GenePharma

RNA oligo

高 分 文 献 集 锦

High Impact Factor References

吉玛基因

www.genepharma.com

目录

介绍

吉玛基因由入选国家重大人才引进工程的张佩琢博士领衔的海归创业团队，于 2003 年在上海张江高科技园区创立，2007 年在苏州生物医药产业园设立总部。

目前公司拥有处于国际先进水平的 siRNA 化学合成的全部核心技术，包括 RNA 单体合成技术、普通和修饰的 siRNA oligo 合成技术、核酸荧光标记技术、多种核苷酸化学修饰技术、shRNA 质粒载体构建技术，慢病毒载体构建以及包装技术、microRNA 荧光定量 PCR 检测试剂盒、荧光定量 PCR 探针合成技术及其荧光定量 PCR、RNA Fish 检测技术等。在基因编辑技术上，公司拥有化学合成 gRNA、载体构建、病毒包装等多种平台，结合载体构建及直接使用 Cas-9 蛋白等方法实现基因编辑。在此基础上，吉玛公司已经发展形成强大的细胞技术平台，包括细胞增殖检测(MTT & CCK-8)、细胞凋亡检测 (Annexin V/PI)、细胞迁移&侵袭实验(Transwell)、酶联免疫吸附实验（ELISA）等。此外，公司也建立了规范的 SPF 级动物房，开展转基因动物、PDX 模型建立和应用等技术服务。拥有一个近千平米的三类诊断试剂 GMP 生产车间和 1500 平方米的 RNA 药物中试车间。

公司产品涵盖化学合成的 RNA 单体，普通和修饰的 siRNA oligo，生物大分子标记用荧光染料；生物合成 siRNA、shRNA；转录编码 shRNA 的 DNAs、转录编码 shRNA 的质粒载体；慢病毒载体 lentiviurs 的构建以及包装，基于化学合成的 RNAi 的全程服务；基于载体调控的 shRNA RNAi全程服务；siRNA 相关试剂和 RNA 技术相关产品的销售；microRNA 荧光定量 PCR 检测试剂盒、荧光定量 PCR 探针和引物、荧光定量 PCR 检测服务；基因编辑相关试剂和技术服务；转基因动物；常用的分子生物学试剂、实验耗材销售等。

RESEARCH

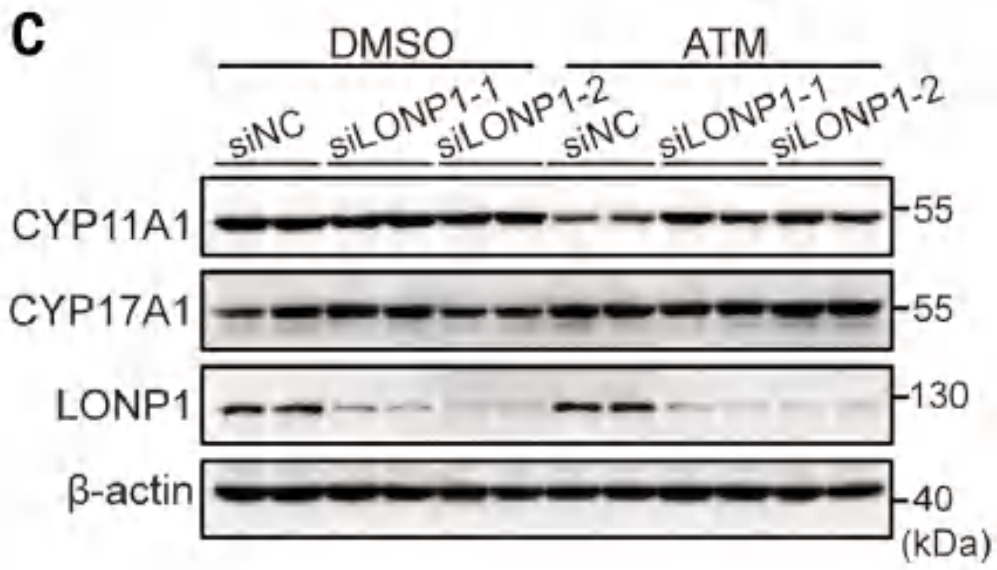
RESEARCH ARTICLE SUMMARY

ENDOCRINOLOGY

Artemisinins ameliorate polycystic ovarian syndrome by mediating LONP1-CYP11A1 interaction

Yang Liu†, Jing-jing Jiang†, Shao-yue Du†, Liang-shan Mu, Jian-jun Fan, Jun-chi Hu, Yao Ye, Meng Ding, Wei-yu Zhou, Qiu-han Yu, Yi-fan Xia, Hong-yu Xu, Yi-jie Shi, Shu-wen Qian, Yan Tang, Wei Li, Yong-jun Dang, Xi Dong, Xiao-ying Li, Cong-jian Xu, Qi-qun Tang*

Polycystic ovarian syndrome(PCOS), a prevalent reproductive endocrinedisorder affecting 10 to 13%ofwomen in theirreproductive age, is characterized by hyperandrogenemia,ovulatory dysfunction, polycysticovarian morphology, and often by associatedmetabolic disorders. Androgen excess is a keyfactor driving the phenotypic features of PCOS.Despite the high prevalence of PCOS, pharmacologicinterventions for such a complicatedsyndrome encounter substantial challenges.The treatment options currently available forPCOS are limited and mainly tailored to managementof specific symptoms. Consequently,there is a compelling and urgent need for thedevelopment of innovative therapeutic strategies.



SCIENCE

Liu et al., Science 384, eadk5382 (2024) 14 June 2024
Impact Factor: 44.7

Materials and Method

The **siRNAs** were generated by **GenePharma**

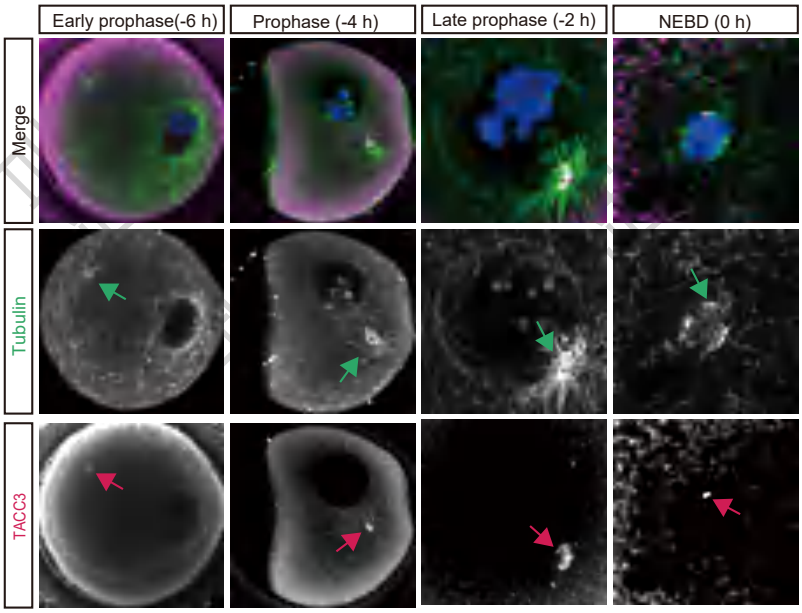
RESEARCH ARTICLE SUMMARY

HUMAN FERTILITY

The mechanism of acentrosomal spindle assembly in human oocytes

INTRODUCTION: Spindle assembly is essential for ensuring accurate chromosome transmission in both meiosis and mitosis. In somatic cells, mitotic spindle assembly is mediated by dupli-cated centrosomes, but canonical centrosomes are absent in the oocytes of many species. In rodents, acentriolar microtubule organizing centers (aMTOCs) are responsible for meiotic spindle assembly, but it has long been sup-posed that human oocytes lack prominent aMTOCs on the meiotic spindle, and the exact mechanism of acentrosomal spindle assembly in human oocytes has remained unclear.

RATIONALE: Microtubule nucleation and en-suring spindle assembly are core events reg-ulating oocyte nuclear maturation. To identify the potential proteins driving spindle micro-tubule nucleation in human oocytes, we sys-tematically localized 86 human centrosome and microtubule-related proteins by immunofluo-rescence or three-dimensional high-resolution live cell imaging in more than 2000 human oocytes. We then tracked the dynamic migra-tion of identified microtubule nucleators at different time points before and after nuclear envelope breakdown (NEBD). We further down-regulated corresponding proteins to confirm their role in microtubule nucleation and spin-dle assembly. Given that spindle microtubule nucleation defects result in impaired spindle assembly and abnormal oocyte maturation, we screened for mutations in genes encoding components of microtubule nucleators in a cohort of 1394 infertile female patients characterized by oocyte maturation arrest.



SCIENCE
2022 Nov;378 (6621)
Impact Factor:56.9

Materials and Method
The **siRNAs** were provided by **GenePharma**.

Science
AAAS

RESEARCH ARTICLE

METABOLISM

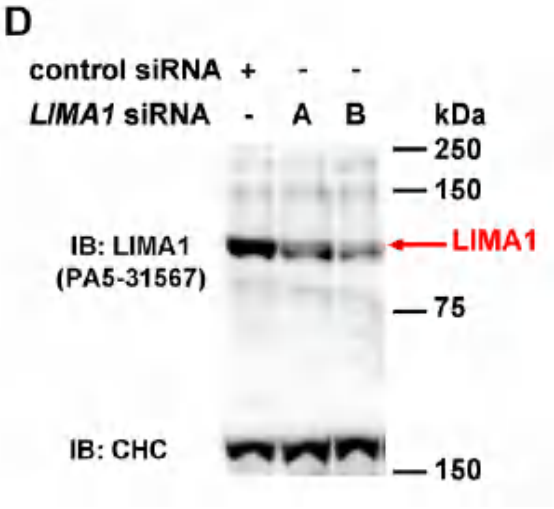
A *LIMA1* variant promotes low plasma LDL cholesterol and decreases intestinal cholesterol absorption

Ying-Yu Zhang[1,2*], Zhen-Yan Fu[3*], Jian Wei[2*], Wei Qi[4], Gulinaer Baituola[3], Jie Luo[2], Ya-Jie Meng[3], Shu-Yuan Guo[4,5], Huiyong Yin[4,5], Shi-You Jiang[2], Yun-Feng Li[2], Hong-Hua Miao[1], Yong Liu[2], Yan Wang[2], Bo-Liang Li[1], Yi-Tong Ma[3]†, Bao-Liang Song[2]†

A high concentration of low-density lipoprotein cholesterol (LDL-C) is a major risk factor for cardiovascular disease. Although LDL-C levels vary among humans and are heritable, the genetic factors affecting LDL-C are not fully characterized.We identified a rare frameshift variant in the LIMA1 (also known as EPLIN or SREBP3) gene from a Chinese family of Kazakh ethnicity with inherited low LDL-C and reduced cholesterol absorption. In a mouse model, LIMA1 was mainly expressed in the small intestine and localized on the brush border membrane. LIMA1 bridged NPC1L1, an essential protein for cholesterol absorption, to a transportation complex containing myosin Vb and facilitated cholesterol uptake. Similar to the human phenotype, Lima1-deficient mice displayed reduced cholesterol absorption and were resistant to diet-induced hypercholesterolemia. Through our study of both mice and humans, we identify LIMA1 as a key protein regulating intestinal cholesterol absorption.

Science
2018 Jun 8; 360(6393): 1087-92
Impact Factor: 56.9

Materials and Methods
Duplexes of **siRNA** were synthesized by **Genepharma** (Shanghai, China).



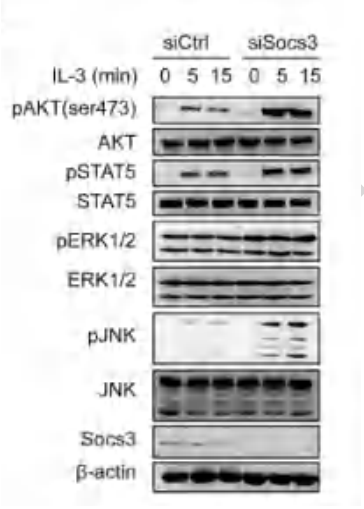
LETTER

doi:10.1038/nature25434

Tet2 promotes pathogen infection–induced myelopoiesis through mRNA oxidation

Qicong Shen[1]*, Qian Zhang[1,2]*, Yang Shi[3], Qingzhu Shi[3], Yanyan Jiang[1], Yan Gu[1], Zhiqing Li[3], Xia Li[2], Kai Zhao[2], Chunmei Wang[2], Nan Li[1] & Xuetao Cao[1,2]

Varieties of RNA modification form the epitranscriptome for posttranscriptional regulation1. 5-Methylcytosine (5-mC) is a sparse RNA modification in messenger RNA (mRNA) under physiological conditions2. The function of RNA 5-hydroxymethylcytosine (5-hmC) oxidized by ten-eleven translocation (Tet) proteins in Drosophila has been revealed more recently3,4. However, the turnover and function of 5-mC in mammalian mRNA have been largely unknown. Tet2 suppresses myeloid malignancies mostly in an enzymatic activity-dependent manner5, and is important in resolving inflammatory response in an enzymatic activityindependent way6. Myelopoiesis is a common host immune response in acute and chronic infections; however, its epigenetic mechanism needs to be identified. Here we demonstrate that Tet2 promotes infection-induced myelopoiesis in an mRNA oxidation-dependent manner through Adar1-mediated repression of Socs3 expression at the post-transcription level. Tet2 promotes both abdominal sepsis-induced emergency myelopoiesis and parasite-induced mast cell expansion through decreasing mRNA levels of Socs3, a key negative regulator of the JAK–STAT pathway that is critical for cytokine-induced myelopoiesis. Tet2 represses Socs3 expression through Adar1, which binds and destabilizes Socs3 mRNA in a RNA editing-independent manner. For the underlying mechanism of Tet2 regulation at the mRNA level, Tet2 mediates oxidation of 5-mC in mRNA. Tet2 deficiency leads to the transcriptome-wide appearance of methylated cytosines, including ones in the 3′ untranslated region of Socs3, which influences double-stranded RNA formation for Adar1 binding, probably through cytosine methylation-specific readers, such as RNA helicases. Our study reveals a previously unknown regulatory role of Tet2 at the epitranscriptomic level, promoting myelopoiesis during infection in the mammalian system by decreasing 5-mCs in mRNAs. Moreover, the inhibitory function of cytosine methylation on double-stranded RNA formation and Adar1 binding in mRNA reveals its new physiological role in the mammalian system.



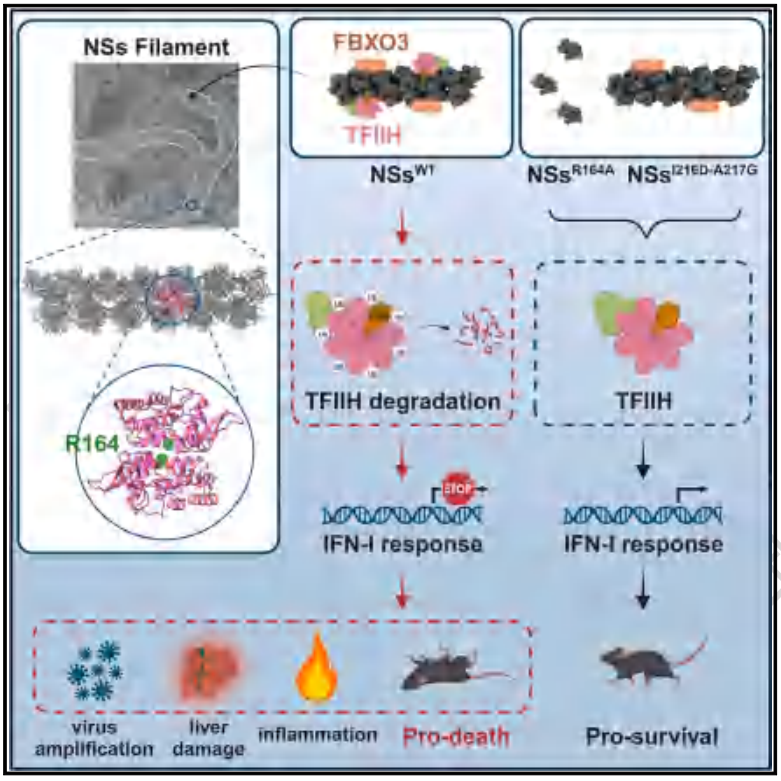
Nature
2018 Feb 1; 554(7690): 123-7
Impact Factor: 64.8

Materials and Method

The mouse-specific **siRNAs** targeting Socs3 and Adar1 were designed and synthesized by **GenePharma** (Shanghai).

Rift Valley fever virus coordinates the assembly of a programmable E3 ligase to promote viral replication

Graphical abstract



Authors

Huiling Li, Yulan Zhang, Guibo Rao, ..., Pierre-Yves Lozach, Sheng Cao, Ke Peng

Correspondence

caosheng@wh.iov.cn (S.C.), pengke@wh.iov.cn (K.P.)

In brief

The non-structural protein NSs of Rift Valley fever virus forms a filamentous E3 ligase to trigger efficient degradation of the cellular TFIIH complex, leading to robust inhibition of antiviral immunity and enhanced viral pathogenesis. The NSs filament structure can be programmed to target other proteins for proteasome-dependent degradation, serving as a versatile targeted protein degrader.

Cell

Li et al., 2024, Cell 187, 1–18

Impact Factor: 45.5

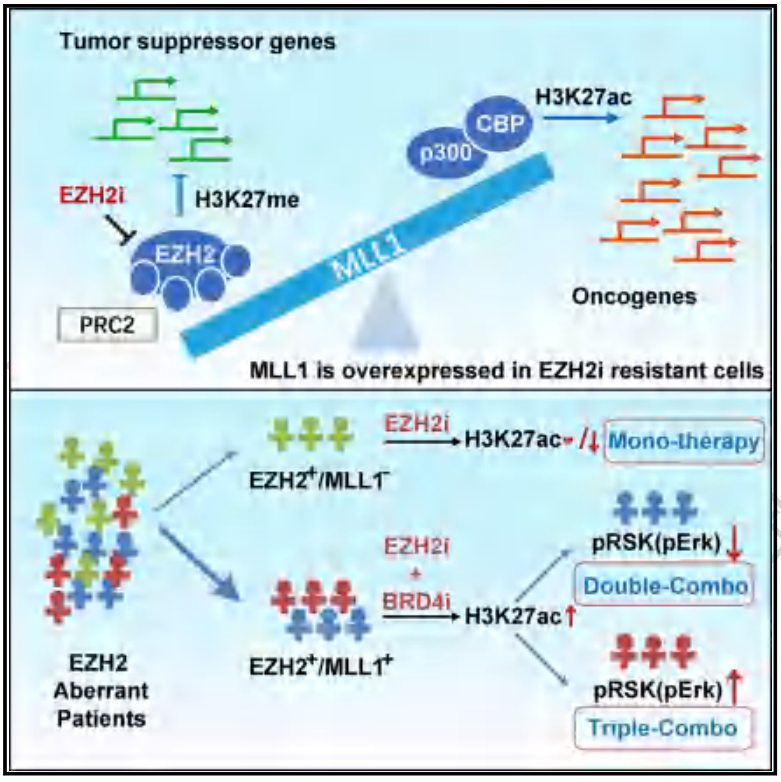
Materials and Method

P62 siRNA-1	GenePharma	CCAACUCCAAUCCAGUCAC
P62 siRNA-2	GenePharma	GCUGCCAUCAUCAAGAGAU
P44 siRNA-1	GenePharma	AGACCAACAUGUUUAUGUUUGUGCU
P44 siRNA-2	GenePharma	CUGGCUGUAUUCAUAAGAU
XPB siRNA-1	GenePharma	CCGGAAGCAAAUGUCCUCA
XPB siRNA-2	GenePharma	GCCCUAAAGGAAUAUGCCA
P34 siRNA-1	GenePharma	GCUGGGAAAUUCGCAUUUA
P34 siRNA-2	GenePharma	GCCUUCUCUUCUGCAGUAU
P52 siRNA-1	GenePharma	UACAAUGCAGGAAUCUGCAGGAAUU
P52 siRNA-2	GenePharma	CAGCAAGGCUCAGGAGGAAAGUACA

Cell

Targeting Epigenetic Crosstalk as a Therapeutic Strategy for EZH2-Aberrant Solid Tumors

Graphical Abstract



Authors

Xun Huang, Juan Yan, Min Zhang, ..., Minjia Tan, Jian Ding, Meiyu Geng

Correspondence

mjtan@simm.ac.cn (M.T.),
jding@simm.ac.cn (J.D.),
mygeng@simm.ac.cn (M.G.)

In Brief

Epigenetic crosstalk targeting together with MLL1-based stratification and inhibiting feedback MAPK activation expand EZH2 inhibitors' therapeutic utility and efficacy in patient-derived solid tumor models.

Cell
2018 Sep 13;175(1):186-199.e19
Impact Factor:64.5

Materials and Method

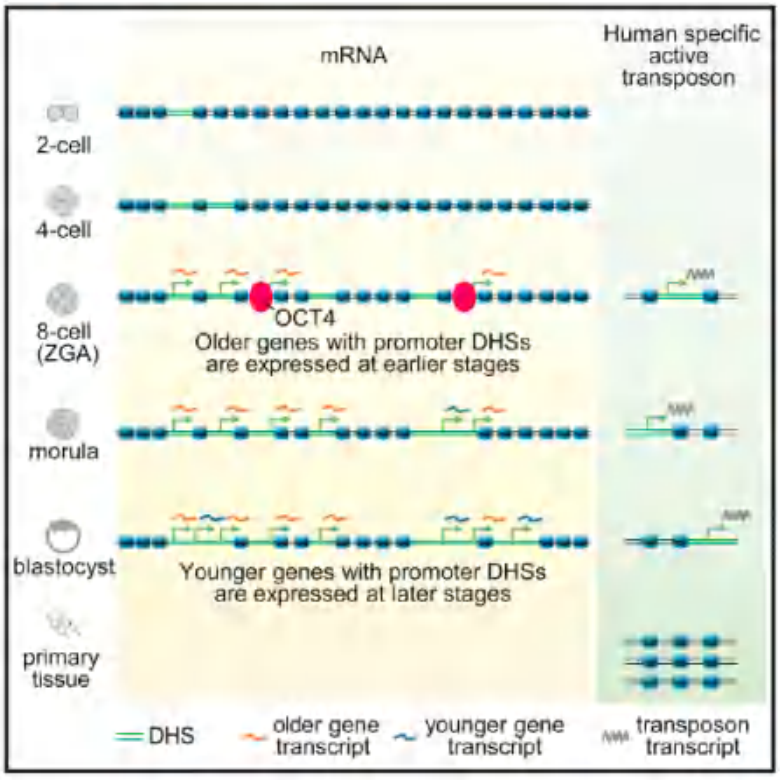
siRNAs were ordered as RPHPLC-purified duplexes from **GenePharma**.

siRNAs	Oligonucleotide (5'–3')
siEZH2 #1	GCUGAAGCCUCAAUGUUUA
siEZH2 #2	GAAUGGAAACAGCGAAGGA
sip300	GGACUACCCUAUCAAGUAATT
siCBP	GAGCCAUCUAGUGCAUAAATT
siMAPK3 #1	GAGAUGUCUACAUUGUGCATT
siMAPK3 #2	CUCGCGUGGCCAUCAAGAATT
siBRD4 #1	GAACCUCCCUGAUUACUAU
siBRD4 #2	GAGCUACCCACAGAAGAAATT
siSUZ12	GGCCAUGGAAAUGCUAUCATT
siMLL1#1	AGGAGGATTGTGAAGCAG
siMLL1#2	CGAAACAGCTATCACCTT

Cell

Chromatin Accessibility Landscape in Human Early Embryos and Its Association with Evolution

Graphical Abstract



Authors

Lei Gao, Keliang Wu, Zhenbo Liu, ..., Jianqiao Liu, Zi-Jiang Chen, Jiang Liu

Correspondence

ljq88gz@163.com (J.L.), chenzijiang@hotmail.com (Z.-J.C.), liuj@big.ac.cn (J.L.)

In Brief

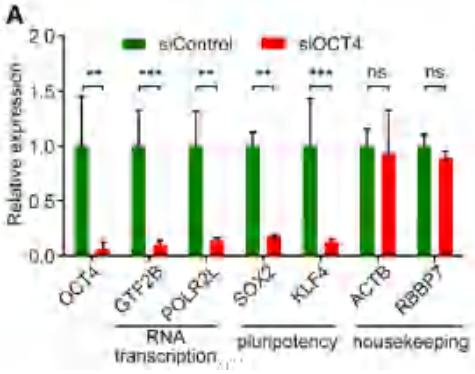
The dynamic landscape of open chromatin during early human embryogenesis provides a rich resource and insights into a zygotic genome activation.

Cell
2018 Mar 22; 173: 248-59
Impact Factor:64.5

Materials

Oligonucleotides

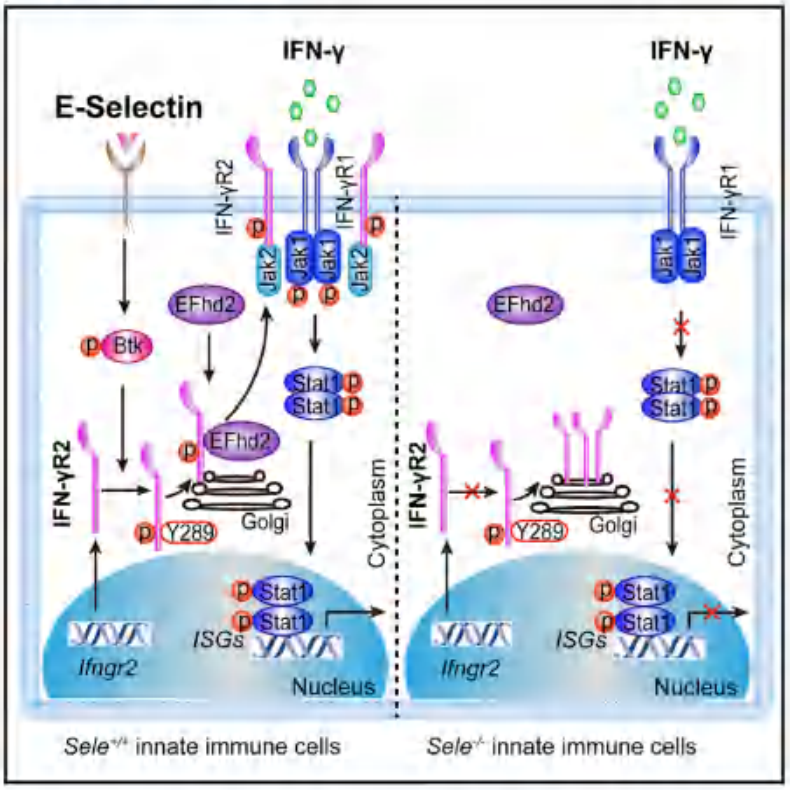
Negative control siRNA: UUCUCCGAACGUGUCACGUdTdT	Synthesized by Shanghai GenePharma
Human OCT4 siRNA #1: AAGGAUGUGGUCCGAGUGUGGdTdT	[illegible] et al., 2004, synthesized by Shanghai GenePharma
Mouse OCT4 siRNA #1: AAGGAUGUGGUUCGAGUAUGGdTdT	[illegible] et al., 2016, synthesized by Shanghai GenePharma
Mouse OCT4 siRNA #2: GGAGUCCCAGGACAUGAAAdTdT	[illegible] et al., 2015, synthesized by Shanghai GenePharma



Cell

Phosphorylation-Mediated IFN-γR2 Membrane Translocation Is Required to Activate Macrophage Innate Response

Graphical Abstract



Authors

Xiaoqing Xu, Jia Xu, Jiacheng Wu, ..., Juan Liu, Bing Liu, Xuetao Cao

Correspondence

caoxt@immunol.org

In Brief

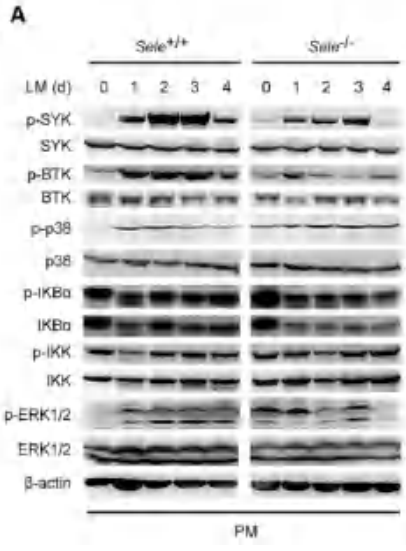
Membrane translocation of cytoplasmic IFN-γR2 is a critical step for the activation of macrophage innate response against intracellular bacterial infection.

Cell
2018 Nov 29; 175: 1-16
Impact Factor: 64.5

Materials

Oligonucleotides

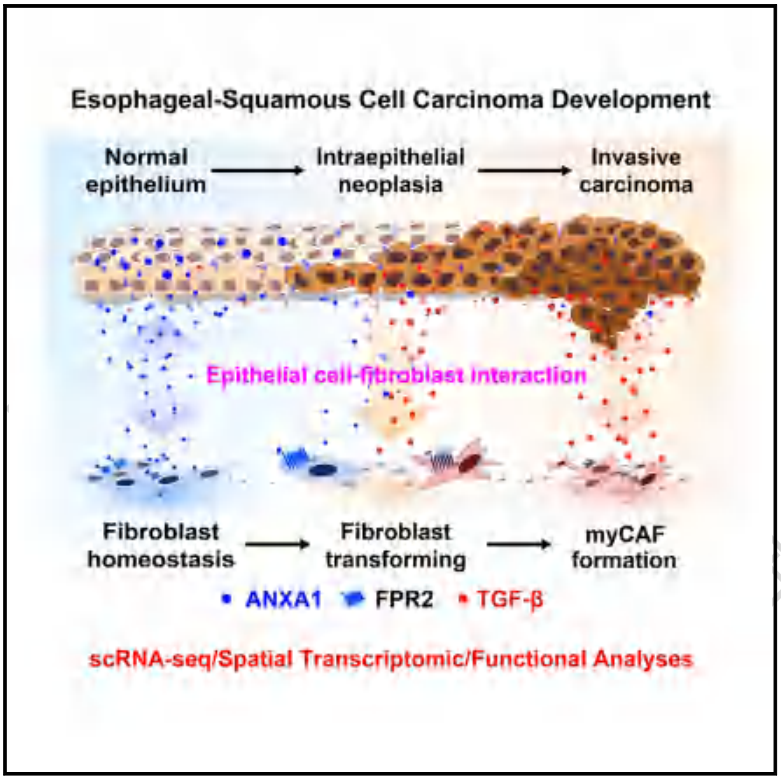
siRNA: *Syk*: 5'-GGCAGCUAGUGGAACAUUATT-3' (sense)	Genepharma
siRNA: *Btk*: 5'-CAUCACCUUUAAACUUCAATT-3' (sense)	Genepharma
siRNA: *p65*: 5'-CUCAAGAUCUGCCGAGUAATT-3' (sense)	Genepharma
siRNA: *Efhd2-1*: 5'-CCAGGAAGCAGAUCAAAGATT-3' (sense)	Genepharma
siRNA: *Efhd2-2*: 5'-GCCGCUUUGAGGAAGAGAUTT-3' (sense)	Genepharma



Cancer Cell

Epithelial cells activate fibroblasts to promote esophageal cancer development

Graphical abstract



Authors

Yamei Chen, Shihao Zhu, Tianyuan Liu, ..., Guoyu Cheng, Dongxin Lin, Chen Wu

Correspondence

lindx@cicams.ac.cn (D.L.), chenwu@cicams.ac.cn (C.W.)

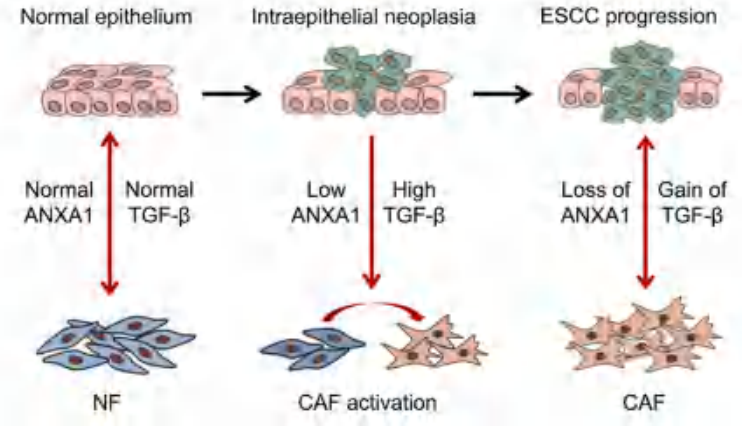
In brief

Chen et al. perform single-cell and spatial transcriptomic analyses of multistage esophageal lesions and reveal gradual loss of ANXA1 expression in epithelial cells during ESCC development. Both in vitro and in vivo experiments demonstrate that suppressed ANXA1-FPR2 ligand-receptor interaction between epithelial-fibroblast leads to cancer-associated fibroblast formation, which promotes ESCC progression.

CANCER CELL
2023 Mar 23;41, 1–16
Impact Factor:50.3

Materials and Method

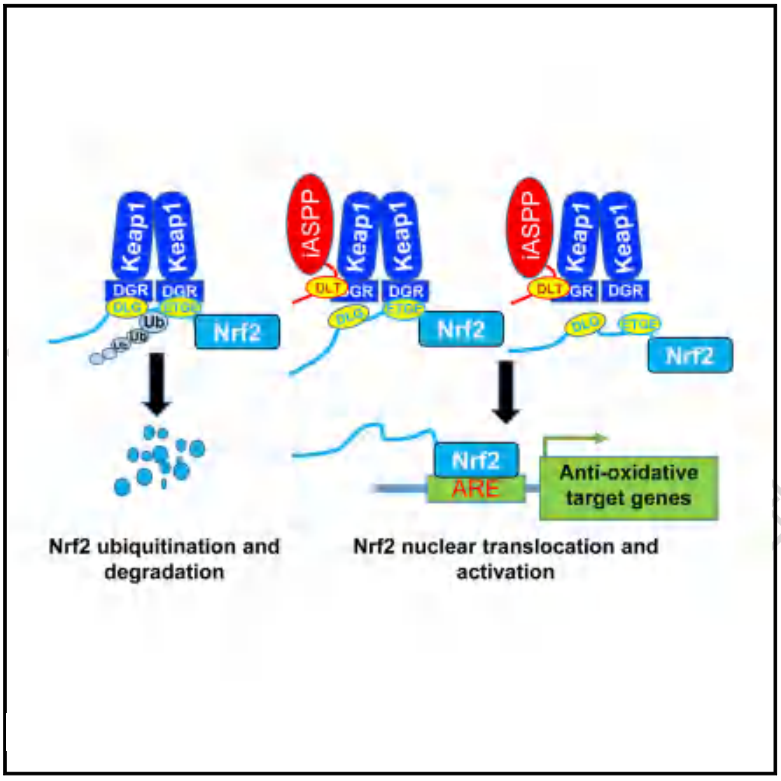
Small interfering RNA (siRNA) targeting FPR2, KLF4, KLF5, CEBPB or FOXA1 (Table S6) was purchased from **GenePharma**.



Cancer Cell

iASPP Is an Antioxidative Factor and Drives Cancer Growth and Drug Resistance by Competing with Nrf2 for Keap1 Binding

Graphical Abstract



Authors

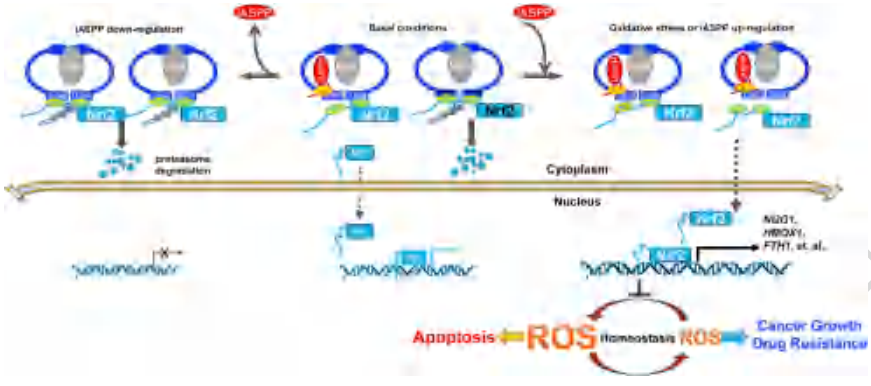
Wenjie Ge, Kunming Zhao, Xingwen Wang, ..., Yiwei Cheng, Shijian Jiang, Ying Hu

Correspondence

huying@hit.edu.cn

In Brief

Ge et al. show that iASPP, a known p53 inhibitor, functions independently of p53 to compete with Keap1 for Nrf2 binding, leading to decreased Nrf2 ubiquitination and increased Nrf2 accumulation and antioxidative transactivation. The iASPP-Keap1-Nrf2 axis promotes cancer growth and drug resistance.



Cancer Cell
2017 Nov 13;32(5):561-573
Impact Factor:50.3

Materials and Method

siRNA specifically targeting iASPP, Nrf2, Keap1, b-TrCP1 or p53 and non-specific si-control were synthesized by **GenePharma**.

nature biotechnology

ARTICLES

https://doi.org/10.1038/s41587-021-01112-1

Check for updates

Optogenetic control of RNA function and metabolism using engineered light-switchable RNA-binding proteins

Renmei Liu[1,2,5], Jing Yang[1,2,5], Jing Yao[1,2], Zhou Zhao[1,2], Wei He[1], Ni Su[1,2], Zeyi Zhang[1,2], Chenxia Zhang[1,2], Zhuo Zhang[1], Haibo Cai[1], Linyong Zhu , Yuzheng Zhao , Shu Quan [1], Xianjun Chen and Yi Yang

Recent studies have reshaped prior conceptions about the func-tions of RNAs, particularly the numerous non-coding RNAs that play important roles in diverse cellular activities1. RNAs exhibit complex dynamics and functions at specific times and loca-tions inside cells, and these dynamics include changes in their expression, degradation, translocation, splicing and other chemical modifications2–4; thus, techniques capable of the precise and spatio-temporal manipulation of RNA dynamics and functions are highly desirable for understanding the physiological functions of RNA in live cells5,6. To this end, light is an ideal trigger because it is easy to obtain, highly tunable, non-toxic and, most importantly, has a high spatiotemporal resolution7. Several studies have attempted to control RNA functions through the activation of chemically caged RNAs using UV light; these efforts allowed for the optical control of gene expression8–12, ribozyme activity13, CRISPR–Cas function14 and protein–RNA crosslinking15,16. However, the acceptance of these methodologies by biologists has been limited, probably because of the toxicity of UV radiation and the technical complexities associ-ated with the synthesis of caged RNAs6,17. Alternatively, RNA func-tions might be optogenetically controlled by genetically encoded photoswitchable RBPs6. Optogenetics is a burgeoning technique in which genetically encoded photoswitchable proteins are used to manipulate biological processes with unsurpassable flexibility and high spatiotemporal precision7,18. In eukaryotic cells, numer-ous proteins are thought to function as RBPs, which govern almost all aspects of RNA metabolism, including transcription, process-ing, translation, turnover and cellular localization19,20. Nevertheless, reports on natural photoswitchable RBPs are extremely rare.

Nature Biotechnology
2022 Jan;40(5):779-786
Impact Factor:46.9

Materials and Method

RAT RNA containing a 5′-terminal TAMRA fluorophore (**GenePharma**) was used for analysis of RNA binding by fluorescence anisotropy.

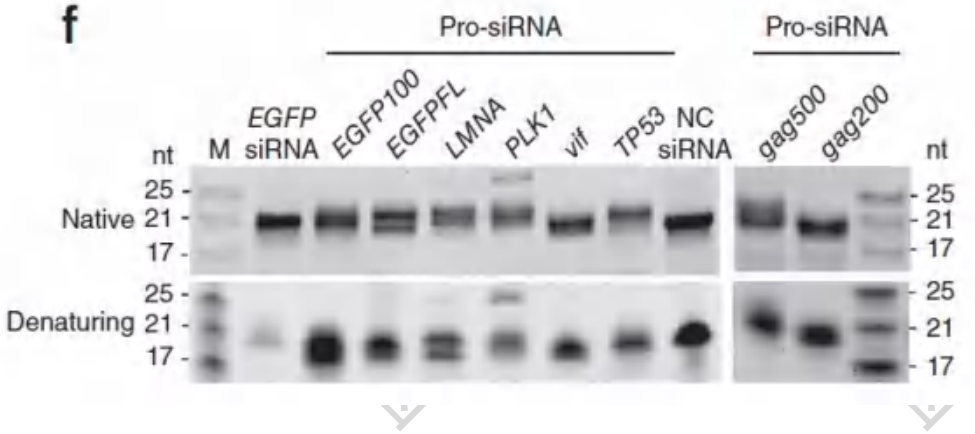
LETTERS

nature biotechnology

Efficient and specific gene knockdown by small interfering RNAs produced in bacteria

Linfeng Huang[1,2], Jingmin Jin[3], Padraig Deighan[4,5], Evgeny Kiner[1,2], Larry McReynolds[3] & Judy Lieberman[1,2]

Synthetic small interfering RNAs (siRNAs) are an indispensable tool to investigate gene function in eukaryotic cells1,2 and may be used for therapeutic purposes to knock down genes implicated in disease3. Thus far, most synthetic siRNAs have been produced by chemical synthesis. Here we present a method to produce highly potent siRNAs in *Escherichia coli*. This method relies on ectopic expression of p19, an siRNAbinding protein found in a plant RNA virus4,5. When expressed in *E. coli*, p19 stabilizes an ~21-nt siRNA-like species produced by bacterial RNase III. When mammalian cells are transfected by them, siRNAs that were generated in bacteria expressing *p19* and a hairpin RNA encoding 200 or more nucleotides of a target gene reproducibly knock down target gene expression by ~90% without immunogenicity or off-target effects. Because bacterially produced siRNAs contain multiple sequences against a target gene, they may be especially useful for suppressing polymorphic cellular or viral genes.



Nature Biotechnology
2013 Apr; 31(4): 350-9
Impact Factor: 46.9

Materials and Method

For each assay, 200 ng of an unmodified synthetic **negative control siRNA** (**GenePharma**). **negative-control siRNA** (NC siRNA, B01001, **GenePharma**); **positive-control siRNA TP53** (B03001, **GenePharma**).

ARTICLE OPEN

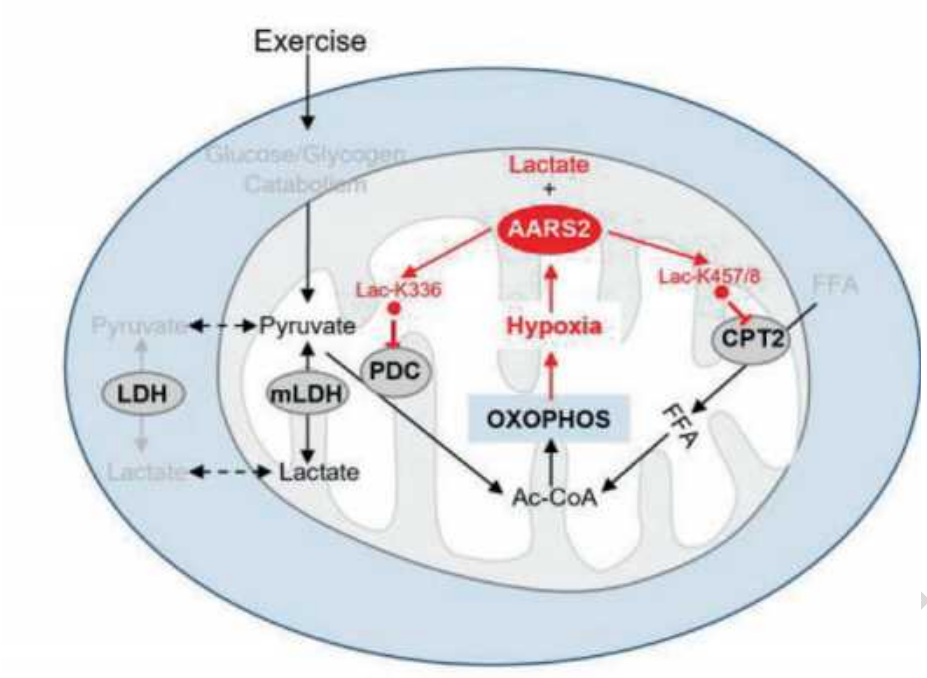
Check for updates

Hypoxia induces mitochondrial protein lactylation to limit oxidative phosphorylation

Yunzi Mao[1,8], Jiaojiao Zhang[1,8], Qian Zhou[1,8], Xiadi He[1,2,3,8], Zhifang Zheng[1], Yun Wei[1,2,3], Kaiqiang Zhou[1], Yan Lin[1,4,5], Haowen Yu[1], Haihui Zhang[1], Yineng Zhou[1], Pengcheng Lin[6], Baixing Wu[7], Yiyuan Yuan[1,4], Jianyuan Zhao[1,4], Wei Xu[1,4,5]✉ and Shimin Zhao[1,4,6]✉

Oxidative phosphorylation (OXPHOS) consumes oxygen to produce ATP. However, the mechanism that balances OXPHOS activity and intracellular oxygen availability remains elusive. Here, we report that mitochondrial protein lactylation is induced by intracellular hypoxia to constrain OXPHOS. We show that mitochondrial alanyl-tRNA synthetase (AARS2) is a protein lysine lactyltransferase, whose proteasomal degradation is enhanced by proline 377 hydroxylation catalyzed by the oxygen-sensing hydroxylase PHD2. Hypoxia induces AARS2 accumulation to lactylate PDHA1 lysine 336 in the pyruvate dehydrogenase complex and carnitine palmitoyltransferase 2 (CPT2) lysine 457/8, inactivating both enzymes and inhibiting OXPHOS by limiting acetyl-CoA influx from pyruvate and fatty acid oxidation, respectively. PDHA1 and CPT2 lactylation can be reversed by SIRT3 to activate OXPHOS. In mouse muscle cells, lactylation is induced by lactate oxidation-induced intracellular hypoxia during exercise to constrain high-intensity endurance running exhaustion time, which can be increased or decreased by decreasing or increasing lactylation levels, respectively. Our results reveal that mitochondrial protein lactylation integrates intracellular hypoxia and lactate signals to regulate OXPHOS.

Cell Research (2024) 34:13–30; https://doi.org/10.1038/s41422-023-00864-6



CELL RESEARCH
2024 Jan;34(1):13-30
Impact Factor:44.1

Materials and Method

Oligonucleotides used for **small interfering RNA (siRNA)**-mediated silencing of VHL, PHD1, PHD2, PHD3, AARS2, and SIRT3 were synthesized by **GenePharma** (Shanghai, China). **Synthetic oligonucleotides** were purchased from **Genepharma**.

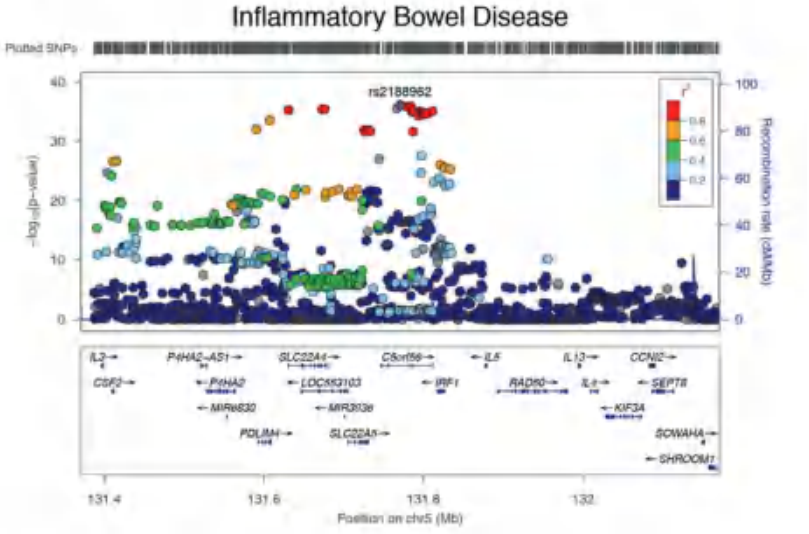
ARTICLE OPEN

Check for updates

A lncRNA from an inflammatory bowel disease risk locus maintains intestinal host-commensal homeostasis

Hongdi Ma[1,2,11], Taidou Hu[1,2,11], Wanyin Tao[1,2], Jiyu Tong[3], Zili Han[1,2], Dietmar Herndler-Brandstetter[3], Zheng Wei[3], Ruize Liu[4], Tingyue Zhou[1,2], Qiuyuan Liu[5], Xuemei Xu[1], Kaiguang Zhang[1], Rongbin Zhou[2], Judy H. Cho[6], Hua-Bing Li[7]✉, Hailiang Huang[4]✉, Richard A. Flavell[3,8]✉ and Shu Zhu[1,2,9,10]✉

Inflammatory bowel diseases (IBD) are known to have complex, genetically influenced etiologies, involving dysfunctional interactions between the intestinal immune system and the microbiome. Here, we characterized how the RNA transcript from an IBD-associated long non-coding RNA locus ("CARINH-Colitis Associated IRF1 antisense Regulator of Intestinal Homeostasis") protects against IBD. We show that CARINH and its neighboring gene coding for the transcription factor IRF1 together form a feedforward loop in host myeloid cells. The loop activation is sustained by microbial factors, and functions to maintain the intestinal host-commensal homeostasis via the induction of the anti-inflammatory factor IL-18BP and anti-microbial factors called guanylate-binding proteins (GBPs). Extending these mechanistic insights back to humans, we demonstrate that the function of the CARINH/IRF1 loop is conserved between mice and humans. Genetically, the T allele of rs2188962, the most probable causal variant of IBD within the CARINH locus from the human genetics study, impairs the inducible expression of the CARINH/IRF1 loop and thus increases genetic predisposition to IBD. Our study thus illustrates how an IBD-associated lncRNA maintains intestinal homeostasis and protects the host against colitis.



CELL RESEARCH
2023 Apr ;33(5):372-388
Impact Factor:44.1

Materials and Methods

siRNA and **non-targeting control siRNA** were purchased from **GenePharma**.
For FISH, complementary probes targeting human CARINH were designed, synthesized and labeled by **Cy3** (**GenePharma**).
The **donor DNA** containing mutation of rs2188962 was synthesized (**GenePharma**).

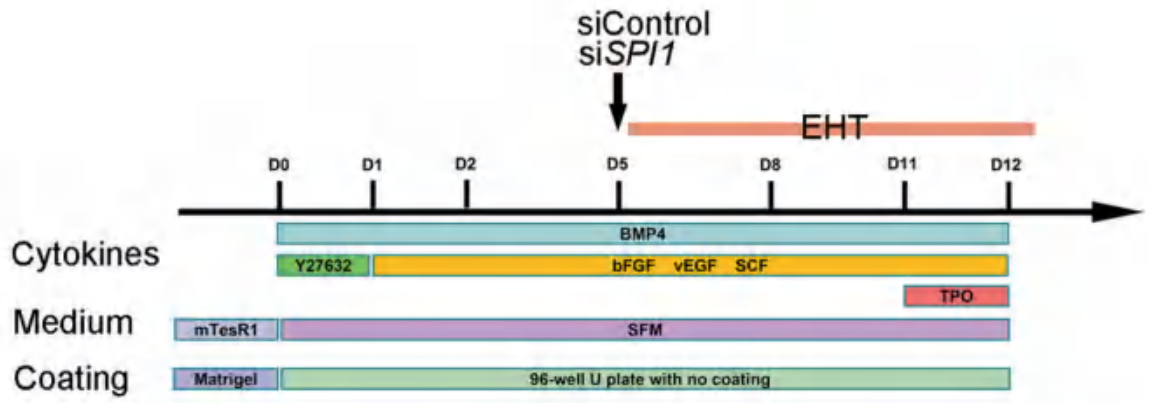
ARTICLE

Check for updates

Activation of lineage competence in hemogenic endothelium precedes the formation of hematopoietic stem cell heterogeneity

Jun Xia[1,2,3,6], Mengyao Liu[4,6], Caiying Zhu[4], Shicheng Liu[1,2,3], Lanlan Ai[4], Dongyuan Ma[1,2,3], Ping Zhu[4], Lu Wang[4]✉ and Feng Liu[1,2,3,5]✉

Hematopoietic stem and progenitor cells (HSPCs) are considered as a heterogeneous population, but precisely when, where and how HSPC heterogeneity arises remain largely unclear. Here, using a combination of single-cell multi-omics, lineage tracing and functional assays, we show that embryonic HSPCs originate from heterogeneous hemogenic endothelial cells (HECs) during zebrafish embryogenesis. Integrated single-cell transcriptome and chromatin accessibility analysis demonstrates transcriptional heterogeneity and regulatory programs that prime lymphoid/myeloid fates at the HEC level. Importantly, spi2+ HECs give rise to lymphoid/myeloid-primed HSPCs (L/M-HSPCs) and display a stress-responsive function under acute inflammation. Moreover, we uncover that Spi2 is required for the formation of L/M-HSPCs through tightly controlling the endothelial-to-hematopoietic transition program. Finally, single-cell transcriptional comparison of zebrafish and human HECs and human induced pluripotent stem cell-based hematopoietic differentiation results support the evolutionary conservation of L/M-HECs and a conserved role of SPI1 (spi2 homolog in mammals) in humans. These results unveil the lineage origin, biological function and molecular determinant of HSPC heterogeneity and lay the foundation for new strategies for induction of transplantable lineage-primed HSPCs in vitro.



Cell Research
2023 Jun;33(6):448-463.
Impact Factor:44.1

Materials and Method

For SPI1 siRNA KD assay, the **siRNAs** for SPI1 (NM_003120.3) were designed and synthesized by **GenePharma** (Supplementary information, Table S10).ntary information, Table S10).

ARTICLE

Check for updates

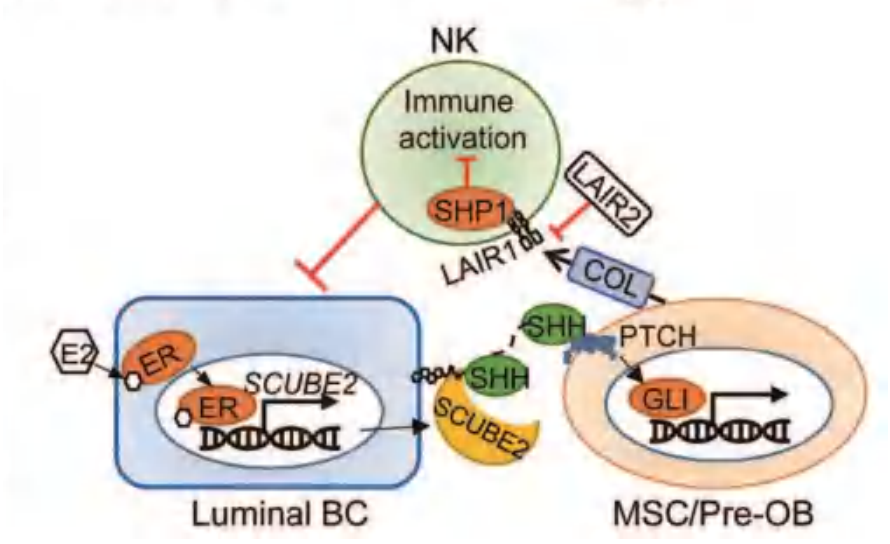
SCUBE2 mediates bone metastasis of luminal breast cancer by modulating immune-suppressive osteoblastic niches

Qiuyao Wu[1], Pu Tian[1], Dasa He[1], Zhenchang Jia[1], Yunfei He[1], Wenqian Luo[1], Xianzhe Lv[1], Yuan Wang[1], Peiyuan Zhang[1], Yajun Liang[1], Wenjin Zhao[2], Jun Qin[1], Peng Su[3], Yi-Zhou Jiang[4], Zhi-Ming Shao[4], Qifeng Yang[5]✉ and Guohong Hu[1]✉

Estrogen receptor (ER)-positive luminal breast cancer is a subtype with generally lower risk of metastasis to most distant organs. However, bone recurrence occurs preferentially in luminal breast cancer. The mechanisms of this subtype-specific organotropism remain elusive. Here we show that an ER-regulated secretory protein SCUBE2 contributes to bone tropism of luminal breast cancer. Single-cell RNA sequencing analysis reveals osteoblastic enrichment by SCUBE2 in early bone-metastatic niches. SCUBE2 facilitates release of tumor membrane-anchored SHH to activate Hedgehog signaling in mesenchymal stem cells, thus promoting osteoblast differentiation. Osteoblasts deposit collagens to suppress NK cells via the inhibitory LAIR1 signaling and promote tumor colonization. SCUBE2 expression and secretion are associated with osteoblast differentiation and bone metastasis in human tumors. Targeting Hedgehog signaling with Sonidegib and targeting SCUBE2 with a neutralizing antibody both effectively suppress bone metastasis in multiple metastasis models. Overall, our findings provide a mechanistic explanation for bone preference in luminal breast cancer metastasis and new approaches for metastasis treatment.

CELL RESEARCH
2023 May 4;33:464–478
Impact Factor:44.1

Materials and Method
siRNAs were purchased from **GenePharma**.



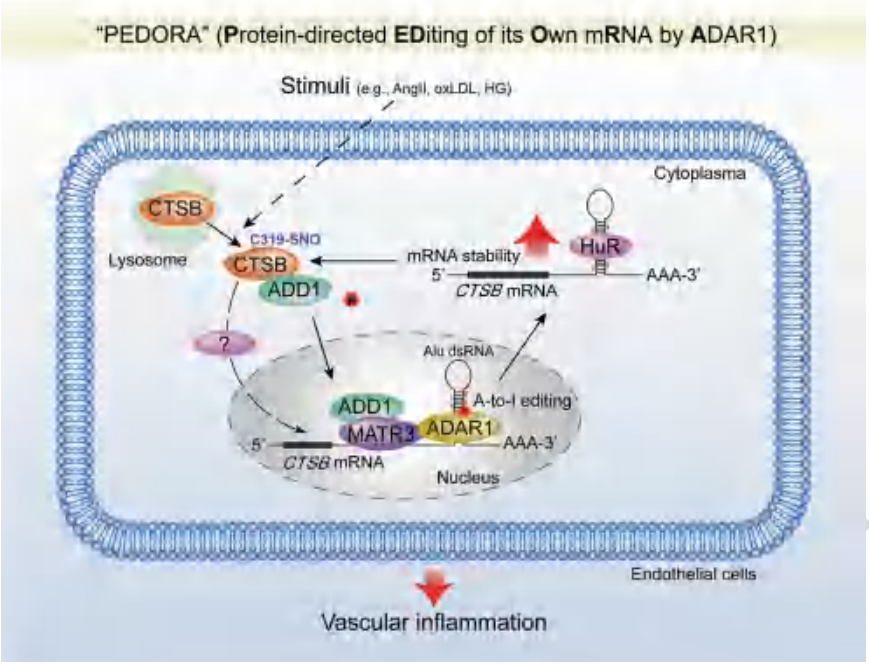
ARTICLE

Check for updates

Cathepsin B S-nitrosylation promotes ADAR1-mediated editing of its own mRNA transcript via an ADD1/MATR3 regulatory axis

Zhe Lin[1,11], Shuang Zhao[1,11], Xuesong Li[1,11], Zian Miao[1], Jiawei Cao[1], Yurong Chen[1], Zhiguang Shi[1], Jia Zhang[1], Dongjin Wang[2], Shaoliang Chen[3], Liansheng Wang[4], Aihua Gu[5], Feng Chen[6], Tao Yang[7], Kangyun Sun[8], Yi Han[9✉], Liping Xie[1✉], Hongshan Chen[1✉] and Yong Ji[1,10✉]

Genetic information is generally transferred from RNA to protein according to the classic “Central Dogma”. Here, we made a striking discovery that post-translational modification of a protein specifically regulates the editing of its own mRNA. We show that S-nitrosylation of cathepsin B (CTSB) exclusively alters the adenosine-to-inosine (A-to-I) editing of its own mRNA. Mechanistically, CTSB S-nitrosylation promotes the dephosphorylation and nuclear translocation of ADD1, leading to the recruitment of MATR3 and ADAR1 to CTSB mRNA. ADAR1-mediated A-to-I RNA editing enables the binding of HuR to CTSB mRNA, resulting in increased CTSB mRNA stability and subsequently higher steady-state levels of CTSB protein. Together, we uncovered a unique feedforward mechanism of proteinexpression regulation mediated by the ADD1/MATR3/ADAR1 regulatory axis. Our study demonstrates a novel reverse flow of information from the post-translational modification of a protein back to the post-transcriptional regulation of its own mRNA precursor. We coined this process as “Protein-directed EDiting of its Own mRNA by ADAR1 (PEDORA)” and suggest that this constitutes an additional layer of protein expression control. “PEDORA” could represent a currently hidden mechanism in eukaryotic gene expression regulation.



CELL RESEARCH
2023 May 8;0:1–16
Impact Factor:44.1

Materials and Method

siRNAs were purchased from **GenePharma** (Shanghai, China) (Supplementary information, Table S6) .

ARTICLE OPEN

Check for updates

NudCL2 is an autophagy receptor that mediates selective autophagic degradation of CP110 at mother centrioles to promote ciliogenesis

Min Liu[1,2,6], Wen Zhang[2,3,6], Min Li[2], Jiaxing Feng[2], Wenjun Kuang[2], Xiying Chen[2], Feng Yang[2], Qiang Sun[2], Zhangqi Xu[2], Jianfeng Hua[2], Chunxia Yang[2], Wei Liu[2], Qiang Shu[1], Yuehong Yang[2], Tianhua Zhou[2,3,4,5]✉ and Shanshan Xie[1]✉

INTRODUCTION

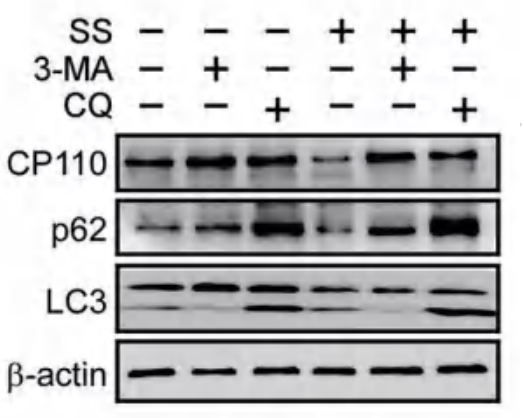
Primary cilia are microtubule-based organelles that project from the surface of vertebrate cells to transduce extracellular signals into intracellular responses,1,2 and are of crucial importance in vertebrate development and homeostasis maintenance.3–7 Defects in cilia function are involved in multiple human syndromes that are collectively called ciliopathies, including situs inversus, congenital heart defects, cystic kidney disease and so on.8–12 Primary cilia form in the interphase, and are resorbed prior to mitosis.13–15 In G0 or early G1 phase, mother centrioles convert into basal bodies, dock to the plasma membrane through their distal appendages, and nucleate ciliary axonemes to form primary cilia.16 Although ciliogenesis regulation has been intensively studied, the mechanism of ciliogenesis initiation remains unclear.

Centriolar coiled-coil protein 110 (CP110), originally character-ized as a cyclin-dependent kinase substrate, caps the distal ends of both mother and daughter centrioles, and is essential for centriole duplication and ciliogenesis initiation in mammalian cells.7,17–23 The removal of CP110 from mother centrioles is prerequisite for enabling axoneme outgrowth and appears to be one of the earliest steps in initiating ciliogenesis.7,19–23 CP110 antagonizes the action of centrosomal protein of 290 kDa (CEP290) to suppress the recruitment of small GTPase Rab8a, resulting in the inhibition of cilia formation.21 However, the mechanism by which mother centriole-localized CP110 is degraded to promote ciliogenesis remains unknown.

Autophagy is a lysosome-dependent program that degrades cytoplasmic proteins or organelles to maintain cellular homeostasis in response to different types of stresses.24,25 Previous reports have shown that autophagy is involved in the regulation of ciliogenesis by degrading ciliary proteins such as satellite oral-facial-digital syndrome 1 (OFD1) and intraflagellar transport 20 (IFT20).26–28 Nevertheless, it is unknown whether autophagy plays a role in CP110 degradation to initiate ciliogenesis.

In this manuscript, we find that autophagy is crucial for the specific removal of CP110 from mother centrioles and ciliogenesis. Further data show that after serum starvation, an Hsp90 co-chaperone NudC-like protein 2 (NudCL2) functions as a previously uncharacterized autophagy receptor mediating the selective autop-hagic degradation of CP110 at mother centrioles, which is essential for ciliogenesis initiation and vertebrate development.

Cell Research
2021 Sep;31(11):1199-1211
Impact Factor:44.1



Materials and Method

Oligos corresponding to the following sequences were synthesized by **GenePharma**.

Cell Research

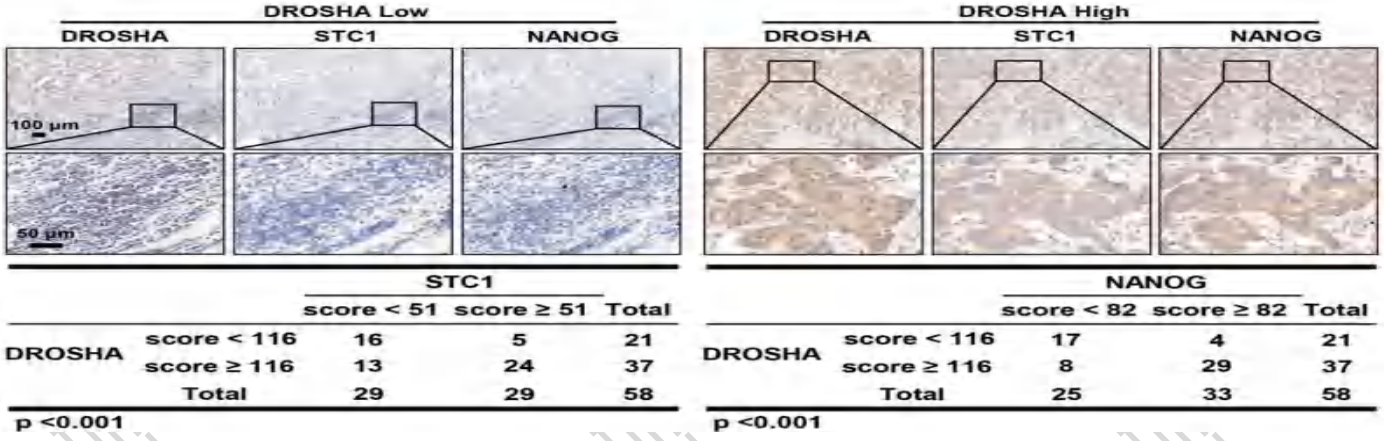
www.nature.com/cr
www.cell-research.com

ARTICLE

Oncogenic AURKA-enhanced N^6-methyladenosine modification increases DROSHA mRNA stability to transactivate STC1 in breast cancer stem-like cells

Fei Peng[1,2], Jie Xu[1], Bai Cui[1], Qilan Liang[1], Sai Zeng[1], Bin He[2], Hong Zou[1], Manman Li[1], Huan Zhao[1], Yuting Meng[1], Jin Chen[3], Bing Liu[1], Shasha Lv[1], Peng Chu[1,4], Fan An[1], Zifeng Wang [2], Junxiu Huang[1], Yajing Zhan[1], Yuwei Liao[1], Jinxin Lu[1], Lingzhi Xu[5], Jin Zhang[6], Zhaolin Sun[4], Zhiguang Li[1], Fangjun Wang[3], Eric W.-F. Lam [7] and Quentin Liu[1,2]

RNase III DROSHA is upregulated in multiple cancers and contributes to tumor progression by hitherto unclear mechanisms. Here, we demonstrate that DROSHA interacts with β-Catenin to transactivate STC1 in an RNA cleavage-independent manner, contributing to breast cancer stem-like cell (BCSC) properties. DROSHA mRNA stability is enhanced by N6-methyladenosine (m6A) modification which is activated by AURKA in BCSCs. AURKA stabilizes METTL14 by inhibiting its ubiquitylation and degradation to promote DROSHA mRNA methylation. Moreover, binding of AURKA to DROSHA transcript further strengthens the binding of the m6A reader IGF2BP2 to stabilize m6A-modified DROSHA. In addition, wild-type DROSHA, but not an m6A methylation-deficient mutant, enhances BCSC stemness maintenance, while inhibition of DROSHA m6A modification attenuates BCSC traits. Our study unveils the AURKA-induced oncogenic m6A modification as a key regulator of DROSHA in breast cancer and identifies a novel DROSHA transcriptional function in promoting the BCSC phenotype.



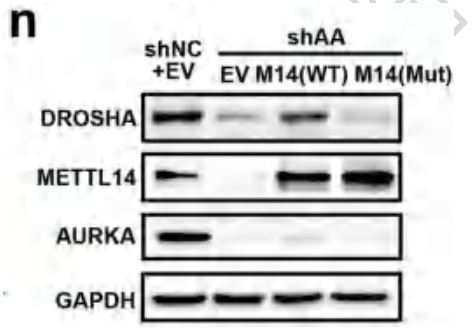
		STC1 score < 51	STC1 score ≥ 51	Total
DROSHA	score < 116	16	5	21
	score ≥ 116	13	24	37
	Total	29	29	58

p <0.001

		NANOG score < 82	NANOG score ≥ 82	Total
DROSHA	score < 116	17	4	21
	score ≥ 116	8	29	37
	Total	25	33	58

p <0.001

Cell Research
2020 Aug 28 ; 29,233-247
Impact Factor:44.1



Materials and Method

Transfection, lentivirus package and stable cell line generation Transient transfection with siRNAs (GenePharma, Suzhou, China) or plasmids was performed using Lipofectamine 3000 (Lipo3000, Invitrogen, L3000015) according to the manufacturers' protocols.

Cell Research

www.nature.com/cr
www.cell-research.com

ARTICLE

PARylation regulates stress granule dynamics, phase separation, and neurotoxicity of disease-related RNA-binding proteins

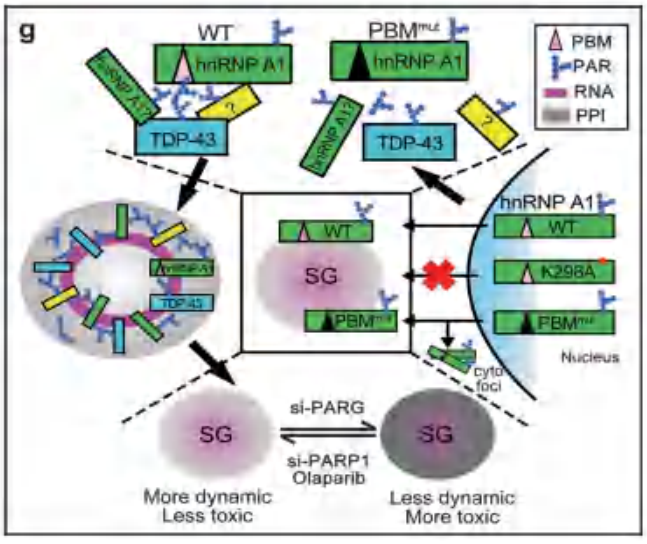
Yongjia Duan[1,2], Aiying Du[1], Jinge Gu[1,2], Gang Duan[1], Chen Wang[1,2], Xinrui Gui[1,2], Zhiwei Ma[1,3], Beituo Qian[1,2], Xue Deng[1,2], Kai Zhang[1,2], Le Sun[1,2], Kuili Tian[1], Yaoyang Zhang[1,2], Hong Jiang[1,2], Cong Liu[1,2] and Yanshan Fang[1,2]

Mutations in RNA-binding proteins (RBPs) localized in ribonucleoprotein (RNP) granules, such as hnRNP A1 and TDP-43, promote aberrant protein aggregation, which is a pathological hallmark of various neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Protein posttranslational modifications (PTMs) are known to regulate RNP granules. In this study, we investigate the function of poly(ADP-ribosyl)ation (PARylation), an important PTM involved in DNA damage repair and cell death, in RNP granule-related neurodegeneration. We reveal that PARylation levels are a major regulator of the assembly-disassembly dynamics of RNP granules containing disease-related RBPs, hnRNP A1 and TDP-43. We find that hnRNP A1 can both be PARylated and bind to PARylated proteins or poly(ADP-ribose) (PAR). We further uncover that PARylation of hnRNP A1 at K298 controls its nucleocytoplasmic transport, whereas PAR-binding via the PAR-binding motif (PBM) of hnRNP A1 regulates its association with stress granules. Moreover, we reveal that PAR not only dramatically enhances the liquid-liquid phase separation of hnRNP A1, but also promotes the co-phase separation of hnRNP A1 and TDP-43 in vitro and their interaction in vivo. Finally, both genetic and pharmacological inhibition of PARP mitigates hnRNP A1- and TDP-43-mediated neurotoxicity in cell and Drosophila models of ALS. Together, our findings suggest a novel and crucial role for PARylation in regulating the dynamics of RNP granules, and that dysregulation in PARylation and PAR levels may contribute to ALS disease pathogenesis by promoting protein aggregation.

Cell Research
2019 Feb 6 ; 29,233-247
Impact Factor:44.1

Materials and Method

For knockdown experiments, the **siRNA** (**Genepharma**, Shanghai) was transfected into the cells using the Lipofectamine™ RNAiMAX Transfection Reagent (Invitrogen, 13778150), according to the manufacturer's instruction.



Cell Research (2017) :1-15.

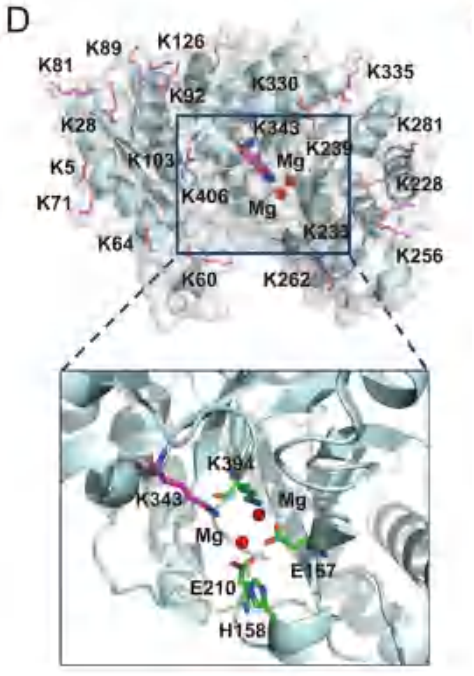
www.nature.com/cr

ORIGINAL ARTICLE

Landscape of the regulatory elements for lysine 2-hydroxyisobutyrylation pathway

He Huang[1, *], Zhouqing Luo[2, 3, *], Shankang Qi[1, *], Jing Huang[3, *], Peng Xu[3], Xiuxuan Wang[4], Li Gao[4], Fangyi Li[5], Jian Wang[5], Wenhui Zhao[6], Wei Gu[7], Zhucheng Chen[3], Lunzhi Dai[4], Junbiao Dai[2, 3], Yingming Zhao[1]

Short-chain fatty acids and their corresponding acyl-CoAs sit at the crossroads of metabolic pathways and play important roles in diverse cellular processes. They are also precursors for protein post-translational lysine acylation modifications. A noteworthy example is the newly identified lysine 2-hydroxyisobutyrylation (K_{hib}) that is derived from 2-hydroxyisobutyrate and 2-hydroxyisobutyryl-CoA. Histone K_{hib} has been shown to be associated with active gene expression in spermatogenic cells. However, the key elements that regulate this post-translational lysine acyla-tion pathway remain unknown. This has hindered characterization of the mechanisms by which this modification exerts its biological functions. Here we show that Esa1p in budding yeast and its homologue Tip60 in human could add K_{hib} to substrate proteins both *in vitro* and *in vivo*. In addition, we have identified HDAC2 and HDAC3 as the major enzymes to remove K_{hib}. Moreover, we report the first global profiling of K_{hib} proteome in mammalian cells, identifying 6 548 K_{hib} sites on 1 725 substrate proteins. Our study has thus discovered both the "writers" and "erasers" for histone K_{hib} marks, and major K_{hib} protein substrates. These results not only illustrate the landscape of this new lysine acylation pathway, but also open new avenues for studying diverse functions of cellular metabolites associated with this pathway.



ORIGINAL ARTICLE
2018 Jan;28(1):111-125
Impact Factor:44.1

Materials and Method

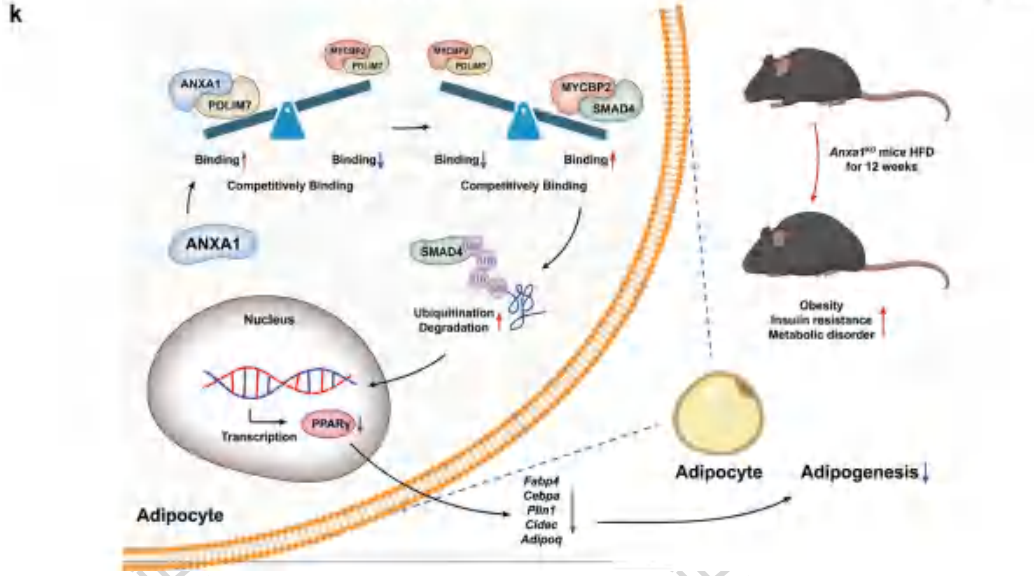
The HDAC2 knockout HEK293T cells transfected twice with **siRNA** (**Genepharma**, 5′-UUCUCCGAACGUGUCACGUTT-3′) were used as negative control.

ARTICLE OPEN

Annexin A1 binds PDZ and LIM domain 7 to inhibit adipogenesis and prevent obesity

Lu Fang[1], Changjie Liu[2], Zong-zhe Jiang[3,4], Mengxiao Wang[1], Kang Geng[4,5], Yangkai Xu[1], Yujie Zhu[1], Yiwen Fu[1], Jing Xue[6], Wenxin Shan[1], Qi Zhang[1], Jie Chen[1], Jiahong Chen[1], Mingming Zhao[7], Yuxuan Guo[1], K. W. Michael Siu[8,9], Y. Eugene Chen[10], Yong Xu[3,4] ✉, Donghui Liu[11] ✉ and Lemin Zheng[1] ✉

Obesity is a global issue that warrants the identification of more effective therapeutic targets and a better understanding of the pivotal molecular pathogenesis. Annexin A1 (ANXA1) is known to inhibit phospholipase A2, exhibiting anti-inflammatory activity. However, the specific effects of ANXA1 in obesity and the underlying mechanisms of action remain unclear. Our study reveals that ANXA1 levels are elevated in the adipose tissue of individuals with obesity. Whole-body or adipocyte-specific ANXA1 deletion aggravates obesity and metabolic disorders. ANXA1 levels are higher in stromal vascular fractions (SVFs) than in mature adipocytes. Further investigation into the role of ANXA1 in SVFs reveals that ANXA1 overexpression induces lower numbers of mature adipocytes, while ANXA1-knockout SVFs exhibit the opposite effect. This suggests that ANXA1 plays an important role in adipogenesis. Mechanistically, ANXA1 competes with MYC binding protein 2 (MYCBP2) for interaction with PDZ and LIM domain 7 (PDLIM7). This exposes the MYCBP2-binding site, allowing it to bind more readily to the SMAD family member 4 (SMAD4) and promoting its ubiquitination and degradation. SMAD4 degradation downregulates peroxisome proliferator-activated receptor gamma (PPARγ) transcription and reduces adipogenesis. Treatment with Ac2-26, an active peptide derived from ANXA1, inhibits both adipogenesis and obesity through the mechanism. In conclusion, the molecular mechanism of ANXA1 inhibiting adipogenesis



Signal Transduction and Targeted Therapy
Signal Transduction and Targeted Therapy (2024) 9:218
Impact Factor:40.8

Materials and Method

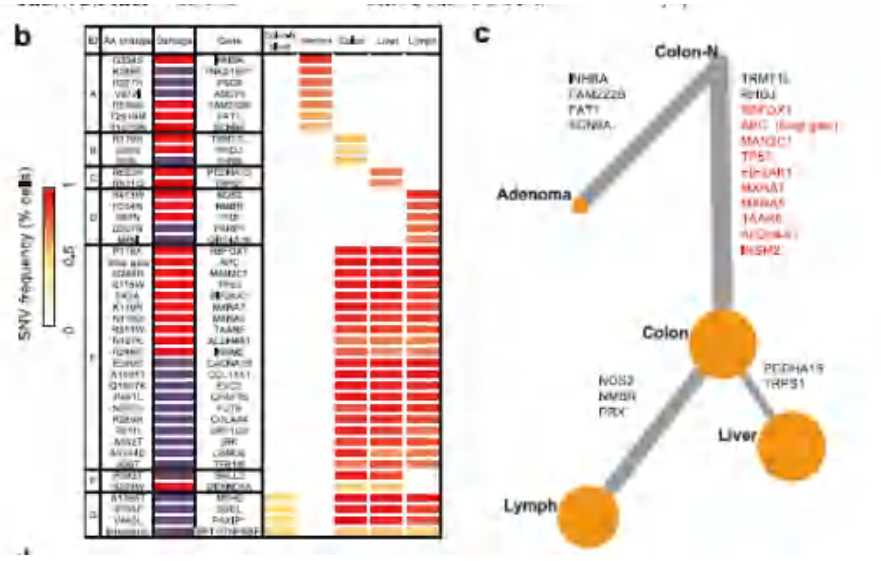
the **siRNA** was constructed by **Suzhou GenePharma Co** .

ARTICLE OPEN

Single-cell exome sequencing reveals polyclonal seeding and TRPS1 mutations in colon cancer metastasis

Jianqiang Cai[1,2], Weilong Zhang[3], Yalan Lu[4,5], Wenjie Liu[2,6], Haitao Zhou[2,6], Mei Liu[7], Xinyu Bi[2,6], Jianmei Liu[1,2], Jinghua Chen[1,2], Yanjiang Yin[1,2], Yiqiao Deng[1,2], Zhiwen Luo[1,2], Yi Yang[1,2], Qichen Chen[1,2], Xiao Chen[1,2], Zheng Xu[2,6], Yueyang Zhang[2,6], Chaoling Wu[3], Qizhao Long[3], Chunyuan Huang[3], Changjian Yan[3], Yan Liu[3], Lei Guo[8], Weihua Li[8], Pei Yuan[8], Yucheng Jiao[7], Wei Song[5], Xiaobing Wang[7], Zhen Huang[1,2]✉, Jianming Ying[2,8]✉ and Hong Zhao[1,2]✉

Liver metastasis remains the primary cause of mortality in patients with colon cancer. Identifying specific driver gene mutations that contribute to metastasis may offer viable therapeutic targets. To explore clonal evolution and genetic heterogeneity within the metastasis, we conducted single-cell exome sequencing on 150 single cells isolated from the primary tumor, liver metastasis, and lymphatic metastasis from a stage IV colon cancer patient. The genetic landscape of the tumor samples revealed that both lymphatic and liver metastases originated from the same region of the primary tumor. Notably, the liver metastasis was derived directly from the primary tumor, bypassing the lymph nodes. Comparative analysis of the sequencing data for individual cell pairs within different tumors demonstrated that the genetic heterogeneity of both liver and lymphatic metastases was also greater than that of the primary tumor. This finding indicates that liver and lymphatic metastases arose from clusters of circulating tumor cell (CTC) of a polyclonal origin, rather than from a single cell from the primary tumor. Single-cell transcriptome analysis suggested that higher EMT score and CNV scores were associated with more polyclonal metastasis. Additionally, a mutation in the TRPS1 (Transcriptional repressor GATA binding 1) gene, TRPS1 R544Q, was enriched in the single cells from the liver metastasis. The mutation significantly increased CRC invasion and migration both in vitro and in vivo through the TRPS1^{R544Q}/ZEB1 axis. Further TRPS1 mutations were detected in additional colon cancer cases, correlating with advanced-stage disease and inferior prognosis. These results reveal polyclonal seeding and TRPS1 mutation as potential mechanisms driving the development of liver metastases in colon cancer.



Signal Transduction and Targeted Therapy
Signal Transduction and Targeted Therapy (2024) 9:247 **Impact Factor:40.8**

Materials and Method

All siRNAs were synthesized by **Shanghai GenePharma Co.**

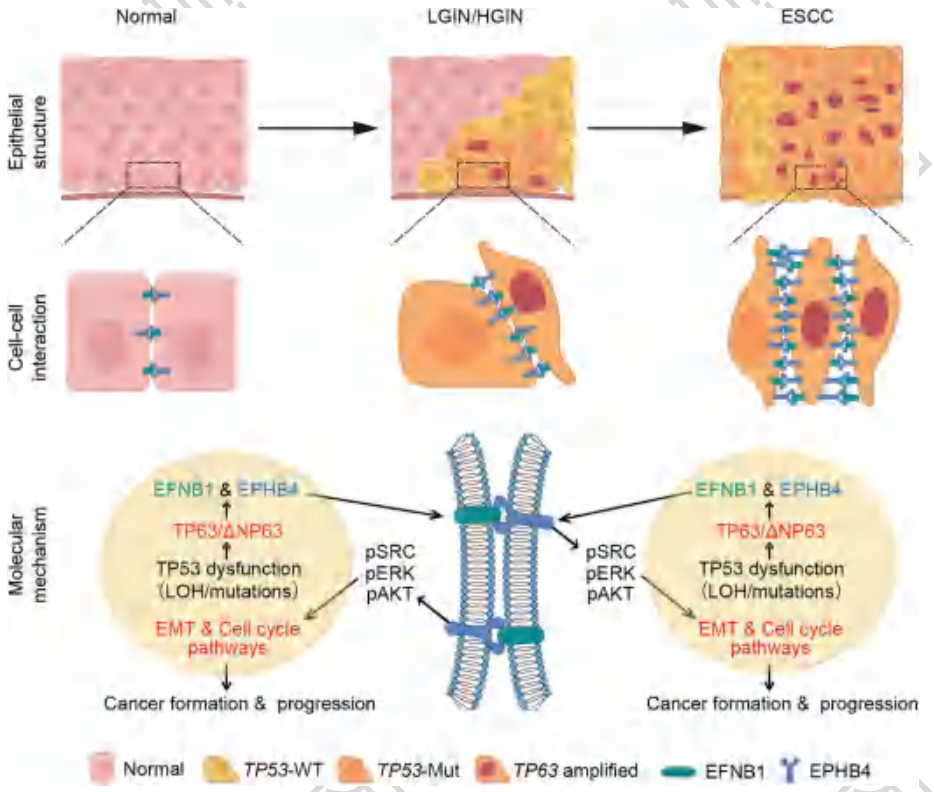
ARTICLE OPEN

Aberrant epithelial cell interaction promotes esophageal squamous-cell carcinoma development and progression

Liping Chen[1], Shihao Zhu[1], Tianyuan Liu[1], Xuan Zhao[1], Tao Xiang[1], Xiao Hu[1], Chen Wu[1,2,3,4]✉ and Dongxin Lin[1,2,3,5]✉

Epithelial-mesenchymal transition (EMT) and proliferation play important roles in epithelial cancer formation and progression, but what molecules and how they trigger EMT is largely unknown. Here we performed spatial transcriptomic and functional analyses on samples of multistage esophageal squamous-cell carcinoma (ESCC) from mice and humans to decipher these critical issues. By investigating spatiotemporal gene expression patterns and cell–cell interactions, we demonstrated that the aberrant epithelial cell interaction via EFNB1-EPHB4 triggers EMT and cell cycle mediated by downstream SRC/ERK/AKT signaling. The aberrant epithelial cell interaction occurs within the basal layer at early precancerous lesions, which expands to the whole epithelial layer and strengthens along the cancer development and progression. Functional analysis revealed that the aberrant EFNB1-EPHB4 interaction is caused by overexpressed ΔNP63 due to TP53 mutation, the culprit in human ESCC tumorigenesis. Our results shed new light on the role of TP53-TP63/ΔNP63-EFNB1-EPHB4 axis in EMT and cell proliferation in epithelial cancer formation.

Signal Transduction and Targeted Therapy (2023)8:453 ; https://doi.org/10.1038/s41392-023-01710-2



Signal Transduction and Targeted Therapy
2023 Dec 15;8(1):453
Impact Factor:39.3

Materials and Method

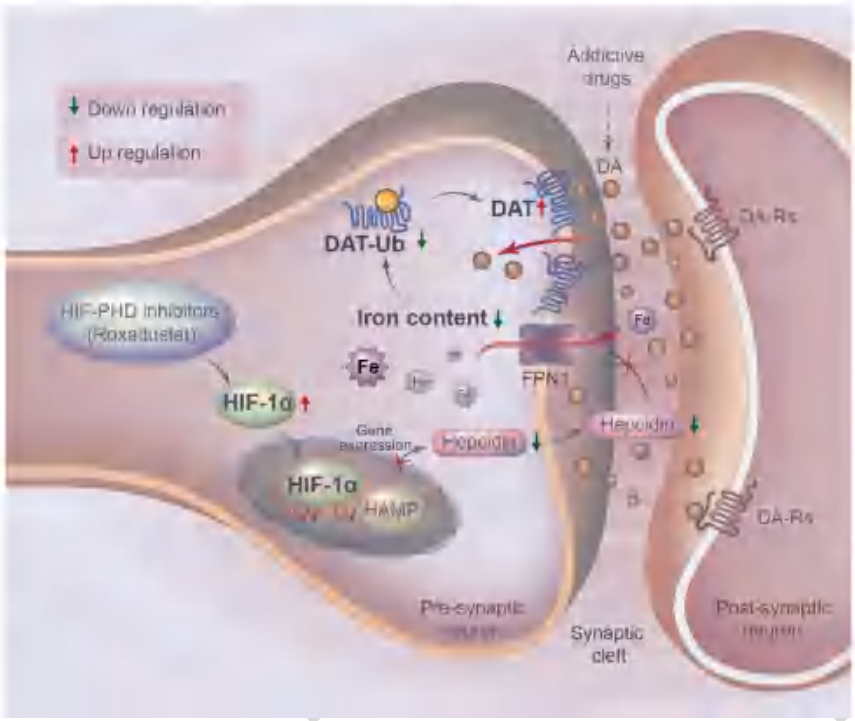
Small interfering RNAs targeting mouse Efnb1/Ephb4/Creb1/Zfp263/Trp63 and human EFNB1/EPHB4/CREB1/ZNF263/TP63 were purchased from **GenePharma** (Supplementary Table S8).

ARTICLE OPEN

Hypoxia-inducible factor upregulation by roxadustat attenuates drug reward by altering brain iron homoeostasis

Pengju Yan[1], Ningning Li[1], Ming Ma[1], Zhaoli Liu[1], Huicui Yang[1], Jinnan Li[2], Chunlei Wan[1], Shuliu Gao[1], Shuai Li[1], Longtai Zheng[1], John L. Waddington[1,3], Lin Xu[2]✉ and Xuechu Zhen[1]✉

Substance use disorder remains a major challenge, with an enduring need to identify and evaluate new, translational targets for effective treatment. Here, we report the upregulation of Hypoxia-inducible factor-1 α (HIF-1 α) expression by roxadustat (Rox), a drug developed for renal anemia that inhibits HIF prolyl hydroxylase to prevent degradation of HIF-1 α, administered either systemically or locally into selected brain regions, suppressed morphine (Mor)-induced conditioned place preference (CPP). A similar effect was observed with methamphetamine (METH). Moreover, Rox also inhibited the expression of both established and reinstated Mor-CPP and promoted the extinction of Mor-CPP. Additionally, the elevation of HIF-1 α enhanced hepcidin/ferroportin 1 (FPN1)-mediated iron efflux and resulted in cellular iron deficiency, which led to the functional accumulation of the dopamine transporter (DAT) in plasma membranes due to iron deficiency-impaired ubiquitin degradation. Notably, iron-deficient mice generated via a low iron diet mimicked the effect of Rox on the prevention of Mor- or METH-CPP formation, without affecting other types of memory. These data reveal a novel mechanism for HIF-1 α and iron involvement in substance use disorder, which may represent a potential novel therapeutic strategy for the treatment of drug abuse. The findings also repurpose Rox by suggesting a potential new indication for the treatment of substance use disorder.



Signal Transduction and Targeted Therapy
2023 Sep 18;8(1):355
Impact Factor:39.3

Materials and Method

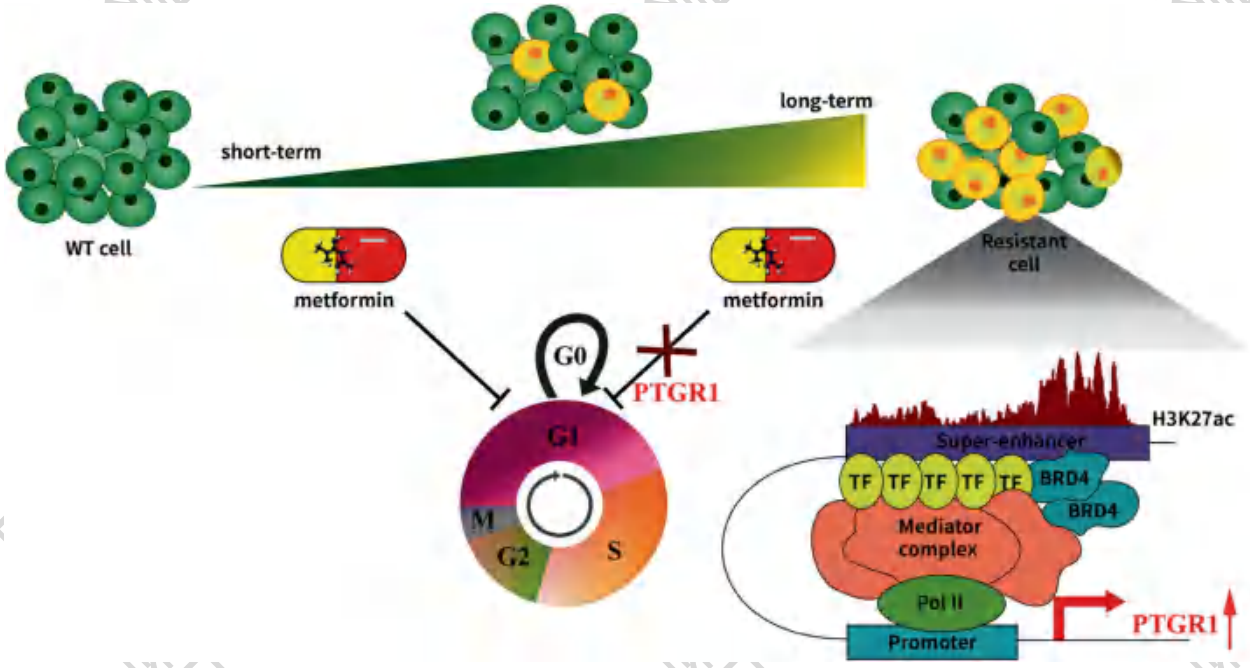
HIF-1α siRNA was purchased from **GenePharma** Co., Ltd.(Shanghai, China) with the following sequences: sense 5'-CCAUGUGACCAUGAGGAAATT-3', antisense 5'-UUUCCUCAUGGU-CACAUGGTT-3'; negative control (NC): sense 5'-UUCUCCGAACGU-GUCACGUTT-3', antisense 5'-ACGUGACACGUUCGGAGAATT-3'.

ARTICLE OPEN

Metformin escape in prostate cancer by activating the PTGR1 transcriptional program through a novel super-enhancer

Jianheng Ye[1], Shanghua Cai[1,2,3], Yuanfa Feng[1,2], Jinchuang Li[1], Zhiduan Cai[1], Yulin Deng[2], Ren Liu[1], Xuejin Zhu[1], Jianming Lu[1], Yangjia Zhuo[1], Yingke Liang[1], Jianjiang Xie[1], Yanqiong Zhang[4], Huichan He[2], Zhaodong Han[1]✉, Zhenyu Jia[5,6]✉ and Weide Zhong[1,2,3,7]✉

The therapeutic efficacy of metformin in prostate cancer (PCa) appears uncertain based on various clinical trials. Metformin treatment failure may be attributed to the high frequency of transcriptional dysregulation, which leads to drug resistance. However, the underlying mechanism is still unclear. In this study, we found evidences that metformin resistance in PCa cells may be linked to cell cycle reactivation. Super-enhancers (SEs), crucial regulatory elements, have been shown to be associated with drug resistance in various cancers. Our analysis of SEs in metformin-resistant (MetR) PCa cells revealed a correlation with Prostaglandin Reductase 1 (PTGR1) expression, which was identified as significantly increased in a cluster of cells with metformin resistance through single-cell transcriptome sequencing. Our functional experiments showed that PTGR1 overexpression accelerated cell cycle progression by promoting progression from the G0/G1 to the S and G2/M phases, resulting in reduced sensitivity to metformin. Additionally, we identified key transcription factors that significantly increase PTGR1 expression, such as SRF and RUNX3, providing potential new targets to address metformin resistance in PCa. In conclusion, our study sheds new light on the cellular mechanism underlying metformin resistance and the regulation of the SE-TFs-PTGR1 axis, offering potential avenues to enhance metformin's therapeutic efficacy in PCa.



Signal Transduction and Targeted Therapy
2023 Aug 16;8(1):303
Impact Factor:39.3

Materials and Method

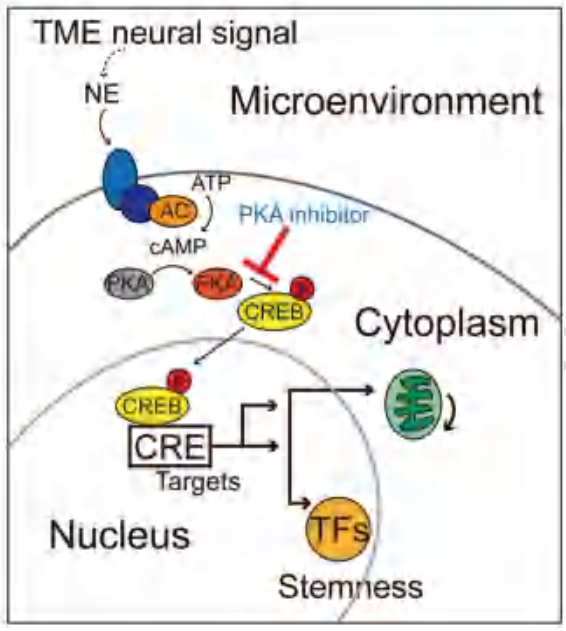
The targeting siRNA and **negative control siRNA** and **the transfection reagent** were obtained from **GenePharma**.

ARTICLE OPEN

Cancer cell employs a microenvironmental neural signal trans-activating nucleus-mitochondria coordination to acquire stemness

Bin He[1], Rui Gao[1,2], Shasha Lv[1,3], Ailin Chen[1], Junxiu Huang[4], Luoxuan Wang[3], Yunxiu Feng[3], Jiesi Feng[5], Bing Liu[1], Jie Lei[1], Bing Deng[1], Bin He[3], Bai Cui[3], Fei Peng[3], Min Yan[1], Zifeng Wang[1], Eric W-F Lam[6], Bilian Jin[3], Zhiming Shao[7], Yulong Li[5], Jianwei Jiao[8], Xi Wang[1]✉ and Quentin Liu[1,2,3]✉

Cancer cell receives extracellular signal inputs to obtain a stem-like status, yet how tumor microenvironmental (TME) neural signals steer cancer stemness to establish the hierarchical tumor architectures remains elusive. Here, a pan-cancer transcriptomic screening for 10852 samples of 33 TCGA cancer types reveals that cAMP-responsive element (CRE) transcription factors are convergent activators for cancer stemness. Deconvolution of transcriptomic profiles, specification of neural markers and illustration of norepinephrine dynamics uncover a bond between TME neural signals and cancer-cell CRE activity. Specifically, neural signal norepinephrine potentiates the stemness of proximal cancer cells by activating cAMP-CRE axis, where ATF1 serves as a conserved hub. Upon activation by norepinephrine, ATF1 potentiates cancer stemness by coordinated trans-activation of both nuclear pluripotency factors MYC/NANOG and mitochondrial biogenesis regulators NRF1/TFAM, thereby orchestrating nuclear reprograming and mitochondrial rejuvenating. Accordingly, single-cell transcriptomes confirm the coordinated activation of nuclear pluripotency with mitochondrial biogenesis in cancer stem-like cells. These findings elucidate that cancer cell acquires stemness via a norepinephrine-ATF1 driven nucleus-mitochondria collaborated program, suggesting a spatialized stemness acquisition by hijacking microenvironmental neural signals.



Signal Transduction and Targeted Therapy
2023 July;8:275
Impact Factor:39.3

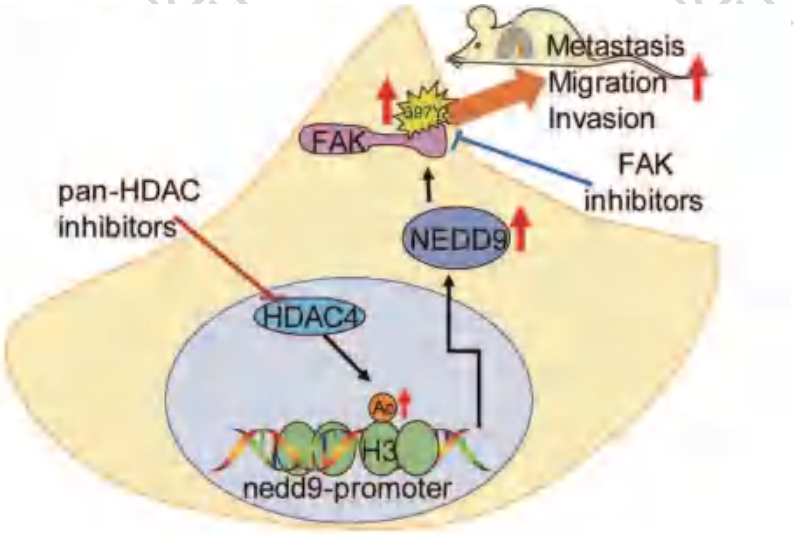
Materials and Method
The **siRNAs** were purchased from **GenePharma**.

ARTICLE OPEN

Histone deacetylase inhibitors promote breast cancer metastasis by elevating NEDD9 expression

Zonglong Hu[1,2], Fan Wei[1], Yi Su[1], Yafang Wang[1], Yanyan Shen[1], Yanfen Fang[1], Jian Ding[1,2,3]✉ and Yi Chen[1,2]✉

Histone deacetylase (HDAC) is a kind of protease that modifies histone to regulate gene expression, and is usually abnormally activated in tumors. The approved pan-HDAC inhibitors have demonstrated clinical benefits for patients in some hematologic malignancies. Only limited therapeutic success in breast cancer has been observed in clinical trials. In this study, we declare that pan-HDAC inhibitors targeting NEDD9-FAK pathway exacerbate breast cancer metastasis in preclinical models, which may severely impede their clinical success. NEDD9 is not an oncogene, however, it has been demonstrated recently that there are high level or activity changes of NEDD9 in a variety of cancer, including leukemia, colon cancer, and breast cancer. Mechanistically, pan-HDAC inhibitors enhance H3K9 acetylation at the nedd9 gene promoter via inhibition of HDAC4 activity, thus increase NEDD9 expression, and then activate FAK phosphorylation. The realization that pan-HDAC inhibitors can alter the natural history of breast cancer by increasing invasion warrants clinical attention. In addition, although NEDD9 has been reported to have a hand in breast cancer metastasis, it has not received much attention, and no therapeutic strategies have been developed. Notably, we demonstrate that FAK inhibitors can reverse breast cancer metastasis induced by upregulation of NEDD9 via pan-HDAC inhibitors, which may offer a potential combination therapy for breast cancer.



Signal Transduction and Targeted Therapy
2023 Jan 6;8:11
Impact Factor:39.3

Materials and Method

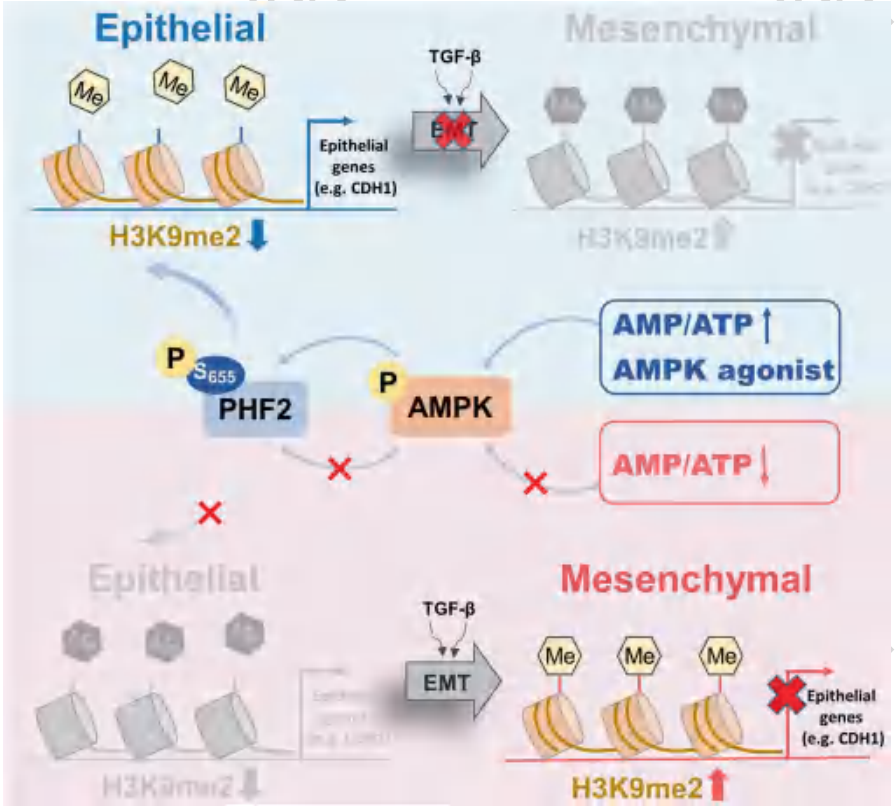
siRNAs ordered from **GenePharma** (Shanghai, China) were transfected with Lipofectamine RNAi MAX Reagent (#13778150, Invitrogen) for 48 h.

ARTICLE

Phosphorylation of PHF2 by AMPK releases the repressive H3K9me2 and inhibits cancer metastasis

Ying Dong[1,2], Hao Hu[1], Xuan Zhang[1,2], Yunkai Zhang[1,2], Xin Sun[1,3], Hanlin Wang[1,4], Weijuan Kan[1], Min-jia Tan[1,2], Hong Shi[5]✉, Yi Zang[1,6,7]✉ and Jia Li[1,2,7,8,9]✉

Epithelial to mesenchymal transition (EMT) plays a crucial role in cancer metastasis, accompanied with vast epigenetic changes. AMP-activated protein kinase (AMPK), a cellular energy sensor, plays regulatory roles in multiple biological processes. Although a few studies have shed light on AMPK regulating cancer metastasis, the inside epigenetic mechanisms remain unknown. Herein we show that AMPK activation by metformin relieves the repressive H3K9me2-mediated silencing of epithelial genes (e.g., CDH1) during EMT processes and inhibits lung cancer metastasis. PHF2, a H3K9me2 demethylase, was identified to interact with AMPKα2. Genetic deletion of PHF2 aggravates lung cancer metastasis and abolishes the H3K9me2 downregulation and anti-metastasis effect of metformin. Mechanistically, AMPK phosphorylates PHF2 at S655 site, enhancing PHF2 demethylation activity and triggering the transcription of CDH1. Furthermore, the PHF2-S655E mutant that mimics AMPK-mediated phosphorylation status further reduces H3K9me2 and suppresses lung cancer metastasis, while PHF2-S655A mutant presents opposite phenotype and reverses the anti-metastasis effect of metformin. PHF2-S655 phosphorylation strikingly reduces in lung cancer patients and the higher phosphorylation level predicts better survival. Altogether, we reveal the mechanism of AMPK inhibiting lung cancer metastasis via PHF2 mediated H3K9me2 demethylation, thereby promoting the clinical application of metformin and highlighting PHF2 as the potential epigenetic target in cancer metastasis.



Signal Transduction and Targeted Therapy
2023 Mar;8(1):95
Impact Impact Factor:39.3

Materials and Method

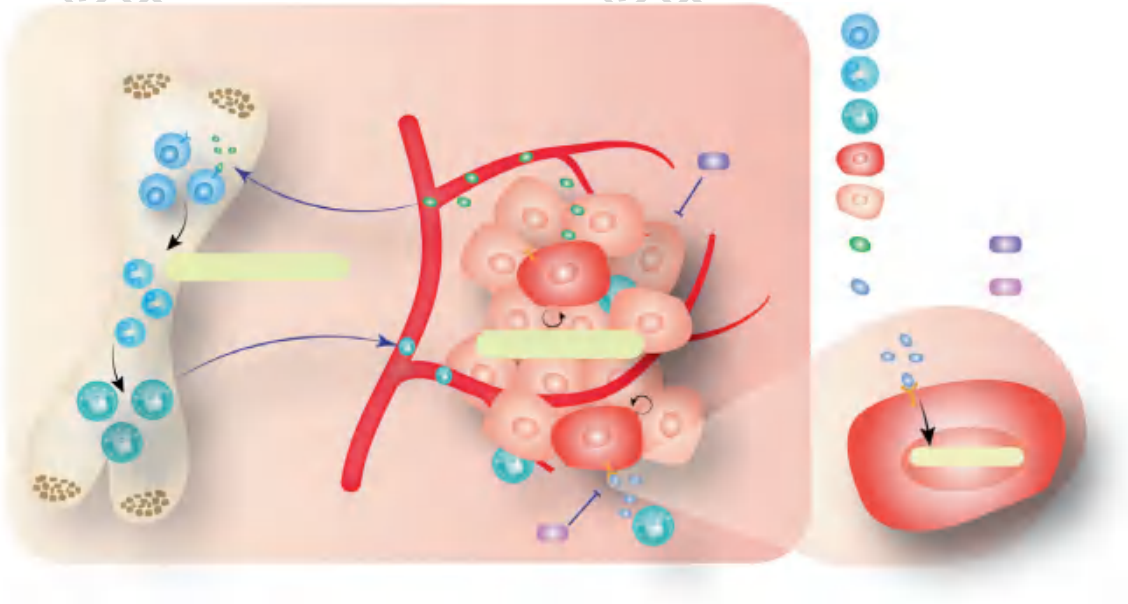
The **siRNA** was synthesised in **Genepharma** (Shanghai) and listed in Table S3.

ARTICLE OPEN

PMN-MDSCs modulated by CCL20 from cancer cells promoted breast cancer cell stemness through CXCL2-CXCR2 pathway

Rui Zhang[1], Mengxue Dong[1], Juchuanli Tu[1], Fengkai Li[1], Qiaodan Deng[1], Jiahui Xu[1], Xueyan He[1], Jiajun Ding[1,2], Jie Xia[1], Dandan Sheng[1], Zhaoxia Chang[1], Wei Ma[1], Haonan Dong[1], Yi Zhang[3], Lixing Zhang[1], Lu Zhang[1]✉ and Suling Liu[1,4]✉

Our previous studies have showed that C-C motif chemokine ligand 20 (CCL20) advanced tumor progression and enhanced the chemoresistance of cancer cells by positively regulating breast cancer stem cell (BCSC) self-renewal. However, it is unclear whether CCL20 affects breast cancer progression by remodeling the tumor microenvironment (TME). Here, we observed that polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) were remarkably enriched in TME of CCL20-overexpressing cancer cell orthotopic allograft tumors. Mechanistically, CCL20 activated the differentiation of granulocyte-monocyte progenitors (GMPs) via its receptor C-C motif chemokine receptor 6 (CCR6) leading to the PMN-MDSC expansion. PMN-MDSCs from CCL20-overexpressing cell orthotopic allograft tumors (CCL20-modulated PMN-MDSCs) secreted amounts of C-X-C motif chemokine ligand 2 (CXCL2) and increased ALDH + BCSCs via activating CXCR2/NOTCH1/HEY1 signaling pathway. Furthermore, C-X-C motif chemokine receptor 2 (CXCR2) antagonist SB225002 enhanced the docetaxel (DTX) effects on tumor growth by decreasing BCSCs in CCL20high-expressing tumors. These findings elucidated how CCL20 modulated the TME to promote cancer development, indicating a new therapeutic strategy by interfering with the interaction between PMN-MDSCs and BCSCs in breast cancer,especially in CCL20high-expressing breast cancer.



Signal Transduction and Targeted Therapy
2023 Mar;8(1):97
Impact Factor:39.3

Materials and Method

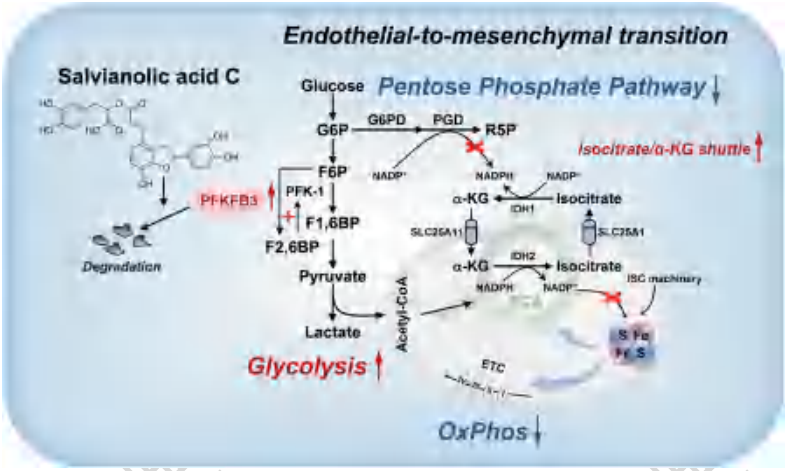
Murine CCR6-siRNA and **non-silencing scrambled control (SCR) siRNA** were purchased from **GenePharma** Biotech.

ARTICLE OPEN

Suppression of PFKFB3-driven glycolysis restrains endothelial-to-mesenchymal transition and fibrotic response

Hao Zeng[1], Ting Pan[1], Meiling Zhan[1], Renaguli Hailiwu[1], Baolin Liu[1], Hua Yang[1]✉ and Ping Li[1]✉

Endothelial-to-mesenchymal transition (EndoMT), the process wherein endothelial cells lose endothelial identity and adopt mesenchymal-like phenotypes, constitutes a critical contributor to cardiac fibrosis. The phenotypic plasticity of endothelial cells can be intricately shaped by alteration of metabolic pathways, but how endothelial cells adjust cellular metabolism to drive EndoMT is incompletely understood. Here, we identified 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) as a critical driver of EndoMT via triggering abnormal glycolysis and compromising mitochondrial respiration. Pharmacological suppression of PFKFB3 with salvianolic acid C (SAC), a phenolic compound derived from Salvia miltiorrhiza, attenuates EndoMT and fibrotic response. PFKFB3-haplodeficiency recapitulates the anti-EndoMT effect of SAC while PFKFB3-overexpression augments the magnitude of EndoMT and exacerbates cardiac fibrosis. Mechanistically, PFKFB3-driven glycolysis compromises cytoplasmic nicotinamide adenine dinucleotide phosphate (reduced form, NADPH) production via hijacking glucose flux from pentose phosphate pathway. Efflux of mitochondrial NADPH through isocitrate/α-ketoglutarate shuttle replenishes cytoplasmic NADPH pool but meanwhile impairs mitochondrial respiration by hampering mitochondrial iron-sulfur cluster biosynthesis. SAC disrupts PFKFB3 stability by accelerating its degradation and thus maintains metabolic homeostasis in endothelial cells, underlying its anti-EndoMT effects. These findings for the first time identify the critical role of PFKFB3 in triggering EndoMT by driving abnormal glycolysis in endothelial cells, and also highlight the therapeutic potential for pharmacological intervention of PFKFB3 (with SAC or other PFKFB3 inhibitors) to combat EndoMT-associated fibrotic responses via metabolic regulation.



Signal Transduction and Targeted Therapy
2022 Sep;7(1):1-17
Impact Factor:39.3

Materials and Method

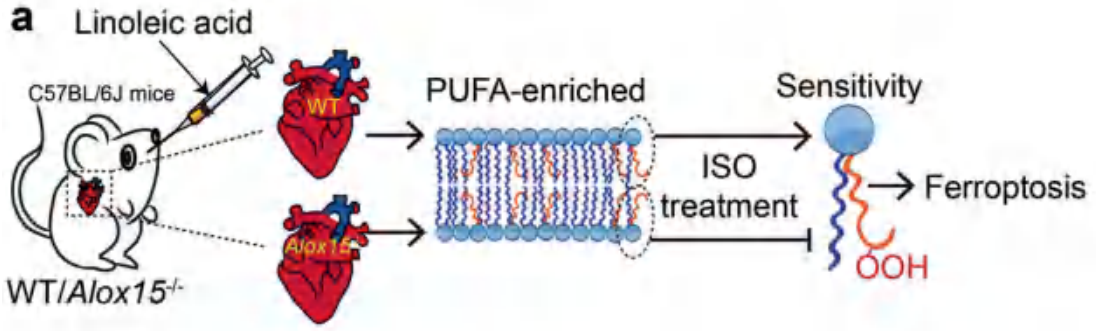
For RNAi experiments, siRNA targeting Pfkfb3, Nfs-1, and scrambled siRNA (GenePharma, Shanghai, China, siRNA sequences were listed in Supplementary Table 2) were used.

ARTICLE OPEN

ALOX15-launched PUFA-phospholipids peroxidation increases the susceptibility of ferroptosis in ischemia-induced myocardial damage

Xiao-Hui Ma[1,2,3,4], Jiang-Han-Zi Liu[1,2,3], Chun-Yu Liu[1,2,3], Wan-Yang Sun[1,2,3], Wen-Jun Duan[1,2,3], Guan Wang[5], Hiroshi Kurihara[1,2,3], Rong-Rong He[1,2,3]✉, Yi-Fang Li[1,2,3]✉, Yang Chen[6]✉ and Hongcai Shang[7]✉

Myocardial ischemia/reperfusion (I/R) injury is a classic type of cardiovascular disease characterized by injury to cardiomyocytes leading to various forms of cell death. It is believed that irreversible myocardial damage resulted from I/R occurs due to oxidative stress evoked during the reperfusion phase. Here we demonstrate that ischemia triggers a specific redox reaction of polyunsaturated fatty acids (PUFA)-phospholipids in myocardial cells, which acts as a priming signaling that initiates the outbreak of robust oxidative damage in the reperfusion phase. Using animal and in vitro models, the crucial lipid species in I/R injury were identified to be oxidized PUFAs enriched phosphatidylethanolamines. Using multi-omics, arachidonic acid 15-lipoxygenase-1(ALOX15) was identified as the primary mediator of ischemia-provoked phospholipid peroxidation, which was further confirmed using chemogenetic approaches. Collectively, our results reveal that ALOX15 induction in the ischemia phase acts as a "burning point" to ignite phospholipid oxidization into ferroptotic signals. This finding characterizes a novel molecular mechanism for myocardial ischemia injury and offers a potential therapeutic target for early intervention of I/R injury.



Signal Transduction and Targeted Therapy
2022 Aug;7(1):1-13
Impact Factor:39.3

Materials and Method

The **siRNA** against CENP-L (AAGAUUAGUUCGUGUUUCA) was obtained from **GenePharma** and was previously confirmed.

Circulation

ORIGINAL RESEARCH ARTICLE

Carbonylation of Runx2 at K176 by 4-Hydroxynonenal Accelerates Vascular Calcification

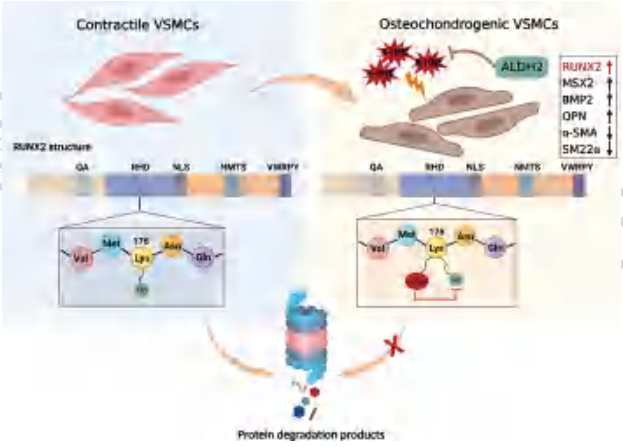
Xiaoxuan Zhai, MD*; Shengchuan Cao, MD, PhD*; Jiali Wang, MD, PhD; Bao Qiao, MD; Xuehao Liu, MD; Rui Hua, MD; Menglin Zhao, MD; Shukun Sun, MD; Yu Han, MD; Shuo Wu, MD; Jiaojiao Pang, MD, PhD; Qiuhuan Yuan, PhD; Bailu Wang, MD; Feng Xu, MD, PhD; Shujian Wei, MD, PhD; Yuguo Chen, MD, PhD

BACKGROUND: Vascular calcification, which is characterized by calcium deposition in arterial walls and the osteochondrogenic differentiation of vascular smooth muscle cells, is an actively regulated process that involves complex mechanisms. Vascular calcification is associated with increased cardiovascular adverse events. The role of 4-hydroxynonenal (4-HNE), which is the most abundant stable product of lipid peroxidation, in vascular calcification has been poorly investigated.

METHODS: Serum was collected from patients with chronic kidney disease and controls, and the levels of 4-HNE and 8-iso-prostaglandin F2α were measured. Sections of coronary atherosclerotic plaques from donors were immunostained to analyze calcium deposition and 4-HNE. A total of 658 patients with coronary artery disease who received coronary computed tomography angiography were recruited to analyze the relationship between coronary calcification and the rs671 mutation in aldehyde dehydrogenase 2 (ALDH2). ALDH2 knockout ($ALDH2^{-/-}$) mice, smooth muscle cell–specific ALDH2 knockout mice, ALDH2 transgenic mice, and their controls were used to establish vascular calcification models. Primary mouse aortic smooth muscle cells and human aortic smooth muscle cells were exposed to medium containing β-glycerophosphate and $CaCl_2$ to investigate cell calcification and the underlying molecular mechanisms.

RESULTS: Elevated 4-HNE levels were observed in the serum of patients with chronic kidney disease and model mice and were detected in calcified artery sections by immunostaining. ALDH2 knockout or smooth muscle cell–specific ALDH2 knockout accelerated the development of vascular calcification in model mice, whereas overexpression or activation prevented mouse vascular calcification and the osteochondrogenic differentiation of vascular smooth muscle cells. In patients with coronary artery disease, patients with ALDH2 rs671 gene mutation developed more severe coronary calcification. 4-HNE promoted calcification of both mouse aortic smooth muscle cells and human aortic smooth muscle cells and their osteochondrogenic differentiation in vitro. 4-HNE increased the level of Runx2 (runt-related transcription factor-2), and the effect of 4-HNE on promoting vascular smooth muscle cell calcification was ablated when Runx2 was knocked down. Mutation of Runx2 at lysine 176 reduced its carbonylation and eliminated the 4-HNE–induced upregulation of Runx2.

CONCLUSIONS: Our results suggest that 4-HNE increases Runx2 stabilization by directly carbonylating its K176 site and promotes vascular calcification. ALDH2 might be a potential target for the treatment of vascular calcification.



CIRCULATION
2024 Feb 13
Impact Factor:37.8

Materials and Method

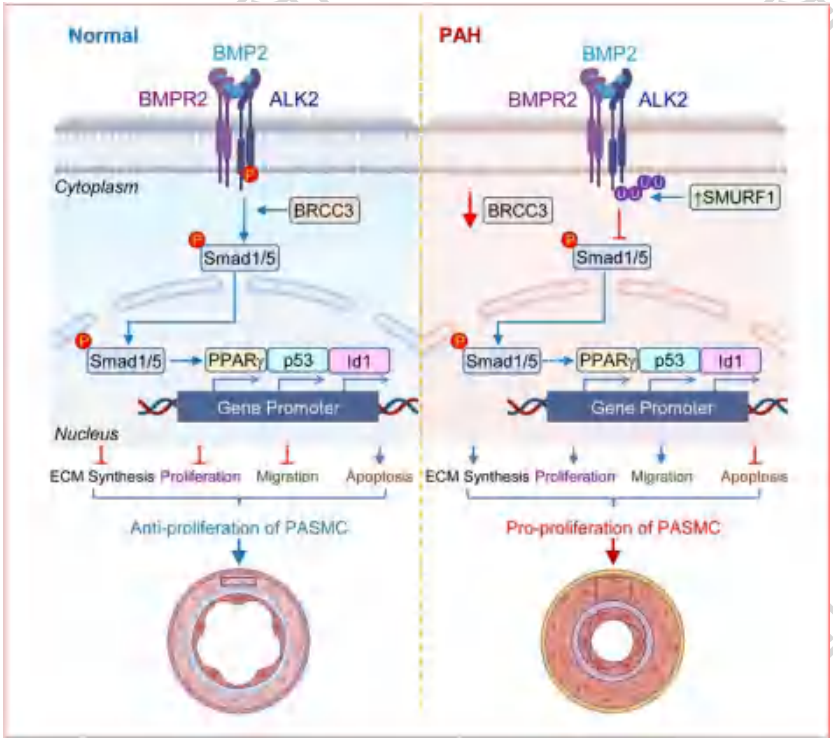
Short interfering RNAs targeting Runx2 were purchased from **GenePharma** (Shanghai, China).

ORIGINAL RESEARCH ARTICLE

BRCC3 Regulation of ALK2 in Vascular Smooth Muscle Cells: Implication in Pulmonary Hypertension

Hui Shen, MD, PhD*; Ya Gao , MS*; Dedong Ge, MD; Meng Tan, MD; Qing Yin, MS; Tong-You Wade Wei , PhD; Fangzhou He , MD; Tzong-Yi Lee, PhD; Zhongyan Li, PhD; Yuqin Chen, PhD; Qifeng Yang, BS; Zhangyu Liu, BS; Xinxin Li, PhD; Zixuan Chen , BS; Yi Yang, PhD; Zhengang Zhang, PhD; Patricia A. Thistlethwaite , MD, PhD; Jian Wang , MD, PhD; Atul Malhotra, MD; Jason X.-J. Yuan , MD, PhD; John Y.-J. Shyy, PhD; Kaizheng Gong , MD, PhD

BACKGROUND: An imbalance of antiproliferative BMP (bone morphogenetic protein) signaling and proliferative TGF-β (transforming growth factor-β) signaling is implicated in the development of pulmonary arterial hypertension (PAH). The posttranslational modification (eg, phosphorylation and ubiquitination) of TGF-β family receptors, including BMPR2 (bone morphogenetic protein type 2 receptor)/ALK2 (activin receptor-like kinase-2) and TGF-βR2/R1, and receptor-regulated (R) Smads significantly affects their activity and thus regulates the target cell fate. BRCC3 modifies the activity and stability of its substrate proteins through K63-dependent deubiquitination. By modulating the posttranslational modifications of the BMP/TGF-β–PPARγ pathway, BRCC3 may play a role in pulmonary vascular remodeling, hence the pathogenesis of PAH.



CIRCULATION Circulation. 2024;149:00–00. DOI: 10.1161/CIRCULATIONAHA.123.066430
Factor:37.8

Materials and Method

For **siRNA** transfection experiments, ALK2 siRNA or scramble control RNA (**Genepharma**)

Molecular Cancer

RESEARCH Open Access

LINC01852 inhibits the tumorigenesis and chemoresistance in colorectal cancer by suppressing SRSF5-mediated alternative splicing of PKM

Zehua Bian[1,2†], Fan Yang[1,2†], Peiwen Xu[1,2†], Ge Gao[1,2], Chunyu Yang[1,2], Yulin Cao[2], Surui Yao[1,2], Xue Wang[2], Yuan Yin[1,2], Bojian Fei[1,2,3] and Zhaohui Huang[1,2*]

Abstract

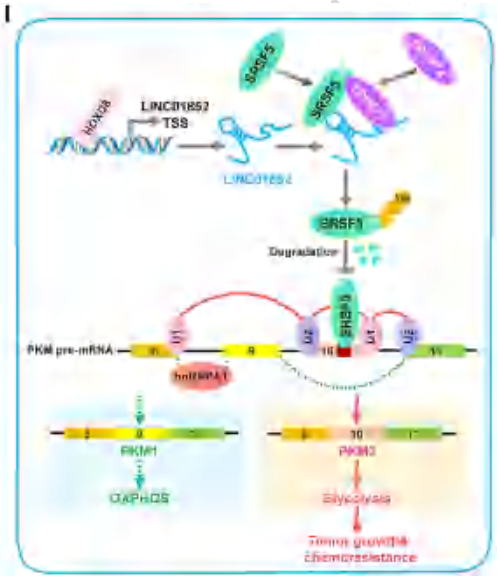
Background Colorectal cancer (CRC) is a major cause of cancer-related deaths worldwide, and chemoresistance is a major obstacle in its treatment. Despite advances in therapy, the molecular mechanism underlying chemoresistance in CRC is not fully understood. Recent studies have implicated the key roles of long noncoding RNAs (lncRNAs) in the regulation of CRC chemoresistance.

Methods In this study, we investigated the role of the lncRNA LINC01852 in CRC chemoresistance. LINC01852 expression was evaluated in multiple CRC cohorts using quantitative reverse transcription PCR. We conducted in vitro and in vivo functional experiments using cell culture and mouse models. RNA pull-down, RNA immunoprecipitation, chromatin immunoprecipitation, and dual luciferase assays were used to investigate the molecular mechanism of LINC01852 in CRC.

Results Our findings revealed that a lncRNA with tumor-inhibiting properties, LINC01852, was downregulated in CRC and inhibited cell proliferation and chemoresistance both in vitro and in vivo. Further mechanistic investigations revealed that LINC01852 increases TRIM72-mediated ubiquitination and degradation of SRSF5, inhibiting SRSF5-mediated alternative splicing of PKM and thereby decreasing the production of PKM2. Overexpression of LINC01852 induces a metabolic switch from aerobic glycolysis to oxidative phosphorylation, which attenuates the chemoresistance of CRC cells by inhibiting PKM2-mediated glycolysis.

Conclusions Our results demonstrate that LINC01852 plays an important role in repressing CRC malignancy and chemoresistance by regulating SRSF5-mediated alternative splicing of PKM, and that targeting the LINC01852/TRIM72/SRSF5/PKM2 signaling axis may represent a potential therapeutic strategy for CRC.

Keywords Colorectal cancer, lncRNA, Chemoresistance, Aerobic glycolysis, Alternative splicing



Molecular Cancer
2024 Jan 24;23(1):23
Impact Factor:37.3

Materials and Method
SiRNAs targeting SRSF5 or HOXD8 were obtained from Shanghai **GenePharma** Co., Ltd.

Fang *et al. Molecular Cancer* (2023) 22:99
https://doi.org/10.1186/s12943-023-01791-1

Molecular Cancer

RESEARCH Open Access

m^{6}A methylation reader IGF2BP2 activates endothelial cells to promote angiogenesis and metastasis of lung adenocarcinoma

Han Fang[1,2†], Qi Sun[1,2†], Jin Zhou[2,3†], Huijuan Zhang[4†], Qiong Song[2], Hua Zhang[1,2], Guohua Yu[5], Ying Guo[1,2], Chengyu Huang[2], Yakui Mou[1,2,6], Chuanliang Jia[2], Yingjian Song[7], Aina Liu[4], Kaiyu Song[2,3], Congxian Lu[1,2], Ruxian Tian[1,2], Shizhuang Wei[1,2], Dengfeng Yang[8], Yixuan Chen[2,9], Ting Li[2,9], Kejian Wang[8,10], Yilan Yu[8,10], Yufeng Lv[9], Ke Mo[2,9,10*], Ping Sun[4*], Xiaofeng Yu[7*] and Xicheng Song[1,2*]

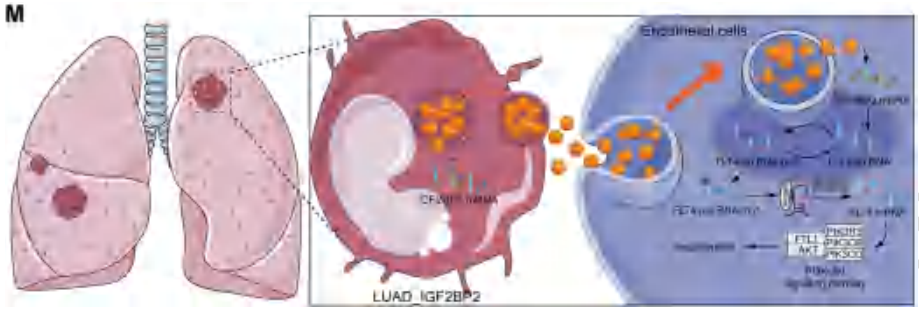
Abstract

Background Lung adenocarcinoma (LUAD) is a common type of lung cancer with a high risk of metastasis, but the exact molecular mechanisms of metastasis are not yet understood.

Methods This study acquired single-cell transcriptomics profiling of 11 distal normal lung tissues, 11 primary LUAD tissues, and 4 metastatic LUAD tissues from the GSE131907 dataset. The lung multicellular ecosystems were characterized at a single-cell resolution, and the potential mechanisms underlying angiogenesis and metastasis of LUAD were explored.

Results We constructed a global single-cell landscape of 93,610 cells from primary and metastatic LUAD and found that IGF2BP2 was specifically expressed both in a LUAD cell subpopulation (termed as LUAD_IGF2BP2), and an endothelial cell subpopulation (termed as En_IGF2BP2). The LUAD_IGF2BP2 subpopulation progressively formed and dominated the ecology of metastatic LUAD during metastatic evolution. IGF2BP2 was preferentially secreted by exosomes in the LUAD_IGF2BP2 subpopulation, which was absorbed by the En_IGF2BP2 subpopulation in the tumor microenvironment. Subsequently, IGF2BP2 improved the RNA stability of FLT4 through m^{6}A modification, thereby activating the PI3K-Akt signaling pathway, and eventually promoting angiogenesis and metastasis. Analysis of clinical data showed that IGF2BP2 was linked with poor overall survival and relapse-free survival for LUAD patients.

Conclusions Overall, these findings provide a novel insight into the multicellular ecosystems of primary and metastatic LUAD, and demonstrate that a specific LUAD_IGF2BP2 subpopulation is a key orchestrator promoting



Molecular Cancer
2023 Jun;22:99
Impact Factor:37.3

Materials and Method

Small interfering RNA (siRNA) of IGF2BP2 and negative control (si-NC)(**GenePharma**, Shanghai, China) were synthesized and transfected into LUAD cells through Lipofectamine RNAiMAX transfection reagent .

Li *et al. Molecular Cancer* (2022) 21:181
https://doi.org/10.1186/s12943-022-01654-1

Molecular Cancer

RESEARCH Open Access

Micropeptide MIAC inhibits the tumor progression by interacting with AQP2 and inhibiting EREG/EGFR signaling in renal cell carcinoma

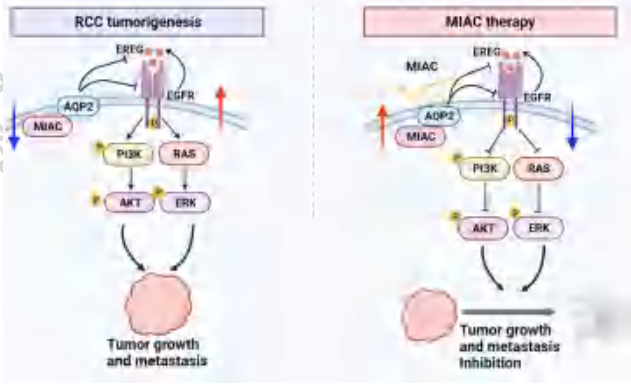
Abstract

Background: Although, micropeptides encoded by non-coding RNA have been shown to have an important role in a variety of tumors processes, there have been no reports on micropeptide in renal cell carcinoma (RCC). Based on the micropeptide MIAC (micropeptide inhibiting actin cytoskeleton) discovered and named in the previous work, this study screened its tumor spectrum, and explored its mechanism of action and potential diagnosis and treatment value in the occurrence and development of renal carcinoma.

Methods: The clinical significance of MIAC in RCC was explored by bioinformatics analysis through high-throughput RNA-seq data from 530 patients with kidney renal clear cell carcinoma (KIRC) in the TCGA database, and the detection of clinical samples of 70 cases of kidney cancer. In vitro and in vivo experiments to determine the role of MIAC in renal carcinoma cell growth and metastasis; High-throughput transcriptomics, western blotting, immunoprecipitation, molecular docking, affinity experiments, and Streptavidin pulldown experiments identify MIAC direct binding protein and key regulatory pathways.

Results: The analysis of 600 renal carcinoma samples from different sources revealed that the expression level of MIAC is significantly decreased, and corelated with the prognosis and clinical stage of tumors in patients with renal carcinoma. Overexpression of MIAC in renal carcinoma cells can significantly inhibit the proliferation and migration ability, promote apoptosis of renal carcinoma cells, and affect the distribution of cells at various stages. After knocking down MIAC, the trend is reversed. In vivo experiments have found that MIAC overexpression inhibit the growth and metastasis of RCC, while the synthetized MIAC peptides can significantly inhibit the occurrence and development of RCC in vitro and in vivo. Further mechanistic studies have demonstrated that MIAC directly bind to AQP2 protein, inhibit EREG/EGFR expression and activate downstream pathways PI3K/AKT and MAPK to achieve anti-tumor effects.

Conclusions: This study revealed for the first time the tumor suppressor potential of the lncRNA-encoded micro-peptide MIAC in RCC, which inhibits the activation of the EREG/EGFR signaling pathway by direct binding to AQP2



Molecular Cancer
2021 Sep;31(11):1199-1211
Impact Factor:37.3

Materials and Method

Cell transfections with plasmids or siRNAs were performed using Lipofectamine 3000 or **GP-transfect-mate** (**GenePharma**, Shanghai, China).
All the **siRNAs** were obtained from **GenePharma**.

Pan et al. Molecular Cancer (2020) 19:9
https://doi.org/10.1186/s12943-020-1133-9

Molecular Cancer

RESEARCH Open Access

lncRNA JPX/miR-33a-5p/Twist1 axis regulates tumorigenesis and metastasis of lung cancer by activating Wnt/β-catenin signaling

Jinchang Pan[1,2], Shuai Fang[1,2], Haihua Tian[1,2,3], Chengwei Zhou[4], Xiaodong Zhao[4], Hui Tian[5], Jinxian He[5], Weiyu Shen[5], Xiaodan Meng[1,2], Xiaofeng Jin[1,2] and Zhaohui Gong[1,2*]

Abstract

Background: MicroRNAs (miRNAs) and Twist1-induced epithelial-mesenchymal transition (EMT) in cancer cell dissemination are well established, but the involvement of long noncoding RNAs (lncRNAs) in Twist1-mediated signaling remains largely unknown.

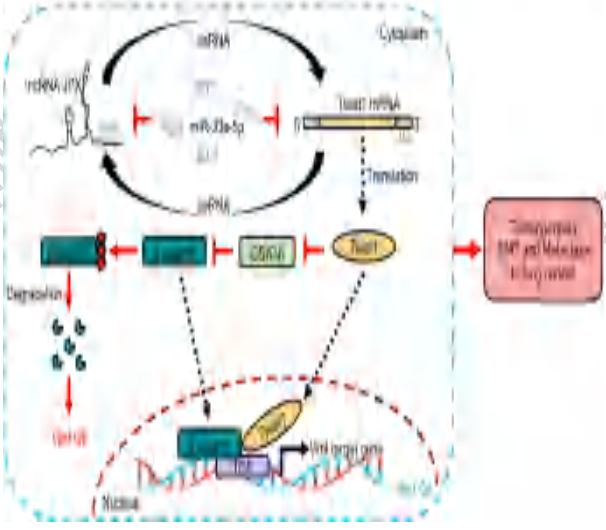
Methods: RT-qPCR and western blotting were conducted to detect the expression levels of lncRNA JPX and Twist1 in lung cancer cell lines and tissues. The impact of JPX on Twist1 expression, cell growth, invasion, apoptosis, and in vivo tumor growth were investigated in lung cancer cells by western blotting, rescue experiments, colony formation assay, flow cytometry, and xenograft animal experiment.

Results: We observed that lncRNA JPX was upregulated in lung cancer metastatic tissues and was closely correlated with tumor size and an advanced stage. Functionally, JPX promoted lung cancer cell proliferation in vitro and facilitated lung tumor growth in vivo. Additionally, JPX upregulated Twist1 by competitively sponging miR-33a-5p and subsequently induced EMT and lung cancer cell invasion. Interestingly, JPX and Twist1 were coordinately upregulated in lung cancer tissues and cells. Mechanically, the JPX/miR-33a-5p/Twist1 axis participated in EMT progression by activating Wnt/β-catenin signaling.

Conclusions: These findings suggest that lncRNA JPX, a mediator of Twist1 signaling, could predispose lung cancer cells to metastasis and may serve as a potential target for targeted therapy.

Keywords: Epithelial-mesenchymal transition, Twist1, Long noncoding RNA, Wnt/β-catenin signaling, Lung cancer

Molecular Cancer
2020 Jan 15;19(1):9.
Impact Factor:37.3



Materials and Methods

JPX small interfering RNA (**siRNA**, **GenePharma**, China) and Twist1 siRNA with the corresponding control RNA (siRNA NC),or miR-33a-5p **mimics** (**GenePharma**, China) with corresponding control RNA (mimics NC) were transfected into cells in logarithmic growth phase.

Liang et al. Cell Discovery (2024)10:13
https://doi.org/10.1038/s41421-023-00633-0

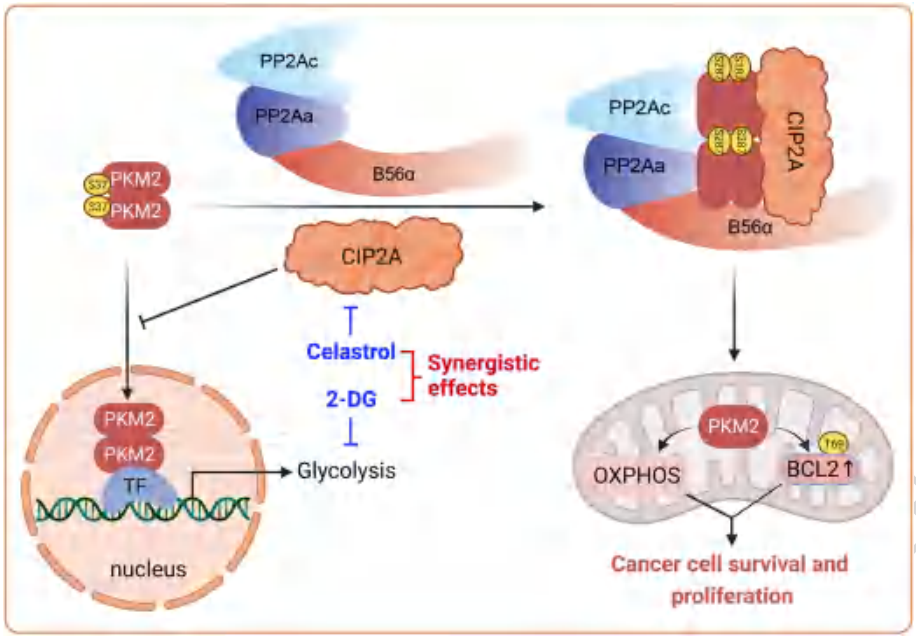
Cell Discovery
www.nature.com/celldisc

ARTICLE Open Access

CIP2A induces PKM2 tetramer formation and oxidative phosphorylation in non-small cell lung cancer

Li-Jun Liang[1,2], Fu-Ying Yang[1], Di Wang[1,3], Yan-Fei Zhang[1,4], Hong Yu[1,5], Zheng Wang[1], Bei-Bei Sun[1], Yu-Tao Liu[1]✉, Gui-Zhen Wang[1]✉ and Guang-Biao Zhou[1]✉

Abstract
Tumor cells are usually considered defective in mitochondrial respiration, but human non-small cell lung cancer (NSCLC) tumor tissues are shown to have enhanced glucose oxidation relative to adjacent benign lung. Here, we reported that oncoprotein cancerous inhibitor of protein phosphatase 2A (CIP2A) inhibited glycolysis and promoted oxidative metabolism in NSCLC cells. CIP2A bound to pyruvate kinase M2 (PKM2) and induced the formation of PKM2 tetramer, with serine 287 as a novel phosphorylation site essential for PKM2 dimer-tetramer switching. CIP2A redirected PKM2 to mitochondrion, leading to upregulation of Bcl2 via phosphorylating Bcl2 at threonine 69. Clinically, CIP2A level in tumor tissues was positively correlated with the level of phosphorylated PKM2 S287. CIP2A-targeting compounds synergized with glycolysis inhibitor in suppressing cell proliferation in vitro and in vivo. These results indicated that CIP2A facilitates oxidative phosphorylation by promoting tetrameric PKM2 formation, and targeting CIP2A and glycolysis exhibits therapeutic potentials in NSCLC.



Cell Discovery
2024 Feb 6;10(1):13
Impact Factor:33.5

Materials and Method

All **siRNAs** were synthesized by **GenePharma** (Shanghai, China) and the sequences are shown in Supplementary Table S2.

Qiao et al. Cell Discovery (2024)10:17
https://doi.org/10.1038/s41421-023-00636-x

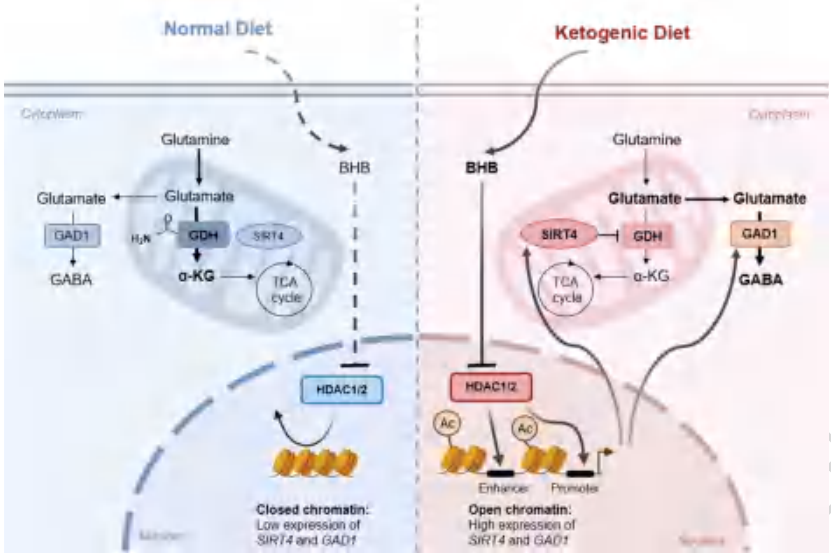
Cell Discovery
www.nature.com/celldisc

ARTICLE Open Access

Ketogenic diet-produced β-hydroxybutyric acid accumulates brain GABA and increases GABA/glutamate ratio to inhibit epilepsy

Ya-Nan Qiao[1], Lei Li[2], Song-Hua Hu[3], Yuan-Xin Yang[1], Zhen-Zhen Ma[1], Lin Huang[1], Yan-Peng An[1], Yi-Yuan Yuan[1], Yan Lin[1], Wei Xu[1], Yao Li[1], Peng-Cheng Lin[4], Jing Cao[2], Jian-Yuan Zhao[5] and Shi-Min Zhao[1,3,4]✉

Abstract
Ketogenic diet (KD) alleviates refractory epilepsy and reduces seizures in children. However, the metabolic/cell biologic mechanisms by which the KD exerts its antiepileptic efficacy remain elusive. Herein, we report that KD-produced β-hydroxybutyric acid (BHB) augments brain gamma-aminobutyric acid (GABA) and the GABA/glutamate ratio to inhibit epilepsy. The KD ameliorated pentetrazol-induced epilepsy in mice. Mechanistically, KD-produced BHB, but not other ketone bodies, inhibited HDAC1/HDAC2, increased H3K27 acetylation, and transcriptionally upregulated SIRT4 and glutamate decarboxylase 1 (GAD1). BHB-induced SIRT4 de-carbamylated and inactivated glutamate dehydrogenase to preserve glutamate for GABA synthesis, and GAD1 upregulation increased mouse brain GABA/glutamate ratio to inhibit neuron excitation. BHB administration in mice inhibited epilepsy induced by pentetrazol. BHB-mediated relief of epilepsy required high GABA level and GABA/glutamate ratio. These results identified BHB as the major antiepileptic metabolite of the KD and suggested that BHB may serve as an alternative and less toxic antiepileptic agent than KD.



Cell Discovery
2024 Feb 13;10(1):17
Impact Factor:33.5

Materials and Method

In RNA interference, **double-stranded siRNAs** targeting GDH and BDH1, respectively, were purchased from **GenePharma** and transfected into cells via RNAiMax (Invitrogen) according to the manu-facturer's instructions.z

Wei et al. Cell Discovery (2024)10:43
https://doi.org/10.1038/s41421-024-00659-y

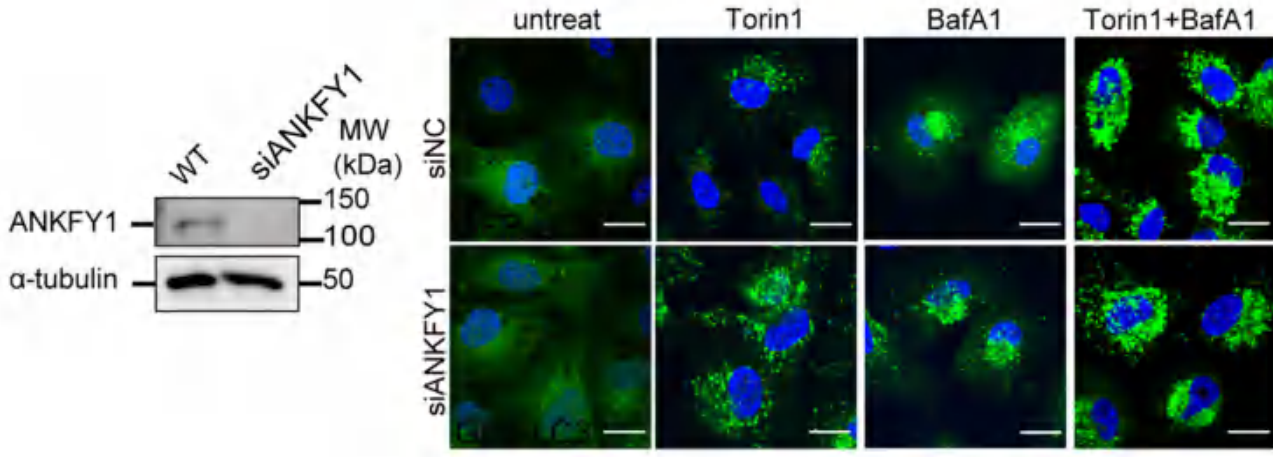
Cell Discovery
www.nature.com/celldisc

ARTICLE Open Access

ANKFY1 bridges ATG2A-mediated lipid transfer from endosomes to phagophores

Bin Wei[1], Yuhui Fu[1], Xiuzhi Li[1], Fang Chen[1], Yiqing Zhang[1], Hanmo Chen[1], Mindan Tong[1], Linsen Li[1], Yi Pan[1], Shen Zhang[1], She Chen[2], Xiaoxia Liu[1]✉ and Qing Zhong[1]✉

Abstract
Macroautophagy is a process that cells engulf cytosolic materials by autophagosomes and deliver them to lysosomes for degradation. The biogenesis of autophagosomes requires ATG2 as a lipid transfer protein to transport lipids from existing membranes to phagophores. It is generally believed that endoplasmic reticulum is the main source for lipid supply of the forming autophagosomes; whether ATG2 can transfer lipids from other organelles to phagophores remains elusive. In this study, we identified a new ATG2A-binding protein, ANKFY1. Depletion of this endosome-localized protein led to the impaired autophagosome growth and the reduced autophagy flux, which largely phenocopied ATG2A/B depletion. A pool of ANKFY1 co-localized with ATG2A between endosomes and phagophores and depletion of UVRAG, ANKFY1 or ATG2A/B led to reduction of PI3P distribution on phagophores. Purified recombinant ANKFY1 bound to PI3P on membrane through its FYVE domain and enhanced ATG2A-mediated lipid transfer between PI3P-containing liposomes. Therefore, we propose that ANKFY1 recruits ATG2A to PI3P-enriched endosomes and promotes ATG2A-mediated lipid transfer from endosomes to phagophores. This finding implicates a new lipid source for ATG2A-mediated phagophore expansion, where endosomes donate PI3P and other lipids to phagophores via lipid transfer.



Cell Discovery
Wei et al. Cell Discovery (2024) 10:43
Impact Factor:33.5

Materials and Method
For **siRNA**-mediated gene knockdown
siRNA duplexes were purchased from **GenePharma**.

Wu et al. Cell Discovery (2023)9:29
https://doi.org/10.1038/s41421-022-00514-y

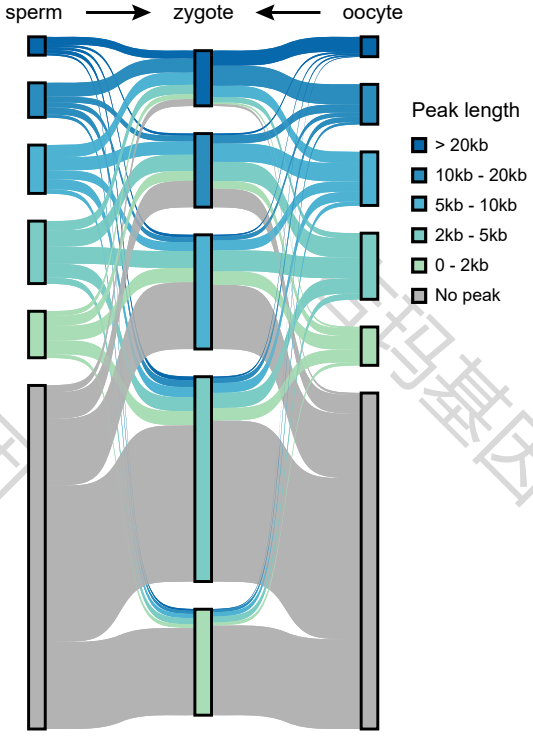
Cell Discovery
www.nature.com/celldisc

ARTICLE Open Access

Dynamics of histone acetylation during human early embryogenesis

Keliang Wu[1], Dongdong Fan[2,3], Han Zhao[1], Zhenbo Liu[4], Zhenzhen Hou[1], Wenrong Tao[1], Guanling Yu[1], Shenli Yuan[2,4], Xiaoxiao Zhu[2,3], Mengyao Kang[2,4], Yong Tian[2,3]✉, Zi-Jiang Chen[1,5,6]✉, Jiang Liu[2,4,7]✉ and Lei Gao[4]✉

Abstract
It remains poorly understood about the regulation of gene and transposon transcription during human early embryogenesis. Here, we report that broad H3K27ac domains are genome-widely distributed in human 2-cell and 4-cell embryos and transit into typical peaks in the 8-cell embryos. The broad H3K27ac domains in early embryos before zygotic genome activation (ZGA) are also observed in mouse. It suggests that broad H3K27ac domains play conserved functions before ZGA in mammals. Intriguingly, a large portion of broad H3K27ac domains overlap with broad H3K4me3 domains. Further investigation reveals that histone deacetylases are required for the removal or transition of broad H3K27ac domains and ZGA. After ZGA, the number of typical H3K27ac peaks is dynamic, which is associated with the stage-specific gene expression. Furthermore, P300 is important for the establishment of H3K27ac peaks and the expression of associated genes in early embryos after ZGA. Our data also indicate that H3K27ac marks active transposons in early embryos. Interestingly, H3K27ac and H3K18ac signals rather than H3K9ac signals are enriched at ERVK elements in mouse embryos after ZGA. It suggests that different types of histone acetylations exert distinct roles in the activation of transposons. In summary, H3K27ac modification undergoes extensive reprogramming during early embryo development in mammals, which is associated with the expression of genes and transposons.



Materials and Method
All the **siRNAs** used in this study were synthesized by **GenePharma** company.

Tian et al. Cell Discovery (2022)8:90
https://doi.org/10.1038/s41421-022-00439-6

Cell Discovery
www.nature.com/celldisc

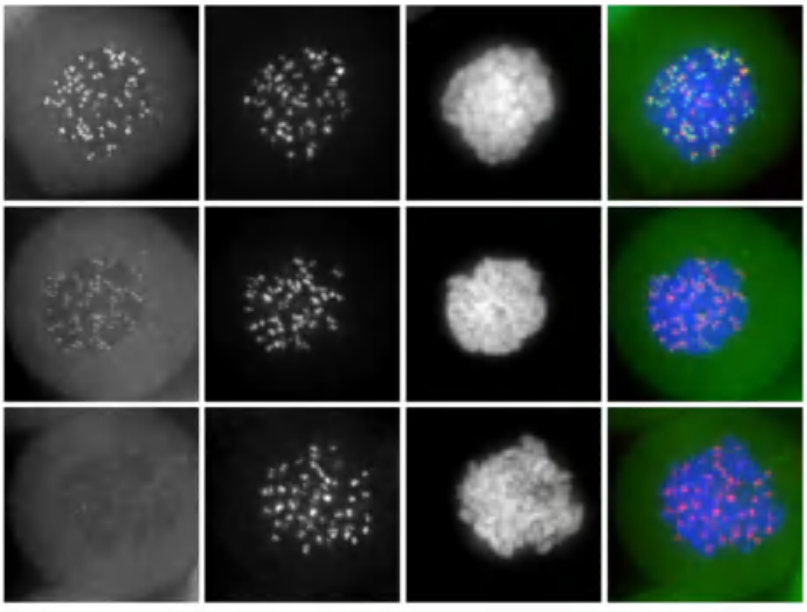
ARTICLE Open Access

Structural insights into human CCAN complex assembled onto DNA

Tian Tian[1], Lili Chen[1], Zhen Dou[1,2], Zhisen Yang[1], Xinjiao Gao[1,2]✉, Xiao Yuan[1,2], Chengliang Wang[1], Ran Liu[1,2], Zuojun Shen[1], Ping Gui[1,2], Maikun Teng[1], Xianlei Meng[1], Donald L. Hill[3], Lin Li[4], Xuan Zhang[1], Xing Liu[1,2], Linfeng Sun[1]✉, Jianye Zang[1]✉ and Xuebiao Yao[1,2]✉

Abstract

In mitosis, accurate chromosome segregation depends on kinetochores that connect centromeric chromatin to spindle microtubules. The centromeres of budding yeast, which are relatively simple, are connected to individual microtubules via a kinetochore constitutive centromere associated network (CCAN). However, the complex centromeres of human chromosomes comprise millions of DNA base pairs and attach to multiple microtubules. Here, by use of cryo-electron microscopy and functional analyses, we reveal the molecular basis of how human CCAN interacts with duplex DNA and facilitates accurate chromosome segregation. The overall structure relates to the cooperative interactions and interdependency of the constituent sub-complexes of the CCAN. The duplex DNA is topologically entrapped by human CCAN. Further, CENP-N does not bind to the RG-loop of CENP-A but to DNA in the CCAN complex. The DNA binding activity is essential for CENP-LN localization to centromere and chromosome segregation during mitosis. Thus, these analyses provide new insights into mechanisms of action underlying kinetochore assembly and function in mitosis.



Cell Discovery
2022 Sep;8(1):1-15
Impact Factor:33.5

Materials and Method

The **siRNA** against CENP-L (AAGAUUAGUUCGUGUUUCA) was obtained from **GenePharma** and was previously confirmed.

Zhang et al. Cell Discovery (2022)8:94
https://doi.org/10.1038/s41421-022-00459-2

Cell Discovery
www.nature.com/celldisc

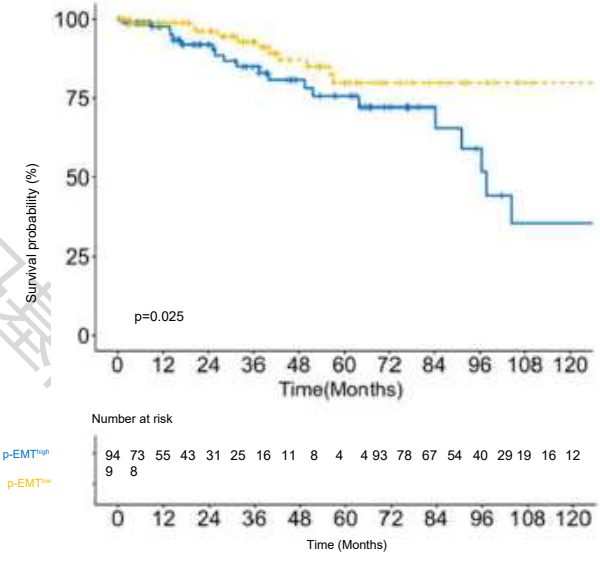
ARTICLE Open Access

Single-cell transcriptome reveals cellular hierarchies and guides p-EMT-targeted trial in skull base chordoma

Qilin Zhang[1,2], Lijiang Fei[3], Rui Han[1,2], Ruofan Huang[2,4], Yongfei Wang[1,2], Hong Chen[2,5], Boyuan Yao[1,2], Nidan Qiao[1,2], Zhe Wang[6], Zengyi Ma[1,2], Zhao Ye[1,2], Yichao Zhang[1,2], Weiwei Wang[2,7], Ye Wang[1,2], Lin Kong[8], Xuefei Shou[1,2], Xiaoyun Cao[1,2], Xiang Zhou[1,2], Ming Shen[1,2], Haixia Cheng[2,5], Zhenwei Yao[2,7], Chao Zhang[6], Guoji Guo[3]✉ and Yao Zhao[1,2,9,10,11,12]✉

Abstract

Skull base chordoma (SBC) is a bone cancer with a high recurrence rate, high radioresistance rate, and poorly understood mechanism. Here, we profiled the transcriptomes of 90,691 single cells, revealed the SBC cellular hierarchies, and explored novel treatment targets. We identified a cluster of stem-like SBC cells that tended to be distributed in the inferior part of the tumor. Combining radiated UM-Chor1 RNA-seq data and in vitro validation, we further found that this stem-like cell cluster is marked by cathepsin L (CTSL), a gene involved in the packaging of telomere ends, and may be responsible for radioresistance. Moreover, signatures related to partial epithelial–mesenchymal transition (p-EMT) were found to be significant in malignant cells and were related to the invasion and poor prognosis of SBC. Furthermore, YL-13027, a p-EMT inhibitor that acts through the TGF-β signaling pathway, demonstrated remarkable potency in inhibiting the invasiveness of SBC in preclinical models and was subsequently applied in a phase I clinical trial that enrolled three SBC patients. Encouragingly, YL-13027 attenuated the growth of SBC and achieved stable disease with no serious adverse events, underscoring the clinical potential for the precision treatment of SBC with this therapy. In summary, we conducted the first single-cell RNA sequencing of SBC and identified several targets that could be translated to the treatment of SBC.



Cell Discovery
2022 Sep;8(1):1-20
Impact Factor:33.5

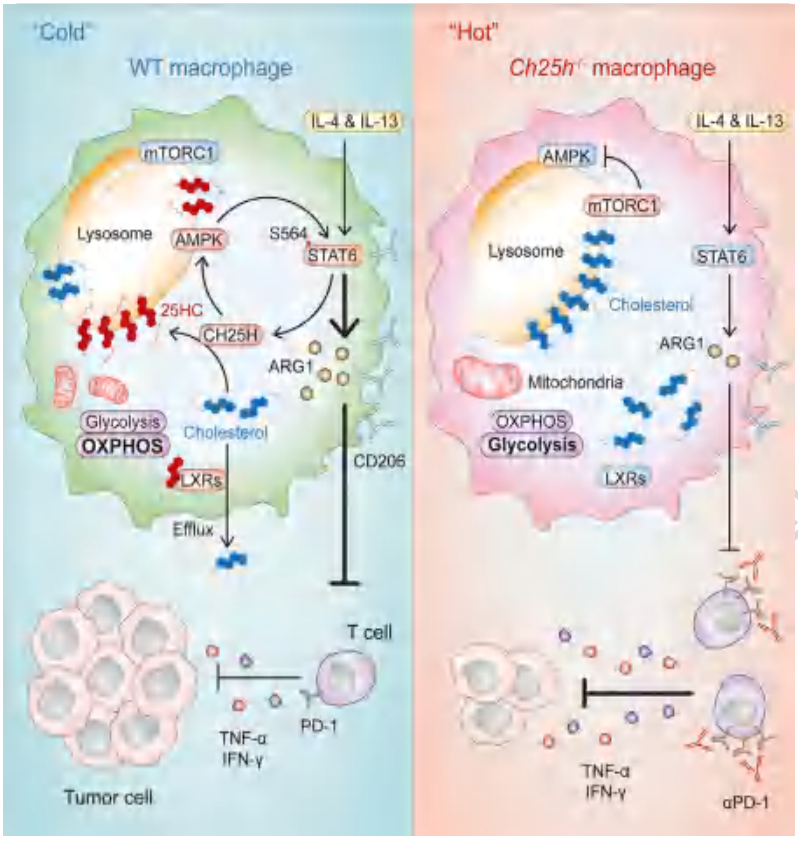
Materials and Method

The siRNA sequences of target gene markers were synthesized by GenePharma.

Immunity

25-Hydroxycholesterol regulates lysosome AMP kinase activation and metabolic reprogramming to educate immunosuppressive macrophages

Graphical abstract



Authors

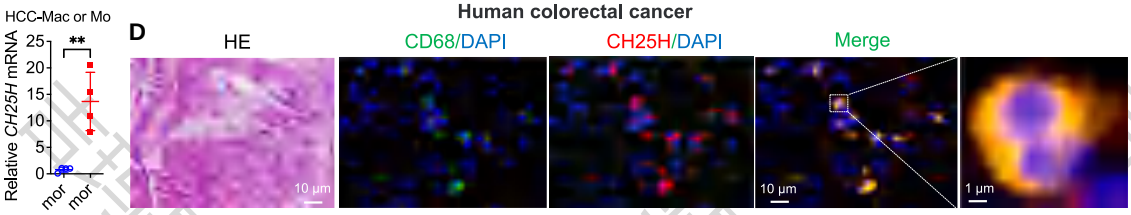
Jun Xiao, Shuang Wang, Longlong Chen, ..., Huiru Tang, Bin Wei, Hongyan Wang

Correspondence

youqiong.ye@shsmu.edu.cn (Y.Y.), huiru_tang@fudan.edu.cn (H.T.), weibinwhy@shu.edu.cn (B.W.), hongyanwang@sibcb.ac.cn (H.W.)

In brief

Cholesterol increases macrophage-mediated inflammation, but how oxysterols control tumor-associated macrophages (TAMs) remains unclear. Xiao et al. show that TAMs exhibit elevated expression of CH25H, resulting in lysosome-accumulated 25HC that activates AMPKa to promote STAT6-dependent ARG1 production. CH25H-deficient macrophages switch ‘‘cold tumors’’ into ‘‘hot tumors’’ and improve anti-PD-1-mediated anti-tumor efficacy.



IMMUNITY
Immunity 57, 1087–1104.e1–e7, May 14, 2024
Impact Factor:32.4

Materials and Method
The synthesized **siRNAs** (**GenePharma**)..

nature immunology

Article

https://doi.org/10.1038/s41590-023-01672-1

Oleic acid availability impacts thymocyte preprogramming and subsequent peripheral T_{reg} cell differentiation

Received: 6 January 2023

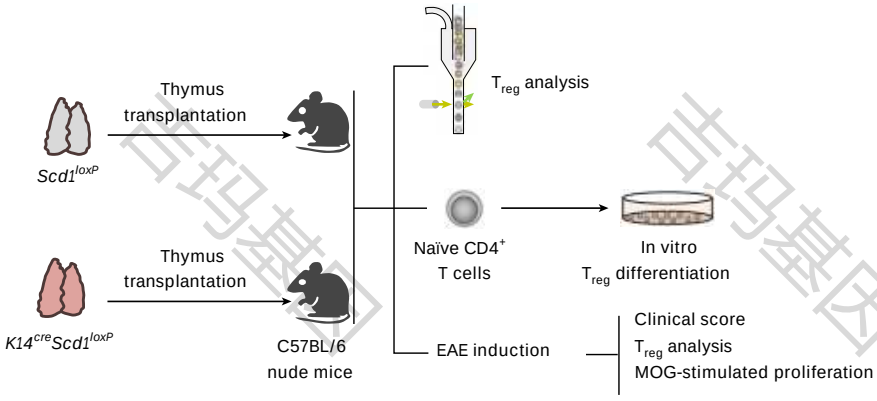
Accepted: 5 October 2023

Published online: 7 December 2023

Check for updates

Liangyu Lin[1,7], Mingyuan Hu[1,7], Qing Li[1], Liming Du[1], Li Lin[2], Yueqing Xue[1], Fanjun Zheng[1], Fei Wang[1], Keli Liu[2], Yu Wang[1], Jiayin Ye[1], Xu Jiang[1], Xuefeng Wang[1], Jiaqi Wang[1], Jingjie Zhai[1], Benming Liu[1], Hongzhen Xie[1], Yanqin You[3], Jinyong Wang[4], Xiangyin Kong[1], Dechun Feng[1], Douglas R. Green[5], Yufang Shi[1,6] ✉ & Ying Wang[1] ✉

The nature of activation signals is essential in determining T cell subset differentiation; however, the features that determine T cell subset preference acquired during intrathymic development remain elusive. Here we show that naive CD4$^+$ T cells generated in the mouse thymic microenvironment lacking *Scd1*, encoding the enzyme catalyzing oleic acid (OA) production, exhibit enhanced regulatory T (T_{reg}) cell differentiation and attenuated development of experimental autoimmune encephalomy-elitis. *Scd1* deletion in K14$^+$ thymic epithelia recapitulated the enhanced T_{reg} cell differentiation phenotype of *Scd1*-deficient mice. The dearth of OA permitted DOT1L to increase H3K79me2 levels at the *Atp2a2* locus of thymocytes at the DN2–DN3 transition stage. Such epigenetic modification persisted in naive CD4$^+$ T cells and facilitated *Atp2a2* expression. Upon T cell receptor activation, ATP2A2 enhanced the activity of the calcium– NFAT1–Foxp3 axis to promote naive CD4$^+$ T cells to differentiate into T_{reg} cells. Therefore, OA availability is critical for preprogramming thymocytes with T_{reg} cell differentiation propensities in the periphery.



NATURE IMMUNOLOGY
2024 Jan;25(1):54-65
Impact Factor:30.5

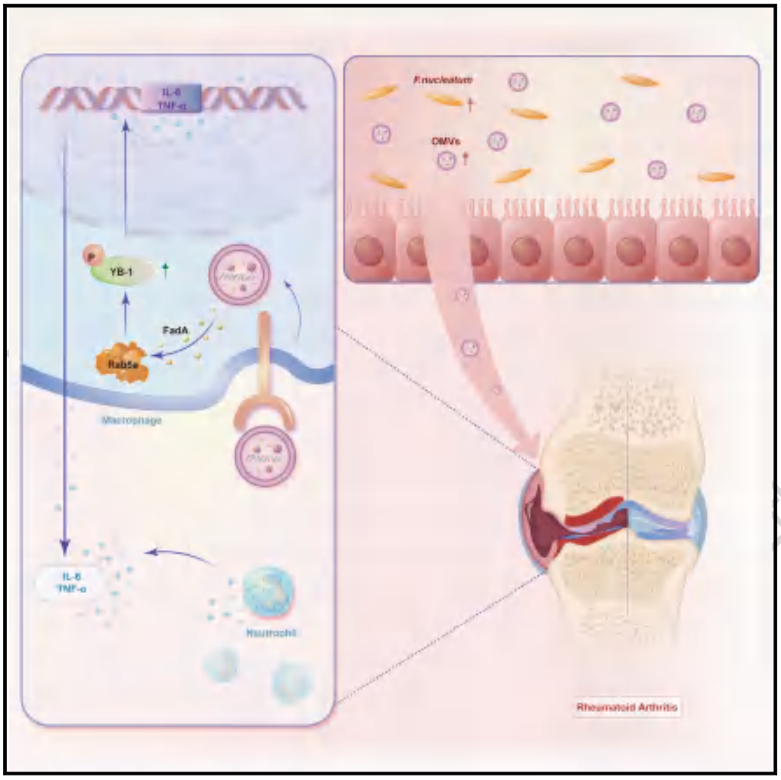
Materials and Method

Atp2a2-targeting siRNA and **scramble controls** were purchased from **Gene Pharma**.

Cell Host & Microbe

Fusobacterium nucleatum aggravates rheumatoid arthritis through FadA-containing outer membrane vesicles

Graphical abstract



Authors

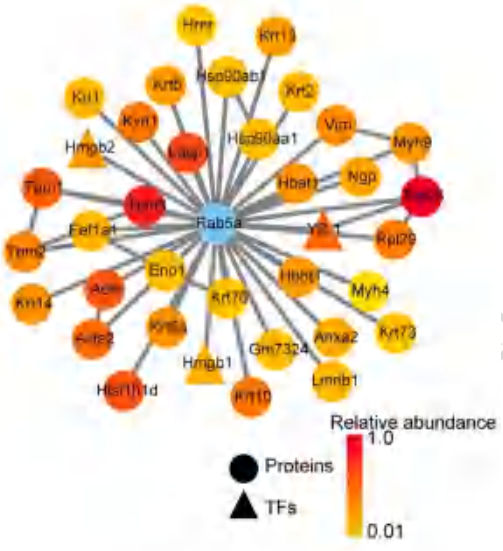
Mukeng Hong, Zhuang Li, Haihua Liu, ..., Shixian Chen, Hongwei Zhou, Juan Li

Correspondence

shixian@smu.edu.cn (S.C.), biodegradation@gmail.com (H.Z.), lijuan@smu.edu.cn (J.L.)

In brief

Hong et al. show that Fusobacterium nucleatum is enriched in the gut of RA patients and aggravates arthritis by delivering the virulence factor FadA to the joints via outer membrane vesicles. Mechanistically, FadA triggers synovial inflammation by activating the Rab5a-YB-1 axis in synovial macrophages.



Cell Host & Microbe
2023 May;31, 798–810
Impact Factor:30.3

Materials and Method

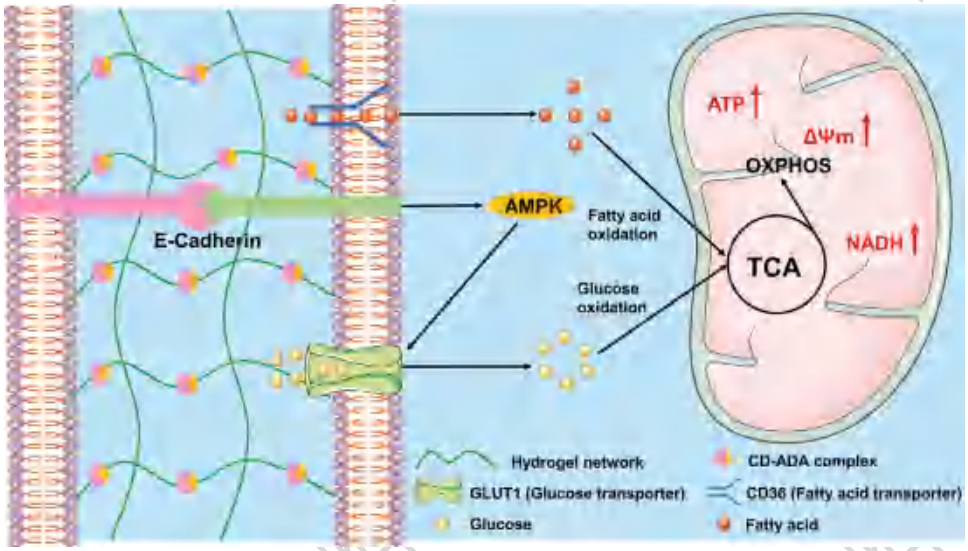
Then BMDMs were transfected with nonspecific con-trol siRNA or **mouse YB-1 siRNA nucleotide fragment** (**GenePharma)** using the LipofectaminTM RNAiMAX (Invitrogen) for 36 h.

ADVANCED MATERIALS
www.advmat.de

Supramolecular Hydrogel with Ultra-Rapid Cell-Mediated Network Adaptation for Enhancing Cellular Metabolic Energetics and Tissue Regeneration

Zhuo Li, Boguang Yang, Zhengmeng Yang, Xian Xie, Zhengnan Guo, Jianyang Zhao, Ruinan Wang, Hao Fu, Pengchao Zhao, Xin Zhao, Guosong Chen, Gang Li, Fuxin Wei,* and Liming Bian**

Cellular energetics plays an important role in tissue regeneration, and the enhanced metabolic activity of delivered stem cells can accelerate tissue repair and regeneration. However, conventional hydrogels with limited network cell adaptability restrict cell–cell interactions and cell metabolic activities. In this work, it is shown that a cell-adaptable hydrogel with high network dynamics enhances the glucose uptake and fatty acid β-oxidation of encapsulated human mesenchymal stem cells (hMSCs) compared with a hydrogel with low network dynamics. It is further shown that the hMSCs encapsulated in the high dynamic hydrogels exhibit increased tricarboxylic acid (TCA) cycle activity, oxidative phosphorylation (OXPHOS), and adenosine triphosphate (ATP) biosynthesis via an E-cadherin- and AMP-activated protein kinase (AMPK)-dependent mechanism. The in vivo evaluation further showed that the delivery of MSCs by the dynamic hydrogel enhanced in situ bone regeneration in an animal model. It is believed that the findings provide critical insights into the impact of stem cell–biomaterial interactions on cellular metabolic energetics and the underlying mechanisms.



ADVANCED MATERIALS
2024 Jan 31:e2307176
Impact Factor:29.4

Materials and Method
All **siRNAs** were synthesized by **GenePharma** (China).

Gastroenterology 2023; - :1–17

Pancreatic Acinar Cells-Derived Sphingosine-1-Phosphate Contributes to Fibrosis of Chronic Pancreatitis via Inducing Autophagy and Activation of Pancreatic Stellate Cells

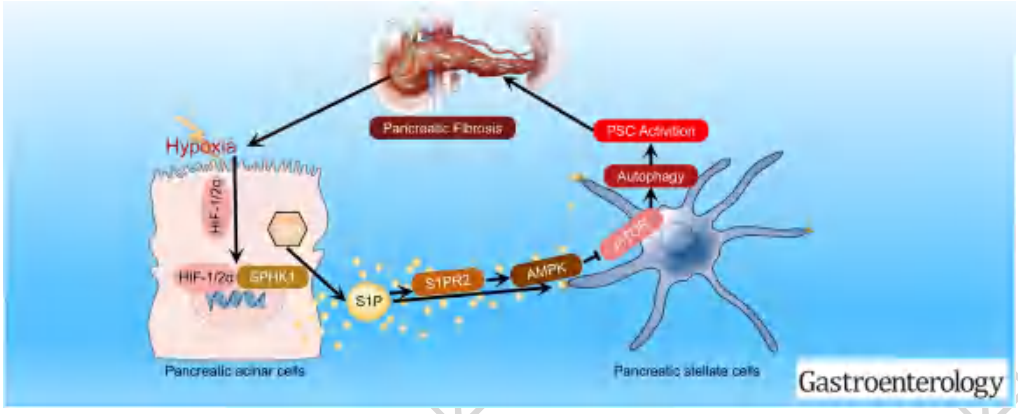
Decai Wang,[1,*] Shengbo Han,[1,*] Guozheng Lv,[1,*] Yuhang Hu,[1,*] Wenfeng Zhuo,[1] Zhu Zeng,[1] Jiang Tang,[1] Yan Huang,[1] Fan Wang,[1] Jie Wang,[1] Yong Zhao,[1] and Gang Zhao[1]

[1]Department of Emergency Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan China

BACKGROUND & AIMS: Studies have demonstrated that activated pancreatic stellate cells (PSCs) play a crucial role in pancreatic fibrogenesis in chronic pancreatitis (CP); however, the precise mechanism for PSCs activation has not been fully elucidated. We analyzed the role of injured pancreatic acinar cells (iPACs) in the activation of PSCs of CP.

METHODS: Sphingosine kinase 1 (SPHK1)/sphingosine-1-phosphate (S1P) signaling was evaluated in experimental CP induced by cerulein injection or pancreatic duct ligation, as well as in PACs injured by cholecystokinin. The activation of PSCs and pancreatic fibrosis in CP samples was evaluated by immunohistochemical and immunofluores-cence analyses. In vitro coculture assay of iPACs and PSCs was created to evaluate the effect of the SPHK1/S1P pathway and S1P receptor 2 (SIPR2) on autophagy and activation of PSCs. The pathogenesis of CP was assessed in SPHK1$^{-/-}$ mice or PACs-specific SPHK1-knockdown mice with recombinant adeno-associated virus serotypes 9-SPHK1-knockdown, as well as in mice treated with inhibi-tor of SPHK1 and S1P receptor 2 (S1PR2).

RESULTS: SPHK1/S1P was remarkably increased in iPACs and acinar cells in pancreatic tissues of CP mice. Meanwhile, the pathogenesis, fibrosis, and PSCs activation of CP was significantly prevented in SPHK1 / mice and recombinant adeno-associated virus serotypes 9-SPHK1-knockdown mice. Meanwhile, iPACs obviously activated PSCs, which was prevented by SPHK1 knockdown in iPACs. Moreover, iPACs-derived S1P specifically combined to S1PR2 of PSCs, by which modulated 50 adenosine monophosphate-activated protein kinase/mechanistic target of rapamycin pathway and consequently induced autophagy and activation of PSCs. Furthermore, hypoxia-inducible factor 1-a and -2a promoted SPHK1 transcription of PACs under hypoxia conditions, which is a distinct characteristic of the CP microenvironment. Coincidently, inhibition of SPHK1 and S1PR2 activity with inhibitor PF-543 and JTE-013 obviously impeded pancreatic fibrogenesis of CP mice.



GASTROENTEROLOGY
2023 Aug 25;S0016-5085(23)04912-0
Impact Factor:29.4

Materials and Method

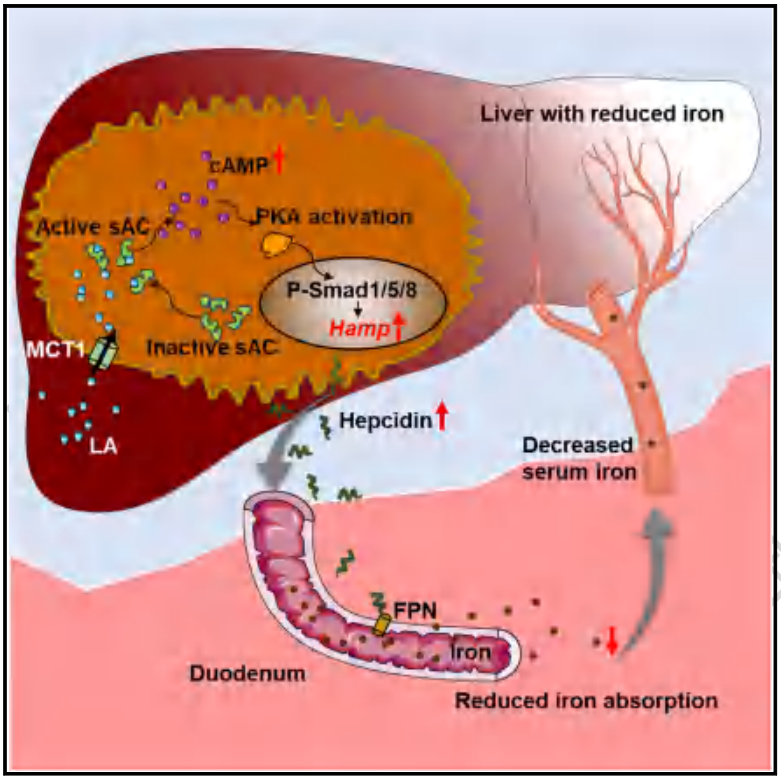
Specific siRNAs and **scrambled siRNA** were synthesized by **GenePharma**.

Cell Metabolism

Article

Lactate modulates iron metabolism by binding soluble adenylyl cyclase

Graphical abstract



Authors

Wei Liu, Shuping Zhang, Quanjin Li, ..., Pu Gao, Tomas Ganz, Sijin Liu

Correspondence

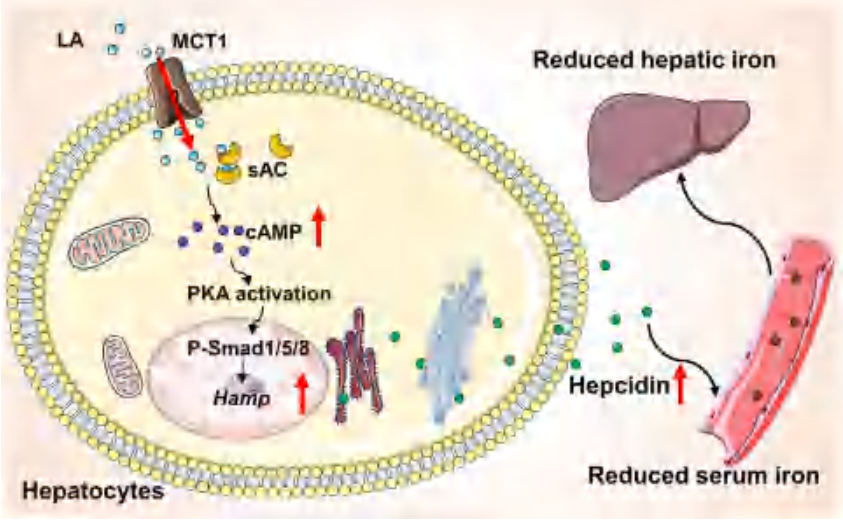
sjliu@rcees.ac.cn

In brief

Liu et al. report that intracellular LA imported by MCT1 binds to sAC to increase cAMP level and thereafter promotes PKA-Smad1/5/8 signaling to induce hepatic hepcidin expression, thereby modulating systemic iron homeostasis.

Cell Metabolism
2023 Jul 21;35:1–16
Impact Factor:29

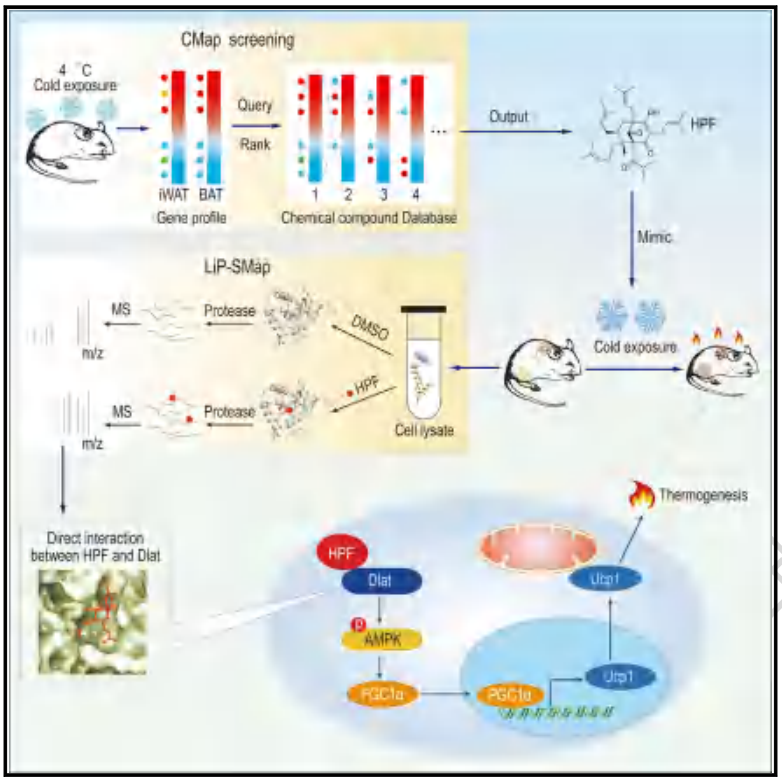
Materials and Method
For in vitro cultured cells, when the confluence reached 70-80%, siRNA (Table S3) molecules (GenePharma, China) were transfected into cells with Lipofectamine 2000 (Thermo Fisher Scientific, USA), following the instructions from the manufacturer.



Cell Metabolism

The phytochemical hyperforin triggers thermogenesis in adipose tissue via a Dlat-AMPK signaling axis to curb obesity

Graphical abstract



Authors

Suzhen Chen, Xiaoxiao Liu, Chao Peng, ..., Xiaojun Xu, Junfeng Han, Junli Liu

Correspondence

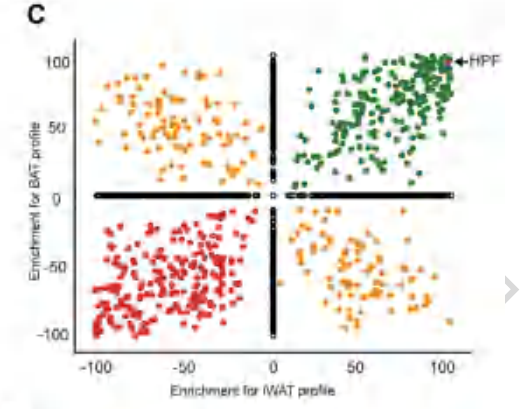
cszdream@163.com (S.C.), 1020122236@cpu.edu.cn (X.X.), tjhjf@163.com (J.H.), liujunli@sjtu.edu.cn (J.L.)

In Brief

Chen et al. reveal that hyperforin (HPF), a natural compound extracted from Hypericum perforatum, promotes adipose tissue thermogenesis to suppress obesity. Using a form of mass spectrometry, they identify Dlat as the direct molecular target of HPF and that it is essential for HPF-mediated adipocyte thermogenesis.

Highlights

- Use of CMap identified the phytochemical hyperforin as an anti-obesity agent in mice
- Hyperforin promotes adipose tissue thermogenesis to promote weight loss
- Dlat was identified and validated as a direct molecular target of hyperforin
- Hyperforin-induced thermogenesis is modulated by a Dlat-AMPK-PGC1a axis



Cell Metabolism
2021 Mar 2;33(3):565-580.e7
Impact Factor:29

Materials and Method

For siRNA transfection, differentiated mature adipocytes were digested with trypsin and incubated with **siRNAs** (**GenePharma**, China) .

nature microbiology

Article

https://doi.org/10.1038/s41564-022-01279-6

Akkermansia muciniphila protects mice against an emerging tick-borne viral pathogen

Received: 26 April 2022

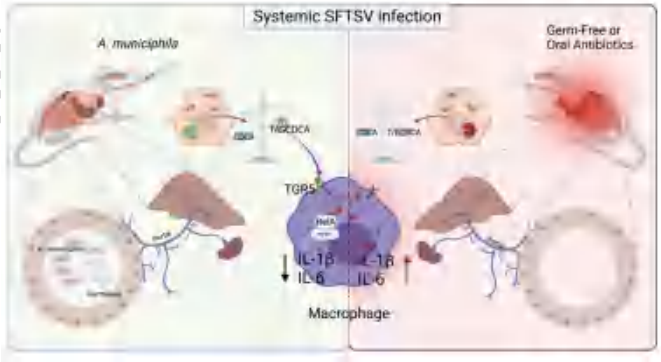
Accepted: 26 October 2022

Published online: 5 January 2023

Check for updates

Jinyan Xie[1,6], Hao Li[2,6], Xiaoai Zhang[2,6], Tong Yang[2,6], Mengjia Yue[1], Yunfa Zhang[2], Shuxian Chen[1], Ning Cui[3], Chun Yuan[3], Jingyun Li[2], Shu Jeffrey Zhu[1,4] ✉ & Wei Liu[2,5] ✉

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne disease caused by a *phlebovirus* in the Bunyaviridae family. Infection can result in systemic inflammatory response syndrome with a high fatality rate, and there are currently no treatments or vaccines available. The microbiota has been implicated in host susceptibility to systemic viral infection and disease outcomes, but whether the gut microbiota is implicated in severe fever with thrombocytopenia syndrome virus (SFTSV) infection is unknown. Here, we analysed faecal and serum samples from patients with SFTS using 16S ribosomal RNA-sequencing and untargeted metabolomics, respectively. We found that the gut commensal *Akkermansia muciniphila* increased in relative abundance over the course of infection and was reduced in samples from deceased patients. Using germ-free or oral antibiotic-treated mice, we found that *A. muciniphila* produces the β-carboline alkaloid harmaline, which protects against SFTSV infection by suppressing NF-κB-mediated systemic inflammation. Harmaline indirectly modulated the virus-induced inflammatory response by specifically enhancing bile acid-CoA: amino a ci d N -a cy lt ra ns ferase expression in hepatic cells to increase conjugated primary bile acids, g l-ycochenodeoxycholic acid and taurochenodeoxycholic acid. These bileacids induced transmembrane G-protein coupled receptor-5-dependent anti-inflammatory responses. These results indicate the probiotic potential of *A. muciniphila* in mitigating SFTSV infection.



Nature Microbiology
2023 Jan 5;91–106
Impact Factor:28.3

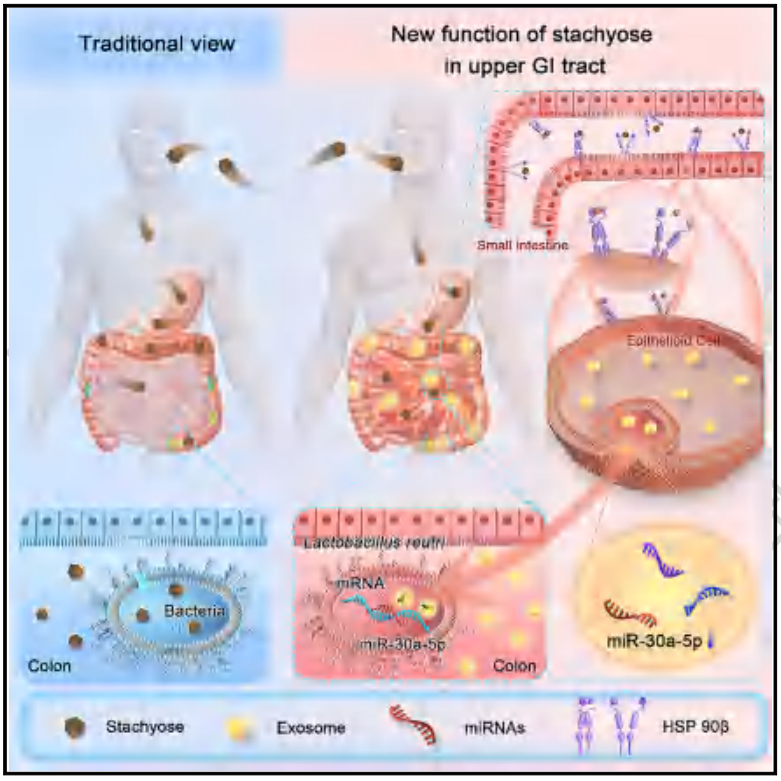
Materials and Method

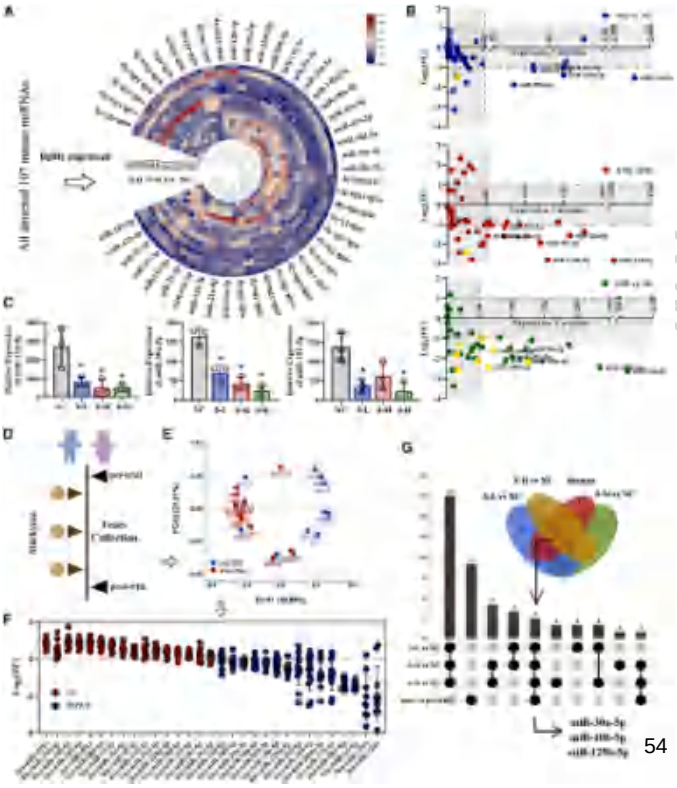
Human TGR5- and FXR-specific siRNAs were designed and synthesized by Santa Cruz Biotechnology, and **mouse Baat-specific siRNAs** were designed and synthesized by **GenePharma**.

Cell Metabolism

Nondigestible stachyose binds membranous HSP90b on small intestinal epithelium to regulate the exosomal miRNAs: A new function and mechanism

Graphical abstract





Authors

Ting Li, Yueyue Liu, Tianchi Duan, ..., Lin Shi, Honglei Tian, Xingbin Yang

Correspondence

tingli@snnu.edu.cn (T.L.),
xbyang@snnu.edu.cn (X.Y.)

In brief

Oligosaccharides are conventionally recognized as ‘‘passersby’’ in the small intestine. However, Li et al. have uncovered that the oligosaccharide stachyose can reprogram the exosomal miRNA profile of small intestinal epithelial cells by binding HSP90b, thereby remodulating the microbiome. These findings reveal a new regulatory axis of stachyose-intestinal miRNAs-gut microbiota crosstalk.

Cell Metabolism
Li et al., 2025, Cell Metabolism 37, 1–16
Impact Factor:27.7

Materials and Method
The **siRNAs** targeting HSP90ab1 (the gene of HSP90b) were synthesized by **GenePharma (Shanghai, China)**

nature microbiology

Article

https://doi.org/10.1038/s41564-024-01695-w

Peptostreptococcus anaerobius mediates anti-PD1 therapy resistance and exacerbates colorectal cancer via myeloid-derived suppressor cells in mice

Received: 12 January 2023

Accepted: 4 April 2024

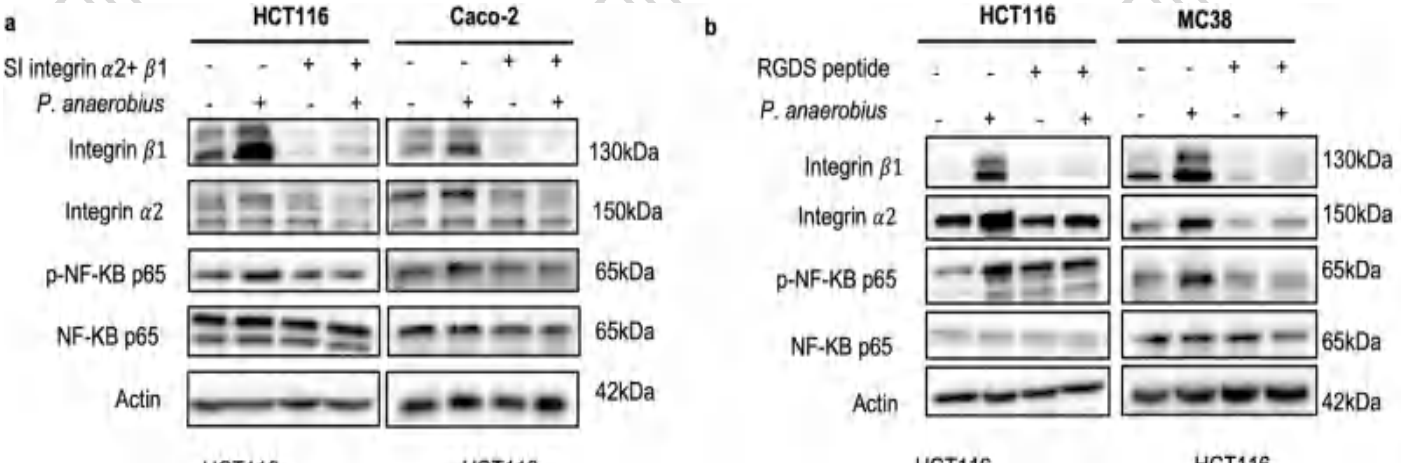
Published online: 15 May 2024

Check for updates

Yali Liu[1], Chi Chun Wong[1], Yanqiang Ding[1], Mengxue Gao[2], Jun Wen[1], Harry Cheuk-Hay Lau[1], Alvin Ho-Kwan Cheung[3], Dan Huang[4], He Huang[2] & Jun Yu[1]

Bacteria such as the oral microbiome member *Peptostreptococcus anaerobius* can exacerbate colorectal cancer (CRC) development. Little is known regarding whether these immunomodulatory bacteria also affect antitumour immune checkpoint blockade therapy. Here we show that administration of *P. anaerobius* abolished the efficacy of anti-PD1 therapy in mouse models of CRC. *P. anaerobius* both induced intratumoral myeloid-derived suppressor cells (MDSCs) and stimulated their immunosuppressive activities to impair effective T cell responses. Mechanistically, *P. anaerobius* administration activated integrin $\alpha_2\beta_1$–NF-κB signalling in CRC cells to induce secretion of CXCL1 and recruit $CXCR2^+$ MDSCs into tumours. The bacterium also directly activated immunosuppressive activity of intratumoral MDSCs by secreting lytC_22, a protein that bound to the Slamf4 receptor on MDSCs and promoted ARG1 and iNOS expression. Finally, therapeutic targeting of either integrin $\alpha_2\beta_1$ or the Slamf4 receptor were revealed as promising strategies to overcome *P. anaerobius*-mediated resistance to anti-PD1 therapy in CRC.

Materials and Method
were transiently silenced using a pool of two different **siRNAs** that ism siRNA to ITGA2 (Ambion, S7537) and ITGB1 (**GenePharma**).



Research Article
Hepatic and Biliary Cancer

JOURNAL OF HEPATOLOGY

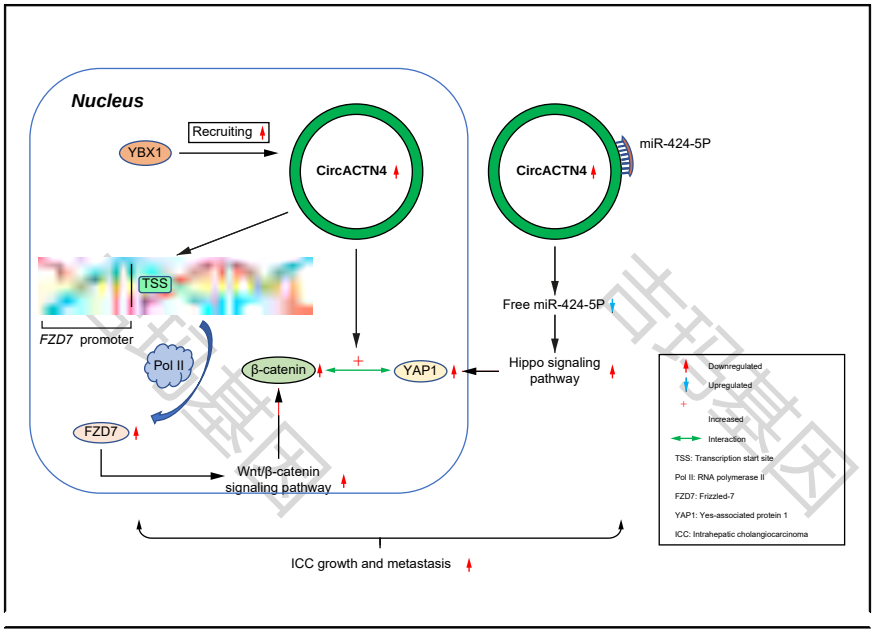
Circular RNA ACTN4 promotes intrahepatic cholangiocarcinoma progression by recruiting YBX1 to initiate FZD7 transcription

Qinjunjie Chen[1,†], Haibo Wang[1,†], Zheng Li[1,†], Fengwei Li[1,2], Leilei Liang[3], Yiran Zou[1], Hao Shen[4], Jun Li[1], Yong Xia[1], Zhangjun Cheng[5], Tian Yang[4], Kui Wang[2], Feng Shen[1,*]

Background & Aims:
Intrahepatic cholangiocarcinoma (ICC) is a primary liver cancer with high aggressiveness and extremely poor prognosis. The role of circular RNAs (circRNAs) in ICC carcinogenesis and progression remains to be determined. Methods: CircRNA microarray was performed to screen signifi-cantly upregulated circRNAs in paired ICC and non-tumor tis-sues. Colony formation, transwell, and xenograft models were used to examine the role of circRNAs in ICC proliferation and metastasis. RNA pulldown, mass spectrometry, chromatin immunoprecipitation, RNA-binding protein immunoprecipita-tion, chromatin isolation by RNA purification, electrophoretic mobility shift assay, and luciferase reporter assays were used to explore the molecular sponge role of the circRNA (via miRNA binding), and the interaction between circRNA and RNA-binding proteins.

Results:
Hsa_circ_0050898, which originated from exon 1 to exon 20 of the ACTN4 gene (named circACTN4), was significantly upregulated in ICC. High circACTN4 expression was associated with enhanced tumor proliferation and metastasis in vitro and in vivo, as well as a worse prognosis following ICC resection. In addition, circACTN4 upregulated Yes-associated protein 1 (YAP1) expression by sponging miR-424-5p. More importantly, cir-cACTN4 also recruited Y-box binding protein 1 (YBX1) to stim-ulate Frizzled-7 (FZD7) transcription. Furthermore, circACTN4 overexpression in ICC cells enhanced the interaction between YAP1 and b-catenin, which are the core components of the Hippo and Wnt signaling pathways, respectively.

Conclusions: CircACTN4 was upregulated in ICC and promoted ICC proliferation and metastasis by acting as a molecular sponge of miR-424-5p, as well as by interacting with YBX1 to tran-scriptionally activate FZD7. These results suggest that circACTN4 is a potential prognostic marker and therapeutic target for ICC.



Journal Of Hepatology
2022 Jan;76(1):135-147.
Impact Factor:25.7

Materials and Method

Small-interfering RNA targeting the junction sites of the circRNA were designed and synthesized by **GenePharma** (Shanghai).

Drug Resistance Updates 71 (2023) 101014

Contents lists available at ScienceDirect

Drug Resistance Updates

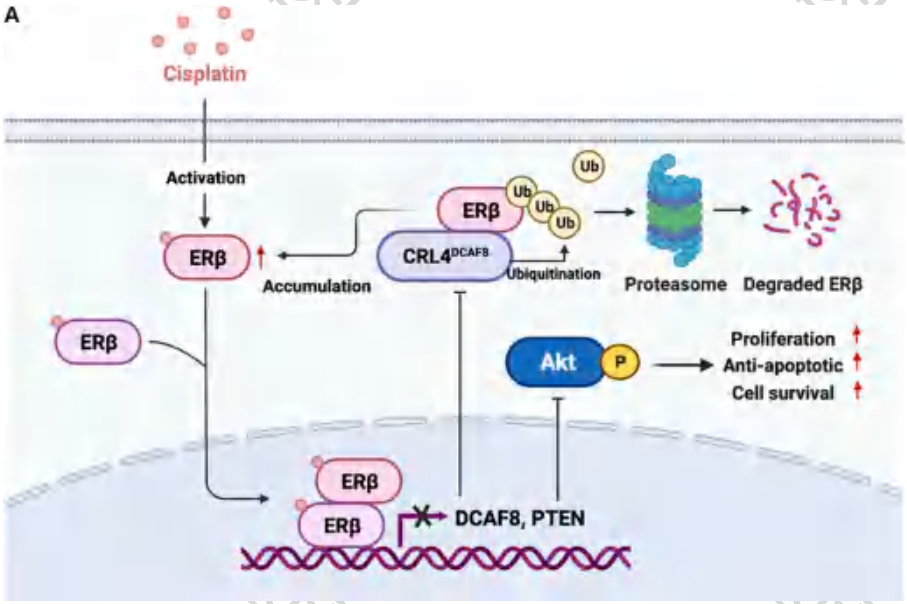
journal homepage: www.elsevier.com/locate/drup

Cisplatin-activated ERβ/DCAF8 positive feedback loop induces chemoresistance in non-small cell lung cancer via PTEN/Akt axis

Yumeng Hu [a,b,1], Yongjie Xu [c,1], Ting Zhang [d], Qianying Han [a], Li Li [a], Mingyang Liu [b,*], Ni Li [c,*], Genze Shao [a,2,*]

A B S T R A C T

High levels of the estrogen receptor β (ERβ) predict poor prognosis following platinum-containing adjuvant chemotherapies in patients with non-small cell lung cancer (NSCLC). However, the precise role of ERβ remains elusive. In this study, we demonstrated that targeting ERβ could significantly increase the cytotoxicity of cisplatin both *in vitro* and *in vivo*. Mechanically, cisplatin directly binds to ERβ, which facilitates its homodimerization and nuclear translocation. ERβ activation transcriptionally represses the expression of DCAF8, an adaptor of CRL4 E3 ubiquitin ligase, which in turn attenuates the proteasomal degradation of ERβ, leading to ERβ accumulation; this positive feedback loop results in Akt activation and eventually cisplatin resistance in NSCLC through PTEN inhibition. Moreover, low expression of DCAF8 and high expression of ERβ are associated with treatment resistance in patients receiving cisplatin-containing adjuvant chemotherapy. The present results provide insights into the underlying mechanism of ERβ-induced cisplatin resistance and offer an alternative therapeutic strategy to improve the efficacy of platinum-based chemotherapy in patients with NSCLC.



DRUG RESISTANCE UPDATES
2023 Nov:71:101014
Impact Factor:24.3

Materials and Method

For RNAi, the following **siRNAs** were used (synthesized from **Genepharma**).

Drug Resistance Updates 70 (2023) 100977

Contents lists available at ScienceDirect

Drug Resistance Updates

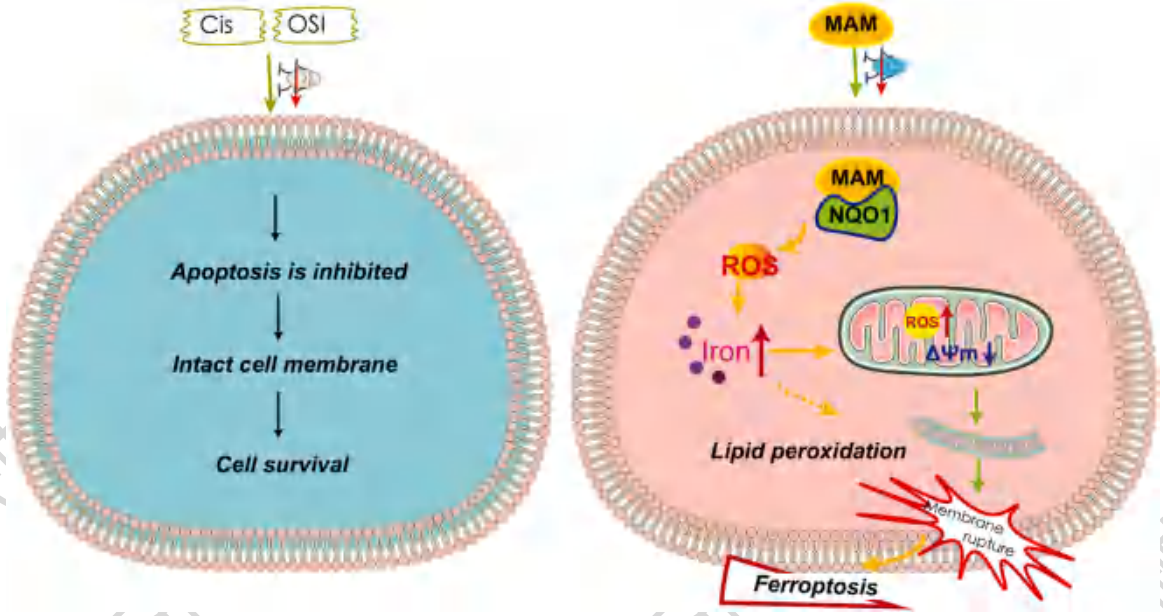
journal homepage: www.elsevier.com/locate/drup

Fighting drug-resistant lung cancer by induction of NAD(P)H:quinone oxidoreductase 1 (NQO1)-mediated ferroptosis

Jie Yu [a,b], Bingling Zhong [a], Lin Zhao [a], Ying Hou [a], Nana Ai [c], Jin-Jian Lu [a], Wei Ge [c], Xiuping Chen [a,d,e,*]

A B S T R A C T

Drug resistance is a major challenge in cancer treatment. The substrates of NAD(P)H:quinone oxidoreductase 1 (NQO1) show a promising anticancer effect in clinical trials. We previously identified a natural NQO1 substrate 2-methoxy-6-acetyl-7-methyljuglone (MAM) with a potent anticancer effect. The present study was designed to explore the efficacy of MAM in fighting against drug-resistant non-small cell lung cancer (NSCLC). The anticancer effect of MAM was evaluated in cisplatin-resistant A549 and AZD9291-resistant H1975 cells. The interaction of MAM with NQO1 was measured by cellular thermal shift assay and drug affinity responsive target stability assay. The NQO1 activity and expression were measured using NQO1 recombinant protein, Western blotting, and immunofluorescence staining assay. The roles of NQO1 were examined by NQO1 inhibitor, small interfering RNA (siRNA), and short hairpin RNA (shRNA). The roles of reactive oxygen species (ROS), labile iron pool (LIP), and lipid peroxidation were determined. MAM induced significant cell death in drug-resistant cells with similar potency to that of parental cells, which were completely abolished by NQO1 inhibitor, NQO1 siRNA, and iron chelators. MAM activates and binds to NQO1, which triggers ROS generation, LIP increase, and lipid peroxi-dation. MAM significantly suppressed tumor growth in the tumor xenograft zebrafish model. These results showed that MAM induced ferroptosis by targeting NQO1 in drug-resistant NSCLC cells. Our findings provided a novel therapeutic strategy for fighting against drug resistance by induction of NQO1-mediated ferroptosis.



DRUG RESISTANCE UPDATES
2023 Jun;70:100977
Impact Factor:24.3

Materials and Method

The **NQO1 siRNA** (5'-GAACCUCAACUGA-CAUAUA-3') and **scrambled siRNA** were purchased from **Genepharma** (Shanghai, China).

Drug Resistance Updates 68 (2023) 100957

Contents lists available at ScienceDirect

Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

A phosphoglycerate mutase 1 allosteric inhibitor overcomes drug resistance to EGFR-targeted therapy *via* disrupting IL-6/JAK2/STAT3 signaling pathway in lung adenocarcinoma

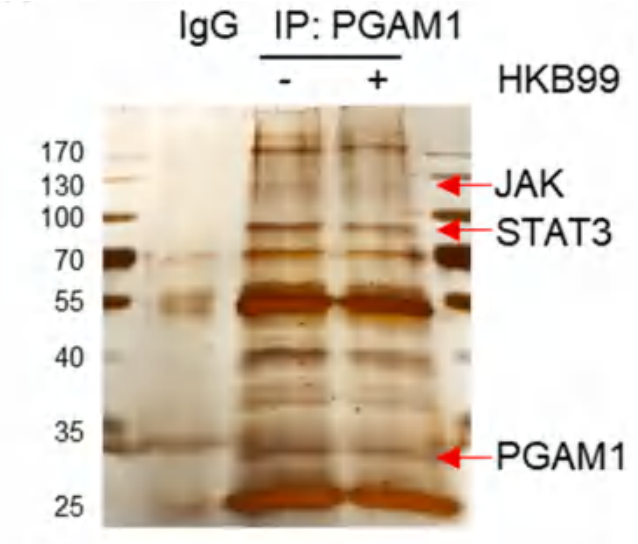
Qian Liang [a,b,1], Miaomiao Gong [a,b,1], Jing-Hua Zou [a,b,1], Ming-yu Luo [a,b,1], Lu-lu Jiang [c], Cheng Wang [a,b], Ning-xiang Shen [a,b], Mo-cong Zhang [a,b], Lu Xu [a,b], Hui-min Lei [a,b], Ke-Ren Zhang [a,b], Rui Zhang [a,b], Guanglei Zhuang [d], Liang Zhu [a,b], Hong-zhuan Chen [e,*], Lu Zhou [c,**], Ying Shen [a,b,***]

ABSTRACT

Resistance to epidermal growth factor receptor (EGFR) inhibitors, from the first-generation erlotinib to the third generation osimertinib, is a clinical challenge in the treatment of patients with EGFR-mutant lung adenocarci-noma. Our previous work found that a novel allosteric inhibitor of phosphoglycerate mutase 1 (PGAM1), HKB99, restrains erlotinib resistance in lung adenocarcinoma cells. However, the role of HKB99 in osimertinib resistance and its underlying molecular mechanism remains to be elucidated. Herein, we found that IL-6/JAK2/STAT3 signaling pathway is aberrantly activated in both erlotinib and osimertinib resistant cells. Importantly, HKB99 significantly blocks the interaction of PGAM1 with JAK2 and STAT3 *via* the allosteric sites of PGAM1, which leads to inactivation of JAK2/STAT3 and thereby disrupts IL-6/JAK2/STAT3 signaling pathway. Consequently, HKB99 remarkably restores EGFR inhibitor sensitivity and exerts synergistic tumoricidal effect. Additionally, HKB99 alone or in combination with osimertinib down-regulated the level of p-STAT3 in xenograft tumor models. Collectively, this study identifies PGAM1 as a key regulator in IL-6/JAK2/STAT3 axis in the development of resistance to EGFR inhibitors, which could serve as a therapeutic target in lung adenocarcinoma with acquired resistance to EGFR inhibitors.

DRUG RESISTANCE UPDATES
2023 Mar;68:100957
Impact Factor:24.3

Materials and Method
RNA interference of PGAM1 was performed using **siRNA duplexes** purchased from **GenePharma** (Shanghai, China).



Drug Resistance Updates 69 (2023) 100976

Contents lists available at ScienceDirect

Drug Resistance Updates

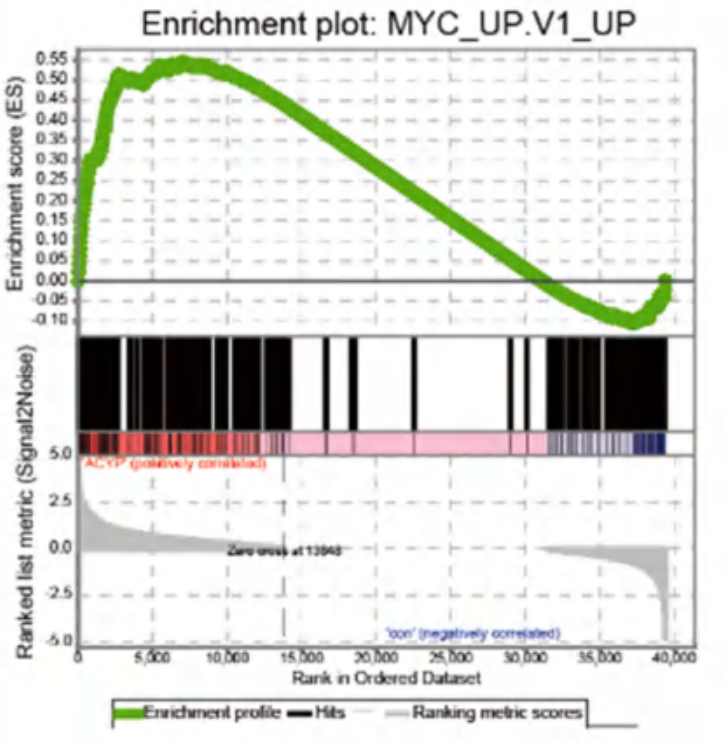
journal homepage: www.elsevier.com/locate/drup

Targeting ACYP1-mediated glycolysis reverses lenvatinib resistance and restricts hepatocellular carcinoma progression

Shuai Wang [a,f,1], Lingyi Zhou [b,1], Ning Ji [c,1], Chengtao Sun [d,1], Linlin Sun [a], Jiao Sun [a], Yawei Du [a], Ningning Zhang [a,*], Yueguo Li [c,**], Weishuai Liu [e,**], Wei Lu [a,*]

A B S T R A C T

Acylphosphatase 1 (ACYP1), a protein located in the mammalian cell cytoplasm, has been shown to be associated with tumor initiation and progression by functioning as a metabolism-related gene. Here we explored the po-tential mechanisms by which ACYP1 regulates the development of HCC and participates in the resistance to lenvatinib. ACYP1 can promote the proliferation, invasion, and migration capacities of HCC cells in vitro and in vivo. RNA sequencing reveals that ACYP1 markedly enhances the expression of genes related to aerobic glycolysis, and LDHA is identified as the downstream gene of ACYP1. Overexpression of ACYP1 upregulates LDHA levels, which then increases the malignancy potential of HCC cells. GSEA data analysis reveals the enrichment of differentially expressed genes in the MYC pathway, indicating a positive correlation between MYC and ACYP1 levels. Mechanistically, ACYP1 exerts its tumor-promoting roles by regulating the Warburg effect through activating the MYC/LDHA axis. Mass spectrometry analysis and Co-IP assays confirm that ACYP1 can bind to HSP90. The regulation of c-Myc protein expression and stability by ACYP1 is HSP90 dependent. Importantly, lenvatinib resistance is associated with ACYP1, and targeting ACYP1 remarkably decreases len-vatinib resistance and inhibits progression of HCC tumors with high ACYP1 expression when combined with lenvatinib in vitro and in vivo. These results illustrate that ACYP1 has a direct regulatory role in glycolysis and drives lenvatinib resistance and HCC progression via the ACYP1/HSP90/MYC/LDHA axis. Targeting ACYP1 could synergize with lenvatinib to treat HCC more effectively.



DRUG RESISTANCE UPDATES
2023 May 16;69:100976
Impact Factor:24.3

Materials and Method
Small-interfering RNA (siRNA) targeting human LDHA, MYC, and scrambled control siRNA were designed and synthesized by **GenePharma** (Shanghai, China).

www.nature.com/cmi

ARTICLE OPEN

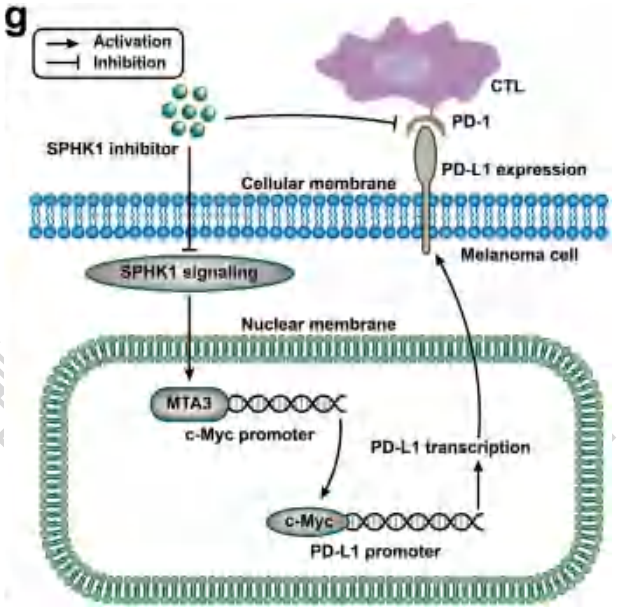
Check for updates

Sphingosine kinase 1 promotes tumor immune evasion by regulating the MTA3-PD-L1 axis

Poyee Lau[1,2,3,4,11], Guanxiong Zhang[1,2,3,4,11], Shuang Zhao[1,2,3,4,11], Long Liang[1,5], Hailun Zhang[6], Guowei Zhou[1,2,3,4], Mien-Chie Hung[7,8,9], Xiang Chen[1,2,3,4,10]✉ and Hong Liu[1,2,3,4,10]✉

Immune checkpoint blockade (ICB) exhibits considerable benefits in malignancies, but its overall response rate is limited. Previous studies have shown that sphingosine kinases (SPHKs) are critical in the tumor microenvironment (TME), but their role in immunotherapy is unclear. We performed integrative analyses including bioinformatics analysis, functional study, and clinical validation to investigate the role of SPHK1 in tumor immunity. Functionally, we demonstrated that the inhibition of
SPHK1 significantly suppressed tumor growth by promoting antitumor immunity in immunocompetent melanoma mouse models and tumor T-cell cocultures. A mechanistic analysis revealed that MTA3 functions as the downstream target of SPHK1 in transcriptionally regulating tumor PD-L1. Preclinically, we found that anti-PD-1 monoclonal antibody (mAb) treatment significantly rescued tumor SPHK1 overexpression or tumor MTA3 overexpression-mediated immune evasion. Significantly, we identified SPHK1 and MTA3 as biological markers for predicting the efficacy of anti-PD-1 mAb therapy in melanoma patients. Our findings revealed a novel role for SPHK1 in tumor evasion mediated by regulating the MTA3-PD-L1 axis, identified SPHK1 and MTA3 as predictors for assessing the efficacy of PD-1 mAb treatment, and provided a therapeutic possibility for the treatment of melanoma patients.

Keywords: Sphingosine kinase; Programmed cell death ligand 1; Programmed cell death protein 1; Melanoma; Tumor microenvironment; Immune checkpoint blockade



Cellular & Molecular Immunology
2022 Oct;19(10):1153-1167
Impact Factor:24.1

Materials and Method

RNA oligos were synthesized and purchased from **GenePharma.**

Cell Stem Cell

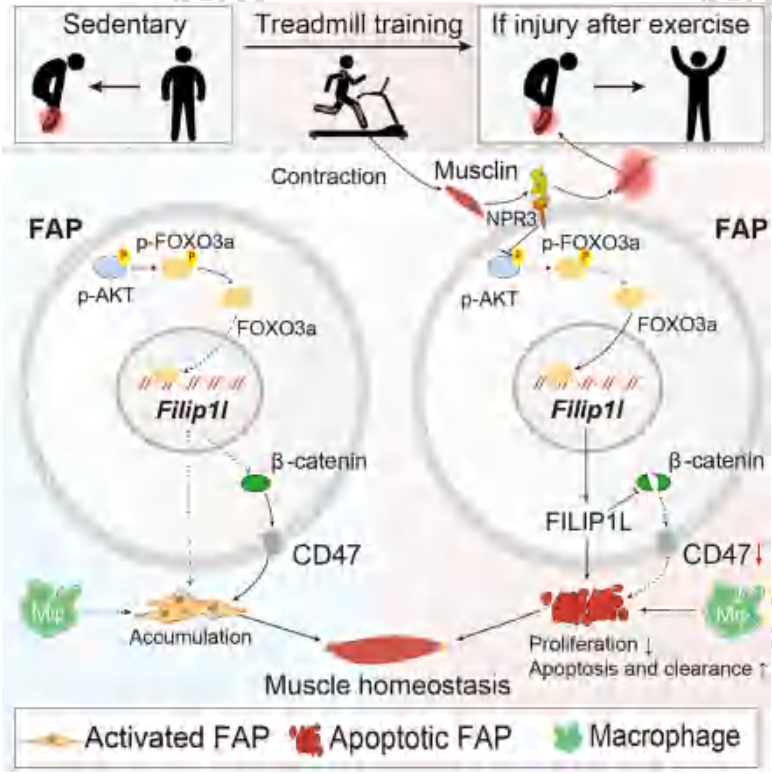
Article

Exercise-induced Musclin determines the fate of fibro-adipogenic progenitors to control muscle homeostasis

Xia Kang,[1,3,8,9,*] Jin Qian,[1,8] You-xing Shi,[2,8] Xu-ting Bian,[2,8] Li-dan Zhang,[6,8] Gao-ming Li,[7] Li-ting Wang,[5] Jing Zhao,[5] Zhen-yu Dong,[2] Meng-meng Yang,[6] Yu-Jia-Nan Chen,[2] Kang-lai Tang,[2,*] and Hong-ming Miao[1,4,*]

SUMMARY

The effects of exercise on fibro-adipogenic progenitors (FAPs) are unclear, and the direct molecular link is still unknown. In this study, we reveal that exercise reduces the frequency of FAPs and attenuates collagen deposition and adipose formation in injured or disused muscles through Musclin. Mechanistically, Musclin inhibits FAP proliferation and promotes apoptosis in FAPs by upregulating FILIP1L. Chromatin immunoprecipitation (ChIP)-qPCR confirms that FoxO3a is the transcription factor of FILIP1L. In addition, the Musclin/FILIP1L pathway facilitates the phagocytosis of apoptotic FAPs by macrophages through downregulating the expression of CD47. Genetic ablation of FILIP1L in FAPs abolishes the effects of exercise or Musclin on FAPs and the benefits on the reduction of fibrosis and fatty infiltration. Overall, exercise forms a microenvi-ronment of myokines in muscle and prevents the abnormal accumulation of FAPs in a Musclin/FILIP1L-dependent manner. The administration of exogenous Musclin exerts a therapeutic effect, demonstrating a potential therapeutic approach for muscle atrophy or acute muscle injury.



Cell Stem Cell
2024 Feb 1;31(2):212-226.e7
Impact Factor:23.9

Materials and Method

All **siRNAs** were generated by Shanghai **GenePharma** Co.,Ltd (Shanghai, China), the siRNA sequences are listed in the key resources table.

Xiong et al. Military Medical Research (2023) 10:68
https://doi.org/10.1186/s40779-023-00501-8

MMR MILITARY MEDICAL RESEARCH

RESEARCH Open Access

Elevated FBXL6 activates both wild-type KRAS and mutant KRAS^{G12D} and drives HCC tumorigenesis via the ERK/mTOR/PRELID2/ROS axis in mice

Hao-Jun Xiong[1], Hong-Qiang Yu[1], Jie Zhang[1], Lei Fang[1], Di Wu[1], Xiao-Tong Lin[1] and Chuan-Ming Xie[1*]

Abstract

Background Kirsten rat sarcoma (KRAS) and mutant KRAS^{G12D} have been implicated in human cancers, but it remains unclear whether their activation requires ubiquitination. This study aimed to investigate whether and how F-box and leucine-rich repeat 6 (FBXL6) regulates KRAS and KRAS^{G12D} activity in hepatocellular carcinoma (HCC).

Methods We constructed transgenic mouse strains LC (*LSL-Fbxl6$^{KI/+}$;Alb-Cre*, $n=13$), KC (*LSL-Kras$^{G12D/+}$;Alb-Cre*, $n=10$) and KLC (*LSL-Kras$^{G12D/+}$;LSL-Fbxl6$^{KI/+}$;Alb-Cre*, $n=12$) mice, and then monitored HCC for 320 d. Multiomics approaches and pharmacological inhibitors were used to determine oncogenic signaling in the context of elevated FBXL6 and KRAS activation. Co-immunoprecipitation (Co-IP), Western blotting, ubiquitination assay and RAS activity detection assay were employed to investigate the underlying molecular mechanism by which FBXL6 activates KRAS. The pathological relevance of the FBXL6/KRAS/extracellular signal-regulated kinase (ERK)/mammalian target of rapamycin (mTOR)/proteins of relevant evolutionary and lymphoid interest domain 2 (PRELID2) axis was evaluated in 129 paired samples from HCC patients.

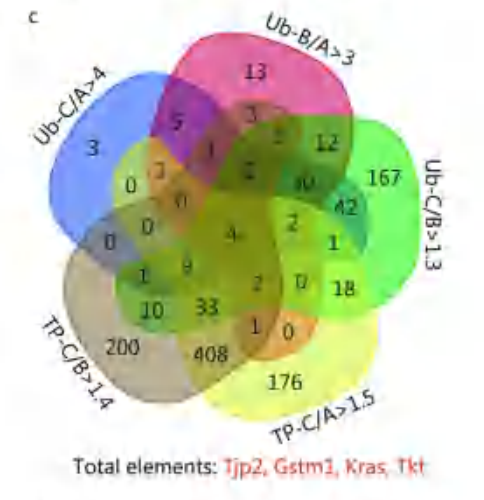
Results FBXL6 is highly expressed in HCC as well as other human cancers ($P<0.001$). Interestingly, FBXL6 drives HCC in transgenic mice. Mechanistically, elevated FBXL6 promotes the polyubiquitination of both wild-type KRAS and KRAS^{G12D} at lysine 128, leading to the activation of both KRAS and KRAS^{G12D} and promoting their binding to the serine/threonine-protein kinase RAF, which is followed by the activation of mitogen-activated protein kinase kinase (MEK)/ERK/mTOR signaling. The oncogenic activity of the MEK/ERK/mTOR axis relies on PRELID2, which induces reactive oxygen species (ROS) generation. Furthermore, hepatic FBXL6 upregulation facilitates KRAS^{G12D} to induce more severe hepatocarcinogenesis and lung metastasis via the MEK/ERK/mTOR/PRELID2/ROS axis. Dual inhibition of MEK and mTOR effectively suppresses tumor growth and metastasis in this subtype of cancer in vivo. In clinical samples, FBXL6 expression positively correlates with p-ERK ($\chi^2=85.067$, $P<0.001$), p-mTOR ($\chi^2=66.919$, $P<0.001$) and PRELID2 ($\chi^2=20.891$, $P<0.001$). The Kaplan–Meier survival analyses suggested that HCC patients with high FBXL6/p-ERK levels predicted worse overall survival (log-rank $P<0.001$).

Conclusions FBXL6 activates KRAS or KRAS^{G12D} via ubiquitination at the site K128, leading to activation of the ERK/mTOR/PRELID2/ROS axis and tumorigenesis. Dual inhibition of MEK and mTOR effectively protects

Military Medical Research
2023 Dec 20;10(1):68
Impact Factor:21.1

Materials and Method

siRNAs targeting Prelid2 were designed and synthe-sized by GenePharma (Shanghai, China).



nature metabolism

Article

https://doi.org/10.1038/s42255-023-00883-y

ENO2-derived phosphoenolpyruvate functions as an endogenous inhibitor of HDAC1 and confers resistance to antiangiogenic therapy

Received: 14 April 2022

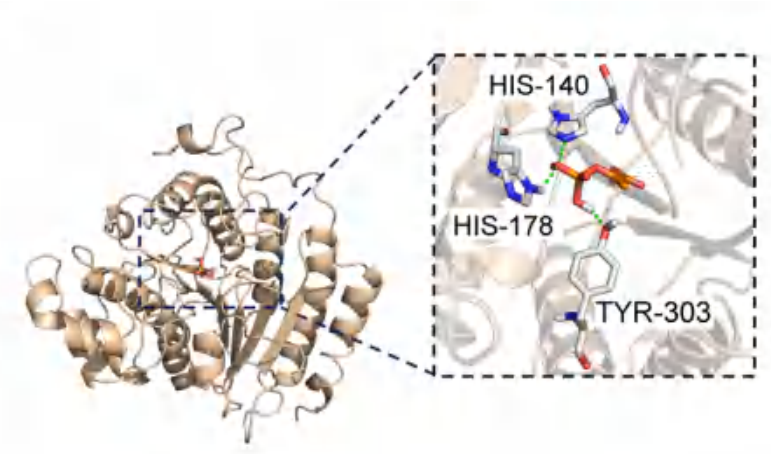
Accepted: 31 July 2023

Published online: 4 September 2023

Check for updates

Chenran Wang[1,2,3,6], Maohua Huang[1,3,6], Yuning Lin[1,3,6], Yiming Zhang[1,3], Jinghua Pan[2], Chang Jiang[4], Minjing Cheng[1,3], Shenrong Li[1,3], Wenzhuo He[4], Zhengqiu Li[1,3], Zhengchao Tu[1,3], Jun Fan[5], Huhu Zeng[1,3], Jiahui Lin[1,3], Yongjin Wang[1,3], Nan Yao[5], Tongzheng Liu[1,3], Qi Qi[5], Xiangning Liu[2], Zhimin Zhang[1,3], Minfeng Chen[1,3] ✉, Liangping Xia[4] ✉, Dongmei Zhang[1,3] ✉ & Wencai Ye[1,3] ✉

Metabolic reprogramming is associated with resistance to antiangiogenic therapy in cancer. However, its molecular mechanisms have not been clearly elucidated. Here, we identify the glycolytic enzyme enolase 2 (ENO2) as a driver of resistance to antiangiogenic therapy in colorectal cancer (CRC) mouse models and human participants. ENO2 overexpression induces neuroendocrine differentiation, promotes malignant behaviour in CRC and desensitizes CRC to antiangiogenic drugs. Mechanistically, the ENO2-derived metabolitephosphoenolpyruvate (PEP) selectively inhibits histone deacetylase 1 (HDAC1) activity, which increases the acetylation of β-catenin and activates the β-catenin pathway in CRC. Inhibition of ENO2 with enolase inhibitors AP-III-a4 or POMHEX synergizes the efficacy of antiangiogenic drugs in vitro and in mice bearing drug-resistant CRC xenograft tumours. Together, our findings reveal that ENO2 constitutes a useful predictive biomarker and therapeutic target for resistance to antiangiogenic therapy in CRC, and uncover a previously undefined and metabolism-independent role of PEP in regulating resistance to antiangiogenic therapy by functioning as an endogenous HDAC1 inhibitor.



Nature Metabolism
2023 Sep 4:5(10):1765-1786
Impact Factor:20.8

Materials and Method

The siRNAs were provided by OBiO Technology and GenePharma, and their sequences are listed in Supplementary Table.

Chen K, Liu J, Liu S, Xia M, Zhang X, Han D, Jiang Y, Wang C, Cao X. Methyltransferase SETD2-Mediated Methylation of STAT1 Is Critical for Interferon Antiviral Activity. Cell. 2017 Jul 27;170(3):492-506.e14. **IF:64.5**
Xu, X., Ding, G., Liu, C. et al. Nuclear UHRF1 is a gate-keeper of cellular AMPK activity and function. Cell Res (2021). **IF:44.1**
Wang, X., Cheng, H., Zhao, J. et al. Long noncoding RNA DLGAP1-AS2 promotes tumorigenesis and metastasis by regulating the Trim21/ELOA/LHPP axis in colorectal cancer. Mol Cancer 21, 210 (2022). **IF:37.3**
Wu Q, Luo X. et al.DDX56 modulates post-transcriptional Wnt signaling through miRNAs and is associated with early recurrence in squamous cell lung carcinoma. Mol Cancer. 2021 Aug 26; 20 (1) :108. **IF:37.3**
Zhaokui Jin, Yanhong Duo, et al.A novel NIR-responsive CO gas-releasing and hyperthermia-generating nanomedicine provides a curative approach for cancer therapy,Nano Today,Volume 38,2021,101197. **IF:32.4**
Zhang F, Li R, Yang Y, et al. Specific Decrease in B-Cell-Derived Extracellular Vesicles Enhances Post-Chemotherapeutic CD8+ T Cell Responses. Immunity. 2019 Mar 19; 50: 738-50. **IF: 32.4**
Fu B, Zhou Y, Ni X, et al. Natural Killer Cells Promote Fetal Development through the Secretion of Growth-Promoting Factors. Immunity. 2017 Dec 19; 47: 1100-13. **IF:32.4**
Huang K, Liang Q, Zhou Y, et al. A Novel Allosteric Inhibitor of Phosphoglycerate Mutase 1 Suppresses Growth and Metastasis of Non-SamII-Cell Lung Cancer. Cell Metabolism. 2019 Dec 3; 30: 1-13. **IF:29**
Zhang, C., Li, T., Yin, S. et al. Monocytes deposit migrasomes to promote embryonic angiogenesis. Nat Cell Biol 24, 1726–1738 (2022). **IF:21.3**
Bing D ,Yumin Q ,Zhefu L , et al.Manipulating bioactivities of endothelial progenitor cell-derived exosomes for promoting angiogenesis in ischemic vascular diseases[J].Nano Today,2023,48. **IF:17.4**
Feng J, Chen S, Ge X, et al. Precise Assembly of Synthetic Carriers of siRNA through a Series of Interlocked Thermodynamically Self Regulated Processes. Advanced Functional Materials, 2018, 28(6): 1703207. **IF:19**
Yang, Y., Zhu, H., Liu, D., Luo, H., Chang, R., Ji, Y., Yao, W., Yin, J., & Gao, X. (2023). A Versatile Platform for the Tumor–Targeted Intracellular Delivery of Peptides, Proteins, and siRNA. Advanced Functional Materials, 33. **IF:19**
Tan S, Wang D, Fu Y, Zheng H, Liu Y, Lu B. Targeted clearance of mitochondria by an autophagy-tethering compound (ATTEC) and its potential therapeutic effects. Sci Bull (Beijing). Published online October 26, 2023. **IF:18.9**
Qin W, Weng J. Hepatocyte NLRP3 interacts with PKCε to drive hepatic insulin resistance and steatosis. Sci Bull (Beijing). 2023 Jul 15;68(13):1413-1429. doi: 10.1016/j.scib.2023.06.003. Epub 2023 Jun 7. PMID: 37336688. **IF:18.9**
Zhang J, Zhang M, Huo XK, Ning J, Yu ZL, Morisseau C, Sun CP, Hammock BD, Ma XC. Macrophage Inactivation by Small Molecule Wedelolactone via Targeting sEH for the Treatment of LPS-Induced Acute Lung Injury. ACS Cent Sci. 2023 Feb 21;9(3):440-456. **IF:18.2**
Wu S, Yun J, Tang W, Familiari G, Relucenti M, Wu J, Li X, Chen H, Chen R. Therapeutic m6A Eraser ALKBH5 mRNA-Loaded Exosome-Liposome Hybrid Nanoparticles Inhibit Progression of Colorectal Cancer in Preclinical Tumor Models. ACS Nano. 2023 Jun 27;17(12):11838-11854. **IF:17.1**
Zhang R, Li R, Zhang L, Chen G, Mo L, Jiang R, Xu X, Wang X, Zhao Y, Zhang L, Wang Y, Zhang B. A Dual-Mechanism Based Nutrient Partitioning Nanoregulator for Enhanced Immunotherapy against Anti-PD-1 Resistant Tumors. ACS Nano. 2023 Jul 25;17(14):13461-13473. **IF:17.1**

Fang Ya, Wan Jia-Ping, Wang Zheng, Song Shi-Yang, Zhang Cao-Xu, Deficiency of the HGF/Met pathway leads to thyroid dysgenesis by impeding late thyroid expansion Nature Communications.Published: 11 April 2024. **IF:16.6**

Shi Yu, Huang Daochao, Song Cui, Cao Ruixue, Wang Zhao, Wang Dan. Diphthamide deficiency promotes association of eEF2 with p53 to induce p21 expression and neural crest defects. Nature Communications | (2024) 15:3301 **IF:16.6**

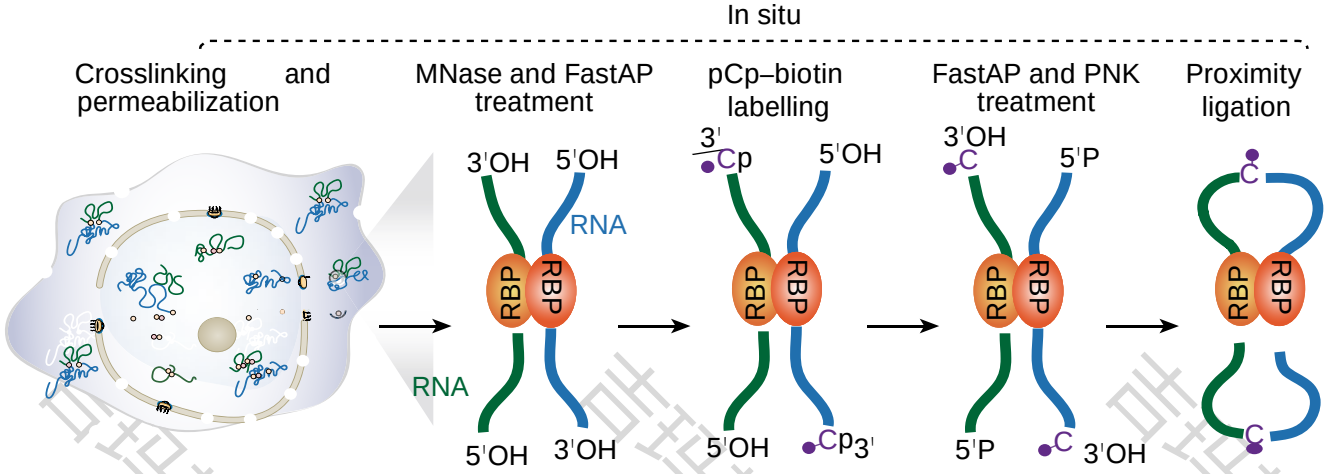
Jie Yang, Xiaofang Huang, Qing Yu, Shibo Wang.Extracellular vesicles derived from M2-like macrophages alleviate acute lung injury in a miR-709-mediated manner
J Extracell Vesicles. 2024;13:e12437.**IF:16**

Article

RIC-seq for global in situ profiling of RNA–RNA spatial interactions

Zhaokui Cai[1,2,5], Changchang Cao[1,5], Lei Ji[1,5], Rong Ye[1,2], Di Wang[1,2], Cong Xia[3], Sui Wang[1,2], Zongchang Du[1,2], Naijing Hu[1,2], Xiaohua Yu[1], Juan Chen[1], Lei Wang[1,4], Xianguang Yang[3], Shunmin He[1] & Yuanchao Xue[1,2]✉

Highly structured RNA molecules usually interact with each other, and associate with various RNA-binding proteins, to regulate critical biological processes. However, RNA structures and interactions in intact cells remain largely unknown. Here, by coupling proximity ligation mediated by RNA-binding proteins with deep sequencing, we report an RNA in situ conformation sequencing (RIC-seq) technology for the global profiling of intra- and intermolecular RNA–RNA interactions. This technique not only recapitulates known RNA secondary structures and tertiary interactions, but also facilitates the generation of three-dimensional (3D) interaction maps of RNA in human cells. Using these maps, we identify noncoding RNA targets globally, and discern RNA topological domains and *trans*-interacting hubs. We reveal that the functional connectivity of enhancers and promoters can be assigned using their pairwise-interacting RNAs. Furthermore, we show that *CCAT1-5L*—a super-enhancer hub RNA—interacts with the RNA-binding protein hnRNPK, as well as RNA derived from the *MYC* promoter and enhancer, to boost *MYC* transcription by modulating chromatin looping. Our study demonstrates the power and applicability of RIC-seq in discovering the 3D structures, interactions and regulatory roles of RNA.



Nature
2020 May;582(7812):432-437
Impact Factor:64.8

Materials and Method

To block snoRNA, we designed two **ASOs** targeting different regions of SNORD22 and synthesized two **sense oligonucleotides** as negative controls (**GenePharma**).

Cell Research

www.nature.com/cr
www.cell-research.com

ARTICLE OPEN

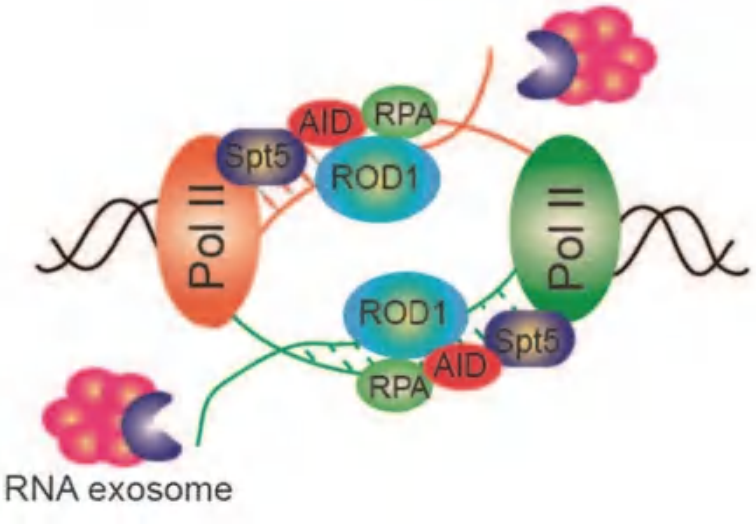
The RNA-binding protein ROD1/PTBP3 cotranscriptionally defines AID-loading sites to mediate antibody class switch in mammalian genomes

Juan Chen[1,2], Zhaokui Cai[1,2], Meizhu Bai[3,4], Xiaohua Yu[1,2], Chao Zhang[5], Changchang Cao[1,2], Xihao Hu[1,2], Lei Wang[1,6], Ruibao Su[1,2], Di Wang[1,2], Lei Wang[1,2], Yingpeng Yao[7], Rong Ye[1,2], Baidong Hou[5], Yang Yu[1], Shuyang Yu[7], Jinsong Li[3,4] and Yuanchao Xue[1,2]

Activation-induced cytidine deaminase (AID) mediates class switching by binding to a small fraction of single-stranded DNA (ssDNA) to diversify the antibody repertoire. The precise mechanism for highly selective AID targeting in the genome has remained elusive. Here, we report an RNA-binding protein, ROD1 (also known as PTBP3), that is both required and sufficient to define AID-binding sites genome-wide in activated B cells. ROD1 interacts with AID via an ultraconserved loop, which proves to be critical for the recruitment of AID to ssDNA using bi-directionally transcribed nascent RNAs as stepping stones. Strikingly, AID-specific mutations identified in human patients with hyper-IgM syndrome type 2 (HIGM2) completely disrupt the AID interacting surface with ROD1, thereby abolishing the recruitment of AID to immunoglobulin (Ig) loci. Together, our results suggest that bi-directionally transcribed RNA traps the RNA-binding protein ROD1, which serves as a guiding system for AID to load onto specific genomic loci to induce DNA rearrangement during immune responses.

Cell Research
2018 Aug;28:981–995
Impact Factor:44.1

Materials and Method
ASO oligos were designed and synthesized by **GenePharma**.



Cell Research (2017) 27:540-558.

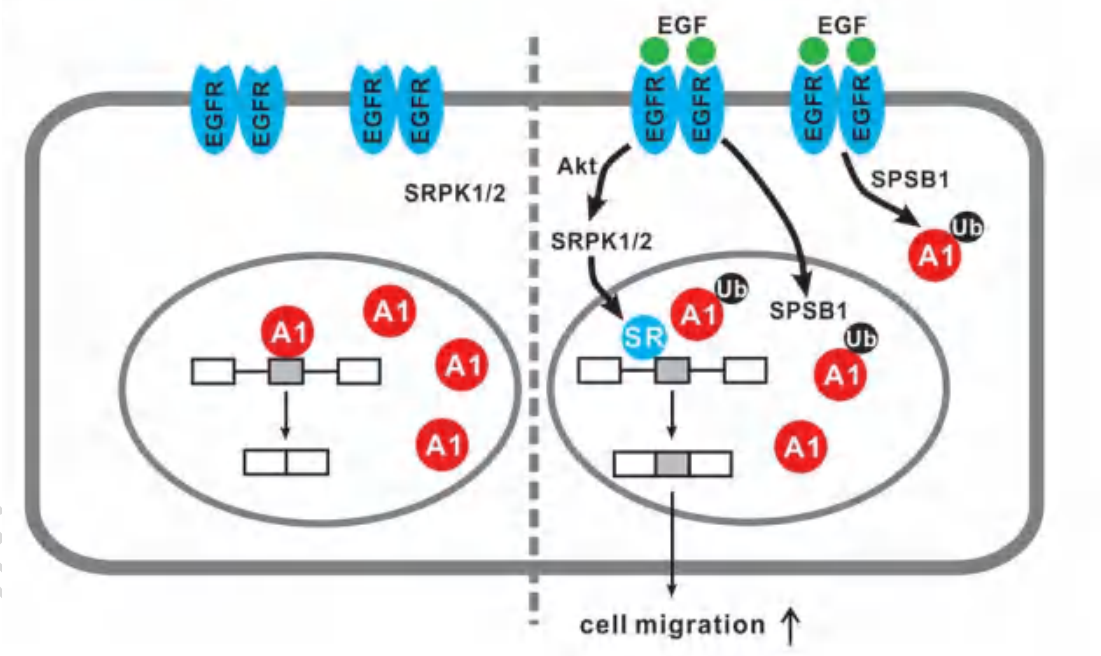
www.nature.com/cr

ORIGINAL ARTICLE

SPSB1-mediated HnRNP A1 ubiquitylation regulates alternative splicing and cell migration in EGF signaling

Feng Wang[1], Xing Fu[2], Peng Chen[3], Ping Wu[4, 5], Xiaojuan Fan[6], Na Li[1], Hong Zhu[1], Ting-Ting Jia[1], Hongbin Ji[3], Zefeng Wang[6], Catherine C L Wong[4, 5], Ronggui Hu[3], Jingyi Hui[1]

Extracellular signals have been shown to impact on alternative pre-mRNA splicing; however, the molecular mechanisms and biological significance of signal-induced splicing regulation remain largely unknown. Here, we report that epidermal growth factor (EGF) induces splicing changes through ubiquitylation of a well-known splicing regulator, hnRNP A1. EGF signaling upregulates an E3 ubiquitin (Ub) ligase adaptor, SPRY domain-containing SOCS box protein 1 (SPSB1), which recruits Elongin B/C-Cullin complexes to conjugate lysine 29-linked polyUb chains onto hnRNP A1. Importantly, SPSB1 and ubiquitylation of hnRNP A1 have a critical role in EGF-driven cell migration. Mechanistically, EGF-induced ubiquitylation of hnRNP A1 together with the activation of SR protein kinases (SRPKs) results in the upregulation of a Rac1 splicing isoform, Rac1b, to promote cell motility. These findings unravel a novel crosstalk between protein ubiquitylation and alternative splicing in EGF/EGF receptor signaling, and identify a new EGF/SPSB1/hnRNP A1/Rac1 axis in modulating cell migration, which may have important implications for cancer treatment.



Original Article
2017 Jan 13;27:540-558
Impact Factor:44.1

Materials and Methods

GenePharma (ASO) for this study are listed in Supplementary information, Table S4.

Sun et al. Molecular Cancer (2015) 14:96
DOI 10.1186/s12943-015-0344-y

MOLECULAR CANCER

RESEARCH Open Access

MiR-320a acts as a prognostic factor and Inhibits metastasis of salivary adenoid cystic carcinoma by targeting ITGB3

Lijuan Sun[1,2,3†], Bodu Liu[1,3†], Zhaoyu Lin[1,2†], Yandan Yao[1,3], Yanyang Chen[4], Yang Li[4], Jianing Chen[1,3], Dongsheng Yu[5], Zhangui Tang[6], Bosheng Wang[6], Shuguang Zeng[7], Song Fan[1,2], Youyuan Wang[1,2], Yilin Li[8], Erwei Song[1,3,9*] and Jinsong Li[1,2,9*]

Abstract

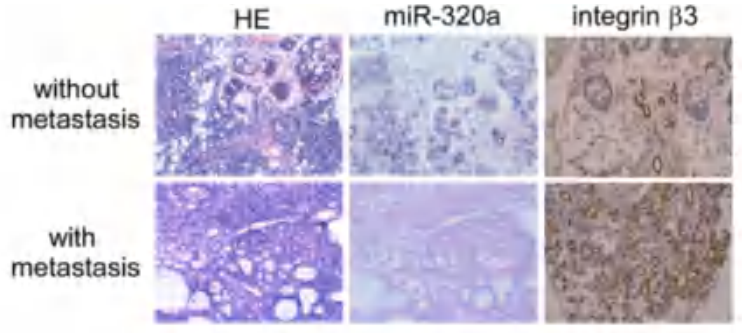
Background: Salivary Adenoid cystic carcinoma (SACC) patients with local invasion and lung metastasis are often resistant to conventional therapy such as operation, chemotherapy and radiotherapy. To explore the underling mechanisms, we studied the roles of miRNA in regulating invasiveness of SACC cells.

Methods: MicroRNA profiling was done in SACC cells with microarray. MiRNA mimics or antisense oligonucleotide was transfected and invasiveness of SACC cells was evaluated by adhesion assay and transwell assay. The target gene of miRNA was identified by luciferase reporter assay and "rescue" experiment. Tumor metastasis was evaluated by BALB/c-nu mice xenografts. MiRNA and its target gene expression were identified by in-situ hybridization and immunohistochemistry respectively, in 302 patients from affiliated hospitals of Sun Yat-sen University and in 148 patients from affiliated hospitals of Central South University, and correlated to the clinicopathological status of the patients.

Results: MiR-320a was down-regulated in high lung metastatic ACCM and SACC-LM cells compared with the corresponding low metastatic ACC2 and SACC-83 cells, and inhibited adhesion, invasion and migration of SACC cells by targeting integrin beta 3 (ITGB3). In vivo, enforced miR-320a expression suppressed metastasis of SACC xenografts. In the two independent sets, miR-320a was downregulated in primary SACCs with metastasis compared to those without metastasis, and low expression of this miRNA predicts poor patient survival and rapid metastasis. Multivariate analysis showed that miR-320a expression was an independent indicator of lung metastasis.

Conclusions: MiR-320a inhibits metastasis in SACCs by targeting ITGB3 and may serve as a therapeutic target and prognostic marker in salivary cancers.

Keywords: Metastasis, miR-320a, ITGB3, Adenoid cystic carcinoma, Prognosis



Molecular Cancer
2015 Apr;14:96
Impact Factor:37.3

Materials and Method

All miRNA mimics and **antisense oligonucleotides (ASOs)** for miRNA were obtained from **GenePharma** (Shanghai, China).
Reactions were run in triplicate in three independent experiments. qRT-PCR for miRNA was performed using the **Real-time PCR Universal Reagent** (**GenePharma**).

MOLECULAR CANCER

RESEARCH Open Access

Microvesicles secreted by macrophages shuttle invasion-potentiating microRNAs into breast cancer cells

Mei Yang[1,2], Jingqi Chen[1], Fang Su[3], Bin Yu[2], Fengxi Su[1], Ling Lin[1,4], Yujie Liu[1], Jian-Dong Huang[2*] and Erwei Song[1*]

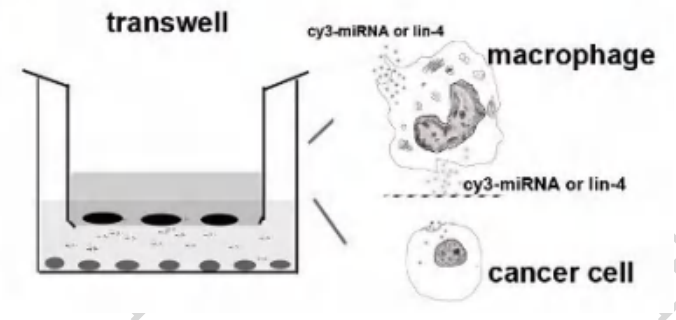
Abstract

Background: Tumor-associated macrophages (TAMs) are alternatively activated cells induced by interleukin-4 (IL-4)-releasing $CD4^+$ T cells. TAMs promote breast cancer invasion and metastasis; however, the mechanisms underlying these interactions between macrophages and tumor cells that lead to cancer metastasis remain elusive. Previous studies have found microRNAs (miRNAs) circulating in the peripheral blood and have identified microvesicles, or exosomes, as mediators of cell-cell communication. Therefore, one alternative mechanism for the promotion of breast cancer cell invasion by TAMs may be through macrophage-secreted exosomes, which would deliver invasion-potentiating miRNAs to breast cancer cells.

Results: We utilized a co-culture system with IL-4-activated macrophages and breast cancer cells to verify that miRNAs are transported from macrophages to breast cancer cells. The shuttling of fluorescently-labeled exogenous miRNAs from IL-4-activated macrophages to co-cultivated breast cancer cells without direct cell-cell contact was observed. miR-223, a miRNA specific for IL-4-activated macrophages, was detected within the exosomes released by macrophages and was significantly elevated in the co-cultivated SKBR3 and MDA-MB-231 cells. The invasiveness of the co-cultivated breast cancer cells decreased when the IL-4-activated macrophages were treated with a miR-223 antisense oligonucleotide (ASO) that would inhibit miR-223 expression. Furthermore, results from a functional assay revealed that miR-223 promoted the invasion of breast cancer cells via the Mef2c-b-catenin pathway.

Conclusions: We conclude that macrophages regulate the invasiveness of breast cancer cells through exosome-mediated delivery of oncogenic miRNAs. Our data provide insight into the mechanisms underlying the metastasis-promoting interactions between macrophages and breast cancer cells.

Molecular Cancer
2011 Sep 22;10:117
Impact Factor:33.1



Materials and Methods

MicroRNA mimics and **inhibitors** (**miRNA antisense oli-gonucleotides (ASO)**) were purchased from **GenePharma** Co., Ltd.

Quantitative real-time reverse transcription-PCR (qRT-PCR) for miR-223 was conducted using **Real-Time PCR Universal Reagent** (**GenePharma** Co., Ltd.) and the MX-3000P Real-Time PCR machine (Stratagene).

To further visualize the shuttling of miRNAs, **Cy3-labeled miRNAs** (**GenePharma**) were transfected into macrophages, as described above.

nature genetics

Article

https://doi.org/10.1038/s41588-023-01620-7

Computational prediction and experimental validation identify functionally conserved lncRNAs from zebrafish to human

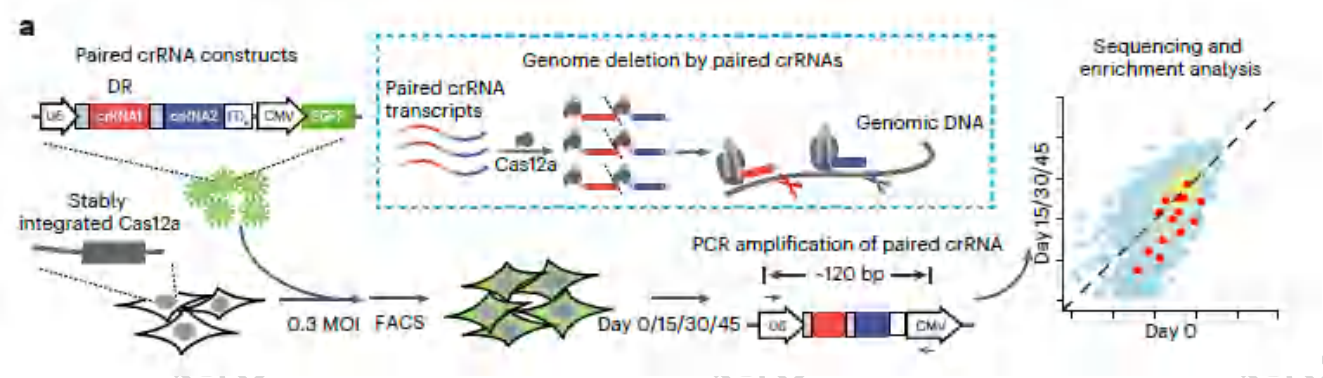
Received: 19 August 2022

Accepted: 21 November 2023

Published online: 9 January 2024

Wenze Huang[1,2,3,11], Tuanlin Xiong[1,2,3,11], Yuting Zhao[4,5,11], Jian Heng[6,7], Ge Han[1,2,3], Pengfei Wang[1,2,3], Zhihua Zhao[8], Ming Shi[4,5], Juan Li[8], Jiazhen Wang[4], Yixia Wu[4], Feng Liu[6,7,9,10], Jianzhong Jeff Xi[8] ✉, Yangming Wang[4] ✉ & Qiangfeng Cliff Zhang[1,2,3] ✉

Functional studies of long noncoding RNAs (lncRNAs) have been hindered by the lack of methods to assess their evolution. Here we present lncRNA Homology Explorer (lncHOME), a computational pipeline that identifies a unique class of long noncoding RNAs (lncRNAs) with conserved genomic locations and patterns of RNA-binding protein (RBP) binding sites (coPARSE-lncRNAs). Remarkably, several hundred human coPARSE-lncRNAs can be evolutionarily traced to zebrafish. Using CRISPR–Cas12a knockout and rescue assays, we found that knocking out many human coPARSE-lncRNAs led to cell proliferation defects, which were subsequently rescued by predicted zebrafish homologs. Knocking down coPARSE-lncRNAs in zebrafish embryos caused severe developmental delays that were rescued by human homologs. Furthermore, we verified that human, mouse and zebrafish coPARSE-lncRNA homologs tend to bind similar RBPs with their conserved functions relying on specific RBP-binding sites. Overall, our study demonstrates a comprehensive approach for studying the functional conservation of lncRNAs and implicates numerous lncRNAs in regulating vertebrate physiology.



NATURE GENETICS
2024 Jan;56(1):124-135
Impact Factor:30.8

Materials and Method

ASOs were synthesized by **GenePharma,** and 80 pg per embryo was injected.

Received: 2 July 2021 | Revised: 29 November 2021 | Accepted: 5 January 2022

DOI: 10.1002/jev2.12187

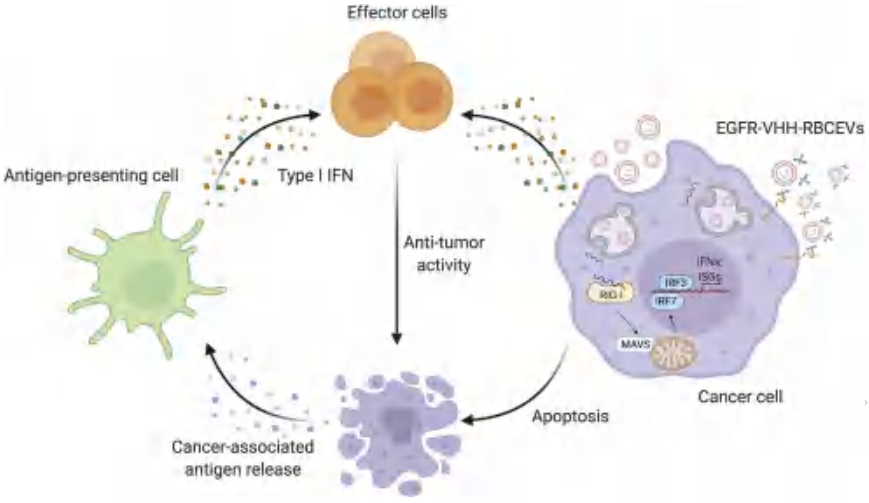
RESEARCH ARTICLE

Robust delivery of RIG-I agonists using extracellular vesicles for anti-cancer immunotherapy

Boya Peng[1,2] | **Trinh Mai Nguyen**[3,4] | **Migara Kavishka Jayasinghe**[1,2] | **Chang Gao**[1,2] | **Thach Tuan Pham**[1,2] | **Luyen Tien Vu**[1,2] | **Eric Yew Meng Yeo**[1,2] | **Gracemary Yap**[1,2] | **Lingzhi Wang**[5] | **Boon Cher Goh**[5] | **Wai Leong Tam**[5,6] | **Dahai Luo**[3,4] | **Minh TN Le**[1,2]

Abstract

The RIG-I pathway can be activated by RNA containing 5′ triphosphate, leading to type I interferon release and immune activation. Hence, RIG-I agonists have been used to induce immune responses against cancer as potential immunotherapy. How-ever, delivery of 5′ triphosphorylated RNA molecules as RIG-I agonists to tumour cells in vivo is challenging due to the susceptibility of these molecules to degrada-tion. In this study, we demonstrate the use of extracellular vesicles (EVs) from red blood cells (RBCs), which are highly amenable for RNA loading and taken up robustly by cancer cells, for RIG-I agonist delivery. We evaluate the anti-cancer activity of two novel RIG-I agonists, the immunomodulatory RNA (immRNA) with a unique secondary structure for efficient RIG-I activation, and a 5′ triphosphorylated anti-sense oligonucleotide with dual function of RIG-I activation and miR-125b inhibition (3p-125b-ASO). We find that RBCEV-delivered immRNA and 3p-125b-ASO trigger the RIG-I pathway, and induce cell death in both mouse and human breast cancer cells. Furthermore, we observe a significant suppression of tumour growth coupled with increased immune cell infiltration mediated by the activation of RIG-I cascade after multiple intratumoral injections of RBCEVs loaded with immRNA or 3p-125b-ASO. Targeted delivery of immRNA using RBCEVs with EGFR-binding nanobody administrated via intrapulmonary delivery facilitates the accumulation of RBCEVs in metastatic cancer cells, leading to potent tumour-specific CD8+ Tcellsimmune response. This contributes to prominent suppression of breast cancer metastasis in the lung. Hence, this study provides a new strategy for efficient RIG-I agonist deliv-ery using RBCEVs for immunotherapy against cancer and cancer metastasis.



Research Article
2022 Jan;11:e12187
Impact Factor:20.6

Materials and Methods

ImmRNA and ′5 triphosphate 125b-ASO (3p-125b-ASO) were synthesized by in vitro transcription, as described in the next section. **Anti-miR-125b ASO (125b-ASO)** , **negative control RNA (NC RNA)** and **FAM-labelled NC-ASO** were synthesized with 2′ O-methyl modification at every ribonucleotide by Shanghai **GenePharma** (Shanghai, China).

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-04791-8 OPEN

Efficient RNA drug delivery using red blood cell extracellular vesicles

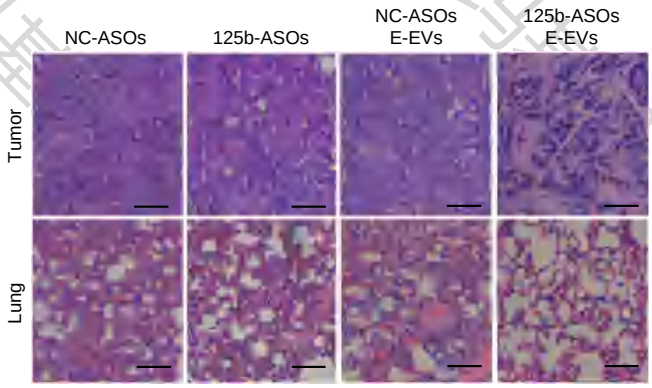
Waqas Muhammad Usman[1], Tin Chanh Pham[1], Yuk Yan Kwok[2], Luyen Tien Vu[1], Victor Ma[2], Boya Peng[1], Yuen San Chan[1], Likun Wei[1], Siew Mei Chin[1], Ajijur Azad[1], Alex Bai-Liang He[3], Anskar Y.H. Leung[3], Mengsu Yang[1,4], Ng Shyh-Chang[5], William C. Cho[2], Jiahai Shi[1,6] & Minh T.N. Le[1,6]

Most of the current methods for programmable RNA drug therapies are unsuitable for the clinic due to low uptake efficiency and high cytotoxicity. Extracellular vesicles (EVs) could solve these problems because they represent a natural mode of intercellular communication. However, current cellular sources for EV production are limited in availability and safety in terms of horizontal gene transfer. One potentially ideal source could be human red blood cells (RBCs). Group O-RBCs can be used as universal donors for large-scale EV production since they are readily available in blood banks and they are devoid of DNA. Here, we describe and validate a new strategy to generate large-scale amounts of RBC-derived EVs for the delivery of RNA drugs, including antisense oligonucleotides, Cas9 mRNA, and guide RNAs. RNA drug delivery with RBCEVs shows highly robust microRNA inhibition and CRISPR–Cas9 genome editing in both human cells and xenograft mouse models, with no observable cytotoxicity.

Nature Communications
2018 Jun 15 ; 2359
Impact Factor:16.6

Materials and Methods

Anti-miR-125b ASOs (5′-UCACAAGUUAGGGUCUCAGGGA-3′)and **negative control ASOs** (5′-CAGUACUUUUGUGUAGUACAA-3′) were synthesized with 2′ O-methyl modification at every ribonucleotide by Shanghai **Genepharma** (Shanghai, China).



MiR-21 Indicates Poor Prognosis in Tongue Squamous Cell Carcinomas as an Apoptosis Inhibitor

Jinsong Li,[1] Hongzhang Huang,[1] Lijuan Sun,[2] Mei Yang,[2] Chaobin Pan,[1] Weiliang Chen,[1] Donghui Wu,[1] Zhaoyu Lin,[1] Chunxian Zeng,[3] Yandan Yao,[2] Peter Zhang,[4] and Erwei Song[2,3]

Abstract

Purpose: We aim to examine miR-21 expression in tongue squamous cell carcinomas (TSCC) and correlate it with patient clinical status, and to investigate its contribution to TSCC cell growth, apoptosis, and tumorigenesis.

Experimental Design: MicroRNA profiling was done in 10 cases of TSCC with micro-array. MiR-21 overexpression was quantitated with quantitative reverse transcrip-array. MiR-21 overexpression was quantitated with quantitative reverse transcrip-array. MiR-21 overexpression was quantitated with quantitative reverse transcrip-tion-PCR in 103 patients, and correlated to the pathoclinical status of the patients.Immunohistochemistry was used to examine the expression of TPM1 and PTEN,and terminal deoxynucleotidyl transferase–mediated dUTP labeling to evaluate apoptosis.Moreover, miR-21 antisense oligonucleotide (ASO) was transfected in SCC-15 and CAL27 cell lines, and tumor cell growth was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, adherent colony formation, and soft agar assay,whereas apoptosis was determined by Annexin V assay, cytochrome c release, and cas-pase 3 assay. Tumorigenesis was evaluated by xenografting SCC-15 cells in nude mice.

Results: MiR-21 is overexpressed in TSCC relative to adjacent normal tissues. The level of miR-21 is reversely correlated with TPM1 and PTEN expression and apoptosis of can-cer cells. Multivariate analysis showed that miR-21 expression is an independent prog-nostic factor indicating poor survival. Inhibiting miR-21 with ASO in TSCC cell lines reduces survival and anchorage-independent growth, and induces apoptosis in TSCC cell lines. Simultaneous silencing of TPM1 with siRNA only partially recapitulates the effect of miR-21 ASO. Furthermore, repeated injection of miR-21 ASO suppresses tu-mor formation in nude mice by reducing cell proliferation and inducing apoptosis.

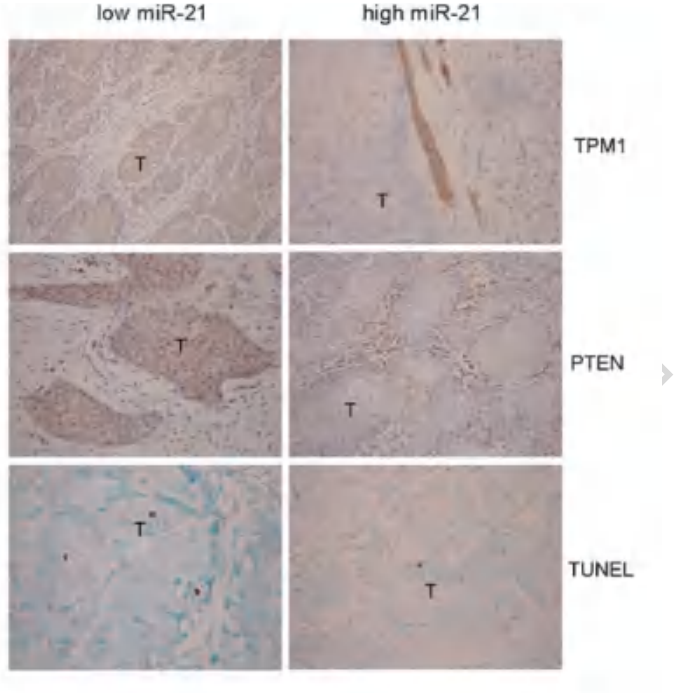
Conclusions: miR-21 is an independent prognostic indicator for TSCC, and may play a role in TSCC development by inhibiting cancer cell apoptosis partly via TPM1 silencing.

Human Cancer Biology
2009 Jun 15 (12): 3998–4008
Impact Factor:12.5

Materials and Methods

All miRNA ASOs and **siRNAs** were obtained from **GenePharma**, and their sequences were shown in Supplementary Table S3.

Real-time reverse transcrip-tion PCR for miR-21 was done using **Real-time PCR Universal Reagent** (**GenePharma** Co., Ltd.) and MX-3000P Real-time PCR machine (Stra-tagen).



Received: 16 August 2023 | Revised: 16 December 2023 | Accepted: 23 December 2023

DOI: 10.1002/ctm2.1531

RESEARCH ARTICLE

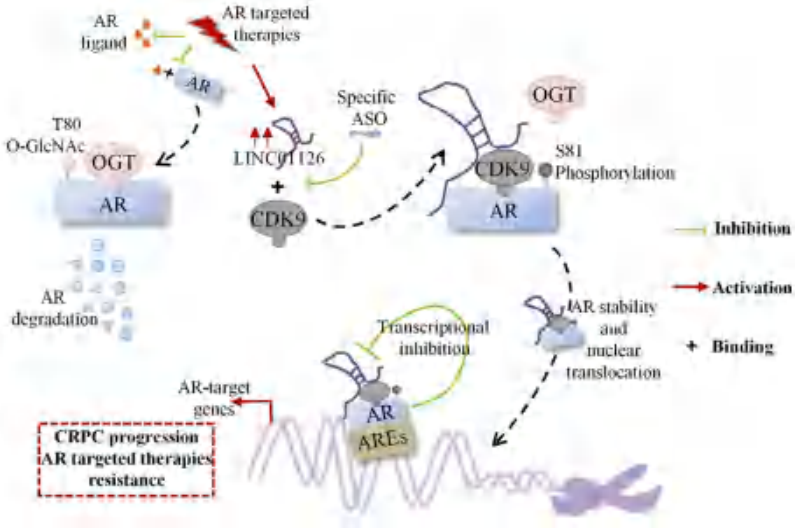
Androgen-repressed lncRNA LINC01126 drives castration-resistant prostate cancer by regulating the switch between O-GlcNAcylation and phosphorylation of androgen receptor

Yi Cai[1] | Minfeng Chen[1] | Yuchen Gong[1] | Guyu Tang[1] | Zhiwei Shu[1] | Jiaxian Chen[1] | Hengfeng Zhou[2] | Yao He[1] | Zhi Long[2] | Yu Gan[1]

Graphical Abstract

LINC01126 is highly expressed in castration-resistant prostate cancer and is correlated with poor prognosis. AR-targeted therapies upregulate LINC01126 expression through relieving its transcriptional repression by AR. LINC01126 facilitates the activation of AR signalling independent of androgen. LINC01126 promotes the transition from O-GlcNAcylation at threonine 80 to phosphorylation at S81 within the AR protein.

AR-targeted therapies inhibit synthesis of AR ligand or block binding of AR ligand to AR. Without AR ligand, AR protein is O-GlcNAcylated at threonine 80 and degrades rapidly. LINC01126 is transcriptionally repressed by AR. AR-targeted therapies thereby upregulate LINC01126 expression through relieving



Clinical and Translational Medicine
2024 Jan;14(1):e1531
Impact Factor:10.6

Materials and Methods

Antisense oligos (ASO) targeting LINC01126 for steri-cally blocking its interaction with the CDK9 protein, ASO with the target sequence mutated, and ASO with non-target sequence were designed with 2′-O-methoxyethyl modification and synthesised by **GenePharma** (Shanghai).

All these **plasmids** were constructed by **GenePharma**.

Tuan Thach Pham, Huan Chen, et al.Endosomal escape of nucleic acids from extracellular vesicles mediates functional therapeutic delivery,Pharmacological Research,Volume 188,2023,106665. **IF**:**9.3**

Chen S, Wang J, Zhang K, et al. LncRNA Neat1 targets NonO and miR-128-3p to promote antigen-specific Th17 cell responses and autoimmune inflammation[J]. Cell Death & Disease, 2023, 14(9): 610. **IF:9.2**

Li M, Ding X, Zhang Y, et al. Antisense oligonucleotides targeting lncRNA AC104041. 1 induces antitumor activity through Wnt2B/β-catenin pathway in head and neck squamous cell carcinomas[J]. Cell Death & Disease, 2020, 11(8): 672. **IF:9**

Ma C, Wang X, Zhang L, et al. Super Enhancer-Associated Circular RNA-CircKrt4 Regulates Hypoxic Pulmonary Artery Endothelial Cell Dysfunction in Mice[J]. Arteriosclerosis, Thrombosis, and Vascular Biology, 2023. **IF:8.7**

Wu Z, Wu Q, Wang C, et al. miR-340 inhibition of breast cancer cell migration and invasion through targeting of oncoprotein c-Met[J]. Cancer, 2011, 117(13): 2842-2852. **IF:6.8**

Lin Z, Sun L, Chen W, et al. miR-639 regulates transforming growth factor beta-induced epithelial–mesenchymal transition in human tongue cancer cells by targeting FOXC 1[J]. Cancer science, 2014, 105(10): 1288-1298. **IF:5.7**

Li Y, Chen Y, Li J, et al. Co-delivery of micro RNA-21 antisense oligonucleotides and gemcitabine using nanomedicine for pancreatic cancer therapy[J]. Cancer Science, 2017, 108(7): 1493-1503. **IF:5.7**

Li M, Liu Q, Xie S, et al. LncRNA TCONS_00323213 Promotes Myogenic Differentiation by Interacting with PKNOX2 to Upregulate MyoG in Porcine Satellite Cells[J]. International Journal of Molecular Sciences, 2023, 24(7): 6773. **IF:5.6**

Qian X, Qu H, Zhang F, et al. Exosomal long noncoding RNA AGAP2-AS1 regulates trastuzumab resistance via inducing autophagy in breast cancer[J]. American journal of cancer research, 2021, 11(5): 1962. **IF:5.6**

Zhang W, Lin J, Shi P, et al. Small extracellular vesicles derived from MSCs have immunomodulatory effects to enhance delivery of ASO-210 for psoriasis treatment[J]. Frontiers in Cell and Developmental Biology, 2022, 10: 842813. **IF:5.5**

Liu S, Yang S, Zhou X, et al. Nerve injury-induced upregulation of apolipoprotein E in dorsal root ganglion participates in neuropathic pain in male mice[J]. Neuropharmacology, 2023, 224: 109372. **IF:4.8**

Yang L, Qiu M, Xu Y, et al. Upregulation of long non-coding RNA PRNCR1 in colorectal cancer promotes cell proliferation and cell cycle progression[J]. Oncology reports, 2016, 35(1): 318-324. **IF:4.2**

Xiao H, Yu L, Li F, et al. MiR-340 suppresses the metastasis by targeting EphA3 in cervical cancer[J]. Cell Biology International, 2018, 42(9): 1115-1123. **IF:3.8**

Chen T, Sun Z, Cui Y, et al. Identification of long noncoding RNA NEAT1 as a key gene involved in the extramedullary disease of multiple myeloma by bioinformatics analysis[J]. Hematology, 2023, 28(1): 2164449. **IF:2.1**

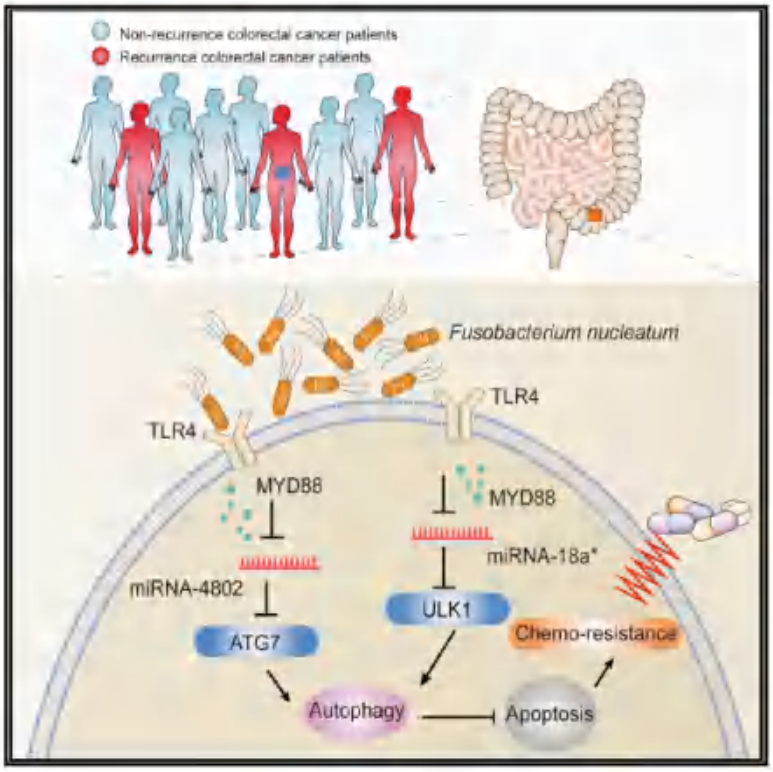
Tian L, Chen Y, Chang S, et al. Antisense oligonucleotides targeting alternative splicing of Nrcam exon 10 suppress neurite outgrowth of ganglion sensory neurons in vitro[J]. NeuroReport, 2021, 32(7):548-554. **IF:1.7**

Article

Cell

Fusobacterium nucleatum Promotes Chemoresistance to Colorectal Cancer by Modulating Autophagy

Graphical Abstract



Authors

TaChung Yu, Fangfang Guo, Yanan Yu, ..., Jie Hong, Weiping Zou, Jing-Yuan Fang

Correspondence

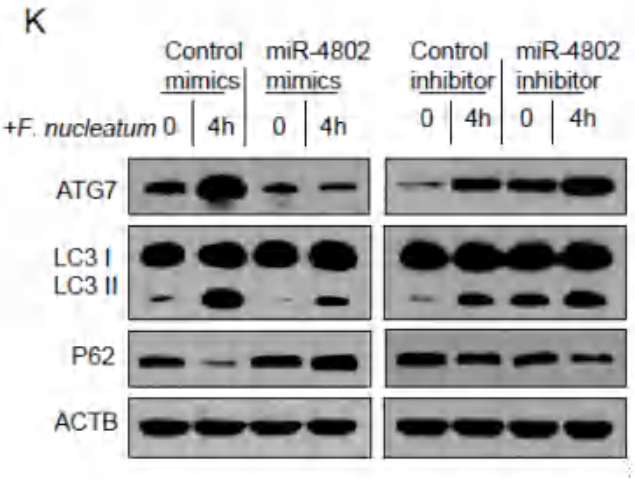
yingxuanchen71@126.com (Y.C.), haoyanchen@shsmu.edu.cn (H.C.), jiehong97@shsmu.edu.cn (J.H.), wzou@med.umich.edu (W.Z.), jingyuanfang@sjtu.edu.cn (J.-Y.F.)

In Brief

Reducing a specific gut microbe in colorectal cancer patients may improve their response to chemotherapy and reduce cancer recurrence.

Cell
2017 Jul 27; 170: 548-63
Impact Factor: 64.5

Materials and Method
siRNAs, miRNA mimics, and **inhibitors** were purchased from **Genepharma** (Shanghai, China) (Table S7).



Open
ORIGINAL ARTICLE

Cell Research (2015) 25:930-945
www.nature.com/cr

An HNF1α-regulated feedback circuit modulates hepatic fibrogenesis via the crosstalk between hepatocytes and hepatic stellate cells

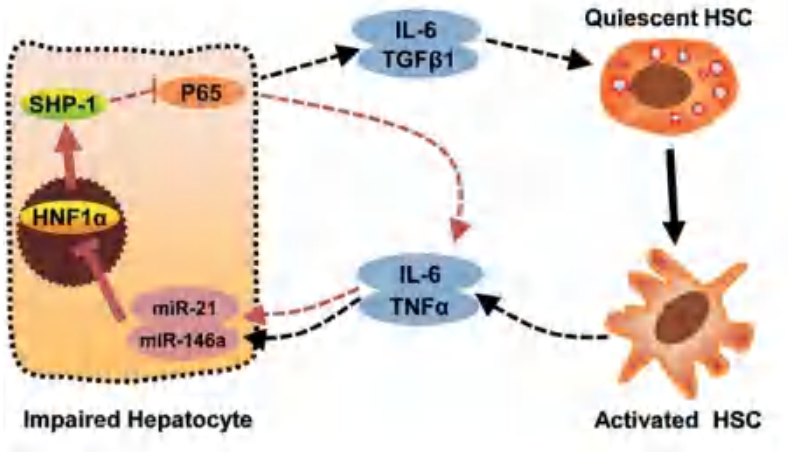
Hui Qian[1, 4, *], Xing Deng[1, *], Zhao-Wei Huang[1, 4, *], Ji Wei[1], Chen-Hong Ding[1], Ren-Xin Feng[1], Xin Zeng[1], Yue-Xiang Chen[1], Jin Ding[3], Lei Qiu[2], Zhen-Lin Hu[2], Xin Zhang[1], Hong-Yang Wang[3], Jun-Ping Zhang[2], Wei-Fen Xie[1]

Hepatocytes are critical for the maintenance of liver homeostasis, but its involvement in hepatic fibrogenesis remains elusive. Hepatocyte nuclear factor 1 α (HNF1 α) is a liver-enriched transcription factor that plays a key role in hepatocyte function. Our previous study revealed a significant inhibitory effect of HNF1 α on hepatocellular carcinoma. In this study, we report that the expression of HNF1 α is significantly repressed in both human and rat fibrotic liver. Knockdown of HNF1 α in the liver significantly aggravates hepatic fibrogenesis in either dimethylnitrosamine (DMN) or bile duct ligation (BDL) model in rats. In contrast, forced expression of HNF1 α markedly alleviates hepatic fibrosis. HNF1 α regulates the transcriptional expression of SH2 domain-containing phosphatase-1 (SHP-1) via directly binding to SHP-1 promoter in hepatocytes. Inhibition of SHP-1 expression abrogates the anti-fibrotic effect of HNF1 α in DMN-treated rats. Moreover, HNF1 α repression in primary hepatocytes leads to the activation of NF-κB and JAK/ STAT pathways and initiates an inflammatory feedback circuit consisting of HNF1 α, SHP-1, STAT3, p65, miR-21 and miR-146a, which sustains the deregulation of HNF1 α in hepatocytes. More interestingly, a coordinated crosstalk between hepatocytes and hepatic stellate cells (HSCs) participates in this positive feedback circuit and facilitates the progression of hepatocellular damage. Our findings demonstrate that impaired hepatocytes play an active role in hepatic fibrogenesis. Early intervention of HNF1 α-regulated inflammatory feedback loop in hepatocytes may have beneficial effects in the treatment of chronic liver diseases.

Cell research
2015 Aug;25(8):930-45
Impact Factor:44.1

Materials and Methods

siRNA, miRNA mimics, miRNA inhibitors and **their negative controls (NC or NC inhibitors)** were synthesized by **GenePharma** (Shanghai GenePharma Co., Ltd., Shanghai, China) .

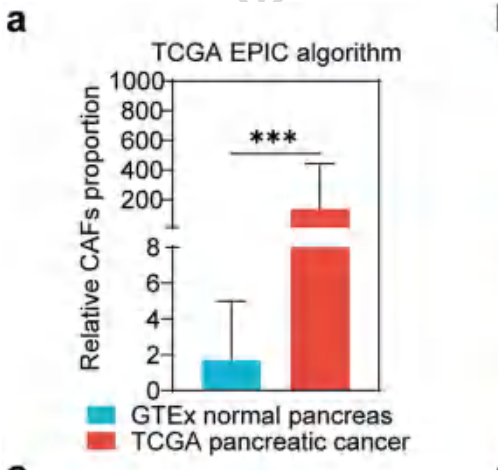


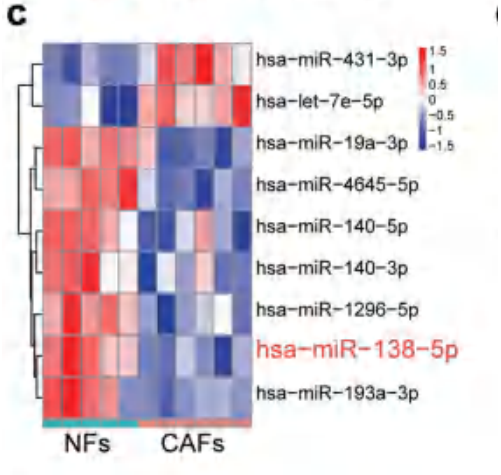
ARTICLE OPEN

Engineered extracellular vesicles for targeted reprogramming of cancer-associated fibroblasts to potentiate therapy of pancreatic cancer

Pengcheng Zhou[1,2], Xuanlong Du[2], Weilu Jia[2], Kun Feng[3] and Yewei Zhang[4]✉

Pancreatic cancer is one of the deadly malignancies with a significant mortality rate and there are currently few therapeutic options for it. The tumor microenvironment (TME) in pancreatic cancer, distinguished by fibrosis and the existence of cancer-associated fibroblasts (CAFs), exerts a pivotal influence on both tumor advancement and resistance to therapy. Recent advancements in the field of engineered extracellular vesicles (EVs) offer novel avenues for targeted therapy in pancreatic cancer. This study aimed to develop engineered EVs for the targeted reprogramming of CAFs and modulating the TME in pancreatic cancer. EVs obtained from bone marrow mesenchymal stem cells (BMSCs) were loaded with miR-138-5p and the anti-fibrotic agent pirfenidone (PFD) and subjected to surface modification with integrin α5-targeting peptides (named IEVs-PFD/138) to reprogram CAFs and suppress their pro-tumorigenic effects. Integrin α5-targeting peptide modification enhanced the CAF-targeting ability of EVs. miR-138-5p directly inhibited the formation of the FERMT2-TGFBR1 complex, inhibiting TGF-β signaling pathway activation. In addition, miR-138-5p inhibited proline-mediated collagen synthesis by directly targeting the FERMT2-PYCR1 complex. The combination of miR-138-5p and PFD in EVs synergistically promoted CAF reprogramming and suppressed the pro-cancer effects of CAFs. Preclinical experiments using the orthotopic stroma-rich and patient-derived xenograft mouse models yielded promising results. In particular, IEVs-PFD/138 effectively reprogrammed CAFs and remodeled TME, which resulted in decreased tumor pressure, enhanced gemcitabine perfusion, tumor hypoxia amelioration, and greater sensitivity of cancer cells to chemotherapy. Thus, the strategy developed in this study can improve chemotherapy outcomes. Utilizing IEVs-PFD/138 as a targeted therapeutic agent to modulate CAFs and the TME represents a promising therapeutic approach for pancreatic cancer.





Signal Transduction and Targeted Therapy

Published: 24 June 2024

Impact Factor:40.8

Materials and Methods

the cells with 100 pmol **NC-mimic** and **miR-138-5p mimic** (**GenePharma**),

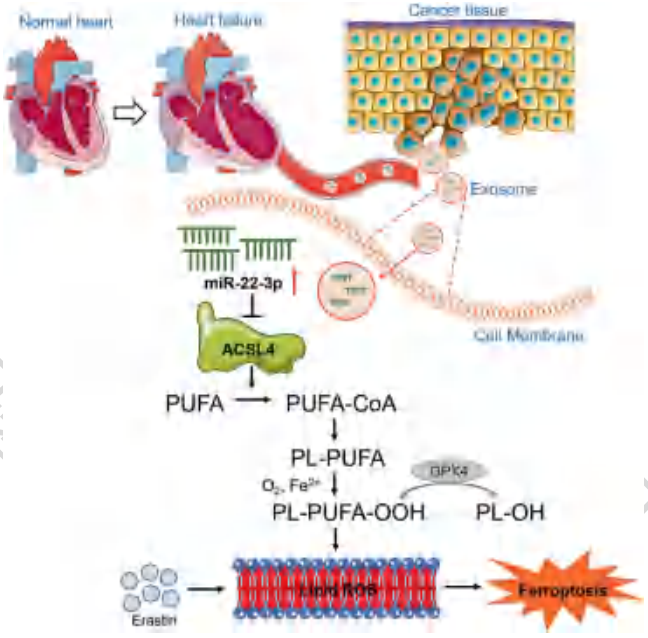
ARTICLE

Exosomes secreted from cardiomyocytes suppress the sensitivity of tumor ferroptosis in ischemic heart failure

Ye Yuan[1,2,3,4], Zhongting Mei[1], Zhezhe Qu[1], Guanghui Li[1], Shuting Yu[1], Yingqi Liu[1], Kuiwu Liu[1], Zhihua Shen[2,4], Jiaying Pu[2,4], Yanquan Wang[1], Changhao Wang[1], Zhiyong Sun[1], Qian Liu[1], Xiaochen Pang[1], Ao Wang[2,4], Zijing Ren[1,2], Tong Wang[1], Ying Liu[1], Jinhuan Hong[2,4], Jiajie Xie[2,4], Xin Li[1], Zhonghua Wang[5], Weijie Du[1,3,6]✉ and Baofeng Yang[1,3,6]✉

Heart failure (HF) patients in general have a higher risk of developing cancer. Several animal studies have indicated that cardiac remodeling and HF remarkably accelerate tumor progression, highlighting a cause-and-effect relationship between these two disease entities. Targeting ferroptosis, a prevailing form of non-apoptotic cell death, has been considered a promising therapeutic strategy for human cancers. Exosomes critically contribute to proximal and distant organ-organ communications and play crucial roles in regulating diseases in a paracrine manner. However, whether exosomes control the sensitivity of cancer to ferroptosis via regulating the cardiomyocyte-tumor cell crosstalk in ischemic HF has not yet been explored. Here, we demonstrate that myocardial infarction (MI) decreased the sensitivity of cancer cells to the canonical ferroptosis activator erastin or imidazole ketone erastin in a mouse model of xenograft tumor. Post-MI plasma exosomes potently blunted the sensitivity of tumor cells to ferroptosis inducers both in vitro in mouse Lewis lung carcinoma cell line LLC and osteosarcoma cell line K7M2 and in vivo with xenograft tumorigenesis model. The expression of miR-22-3p in cardiomyocytes and plasma-exosomes was significantly upregulated in the failing hearts of mice with chronic MI and of HF patients as well. Incubation of tumor cells with the exosomes isolated from post-MI mouse plasma or overexpression of miR-22-3p alone abrogated erastin-induced ferroptotic cell death in vitro. Cardiomyocyte-enriched miR-22-3p was packaged in exosomes and transferred into tumor cells. Inhibition of cardiomyocyte-specific miR-22-3p by AAV9 sponge increased the sensitivity of cancer cells to ferroptosis. ACSL4, a pro-ferroptotic gene, was experimentally established as a target of miR-22-3p in tumor cells. Taken together, our findings uncovered for the first time that MI suppresses erastin-induced ferroptosis through releasing miR-22-3p-enriched exosomes derived from cardiomyocytes. Therefore, targeting exosome-mediated cardiomyocyte/tumor pathological communication may offer a novel approach for the ferroptosis-based antitumor therapy.

Signal Transduction and Targeted Therapy (2023)8:121 ; https://doi.org/10.1038/s41392-023-01336-4



Signal Transduction and Targeted Therapy
2023 Mar;8(1):121
Impact Factor:39.3

Materials and Methods

The miR-22-3p mimics and **miR-22-3p anti-miRNA oligonucleotide (AMO)** were obtained from **GenePharma** (China).

Molecular Cancer

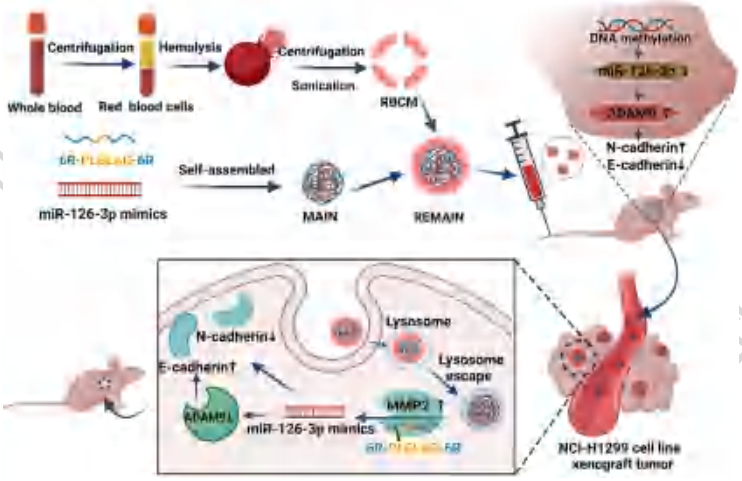
RESEARCH Open Access

The reversion of DNA methylation-induced miRNA silence via biomimetic nanoparticles-mediated gene delivery for efficient lung adenocarcinoma therapy

Abstract

Background: Lung cancer is one of the fatal cancers worldwide, and over 60% of patients are lung adenocarcinoma (LUAD). Our clinical data demonstrated that DNA methylation of the promoter region of miR-126-3p was upregulated, which led to the decreased expression of miR-126-3p in 67 cases of lung cancer tissues, implying that miR-126-3p acted as a tumor suppressor. Transduction of miR-126-3p is a potential therapeutic strategy for treating LUAD, yet the physiological environment and properties of miRNA challenge current transduction approaches.

Methods: We evaluated the expression of miR-126-3p in 67 pairs of lung cancer tissues and the corresponding adja-cent non-tumorous tissues by Reverse transcription-quantitative polymerase chain reaction (RT-qPCR). The relation-ship between the overall survival of lung cancer patients and miR-126-3p was analyzed by the Cancer Genome Atlas cohort database (Oncolnc, http:// www. oncol nc. org). We analyzed DNA methylation Methylation-specific PCR (MSP) analysis. To determine whether ADAM9 is the direct target of miR-126-3p, we performed the 3′-UTR luciferase reporter assay. The protein levels in the cells or tissues were evaluated with western blotting (WB) analysis. The biodistribution of nanoparticles were monitored by in vivo tracking system.



Molecular Cancer
2022 Dec;21(1):1-19
Impact Factor:37.3

Materials and Methods

6R-PLGLAG-6R (GL Biochem Ltd, Shang-hai, China) and miR-126-3p (Genepharma, Shanghai, China) were dissolved in RNase free water to prepare at concentrations of 10 mg/mL and 1 mg/mL, respectively.

Molecular Cancer

RESEARCH Open Access

METTL14-mediated m^{6}A modification of circORC5 suppresses gastric cancer progression by regulating miR-30c-2-3p/AKT1S1 axis

Hui-Ning Fan†, Zhao-Yu Chen†, Xiao-Yu Chen, Ming Chen, You-Cai Yi, Jin-Shui Zhu* and Jing Zhang*

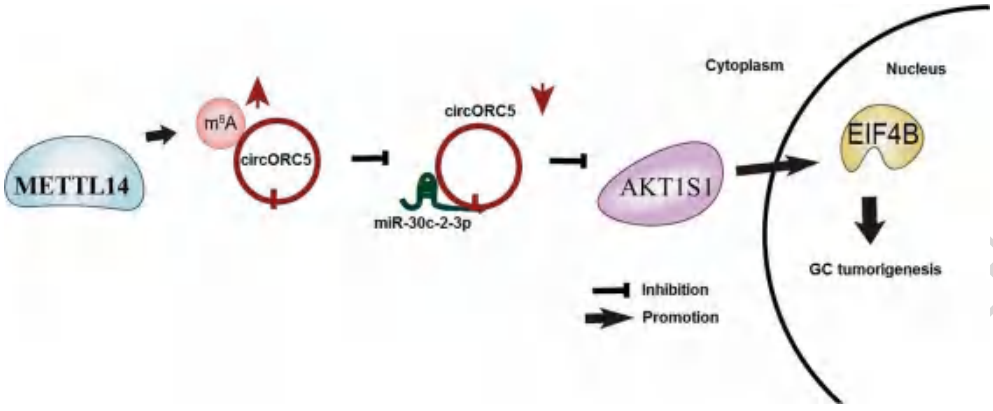
Abstract

Background: N6-methyladenosine (m^{6}A) RNA methylation and circular RNAs (circRNAs) have been shown to act vital roles in multiple malignancies including gastric cancer (GC). However, there is little knowledge about how m6A modification of circRNAs contributes to GC progression.

Methods: The association of METTL14 expression with the clinicopathological characteristics and prognosis in patients with GC was assessed by Western blot, Immunohistochemistry and public datasets. In vitro and vivo function experiments were conducted to investigate the role of METTL14 in GC. Furthermore, m^{6}A circRNA epitranscrip tomic microarray was utilized to identify METTL14 mediated m6A modification of circRNAs, which were validated by methylated RNA immunoprecipitation (Me RIP), RT qPCR and rescue experiments in GC cells. The sponge of circORC5 with miR-30c-2-3p was confirmed by luciferase gene report and RNA immunoprecipitation assays. The expression, localization and prognosis of circORC5 in GC were evaluated by fluorescence in situ-hybridization. The effects of METTL14 and (or) circORC5 on miR-30c-2-3p mediated AKT1S1 and EIF4B were estimated by RT qPCR and Western blot analyses.

Conclusion: Our findings demonstrate that METTL14 mediated m^{6}A modification of circORC5 suppresses gastric cancer progression by regulating miR-30c-2-3p/AKT1S1 axis.

Keywords: m^{6}A, METTL14, circORC5, miR-30c-2-3p, Gastric cancer



Molecular Cancer
2022 Dec;21(1):1-14
Impact Factor:37.3

Materials and Methods

METTL14 **plasmid vector, siRNA** targeting METTL14 (si-METTL14, 5'-CCG ACA GCA TTG GTG CCG TGT TAAA -3') or circORC5 (si-circORC5, 5'- AGCT AT TGC AAG CAT CAT GGA-3'), **miR-30c-2-3p mimics and inhibitor** were purchased from **GenePharma** (Shanghai, China).

Liu et al. Mol Cancer (2021) 20:139
https://doi.org/10.1186/s12943-021-01395-7

Molecular Cancer

RESEARCH Open Access

CircRNF220, not its linear cognate gene RNF220, regulates cell growth and is associated with relapse in pediatric acute myeloid leukemia

Xiaodan Liu[1,2†], Xiaoping Liu[2,3†], Mansi Cai[2,3], Ailing Luo[2,3], Yingyi He[2], Sha Liu[2], Xiaohong Zhang[2], Xu Yang[2,3], Ling Xu[2*] and Hua Jiang[2*]

Abstract

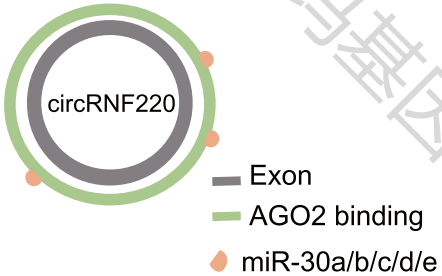
Background: Circular RNAs (circRNAs) constitute a family of transcripts with unique structures and have been confirmed to be critical in tumorigenesis and to be potential biomarkers or therapeutic targets. However, only a few circRNAs have been functionally characterized in pediatric acute myeloid leukemia (AML).

Methods: Here, we investigated the expression pattern of circRNAs in pediatric AML using a circRNA microarray. The characteristics, potential diagnostic value, and prognostic significance of circRNF220 were evaluated. A series of functional experiments were performed to investigate the role of circRNF220 in primary pediatric AML cells. Then we investigated the aberrant transcriptional networks regulated by circRNF220 in primary AML cells by RNA-seq. Further-more, biotin RNA pulldown assays were implemented to verify the relationship between circRNF220 and miR-30a.

Results: We identified a circRNA, circRNF220, which was specifically abundant in and accumulated in the peripheral blood and bone marrow of pediatric patients with AML. It could distinguish AML from ALL and other hematologi-cal malignancies with high sensitivity and specificity. Significantly, circRNF220 expression independently predicted prognosis, while high expression of circRNF220 was an unfavorable prognostic marker for relapse. Furthermore, we characterized the function of circRNF220 and found that circRNF220 knockdown specifically inhibited proliferation and promoted apoptosis in AML cell lines and primary cells. Mechanistically, circRNF220 may act as an endogenous sponge of miR-30a to sequester miR-30a and inhibit its activity, which increases the expression of its targets MYSM1 and IER2 and implicated in AML relapse.

Conclusions: Collectively, these findings demonstrated that circRNF220 could be highly efficient and specific for the accurate diagnosis of pediatric AML, with implications for relapse prediction.

Keywords: Circular RNA, RNF220, miR-30a, Acute myeloid leukemia



Molecular Cancer
2021 Dec;20(1):1-18
Impact Factor:37.3

Materials and Methods

The **miR-30a mimics (miR-30a)** or its **inhibitor (inhibitor-miR-30a)** and **scrambled oligonucleo-tides (miR-NC or inhibitor-NC)** were purchased from **GenePharma** Biotech (Shanghai, China).

Rong et al. Molecular Cancer (2021) 20:106
https://doi.org/10.1186/s12943-021-01400-z

Molecular Cancer

RESEARCH Open Access

Circular RNA CircEYA3 induces energy production to promote pancreatic ductal adenocarcinoma progression through the miR-1294/c-Myc axis

Zeyin Rong[1,2,3,4†], Si Shi[1,2,3,4†], Zhen Tan[1,2,3,4†], Jin Xu[1,2,3,4†], Qingcai Meng[1,2,3,4], Jie Hua[1,2,3,4], Jiang Liu[1,2,3,4], Bo Zhang[1,2,3,4], Wei Wang[1,2,3,4], Xianjun Yu[1,2,3,4*] and Chen Liang[1,2,3,4*]

Abstract

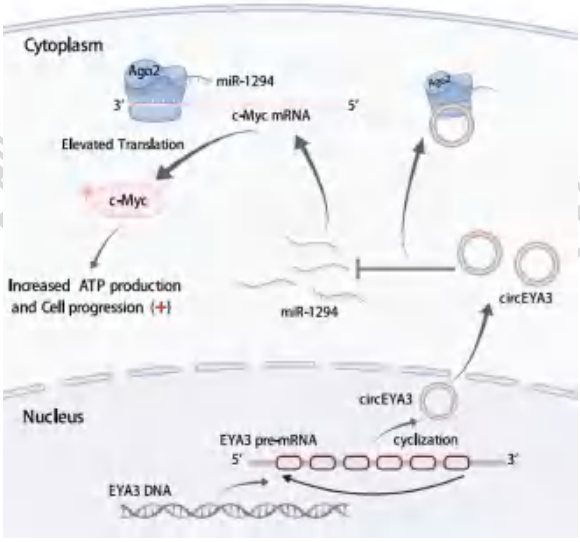
Background: Extensive studies have demonstrated the pivotal roles of circular RNAs (circRNAs) in the occurrence and development of different human cancers. However, the expression and regulatory roles of circRNAs in pancreatic ductal adenocarcinoma (PDAC) are unclear.

Methods: CircEYA3 was explored based on Gene Expression Omnibus (GEO) dataset analysis. qRT-PCR was applied to determine the expression of circRNAs, miRNAs and mRNAs in PDAC cells and tissues. The biological roles of circEYA3 in vitro and in vivo were determined by performing a series of functional experiments. Further, dual luciferase reporter, fluorescence in situ hybridization (FISH), RNA pull-down assays, and RNA immunoprecipitation (RIP) assays were used to confirm the interaction of circEYA3 with miR-1294.

Results: CircEYA3 was elevated in PDAC tissues and cells, and a higher level of circEYA3 was significantly associated with a poorer prognosis in patients with PDAC. Functionally, circEYA3 increased energy production via ATP synthesis to promote PDAC progression in vitro and in vivo. Mechanistically, circEYA3 functions as an endogenous miR-1294 sponge to elevate c-Myc expression, thus exerting its oncogenic functions.

Conclusion: CircEYA3 promotes the progression of PDAC through the miR-1294/c-Myc signalling axis, and circEYA3 may be an efficient molecular therapeutic target in PDAC.

Keywords: CircEYA3, miR-1294, C-Myc, ATP production, Pancreatic ductal adenocarcinoma



Molecular Cancer
2021 Aug 21;20(1):106
mpact Factor:37.3

Materials and Method
The **mimics, inhibitor** and **corresponding negative controls (NCs)** for miR-1294 were synthesized by and purchased from **GenePharma** (Shanghai, China).

Zhang et al. Molecular Cancer (2019) 18:20
https://doi.org/10.1186/s12943-018-0935-5

Molecular Cancer

RESEARCH Open Access

Circular RNA circNRIP1 acts as a microRNA-149-5p sponge to promote gastric cancer progression via the AKT1/mTOR pathway

Xing Zhang[1†], Sen Wang[1†], Haixiao Wang[4†], Jiacheng Cao[1†], Xiaoxu Huang[1], Zheng Chen[2], Penghui Xu[1], Guangli Sun[1], Jianghao Xu[1], Jialun Lv[1] and Zekuan Xu[1,3*]

Abstract

Background: CircRNA has emerged as a new non-coding RNA that plays crucial roles in tumour initiation and development. 'MiRNA sponge' is the most reported role played by circRNAs in many tumours. The AKT/mTOR axis is a classic signalling pathway in cancers that sustains energy homeostasis through energy production activities, such as the Warburg effect, and blocks catabolic activities, such as autophagy. Additionally, the AKT/mTOR axis exerts a positive effect on EMT, which promotes tumour metastasis. Methods: We detected higher circNRIP1 expression in gastric cancer by performing RNA-seq analysis. We verified the tumour promotor role of circNRIP1 in gastric cancer cells through a series of biological function assays. We then used a pull-down assay and dual-luciferase reporter assay to identify the downstream miR-149-5p of circNRIP1. Western blot analysis and immunofluorescence assays were performed to demonstrate that the circNRIP1-miR-149-5p-AKT1/mTOR axis is responsible for the altered metabolism in GC cells and promotes GC development. We then adopted a co-culture system to trace circNRIP1 transmission via exosomal communication and RIP experiments to determine that quaking regulates circNRIP1 expression. Finally, we confirmed the tumour suppressor role of microRNA-133a-3p in vivo in PDX mouse models.

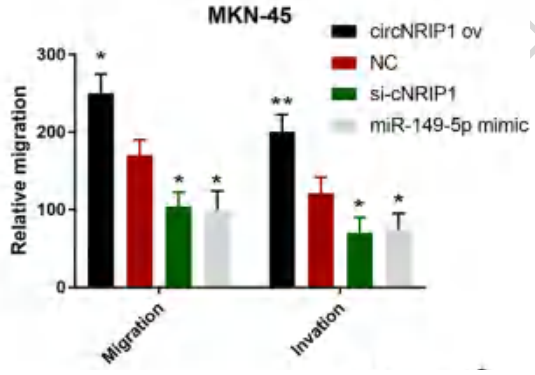
Results: We discovered that knockdown of circNRIP1 successfully blocked proliferation, migration, invasion and the expression level of AKT1 in GC cells. MiR-149-5p inhibition phenocopied the overexpression of circNRIP1 in GC cells, and overexpression of miR-149-5p blocked the malignant behaviours of circNRIP1. Moreover, it was proven that circNRIP1 can be transmitted by exosomal communication between GC cells, and exosomal circNRIP1 promoted tumour metastasis in vivo. We also demonstrated that quaking can promote circNRIP1 transcription. In the final step, the tumour promotor role of circNRIP1 was verified in PDX models.

Conclusions: We proved that circNRIP1 sponges miR-149-5p to affect the expression level of AKT1 and eventually acts as a tumour promotor in GC.

Keywords: Gastric cancer, circRNA, miRNA, ceRNA, AKT1, Organoid, PDX model

Molecular Cancer
2019 February 4 ; 18:20
Impact Factor:37.3

Materials and Method
CircNRIP1 siRNA, **miRNA mimics** and **inhibitors**(**GenePharma**,Shanghai,China).

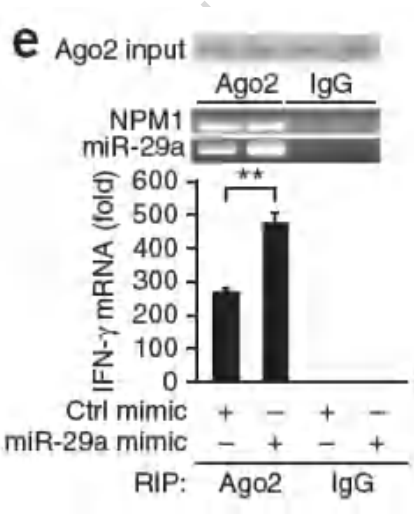


nature immunology

The microRNA miR-29 controls innate and adaptive immune responses to intracellular bacterial infection by targeting interferon-γ

Feng Ma[1,2,5], Sheng Xu[1,5], Xingguang Liu[1], Qian Zhang[1], Xiongfei Xu[1], Mofang Liu[3], Minmin Hua[3], Nan Li[1], Hangping Yao[2] & Xuetao Cao[1,2,4]

Interferon-g (IFN-g) has a critical role in immune responses to intracellular bacterial infection. MicroRNAs (miRNAs) are important in the regulation of innate and adaptive immunity. However, whether miRNAs can directly target IFN-g and regulate IFN-g production post-transcriptionally remains unknown. Here we show that infection of mice with Listeria monocytogenes or Mycobacterium bovis bacillus Calmette-Guérin (BCG) downregulated miR-29 expression in IFN-g-producing natural killer cells, CD4+ T cells and CD8+ T cells. Moreover, miR-29 suppressed IFN-g production by directly targeting IFN-g mRNA. We developed mice with transgenic expression of a 'sponge' target to compete with endogenous miR-29 targets (GS29 mice). We found higher serum concentrations of IFN-g and lower L. monocytogenes burdens in L. monocytogenes–infected GS29 mice than in their littermates. GS29 mice had enhanced T helper type 1 (TH1) responses and greater resistance to infection with BCG or Mycobacterium tuberculosis. Therefore, miR-29 suppresses immune responses to intracellular pathogens by targeting IFN-g.



Nature Immunology
2011 Sep; 12(9): 861-70
Impact Factor: 30.5

Materials and Methods

PPD was from the China Institute of Veterinary Drug Control, and **miRNA mimics** were from **GenePharma**.

RESEARCH

Open Access

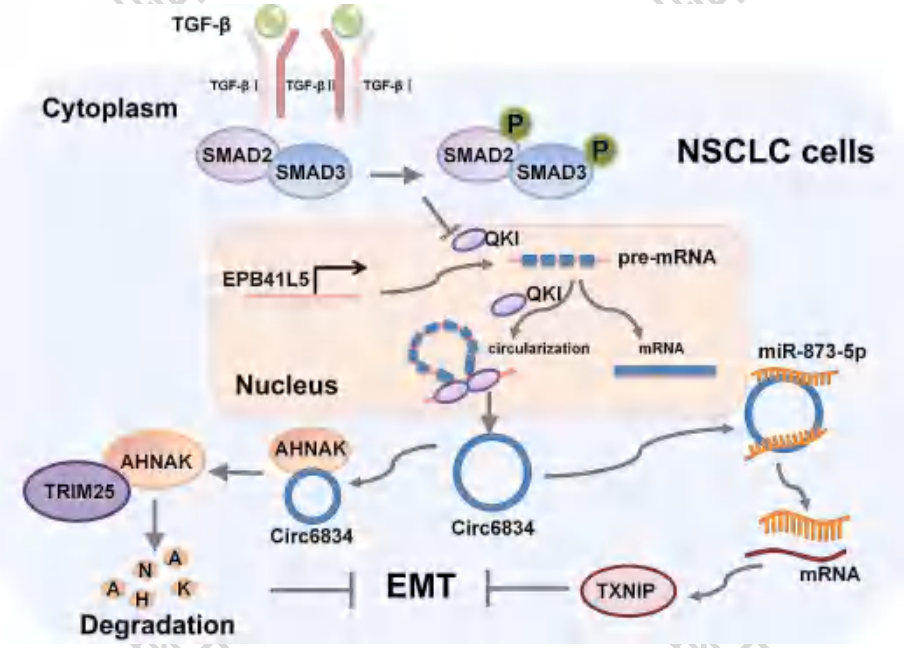
Circ6834 suppresses non-small cell lung cancer progression by destabilizing ANHAK and regulating miR-873-5p/TXNIP axis

Maoye Wang[1†], Xiaoge Ding[1†], Xinjian Fang[4†], Jing Xu[1], Yanke Chen[1], Yu Qian[1], Jiahui Zhang[1], Dan Yu[1], Xiaoxin Zhang[1], Xiuqin Ma[3], Taofeng Zhu[3*], Jianmei Gu[2*] and Xu Zhang[1*]

Abstract

Background Circular RNAs (circRNAs) play important roles in cancer progression and metastasis. However, the expression profiles and biological roles of circRNAs in non-small cell lung cancer (NSCLC) remain unclear.

Methods In this study, we identified a novel circRNA, hsa_circ_0006834 (termed circ6834), in NSCLC by RNA-seq and investigated the biological role of circ6834 in NSCLC progression in vitro and in vivo. Finally, the molecular mechanism of circ6834 was revealed by tagged RNA affinity purification (TRAP), western blot, RNA immunoprecipitation, dual luciferase reporter gene assays and rescue experiments.



Molecular Cancer
Wang et al. Molecular Cancer (2024) 23:128
Impact Factor:27.7

Materials and Methods

SiRNAs and **miRNA mimics** were synthesized by **GenePharma** (Shanghai, China)

Drug Resistance Updates 71 (2023) 101015

Contents lists available at ScienceDirect

Drug Resistance Updates

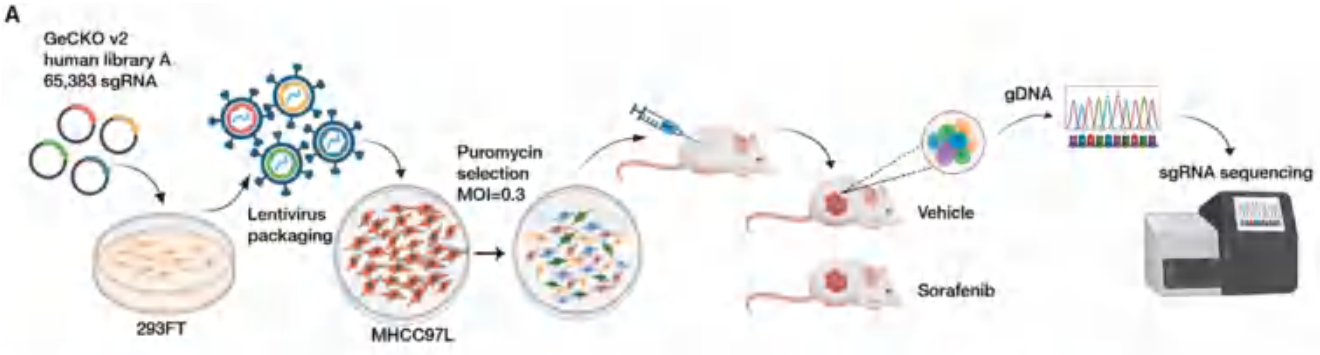
journal homepage: www.elsevier.com/locate/drup

CRISPR/Cas9 screens unravel miR-3689a-3p regulating sorafenib resistance in hepatocellular carcinoma via suppressing CCS/SOD1-dependent mitochondrial oxidative stress

Yuanjun Lu [a], Yau-Tuen Chan [a], Junyu Wu [a], Zixin Feng [a], Hongchao Yuan [a], Qiucheng Li [a], Tingyuan Xing [a], Lin Xu [a], Cheng Zhang [a], Hor-Yue Tan [b], Terence Kin-Wah Lee [c], Yibin Feng [a], Ning Wang [a,*]

A B S T R A C T

Aims: Therapeutic outcome of sorafenib in hepatocellular carcinoma (HCC) is undermined by the development of drug resistance. This study aimed to identify the critical microRNA (miRNA) which is responsible for sorafenib resistance at the genomic level.
Methods: CRISPR/Cas9 screen followed by gain- and loss-of-function assays both in vitro and in vivo were applied to identify the role of miR-3689a-3p in mediating sorafenib response in HCC. The upstream and downstream molecules of miR-3689a-3p and their mechanism of action were investigated.
Results: CRISPR/Cas9 screening identified miR-3689a-3p was the most up-regulated miRNA in sorafenib sensitive HCC. Knockdown of miR-3689a-3p significantly increased sorafenib resistance, while its overexpression sensi-tized HCC response to sorafenib treatment. Proteomic analysis revealed that the effect of miR-3689a-3p was related to the copper-dependent mitochondrial superoxide dismutase type 1 (SOD1) activity. Mechanistically, miR-3689a-3p targeted the 3′ UTR of the intracellular copper chaperone for superoxide dismutase (CCS) and suppressed its expression. As a result, miR-3689a-3p disrupted the intracellular copper trafficking and reduced SOD1-mediated scavenge of mitochondrial oxidative stress that eventually caused HCC cell death in response to sorafenib treatment. CCS overexpression blunted sorafenib response in HCC. Clinically, miR-3689a-3p was down- regulated in HCC and predicted favorable prognosis for HCC patients.
Conclusion: Our findings provide comprehensive evidence for miR-3689a-3p as a positive regulator and potential druggable target for improving sorafenib treatment in HCC.



DRUG RESISTANCE UPDATES
2023 Nov:71:101015
Impact Factor:24.3

Materials and Methods

The **miR-3689–3p mimics** and **NC**, **Anti-miR-3689a-3p** and **Anti-NC, STAT1 siRNAs**, were commercially obtained from **GenePharma**, China.

Drug Resistance Updates 68 (2023) 100936

Contents lists available at ScienceDirect

Drug Resistance Updates

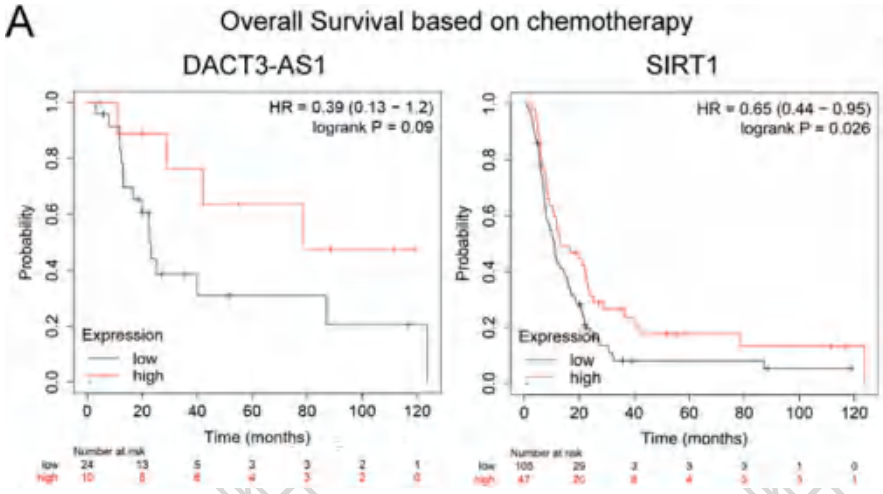
journal homepage: www.elsevier.com/locate/drup

Loss of cancer-associated fibroblast-derived exosomal DACT3-AS1 promotes malignant transformation and ferroptosis-mediated oxaliplatin resistance in gastric cancer

Xianlin Qu [a,1], Bing Liu [a,1], Longgang Wang [a], Luguang Liu [a], Weizhu Zhao [b,c], Changlei Liu [d], Jishuang Ding [a], Siwei Zhao [a], Botao Xu [a], Hang Yu [a], Xiang Zhang [d], Jie Chai [a,*]

A B S T R A C T

Aims: Long non-coding RNAs (lncRNAs), as one of the components of exosomes derived from cancer-associated fibroblasts (CAFs), exhibit a crucial role in the pathogenesis and chemoresistance of gastric cancer (GC). Herein, we investigated the role and mechanism of a novel lncRNA disheveled binding antagonist of beta catenin3 antisense1 (DACT3-AS1) and its involvement in GC.
Methods: DACT3-AS1 was identified by RNA-sequencing and verified by quantitative reverse transcription po-lymerase chain reaction (qRT-PCR). The functional role of DACT3-AS1 in GC was evaluated using *in vitro* and *in vivo* experiments including Transwell assay, 5-Ethynyl-2′-deoxyuridine (EdU) assay, immunoblotting, and xenograft tumor mouse model. Dual-luciferase reporter assay was performed to assess the association between genes.
Results: DACT3-AS1 was downregulated and involved in poor prognosis of patients with GC. The results from both *in vitro* and *in vivo* experiments showed that DACT3-AS1 suppressed cell proliferation, migration, and in-vasion through targeting miR-181a-5p/sirtuin 1 (SIRT1) axis. Additionally, DACT3-AS1 was transmitted from CAFs to GC cells mainly via exosomes. Exosomal DACT3-AS1 alleviated xenograft tumor growth. DACT3-AS1 conferred sensitivity of cancer cells to oxaliplatin through SIRT1-mediated ferroptosis both *in vitro* and *in vivo*. *Conclusions:* CAFs-derived exosomal DACT3-AS1 is a suppressive regulator in malignant transformation and oxaliplatin resistance. DACT3-AS1 could be used for diagnosis and treatment of GC.



DRUG RESISTANCE UPDATES
2023 Jan 31;68:100936
Impact Factor: 24.3

Materials and Methods

The mimics and inhibitors of indicated miR-181a-5p **(miR-181a-5p mimic and miR-181a-5p inhibitor, namely anti-miR-181a-5p)** and the corresponding negative controls **(mimic NC and inhibitor NC, namely anti-NC)** were constructed by **GenePharma**.

nature cell biology

miR-126 and miR-126* repress recruitment of mesenchymal stem cells and inflammatory monocytes to inhibit breast cancer metastasis

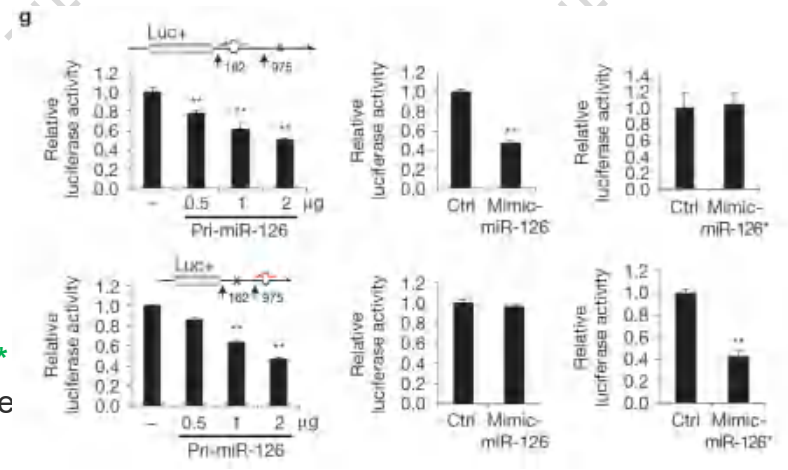
Yun Zhang[1,7], Pengyuan Yang[1,2,7], Tao Sun[1], Dong Li[2,8], Xin Xu[1], Yaocheng Rui[2], Chaoran Li[3], Mengyang Chong[1], Toni Ibrahim[4], Laura Mercatali[4], Dino Amadori[4], Xincheng Lu[5], Dong Xie[6], Qi-Jing Li[3,9] and Xiao-Fan Wang[1,9]

The tumour stroma is an active participant during cancer progression. Stromal cells promote tumour progression and metastasis through multiple mechanisms including enhancing tumour invasiveness and angiogenesis, and suppressing immune surveillance. We report here that miR-126/miR-126_, a microRNA pair derived from a single precursor, independently suppress the sequential recruitment of mesenchymal stem cells and in_ammatory monocytes into the tumour stroma to inhibit lung metastasis by breast tumour cells in a mouse xenograft model. miR-126/miR-126_ directly inhibit stromal cell-derived factor-1 alpha (Sdf-1_) expression, and indirectly suppress the expression of chemokine (C_C motif) ligand 2 (Ccl2) by cancer cells in an Sdf-1_- dependent manner. miR-126/miR-126_ expression is downregulated in cancer cells by promoter methylation of their host gene Eg_7. These _ndings determine how this microRNA pair alters the composition of the primary tumour microenvironment to favour breast cancer metastasis, and demonstrate a correlation between miR-126/126_ downregulation and poor metastasis-free survival of breast cancer patients.

Nature Cell Biology
2013 Mar; 15(3): 284-304
Impact Factor: 21.3

Materials and Methods

Mature miR-126 mimic, miR-126* mimic and **controlRNA duplexes** were obtained from **GenePharma**.



Bioactive Materials xxx (xxxx) xxx

Contents lists available at ScienceDirect

Bioactive Materials

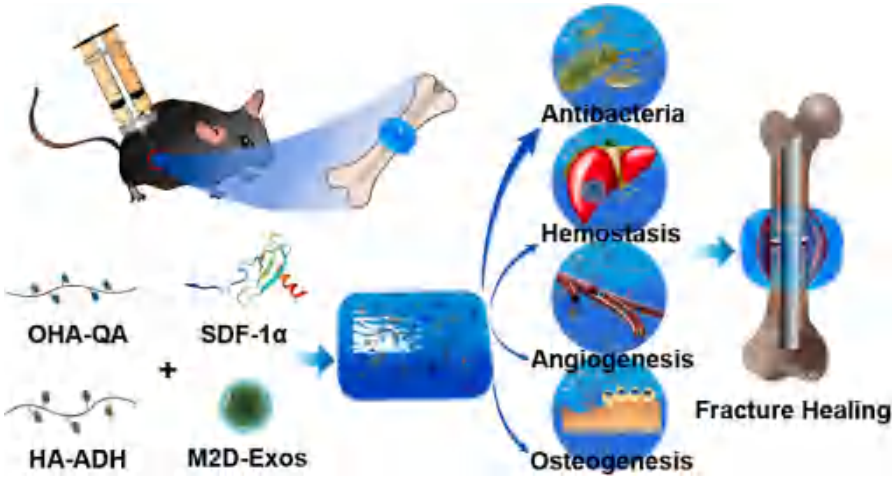
journal homepage: www.keaipublishing.com/en/journals/bioactive-materials

Multifunctional hydrogel enhances bone regeneration through sustained release of Stromal Cell-Derived Factor-1α and exosomes

Lang Chen [a,b,c,1], Chenyan Yu [a,b,1], Yuan Xiong [a,b,1], Kai Chen [a,d,1], Pei Liu [a,d], Adriana C. Panayi [e], Xiufeng Xiao [a,d,****], Qian Feng [a,d,f,***], Bobin Mi [a,b,**], Guohui Liu [a,b,*]

ABSTRACT

Fracture nonunion remains a great challenge for orthopedic surgeons. Fracture repair comprises of three phases, the inflammatory, repair and remodeling stage. Extensive advancements have been made in the field of bone repair, including development of strategies to balance the M1/M2 macrophage populations, and to improve osteogenesis and angiogenesis. However, such developments focused on only one or the latter two phases, while ignoring the inflammatory phase during which cell recruitment occurs. In this study, we combined Stromal Cell- Derived Factor-1α (SDF-1α) and M2 macrophage derived exosomes (M2D-Exos) with a hyaluronic acid (HA)- based hydrogel precursor solution to synthesize an injectable, self-healing, adhesive HA@SDF-1α/M2D-Exos hydrogel. The HA hydrogel demonstrated good biocompatibility and hemostatic ability, with the 4% HA hydrogels displaying great antibacterial activity against gram-negative E. coli and gram-positive S. aureus and Methicillin-resistant Staphylococcus aureus (MRSA). Synchronously and sustainably released SDF-1α and M2D- Exos from the HA@SDF-1α/M2D-Exos hydrogel enhanced proliferation and migration of human bone marrow mesenchymal stem cell (HMSCs) and Human Umbilical Vein Endothelial Cells (HUVECs), promoting osteo-genesis and angiogenesis both in vivo and in vitro. Overall, the developed HA@ SDF-1α/M2D-Exos hydrogel was compatible with the natural healing process of fractures and provides a new modality for accelerating bone repair by coupling osteogenesis, angiogenesis, and resisting infection at all stages.



Bioactive Materials
2022 Aug12;25:460-471
Impact Factor: 18.9

Materials and Methods

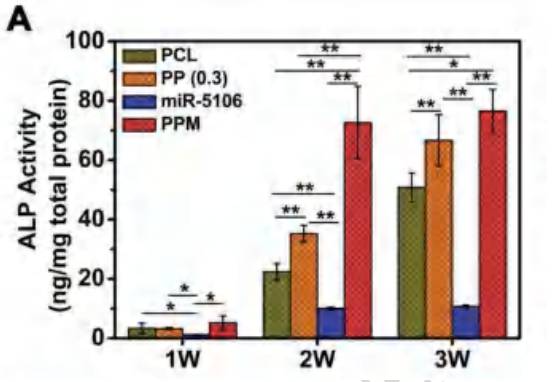
AgomiR-5106 and **antagomiR-5106** were synthesized by **GenePharma** (Shanghai, China).

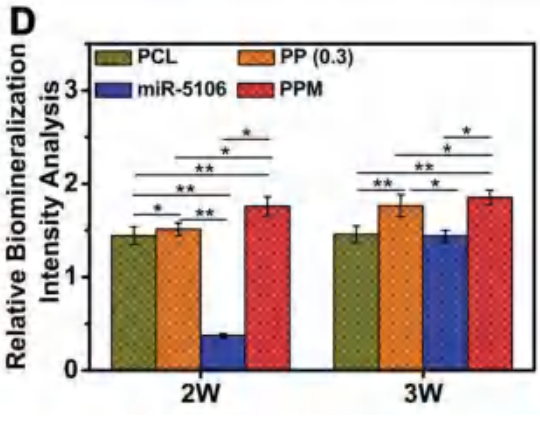
ADVANCED FUNCTIONAL MATERIALS
www.afm-journal.de

Biomimetic Elastomeric Bioactive Siloxane-Based Hybrid Nanofibrous Scaffolds with miRNA Activation: A Joint Physico-Chemical-Biological Strategy for Promoting Bone Regeneration

*Meng Yu, Yuzhang Du, Yong Han, and Bo Lei**

Rapid and efficient disease-induced or critical-size bone regeneration remains a challenge in tissue engineering due to the lack of highly bioactive biomaterial scaffolds. Physical structures such as nanostructures, chemical components such as silicon elements, and biological factors such as genes have shown positive effects on bone regeneration. Herein, a bioactive photoluminescent elastomeric silicate-based nanofibrous scaffold with sustained miRNA release is reported for promoting bone regeneration based on a joint physico chemical-biological strategy. Bioactive nanofibrous scaffolds are fabricated by cospinning poly (ε-caprolactone) (PCL), elastomeric poly (citrates-siloxane) (PCS), and bioactive osteogenic miRNA nanocomplexes (denoted PPM nanofibrous scaffolds). The PPM scaffolds possess uniform nanostructures, significantly enhanced tensile stress (≈15 MPa) and modulus (≈32 MPa), improved hydrophilicity (30–60°), controlled biodegradation, and strong blue fluorescence. Bioactive miRNA complexes are efficiently loaded into the nanofibrous matrix and exhibit long-term release for up to 70 h. The PPM scaffolds significantly promote the adhesion, proliferation, and osteoblast differentiation of bone marrow stem cells in vitro and enhanced rat cranial defect restoration (12 weeks) in vivo. This work reports an attractive joint physico-chemical-biological strategy for the design of novel cell/protein-free bioactive scaffolds for synergistic tissue regeneration.





Advanced Science
2019 Sep 29 ; 190613
Impact Factor: 19.0

Materials and Methods

In this study, PCL-PCS (0.3) was used as the substance to load miRNA.For preparing miRNA complexes-loaded nanofibrous scaffolds, the freeze-dried power of **miRNA** (**GenePharma**, China) .

Bioactive Materials 27 (2023) 1–14

Contents lists available at ScienceDirect

Bioactive Materials

journal homepage: www.keaipublishing.com/en/journals/bioactive-materials

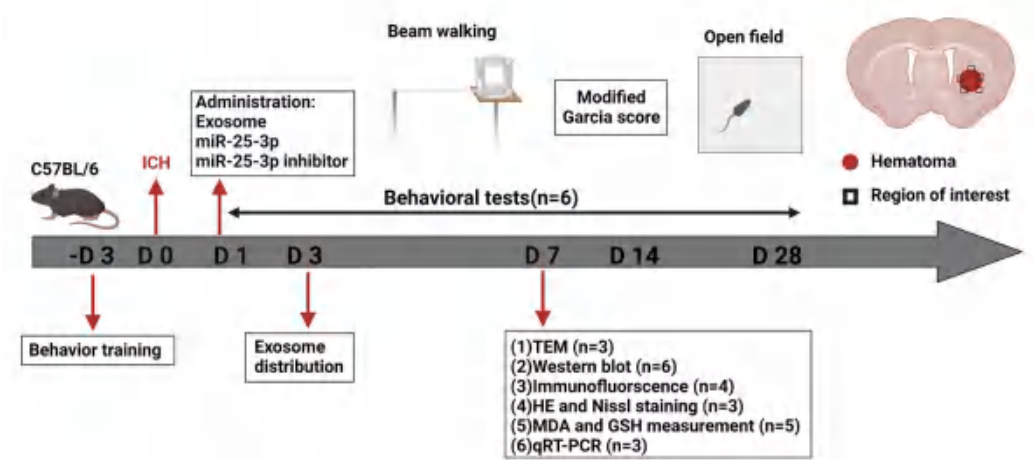
Exosomes from young healthy human plasma promote functional recovery from intracerebral hemorrhage via counteracting ferroptotic injury

Wenqin Yang [a,b,1], Ning Ding [a,1], Ran Luo [a,1], Qian Zhang [c], Zhenhua Li [d], Fengchun Zhao [a], Shuixian Zhang [a], Xuyang Zhang [a], Tengyuan Zhou [a], Haomiao Wang [a], Long Wang [a], Shengli Hu [a], Guixue Wang [e,f], Hua Feng [a], Rong Hu [a,f,*]

ABSTRACT

Intracerebral hemorrhage (ICH), as a type of life-threatening and highly disabled disease, has limited therapeutic approaches. Here, we show that exosomes derived from young healthy human plasma exhibiting typical exo-somes features could facilitate functional recovery of ICH mice. When these exosomes are intraventricularly delivered into the brain after ICH, they mainly distribute around the hematoma and could be internalized by neuronal cells. Strikingly, exosomes administration markedly enhanced the behavioral recovery of ICH mice through reducing brain injury and cell ferroptosis. MiRNA sequencing revealed that microRNA-25-3p (miR-25- 3p) was differentially expressed miRNA in the exosomes from young healthy human plasma, compared with exosomes from the old control. Importantly, miR-25-3p mimicked the treatment effect of exosomes on behavioral improvement, and mediated the neuroprotective effect of exosomes against ferroptosis in ICH. Furthermore, luciferase assay and western blotting data illustrated that P53 as assumed the role of a downstream effector of miR-25-3p, thereby regulating SLC7A11/GPX4 pathway to counteract ferroptosis. Taken together, these findings firstly reveal that exosomes from young healthy human plasma improve functional recovery through counter-acting ferroptotic injury by regulating P53/SLC7A11/GPX4 axis after ICH. Given the easy availability of plasma exosomes, our study provides a potent therapeutic strategy for ICH patients with quick clinical translation in the near future.

Materials and Methods
MiR-25-3p inhibitors and **negative control (NC)** were synthesized by **GenePharma**.



Bioactive Materials 27 (2023) 257–270

Contents lists available at ScienceDirect

Bioactive Materials

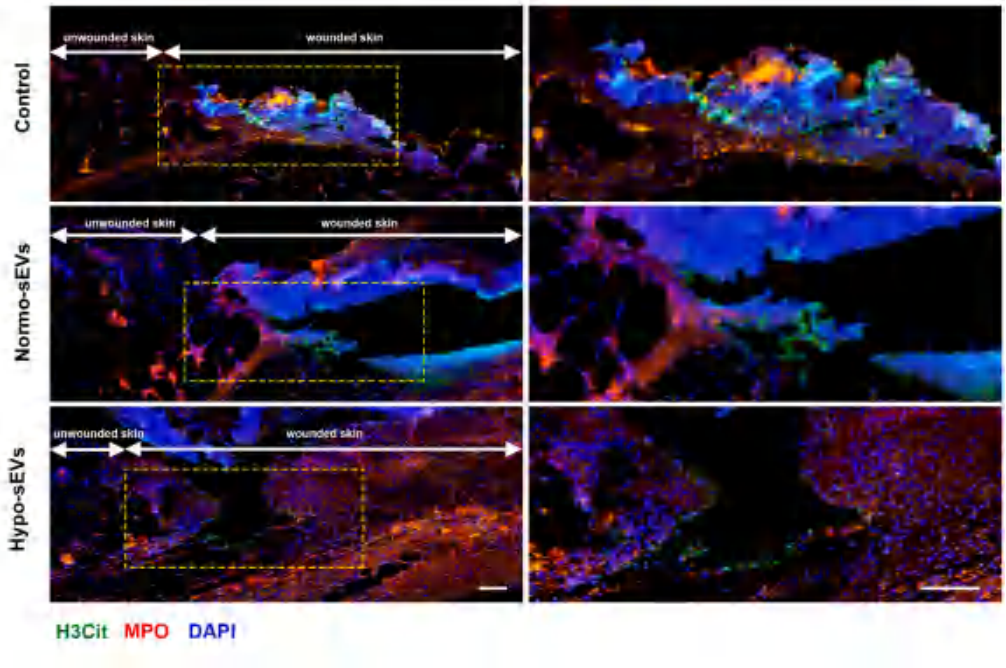
journal homepage: www.keaipublishing.com/en/journals/bioactive-materials

Novel neutrophil extracellular trap-related mechanisms in diabetic wounds inspire a promising treatment strategy with hypoxia-challenged small extracellular vesicles

Ziqiang Chu [a,b,1], Qilin Huang [c,1], Kui Ma [a,d,e,1], Xi Liu [a,d,e], Wenhua Zhang [a,d,e], Shengnan Cui [a,f], Qian Wei [a,b], Huanhuan Gao [a,b], Wenzhi Hu [a], Zihao Wang [a,b], Sheng Meng [a,b], Lige Tian [c], Haihong Li [g,*], Xiaobing Fu [a,b,c,d,e,f,**], Cuiping Zhang [a,d,e,***]

ABSTRACT

Neutrophil extracellular traps (NETs) have been considered a significant unfavorable factor for wound healing in diabetes, but the mechanisms remain unclear. The therapeutic application of small extracellular vesicles (sEVs) derived from mesenchymal stem cells (MSCs) has received considerable attention for their properties. Hypoxic preconditioning is reported to enhance the therapeutic potential of MSC-derived sEVs in regenerative medicine. Therefore, the aim of this study is to illustrate the detailed mechanism of NETs in impairment of diabetic wound healing and develop a promising NET-targeting treatment based on hypoxic pretreated MSC-derived sEVs (Hypo- sEVs). Excessive NETs were found in diabetic wounds and in high glucose (HG)-induced neutrophils. Further research showed that high concentration of NETs impaired the function of fibroblasts through activating endoplasmic reticulum (ER) stress. Hypo-sEVs efficiently promoted diabetic wound healing and reduced the excessive NET formation by transferring miR-17–5p. Bioinformatic analysis and RNA interference experiment revealed that miR-17–5p in Hypo-sEVs obstructed the NET formation by targeting TLR4/ROS/MAPK pathway. Additionally, miR-17–5p overexpression decreased NET formation and overcame NET-induced impairment in fibroblasts, similar to the effects of Hypo-sEVs. Overall, we identify a previously unrecognized NET-related mechanism in diabetic wounds and provide a promising NET-targeting strategy for wound treatment.



Bioactive Materials
2023 Apr 14;27:257-270
Impact Factor: 18.9

Materials and Methods

Small interfering RNAs (TLR4 siRNAs), miR-17–5p mimics, and **miR- 17–5p inhibitors** as well as their corresponding control oligonucleotides were purchased from **GenePharma**.

Nano Today 51 (2023) 101898

Contents lists available at ScienceDirect

Nano Today

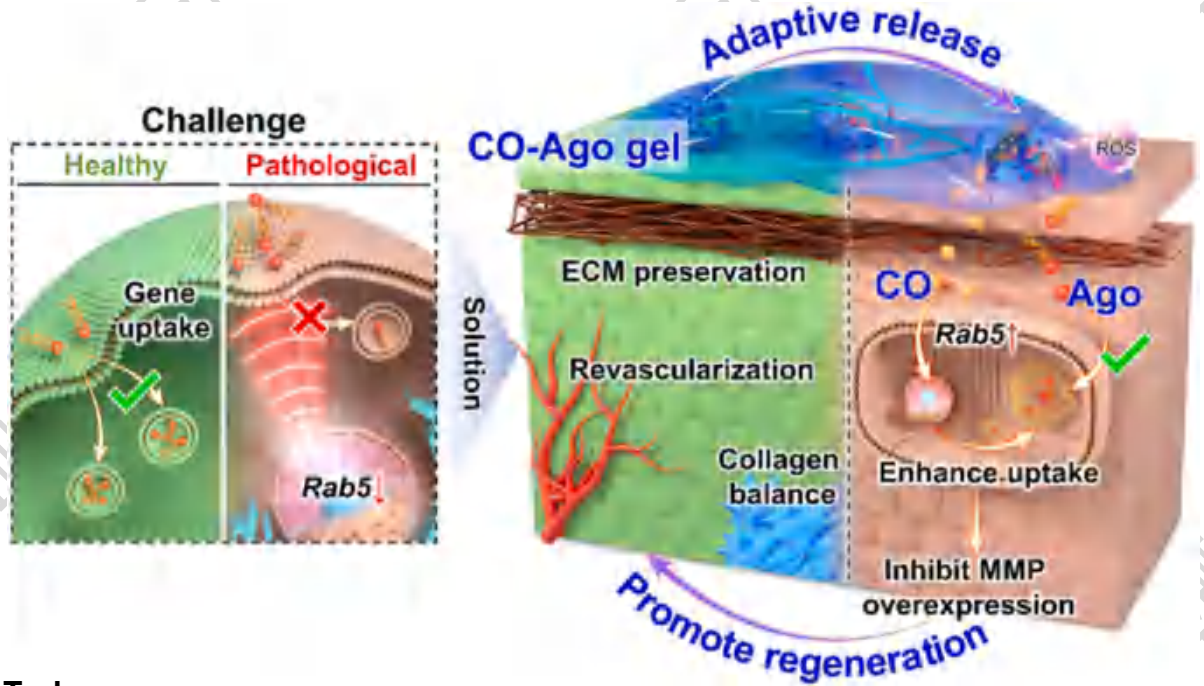
journal homepage: www.elsevier.com/locate/nanotoday

CO enhances agomir transfection under pathological conditions to inhibit MMP overexpression

Xin Jin [a,1], Zelin Ou [b,1], Xue Huang [b,1], Lin Shi [b], Rong Shi [b], Jue Wang [b], Jumin Yang [a], Kejing Fang [d], Jing Yang [b], Dalun Lv [e,f], Chang Wang [b], Zhixian Yuan [b], Wenhong li [f], Wenguang Liu [a], Gaoxing Luo [b,*], Jun Deng [b,*], Wei Wang [c,g,**]

A B S T R A C T

Cellular uptake of exogenous nucleic acids is inhibited in pathological tissues accompanied by excessive expression of matrix metalloproteinases (MMPs). We show that CO, as a regulator of membrane function, can reactivate uptake of agomir (Ago) in pathological condition via RAB5-mediated endocytic pathway. Herein, a responsive nanoparticle-crosslinked injectable hydrogel (CO-Ago gel) was engineered as a pro-totype for co-delivering CO and Ago to inhibit MMP overexpression in accordance with the disease severity. Compared to a typical matrix-enhanced gene therapy (Ago gel), CO-Ago gel significantly promoted Ago uptake, achieving an order of magnitude improvement of targeted gene expression under pathological conditions (11.2-fold for cardiomyocyte and 15.3-fold for primary fibroblasts). The therapeutic effect of CO- Ago gel on MMP overexpression was assessed in rat models of myocardial ischemia reperfusion and diabetic skin wound healing. The results suggest CO-enhanced transfection could contribute to the development of next-generation adjuvants for gene-based therapies and vaccines in vivo.



Nano Today
2023 Jan;51:101898
Impact Factor: 17.4

Materials and Methods

Ago was synthesized by **GenePharma** (Shanghai, China).

ACS NANO

www.acsnano.org

ARTICLE

Mesenchymal Stem Cell Derived Exosomes Repair Uterine Injury by Targeting Transforming Growth Factor-β Signaling

Huidong Liu, Xiao Zhang, Mengtong Zhang, Sichen Zhang, Jin Li, Yingmin Zhang, Qingyu Wang, Jian Ping Cai, Ke Cheng,* and Shaowei Wang*

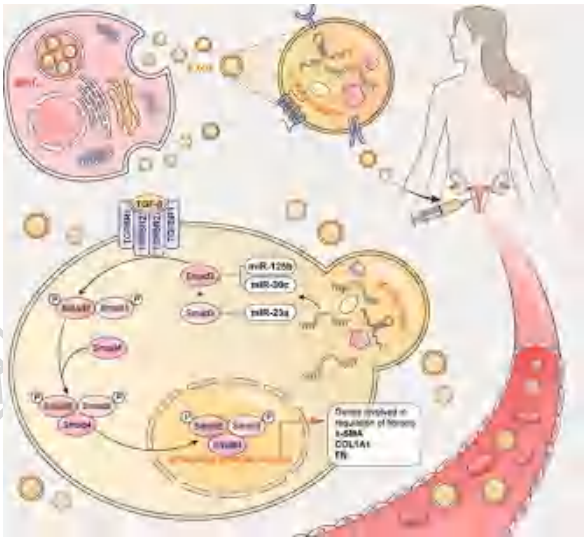
Cite This: *ACS Nano* 2024, 18, 3509−3519

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Intrauterine adhesions (IUA) refer to adhesions within the uterine cavity and cervix caused by injuries from uterine surgery. They are a significant cause of female infertility. Exosomes derived from mesenchymal stem cells (MSCs) play an active role in the treatment of IUA. However, the mechanism by which they reduce fibrosis in the damaged endometrium remains unclear. In this paper, we demonstrate that exosomes derived from placental mesenchymal stem cells (PMSCs) can restore uterine functions and improve the fertility rate of injured animals. This is achieved by promoting cell proliferation, increasing endometrial thickness, and reversing fibrosis. Regarding the molecular mechanism behind these therapeutic effects, we identify three specific miRNAs, namely, miR-125b-5p, miR-30c-5p, and miR-23a-3p, enriched in PMSC-exosomes, as the key players in the treatment of IUA. Specifically, miR-125b-5p/miR-30c-5p and miR-23a-3p inhibit the expression of smad2 and smad3 by targeting their 3′-untranslated regions, resulting in the downregulation of the transforming growth factor-β (TGF-β)/smad signalingpathway and the reversal of fibrosis. Notably, the safety of PMSC-exosomes in intrauterine treatment was also been confirmed. In conclusion, we illustrate that exosomes derived from PMSCs possess the capability to repair endometrial damage and enhance fertility in injured animals by regulating the TGF-β/smad pathway via miR-125b-5p, miR-30c-5p, and miR-23a-3p. This provides insights into the precision treatment of IUA through exosome-based cell-free therapy.

KEYWORDS: *intrauterine adhesion, PMSCs, exosomes, miRNAs, TGF-β*



ACS Nano
2024 Jan 30;18(4):3509-3519
Impact Factor: 17.1

Materials and Methods

Additionally, **miR-125b-5p mimics**, **miR-30c-5p mimics**, **miR-23a-3p mimics**, and **negative control (NC)** were sourced from **GenePharma** (Shanghai, China).

nature COMMUNICATIONS

ARTICLE

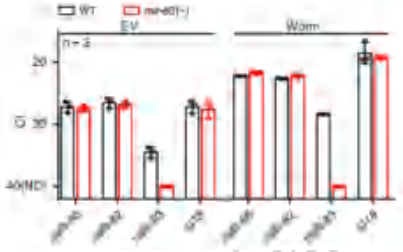
https://doi.org/10.1038/s41467-019-12821-2 OPEN

A secreted microRNA disrupts autophagy in distinct tissues of Caenorhabditis elegans upon ageing

Yifei Zhou[1], Xueqing Wang[1], Mengjiao Song[1], Zhidong He[1], Guizhong Cui[1], Guangdun Peng[2,3], Christoph Dieterich[4], Adam Antebi[5,6], Naihe Jing[1] & Yidong Shen[1*]

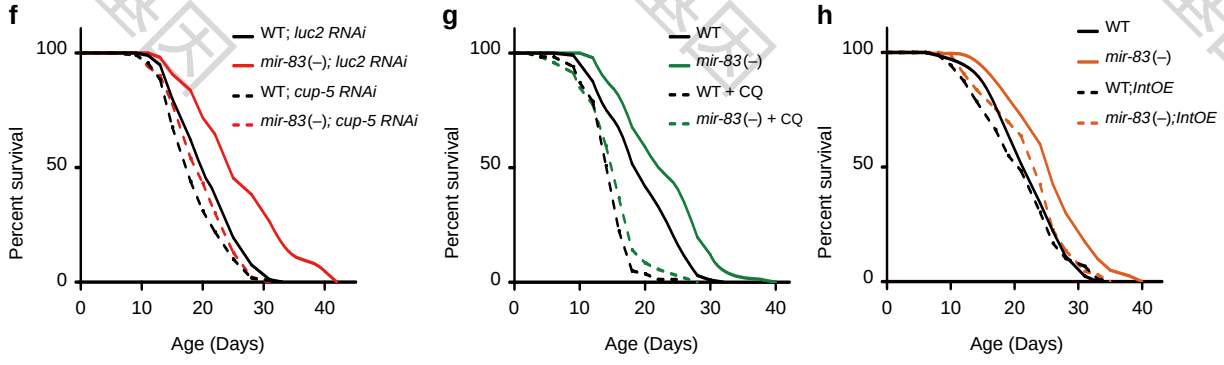
Macroautophagy, a key player in protein quality control, is proposed to be systematically impaired in distinct tissues and causes coordinated disruption of protein homeostasis and ageing throughout the body. Although tissue-specific changes in autophagy and ageing have been extensively explored, the mechanism underlying the inter-tissue regulation of autop-hagy with ageing is poorly understood. Here, we show that a secreted microRNA, mir-83/miR-29, controls the age-related decrease in macroautophagy across tissues in Caenorhabditis elegans. Upregulated in the intestine by hsf-1/HSF1 with age, mir-83 is transported across tissues potentially via extracellular vesicles and disrupts macroautophagy by suppressing CUP-5/MCOLN, a vital autophagy regulator, autonomously in the intestine as well as non-autonomously in body wall muscle. Mutating mir-83 thereby enhances macroautophagy in different tissues, promoting protein homeostasis and longevity. These findings thus identify a microRNA-based mechanism to coordinate the decreasing macroautophagy in various tis-sues with age.

Nature communications
2019 Oct 23 ; 10:4827
Impact Factor: 16.6



Materials and Methods

MicroRNA mimics were ordered from **GenePharma**.



nature COMMUNICATIONS

ARTICLE

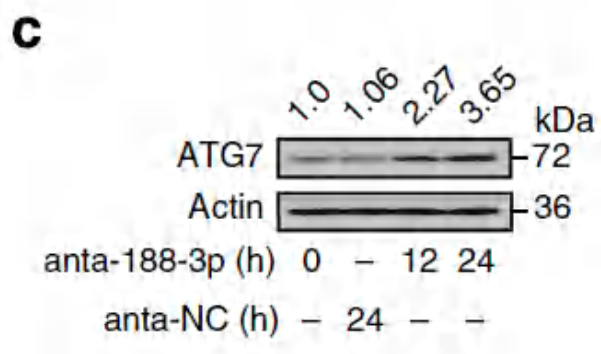
Received 10 Jul 2014 | Accepted 26 Feb 2015 | Published 10 Apr 2015

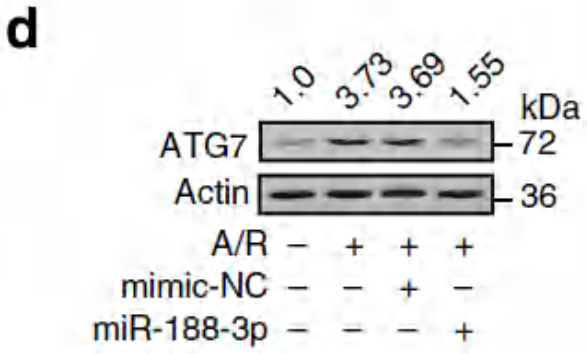
DOI: 10.1038/ncomms7779

APF lncRNA regulates autophagy and myocardial infarction by targeting miR-188-3p

Kun Wang[1], Cui-Yun Liu[2], Lu-Yu Zhou[1], Jian-Xun Wang[1], Man Wang[1], Bing Zhao[1], Wen-Ke Zhao[1], Shi-Jun Xu[3], Li-Hua Fan[2], Xiao-Jie Zhang[2], Chang Feng[2], Chao-Qun Wang[1], Yan-Fang Zhao[1] & Pei-Feng Li[1]

The abnormal autophagy is associated with a variety of cardiovascular diseases. Long noncoding RNAs (lncRNAs) are emerging as new factors in gene regulation, but how lncRNAs operate in the regulation of autophagy in the heart is unclear. Here we report that a long noncoding RNA, named autophagy promoting factor (APF), can regulate autophagic cell death by targeting miR-188-3p and ATG7. The results show that miR-188-3p suppresses autophagy and myocardial infarction by targeting ATG7. Further, we find that APF lncRNA regulates miR-188-3p, and thus affects ATG7 expression, autophagic cell death and myocardial infarction. Our present study reveals a novel regulating model of autophagic programme, which comprises APF, miR-188-3p and ATG7 in the heart. Modulation of their levels may serve as potential targets and diagnostic tools for novel therapeutic strategies of myocardial infarction and heart failure.





Nature communications
2015 Apr 10;6:6779
Impact Factor: 16.6

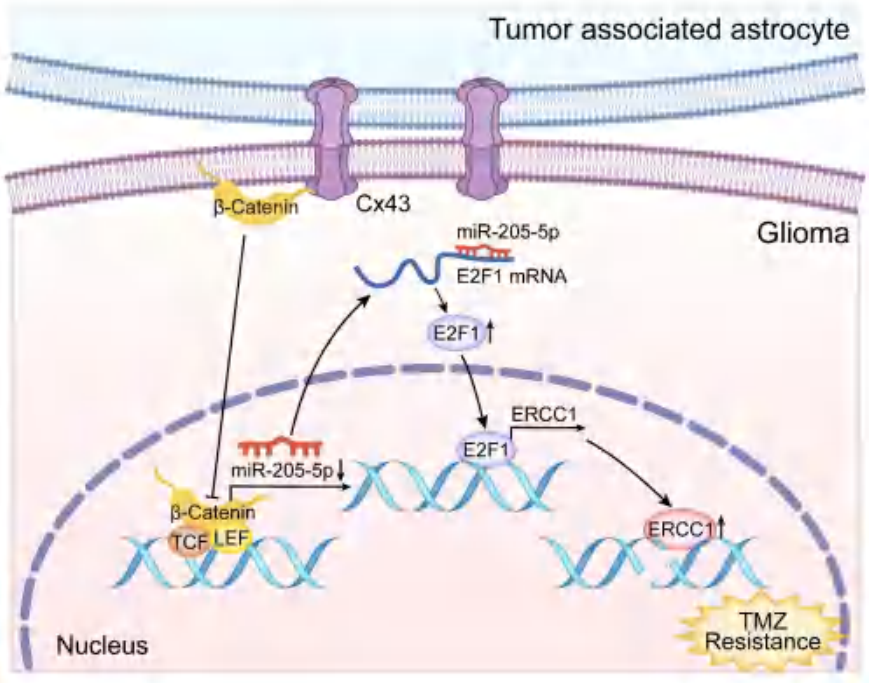
Materials and Methods

The chemically modified **antagomirs complementary to miR-188-3p** designed to inhibit endogenous miR-188-3p expression,and the **antagomir-negative control (antagomir-NC)** was **obtained from GenePharma.**

Glioma–Astrocyte connexin43 confers temozolomide resistance through activation of the E2F1/ERCC1 axis

Yanping Gui[1†], Hongkun Qin[1†], Xinyu Zhang[1], Qianqian Chen[1], Fangyu Ye[1], Geng Tian[1], Shihe Yang[2], Yuting Ye[2], Di Pan[3], Jieying Zhou[5], Xiangshan Fan[4*], Yajing Wang[1*], Li Zhao[1,2*]

Background: Glioma is the most prevalent and lethal tumor of the central nervous system. Routine treatment with Temozolomide (TMZ) would unfortunately result in inevitable recurrence and therapy resistance, severely limiting therapeutic efficacy. Tumor associated astrocytes (TAAs) are key components of the tumor microenvironment and increasing evidence has demonstrated that aberrant expression of Connexin43 (Cx43) was closely associated with glioma progression and TMZ resistance. However, the specific role of Cx43 in mediating TMZ resistance through glioma and astrocyte interactions has not been fully explored.



NEURO-ONCOLOGY
Fudan University user on 20 December 2024
Impact Factor: 16.4

Materials and Methods
The **miR-205-5p mimic** (miR-205-5p) and the human miRNA negative control **(miR-NC)** were purchased from **GenePharma** (Shanghai, China)

JCI The Journal of Clinical Investigation

Platelet-derived miR-223 promotes a phenotypic switch in arterial injury repair

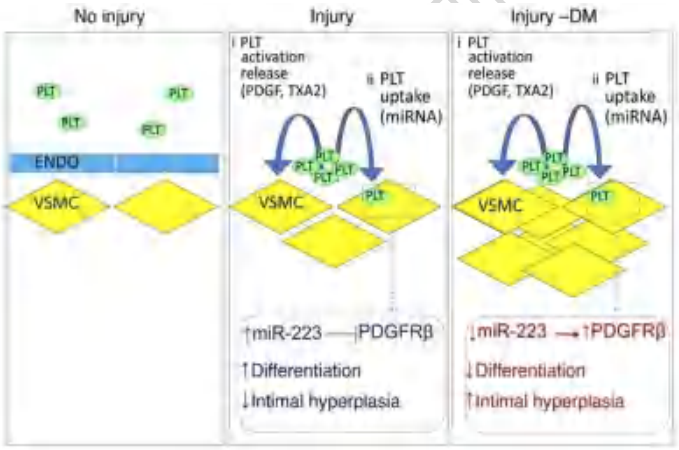
Zhi Zeng[1], Luoxing Xia,[1] Xuejiao Fan,[1] Allison C. Ostriker,[2] Timur Yarovinsky,[2] Meiling Su,[1] Yuan Zhang,[1] Xiangwen Peng,[1] Yi Xie,[2] Lei Pi,[3] Xiaoqiong Gu,[4] Sookja Kim Chung,[5] Kathleen A. Martin,[2] Renjing Liu,[6,7] John Hwa,[2] and Wai Ho Tang[1]

Upon arterial injury, endothelial denudation leads to platelet activation and delivery of multiple agents (e.g., TXA2, PDGF), promoting VSMC dedifferentiation and proliferation (intimal hyperplasia) during injury repair. The process of resolution of vessel injury repair, and prevention of excessive repair (switching VSMCs back to a differentiated quiescent state), is poorly understood. We now report that internalization of APs by VSMCs promotes resolution of arterial injury by switching on VSMC quiescence. Ex vivo and in vivo studies using lineage tracing reporter mice (PF4-cre × mT/mG) demonstrated uptake of GFPlabeled platelets (mG) by mTomato red–labeled VSMCs (mT) upon arterial wire injury. Genome-wide miRNA sequencing of VSMCs cocultured with APs identified significant increases in platelet-derived miR-223. miR-223 appears to directly target PDGFRβ (in VSMCs), reversing the injury-induced dedifferentiation. Upon arterial injury, platelet miR-223–KO mice exhibited increased intimal hyperplasia, whereas miR-223 mimics reduced intimal hyperplasia. Diabetic mice with reduced expression of miR-223 exhibited enhanced VSMC dedifferentiation and proliferation and increased intimal hyperplasia. Our results suggest that horizontal transfer of latelet-derived miRNAs into VSMCs provides a novel mechanism for regulating VSMC phenotypic switching. Platelets thus play a dual role in vascular injury repair, initiating an immediate repair process and, concurrently, a delayed process to prevent excessive repair.

The Journal of Clinical Investigation
2019 Jan 15; 129(3):1372-1386
Impact Factor: 15.9

Materials and Methods

To determine the functional role of target miRNAs in VSMCs, VSMCs were transfected with **miR-143 mimic, miR-145 mimic, miR-223 mimic,** or **NC** (**GenePharma**) at 100 nM by using Lipofectamine RNAiMAX reagent (Invitrogen) according to the manufacturer's protocols. **The micrON miRNA agomiRs** were purchased from Shanghai **GenePharma** Co.

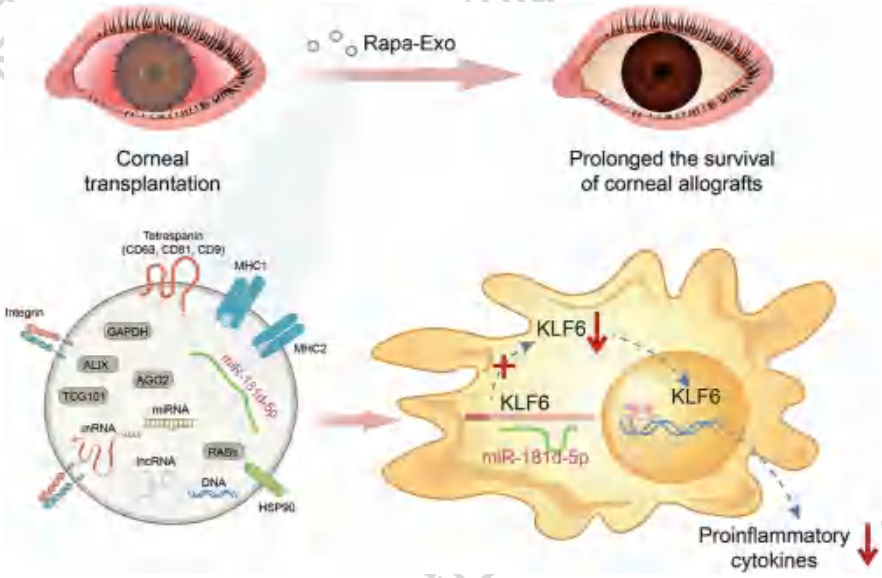


ADVANCED SCIENCE Open Access
www.advancedscience.com

Exosomal miR-181d-5p Derived from Rapamycin-Conditioned MDSC Alleviated Allograft Rejection by Targeting KLF6

*Chao Wei, Yaru Sun, Fanxing Zeng, Xiunian Chen, Li Ma, Xiaoxue Liu, Xiaolin Qi, Weiyun Shi, and Hua Gao**

Immune rejection and side effects of long-term administration of immunosuppressants are the two major obstacles to allograft acceptance and tolerance. The immunosuppressive extracellular vesicles (EVs)-based approach has been proven to be effective in treating autoimmune/inflammatory disorders. Herein, the anti-rejection advantage of exosomes (Rapa-Exo) from rapamycin-conditioned myeloid-derived suppressor cells (MDSCs) over exosomes (Exo-Nor) from the untreated MDSCs is shown. The exosomal small RNA sequencing and loss-of-function assays reveal that the anti-rejection effect of Rapa-Exo functionally relies on miR-181d-5p. Through target prediction and double-luciferase reporter assay, Kruppel-like factor (KLF) 6 is identified as a direct target of miR-181d-5p. Finally, KLF6 knockdown markedly resolves inflammation and prolongs the survival of corneal allografts. Taken together, these findings support that Rapa-Exo executes an anti-rejection effect, highlighting the immunosuppressive EVs-based treatment as a promising approach in organ transplantation.



Advanced Science
2023 Dec;10(34):e2304922
Impact Factor: 15.1

Materials and Methods

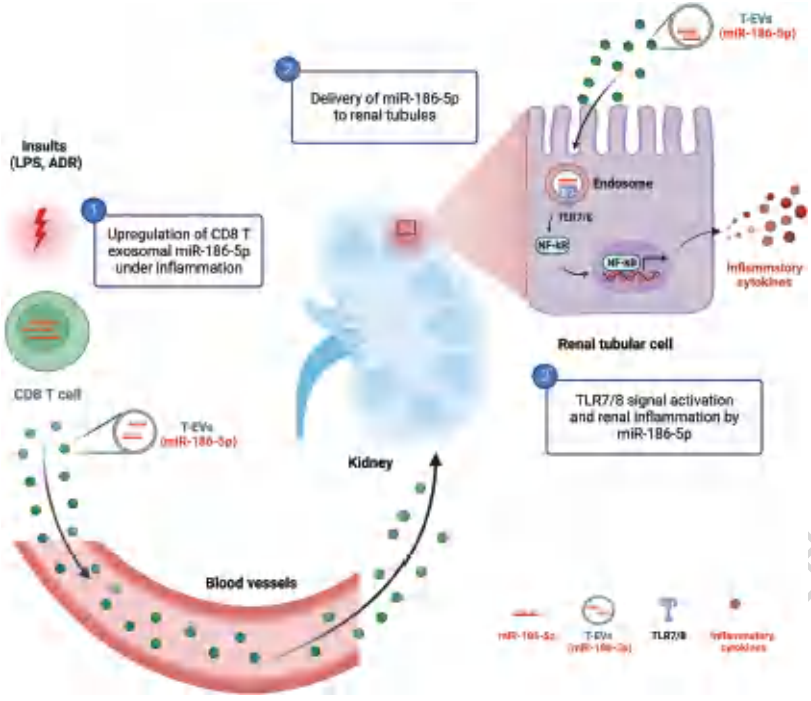
the recipient mice received 10 μL mixture containing Rapa-Exo and **miR-181d-5p an-tagomir** (1000 μgmL−1, **GenePharma**, Shanghai, China) through subcon-junctival injection on postoperative days 3, 6, and 9.
The recipient mice were subconjunctivally trans-fected with **siKLF6** (1000 μgmL−1, **GenePharma**, Shanghai, China) on postoperative days 3, 6, and 9, and PBS was used as the control.

ADVANCED SCIENCE Open Access
www.advancedscience.com

CD8 T Cell-Derived Exosomal miR-186-5p Elicits Renal Inflammation via Activating Tubular TLR7/8 Signal Axis

Xiaodong Xu, Shuang Qu, Changming Zhang, Mingchao Zhang, Weisong Qin, Guisheng Ren, Hao Bao, Limin Li, Ke Zen, and Zhihong Liu**

T cells play an important role in the development of focal segmental glomerulosclerosis (FSGS). The mechanism underlying such T cell-based kidney disease, however, remains elusive. Here the authors report that activated CD8 T cells elicit renal inßammation and tissue injury via releasing miR-186-5p-enriched exosomes. Continuing the cohort study identifying the correlation of plasma level of miR-186-5p with proteinuria in FSGS patients, it is demonstrated that circulating miR-186-5p is mainly derived from activated CD8 T cell exosomes. Renal miR-186-5p, which is markedly increased in FSGS patients and mice with adriamycin-induced renal injury, is mainly delivered by CD8 T cell exosomes. Depleting miR-186-5p strongly attenuates adriamycin-induced mouse renal injury. Supporting the function of exosomal miR-186-5p as a key circulating pathogenic factor, intravenous injection of miR-186-5p or miR-186-5p-containing T cell exosomes results in mouse renal inßammation and tissue injury. Tracing the injected T cell exosomes shows their preferential distribution in mouse renal tubules, not glomerulus. Mechanistically, miR-186-5p directly activates renal tubular TLR7/8 signal and initiates tubular cell apoptosis. Mutating the TLR7-binding sequence on miR-186-5p or deleting mouse TLR7 largely abolishes renal tubular injuries induced by miR-186-5p or adriamycin. These Pndings reveal a causative role of exosomal miR-186-5p in T cell-mediated renal dysfunction.



Advanced Science
2023 Sep 3;10(25):e2301492
Impact Factor: 15.1

Materials and Methods

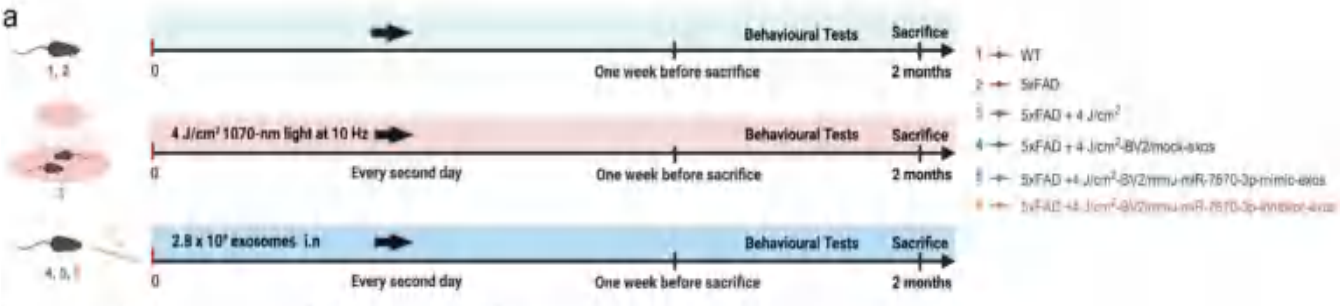
To calculate the absolute expression levels of miR-186-5p, synthetic **miR-186-5p oligonucleotides** (**Genepharma**, Shanghai, China) at known concentrations were used to build a standard curve and formula, then the absolute amount of miR-186-5p was calculated.

ADVANCED SCIENCE
Open Access
www.advancedscience.com

Exosomes Derived from M2 Microglial Cells Modulated by 1070-nm Light Improve Cognition in an Alzheimer's Disease Mouse Model

Chengwei Chen, Yuting Bao, Lu Xing, Chengyong Jiang, Yu Guo, Shuangmei Tong, Jiayi Zhang, Liang Chen,* and Ying Mao**

Near-infrared photobiomodulation has been identified as a potential strategy for Alzheimer's disease (AD). However, the mechanisms underlying this therapeutic effect remain poorly characterize. Herein, it is illustrate that 1070-nm light induces the morphological alteration of microglia from an M1 to M2 phenotype that secretes exosomes, which alleviates the β-amyloid burden to improve cognitive function by ameliorating neuroinflammation and promoting neuronal dendritic spine plasticity. The results show that 4 J cm^{-2} 1070-nm light at a 10-Hz frequency prompts microglia with an M1 inflammatory type to switch to an M2 anti-inflammatory type. This induces secretion of M2 microglial-derived exosomes containing miR-7670-3p, which targets activating transcription factor 6 (ATF6) during endoplasmic reticulum (ER) stress. Moreover, it is found that miR-7670-3p reduces ATF6 expression to further ameliorate ER stress, thus attenuating the inflammatory response and protecting dendritic spine integrity of neurons in the cortex and hippocampus of 5xFAD mice, ultimately leading to improvements in cognitive function. This study highlights the critical role of exosomes derive from 1070-nm light-modulated microglia in treating AD mice, which may provide a theoretical basis for the treatment of AD with the use of near-infrared photobiomodulation.



Advanced Science
2023 Sep 13:e2304025
Impact Factor: 15.1

Materials and Methods

Mimics and inhibitors of mmu-miR-7670-3p were synthesized by **GenePharma** (Suzhou, China).

Chemical Engineering Journal 457 (2023) 141315

Contents lists available at ScienceDirect

Chemical Engineering Journal

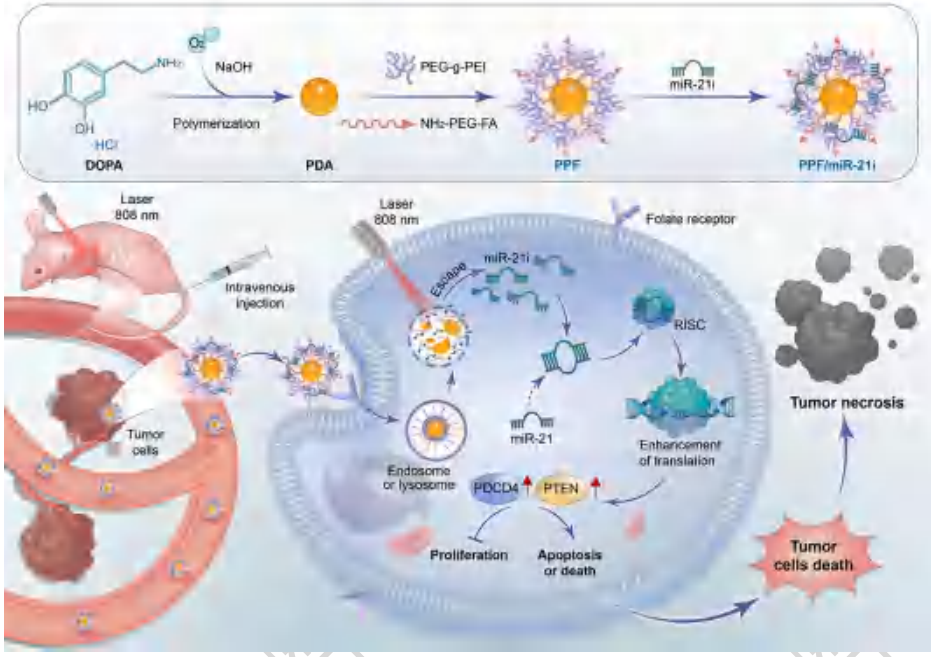
journal homepage: www.elsevier.com/locate/cej

Tumor-targeting gene-photothermal synergistic therapies based on multifunctional polydopamine nanoparticles

Ying Zhang [a,b], Shiqi Tang [b], Xiaoyun Feng [c], Xiang Li [b], Jingyu Yang [b], Qiqi Liu [b], Meirong Li [a,b], Yujuan Chai [b], Chengbin Yang [b,*], Suxia Lin [d,*], Jia Liu [a,*]

A B S T R A C T

Gene-photothermal synergistic therapy shows great potential for breast cancer treatment. Polydopamine (PDA) is a widely used photothermal therapeutic agent and delivery vector. Herein, a tumor-targeted nanoplatform of PDA grafted with PEG-g-PEI and folic acid (FA) (PPF) was elaborately fabricated for precisely intracellular de-livery of microRNA-21 inhibitor (miR-21i). The multifunctional nanoplatform possessed a narrow size distri-bution, good stability, and excellent photothermal conversion efficiency. *In vitro* FA modification more effectively promoted the intracellular uptake of the nanocomposites by MCF-7 and 4T1 cells, and facilitated the miR-21i escape from the lysosomes, thus significantly inhibiting cell proliferation and inducing tumor cell apoptosis. More importantly, *in vivo* satisfactory tumor growth inhibition effects were observed in PPF/miR21 and laser co-treated group due to the near-infrared (NIR) responsive PDA and conjugated tumor-targeting FA. In conclusion, this nanocarrier delivery system exhibit enhanced anti-cancer effect, indicating the outstanding advantages of synergistic therapy by intergrating photothermal, gene, and accurate cancer-targeted treatment into one system, which will provide a valuable strategy for the clinical treatment of breast cancer.



CHEMICAL ENGINEERING JOURNAL
2023 Jan;457:141315
Impact Factor: 15.1

Materials and Methods

miR- 21i, Cy3-miR-21i, FAM-miR-21i, miR-NC, and all the **primer sequences** were synthesized by Shanghai **GenePharma**.

Chemical Engineering Journal 452 (2023) 139553

Contents lists available at ScienceDirect

Chemical Engineering Journal

journal homepage: www.elsevier.com/locate/cej

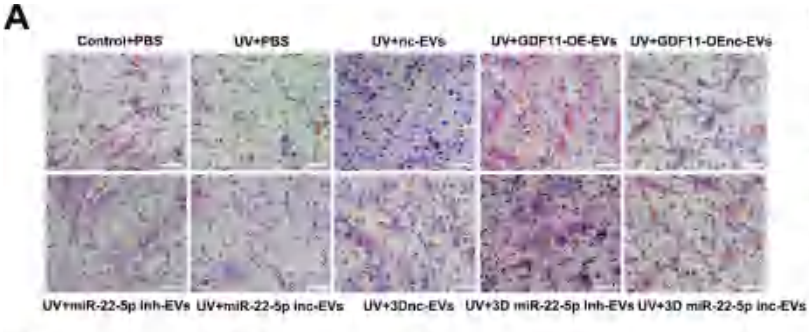
Extracellular vesicles derived from human dermal fibroblast effectively ameliorate skin photoaging via miRNA-22-5p-GDF11 axis

Hao Wu [a,1], Jie Wang [a,1], Yue Zhao [a], Youyou Qin [a], Xi Chen [b], Yongting Zhou [a], Hao Pang [a], Zidi Xu [a], Xueyi Liu [a], Ying Yu [a], Zhibo Xiao [a,*]

[a] Department of Plastic and Aesthetic Surgery, the Second Affiliated Hospital of Harbin Medical University, Harbin 150081, People's Republic of China
[b] Department of General Surgery, the Second Affiliated Hospital of Harbin Medical University, Harbin 150081, People's Republic of China

Abstract

Aging is the leading cause of several degenerative diseases. Photoaging due to ultraviolet (UV) exposure accounts for more than 80% of facial aging, which is a complex and incompletely understood process. Here, we explored the mechanisms of skin photoaging and increased chromatin accessibility in UVB-irradiated human dermal fi-broblasts (UVB-HDFs). Especially, we investigated key skin photoaging pathways and inflammatory responses characterized by exons occupied by active and repressive chromatin marks. mRNA sequencing revealed changes in mRNA expression levels—1180 genes were upregulated, and 1080 genes were downregulated in UVB-HDFs. In addition, 393 differentially expressed microRNAs (miRNAs) were detected in the extracellular vesicles (EVs) derived from UVB-HDFs; among these miRNAs, miRNA-22-5p (miR-22-5p) was significantly upregulated and targeted growth differentiation factor 11 (GDF11). We determined that GDF11 expression in human skin tissues was strongly associated with age, and GDF11 overexpression in HDFs attenuated UVB-induced damage. Furthermore, when EVs derived from miR-22-5p-inhibited HDF spheroids were administered to UVB-irradiated nude mice, they ameliorated skin photoaging. These findings suggest that the downregulation of miR-22-5p in EVs of HDFs can regulate GDF11 to treat skin photoaging. Our study provides a potential cell-free approach for promoting skin repair and treating skin photoaging.



CHEMICAL ENGINEERING JOURNAL
2023 Jan;452:139553
Impact Factor: 15.1

Materials and Methods

The **miRNA-22-5p mimics (mic), negative control (nc), miRNA-22- 5p inhibitor (Inh),** and **inhibitor negative control (Inc)** were obtained from **GenePharma** Biotechnology (Suzhou, China).

3580–3593 Nucleic Acids Research, 2019, Vol. 47, No. 7 Published online 1 March 2019
doi: 10.1093/nar/gkz141

circ-Sirt1 controls NF-κB activation via sequence-specific interaction and enhancement of SIRT1 expression by binding to miR-132/212 in vascular smooth muscle cells

Peng Kong[1,†], Yuan Yu[1,†], Lu Wang[1], Yong-Qing Dou[1], Xu-Hui Zhang[1], Yan Cui[1], Hai-Yue Wang[1], Yu-Tao Yong[1], Ya-Bin Liu[2], Hai-Juan Hu[3], Wei Cui[3], Shao-Guang Sun[1], Bing-Hui Li[2], Fan Zhang[1] and Mei Han[1,*]

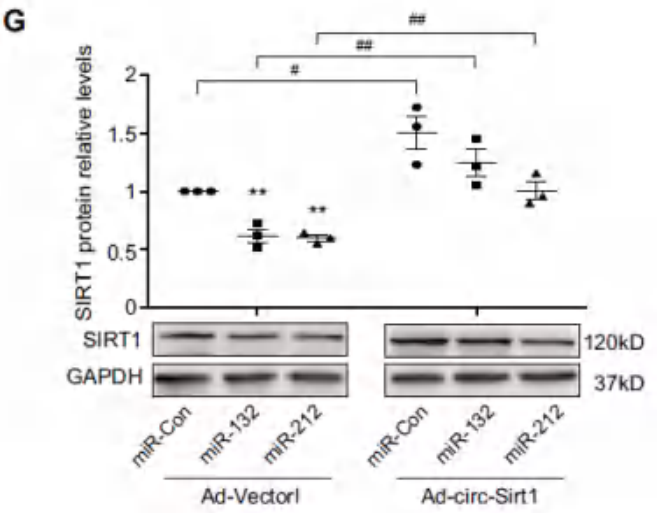
ABSTRACT

NF- kB-mediated inflammatory phenotypic switching of vascular smooth muscle cells (VSMCs) plays a central role in atherosclerosis and neointimal formation. However, little is known about the roles of circRNAs in the regulation of NF-kB signaling. Here, we identify the involvement of circ-Sirt1 that was one of transcripts of SIRT1 host gene in VSMC inflammatory response and neointimal hyperplasia. First, in the cytoplasm, circ-Sirt1 directly interacts with and sequesters NF-kB p65 from nuclear translocation induced by TNF-α in a sequence-dependent manner. The inhibitory complex of circ-Sirt1-NF-kB p65 is not dependent on IkBα. Second, circ-Sirt1 binds to miR- 132/212 that interferes with SIRT1 mRNA, and facilitates the expression of host gene SIRT1. Increased SIRT1 results in deacetylation and inactivation of the nuclear NF-kB p65. These findings illustrate that circ- Sirt1 is a novel non-coding RNA regulator of VSMC phenotype.

Nucleic Acids Research
2019 Mar; 47(7): 3580-3593
Impact Factor: 14.9

Materials and Methods

Human embryonic kidney 293A cells were co-transfected with a **miR132/212 mimic** (**GenePharma**) or NC mimic combined with 400 ng luciferase reporter or an empty vector.



Acta Pharmaceutica Sinica B 2023;13(6):2645e2662

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com

ORIGINAL ARTICLE

The suppression of cervical cancer ferroptosis by macrophages: The attenuation of ALOX15 in cancer cells by macrophages-derived exosomes

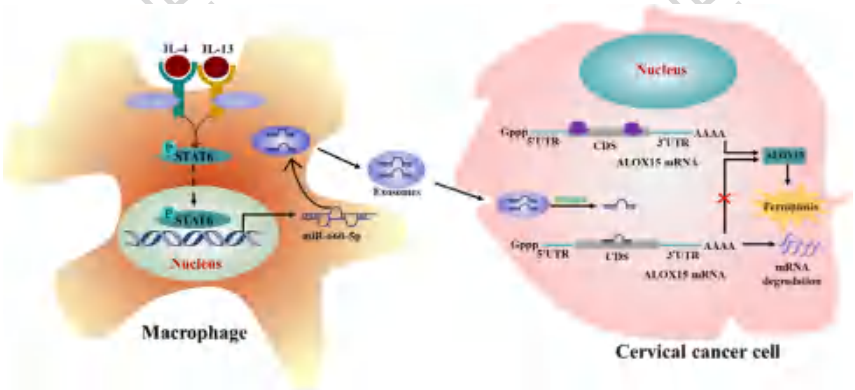
Yanlin Luo[a,b,c,†], Yibing Chen[d,*,†], Huan Jin[b], Benxin Hou[e], Hongsheng Li[f], Xiang Li[g], Lingfeng Liu[b], Yuan Zhou[b], Yonghua Li[b], Yong Sang Song[h], Quentin Liu[i], Zhengzhi Zou[b,j,*]

Abstract

Induction of cancer cell ferroptosis has been proposed as a potential treatment in several cancer types. Tumor-associated macrophages (TAMs) play a key role in promoting tumor malignant progression and therapy resistance. However, the roles and mechanisms of TAMs in regulating tumor ferroptosis is still unexplored and remains enigmatic. This study shows ferroptosis inducers has shown therapeutic outcomes in cervical cancer in vitro and in vivo. TAMs have been found to suppress cervical cancer cells ferroptosis. Mechanistically, macrophage-derived miRNA-660-5p packaged into exosomes are transported into cancer cells. In cancer cells, miRNA-660-5p attenuates ALOX15 expression to inhibit ferroptosis. Moreover, the upregulation of miRNA-660-5p in macrophages depends on autocrine IL4/IL13-activated STAT6 pathway. Importantly, in clinical cervical cancer cases, ALOX15 is negatively associated with macrophages infiltration, which also raises the possibility that macrophages reduce ALOX15 levels in cervical cancer. Moreover, both univariate and multivariate Cox analyses show ALOX15 expression is independent prognostic factor and positively associated with good prognosis in cervical cancer. Altogether, this study reveals the potential utility of targeting TAMs in ferroptosis-based treatment and ALOX15 as prognosis indicators for cervical cancer.

Acta Pharmaceutica Sinica B
2023 Jun;13(6):2645-2662
Impact Factor:14.5

Materials and Methods
MiR-660-5p mimics labeled by Cy3 were obtained from **GenePharma**.



Acta Pharmaceutica Sinica B xxxx;xxx(xxx):xxx

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

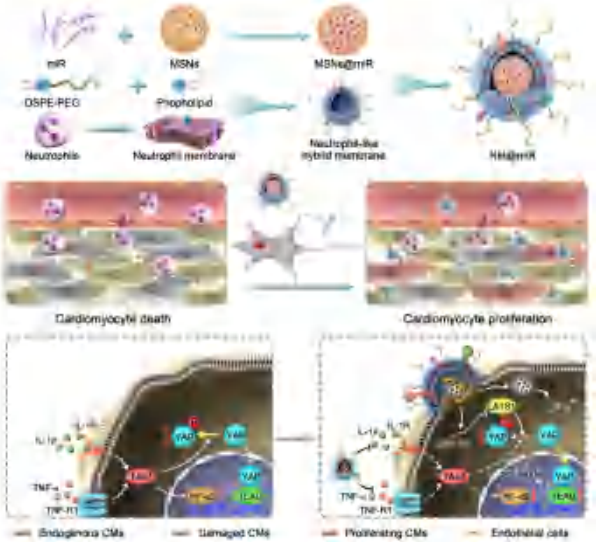
www.elsevier.com/locate/apsb
www.sciencedirect.com

ORIGINAL ARTICLE

Hippo pathway-manipulating neutrophil-mimic hybrid nanoparticles for cardiac ischemic injury via modulation of local immunity and cardiac regeneration

Qiaozi Wang[a,d,†], Yanan Song[a,d,†], Jinfeng Gao[a,d,†], Qiyu Li[a,d], Jing Chen[a,d], Yifang Xie[b], Zhengmin Wang[a,d], Haipeng Tan[a,d], Hongbo Yang[a,d], Ning Zhang[a,d], Juying Qian[a,d], Zhiqing Pang[c,*], Zheyong Huang[a,d,*], Junbo Ge[a,b,d,*]

Abstract The promise of regeneration therapy for restoration of damaged myocardium after cardiac ischemic injury relies on targeted delivery of proliferative molecules into cardiomyocytes whose healing benefits are still limited owing to severe immune microenvironment due to local high concentration of proinflammatory cytokines. Optimal therapeutic strategies are therefore in urgent need to both modulate local immunity and deliver proliferative molecules. Here, we addressed this unmet need by developing neutrophil-mimic nanoparticles NM@miR, fabricated by coating hybrid neutrophil membranes with arti-ficial lipids onto mesoporous silica nanoparticles (MSNs) loaded with microRNA-10b. The hybrid mem-brane could endow nanoparticles with strong capacity to migrate into inflammatory sites and neutralize proinflammatory cytokines and increase the delivery efficiency of microRNA-10b into adult mammalian cardiomyocytes (CMs) by fusing with cell membranes and leading to the release of MSNs-miR into cytosol. Upon NM@miR administration, this nanoparticle could home to the injured myocardium, restore the local immunity, and efficiently deliver microRNA-10b to cardiomyocytes, which could reduce the activation of Hippo-YAP pathway mediated by excessive cytokines and exert the best proliferative effect of miR-10b. This combination therapy could finally improve cardiac function and mitigate ventricular remodeling. Consequently, this work offers a combination strategy of immunity modulation and prolif-erative molecule delivery to boost cardiac regeneration after injury.



Acta Pharmaceutica Sinica B
2023 Aug 19;2211-3835
Impact Factor: 14.5

Materials and Methods

Mir-10b mimics and their **negative controls** (**GenePharma**, Shanghai, China) were transfected into CMs using Lipofectamine RNAiMAX (Invitrogen, Carlsbad, CA, USA) according to the instructions at a final concentration of 50 mmol/L.

Biomaterials 275 (2021) 120902

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

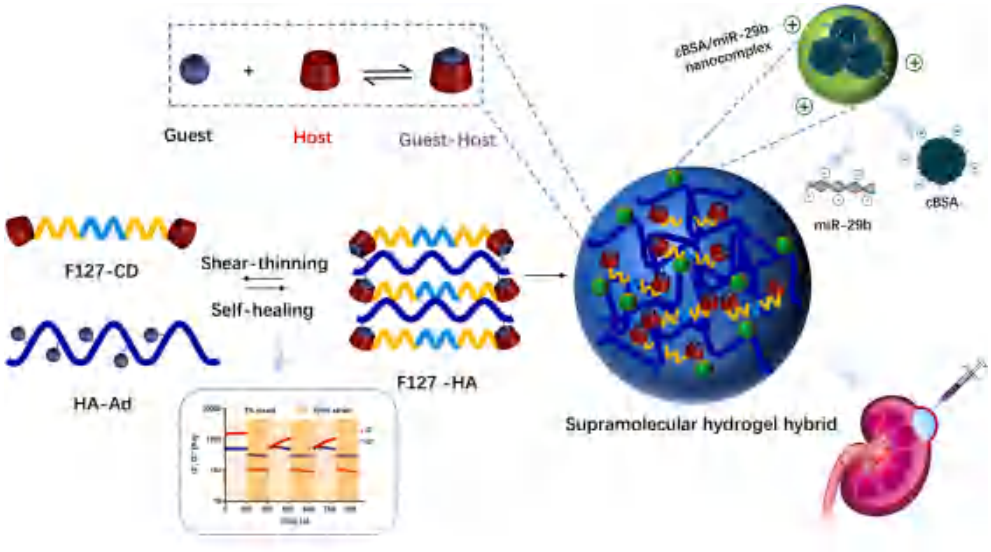
Extended-release of therapeutic microRNA via a host-guest supramolecular hydrogel to locally alleviate renal interstitial fibrosis

Yingying Xu [a], Yining Niu [a], Beibei Wu [a], Xi Cao [b], Tao Gong [a], Zhi-Rong Zhang [a], Yao Fu [a,*]

[a] Key Laboratory of Drug-Targeting and Drug Delivery System of the Education Ministry and Sichuan Province, Sichuan Engineering Laboratory for Plant-Sourced Drug and Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu, 610041, China
[b] Department of Pharmacy, the First Affiliated Hospital of Anhui Medical University, and the Grade 3 Pharmaceutical Chemistry Laboratory of State Administrate of Traditional Chinese Medicine, Hefei, China

Abstract

Activated fibroblasts are critical contributors to renal interstitial fibrosis thus becoming the cellular target for fibrosis treatment. Previously, microRNA 29 b (miR-29 b) is shown to be down-regulated in various animal models of renal fibrosis. Herein, we describe a facile strategy to achieve localized and sustained delivery of therapeutic microRNA to the kidney via a host-guest supramolecular hydrogel. Specifically, cationic bovine serum albumin is used to complex with miR-29 b to afford nanocomplexes (cBSA/miR-29 b), which is proven to specifically inhibit fibroblast activation in a dose-dependent manner in vitro. Following unilateral ureteral obstruction in mice, a single injection of the hydrogel loaded with cBSA/miR-29 b in vivo, significantly down- regulated proteins and genes related to fibrosis for up to 21 days without affecting the normal liver or kidney functions. Overall, the localized delivery of cBSA/miR-29 b via a host-guest supramolecular hydrogel represents a safe and effective intervention strategy to delay and reverse the progression of interstitial renal fibrosis.



Biomaterials
2021 May 27 ; 120902
Impact Factor:14

Materials and Methods

miR-29b mimics (sense: 5′- UAGCACCAUUUGAAAUCAGUGUU-3’; anti-sense: 5′-CACUGAUUU-CAAAUGGUGCUAUU-3′), **Cy5-miR-29 b mimics, miR-NC** were supplied by **GenePharma** (Shanghai, China).

Plant Biotechnology Journal

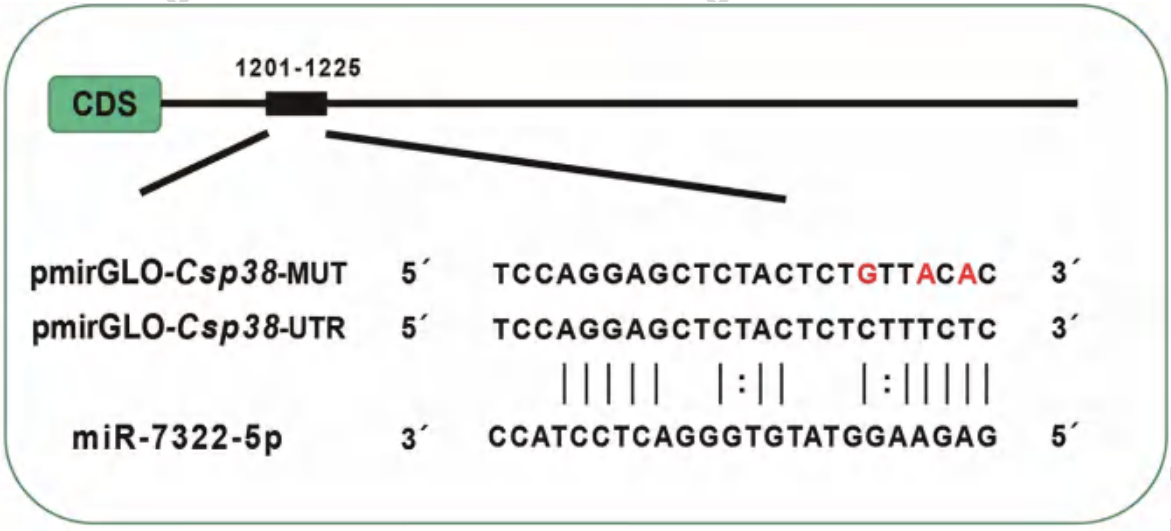
Plant Biotechnology Journal (2023) 21, pp. 1827–1838 doi: 10.1111/pbi.14095

The microRNA-7322-5p/p38/Hsp19 axis modulates Chilo suppressalis cell-defences against Cry1Ca: an effective target for a stacked transgenic rice approach

Yan Wu[1,2,†], Zijin Weng[1,3,†], Haixia Yan[1,3], Zhuotian Yao[1,2], Zhenzhen Li[2], Yajie Sun[2], Kangsheng Ma[2], J. Joe Hull[4], Delin Zhang[1,3,*], Weihua Ma[1,2,*], Hongxia Hua[2] and Yongjun Lin[1,3]

Summary

Bacillus thuringiensis (Bt)-secreted crystal (Cry) toxins form oligomeric pores in host cell membranes and are a common element in generating insect-resistant transgenic crops. Although Cry toxin function has been well documented, cellular defences against pore-formation have not been as well developed. Elucidation of the processes underlying this defence, however, could contribute to the development of enhanced Bt crops. Here, we demonstrate that Cry1Ca-mediated downregulation of microRNA-7322-5p (miR-7322-5p), which binds to the 3′ untranslated region of p38, negatively regulates the susceptibility of Chilo suppressalis to Cry1Ca. Moreover, Cry1Ca exposure enhanced phosphorylation of Hsp19, and hsp19 downregulation increased susceptibility to Cry1Ca. Further, Hsp19 phosphorylation occurs downstream of p38, and pull-down assays confirmed the interactions between Hsp19 and Cry1Ca, suggesting that activation of Hsp19 by the miR-7322-5p/p38/Hsp19 pathway promotes Cry1Ca sequestration. To assess the efficacy of targeting this pathway in planta, double-stranded RNA (dsRNA) targeting C. suppressalis p38 (dsp38) was introduced into a previously generated cry1Ca-expressing rice line (1CH1-2) to yield a single-copy cry1Ca/dsp38 rice line (p38-rice). Feeding on this rice line triggered a significant reduction in C. suppressalis p38 expression and the line was more resistant to C. suppressalis than 1CH1-2 in both short term (7-day) and continuous feeding bioassays as well as field trials. These findings provide new insights into invertebrate epithelium cellular defences and demonstrate a potential new pyramiding strategy for Bt crops.



PLANT BIOTECHNOLOGY JOURNAL
2023 Jun;21:1827–1838
Impact Factor:13.8

Materials and Methods

All miRNA mimics, inhibitors, and their respective **negative controls (NC)** were commercially synthesized (Shanghai **Genepharma** Co., Ltd, Shanghai, China).

Journal of Hazardous Materials 462 (2024) 132749

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

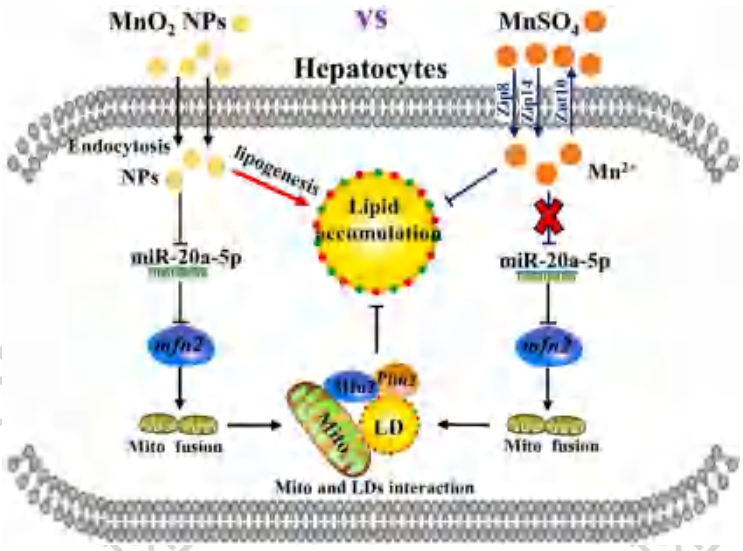
Research Paper

miR-20a-5p targeting *mfn2*-mediated mitochondria-lipid droplet contacts regulated differential changes in hepatic lipid metabolism induced by two Mn sources in yellow catfish

Tao Zhao [a], Xiao-Ying Tan [a], Kostas Pantopoulos [c], Jie-Jie Xu [a], Hua Zheng [a], Yi-Chuang Xu [a], Yu-Feng Song [a], Zhi Luo [a,b,*]

A B S T R A C T

Understanding the hazards of different forms of metal elements provided innovative insights into their toxicity and environmental risk assessment. To date, few studies had been conducted to investigate the differential effects and mechanisms of MnO_2 NPs and $MnSO_4$, two widely distributed environmental pollutants, on hepatic toxicityand lipid metabolism since lipid metabolism-relevant parameters were broadly used as biomarkers for risk assessment of hazardous contaminants. Thus, using yellow catfish Pelteobagrus fulvidraco, an ecologically and economically important freshwater fish as the model, the present study investigated the differential effects and mechanisms of MnO2 NPs and MnSO4 influencing hepatic lipid metabolism. Compared to MnSO4, MnO2 NPs increased hepatic Mn content, induced lipotoxicity, up-regulated the mRNA expression of lipogenic genes, increased peridroplet mitochondrial (PDM) contents, intensified the contact between mitochondria and lipid droplets (LDs), and downregulated miR-20a-5p abundance. Importantly, miR-20a-5p targeted mfn2, which mediated the contact between mitochondria and LDs and influenced changes in lipid metabolism induced by MnO2 NPs. Mechanistically, the direct Mfn2-Plin2 binding and Mfn2 GTPase activity promoted the MnO2 NPs- induced interactions between mitochondria and LDs, which in turn influenced MnO2 NPs-induced changes in hepatic lipid metabolism. For the first time, our findings indicated the significant differences between the changes in body metabolism induced by nanoparticles and inorganic elements, which helped to illuminate different mechanisms governing the responses of aquatic vertebrates to hazardous metal pollutants (MnO2 NPs and MnSO4).



JOURNAL OF HAZARDOUS MATERIALS
2023 Oct 10 ; 462:132749
Impact Factor:13.6

Materials and Methods

The mfn2 **siRNAs** and **miR-20a-5p mimic,** and the **negative mimic control (NC)** were synthesized by the **GenePharma** (Shanghai, China).

Journal of Hazardous Materials 460 (2023) 132391

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

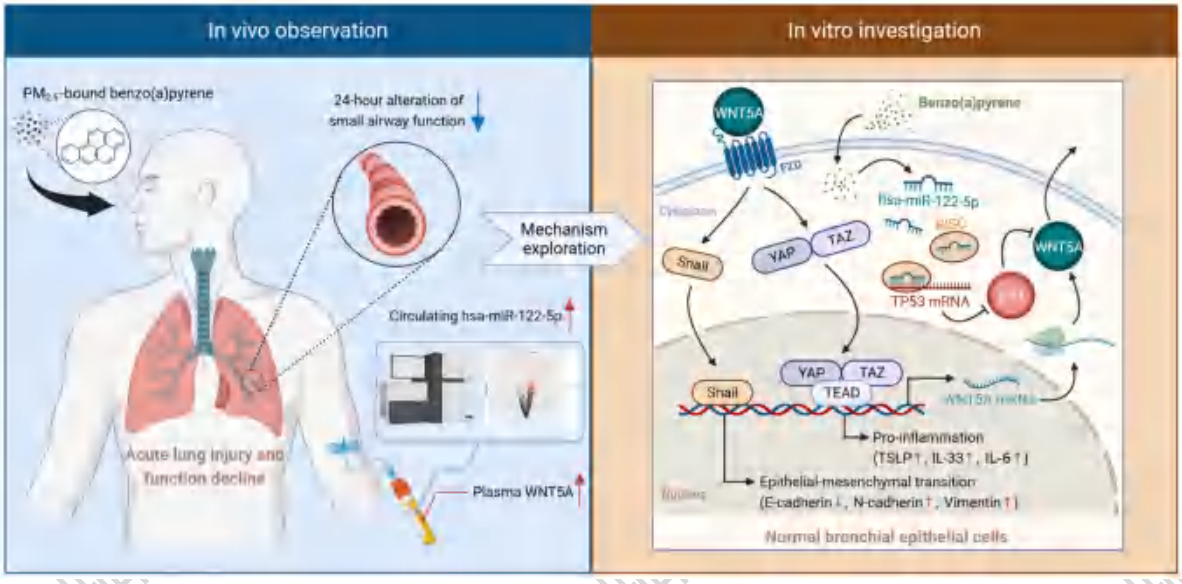
Research Paper

Role and mechanism of WNT5A in benzo(a)pyrene-induced acute lung injury and lung function decline

Lieyang Fan [a,b,1], Bin Wang [a,b,1], Jixuan Ma [a,b], Zi Ye [a,b], Xiuquan Nie [a,b], Man Cheng [a,b], Yujia Xie [a,b], Pei Gu [a,b], Yingdie Zhang [a,b], Xiaojie You [a,b], Yun Zhou [c,*], Weihong Chen [a,b,**]

A B S T R A C T

Benzo(a)pyrene was sparsely studied for its early respiratory impairment. The non-canonical ligand WNT5A play a role in pneumonopathy, while its function during benzo(a)pyrene-induced adverse effects were largely unexplored. Individual benzo(a)pyrene, plasma WNT5A, and spirometry 24-hour change for 87 residents from Wuhan-Zhuhai cohort were determined to analyze potential role of WNT5A in benzo(a)pyrene-induced lung function alternation. Normal bronchial epithelial cell lines were employed to verify the role of WNT5A after benzo(a)pyrene treatment. RNA sequencing was adopted to screen for benzo(a)pyrene-related circulating microRNAs and differentially expressed microRNAs between benzo(a)pyrene-induced cells and controls. The most potent microRNA was selected for functional experiments and target gene validation, and their mechanistic link with WNT5A-mediated non-canonical Wnt signaling was characterized through rescue assays. We found significant associations between increased benzo(a)pyrene and reduced 24-hour changes of FEF50% and FEF75%, as well as increased WNT5A. The benzo(a)pyrene-induced inflammation and epithelial-mesenchymal transition in BEAS-2B and 16HBE cells were attenuated by WNT5A silencing. hsa-miR-122–5p was significantly and positively associated with benzo(a)pyrene and elevated after benzo(a)pyrene induction, and exerted its effect by downregulating target gene TP53. Functionally, WNT5A participates in benzo(a)pyrene-induced lung epithelial injury via non-canonical Wnt signaling modulated by hsa-miR-122–5p/TP53 axis, showing great potential as a preventive and therapeutic target.



JOURNAL OF HAZARDOUS MATERIALS
2023 Aug 24;460:132391
Impact Factor: 13.6

Materials and Methods

All the **siRNAs**, **miRNA mimic** and **inhibitor** were designed and synthesized by **Genepharma** Inc. (Shanghai, China), and were trans-fected using Lipofectamine 3000 (Invitrogen, USA) according to the manufacturers' instructions.

Journal of Hazardous Materials 458 (2023) 131908

Contents lists available at ScienceDirect

Journal of Hazardous Materials

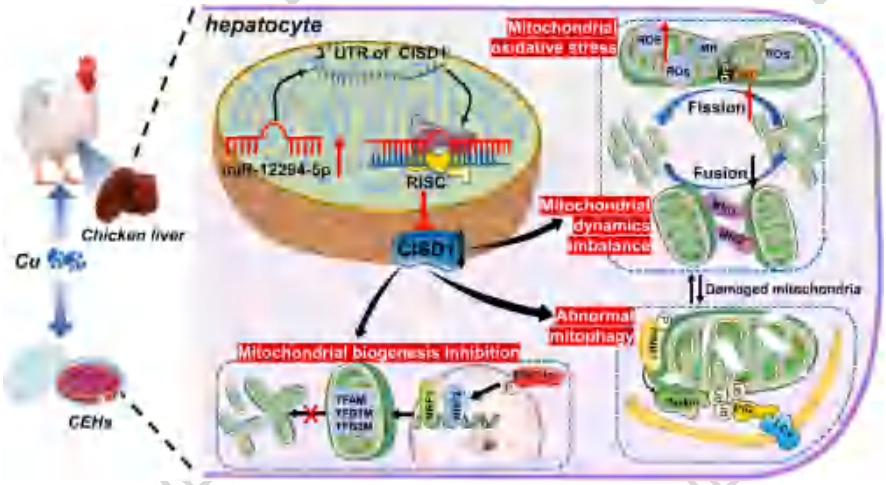
journal homepage: www.elsevier.com/locate/jhazmat

Mitochondrial miR-12294-5p regulated copper-induced mitochondrial oxidative stress and mitochondrial quality control imbalance by targeted inhibition of CISD1 in chicken livers

Gaolong Zhong, Yuanxu Li, Lei Li, Yihui Huo, Wenting Zhang, Tingyu Li, Feiyang Ma, Jianzhao Liao, Ying Li, Hui Zhang, Jianying Guo, Jiaqiang Pan, Wenlan Yu, Lianmei Hu, Zhaoxin Tang *

A B S T R A C T

Copper (Cu) is hazardous metal contaminant, which induced hepatotoxicity is closely related to mitochondrial disorder, but exact regulatory mechanism has not yet been revealed. Mitochondrial microRNAs (mitomiRs) are a novel and critical regulator of mitochondrial function and mitochondrial homeostasis. Hence, this study revealed the impact of Cu-exposure on mitomiR expression profiles in chicken livers, and further identified mitomiR- 12294–5p and its target gene CISD1 as core regulators involved in Cu-induced hepatotoxicity. Additionally, our results showed that Cu-exposure induced mitochondrial oxidative damage, and mitochondrial quality control imbalance mediated by mitochondrial dynamics disturbances, mitochondrial biogenesis inhibition and abnormal mitophagy flux in chicken livers and primary chicken embryo hepatocytes (CEHs). Meaningfully, we discovered that inhibition of the expression of mitomiR-12294-5p effectively alleviated Cu-induced mitochondrial oxidative stress and mitochondrial quality control imbalance, while the up-regulation of mitomiR-12294-5p expression exacerbated Cu-induced mitochondrial damage. Simultaneously, the above Cu-induced mitochondrial damage can be effectively rescued by the overexpression of CISD1, while knockdown of CISD1 dramatically reverses the



JOURNAL OF HAZARDOUS MATERIALS
2023 Jun 21;458:131908
Impact Factor:13.6

Materials and Methods

miR-12294–5p mimic, miR- 12294–5p inhibitor, miR-12294–5p mimic NC (negative control) and **miR-12294–5p inhibitor NC** were designed and synthesized by **Genepharma** Co., Ltd. (Suzhou, China).

Meanwhile,the **sequences of siRNA targeting CISD1 (si-CISD1)** and **siRNA-NC** were also synthesized by **Genepharma** Co., Ltd (Suzhou, China).

Journal of Hazardous Materials 457 (2023) 131749

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

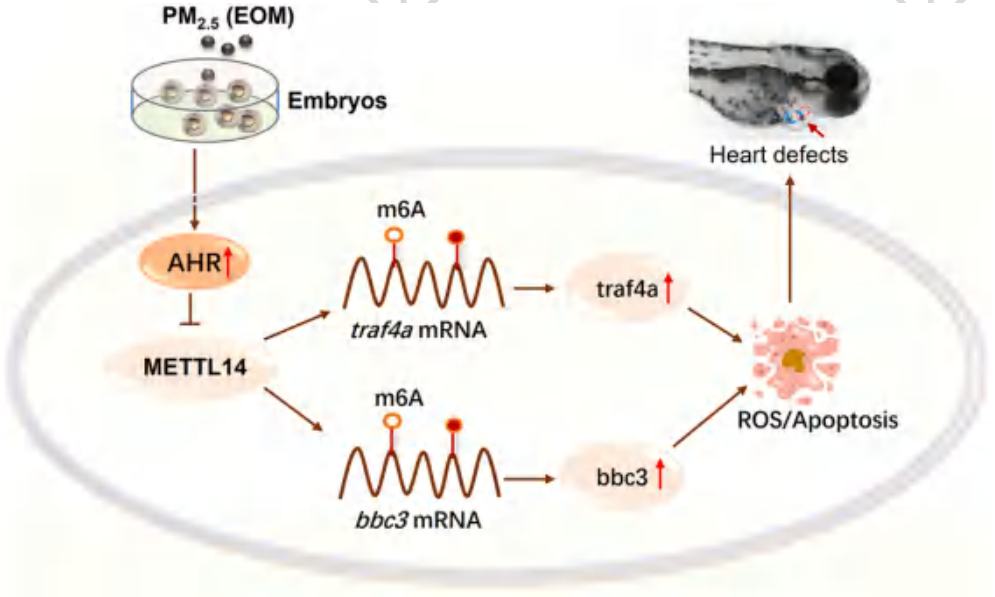
AHR-mediated m^{6}A RNA methylation contributes to $PM_{2.5}$-induced cardiac malformations in zebrafish larvae

Cheng Ji [a,1], Yizhou Tao [a,1], Xiaoxiao Li [a,b], Jin Wang [a,b], Jin Chen [a,b], Stanley Aniagu [c], Yan Jiang [a,*], Tao Chen [a,b,**]

A B S T R A C T

A growing body of evidence indicates that ambient fine particle matter ($PM_{2.5}$) exposure inhibits heart devel-opment, but the underlying mechanisms remain elusive. We hypothesized that m^{6}A RNA methylation plays an important role in the cardiac developmental toxicity of $PM_{2.5}$. In this study, we demonstrated that extractable organic matter (EOM) from PM2.5 significantly decreased global m^{6}A RNA methylation levels in the heart of zebrafish larvae, which were restored by the methyl donor, betaine. Betaine also attenuated EOM-induced ROS overgeneration, mitochondrial damage, apoptosis and heart defects. Furthermore, we found that the aryl hy-drocarbon receptor (AHR), which was activated by EOM, directly repressed the transcription of methyl-transferases *mettl14* and *mettl3*. EOM also induced genome-wide m^{6}A RNA methylation changes, which led us to focus more on the aberrant m^{6}A methylation changes that were subsequently alleviated by the AHR inhibitor, CH223191. In addition, we found that the expression levels of *traf4a* and *bbc3*, two apoptosis related genes, were upregulated by EOM but restored to control levels by the forced expression of *mettl14*. Moreover, knockdown of

either *traf4a* or *bbc3* attenuated EOM-induced ROS overproduction and apoptosis. In conclusion, our results indicate that $PM_{2.5}$ induces m^{6}A RNA methylation changes via AHR-mediated *mettl14* downregulation, which upregulates *traf4a* and *bbc3*, leading to apoptosis and cardiac malformations.



JOURNAL OF HAZARDOUS MATERIALS
2023 Jun 2;457:131749
Impact Factor:13.6

Materials and Methods

Traf4a antago , bbc3-antago , and non-specific control antago were designed and synthesized by **GenePharma** (Suzhou, China).

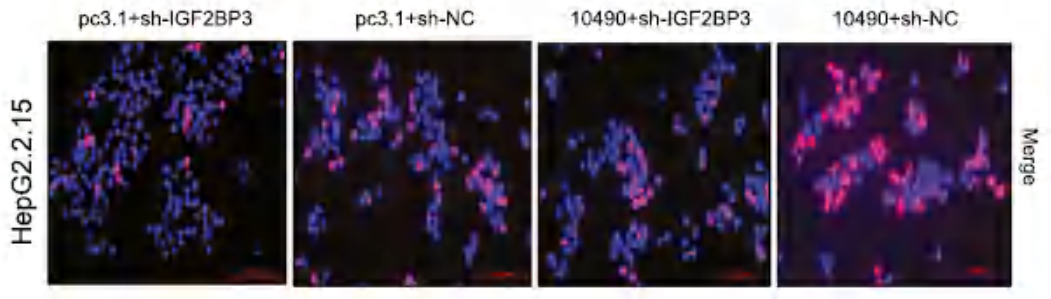
HEPATOLOGY

HEPATOLOGY, VOL. 0, NO. 0, 2021

HBV/Pregenomic RNA Increases the Stemness and Promotes the Development of HBV-Related HCC Through Reciprocal Regulation With Insulin- Like Growth Factor 2 mRNA- Binding Protein 3

Wen-bin Ding,[1-3*] Meng-chao Wang,[1-3*] Jian Yu,[1-3*] Gang Huang,[1-3*] Da-peng Sun,[1-3*] Lei Liu,[1-3] Jia-ning Zhang,[1-3] Yuan Yang,[1-3] Hui Liu ,[1-3] Wei-ping Zhou,[1-3] Fu Yang,[4] and Sheng-xian Yuan[1-3]

Rapid and efficient disease-induced or critical-size bone regeneration remains a challenge in tissue engineering due to the lack of highly bioactive biomaterial scaffolds. Physical structures such as nanostructures, chemical components such as silicon elements, and biological factors such as genes have shown positive effects on bone regeneration. Herein, a bioactive photoluminescent elastomeric silicate-based nanofibrous scaffold with sustained miRNA release is reported for promoting bone regeneration based on a joint physico chemical-biological strategy. Bioactive nanofibrous scaffolds are fabricated by cospinning poly (ε-caprolactone) (PCL), elastomeric poly (citrates-siloxane) (PCS), and bioactive osteogenic miRNA nanocomplexes (denoted PPM nanofibrous scaffolds). The PPM scaffolds possess uniform nanostructures, significantly enhanced tensile stress (≈15 MPa) and modulus (≈32 MPa), improved hydrophilicity (30–60°), controlled biodegradation, and strong blue fluorescence. Bioactive miRNA complexes are efficiently loaded into the nanofibrous matrix and exhibit long-term release for up to 70 h. The PPM scaffolds significantly promote the adhesion, proliferation, and osteoblast differentiation of bone marrow stem cells in vitro and enhanced rat cranial defect restoration (12 weeks) in vivo. This work reports an attractive joint physico-chemical-biological strategy for the design of novel cell/protein-free bioactive scaffolds for synergistic tissue regeneration.



HEPATOLOGY
2021 Sep;74(3):1480-1495
Impact Factor: 13.5

Materials and Methods

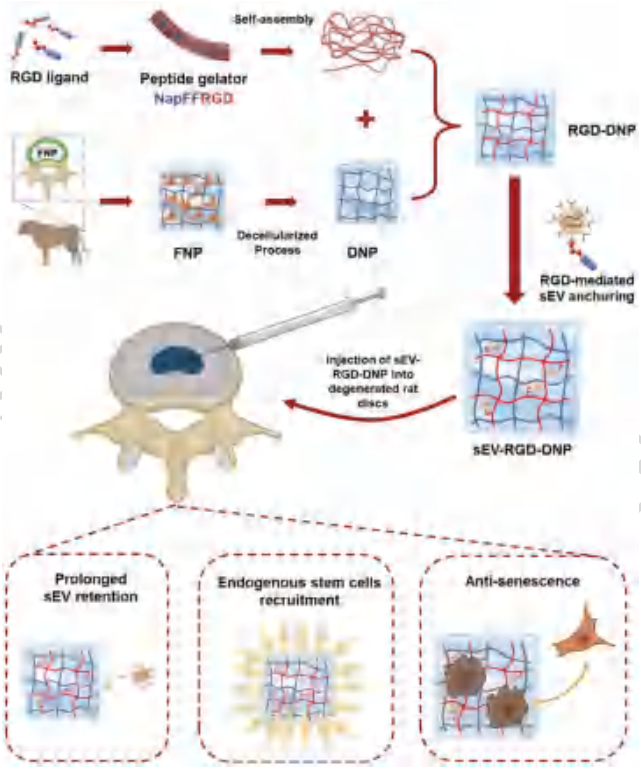
The mimics and inhibitor of miR-let-7e-5p and corresponding **miR-NC** were designed and synthesized by the Shanghai **Genepharma** Company (Shanghai, China).

NANO · MICRO small
www.small-journal.com

Extracellular Vesicle-Conjugated Functional Matrix Hydrogels Prevent Senescence by Exosomal miR-3594-5p-Targeted HIPK2/p53 Pathway for Disc Regeneration

Yizhong Peng, Xuanzuo Chen, Sheng Liu, Wei Wu, Hongyang Shu, Shuo Tian, Yan Xiao, Kanglu Li, BaiChuan Wang, Hui Lin, Xiangcheng Qing,* and Zengwu Shao**

Nucleus pulposus stem cells (NPSCs) senescence plays a critical role in the progression of intervertebral disc degeneration (IDD). Stem cell-derived extracellular vesicles (EV) alleviate cellular senescence. Whereas, the underlying mechanism remains unclear. Low stability largely limited the administration of EV in vivo. RGD, an arginine-glycine-aspartic acid tripeptide, strongly binds integrins expressed on the EV membranes, allowing RGD to anchor EV and prolong their bioavailability. An RGD-complexed nucleus pulposus matrix hydrogel (RGD-DNP) is developed to enhance the therapeutic effects of small EV (sEV). RGD-DNP prolonged sEV retention in vitro and ex vivo. sEV-RGD-DNP promoted NPSCs migration, decreased the number of SA-β-gal-positive cells, alleviated cell cycle arrest, and reduced p16,p21, and p53 activation. Small RNA-seq showed that miR-3594-5p is enriched in sEV, and targets the homeodomain-interacting protein kinase 2 (HIPK2)/p53 pathway. The HIPK2 knockdown rescues the impaired therapeutic effects of sEV with downregulated miR-3594-5p. RGD-DNP conjugate with lower amounts of sEV achieved similar disc regeneration with free sEV of higher concentrations in DNP. In conclusion, sEV-RGD-DNP increases sEV bioavailability and relieves NPSCs senescence by targeting the HIPK2/p53 pathway, thereby alleviating IDD. This work achieves better regenerative effects with fewer sEV and consolidates the theoretical basis for sEV application for IDD treatment.



Small
2023 May 10 ; 2206888
Impact Factor:13.3

Materials and Methods

MicroRNA-inhibitor and siRNA Transfection: A **miR-3594-inhibitor** was constructed from **GenePharma** (Shanghai).

Received: 2 December 2022 | Accepted: 30 March 2023

DOI: 10.1002/jmv.28725

RESEARCH ARTICLE

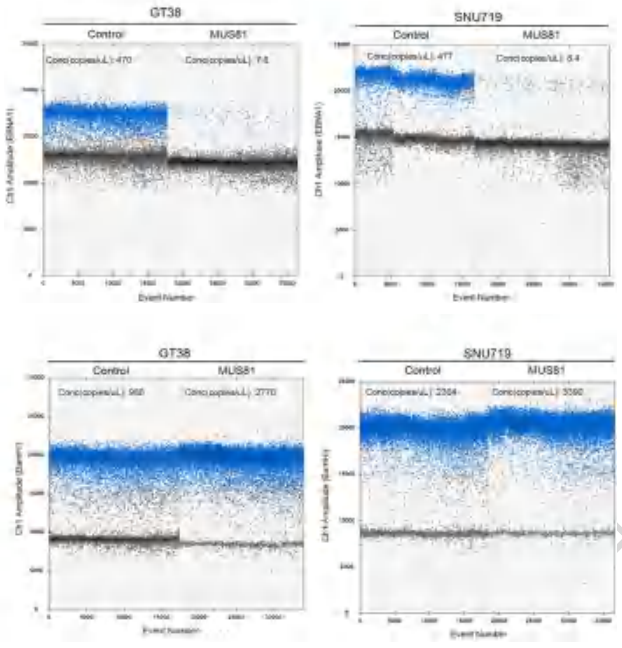
JOURNAL OF MEDICAL VIROLOGY WILEY

Downregulation of MUS81 expression inhibits cell migration and maintains EBV latent infection through miR-BART9-5p in EBV-associated gastric cancer

Yan Zhang[1,2] | Duo Shi[1] | Xing Zhang[1] | Shuo Wu[1,3] | Wen Liu[1] | Bing Luo[1]

Abstract

Epstein–Barr virus (EBV) infection is associated with the occurrence and development of gastric cancer (GC). Methyl methanesulfonate and ultraviolet-sensitive gene 81 (MUS81) is the catalytic component of a structure-specific endonuclease and plays an important role in chromosomal stability. However, the link between EBV infection and MUS81 remains unclear. In the present study, we found that MUS81 expression was much lower in EBV-associated GC cells than in EBV-negative GC. MUS81 acts as an oncogene in GC by inducing the cell migration and proliferation. Western blot and luciferase reporter assays revealed that miR-BART9-5p directly targeted MUS81 and downregulated its expression. Additionally, overexpression of MUS81 in EBV-positive GC cells inhibited the expression of EBV nuclear antigen 1 (EBNA1). EBNA1 is critical for the pathogenesis of EBV-associated tumors and the maintenance of a stable copy number of the viral genomes. Altogether, these results indicated that the lowering MUS81 expression might be a mechanism by EBV to maintain its latent infection.



JOURNAL OF MEDICAL VIROLOGY
2023 Apr 13;95:e28725
Impact Factor: 12.7

Materials and Methods

Small interfering RNAs and **negative control siRNA** were designed and synthesized from **GenePharma**.

The **miR-BART9-5p mimics** , **miR-BART9-5p inhibitor** , **negative control** , and **inhibitor control** were also provided from **GenePharma**.

Cell Death & Differentiation
https://doi.org/10.1038/s41418-021-00779-y

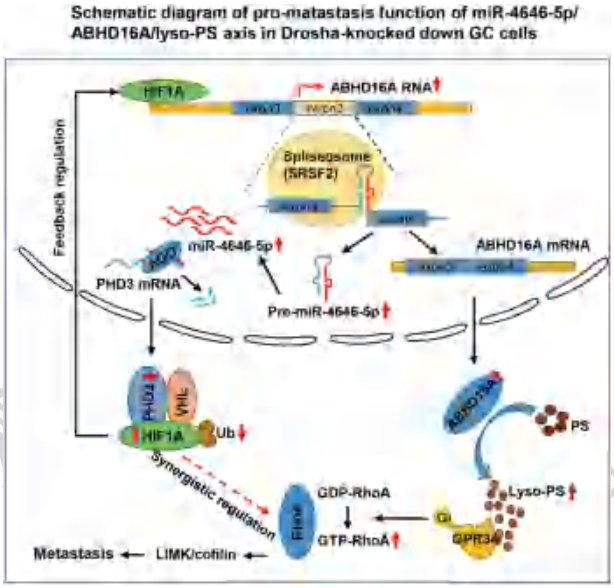
ARTICLE

Mirtronic miR-4646-5p promotes gastric cancer metastasis by regulating ABHD16A and metabolite lysophosphatidylserines

Liping Yang[1]·Yixuan Hou[2]·Yan-e Du[3]·Qiao Li[1]·Fanlin Zhou[4]·Yu Li[4]·Huan Zeng[1]·Ting Jin[1]·Xueying Wan[1]·Shengdong Guan[1]·Rui Wang[1]·Manran Liu[1]

Abstract

The aberrant classical miRNAs are considered to play significant roles in tumor progression. However, it remains unclear for nonclassical miRNAs, a set of Drosha-independent miRNAs in the process of various biology. Here, we reveal that a nonclassical miR-4646-5p plays a pivotal role in gastric cancer (GC) metastasis. MiR-4646-5p, one of Drosha-independent mirtronic miRNA, is aberrant up-regulated in Drosha-low expressed GC and Drosha-knockdown gastric cancer cells. Mirtronic miR-4646-5p is a specific transcription splicing product of intron 3 of the host gene Abhd16a with the aid of SRSF2. The enhanced miR-4646-5p can stabilize HIF1A by targeting PHD3 to positive feedback regulate Abhd16a and miR-4646-5p itself expressions. ABHD16A, as an emerging phosphatidylserine-specific lipase, involves in lipid metabolism leading to lysophosphatidylserines (lyso-PSs) accumulation, which stimulates RhoA and downstream LIMK/cofilin cascade activity through GPR34/Gi subunit, thus causes metastasis of gastric cancer. In addition, miR-4646-5p/PHD3/HIF1A signaling can also up-regulate RhoA expression and synergistically promote gastric cancer cell invasion and metastasis. Our study provides new insights of nonclassical mirtronic miRNA on tumor progress and may serve as a new diagnostic biomarker for gastric cancer. MiR-4646-5p and its host gene Abhd16a mediated abnormal lipid metabolism may be a new target for clinical treatment of gastric cancer.



Cell Death & Differentiation
2021 Apr 19;28(9):2708-2727
Impact Factor: 12.4

Materials and Methods

And the lentivirus expression vectors of shRNAs against Drosha, **HIF1A, PHD3, ABHD16A, GPR34, SRSF2, and the control shRNA** were purchased from **GenePharma** .
Mimics, inhibitors and antagomir of miR-4646-5p were also purchased from **GenePharma** .

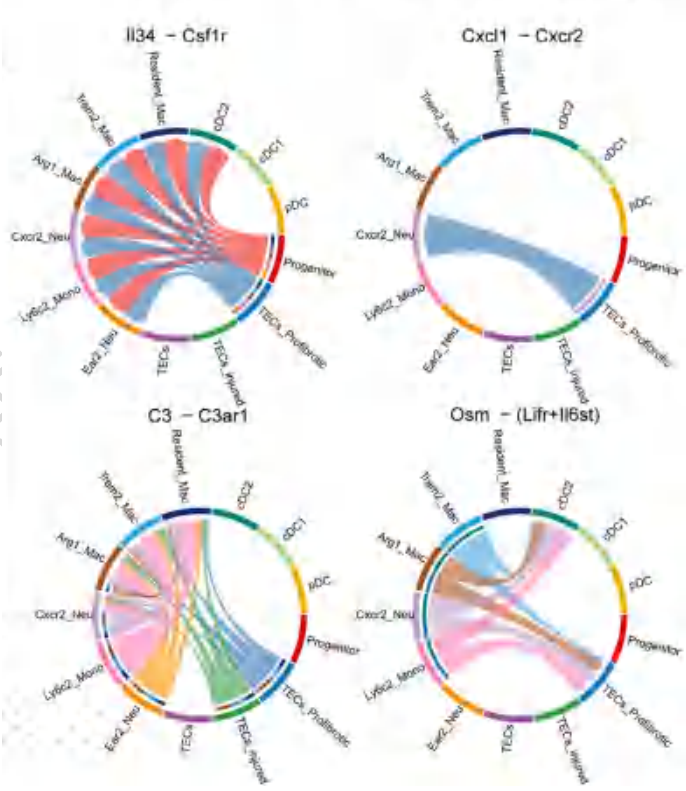
Please cite this article in press as: Wang et al., Single-cell dissection of cellular and molecular features underlying mesenchymal stem cell therapy in ischemic acute kidney injury, Molecular Therapy (2023), https://doi.org/10.1016/j.ymthe.2023.07.024

Molecular Therapy
Original Article

Single-cell dissection of cellular and molecular features underlying mesenchymal stem cell therapy in ischemic acute kidney injury

Wenjuan Wang,[1,2,4] Min Zhang,[2,4] Xuejing Ren,[3] Yanqi Song,[2] Yue Xu,[2] Kaiting Zhuang,[2] Tuo Xiao,[2] Xinru Guo,[1,2] Siyang Wang,[2] Quan Hong,[2] Zhe Feng,[2] Xiangmei Chen,[2] and Guangyan Cai[1,2]

Mesenchymal stem cells (MSCs) exert beneficial therapeutic ef-fects in acute kidney injury (AKI), while the detailed repair mechanism remains unclear. Herein, we probed the underlying mechanisms of MSC therapy in AKI by performing unbiased single-cell RNA sequencing in IRI model with/without MSC treatment. Our analyses uncovered the tubular epithelial cells (TECs) and immune cells transcriptomic diversity and high-lighted a repair trajectory involving renal stem/progenitor cell differentiation. Our findings also suggested that profibrotic TECs expressing pro-fibrotic factors such as Zeb2 and Pdgfb promoted the recruitment of inflammatory monocytes and Th17 cells to injured kidney tissue, inducing TGF-b1 secretion and renal fibrosis. Finally, in addition to activating the repair properties of renal progenitor/stem cells, we uncovered a role for MSC-derived miR-26a-5p in mediating the therapeutic ef-fects of MSCs by inhibiting Zeb2 expression and suppressing pro-fibrotic TECs and its subsequent recruitment of immune cell subpopulations. These findings may help to optimize future AKI treatment strategies



MOLECULAR THERAPY
2023 Aug 2;31(10):3067-3083
Impact Factor:12.4

Materials and Methods

MSCs or HK2 cells were grown to 50% confluence before being trans-fected with 30 nmol/L synthetic **miR-26a-5p mimic, inhibitor, or nega-tive control (NC)** (**Gene Pharma**, Nanjing, China) using Lipofectamine 3000 in Opti-MEM (Invitrogen, Carlsbad, CA).

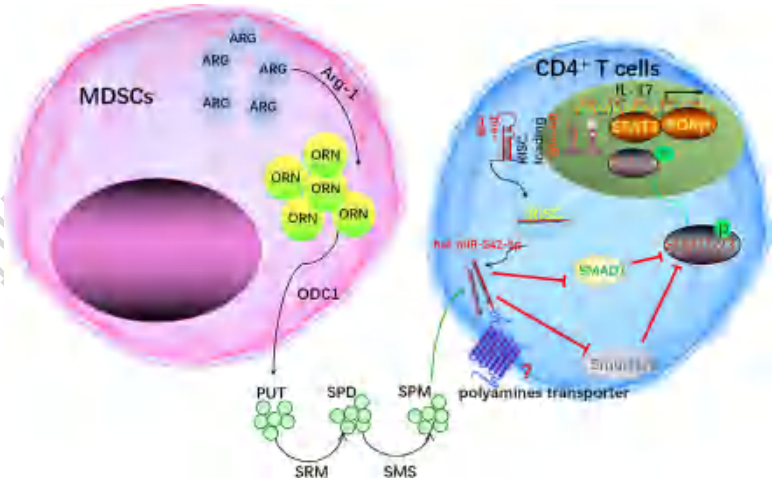
Please cite this article in press as: Hu et al., Polyamines from myeloid-derived suppressor cells promote Th17 polarization and disease progression, Molecular Therapy (2022), https://doi.org/10.1016/j.ymthe.2022.10.013

Molecular Therapy
Original Article

Polyamines from myeloid-derived suppressor cells promote Th17 polarization and disease progression

Cong Hu,[1,2,3] Yu Zhen,[4] Zhanchuan Ma,[1,2] Li Zhao,[5] Hao Wu,[6] Chang Shu,[7] Bo Pang,[1,8] Jinyu Yu,[9] Ying Xu,[6] Xin Zhang,[10] Xiang-yang Wang,[11] and Huanfa Yi[1,2]

Myeloid-derived suppressor cells (MDSCs) are a group of immature myeloid cells that play an important role in diseases. MDSCs promote Th17 differentiation and aggravate sys-temic lupus erythematosus (SLE) progression by producing arginase-1 to metabolize arginine. However, the metabolic reg-ulators remain unknown. Here, we report that MDSC deriva-tive polyamines can promote Th17 differentiation via miR-542–5p in vitro. Th17 polarization was enhanced in response to polyamine treatment or upon miR-542–5p overexpression. The TGF-b/SMAD3 pathway was shown to be involved in miR-542-5p-facilitated Th17 differentiation. Furthermore, miR-542–5p expression positively correlated with the levels of polyamine synthetases in peripheral blood mononuclear cells of patients with SLE as well as disease severity. In humanized SLE model mice, MDSC depletion decreased the levels of Th17 cells, accompanied by reduced expression of miR-542–5p and these polyamine synthetases. In addition, miR-542–5p expression positively correlated with the Th17 level and disease severity in both patients and humanized SLE mice. Together, our data reveal a novel molecular pathway by which MDSC-derived polyamine metabolism enhances Th17 differentiation and aggravates SLE.



MOLECULAR THERAPY
2022 Oct;31(2):569-584
Impact Factor:12.4

Materials and Methods

HiPerFect trans-fection reagent (0.6 mL, Qiagen) and **hsa-miR542–5p mimics, inhibitor, or control** (0.3 mL, **GenePharma**) were prepared in 20 mLof complete 1640 medium.
Invivofectamine 3.0 reagent (Invitrogen) and **hsa-miR542–5p agomir, antagomir, or control** (**GenePharma**) were used for in vivo transfec-tion according to the manufacturer's instructions and intravenously injected into NSG mice, which were transfected for 3 weeks.

Environment International 172 (2023) 107807

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

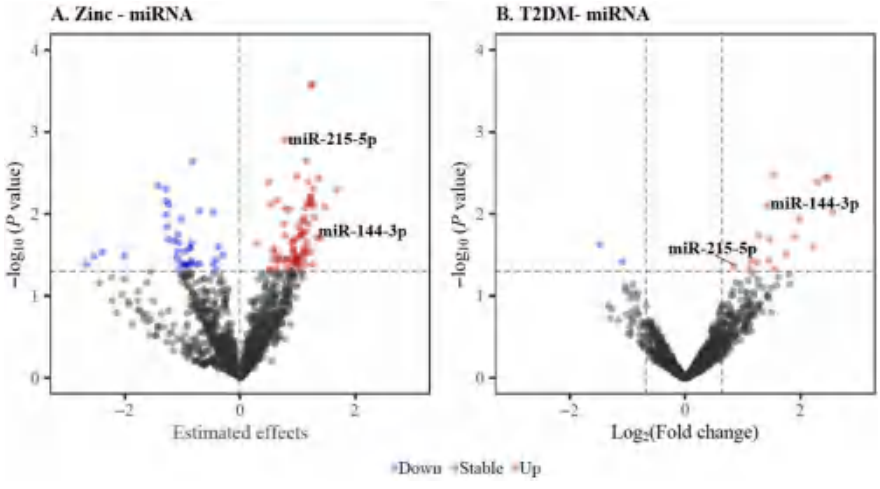
Full length article

Plasma microRNA expression profiles associated with zinc exposure and type 2 diabetes mellitus: Exploring potential role of miR-144-3p in zinc-induced insulin resistance

Zi Ye, Man Cheng, Lieyang Fan, Jixuan Ma, Yingdie Zhang, Pei Gu, Yujia Xie, Xiaojie You, Min Zhou, Bin Wang, Weihong Chen *

Abstract

Zinc exposure has been linked with disordered glucose metabolism and type 2 diabetes mellitus (T2DM) development. However, the underlying mechanism remains unclear. We conducted population-based studies and in vitro experiments to explore potential role of microRNAs (miRNAs) in zinc-related hyperglycemia and T2DM. In the discovery stage, we identified plasma miRNAs expression profile for zinc exposure based on 87 community residents from the Wuhan-Zhuhai cohort through next-generation sequencing. MiRNAs profiling for T2DM was also performed among 9 pairs newly diagnosed T2DM-healthy controls. In the validating stage, plasma miRNA related to both of zinc exposure and T2DM among the discovery population was measured by qRT-PCR in 161 general individuals derived from the same cohort. Furthermore, zinc treated HepG2 cells with mimic or inhibitor were used to verify the regulating role of miR-144-3p. Based on the discovery and validating populations, we observed that miR-144-3p was positively associated with urinary zinc, hyperglycemia, and risk of T2DM. In vitro experiments confirmed that zinc-induced increase in miR-144-3p expression suppressed the target gene Nrf2 and downstream antioxidant enzymes, and aggravated insulin resistance. Our findings provided a novel clue for mechanism underlying zinc-induced glucose dysmetabolism and T2DM development, emphasizing the important role of miR-144-3p dysregulation.



Materials and Methods

MiRNA mimic, inhibitor, and **corresponding negative controls** were synthesized by **GenePharma**. **Dual Luciferase Reporter Gene Assay Kit** (**GenePharma**, Shang, China) were used to detect Firefly and Renilla luciferase activity in accordance with the manufacture's instruction.

Redox Biology 64 (2023) 102782

Contents lists available at ScienceDirect

Redox Biology

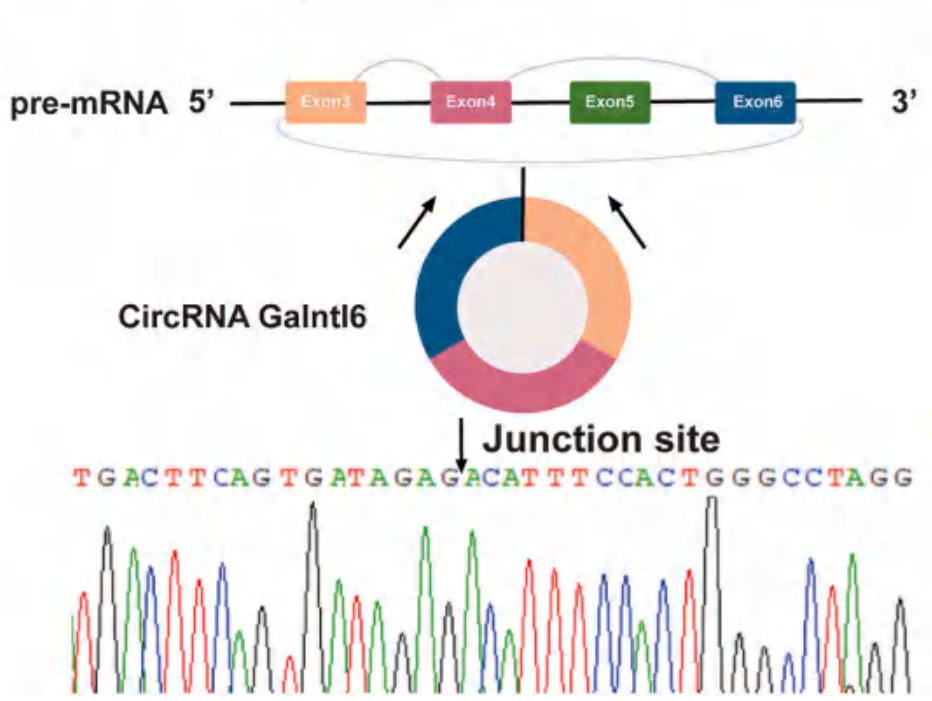
journal homepage: www.elsevier.com/locate/redox

CircRNA Galntl6 sponges miR-335 to ameliorate stress-induced hypertension through upregulating Lig3 in rostral ventrolateral medulla

Shuai Zhang [a], Xueping Wang [b], Gaojun Chen [b], Lei Tong [b], Tengteng Dai [b], Linping Wang [b], Liucun Zhu [b], Haili Zhang [c], Dongshu Du [b,c,d,*]

A B S T R A C T

Rostral ventrolateral medulla (RVLM) is thought to serve as a major vasomotor center that participates in controlling the progression of stress-induced hypertension (SIH). Circular RNAs (circRNAs) perform important functions in the regulation of diverse physiological and pathological processes. However, information concerning the functions of RVLM circRNAs on SIH remains limited. RNA sequencing was performed to profile circRNA expression in RVLMs from SIH rats, which were induced by electric foot shocks and noises. The functions of circRNA Galntl6 in reducing blood pressure (BP) and its potential molecular mechanisms on SIH were investi-gated via various experiments, such as Western blot and intra-RVLM microinjection. A total of 12,242 circRNA transcripts were identified, among which circRNA Galntl6 was dramatically downregulated in SIH rats. The upregulation of circRNA Galntl6 in RVLM effectively decreased the BP, sympathetic outflow, and neuronal excitability in SIH rats. Mechanistically, circRNA Galntl6 directly sponged microRNA-335 (miR-335) and restrained it to reduce oxidative stress. Reintroduction of miR-335 observably reversed the circRNA Galntl6- induced attenuation of oxidative stress. Furthermore, Lig3 can be a direct target of miR-335. MiR-335 inhibi-tion substantially increased the expression of Lig3 and suppressed oxidative stress, and these favorable effects were blocked by Lig3 knockdown. CircRNA Galntl6 is a novel factor that impedes SIH development, and the circRNA Galntl6/miR-335/Lig3 axis represents one of the possible mechanisms. These findings demonstrated circRNA Galntl6 as a possibly useful target for the prevention of SIH.



Redox Biology
2023 Jun 9;64:102782
Impact Factor:11.4

Materials and Methods

As shown in Table S3, **miR-335 agomir, miR-335 antagomir, and miR-335 antagomir NC** were synthesized by **GenePharma** (China).
LV5 > circRNA Galntl6 and **control LV5 > NC plasmids** were synthesized by **GenePharma** (China).

Zheng *et al. J Exp Clin Cancer Res* (2023) 42:63
https://doi.org/10.1186/s13046-023-02624-1

Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

CircFOXK2 promotes hepatocellular carcinoma progression and leads to a poor clinical prognosis via regulating the Warburg effect

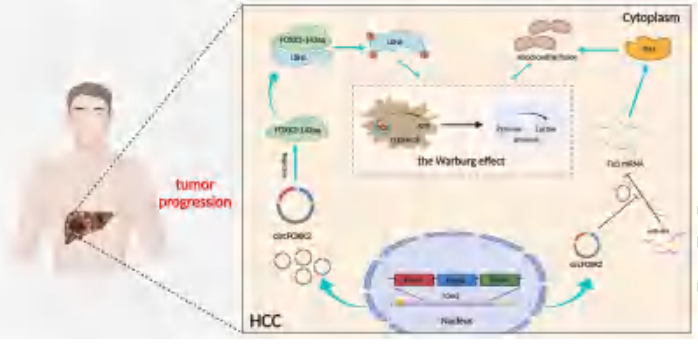
Jun Zheng[1,2†], Xijing Yan[1,2†], Tongyu Lu[1,2†], Wen Song[3†], Yang Li[1,2], Jinliang Liang[2], Jiebin Zhang[1,2], Jianye Cai[1,2], Xin Sui[4], Jiaqi Xiao[1,2], Haitian Chen[1,2], Guihua Chen[1,2], Qi Zhang[1,2*], Yubin Liu[5*], Yang Yang[1,2*], Kanghong Zheng[6*] and Zihao Pan[5*]

Abstract

Background The Warburg effect is well-established to be essential for tumor progression and accounts for the poor clinical outcomes of hepatocellular carcinoma (HCC) patients. An increasing body of literature suggests that circular RNAs (circRNAs) are important regulators for HCC. However, few circRNAs involved in the Warburg effect of HCC have hitherto been investigated. Herein, we aimed to explore the contribution of circFOXK2 to glucose metabolism reprogramming in HCC.

Methods In the present study, different primers were designed to identify 14 circRNAs originating from the *FOXK2* gene, and their differential expression between HCC and adjacent liver tissues was screened. Ultimately, circFOXK2 (hsa_circ_0000817) was selected for further research. Next, the clinical significance of circFOXK2 was evaluated. We then assessed the pro-oncogenic activity of circFOXK2 and its impact on the Warburg effect in both HCC cell lines and animal xenografts. Finally, the molecular mechanisms of how circFOXK2 regulates the Warburg effect of HCC were explored.

Results CircFOXK2 was aberrantly upregulated in HCC tissues and positively correlated with poor clinical outcomes in patients that underwent radical hepatectomy. Silencing of circFOXK2 significantly suppressed HCC progression both in vitro and in vivo. Mechanistically, circFOXK2 upregulated the expression of protein FOXK2-142aa to promote



JOURNAL OF EXPERIMENTAL & CLINICAL CANCER RESEARCH
2023 Mar 15;42(1):63
Impact Factor:11.3

Materials and Methods

The **biotin-labeled miR-484 mimic** (**GenePharma**, China) was transfected into the stably overexpressing circFOXK2 HCC cells for 48 h.
ShRNA knocking down circFOXK2, **siRNA targeting LDHA and miR-484 mimics or inhibitors** were purchased from **GenePharma.**

Chang *et al. J Exp Clin Cancer Res* (2023) 42:13
https://doi.org/10.1186/s13046-022-02572-2

Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

Parvimonas micra activates the Ras/ERK/c-Fos pathway by upregulating miR-218-5p to promote colorectal cancer progression

Yuxiao Chang[1], Ziran Huang[1], Fengyi Hou[1], Yuejiao Liu[1], Likun Wang[1], Zhen Wang[1], Yifan Sun[1], Zhiyuan Pan[1], Yafang Tan[1], Lei Ding[2], Hong Gao[2], Ruifu Yang[1*] and Yujing Bi[1*]

Abstract

Background Colorectal cancer (CRC) is the third most common cancer in the world, and a strong relationship exists between CRC and gut microbiota, which affects the occurrence, development, and metastasis of cancer. Bioinformatics-based analyses revealed that the abundance of *Parvimonas micra* (*P. micra*) in the feces of patients with cancer is significantly higher than that in healthy people. Therefore, an important relationship may exist between *P. micra* and CRC.

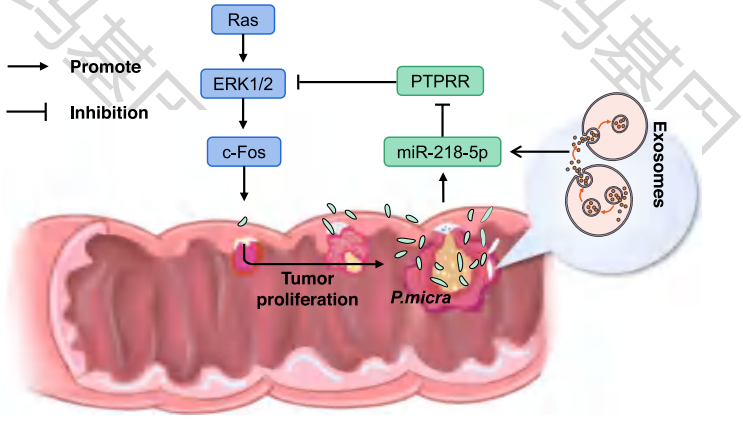
Methods We first confirmed that *P. micra* can promote the proliferation of cell lines through cell experiments and mouse models. Then we selected the signaling pathways and content of exosomes to promote the development of CRC by transcriptomics and microRNA sequencing. Finally, we confirmed that *P. micra* promoted CRC development through miR-218-5p/Ras/ERK/c-Fos pathway through the in vivo and in vitro experiments.

Results First, it was confirmed by in vitro and in vivo experiments that *P. micra* can promote the development of CRC. Transcriptome analysis after the coincubation of bacteria and cells revealed that *P. micra* promoted cell proliferation by activating the Ras/ERK/c-Fos pathway. Furthermore, microRNA sequencing analysis of the cells and exosomes showed that miR-218-5p and protein tyrosine phosphatase receptor R (PTPRR) were the key factors involved in activating the Ras/ERK/c-Fos pathway, and the miR-218-5p inhibitor was used to confirm the role of microRNA in xenograft mice.

Conclusion This experiment confirmed that *P. micra* promoted the development of CRC by upregulating miR-218-5p expression in cells and exosomes, inhibiting *PTPRR* expression, and ultimately activating the Ras/ERK/c-Fos signaling pathway.

Keywords Parvimonas micra, CRC, Exosomes, microRNA, Colorectal cancer, Ras/ERK/c-Fos signaling pathway

Materials and Methods
Tumor-bearing nude mice treated with the **antago-mir** (**GenePharma**, China) were subcutaneously injected with cells using the same protocol.



RESEARCH Open Access

Gastric cancer-derived exosomal miR-519a-3p promotes liver metastasis by inducing intrahepatic M2-like macrophage-mediated angiogenesis

Shengkui Qiu[1,2†], Li Xie[1†], Chen Lu[1†], Chao Gu[1†], Yiwen Xia[1], Jialun Lv[1], Zhe Xuan[1], Lang Fang[1], Jing Yang[1], Lu Zhang[1], Zheng Li[1], Weizhi Wang[1], Hao Xu[1,3], Bowen Li[1*] and Zekuan Xu[1,3*]

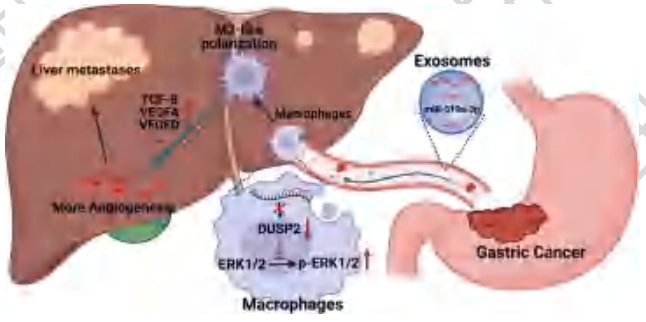
Abstract

Background: Liver metastasis (LM) is a major obstacle to the prognosis of gastric cancer (GC) patients, but the molecular mechanism underlying gastric cancer liver metastasis (GC-LM) remains unknown. Exosomes have been identified as an important mediator of communication between tumor cells and the microenvironment. Therefore, we sought to investigate the effects of primary GC cells on the liver microenvironment and the role of exosomal microRNAs (exo-miRNA) in GC-LM.

Methods: Sequential differential centrifugation, transmission electron microscopy and NanoSight analysis were used to extract and characterize exosomes. MicroRNA sequencing in GC-derived exosomes and mRNA sequencing in PMA-treated THP-1 cells were used to identify differentially expressed miRNAs in exosomes and the functional targets of exosomal miR-519a-3p (exo-miR-519a-3p) in macrophages, respectively. Tracing and internalization of exosomes and transfer of exo-miR-519a-3p were observed by immunofluorescence. Tubule formation assays, aortic ring assays, and exosome-educated GC-LM model were used to investigate the roles of GC-derived exosomes and exo-miR-519a-3p in angiogenesis and GC-LM. Luciferase reporter assay, qRT-PCR, Western blot, ELISA, flow cytometry and immunofluo-rescence were used to investigate the regulatory mechanism of exo-miR-519a-3p at GC-LM.

Results: The expression level of miR-519a-3p in serum exosomes was significantly higher in GC-LM patients than in patients without LM, and high expression of exo-miR-519a-3p indicates a worse prognosis. GC-derived exosomes are mainly accumulated in the liver and internalized by intrahepatic macrophages. Mechanistically, exo-miR-519a-3p activates the MAPK/ERK pathway by targeting DUSP2, thereby causing M2-like polarization of macrophages. M2-like polarized macrophages accelerate GC-LM by inducing angiogenesis and promoting intrahepatic premetastatic niche formation.

Conclusions: Our results indicate that exo-miR-519a-3p plays a critical role in mediating crosstalk between primary GC cells and intrahepatic macrophages and is a potential therapeutic target for GC-LM.



JOURNAL OF EXPERIMENTAL & CLINICAL CANCER RESEARCH
2022 Dec;41(1):1-20
Impact Factor:11.3

Materials and Methods

The **miR-519a-3p inhibitor/mimics** or **negative controls** were purchased from **GenePharma** Co.

Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

Exosomal miR-106b-5p derived from melanoma cell promotes primary melanocytes epithelial-mesenchymal transition through targeting EphA4

Wenkang Luan[1*†], Yuting Ding[2†], Haolan Xi[3†], Hongru Ruan[1], Feng Lu[1], Shaojun Ma[1] and Jinlong Wang[1]

Abstract

Background: Cancer-secreted exosomal miRNAs regulates the biological processes of many tumours. The serum level of exosomal miR-106b-5p is significantly increased in melanoma patients. However, the role and molecular mechanisms of exosomal miR-106b-5p in melanoma remains unclear.

Methods: Quantitative real-time polymerase chain reaction (qRT-PCR) was used to detect the expression of miR-106b-5p and EphA4 in melanoma tissues. Transmission electron microscopy (TEM) and western blotting were used to identify exosome. QRT-qPCR and Cy3-labelled miR-106b-5p were used to demonstrated the transmission of melanoma cell-secreted exosomal miR-106b-5p. Western blotting, Immunofluorescence, adhesion, transwell and scratch wound assay were used to explore the role of exosomal miR-106b-5p in melanocytes. Luciferase reporter assays and RNA-Chromatin Immunoprecipitation (ChIP) assay were used to confirm whether erythropoietin-producing hepatocellular carcinoma receptor A4 (EphA4) was a direct target of miR-106b-5p.

Results: We found that miR-106b-5p levels were increased in melanoma tissue, and high miR-106b-5p expression is an independent risk factor for the overall survival of patients with melanoma. miR-106b-5p is enriched in melanoma cell-secreted exosomes and transferred to melanocytes. Exosomal miR-106b-5p promotes the epithelial-to-mesenchymal transition (EMT), migration, invasion and adhesion of melanocytes. Exosomal miR-106b-5p exerted its role by targeting EphA4 to activate the ERK pathway. We demonstrated that exosomal miR-106b-5p promoted melanoma metastasis in vivo through pulmonary metastasis assay.

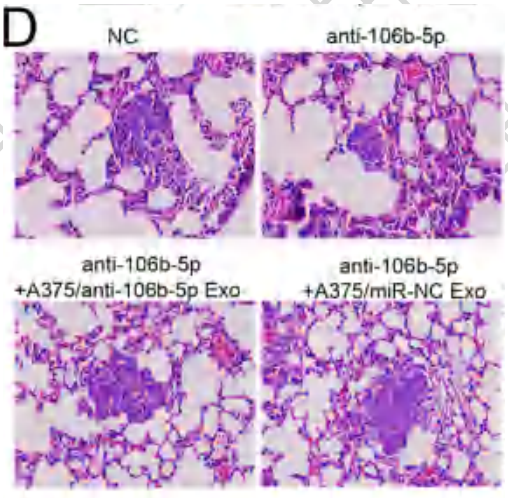
Conclusions: Thus, melanoma cell-secreted exosomal miR-106b-5p may serve as a diagnostic indicator and potential therapeutic target in melanoma patients.

Keywords: Melanoma, Exosomal, miR-106b-5p, EphA4, EMT

Journal of Experimental & Clinical Cancer Research
2021 Mar 19; 40:107
Impact Factor: 11.3

Materials and Methods

miR-106b-5p mimic, miR-106b-5p inhibitor and negative controls were chemically synthesized by **GenePharma** , and the **small interference RNAs (siRNAs)** for the reduceion of EphA4 expression were also obtained from **GenePharma**. Melanoma cells were transfected with **Cy3-labelled miR-106b-5p** (**GenePharma**).



Lv et al. Journal of Experimental & Clinical Cancer Research (2021) 40:76
https://doi.org/10.1186/s13046-021-01864-3

Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

CircAGAP1 promotes tumor progression by sponging miR-15-5p in clear cell renal cell carcinoma

Qi Lv[1†], Gangmin Wang[2†], Yinan Zhang[3], Aijun Shen[1], Junjun Tang[1], Yi Sun[5], Chunhui Ma[4*] and Peijun Wang[1*]

Abstract

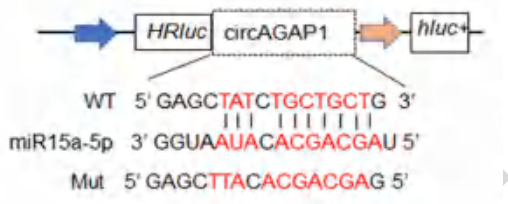
Background: Accumulating evidence has revealed that circular RNAs (circRNAs), as novel noncoding RNAs, play critical roles in carcinogenesis and tumor progression. However, the functions and molecular mechanisms of circRNAs in clear cell renal cell carcinoma (ccRCC) are largely unknown.

Methods: The expression and functions of circAGAP1 were identified in clinical samples, ccRCC cells and in vivo animal models. The molecular mechanism of circAGAP1 was investigated by fluorescence in situ hybridization, RNA immunoprecipitation and luciferase assays.

Results: circAGAP1 (circ0058792) expression was significantly upregulated in ccRCC tissues compared to adjacent nontumor tissues. Moreover, the expression of circAGAP1 was closely related to the tumor size, nuclear grade and clinical stage of ccRCC in patients. Mechanistic studies demonstrated that cytoplasmic circAGAP1 targeted miR-15-5p in an RNA-induced silencing complex. Additionally, miR-15-5p expression was downregulated in ccRCC. Luciferase reporter assays showed that E2F transcription factor 3 (E2F3) was a target of miR-15-5p, and upregulated E2F3 expression was positively correlated with circAGAP1 in ccRCC. Furthermore, the tumor-promoting functions of circAGAP1 could be alleviated by miR-15-5p mimics in vitro and in vivo.

Conclusion: Our results clarify that circAGAP1 exerts its oncogenic functions as a competitive endogenous RNA
(ceRNA) by sponging miR-15-5p, which promotes E2F3 expression. Targeting circAGAP1 might be a new attractive therapeutic strategy in ccRCC.

Keywords: Clear cell renal carcinoma, circRNA, miR-15, E2F3, ceRNA



Journal of Experimental & Clinical Cancer Research 2021 Feb 22; 40:76
Impact Factor: 11.3

Materials and Methods

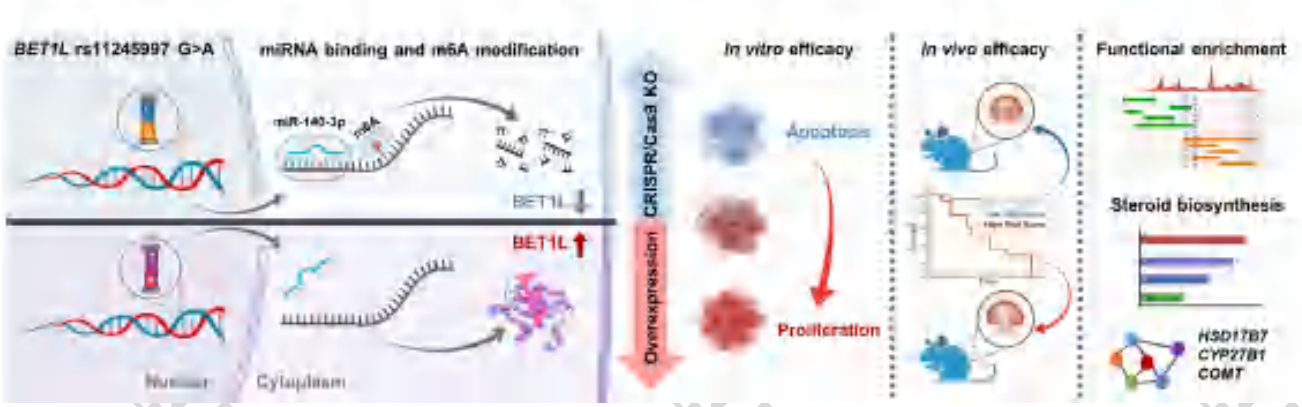
miR-15a-5p mimic and **corresponding control (NC)** were purchased from **GenePharma**. **circAGAP1 siRNA** (5′-GACGATGCCTTCGTGAACA-3′) and **control siRNA** (5′-TTCTCCGAACGTGTCACGT-3′) were produced by **GenePharma**.

A germline variant in the BET1L 3'-UTR confers colorectal cancer susceptibility by reducing miRNA binding and m6A modification

Shuwei Li[a,b,*], Mulong Du[b,c,*], Kaili Xu[a,b], Shuai Ben[a,b], Tianru Zhu[a,b], Mengfan Guo[a,b], Junyi Xin[a,b], Lingjun Zhu[d], Dongying Gu[e], Zhengdong Zhang[a,b], Meilin Wang[a,b,f,†]

ABSTRACT

Genetic variants in regions encoding 3'-untranslated regions (UTR) of mRNA potentially alter miRNA binding affinity and N6-methyladenosine (m6A) levels to affect gene expression. A better understanding of the association of these variants with colorectal cancer susceptibility could facilitate development of cancer prevention and treatment approaches. Here, we analyzed miRNA expression profiles and integrated genetic analyses from 8,533 individuals to evaluate the effects of altered miRNA-binding sites on colorectal cancer risk. The single nucleotide polymorphism rs11245997 in the BET1L 3'-UTR was significantly associated with colorectal cancer risk. The rs11245997 A allele facilitated BET1L expression by disrupting miR-140-3p binding. It also reduced BET1L m6A modification, which upregulated BET1L mRNA and protein expression levels through a mechanism mediated by the m6A methyltransferases (METTL14 and WTAP) and the m6A demethylase ALKBH5. Moreover, higher expression of BET1L was associated with advanced tumor stages and poor patient prognosis. Increased BET1L expression promoted growth of colorectal cancer cells in vitro and in vivo, which could be partially rescued with miR-140-3p overexpression. RNA-Seq and pathway analyses indicated that BET1L is associated with the steroid biosynthesis pathway through regulation of HSD17B7, CYP27B1 and COMT. These findings provide insights into the involvement of genetic variants of BET1L in the development and progression of colorectal cancer.



CANCER RESEARCH
2023 Apr;83 (13): 2142–2154
Impact Factor:11.2

Materials and Methods

Mimics and inhibitors of miRNA-140-3p and **the negative control miRNA** were purchased from **GenePharma** Tech (Shanghai, China).

Liu, Z., Wang, T., She, Y. et al. N6-methyladenosine-modified circIGF2BP3 inhibits CD8+ T-cell responses to facilitate tumor immune evasion by promoting the deubiquitination of PD-L1 in non-small cell lung cancer. Mol Cancer 20, 105 (2021). **IF:37.3**
Yang, C., Yuan, W., Yang, X., Li, P., Wang, J., Han, Zhang, W. (2018). Circular RNA circ-ITCH inhibits bladder cancer progression by sponging miR-17/miR-224 and regulating p21, PTEN expression. Molecular cancer, 17(1), 19. **IF:37.3**
Liu H, Bi J, Dong W, et al. Invasion-related circular RNA circFNDC3B inhibits bladder cancer progression through the miR-1178-3p/G3BP2/SRC/FAK axis. Molecular Cancer. 2018; 17: 161-80. **IF: 37.3**
Lin, X., Wang, S., Sun, M., Zhang, C., Wei, C., Yang, C. Xiong, B. (2019). miR-195-5p/NOTCH2-mediated EMT modulates IL-4 secretion in colorectal cancer to affect M2-like TAM polarization. Journal of hematology & oncology, 12(1), 1-14. **IF:28.5**
Chen, X., Wang, L., Huang, R., Qiu, H., Wang, P., Wu, D., Na, J. (2019). Dgcr8 deletion in the primitive heart uncovered novel microRNA regulating the balance of cardiac-vascular gene program. Protein & cell, 10(5), 327-346. **IF:21.1**
Li ZL, Lv LL, Tang TT, et al. HIF-1a inducing exosomal microRNA-23a expression mediates the cross-talk between tubular epithelial cells and macrophages in tubulointerstitial inflammation. Kidney International. 2019; 95: 388-404. **IF:19.6**
Wang, C., Li, X., Xue, B. et al. RasGRP1 promotes the acute inflammatory response and Wang, C., Li, X., Xue, B. et al. RasGRP1 promotes the acute inflammatory response and restricts inflammation-associated cancer cell growth. Nat Commun 13, 7001 (2022). **IF:16.6**
Wang YM, Zheng YF, Yang SY, et al. MicroRNA-197 controls ADAM10 expression to mediate McCP2's role in the differentiation of neuronal progenitors. Cell Death & Differentiation. 2018 Dec 3. **IF: 12.4**
Yuan H, Xu X, Feng X, et al. A novel long noncoding RNA PGC1β-OT1 regulates adipocyte and osteoblast differentiation through antagonizing miR-148a-3p. Cell Death & Differentiation. 2019 Jan 14. **IF: 12.4**
Pan S, Zhu J, Liu P, Wei Q, Zhang S, An W, Tong Y, Cheng Z, Liu F. FN1 mRNA 3'-UTR supersedes traditional fibronectin 1 in facilitating the invasion and metastasis of gastric cancer through the FN1 3'-UTR-let-7i-5p-THBS1 axis. Theranostics. 2023 Sep 25;13(14):5130-5150. **IF:12.4**
Zhang H, Du Z, Tu C, Zhou X, Menu E, Wang J. Hypoxic bone marrow stromal cells secrete miR-140-5p and miR-28-3p target SPRED1 to confer drug resistance in multiple myeloma. Cancer Res. 2023 Sep 26. **IF:11.2**
Lozano J, Montañez R, Belles X. MiR-2 family regulates insect metamorphosis by controlling the juvenile hormone signaling pathway. PNAS. 2015 Feb 4. **IF: 11.1**
Ning Y, Huang P, Chen G, Xiong Y, Gong Z, Wu C, Xu J, Jiang W, Li X, Tang R, Zhang L, Hu M, Xu J, Xu J, Qian H, Jin C, Yang Y. Atorvastatin-pretreated mesenchymal stem cell-derived extracellular vesicles promote cardiac repair after myocardial infarction via shifting macrophage polarization by targeting microRNA-139-3p/Stat1 pathway. BMC Med. 2023 Mar 16;21(1):96. **IF: 9.3**
Jin H, Sun W, Zhang Y, et al. MicroRNA-411 downregulation enhances tumor growth by upregulating MLLT11 expression in human bladder cancer[J]. Molecular Therapy-Nucleic Acids, 2018, 11:312-322. **IF: 8.8**
Liu L, He J, Wei X, Wan G, et al. MicroRNA-20a-mediated loss of autophagy contributes to breast tumorigenesis by promoting genomic damage and instability. Oncogene. 2017 Oct 19; 36: 5874-84. **IF: 8**

适配体

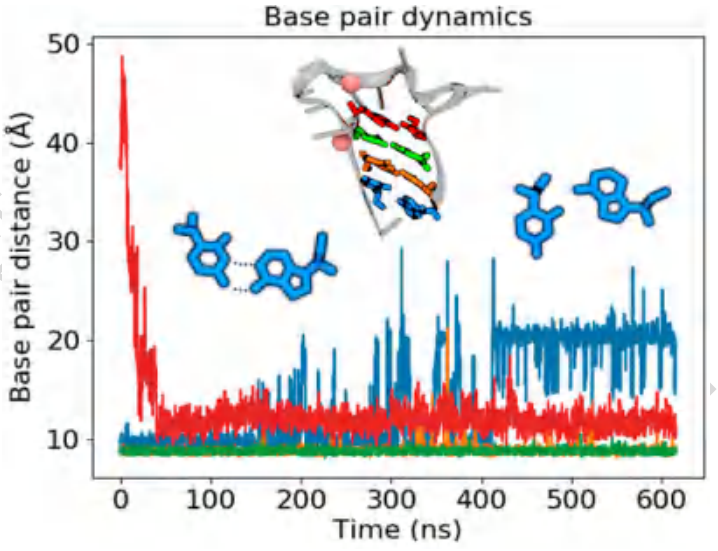
In silico design and validation of high-affinity RNA aptamers targeting epithelial cellular adhesion molecule dimers

David R. Bell[a,b,1], Jeffrey K. Weber[b,1], Wang Yin[c,1], Tien Huynh[b], Wei Duan[c,2], and Ruhong Zhou[a,b,d,2]

Nucleic acid aptamers hold great promise for therapeutic applica-tions due to their favorable intrinsic properties, as well as high-throughput experimental selection techniques. Despite the utility of the systematic evolution of ligands by the exponential enrich-ment (SELEX) method for aptamer determination, complementary in silico aptamer design is highly sought after to facilitate virtual screening and increased understanding of important nucleic acid–protein interactions. Here, with a combined experimental and the-oretical approach, we have developed two optimal epithelial cellular adhesion molecule (EpCAM) aptamers. Our structure-based in silico method first predicts their binding modes and then optimizes them for EpCAM with molecular dynamics simulations, docking, and free energy calculations. Our isothermal titration calorimetry experiments further confirm that the EpCAM aptamers indeed exhibit enhanced affinity over a previously patented nanomolar aptamer, EP23. More-over, our study suggests that EP23 and the de novo designed aptamers primarily bind to EpCAM dimers (and not monomers, as hypothesized in previous published works), suggesting a paradigm for developing EpCAM-targeted therapies. RNA aptamer | rational design | molecular dynamics | isothermal titration calorimetry | epithelial cellular adhesion molecule

PNAS
2020 Apr 14; 8486–8493
Impact Factor: 11.1

Materials and Methods
The **original EpCAM aptamer EP23** and the **mutant aptamers A5U and G15U** were synthesized by Suzhou **Genepharma** (Suzhou, China), followed by HPLC purification.



International Journal of Nanomedicine

Dovepress
open access to scienti ic and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Poly(lactic-co-glycolic acid) nanoparticles conjugated with CD133 aptamers for targeted salinomycin delivery to CD133$^+$ osteosarcoma cancer stem cells

Background: Cancer stem cells (CSCs) possess the characteristics associated with normal stem cells and are responsible for cancer initiation, recurrence, and metastasis. CD133 is regarded as a CSCs marker of osteosarcoma, which is the most common primary bone malignancy in childhood and adolescence. Salinomycin, a polyether ionophore antibiotic, has been shown to kill various CSCs, including osteosarcoma CSCs. However, salinomycin displayed poor aqueous solubility that hinders its clinical application. The objective of this study was to develop salinomycin-loaded nanoparticles to eliminateCD133+ osteosarcoma CSCs.

Methods: The salinomycin-loaded PEGylated poly(lactic-co-glycolic acid) nanoparticles (SAL-NP) conjugated with CD133 aptamers (Ap-SAL-NP) were developed by an emulsion/solvent evaporation method, and the targeting and cytotoxicity of Ap-SAL-NP to CD133+ osteosarcoma CSCs were evaluated.

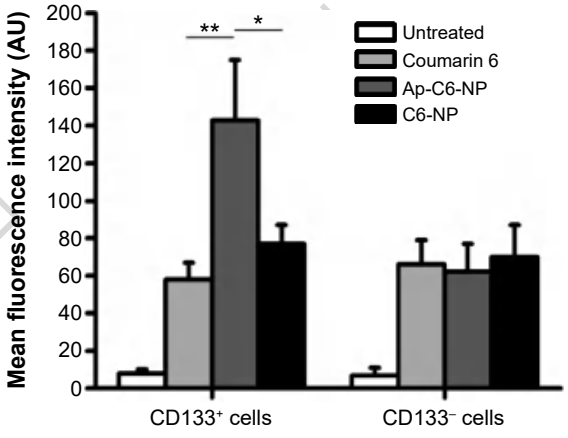
Results: The nanoparticles are of desired particle size (~150 nm), drug encapsulation efficiency (~50%), and drug release profile. After 48 hours treatment of the Saos-2 CD133+ osteosarcoma cells with drugs formulated in Ap-SAL-NP, SAL-NP, and salinomycin, the concentrations needed to kill 50% of the incubated cells were found to be 2.18, 10.72, and 5.07 μg/mL, respec-tively, suggesting that Ap-SAL-NP could be 4.92 or 2.33 fold more effective than SAL-NP or salinomycin, respectively. In contrast, Ap-SAL-NP was as effective as SAL-NP, and less effective than salinomycin in Saos-2 CD133- cells, suggesting that Ap-SAL-NP possess specific cytotoxicity toward Saos-2 CD133+ cells. Ap-SAL-NP showed the best therapeutic effect in Saos-2 osteosarcoma xenograft mice, compared with SAL-NP or salinomycin. Significantly, Ap-SAL-NP could selectively kill CD133+ osteosarcoma CSCs both in vitro and in vivo, as reflected by the tumorsphere formation and proportion of Saos-2 CD133+ cells. Conclusion: Our results suggest that CD133 is a potential target for drug delivery to osteo-sarcoma CSCs and that it is possible to significantly inhibit the osteosarcoma growth by killing CD133+ osteosarcoma CSCs. We demonstrated that Ap-SAL-NP have the potential to target and kill CD133+ osteosarcoma CSCs.

Keywords: targeted therapy, ligand-conjugated nanomedicines, cancer initiating cells

International Journal of Nanomedicine
2015 Mar 31; 10 2537–2554
Impact Factor: 8

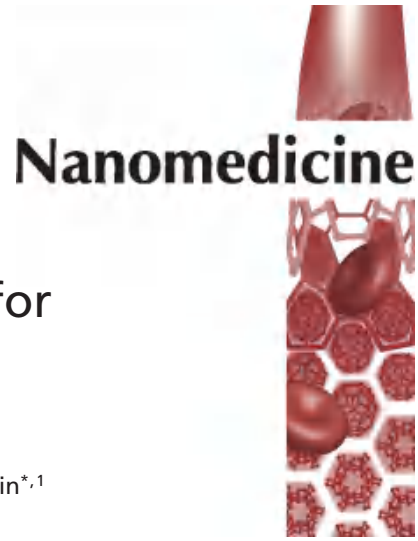
Materials and Methods

A15 aptamers (sequence: 5′-NH2 CCCUCCUACAUAGGG-3′) were synthesized by **GenePharma** Co., Ltd (Shanghai, People's Republic of China).



Research Article

For reprint orders, please contact: reprints@futuremedicine.com



PLGA nanoparticles with CD133 aptamers for targeted delivery and sustained release of propranolol to hemangioma

Xiaonan Guo[1], Xiaoshuang Zhu[2], Jie Gao[3], Dakan Liu[2], Changxian Dong[**,2] & Xing Jin[*,1]

Aim: To develop propranolol-loaded poly(lactic-co-glycolic acid) nanoparticle with CD133 aptamers (PPN-CD133) to treat infantile hemangioma.

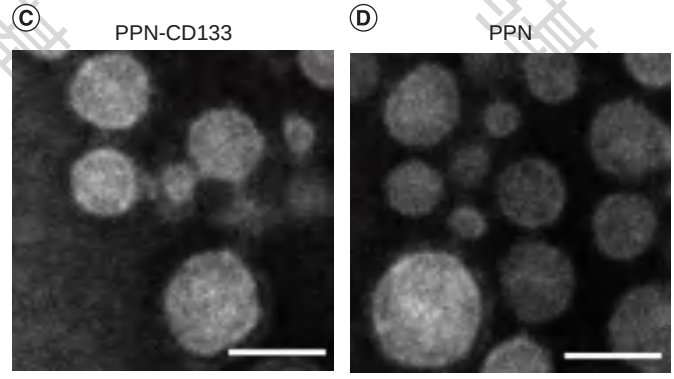
Materials & methods: The antihemangioma activity and mecha-nism of PPN-CD133 were evaluated.

Results & conclusion: PPN-CD133 are of desired size (143.7 nm), drug encapsulation efficiency (51.8%) and sustained drug release for 8 days. PPN-CD133 could effectively bind to $CD133^+$ hemangioma stem cells, resulting in enhanced cytotoxic effect and reduced expression of an-giogenesis factors in hemangioma stem cells. The therapeutic effect of PPN-CD133 in hemangioma was superior to that of untargeted PPN and propranolol *in vivo*, as reflected by reduced hemangioma volume, weight and microvessel density. PPN-CD133 represents a very promising approach to locally and efficiently deliver propranolol leading to significant inhibition of infantile hemangioma.

Nanomedicine
2017 Sep 29; 1743-5889
Impact Factor: 5.5

Materials and Methods

A15 aptamers (sequence: 5'-NH2-CCCUCCUACAUAGGG-3') were synthesized by **GenePharma** Co., Ltd (Shanghai, PR China).



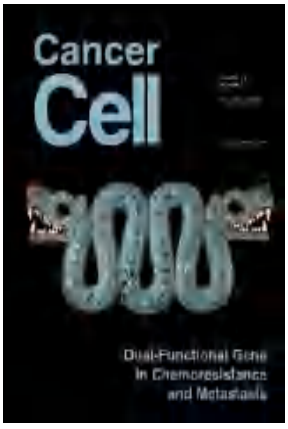
AlShamaileh, H., Wang, T., Xiang, D., Yin, W., Tran, P. H., Barrero, R. A., Zhang, P. Z., Li, Y., Kong, L., Liu, K., Zhou, S. F., Hou, Y., Shigdar, S., & Duan, W. (2017). Aptamer-mediated survivin RNAi enables 5-fluorouracil to eliminate colorectal cancer stem cells. Scientific reports, 7(1), 5898. **IF:4.6**
Wang T, Yin W, AlShamaileh H, et al. A Detailed Protein-SELEX Protocol Allowing Visual Assessments of Individual Steps for a High Success Rate. Hum Gene Ther Methods. 2019;30(1):1-16. **IF:4.2**

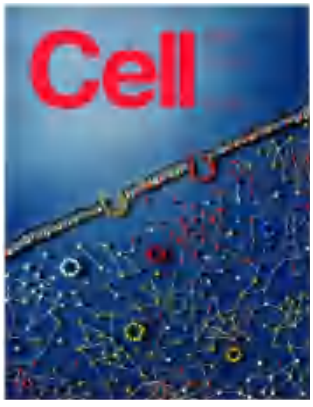
So far GenePharma products have been used in more than 60,000 articles published on magazines domestic and overseas.


nature
MICROBIAL MENAGERIE


PNAS
Artificial photosynthesis and solar fuels


nature biotechnology


Cancer Cell
Dual-Functional Gene in Chemoresistance and Metastasis

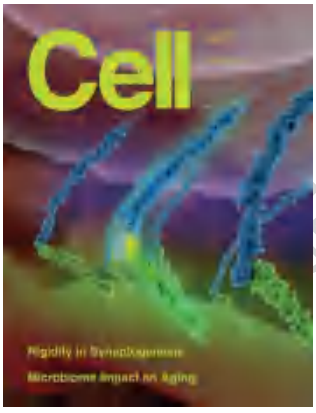

Cell


Cell
Catching Cellular Kinase-Substrate Relationships
Review
Looking downstream of AKT

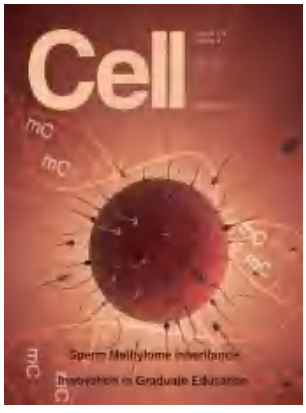

Cell
Organizing Stable Micromuscle Arrays
Review
Rethinking Morphogen Gradients


nature biotechnology


Cell Research


Cell
Rigidity in Synaptogenesis
Microbiome Impact on Aging


ADVANCED SCIENCE
Open Access


Cell
Sperm Methylome Inheritance
Innovation in Graduate Education

Shanghai GenePharma Co., Ltd.

Add: Building 2, 368 Zhangjiang Road，
Pudong New Area, Shanghai, 201203
Tel: 021-51320195，51370738，51370739
Fax: 021-51320295
Email: order@genepharma.com
support@genepharma.com

Suzhou GenePharma Co., Ltd.

Add: 199 Dongping Street, Suzhou, 215123
Tel: 0512-86668828
Fax: 0512-86665900
Email: szorder@genepharma.com
szsupport@genepharma.com

A003-V008-20231221