GenePharma

载体及病毒
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。

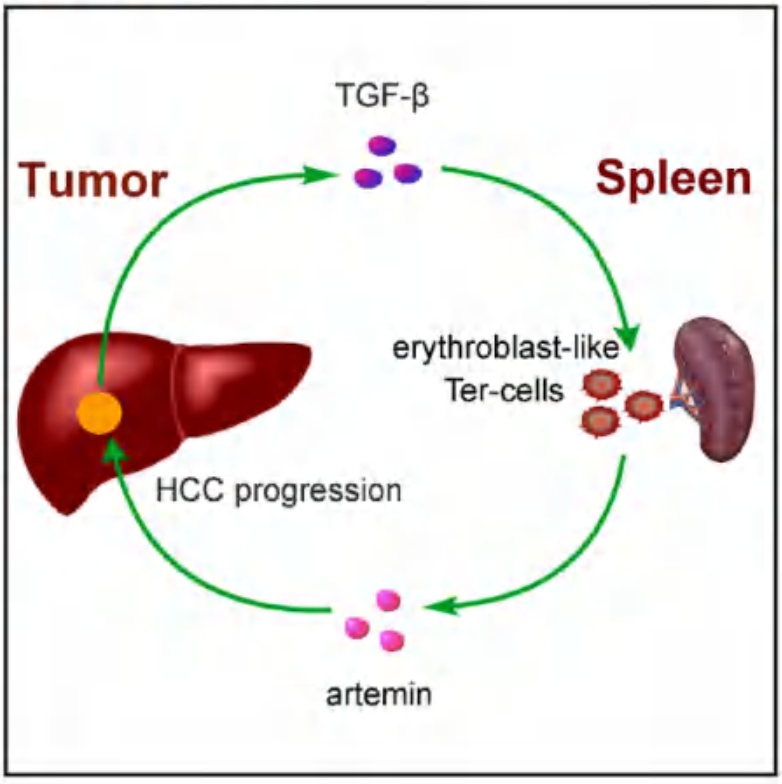
公司产品涵盖化学合成的 RNA 单体，普通和修饰的 siRNA oligo，生物大分子标记用荧光染料；生物合成 siRNA、shRNA；转录编码 shRNA 的 DNAs、转录编码 shRNA 的质粒载体；慢病毒载体 lentiviurs 的构建以及包装，基于化学合成的 RNAi 的全程服务；基于载体调控的 shRNA RNAi全程服务；siRNA 相关试剂和 RNA 技术相关产品的销售；microRNA 荧光定量 PCR 检测试剂盒、荧光定量 PCR 探针和引物、荧光定量 PCR 检测服务；基因编辑相关试剂和技术服务；转基因动物；常用的分子生物学试剂、实验耗材销售等。

DNA 克隆和突变——shRNA

Cell

Tumor-Induced Generation of Splenic Erythroblast-like Ter-Cells Promotes Tumor Progression

Graphical Abstract



Authors

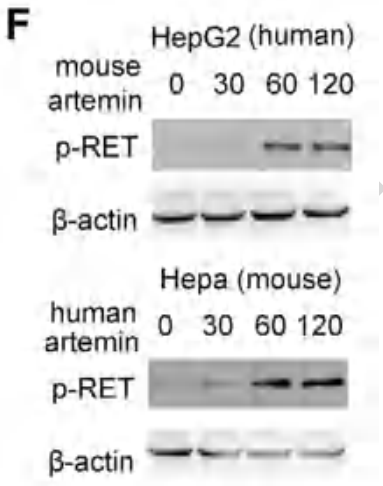
Yanmei Han, Qiuyan Liu, Jin Hou, ...,
Yizhi Yu, Nan Li, Xuetao Cao

Correspondence

caoxt@immunol.org

In Brief

A population of immune cells in the erythroid lineage are induced in a mouse model of hepatocellular carcinoma, which promotes tumor progression through artemin production.



Cell
2018 Apr 19; 173: 634-48
Impact Factor: 64.5

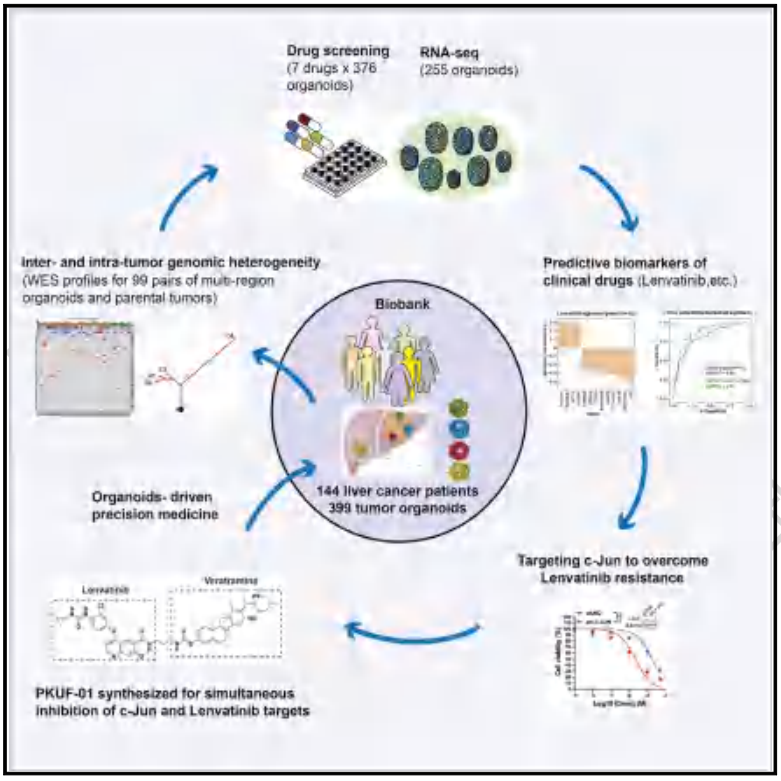
Materials and Method

$2x10^5$ HepG2 cells were seeded into each well of 6-well plates and incubated overnight, then transfected with GFRα3 **shRNA plasmids** (design by **GenePharma**, China).

Cancer Cell

Pharmacogenomic profiling of intra-tumor heterogeneity using a large organoid biobank of liver cancer

Graphical abstract



Authors

Hui Yang, Jinghui Cheng, Hao Zhuang, ..., Jiangong Zhang, Jianmin Wu, Ning Zhang

Correspondence

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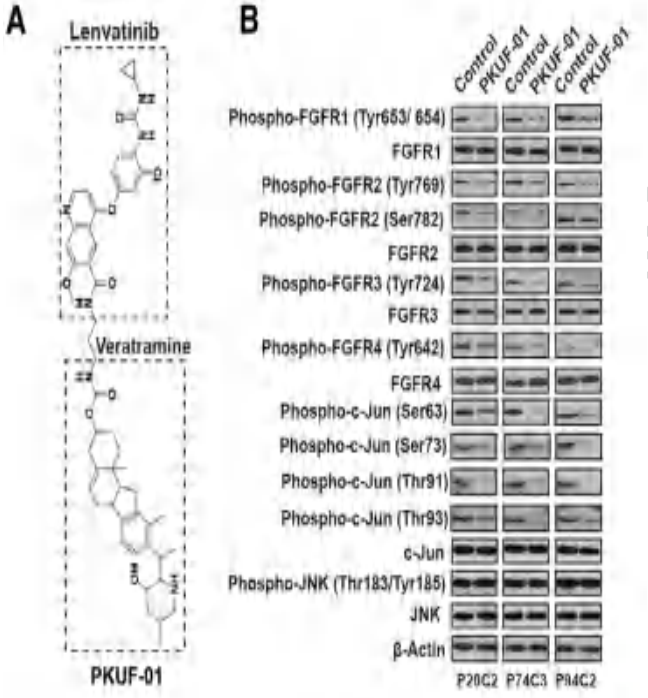
wujm@bjmu.edu.cn (J.W.),
zhangning@bjmu.edu.cn (N.Z.)

In brief

Yang et al. reveal the genomic and phenotypic inter- and intra-tumor heterogeneity of liver cancer using a biobank of 399 tumor organoids from 144 patients. Pharmacogenomic profiling and mechanistic investigation generate biomarker panels predicting drug responses and identify c-Jun overexpression as a key factor leading to lenvatinib resistance.



CANCER CELL
Cancer Cell 42, 535–551, April 8, 2024
Impact Factor:50.3

Materials and Methods

sh c-JUN vector GenePharma

Jiang et al. Molecular Cancer (2022) 21:150
https://doi.org/10.1186/s12943-022-01605-w

Molecular Cancer

RESEARCH Open Access

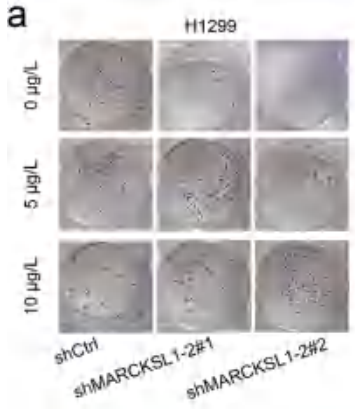
MARCKSL1–2 reverses docetaxel-resistance of lung adenocarcinoma cells by recruiting SUZ12 to suppress HDAC1 and elevate miR-200b

Min Jiang[1†], Feng Qi[2†], Kai Zhang[3†], Xiaofei Zhang[4†], Jingjing Ma[5], Suhua Xia[1], Longbang Chen[6], Zhengyuan Yu[1*], Jing Chen[7*] and Dongqin Chen[4,8,9*]

Abstract

Background: Long non-coding RNAs (lncRNAs) are implicated in the development of multiple cancers. In our previ-ous study, we demonstrated that HDAC1/4-mediated silencing of microRNA-200b (miR-200b) enhances docetaxel (DTX)-resistance of human lung adenocarcinoma (LAD) cells.

Methods and results: Herein, we probed the function of LncRNA MARCKSL1–2 (MARCKSL1-transcript variant 2, NR_052852.1) in DTX resistance of LAD cells. It was found that MARCKSL1–2 expression was markedly reduced in DTX-resistant LAD cells. Through gain- or loss- of function assays, colony formation assay, EdU assay, TUNEL assay, and flow cytometry analysis, we found that MARCKSL1–2 suppressed the growth and DTX resistance of both parental and DTX-resistant LAD cells. Moreover, we found that MARCKSL1–2 functioned in LAD through increasing miR-200b expression and repressing HDAC1. Mechanistically, MARCKSL1–2 recruited the suppressor of zeste 12 (SUZ12) to the promoter of histone deacetylase 1 (HDAC1) to strengthen histone H3 lysine 27 trimethylation (H3K27me3) of HDAC1 promoter, thereby reducing HDAC1 expression. MARCKSL1–2 up-regulated miR-200b by blocking the suppressive effect of HDAC1 on the histone acetylation modification at miR-200b promoter. Furthermore, in vivo analysis using mouse xenograft tumor model supported that overexpression of MARCKSL1–2 attenuated the DTX resistance in LAD tumors.



Molecular Cancer
2022 Dec;21(1):1-16
Impact Factor:37.3

Materials and Methods

The specific **shRNAs** targeting MARCKSL1–2 (shMARCKSL1–2#1 and shMARCKSL1–2#2), HDAC1 (sh/HDAC1), or SUZ12 (shSUZ12#1 and shSUZ12#2), as well as relative control shRNAs (sh/Ctrl), were procured from **GenePharma** (Shanghai, China).

Ni et al. Journal of Hematology & Oncology (2018) 11:17
https://doi.org/10.1186/s13045-018-0562-z

Journal of Hematology & Oncology

RESEARCH Open Access

CBX7 regulates stem cell-like properties of gastric cancer cells via p16 and AKT-NF-κB-miR-21 pathways

Su-Jie Ni[1,2,4†], Li-Qin Zhao[1,2†], Xiao-Feng Wang[1,2†], Zhen-Hua Wu[1,2], Rui-Xi Hua[1,2], Chun-Hua Wan[5], Jie-Yun Zhang[1,2], Xiao-Wei Zhang[1,2], Ming-Zhu Huang[1,2], Lu Gan[1,2], Hua-Lin Sun[6], Goberdhan P. Dimri[3] and Wei-Jian Guo[1,2*]

Abstract

Background: Chromobox protein homolog 7 (CBX7), a member of the polycomb group (PcG) family of proteins, is involved in the regulation of cell proliferation and cancer progression. PcG family members, such as BMI, Mel-18, and EZH2, are integral constituents of the polycomb repressive complexes (PRCs) and have been known to regulate cancer stem cell (CSC) phenotype. However, the role of other PRCs' constituents such as CBX7 in the regulation of CSC phenotype remains largely elusive. This study was to investigate the role of CBX7 in regulating stem cell-like properties of gastric cancer and the underlying mechanisms.

Methods: Firstly, the role of CBX7 in regulating stem cell-like properties of gastric cancer was investigated using sphere formation, Western blot, and xenograft tumor assays. Next, RNA interference and ectopic CBX7 expression were employed to determine the impact of CBX7 on the expression of CSC marker proteins and CSC characteristics. The expression of CBX7, its downstream targets, and stem cell markers were analyzed in gastric stem cell spheres, common cancer cells, and gastric cancer tissues. Finally, the pathways by which CBX7 regulates stem cell-like properties of gastric cancer were explored.

Results: We found that CBX7, a constituent of the polycomb repressive complex 1 (PRC1), plays an important role in maintaining stem cell-like characteristics of gastric cancer cells via the activation of AKT pathway and the downregulation of p16. Spearman rank correlation analysis showed positive correlations among the expression of CBX7 and phospho-AKT (pAKT), stem cell markers OCT-4, and CD133 in gastric cancer tissues. In addition, CBX7 was found to upregulate microRNA-21 (miR-21) via the activation of AKT-NF-κB pathway, and miR-21 contributes to CBX7-mediated CSC characteristics.

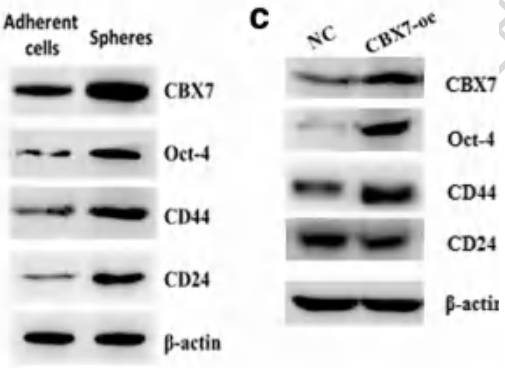
Conclusions: CBX7 positively regulates stem cell-like characteristics of gastric cancer cells by inhibiting p16 and activating AKT-NF-κB-miR-21 pathway.

Keywords: CBX7, p16, AKT, miR-21, Gastric cancer, Stem cells

Journal of Hematology & Oncology
2018 Feb 8; 11:17
Impact Factor: 28.5

Materials and Methods

Retroviral vectors (pGPU/Hygro and pEX-2/Hygro) expressing CBX7, CBX7 **shRNA,** and **p16 shRNA** were obtained from Shanghai **GenePharma** Co Ltd.



Research Article

EASL | JOURNAL OF HEPATOLOGY

Human hepatitis B virus surface and e antigens inhibit major vault protein signaling in interferon induction pathways

Shi Liu, Nanfang Peng, Jiajia Xie, Qian Hao, Mo Zhang, Yi Zhang, Zhangchuan Xia, Gang Xu, Fanpeng Zhao, Qing Wang, Tao Han, Ying Zhu*

State Key Laboratory of Virology and College of Life Sciences, Wuhan University, Wuhan 430072, China

Background & Aims: We previously demonstrated that major vault protein (MVP) is a novel virus-induced host factor and its expression upregulates type-I interferon production, leading to cellular antiviral response. However, it remains unclear whether the antiviral function of MVP is impaired during hepatitis B virus (HBV) infection and what mechanisms are involved. Therefore, the aim of this study was to assess whether HBV can alter MVP expression despite the lack of type-I IFN induction and shed light on the underlying mechanisms HBV utilizes to evade host innate immune response.

Methods: The ability of HBV surface and e antigens to inhibit MVP signaling in interferon induction pathways was evaluated by co-immunoprecipitation, immunofluorescence, quantitative RT-PCR, Western blot and reporter assays.

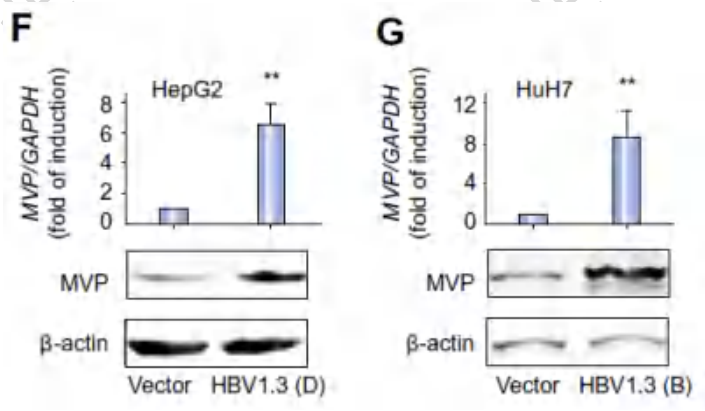
Results: In our current study, we found high levels of MVP in peripheral blood mononuclear cells, sera, and liver tissue from HBV-infected patients relative to healthy individuals. We determined that MVP intracellularly associates with MyD88, an adapter protein involved in virus-triggered induction of type-I IFN. Protein truncation analysis revealed that the middle domain of MVP (amino acid residues 310–620) was essential for MyD88 binding. Conversely, HBV inhibited MVP–induced type-I IFN production by suppressing MVP/MyD88 interaction. HBV antigens, both HBsAg and HBeAg, suppressed this interaction by competitively binding to the essential MyD88 binding region of MVP and limiting downstream IFN signaling.

Conclusions: MVP is a virus-induced protein capable of binding with MyD88 leading to type-I IFN production. HBV may evade an immune response by disrupting this interaction and limiting type-I IFN antiviral activity.

Journal of Hepatology
2015 May; 62(5): 1015-23
Impact Factor: 25.7

Materials and Methods

MVP shRNA and **irrelevant shRNA control (shRNA-control)** were purchased **GenePharma** (Shanghai GenePharma) .



Drug Resistance Updates 71 (2023) 101003

Contents lists available at ScienceDirect

Drug Resistance Updates

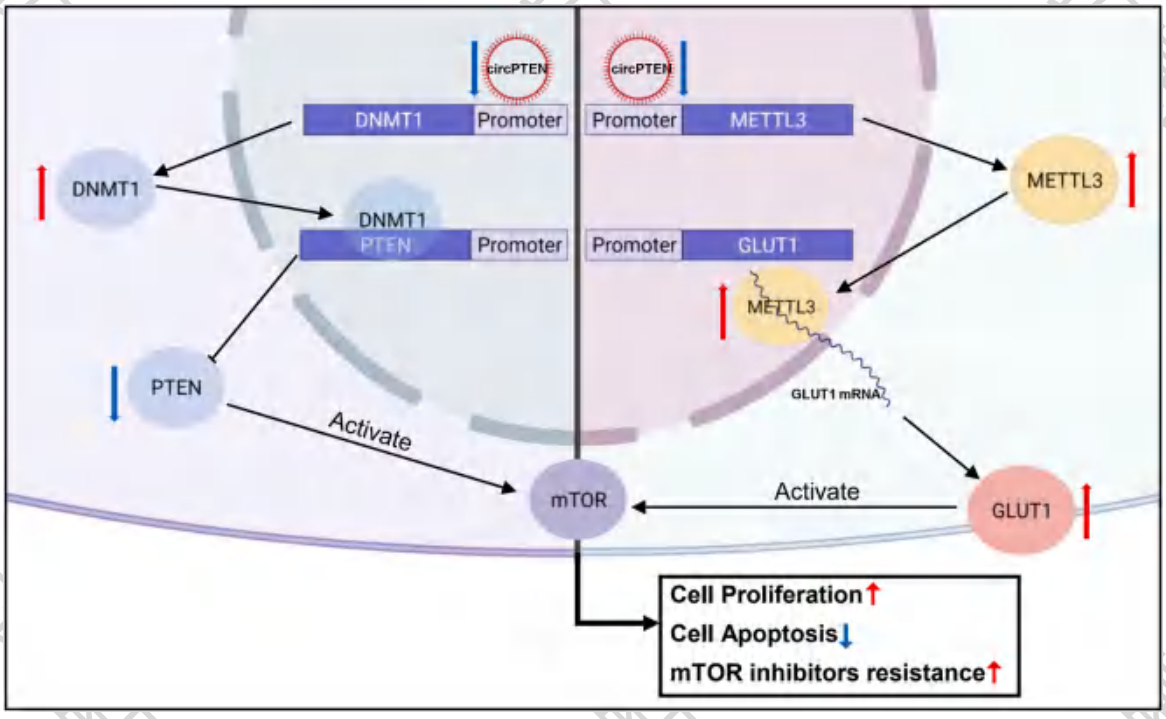
journal homepage: www.elsevier.com/locate/drup

CircPTEN suppresses human clear cell renal carcinoma progression and resistance to mTOR inhibitors by targeting epigenetic modification

Yangyang Zhan [a,1], Yang Liu [c,1], Rui Yang [d,1], Qiong Chen [b,1], Fei Teng [e,1], Yueying Huang [a], Xin Jiang [d], Yueming Wang [b], Bin Yu [g], Ding Zhang [h], Leilei Bao [a,*], Xinli Liu [f,*], Jiwei Huang [b,*]

A B S T R A C T

Renal cell carcinoma (RCC) is known to be the most commonly diagnosed kidney cancer. Clear cell RCC (ccRCC) represents approximately 85 % of diagnosed RCC cases. Targeted therapeutics, such as multi-targeted tyrosine kinase inhibitors (TKI) and mTOR inhibitors, are widely used in ccRCC therapy. However, patients treated with mTOR and TKI inhibitors easily acquire drug resistance, making the therapy less effective. Here, we demon-strated that circPTEN inhibits the expression of its parental gene PTEN by reducing methylation of the PTEN promotor and inhibits GLUT1 expression by reducing m6A methylation of GLUT1, which suppresses ccRCC progression and resistance to mTOR inhibitors.



DRUG RESISTANCE UPDATES
2023 Sep 2;71:101003
Impact Factor:24.3

Materials and Methods

CircPTEN, vector, short hairpin (sh)-circ-PTEN, and sh-negative control (NC) were synthesized by **GenePharma** Co. (GenePharma, Shanghai, China).

Contents lists available at ScienceDirect

Drug Resistance Updates

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

N6-methyladenosine-modified circular RNA QSOX1 promotes colorectal cancer resistance to anti-CTLA-4 therapy through induction of intratumoral regulatory T cells

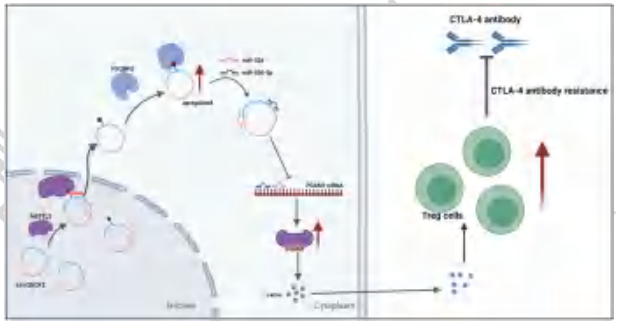
Zhihua Liu [b,1], Nanxin Zheng [a,d,1], Juan Li [e,1], Chao Li [b], Dan Zheng [c], Xue Jiang [c], Xiaoying Ge [c], Min Liu [b], Lianjie Liu [a,d], Zhen Song [b], Leilei Bao [c,*], Yangyang Zhan [c,*], Xianhua Gao [a,d,**]

Abstract

Background: Colorectal cancer (CRC) is the 3rd most common cancer worldwide. CircRNAs are promising novel biomarkers for CRC. T regulatory (Treg) cells express the immune checkpoint receptor of cytotoxic T-lympho-cyte-associated antigen-4 (CTLA-4) and promote tumor immunological tolerance. We therefore investigate the biological functions and mechanisms of circQSOX1 in CRC tumorigenesis; involvement of circQSOX1 in pro-moting Treg cell-mediated CRC immune escape in anti-CTLA-4 therapy.

Methods: Bioinformatics analyses were performed for circQSOX1expressions, specific binding sites, and N6-methyladenosine (m6A) motifs of circQSOX1, thatwere further validated with a series of experiments. Func-tions of circQSOX1 in promoting CRC development, Treg cells-based immune escape, and anti-CTLA-4 therapy response were investigated both in vitro and in vivo.

Results: High circQSOX1 expression was associated with carcinogenesis and poor clinical outcome of CRC patients. METTL3-mediated RNA m6A modification on circQSOX1 could be read by IGF2BP2 in CRC cells. CircQSOX1 promoted CRC development by regulating miR-326/miR-330–5p/PGAM1 axis. CircQSOX1 regulated glycolysis and promoted immune escape of CRC cells, and inhibits anti-CTLA-4 therapy response in CRC patients. Conclusion: m6A-modified circQSOX1 facilitated CRC tumorigenesis by sponging miR-326 and miR-330–5p to promotes PGAM1 expression, which further promoted CRC immune escape by activating glycolysis and inacti-vating the anti-CTLA-4 therapy response of CRC. Combined treatment with sh-circQSOX1 and anti-CTLA-4 could be a strategy to overcome Treg cell-mediated CRC immune therapy resistance.



DRUG RESISTANCE UPDATES
2022 Dec;65:100886
Impact Factor:24.3

Materials and Methods

Two **specific small hairpin RNAs (shRNAs)** targeted to circQSOX1 were synthesized from **GenePharma** (Shanghai, China) and cloned into pLKO.1 lentiviral vector to stably knock down target genes in CRC cells as previous report .

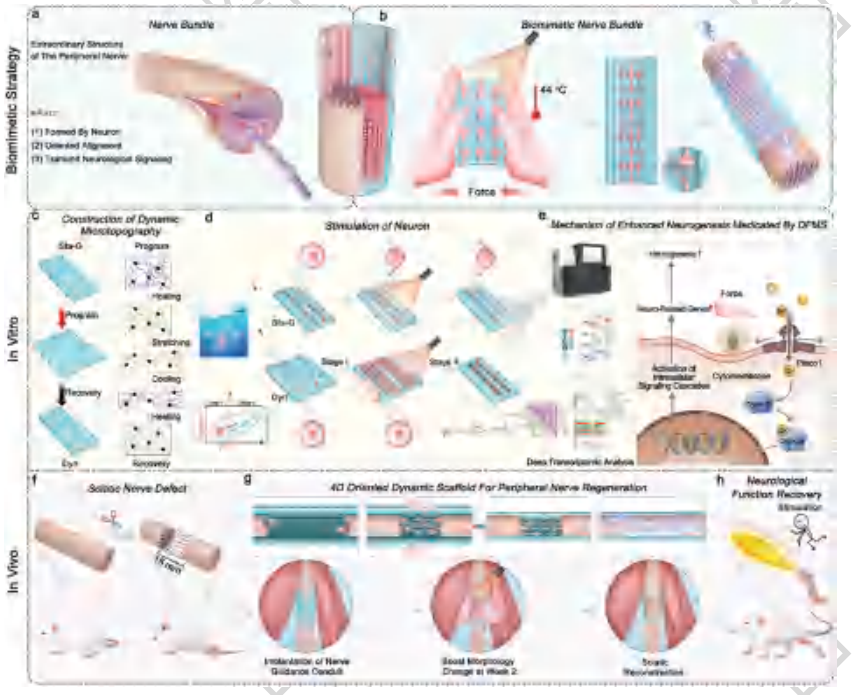
Biotin-labeled circQSOX1 and negative control (NC) probes were synthesized by **GenePharma** (Shanghai, China).

ADVANCED FUNCTIONAL MATERIALS
www.afm-journal.de

4D Oriented Dynamic Scaffold for Promoting Peripheral Nerve Regeneration and Functional Recovery

Mouyuan Sun, Dongqi You, Ning Zhan, Chao Liu, Xiaoting Zhang, Lining Lin, Jingyu Zhang, Yiting Lou, Yuewei Chen, Chundi Liu, Huiming Wang, Yong He,* and Mengfei Yu**

Neurological function recovery after peripheral nerve injury (PNI) is exceptionally challenging, chiefly because neurons cannot efficiently proliferate, differentiate, and form regenerated axons to pass through the defect region expeditiously and transmit neurological signals. In this study, a four-dimensional (4D) oriented dynamic scaffold is constructed based on shape memory polymer (SMP), which can regulate spatiotemporally controllable neuronal early adequate proliferation, subsequently effective differentiation and axon formation by synergizing the on-demand microtopography and deformation force-based mechanical stimuli (DFMS). This dynamic scaffold can accelerate the restoration of large segmental nerve defects, elevate the neural signaling efficiency by 60% compared with static scaffold, and finally form the functionalized robust regenerating nerve fascicles with comparable therapeutic effects on autologous nerve transplantation. Furthermore, the crucial role of Piezo1/Camk2b modulated neuronal differentiation and axon extension is also revealed through deep transcriptomic analysis. In summary, the 4D oriented dynamic scaffold can precisely and remotely regulate neuronal behavior and fate in a non-invasive way, which has excellent potential for clinical application in peripheral nerve restoration.



ADVANCED FUNCTIONAL MATERIALS
2023 Sep 12;2305827
Impact Factor:19.0

Materials and Methods

Rat-Piezo1-shRNA, GMPO polybrene, and puromycin dihydrochloride were derived by Shanghai **GenePharma** Co. (China).

nature communications

Article

https://doi.org/10.1038/s41467-023-42508-8

The Lin28b/Wnt5a axis drives pancreas cancer through crosstalk between cancer associated fibroblasts and tumor epithelium

Received: 27 November 2022

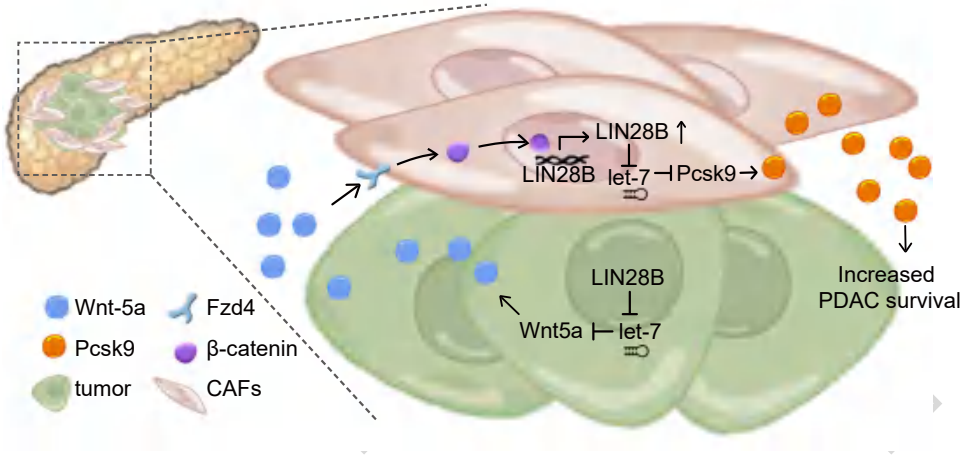
Accepted: 13 October 2023

Published online: 28 October 2023

Check for updates

Zhaoqi Shu[1,2,11], Minghe Fan[1,2,11], Bo Tu[3,4,11], Zhiheng Tang[5], Haojie Wang[6], Haimeng Li[1,2], Hengchao Li[7], Meng Yuan[1,2], Jingru Bai[8,9], Sihan Huo[1,2], Lina Wang[1], Wei-Guo Zhu[8,9], Wei Wang[10], Xiaoyun Liu[5], Shaokun Shu[2] & Ying Zhao[1,2]

Bidirectional signal transduction between tumor epithelial cells and tumor microenvironment (TME) is important for tumor development. Here we show that Lin28b/let-7 pathway is indispensable for modulating the expression of Wnt5a in tumor epithelium, which could be secreted and then up-regulates Lin28b in cancer-associated fibroblasts (CAFs). Moreover, we demonstrate that Lin28b in CAFs promoted growth of PDAC by inducing cytokine PCSK9's production. Using an orthotopic mouse model of PDAC, we find that depletion of Lin28b in CAFs reduced tumor weight, highlighting the importance of Lin28b in PDAC stroma. Thus, our study shows that the Lin28b-Wnt5a axis plays a critical role in bidirectional crosstalk between pancreatic tumor epithelium and TME and results in a pro-tumorigenic contexture.



Nature Communications
2023 Oct 28;14:6885
Impact Factor:16.6

Materials and Methods

Puromycin-resistance **shRNA plasmids** were purchased from Suzhou **GenePharma**.

Received: 10 November 2022 | Revised: 23 February 2023 | Accepted: 16 May 2023

DOI: 10.1002/cac2.12443

ORIGINAL ARTICLE

N6-methyladenosine modification of CENPF mRNA facilitates gastric cancer metastasis via regulating FAK nuclear export

Penghui Xu[1,†] | **Jing Yang**[1,†] | **Zetian Chen**[1,†] | **Xing Zhang**[1,†] | **Yiwen Xia**[1] | **Sen Wang**[1] | **Weizhi Wang**[1] | **Zekuan Xu**[1,2,3]

Abstract

Background: N6-methyladenosine (m^6A) modification is the most common modification that occurs in eukaryotes. Although substantial effort has been made in the prevention and treatment of gastric cancer (GC) in recent years, the prognosis of GC patients remains unsatisfactory. The regulatory mechanism between m^6A modification and GC development needs to be elucidated. In this study, we examined m^6A modification and the downstream mechanism in GC.

Methods: Dot blotting assays, The Cancer Genome Atlas analysis, and quan-titative real-time PCR (qRT-PCR) were used to measure the m^6A levels in GC tissues. Methylated RNA-immunoprecipitation sequencing and RNA sequenc-ing were performed to identify the targets of m^6A modification. Western blotting, Transwell, wound healing, and angiogenesis assays were conducted to examine the role of centromere protein F (CENPF) in GC in vitro. Xenograft, immuno-histochemistry, and in vivo metastasis experiments were conducted to examine the role of CENPF in GC in vivo. Methylated RNA-immunoprecipitation-qPCR, RNA immunoprecipitation-qPCR and RNA pulldown assays were used to verify the m^6A modification sites of *CENPF*. Gain/loss-of-function and rescue experiments were conducted to determine the relationship between CENPF and the mitogen-activated protein kinase (MAPK) signaling pathway in GC cells. Coimmunoprecipitation, mass spectrometry, qRT-PCR, and immunofluores-cence assays were performed to explore the proteins that interact with CENPF and elucidate the regulatory mechanisms between them.

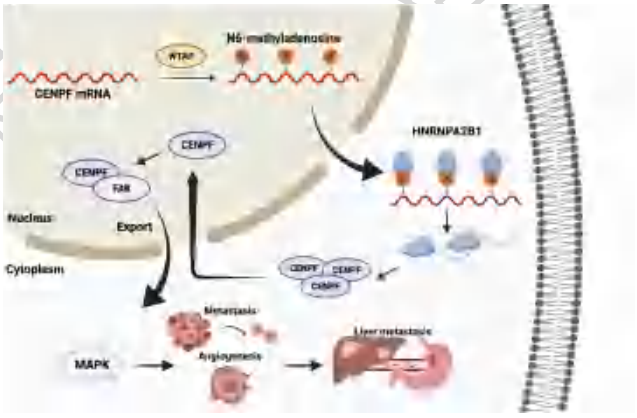
Results: CENPF was upregulated in GC and facilitated the metastasis of GC both in vitro and in vivo. Mechanistically, increased m^6A modification of *CENPF* was mediated by methyltransferase 3, and this modified molecule could be recognized by heterogeneous nuclear ribonucleoprotein A2/B1 (HNRNPA2B1), thereby promoting its mRNA stability. In addition, the metastatic phenotype of CENPF was dependent on the MAPK signaling pathway. Furthermore, CENPF could bind to FAK and promote its localization in the cytoplasm. Moreover, we discovered that high expression of CENPF was related to lymphatic invasion and overall survival in GC patients.

Conclusions: Our findings revealed that increased m6A modification of CENPF facilitates the metastasis and angiogenesis of GC through the CENPF/FAK/MAPK and epithelial-mesenchymal transition axis. CENPF expression was correlated with the clinical features of GC patients; therefore, CENPF may serve as a prognostic marker of GC.

Cancer Communications
2023 May 16; 43:685–705
Impact Factor: 16.2

Materials and Methods

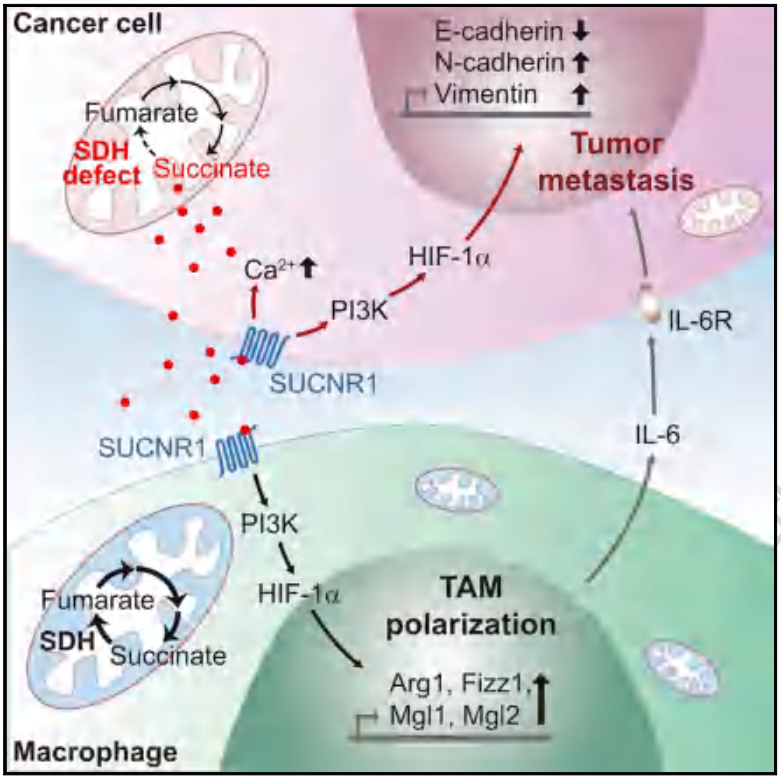
Small interfering RNA (siRNA) and **short hairpin RNA (shRNA)** for gene knockdown and **plasmids** for overex-pression were designed and synthesized by **GenePharma** (Shanghai, China).



Molecular Cell

Cancer-Derived Succinate Promotes Macrophage Polarization and Cancer Metastasis via Succinate Receptor

Graphical Abstract



Authors

Jing-Yiing Wu, Tsai-Wang Huang, Yi-Ting Hsieh, ..., Hsing-Jien Kung, Yu-Juei Hsu, Cheng-Chin Kuo

Correspondence

kuocc@nhri.org.tw

In Brief

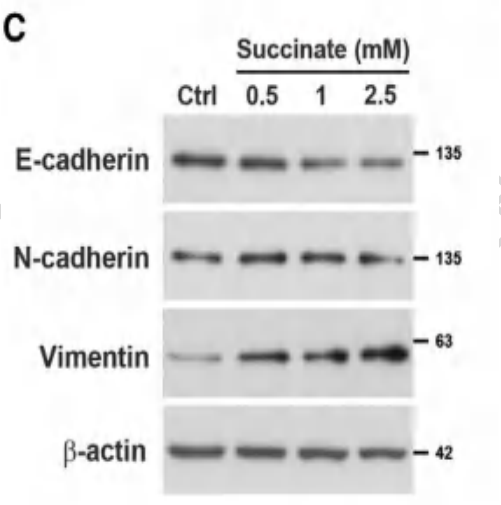
We have shown that cancer cells secrete succinate into extracellular milieu, which mediates TAM polarization and promotes cancer metastasis. Succinate exerts its effects on TAM polarization and cancer metastasis via a specific membrane receptor, SUCNR1, which transmits signaling through the PI3K/HIF-1a pathway.

Molecular Cell
2020 Jan 16;77, 213–227
Impact Factor:16

Materials

Recombinant DNA

pGPU6/Neo-human SUCNR1 shRNA	GenePharma
pGPU6/Neo-human HIF1a shRNA	GenePharma
pGPU6/Neo-mosue SUCNR1 shRNA	GenePharma



nature communications

Article

https://doi.org/10.1038/s41467-024-54400-0

High mobility group A1 (HMGA1) promotes the tumorigenesis of colorectal cancer by increasing lipid synthesis

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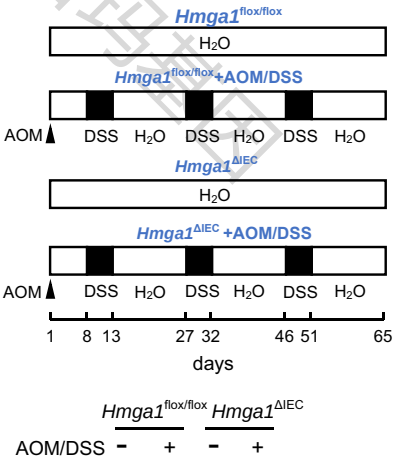
Check for updates

Yuan Zhao, Meng-Jie Liu, Lei Zhang, Qi Yang, Qian-Hui Sun, Jin-Rong Guo, Xin-Yuan Lei, Kai-Yue He, Jun-Qi Li, Jing-Yu Yang, Yong-Ping Jian ✉ & Zhi-Xiang Xu ✉

Metabolic reprogramming is a hallmark of cancer, enabling tumor cells to meet the high energy and biosynthetic demands required for their proliferation. High mobility group A1 (HMGA1) is a structural transcription factor and frequently overexpressed in human colorectal cancer (CRC). Here, we show that HMGA1 promotes CRC progression by driving lipid synthesis in a AOM/DSS-induced CRC mouse model. Using conditional knockout ($Hmga1^{\triangle IEC}$) and knock-in ($Hmga1^{IEC\text{-}OE/+}$) mouse models, we demonstrate that HMGA1 enhances CRC cell proliferation and accelerates tumor development by upregulating fatty acid synthase (FASN). Mechanistically, HMGA1 increases the transcriptional activity of sterol regulatory element-binding protein 1 (SREBP1) on the FASN promoter, leading to increased lipid accumulation in intestinal epithelial cells. Moreover, a high-fat diet exacerbates CRC progression in $Hmga1^{\triangle IEC}$ mice, while pharmacological inhibition of FASN by orlistat reduces tumor growth in $Hmga1^{IEC\text{-}OE/+}$ mice. Our findings suggest that targeting lipid metabolism could offer a promising therapeutic strategy for CRC.



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Nature Communications

Nature Communications | (2024) 15:9909

Impact Factor:14.7

Materials

shHMGA1 plasmids were purchased from **Genepharma** (Shanghai, China).

Received: 8 October 2022 | Accepted: 3 March 2023

DOI: 10.1002/jmv.28637

RESEARCH ARTICLE

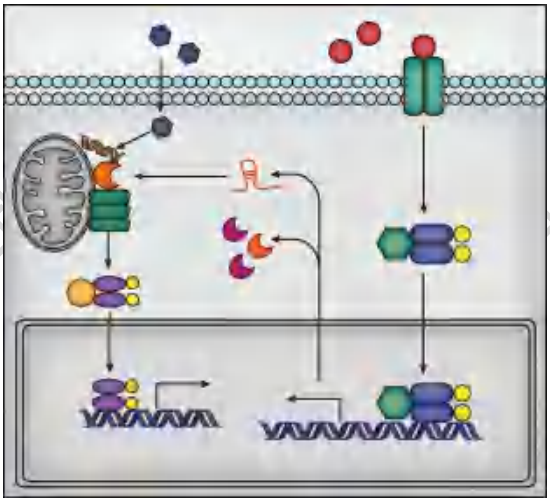
JOURNAL OF MEDICAL VIROLOGY WILEY

ZNFX1 antisense RNA1 promotes antiviral innate immune responses via modulating ZNFX1 function

Xin Jia[1] | Meiqi Zhang[1] | Haojia Wang[2] | Cuiqin Cheng[2] | Qiqi Li[1] | Yiying Li[2] | Lingdong Kong[1] | Xihong Lan[3] | Yuxi Wang[2] | Xue Liang[2] | Shaochun Yuan[4] | Yao Wang[2,5] | Anlong Xu[2,4,5]

Abstract

Increasing evidence suggests that natural antisense transcriptional lncRNAs regulate their adjacent coding genes to mediate diverse aspects of biology. Bioinformatics analysis of the previously identified antiviral gene ZNFX1 revealed neighboring lncRNA ZFAS1 transcribed on the opposite strand from ZNFX1. Whether ZFAS1 exerts antiviral function via regulating the dsRNA sensor ZNFX1 is unknown. Here we found that ZFAS1 was upregulated by RNA and DNA viruses and type I IFNs (IFN-I) dependent on Jak-STAT signaling, similar to the transcription regulation of ZNFX1. Knockdown of endogenous ZFAS1 partially facilitated viral infection, while ZFAS1 overexpression showed opposite effects. In addition, mice were more resistant to VSV infection with the delivery of human ZFAS1. We further observed that ZFAS1 knockdown significantly inhibited IFNB1 expression and IFR3 dimeriza-tion, whereas ZFAS1 overexpression positively regulated antiviral innate immune pathways. Mechanistically, ZFAS1 positively regulated ZNFX1 expression and antiviral function by enhancing the protein stability of ZNFX1, thereby establishing a positive feedback loop to enhance antiviral immune activation status. In short, ZFAS1 is a positive regulator of antiviral innate immune response via regulating its neighbor gene ZNFX1, adding new mechanistic insight into lncRNA-mediated regulation of signaling in innate immunity.



JOURNAL OF MEDICAL VIROLOGY
2023 Mar 9;95(3):e28637
Impact Factor:12.7

Materials and Methods

Plasmids encoding shRNAs were obtained from Shanghai **GenePharma**.

DNA 克隆和突变——过表达质粒

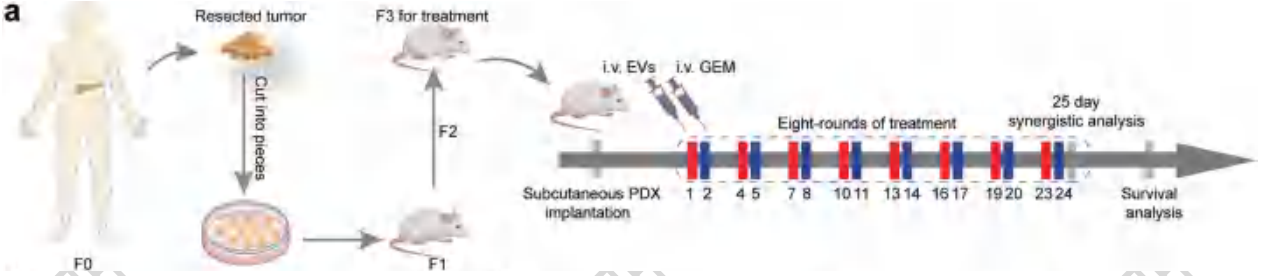
Signal Transduction and Targeted Therapy www.nature.com/sigtrans

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

Signal Transduction and Targeted Therapy (2024) 9:151

Impact Factor:40.8

Materials and Methods

100 pmol **si-FERMT2** (RioBio) and 2 μg **plasmid expressing** PYCR1 (**GenePharma**)

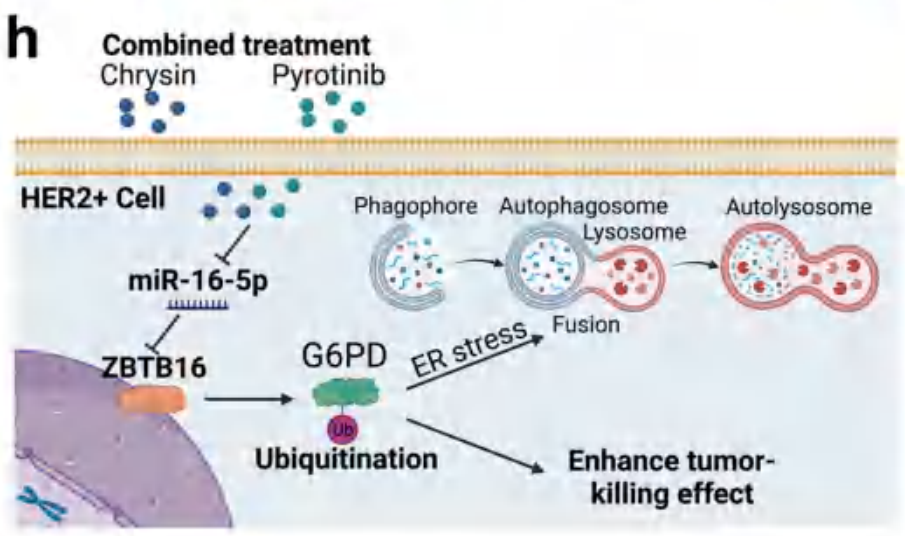
ARTICLE OPEN

Pyrotinib and chrysin synergistically potentiate autophagy in HER2-positive breast cancer

Xiaoxiao Liu[1,2], Xing Zhang[3], Zhiying Shao[4], Xiaorong Zhong[1], Xin Ding[2], Liang Wu[5], Jie Chen[6], Ping He[1], Yan Cheng[1], Kunrui Zhu[1], Dan Zheng[1], Jing Jing[7]✉ and Ting Luo[1]✉

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC) has been the most challenging subtype of BC, consisting of 20% of BC with an apparent correlation with poor prognosis. Despite that pyrotinib, a new HER2 inhibitor, has led to dramatic improvements in prognosis, the efficacy of pyrotinib monotherapy remains largely restricted due to its acquired resistance. Therefore, identifying a new potential antitumor drug in combination with pyrotinib to amplify therapeutic efficacy is a pressing necessity. Here, we reported a novel combination of pyrotinib with chrysin and explored its antitumor efficacy and the underlying mechanism in HER2-positive BC. We determined that pyrotinib combined with chrysin yielded a potent synergistic effect to induce more evident cell cycle arrest, inhibit the proliferation of BT-474 and SK-BR-3 BC cells, and repress in vivo tumor growth in xenograft mice models. This may be attributed to enhanced autophagy induced by endoplasmic reticulum stress. Furthermore, the combined treatment of pyrotinib and chrysin induced ubiquitination and glucose-6-phosphate dehydrogenase (G6PD) degradation by upregulating zinc finger and BTB/POZ domain-containing family protein 16 (ZBTB16) in tumorigenesis of BC. Mechanistically, we identified that miR-16-5p was a potential upstream regulator of ZBTB16, and it showed a significant inverse correlation with ZBTB16. Inhibition of miR-16-5p overexpression by restoring ZBTB16 significantly potentiated the overall antitumor efficacy of pyrotinib combined with chrysin against HER2-positive BC. Together, these findings demonstrate that the combined treatment of pyrotinib and chrysin enhances autophagy in HER2-positive BC through an unrecognized miR-16-5p/ZBTB16/G6PD axis.

Signal Transduction and Targeted Therapy (2023)8:463 ; https://doi.org/10.1038/s41392-023-01689-w



Signal Transduction and Targeted Therapy
2023 Dec 18;8(1):463
Impact Factor:39.3

Materials and Methods

G6PD overexpression plasmid and **miR-16-5p mimic** were designed and synthesized by **GenePharma** (Shanghai, China).

ARTICLE OPEN

Global profiling of O-GlcNAcylated and/or phosphorylated proteins in hepatoblastoma

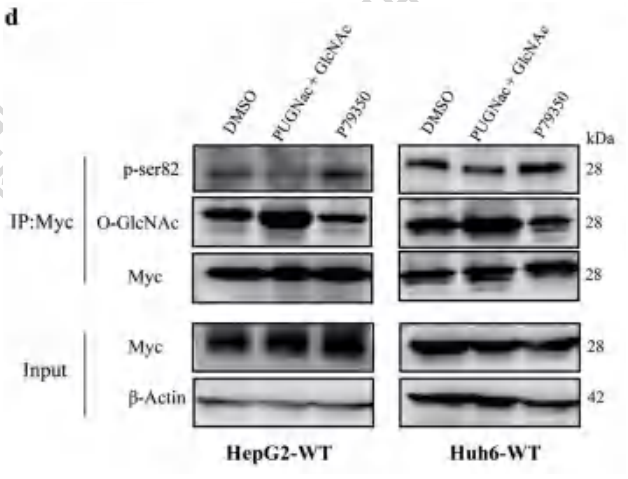
Hang Song[1], Ji Ma[1], Zhixuan Bian[1], Shuhua Chen[2], Jiabei Zhu[1], Jing Wang[3], Nan Huang[4], Minzhi Yin[5], Fenyong Sun[4], Min Xu[3] and Qiuhui Pan[1]

O-linked-β-N-acetylglucosamine (O-GlcNAc) glycosylation (O-GlcNAcylation) and phosphorylation are critical posttranslational modifications that are involved in regulating the functions of proteins involved in tumorigenesis and the development of various solid tumors. However, a detailed characterization of the patterns of these modifications at the peptide or protein level in hepatoblastoma (HB), a highly malignant primary hepatic tumor with an extremely low incidence in children, has not been performed. Here, we examined O-GlcNAc-modified or phospho-modified peptides and proteins in HB through quantitative proteomic analysis of HB tissues and paired normal liver tissues. Our results identified 114 O-GlcNAcylated peptides belonging to 78 proteins and 3494 phosphorylated peptides in 2088 proteins. Interestingly, 41 proteins were modified by both O-GlcNAcylation and phosphorylation. These proteins are involved in multiple molecular and cellular processes, including chromatin remodeling, transcription, translation, transportation, and organelle organization. In addition, we verified the accuracy of the proteomics results and found a competitive inhibitory effect between O-GlcNAcylation and phosphorylation of HSPB1. Further, O-GlcNAcylation modification of HSPB1 promoted proliferation and enhanced the chemotherapeutic resistance of HB cell lines in vitro. Collectively,our research suggests that O-GlcNAc-modified and/or phospho-modified proteins may play a crucial role in the pathogenesis of HB.

Signal Transduction and Targeted Therapy
2019 Oct 11;4:40
Impact Factor: 39.3

Materials and Methods

Myc-tagged wild-type HSPB1 and **mutants,** including Myc-HSPB1-T180A, Myc-HSPB1-S187G, and Myc-HSPB1-T180A/S187G, were chemically synthesized by **GenePharma** (Shanghai, China) and subcloned into the **pEX-3 expression plasmid** (**GenePharma**, Shanghai, China).



Tang *et al. Molecular Cancer* (2024) 23:91
https://doi.org/10.1186/s12943-024-01998-w

RESEARCH

Open Access

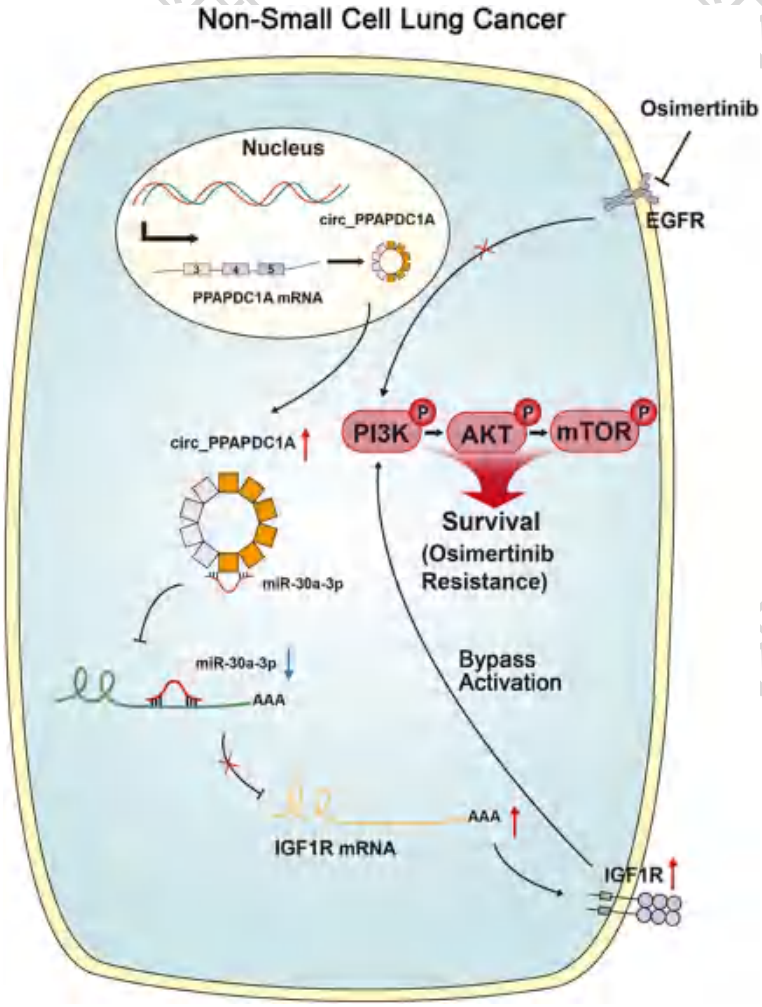
circ_PPAPDC1A promotes Osimertinib resistance by sponging the miR-30a-3p/ IGF1R pathway in non-small cell lung cancer (NSCLC)

Yi-fang Tang[1], Zheng-hua Liu[2], Lei-yi Zhang[3], Sheng-hao Shi[4], Shun Xu[2], Jin-An Ma[4], Chun-Hong Hu[4] and Fang-wen Zou[4*]

Abstract

Background Recent evidence has demonstrated that abnormal expression and regulation of circular RNA (circR- NAs) are involved in the occurrence and development of a variety of tumors. The aim of this study was to investigate the effects of circ_PPAPDC1A in Osimertinib resistance in NSCLC.

Methods Human circRNAs microarray analysis was conducted to identify differentially expressed (DE) circRNAs in Osimertinib-acquired resistance tissues of NSCLC. The effect of circ_PPAPDC1A on cell proliferation, invasion, migra- tion, and apoptosis was assessed in both in vitro and in vivo. Dual-luciferase reporter assay, RT-qPCR, Western-blot, and rescue assay were employed to confirm the interaction between circ_PPAPDC1A/miR-30a-3p/IGF1R axis.



Molecular Cancer Tang et al. Molecular Cancer (2024) 23:91
Impact Factor:37.3

Materials and Methods
Reporter plasmids containing **Wild-type (WT)** and **mutant (MUT) circ_PPAPDC1A (3′UTR) or IGF1R (IGF1R-WT** and **IGF1R-MUT) (3′ UTR)** sequences were synthesized by Shanghai **Gene Pharma** Co

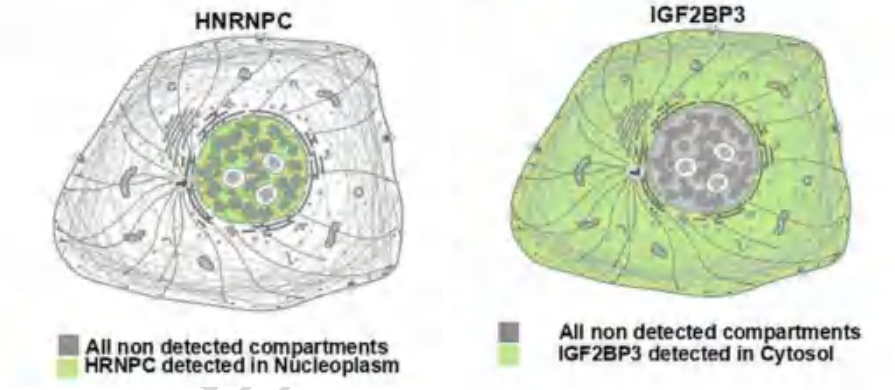
RESEARCH Open Access

CircZBTB44 promotes renal carcinoma progression by stabilizing HK3 mRNA structure

Tushuai Li[1,2,3], Yue Gu[4], Baocai Xu[1], Kamil Kuca[6], Jie Zhang[5*] and Wenda Wu[1,3,6*]

Abstract

CircZBTB44 (hsa_circ_0002484) has been identified to be upregulated in renal cell carcinoma (RCC) tissues, while its role and contribution in RCC remain elusive. We confirmed the overexpression of circZBTB44 in RCC cells compared to normal kidney cell HK-2. CircZBTB44 knockdown suppressed the viability, proliferation, and migration of RCC cells and inhibited tumorigenesis in xenograft mouse models. Heterogeneous Nuclear Ribonucleoprotein C (HNRNPC) and Insulin-like growth factor 2 mRNA-binding protein 3 (IGF2BP3) are two RNA binding proteins of circZBTB44. HNRNPC facilitated the translocation of circZBTB44 from nuclei to cytoplasm via m6A modification, facilitating the interaction of IGF2BP3 and circZBTB44 in the cytoplasm of RCC cells. Furthermore, circZBTB44 upregulated Hexokinase 3 (HK3) expression by binding to IGF2BP3 in RCC cells. HK3 exerted oncogenic effects on RCC cell malignant behaviors and tumor growth. In the co-culture of RCC cells with macrophages, circZBTB44 promoted M2 polarization of macrophages by up-regulating HK3. In summary, HNRNPC mediated circZBTB44 interaction with IGF2BP3 to up-regulate HK3, promoting the proliferation and migration of RCC cells *in vitro* and tumorigenesis *in vivo*. The results of the study shed new light on the targeted therapy of RCC.



Molecular Cancer
2023 Apr 27;22(1):77
Impact Factor:37.3

Materials and Methods

si-IGF2BP3-1/-2/-3), HK3 (si-HK3-1/-2/-3), and the nega-tive control (si-NC) were provided by **GenePharma** (Shanghai, China).

The **pcDNA3.1/HK3 vectors** used for HK3 overexpression were sup-plied by **GenePharma** with empty pcDNA3.1 vectors as the negative control.

Molecular Cancer

RESEARCH

Open Access

Exosome-derived circCCAR1 promotes CD8 + T-cell dysfunction and anti-PD1 resistance in hepatocellular carcinoma

Zongqiang Hu, Gang Chen, Yingpeng Zhao, Hongqiang Gao, Laibang Li, Yanfeng Yin, Jie Jiang, Li Wang, Yuanyi Mang, Yang Gao, Shengning Zhang*, Jianghua Ran* and Li Li*

Abstract

Background Circular RNAs (circRNAs) can be encapsulated into exosomes to participate in intercellular communication, affecting the malignant progression of a variety of tumors. Dysfunction of CD8 + T cells is the main factor in immune escape from hepatocellular carcinoma (HCC). Nevertheless, the effect of exosome-derived circRNAs on CD8 + T-cell dysfunction needs further exploration.

Methods The effect of circCCAR1 on the tumorigenesis and metastasis of HCC was assessed by in vitro and in vivo functional experiments. The function of circCCAR1 in CD8 + T-cell dysfunction was measured by enzyme-linked immunosorbent assay (ELISA), western blotting and flow cytometry. Chromatin immunoprecipitation, biotinylated RNA pull-down, RNA immunoprecipitation, and MS2 pull-down assays were used to the exploration of mechanism. A mouse model with reconstituted human immune system components (huNSG mice) was constructed to explore the role of exosomal circCCAR1 in the resistance to anti-PD1 therapy in HCC.

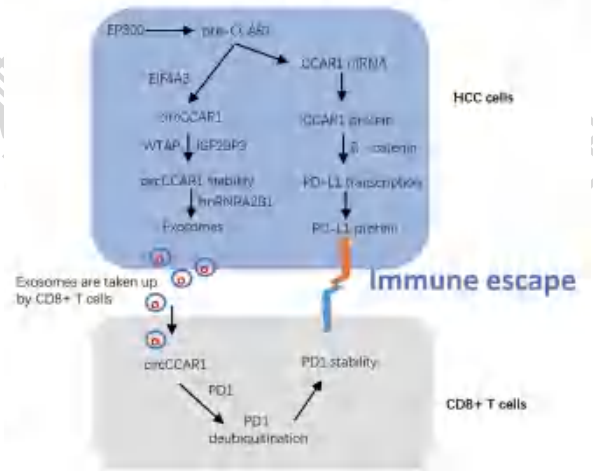
Results Increased circCCAR1 levels existed in tumor tissues and exosomes in the plasma of HCC patients, in the culture supernatant and HCC cells. CircCCAR1 accelerated the growth and metastasis of HCC in vitro and in vivo. E1A binding protein p300 (EP300) and eukaryotic translation initiation factor 4A3 (EIF4A3) promoted the biogenesis of circCCAR1, and Wilms tumor 1-associated protein (WTAP)-mediated m6A modification enhanced circCCAR1 stability by binding insulin-like growth factor 2 mRNA-binding protein 3 (IGF2BP3). CircCCAR1 acted as a sponge for miR-127-5p to upregulate its target WTAP and a feedback loop comprising circCCAR1/miR-127-5p/WTAP axis was formed. CircCCAR1 is secreted by HCC cells in a heterogeneous nuclear ribonucleoprotein A2/B1 (hnRNPA2B1)-dependent manner. Exosomal circCCAR1 was taken in by CD8 + T cells and caused dysfunction of CD8 + T cells by stabilizing the PD-1 protein. CircCCAR1 promoted resistance to anti-PD1 immunotherapy. Furthermore, increased cell division cycle and apoptosis regulator 1 (CCAR1) induced by EP300 promoted the binding of CCAR1 and β-catenin protein, which further enhanced the transcription of PD-L1.

Conclusions The circCCAR1/miR-127-5p/WTAP feedback loop enhances the growth and metastasis of HCC. Exosomal circCCAR1 released by HCC cells contributes to immunosuppression by facilitating CD8 + T-cell dysfunction in

Molecular Cancer
2023 Mar 18;22(1):55
Impact Factor:37.3

Materials and Methods

The recombinant plasmids pCCAR1-MS2, pEmpty-MS2, and pMS2-GST were constructed by **GenePharma**.
All primers were synthesized by **GenePharma** and are listed in Table S2.
The biotin-labeled circCCAR1 and **control probes** were synthesized by **GenePharma**.



Molecular Cancer

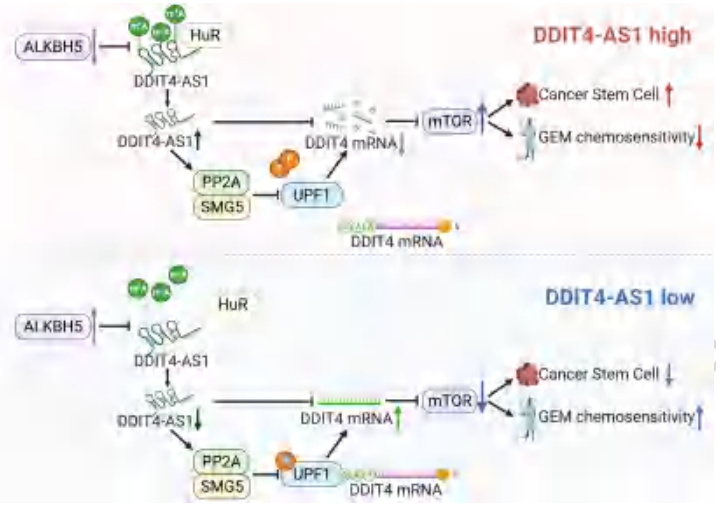
RESEARCH Open Access

The m^{6}A demethylase ALKBH5-mediated upregulation of DDIT4-AS1 maintains pancreatic cancer stemness and suppresses chemosensitivity by activating the mTOR pathway

Abstract

Background: Chemoresistance is a major factor contributing to the poor prognosis of patients with pancreatic cancer, and cancer stemness is one of the most crucial factors associated with chemoresistance and a very promis-ing direction for cancer treatment. However, the exact molecular mechanisms of cancer stemness have not been completely elucidated.

Methods: m6A-RNA immunoprecipitation and sequencing were used to screen m6A-related mRNAs and lncRNAs. qRT-PCR and FISH were utilized to analyse DDIT4-AS1 expression. Spheroid formation, colony formation, Western blot and flow cytometry assays were performed to analyse the cancer stemness and chemosensitivity of PDAC cells. Xenograft experiments were conducted to analyse the tumour formation ratio and growth in vivo. RNA sequencing, Western blot and bioinformatics analyses were used to identify the downstream pathway of DDIT4-AS1. IP, RIP and RNA pulldown assays were performed to test the interaction between DDIT4-AS1, DDIT4 and UPF1. Patient-derived xenograft (PDX) mouse models were generated to evaluate chemosensitivities to GEM.



Molecular Cancer
2022 Dec;21(1):1-20
Impact Factor:37.3

Materials and Methods

Fragments encoding UPF1 amino acid residues were generated by PCR and inserted into a **pcDNA3.1-Flag vector**, which was synthesized by **GenePharma** (Shanghai, China).

Zang et al. Molecular Cancer (2022) 21:141
https://doi.org/10.1186/s12943-022-01606-9

Molecular Cancer

RESEARCH Open Access

Circular RNA EIF4G3 suppresses gastric cancer progression through inhibition of β-catenin by promoting δ-catenin ubiquitin degradation and upregulating SIK1

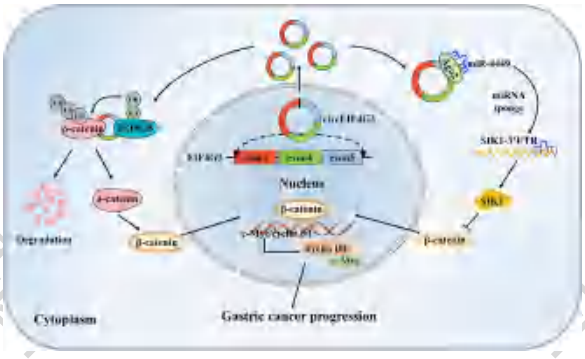
Xueyan Zang[1,2†], Jiajia Jiang[1,2†], Jianmei Gu[3†], Yanke Chen[2], Maoye Wang[2], Yu Zhang[2], Min Fu[2], Hui Shi[2,4], Hui Cai[4], Hui Qian[1,2], Wenrong Xu[1,2*] and Xu Zhang[1,2,4*]

Abstract

Background: Increasing studies suggest that circular RNAs (circRNAs) are critical regulators of cancer development and progression. However, the biological roles and mechanisms of circRNAs in gastric cancer (GC) remain largely unknown.

Methods: We identified the differentially expressed circRNAs in GC by analyzing Gene Expression Omnibus (GEO) datasets. We explored the biological roles of circRNAs in GC by in vitro functional assays and in vivo animal studies. We performed tagged RNA affinity purification (TRAP), RNA immunoprecipitation (RIP), mass spectrometry (MS), RNA sequencing, luciferase reporter assays, and rescue experiments to investigate the mechanism of circRNAs in GC.

Results: Downregulated expression of circular RNA EIF4G3 (circEIF4G3; hsa_circ_0007991) was found in GC and was associated with poor clinical outcomes. Overexpression of circEIF4G3 suppressed GC growth and metastasis through the inhibition of β-catenin signaling, whereas knockdown of circEIF4G3 showed the opposite effects. Mechanistic studies revealed that circEIF4G3 bound to δ-catenin protein to promote its TRIM25-mediated ubiquitin degradation and interacted with miR-4449 to upregulate SIK1 expression.



Molecular Cancer
2022 Dec;21(1):1-16
Impact Factor:37.3

Materials and Methods

Specific targeting **siRNAs** and **overexpressing plasmid** were designed and synthesized by **GenePharma** (Shanghai, China) .

Cells were cultured in 24-well plates and transfected with control vector, miRNA-binding site containing **wild type (WT)** or **mutant (MUT)** vector, as well as predicted **miRNA mimics or controls** (**GenePharma**, Suzhou, China).

Zhu et al. Molecular Cancer (2019) 18:126
https://doi.org/10.1186/s12943-019-1054-7

Molecular Cancer

RESEARCH Open Access

Circular RNA circNHSL1 promotes gastric cancer progression through the miR-1306-3p/SIX1/vimentin axis

Zhonglin Zhu†, Zeyin Rong†, Zai Luo†, Zhilong Yu, Jing Zhang, Zhengjun Qiu and Chen Huang*

Abstract

Background: Mounting evidences indicate that circular RNAs (circRNAs) play vital roles in the development and progression of various cancers. However, the detail functions and underlying mechanisms of circRNAs in gastric cancer remain largely unknown.

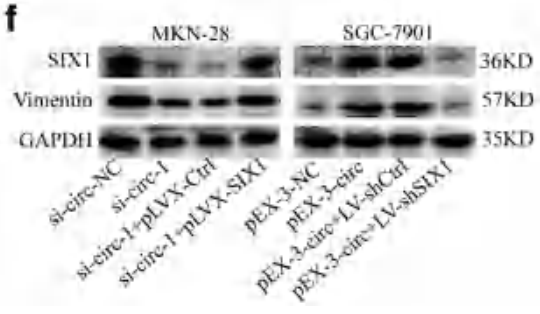
Methods: The expression profile of metastasis-related circRNAs was screened by RNA-seq analysis. qRT-PCR was used to determine the level and prognostic values of circNHSL1 in gastric cancer tissues. In vitro cell wound healing and transwell (migration and invasion) and in vivo tumorigenesis and metastasis assays were performed to evaluate the functions of circNHSL1. Luciferase reporter, RNA immunoprecipitation (RIP) and rescued assays were employed to confirm the interactions between circNHSL1, miR-1306-3p and SIX1. It's widely accepted that as a mesenchymal marker, Vimentin promotes invasion and metastasis in various cancers. Luciferase reporter assay was used to determine the regulation of SIX1 on Vimentin. In addition, In situ hybridization (ISH) was performed to detect the level and prognostic values of miR-1306-3p.

Results: We found that the level of circNHSL1 was significantly up-regulated in gastric cancer, and positively correlated with clinicopathological features and poor prognosis of patients with gastric cancer. Functionally, circNHSL1 promoted cell mobility and invasion, as well as in vivo tumorgenesis and metastasis. Mechanistically, circNHSL1 acted as a miR-1306-3p sponge to relieve the repressive effect of miR-1306-3p on its target SIX1. Moreover, SIX1 enhanced Vimentin expression in the transcriptional level through directly binding to the promoter domain of Vimentin, thereby promoting cell migration and invasion. In addition, miR-1306-3p was down-regulated and negatively correlated with pathological features and poor prognosis in gastric cancer.

Conclusions: CircNHSL1 promotes gastric cancer progression through miR-1306-3p/SIX1/Vimentin axis, and may serve as a novel diagnostic marker and target for treatment of gastric cancer patients.

Keywords: CircNHSL1, miR-1306-3p, SIX1, Vimentin, Metastasis, Gastric cancer

Molecular Cancer
2019 Aug 22; 18: 126
Impact Factor: 37.3



Materials and Methods

Full length circNHSL1 was cloned into the pEX-3 (GenePharma, Shanghai, China).

Zhang et al. Molecular Cancer (2019) 18:80
https://doi.org/10.1186/s12943-019-1015-1

Molecular Cancer

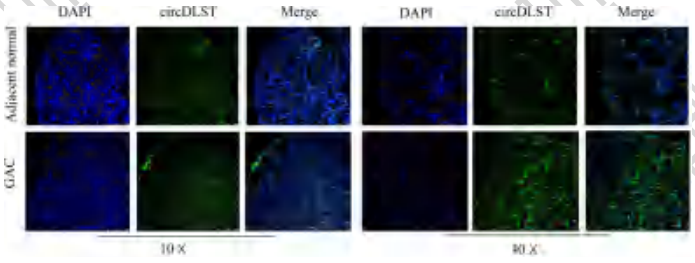
RESEARCH Open Access

CircDLST promotes the tumorigenesis and metastasis of gastric cancer by sponging miR-502-5p and activating the NRAS/MEK1/ERK1/2 signaling

Jing Zhang[1*†], Lidan Hou[2†], Rui Liang[1†], Xiaoyu Chen[1], Rui Zhang[1], Wei Chen[1] and Jinshui Zhu[1*]

Abstract

Background: Accumulating evidence shows that, the dysregulation of circular RNAs (circRNAs) is associated with the progression of multiple malignancies. But, the underlying mechanisms by which has_circ_0032627 (circDLST) contributed to gastric cancer (GC) remain undocumented. **Methods**: The expression and cellular localization of circDLST and its association with clinicopathological characteristics and prognosis in patients with GC was analysed by using fluorescence in situ hybridization. Gain-and loss-of-function experiments as well as a subcutaneous xenograft tumor model and a liver metastasis model from orthotopic implantation of GC tissues were conducted to assess the role of circDLST in GC cells. CircDLST specific binding with miR-502-5p was confirmed by dual luciferase gene report, RNA immunoprecipitation (RIP) assays and RIP-miRNA expression profiling. qRT-PCR and Western blot analysis was used to detect the effects of circDLST on miR-502-5p-mediated NRAS/MEK1/ERK1/2 signaling in GC cells. **Results**: The expression levels of circDLST were dramatically elevated in GC tissues as compared with the adjacent normal tissues, and acted as an independent prognostic factor of poor survival in patients with GC. Knockdown of circDLST inhibited the cell viability, colony formation, DNA synthesis, cell invasion and liver metastasis in vitro and in vivo, whereas overexpression of circDLST had the opposite effects. Furthermore, circDLST was co-localized with miR-502-5p in the cytoplasm of GC cells, and acted as a sponge of miR-502-3p in GC cells, which abrogated the tumor promoting effects of circDLST by inactivating the NRAS/MEK1/ERK1/2 signaling in GC cells.



Molecular Cancer
2019 Apr 5; 18:80
Impact Factor: 37.3

Materials and Methods

Plasmid mediated circDLST vector, shRNA targeting circDLST vector (sh-circDLST, 5′-CAGGUGGGAGAAAGCAUUATT-3′), **siRNA targeting NRAS gene** (si-NRAS, 5′-GCGCACTGACAATCCAGCTAATCCA-3′), **miR-502-5p mimic, inhibitor and NRAS plasmid** were purchased from **GenePharma** (Shanghai, China).

Su et al. Molecular Cancer (2019) 18:27
https://doi.org/10.1186/s12943-019-0951-0

Molecular Cancer

RESEARCH Open Access

Circular RNA cTFRC acts as the sponge of MicroRNA-107 to promote bladder carcinoma progression

Hongwei Su[1†], Tao Tao[2,3†], Zhao Yang[4,5†], Xing Kang[2], Xu Zhang[2], Danyue Kang[6], Song Wu[3,7,8,9*] and Chong Li[1,2,3,5,10*]

Abstract

Background: Circular RNA (circRNA) represents a broad and diverse endogenous RNAs that can regulate gene expression in cancer. However, the regulation and function of bladder cancer (BC) circRNAs remain largely unknown.

Methods: Here we generated circRNA microarray data from three BC tissues and paired non-cancerous matched tissues, and detected circular RNA-cTFRC up-regulated and correlated with tumor grade and poor survival rate of BC patients. We subsequently performed functional analyses in cell lines and an animal model to support clinical findings. Mechanistically, we demonstrated that cTFRC could directly bind to miR-107 and relieve suppression for target TFRC expression.

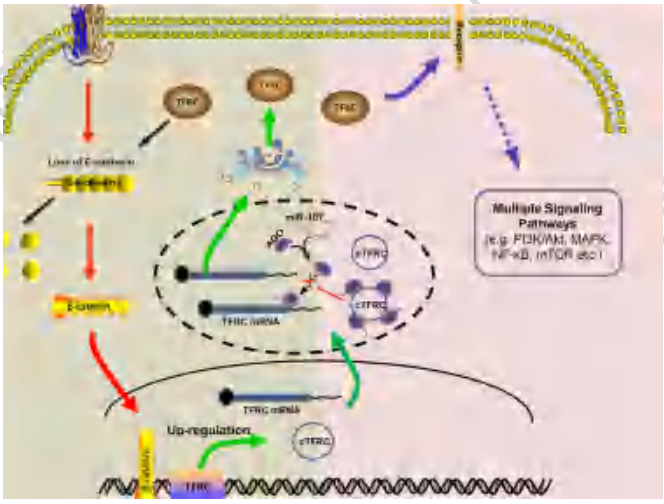
Results: We detected circular RNA-cTFRC up-regulated and correlated with tumor grade and poor survival rate of BC patients. Knock down of cTFRC inhibited invasion and proliferation of BC cell lines in vitro and tumor growth in vivo. Furthermore, the expression of cTFRC correlated with TFRC and negatively correlated with miR-107 both in BC cell lines and BC clinical samples. In addition, up-regulation of cTFRC promoted TFRC expression and contributed to an epithelial to mesenchymal transition phenotype in BC cells. Finally, we found that cTFRC acts as a competing endogenous RNA (ceRNA) for miR-107 to regulate TFRC expression.

Molecular Cancer
2019 Feb 19; 18:27
Impact Factor: 37.3

Materials and Methods

Short hairpin RNA (shRNA) of cTFRC were synthesized by **GenePharma** (Shanghai, China), shcTFRC targeting to the junction region of the cTFRC sequence.

For luciferase reporter assay, **pmirGLO Dual-luciferase vectors** (**GenePharma**, Shanghai, China) were used to construct dual luciferase reporter plasmids.



nature immunology

Article

https://doi.org/10.1038/s41590-023-01634-7

The ligation between ERMAP, galectin-9 and dectin-2 promotes Kupffer cell phagocytosis and antitumor immunity

Received: 18 January 2023

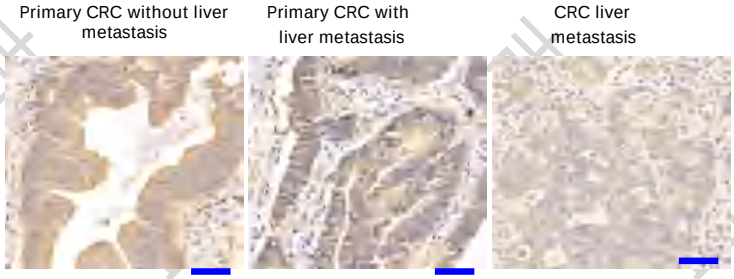
Accepted: 1 September 2023

Published online: 9 October 2023

Check for updates

Jie Li[1,8], Xiao-gang Liu[2,8], Rui-liang Ge[3,8], Yu-peng Yin[1], Yong-da Liu[1], Wan-peng Lu[1], Mei Huang[1], Xue-ying He[1], Jinghan Wang[4], Guoxiang Cai[5,6] ✉, Shu-han Sun[1] ✉ & Ji-hang Yuan[1,7] ✉

Kupffer cells, the liver tissue resident macrophages, are critical in the detection and clearance of cancer cells. However, the molecular mechanisms underlying their detection and phagocytosis of cancer cells are still unclear. Using in vivo genome-wide CRISPR-Cas9 knockout screening, we found that the cell-surface transmembrane protein ERMAP expressed on various cancer cells signaled to activate phagocytosis in Kupffer cells and to control of liver metastasis. ERMAP interacted with β-galactoside binding lectin galectin-9 expressed on the surface of Kupffer cells in a manner dependent on glycosylation. Galectin-9 formed a bridging complex with ERMAP and the transmembrane receptor dectin-2, expressed on Kupffer cells, to induce the detection and phagocytosis of cancer cells by Kupffer cells. Patients with low expression of ERMAP on tumors had more liver metastases. Thus, our study identified the ERMAP–galectin–9-dectin-2 axis as an 'eat me' signal for Kupffer cells.



NATURE IMMUNOLOGY
2023 Nov;24(11):1813-1824
Impact Factor:30.5

Materials and Methods

Two independent cDNA oligonucleotides suppressing Ermap expres-sion were designed, synthesized and subcloned into the SuperSilencing **shRNA expression vector** pGPU6/Neo (**GenePharma**), designated as shErmap-1 and shErmap-2.

Received: 28 September 2023 | Revised: 30 April 2024 | Accepted: 14 May 2024

DOI: 10.1002/cac2.12574

ORIGINAL ARTICLE

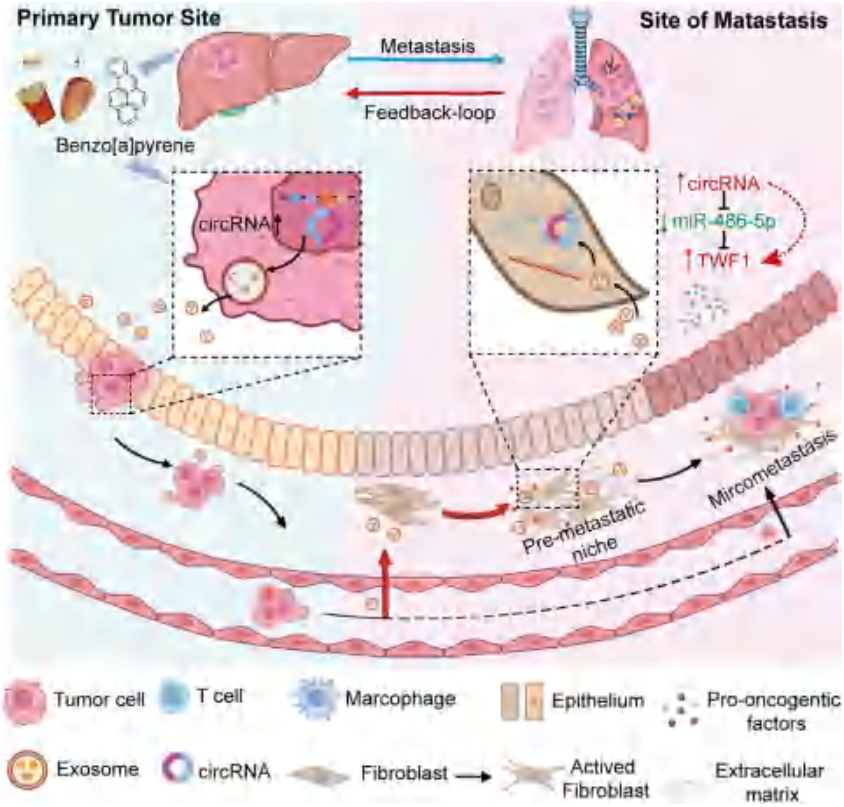
Exposure of benzo[a]pyrene induces HCC exosome-circular RNA to activate lung fibroblasts and trigger organotropic metastasis

Wei Mu[1] | **Pengfei Gu**[1] | **Huating Li**[2] | **Jinjin Zhou**[1] | **Yulun Jian**[1] | **Weiping Jia**[2] | **Yang Ge**[1]

Abstract

Background: Benzo[a]pyrene (B[a]P), a carcinogen pollutant produced by com-bustion processes, is present in the western diet with grilled meats. Chronic exposure of B[a]P in hepatocellular carcinoma (HCC) cells promotes metas-tasis rather than primary proliferation, implying an unknown mechanism of B[a]P-induced malignancy. Given that exosomes carry bioactive molecules to distant sites, we investigated whether and how exosomes mediate cancer-stroma communications for a toxicologically associated microenvironment.

Method: Exosomes were isolated from B[a]P stimulated BEL7404 HCC cells (7404-100Bap Exo) at an environmental relevant dose (100 nmol/L). Lung pre-education animal model was prepared via injection of exosomes and cytokines. The inflammatory genes of educated lungs were evaluated using quantita-tive reverse transcription PCR array. HCC LM3 cells transfected with firefly luciferase were next injected to monitor tumor burdens and organotropic metas-tasis. Profile of B[a]P-exposed exosomes were determined by ceRNA microarray. Interactions between circular RNA (circRNA) and microRNAs (miRNAs) were detected using RNA pull-down in target lung fibroblasts. Fluorescence in situ



Bioactive Materials 30 (2023) 169–183

Contents lists available at ScienceDirect

Bioactive Materials

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

Dual-engineered cartilage-targeting extracellular vesicles derived from mesenchymal stem cells enhance osteoarthritis treatment via miR-223/NLRP3/pyroptosis axis: Toward a precision therapy

Weixuan Liu [a,b,1], Anqi Liu [d,e,1], Xujun Li [f,1], Ziyang Sun [b,c], Zhenghua Sun [b], Yaru Liu [b], Gang Wang [b], Dan Huang [b], Hao Xiong [b,c,****], Shiyang Yu [b,c,***], Xintao Zhang [a,**], Cunyi Fan [b,c,*]

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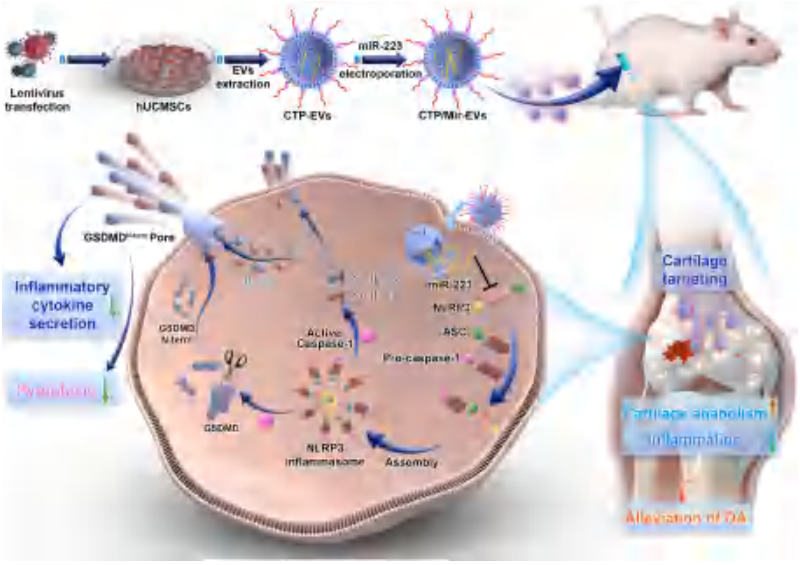
[f] Minhang Hospital, Fudan University, Shanghai, 201199, China

A B S T R A C T

Osteoarthritis (OA) is the most common disabling joint disease with no effective disease modifying drugs. Extracellular vesicles released by several types of mesenchymal stem cells could promote cartilage repair and ameliorate OA pathology in animal models, representing a novel therapeutic strategy. In this study, we demonstrated that extracellular vesicles derived from human umbilical cord mesenchymal stem cells (hUC-EVs) could maintain chondrocyte homeostasis and alleviate OA, and further revealed a novel molecular mechanism of this therapeutic effect. miR-223, which could directly bind with the 3′UTR of NLRP3 mRNA, was found to be a key miRNA for hUC-EVs to exert beneficial effects on inflammation inhibiting and cartilage protecting. For enhancing the effect on mitigating osteoarthritis, exogenous miR-223 was loaded into hUC-EVs by electropo-ration, and a collagen II-targeting peptide (WYRGRL) was modified onto the surface of hUC-EVs by genetic engineering to achieve a more targeted and efficient RNA delivery to the cartilage. The dual-engineered EVs showed a maximal effect on inhibiting the NLRP3 inflammasome activation and chondrocyte pyroptosis, and offered excellent results for the treatment of OA. This study provides a novel theoretical basis and a promising therapeutic strategy for the application of engineered extracellular vesicles in OA treatment.



Bioactive Materials
2023 Aug 4;30:169-183
Impact Factor: 18.9

Materials and Methods

A **dual-luciferase miRNA target expression vector** (**GP-miRGLO**, **GenePharma**, Shanghai, China) was cloned from the 3′UTR region of NLRP3 mRNA containing the miR-223 binding site, wild or mutant (AACUGAC mutated to GGAGUCU).

Nano Today 51 (2023) 101915

Contents lists available at ScienceDirect

Nano Today

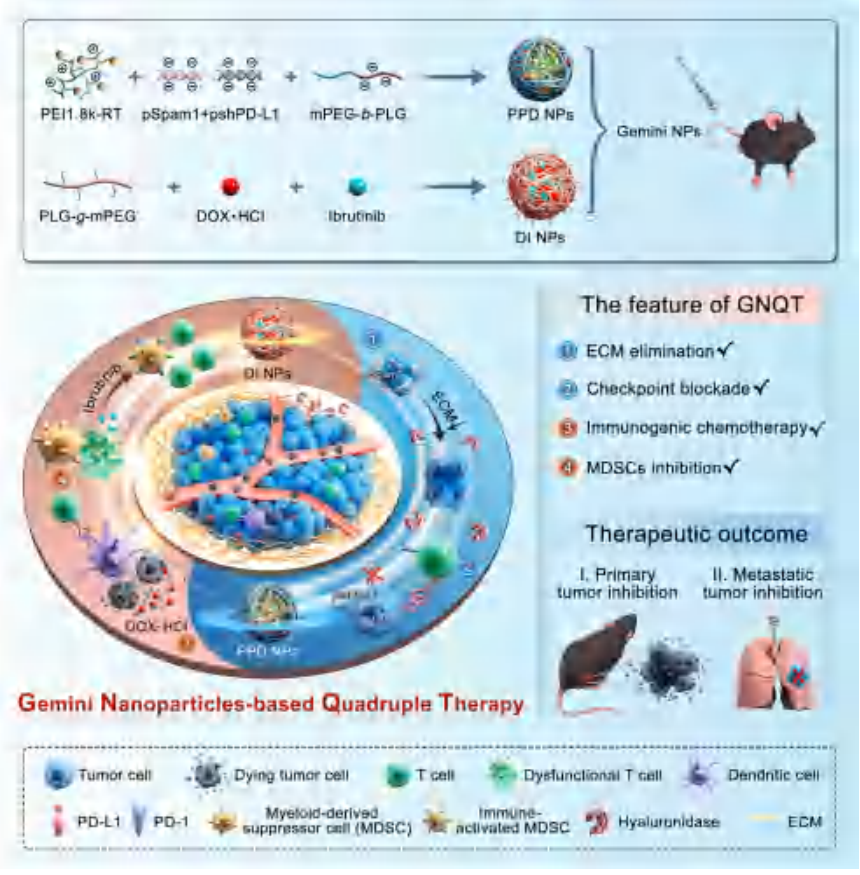
journal homepage: www.elsevier.com/locate/nanotoday

Gemini nanoparticles-based quadruple therapy (GNQT) achieved effective tumor immunotherapy by comprehensive regulation of tumor microenvironment

Xiaoya Guo [a,b], Jiayan Wu [a,b], Yuanji Feng [c], Zhiyu Yang [a,b], Huapan Fang [c,d], Jie Chen [a], Zhaopei Guo [a], Lin Lin [a], Xuan Pang [a,b], Huayu Tian [a,b,c,d,*]

A B S T R A C T

Even though immune checkpoint blockade (ICB) therapy has advanced cancer immunotherapy greatly due to its quick development, and scientists have also tried a variety of combination therapies to further amplify the therapeutic impact, the therapeutic outcome is still limited because of the complex immunosuppressive microenvironment of tumor tissue. To improve the antitumor effect of immunotherapy, developing more comprehensive and effective tumor microenvironment regulation strategy is necessary. In this work, we prepared Gemini NPs composed of drug-loaded nanoparticles DI NPs (Doxorubicin and Ibrutinib were si-multaneously encapsulated by PLG-g-mPEG) and gene-loaded nanoparticles PPD NPs (pSpam1 and pshPD- L1 were simultaneously encapsulated by PEI1.8k-RT), and proposed a Gemini nanoparticles-based quad-ruple therapy (GNQT). Compared with triple therapy and four-drug combination therapy, GNQT demon-strated comprehensive modulation of the tumor microenvironment and had exceptional anticancer ability in melanoma model without obvious toxicity. In addition, by establishing a persistent immunological memory effect, GNQT could also successfully prevent tumor lung metastasis in mice. The GNQT proposed here provided new insights into tumor immunotherapy and had important implications for the research of preclinical antitumor immunotherapy.



Nano Today
2023 Jun;51:101915
Impact Factor:17.4

Materials and Methods
The **plasmid DNA** expressed mouse Spam1 was syn-thesized by **Gene Pharma** (Shanghai, China).

Nano Today 50 (2023) 101839

Contents lists available at ScienceDirect

Nano Today

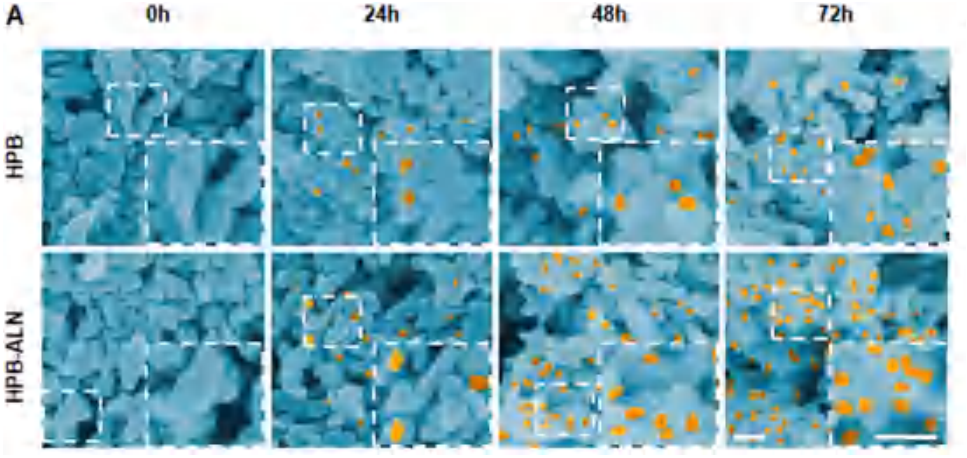
journal homepage: www.elsevier.com/locate/nanotoday

Targeting ROS-induced osteoblast senescence and RANKL production by Prussian blue nanozyme based gene editing platform to reverse osteoporosis

Ke Li [a,b,1], Sihan Hu [c,1], Jinhua Huang [a,1], Yu Shi [a,c], Wenzheng Lin [a,b], Xiangyu Liu [a,b], Wenwen Mao [a,b], Chunbiao Wu [a], Chun Pan [b], Zhuobin Xu [b], Huihui Wang [a,b,*], Lizeng Gao [d,**], Hao Chen [a,**]

ABSTRACT

Blocking the reactive oxygen species (ROS) induced osteoblast senescence and massive RANKL release is the key to alleviate the vicious osteoporotic micro-environment in aged skeleton. In this study, we constructed a composite nanoparticle by confining the growth of Prussian blue nanozyme (PBzyme) on the surface of a sub-50 nm hollow mesoporous silica nanoparticles (HPB), which presented strong ROS scavenging ability. The abundant mesoporous structure made it available to combine receptor activator of nuclear factor kappa-B ligand (RANKL) CRISPR/Cas9 plasmid and skeletal targeting agent alendronate (HPB@RC-ALN) together to modulate the osteoporotic micro-environment. Our results indicate HPB@RC-ALN confined ROS generation and alleviated osteoblast senescence as revealed by dihydroethidium and senescence-associated β-galactosidase staining. The rejuvenated osteoblasts presented robust osteogenic ability as shown by al-kaline phosphatase and alizarin red staining *in vitro*, as well as the micro-computed tomography (μCT) *in vivo*. Meanwhile, efficient transfection of CRISPR/Cas9 plasmid by HPB@RC-ALN precisely achieved RANKL gene editing target and knocked the RANKL gene out in osteoblasts as confirmed by T7E1 digestion and western blot assays. Hence, the osteoclast formation was significantly suppressed as shutting down the RANKL production by HPB@RC-ALN in the senescent osteoblast. At last, the μCT revealed fully reversed bone volume in ovariectomized mice after HPB@RC-ALN injection into the bone remodeling site. Overall, the constructed nanozyme based gene editing platform achieved bidirectional regulation of osteoblast-osteo-clast through rescuing cellular senescence and blocking RANKL production. This strategy provides a new theoretical base for osteoporosis management.



Nano Today
2023 Mar;50:101839
Impact Factor:17.4

Materials and Methods

The **RANKLCRISPR/Cas9 plasmid** was synthesized by **GenePharma** (Shanghai, China),

nature communications

Article

https://doi.org/10.1038/s41467-023-35998-z

Circular RNA circGlis3 protects against islet β-cell dysfunction and apoptosis in obesity

Received: 1 September 2022

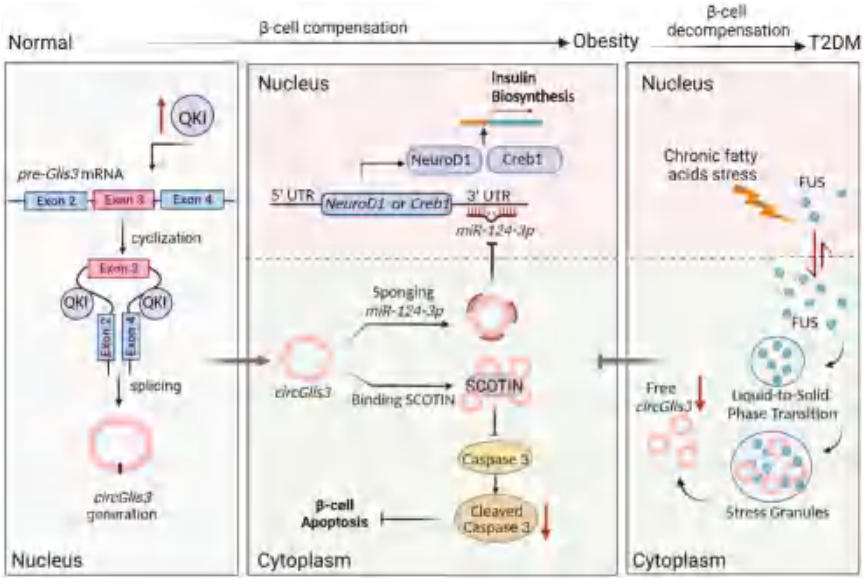
Accepted: 12 January 2023

Published online: 21 January 2023

Check for updates

Yue Liu[1], Yue Yang[1], Chenying Xu[1], Jianxing Liu[1], Jiale Chen[1], Guoqing Li[2], Bin Huang[1], Yi Pan[1], Yanfeng Zhang[1], Qiong Wei[2], Stephen J. Pandol[3], Fangfang Zhang[1] ✉, Ling Li[2] ✉ & Liang Jin[1] ✉

Pancreatic β-cell compensation is a major mechanism in delaying T2DM pro-gression. Here we report the abnormal high expression of circGlis3 in islets of male mice with obesity and serum of people with obesity. Increasing circGlis3 is regulated by Quaking (QKI)-mediated splicing circularization. circGlis3 overexpression enhances insulin secretion and inhibits obesity-induced apoptosis in vitro and in vivo. Mechanistically, circGlis3 promotes insulin secretion by up-regulating NeuroD1 and Creb1 via sponging miR-124-3p and decreases apoptosis via interacting with the pro-apoptotic factor SCOTIN. The RNA binding protein FUS recruits circGlis3 and collectively assemble abnormal stable cytoplasmic stress granules (SG) in response to cellular stress. These findings highlight a physiological role for circRNAs in β-cell compensation and indicate that modulation of circGlis3 expression may represent a potential strategy to prevent β-cell dysfunction and apoptosis after obesity.



Nature Communications
2023 Jan 21;14:351
Impact Factor:16.6

Materials and Methods

circGlis3 was amplified from mouse genomic DNA, and the sequence of exon 3 of the Glis3 gene was inserted into a **pEx-3 ciR vector** (**GenePharma** Co., Shanghai, China) .

nature communications

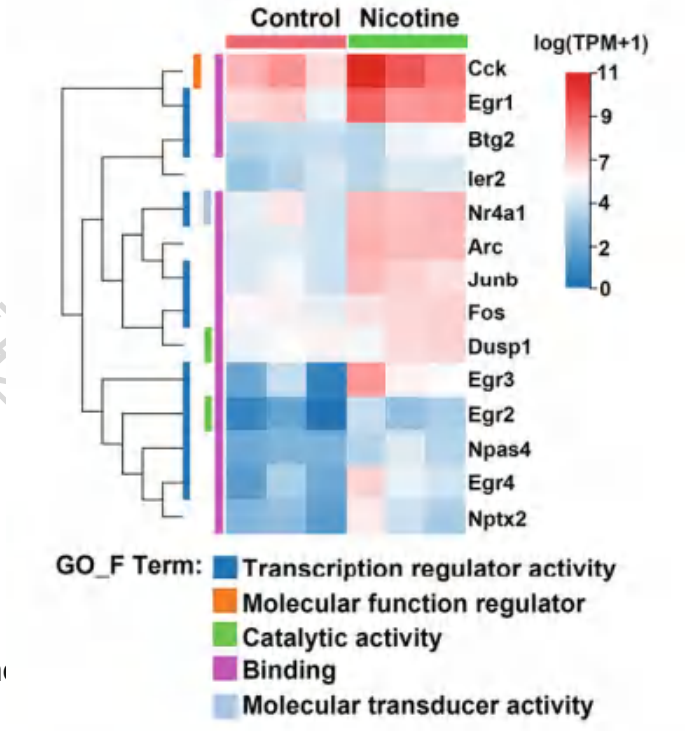
Article

https://doi.org/10.1038/s41467-023-36543-8

Nicotine rebalances NAD$^+$ homeostasis and improves aging-related symptoms in male mice by enhancing NAMPT activity

Liang Yang[1,2,3], Junfeng Shen[1,4], Chunhua Liu[1,2,3], Zhonghua Kuang[1,5,6], Yong Tang[1,2], Zhengjiang Qian[1,2], Min Guan[1,7], Yongfeng Yang[1,5,6], Yang Zhan[1,2], Nan Li[1,4,8] & Xiang Li[1,3]

Imbalances in NAD$^+$ homeostasis have been linked to aging and various dis-eases. Nicotine, a metabolite of the NAD$^+$ metabolic pathway, has been found to possess anti-inflammatory and neuroprotective properties, yet the under-lying molecular mechanisms remained unknown. Here we find that, indepen-dent of nicotinic acetylcholine receptors, low-dose nicotine can restore the age-related decline of NAMPT activity through SIRT1 binding and subsequent deacetylation of NAMPT, thus increasing NAD$^+$ synthesis. ^{18}F-FDG PET imaging revealed that nicotine is also capable of efficiently inhibiting glucose hyper-metabolism in aging male mice. Additionally, nicotine ameliorated cellular energy metabolism disorders and deferred age-related deterioration and cognitive decline by stimulating neurogenesis, inhibiting neuroinflammation, and protecting organs from oxidative stress and telomere shortening. Col-lectively, these findings provide evidence for a mechanism by which low-dose nicotine can activate NAD$^+$ salvage pathways and improve age-related symptoms.



Nature Communications
2023 Feb 17; 14:900
Impact Factor:16.6

Materials and Methods

The **plasmids** of targeting mouse NAMPT-Flag and NAMPT-K53Q were purchased from **GenePharma**. The **siRNA** oligonucleotides targeting mouse sirt1 an sirt6 were purchased from **GenePharma**.

nature communications

Article

https://doi.org/10.1038/s41467-023-39414-4

K235 acetylation couples with PSPC1 to regulate the m^{6}A demethylation activity of ALKBH5 and tumorigenesis

Received: 20 June 2020

Accepted: 12 June 2023

Published online: 27 June 2023

Check for updates

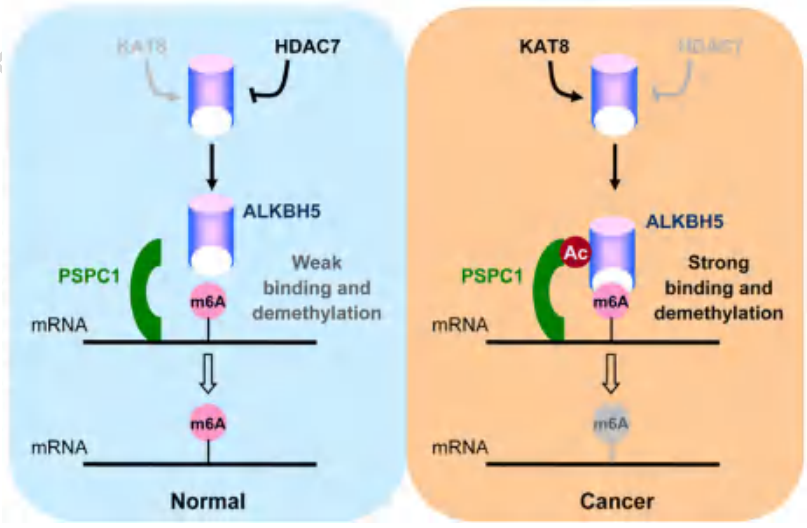
Xiao-Lan Zhang[1,5], Xin-Hui Chen[1,5], Binwu Xu[2,5], Min Chen[1,5], Song Zhu[1,3,5], Nan Meng[1], Ji-Zhong Wang[1], Huifang Zhu[1], De Chen[1] ✉, Jin-Bao Liu[4] ✉ & Guang-Rong Yan[1] ✉

N6-methyladenosine (m^{6}A) modification plays important roles in bioprocesses and diseases. AlkB homolog 5 (ALKBH5) is one of two m^{6}A demethylases. Here, we reveal that ALKBH5 is acetylated at lysine 235 (K235) by lysine acetyltransferase 8 and deacetylated by histone deacetylase 7. K235 acetylation strengthens the m^{6}A demethylation activity of ALKBH5 by increasing its recognition of m^{6}A on mRNA. RNA-binding protein paraspeckle component 1 (PSCP1) is a regulatory subunit of ALKBH5 and preferentially interacts with K235-acetylated ALKBH5 to recruit and facilitate the recognition of m^{6}A mRNA by ALKBH5, thereby promoting m^{6}A erasure. Mitogenic signals promote ALKBH5 K235 acetylation. K235 acetylation of ALKBH5 is upregulated in cancers and promotes tumorigenesis. Thus, our findings reveal that the m^{6}A demethylation activity of ALKBH5 is orchestrated by its K235 acetylation and regulatory subunit PSPC1 and that K235 acetylation is necessary for the m^{6}A demethylase activity and oncogenic roles of ALKBH5.

Nature Communications
2023 Jun 27;14:3815
Impact Factor:16.6

Materials and Methods

The **ALKBH5 Cas9/sgRNA vector** pGE-4 (pU6-gRNA1 Cas9-puroU6-gRNA2) was constructed by **GenePharma** (Shanghai, China). The anti-ALKBH5, anti-KAT8, anti-HDAC7, or anti-PSPC1 **siRNAs or negative control siRNA** (**GenePharma**) were transfected into the cells with RNAiMAX for 48 h .



nature communications

Article

https://doi.org/10.1038/s41467-023-41160-6

Cold-activated brown fat-derived extracellular vesicle-miR-378a-3p stimulates hepatic gluconeogenesis in male mice

Received: 13 February 2023

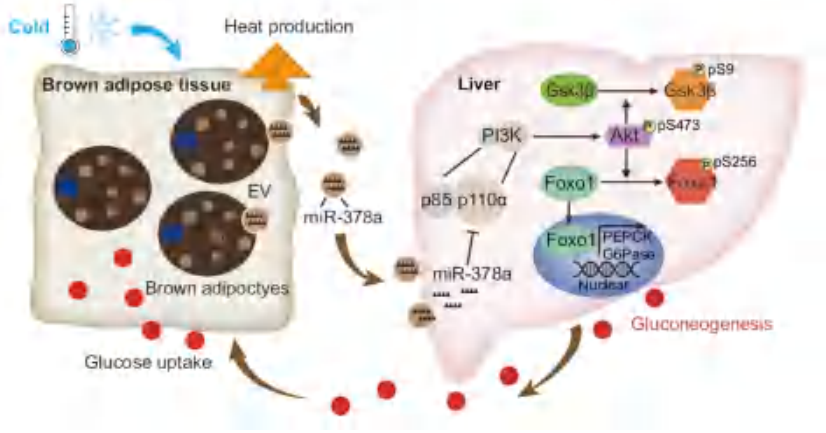
Accepted: 24 August 2023

Published online: 06 September 2023

Check for updates

Jinhong Xu[1,7], Le Cui[1,7], Jiaqi Wang[1,7], Shasha Zheng[1,7], Huahua Zhang[1], Shuo Ke[1], Xiaoqin Cao[1], Yanteng Shi[1], Jing Li[1], Ke Zen[1], Antonio Vidal-Puig[2,3] ✉, Chen-Yu Zhang[1,4,5,6] ✉, Liang Li[1,4] ✉ & Xiaohong Jiang[1,3,4] ✉

During cold exposure, activated brown adipose tissue (BAT) takes up a large amount of circulating glucose to fuel non-shivering thermogenesis and defend against hypothermia. However, little is known about the endocrine function of BAT controlling glucose homoeostasis under this thermoregulatory challenge. Here, we show that in male mice, activated BAT-derived extracellular vesicles (BDEVs) reprogram systemic glucose metabolism by promoting hepatic glu-coneogenesis during cold stress. Cold exposure facilitates the selective packaging of miR-378a-3p—one of the BAT-enriched miRNAs—into EVs and delivery into the liver. BAT-derived miR-378a-3p enhances gluconeogenesis by targeting p110α. miR-378 KO mice display reduced hepatic gluconeogenesis during cold exposure, while restoration of miR-378a-3p in iBAT induces the expression of gluconeogenic genes in the liver. These findings provide a mechanistic understanding of BDEV-miRNA as stress-induced batokine to coordinate systemic glucose homoeostasis. This miR-378a-3p-mediated interorgan communication highlights a novel endocrine function of BAT in preventing hypoglycemia during cold stress.



Nature Communications
2023 Sep 6;:14(1):5480
Impact Factor:16.6

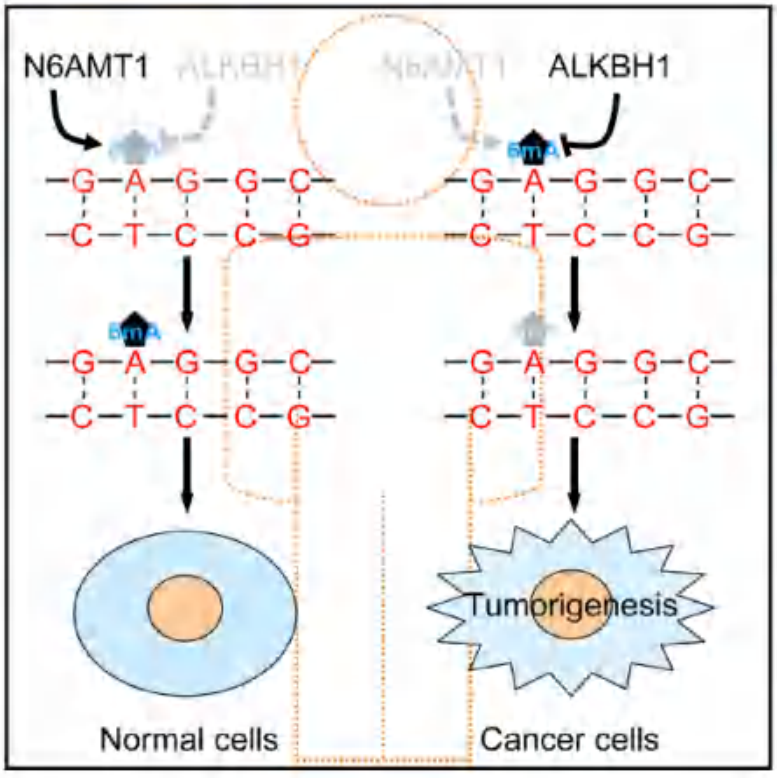
Materials and Methods

The **recombinant viral plasmids** encoding lentiviral particles and the **packaging plasmids** pGag/Pol, pRev and PVSV-G were constructed and prepared by **GenePharma**(Shanghai, China).

Molecular Cell

N^6-Methyladenine DNA Modification in the Human Genome

Graphical Abstract



Authors

Chuan-Le Xiao, Song Zhu, Minghui He, ..., Xiao-Feng Gu, Kai Wang, Guang-Rong Yan

Correspondence

boxc@bmi.ac.cn (X.-C.B.), guxiaofeng@caas.cn (X.-F.G.), wangk@email.chop.edu (K.W.), jxygr007@yahoo.com (G.-R.Y.)

In Brief

Xiao et al. show that DNA methylation on N^6-adenine exists in the human genome. The mark is added by the methyltransferase N6AMT1 and it is removed by the demethylase ALKBH1. Decrease of genomic DNA 6mA promotes tumorigenesis and is associated with poor prognosis for cancer patients.

Molecular Cell
2018 Jul 19; 71: 306-18
Impact Factor: 16

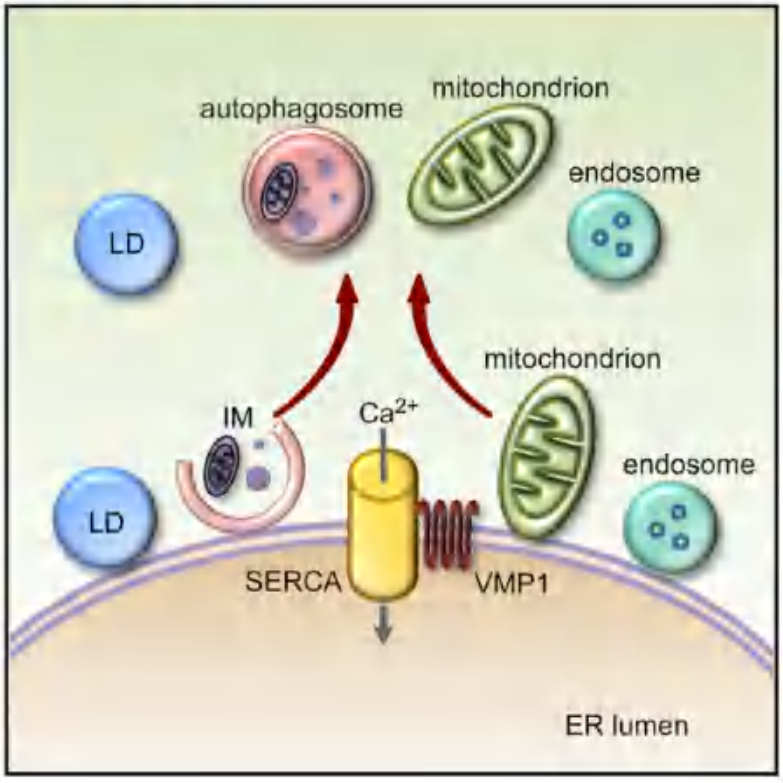
Materials and Methods

The ALKBH1 and N6AMT1 **Cas9/sgRNAs plasmids** pGE-4 (pU6gRNA1Cas9puroU6gRNA2) were purchased from **Genepharma** (Shanghai, China).

Molecular Cell

The ER-Localized Transmembrane Protein EPG-3/VMP1 Regulates SERCA Activity to Control ER-Isolation Membrane Contacts for Autophagosome Formation

Graphical Abstract



Authors

Yan G. Zhao, Yong Chen, Guangyan Miao, ..., Pingsheng Liu, Du Feng, Hong Zhang

Correspondence

hongzhang@ibp.ac.cn

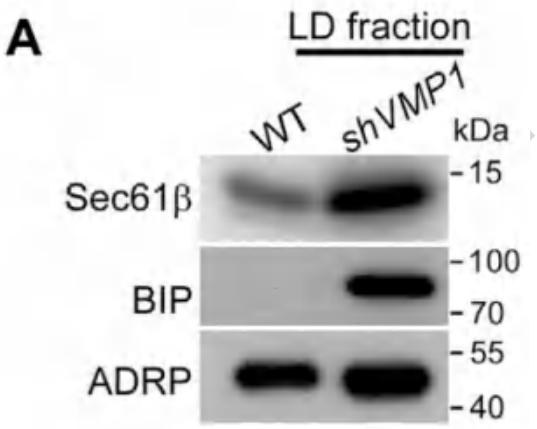
In Brief

Zhao et al. demonstrate that the ER-localized metazoan-specific autophagy protein VMP1 controls ER contacts with IMs and other organelles. VMP1 controls contact maintenance by modulating SERCA activity. VMP1 interacts with SERCA and prevents formation of the SERCA/PLN/SLN inhibitory complex.

Molecular Cell
2017 Sep 21; 67: 974-89
Impact Factor: 16

Materials and Methods

shVMP1 cells were generated by transfecting HeLa cells with **pGPU6/Neo plasmid** containing shRNA sequence targeting human VMP1 (**GenePharma**).



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Injectable engineered micro/nano-complexes trigger the reprogramming of bone immune epigenetics

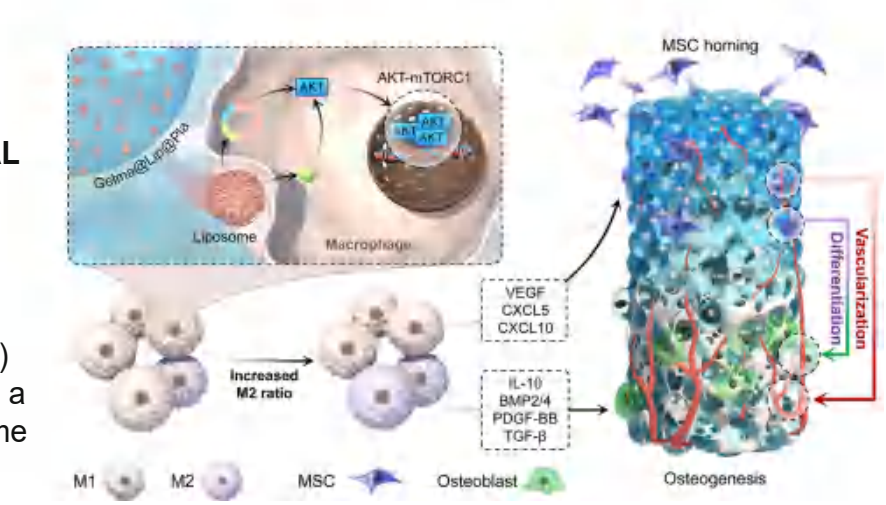
Xindie Zhou [a,b,c,d,1], Kun Xi [a,1], Jiang Bian [b,c,1], Ziang Li [a], Liang Wu [a], Jincheng Tang [a], Chenwei Xiong [b,c], Zhentang Yu [b,c], Junjie Zhang [b,c], Yong Gu [a], Yong Huang [b,c,*], Feng Cai [a,*], Liang Chen [a,*]

ABSTRACT

Imbalance in the local immune microenvironment plays a vital role in the nonunion or delayed healing of bone defects. Additionally, there exists a cross-connection between material design of microfluidics and immune regulation. Therefore, we aimed to investigate whether epigenetic reprogramming of the microfluidic micro-sphere systems could regulate microenvironmental homeostasis in the acute phase of fracture and facilitate bone regeneration. To this end, we used Gelma hydrogel microspheres as the base carriers to design and fabricate an injectable, macrophage-targeted, engineered micro/nano microsphere reprogramming system (Gelma@Lip@-Pla). Liposome (Lip) coating and macrophage targeting were improved by adding DSPE-PEG-CHO and phos-phatidylserine (Pla). the surface of Gelma was coated with a lipid membrane, Schiff base, and hydrogel matrix network; the resultant macrophage-targeted liposomes activated AKT signaling in the local microenvironment by releasing the AKT signal activator dihydrocapsaicin and amplifiers (pcDNA3.1-AKT), triggering gene reprog-ramming in the local microenvironment and restarting the bone healing process. Compared with pcDNA3.1-AKT and dihydrocapsaicin-loaded liposomes (Lip@Pla) and pure Gelma hydrogel microgels (Gelma), the Gelma@-Lip@Pla group significantly prolonged the release time of active ingredients. They also promoted the polari-zation of macrophages to the M2 phenotype, leading to the reactivation of bone marrow-derived mesenchymal stem cell osteogenic differentiation and human umbilical vein endothelial cell angiogenesis. Furthermore, in vivo experiments confirmed that local injection of Gelma@Lip@Pla could significantly accelerate the regeneration of a defective rat femoral condyle. Collectively, the Gelma@Lip@Pla microgel exhibits considerable potential as an extended delivery platform for treating bone defects and other immune-related diseases involving macrophages.

Materials and Methods

pcDNA3.1-AKT (GenePharma, China) was added to the tubes and mixed into a solution with a pcDNA3.1-AKT: liposome ratio of 1:2.5.

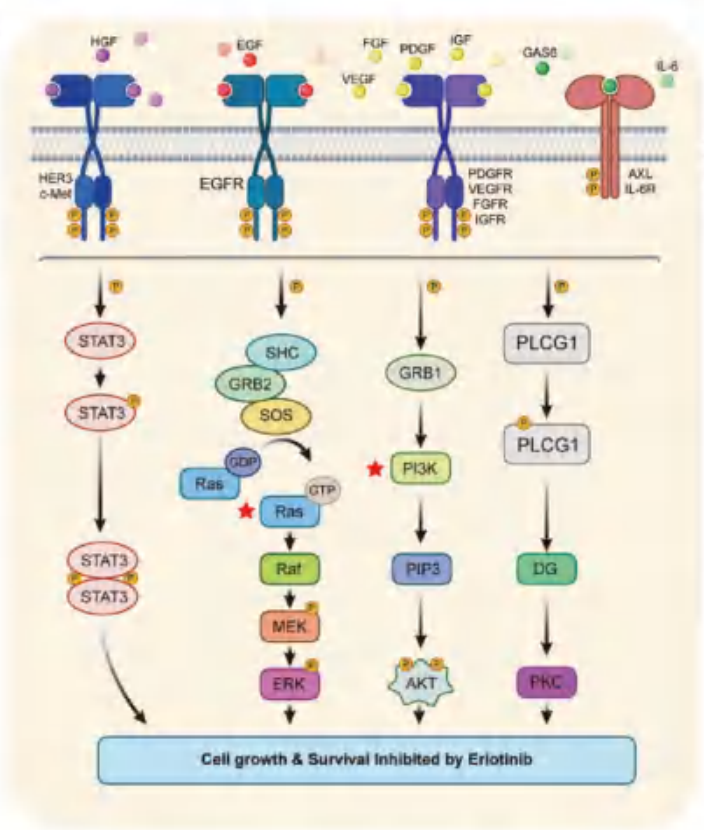


ADVANCED SCIENCE Open Access
www.advancedscience.com

BPTF Drives Gastric Cancer Resistance to EGFR Inhibitor by Epigenetically Regulating the C-MYC/PLCG1/Perk Axis

Fangyuan Li, Junxian Yu, Tao Pan, Haoran Feng, Jianfang Li, Beiqin Yu, Zhiyuan Fan, Qingqing Sang, Mengdi Chen, Mingde Zang, Junyi Hou, Xiongyan Wu, Yingyan Yu, Yuan-Yuan Li, Chao Yan, Zhenggang Zhu, Liping Su, and Bingya Liu**

Erlotinib, an EGFR tyrosine kinase inhibitor, is used for treating patients with cancer exhibiting EGFR overexpression or mutation. However, the response rate of erlotinib is low among patients with gastric cancer (GC). The findings of this study illustrated that the overexpression of bromodomain PHD finger transcription factor (BPTF) is partially responsible for erlotinib resistance in GC, and the combination of the BPTF inhibitor AU-1 with erlotinib synergistically inhibited tumor growth both in vivo and in vitro. AU-1 inhibited the epigenetic function of BPTF and decreased the transcriptional activity of c-MYC on PLCG1 by attenuating chromosome accessibility of the PLCG1 promoter region, thus decreasing the expression of p-PLCG1 and p-Erk and eventually improving the sensitivity of GC cells to erlotinib. In patient-derived xenograft (PDX) models, AU-1 monotherapy exhibited remarkable tumor-inhibiting activity and is synergistic anti-tumor effects when combined with erlotinib. Altogether, the findings illustrate that BPTF affects the responsiveness of GC to erlotinib by epigenetically regulating the c-MYC/PLCG1/pErk axis, and the combination of BPTF inhibitors and erlotinib is a viable therapeutic approach for GC.



Advanced Science
2023 Dec;10(34):e2303091
Impact Factor:15.1

Materials and Methods

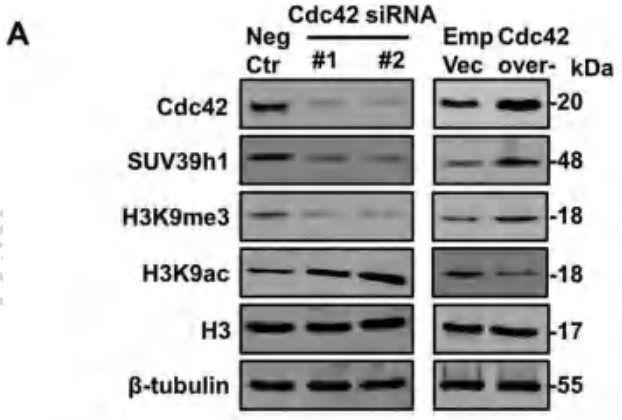
In brief, BPTF complementary oligonucleotides with BpiI restriction sites for guide RNAs (gRNAs) were synthesized and cloned into the **pU6gRNACas9purovector** (**GenePharma**, C051005).

ADVANCED SCIENCE Open Access
www.advancedscience.com

Synthetic Retinoid Kills Drug-Resistant Cancer Stem Cells via Inducing RARγ-Translocation-Mediated Tension Reduction and Chromatin Decondensation

Yao Zhang, Qi Dong, Quanlin An, Chumei Zhang, Erfan Mohagheghian, Bing Niu, Feng Qi, Fuxiang Wei, Sihan Chen, Xinman Chen, Anqi Wang, Xin Cao, Ning Wang,* and Junwei Chen**

A recently developed synthetic retinoid abrogates proliferation and induces apoptosis of drug-resistant malignant-cancer-stem-cell-like cells. However, the underlying mechanisms of how the synthetic retinoid induces cancer-stem-cell-like cell tumor-repopulating cell (TRC) apoptosis are elusive. Here, it is shown that although the retinoid and conventional anticancer drugs cisplatin, all-trans retinoic acid, and tazarotene all inhibit cytoskeletal tension and decondense chromatin prior to inducing TRC apoptosis,half-maximal inhibitory concentration of the retinoid is 20-fold lower than those anticancer drugs. The synthetic retinoid induces retinoic acid receptor gamma (RAR) translocation from the nucleus to the cytoplasm, leading to reduced RAR binding to Cdc42 promoter and Cdc42 downregulation, which decreases filamentous-actin (F-actin) and inhibits cytoskeletal tension. Elevating F-actin or upregulating histone 3 lysine 9 trimethylation decreases retinoid-induced DNA damage and apoptosis of TRCs. The combinatorial treatment with a chromatin decondensation molecule and the retinoid inhibits tumor metastasis in mice more effectively than the synthetic retinoid alone. These findings suggest a strategy of lowering cell tension and decondensing chromatin to enhance DNA damage to abrogate metastasis of cancer-stem-cell-like cells with high efficacy.



Advanced Science
2022 Aug;:2203173
Impact Factor:15.1

Materials and Methods

plasmid cloning DNA (pcDNA)3.1–Cdc42 plasmid or pcDNA3.1–GFP (Emp Vec) were purchased from **GenePharma** (Shanghai, China).

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

Acta Pharmaceutica Sinica B

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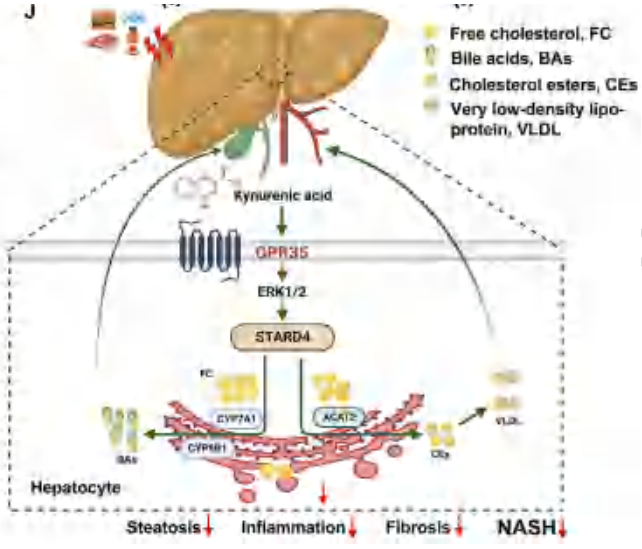
ORIGINAL ARTICLE

G protein-coupled receptor 35 attenuates nonalcoholic steatohepatitis by reprogramming cholesterol homeostasis in hepatocytes

ABSTRACT: Tumor heterogeneity has been one of the most important factors leading to the failure of conventional cancer therapies due to the accumulation of genetically distinct tumor-cell subpopulations during the tumor development process. Due to the diversity of genetic mutations during tumor growth, combining the use of multiple drugs has only achieved limited success in combating heterogeneous tumors. Herein, we report a novel antitumor strategy that effectively addresses tumor heterogeneity by using a CRISPR/Cas9-based nanoRNP carrying a combination of sgRNAs. Such nanoRNP is synthesized from Cas9 ribonucleoprotein, any combinations of required sgRNAs, and a rationally designed responsive polymer that endows nanoRNP with high circulating stability, enhanced tumor accumulation, and the efficient gene editing in targeted tumor cells eventually. By carrying a combination of sgRNAs that targets STAT3 and RUNX1, the nanoRNP exhibited efficient gene expression disruptions on a heterogeneous tumor model with two subsets of cells whose proliferations were sensitive to the reduced expression of STAT3 and RUNX1, respectively, leading to the effective growth inhibition of the heterogeneous tumor. Considering the close relationship between tumor heterogeneity and cancer progression, resistance to therapy, and recurrences, nanoRNP provides a feasible strategy to overcome tumor heterogeneity in the development of more advanced cancer therapy against malignant tumors.

Acta Pharmaceutica Sinica B
2022 Oct;:2211-3835
Impact Factor: 14.5



Materials and Methods

The pEX-3 (pGCMV/MCS/Neo)-control or **pEX-3-Mus Gpr35 plasmid** (**GenePharma**, Shanghai, China) was transfected into AML-12 cells using Lipofectamine 2000 .

COGNITIVE NEUROSCIENCE

The *FAM171A2* gene is a key regulator of progranulin expression and modifies the risk of multiple neurodegenerative diseases

Wei Xu[1,2]*, Si-Da Han[1]*, Can Zhang[3], Jie-Qiong Li[4], Yan-Jiang Wang[5], Chen-Chen Tan[2], Hong-Qi Li[1], Qiang Dong[1], Cui Mei[1], Lan Tan[2], Jin-Tai Yu[1†]

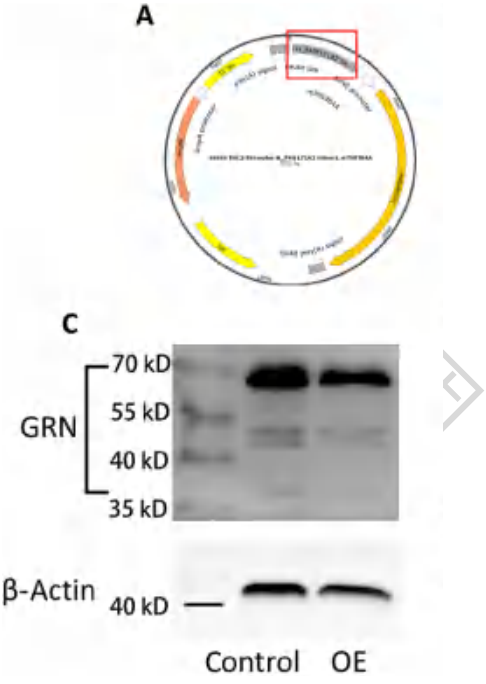
Progranulin (PGRN) is a secreted pleiotropic glycoprotein associated with the development of common neuro-degenerative diseases. Understanding the pathophysiological role of PGRN may help uncover biological under-pinnings. We performed a genome-wide association study to determine the genetic regulators of cerebrospinal fluid (CSF) PGRN levels. Common variants in region of *FAM171A2* were associated with lower CSF PGRN levels (rs708384, $P = 3.95 \times 10^{-12}$). This was replicated in another independent cohort. The rs708384 was associated with increased risk of Alzheimer's disease, Parkinson's disease, and frontotemporal dementia and could modify the expression of the *FAM171A2* gene. FAM171A2 was considerably expressed in the vascular endothelium and microglia, which are rich in PGRN. The in vitro study further confirmed that the rs708384 mutation up-regulated the expression of FAM171A2, which caused a decrease in the PGRN level. Collectively, genetic, molecular, and bioinformatic findings suggested that *FAM171A2* is a key player in regulating PGRN production.

SCIENCE ADVANCES
2020 Oct 21;6 : eabb3063
Impact Factor: 13.6

Materials and Methods

The in vitro FAM171A2 knockdown was achieved by siRNA, purchased from **GenePharma** Co. Ltd, Shanghai, China. Sequence:5′-GCAAUGGCACUGGUGUAAUTT, AUUACACCAGUGCCAUUGCTT-3′.

The FAM171A2 overexpression plasmid was purchased from **GenePharma**. The pEX-3 vector was used for plasmid construction.



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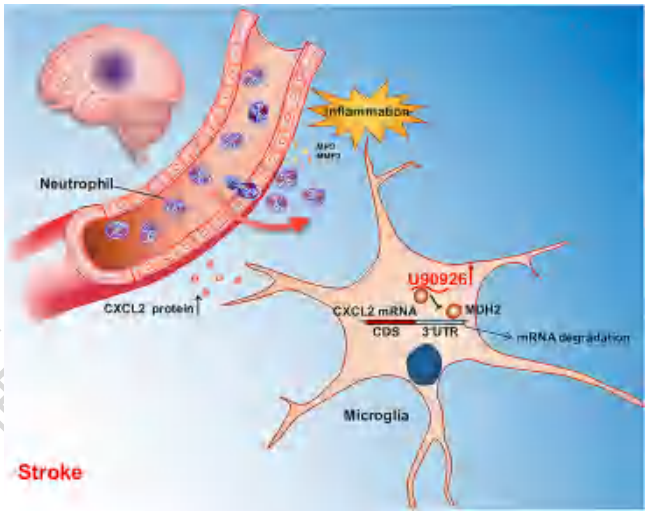
Molecular Therapy
Original Article

Microglial lnc-U90926 facilitates neutrophil infiltration in ischemic stroke via MDH2/CXCL2 axis

Jian Chen, Jiali Jin,Xi Zhang,Hailong Yu, Xiaolei Zhu, Linjie Yu,
Yanting Chen, Pinyi Liu, Xiaohong Dong, Xiang Cao, Yue Gu,Xinyu Bao,Shengnan Xia,and Yun Xu

Dysregulated long non-coding RNAs (lncRNAs) have been shown to contribute to the pathogenesis of ischemic stroke. However, the potential role of lncRNAs in post-stroke micro-glial activation remains largely unknown. Here, we uncovered that lncRNA-U90926 was significantly increased in microglia exposed to ischemia/reperfusion both in vivo and in vitro.In addition, adenovirus-associated virus (AAV)-mediated micro-glial U90926 silencing alleviated neurological deficits and reduced infarct volume in experimental stroke mice. Microglial U90926 knockdown could reduce the infiltration of neutro-phils into ischemic lesion site, which might be attributed to the downregulation of C-X-C motif ligand 2 (CXCL2). Mecha-nistically, U90926 directly bound to malate dehydrogenase 2 (MDH2) and competitively inhibited the binding of MDH2 to the CXCL2 30 untranslated region (UTR), thus protecting against MDH2-mediated decay of CXCL2 mRNA. Taken together, our study demonstrated that microglial U90926 aggravated ischemic brain injury via facilitating neutrophil infiltration, suggesting that U90926 might be a potential biomarker and therapeutic target for ischemic stroke.



Molecular Therapy
2021 Apr 19; 29 No 9
Impact Factor: 12.4

Materials and Methods

Biotin-labeled RNA oligonucleotides (U90926: biotin-ACAGUA-GUUCUUCUGCUCAGUGGCG) were synthesized by **GenePharma** Technologies (Shanghai, China) .

Lentivirus carrying U90926/MDH2 shRNA was used to knockdown U90926 or MDH2, while **gene-overexpression (U90926, MDH2) plasmid** (**GenePharma** Techniques, Shanghai, China) was used to overexpress the target gene.

GUT MICROBES
2023, VOL. 15, NO. 1, 2240035
https://doi.org/10.1080/19490976.2023.2240035

Taylor & Francis
Taylor & Francis Group

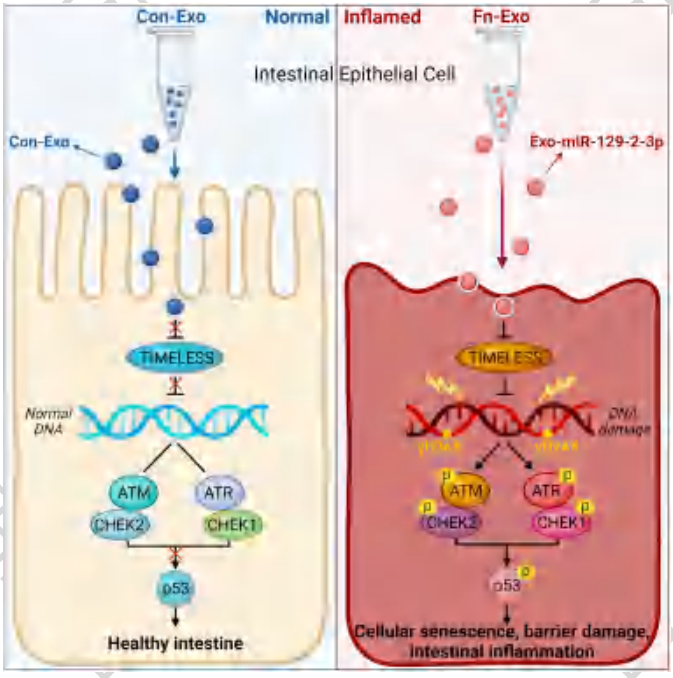
Exosomal-miR-129-2-3p derived from *Fusobacterium nucleatum*-infected intestinal epithelial cells promotes experimental colitis through regulating TIMELESS-mediated cellular senescence pathway

Shuchun Wei[a,b*], Xiaohan Wu[a,c*], Meilin Chen[a,c*], Zixuan Xiang[a,c], Xiangyun Li[a,c], Jixiang Zhang[a], and Weiguo Dong[a]

[a]Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan, Hubei Province, China; [b]Department of Gastroenterology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, China; [c]Key Laboratory of Hubei Province for Digestive System Disease, Renmin Hospital of Wuhan University, Wuhan, Hubei Province, China

ABSTRACT

Fusobacterium nucleatum (Fn) infection is known to exacerbate ulcerative colitis (UC). However, the link between Fn-infected intestinal epithelial cell (IEC)-derived exosomes (Fn-Exo) and UC progres-sion has not been investigated. Differentially expressed miRNAs in Fn-Exo and non-infected IECs- derived exosomes (Con-Exo) were identified by miRNA sequencing. Then, the biological role and mechanism of Fn-Exo in UC development were determined *in vitro* and *in vivo*. We found that exosomes delivered miR-129-2-3p from Fn-infected IECs into non-infected IECs, exacerbating epithelial barrier dysfunction and experimental colitis. Mechanically, Fn-Exo induces DNA damage via the miR-129-2-3p/TIMELESS axis and subsequently activates the ATM/ATR/p53 pathway, ulti-mately promoting cellular senescence and colonic inflammation. In conclusion, Exo-miR-129-2-3p/ TIMELESS/ATM/ATR/p53 pathway aggravates cellular senescence, barrier damage, and experimen-tal colitis. The current study revealed a previously unknown regulatory pathway in the progression of Fn-infectious UC. Furthermore, Exosomal-miR-129-2-3p in serum and TIMELESS may function as novel potential diagnostic biomarkers for UC and Fn-high-UC.



Gut Microbes
2023 Aug;15(1):2240035
Impact Factor:12.2

Materials and Methods

Negative control RNA (NC), miR-129-2-3p-mimics, miR-129-2-3p-inhibitor/scrambled negative control RNA (inhibitor-NC), and **siRNAs** targeting the human TIMELESS gene (siTIMELESS) were purchased from **GenePharma** (Shanghai, China), the sequences of which were documented in Table S5.

The **pmirGLO dual-luciferase miRNA targeting expression vector** cloned with the binding sites between miR-129-2-3p and TIMELESS was con-structed by **GenePharma** (Shanghai, China).

Lv et al. J Exp Clin Cancer Res (2023) 42:41
https://doi.org/10.1186/s13046-023-02614-3

Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

HNRNPL induced circFAM13B increased bladder cancer immunotherapy sensitivity via inhibiting glycolysis through IGF2BP1/PKM2 pathway

Jiancheng Lv†, Kai Li†, Hao Yu†, Jie Han†, Juntao Zhuang, Ruixi Yu, Yidong Cheng, Qiang Song, Kexin Bai, Qiang Cao, Haiwei Yang*, Xiao Yang* and Qiang Lu*

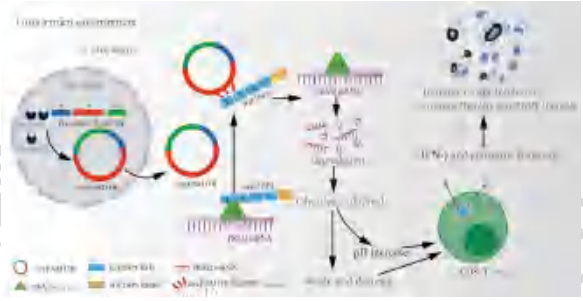
Abstract

Background The response rate to immunotherapy in patients with bladder cancer (BCa) remains relatively low. Considering the stable existence and important functions in tumour metabolism, the role of circRNAs in regulating immune escape and immunotherapy sensitivity is receiving increasing attention.

Methods Circular RNA (circRNA) sequencing was performed on five pairs of BCa samples, and circFAM13B (hsa_circ_0001535) was screened out because of its remarkably low expression in BCa. Further mRNA sequencing was conducted, and the association of circFAM13B with glycolysis process and $CD8^+$ T cell activation was confirmed. The functions of circFAM13B were verified by proliferation assays, glycolysis assays, BCa cells-$CD8^+$ T cell co-culture assays and tumorigenesis experiment among human immune reconstitution NOG mice. Bioinformatic analysis, RNA–protein pull down, mass spectrometry, RNA immunoprecipitation, luciferase reporter assay and fluorescence in situ hybridization were performed to validate the HNRNPL/circFAM13B/IGF2BP1/PKM2 cascade.

Results Low expression of circFAM13B was observed in BCa, and it was positively associated with lower tumour stage and better prognosis among patients with BCa. The function of $CD8^+$ T cells was promoted by circFAM13B, and it could attenuate the glycolysis of BCa cells and reverse the acidic tumour microenvironment (TME). The production of granzyme B and IFN-γ was improved, and the immunotherapy (PD-1 antibodies) sensitivity was facilitated by the inhibition of acidic TME. Mechanistically, circFAM13B was competitively bound to the KH3-4 domains of IGF2BP1 and subsequently reduced the binding of IGF2BP1 and PKM2 3'UTR. Thus, the stability of the PKM2 mRNA decreased, and glycolysis-induced acidic TME was inhibited. The generation of circFAM13B was explored by confirming whether heterogeneous nuclear ribonucleoprotein L (HNRNPL) could promote circFAM13B formation via pre-mRNA back-splicing.

JOURNAL OF EXPERIMENTAL & CLINICAL CANCER RESEARCH
2023 Feb 6;42:41
Impact Factor: 11.3



Materials and Methods

Overexpres-sion plasmids and **small interfering RNAs (siRNAs)** of IGF2BP1, HNRNPL and PKM2 were obtained from **GenePharma** Co.

Cy3-labeled circFAM13B probes were acquired from **GenePharma**.

The cells were stained by incubation with the circFAM13 probe by using the **RNA-FISH kit** (**Genep-harma**, Shanghai, China) .

The PKM2 3' UTR wild type (WT) **luciferase reporter plasmid** and binding motif-mutated **lucif-erase reporter plasmid** (WT) by **GenePharma**.

Wang et al. J Exp Clin Cancer Res (2022) 41:303
https://doi.org/10.1186/s13046-022-02477-0

Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

PCSK9 promotes the progression and metastasis of colon cancer cells through regulation of EMT and PI3K/AKT signaling in tumor cells and phenotypic polarization of macrophages

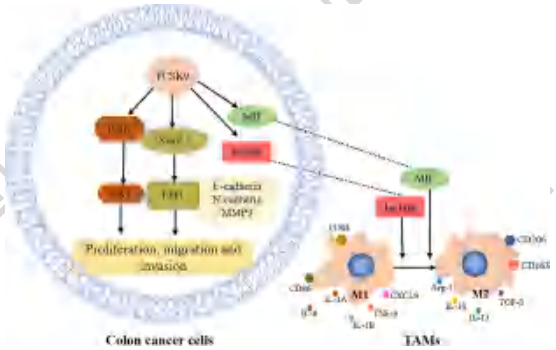
Abstract

Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is the ninth member of the proprotein convertase family that regulates lipoprotein homeostasis and altered PCSK9 expression was reportedly associated with tumor development and progression. This study assessed PCSK9 expression and functions in human colon cancer and then explored the underlying molecular events.

Methods: Colon cancer tissues were utilized for analysis of PCSK9 expression for association with clinicopathological factors from patients by immunohistochemistry assay. Manipulation of PCSK9 expression was assessed in vitro and in vivo for colon cancer cell proliferation, migration, and invasion using cell viability CCK-8, Transwell tumor cell migra-tion and invasion, and wound-healing assays. Next, proteomic analysis, Western blot, qRT-PCR and Flow cytometry were conducted to assess downstream targets and tumor cell-derived PCSK9 action on macrophage polarization.

Results: PCSK9 expression was upregulated in colon cancer tissues versus the normal tissues, and associated with advanced tumor pathological grade. Knockdown of PCSK9 expression reduced colon cancer cell proliferation, migra-tion, and invasion and suppressed tumor metastasis in vivo. PCSK9 directly or indirectly upregulated Snail 1 and in turn to downregulate E-cadherin expression, but upregulate N-cadherin and MMP9 levels and thereafter, to induce colon cancer cell epithelial-mesenchymal transition (EMT) process and activated PI3K/AKT signaling. However, PCSK9 overexpression showed the inverse effects on colon cancer cells. Knockdown of PCSK9 expression inhibited M2 mac-rophage polarization, but also promoted M1 macrophage polarization by reduction of lactate, protein lactylation and macrophage migration inhibitory factor (MIF) levels.

JOURNAL OF EXPERIMENTAL & CLINICAL CANCER RESEARCH
2022 Dec;41(1):1-21
Impact Factor: 11.3



Materials and Methods

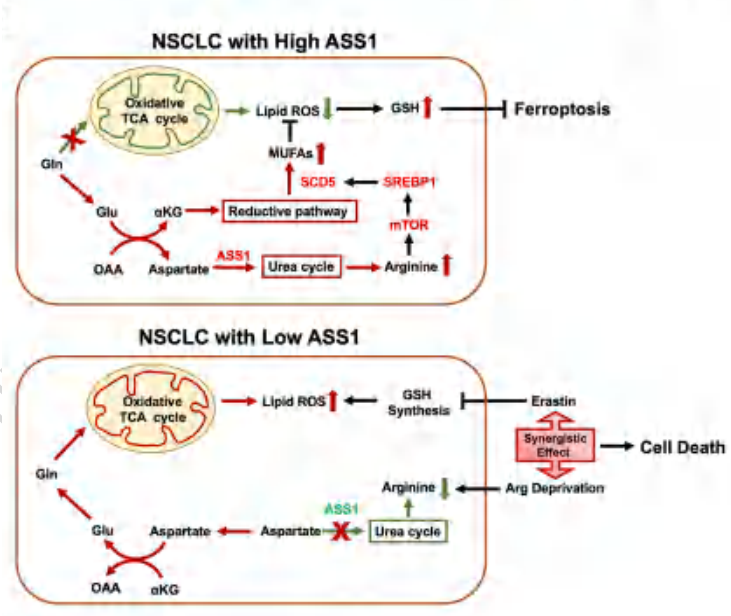
To overexpress PCSK9, we transiently transfected the **PCSK9 plasmid** (**GenePharma** Technologies, Shanghai, China).

ASS1-mediated reductive carboxylation of cytosolic glutamine confers ferroptosis resistance in cancer cells

Qiangsheng Hu1*, Jie Dai1*, Zheng Zhang5*, Huansha Yu3, Jing Zhang1, Xinsheng Zhu1, Yi Qin4#, Lele Zhang2# and Peng Zhang1#

ABSTRACT

Induction of ferroptosis, a recently defined form of nonapoptotic cell death caused by iron-dependent lipid peroxidation, has emerged as an anti-cancer strategy. Erastin is a ferroptosis activator that promotes cell death that not only depends on the depletion of cellular cysteine but also relies on mitochondrial oxidative metabolism of glutamine. Here, we demonstrate that ASS1, a key enzyme involved in the urea cycle, plays a crucial role in ferroptosis resistance. Loss of ASS1 increased the sensitivity of non-small cell lung cancer (NSCLC) cells to erastin in vitro and decreased tumor growth in vivo. Metabolomics analysis with stable isotope-labeled glutamine showed that ASS1 promotes reductive carboxylation of cytosolic glutamine and compromises the oxidative TCA cycle from glutamine anaplerosis, reducing mitochondrial-derived lipid reactive oxygen species. Moreover, transcriptome sequencing showed that ASS1 activates the mTORC1-SREBP1-SCD5 axis to promote de novo monounsaturated fatty acid synthesis by utilizing acetyl-CoA derived from the glutamine reductive pathway. Treating ASS1-deficient NSCLC cells with erastin combined with arginine deprivation significantly enhanced cell death compared to either treatment alone. Collectively, these results reveal a previously unknown regulatory role of ASS1 in ferroptosis resistance and provide a potential therapeutic target for ASS1-deficient NSCLC.



CANCER RESEARCH
2023 May 15; 83 (10): 1646–1665
Impact Factor: 11.2

Materials and Methods

The SREBP1 sequence was synthesized by **GenePharma** (Shanghai, China) and cloned into the pcDNA3.1(+) vector.
GOT1-specific siRNA and **GOT2-specific siRNA** were obtained from **GenePharma** (Shanghai, China).

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Lou, M. D., Li, J., Cheng, Y., Xiao, N., Ma, G., Li, P.(2019). Glucagon up‐regulates hepatic mitochondrial pyruvate carrier 1 through cAMP‐responsive element‐binding protein; inhibition of hepatic gluconeogenesis by ginsenoside Rb1. British journal of pharmacology, 176(16), 2962-2976. **IF:7.3**
Lou MD, Li J, Cheng Y, et al. Glucagon up‐regulates hepatic mitochondrial pyruvate carrier 1 through cAMP responsive element‐binding protein; inhibition of hepatic gluconeogenesis by ginsenoside Rb1. British Pharmacological Society. 2019 May 19; 176: 2962-76. **IF: 7.3**
Liao, J., Xie, Y., Lin, Q., Yang, X., An, X., Xia, Y(2020). Immunoproteasome subunit β5i regulates diet‐induced atherosclerosis through altering MERTK‐mediated efferocytosis in Apoe knockout mice. The Journal of Pathology, 250(3), 275-287. 1.7. **IF: 7.3**
Jiang C, Qi Z, Jia H, et al. ATP-Responsive Low-Molecular-Weight Polyethylenimine-Based Supramolecular Assembly via Host−Guest Interaction for Gene Delivery. Biomacromolecules. 2019 Jan 14; 20(1): 478-89. **IF:6.2**
Yuan, Z., Yuan, Z., Hasnat, M., Zhang, H., Liang, P., Sun, L.(2020). A new perspective of triptolide-associated hepatotoxicity: the relevance of NF-κB and NF-κB-mediated cellular FLICE-inhibitory protein. Acta Pharmaceutica Sinica B. **IF:4.5**

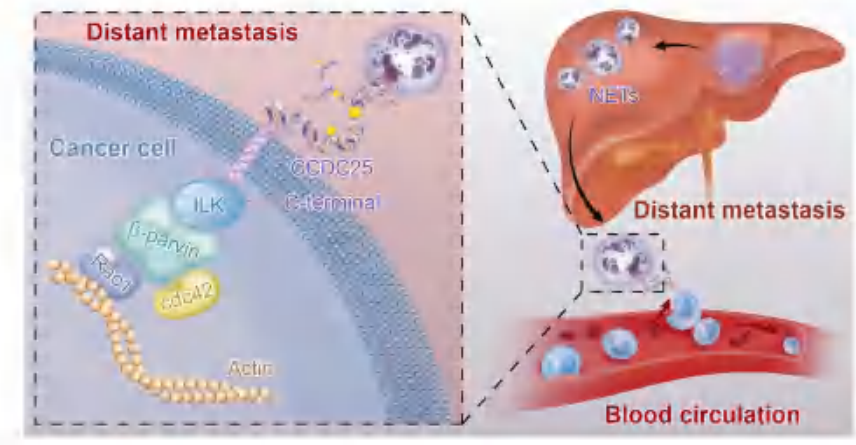
病毒——慢病毒

Article

DNA of neutrophil extracellular traps promotes cancer metastasis via CCDC25

Linbin Yang[1,2], Qiang Liu[1,2], Xiaoqian Zhang[1,2], Xinwei Liu[1,2], Boxuan Zhou[1,2], Jianing Chen[1,2], Di Huang[1,2], Jiaqian Li[1,2], Heliang Li[1,2], Fei Chen[1,2], Jiang Liu[1,2], Yue Xing[1,2], Xueman Chen[1,2], Shicheng Su[1,2]✉ & Erwei Song[1,2,3,4]✉

Neutrophil extracellular traps (NETs), which consist of chromatin DNA filaments coated with granule proteins, are released by neutrophils to trap microorganisms[1–3]. Recent studies have suggested that the DNA component of NETs (NET-DNA) is associated with cancer metastasis in mouse models[4–6]. However, the functional role and clinical importance of NET-DNA in metastasis in patients with cancer remain unclear. Here we show that NETs are abundant in the liver metastases of patients with breast and colon cancers, and that serum NETs can predict the occurrence of liver metastases in patients with early-stage breast cancer. NET-DNA acts as a chemotactic factor to attract cancer cells, rather than merely acting as a 'trap' for them; in several mouse models, NETs in the liver or lungs were found to attract cancer cells to form distant metastases. We identify the transmembrane protein CCDC25 as a NET-DNA receptor on cancer cells that senses extracellular DNA and subsequently activates the ILK–β-parvin pathway to enhance cell motility. NET-mediated metastasis is abrogated in CCDC25-knockout cells. Clinically, we show that the expression of CCDC25 on primary cancer cells is closely associated with a poor prognosis for patients. Overall, we describe a transmembrane DNA receptor that mediates NET-dependent metastasis, and suggest that targeting CCDC25 could be an appealing therapeutic strategy for the prevention of cancer metastasis.



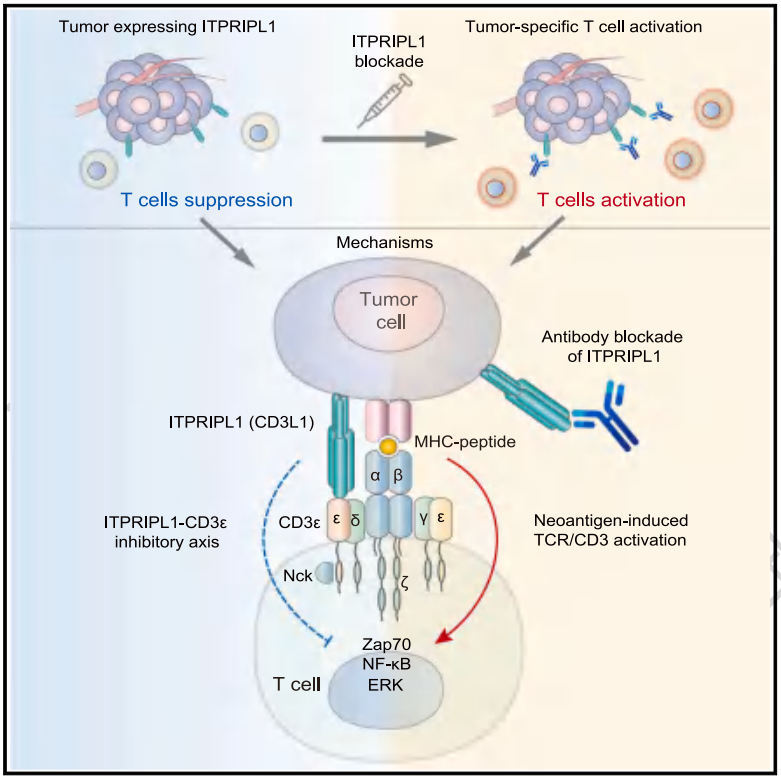
Nature
2020 Jun 11;583(7814):133-138
Impact Factor: 64.8

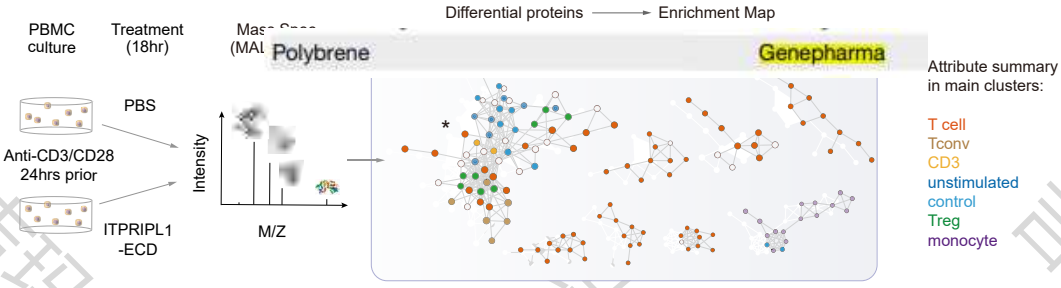
Materials and Methods

The **Cas9 lentivirus** and **gRNA1/2 lentivirus** were purchased from **GenePharma** and transduced to MDA-MB-231 tumour cells.

ITPRIPL1 binds CD3ε to impede T cell activation and enable tumor immune evasion

Graphical abstract





Authors

Shouyan Deng, Yibo Zhang, Huanbin Wang, ..., Grace Liu, Yingfei Quan, Jie Xu

Correspondence

jie_xu@fudan.edu.cn

In brief

An inhibitory ligand acts directly on CD3e to regulate T cell activation, and disruption of the interaction boosts tumor-specific T cell cytotoxicity to limit tumor growth.

CELL
Deng et al., 2024, Cell 187, 2305–2323

Impact Factor: 64.5

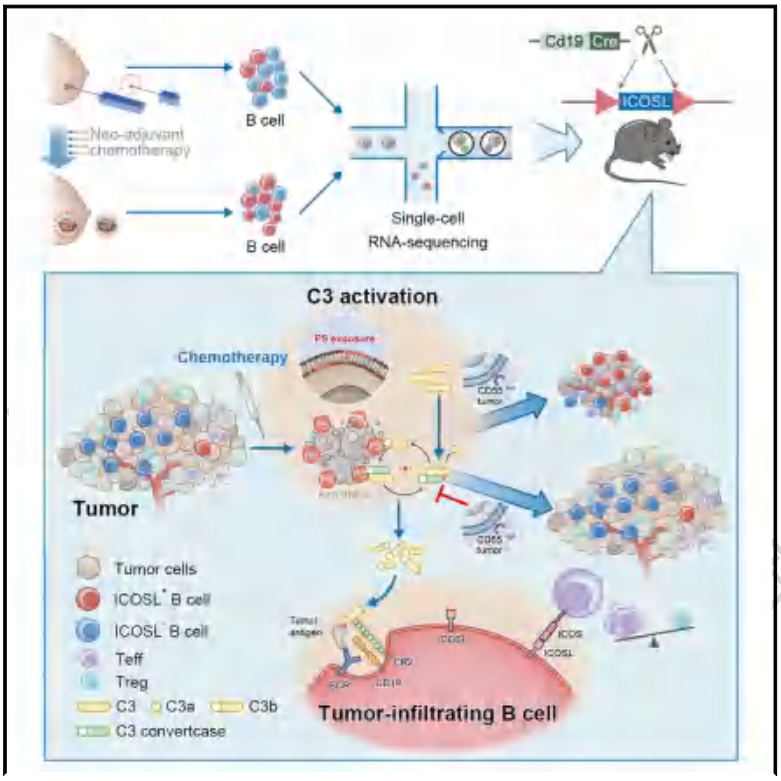
Materials

Polybrene Genepharma

Cell

Complement Signals Determine Opposite Effects of B Cells in Chemotherapy-Induced Immunity

Graphical Abstract



Authors

Yiwen Lu, Qiyi Zhao, Jian-You Liao, ..., Shubin Yu, Yunjie Zeng, Shicheng Su

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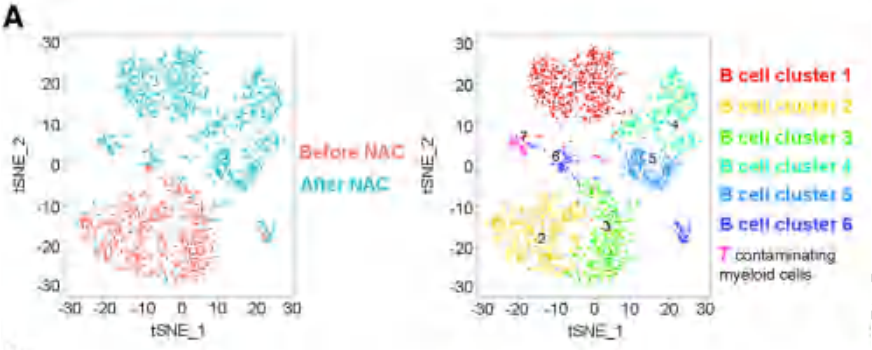
sushch@mail.sysu.edu.cn

In Brief

An anti-tumoral B cell subset emerges in the tumor microenvironment in response to chemotherapy-induced immunogenic cell death and complement signaling.

Cell
2020 Mar;180:1081
Impact Factor: 64.5



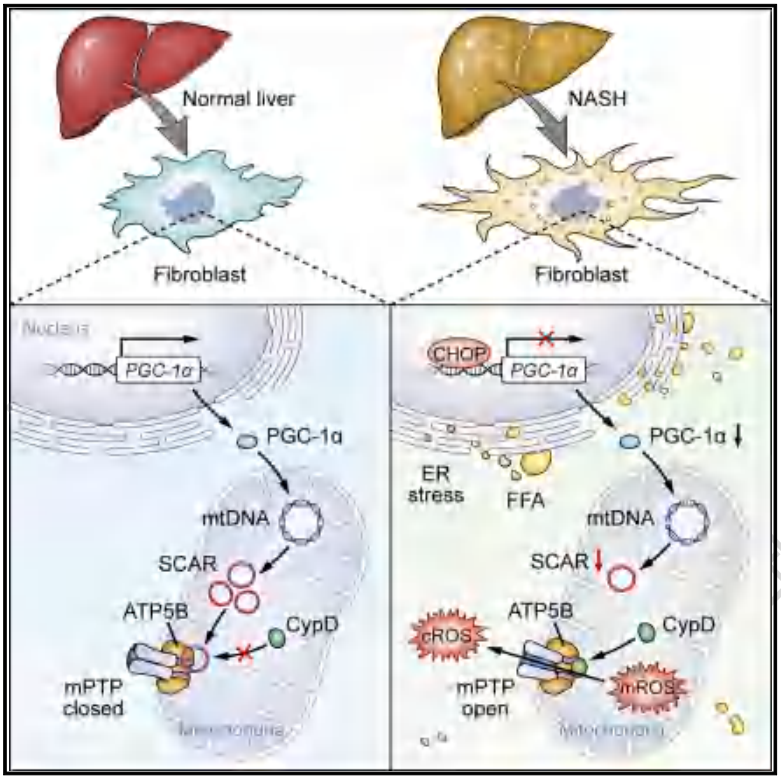
Materials

Bacterial and Virus Strains

LV5 lentiviral vetor	Genepharma,Shanghai
LV3 lentiviral vetor	Genepharma,Shanghai

Targeting Mitochondria-Located circRNA SCAR Alleviates NASH via Reducing mROS Output

Graphical Abstract



Authors

Qiyi Zhao, Jiayu Liu, Hong Deng, ..., Xiaoding Xu, Zhiliang Gao, Shicheng Su

Correspondence

xuxiaod5@mail.sysu.edu.cn (X.X.), gaozhl@mail.sysu.edu.cn (Z.G.), sushch@mail.sysu.edu.cn (S.S.)

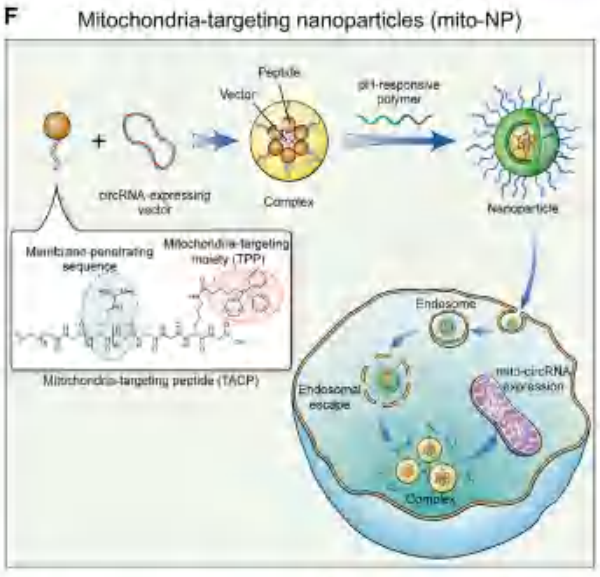
In Brief

A mitochondrial circRNA that is dysregulated in NAFLD patients' liver fibroblasts directly binds and regulates the mitochondrial permeability transition pore to modulate mitochondrial metabolism and inflammation, providing a potential therapeutic angle.

Cell
2020 Oct 1; 183: 76-93
Impact Factor: 64.5

Materials and Methods

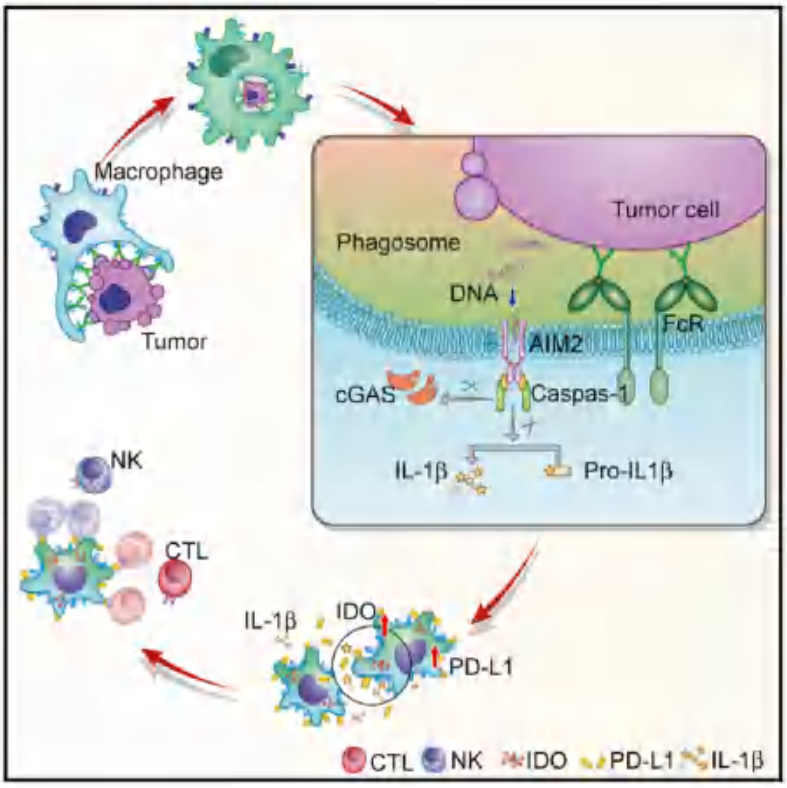
For shRNA transduction, a **lentiviral vector plasmid pLKO.1-puro** (**GenePharma** Inc, Shanghai, China) was used to construct the stable clones.



Cell

Immune Checkpoint Inhibition Overcomes ADCP-Induced Immunosuppression by Macrophages

Graphical Abstract



Authors

Shicheng Su, Jinghua Zhao, Yue Xing, ..., Fengxi Su, Qiang Liu, Erwei Song

Correspondence

victorlq@hotmail.com (Q.L.), songew@mail.sysu.edu.cn (E.S.)

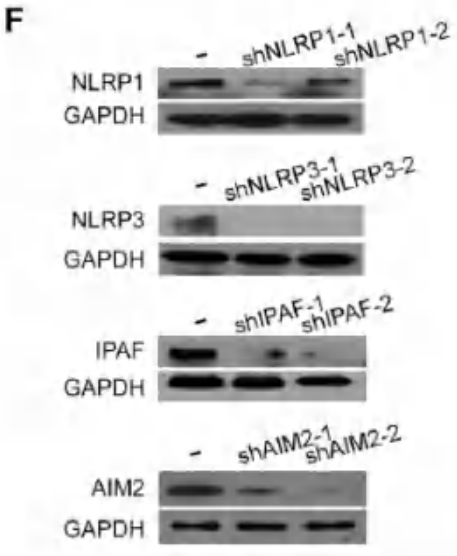
In Brief

Therapeutic antibody-based cancer treatment leads to ADCP-induced, AIM2-mediated immunosuppression by macrophages that can be overcome with concomitant immune checkpoint blockade.

Cell
2018 Oct 4; 175: 442-57
Impact Factor: 64.5

Materials and Methods

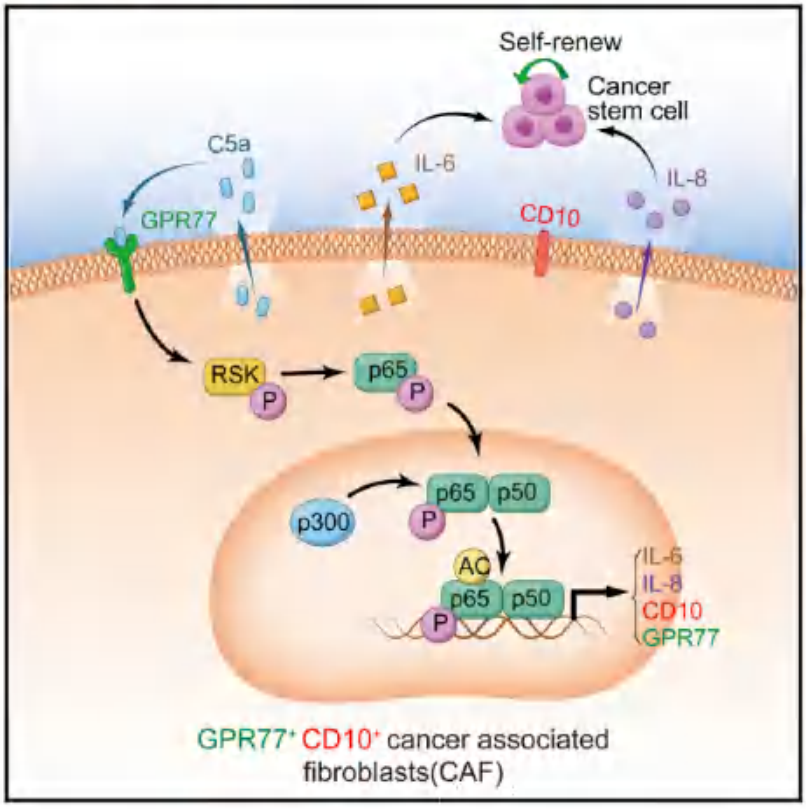
Lentivirus packaging was made by **GenePharma** Inc (Shanghai, China). A lentiviral vector plasmid pGag/Pol was used in our study to construct the stable clones. **Lentiviral shRNAs** targeting AIM2, NLRP1, NLRP3, IPAF, STING, TLR9, p65, STAT1, TBK1 and AMPK were obtained from **Genepharma** and shRNA Silencing sequences are listed in Table S2.



Cell

CD10+GPR77+ Cancer-Associated Fibroblasts Promote Cancer Formation and Chemoresistance by Sustaining Cancer Stemness

Graphical Abstract



Authors

Shicheng Su, Jianing Chen, Herui Yao, ..., Mengfeng Li, Qiang Liu, Erwei Song

Correspondence

songew@mail.sysu.edu.cn

In Brief

CD10 and GPR77 identify a cancer stemness-sustaining cancer-associated fibroblast subset.

Cell
2018 Feb 8; 172: 1-16
Impact Factor: 64.5

Materials and Methods

Lentivirus packaging was provided by **GenePharma** (Shanghai, China).

RESEARCH

Science
AAAS

SEX DETERMINATION

The histone demethylase KDM6B regulates temperature-dependent sex determination in a turtle species

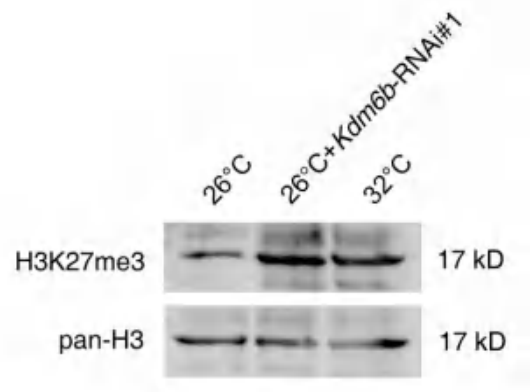
Chutian Ge,[1*†] Jian Ye,[2*] Ceri Weber,[3] Wei Sun,[1] Haiyan Zhang,[1] Yingjie Zhou,[1] Cheng Cai,[1] Guoying Qian,[1†] Blanche Capel[3†]

Temperature-dependent sex determination is a notablemodel of phenotypic plasticity. Inmany reptiles, including the red-eared slider turtle Trachemys scripta elegans (T. scripta), the individual's sex is determined by the ambient temperature during egg incubation. In this study, we show that the histone H3 lysine 27 (H3K27) demethylase KDM6B exhibits temperaturedependent sexually dimorphic expression in early T. scripta embryos before the gonad is distinct. Knockdown of Kdm6b at 26°C (a temperature atwhich all offspring develop into males) triggers male-to-female sex reversal in >80%of surviving embryos. KDM6B directly promotes the transcription of the male sex-determining gene Dmrt1 by eliminating the trimethylation of H3K27 near its promoter. Additionally, overexpression of Dmrt1 is sufficient to rescue the sex reversal induced by disruption of Kdm6b.This study establishes causality and a direct genetic link between epigenetic mechanisms and temperature-dependent sex determination in a turtle species.

Science
2018 May 11; 360(6389): 645-8
Impact Factor: 56.9

Materials and Methods

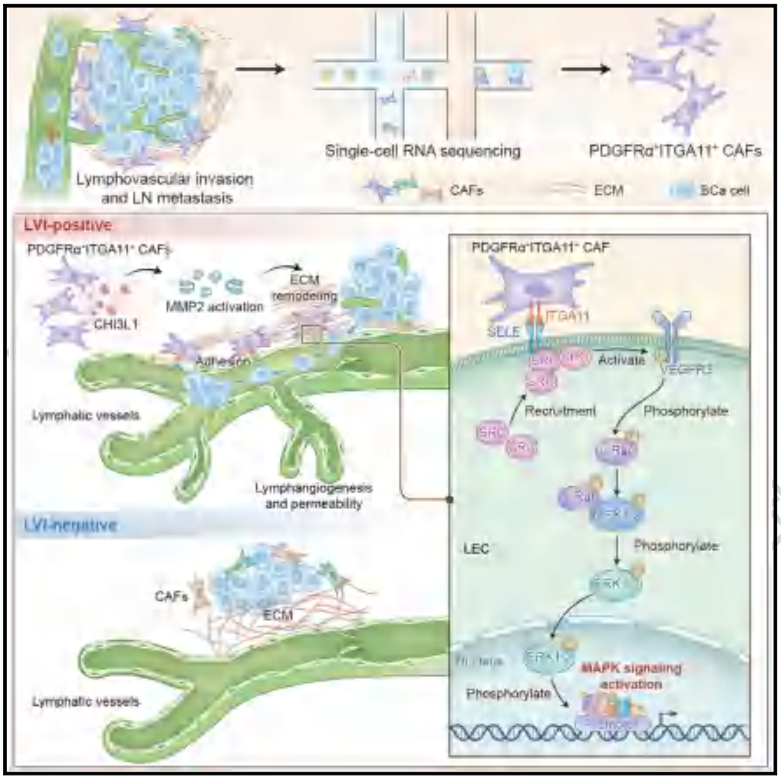
The pGP-U6-Kdm6b-shRNA construct was digested with AgeI-EcoRI and inserted into the EcoRI site of **pGLV-U6-GFP** (**GenePharma**, Shanghai, China).
The PCR product was digested with EcoRI and cloned to **pGLV-EF1a-GFP** (**LV-4**, **GenePharma**, Shanghai, China).



Cancer Cell

PDGFRa^{+}ITGA11^{+} fibroblasts foster early-stage cancer lymphovascular invasion and lymphatic metastasis via ITGA11-SELE interplay

Graphical abstract



Authors

Hanhao Zheng, Mingjie An, Yuming Luo, ..., Jian Huang, Changhao Chen, Tianxin Lin

Correspondence

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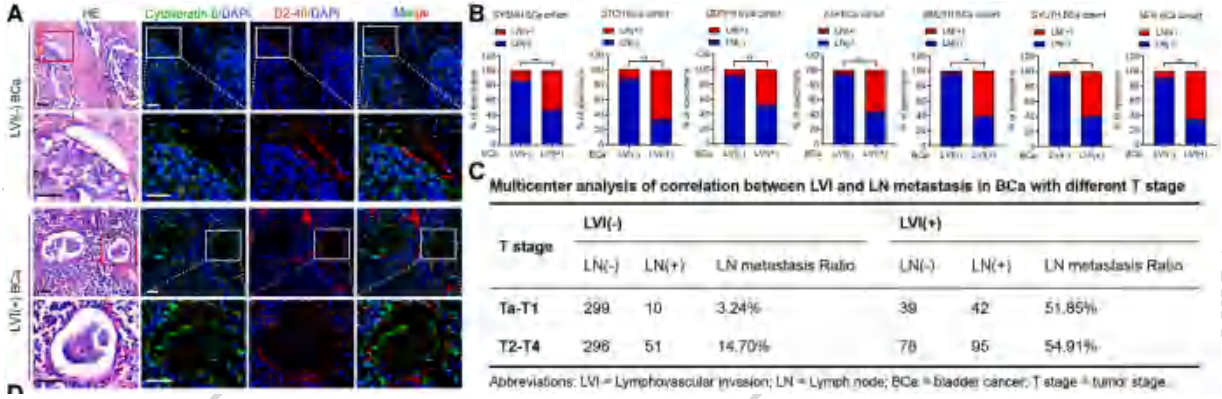
In brief

Zheng et al. uncover the cellular landscape in early-stage BCa and report a CAF subset characterized by PDGFRa and ITGA11. They demonstrate that PDGFR ITGA11^{+} CAFs stimulate lymphangiogenesis and align ECM to assist BCa cell intravasation, facilitating the LVI and LN metastasis of early-stage BCa, which provides a potential therapeutic target.



CANCER CELL
Cancer Cell 42, 682–700.e1–e12, April 8, 2024
Impact Factor: 50.3

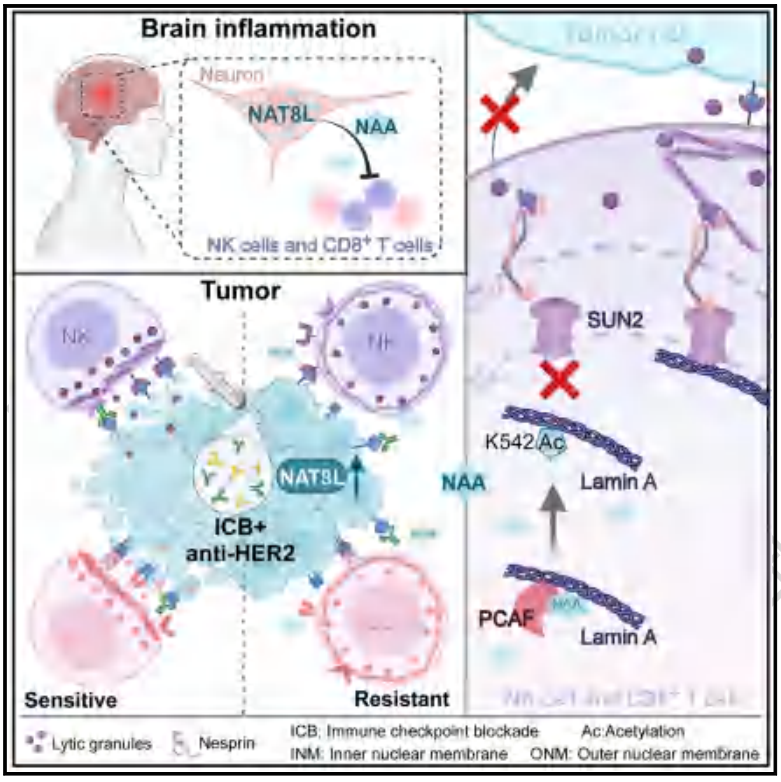
Materials and Methods

LV3 lentiviral vector Genepharma

Cancer Cell

Tumor cells impair immunological synapse formation via central nervous system-enriched metabolite

Graphical abstract



Authors

Yihong Li, Min Huang, Minger Wang, ..., Jinghua Zhao, Yiwen Lu, Shicheng Su

Correspondence

luyw8@mail.sysu.edu.cn (Y.L.),
sushch@mail.sysu.edu.cn (S.S.)

In brief

Li et al. reveal that tumor cells mimic the anti-inflammatory mechanism of central nervous system to evade anti-tumor immunity by expressing brain-enriched N-acetyltransferase 8-like (NAT8L) and its metabolite N-acetylaspartate (NAA). NAA impairs the formation of immunological synapse by cytotoxic immune cells. NAT8L is a potential target for cancer immunotherapy.

Tumors employ various strategies to evade immune surveillance. Central nervous system (CNS) has multiple features to restrain immune response. Whether tumors and CNS share similar programs of immunosuppression is elusive. Here, we analyze multi-omics data of tumors from HER2$^+$ breast cancer patients receiving trastuzumab and anti-PD-L1 antibody and find that CNS-enriched N-acetyltransferase 8-like (NAT8L) and its metabolite N-acetylaspartate (NAA) are overexpressed in resistant tumors. In CNS, NAA is released during brain inflammation. NAT8L attenuates brain inflammation and impairs anti-tumor immunity by inhibiting cytotoxicity of natural killer (NK) cells and CD8$^+$ T cells via NAA. NAA disrupts the formation of immunological synapse by promoting PCAF-induced acetylation of lamin A-K542, which inhibits the integration between lamin A and SUN2 and impairs polarization of lytic granules. We uncover that tumor cells mimic the anti-inflammatory
mechanism of CNS to evade anti-tumor immunity and NAT8L is a potential target to enhance efficacy of anti-cancer agents.

CANCER CELL
Cancer Cell 42, 985–1002

Impact Factor: 50.3

Materials and Methods
Lentivirus vector LV5-pGLV Genepharma

Cell Research

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

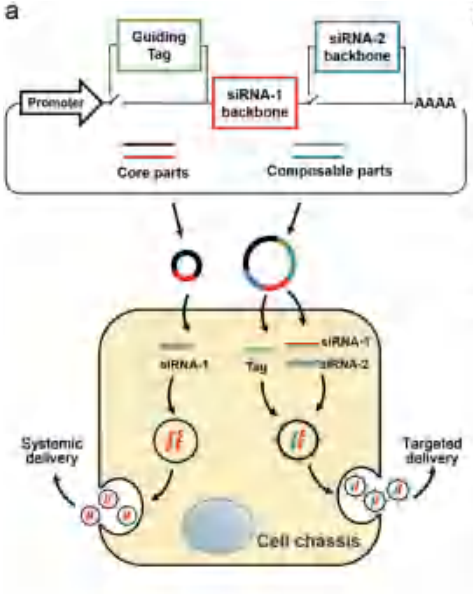
ARTICLE OPEN

In vivo self-assembled small RNAs as a new generation of RNAi therapeutics

Zheng Fu[1,2,3], Xiang Zhang[1], Xinyan Zhou[1], Uzair Ur-Rehman[1], Mengchao Yu[1,4], Hongwei Liang[1], Hongyuan Guo[1], Xu Guo[1], Yan Kong[1], Yuanyuan Su[1], Yangyang Ye[1], Xiuting Hu[1], Wei Cheng[5], Jinrong Wu[6], Yanbo Wang[1], Yayun Gu[3], Sheng-feng Lu[7], Dianqing Wu[8], Ke Zen[1], Jing Li[1], Chao Yan[1,2,3], Chen-Yu Zhang[1] and Xi Chen[1,2,3]

INTRODUCTION

RNA interference (RNAi) offers an opportunity to specifically target mRNAs and modulate the expression of corresponding proteins before their biogenesis, and has therefore been proposed as a promising therapeutic tool to manipulate the expression of disease-related genes, especially the genes that are considered undruggable using traditional approaches.1–3 However, RNAi therapy has encountered many problems and falls way behind expectation during clinical translation. The development of RNAi therapy has undergone two major stages. In the first stage, naked small interfering RNAs (siRNAs) or chemically modified stable siRNAs were synthesized and directly injected for systematic delivery; yet these siRNAs cannot effectively pass biological barriers and reach target genes.3 In the second stage, various delivery vehicles (e.g., lipid nanoparticles, cationic polymers and viruses) or conjugated ligands (e.g., triantennary N-acetylgalactosamine (GalNAc)) were invented to increase the efficiency of siRNA delivery in vivo.4,5 The recent FDA approval of the first (Patisiran, siRNA is formulated as a lipid complex for the delivery to hepatocytes6) and second (Givosiran, siRNA is conjugated to a GalNAc ligand that enables asialoglycoprotein receptors-mediated targeted delivery to hepatocytes7) siRNA drugs marked the beginning of the era of RNAi therapeutics. Despite some successful cases, in general the translation of siRNA therapeutics to wide clinical use is still hindered by a major hurdle associated with in vivo delivery, especially for extrahepatic delivery. A common feature of the current delivery strategies is that the siRNAs are pre-assembled with vehicles or ligands in vitro. However, these artificial complexes are often plagued by problems like low immunocompatibility, high toxicity, insufficient circulation stability and limited tissue accessibility (mainly liver) when administered in vivo.8 Thus, a more concerted effort towards developing a safe, precise and efficient delivery platform for siRNAs is crucial for next-generation RNAi therapeutics.



Cell Research
2021 Mar;31(6):631-648
Impact Factor: 44.1

Materials and Methods

The lentiviral vector pLv-Luc encoding luciferase and puromycin was purchased from GenePharma.

Cell Research (2015) :1-15.

www.nature.com/cr

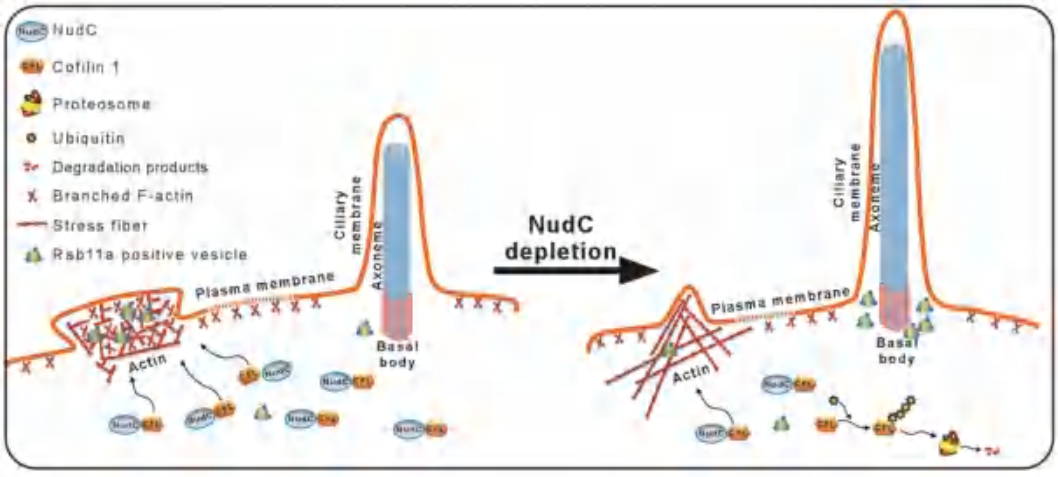
ORIGINAL ARTICLE

NudC regulates actin dynamics and ciliogenesis by stabilizing cofilin 1

Cheng Zhang[1,*], Wen Zhang[1,*], Yi Lu[1,*], Xiaoyi Yan[1,2], Xiumin Yan[3], Xueliang Zhu[3], Wei Liu[1], Yuehong Yang[1,2], Tianhua Zhou[1,2]

Emerging data indicate that actin dynamics is associated with ciliogenesis. However, the underlying mechanism remains unclear. Here we find that nuclear distribution gene C (NudC), an Hsp90 co-chaperone, is required for actin organization and dynamics. Depletion of NudC promotes cilia elongation and increases the percentage of ciliated cells. Further results show that NudC binds to and stabilizes cofilin 1, a key regulator of actin dynamics. Knockdown of cofilin 1 also facilitates ciliogenesis. Moreover, depletion of either NudC or cofilin 1 causes similar ciliary defects in zebrafish, including curved body, pericardial edema and defective left-right asymmetry. Ectopic expression of cofilin 1 significantly reverses the phenotypes induced by NudC depletion in both cultured cells and zebrafish. Thus, our data suggest that NudC regulates actin cytoskeleton and ciliogenesis by stabilizing cofilin 1.

Keywords: NudC; actin dynamics; ciliogenesis; cofilin 1; zebrafish development



Cell Research
2016 Feb; 26: 239-53
Impact Factor: 44.1

Materials and Methods

pGLV3/H1/GFP **lentiviral vectors** were purchased from **GenePharma**.
Oligos corresponding to the following sequences were synthesized by **GenePharma**: 5′-GGATCAAGCATGAATTGCAAGCAAA-3′ for cofilin 1 RNAi-1 and 5′-CATG GAAGCAGGACCAGTA-3′ for cofilin 1 RNAi-2.

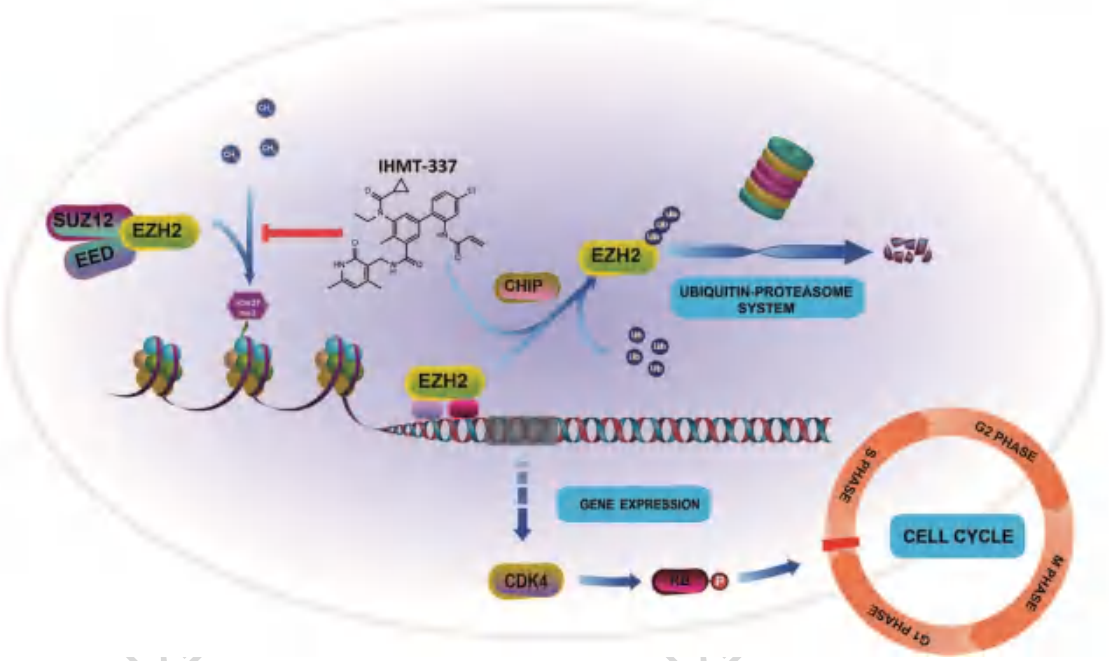
ARTICLE OPEN

Discovery of IHMT-337 as a potent irreversible EZH2 inhibitor targeting CDK4 transcription for malignancies

Husheng Mei[1,2], Hong Wu[1,3], Jing Yang[1,3], Bin Zhou[1,2], Aoli Wang[1,3], Chen Hu[1,3], Shuang Qi[1,3], Zongru Jiang[1,3], Fengming Zou[1,3], Beilei Wang[1,3], Feiyang Liu[1,3], Yongfei Chen[1,3], Wenchao Wang[1,3]✉, Jing Liu[1,3]✉ and Qingsong Liu[1,2,3,4]✉

Enhancer of zeste homolog 2 (EZH2), an enzymatic subunit of PRC2 complex, plays an important role in tumor development and progression through its catalytic and noncatalytic activities. Overexpression or gain-of-function mutations of EZH2 have been significantly associated with tumor cell proliferation of triple-negative breast cancer (TNBC) and diffuse large B-cell lymphoma (DLBCL). As a result, it has gained interest as a potential therapeutic target. The currently available EZH2 inhibitors, such as EPZ6438 and GSK126, are of benefit for clinical using or reached clinical trials. However, certain cancers are resistant to these enzymatic inhibitors due to its noncatalytic or transcriptional activity through modulating nonhistone proteins. Thus, it may be more effective to synergistically degrade EZH2 in addition to enzymatic inhibition. Here, through a rational design and chemical screening, we discovered a new irreversible EZH2 inhibitor, IHMT-337, which covalently bounds to and degrades EZH2 via the E3 ligase CHIP-mediated ubiquitination pathway. Moreover, we revealed that IHMT-337 affects cell cycle progression in TNBC cells through targeting transcriptional regulating of CDK4, a novel PRC2 complex- and enzymatic activity-independent function of EZH2. More significantly, our compound inhibits both DLBCL and TNBC cell proliferation in different preclinical models in vitro and in vivo. Taken together, our findings demonstrate that in addition to enzymatic inhibition, destroying of EZH2 by IHMT-337 could be a promising therapeutic strategy for TNBC and other malignancies that are independent of EZH2 enzymatic activity.

Signal Transduction and Targeted Therapy (2023)8:18 ; https://doi.org/10.1038/s41392-022-01240-3



Signal Transduction and Targeted Therapy
2023 Jan 16;8:18
Impact Factor: 39.3

Materials and Methods

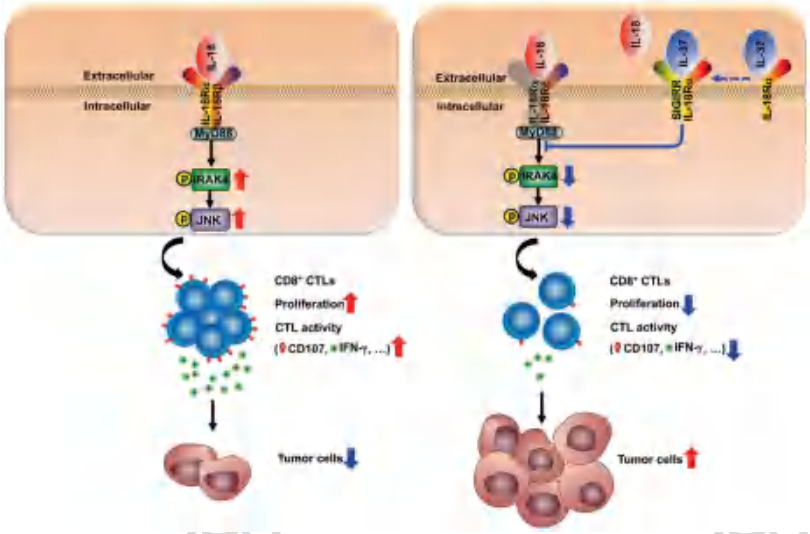
EZH2 and CDK4 knockdown lentivirus were purchased from **GenePharma**.

ARTICLE OPEN

Interleukin-37 promotes colitis-associated carcinogenesis via SIGIRR-mediated cytotoxic T cells dysfunction

Zhen Wang[1,2,3], Fan-lian Zeng[1], Ya-wen Hu[1], Xiao-yan Wang[1], Fu-lei Zhao[1], Pei Zhou[1], Jing Hu[1], Yuan-yuan Xiao[1,4,5], Zhong-lan Hu[1], Ming-feng Guo[1], Xiao-qiong Wei[1], Xiao Liu[1], Nong-yu Huang[1], Jun Zhang[1], Shu-wen Chen[1], Juan Cheng[1], Hua-ping Zheng[1], Hong Zhou[1], Qi-xiang Zhao[1], Chen Zhang[1], Yan Hao[1], Song Zou[6], Yi-yue Gui[6], Jia-dong Yu[1], Lin-na Gu[1], Cheng-cheng Yue[1], Hao-zhou Zhang[1], Wen-ling Wu[1], Yi-fan Zhou[1], Xi-kun Zhou[1], Guo-bo Shen[1], Xiu Teng[1,7]✉ and Jiong Li[1]✉

Interleukin-37b (hereafter called IL-37) was identified as fundamental inhibitor of natural and acquired immunity. The molecular mechanism and function of IL-37 in colorectal cancer (CRC) has been elusive. Here, we found that IL-37 transgenic (IL-37tg) mice were highly susceptible to colitis-associated colorectal cancer (CAC) and suffered from dramatically increased tumor burdens in colon. Nevertheless, IL-37 is dispensable for intestinal mutagenesis, and CRC cell proliferation, apoptosis, and migration. Notably, IL-37 dampened protective cytotoxic T cell-mediated immunity in CAC and B16-OVA models. CD8+ T cell dysfunction is defined by reduced retention and activation as well as failure to proliferate and produce cytotoxic cytokines in IL-37tg mice, enabling tumor evasion of immune surveillance. The dysfunction led by IL-37 antagonizes IL-18–induced proliferation and effector function of CD8+ T cells, which was dependent on SIGIRR (single immunoglobulin interleukin-1 receptor-related protein). Finally, we observed that IL-37 levels were significantly increased in CRC patients, and positively correlated with serum CRC biomarker CEA levels, but negatively correlated with the CD8+ T cell infiltration in CRC patients. Our findings highlight the role of IL-37 in harnessing antitumor immunity by inactivation of cytotoxic T cells and establish a new defined inhibitory factor IL-37/SIGIRR in cancer-immunity cycle as therapeutic targets in CRC.



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

Materials and Methods

The human IL-37b gene **overexpression lentivirus and control lentivirus** were obtained from Shanghai **GenePharma** Co., Ltd.

Molecular Cancer

RESEARCH Open Access

ZNF460-mediated circRPPH1 promotes TNBC progression through ITGA5-induced FAK/PI3K/AKT activation in a ceRNA manner

Chuanpeng Zhang[1†], Ziyi Yu[1†], Susu Yang[1†], Yitao Liu[1†], Jiangni Song[1], Juan Mao[1], Minghui Li[1] and Yi Zhao[1*]

Abstract

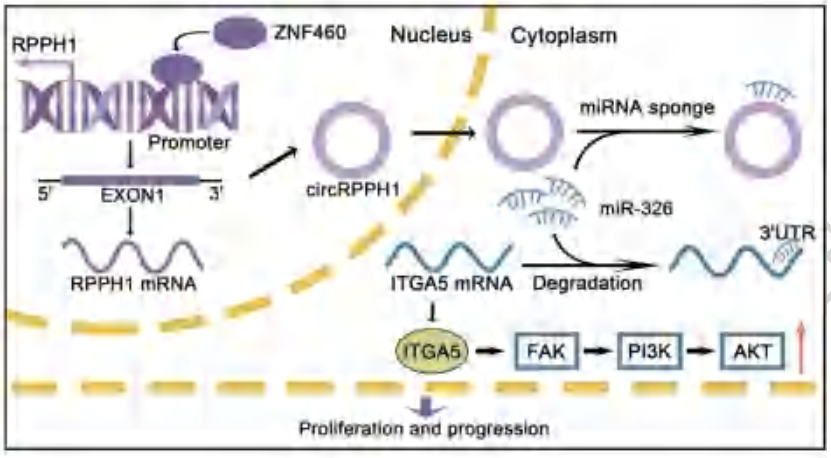
Background Circular RNAs are highly stable regulatory RNAs that have been increasingly associated with tumorigenesis and progression. However, the role of many circRNAs in triple-negative breast cancer (TNBC) and the related mechanisms have not been elucidated.

Methods In this study, we screened circRNAs with significant expression differences in the RNA sequencing datasets of TNBC and normal breast tissues and then detected the expression level of circRPPH1 by qRT–PCR. The biological role of circRPPH1 in TNBC was then verified by in vivo and in vitro experiments. Mechanistically, we verified the regulatory effects between circRPPH1 and ZNF460 and between circRPPH1 and miR-326 by chromatin immunoprecipitation (ChIP), fluorescence in situ hybridization assay, dual luciferase reporter gene assay and RNA pull-down assay. In addition, to determine the expression of associated proteins, we performed immunohistochemistry, immunofluorescence, and western blotting.

Results The upregulation of circRPPH1 in TNBC was positively linked with a poor prognosis. Additionally, both in vivo and in vitro, circRPPH1 promoted the biologically malignant behavior of TNBC cells. Additionally, circRPPH1 may function as a molecular sponge for miR-326 to control integrin subunit alpha 5 (ITGA5) expression and activate the focal adhesion kinase (FAK)/PI3K/AKT pathway.

Conclusion Our research showed that ZNF460 could promote circRPPH1 expression and that the circRPPH1/miR-326/ITGA5 axis could activate the FAK/PI3K/AKT pathway to promote the progression of TNBC. Therefore, circRPPH1 can be used as a therapeutic or diagnostic target for TNBC.

Keywords TNBC, circRPPH1, miR-326, ITGA5



Molecular Cancer
2024 Feb 13
Impact Factor: 37.3

Materials and Methods

To knock down circRPPH1, **siRNAs (si-circ1, si-circ2, si-circ3) targeting the reverse splice site of circRPPH1** and **lentiviral vectors** and **control vectors containing shRNAs targeting circRPPH1** were purchased from **GenePharma** (Shanghai, China).

Molecular Cancer

RESEARCH Open Access

hsa_circ_0007919 induces LIG1 transcription by binding to FOXA1/TET1 to enhance the DNA damage response and promote gemcitabine resistance in pancreatic ductal adenocarcinoma

Lei Xu[1,2,3†], Xiao Ma[1,2,4†], Xiuzhong Zhang[1†], Chong Zhang[1], Yi Zhang[1], Shuai Gong[1], Nai Wu[1], Peng Zhang[1,2,5], Xinyu Feng[1,2], Jiaxuan Guo[1,2], Mengmeng Zhao[1,2], Zeqiang Ren[1*] and Pengbo Zhang[1*]

Abstract

Background Circular RNAs (circRNAs) play important roles in the occurrence and development of cancer and chemoresistance. DNA damage repair contributes to the proliferation of cancer cells and resistance to chemotherapy-induced apoptosis. However, the role of circRNAs in the regulation of DNA damage repair needs clarification.

Methods RNA sequencing analysis was applied to identify the differentially expressed circRNAs. qRT-PCR was conducted to confirm the expression of hsa_circ_0007919, and CCK-8, FCM, single-cell gel electrophoresis and IF assays were used to analyze the proliferation, apoptosis and gemcitabine (GEM) resistance of pancreatic ductal adenocarcinoma (PDAC) cells. Xenograft model and IHC experiments were conducted to confirm the effects of hsa_circ_0007919 on tumor growth and DNA damage in vivo. RNA sequencing and GSEA were applied to confirm the downstream genes and pathways of hsa_circ_0007919. FISH and nuclear-cytoplasmic RNA fractionation experiments were conducted to identify the cellular localization of hsa_circ_0007919. ChIRP, RIP, Co-IP, ChIP, MS-PCR and luciferase reporter assays were conducted to confirm the interaction among hsa_circ_0007919, FOXA1, TET1 and the LIG1 promoter.

Results We identified a highly expressed circRNA, hsa_circ_0007919, in GEM-resistant PDAC tissues and cells. High expression of hsa_circ_0007919 correlates with poor overall survival (OS) and disease-free survival (DFS) of PDAC patients. Hsa_circ_0007919 inhibits the DNA damage, accumulation of DNA breaks and apoptosis induced by GEM in a LIG1-dependent manner to maintain cell survival. Mechanistically, hsa_circ_0007919 recruits FOXA1 and TET1 to

Molecular Cancer
2023 Dec 4;22(1):195
Impact Factor: 37.3

Materials and Methods

PANC-1 and CFPAC-1 GEM-resistant cells were infected by hsa_circ_0007919 **inhibition lentivirus** (**GenePharma**, China) .

All small interfering RNA (siRNA) and **full-length plasmid** of hsa_circ_0007919, LIG1, FOXA1, TET1 and nega-tive control were purchased from **GenePharma** (Suzhou, China) .

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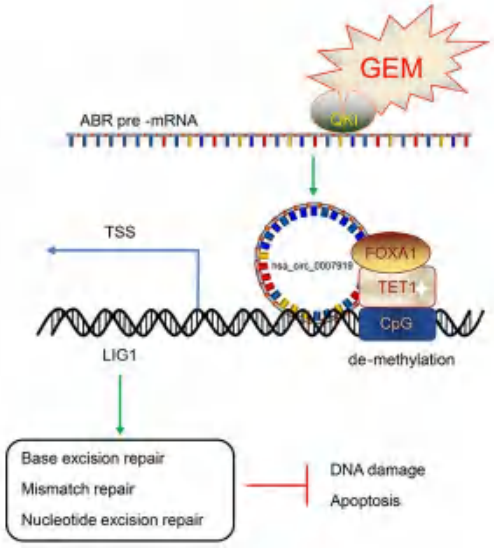


Liao *et al. Molecular Cancer* (2023) 22:163
https://doi.org/10.1186/s12943-023-01859-y

Molecular Cancer

RESEARCH Open Access

LINC00922 decoys SIRT3 to facilitate the metastasis of colorectal cancer through up-regulation the H3K27 crotonylation of ETS1 promoter

Meijian Liao[1†], Xiaolin Sun[1†], Wendan Zheng[1], Mengdi Wu[1], Yifan Wang[1], Jia Yao[1], Yu Ma[1], Shoucui Gao[1*] and Dongsheng Pei[1*]

Abstract

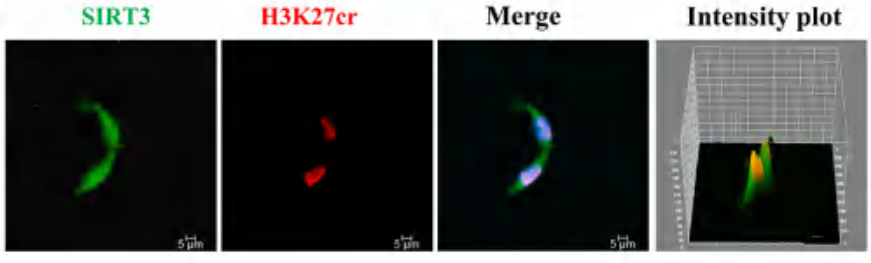
Background Lysine crotonylation (Kcr) is up-regulation in colorectal cancer (CRC) tissues, while its specific contribution remains uncertain. This study aimed to elucidate the role and mechanism of crotonylation on Lys27 of histone H3 (H3K27cr) in facilitating CRC metastasis.

Methods Immunohistochemistry was employed to investigate the correlation between H3K27cr and CRC metastasis. Both in vitro and in vivo assays employing loss function or gain function approaches were conducted to elucidate the role of LINC00922 in promoting CRC metastasis. ScRNA-seq analysis and immunoprecipitation analyses were employed to explore the underlying mechanism by which LINC00922 facilitates CRC metastasis through H3K27cr.

Results Clinically, H3K27cr was upregulated in metastatic CRC tissues and positively correlated with advanced clinical stages. Functionally, knockdown of LINC00922 inhibited migration of CRC cells both in vitro and in vivo. Furthermore, the supplementation of NaCr restored the migration and invasion levels of LINC00922 stable knockdown cells by restoring the H3K27cr level. Mechanistically, LINC00922 promoted invasion and migration through H3K27cr mediated cell adhesion molecules (CAMs) in epithelial cells. Notably, LINC00922 interacted with the protein sirtuin 3 (SIRT3) and obstructed its binding to the promoter region of ETS1, leading to an elevation in the level of H3K27cr in this promoter region and the subsequent activation of ETS1 transcription.

Conclusions Our findings uncovered a novel regulatory function of H3K27cr, regulated by LINC00922, in facilitating CRC metastasis. This discovery contributed to a deeper comprehension of the involvement of histone crotonylation in the metastatic process of CRC.

Keywords Colorectal cancer, Metastasis, LINC00922, H3K27cr, SIRT3



Materials and Methods

The sh-LINC00922 plasmid was constructed and then packaged into **lentivirus** by **GenePharma** (Shanghai, China).

He *et al. Molecular Cancer* (2023) 22:117
https://doi.org/10.1186/s12943-023-01824-9

RESEARCH Open Access

Extracellular vesicle-circEHD2 promotes the progression of renal cell carcinoma by activating cancer-associated fibroblasts

Tao He[1,2†], Qiansheng Zhang[1,2†], Peng Xu[2,3], Wen Tao[1,2], Fuyang Lin[1,2], Renfei Liu[1,2], Mingzhao Li[1,2], Xiaolu Duan[1,2], Chao Cai[1,2], Di Gu[1,2], Guohua Zeng[1,2] and Yongda Liu[1,2*]

Abstract

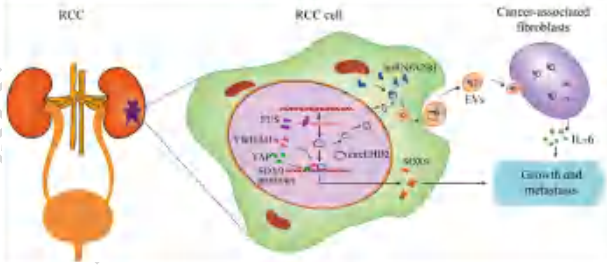
Background The encapsulation of circular RNAs (circRNAs) into extracellular vesicles (EVs) enables their involvement in intercellular communication and exerts an influence on the malignant advancement of various tumors. However, the regulatory role of EVs-circRNA in renal cell carcinoma (RCC) remains elusive.

Methods The in vitro and in vivo functional experiments were implemented to measure the effects of circEHD2 on the phenotype of RCC. The functional role of EVs-circEHD2 on the activation of fibroblasts was assessed by collagen contraction assay, western blotting, and enzyme-linked immunosorbent assay (ELISA). The mechanism was investigated by RNA pull-down assay, RNA immunoprecipitation, chromatin isolation by RNA purification, luciferase assay, and co-immunoprecipitation assay.

Results We demonstrated that circEHD2 was upregulated in RCC tissues and serum EVs of RCC patients with metastasis. Silencing circEHD2 inhibited tumor growth in vitro and in vivo. Mechanistic studies indicated that FUS RNA -binding protein (FUS) accelerated the cyclization of circEHD2, then circEHD2 interacts with tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein eta (YWHAH), which acts as a bridge to recruit circEHD2 and Yes1-associated transcriptional regulator (YAP) to the promoter of SRY-box transcription factor 9 (SOX9); this results in the sustained activation of SOX9. Heterogeneous nuclear ribonucleoprotein A2/B1 (hnRNPA2B1) regulates the package of circEHD2 into EVs, then EVs-circEHD2 transmits to fibroblasts, converting fibroblasts to cancer-associated fibroblasts (CAFs). Activated CAFs promote the metastasis of RCC by secreting pro-inflammatory cytokines such as IL-6. Furthermore, antisense oligonucleotides (ASOs) targeting circEHD2 exhibited a strong inhibition of tumor growth in vivo.

Conclusions The circEHD2/YWHAH/YAP/SOX9 signaling pathway accelerates the growth of RCC. EVs-circEHD2 facilitates the metastasis of RCC by converting fibroblasts to CAFs. Our results suggest that EVs-circEHD2 may be a useful biomarker and therapeutic target for RCC.

Keywords RCC, Extracellular vesicles, circEHD2, Progression, ASO



Molecular Cancer
2023 Jul 22;22:117
Factor: 37.3

Materials and Methods

A **lentiviral vector** carrying the full length circEHD2 was designed to overexpress circEHD2, which was also syn-thesized by **GenePharma** .

OSRC-2 and 786-O cells were retrovirally infected with the lentiviruses combined with 1 μl **Polybrene** (5 μg/μl) (**GenePharma**, Suzhou, China).

The **circEHD2 probe** was designed to target the back-spliced site of circEHD2 by **GenePharma** (Suzhou, China).

Xi et al. Molecular Cancer (2022) 21:145
https://doi.org/10.1186/s12943-022-01615-8

Molecular Cancer

RESEARCH Open Access

CircBCAR3 accelerates esophageal cancer tumorigenesis and metastasis via sponging miR-27a-3p

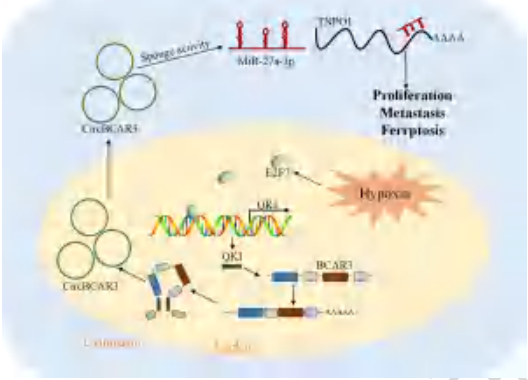
Yong Xi[1*†], Yaxing Shen[2†], Donglei Wu[3], Jingtao Zhang[4], Chengbin Lin[1], Lijie Wang[1], Chaoqun Yu[1], Bentong Yu[4*] and Weiyu Shen[1*]

Abstract

Rationale: Circular RNAs (circRNAs) have been demonstrated to contribute to esophageal cancer progression. CircB-CAR3 (hsa_circ_0007624) is predicted to be differentially expressed in esophageal cancer by bioinformatics analysis. We investigated the oncogenic roles and biogenesis of circBCAR3 in esophageal carcinogenesis.

Methods: Functions of circBCAR3 on cancer cell proliferation, migration, invasion, and ferroptosis were explored using the loss-of-function assays. A xenograft mouse model was used to reveal effects of circBCAR3 on xenograft growth and lung metastasis. The upstream and downstream mechanisms of circBCAR3 were investigated by bioinfor-matics analysis and confirmed by RNA immunoprecipitation and luciferase reporter assays. The dysregulated genes in hypoxia-induced esophageal cancer cells were identified using RNA-seq.

Results: CircBCAR3 was highly expressed in esophageal cancer tissues and cells and its expression was increased by hypoxia in vitro. Silencing of circBCAR3 repressed the proliferation, migration, invasion, and ferroptosis of esopha-geal cancer cells in vitro, as well as inhibited the growth and metastasis of esophageal xenograft in mice in vivo. The hypoxia-induced promotive effects on esophageal cancer cell migration and ferroptosis were rescued by circBCAR3 knockdown. Mechanistically, circBCAR3 can interact with miR-27a-3p by the competitive endogenous RNA mecha-nism to upregulate transportin-1 (TNPO1). Furthermore, our investigation indicated that splicing factor quaking (QKI) is a positive regulator of circBCAR3 via targeting the introns flanking the hsa_circ_0007624-formed exons in BCAR3 pre-mRNA. Hypoxia upregulates E2F7 to transcriptionally activate QKI.



Molecular Cancer
2022 Dec;21(1):1-20
Impact Factor: 37.3

Materials and Methods

CircBCAR3 **overexpressing plasmid** (pcDNA circB-CAR3), **silencing plasmid** (sh-circBCAR3), and their **negative controls** (empty pcDNA and sh-NC) were com-mercially provided by **GenePharma** (Shanghai, China).

The EC109 cells stably expressing sh-circBCAR3 or sh-nc were establishedby infection with corresponding **lentivirus vectors** (backbone: pGLVU6/Puro; #C06002; **GenePharma**).

Shen et al. Molecular Cancer (2021) 20:51
https://doi.org/10.1186/s12943-021-01333-7

Molecular Cancer

RESEARCH ARTICLE Open Access

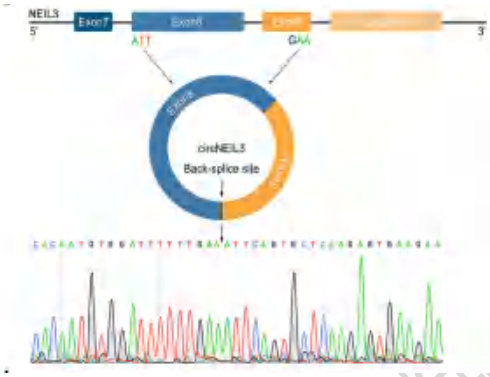
CircNEIL3 regulatory loop promotes pancreatic ductal adenocarcinoma progression via miRNA sponging and A-to-I RNA-editing*

Abstract

Background: A growing number of studies have focused on investigating circRNAs as crucial regulators in the progression of multiple cancer types. Nevertheless, the biological effects and underlying mechanisms of circRNAs in pancreatic ductal adenocarcinoma (PDAC) remain unclear.

Methods: Differentially expressed circRNAs between cancerous tissue and adjacent normal tissues were identified by RNA sequencing in PDAC. Subsequently, in vitro and in vivo functional experiments were performed to investigate the functional roles of circNEIL3 in PDAC tumour growth and metastasis. Furthermore, RNA pull-down, dual-luciferase reporter assays, RNA immunoprecipitation (RIP) assays, fluorescent in situ hybridization (FISH) and Sanger sequencing assays were performed to examine the circular interaction among circNEIL3, miR-432-5p and adenosine deaminases acting on RNA 1 (ADAR1).

Results: CircNEIL3 was upregulated in PDAC and promoted the progression of PDAC cells both in vitro and in vivo. Mechanistically, circNEIL3 was shown to regulate the expression of ADAR1 by sponging miR-432-5p to induce RNA editing of glioma-associated oncogene 1 (GLI1), ultimately influencing cell cycle progression and promoting epithelial-to-mesenchymal transition (EMT) in PDAC cells. Moreover, we discovered that the circNEIL3/miR-432-5p/ADAR1 axis was correlated with the PDAC clinical stage and overall survival of PDAC patients, while ADAR1 may reduce the biogenesis of circNEIL3.



Molecular Cancer
2021 Dec;20(1):1-22
Impact Factor: 37.3

Materials and Methods

CircNEIL3 **siRNA sequences** were syn-thesized by **GenePharma** (Shanghai, China), and a scrambled siRNA was synthesized as a negative con-trol.

The **miR-432-5p mimics and inhibitor**, **ADAR1-overexpressing lentivirus and ADAR1 shRNAs** were synthesized by **GenePharma** (Shanghai, China) and transfected as described above.

Wild-type and mutant (mut-circNEIL3 or mut-ADAR1) **cirCNEIL3 and ADAR1** fragments were constructed and inserted downstream of the luciferase reporter gene in the **reporter plasmid pRL-SV40** (**GenePharma**, Shanghai, China).

Xie et al. Molecular Cancer (2020) 19:112
https://doi.org/10.1186/s12943-020-01208-3

Molecular Cancer

RESEARCH Open Access

Exosomal circSHKBP1 promotes gastric cancer progression via regulating the miR-582-3p/HUR/VEGF axis and suppressing HSP90 degradation

Mengyan Xie[1†], Tao Yu[1†], Xinming Jing[1†], Ling Ma[1], Yu Fan[4], Fengming Yang[1], Pei Ma[1], Huning Jiang[1], Xi Wu[1], Yongqian Shu[1,2,3*] and Tongpeng Xu[1]

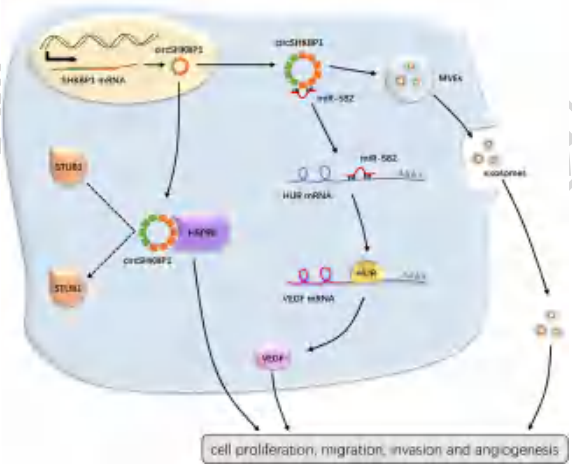
Abstract

Background: Circular RNAs (circRNAs) play important regulatory roles in the development of various cancers. However, biological functions and the underlying molecular mechanism of circRNAs in gastric cancer (GC) remain obscure.

Methods: Differentially expressed circRNAs were identified by RNA sequencing. The biological functions of circSHKBP1 in GC were investigated by a series of in vitro and in vivo experiments. The expression of circSHKBP1 was evaluated using quantitative real-time PCR and RNA in situ hybridization, and the molecular mechanism of circSHKBP1 was demonstrated by western blot, RNA pulldown, RNA immunoprecipitation, luciferase assays and rescue experiments. Lastly, mouse xenograft and bioluminescence imaging were used to exam the clinical relevance of circSHKBP1 in vivo.

Results: Increased expression of circSHKBP1(hsa_circ_0000936) was revealed in GC tissues and serum and was related to advanced TNM stage and poor survival. The level of exosomal circSHKBP1 significantly decreased after gastrectomy. Overexpression of circSHKBP1 promoted GC cell proliferation, migration, invasion and angiogenesis in vitro and in vivo, while suppression of circSHKBP1 plays the opposite role. Exosomes with upregulated circSHKBP1 promoted cocultured cells growth. Mechanistically, circSHKBP1 sponged miR-582-3p to increase HUR expression, enhancing VEGF mRNA stability. Moreover, circSHKBP1 directly bound to HSP90 and obstructed the interaction of STUB1 with HSP90, inhibiting the ubiquitination of HSP90, resulting in accelerated GC development in vitro and in vivo.

Molecular Cancer
2020 Jun 29; 19:112
Impact Factor: 37.3



Materials and Methods

The lentivirus vector (pGLV3/GFP/Puro) containing shRNAs targeting circSHKBP1 and vector (pGLV5/GFP/Puro) overerexpressing circSHKBP1 were generated by GenePharma (Shanghai, China).

Zhang et al. Molecular Cancer (2020) 19:101
https://doi.org/10.1186/s12943-020-01221-6

Molecular Cancer

RESEARCH Open Access

Circular RNA circSATB2 promotes progression of non-small cell lung cancer cells

Nan Zhang[1,2†], Aruo Nan[1,2†], Lijian Chen[2], Xin Li[2], Yangyang Jia[2], Miaoyun Qiu[2], Xin Dai[2], Hanyu Zhou[2], Jialu Zhu[2], Han Zhang[2] and Yiguo Jiang[1,2*]

Abstract

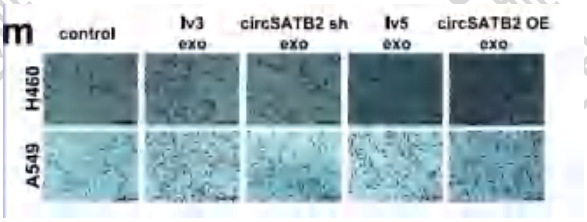
Background:Lung cancer has high morbidity and mortality worldwide with non-small cell lung cancer (NSCLC) accounting for 85% of the cases. Therapies for lung cancer have relatively poor outcomes and further improvements are required. Circular RNAs have been reported to participate in the occurrence and progression of cancer. Information on the functions and mechanism of circRNAs in lung cancer is limited and needs more exploration.

Methods: We detected expression of genes and proteins by qPCR and western blot. Function of circSATB2 was investigated using RNA interference and overexpression assays. Location of circSATB2 was assessed by fluorescence in situ hybridization (FISH). Interaction of circSATB2, miR-326 and FSCN1 was confirmed by dual-luciferase reporter assay.

Results: Data from the investigation showed that circSATB2 was highly expressed in NSCLC cells and tissues. circSATB2 positively regulated fascin homolog 1, actin-bundling protein 1 (FSCN1) expression via miR-326 in lung cancer cells. Furthermore, circSATB2 can be transferred by exosomes and promote the proliferation, migration and invasion of NSCLC cells, as well as induce abnormal proliferation in normal human bronchial epithelial cells. Also, circSATB2 was highly expressed in serumal exosomes from lung cancer patients with high sensitivity and specificity for clinical detection and was related to lung cancer metastasis.

Conclusions:circSATB2 participated in the progression of NSCLC and was differentially expressed in lung cancer tissue and serumal exosomes. circSATB2 may be potential biomarker for the diagnosis of NSCLC.

Keywords: Lung cancer, Progression, circRNA, Exosome, miRNA



Molecular Cancer
2020 Jun 3 ; 19: 101
Impact Factor: 37.3

Materials and Methods

Stable lentivirus-3 circSATB2-shRNA and **lentivirus-5 circSATB2--OE vectors** were constructed and the lentiviruses were packaged and purified by Shanghai **GenePharma** Co., Ltd. (Suzhou, China).

Ding et al. Molecular Cancer (2019) 18:45
https://doi.org/10.1186/s12943-019-1006-2

Molecular Cancer

RESEARCH Open Access

Circular RNA circ-DONSON facilitates gastric cancer growth and invasion via NURF complex dependent activation of transcription factor SOX4

Lixian Ding[1,2†], Yuying Zhao[3†], Shuwei Dang[1,2†], Yue Wang[4], Xinglong Li[1,2], Xiaotong Yu[1,2], Zhongsheng Li[1,2], Jiufeng Wei[1,2], Ming Liu[1,2] and Guodong Li[1,2*]

Abstract

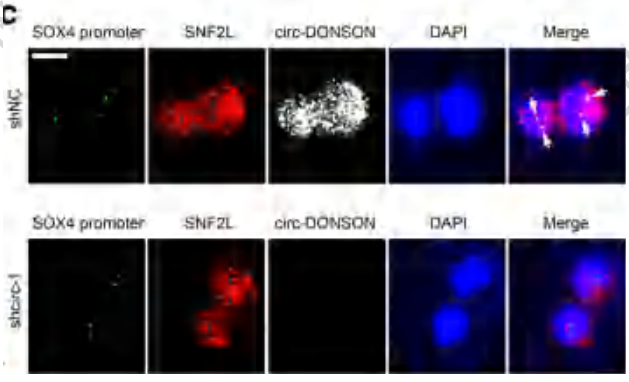
Background: Circular RNAs (circRNAs) are a novel type of noncoding RNAs and play important roles in tumorigenesis, including gastric cancer (GC). However, the functions of most circRNAs remain poorly understood. In our study, we aimed to investigate the functions of a new circRNA circ-DONSON in GC progression.

Methods: The expression of circ-DONSON in gastric cancer tissues and adjacent normal tissues was analyzed by bioinformatics method, qRT-PCR, Northern blotting and in situ hybridization (ISH). The effects of circ-DONSON on GC cell proliferation, apoptosis, migration and invasion were measured by using CCK8, colony formation, EdU, immunofluorescence (IF), FACS and Transwell assays. qRT-PCR and Western blotting were utilized to validate how circ-DONSON regulates SOX4 expression. ChIP, DNA fluorescence in situ hybridization (DNA-FISH) and DNA accessibility assays were used to investigate how circ-DONSON regulates SOX4 transcription. The interaction between circ-DONSON and NURF complex was evaluated by mass spectrum, RNA immunoprecipitation (RIP), pulldown and EMSA assays. Xenograft mouse model was used to analyze the effect of circ-DONSON on GC growth in vivo.

Molecular Cancer
2019 Mar 28; 18:45
Impact Factor: 37.3

Materials and Methods

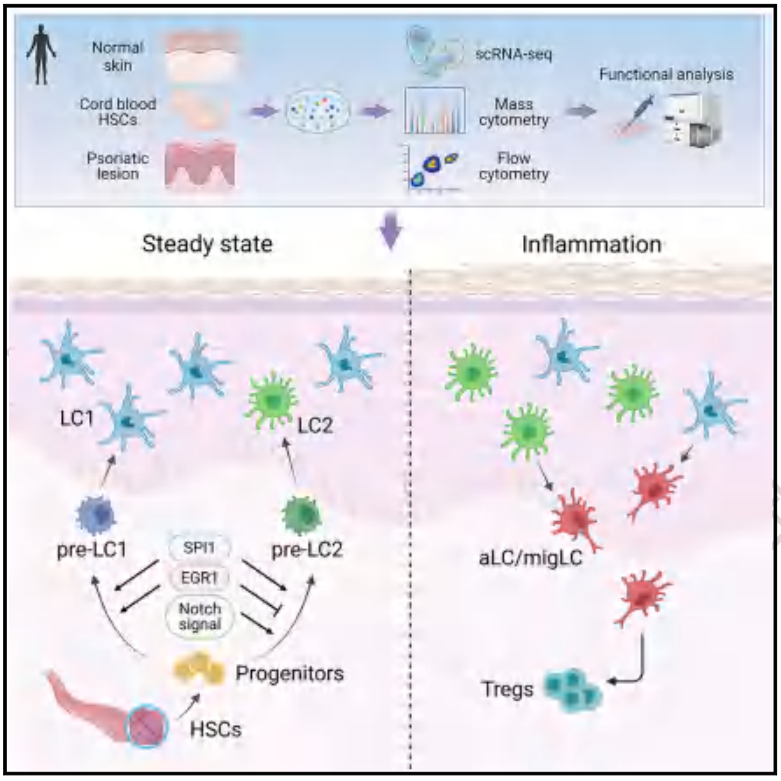
The **lentivirus-containing short hairpin RNA (shRNA)** targeting circ-DONSON, BPTF, SNF2L or RBBP4 was purchased from **GenePharma** (Shanghai, China).



Immunity

Distinct human Langerhans cell subsets orchestrate reciprocal functions and require different developmental regulation

Graphical abstract



Authors

Xiaochun Liu, Ronghui Zhu, Yang Luo, ..., Xu Yao, Xiao Li, Wei Li

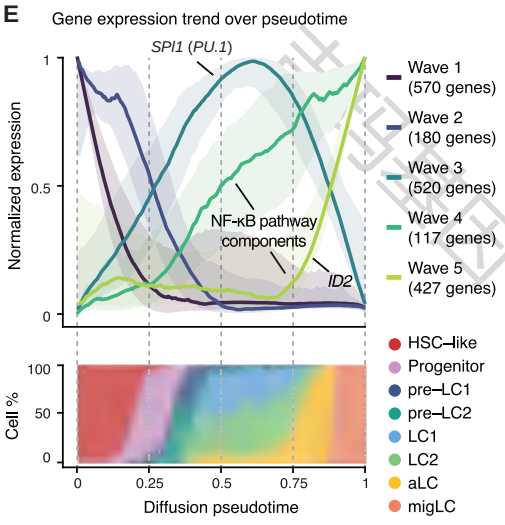
Correspondence

dryao_xu@126.com (X.Y.), xli@texasheart.org (X.L.), liweiderma@fudan.edu.cn (W.L.)

In brief

The heterogeneity of Langerhans cells has long been considered. Liu et al. reveal four subpopulations of primary and HSC-derived Langerhans cells in human, which are phenotypically and functionally distinct and require different developmental regulation.

Immunity
2021 Oct 12;54(10):2305-2320.e11
Impact Factor: 32.4



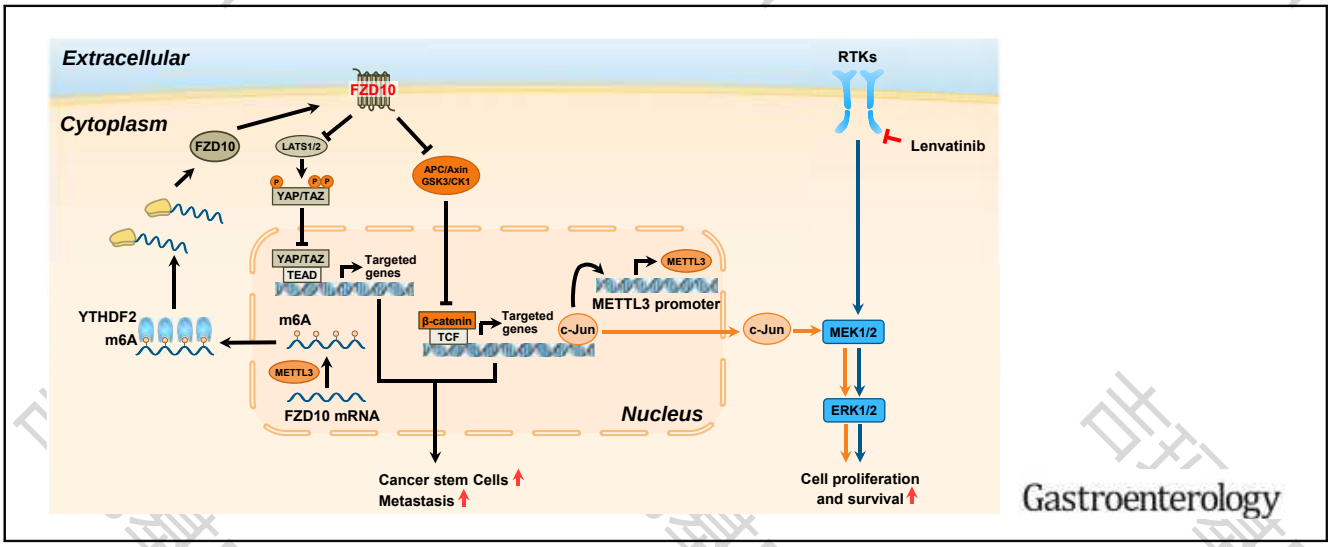
Materials and Methods

Overexpression or shRNA lentivirus as well as **negative control lentivirus** were purchased from **GenePharma** (China).

N6-Methyladenosine–Mediated Up-Regulation of FZD10 Regulates Liver Cancer Stem Cells' Properties and Lenvatinib Resistance Through WNT/b-Catenin and Hippo Signaling Pathways

Jinghan Wang,[1] Hongming Yu,[2] Wei Dong,[3] Cheng Zhang,[4] Mingtai Hu,[1] Wencong Ma,[1] Xiaoqing Jiang,[2] Hengyu Li,[5] Pinghua Yang,[2] and Daimin Xiang[1,6]

Temperature-dependent sex determination is a notablemodel of phenotypic plasticity. Inmany reptiles, including the red-eared slider turtle Trachemys scripta elegans (T. scripta), the individual's sex is determined by the ambient temperature during egg incubation. In this study, we show that the histone H3 lysine 27 (H3K27) demethylase KDM6B exhibits temperaturedependent sexually dimorphic expression in early T. scripta embryos before the gonad is distinct. Knockdown of Kdm6b at 26°C (a temperature atwhich all offspring develop into males) triggers male-to-female sex reversal in >80%of surviving embryos. KDM6B directly promotes the transcription of the male sex-determinin gene Dmrt1 by eliminating the trimethylation of H3K27 near its promoter. Additionally, overexpression of Dmrt1 is sufficient to rescue the sex reversal induced by disruption of Kdm6b.This study establishes causality and a direct genetic link between epigenetic mechanisms and temperature-dependent sex determination in a turtle species.



GASTROENTEROLOGY
2023 Jan;164:990–1005
Factor: 29.4

Materials and Methods

FZD10 knockdown, **β-catenin knockdown**, **YAP1 knockdown**, **c-Jun overexpression**, and **control lentiviruses** were purchased from **GenePharma**.

Please cite this article in press as: Zhang et al., Methionine secreted by tumor-associated pericytes supports cancer stem cells in clear cell renal carcinoma, Cell Metabolism (2024), https://doi.org/10.1016/j.cmet.2024.01.018

Cell Metabolism

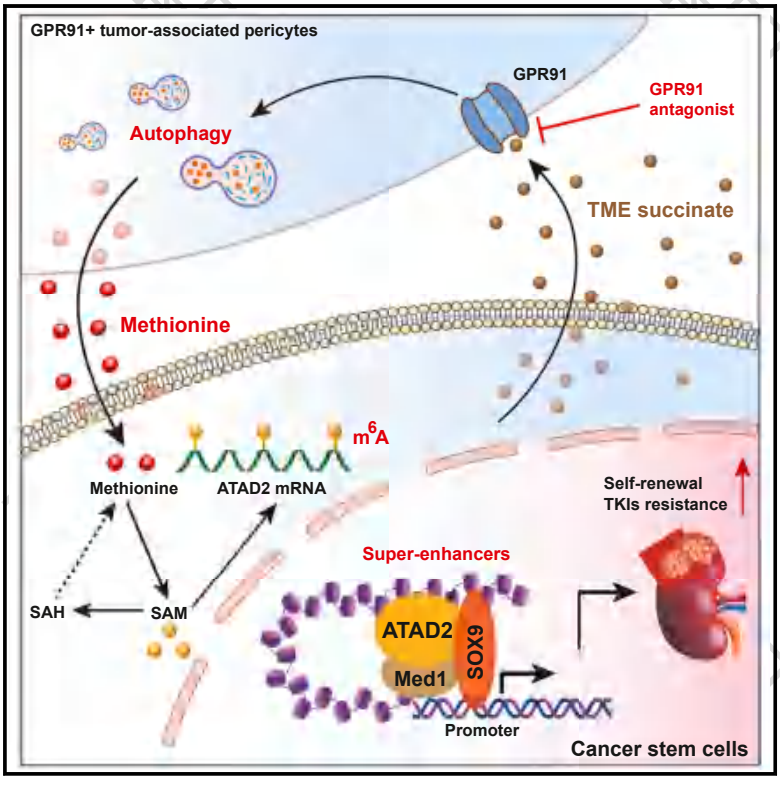
CellPress

Article

Methionine secreted by tumor-associated pericytes supports cancer stem cells in clear cell renal carcinoma

SUMMARY

Here, we identify a subset of vascular pericytes, defined by expression of platelet-derived growth factor receptor beta (PDGFR-b) and G-protein-coupled receptor 91 (GPR91), that promote tumorigenesis and tyrosine kinase inhibitors (TKIs) resistance by functioning as the primary methionine source for cancer stem cells (CSCs) in clear cell renal cell carcinoma (ccRCC). Tumor-cell-derived succinate binds to GPR91 on pericyte to activate autophagy for methionine production. CSCs use methionine to create stabilizing N6-methyladeno-sine in ATPase-family-AAA-domain-containing 2 (ATAD2) mRNA, and the resulting ATAD2 protein complexes with SRY-box transcription factor 9 to assemble super enhancers and thereby dictate its target genes that feature prominently in CSCs. Targeting PDGFR-b+GPR91+ pericytes with specific GRP91 antagonists reduce intratumoral methionine level, eliminate CSCs, and enhance TKIs sensitivity. These results unraveled the mechanisms by which PDGFR-b+GPR91+ pericytes provide supportive niche for CSCs and could be used to develop targets for treating ccRCC.



Cell Metabolism
2024 Apr 2;36(4):778-792.e10
Impact Factor: 29

Materials and Methods

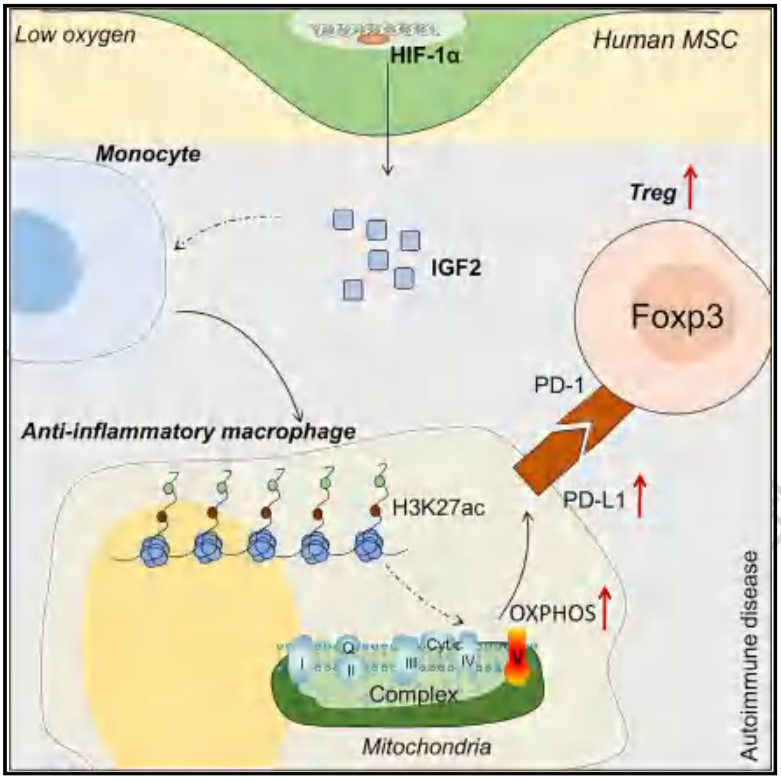
LV3 lentiviral vector	Genepharma,Shanghai	N/A

Article

Cell Metabolism

IGF-2 Preprograms Maturing Macrophages to Acquire Oxidative Phosphorylation-Dependent Anti-inflammatory Properties

Graphical Abstract



Authors

Liming Du, Liangyu Lin, Qing Li, ..., Changshun Shao, Ying Wang, Yufang Shi

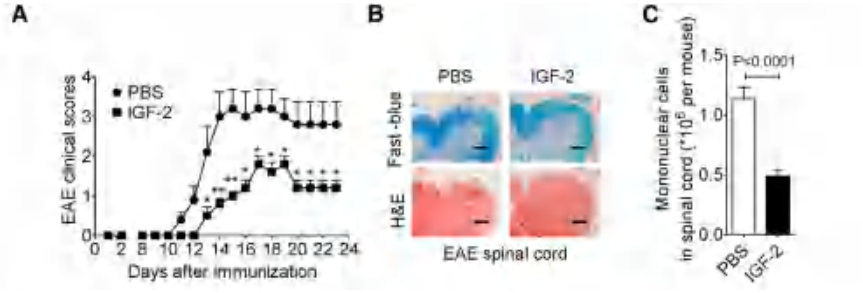
Correspondence

yingwang@sibs.ac.cn (Y.W.), yfshi@suda.edu.cn (Y.S.)

In Brief

Du and Lin et al. show that insulin-like growth factor 2 (IGF-2) modulates the innate immune memory of macrophages during their maturation and enables macrophages to have persistent oxidative phosphorylation (OXPHOS). Such metabolic commitment allows macrophages to highly express PD-L1 even upon pro-inflammation stimulation and determines their anti-inflammatory phenotype.

Cell Metabolism
2019 Jun 4; 29, 1363–1375
Impact Factor: 29



Materials

REAGENT or RESOURCE	SOURCE	IDENTIFIER
PGLV3/H1/GFP/Puro	Gene Pharma	N/A

OPEN ACCESS

CLINICAL SCIENCE

TGFβ attenuates cartilage extracellular matrix degradation via enhancing FBXO6-mediated MMP14 ubiquitination

Gangliang Wang [1,2], Shuai Chen,[1,2] Ziang Xie,[1,2] Shuying Shen,[1,2] Wenbin Xu,[1,2] Wenxiang Chen,[1,2] Xiang Li,[1,2] Yizheng Wu,[1,2] Liangping Li,[1,2] Bin Liu,[3] Xianjun Ding,[1,2] An Qin,[4] Shunwu Fan[1,2]

Abstract

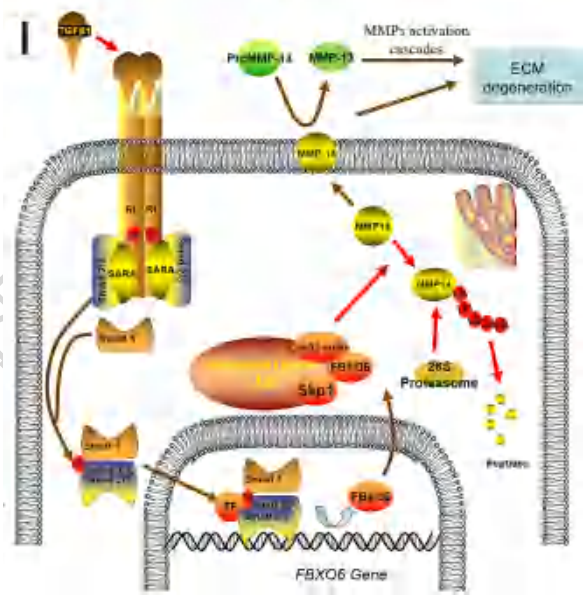
Objectives:FBXO6, a component of the ubiquitin E3 ligases, has been shown to bind high mannose N-linked glycoproteins and act as ubiquitin ligase subunits. Most proteins in the secretory pathway, such as matrix metalloproteinases, are modified with N-glycans and play important roles in the development of osteoarthritis (OA). However, whether FBXO6 exerts regulatory effects on the pathogenesis of OA remains undefined.

Methods: The expression of FBXO6 was examined in the cartilage of human and multiple mouse OA models. The role of FBXO6 in cartilage degeneration was analysed with global FBXO6 -/- mice, transgenic Col2a1-CreERT2;FBXO6f/f mice. The FBXO6 interacting partner MMP14 and its regulatory transcriptional factor SMAD2/3 were identified and validated in different pathological models as well as SMAD2 -/- mice.

Results: The expression of FBXO6 decreased in the cartilage from human OA samples, anterior cruciate ligament transaction (ACLT) -induced OA samples, spontaneous OA STR/ort samples and aged mice samples. Global knockout or conditional knockout of FBXO6 in cartilage promoted experimental OA process. The molecular mechanism study revealed that FBXO6 decreased MMP14 by ubiquitination and degradation, leading to inhibited proteolytic activation of MMP13. Interestingly, FBXO6 expression is regulated by transforming growth factor β (TGFβ)-SMAD2/3 signalling pathway. Therefore, the overexpression of FBXO6 protected mice from post-injury OA development.

Conclusions:TGFβ-SMAD2/3 signalling pathway suppressed MMP13 activation by upregulating of FBXO6 transcription and consequently promoting MMP14 proteasomal degradation. Inducement of FBXO6 expression in OA cartilage might provide a promising OA therapeutic strategy.

Keywords: osteoarthritis, chondrocytes, cytokines



CLINICAL SCIENCE
2020 Oct 1; 183: 76-93
Impact Factor: 27.4

Materials and Methods

10μl of concentrated lentiviral particles expressing mouse **FBXO6(LV-FBXO6)** or **negative control LV-Con** (**GenePharma**, Shanghai, China) .

ORIGINAL ARTICLE

METTL3-mediated m^{6}A modification of HDGF mRNA promotes gastric cancer progression and has prognostic significance

Qiang Wang,[1] Chen Chen,[2] Qingqing Ding,[3] Yan Zhao,[4] Zhangding Wang,[4] Junjie Chen,[2] Zerun Jiang,[2] Yan Zhang,[1] Guifang Xu,[4] Jingjing Zhang,[5] Jianwei Zhou,[2] Beicheng Sun,[1] Xiaoping Zou,[4] Shouyu Wang [1,2,6,7]

ABSTRACT

Objective N6-methyladenosine (m6A) RNA methylation and its associated methyltransferase METTL3 are involved in tumour initiation and progression via the regulation of RNA function. This study explored the biological function and clinical significance of METTL3 in gastric cancer (GC).

Design The prognostic value of METTL3 expression was evaluated using tissue microarray and immunohistochemical staining analyses in a human GC cohort. The biological role and mechanism of METTL3 in GC tumour growth and liver metastasis were determined in vitro and in vivo.

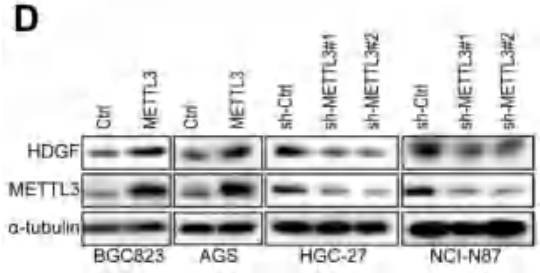
Results The level of m6A RNA was significantly increased in GC, and METTL3 was the main regulator involved in the abundant m6A RNA modification. METTL3 expression was significantly elevated in GC tissues and associated with poor prognosis. Multivariate Cox regression analysis revealed that METTL3 expression was an independent prognostic factor and effective predictor in human patients with GC. Moreover, METTL3 overexpression promoted GC proliferation and liver metastasis in vitro and in vivo. Mechanistically, P300-mediated H3K27 acetylation activation in the promoter of METTL3 induced METTL3 transcription, which stimulated m6A modification of HDGF mRNA, and the m6A reader IGF2BP3 then directly recognised and bound to the m6A site on HDGF mRNA and enhanced HDGF mRNA stability. Secreted HDGF promoted tumour angiogenesis, while nuclear HDGF activated GLUT4 and ENO2 expression, followed by an increase in glycolysis in GC cells, which was correlated with subsequent tumour growth and liver metastasis.

Conclusions Elevated METTL3 expression promotes tumour angiogenesis and glycolysis in GC, indicating that METTL3 expression is a potential prognostic biomarker and therapeutic target for human GC.

Gut
2020 Jul;69(7):1193-1205
Impact Factor: 24.5

Materials and Methods

METTL3, HDGF, and IGF2BP3 shRNAs designed based on the siRNA sequences and METTL3 cDNA were cloned into the **pGLV3/H1/GFP** and GV358 **lentiviral vectors** (**GenePharma**, Shanghai, China) or pBabe retroviral vector, respectively.



www.nature.com/cmi

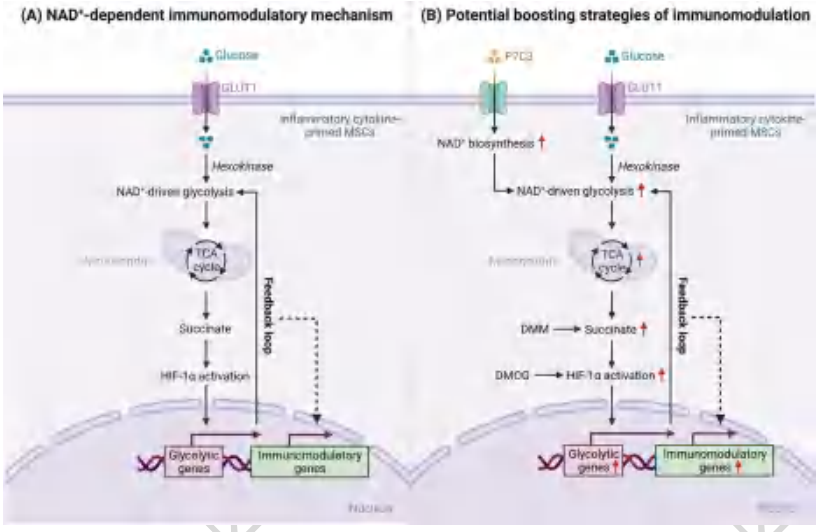
ARTICLE

Check for updates

NAD^+ salvage governs the immunosuppressive capacity of mesenchymal stem cells

Jiankai Fang[1], Pengbo Hou[1,2], Shisong Liu[1], Muqiu Zuo[1], Zhanhong Liu[1,2], Wangwang Chen[3], Yuyi Han[1,2], Yanan Li[1,2], Tingting Wang[1], Chao Feng[1,2], Peishan Li[1], Changshun Shao[1]✉ and Yufang Shi[1,4]✉

Mesenchymal stem/stromal cells (MSCs) possess robust immunoregulatory functions and are promising therapeutics for inflammatory disorders. This capacity is not innate but is activated or 'licensed' by inflammatory cytokines. The licensing mechanism remains unclear. Here, we examined whether inflammatory cytokines metabolically reprogrammed MSCs to confer this immunoregulatory capacity. In response to stimulation by inflammatory cytokines, MSCs exhibited a dramatic increase in the consumption of glucose, which was accompanied by an enhanced use of nicotinamide adenine dinucleotide (NAD^+) and increased expression of nicotinamide phosphoribosyltransferase (NAMPT), a central enzyme in the salvage pathway for NAD^+ production. When NAD^+ synthesis was blocked by inhibiting or depleting NAMPT, the immunosuppressive function of MSCs induced by inflammatory cytokines was greatly attenuated. Consequently, when NAD^+ metabolism in MSCs was perturbed, their therapeutic benefit was decreased in mice suffering from inflammatory bowel disease and acute liver injury. Further analysis revealed that NAMPT-driven production of NAD^+ was critical for the inflammatory cytokine-induced increase in glycolysis in MSCs. Furthermore, the increase in glycolysis led to succinate accumulation in the tricarboxylic acid cycle, which led to hypoxia-inducible factor 1α (HIF-1α) stabilization and subsequently increased the transcription of key glycolytic genes, thereby persistently maintaining glycolytic flux. This study demonstrated that unlike its proinflammatory role in immune cells, NAD^+ metabolism governs the anti-inflammatory function of MSCs during inflammation.



Cellular & Molecular Immunology
2023 Aug 14;20(10):1171-1185
Impact Factor: 24.1

Materials and Methods

To achieve NAMPT knockdown, MSCs were transfected with NAMPT-targeting short hairpin RNA (shRNA) carried by **a lentiviral vector** (PGLV3/H1/GFP/Puro, **GenePharma**, Shanghai, China) and incubated with poly-brene (5 μg/mL, GenePharma) for 12 h.

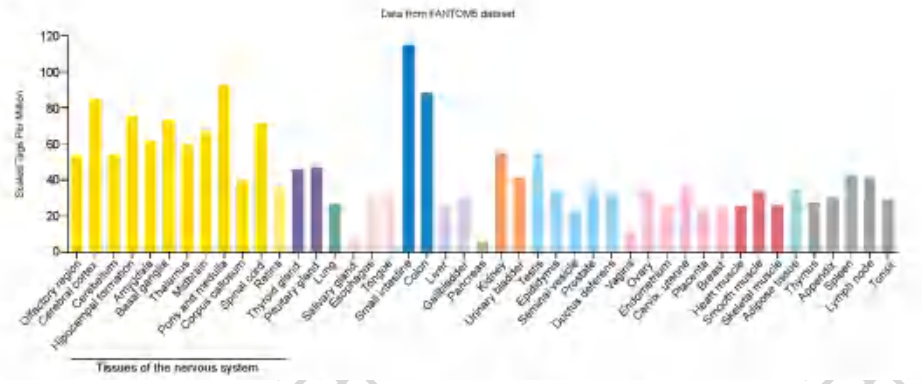
ARTICLES
https://doi.org/10.1038/s41556-021-00762-2
nature cell biology

Check for updates

Eosinophil extracellular traps drive asthma progression through neuro-immune signals

Yiwen Lu[1,2,9], Yijiao Huang[1,3,9], Jiang Li[1,2,9], Jingying Huang[1,2,9], Lizhi Zhang[1,3,9], Jingwei Feng[1,2], Jiaqian Li[1,2], Qidong Xia[1,2], Qiyi Zhao[4,5,6], Linjie Huang[1,3,7], Shanping Jiang[1,3,7] ✉ and Shicheng Su[1,2,4,8] ✉

Eosinophilic inflammation is a feature of allergic asthma. Despite mounting evidence showing that chromatin filaments released from neutrophils mediate various diseases, the understanding of extracellular DNA from eosinophils is limited. Here we show that eosinophil extracellular traps (EETs) in bronchoalveolar lavage fluid are associated with the severity of asthma in patients. Functionally, we find that EETs augment goblet-cell hyperplasia, mucus production, infiltration of inflammatory cells and expressions of type 2 cytokines in experimental non-infection-related asthma using both pharmaceutical and genetic approaches. Multiple clinically relevant allergens trigger EET formation at least partially via thymic stromal lymphopoietin in vivo. Mechanically, EETs activate pulmonary neuroendocrine cells via the CCDC25–ILK–PKCα–CRTC1 pathway, which is potentiated by eosinophil peroxidase. Subsequently, the pulmonary neuroendocrine cells amplify allergic immune responses via neuropeptides and neurotransmitters. Therapeutically, inhibition of CCDC25 alleviates allergic inflammation. Together, our findings demonstrate a previously unknown role of EETs in integrating immunological and neurological cues to drive asthma progression.



Nature Cell Biology
2021 Oct;23(10):1060-1072
Impact Factor: 21.3

Materials and Methods

CCDC25 was knocked out of H146 cells using the CRISPR–Cas9 system with the **Cas9 lentivirus and gRNA lentivirus** (**GenePharma**)
Lentiviral vector LV3-pGLV-H1-GFP/Puro (**GenePharma**) was used for knockdown experiments.

nature communications

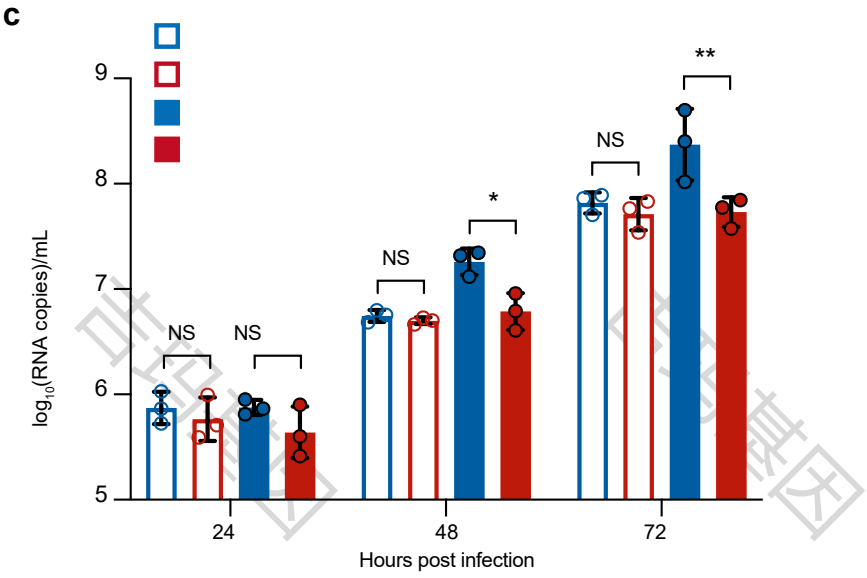
Article

https://doi.org/10.1038/s41467-023-36838-w

Zika virus RNA structure controls its unique neurotropism by bipartite binding to Musashi-1

Xiang Chen[1,6], Yan Wang[2,6], Zhonghe Xu[2,6], Meng-Li Cheng[1], Qing-Qing Ma[1], Rui-Ting Li[1], Zheng-Jian Wang[1], Hui Zhao[1], Xiaobing Zuo[3], Xiao-Feng Li[1], Xianyang Fang[2,4] ✉ & Cheng-Feng Qin[1,5] ✉

Human RNA binding protein Musashi-1 (MSI1) plays a critical role in neural progenitor cells (NPCs) by binding to various host RNA transcripts. The canonical MSI1 binding site (MBS), A/GU$_{(1-3)}$AG single-strand motif, is present in many RNA virus genomes, but only Zika virus (ZIKV) genome has been demonstrated to bind MSI1. Herein, we identified the AUAG motif and the AGAA tetraloop in the Xrn1-resistant RNA 2 (xrRNA2) as the canonical and non-canonical MBS, respectively, and both are crucial for ZIKV neurotropism. More importantly, the unique AGNN-type tetraloop is evolutionally conserved, and distinguishes ZIKV from other known viruses with putative MBSs. Integrated structural analysis showed that MSI1 binds to the AUAG motif and AGAA tet-raloop of ZIKV in a bipartite fashion. Thus, our results not only identified an unusual viral RNA structure responsible for MSI recognition, but also revealed a role for the highly structured xrRNA in controlling viral neurotropism.



Nature Communications
2023 Feb 28;14:1134
Impact Factor:16.6

Materials and Methods

For the BHK-21-Msi1 cells stably expressing MSI1, the MSI1 encoding sequence (NM_002442.4) was constructed into **lentiviral vector LV-6**, containing a puromycin resistance gene by **Genepharma**.

nature communications

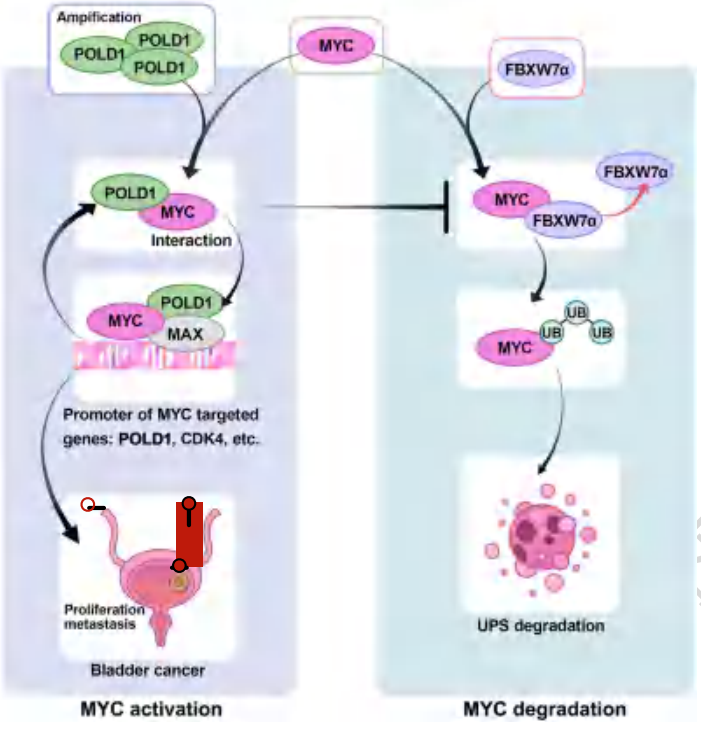
Article

https://doi.org/10.1038/s41467-023-38160-x

DNA polymerase POLD1 promotes proliferation and metastasis of bladder cancer by stabilizing MYC

Yejinpeng Wang[1,9], Lingao Ju [2,3,4,9], Gang Wang[1,2,3], Kaiyu Qian [1,2,3], Wan Jin[5], Mingxing Li[1], Jingtian Yu[1], Yiliang Shi[1], Yongzhi Wang[1], Yi Zhang [5,6] ✉, Yu Xiao [1,2,3,4] ✉ & Xinghuan Wang [1,4,7,8] ✉

To date, most studies on the DNA polymerase, POLD1, have focused on the effect of POLD1 inactivation mutations in tumors. However, the implications of high POLD1 expression in tumorigenesis remains elusive. Here, we determine that POLD1 has a pro-carcinogenic role in bladder cancer (BLCA) and is asso-ciated to the malignancy and prognosis of BLCA. Our studies demonstrate that POLD1 promotes the proliferation and metastasis of BLCA via MYC. Mechan-istically, POLD1 stabilizes MYC in a manner independent of its' DNA poly-merase activity. Instead, POLD1 attenuates FBXW7-mediated ubiquitination degradation of MYC by directly binding to the MYC homology box 1 domain competitively with FBXW7. Moreover, we find that POLD1 forms a complex with MYC to promote the transcriptional activity of MYC. In turn, MYC increases expression of POLD1, forming a POLD1-MYC positive feedback loop to enhance the pro-carcinogenic effect of POLD1-MYC on BLCA. Overall, our study identifies POLD1 as a promotor of BCLA via a MYC driven mechanism and suggest its potential as biomarker for BLCA.



Nature Communications
2023 Apr 27;14:2421
Impact Factor:16.6

Materials and Methods

T24, 5637 or UM-UC-3 cells were transfected with **lentivirus** purchased from **GenePharma**. All **siRNAs** used in this study were purchased from **GenePharma** (Shanghai, China).

Received: 27 January 2022 | Revised: 26 June 2022 | Accepted: 5 August 2022

DOI: 10.1002/cac2.12349

ORIGINAL ARTICLE

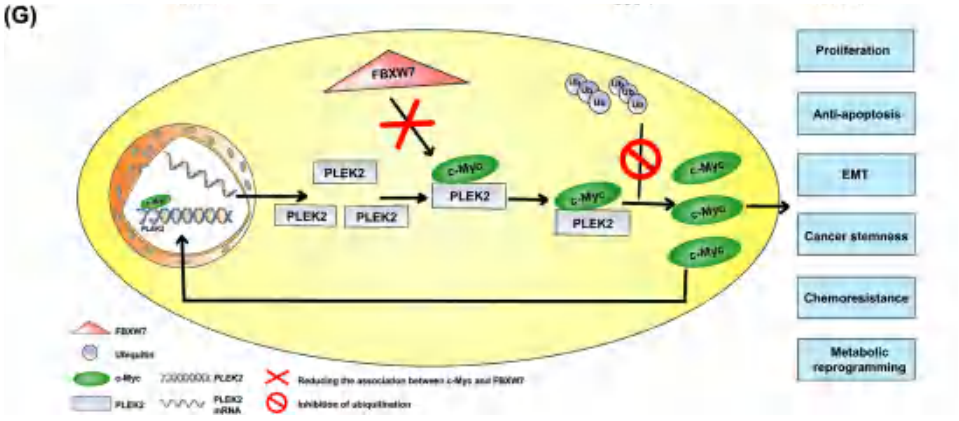
PLEK2 promotes cancer stemness and tumorigenesis of head and neck squamous cell carcinoma via the c-Myc-mediated positive feedback loop

Xinyuan Zhao[1] | Dalong Shu[2] | Wenjuan Sun[3] | Shanshan Si[4] | Wei Ran[2] | Bing Guo[2,5] | Li Cui[6,7]

Abstract

Background: Head and neck squamous cell carcinoma (HNSCC) is one of the most frequent malignancies worldwide and is characterized by unfavorable prog-nosis, high lymph node metastasis and early recurrence. However, the molecular events regulating HNSCC tumorigenesis remain poorly understood. Therefore, uncovering the underlying mechanisms is urgently needed to identify novel and promising therapeutic targets for HNSCC. In this study, we aimed to explore the role of pleckstrin-2 (PLEK2) in regulating HNSCC tumorigenesis.

Methods: The expression pattern of PLEK2 and its clinical significance in HNSCC were determined by analyzing publicly assessable datasets and our own independent HNSCC cohort. In vitro and in vivo experiments, including cell proliferation, colony formation, Matrigel invasion, tumor sphere formation,ALDEFLUOR, Western blotting assays and xenograft mouse models, were used to investigate the role of PLEK2 in regulating the malignant behaviors of HNSCC cells. The underlying molecular mechanisms for the tumor-promoting role of PLEK2 were elucidated using co-immunoprecipitation, cycloheximide chase analysis, ubiquitination assays, chromatin immunoprecipitation-quantitative polymerase chain reaction, luciferase reporter assays and rescue experiments.



Cancer Communications
2022 Oct;42(10):987-1007
Impact Factor: 16.2

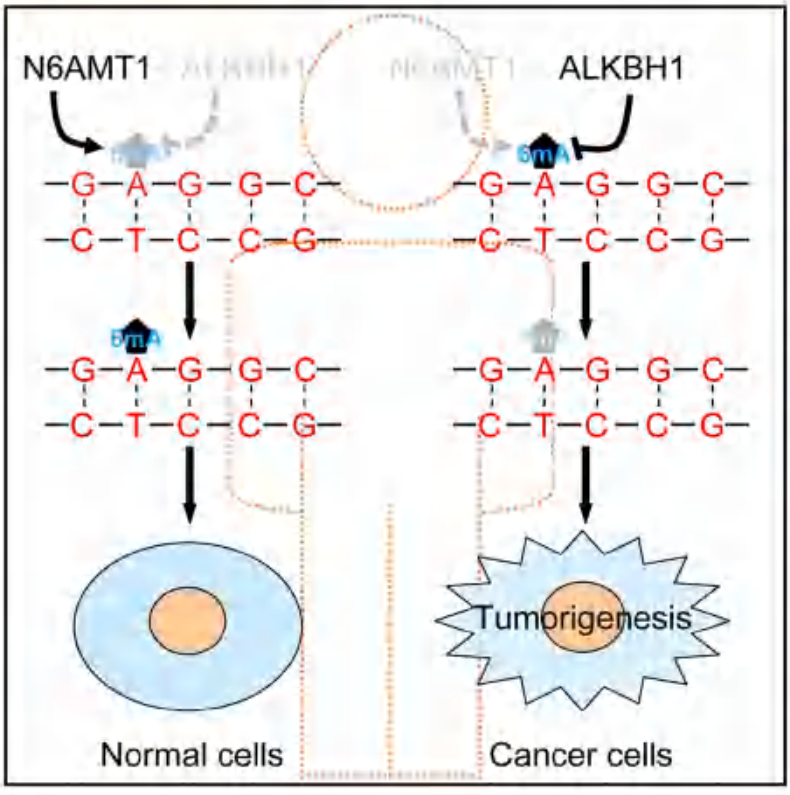
Materials and Methods

The short hairpin RNAs (shRNAs) targeting PLEK2 were inserted into the **LV3-pGLV-h1-GFP-puro vector** (**GenePharma**, Shanghai, China) to establish recombi-nant lentiviral expression plasmids.

Molecular Cell

N^6-Methyladenine DNA Modification in the Human Genome

Graphical Abstract



Authors

Chuan-Le Xiao, Song Zhu, Minghui He, ..., Xiao-Feng Gu, Kai Wang, Guang-Rong Yan

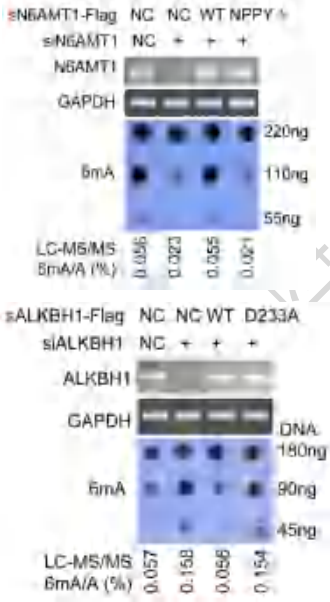
Correspondence

boxc@bmi.ac.cn (X.-C.B.), guxiaofeng@caas.cn (X.-F.G.), wangk@email.chop.edu (K.W.), jxygr007@yahoo.com (G.-R.Y.)

In Brief

Xiao et al. show that DNA methylation on N^6-adenine exists in the human genome. The mark is added by the methyltransferase N6AMT1 and it is removed by the demethylase ALKBH1. Decrease of genomic DNA 6mA promotes tumorigenesis and is associated with poor prognosis for cancer patients.

Molecular Cell
2018 Jul 19; 71: 306-18
Impact Factor: 16



Materials

Bacterial and Virus Strains	
Lentivirus pLV5-GFP-Luc	This paper, Genepharma
Lentivirus pLV3-NC shRNA	Genepharma
Lentivirus pLV3-N6AMT1 shRNA	This paper, Genepharma
Lentivirus pLV3-ALKBH1 shRNA	This paper, Genepharma

Chemical Engineering Journal 474 (2023) 145796

Contents lists available at ScienceDirect

Chemical Engineering Journal

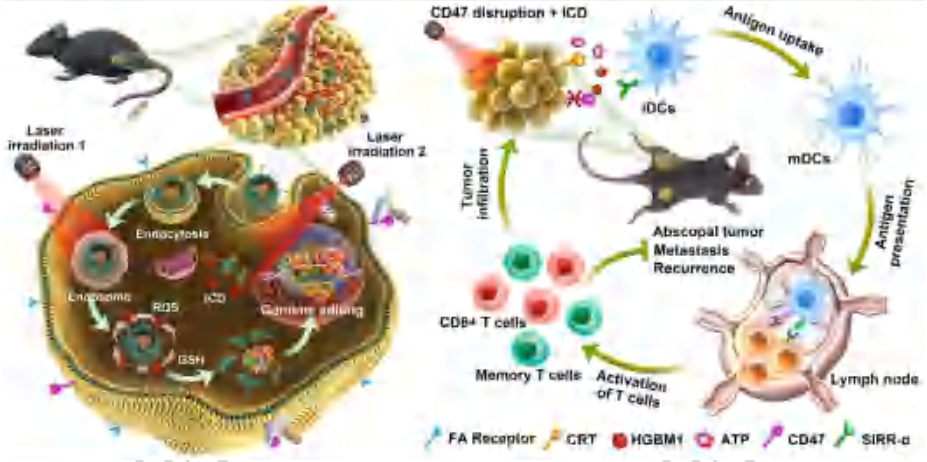
journal homepage: www.elsevier.com/locate/cej

Time-programmed activation of CD47 disruption and immunogenic cell death with Cas9 ribonucleoprotein nanocapsule for improved cancer immunotherapy

Yumeng Xing [a,b], Jianhui Yang [a,b], Chun Wang [c], Ziyao Kang [c], Zheng Pan [c], Jihui Tang [b], Fenghe Li [b], Xiao Wang [e], Xiao-ming Meng [b], Zhifei Cheng [d,*], Yang Liu [c,**], Qi Liu [a,b,***]

A B S T R A C T

Cancer immunotherapy refers to activating the body's antitumor immunity to fight cancer cells, showing great potential in long-term inhibition of tumor growth and recurrence. However, adequate activation of antitumor immunity remains challenging due to overactivated immune checkpoints and poor tumor immunogenicity. To address these challenges, herein, a Cas9 ribonucleoprotein (RNP) nanocapsule (Cas9NC) is described to syner-gistically activate antitumor immunity by time-programmed activation of CD47 disruption and immunogenic cell death (ICD) of tumor cells. Such Cas9NC is formed by coating RNP with a thin polymer shell made of multiple functional monomers, which not only endows Cas9NC with the capability to deliver payloads into tumor tissues, but also activates CRISPR-Cas9 system and ICD in a time-programmed manner. This time-programmed activation strategy significantly promotes the synergy of two payloads with different onset times. Additionally, CD47 disruption achieve superior therapeutic effects than antibody that achieve temporary conformational blockade. As a result, Cas9NC initiates robust and durable antitumor immune responses, and remarkably inhibits the growth of both primary and abscopal tumors, prevents the malignant tumor recurrence and metastasis. Collectively, this time-programmed activation strategy for synergistic CD47 disruption and ICD provides a promising approach for improved cancer immunotherapy.



CHEMICAL ENGINEERING JOURNAL
2023 Sep 3 ; 1385-8947
Impact Factor: 15.1

Materials and Methods

B16F10 cells with a single copy of destabilized EGFP gene inte-grated into the genome was first constructed by transduced with **Lentivirus** (**GenePharma**, Shanghai, China) encoding EGFP as described in our previous studies.

The **positive primers containing target genes** were purchased from **GenePharma** Biotech (Shanghai, China) and the sequences are follows in Table S2.

ADVANCED SCIENCE Open Access
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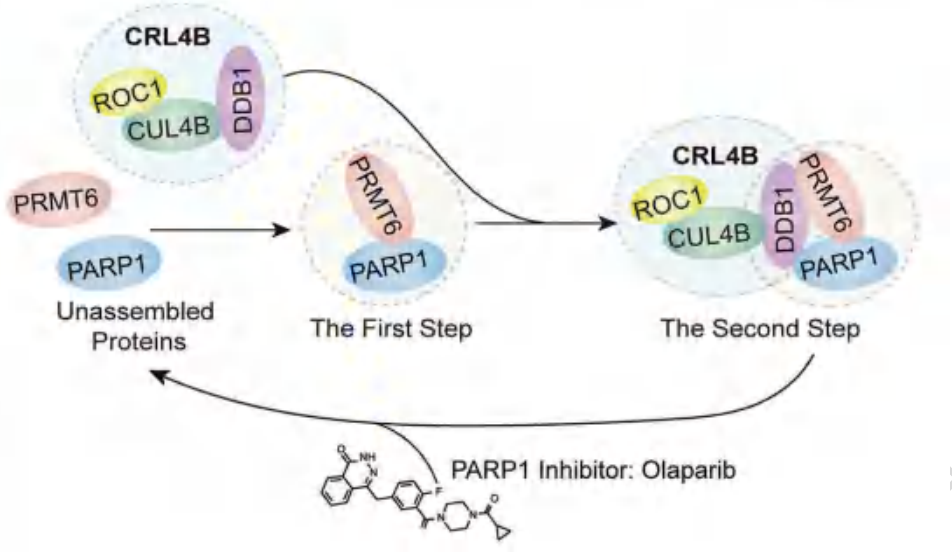
The PRMT6/PARP1/CRL4B Complex Regulates the Circadian Clock and Promotes Breast Tumorigenesis

*Tianshu Yang, Wei Huang, Tianyu Ma, Xin Yin, Jingyao Zhang, Miaomiao Huo, Ting Hu, Tianyang Gao, Wei Liu, Die Zhang, Hefen Yu, Xu Teng, Min Zhang, Hao Qin, Yunkai Yang, Baowen Yuan, and Yan Wang**

Abstract

Circadian rhythms, as physiological systems with self-regulatory functions in living organisms, are controlled by core clock genes and are involved in tumor development. The protein arginine methyltransferase 6 (PRMT6) serves as an oncogene in a myriad of solid tumors, including breast cancer. Hence, the primary aim of the current study is to investigate the molecular mechanisms by which the PRMT6 complex promotes breast cancer progression. The results show that PRMT6, poly(ADP-ribose) polymerase 1 (PARP1), and the cullin 4 B (CUL4B)-Ring E3 ligase (CRL4B) complex interact to form a transcription-repressive complex that co-occupies the core clock gene PER3 promoter. Moreover, genome-wide analysis of PRMT6/PARP1/CUL4B targets identifies a cohort of genes that is principally involved in circadian rhythms. This transcriptional-repression complex promotes the proliferation and metastasis of breast cancer by interfering with circadian rhythm oscillation. Meanwhile, the PARP1 inhibitor Olaparib enhances clock gene expression, thus, reducing breast carcinogenesis, indicating that PARP1 inhibitors have potential antitumor effects in high-PRMT6 expression breast cancer.



Advanced Science
2023 Mar 20;10:202737
Impact Factor: 15.1

Materials and Methods

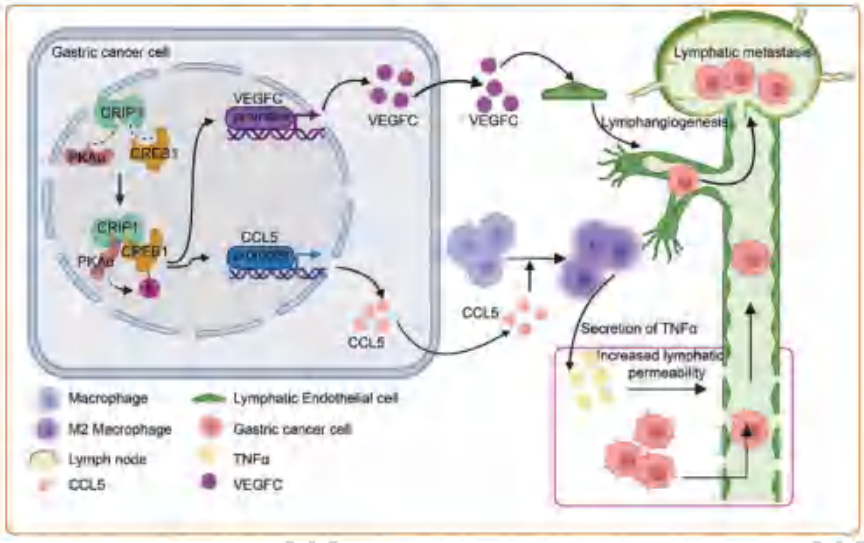
Lentiviral Production and Infection: Recombinant lentiviruses express-ing GFP-tagged shPRMT6, shPARP1 were constructed by Shanghai **GenePharma** Co., Ltd.

ADVANCED SCIENCE Open Access
www.advancedscience.com

CRIP1 Reshapes the Gastric Cancer Microenvironment to Facilitate Development of Lymphatic Metastasis

Zhonghua Wu, Bicheng Qu, Minxian Yuan, Jingjing Liu, Cen Zhou, Mingwei Sun, Zhexu Guo, Yaqing Zhang, Yongxi Song, and Zhenning Wang**

Lymphangiogenesis in tumors provides an auxiliary route for cancer cell invasion to drainage lymph nodes, facilitating the development of lymphatic metastasis (LM). However, the mechanisms governing tumor lymphangiogenesis and lymphatic permeability in gastric cancer (GC) remain largely unknown. Here, the unprecedented role and mechanism of cysteine-rich intestinal protein-1 (CRIP1) in mediating the development of GC LM is uncovered. A series of assays are performed to identify downstream targets of CRIP1, and rescue experiments are performed to conÞrm the effects of this regulatory axis on LM. CRIP1 overexpression facilitates LM in GC by promoting lymphangiogenesis and lymphatic vessel permeability. CRIP1 promotes phosphorylation of cAMP responsive element binding protein 1(CREB1), which then mediates vascular endothelial growth factor C (VEGFC) expression necessary for CRIP1-induced lymphangiogenesis and transcriptionally promotes C-C motif chemokine ligand 5 (CCL5) expression. CCL5 recruits macrophages to promote tumor necrosis factor alpha (TNF-α) secretion, eventually enhancing lymphatic permeability. The study highlights CRIP1 regulates the tumor microenvironment to promote lymphangiogenesis and LM in GC. Considering the current limited understanding of LM development in GC, these pathways provide potential targets for future therapeutics.



Advanced Science
2023 Sep 6 ; 10(26):e2303246
Impact Factor: 15.1

Materials and Methods

The open reading frames (ORF) of CRIP1 and CREB1 were cloned into **pCDNA3.1 vectors**. Short hairpin RNAs (shRNA) were cloned into a **lentivirus vector**. All vectors were purchased from **GenePharma** (Shanghai, China).

ADVANCED SCIENCE Open Access
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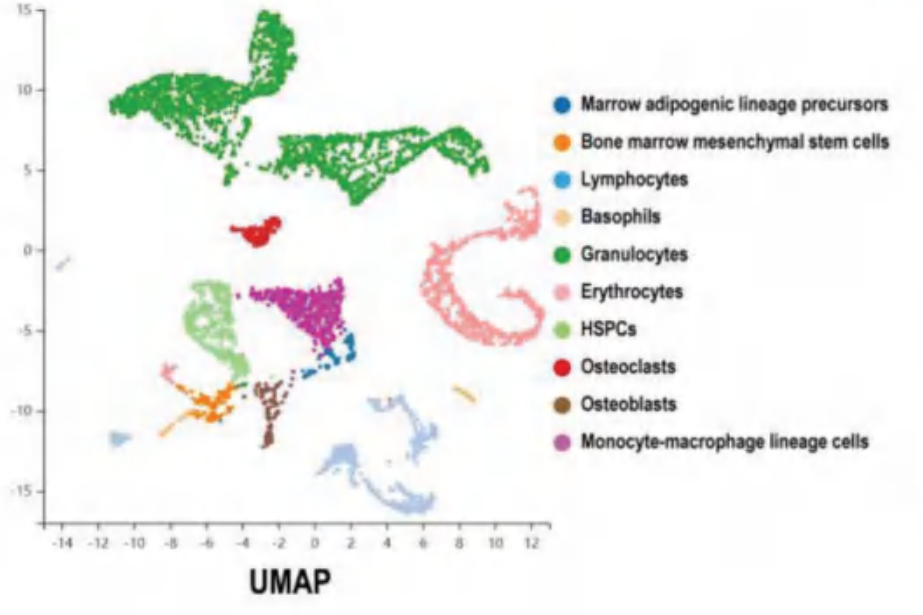
The Critical Role of The Piezo1/β-catenin/ATF4 Axis on The Stemness of Gli1$^+$ BMSCs During Simulated Microgravity-Induced Bone Loss

Yuxiang Hu, Hongtao Tian, Wei Chen, Yunlu Liu, Yulin Cao, Hongxin Pei, Chaochang Ming, Cunqing Shan, Xihui Chen, Zhipeng Dai, Shuhua Yang, Zengwu Shao, Shenghui Lan, Yong Liu,* and Wei Tong**

Disuse osteoporosis is characterized by decreased bone mass caused by abnormal mechanical stimulation of bone. Piezo1 is a major mechanosensitive ion channel in bone homeostasis. However, whether intervening in the action of Piezo1 can rescue disuse osteoporosis remains unresolved. In this study, a commonly-used hindlimb-unloading model is employed to simulate microgravity. By single-cell RNA sequencing, bone marrow-derived mesenchymal stem cells (BMSCs) are the most downregulated cell cluster, and coincidentally, Piezo1 expression is mostly enriched in those cells, and is substantially downregulated by unloading. Importantly, activation of Piezo1 by systemically-introducing yoda1 mimics the effects of mechanical stimulation and thus ameliorates bone loss under simulated microgravity. Mechanistically, Piezo1 activation promotes the proliferation and osteogenic differentiation of Gli1+ BMSCs by activating the -catenin and its target gene activating transcription factor 4 (ATF4). Inhibiting -catenin expression substantially attenuates the effect of yoda1 on bone loss, possibly due to inhibited proliferation and osteogenic differentiation capability of Gli1+ BMSCs mediated by ATF4. Lastly, Piezo1 activation also slightly alleviates the osteoporosis of OVX and aged mice. In conclusion, impaired function of Piezo1 in BMSCs leads to insufficient bone formation especially caused by abnormal mechanical stimuli, and is thus a potential therapeutic target for osteoporosis.



Advanced Science
2023 Sep 27:e2303375
Impact Factor: 15.1

Materials and Methods

Lentivirus (Lv)-shPiezo1 (**GenePharma** Co. Ltd., Shanghai, China) at a multiplicity of infection (MOI) of 50 was incubated with the cells for 12 h.

ADVANCED SCIENCE Open Access
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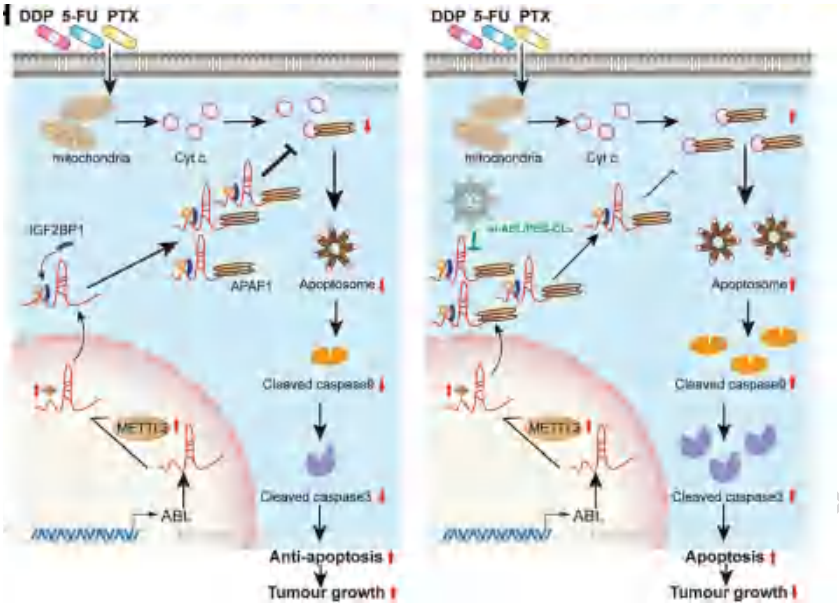
APAF1-Binding Long Noncoding RNA Promotes Tumor Growth and Multidrug Resistance in Gastric Cancer by Blocking Apoptosome Assembly

Qiang Wang, Chen Chen, Xiao Xu, Chuanjun Shu, Changchang Cao, Zhangding Wang, Yao Fu, Lei Xu, Kaiyue Xu, Jiawen Xu, Anliang Xia, Bo Wang, Guifang Xu, Xiaoping Zou, Ruibao Su, Wei Kang, Yuanchao Xue, Ran Mo,* Beicheng Sun,* and Shouyu Wang**

Chemotherapeutics remain the first choice for advanced gastric cancers(GCs). However, drug resistance and unavoidable severe toxicity lead to chemotherapy failure and poor prognosis. Long noncoding RNAs (lncRNAs) play critical roles in tumor progression in many cancers, including GC. Here, through RNA screening, an apoptotic protease-activating factor 1(APAF1)-binding lncRNA (ABL) that is significantly elevated in cancerous GC tissues and an independent prognostic factor for GC patients is identified. Moreover, ABL overexpression inhibits GC cell apoptosis and promotes GC cell survival and multidrug resistance in GC xenograft and organoid models. Mechanistically, ABL directly binds to the RNA-binding protein IGF2BP1 via its KH1/2 domain, and then IGF2BP1 further recognizes the METTL3-mediated m6A modification on ABL, which maintains ABL stability. In addition, ABL can bind to the WD1/WD2 domain of APAF1, which competitively prevent cytochrome c from interacting with APAF1, blocking apoptosome assembly and caspase-9/3 activation; these events lead to resistance to cell death in GC cells. Intriguingly, targeting ABL using encapsulated liposomal siRNA can significantly enhance the sensitivity of GC cells to chemotherapy. Collectively, the results suggest that ABL can be a potential prognostic biomarker and therapeutic target in GC.



Advanced Science
2022 Oct;9(28):e2201889
Impact Factor: 15.1

Materials and Methods

shRNAs targeting ABL or METTL3 were designed based on siRNA sequences and subcloned into **LV3 vectors** (pGLV-h1-EGFP-puro), which were con-structed by **GenePharma** (Shanghai, China).

Contents lists available at ScienceDirect

Biomaterials

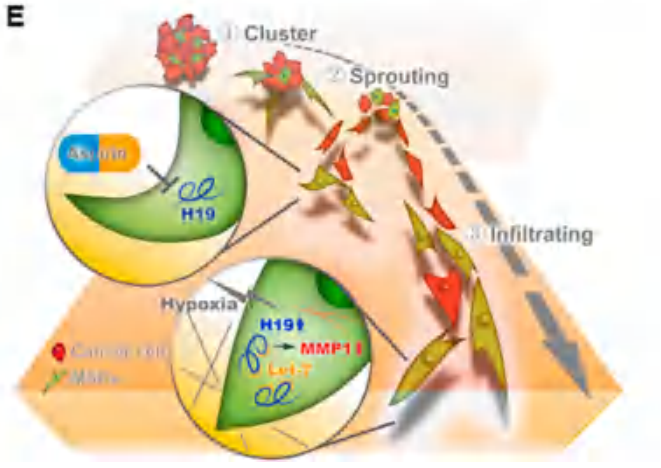
journal homepage: www.elsevier.com/locate/biomaterials

A microfluidic demonstration of "cluster-sprout-infiltrating" mode for hypoxic mesenchymal stem cell guided cancer cell migration

Fan An [a,1], Zhijie Hou [a,g,1], Xiaochao Wang [a,1], Zhongmin Wang [f,1], Chenying Jing [a], Ran Sui [a], Yameng Wu [a], Yunfeng Ma [a], Cheng Chang [a], Shuai Liu [a], Manman Li [a], Lijie Sun [c], Ziqi Gao [a], Wenjuan Zhang [a], Zhenghui Lang [a], Jiaqi Zhao [a], Yueyang Qu [d], Lingzhi Xu [c], Yong Luo [e], Jinsong Yan [g], Yuesheng Wang [a], Jie Xu [a,*], Quentin Liu [a,b,**]

Abstract

Mesenchymal stem cells (MSCs) play a critical role in tumor metastasis. However, the dynamic process of MSCs-mediated cancer cell invasion remains inconclusive. In breast cancer mouse models, we observed that MSCs promoted lung metastasis. We constructed a microfluidic-based 3D co-culture device to monitor MSCs-mediated cancer cell invasion in a nutrient-deficient hypoxic microenvironment. On biomimetic microfluidic devices, MSCs guided cancer cell migration in a "cluster-sprout-infiltrating" mode. Importantly, hypoxic conditions significantly promoted MSCs migration at the infiltration stage, leading to accelerated breast cancer cell inva-sion. Moreover, hypoxia related LncRNA analysis showed that H19 was dramatically upregulated in response to hypoxic conditions. Conversely, H19 depletion impaired MSCs-directed breast cancer cell invasion. Mechanis-tically, H19 functions as a competitive endogenous RNA (ceRNA) which sequesters miRNA let-7 to release its target matrix metalloproteinase-1 (MMP1). Intriguingly, aspirin dramatically suppressed H19 and MMP1 expression and blocked MSCs infiltration under hypoxic conditions, resulting in alleviated breast cancer cell invasion. These findings point to the metastatic promoting role of MSCs in tumor stroma and suggest that MSCs might be a therapeutic target for metastatic breast cancer.



BIOMATERIALS
2022 Oct;:121848
Impact Factor: 14

Materials and Methods

MSCs were infected with **shRNA lentiviruses** of H19 (**Genepharma**).

Journal of Hazardous Materials 457 (2023) 131750

Contents lists available at ScienceDirect

Journal of Hazardous Materials

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

MDM2 upregulation induces mitophagy deficiency via Mic60 ubiquitination in fetal microglial inflammation and consequently neuronal DNA damage caused by exposure to ZnO-NPs during pregnancy

Yanli Zhang [a,b,1], Yulin Zhang [a,1], Ye Lei [c], Junrong Wu [a], Yiyuan Kang [a], Shuo Zheng [a], Longquan Shao [a,b,*]

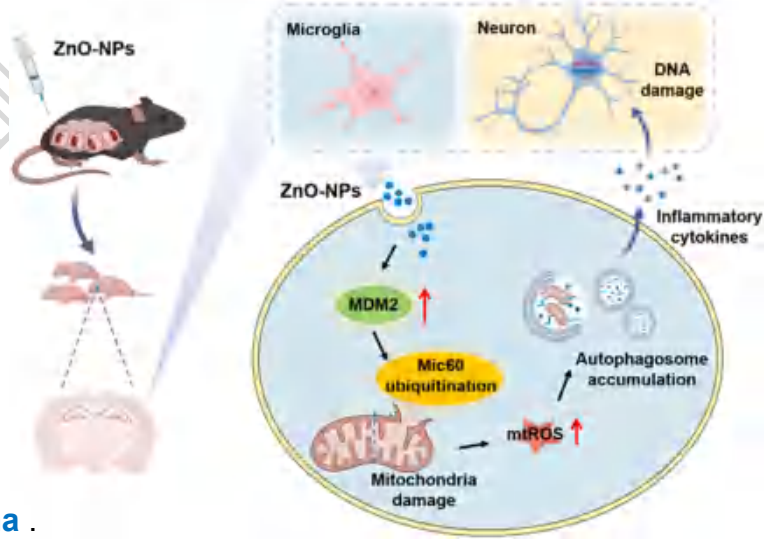
ARTICLE INFO

Editor: Dr. S.Y. Chen

Key words:
Zinc oxide nanoparticles
Neurodevelopmental toxicity
Paracrine effect
Mitochondrial homeostasis
Oxidation respiratory chain

ABSTRACT

During pregnancy, the human body is quite vulnerable to external stimuli. Zinc oxide nanoparticles (ZnO-NPs) are widely used in daily life, and they enter the human body via environmental or biomedical exposure, thus having potential risks. Although accumulating studies have demonstrated the toxic effects of ZnO-NPs, few studies have addressed the effect of prenatal ZnO-NP exposure on fetal brain tissue development. Here, we systematically studied ZnO-NP-induced fetal brain damage and the underlying mechanism. Using in vivo and in vitro assays, we found that ZnO-NPs could cross the underdeveloped blood—brain barrier and enter fetal brain tissue, where they could be endocytosed by microglia. ZnO-NP exposure impaired mitochondrial function and induced autophagosome overaccumulation by downregulation of Mic60, thus inducing microglial inflammation. Mechanistically, ZnO-NPs increased Mic60 ubiquitination by activating MDM2, resulting in imbalanced mitochondrial homeostasis. Inhibition of Mic60 ubiquitination by MDM2 silencing significantly attenuated the mitochondrial damage induced by ZnO-NPs, thereby preventing autophagosome overaccumulation and reducing ZnO-NP-mediated inflammation and neuronal DNA damage. Our results demonstrate that ZnO-NPs are likely to disrupt mitochondrial homeostasis, inducing abnormal autophagic flux and microglial inflammation and secondary neuronal damage in the fetus. We hope the information provided in our study will improve the understanding of the effects of prenatal ZnO-NP exposure on fetal brain tissue development and draw more attention to the daily use of and therapeutic exposure to ZnO-NPs among pregnant women.



JOURNAL OF HAZARDOUS MATERIALS
2023 Jun 1;457:131750.
Impact Factor: 13.6

Materials and Methods

Lentiviruses were provided by **Genepharma** .

Emerging Microbes & Infections
2022, VOL. 11
https://doi.org/10.1080/22221751.2022.2125344

RESEARCH ARTICLE

OPEN ACCESS

Compartmentalisation of Hepatitis B virus X gene evolution in hepatocellular carcinoma microenvironment and the genotype-phenotype correlation of tumorigenicity in HBV-related patients with hepatocellular carcinoma

Ya Fu [a,b,c,d], Fengling Fang[a,b,c,d], Hongyan Guo[a,b,c,d], Xialin Xiao[a,b,c,d], Yuhai Hu[e], Yongbin Zeng[a,b,c,d], Tianbin Chen[a,b,c,d], Songhang Wu[a,b,c,d], Ni Lin[a,b,c,d], Jinlan Huang[a,b,c,d], Ling Jiang[a,b,c,d], Qishui Ou[a,b,c,d] and Can Liu[a,b,c,d]

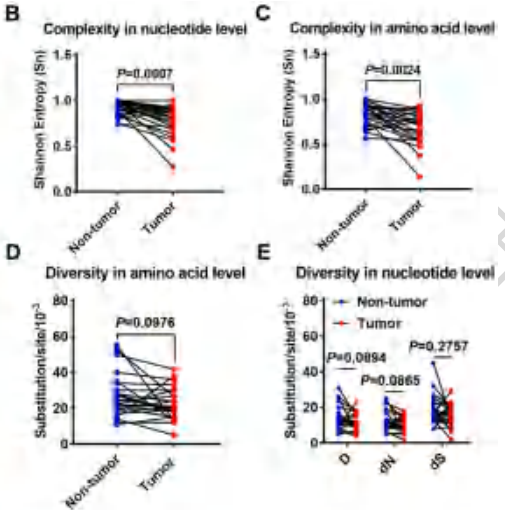
Abstract

Hepatitis B virus (HBV) exists as quasispecies (QS). However, the evolutionary characteristics of haplotypes of HBV X gene in the hepatocellular carcinoma (HCC) microenvironment remain unclear. Mutations across X gene are essential for the tumorigenicity of HBV X protein (HBx). However, the functional phenotypes of many mutant HBx remain unknown. This study aims to compare the characteristics of X gene evolution between tumour and non-tumour tissues in HCC patients and investigate the tumorigenic phenotype of HBx harbouring mutation T81P/S101P/L123S. This study included 24 HCC patients. Molecular cloning of X gene was performed to analyse characteristics of haplotypes in liver tissues. HCC cell lines stably expressing wild-type or mutant HBx and subcutaneous tumour xenograft mouse model were used to assess HBx-T81P/S101P/L123S tumorigenicity. The mean heterogeneity of HBV QS across X gene in tumour tissues was lower than that in non-tumour tissues. A location bias was observed in X gene clones with genotype C or D in tumour tissues compared to those with genotype B. Mutations in genotype-C or – D clones were mainly clustered in the dimerization region and aa110-aa140 within the transactivation region. A novel mutation combination at residues 81, 101 and 123 was identified in tumour tissues. Further, HBx-T81P/S101P/L123S promotes cell proliferation and increases genomic instability, which was mediated by MYC. This study elucidates the compartmentalized evolution patterns of HBV X gene between intra tumour and non-tumour tissues in HCC patients and provides a new mechanism underlying HBV-driven hepatocarcinogenesis, suggesting a potential viral marker for monitoring HCC.

Emerging Microbes & Infections
2022 Dec;11(1):2486-2501
Impact Factor: 13.2

Materials and Methods

To obtain HCC cell lines stably expressing wild-type and mutated HBx, Huh 7 and Bel-7404 cells were infected with the Lv-HBx-WT, Lv-HBx-L123S, Lv-HBx-S101P/L123S, Lv-HBx-T81P/S101P/L123S and **lentivirus empty vector** (**GenePharma**, China).



CDD press

www.nature.com/cdd

ARTICLE

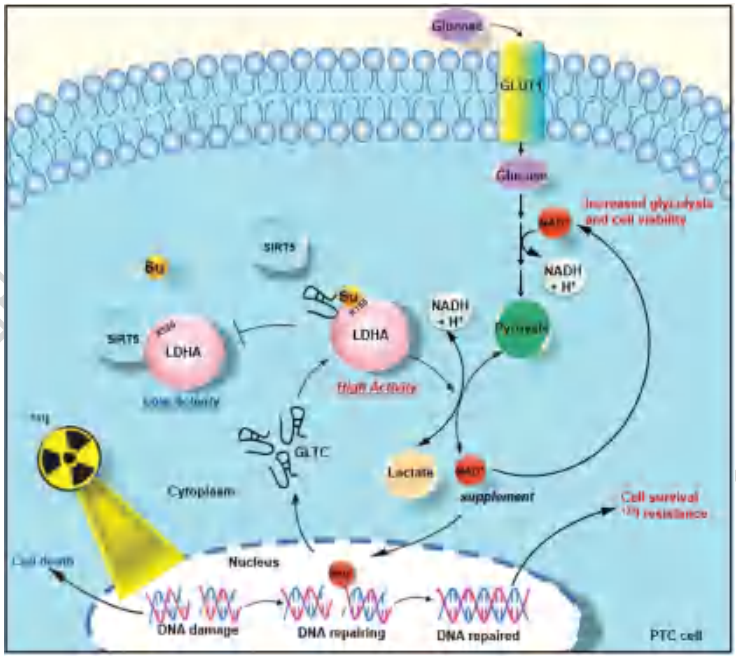
Check for updates

LncRNA GLTC targets LDHA for succinylation and enzymatic activity to promote progression and radioiodine resistance in papillary thyroid cancer

Liang Shi[1,7], Rui Duan[1,2,7], Zhenhua Sun[3,7], Qiong Jia[4], Wenyu Wu[1], Feng Wang[1], Jianjun Liu[5]✉, Hao Zhang[6]✉ and Xue Xue[1]✉

Dysregulation of long noncoding RNAs (lncRNAs) has been associated with the development and progression of many human cancers. Lactate dehydrogenase A (LDHA) enzymatic activity is also crucial for cancer development, including the development of papillary thyroid cancer (PTC). However, whether specific lncRNAs can regulate LDHA activity during cancer progression remains unclear. Through screening, we identified an LDHA-interacting lncRNA, GLTC, which is required for the increased aerobic glycolysis and cell viability in PTC. GLTC was significantly upregulated in PTC tissues compared with nontumour thyroid tissues. High expression of GLTC was correlated with more extensive distant metastasis, a larger tumour size, and poorer prognosis. Mass spectrometry revealed that GLTC, as a binding partner of LDHA, promotes the succinylation of LDHA at lysine 155 (K155) via competitive inhibition of the interaction between SIRT5 and LDHA, thereby promoting LDHA enzymatic activity. Overexpression of the succinylation mimetic LDHA^{K155E} mutant restored glycolytic metabolism and cell viability in cells in which metabolic reprogramming and cell viability were ceased due to GLTC depletion. Interestingly, GLTC inhibition abrogated the effects of K155-succinylated LDHA on radioiodine (RAI) resistance in vitro and in vivo. Taken together, our results indicate that GLTC plays an oncogenic role and is an attractive target for RAI sensitisation in PTC treatment.

Cell Death & Differentiation; https://doi.org/10.1038/s41418-023-01157-6



CELL DEATH AND DIFFERENTIATION
2023 Apr 8;30:1517–1532
Impact Factor: 12.4

Materials and Methods

All **plasmids**, **siRNAs and lentiviruses** were purchased from **GenePharma** Technology.

IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2023; 13(7): 2337-2349. doi: 10.7150/thno.82538

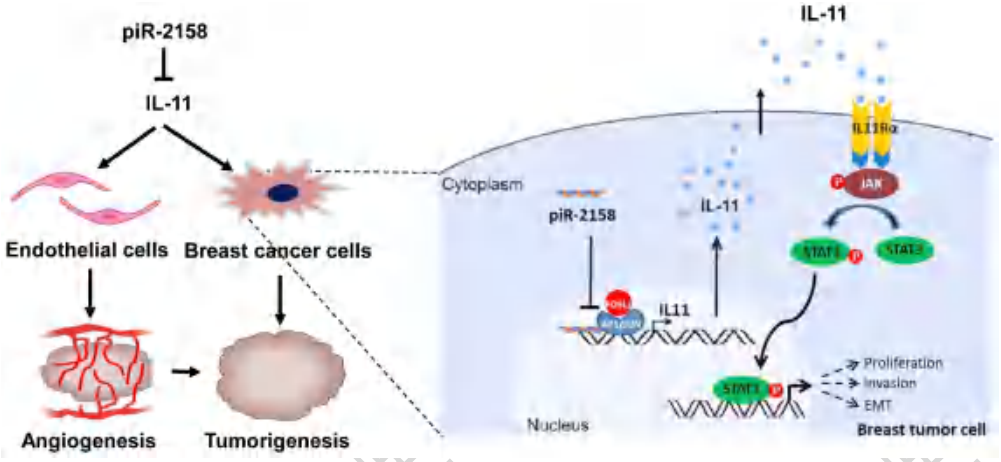
Research Paper

IL11 signaling mediates piR-2158 suppression of cell stemness and angiogenesis in breast cancer

Qian Zhao[1†], Lu Qian[1†], Yuefan Guo[1†], Jinhui Lü[1], Danni Li[1], Heying Xie[1,2], Qiong Wang[1], Wenjing Ma[1], Pengfei Liu[1], Yu Liu[1,2], Tao Wang[1], Xuebiao Wu[3], Junyi Han[1✉] and Zuoren Yu[1✉]

Abstract

Emerging evidence has indicated the aberrant expression of PIWI-interacting RNAs (piRNAs) in human cancer cells to regulate tumor development and progression by governing cancer cell stemness. Herein, we identified downregulation of piR-2158 in human breast cancer tumors, especially in ALDH+ breast cancer stem cells (BCSCs) from patients and cell lines, which was further validated in two types of genetically engineered mouse models of breast cancer (MMTV-Wnt and MMTV-PyMT). Enforced overexpression of piR-2158 in basal-like or luminal subtypes of breast cancer cells suppressed cell proliferation, migration, epithelial-mesenchymal transition (EMT) and stemness *in vitro*. Administration of a dual mammary tumor-targeting piRNA delivery system in mice reduced tumor growth *in vivo*. RNA-seq, ChIP-seq and luciferase reporter assays demonstrated piR-2158 as a transcriptional repressor of *IL11* by competing with AP-1 transcription factor subunit FOSL1 to bind the promoter of *IL11*. STAT3 signaling mediated piR-2158-IL11 regulation of cancer cell stemness and tumor growth. Moreover, by co-culturing of MDA-MB-231 and HUVECs *in vitro* and CD31 staining of tumor endothelial cells *in vivo*, we demonstrated inhibition of angiogenesis by piR-2158-IL11 in breast cancer. In conclusion, the current study not only reveals a novel mechanism through which piR-2158 inhibits mammary gland tumorigenesis *via* regulating cancer stem cells and tumor angiogenesis, but also provides a novel therapeutic strategy in treatment of breast cancer.



Theranostics
2023 Apr 17; 13(7): 2337-2349.
Impact Factor: 12.4

Materials and Methods

Lentivirus vector LV3(H1/GFP&Puro)- piR-2158 was purchased from **GenePharma** (Shanghai, China), using a sequence not homology to any known mammalian gene as negative control (NC).

CDD press

www.nature.com/cdd

ARTICLE OPEN

Check for updates

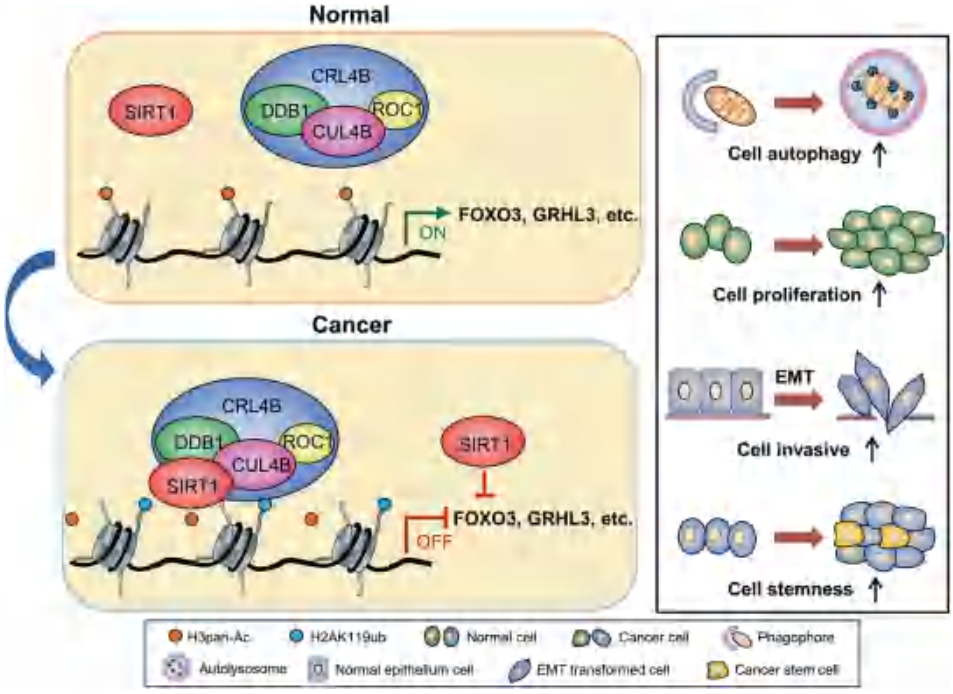
SIRT1 coordinates with the CRL4B complex to regulate pancreatic cancer stem cells to promote tumorigenesis

Shuai Leng[1], Wei Huang[2], Yang Chen[1], Yang Yang[1], Dandan Feng[1], Wei Liu[1], Tianyang Gao[1], Yanli Ren[1], Miaomiao Huo[3], Jingyao Zhang[3], Yunkai Yang[3] and Yan Wang[1,3]✉

Pancreatic cancer is a common malignant tumor with poor prognosis. Recently, cancer stem cells (CSCs) were identified in several solid tumors, including pancreatic cancer. Although accumulating evidence indicates that sirtuin 1 (SIRT1) exerts biological functions in various cancers, how it contributes to tumorigenesis and metastasis of pancreatic cancer, as well as its role in CSCs, is still poorly defined. Here we show that SIRT1 interacts with the Cullin 4B (CUL4B)-Ring E3 ligase (CRL4B) complex, which is responsible for H2AK119 monoubiquitination (H2AK119ub1), collaborating as a functional unit. Genome-wide analysis of SIRT1/CUL4B targets identified a cohort of genes, including GRHL3 and FOXO3, critically involved in cell differentiation, growth, and migration. Furthermore, we found that SIRT1 and CUL4B collectively promote the proliferation, autophagy, and invasion of pancreatic cancer cells. Remarkably, we demonstrate that SIRT1/CUL4B promotes CSC-like properties, including increased stemness marker expression and sphere formation. In vivo experiments implied that SIRT1 promoted established tumor xenograft growth, increased tumor-initiating capacity in NOD/SCID mice, and increased CSC frequency. Strikingly, SIRT1 and CUL4B expression is markedly upregulated in a variety of human cancers, including pancreatic cancer. Our data provide a molecular basis for the functional interplay between histone deacetylation and ubiquitination. The results also implicate the SIRT1/CRL4B complex in pancreatic cancer metastasis and stem cell properties, thus supporting SIRT1 as a promising potential target for cancer therapy development.

Cell Death & Differentiation
2021 Jun 23
Impact Factor: 12.4

Materials and Methods
short hairpin RNAs **(shRNAs)** from **GenePharma** Co., Ltd. (Shanghai, China). **Recombinant lentivirus** expressing shSCR (control scrambled shRNA), shSIRT1, and shCUL4B were constructed according to the instructions from Shanghai **GenePharma**.



IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2021; 11(2): 925-940. doi: 10.7150/thno.46655

Research Paper

LncRNA BCYRN1-induced autophagy enhances asparaginase resistance in extranodal NK/T-cell lymphoma

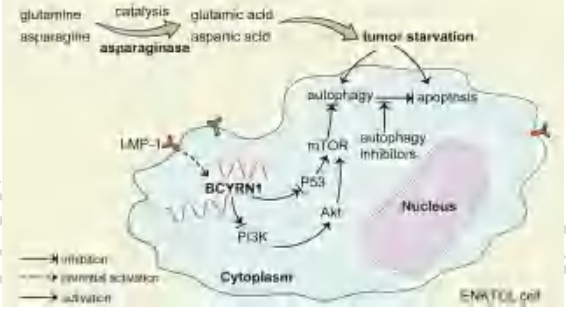
Liang Wang[1,2], Jing Yang[1], He-nan Wang[1], Rui-ying Fu[1], Xin-di Liu[1], Ying-shi Piao[3,4], Li-qiang Wei[1], Jing-wen Wang[1], Luo Zhang[5,6]✉

Abstract

Background: Asparaginase (ASP) is the cornerstone drug in the treatment of extranodal NK/T-cell lymphoma (ENKTCL), and the mechanisms of resistance to ASP remain largely unknown. Long non-coding RNAs play important roles in chemotherapy resistance in various cancers. However, the expression of BCYRN1 and its role in ENKTCL still remain unidentified.

Methods: Lentivirus-mediated BCYRN1 overexpression and knockdown were performed in SNK-6 cells. Cell autophagy was analyzed by adenovirus expressing GFP-LC3B fusion protein. RNA pull-down and RNA Binding Protein Immunoprecipitation Assay were performed to investigate the relationship between BCYRN1 and p53. Western blot analysis was performed to assess the effect of BCYRN1 on different autophagy pathways. Finally, in vivo xenograft tumor model was constructed to analyze the effect of BCYRN1 on tumor growth and ASP resistance.

Results: BCYRN1 was overexpressed in ENKTCL than normal NK cells, and patients with higher expression had significantly inferior progression-free survival (PFS). The IC50 value of ASP was significantly increased in BCYRN1-overexpressed SNK-6 cells and BCYRN1 overexpression could resist the inhibitory effect of ASP on proliferation. ASP could induce concurrent apoptosis and autophagy in ENKTCL, and the latter process was enhanced by overexpression of BCYRN1, mainly through affecting both PI3K/AKT/mTOR and p53/mTOR pathways. BCYRN1 could induce the degradation of p53 via ubiquitination, thus resulting in enhancement of autophagy and ASP resistance, which could be reversed by drug-induced autophagy inhibition. The effect of BCYRN1 on tumor growth and autophagy were confirmed in vivo xenograft model.



Theranostics
2021 Jan 1; 11(2): 925-940
Impact Factor: 12.4

Materials and Methods

Briefly, the full-length BCYRN1 cDNA and step-loop for the shBCYRN1 was inserted into the **LV5 vector** (**GenePharma**) at NotI and BamHI sites.

The LV5-BCYRN1 vector, LV5-shBCYRN1 vector and LV5 control vector (LV5-NC) were, respectively, co-transfected with the packaging vectors **pGag/Pol, pRev, and pVSV-G** (**GenePharma**) into HEK293T cells.

shRNA for p53 (shp53) was obtained from **GenePharma** (Shanghai, China).

Cell Death & Differentiation
https://doi.org/10.1038/s41418-021-00786-z

Cell Death & Differentiation

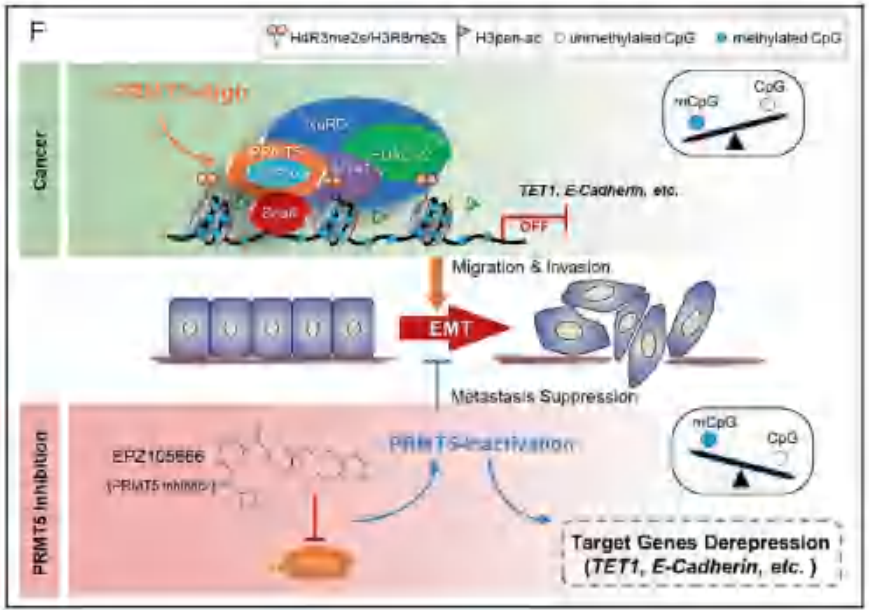
ARTICLE

Snail/PRMT5/NuRD complex contributes to DNA hypermethylation in cervical cancer by TET1 inhibition

Jie Gao[1,2]·Ruiqiong Liu[2]·Dandan Feng[1]·Wei Huang[3]·Miaomiao Huo[4]·Jingyao Zhang[4]·Shuai Leng[1]·Yang Yang[1]·Tianshu Yang[3]·Xin Yin[3]·Xu Teng[3]·Hefen Yu[3]·Baowen Yuan[4]·Yan Wang [1,]

Abstract

The biological function of PRMT5 remains poorly understood in cervical cancer metastasis. Here, we report that PRMT5 physically associates with the transcription factor Snail and the NuRD(MTA1) complex to form a transcriptional-repressive complex that catalyzes the symmetrical histone dimethylation and deacetylation. This study shows that the Snail/PRMT5/NuRD(MTA1) complex targets genes, such as TET1 and E-cadherin, which are critical for epithelial-mesenchymal transition (EMT). This complex also affects the conversion of 5mC to 5hmC. This study demonstrates that the Snail/PRMT5/NuRD(MTA1) complex promotes the invasion and metastasis of cervical cancer in vitro and in vivo. This study also shows that PRMT5 expression is upregulated in cervical cancer and various human cancers, and the PRMT5 inhibitor EPZ015666 suppresses EMT and the invasion potential of cervical cancer cells by disinhibiting the expression of TET1 and increasing 5hmC, suggesting that PRMT5 is a potential target for cancer therapy.



Cell Death & Differentiation
22021 Sep;28(9):2818-2836
Impact Factor: 12.4

Materials and Methods

Recombinant lentiviruses expressing shPRMT5, shSnail, and shMTA1 were con-structed by Shanghai **GenePharma** (Shanghai, China).

Cell Death & Differentiation
https://doi.org/10.1038/s41418-021-00813-z

Cell Death & Differentiation

ARTICLE

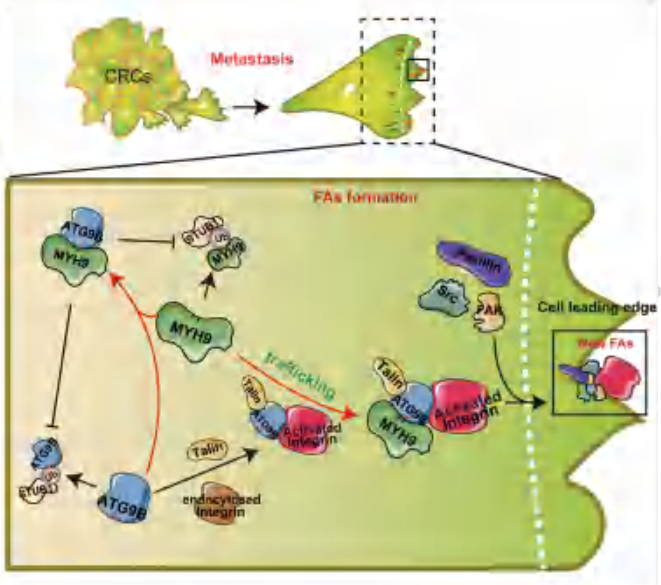
MYH9-dependent polarization of ATG9B promotes colorectal cancer metastasis by accelerating focal adhesion assembly

Yan Zhong[1,2]·Ting Long[1]·Chuan-Sha Gu[2,3]·Jing-Yi Tang[2,3]·Ling-Fang Gao[1,2]·Jia-Xian Zhu[1,2]·Zhi-Yan Hu[2,3,4]·Xia Wang[2,3]·Yi-Dan Ma[2,3]·Yan-Qing Ding [2,3,4]·Zu-Guo Li[1,3]·Xiao-Yan Wang [2,3,4]

Abstract

Tumour metastasis is a major reason accounting for the poor prognosis of colorectal cancer (CRC), and the discovery of targets in the primary tumours that can predict the risk of CRC metastasis is now urgently needed. In this study, we identified autophagy-related protein 9B (ATG9B) as a key potential target gene for CRC metastasis. High expression of ATG9B in tumour significantly increased the risk of metastasis and poor prognosis of CRC. Mechanistically, we further find that ATG9B promoted CRC invasion mainly through autophagy-independent manner. MYH9 is the pivotal interacting protein for ATG9B functioning, which directly binds to cytoplasmic peptide segments aa368–411 of ATG9B by its head domain. Furthermore, the combination of ATG9B and MYH9 enhance the stability of each other by decreasing their binding to E3 ubiquitin ligase STUB1, therefore preventing them from ubiquitin-mediated degradation, which further amplified the effect of ATG9B and MYH9 in CRC cells. During CRC cell invasion, ATG9B is transported to the cell edge with the assistance of MYH9 and accelerates focal adhesion (FA) assembly through mediating the interaction of endocytosed integrin β1 and Talin-1, which facilitated to integrin β1 activation. Clinically, upregulated expression of ATG9B in human CRC tissue is always accompanied with highly elevated expression of MYH9 and associated with advanced CRC stage and poor prognosis. Taken together, this study highlighted the important role of ATG9B in CRC metastasis by promoting focal adhesion assembly, and ATG9B together with MYH9 can provide a pair of potential therapeutic targets for preventing CRC progression.

Cell Death & Differentiation
2021 Dec;28(12):3251-3269
Impact Factor: 12.4



Materials and Methods

In light of the manufacturer's instructions, lentiviral con-structs containing the indicated **ATG9B-repressing short hairpin RNA** sequence (GAUCCCUGAA-CAGGAUUAUTT) purchased from **GenePharma** (Suzhou, China) were used to establish cell lines constitutively repressing ATG9B. **A stable lentiviral vector with over-expression of ATG9B** (**GenePharma**, Suzhou, China).

Cell Death & Differentiation (2019) 26:2652–2666
https://doi.org/10.1038/s41418-019-0328-3

Cell Death & Differentiation

ARTICLE

TRAF4 positively regulates the osteogenic differentiation of mesenchymal stem cells by acting as an E3 ubiquitin ligase to degrade Smurf2

Jinteng Li[1,2] · Peng Wang[1,2] · Zhongyu Xie[1,2] · Shan Wang[3] · Shuizhong Cen[2] · Ming Li[2] · Wenjie Liu[2] · Su'an Tang[2] · Guiwen Ye[2] · Guan Zheng[2] · Hongjun Su[3] · Mengjun Ma[1,2] · Xiaohua Wu[3] · Yanfeng Wu[3] · Huiyong Shen[1,2]

Received: 4 October 2018 / Revised: 13 March 2019 / Accepted: 22 March 2019 / Published online: 10 May 2019

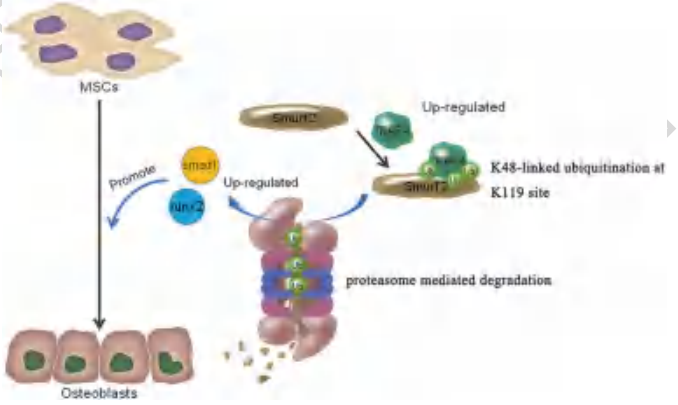
Abstract

TNF receptor-associated factor 4 (TRAF4), a member of the TRAF family, plays an important role in the embryogenesis and development of the bone system. Mesenchymal stem cells (MSCs), which are the primary origin of osteoblasts in vivo, are key cells in bone development; however, whether TRAF4 modulates the osteogenic capacity of MSCs has never been explored. In this study, we demonstrated that TRAF4 positively regulates the osteogenic process of MSCs both in vitro and in vivo. In addition, we further demonstrated that TRAF4 modulates the osteogenic process of MSCs by acting as an E3 ubiquitin ligase to mediate the K48-linked ubiquitination of Smurf2 at the K119 site and cause degradation. Furthermore, TRAF4 was abnormally decreased in bone sections of ovariectomized rat and osteoporosis patients. Taken together, our findings suggest that TRAF4 positively regulates the osteogenic differentiation of MSCs by acting as an E3 ubiquitin ligase to degrade Smurf2. These results emphasize the critical role of TRAF4 in bone formation and could not only improve the clinical use of MSCs in tissue engineering but also clarify the pathogenesis of bone metabolism disorders.

Cell Death & Differentiation
2019 May 10; 26:2652–2666
Impact Factor: 12.4

Materials and Methods

Lentiviruses encoding short hairpin RNA (**shRNA**, **GenePharma**) targeting TRAF4 (Sh-TRAF4).



Redox Biology 62 (2023) 102679

Contents lists available at ScienceDirect

Redox Biology

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

TRIM21 deficiency protects against atrial inflammation and remodeling post myocardial infarction by attenuating oxidative stress

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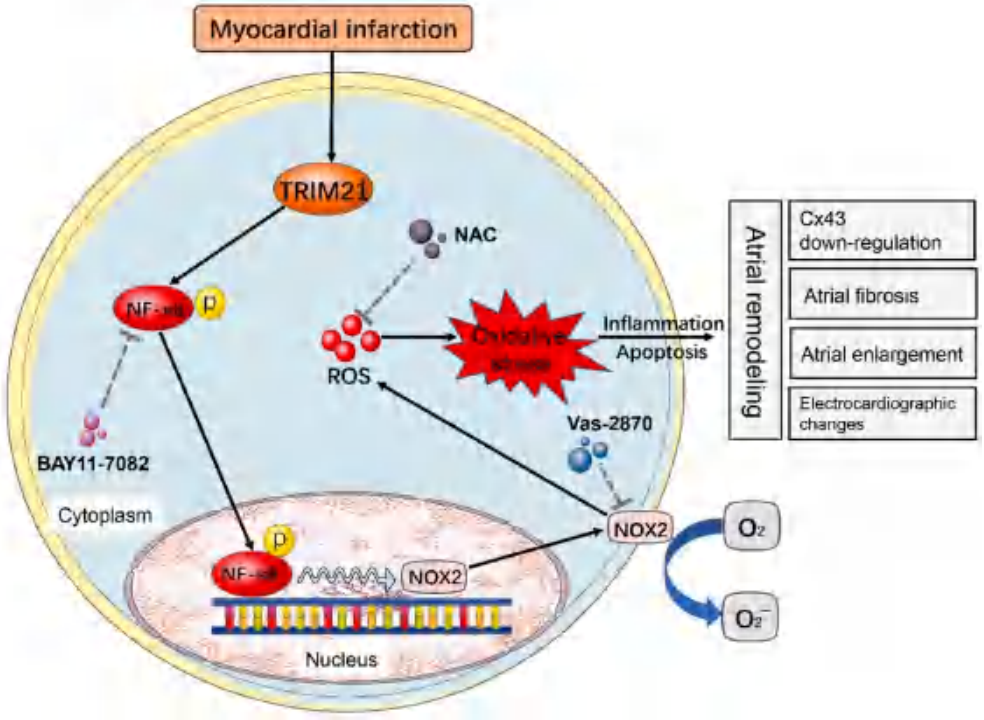
ABSTRACT

Atrial remodeling is a major contributor to the onset of atrial fibrillation (AF) after myocardial infarction (MI). Tripartite motif-containing protein 21 (TRIM21), an E3 ubiquitin protein ligase, is associated with pathological cardiac remodeling and dysfunction. However, the role of TRIM21 in postmyocardial infarction atrial remodeling and subsequent AF remains unclear. This study investigated the role of TRIM21 in post myocardial infarction atrial remodeling using TRIM21 knockout mice and explored the underlying mechanisms by overexpressing TRIM21 in HL-1 atrial myocytes using a lentiviral vector. The expression of TRIM21 in the left atrium of the mouse MI model was significantly elevated. TRIM21 deficiency alleviated MI-induced atrial oxidative damage, Cx43 downregulation, atrial fibrosis and enlargement, and abnormalities in electrocardiogram parameters (prolongation of the P-wave and PR interval). TRIM21 overexpression in atrial myocyte HL-1 cells further enhanced oxidative damage and Cx43 downregulation, whereas these effects were reversed by the reactive oxygen species scavenger N-acetylcysteine. The findings suggest that TRIM21 likely induces Nox2 expression mechanistically by activating the NF-κB pathway, which in turn leads to myocardial oxidative damage, inflammation, and atrial remodeling.



Redox Biology
2023 Mar;62:102679
Impact Factor: 11.4

Materials and Methods

GenePharma (Shanghai, China) constructed a TRIM21 **overexpression lentiviral vector** (Lenti-TRIM21) and a **negative control (NC)** Lenti-green fluorescent protein (Lenti-GFP) vector.

Yao et al. J Exp Clin Cancer Res (2023) 42:330
https://doi.org/10.1186/s13046-023-02916-6

Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

Circular RNA circATP9A promotes non-small cell lung cancer progression by interacting with HuR and by promoting extracellular vesicles-mediated macrophage M2 polarization

Yuanshan Yao[1†], Chunji Chen[1†], Jing Wang[1†], Haojie Xuan[1†], Xiuxiu Chen[1†], Zheng Li[1], Fuzhi Yang[1], Bin Wang[1], Siyun Lin[1], Saitian Li[1], Dongfang Tang[1†], Libao Gong[2†] and Wen Gao[1*†]

Abstract

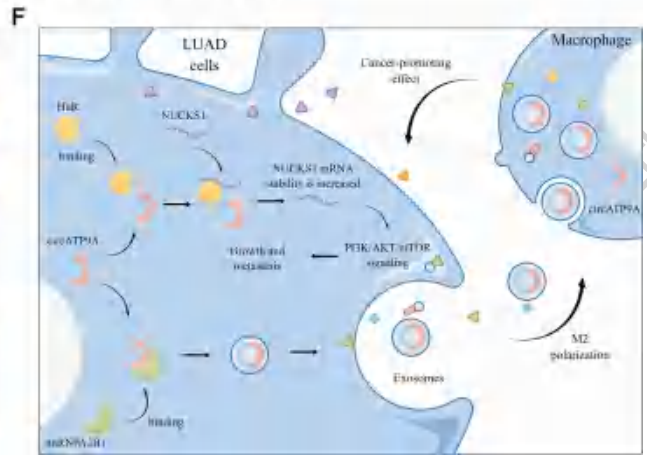
Background CircRNA is recognized for its significant regulatory function across various cancers. However, its regulatory role in non-small cell lung cancer (NSCLC) is still largely uncharted.

Methods Analysis based on public databases is completed using R software. circATP9A was identified by two circRNA datasets of NSCLC from the Gene Expression Omnibus database. To examine the impact of circATP9A on the phenotype of NSCLC, we conducted both in vitro and in vivo functional experiments. The mRNA and protein levels of specific molecules were determined through quantitative real-time PCR and western blot assays. RNA pulldown and RNA immunoprecipitation assays were performed to verify the interaction between RNA and protein. The functional role of extracellular vesicles (EVs)-circATP9A on tumor-associated macrophage (TAM) polarization was assessed using co-culture system and cell flow cytometry.

Results Here, we elucidates the functional role of circATP9A in NSCLC. We demonstrated that circATP9A can foster the progression of NSCLC through in vivo and in vitro experiments. From a mechanistic standpoint, circATP9A can interact with the HuR protein to form an RNA–protein complex, subsequently amplifying the mRNA and protein levels of the target gene NUCKS1. Further, the PI3K/AKT/mTOR signaling was identified as the downstream pathways of circATP9A/HuR/NUCKS1 axis. More notably, hnRNPA2B1 can mediate the incorporation of circATP9A into EVs. Subsequently, these EVs containing circATP9A induce the M2 phenotype of TAMs, thereby facilitating NSCLC development.

Conclusions Our discoveries indicate that circATP9A could serve as a promising diagnostic indicator and a therapeutic target for NSCLC.

Keywords NSCLC, circATP9A, Extracellular vesicles, HuR, Macrophages



Materials and Methods

Additionally, a **full-length circATP9A lentiviral vector**, also synthesized by **GenePharma**, was employed for circATP9A overexpression, with a control vector lacking any circATP9A sequence used as the reference group.

Yang *et al. J Exp Clin Cancer Res* (2023) 42:155
https://doi.org/10.1186/s13046-023-02698-x

Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

Epigenetic reprogramming-induced guanidinoacetic acid synthesis promotes pancreatic cancer metastasis and transcription-activating histone modifications

Jinshou Yang[1,2†], Bo Ren[1,2†], Jie Ren[1,2†], Gang Yang[1,2], Yuan Fang[1,2], Xing Wang[1,2], Feihan Zhou[1,2], Lei You[1,2*] and Yupei Zhao[1,2,3*]

Abstract

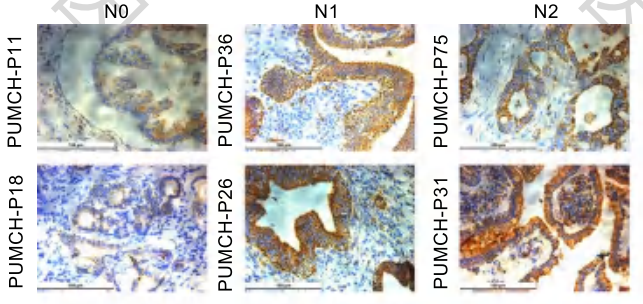
Background Pancreatic ductal adenocarcinoma (PDAC) tends to undergo distant metastasis, especially liver metastasis, leading to a poor prognosis. Metabolic remodelling and epigenetic reprogramming are two important hallmarks of malignant tumours and participate in regulating PDAC tumorigenesis and metastasis. However, the interaction between these two processes during PDAC metastasis has not been fully elucidated.

Methods We performed metabolomics analysis to identify the critical metabolites associated with PDAC liver metastasis and focused on guanidinoacetic acid (GAA). Intracellular GAA content was significantly increased in liver metastatic PDAC cells compared to primary cancer cells in mouse xenograft tumour models. The effects of GAA supplementation and glycine amidinotransferase (GATM) knockdown on PDAC metastasis were assessed by analysing cell migration, filopodia formation, epithelial-mesenchymal transition (EMT), and in vivo metastasis in different cell and animal models. Next, ChIP–qPCR, 3C–qPCR, and CRISPRi/dCas9-KRAB experiments were used to validate the "epigenome-metabolome" mechanism. Finally, the results of in vitro approaches, including RNA-seq, CUT&RUN, RT–qPCR, and western blot analyses, as well as luciferase reporter gene assay and transwell assay, revealed the GAA-c-Myc-HMGA axis and transcription-activating histone modifications reprogramming.

Results A high level of intracellular GAA was associated with PDAC liver metastasis. GAA could promote the migration, EMT, and liver metastasis of pancreatic cancer cells in vitro and in vivo. Next, we explored the role of GATM-mediated de novo GAA synthesis in pancreatic cancer metastasis. High expression of GATM was positively correlated with advanced N stage in PDAC. Knockdown of GATM significantly reduced the intracellular level of GAA, suppressed EMT, and inhibited PDAC liver metastasis, and these effects were attenuated by GAA supplementation. Mechanistically, we identified the active enhancers looped to the *Gatm* gene locus that promoted GATM expression and PDAC liver

Materials and Methods

Lenti-EF1a-dCas9-KRAB-Puro virus was commercially obtained from **GenePharma** Technology Co., Ltd. (Shang-hai, China).



Kong *et al. J Exp Clin Cancer Res* (2023) 42:45
https://doi.org/10.1186/s13046-023-02610-7

Journal of Experimental & Clinical Cancer Research

RESEARCH

Open Access

Procoxacin bidirectionally inhibits osteoblastic and osteoclastic activity in bone and suppresses bone metastasis of prostate cancer

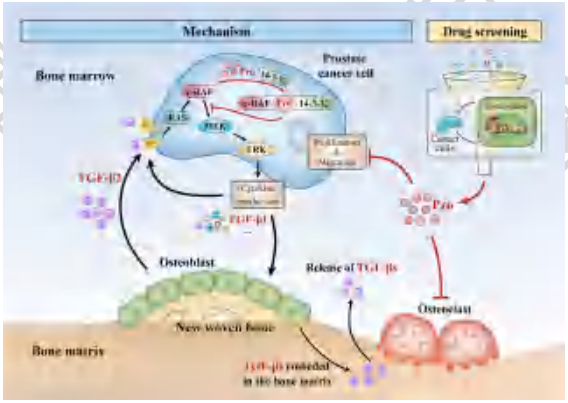
Depei Kong[1,2], Chen Ye[3], Chenxi Zhang[2], Xiaochen Sun[2], Fubo Wang[4], Rui Chen[3], Guangan Xiao[3], Shipeng He[2], Jianrong Xu[5,6], Xiwu Rao[7], Jianzhong Ai[1*], Xu Gao[3*], Hong Li[1*] and Li Su[2*]

Abstract

Background Bone is the most common site of metastasis of prostate cancer (PCa). PCa invasion leads to a disruption of osteogenic-osteolytic balance and causes abnormal bone formation. The interaction between PCa and bone stromal cells, especially osteoblasts (OB), is considered essential for the disease progression. However, drugs that effectively block the cancer-bone interaction and regulate the osteogenic-osteolytic balance remain undiscovered.

Methods A reporter gene system was constructed to screen compounds that could inhibit PCa-induced OB activation from 631 compounds. Then, the pharmacological effects of a candidate drug, Procoxacin (Pro), on OBs, osteoclasts (OCs) and cancer-bone interaction were studied in cellular models. Intratibial inoculation, micro-CT and histological analysis were used to explore the effect of Pro on osteogenic and osteolytic metastatic lesions. Bioinformatic analysis and experiments including qPCR, western blotting and ELISA assay were used to identify the effector molecules of Pro in the cancer-bone microenvironment. Virtual screening, molecular docking, surface plasmon resonance assay and RNA knockdown were utilized to identify the drug target of Pro. Experiments including co-IP, western blotting and immunofluorescence were performed to reveal the role of Pro binding to its target. Intracardiac inoculation metastasis model and survival analysis were used to investigate the therapeutic effect of Pro on metastatic cancer.

Results Luciferase reporter gene consisted of Runx2 binding sequence, OSE2, and *Alp* promotor could sensitively reflect the intensity of PCa-OB interaction. Pro best matched the screening criteria among 631 compounds in drug screening. Further study demonstrated that Pro effectively inhibited the PCa-induced osteoblastic changes without killing OBs or PCa cells and directly killed OCs or suppressed osteoclastic functions at very low concentrations. Mechanism study revealed that Pro broke the feedback loop of TGF-β/C-Raf/MAPK pathway by sandwiching into 14–3-3ζ/C-Raf complex and prevented its disassociation. Pro treatment alleviated both osteogenic and osteolytic lesions in PCa-involved bones and reduced the number of metastases of PCa in vivo.



Chen *et al. J Exp Clin Cancer Res* (2023) 42:36
https://doi.org/10.1186/s13046-023-02611-6

Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

Integrated multi-dimensional analysis highlights DHCR7 mutations involving in cholesterol biosynthesis and contributing therapy of gastric cancer

Yuqi Chen[1†], Wenying Yan[2†], Kexi Yang[1], Yiting Qian[1], Yanjun Chen[1], Ruoqin Wang[1], Jinghan Zhu[1], Yuxin He[1], Hongya Wu[3,4,5], Guangbo Zhang[3,4,5], Tongguo Shi[1,3,4,5*] and Weichang Chen[1,3,4,5*]

Abstract

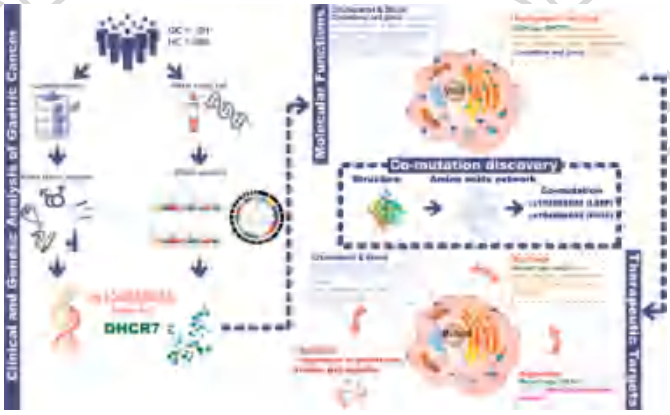
Background Genetic background plays an important role in the occurrence and development of gastric cancer (GC). With the application of genome-wide association study (GWAS), an increasing number of tumor susceptibility genes in gastric cancer have been discovered. While little of them can be further applicated in clinical diagnosis and treatment due to the lack of in-depth analysis.

Methods A GWAS of peripheral blood leukocytes from GC patients was performed to identify and obtain genetic background data. In combination with a clinical investigation, key SNP mutations and mutated genes were screened. Via in vitro and in vivo experiments, the function of the mutated gene was verified in GC. Via a combination of molecular function studies and amino acid network analysis, co-mutations were discovered and further identified as potential therapeutic targets.

Results At the genetic level, the G allele of rs104886038 in DHCR7 was a protective factor identified by the GWAS. Clinical investigation showed that patients with the rs104886038 A/G genotype, age ≥ 60, smoking ≥ 10 cigarettes/day, heavy drinking and *H. pylori* infection were independent risk factors for GC, with odds ratios of 12.33 (95% CI, 2.10 ~ 72.54), 20.42 (95% CI, 2.46 ~ 169.83), and 11.39 (95% CI, 1.82 ~ 71.21), respectively. Then molecular function studies indicated that DHCR7 regulated cell proliferation, migration, and invasion as well as apoptosis resistance via cellular cholesterol biosynthesis pathway. Further amino acid network analysis based on the predicted structure of DHCR7 and experimental verification indicated that rs104886035 and rs104886038 co-mutation reduced the stability of DHCR7 and induced its degradation. DHCR7 mutation suppressed the malignant behaviour of GC cells and induced apoptosis via inhibition on cell cholesterol biosynthesis.

Conclusion In this work, we provided a comprehensive multi-dimensional analysis strategy which can be applied to in-depth exploration of GWAS data. DHCR7 and its mutation sites identified by this strategy are potential theratic targets of GC via inhibition of cholesterol biosynthesis.

JOURNAL OF EXPERIMENTAL & CLINICAL CANCER RESEARCH
2023 Jan; 42:36
Impact Factor: 11.3



Materials and Methods

Lentiviruses carrying DHCR7 cDNA or DHCR7 short hairpin RNA (shRNA) containing the sequence of DHCR7-siRNA-1 were purchased from Shanghai **GeneP-harma** .

Zhang et al. Journal of Experimental & Clinical Cancer Research (2021) 40:200
https://doi.org/10.1186/s13046-021-01994-8

Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

RNA-binding protein IMP3 is a novel regulator of MEK1/ERK signaling pathway in the progression of colorectal Cancer through the stabilization of MEKK1 mRNA

Meng Zhang[1,2,3†], Senlin Zhao[3,4†], Cong Tan[1,2,3†], Yanzi Gu[2,3,5], Xuefeng He[3,4], Xiang Du[1,2,3*], Dawei Li[3,4*] and Ping Wei[1,2,3,6*]

Abstract

Background: MEK1/ERK signaling pathway plays an important role in most tumor progression, including colorectal cancer (CRC), however, MEK1-targeting therapy has little effective in treating CRC patients, indicating there may be a complex mechanism to activate MEK1/ERK signaling pathway except RAS activated mechanism.

Methods: To investigate the clinical significance of IMP3, we analyzed its expression levels in publicly available dataset and samples from Fudan University Shanghai Cancer Center. The effects of IMP3 on proliferation, migration, and invasion were determined by in vitro and in vivo experiments. To investigate the role of IMP3 in colon carcinogenesis, conditional IMP3 knockout C57BL/6 mice was generated. The IMP3/MEKK1/MEK/ERK signaling axis in CRC was screened and validated by RNA-sequencing, RNA immunoprecipitation, luciferase reporter and western blot assays.

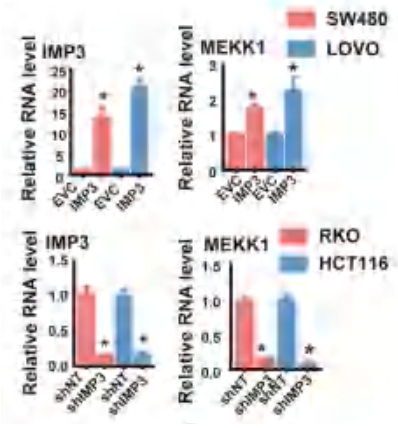
Results: We find RNA binding protein IMP3 directly bind to MEKK1 mRNA 3′-UTR, which regulates its stability, promote MEKK1 expression and sequentially activates MEK1/ERK signaling. Functionally, IMP3 promote the malignant biological process of CRC cells via MEKK1/MEK1/ERK signaling pathway both in vitro and in vivo, Moreover, IMP3−/− mice show decreased the expression of MEKK1 as well as colorectal tumors compared with wild-typemiceaftertreatmentwith azoxymethane/dextran sodium sulfate. Clinically, the expression of IMP3 and MEKK1 are positive correlated, and concomitant IMP3 and MEKK1 protein levels negatively correlate with metastasis in CRC patients. In addition, MEK1 inhibitor in combination with shRNA-IMP3 have a synergistic effect both in vitro and in vivo.

Keywords: IMP3, MEK1/ERK pathway, MEKK1, Colorectal Cancer

Journal of Experimental & Clinical Cancer Research
2021 Jun 21; 40:200
Impact Factor: 11.3

Materials and Methods

The human full cDNA sequence of **IMP3 and MEKK1** was purchased from **GenePharma** (China). **lentiviruses of IMP3-shRNA and non-target control, lentiviruses of IMP3, MEKK1 and empty vector control** were also pur-chased from **GenePharma** (China).



Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

LncRNA CARMN overexpression promotes prognosis and chemosensitivity of triple negative breast cancer via acting as miR143-3p host gene and inhibiting DNA replication

Xiaonan Sheng†, Huijuan Dai†, Yueyao Du†, Jing Peng, Rui Sha, Fan Yang, Liheng Zhou, Yanping Lin, Shuguang Xu, Yifan Wu, Wenjin Yin* and Jinsong Lu*

Abstract

Background: Triple negative breast cancer (TNBC) is a subtype of breast cancer with poor prognosis and lack of effective treatment target. Here we screened differentially expressed lncRNAs through bioinformatics analysis and identified CARMN as a downregulated lncRNA which is lowest expressed in TNBC. We aimed to identify the potential role and molecular mechanisms of CARMN in TNBC.

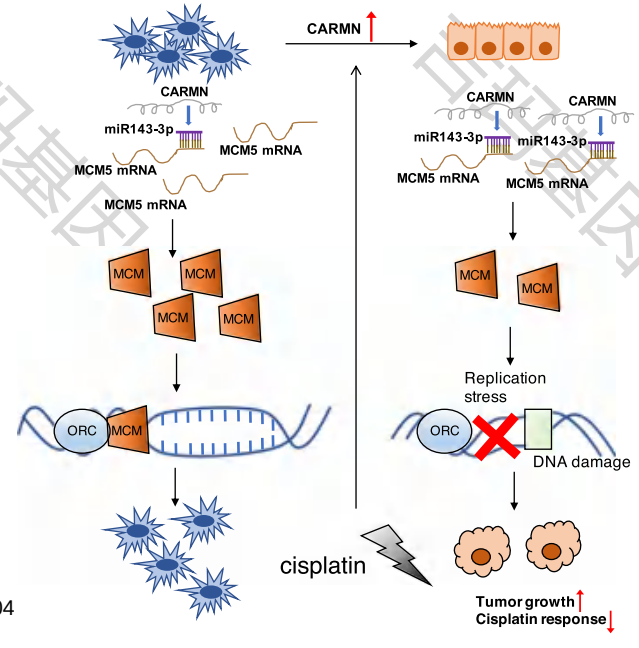
Methods: Predictive value of CARMN was explored in breast cancer cohorts. TNBC cell lines with CARMN overexpression or CARMN silence and were used for in vitro and in vivo experiments. RNA-seq of CARMN overexpressed cells was performed for exploring downstream of CARMN.

Results: CARMN is downregulated at different phase of malignant transformation of breast tissue. CARMN can predict both better prognosis and higher response rate of cisplatin-based neoadjuvant chemotherapy in breast cancer. A nomogram is built to predict cisplatin-based chemotherapy response in breast cancer. Through in vitro and in vivo studies, we confirmed CARMN can also inhibit tumorigenesis and enhance sensitivity to cisplatin in TNBC cells. RNA-seq and further experiments revealed CARMN can inhibit DNA replication. MCM5, an important DNA replication initiation factor, is the most downregulated gene in DNA replication pathway following CARMN overexpression. We confirmed CARMN can produce miR143-3p from its exon5 which is DROSHA and DICER dependent, resulting binding and decrease of MCM5. Moreover, suppressing miR143-3p can weaken function of CARMN in suppressing tumorigenesis and promoting chemosensitivity.

Journal of Experimental &Clinical Cancer Research
2021 Jun 23; 40:205
Impact Factor: 11.3

Materials and Methods

Cells were transfected with **lentivirus vectors overex-pressing CARMN or control ones** (purchased from **GenePharma** Shanghai, China) for stably overexpressing CARMN.



Journal for ImmunoTherapy of Cancer

ANKRD22 is a potential novel target for reversing the immunosuppressive effects of PMN-MDSCs in ovarian cancer

Huanhuan Chen, Keqing Yang, Lingxiao Pang, Jing Fei, Yongliang Zhu , Jianwei Zhou

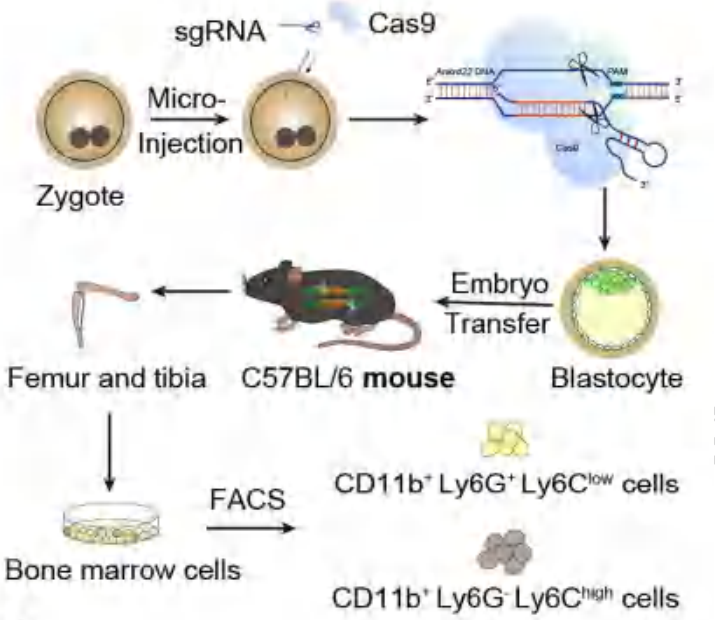
ABSTRACT

Background Ovarian cancer is the deadliest type of malignant gynecological tumor. Polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) are involved ovarian cancer and are closely related to adverse outcomes. However, the immunosuppressive mechanism of PMN-MDSCs remains elusive.

Methods The types and numbers of ANKRD22-expressing cells were investigated by bioinformatics analysis and immunohistochemical staining. *Ankrd22*$^{-/-}$ C57BL/6 mice were constructed with CRISPR-Cas9 technology. Mouse PMN-MDSCs were obtained from bone marrow (BM)- derived CD11b^{+}Ly6G^{+}Ly6C^{low} cells sorted by fluorescence- activated cell sorting with treatment of GM-CSF and IL-6, and the immunosuppressive activity of PMN-MDSCs
was evaluated by flow cytometry (FCM) and ELISA. The expression level of CCR2 and the exogenous glucose uptake capacity were determined by FCM. RT- qPCR was used to detect *ANKRD22* expression in CD11b^{+}HLA- DR^{-}CD14^{-}CD15^{+} cells from human ovarian cancer tissues, and the correlations of *ANKRD22* expression with the clinical characteristics and prognosis of patients were evaluated by the χ^2 test.

Results We identified a novel protein involved in regulating the immunosuppressive ability of PMN- MDSCs, ANKRD22. *Ankrd22* expression was high
in mouse CD11b^{+}Ly6G^{+}Ly6C^{low} cells and could be significantly downregulated after exposure to a
simulated microenvironmental stimulus. Knockout of *Ankrd22* increased the expression level of CCR2 of CD11b^{+}Ly6G^{+}Ly6C^{low} cells and the immunosuppressive activity of PMN-MDSCs. BM-derived CD11b^{+}Ly6G^{+}Ly6C^{low} cells of *Ankrd22*$^{-/-}$ mice significantly promoted the proliferation of ovarian cancer cells in tumor xenograft mouse models. Mechanistically, RNA sequencing showed that *Wdfy1* expression was obviously increased in *Ankrd22*-knockout BM-derived CD11b^{+}Ly6G^{+} Ly6C^{low} cells and that ectopic expression of *Wdfy1* increased the levels of *Arg1*, *Inos*, *Ido* and *Pdl1* in *Ankrd22*$^{+/+}$ PMN-MDSCsderived from BM-derived CD11b^{+}Ly6G^{+}Ly6C^{low} cells. Surprisingly, an ANKRD22-activating candidate small- molecule compound attenuated the immunosuppressive activity of *Ankrd22*$^{+/+}$ PMN-MDSCs. Finally, we found that low *ANKRD22* levels in CD11b^{+}HLA-DR^{-}CD14^{-}CD15^{+} cells derived from primary ovarian tissues were associated with a more advanced International Federation of Gynecology and Obstetrics stage, a higher recurrence rate, and a higher neutrophil- to- lymphocyte ratio.

Conclusions These results suggest that ANKRD22 is a potential novel target for reversing the immunosuppressive effects of PMN- MDSCs.



Journal for ImmunoTherapy of Cancer
2023 Feb; 11:e005527
Impact Factor: 10.9

Materials and Methods

Construction and production of the **recombinant lentivirus** expressing Ankrd22 and Mlixp was performed by **GenePharma** Corporation.

Journal of Controlled Release 358 (2023) 142–160

Contents lists available at ScienceDirect

Journal of Controlled Release

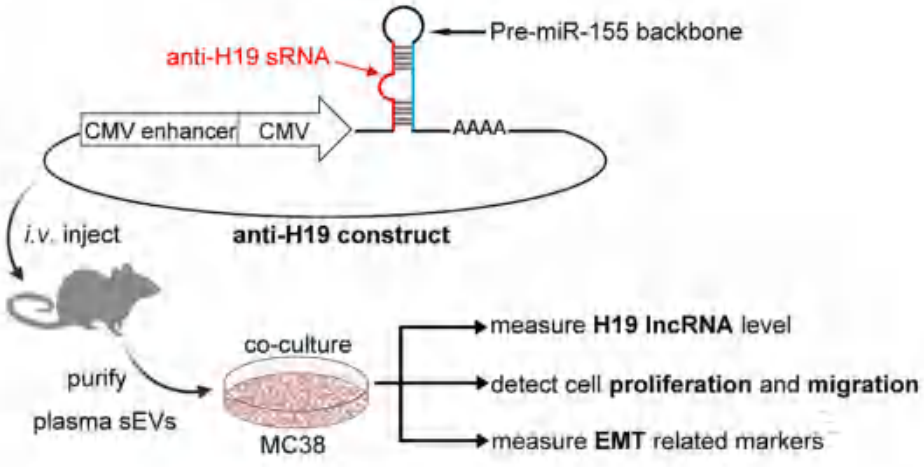
journal homepage: www.elsevier.com/locate/jconrel

In vivo self-assembled small RNA targets H19 lncRNA for the treatment of colorectal cancer

Ying Sun [a,1], Yixuan Zhao [a,1], Xue Ni [a,1], Yixuan Yang [a,1], Zheng Fu [a,b,*], Rui Liu [c,**], Chen-Yu Zhang [a,d,e,f,*], Xi Chen [a,b,e,f,*]

A B S T R A C T

The majority of molecularly targeted therapies in clinical use target disease-related proteins, but only a small fraction (~1.5%) of human genome is protein-coding region. Considering that ~70% of human genome is transcribed to noncoding RNAs, targeting noncoding RNAs rather than protein-coding RNAs can significantly expand the proportion of human genome that can be manipulated. H19 long noncoding RNA (lncRNA) is aberrantly expressed in a variety of cancer types and actively contributes to multiple steps of tumorigenesis. Therefore, we selected H19 as a representative target and designed synthetic anti-H19 construct for the self- assembly and delivery of anti-H19 small RNA (sRNA) to prevent colorectal cancer development and metas-tasis based on the natural ability of the host liver to package sRNA-encapsulating small extracellular vesicles (sEVs) and the endogenous circulating sEVs to transfer sRNA. As anticipated, the synthetic anti-H19 construct successfully generated anti-H19 sRNA-encapsulating sEVs and exhibited high silencing efficiency on H19 lncRNA in an *ex vivo* model. In orthotopic and lung metastasis mouse models of colorectal cancer, the anti-H19 construct exhibited significantly superior therapeutic efficacy over 5-fluorouracil (5-Fu) in preventing primary tumor growth and lung metastasis. Particularly, the anti-H19 sRNA-encapsulating sEVs were generated in a nontoxic, nonimmunogenic and biocompatible manner. In summary, this study demonstrates that the *in vivo* self-assembled anti-H19 sRNA can serve as a new therapeutic agent for colorectal cancer.



JOURNAL OF CONTROLLED RELEASE
2023 Apr 30;358;142–160
Impact Factor: 10.8

Materials and Methods

The **luciferase-encoding lentiviral vector** pLv-Luc with puromycin resistance gene were bought from **GenePharma** (Shanghai, China).

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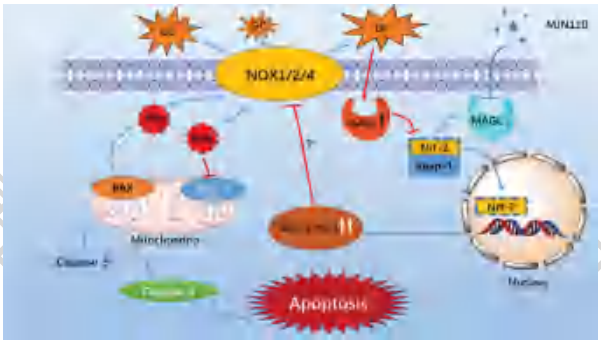
DOI: 10.1002/ctm2.447

RESEARCH ARTICLE

Inhibition of MAGL activates the Keap1/Nrf2 pathway to attenuate glucocorticoid-induced osteonecrosis of the femoral head

Abstract

Glucocorticoids (GCs) are used in treating viral infections, acute spinal cord injury, autoimmune diseases, and shock. Several patients develop GC-induced osteonecrosis of the femoral head (ONFH). However, the pathogenic mecha-nisms underlying GC-induced ONFH remain poorly understood. GC-directed bone marrow mesenchymal stem cells (BMSCs) fate is an important factor that determines GC-induced ONFH. At high concentrations, GCs induce BMSC apoptosis by promoting oxidative stress. In the present study, we aimed to elu-cidate the molecular mechanisms that relieve GC-induced oxidative stress in BMSCs, which would be vital for treating ONFH. The endocannabinoid system regulates oxidative stress in multiple organs. Here, we found that monoacylglyc-erol lipase (MAGL), a key molecule in the endocannabinoid system, was sig-nificantly upregulated during GC treatment in osteoblasts both in vitro and in vivo. MAGL expression was positively correlated with expression of the NADPH oxidase family and apoptosis-related proteins. Functional analysis showed that MAGL inhibition markedly reduced oxidative stress and partially rescued BMSC apoptosis. Additionally, in vivo studies indicated that MAGL inhibition effec-tively attenuated GC-induced ONFH. Pathway analysis showed that MAGL inhi-bition regulated oxidative stress in BMSCs via the Kelch-like ECH-associated protein 1 (Keap1)/nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. The expression of Nrf2, a major regulator of intracellular antioxidants, was upregu-lated by inhibiting MAGL. Nrf2 activation can mimic the effect of MAGL inhi-bition and significantly reduce GC-induced oxidative damage in BMSCs. The beneficial effects of MAGL inhibition were attenuated after the blockade of the Keap1/Nrf2 antioxidant signaling pathway. Notably, pharmacological blockade of MAGL conferred femoral head protection in GC-induced ONFH, even after oxidative stress responses were initiated. Therefore, MAGL may represent a novel target for the prevention and treatment of GC-induced ONFH.



CLINICAL AND TRANSLATIONAL MEDICINE
2021 Jun 2; 11:e447
Impact Factor: 10.6

Materials and Methods

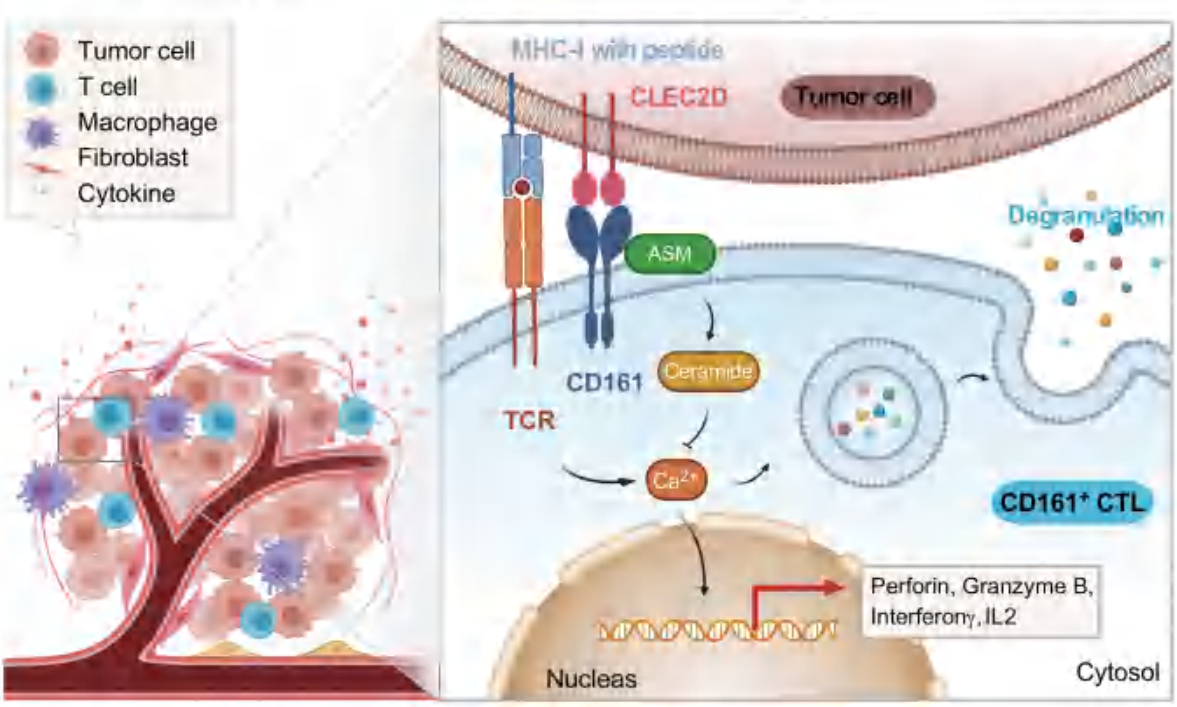
A lentiviral vector [LV3 (H1/GFP&Puro)] encoding shMAGL was obtained from **GenePharma**. **siRNA** (RNA oligo) and **overexpression plasmids** (pcDNA3.1) were provided by **GenePharma**.

CD8$^+$ T cell–Dependent Remodeling of the Tumor Microenvironment Overcomes Chemoresistance

Liyan Lao[1,2,3], Wenfeng Zeng[1,2,3], Penghan Huang[1,2,3], Huiping Chen[1,2,3], Zishuo Jia[1,2,3], Pei Wang[1,2,3], Di Huang[1,2,3], Jianing Chen[1,2,3], Yan Nie[1,2,3], Linbin Yang[1,2,3], Wei Wu[1,2,3], and Jiang Liu[1,2,3]

ABSTRACT

The therapeutic efficacy of chemotherapy is in part a result of its ability to enhance adaptive antitumor immune responses. However, tumor cells exploit various evasion mechanisms to escape the immune attack and blunt chemosensitivity. Herein, we report that through single-cell profiling of the tumor immune microenvironment, we identified a subset of CD161-overexpressing CD8+ T cells enriched in chemoresistant tumors. CD161 engagement repressed the calcium influx and cytolytic capacity of CD8+ T cells through acid sphingomyelinase activation and ceramide generation. Targeting CD161 in adoptively transferred cytotoxic T lymphocytes enhanced antitumor immunity and reversed chemoresistance in patient-derived xenografts in vivo. Clinically, CD161 expression on CD8+ T cells was associated with chemoresistance and shortened patient survival. Our findings provide insights into novel immunosuppressive mechanisms in chemoresistance and highlight targeting CD161 as a potential therapeutic strategy.



Cancer Immunology Research
2023 Mar 1;11(3): 320–338.
Impact Factor: 10.1

Materials and Methods

Lentivirus packaging was provided by **GenePharma** Inc using LV3/LV5 lentiviral vectors. Freshly isolated human T cells or ESO CTLs were transduced with the **Cas9 lentivirus and CD161 gRNA1/2 lentivirus** purchased from **GenePharma**.
Lentivirus containing shRNAs against acid sphingomyelinase (ASM) were constructed by **GenePharma**.

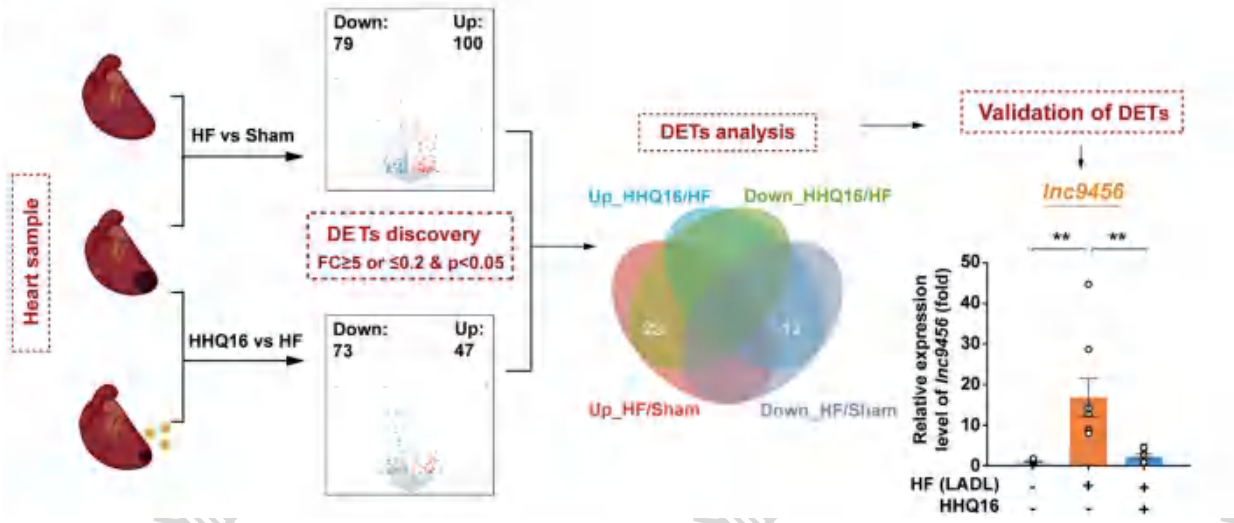
www.nature.com/sigtrans

ARTICLE OPEN

Astragaloside IV derivative HHQ16 ameliorates infarction-induced hypertrophy and heart failure through degradation of lncRNA4012/9456

Jingjing Wan[1], Zhen Zhang[1], Chennan Wu[1], Saisai Tian[1], Yibei Zang[1], Ge Jin[1], Qingyan Sun[2], Pin Wang[3], Xin Luan[4], Yili Yang[5], Xuelin Zhan[5,6], Lingyu Linda Ye[7], Dayue Darrel Duan[7,8]✉, Xia Liu[1]✉ and Weidong Zhang[1,9]✉

Reversing ventricular remodeling represents a promising treatment for the post-myocardial infarction (MI) heart failure (HF). Here, we report a novel small molecule HHQ16, an optimized derivative of astragaloside IV, which effectively reversed infarction-induced myocardial remodeling and improved cardiac function by directly acting on the cardiomyocyte to reverse hypertrophy. The effect of HHQ16 was associated with a strong inhibition of a newly discovered Egr2-affiliated transcript lnc9456 in the heart. While minimally expressed in normal mouse heart, lnc9456 was dramatically upregulated in the heart subjected to left anterior descending coronary artery ligation (LADL) and in cardiomyocytes subjected to hypertrophic stimulation. The critical role of lnc9456 in cardiomyocyte hypertrophy was confirmed by specific overexpression and knockout in vitro. A physical interaction between lnc9456 and G3BP2 increased NF-κB nuclear translocation, triggering hypertrophy-related cascades. HHQ16 physically bound to lnc9456 with a high-affinity and induced its degradation. Cardiomyocyte-specific lnc9456 overexpression induced, but knockout prevented LADL-induced, cardiac hypertrophy and dysfunction. HHQ16 reversed the effect of lnc9456 overexpression while lost its protective role when lnc9456 was deleted, further confirming lnc9456 as the bona fide target of HHQ16. We further identified the human ortholog of lnc9456, also an Egr2-affiliated transcript, lnc4012. Similarly, lnc4012 was significantly upregulated in hypertrophied failing hearts of patients with dilated cardiomyopathy. HHQ16 also specifically bound to lnc4012 and caused its degradation and antagonized its hypertrophic effects. Targeted degradation ofpathological increased lnc4012/lnc9456 by small molecules might serve as a novel promising strategy to regress infarction-induced cardiac hypertrophy and HF.



Signal Transduction and Targeted Therapy
2023 Oct 19;8(1):414
Impact Factor: 39.3

Materials and Methods

The **overexpression plasmid** of lnc9456 or lnc4012 and their negative control vectors were constructed by **GenePharma**.
plasmids were transfected by **GP-transfect-Mate** (**GenePharma**).
The **adenovirus** harboring lnc9456 (AdV-lnc9456) was also constructed by **GenePharma**.

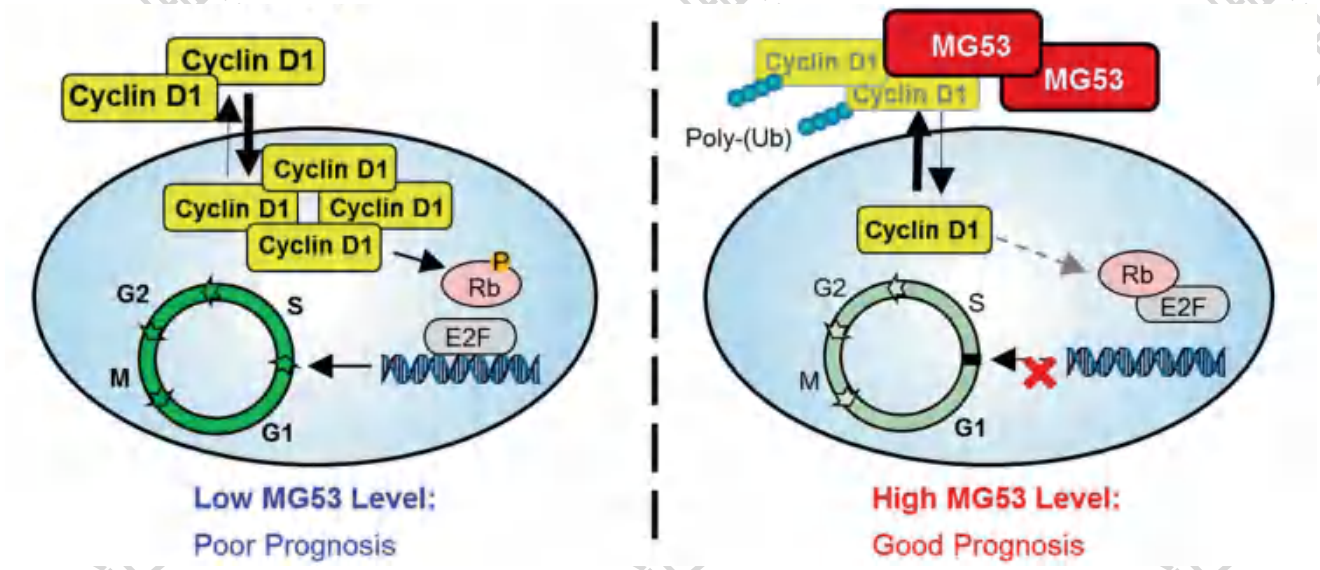
ARTICLE OPEN

E3 ligase MG53 suppresses tumor growth by degrading cyclin D1

Meng Fang[1,2], Hong-Kun Wu[3,4], Yumeng Pei[1,2], Yan Zhang[1,5], Xiangyu Gao[6], Yanyun He[1,2], Gengjia Chen[1], Fengxiang Lv[1,5], Peng Jiang[1], Yumei Li[1], Wenwen Li[1], Peng Jiang[7], Lin Wang[8], Jiafu Ji[6]✉, Xinli Hu[1,5]✉ and Rui-Ping Xiao[1,2,5]✉

Due to the essential role of cyclin D1 in regulating transition from G1 to S phase in cell cycle, aberrant cyclin D1 expression is a major oncogenic event in many types of cancers. In particular, the dysregulation of ubiquitination-dependent degradation of cyclin D1 contributes to not only the pathogenesis of malignancies but also the refractory to cancer treatment regiments with CDK4/6 inhibitors. Here we show that in colorectal and gastric cancer patients, MG53 is downregulated in more than 80% of tumors compared to the normal gastrointestinal tissues from the same patient, and the reduced MG53 expression is correlated with increased cyclin D1 abundance and inferior survival. Mechanistically, MG53 catalyzes the K48-linked ubiquitination and subsequent degradation of cyclin D1. Thus, increased expression of MG53 leads to cell cycle arrest at G1, and thereby markedly suppresses cancer cell proliferation in vitro as well as tumor growth in mice with xenograft tumors or AOM/DSS induced-colorectal cancer. Consistently, MG53 deficiency results in accumulation of cyclin D1 protein and accelerates cancer cell growth both in culture and in animal models. These findings define MG53 as a tumor suppressor via facilitating cyclin D1 degradation, highlighting the therapeutic potential of targeting MG53 in treating cancers with dysregulated cyclin D1 turnover.

Signal Transduction and Targeted Therapy (2023)8:263 ; https://doi.org/10.1038/s41392-023-01458-9



Signal Transduction and Targeted Therapy
2023 July;8:263
Impact Factor: 39.3

Materials and Methods

When cells reached 90% confluency, gene transfer was performed by **adenoviral or lentiviral infection** (Suzhou **GenePharma**), or plasmid transfection using Lipofecta-mine 3000TM (Invitrogen, L3000015).

IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2019; 9(15): 4558-4566. doi: 10.7150/thno.31052

Research Paper

LncRNA DCRF regulates cardiomyocyte autophagy by targeting miR-551b-5p in diabetic cardiomyopathy

Yu Feng[1,2,#], Weiting Xu[3,#], Wei Zhang[3,#], Wenjing Wang[3], Tong Liu[2], Xiang Zhou[3,✉]

Abstract

Background: We generated a rat model of diabetic cardiomyopathy (DCM) and reported significant upregulation of the long non-coding RNA DCRF. This study was designed to determine the molecular mechanisms of DCRF in the development of DCM.

Methods: Real-time PCR and RNA fluorescent in situ hybridization were conducted to detect the expression pattern of DCRF in cardiomyocytes. Histological and echocardiographic analyses were used to assess the effect of DCRF knockdown on cardiac structure and function in diabetic rats. mRFP-GFP-LC3 fluorescence microscopy, transmission electron microscopy, and Western blotting were carried out to determine cardiomyocyte autophagy. RNA immunoprecipitation and luciferase reporter assays were performed to elucidate the regulatory role of DCRF/miR-551b-5p/PCDH17 pathway in cardiomyocyte autophagy.

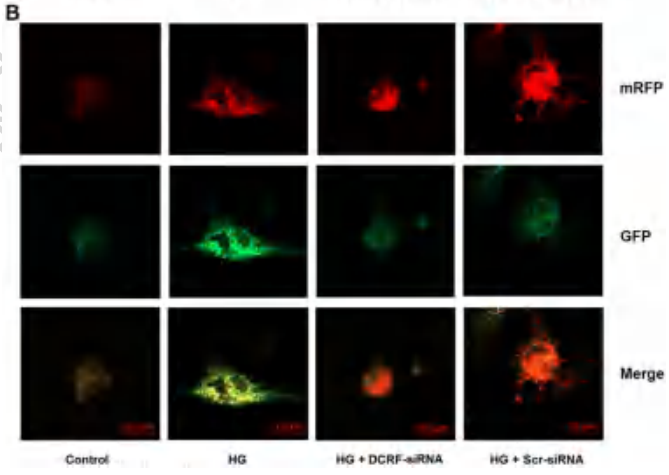
Results: Our findings showed that DCRF knockdown reduced cardiomyocyte autophagy, attenuated myocardial fibrosis, and improved cardiac function in diabetic rats. High glucose increased DCRF expression and induced autophagy in cardiomyocytes. RNA immunoprecipitation and luciferase reporter assays indicated that DCRF was targeted by miR-551b-5p in an AGO2-dependent manner and PCDH17 was the direct target of miR-551b-5p. Forced expression of DCRF was found to attenuate the inhibitory effect of miR-551b-5p on PCDH17. Furthermore, DCRF knockdown decreased PCDH17 expression and suppressed autophagy in cardiomyocytes treated with high glucose.

Conclusion: Our study suggests that DCRF can act as a competing endogenous RNA to increase PCDH17 expression by sponging miR-551b-5p, thus contributing to increased cardiomyocyte autophagy in DCM.

Keywords: autophagy; DCRF; diabetic cardiomyopathy; miR-551b-5p

Materials and Methods

Myocardial cells were transfected with **adenovirus expressing mRFP-GFP-LC3** (**GenePharma**, Suzhou, China) at 10 MOI for 24 h and were observed under a confocal laser scanning microscope (LSM 510; Carl Zeiss, Germany).



Journal of Advanced Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Advanced Research

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

Original Manuscript

Kaempferol alleviates myocardial ischemia injury by reducing oxidative stress via the HDAC3-mediated Nrf2 signaling pathway

Zejun Yue [a,b,1], Yirong Zhang [a,b,1], Wei Zhang [c], Nanbo Zheng [d], Jiazheng Wen [a,b], Lingxuan Ren [d], Xiaoyu Rong [a,b], Liang Bai [a,b], Rong Wang [a,b], Sihai Zhao [a,b], Enqi Liu [a,b], Weirong Wang [a,b,*]

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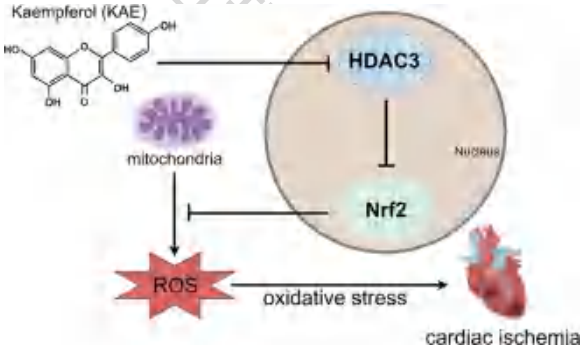
[b] Laboratory Animal Center, Xi'an Jiaotong University, Xi'an 710061, China
[c] Department of Cardiovascular Surgery, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China
[d] Department of Pharmacology, Xi'an Jiaotong University Health Science Center, Xi'an 710061, China

highlights

- KAE alleviates myocardial ischemia injury and improves cardiac function in rats.
- KAE attenuates myocardial injury and oxidative stress by inhibiting HDAC3.
- KAE protects against myocardial ischemia via HDAC3-mediated Nrf2 signaling pathway.

graphical abstract



abstract

Introduction: Kaempferol (KAE) is a flavonoid found in various plants. Recent studies showed that high dietary intake of KAE was associated with a lower risk of myocardial infarction; however, the cardioprotective mechanism of KAE remains unknown.

Objectives: To determine the effect of KAE on cardiac injury in isoproterenol (ISO)-induced rats and cobalt chloride ($CoCl_2$)-treated cardiomyocytes, and the underlying mechanisms.

Methods: Male rats were pretreated with different doses of KAE for 14 days, and then injected with ISO to induce myocardial ischemia injury. We also established a model of myocardial cell injury using rat H9c2 cardiomyocytes stimulated with $CoCl_2$.

Results: We found that KAE pretreatment significantly alleviated myocardial injury and improved cardiac function in ISO-injected rats. In addition, KAE reduced oxidative stress in rats with myocardial ischemia by decreasing malondialdehyde concentration and increasing superoxide dismutase activity, and protection of the myocardial mitochondrial structure. KAE also attenuated $CoCl_2$-induced injury of H9c2 cardiomyocytes via suppression of oxidative stress. With regard to the mechanism, we found that KAE down-regulated HDAC3 expression and up-regulated Nrf2 expression in ISO-induced rats and $CoCl_2$-stimulated cardiomyocytes. Incubation of cardiomyocytes with HDAC3-selective inhibitor RGFP966 augmented the protective effect of KAE and reduced oxidative stress. By contrast, HDAC3 overexpression by adenovirus attenuated the effect of KAE on oxidative stress compared with KAE treatment group. HDAC3 also regulated Nrf2 expression in the cardiomyocytes with RGFP966 or an adenovirus overexpressing HDAC3; but Nrf2 inhibition reduced the effect of KAE on ROS generation in $CoCl_2$-induced

Journal of Advanced Research
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Impact Factor: 11.4

Materials and Methods

HDAC3 **adenovirus (Ad-HDAC3)** and control **adenovirus (Ad-GFP)** were purchased by **GenePharma** (Shanghai, China).

Redox Biology 45 (2021) 102051

Contents lists available at ScienceDirect

Redox Biology

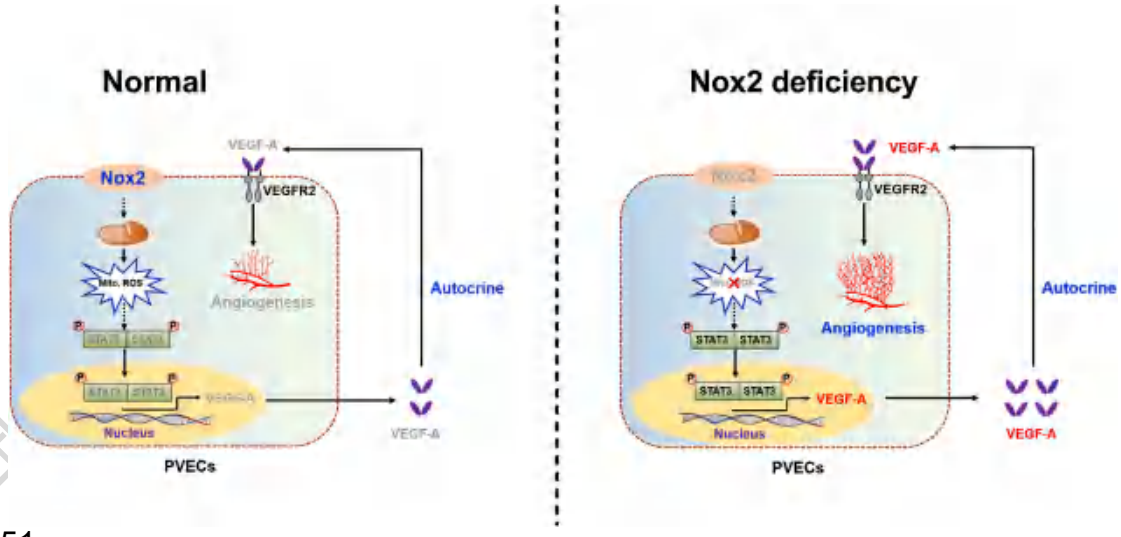
journal homepage: www.elsevier.com/locate/redox

Nox2 impairs VEGF-A-induced angiogenesis in placenta *via* mitochondrial ROS-STAT3 pathway

Chengjun Hu [a,b], Zifang Wu [a], Zihao Huang [a], Xiangyu Hao [a], Shuqi Wang [a], Jinping Deng [a], Yulong Yin [c], Chengquan Tan [a,]

Abstract

Aberrant placental angiogenesis is associated with fetal intrauterine growth restriction (IUGR), but the mecha-nism underlying abnormal placental angiogenesis remains largely unknown. Here, lower vessel density and higher expression of NADPH oxidases 2 (Nox2) were observed in the placentae for low birth weight (LBW) fe-tuses versus normal birth weight (NBW) fetuses, with a negative correlation between Nox2 and placental vessel density. Moreover, it was revealed for the first time that Nox2 deficiency facilitates angiogenesis in vitro and in vivo, and vascular endothelial growth factor-A (VEGF-A) has an essential role in Nox2-controlled inhibition of angiogenesis in porcine vascular endothelial cells (PVECs). Mechanistically, Nox2 inhibited phospho-signal transducer and activator of transcription 3 (p-STAT3) in the nucleus by inducing the production of mitochon-drial reactive oxygen species (ROS). Dual-luciferase assay confirmed that knockdown of Nox2 reduces the expression of VEGF-A in an STAT3 dependent manner. Our results indicate that Nox2 is a potential target for therapy by increasing VEGF-A expression to promote angiogenesis and serves as a prognostic indicator for fetus with IUGR.



Redox Biology
2021 Jun 18; 102051
Impact Factor: 11.4

Materials and Methods

The **siRNA** was purchased from **GenePharma** Co., Ltd (Shanghai, China).
The **Ad-Nox2 adenovirus** was generated from **GenePharma** Co., Ltd. (Shanghai, China).

病毒——腺相关病毒

RESEARCH Open Access

CircMYH9 drives colorectal cancer growth by regulating serine metabolism and redox homeostasis in a p53-dependent manner

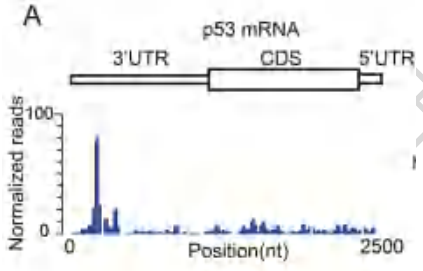
Xin Liu[1,2†], Yunze Liu[2,3†], Zhao Liu[4†], Changwei Lin[4,5†], Fanchao Meng[4], Lei Xu[4], Xiuzhong Zhang[4], Chong Zhang[4], Penbo Zhang[4], Shuai Gong[4], Nai Wu[4], Zeqiang Ren[4], Jun Song[4] and Yi Zhang[2,4*]

Abstract

Background: Circular RNAs (circRNAs) play important roles in cancer progression and metabolism regulation. Serine/glycine metabolism supports the growth of cancer cells by contributing to their anabolic demands and epigenome as well as by regulating their redox state. However, the role of circRNA in the regulation of serine/glycine metabolism has not been well elucidated.

Methods: Microarray analysis was used to screen differentially expressed novel circRNAs. qRT-PCR and FISH were utilized to analyzed the expression of circMYH9. CCK8, colony formation and FACS were used to analyze proliferation of colorectal cancer (CRC) cells. Xenograft experiments were used to analyze tumor growth in vivo. RNA-sequencing, immunoblot and LC–MS were used to identify the downstream metabolic pathway of circMYH9. ChIRP, Mass Spec-trometry, RIP and RNA pulldown were utilized to test the interaction between circMYH9, hnRNPA2B1 and p53 pre-mRNA. ChIP-qPCR was used to analyze the binding sites of HIF-1α. Chemically-induced CRC mice were generated to evaluate the role of circMYH9 in tumorigenesis.

Results: We identified an intron-derived circRNA, circMYH9, which was significantly upregulated in CRC tissues. A higher circMYH9 level correlated with shorter relapse-free survival and overall survival of CRC patients. CircMYH9 pro-moted serine/glycine metabolism, the NAD + /NADH ratio, and glutathione recycling and inhibited reactive oxygen species (ROS) in a p53-dependent manner, impacting tumour growth. Mechanistically, circMYH9 destabilized the pre-mRNA of p53 by recruiting hnRNPA2B1 in the nucleus. hnRNPA2B1 bound to N6-methyladenosine sites on the 3' untranslated region of p53 pre-mRNA and maintained its stability. Moreover, a lack of amino acids led to an elevated level of ROS, resulting in increased HIF1α, which promoted circMYH9 expression by binding to the promoter region. Furthermore, in vivo AAV9-mediated transfection of circMYH9 could drive chemically-induced carcinogenesis by sup-pressing p53 in mice.



Molecular Cancer
2021 Dec;20(1):1-19
Impact Factor: 37.3

Materials and Methods

Short interfering RNA (siRNA) sequences were directly synthesized (**GenePharma**). For **overexpression of circMYH9**, Human circ-MYH9 linear sequence (**GenePharma**) One week before the experiment, **AAV9-circMYH9** (**GenePharma**).

nature communications

Article

https://doi.org/10.1038/s41467-023-44088-z

BACH1 controls hepatic insulin signaling and glucose homeostasis in mice

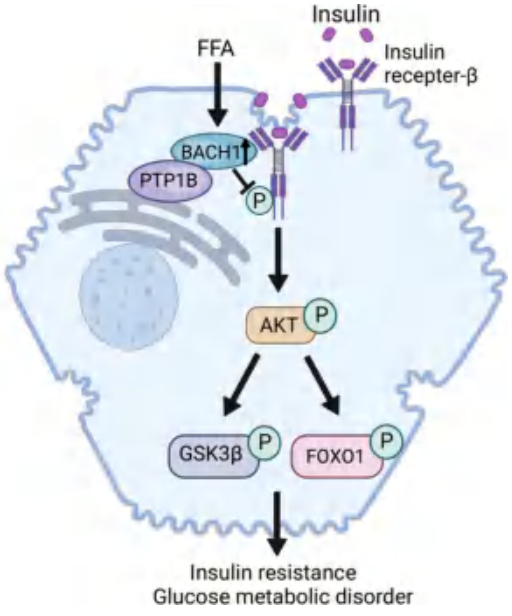
Received: 18 January 2023

Accepted: 27 November 2023

Published online: 21 December 2023

Jiayu Jin[1,5], Yunquan He[1,5], Jieyu Guo[1,5], Qi Pan[1], Xiangxiang Wei[1], Chen Xu[2], Zhiyuan Qi[1], Qinhan Li[1], Siyu Ma[1], Jiayi Lin[1], Nan Jiang[1], Jinghua Ma[1], Xinhong Wang[1], Lindi Jiang[1], Qiurong Ding[3], Elena Osto[4], Xiuling Zhi[1] ✉ & Dan Meng[1] ✉

Hepatic insulin resistance is central to the metabolic syndrome. Here we investigate the role of BTB and CNC homology 1 (BACH1) in hepatic insulin signaling. BACH1 is elevated in the hepatocytes of individuals with obesity and patients with non-alcoholic fatty liver disease (NAFLD). Hepatocyte-specific Bach1 deletion in male mice on a high-fat diet (HFD) ameliorates hyperglyce-mia and insulin resistance, improves glucose homeostasis, and protects against steatosis, whereas hepatic overexpression of Bach1 in male mice leads to the opposite phenotype. BACH1 directly interacts with the protein-tyrosine phosphatase 1B (PTP1B) and the insulin receptor β (IR-β), and loss of BACH1 reduces the interaction between PTP1B and IR-β upon insulin stimulation and enhances insulin signaling in hepatocytes. Inhibition of PTP1B significantly attenuates BACH1-mediated suppression of insulin signaling in HFD-fed male mice. Hepatic BACH1 knockdown ameliorates hyperglycemia and improves insulin sensitivity in diabetic male mice. These results demonstrate a critical function for hepatic BACH1 in the regulation of insulin signaling and glucose homeostasis.



Nature Communications
2023 Dec 21;14(1):8428
Impact Factor: 16.6

Materials and Methods

For the rescue experiment, we silenced Ptpn1 by administering an AAV containing a construct encoding mur-ine Ptpn1 short hairpin RNA (shRNA) under the TBG promoter for hepatocyte-specific expression (**AAV-shPtpn1**, designed and synthe-sized by **Gene Pharma**, Shanghai, China).

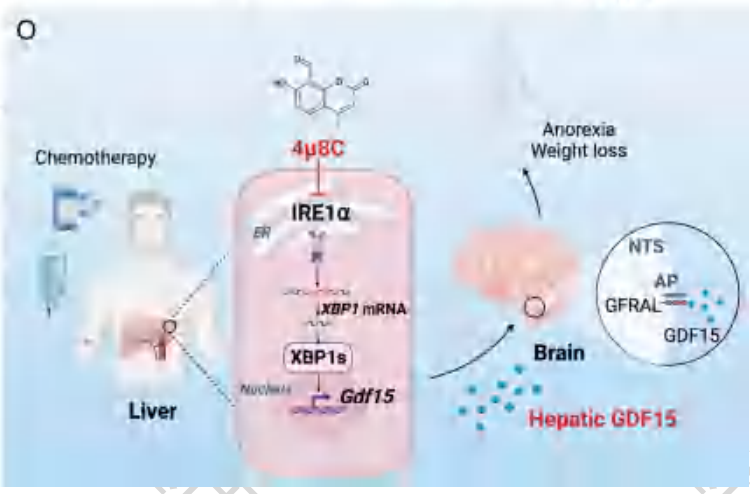
JEM Journal of Experimental Medicine

BRIEF DEFINITIVE REPORT

Hepatic IRE1α-XBP1 signaling promotes GDF15-mediated anorexia and body weight loss in chemotherapy

Yuexiao Tang[1,2*], Tao Yao[1,2,3*], Xin Tian[1,2,3], Xintong Xia[2,3], Xingxiao Huang[1], Zhewen Qin[1], Zhong Shen[4], Lin Zhao[1], Yaping Zhao[5], Bowen Diao[1], Yan Ping[1], Xiaoxiao Zheng[2], Yonghao Xu[1], Hui Chen[1], Tao Qian[6], Tao Ma[6], Ben Zhou[7], Suowen Xu[5], Qimin Zhou[8], Yong Liu[9], Mengle Shao[10], Wei Chen[2,3], Bo Shan[1,11], and Ying Wu[2,3]

Platinum-based chemotherapy drugs can lead to the development of anorexia, a detrimental effect on the overall health of cancer patients. However, managing chemotherapy-induced anorexia and subsequent weight loss remains challenging due to limited effective therapeutic strategies. Growth differentiation factor 15 (GDF15) has recently gained significant attention in the context of chemotherapy-induced anorexia. Here, we report that hepatic GDF15 plays a crucial role in regulating body weight in response to chemo drugs cisplatin and doxorubicin. Cisplatin and doxorubicin treatments induce hepatic Gdf15 expression and elevate circulating GDF15 levels, leading to hunger suppression and subsequent weight loss. Mechanistically, selective activation by chemotherapy of hepatic IRE1α-XBP1 pathway of the unfolded protein response (UPR) upregulates Gdf15 expression. Genetic and pharmacological inactivation of IRE1α is sufficient to ameliorate chemotherapy-induced anorexia and body weight loss. These results identify hepatic IRE1α as a molecular driver of GDF15-mediated anorexia and suggest that blocking IRE1α RNase activity offers a therapeutic strategy to alleviate the adverse anorexia effects in chemotherapy.



JOURNAL OF EXPERIMENTAL MEDICINE

J. Exp. Med. 2024 Vol. 221 No. 7 e20231395

Impact Factor: 15.3

Materials and Methods

pAAV-U6-shNC-EGFP, pAAV-U6-shGdf15-1-EGFP, and pAAV-U6-shGdf15-2-EGFP plasmids were constructed at **GenePharma** Co. Ltd. The plasmids were packaged into **AAV vector serotype DJ (AAV-DJ)** by **GenePharma**

IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2024; 14(19): 7569-7588. doi: 10.7150/thno.102593

Research Paper

FBLN7 mediates vascular smooth muscle cell phenotype switching and vascular remodeling in hypertension

Guoqing Yao, Xuehui Zheng, Yang Hu, Yuan Zhao, Binghui Kong, Yun Ti✉, Pei li Bu✉

State Key Laboratory for Innovation and Transformation of Luobing Theory; Key Laboratory of Cardiovascular Remodeling and Function Research, Chinese Ministry of Education, Chinese National Health Commission and Chinese Academy of Medical Sciences; Department of Cardiology, Qilu Hospital of Shandong University, Jinan, 250012, China

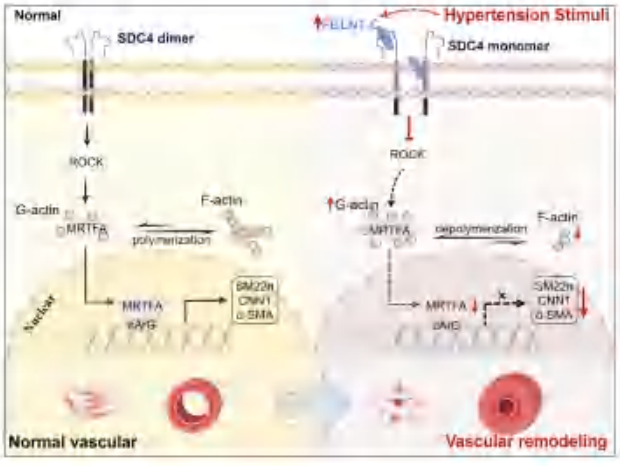
Abstract

Rationale: Arterial remodeling serves as a pivotal mechanism underlying the development of diseases such as hypertension. Fibulin-7 (FBLN7), an adhesion protein, remains enigmatic regarding its role in these pathological processes. This study aims to explore whether FBLN7 influences vascular remodeling and its underlying mechanisms.

Methods: We generated FBLN7 knockout mice and smooth muscle-specific FBLN7 overexpression mice. Vascular remodeling models were established by administering angiotensin II (Ang II) for 28 days. RNA sequencing, western blot, and immunofluorescence assays were employed to investigate the biological function of FBLN7 in vascular smooth muscle cells (VSMCs). The interaction mechanism between FBLN7 and cell membrane receptors was explored through mass spectrometry analysis, co-immunoprecipitation techniques and molecular dynamics simulations.

Results: Bioinformatics analysis revealed an upregulation of FBLN7 expression in the vascular remodeling model, with FBLN7 predominantly localized in VSMCs. Subsequent *in vivo* validation demonstrated that FBLN7 knockout attenuated Ang II-induced vascular remodeling, reducing aortic wall thickness and collagen formation. Conversely, VSMC-specific overexpression of FBLN7 via AAV vectors exacerbating the remodeling phenotype. Functionally speaking, FBLN7 potentiates Ang II-mediated phenotypic transformation. Mechanistically, FBLN7 interacts with the extracellular and transmembrane domains of syndecan-4 (SDC4) via its C-terminal region, affecting SDC4 signaling and dimer formation. This interaction inhibits SDC4-mediated activation of the Rho-associated protein kinase pathway, subsequently reducing nuclear translocation of myocardin-related transcription factor A, leading to decreased transcription of genes associated with the contractile VSMCs phenotype.

Conclusions: These findings reveal FBLN7 promotes the transition of VSMCs from a contractile to a synthetic phenotype, thereby aggravating vascular remodeling. This provides further insights into the pathogenesis of vascular remodeling and potential therapeutic strategies.



Materials and Methods

The specific overexpression of FBLN7 in mice was achieved using adeno-associated **virus-9 (AAV9)**provided by **GenePharma** (Shanghai, China),

CDD press

www.nature.com/cdd

ARTICLE

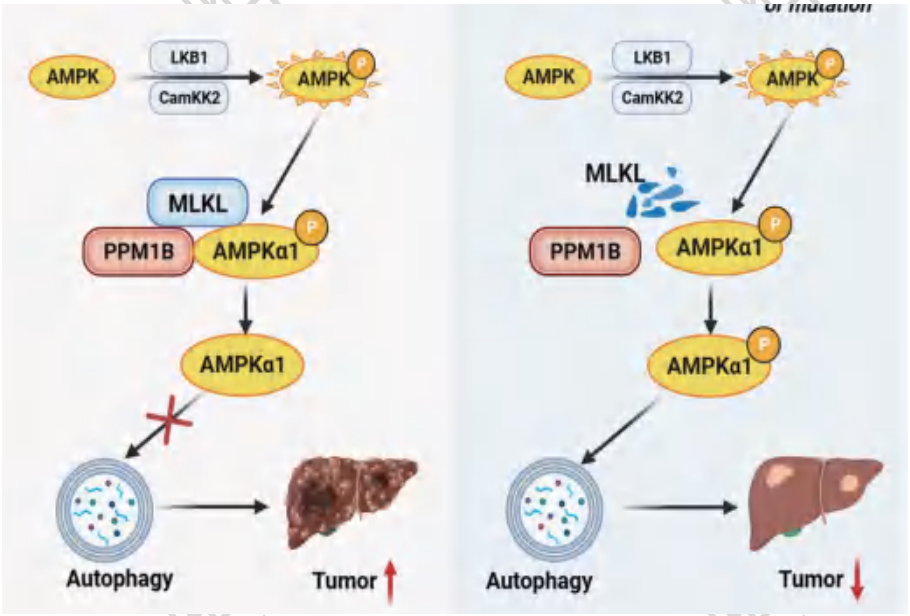
Check for updates

MLKL promotes hepatocarcinogenesis through inhibition of AMPK-mediated autophagy

Xianjun Yu[1,2], Mengyuan Feng[1,2], Jian Guo[2], Haoyu Wang[1,2], Jun Yu[3], Anjie Zhang[1,2], Jingyi Wu[1,2], Yamei Han[4], Zequn Sun[1], Yingying Liao[1] and Qun Zhao[1,2]✉

The pseudokinase mixed lineage kinase domain-like (MLKL) is an essential component of the activation of the necroptotic pathway. Emerging evidence suggests that MLKL plays a key role in liver disease. However, how MLKL contributes to hepatocarcinogenesis has not been fully elucidated. Herein, we report that MLKL is upregulated in a diethylnitrosamine (DEN)-induced murine HCC model and is associated with human hepatocellular carcinomas. Hepatocyte-specific MLKL knockout suppresses the progression of hepatocarcinogenesis. Conversely, MLKL overexpression aggravates the initiation and progression of DEN-induced HCC. Mechanistic study reveals that deletion of MLKL significantly increases the activation of autophagy, thereby protecting against hepatocarcinogenesis. MLKL directly interacts with AMPKα1 and inhibits its activity independent of its necroptotic function. Mechanistically, MLKL serves as a bridging molecule between AMPKα1 and protein phosphatase 1B (PPM1B), thus enhancing the dephosphorylation of AMPKα1. Consistently, MLKL expression correlates negatively with AMPKα1 phosphorylation in HCC patients. Taken together, our findings highlight MLKL as a novel AMPK gatekeeper that plays key roles in inhibiting autophagy and driving hepatocarcinogenesis, suggesting that the MLKL-AMPKα1 axis is a potential therapeutic target for HCC.

Cell Death & Differentiation; https://doi.org/10.1038/s41418-024-01314-5



CELL DEATH AND DIFFERENTIATION
Received: 16 January 2024 Revised: 7 May 2024 Accepted: 8 May 2024
Impact Factor: 12.4

Materials and Methods

AAV8 cells harboring PPM1B interference sequences (**AAV8-shPPM1B**) and the negative control (**AAV8-shNC)** were generated by **GenePharma** (Shanghai,China).

Molecular Therapy
Original Article

Endocrine modulation of brain-skeleton axis driven by neural stem cell-derived perilipin 5 in the lipid metabolism homeostasis for bone regeneration

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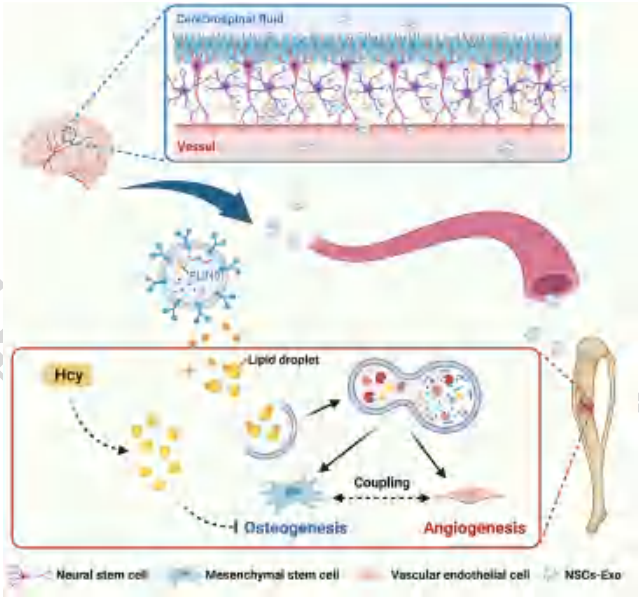
Abstract

Factors released from the nervous system always play crucial roles in modulating bone metabolism and regeneration. How the brain-driven endocrine axes maintain bone homeostasis, especially under metabolic disorders, remains obscure. Here, we found that neural stem cells (NSCs) residing in the subven-tricular zone participated in lipid metabolism homeostasis of regenerative bone through exosomal perilipin 5 (PLIN5). Fluo-rescence-labeled exosomes tracing and histological detection identified that NSC-derived exosomes (NSC-Exo) could travel from the lateral ventricle into bone injury sites. Homocysteine (Hcy) led to osteogenic and angiogenic impairment, whereas the NSC-Exo were confirmed to restore it. Mecobalamin, a clin-ically used neurotrophic drug, further enhanced the protective effects of NSC-Exo through increased PLIN5 expression. Mech-anistically, NSC-derived PLIN5 reversed excessive Hcy-induced lipid metabolic imbalance and aberrant lipid droplet accumu-lation through lipophagy-dependent intracellular lipolysis. Intracerebroventricular administration of mecobalamin and/or AAV-shPlin5 confirmed the effects of PLIN5-driven endo-crine modulations on new bone formation and vascular recon-struction in hyperhomocysteinemic and high-fat diet models. This study uncovered a novel brain-skeleton axis that NSCs in the mammalian brain modulated bone regeneration through PLIN5-driven lipid metabolism modulation, providing evi-dence for lipid- or bone-targeted medicine development.



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Materials and Methods

The **AAV-shPlin5 vector** (**GenePharma**, Shanghai, China) was gener-ated by replacing the Plin5 transcript sequence with the shRNA target for Plin5, with the AAV-shCtrl as negative control.

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RESEARCH Open Access

PARD3 drives tumorigenesis through activating Sonic Hedgehog signalling in tumour-initiating cells in liver cancer

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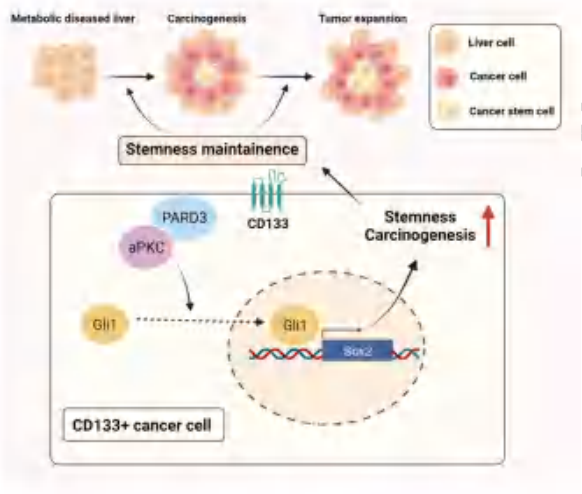
Abstract

Background Par-3 Family Cell Polarity Regulator (PARD3) is a cellular protein essential for asymmetric cell division and polarized growth. This study aimed to study the role of PARD3 in hepatic tumorigenesis.

Methods The essential role of PARD3 in mediating hepatic tumorigenesis was assessed in diet-induced spontaneous liver tumour and syngeneic tumour models. The mechanism of PARD3 was delineated by bulk and single-cell RNA sequencing. The clinical significance of PARD3 was identified by tissue array analysis.

Results PARD3 was overexpressed in tumour tissues and PARD3 overexpression was positively correlated with high tumour stage as well as the poor prognosis in patients. In models of spontaneous liver cancer induced by choline-deficient, amino acid-defined (CDAA) and methionine-choline-deficient (MCD) diets, upregulation of PARD3 was induced specifically at the tumorigenesis stage rather than other early stages of liver disease progression. Site-directed knockout of PARD3 using an adeno-associated virus 8 (AAV8)-delivered CRISPR/Cas9 single-guide RNA (sgRNA) plasmid blocked hepatic tumorigenesis, while PARD3 overexpression accelerated liver tumour progression. In particular, single-cell sequencing analysis suggested that PARD3 was enriched in primitive tumour cells and its overexpression enhanced tumour-initiating cell (TICs). Overexpression of PARD3 maintained the self-renewal ability of the $CD133^+$ TIC population within hepatocellular carcinoma (HCC) cells and promoted the in vitro and in vivo tumorigenicity of $CD133^+$ TICs. Transcriptome analysis revealed that Sonic Hedgehog (SHH) signalling was activated in PARD3-overexpressing $CD133^+$ TICs. Mechanistically, PARD3 interacted with aPKC to further activate SHH signalling and downstream stemness-related genes. Suppression of SHH signalling and aPKC expression attenuated the in vitro and in vivo tumorigenicity of PARD3-overexpressing $CD133^+$ TICs. Tissue array analysis revealed that PARD3 expression was positively associated with the phosphorylation of aPKC, SOX2 and Gli1 and that the combination of these markers could be used to stratify HCC patients into two clusters with different clinicopathological characteristics and overall survival prognoses. The natural compound berberine was selected as a potent suppressor of PARD3 expression and



Materials and Methods

To examine the effects of PARD3 overexpression on carcinogenesis in vivo, mice were and subjected to intravenous injection of either (i) AAV8-vector or (ii) **AAV8-PARD3Act** (1 × 1011 viral genomes/mouse) (**GenePharma**, P.R. China) every two weeks (n = 10).

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Research paper

Altered DNA methylation of TRIM13 in diabetic nephropathy suppresses mesangial collagen synthesis by promoting ubiquitination of CHOP

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Abstract

Background: Mesangial collagen synthesis in renal glomeruli contributes to the pathogenesis of diabetic nephropathy (DN) which is one of the most serious complications of diabetes mellitus. However, the under-lying mechanism of mesangial collagen synthesis is largely unknown.

Methods: The differential expression of CHOP and TRIM13 which is a well-defined E3 ubiquitin ligase was compared in renal biopsy samples from DN/normal renal tissues, in isolated glomeruli of diabetic/control mice, as well as in high glucose (HG) or TGF-b1-stimulated renal mesangial cells. Then the relationship between TRIM13 and CHOP was explored using the ubiquitination assay.

Findings: We found that the expression of TRIM13 was downregulated in renal biopsies, isolated glomeruli of diabetic mice, and HG/TGF-b1-stimulated renal mesangial cells, while the expression of CHOP was upregu-lated. An increased level of TRIM13 promoter methylation contributed to the deregulation of TRIM13 in renal glomeruli of DN. The ubiquitination assay confirmed that TRIM13 promoted ubiquitination and degradation of CHOP. Meanwhile, overexpressing TRIM13 attenuated DN-induced collagen synthesis and restored renal function in vitro and in vivo via downregulating CHOP.

Interpretation: Our findings demonstrated that overexpressed TRIM13 suppresses mesangial collagen synthesis in DN by promoting ubiquitination of CHOP, suggesting TRIM13 as a potential therapeutic target in treating DN.
Keywords:Diabetic nephropathy;DNA ethylation ; TRIM13; CHOP;Ubiquitination

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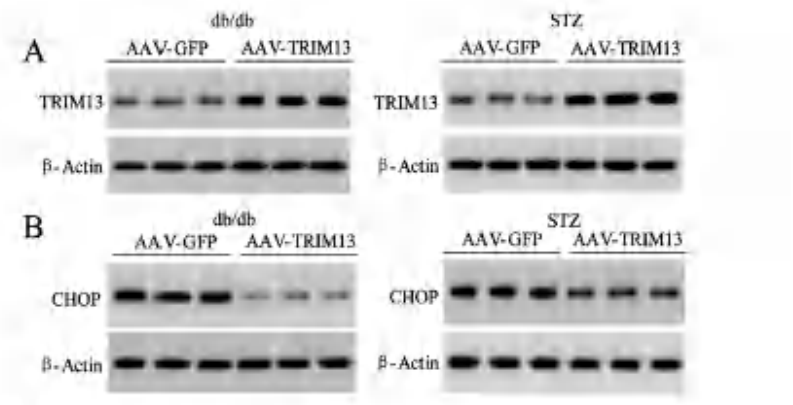
Materials and Methods

The TRIM13,CHOP or GFP cDNA was cloned into the **AAV9** capsid and the recombinant **AAV9** was manufactured by Shanghai **GenePharma** Co.,Ltd.



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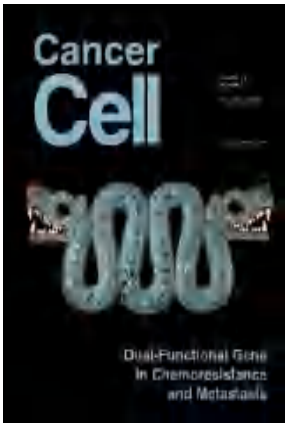
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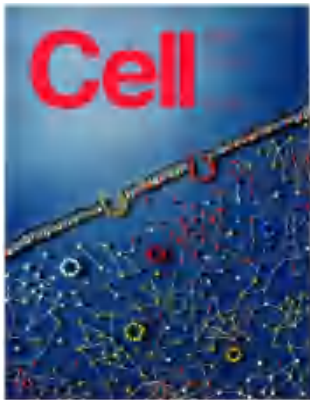
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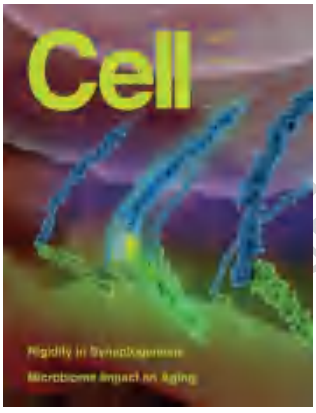
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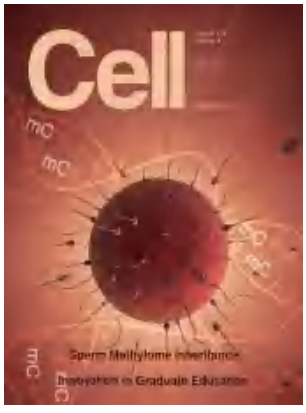
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