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文献综述 REVIEW

# miR-148a在消化系恶性肿瘤中的研究进展

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■背景资料
近年来大量研究报道证实, miR-148a在多种消化系恶性肿瘤中都存在异常表达下调, 并且miR-148a的下调在肿瘤的发病及进展中具有重要作用. 上调miR-148a的表达在肿瘤的增殖、迁移、侵袭等方面具有一定的抑制效应, 为消化系肿瘤的治疗提供了新的潜在治疗靶点.

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## Progresses in research of miR-148a in digestive system cancers

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## Abstract
MicroRNAs (miRNAs) are a class of small non-protein-coding RNAs, which are often aberrantly expressed in the progression of various malignant tumors. Digestive system cancers are major causes of death all over the world. The finding of miRNAs provides a new direction for the diagnosis and therapy of digestive system cancers. Recent studies have demonstrated that miR-148a is aberrantly down-regulated in various digestive system cancers, including gastric cancer, hepatocellular cancer, pancreatic cancer and colorectal cancer. MiR-148a play a crucial role in the progression of these tumors as a tumor suppressor gene. This article will review the progress in research of miR-148a in digestive system cancers.



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Key Words: miR-148a; Digestive system cancers

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## 摘要
MicroRNAs(miRNAs)是一类非蛋白编码的短小RNA, 目前已证实在多种恶性肿瘤的发生和进展中都存在异常表达. 消化系恶性肿瘤是目前全球主要的疾病致死原因之一. miRNAs的发现为消化系恶性肿瘤的诊断和治疗提供了新的方向. 近年来许多研究表明, miR-148a在多种消化系恶性肿瘤如胃癌、肝癌、胰腺癌及结直肠癌等中都存在异常表达下调, 他以肿瘤抑制因子的身份在这些肿瘤的发生、发展中发挥重要作用. 本文就miR-148a在消化系恶性肿瘤中的作用的研究进展作一综述.



关键词: miR-148a; 消化系恶性肿瘤

**核心提示**: miR-148a以肿瘤抑制因子的身份在多种消化系恶性肿瘤, 如胃癌、肝癌、胰腺癌及结直肠癌等中都存在异常表达下调, 上调miR-148a的表达有望从发病机制上达到有效抑癌作用, 为消化系恶性肿瘤的治疗提供了新的方向.

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## 0 引言
MicroRNAs(miRNAs)是一类大小为19-25个核苷酸的非蛋白编码的微小RNA, 主要通过与靶信使RNA(mRNA)的3'-非翻译区(3'-untranslated region, 3'-UTR)碱基配对的方式来执行对靶mRNA的切割或者翻译抑制功能, 抑制靶基因表达而起调控作用[1]. 越来越多的研究表明miR-

NAs参与了人体内许多重要的生理过程, 包括细胞分化、细胞增殖及细胞凋亡等, 更重要的是他与恶性肿瘤的发生发展也密切相关[2,3]. miRNAs在许多肿瘤中都存在异常表达, 他们在不同类型的肿瘤中分别发挥致癌基因或抑癌基因的作用[4-7]. miR-148a是miR-148/152家族的成员之一, 基因定位于7p15.2, miR-148a成熟体由22个核苷酸组成, 含有一个8个核苷酸区域的“种子序列”. 近年来许多研究表明, miR-148a在多种恶性肿瘤中异常表达下调, 并通过作用于不同的靶基因对肿瘤细胞的活性、增殖、侵袭及转移等发挥调控作用[8,9]. 本文就miR-148a在消化系恶性肿瘤中的研究进展作一综述.

## 1 miR-148a与胃癌

胃癌为消化系最常见的恶性肿瘤, 近年来研究发现, 异常表达的miRNAs在胃癌的发生发展过程中具有重要作用[10-14]. 其中, miR-148a在大多数的胃癌组织和胃癌细胞株中表达均存在显著下调[15-20]. Zhu等[21]研究认为, miR-148a的表达下调与DNA甲基转移酶1(DNA methyltransferase 1, DNMT1)有关, DNMT1可以甲基化miR-148a的启动子区域使其失活, 从而使得miR-148a在胃癌中表达明显降低, miR-148a的表达水平与DNMT1的表达成负相关性. miR-148a表达的下调与胃癌的发生、癌肿的大小、肿瘤分期、淋巴结转移及临床预后密切相关[15,20]. miR-148a能够通过介导DNMT1依赖的甲基化来调节胃癌组织及细胞内RUNT相关转录因子3(runt-related transcription factor 3, RUNX3)的表达[22], 而RUNX3的甲基化与胃癌的组织学类型及分化程度有关[23]. miR-148a在Ⅲ/Ⅳ期胃癌中的表达水平比Ⅰ/Ⅱ期更低, 这表明miR-148a低表达与胃癌的进展有关[20].

另一方面, 目前已有研究证实上调miR-148a的表达可以抑制胃癌侵袭和转移. Sakamoto等[15]研究显示, miR-148a可通过直接靶向MMP7而发挥抑制胃癌细胞侵袭的作用. 高表达的miR-148a还可以直接结合至Rho相关蛋白激酶1(Rho-associated coiled-coil containing protein kinase 1, ROCK1)的3'-UTR端从而降低ROCK1的mRNA和蛋白水平, 继而抑制GC细胞的迁移和侵袭, 阻止体内淋巴结和肺转移的形成[20]. 不论是转染上调miR-148a基因表达, 还是敲除*DNMT1*基因, 或是加用DNA甲基化抑制剂作用后, 胃癌细胞内RUNX3的mRNA及蛋白水平则均上升[22], RUNX3的增加又能够通过上调TIMP1的水平使MMP9失活, 继而阻止胃癌细胞的转移[24]. Wang等[18]研究认为, *SMAD2*基因也是miR-148a直接的作用靶点之一, 高表达的miR-148a抑制胃癌代谢和上皮-间质转化(epithelial-mesenchymal transition, EMT)很可能就是通过靶向SMAD2实现的. 此外, 胃癌中miR-148a可通过靶向*DNMT1*基因抑制其甲基化而发挥某些抑癌效应[21].

## 2 miR-148a与胰腺癌

在胰腺癌的研究中, Bloomston等[25]采用基因芯片技术检测了65份胰腺癌组织及癌旁正常胰腺组织和42份慢性胰腺炎组织中miRNAs的表达情况, 结果发现miR-148a在胰腺癌组织中异常表达下调. Szafranska等[26,27]的研究也发现在胰腺癌组织和多种胰腺癌细胞株中miR-148a表达明显下调. 在胰腺癌中miR-148a低表达导致DNMT1对抑癌基因过度甲基化从而促进了癌肿的发展[25,28]. Hanoun等[29]研究认为胰腺癌和胰腺导管内上皮肿瘤组织中miR-148a低表达与其基因编码区的高甲基化状态有关, 同时指出miR-148a及其甲基化检测可以成为对胰腺癌和慢性胰腺炎鉴别诊断的辅助标志.

Liffers等[30]报道胰腺癌细胞miR-148a表达比正常胰腺导管细胞下调4倍, 同时他们在体外实验中发现, miR-148a能直接靶向结合CDC25B的3'-UTR, miR-148a高表达能有效下调胰腺癌细胞中CDC25B的蛋白表达. CDC25B可以在$G_2$/M期激活细胞周期依赖蛋白激酶/细胞周期蛋白B复合体(cyclin-dependent protein kinases/cyclinB, CDK/cyclinB)而启动细胞的有丝分裂, 在胰腺癌组织中CDC25B呈高表达[31,32]. 因此上调miR-148a能够通过抑制CDC25B的蛋白表达而抑制癌细胞的生长并阻碍癌细胞集落的形成. 然而, 最近Delpu等[33]的研究结果显示, 上调胰腺癌细胞株的miR-148a表达水平后, 癌细胞的增殖以及对化疗的敏感性并没有显著改变, 并且调节上皮肿瘤细胞和/或肿瘤微环境中的miR-148a表达都不能阻碍癌细胞的生长. 因此, 靶向miR-148a对胰腺癌的治疗作用仍有待进一步研究.

## 3 miR-148a与肝癌

大量研究表明, 包括miR-148a在内的某些特定的miRNAs的表达失调与肝癌细胞的临床病理特点, 如转移、复发和预后密切相关[34,35]. miR-148a在肝癌组织和肝癌细胞株内表达显著下

**■研究前沿**

研究确定miR-148a在消化系恶性肿瘤中的具体作用机制, 以miR-148a为靶点, 特异性上调miR-148a在消化系恶性肿瘤细胞内的表达, 阻断其的对机体靶基因的修饰介导来抑制肿瘤的发生发展具有一定的可行性, 但仍需进一步研究探索.

**■相关报道**

据研究报道, miR-148a的表达下调与DNA甲基转移酶1(DNA methyltransferase 1, DNMT1)有关, DNMT1能够甲基化miR-148a的启动子区域使其失活, miR-148a在消化系肿瘤中表达明显降低使其对*DNMT1*基因的靶向抑制作用也减弱, DNMT1表达的上调增加了多种抑癌基因的甲基化修饰, 进而促进了肿瘤的发生.

■创新盘点
本文总结了大量文献，分别介绍了miR-148a在胃癌、胰腺癌、肝癌以及结直肠癌的发病及抑制肿瘤生长中的突出作用，内容较为全面.

调[36-38]. Gailhouste等[36]发现miR-148a通过调节DNMT1促进肝脏内成熟肝细胞特异性表型的生成, 在肝细胞分化中发挥重要作用. 在胆管细胞型肝癌中, 白介素(interleukin, IL)-6能够通过介导miR-148a和miR-152的表达来调节DNMT1的活性和甲基化依赖性肿瘤抑制基因的表达[39]. 另外一方面, miR-148a与DNMT1之间相互形成负反馈调节回路. 在肝癌细胞株内, miR-148a启动子的CpG岛被DNMT1甲基化而表达下调, 使用DNMT抑制剂5-杂氮-2'-脱氧胞苷(5-aza-2-dC)处理细胞后, miR-148a的水平则明显上调[38].

miR-148a表达下调诱发了肝癌的发生. Yan等[40]的研究表明, 低分化肝癌组织中miR-148a表达水平低于高分化肝癌组织, miR-148a的过度表达能够阻断EMT过程, 降低肝癌干细胞的生物标志物CD90和CD44的表达. 乙型肝炎病毒相关肝癌中, 与肿瘤发生密切相关的乙型肝炎病毒X蛋白能够抑制p53介导的miR-148a活化而降低其表达水平而促进肝癌的发生[41]. 此外, miR-148a表达降低还能靶向降低泛素特异性蛋白酶4(ubiquitin specific protease 4, USP4)表达而促进肿瘤细胞的迁移和增殖[37].

miR-148a表达上调在抑制肝癌的增殖、转移和复发中也发挥着重要作用. miR-148a过度表达能够通过阻滞细胞周期显著抑制肝癌细胞的增殖, 但对癌细胞凋亡并没有影响[38]. miR-148a通过阻滞EMT和肝癌细胞获得肿瘤干细胞样细胞(stem-like cancer cells, CSCs)属性的而抑制肝癌细胞的转移, 在该过程中, miR-148a靶向抑制Wnt信号通路来实现的[38]. miR-148a还可以通过靶向Met/Snail信号通路可抑制肝癌细胞的EMT和转移, miR-148a可降低HPIP的表达, 引起AKT和ERK信号抑制, 随后通过AKT/ERK/FOXO4/ATF5信号通路而抑制mTOR水平而抑制肝癌细胞生长、EMT、侵袭和转移发挥抑癌作用[42].

## 4 miR-148a与结直肠癌

结直肠癌(colorectal carcinoma, CRC)在目前癌症致死疾病中排名第2位, 他也是全球病死率排名第4的疾病. 研究发现, miR-148a在结肠癌组织和癌细胞株中的表达显著低于正常的癌旁正常组织[43]. 结直肠癌细胞中的转录因子MYB能够作用于miR-148a基因的转录因子结合位点2(transcription factor binding site 2, TFBS-2)而直接抑制miR-148a的转录表达[44]. Takahashi等[45]在一项临床研究中从可能与CRC相关的21种miRNAs中筛选出了miR-148a, 发现他在大多数的进展期CRC患者肿瘤组织中表达明显下调, 并且发现在Ⅲ期和Ⅳ期CRC中miR-148a低表达与无病生存期短、治疗反应差和总存活率低有关. 在CRC中, miR-148a还与肿瘤pT分期有关[43]. 此外, 研究发现miR-148a的靶基因之一的*DNMT1*与CRC患者的发病也密切相关, 他能够维持CRC细胞获得CSCs样属性[46]. Kalimutho等[47]研究认为, miR-148a的表观遗传沉默与CRC的预后差有关, miR-148a的异常甲基化能够作为CRC疾病进展的有效随访标志物. Tsai等[48]最新研究发现在早期与非早期的复发型Ⅱ、Ⅲ期CRC患者中, miR-148a表达均出现异常水平, 因此, CRC患者的miR-148a血清水平还可作为CRC进行根治切除术后早期复发的生物学标志物. Zhang等[44]发现, miR-148a在CRC细胞中可发挥细胞凋亡激活因子的作用, 触发癌细胞早期凋亡, 在CRC细胞中, miR-148a不仅可以在转录后直接结合于Bcl-2的3'-UTR沉默Bcl-2的表达, 也可以先抑制miR-148a的另一靶点PXR的表达后间接降低Bcl-2的表达, Bcl-2表达的降低继而激活细胞色素Caspase9-Caspase3-PARP固有凋亡通路而诱发癌细胞凋亡发挥抗癌作用.

## 5 结论

MiR-148a通过作用于不同的基因靶点和信号通路来抑制消化系肿瘤细胞的增殖、侵袭和转移, 在消化系恶性肿瘤的发生发展中具有重要作用. 以miR-148a为治疗靶点, 特异性上调miR-148a的表达有望成为一种新的有效的治疗方法. 同时, miR-148a也可作为一种消化系恶性肿瘤的诊断及判断预后的生物学标志物. 但miR-148a在消化系恶性肿瘤中异常表达及其抑癌作用的机制仍有待深入研究.

## 6 参考文献

1 Ambros V. The functions of animal microRNAs. *Nature* 2004; 431: 350-355 [PMID: 15372042]
2 Iorio MV, Croce CM. microRNA involvement in human cancer. *Carcinogenesis* 2012; 33: 1126-1133 [PMID: 22491715 DOI: 10.1093/carcin/bgs140]
3 Lujambio A, Lowe SW. The microcosmos of cancer. *Nature* 2012; 482: 347-355 [PMID: 22337054 DOI: 10.1038/nature10888]
4 Di Leva G, Croce CM. Roles of small RNAs in tumor formation. *Trends Mol Med* 2010; 16: 257-267 [PMID: 20493775 DOI: 10.1016/j.molmed.2010.04.001]
5 Ichikawa D, Komatsu S, Konishi H, Otsuji E. Circulating microRNA in digestive tract cancers. *Gastroenterology* 2012; 142: 1074-1078.e1 [PMID: 22433392]
6 Song S, Ajani JA. The role of microRNAs in cancers

of the upper gastrointestinal tract. *Nat Rev Gastroenterol Hepatol* 2013; 10: 109-118 [PMID: 23165235 DOI: 10.1038/nrgastro.2012.210]
7 Leidner RS, Li L, Thompson CL. Dampening enthusiasm for circulating microRNA in breast cancer. *PLoS One* 2013; 8: e57841 [PMID: 23472110 DOI: 10.1371/journal.pone.0057841]
8 Xu Q, Jiang Y, Yin Y, Li Q, He J, Jing Y, Qi YT, Xu Q, Li W, Lu B, Peiper SS, Jiang BH, Liu LZ. A regulatory circuit of miR-148a/152 and DNMT1 in modulating cell transformation and tumor angiogenesis through IGF-IR and IRS1. *J Mol Cell Biol* 2013; 5: 3-13 [PMID: 22935141 DOI: 10.1093/jmcb/mjs049]
9 Aprelikova O, Palla J, Hibler B, Yu X, Greer YE, Yi M, Stephens R, Maxwell GL, Jazaeri A, Risinger JI, Rubin JS, Niederhuber J. Silencing of miR-148a in cancer-associated fibroblasts results in WNT10B-mediated stimulation of tumor cell motility. *Oncogene* 2013; 32: 3246-3253 [PMID: 22890324 DOI: 10.1038/onc.2012.351]
10 Zhang J, Zhang XH, Wang CX, Liu B, Fan XS, Wen JJ, Shi QL, Zhou XJ. Dysregulation of microRNA biosynthesis enzyme Dicer plays an important role in gastric cancer progression. *Int J Clin Exp Pathol* 2014; 7: 1702-1707 [PMID: 24817967]
11 Kim JG, Kim TO, Bae JH, Shim JW, Kang MJ, Yang K, Ting AH, Yi JM. Epigenetically regulated MIR941 and MIR1247 target gastric cancer cell growth and migration. *Epigenetics* 2014; 9: 1018-1030 [PMID: 24785261 DOI: 10.4161/epi.29007]
12 Wu WK, Lee CW, Cho CH, Fan D, Wu K, Yu J, Sung JJ. MicroRNA dysregulation in gastric cancer: a new player enters the game. *Oncogene* 2010; 29: 5761-5771 [PMID: 20802530 DOI: 10.1038/onc.2010.352]
13 Kogo R, Mimori K, Tanaka F, Komune S, Mori M. Clinical significance of miR-146a in gastric cancer cases. *Clin Cancer Res* 2011; 17: 4277-4284 [PMID: 21632853 DOI: 10.1158/1078-0432.CCR-10-2866]
14 Ueda T, Volinia S, Okumura H, Shimizu M, Taccioli C, Rossi S, Alder H, Liu CG, Oue N, Yasui W, Yoshida K, Sasaki H, Nomura S, Seto Y, Kaminishi M, Calin GA, Croce CM. Relation between microRNA expression and progression and prognosis of gastric cancer: a microRNA expression analysis. *Lancet Oncol* 2010; 11: 136-146 [PMID: 20022810]
15 Sakamoto N, Naito Y, Oue N, Sentani K, Uraoka N, Zarni Oo H, Yanagihara K, Aoyagi K, Sasaki H, Yasui W. MicroRNA-148a is downregulated in gastric cancer, targets MMP7, and indicates tumor invasiveness and poor prognosis. *Cancer Sci* 2014; 105: 236-243 [PMID: 24283384 DOI: 10.1111/cas.12330]
16 Chen Z, Saad R, Jia P, Peng D, Zhu S, Washington MK, Zhao Z, Xu Z, El-Rifai W. Gastric adenocarcinoma has a unique microRNA signature not present in esophageal adenocarcinoma. *Cancer* 2013; 119: 1985-1993 [PMID: 23456798 DOI: 10.1002/cncr.28002]
17 Zheng G, Xiong Y, Xu W, Wang Y, Chen F, Wang Z, Yan Z. A two-microRNA signature as a potential biomarker for early gastric cancer. *Oncol Lett* 2014; 7: 679-684 [PMID: 24527072]
18 Wang SH, Li X, Zhou LS, Cao ZW, Shi C, Zhou CZ, Wen YG, Shen Y, Li JK. microRNA-148a suppresses human gastric cancer cell metastasis by reversing epithelial-to-mesenchymal transition. *Tumour Biol* 2013; 34: 3705-3712 [PMID: 23873106 DOI: 10.1007/s13277-013-0954-1]
19 Tseng CW, Lin CC, Chen CN, Huang HC, Juan HF. Integrative network analysis reveals active microRNAs and their functions in gastric cancer. *BMC Syst Biol* 2011; 5: 99 [PMID: 21703006 DOI: 10.1186/1752-0509-5-99]
20 Zheng B, Liang L, Wang C, Huang S, Cao X, Zha R, Liu L, Jia D, Tian Q, Wu J, Ye Y, Wang Q, Long Z, Zhou Y, Du C, He X, Shi Y. MicroRNA-148a suppresses tumor cell invasion and metastasis by downregulating ROCK1 in gastric cancer. *Clin Cancer Res* 2011; 17: 7574-7583 [PMID: 21994419 DOI: 10.1158/1078-0432.CCR-11-1714]
21 Zhu A, Xia J, Zuo J, Jin S, Zhou H, Yao L, Huang H, Han Z. MicroRNA-148a is silenced by hypermethylation and interacts with DNA methyltransferase 1 in gastric cancer. *Med Oncol* 2012; 29: 2701-2709 [PMID: 22167392 DOI: 10.1007/s12032-011-0134-3]
22 Zuo J, Xia J, Ju F, Yan J, Zhu A, Jin S, Shan T, Zhou H. MicroRNA-148a can regulate runt-related transcription factor 3 gene expression via modulation of DNA methyltransferase 1 in gastric cancer. *Mol Cells* 2013; 35: 313-319 [PMID: 23549984 DOI: 10.1007/s10059-013-2314-9]
23 Fan XY, Hu XL, Han TM, Wang NN, Zhu YM, Hu W, Ma ZH, Zhang CJ, Xu X, Ye ZY, Han CM, Pan WS. Association between RUNX3 promoter methylation and gastric cancer: a meta-analysis. *BMC Gastroenterol* 2011; 11: 92 [PMID: 21867527 DOI: 10.1186/1471-230X-11-92]
24 Chen Y, Wei X, Guo C, Jin H, Han Z, Han Y, Qiao T, Wu K, Fan D. Runx3 suppresses gastric cancer metastasis through inactivation of MMP9 by upregulation of TIMP-1. *Int J Cancer* 2011; 129: 1586-1598 [PMID: 21128246 DOI: 10.1002/ijc.25831]
25 Bloomston M, Frankel WL, Petrocca F, Volinia S, Alder H, Hagan JP, Liu CG, Bhatt D, Taccioli C, Croce CM. MicroRNA expression patterns to differentiate pancreatic adenocarcinoma from normal pancreas and chronic pancreatitis. *JAMA* 2007; 297: 1901-1908 [PMID: 17473300]
26 Szafranska AE, Davison TS, John J, Cannon T, Sipos B, Maghnouj A, Labourier E, Hahn SA. MicroRNA expression alterations are linked to tumorigenesis and non-neoplastic processes in pancreatic ductal adenocarcinoma. *Oncogene* 2007; 26: 4442-4452 [PMID: 17237814]
27 Szafranska AE, Doleshal M, Edmunds HS, Gordon S, Luttges J, Munding JB, Barth RJ, Gutmann EJ, Suriawinata AA, Marc Pipas J, Tannapfel A, Korc M, Hahn SA, Labourier E, Tsongalis GJ. Analysis of microRNAs in pancreatic fine-needle aspirates can classify benign and malignant tissues. *Clin Chem* 2008; 54: 1716-1724 [PMID: 18719196 DOI: 10.1373/clinchem.2008.109603]
28 Mees ST, Schleicher C, Mardin WA, Senninger N, Colombo-Benkmann M, Haier J. Analyzing miRNAs in ductal adenocarcinomas of the pancreas. *J Surg Res* 2011; 169: 241-246 [PMID: 20080250 DOI: 10.1016/j.jss.2009.10.005]
29 Hanoun N, Delpu Y, Suriawinata AA, Bournet B, Bureau C, Selves J, Tsongalis GJ, Dufresne M, Buscail L, Cordelier P, Torrisani J. The silencing of microRNA 148a production by DNA hypermethylation is an early event in pancreatic carcinogenesis. *Clin Chem* 2010; 56: 1107-1118 [PMID: 20431052 DOI: 10.1373/clinchem.2010.144709]

**■应用要点**

本文全面总结阐述了近几年来miR-148a在消化系恶性肿瘤中的研究进展, 为靶向miR-148a治疗消化系恶性肿瘤提供了坚实的理论依据, 有望为消化系恶性肿瘤的诊治带来新的突破.

**■同行评价**
本文具有一定指导意义.


30 Liffers ST, Munding JB, Vogt M, Kuhlmann JD, Verdoodt B, Nambiar S, Maghnouj A, Mirmohammadsadegh A, Hahn SA, Tannapfel A. MicroRNA-148a is down-regulated in human pancreatic ductal adenocarcinomas and regulates cell survival by targeting CDC25B. *Lab Invest* 2011; 91: 1472-1479 [PMID: 21709669 DOI: 10.1038/labinvest.2011.99]

31 Lindqvist A, Källström H, Lundgren A, Barsoum E, Rosenthal CK. Cdc25B cooperates with Cdc25A to induce mitosis but has a unique role in activating cyclin B1-Cdk1 at the centrosome. *J Cell Biol* 2005; 171: 35-45 [PMID: 16216921]

32 Guo J, Kleeff J, Li J, Ding J, Hammer J, Zhao Y, Giese T, Korc M, Büchler MW, Friess H. Expression and functional significance of CDC25B in human pancreatic ductal adenocarcinoma. *Oncogene* 2004; 23: 71-81 [PMID: 14712212]

33 Delpu Y, Lulka H, Sicard F, Saint-Laurent N, Lopez F, Hanoun N, Buscail L, Cordelier P, Torrisani J. The rescue of miR-148a expression in pancreatic cancer: an inappropriate therapeutic tool. *PLoS One* 2013; 8: e55513 [PMID: 23383211 DOI: 10.1371/journal.pone.0055513]

34 Ladeiro Y, Couchy G, Balabaud C, Bioulac-Sage P, Pelletier L, Rebouissou S, Zucman-Rossi J. MicroRNA profiling in hepatocellular tumors is associated with clinical features and oncogene/tumor suppressor gene mutations. *Hepatology* 2008; 47: 1955-1963 [PMID: 18433021 DOI: 10.1002/hep.22256]

35 Mott JL. MicroRNAs involved in tumor suppressor and oncogene pathways: implications for hepatobiliary neoplasia. *Hepatology* 2009; 50: 630-637 [PMID: 19585622 DOI: 10.1002/hep.23010]

36 Gailhouste L, Gomez-Santos L, Hagiwara K, Hatada I, Kitagawa N, Kawaharada K, Thirion M, Kosaka N, Takahashi RU, Shibata T, Miyajima A, Ochiya T. miR-148a plays a pivotal role in the liver by promoting the hepatospecific phenotype and suppressing the invasiveness of transformed cells. *Hepatology* 2013; 58: 1153-1165 [PMID: 23532995 DOI: 10.1002/hep.26422]

37 Heo MJ, Kim YM, Koo JH, Yang YM, An J, Lee SK, Lee SJ, Kim KM, Park JW, Kim SG. microRNA-148a dysregulation discriminates poor prognosis of hepatocellular carcinoma in association with USP4 overexpression. *Oncotarget* 2014; 5: 2792-2806 [PMID: 24798342]

38 Long XR, He Y, Huang C, Li J. MicroRNA-148a is silenced by hypermethylation and interacts with DNA methyltransferase 1 in hepatocellular carcinogenesis. *Int J Oncol* 2014; 44: 1915-1922 [PMID: 24714841 DOI: 10.3892/ijo.2014.2373]

39 Braconi C, Huang N, Patel T. MicroRNA-dependent regulation of DNA methyltransferase-1 and tumor suppressor gene expression by interleukin-6 in human malignant cholangiocytes. *Hepatology* 2010; 51: 881-890 [PMID: 20146264 DOI: 10.1002/hep.23381]

40 Yan H, Dong X, Zhong X, Ye J, Zhou Y, Yang X, Shen J, Zhang J. Inhibitions of epithelial to mesenchymal transition and cancer stem cells-like properties are involved in miR-148a-mediated anti-metastasis of hepatocellular carcinoma. *Mol Carcinog* 2014; 53: 960-969 [PMID: 23861222 DOI: 10.1002/mc.22064]

41 Xu X, Fan Z, Kang L, Han J, Jiang C, Zheng X, Zhu Z, Jiao H, Lin J, Jiang K, Ding L, Zhang H, Cheng L, Fu H, Song Y, Jiang Y, Liu J, Wang R, Du N, Ye Q. Hepatitis B virus X protein represses miRNA-148a to enhance tumorigenesis. *J Clin Invest* 2013; 123: 630-645 [PMID: 23321675 DOI: 10.1172/JCI64265]

42 Zhang JP, Zeng C, Xu L, Gong J, Fang JH, Zhuang SM. MicroRNA-148a suppresses the epithelial-mesenchymal transition and metastasis of hepatoma cells by targeting Met/Snail signaling. *Oncogene* 2014; 33: 4069-4076 [PMID: 24013226 DOI: 10.1038/onc.2013.369]

43 Chen Y, Song Y, Wang Z, Yue Z, Xu H, Xing C, Liu Z. Altered expression of MiR-148a and MiR-152 in gastrointestinal cancers and its clinical significance. *J Gastrointest Surg* 2010; 14: 1170-1179 [PMID: 20422307 DOI: 10.1007/s11605-010-1202-2]

44 Zhang H, Li Y, Huang Q, Ren X, Hu H, Sheng H, Lai M. MiR-148a promotes apoptosis by targeting Bcl-2 in colorectal cancer. *Cell Death Differ* 2011; 18: 1702-1710 [PMID: 21455217 DOI: 10.1038/cdd.2011.28]

45 Takahashi M, Cuatrecasas M, Balaguer F, Hur K, Toiyama Y, Castells A, Boland CR, Goel A. The clinical significance of MiR-148a as a predictive biomarker in patients with advanced colorectal cancer. *PLoS One* 2012; 7: e46684 [PMID: 23056401 DOI: 10.1371/journal.pone.0046684]

46 Morita R, Hirohashi Y, Suzuki H, Takahashi A, Tamura Y, Kanaseki T, Asanuma H, Inoda S, Kondo T, Hashino S, Hasegawa T, Tokino T, Toyota M, Asaka M, Torigoe T, Sato N. DNA methyltransferase 1 is essential for initiation of the colon cancers. *Exp Mol Pathol* 2013; 94: 322-329 [PMID: 23064049 DOI: 10.1016/j.yexmp.2012.10.004]

47 Kalimutho M, Di Cecilia S, Del Vecchio Blanco G, Roviello F, Sileri P, Cretella M, Formosa A, Corso G, Marrelli D, Pallone F, Federici G, Bernardini S. Epigenetically silenced miR-34b/c as a novel faecal-based screening marker for colorectal cancer. *Br J Cancer* 2011; 104: 1770-1778 [PMID: 21610744 DOI: 10.1038/bjc.2011.82]

48 Tsai HL, Yang IP, Huang CW, Ma CJ, Kuo CH, Lu CY, Juo SH, Wang JY. Clinical significance of microRNA-148a in patients with early relapse of stage II stage and III colorectal cancer after curative resection. *Transl Res* 2013; 162: 258-268 [PMID: 23933284 DOI: 10.1016/j.trsl.2013.07.009]


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