·综 述·

miR-29在肿瘤中的研究进展*

任雪维[①] 综述 张吉才[①②] 审校

摘要 微小RNA(microRNA,miRNA)是生物体内一种重要的基因调控分子,参与多种疾病的发生过程,与肿瘤关系密切,已成为近年来肿瘤学研究的新方向。研究发现,miRNA-29(miR-29)在多种肿瘤中均有涉及,具有抑癌和促癌双重作用,且其表达水平在肿瘤组织和非肿瘤组织中也存在差异。因此,miR-29有望成为恶性肿瘤诊断及预后的生物标记物或治疗靶点。本文就miR-29家族在恶性肿瘤中的研究进展进行综述。

关键词 microRNA miR-29 肿瘤
doi:10.3969/j.issn.1000-8179.2016.17.362

Research progress of microRNA-29 in tumors

Xuewei REN[1], Jicai ZHANG[1,2]
Correspondence to: Jicai ZHANG; E-mail: 3561361@qq.com
[1]Hubei University of Medicine, Shiyan Dali 442000, China; [2]Clinical Laboratory, Taihe Hospital Affiliated to Hubei University of Medicine, Shiyan Dali 442000, China

This work was supported by Hubei Provincial Natural Science Foundation of China (No. 2014CFB304).

Abstract MicroRNA (miRNA) is an important gene regulatory molecule involved in the occurrence of a variety of diseases and is related to tumors. MicroRNA has become a new direction of oncology research in recent years. Studies showed that miR-29 plays dual roles, as tumor suppressor and tumor promoter. The expression of miR-29 significantly differs between cancer and normal tissues. miR-29 is predicted to be a biomarker for early diagnosis and prognosis prediction of certain cancer. This paper reviews the role of miR-29 in the pathogenesis of cancer.

Keywords: microRNAs (miRNAs), miR-29, cancer

microRNAs(miRNAs)是一组内源性、高度保守、大小为18~25个碱基的非编码单链RNA分子,其通过与分布在转录组上的miRNA应答元件(miRNA response element,MRE)结合而发挥生物学功能。当miRNA上的"种子序列"(seed sequence)与蛋白编码转录组即mRNA上的MRE结合时,可抑制mRNA的翻译过程或降低mRNA的稳定性,进而导致基因表达下调,发挥转录后表达的调节作用。当miRNA与假基因、长链非编码RNA和环形RNA等非编码转录组的MRE结合时,可以降低miRNA的含量,从而间接影响miRNA对基因转录后表达的调节作用[1]。miRNA的表达具有时间和组织特异性,是调控基因表达的重要一员,影响着细胞的分化、增殖、凋亡和转移,与肿瘤关系密切。本文将对miR-29在肿瘤中的研究进展进行综述。

1 miR-29的来源

成熟的miRNA由前体基因mRNA的茎环结构或发夹结构(pre-miRNA)剪切而来,一般只来自于pre-miRNA的3′(3p)或5′(5p)端中的一条臂,成熟的miR-29主要由pre-miRNA的3p端剪切而来。人类miR-29家族分布于1号染色体和7号染色体,主要有3个成员,包括miR-29a、miR-29b和miR-29c。其中miR-29a位于7号染色体(7q32),miR-29b位于7号染色体(7q32)和1号染色体(1q32),miR-29c位于1号染色体(1q32)[2](表1)。

2 miR-29在肿瘤中的表达情况

大量研究表明,miR-29在肿瘤发生中的作用机制复杂,具有抑癌和促癌的双重作用。同时,与对应的正常组织相比,miR-29在多数肿瘤组织中表达下调,在少数肿瘤组织中表达上调(表2)。

3 miR-29在肿瘤中表达的上游调控

miR-29由其前体基因转录加工为成熟miRNA的过程受多种信号分子调控,如转录因子MYC、YY1和GATA3,组蛋白甲基转移酶2(enhancer of zeste ho-

作者单位:①湖北医药学院(湖北省十堰市442000);②湖北医药学院附属太和医院检验科
*本文课题受湖北省自然科学基金(编号:2014CFB304)资助
通信作者:张吉才 3561361@qq.com

molog 2，EZH2），组蛋白去乙酰化酶（histone deacetylases，HDACs）等。

表1 miR-29的分布及子序列

Table 1 Introduction to the miR-29 family

Name	Location	Subsequence
miR-29a	7q32	UAGCACCAUCUGAAAUCGGUUA
miR-29b	7q32、1q32	UAGCACCAUUUGAAAUCAGUGUU
miR-29c	1q32	UAGCACCAUUUGAAAUCGGUUA

在慢性淋巴细胞性白血病中[3]，HDACs可下调miR-29的表达，HDAC3是HDAC3-EZH2复合体的组成成分，MYC通过HDAC3-EZH复合体抑制miR-29的表达。另外，miR-29参与了涉及核转录因子-κB（nuclear factor Kappa-light-chain-enhancer of activated B cells，NF-κB）和YY1的调节回路，YY1可抑制miR-29的表达，NF-κB可促进miR-29的表达。另一方面，miR-29也可以逆向调节YY1，并阻碍YY1的翻译，而YY1抑制miR-29转录，形成一个负反馈环，而NF-κB可以直接活化YY1从而调控这个负反馈环，间接调控miR-29。除了MYC和YY1，造血因子CEBPA可诱导miR-29的表达，且由于CEBPA位于染色体7q，CEBPA选择性的上调位于染色体7q32上的miR-29a和miR-29b的表达，而不影响位于染色体1q32上的miR-29b和miR-29c。

表2 miR-29在肿瘤组织中的表达情况

Table 2 Expression of miR-29 in cancer

Tumor tissue	Regulation of miR-29	Functions of miR-29
Non-small cell lung cancer[25]	↓	Targeting DNA methyltransferases 3A and 3B and FHIT
Lung adenocarcinoma[26]	↓	Regulate specific genes associated with tissue invasion and metastasis
Esophageal carcinoma[27]	↓	Induced cell cycle G1/G0 arrest through suppression of cyclin E expression
Stomach cancer[28]	↓	Acted as tumor suppressors through targeting CCND2 and matrix metalloproteinase-2 genes
Hepatocellular carcinoma[29]	↓	Promote apoptosis through a mitochondrial pathway that involves Mcl-1 and Bcl-2
Cholangiocarcinoma[30]	↓	Regulates Mcl-1 protein expression and apoptosis
Glioblastomas[31]	↓	Regulate podoplanin and suppress invasion
Neuroblastoma [32]	↓	Modulates expression of immunoinhibitory molecule B7-H3
Osteoblastoma[33-34]	↓	Silencing Bcl-2 and Mcl-1 and inducing E2F1 and E2F3 expression
Rhabdomyosarcoma[35-36]	↓	Involve in NF-kappaB-YY1-miR-29 regulatory circuit, reduce the expression of CCND2 and E2F7, induce G1 rerest
Bladder cancer[37-38]	↓	Reduce DNA methyltransferases,promote PTEN expression
Prostate cancer[39]	↓	Suppresses metastasis by regulating EMT signaling
Renal carcinoma[40-41]	↓	Suppresses DNMT-3A and DNMT-3B expression, reduce LOXL2
Ovarian cancer[42-43]	↓	Reduce COL1A1
Endometrial cancer[44]	↓	Reduce metastasis
Acute lymphoblastic leukemia[3, 45]	↓	Reduce Tcl-1, Mcl-1 and DNA methyltransferases
Acute myeloid leukemia[3]	↓	Reduce Tcl-1, Mcl-1 and DNA methyltransferases
Chronic lymphocytic leukemia[3]	↓	Reduce Tcl-1, Mcl-1 and DNA methyltransferases
Mantle cell lymphoma[3]	↓	Reduce Tcl-1, Mcl-1 and DNA methyltransferases
Basal cell carcinoma[46]	↓	Reduce DNA methyltransferases
Nasopharyngeal carcinomas[47]	↓	Reduce Tcl-1, Mcl-1
Colon cancer[48]	↑	Targeted regulate COL11A1
Breast cancer[49]	↑	Suppresses ATP1B1,reduce metastasis
Diffuse large B lymphoma[50]	↑	Downregulate Tcl-1, Mcl-1 and DNA methyltransferases
Malignant pleural mesothelioma[51]	↑	Downregulate DNA methyltransferases

在黑色素瘤细胞中[4]，转录因子STAT1上调miR-29，而miR-29靶向作用于干扰素（interferon，IFN），IFN-γ表达的增加导致受周期蛋白依赖性激酶CDK6抑制的黑色素瘤细胞G_1期重启（G1-arrest）。

在乳腺癌中[5]，转录因子GATA3通过诱导miR-29b的表达，来抑制乳腺癌的远端转移和改变肿瘤微环境，抑癌基因GATA3的缺失使乳腺癌患者的预后情况更差。

4 miR-29在肿瘤中的作用机制

4.1 抑制DNA甲基转移酶的表达

癌基因的低甲基化和抑癌基因的高甲基化是肿瘤发病的表观遗传学机制。miR-29家族(miR-29s,即miR-29a,miR-29b和miR-29c)能与DNA甲基转移酶3A(DNMT-3A)和DNA甲基转移酶3B(DNMT-3B)的3′-UTRs互补,从而调控DNA甲基化,诱导基因沉默。Fabbri等[6]发现在非小细胞型肺癌细胞系中,一些抑癌基因如PTEN和WWOX由于甲基化作用而表达较少,增加miR-29s的表达后,抑癌基因的DNA甲基化程度正常化,从而促进抑癌基因的表达。Garzon等[7]发现,miR-29b不仅能直接的与DNMT-3A和DNMT-3B的3′-UTRs结合,还能与DNMT-1基因的反式激活因子Sp1结合,从而间接的抑制DNMT-1。Li等[8]与Wang等[9]研究证实,miR-29b阻碍甲基转移酶的表达,导致抑癌基因PTEN启动子甲基化降低,最终导致PTEN基因表达上调,抑制肿瘤的发展。上述研究显示,miR-29能够通过抑制DNA甲基转移酶的表达,降低基因组的甲基化作用,增强抑癌基因的表达,从而发挥肿瘤抑制作用。

4.2 通过促进细胞凋亡发挥抑癌作用

p53依赖的信号通路是经典的细胞凋亡途径,miR-29s可间接增加p53水平,通过p53依赖的途径引发细胞凋亡。Park等[10]发现miR-29s可以直接抑制磷脂酰肌醇激酶调节亚基p85a和Rho家族的GTP酶CDC42,然后p85a和CDC42再负向调节p53。

B细胞淋巴瘤/白血病-2基因(B-cell lymphoma-2,Bcl-2)是一种原癌基因,它具有抑制凋亡的作用,而髓细胞白血病因子-1(myeloid cell leukemia-1,Mcl-1)含有BH-1、BH-2和BH-3保守结构域,此结构域是Bcl-2基因的同源亚基。内源性miR-29直接与Mcl-1的3′-UTRs端结合,阻止Mcl-1蛋白的表达,促进细胞凋亡。在胆管癌细胞系中,miR-29b下调使Mcl-1表达增加。过表达miR-29b,可降低细胞内Mcl-1蛋白含量,增加癌细胞对肿瘤坏死因子相关凋亡诱导配体(tumor necrosis factor-related apoptosis-inducing ligand,TRAIL)的敏感性。

细胞色素C与细胞凋亡有关,从线粒体中泄漏的细胞色素C有诱导细胞凋亡的作用。当线粒体外膜电压依赖的阴离子通道(voltage-dependent anion channel,VDAC)通透性增加,细胞色素C可通过VDAC释放。最新的研究表明,miR-29a靶向作用于VDAC1和VDAC2的3-UTRs,过表达miR-29a可导致VDAC1和VDAC2表达水平降低,从而减少细胞色素C的泄漏[11]。

此外,miR-29a和miR-29b也可上调促凋亡基因BIM(bcl-2-like 11,BCL2L11)和程序性细胞死亡因子4肿瘤抑制基因(programmed cell death factor 4,PDCD4)。

4.3 改变肿瘤的侵袭性

髓细胞白血病基因-1(T-cell leukemia 1,Tcl-1)与肿瘤的侵袭性有关,miR-29可降低Tcl-1在慢性淋巴细胞性白血病中的表达。其他研究表明,miR-29b通过下调转录抑制因子-1(inhibitor of DNA binding/differentiation 1,ID1)和基质金属蛋白酶-9(matrix metalloprotein 9,MMP9)调控肿瘤细胞转移和侵袭。miR-29b可结合到ID1的3′-UTR上,抑制内源性的miR-29b表达可上调ID1和MMP9,从而增加肿瘤细胞的侵袭性,相反增加miR-29b的表达则下调ID1和MMP9,显著的降低肿瘤细胞的侵袭性[12]。

乳腺癌中的miR-29也具有增加肿瘤细胞侵袭性的作用,这一作用可能通过抑制Na/K-ATP酶β1转运肽(sodium/potassium-transporting ATPase subunit beta-1,ATP1B1)而实现,而后者是抑制乳腺癌细胞的转移和侵袭的重要因子。Cochrane等[13]发现黄体酮治疗能降低miR-29表达水平,从而间接降低对ATP1B1基因靶点的抑制,从而使ATP1B1表达增加,最终降低肿瘤细胞的侵袭性。

4.4 诱导细胞周期阻滞抑制肿瘤细胞增殖

Ding等[14]在食管鳞状细胞癌的组织和细胞系中均发现miR-29c表达下调,上调miR-29可导致细胞周期蛋白E减少,使细胞周期停滞在G_1/G_0从而抑制细胞生长。Lee等[15]发现体外和移植瘤细胞中,miR-29s可抑制干扰素诱导核酸内切酶(ribonuclease-L,RNase-L)的表达,RNase-L是干扰素调控RNA衰减途径的关键成分,RNase-L的缺失可显著抑制细胞增殖。

4.5 miR-29在上皮细胞间质转型中的作用

上皮细胞间质转型(epithelial-mesenchymal transition,EMT)是上皮细胞通过特定的程序转化为具有间质表型细胞的生物学过程。EMT伴随着显著的细胞形态学变化、细胞黏附性丢失及重塑,是上皮细胞来源的恶性肿瘤细胞获得迁移和侵袭能力的重要生物学过程。miR-29a可增加乳腺癌细胞的侵袭性,而侵袭性增加和EMT密切相关。Gebeshuber等[16]在比较转移性RasXT细胞与上皮EpRas细胞时发现,过表达的miR-29a抑制锌指蛋白36(tristetraprolin,TTP)的表达,而TTP对EMT具有抑制作用,故miR-29a间接地促进了EMT的发生。此外,过表达miR-29a还可通过与致癌Ras信号通路协同后抑制TPP,最终导致肿瘤转移的发生。miR-29可以上调多基因编码细胞外基质蛋白(extra cellular matrix,ECM蛋白),包括胶原蛋白、肌原纤维蛋白和弹性蛋白,这些蛋白是

EMT过程中的动力因子，miR-29可通过上调ECM蛋白诱发EMT。

Li等[17]在乳腺癌中发现，miR-29的过表达可下调乳腺癌相关基因ADAM12从而阻止EMT，降低了肿瘤细胞的侵袭性。乳腺癌中的锌指转录因子GATA3可提高miR-29b的水平，而miR-29b缺失会促进EMT，增加癌细胞的侵袭性。此外，miR-29b还通过靶向调节转移前动力蛋白来抑制癌细胞转移[18]，间接的影响细胞分化和EMT，这些蛋白（包括VEGFA、ANGPTL4、PDGF、LOX和MMP9，靶点为ITGA6、ITGB1和TGFB）涉及血管新生、胶原重建和蛋白酶解。

5 miR-29与临床

综上所述，miR-29参与肿瘤的发生发展中的多个过程，机制复杂，且其表达水平也存在差异，因此miR-29在癌症的诊断分期、预后评估以及提高化疗药物的敏感性等方面具有广阔的应用前景。

研究表明，在弥漫性大B细胞淋巴瘤[19]、脑膜瘤[20]、急性髓细胞性白血病[21]、神经胶质瘤[22]等肿瘤中，miR-29在血清中的表达水平有望成为辅助诊断肿瘤的新型生物标记物。在大肠癌中，miR-29a的表达水平越高，癌症的分级越低、预后越好[23]。在小儿急性髓细胞白血病中，低水平的miR-29a提示更高临床分期和预后不良，并预示着患者复发的可能性越大和生存期越短[24]。在急性髓细胞性白血病的化疗过程中，硼替佐米上调miR-29b，而miR-29b可提高肿瘤患者对地西他滨的敏感性，因此将地西他滨和硼替佐米联合用药能显著提高药效。

6 结语

miR-29s在肿瘤的发生、发展、侵袭和转移过程中均扮演了重要角色。大多数肿瘤中，miR-29s通过调控细胞凋亡、甲基化、细胞的侵袭增殖以及化疗敏感性起到抑癌的作用。然而，在部分肿瘤中miR-29s可促进细胞转移，发挥促癌效应。目前miR-29的多重肿瘤调控机制还缺乏充分的解释，其作用机制中还需要更进一步的研究。

miR-29的差异性表达在肿瘤的临床诊断分期和预后判断中具有广阔的应用前景。同时，阐明miR-29在肿瘤病理生理进程中的调控作用，进一步探索抗肿瘤药物发挥作用时miR-29的效应及分子机制，有助于针对miR-29进行药物研发，为肿瘤治疗开发新方案。

参考文献

[1] Tay Y, Rinn J, Pandolfi PP. The multilayered complexity of ceRNA crosstalk and competition[J]. Nature, 2014, 505(7483):344-352.

[2] Jiang H, Zhang G, Wu JH, et al. Diverse roles of miR-29 in cancer (review)[J].Oncol Rep, 2014, 31(4):1509-1516.

[3] Kollinerova S, Vassanelli S, Modriansky M. The role of miR-29 family members in malignant hematopoiesis[J]. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub, 2014, 158(4):489-501.

[4] Schmitt MJ, Philippidou D, Reinsbach SE, et al. Interferon-gamma-induced activation of signal transducer and activator of transcription 1 (STAT1) up-regulates the tumor suppressing microRNA-29 family in melanoma cells[J]. Cell Commun Signal, 2012, 10(1):41.

[5] Melo SA, Kalluri R. miR-29b moulds the tumour microenvironment to repress metastasis[J]. Nat Cell Biol, 2013, 15(2):139-140.

[6] Fabbri M, Garzon R, Cimmino A, et al. MicroRNA-29 family reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B[J]. Proc Natl Acad Sci USA, 2007, 104(40):15805-15810.

[7] Garzon R, Liu S, Fabbri M, et al. MicroRNA-29b induces global DNA hypomethylation and tumor suppressor gene reexpression in acute myeloid leukemia by targeting directly DNMT3A and 3B and indirectly DNMT1[J]. Blood, 2009, 113(25):6411-6418.

[8] Li G, Zhao J, Peng X, et al. The mechanism involved in the loss of PTEN expression in NSCLC tumor cells[J]. Biochem Biophys Res Commun, 2012, 418(3):547-552.

[9] Wang X, Zhao J, Huang J, et al. The regulatory roles of miRNA and methylation on oncogene and tumor suppressor gene expression in pancreatic cancer cells[J]. Biochem Biophys Res Commun, 2012, 425(1):51-57.

[10] Park SY, Lee JH, Ha M, et al. miR-29 miRNAs activate p53 by targeting p85 alpha and CDC42[J]. Nat Struct Mol Biol, 2009,16(1):23-29.

[11] Bargaje R, Gupta S, Sarkeshik A, et al. Identification of novel targets for miR-29a using miRNA proteomics[J]. PLoS One, 2012, 7(8):e43243.

[12] Rothschild SI, Tschan MP, Federzoni EA, et al. MicroRNA-29b is involved in the Src-ID1 signaling pathway and is dysregulated in human lung adenocarcinoma[J]. Oncogene, 2012, 31(38):4221-4232.

[13] Cochrane DR, Jacobsen BM, Connaghan KD, et al. Progestin regulated miRNAs that mediate progesterone receptor action in breast cancer[J]. Mol Cell Endocrinol, 2012, 355(1):15-24.

[14] Ding DP, Chen ZL, Zhao XH, et al. miR-29c induces cell cycle arrest in esophageal squamous cell carcinoma by modulating cyclin E expression[J]. Carcinogenesis, 2011, 32(7):1025-1032.

[15] Lee TY, Ezelle HJ, Venkataraman T, et al. Regulation of human RNase-L by the miR-29 family reveals a novel oncogenic role in chronic myelogenous leukemia[J]. J Interferon Cytokine Res, 2013,33(1):34-42.

[16] Gebeshuber CA, Zatloukal K, Martinez J. miR-29a suppresses tristetraprolin, which is a regulator of epithelial polarity and metastasis [J]. EMBO Rep, 2009, 10(4):400-405.

[17] Li H, Solomon E, Duhachek MS, et al. Metalloprotease-disintegrin ADAM12 expression is regulated by Notch signaling via microRNA-29[J]. J Biol Chem, 2011, 286(24):21500-21510.

[18] Chou J, Lin JH, Brenot A, et al. GATA3 suppresses metastasis and modulates the tumour microenvironment by regulating microRNA-29b expression[J]. Nat Cell Biol, 2013, 15(2):201-213.

[19] Fang C, Zhu DX, Dong HJ, et al. Serum microRNAs are promising novel biomarkers for diffuse large B cell lymphoma[J]. Ann Hematol, 2012, 91(4):553-559.

[20] Zhi F, Zhou G, Wang S, et al. A microRNA expression signature predicts meningioma recurrence[J]. Int J Cancer, 2013, 132(1):128-136.

[21] Wang F, Wang XS, Yang GH, et al. miR-29a and miR-142-3p down-regulation and diagnostic implication in human acute myeloid leu-

kemia[J]. Mol Biol Rep, 2012, 39(3):2713-2722.
[22] Wu J, Li L, Jiang C. Identification and Evaluation of Serum MicroRNA-29 Family for Glioma Screening[J]. Mol Neurobiol, 2015, 52(3): 1540-1546.
[23] Weissmann-Brenner A, Kushnir M, Lithwick YG, et al. Tumor microRNA-29a expression and the risk of recurrence in stage II colon cancer[J]. Int J Oncol, 2012, 40(6):2097-2103.
[24] Zhu C, Wang Y, Kuai W, et al. Prognostic value of miR-29a expression in pediatric acute myeloid leukemia[J]. Clin Biochem, 2013, 46(1-2):49-53.
[25] Wu DW, Hsu NY, Wang YC, et al. c-Myc suppresses microRNA-29b to promote tumor aggressiveness and poor outcomes in non-small cell lung cancer by targeting FHIT[J]. Oncogene, 2015, 34(16):2072-2082.
[26] Plaisier CL, Pan M, Baliga NS. A miRNA-regulatory network explains how dysregulated miRNAs perturb oncogenic processes across diverse cancers[J]. Genome Res, 2012, 22(11):2302-2314.
[27] Ding DP, Chen ZL, Zhao XH, et al. miR-29c induces cell cycle arrest in esophageal squamous cell carcinoma by modulating cyclin E expression[J]. Carcinogenesis, 2011, 32(7):1025-1032.
[28] Gong J, Li J, Wang Y, et al. Characterization of microRNA-29 family expression and investigation of their mechanistic roles in gastric cancer[J]. Carcinogenesis, 2014, 35(2):497-506.
[29] Xiong Y, Fang JH, Yun JP, et al. Effects of microRNA-29 on apoptosis, tumorigenicity, and prognosis of hepatocellular carcinoma[J]. Hepatology, 2010, 51(3):836-845.
[30] Mott JL, Kobayashi S, Bronk SF, et al. miR-29 regulates Mcl-1 protein expression and apoptosis[J]. Oncogene, 2007, 26(42):6133-6140.
[31] Cortez MA, Nicoloso MS, Shimizu M, et al. miR-29b and miR-125a regulate podoplanin and suppress invasion in glioblastoma[J]. Genes Chromosomes Cancer, 2010, 49(11):981-990.
[32] Xu H, Cheung IY, Guo HF, et al. MicroRNA miR-29 modulates expression of immunoinhibitory molecule B7-H3: potential implications for immune based therapy of human solid tumors[J]. Cancer Res, 2009, 69(15):6275-6281.
[33] Namlos HM, Meza-Zepeda LA, Baroy T, et al. Modulation of the osteosarcoma expression phenotype by microRNAs[J]. PLoS One, 2012, 7(10):e48086.
[34] Zhang W, Qian JX, Yi HL, et al. The microRNA-29 plays a central role in osteosarcoma pathogenesis and progression[J]. Mol Biol (Mosk), 2012, 46(4):622-627.
[35] Wang H, Garzon R, Sun H, et al. NF-kappaB-YY1-miR-29 regulatory circuitry in skeletal myogenesis and rhabdomyosarcoma[J]. Cancer Cell, 2008, 14(5):369-381.
[36] Ciesla M, Dulak J, Jozkowicz A. MicroRNAs and epigenetic mechanisms of rhabdomyosarcoma development[J]. Int J Biochem Cell Biol, 2014, 53:482-492.
[37] Ratert N, Meyer HA, Jung M, et al. Reference miRNAs for miRNAome analysis of urothelial carcinomas[J]. PLoS One, 2012, 7(6):e39309.
[38] Palmbos PL, Wang L, Yang H, et al. ATDC/TRIM29 drives invasive bladder cancer formation through mirna-mediated and epigenetic mechanisms[J]. Cancer Res, 2015, 75(23):5155-5166.
[39] Ru P, Steele R, Newhall P, et al. miRNA-29b suppresses prostate cancer metastasis by regulating epithelial-mesenchymal transition signaling[J]. Mol Cancer Ther, 2012, 11(5):1166-1173.
[40] Heinzelmann J, Henning B, Sanjmyatav J, et al. Specific miRNA signatures are associated with metastasis and poor prognosis in clear cell renal cell carcinoma[J]. World J Urol, 2011, 29(3):367-373.
[41] Nishikawa R, Chiyomaru T, Enokida H, et al. Tumour-suppressive microRNA-29s directly regulate LOXL2 expression and inhibit cancer cell migration and invasion in renal cell carcinoma[J]. FEBS Lett, 2015, 589(16):2136-2145.
[42] Petrillo M, Zannoni GF, Beltrame L, et al. Identification of high-grade serous ovarian cancer miRNA species associated with survival and drug response in patients receiving neoadjuvant chemotherapy: a retrospective longitudinal analysis using matched tumor biopsies[J]. Ann Oncol, 2016, 27(4):625-634.
[43] Yu PN, Yan MD, Lai HC, et al. Downregulation of miR-29 contributes to cisplatin resistance of ovarian cancer cells[J]. Int J Cancer, 2014, 134(3):542-551.
[44] Hiroki E, Akahira J, Suzuki F, et al. Changes in microRNA expression levels correlate with clinicopathological features and prognoses in endometrial serous adenocarcinomas[J]. Cancer Sci, 2010, 101(1):241-249.
[45] Oliveira LH, Schiavinato JL, Fraguas MS, et al. Potential roles of microRNA-29a in the molecular pathophysiology of T-cell acute lymphoblastic leukemia[J]. Cancer Sci, 2015, 106(10):1264-1277.
[46] Sand M, Skrygan M, Sand D, et al. Expression of microRNAs in basal cell carcinoma[J]. Br J Dermatol, 2012, 167(4):847-855.
[47] Zeng X, Xiang J, Wu M, et al. Circulating miR-17, miR-20a, miR-29c, and miR-223 combined as non-invasive biomarkers in nasopharyngeal carcinoma[J]. PLoS One, 2012, 7(10):e46367.
[48] Wang J, Yu H, Ye L, et al. Integrated regulatory mechanisms of miRNAs and targeted genes involved in colorectal cancer[J]. Int J Clin Exp Pathol, 2015, 8(1):517-529.
[49] Wu Q, Wang C, Lu Z, et al. Analysis of serum genome-wide microRNAs for breast cancer detection[J]. Clin Chim Acta, 2012, 413(13-14):1058-1065.
[50] Fang C, Zhu DX, Dong HJ, et al. Serum microRNAs are promising novel biomarkers for diffuse large B cell lymphoma[J]. Ann Hematol, 2012, 91(4):553-559.
[51] Pass HI, Goparaju C, Ivanov S, et al. hsa-miR-29c* is linked to the prognosis of malignant pleural mesothelioma[J]. Cancer Res, 2010, 70(5):1916-1924.

（2016-03-30收稿）
（2016-08-31修回）
（编辑：武斌 校对：杨红欣）

作者简介

任雪维 专业方向为临床检验诊断学，肿瘤分子诊断等。

E-mail：369385102@qq.com