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内皮特异和富含miRNAs对血管功能的影响

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[摘　要] MicroRNAs (miRNAs)是广泛存在于真核生物中的一组不编码蛋白的小分子RNA，由含茎环结构的miRNA前体经核糖核酸酶(Dicer)加工后形成。在真核生物中，miRNAs具有组织特异性和时序性，只在特定的组织和发育阶段表达，在细胞的分化、生长和凋亡过程中发挥广泛的作用。大量研究表明内皮特异和内皮富含的miRNAs对血管功能的调节有重要作用，如内皮细胞特异性miR-126在维持血管内皮完整性、炎症反应以及血管新生过程中均有显著作用；内皮富含的miR-221/222、miR-21等参与炎症反应、血管新生、内皮衰老等功能的调节。

[关键词] 内皮特异miRNAs；内皮富含的miRNAs；血管功能

Effects of endothelial-specific and endothelial-enriched miRNAs on vascular function

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Abstract miRNAs, widely presenting in eukaryotes, are a group of non-coding small RNAs generated from hairpin miRNA precursors (pre-miRNAs) by Rnase-Dicer. It has been demonstrated that miRNAs possess the characteristics of tissue specificity and sequential expression and only express in particular organs at stages of special developments. miRNAs play an essential role in cell differentiation, proliferation and apoptosis. Numerous studies show that endothelial-specific and endothelial-enriched miRNAs exert effects on vascular function. For example, endothelial-specific miR-126 plays a vital role in inflammation, angiogenesis, as well as endothelial integrity, while endothelial-enriched miR-221/222 and miR-21 participate in regulation of inflammation, angiogenesis, and endothelial senescence and so on.

Key words endothelial-specific miRNAs; endothelial-enriched miRNAs; vascular function

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MicroRNAs (miRNAs)是单链的含18~25个核苷酸长度的非蛋白编码RNA，主要通过作用于靶基因mRNA的3′非翻译区域调节mRNA的降解和蛋白翻译。到目前为止，已被发现的人类miRNAs序列就有1 400多个，有人推测至少有30%的基因是直接受miRNAs所调节[1]，因此对于这些miRNAs功能的研究已成为生物学和医学上的一大热点。

miRNAs参与体内多种生物学功能的调节，包括细胞增殖、凋亡、衰老、分化、代谢等。最近的研究表明，在血管内皮中存在内皮特异miRNAs (endothelial-specific miRNAs)和内皮富含miRNAs (endothelial-enriched miRNAs)，这些miRNAs对维持血管的正常功能具有重要作用。

1 内皮特异和富含miRNAs

随着对miRNAs认识的加深，人们逐渐发现某些miRNAs的表达存在组织或细胞特异性，如miR-9、miR-124a为脑特异性miRNAs[2-3]，miR-1、miR-133为肌肉特异性miRNAs[4]。而在血管内皮，至少有miR-126、miR-15a被认为是内皮特异性miRNAs[5-6]。除具备组织或细胞特异性外，miRNAs在不同的组织和细胞表达水平差别很大。在某些组织或细胞表达水平高的miRNAs，通常被称为组织或细胞富含的miRNAs。相对于内皮特异性miRNAs，目前报道的内皮富含的miRNAs数量则更多，如miR-21、miR-155、miR-221/222、miR-146等均在内皮细胞表达丰富[7-9]。近年研究表明，这些内皮特异或富含的miRNAs通过影响靶基因表达水平参与了血管内皮细胞、平滑肌细胞等病理生理功能的调节，对维持血管功能发挥重要作用(表1)。

2 内皮特异和富含miRNAs与血管新生

血管新生(angiogenesis)是指从已有的毛细血管或毛细血管后静脉发展而形成新的血管，是

表 1 内皮特异和富含的 miRNAs 及其对血管功能的影响

Table 1 Endothelial-specific and endothelial-enriched miRNAs and their effects on vascular function

内皮特异或富含的 miRNAs	对血管功能的影响				肿瘤	参考文献
	血管新生	内皮炎症	内皮损伤	动脉粥样硬化		
miR-126	+	–	–	–	–	[10-13]
miR-15a/16	–	?	?	?	–	[14-16]
miR-21	–	+	–	+	+	[7,16-18]
miR-155	+	–	+	–	+	[8,16,17,19,20]
miR-221/222	–	–	–	+	–	[1,8,17,19,21]
miR-146	?	–	+	+	–	[9,17,20,22]
miR-125a/b-5p	?	?	–	?	+	[22,23]
miR-17-92cluster	–	+	–	?	+	[11,19,22,24]
miR-23-27-24 cluster	+	?	?	+	?	[11]
miR-320	–	?	?	?	–	[25-27]
miR-103	+	?	?	?	+	[25,28,29]
miR-199a-5p	+	?	?	?	+	[30,31]
miR-130a	+	?	?	+	?	[25,32,33]
let-7	+	?	–	–	–	[16,25,28,34]
miR-150	+	?	?	?	+	[35-37]
miR-378	+	–	?	?	+	[35,38]
miR-30c	+	?	?	–	–	[35,39,40]
miR-31	+	–	–	?	+	[25,41,42]
miR-100	–	–	–	–	–	[17,25,43,44]
miR-191	?	?	?	?	+	[25,45]
miR-197	?	?	?	?	?	[10]
miR-625	?	?	?	?	–	[10,46]
miR-99a	?	?	?	?	–	[25,47]
miR-181a	?	?	?	?	+	[25,48]

+：促进；–：抑制；?：不确定。

一个涉及多种细胞和分子的复杂过程。血管的形成依赖于一系列血管生成调节因子的高度协调作用，例如血管内皮生长因子(vascular endothelial growth factor，VEGF)和它的内皮细胞特异性受体在血管形成的各个环节中均发挥重要作用。最近有大量研究表明，miRNAs能够在各种不同的环境下通过直接作用于VEGF信号通路的下游基因而调节血管新生[11,14,15]，其中，某些内皮特异或含量丰富的miRNAs，如miR-126、miR-15a/16、miR-21等，参与了血管新生的调节[7,11,15]。

miR-126是内皮特异性的miRNA，有证据表明它能够在体内调节血管新生。在小鼠和斑马鱼中敲除miR-126能够降低血管的完整性，抑制内皮细胞增殖、迁移以及血管生成[11]；在小鼠血管组织中特异性敲除miR-126，则能够导致血管渗漏、出血以及胚胎致死，这些现象可能是因为miR-126敲除后，血管生长因子表达下调，从而导致内皮细胞生长、增殖以及粘附能力减弱[11]。miR-126能够通过很多途径调节血管新生。它能通过抑制Spred-1(sprouty-related protein)和磷酸肌醇3激酶调节亚基2 (Phosphatidylinositol 3-kinase regulatory subunit 2，PIK3R2)基因(均为VEGF信号通路的负调节因子)表达，增强VEGF信号而促进血管新生[11]；miR-126促血管新生机制还涉及对金属蛋白酶-9(matrix metalloproteinase-9，MMP-9)的调节。MMP-9被认为是在血管新生过程中内皮细胞迁移的关键蛋白。低氧条件下，猴视网膜血管内皮细胞中miR-126的表达下调，MMP-9表达受到抑制，伴随血管新生受阻[49]。在肿瘤组织，miR-126则表现为抑制血管新生。在结直肠癌的原癌组织，miR-126表达下调，当恢复miR-126在这些细胞中的表达时，它能够抑制细胞的生长、迁移及侵袭[12]。进一步研究[12]发现，miR-126主要是通过下调VEGF表达抑制血管新生。miR-126在不同情况下对血管新生的调节表现出的矛盾现象值得深入探讨。

miR-15a/16也被认为是内皮特异性miRNA，位于人体的第13号染色体，聚集在13q14区域。miR-15a/16-1集落是首个被认为与哺乳动物癌症相关的miRNA基因[50]。而最近有研究表明miR-15a/16能够通过直接作用于成纤维生长因子2(fihroblast growth factor，FGF2)和VEGF-A抑制血管新生[14-15]。

miR-21在血管内皮表达丰富，一直以来都被认为对多种肿瘤发生关键基因表达具有调节作用。在肿瘤组织中，miR-21通过增强低氧诱导因子-1α(hypoxia inducible factor-1α，HIF-1α)和VEGF的表达促进血管新生，其作用机制涉及Akt/$ERK_{1/2}$信号通路的激活[51]。而Sabatel等[7]发现，在内皮细胞中，miR-21过表达能够减弱内皮细胞的增殖、迁移及其形成血管网状组织的能力，而抑制miR-21表达则作用相反，进一步研究发现miR-21是通过抑制人ras同源物基因家族成员b(human ras homolog gene family, memmber B，RhoB)表达而抑制血管新生。此外，与血管新生相关的内皮特异或富含miRNAs还有miR-17-92，miR-320，miR-320等(表1)。

3 内皮特异和富含miRNAs对血管内皮(祖)细胞功能的调节

内皮祖细胞(endothelial progenitor cells，EPCs)是血管内皮细胞的前体细胞，骨髓中含量丰富，可动员到外周血参与血管内皮损伤的修复。近年来的研究表明很多内皮特异或富含的miRNAs，如miR-21、miR-126等，参与了内皮(祖)细胞功能的调节[5,52]。

miR-126在内皮(祖)细胞中特异性表达，对内皮(祖)细胞功能的调节具有重要作用。Meng等[53]发现在糖尿病患者的内皮祖细胞中，miR-126主要通过下调Spred-1表达影响Ras/ERK/VEGF和PI3K/Akt/eNOS信号通路来调节内皮祖细胞功能；miR-126具有促进内皮祖细胞的增殖、动员和迁移作用，但不影响其向成熟内皮细胞分化[53]；过表达miR-126可以抑制内皮祖细胞向间质转化[5]，同时促进间质干细胞向内皮细胞分化[54]，该过程主要由PI3K/Akt信号通路所介导。

miR-21在内皮(祖)细胞表达丰富，也参与了内皮(祖)细胞功能的调节。通过PTEN/Akt途径，miR-21能调节TGF-β(诱导内皮间质转化和各种组织纤维化的主要细胞因子)介导的内皮间质转化(endothelial-to-mesenchymal transition, EndMT)[11]；通过TGF-β2信号通路，miR-21参与了多功能干细胞向内皮细胞系分化的调节[55]；通过下调高迁移率族蛋白A2(High mobility group A2，HMGA2)的表达，miR-21促进了内皮祖细胞的衰老[52]。最新的研究表明[56]，高糖能够刺激miR-21的表达，而miR-21的过表达又能够通过抑制死亡结构域相关蛋白(death domain-associated protein，DAXX)的表达对抗高糖对内皮细胞的毒性作用。

4 内皮特异和富含miRNAs与血管内皮损伤

血管内皮形态结构和功能完整对维持正常的血管通透性、张力和免疫防御等具有重要生理和病理学意义，而血管内皮损伤是多种心血管疾病的始动因素。多种miRNAs在血管的内皮损伤中发挥了重要作用，其中也包含内皮特异和内皮富含的miRNAs，如miR-155、miR-221/222等[8]。

miR-155是典型的多功能miRNA，参与造血、炎症、免疫等多种生物学功能的发生[19]。Zhu等[8]发现miR-155和miR-221/222在人脐静脉内皮细胞表达丰富，能调节血管紧张素Ⅱ(AngⅡ)诱导的内皮细胞炎症及迁移。AngⅡ是内皮细胞炎症及心血管疾病发生的重要调节因子，其大部分生物学功能是由血管紧张素Ⅱ受体1(AT1R)所介导，而AT1R是miR-155的靶基因，后者通过转录后机制抑制AT1R的表达[8]。进一步研究发现，miR-155和miR-221/222对内皮功能的调节还涉及Ets-1 (E-Twenty-Six-1)[8]。Ets-1是血管新生、血管重构及炎症的关键转录因子，是miR-155和miR-221/222共同靶基因。AngⅡ能诱导Ets-1及其下游靶基因的表达，过表达miR-155或miR-221/222则能够抑制Ets-1的表达[8]。由于Ets-1和AT1R均为miR-155的靶基因，miR-155可通过影响Ets-1和AT1R表达抑制内皮细胞炎症损伤。

miR-221和miR-222属于同一个家族并调节共同的靶基因，在血管平滑肌细胞(vascular smooth muscle cells，VSMCs)和血管内皮细胞(endothelial cells，ECs)中均表达丰富，并参与细胞增殖、迁移及凋亡的调节，但miR-221/222对VSMCs和ECs的作用存在差别。在VSMCs中，miR-221/222能促细胞增殖、迁移及抑制细胞凋亡[1]；而在ECs中，miR-221/222则表现出抑制细胞增殖、迁移及促进细胞凋亡的作用[1]。miR-221/222在不同细胞中功能差异的机制尚未阐明。此外，miR-221/222还与内皮细胞炎症、损伤修复以及血管新生等有关。miR-221/222能通过影响c-Kit，转录激活因子-5a (signal transducers and activators of transcription-5a，STAT5a)和锌指E盒结合同源盒蛋白2(zinc finger E-box binding homeobox protein-2, ZEB2)等信号分子而促进血管新生[1,19]，通过影响p27和p57等促进血管平滑肌细胞增殖及新生内膜增厚[1,19]，通过影响Est-1而调节内皮细胞炎症[8]。这些发现提示miR-221/222参与了血管内皮损伤的调节。

5 内皮特异和富含miRNAs对血管内皮素-1的表达调节作用

内皮素1 (endothelin 1, ET-1)是最初从血管内皮细胞中分离纯化出的一种活性多肽，是迄今所知最强的缩血管物质，对维持基础血管张力与心血管系统稳态起重要作用。ET-1基因的稳定表达不仅仅受其合成速率的影响，同时也涉及转录后调节机制。Li等[23]首先证明了miRNAs能够参与ET-1的转录后调节，他们还发现miR-125a/b-5p在血管内皮细胞中表达丰富，能直接与ET-1mRNA的3'-UTR结合而抑制ox-LDL诱导的ET-1的表达。

6 结语

在真核生物中，miRNAs只在特定的组织和发育阶段表达，具有组织特异性和时序性， miRNAs的这种特性在一定程度上决定了组织和细胞功能的特异性。随着人们对miRNAs认识的提高和研究的深入，在血管领域，内皮特异性或富含miRNAs逐渐步入人们的视野，对这一类miRNAs功能及机制的研究不仅有助于加深我们对各种血管疾病发生机制的认识，而且还能为疾病防治提供新的思路。目前，循环中miRNAs可能成为临床上疾病诊断的新型标志物，检测血液中内皮特异性或富含miRNAs的变化将有助于诊断与血管内皮功能紊乱相关的疾病，而外源性miRNAs的类似物或抑制剂则可能用于相关疾病的防治。需要指出的是，内皮特异性或富含miRNAs要用于临床疾病的治疗还面临诸多问题，如：影响心血管疾病发生发展的关键miRNAs是哪些？他们如何参与心血管疾病的发生发展？如何有效干预这些miRNAs的表达？随着人们对内皮特异和富含miRNAs研究的深入，以miRNAs为基础的血管新生疗法将为冠心病等血管相关性疾病的治疗指明新的方向。

参考文献

1. Liu X, Cheng Y, Yang J, et al. Cell-specific effects of miR-221/222 in vessels: molecular mechanism and therapeutic application[J]. J Mol Cell Cardiol, 2012, 52(1): 245-255.
2. Jung HJ, Coffinier C, Choe Y, et al. Regulation of prelamin A but not lamin C by miR-9, a brain-specific microRNA[J]. Proc Natl Acad Sci U S A, 2012, 109(7): E423-E431.

3. Kynast KL, Russe OQ, Möser CV, et al. Modulation of central nervous system-specific microRNA-124a alters the inflammatory response in the formalin test in mice[J]. Pain, 2013, 154(3): 368-376.
4. Nielsen S, Hvid T, Kelly M, et al. Muscle specific miRNAs are induced by testosterone and independently upregulated by age [J]. Front Physiol, 2014, 4: 394.
5. Zhang J, Zhang Z, Zhang DY, et al. microRNA 126 inhibits the transition of endothelial progenitor cells to mesenchymal cells via the PIK3R2-PI3K/Akt signalling pathway [J]. PLoS One, 2013, 8(12): e83294.
6. Yin KJ, Olsen K, Hamblin M, et al. Vascular endothelial cell-specific microRNA-15a inhibits angiogenesis in hindlimb ischemia[J]. J Biol Chem, 2012, 287(32): 27055-27064.
7. Sabatel C, Malvaux L, Bovy N, et al. MicroRNA-21 exhibits antiangiogenic function by targeting RhoB expression in endothelial cells [J]. PLoS One, 2011, 6(2): e16979.
8. Zhu N, Zhang D, Chen S, et al. Endothelial enriched microRNAs regulate angiotensin II-induced endothelial inflammation and migration[J]. Atherosclerosis, 2011, 215(2): 286-293.
9. Cheng HS, Sivachandran N, Lau A, et al. MicroRNA-146 represses endothelial activation by inhibiting pro-inflammatory pathways[J]. EMBO Mol Med, 2013, 5(7): 949-966.
10. Fish JE, Santoro MM, Morton SU, et al. miR-126 regulates angiogenic signaling and vascular integrity[J]. Dev Cell, 2008, 15(2): 272-284.
11. Yamakuchi M. MicroRNAs in Vascular Biology[J]. Int J Vasc Med, 2012, 2012: 794898.
12. Zhang Y, Wang X, Xu B, et al. Epigenetic silencing of miR-126 contributes to tumor invasion and angiogenesis in colorectal cancer[J]. Oncol Rep, 2013, 30(4): 1976-1984.
13. Schober A, Nazari-Jahantigh M, Wei Y, et al. MicroRNA-126-5p promotes endothelial proliferation and limits atherosclerosis by suppressing Dlk1[J]. Nat Med, 2014, 20(4): 368-376.
14. Xue G, Yan HL, Zhang Y, et al. c-Myc-mediated repression of miR-15-16 in hypoxia is induced by increased HIF-2α and promotes tumor angiogenesis and metastasis by upregulating FGF2 [J]. Oncogene, 2014. [Epub ahead of print].
15. Sun CY, She XM, Qin Y, et al. miR-15a and miR-16 affect the angiogenesis of multiple myeloma by targeting VEGF[J]. Carcinogenesis, 2013, 34(2): 426-435.
16. Tong AW, Nemunaitis J. Modulation of miRNA activity in human cancer: a new paradigm for cancer gene therapy?[J]. Cancer Gene Ther, 2008, 15(6): 341-355.
17. Jovanović I, Zivković M, Jovanović J, et al. The co-inertia approach in identification of specific microRNA in early and advanced atherosclerosis plaque[J]. Med Hypotheses, 2014, 83(1): 11-15.
18. Zhou J, Wang KC, Wu W, et al. MicroRNA-21 targets peroxisome proliferators-activated receptor-alpha in an autoregulatory loop to modulate flow-induced endothelial inflammation[J]. Proc Natl Acad Sci U S A, 2011, 108(25): 10355-10360.
19. Qin B, Yang H, Xiao B. Role of microRNAs in endothelial inflammation and senescence[J]. Mol Biol Rep, 2012, 39(4): 4509-4518.
20. Huang Y, Liu Y, Li L, et al. Involvement of inflammation-related miR-155 and miR-146a in diabetic nephropathy: implications for glomerular endothelial injury [J]. BMC Nephrol, 2014, 15: 142.
21. Dentelli P, Traversa M, Rosso A, et al. miR-221/222 control luminal breast cancer tumor progression by regulating different targets[J]. Cell Cycle, 2014, 13(11): 1811-1826.
22. Alemdehy MF, Erkeland SJ. MicroRNAs: key players of normal and malignant myelopoiesis[J]. Curr Opin Hematol, 2012, 19(4): 261-267.
23. Li D, Yang P, Xiong Q, et al. MicroRNA-125a/b-5p inhibits endothelin-1 expression in vascular endothelial cells[J]. J Hypertens, 2010, 28(8): 1646-1654.
24. Liu SQ, Jiang S, Li C, et al. miR-17-92 cluster targets phosphatase and tensin homology and Ikaros Family Zinc Finger 4 to promote TH17-mediated inflammation[J]. J Biol Chem, 2014, 289(18): 12446-12456.
25. Suárez Y, Sessa WC. MicroRNAs as novel regulators of angiogenesis[J]. Circ Res, 2009, 104(4): 442-454.
26. Wu YY, Chen YL, Jao YC, et al. miR-320 regulates tumor angiogenesis driven by vascular endothelial cells in oral cancer by silencing neuropilin 1[J]. Angiogenesis, 2014, 17(1): 247-260.
27. Wang XH, Qian RZ, Zhang W, et al. MicroRNA-320 expression in myocardial microvascular endothelial cells and its relationship with insulin-like growth factor-1 in type 2 diabetic rats[J]. Clin Exp Pharmacol Physiol, 2009, 36(2): 181-188.
28. Chen Z, Lai TC, Jan YH, et al. Hypoxia-responsive miRNAs target argonaute 1 to promote angiogenesis[J]. J Clin Invest, 2013, 123(3): 1057-1067.
29. Geng L, Sun B, Gao B, et al. MicroRNA-103 promotes colorectal cancer by targeting tumor suppressor DICER and PTEN[J]. Int J Mol Sci, 2014, 15(5): 8458-8472.
30. Zhang S, Liu L, Wang R, et al. MiR-199a-5p promotes migration and tube formation of human cytomegalovirus-infected endothelial cells through downregulation of SIRT1 and eNOS[J]. Arch Virol, 2013, 158(12): 2443-2452.
31. Chen R, Alvero AB, Silasi DA, et al. Regulation of IKKbeta by miR-199a affects NF-kappaB activity in ovarian cancer cells[J]. Oncogene, 2008, 27(34): 4712-4723.
32. Chen Y, Gorski DH. Regulation of angiogenesis through a microRNA (miR-130a) that down-regulates antiangiogenic homeobox genes GAX and HOXA5[J]. Blood, 2008, 111(3): 1217-1226.
33. Li T, Cao H, Zhuang J, et al. Identification of miR-130a, miR-27b and miR-210 as serum biomarkers for atherosclerosis obliterans[J]. Clin

Chim Acta, 2011, 412(1-2): 66-70.

34. Bao MH, Zhang YW, Lou XY, et al. Protective effects of let-7a and let-7b on oxidized low-density lipoprotein induced endothelial cell injuries [J]. PLoS One, 2014, 9(9): e106540.
35. Wagner J, Riwanto M, Besler C, et al. Characterization of levels and cellular transfer of circulating lipoprotein-bound microRNAs[J]. Arterioscler Thromb Vasc Biol, 2013, 33(6): 1392-1400.
36. Liu Y, Zhao L, Li D, et al. Microvesicle-delivery miR-150 promotes tumorigenesis by up-regulating VEGF, and the neutralization of miR-150 attenuate tumor development[J]. Protein Cell, 2013, 4(12): 932-941.
37. Li J, Zhang Y, Liu Y, et al. Microvesicle-mediated transfer of microRNA-150 from monocytes to endothelial cells promotes angiogenesis[J]. J Biol Chem, 2013, 288(32): 23586-23596.
38. Yu BL, Peng XH, Zhao FP, et al. MicroRNA-378 functions as an onco-miR in nasopharyngeal carcinoma by repressing TOB2 expression[J]. Int J Oncol, 2014, 44(4): 1215-1222.
39. Soh J, Iqbal J, Queiroz J, et al. MicroRNA-30c reduces hyperlipidemia and atherosclerosis in mice by decreasing lipid synthesis and lipoprotein secretion[J]. Nat Med, 2013, 19(7): 892-900.
40. Zhong K, Chen K, Han L, et al. MicroRNA-30b/c inhibits non-small cell lung cancer cell proliferation by targeting Rab18 [J]. BMC Cancer, 2014, 14: 703.
41. Suárez Y, Wang C, Manes TD, et al. Cutting edge: TNF-induced microRNAs regulate TNF-induced expression of E-selectin and intercellular adhesion molecule-1 on human endothelial cells: feedback control of inflammation [J]. J Immunol, 2010, 184(1): 21-25.
42. Wu YH, Hu TF, Chen YC, et al. The manipulation of miRNA-gene regulatory networks by KSHV induces endothelial cell motility[J]. Blood, 2011, 118(10): 2896-2905.
43. Leonhardt F, Grundmann S, Behe M, et al. Inflammatory neovascularization during graft-versus-host disease is regulated by αv integrin and miR-100[J]. Blood, 2013,121(17):3307-3318.
44. Deng L, Shang L, Bai S, et al. MicroRNA100 Inhibits Self-Renewal of Breast Cancer Stem-like Cells and Breast Tumor Development[J]. Cancer Res, 2014, 74(22): 6648-6660.
45. Liu H, Xu XF, Zhao Y, et al. MicroRNA-191 promotes pancreatic cancer progression by targeting USP10[J]. Tumour Biol, 2014. [Epub ahead of print].
46. Lou X, Qi X, Zhang Y, et al. Decreased expression of microRNA-625 is associated with tumor metastasis and poor prognosis in patients with colorectal cancer[J]. J Surg Oncol, 2013, 108(4): 230-235.
47. Yu S, Zhang C, Deng F, et al. miR-99a suppresses the metastasis of human non-small cell lung cancer cells by targeting AKT1 signaling pathway [J]. J Cell Biochem, 2014. [Epub ahead of print].
48. Ji D, Chen Z, Li M, et al. MicroRNA-181a promotes tumor growth and liver metastasis in colorectal cancer by targeting the tumor suppressor WIF-1[J]. Mol Cancer, 2014, 13: 86.
49. Ye P, Liu J, He F, et al. Hypoxia-induced deregulation of miR-126 and its regulative effect on VEGF and MMP-9 expression[J]. Int J Med Sci, 2013, 11(1): 17-23.
50. Calin GA, Dumitru CD, Shimizu M, et al. Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia[J]. Proc Natl Acad Sci U S A, 2002, 99(24): 15524-15529.
51. Liu LZ, Li C, Chen Q, et al. MiR-21 induced angiogenesis through AKT and ERK activation and HIF-1α expression [J]. PLoS One, 2011, 6(4): e19139.
52. Zhu S, Deng S, Ma Q, et al. MicroRNA-10A* and MicroRNA-21 modulate endothelial progenitor cell senescence via suppressing high-mobility group A2[J]. Circ Res, 2013, 112(1): 152-164.
53. Meng S, Cao JT, Zhang B, et al. Downregulation of microRNA-126 in endothelial progenitor cells from diabetes patients, impairs their functional properties, via target gene Spred-1[J]. J Mol Cell Cardiol, 2012, 53(1): 64-72.
54. Huang F, Fang ZF, Hu XQ, et al. Overexpression of miR-126 promotes the differentiation of mesenchymal stem cells toward endothelial cells via activation of PI3K/Akt and MAPK/ERK pathways and release of paracrine factors[J]. Biol Chem, 2013, 394(9): 1223-1233.
55. Di Bernardini E, Campagnolo P, Margariti A, et al. Endothelial lineage differentiation from induced pluripotent stem cells is regulated by microRNA-21 and transforming growth factor β2 (TGF-β2) pathways[J]. J Biol Chem, 2014, 289(6): 3383-3393.
56. Zeng J, Xiong Y, Li G, et al. MiR-21 is overexpressed in response to high glucose and protects endothelial cells from apoptosis[J]. Exp Clin Endocrinol Diabetes, 2013, 121(7): 425-430.

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