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综 述

血管发育相关microRNAs的研究进展

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摘 要：脊椎动物血管系统的发育是一个极其重要且复杂的过程。MicroRNAs在转录及转录后水平对基因表达起调控作用，参与了诸多重要的生理、病理过程。MicroRNAs主要在血管平滑肌细胞和血管内皮细胞的发育调控中发挥着重要作用。本文归纳了近年来有关microRNAs在血管发育中的研究进展，着重阐述了miR-126、miR-17/92家族等在血管内皮细胞中的调控作用机制，以及miR-143/145家族、miR-21等在血管平滑肌细胞中的调控作用机制。本文还对microRNAs在血管发育中作用的研究前景作了展望。

关键词：血管发育；microRNAs；调控
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Research progress on microRNAs involved in vascular development

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Abstract: The vertebrate vascular system development is a very important and complicated process. MicroRNAs regulate gene expression at transcriptional and post-transcriptional levels and play important roles in many physiological and pathological processes. MicroRNAs mainly participate in the regulation of vascular smooth muscle cell and vascular endothelial cell development. In this paper, we summarize the recent progress regarding the microRNAs involved in the vascular development. In particular, we focus on the microRNAs including miR-126, miR-17/92 family in endothelial cell's regulation, and miR-143/145 family, miR-21 in vascular smooth muscle cell's regulation. The future research on the role of microRNAs in vascular development is also prospected.

Key words: vascular development; microRNAs; regulation

20 世纪 50 年代，科学家借助光学显微镜发现，无脊椎动物的血液循环系统中缺少内皮细胞，因此无脊椎动物无法像脊椎动物一样进行一系列演变，形成一个闭锁型血管系统[1]。脊椎动物体内出现闭锁型血管系统有助于脊椎动物的生长发育，也是生物进化过程中的重要环节。血管系统为生物个体的生长、发育、存活提供氧气输送及各种养分供给。在胚胎发育时期，血管系统发育出现障碍可能导致胚胎死亡或个体发育障碍致残。

在高等脊椎动物中，血管发育是一个非常复杂的过程。在高等脊椎动物体内存在两个血管系统，血液血管系统与淋巴血管系统[2]。血液血管系统发育又可分为血管发生和血管生成两个部分。淋巴血管系统与血液血管系统存在一定的不同：血液血管

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是一个环状的系统，而淋巴血管系统则是一个线性系统；毛细血管是由血管内皮细胞包绕而形成，而组成毛细淋巴的内皮细胞之间的连接呈叠瓦状，即一个细胞边缘叠于另一个边缘[3]。二者在组织液的再吸收[2]等功能上相互联系。血液血管系统与淋巴血管系统的存在以及二者之间的紧密联系在高等脊椎动物中是必不可少的[4]。

MicroRNAs是一类长21~23 nt的单链非编码小RNA，通过识别靶mRNA的3’非翻译区序列与其靶向结合，在转录后抑制其靶基因的翻译水平而发挥作用[5]。目前已有许多关于microRNAs调控血管发育的研究报道，本文主要对microRNAs在血管发育中的调控机制的研究进展作一综述。

1 MicroRNAs在血管发育中的研究

MicroRNAs广泛存在于各种动植物基因组中，在物种进化过程中保持高度同源性和保守性，并且在物种中具有严格的表达特异性和时序性[6]。1993年，Lee等在秀丽隐杆线虫中发现第1个microRNA，与调控幼虫胚胎发育的时序性基因*lin-4*反义互补[7]。到目前为止，已有数以千计的microRNAs在果蝇、线虫、小鼠和人等多种物种中被发现。研究显示，microRNAs不仅能在转录后mRNA水平上起调控作用，也能在转录水平介导很多关键的生理进程和病理过程，包括细胞增殖、细胞命运决定、细胞分化、细胞代谢、细胞凋亡等，是一类重要的非编码RNA[8]。

1.1 与血液血管系统发育相关的microRNAs的研究

1.1.1 影响血管平滑肌细胞的microRNAs

迄今为止，许多与血管发育相关的microRNAs已被研究报道，有许多是与血管平滑肌细胞相关的，如miR-21在血管平滑肌细胞增殖和迁移中有重要的调节作用[9]，在内皮细胞中也有较高水平的表达[10]。下调miR-21的表达会增加细胞凋亡，抑制动脉外膜成纤维细胞和肌成纤维细胞的增殖[11]。miR-21通过影响骨形态生成蛋白4 (bone morphogenetic protein 4, BMP4)和转化生长因子-β (transforming growth factor β, TGF-β)信号转导通路来调控血管平滑肌细胞的分化[12]。miR-21也调节平滑肌细胞和内皮细胞，影响血管重构[10]。研究显示，在人动脉粥样硬化病变中miR-21的表达量增加[13]。在去除血清条件的体外实验中，人或小鼠的大动脉平滑肌细胞分化会减少miR-21的表达[10]。在体外实验的小鼠主动脉平滑肌细胞以及损伤的小鼠颈动脉中，沉默miR-21将会抑制细胞增殖，增加细胞凋亡[10]。在小鼠中，敲降miR-21会抑制颈动脉球囊损伤中的血管重建[10]。研究显示，miR-21在多种实体瘤中相对于正常细胞有较高的表达量[14]，因此miR-21既有促进细胞增殖的作用，也有抑制细胞增殖的作用。

研究显示，miR-146a能在体外促进血管平滑肌细胞增殖，在体内能促进血管新生内膜增生[15]。转染反义miR-146a寡核苷酸到颈动脉球囊损伤的小鼠中可显著减少新生内膜增生[15]，这表明miR-146a能促进血管平滑肌增殖。同时miR-146能形成一个负反馈回路抑制Toll样受体(Toll-like receptor, TLR)信号通路，这种负反馈在一定程度上导致了内毒素诱导的耐受性，并且能抑制炎症因子的产生[16]。研究还显示，miR-147和miR-155也具有相似的功能[17]。

有许多研究表明，血管细胞运动在各种癌症和心血管疾病的发展中起着至关重要的作用，而miR-143/145家族可以调节血管细胞运动[18]。在小鼠中，敲除miR-143和miR-145都可导致血管张力异常和血管平滑肌细胞的特异基因的表达下调[19]。有研究表明，缺失这个家族将导致血管损伤中的内膜增殖应答减少[19]。miR-143/145家族在正常的血管平滑肌细胞中有较高的表达量，但是该家族在急性和慢性血管压力以及人类主动脉瘤中的表达量都较少[18]，并且在增生的血管平滑肌细胞中的表达有所下降[20,21]。在该家族中，miR-145与miR-143相互作用，上调众多靶基因的表达，包括Kruppel样因子4 (Kruppel-like factor 4, KLF4)、Elk-1 (ETS癌基因家族成员)[21]、血管紧张素转化酶(angiotensin-converting enzyme, ACE)[22]、血清应答因子(serum response factor, SRF)以及它的共活化剂——心肌素[19]，表明miR-145可调控人胚胎干细胞的分化和骨髓干细胞的自我更新。miR-143可通过多功能蛋白聚糖抑制血管平滑肌细胞的迁移[23]。

血小板源性生长因子可诱导miR-24转录，从而诱导出血管平滑肌细胞合成表型[24]。上调血小板源性生长因子的刺激，miR-24的表达将会提高。miR-24在应激状态下的内皮细胞中高表达，如氧化应激。在小鼠体内，反义表达miR-24会提高血管的形成和心脏功能[25]。

在血管平滑肌细胞中转染反义miR-155抑制剂，可上调内源性血管紧张素II-1型受体(angiotensin II type 1 receptor, AGTR1)的表达[26]。miR-155在平滑肌细胞中表达，在动脉粥样硬化的形成中缺少miR-155可减少巨噬细胞的脂肪堆积[27]。在动脉粥样硬化损伤的小鼠和人体内miR-155表达上调，虽然miR-155表达上调可促进人动脉粥样硬化损伤，但是冠状动脉疾病患者miR-155的循环水平却是下降的[13]。有研究表明，在miR-155缺陷型的小鼠骨髓中植入高脂饮食的LDLR缺陷型小鼠骨髓，将加重粥样硬化病变和炎症反应[27]。

miR-30b和miR-30c表达下调可导致血管平滑肌细胞钙化加重[28]。抑制miR-26a可加速血管平滑肌细胞分化，miR-26a调控TGF-β信号通路可能会改变血管平滑肌表型[29]。在血管平滑肌增殖和血管壁新生内膜的生长过程中，miR-31的表达显著增加[30]；敲除miR-31可下调血清和血小板源性生长因子，从而诱导血管平滑肌细胞增殖[30]。过表达miR-208能促进血管平滑肌细胞增殖，并可增加胰岛素对血管平滑肌细胞增殖的调节作用[31]。在血管平滑肌细胞中，过表达miR-181a下调血管紧张素II (angiotensin II, Ang II)表达，上调骨调素(osteopontin, OPN)表达，并增强血管平滑肌细胞与胶原蛋白的附着力[32]。在人主动脉平滑肌细胞中，过表达心肌素可上调miR-1的表达，并抑制血管平滑肌细胞的增殖[33]。

1.1.2 影响血管内皮细胞的microRNAs

除了上述与血管平滑肌细胞相关的microRNAs，还有不少microRNAs是通过影响内皮细胞进而影响血管系统的发育。

miR-17/92家族包括6个microRNAs：17、18a、19a、20a、19b-1和92a-1[34]。研究表明，缺少这个microRNA家族将导致小鼠出生后由于心脏间隔缺损而死亡[18, 35]。这个家族在内皮细胞中高表达，通过阻碍内皮细胞运动从而抑制血管生成[36]。miR-17/92家族调控原癌基因的表达，该microRNAs家族下调抗血管生成分子——血小板反应蛋白和结缔组织生长因子的表达[37]。对于该家族中单独的microRNA的研究较多，例如，抑制miR-92a的表达可提高在缺血损伤或心肌梗死时血管的生长[38]。在体外实验中，过表达miR-92a能抑制血管出芽形成和血管网络形成；而在动物实验中，过表达miR-92a则抑制血管生长因子表达[39]。miRNA-17/92家族别的成员，包括miR-17和miR-20a也同样可以抑制血管生长[40]。

研究显示，miR-126在内皮细胞中高表达[41]。miR-126抑制PI3K和MAPK信号通路从而促进血管生成，下调炎症性黏附分子和血管细胞黏附分子1 (vascular cell adhesion molecule 1, VCAM1)的表达(图1)[42]。miR-126可以抑制动脉粥样硬化的形成并且能增加血小板的稳定性，可以调控生成血管信号级联放大，在内皮细胞中可以作为一个抗炎症介质抑制炎症反应[43]。以上研究表明miR-126可调控一系列病理条件下的血管生成，提示其可在将来的癌症治疗中起到一定作用。在人脐静脉内皮细胞损伤时，过表达miR-126会显著增强PI3K/Akt信号通路[44]。在小鼠中，敲除miR-126后，其在胚胎期的血管出现破裂，其在成体组织的血管损伤中能提高促血管新生因子的活性，对新生血管形成有促进作用[45]。

最近的研究显示，miR-221能通过调控PI3K调节亚基下调血管内皮生长因子(vascular endothelial growth factor, VEGF)受体信号[46]。miR-221/222家族是c-Kit和let-7f的靶基因，该家族能通过血小板反应蛋白1促进血管生成[11]。深度测序结果显示，

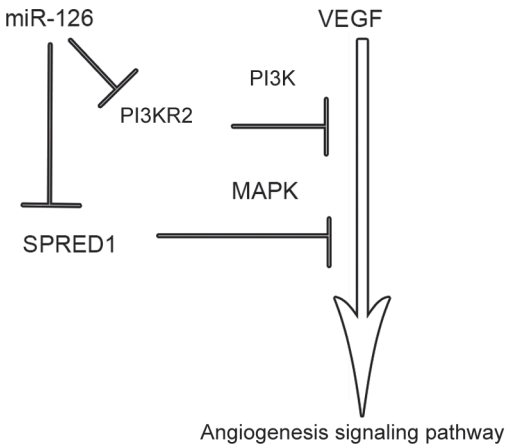

图 1. miR-126调控血管生成信号通路示意图

Fig. 1. Schematic diagram of signal pathways for miR-126 to regulate angiogenesis. VEGF, vascular endothelial growth factor; PI3K, phosphoinositide 3-kinase pathway; MAPK, mitogen-activated protein kinase pathway; PI3KR2, phosphoinositide 3-kinase, regulatory subunit 2; SPRED1, Sprouty-related, EVH1 domain-containing 1.

表1. 部分已报道的与血管发育相关的microRNAs

Table 1. Some microRNAs involved in the vascular development which have been reported

miRNA	Subject	Method	Target gene	Function
miR-126	Mouse	Knockout	*F4C*	Plays a role in the formation of new blood vessels [55]
	Mouse	Knockout	*Egfl7*	Plays an important role in embryonic blood vessel formation development [55]
	Mouse	Injection of miR-126	*Cxcl12*	Regulation of apoptotic body makes it have the function of anti-atherosclerosis [43]
	Human umbilical vein endothelial cells	Transfection of miR-126	*VCAM-1*	Inhibits VCAM-1 and regulates vascular inflammation [56]
	Zebrafish	Knockdown	*Flt4*	Inhibits the development of lymphatic vessels in the face and torso [57]
	Mouse	Knockout	*Flt4*	Regulates the development of the lymphatic network [58]
	Zebrafish	Knockdown	*Spred1*	Enhances *Spred1* activity [57]
	Human coronary endothelial cells	Knockdown	*Spred1*	Regulates *Spred1* expression [58]
	Endothelial progenitor cell	Overexpression	*PI3KR2*	Regulates angiogenesis via targeting PI3KR2 [59]
	Zebrafish	Knockdown	*Pak1*	Regulates the expression of Pak1 in endothelial cells and causing head hemorrhage in zebrafish [60]
miR-126a	Zebrafish embryos	Knockdown	*Cxcl12a*	Regulates the formation of lymphatic vascular cavity [61]
miR-92a	Vascular smooth muscle cells	Overexpression	*MKK4*, *JNK1*	Down-regulates MKK4 and JNK1 [62]
	Mouse	Knockout	*Itga5*	Damages the development of the neointima [63]
miR-19a	Endothelial cells	Overexpression	*Cyclin D1*	Inhibits endothelial cell proliferation via negatively regulating Cyclin D1 [64]
miR-146a, miR-21	Human coronary smooth muscle cells	Overexpression	*Notch2*	Inhibits expression of Notch2 to regulate proliferation of smooth muscle cells [65]
miR-146a	Human umbilical vein endothelial cells	Overexpression	*IRAK1*	Down-regulates IRAK1 [66]
	Vascular smooth muscle cells	Knockdown	*NF-κB*, *KLF4*	Regulates the proliferation and migration of vascular smooth muscle cells via targeting NF-κB and KLF4 [67, 68]
miR-155	Mouse	Knockout	*MST2*	Regulates vascular smooth muscle cells by down-regulating MST2 [69]
	Mouse	Knockout	*TNF-α*	Regulates vascular inflammatory response and proliferation of neointima [70]
	Mouse	Knockout	*CCN1*	Promotes angiogenesis [71]
miR-10a	Mouse umbilical vein endothelial cells	Overexpression	*BMP2*	Reduces proliferation and migration of umbilical vein endothelial cells and the formation of lumen [72]
	Mouse smooth muscle cells	Transfection of miR-10a mimics	*HDAC4*	Reduces smooth muscle cell differentiation [73]
	Human arterial endothelial cells	Knockdown	*HOXA1*	Inhibits the expression of HOXA1 [74]
miR-10a, miR-22	Endothelial progenitor cell	Overexpression	*Hmga2*	Inhibits Hmga2 expression [75]
miR-100	Mouse	Silent expression	*mTOR*	Inhibits the formation of blood vessels [76]
miR-296	Human umbilical vein endothelial cells	Overexpression	*HGS*	Regulates HGS and promotes angiogenesis [77]
miR-378	NCI-H292 cells	Overexpression	*HMOX1*	Regulates HMOX1 and affects angiogenesis and growth of non-small cell lung cancer [78]
	Mouse	Injection of miR-378-transfected cancer cells	*VEGF*	Affects angiogenesis [48]
miR-23/27	Endothelial cells	Overexpression	*Sprouty*, *Sema6A*	Inhibits the expression of SEMA6A and SPROUTY and promotes angiogenesis [50]
miR-96	Vascular smooth muscle cells	Injection of anti-miR-96	*BMP4*	Regulates vascular smooth muscle cells via targeting BMP4 [79]
miR-34a	Vascular smooth muscle cells	Overexpression	*SIRT1*	Down-regulates SIRT1 and promotes senescence of vascular smooth muscle cells [80]
miR-217	Vascular smooth muscle cells	Transfection of mimics	*NMDAR*	Inhibits proliferation of vascular smooth muscle cells [81]
	Human umbilical vein endothelial cells	Transfection of mimics	*SIRT1*	Inhibits SIRT1 and regulates FoxO1 resulting in angiogenesis damage and promotes endothelial cell senescence [82]
miR-182	Zebrafish	Knockout	*FoxO1*	Regulates angiogenesis via targeting FoxO1 [83]

miR-221 在斑马鱼胚胎中可使内皮细胞增多 [46]。敲除 miR-221 并不影响胚胎的血管发育，但是可使血管生成和淋巴血管系统产生缺陷，这与缺少血管内皮细胞生长因子受体 -3 (vascular endothelial growth factor receptor 3, VEGFR-3) 相似 [46]。而过表达 miR-221 可以引起顶端细胞行为改变，例如增殖和迁移的增多 [47]。

miR-378 通过与 miR-125a 竞争 VEGF 3'-UTR 的同一个区域来促进 VEGF 表达 [48]。miR-378 通过靶基因 *Sufu* 和 *Fus-1* 来促进细胞存活，并且通过间接上调 VEGF 来调控肿瘤血管发生。研究显示，在小鼠中注射 miR-378 转染的癌细胞和单纯注射癌细胞相比，产生的血管更大；在肿瘤细胞中过表达 miR-378，会增加细胞存活力，减少细胞死亡，促进肿瘤生长和血管生成 [49]。

miR-23/27/24 家族在血管化的组织和内皮细胞中广泛存在。沉默 miR-23 和 miR-27 可抑制 VEGF 对 MAPK 和 PI3K/PKB 信号通路的激活作用，从而抑制血管新生，并且能抑制激光损伤后的脉络膜血管再生 [50]。在斑马鱼胚胎缺失节间血管的条件下，下调 miR-27 将诱导静脉重构和血管生成 [51]。miR-27 功能缺失表型可以通过抑制 *Sprouty* 或 *DLL4* 基因中的其中一个进行补偿，因此，在斑马鱼的血管发育中这两个基因可能是 miR-27 主要的靶基因 [51]。

在血管内皮细胞中，低氧可引起 miR-210 的表达 [52]。miR-210 能在低氧条件下通过抑制 Ephrin-A3 促进毛细血管出芽的形成，减少细胞凋亡 [52]。皮肤受损时，miR-200b 下调可促进内皮细胞中的血管生成 [53]。在内皮细胞中，过表达 miR-181b 可抑制核因子 -κB (nuclear factor κB, NF-κB) 应答基因的表达；在小鼠血管内皮细胞对促炎性因子的刺激性应答中，miR-181b 的表达量减少 [54]。

除了上述提到的 microRNAs 外，还有不少 microRNAs 也影响着血管的发育，表 1 罗列出了部分影响血液血管系统发育的 microRNAs，并列出其靶基因以及功能。

1.2 与淋巴血管系统发育相关的microRNAs的研究

microRNAs 不仅调控血液血管系统的发育，也调控淋巴血管系统的发育。

miR-31 在非洲爪蟾早期胚胎淋巴血管系统发育中起作用 [84]。研究显示，在淋巴内皮细胞中，敲降 *FAT4* 能增强细胞迁移，而 *FAT4* 是 miR-31 的靶基因 [85]。研究显示，在斑马鱼胚胎淋巴血管形成过程中，miR-31 和 miR-181a 都在血管内皮细胞中表达，并且 miR-31 或 miR-181a 通过调控 BMP2b/BMP2 信号通路进而调节淋巴血管形成 [86]。体外实验证明，miR-184 抑制角膜淋巴血管生成，过表达 miR-184 会降低淋巴内皮细胞的迁移，并且抑制淋巴内皮细胞管腔形成 [87]。在人淋巴内皮细胞中，过表达 miR-27a 会减少淋巴管腔形成和迁移，miR-27a 的靶基因是 *SMAD4*，*SMAD4* 在人淋巴内皮细胞的形成和迁移中负调控淋巴血管的长度 [88]。miR-206 在胰腺导管腺癌细胞中抑制肿瘤淋巴血管形成，因而使肿瘤生长延缓，在癌症治疗研究中具有一定的意义 [89]。对斑马鱼淋巴血管形态形成的研究显示，敲降 miR-182 的斑马鱼脊索旁淋巴血管存在缺陷 [83]。

2 问题与展望

血管发育是一个极其重要且复杂的过程，包含内皮细胞的分化、血管生成和血管发生以及淋巴血管系统的形成等过程，同时涉及到诸如 Notch、BMP 等众多信号通路与转录因子，这些调控因子控制着内皮细胞的分化、运动等，从而调控着血管的发育。因此，研究血管发育机制及其相关的信号通路对动物的进化、生长发育、繁殖等具有一定的推进作用。

许多血管发育相关的研究表明，microRNAs 在血管发育中起着重要的作用，microRNAs 主要通过调控其靶基因进而抑制血管发育或使血管增生，在血液血管系统中的血管平滑肌细胞和血管内皮细胞中具有重要的调控作用。虽然已有许多研究揭示了 microRNAs 在血管发育中的调控机制，但是还有很多在血管发育过程中具有重要功能的 microRNAs 没有被发现。进一步探索 microRNAs 对血管发育的调控，将有助于我们深入了解生命发生过程，对于生物进化的研究具有重要意义。

* * *

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