

·综述·

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## microRNAs 在高血压疾病中的作用机制

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**摘要** 高血压作为一种多因素的慢性疾病,其引起的一系列并发症是导致心血管疾病死亡的主要原因。微RNA(microRNA, miRNAs)作为内源性单链非编码RNA,在高血压的病理生理过程中发挥重要作用。miRNAs通过调控血管内皮细胞损伤、血管平滑肌细胞功能障碍、单核/巨噬细胞介导的免疫炎症反应、氧化应激、一氧化氮合成异常、肾素-血管紧张素-醛固酮系统的激活、交感神经激活、肾水钠潴留和胰岛素抵抗等过程,进而广泛参与高血压的发病过程。本文就miRNAs在高血压发生发展中的作用机制及其研究进展进行简要综述,为高血压早期诊断及治疗提供新思路。

**关键词** 高血压;微小核糖酸;血管重塑

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## Mechanisms of MicroRNAs in Hypertension

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**Abstract** Hypertension, as a multi-factor chronic disease, causes a series of complications that are the main causes of cardiovascular deaths. MicroRNAs (miRNAs), as endogenous single-strand non-coding RNAs, play an important role in the pathophysiological process of hypertension. miRNAs are involved in the pathogenesis of hypertension through regulating vascular endothelial cell injury, vascular smooth muscle cell dysfunction, monocyte/macrophage-mediated immune inflammatory response, oxidative stress, abnormal synthesis of nitric oxide, activation of renin-angiotensin-aldosterone system, sympathetic activation, sodium retention and insulin resistance. This review summarizes the role of miRNAs in the development of hypertension and provides new ideas for early diagnosis and therapy of hypertension.

**Key words** hypertension; microRNAs(miRNAs); vasculature remodeling

微RNA(microRNA, miRNAs)是长度约22 nt的内源性单链非编码RNA,通过与靶基因mRNA 3'非编码区(3'-UTR)互补配对,促使靶基因降解或抑制其翻译过程,从而调节多种生物学过程,包括器官发育、细胞分化、增殖、凋亡和代谢等<sup>[1-3]</sup>。高血压是以血压持续升高为特点的一种临床常见慢性疾病,其主要并发症有脑卒中、心肌梗死、心力衰竭及慢性肾功能衰竭等。据世界卫生组织卫生数据统计,高血压影响到25岁以上40%的成年人,其发病率和死亡率很高,严重危害公众健康,但其发病机制仍不清楚<sup>[4]</sup>。目前研究认为,高血压的发病机制主要包括血管内皮细胞损伤、血管平滑肌细胞功能障碍、单核/巨噬细胞介导的免疫炎症反应、氧化应激、一氧

化氮(nitric oxide, NO)合成异常、肾素-血管紧张素-醛固酮系统(renin-angiotensin-aldosterone system, RAAS)激活、交感神经激活、肾水钠潴留和胰岛素

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抵抗等过程。而表达异常的 miRNAs 可通过调控上述机制, 从而对高血压的发生产生重要影响<sup>[5,6]</sup>。因此, 全面了解 miRNAs 在高血压发生过程中的调控作用及其病理生理机制, 对高血压的防治具有重要意义。

## 1 miRNAs 参与调节血管细胞的生物学过程

### 1.1 miRNAs 调节血管内皮细胞增殖、迁移、凋亡以及炎症过程

血管内皮细胞是介于血管平滑肌细胞和血液间的机械屏障, 可分泌血管舒张因子和收缩因子。血管内皮障碍导致血管舒缩状态异常、凝血及纤溶系统失衡、血管平滑肌细胞功能异常以及炎性细胞聚集等, 引起高血压等一系列心血管疾病<sup>[7]</sup>。miRNAs 通过调控血管内皮细胞生物学功能参与高血压的发生与发展<sup>[8]</sup>。miR-126 和 miR-92a 参与调控血管内皮细胞的增殖和迁移过程。过表达 miR-126 上调血管内皮生长因子 (vascular endothelial growth factor, VEGF) 和成纤维细胞生长因子 (fibroblast growth factor, FGF) 表达, 促进小鼠主动脉内皮细胞增殖和血管生成<sup>[9]</sup>。大鼠主动脉内皮细胞中抑制 miR-92a 表达, 上调细胞外调节蛋白激酶 (extracellular regulated protein kinase, ERK) 1/2、c-Jun 氨基末端激酶 (c-Jun N-terminal kinase, JNK) 以及内皮型一氧化氮合酶 (endothelial nitric oxide synthase, eNOS) 表达, 促进内皮细胞的增殖和迁移, 抑制大鼠颈动脉球囊损伤后的血管内膜增生<sup>[10]</sup>。相反, 过表达 miR-92a 可以抑制靶基因整合素  $\alpha 5$  和沉默信息调节因子 2 相关酶 1 (silence information regulator two 1, SIRT1) 表达, 降低 eNOS 表达, 从而抑制人冠状动脉内皮细胞增殖和迁移<sup>[11]</sup>。另外, miR-24、miR-34a 以及 miR-506 参与调控血管内皮细胞的凋亡过程。miR-24 通过抑制重组 GATA 结合蛋白 2 (recombinant GATA binding protein 2) 和重组 p21 活化激酶 4 (recombinant p21 protein activated kinase 4) 表达, 从而引起人脐静脉内皮细胞的凋亡<sup>[12]</sup>。过表达 miR-34a 和 miR-506-3p 可分别抑制转化生长因子  $\beta$  诱导因子 2 (transforming growth factor- $\beta$ -induced factor 2, Tgif2), 以及肌球蛋白样 BCL2 结合蛋白 (coiled-coil, myosin-like BCL-2 interacting protein, BECN1) 表达, 促进人脐静脉内皮细胞凋亡, 引起血管损伤<sup>[13,14]</sup>。此外, miR-132、miR-126 在调控血管内皮细胞的炎症过程也发挥着重要作用。

miR-132 通过抑制 SIRT1、固醇调节元件结合蛋白 1c (sterol-regulatory elementary binding protein-1c, SREBP-1c)、脂肪酸合成酶 (fatty acid synthase, FASN) 和 HMG-CoA 还原酶 (3-hydroxy-3-methyl glutaryl-CoA reductase, HMGCR) 表达, 从而促进肿瘤坏死因子  $\alpha$  (tumor necrosis factor  $\alpha$ , TNF- $\alpha$ ) 诱导的人脐静脉内皮细胞炎症过程<sup>[15]</sup>。而过表达 miR-126 则通过抑制血管细胞黏附分子 (vascular cell adhesion molecule 1, VCAM-1) 表达, 抑制单核细胞黏附和入脐静脉内皮细胞的炎症过程<sup>[16]</sup>。

### 1.2 miRNAs 调节血管平滑肌细胞表型转换

血管舒缩功能异常是高血压重要的病理改变, 主要取决于血管平滑肌细胞的结构与功能。当血管壁损伤时, 血管平滑肌细胞表型由收缩型转换为合成型, 表现为细胞增殖和迁移、胶原沉积以及细胞外基质合成增加。miRNAs 通过调节血管平滑肌细胞增殖、分化及表型转换参与高血压的发生与发展<sup>[17]</sup>。大鼠体内过表达 miR-145 或抑制 miR-146a 表达可分别通过下调 kruppel-样因子 5 (krueppel-like factor 5, KLF5) 表达, 或促进 kruppel-样因子 4 (krueppel-like factor 4, KLF4) 表达, 从而抑制血管平滑肌细胞增殖和分化, 减少大鼠颈动脉球囊损伤后的血管内膜增生<sup>[18,19]</sup>。小鼠血管平滑肌细胞中, 过表达 miR-143/145 可以下调血管紧张素转化酶 (angiotensin converting enzyme, ACE) 和血管紧张素 II 1 型受体 (angiotensin II type 1 receptor, AT1R) 表达, 抑制平滑肌细胞的增殖和分化<sup>[20-22]</sup>。相反, 抑制 miR-16 表达则通过调控 ERK1/2 和 p38 信号通路, 从而促进 Ang II 诱导的小鼠血管平滑肌细胞的增殖和迁移<sup>[23]</sup>。miR-365 通过下调细胞周期蛋白 D1 (cyclin D1) 表达, 抑制血小板衍生生长因子 BB (platelet derived growth factor BB, PDGF-BB) 和血管紧张素 II (angiotensin II, Ang II) 诱导的大鼠主动脉平滑肌细胞增殖<sup>[24]</sup>。miR-424/322 和 miR-34b 可分别下调大鼠主动脉血管平滑肌细胞中的细胞周期蛋白 D1、 $\text{Ca}^{2+}$ -调节蛋白、基质相互作用分子 1 (stromal interaction molecule 1, STIM1) 和细胞周期蛋白依赖性激酶 6 (cyclin-dependent kinases 6, CDK6) 的表达, 抑制平滑肌细胞增殖和迁移<sup>[25,26]</sup>。此外, miR-26a 通过抑制信号转导与转录激活因子 1 (signal transducers and activators of transcription 1, SMAD-1) 的表达, 促进人主动脉血管平滑肌细胞增殖和迁移<sup>[27]</sup>。

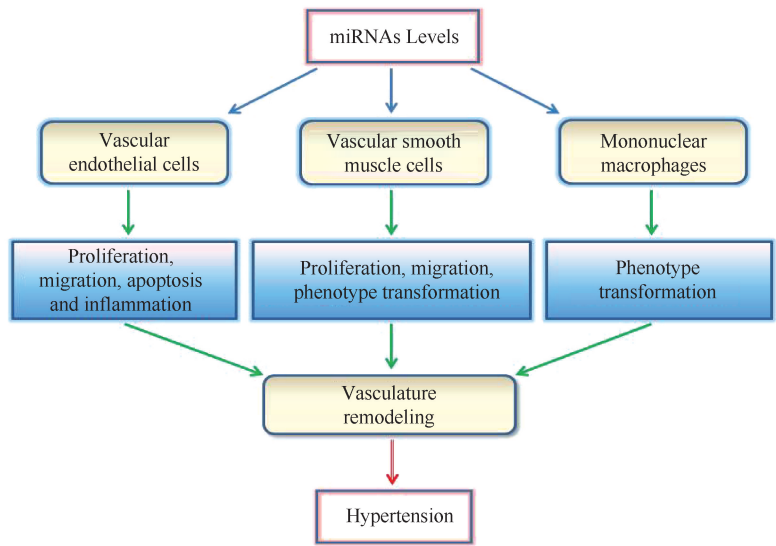
### 1.3 miRNAs 调节单核/巨噬细胞表型转换

在高血压发生过程中, 血管、心脏以及肾等靶器

官中有大量单核/巨噬细胞聚集,产生多种炎性因子及活性氧(reactive oxygen species, ROS),进一步损伤靶器官。巨噬细胞分为经典活化的 M1 型和选择性活化的 M2 型。M1 型巨噬细胞分泌大量的白细胞介素-1 $\beta$ (interleukin-1 beta, IL-1 $\beta$ )、白细胞介素-6(interleukin-6, IL-6)和 TNF- $\alpha$  等炎性细胞因子,促进 ROS 的合成,参与抗原呈递及 Th1 型免疫反应。M2 型巨噬细胞则分泌大量白细胞介素-10(interleukin-10, IL-10)、TGF- $\beta$  及精氨酸酶,从而抑制炎症反应,参与组织重塑以及免疫调节过程<sup>[28]</sup>。miRNAs 参与巨噬细胞表型转换,调节单核/巨噬细胞介导的炎症反应,从而影响高血压的发生与发展。小鼠骨髓巨噬细胞中过表达 miR-148a-3p 能通过下调 PTEN 的表达,促进 ROS 的产生,从而促进 M1 型巨噬细胞分化,抑制 M2 型巨噬细胞分化<sup>[29]</sup>。相反,

过表达 miR-125a-5p 则下调小鼠骨髓巨噬细胞中 krueppel 样因子 13(krueppel-like factor 13, KLF13)表达,促进 M2 型巨噬细胞分化<sup>[30]</sup>。人单核巨噬细胞(human mononuclear macrophage, THP-1)中过表达 miR-195 可以抑制 Toll 样受体 2(Toll-like receptor 2, TLR2)表达,促进 M2 型巨噬细胞分化,抑制细胞炎症因子分泌<sup>[31]</sup>。未经治疗的初诊高血压患者外周血单核细胞中,miR-208b 和 miR-133a 的表达水平与尿蛋白排泄水平呈强相关,其机制可能是过表达的 miR-208b 和 miR-133a 通过促进尿蛋白表达,引起血管内皮功能紊乱,从而引发高血压<sup>[32]</sup>。

miRNAs 在血管重构过程中发挥着重要作用。miRNAs 通过调节血管内皮细胞、血管平滑肌细胞和单核巨噬细胞生物学功能,进而影响高血压的发生与发展(Fig.1)。



**Fig.1 The role of miRNAs in vasculature remodeling in relation to hypertension** miRNAs regulates the biological functions of vascular endothelial cells, vascular smooth muscle cells and mononuclear macrophages, causing vascular remodeling and affecting development of hypertension

## 2 miRNAs 参与调节高血压的分子机制

### 2.1 miRNAs 调节一氧化氮的合成与释放

一氧化氮(NO)是血管内皮细胞分泌的一种重要的血管舒张调节因子。miRNAs 通过调节 NO 的合成和释放,影响血管内皮细胞功能,调节血管张力,进而参与高血压的发生和发展过程。人脐静脉内皮细胞中过表达 miR-122 能抑制溶质载体家族 7 成员 1(recombinant solute carrier family 7, member 1, SLC7A1)表达<sup>[33]</sup>,过表达 miR-155 则下调 eNOS 表达<sup>[34]</sup>,过表达 miR-24 下调特异性蛋白 1(specific protein 1, SP1)和 eNOS 表达<sup>[35]</sup>,以上均导致 NO 水

平降低,引起内皮细胞功能障碍。另有研究发现,过表达 miR-27b 能够下调肺动脉高血压大鼠体内过氧化物酶体增殖物激活受体- $\gamma$ (peroxisome proliferator-activated receptors- $\gamma$ , PPAR- $\gamma$ ),促进 eNOS 表达以及 NO 产生,从而抑制野百合碱诱导的血管内皮功能损伤<sup>[36]</sup>。

### 2.2 miRNAs 调节氧化应激过程

ROS 在调节血管舒缩及维持心血管功能方面发挥了重要作用。体内 ROS 活性增加会导致氧化应激状态发生,引起血管细胞增殖、迁移和凋亡,脂质过氧化、炎症反应以及细胞外基质蛋白质沉积,最终导致血管损伤引发高血压。miR-590-5p

通过影响 ROS 水平进而调节血管内皮细胞凋亡过程。过表达 miR-590-5p 下调凝集素样氧化的低密度脂蛋白受体 1 (lectin-like oxidized low density lipoprotein receptor -1, LOX-1) 表达,降低 ROS 水平,抑制 Ang II 诱导的人脐静脉内皮细胞凋亡<sup>[37]</sup>。miR-146、miR-155 以及 miR-135b-5p 等参与调节 ROS 引起的细胞炎症反应。人主动脉血管内皮细胞中,过表达 miR-146,抑制 NADPH 氧化酶 4 (NADPH oxidase 4, Nox4) 表达,降低 ROS 水平,从而抑制高糖/凝血酶诱导的内皮细胞炎症<sup>[38]</sup>。人主动脉血管平滑肌细胞中,过表达 miR-155,能通过抑制胆固醇酰基转移酶-1 (acyl-CoA: cholesterol acyltransferases-1, ACAT-1) 和 VCAM-1 的表达,从而抑制平滑肌细胞中 ROS 的产生与单核细胞粘附和脂质积累<sup>[39]</sup>。同样,人单核/巨噬细胞中过表达 miR-135b-5p,可以通过下调  $Mg^{2+}/Mn^{2+}$  依赖性蛋白磷酸酶 1e (protein phosphatase,  $Mg^{2+}/Mn^{2+}$  dependent 1e, Ppm1e) 表达,抑制脂多糖诱导的 ROS 及 TNF $\alpha$  产生,从而抑制巨噬细胞炎症反应<sup>[40]</sup>。

### 2.3 miRNAs 调节肾素-血管紧张素-醛固酮系统

肾素-血管紧张素-醛固酮系统 (renin-angiotensin-aldosterone system, RAAS) 由一系列酶、激素、肽类以及受体组成,在调节体液平衡、心血管发育以及血管重构过程中发挥重要作用。RAAS 过度激活会促进血管紧张素原 (angiotensinogen, AGT)、ACE-1 和 Ang II 等形成,引发高血压。研究表明,miRNAs 通过多种途径参与调节 RAAS,从而影响高血压的发生与发展<sup>[41]</sup>。Ang II 诱导的大鼠高血压模型中过表达 miR-132 或 miR-212,能通过抑制内皮素-1 (endothelin-1, ET-1) 表达,从而改善大鼠心肌肥厚<sup>[42]</sup>。人脐静脉内皮细胞中过表达 miR-155 和 miR-221,下调 AT1R、ET-1 及其下游因子 VCAM1、单核细胞趋化蛋白 1 (monocyte chemoattractant protein 1, MCP1) 和 fms 样酪氨酸激酶 (fms-like tyrosine kinase, FLT-1) 的表达,从而抑制 Ang II 诱导的血管内皮细胞迁移<sup>[43]</sup>。同样,miR-155 通过下调 AT1R 表达,抑制 ERK1/2 通路激活,抑制 AngII 诱导的人脐静脉内皮细胞凋亡<sup>[44]</sup>。此外,大鼠血管平滑肌细胞中过表达 miR-483-3p,通过抑制 Ang II 诱导的 AGT 和 ACE-1 表达,从而减少平滑肌细胞的增殖和迁移<sup>[45]</sup>。

### 2.4 miRNAs 调节交感神经系统

交感神经过度激活可引起血管收缩和血压升

高。miRNAs 通过调节神经递质 (肾上腺素、去甲肾上腺素、多巴胺) 调节血管收缩,从而影响高血压的发生与发展。与血压正常 BPN/3J 小鼠相比,遗传性高血压 BPH/2J 小鼠体内交感神经过度激活,miR-181a 表达降低,肾素/血管紧张素形成酶 (renin / angiotensin forming enzyme, Ren1) 表达升高<sup>[46]</sup>。自发性高血压大鼠 (spontaneously hypertensive rats, SHR) 肾去交感神经手术 (renal sympathetic denervation, RSD) 处理,发现其血压显著下降,并且主动脉和血清中 miR-150、miR-155、miR-124、miR-135a 和 miR-143/145 表达水平均降低<sup>[47]</sup>。同样,左心室心肌梗死的大鼠进行 RSD 处理,发现其体内 miR-101a、miR-133a 和 miR-21 表达下调,结缔组织生长因子 (connective tissue growth factor, CTGF) mRNA 和蛋白质水平降低,大鼠血压和心功能都获得改善<sup>[48]</sup>。此外,通过对 90 例肾交感神经切除术患者进行为期 6 个月的观察,发现其体内 miR-133a 显著增加,且血压得到明显改善<sup>[49]</sup>。

### 2.5 miRNAs 调节肾的水钠潴留过程

肾的水钠潴留导致交感神经兴奋性增加。miRNAs 通过调控肾的水钠排泄,改变血管平滑肌细胞结构,影响肾对血管活性物质的敏感性,改变外周血管阻力,引起血压变化。盐皮质激素能够有效调节机体水盐水平,引起水钠潴留,进而引发高血压。HeLa 细胞中,过表达 miR-124 和 miR-135a 能通过抑制盐皮质激素受体基因 NR3C2 (nuclear receptor subfamily 3, group C, member 2) 的表达,阻断其 mRNA 的翻译过程,降低盐皮质激素受体水平<sup>[50]</sup>。单侧肾切除大鼠体内抑制 miR-429 表达,促进缺氧诱导因子脯氨酰羟化酶 2 (prolyl hydroxylase domain-containing protein 2, PHD2) 的表达,抑制尿钠排泄,增加肾的钠潴留,导致大鼠盐敏感性高血压<sup>[51]</sup>。研究还发现,高盐摄入会抑制盐敏感性大鼠体内 miR-133a 的表达,促进心肌 I 型胶原和 CTGF 的表达,从而导致盐敏感性大鼠高血压心肌纤维化<sup>[52]</sup>。

## 3 miRNAs 与其他病理表现的关系

胰岛素抵抗与原发性高血压关系密切。胰岛素通过促进肾小管对钠的重吸收使血浆  $Na^+$  浓度增加,导致血浆渗透压升高,引起血容量增加,最终造成血压升高。胰岛素可引起交感神经激活,导致体内磷酸化与去磷酸化的发生,引起去甲肾上腺素增加,造成血压升高。胰岛素可影响多种

跨膜离子系统导致血管平滑肌细胞  $\text{Ca}^{2+}$  浓度增加,导致平滑肌收缩,导致外周阻力增加,造成血压升高。miRNAs 通过调节胰岛素抵抗过程,进而影响高血压的发生与发展。在  $\text{TNF-}\alpha$  诱导的 HepG2 细胞胰岛素抵抗过程中,抑制 miR-543 的表达,促进 SIRT1 mRNA 和蛋白质表达,减轻胰岛素抵抗<sup>[53]</sup>。SHR 进行补肾减压(中医疗法)治疗,通过上调 miR-145 水平,促进脂联素表达,调节胰岛素 PI3K-Akt 信号通路,改善胰岛素抵抗,降低大鼠血压,并减轻靶器官损害<sup>[54]</sup>。二甲双胍可抑制高脂饮食大鼠体内 miR-21 表达,上调信号转导与转录激活因子 7(signal transducers and activators of transcription 7, SMAD-7)表达,改善骨骼肌胰岛素抵抗<sup>[55]</sup>。miRNA 对胰岛素信号通路的调控可能成为改善胰岛素型高血压的新靶点。

Table 1 Role of miRNAs in regulating hypertension

miRNAs	Study models	Validate target	Function	References
miRNAs and vascular endothelial cells				
↑ miR-126	Mouse aortic ECs	↑ VEGF, ↑ FGF	Promoting ECs proliferation and angiogenesis in mouse	[ 9 ]
↓ miR-92a	Rat aortic ECs	↑ ERK1/2, ↑ JNK, ↑ eNOS	Promoting ECs proliferation and inhibits intimal hyperplasia in rats	[ 10 ]
↑ miR-92a	Human coronary artery ECs	↓ Integrin $\alpha$ 5, ↓ SIRT1, ↓ eNOS	Decrease ECs proliferation and migration	[ 11 ]
↑ miR-24	HUVECs	↓ GATA2, ↓ PAK4	Regulation of ECs apoptosis	[ 12 ]
↑ miR-34a	HUVECs	↓ Tgif2	Regulation of ECs apoptosis	[ 13 ]
↑ miR-506-3p	HUVECs	↓ BECN1	Regulation of ECs apoptosis	[ 14 ]
↑ miR-132	HUVECs	↓ SIRT1, ↓ SREBP-1c, ↓ FAS, ↓ HMGCR	Promoting $\text{TNF-}\alpha$ -induced ECs inflammation	[ 15 ]
↑ miR-126	HUVECs	↓ VCAM-1	Decrease ECs inflammation	[ 16 ]
miRNAs and vascular smooth muscle cells				
↑ miR-145	Rat carotid artery balloon injury	↓ KLF5	Inhibit VSMCs proliferation and differentiation and rat intimal hyperplasia	[ 18 ]
↓ miR-146a	Rat carotid artery balloon injury	↑ KLF4	Inhibit VSMCs proliferation and differentiation and rat intimal hyperplasia	[ 19 ]
↑ miR-143/145	Mouse VSMCs	↓ ACE, ↓ AT1R	Inhibit VSMCs proliferation and differentiation	[ 20-22 ]
↓ miR-16	Mouse VSMCs	↑ ERK1/2, ↑ p38	Promoting AngII-induced VSMCs proliferation and migration	[ 23 ]
↑ miR-365	Rat primary aortic VSMCs	↓ Cyclin D1	Inhibits PDGF-BB and Ang II-induced VSMCs proliferation	[ 24 ]
↑ miR-424/322	Rat VSMCs	↓ Cyclin D1, ↓ STIM1, ↓ $\text{Ca}^{2+}$ -regulating proteins, calumenin	Inhibits VSMCs proliferation and migration	[ 25 ]
↑ miR-34b	Rat VSMCs	↓ CDK6	Inhibits VSMCs proliferation and migration	[ 26 ]
↑ miR-26a	Human aortic VSMCs	↓ SMAD-1	Promoting VSMCs proliferation and migration	[ 27 ]

4 问题与展望

随着对 miRNAs 生物学功能和作用机制的研究,大量的 miRNAs 被发现参与调控高血压的发生与发展( Table 1)。特别是 miR-143/145、miR-133a、miR-155 等 in 高血压的发病过程中发挥重要作用,这对高血压疾病早期诊断及治疗具有重要的意义。但 miRNAs 对高血压的调控机制是非常复杂的,一个 miRNAs 可以同时调节多个靶基因,而多个 miRNAs 又可以同时调节一个靶基因,如何克服 miRNAs 的多靶点调控,安全有效地定向干预特定靶基因的表达,需要进一步研究。另外,miRNAs 表达是否存在个体差异,在作用靶基因改善高血压的同时是否对机体的其他功能产生影响,miRNAs 与其他基因调控因子之间有无相互作用等都是今后有待解决的问题。

Continued Table 1

miRNAs	Study models	Validate target	Function	References
miRNAs and mononuclear macrophages				
↑ miR-148a-3p	Mouse BM cells	↓ PTEN	Promoting ROS production and differentiation of M1 macrophages, inhibits the differentiation of M2 macrophages	[ 29 ]
↑ miR-125a-5p	Mouse BM cells	↓ KLF13	Promoting differentiation of M2 macrophages	[ 30 ]
↑ miR-195	THP-1	↓ TLR2	Promoting differentiation of M2 macrophages and inhibits secretion of cellular inflammatory factors	[ 31 ]
↑ miR-208b, ↑ miR-133a	Peripheral blood mononuclear cells in newly diagnosed hypertensive patients	↑ Urinary albumin	Promoting vascular endothelial dysfunction, leading to hypertension	[ 32 ]
miRNAs and nitric oxide				
↑ miR-122	HUVECs	↓ SLC7A1	Inhibits NO production, leading to ECs dysfunction	[ 33 ]
↑ miR-155	HUVECs	↓ eNOS	Inhibits NO production, leading to ECs injury	[ 34 ]
↑ miR-24	HUVECs	↓ SP1, ↓ eNOS	Inhibits NO production and ECs proliferation	[ 35 ]
↑ miR-27b	Pulmonary hypertension rat	↓ PPAR-γ; ↑ eNOS	Promoting NO production and inhibits monocrotaline-induced vascular endothelial injury	[ 36 ]
miRNAs and oxidative-stress				
↑ miR-590-5p	HUVECs	↓ LOX-1	Decrease ROS and inhibits AngII-induced ECs apoptosis	[ 37 ]
↑ miR-146	HAECs	↓ Nox4	Decrease ROS production and inhibits high glucose/thrombin-induced ECs inflammation	[ 38 ]
↑ miR-155	Human aortic VSMCs	↓ ACAT-1, ↓ VCAM-1	Inhibits ROS production, monocyte adhesion and lipid accumulation in SMCM	[ 39 ]
↑ miR-135b-5p	Human monocyte cell lines, U937 and THP-1	↓ Ppm1e	Inhibits lipopolysaccharide- induced ROS production and TNFα, macrophage inflammation	[ 40 ]
miRNAs and renin angiotensin aldosterone system				
↑ miR-132, ↑ miR-212	AngII mediated hypertension in rats	↓ ET-1	Regulation of rat cardiac hypertrophy	[ 42 ]
↑ miR-155, ↑ miR-221	HUVECs	↓ AT1R, ↓ ET-1, ↓ VCAM1, ↓ MCP1, ↓ FLT-1	Inhibits AngII-induced ECs migration	[ 43 ]
↑ miR-155	HUVECs	↓ AT1R	Inhibits AngII-induced ECs apoptosis	[ 44 ]
↑ miR-483-3p	Rat VSMCs	↓ AGT, ↓ ACE-1	Inhibits SMCs proliferation and migration	[ 45 ]
miRNAs and sympathetic system				
↓ miR-181a	BPH/2 J	↑ Ren1	Inducing hypertension in mice	[ 46 ]
↓ miR-150, ↓ miR-155, ↓ miR-124, ↓ miR-135a, ↓ miR-143/145	SHR	——	Decrease blood pressure	[ 47 ]
↓ miR-101a, ↓ miR-133a, ↓ miR-21	SD rats by ligating left coronary artery and denervating bilateral renal nerves	↓ CTGF	Regulation of rat blood pressure and heart function	[ 48 ]
↑ miR-133a	Patients undergoing RSD	——	Regulation of blood pressure	[ 49 ]
miRNAs and water-sodium retention				
↑ miR-124, ↑ miR-135a	HeLa cells	↓ NR3C2	Decrease mineralocorticoid receptor levels	[ 50 ]

Continued Table 1

miRNAs	Study models	Validate target	Function	References
↓ miR-429	Uninephrectomized rat	↑ PHD2	Inhibits urinary sodium excretion, increase renal sodium retention, leading to rats salt-sensitive hypertension	[ 51 ]
↓ miR-133a	Salt-sensitive(SS) rats	↑ Collagen I, ↑ CTGF	Salt-sensitive hypertensive myocardial fibrosis	[ 52 ]
miRNAs and insulin resistance				
↓ miR-543	Insulin-resistant HepG2 cells induced by TNF-α	↑ SIRT1	Reduce HepG2 insulin resistance	[ 53 ]
↑ miR-145	SHR	↑ Adiponectin	Decrease rats blood pressure, regulation of insulin resistance, and reduce target organ damage	[ 54 ]
↓ miR-21	High-fat diet rat	↑ SMAD-7	Regulation of skeletal muscle insulin resistance	[ 55 ]

Note: —— no specific regulatory genes are mentioned in the article

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