Review

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Noncoding RNAs in Hypertension

Amela Jusic, Yvan Devaux; on behalf of the EU-CardioRNA COST Action (CA17129)

High blood pressure or hypertension is an outstanding public health problem affecting nearly 40% of the World's adult population. Prevalence of hypertension has a strong socioeconomic impact and health burden. Recently, hypertension has reached epidemic proportions, and it is estimated that ≈25% of adult individuals will be hypertensive in the World by 2025.[1] Untreated hypertension can result in various health complications, such as stroke, myocardial infarction, vascular disease, and chronic kidney diseases.[2]

Generally, hypertension is categorized as either primary or secondary according to its cause. However, there are several types of hypertension that are more or less common such as essential hypertension (EHT), pulmonary hypertension (PHT), pulmonary arterial hypertension (PAHT), white coat hypertension, and nocturnal hypertension. This article focuses on the 3 first types for which a significant amount of information on the role of noncoding RNAs (ncRNAs) is available. Essential, primary, or idiopathic hypertension refers to elevated blood pressure in which secondary causes such as renovascular disease, renal failure, pheochromocytoma, aldosteronism, or other causes of secondary hypertension, or Mendelian forms are not present.[3] EHT is the most frequent type of hypertension, which accounts for 95% of all cases.

PHT refers to an elevation of the pulmonary arterial pressure above 25 mm Hg at rest as assessed by right heart catheterization.[4] This elevation can be caused by different underlying diseases, such as liver disease, thromboembolic disease, rheumatic disorders, lung conditions, including tumors, chronic obstructive pulmonary disease, pulmonary fibrosis, or cardiovascular diseases, including aortic valve disease, heart failure, and congenital heart disease. According to the latest World Health Organization classification, PHT is classified depending on its cause into 5 groups: PAHT, PHT caused by left heart disease, PHT caused by lung disease, PHT caused by chronic blood clots, and PHT associated with other unclear conditions.

PAHT is defined as pulmonary vasculopathy and progressive pulmonary vasculature remodeling that cause the rise of pulmonary arterial pressure.[5] Although PAHT is classified as a specific subgroup of PHT, in the literature, PHT is often used instead of PAHT. Thus, while PHT refers to an elevation of pressure in the lung arteries caused by a side disease, PAHT is caused by remodeling of pulmonary blood vessels.

Owing to the fact that blood pressure is regulated by multiple physiological pathways, it is difficult to decipher a single causative agent of hypertension. Recent studies have shown that complex multifactorial cause of hypertension results from a dynamic interplay of genetic and environmental factors.[6] Polygenic nature of hypertension involves many genes each with mild cumulative effects reacting to environmental factors that contribute to hypertension. Population-based studies have demonstrated that Mendelian forms of hypertension can be found in about 20% of families and reach 60% in twins.[7,8] Integration of data from genome-wide linkage and association studies and system genetics approaches allowed the identification of >100 single nucleotide polymorphisms implicated in high blood pressure.[9,10] Studies aiming to decipher the molecular pathways of high blood pressure have identified genes involved in the renin-angiotensin-aldosterone system (RAAS), signaling through G protein-coupled receptors, vascular inflammation, remodeling, and in the structure and regulation of vascular senescence and developmental programming.[11]

Although significant progress has been achieved in elucidating the molecular pathways involved in the pathophysiology of hypertension, the regulatory function of these pathways remains to be fully elucidated. Recent advances in epigenetics may provide at least some of the missing pieces of the hereditary puzzle that can explain the fact that a same genome can provide distinct phenotypes, without alterations in primary DNA structure.[12] The key factor in figuring out the complex multifactorial nature of hypertension might well hence be the dark matter of the human genome. Indeed, while it used to be commonly accepted that each of human genes would encode proteins, it has more recently been discovered that the majority (>95%) of these genes are unable to produce proteins.[13] These genes are transcribed into ncRNA molecules and they play multiple important roles in regulating protein-coding genes. The ubiquitous expression of ncRNAs allows them to regulate many physiological and pathological processes, in virtually all cell types. Because their discovery, ncRNAs have attracted an exponential interest by the biomedical research community, notably in the area of cardiovascular diseases and their major risk factor, hypertension.[14] NcRNAs have been arbitrarily classified into short and long ncRNAs with a threshold of 200 nucleotides.[15] In addition, ncRNAs have been classified according to their cellular localization (nuclear versus cytoplasmic), mechanism of action and

From the Department of Biology, Faculty of Natural Sciences and Mathematics, University of Tuzla, Bosnia and Herzegovina (A.J.); and Cardiovascular Research Unit, Luxembourg Institute of Health (Y.D.).

Correspondence to Yvan Devaux, Cardiovascular Research Unit, Luxembourg Institute of Health, 1A-B rue Edison, L-1445 Strassen, Luxembourg. Email yvan.devaux@lih.lu

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structure.[15,16] This review presents a comprehensive overview of the current knowledge of the role of ncRNAs in the complex regulatory processes involved in the pathophysiology of hypertension. We focus on microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs). Because different ncRNAs regulate different types of hypertension, we separately review existing data on the 3 most prevalent types of hypertension, namely EHT, PHT, and PAHT.

Search Strategy, Data Synthesis, and Data Analysis

We searched all published studies in the PubMed database (up to March 31, 2019) using the following combination of keywords: "noncoding RNA AND hypertension" (Figure 1A). Furthermore, manual searches for related articles were performed to avoid missing any relevant study. A total of 1476 records were initially identified by searching the PubMed database. After reading the titles and abstracts, we excluded 269 articles with inadequate data, 6 articles not written in English, 39 reviews or commentaries, and 1046 that did not focus on ncRNAs and hypertension (Figure 1B). The remaining 116 full articles were then assessed according to following criteria: studies aimed to investigate the relationship between ncRNAs and hypertension, clinical, animal, in vitro and in silico studies, available data on ncRNAs expression levels, proposed functional role, target gene, and biomarker potential. This filtering step resulted in excluding 14 articles focused on other cardiovascular disease than hypertension, messenger RNAs (mRNAs) or single nucleotide polymorphisms in hypertension. Finally, 102 original articles were included in the present review and were stratified according to the type of hypertension (Figure 1B). The following information was extracted from each article: first author, year of publication, type of ncRNAs, method of detection, species, type of samples, expression of ncRNAs in hypertension, ncRNA's target gene and method of target gene detection, and proposed role of ncRNAs in hypertension.

MiRNAs and Hypertension

MiRNAs are short endogenous conserved ncRNAs with important roles in regulating gene expression programs that underlie normal and pathological cellular processes, including cardiovascular diseases.[17] Individual miRNAs have the capacity to simultaneously regulate a large number of genes through their coordinated activities on different pathways and networks. Increasing data have revealed that abnormal miRNAs expression and function can be related to pathogenesis or target organ damages of hypertension. MiRNAs

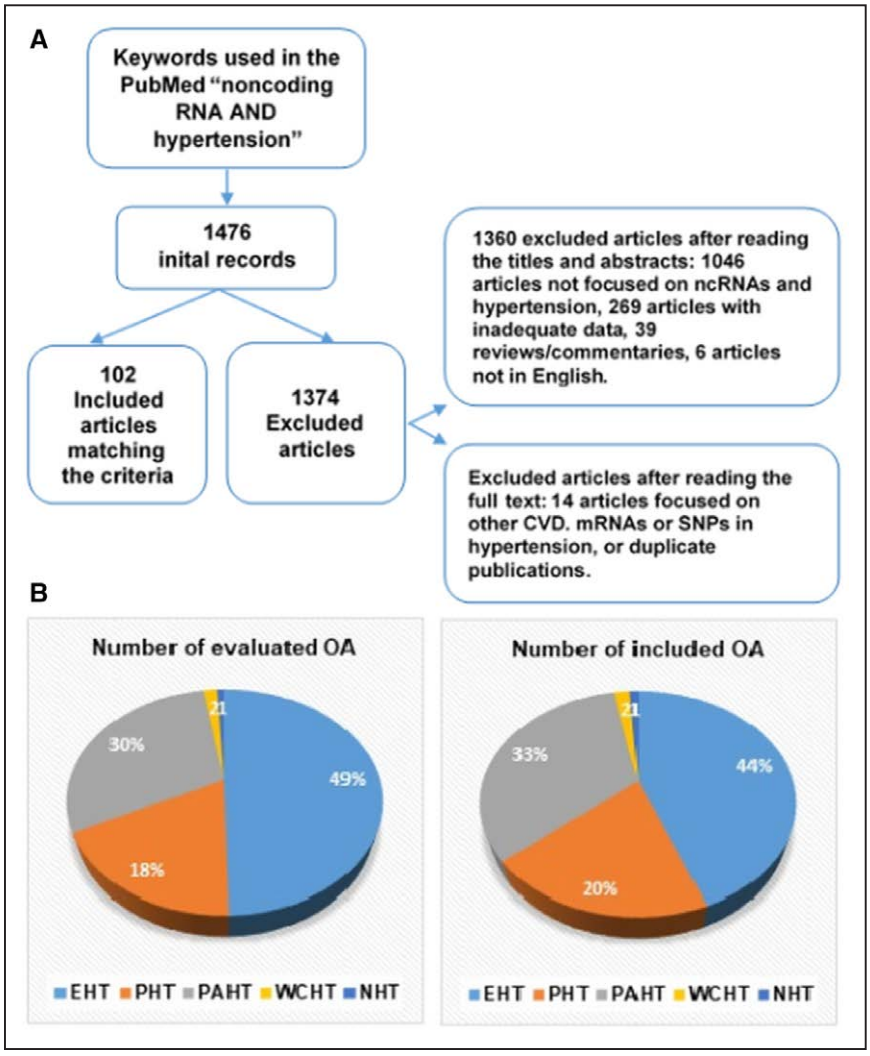

Figure 1. Literature search. **A**, Flow chart methodology used for data extraction (original articles). PubMed search was performed using the keywords "noncoding RNA AND hypertension." **B**, Distribution of evaluated and included original articles according to type of hypertension. CVD indicates cardiovascular disease; EHT, essential hypertension; mRNA, messenger RNA; ncRNA, noncoding RNA; NHT, nocturnal hypertension; OA, original articles; PAHT, pulmonary arterial hypertension; PHT, pulmonary hypertension; SNPs, single nucleotide polymorphisms; and WCHT, white coat hypertension.

are remarkably stable and are present in circulating cells or exosomes found in body fluids, such as blood, serum, and urine.[14] Because of miRNAs presence in body fluids and their altered expression levels in elevated blood pressure, they have drawn attention as potential biomarkers for different types of hypertension.

MiRNAs in EHT

The expression profiles, target genes, and proposed functional roles of miRNAs shown to be associated with EHT are shown in Table 1. Regulation of miRNA expression levels was obtained either by comparing patients with hypertension and healthy individuals, or in animal models of hypertension, or in cultured cells. This heterogeneity accounts for some of the variability between reports. Owing to the fact that miRNAs and their target genes are involved in a complex molecular network of vascular metabolism, they may affect EHT development in several ways.

The RAAS represents a well-tuned network of peptides, substrates, enzymes, hormones, and receptors that act together to regulate blood pressure. Multiple miRNAs interact with the RAAS system. Downregulated miR-34b, miR-361-5p, miR-362-5p, and miR-181a, acting via their target genes, may alter homeostasis of the RAAS.[18–20] MiR-29b alters Sp1-TGF (transforming growth factor)-β/Smad-nuclear factor-kappa B signaling pathways in human and rats.[21] Furthermore, upregulation of miR-34c-5p, miR-449b, miR-571, miR-765, miR-483-3p, miR-143/145, miR-21, miR-126, miR-196a, miR-132, miR-212, and miR-451 may induce an imbalance in RAAS system resulting in elevated blood pressure.[45] MiR-663 can regulate REN (renin) and APOE (apolipoprotein E) mRNA levels via binding to REN and APOE 3′ untranslated regions whereas miR-181a regulates REN and AIFM1 (apoptosis-inducing factor mitochondria-associated 1) mRNAs.[22] Three studies reported that downregulation of miR-31a-5p,[23] miR-142-3p,[24] miR-4763-5p,[25] and miR-4717-3p[25] can induce a loss of control of cell proliferation and apoptosis in pulmonary artery smooth muscle cell (PASMCs) and platelets in rats, while downregulated miR-4709-3p via target gene apolipoprotein L3 gene (*APOL3*) induces apoptosis of human peripheral blood mononuclear cells.[25] Cardiac hypertrophy in patients with EHT might be caused by the presence of the C allele of rs17168525 located in the let-7/miR-98-binding site of myotrophin gene (*MTPN*).[26] Thus, let-7c overexpression can cause a significant decrease in the level of myotrophin protein. Furthermore, overexpression of miR-103a-2-5p or miR-585-5p may affect oxidative DNA damage and cell survival by regulating poly-(ADP-ribose) polymerase 1 (PARP-1) gene expression in human aortic endothelial cells (ECs) and human umbilical vein ECs.[30]

It is widely known that elevated oxygen levels may induce vascular wall remodeling associated with endothelial dysfunction, inflammation, and cell migration. Overexpression of miR-21 is positively correlated with elevated blood pressure in humans, and it has been shown to directly target mitochondrial genome-encoded cytochrome b (mt-Cytb), thereby enhancing the production of reactive oxygen species in the spontaneously hypertensive rat model.[31] Moreover, overexpression of miR-21 can trigger the atherosclerotic process in patients with EHT by targeting eNOS (endothelial nitric oxide synthase).[32] Upregulation of miR-135a, miR-376a, hcmv-miR-UL112, miR-296-5p, and miR-let-7e may induce neuromodulation and catecholaminergic regulation, together with immunologic, inflammatory, and anti-infection responses in human and rat.[33,34] In addition to hypothalamic hormone regulation of blood pressure, hypothalamic inflammation can be a trigger of pathological events, such as oxidative stress and endothelial dysfunction in hypertensive patients.

ECs play a crucial role in the development, maintenance, and remodeling of vascular network.[46] Dysfunctional vascular endothelium leads to impaired vasodilatation and a proinflammatory and prothrombic phenotype of the vessel wall.[47] MiRNAs play significant roles in the vascular wall and their deregulation may alter the function of ECs. MiR-505 and miR-126 are necessary for angiogenesis and endothelial migration.[35,46] MiR-130a and miR-487b regulate the proliferation of vascular smooth muscle cells (VSMCs) and medial smooth muscle cells via downregulation of GAX (growth arrest homeobox transcription factor)[36] and IRS1 (insulin receptor substrate 1)[37] expression, which may contribute to vascular remodeling in vascular disorders such as EHT. Finally, many of the miRNAs listed in Table 1 have been shown to be downregulated or upregulated in hypertensive subjects or in animal models,[27–29,38–44] although their role in the development and progression of EHT remains to be elucidated.

MiRNAs in PHT

MiRNAs have an important role in the maintenance of pulmonary vascular homeostasis and in the pathogenesis of PHT[48] (Table 2). MiR-let-7b might be involved in the pathogenesis of chronic thromboembolic PHT by affecting ET-1 (endothelin-1) expression and the migration of pulmonary artery ECs and PASMCs.[49] Downregulation of miR-208 was observed during the progression towards right ventricular failure and its inhibition activates the complex mediator of transcription 13/nuclear receptor corepressor 1 axis, which, in turn, promotes Mef2 inhibition.[50] By targeting androgen receptor and protein kinase C-α, miR-3148, which is downregulated in chronic thromboembolic PHT, might play a role in the development of chronic thromboembolic PHT.[51] In female mice carrying a heterozygous mutation of the bone morphogenetic protein receptor II gene (*BMPRII*), downregulation of miR-96 was associated with a concomitant upregulation of the 5-hydroxytryptamine 1B receptor and an increase in the proliferation of PASMCs, which may explain the association between miR-96 and the development of PHT in women.[52]

The ubiquitous miR-21 display upregulated expression levels in plasma samples from humans and mice with PHT, lung, right ventricular tissues, and human pulmonary arterial ECs.[53,54] Integration of data obtained by different approaches such as combination of in silico predictions, cell culture data, and animal experiments, demonstrated that miR-21 acts in Rho/Rho kinase signaling pathway as well as in pathways associated with hypoxia, inflammation, and genetic haploinsufficiency of the *BMPRII* gene to control the development of PHT.[53]

MiRNA-328 regulates hypoxic PHT by targeting IGF-1R (insulin growth factor 1 receptor) and L-type calcium

Table 1. MicroRNAs Associated With EHT

miRNA	Method of Detection	Species	Type of Sample	Regulation	Target Gene	Proposed Role	References
miR-34b	qRT-PCR	Rats	VSMCs	Down	CDK6*	Signaling pathways	18
miR-361-5p, miR-362-5p	microRNA-sequencing/ qRT-PCR	Human	Blood	Down	PIK3CA, RGL1, CALM1, RHOA, AKT3, MET, MAP2K1, PRKCA, IKBKB, PIK3R3†	RAAS system	19
mirR-181a	qRT-PCR	BPH/2J rats	Kidney tissue	Down	Ren1	RAAS system	20
miR-29b	qRT-PCR	Mice	LV	Down	TGF-β/Smad3, NF-κB-YY1‡	Sp1-TGF-β/Smad-NF-κB signaling pathways	21
miR-181a	qPCR-array	Human	Kidney tissue	Down	REN, AIFM1*	Posttranscriptional control	22
miR-663					REN*		
miR-31a-5p	qPCR-array	Rats	PASMCs	Down	TP53*	The control of cell proliferation and apoptosis	23
miR-142-3p	qPCR-array	Rats	Platelet	Down	BCL2L1*	Endothelial cell apoptosis	24
miR-4763-5p, miR -4717-3p, miR -4709-3p	qPCR-array	Human	PBMCs	Down	APOL†	Programmed cell death	25
miR-let-7c	qRT-PCR	Human	Blood	Down	MTPN*	Cardiac hypertrophy	26
miR-133a, miR-26b	qRT-PCR	Human	PBMCs	Down	…	…	27
miR-1, miR-208b, miR-499, miR-21				Up			
miR-9, miR-126	qRT-PCR	Human	PBMCs	Down	…	…	28
miR-93, miR-200b, miR-92a, miR-192, miR-433	qRT-PCR	Human	Urine	Down	…	…	29
miR-21				Up			
miR-103a-2-5p, miR-585-5p	qPCR-array	Human	HAECs, HUVECs	Up	PARP1*	Regulating oxidative DNA damage in hypertension	30
miR-21	qRT-PCR	Rats	Blood	Up	Cytb†	ROS production	31
miR-21	qRT-PCR	Human	Plasma	Up	eNOS‡	The early stages of atherosclerotic process in hypertensive patients	32
miR-135a, miR-376a	qRT-PCR	Rats	BSC	Up	Agtrap, Ptgr1, Il1rn†	Neuromodulation, inflammation, and catecholaminergic regulation	33
hcmv-miR-UL112, miR-296-5p, miR-let-7e	qPCR-array	Human	Plasma	Up	IRF-1, MICB§	Immunologic, inflammatory, and anti-infection responses	34
miR-505	qPCR-array	Human	Plasma	Up	FGF18*	Angiogenesis, endothelial migration, tube formation in culture	35
miR-130a	qRT-PCR	Rats	VSMCs	Up	GAX‖	Proliferation of VSMCs	36
miR-487b	qPCR-array	Human, rats	HUAAFs, HUASMCs	Up	IRS1†	Survival of adventitial fibroblasts and medial smooth muscle cells under stress	37
miR-145	qRT-PCR	Human	AP	Up	…	…	38
miR-510	qRT-PCR	Human	Blood	Up	…	…	39
miR-let-7	qRT-PCR	Human	Plasma	Up	…	…	40
miR-29a, miR-29b, miR-29c	qRT-PCR	Human	Plasma	Up	…	…	41

(*Continued*)

Table 1. Continued

miRNA	Method of Detection	Species	Type of Sample	Regulation	Target Gene	Proposed Role	References
miR-92a	qRT-PCR	Human	Plasma	Up	…	…	42
miR-155	qRT-PCR	Human	Blood	Up	…	…	43
miR-208b, miR-499	qRT-PCR	Human	PBMC	Up	…	…	44
miR-26b				Down			

AP indicates atherosclerotic plaques; BSC, brain stem cells; EHT, essential hypertension; HAECs, human aortic endothelial cells; HUAAFs, human umbilical arterial adventitial fibroblasts; HUASMCs, human umbilical arterial smooth muscle cells; HUCARs, human umbilical cord arterial cells; HUVECs, human umbilical vein endothelial cells; LV, left ventricle; PASMCs, pulmonary artery smooth muscle cells; PBMC, peripheral blood mononuclear cells; qRT-PCR, quantitative real-time polymerase chain reaction; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; TGF-β, transforming growth factor β; and VSMCs, vascular smooth muscle cells.

Target gene validation:

*Luciferase assay.

†Bioinformatics tools: DIANA-microT v5.0, miRWalk, OmicsBean, and RNAhybrid software.

‡Immuno assay.

§Fluorescent Reporter Assay.

‖Western blot.

channel-1C (CaV1.2), causing pulmonary vascular remodeling in human and rats.[55] Upregulated miR-214 and miR-125a may cause proliferation of PASMCs and pulmonary ECs in PHT.[56–58] The miR-130/301 family plays an important role in the regulation of multiple proliferation pathways in PHT, such as apelin-miR-424/503-FGF2 signaling in smooth muscular cells, miR-130/301 modulated STAT3-miR-204 signaling, and endothelial signaling.[59,60] Thus, these findings suggest that inhibition of miR-130/301 may prevent PHT pathogenesis.

MiRNAs in PAHT

A summary of miRNAs, their targets and proposed role associated with PAHT is presented in Table 3. MiR-124, via targeting the splicing factor PTPB1 (polypyrimidine-tract binding protein) and PKM1/PKM2 (pyruvate kinase M2), may cause highly proliferative, migratory, inflammatory and metabolic abnormalities in PASMCs and fibroblasts.[64] Modification of the dysregulated miR-124, PTBP1 and PKM2 pathways may restore the normal glycolytic flux in ECs. The association between PAHT and APLN (apelin) and FGF (fibroblast growth factor) signaling pathways in the pulmonary vasculature is mediated by miR-424 and miR-503.[65] MiR-125-3p, miR-148-3p, and miR-193 may contribute to PAHT pathogenesis via dysregulation of TGF-β pathway, which plays an important role in pulmonary blood vessel angiogenesis, macrophage infiltration, and cytokine expression in the lungs.[66] The miR-143/145 cluster is abundantly expressed in smooth muscle cells, and its promoter responds to TGF-β by increasing the expression of mature forms of miRNAs.[67] Moreover, miR-22, miR-30, miR-let-7f,[68] and miR-140-5p[69] have been reported as important players in the dysregulation of TGF-β and BMP (bone morphogenetic protein) signaling pathways in PAHT. Downregulation of miR-140-5p and upregulation of TNF-α (tumor necrosis factor-α) may induce pathological events in PAHT.[70]

Several miRNAs are involved in the regulation of VEGFA (vascular endothelial growth factor A) pathway. Specifically, miR-126 is enriched in ECs and its dysregulation enhances the proangiogenic response of ECs to VEGF by repressing mRNA expression of VEGFA suppressor SPRED-1 (Sprouty-related EVH1 domain-containing protein 1) and PI3KR2 (phosphatidylinositol 3-kinase regulatory subunit β).[71,72] In addition, loss of miR-126 diminishes MAPK (mitogen-activated protein kinase) signaling in response to VEGFA and FGF, whereas gain of miR-126 enhances angiogenesis signaling.[73]

While most miRNAs are synthesized by a canonical pathway, deep sequencing technologies have revealed a class of miRNAs that can be generated by noncanonical biogenesis. Interestingly, mutations in BMPRII (causing heritable PAHT) or downstream mediator mothers against decapentaplegic homolog 9 (SMAD9) abrogated noncanonical processing of miR-21 and miR-27a which show antiproliferative properties on human pulmonary artery ECs and human PASMCs, providing a link between miR-21, miR-27a, and PAHT.[74] These findings emphasize the importance of the identification of heterozygous mutations of SMAD9 gene that can effectively distinguish between the canonical and noncanonical pathways in the pathogenesis of PAHT.

Downregulated miR-223 in human and rat lung tissue can be correlated to pathological DNA repair, increased proliferation, and suppressed apoptosis.[75] MiR-204 and its putative targets are implicated in pathways correlated to cell proliferation and resistance to apoptosis. Despite the fact that miR-204 might regulate several pathways in PAH-PASMCs including Rho-associated, coiled-coil–containing protein kinase (RhoA-ROCK), and NFAT (nuclear factor of activated T cells) pathways, aberrant expression of miR-204 might be critical for PAHT pathogenesis.[76] However, downregulation of several miRNAs might protect against the development of PAHT. MiR-145 was shown to be abundantly expressed in the vessel wall,[88] and mutations in BMPRII lead to upregulation of miR-145 in mice and patients with PAHT.[68] In line with these findings, manipulation of miR-145 may represent a novel strategy in PAHT treatment. Wnt/β-catenin signaling pathway is a key mediator of cell-cell signaling during embryonic development, cell proliferation, cell migration, cell polarity, neural patterning, and carcinogenesis. It is a highly conserved pathway that consists of the canonical or Wnt/β-catenin dependent pathway and the noncanonical or

Table 2. MicroRNAs Associated With PHT

miRNA	Method of Detection	Species	Type of Sample	Expression	Target	Proposed Role	References
miR-let-7b	qPCR-array	Human	Plasma	Down	ET-1, TGFBR1*	10 pathways	49
miR-208	qPCR-array	Rats	RV	Down	TNF-α, MED13/NCoR1 axis†	Glycolysis (glucose oxidation), angiogenesis	50
miR-3148	qPCR-array	Human	Blood	Down	AR, PRKCA†	Cancer, glioma and ErbB signaling pathways	51
miR-96	qRT-PCR	Mice	PASMCs	Down	5-HT_{1B}R‡	Serotonin-induced Proliferation of PASMCs	52
miR-21	qRT-PCR	Human, mice	HPAECs, lung tissue	Up	BMPRII†	Rho/Rho kinase signaling, pathways associated with hypoxia, inflammation, and genetic haploinsufficiency of the BMPRII	53
miR-21	qRT-PCR	Human, rats	Plasma, lung, RV	Up	…	…	54
miR-17, miR-130b, miR-145, miR-204, miR-424, miR-503				Down			
miRNA-328	qPCR-array	Human, rats	Lung tissue	Up	IGF-1R, CaV1.2§	HPV and hypoxic pulmonary vessel remodeling	55
miR-214	qRT-PCR	Human, mice	PASMCs	Up	CCNL2§	Proliferation of PASMCs by suppressing cell apoptosis	56
miR-214	qRT-PCR	Human	PASMCs	Up	PTEN§	Regulation of cardiomyocyte survival and hypertrophy, the survival and proliferation of PASMCs, the Akt pathway	57
miR-125a	qRT-PCR	Human, mice	Blood, HPASMC	Up	BMPRII, CDKN1A‡	Proliferative phenotype of pulmonary endothelial cells	58
miR-130/301	qPCR-array	Human, rats	Lung tissue, Plasma	Up	PPARγ§	ECs: apelin-miR-424/503-FGF2 signaling, SMCs: miR-130/301 modulated STAT3-miR-204 signaling;	59,60
			PAECs, PASMCs		EDN1†	Endothelin signaling	
miR-206	qRT-PCR	Human	Blood	Down	…	…	61
miR-451, miR-1246	qPCR-array	Human	Blood	Down	…	…	62
miR-23b, miR-130a, miR-191				Up			
miR-451	qRT-PCR	Human, mice	Plasma	Down	…	…	63
miR-26a	qPCR-array	Human, rats	Plasma	Down	…	…	54

ECs indicates endothelial cells; HPASMC, human pulmonary artery smooth muscle cells; HPV, hypoxic pulmonary vasoconstriction; PAECs, pulmonary artery endothelial cell; PASMCs, pulmonary artery smooth muscle cell; PHT, pulmonary hypertension; qPCR, quantitative polymerase chain reaction; and RV, right ventricle.

Target gene validation:

*Fluorescence reporter assay.

†Immunoblotting.

‡Densitometric analysis.

§Luciferase assay.

β-catenin–independent pathway. Interestingly, the Wnt/β-catenin signaling pathway is one of the critical pathways in PAHT pathogenesis. Aberrantly expressed miR-let-7a-5p, miR-26b-5p, miR-27b-3p, miR-199a-3p, miR-656,[78] and miR-199a-3p[79] strongly correlate to major PAHT-related pathways, including Wnt/β-catenin signaling pathway. Moreover, upregulated miR-27b targets NOTCH1 (notch receptor 1)[80] and PPAR-γ (peroxisome proliferator-activated receptor γ)[81] in the NOTCH, Hsp90-eNOS, and nitric oxide signaling pathways respectively, leading to progression of PAHT.

A common feature of miRNAs is their pleiotropic effects because of regulation of several target genes and thereby several biological pathways. As an example, miR-23a has shown a pleiotropic effect on the function of several PAHT-related

Table 3. MicroRNAs Associated With PAHT

miRNA	Method of Detection	Species	Type of Sample	Expression	Target	Proposed role	References
miR-124	qPCR-array	Human, rats	BOECs, lung tissue	Down	PTBP1*	Splicing factor, polyadenylation, mRNA stability, translation initiation	64
miR-424, miR-503	qPCR-array	Human/Apln knockout mice	Lung tissue	Down	FGF2, FGFR1†	APLN and FGF2 pathways	65
miR-125-3p, miR-148-3p, miR-193	qPCR-array	Wistar rats	Lung tissue	Down	PPP1CB, TGF-β2*	26 signal transduction pathways with MAPK, TGF-β and cell cycle signaling	66
miR-143-3p	qPCR-array	Human, mice	Lung tissue, RV	Up	TGF-β1†	PASMC migration and apoptosis, PAEC migration and tube formation	67
miR-22, miR-30, miR-let-7f	qPCR-array	Human, rats	Lung tissue, serum	Down	TGFBR1, YWHAZ, TNRC6A, KCNJ6, TACC1, PPP2R5E, TGF-β1‡	BMP and TGF-β signaling	68
miR-322, miR-451, miR-21				Up			
miR-140-5p	qRT-PCR	Human, rats	Blood, PASMCs, lung tissue	Down	SMURF†	BMP signaling	69
miR-140-5p	qPCR-array	Rats	Lung tissue	Down	TNF-α†	TNF signaling pathway	70
miR-126	qPCR-array	Human, rats	Muscle tissue, RV	Down	SPRED-1,‡ PI3KR2‡	VEGF/VEGFR2/MAPK pathway and p-Raf/Raf and p-ERK/ERK	71,72
miR-21	qRT-PCR	Human	Lung tissue	Up	SPRED-1§	VEGF signaling pathway	73
miR-143/145, miR-126, miR-204,				Down			
miR-21,	qRT-PCR	Human	Lung tissue	Up	SMAD9†	Noncanonical Smad-mediated microRNA (miR) processing.	74
miR-27a, miR-100				Down			
miR-223	qRT-PCR	Human, rats	Lung tissue	Down	PARP-1‡	Pathological DNA repair, increased proliferation, and suppressed apoptosis.	75
miR-204	qPCR-array	Human, rats	Lung tissue	Down	SHP2†	RhoA-ROCK pathway in PAH-PASMCs	76
miR-150	qPCR-array	Human, rats	Plasma, circulating blood cells, lung tissue	Down	…	…	77
miR-145	qPCR-array	Human, mice	Lung tissue	Up	KLF4, KLF5, SMAD4, SMAD5*	SMCs proliferation and differentiation; signaling intermediaries for the TGF-β superfamily.	68
miR-let-7a-5p, miR-26b-5p, miR-27b-3p, miR-199a-3p, miR-656	qPCR-array	Human	Lung tissue	Up	FZD4, FZD5, CTNNB1, CCND1, VEGFA, AXIN2*	Major PAHT-related pathways; Wnt/β-catenin pathway activation	78
miR-199b-5p	Bioinformatics tools	Human, mice	-	Up	GSK3*	Wmt/β-catenin pathway	79
miR-27b	qPCR-array	Human	Lung tissue	Up	NOTCH1†	NOTCH pathway	80
miR-27b	qRT-PCR	Human	HPAECs	Up	PPARγ†	Hsp90-eNOS and NO signaling	81
miR-23a	qPCR-array	Human	Blood, HSVPAEC	Up	PGC1α, CYC, SOD, NRF2, HO1‡	Coactivator of PPARγ	82
miR-322-5p	qRT-PCR	Rats	RV	Up	IGF-1†	PAH-related RV hypertrophy.	83
miR-130a	qPCR-array	PAH mouse model	MVEC	Up	BMPR2†	Lung vascular remodeling.	84
miR-19a	qPCR-array	Human	Blood, lung tissues	Up	…	…	85

(*Continued*)

Table 3. MicroRNAs Associated With PAHT

miRNA	Method of Detection	Species	Type of Sample	Expression	Target	Proposed role	References
32 circulating miRNAs	miRNA arrays	Human	Serum	…	…	…	86
miR-17, miR-*21,* miR-223	qRT-PCR	rMCT-PAH rats	Lungs, PA, RV	Up	…	…	87
miR-126, miR-145, miR-150, miR-204, miR-424, miR-503				Down			

Apln KM indicates Apln knockout mice; BOECs, blood outgrowth endothelial cells; HSVPAEC, human small vascular pulmonary artery endothelial cells; MCT-PAH, monocrotaline pulmonary arterial hypertension rats; MVEC, microvascular endothelial cells; PA, pulmonary artery; PAEC, pulmonary arterial endothelial cell; PAHT, pulmonary arterial hypertension; PASMCs, pulmonary artery smooth muscle cells; qPCR, quantitative polymerase chain reaction; RV, right ventricle; and SD, Sprague-Dawley rats.

Target gene validation:

*Bioinformatic tools: miRanda, mirTarget2, miRWalk, PicTar, TargetScan.

†Luciferase assay.

‡Immunoblot analysis.

§Coimmunoprecipitation assays.

genes including PGC1-α (PPAR-γ coactivator 1-α), CYTC (cytochrome C), SOD (superoxide dismutase), NRF2 (nuclear factor 2), and HO1 (heme oxygenase 1).[82]

Right ventricular hypertrophy and lung vascular remodeling are strongly correlated with PAHT. Reduced miR-322-5p contributes to the PAH-related right ventricular hypertrophy by increasing the expression of IGF-1 (insulin-like growth factor 1).[83] Overexpression of miR-130a in lung microvascular ECs is critical in lung vascular remodeling, an effect involving its target gene *BMPRII*.[84] Multiple other miRNAs have been shown to be aberrantly expressed, and their role in the pathogenesis of PAHT needs to be further explored.[77,85–87]

Common miRNAs in EHT, PHT, and PAHT Pathogenesis

Integration of published data revealed that multiple miRNAs are associated with the pathogenesis of different types of hypertension (Figure 2). This was expected considering their pleiotropic properties, their ability to regulate the expression of numerous target genes, and their involvement in complex regulatory networks. However, only 2 miRNAs, miR-21 and miR-130a, were found to be upregulated in EHT, PHT, and PAHT. MiR-21 is highly expressed and its role in VSMC proliferation and apoptosis, cardiac cell growth and death, cardiac fibroblast functions, and hypertension has been extensively reported.[89] Blood pressure-related changes in circulating concentrations of miR-21 may play a role in the increased risk of vascular disease and associated events in adults with hypertension.[90] The dysregulation of miR-21 expression induced by the hypobaric hypoxia closely correlates to decreased arterial blood oxygen content parameters in healthy humans that may cause proliferative status of PASMCs and pulmonary artery ECs in the early phase of hypoxic exposure.[91] Increased levels of miR-21 and BNP (B-type natriuretic peptide) have been shown in patients with pregnancy-induced hypertension.[92] Additionally, the elevated expression of miR-21 correlates with white coat hypertension.[93,94]

MiRNA-130a is the most abundantly expressed member of the miR-130 family and correlates with vascular remodeling. Recent data offer evidence that the elevated expression levels of miR-130a may participate in the pathogenesis of different types of hypertension through pleiotropic effects on several target genes involved in vascular remodeling.[95] However, its therapeutic potential in hypertension remains to be addressed. Additionally, we observed that downregulated miR-126 and upregulated miR-145 are common for EHT and PAHT, while miR-204, miR-424, and miR-503 are downregulated in PAHT and PHT. These findings motivate future research on the role of miRNAs in the complex regulatory networks responsible for the development of different types of hypertension.

Interaction Between Host miRNAs and the Gut Microbiota in Hypertension

In the last decade, the role of gut microbiota in the pathogenesis of hypertension has attracted some interest. The gut microbiota consists of a plethora of different microbes that play essential roles in the development of immune function, cell proliferation, and metabolism, by regulating roughly 10% of the host's transcriptome.[96] Increased population of 2 main species of microbes in the gut, Firmicutes and Bacterioidetes, has been shown in experimental models of hypertension, including spontaneously hypertensive rats, salt-induced models, and Ang II (angiotensin II)–induced hypertension.[97] Recent data suggest the existence of a crosstalk between host cells and microbes that could be mediated through host miRNAs. Microbes might take up host miRNAs that are able to affect their microbiome, while they might also produce metabolites that can regulate the expression of host genes, including miRNAs.[98] The gut microbiota could cause endothelial dysfunction through downregulation of miR-204 expression in the vessel wall.[99] The expression of miR-21-5p could be induced by commensal microbiota, such as *Helicobacter pylori*, *Salmonella typhimurium*, and Mycobacterium species, leading to excessive immune responses.[100] Overall, the significance of a crosstalk between host miRNAs and the gut microbiota in the pathophysiology of hypertension remains to be further explored.

LncRNAs and Hypertension

LncRNAs are transcripts of >200 nucleotides without known protein-coding function. They are implicated in epigenetic

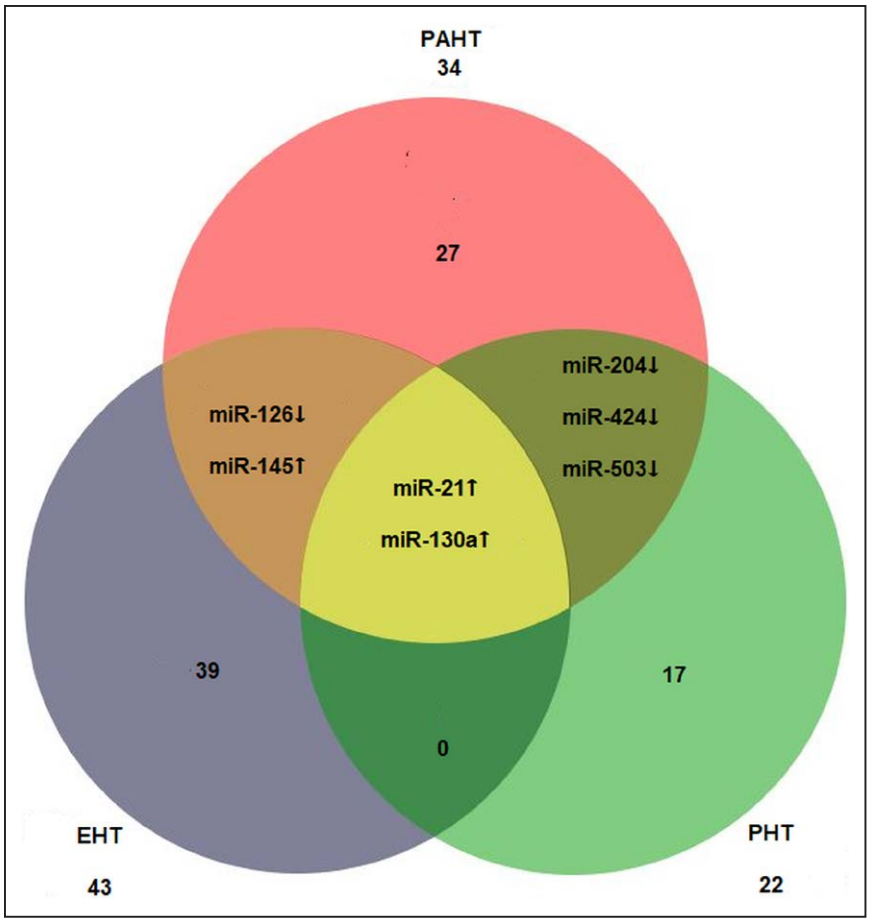

Figure 2. Venn diagram of the number of microRNAs (miRNAs) overlap between different types of hypertension. MiRNA-21↑ and miR-130a↑ are upregulated in all types of hypertension. MiRNA-126↓ and miR-145↑ are common for essential hypertension (EHT) and pulmonary arterial hypertension (PAHT), while miR-204↓, miR-424↓ and miR-503↓ are downregulated in PAHT and PHT. ↑, upregulated; ↓, downregulated.

processes in the nucleus, including chromatin modification, transcription modulation, and alternative splicing regulation, while cytoplasmic lncRNAs interact with proteins and other RNAs to modulate gene expression.[15] Despite remarkable breakthroughs of high-throughput sequencing technologies, the function and biological significance of lncRNAs in the cardiovascular system including pathological events related to hypertension is still limited. A few studies showed that lncRNAs are expressed in the circulation and might be useful disease markers.[101,102] Yet, their potential biomarker value in the context of hypertension has received little attention.

LncRNAs shown to be associated with elevated blood pressure are summarized in Table 4. The GAS5 (growth arrest-specific 5) lncRNA is widely expressed in adult tissues and, during embryonic development, it regulates ECs and VSMCs function through β-catenin signaling.[103] Because dysfunction of ECs and VSMCs strongly correlates to vascular remodeling, these data suggest that GAS5 may play an important role in EHT.[103] Using a sequence-based bioinformatics method named LncDisease to predict potential associations between lncRNAs and specific diseases, 3 lncRNAs (lnc-C16orf95–1:5, lnc-SPATA9-1:2, lnc-SLC17A9–1:1) have been shown to be downregulated in Ang II–treated VSMCs.[104] However, this method did not predict an association between the lncRNA GAS5 and EHT, as suggested by a previous study.[103] In a discovery phase with RNA-sequencing and a validation phase by quantitative polymerase chain reaction, 2 lncRNAs (TCONS_00028980 and TCONS_00029009) displayed differential expression between Dahl salt-sensitive rats and salt-insensitive, congenic Brown Norway SS.13 rats exposed to a high-salt diet, suggesting a role for these 2 lncRNAs in hypertension.[105] Results from a genetic study in human support a role for polymorphisms rs10757274, rs2383207, rs10757278, and rs1333049 within the lncRNA CDKN2B-AS1 in increasing the susceptibility to develop EHT.[106] A microarray analysis of ipsilateral renal cortex tissue revealed 145 differentially expressed lncRNAs between spontaneously hypertensive rats and normotensive Wistar-Kyoto rats, thus further supporting that lncRNAs might be involved in the pathogenesis of hypertension.[107] Additionally, the 4 lncRNAs TCONS_00052110, TCONS_00201718, TCONS_00094247, and TCONS_00296056 were upregulated in failing right ventricles of Sprague-Dawley rats treated with monocrotaline to establish PAHT and lipopolysaccharide to induce acute inflammation and heart failure.[5] A lncRNA termed MANTIS was downregulated in patients with PAHT, as well as in rats after administration of monocrotaline, and played a role in the angiogenic function of ECs.[108] Inhibition of MANTIS through CRISPR/Cas9-mediated gene editing, small interfering RNAs, or GapmeRs had favorable effects on ECs subjected to shear stress, suggesting that this lncRNA, which is also altered in patients with PAHT, might constitute an interesting therapeutic option for hypertension.[108] A lncRNA called Giver (growth factor- and proinflammatory cytokine-induced vascular cell-expressed RNA) is involved in Ang II–mediated VSMC dysfunction, is upregulated in arteries from

Table 4. Long and Circular Noncoding RNAs Associated With Hypertension

Noncoding RNAs	Method of Detection	Species	Type of Sample	Expression	Target	Proposed Role	Type of HT	References
lncRNA								
GAS5	qRT-PCR	Endothelial, VSMC, WKY, SHR	HUVECs, VSMCs	Down	β-Catenin	Regulates EC and VSMC function through β-catenin signaling	EHT	103
lnc-C16orf95–1:5, lnc-SPATA9-1:2, lnc-SLC17A9–1:1	LncDisease b.tool/qRT-PCR	Human	VSMCs	Down	…	…	EHT	104
TCONS_00028980, TCONS_00029009	qRT-PCR, RNA-seq	Rats	Brain tissue	Differential expression between salt-sensitive and salt-insensitive rats	…	…	EHT	105
CDKN2B-AS1	qRT-PCR	Human	Blood	Up	…	…	EHT	106
145 lncRNAs	Microarray	SHR, WKY	Ipsilateral renal cortex	Differential expression between SHR and normotensive rats	…	…	EHT	107
TCONS_00052110, TCONS_00201718, TCONS_00094247, TCONS_00296056	qRT-PCR/ RNA-sequencing	SD rats	Rat C6 cells, tail	Up	…	…	PAHT	5
MANTIS	qRT-PCR	Human, mice, rats, monkey	Lung, vessels, LVECs, brain	Down	SOX18, SMAD6, COUP-TFII	Regulates EC function by acting as a scaffolding lncRNA within a chromatin-remodeling complex	PAHT	108
Giver	qRT-PCR	Human, rats	VSMCs, HUVECs	Up	NR4A3	Promoting inflammatory gene expression, oxidative stress, and proliferation	EHT	109
H19	qRT-PCR	Rats/mice	Serum	Up	AT_1R	H19-let-7b-AT_1R axis contributes to the pathogenesis of PAHT by stimulating PASMCs proliferation	PAHT	110
AK098656	Microarray, qRT-PCR	Human	Plasma, VSMCs	Up	MYH11, FN1	Promotes VSMCs proliferation and migration	EHT	111
LnRPT	qRT-PCR	SD rats	PASMCs	Down	Notch3	A signaling axis, PDGF-PI3K-LnRPT-Notch3 regulates PASMC proliferation	PAHT	112
MRAK048635_P1	qRT-PCR	SHR, WKY rats	Serum, VSMCs	Down	CyclinD1/E, CDK2/4	Promotes VSMCs proliferation and migration	EHT	113
UCA1	Microarray, qRT-PCR	Human	HPASMCs	Up	ING5, hnRNP I	Promotes proliferation and restrained apoptosis by competing with ING5 for hnRNP I	PHT	114
Hoxaas3	qRT-PCR	Mice	PASMCs	Up	Homeobox a3	Regulates cell proliferation by accelerating the cell cycle	PHT	115
Circular RNAs								
hsa_circ_0037911	qRT-PCR-array	Human	Blood	Up	…	…	EHT	116

(*Continued*)

Table 4. Continued

Noncoding RNAs	Method of Detection	Species	Type of Sample	Expression	Target	Proposed Role	Type of HT	References
hsa-circ-0000437, hsa-circ-0008139, hsa-circ-0040809, hsa-circ-0005870	microarray/ qRT-PCR	Human	Plasma	Down	hsa-miR-6807-3p, hsa-miR-5095, hsa-miR-1273g-3p, hsa-miR-5096, hsa-miR-619-5p	TGF-β signaling pathway, glycosphingolipid biosynthesis - globo series, O-glycan biosynthesis	EHT	117
hsa_circ_0014243	microarray/ qRT-PCR	Human	Blood	Up	miR-10a-5p	…	EHT	118
rno_circRNA_006016	qRT-PCR-array	Rat	Kidney tissue	Down	rno-miR-297, rno-miR-466b-5p, rno-miR-423-5p, rno-miR-3573-5p, rno-miR-185-5p	Small GTPase-mediated signal transduction, ion transmembrane transport, regulation of N-methyl-D-aspartate selective glutamate receptor activity, MAPK and Wnt signaling pathways	EHT	119
hsa_circ_0002062	Agilent circRNA chip	Human	Blood	Down	hsa-miR-942–5p	hsa_circ_0002062–hsa-miR-942–5p–CDK6–pathways involved in cancer	PHT	51
hsa_circ_0022342					hsa-miR-940	hsa_circ_0022342–hsa-miR-940–CRKL–ErbB signaling pathway		

DSS indicates Dahl salt-sensitive rats; EHT, essential hypertension; HPASMCs, human pulmonary artery smooth muscle cells; HUVECs, human umbilical vein endothelial cells; LVECs, lung vascular endothelial cells; PAHT, pulmonary arterial hypertension; PHT, pulmonary hypertension; qRT-PCR, quantitative reverse transcription polymerase chain reaction; RNA-seq, RNA-sequencing; SD, Sprague-Dawley rats; SHRs, spontaneously hypertensive rats; VSMCs, vascular smooth muscle cells; and WKY, Wistar-Kyoto rats.

hypertensive patients and downregulated after treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, observations that support its potential as antihypertensive drug.[109] The lncRNA H19 was upregulated in serum and lung samples from rats and mice after monocrotaline treatment, and this was associated with PASMCs proliferation.[110] Knocking-down H19 had protective effects on pulmonary artery remodeling and PAHT development in mice treated with monocrotaline.[110] The lncRNA-AK098656 was upregulated in the plasma of patients with hypertension and promoted VSMC proliferation.[111] LncRNA-AK098656 transgenic rats developed spontaneous hypertension with narrowed resistant arteries.[111] Depletion of LnRPT (lncRNA regulated by platelet-derived growth factor and TGF-β) promoted PASMCs proliferation and this lncRNA was downregulated in pulmonary arteries from rats after monocrotaline-induced PAHT, consistent with a role in the development of PAHT.[112] LncRNA MRAK048635_P1 was weakly expressed in spontaneously hypertensive rats and its downregulation in VSMC stimulated the proliferation and migration of VSMCs, concomitantly with a phenotypic switch from a contractile to a secretory phenotype, key features of EHT.[113] Two lncRNAs, UCA1 and Hoxaas3, participated in the induction of proliferation of PASMCs on hypoxic stress.[114,115] Together, these preclinical studies support a role for lncRNAs in the development of hypertension and the potential for drugs targeting lncRNAs to treat hypertension.

CircRNAs and Hypertension

CircRNAs are lncRNAs characterized by their structure and highly evolutionary conservation. Unlike linear lncRNAs, circRNAs have a covalently closed loop structure generated during a back-splicing event between 2 or more exons.[120,121] This loop structure protects circRNAs from degradation by exonucleases and thereby confers them with a high stability, in opposite to linear lncRNAs which are relatively unstable because of digestion by exonucleases. Although circRNAs are still looking for a place in the complex regulatory network of gene expression, they have been reported to orchestrate gene expression either by acting as miRNA sponges or through interactions with RNA binding proteins.[122] Recently, circRNAs have gained attention in cardiovascular pathology, because of their tissue-specificity and their presence in the circulation, which makes them potential disease markers.[123,124] However, their role in hypertension is still poorly characterized.

The latest findings of the role of circRNAs in hypertension are summarized in Table 4. The hsa_circ_0037911 has been suggested to play a role in the development of EHT because of significantly increased expression in patients with hypertension.[116] The 4 circRNAs hsa-circ-0000437, hsa-circ-0008139,

hsa-circ-0040809, and hsa-circ-0005870 seem to be dysregulated in plasma samples obtained from patients with EHT.[117] Hsa_circ_0014243 is upregulated in whole blood of patients with EHT.[118] The rat circRNA rno_circRNA_006016 may play a role in the regulatory network of blood pressure through circRNA-miRNA-gene interaction in different signaling pathways such as the small GTPase-mediated signal transduction, ion transmembrane transport regulation of N-methyl-D-aspartate selective glutamate receptor activity, MAPK, and Wnt signaling pathways.[119] Hsa_circ_0002062 and hsa_circ_0022342 are associated with chronic thromboembolic PHT development.[51]

Biomarker Potential of ncRNAs in Hypertension

Several properties of ncRNAs suggest their potential value as biomarkers of hypertension: they are present and stable in the circulation, they are measurable using reliable and sensitive techniques, their expression is dynamic and changes on disease status, and they participate in disease evolution.

Among ncRNAs, miRNAs have been mostly investigated and their diagnostic potential for different types of hypertension has been suggested. Reports (61–64) have shown that miR-206, miR-451, miR-1246, miR-23b, miR-130a, miR-191, miR-451, and miR-26a are dysregulated in human blood samples. Several miRNAs, such as miR-199a-3p, miR-208a-3p, 122-5p, and 223-3p have shown good diagnostic performance for hypertension.[125] Dysregulation of those miRNAs may impact risk of EHT. Downregulated (miR-451 and miR-1246) and upregulated (miR-23b, miR-130a, and miR-191) may be considered as potential biomarker for early detection of PHT.[62] Combination of expression levels of plasma miR-451 with echocardiography may serve as a diagnostic reference for PHT.[63] Enhanced expression of circulating miR-19a in PAHT suggests that it may be proposed as novel biomarker for the diagnosis of PAHT.[85] A muscle-specific miRNA, miR-206 regulates the growth of cardiac myocytes and PASMCs. Combination of dysregulated miR-206 expression, cardiac remodeling, and neuroendocrine biomarkers may be helpful for the screening and identification of PHT.[61] The diagnostic or prognostic value of lncRNAs and circRNAs for hypertension has been so far poorly addressed. Differentially expressed lncRNAs: NR_027032, NR_034083, and NR_104181 in patients with hypertension and healthy individuals, support their roles in the pathogenesis of EHT.[126] The circRNAs hsa_circ_0014243 may find utility as a diagnostic biomarker of EHT.[118] Additionally, the combination of hsa_circ_0037911 and hsa-miR-637 may serve as significant biomarker for early diagnosis of EHT.[127]

Therapeutic Potential of ncRNAs in Hypertension

Despite continuous progress in the development of antihypertensive drugs, an epidemic proportion of hypertension worldwide pinpoints necessity for identification of novel and vigorous antihypertensive therapy. Multiple advantages of miRNAs, such as small size, evolutionary conservation among species, and their known sequence, are promising features for tailoring new therapeutic strategies for different diseases, including hypertension. Restoring altered miRNAs expression in hypertension can be achieved by introducing miRNA mimetics (miRNA-mimic) or anti-miRNA oligonucleotide inhibitors known as antagomiRs. Recent evidence has demonstrated the antihypertensive effect of recombinant adeno-associated virus-mediated delivery of miR-21-3p in hypertensive rats via miR-21-3p-mediated positive modulation of mt-Cytb translation in mitochondria.[128] AntagomiR-155 markedly decreased systolic and diastolic blood pressures, jointly with an elevation of the cell cycle regulator p27 (a direct target of miR-155) and α-smooth muscle actin expression in thoracic aortic media and a reduction of the thickness of tunica media in a rat model of hypertension.[129] Therapeutic inhibition of cardiac-specific miR-208a by subcutaneous delivery of miR-208a antisense prevents pathological cardiac remodeling during hypertension-induced heart failure in rats.[130] In experimental models of PAHT induced by hypoxia or monocrotaline in rodents, injection of antagomiRs against miR-17 improved cardiac and pulmonary function through interference with pulmonary and right ventricular vascular remodeling.[131] AntagomiR-20a prevented the development of vascular remodeling, in parallel with a restoration of functional levels of BMPRII, in a hypoxia-induced mouse model of PHT.[132] Although miRNAs have demonstrated some therapeutic potential in preclinical studies, the implementation of miRNAs antihypertension therapy in patients should be considered with caution due notably to their pleiotropic nature associated with multiple cellular pathways in different cell types and tissues. Modulation of a miRNA could be beneficial in a particular cell type or tissue but may also induce detrimental side effects. To date, whether targeting lncRNAs and circRNAs may help to treat hypertension remains an open question.

Conclusions and Future Directions

The available data summarized in this review article provide evidence that ncRNAs control numerous genes and biological processes, as well as navigate different signaling pathways involved in the regulatory network of hypertension. Furthermore, a dysregulation of ncRNAs expression can trigger cellular dysfunction and promote the development of pathological events related to hypertension. Owing to a certain tissue-specificity, ncRNAs might be considered as a novel class of antihypertensive drugs. AntagomiRs against miR-20a and miR-155 showed interesting protective effects in rodent models of hypertension. MiR-21 and miR-130a seem to be commonly regulated in EHT, PHT, and PAHT, while most miRNAs show distinct profiles of regulation between different types of hypertension, consistently with different features of each type of hypertension. It is tempting to speculate that miRNAs might be used both as diagnostic markers and therapeutic targets and thereby have the capacity to move the Theranostics field a step forward.

The present review shows that only a fraction of hypertension-related lncRNAs and circRNAs have been discovered and studied. Only a couple of lncRNAs have been tested for their ability to prevent or treat hypertension. No circRNAs have, so far, been engaged in such studies. The biomarker potential of lncRNAs and circRNAs as well has been poorly addressed. As a matter of fact, there is a substantial gap in knowledge of

diagnostic and therapeutic potential for hypertension between miRNAs and other types of lncRNAs or circRNAs. Although significant progress has been made in the technologies used for the discovery and validation of novel ncRNAs, their clinical applicability (both as biomarker and therapeutic target) still needs to be demonstrated. Suitable delivery methods shall be implemented and the side effects and toxicity of modulating gene expression needs to be carefully examined. Properly sized and properly designed patient cohorts shall be engaged into biomarker studies. Use of extensively validated and homogenized experimental protocols is paramount to generate robust and reproducible results translatable into high-impact outcomes for public health. Finally, whether ncRNAs have the capacity to aid in advancing personalized healthcare is still an open question.

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Disclosures

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References

1. Adler AJ, Prabhakaran D, Bovet P, Kazi DS, Mancia G, Mungal-Singh V, Poulter N. Reducing cardiovascular mortality through prevention and management of raised blood pressure: a World Heart Federation Roadmap. *Glob Heart*. 2015;10:111–122. doi: 10.1016/j.gheart.2015.04.006
2. Sekar D, Shilpa BR, Das AJ. Relevance of microRNA 21 in different types of hypertension. *Curr Hypertens Rep*. 2017;19:57. doi: 10.1007/s11906-017-0752-z
3. Carretero OA, Oparil S. Essential hypertension: part II: treatment. *Circulation*. 2000;101:446–453. doi: 10.1161/01.cir.101.4.446
4. Humbert M, Montani D, Evgenov OV, Simonneau G. Definition and classification of pulmonary hypertension. *Handb Exp Pharmacol*. 2013;218:3–29. doi: 10.1007/978-3-642-38664-0_1
5. Cao Y, Yang Y, Wang L, Li L, Zhang J, Gao X, Dai S, Zhang Y, Guo Q, Peng YG, Wang E. Analyses of long non-coding RNA and mRNA profiles in right ventricle myocardium of acute right heart failure in pulmonary arterial hypertension rats. *Biomed Pharmacother*. 2018;106:1108–1115. doi: 10.1016/j.biopha.2018.07.057
6. Levy E, Spahis S, Bigras JL, Delvin E, Borys JM. The epigenetic machinery in vascular dysfunction and hypertension. *Curr Hypertens Rep*. 2017;19:52. doi: 10.1007/s11906-017-0745-y
7. Butler MG. Genetics of hypertension. Current status. *J Med Liban*. 2010;58:175–178.
8. Ruppert V, Maisch B. Genetics of human hypertension. *Herz*. 2003;28:655–662. doi: 10.1007/s00059-003-2516-6
9. Russo A, Di Gaetano C, Cugliari G, Matullo G. Advances in the genetics of hypertension: the effect of rare variants. *Int J Mol Sci*. 2018;19:E688. doi:10.3390/ijms19030688
10. Langley SR, Kunes J, Zicha J, Zidek V, Hubner N, Cook SA, Pravenec M, Aitman TJ, Petretto E. Systems level approaches reveal conservation of trans-regulated genes in the rat and genetic determinants of blood pressure in humans. *Cardiovasc Res*. 2013;97:653–665. doi:10.1093/cvr/cvs329
11. Sedeek M, Hébert RL, Kennedy CR, Burns KD, Touyz RM. Molecular mechanisms of hypertension: role of Nox family NADPH oxidases. *Curr Opin Nephrol Hypertens*. 2009;18:122–127. doi: 10.1097/MNH.0b013e32832923c3
12. Raftopoulos L, Katsi V, Makris T, Tousoulis D, Stefanadis C, Kallikazaros I. Epigenetics, the missing link in hypertension. *Life Sci*. 2015;129:22–26. doi: 10.1016/j.lfs.2014.08.003
13. Dunham I, Kundaje A, Aldred SF, et al. An integrated encyclopedia of DNA elements in the human genome. *Nature*. 2012;489:57–74. doi: 10.1038/nature11247
14. Wu G, Jose PA, Zeng C. Noncoding RNAs in the regulatory network of hypertension. *Hypertension*. 2018;72:1047–1059. doi: 10.1161/HYPERTENSIONAHA.118.11126
15. Devaux Y, Zangrando J, Schroen B, Creemers EE, Pedrazzini T, Chang CP, Dorn GW II, Thum T, Heymans S; Cardiolinc Network. Long noncoding RNAs in cardiac development and ageing. *Nat Rev Cardiol*. 2015;12:415–425. doi: 10.1038/nrcardio.2015.55
16. Beermann J, Piccoli MT, Viereck J, Thum T. Non-coding RNAs in development and disease: background, mechanisms, and therapeutic approaches. *Physiol Rev*. 2016;96:1297–1325. doi: 10.1152/physrev.00041.2015
17. Thum T, Catalucci D, Bauersachs J. MicroRNAs: novel regulators in cardiac development and disease. *Cardiovasc Res*. 2008;79:562–570. doi: 10.1093/cvr/cvn137
18. Yang F, Li H, Du Y, Shi Q, Zhao L. Downregulation of microRNA-34b is responsible for the elevation of blood pressure in spontaneously hypertensive rats. *Mol Med Rep*. 2017;15:1031–1036. doi: 10.3892/mmr.2017.6122
19. Qi H, Liu Z, Liu B, Cao H, Sun W, Yan Y, Zhang L. micro-RNA screening and prediction model construction for diagnosis of salt-sensitive essential hypertension. *Medicine (Baltimore)*. 2017;96:e6417. doi: 10.1097/MD.0000000000006417
20. Jackson KL, Marques FZ, Watson AM, Palma-Rigo K, Nguyen-Huu TP, Morris BJ, Charchar FJ, Davern PJ, Head GA. A novel interaction between sympathetic overactivity and aberrant regulation of renin by miR-181a in BPH/2J genetically hypertensive mice. *Hypertension*. 2013;62:775–781. doi: 10.1161/HYPERTENSIONAHA.113.01701
21. Wei LH, Huang XR, Zhang Y, Li YQ, Chen HY, Heuchel R, Yan BP, Yu CM, Lan HY. Deficiency of Smad7 enhances cardiac remodeling induced by angiotensin II infusion in a mouse model of hypertension. *PLoS One*. 2013;8:e70195. doi: 10.1371/journal.pone.0070195
22. Marques FZ, Campain AE, Tomaszewski M, Zukowska-Szczechowska E, Yang YH, Charchar FJ, Morris BJ. Gene expression profiling reveals renin mRNA overexpression in human hypertensive kidneys and a role for microRNAs. *Hypertension*. 2011;58:1093–1098. doi: 10.1161/HYPERTENSIONAHA.111.180729
23. Feng Q, Tian T, Liu J, Zhang L, Qi J, Lin X. Deregulation of microRNA-31a-5p is involved in the development of primary hypertension by suppressing apoptosis of pulmonary artery smooth muscle cells via targeting TP53. *Int J Mol Med*. 2018;42:290–298. doi: 10.3892/ijmm.2018.3597
24. Bao H, Yao QP, Huang K, Chen XH, Han Y, Jiang ZL, Gao LZ, Qi YX. Platelet-derived miR-142-3p induces apoptosis of endothelial cells in hypertension. *Cell Mol Biol (Noisy-le-grand)*. 2017;63:3–9. doi: 10.14715/cmb/2017.63.4.1
25. Dluzen DF, Noren Hooten N, Zhang Y, Kim Y, Glover FE, Tajuddin SM, Jacob KD, Zonderman AB, Evans MK. Racial differences in microRNA and gene expression in hypertensive women. *Sci Rep*. 2016;6:35815. doi: 10.1038/srep35815
26. Wang Y, Chen J, Song W, Wang Y, Chen Y, Nie Y, Ye Z, Hui R. The human myotrophin variant attenuates microRNA-Let-7 binding ability but not risk of left ventricular hypertrophy in human essential hypertension. *PLoS One*. 2015;10:e0135526. doi:10.1371/journal.pone.0135526
27. Kontaraki JE, Marketou ME, Zacharis EA, Parthenakis FI, Vardas PE. Differential expression of vascular smooth muscle-modulating microRNAs in human peripheral blood mononuclear cells: novel targets in essential hypertension. *J Hum Hypertens*. 2014;28:510–516. doi: 10.1038/jhh.2013.117
28. Kontaraki JE, Marketou ME, Zacharis EA, Parthenakis FI, Vardas PE. MicroRNA-9 and microRNA-126 expression levels in patients with essential hypertension: potential markers of target-organ damage. *J Am Soc Hypertens*. 2014;8:368–375. doi: 10.1016/j.jash.2014.03.324
29. Kwon SH, Tang H, Saad A, Woollard JR, Lerman A, Textor SC, Lerman LO. Differential expression of microRNAs in urinary extracellular vesicles obtained from hypertensive patients. *Am J Kidney Dis*. 2016;68:331–332. doi: 10.1053/j.ajkd.2016.01.027
30. Dluzen DF, Kim Y, Bastian P, Zhang Y, Lehrmann E, Becker KG, Noren Hooten N, Evans MK. MicroRNAs modulate oxidative stress in hypertension through PARP-1 regulation. *Oxid Med Cell Longev*. 2017;2017:3984280. doi: 10.1155/2017/3984280
31. Li H, Zhang X, Wang F, Zhou L, Yin Z, Fan J, Nie X, Wang P, Fu XD, Chen C, Wang DW. MicroRNA-21 lowers blood pressure in spontaneous hypertensive rats by upregulating mitochondrial translation. *Circulation*. 2016;134:734–751. doi: 10.1161/CIRCULATIONAHA.116.023926
32. Cengiz M, Yavuzer S, Kılıçkıran Avcı B, Yürüyen M, Yavuzer H, Dikici SA, Karataş ÖF, Özen M, Uzun H, Öngen Z. Circulating miR-21

and eNOS in subclinical atherosclerosis in patients with hypertension. *Clin Exp Hypertens*. 2015;37:643–649. doi: 10.3109/10641963.2015.1036064
33. DeCicco D, Zhu H, Brureau A, Schwaber JS, Vadigepalli R. MicroRNA network changes in the brain stem underlie the development of hypertension. *Physiol Genomics*. 2015;47:388–399. doi: 10.1152/physiolgenomics.00047.2015
34. Li S, Zhu J, Zhang W, et al. Signature microRNA expression profile of essential hypertension and its novel link to human cytomegalovirus infection. *Circulation*. 2011;124:175–184. doi: 10.1161/CIRCULATIONAHA.110.012237
35. Yang Q, Jia C, Wang P, Xiong M, Cui J, Li L, Wang W, Wu Q, Chen Y, Zhang T. MicroRNA-505 identified from patients with essential hypertension impairs endothelial cell migration and tube formation. *Int J Cardiol*. 2014;177:925–934. doi: 10.1016/j.ijcard.2014.09.204
36. Wu WH, Hu CP, Chen XP, Zhang WF, Li XW, Xiong XM, Li YJ. MicroRNA-130a mediates proliferation of vascular smooth muscle cells in hypertension. *Am J Hypertens*. 2011;24:1087–1093. doi: 10.1038/ajh.2011.116
37. Nossent AY, Eskildsen TV, Andersen LB, Bie P, Brønnum H, Schneider M, Andersen DC, Welten SM, Jeppesen PL, Hamming JF, Hansen JL, Quax PH, Sheikh SP. The 14q32 microRNA-487b targets the antiapoptotic insulin receptor substrate 1 in hypertension-induced remodeling of the aorta. *Ann Surg*. 2013;258:743; discussion 752–751; discussion 752. doi: 10.1097/SLA.0b013e3182a6aac0
38. Santovito D, Mandolini C, Marcantonio P, De Nardis V, Bucci M, Paganelli C, Magnacca F, Ucchino S, Mastroiacovo D, Desideri G, Mezzetti A, Cipollone F. Overexpression of microRNA-145 in atherosclerotic plaques from hypertensive patients. *Expert Opin Ther Targets*. 2013;17:217–223. doi: 10.1517/14728222.2013.745512
39. Krishnan R, Mani P, Sivakumar P, Gopinath V, Sekar D. Expression and methylation of circulating microRNA-510 in essential hypertension. *Hypertens Res*. 2017;40:361–363. doi: 10.1038/hr.2016.147
40. Huang YQ, Huang C, Chen JY, Li J, Feng YQ. Plasma expression level of miRNA let-7 is positively correlated with carotid intima-media thickness in patients with essential hypertension. *J Hum Hypertens*. 2017;31:843–847. doi: 10.1038/jhh.2017.52
41. Huang Y, Tang S, Huang C, Chen J, Li J, Cai A, Feng Y. Circulating miRNA29 family expression levels in patients with essential hypertension as potential markers for left ventricular hypertrophy. *Clin Exp Hypertens*. 2017;39:119–125. doi: 10.1080/10641963.2016.1226889
42. Huang Y, Tang S, Ji-Yan C, Huang C, Li J, Cai AP, Feng YQ. Circulating miR-92a expression level in patients with essential hypertension: a potential marker of atherosclerosis. *J Hum Hypertens*. 2017;31:200–205. doi: 10.1038/jhh.2016.66
43. Huang Y, Chen J, Zhou Y, Tang S, Li J, Yu X, Mo Y, Wu Y, Zhang Y, Feng Y. Circulating miR155 expression level is positive with blood pressure parameters: potential markers of target-organ damage. *Clin Exp Hypertens*. 2016;38:331–336. doi: 10.3109/10641963.2015.1116551
44. Kontaraki JE, Marketou ME, Parthenakis FI, Maragkoudakis S, Zacharis EA, Petousis S, Kochiadakis GE, Vardas PE. Hypertrophic and antihypertrophic microRNA levels in peripheral blood mononuclear cells and their relationship to left ventricular hypertrophy in patients with essential hypertension. *J Am Soc Hypertens*. 2015;9:802–810. doi: 10.1016/j.jash.2015.07.013
45. Leimena C, Qiu H. Non-coding RNA in the pathogenesis, progression and treatment of hypertension. *Int J Mol Sci*. 2018;19:927. doi:10.3390/ijms19040927
46. Bátkai S, Thum T. MicroRNAs in hypertension: mechanisms and therapeutic targets. *Curr Hypertens Rep*. 2012;14:79–87. doi: 10.1007/s11906-011-0235-6
47. Landmesser U, Drexler H. Endothelial function and hypertension. *Curr Opin Cardiol*. 2007;22:316–320. doi: 10.1097/HCO.0b013e3281ca710d
48. Kim J, Kang Y, Kojima Y, Lighthouse JK, Hu X, Aldred MA, McLean DL, Park H, Comhair SA, Greif DM, Erzurum SC, Chun HJ. An endothelial apelin-FGF link mediated by miR-424 and miR-503 is disrupted in pulmonary arterial hypertension. *Nat Med*. 2013;19:74–82. doi: 10.1038/nm.3040
49. Guo L, Yang Y, Liu J, Wang L, Li J, Wang Y, Liu Y, gu S, Gan H, Cai J, Yuan JX, Wang J, Wang C. Differentially expressed plasma microRNAs and the potential regulatory function of Let-7b in chronic thromboembolic pulmonary hypertension. *PLoS One*. 2014;9:e101055. doi: 10.1371/journal.pone.0101055
50. Paulin R, Sutendra G, Gurtu V, Dromparis P, Haromy A, Provencher S, Bonnet S, Michelakis ED. A miR-208-Mef2 axis drives the decompensation of right ventricular function in pulmonary hypertension. *Circ Res*. 2015;116:56–69. doi: 10.1161/CIRCRESAHA.115.303910
51. Miao R, Wang Y, Wan J, Leng D, Gong J, Li J, Liang Y, Zhai Z, Yang Y. Microarray expression profile of circular RNAs in chronic thromboembolic pulmonary hypertension. *Medicine (Baltimore)*. 2017;96:e7354. doi: 10.1097/MD.0000000000007354
52. Wallace E, Morrell NW, Yang XD, Long L, Stevens H, Nilsen M, Loughlin L, Mair KM, Baker AH, MacLean MR. A sex-specific microRNA-96/5-hydroxytryptamine 1B axis influences development of pulmonary hypertension. *Am J Respir Crit Care Med*. 2015;191:1432–1442. doi: 10.1164/rccm.201412-2148OC
53. Parikh VN, Jin RC, Rabello S, et al. MicroRNA-21 integrates pathogenic signaling to control pulmonary hypertension: results of a network bioinformatics approach. *Circulation*. 2012;125:1520–1532. doi: 10.1161/CIRCULATIONAHA.111.060269
54. Schlosser K, White RJ, Stewart DJ. miR-26a linked to pulmonary hypertension by global assessment of circulating extracellular microRNAs. *Am J Respir Crit Care Med*. 2013;188:1472–1475. doi: 10.1164/rccm.201308-1403LE
55. Guo L, Qiu Z, Wei L, Yu X, Gao X, Jiang S, Tian H, Jiang C, Zhu D. The microRNA-328 regulates hypoxic pulmonary hypertension by targeting at insulin growth factor 1 receptor and L-type calcium channel-α1C. *Hypertension*. 2012;59:1006–1013. doi: 10.1161/HYPERTENSIONAHA.111.185413
56. Liu H, Yin T, Yan W, Si R, Wang B, Chen M, Li F, Wang Q, Tao L. Dysregulation of microRNA-214 and PTEN contributes to the pathogenesis of hypoxic pulmonary hypertension. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1781–1791. doi: 10.2147/COPD.S104627
57. Liu H, Tao Y, Chen M, Yu J, Li WJ, Tao L, Li Y, Li F. Up-regulation of microRNA-214 contributes to the development of vascular remodeling in hypoxia-induced pulmonary hypertension via targeting CCNL2. *Sci Rep*. 2016;6:24661. doi: 10.1038/srep24661
58. Huber LC, Ulrich S, Leuenberger C, Gassmann M, Vogel J, von Blotzheim LG, Speich R, Kohler M, Brock M. Featured article: microRNA-125a in pulmonary hypertension: regulator of a proliferative phenotype of endothelial cells. *Exp Biol Med (Maywood)*. 2015;240:1580–1589. doi: 10.1177/1535370215579018
59. Bertero T, Lu Y, Annis S, et al. Systems-level regulation of microRNA networks by miR-130/301 promotes pulmonary hypertension. *J Clin Invest*. 2014;124:3514–3528. doi: 10.1172/JCI74773
60. Bertero T, Cottrill K, Krauszman A, Lu Y, Annis S, Hale A, Bhat B, Waxman AB, Chau BN, Kuebler WM, Chan SY. The microRNA-130/301 family controls vasoconstriction in pulmonary hypertension. *J Biol Chem*. 2015;290:2069–2085. doi: 10.1074/jbc.M114.617845
61. Jin P, Gu W, Lai Y, Zheng W, Zhou Q, Wu X. The circulating microRNA-206 level predicts the severity of pulmonary hypertension in patients with left heart diseases. *Cell Physiol Biochem*. 2017;41:2150–2160. doi: 10.1159/000475569
62. Wei C, Henderson H, Spradley C, Li L, Kim IK, Kumar S, Hong N, Arroliga AC, Gupta S. Circulating miRNAs as potential marker for pulmonary hypertension. *PLoS One*. 2013;8:e64396. doi: 10.1371/journal.pone.0064396
63. Song XW, Zou LL, Cui L, Li SH, Qin YW, Zhao XX, Jing Q. Plasma miR-451 with echocardiography serves as a diagnostic reference for pulmonary hypertension. *Acta Pharmacol Sin*. 2018;39:1208–1216. doi: 10.1038/aps.2018.39
64. Caruso P, Dunmore BJ, Schlosser K, et al. Identification of microRNA-124 as a major regulator of enhanced endothelial cell glycolysis in pulmonary arterial hypertension via PTBP1 (Polypyrimidine Tract Binding Protein) and pyruvate kinase M2. *Circulation*. 2017;136:2451–2467. doi: 10.1161/CIRCULATIONAHA.117.028034
65. Kim JD, Lee A, Choi J, Park Y, Kang H, Chang W, Lee MS, Kim J. Epigenetic modulation as a therapeutic approach for pulmonary arterial hypertension. *Exp Mol Med*. 2015;47:e175. doi: 10.1038/emm.2015.45
66. Xiao T, Xie L, Huang M, Shen J. Differential expression of microRNA in the lungs of rats with pulmonary arterial hypertension. *Mol Med Rep*. 2017;15:591–596. doi: 10.3892/mmr.2016.6043
67. Deng L, Blanco FJ, Stevens H, et al. MicroRNA-143 activation regulates smooth muscle and endothelial cell crosstalk in pulmonary arterial hypertension. *Circ Res*. 2015;117:870–883. doi: 10.1161/CIRCRESAHA.115.306806
68. Caruso P, MacLean MR, Khanin R, McClure J, Soon E, Southgate M, MacDonald RA, Greig JA, Robertson KE, Masson R, Denby L, Dempsie Y, Long L, Morrell NW, Baker AH. Dynamic changes in lung microRNA profiles during the development of pulmonary hypertension due to chronic

hypoxia and monocrotaline. *Arterioscler Thromb Vasc Biol*. 2010;30:716–723. doi: 10.1161/ATVBAHA.109.202028
69. Rothman AM, Arnold ND, Pickworth JA, Iremonger J, Ciuclan L, Allen RM, Guth-Gundel S, Southwood M, Morrell NW, Thomas M, Francis SE, Rowlands DJ, Lawrie A. MicroRNA-140-5p and SMURF1 regulate pulmonary arterial hypertension. *J Clin Invest*. 2016;126:2495–2508. doi: 10.1172/JCI83361
70. Zhu TT, Zhang WF, Yin YL, Liu YH, Song P, Xu J, Zhang MX, Li P. MicroRNA-140-5p targeting tumor necrosis factor-α prevents pulmonary arterial hypertension. *J Cell Physiol*. 2019;234:9535–9550. doi: 10.1002/jcp.27642
71. Potus F, Malenfant S, Graydon C, Mainguy V, Tremblay È, Breuils-Bonnet S, Ribeiro F, Porlier A, Maltais F, Bonnet S, Provencher S. Impaired angiogenesis and peripheral muscle microcirculation loss contribute to exercise intolerance in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2014;190:318–328. doi: 10.1164/rccm.201402-0383OC
72. Potus F, Ruffenach G, Dahou A, et al. Downregulation of MicroRNA-126 contributes to the failing right ventricle in pulmonary arterial hypertension. *Circulation*. 2015;132:932–943. doi: 10.1161/CIRCULATIONAHA.115.016382
73. Bockmeyer CL, Maegel L, Janciauskiene S, Rische J, Lehmann U, Maus UA, Nickel N, Haverich A, Hoeper MM, Golpon HA, Kreipe H, Laenger F, Jonigk D. Plexiform vasculopathy of severe pulmonary arterial hypertension and microRNA expression. *J Heart Lung Transplant*. 2012;31:764–772. doi: 10.1016/j.healun.2012.03.010
74. Drake KM, Zygmunt D, Mavrakis L, Harbor P, Wang L, Comhair SA, Erzurum SC, Aldred MA. Altered MicroRNA processing in heritable pulmonary arterial hypertension: an important role for Smad-8. *Am J Respir Crit Care Med*. 2011;184:1400–1408. doi: 10.1164/rccm.201106-1130OC
75. Meloche J, Le Guen M, Potus F, Vinck J, Ranchoux B, Johnson I, Antigny F, Tremblay E, Breuils-Bonnet S, Perros F, Provencher S, Bonnet S. miR-223 reverses experimental pulmonary arterial hypertension. *Am J Physiol Cell Physiol*. 2015;309:C363–C372. doi: 10.1152/ajpcell.00149.2015
76. Courboulin A, Paulin R, Giguère NJ, Saksouk N, Perreault T, Meloche J, Paquet ER, Biardel S, Provencher S, Côté J, Simard MJ, Bonnet S. Role for miR-204 in human pulmonary arterial hypertension. *J Exp Med*. 2011;208:535–548. doi: 10.1084/jem.20101812
77. Rhodes CJ, Wharton J, Boon RA, et al. Reduced microRNA-150 is associated with poor survival in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2013;187:294–302. doi: 10.1164/rccm.201205-0839OC
78. Wu D, Talbot CC Jr, Liu Q, Jing ZC, Damico RL, Tuder R, Barnes KC, Hassoun PM, Gao L. Identifying microRNAs targeting Wnt/β-catenin pathway in end-stage idiopathic pulmonary arterial hypertension. *J Mol Med (Berl)*. 2016;94:875–885. doi: 10.1007/s00109-016-1426-z
79. Boucherat O, Bonnet S. MicroRNA signature of end-stage idiopathic pulmonary arterial hypertension: clinical correlations and regulation of WNT signaling. *J Mol Med (Berl)*. 2016;94:849–851. doi: 10.1007/s00109-016-1431-2
80. Ma K, Zhao Q, Chen W, Zhang H, Li S, Pan X, Chen Q. Human lung microRNA profiling in pulmonary arterial hypertension secondary to congenital heart defect. *Pediatr Pulmonol*. 2015;50:1214–1223. doi: 10.1002/ppul.23181
81. Bi R, Bao C, Jiang L, Liu H, Yang Y, Mei J, Ding F. MicroRNA-27b plays a role in pulmonary arterial hypertension by modulating peroxisome proliferator-activated receptor γ dependent Hsp90-eNOS signaling and nitric oxide production. *Biochem Biophys Res Commun*. 2015;460:469–475. doi: 10.1016/j.bbrc.2015.03.057
82. Sarrion I, Milian L, Juan G, Ramon M, Furest I, Carda C, Cortijo Gimeno J, Mata Roig M. Role of circulating miRNAs as biomarkers in idiopathic pulmonary arterial hypertension: possible relevance of miR-23a. *Oxid Med Cell Longev*. 2015;2015:792846. doi: 10.1155/2015/792846
83. Connolly M, Garfield BE, Crosby A, Morrell NW, Wort SJ, Kemp PR. miR-322-5p targets IGF-1 and is suppressed in the heart of rats with pulmonary hypertension. *FEBS Open Bio*. 2018;8:339–348. doi: 10.1002/2211-5463.12369
84. Li L, Kim IK, Chiasson V, Chatterjee P, Gupta S. NF-κB mediated miR-130a modulation in lung microvascular cell remodeling: implication in pulmonary hypertension. *Exp Cell Res*. 2017;359:235–242. doi: 10.1016/j.yexcr.2017.07.024
85. Chen W, Li S. Circulating microRNA as a novel biomarker for pulmonary arterial hypertension due to congenital heart disease. *Pediatr Cardiol*. 2017;38:86–94. doi: 10.1007/s00246-016-1487-3
86. Kheyfets VO, Sucharov CC, Truong U, Dunning J, Hunter K, Ivy D, Miyamoto S, Shandas R. Circulating miRNAs in pediatric pulmonary hypertension show promise as biomarkers of vascular function. *Oxid Med Cell Longev*. 2017;2017:4957147. doi: 10.1155/2017/4957147
87. Gubrij IB, Pangle AK, Pang L, Johnson LG. Reversal of MicroRNA dysregulation in an animal model of pulmonary hypertension. *PLoS One*. 2016;11:e0147827. doi: 10.1371/journal.pone.0147827
88. Cheng Y, Liu X, Yang J, Lin Y, Xu DZ, Lu Q, Deitch EA, Huo Y, Delphin ES, Zhang C. MicroRNA-145, a novel smooth muscle cell phenotypic marker and modulator, controls vascular neointimal lesion formation. *Circ Res*. 2009;105:158–166. doi: 10.1161/CIRCRESAHA.109.197517
89. Cheng Y, Zhang C. MicroRNA-21 in cardiovascular disease. *J Cardiovasc Transl Res*. 2010;3:251–255. doi: 10.1007/s12265-010-9169-7
90. Hijmans JG, Diehl KJ, Bammert TD, Kavlich PJ, Lincenberg GM, Greiner JJ, Stauffer BL, DeSouza CA. Association between hypertension and circulating vascular-related microRNAs. *J Hum Hypertens*. 2018;32:440–447. doi: 10.1038/s41371-018-0061-2
91. Blissenbach B, Nakas CT, Krönke M, Geiser T, Merz TM, Pichler Hefti J. Hypoxia-induced changes in plasma micro-RNAs correlate with pulmonary artery pressure at high altitude. *Am J Physiol Lung Cell Mol Physiol*. 2018;314:L157–L164. doi: 10.1152/ajplung.00146.2017
92. Kan C, Cao J, Hou J, Jing X, Zhu Y, Zhang J, Guo Y, Chen X. Correlation of miR-21 and BNP with pregnancy-induced hypertension complicated with heart failure and the diagnostic value. *Exp Ther Med*. 2019;17:3129–3135. doi: 10.3892/etm.2019.7286
93. Huang YQ, Huang C, Chen JY, Li J, Feng YQ. The association of circulating miR-30a, miR-29 and miR-133 with white-coat hypertension. *Biomark Med*. 2016;10:1231–1239. doi: 10.2217/bmm-2016-0215
94. Cengiz M, Karatas OF, Koparir E, Yavuzer S, Ali C, Yavuzer H, Kirat E, Karter Y, Ozen M. Differential expression of hypertension-associated microRNAs in the plasma of patients with white coat hypertension. *Medicine (Baltimore)*. 2015;94:e693. doi: 10.1097/MD.0000000000000693
95. Bertero T, Handen AL, Chan SY. Factors associated with heritable pulmonary arterial hypertension exert convergent actions on the miR-130/301-vascular matrix feedback loop. *Int J Mol Sci*. *2018*;19:E2289. doi: 10.3390/ijms19082289
96. Jose AJ, Ray D. Gut microbiota in hypertension. *Curr Opin Nephrol Hypertens*. 2016;24:403–409.
97. Pevsner-Fischer M, Blacher E, Tatirovsky E, Ben-Dov IZ, Elinav E. The gut microbiome and hypertension. *Curr Opin Nephrol Hypertens*. 2017;26:1–8. doi: 10.1097/MNH.0000000000000293
98. Zhao L, Zhou X, Cai W, Shi R, Yang G, Yang L. Host intestinal epithelium derived miRNAs shape the microbiota and its implication in cardiovascular diseases. *J. Am. College Cardiol*. 2017;69:1075. doi: 10.1016/S0735-1097(17)34464–9
99. Vikram A, Kim YR, Kumar S, Li Q, Kassan M, Jacobs JS, Irani K. Vascular microRNA-204 is remotely governed by the microbiome and impairs endothelium-dependent vasorelaxation by downregulating Sirtuin1. *Nat Commun*. 2016;7:12565. doi: 10.1038/ncomms12565
100. Nakata K, Sugi Y, Narabayashi H, Kobayakawa T, Nakanishi Y, Tsuda M, Hosono A, Kaminogawa S, Hanazawa S, Takahashi K. Commensal microbiota-induced microRNA modulates intestinal epithelial permeability through the small GTPase ARF4. *J Biol Chem*. 2017;292:15426–15433. doi: 10.1074/jbc.M117.788596
101. Gomes CPC, Spencer H, Ford KL, Michel LYM, Baker AH, Emanueli C, Balligand JL, Devaux Y; Cardiolinc Network. The function and therapeutic potential of long non-coding RNAs in cardiovascular development and disease. *Mol Ther Nucleic Acids*. 2017;8:494–507. doi: 10.1016/j.omtn.2017.07.014
102. Greco S, Salgado Somoza A, Devaux Y, Martelli F. Long noncoding RNAs and cardiac disease. *Antioxid Redox Signal*. 2018;29:880–901. doi: 10.1089/ars.2017.7126
103. Wang YN, Shan K, Yao MD, Yao J, Wang JJ, Li X, Liu B, Zhang YY, Ji Y, Jiang Q, Yan B. Long noncoding RNA-GAS5: a novel regulator of hypertension-induced vascular remodeling. *Hypertension*. 2016;68:736–748. doi: 10.1161/HYPERTENSIONAHA.116.07259
104. Wang J, Ma R, Ma W, Chen J, Yang J, Xi Y, Cui Q. LncDisease: a sequence based bioinformatics tool for predicting lncRNA-disease associations. *Nucleic Acids Res*. 2016;44:e90. doi: 10.1093/nar/gkw093
105. Wang F, Li L, Xu H, Liu Y, Yang C, Cowley AW Jr, Wang N, Liu P, Liang M. Characteristics of long non-coding RNAs in the brown norway rat and alterations in the Dahl salt-sensitive rat. *Sci Rep*. 2014;4:7146. doi: 10.1038/srep07146
106. Bayoglu B, Yuksel H, Cakmak HA, Dirican A, Cengiz M. Polymorphisms in the long non-coding RNA CDKN2B-AS1 may contribute to higher systolic blood pressure levels in hypertensive patients. *Clin Biochem*. 2016;49:821–827. doi: 10.1016/j.clinbiochem.2016.02.012
107. Hou L, Lin Z, Ni Y, Wu Y, Chen D, Song L, Huang X, Hu H, Yang D. Microarray expression profiling and gene ontology analysis

of long non-coding RNAs in spontaneously hypertensive rats and their potential roles in the pathogenesis of hypertension. *Mol Med Rep*. 2016;13:295–300. doi: 10.3892/mmr.2015.4554

108. Leisegang MS, Fork C, Josipovic I, et al. Long noncoding RNA MANTIS facilitates endothelial angiogenic function. *Circulation*. 2017;136:65–79. doi: 10.1161/CIRCULATIONAHA.116.026991
109. Das S, Zhang E, Senapati P, et al. A novel angiotensin II-induced long noncoding RNA giver regulates oxidative stress, inflammation, and proliferation in vascular smooth muscle cells. *Circ Res*. 2018;123:1298–1312. doi: 10.1161/CIRCRESAHA.118.313207
110. Su H, Xu X, Yan C, Shi Y, Hu Y, Dong L, Ying S, Ying K, Zhang R. LncRNA H19 promotes the proliferation of pulmonary artery smooth muscle cells through AT1R via sponging let-7b in monocrotaline-induced pulmonary arterial hypertension. *Respir Res*. 2018;19:254. doi: 10.1186/s12931-018-0956-z
111. Jin L, Lin X, Yang L, Fan X, Wang W, Li S, Li J, Liu X, Bao M, Cui X, Yang J, Cui Q, Geng B, Cai J. AK098656, a novel vascular smooth muscle cell-dominant long noncoding RNA, promotes hypertension. *Hypertension*. 2018;71:262–272. doi: 10.1161/HYPERTENSIONAHA.117.09651
112. Chen J, Guo J, Cui X, Dai Y, Tang Z, Qu J, Raj JU, Hu Q, Gou D. The long noncoding RNA LnRPT Is regulated by PDGF-BB and modulates the proliferation of pulmonary artery smooth muscle cells. *Am J Respir Cell Mol Biol*. 2018;58:181–193. doi: 10.1165/rcmb.2017-0111OC
113. Fang G, Qi J, Huang L, Zhao X. LncRNA MRAK048635_P1 is critical for vascular smooth muscle cell function and phenotypic switching in essential hypertension. *Biosci Rep*. 2019;39:BSR20182229. doi: 10.1042/BSR20182229
114. Zhu TT, Sun RL, Yin YL, Quan JP, Song P, Xu J, Zhang MX, Li P. Long noncoding RNA UCA1 promotes the proliferation of hypoxic human pulmonary artery smooth muscle cells. *Pflugers Arch*. 2019;471:347–355. doi: 10.1007/s00424-018-2219-8
115. Zhang H, Liu Y, Yan L, Wang S, Zhang M, Ma C, Zheng X, Chen H, Zhu D. Long noncoding RNA Hoxaas3 contributes to hypoxia-induced pulmonary artery smooth muscle cell proliferation. *Cardiovasc Res*. 2019;115:647–657. doi: 10.1093/cvr/cvy250
116. Bao X, Zheng S, Mao S, Gu T, Liu S, Sun J, Zhang L. A potential risk factor of essential hypertension in case-control study: circular RNA hsa_circ_0037911. *Biochem Biophys Res Commun*. 2018;498:789–794. doi: 10.1016/j.bbrc.2018.03.059
117. Wu N, Jin L, Cai J. Profiling and bioinformatics analyses reveal differential circular RNA expression in hypertensive patients. *Clin Exp Hypertens*. 2017;39:454–459. doi: 10.1080/10641963.2016.1273944
118. Zheng S, Gu T, Bao X, Sun J, Zhao J, Zhang T, Zhang L. Circular RNA hsa_circ_0014243 may serve as a diagnostic biomarker for essential hypertension. *Exp Ther Med*. 2019;17:1728–1736. doi: 10.3892/etm.2018.7107
119. Cheng X, Joe B. Circular RNAs in rat models of cardiovascular and renal diseases. *Physiol Genomics*. 2017;49:484–490. doi: 10.1152/physiolgenomics.00064.2017
120. Gomes CPC, Salgado-Somoza A, Creemers EE, Dieterich C, Lustrek M, Devaux Y; Cardiolinc™ Network. Circular RNAs in the cardiovascular system.*NoncodingRNARes*.2018;3:1–11.doi:10.1016/j.ncrna.2018.02.002
121. Devaux Y, Creemers EE, Boon RA, Werfel S, Thum T, Engelhardt S, Dimmeler S, Squire I; Cardiolinc Network. Circular RNAs in heart failure. *Eur J Heart Fail*. 2017;19:701–709. doi: 10.1002/ejhf.801
122. Devaux Y. Transcriptome of blood cells as a reservoir of cardiovascular biomarkers. *Biochim Biophys Acta Mol Cell Res*. 2017;1864:209–216. doi: 10.1016/j.bbamcr.2016.11.005
123. Vausort M, Salgado-Somoza A, Zhang L, Leszek P, Scholz M, Teren A, Burkhardt R, Thiery J, Wagner DR, Devaux Y. Myocardial infarction-associated circular RNA predicting left ventricular dysfunction. *J Am Coll Cardiol.* 2016;68:1247–1248. doi: 10.1016/j.jacc.2016.06.040
124. Salgado-Somoza A, Zhang L, Vausort M, Devaux Y. The circular RNA MICRA for risk stratification after myocardial infarction. *Int J Cardiol Heart Vasc.* 2017;17:33–36. doi: 10.1016/j.ijcha.2017.11.001
125. Zhang X, Wang X, Wu J, Peng J, Deng X, Shen Y, Yang C, Yuan J, Zou Y. The diagnostic values of circulating miRNAs for hypertension and bioinformatics analysis. *Biosci Rep*. 2018;38:BSR20180525. doi: 10.1042/BSR20180525
126. Chen S, Chen R, Zhang T, Lin S, Chen Z, Zhao B, Li H, Wu S. Relationship of cardiovascular disease risk factors and noncoding RNAs with hypertension: a case-control study. *BMC Cardiovasc Disord*. 2018;18:58. doi:10.1186/s12872-018-0795-3
127. Bao X, He X, Zheng S, Sun J, Luo Y, Tan R, Zhao J, Zhong F, Zhang L. Up-regulation of circular RNA hsa_circ_0037909 promotes essential hypertension. *J Clin Lab Anal*. 2019;12:e22853. doi: 10.1002/jcla.22853
128. Wang F, Fang Q, Chen C, Zhou L, Li H, Yin Z, Wang Y, Zhao CX, Xiao X, Wang DW. Recombinant adeno-associated virus-mediated delivery of microRNA-21-3p lowers hypertension. *Mol Ther Nucleic Acids.* 2018;11:354–366. doi: 10.1016/j.omtn.2017.11.007
129. Xu D, Liao R, Wang XX, Cheng Z. Effects of miR-155 on hypertensive rats via regulating vascular mesangial hyperplasia. *Eur Rev Med Pharmacol Sci*. 2018;22:7431–7438. doi: 10.26355/eurrev_201811_16283
130. Montgomery RL, Hullinger TG, Semus HM, Dickinson BA, Seto AG, Lynch JM, Stack C, Latimer PA, Olson EN, van Rooij E. Therapeutic inhibition of miR-208a improves cardiac function and survival during heart failure. *Circulation*. 2011;124:1537–1547. doi: 10.1161/CIRCULATIONAHA.111.030932
131. Pullamsetti SS, Doebele C, Fischer A, Savai R, Kojonazarov B, Dahal BK, Ghofrani HA, Weissmann N, Grimminger F, Bonauer A, Seeger W, Zeiher AM, Dimmeler S, Schermuly RT. Inhibition of microRNA-17 improves lung and heart function in experimental pulmonary hypertension. *Am J Respir Crit Care Med*. 2012;185:409–419. doi: 10.1164/rccm.201106-1093OC
132. Brock M, Samillan VJ, Trenkmann M, Schwarzwald C, Ulrich S, Gay RE, Gassmann M, Ostergaard L, Gay S, Speich R, Huber LC. AntagomiR directed against miR-20a restores functional BMPR2 signalling and prevents vascular remodelling in hypoxia-induced pulmonary hypertension. *Eur Heart J*. 2014;35:3203–3211. doi: 10.1093/eurheartj/ehs060