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REVIEW ARTICLE

microRNA-21 and hypertension

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Abstract

Hypertension, a multifactorial disease, is a major risk factor for the development of stroke, coronary artery disease, heart failure, and chronic renal failure. However, its underlying cellular and molecular mechanisms remain largely elusive. Numerous studies have shown that microRNAs (miRNAs) are involved in a variety of cellular processes, including cellular proliferation, apoptosis, differentiation, and the development of diseases. microRNA-21 (miR-21), a conserved single-stranded non-coding RNA that is composed of approximately 22 nucleotides, is one of the most intensively studied miRNAs in recent years, and it can regulate gene expression at the post-transcriptional level. miR-21 is expressed in many kinds of tumors and in the cardiovascular system, and it plays an important role in the occurrence and development of cardiovascular diseases. In recent years, more and more evidence indicates that miR-21 plays an important role in hypertension. This article reviews the source, function, and altered levels of miR-21 in hypertension and the role of miR-21 in the pathogenesis of hypertension and target organ damage (TOD). The potential role of miR-21 as a new target for predicting and treating hypertension is also explored.

Introduction

Hypertension is a major risk factor of stroke, coronary artery disease, heart failure, peripheral vascular disease, and chronic renal disease [1]. Moreover, hypertension is one of the most common chronic diseases. Hypertension influences approximately 25% of the adult population worldwide, and the number of adults with hypertension in 2025 is predicted to increase by approximately 60% to a total of 1.56 billion [2]. In the United States, it influenced over 30% of the population in 2015, and its direct medical costs alone have been estimated at almost 100 billion dollars [3]. Moreover, in northeast China, a recent study shows that the awareness and treatment rates of hypertension are 47.4 and 78.8%, respectively. However, the control rate of hypertension is only 10.2% [4]. According to the 2017 High Blood Pressure Clinical Practice Guideline, the prevalence of hypertension among U.S. adults substantially increased when the definition in the present guideline was used vs. the JNC 7 definition (46 vs. 32%) [5].

The pathophysiology of hypertension is complex; in addition to its common pathogenesis, such as neural mechanisms, renal mechanisms, hormonal mechanisms, vascular mechanisms, and insulin resistance mechanisms, there is evidence that inflammation is involved in the pathogenesis of hypertension [6–8], and its occurrence and development are determined by the combination of genetic susceptibility, environmental factors, compensatory factors and time factors [9]. Long-lasting and inadequately treated hypertension evinces as pathological changes in organs throughout the body, including atherosclerosis and vascular disease, cardiac hypertrophy and fibrosis, heart failure, renal fibrosis, kidney failure, eye disease and hemorrhagic stroke, known as TOD [10]. Furthermore, although effective antihypertensive agents, including sartans and dihydropyridines, are used, TOD still exists in many HT patients [11–15]. Recently, more and more evidence shows that the pathogenesis of essential hypertension (EH) and its complications is associated with the abnormal expression of

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many genes [16–18]. However, despite extensive and continuous efforts to understand the pathogenesis of EH in genetics, its molecular mechanism remains largely elusive.

miRNAs include endogenous, small noncoding RNAs that are approximately 21–25 nucleotides in length. These small miRNAs play important regulatory roles by inhibiting translation of the target mRNAs or promoting degradation of the target mRNAs [19]. In 1993, Lee et al. found the first miRNA while studying the development process of nematodes and named it lin-4 [20]. Today, more than 3000 human genes have been cloned and sequenced according to the Ensembl-database, and the number of miRNAs is expected to be more than 4500. Approximately 30% of human genes might be regulated by miRNAs due to the in silico estimation by Rajewsky [21].

miRNAs have been detected in humans and in animals, viruses and plants, and they are involved in a variety of processes, including proliferation, differentiation, apoptosis and metabolism, and other cellular processes [22]. miRNAs have non-selective and non-specific characteristics: a miRNA can act on multiple mRNAs, and a mRNA can be regulated by multiple miRNAs.

A growing body of recent research indicates that miRNAs, such as miR-1, 21, 133, 145, 505, and 510, are important in the pathogenesis of EH [23–25]. miR-126a-5p is involved in the hypoxia-induced endothelial-to-mesenchymal transition of neonatal pulmonary hypertension [26]. Furthermore, miRNAs, including miR-9, 21, 26, 126, and 155, play important roles in TOD during hypertension [10, 27]. miR-21 is one of the most intensively studied miRNAs in recent years. It is highly expressed in the organs and tissues of mammals. It has a close relationship with hypertension. In this review, we focus on the relationship between miR-21 and EH, such as the source and function of miR-21, the level of changes in hypertension, and the role of miR-21 in the pathogenesis of hypertension and TOD during hypertension, and thus speculate that miR-21 may be a new target for predicting and treating hypertension.

Source of miR-21

Mature miR-21 is a 22 nt long non-coding RNAs with homologous sequences in humans, rats, and mice. Its sequence is 5′-UAGCUUAUCAGACUGAUGUUGA.

The transcription process of miR-21 is that RNA polymerase II transcribes the miR-21 genes, generating long primary transcripts (pri-miR-21). Subsequently, the precursor of nuclease Drosha processes pri-miR-21 into the hairpin structure (pre-miR-21), then pre-miR-21 is transferred to the cytoplasm by exportin 5, and the complex is further processed by dicer protein (Dicer), transactivation response RNA binding protein (TRBP) and protein kinase RNA activator (PACT) to form double-stranded miRNA, which finally unwinds into mature miRNA. Similar to other mature miRNAs, mature miR-21 is involved in the formation of RNA-induced silencing complex (RISC), which functions by combining with mRNA. The combination of miRNA and the target genes into the RISC inhibits the translation of the latter and (or) the promotion of its degradation [28]. Translation inhibition is the main form of miRNA regulation in the mammalian body, but the mRNA level is often decreased, which may be due to the decreased stability of mRNA (Fig. 1) [29].

miR-21 is encoded by a single gene and is highly conserved across evolution. The human miR-21 gene is located on chromosome 17q23.2 and overlaps with the transmembrane protein-encoding gene vacuole membrane protein 1 (VMP1 and TMEM49) and is pre-transcribed independently

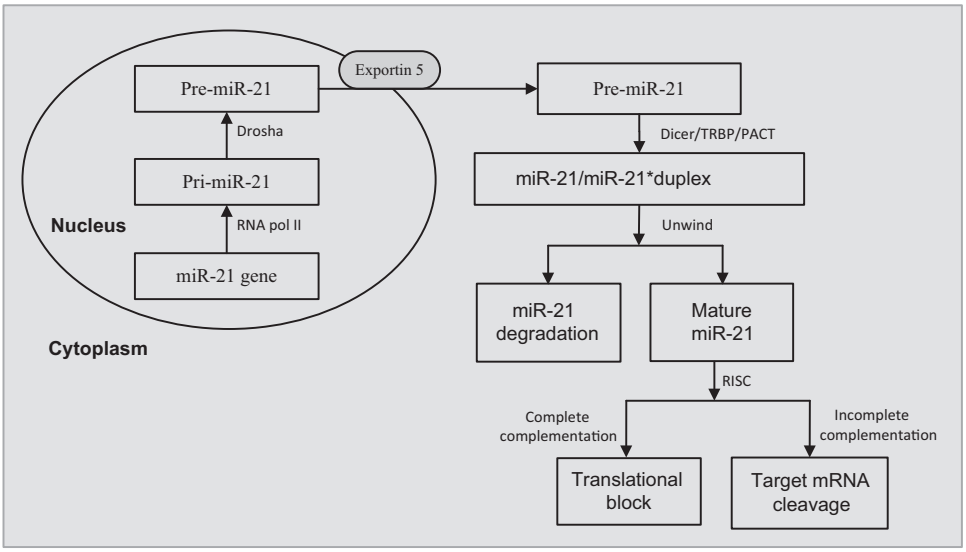

Fig. 1 Biological source of mature miRNA-21. miR-21, microRNA-21; pri-miR-21, primary microRNA-21; pre-miR-21, precursor microRNA-21; Dicer, dicer protein; TRBP, transactivation response RNA binding protein; PACT, protein kinase RNA activator; RISC, RNA-induced silencing complex

by miR-21 as pri-miR-21 in a relatively conserved promoter [30, 31]. miR-21 has been found to be over expressed in many tumor tissues and many organs, including the heart, spleen, small intestine, colon, breast and brain of mammals [32], so it has been considered to have carcinogenic activity and can be classified as carcinogenic miRNA [33]. Many scholars have proposed a non-transcriptional mechanism for miR-21 upregulation, implying gene amplification rather than promoter hyper-activation [34].

The generation of miR-21 is regulated mainly at two levels. One level is the level of transcription (the generation of pri-miRNA). The miR-21 gene has its own promoter, and its expression is not regulated by the promoter of the overlapping protein coding gene [35], which is very different from that of other miRNAs sharing a promoter with their overlapping protein-coding genes. The promoter of miR-21 has multiple enhancer-binding sites, including activation protein-1 (AP-1), signal transducer and activator of transcription (STAT3) and nuclear factor 1 (NF1), which can mediate miR-21 expression through different signaling pathways. It has been demonstrated that AP-1, Ets/PU.1, p53, RELA, DeltaEF1/ZEB1, and Stat3 can induce the transcription of miR-21; however, CCAAT/enhancer-binding protein (C/EBPα), NFI, Gfil, and estrogen receptor (ER) pathways can inhibit the transcription of miR-21 [31, 36–41]. The other level is the post-transcriptional level. Transforming growth factor-B (TGF-B) and bone morphogenetic proteins (BMPs) accelerate miR-21 production by activating Drosha complexes, whereas the bone morphogenetic protein receptor type-1A (BMPR1a) pathway can inhibit the production of miR-21 without changing the level of pri-miR-21 [42, 43].

Function of miR-21

The role of miR-21 in vivo depends on the action target. It has been found and confirmed that miR-21-induced effects should be the result of multiple target genes. However, because there are differences in the expression of genes in different cells, the number and type of miR-21 target genes should be different in specific cells. Until now, there has been a lack of research in this area [44]. Recent studies have suggested that miR-21 showed different expression levels in many major cardiovascular cell types, including vascular smooth muscle cells (VSMC), vascular endothelial cells, myocardial cells and cardiac fibroblasts and other cells, tissues, and blood (Table 1) [23, 45–65], suggesting that it may be involved in the pathophysiologic process of many diseases. These studies suggest that miR-21 inhibits cell apoptosis and promotes cell proliferation and the development of interstitial fibrosis. However, whether the distributions of miR-21 in different cells contribute to

Table 1 The specific expressions and the relative effects of miR-21 in ECs, VSMCs, cardiomyocytes and other cells, tissue, and blood

Cell, tissue or blood	Species	Expression level of miR-21	Function of miR-21
Proliferative ECs	Mouse	↑	Stimulating cell proliferation/ suppressing cell apoptosis [53]
Proliferative VSMCs	Rat, mouse, and human	↑	miR-21 promotes cell proliferation, differentiation and inhibits apoptosis of VSMCs [54, 56–60]
Hypertrophic cardiomyocytes	Rat, mouse	↑	Modulating miR-21 expression via antisense-mediated depletion (knockdown) had a significant negative effect on cardiomyocyte hypertrophy, while studies in cardiac myocytes suggested a protective role in this cell type [46, 61–63]
Prostrated cardiac fibroblasts	Rat, mouse	↑	In vivo silencing of miR-21 by a specific antagomir in a mouse pressure-overload-induced disease model reduces cardiac ERK–MAP kinase activity, inhibits interstitial fibrosis and attenuates cardiac dysfunction [49, 64, 65]
Peripheral blood mononuclear cells of HT patients	Human	↑	HT patients showed higher miR-21 expression levels compared with controls. However, the specific mechanism of miR-21 needs to be studied [23]
Blood plasma of HT patients	Human	↑	miR-21 expression levels were significantly upregulated in the HT groups compared with the NT groups. However, the specific mechanism of miR-21 needs to be studied [50]
Serum of HT patients	Human	↑	The hypertensive ocean seamen had significantly higher expression levels of miR-21. However, the specific mechanism of miR-21 needs to be studied [51]
Renal cortex of HT patients	Human	↑	Hsa-miR-21 was highly expressed in renal cortex of HT patients compared with NT subjects. However, the specific mechanism of miR-21 needs to be studied [52]
Renal tubular epithelial cells	Rat	↓	Overexpression of miR-21 may inhibit the proliferation of rat renal tubular epithelial cells [55]

miR-21 microRNA-21, *ECs* endothelial cells, *VSMCs* vascular smooth muscle cells, *HT* hypertensive, *NT* normotensive, ↑ increase, ↓ decrease

hypertension remains to be verified. Human miR-21-5p has approximately 382 target genes and miR-21-3p has approximately 3673 as predicted by Target Scan [66, 67]. Among these target genes, genes involved in the pathophysiology of hypertension are shown in Table 2. Even more importantly, it has been proven that target genes, such as JAG1 and BCL-2, are associated with hypertension and that asporin (ASPN) and COL12A1 are associated with TOD during hypertension [68–70].

miR-21 and hypertension

miR-21 level in EH patients

miR-21 is usually highly expressed in both animal models and human hypertension plasma or tissues.

In 2012, a study showed that miR-21 levels were increased in the skeletal muscle of hypertensive rats compared with normotensive rats [69]. More significantly, in human disease research studies, the expression levels of miR-21 in the circulatory system of EH patients were higher than those of healthy volunteers (HVs) [71]. In addition, it has been validated that selected mRNAs and miRNAs are differentially expressed in the renal cortex between HT and normotensive subjects. miR-21 levels in the renal cortex of HT patients were higher than those in normotensive subjects [52]. Subsequently, the miR-21 level was quantified in peripheral blood mononuclear cells by quantitative reverse transcription polymerase chain reaction (qRT-PCR). HT patients showed higher miR-21 levels than controls. The study observed correlations of miR-21 expression levels with 24-h diastolic blood pressure (BP). In HT patients, the authors observed significant negative correlations of miR-21 levels with 24-h diastolic BP and with mean BP. Furthermore, the study observed a correlation between miR-21 and dipping status. An association between miR-21 levels and 24-h mean pulse pressure was also found [23]. Another study used qRT-PCR to measure the serum levels of miR-21 in seamen with hypertension. The ocean seamen with hypertension had significantly higher expression levels of miR-21 than healthy ocean seamen [51]. Interestingly, in a study group consisting of 30 untreated white coat hypertension (WCH) patients, 30 newly diagnosed and untreated HT patients and 30 normotensive (NT) healthy volunteers, plasma miR-21 levels were significantly upregulated in HT patients compared with WCH patients and NT healthy volunteers, and these miRNAs were proposed as diagnostic markers [50]. All these clinical and experimental studies suggested that miR-21 expression levels were positively associated with high BP.

In addition, in terms of TOD during hypertension, plasma miR-21 expression levels were significantly higher in the HT group than in the control group. miR-21 levels were positively correlated with clinical systolic blood pressure, clinical diastolic blood pressure, C-reactive protein (CRP), and carotid intima media thickness (CIMT) [72]. A recent study also showed that plasma miR-21 expression levels were significantly higher in HT patients than in healthy controls and that they were positively associated with left ventricular (LV) mass index in HT patients [73]. However, the potential mechanism of increased miR-21 in TOD remains unclear.

Prognostic role of miR-21 in hypertension

In 2008, miRNAs were discovered to circulate in the bloodstream. Until now, they have been detected in all blood components, including plasma, platelets, erythrocytes, red blood cells and nucleated blood cells [74–76]. Because they have many important features, including stability in the circulation, evolutionarily conserved sequences, tissue- or pathology-specific expression and detection based on sequence-specific amplification [77], circulating miRNAs are promising biomarkers for early diagnosis and are new drug targets for many diseases [78, 79].

qRT-PCR is the gold standard for profiling miRNA expression patterns with high sensitivity, specificity, accuracy, speed, and reproducibility [80–82]. This method requires proper data normalization. An ideal normalizer needs to have expression stability in different disease conditions, along with experimental variables. Unfortunately, a universal endogenous normalizer is unlikely to exist. Therefore, to acquire accurate normalization of qRT-PCR data, normalizers need to be evaluated under every experimental condition, and the stability of each candidate normalizer must be validated before conducting the experiment [83, 84]. Accordingly, accurate normalization of miRNA expression is necessary.

More importantly, a recent study has shown that hsa-miR-21-5p may be used to normalize plasma miRNA qRT-PCR expression data in EH studies [85]. Previous studies have shown that miR-21 can be used as a marker for the diagnosis and prognosis of some cancers, such as colorectal cancer, hepatocellular carcinoma, and pancreatic ductal adenocarcinoma [86–88]. In addition, miR-21 is stable in the circulation and is often regulated in a tissue- and pathology-specific manner, and moreover, it can be detected with high sensitivity and specificity using sequence-specific amplification [77]. Of note, Cengiz et al. reported that circulating miR-21 is specially overexpressed in subclinical atherosclerosis in patients with hypertension [72]. Given the above two findings, it can be concluded that the levels of miR-21 in patients with hypertension are elevated and that miR-21 may be used as normalizers for plasma miRNA expression data in EH studies. Therefore, miR-21 has the

Table 2 Target genes of miR-21 involved in the pathophysiology of hypertension

Function	Ortholog of target gene	GO class (direct)	Number of 3P-seq tags supporting UTR + 5
Vascular remodeling	RTN4	Sprouting angiogenesis	34030
	PCBP2	Ubiquitin protein ligase binding	24310
	Mar-06	Ubiquitin protein ligase activity involved in ERAD pathway	14086
	COL4A1	Collagen trimer	6549
	TGFBI	Transforming growth factor beta receptor signaling pathway	6307
	RAB11A	angiogenesis	5781
	HSPA13	Cellular component	2175
	TGFBR2	Type II transforming growth factor beta receptor binding	2168
	KLHL42	Cul3-RING ubiquitin ligase complex	2120
	ARHGEF12	Regulation of Rho protein signal transduction	815
	MEGF9	Basement membrane	689
	CADM1	Cell-matrix adhesion	676
	RFFL	Ubiquitin protein ligase binding	670
	KRIT1	Angiogenesis	574
	SESTD1	Blood vessel morphogenesis	478
	SKP2	Mitotic G2 DNA damage checkpoint	340
	BMPR2	Blood vessel remodeling	287
	RALGPS2	Ubiquitin protein ligase binding	201
	UBR3	Protein ubiquitination	200
	ERG	Angiogenesis	184
	FRS2	Fibroblast growth factor receptor signaling pathway	176
	WWP1	Protein ubiquitination	161
	TGFB2	Transforming growth factor beta receptor binding	157
	MAP3K1	Negative regulation of epidermal growth factor-activated receptor activity	137
	SPRY4	Regulation of fibroblast growth factor receptor signaling pathway	110
	GID4	Ubiquitin protein ligase activity	79
	VASH2	Regulation of angiogenesis	70
	KBTBD6	Cul3-RING ubiquitin ligase complex	51
	KLHL15	Cul3-RING ubiquitin ligase complex	42
	HECTD1	Protein ubiquitination	34
	HDAC9	Angiogenesis	13
	RECK	Blood vessel maturation	10
	ESM1	Angiogenesis	10
	ARHGAP24	Protein binding	9
	FGF18	Fibroblast growth factor binding	5
	FGF7	Transforming growth factor beta receptor signaling pathway	5

Table 2 (continued)

Function	Ortholog of target gene	GO class (direct)	Number of 3P-seq tags supporting UTR + 5
	EDNRB	Endothelin receptor activity	5
Renin angiotensin system	RHOB	GTPase activity	6532
	RASA1	GTPase binding	1700
	RASEF	GTPase activity	298
	RASA2	GTPase activator activity	170
	RASGRP1	GTPase activating protein binding	7
Oxidative stress	CMC1	Mitochondrion	1203
	SESN3	Regulation of response to reactive oxygen species	260
	ZADH2	Oxidation-reduction process	207
	GLYR1	Oxidoreductase activity	31
Inflammatory cytokines	IL6ST	Interleukin-6 receptor activity	213
	ST3GAL6	Cellular response to interleukin-6	150
	CCL20	Chemokine activity	16
	IL6R	Interleukin-6 receptor complex	13

The target genes of miR-21 are predicted by the TargetScanHuman software (http://www.targetscan.org/vert_71/).

3P-seq tags supporting UTR + 5, the 3′-UTR profiles were constructed using 3P-seq tags, which indicate the location and usage of mRNA cleavage and polyadenylation sites [66, 67]. The number of 3P-seq tags supporting UTR + 5 also includes 5 pseudocounts added at the distal end of the Gencode annotation. *RTN4* reticulon 4, *PCBP2* poly(rC) binding protein 2, *MARCH6* membrane-associated ring finger (C3HC4) 6, E3 ubiquitin protein ligase, *COL4A1* collagen, type IV, alpha 1, *TGFBI* transforming growth factor, beta-induced, 68 kDa, *RAB11A*, member RAS oncogene family, *HSPA13* heat shock protein 70 kDa family, member 13, *TGFBR2* transforming growth factor, beta receptor II (70/80 kDa), *KLHL42* kelch-like family member 42, *ARHGEF12* Rho guanine nucleotide exchange factor (GEF) 12, *MEGF9* multiple EGF-like-domains 9, *CADM1* cell adhesion molecule 1, *RFFL* ring finger and FYVE-like domain containing E3 ubiquitin protein ligase, *KRIT1* ankyrin repeat containing, *SESTD1* SEC14 and spectrin domains 1, *SKP2* S-phase kinase-associated protein 2, E3 ubiquitin protein ligase, *BMPR2* bone morphogenetic protein receptor, type II (serine/threonine kinase), *RALGPS2* Ral GEF with PH domain and SH3 binding motif 2, *UBR3* ubiquitin protein ligase E3 component n-recognin 3 (putative), *ERG* v-ets avian erythroblastosis virus E26 oncogene homolog, *FRS2* fibroblast growth factor receptor substrate 2, *WWP1* WW domain containing E3 ubiquitin protein ligase 1, *TGFB2* transforming growth factor, beta 2, *MAP3K1* mitogen-activated protein kinase kinase kinase 1, E3 ubiquitin protein ligase, *SPRY4* sprouty homolog 4 (Drosophila), *GID4* GID complex subunit 4, *VASH2* vasohibin 2, *KBTBD6* kelch repeat and BTB (POZ) domain containing 6, *KLHL15* kelch-like family member 15, *HECTD1* HECT domain containing E3 ubiquitin protein ligase 1, *HDAC9* histone deacetylase 9, *RECK* reversion-inducing-cysteine-rich protein with kazal motifs, *ESM1* endothelial cell-specific molecule 1, *ARHGAP24* Rho GTPase activating protein 24, *FGF18* fibroblast growth factor 18, *SRL* sarcalumenin, *FGF7* fibroblast growth factor 7, *EDNRB* endothelin receptor type B, *RHOB* ras homolog family member B, *RASA1* RAS p21 protein activator (GTPase activating protein) 1, *RASEF* RAS and EF-hand domain containing, *RASA2* RAS p21 protein activator 2, *RASGRP1* RAS guanyl releasing protein 1 (calcium and DAG-regulated), *CMC1* COX assembly mitochondrial protein 1 homolog (S. cerevisiae), *SESN3* sestrin 3, *ZADH2* zinc binding alcohol dehydrogenase domain containing 2, *GLYR1* glyoxylate reductase 1 homolog (Arabidopsis), *IL6ST* interleukin 6 signal transducer (gp130, oncostatin M receptor), *ST3GAL6* ST3 beta-galactoside alpha-2,3-sialyltransferase 6, *CCL20* chemokine (C-C motif) ligand 20, *IL6R* interleukin 6 receptor

potential to be used for the diagnosis and prognosis of hypertension.

miR-21 in the pathogenesis of hypertension

Marques et al. carried out the first transcriptome-wide study of differential expression of mRNAs and miRNAs in the kidney in human hypertension. Their data first confirmed that miRNAs could regulate renin expression and thus provide new insights into hypertension etiology. However, their functional experiments in human embryonic kidney (HEK-293) cells demonstrated that hsa-miR-663 and hsa-miR-181a can regulate renin mRNA levels. In their study, hsa-miR-21 was validated to have different expression in the renal cortex between HT and normotensive subjects by qRT-PCR [52]. Therefore, miR-21 may play an important role in renin expression regulation, whereas the concrete regulation mechanism still needs to be further explored.

The main manifestation of hypertension is the continuous elevation of peripheral vascular tension, which leads to abnormal vasomotor activity, whereas vasomotor activity is mainly determined by VSMC [89]. The VSMCs of normal mature vascular walls are in the states of contraction. The VSMCs in differentiation states belong to differentiation phenotypic VSMCs, synthesizing a small amount of osteopontin (OPN) and matrix proteins [90]. Vascular injury triggers a VSMC phenotypic switch from the contractile to the proliferating state, and dedifferentiated

proliferative VSMCs and increased secretion of extracellular matrix lead to vessel wall thickening and participation in vascular remodeling, which are a key structural feature of hypertension and constitute an important structural basis for elevated blood pressure [91].

miR-21 is a key molecule in the regulation of vascular remodeling during EH. The main reasons are as follows. First, miR-21 has been shown to participate in VSMCs differentiation and phenotypic regulation [33]. Research data provide important evidence that VSMC-modulating miRNAs are closely related to EH in humans. This work is the first study to reveal that miRNAs involved in VSMC phenotypic modulation are related to EH in humans [23]. Second, hypertensive vascular remodeling leads to increased expression of extracellular matrix (ECM) proteins and miR-21 in the thoracic aorta of rats. The cyclic strain causes the high expression of miR-21, which via mothers against decapentaplegic homolog 7 (Smad7) protein, increases the expression of ECM, especially collagen III, in VSMCs under vascular remodeling of hypertension. However, how Smad7 accurately and negatively regulates the expression of vascular collagen protein and then negatively regulates vascular fibrosis must be further explored [92]. Third, arterial stiffness has been recognized as a predictor of cardiovascular and all-cause mortality in HT patients [93]. miR-21 levels were positively correlated with carotid-femoral pulse wave velocity (CFPWV) and carotid radial pulse wave velocity (CRPWV). Accordingly, studies have confirmed that low levels of miR-21 were strongly associated with an improvement in arterial stiffness in patients with well-controlled EH independently of their blood pressure levels. These data emphasized the significance of miR-21 in vascular remodeling [94]. Thus, miR-21 may be involved in the regulation of vascular remodeling in EH.

Reactive oxygen species (ROS) are products of normal cellular metabolism and come from various sources in different cellular compartments. Oxidative stress resultant from imbalance between ROS generation and antioxidant defense mechanisms plays an important role in the pathogenesis of hypertension [95]. In a recent study, researchers observed a reduction of mtDNA-encoded cytochrome b (mt-Cytb) in spontaneous hypertensive rats (SHRs), which appeared to directly cause an increase in mitochondrial reactive oxygen species (mt-ROS). The authors found that miR-21 was able to translocate into the mitochondria to inhibit the downregulation of mt-Cytb gene downregulation, which may represent part of the compensatory mechanism of hypertension. This study revealed that miR-21 directly targeted mt-Cytb to positively modulate mt-Cytb translation in mitochondria by computational prediction coupled with biochemical analysis. These findings show a positive function of miR-21 in mitochondrial translation that is sufficient to lower blood pressure and alleviate cardiac hypertrophy in SHRs [96]. This discovery suggests that miR-21 induction is part of the compensatory program.

Potential roles for miR-21 in mediating the pathophysiology of hypertension are as follows (Fig. 2) [97–99].

Taken together, there is growing evidence for the regulatory role of miR-21 in the pathogenesis of hypertension.

miR-21 and TOD of hypertension

miR-21 was highly expressed in the hypertrophic left ventricle and the proximal medullary cortex tissue of fibrotic kidney in the SHR model. miR-21 may be involved in the pathological process of cardiac hypertrophy and renal fibrosis induced by hypertension [100]. A recent study observed higher levels of miR-21 in HT patients than in

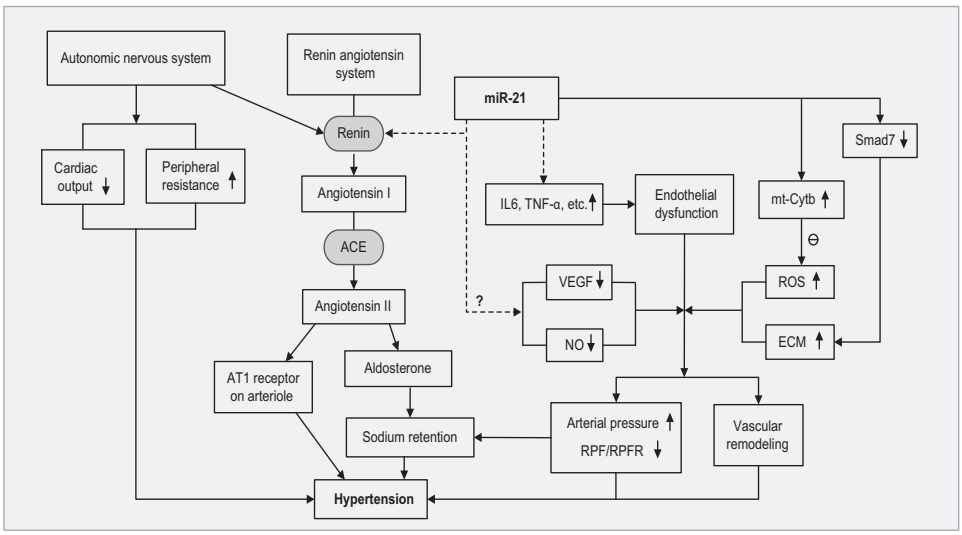

Fig. 2 Potential roles for miR-21 in mediating the pathophysiology of hypertension. miR-21, microRNA-21; ACE, angiotensin converting enzyme; IL, interleukin; TNF, tumor necrosis factor; Smad7, mothers against decapentaplegic homolog 7; mt-Cytb, mtDNA-encoded cytochrome b; ROS, reactive oxygen species; ECM, extracellular matrix; VEGF, vascular endothelial growth factor; NO, nitric oxide; RPF, renal plasma flow; GFR, glomerular filtration rate; ↓, decrease; ↑, increase;?, not reported; Θ, inhibited

healthy controls. These data revealed that miR-21 was linked to left ventricular hypertrophy (LVH) in patients with EH. Therefore, it may be related to heart hypertrophy in HT patients and is possibly a candidate therapeutic target in hypertensive heart disease [73]. However, the mechanism of miR-21 involved in hypertensive ventricular myocardial hypertrophy is not completely clear.

Sustained pressure overload of the myocardium causes cardiac fibrosis, and miR-21 has been extensively investigated in this regard [101]. It is noteworthy that study results are inconsistent. Thum et al. convincingly showed that miR-21 contributed to myocardial fibrosis by stimulating mitogen-activated protein kinase signaling in fibroblasts, and inhibiting miR-21 with a cholesterol-modified antagomir prevented cardiac failure and fibrosis development [49]. However, Patrick et al. reported that inhibition of miR-21 through the intravenous delivery of a locked nucleic acid-modified (LNA-modified) antimiR oligonucleotide failed to block the remodeling response of the heart to stress, indicating that miR-21 was not essential for pathological cardiac remodeling [102]. In contrast, another study showed that via its target programmed cell death protein 4 (PDCD4), miR-21 protected myocytes from the injury induced by reactive oxygen species [103].

Furthermore, miR-21 plays a crucial role in the development of renal fibrosis by mediating complex signaling. Smad-3-mediated upregulation of miR-21 contributes to the development of renal fibrosis [104, 105]. Microalbuminuria level is a sensitive biomarker in the diagnosis of kidney damage [106, 107], but unfortunately, previous studies found no significant correlation between miR-21 expression levels and patients' 24-h urinary albumin levels [108].

The VSMC phenotypic switch is one of the main factors leading to hypertension [91]. In addition, VSMCs play a key role in the functional and structural changes of the arterial walls in response to atherogenic factors [109–111]. Previous studies confirmed that VSMC apoptosis alone is enough to induce multiple features of atherosclerotic plaque vulnerability [112]. Moreover, there is close contact between hypertension and atherosclerosis. Hypertension is an important risk factor of carotid atherosclerotic plaques [113]. Meanwhile, hypertension is a high-risk symptom of systemic atherosclerotic disease [114]. In 2014, Kontaraki et al. reported that miR-21 was upregulated in hypertensive patients compared with controls, which contradicts its negative association with 24-h diastolic BP, mean BP, and target organ damage [23]. Subsequently, recent studies have also demonstrated that circulating miR-21 was significantly upregulated in HT patients. However, these studies showed that the miR-21 level was positively correlated with clinical systolic blood pressure, clinical diastolic blood pressure, CRP, and CIMT, indicating that miR-21 might be involved in the early stages of atherosclerotic process in HT patients and could be used as a novel marker to indicate asymptomatic organ damage in HT patients [72, 115]. Therefore, the association between miR-21 and the level of blood pressure and target organ damage in HT patients needs to be further verified.

These results indicate that miR-21 has a close relationship with TOD during hypertension, which includes the heart, kidney and blood vessels.

miR-21 and treatment of hypertension

miR-21 expression levels were upregulated in response to treatment with TGF-β1 or tumor necrosis factor α (TNF-α) in human renal tubular epithelial cells in vitro. Furthermore, previous studies found that blocking miR-21 in vivo alleviated unilateral ureteral obstruction (UUO)-induced renal fibrosis, presumably by diminishing the expression of profibrotic proteins and reducing the infiltration of inflammatory macrophages in UUO kidneys [104]. These data suggest that targeting specific miR-21 could be a novel therapeutic approach to treat renal fibrosis.

miR-21 levels in SHRs were elevated compared with the normotensive group, whereas exercise training (ET) in trained SHRs (SHR-Ts) reduced miR-21 levels and elevated vascular endothelial growth factor (VEGF) and Bcl-2 levels. In addition, ET restored soleus endothelial nitric oxide (NO) synthase levels together with proapoptotic and antiapoptotic mediators in SHR-Ts, suggesting that the balance between angiogenic and apoptotic factors may avert microvascular abnormalities during hypertension [69]. A recent study has shown that hypertension is characterized by an imbalance of pro-angiogenic and anti-angiogenic factors in the background of inflammation [116]. Moreover, miR-21 plays a well-known role in the control of angiogenesis and vascular integrity [117–122]. According to prediction algorithms, miR-21 is identified as one of the antiangiogenic miRNAs [119–121]. Meanwhile, miR-21 is also an antiapoptotic miRNA targeting Bcl-2, suggesting its important roles in regulating cell-intrinsic angiogenic activity [117–122]. Therefore, Fernandes et al. concluded that ET restored the levels of miR-21 associated with peripheral revascularization in hypertension, indicating the potential therapeutic application of miR-21 in vascular diseases [69].

In addition, tail artery diastolic pressure and average blood pressure declines and thoracic aorta reconstruction occurred in mice after specifically knocking out endothelial cell (EC) miR-21. EC miR-21 is a key molecule that can regulate blood vessel reconstruction, but its specific mechanism needs to be further explored [123]. A recent study has shown that low levels of miR-21 were strongly associated with an improvement in arterial stiffness in patients with well-controlled EH. Their data also indicated the role of miR-21 as a potential prognostic marker and future therapeutic target [94].

There is evidence that inflammation is closely associated with the occurrence and development of many cardiovascular diseases [124]. More and more basic and clinical research shows that proinflammatory factors are closely related to the occurrence and development of EH, especially in obese patients with EH [125]. In addition, inflammatory factors are closely related to TOD in patients with EH, such as the relationships between CRP, TNF-a, interleukin (IL)-6 and blood vessels [126, 127], IL-2, IL-6, IL-16, and brain [128, 129], IL-1, IL-6, IL-8, TNF-α, interferon-Y (IFN-Y), Apo-1/Fas and heart and CRP, TNF-a, IL-Iβ, IL-6, and kidney [130–132].

Previous research results indicated that compared with in the placebo or the GE group, the observed downregulation of the proinflammatory cytokines in peripheral blood mononuclear cells (PBMCs) was concomitant with higher levels of miR-21 in the HT group consuming RES-containing grape extract (GE-RES) for 12 months. miR-21 was found to be highly correlated and altered in the group consuming GE-RES for 12 months. The possibility of targeting the effects of miR-21 on the inflammatory pathway by dietary supplementation with resveratrol (RES) offers new perspectives on the prevention and treatment of hypertension [133].

A recent study found that recombinant adeno-associated virus-mediated delivery of miR-21 was sufficient to reduce blood pressure and attenuate cardiac hypertrophy in SHRs. This finding indicates a novel theoretical ground for developing miR-21-based therapeutics against hypertension [96].

Although these studies demonstrated that miR-21 exerts crucial effects on the treatment of hypertension, the idiographic action mechanism and clinical application still need to be further explored and validated repeatedly.

Conclusion

In summary, miR-21 is closely related to hypertension, and it is involved in the development and progression of hypertension and related TOD, including renin angiotensin system, inflammatory cytokines, and endothelial dysfunction. It is expected to be a new target for the prediction and treatment of hypertension.

However, investigation of the relationship between miR-21 and hypertension is just a beginning; there is still a long way to go. We need more rigorous clinical trials and more samples to evaluate the changes and significance of miR-21 in hypertension. Moreover, the corresponding targets and functional roles of miR-21 involved in hypertension still need to be further explored. In addition, considering that most of the previous studies on miR-21 are limited to animal experiments, the diagnostic and prognostic value of miR-21 should be further explored and validated in large hypertensive patient cohorts.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903–13.
2. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365:217–23.
3. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Finkelstein EA, Hong Y, Johnston SC, Khera A, Lloyd-Jones DM, Nelson SA, Nichol G, Orenstein D, Wilson PW, Woo YJ. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation. 2011;123:933–44.
4. Zhang FL, Guo ZN, Xing YQ, Wu YH, Liu HY, Yang Y. Hypertension prevalence, awareness, treatment, and control in northeast China: a population-based cross-sectional survey. J Hum Hypertens. 2017;32:54–65.
5. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017;70:776–803.
6. Wang Q, Li F. Research progress on the relationship between essential hypertension and inflammatory factors. J Guangxi Tradit Chin Med Univ. 2006;9:79–82.
7. Grundy SM. Inflammation, hypertension and the metabolic syndrome. JAMA. 2003;290:3000–2.
8. Shi W, Sun X. Inflammation and hypertension. Clin Focus. 2004;19:1255–6.
9. Wang Z, Peng X. Pathogenesis of essential hypertension: development of a 4-dimensional model. Hypothesis. 2013;11:1–7.
10. Heggermont WA, Heymans S. MicroRNAs are involved in end-organ damage during hypertension. Hypertension. 2012;60:1088–93.
11. Tsioufis K, Tsioufis C, Dimitriadis K, Mantzouranis E, Mani I, Tousoulis D. Differential effects of lercanidipine/enalapril versus amlodipine/enalapril and hydrochlorothiazide/enalapril on target organ damage and sympathetic activation in non-obese essential hypertensive subjects. Curr Med Res Opin. 2016;32:35–41.

12. Weir MR. Effects of renin-angiotensin system inhibition on end-organ protection: can we do better? Clin Ther. 2007;29: 1803–1024.
13. Kurtz TW, Kajiya T. Differential pharmacology and benefit/risk of azilsartan compared to other sartans. Vasc Health Risk Manage. 2012;8:133–43.
14. Biala A, Finckenberg P, Korpi A, Loytainen M, Martonen E, Levijoki J, Mervaala E. Cardiovascular effects of the combination of levosimenan and valsartan in hypertensive Dahl/Rapp rats. J Physiol Pharmacol. 2011;62:275–85.
15. Cheung BM. Therapeutic potential of angiotensin receptor blockers in hypertension. Expert Opin Investig Drugs. 2006;15:625–35.
16. Zhao P, Chang P. The research progress of essential hypertension-related genes. J Inn Mong Med Univ. 2013;35: 417–20.
17. Zhang H, Zhang Z. Relationship between aldosterone synthase gene polymorphism and target organ damage in patients with essential hypertension. Mod Prev Med. 2016;43:1–4.
18. Chen H, Yin X, Cheng J. RAAS gene polymorphisms and essential hypertension and its target organ damage in Chinese Han. Chin J Clin Res. 2011;24:71–73.
19. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 2004;116:281–97.
20. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993;75:843–54.
21. Rajewsky N. microRNA target predictions in animals. Nat Genet. 2006;38:S8–13.
22. Faraoni I, Antonetti FR, Cardone J, Bonmassar E. miR-155 gene: a typical multifunctional microRNA. Biochim Biophys Acta. 2009;1792:497–505.
23. 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;28:510–6.
24. 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;177:925–34.
25. Krishnan R, Mani P, Sivakumar P, Gopinath V, Sekar D. Expression and methylation of circulating microRNA-510 in essential hypertension. Hypertens Res. 2017;40:361–3.
26. Xu YP, He Q, Shen Z, Shu XL, Wang CH, Zhu JJ, Shi LP, Du LZ. MiR-126a-5p is involved in the hypoxia-induced endothelial-to-mesenchymal transition of neonatal pulmonary hypertension. Hypertens Res. 2017;40:552–61.
27. 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;8:368–75.
28. Denli AM, Tops BB, Plasterk RH, Ketting RF, Hannon GJ. Processing of primary microRNAs by microRNAs by the microprocessor complex. Nature. 2004;432:231–5.
29. Baek D, Villen J, Shin C, Camargo FD, Gygi SP, Bartel DP. The impact of microRNAs on protein output. Nature. 2008;455: 64–71.
30. Selcuklu SD, Donoghue MT, Spillane C. miR-21 as a key regulator of oncogenic processes. Biochem Soc Trans. 2009;37: 918–25.
31. Krichevsky AM, Gabriely G. miR-21: a small multi-faceted RNA. J Cell Mol Med. 2009;13:39–53.
32. Lagos-Quintana M, Rauhut R, Yalcin A, Meyer J, Lendeckel W, Tuschl T. Identification of tissue-specific microRNAs from mouse. Curr Biol. 2002;12:735–9.
33. Ji R, Cheng Y, Yue J, Yang J, Liu X, Chen H, Dean DB, Zhang C. MicroRNA expression signature and antisense-mediated depletion reveal an essential role of MicroRNA in vascular neointimal lesion formation. Circ Res. 2007;100:1579–88.
34. Haverty PM, Fridlyand J, Li L, Getz G, Beroukhim R, Lohr S, Wu TD, Cavet G, Zhang Z, Chant J. High-resolution genomic and expression analyses of copy number alterations in breast tumors. Genes Chromosomes Cancer. 2008;47:530–42.
35. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, Shimizu M, Rattan S, Bullrich F, Negrini M, Croce CM, Croce CM. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proc Natl Acad Sci USA. 2004;101:2999–3004.
36. Fujita S, Ito T, Mizutani T, Minoguchi S, Yamamichi N, Sakurai K, Iba H. miR-21 Gene expression triggered by AP-1 is sustained through a double-negative feedback mechanism. J Mol Biol. 2008;378:492–504.
37. Du J, Yang S, An D, Hu F, Yuan W, Zhai C, Zhu T. BMP-6 inhibits microRNA-21 expression in breast cancer through repressing δEF1 and AP-1. Cell Res. 2009;19:487–96.
38. Velu CS, Baktula AM, Grimes HL. Gfi1 regulates miR-21 and miR-196b to control myelopoiesis. Blood. 2009;113:4720–8.
39. Wickramasinghe NS, Manavalan TT, Dougherty SM, Riggs KA, Li Y, Klinge CM. Estradiol downregulates miR-21 expression and increases miR-21 target gene expression in MCF-7 breast cancer cells. Nucleic Acids Res. 2009;37:2584–95.
40. Loffler D, Brocke-Heidrich K, Pfeifer G, Stocsits C, Hackermuller J, Kretzschmar AK, Burger R, Gramatzki M, Blumert C, Bauer K, Cvijic H, Ullmann AK, Stadler PF, Horn F. Interleukin-6 dependent survival of multiple myeloma cells involves the Stat3-mediated induction of microRNA-21 through a highly conserved enhancer. Blood. 2007;110:1330–3.
41. Choy MK, Movassagh M, Siggens L, Vujic A, Goddard M, Sanchez A, Perkins N, Figg N, Bennett M, Carroll J, Foo R. High-throughput sequencing identifies STAT3 as the DNA-associated factor for p53-NF-kappaB-complex-dependent gene expression in human heart failure. Genome Med. 2010;2:1–14.
42. Davis BN, Hilyard AC, Lagna G, Hata A. SMAD proteins control DROSHA-mediated microRNA maturation. Nature. 2008;454:56–61.
43. Sahni V, Mukhopadhyay A, Tysseling V, Hebert A, Birch D, McGuire TL, Stupp SI, Kessler JA. BMPR1a and BMPR1b signaling exert opposing effects on gliosis after spinal cord injury. J Neurosci. 2010;30:1839–55.
44. Wu W, Hu C. The role of MicroRNA-21 in cardiovascular diseases. Chin J Clin Pharmacol Ther. 2012;17:709–14.
45. Suarez Y, Fernandez-Hernando C, Pober JS, Sessa WC. Dicer dependent microRNAs regulate gene expression and functions in human endothelial cells. Circ Res. 2007;100:1164–73.
46. Cheng Y, Ji R, Yue J, Yang J, Liu X, Chen H, Dean DB, Zhang C. MicroRNAs are aberrantly expressed in hypertrophic heart: do they play a role in cardiac hypertrophy? Am J Pathol. 2007;170:1831–40.
47. Roy S, Khanna S, Hussain SR, Biswas S, Azad A, Rink C, Gnyawali S, Shilo S, Nuovo GJ, Sen CK. MicroRNA expression in response to murine myocardial infarction: miR-21 regulates fibroblast metalloprotease-2 via phosphatase and tensin homologue. Cardiovasc Res. 2009;82:21–9.
48. Oudit GY, Sun H, Kerfant BG, Crackower MA, Penninger JM, Backx PH. The role of phosphoinositide-3 kinase and PTEN in cardiovascular physiology and disease. J Mol Cell Cardiol. 2004;37:449–71.
49. Thum T, Gross C, Fiedler J, Fischer T, Kissler S, Bussen M, Galuppo P, Just S, Rottbauer W, Frantz S, Castoldi M, Soutschek J, Koteliansky V, Rosenwald A, Basson MA, Licht JD, Pena JT, Rouhanifard SH, Muckenthaler MU, Tuschl T, Martin GR,

Bauersachs J, Engelhardt S. MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. Nature. 2008;456:980–4.
50. 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. 2015; 94:1–7.
51. Lin J, Chai W, Zhang J, Wang Y, Lin S, Li H, Wu S. Association between hypertension and serum microRNA21 and microRNAl33a in ocean seamen. Chin J Ind Hyg Occup Dis. 2014;34: 412–5.
52. 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;58:1093–8.
53. Rippe C, Blimline M, Magerko KA, Lawson BR, LaRocca TJ, Donato AJ, Seals DR. MicroRNA changes in human arterial endothelial cells with senescence: relation to apoptosis, eNOS and inflammation. Exp Gerontol. 2012;47:45–51.
54. Li J, Zhao L, He X, Yang T, Yang K. MiR-21 inhibits c-Ski signaling to promote the proliferation of rat vascular smooth muscle cells. Cell Signal. 2014;26:724–9.
55. Lin L, Gan H, Zhang H, Tang W, Sun Y, Tang X, Kong D, Zhou J, Wang Y, Zhu Y. MicroRNA21 inhibits SMAD7 expression through a target sequence in the 3' untranslated region and inhibits proliferation of renal tubular epithelial cells. Mol Med Rep. 2014;10:707–12.
56. Wang XW, Zhang C, Lee KC, He XJ, Lu ZQ, Huang C, Wu QC. Adenovirus-mediated gene transfer of microRNA-21 sponge inhibits neointimal hyperplasia in rat vein grafts. Int J Biol Sci. 2017;13:1309–19.
57. Zhao J, Schnitzler GR, Iyer LK, Aronovitz MJ, Baur WE, Karas RH. MicroRNA-offset RNA alters gene expression and cell proliferation. PLoS ONE. 2016;11:e0156772.
58. Stein JJ, Iwuchukwu C, Maier KG, Gahtan V. Thrombospondin-1-induced vascular smooth muscle cell migration and proliferation are functionally dependent on microRNA-21. Surgery. 2014;155:228–33.
59. Albinsson S, Sessa WC. Can microRNAs control vascular smooth muscle phenotypic modulation and the response to injury? Physiol Genom. 2011;43:529–33.
60. Li Y, Yan L, Zhang W, Hu N, Chen W, Wang H, Kang M, Ou H. MicroRNA-21 inhibits platelet-derived growth factor-induced human aortic vascular smooth muscle cell proliferation and migration through targeting activator protein-1. Am J Transl Res. 2014;6:507–16.
61. Dubois-Deruy E, Cuvelliez M, Fiedler J, Charrier H, Mulder P, Hebbar E, Pfanne A, Beseme O, Chwastyniak M, Amouyel P, Richard V, Bauters C, Thum T, Pinet F. MicroRNAs regulating superoxide dismutase 2 are new circulating biomarkers of heart failure. Sci Rep. 2017;7:14747.
62. Ramanujam D, Sassi Y, Laggerbauer B, Engelhardt S. Viral vector-based targeting of miR-21 in cardiac nonmyocyte cells reduces pathologic remodeling of the heart. Mol Ther. 2016;24: 1939–48.
63. Huang W, Tian SS, Hang PZ, Sun C, Guo J, Du ZM. Combination of microRNA-21 and microRNA-146a attenuates cardiac dysfunction and apoptosis during acute myocardial infarction in mice. Mol Ther Nucleic Acids. 2016;5:e296.
64. Dong S, Ma W, Hao B, Hu F, Yan L, Yan X, Wang Y, Chen Z, Wang Z. microRNA-21 promotes cardiac fibrosis and development of heart failure with preserved left ventricular ejection fraction by up-regulating Bcl-2. Int J Clin Exp Pathol. 2014;7:565–74.
65. Villar AV, García R, Merino D, Llano M, Cobo M, Montalvo C, Martín-Durán R, Hurlé MA, Nistal JF. Myocardial and circulating levels of microRNA-21 reflect left ventricular fibrosis in aortic stenosis patients. Int J Cardiol. 2013;167:2875–81.
66. Jan CH, Friedman RC, Ruby JG, Bartel DP. Formation, regulation and evolution of Caenorhabditis elegans 3'UTRs. Nature. 2011;469:97–101.
67. Agarwal V, Bell GW, Nam JW, Bartel DP. Predicting effective microRNA target sites in mammalian mRNAs. eLife. 2015;4: 1–38.
68. Kriegel AJ, Baker MA, Liu Y, Liu P, Cowley AW Jr, Liang M. Endogenous microRNAs in human microvascular endothelial cells regulate mRNAs encoded by hypertension-related genes. Hypertension. 2015;66:793–9.
69. Fernandes T, Magalhaes FC, Roque FR, Phillips MI, Oliveira EM. Exercise training prevents the microvascular rarefaction in hypertension balancing angiogenic and apoptotic factors: role of microRNAs-16, -21, and -126. Hypertension. 2012;59:513–20.
70. Wang G, Wu L, Chen Z, Sun J. Identification of crucial miRNAs and the targets in renal cortex of hypertensive patients by expression profiles. Ren Fail. 2017;39:92–99.
71. Park MY, Herrmann SM, Saad A, Widmer RJ, Tang H, Zhu XY, Lerman A, Textor SC, Lerman LO. Circulating and renal vein levels of microRNAs in patients with renal artery stenosis. Int J Nephrol. 2011;30:480–90.
72. Cengiz M, Yavuzer S, Kilickiran AB, Yuruyen M, Yavuzer H, Dikici SA, Karatas OF, Ozen M, Uzun H, Ongen Z. Circulating miR-21 and eNOS in subclinical atherosclerosis in patients with hypertension. Clin Exp Hypertens. 2015;37:643–9.
73. 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;9:802–10.
74. Mitchell PS, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova-Agadjanyan EL, Peterson A, Noteboom J, O'Briant KC, Allen A, Lin DW, Urban N, Drescher CW, Knudsen BS, Stirewalt DL, Gentleman R, Vessella RL, Nelson PS, Martin DB, Tewari M. Circulating microRNAs as stable blood-based markers for cancer detection. Proc Natl Acad Sci USA. 2008;105:10513–8.
75. Lawrie CH, Gal S, Dunlop HM, Pushkaran B, Liggins AP, Pulford K, Banham AH, Pezzella F, Boultwood J, Wainscoat JS, Hatton CS, Harris AL. Detection of elevated levels of tumour-associated microRNAs in serum of patients with diffuse large B-cell lymphoma. Br J Haematol. 2008;141:672–5.
76. Chen X, Ba Y, Ma L, Cai X, Yin Y, Wang K, Guo J, Zhang Y, Chen J, Guo X, Li Q, Li X, Wang W, Zhang Y, Wang J, Jiang X, Xiang Y, Xu C, Zheng P, Zhang J, Li R, Zhang H, Shang X, Gong T, Ning G, Wang J, Zen K, Zhang J, Zhang CY. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. Cell Res. 2008;18: 997–1006.
77. Tijsen AJ, Pinto YM, Creemers EE. Circulating microRNAs as diagnostic biomarkers for cardiovascular diseases. Am J Physiol Heart Circ Physiol. 2012;303:H1085–95.
78. Kosaka N, Iguchi H, Ochiya T. Circulating microRNA in body fluid: a new potential biomarker for cancer diagnosis and prognosis. Cancer Sci. 2010;101:2087–92.
79. Yu DC, Li QG, Ding XW, Ding YT. Circulating microRNAs: potential biomarkers for cancer. Int J Mol Sci. 2011;12:2055–63.
80. Roberts TC, Coenen-Stass AM, Wood MJ. Assessment of RT-qPCR normalization strategies for accurate quantification of extracellular microRNAs in murine serum. PLoS One. 2014;9: e89237.

81. McDermott AM, Kerin MJ, Miller N. Identification and validation of miRNAs as endogenous controls for RQ-PCR in blood specimens for breast cancer studies. PLoS One. 2013;8:e83718.
82. Heid CA, Stevens J, Livak KJ, Williams PM. Real time quantitative PCR. Genome Res. 1996;6:986–94.
83. Vandesompele J, De Preter K, Pattyn F, Poppe B, Van Roy N, DePaepe A, Speleman F. Accurate normalization of real-time quantitative RT-PCR data by geometric averaging of multiple internal control genes. Genome Biol. 2002;3:1–12.
84. Schmittgen TD, Zakrajsek BA. Effect of experimental treatment on housekeeping gene expression: validation by real-time, quantitative RT-PCR. J Biochem Biophys Methods. 2000;46: 69–81.
85. Solayman MH, Langaee T, Patel A, El-Wakeel L, El-Hamamsy M, Badary O, Johnson JA. Identification of suitable endogenous normalizers for qRT-PCR analysis of plasma microRNA expression in essential hypertension. Mol Biotechnol. 2016;58: 179–87.
86. Liu GH, Zhou ZG, Chen R, Wang MJ, Zhou B, Li Y, Sun XF. Serum miR-21 and miR-92a as biomarkers in the diagnosis and prognosis of colorectal cancer. Tumour Biol. 2013;34:2175–81.
87. Yan SR, Liu ZJ, Yu S, Bao YX. Investigation of the value of miR-21 in the diagnosis of early stage HCC and its prognosis: a meta-analysis. Genet Mol Res. 2015;14:11573–86.
88. Vychytilova-Faltejskova P, Kiss I, Klusova S, Hlavsa J, Prochazka V, Kala Z, Mazanec J, Hausnerova J, Kren L, Hermanova M, Lenz J, Karasek P, Vyzula R. Slaby O. MiR-21, miR-34a, miR-198 and miR-217 as diagnostic and prognostic biomarkers for chronic pancreatitis and pancreatic ductal adenocarcinoma. Int J Clin Exp Pathol. 2015;8:7131–9.
89. Gerthoffer WT. Mechanisms of vascular smooth muscle cell migration. Circ Res. 2007;100:607–21.
90. Shang Y, Yoshida T, Amendt BA, Martin JF, Owens GK. Pitx2 is functionally important in the early stages of vascular smooth muscle cell differentiation. J Cell Biol. 2008;181:461–73.
91. Feihl F, Liaudet L, Levy BI, Waeber B. Hypertension and microvascular remodelling. Cardiovasc Res. 2008;78:274–85.
92. Shen B, Yao Q, Wu G, Qi Y, Jiang Z. Regulating effect of microRNA-21 on the expression of extracellular matrix of vascular smooth muscle cells under vascular remodeling of hypertension. J Mol Biol. 2015;30:1–7.
93. Lin X, Chen G, Qi J, Chen X, Zhao J, Lin Q. Effect of continuous positive airway pressure on arterial stiffness in patients with obstructive sleep apnea and hypertension: a meta-analysis. Eur Arch Otorhinolaryngol. 2016;273:4081–8.
94. Parthenakis F, Marketou M, Kontaraki J, Patrianakos A, Nakou H, Touloupaki M, Vernardos M, Kochiadakis G, Chlouverakis G, Vardas P. Low levels of microRNA-21 are a marker of reduced arterial stiffness in well-controlled hypertension. J Clin Hypertens. 2017;19:235–40.
95. Majzunova M, Dovinova I, Barancik M, Chan JY. Redox signaling in pathophysiology of hypertension. J Biomed Sci. 2013;20:1–10.
96. 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;134:734–51.
97. Beevers G, Gregory YHL, O'Brien E. ABC of hypertension: the pathophysiology of hypertension. BMJ. 2001;322:912–6.
98. Lamarca B. The role of immune activation in contributing to vascular. Minerva Ginecol. 2010;62:105–20.
99. Montezano AC, Tsiropoulou S, Dulak-Lis M, Harvey A, Camargo Lde L, Touyz RM. Redox signaling, Nox5 and vascular remodeling. Curr Opin Nephrol Hypertens. 2015;24: 425–33.
100. Romero DG, Plonczynski MW, Carvajal CA, Gomez-Sanchez EP, Gomez-Sanchez CE. Microribonucleic acid-21 increases aldosterone secretion and proliferation in H295R human adrenocortical cells. Endocrinology. 2008;149:2477–83.
101. Kumarswamy R, Volkmann I, Thum T. Regulation and function of miRNA-21 in health and disease. RNA Biol. 2011;8:706–13.
102. Patrick DM, Montgomery RL, Qi X, Obad S, Kauppinen S, Hill JA, van Rooij E, Olson EN. Stress-dependent cardiac remodeling occurs in the absence of microRNA-21 in mice. J Clin Invest. 2010;120:3912–6.
103. Cheng Y, Liu X, Zhang S, Lin Y, Yang J, Zhang C. MicroRNA-21 protects against the H_2O_2-induced injury on cardiac myocytes via its target gene PDCD4. J Mol Cell Cardiol. 2009;47:5–14.
104. Zarjou A, Yang S, Abraham E, Agarwal A, Liu G. Identification of a microRNA signature in renal fibrosis: role of miR-21. Am J Physiol Ren Physiol. 2011;301:F793–801.
105. Zhong X, Chung AC, Chen HY, Meng XM, Lan HY. Smad3-mediated upregulation of miR-21 promotes renal fibrosis. J Am Soc Nephrol. 2011;22:1668–81.
106. Bigazzi R, Bianchi S, Baldari D, Campese VM. Microalbuminuria predicts cardiovascular events and renal insufficiency in patients with essential hypertension. J Hypertens. 1998;16:1325–33.
107. Zulu M, Kaile T, Kantenga T, Chileshe C, Nkhoma P, Sinkala M. Kidney injury molecule-1 and microalbuminuria levels in Zambian population: biomarkers of kidney injury. Pan Afr Med J. 2016;24:1–6.
108. Parthenakis FI, Marketou ME, Kontaraki JE, Maragoudakis F, Maragkoudakis S, Nakou H, Roufas K, Patrianakos A, Chlouverakis G, Malliaraki N, Vardas PE. Comparative microRNA profiling in relation to urinary albumin excretion in newly diagnosed hypertensive patients. J Hum Hypertens. 2016;30: 685–9.
109. Rosenfeld ME, Ross R. Macrophage and smooth muscle cell proliferation in atherosclerotic lesions of WHHL and comparably hypercholesterolemic fat-fed rabbits. Arteriosclerosis. 1990;10: 680–7.
110. Allahverdian S, Chehroudi AC, McManus BM, Abraham T, Francis GA. Contribution of intimal smooth muscle cells to cholesterol accumulation and macrophage-like cells in human atherosclerosis. Circulation. 2014;129:1551–9.
111. Shanahan CM, Weissberg PL. Smooth muscle cell phenotypes in atherosclerotic lesions. Curr Opin Lipidol. 1999;10:507–13.
112. Clarke MC, Figg N, Maguire JJ, Davenport AP, Goddard M, Littlewood TD, Bennett MR. Apoptosis of vascular smooth muscle cells induces features of plaque vulnerability in atherosclerosis. Nat Med. 2006;12:1075–80.
113. Chen Z, Wang F, Zheng Y, Zeng Q, Liu H. H-type hypertension is an important risk factor of carotid atherosclerotic plaques. Clin Exp Hypertens. 2016;38:424–8.
114. Román AO, Badilla SM, Dussaubat AAM. Hypertension as a biological marker of systemic atherosclerotic disease. Rev Med Chil. 2010;138:346–51.
115. Erkan Y, Kamuran K, Ip Emrah, Ugur A, Selami D, Emrah E, Mustafa Ö, Hikmet H. A novel marker for asymptomatic organ damage in the patients with hypertension: MIR-21. Am J Cardiol. 2016;117:S19.
116. Marek-Trzonkowska N, Kwieczynska A, Reiwer-Gostomska M, Kolinski T, Molisz A, Siebert J. Arterial hypertension is characterized by imbalance of pro-angiogenic versus anti-angiogenic factors. PLoS ONE. 2015;10:e0126190.
117. Batkai S, Thum T. MicroRNAs in hypertension: mechanisms and therapeutic targets. Curr Hypertens Rep. 2012;14:79–87.
118. Weber M, Baker MB, Moore JP, Searles CD. MiR-21 is induced in endothelial cells by shear stress and modulates apoptosis and

eNOS activity. Biochem Biophys Res Commun. 2010;393: 643–8.
119. Quintavalle C, Garofalo M, Croce CM, Condorelli G. "ApoptomiRs" in vascular cells: their role in physiological and pathological angiogenesis. Vasc Pharmacol. 2011;55:87–91.
120. Urbich C, Kuehbacher A, Dimmeler S. Role of microRNAs in vascular diseases, inflammation, and angiogenesis. Cardiovasc Res. 2008;79:581–8.
121. Suarez Y, Sessa WC. MicroRNAs as novel regulators of angiogenesis. Circ Res. 2009;104:442–54.
122. Sen CK, Gordillo GM, Khanna S, Roy S. Micromanaging vascular biology: tiny microRNAs play big band. J Vasc Res. 2009;46:527–40.
123. Zhang XY, Shen BR, Zhang YC, Wan XJ, Yao QP, Wu GL, Wang JY, Chen SG, Yan ZQ, Jiang ZL. Induction of thoracic aortic remodeling by endothelial-specific deletion of microRNA-21 in mice. PLoS ONE. 2013;8:e59002.
124. Badr K, Wainwright CL. Inflammation in the cardiovascular system: here, there and everywhere. Curr Opin Pharmacol. 2004;4:107–9.
125. Recasens M, Ricart W, Fernández-Real JM. Obesity and inflammation. Rev Med Univ Navar. 2004;48:49–54.
126. Blake GJ, Ridker PM. Novel clinical markers of vascular wall inflammation. Circ Res. 2001;89:763–71.
127. Hayaishi-Okano R, Yamasaki Y, Katakami N, Katakami N, Ohtoshi K, Gorogawa S, Kuroda A, Matsuhisa M, Kosugi K, Nishikawa N, Kajimoto Y, Hori M. Elevated C-reactive protein associates with early-stage carotid atherosclerosis in young subjects with type 1 diabetes. Diabetes Care. 2002;25:1432–8.
128. Luo X, Wu W, Cheng T, Zheng M. Changes and significance of serum IL-2,IL-6 and IL,16 in patients with hypertensive cerebral hemorrhage. Chin J Clin Neurosci. 2004;12:309–10.
129. Yuan Z, Zhang Y. The relationship between the level of C-reactive protein and the prognosis of patients with hypertensive cerebral hemorrhage. Chin J Cerebrovasc Dis. 2005;2:276–7.
130. Zhu J, Chen X, Ma S, Wang C. Study on the relationship between essential hypertension complicated with cardiac dysfunction and cytokines. Chin J Gerontol. 2004;24:394–5.
131. Yu Q, Li X, Zhao C. Relationship between the cytokines release and left ventricular function in patients with essential hypertension patients. Chin J Cardiovasc Rev. 2004;2:187–9.
132. Wu X, Yang C, Yu J, Zhang B. The significance of inflammation on renal damage in patients with essential hypertension. Chin J Hypertens. 2003;11:16–8.
133. Tome-Carneiro J, Larrosa M, Yanez-Gascon MJ, Davalos A, Gil-Zamorano J, Gonzalvez M, Garcia-Almagro FJ, Ruiz Ros JA, Tomas-Barberan FA, Espin JC, Garcia-Conesa MT. One-year supplementation with a grape extract containing resveratrol modulates inflammatory-related microRNAs and cytokines expression in peripheral blood mononuclear cells of type 2 diabetes and hypertensive patients with coronary artery disease. Pharmacol Res. 2013;72:69–82.