MicroRNAs Are Involved in End-Organ Damage During Hypertension

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Abstract—Even in the new millennium, arterial hypertension remains a serious condition, with considerable morbidity and mortality worldwide. Crucial in managing the disease is not only lowering arterial blood pressure but also preventing or treating the typical end-organ damage caused by long-lasting and inadequately treated hypertension. In the past decade, it has been shown that microRNAs (miRs) are involved in several hypertension-related pathologies, such as cardiac hypertrophy and fibrosis, hypertensive heart failure, renal fibrosis, kidney failure, and, to a lesser extent, eye disease and hemorrhagic stroke. Whereas others extensively reviewed the role of miRs in atherosclerosis and vascular disease, this review focuses on their role in target organ damage during arterial hypertension. We emphasize the involvement of miRs in pathological end-organ remodeling processes and try to demonstrate some common miR signatures in distinct end organs. Hence, we aimed to provide proof of arterial hypertension being a systemic disease, similar to diabetes mellitus or metabolic syndrome. Furthermore, miRs that act on one particular process in different end organs are interesting therapeutic targets. Some future perspectives in miR research are highlighted with respect to novel therapeutic strategies in the cardiovascular field. **(*Hypertension*. 2012;60:1088-1093.)**

Key Words: general categories: basic science ■ genetics/genomics: gene expression/regulation ■ heart/cardiac: failure ■ kidney: chronic failure ■ vascular biology: hypertrophy/remodeling ■ microRNA

Even in the new millennium, arterial hypertension remains a serious condition, with considerable morbidity and mortality worldwide. Crucial in managing the disease is not only lowering arterial blood pressure but also preventing or treating the concomitant end-organ damage. Crucial organs, such as the heart, kidneys, vessels, eyes, and brain, are sensitive to high blood pressure.[1,2]

In the past decade, microRNAs (miRs) have become among the most popular kids on the cardiovascular block, being the subject of numerous studies on their involvement in hypertension-related manifestations.[3,4] MiRs are small, double-stranded RNA molecules of 20 to 23 nucleotides in length. They are synthesized in the nucleus of every cell, after which they undergo different maturation processes before being included in the RNA-induced silencing complex. This complex blocks translation of mRNA into protein and to some extent degrades mRNA. MiRs, with their often imperfect complementarity to the 3′ untranslated region of untranslated mRNA, are widely conserved among mammals. They typically act in clusters to influence a specific process, but 1 miR is often involved in different miR-mRNA interactions.[5] Large-scale expression analyses with microarrays led to subsequent in-depth functional studies of ≥1 differentially regulated miR(s), using a transgenic approach (miR-knockout or miR-overexpressing animals), or pharmacological blockade of miRs using highly specific oligonucleotides. Whereas other groups extensively reviewed the implication of miRs in atherosclerosis and vascular disease,[6–8] this review focuses on their potential role in hypertension-related end-organ damage. Nevertheless, it needs to be affirmed that the contribution of arterial hypertension itself to end-organ damage is difficult to investigate, because end-organ damage is multifactorial and is a combination of genetic susceptibility and environmental factors. Even more challenging is determining the influence of individual miRs on these complex processes.

Are MiRs of Pathogenetic Importance in Arterial Hypertension Anyway?

Little is known about the involvement of miRs in essential hypertension as such. A recent study showed a miR signature in plasma of patients with essential hypertension, which differed from their healthy counterparts: 27 miRs were differentially expressed.[9] The evidence for the interplay among miR-155, the angiotensin receptor 1, A1166C polymorphism, and angiotensin receptor 1 protein expression levels[10,11] provides a possible pathogenetic role for a miR in cardiac hypertrophy, whereas the description of a genetic variant in the 3′ untranslated region of vacuolar H+ ATPase ATPV0A1 creates a miR-637–binding motif related to hypertension risk by interfering with the fine-tuning of several vasoactive substances, including chromogranin A as precursor of catestatin, an inhibitor of catecholamine release.[12]

A refreshing point of view would be to study the effect of antihypertensive medication on miR profiles. Until now, such

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studies in hypertension are generally lacking. This approach could, however, be promising.[13,14] Lu et al[13] observed that the cardioprotective effect of propanolol after myocardial infarction is at least partially mediated by downregulation of miR-1 in the heart. A similar approach in hypertension studies could lead to the discovery of miRs with a causal importance.

Heart: Cardiac Fibrosis, Hypertrophy, and Hypertensive Heart Failure

Studies in Models of Pressure Overload

Hypertensive heart disease and concomitant cardiac fibrosis have been the subject of numerous investigations, albeit not always in models of hypertension. These important manifestations of long-lasting arterial hypertension also occur on other stressors.[15–17] MiRs are essential in different pathophysiological processes underlying cardiomyocyte growth, remodeling, interstitial fibrosis, and heart failure.[18] The expression of miRs during cardiomyocyte hypertrophy is dynamically regulated[19] and differs between hypertension-related hypertrophy and physiological hypertrophy,[20,21] suggesting that different cell signaling pathways are involved in these 2 distinct processes. MiR-133a, constitutionally expressed in the heart, protects against myocardial fibrosis without affecting hypertrophy in pressure-overloaded hearts.[22] MiR-133a and miR-30 are involved in myocardial matrix remodeling, in part by their regulation of connective tissue growth factor.[23] MiR-199a/b functions as an important negative regulator of hypertrophy,[24] targeting dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1a[25] and calcineurin/nuclear factor of activated T-cells (NFAT) signaling,[26] the latter also controlled by miR-23a.[27]

Studies in Other Cardiac Disease Models

The role of miRs in cardiovascular adaptation to stress has been extensively studied in other models, for example, doxorubicin-induced cardiomyopathy, transgenic rodent strains, and adeno-associated virus vector–mediated approaches. Several groups already showed that targeted deletion of Dicer, the endoribonuclease of the RNAse-III family that cleaves immature forms of miRs, not only provokes spontaneous cardiac remodeling but also leads to dilated cardiomyopathy and heart failure.[28,29] These crucial findings clearly indicate that the normal heart is delicately fine-tuned by different miRs, in line with downregulation of Dicer in end-stage failing hearts.[30]

The constitutively expressed cardiac miRs, miR-1 and miR-133, are among influential regulators of cardiomyocyte biology. They are implicated in differentiation of embryonic stem cells into cardiomyocytes.[31] MiR-1-1 and miR-1-2, representing 40% of all expressed cardiac miRs, derepress certain elements of the cytoskeleton, such as twinfilin-1, to provoke cardiac hypertrophy.[32] MiR-1 negatively regulates expression of several hypertrophy-associated genes, such as calmodulin and myocyte enhancer factor 2a,[33] sarco/endoplasmic reticulum calcium-dependent ATPase 2a,[34] and insulin growth factor 1.[35,36] MiR-133 itself is downregulated in cardiac hypertrophy.[37] Other known targets in hypertrophy, such as calcineurin and NFATc4, are also controlled by miR-133.[38,39]

Continuous pressure overload of myocardium gives rise to cardiac fibrosis, and miR-21 has been extensively investigated in this regard.[40] Myocytes are at least partially protected from reactive oxygen species by miR-21, via its target programmed cell death protein 4,[41] but miR-21 does contribute to myocardial fibrosis by stimulating mitogen-activated protein kinase signaling in fibroblasts.[42] However, Thum et al[42] convincingly showed that inhibiting miR-21 with a cholesterol-modified antago-miR prevented cardiac failure and fibrosis development; similar, but not identical, experiments by Patrick et al[43] did not show this protective effect: their treatment with a locked nucleic acid–based anti-miR-21 was not able to prevent or treat cardiac fibrosis on transaortic banding. Probably other subtle factors are at stake when a specific miR is inhibited: the pharmacological blockade of miRs is not only dose dependent but also differs according to the oligonucleotide chemistry (antago-miR versus anti-miR) and the time of administration, factors that differed between both publications.

Downregulation of miR-29 induces the expression of collagens in vitro and in vivo and enhances the fibrotic response in the myocardium.[44] Furthermore, miR-21 and -29 also mediate complex signaling in the development of renal fibrosis[45–48] and thus seem to modulate similar processes in different target organs (Figure). MiR-133a regulates collagen 1A1 expression,[49] and miR-199 also links antiapoptotic Akt signaling with β-adrenergic stimulation.[50] Finally, miR-199a-5p is regulated by signal transducer and activator of transcription 3, thereby linking cardiomyocyte and endothelial cell function.[51] MiR-9 regulates myocardin expression together with NFATc3,[52] the latter being controlled by miR-23a.[53] Furthermore, phosphatase and tensin homolog is also derepressed by miR-22, hence protecting rat cardiomyocytes from hypertrophy.[54] Mitogen-activated protein kinase, which is regulated by miR-21 in fibroblasts, is under the control of miR-142.[55] Others report that both miR-221[56] and miR-27b[57] promote cardiac hypertrophy, whereas miR-206 attenuates cardiac remodeling by inhibiting metalloproteinase inhibitor 3.[58]

MiRs as Biomarkers for Cardiomyocyte Injury

A few miRs implicated in cardiac function are possible biomarkers for cardiomyocyte injury. MiR-208a/b is encoded together with the cardio-specific α- and β-myosin heavy chains. Elevated plasma miR-208 levels were reported in myocardial infarction[59] and are associated with adverse clinical outcomes in human dilated cardiomyopathy.[60] When miR-208a is inhibited in Dahl hypertensive rats, cardiac function and survival improve during hypertension-induced heart failure.[61] MiR-208a functions as a regulator of hypertrophy and conduction[62] by downregulating the expression of α-myosin heavy chain.[63] Together with miR-208b, circulating miR-499 also reflects myocardial damage in cardiovascular disease, in general,[64] and, more particularly, in myocardial infarction.[65] In 2011, Wang et al[66] showed that miR-499 targets calcineurin and dynamin-related protein 1, thereby regulating mitochondrial dynamics. Furthermore, also miR-423-5p was reported to be a possible candidate biomarker for heart failure.[67,68] These biomarker miRs are not only part of a disease-specific miR signature, but their up- or downregulation might bring cardiovascular signaling networks to light that are involved in heart failure.[69,70]

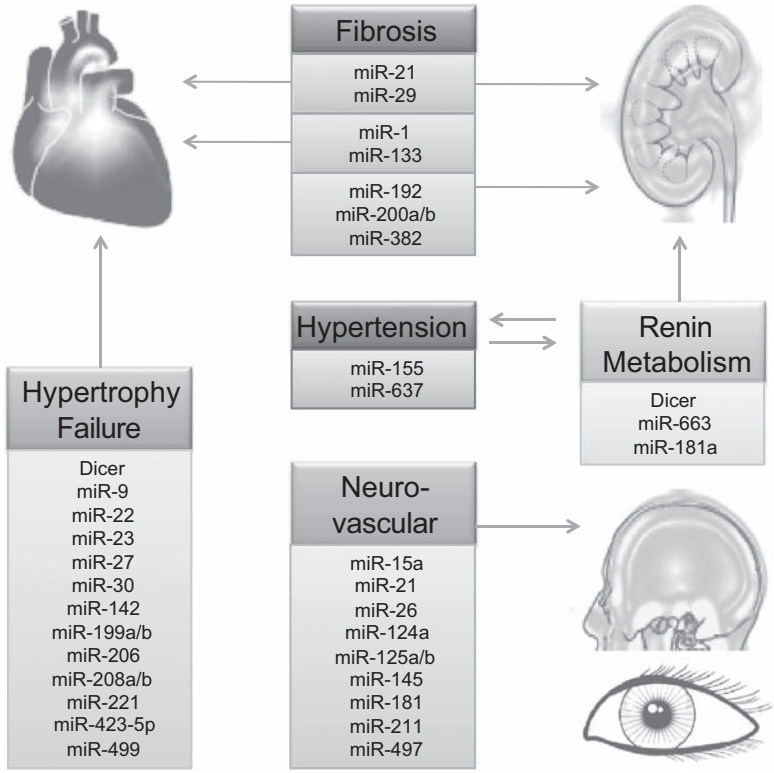

Figure. Nonlimitative list of microRNAs (miRs) implied in hypertension and end-organ damage.

Kidney: Renal Fibrosis and Hypertensive Kidney Failure

Studies in Models of Arterial Hypertension

Because of its enormous reserve capacity, kidney failure is only an end-stage manifestation of arterial hypertension.[71] Pre-emptive screening by measuring serum creatinine clearance is insufficient to detect early hypertensive kidney failure. Already in 2010, miR-200a/b, miR-141, miR-192, miR-205, and miR-429 were described to be highly expressed in the kidneys of patients with hypertensive nephrosclerosis.[72] However, few studies have investigated these miRs in models of arterial hypertension but rather in models of kidney disease, such as the unilateral ureteral obstruction model.[73] However, some pathogenetic links might shed more light on these complex processes. The renal juxtaglomerular cells are responsible for renin production. MiR-663 and miR-181a clearly interfere in the metabolism of renin: in vitro experiments in HEK293 cells demonstrated that miR-663 binds to the renin and apolipoprotein E 3′ untranslated region and regulates both mRNA levels; miR-181a, on the other hand, binds to and regulates renin and mitochondria-associated apoptosis-inducing factor (AIFM1) mRNA.[74] Furthermore, Dicer-knockout mice lose numerous juxtaglomerular cells and develop marked renal fibrosis.[75] This implies at least a role for these miRs in the pathogenesis of hypertensive renal injury, but further studies are certainly needed to elaborate these findings.

Studies in Other Models of Kidney Disease

A histological hallmark of long-lasting kidney damage is renal fibrosis. MiR-29b is partially protective in renal fibrosis because it mediates the downregulation of several collagens in renal medullary injury,[45] and suppression of miR-29 by transforming growth factor β-1 (TGF-β1) contributes to enhanced renal collagen expression and resulting fibrosis.[46] Smad-3–mediated upregulation of miR-21 promotes the development of renal fibrosis.[47,48] TGF-β modulates a lot of the compensatory mechanisms observed in diabetic nephropathy, which is also accompanied by renal fibrosis and glomerulosclerosis. A miR circuit composed of miR-192 and miR-200b/c induces TGF-β expression, responsible for an acceleration of the profibrotic process in the kidney.[76] Inhibition of these miRs with specific antisense oligonucleotides results in partial amelioration of renal fibrosis in mice[77,78] and rats.[79] However, there is debate regarding whether miR-192 is profibrotic or antifibrotic in the kidney. Although a profibrotic effect of miR-192 was reported via TGF-β1 signaling,[80] loss of miR-192 did promote fibrogenesis in diabetic nephropathy.[81] Possible explanations are the differences in animal models, cell types, and stimuli used in the assays and differences in seed-binding sites between rodent and human miR-192 targets. Also, miR-382 is at play in the development of inner medullary interstitial fibrosis in mice by targeting kallikrein-5[82] and TGF-β.[83] On the other hand, miR-200a is able to inhibit renal fibrosis by downregulating TGF-β.[84]

Eyes and Brain: Toward a MiR Signature for Organ Damage?

Hypertensive retinopathy and stroke are manifestations of inadequately treated, long-lasting arterial hypertension. Evidence for miRs contributing to these processes is scarce. A detrimental feature of retinopathy is that its consequence—visual loss—only manifests at a late stage when the damage to the retina is mostly irreversible. Patients with known hypertension under adequate follow-up should be screened on an annual basis for the development of hypertensive retinopathy.[85]

Several miRs seem to be involved in diabetic retinopathy.[86–88] Recently, a comprehensive atlas of the complete mouse eye, including the retina, has been developed,[89] and a tool for miR-restricted transgene expression in the retina has been set up.[90] Until now, evidence for a miR signature in hypertensive retinopathy is lacking, yet the premise of miR-oriented research on this topic could be promising.

MiR expression profiling has been performed in animal models of intracerebral hemorrhage[91,92] and in ischemic stroke.[93–95] Also in the repair phase after stroke in general, there is growing evidence that miRs regulate an important part of the process of controlled neuronal death,[96,97] reviewed in Reference [98]. One of the most dangerous consequences of ischemic stroke is hemorrhagic transformation, and here arterial hypertension plays a crucial role. MiR-211 as a regulator of angiopoietin-1[99] and miR-125a/b-5p inhibiting endothelin-1 expression in vascular endothelial cells[100] do point toward the importance of miRs in vasculogenesis and vascular solidity. Furthermore, there is evidence for involvement of miRs in vascular neointimal lesion formation,[101,102] reviewed in Reference [103].

Perspectives in Cardiovascular MiR Research

In the past decade, knowledge on the function of specific miRs in development, health, and disease has boomed. We appreciate miRs as delicate fine-tuners of developmental and pathophysiological processes. In addition, this research field still leads to the discovery of previously unknown molecular targets in different diseases.

Furthermore, blocking of miRs with specific antisense oligonucleotides could be of therapeutic use, also in the cardiovascular field. Referring to the end-organ damage described here, for example, administration of miR inhibitors in ophthalmology, is a challenging perspective. One of the theoretical advantages of miR-blocking therapy is that several miRs are often time-, organ-, and disease-specifically altered. However, contrasting effects of miR blockade should make us think about the clinical usefulness. The development of specific galenic forms, for example, anti-miR sponges, is under investigation.[104] The discovery of highly disease-specific miR signatures is an interesting screening tool to detect a disease faster and more accurately, of course taking into account all the possible drawbacks.

In conclusion, miRs still remain an exciting subdomain in cardiovascular research. Process-specific miR signatures are revealed little by little in systemic diseases, such as arterial hypertension and diabetes mellitus. Those miR-rich networks form interesting therapeutic targets. However, we have to realize that miRs are only a micro-part of the vast number of noncoding RNAs,[105] such as long noncoding RNAs, PIWI-interacting RNAs, small nucleolar RNAs, transcribed ultraconserved regions, and large intergenic noncoding RNAs, which definitely merit our attention to better understand and treat diseases, including hypertension.

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Disclosures

None.

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