

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 al¹³ observed that the cardioprotective effect of propranolol 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 regulated¹⁹ 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, constitutively 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 1a²⁵ 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 al⁴² 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 al⁴³ 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-221⁵⁶ and miR-27b⁵⁷ 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 infarction⁵⁹ 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 conduction⁶² 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 al⁶⁶ 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}

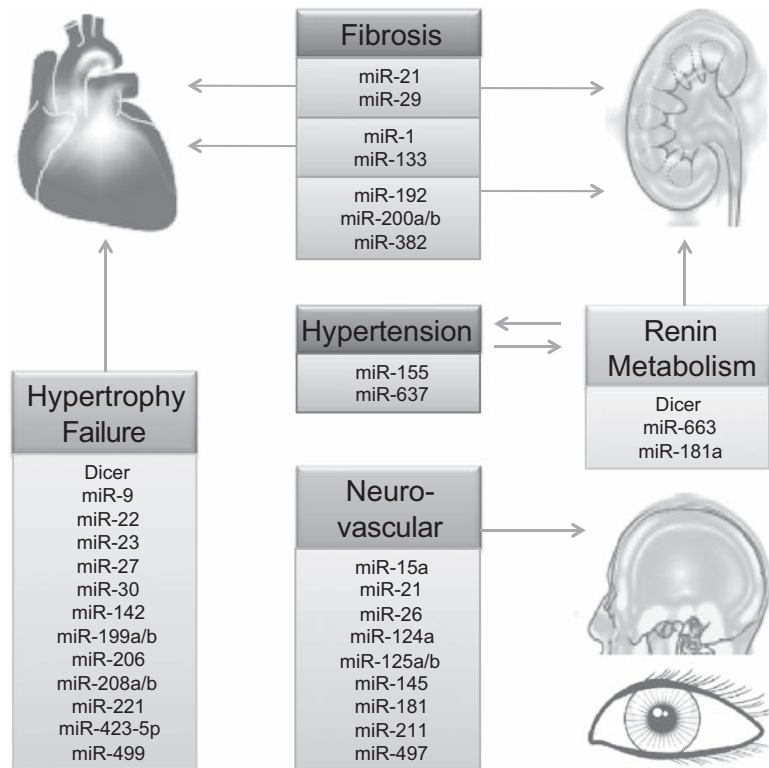


Figure. Nonlimitative list of microRNAs (miRs) implied in hypertension and end-organ damage.

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- β 1) 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- β 1 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-5⁸² 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 miRNAs 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 miRNAs regulate an important part of the process of controlled neuronal death,^{96,97} reviewed in Reference⁹⁸. 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 angiotensin-1⁹⁹ and miR-125a/b-5p inhibiting endothelin-1 expression in vascular endothelial cells¹⁰⁰ do point toward the importance of miRNAs in vasculogenesis and vascular solidity. Furthermore, there is evidence for involvement of miRNAs in vascular neointimal lesion formation,^{101,102} reviewed in Reference¹⁰³.

Perspectives in Cardiovascular MiR Research

In the past decade, knowledge on the function of specific miRNAs in development, health, and disease has boomed. We appreciate miRNAs 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 miRNAs 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 miRNAs 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, miRNAs 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 miRNAs 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

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References

- McCormack T, Krause T, O'Flynn N. Management of hypertension in adults in primary care: NICE guideline. *Br J Gen Pract.* 2012;62:163–164.
- Susic D, Frohlich ED. Hypertensive cardiovascular and renal disease and target organ damage: lessons from animal models. *Cardiorenal Med.* 2011;1:139–146.
- Thum T, Catalucci D, Bauersachs J. MicroRNAs: novel regulators in cardiac development and disease. *Cardiovasc Res.* 2008;79:562–570.
- Lorenzen JM, Haller H, Thum T. MicroRNAs as mediators and therapeutic targets in chronic kidney disease. *Nat Rev Nephrol.* 2011;7:286–294.
- Ambros V. The functions of animal microRNAs. *Nature.* 2004;431:350–355.
- Quintavalle M, Condorelli G, Elia L. Arterial remodeling and atherosclerosis: miRNAs involvement. *Vascul Pharmacol.* 2011;55:106–110.
- Hulsmans M, De Keyzer D, Holvoet P. MicroRNAs regulating oxidative stress and inflammation in relation to obesity and atherosclerosis. *FASEB J.* 2011;25:2515–2527.
- Urbich C, Kuehnbacher A, Dimmeler S. Role of microRNAs in vascular diseases, inflammation, and angiogenesis. *Cardiovasc Res.* 2008;79:581–588.
- Li S, Zhu J, Zhang W, Chen Y, Zhang K, Popescu LM, Ma X, Lau WB, Rong R, Yu X, Wang B, Li Y, Xiao C, Zhang M, Wang S, Yu L, Chen AF, Yang X, Cai J. Signature microRNA expression profile of essential hypertension and its novel link to human cytomegalovirus infection. *Circulation.* 2011;124:175–184.
- Ceolotto G, Papparella I, Bortoluzzi A, Strapazon G, Ragazzo F, Bratti P, Fabricio AS, Squarcina E, Gion M, Palatini P, Semplicini A. Interplay between miR-155, AT1R A1166C polymorphism, and AT1R expression in young untreated hypertensives. *Am J Hypertens.* 2011;24:241–246.
- Jin Y, Kuznetsova T, Thijs L, Schmitz B, Liu Y, Asayama K, Brand SM, Heymans S, Brand E, Fagard R, Staessen JA. Association of left ventricular mass with the AGTR1 A1166C polymorphism. *Am J Hypertens.* 2012;25:472–478.
- Wei Z, Biswas N, Wang L, Courel M, Zhang K, Soler-Jover A, Taupenot L, O'Connor DT. A common genetic variant in the 3'-UTR of vacuolar H⁺-ATPase ATP6V0A1 creates a micro-RNA motif to alter chromogranin A processing and hypertension risk. *Circ Cardiovasc Genet.* 2011;4:381–389.
- Lu Y, Zhang Y, Shan H, Pan Z, Li X, Li B, Xu C, Zhang B, Zhang F, Dong D, Song W, Qiao G, Yang B. MicroRNA-1 downregulation by propranolol in a rat model of myocardial infarction: a new mechanism for ischaemic cardioprotection. *Cardiovasc Res.* 2009;84:434–441.
- Zhu W, Yang L, Shan H, Zhang Y, Zhou R, Du Z. MicroRNA expression analysis: clinical advantage of propranolol reveals key microRNAs in myocardial infarction. *PLoS One.* 2011;6:e14736 (1–6).
- Charchar FJ, Kaiser M, Bingham AJ, Fotinatos N, Ahmady F, Tomaszewski M, Samani NJ. Whole genome survey of copy number variation in the spontaneously hypertensive rat: relationship to quantitative trait loci, gene expression, and blood pressure. *Hypertension.* 2010;55:1231–1238.
- Naraba H, Iwai N. Assessment of the microRNA system in salt-sensitive hypertension. *Hypertens Res.* 2005;28:819–826.
- Wang J, Xu R, Lin F, Zhang S, Zhang G, Hu S, Zheng Z. MicroRNA: novel regulators involved in the remodeling and reverse remodeling of the heart. *Cardiology.* 2009;113:81–88.
- 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;170:1831–1840.
- Tatsuguchi M, Seok HY, Callis TE, Thomson JM, Chen JF, Newman M, Rojas M, Hammond SM, Wang DZ. Expression of microRNAs is dynamically regulated during cardiomyocyte hypertrophy. *J Mol Cell Cardiol.* 2007;42:1137–1141.
- Fernandes T, Hashimoto NY, Magalhães FC, Fernandes FB, Casarini DE, Carmona AK, Krieger JE, Phillips MI, Oliveira EM. Aerobic exercise training-induced left ventricular hypertrophy involves regulatory MicroRNAs, decreased angiotensin-converting enzyme-angiotensin II, and synergistic regulation of angiotensin-converting enzyme 2-angiotensin (1-7). *Hypertension.* 2011;58:182–189.

21. Busk PK, Cirera S. MicroRNA profiling in early hypertrophic growth of the left ventricle in rats. *Biochem Biophys Res Commun.* 2010;396:989–993.
22. Matkovich SJ, Wang W, Tu Y, Eschenbacher WH, Dorn LE, Condorelli G, Diwan A, Nerbonne JM, Dorn GW 2nd. MicroRNA-133a protects against myocardial fibrosis and modulates electrical repolarization without affecting hypertrophy in pressure-overloaded adult hearts. *Circ Res.* 2010;106:166–175.
23. Duisters RF, Tijssen AJ, Schroen B, Leenders JJ, Lentink V, van der Made I, Herias V, van Leeuwen RE, Schellings MW, Barenbrug P, Maessen JG, Heymans S, Pinto YM, Creemers EE. miR-133 and miR-30 regulate connective tissue growth factor: implications for a role of microRNAs in myocardial matrix remodeling. *Circ Res.* 2009;104:170–8, 6p following 178.
24. Song XW, Li Q, Lin L, Wang XC, Li DF, Wang GK, Ren AJ, Wang YR, Qin YW, Yuan WJ, Jing Q. MicroRNAs are dynamically regulated in hypertrophic hearts, and miR-199a is essential for the maintenance of cell size in cardiomyocytes. *J Cell Physiol.* 2010;225:437–443.
25. Kuhn C, Frank D, Will R, Jaschinski C, Frauen R, Katus HA, Frey N. DYRK1A is a novel negative regulator of cardiomyocyte hypertrophy. *J Biol Chem.* 2009;284:17320–17327.
26. da Costa Martins PA, Salic K, Gladka MM, Armand AS, Leptidis S, el Azzouzi H, Hansen A, Coenen-de Roo CJ, Bierhuizen MF, van der Nagel R, van Kuik J, de Weger R, de Bruin A, Condorelli G, Arbones ML, Eschenhagen T, De Windt LJ. MicroRNA-199b targets the nuclear kinase Dyrk1a in an auto-amplification loop promoting calcineurin/NFAT signaling. *Nat Cell Biol.* 2010;12:1220–1227.
27. Wang K, Lin ZQ, Long B, Li JH, Zhou J, Li PF. Cardiac hypertrophy is positively regulated by MicroRNA miR-23a. *J Biol Chem.* 2012;287:589–599.
28. da Costa Martins PA, Bourajaj M, Gladka M, Kortland M, van Oort RJ, Pinto YM, Molkenin JD, De Windt LJ. Conditional dicer gene deletion in the postnatal myocardium provokes spontaneous cardiac remodeling. *Circulation.* 2008;118:1567–1576.
29. Rao PK, Toyama Y, Chiang HR, Gupta S, Bauer M, Medvid R, Reinhardt F, Liao R, Krieger M, Jaenisch R, Lodish HF, Blalock R. Loss of cardiac microRNA-mediated regulation leads to dilated cardiomyopathy and heart failure. *Circ Res.* 2009;105:585–594.
30. Chen JF, Murchison EP, Tang R, Callis TE, Tatsuguchi M, Deng Z, Rojas M, Hammond SM, Schneider MD, Selzman CH, Meissner G, Patterson C, Hannon GJ, Wang DZ. Targeted deletion of Dicer in the heart leads to dilated cardiomyopathy and heart failure. *Proc Natl Acad Sci USA.* 2008;105:2111–2116.
31. Takaya T, Ono K, Kawamura T, Takanabe R, Kaichi S, Morimoto T, Wada H, Kita T, Shimatsu A, Hasegawa K. MicroRNA-1 and MicroRNA-133 in spontaneous myocardial differentiation of mouse embryonic stem cells. *Circ J.* 2009;73:1492–1497.
32. Li Q, Song XW, Zou J, Wang GK, Kremneva E, Li XQ, Zhu N, Sun T, Lappalainen P, Yuan WJ, Qin YW, Jing Q. Attenuation of microRNA-1 derepresses the cytoskeleton regulatory protein twinfilin-1 to provoke cardiac hypertrophy. *J Cell Sci.* 2010;123(pt 14):2444–2452.
33. Ikeda S, He A, Kong SW, Lu J, Bejar R, Bodyak N, Lee KH, Ma Q, Kang PM, Golub TR, Pu WT. MicroRNA-1 negatively regulates expression of the hypertrophy-associated calmodulin and Mef2a genes. *Mol Cell Biol.* 2009;29:2193–2204.
34. Kumarswamy R, Lyon AR, Volkmann I, Mills AM, Bretthauer J, Pahuja A, Geers-Knorr C, Kraft T, Hajjar RJ, Macleod KT, Harding SE, Thum T. SERCA2a gene therapy restores microRNA-1 expression in heart failure via an Akt/FoxO3a-dependent pathway. *Eur Heart J.* 2012;33:1067–1075.
35. Hua Y, Zhang Y, Ren J. IGF-1 deficiency resists cardiac hypertrophy and myocardial contractile dysfunction: role of microRNA-1 and microRNA-133a. *J Cell Mol Med.* 2012;16:83–95.
36. Elia L, Contu R, Quintavalle M, Varrone F, Chimenti C, Russo MA, Cimino V, De Marinis L, Frustaci A, Catalucci D, Condorelli G. Reciprocal regulation of microRNA-1 and insulin-like growth factor-1 signal transduction cascade in cardiac and skeletal muscle in physiological and pathological conditions. *Circulation.* 2009;120:2377–2385.
37. Carè A, Catalucci D, Felicetti F, Bonci D, Addario A, Gallo P, Bang ML, Segnalini P, Gu Y, Dalton ND, Elia L, Latronico MV, Høydal M, Autore C, Russo MA, Dorn GW 2nd, Ellingsen O, Ruiz-Lozano P, Peterson KL, Croce CM, Peschle C, Condorelli G. MicroRNA-133 controls cardiac hypertrophy. *Nat Med.* 2007;13:613–618.
38. Dong DL, Chen C, Huo R, Wang N, Li Z, Tu YJ, Hu JT, Chu X, Huang W, Yang BF. Reciprocal repression between microRNA-133 and calcineurin regulates cardiac hypertrophy: a novel mechanism for progressive cardiac hypertrophy. *Hypertension.* 2010;55:946–952.
39. Li Q, Lin X, Yang X, Chang J. NFATc4 is negatively regulated in miR-133a-mediated cardiomyocyte hypertrophic repression. *Am J Physiol Heart Circ Physiol.* 2010;298:H1340–H1347.
40. Kumarswamy R, Volkmann I, Thum T. Regulation and function of miRNA-21 in health and disease. *RNA Biol.* 2011;8:706–713.
41. Cheng Y, Liu X, Zhang S, Lin Y, Yang J, Zhang C. MicroRNA-21 protects against the H(2)O(2)-induced injury on cardiac myocytes via its target gene PDCD4. *J Mol Cell Cardiol.* 2009;47:5–14.
42. Thum T, Gross C, Fiedler J, Fischer T, Kissler S, Bussen M, Galuppo P, Just S, Rottbauer W, Frantz S, Castoldi M, Soutschek J, Kotliansky 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;456:980–984.
43. 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;120:3912–3916.
44. van Rooij E, Sutherland LB, Thatcher JE, DiMaio JM, Naseem RH, Marshall WS, Hill JA, Olson EN. Dysregulation of microRNAs after myocardial infarction reveals a role of miR-29 in cardiac fibrosis. *Proc Natl Acad Sci USA.* 2008;105:13027–13032.
45. Liu Y, Taylor NE, Lu L, Usa K, Cowley AW Jr, Ferreri NR, Yeo NC, Liang M. Renal medullary microRNAs in Dahl salt-sensitive rats: miR-29b regulates several collagens and related genes. *Hypertension.* 2010;55:974–982.
46. Wang B, Komers R, Carew R, Winbanks CE, Xu B, Herman-Edelstein M, Koh P, Thomas M, Jandeleit-Dahm K, Gregorevic P, Cooper ME, Kantharidis P. Suppression of microRNA-29 expression by TGF-β1 promotes collagen expression and renal fibrosis. *J Am Soc Nephrol.* 2012;23:252–265.
47. 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 Renal Physiol.* 2011;301:F793–F801.
48. Zhong X, Chung AC, Chen HY, Meng XM, Lan HY. Smad3-mediated upregulation of miR-21 promotes renal fibrosis. *J Am Soc Nephrol.* 2011;22:1668–1681.
49. Castoldi G, Di Gioia CR, Bombardi C, Catalucci D, Corradi B, Gualazzi MG, Leopizzi M, Mancini M, Zerbini G, Condorelli G, Stella A. MiR-133a regulates collagen 1A1: potential role of miR-133a in myocardial fibrosis in angiotensin II-dependent hypertension. *J Cell Physiol.* 2012;227:850–856.
50. Rane S, He M, Sayed D, Yan L, Vatner D, Abdellatif M. An antagonism between the AKT and beta-adrenergic signaling pathways mediated through their reciprocal effects on miR-199a-5p. *Cell Signal.* 2010;22:1054–1062.
51. Haghikia A, Missol-Kolka E, Tsikas D, Venturini L, Brundiers S, Castoldi M, Muckenthaler MU, Eder M, Stapel B, Thum T, Haghikia A, Petrasch-Parwez E, Drexler H, Hilfiker-Kleiner D, Scherr M. Signal transducer and activator of transcription 3-mediated regulation of miR-199a-5p links cardiomyocyte and endothelial cell function in the heart: a key role for ubiquitin-conjugating enzymes. *Eur Heart J.* 2011;32:1287–1297.
52. Wang K, Long B, Zhou J, Li PF. miR-9 and NFATc3 regulate myocardin in cardiac hypertrophy. *J Biol Chem.* 2010;285:11903–11912.
53. Lin Z, Murtaza I, Wang K, Jiao J, Gao J, Li PF. miR-23a functions downstream of NFATc3 to regulate cardiac hypertrophy. *Proc Natl Acad Sci USA.* 2009;106:12103–12108.
54. Xu XD, Song XW, Li Q, Wang GK, Jing Q, Qin YW. Attenuation of microRNA-22 derepressed PTEN to effectively protect rat cardiomyocytes from hypertrophy. *J Cell Physiol.* 2012;227:1391–1398.
55. Sharma S, Liu J, Wei J, Yuan H, Zhang T, Bishopric NH. Repression of miR-142 by p300 and MAPK is required for survival signalling via gp130 during adaptive hypertrophy. *EMBO Mol Med.* 2012;4:617–632.
56. Wang C, Wang S, Zhao P, Wang X, Wang J, Wang Y, Song L, Zou Y, Hui R. MiR-221 promotes cardiac hypertrophy *in vitro* through the modulation of p27 expression. *J Cell Biochem.* 2012;113:2040–2046.
57. Wang J, Song Y, Zhang Y, Xiao H, Sun Q, Hou N, Guo S, Wang Y, Fan K, Zhan D, Zha L, Cao Y, Li Z, Cheng X, Zhang Y, Yang X. Cardiomyocyte overexpression of miR-27b induces cardiac hypertrophy and dysfunction in mice. *Cell Res.* 2012;22:516–527.
58. Limana F, Esposito G, D'Arcangelo D, Di Carlo A, Romani S, Melillo G, Mangoni A, Bertolami C, Pompilio G, Germani A, Capogrossi MC. HMGB1 attenuates cardiac remodeling in the failing heart via enhanced cardiac regeneration and miR-206-mediated inhibition of TIMP-3. *PLoS ONE.* 2011;6:e19845.

59. Ji X, Takahashi R, Hiura Y, Hirokawa G, Fukushima Y, Iwai N. Plasma miR-208 as a biomarker of myocardial injury. *Clin Chem*. 2009;55:1944–1949.
60. Satoh M, Minami Y, Takahashi Y, Tabuchi T, Nakamura M. Expression of microRNA-208 is associated with adverse clinical outcomes in human dilated cardiomyopathy. *J Card Fail*. 2010;16:404–410.
61. 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.
62. Callis TE, Pandya K, Seok HY, Tang RH, Tatsuguchi M, Huang ZP, Chen JF, Deng Z, Gunn B, Shumate J, Willis MS, Selzman CH, Wang DZ. MicroRNA-208a is a regulator of cardiac hypertrophy and conduction in mice. *J Clin Invest*. 2009;119:2772–2786.
63. van Rooij E, Sutherland LB, Qi X, Richardson JA, Hill J, Olson EN. Control of stress-dependent cardiac growth and gene expression by a microRNA. *Science*. 2007;316:575–579.
64. Corsten MF, Dennert R, Jochems S, Kuznetsova T, Devaux Y, Hofstra L, Wagner DR, Staessen JA, Heymans S, Schroen B. Circulating MicroRNA-208b and MicroRNA-499 reflect myocardial damage in cardiovascular disease. *Circ Cardiovasc Genet*. 2010;3:499–506.
65. Devaux Y, Vausort M, Goretti E, Nazarov PV, Azuaje F, Gilson G, Corsten MF, Schroen B, Lair ML, Heymans S, Wagner DR. Use of circulating microRNAs to diagnose acute myocardial infarction. *Clin Chem*. 2012;58:559–567.
66. Wang JX, Jiao JQ, Li Q, Long B, Wang K, Liu JP, Li YR, Li PF. miR-499 regulates mitochondrial dynamics by targeting calcineurin and dynamin-related protein-1. *Nat Med*. 2011;17:71–78.
67. Tijssen AJ, Creemers EE, Moerland PD, de Windt LJ, van der Wal AC, Kok WE, Pinto YM. MiR423-5p as a circulating biomarker for heart failure. *Circ Res*. 2010;106:1035–1039.
68. Kumarswamy R, Anker SD, Thum T. MicroRNAs as circulating biomarkers for heart failure: questions about MiR-423-5p. *Circ Res*. 2010;106:e8; author reply e9.
69. Naga Prasad SV, Duan ZH, Gupta MK, Surampudi VS, Volinia S, Calin GA, Liu CG, Kotwal A, Moravec CS, Starling RC, Perez DM, Sen S, Wu Q, Plow EF, Croce CM, Karnik S. Unique microRNA profile in end-stage heart failure indicates alterations in specific cardiovascular signaling networks. *J Biol Chem*. 2009;284:27487–27499.
70. Zampetaki A, Willeit P, Drozdov I, Kiechl S, Mayr M. Profiling of circulating microRNAs: from single biomarkers to re-wired networks. *Cardiovasc Res*. 2012;93:555–562.
71. Udani S, Lazich I, Bakris GL. Epidemiology of hypertensive kidney disease. *Nat Rev Nephrol*. 2011;7:11–21.
72. Wang G, Kwan BC, Lai FM, Choi PC, Chow KM, Li PK, Szeto CC. Intrarenal expression of miRNAs in patients with hypertensive nephrosclerosis. *Am J Hypertens*. 2010;23:78–84.
73. Chevalier RL, Forbes MS, Thornhill BA. Ureteral obstruction as a model of renal interstitial fibrosis and obstructive nephropathy. *Kidney Int*. 2009;75:1145–1152.
74. Marques FZ, Campaign 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.
75. Sequeira-Lopez ML, Weatherford ET, Borges GR, Monteagudo MC, Pentz ES, Harfe BD, Carretero O, Sigmund CD, Gomez RA. The microRNA-processing enzyme dicer maintains juxtaglomerular cells. *J Am Soc Nephrol*. 2010;21:460–467.
76. Kato M, Arce L, Wang M, Putta S, Lanting L, Natarajan R. A microRNA circuit mediates transforming growth factor-1 autoregulation in renal glomerular mesangial cells. *Kidney Int*. 2011;80:358–368.
77. Putta S, Lanting L, Sun G, Lawson G, Kato M, Natarajan R. Inhibiting microRNA-192 ameliorates renal fibrosis in diabetic nephropathy. *J Am Soc Nephrol*. 2012;23:458–469.
78. Oba S, Kumano S, Suzuki E, Nishimatu H, Takahashi M, Takamori H, Kasuya M, Ogawa Y, Sato K, Kimura K, Homma Y, Hirata Y, Fujita T. MiR-200b precursor can ameliorate renal tubulointerstitial fibrosis. *PLoS One*. 2010;25:e13614 (1–6).
79. Sun L, Zhang D, Liu F, Xiang X, Ling G, Xiao L, Liu Y, Zhu X, Zhan M, Yang Y, Kondeti VK, Kanwar YS. Low-dose paclitaxel ameliorates fibrosis in the remnant kidney model by down-regulating miR-192. *J Pathol*. 2011;225:364–377.
80. Chung AC, Huang XR, Meng X, Lan HY. miR-192 mediates TGF- β /Smad3-driven renal fibrosis. *J Am Soc Nephrol*. 2010;21:1317–1325.
81. Krupa A, Jenkins R, Luo DD, Lewis A, Phillips A, Fraser D. Loss of MicroRNA-192 promotes fibrogenesis in diabetic nephropathy. *J Am Soc Nephrol*. 2010;21:438–447.
82. Kriegl AJ, Liu Y, Cohen B, Usa K, Liu Y, Liang M. MiR-382 targeting of kallikrein 5 contributes to renal inner medullary interstitial fibrosis. *Physiol Genomics*. 2012;44:259–267.
83. Kriegl AJ, Fang Y, Liu Y, Tian Z, Mladinov D, Matus IR, Ding X, Greene AS, Liang M. MicroRNA-target pairs in human renal epithelial cells treated with transforming growth factor beta 1: a novel role of miR-382. *Nucleic Acids Res*. 2010;38:8338–8347.
84. Wang B, Koh P, Winbanks C, Coughlan MT, McClelland A, Watson A, Jandeleit-Dahm K, Burns WC, Thomas MC, Cooper ME, Kantharidis P. miR-200a Prevents renal fibrogenesis through repression of TGF- β 2 expression. *Diabetes*. 2011;60:280–287.
85. Chatziralli IP, Kanonidou ED, Kerytopoulos P, Dimitriadis P, Papazisis LE. The value of funduscopy in general practice. *Open Ophthalmol J*. 2012;6:4–5.
86. Kantharidis P, Wang B, Carew RM, Lan HY. Diabetes complications: the microRNA perspective. *Diabetes*. 2011;60:1832–1837.
87. Kovacs B, Lumayag S, Cowan C, Xu S. MicroRNAs in early diabetic retinopathy in streptozotocin-induced diabetic rats. *Invest Ophthalmol Vis Sci*. 2011;52:4402–4409.
88. McArthur K, Feng B, Wu Y, Chen S, Chakrabarti S. MicroRNA-200b regulates vascular endothelial growth factor-mediated alterations in diabetic retinopathy. *Diabetes*. 2011;60:1314–1323.
89. Karali M, Peluso I, Gennarino VA, Bilio M, Verde R, Lago G, Dollé P, Banfi S. miRNeys: a microRNA expression atlas of the mouse eye. *BMC Genomics*. 2010;11:715.
90. Karali M, Manfredi A, Puppo A, Marrocco E, Gargiulo A, Allocca M, Corte MD, Rossi S, Giunti M, Bacci ML, Simonelli F, Surace EM, Banfi S, Auricchio A. MicroRNA-restricted transgene expression in the retina. *PLoS ONE*. 2011;6:e22166.
91. Liu DZ, Tian Y, Ander BP, Xu H, Stamova BS, Zhan X, Turner RJ, Jickling G, Sharp FR. Brain and blood microRNA expression profiling of ischemic stroke, intracerebral hemorrhage, and kainate seizures. *J Cereb Blood Flow Metab*. 2010;30:92–101.
92. Bai Y, Wang L, Sun L, Ye P, Hui R. Circulating microRNA-26a: potential predictors and therapeutic targets for non-hypertensive intracerebral hemorrhage. *Med Hypotheses*. 2011;77:488–490.
93. Gan CS, Wang CW, Tan KS. Circulatory microRNA-145 expression is increased in cerebral ischemia. *Genet Mol Res*. 2012;11:147–152.
94. Buller B, Liu X, Wang X, Zhang RL, Zhang L, Hozeska-Solgot A, Chopp M, Zhang ZG. MicroRNA-21 protects neurons from ischemic death. *FEBS J*. 2010;277:4299–4307.
95. Ouyang YB, Lu Y, Yue S, Xu LJ, Xiong XX, White RE, Sun X, Giffard RG. miR-181 regulates GRP78 and influences outcome from cerebral ischemia *in vitro* and *in vivo*. *Neurobiol Dis*. 2012;45:555–563.
96. Yin KJ, Deng Z, Huang H, Hamblin M, Xie C, Zhang J, Chen YE. miR-497 regulates neuronal death in mouse brain after transient focal cerebral ischemia. *Neurobiol Dis*. 2010;38:17–26.
97. Liu XS, Chopp M, Zhang RL, Tao T, Wang XL, Kassiss H, Hozeska-Solgot A, Zhang L, Chen C, Zhang ZG. MicroRNA profiling in subventricular zone after stroke: MiR-124a regulates proliferation of neural progenitor cells through Notch signaling pathway. *PLoS ONE*. 2011;6:e23461.
98. Shafi G, Aliya N, Munshi A. MicroRNA signatures in neurological disorders. *Can J Neurol Sci*. 2010;37:177–185.
99. Chen J, Yang T, Yu H, Sun K, Shi Y, Song W, Bai Y, Wang X, Lou K, Song Y, Zhang Y, Hui R. A functional variant in the 3'-UTR of angiopoietin-1 might reduce stroke risk by interfering with the binding efficiency of microRNA 211. *Hum Mol Genet*. 2010;19:2524–2533.
100. Li D, Yang P, Xiong Q, Song X, Yang X, Liu L, Yuan W, Rui YC. MicroRNA-125a/b-5p inhibits endothelin-1 expression in vascular endothelial cells. *J Hypertens*. 2010;28:1646–1654.
101. 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;100:1579–1588.
102. Yin KJ, Deng Z, Hamblin M, Xiang Y, Huang H, Zhang J, Jiang X, Wang Y, Chen YE. Peroxisome proliferator-activated receptor delta regulation of miR-15a in ischemia-induced cerebral vascular endothelial injury. *J Neurosci*. 2010;30:6398–6408.
103. Sen CK, Gordillo GM, Khanna S, Roy S. Micromanaging vascular biology: tiny microRNAs play big band. *J Vasc Res*. 2009;46:527–540.
104. Kluijver J, Gibcus JH, Hettinga C, Adema A, Richter MK, Halsema N, Slezak-Prochazka I, Ding Y, Kroesen BJ, van den Berg A. Rapid generation of microRNA sponges for microRNA inhibition. *PLoS ONE*. 2012;7:e29275.
105. Wapinski O, Chang HY. Long noncoding RNAs and human disease. *Trends Cell Biol*. 2011;21:354–361.

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