Role of MicroRNAs in Renin-Angiotensin-Aldosterone System-Mediated Cardiovascular Inflammation and Remodeling

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1. Introduction

The role of microRNAs in RAAS system is at early stages of investigations; however, few microRNAs have been shown to be implicated in the RAAS mediated hypertension cardiovascular diseases [1]. Blocking RAAS is a primary approach for the treatment of hypertension, cardiovascular inflammation, and cardiac hypertrophy [2]. The discovery of microRNAs in 1993 in nematode Caenorhabditis elegans has led to a new research avenue and provided novel and innovative tools to understand gene regulation that sometimes could not be explained. Since then, more than 2,518 microRNAs have been identified and listed in current databases [3]. Angiotensin II (Ang II) is the main active effector of the RAAS with profound signaling effects on the cardiac and vascular systems. Ang II impacts the cardiovascular system particularly regulating the proliferation and migration of vascular smooth muscle cells (VSMC) therefore affecting cardiovascular remodeling. Ang II signaling is mediated via Ang II type I receptor (ATIR), and both the Ang II and ATRI are highly expressed in the VSMC of some of cardiovascular disease (CVD). In addition to Ang II, tumor necrosis factor alpha (TNFalpha) plays an important role in the development of cardiovascular inflammation, sometimes in tandem with Ang II. MicroRNAs regulate many important biological functions and abnormal levels of microRNAs are involved in cardiovascular and other pathologies.

In this review, we attempt to provide information of microRNAs that have been shown to play a role in the RAAS signaling and cardiovascular inflammation/remodeling and related CVD.

2. MicroRNA Biogenesis and Stability

The main function of microRNA is to bind to 3' UTR of its target gene and suppress its expression. MicroRNAs are
3. MicroRNA and RAAS Effectors

Recent estimates suggest that one-third of all genes are regulated by microRNAs. In mouse primary cultured VSMC, overexpression of miR-155 inhibited Ang II-induced cell proliferation and viability via decreasing ATIR mRNA and protein [11]. Numerous studies showed that miR-155 plays an important role mediating inflammatory and immune responses and hematopoiesis [12]. However, miR-155 is also highly expressed in numerous types of cancer, and thus it seems that miR-155 may indeed regulate diverse biological functions [12]. Alexy and coworkers examined the formation of miR-155 encapsulated microvesicles (MP) by endothelial cells (EC) following TNFalpha treatment. In the presence of TNFalpha, EC released a higher level of miR-155/MP but tremendously decreased the level of miR-126 and miR-21/MP. The TNFalpha-induced miR-MP exerted antiapoptotic effect, whereas the low miR-MPs were proapoptotic. These results suggested also a role of microRNAs in cell to cell communication signaling pathway [13]. MiR-155 plays a key role in mediating cardiac injury, cardiac remodeling, and inflammation in hypertensive or pressure overload heart via regulating ATIR, eNOS, and inflammatory cytokines. In aortic adventitial fibroblast, miR-155 regulates ATIR [14]. Overexpression of miR-155 decreased the expression of ATIR and prevented Ang II-induced ERK1/2 activation and increased the expression of α-smooth muscle actin (α-SMA) [14]. Moreover, miR-155 targets endothelial nitric oxide synthase (eNOS), thus directly regulating endothelium-dependent vasorelaxation [15, 16]. Patients with nephrolithiasis exhibited high levels of miR-155 in blood and urine [17]. Urine MiR-155 level negatively correlated with IL-6, IL-1β, IL-6, and TNF-α and positively with RANTES [17]. Another level of intricacy between RAAS, microRNA, exercise, and hypertension was explored by Sun et al. [15]. In this study, exercise attenuated aortic remodeling and improved endothelium-mediated vasorelaxation in SHR rats. Exercise increased miR-27a and miR-155 and decreased miR-143. Exercise also reduced Ang II level, increased Ang (1–7) levels, ACE2, AT2R, and Mas receptors, and suppressed ACE a target of miR-27a and AT1R which is a target of miR-155. This study provided an insight into the possible mechanism by which exercise improves RAAS in aorta and might explain the beneficial effect of exercise on cardiovascular system [15].

Ang II plays an important role in vascular remodeling by increasing the expression of TGFbeta, ColIAl, and alpha-smooth muscle actin (α-SMA). Pan et al. examined the effect of Ang II on miR-29b expression in the kidney of spontaneously hypertensive rats (SHRs). Ang II decreased the expression of miR-29b in the renal cortex of SHRs and in NRK-52E treated cells. In NRK-52E cells, miR-29b targets TGFbeta and α-SMA, and ColIAl, ColIIIAl, and overexpression of miR-29b abolished Ang II-induced genes [18]. In HEK293N cells overexpressing AT1R, Ang II increased miR-132 and miR-212 via AT1R/Goq/ERK1/2-dependent axis. In primary cardiac fibroblast, Ang II induced the expression of miR-132 and miR-212 in the heart, arteries wall, and kidney but no Ang II effect on these microRNAs in primary myocytes [19]. In hypertensive rats, Ang II induced the expression of miR-132 or miR-212. Moreover, patients taking ATIR blockers (losartan, candesartan, irbesartan, and telmisartan) exhibited decreased levels of miR-132 and miR-122 [20]. Both miR-132 and miR-212 are highly conserved miRNAs, closely clustered and regulated by cAMP response element binding protein (CREB), which is Ang II target gene. In most tissues, the level of miR-132 is much higher than that of miR-212, and the exact role of such difference is not known; however, it is proposed that miR-132 may indeed have a regulatory effect on miR-212 [21]. Overexpression of miR-132/212 in fibroblasts resulted in differential expression of 24 genes of which 7 genes (AGTR1, AC, PKC, EGRI, JAK2, cJUN, and SOD2) are involved in Ang II signaling. Functionally, overexpression of miR-132/212 induces increased fibroblast size and increased expression level of Ang II. Among the modulated genes, DYSR2 and MAP3K3 were found to be downregulated and known to be involved in endothelial to mesenchymal transition [22]. These results suggested that miR-132/212 regulates many genes of Ang II signaling pathway [19] (Table I).

In patients with renal carcinoma, miR-129-3p and miR-129-5p were significantly attenuated compared to normal biopsy specimens. Moreover, ectopic expression of miR-129-3p inhibited cell migration and invasiveness, whereas
Table 1: MicroRNAs affected by RAAS effectors.

| Effector | MicroRNA target gene | Reference |
|----------|----------------------|-----------|
| miR-155  | ATRI, eNOS, α-SMA, NF-κB, AP-1 | [11–14, 16, 48] |
| ↓ miR-29-b | TGFβeta, Col 1A, α-SMA | [18, 24, 33–35] |
| ↓ miR-483-3p | AGT, ACE-1, ACE-2, AT2R | [29] |
| ↓ miR-129-3p | FAK, MMP-2, MMP-9 | [23] |
| ↑ miR-132/212 | AT1R, MSK, Gα/β/ERK1/2 | [19, 21] |
| ↓ miR-34 | ANP, β-MHC | [46, 49] |
| miR-766 | Cyp11B2 | [25] |
| miR-16 | Ang II, CCDNI, CCDN2, CCDNE | [47] |

Note: ↓ decreased expression level; ↑ increased expression level.

Table 1: MicroRNAs affected by RAAS effectors.

The effect of RAAS inhibition on microRNAs was investigated by Deiuliis et al. in patients with atherosclerosis plaque progression [26]. Patients were given aliskiren for 12 weeks and peripheral blood mononuclear cells were collected and microRNAs arrays were performed. Aliskiren-treated patients had significantly downregulated miR-106b-5p, miR-27a-3p, and miR-18b-5p compared to placebo-treated patients. The level of microRNAs positively correlated with thoracic and abdominal aorta wall in patients treated with Aliskiren. In a different clinical setting such as in patients with acute stroke, plasma miR-106b-5p was found to be highly elevated compared to healthy patients [27]. Although the function of miR-106b-5p is not known yet, these findings suggest that miR-106-5p may play a role in hemodynamics. MiR-27a-3p has been shown to regulate EGFR/AKT1/mTOR axis thus to decrease cell viability and increase apoptosis, whereas overexpression of EGFR, AKT, or mTOR decreases miR-27a-3p-induced cell viability [28]. To identify angiotensin II (Ang II) regulated microRNAs, Kemp et al. performed genome-wide microarrays analysis in vascular smooth muscle cells treated with Ang II or losartan [29]. A high number of microRNAs (468) were regulated by Ang-II and losartan. Only 32 microRNAs were regulated by Ang II/AT2R, whereas 52 miRNAs were regulated via AT1R and 18 microRNAs were commonly regulated via AT1R and AT2R. Of all microRNAs, miR-483-3p expression was significantly downregulated in response to chronic activation of AT1R. AT1R antagonist candesartan significantly increased miR-483-3p. Kemp et al. [29] also shed some insight on Ang II feed-forward regulation of RAAS effectors AGT, ACE-1, ACE-2, and AT2R via miR483-3p. In the presence of Ang II, miR483-3p is depressed, whereas RAAS effectors are highly expressed via 3’UTR binding sites of miR483-3p present on RAAS effectors [29]. A recent study of patients with coronary artery disease (CAD) receiving ARB, ACEI, and statins for 12 months provided evidence of Toll-like receptor 4 (TLR-4) regulated microRNAs. Four microRNAs including miR-31, miR-181a, miR-16, and miR-145 were downregulated in CAD patients compared to non-CAD patients. The treatment combination of ARB telmisartan and atorvastatin or ACEI enalapril and atorvastatin increased the TLR-4 responsive microRNAs and decreased TLR-4 protein level. ARB treatment induced a greater change of the four microRNAs compared to ACEI [30]. Another microRNA, miR-146a/b, was found at high levels in the blood of CAD patients, and its expression positively correlated with IRAK, TRAF, TLR4 mRNA, or protein [31]. After 12 months of treatment with atorvastatin and telmisartan or atorvastatin and enalapril, miR-146a/b, IRAK, TLR4 mRNA, or protein decreased in the blood of CAD patients. Correlation analysis revealed that miR-146-a and TLR4 were independent predictors of cardiac events [31] (Table 2).

5. MicroRNA in Cardiovascular Disease

Cardiovascular disease (CVD) still remains the major cause of worldwide death, and identifying new molecular factors with roles in the development of CVD may offer novel diagnostic markers for cardiovascular events. In patients with atypical coronary artery disease, a signature of five microRNAs miR-487a, miR-502, miR-208, miR-215, and miR-29b was found to be altered and thus may be considered potential novel diagnostic biomarkers [32]. Molecular targets for several of the five microRNAs were found to be mediators of local inflammation, such as miR-215 targets catenin-beta interacting protein 1 in TGFbeta stimulated rat mesangial cells, whereas miR-29b plays an important role in modulating myocardial injury and idiopathic fibrosis [33–35]. MiR-29 family regulates extracellular matrix proteins and thus also influences remodeling. Potential therapeutic applicability of miR-29 has been experimentally tested in the settings of induced pulmonary fibrosis. In the bleomycin-induced pulmonary fibrosis, treatment with miR-29 reversed fibrosis by decreasing collagen (Col1A1 and Col3A1) synthesis.
| Inhibitor   | MicroRNA target gene          | Reference |
|------------|-------------------------------|-----------|
| **Aliskiren** |                               |           |
| ↓ miR-106-5p  | EGFR/AKT/mTOR, ACE            | [27]      |
| ↓ miR-27a-3p  | EGFR/AKT/mTOR, ACE            | [26–28, 38] |
| ↓ miR-18b-5p  | EGFR, ACE                    | [29]      |
| ↓ miR-155     | AT1R                         |           |
| **Candesartan** |                               |           |
| ↑ miR-483-3p  | AGT, ACE-1, ACE-2, AT2R       | [26, 38]  |
| ↓ miR-132/122 | Ang II                       | [38]      |
| ↓ miR-29b     | Col1A, Col3A1                | [26, 38]  |
| ↓ miR-212     | AT2R                         |           |
| **Telmisartan** |                               |           |
| ↑ miR-31      |                              | [30]      |
| ↑ miR-181a    | TNFalpha                     | [30]      |
| ↑ miR-16      | VEGF                         | [30]      |
| ↑ miR-143/145 | KLF4, KLF6, ACE-2            | [30]      |
| ↑ miR-146a/b  | TRAF6, KLF4, TLR4            | [31]      |
| **Atorvastatin** |                               |           |
| ↑ miR-146a/b  | TRAF6, KLF4, TLR4            | [31]      |
| ↓ miR-221/222 | p27, p57                     | [50]      |
| **Enalapril** |                               |           |
| ↑ miR-31      |                              | [30]      |
| ↑ miR-181a    | TNFalpha                     | [30]      |
| ↑ miR-145     | KLF4, KLF6, ACE-2            | [30]      |
| ↑ miR-16      | VEGF, CCND1, CCND2, CCNE     | [30, 47]  |
| **Captopril** |                               |           |
| ↑ miR-16      | VEGF                         | [30, 47]  |
| ↑ miR-19b     | βMHC                         | [47, 51]  |
| ↑ miR-20b     |                             | [47]      |
| ↑ miR-93      |                             | [47]      |
| ↑ miR-106b    |                             | [47]      |
| ↑ miR-223     |                             | [47]      |
| ↑ miR-423-5p  |                             | [47]      |

Note: ↓: decreased expression level; ↑: increased expression level.

Moreover, tissue analysis revealed the presence of intravenously injected miR-29b not only in the lungs but also in the cardiac muscle and spleen [35].

In a different cardiovascular pathology such as in patients with failing heart, ischemic cardiomyopathy, or aortic stenosis, miR-320 was found to be highly expressed compared to control patients [36]. The functional analysis of miR-320 via ectopic expression in cultured cardiomyocytes indicated that miR-320 regulates cell death and apoptosis gene [37]. MicroRNA analysis in the blood and cerebrospinal fluid (CSF) of patients that suffered a stroke showed a differential profile of the two tissues, and hence some microRNAs were absent in one tissue but present in the other. In the CSF, microRNAs were detected out of which let-7c and miR-221-3p were upregulated and correlated with stroke [26]. Also, patients with atherosclerosis and receiving aliskiren for 12 weeks had a decreased blood level of miR-18b-5p, miR-106b-5, and miR-27a-3p [38]. Although both cardiovascular diseases, stroke and atherosclerosis, are due to blood clots formation, some microRNAs might just be disease specific, as, for example, miR-18b-5p is decreased in the blood of stroke patients but not in patients with atherosclerosis [26, 38] (Table 2). Recent studies support microRNAs role in cardiac hypertrophy [22]. For example, inhibition of miR-1, miR-23a, and miR-133 increased cardiomyocytes hypertrophy, whereas miR-22 or miR-30a regulates cardiac hypertrophy in mice [39–43]. MicroRNA signaling is complex; for example, one microRNA can target multiple genes. MiR-34 targets cell cycle genes and cardiac autophagy [44]. In addition to microRNAs modulating cardiomyocytes, Ang II is also
Ang II regulates its level via stimulating miR-132, miR-212, and its downstream signaling via suppressing miR-483-3p, miR-129-3p, miR-29b, and miR-34 by increasing the expression of AT1R, AT2R, ACE1, ACE2, Col1A, and TGFbeta. Several microRNAs regulate RAAS signaling independent of Ang II via regulating inflammation and remodeling miR-146a/b, miR-132, miR-212, miR-129-3b, and miR-29b. RAAS inhibitors differentially regulate microRNAs: telmisartan, atorvastatin, aliskiren, and candesartan inhibit miR-146a/b, miR-132, miR-212, miR-129-3s, and miR-29b. Enalapril stimulates the expression of miR-181a which targets TNFα therefore regulating inflammation and remodeling. ↑: increased level, ↓: decreased level; ⊥: inhibition, and →: stimulation. AT1R: angiotensin II type 1 R; ACE: angiotensin converting enzymes; AGT: angiotensinogen; TLR4: toll-like receptor 4; TRAF6: TNF receptor associated factor 6.

**Figure 1**: Dependent and independent RAAS-regulated microRNAs signaling in cardiovascular inflammation/remodeling and hypertension. Ang II regulates its level via stimulating miR-132, miR-212, and its downstream signaling via suppressing miR-483-3p, miR-129-3p, miR-29b, and miR-34 by increasing the expression of AT1R, AT2R, ACE1, ACE2, Col1A, and TGFbeta. Several microRNAs regulate RAAS signaling independent of Ang II via regulating inflammation and remodeling miR-146a/b, miR-181a, miR-155, miR-129-3p, and miR-29b. RAAS inhibitors differentially regulate microRNAs: telmisartan, atorvastatin, aliskiren, and candesartan inhibit miR-146a/b, miR-132, miR-212, miR-155, miR-129-3b, and miR-29b. Enalapril stimulates the expression of miR-181a which targets TNFα therefore regulating inflammation and remodeling. ↑: increased level, ↓: decreased level; ⊥: inhibition, and →: stimulation. AT1R: angiotensin II type 1 R; ACE: angiotensin converting enzymes; AGT: angiotensinogen; TLR4: toll-like receptor 4; TRAF6: TNF receptor associated factor 6.

a regulator of cardiomyocytes hypertrophy [45]. With regard to this relationship, Huang et al. [45] have shown that Ang II-induced myocardial hypertrophy was antagonized by miR-34, whereas inhibition of miR-34 promoted Ang II signaling via ANP and β-MHC [46]. Another microRNA regulating cardiomyocytes hypertrophy is miR-16 [16, 47]. Huang et al. [47] showed that overexpressing miR-16 in cardiomyocytes decreases Ang II, whereas overexpressing miR-16 resulted in decreased expression of cyclins D2, D2, and E in the myocardium of mice. As shown in Figure 1, based on the existing experimental evidence, microRNAs and RAAS signaling are complex particularly such that RAAS effector Ang II coregulates its level via microRNA-132 and microRNA-212 which also targets Ang II signaling via AT1R. RAAS inhibitors mostly target microRNAs by suppressing their expression thus alleviating cardiovascular inflammation and remodeling.

**6. Conclusion**

Considering the fact that millions of people worldwide are affected by hypertension and knowing the role played by RAAS in cardiovascular inflammation and remodeling, the determination of microRNAs role in regulating RAAS signaling may represent a new strategy in the development of novel therapeutics as well as a new treatment combination for patients suffering from high blood pressure and other cardiovascular diseases. Although scientific evidence on the role of microRNAs in RAAS signaling is scarce, the few published studies on circulating microRNAs in patients with coronary artery diseases do indeed indicate that some of these circulating microRNAs may be used as biomarkers of therapeutic approaches targeting RAAS and cardiovascular diseases.

**Abbreviations**

AS: Aldosterone synthase  
ASI: Aldosterone synthase inhibitors  
ANG: Angiotensin  
ACE: Angiotensin converting enzyme  
ARB: Angiotensin receptor blockers  
CRP: C-reactive protein  
CVD: Cardiovascular disease  
DRI: Direct rennin inhibitors  
EPC: Endothelial progenitor cells  
ERK: Extracellular receptor kinase  
EGFR: Epidermal growth factor receptor  
eNOS: Endothelial nitric oxide synthase
EDHF: Endothelium-derived hyperpolarizing factor
ET-1: Endothelin 1
IL-1β: Interleukin 1 beta
IL-6: Interleukin 6
ICAM-1: Intracellular cell adhesion molecule 1
IGF: Insulin growth factor
MCP-1: Monocytes chemoattractant protein 1
MIP-1: Monocytes inflammatory protein 1
miR: MicroRNA
MRA: Mineralocorticoid receptor antagonist
NF-κB: Nuclear factor kappa B
NO: Nitric oxide
PPARγ: Peroxisome proliferators-activated receptor gamma
RAAS: Renin-angiotensin-aldosterone system
TGFβ: Transforming growth factor beta
TNFα: Tumor necrosis factor alpha
VCAM-1: Vascular cell adhesion molecule 1

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

[1] J. Deiuliis, G. Mihai, J. Zhang et al., “Renin-sensitive microRNAs correlate with atherosclerosis plaque progression,” Journal of Human Hypertension, vol. 28, no. 4, pp. 251–258, 2014.
[2] M. Pacurari, R. Kafoury, P. B. Tchounwou, and K. Ndebele, “The renin-angiotensin-aldosterone system in vascular inflammation and remodeling,” International Journal of Inflammation, vol. 2014, Article ID 689360, 13 pages, 2014.
[3] R. C. Lee, R. L. Feinbaum, and V. Ambros, “The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14,” Cell, vol. 75, no. 5, pp. 843–854, 1993.
[4] M. S. Jamaluddin, S. M. Weakley, L. Zhang et al., “MiRNAs: roles and clinical applications in vascular disease,” Expert Review of Molecular Diagnostics, vol. 11, no. 1, pp. 79–89, 2011.
[5] J. G. Doench, C. P. Petersen, and P. A. Sharp, “siRNAs can function as microRNAs,” Genes and Development, vol. 17, no. 4, pp. 438–442, 2003.
[6] J. Krol, I. Loedige, and W. Filipowicz, “The widespread regulation of microRNA biogenesis, function and decay,” Nature Reviews Genetics, vol. 11, no. 9, pp. 597–610, 2010.
[7] M. Ha and V. N. Kim, “Regulation of microRNA biogenesis,” Nature Reviews Molecular Cell Biology, vol. 15, no. 8, pp. 509–524, 2014.
[8] S. Diederichs and D. A. Haber, “Dual role for argonautes in microRNA processing and posttranscriptional regulation of microRNA expression,” Cell, vol. 131, no. 6, pp. 1097–1108, 2007.
of retinal pigment epithelial cells by targeting AKT2," Experimental Cell Research, 2014.

[25] S. Maharjan, B. Mopidevi, M. K. Kaw, N. Puri, and A. Kumar, "Human aldosterone synthase gene polymorphism promotes miRNA binding and regulates gene expression," Physiological Genomics, vol. 46, no. 24, pp. 860–865, 2014.

[26] J. Deiuliis, G. Mihai, J. Zhang et al., "Renin-sensitive microRNA correlate with atherosclerosis plaque progression," Journal of Human Hypertension, vol. 28, no. 4, pp. 251–258, 2014.

[27] W. Wang, G. Sun, L. Zhang, L. Shi, and Y. Zeng, "Circulating microRNAs as novel potential biomarkers for early diagnosis of acute stroke in humans," Journal of Stroke and Cerebrovascular Diseases, vol. 23, no. 10, pp. 2607–2613, 2014.

[28] X. Wu, M. K. Bhayani, C. T. Dodge et al., "Coordinated targeting of the EGFR signaling axis by MicroRNA-27a," Oncotarget, vol. 4, no. 9, pp. 1388–1398, 2013.

[29] J. R. Kemp, H. Unal, R. Desnoyer, H. Yue, A. Bhattacharjee, and S. S. Sørensen, "Angiogenesis II-regulated microRNA 483-3p directly targets multiple components of the renin–angiotensin system," Journal of Molecular and Cellular Cardiology, vol. 75, pp. 25–39, 2014.

[30] M. Satoh, Y. Takahashi, T. Tabuchi et al., "Circulating Toll-like receptor 4-responsive microRNA panel in patients with coronary artery disease: results from prospective and randomized study of treatment with renin–angiotensin system blockade," Clinical Science, vol. 128, no. 8, pp. 483–491, 2015.

[31] Y. Takahashi, M. Satoh, Y. Minami, T. Tabuchi, T. Itoh, and M. Nakamura, "Expression of miR-146a/b is associated with the Toll-like receptor 4 signal in coronary artery disease: effect of renin-angiotensin system blockade and statins on miRNA-146a/b and Toll-like receptor 4 levels," Clinical Science, vol. 119, no. 9, pp. 395–405, 2010.

[32] J. Wang, Y. Pei, Y. Zhong et al., "Altered serum microRNAs as novel diagnostic biomarkers for atypical coronary artery disease," PLoS ONE, vol. 9, no. 9, Article ID e107012, 2014.

[33] J. Mu, Q. Pang, Y.-H. Guo et al., "Functional implications of microRNA-215 in TGF-b1 induced phenotypic transition of mesangial cells by targeting CTNNBIP1," PLoS ONE, vol. 8, no. 3, Article ID e58622, 2013.

[34] E. van Rooij, L. B. Sutherland, J. E. Thatcher et al., "Dysregulation of microRNAs after myocardial infarction reveals a role of miR-29 in cardiac fibrosis," Proceedings of the National Academy of Sciences of the United States of America, vol. 105, no. 35, pp. 13027–13032, 2008.

[35] R. L. Montgomery, G. Yu, P. A. Latimer et al., "MicroRNA mimicer blocks pulmonary fibrosis," EMBO Molecular Medicine, vol. 6, no. 10, pp. 1347–1356, 2014.

[36] S. Ikeda, S. W. Kong, J. Lu et al., "Altered microRNA expression in human heart disease," Physiological Genomics, vol. 31, no. 3, pp. 367–373, 2007.

[37] A. S. Kim and S. C. Johnston, "Global variation in the relative burden of stroke and ischemic heart disease," Circulation, vol. 124, no. 3, pp. 314–323, 2011.

[38] S. S. Serensen, A. Nygaard, M. Nielsen, K. Jensen, and T. Christensen, "MiRNA expression profiles in cerebrospinal fluid and blood of patients with acute ischemic stroke," Translational Stroke Research, vol. 5, no. 6, pp. 711–718, 2014.

[39] S. Ikeda, A. He, S. W. Kong et al., "MicroRNA-1 negatively regulates expression of the hypertrophy-associated calmodulin and Mef2a genes," Molecular and Cellular Biology, vol. 29, no. 8, pp. 2193–2204, 2009.

[40] Z. Lin, I. Murtaza, K. Wang, J. Jiao, J. Gao, and P.-F. Lia, "miR-23a functions downstream of NFATc3 to regulate cardiac hypertrophy," Proceedings of the National Academy of Sciences of the United States of America, vol. 106, no. 29, pp. 12103–12108, 2009.

[41] A. Caré, D. Catalucci, F. Felicetti et al., "MicroRNA-133 controls cardiac hypertrophy," Nature Medicine, vol. 13, no. 5, pp. 613–618, 2007.

[42] Z.-P. Huang, J. Chen, H. Y. Seok et al., "MicroRNA-22 regulates cardiac hypertrophy and remodeling in response to stress," Circulation Research, vol. 112, no. 9, pp. 1234–1243, 2013.

[43] X. Yin, C. Peng, W. Ning et al., "MiR-30a downregulation aggravates pressure overload-induced cardiomyocyte hypertrophy," Molecular and Cellular Biochemistry, vol. 379, no. 1-2, pp. 1–6, 2013.

[44] T.-C. Chang, E. A. Wentzel, O. A. Kent et al., "Transactivation of miR-34a by p53 broadly influences gene expression and promotes apoptosis," Molecular Cell, vol. 26, no. 5, pp. 745–752, 2007.

[45] J. Huang, W. Sun, H. Huang et al., "miR-34a modulates angiotensin II-induced myocardial hypertrophy by direct inhibition of ATG9A expression and autophagic activity," PLoS ONE, vol. 9, no. 4, Article ID e94382, 2014.

[46] R. A. Boon, K. Iejushi, S. Lechner et al., "MicroRNA-31a regulates cardiac ageing and function," Nature, vol. 495, pp. 107–110, 2013.

[47] S. Huang, X. Zou, J.-N. Zhu et al., "Attenuation of microRNA-16 derepresses the cyclins D1, D2 and E1 to provoke cardiomyocyte hypertrophy," Journal of Cellular and Molecular Medicine, vol. 19, no. 3, pp. 608–619, 2015.

[48] L. Shi and I. Fleming, "One miR level of control: microRNA-155 directly regulates endothelial nitric oxide synthase mRNA and protein level," Hypertension, vol. 60, no. 6, pp. 1381–1382, 2012.

[49] E. R. Porrello and L. M. D. Delbridge, "Cardiomyocyte autophagy is regulated by angiotensin II type 1 and type 2 receptors," Autophagy, vol. 5, no. 8, pp. 1215–1216, 2009.

[50] D. Hartmann and T. Thum, "MicroRNAs and vascular (dys)function," Vascular Pharmacology, vol. 55, no. 4, pp. 92–105, 2011.

[51] B. S. Dickinson, H. M. Semus, R. L. Montgomery et al., "Plasma microRNAs serve as biomarkers of therapeutic efficacy and disease progression in hypertension-induced heart failure," European Journal of Heart Failure, vol. 15, no. 6, pp. 650–659, 2013.