Chapter 3

Implications of MicroRNAs in the Vascular Homeostasis and Remodeling

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Abstract

Vascular remodeling or arterial remodeling is a process of adaptive alteration of vascular wall architecture and leads to the endothelial cell (EC) dysfunction and synthetic or contractile phenotypic change of VSMCs, and the infiltration of monocytes and Macrophages that promotes vascular diseases including atherosclerosis. Recent findings have demonstrated that microRNAs (miRNAs) are involved in regulating gene expression at posttranscriptional level and disease pathogenesis. A change of miRNA expression profiles plays key roles in the gene expressions and the regulation of cellular functions. In this chapter, we summarize the vascular remodeling-related miRNAs and their functions in vascular biology.

Keywords: Vascular remodeling, vascular homeostasis, smooth muscle cells, endothelial cells, macrophage, microRNAs, vascular smooth muscle cell phenotypic switch

1. Introduction

Vascular remodeling (or arterial remodeling) is a process of adaptive alteration of vascular wall architecture and is caused by variety of environmental stimuli such as oxidative stress, vascular injury, and hemodynamic stress [1]. Endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) compose the arteries and play critical roles in vascular remodeling in conjunction with inflammatory cells such as monocytes or macrophages [2]. During vascular

remodeling, the EC dysfunction, synthetic or contractile phenotypic change of VSMCs, and the infiltration of monocytes and macrophages promote vascular diseases including atherosclerosis [3, 4]. Therefore, modulation of VSMC phenotype, maintenance of ECs, and regulation of inflammation in the vessel wall are important in arterial function and homeostasis.

Recent findings have been demonstrated that microRNAs (miRNAs) are involved in regulating gene expressions at posttranscriptional level and disease pathogenesis [5, 6]. Importantly, altered specific set of miRNAs is closely related to cell fate determination, tissue function, and homeostasis [7, 8], indicating that miRNAs plays key roles in the gene expressions and the regulation of cellular functions [9]. Consequently, the change of miRNA expressions can lead to VSMC phenotype switch, EC dysfunction, and the inflammatory response and lipid accumulation of macrophage in vascular pathophysiology [10–12].

In this chapter, we summarize the vascular remodeling-related miRNAs and the function of these miRNAs in vascular biology, and suggest novel therapeutic strategies for the treatment and/or prevention of vascular diseases via controlling the expressions of miRNA regulation.

2. MicroRNAs

MicroRNAs (miRNAs or miRs) are small noncoding RNA molecules approximately 18–25 nucleotides in length that participate in controlling gene expression at the posttranscriptional level [13]. MicroRNAs directly bind to 3 untranslated regions (3UTR) of target mRNAs, leading to translational inhibition and/or mRNA degradation [9]. One miRNA can suppress multiple target protein-coding mRNAs, which also means that a single protein can be regulated by numerous miRNAs [14]. Interestingly, about two-thirds of the coding-mRNA genes are regulated by miRNAs [15]. Since the first discovery of miRNAs in *Caenorhabditis elegans* in 1993, more than 1800 miRNAs in human have been identified and recorded in miRBase 21 (www.mirbase.org) [16].

The biogenesis of miRNAs are initiated by transcription from their genes by RNA polymerase II, which produces primary miRNAs (pri-miRNAs) with hundreds to thousands of nucleotides and single or multiple stem-loop-like structures [17]. After transcription, the pri-miRNAs are cleaved at ~70-nucleotide hairpin-shaped precursor miRNA (pre-miRNA) by RNase-III endonuclease (Drosha) and DiGeorge syndrome Critical Region 8 protein (DGCR8) complex [18]. The pre-miRNAs are transferred from nuclear to cytoplasm through the nuclear export protein exportin-5 [19]. In the cytoplasm, the pre-miRNAs are processed to produce mature miRNA duplex mediated by RNase-III endonuclease, Dicer: the passenger strand and the guide strand (~22 nucleotides long) [20]. The guide strand is loaded to RNA-induced silencing complex (RISC), and the passenger strand is degraded [21]. The miRNA–RISC complex recognizes and binds the miRNA based on the complementary match between the miRNA seed sequence (2–8 nucleotides in the 5' end) and the 3 UTR of the target mRNA, and this results in translational suppression and/or mRNA degradation (Figure 1) [22, 23].

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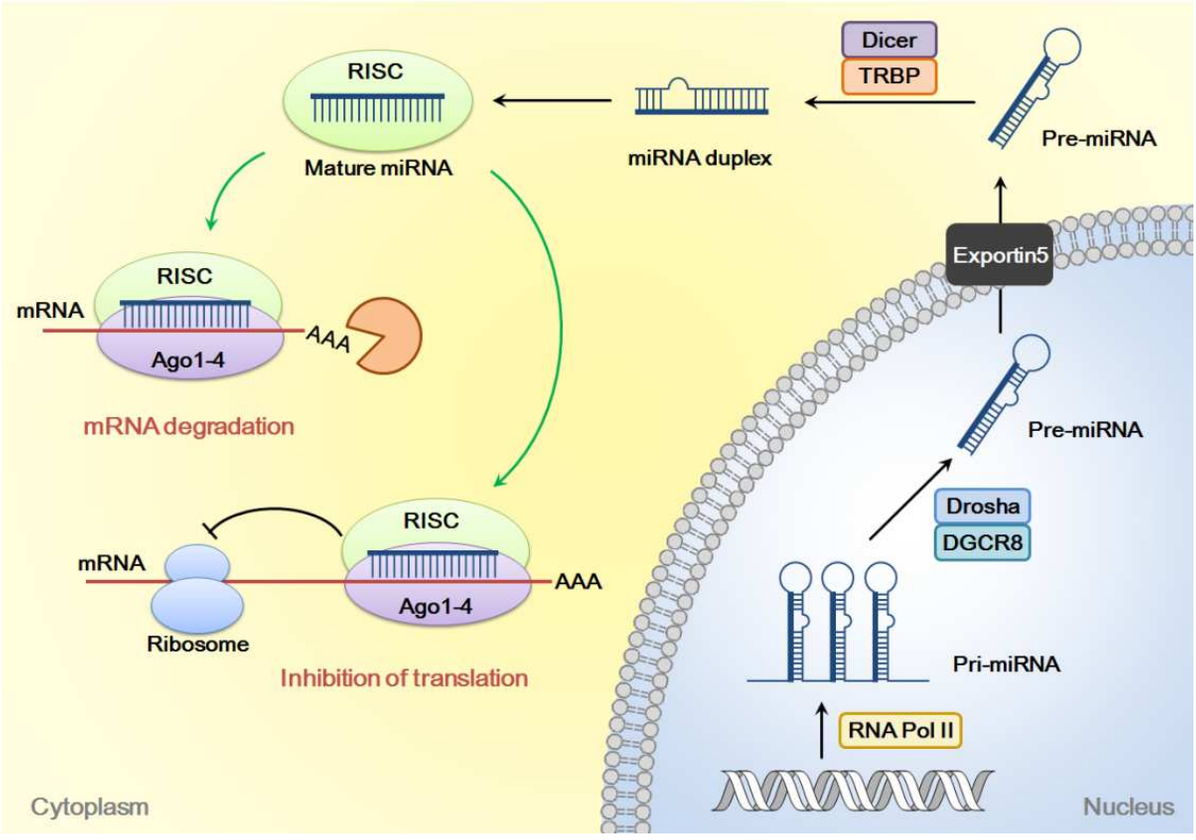

Figure 1. The biogenesis of miRNAs.

Increasing evidence suggests that miRNAs play important roles in a wide range of biological functions and processes, including but not limited to, development, growth, pathophysiology, regeneration, inflammation, stem cell fate regulation, and aging [24–29]. Because the changes of miRNA expression profiles are related to various human diseases, such as cardiovascular diseases, cancer, neuropathy, infection, and metabolic disorders [9, 30–34], the modulation of miRNA expressions consider as a novel therapeutic target and may inspire a new strategy for treatment of these diseases [35–37].

3. Vascular smooth muscle cells

The VSMCs of blood vessels in adult generally show a low proliferation rate and well-maintained homeostasis [38]. However, upon external stimuli, such as cytokines, blood flow rates, shear stress, hormones, injury, and inflammation, provoke the phenotypic switch of VSMCs from contractile to synthetic [2, 39]. The contractile or differentiated VSMCs express contractile markers, smooth muscle myosin heavy chain (SM-MHC), alpha smooth muscle actin (SM α-actin), and calponin; whereas the synthetic or dedifferentiated VSMCs show an increase of cell proliferation, migration, upregulation of extracellular matrix proteins,

such as collagen, elastin, and proteoglycans, and a decrease in the expression of contractile markers [16, 40]. The plasticity of VSMCs plays important roles in the vascular development and pathological/physiological vascular remodeling. The contractile phenotype is required to maintain the normal arterial wall structure and function, while the synthetic phenotype is involved in the development of atherosclerosis, restenosis after angioplasty, and hypertension [1, 39, 41].

The recent studies show that the regulation of VSMC phenotypic change is associated with the alteration of local environment as well as the modulation of gene expressions by miRNAs. Albinsson et al. reported that VSMC-specific deletion of Dicer-induced embryonic lethality at embryonic days 16 to 17 due to the thin and hypotensive vessel walls, impaired contractility, and hemorrhage [42]. In addition, the loss of Dicer in VSMCs of adult mice also showed a dramatic decrease in blood pressure, the impairment of contractile function, morphology, and phenotypic modulation [43]. These results strongly suggest that miRNAs are essential to vascular development and keep a balance of VSMC phenotype (Figure 2).

3.1. miRNAs in the contractile phenotype of VSMCs

3.1.1. miR-143 and miR-145

MiR-143 and miR-145 are the most well-known and enriched miRNAs in VSMCs and are in a bicistronic miRNA cluster on human chromosome 5 [44]. The significant role of miR-143 and miR-145 is to drive VSMC development and differentiation from human embryonic stem cells via targeting the stem cell pluripotency factors OCT4 (octamer-binding transcription factor 4), SOX2 [SRY (sex-determining region Y)-box 2], and KLF4 (Krüppel-like factor 4) [45]. After VSMC development, miR-143 and miR-145 are required for maintaining homeostasis of VSMCs through the suppression of multiple target proteins, such as KLF4, KLF5, E twenty-six (ETS)-like transcription factor 1 (ELK1), versican, several actin remodeling proteins, and angiotensin-converting enzyme. The transcriptional activation of miR-143 and miR-145 also leads to the expression of contractile genes [41, 46–48].

The maintenance of the VSMC contractile phenotype is modulated by several signaling pathways including serum response factor (SRF)/myocardin, transforming growth factor β (TGF-β), bone morphogenetic proteins 4 (BMP4), and Jagged-1 (Jag-1)/Notch signaling, which regulates the expression of miR-143 and miR-145 (Figure 3) [46]. The promoter region of miR-143 and miR-145 represents highly conserved *cis* elements and potential binding sites containing CArG box of SRF and Nkx2.5. In addition, myocardin and myocardin-related transcription factor A (MRTF-A), cofactors of SRF, synergistically and strongly activate the miR-143 and miR-145 transcription [49, 50]. The upregulation of miR-143 and miR-145 by TGF-β and BMP4 mediates the induction of SRF cofactors: TGF-β upregulates myocardin via the activation of parallel pathways of p38MAPK and SMAD dependent [51], whereas BMP4 stimulates the nuclear translocation of MRTF-A [52]. The Jag-1-mediated activation of Notch receptors is also activating miR-143 and miR-145 transcription [46]. Activation of Notch receptor by Jag-1 results in proteolytic cleavage and translocation to the nucleus of the Notch

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intracellular domain (NICD). In the nucleus, NICD forms complex with C promoter binding factor 1 (CBF1), which is binding to miR-143 and miR-145 promoter and increases in miR-145 and miR-145 expression [46].

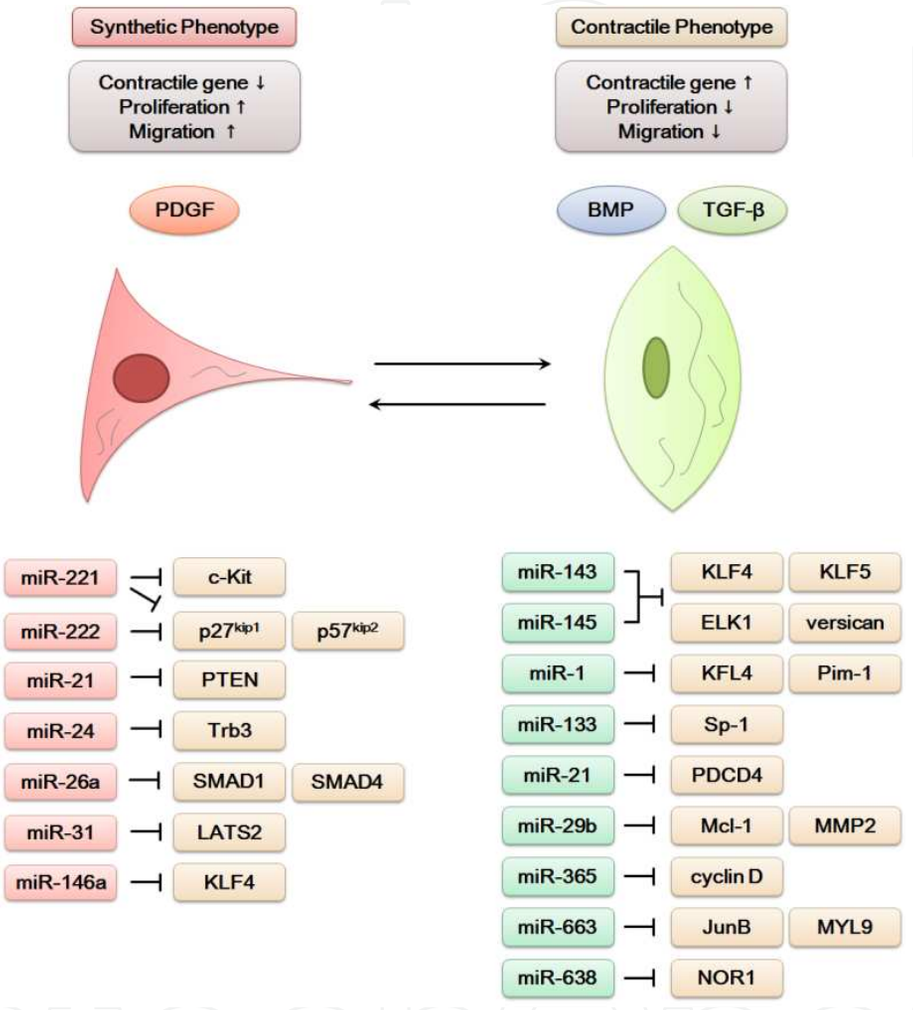

Figure 2. miRNAs in phenotypic switch of VSMCs.

The expression levels of miR-143 and miR-145 significantly decrease in animal vascular diseases models including apolipoprotein E knockout mice ($ApoE^{-/-}$), carotid artery ligation injury models, carotid balloon injury models, and in aortas from patients with aortic aneurism [53, 54]. MiR-143 and miR-145 knockout murine VSMCs showed a shift from contractile to synthetic state and the development of neointimal lesions [55], whereas the VSMC-specific overexpression of miR-143 and 145 increased the plaque stability and the expression of contractile proteins, and decreased macrophage infiltration, the expression of KLF4 and KLF5, and neointimal lesion formation [54, 56]. Altogether, these data indicate that miR-143 and miR-145 play an important role in the VSMC homeostasis and strengthen the VSMC contractile phenotype.

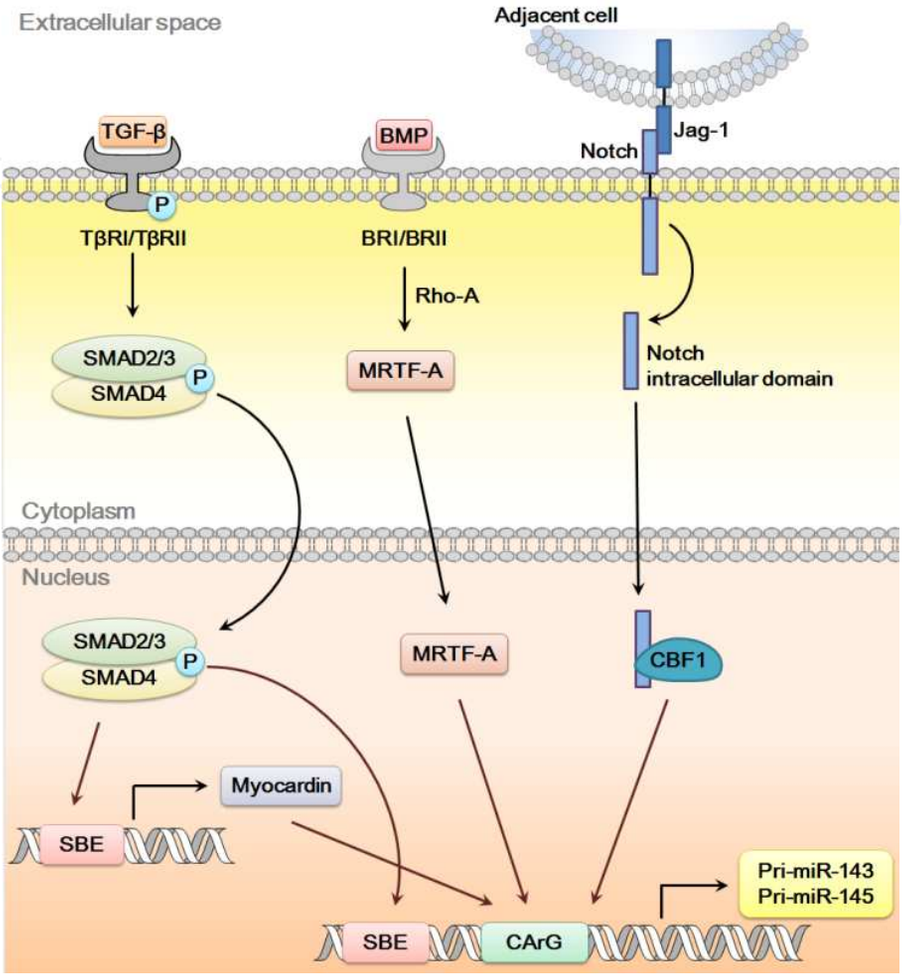

Figure 3. The signaling pathway of miR-143 and miR-145 expression.

3.1.2. miR-1 and miR-133

Similar to miR-143 and miR-145, miR-1 and miR-133 are also in bicistronic miRNA clusters and are induced by myocardin in VSMCs [57]. During differentiation of mouse ESC to VSMCs, the expression level of miR-1 is gradually increased, which results in the upregulation of VSMC-specific contractile proteins by repressing KLF4 [58]. Chen et al. demonstrated that overexpression of myocardin in VSMCs increased miR-1 expression and inhibited VSMC proliferation, which mediated the repression of Pim-1, a serine/threonine kinase [59].

The expression level of miR-133 is downregulated in proliferating VSMCs and after vascular injury. Overexpression of miR-133 reduces VSMC growth, but the downregulation of miR-133 induces VSMC proliferation *in vitro* [57]. Both the transcription factor Sp-1 (specificity protein 1) which regulates VSMC phenotypic switch and the actin-binding protein moesin that modulates VSMC migration are direct targets of miR-133. Accordingly, miR-133 overexpres-

sion in the rat carotid artery reduced neointimal hyperplasia, whereas anti-miR-133 increased VSMC proliferation and neointimal formation after balloon injury [57].

3.1.3. miR-21

The expression of miR-21 mediates TGF-β and BMP4 signaling pathway and promotes the contractile phenotype of VSMCs via downregulating programmed cell death 4 (PDCD4), a negative regulator of smooth muscle contractile genes [60]. Another target of miR-21 is the family of the dedicator of cytokinesis (DOCK) proteins, which promote VSMC migration by modulating the activity of small Rac1 GTPase [61]. On the other hand, Horita et al. reported that Fos-related antigen (FRA)-1, a direct target of miR-143, was a positive regulator of increased miR-21 expression [62]. The upregulation of miR-143 by SRF repressed FRA-1 expression, which led to the decrease of VSMC proliferation via the repression of miR-21 and subsequent increase of phosphatase and tensin homolog (PTEN), one of the target proteins of miR-21 [62]. The dual function of miR-21 in promoting both contractile and synthetic phenotype of VSMCs may suggest that diverse targets of miR-21 are involved in different biological processes depending on the cellular environments or context.

3.1.4. Other miRNAs

Our group has reported that miR-29b and miR-365 inhibit the proliferation and migration of VSMCs [63, 64]. The interleukin-3 (IL-3) is known to stimulate proliferation and migration in vascular diseases, and it downregulates miR-29b expression. Mir-29b significantly decreases the proliferation and migration of VSMCs through the inhibition of the signaling pathway related to Mcl-1 (myeloid cell leukemia 1) and MMP2 (matrix metallopeptidase 2). Consistent with the declined miR-29b expression in balloon-injured rat carotid arteries, overexpression of miR-29b by local oligonucleotide delivery can inhibit neointimal formation [64]. The proliferation of VSMCs by various stimuli, including platelet-derived growth factor (PDGF)-BB, angiotensin II (Ang II), and serum, led to the downregulation of miR-365 expression levels. The cell-cycle-specific cyclin D1 was found to be a potential target of miR-365; thus exogenous miR-365 overexpression reduced VSMC proliferation and proliferating cell nuclear antigen (PCNA) expression, blocking transition of G1/S [63, 65].

Li et al. reported that miR-663 is related to human VSMC phenotypic switch and the development of neointimal formation [66]. According to this particular study, overexpression of miR-663 upregulated VSMC differentiation marker genes and inhibited PDGF-induced VSMC proliferation and migration via targeting the transcription factor JunB and myosin light chain 9 (MYL9). Overexpression of miR-663 also dramatically attenuated the neointimal lesion formation in mice after carotid artery ligation [66]. In addition, the same group identified that miR-638 also is markedly downregulated by PDGF-stimulated human VSMCs, whereas upregulated in human VSMCs cultured in differentiation medium, a condition that inhibits proliferation [67]. Furthermore, the orphan nuclear receptor NOR1 (neuron-derived orphan receptor 1) was identified as a target of miR-638 and downregulation of NOR1 was implicated in the miR-638-mediated inhibitory effects on cyclin D1 expression, cell growth, and migration of PDGF-induced VSMCs.

3.2. miRNAs in the synthetic phenotype of VSMCs

3.2.1. miR-221 and miR-222

Similar to TGF-β and BMP4 promote VSMC contractile phenotype, PDGF induces VSMC phenotype switch from contractile to synthetic type [41]. Mir-221 and miR-222 are well characterized in VSMC phenotype switch and clustered on the X chromosome, and have same seed sequence [68]. Mir-221 and miR-222 are transcriptionally induced by activating PDGF pathway, which reduces the expression of contractile genes and promotes VSMC proliferation and migration [69]. In addition, the expression of miR-221 and miR-222 are elevated in neointimal lesion from balloon-injured rat carotid arteries [70]. The targets of miR-221 and miR-22 include $p27^{Kip1}$ and $p57^{kip2}$, both of which are a negative regulator of VSMC proliferation [70, 71]. Interestingly, miR-221 decreased the expression of c-kit, and this reduced c-kit expression subsequently repressed the expression of a VSMC-specific nuclear coactivator myocardin [69]. As the PDGF-treatment stimulated phenotype change of VSMCs, overexpression of miR-221 and miR-222 accelerated VSMC proliferation and migration, while downregulation of them attenuated VSMC proliferation and neointimal formation in rat carotid artery after angioplasty [70]. These data indicate that miR-221 and miR-222 have a crucial role in regulating VSMC phenotype change, and suggest their therapeutic potential in pathological vascular remodeling.

3.2.2. miR-146a

Recent study has shown that miR-146a is upregulated in rat balloon-injured arteries and serum-induced proliferative VSMCs [72, 73]. KLF4, a negative regulator of VSMC proliferation, was downregulated by miR-146a, and in turn, KLF4 repressed miR-146a expression through binding to CACCC (or GGGTG) elements on the miR-146a promoter. This negative feedback regulatory network between miR-146a and KLF4 regulates transcription of each other, controlling VSMC proliferation *in vitro* and vascular neointimal hyperplasia *in vivo* [72]. Dong et al. demonstrated that miR-146a upregulation is related to the downregulation of critical transcriptional factors such as the protein expression of nuclear factor-κBp65 (NF-κBp65) and PCNA. In contrast, miR-146a knockdown is linked to the increase in pro-apoptotic protein Bax expression [73]. Therefore, miR-146a is a novel regulator of VSMC proliferation in cardiovascular diseases.

3.2.3. miR-24

Both TGF-β and BMP4 signaling are important in maintaining the VSMC contractile phenotype, whereas PDGF signaling pathways can promote the synthetic phenotype conversion of VSMCs. Although these signaling pathways play key roles in VSMC phenotypic changes, the crosstalk between these pathways is not elucidating until quite recently. Chan et al. reported that despite of BMP4 stimulation, the contractile genes are downregulated by co-treatment with PDGF in human primary pulmonary SMCs (PASMCs) [74]. Furthermore, PDGF stimulation decreases the expression of Tribbles-like protein-3 (Trb3), an important modulator of the BMP and TGF-β signaling pathway. Interestingly, the result of Trb3 promoter-luciferase-

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reporter assay showed that the downregulation mechanism of Trb3 expression by PDGF is associated with the effect of PDGF-induced miR-24, directly targeting 3URT of Trb3 mRNA, rather than PDGF stimulation [74]. The knockout endogenous miR-24 by antisense oligonucleotides restored Trb3 expression as well as attenuates PDGF-mediated synthetic activity, suggesting that PDGF-induced miR-24 expression which downregulated Trb3, and this miR-24-mediated downregulation of Trb3 is sufficient to induce synthetic phenotypic changes of VSMCs [74].

3.2.4. miR-26a

Leeper et al. demonstrated that serum-starved human aortic SMCs upregulates the expression of contractile marker genes, and miR-26a is significantly downregulated during serum-starvation and in murine abdominal aortic aneurysm (AAA) development models [75]. Overexpression of miR-26a promoted VSMC proliferation and migration as well as inhibited apoptosis, whereas downregulation of miR-26a induced contractile gene expression and reduced proliferation and migration. The potential targets of miR-26a include SMAD1 and SMAD4, members of TGF-β and BMP superfamily downstream signaling cascade. Consistently, knockdown of miR-26a led to SMAD1 and Samd4 upregulation and activates TGF-β and BMP signaling pathway. Thus, miR-26a is expected to actively participate in the regulation of VSMCs as an enhancer of cell growth and migration, and an inhibitor of apoptosis, modulating TGF-β and BMP signaling [75].

3.2.5. miR-31

Although miR-31 plays an important role in cancer cell growth and proliferation [76–78], the biological function of miR-31 in VSMCs remains unclear. Recently, Liu et al. found that miR-31 was an abundant miRNA in VSMCs of vascular walls, and was significantly upregulated in proliferative VSMCs and rat carotid arteries with neointimal growth after balloon injury [79]. The serum- or PDGF-induced VSMC proliferation is inhibited by miR-31 inhibitor, 2′OMe-miR-31 (the antisense oligonucleotide for miR-31 that is modified at each nucleotide by an O-methyl moiety at the 2′-ribose position). On the contrary, overexpression of miR-31 using the adenoviruses expressing rat miR-31 promotes VSMC proliferation [79]. The pro-proliferative effect of miR-31 is mediated by the direct inhibition of the large tumor suppressor homolog 2 (LATS2) expression, and is accelerated by the activation of mitogen-activated protein kinase/extracellular regulated kinase (MAPK/ERK) [79].

4. Endothelial cells

Vascular endothelial cells (ECs) cover the internal surface of blood vessels. The primary role of ECs is the maintenance of vessel wall permeability and function as a sensor for the altered physical and chemical signals by physiological or pathological processes including thrombosis, inflammation, and vascular wall remodeling [80–82]. The knockdown of Dicer in human ECs resulted in the change of several key regulator proteins of EC biology and angiogenesis,

such as TEK (Tie-2), KDR (VEGFR2), adhesion molecules and proteins, cytokine, chemokine, and IL-8. Furthermore, EC-specific knockdown of Dicer activated the endothelial nitric oxide synthase (eNOS) pathway, which reduces proliferation and capillary formation of EC, and the endogenous miRNA expression levels were also significantly altered [83]. These results indicate that altered miRNA expression in ECs affects the maintenance and functions of ECs (Figure 4).

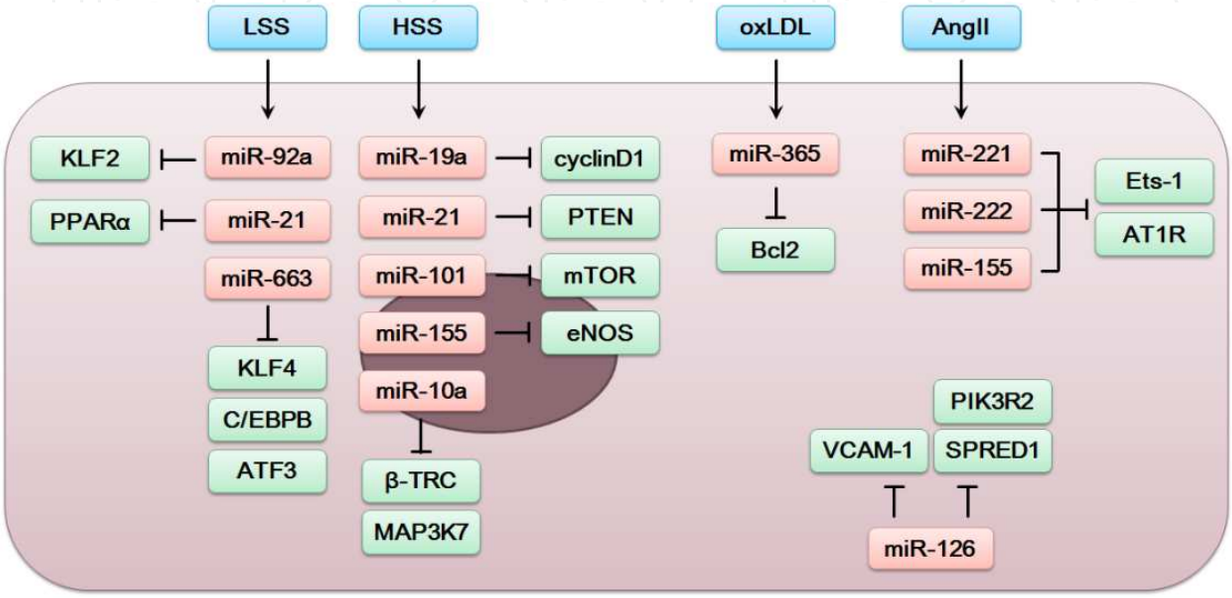

Figure 4. miRNAs in ECs regulating during vascular remodeling.

4.1. miR-126

Adhesion molecules in ECs are directly associated with leukocyte trafficking to the region of the injury and/or inflammation [84]. Generally, resting ECs do not express adhesion molecules, but activated ECs express adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1), which plays an important role in modulating leukocyte trafficking and inflammation [85]. Based on microarray and Northern analysis, Harris et al. showed that miR-126 is the most frequently expressed in HUVECs as well as other origin ECs from dermal, brain, and vein [86]. *In silico* analysis suggests that VCAM-1 is one of the targets of miR-126. The upregulation of miR-126 by transfection of pre-miR-126 results in inhibiting TNF-α induced VCAM-1 expression, whereas the knockdown of miR-126 by antisense miR-126 oligonucleotide is causing TNF-α induced VCAM-1 upregulation in a dose-dependent manner. In addition, overexpression of miR-126 mediated a decrease of VCAM-1 downregulating leukocyte adherence to ECs. These data suggest that miR-126 regulates the expression of adhesion molecules and plays a crucial role in the control of vascular inflammation [86].

Fish et al. found that EC-specific miRNA miR-126 is also highly enriched in Flk-1 positive vascular progenitors from differentiating mouse embryonic stem cells in the embryonic body [87]. Nevertheless, overexpression of miR-126 using miR-126 mimic does not promote

endothelial differentiation of embryonic stem cells. The loss-of-function of miR-126 by a morpholino antisense to miR-126 shows that the EC migration and the formation/stability of capillary tubes are decreased compared to normal HUVECs. In addition, EC-targeted deletion of miR-126 results in vascular abnormalities such as vascular leakage, hemorrhaging, and embryonic lethality in both zebrafish [87] and mice [88], because of reduced EC growth, sprouting, and adhesion by decrease in angiogenic growth factor signaling. The pro-angiogenic function of miR-126 was due to its ability to repress two negative regulators of angiogenic process, namely sprouty-related EVH1 domain-containing protein 1 (SPRED1) and phosphoinositol-3 kinase regulatory subunit 2 (PIK3R2) [87, 88]. Taken together, miR-126 is considered as new therapeutic implication for modulating vascular formation, function, leakage, and abnormal angiogenesis.

4.2. Endothelial Shear Stress (ESS) and miRNAs

The atherosclerotic lesions form at specific arterial regions such as the vicinity of branch points, the outer wall of bifurcations, and the inner wall of curvatures, where they show the disturbed flow and the change of hemodynamic forces, especially endothelial shear stress (ESS) [89]. ESS has been reported to regulate endothelial gene expression and promotes EC activation and atherosclerotic plaque progression and vascular remodeling [90, 91].

By miRNA microarray analysis using human umbilical vein endothelial cells (HUVECs), Ni et al. identified that the expression of miR-663 was mediated by low ESS (LSS) and LSS-induced miR-663 expression improved monocyte adhesion to ECs, but it had no effect on EC apoptosis. MicroRNA-663 has been reported to regulate several transcription factors related to inflammatory responses, such as KLF4, C/EBPB, and ATF3 [92].

In addition, miR-21 was also upregulated by LSS at transcriptional level in HUVECs through an increased activity and binding of c-Jun, a component of transcription factor activator protein-1 (AP-1), to the promoter region of miR-21 [93]. Mir-21 upregulated the expression of VCAM-1 and monocyte chemotactic protein-1 (MCP-1) by suppressing the peroxisome proliferators-activated receptor-α (PPARα), increasing adhesion of monocytes to ECs and pro-inflammatory responses [93].

MicroRNA-92a, a member of miR-17~92 cluster, was upregulated by LSS in HUVECs [94]. The decreased expression of miR-92a was correlated to the upregulation of KLF2 and subsequent KLF2-mediated eNOS and thrombomodulin (TM) expression and NO production, all of which are considered as potent anti-thrombotic, anti-adhesive, and anti-inflammatory properties [94, 95]. Therefore, LSS-induced miR-92a inhibited KLF2-mediated eNOS and TM expression that resulted in impaired EC functions.

In contrast to LSS, high ESS (HSS) appears to be protective against atherosclerosis, but the precise functions still remain unclear [96]. Mir-10a is one of the flow-induced miRNAs in ECs and is known to be downregulated in athero-susceptible regions of the inner aortic arch and aorto-renal branches than other regions [97]. The knockout of miR-10a led to IκB/NF-κB-mediated inflammation, which suggested anti-inflammatory role of miR-10a. Interestingly, two key regulators of IκBα degradation, mitogen-activated kinase kinase kinase 7 (MAP3K7;

TAK1) and β-transducin repeat-containing gene (β-TRC), are putative targets of miR-10a [97]. Therefore, miR-10a contributes to anti-inflammatory endothelial phenotype through the inhibition of pro-inflammatory molecules in athero-susceptible regions.

In addition, Qin et al. found that laminar shear stress induced miR-19a that suppressed cyclin D1 expression, leading to an arrest of cell cycle at G1/S transition [98]. Similar research by Chen et al. showed that miR-101 was also induced by laminar shear stress and cell cycle arrest at the G1/S transition and suppressed endothelial cell proliferation via targeting mTOR [99].

MicroRNA-155 is upregulated by prolonged HSS in HUVECs and it modulated endothelium-dependent vasorelaxation by repressing eNOS. Therefore, the inhibition of miR-155 improved endothelial dysfunction during the development of atherosclerosis [100].

MicroRNA-21 and miR-92a were induced by both LSS and HSS. Compared with LSS-induced miR-21, HSS-induced miR-21 decreased EC apoptosis and activated the NO pathway by targeting PTEN [101]. As mentioned earlier, downregulation of miR-92a led to upregulation of KLF2 and subsequent KLF2-mediated eNOS and TM, which facilitated the maintenance of EC homeostasis and functions against inflammation and pro-atherosclerotic effects [94, 95].

4.3. Angiotensin II (AngII) and miRNAs

Angiotensin II (AngII) has been implicated in the development and progression of cardiovascular diseases such as hypertension, atherosclerosis, and restenosis after vascular injury [102]. AngII-mediated intracellular singling is activated through its G-protein-coupled AngII Type 1 receptor (AT1R). In both VSMCs and ECs, AngII leads to vascular and endothelial dysfunctions by generating intracellular reactive oxygen species (ROS) and negatively regulating NO signaling pathway, respectively [103, 104]. Zhu et al. found that miR-155, miR-221, and miR-222 were highly expressed in both HUVECs and VSMCs, and a key endothelial transcription factor for inflammation and tube formation Ets-1 was a putative target of miR-155, miR-221, and miR-222 [105]. Interestingly, miR-155 also targeted AT1R, and AngII-stimulated HUVECs upregulates Ets-1 and its downstream genes, including VCAM1, MCP1, and FLT1 [105]. These results indicated that miR-155, miR-221, and miR-222 act as negative regulators to inflammatory response of ECs caused by AngII stimulation.

4.4. Oxidized low-density lipoprotein (oxLDL) and miRNAs

Oxidized low-density lipoprotein (oxLDL) induces EC death and dysfunction through the activation of NF-κB and AP-1 pathways, and it also activates pro-inflammatory response during the progression of atherosclerotic vascular diseases [2, 106]. Based on microarray and qRT-PCR analysis with oxLDL-stimulated HUVECs, Qin et al. found that four miRNAs are upregulating including miR-365 and miR-142-3p, whereas eleven miRNAs are downregulating including miR-590-5p and miR-33a in microarray, which expression levels are validated with qRT-PCR [107]. Using computational prediction algorithms (TargetScan, microRNA.org, and MicroCosm v5), the gene ontology (GO) database (www.geneontology.org), and KEGG pathway database (www.genome.ad.jp/kegg), the authors predicted and identified the functions of miRNA-targeted genes. As a result, miR-365 has been reported to be involved in

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oxLDL-induced apoptosis of ECs by suppressing the anti-apoptotic protein Bcl-2 [107]. Therefore, the inhibition of miR-365 may reduce EC apoptosis and inhibit the pro-atherogenic progression caused by oxLDL.

5. Macrophage

The accumulation and activation of macrophages within the vascular wall are a crucial event in vascular remodeling and implicate the progression of atherogenesis, which is initiated by inflammation, a rise in circulating LDL levels, and the accumulation of oxLDL in macrophages [108, 109]. Inflammation triggers the recruitment and infiltration of monocytes and macrophage in atherosclerotic lesions, continuously accumulating lipids and oxLDL [110]. The macrophages respond to various inflammatory stimuli, which lead to the changes in expression of many genes and several miRNAs, including miR-155, miR-125a, miR-146a, and miR-146b [111, 112]. Although the microRNAs involved in oxLDL accumulation and inflammatory response in macrophages are currently unclear, considering the role of miRNAs in VSMCs and ECs during arterial remodeling, the idea of miRNAs that also contribute the macrophage functions does not seem to be illogical (Figure 5) [2].

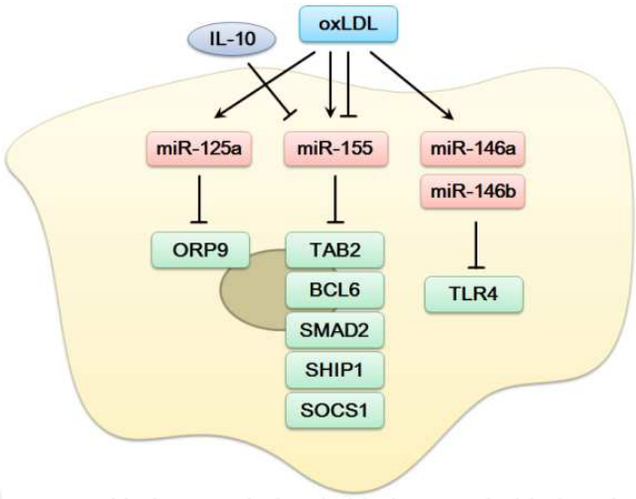

Figure 5. miRNAs in macrophages during vascular remodeling.

5.1. miR-155

The expression of miR-155 increased in human atherosclerotic lesions, but circulating miR-155 is known to be downregulated in patients with coronary artery diseases [113, 114]. During vascular remodeling, miR-155 is expressed in VSMCs, ECs, as well as activated macrophages [115]. The oxLDL and/or ESS promote the recruitment of monocytes into the arterial wall through ECs and then monocytes are differentiated toward macrophages and dendritic cells (DCs) [108]. MiR-155 is the most important miRNA in macrophage-mediated inflammation [116], and its expression is increased by several Toll-like receptor (TLR) ligands via myeloid

differentiation primary response gene (MyD88) and/or TIR-domain-containing adapter-inducing interferon-β (TRIF)-dependent signaling in the inflammatory activation of macrophages [117]. In addition, the lipopolysaccharide (LPS) is also known to induce miR-155 in monocytes and DCs. LPS-induced miR-155 expression is mediated by the single-strand RNA-binding protein KH-type splicing regulatory protein (KSRP) in bone marrow-derived macrophages [118]. In activated primary human monocyte-derived DCs, LPS-induced upregulation of miR-155 inhibited Toll-like receptor/interleukin-1 (TLR/IL-1) inflammatory pathway as well as TAB2 (an adaptor in the TLR/IL-1 signaling cascade), attenuating IL-1β and inflammatory signals [119]. Furthermore, oxLDL and cytokine IFN-γ induced the expression of miR-155 that modulated the inflammatory response in macrophages by repressing BCL6, a negative regulator of pro-inflammatory NF-κB signaling. The attenuation of BCL6 was correlated to upregulation of chemokine CCL2, an activator of monocyte recruiting into atherosclerotic plaques [120]. MicroRNA-155 also regulates TGF-β signaling in macrophages by targeting SMAD2. Overexpression of miR-155 inhibited TGF-β induction of SMAD2 phosphorylation, which repressed TGF-β-dependent transcription of cytokines, such as IL-1β [121].

On the other hand, a potent anti-inflammatory cytokine IL-10 inhibited LPS-induced miR-155 expression via STAT3-dependent manner, which led to upregulation of the target proteins of miR-155 such as Src homology 2 domain-containing inositol-5-phosphatase 1 (SHIP1) and anti-inflammatory genes [122]. Moreover, LPS-activated PI3K/Akt1 pathway inhibited expressions of miR-155 and pro-inflammatory mediators [123]. Paradoxically, a small number of studies reported that miR-155 is also downregulated in oxLDL simulation and reduces lipid uptake and accumulation in macrophages [120, 124]. Therefore, miR-155 in macrophages maintains the balance between pro- and anti-inflammatory responses, which is influenced by the diseases context or extracellular microenvironments.

5.2. miR-125a

Similar to miR-155, upregulation of miR-125a seems to decrease lipid accumulation by directly targeting oxysterol-binding protein-like 9 (ORP9), but the functional role of miR-125a in oxLDL-stimulated monocytes and macrophage still remains unclear [125]. MicroRNA-125a has been reported to be upregulated through oxLDL in primary human monocytes, and inhibition of miR-125a increased the secretion of IL-6, TNF-α, IL-2, and TGF-β, possibly due to enhanced expression of scavenger receptors (LOX-1, CD68).

5.3. miR-146a and miR-146b

MicroRNA-146a/b is upregulated after stimulation with oxLDL in primary human monocytes [125]. MiR-146a and -b are located on different chromosomes, and differ by two nucleotides. Stimulation of TLR-2, 4, and 5 has been reported to induce miR-146a/b expressions in macrophages through NF-κB activation [126]. The oxLDL-mediated suppression of miR-146a promoted lipid uptake and cytokine release, most likely due to reduced suppression of TLR-4 (target of miR-146a) in macrophage [124]. Additionally, miR-146a and b are known to upregulated in human atherosclerotic plaques [127].

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6. Circulating miRNAs as biomarkers

In addition to the significance of miRNAs regulating gene expression at the intracellular regions, some miRNAs have been discovered in the extracellular body fluids including serum/plasma and bloodstream [128, 129]. Interestingly, the extracellular circulating miRNAs show remarkably stable and resistant against ribonucleases, freezing, boiling, low or high pH, and so on, which signifies that some protective mechanisms can countervail degradation [130–132]. The mature miRNAs are released from intracellular to extracellular environment via the complex with RNA-binding proteins such as Argonaute-2 (Ago2), binding to high-density lipoprotein (HDL), and loading into microvesicle bodies such as microvesicles, exosomes, or apoptotic bodies (Figure 6) [133–136].

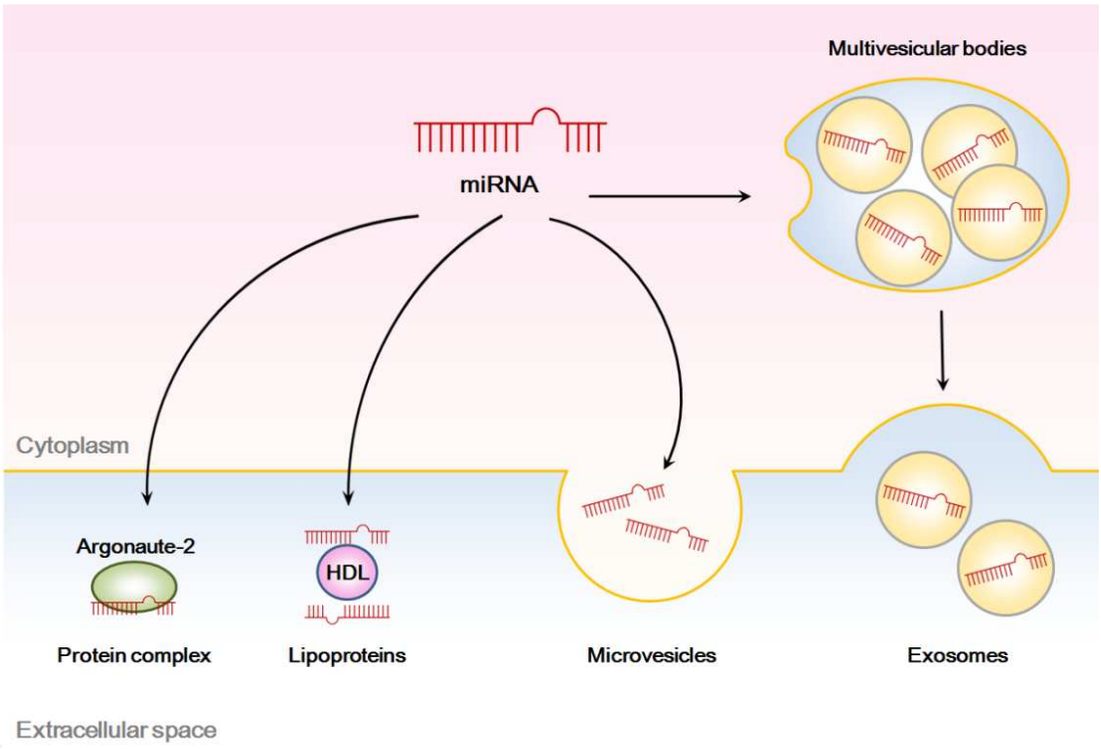

Figure 6. The cellular release mechanisms of miRNAs.

Although the cellular origin and function of the circulating miRNAs remain uncertain, their expression profiles are changed by fluid types and physiology or pathology conditions [137, 138]. The extraordinarily stable and tissue/diseases specific profiles of circulating miRNAs have been considered as promising biomarkers for diagnosis of diseases [139, 140].

Several studies suggest that circulating miRNAs may be taken into the recipient cells and regulate target gene expression [141–143]. In vascular diseases, a few studies showed that circulating miRNAs modulate the function of ECs [144, 145]. Zhang et al. found that the secretion of microvesicles containing miR-150 from human monocytic cells THP-1 is increased in the plasma of patients with atherosclerosis. Secreted monocytic miR-150 is transported into human microvascular endothelial cells (HMEC-1) and then promotes HMEC-1 migration via downregulating the miR-150 target gene c-Myb [144]. Likewise, Zernecke et al. showed that

EC-derived apoptotic bodies, containing miR-126, upregulates the production of CXC chemokine CXCL12, which promotes the recruitment of Sca-1^{+} progenitor cells and reduces the atherosclerotic lesion formation in ApoE$^{-/-}$ mice. These results suggest that circulating miR-126 in apoptotic bodies may have protective potential against atherosclerosis [145].

7. Conclusion

Vascular remodeling encompasses a series of complex biological pathways and involves the phenotype change of VSMCs, EC dysfunction, as well as macrophage activation. The alteration of VSMCs, ECs, and macrophage cellular functions is related to the various extracellular stimulus-dependent changes in transcriptional regulation, which is regulated by miRNAs. Thus, the identification of stimuli-dependent vascular remodeling which affects miRNA expression in different vascular cell types is imperative. The augmenting or inhibiting of the expression levels of specific miRNAs may provide opportunity for the development of miRNA-based therapeutic application to treating diverse vascular pathologies. In addition, extracellular circulating miRNAs have been reported to be altered under specific pathologic conditions, implicating their usage as biomarkers for specific diseases including cardiovascular disease. Although there are unsolved issues of the efficiency and safety of using miRNAs in diagnosis and therapy, accumulating evidence indicate that continuous research on the functions and mechanisms of miRNAs and the identification of a network between miRNAs and their targets is highly recommended and the results will expand our understanding of vascular remodeling and diseases.

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References

[1] Salabei JK, Hill BG.. Autophagic regulation of smooth muscle cell biology. Redox Biol 2014;4C:97–103.

[2] Nazari-Jahantigh M, Wei Y, Schober A. The role of microRNAs in arterial remodelling. Thromb Haemost 2012;107(4):611–8.

[3] McDonald RA, Hata A, MacLean MR, Morrell NW, Baker AH. MicroRNA and vascular remodelling in acute vascular injury and pulmonary vascular remodelling. Cardiovasc Res 2012;93(4):594–604.

[4] Heusch G, Libby P, Gersh B, Yellon D, Bohm M, Lopaschuk G, et al. Cardiovascular remodelling in coronary artery disease and heart failure. Lancet 2014;383(9932):1933–43.

[5] Yu X, Li Z. MicroRNAs regulate vascular smooth muscle cell functions in atherosclerosis (review). Int J Mol Med 2014;34(4):923–33.

[6] Kataoka M, Wang DZ. Non-coding RNAs including miRNAs and lncRNAs in cardiovascular biology and disease. Cells 2014;3(3):883–98.

[7] Nazari-Jahantigh M, Egea V, Schober A, Weber C. MicroRNA-specific regulatory mechanisms in atherosclerosis. J Mol Cell Cardiol 2014.

[8] Runtsch MC, Round JL, O'Connell RM. MicroRNAs and the regulation of intestinal homeostasis. Front Genet 2014;5:347.

[9] Song MA, Paradis AN, Gay MS, Shin J, Zhang L. Differential expression of microRNAs in ischemic heart disease. Drug Discov Today 2014.

[10] Zampetaki A, Dudek K, Mayr M. Oxidative stress in atherosclerosis: the role of microRNAs in arterial remodeling. Free Rad Biol Med 2013;64:69–77.

[11] Tousoulis D, Androulakis E, Papageorgiou N, Siasos G, Latsios G, Charakida M, et al. Novel biomarkers assessing endothelial dysfunction: role of microRNAs. Curr Top Med Chem 2013;13(13):1518–26.

[12] Urbich C, Kuehbacher A, Dimmeler S. Role of microRNAs in vascular diseases, inflammation, and angiogenesis. Cardiovasc Res 2008;79(4):581–8.

[13] Beavers KR, Nelson CE, Duvall CL. miRNA inhibition in tissue engineering and regenerative medicine. Adv Drug Delivery Rev 2014.

[14] Thomson DW, Bracken CP, Goodall GJ. Experimental strategies for microRNA target identification. Nucleic Acids Res 2011;39(16):6845–53.

[15] Luo X, Yang B, Nattel S. MicroRNAs and atrial fibrillation: mechanisms and translational potential. Nat Rev Cardiol 2014.

[16] Song X, Shan D, Chen J, Jing Q. miRNAs and lncRNAs in vascular injury and remodeling. Sci China Life Sci 2014;57(8):826–35.

[17] Romero-Cordoba SL, Salido-Guadarrama I, Rodriguez-Dorantes M, Hidalgo-Miranda A. miRNA biogenesis: biological impact in the development of cancer. Cancer Biol Ther 2014;15(11):1444–55.

[18] Han J, Lee Y, Yeom KH, Nam JW, Heo I, Rhee JK, et al. Molecular basis for the recognition of primary microRNAs by the Drosha-DGCR8 complex. Cell 2006;125(5):887–901.

[19] Yi R, Qin Y, Macara IG, Cullen BR. Exportin-5 mediates the nuclear export of pre-microRNAs and short hairpin RNAs. Genes Dev 2003;17(24):3011–6.

[20] Pulito C, Donzelli S, Muti P, Puzzo L, Strano S, Blandino G. microRNAs and cancer metabolism reprogramming: the paradigm of metformin. Ann Trans Med 2014;2(6): 58.

[21] Berezikov E. Evolution of microRNA diversity and regulation in animals. Nat Rev Genet 2011;12(12):846–60.

[22] Pasquinelli AE. MicroRNAs and their targets: recognition, regulation and an emerging reciprocal relationship. Nat Rev Genet 2012;13(4):271–82.

[23] Ha M, Kim VN. Regulation of microRNA biogenesis. Nature reviews Mol Cell Biol 2014;15(8):509–24.

[24] Frith JE, Porrello ER, Cooper-White JJ. Concise review: new frontiers in microRNA-based tissue regeneration. Stem Cells Trans Med 2014;3(8):969–76.

[25] Joladarashi D, Thandavarayan RA, Babu SS, Krishnamurthy P. Small engine, big power: microRNAs as regulators of cardiac diseases and regeneration. Int J Mol Sci 2014;15(9):15891–911.

[26] Harries LW. MicroRNAs as mediators of the ageing process. Genes 2014;5(3):656–70.

[27] Shenoy A, Blelloch RH. Regulation of microRNA function in somatic stem cell proliferation and differentiation. Nat Rev Mol Cell Biol 2014;15(9):565–76.

[28] Pourrajab F, Babaei Zarch M, BaghiYazdi M, Hekmatimoghaddam S, Zare-Khormizi MR. MicroRNA-based system in stem cell reprogramming; differentiation/dedifferentiation. Int J Biochem Cell Biol 2014;55C:318–28.

[29] Clark EA, Kalomoiris S, Nolta JA, Fierro FA. Concise review: MicroRNA function in multipotent mesenchymal stromal cells. Stem Cells 2014;32(5):1074–82.

[30] Haga H, Yan I, Takahashi K, Wood J, Patel T. Emerging insights into the role of microRNAs in the pathogenesis of cholangiocarcinoma. Gene Expr 2014;16(2):93–9.

[31] Bronze-da-Rocha E. MicroRNAs expression profiles in cardiovascular diseases. BioMed Res Int 2014;2014:985408.

[32] Lawless N, Vegh P, O'Farrelly C, Lynn DJ. The role of microRNAs in bovine infection and immunity. Front Immunol 2014;5:611.

[33] Shivarov V, Bullinger L. Expression profiling of leukemia patients: key lessons and future directions. Exper Hematol 2014;42(8):651–60.

[34] Di Y, Lei Y, Yu F, Changfeng F, Song W, Xuming M. MicroRNAs expression and function in cerebral ischemia reperfusion injury. J Mol Neurosci: MN 2014;53(2):242–50.

[35] Guo CJ, Pan Q, Xiong H, Qiao YQ, Bian ZL, Zhong W, et al. Therapeutic potential of microRNA: a new target to treat intrahepatic portal hypertension? BioMed Res Int 2014;2014:797898.

[36] Li Z, Rana TM. Therapeutic targeting of microRNAs: current status and future challenges. Nat Rev Drug Discov 2014;13(8):622–38.

[37] Tong L, Yuan Y, Wu S. Therapeutic microRNAs targeting the NF-kappa B signaling circuits of cancers. Adv Drug Delivery Rev 2015;81C:1–15.

[38] Rostama B, Peterson SM, Vary CP, Liaw L. Notch signal integration in the vasculature during remodeling. Vasc Pharmacol 2014;63(2):97–104.

[39] Robinson HC, Baker AH. How do microRNAs affect vascular smooth muscle cell biology? Curr Opin Lipidol 2012;23(5):405–11.

[40] Rzucidlo EM, Martin KA, Powell RJ. Regulation of vascular smooth muscle cell differentiation. J Vasc Surg 2007;45 Suppl A:A25–32.

[41] Davis-Dusenbery BN, Wu C, Hata A. Micromanaging vascular smooth muscle cell differentiation and phenotypic modulation. Arterioscler Thromb Vasc Biol 2011;31(11):2370–7.

[42] Albinsson S, Suarez Y, Skoura A, Offermanns S, Miano JM, Sessa WC. MicroRNAs are necessary for vascular smooth muscle growth, differentiation, and function. Arterioscler Thromb Vasc Biol 2010;30(6):1118–26.

[43] Albinsson S, Skoura A, Yu J, DiLorenzo A, Fernandez-Hernando C, Offermanns S, et al. Smooth muscle miRNAs are critical for post-natal regulation of blood pressure and vascular function. PloS one 2011;6(4):e18869.

[44] Albinsson S, Sward K. Targeting smooth muscle microRNAs for therapeutic benefit in vascular disease. Pharmacol Res: Off J Italian Pharmacol Soc 2013;75:28–36.

[45] Xu N, Papagiannakopoulos T, Pan G, Thomson JA, Kosik KS. MicroRNA-145 regulates OCT4, SOX2, and KLF4 and represses pluripotency in human embryonic stem cells. Cell 2009;137(4):647–58.

[46] Boucher JM, Peterson SM, Urs S, Zhang C, Liaw L. The miR-143/145 cluster is a novel transcriptional target of Jagged-1/Notch signaling in vascular smooth muscle cells. J Biol Chem 2011;286(32):28312–21.

[47] Rangrez AY, Massy ZA, Metzinger-Le Meuth V, Metzinger L. miR-143 and miR-145: molecular keys to switch the phenotype of vascular smooth muscle cells. Circ Cardiovasc Genet 2011;4(2):197–205.

[48] Kang H, Hata A. MicroRNA regulation of smooth muscle gene expression and phenotype. Curr Opin Hematol 2012;19(3):224–31.

[49] Cordes KR, Sheehy NT, White MP, Berry EC, Morton SU, Muth AN, et al. miR-145 and miR-143 regulate smooth muscle cell fate and plasticity. Nature 2009;460(7256): 705–10.

[50] Xin M, Small EM, Sutherland LB, Qi X, McAnally J, Plato CF, et al. MicroRNAs miR-143 and miR-145 modulate cytoskeletal dynamics and responsiveness of smooth muscle cells to injury. Gene Dev 2009;23(18):2166–78.

[51] Long X, Miano JM. Transforming growth factor-beta1 (TGF-beta1) utilizes distinct pathways for the transcriptional activation of microRNA 143/145 in human coronary artery smooth muscle cells. J Biol Chem 2011;286(34):30119–29.

[52] Davis-Dusenbery BN, Chan MC, Reno KE, Weisman AS, Layne MD, Lagna G, et al. Down-regulation of Kruppel-like factor-4 (KLF4) by microRNA-143/145 is critical for modulation of vascular smooth muscle cell phenotype by transforming growth factor-beta and bone morphogenetic protein 4. J Biol Chem 2011;286(32):28097–110.

[53] Elia L, Quintavalle M, Zhang J, Contu R, Cossu L, Latronico MV, et al. The knockout of miR-143 and -145 alters smooth muscle cell maintenance and vascular homeostasis in mice: correlates with human disease. Cell Death Differ 2009;16(12):1590–8.

[54] Lovren F, Pan Y, Quan A, Singh KK, Shukla PC, Gupta N, et al. MicroRNA-145 targeted therapy reduces atherosclerosis. Circulation 2012;126(11 Suppl 1):S81–90.

[55] Boettger T, Beetz N, Kostin S, Schneider J, Kruger M, Hein L, et al. Acquisition of the contractile phenotype by murine arterial smooth muscle cells depends on the Mir143/145 gene cluster. J Clin Invest 2009;119(9):2634–47.

[56] Cheng Y, Liu X, Yang J, Lin Y, Xu DZ, Lu Q, et al. MicroRNA-145, a novel smooth muscle cell phenotypic marker and modulator, controls vascular neointimal lesion formation. Circ Res 2009;105(2):158–66.

[57] Torella D, Iaconetti C, Catalucci D, Ellison GM, Leone A, Waring CD, et al. MicroRNA-133 controls vascular smooth muscle cell phenotypic switch in vitro and vascular remodeling in vivo. Circ Res 2011;109(8):880–93.

[58] Xie C, Huang H, Sun X, Guo Y, Hamblin M, Ritchie RP, et al. MicroRNA-1 regulates smooth muscle cell differentiation by repressing Kruppel-like factor 4. Stem Cells Develop 2011;20(2):205–10.

[59] Chen J, Yin H, Jiang Y, Radhakrishnan SK, Huang ZP, Li J, et al. Induction of microRNA-1 by myocardin in smooth muscle cells inhibits cell proliferation. Arterioscler Thromb Vasc Biol 2011;31(2):368–75.

[60] Davis BN, Hilyard AC, Lagna G, Hata A. SMAD proteins control DROSHA-mediated microRNA maturation. Nature 2008;454(7200):56–61.

[61] Kang H, Davis-Dusenbery BN, Nguyen PH, Lal A, Lieberman J, Van Aelst L, et al. Bone morphogenetic protein 4 promotes vascular smooth muscle contractility by activating microRNA-21 (miR-21), which down-regulates expression of family of dedicator of cytokinesis (DOCK) proteins. J Biol Chem 2012;287(6):3976–86.

[62] Horita HN, Simpson PA, Ostriker A, Furgeson S, Van Putten V, Weiser-Evans MC, et al. Serum response factor regulates expression of phosphatase and tensin homolog through a microRNA network in vascular smooth muscle cells. Arterioscler Thromb Vasc Biol 2011;31(12):2909–19.

[63] Kim MH, Ham O, Lee SY, Choi E, Lee CY, Park JH, et al. MicroRNA-365 inhibits the proliferation of vascular smooth muscle cells by targeting cyclin D1. J Cell Biochem 2014;115(10):1752–61.

[64] Lee J, Lim S, Song BW, Cha MJ, Ham O, Lee SY, et al. MicroRNA-29b inhibits migration and proliferation of vascular smooth muscle cells in neointimal formation. J Cell Biochem 2014.

[65] Zhang P, Zheng C, Ye H, Teng Y, Zheng B, Yang X, et al. MicroRNA-365 inhibits vascular smooth muscle cell proliferation through targeting cyclin D1. Int J Med Sci 2014;11(8):765–70.

[66] Li P, Zhu N, Yi B, Wang N, Chen M, You X, et al. MicroRNA-663 regulates human vascular smooth muscle cell phenotypic switch and vascular neointimal formation. Circ Res 2013;113(10):1117–27.

[67] Li P, Liu Y, Yi B, Wang G, You X, Zhao X, et al. MicroRNA-638 is highly expressed in human vascular smooth muscle cells and inhibits PDGF-BB-induced cell proliferation and migration through targeting orphan nuclear receptor NOR1. Cardiovasc Res 2013;99(1):185–93.

[68] Chistiakov DA, Sobenin IA, Orekhov AN, Bobryshev YV. Human miR-221/222 in Physiological and Atherosclerotic Vascular Remodeling. BioMed Res Int.

[69] Davis BN, Hilyard AC, Nguyen PH, Lagna G, Hata A. Induction of microRNA-221 by platelet-derived growth factor signaling is critical for modulation of vascular smooth muscle phenotype. J Biol Chem 2009;284(6):3728–38.

[70] Liu X, Cheng Y, Zhang S, Lin Y, Yang J, Zhang C. A necessary role of miR-221 and miR-222 in vascular smooth muscle cell proliferation and neointimal hyperplasia. Circ Res 2009;104(4):476–87.

[71] Liu X, Cheng Y, Yang J, Xu L, Zhang C. Cell-specific effects of miR-221/222 in vessels: molecular mechanism and therapeutic application. J Mol Cell Cardiol 2012;52(1):245–55.

[72] Sun SG, Zheng B, Han M, Fang XM, Li HX, Miao SB, et al. miR-146a and Kruppel-like factor 4 form a feedback loop to participate in vascular smooth muscle cell proliferation. EMBO Rep 2011;12(1):56–62.

[73] Dong S, Xiong W, Yuan J, Li J, Liu J, Xu X. MiRNA-146a regulates the maturation and differentiation of vascular smooth muscle cells by targeting NF-kappaB expression. Mol Med Rep 2013;8(2):407–12.

[74] Chan MC, Hilyard AC, Wu C, Davis BN, Hill NS, Lal A, et al. Molecular basis for antagonism between PDGF and the TGFbeta family of signalling pathways by control of miR-24 expression. EMBO J 2010;29(3):559–73.

[75] Leeper NJ, Raiesdana A, Kojima Y, Chun HJ, Azuma J, Maegdefessel L, et al. MicroRNA-26a is a novel regulator of vascular smooth muscle cell function. J Cell Physiol 2011;226(4):1035–43.

[76] Slaby O, Svoboda M, Fabian P, Smerdova T, Knoflickova D, Bednarikova M, et al. Altered expression of miR-21, miR-31, miR-143 and miR-145 is related to clinicopathologic features of colorectal cancer. Oncology 2007;72(5-6):397–402.

[77] Wang A, Landen NX, Meisgen F, Lohcharoenkal W, Stahle M, Sonkoly E, et al. MicroRNA-31 is overexpressed in cutaneous squamous cell carcinoma and regulates cell motility and colony formation ability of tumor cells. PloS one 2014;9(7):e103206.

[78] Chen T, Yao LQ, Shi Q, Ren Z, Ye LC, Xu JM, et al. MicroRNA-31 contributes to colorectal cancer development by targeting factor inhibiting HIF-1alpha (FIH-1). Cancer Biol Therap 2014;15(5):516–23.

[79] Liu X, Cheng Y, Chen X, Yang J, Xu L, Zhang C. MicroRNA-31 regulated by the extracellular regulated kinase is involved in vascular smooth muscle cell growth via large tumor suppressor homolog 2. J Biol Chem 2011;286(49):42371–80.

[80] Cines DB, Pollak ES, Buck CA, Loscalzo J, Zimmerman GA, McEver RP, et al. Endothelial cells in physiology and in the pathophysiology of vascular disorders. Blood 1998;91(10):3527–61.

[81] Michiels C. Endothelial cell functions. J Cell Physiol 2003;196(3):430–43.

[82] Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. Circulation 2007;115(10):1285–95.

[83] 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(8):1164–73.

[84] Bevilacqua MP. Endothelial-leukocyte adhesion molecules. Ann Rev Immunol 1993;11:767–804.

[85] Salmi M, Jalkanen S. Cell-surface enzymes in control of leukocyte trafficking. Nat Rev Immunol 2005;5(10):760–71.

[86] Harris TA, Yamakuchi M, Ferlito M, Mendell JT, Lowenstein CJ. MicroRNA-126 regulates endothelial expression of vascular cell adhesion molecule 1. Proc Nat Acad Sci USA 2008;105(5):1516–21.

[87] Fish JE, Santoro MM, Morton SU, Yu S, Yeh RF, Wythe JD, et al. miR-126 regulates angiogenic signaling and vascular integrity. Develop Cell 2008;15(2):272–84.

[88] Wang S, Aurora AB, Johnson BA, Qi X, McAnally J, Hill JA, et al. The endothelial-specific microRNA miR-126 governs vascular integrity and angiogenesis. Develop Cell 2008;15(2):261–71.

[89] Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, Stone PH. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. J Am Coll Cardiol 2007;49(25):2379–93.

[90] Stone PH, Coskun AU, Kinlay S, Popma JJ, Sonka M, Wahle A, et al. Regions of low endothelial shear stress are the sites where coronary plaque progresses and vascular remodelling occurs in humans: an in vivo serial study. Eur Heart J 2007;28(6):705–10.

[91] Neth P, Nazari-Jahantigh M, Schober A, Weber C. MicroRNAs in flow-dependent vascular remodelling. Cardiovasc Res 2013;99(2):294–303.

[92] Ni CW, Qiu H, Jo H. MicroRNA-663 upregulated by oscillatory shear stress plays a role in inflammatory response of endothelial cells. Am J Physiol Heart Circ Physiol 2011;300(5):H1762–9.

[93] Zhou J, Wang KC, Wu W, Subramaniam S, Shyy JY, Chiu JJ, et al. MicroRNA-21 targets peroxisome proliferators-activated receptor-alpha in an autoregulatory loop to modulate flow-induced endothelial inflammation. Proc Nat Acad Sci USA 2011;108(25):10355–60.

[94] Wu W, Xiao H, Laguna-Fernandez A, Villarreal G, Jr., Wang KC, Geary GG, et al. Flow-dependent regulation of Kruppel-like factor 2 is mediated by microRNA-92a. Circulation 2011;124(5):633–41.

[95] Atkins GB, Jain MK. Role of Kruppel-like transcription factors in endothelial biology. Circ Res 2007;100(12):1686–95.

[96] Wentzel JJ, Chatzizisis YS, Gijsen FJ, Giannoglou GD, Feldman CL, Stone PH. Endothelial shear stress in the evolution of coronary atherosclerotic plaque and vascular remodelling: current understanding and remaining questions. Cardiovasc Res 2012;96(2):234–43.

[97] Fang Y, Shi C, Manduchi E, Civelek M, Davies PF. MicroRNA-10a regulation of proinflammatory phenotype in athero-susceptible endothelium in vivo and in vitro. Proc Nat Acad Sci USA 2010;107(30):13450–5.

[98] Qin X, Wang X, Wang Y, Tang Z, Cui Q, Xi J, et al. MicroRNA-19a mediates the suppressive effect of laminar flow on cyclin D1 expression in human umbilical vein endothelial cells. Proc Nat A Sci USA 2010;107(7):3240–4.

[99] Chen K, Fan W, Wang X, Ke X, Wu G, Hu C. MicroRNA-101 mediates the suppressive effect of laminar shear stress on mTOR expression in vascular endothelial cells. Biochem Biophys Res Commun 2012;427(1):138–42.

[100] Sun HX, Zeng DY, Li RT, Pang RP, Yang H, Hu YL, et al. Essential role of microRNA-155 in regulating endothelium-dependent vasorelaxation by targeting endothelial nitric oxide synthase. Hypertension 2012;60(6):1407–14.

[101] 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(4):643–8.

[102] Wynne BM, Chiao CW, Webb RC. Vascular smooth muscle cell signaling mechanisms for contraction to angiotensin II and endothelin-1. J Am Soc Hypertension: JASH. 2009;3(2):84–95.

[103] Nakashima H, Suzuki H, Ohtsu H, Chao JY, Utsunomiya H, Frank GD, et al. Angiotensin II regulates vascular and endothelial dysfunction: recent topics of angiotensin II type-1 receptor signaling in the vasculature. Curr Vasc Pharmacol 2006;4(1):67–78.

[104] Higuchi S, Ohtsu H, Suzuki H, Shirai H, Frank GD, Eguchi S. Angiotensin II signal transduction through the AT1 receptor: novel insights into mechanisms and pathophysiology. Clin Sci 2007;112(8):417–28.

[105] Zhu N, Zhang D, Chen S, Liu X, Lin L, Huang X, et al. Endothelial enriched microRNAs regulate angiotensin II-induced endothelial inflammation and migration. Atherosclerosis 2011;215(2):286–93.

[106] Valente AJ, Irimpen AM, Siebenlist U, Chandrasekar B. OxLDL induces endothelial dysfunction and death via TRAF3IP2: inhibition by HDL3 and AMPK activators. Free Rad Biol Med 2014;70:117–28.

[107] Qin B, Xiao B, Liang D, Xia J, Li Y, Yang H. MicroRNAs expression in ox-LDL treated HUVECs: MiR-365 modulates apoptosis and Bcl-2 expression. Biochem Biophys Res Commun 2011;410(1):127–33.

[108] Chinetti-Gbaguidi G, Colin S, Staels B. Macrophage subsets in atherosclerosis. Nat Rev Cardiology 2015;12(1):10–7.

[109] Tellides G, Pober JS. Inflammatory and immune responses in the arterial media. Circ Res 2015;116(2):312–22.

[110] Libby P, Aikawa M, Schonbeck U. Cholesterol and atherosclerosis. Biochim Biophys Acta 2000;1529(1-3):299–309.

[111] O'Connell RM, Rao DS, Chaudhuri AA, Baltimore D. Physiological and pathological roles for microRNAs in the immune system. Nat Rev Immunol 2010;10(2):111–22.

[112] Graff JW, Dickson AM, Clay G, McCaffrey AP, Wilson ME. Identifying functional microRNAs in macrophages with polarized phenotypes. J biol chem 2012;287(26): 21816–25.

[113] van Empel VP, De Windt LJ, da Costa Martins PA. Circulating miRNAs: reflecting or affecting cardiovascular disease? Curr Hypertension Rep 2012;14(6):498–509.

[114] Wei Y, Nazari-Jahantigh M, Neth P, Weber C, Schober A. MicroRNA-126, -145, and -155: a therapeutic triad in atherosclerosis? Arterioscler Thromb Vasc Biol 2013;33(3): 449–54.

[115] Wei Y, Schober A, Weber C. Pathogenic arterial remodeling: the good and bad of microRNAs. Am J Physiol Heart Circ Physiol 2013;304(8):H1050–9.

[116] Mosser DM. The many faces of macrophage activation. J Leukocyte Biol 2003;73(2): 209-12.

[117] O'Connell RM, Taganov KD, Boldin MP, Cheng G, Baltimore D. MicroRNA-155 is induced during the macrophage inflammatory response. Proc Nat Acad Sci USA 2007;104(5):1604–9.

[118] Ruggiero T, Trabucchi M, De Santa F, Zupo S, Harfe BD, McManus MT, et al. LPS induces KH-type splicing regulatory protein-dependent processing of microRNA-155 precursors in macrophages. FASEB J: Off Pub Fed Am Soc Experimental Biol 2009;23(9):2898–908.

[119] Ceppi M, Pereira PM, Dunand-Sauthier I, Barras E, Reith W, Santos MA, et al. MicroRNA-155 modulates the interleukin-1 signaling pathway in activated human monocyte-derived dendritic cells. Proc Nat Acad Sci USA. 2009;106(8):2735–40.

[120] Nazari-Jahantigh M, Wei Y, Noels H, Akhtar S, Zhou Z, Koenen RR, et al. MicroRNA-155 promotes atherosclerosis by repressing Bcl6 in macrophages. J Clin Investig 2012;122(11):4190–202.

[121] Louafi F, Martinez-Nunez RT, Sanchez-Elsner T. MicroRNA-155 targets SMAD2 and modulates the response of macrophages to transforming growth factor-{beta}. J Biol Chem 2010;285(53):41328–36.

[122] McCoy CE, Sheedy FJ, Qualls JE, Doyle SL, Quinn SR, Murray PJ, et al. IL-10 inhibits miR-155 induction by toll-like receptors. J Biol Chem. 2010;285(27):20492–8.

[123] Androulidaki A, Iliopoulos D, Arranz A, Doxaki C, Schworer S, Zacharioudaki V, et al. The kinase Akt1 controls macrophage response to lipopolysaccharide by regulating microRNAs. Immunity 2009;31(2):220–31.

[124] Yang K, He YS, Wang XQ, Lu L, Chen QJ, Liu J, et al. MiR-146a inhibits oxidized low-density lipoprotein-induced lipid accumulation and inflammatory response via targeting toll-like receptor 4. FEBS Lett 2011;585(6):854–60.

[125] Chen T, Huang Z, Wang L, Wang Y, Wu F, Meng S, et al. MicroRNA-125a-5p partly regulates the inflammatory response, lipid uptake, and ORP9 expression in oxLDL-stimulated monocyte/macrophages. Cardiovasc Res 2009;83(1):131–9.

[126] Taganov KD, Boldin MP, Chang KJ, Baltimore D. NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. Proc Nat Acad Sci USA 2006;103(33):12481–6.

[127] Raitoharju E, Lyytikainen LP, Levula M, Oksala N, Mennander A, Tarkka M, et al. miR-21, miR-210, miR-34a, and miR-146a/b are up-regulated in human atherosclerotic plaques in the Tampere Vascular Study. Atherosclerosis 2011;219(1):211–7.

[128] Guay C, Regazzi R. Circulating microRNAs as novel biomarkers for diabetes mellitus. Nat Rev Endocrinol 2013;9(9):513–21.

[129] Witwer KW. Circulating microRNA biomarker studies: pitfalls and potential solutions. Clin Chem 2015;61(1):56–63.

[130] Creemers EE, Tijsen AJ, Pinto YM. Circulating microRNAs: novel biomarkers and extracellular communicators in cardiovascular disease? Circ Res 2012;110(3):483–95.

[131] Mitchell PS, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova-Agadjanyan EL, et al. Circulating microRNAs as stable blood-based markers for cancer detection. Proc Nat Acad Sci USA 2008;105(30):10513–8.

[132] Bitzer M, Ben-Dov IZ, Thum T. Microparticles and microRNAs of endothelial progenitor cells ameliorate acute kidney injury. Kidney Int 2012;82(4):375–7.

[133] Fujita Y, Kuwano K, Ochiya T, Takeshita F. The impact of extracellular vesicle-encapsulated circulating microRNAs in lung cancer research. BioMed Res Int 2014;2014:486413.

[134] Kinet V, Halkein J, Dirkx E, Windt LJ. Cardiovascular extracellular microRNAs: emerging diagnostic markers and mechanisms of cell-to-cell RNA communication. Front Genet 2013;4:214.

[135] Turchinovich A, Weiz L, Burwinkel B. Extracellular miRNAs: the mystery of their origin and function. Trend Biochem Sci 2012;37(11):460–5.

[136] Russo F, Di Bella S, Nigita G, Macca V, Lagana A, Giugno R, et al. miRandola: extracellular circulating microRNAs database. PloS one 2012;7(10):e47786.

[137] Allegra A, Alonci A, Campo S, Penna G, Petrungaro A, Gerace D, et al. Circulating microRNAs: new biomarkers in diagnosis, prognosis and treatment of cancer (review). Int J Oncol 2012;41(6):1897–912.

[138] Jung HJ, Suh Y. Circulating miRNAs in ageing and ageing-related diseases. J Genet Genomic = Yi chuan xue bao. 2014;41(9):465–72.

[139] Van Aelst LN, Heymans S. MicroRNAs as biomarkers for ischemic heart disease. J Cardiovasc Trans Res 2013;6(4):458–70.

[140] Mayr M, Zampetaki A, Willeit P, Willeit J, Kiechl S. MicroRNAs within the continuum of postgenomics biomarker discovery. Arterioscler Thromb Vasc Biol 2013;33(2):206–14.

[141] Fichtlscherer S, Zeiher AM, Dimmeler S. Circulating microRNAs: biomarkers or mediators of cardiovascular diseases? Arterioscler Thromb Vasc Biol 2011;31(11):2383–90.

[142] Reid G, Kirschner MB, van Zandwijk N. Circulating microRNAs: association with disease and potential use as biomarkers. Crit Rev Oncol/Hematol 2011;80(2):193–208.

[143] Turchinovich A, Samatov TR, Tonevitsky AG, Burwinkel B. Circulating miRNAs: cell–cell communication function? Front Genet 2013;4:119.

[144] Zhang Y, Liu D, Chen X, Li J, Li L, Bian Z, et al. Secreted monocytic miR-150 enhances targeted endothelial cell migration. Mol Cell 2010;39(1):133–44.

[145] Zernecke A, Bidzhekov K, Noels H, Shagdarsuren E, Gan L, Denecke B, et al. Delivery of microRNA-126 by apoptotic bodies induces CXCL12-dependent vascular protection. Sci Signal 2009;2(100):ra81.

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