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MicroRNAs in Vascular Biology and Vascular Disease

Chunxiang Zhang

RNA and Cardiovascular Research Laboratory, Department of Anesthesiology, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, 185 South Orange Avenue, MSB-E548, Newark, NJ 07101, USA, zhangc3@umdnj.edu

Abstract

MicroRNAs (miRNAs) have emerged as a novel class of endogenous, small, non-coding RNAs that negatively regulate over 30% of genes in a cell via degradation or translational inhibition of their target mRNAs. Functionally, an individual miRNA is important as a transcription factor because it is able to regulate the expression of its multiple target genes. Recent studies have identified that miRNAs are highly expressed in vasculature and their expression is deregulated in diseased vessels. miRNAs are found to be critical modulators for vascular cell functions such as cell differentiation, migration, proliferation, and apoptosis. Accordingly, miRNAs are involved in the angiogenesis and in the pathogenesis of vascular diseases. miRNAs may serve as novel biomarkers and therapeutic targets for vascular disease. This review article summarizes the research progress regarding the roles of miRNAs in vascular biology and vascular disease.

Keywords

MicroRNAs; Gene Regulation; Vascular Biology; Vascular Disease

Introduction

MicroRNAs (miRNAs) are a class of endogenous, small, non-coding RNAs that can pair with sites in 3' untranslated regions in mRNAs of protein-coding genes to downregulate their expression [1]. miRNAs are initially transcribed by RNA polymerase II (Pol II) in the nucleus to form large pri-miRNA transcripts. The pri-miRNAs are processed by the RNase III enzymes, Drosha and Dicer, to generate 18- to 24-nucleotide mature miRNAs [1]. The first miRNA, lin-4, was discovered in *Caenorhabditis elegans* in 1993 [2, 3]. The presence of miRNAs in vertebrates was confirmed in 2001 [4]. Currently, more than 800 miRNAs have been cloned and sequenced in human [5], and the estimated number of miRNA genes is as high as 1,000 in the human genome [6]. More importantly, one miRNA is able to regulate the expression of multiple genes because it can bind to its mRNA targets as either an imperfect or a perfect complement. Thus, a miRNA can be functionally as important as a transcription factor [7]. As a group, miRNAs may directly regulate at least 30% of the genes in a cell [8]. It is therefore not surprising that miRNAs are involved in the regulation of all major cellular functions [9].

It is well established that vascular diseases such as atherosclerosis, coronary artery disease, post-angioplasty restenosis, transplantation arteriopathy, and diabetic vascular complication are among the leading causes of morbidity and mortality in developed countries. In addition, angiogenesis is a common vascular consequence in many diseases including cancer [10],

atherosclerosis [11], and ischemic heart disease [12]. Cell differentiation, migration, proliferation, and apoptosis of vascular smooth muscle cells (VSMCs) and endothelial cells (ECs) are critical cellular events responsible for the development of angiogenesis and vascular disease. Recent studies have demonstrated that miRNAs are highly expressed in vascular walls and their expression is deregulated in diseased vessels [13–15]. miRNAs are found to play important roles in angiogenesis and vascular disease via regulating vascular cell differentiation, migration, proliferation, and apoptosis through their target genes [13–18]. The current review article is for summarizing the research progress regarding the roles of miRNAs in vascular biology and vascular disease.

miRNAs in Angiogenesis

Angiogenesis is an important mechanism for the maintenance of adequate blood supply to the tissues both in normal development and in the process of diseases such as ischemic heart disease, cancer, and atherosclerosis [10–12]. The first evidence showing miRNAs in the regulation of angiogenesis came from Dicer knockout mice [17]. Dicer is a critical enzyme for miRNA synthesis [17]. These Dicer-deficient mice died early during development due to the thinning of vascular walls and severe disorganization of the network of blood vessels [17]. Similarly, knockdown of Dicer in both human and animal vascular ECs via RNAi approach significantly reduced EC migration, capillary sprouting, and tube formation [18]. Dicer knockout and knockdown accompanied the expression changes of a number of angiogenesis-related genes including vascular endothelial growth factor and its receptor, tek-TIE-2, Tie-1, endothelial nitric oxide synthase, and interleukin-8 [17, 18].

The above phenotypic change in angiogenesis observed in these Dicer-deficient animals and ECs led to an explosion in studying the biological roles of individual miRNAs in EC biology and angiogenesis. In this respect, Poliseno et al. [16] identified that miR-221 and miR-222 had significant inhibitory effects on EC migration, tube formation, and wound healing in cultured ECs. These investigators further identified that miR-221/miR-222-mediated effects on ECs occurred, at least in part, through their target gene, *c-Kit*. More recently, a series of studies were conducted by different research groups in this new research area to identify the angiogenesis-related miRNAs [18–30]. Based on the results, these miRNAs can be divided into two groups: pro-angiogenic miRNAs or anti-angiogenic miRNAs. Pro-angiogenic miRNAs include miR-126 [19, 20], miR-17-92 [21], Let-7 [17], miR-130a [22], miR-210 [23], miR-378 [24], and miR-296 [25]. In contrast, the current known anti-angiogenic miRNAs include miR-221/222 [16, 26, 27], miR-328 [28], miR-92a [29], and miR-214 [30]. The currently identified angiogenesis-related miRNAs and their target genes are listed in Table 1. It should be noted that the effects of these miRNAs on EC biology and angiogenesis are not only identified in cultured ECs in vitro but also in ischemia-induced angiogenesis in vivo using limb ischemia and myocardial infarction models [20, 29].

miRNAs in Vascular Disease

The formation of neointimal lesions is a common pathological feature of diverse vascular diseases. It is well established that neointimal formation is resulted from EC injury and activation followed by white blood cell infiltration, lipid deposition, and VSMC dedifferentiation, proliferation, and migration in the vascular walls. Ji et al. [13] were the first group to identify the potential involvement of miRNAs in vascular neointimal growth. Using microarray analysis, these investigators demonstrated that miRNAs were highly expressed in normal rat arteries. Interestingly, in vascular walls with neointimal growth induced by balloon-catheter angioplasty, many of the detected miRNAs are aberrantly expressed [13]. The broadly deregulated miRNAs in injured arteries indicated that multiple miRNAs are involved in vascular injury responses that match the complex feature of

neointimal growth in diverse vascular diseases in which multiple genes participated. The aberrant expression of miRNA was not limited to rat model. In mouse arteries with neointimal growth after ligation injury, both miR-143 and miR-145 were downregulated as reported by Cordes et al. [31] and our group [32]. Moreover, in atherosclerotic human and mouse arteries without mechanical injuries, some of miRNAs were also deregulated as demonstrated in recent reports by Elia et al. [33] as well as our group [32]. Table 2 shows the miRNAs that are highly expressed in vascular walls and are aberrantly expressed in animal and human arteries with neointimal lesion formation. The putative cellular functions of these miRNAs are also listed (Table 2).

VSMC dedifferentiation, migration, proliferation, and apoptosis are critical cellular events responsible for the development of a number of proliferative vascular diseases. Indeed, VSMCs are the major cells within neointimal lesions in these vascular diseases. The biological roles of miRNAs in VSMCs have been identified by recent studies [13, 14, 32–35]. We demonstrated that miR-21, a miRNA that is upregulated in vascular walls with neointima, was a critical regulator for VSMC proliferation and apoptosis [13]. In cultured cells, upregulation of miR-21 via pre-miR-21 resulted in an increased VSMC proliferation, but decreased VSMC apoptosis. In contrast, VSMC proliferation was decreased, but apoptosis was increased via miR-21 inhibition through its inhibitor. In addition, we identified that the target genes of miR-21 involved in miR-21-mediated cellular effects on VSMCs were phosphatase and tensin homology deleted from chromosome 10 (*PTEN*) [13] and programmed cell death 4 (*PDCD4*) [32]. In our study targeting miR-221/222, we identified that miR-221/222 were critical pro-proliferative miRNAs in cultured VSMCs via their target genes, *p27(Kip1)* and *p57(Kip2)* [14]. The proliferative effect of miR-221/222 on VSMCs was further confirmed by another independent research group in which Davis et al. demonstrated that miR-221 increased the proliferation and migration of VSMCs through its target gene, *p27(Kip1)* [33].

More recently, the roles of miR-145 and miR-143 in VSMC biology have received special attention because they are abundant miRNAs in normal vascular walls and their expression is downregulated in diseased arteries [13, 15, 31–33, 36, 37]. We identified that miR-145 was selectively expressed in VSMCs of arterial walls and its expression was significantly downregulated in differentiated, proliferative VSMCs [15]. Both in cultured cells in vitro and in balloon-injured rat carotid arteries in vivo, we demonstrated that miR-145 was a novel biomarker and a critical modulator for VSMC phenotype [15]. Indeed, the expression of miR-145 was consistent with that of VSMC differentiation marker genes, SM α -actin, calponin, and SM-MHC. Moreover, the expression of VSMC differentiation marker genes was significantly upregulated by overexpression of miR-145, but was downregulated by miR-145 inhibition. Furthermore, VSMC proliferation was inhibited by miR-145 overexpression via pre-miR145. To determine the potential gene targets of miR-145 in VSMCs, both bioinformatic and experimental approaches were applied. We identified that Kruppel-like factor 5 (KLF5) was one of the critical target genes responsible for miR-145-mediated cellular effects on VSMCs [15]. Although Kruppel-like factor 4 (KLF4) was also a potential target gene of miR-145 in VSMCs, the time course change of its expression in cultured VSMCs after PDGF stimulation and in balloon-injured rat carotid arteries did not match perfectly with the expression change of miR-145 [32]. Thus, the role of KLF4 in miR-145-mediated biological effects on VSMCs should be further studied. The role of miR-145 in VSMC biology was further confirmed by Cordes et al. [31]. These investigators demonstrated that KLF4 and calmodulin kinase IIdelta (CamkII δ) are two target genes of miR-145 in VSMCs [31]. In addition, they also found that myocardin may be a direct target gene of miR-145 in VSMCs. However, in contrast to the inhibitory effect of a miRNA on its target genes, overexpression of miR-145 increased the expression of myocardin. We also found that the expression of myocardin was increased in miR-145-overexpressed VSMCs

[15]. However, our explanation was that at least in part, the upregulated myocardin is induced by an indirect effect of miR-145 through its target gene KLF5 [15]. If myocardin is indeed a direct target of miR-145 but the expression is increased by miR-145, it could be a new discovery because recent studies revealed that some small RNAs may be able to increase their target gene expression via RNA activation mechanisms (RNAa) [38]. In addition to the above studies, Boettger et al. [36] identified that angiotensin-converting enzyme (ACE) is also a target gene of miR-145 related to its biological effect on VSMCs. More excitedly, miR-145 was found to play a critical role in keeping the contractive functions of VSMCs and vessels [36], which matched our finding regarding the role of miR-145 in VSMC phenotype. miR-143 is another important miRNA in VSMC biology [31, 33, 36, 37]. It was found that miR-143 was an important regulator for proliferation and contractive function of VSMC by targeting Elk-1 [31] and ACE [36]. The roles of miR-143 and miR-145 in VSMC biology were further verified by miR-143/145 knockout approach [33, 36, 37]. Boettger et al. [36] demonstrated that VSMCs from miR-143/145-deficient mice were locked in the synthetic state (dedifferentiated phenotype), which incapacitated their contractile abilities. The incomplete differentiation of VSMCs in miR-143/145-deficient mice was also demonstrated by Condorelli's group [33]. Disarray of actin stress fibers of VSMCs in miR-143/145-deficient mice was identified by Xin et al. [37]. In addition, decreased blood pressure was found in these miR-143/145-deficient mice due to the decreased contractile abilities of the vessels [36, 37]. The biological roles of miR-143/145 in VSMCs and their identified targets were summarized in Fig. 1.

miR-126 is also a well-studied miRNA in vascular biology. In addition to its critical roles in angiogenesis and vascular integrity by targeting *Spred1*, *PIK3R2/p85-beta*, *VEGF*, and *FGF* [19, 20, 39–41], miR-126 may also be a regulator for EC activation and vascular inflammation via its target, vascular cell adhesion molecule 1 (*VCAM-1*).

The effects of miRNAs on vascular disease have recently been intensively explored [13–15, 36–38, 42]. We demonstrated that miR-21, miR-221/222, and miR-145 were deregulated in balloon-injured rat carotid arteries [13–15]. Inhibition of the upregulated miR-21 [13] and miR-221/222 [14] inhibited vascular neointimal growth. In addition, the neointimal formation in carotid arteries was also significantly reduced by restoration of miR-145 after angioplasty [15]. The negative effect of miR-145 on vascular neointimal growth was also demonstrated in another study using the same rat model [33]. More recently, the role of miR-143/145 in neointimal formation was further confirmed using gene knockout approach in which Boettger et al. [36] found that spontaneous huge neointimal lesion formation was displayed in arteries from miR-143/145 knockout mice without any additional injuries. However, Xin et al. [37] reported that neointimal formation after carotid artery ligation injury was decreased in these miR-143/145 knockout mice. Obviously the result was different from that obtained in Dr. Braun's study [36] and also different from our unpublished data in mouse carotid artery guide-wire injury and air drying injury models using the pharmacological approaches. The mechanism for the different results is unclear. We think it might be related to the following reasons: First, miR-143/145 knockout may affect the normal development of VSMCs and vessels; thus, the real direct effect of miR-145 on vascular neointimal growth is affected. Thus, inducible miR-143/145 knockout should be needed to overcome the pitfall of the regular knockout approach. Second, neointimal formation in ligation model is dependent on the distance to the ligation site, which is difficult for the correct histological analysis. In addition, the neointimal response in carotid artery ligation model often has big difference even among the same group. Other injury models such as air drying injury and guide-wire injury (guide-wire injury should be performed in ApoE mice) should be tested in these knockout mice. More recently, Zernecke et al. [42] demonstrated that delivery of miR-126 by apoptotic body limited atherosclerosis,

promoted the incorporation of Sca-1+ progenitor cells, and conferred features of plaque stability in mouse models of atherosclerosis via CXCL12-dependent mechanisms.

Genetic variations of pre-miRNAs, mature miRNAs, and their target genes determined by gene polymorphisms and single-nucleotide polymorphisms have revealed that the variations of pre-miRNAs, mature miRNAs, and miRNA binding sites in their target genes are related to many human diseases such as cancer and heart disease [43–45]. It is well known that polymorphism ss52051869 in the 3' UTR of human SLC7A1 with the binding sites of miR-122 is related to human hypertension [46]. Polymorphism study revealed that the variants of the miR-122 binding sites of 3' UTR in SLC7A1 might be related to the development of hypertension in human [46]. More polymorphism studies on miRNAs and their targets involved in vascular diseases should be performed.

Unlike cancer tissues, human vessel tissues with vascular diseases are not easy to be obtained. However, exciting results from animal studies have revealed that many critical genes related to vascular diseases are regulated by miRNAs. Some miRNAs have strong effects on vascular cell functions and vascular lesions in animals. Limited human atherosclerotic studies have also revealed that multiple miRNAs are deregulated [32, 33]. Clearly, more clinical studies should be performed using human vessel tissues. In addition, human miRNA studies using blood cells isolated from patients with vascular diseases could be an alternative approach for the clinical studies in this area.

Conclusion and Perspective

miRNAs in vascular biology and vascular disease has emerged as a new research area. The initial exciting results have demonstrated that multiple miRNAs are involved in the development of both human and animal vascular diseases via regulating vascular cell differentiation, migration, proliferation, and apoptosis through their target genes. Several in vivo animal studies have revealed the promising therapeutic results in vascular disease. Thus, miRNAs may represent new biomarkers and therapeutic targets for diverse vascular diseases. miRNA-based therapy may have both advantages and disadvantages. As we know well, the vascular diseases are multifactorial complex diseases in which many genes are involved. miRNA-based therapy may have some advantages compared with those for other molecular targets because one endogenous miRNA can target its multiple target genes. On the other hand, multiple target genes might induce some unexpected side effects, and this could be the disadvantage [47]. However, as miRNAs are endogenous, restoration of the aberrantly expressed miRNAs to the physiological levels should not have major unexpected side effects.

miRNAs are aberrantly expressed in vascular diseases, some being upregulated and others downregulated. Thus, two major miRNA-based therapeutic strategies are restoring the expression of miRNAs reduced in diseases and, conversely, inhibiting overexpressed miRNAs. We should realize that we are still at the early stages in miRNA-based therapy. The following studies should be performed before it can be used in the clinic. First, the critical miRNAs responsible for the development of vascular diseases should be further identified. Second, the detailed cellular and molecular mechanisms of these critical miRNAs in the prevention and treatment of vascular diseases should be studied. Third, in addition to the biological effects of these miRNAs on ECs and VSMCs, their effects on other vascular disease-related cellular events should be identified. Fourth, although methods are available to downregulate miRNA in vivo, technology for upregulating miRNA in the vascular walls in vivo requires development. Finally, the potential side effects of miRNA-based therapy should be studied before application in the clinic.

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Fig. 1.

Regulation of vascular smooth muscle cell functions by miR-143 and miR-145. miR-143 and miR-145 are two abundant miRNAs in vascular smooth muscle cells (VSMCs). Kruppel-like factor 5 (*KLF5*), Kruppel-like factor 4 (*KLF4*), myocardin, and calmodulin kinase IIdelta (*CamkIIδ*) are found to be the target genes of miR-145, whereas Elk-1 is a target gene of miR-143 within VSMCs. In addition, angiotensin-converting enzyme (*ACE*) is target gene for both miR-143 and miR-145. These targets are able to regulate VSMC cell differentiation, proliferation, and contraction directly or indirectly via interaction with serum response factor (*SRF*)

Table 1

Angiogenesis-related miRNAs and their target genes

Pro-angiogenic miRNA	Target genes	Anti-angiogenic miRNAs	Target genes
miR-126	Spred1, PIK3R2/p85-beta, VEGF, FGF	miR-221	c-kit
miR-17-92	Tsp1, CTGF	miR-222	c-kit
Let-7	thrombospondin-1	miR-328	CD44
miR-130a	GAX, HOXA5	miR-92a	integrin subunit alpha5
miR-210	Ephrin-A3	miR-214	eNOS
miR-378	SuFu, Fus-1		
miR-296	HGS		

Table 2

Aberrantly expressed miRNAs in diseased vascular walls and their potential cellular functions

Upregulated miRNAs	Putative cellular functions	Downregulated miRNAs	Putative cellular functions
miR-21	Anti-apoptosis, anti-proliferation	miR-125a	Anti-proliferation
miR-31	Pro-proliferation, anti-metastasis	miR-125b	Anti-proliferation
miR-146	Anti-inflammation	miR-133a	Anti-proliferation, anti-fibrosis, pro-differentiation
miR-221	Anti- or pro-proliferation, Anti- or pro-migration	miR-143	Anti-proliferation
miR-222	Anti- or pro-proliferation, Anti- or pro-migration	miR-145	Pro-differentiation, anti-proliferation
miR-352	n/a	miR-347	n/a
		miR-365	n/a