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MicroRNAs and Endothelial (Dys) Function

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Abstract

Accumulating evidence indicates that microRNAs (miRs)—non-coding RNAs that can regulate gene expression via translational repression and/or post-transcriptional degradation—are becoming one of the most fascinating areas of physiology, given their fundamental roles in countless pathophysiological processes. The relative roles of different miRs in vascular biology as direct or indirect post-transcriptional regulators of fundamental genes implied in vascular remodeling designate miRs as potential biomarkers and/or promising drug targets. The mechanistic importance of miRs in modulating endothelial cell (EC) function in physiology and in disease is addressed here. Drawbacks of currently available therapeutic options are also discussed, pointing at the challenges and clinical opportunities provided by miR-based treatments.

Endothelial cells (EC) form the inner thin monolayer that acts as anatomic and functional interface between circulating fluid in the lumen and the rest of the vessel wall. The main functions of EC include regulation of vascular tone, fluid filtration, cell recruitment, hormone trafficking, and hemostasis (Santulli et al., 2009).

MicroRNAs (miRs) are small, generally non-coding RNAs, that regulate gene expression via post-transcriptional degradation or translational repression. Indisputably, miRs are fundamental regulators of numerous biological processes. More than 30,000 mature miR products have been identified (~200 in the human genome) and the number of published miR sequences continues to increase rapidly (Wronska et al., 2015). Importantly, several investigators determined that some transcripts previously identified as non-coding RNAs may actually encode micropeptides (Carninci et al., 2005; Andrews and Rothnagel, 2014; Anderson et al., 2015; Santulli, 2015a).

The key importance of miRs in endothelial physiology is clearly indicated by the phenotype obtained following the EC-specific inactivation of Dicer, an enzyme involved in miR biogenesis and processing which cleaves precursor-miRs to mature forms (Suarez et al., 2008; Wronska et al., 2015). The lack of Dicer in the endothelium leads to altered expression of fundamental regulators of endothelial function, including endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF) receptor 2, interleukin-8, Tie-1 and Tie-2. As mentioned above, vascular endothelium plays a pivotal role in regulating

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vessel biology and homeostasis. Alterations of its function partake in various cardiovascular disorders including hypertension, atherosclerosis, and impaired angiogenesis (Cimpean et al., 2013; Lampri and Elli, 2013; Santulli et al., 2012).

The Orchestrator of Endothelial Physiology: miR-126

Two independent research groups have established in 2008 that miR-126 is a master regulator of vascular integrity (Fish et al., 2008; Wang et al., 2008). It is encoded by intron 7 of the vascular endothelial-statin (VE-statin) gene, also known as EGF-like domain 7 (EGFL7), which is under the transcriptional control of the E-twenty-six family of transcription factors ETS1/2. In resting conditions ETS1 is expressed at a very low level while it is transiently highly expressed during angiogenesis or (re)-endothelialization. Therefore, during replicative senescence an augmented expression of ETS1 increases miR-126 levels. Intriguingly, one of the main targets of miR-126 is its own host gene EGFL7, which regulates the correct spatial organization of the endothelium. The cardiovascular phenotype of EGFL7 deficient mice is recapitulated by the ablation of miR-126, causing ruptured blood vessels, systemic edema, and multifocal hemorrhages (~40% of mir-126$^{-/-}$ mice die embryonically) (Wang et al., 2008).

miR-126 plays a crucial role in modulating vascular development and homeostasis, targeting specific mRNAs including the Sprouty-related protein 1 (SPRED-1), CXCL12, SDF-1, and phosphoinositol-3 kinase regulatory subunit 2 (PIK3R2) (Feng et al., 2015; Hu et al., 2015). Confirming its essential function in maintaining vascular integrity, among the numerous targets of miR-126 there is a key mediator of leukocyte adhesion and inflammation: vascular cell adhesion molecule 1 (VCAM-1). This miR has been also identified as an efficient marker in the detection and purification of EC (Miki et al., 2015), due to its abundance in these cells (Santulli et al., 2014).

Circulating miR-126 can be modulated by diverse stimuli inducing dissimilar cellular fates in different cell types. It acts as an intercellular messenger mainly released by EC and internalized by vascular smooth muscle cells (VSMC) and monocytes (Wang et al., 2008). A significant increase in circulating miR-126 has been detected in patients with acute myocardial infarction and angina whereas miR-126 down-regulation has been reported in plasma from patients with diabetes, heart failure, or cancer (Wronska et al., 2015). Circulating miR-126-3p has been shown to be a reliable biomarker of physiological endothelial senescence in normoglycemic elderly subjects and underlies a mechanism that may be disrupted in aged diabetic patients (Olivieri et al., 2014). Diabetes mellitus is known to lead to dysregulated activation of ETS, which in turn blocks the functional activity of progenitor cells and their commitment towards the endothelial cell lineage.

Remarkably, endothelial function can also be regulated by miRs not commonly expressed by EC. One of the best examples of this condition is given by miR-223, a critical regulator of cholesterol homeostasis. In particular, miR-223 is one of the most abundant miRs in HDL and is also present in LDL particles (Vickers et al., 2011). This miR is transferred within microvesicles and within HDL and LDL particles. The transfer of miR-223 from HDL to EC could be a potential mechanism underlying the anti-inflammatory properties of HDL (Novák

et al., 2015). Indeed, miR-223 targets NOD-like receptor pyrin domain containing 3 (NLRP3) and intercellular adhesion molecule I (ICAM-1), thereby suppressing leukocyte infiltration and inflammation intimately linked with atherosclerosis. Likewise, macrophages and platelets have been shown to produce—and transfer to other cells—microvesicles/exosomes containing miR-223, regulating post-transcriptionally gene expression. Specifically, the transfer of miR-223 to EC has been shown to increase the rate of apoptosis induced by advanced glycation products (Pan et al., 2014). Intriguingly, miR-223 is also involved in the development of insulin sensitivity and in the regulation of thrombosis and platelet function. Indeed, miR-223$^{-/-}$ mice receiving high-fat diet display profound insulin resistance, which has been attributed to an altered expression of the glucose transporter 4 (GLUT4).

A recent study has identified miR-19a as a specific molecular player in the functional association linking endothelial dysfunction, hyperlipidemia, inflammation, and atherosclerosis unraveling a vicious circle comprising the activation of endothelial Hif-1a hyperlipidemia and the upregulation of miR-19a, promoting CXCR2-dependent adhesion of monocytes by increasing endothelial CXCL1 expression (Akhtar et al., 2015). Of note, miRs are also involved in the VSMC phenotypic switch between the quiescent (pro-contractile, differentiated) state and the proliferative (pro-synthetic, de-differentiated) state (Liu et al., 2013), a determinant step in the pathophysiology of atherosclerosis.

Angiogenesis and miRs

Various events are involved in angiogenesis, including EC division, selective degradation of the basal membrane and the surrounding extracellular matrix, with the subsequent EC migration and the formation of neovessels (Berthod, 2013; Duscha et al., 2013; Santulli, 2014). A proper endothelial maturation is finely guided by a variety of signals from other cell types including VSMC and pericytes: the communication between these cells eventually leads to the maturation and stabilization of the vessel (Santulli et al., 2011, 2013; Lampri and Elli, 2013). Numerous studies investigated the mechanistic role of miRs in regulating EC function during angiogenesis; they are summarized, alongside with their main target genes, in Table 1.

Mounting evidence indicates that miRs can be considered as a language that allows cells to communicate: indeed, as mentioned above, some cells can release miRs to specifically modulate physiological processes in recipient cells. Ergo, miRs have inter-cellular signal transduction capabilities. For instance, EC/VSMC contacts induce the activation of miR-143/145 transcription in VSMC, promoting the transfer of these miRs to the endothelium: VSMC can deliver miR-143/145 to EC via fine intercellular tubes, named membrane nanotubes or tunneling nanotubes (Climent et al., 2015). The level of miR-143/145, but not that of its precursor molecule (pri-miR-143/145), is significantly augmented in EC when these cells are co-cultured with VSMC. A molecular pathway has been proposed, in which secretion of transforming growth factor-β (TGF-β) by EC stimulates the transfer of miR-143/145 from VSMC to EC. Once in the EC, miR-143/145 represses hexokinase II and integrin β8 and thereby the angiogenic potential of the recipient cell (Climent et al., 2015). The expression of miR-143/145 in EC could not be achieved by

the simple transfer of conditioned medium or VSMC-derived exosomes and was not sensitive to gap junction uncoupling agents—both exosomes and gap junctions had been reported as potential routes for intercellular transfer of miRs. Instead, the transfer of miR-143/145 was sensitive to lantrunculin A, an inhibitor of the formation of tiny membrane connections among cultured cells. High-resolution imaging allowed the direct visualization of tunneling nanotubes between EC and VSMC and the transport of miRs within them (Climent et al., 2015). Supporting these results, the intercellular transfer of miRs through tunneling nanotubes had been previously reported in ovarian cancer (Thayanithy et al., 2014).

The actual role of miR-155 in angiogenesis deserves to be addressed in more detail. This so-called “angiomiR” is expressed on the BIC locus on chromosome 21, and was recognized in 2007 as a translational repressor of the type I angiotensin II receptor (Martin et al., 2007). A study in brain microvasculature reported an attenuating effect of miR-155 on EC morphogenesis (Roitbak et al., 2011). A significant downregulation of miR-155 has been identified during hindlimb ischemia. Correspondingly, inhibition of miR-155 in EC has a stimulatory effect on proliferation and angiogenic tube formation via derepression of its direct target gene type I angiotensin II receptor. Nevertheless, miR-155$^{-/-}$ mice exhibit an unexpected phenotype in vivo, with a strong reduction of blood flow recovery after femoral artery ligation (arteriogenesis) dependent on the attenuation of leukocyte-endothelial interaction and a reduction of proarteriogenic cytokine expression. Consistently, miR-155-deficient macrophages exhibit a specific alteration of the proarteriogenic cytokine expression profile, which is partly mediated by the direct miR-155 target gene SOCS-1. Therefore, miR-155 exerts an antiangiogenic but proarteriogenic function in the regulation of neovascularization via the suppression of divergent cell-specific target genes and that its expression in both EC and bone marrow-derived cells is essential for arteriogenesis in response to hindlimb ischemia (Pankratz et al., 2015).

Hypertension and miRs

Essential hypertension affects approximately a billion people worldwide and is considered to be causing more than 7 million deaths per year (Santulli, 2013). It is a complex heritable trait involving multiple genes that interact with environmental factors. Notably, only up to 2.2% of inter-individual variance in blood pressure (BP) may be explained by common single nucleotide polymorphisms (SNPs) associated with hypertension identified by genome-wide association (GWA) studies (Ehret et al., 2011; Marques et al., 2015). This aspect and the fact that coding regions account for less than 2% of the entire human genome support the theory that other mechanisms besides coding genes contribute to BP regulation. The mechanistic importance of non-coding regions of the genome in the pathophysiology of hypertension has been suggested by several investigators. In particular, the role of miRs—which represent only a small fraction of the non-coding RNAs—in the regulation of BP has emerged from seminal preclinical studies in which Dicer, the endoribonuclease that processes double-stranded RNA including pre-miRs, has been deleted in VSMC (Albinsson et al., 2011) or in juxtaglomerular cells, the renal cells that produce renin, the rate-limiting enzyme of the renin-angiotensin-aldosterone system (RAAS) (Sequeira-Lopez et al., 2010). Both murine models displayed a drop in BP. A less pronounced reduction in BP values was

observed in the miR-143/miR-145 knockout mouse, which also exhibited thin arteries with an overall reduced vascular tone (Xin et al., 2009).

Animal studies provided functional insights on the role of miRs in hypertension and also allowed to test miR-based therapeutic approaches to treat such a disease. For instance, a neurogenic model of hypertension with marked circadian elevation of BP, the Schlager BHP/2J mouse, exhibits low levels of miR-181a and high renin mRNA during the active period (Head et al., 2015). This is consistent with the down-regulation of miR-181a observed in kidneys of hypertensive patients (Marques et al., 2015). When treated with a miR-181a mimic, a reduction in BP and renal renin mRNA were observed (Head et al., 2015). Another example of therapeutic use of a miR in hypertension is miR-22, targeting chromogranin A mRNA, which has been associated with human hypertension (Sahu et al., 2010). Spontaneously hypertensive rats (SHR) treated with miR-22 inhibitor displayed a decrease in BP (Friese et al., 2013). Interestingly, a polymorphism in the 3′UTR of chromogranin A, which increases the binding of miR-22, has been identified in SHR (Friese et al., 2013).

Studies in rodents greatly contributed also to the identification of several miRs implicated in the pathogenesis of pulmonary hypertension, including miR-21, miR-26a, miR-29a-3p, miR-30c, miR-17-92, miR-96, miR-125a, miR-126, miR130-301, miR143/145, miR-204, miR-206, miR-210, miR-223, miR-424, and miR 503 (Kim et al., 2013; Potus et al., 2014; Courboulin et al., 2015; Luo et al., 2015; Meloche et al., 2015; Schlosser et al., 2015; Tang et al., 2015). However, discordant results have been found when comparing preclinical and clinical studies, due to the existence of multiple experimental models of pulmonary hypertension (Schlosser et al., 2015).

Some miRs have been shown to partake into the pathogenesis of essential hypertension due to their ability in modulating the expression of key molecules involved in the regulation of vascular tone. For instance, miR-125a-5p and miR125b-5p suppress endothelin-1 expression in EC (Li et al., 2010). These findings are supported by the decreased levels of miR125a/b in hypertensive rats. Another example is given by miR-155, which can modulate the expression of two main players in vascular homeostasis, namely endothelial nitric oxide synthase (eNOS) and type I angiotensin II receptor (Sun et al., 2012; Pankratz et al., 2015).

Most recently, Liao and colleagues demonstrated that Let-7g, one of the members of the most studied and highly conserved miRs, is able to preserve endothelial function and suppress inflammation induced by metabolic dysregulation (Liao et al., 2014). Using both in vivo experiments in animals and samples from patients, Let-7g was shown to finely modulate the TGF-β/plasminogen activator inhibitor 1 (PAI-1) axis (Liao et al., 2014).

Furthermore, independent research groups have sought to directly study the association of miRs and hypertension in humans, mostly focusing on miRs as potential biomarkers, as summarized in Table 2. Indeed, miRs in biological fluids are protected from endogenous RNase-activity because they are carried in extracellular vesicles, RNA-binding proteins and lipoprotein complexes. These miRs are therefore considered unique and highly stable also in extreme conditions (Tijsen et al., 2012; Marques et al., 2015).

Three miRs were found to be up-regulated in hypertension via a microarray analysis in a Chinese population: miR-210, miR-425, and miR-505 (Yang et al., 2014). In particular, levels of miR-505 were consistently higher in other cohorts of hypertensive patients and this miR impairs EC migration and tube formation via the regulation of the gene encoding for fibroblast growth factor 18 (*FGF18*) (Yang et al., 2014).

A genome-wide analysis compared miR expression in plasma from hypertensive and normotensive subjects identifying 27 differentially expressed miRs (9 were up-regulated and 18 were down-regulated in hypertensive patients (Li et al., 2011)). Three miRs were then validated using qPCR: hcmv-miR-UL112, miR-296–5p, and let-7e. Intriguingly, hcmv-miR-UL112 is a human cytomegalovirus (CMV)–encoded miR that interacts with interferon regulatory factor-1, a receptor involved in infectious and inflammatory responses. Moreover, high titres of CMV have been found in hypertensive patients, leading to the speculative conjecture that CMV could contribute to hypertension by modulating miR pathways.

A recent study aiming to investigate the differential expression of hypertension-associated miRs in the plasma of patients with white coat hypertension revealed that miR-21, miR-122, miR-637, and let-7e are up-regulated in hypertensive subjects, whereas miR-122 and miR-637 are higher in white-coat patients than in control subjects (Cengiz et al., 2015). BP values were negatively correlated with miR-296-5p.

Interestingly, miR-296-5p was downregulated in hypertensive patients but up-regulated in white-coat hypertensives. The authors concluded that the expression analysis of miR-296-5p and miR-637 allows to distinguish between white-coat and non-white-coat hypertensive individuals (Cengiz et al., 2015).

In a report evaluating metabolic syndrome and its risk factors, differentially expressed miRs were identified in the blood and in exosomes isolated from serum of healthy controls compared with patients with metabolic syndrome, type 2 diabetes, hypercholesterolemia or hypertension (Karolina et al., 2012). The analysis revealed that miR-150, miR-192, and miR-27a were down-regulated in subjects with hypercholesterolemia or hypertension; miR-130a, miR-195, and miR-92a were up-regulated in patients with hypertension and with metabolic syndrome and positively correlated with BP values (Karolina et al., 2012). Consistent with these results, preclinical investigations have demonstrated that miR-27a is down-regulated in aortas of spontaneously hypertensive rat (SHR) compared to Wistar–Kyoto (WKY) normotensive animals (Gu et al., 2014). On the other side, the finding of the upregulation of miR-92a, predicted to target angiotensin II (Ang II) receptor type I (Karolina et al., 2012), is somehow in contrast with studies in mice deficient in miR-92a, which do not exhibit significant changes in BP (Charan Reddy, 2015).

Most recently, Kriegel and colleagues identified 35 miR-target pairs, in which mRNA encoded by hypertension-related genes was suppressed by endogenous miRs in human vascular EC (Kriegel et al., 2015). Such a finding indicates widespread, tonic control of gene expression relevant to BP regulation by endothelial miRs.

Several investigators have also analyzed whether SNPs in miR sequences (Fu et al., 2014) or in the 3′ untranslated region (UTR) of a messenger RNA (mRNA) of genes known to be

functionally involved in the regulation of BP (Marques et al., 2015) were associated with hypertension, yielding encouraging findings (Fu et al., 2014; Marques et al., 2015). For instance, miR-155 binds more efficiently to the A allele than to the C allele at position +1166 of the SNP rs5186 in the 3′UTR of the Angiotensin II Receptor 1 mRNA. The C allele is also more prevalent in hypertensive patients than in normotensive subjects (Sethupathy et al., 2007). Additionally, SNPs in the arginine vasopressin 1A receptor (AVPR1A) gene, bradykinin 2 receptor (BDKRB2) gene and thromboxane A2 receptor (TBXA2R) gene can modify the binding site for several miRs (Nossent et al., 2011).

Endothelial miRs in the Clinical Scenario: New Hopes in Interventional Cardiology

Percutaneous coronary intervention (PCI) is one of the most commonly performed interventions (Stefanini and Holmes, 2013), representing the main option for revascularization in cardiovascular disease (Stefanini and Holmes, 2013). Millions of procedures to intervene on occlusive vascular lesions are performed worldwide each year (~700,000 angioplasties are performed annually only in US) and 70–90% of all angioplasty patients receive a stent (Santulli, 2013), inserted permanently at the site of the vascular blockage to form an internal scaffolding that keeps the angioplastied vessel from closing.

Recurrent lumen narrowing has been a substantial limitation of PCI from its inception. A major breakthrough in the field was the introduction of bare metal stents (BMS), to prevent the elastic recoil of the treated vessels (Sigwart et al., 1987). However, the major drawback of this procedure is the induction of proliferation/migration and subsequent accumulation of VSMC, macrophages, and lymphocytes in the arterial wall, eventually leading to restenosis. To reduce rates of restenosis, drug-eluting stents (DES) were introduced in the clinical scenario (Marks, 2003), in order to deliver in situ drugs that could inhibit cell proliferation. Nevertheless, concerns have been raised over the long-term safety of DES, with particular reference to stent thrombosis, essentially attributable to impaired re-endothelization caused by the non-selective anti-proliferative properties of DES. Hence, when the obstacle of restenosis seemed finally overcome, enthusiasm and euphoria were considerably tempered by epidemiologic data reporting that DES did not ameliorate mortality rates when compared to BMS (Wijns and Krucoff, 2006). Basic research revealed that the main reason underlying these findings was the non-selective properties of the antiproliferative drugs eluted by the stents, thereby inhibiting not only the proliferation and migration of the cells responsible for restenosis (primarily VSMC), but also the growth and mobility of EC, indispensable for the healing of the vessel following stent implantation. Ergo, the lack of proper endothelial coverage eventually leads to an increased risk of thrombosis, with catastrophic clinical consequences for the patients.

The effect of stent deployment on EC behavior remains poorly understood. Stent implantation and balloon angioplasty lead to mechanical damage of the thin endothelial layer. Endothelial denudation and medial wall injury are generally considered the initial effects of angioplasty-induced injury (Popma and Topol, 1990; Chaabane et al., 2013). Given the essential role of EC in suppressing inflammation and thrombosis and overall in

controlling vascular tone and function, the restoration of a healthy endothelial layer is an imperative therapeutic goal in order to prevent restenosis and to avoid the detrimental consequences of in-stent thrombosis (Santulli et al., 2014). Unquestionably, re-endothelialization of injured coronary arteries is affected by the presence of a stent since such a structure provides a non-physiological surface for adhesion and generates perturbations in blood flow (Alexander, 2004). Notably, drugs eluted by the stents currently available in clinical practice—including rapamycin (sirolimus), everolimus, zotarolimus, umirolimus (biolimus A9), novolimus, myolimus, paclitaxel—are not able to differentiate EC from VSMC, T-cells or macrophages. Therefore the inhibition of proliferation and migration affects all these cellular types, leading to an increased risk for late thrombosis, due to delayed/incomplete re-endothelization. Thus, impaired endothelial coverage after angioplasty prolongs the window of vulnerability to thrombosis, requiring thereby a prolonged dual anti-platelet therapy.

Diverse vasculoprotective methods have been proposed to overcome the restenosis problem following PCI, in order to preserve endothelial function (Kipshidze et al., 2004; Yu et al., 2007; Torella et al., 2009). However, vascular restenosis and thrombosis continue to be a major problem in interventional cardiology, limiting the actual effectiveness of revascularization procedures. The ideal DES should display a selective anti-proliferative effect on VSMC, macrophages, and T-lymphocytes, without affecting EC (Stefanini and Holmes, 2013).

Since EC injury is a fundamental element in the pathophysiology of atherogenesis (Cirillo et al., 2015), understanding EC repair is of critical importance in developing therapeutic approaches to preserve endothelial integrity and vascular health. In this sense miRs and their intrinsic properties represent an ideal opportunity to specifically attenuate neointimal formation. Several miRs have been implicated in restenosis after interventional endothelial injury. For instance, inducing miR-221 in VSMC causes $p27^{Kip1}$ inhibition (Davis et al., 2009), thereby increasing VSMC proliferation; on the contrary, overexpression of miR-145 reduces neointima formation in response to balloon injury (Cheng et al., 2009). Antisense knockdown of miR-21, which is moderately increased after vessel injury (Ji et al., 2007), has been shown to blunt the formation of neointimal lesions in response to balloon injury and the knockout of miR-21 attenuates post-stenting restenosis modulating inflammation and VSMC response (McDonald et al., 2015). The mechanistic role of miRs in the restenosis process has been also confirmed by the identification of multiple miRs (including miR-21, miR-146, and miR142-3p) aberrantly expressed in stented swine arteries (McDonald et al., 2015).

Harnessing the EC-specific expression of miR-126, we were able to obtain in one fell swoop both the inhibition of restenosis, targeting VSMC, and the prevention of restenosis and thrombosis, preserving the endothelial function (Santulli et al., 2014). A major challenge remains the delivery of miR-based therapies. Indeed, while in preclinical studies, miR mimetics and antagomiRs (chemically derived oligonucleotides that have been developed in order to specifically silence miRs) have been successfully (Care et al., 2007) delivered systemically (intravenously injected), they are preferentially targeted to liver, spleen, and kidney. The specific application of miR-based agents to the vasculature, for instance during

PCI, can be considered as an effective therapeutic strategy. The direct intravascular delivery could be combined to new-generation bioresorbable stents with biodegradable scaffolds (Ellis et al., 2015; Kraak et al., 2015; Santulli, 2015b). Other potential alternatives include the stabilization of miR-based agents: various chemical modifications of nucleotides can enhance their stability *in vivo*, for instance by using cholesterol-conjugated, 2′-O-methyl–modified antagomiRs; miR-based drugs can be also conjugated to targeting molecules including antibodies, peptides, or other bioactive molecules, which may promote the specific homing to the site of the injury.

Conclusions

This review highlights the complex interactions linking miRs, expression of genes, and molecular pathways leading to endothelial dysfunction. The potential therapeutic use of miRs is currently being explored through several approaches, including inhibition and over-expression, in many cardiovascular disorders.

Acknowledgments

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TABLE 1

Angiogenesis and miRs

Pro-angiogenic miRs	**Target gene**	**Ref.**
miR-9	*SOCS5*	Zhuang et al. (2012)
miR-10a	*MAP3K7; HOXA1; bTRC*	Fang et al. (2010)
miR-21	*STAT3*	Liu et al. (2015)
miR-23/27	*SEMA6A; SPROUTY2*	Zhou et al. (2011a)
miR-107	*DICER1*	Li et al. (2015)
miR-126	*PI3KR2; SPRED1;VCAM1; SDF1*	Nicoli et al. (2010)
miR-130	*HOXA5, GAX*	Li et al. (2015)
miR-132/212	*RASA1, SPRED2*	Lei et al. (2015)
miR-210	*EFNA3*	Wang et al. (2013)
miR-217	*SIRT1- FOXO/eNOS*	Menghini et al. (2009)
miR-424	*HIF-1α*	Kim et al. (2013)
miR891a-5p	*NF-κB*	Yao et al. (2015)
Anti-angiogenic miRs		
miR-17	*JAK-1*	Katz et al. (2014)
miR-21	*RhoB;PPARγ*	Zhou et al. (2011b)
miR-24	*GATA-2; PAK4*	Zhou et al. (2014)
miR-92a	*SIRT1; ITGA5; KLF4* and *MKK4*	Ohyagi-Hara et al. (2013)
miR-200	*Ets-1; IL-8; CXCL1*	Chan et al. (2011)
miR-221/222	*STA5a; c-KIT; eNOS*	Nicoli et al. (2012)
miR-492	*eNOS*	Patella et al. (2013)
14q32 miR cluster (329, 487b, 494, 495)	Multiple neovascularization genes	Welten et al. (2014)
miR-497	*VEGFR2*	Tu et al. (2015)
miR-505	*FGF18*	Yang et al. (2014)
miR-506	*SPHK1*	Lu et al. (2015)

EFNA3, Ephrin-A3; *eNOS*, Endothelial Nitric Oxide Synthase; *FGF18*, Fibroblast growth factor 18; *JAK1*, Janus kinase 1; *KLF4*, Kruppel-like factor 4; *PPAR-γ*, Peroxisome proliferator-activated receptor gamma; *RhoB*, Ras homolog gene family, member B; *SIRT1*, sirtuin (silent mating type information regulation 2 homolog) 1; *SOCS5*, suppressor of cytokine signaling 5; *PI3KR2*, phosphoinositol-3 kinase regulatory subunit 2; *RASA1*, RAS p21 protein activator; *SPRED2*, sprouty-related, EVH1 domain containing 1; *SEMA6A*, Semaphorin-6A; *SPHK1*, sphingosine kinase 1; *STAT3*, Signal transducer and activator of transcription 3; *VCAM-1*, vascular cell adhesion molecule 1; *VEGFR2*, vascular endothelial growth factor receptor 2.

TABLE 2

Regulation of miRs in human tissues during hypertension

miRs upregulated in hypertension	**Tissue**
miR-1, miR-21, miR-92a, miR-130a, miR-195, miR-221, miR-222, let-7e, hcmv-miR-UL112	Systemic circulation and urine
miR-21, miR-132, miR-196a, miR-451	Kidney
miR-132, miR-145, miR-212, miR-221, miR-222	VSMC
miR-132, miR-212	Heart
miRs downregulated in hypertension	
miR-9, miR-27a, miR-126, miR-133a, miR-143, miR-145, miR-150, miR-192, miR-296-5p	Systemic circulation and urine
miR-181a, miR-638, miR-663	Kidney

VSMC, vascular smooth muscle cell.