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MicroRNAs as regulators of endothelial cell functions in cardiometabolic diseases ☆

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ABSTRACT

Endothelial cells (ECs) provide nutrients and oxygen essential for tissue homeostasis. Metabolic imbalances and other environmental stimuli, like cytokines or low shear stress, trigger endothelial inflammation, increase permeability, compromise vascular tone, promote cell proliferation, and ultimately cause cell death. These factors contribute to EC dysfunction, which is crucial in the development of cardiometabolic diseases. microRNAs (miRNAs) are small non-coding RNAs that have important functions in the regulation of ECs. In the present review, we discuss the role of miRNAs in various aspects of EC pathology in cardiometabolic diseases like atherosclerosis, type 2 diabetes, obesity, and the metabolic syndrome, and in complication of those pathologies, like ischemia. We also discuss the potential therapeutic applications of miRNAs in promoting angiogenesis and neovascularization in tissues where the endothelium is damaged in different cardiometabolic diseases. This article is part of a Special Issue entitled: MicroRNAs and lipid/energy metabolism and related diseases edited by Carlos Fernández-Hernando and Yajaira Suárez.

1. Introduction

Cardiometabolic diseases are reaching epidemic proportions in both industrialized and developing countries [1,2]. Cardiometabolic diseases are a combination of metabolic abnormalities that are risk factors for cardiovascular disease. Indeed, defects in homeostatic regulation of cholesterol, fatty acids, and glycemia are associated with the major risk factors that are prevalent in atherosclerosis, type 2 diabetes, obesity, and metabolic syndrome [3–6].

The endothelium is the main regulator of vascular homeostasis. Endothelial cells (ECs) maintain a relaxed vascular tone and low levels of oxidative stress by releasing mediators such as nitric oxide (NO), prostacyclin (PGI2), and endothelin (ET-1), and controlling local angiotensin-II activity. The endothelium also actively regulates vascular permeability to plasma constituents, platelet and leukocyte adhesion and aggregation, and thrombosis [7–9]. All of the traditional cardiovascular risk factors (dyslipidemia, arterial hypertension, hyperglycemia, and diabetes) are associated with endothelial dysfunction. Oxidized low-density lipoproteins, the renin–angiotensin axis, and insulin resistance play important roles in the pathogenesis of impaired endothelial function [10–15]. When the endothelium is dysfunctional, it loses its physiological properties and this leads to a disruption of the balance between vasoconstriction and vasodilation, the initiation of a number of events that trigger activation and predispose the vessel wall to increased endothelial permeability, leukocyte adherence, endothelial proliferation, pro-oxidation, and thrombosis [7–9,11,13,15–19]. Therefore, endothelial dysfunction is an early step in the development of atherosclerosis and appears to be a consistent finding in patients with type 2 diabetes and obesity.

Despite aggressive treatment of the individual cardiometabolic risk factors, death from cardiometabolic conditions remains unacceptably high. Several agents, including statins and blockers/inhibitors of the renin–angiotensin–aldosterone system, can ameliorate endothelial dysfunction [12]. However, the improvement of endothelial function cannot be used as a surrogate end point to predict reduction in cardiovascular morbidity and mortality. Therefore, there is an urgent need to identify new strategies for treating and preventing cardiometabolic diseases. Recently, microRNAs (miRNAs) have gained considerable attention as potential therapeutic targets [20–22]. MiRNAs are evolutionary conserved small non-coding RNAs that regulate gene expression by mediating post-transcriptional silencing of target genes [23–25]. Since miRNAs are involved in fine-tuning of physiological responses, they have become of interest for diagnosis and therapy of a number of diseases including cardiometabolic diseases [26–30]. However, a clear understanding of the role of miRNAs in regulating endothelial function and dysfunction in cardiometabolic diseases may allow the development of preventive and early therapeutic measures.

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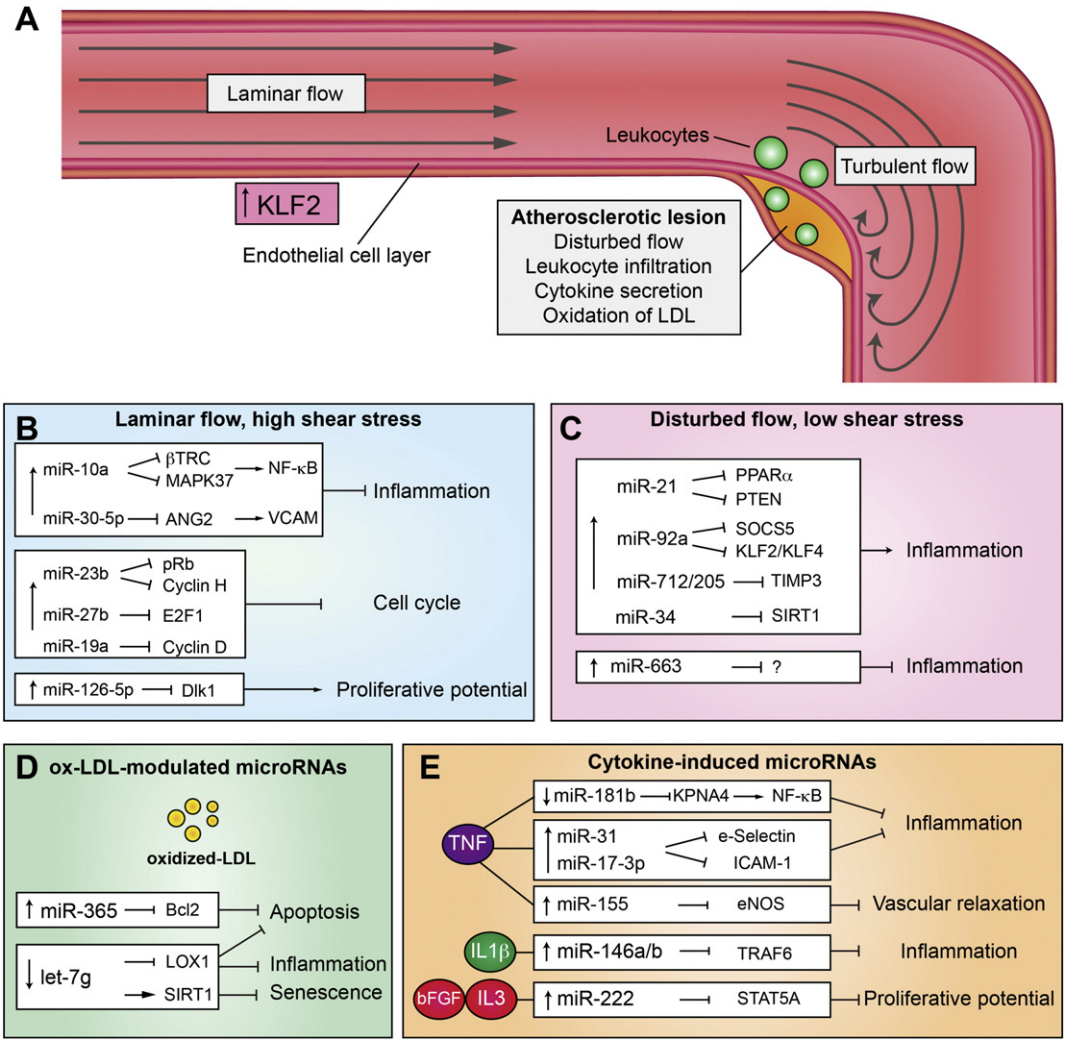

Fig. 1. microRNAs affect the functions of ECs in atherosclerosis. A. In unbranched arteries, ECs are subject to laminar flow and high shear stress. In atheroprone sites, where curvatures and arterial bifurcations permanently perturb the blood flow, ECs are exposed to low shear stress. This causes EC dysfunction and promotes the development of atherosclerotic lesions, where leukocytes infiltrate in the subendothelial space, secrete cytokines, and LDLs are oxidized, further promoting the inflammatory microenvironment. Most of the cues that favor EC dysfunction also affect the expression of specific miRNAs, which can either exacerbate or improve the phenotype of ECs. B. Laminar flow-induced miRNAs: miRNAs -10a, -30-5p, -23b, -27b, -19a, and -126-5p are induced in high shear stress in areas of laminar flow and through the action of their targets, they overall decrease inflammation, inhibit proliferation by blocking the cell cycle, and promote the proliferative potential. C. Disturbed flow-induced miRNAs: miRNAs -21, -92a, -712/205, -34 are induced in disturbed flow and promote inflammation. On the other hand, miR-663 is induced in low shear stress, but it inhibits inflammation through the action of unknown targets. D. Ox-LDL is responsible for the upregulation of miR-365, while it downregulates let-7g. Overall, the regulation of these miRNAs contributes to reduce inflammation, apoptosis, and inhibit senescence in ECs. E. Inflammatory cytokine-induced miRNAs: TNFα induces the expression of miR-31, miR-17-3p, miR-155, while it decreases the expression of miR-181b; IL1β increases miR-146a/b, while IL3 in conjunction with bFGF induces the expression of miR-222. The combined action of cytokine-induced miRNAs is to reduce inflammation, vascular relaxation, and inhibit the proliferation of ECs.

In the present review, we summarize the role of miRNAs in regulating EC functions linked to cardiometabolic diseases and discuss their therapeutic potential.

2. Endothelial miRNAs and atherosclerosis

Atherosclerosis is one of the leading causes of morbidity and mortality in Western countries [1], and it is characterized by the buildup of cholesterol-rich plaque in the arteries. Atherosclerosis causes narrowing of vessel lumen that in its extreme clinical manifestation results in ischemic symptoms, as well as plaque rupture or thrombosis that can lead to death by myocardial infarction or stroke [31]. The natural predisposition of the disease has its basis in the vulnerability of the endothelium in sites of turbulent arterial flow in bifurcated arteries [32]. The damaged endothelial layer at arterial branches, characterized by decreased endothelial nitric oxide synthase (eNOS) expression and increased nuclear factor kappa light chain enhancer of activated B cells (NF-κB) activity is more prone to infiltration of low-density lipoproteins (LDLs), leukocyte adhesion, and inflammation. In the subendothelial space, lipids in LDL become oxidized and the lysine residues in apolipoprotein B (ApoB) are modified [31]. The infiltration of LDL causes the recruitment of immune cells, mostly monocytes, to the sites of the lesions and is accompanied by secretion of inflammatory cytokines and recruitment of other immune cells [33]. Accumulation of inflammatory cells in the intima further promotes activation of ECs and, in advanced stages of plaque formation, smooth muscle cells (SMCs) proliferate and migrate into the subendothelial space where they promote the formation of a fibrous cap at the site of lesion by secreting extracellular matrix proteins [31].

2.1. Shear stress, endothelium, and microRNAs

Most atherosclerotic lesions occur at the site of arterial bifurcation, where the flow exhibits turbulent dynamics. The flow in linear arteries is laminar and in parallel layers, exerting a high, physiological shear stress on the endothelium. Up to 15% of genes regulated in physiological shear stress are modulated by the transcription factor Krüppel-like

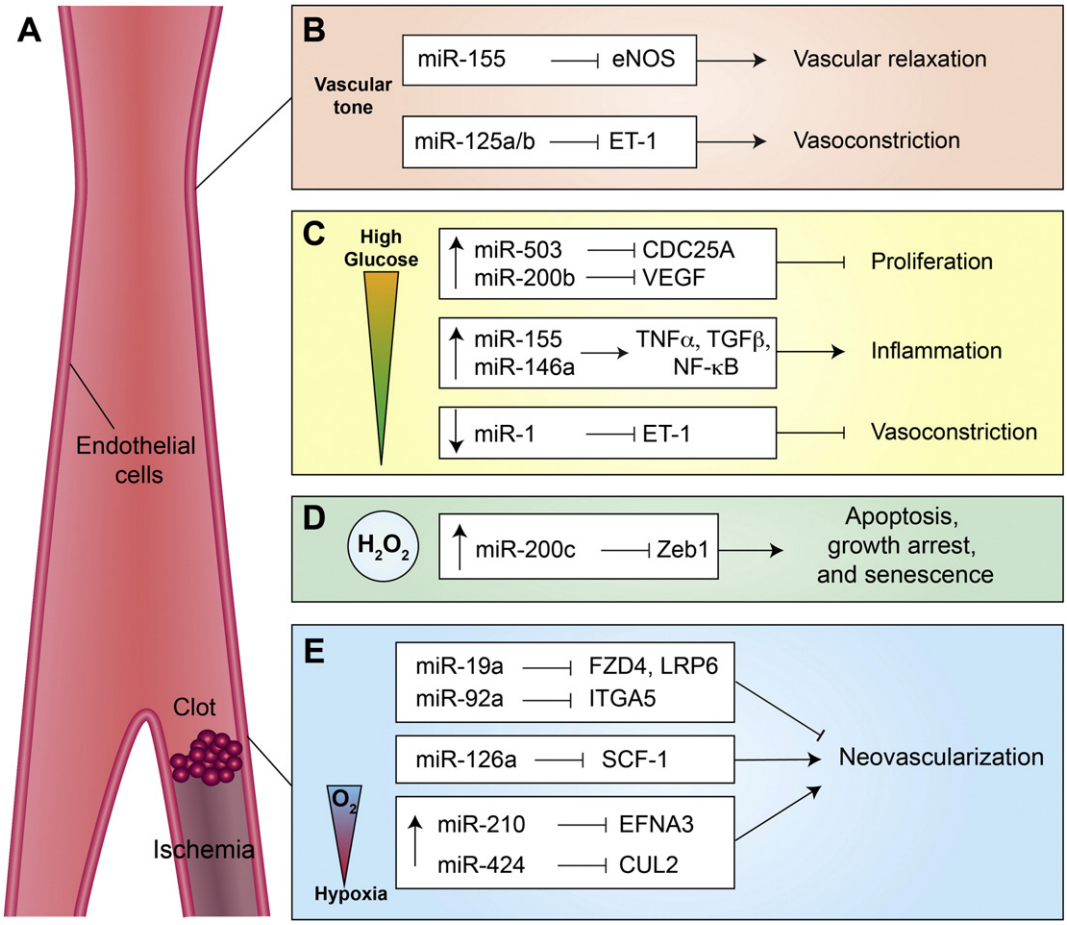

Fig. 2. Endothelial cell dysfunction in diabetes. A. Hyperglycemia and other pathological insults resulting from the metabolic syndrome can cause EC dysfunction. Often, diabetic patients have insufficient vasodilation, which can result in ischemia. Complications from atherosclerosis, like atherothrombotic clots, can block capillaries and further enhance ischemia in peripheral areas. miRNAs have been shown to be interesting targets to prevent endothelial dysfunction associated with complications of diabetes and the metabolic syndrome. B. miRNAs can modulate vascular tone. miR-155 and miR-125a/b can promote and reduce vasorelaxation, respectively. C. High glucose levels similar to the ones found in diabetic patients can modulate the expression of several miRNAs, like miRNAs-503, -200b, -155, -146a, -1, which overall promote inflammation, decrease proliferation, and induce vasoconstriction, therefore worsening EC dysfunction. D. Oxidative agents, like hydrogen peroxide, can induce the expression of miRNAs, like miR-200c, which promote apoptosis, growth arrest, and senescence. E. In ischemia, several miRNAs are upregulated by the low oxygen tension, or hypoxia. MiR-210 and miR-424 are induced and promote neovascularization by targeting EFNA3 and CUL2, respectively. Other miRNAs can be potential targets for neovascularization in ischemia, like miR-19a and miR-92a, which impair neovascularization, or miR-126-5a, which favors angiogenesis.

factor 2 (KLF2), which is induced by flow in a mechanism that involves AMP-activated protein kinase (AMPK) [34–36]. KLF2 in turn induces the flow-induced antioxidant transcription factor nuclear factor erythroid 2-related factor (Nrf2). The combined action of KLF2 and NRF2 results in quiescent endothelial phenotype that suppresses inflammation. In areas of bifurcation, there is disturbed flow that decreases shear stress [37,38]. The disturbed arterial flow in arterial braches results in EC death, inflammation, and activation of vascular repair [39–41].

Global ablation of miRNAs in ECs by silencing the miRNA processing enzyme Dicer increases the expression of the key shear stress transcription factor KLF2 [42], suggesting that miRNAs have a direct impact on flow-regulated genes by repressing KLF2 in shear stress. Additionally, hemodynamics itself has a profound effect on miRNA expression, and differentially regulated miRNAs contribute to the regulation of shear stress-mediated transcriptional programs (See Fig. 1 A-C).

2.1.1. High-shear stress-induced microRNAs

2.1.1.1. miR10a. miR-10a expression is decreased in area of disturbed flow in vivo, while it is highly present in areas of laminar flow [43]. In vitro analysis of ECs in which miR-10a is inhibited reveals that the NF-κB pathway is upregulated and transcription of NF-κB target genes is increased [43], suggesting that the absence of miR-10a in branching points makes ECs more susceptible to inflammation. MiR-10a exerts this effect on NF-κB by directly targeting the main regulators of nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor (IkB)α degradation, mitogen-activated kinase kinase kinase 7 (MAP3K7) and β-transducin repeat containing gene (β-TRC) [43]. Interestingly, it has been recently shown that ECs secrete extracellular vesicles that have potent anti-inflammatory activities that can be attributable in part to the transfer of miR-10a to monocytes/macrophages and suppression of several components of the NF-κB pathway, including interleukin-1 receptor-associated Kinase 4 (IRAK4), β-TRC, and MAP3K7 [44].

2.1.1.2. miR-30-5p family. The 3′UTR sequences of genes highly downregulated by KLF2 are enriched in miR-30-5p seed sequences. Consistently, miR-30 family members are induced in shear stress in a KLF2-dependent manner [45]. miR-30-5p members directly target angiopoietin 2, and, through Ang2 downregulation, miR-30 inhibits cell–cell adhesion molecules, like vascular cell adhesion molecule 1 (VCAM1), reducing EC inflammation and possibly conferring protection in atherogenesis [45].

2.1.1.3. miR-23b/miR-27b. The expression of miR-23b is in part stimulated by KLF2 in areas of pulsatile laminar shear flow [46,47]. Direct targeting of cyclin H mediated by miR-23b causes cell cycle arrest,

which is released when miR-23b is inhibited. Additionally, antago-miR-23 treatment in human umbilical vein ECs (HUVECs) increases the phosphorylation of the retinoblastoma protein (Rb) and stabilization of E2F transcription factor 1 (E2F1) in shear stress, causing the inhibition of cell cycle arrest seen in shear stress-exposed ECs. MiR-27b is similarly increased in high shear stress and it causes an increase in cell proliferation when inhibited, but it only affects E2F1 expression rather than Rb phosphorylation [46].

2.1.1.4. miR-19a. In areas of laminar flow, there is high shear stress and ECs are arrested in G1 phase due to the downregulation of cyclin D1. Laminar shear stress induces the expression of miR-19a, which directly targets cyclin D1 [48]. Administration of anti-miR-19a in human endothelial vein ECs releases cyclin D1 downregulation in shear stress and favors cell proliferation. The targeting activity of this miRNA on cyclin D1 is highly conserved among vertebrates; therefore, this mechanism could explain the loss of proliferative potential in ECs in areas of laminar flow across phyla [48].

2.1.1.5. miR-126. The precursor miRNA pre-miR-126 gives rise to two mature strands, miR-126-3p and miR-126-5p, which are among the most abundant miRNAs in ECs [49,50]. Furthermore, both strands (guide or miR-126-3p and passenger or miR-126-5p) are expressed at appreciable levels. The expression of the passenger strand miR-126-5p is increased in shear stress in a KLF2-dependent manner and it decreases in atheroprone areas where the flow is disturbed [51], suggesting an involvement of this miRNA in arterial response to shear stress. Whole body knockout of pri-miR-126a in mice favors atherosclerotic lesion, as endothelial repair in injured vascular bed is impaired. Treatment of animals with locked nucleic acid (LNA) inhibitor of miR-126-5p, but not of miR-126-3p, mimics the effects of the universal miR-126a knockout in increasing lesion area, promoting macrophage infiltration and decreasing endothelial repair [51]. The authors demonstrate that miR-126-5p exerts its action by downregulating the Notch1 inhibitor delta-like 1 homolog (Dlk1), therefore promoting Notch-mediated endothelial proliferative potential after injury. Consistently, administration of miR-126a-5p mimic protects against atherosclerotic lesions similarly to Dlk1 siRNA [51]. These data suggest that miR-126-5p mimic could be used to ameliorate atherosclerotic lesions at the sites where EC proliferation needs to be enhanced.

Overall, miRNAs, induced in high shear stress decrease inflammation (miR-10a, and miR-30-5p), suppress cell cycle (miR-19a and miR-23b), while increasing the proliferative potential of ECs. The action of high-shear stress-induced miRNAs is specific to ECs and it is protective to the integrity of endothelium. Mimic treatment of these miRNAs into atheroprone mice should ameliorate atherosclerotic lesions.

2.1.2. Disturbed flow-induced microRNAs

2.1.2.1. miR-21. In HUVECs under conditions of oscillatory shear stress, c-Jun binds to the promoter of miR-21, inducing its expression. Upregulation of miR-21 in response to disturbed arterial flow has a dual effect on ECs. By targeting peroxisome proliferator-activated receptor α (PPARα) mRNA, miR-21 upregulates AP-1 and induces the expression of VCAM1 and C-C motif chemokine 2/monocyte chemoattractant protein1- (CCL2/MCP1), therefore promoting inflammation, monocyte adhesion, and also amplifying its own expression [52]. On the other hand, miR-21 upregulation decreased apoptosis [53]. miR-21 targets phosphatase and tensin homolog (PTEN), which antagonizes phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/v-akt murine thymoma viral oncogene (Akt) pathway. miR-21 transfected in ECs promotes phosphorylation of eNOS and NO production, resulting in a further protection against apoptosis [53].

2.1.2.2. miR-92a. Turbulent flow in synergy with oxidated LDL treatment (ox-LDL) induces the expression of miR-92a in HUVECs in a signal transducer and activator of transcription 3 (STAT3)-dependent manner [42,54,55]. Consistently, miR-92a is upregulated in atherogenic sites in LDL receptor-deficient mice ($LDLR^{-/-}$) fed a high-fat diet and in swine inner aortic arch endothelium [54,55]. Interestingly, inhibition of miR-92a in a murine model of atherosclerosis blunts inflammatory cytokine secretion in aortas, decreases leukocyte recruitment and adhesion, and prevents endothelial dysfunction, overall decreasing atherosclerotic lesions [54]. miR-92a directly downregulates the anti-inflammatory gene suppressor of cytokine signaling 5 (SOCS5), and it also affects the expression of the transcription factors KLF2 and KLF4, thereby decreasing the activation of NF-kB and the expression of cell adhesion molecules, and stimulating the production of NO in arteries [42, 54] [55]. Intriguingly, by targeting KLF2 and KLF4, miR-92a could indirectly modulate the expression of most shear stress-induced genes and miRNAs.

2.1.2.3. miR-712/miR-205. The expression of the mechanosensitive miR-712 is stimulated in conditions of disturbed flow in vitro and in vivo in murine endothelium. This miRNA inhibits the expression of tissue inhibitor of metalloproteinase 3 (TIMP3), therefore activating matrix metalloproteinases (MMP2 and MMP9) and a disintegrin and metalloproteases (especially ADAM10/17) [56]. The overall effect of disturbed flow-induced expression miR-712 is pro-atherogenic, as it promotes endothelial inflammation and permeability. Consistently, in vivo silencing of miR-712 prevents atherosclerotic lesions in murine models of atherosclerosis [56]. Interestingly, this miRNA is atypical, as it is derived from pre-ribosomal RNA in a DiGeorge syndrome critical region 8 (DGCR8)-independent mechanism. In normal conditions, miR-712 is degraded by the exoribonuclease 1 (XRN1), by an unknown mechanism, XNR1 expression decreases in disturbed flow and miR-712 is stabilized. The human homolog of miR-712, hsa-miR-205, shares target specificity for TIMP3, and it is also upregulated by disturbed flow, therefore it could be envisioned to be a therapeutic target for atherosclerosis intervention [56].

2.1.2.4. miR-663. Oscillatory shear stress in vitro induces miR-663 expression in HUVECs [57]. Silencing this miRNA in ECs increases several pro-inflammatory cytokines and adhesion molecules, like IL8, and E-selectin, although the mechanism for this modulation is not clear. Overall, miR-663 increase seems to blunt gene expression associated with inflammatory responses and monocyte adhesion on ECs [57]. Notably, expression of KLF4, an atheroprotective effector which is downregulated during oscillatory stress, is modulated by miR-663, suggesting a cooperative action of miR-663 in preventing shear stress-induced damage to ECs [57]. Similarly to murine miR-712, human miR-663 is also encoded in a non-canonical ribosomal transcript, suggesting that its stability in oscillatory shear stress could also be influenced by XNR1 [56].

2.1.2.5. miR-34. Disturbed flow in vivo and in vitro promotes endothelial senescence through a p53/p21-dependent mechanism [58]. Interestingly, both p53 and oscillatory flow induce the expression of miR-34 [59]. Mir-34 overexpression in ECs, both in static flow and in oscillatory flow, causes the upregulation of intercellular adhesion molecule 1 ICAM1 and VCAM1 expression and an increase in leukocyte adhesion [60]. miR-34 indirectly decreases the protein levels of sirtuin 1 (SIRT1), which is a known inhibitor of NF-kB/p65 acetylation. In fact, miR-34 overexpression induces the acetylation of NF-kB subunit p65, further contributing to the increase of VCAM1 and ICAM1 expression [60].

2.1.3. Endothelial-smooth muscle cell interaction in shear stress

SMCs play an important role in the physiological development of atherosclerosis and their response to shear stress contributes to affect EC functions.

Co-culturing ECs with SMCs in static conditions induces the expression of NF-κB and therefore promotes the transcription of four anti-inflammatory miRNAs, namely, miR-146a, miR-708, miR-451, and

miR-98, through a mechanism that requires the synergistic action of integrin β1 and β3 [61]. miR-146a is upregulated by nuclear factor erythroid 2 [NF-E2]-related factor 2 (Nrf2) in shear stress both in vivo and in vitro in co-culture with SMCs, while the regulation of the other miRNA is Nrf2-independent. Expression of miR-146a, miR-708, miR-451, and miR-98 is further increased in shear stress and in injured arteries under physiological levels of flow, while their expression is barely detectable in conditions of flow stagnation. The anti-inflammatory activity of these miRNAs on ECs is due to the silencing of IRAK1 (miR-146a), IκB kinase γ (IKKγ) (miR-708), IL6R (miR-451), and IKKα (miR-98). The targeting activity of these miRNA blunts NF-κB and therefore negatively regulates their expression [61].

Interestingly, ECs overexpressing KLF2, which are in a shear stress-like state, can secrete miR-143/145 into microvesicles [62]. These miR-143/145-rich vesicles can be transferred to SMCs and promote an atheroprotective phenotype both in vivo and in vitro by downregulating key target genes like member of ETS oncogene family (ELK1), KLF4, calcium/calmodulin-dependent protein kinase II delta (CAMK2d), slingshot homolog 2 (SSH2), phosphatase and actin regulator 4 (PHACTR4), and cofilin 1 (CFL1) [62].

2.2. miRNAs involved in the regulation of the inflammatory state

During atherosclerotic plaque progression, several inflammatory cytokines are secreted from recruited leukocytes at the site of lesion. Additionally, low-density lipoproteins are oxidized (ox-LDL), contributing to sustain an inflammatory response and to induce apoptosis in ECs. Both inflammatory cytokines and ox-LDL contribute to the regulation of miRNAs, which in turn regulate cellular responses to these insults. Below are few examples of the role of miRNA in inflammatory conditions (See Fig. 1 D-E).

2.2.1. Cytokine-modulated miRNAs

2.2.1.1. miR-146a/b. Pro-inflammatory cytokines, such as tumor necrosis factor α (TNFα) or interleukin 1β (IL1β), induce the expression of miR-146a and miR-146b in ECs [63]. miR-146a/b upregulation favors the downregulation of adhesion molecules and pro-inflammatory genes, by suppressing NF-κB and MAP kinase/early growth response (EGR) pathways by direct targeting of TNF receptor-associated factor 6 (TRAF6) and IRAK1 [63]. In addition to its direct effect on inflammatory pathways, miR-146a targets human antigen R (HuR) [63]. This RNA binding protein (also known as ELAV-like protein 1) facilitates EC activation and leukocyte adhesion, by destabilizing eNOS. In the context of IL1β-mediated upregulation of miR-146a in ECs, the 3′UTR of HuR is targeted and loss of this protein decreases cell adhesion molecules and inhibits endothelial activation by releasing the suppression on eNOS, probably by stabilization of the transcription factor KLF2 [63].

2.2.1.2. miR-181b. The expression of miR-181b in ECs is reduced by TNFα [64]. Interestingly, miR-181b is upregulated also in laminar flow [48,56], while its expression is reduced in the aortic intima of ApoE deficient over time after high-fat diet and in individuals with coronary artery disease [65]. Importin-α3 (KPNA4) is a direct target of miR-181b and its inhibition decreases NF-κB nuclear translocation in ECs but not in circulating leukocytes. Additionally, TNFα-induced expression of adhesion molecules in ECs is blunted by miR-181b through indirect targeting [64]. Systemic administration of miR-181b to atheroprone mice decreases NF-kB activation exclusively in ECs, while leukocyte NF-kB activation is mediated by importin-α5 in a miR-181b-independent fashion [65]. Overall, delivery of miR-181b is protective against atherosclerosis, by inhibiting vascular inflammation and leukocyte recruitment to the sites of lesion.

2.2.1.3. miR-222. Two inflammatory stimuli produced by T-cells infiltrating the atherosclerotic plaque, namely, IL3 and basic fibroblast growth factor (bFGF), are able to reduce the expression of miR-222 [66]. STAT5A, the main intracellular mediator of IL3 and bFGF signaling, is the main target of miR-222, therefore the IL3 and bFGF-mediated downregulation of miR-222 contributes to fully activate STAT5A signaling in response to these cytokines [66]. Accordingly, miR-222 decreases neoangiogensis in vivo by reducing STAT5A signaling [66]. In advanced human atherosclerotic plaque miR-222 is also less abundant than in healthy plaque and its expression inversely correlates with increased STAT5A and EC proliferation [66]. In a previous study, miR-222 was shown to inhibit EC proliferation and migration by targeting c-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog [67]. These data suggests that therapeutic repression of miR-222 might improve EC proliferation in atherosclerosis.

2.2.1.4. miR-17-3p and miR-31. In ECs, TNFα stimulates the expression of miR-17-3p and miR-31. These miRNAs can downregulate the expression of ICAM1 and E-selectin, respectively, through specific target to their 3′UTR [68]. Overexpression of these miRNAs diminishes neutrophil adhesion to TNFα-activated ECs, while their specific antagonism increases neutrophil binding to cultured ECs. miR-17-3p and miR-31 provide a negative feedback control of inflammation. In this system, miRNA delivery designed to simulate, rather than antagonize, the function of endogenous mature miRNAs could be useful in the context of atherosclerosis as an anti-inflammatory therapy to decrease the expression of adhesion molecules (i.e. E-selectin SELE and ICAM1).

2.2.2. Oxidized-LDL-regulated microRNAs

2.2.2.1. miR-365. One of the most upregulated miRNAs in ECs treated with ox-LDL is miR-365 [69]. It is well known that ox-LDL increases inflammation and apotosis in ECs through the downregulation of the anti-apoptotic gene B-cell CLL-lymphoma 2 (Bcl2). Intrestingly, miR-365 targets Bcl2, and, consistently, delivery of anti-miR-365 rescues the ox-LDL-mediated apoptosis [70].

2.2.2.2. Let-7 family. Ox-LDL induces the downregulation of let-7g in ECs through the binding of OCT-1 to the let-7g promoter [71]. Interestingly, let-7g [71], as well as let-7a and let-7b [72], targets the lectin-like low-density lipoprotein receptor 1 (LOX-1), which is the receptor for ox-LDL in ECs. While overexpression of let-7a and let-7b decreases the production of reactive oxygen species (ROS) and reduce ox-LDL-mediated EC apoptosis and NF-κB activation, let-7g indirectly decreases senescence by upregulating SIRT1 [73]. Administration of let-7 g in ox-LDL treatment results in a downregulation of LOX-1 and in decreased EC proliferation and increased migration [71]. These data suggest that the members of the let-7 family are protective against endothelial dysfunction.

3. Endothelial miRNAs and type 2 diabetes, obesity, or metabolic syndrome

Type 2 diabetes is a chronic condition that results in the body's ineffective use of insulin. In 2014, 9% of adults had diabetes, with type 2 diabetes affecting 90% of all diabetic patients [2]. While the causes of type 1 diabetes are unknown, type 2 diabetes mostly affects individuals that are overweight and that conduct a sedentary life. The association of obesity with type 2 diabetes has been recognized for decades and it is well established that obesity engender insulin resistance [74].

Worldwide obesity has more than doubled since 1980, and in 2014, more than 1.9 billion adults were overweight, with a staggering 600 million of obese individuals [2]. Obesity, defined as body mass index greater than 30, is a component of the metabolic syndrome, a constellation of metabolic risk factors that consist of serum elevations of triglycerides, low levels of high-density lipoprotein, elevated blood pressure, elevated glucose associated with insulin resistance, a prothrombotic state and a pro-inflammatory state and overall endothelial dysfunction [6] (See Fig. 2).

3.1. microRNAs involved in the regulation of vascular tone

Endothelial dysfunction is an important component of the metabolic or insulin resistance syndrome. Patients with these syndromes have inadequate vasodilation and/or paradoxical vasoconstriction in coronary and peripheral arteries. In addition to its role in glucose homeostasis, insulin is also a vascular hormone that has both physiologic and pathophysiologic roles in the vasculature. Insulin stimulates NO and ET-1 production in the endothelium. Under pathological state, as in type 2 diabetes individuals, glucotoxicity, lipotoxicity, and insulin resistance compromise the ability of insulin to stimulate NO and ET-1 production in ECs, while further interfering with insulin signaling [75]. Additionally, NO deficiency results from decreased synthesis and/or release, in combination with exaggerated consumption in tissues by high levels of ROS and reactive nitrogen species (RNS), which are produced by cellular disturbances in glucose and lipid metabolism [76] (see Fig. 2 B).

Regarding the role of miRNAs in the regulation of the vascular tone, preliminary studies show that knockdown of Dicer, the enzyme necessary for miRNA maturation, increases eNOS expression in ECs [77].

3.1.1. miR-155

Several reports provide evidence that miR-155 downregulate eNOS expression through decreasing eNOS mRNA stability by binding to its 3-UTR [78]. Interestingly, TNF increases miR-155 expression in ECs [68] and knockdown of miR-155 prevent cytokine-induced downregulation of eNOS expression, reduction of NO production, and impairment of endothelium-dependent vascular relaxation [78]. These findings indicate that miR-155 is an essential regulator of eNOS expression and endothelium-dependent vasorelaxation. Inhibition of miR-155 may be a new therapeutic approach to improve endothelial dysfunction during the development of cardiovascular diseases.

3.1.2. miR-125a/b

In addition to producing the potent vasodilator NO, ECs also synthesize ET-1, one of the most potent and long-lasting vasoconstrictive peptides [79]. In non-stimulated physiological conditions, ET-1 mRNA levels are very low, while its expression and secretion from ECs is stimulated by hypoxia, shear stress, and ischemia. Upon release, ET-1 binds to ET-A receptor on vascular SMCs, resulting in an increase in calcium concentration and vascular SMC tone. NO controls the duration of these effects by accelerating the restoration of intracellular basal calcium levels. Therefore, in states of EC dysfunction, such as type 2 diabetes, where NO levels are reduced, ET-1 promotes vasoconstriction [80]. MiR-125a/b is involved in the regulation of the ET-1. However, it is not known whether this effect is indirect or through direct targeting of the ET-1 3′UTR. Interestingly, aortas in stroke-prone spontaneously hypertensive rats compared to normotensive rats have an inverse correlation between the levels of miR-125a/b and the precursor protein ET-1 (preproET-1) [81]. Additionally, miR-125a/b is upregulated in response to oxidized LDL (ox-LDL) in both ECs [81] and macrophages [82]. Due to the relevance of ET-1 in many vascular diseases such as hypertension, type 2 diabetes, atherosclerosis, and stroke, targeting of miR-125a/b could provide an important therapeutic approach.

3.1.3. miR-1

In hyperglycemic conditions, miR-1 expression is reduced in ECs. This is accompanied by an increase in ET-1 expression. Overexpression of miR-1, in high glucose cultured conditions, prevented ET-1 induction as well as ET-1-mediated upregulation of fibronectin [83]. However, the direct effect of miR-1 on the ET-1 3′UTR was not assessed. Despite this, streptozotocin-induced diabetic mice show a decreased in the expression of miR-1 in the retina, heart, and kidneys, while the mRNA levels of ET-1 and fibronectin are upregulated, thus facilitating extracellular matrix accumulation observed in diabetic complications [83].

3.2. miRNAs involved in the regulation of neovascularization in diabetes

EC function and postischemic reparative neovascularization in diabetes mellitus is impaired; however, the molecular mechanisms are not fully understood. Hyperglycemia is responsible for the initiation and the progression of chronic diabetes complications, and this contributes to the pathogenesis of vascular abnormalities of the retina, kidneys, and impaired formation of coronary collaterals. miRNAs contribute to modulate the phenotype of ECs in hyperglycemia [84] (see Fig. 2 C).

3.2.1. miR-503

In culture conditions mimicking diabetes mellitus (high D-glucose) and ischemia-associated starvation (low growth factors) in ECs, miR-503 is upregulated [85]. MiR-503 decreases EC proliferation, migration, and cord formation by targeting cell division cycle 25 (CDC25A) and cyclin E1 (CCNE1). Importantly, miR-503 expression was remarkably higher, and it inversely correlated with CDC25A protein expression in diabetic muscles when compared to calf biopsies of non-diabetic and non-ischemic patients undergoing saphenous vein stripping. Interestingly, miR-503 expression is increased in ischemic limb muscles of streptozotocin-diabetic mice and in ECs enriched from these muscles. Administration of anti-miR-503 improved blood flow recovery and angiogenesis in diabetic mice with limb ischemia. All these data suggest miR-503 modulation as a possible therapeutic tool in diabetic patients with critical limb ischemia [85].

3.2.2. miR-200b

A number of growth factors and vasoactive factors are increased in response to hyperglycemia, including endothelins and vascular endothelial growth factor (VEGF) [86]. In response to VEGF, ECs undergo functional alterations, including increased proliferation that causes neovascularization [87]. miR-200b expression is decreased in the human retina in diabetes. Such downregulation was validated in the retina of diabetic rats and in ECs incubated in glucose. In the retina, miR-200b is localized in neuronal, glial, and vascular elements. Interestingly, VEGF mRNA and protein are elevated due to the lack of targeting activity of miR-200b on VEGF. Moreover, transfection of ECs or intravitreal injection of miR-200b mimic prevents diabetes-induced increased VEGF as well as glucose-induced increased permeability and angiogenesis. Furthermore, transfection of miR-200b antagonists (antagomir) leads to increased VEGF production [88].

3.3. microRNAs in diabetic injury of glomerular ECs

Complications affecting the macro- and microvasculature are major causes of illness and death among diabetic patients. For example, diabetic nephropathy, one of the microvascular complications of diabetes mellitus, leads to the development of end-stage renal disease [89]. miR-155 and miR-146a levels are increased and primarily distributed in the glomerular ECs. Interestingly, high glucose induces the overexpression of miR-155 and miR-146a in the human renal glomerular ECs, which, in turn, increase the TNFα, transforming growth factor β1 (TGF-β1), and NF-κB expression [90]. These findings indicate that the increased expression of miR-155 and miR-146a in the diabetic nephropathy patients and in the experimental diabetic nephropathy animal models contributes to inflammation-mediated glomerular endothelial injury. The pro-inflammatory effect of these miRNA in the present setting appears to be paradoxical with the anti-inflammatory roles described for these miRNAs. Determination of the detailed mechanisms by which miR-155 and miR-146a cause renal damage and pro-inflammatory actions in the setting of diabetes could elucidate the pathogenesis of diabetic nephropathy and enable the development of improved treatment strategies.

4. Oxidative stress and microRNAs

Hypertension, hyperlipidemia, hyperglycemia, aging, and other pathophysiological conditions cause inflammatory responses in ECs, which serve to produce pro-inflammatory cytokines and chemokines and to recruit immune cells. Chronic, low-grade inflammation sustained by immune cells produces reactive oxygen species and oxidize lipoproteins, which affect EC biology and expression of miRNAs.

ECs produce endogenously low concentration of ROS as signaling messengers to favor angiogenesis [91]. The importance of miRNAs in physiological redox signaling in ECs is evident as ECs lacking Dicer produce less ROS, suggesting an involvement of certain miRNAs in the production of ROS essential for VEGF-induced angiogenesis [92]. Importantly, the angiogenic impairment given by depletion of Dicer in ECs is rescued by micromolar hydrogen peroxide [92]. Although the miRNAs responsible for physiological production of ROS have not been identified, the regulation and function of other miRNAs in response to external and excessive oxidative stress has been well described and it is reported below (See Fig. 2D).

4.1. miR-200c

miR-200c and the co-transcribed miR-141 are some of the most upregulated miRNAs in HUVEC treated with hydrogen peroxide [93]. The zinc finger E-box binding homeobox 1 protein (Zeb1) is a target of miR-200c, it is inversely regulated during ROS administration, and its downregulation induces EC growth arrest, apoptosis, and senescence [93].

5. Ischemic injury and microRNAs

Complications of cardiometabolic diseases include critical limb ischemia, myocardial infarction, and stroke [6,84,94]. Rupture of the atherosclerotic plaque causes blockage of coronary arteries and oxygen deprivation, or hypoxia, in affected tissues. Thickening of the arterial wall caused by plaque buildup also narrows blood flow and deprives tissues of oxygenated hemoglobin [31]. In diabetes, loss of vascular tone caused by high glucose induces a progressive loss of blood flow in the periphery that leads to ischemia. When ischemic tissues are damaged by chronic hypoxia or acute hypoxic injury and reperfusion, angiogenic stimuli are produced to restore tissue homeostasis by prompting EC into forming new vessels to contribute to the restoration of flow in affected areas [17]. The formation of new vessels, also called *de novo* angiogenesis, is essential as it provides oxygen and nutrients to tissues damaged by hypoxia or where malfunctioning EC cannot provide enough blood to sustain physiological functions [95]. This process is mediated by key angiogenic stimuli, like the VEGF or FGF [96]. Interestingly, several of miRNAs have been reported to be regulated by angiogenic growth factors and been implicated in regulation of angiogenic functions of ECs [97–99]. Stimulating and sustaining de novo angiogenesis might be an effective way to repair malfunctioning ECs or replace damaged capillaries in cardiometabolic diseases. miRNAs are excellent targets for improving de novo angiogenesis, and the literature is abundant with such examples.

5.1. microRNAs induced by hypoxia

5.1.1. miR-210

Decreased oxygen tension in sites of ischemia promotes the stabilization of hypoxia inducible factors (HIF) HIF-1α and HIF-2α, which transcriptionally induce the expression of genes that promote survival of cells, anaerobic metabolism switch, and angiogenic programs. Hypoxia also regulates miRNAs. The most notable hypoxia-miR, miR-210, is induced in ECs in an HIF-1α-dependent manner [100]. Notably, miR-210 is upregulated also in cardiomyocytes undergoing hypoxia [101] and in whole ischemic muscles [102]. Induction of miR-210 in ECs is instrumental in downregulating genes that impair tubulogenesis and VEGF-induced chemotaxis, like EphrinA3 (EFNA3) [100] and apoptosis [101]. Delivery of miR-210 LNA in a model of hind-limb ischemia increases cell apoptosis and necrosis, further decreases capillary density, and impairs limb perfusion. Gene expression analysis of ischemic gastrocnemius shows that the most affected pathways following by miR-210 inhibition were redox balance in cells and mitochondria function [102].

5.1.2. miR-424

miR-424 is upregulated in ECs in hypoxia and in a murine model of ischemia. Intriguingly, miR-424 stabilizes HIF-1a and HIF2a, by targeting Cullin2 (Cul2), a scaffolding protein that is critical to the assembly of the ubiquitin ligase complex that degrades HIFs [103]. Therefore, overexpression of miR-424 stabilizes the hypoxia transcriptional program, enhancing proliferation and migratory capabilities of ECs [103]. Overall, miR-424 promotes angiogenesis in vivo and in vitro.

5.2. microRNAs involved in limb ischemia

The first evidence of the importance of miRNAs in limb ischemia was shown by inactivation of Dicer in the endothelium [104]. Examples that illustrate the roles of individual miRNAs in limb ischemia are presented below.

5.2.1. miR-126

miR-126, is a constitutively expressed but EC-restricted miRNA and it is involved in vascular integrity and angiogenesis [49,50,105,106]. Consistent with the angiogenic properties of miR-126, inhibiting its action via antagomir injection impairs ischemia-induced angiogenesis [107]. Furthermore, miR-126 regulates vasculogenesis by modulating the endothelial expression of stromal cell-derived factor-1 (SDF-1). In a murine model of hind-limb ischemia, the number of circulating Sca-1(+)/Lin(−) progenitor cells in antagomir-126-treated mice is increased when compared with scramble mir-treated controls. This effect correlates with an elevated SDF-1 expressing CD31-positive capillaries. Therefore, in the context of an ischemic event, systemic silencing of miR-126 leads to the mobilization of Sca-1(+)/Lin(−) progenitor cells into the peripheral circulation, potentially in response to elevated SDF-1 expression by ECs present in the ischemic tissue [107,108].

5.2.2. miR-19a

In a genetic model where the miR-17-92 cluster is ablated in Tie2-expressing cells, there is an increase in density of small arteries in the limbs and in the heart in adult mice in physiological conditions [109]. In a model of hind-limb ischemia, collateral arteries are more developed in animals lacking endothelial miR-17-92, and this correlates with improved blood flow recovery [109]. These data suggest that miR-17-92 is involved in arteriogenesis. Further experiments reveal that miR-19a inhibits arterial development by targeting genes in the Wnt pathway, namely, the Wnt receptor frizzled class receptor 4 (Fzd4) and the coreceptor low-density lipoprotein receptor-related protein 6 (Lrp6). Administration of anti-miR-19a significantly improves the recovery to hind-limb ischemia and increases the presence of collateral arteries and it correlates with augmented expression of Fzd4 and Lrp6. Overall, these data suggest that in hind-limb ischemia in the adult, miR-19a acts as an anti-arterogenic miRNA.

5.2.3. miR-92a

Overexpression of miR-92a blocks neoangiogenesis in vitro and in vivo. The first report of miR-92a function in ECs came from a seminal work reporting that miR-92a inhibition in a mouse model of hind-limb ischemia and myocardial infarction improves blood vessel formation and recovery of the damaged tissue [110]. The putative target that mediates the beneficial effects of miR-92a is integrin subunit alpha5 (ITGA5) [110]. Several other studies proved in vitro and in vivo the

role of miR-92a as an antiangiogenic miRNA. In a rat model of balloon injuring or arterial stenting in vivo, miR-92a functional inhibition leads to an enhancement of re-endothelialization in injured arteries [111]. This study also provides evidence of increased proliferation and migration of rat ECs after administration of miR-92a inhibitor, while the effect was not present in SMCs [111]. KLF4 and MKK4 were identified as putative targets of miR-92a. More recently, in a pre-clinical porcine model of myocardial infarction, inhibition of miR-92a was shown to be beneficial if administered at the site of ischemia/reperfusion [112]. It reduces leukocyte adhesion to ischemic ECs and increases capillary density, while protecting cardiomyocytes from necrosis and apoptosis. MiR-92a inhibition in this model of myocardial ischemia overall decreases infarct size [112]. Genetic deletion of miR-92a in ECs also attenuates neointimal lesion formation by accelerating re-endothelialization, decreasing leukocyte infiltration and inhibiting SMC proliferation, through increase in ITGA5 and SIRT1 expression [113].

5.2.4. miR-106b-25

Knocking out of the miR-17~92 paralog, miR-106b~25, results in impaired vascularization after hind-limb ischemia. This observation was correlated with an impairment of stromal cell function in miR-106~25 knockout, including regulation of apoptosis, cytokine secretion, and expression of the stem cell marker Sca1 [114].

6. Therapeutic potential and concluding remarks

EC dysfunction is a term that implies the dysregulation of normal EC functions, including impairment of the barrier functions, control of vascular tone, disturbance of proliferative, migratory and morphogenic capacities of ECs, as well as control of leukocyte trafficking. Several studies have demonstrated the implication of endothelial dysfunction in the progression of cardiometabolic diseases, which in turn accelerates the manifestation of vascular complications. miRNAs are short non-coding RNAs that have emerged as critical regulators of gene expression acting predominantly at the post-transcriptional level. The coexistence of endothelial dysfunction with risks factors associated with cardiometabolic diseases suggests the involvement of common regulators between these entities. Indeed, dysregulation of miRNAs is a common feature in various human diseases including atherosclerosis and obese/diabetes-associated vascular complications. Based on their ability to coherently target multiple pathways, miRNAs are now recognized to have valuable therapeutic interest, as we have discussed in the present review. The biologically diverse functions of miRNAs underscore the need for targeted delivery and desirable pharmacokinetic profiles of inhibitory and mimic miRNA chemistries for reparative therapeutics. Although delivery of miRNA mimics or inhibitors raises concerns over potential off-target effects, the expectations for the clinical application of miRNA discoveries are promising [115]. Current work has demonstrated that anti-miRNA therapies may prove more effective when used complimentary to existing therapeutic options for cardiometabolic diseases [115][REF]. miRNA diagnostics and therapeutics, such as the use of cardiovascular miRNA biomarkers [116] and ongoing phase II clinical trials of miRNA inhibitory molecules [117], exemplify this potential.

Transparency document

The Transparency document associated with this article can be found in the online version.

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