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Effect on MicroRNA-92a in Atherosclerosis along with Flow-Mediated Vasodilation Study

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Review Article

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Abstract

Atherosclerosis has been regarded as an inflammatory disease. The vascular endothelium is considered as having multiple functions, regulating vascular tone, thrombosis, haematosis, permeability and cell adhesion. The emergence of microRNAs (miRNAs) as significant regulators of pathophysiological processes has indicated novel molecular insights and provided new therapeutic targets in atherosclerotic condition. Many studies have revealed that miRNA are associated with cardiovascular disease (CVD). With respect to miR-92a, miR -92a, a member of the miR-17 to miR-92 cluster, is expressed highly in endothelial cells (ECs) and regulated by shear stress. Both In vitro and vivo, miR-92a expression is highly induced in atheroprone regions compared with atheroresistant regions under disturbed flow (d-flow) condition. The clinical and experimental studies have suggested that inhibition of miR-92a can contribute to the improvement of endothelial dysfunction, inflammation, and oxidative stress in atherosclerosis. Recent reports showed that antimiR-92a as novel therapeutic options can be attributed to the endothelial cell autophagy and cardiomyocyte metabolism and that mechanistically, atherosclerotic status promote the packaging of functional miR-92a-3p into endothelial microvesicles, thereby promoting angiogenic response into recipient endothelial cells. It is strongly suggested that miR-92a-3p, having novel biological function and mechanism is a potent therapeutic target in atherosclerosis-related diseases. It is putative that flow-mediated vasodilation (FMD) study, early surrogate marker of endothelial function may in part reflect miR-92a, multifunctional biomarker.

Keywords: Endothelial dysfunction; miR-92a-3p; Flow-sensitive microRNA; Atherosclerosis-related disease; Flow-mediated vasodilation

Introduction

The vascular endothelium is considered as having multiple functions, regulating vascular tone, thrombosis, haematosis, permeability and cell adhesion [1]. The emergence of microRNAs (miRNA) as significant regulators of pathophysiological processes has indicated novel molecular insights and provided new therapeutic strategies in atherosclerotic status [2]. In clinical and experimental studies, inhibition of miR-92a can contribute to the improvement of endothelial dysfunction, inflammation, and oxidative stress in atherosclerosis [3,4]. The novel biological functions of miR-92a-3p on endothelial cell autophagy and cardiomyocyte metabolism have been demonstrated by analyzing the cell type-specific response to miR-92a-3p inhibition [5]. A recent report provided that mechanistically, the clinical and experimental atherosclerotic status can promote the packaging of functional miR-92a-3p into endothelial microvesicles (EMVs) thereby promoting angiogenic response in the recipient endothelial cells by a STAT3 (signal transducer and activator of transcription 3)-THBS1 (thrombospondin 1) -dependent manner [6].

Chang et al. [7] have also revealed that extracellular miR-92a mediate endothelial cell-macrophage communication. In addition, the relationship between FMD examination, early surrogate marker of endothelial dysfunction and miR-92a, gene expression has been identified [8,9]. The current knowledges of miR-92a, so-called flow-sensitive microRNA (mechano-miR) [10,11] and/or atheromiR [3] which have the novel biological function and mechanism will be reviewed in this article.

Endothelial Dysfunction in Atherosclerosis

Endothelial dysfunction was first indicated in essential hypertension in the forearm vasculature [12] and has been well characterized in the pathophysiological process of numerous other forms of cardiovascular disease (CVD) such as both hereditary and acquired dyslipidemia, coronary artery disease (CAD), congestive heart failure (CHF) and peripheral artery disease. Endothelial dysfunction has been also associated with smoking, type 1 and type 2 diabetes and obesity in patients without overt CVD [1]. Flow-mediated vasodilation (FMD) and nitroglycerin-mediated vasodilation (NMD) in the brachial artery is a potent procedure for estimating vascular endothelial and vascular smooth muscle cell (VSMC) function [13]. FMD and NMD examinations are useful tool of the vascular reactivity. The author has reported some studies on FMD and NMD including migraine, CVD, chronic kidney disease (CKD) and dyslipidema [14-18]. The vascular endothelium is considered as having multiple functions, regulating vascular tone, thrombosis, haematosis, permeability and cell adhesion. Vasodilatory substances including nitric oxide (NO), prostacycrin, C-type natriuretic peptide and endothelium-derived hyperporlarization factors (EDHF), as well as vasoconstrictions such as endothelin-1 (ET-1), angiotensin II (Ang II) and thromboxane A2 were released from endothelium [1,12]. Endothelial dysfunction, namely, endothelial activation is regarded as an important initiation process in atherosclerotic condition and also contribute to arteriosclerosis, so-called arterial stiffening.

MicroRNA in Atherosclerosis

MicroRNAs (miRNAs) were first identified in *Caenorhabditis elegans* [19]. MiRNAs are evolutionarily conserved, small, single-stranded noncoding RNAs that regulate gene expression at the post-transcriptional level typically binding to the 3'-untranslated region (UTR) of specific target mRNA sequences [2,20-25]. Feinberg et al. [2] described that the emergence of miRNAs as an important regulators of pathophysiological processes has indicated novel molecular insights and provided new therapeutic strategies in atherosclerotic status. Numerous studies have revealed that miRNA are associated with diseases such as CVD [26], kidney disease [27], liver disease [28], autoimmune disease [29] and cancer [30]. Atherosclerotic changes mainly occur at arterial branch points, bifurcations, and lesser curvature of the aorta in mice and human [31]. These findings are recognized, partially, under disturbed flow (d-flow) condition in these regions, which increases endothelial permeability and pro-inflammatory signaling. While, anti-inflammatory, anti-adhesive and antithrombotic properties occur under the laminar flow (l-flow) state in the vessel wall. A large number of miRNAs have been demonstrated as shear stress response under either d-flow or l-flow condition [2]. With respect to miR-92a, miR -92a, a member of the miR-17 to miR-92 cluster, is expressed highly in endothelial cells and regulated by shear stress [3,32]. In vitro condition, the exposing of endothelial cells to laminar flow (l-flow) decreased miR-92a expression. While disturbed flow (d-flow) increases its expression. In vivo status, miR-92a expression is also highly activated in atheroprone areas compared with atheroresistant regions [33].

The evidence that endothelial microRNAs (miRNAs) regulate vascular inflammation has been indicated. In response to biochemical and biomechanical stimuli, miRNAs regulate specific targets in endothelial cells that change the balance of pro- or anti-inflammatory signaling pathways. With regard to miR-92a, it targets the transcription factors Kruppel-like factor 2 (KLF2) and 4 (KLF4), and suppressor of cytokine signaling 5 (SOCS5) expression and increase monocyte chemoattractant protein (MCP)-1 and interleukin (IL)-6 [2]. Overexpression of miR-92a in endothelial cells decreased KLF2 and KLF4 expression, which are flow-responsive transcription factors. In contract, miR-92a antagonism decreased endothelial cell inflammation [3]. According to Loyer's report, miR-92a mechanistically, targets SOCS5 in endothelial cells under oxidized low-density lipoprotein (ox LDL) and low share stress status [3].

Flow-Sensitive MicroRNAs (Mechano-miRs)

Disturbed flow occurs in branched or curved arteries and has the characteristic of low-magnitude and oscillatory shear stress. While, laminar flow (stable flow) occurs in straight sections of the vasculature and has the aspect of high-magnitude and laminar shear stress which remain heathy [10]. Kumar et al. [10] mentioned that atherosclerosis occurs in arterial regions under disturbed flow condition, partially caused by changings in gene expression. MiRNAs are small, noncoding genes that post-transcriptionally regulate gene expression by targeting messenger RNA transcripts. MiRNAs including miR-10a, miR-19a, miR-23b, miR-17-92, miR-21, miR-663, miR-92a, miR143/145, miR-101, miR-126, miR-712, miR-205, and miR-155 have been recognized as flow-sensitive microRNAs (mechano-miRs). MiR -92a is one of the flow-sensitive miRNA, so-called mechano-miRs, regulate endothelial gene expression, endothelial dysfunction, and

atherosclerotic condition. The key signaling pathways that are targeted by these flow-sensitive microRNAs include the endothelial cell cycle, inflammation, apoptosis, and NO signaling [10]. Furthermore, Kumar et al. [11] also studied the role of flow-sensitive microRNAs and long noncoding RNAs (lncRNAs) in vascular dysfunction and atherosclerosis. They focused on multiple flow-sensitive miRNAs such as, miR-10a, -19a, -23b, -17 ˆ 92, -21, -663, -92a, -143/145, -101, -126, -712, -205, and -155 that play an important role of the endothelial function in atherosclerosis by targeting inflammation, cell cycle, proliferation, migration, apoptosis, and NO signaling [11]. They have discussed the flow-sensitive lncRNA STEEL along with other lncRNAs [11].

MiR-92a as Multifunctional Biomarker in Atherosclerosis

Loyer et al. [3] mentioned that microRNA, selectively regulated by ox LDL and share stress are called as atheromiRs. They identified miR-92a as an atheromiR and SOCS5 as novel miR-92a target [3]. They suggested that increased miR-92a expression and proinflammatory markers are recognized under the exposure condition of endothelial cells to oxidized LDL and low share stress [3]. Furthermore, they demonstrated that inhibition of microRNA-92a prevents endothelial dysfunction and atherosclerosis in mice. MiR-92a is a member of the miR-17-92 cluster, having numerous effects on the cardiovascular disease. Inhibition of miR-92a improves neovasculization after myocardial or hind limb ischemia [34]. Hinkel et al. [35] suggested that inhibition of microRNA-92a protected against ischemia/reperfusion injury in a large-animal study. In addition, several studies both in vitro and vivo [4,32,36] also have indicated a vasculoprotective effect for miR-92a inhibition. Daniel et al. indicated that inhibition of endothelial miR-92a improves re-endothelialization and prevents neointima lesion after vascular injury [4]. These evidences have provided endothelial and cardioprotective effects of genetic inhibition of miR-92a. MiR-92a-3p has many targets including KLF2, KLF4 [32,37], the fibronectin adhesion molecule integrin α5 (ITGA5), SOCS5, and SIRT1 [5,38]. Recently, Rogg et al. [5] indicated that inhibition of miR-92a-3p regulates endothelial cell autophagy through Atg4a and cardiomyocyte metabolic switching through Abca8b and Cd36 regulation. Rogg et al. [5] studied miR target regulation using miR-92a-3p and suggested that miRs have cell type-specific effects in vivo. A novel function of miR-92a-3p in endothelial cell autophagy and cardiomyocyte metabolism was discovered by analysis of miR-92a targets in cell subtypes. Gou et al. [39] also suggested that miR-92a overexpression reduces endothelial function and suppresses heme oxygenase-1 (HO-1) expression, namely, a critical cytoprotective enzyme, in endothelial cells. They demonstrated that inhibition of miR-92a suppresses oxidative stress and improves endothelial function by upregulating HO-1 in db/db mice. While, extracellular vesicles (EVs) are emerging as important regulators of vascular homeostasis and cardiovascular disease progression [6]. Atherosclerotic stimulation such as oxLDL or IL-6, increase miR-92a-3p expression in endothelial cells, as well as in corresponding endothelial microvesicles in vitro [6]. Liu et al. [6] demonstrated that clinical and experimental atherosclerotic conditions such as oxLDL and IL-6 can promote the packaging of functional miR-92a-3p into endothelial microvesicles, thereby promoting angiogenic responses in the recipient endothelial cells in a STAT3-THBS1- dependent manner [6]. Chang et al. [7] suggested that miR-92a exerts its effects on physiological responses in a novel biological manner. They have demonstrated that miR-92a-containing extracellular vesicles from endothelial cells modulate macrophage functions and phenotypes [6].

Inverse Correlation between MiR-92a Expression and FMD Study

Endothelial innate immunity has emerged as a significant mechanism underlying the interaction among oxidative stress condition, inflammation status, and endothelial dysfunction. Chen et al. [8] reported that miR-92a is inversely correlated with endothelial function assessed by FMD study and is positively correlated with serum interleukin-1β in patient with CAD. They suggested that sterol regulatory element-binding protein 2 (SREBP2) –miR-92a-inflammasome exacerbates endothelial dysfunction under oxidative stress condition. The miR-17-92 cluster is upregulated by c-Myc and NF-κB in cancer cells, fibroblasts, and epithelial cells [40,41]. They think that oxidative stress activates SREBP2 and miR-92a, in turn inducing innate immunity reaction and leading to endothelial dysfunction [8]. Finally, the reports [8,9] indicated the significant relationship between miR-92a and FMD study, showing close relation vascular reactivity and gene expression, thereby it is putative that FMD examination may partially reflect miR-92a expression.

In summary, the clinical and experimental studies have suggested that inhibition of miR-92a can contribute to the improvement of endothelial dysfunction, inflammation, and oxidative stress in atherosclerosis. The current knowledges indicated that miR-92a-3p can be attributed to the new novel biological function and mechanism in endothelial autophagy, cardiomyocyte metabolism, and angiogenesis and that antimiR-92a-3p treatment can also contribute to the new therapeutic strategies in atherosclerotic condition. It is strongly suggested that miR-92a-3p, having pleiotropic manner is a potent therapeutic target in atherosclerosis-related disease. The author will also suggest that it is plausible that FMD study, early endothelial surrogate marker may in part reflect miR-92a, multifunctional biomarker.

Conclusion

The author strongly suggests that miR-92a-3p, having pleiotropic manner is a potential therapeutic target in atherosclerosis-related diseases.

The author will also suggest that it is putative that flow-mediated vasodilation study, early endothelial surrogate marker may partially reflect miR-92a, multifunctional biomarker.

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Conflict of interest

The author declares that I have no conflicts of interest.

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