The Importance of Krüppel-Like Factors in Cardiovascular Diseases

Subjects: Biochemistry & Molecular Biology

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Krüppel-like factors (KLFs) are a set of DNA-binding proteins belonging to a family of zinc-finger transcription factors, which have been associated with many biological processes related to the activation or repression of genes, inducing cell growth, differentiation, and death, and the development and maintenance of tissues. In response to metabolic alterations caused by disease and stress, the heart will undergo cardiac remodeling, leading to cardiovascular diseases (CVDs). KLFs are among the transcriptional factors that take control of many physiological and, in this case, pathophysiological processes of CVD. KLFs seem to be associated with congenital heart disease-linked syndromes, malformations because of autosomal diseases, mutations that relate to protein instability, and/or loss of functions such as atheroprotective activities. Ischemic damage also relates to KLF dysregulation because of the differentiation of cardiac myofibroblasts or a modified fatty acid oxidation related to the formation of a dilated cardiomyopathy, myocardial infarctions, left ventricular hypertrophy, and diabetic cardiomyopathies.

cardiovascular Krüppel-like factors regulation miRNAs

1. Introduction

In response to metabolic alterations caused by disease and stress, the heart undergoes changes that are referred to as pathological remodeling, which involves hypertrophy and fibrosis, eventually leading to cardiac failure [1][2]. Similar metabolic changes can also affect the blood vasculature, which leads to structural alterations that potentially evolve into angiogenesis and atherosclerosis. These affections of heart and blood vessels are termed cardiovascular diseases (CVDs) [3][4][5]. To date, CVDs remain as the leading cause of mortality worldwide, claiming up to 18.56 million lives just in 2019, according to data of the Global Burden of Disease Study [6]. For the United States (U.S.), CVDs and stroke continue to be in the top 10 causes of death according to 2021 reports, with 173.8 and 41.1 deaths per 100,000 U.S. habitants, respectively [7]. Additionally, some of the most prevalent risk factors associated with premature death, such as high blood pressure, smoking, high blood sugar, and obesity, are well-known to be associated with the development of CVDs [6].

Cardiovascular diseases have a multifactorial etiology, which has not been fully clarified up to now. In recent years, the family of Krüppel-like transcription factors (KLFs) have acquired traction, as new developments have shed light on their involvement in various processes, including those associated with CVDs. The KLFs were first identified

and characterized in the early 1990s as erythroid cell-specific transcription factors [8], yet since then, several KLFs have been isolated in plenty of organs and tissues. Krüppel-like factors are a set of DNA-binding proteins belonging to the family of zinc-finger transcription factors [9]. Krüppel-like factors were named after their similarity to the *Drosophila melanogaster* Krüppel protein (from German, “crippled” protein), a member of the *gap* gene class involved in the thorax and anterior abdomen segmentation of *Drosophila* embryos [10], which, when presenting alterations, result in severe body abnormalities [11]. Krüppel-like factors are important regulators of gene transcription and can activate or repress the expression of genes involved in a variety of processes, including cell growth, differentiation, and death, and the development and maintenance of specialized tissues, under both physiological and pathological conditions [12]. Over the past few decades, numerous studies have explored the role of KLFs in CVDs, revealing that KLFs are involved in the regulation of a wide range of processes that are relevant to CVDs, including inflammation, oxidative stress, and cell proliferation [13][14][15][16]. For instance, KLF-2 has been associated with endothelial activation, possessing an anti-inflammatory effect and thus, being protective against CVDs [13]. On the other hand, KLF-5 has been found to be pro-inflammatory and pro-proliferative and has been implicated in the progression of CVDs [17].

2. Krüppel-like Factors and miRNA in Cardiovascular Diseases

MicroRNAs (miR) are small non-coding RNAs that regulate gene expression by binding to specific messenger RNAs and either inhibiting their translation or promoting their degradation [18]. Recent studies have found that miRNAs can modulate the expression of KLFs in the context of CVDs. MicroRNA (miR)-145 is the most abundant miR in VSMC, overseeing the maintenance of cells in their contractile phenotype by promoting contractile genes [19]. The phenotype that cells are is an important factor to take into account in the pathogenesis of atherosclerosis [20]. The VSMC phenotype increases atherosclerotic development because of its facility to migrate, proliferate, and generate extracellular matrix proteins [21]. This phenotype switching is regulated by *KLF-4*, as suggested in several studies [22][23]. The overexpression of KLF-4 inhibits VSMC proliferation induced by PDGF [24][25]. miR-145 also has a role as a key regulator of *KLF-5*, *KLF-4*, and *MYOCD*, as it downregulates the first two genes by suppressing their transcription (which are repressors of MYOCD) and directly stimulates the translation of myocardin [23]. Researchers have found that miR-145 expression (KLF-5 is its target) was found to be considerably higher in the normal aortic samples group, accompanied by a higher expression of contractile proteins such as calponin and α-SMA, compared to the atherosclerotic group, where the circulating levels of miR-145 were reduced [22][26]. In animal models of vascular diseases, miR-143/miR-145 were found to be downregulated, albeit this has not been confirmed in humans. Current research further proposes that miR-145 or miR-143 are part of the regulatory loop for KLF-4, KLF-5, MYOCD, and SRF; critical transcription factors the development of SMC phenotype, and lacking SMC correct differentiation could lead more easily to the development of atherosclerosis [27][28]. *KLF-5* inhibition via miR-145 results in the failure to repress MYOCD, a transcriptional cofactor for SRF, which commands the expression of multiple smooth and cardiac muscle-specific genes, such *SM-22*, *ANP*, *MLC-2V*, and *α-MHC* [26][29][30]. The transient decease in miR-145 expression 3 days post-myocardial infarction was associated with an increase in *KLF-5* and a decrease in *MYOCD*. In addition, miR-145 is necessary for the myocardin-induced cell

reprograming of adult fibroblasts into SMC and to induce the differentiation of multipotent neural crest stem cells into VSMC [31]. These data suggest that the miR-145/KLF-5/MYOCD path might be a critical modulator of VSMC in atherosclerosis.

A study using human coronary artery smooth muscle cells (HCASMCs) cultured under hyperglycemic conditions found that the repression of miR-145 resulted in *KLF-4* upregulation and thus, a decrease in MYOCD expression. This response, mediated by Ang II secretion in HCASMCs, resulted as a reaction to high glucose conditions, which developed in the facilitating migration of VSMC, as well as reduced the expression of VSMC differentiation marker genes, such as *α-SMA*, *transgelin*, and *smoothelin*, among others [23].

MiR-133 has also been associated with VSMC phenotypic modulation. miR-133 is capable of downregulating *KLF-4* via the suppression of its coactivator transcription factor, Sp1. In this process, miR-133 targets Sp-1, preventing KLF-4 activation, and making it unable to displace MYOCD from the SRF complex, determining the upregulation of smooth muscle genes, such as *MYH11* [32].

Horie et al. assessed the role of miR-133 in chronic heart failure, identifying *KLF-15* as another miR-133 target. In their study, miR-133 was shown to reduce KLF-15 and GLUT4 protein expression [33]. KLF-15 and MEF2A synergistically bind to the GLUT4 promoter, therefore increasing the glucose uptake in cardiomyocytes, a process of vital importance for the maintenance of myocardial energetic supply [34][35]. These results suggest that miR-133 may play a role in the perturbed energetics of heart failure.

In another study, rats were infarcted to assess the role of miR-92a and its relation to *Klf-2* and *Klf-4* in endothelial injury after left coronary artery ligation. Herein, this study demonstrated that in animal models, endothelial injury markers, *H-Fabp*, *vWF*, and miR-92a, were significantly higher than the control group, while vasoprotective factors, *Klf-2* and *Klf-4*, were downregulated through miR-92a binding to their 3′ UTR. The suppression of miR-92a seems to promote endothelial activation, cardiac cell proliferation, and the decrease in apoptosis after AMI, proving that both *Klf-2* and *Klf-4* are involved in the protection and modulation of endothelial cells [36]. Similar results were obtained when using antimiR-92a, decreased macrophage and T lymphocyte accumulation, and a marked reduction in atherosclerosis (32%, as compared to the non-treated group) [37].

miR-32-5p targets the expression of *KLF-2*. In a recent study, researchers found elevated serum levels of miR-32-5p in patients with AMI, and reduced expressions of KLF-2 [38]. KLF-2 possesses atheroprotective properties [36]; therefore, having an adequate expression of this gene could prevent the development of a cardiovascular disease. In another study, miR-363-3p was upregulated in the serum of AMI patients, showing that the expression of this miR was positively correlated with the concentration of endothelial injury biomarkers. As confirmed in rat studies with a knockdown of miR-363-3p, which showed that endothelial injury biomarkers are reduced. In the same study, they observed that the activity of KLF-2 was inhibited with the upregulation of miR-363-3p, leading patients toward a higher probability of suffering AMI [39].

Regarding ischemic damage, miR-125b-5p was linked to a cardioprotective effect in the onset of AMI. Using several prediction algorithms, researchers have identified proapoptotic *BAX1* and *KLF-13* as miR-125b-5p targets. This research group showed that in vivo repression of miR-125b-5p is associated with a higher mortality after left coronary artery ligation, left ventricular disfunction, enhanced susceptibility to cardiac rupture, higher levels of *ANP* and *TNF-α*, and larger fibrotic regions. An in vitro analysis showed that miR-125b-5p could induce an increase in p-AKT levels, suggesting a function as a pro-survival miR in cardiomyocytes. Furthermore, researcher proved that β-blocker carvedilol was capable of upregulating miR-125b-5p (a process accompanied by a decrease in BAX1 and KLF-13) [40]. These findings suggest miR-125b-5p to be a carvedilol-responsive miR, a mediator of improved cardiac function after AMI, via the blockage of pro-apoptotic proteins.

miR-let-7g demonstrated an increase in the expression of α-SMA and calponin by the downregulation of PDGF-β, leading to a reduced interaction between KLF-4 and SRF, which de-repressed MYOCD; this maintains VSMC contractile phenotype and therefore reduced the formation of atherosclerotic plaques [41]. There have been some miRNAs that are related with the AMI but not associated with KLF signaling. miR-139-5p has been involved in regulating cardiomyocyte proliferation and apoptosis. Finally, further research has also confirmed that miR-139-5p increases in the serum of AMI patients [42]. An overview of miRs involved in the regulation of CVDs, as well as their target and response can be seen on **Table 1**.

Table 1. miRNAs involvement in KLF regulation during CVDs.

MiRNAs	Cardiovascular Diseases	Target	Response	Ref.
miR-143/145 miR-1 miR-137-3p	Promotes atherosclerosis	KLF-4/5 KLF-4 KLF-15	• ↓ Expression; • MiR-1 induces SMC differentiation through the repression of Klf4; • Promote ischemia.	[43] [44] [45]
miR126	Promotes atherosclerosis	KLF-2	• ↑ expression of miR-126 ↑ KLF-2 activated VEGF.	[46]
miR29a	Promotes atherosclerosis	KLF-15	• ↑ expression of miR-29a ↑ miR29 increased KLF-15 stability by Fbw7/CDC4.	[47]
miR-410 mmu-miR-107, mmu-miR-142-5p, mmu-miR-	Anti-atherosclerosis	KLF-5 KLF-2	• HDAC1; • KLF-5 promotes IKB alpha ↓ NFκB;	[48] [49]

MiRNAs	Cardiovascular Diseases	Target	Response	Ref.
143, mmu-miR-155			• FOXO1 regulates the expression of the downstream transcription factor KLF-2 in endothelial cells.	
miR-10a	Myocardial infarction	KLF-4	• miR-10a rejuvenated aged hBM-MSCs, which improved angiogenesis and cardiac function in injured mouse hearts.	[50]
miR-27a	Myocardial infarction	KLF-5	• miR-27a expression could be transcriptionally suppressed by KLF-5 and inactivated by the TGF-β/Smad2/3 signaling pathway.	[51]
mIR-363-3p	Myocardial infarction	KLF-2	• ↓ miR-363-3p reduces the concentration of endothelial biomarkers and promotes the vascular endothelial cell proliferation, and this protective effect on endothelial injury may be exerted by targeting KLF2.	[39]
miR32-5p	Myocardial infarction	KLF-2	• miR-32-5p promotes endothelial cell viability.	[38]
miR-125b-5p	Myocardial infarction	KLF-13	• miR-125b-5p protects the heart against AMI by blunting CM death in response to injury in part through its repression of bak1 and klf13.	[40]
miR-150	Myocardial infarction	KLF-13	• Increasing KLF-13 expression via ↓ miR-150.	[52]
mIR-92a	Myocardial infarction	KLF-2 KLF-4	• miR-92a promoted endothelial activation, cardiac cell proliferation. and apoptosis decrease after AMI, proving that both KLF-	[53]

MiRNAs	Cardiovascular Diseases	Target	Response	Ref.
			2 and KLF-4 are involved in the protection and modulation of endothelial cells.	
miR-124	Atherosclerosis	KLF-6 and STAT3	• Downregulation of miR-124 and Sp1 levels was found in human aortic media from clinical specimens of aortic dissection.	[54] [55]
miR-let-7g	Atherosclerosis	KLF-4, SRF, α-SMA, calponin, and PDGF-B	• ↑ α-SMA expression via ↓ KLF-4 & SRF which depresses Myod.	[41]

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