

Is Mir-133a a Promising Therapeutic Target for Heart Failure?

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Abstract

Although miR-133 mitigates cardiac hypertrophy and fibrosis, fine tunes β 1-AR signaling, and protects against oxidative stress mediated apoptosis, it is unclear whether overexpression of miR-133a can ameliorate left ventricular function in failing hearts. Considering its multidisciplinary role in the heart, it is suggested that miR-133a is a master regulator of several networks that controls pathological cardiac remodeling. Therefore, it is a promising therapeutic target for heart failure.

Keywords: MicroRNA; Diabetes; Remodeling; Therapy; Regulation

Introduction

Despite gigantic stride made towards understanding Cardiovascular Diseases (CVD), heart failure remains the number one cause of morbidity and mortality across the globe, and accounts for 31.9% of all deaths in USA [1]. Heart is a highly sophisticated, vulnerable, and unique organ, which has responsibility to incessantly and efficiently function for survival of the individual. The heart is regulated at several levels by tiny regulatory RNAs called miRNAs [2-8]. MiRNAs are endogenous, evolutionary conserved and ~ 23 nucleotide long, non-coding RNAs that modulate genes by post transcription repression [9]. Differential expression of miRNAs are documented in pathological hearts that leads to cardiovascular diseases [2,10]. MiRNAs are emerged as a biomarker and promising therapeutic target for cardiovascular disease [2,3,11]. The human heart expresses more than 800 miRNAs amongst which miR-133a is the most abundant in human myocardium [12-14]. Abrogation of miR-133a impairs cardiac development at embryonic and postnatal stages [15]. The inhibition of only miR-133a can cause development of cardiac hypertrophy in adult mice [16]. Interestingly, transgenic overexpression of miR-133a does not show any phenotype but mitigates cardiac fibrosis in pressure overload (trans-aortic constriction) hearts [17]. MiR-133a is attenuated and contributes to cardiac hypertrophy in the diabetic hearts. Interestingly, overexpression of miR-133a mitigates cardiac fibrosis in diabetics [18-20].

However, whether overexpression of miR-133a can mitigate cardiac dysfunction in the failing heart is unclear. Here, a brief account of miR-133a transcription and its potential role in amelioration of cardiac dysfunction will be discussed.

Types of Mir-133 and their Transcription

There are two types of miR-133: miR-133a and miR-133b. MiR-133a has two alleles: miR-133a-1 and miR-133a-2. Both alleles of miR-133a are identical in sequence and differ from miR-133b by only two nucleotides. MiR-133a is expressed in the heart and in the skeletal muscle, whereas miR-133b is expressed only in the skeletal muscle and not in the heart. Both alleles of miR-133a and miR-133b are transcribed as bicistronic transcripts. MiR-133a-1 is encoded by chromosome 18 and transcribed as bicistronic cluster with miR-1-2. On the other hand miR-133a-2 is encoded by chromosome 2 and it transcribed as bicistronic transcript with miR-1-1. MiR-133b is located on chromosome 1 and is transcribed as a cluster with miR-206 [15]. The expression of miR-133a is regulated by myosin enhancer factor-2 (Mef2) and Serum Response Factor (SRF) in the myocardium [21,22].

Multidisciplinary Role of Mir-133a in Pathological Cardiac Remodeling

The two common pathological remodeling in the heart is hypertrophy and fibrosis. It is documented that miR-133a mitigates both hypertrophy and fibrosis suggesting that it is cardioprotective [16-18,20,23-25]. Recently, it is reported that miR-133a regulates several genes in the beta1-adrenergic receptor (β 1-AR) signaling cascade. The cardiac specific overexpression of miR-133 attenuates β 1-AR mediated induction of apoptosis and fibrosis in the heart, and mitigates cardiac dysfunction in mice with transaortic constriction [23]. This is corroborated by the finding that carvedilol (a β -blocker) protects cardiomyocytes against oxidative stress induced apoptosis by up regulating miR-133 [24]. In human mesenchymal stem cell, miR-133a is demonstrated to promote cardiogenic differentiation by targeting epidermal growth factor receptor [25]. The cardiogenic differentiation is crucial for regeneration of myocardium and replenishment of damaged cardiomyocytes. In pathological hearts, fibroblasts turnover is increased and accumulated fibroblast causes fibrosis. This fibroblast can be reprogrammed into cardiomyocytes by a cocktail of miR-1, -133, -208, and -499 in mice [26]. Since cardiomyocytes undergoes apoptosis and their number is less in failing hearts, the trans- differentiation of fibroblasts that causes fibrosis into cardiomyocytes is like converting devil into god and it can be harnessed for reverting pathological remodeling. Further analyses using human foreskin fibroblasts revealed that miR-133a in concert with other transcription factors contributes to reprogramming of fibroblast into cardiomyocytes [27].

It is established that miRNAs inhibits gene by binding to the 3' UTR of the gene. Interestingly, recent studies revealed that mature miRNA can reenter into nucleus and bind to promoter region to up- or down-regulates a gene [28-32]. The binding of miRNA to promoter region is facilitated by recruitment of Chromatin Modifying Proteins (CMPs).

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The binding of miRNA to promoter region can activate transcription (RNA activation) if CMP recruitment increases H3K4 methylation. On the other hand, miRNA binding at promoter can silence gene transcription (transcriptional gene silencing) if CMP recruitment increases H3K9/27 methylation [28]. We have reported that miR-133a controls DNA methylation by regulating DNA methyl transferases in diabetic cardiomyocytes [18]. These findings suggest miR-133a has multiple roles and could be a master regulator of several regulatory networks in the heart.

Potentials and Limitations of Mir-133a as Therapeutic Target for Heart Failure

Considering the role of miR-133a in regulation of cardiac hypertrophy, fibrosis, epigenetic modification, and β -AR signaling and our unpublished data on cardiac autophagy homeostasis, it is justified to suggest that miR-133a is a promising therapeutic target for cardiomyopathy [16-20,23,24]. However, more empirical data pertaining to improvement of left ventricular function and on toxicity in different heart failure models are required before it can be translated from bench to bedside.

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