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Macro advances in microRNAs and myocardial regeneration

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Abstract

Purpose of review—Myocardial injury and disease often results in heart failure, the leading cause of death worldwide. To achieve myocardial regeneration and foster development of efficient therapeutics for cardiac injury, it is essential to uncover molecular mechanisms that will promote myocardial regeneration. In this review, we examine the latest progress made in elucidation of the roles of small non coding RNAs called microRNAs (miRs) in myocardial regeneration.

Recent findings—Promising progress has been made in studying cardiac regeneration. Several miRs, which includes *miR-590*, *miR-199a*, *miR-17-92* cluster, *miR-199a-214* cluster, *miR-34a*, and *miR-15* family, have been recently shown to play an essential role in myocardial regeneration by regulating different processes during cardiac repair, including cell death, proliferation and metabolism. For example, *miR-590* promotes cardiac regeneration through activating cardiomyocytes proliferation, while *miR-34a* inhibits cardiac repair through inducing apoptosis.

Summary—These recent findings shed new light on our understanding of myocardial regeneration and suggest potential novel therapeutic targets to treat cardiac disease.

Keywords

MicroRNA; cardiomyocyte; cardiac injury; regeneration

1. Introduction

Compromised myocardial function with heart failure is the worldwide leading cause of morbidity and mortality [1,2]. Heart transplantation remains the most effective treatment strategy for end-stage heart failure but can barely meet the increasing global demand because of the scarcity of donor hearts[3]. Unlike amphibians and fish [4-8], mammalian cardiomyocytes have limited renewal capacity compromising the ability of mammalian hearts to efficiently repair after injury [9-13]. Because of these limitations, researchers are

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constantly pursuing novel approaches towards therapies that could ameliorate heart failure. Currently, there is no available approach to reverse the loss of functional myocardium [14]. Efficacious regenerative therapeutics to reverse the progress of heart failure has become an urgent and critical goal of modern cardiovascular research.

Considerable effort has been extended to develop therapies based on transplantation of stem cells or different types of progenitor cells to help a failing heart repopulate with newly made cardiomyocytes [15-24]. An alternative and promising cell-free tactic is to use small molecules or paracrine factors to stimulate cardiomyocyte proliferation or differentiation of resident cardiac progenitor cells [25-31]. Recent progress made in reprogramming and trans-differentiation of non-cardiomyocytes also shows great promise to advance cardiac regeneration [32-45]. Moreover, additional investigations aim to dissect signaling pathways regulating endogenous cardiomyocytes regenerative capacity [46-51].

MicroRNAs (miRs) are small endogenous non-coding single-stranded RNAs that function in biologic processes primarily via post-transcriptional gene silencing in diverse organisms [52,53]. MiRs generally repress target gene expression by promoting mRNA degradation and/or inhibiting translation. Genes targeted by a miR have conserved Watson–Crick base pairing to the miR “seed” site, which is centered at the 5′end of the miR[54,55]. The essential roles of miRs have been shown in regeneration of different tissues and organs. For example, *miR-133* promotes appendage regeneration in zebra fish [56], while *miR-206* promotes the regeneration of neuromuscular synapses[57] and skeletal muscle[58] in mice. Though the mechanisms remain largely unknown, miRs have been shown to have critical functions in cardiac regeneration. For example, previous studies showed a combination of miRs (miR-1, miR-133, miR-208 and miR-499) has the capability of reprogramming cardiac fibroblasts into cardiomyocytes [40]. Previous reviews have summarized the previous progress made in studying reprograming and regenerating cardiac tissue, including critical miRs involved in cardiac development and homeostasis [59-69]. Here, we summarize the most recent investigations into the function of miRs in myocardial regeneration.

2. miRs play an essential role in myocardial regeneration

has-miR-590 and has-miR-199a

To identify miRs that function in cardiomyocytes proliferation, a recent study cultured neonatal rat ventricular cardiomyocytes and transfected them with a library of 875 human miR mimics in a high-throughput screening approach [70]. Based on that screening, 204 miRs significantly increased neonatal rat cardiomyocyte proliferation and 40 miRs from the original 204 miRs also increased cytokinesis and karyokinesis in neonatal mouse cardiomyocytes[70]. Among the 40 miRs, *hsa-miR-590-3p*, *hsa-miR-199a-3p*, *hsa-miR-33b* and *hsa-miR-1825* can significantly increase the proliferation of 7-day postnatal cardiomyocyte, and even more remarkably, *hsa-miR-590-3p* and *hsa-miR-199a-3p* can significantly increase 2 month adult cardiomyocyte proliferation [70]. *Hsa-miR-33b* has been previously shown to have a role in regulating cell proliferation and fatty acid metabolism [71-73] while *hsa-miR-1825* function was previously unclear. This study chose to focus on *hsa-miR-590-3p* and *hsa-miR-199a-3p* for further miR targets studies, given that

these two miRs were the most effective at promoting proliferation in rat and mouse cardiomyocytes.

The miR target genes controlling cardiomyocytes proliferation were globally identified using a combined RNA deep-sequencing and siRNA screening approach [70]. The authors were able to identify three targets, *Homer protein homolog 1* (*Homer1*), *Homeodomain-only protein x* (*Hopx*) and *Chloride intracellular channel protein 5* (*Clic5*), that are miR regulated and also modulate cardiomyocyte cell proliferation. Further luciferase reporter assays indicated *Homer1* and *Hopx* are targeted by both *hsa-miR-590-3p* and *hsa-miR-199a-3p*, while *Clic5* is only targeted by *hsa-miR-590-3p*. *Homer1* previously has been shown to interact with ryanodin receptor (RyR) to control intracellular calcium signaling and with PI3 kinase to prevent cell apoptosis [74-77]. *Hopx*, an atypical homeodomain-protein, regulates proliferation and differentiation of different cell types, including cadiomyocyte proliferation by modulating Gata4 acetylation and SRF-dependent gene expression [78-82]. *Hopx* is expressed in both embryonic and postnatal cardiomyocytes and was found to be significantly reduced in both human and mouse hearts with heart failure [78,79,83].

Consistent with the *in vitro* data, *in vivo* analysis using synthetic miRs indicated that overexpression of *hsa-miR-590-3p* and *hsa-miR-199a-3p* increased cardiomyocyte proliferation in neonatal mice [70]. After myocardial infarction (MI), mouse hearts transduced with AAV9-*miR-590-3p* and AAV9-*miR-199a-3p* had improved cardiac function and reduced fibrotic scar size compared to controls [70]. Together, this study suggested that *hsa-miR-590-3p* and *hsa-miR-199a-3p* can stimulate cardiac regeneration by promoting mature cardiomyocytes to re-enter cell cycle and progress through mitosis [70].

miR-199a-214 cluster

In addition to the work investigating *miR-199a* discussed above, other studies indicated that *miR-199a* repressed hypoxia-inducible factor-1alpha and Sirtuin 1 [84], as well as, the ubiquitin-proteasome system [85] in mouse hearts. Meanwhile, *miR-199a* was modulated by high glucose and hypoxia in heart failure patients [86] and *miR-199a-214* cluster was down-regulated in explanted cardiac tissue from patients with dilated cardiomyopathy [87]. A recent study indicated that *miR-199a-214* is cluster involved in heart failure by facilitating a cardiac metabolic shift from predominantly fatty acid utilization in healthy myocardium toward increased glucose metabolism in failing hearts [88]. Using a cardiac disease mouse model with transverse aortic constriction (TAC) pressure overload, the authors found that mice treated with antagomirs of *miR-199a* and *miR-214* had improved cardiac function as well as normal arrangement of cardiomyocytes, significantly reduced cardiac fibrosis and hypertrophy, while vehicle-treated control hearts had impaired cardiac function and displayed cardiomyocyte disarray, interstitial fibrosis and hypertrophied myofibers [88]. The mechanistic studies indicated that both *miR-199a* and *miR-214* directly repressed *PPARδ*, a critical regulator of mitochondrial fatty acid metabolism in heart, but didn't alter expression of genes involved in glucose metabolism [88].

miR-17-92 cluster

The *miR-17-92* cluster encodes six polycistronic miRs (*miR-17*, *miR-18a*, *miR-19a*, *miR-20a*, *miR-19b,* and *miR-92a miR-92a*), of which some miRs have the same seed site. *MiR-17-92* germ-line loss-of-function resulted in abnormal myocardial differentiation from second heart field cardiac progenitors, by repressing the cardiac progenitor gene *Isl1* during embryonic cardiac development [89]. *MiR-17-92* also represses T-box genes during cardiac and craniofacial morphogenesis [89,90]. *MiR-92a* inhibits endothelial cell migration and angiogenesis in adult mice, while inhibition of *miR-92a* improves heart function and angiogenesis after MI or vascular injury [91,92]. A recent study reported that *miR-17-92*, particularly *miR-19* as a key component, can induce proliferation of cardiomyocytes and help protect the heart from ischemic injury caused by MI [93]. Compared with controls, proliferation of cardiomyocytes was decreased in *miR-17-92* loss-of-function hearts and increased in *miR-17-92* gain-of-function hearts. Importantly, after MI, *miR-17-92* gain-of-function hearts had improved cardiac function, reduced scar size and more proliferating cardiomyocytes at the border zone when compared with controls, suggesting an essential role in cardiac regeneration. *In vitro* analysis suggests that *miR-17-92* induces cardiomyocyte proliferation through direct repression of PTEN by miR-19, a tumor suppressor previously shown to be a *miR-17-92* target in tumorgenesis [94].

miR-34a

Aging is a critical risk factor for heart diseases and old patients with cardiac injury usually have worse outcome than young patients [95]. Compared to young mice, the aged mouse heart has increased cardiomyocyte apoptosis, fibrosis and hypertrophy, with decreased telomere length [96]. The expression levels of *miR-34a*, which previously had been shown as a regulator in apoptosis and senescence [97-101], were higher in older human and mouse hearts compared to young hearts [96]. *In vitro* data indicated this age induced miR promoted H_2O_2-induced apoptosis in rat neonatal cardiomyocytes [96]. *In vivo* assays using *miR-34a* antagomir treatment further indicated *miR-34a* induced cell death [96]. Moreover, *miR-34a* knock-out mice had less cell death and hypertrophy, as well as better cardiac contractile function compared to wild-type mice [96]. Notably, after acute MI, *miR-34a* expression was significantly increased at the border zone and treatment with *miR-34a* antagomirs or locked nucleic acid (LNA) based anti-miRs significantly improved cardiac function [96]. A key target of *miR-34a* identified in this study is *Pnuts* (also known as *Ppp1r10*), which is a gene previously reported in modulating apoptosis, telomere shortening and DNA repair [102].

miR-15 family

Mouse neonatal hearts can regenerate after injury, but this ability is gradually lost by postnatal day (P) 7 [49]. The expression levels of *miR-15*, *miR-30* and *let-7* families were increased in P10 compared to P1 mouse heart, suggesting a functional role in the transition to non-regenerative myocardium [103]. Transfection data in rat cardiomyocytes indicated that *miR-518* and *miR-302* family promoted cardiomyocyte proliferation while *Let-7* and *miR-15* family inhibited proliferation [70].

The *miR-15* family, consisting of 6 closely related miRs (*miR-15a*, *miR-15b*, *miR-16-1*, *miR-16-2*, *miR-195*, and *miR-497*), was up-regulated in different heart diseases [104].

Cardiac-specific overexpression of *miR-195* (*MYH7-miR-195* TG) resulted in premature cell cycle arrest at G2 phase leading to reduced heart size and congenital heart abnormalities such as ventricular hypoplasia and ventricular septal defects [103]. Mouse hearts treated with LNA anti-*miR15* to inhibit *miR-15* had reduced infarct size and enhanced cardiac function after ischemia reperfusion surgery [105]. Wild type (WT) P1 mouse hearts regenerate after MI and the newly formed cardiomyocytes are derived mainly from pre-existing cardiomyocytes [106]. However, after MI, *MYH7-miR-195* TG hearts fail to regenerate and had significantly impaired cardiac function compared to WT hearts, perhaps due to induction of inflammatory genes and repression of mitochondrial and cell cycle genes [106]. Conversely, LNA anti-*miR15* treatment increased proliferation of cardiomyocytes and improved left ventricular systolic function after adult MI [106].

It has been reported that *miR-195* contributed to the repression of a number of cell cycle genes including checkpoint kinase 1 (*Chek1*), cyclin-dependent kinase 1 (*Cdk1*), baculoviral IAP repeat-containing 5 (*Birc5*), nucleolar and spindle associated protein 1 (*Nusap1*), and sperm associated antigen 5 (*Spag5*) [103]. Among these cell cycle genes, *Chek1* has the *miR-195* seed site conserved between mice and humans and was directly targeted by *miR-195* based on the luciferase reporter analysis [103]. *Chek1* is a cell cycle gene that coordinates mitotic progression with spindle checkpoints [103]. Recently a hepatocellular carcinoma study found *miR-195* suppressed cancer cell proliferation and led to reduced tumor size through directly targeting NF-κB signaling related genes IKKα and TAB3 [107-109].

3. Conclusions and Perspectives

Important recent progress has been made in the field of cardiac regeneration research. The success of cell-based therapies for heart repair, although measurable, has been modest to date likely because the infused cells fail to efficiently integrate into the heart. Moreover, reprogramming and trans-differentiation of non-cardiomyocytes are limited by poor efficiency and other technical challenges [15-20,32-40,64]. Thus, new innovative strategies are needed to enhance cardiac regeneration and one of the alternative compelling strategies is to trigger the endogenous cardiomyocyte regenerative capacity. Exciting new findings, revealed in the last few years, indicate that resident cardiomyocytes can be induced to reenter the cell cycle and undergo cytokinesis. More work is needed to investigate the underlying molecular mechanisms for induced cardiomyocyte cell cycle reentry. The studies summarized in this review indicate that miR-based therapeutics, using miR antagonists or mimics, has strong potential to be used to promote cardiomyocyte cell cycle re-entry and improve cardiac function after cardiac injury.

A majority of myocardial regeneration related miRs, or regenerative miRs, play essential roles in cell proliferation (Figure 1), not only in cardiomyocyte but also many other cell types. Moreover, their functions in proliferation are conserved between species from mouse to human. For examples, *miR-17-92* cluster was the first described oncogenic miR [110,111], while *miR-15a* and *miR-16* are the first identified tumor suppressor miRs [112]. Notably, regenerative miRs could share the same target genes during myocardial regeneration as they do in other contexts. For example, individual *miR-15* family members,

that have the same seed site, have characterized targets in contexts other than heart regeneration [107-109]. These characteristics would enable cardiac researchers to investigate candidate target genes for the *miR-15* family in the context of cardiac regeneration.

Other regenerative miRs have different mechanisms of modulating cardiac function after injury (Figure 1). As an example, *miR-34a* mainly regulated apoptosis and senescence during cardiac repair [96]. Notably, within the same cluster, miRs may modulate cardiac function via independent mechanisms, like *miR-19* induced cardiomyocytes proliferation while *miR-92a* inhibited angiogenesis [91,92]. Moreover, the same miR could play different roles after different types of cardiac injury. Take *miR-199a* as an example, in mice with transvers aortic constriction (TAC) pressure overload, *miR-199a* inhibition with antagomir-199a improved cardiac contractility [88]. In contrast, overexpression of *miR-199a* using AAV9-199a induced cardiac regeneration in mice after MI [70]. A potential explanation, worthy of further investigation, for those observations is that miRs have multiple targets and repress different targets in the context of different injury types.

Although progress is promising, current miR studies in myocardial regeneration are limited to some extent due to the lack of cardiomyocyte specificity of *in vivo* anti-miR administration protocols, therefore new technologies or further studies are still needed to address these limitations. For example, LNA anti-*miR15* treatment increased cardiomyocytes proliferation after MI, but also robustly induced proliferation of the non-cardiomyocytes compartment [106]. It is unknown if this non-cardiomyocyte effect is necessary for cardiac repair and so has therapeutic relevance. Moreover, treatment using anti-*miR* chemistries could efficiently improve cardiac function in mouse and some cases even pig, but whether these approaches could sufficiently repair injured human hearts remains to be demonstrated. Studies in non-human primates and eventually human patients are needed.

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Key Points

- MiRs have the capabilities to regulate cardiac reprogramming and regeneration
- MiRs function in cardiac repair by regulating proliferation, apoptosis, metabolism, angiogenesis and senescence.
- MiRs have multiple targets, making the molecular mechanisms more complicated such that the same miR may function differently after different types of cardiac injuries.
- Manipulation of miR levels can be achieved by antagomirs/LNA anti-miR and miR mimics/AAV9-miR, making miR-based therapeutics feasible.

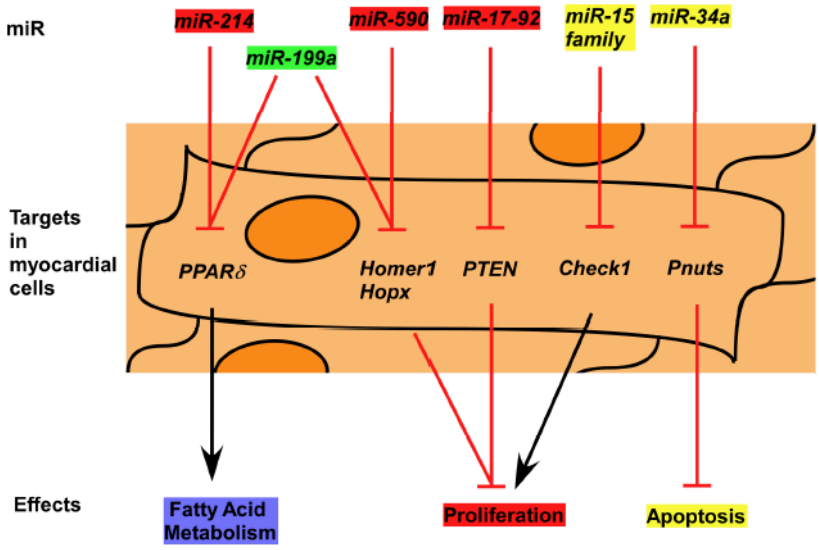

Figure 1.

Summary of recently reported miRs that play essential roles in myocardial regeneration. MiRs could promote (in red) or inhibit (in yellow) myocardial regeneration, or play a dual-role (in green) in myocardial regeneration.

Table 1

Recently published reports of miRs that function in cardiomyocyte regeneration

Ref	miR	Function in cardiomyocyte (CM) regeneration	Target genes in heart
34	*miR-590*	promote 7-day and 2 month postnatal CMs to re-enter cell cycle and progress through mitosis	*Homer1,Hopx and Clic5*
34	*miR-1825*	increase the proliferation of 7-day postnatal CMs	unclear
34	*miR-33b*	increase the proliferation of 7-day postnatal CMs	unclear
34, 52	*miR-199a*	promote 7-day and 2 month CMs to re-enter cell cycle and progress through mitosis; facilitate a cardiac metabolic shift from fatty acid toward glucose metabolism	*Homer1, Hopx and PPARδ*
52	*miR-214*	facilitate a cardiac metabolic shift from fatty acid toward glucose metabolism	*PPARδ*
53, 57	*miR-17-92*	induce proliferation of CMs	*PTEN, Isl1 and Tbx1*
60	*miR-34a*	induce cell death and hypertrophy of CMs	*Pnuts*
67, 69, 70,	*miR-15* family	repress proliferation of CMs	*Chek1*