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ORIGINAL ARTICLE

The Role of Non-coding RNAs in Ischemic Myocardial Reperfusion Injury

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Abstract

MicroRNAs (miRNA) are non-coding RNAs that regulate gene expression in up to 90% of the human genome through interactions with messenger RNA (mRNA). The expression of miRNAs varies and changes in diseased and healthy states, including all stages of myocardial ischemia-reperfusion and subsequent ischemia-reperfusion injury (IRI). These changes in expression make miRNAs an attractive potential therapeutic target. Herein, we review the differences in miRNA expression prior to ischemia (including remote ischemic conditioning and ischemic pre-conditioning), the changes during ischemia-reperfusion, and the changes in miRNA expression after IRI, with an emphasis on inflammatory and fibrotic pathways. Additionally, we review the effects of manipulating the levels of certain miRNAs on changes in infarct size, inflammation, remodeling, angiogenesis, and cardiac function after either ischemia-reperfusion or permanent coronary ligation. Levels of target miRNA can be increased using molecular mimics ("agomirs"), or can be decreased by using "antagomirs" which are antisense molecules that act to bind and thus inactivate the target miRNA sequence. Other non-coding RNAs, including long non-coding RNAs and circular RNAs, also regulate gene expression and have a role in the regulation of IRI pathways. We review the mechanisms and downstream effects of the miRNAs that have been studied as therapy in both permanent coronary ligation and ischemia-reperfusion models.

Keywords microRNA · Ischemic heart disease · Reperfusion injury

Introduction

Ischemic cardiovascular disease remains a primary cause of global morbidity and mortality. Great efforts have been made to decrease the burden of myocardial infarction (MI) through early reperfusion with primary percutaneous coronary intervention (PCI) and thrombolytic agents. Despite substantial improvements in door-to-balloon times, attempts to further reduce infarct size have not been successful, as clinical outcomes such as in-hospital mortality have plateaued, and rates of heart failure continue to increase [6, 46].

MicroRNAs (miRNA) are non-coding RNAs of 20 to 23 nucleotides in length, which act to regulate gene expression, primarily through inhibiting transcription or degrading messenger RNA (mRNA) [5, 47, 78]. Recent investigations have demonstrated that miRNAs may regulate as much as 90% of the human genome, including gene alterations associated with various aspects of heart disease, such as ischemic myocardial reperfusion injury, ventricular remodeling, arrhythmia, and ventricular hypertrophy. There are complex, variable changes in miRNA expression before, during, and after myocardial ischemia and reperfusion. Many studies have shown the significant role of miRNAs in modulating the cascade of myocardial ischemia-reperfusion injury (IRI), and the effect certain therapies have on miRNA expression. Because of their significant role in all stages of IRI, modulating miRNAs is a

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promising therapeutic strategy. For example, protective non-coding RNAs may have a role in the setting of anticipated ischemia (i.e., before elective surgery or PCI) [78].

IRI evolves over minutes to hours to days after reperfusion. In prolonged ischemia with irreversible myocardial damage, pro-apoptotic miRNAs dominate signaling in the myocardium and the endothelium. Subsequently, certain miRNAs promote fibrosis in the infarcted myocardium, as well as angiogenesis and remodeling of the peri-infarct border zones (Tables 1, 2, 3, 4, and 5). The differential expression patterns of miRNAs can thus link multiple unique cellular pathways involved in IRI [16, 57]. However, non-coding RNAs could have opposite effects in the acute and recovery phases of IRI. For example, certain miRNAs can promote cell survival and reduce myocardial infarct size when given before or during ischemia, but could promote fibrosis, hypertrophy, and adverse remodeling if given in the recovery phase.

There are other types of non-coding RNAs besides miRNAs that have been shown to regulate gene expression in the context of IRI. Long non-coding RNAs (lncRNA) are non-translated RNA molecules varying in length from 200 to 100,000 nucleotides that function as regulators of gene expression [60]. Circular RNAs (circRNA) are endogenous non-coding RNAs that regulate gene expression. Due to their circular nature lacking an open end and cytoplasmic origin, they are more stable in vivo than either miRNA or lncRNAs [17]. Compared with miRNA, lncRNAs and circRNAs have more complex roles in regulating gene expression, as they can activate gene expression, repress gene expression, and interact with the chromatin structure [60]. lncRNA and circRNA mostly act via direct binding to miRNA thus forming a regulatory complex consisting of lncRNA/circRNA-miRNA [25]. The role of both lncRNA and circRNAs is currently being investigated in IRI.

The effects of miRNA are non-specific, and each miRNA can affect multiple mRNAs, and each mRNA is affected by multiple different miRNA, leading to interdependence among different miRNA and the other non-coding RNAs. For example, miR-24 has been shown to have anti-apoptotic activity as well as anti-fibrotic activities in MI [63]. There is also cross-

Table 1 Permanent ischemic model

Treatment before ischemia

Study	miRNA	Animal	Therapy	Ischemia	Downstream effects	Mechanism of action
Yang 2018 [76]	miR-21	Mice	miR-21 conditional knockout (KO)	Permanent LAD ligation	Decreased survival, decreased LVEF, increased infarct size	miR-21 inhibits inflammatory response by targeting KBTBD7 and impairing MKK3/6 activation
He 2018 [28]	miR-144	Mice	miR-144 conditional KO	Permanent LAD ligation	Increased infarct size; reduced scar thickness; increased collagen content; decreased LVEF	Loss of miR-144 led to abnormal collagen deposition, adverse remodeling; possibly through Zeb1/LOX1 axis
Wang 2008 [61]	miR-126	Mice	miR-126 conditional KO	Permanent LAD ligation	Decreased survival at 3 weeks, decreased angiogenesis, increased heart failure	miR-126 enhances the proangiogenic actions of VEGF and FGF and promotes neoangiogenesis
Hu 2019 [31]	miR-155	Mice	IV injection of anti-miR-155 daily for 3 days prior to ischemia	Permanent LAD ligation	miR-155 inhibition reduced sympathetic neural remodeling and decreased arrhythmias	miR-155 inhibition decreases inflammation via SOCS1/NF-κB pathway
Xu 2017 [73]	miR-145	Rats	Intramyocardial injection of lentivirus vector miR-145 3 days prior to ischemia	Permanent LAD ligation	Improved LVEF at 2 weeks; reduced infarct size	miR-145 is cardioprotective through decreased apoptosis and mitochondrial dysfunction after ischemia
Lu 2015 [42]	miR-130a	Mice	IV injection of lentivirus-transfected miR-130a 7 days prior to ischemia	Permanent LAD ligation	Improves cardiac function, attenuates post-MI remodeling; increased LVEF at 21 days	miR-130a mediated increased angiogenesis, and decreased collagen deposition

talk among mRNAs, lncRNAs, and circRNAs [74]. Because of the extent of interactions non-coding RNAs have, changes in expression of non-coding RNAs are expected following every physical or pharmacological intervention. Some of the altered expression can be related to the direct effect of the intervention, while others may be part of counter-regulatory mechanisms. There is an interest in using non-coding RNA-based therapy to induce cardioprotection in patients with ST elevation myocardial infarction (STEMI) to attenuate IRI and reduce infarct size. When using miRNA-based therapies for IRI, there are a number of delivery mechanisms that have been used, and each has specific advantages and disadvantages. Therapeutic strategies include using miRNA mimics or "agomirs" or using "antagomirs." Antagomirs are antisense oligonucleotides containing a partial or full complementary sequence of the target miRNA, which act as a molecular sponge to reduce endogenous levels of the target miRNA upon binding of the antagomir and target sequence of the miRNA [53, 56]. In addition, non-coding RNA therapy can be used after ischemia/reperfusion to reduce inflammation, apoptosis, fibrosis and adverse remodeling, and to increase angiogenesis and recovery (Table 2 and Table 5). However, due to the non-specific action of non-coding RNAs, the multiple targets of miRNA and the complex cross-talk among non-coding RNAs, the downstream clinical effects of miRNA-based therapy can be unpredictable, especially if used chronically [15].

miRNA Prior to Ischemia-Reperfusion

IRI is caused by a transient decrease in tissue oxygen delivery secondary to acute arterial occlusion, followed by rapid restoration of blood flow. This initiates a cascade of injuries leading to cardiomyocyte dysfunction and death: an initial ischemic injury caused by tissue hypoxia, and a second injury pattern following reperfusion characterized by a burst of reactive oxygen species, reactive nitrogen species, and inflammation secondary to mitochondrial dysregulation following reperfusion [24, 41, 47]. Prior to ischemia, there are a few possible therapeutic roles for miRNA to decrease necrosis and MI size. Ischemic preconditioning (IPC) and remote ischemic conditioning (RIC) are both cardioprotective pathways in which miRNAs are involved. IPC is a form of cardioprotection achieved through the controlled local application of transient, sub-injurious ischemic episodes prior to the index ischemic event. Cellular damage during the index ischemic event is then attenuated because of the "preconditioned" myocardium [55]. There are two miRNA shown in vitro to mediate IPC: miR-21 and miR-451 [47]. The protective roles of these miRNAs were demonstrated in experimental knockout (KO) mice and rat models, in which the protective effects of IPC were ameliorated in the KO animals (Table 6). Levels of miR-21 and miR-451 were both increased following IPC [11, 64]. The cardioprotective effect of miR-451 is thought to be mediated by a decrease in oxidative stress signaling [64], while the protective effect of miR-21 is thought to be through regulation of PDCD4, a potential mediator of cardiomyocyte apoptosis [11].

RIC is a form of myocardial protection similar to IPC, but in RIC, the sub-lethal ischemic events are applied to organs remote from the heart itself [7]. The mechanism is thought to involve three steps: signal generation at the remote site; a connection or pathway between the remote organ and the target organ; and the activation of protective mechanisms within the target organ itself [54]. There are no known studies investigating miRNA expression at the site that is being ischemically conditioned remotely; however, there has been investigation into miRNA expression within cardiac tissue during RIC, as well as research into the role of circulating miRNA as the signal transducer of RIC [36, 49]. Li showed an elevation in the plasma levels and cardiac expression of miR-144 following RIC, as well as the protective effect of miR-144 following ischemia-reperfusion (Table 6) [36].

There are many other miRNAs that have various protective mechanisms that have been studied in animal models. In models of permanent coronary artery occlusion, knocking out miR-21 [76], miR-144 [28], or miR-126 [61] prior to ischemia resulted in increased infarct size, pointing to the protective role of these miRNAs. On the other hand, pretreatment with miR-155 [31], miR-130a [42], or miR-145 [73] prior to permanent coronary ligation led to a reduced infarct size and increased left ventricular (LV) function (Table 1). In models of ischemia-reperfusion, pretreatment with miR-22 [9] led to decreased infarct size, while inhibiting miR-494 [62] led to increased infarct size (Table 3), indicating the cardioprotective nature of both miR-22 and miR-494.

miRNA and Cardiac Remodeling After MI

miRNAs have an integral role in cardiac remodeling after ischemic cardiac injury, and a large number of miRNAs have been implicated in several stages of remodeling [10]. A comprehensive review of all miRNAs involved in cardiac remodeling is beyond the scope of this review; herein, we focus on miRNAs implicated in remodeling after ischemia-reperfusion.

Cardiac remodeling after ischemic injury is a dynamic process involving hypertrophy, inflammation, fibrosis, and angiogenesis, and miRNA are intimately involved in the regulation of these processes [10]. There is a normal inflammatory response after MI; however, this process must be controlled and suppressed in a timely manner, as continued inflammation can lead to increased tissue damage leading to left ventricular dysfunction [20]. To this point, circulating miR-146a and miR-21 levels, both implicated in the inflammatory response, were

Table 2 Permanent ischemic models

Treatment after ischemia has started

Study	miRNA	Animal	Therapy	Ischemia	Downstream effects	Mechanism of action
Bayoumi 2017 [2]	miR-532	Mice	Intramyocardial injection of miR-532 antagomir immediately after induction of ischemia	Permanent LAD ligation	Increased cardiac cell death and fibrosis, decreased vascularization, and impairment of ventricular function	miR-532 is cardioprotective via regulation of endothelial to mesenchymal cell transition
Garikipati 2017 [21]	miR-375	Mice	Subcutaneous injection of anti-miR-375 immediately after induction of ischemia	Permanent LAD ligation	Anti-miR-375 reduced infarct size, improved LV function	Blocking miR-375 activity decreased inflammation, improved neoangiogenesis, reduced apoptosis
Fiedler 2011 [19]	miR-24	Mice	Retroorbital injection of miR-24 antagomir immediately after induction of ischemia	Permanent LAD ligation	Reduced endothelial apoptosis, enhanced vascularization, decreased infarct size, and improved cardiac function	miR-24 regulates endothelial cell survival and angiogenesis; low-dose inhibition showed favorable effects
Wang 2012 [63]	miR-24	Mice	Intramyocardial injection of lentivirus vector miR-24 15 min after induction of ischemia	Permanent LAD ligation	Attenuated fibrosis and decreased infarct size, improved LVEF at 2 weeks	miR-24 regulates cardiac fibrosis via the furin-TGFB pathway
Meloni 2013 [45]	miR-24	Mice	IV injection of adenovirus-vector miR-24 antagomir immediately after induction of ischemia	Permanent LAD ligation	Increased angiogenesis/capillary density, reduced infarct size, improved echocardiographic function at 14 days	miR-24 inhibition initially affects endothelial cells; inhibition leads to increased angiogenesis
Ge 2019 [22]	miR-26b	Mice	IV injection miR-26b agomir 5 min after and 3 days after induction of ischemia	Permanent LCA ligation	Decreased inflammatory response, less fibrosis/LV dilatation	miR-26b reduces inflammatory response; improve myocardial remodeling through MAPK regulation
Hu 2010 [30]	miR-210	Mice	Intramyocardial injection of miR-210 15 min after ischemia	Permanent LAD ligation	Decreased infarct size, improved angiogenesis, and improve LVEF at 8 weeks	miR-210 upregulates angiogenic factors, prevents apoptosis
Xiao 2018 [72]	miR-9-5p	Mice	Intramyocardial injection of miR-9-5p antagomir after induction of ischemia	Permanent LAD ligation	Decreased post-MI apoptosis; attenuated inflammatory response	Suppression of miR-9-5p leads to decreased adverse remodeling/fibrosis after MI
Huang 2014 [32]	miR-34	Mice	IV injection of miR-34 antagomir for 1–3 days after coronary ligation	Permanent LAD ligation	Inhibition of miR-34 led to decreased fibrosis post-MI	miR-34 is profibrotic through interaction with fibroblasts causing increased collagen deposition, modulates TGF-B pathway
Martinez 2017 [43]	miR-31	Rats	Subcutaneous injection of miR-31 antagomir 2 days after coronary ligation	Permanent LAD ligation	miR-31 inhibition improved LVEF at 30 days, attenuated fibrosis	miR-31 regulates several genes implicated in cardiac function and structure post-MI
Pan 2012 [48]	miR-101	Rats	Injection into LV cavity of adenovirus vector miR-101 3 days after coronary ligation	Permanent LAD ligation	Improved LVEF at 1, 2, 4 weeks	miR-101 is antifibrotic via suppression of c-Fos and its downstream protein TGFβ1
Bonauer 2009 [4]	miR-92a	Mice	Intravenous injection of miR-92a antagomir at days 0, 2, 4, 7, 9 after coronary ligation	Permanent LCA occlusion	Improved LVEDV at day 14; improved neovascularization post-MI	miR-92a acts as endogenous repressor of angiogenesis
Li 2018 [39]	miR-144	Mice	IV injection of miR-144 at day 0, 1, 3, then every 3 days until day 28 after coronary ligation	Permanent LAD ligation	Reduced infarct size, improved LV remodeling	miR-144 reduced fibrosis, activated autophagy, decreased inflammation and apoptosis

predictive of adverse LV remodeling after STEMI [40]. In permanent coronary ligation models, the post-infarction inflammatory response was inhibited by experimentally increasing the in vivo activity of miR-26b [22], miR-144 [39], miR-9-5p [72] (Table 2), miR-21 [76], and miR-155 [31] (Table 1). Also, the inhibition of miR-375 activity led to decreased inflammation (Table 2) [21]. miR-21, along with its role in IPC, inhibits the post-infarction inflammatory response, and miR-

Table 3 Ischemia-reperfusion models

Treatment before ischemia-reperfusion						
Study	miRNA	Animal	Therapy	Ischemia	Downstream effects	Mechanism of action
Chen 2015 [9]	miR-22	Rats	Intramyocardial miR-22 agomir 24 h before ischemia	LAD ligation × 30 min/24 h reperfusion	Reduced apoptosis, improved LVEF at 24 h	miR-22 is anti-apoptotic via downregulation of Cav3, leading to restored eNOS activity
Wang 2010 [62]	miR-494	Mice	3× daily IV injections of miR-494 antagomir prior to ischemia on days 2, 1, 0	LAD ligation × 30 min; 24 h of reperfusion	miR-494 antagomir sensitized hearts to IRI; led to increased apoptosis, depressed cardiac function post-MI	miR-494 is cardioprotective via regulation or both pro- and anti-apoptotic mechanisms

21 KO mice had increased inflammation and scar size after permanent coronary ligation (Table 1) [76]. Another miRNA implicated in the inflammatory response is miR-202-3p, and increased activity led to an attenuated inflammatory response after IRI (Table 4) [71].

The fibrotic response post-MI is a complex interplay between various signaling pathways. Initially, a physiological response to infarction, the persistent activation of the fibrosis pathway leads to adverse remodeling. Short-term activation of pro-survival and anti-apoptotic pathways are beneficial by conferring protection against IRI; however, prolonged activation leads to adverse remodeling and resultant ventricular dysfunction [77].

The transforming growth factor β (TGF-β) pathways play a central role in fibrosis and ventricular remodeling, and there are many miRNAs implicated in the TGF-β pathway: miR-101 [48], miR-24 [63], miR-15 family (including miR-15a, miR-15b, miR-16, miR-195, miR-497) [33], miR-34a [32], and miR-155 [10]; miR-29 [58], and miR-22 [9, 10, 13].

In the experiments using permanent coronary ligation, fibrosis and other fibrotic markers (collagen content) were decreased with increased activity of miR-130a [42], miR-24 [63], miR-9-5p [72], miR-34 [32], miR-31 [43], miR-101 [48], and miR-144 (Tables 1 and 2). Both agomir- and antagomir-based models were used to increase expression of the target miRNAs. Knockout of miR-144 led to increased collagen content, and worsened ejection fraction after infarction, pointing to its protective and possibly antifibrotic role [28]. In IRI models, by increasing the expression of miR-202-3p [71] and miR-17-3p [52] using agomir-based therapy, there was decreased fibrosis post-IRI (Tables 4 and 5).

miR-130a acts to decrease fibrosis through the "phosphatase and tensin homologue on chromosome 10" (PTEN) pathway, and increased miR-130a expression in a permanent coronary ligation model led to decreased fibrosis post-MI (Table 1) [13, 42].

Angiogenesis is the process by which myocardial tissue attempts to salvage ischemic tissue, and is a central element in long-term ventricular remodeling [12]. Inadequate capillary concentration post-MI is an integral factor in the development of LV dysfunction after MI, thus increasing angiogenesis post-MI can potentially lead to improved function and decreased MI size [15]. In addition to the anti-fibrotic role of miRNA-130a, increased angiogenesis post-MI has been observed with pretreatment with miR-130a prior to permanent coronary ligation [42]. A knockout model of miR-126 led to decreased survival (Table 1) [61], implicating both of these miRNAs as affecting the pro-angiogenic pathways post-MI. In a permanent coronary ligation model, inhibition of miR-375 [21], miR-24 [19, 45], miR-92a [4] and increasing expression of miR-210 [30] all led to enhanced angiogenesis (Table 2). Using an ischemia-reperfusion model, decreasing the activity of miR-26a [34] and miR-92a [29] using antagomir therapy led to improved angiogenesis (Table 4). These miRNAs may act as endogenous repressors of angiogenesis, hence the improvement with decreased expression. miR-532 is integral for endothelial cell function in vitro, and miR-532 knockout mice had altered cardiac function after permanent coronary ligation, possibly through a loss of neovascularization after MI [2].

The apoptotic pathways following IRI are regulated by a multitude of miRNAs. In experimental models, apoptosis can be evaluated directly or indirectly by assessing scar size or post-infarction ejection fraction, a marker of cardiac contractility and therefore viable, functioning cardiomyocytes. Increasing miR-145 [73], miR-210 [30], and miR-144 [28, 39] activity in a permanent coronary ligation model led to both decreased infarct size and increased ejection fraction; while inhibiting the activity of miR-375 [21], miR-24 [19], and miR-31 [43] ultimately led to the same effects (Tables 1 and 2). Not all of these miRNAs affect only the apoptotic pathway, as miR-210 also has pro-angiogenic properties [30]. Using an ischemia-reperfusion experimental model, miR-22 [9] and

Table 4 Ischemia-reperfusion models

Treatment during ischemia-reperfusion

Study	miRNA	Animal	Therapy	Ischemia	Downstream effects	Mechanism of action
Icli 2013 [34]	miR-26a	Mice	Injection into LV cavity of miR-26a antagomir 5 min after induction of ischemia	LAD ligation × 45 min; 24-h reperfusion	Reduced infarct size; induced early angiogenesis; improved LV function at 7 days	miRNA-26 regulates angiogenic response; overexpression impairs angiogenic response
Hinkel 2013 [29]	miR-92a	Pigs	IV or intracoronary injection of miR-92a antagomir 5 min prior to reperfusion (after 55 min ischemia)	LAD occlusion × 60 min; reperfusion for either 72 h or 7 days	Reduced infarct size; increased LVEF, decreased LVEDV; increased capillary density	Inhibition of miR-92a led to increased proangiogenic factors (endothelial nitric oxide synthase21 and thymosin β4)
Bellera 2014 [3]	miR-92a	Pigs	Intracoronary injection of miR-92a antagomir microspheres 5 min after reperfusion	LAD occlusion × 49 min or 60 min	Lower microvascular resistance at 1 month post-MI	Inhibition of miR-92a leads to increased post-MI neoangiogenesis
Hullinger 2012 [33]	miR-15 family	Mice	IV injection of anti-miR-15 at onset of reperfusion	LCA ligation × 75 min; reperfusion × 24 h or 2 weeks	Anti-miR-15 reduces infarct size, inhibits cardiac remodeling, and improves LVEF, LVEDP at 2 weeks	miR-15 thought to regulate cell survival by regulating pro-survival pathways
Wu 2019 [71]	miR-202-3p	Rats	IV injection of adenovirus-transfected miR-202-3p agomir during reperfusion	LAD ligation × 30 min; 120-min reperfusion; hearts examined at 4 weeks	Improved LV function and ventricular remodeling post-MI at 4 weeks	Upregulation of miR-202-3p alleviated oxidative stress and inflammatory response; inhibited fibrosis

miR-494 [62] were both shown to be protective following IRI and led to decreased apoptosis and increased ejection fraction (Table 3), while inhibiting the miR-15 family of miRNAs had similar effects following IRI (Table 4) [33]. miR-21 [14], miR- 24, miR-210 [30], miR-494 [62], and miR-499 are other miRNAs implicated in apoptosis after IR injury [30, 81]. miR-93 has been studied in ischemic disease states (stroke, peripheral artery disease) and miR-93 knockout mice showed decreased EF 30 days after MI in a mouse model [37]. miR-1 and miR-133a were studied in an ischemia-reperfusion model utilizing ischemic post-conditioning, a process similar to ischemic preconditioning, but the sub-injurious stimuli is applied after ischemia. Mimics of both miR-1 and miR-133a injected into the myocardium prior to ischemia and led to decreased apoptosis after ischemia-reperfusion (Table 6) [27]. Levels of both of these were upregulated following ischemic post-conditioning, and it is possible that these molecules mediate the cardioprotective effects of post-conditioning.

Circular and Non-coding RNAs

The lncRNAs are beginning to be investigated as both biomarkers and therapeutic targets in cardiovascular disease, and recent research efforts have clarified the roles of lncRNAs in multiple aspects of cardiac injury and repair: particularly regeneration, hypertrophy, and endothelial function [26]. An in vitro study of myocardial cells showed the protective effect of suppressing the lncRNA, KCNQ1OT1, in simulated myocardial ischemia, which points to a possible, yet unconfirmed, detrimental role of this lncRNA in myocardial ischemia-reperfusion [38]. Urothelial carcinoma-associated 1 (UCA-1), a lncRNA, was studied as a potential biomarker in acute MI, and levels were inversely associated with miR-1 levels, an miRNA implicated in RIC, demonstrating the interplay between lncRNA and miRNAs in IRI [75]. The lncRNA autophagy-promoting factor (APF) regulates cell authophagy through modulation of miR-188-3p, which suppresses autophagy through the ATG7 pathway known to be involved in IRI [68]. Another lncRNA, cardiac apoptosis-related lncRNA (CARL), inhibits cardiac apoptosis and therefore decreases infarct size following myocardial ischemia-reperfusion through the regulation of the miR-529/PHB2 pathway [65]. H19, another lncRNA, modulates activity of miR-103/107, which regulates necrosis in mice hearts after myocardial IR through the regulation of the expression of Fas-associated protein with death domain (FADD) [67]. The lncRNA necrosis-related factor, NRF, has a regulatory role in myocardial cell death via acting as a sponge to repress miR-873 expression in myocardial IRI [69].

The circRNA, mitochondrial fission and apoptosis-related circRNA (MFACR), a negative regulator of mitochondrial apoptosis, downregulates miR-652-3p following MI in mice

Table 5 Ischemia-reperfusion models

Treatment after ischemia-reperfusion						
Study	miRNA	Animal	Therapy	Ischemia	Downstream effects	Mechanism of action
Shi 2017 [52]	miR-17-3p	Mice	IV injection of miR-17-3p agomir every 3 days × 4 weeks starting 1 day after reperfusion	LAD ligation × 30 min; 4-week reperfusion	Protective against adverse remodeling, decreased apoptosis, improved LV function post-MI	miR-17-3p agomir led to decreased cardiac fibrosis and improved proliferation of cardiomyocytes

[70]. Mitochondrial dynamic related lncRNA (MDRL) targets two miRNAs, miR-484 and miR-361, which are both involved in mitochondrial regulation. In mice that were subject to ischemia-reperfusion, intracoronary delivery of transfected-MDRL reduced apoptosis by sponging and inhibiting miR-361 [66]. The circRNA, autophagy-related circular RNA (ACR), showed a protective role in myocardial ischemia/reperfusion injury in mice by inhibiting autophagy [80]. Cdr1as, a circRNA, acts a sponge for miR-7a, and overexpression of Cdr1as led to increased MI size in mice, partly mediated through decreased miR-7a expression [23]. MICRA, another circRNA, is thought to play a substantial and possibly protective role in myocardial IR, as lower circulating levels of MICRA at the time of reperfusion were indicative of worse LV function at 4 months [51]. lncRNA and circRNAs work mostly through interactions with miRNAs, further affecting downstream translation and post-transcription modifications of target proteins. The role of circRNAs and lncRNAs in myocardial ischemic/reperfusion injury is still being defined, and it is a major topic of research currently [1].

Delivery Mechanisms of miRNA

An efficient and specific delivery system is required for successful miRNA therapy. A delivery system is needed to overcome the inherent instability of the miRNA in circulation, the off-target effects, and inappropriate distribution, yet it also need not limit cell permeability, increase excretion, or accumulate in off-target organs [56, 79]. Because miRNAs are small and water soluble, they can be injected intravenously or subcutaneously [53]. However, because miRNAs are single stranded and open ended, they are either degraded in circulation by systemic nucleases, excreted renally, or are

Table 6 Inducing protection

IPC, RIC, post-conditioning						
Study	miRNA	Animal	Therapy	Ischemia	Downstream effects	Mechanism of action
Cheng 2010 [11]	miR-21	Rats	Injection of LV cavity with adenovirus vector miR-21 antagomir 24 h prior to ischemia	LAD occlusion × 60 min; 3 h reperfusion	miR-21 KO inhibited protective effects of IPC	miR-21 mediates IPC and has anti-apoptotic effects through PDCD4 regulation
Wang 2012 [64]	miR-144/451	Mice	miR-144/451 conditional knockout (KO)	LAD occlusion using 4 cycles of 6-min occlusion/6-min reperfusion; 30 min LAD occlusion/24 h reperfusion	miR-144/451 KO ameliorates protective effect of IPC, led to increased infarct size	miR144/451 mediates IPC via Rac-1 mediated oxidative stress signaling
Li 2018 [36]	miR-144	Mice	IV injections of miR-144 antagomir 60 min prior to RIC or daily injections on days 3, 2, 1	4 cycles of 5-min limb occlusion/5-min reperfusion; global ischemia for 30 min; 60-min reperfusion	Anti-miR-144 abolished RIC, led to increased infarct size	miR-144 induces early and late cardioprotection; possibly through RIC
He 2011 [27]	miR-1/miR-133a	Rats	Intra-myocardial injection of miR-133a and miR-1 mimics 48 h prior to ischemia	Ischemia × 60 min, 180 min reperfusion; ischemic post-conditioning using 30-s ischemia/30-s reperfusion × 3 cycles	miR-1 and miR-133a mimics both attenuated cellular apoptosis; up-regulated following post-conditioning	miR-1 and miR-133a protective against IRI by downregulating apoptotic genes

phagocytized by monocytes, which limit the clinical applicability of naked miRNAs as therapy [35]. Chemically modifying the miRNA using either locked nucleic acids (LNA) or 2'-O-methyl group (OME) can increase stability in vivo, and is the basis for many antagomir therapies. Antagomirs are the most frequently used approach for therapeutic use of miRNA therapy [59]. Other problems arising with certain delivery systems are accumulation in off-target organs (liver, spleen), non-specific uptake, excretion, toxicity, and an immune-mediated response [53]. Systemic delivery requires stability of the delivery system in circulation, and specific targeting to tissues.

Ongoing studies have identified some strategies for systemic delivery. Viral vectors can be utilized to increase stability in circulation during transportation, and the viral capsid can be manipulated for tissue-specific delivery [53]. Adeno-associated viruses have shown high levels of cardiospecificity, and in clinical trials for gene therapy have demonstrated acceptable safety profiles [59]. Viral vectors do have pitfalls including immune reactions and viral integration into the host genome [53]. Other lipid-based vectors, like liposomes, have been used and are protective against nucleases, lysosomal and endosomal degradation in circulation [35]. As natural transporters, exosome delivery systems are an attractive option. These offer specificity by binding in receptor-mediated fashion, limiting off-target side effects [44]. Nanoparticles are another possible strategy, and have been used in an attempt to overcome excessive inflammatory reactions [8]. An intriguing concept for drug delivery for IR injury is "passive drug targeting" where a colloid-based drug delivery system is used. These molecules then accumulate at sites of inflammation, as occurs in IRI, because the endothelium at these sites is compromised and will allow passive diffusion through the vessel [35]. Another possible strategy for systemic delivery are mesenchymal stem cell-derived extracellular vesicles (MSC-EV), which have been studied showing miRNAs are sorted into and delivered via MSC-EVs in vivo [50]. One study showed MSC-EVs with miR-22 were upregulated in ischemic preconditioning [18]. MSC-EV, like the other delivery systems, is still undergoing research for clinical use, but has shown promising early results.

Conclusion

The review highlights the intricate, extensive changes in expression of miRNAs, circRNAs, lncRNAs before, during, and after IRI. By regulating the inhibition of translation and post-transcriptional modification, miRNAs affect several biological pathways involved in IRI. The expanding role of these non-coding RNAs should be integrated into the current framework of IRI. Prior to ischemia, there are protective miRNAs that act to precondition the myocardium locally and remotely. These miRNAs can then protect the myocardium during the index ischemic event, mostly through mitochondrial protective mechanisms and inhibition of apoptosis. After infarction, miRNAs can decrease apoptosis, inflammation, and ultimately inhibit the fibrotic response. The initial fibrotic response to MI is adaptive, so it is vital to target the inhibition to the pathological long-term fibrotic response. Because miRNAs have numerous wide-ranging effects, and there is vast interplay between all non-coding RNAs that can have far-reaching effects throughout the entire body, any therapies must be assessed for risks, benefits, and off-target effects in both the short term and long term. Delivery systems will be required for the therapeutic application of any miRNA-based therapies. Chemical modification to make antagomirs, using various carriers (lipids, exosomes, nanoparticles), or using viral vectors to transfect human cells, has all been used to some effect in animal models. Off-target side effects, unpredictable distribution, and inefficient delivery all must be overcome by whatever delivery system is used. Further research is needed to further define the exact role all of the non-coding RNAs have in IRI, so that adequately designed clinical trials can be performed to translate these findings into human studies. In conclusion, miRNA-based therapy can potentially provide routes for extremely specific and efficacious treatment of ischemic heart disease at all stages of ischemia/reperfusion: prior to, during, after, and preventing adverse remodeling after ischemia to prevent downstream heart failure and other chronic cardiomyopathies.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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