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Mini Review

Systematic review and network analysis of microRNAs involved in cardioprotection against myocardial ischemia/reperfusion injury and infarction: Involvement of redox signalling

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ABSTRACT

Although myocardial ischemia-reperfusion injury (I/R) and its pathological consequences are the leading cause of morbidity and mortality worldwide, cardioprotective therapeutics are still not on the market. Oxidative stress, a major contributing factor to myocardial I/R, changes transcription of coding and non-coding RNAs, alters post-transcriptional modulations, and regulate protein function. MicroRNA (miRNA) expression can be altered by oxidative stress and microRNAs may also regulate cytoprotective mechanisms and exert cardioprotection againts I/R. Transcriptomic analysis of I/R and oxidative stress-induced alterations followed by microRNA-mRNA target interaction network analysis may reveal microRNAs and their mRNA targets that may play a role in cardioprotection and serve as microRNA therapeutics or novel molecular targets for further drug development. Here we provide a summary of a systematic literature review and in silico molecular network analysis to reveal important cardioprotective microRNAs and their molecular targets that may provide cardioprotection via regulation of redox signalling.

Despite advances in myocardial reperfusion therapies, either with percutaneous coronary intervention (PCI) or with coronary artery bypass graft (CABG) surgery, acute myocardial ischemia-reperfusion injury, consequent myocardial infarction and post-ischemic heart failure are still the leading causes of morbidity and mortality in industrialized societies. For this reason, there is a continuous demand for novel cardioprotective approaches to attenuate detrimental effects of myocardial ischemia-reperfusion injury (I/R) [1].

Ischemic conditioning techniques were first described more than 30 years ago as sub-lethal cycles of myocardial ischemia and reperfusion before a longer, potentially fatal ischemia-reperfusion (preconditioning). Ischemic preconditioning is still the most effective and reproducible strategy to reduce myocardial infarct size in preclinical models. Clinically applicable forms of ischemic conditioning, such as postconditioning, when the sub-lethal cycles of ischemia-reperfusion were applied at the time of reperfusion, and remote conditioning, when the ischemia-reperfusion cycles are applied on a remote organ, were described later. On top of ischemic conditionings, pharmacological approches targeting cardioprotective cellular mechanisms were shown to be effective in preclinical models [1]. Although these cardioprotective therapeutic interventions have been shown to be effective in laboratory settings, their clinical translation has not been successful so far due to the presence of several confounding factors [2–6]. One factor seems to be the simplistic hypothesis-driven biased approach to reveal mechanism of ischemic conditioning and to discover and validate cardioprotective targets [7–9].

Therefore, a more complex way of target discovery and validation must be utilized for the successful development of cardioprotective therapies for myocardial ischemia/reperfusion injury, i.e. multitarget

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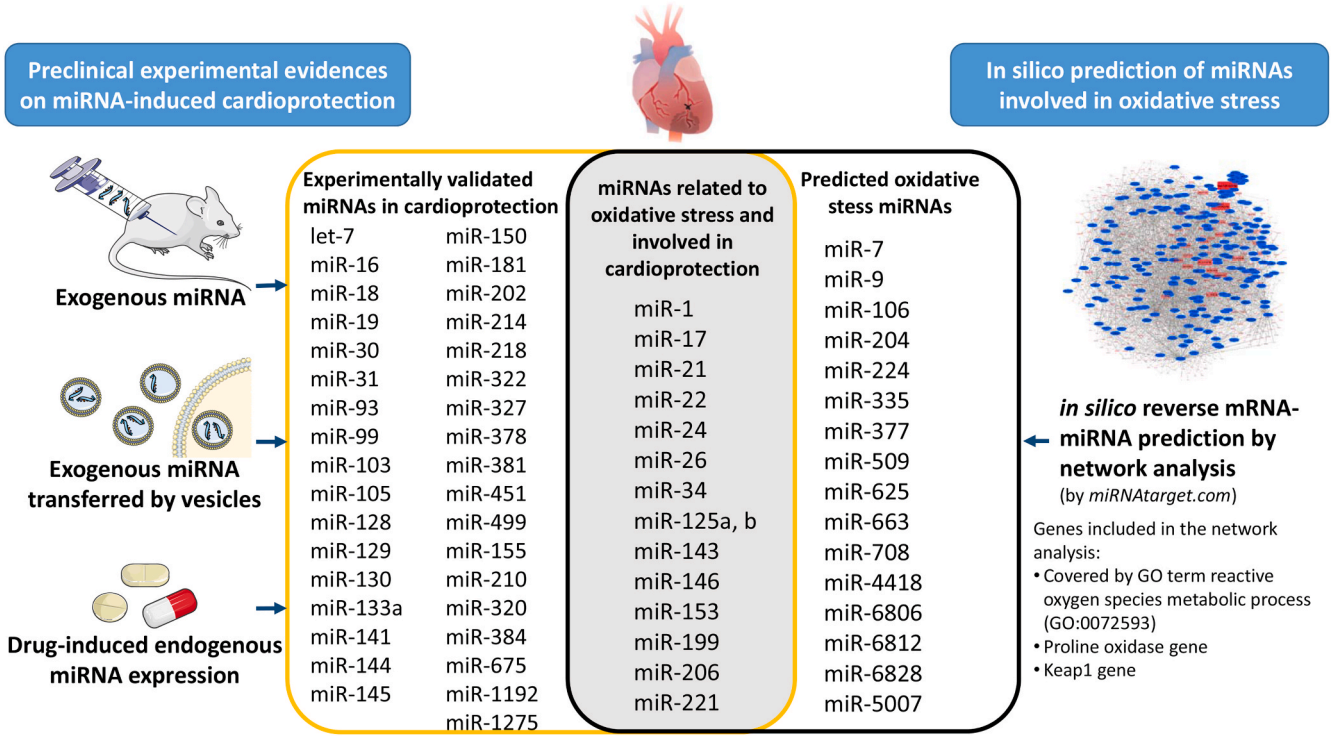

Fig. 1. Graphical summary of systematic collection of microRNAs involved in cardioprotection against myocardial ischemia/reperfusion injury and their association to redox signalling. MicroRNAs are collected based on scientific evidence on their association with cardioprotection (left) or with in silico reverse mRNA-microRNA prediction by network analysis (right). Genes included in the network analysis were covered by GO term: reactive oxygen species metabolic process (GO:0072593), proline oxidase and Keap1 gene manually added. Central section of Venn-diagram highlights microRNAs related to oxidative stress and involved in cardioprotection.

therapeutics and network medicine that include unbiased multiomics approach and network analysis [9,10] that has the potential to reveal the molecular network for I/R and cardioprotection.

1. MicroRNAs as regulators of gene expression in I/R injury and cardioprotection targeting redox signalling

MicroRNAs are non-coding, single stranded RNAs with a size between 20 and 22 nucleotides. Although expression of microRNAs is regulated by transcription factors, microRNAs themselves are involved in fine-tuning of gene expression in cardiac physiology and pathology [11,12]. MicroRNAs are evolutionally conserved regulators of gene expression through incomplete base-paring with their target mRNAs leading to mRNA degradation or halted protein translation [13]. MicroRNAs can be grouped into families, based on the mature microRNA or pre-miRNA structure or sequence [14]. MicroRNAs can also grouped into polycistronic clusters, in which many microRNAs are expressed from a common primary transcript [15]. These functional or structural classes of microRNAs can regulate complex cellular signalling pathways. More than half of the human protein coding genes are estimated to be post-transcriptionally regulated by microRNAs [16]. The precise role of microRNAs in the mechanism of myocardial ischemia-reperfusion injury and cardioprotection was investigated by several groups, revealing the role of microRNAs in many cellular processes including cellular redox signalling [9]. Pathological levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) has been proven to contribute to irreversible tissue injury and may interfere with cardioprotection [17–19]. There are several key endogenous and exogenous oxidant and antioxidant mechanisms, which are responsible for redox balance and can be targeted in cardioprotection as reviewed in detail in the current themed issue (Andreadou et al. FRBM 2021; Bartekova et al. FRBM 2021) and elsewhere [20].

Cardioprotective microRNAs that reduce tissue damage caused by I/R have been previously reviewed in excellent papers. The search term "(cardioprotection OR acute ischemia) AND (miRNA OR microRNA)" provides over 171 review papers in the PubMed database (date of search: Mar 11, 2021), however, none of these have systematically collected and described the role of microRNAs in cardioprotection and have not provided predicted lists of possible microRNAs that may target genes involved in redox signalling and may therefore be involved in cardioprotection.

Therefore, the focus of the current review is to provide a brief summary of a systematic analysis of the literature from the last 6 years focusing on microRNAs that may provide cardioprotection via regulation of cellular redox signalling. Moreover, here we provide a reverse prediction of interacting microRNAs by an unbiased interaction network analysis of oxidative stress genes. Fig. 1 summarizes the methods and the results of the current systematic review and literature and network analysis of genes involved in redox signalling (Fig. 1).

2. MicroRNAs in preclinical models of cardioprotection - association to oxidative stress

Several studies described multiple microRNAs as key regulators of cardiocytoprotection and improvement of cardiac function after myocardial infarction (MI). Here we systematically collected and analyzed microRNAs that were shown to be involved in acute I/R injury and cardioprotection. The following search string combination was used: *"(heart OR myocard*) AND (ischemi* OR reperfus* OR infarct*) AND cardioprot* AND (miRNA OR microRNA OR "non-coding RNA" OR "non coding RNA")"* in PubMed database (search date: from Jan 1, 2014–Mar 11, 2021), that resulted 270 originial research papers. After reviewing all these papers, 118 was found relevant for current topic from 2014 to date and the articles were further classified according to the method of application of the

Table 1
List of microRNAs with *in vivo* experimental evidence on their association with cardioprotection against I/R injury based on systematic literature review limited to the last 6 years. Articles are grouped in three groups based on the method used to deliver microRNAs. **Exogenous native microRNA *in vivo***: *in vivo* preclinical reports where cardioprotection has been induced after direct delivery of exogenous microRNA. **MicroRNA delivery by carrier vesicles *in vivo***: *in vivo* preclinical reports in which a vesicular or other type of transport method was used to deliver exogenous microRNA and thus cardioprotection was achieved. **Induction of endogenous microRNAs by drugs or other treatments *in vivo***: endogenous microRNA changes are induced by a drug or other treatment that lead to cardioprotection. (I/R – ischemia-reperfusion, MI – myocardial infarction, post-MI HF – post-myocardial infarction heart failure). Literature search has been done in PubMed database (from Jan 1, 2014–Mar 11, 2021) and major findings of resulting papers are summarized.

microRNA	Effect on cardioprotection			Oxidative stress related effect	PMID
	Protective approach	MI model	Protective effect		
Exogenous microRNA treatment to induce cardioprotection *in vivo*					
let-7 family	let-7 lentiviral local overexpression	diabetic rat; I/R	Transfection of the let-7 antimiR significantly reduced the infarct size of diabetic rats	Not found	PMID: 27217295
miR-1275	miR-1275 mimic	rat; I/R	miR-1275 mimic attenuated the altered levels of myocardial enzymes and haemodynamic functions seen in MI and also reduced cardiac myocyte apoptosis and ameliorated the altered Wnt/NF-κB pathway	Nuclear factor kappa B (NF-κB) signalling was supressed by miR-1275 mimic.	PMID: 32056105
miR-129-5p	agomiR-129-5p	rat; I/R	Exogenous miR-129-5p restored cardiac function indices, alleviated cardiac injury, revealed inflammatory effects and reduced infarct size and cell apoptosis	Not found	PMID: 33084599
miR-130b-3p	miR-130b-3p inhibitor	diabetic mouse; I/R	miR-130b-3p inhibitor administrations attenuated I/R injury in the diabetic heart via AMP-activated protein kinase (AMPK) α1/α2 and Baculoviral IAP repeat-containing protein 6 (Birc6)	miR-130b-3p mimic decreased Heme oxygenase-1 (HO-1), Uncoupling protein 2 (Ucp2), and Nuclear factor erythroid 2-related factor 2 (Nrf2)	PMID: 31918577
miR-141	miR-141 mimic iv.	mouse; I/R	miR-141 mimic downregulated the expression level of ICAM-1 in heart and decreased infarct size	Not found	PMID: 26371161
miR-145	miR-145 adenoviral overexpression	rat; I/R	Overexpression of miR-145 alleviated I/R-induced myocardial electrophysiological instability and apoptotic and inflammatory response via inhibition of the Calcium/calmodulin-dependent protein kinase II (CaMKII)-mediated antiapoptotic pathways	miR-145 reversed I/R-induced imbalance of Superoxide dismutase (SOD) and Malondialdehyde (MDA) levels, and inhibited NF-κB p65 anti-inflammatory pathways	PMID: 31583047
miR-145	miR-145 encapsulated in liposomes iv.	rabbit; I/R	miR-145 reduced infarct size and improved the cardiac function and remodelling	Not found	PMID: 26432843
miR-146b	miR-146b overexpression	rat; I/R	miR-146b overexpression reduced the infarct size, apoptosis and release of Creatine kinase (CK) and Lactate dehydrogenase (LDH). Smad4 was predicted and verified as target of miR-146b target	Not found	PMID: 28337293
miR-150	miR-150 overexpression	mouse; I/R	miR-150 improved cardiac function, reduced myocardial infarction size, inhibition of apoptosis, and reduced inflammatory Ly-6C(high) monocyte invasion	Not found	PMID: 25466411
miR-153	miR-153 inhibitor adenoviral vector	rat; I/R	Suppression of miR-153 decreased cleaved caspase-3 and Bcl-2-associated X (Bax) expression, and increased B cell lymphoma 2 (Bcl-2) expression	miR-153 inhibition upregulated Nrf2, and Nrf2/HO-1 signalling	PMID: 32517768
miR-202-5p	agomiR-202-5p	rat; I/R	Overexpression of miR-202-5p reduced infarct size, revealed the dysregulation of myocardial enzymes and Ca2+ overload	miR-202-5p reduced ROS production, and increased SOD expression	PMID: 31062423
miR-22	miR-22 adenoviral overexpression	rat; I/R	miR-22 overexpression markedly reduced infarct size, improved cardiac function, and inhibited p38 MAPK, CBP, c-Jun-AP-1, p-c-Jun-AP-1 expression levels and proinflammation mediators	Not found	PMID: 27882145
miR-22	miR-22 adenoviral overexpression	rat; I/R	miR-22 overexpression reduced infarct size, release of creatine kinase (CK) and lactate dehydrogenase (LDH), and cardiomyocytes apoptosis.	Not found	PMID: 24338162

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Table 1 (*continued*)

microRNA	Effect on cardioprotection			Oxidative stress related effect	PMID
	Protective approach	MI model	Protective effect		
miR-24-3p	miR-24-3p-mimic	mouse; I/R	miR-24-3p mimic attenuated the myocardial injury, improved cardiac function and decreased the apoptosis rate	Not found	PMID: 30439713
miR-31	miR-31 antagomiR iv.	mouse; I/R	miR-31 downregulation alleviated myocardial infarct size and decreased LDH activity and MDA content	miR-31 downregulation increased SOD activity, NF-κB was identified as downstream effector.	PMID: 25925791
miR-322	miR-322 mimic	mouse; I/R	miR-322 mimic reduced infarct size via reduced apoptosis	Not found	PMID: 31150734
miR-327	adenoviral miR-327 inhibitor	rat; I/R	Down-regulation of miR-327 reduced myocardial infarct size, attenuated cardiomyocyte destruction, and alleviated inflammation	miR-327 inhibitor suppressed NF-κB signalling	PMID: 30196287
miR-378a-3p	miR-378a-3p mimic	rat; I/R	miR-378a-3p mimic suppressed cell apoptosis and I/R damage score. miR-378a-3p mimic suppressed cell apoptosis, JNK1/2 activation, cleavage of poly (ADP-ribose) polymerase (PARP) and caspase-3, and Bax/Bcl-2 ratio	Not found	PMID: 32463795
miR-499	miR-499 adenoviral upregulation	rat; I/R combined with postconditioning (IPostC)	Postconditioning induced protection and increased miR-499. IPostC + miR-499 mimics significantly inhibited inflammation and the Protein kinase C (PKC) signalling pathway and enhanced the anti-inflammatory and anti-apoptotic effects of IPostC	Not found	PMID: 32377693
miR-93	miR-93 adenoviral overexpression	rat; I/R	miR-93 reduced infarct size, LDH and CK levels and activated PI3K/AKT/PTEN signalling	miR-93 attenuated H/R induced increase in MDA and ROS generation	PMID: 27119510
miR-384-3p	mi-134/384-3p inhibition	rat; I/R	adenoviral knock-down of miR-384-3p decreased infarct size, decreased apoptosis and increased HSP70 level	Not found	PMID: 33635243
miR-1	miR-1 antagomiR	mouse, permanent occlusion; (post-MI HF)	miR-1 antagomiR exerted a significant protective effect on heart function, decreased infarct size, cardiomyocyte apoptosis and alleviating myocardial fibrosis and remodelling after 2 weeks	miR-1 antagomiR decreased 19s proteasome, 20S proteasome and ubiquitin ligase E3	PMID: 31485642
miR-105	miR-105 transfection	rat; permanent occlusion	miR-105 significantly reduced the infarct size via inhibition of Cysteine-rich protein 3 (cRIP3)/phospho-Mixed lineage kinase domain-like (MLKL) necroptotic pathway and Blc2 interacting protein 3 (BNIP3)-dependent apoptosis	Not found	PMID: 30743213
miR-1192	agomiR-1192	mouse; permanent occlusion (post-MI HF)	Exercise increased circulating miR-1192. AgomiR-1192 exerted similar cardioprotective effect as exercise training via anti-apoptotic effects in cardiac myocytes	Not found	PMID: 31733833
miR-128-3p	miR-128 anitmiR adenoviral transfer	mouse; permanent occlusion; (post-MI HF)	Inhibition of mir128-3p preserved Irs1 and ameliorated cardiac dysfunction post-MI	Not found	PMID: 32223896
miR-143	miR-143 antagomiR	mouse; permanent occlusion	MI induced apoptosis and necrosis was reversed by antagomiR-143. MI-mediated upregulation of miR-143 inhibits PKCε expression and interference with cardioprotection	miR-143 antagomiR inhibits mitochondrial membrane potential dissipation	PMID: 28887629
miR-144	miR-144 agomiR	miR-144 KO mouse; permanent occlusion (post-MI HF)	miR-144-reduced infarct size, and improved cardiac function, associated with reduced border zone fibrosis, inflammation and apoptosis	Not found	PMID: 30084039
miR-145	miR-145 adenoviral overexpression	rat; permanent occlusion (post-MI HF)	Up-regulation of miR-145 ameliorated HF-induced myocardial fibrosis and increased L-type calcium current (ICa) density while decreased ICa response to β-adrenergic stimulation with isoproterenol	Not found	PMID: 32554856

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Table 1 (*continued*)

microRNA	Effect on cardioprotection			Oxidative stress related effect	PMID
	Protective approach	MI model	Protective effect		
miR-145	miR-145 lentiviral overexpression	rat; permanent occlusion (post-MI HF)	miR-145 overexpression significantly reduced infarct size and cardiomyocyte apoptosis. MiR-145 attenuates hypoxia-induced cardiomyocyte apoptosis	MiR-145 attenuates hypoxia-induced mitochondrial dysfunction *in vitro*	PMID: 29218098
miR-16	miR-16 lentiviral inhibitor	rat; permanent occlusion	Knockdown of miR-16 alleviated acute cardiac injury and significantly suppressed β2-adrenergic receptor protein expression	oxidative stress upregulated miR-16	PMID: 28423616
miR-181a	miR-181a adenoviral overexpression	mouse; permanent occlusion	Improved cardiac function and deactivated aldosterone-mineralocorticoid receptor pathway post-MI. Adamts1, a direct target of miR-181a, was found to be downregulated with miR-181a overexpression	Not found	PMID: 32304626
miR-18a	miR-18a antagomiR	rat; permanent occlusion (post-MI HF)	Downregulation of miR-18a promoted Brain-derived neurotrophic factor (BDNF) expression, which offers protection against AMI	increased SOD and a decreased MDA level detected in the miR-18a inhibitor group	PMID: 31168354
miR-21	miR-21 lentiviral overexpression in the left ventricle	mouse; permanent occlusion	miR-21 reduced infarct size, collagen I level, fibronectin content and number of α-SMA-positive and apoptotic cells	Not found	PMID: 25809568
miR-214	pre-miR-214 adenoviral transfection	rat; permanent occlusion (post-MI HF)	miR-214 overexpression exerted cardio-protective effects by inhibition of fibrosis and the inhibitory effect involved Transforming growth factor beta 1 (TGF-β1) suppression and matrix metallopeptidase 1 (MMP-1)/Tissue inhibitor of metallopeptidases (TIMP-1) regulation	Not found	PMID: 27357906
miR-218	miR-218 inhibitor	rat; permanent occlusion (post-MI HF)	Suppression of miR-218 alleviated cardiac fibrosis and cardiac function impairment, and stimulated angiogenesis	inhibited miR-218 expression alleviated the oxidative stress: serum levels of MDA were diminished and activity of Plasma glutathione peroxidase (GSH-Px) and SOD was promoted.	PMID: 31408435
mir-221	miR-221 mimic	rat; permanent occlusion (post-MI HF)	miR-221 mimics reduced infarct size and cardiac fibrosis, ameliorated adverse left ventricle remodelling and preserved cardiac function. miR-221 inhibits ischemia-induced apoptosis	Not found	PMID: 31261033
miR-30 family	miR-30 family LNA-inhibitors iv.	mouse; permanent occlusion	miR-30 family inhibitor protected against hypoxic cell injury by elevating cystathionine-γ-lyase (CSE) and H_2S level	miR-30 inhibitor reduced MDA and increased SOD and catalase (CAT)	PMID: 25203395
miR-30d	miR-30d overexpression (genetic, lentivirus, or agomiR-mediated)	rat and mouse; permanent occlusion (post-MI HF)	miR-30d improved cardiac function, decreased myocardial fibrosis, and attenuated cardiomyocyte apoptosis	miR-30d expression is selectively enriched in cardiac myocytes, induced by hypoxic stress	PMID: 33092465
miR-381	miR-381 antagomiR	mouse; permanent occlusion (post-MI HF)	miR-381 antagomir significantly reduced infarct size and attenuated apoptosis. miR-381 inhibition re-established Notch signalling	miR-381 expression was increased by oxidative stress	PMID: 30105734
miR-99	miR-99 lentiviral overexpression	mouse; permanent ischemia	miR-99 overexpression improved in both left ventricular function and survival ratio and decreased cellular apoptosis and increased autophagy in cardiomyocytes	Not found	PMID: 24628978
miR-103	locked nucleid acid (LNA) miR-103 inhibitor	mouse; isoprenalin induced MI	miR-103 silencing induced improvement in the troponin-I and CK-MB levels	Not found	PMID: 33577038
Exogenous microRNA transferred by carrier vesicles to induce cardioprotection in vivo					
miR-181b	Cardiosphere-derived cell (CDC) exosomes	rat; I/R	Exosomes reduced infarct size and reduced the number and polarisation of macrophages within the infarcted tissue. Exosomes were selectively loaded with miR-181b conferred cardioprotection	Not found	PMID: 28411247
miR-182	Mesenchymal stromal cell derived exosomes (MSC-Exo)	mouse; I/R	MSC-Exo reduced infarct size improved cardiac function, reduced hypertrophy of		PMID: 30753344

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Table 1 (*continued*)

microRNA	Effect on cardioprotection			Oxidative stress related effect	PMID
	Protective approach	MI model	Protective effect		
			cardiomyocytes, reduced inflammatory cell infiltration. miR-182 is enriched in MSC-Exo	Inducible nitric oxide synthase (iNOS), Toll like receptor 4 (TLR4), and NF-κB p-P65 was down-regulated	
miR-21	mouse cardiac fibroblast derived iPS cell exosome	mouse; I/R	Exosomes protected against ischemia/reperfusion. iPS-exo delivered miR-21 and miR-210	HIF1α signalling was effected by miR-210	PMID: 26000464
miR-21a-5p	miR-21 KO mesenchymal stem cell (MSC) exosomes	mouse; I/R	Infarct size reduction was abrogated in miR-21 KO exosome group. There were significant decreases in levels of miR-21 target genes in wild type exosome treated mice	Not found	PMID: 29698635
miR-221/222	Adipose-derived stem cells (ADSC-Exo) derived exosome	mouse; I/R	I/R reduced miR-221/222 expression, while ADSC-Exo treatment increased	Not found	PMID: 33344446
miR-24	Remote ischemic conditioning induced plasma exosomes	rat; I/R	miR-24 was expressed in remote conditioning induced plasma exosomes, which reduced infarct size and improved heart function and decreasing apoptosis	miR-24 had anti-apoptotic function under conditions of oxidative stress	PMID: 29476052
miR-26a	Hypoxic human mesenchymal stem cell (MSC) vesicles	rat; I/R	Vesicles reduced infarct size, and diminished arrhythmias. miR-26a was significantly increased in hypoxic MSC vesicles	Not found	PMID: 29978610
miR-125b	Mesenchymal stem cell (MSC) derived exosomes	mouse; permanent occlusion	MSC-exos improved myocardial recovery by impeding autophagy. Exosomes from anti-miR-125b treated MSCs was ineffective	Not found	PMID: 29921652
miR-125b-5p	Hypoxia-conditioned bone marrow mesenchymal stem cell exosomes (Hypo-Exo)	mouse; permanent occlusion (post-MI HF)	miR-125b-5p is enriched in Hypo-Exo. miR-125b knockdown Hypo-Exo significantly increased the infarction area and suppressed cardiomyocyte survival post-MI	Not found	PMID: 30613290
miR-125b-5p	Human umbilical cord mesenchymal stem cell (hucMSC) exosomes	rat; permanent occlusion	HucMSC-exosomes improved cardiac systolic function and protected cardiac myocytes. HucMSC-exosomes inhibited miR-125b-5p expression in injured cardiac myocytes *in vivo*	Not found	PMID: 29484378
miR-146a	miR-146a-modified adipose-derived stem cell (ADSC) exosomes	rat; permanent occlusion (post-MI HF)	ADSC exosomes containing miR-146a decreased infarct size, suppressed myocardial fibrosis, inflammation and myocardial apoptosis	ADSC exosome decreased NF-κB p65 phosphorylation	PMID: 30362610
miR-150	miR-150 mimic-transfected macrophage EVs	mouse; permanent occlusion (post-MI HF)	EV-derived miR-150 reduced infarct size. Further, prevented cardiomyocyte apoptosis *in vitro*, as evidenced by downregulated Bax and cleaved-caspase 3 and upregulated Bcl2	Not found	PMID: 33164579
miR-155-5p	anti-miR-155-5p-AMSCs (aged mesenchymal stem cells)	aged mouse; permanent occlusion (post-MI HF)	Anti-miR-155-5p-AMSC improved cardiac function by enhancing angiogenesis and promoting cell survival	Not found	PMID: 32196916
miR-185	Bone marrow mesenchymal stem cells-derived exosomal (MBSCs-EXO)	mouse; permanent occlusion (post-MI HF)	MBSCs-EXO increased miR-185 expression and reduced infarct size, repressed ventricular remodelling and apoptosis	Not found	PMID: 31945609
miR-19a	GATA4 overexpresing mesenchymal stem cells (MSCs) exosome	rat; permanent occlusion	Exosomes restored cardiac contractile function and reduced infarct size. Enhanced protective effects were diminished by the inhibition of miR-19a	Not found	PMID: 25590961
miR-21	Endometrium mesenchymal stem cell (EnMSC) exosome	rat; permanent occlusion (post-MI HF)	EnMSCs had superior cardioprotection to other mesenchimal stem cells. miR-21 expression was selectively enhanced in exosomes. Anti-miR treatment abolished the antiapoptotic and angiogenic effect	Not found	PMID: 28170197
miR-210	Hypoxic mesenchymal stem cell (MSC) exosomes	mouse; permanent occlusion	ExoH resulted in significantly higher survival, smaller scar size and better cardiac functions recovery. Reduced miR-210 secretion abrogated the beneficial effects of hypoxic exosomes	Not found	PMID: 29141446

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Table 1 (*continued*)

microRNA	Effect on cardioprotection			Oxidative stress related effect	PMID
	Protective approach	MI model	Protective effect		
miR-221	GATA4 overexpressing cardiac colony-forming unit fibroblast (cCFU-Fs) exosome	mouse; permanent occlusion	Intramyocardial transplantation of GATA4-Exo restored cardiac contractile function and reduced infarct size. Significantly increased miR221 expression was revealed in GATA4-Exo	Not found	PMID: 32586406
miR-98	miR-98 inhibitor transfected cardiac progenitor cells (CPC)	mouse; permanent occlusion	Knockdown of miR-98 enhanced the effectiveness of CPCs transplantation therapy for MI. MiR-98 targeted the signal transducer and activator of the transcription 3 (STAT3)	miR-98 inhibitor attenuated the proliferation reduction and apoptosis in presence of oxidative stress	PMID: 29913449
miR-144-3p	miR-144-3p loaded EVs with cardiac targeting peptide (CTP-EVs)	mouse; permanent occlusion	miR-144-3p in CTP-EVs achieved enhanced cardioprotective effect, reduced infarct size and improved cardiac function	Not found	PMID: 33460670
miR-675	Atorvastatin pretreated mesenchymal stem cells (MSC) exosomes	rat, permanent occlusion	MSCATV-Exo improved recovery in cardiac function, reduced in infarct size and promoted angiogenesis and inhibited IL-6 and TNF-α. lncRNA H19 regulating miR-675 was identified as mediator of MSCATV-Exo	Not found	PMID: 31119268
miR-133a-3p	Macrophage migration inhibitory factor engineered umbilical cord mesenchymal stem cells (MIF-Exo)	rat; permanent occlusion (post-MI HF)	MIF-Exo also significantly inhibited cardiomyocyte apoptosis, reduced fibrotic area, and improved cardiac function, mechanism of MIF-Exo involved miR-133a-3p and the downstream AKT kinase signalling pathway	Not found	PMID: 33639970
miR-146a	Human cardiosphere-derived cells (CDCs) exosomes	mouse; acute and chronic MI	miR-146 containing exosomes inhibited apoptosis and promoted proliferation of cardiomyocytes, enhanced angiogenesis. miR-146a mimic reproduced some (but not all) of the benefits of CDC exosomes	Not found	PMID: 24936449
miR-199a-3p	miR-199a-3py enriched mesenchymal stem cell-EV (MSC-EV)	cold ischemia of mouse heart	Cold ischemia reduced miR-199a-3p. MSC-EVs reversed the detrimental effects of prolonged cold ischemia. miR-199a-3p was highly enriched in MSC-EVs	Not found	PMID: 32981709
Induction of endogenous microRNAs by drugs or other treatments in vivo					
miR-1	Telmisartan	rat; I/R	Telmisartan reduced miR-1 expression within the infarcted heart along with increased expression of apoptotic markers	Not found	PMID: 31369209
miR-1	Remote ischemic preconditioning	rat; I/R	miR-1 was downregulated by remote ischemic conditioning	Not found	PMID: 24978894
miR-125a-3p, miR-324-3p, miR-139-3p	Urocortin 1 and 2 (Ucn-1 and Ucn-2)	rat; I/R	Ucn-1 and Ucn-2 protected heart from I/R injuries and upregulated miR-125a-3p, miR-324-3p and downregulated miR-139-3p and promoted dysregulation of genes expression involved in cell death and apoptosis	Not found	PMID: 28827743
miR-128-3p	Tongxinluo (TXL)	rat; I/R	Myocardial infarct size in the TXL group was significantly smaller, while miR-128-3p level was decreased. miR-128-3p mimic eliminated the protective effects of TXL	Not found	PMID: 29163161
miR-133b-5p	Ischemic preconditioning	rat; I/R	Preconditioning restored miR-133b-5p expression, which was negatively regulated by ischemia-reperfusion. Knockdown of miR-133b-5p blocked preconditioning-mediated cardioprotection	Not found	PMID: 29568969
miR-146a-5p	Troxerutin	rat; I/R	Troxerutin alleviated myocardial I/R injury in rats via inhibition of miR-146a-5p and antiapoptotic effect. miR-146a-5p mimic disrupted the protective effect of troxerutin	Not found	PMID: 30417352

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Table 1 (*continued*)

microRNA	Effect on cardioprotection			Oxidative stress related effect	PMID
	Protective approach	MI model	Protective effect		
miR-146b, miR-339-3p	Nitrite	mouse; I/R	miR-125a-5p, miR-146b, miR-339-3p, and miR-433 were significantly down-regulated by nitrite induced protection. miR-146b, and miR-339-3p changed parallel with their target, Interleukin 1 receptor associated kinase (Irak-M)	Not found	PMID: 28090786
miR-155	Sevoflurane	mouse; I/R	Sevoflurane reduced miR-155 expression, reduced infarct size and inhibited cardiomyocyte apoptosis. This effect suspended when miR-155 was overexpressed	Not found	PMID: 31099069
miR-203	Sevoflurane	rat; I/R	miR-203 was poorly expressed after I/R. Sevoflurane elevated miR-203	miR-203 overexpression declined oxidative stress, increased GSH and SOD levels after I//R	PMID: 32783282
miR-206	RNA Component Of Mitochondrial RNA Processing Endoribonuclease (RMPR) lnc-RNA inhibition	rat; I/R	Suppression of RMPR significantly decreased infarct size and improved cardiac function. RMRP and miR-206 showed antagonistic expression	Not found	PMID: 30551524
miR-21	Isoflurane	miR-21 KO mouse; I/R	Isoflurane induced up-regulation of miR-21. Protective effect of isoflurane was abolished in miR-21 knock out	Not found	PMID: 25536091
miR-21-5p	Isoflurane preconditioning	rat; I/R	Isoflurane reduced infarct sizes, while miR-21-5p expression was increased by isoflurane preconditioning	HIF1α signalling is involved in miR-21-5p regulation	PMID: 32789575
miR-214	Ischemic postconditioning	rat; I/R	Ischemic postconditioning group showed decreased CK-MB and upregulated miR-214	Postconditioning decreased MDA and increased SOD	PMID: 26025394
miR-29b, miR-133, miR-146	Ischemic postconditioning	pig; I/R	miR-29b, −133a, and −146b showed potential causal involvement in cardioprotection by postconditioning	Not found	PMID: 24390754
miR-30	Triiodothyronine (T3)	rat; I/R	T3 improved cardiac performance and increased miR-30a expression	Decreased p53 limits mitochondrial membrane depolarization	PMID: 25137026
miR-34b, miR-337	HDL treatment	mouse; I/R	HDL conferred protection against I/R via the modulation of the expression of microRNAs; miR-34b and miR-337 expression increased following HDL treatment	HDL protected against oxidative stress	PMID: 31220137
miR-370	Sevoflurane	mouse; I/R	I/R decreased, but sevoflurane elevated the miR-370 expression. Elevated miR-370 promoted cardiomyocyte proliferation and inhibited cardiomyocyte apoptosis	Sevoflurane increased SOD activity	PMID: 30856533
miR-384	Epigallocatechin gallate (EGCG)	rat; I/R	EGCG up-regulated miR-384 to protect cardiomyocytes from I/R injury by inhibiting excessive autophagy	Not found	PMID: 31802847
miR-451	Propofol	rat; I/R	Propofol treatment reduced infarct size and increased miR-451 expression. Propofol-mediated cardioprotection against myocardial I/R is dependent of miR-451	Not found	PMID: 31188485
miR-499	Ischemic postconditioning	rat; I/R	Postconditioning mediated cardiac protection against I/R injury was inhibited by knockdown of cardiac miR-499	miR-499 inhibition decreased SOD activity and increased MDA level	PMID: 27832626
miR-1	HOX antisense intergenic RNA (HOTAIR) adenoviral vector	mouse; permanent occlusion	Upregulation of HOTAIR inhibited cell death via regulation of apoptosis-related proteins. HOTAIR expression was negatively correlated with the expression of miR-1	Not found	PMID: 29258067
miR-1	Soluble epoxide hydrolase inhibitors (sEHIs)	mouse; permanent occlusion	sEHIs reduced the myocardium infarct size and incidence of inducible arrhythmias, while antagonised the ischemia induced upregulation of miR-1	Not found	PMID: 29212255
miR-122	Lycium barbarum polysaccharides		Lycium barbarum polysaccharides decreased infarct size and improved	Not found	PMID: 30458344

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Table 1 (*continued*)

microRNA	Effect on cardioprotection			Oxidative stress related effect	PMID
	Protective approach	MI model	Protective effect		
		rat; permanent occlusion (post-MI HF)	cardiac function via down-regulation of miR-122 and induced the activation of MEK/ERK and AMPK signalisation		
miR-126	Exercise-training + 1-trifluoromethoxyphenyl-3-(1-propionylpiperidine-4-yl) urea (TPPU)	mouse; permanent occlusion (post-MI HF)	TPPU increased exercise-induced effects on inhibiting cardiac enlargement and improved cardiac function. TPPU could enhance the overexpression of miR-126	Not found	PMID: 29265525
miR-155-5p, miR-145-5p	Sildenafil	pig; cardiac arrest	Cardiac arrest increased miR-155-5p and miR-145-5p levels. Sildenafil treatment decreased the levels of miR-155-5p and miR-145-5p in cardiac arrest	Not found	PMID: 33407761
miR-23a, miR-92a	Astragaloside	rat; permanent occlusion (post-MI HF)	Astragalosid reduced the infarct size, improved cardiac function while the elevated expression of miR-23a and miR-92a was reduced	Not found	PMID: 30257251
miR-29a-3p	Leonurine treatment	mouse; permanent occlusion (post-MI HF)	miR-29 downregulated mice post-MI. 4 week of leonurine treatment significantly upregulated miR-29a-3p expression	Not found	PMID: 33235025
miR-29b	Tanshinone IIA (TSN) treatment	rat; permanent occlusion	TSN downregulated the expression of TGF-β1, Col1a1, Col3a1, and α-SMA but upregulated the expression of miR-29b	Not found	PMID: 25636075
miR-297	miR-297 sponge (hsa_circ_0007623 circRNA)	mouse isoproterenol-induced acute MI	miR-297 was decreased, cardiac function and VEGFA expression level significantly improved after hsa_circ_0007623 circRNA treatment	Not found	PMID: 31973814

microRNAs in the *in vivo* (Table 1) and *in vitro* (Table 2) experimental models.

The *in vivo* studies were subclassified to the following groups (Table 1):

a) **Exogenous microRNA**: this group of papers contain *in vivo* preclinical reports where cardioprotection has been induced after direct delivery of microRNA into animals **(41 original articles, 17 of which deal with oxidative stress).**
b) **Exogenous microRNAs transferred by carrier vesicles:** this group contains *in vivo* preclinical reports in which a vesicular or other type of transport mechanism was used to deliver microRNA directly into animals and thus cardioprotection was achieved **(24 original articles, 5 of which deal with oxidative stress).**
c) **Induction of endogenous microRNA expression:** this group contains publications where microRNA changes are induced by a drug or other molecule that lead to cardioprotection **(29 original articles, 7 of which deal with oxidative stress).**

Ex vivo and *in vitro* studies (24 original article, 3 of which deal with oxidative stress) and publications that present relevant data obtained in ex vivo or *in vitro* models were classified into the same groups: **exogenous microRNA (11 original articles, 1 of which deal with oxidative stress)**, **exogenous microRNAs transferred by carrier vesicles (2 original articles not dealing with oxidative stress), induction of endogenous microRNA expression (11 original articles, 2 of which deal with oxidative stress).** These publications are listed separately in Table 2.

The result of the literature search shows that there is variable amount of information available on the different microRNAs studied in cardioprotection that may act via oxidative stress-mediated processes.

miR-1 has been studied frequently and the published papers are classified both into subclass a and c. miR-1 antagomir delivery exerted a significant protective effect on heart function, decreasing cardiomyocyte apoptosis and alleviating myocardial fibrosis and remodelling in mouse model of MI. In that study, miR-1 antagomir decresased 19s proteasome, 20S proteasome and ubiquitin ligase E3 level, which play a pivotal role in the selective recognition and degradation of oxidized proteins [21]. In rat model of MI, miR-1 was downregulated by remote ischemic preconditioning (RIPC) with or without following ischemia, however, relation to oxidative stress has not been investigated [22].

miR-21 and miR-146a: Both miR-21 and miR-146a showed a protective role against hypoxia-induced myocardial apoptosis and inflammation in the context of I/R injury [23–26]. MiR-21 attenuates cardiomyocyte injury via regulating the programmed cell death 4 (PDCD4) and AKT pathway, whereas miR-146a exerts its protective antiapoptotic effects through modulating interleukin-1 receptor-associated kinase1 (IRAK1), tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) and the NF-κB/TNF-α pathways [27,28]. Adipose-derived stem cell exosomes containing miR-146a decreased infarct size, suppressed myocardial fibrosis, inflammation and myocardial apoptosis in rat post-MI heart failure model and also decreased NF-κB p65 phosphorylation [29].

miR-21 plays role both in pre-, post- and H_2S-mediated cardioprotection [23,30,31]. However, miR-21 and miR-146 pro-survival effects can elicit an adverse fibrotic response [32–34]. In another study it was shown, that iPS-derived exosome treatment can protect against myocardial ischemia-reperfusion (I/R) injury via intramyocardial injection into mouse ischemic myocardium before reperfusion. Furthermore, iPS-derived exosomes deliver cardioprotective microRNAs, including nanog-regulated miR-21 and HIF-1α-regulated miR-210 [35]

miR-145: Overexpression of miR-145 alleviates I/R-induced myocardial electrophysiological instability and apoptotic and inflammatory response via inhibition of the CaMKII-mediated antiapoptotic pathways. miR-145 reversed I/R-induced imbalance of SOD and MDA levels, and inhibited NF-κB p65 anti-inflammatory pathways [36].

miR-30: Silencing the whole miR-30 family can protect against hypoxic cell injury by elevating cystathionine-γ-lyase (CSE) and H_2S levels in rat and mouse MI models, and decrease in p53 protein content reduces Bax expression and limits mitochondrial membrane depolarization resulting in preserved mitochondrial function [37].

miR-133: Antiapoptotic effect of miR-133 under hypoxia was described

Table 2
List of microRNAs with *in vitro* experimental evidence on their association with cardioprotection against I/R injury based on systematic literature review limited to the last 6 years. Articles are grouped in three groups based on the method used to deliver microRNAs. **Exogenous native microRNA *in vitro***: *in vitro* preclinical reports where cardioprotection has been induced after direct delivery of exogenous microRNA. **MicroRNA delivery by carrier vesicles *in vitro***: *in vitro* preclinical reports in which a vesicular or other type of transport mechanism was used to deliver exogenous microRNA and thus cardioprotection was achieved. **Induction of endogenous microRNAs by drugs or other treatments *in vitro***: endogenous microRNA changes are induced by a drug or other treatment that lead to cardioprotection. (I/R – ischemia-reperfusion, H/R – hypoxia-reoxygenation, OGD – oxygen glucose deprivation). Literature search has been done in PubMed database (from Jan 1, 2014–Mar 11, 2021) and major findings of resulting papers are summarized.

microRNA	Effect on cardioprotection			Oxidative stress related effect	PMID
	Protective approach	MI model	Protective effect		
Exogenous microRNA treatment to induce cardioprotection *in vitro*					
miR-125b-5p	miR-125b-5p mimic	HL1 and H9c2 cell line simulated I/R	Overexpression of miR-125b-5p have increased phospho-AKT pro-survival signalling, while lack of miR-125b-5p exhibit increased susceptibility to stress-induced apoptosis	Not found	PMID: 29122578
miR-133b-5p	miR-133b-5p mimic	cardiomyocyte H/R	Overexpression of miR-133b-5p reduced H/R-induced cell injury and apoptosis by inhibiting Fas expression	Not found	PMID: 26919791
miR-139-5p, miR-125b*, let-7b, miR-487b	miR-139-5p mimic, miR-125b* mimic, let-7 mimic, miR-487b antagomiR transfection	rat cardiomyocyte simulated I/R	let-7, miR-139-5p, miR-125b* mimic and miR-487b induced cardioprotection	Not found	PMID: 24858849
miR-144	miR-144 overexpression	mouse ex vivo heart I/R model	miR-144 reduced infarct size and improved functional recovery via increased p-Akt, p-GSK3β and p-p44/42 MAPK, decreased p-mTOR level and induced autophagy signalling	Not found	PMID: 25060662
miR-199a-3p, miR-214	mir-199 and miR-214 overexpression	cardiomyocyte simulated I/R	Overexpression of miR-199 and miR-214 mimicked the protective effects of carvedilol and repressed the predictive or known apoptotic targets	Not found	PMID: 27288437
miR-200a	miR-200a mimic	human cardiomyocyte hypoxia model	Overexpression of miR-200a protected from hypoxia-induced cell damage and the excessive production of reactive oxygen species. Suppression of Keap1 by miR-200a exerted a cardioprotective effect	miR-200a overexpression increased nuclear translocation of Nrf2 and downstream antioxidant enzyme gene expression	PMID: 27573160
miR-208b-3p	miR-208b-3p inhibitor transfection	ex vivo rat heart I/R model	Knockdown of miR-208b-3p expression attenuated apoptosis	Not found	PMID: 26658785
miR-214	miR-214 mimic	H9c2 cells with oxygen glucose deprivation (OGD)	miR-214 mimic reduced apoptosis, decreased LDH and CK activities, rescued the OGD-induced Ca(2+) and down-regulated elevated protein levels of NCX1, BIM, CaMKIIδ and CypD	Not found	PMID: 25593579
miR-22	miR-22 adenoviral overexpression	neonatal rat cardiomyocyte simulated I/R	Overexpression of miR-22 attenuated cardiomyocyte apoptosis and efficiently changed Bcl-2/Bax ratio, and reduced pro-inflammatory cytokines (TNF-α and IL-6).	Not found	PMID: 26707060
miR-221	miR-221 mimic transfection	H9c2 and cardiomyocyte H/R	miR-221 significantly reduced H/R injury in association with inhibition of autophagy	Not found	PMID: 27105917
miR-221, miR-150, miR-206	miR-221, -150, −206 mimics	H9c2 and rat cardiomyocyte H/R	miR-221, -150, and −206 mimics protected H9c2 and rat cardiomyocytes and reduced I/R-induced apoptosis and autophagy	Not found	PMID: 26396139
Exogenous microRNA transferred by carrier vesicles to induce cardioprotection in vitro					
miR-320	Platelet-derived growth factor (PDGF) conditioned human mesenchymal stem cells (MSC)	ex vivo isolated mouse heart I/R model	MSC transfer induced cardioprotection via a c-Jun/miR-320 signalling mechanism	Not found	PMID: 25724494
miR-16-5p, miR-144-3p and miR-451a	Remote ischemic conditioning induced extracellular vesicles (EV)s	ex vivo isolated rat heart I/R model	EV collected from human plasma after remote conditioning reduced infarct size and upregulated miR-16-5p, miR-144-3p and miR-451a	Not found	PMID: 33689033
Induction of endogenous microRNAs by drugs or other treatments in vitro					
miR-125b-1-3p	Preconditioning	ex vivo hypercholesterolemic rat heart I/R	Preconditioning reduced infarct size and upregulated miR-125b-1-3p. In hypercholesterolemic hearts preconditioning failed to induce cardioprotection and also failed increase miR-125b-1-3p	Not found	PMID: 32466450
miR-133a	NQDI-1 + Sunitinib	ex vivo rat heart I/R model	Sunitinib treatment resulted in increased infarct size, increased miR-133a expression. NQDI-1	Not found	PMID: 29248607

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Table 2 (*continued*)

microRNA	Effect on cardioprotection			Oxidative stress related effect	PMID
	Protective approach	MI model	Protective effect		
			attenuated the increased Sunitinib-induced infarct size, reversed miR-133a expression		
miR-17–92 cluster	Rapamycin	ex vivo diabetic rat heart I/R model	Rapamicin reduced infarct size. miR-17 and miR-20a elevated in diabetic hearts following rapamycin treatment	Not found	PMID: 31738412
miR-199a-5p	Atorvastatin	cardiomyocyte and H9C2 cell line oxygen-glucose deprivation	Pretreatment with atorvastatin significantly improved the recovery of cell viability and decreased miR-199a-5p expression	Not found	PMID: 27537066
miR-208b	Dexmedetomidine	H9c2 cell line H/R	Dexmedetomidin increased cell viability and reduced expression of miR-208b. Overexpression of miR-208b-3p attenuated dexmedetomidine exerted protective effects of myocardial cells	Not found	PMID: 32070878
miR-21	Kaempferol (natural flavonioid)	H9c2 cell line H/R	Kaempferol enhanced miR-21 level, miR-21 inhibitor blocked the protection of kaempferol	miR-21 inhibitor reversed kaempferol-induced inhibition on oxidative stress	PMID: 33151961
miR-21	Salidroside	H9c2 cell line H/R	Salidroside induced protection and increased miR-21 level. miR-21 inhibitor also abrogated the protective effect of salidroside	miR-21 inhibitor increased ROS generation and MDA level and reduced the activities of SOD and GSH-Px	PMID: 32104217
miR-30	Postconditioning	aged cardiomyocyte H/R	miR-30a was increased as a result of postconditioning. Overexpression of miR-30a promoted cardioprotective effect of postconditioning, while inhibitor suspended the protection	Not found	PMID: 32115441
miR-665	Dexmedetomidine	ex vivo rat heart I/R model	Dexmedetomidine precondition reduced infarct area and decreased expression of miR-665. Up-regulation of miR-665 attenuated dexmedetomidine induced protection	Not found	PMID: 31026731
miR-30a	Salvionic acid B	cardiac myocytes oxygen-glucose deprivation	Salvionic acid B had a protective role in miR-30a-mediated autophagy through the PI3K/Akt signaling pathway. Knockdown of miR-30a reverse the anti-autophagy effect of Salvionic acid B	Not found	PMID: 27586425
miR-208	Ginsenoside Rb1	cardiac myocytes H/R	Ginsenoside Rb1 reduced apoptosis and increased viability, while miR-208 inhibitor slightly decreased the protective effect of Ginsenoside Rb1	Not found	PMID: 27577116

in bone marrow-derived mesenchymal stem cells (MSCs) [38]. Peri-infarct injection of miR-133 overexpressing MSC lead to attenuated inflammation, smaller infarct size and improved cardiac function in rats [38]. In a different study cardiac function and myocardial miR-133 level was restored by post-MI carvedilol treatment in rats [39].

miR-125b has been studied well, and knockdown of miR-125b-5p after transfection of its inhibitor results in enhanced post-MI mortality and left ventricular dysfunction in mouse model of MI [40]. miR-125b transferred by mesenchymal cell-derived exosomes has shown to be protective in mouse and rat MI models by decreasing infarct size and cardiac myocyte death [41–43]. Interestingly, none of the abovementioned studies investigating the role of miR-125b in cardioprotection has looked at association to oxidative stress.

miR-144/451 cluster: Decrease of miR-144 was noted in I/R injury in mouse myocardium [44], while overexpression of the miR-144/451 cluster reduces cell death in isolated cardiomyocytes subjected to simulated ischemia-reperfusion [45]. *In vivo* cardiac expression of miR-144/451 was increased in response to brief preconditioning ischemia, and preconditioning failed to reduce infarct size in miR-144/451 knockout mice [46].

In the "*clinicaltrials.gov*" database, we performed an additional search for human clinical trials using the following search terms: "Myocardial Infarction and microRNA". This search resulted 17 trials, meanwhile the "heart and microRNA" search term resulted 109 trials. These human clinical trials involved several cardiac pathologies (majority of studies involved patients suffering from acute myocardial infarction, acute coronary syndrome, and heart failure) and focused on measuring circulating levels of microRNAs as potential biomarkers. These data show that testing microRNAs as cardioprotective therapeutic tools has not yet been tested in human clinical trials so far.

3. Transcriptomic approach to identify novel microRNAs that may serve as cardioprotective microRNAs ("protectomiRs")

Omics approaches provide large quantities of data that can be used for unbiased assessment of pathophysiological processes without *a priori* assumption. Analyses of omics data might represent a great opportunity for researchers to gain important novel insights into the mechanisms underlying myocardial I/R. In contrast to other approaches targeting a putative, single molecular target, this strategy might be more helpful to identify multiple key targets determining cardiac dysfunction in response to I/R [9].

Beside the tremendous efforts, application of basic discoveries from the field of genomics and genetics has been failed so far to be translated

into clinical practice [47]. Involvement of further omics techniques may alleviate an effective tool to improve our understanding of the molecular mechanism of myocardial I/R. Since stress signalling induced by I/R activate pathways that lead to gene expression changes, the transcriptomic analysis can provide insight to these changes and their regulation. High-resolution investigations (e.g. microarrays, sequencing) can now provide large amount of information, that requires robust bioinformatics analysis.

The first studies in the literature using high-throughput DNA-chips in case of cardioprotection by ischemic preconditioning showed affected gene expression in rats and rabbits [48,49]. Later multiple further studies confirmed that, ischemic conditionings trigger a cardioprotective transcriptomic profile of the myocardium [7]. The study of Simkhovich et al. [49] showed that regional ischemia led to changes in the gene expression profile in the remote non-ischemic area of the heart. So far one paper has confirmed that remote ischemic

Table 3
List of microRNAs with significantly enriched targeting of oxidative stress-related genes (microRNAs are listed according to decreasing enrichment q-values). MicroRNAs not found in the cardioprotective systematic literature review (see Tables 1 and 2) were highlighted in grey shading. Further systematic literature search has been done for all listed microRNAs. Number of hits resulted in the search with string "(heart OR cardi*) AND miRNA-xxx" was further narrowed by "(heart OR cardi*) AND (oxidative stress OR ROS) AND miR-xxx" (PubMed database, last search date: Mar 11, 2021) and major findings of resulting papers are summarized.

miRNA	Total number of mRNA targets	Degree (number of mRNA targets among oxidative stress genes)	Fold enrichment	Level of significance (q-value)	Available literature in the heart (number of hits); further selected for oxidative stress (number of hits in brackets)	Major findings in heart and oxidative stress related papers articles
hsa-miR-26b-5p	2022	43	2.91	2.09E-05	**72 (2)**	ox-stress relation in hypertension model (PMID: 30416683), related to mitochondrial dynamics in myocardial infarction (PMID: 33667993)
hsa-miR-34a-5p	980	26	3.52	0.0001	**42 (33)**	several article on ox stress relation in myocardial infarction (PMID: 31601093, PMID: 27383330) and in hyperglycaemia (PMID: 33380310, PMID: 32664383), ox-stress relation in endothelial cells (PMID: 33488795, PMID: 30793480)
hsa-miR-335-5p	2685	48	2.44	0.0002	**36 (3)**	ox-stress relation in myocardial infarction (PMID: 33506923) and endothelial cell models (PMID: 31894323, PMID: 30785341)
hsa-miR-125a-5p	318	14	5.80	0.0002	**32 (3)**	ox stress relation in hypoxia injury in cardiomyocyte model (PMID: 33475463)
hsa-miR-9-5p	420	15	4.67	0.0007	**16 (3)**	ox-stress relation in endothelial cell model, diabetes (PMID: 33093269, PMID: 32315958), and one study in ischemia/reperfusion model in mice (PMID: 30101604)
hsa-miR-146a-5p	300	12	5.21	0.0018	**50 (2)**	ox stress relation in diabetes (PMID: 32315958) and doxorubicin induced cardiotoxicity (PMID: 31098627)
hsa-miR-7-5p	735	19	3.36	0.0023	**17 (1)**	ox-stress relation in hypoxia induced injury model in H9C2 cells (PMID: 32945347)
hsa-miR-206	174	9	6.78	0.0024	**124 (11)**	ox-stress relation in macrophages (PMID: 33526034, PMID: 30633352) and mesenchymal stem cells (PMID: 32148656)
hsa-miR-17-5p	1825	33	2.39	0.0030	**71 (3)**	miR-17-5p inhibition protected against oxidative injury in cardiac myocytes (PMID: 25200830, PMID: 24386440) and related to ROS formation (PMID: 23194063)
hsa-miR-377-3p	415	13	4.05	0.0055	**16 (1)**	ox-stress relation in one study in renal ischemia/reperfusion model in mice (PMID: 30612004)
hsa-miR-22-3p	203	9	5.76	0.0058	**146 (7)**	several reviews (PMID: 31336454, PMID: 29063105) and articles on ox stress relation in cardiac myocytes (PMID: 31677784) and in hyperglycaemia (PMID: 29288528)

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Table 3 (*continued*)

hsa-miR-6812-3p	80	6	9.99	0.0058	**0 (0)**	Not found
hsa-miR-24-3p	990	21	2.75	0.0081	**142 (8)**	ox-stress relation in *in vitro* cardiac hypertrophy (PMID: 32898528) and vascular smooth muscle cells (PMID: 31539718)
hsa-miR-509-3-5p	125	7	7.33	0.0081	**0 (0)**	Not found
hsa-miR-21-5p	931	20	2.78	0.0089	**98 (1)**	miR-21-5p regulates mitochondrial respiration in H9c2 cells (PMID: 30657727)
hsa-miR-1-3p	1157	23	2.58	0.0089	**517 (21)**	miR-1 mediates ox-stress induced damage *in vivo* (PMID: 25583113) and *in vitro* (PMID: 22982320, PMID: 22806319)
hsa-miR-125b-5p	534	14	3.37	0.0126	**46 (1)**	No relevant paper found
hsa-miR-204-5p	469	13	3.56	0.0126	**86 (7)**	ox-stress relation in acute ischemia/reperfusion model (PMID: 32730836, PMID: 30213603, PMID: 28235791) in acute coronary syndrome in mice (PMID: 22364258)
hsa-miR-106a-5p	1169	23	2.55	0.0133	**35 (2)**	ox-stress relation endothelial cells (PMID: 32626987) and in cardiac hypertrophy (PMID: 27565029)
hsa-miR-6806-5p	69	5	9.59	0.0189	**0 (0)**	Not found
hsa-miR-143-3p	310	10	4.14	0.0189	**187 (10)**	ox-stress relation in cardiac progenitor cells (PMID: 29858017) and cardiotoxicity model (PMID: 32170053)
hsa-miR-6828-3p	70	5	9.45	0.0192	**0 (0)**	Not found
hsa-miR-625-3p	42	4	12.89	0.0257	**11 (0)**	Not found
hsa-miR-199a-5p	219	8	4.69	0.0300	**63 (3)**	ox-stress relation in in neuronal cells after ischemic injury (PMID: 31990992) and in endothelial cells (PMID: 29976767)
hsa-miR-153-3p	120	6	6.48	0.0300	**17 (4)**	miR-153 is related to Nrf2 signalling in cardiac myocytes in vivo (PMID: 32143647) and in vitro (PMID: 31037501)
hsa-miR-708-5p	124	6	6.26	0.0317	**15 (1)**	ox-stress relation in H9c2 cardiomyocytes exposed to hypoxia/reoxygenation (H/R) (PMID: 32866662)
hsa-miR-509-5p	124	6	6.26	0.0317	**6 (0)**	Not found
hsa-miR-224-5p	172	7	5.23	0.0317	**26 (1)**	ox-stress relation in atrial tachypacing in canine heart. (PMID: 25816284)
hsa-miR-4418	122	6	6.37	0.0317	**0 (0)**	Not found
hsa-miR-221-3p	484	12	3.16	0.0379	**38 (6)**	ox-stress relation in HUVEC cells (PMID: 32947021, PMID: 32401923), H9c2 cells (PMID: 30695715) and in skeletal muscle (PMID: 24308935)
hsa-miR-5007-5p	129	6	6.00	0.0379	**0 (0)**	Not found
hsa-miR-34c-5p	240	8	4.26	0.0436	**37 (2)**	ox-stress relation in endothelial cell model (PMID: 33488795) and in erectile tissue (PMID: 32377289)
hsa-miR-663a	188	7	4.77	0.0468	**19 (0)**	Not found

preconditioning leads to alteration of gene expression profile in the heart of mice [50]. Moreover, after determination of global cardiac microRNA expression changes, systematic comparisons of looking at the direction of individual microRNA expression changes due to I/R with or without conditioning stimuli, potential cardioprotective microRNA targets termed '**protectomiRs**' such as **miR-125b*, miR-139-3p, let-7 and miR 487b** have been identified by our group [51].

4. Predicted microRNAs affecting oxidative stress genes

In order to carry out the widest and most accurate mapping of the microRNAs that may be associated with key elements of oxidative stress, here we used a bioinformatics approach to predict such microRNAs. First we selected Gene Ontology biological process terms containing a list of human genes related to oxidative stress and response to oxidative stress. The term "reactive oxygen species metabolic process" has been selected within the subclass "cellular metabolic process". The 283 (without duplicates) oxidative stress related genes covered by this term were selected for further analysis. Additional literature search has been done to construct a list of relevant redox mediators including relevant recent reviews in the field [52–54]. We have found that the above-mentioned GO term included all relevant oxidant and antioxidant key mediators, except for prolin oxidase and Keap1, which were finally added to complete the gene list used for reverse microRNA prediction (see Fig. 1). Then reverse mRNA-microRNA target prediction was performed by using the *miRNAtarget.com* software [55–57] to identify microRNAs with possible modulatory effect on oxidative stress-related genes. MicroRNA-target mRNA interaction network was constructed and analyzed to identify microRNA hubs associated to oxidative stress-induced alterations. The analysis revealed several microRNAs with high node degree (i.e. high number of interactions with target mRNAs), which were also involved in high number of non-oxidative stress related processes. Since there was a very strong correlation between the number of targets of microRNAs and their degree, enrichment analysis was performed. Enrichment p-values were calculated using Fisher's exact test, after which these p-values were adjusted for multiple comparison by calculating false discovery rate according to Benjamini and Hochberg (q-value). As a result, we obtained 33 microRNAs that show both a high node degree and a significant enrichment for predicted regulation of oxidative stress genes (Table 2 - lists microRNAs with a q-value of less than 0.05). Out of these 33 microRNAs, 19 microRNAs have not been previously studied in the literature in relation to cardioprotection and/or oxidative stress, although they may also play an important role in oxidative stress-mediated cardioprotection. Additional literature search has been performed on each 33 microRNAs to see whether they were studied in relation to heart and oxidative stress. Results of the literature search has been summarized in Table 3. The applied search string using "miR-xxx" resulted reasonable number of hits with the following limitation: The PubMed search strings we applied here specify the microRNA number in the name of microRNAs (miR-xxx), however, they do not specify additional endings like an asterisk (*) or -3p/-5p postfix according to the old or the new microRNA nomenclature. Therefore, all articles that refer to the queried microRNA with the microRNA number alone have been included in this paper, however, articles in which all appearance of the microRNA name is marked with additional asterisk or postfix are omitted. To solve this problem, PubMed search engine should be optimized for microRNA search.

5. Conclusions: development of microRNA therapeutics

MicroRNAs have been proved to be involved in the mechanism of I/R injury and cardioprotection, and mimics or antagomirs of certain microRNAs may serve as potential multitarget drugs for several cardiovascular pathologies. MicroRNAs became the first small non-coding RNAs studied in large animals and recently in clinical trials (see for extensive reviews, example: Huang et al., 2020, Circ Res [58]). Development in nucleotide chemistry to improve druggability of oligonucleotides and their efficacy to modulate certain genes (e.g. locked nucleic acid - LNA nucleotides [59]) will definitely increase the pipeline of development of microRNA compounds in the future. Indeed MiR-92a LNA antagonist showed dose-dependent decreases in circulating miR-92a levels and target gene depression in the peripheral blood compartment as an evidence of target engagement, and specific activity [60]. As miR-92a regulates blood vessel growth, administration of MRG-110 (miR-92a LNA antagonist) may prove to be an efficient treatment strategy following cardiac ischemic injury [61,62]. MiR-132-3p, a member of the heart failure associated miR-212/132 stem-loop cluster, was lately investigated in a first in man clinical trial with microRNA modulators. Intravenous and intracoronary delivery of miR-132-3p LNA inhibitor were effective to improve cardiac function, reduce brain natriuretic peptide (BNP) levels and induce reverse remodelling in heart failure patients [63]. The authors of this review strongly believe that these results will boost further development of microRNA therapeutics in several therapeutic indications including cardioprotection.

Declaration of competing interest

P.F. is the founder and CEO, A.G. and B.Á. is involved in the management of Pharmahungary Group.

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