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Invited Review

MicroRNAs in the regulation of cellular redox status and its implications in myocardial ischemia-reperfusion injury

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ABSTRACT

MicroRNAs (miRNAs) are small RNAs that do not encode for proteins and play key roles in the regulation of gene expression. miRNAs are involved in a comprehensive range of biological processes such as cell cycle control, apoptosis, and several developmental and physiological processes. Oxidative stress can affect the expression levels of multiple miRNAs and, conversely, miRNAs may regulate the expression of redox sensors, alter critical components of the cellular antioxidants, interact with the proteasome, and affect DNA repair systems. The number of publications identifying redox-sensitive miRNAs has increased significantly over the last few years, and some miRNA targets such as Nrf2, SIRT1 and NF- κ B have been identified. The complex interplay between miRNAs and ROS is discussed together with their role in myocardial ischemia-reperfusion injury and the potential use of circulating miRNAs as biomarkers of myocardial infarction. Detailed knowledge of redox-sensitive miRNAs is needed to be able to effectively use individual compounds or sets of miRNA-modulating compounds to improve the health-related outcomes associated with different diseases.

1. Introduction: miRNAs and oxidative stress

Oxidative stress can affect the expression levels of multiple microRNAs (miRNAs) and, conversely, miRNAs can regulate the expression of redox sensors and alter key components of the cellular antioxidant machinery [1]. This complex network between miRNAs and oxidative stress act by modulating cell homeostasis. miRNAs are short RNAs that do not encode for proteins and play key roles in the regulation of gene expression acting at the post-transcriptional level [1]. miRNAs were firstly identified in *C. elegans* [2,3]. miRNAs are expressed in nearly all eukaryotic cells and induce gene silencing by binding to target sites found within the 3'UTR (untranslated region) of the targeted mRNA [1,4]. This interaction prevents protein production by suppressing protein synthesis and/or by initiating mRNA degradation.

miRNAs are involved in a wide range of physiological processes and as such miRNA biogenesis and function are tightly regulated at multiple levels [1,5]. Canonical biogenesis results in miRNAs being encoded as individual monocistronic genes, as a cluster containing a few to several hundreds of different miRNAs, transcribed together as polycistronic transcripts, or in introns of host genes (intronic). Primary pri-miRNAs transcripts are generated by RNA polymerase II. In the next step, pri-miRNAs are processed to pre-miRNAs by a nuclear complex, which

includes the Di George critical Region 8 (DGCR8) dimer and the RNASE III Drosha [6,7]. Pri-miRNAs contained hairpins and 5' and 3' flanking sequences. The microprocessor complex cleaves at the stem of the hairpin and liberates a pre-miRNAs with a 5'phosphate and a 3' hydroxyl group. The pre-miRNAs are exported to the cytoplasm by binding to the export receptor Exportin 5 (XPO5) [8–10], where the RNASE III enzyme Dicer (in humans Dicer functions with a trans-activation-responsive RNA-binding protein TRBP) cleaves them and generates a miRNA duplex intermediate. In the last step, one strand of miRNA duplex assembles with a member of the Argonaute (AGO) to form the RNA-induced silencing complex (RISC). Upon loading of miRNAs into the RISC complex, the miRNA guides RISC to complementary sequences mainly located at the 3'untranslated regions of its target mRNAs. RISC regulates gene expression through translational repression (at the early stages) or mRNA degradation (at the later stages) [11]. Besides the well-established mi-RNA biogenesis pathway, some non-canonical Drosha-independent or Dicer-independent miRNAs processor have been recently described [12–14]. Moreover, several cell regulatory factors such as phosphorylation [15,16], deacetylation [17], ubiquitylation [18] and SUMOylating [19], connect miRNAs biogenesis to different cell signaling pathways. Diverse studies have also revealed that some miRNAs-transcription factors are redox-sensitive [20–23].

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Abbreviations

ADPKD	autosomal dominant polycystic kidney disease
AGO2	Argonaute
AIFM3	mitochondrion-associated 3
AKT	protein kinase B
AREs	antioxidant response elements
ASK	apoptosis-regulating kinase
BMSCs	bone marrow mesenchymal stromal cells
CAMKII	Ca ²⁺ /calmodulin dependent protein kinase II
CAT	catalase
CBD	cAMP response element binding (CREB) binding protein
DRGC8	Di George critical Region 8
GPX	glutathione peroxidase
GR	glutathione reductase
GSH	glutathione
H ₂ O ₂	hydrogen peroxide
HDACs	histone deacetylases
HIF-1 α	Hypoxia-inducible factor-1 α
HMOX1	Heme Oxygenase 1
HUVECs	Human Umbilical Vein Endothelial Cells

KEAP1	Kelch Like ECH Associated Protein
MAPK6	mitogen-activated protein kinase 6
MDA	malondialdehyde
MEFs	mouse embryonic fibroblasts
MI	myocardial infarction
MM	multiple myeloma
NAFT	factor of activated T cell
NF- κ B	nuclear factor κ B
NOX	NADPH oxidase
Nrf2	nuclear factor-erythroid 2 related factor 2
OGD/R	oxygen-glucose deprivation and reoxygenation
POMP	Proteasome maturation protein
PSME4	Proteasome Activator Subunit 4
RISC	RNA-induced silencing complex
RNS	reactive nitrogen species
ROS	reactive oxygen species
SOD	superoxide dismutase
TGF β 1	Transforming growth factor beta 1
UPS	Ubiquitin Proteasome System
XPO5	Exportin 5

Alterations in miRNAs expression profiles occur during organ development, aging [24], and cell death [25]. miRNA expression is also changed during the pathophysiology of complex diseases such as inflammation [25], cardiac [26,27], and neurodegenerative diseases [28], and almost all kinds of cancer [22,29,30]. In addition to their role in regulating gene expression, miRNAs released into body fluids have emerged as potential serum biomarkers. Circulating miRNAs can be either bound to serum proteins and lipoproteins or be encircled in extracellular vesicles including exosomes, microvesicles or apoptotic bodies [25]. Currently, miRNAs are intensely studied as candidates for diagnostic and prognostic biomarkers in liver diseases [25,31], myocardial infarction [27,32] and Alzheimer disease [33].

The link between regulatory factors and miRNAs provide an interesting tool to modulate miRNAs biogenesis in certain pathologies [18,19]. Emerging evidence now suggests that reactive oxygen species

(ROS) modulate some specific miRNAs biogenesis, also called “redoximiRs” [34] and that miRNAs target antioxidant responsive elements and ROS related genes, thus affecting cellular redox status. During normal oxidative metabolism, there is a constant formation of oxidative reactive species in the cell, such as ROS and reactive nitrogen species (RNS). Reactive oxidants include many ROS (such as H₂O₂, O₂⁻, [•]OH, ¹O₂, O₃, RO₂[•], RO[•]) and RNS (such as [•]NO, [•]NO₂, ONOO⁻) [35,36]. Environmental factors, as well as different physiological and pathophysiological conditions, influence the formation of radical species inside the cell. The generation of ROS and RNS elicits oxidative stress, which includes the oxidation and subsequent functional impairment of lipids, proteins and nucleic acids [37]. Increase in intracellular ROS/RNS has also been associated with cell death, having a critical role in the induction of apoptosis [38,39].

A significant disruption of redox homeostasis by ROS/RNS and

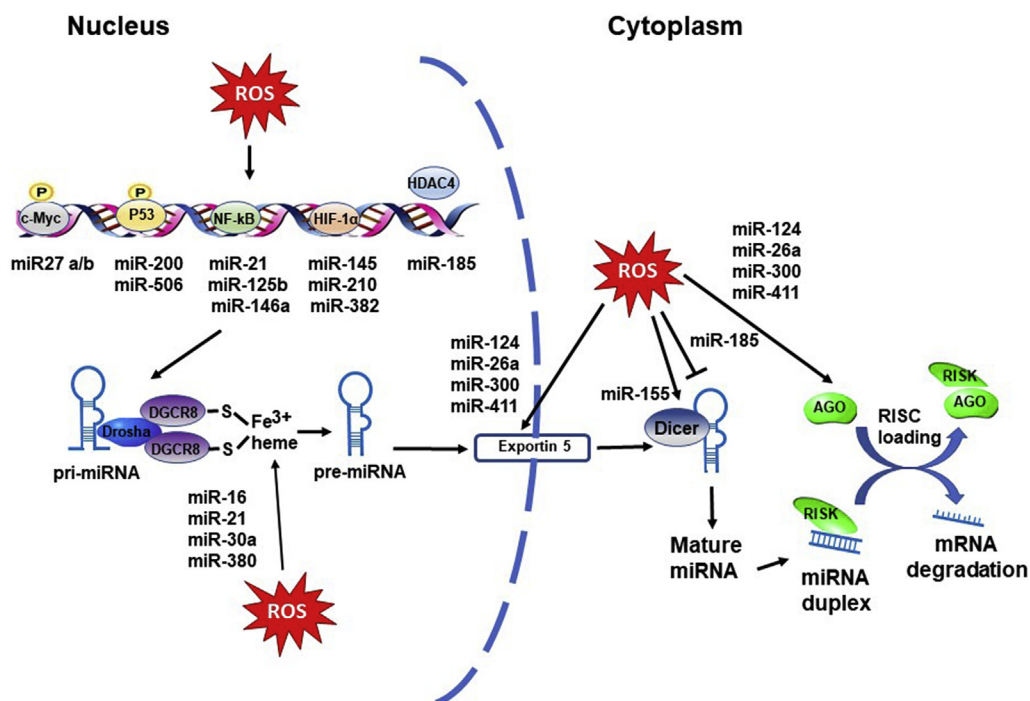


Fig. 1. ROS affecting nuclear and cytoplasmic processing of miRNAs. miRNA transcription can be induced by ROS activating transcription factors (c-Myc, p53, NF- κ B, HIF-1 α). HDAC4 does not directly bind to DNA but suppresses transcription when bound to a promoter. ROS can affect miRNA biogenesis, translocation and maturation through regulating the activity and expression of DGCR8, drosha, exportin 5 and the processing enzyme dicer. (Arrow indicates activation, T arrow indicates inhibition).

antioxidant defense can induce oxidative stress. Under physiological conditions, there is a balance between factors promoting ROS/RNS formation and the cellular antioxidant pool [40,41]. The antioxidant defense system includes molecular antioxidants and enzymes. Antioxidant enzymes are proteins that convert highly reactive species into less reactive particles: superoxide dismutase (SOD) scavenges radical superoxide, while catalase (CAT) and glutathione peroxidase (GPX) detoxify hydroperoxides [42]. A broader look at the ROS/RNS defense system would include enzymes that are able to repair cellular damage [43], including enzymes involved in DNA repair and the proteasome, a system able to recognize and degrade oxidatively-modified proteins [44]. However, while at relatively high concentrations, ROS/RNS become harmful, at low levels can promote cell proliferation and survival [41]. Low ROS levels are also needed because ROS are involved in several signaling pathways [45,46].

A regulatory interplay between miRNAs and redox signaling have been increasingly reported in the literature over the last decade. While some redox-sensitive miRNAs [34] are regulated by oxidative stress, miRNAs can also regulate cellular redox status. Gene silencing by miRNAs can result in changes in ROS activators and ROS scavengers, leading to a complex interplay between oxidative stress and miRNA to modulate cellular redox homeostasis. Research published to date on the relationship between miRNAs and oxidative stress suggests that:

- miRNAs biogenesis can be regulated by cellular redox status.
- miRNAs can target ROS generation and modulate antioxidant signaling
- miRNAs can interact with the proteasome and act as endogenous proteasome inhibitors
- miRNAs cooperate with ROS to regulate cell fate, as oxidative stress-induced apoptosis and autophagy and redox regulation of DNA repair systems
- miRNAs regulate ROS in many diseases such as myocardial and cerebral ischemia-reperfusion injury, as well as cancer.

miRNAs involved in cellular redox status as potential targets for therapeutics and biomarkers

Current concepts about these aspects of miRNA biology are described below.

2. miRNAs biogenesis can be regulated by cellular redox status

The biogenesis and regulation mechanisms of miRNAs are displayed in Fig. 1. Many scientific reports indicate that several miRNAs are regulated by redox status [34,47,48]. ROS acts by activating related transcription factors such as c-Myc, p53, Nuclear factor κ B (NF- κ B) and hypoxia-inducible factor 1 (HIF-1 α) in response to oxidative stress. Table 1 shows a summary of studies that indicate ROS can regulate miRNAs through these transcription factors. c-Myc is a transcription factor involved in oncogenesis, and whose effects have been correlated with exposure to ROS [49]. c-Myc induces the expression of miR27a/b, which, in turn, inhibits the expression of nuclear factor-erythroid 2 related factor 2 (Nrf2) worsening the progression of cholestatic liver injury [50]. P53, a stress-related transcription factor, can be induced by ROS and activate target genes for protecting the genome stability [49]. The members of the miR-200 family are markedly enhanced in hepatic cells by hydrogen peroxide (H₂O₂) treatment. In liver cells, miRNA-200s are upregulated by oxidative stress-induced p38 α -mediated phosphorylation of Ser33 on p53 [51]. Upregulation of miR-200-3p under these conditions promotes H₂O₂-induced cell death [51]. miR-506 was regulated by p53 and lead to apoptosis in lung tumor cells [52].

NF- κ B transcriptionally regulates several miRNAs. NF- κ B is a critical regulator of pro-inflammatory/stress-like responses that play important roles in DNA damage response and apoptosis in different cell type [53,54]. ROS-induced NF- κ B upregulates miR-21, promoting cancer progression [55] and fibrogenesis [56]. Likewise, miR-146a and miR-125b were overexpressed after ROS-NF- κ B activation in human neural

Table 1

ROS-sensitive transcription factors, ROS induced epigenetic modifications of miRNAs, and ROS induced nuclear and cytoplasmatic processing of miRNAs.

ROS inducing model	Transcription factor	Targeted miRNAs	Model and outcomes of miRNAs upregulation	References
ROS-sensitive transcription factors affecting miRNAs biogenesis				
MELAS syndrome	NF κ -B activation	miR-9	Negative regulator of GTPBP3, MTO1 and TRMU leading to aggravated mitochondrial dysfunction in platelet derived cybrids from two patients with MELAS syndrome	[169]
Leptin-NADPH oxidases	NF κ -B activation	miR-21	Fibrogenesis in experimental and human Nonalcoholic Steatohepatitis (NASH)	[56]
High glucose	NF κ -B activation	miR-21	Fibroblasts cells. Promotes migration	[55]
Inhibited GSH synthesis	C Myc overexpression	miR-27a/b	Liver cancer progression	[50]
Aluminium-sulfate	NF κ -B activation	miR-146a miR-125b	Human neural cells. Promotes inflammation	[57,58]
H ₂ O ₂	P38/P53 phosphorylation	miR-200	Liver cell death by inhibiting p38/p53 feed-back loop	[51]
Hypoxia	HIF 1- α	miR-210 miR-382 miR-145	Regulation of mitochondrial metabolism in human cancer cells and tumors Proliferation of pulmonary artery smooth muscle Promotes angiogenesis in human gastric cancer cells Protective effects against apoptosis in cardiomyocytes	[63] [64] [65] [66]
ROS generation	P53 activation	miR-506	Induced cell apoptosis and decreases viability in lung tumor cells	[52]
ROS affecting epigenetic modifications of miRNAs				
Hypoxia	HDAC4 supression	miR-185	Lung epithelial cell death	[70]
Glucose deprivation	HDAC2 inhibition	miR-466h-5p	Increased apoptosis mouse cell line	[69]
ROS affecting nuclear and cytoplasmatic processing of miRNAs				
Hypoxia	DICER	miR-155	Upregulation of miRNA induce glycolysis in lung alveolar epithelial cells	[73]
Chronic Hypoxia	DICER	miR-185	Downregulation of Dicer-dependent miRNA maintains the induction of HIF-1 α and hypoxia-responsive genes	[74]
Nutritional stress	XPO5 and AGO2	miR-124 miR-26a miR-300 miR-411	Xpo5 and Ago2 mRNA levels are altered in malnourished mice The levels of 70% and 50% of the miRNAs, were increased in the hippocampus of LP mice	[78]
Redox state favoring conversion of Fe(II) heme to Fe(III) heme	Drosha-DGCR8 complex	miR-21 miR-30a miR-380 miR-16	Increase the efficiency of pri-miRNA processing	[71] [72]

cells [57,58]. The HIF-1 α transcription factor is a critical oxygen sensor and a major regulator of the hypoxic adaptive response [59]. ROS directly regulate HIF-1 α by oxidizing a cysteine amino residue on HIF-1 α , resulting in a stabilization of the protein. HIF-1 α regulates the expression of genes involved in the adaptation to hypoxia, like EPO (erythropoietin) or VEGF (Vascular endothelial growth factor) [60,61]. Likewise, HIF-1 α overexpression can regulate the expression of a broad range of miRNAs, the so called hypoxamiRs [62], which constitute key regulators of cellular adaptation to hypoxia. Among them: miR-210, which regulates mitochondrial metabolism [63] and proliferation of pulmonary smooth muscle [64]; miR-382 which promotes angiogenesis [65]; and miR-145 which leads protective effects in cardiomyocytes [66].

ROS can also regulate miRNAs expression through epigenetic modifications (Table 1). Like protein coding DNA sequences, miRNAs genes may undergo DNA methylation and histone modifications. Altered epigenetic miRNA expression has been described in cancer cells [18,67,68]. Reduced activities of histone deacetylases (HDACs) under oxidative stress can alter miRNAs expression levels. Accumulation of ROS due to glucose deprivation inhibited HDAC2 in cultured mouse cells, which increased acetylation and induction of miR-466h-5p, leading to increased apoptosis [69]. Likewise, hyperoxia suppresses histone deacetylase 4 (HDAC4) and subsequently affects histone deacetylation, resulting in an elevated miR-185 transcription [70]. Functionally, miR-185 promotes lung epithelial cell death through inducing DNA damage.

ROS can modulate miRNAs biogenesis at many levels, and several enzymes and components of miRNA processing machinery can be affected by oxidative stress (Table 1). In the Drosha-DGCR8 complex, DGCR8 forms a highly stable and active complex with the ferric heme using two endogenous cysteines as axial ligands [71]. The reduction of the heme iron to the ferrous state in DGCR8 abolishes the pri-miRNA processing activity [71,72]. Dicer is a principal component of miRNA processing machinery that processes precursor miRNAs (pre-miRNAs) into mature miRNAs. There is evidence that chronic hypoxia promotes cell glucose metabolism through Dicer regulation of miR-143 and miR-155 [73] and the induction of hypoxia-responsive genes through Dicer regulation of miR-185 [74]. The relationship between the redox state

and the complexes processing miRNA may be more widespread. For example, a mutant p53 inhibited the processing of pri-miRNAs by Drosha, decreasing the levels of certain mature miRNAs in cells involved in cell cycle and cell proliferation regulation [75]. In addition, mutant p53 was also reported to suppress DICER1 expression [76]. Deregulation of the miRNA biogenesis pathway is an emerging mechanism in neurodegenerative diseases. Loss of Dicer [77], as well as downregulation of Drosha and DGCR8 were potentially involved in several neurodegenerative disorders. Moreover, nutritional stress alters the expression of the Xpo5 (Exportin 5) and Ago2 (Argonaute RISC Catalytic Component 2) genes in the hippocampus of restricted protein offspring mice [78].

3. miRNAs can target ROS generation and can modulate antioxidant signaling

Oxidative stress is typically the result of an imbalance between the rate of ROS generation, and the ability to detoxify these reactive species. Strong experimental evidence exists to support that miRNAs can regulate ROS generation and alter key components of the cellular antioxidant machinery. The miRNAs affecting ROS production, antioxidants and repair systems are shown in Fig. 2.

NADPH oxidases (NOXs) are a family of membrane-bound enzymes that oxidize NADPH to produce ROS (either superoxide or hydrogen peroxide) as the primary species during the catalytic metabolism of oxygen for a range of host defense and signaling functions [79] and a target of several miRNAs [80] (Table 2). Enhanced expression of NOX2 isoform has been reported due to miR-34a overexpression in glioma cells [20] and after exosomes enriched miR-3 in a mouse model of cardiac injury [27]. However, other miRNAs inducing inhibition of NOX2 [81] or attenuated NOX4 activity [68] have also been reported. miR-124-5p is selectively expressed within the central nervous system (CNS) and is predicted to bind to NOX2 directly. *In vivo*, miR-124 overexpression improved, whereas miR-124 inhibition aggravated the injury in a cerebral I/R injury model in rats through middle cerebral artery occlusion (MCAO) surgery [81] and increased activity of miR-21a-3p targets and inhibits NOX4 to inhibit tumor formation [68] in endothelial cells. Proline oxidase (POX) is a mitochondrial inner-

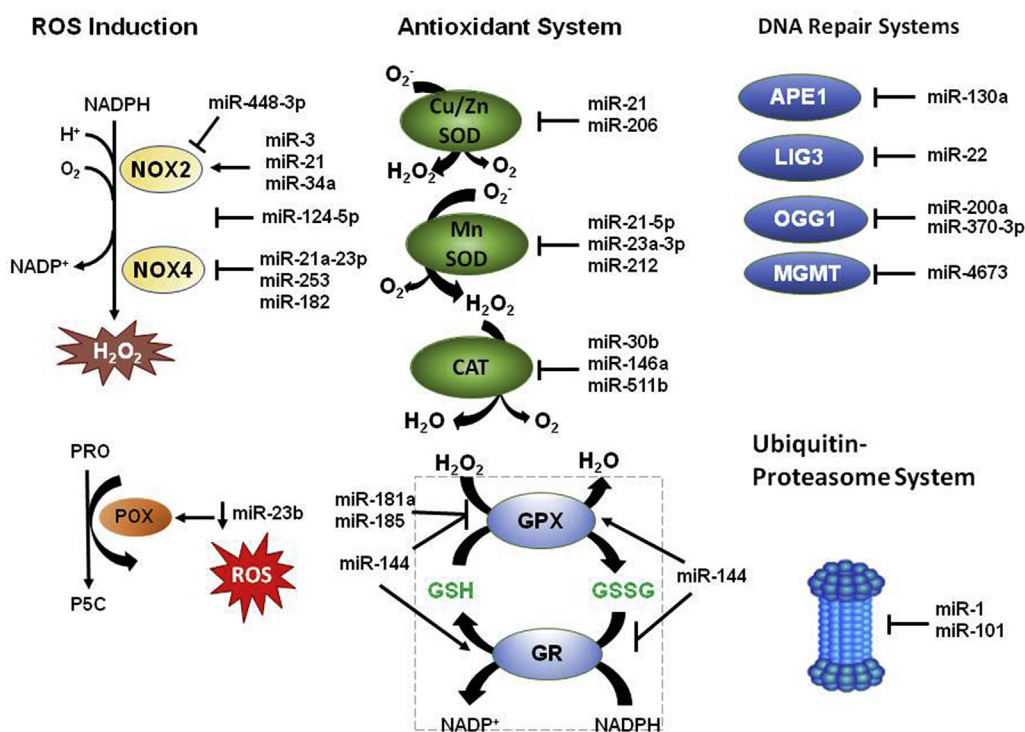


Fig. 2. miRNAs affecting ROS production, antioxidants and repair systems. miRNAs regulate ROS levels by activating or inhibiting NOX2 (NADPH oxidase 2), NOX4 (NADPH oxidase 4) and POX (Proline oxidase) enzymes. miRNAs can affect ROS levels through activation or inhibition of antioxidants including catalase (CAT), superoxide dismutases (Cu/Zn SOD and MnSOD), glutathione peroxidase (GPX) and glutathione reductase (GR). miRNAs can interact with DNA repair systems and ubiquitin proteasome system, which both affect the cellular redox status of the cell. APE1, AP-endonuclease; LIG3, DNA ligase 3, OGG1, 8-oxoguanine glycosylase; MGMT, O-6-methylguanine DNA methyltransferase; PRO, proline; P5C, pyrroline-5-carboxylate. (Arrow indicates activation, T arrow indicates inhibition).

Table 2
miRNAs that modulate ROS production.

miRNAs	Affected ROS producers	Effects	Model	References
Exosomes enriched miR-3	Enhanced NOX2 expression	ROS production Angiogenesis	Mouse model of cardiac injury	[27]
Inhibition of miR-21	Decreased NOX2	Lower ROS production	Renal inflammation in NAFLD	[170]
Up-regulated miR-21a-3p	Attenuated NOX4 activity	Decreased H ₂ O ₂	EOMA cells	[68]
Decreased miR-23b	Enhanced Proline Oxidase	ROS production Apoptosis	Renal tumors	[29]
Overexpression of miR-34a	Enhanced NOX2 expression	ROS production Apoptosis	Glioma cells	[20]
Overexpression of miR-124-5p	Inhibits NOX2	Decreased ROS, MDA	Improved I/R injury in MCAO rats Decreased OS in OC-12 cells	[81]
Overexpression of miR-155	Decreased Nfe2l2, Sod1, and Hmox1	ROS production	Induced ROS production in mesenchymal stem cells (MSCs) from aged mice	[171]
Decreased miR-451	Not determined	Lower ROS production	Bone marrow derived macrophages (BMDM) from wild type and p47 ^{phox} -/- mice	[172]

membrane enzyme that mediates the proline cycle to shuttle redox equivalents between mitochondria and the cytosol. POX is a miR-23b target, and in human renal carcinoma tissues, a negative correlation between miR-23b and POX protein expression has been reported [29].

The list of miRNAs that targets antioxidant enzymes continues to expand in different experimental models (Table 3). Intracellular and extracellular Cu/Zn SOD are downregulated by miRNAs in human bronchial cells [82] and in a model of atrial fibrillation [83], respectively. miR-212 suppressed MnSOD expression in human colorectal tumor [67]. miR-30b [84], miR-146a [85] and miR-551b [86] decreases CAT expression. Glutathione (GSH) is a ubiquitous low molecular antioxidant [87–89]. In a detoxification reaction, two molecules of GSH react with H₂O₂ in a GPX catalyzed reaction, giving GSSG, the disulfide-oxidized form of glutathione, and water. On the other hand, GSSG is a substrate of the glutathione reductase (GR) enzyme, which regenerates GSH. miRNAs have been regarded as potential regulators of glutathione peroxidases expression [90]. Upregulation of miR-181a [91], miR-185 [92,93] and miR-144 [94] decrease GPX expression, while miR-214 increase GPX activity [95] and decrease the GR activity [96]. GSH levels in the CNS show a circadian rhythm; therefore, a role for miRNA in the generation of the GSH rhythm has recently been suggested [97].

miRNAs can also target genes that indirectly modulate the

antioxidant effect. Inhibition or suppression of nuclear Nrf2 expression by miR-27 a/b has been reported in chronic cholestatic liver injury [50], and by miR-200c [98] in lung cancer cells. Nrf2 is a transcriptional factor that controls cellular redox homeostasis. Nrf2 activates the transcription of genes that encode antioxidant enzymes, among others. Diverse miRNAs can decrease (miR-93) [99] or activate (miR-200a, miR-7, miR-455) [100–102] Nrf2 pathway in different cancer models, highlighting the importance of modulating the levels of antioxidant enzymes under tumor processes.

4. miRNAs can interact with the proteasome and act as endogenous proteasome inhibitors

A recent exciting development in the protein homeostasis field was the discovery that miR-101 targets and inhibits the protein POMP (proteasome maturation protein), a protein that is needed for the assembly of constitutive proteasomes and immunoproteasomes [103]. By inhibiting POMP miR-101 causes impaired proteasome assembly and reduced activity. It was previously known that miR-101 is reduced in several cancers [104,105] and restoration of miR-101 inhibits cancer cell proliferation.

The proteasome is part of the ubiquitin-proteasome system (UPS) that is responsible for the degradation of more than 60% of intracellular

Table 3
miRNAs that modulate antioxidant expression or activity.

miRNAs	Targeted Antioxidant	Model	References
miR-7	Inhibit Keap1/activates Nrf2 pathway	Human neuroblastoma cell line	[101]
miR-21	Extracellular Cu/ZnSOD inhibition MnSOD downregulation	Human bronchial epithelial cells	[82]
miR 27ab	Inhibit Nrf2 expression	Chronic cholestatic liver injury	[50]
miR-30b	Inhibit Catalase expression	Retinal pigment epithelial cell line	[84]
miR-93	Decrease Nrf2 level	Breast carcinogenesis	[99]
miR-101	Inhibits Cul3/stabilizes Nrf2	HUVEC cells and aortic rings	[173]
miR-144	GR (modulated?) Decrease GPx expression Decrease Nrf2 level	Primary erythroid progenitor cells Human neuroblastoma SH-SY5Y cells Primary erythroid progenitor cells	[94] [174] [94]
miR-146a	Decrease Catalase expression	Alveolar epithelial dysfunction in HIV-1 transgenic rats	[175]
miR-181a	Decrease GPx expression	Human lung cancer cells	[85]
miR-185	Decrease GPx expression	Rat cardiomyocyte cell line Alcoholic liver disease	[91] [92]
miR-200a	Inhibit Keap1/activates Nrf2 pathway	Human endothelial cells Breast carcinogenesis Liver inflammation	[93] [100] [176]
miR-212	Suppress MnSOD expression	Colorectal tumor	[67]
miR-214	Increase GPx activity Decreased GR activity	Diabetic nephropathy Alcohol induced liver injury	[95] [96]
miR-206	Intracellular Cu/ZnSOD inhibition	Canine model of atrial fibrillation	[83]
miR-200c	Suppress Nrf2 expression	Lung cancer cells	[98]
miR-455	Inhibits Cul3/activates Nrf2	Human osteoblasts	[102]
miR-551b	Decrease Catalase expression	Lung Cancer model	[86]

proteasomes. The proteasome itself is a large complex that could be divided up into two parts, the 20S and the 19S, which together form the 26S proteasome [106,107]. The 20S proteasome is composed of 28 subunits in a barrel shape structure with four rings (two α and two β rings). The 20S proteasome has three independent proteolytic β subunits (each occurring in duplicate) with caspase-like (β 1), trypsin-like (β 2), and chymotrypsin-like activities (β 5) that are responsible for the cleavage of proteins that enters the proteasome. The 19S complex is the regulatory complex that is responsible for recognizing poly-ubiquitinated proteins, removing the ubiquitins attached to proteins targeted for degradation, and unfolding the proteins for entry into the 20S proteolytic core. Inhibition of the proteasome is associated with many diseases, including cardiac diseases, Alzheimer's, Parkinson's, diabetes and others, and significant inhibition of the proteasome leads to cell death [107].

The proteasome is also very important in reduced intracellular oxidative stress by degrading oxidized proteins. Another form of the proteasome, call the immunoproteasome, seems to be optimized for degrading oxidized proteins [108]. Although not measured immunoproteasome activity would also likely decrease if POMP is impaired since POMP is also important in the assembly of immunoproteasomes. The activity of the proteasome can also be regulated by oxidative stress. The apoptosis-regulating kinase ASK1 is activated by oxidative stress (such as H_2O_2), and can interact with and phosphorylate the RPT5 subunit of the 19S complex [109]. Phosphorylation of the proteasome by ASK1 results in all three activities of the proteasome being reduced and may play a role in apoptosis [109]. Formation of a functional proteasome 26S complex is a multifaceted process involving the synthesis of the individual subunits, partial assembly, full assembly, and then maturation. This latter process in humans requires POMP, a chaperone that forms the 20S half-structures by (referred to as 16S proteasome precursors) [110–113]. POMP is degraded after proteasome maturation. The cancer cell proliferation that is inhibited by miR-101 can be rescued by overexpression of POMP. The ability of miR-101 to inhibit proteasome activity is interesting because the proteasome inhibitor, bortezomib (which inhibits the β 5 proteasome subunit) has been used as an anti-cancer drug for over a decade [114]. Other reports also suggest that cancer cells are more vulnerable to proteasome inhibition than control cells [115].

While miR-101 is important in redox cellular biology because of its direct link to regulating proteasome activity and hence the levels of oxidized protein in a cell, many other miRNAs act by regulating the Nrf2 pathway. The Nrf2 pathway is one of the most important pathways for intracellular protection during oxidative stress as Nrf2 regulates the expression of several cytoprotective and stress-related genes including thioredoxin (Trx) and HO-1 [116–118]. In healthy cells, Nrf2 is readily polyubiquitinated by the BCR(KEAP1) ubiquitin ligase complex, and then becomes a substrate for the 26S proteasome, resulting in low levels of Nrf2. KEAP1 (Kelch Like ECH Associated Protein 1) is a substrate adaptor that interacts with Nrf2 and the BCR complex, which under conditions of oxidative stress, undergoes oxidation of its reactive cysteine residues, resulting in Nrf2 dissociating from KEAP1 (Fig. 3) [119]. Free Nrf2 can translocate to the nucleus where it can interact with antioxidant response elements (AREs) [120]. In mammalian cells, most of the genes encoding proteasome subunits, POMP, and other assembly partners contain AREs [121]. Nrf1 and Nrf2 can upregulate the expression of proteasome subunits and POMP by binding to the ARE in response to proteasome inhibition [121,122].

Nrf2 has also been shown to promote biogenesis [123] and regulate ROS levels in mitochondria via many mechanisms including increasing the synthesis of NADPH and GSH, regenerating Trx2 and GSH and increasing the detoxification of peroxides by GPx and Prx3 [124]. Pickering et al., 2012 found that the addition of H_2O_2 induced binding of Nrf2 to the ARE of the proteasome β 5 gene, resulting in increased β 5 mRNA levels. Additionally, inducers of Nrf2 also upregulate proteasome subunits and activity in different cell types [125,126]. As such, induction of proteasome subunits by the Nrf2-pathway is likely to be an important way for a cell undergoing oxidative stress to increase its capacity to remove damaged and oxidized proteins. miR-155 levels were lower in plasma cells from multiple myeloma (MM) patients when compared to control patients [127]. Addition of synthetic miR-155 mimics into MM cell lines resulted in increased pro-apoptotic effects and decreased cell viability. In MM cells resistant to the proteasome inhibitor, bortezomib, when the miR-155 mimics were added, they enhanced bortezomib anti-tumor activity. These results suggest that miR-155, like miR-101 exerts its effect by proteasome inhibition.

Although bortezomib has helped with the management of MM

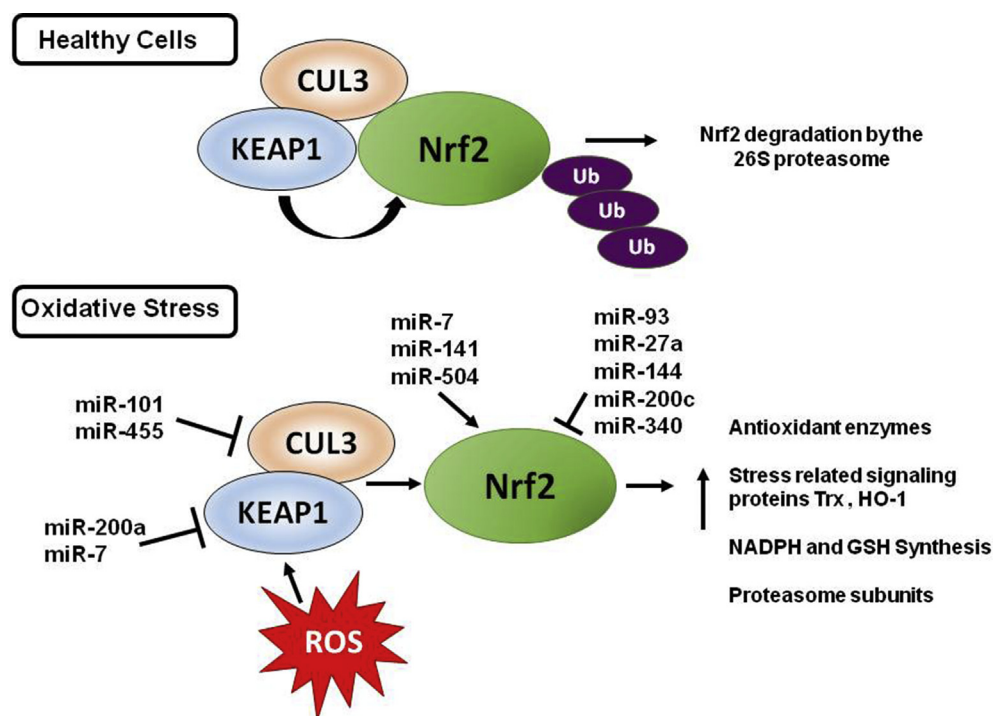


Fig. 3. miRNAs regulating the Nrf2 pathway. In healthy cells, Nrf2 is polyubiquitinated by the KEAP1 ubiquitin ligase complex, becoming a substrate for the 26S proteasome. Under conditions of oxidative stress, KEAP1 undergoes oxidation of its reactive cysteine residues, resulting in Nrf2 dissociating from KEAP1. Free Nrf2 can translocate to the nucleus where it can interact with antioxidant response elements (AREs). CUL3, cullin-3, KEAP1, Kelch-like ECH-associated protein 1, Nrf2, nuclear factor-erythroid 2-related factor 2, Ub, Ubiquitin. (Arrow indicates activation, T arrow indicates inhibition).

patients, resistance to bortezomib occurs over time [128]. Using genome-wide profiling of bortezomib-resistant myeloma cells, miR-29b was significantly reduced in bortezomib-resistant cells [128]. Further investigation showed that miR-29b targeted the proteasome subunit PSME4 (Proteasome Activator Subunit 4). PSME4 encodes one of the subunits of the PA200 complex which can replace the 19S complex and interact with the 20S proteasome. The PA200 has been shown to be involved in degrading histones following DNA double-strand breaks. Synthetic miR-29b mimics diminished the growth of myeloma cells, xenotransplants, and patient tumor cells [128]. These miR-29b mimics also reduced proteasome activity and has the potential to synergistically enhance the anti-tumour effects of proteasome inhibitors.

Using a combination of approaches, miR-200c was identified as a negative regulator of Noxa expression [129]. Noxa is a pro-apoptotic protein that contributes to p53-mediated apoptosis under certain conditions such as radiation exposure. miR-200c overexpression resulted in increased susceptibility to bortezomib in several cell lines. When cells lacking Noxa were used to overexpress miR-200c these cells had greater apoptosis induced by proteasomal inhibition compared to cells treated with proteasome inhibitors but without overexpression of miR-200c, suggesting that miR-200c is an enhancer of bortezomib-induced cell death. The results also suggest that multiple miRNAs may be working together acting on different aspects of the proteasome (proteasome assembly, proteasome subunits, etc.) to intensify the proteasome inhibition. Overall, these results suggest that the miRNAs that act by inhibiting proteasome activity are good targets for potential anti-cancer therapeutic strategies.

Recently, in silico tools were used to determine which miRNAs are involved in oxidative stress regulation [130]. Literature with information on miRNAs that changed expression levels in the presence of oxidative stress damage was reviewed and miRNA data extracted and utilized with several databases and prediction software to gene targets and pathways of oxidative stress-modulated miRNAs. This approach allowed the identification of potential miRNAs that will target the oxidative stress-related miRNA gene targets and pathways. One of the major pathways identified was the ubiquitination pathway. One example of a miRNA affecting the UPS would be miR-501-5p. Autosomal dominant polycystic kidney disease (ADPKD) cells and tissues show upregulated miR501-5p, which induces mTOR kinase activation [131]. The mTOR kinase increases the expression of the E3 ubiquitin ligase MDM2, which ubiquitinates p53, increasing its rate of degradation by the proteasome. miR501-5p overexpression inhibits mTOR activity and increases cell proliferation in kidney cells. Reduced expression of miR501-5p as well as the proteasome and mTOR inhibitors activate apoptosis and lessens cell growth in autosomal dominant polycystic kidney disease (ADPKD) cells [131]. Several miRNAs have also been shown to be associated with both ubiquitination and autophagy, including miR-9, miR-16, miR-17, miR-93, miR-101, miR-124, miR-128, miR-200, miR-429, and miR-497 [130].

5. miRNAs cooperate with ROS to regulate cell fate, as oxidative stress-induced apoptosis and autophagy and redox regulation of DNA repair systems

Several miRNAs are involved in redox regulation of DNA damage and DNA repair pathways (Table 4) [132]. miRNAs play an important role in regulating mitochondrial signaling pathways, including the apoptotic pathway [133]. Ionizing radiation (IR) induces the generation and accumulation of mitochondrial ROS and causes DNA damage, which ultimately results in apoptosis in bone marrow mesenchymal stromal cells (BMSCs). The mitochondrial ROS can damage the mitochondria resulting in a dysfunction mitochondrial antioxidant system, resulting in further ROS buildup. IR is used experimentally to investigate the effects of radiotherapy, which is commonly performed as part of the treatment for many malignancies such as cancer. IR induces miR-22 in many cell types, including bone marrow mesenchymal stromal cells (BMSCs) [134]. Overexpression of miR-22 increases mitochondrial ROS and cellular apoptosis. Redd1 was found to be a target for miR-22 and overexpression of Redd1 diminished the role of miR-22 on mitochondrial ROS generation protecting cells from miR-22 induced cell injury due to IR.

In mouse hippocampal neurons, H₂O₂ upregulated miR-135b and miR-708, and their targets were predicted to be involved in DNA recombination and protein ubiquitination [132]. miRNA-370-3p was the most downregulated miRNA in tissues of glioblastoma multiforme (GBM) chemotherapy cells and temozolomide resistance cells [135]. A miRNA-370-3p mimic repressed the self-reparative ability of GBM cell DNA and increased the sensitivity of these cells to temozolomide. The target gene of miR-370-3p was O(6)-methylguanine-DNA methyltransferase (MGMT). toxicity In A549 and H1299 cells, increased miR-4673 expression due to paclitaxel (PTX) resulted in increased ROS and apoptosis and reduced cell viability [136]. miR-4673 was found to target and reduce 8-Oxoguanine-DNA Glycosylase-1 (OGG1). Increased levels of OGG1 reduced PTX induced ROS, apoptosis and cell death. Although beyond the scope of this review, many miRNAs are pro-apoptotic, including miR-34a, miR-144, miR-155, and miR-200, while others are anti-apoptotic, including miR-210, miR-21, and miR-146a [137]. Experimental data also suggest that miRNAs can initiate apoptotic pathways in mitochondria during myocardial ischemia-reperfusion-injury [133].

6. miRNAs and ROS in cancer and myocardial ischemia-reperfusion injury

Numerous reports provide strong evidence of a reciprocal link between miRNAs and ROS in cancer [138,139]. However, the role of miRNAs and ROS in cancer will not be discussed in detail here as several great recent reviews on that topic are available [140–144]. ROS generation leads to oxidative DNA damage which has been suggested to be one of the first steps in the development of tumors [37,40]. ROS accumulation may activate oncogenic signaling and also control the

Table 4
miRNAs mediated redox regulation of DNA damage and DNA repair pathways.

miRNAs	Target Expression	Effects	References
miR-22 overexpression	Reduces Redd1	Promotes mitochondrial ROS, DNA damage, and apoptosis in bone marrow mesenchymal stromal cells	[134]
Decreased miR-130a	Increase APE1	Confers resistance to temozolomide in glioma cells	[177]
miR-135b overexpression	Not determined	May play a role in Alzheimer's disease	[132]
miR-185 overexpression	Increased the relative apurinic/aprimidinic (AP) sites in genomic DNA	DNA damage in lung epithelial cells	[70]
	Downregulated 14-3-3 δ signaling pathway		
miR-200a overexpression	Down-modulates OGG1, APE1, LIG3 and XRCC1	Required for repairing 8-OH-dG in senescent primary human keratinocytes	[178]
Overexpression of miR-370-3p	Downregulates MGMT	Stimulate sensitization to temozolomide in glioblastoma cells	[135]
miR-4673 overexpression	Down-modulates OGG1	Required for repairing 8-OH-dG in human lung cancer cell line	[136]

expression of various tumor suppressor genes that results in tumor progression [145]. Paradoxically, radiation and various chemotherapeutic agents used to treat cancer mediate their effects through the production of ROS [39,145]. Several miRNAs behave as regulators of gene expression by interacting with oncogenic and tumor suppressor genes that contribute to tumorigenesis. Consistent with this hypothesis, recurrent genetic and epigenetic alterations of individual miRNA have been found in several tumors [20,29,135,136].

ROS-sensitive transcription factors affect the biogenesis of miRNAs with oncogenic roles. For example, ROS generated by p53 dependent mechanisms can induce the expression of miR-506, resulting in decreased viability of lung tumor cells due to apoptosis [52]. It has also been shown that miRNAs can modify ROS homeostasis during the process of cancer. In human renal carcinoma tissue a decrease in miR-23b enhanced proline oxidase protein expression leading to ROS production and apoptosis [29]. Silencing miR-517a promotes oxidative stress in melanoma cells and decreases cell proliferation [146]. Several miRNA modulations can affect the Nrf2 pathway and modify antioxidant enzymes expression in different cancer models. Enhanced expression of miR27a/b inhibits Nrf2, thereby worsening the progression of cholestatic liver injury [50]. In breast cancer cells miR-93 decreases Nrf2 level [99] and miR-28 reduces the stability of Nrf2, increasing colony formation [147]. Attempts to modify ROS production in cancer using mi-RNA as a therapeutic tool have also been reported. The miRNA-mediated targeting of the NOX family of enzymes decreases ROS production and reduces cancer aggressiveness [148]. Although the molecular mechanisms underlying the role of miRNA and ROS in tumorigenesis and chemoresistance are better understood than in other diseases, they are still currently the subject of significant research.

Several reports support a role for miRNAs in myocardial ischemia-reperfusion (I/R) injury (Table 5) [149]. When a patient is admitted to the hospital with myocardial ischemia, that patient usually undergoes re-canalization of the coronary artery to help restore blood supply to the heart. However, this restoration of the blood supply (re-oxygenation), or reperfusion, can cause oxidative stress and inflammation, which leads to tissue damage, apoptosis and necrosis of cardiac cells.

Reperfusion injury results in changes in intracellular free Ca^{2+} concentrations and a key regulator of Ca^{2+} signaling is Ca^{2+} /calmodulin dependent protein kinase II (CaMKII). CaMKII mediates several signaling pathways in the heart, including hypertrophy, apoptosis, and heart disease. In H_2O_2 treated cardiomyocytes, miR-145 targets and reduced CaMKII δ protein expression resulting in suppressed ROS-induced Ca^{2+} increases, which will prevent apoptosis [150].

Oxidative stress following a period of hypoxia causes lipid and protein oxidations, and DNA damage which could eventually lead to cell death. In rat heart, using a myocardial I/R injury model of 30 min ischemia followed by 12h reperfusion, the infarct size, cardiomyocyte apoptosis, and levels of creatine kinase and lactate dehydrogenase released were all decreased when miR-22 was overexpressed [151]. One of the targets of miR-22, CBP (cAMP response element binding (CREB) binding protein), was inhibited by miR-22 overexpression. Down-regulation of CBP resulted in decreased Bax and p21 (pro-apoptotic related genes) and reduced p53 acetylation activity [151]. This data suggest that miR-22 can inhibit cardiomyocyte apoptosis that occurs due to I/R injury by inhibiting CBP. miR-374a-5p expression was decreased in a myocardial hypoxia/reoxygenation (H/R) H9C2 cell model and a mouse I/R model [149]. miR-374a-5p over-expression diminished cardiac cell damage in both *in vivo* the cell H/R model and the mouse I/R models of ischemia. miR-374a-5p was found to regulate mitogen-activated protein kinase 6 (MAPK6) negatively. Increased MAPK6 activity inhibited the protective effect of miR-374a-5p in the H9C2 H/R model [149]. Hence, miR-374a-5p seems to be protective against *in vitro* H/R injury and *in vivo* cardiac I/R injury.

A mouse model of myocardial infarction (MI) showed increased expression of miRNA-1 [152]. To investigate the role of miRNA-1 on MI, mouse hearts that underwent MI, as well as sham hearts, were treated with a miRNA-1 antagonist that inhibited miRNA-1 expression, miRNA-1 lentiviral vectors that increased miRNA levels or bortezomib that decrease proteasome activity [152]. miRNA-1 upregulated components of the UPS, such as an E3 enzyme and 19S and 20S subunits. Reduced miRNA-1 levels or inhibiting proteasome activity both lessened the left ventricular (LV) end-diastolic diameter and LV mass

Table 5
miRNAs involved in oxidative stress induced Cardiac Ischemia/Reperfusion Injury.

miRNAs	Expression	Target	Effects	Model	References
miR-1	Upregulated	E3 enzyme/19S and 20S proteasome subunits	LV end-diastolic diameter and LV mass	Mice I/R	[152]
miR-19a	Downregulated	PTEN/PI3K/pAKT	Cell injury/apoptosis	H9c2	[179]
miR-21	Upregulated	PI3K/AKT	ROS	H9c2	[180]
miR-22	Upregulated	SIRT-1	Apoptosis	Cardiomyocytes	[181]
		PI3K/AKT/ β Catenin	Altered mitochondrial function	H9c2	[182]
		SIRT-1/PGC1 α	Inhibits Apoptosis	Rats I/R	[151]
		CBP		Cardiomyocytes	
miR-34a	Upregulated	SIRT-1	Apoptosis/infarct size	Cardiomyocytes	[183]
miR-93	Downregulated	PTEN/PI3K/pAKT	ROS/Cell injury/apoptosis	H9c2	[184]
miR-126a-5p	Upregulated	Hspb8	Cell injury/apoptosis	H9c2	[185]
				Mice I/R	
miR-129-5p	Downregulated	PI3K/AKT/mTOR	Cell injury/autophagy	H9c2	[186]
miR-141-3p	Upregulated	PI3K/AKT	Apoptosis	H9c2	[187]
miR-142-3p	Downregulated	TLR4/NFk-B	Apoptosis	Mice I/R	[188]
miR-144	Downregulated	FoxO1	Apoptosis	H9c2	[189]
				Rats I/R	
miR-145	Downregulated	CaMKII δ	Apoptosis	Cardiomyocytes	[150]
miR-153	Upregulated	Nrf2/HO-1	ROS/apoptosis	Cardiomyocytes	[160]
miR-181b-5p	Upregulated	PI3K/AKT	Cell injury/apoptosis	H9c2	[190]
				Rats I/R	
miR-181c-5p	Upregulated	PTPN4	Cell injury/apoptosis	H9c2	[191]
miR-208	Downregulated	P21	ROS/apoptosis	Cardiomyocytes	[192]
miR-210	Downregulated	AIFM3	ROS/apoptosis	Cardiomyocytes	[153]
miR-223	Downregulated	NLRP3	Inflammation	H9c2	[193]
miR-374a-5p	Downregulated	MAPK6	Cell injury	H9c2	[149]
				Mice I/R	
miR-486	Downregulated	JNK/C-Jun	Cell injury/apoptosis	H9c2	[194]
		NF-kB			
miR-711	Upregulated	HIF-1 α /NF-kB	apoptosis	H9c2	[195]

increases that occur due to MI. Together with other experiments performed, these results suggest that UPS component are mediators of the effects of miRNA-1 on the cardiac remodeling that occurs after MI. It was disappointing that the latter study did not measure the proteasome activity after reducing miRNA levels since an increase in proteasome expression does not always result in increased proteasome activity.

Overexpression of miR-210 in cardiomyocytes reduces ROS production and cell death, while lower miR-210 levels increase ROS production after hypoxia-reoxygenation [153]. miR-210 targets mitochondrion-associated 3 (AIFM3), an apoptosis-inducing factor, but miR-210 cardioprotective effects do not seem to be via AIFM3. The upregulation of miR-210 may be via protein kinase B (Akt) and p53-dependent pathways since Akt inhibition results in lower miR-210 induction during hypoxia, and p53 overexpression in mouse embryonic fibroblasts (MEFs) induce miR-210. The miR-210 cardioprotective effects in cardiomyocytes seem to be through reducing mitochondrial ROS production and although not investigated may be occurring via Nrf2. Tingle SJ et al. [154] investigated if dual blockade of miR-24-3p and miR-145-5p will synergistically upregulate shared target genes during Human Umbilical Vein Endothelial Cells (HUVECs) I/R injury. Under hypoxic conditions miR-24-3p, miR-145-5p and ROS production are upregulated, and heme oxygenase 1 (HMOX1) and SOD1 are downregulated. miR-24-3p and miR-145-5p were highly expressed in human kidneys following extended cold ischemia. Inhibition of miR-24-3p and miR-145-5p before hypoxia-reoxygenation increased HMOX1 and SOD2, and decreased cellular ROS to lower levels than when either miR-24-3p or miR-145-5p were blocked individually.

An ingredient from the traditional Chinese medicinal plant, *Rhodiola rosea*, Salidroside, was found to be protective (increases antioxidant enzymes, SOD and GSH-Px, reduces ROS and malondialdehyde (MDA) levels and increased cell viability) against myocardial I/R injury *in vitro* and *in vivo*. This protective effect in H9C2 cells was found to be mediated by miR-21 as a miR-21 inhibitor reversed the effects of Salidroside [155].

These changes in miRNA expression occur mainly via modulation Nrf2, sirtuins, calcineurin/nuclear factor of activated T cell (NFAT), or NF- κ B pathways. Several circulating miRNAs have been reported to be potential biomarkers of ROS-related cardiac diseases, including myocardial infarction, hypertrophy, ischemia/reperfusion, and heart failure, such as miRNA-499, miRNA-199, miRNA-21, miRNA-144, miRNA-208a, miRNA-34a, and others. While a lot of research publications and reviews suggest that circulating miRNAs are potential biomarkers for ROS-related cardiac disease and are likely to be good therapeutic targets because of the number of miRNAs and opposing actions of some miRNAs, significantly more experimental research is needed before we will know if miRNAs will be good biomarkers or therapeutic targets [156].

7. miRNAs and ROS in cerebral ischemia-reperfusion injury

Cerebral I/R injury happens when an ischemic stroke occurs, and is characterized by swelling of cells, apoptosis and necrosis [157]. The primary source of ROS in brain tissue comes from NOX2. Data from a rat I/R injury model and an SH-SY5Y cell hypoxia/reoxygenation (H/R) model showed that NOX2 is significantly increased [158]. The miR-652 was decreased in both models (I/R and H/R), and the use of a miRNA-652 agomir (which reduces miR-652 levels) decreased NOX2 expression and ROS production in brain tissue of the rat cerebral I/R model. miR-652 overexpression reduced NOX2 expression and ROS generation in the H/R treated SH-SY5Y cells [158]. These results suggest that miR-652 is protective against cerebral I/R injury by targeting NOX2.

A cellular model to mimic cerebral I/R injury, called oxygen-glucose deprivation/reoxygenation (OGD/R), has been used in several studies. Hippocampal neurons exposed to OGD/R had significantly less miR-148b-3p expression levels [159]. When miR-148b-3p was overexpressed in neurons, ROS levels and apoptosis was increased, and cell

viability decreased after OGD/R. Conversely, inhibition of miR-148b-3p decreased ROS production and apoptosis and improved cell viability [159]. The miR-148b-3p target was a cytoprotective gene, Sestrin2 and Nrf2. Inhibition of miR-148b-3p upregulated both Sestrin2 and Nrf2. Consistent with these results, reducing Sestrin2 or Nrf2 considerably reversed the protective effect of miR-148-3p-inhibition in OGD/R-injured neurons. Treatment of cardiomyocytes using an oxygen-glucose deprivation and reoxygenation (OGD/R) cellular model which should be similar to an I/R model significantly upregulated miR-153 which resulted in increased ROS production and apoptosis [160]. Cardiomyocytes were protected from OGD/R treatment injury when miR-153 levels were reduced. Like many other miRNAs, miR-153 targeted Nrf2, and acts via the inhibiting the Nrf2/HO-1 pathway.

miRNAs are not just regulators of I/R injury in cardiomyocytes but many other cell types and tissues including neuronal tissue. Various miRNAs have also been found to be altered in neuronal injury during cerebral ischemia/reperfusion injury [159]. miR-153 has also been shown to be important in regulating neuron survival during cerebral ischemia/reperfusion (I/R) injury. miR-199a-5p overexpression in HT22 neurons exposed to OGD/R treatment increased ROS production and induced apoptosis, while inhibition of miR-199a-5p prevented OGD/R-induced ROS production and apoptosis [161]. The target gene for miR-199a-5p was Brahma-related gene 1 (Brg1), which activated Nrf2/HO-1 signaling. Knockdown of Brg1 levels prevented the miR-199a-5p inhibition-mediated neuroprotective effect on neurons [161]. Hence the results suggest that lower levels of miR-199a-5p are protective for neurons exposed to OGD/R-induced injury.

More recent studies suggest that miR-224-3p and miR-10a are also involved in modulating ROS levels [162,163]. Using the OGD/R model in N2a cells, miR-224-3p overexpression reduced ROS and apoptosis due to its interaction with the FAK family-interacting protein (FIP200) [162]. The effect of miR-224-3p on apoptosis was partially blocked when FIP200 was overexpressed [162]. A triterpenoid isolated from the *trametes lactinea* (Berk.) Pat (a type of mushroom), Trametenolic acid B (TAB) significantly reduced serum ROS levels, neuronal cell loss and apoptosis in cerebral I/R injury rats [163]. The neuroprotective effect of TAB against OGD/R and I/R injury seems to occur through miR-10a. TAB downregulates miR-10a resulting in increased activation of the PI3K/Akt/mTOR signaling pathway, which reduces mitochondrial-mediated apoptosis [163]. Li et al. found that 115 circulating miRNAs were differentially expressed in acute ischemic stroke, a form of cerebral I/R [164]. As such, several other miRNAs involved in cerebral I/R will likely be identified in the next few years that alter the cellular redox status of cells.

8. miRNAs involved in cellular redox status as potential targets for therapeutics and biomarkers

The number of publications that suggest miRNAs would be quality biomarkers for health conditions has significantly increased over the last few years. As such, the promise of miRNAs being used in the treatment of diseases is high. However, an FDA-approved miRNA for the treatment of any illness is still a few years away. Most advanced candidate miRNAs are now in phase 1 or phase 2 clinical trials. The road to approval is long, and most miRNA candidates are typically withdrawn during different stages of the clinical trials (clinicaltrials.gov). Another type of RNA, single (siRNA), had clinical trials started in 2004 and the first siRNA drug was only approved in 2018 [165]. As of April 2020, nearly 900 clinical research studies on miRNAs as biomarkers or as interventional drugs has been conducted or started (clinicaltrials.gov), with some (28 as of April 20th, 2020) of these trials already being discontinued and some (17 as of April 20th, 2020) withdrawn. miR-21, which when inhibited reduces ROS production, is in phase 1 trial for Alport syndrome (<https://clinicaltrials.gov/ct2/show/NCT03373786>) [166].

It is likely that a miRNA clinical biomarker will be approved before

a miRNA is approved for treating disease since more than half of the current studies are screening for biomarkers or secondary studies focusing on particular miRNAs for specific diseases such as preeclampsia. While in some cases, one miRNA might be able to identify a specific health outcome, it is more likely that health conditions will require several for increased specificity of detection [167].

9. Conclusion

Oxidative stress is a key contributing factor to many diseases, including cancer and cardiovascular disease. The number of publications identifying new redox-sensitive miRNAs, as well as the roles of these miRNAs is increasing at a dramatic pace. Our understanding of the major targets of these redox-sensitive miRNAs has increased dramatically, and a few targets such as Nrf2, SIRT1, and NF- κ B have been identified that are targets for multiple miRNAs. However, more experimental work is needed since miRNAs could have numerous targets and understanding the effect of the miRNA on those targets, as well as the function of these targets, is essential. Research is also needed to further determine the crosstalk between miRNAs, ROS and diseases, as well as to discover redox-sensitive miRNAs that are vital in many diseases but are not currently being investigated. Discovering new redox-sensitive miRNAs is likely to get easier as in silico-based approaches show promise to identify new miRNA targets as well as miRNAs binding to specific targets. miRNA disease association prediction will also continue to improve [168].

While the rush is on to identify miRNA biomarkers of diseases and to develop miRNA based therapeutic targets, the number of redox-sensitive miRNAs in clinical trials is limited. Hence, the use of redox-sensitive miRNAs for biomarkers of disease or as clinical therapeutics is likely several years off as numerous studies are required to validate and elaborate on current findings. Overall, redox-sensitive miRNAs have the potential to allow us to regulate oxidative stress. Once our understanding of redox-sensitive miRNAs is detailed enough to allow us to use individual or pools of miRNA modulating compounds safely, targeting miRNAs will enable us to improve health-related outcomes associated with different diseases.

Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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