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MicroRNA-mediated regulation of Nrf2 signaling pathway: Implications in disease therapy and protection against oxidative stress

Running Title: microRNAs and Nrf2 signaling pathway

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Abstract:

MicroRNAs (miRs) are small non-coding pieces of RNA that are involved in a variety of physiologic processes such as apoptosis, cell proliferation, cell differentiation, cell cycle and cell survival. These multifunctional nucleotides are also capable of preventing oxidative damages by modulating antioxidant defense systems in a variety of milieu, such as in diabetes. Although the exact molecular mechanisms by which miRs modulate the antioxidant defense elements are unclear, some evidence suggests that they may exert these effects via nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway. This intracellular mechanism is crucial in the maintenance of the physiologic redox balance by regulating the expression and activity of various cellular antioxidative defense elements and thereby play a pivotal role in the development of oxidative stress. Any impairment in the Nrf2 signaling pathway may result in oxidative damage-dependent complications such as various diabetic complications, neurological disorders and cancer. In the current review, we discuss the modulatory effects of miRs on the Nrf2 signaling pathway, which can potentially be novel therapeutic targets.

Keywords: MicroRNAs; Oxidative stress; Nrf2 Signaling Pathway; Diabetes Mellitus; Free Radicals

Abbreviations:

ROS, reactive oxygen species; Nrf2, nuclear factor erythroid 2-related factor 2; miR, microRNA; mRNA, messenger RNA; pri-miR, primary-miR; RISC, RNA-induced silencing complex; DOX, doxorubicin; AD, Alzheimer's disease; PD, Parkinson's disease; SCI, spinal cord injury; Keap1, keltch-like ECH-associated protein 1; cul3, cullin-3; Neh2, Nrf2-ECH homology domain 2; ARE, antioxidant response element; HO-1, heme oxygenase-1; NQO1, NADPH quinone reductase-1; SOD, superoxide dismutase; GST, glutathione-s-transferase; lncRNA, long non-coding RNA; OX-LDL, oxidized-low density lipoprotein; MAPK, mitogen activated protein kinase; mTOR, mammalian target of rapamycin; HDACis, histone deacetylase inhibitors; MM, multiple myeloma; FPN1, ferroportin; Tβ-4, thymosin β-4; Dex, dexamethasone; I/R, ischemic/reperfusion; RPE, retinal pigment epithelium; APAP, acetaminophen; SIRT1, sirtuin 1; CPF, chlorpyrifos; OSCC, oral squamous cell carcinoma; PRXL2A, proxiredoxin like 2A; NO, nitric oxide; MnSOD, manganese SOD; GRP78, glucose-regulated protein 78; CHOP, C/EBP homologous protein; T2DM, type 2 diabetes mellitus; MDA, malondialdehyde; OGD/R, oxygen and glucose deprivation/reperfusion; MMP, mitochondrial membrane potential; PQ, paraquat; EPC, endothelial progenitor cells; ERMP1, endoplasmic reticulum metalloprotease 1; NAFLD, non-alcoholic fatty liver disease; HHW, high-content hydrogen water; H_2O_2, hydrogen peroxide; ATO, arsenic trioxide.

1. Introduction

Oxidative stress is defined as a process by which a higher level of reactive oxygen species (ROS) are produced, leading to damages in proteins, lipids, cell membranes and crucially, the genetic material (Farkhondeh et al. , 2019, Yaribeygi et al. , 2019a). Studies have demonstrated that oxidative stress is a crucial factor in various pathological events, particularly in diabetic complications, neurological disorders and cancer (Aggarwal et al. , 2019, Fakhri et al. , 2018, Yaribeygi et al. , 2018a, Yaribeygi et al. , 2019b, Yaribeygi et al. , 2018c). The cells typically adapt to oxidative stress using compensatory mechanisms known as antioxidant defense system (Kobayashi et al. , 2009, Yaribeygi et al., 2018c). Nuclear factor erythroid 2-related factor 2 (Nrf2) is considered as one of the most critical pathways in preserving the cell homeostasis by induction of this redox balance (Francisqueti-Ferron et al. , 2019a, Kubo et al. , 2019). This molecular pathway influences various antioxidant enzymatic systems and thereby, reinforce the antioxidant defense system (Figure 1).

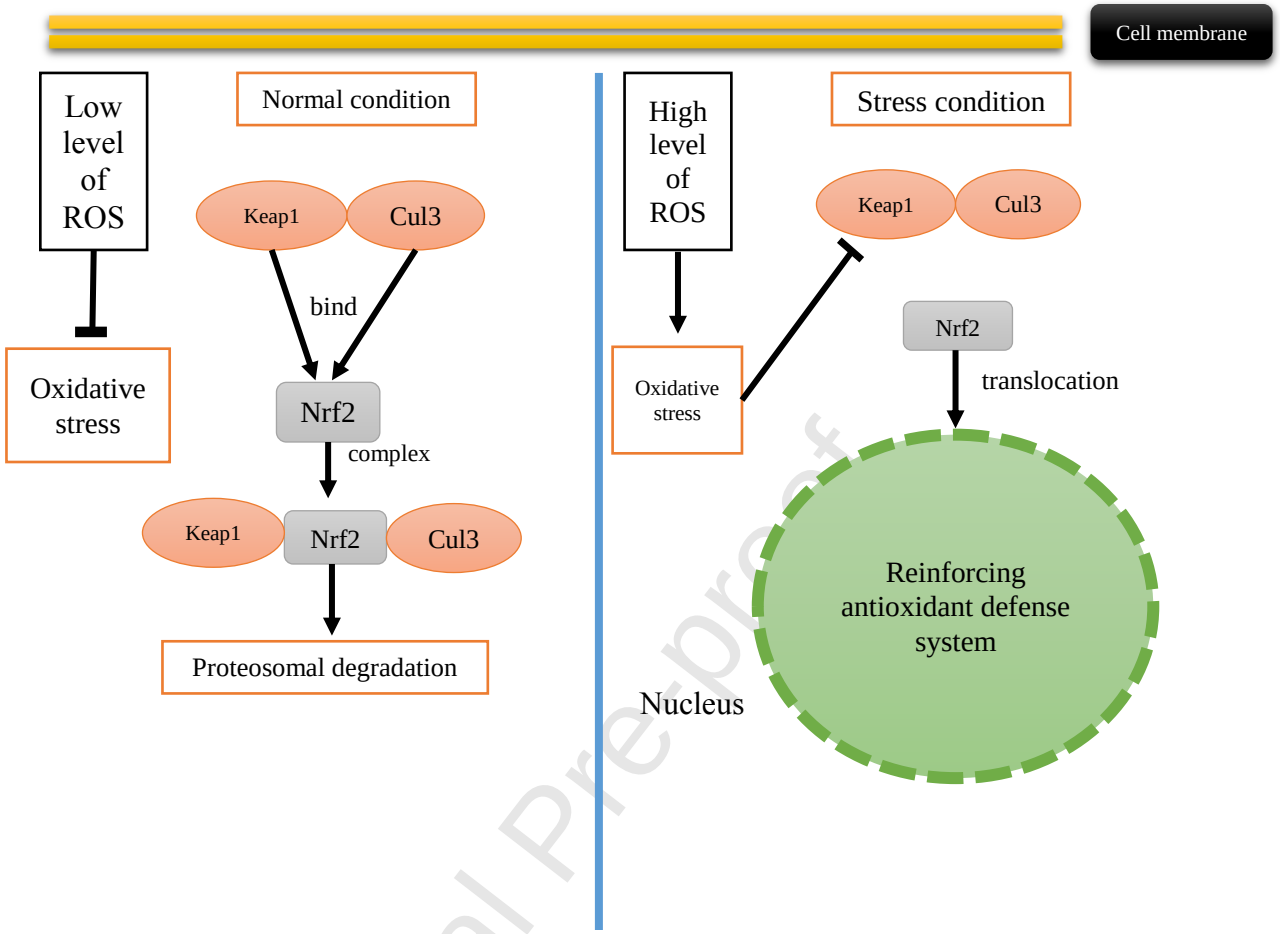

Figure 1: The function of the Nrf2 signaling pathway during the stress condition.

Most of the genome is not transcribed into protein and makes the non-coding RNAs (Humphries et al. , 2019). These non-coding RNAs are now considered as essential players in various physiologic processes such as cell differentiation, cell cycle regulation, apoptosis and proliferation (Mercer et al. , 2009). MicroRNAs (miRs) are small non-coding RNAs with the length of between 20-25 nucleotides (Getaneh et al. , 2019, Yeh et al. , 2019). Although these small pieces of RNAs are considered as non-coding nucleotides, they play significant roles in the regulation of coding genes by binding to the target mRNAs (messenger RNA) and silencing them (Bartel, 2018, Yaribeygi et al. , 2018b). Therefore, miRs regulate the expression of various genes at the post-transcriptional level (MacFarlane and R Murphy, 2010). In the present study, we review the mechanism by which miRs affect the Nrf2 signaling pathway and how these

effects could be developed as potential novel therapeutic targets against oxidative stress-induced complications.

2. Micro RNA synthesis

The biogenesis process of miRs involves complex sequential steps. At the first phase in the nucleus, a primary miR (pri-miR) is produced by RNA polymerase II. RNA polymerase II transcripts pri-miR from relevant genes, then it is cleaved to pre-miRNA by Drosha (a class of ribonuclease enzymes) and exported out of the nucleus into the cytosol by exportin-5 activity where it processed by the DICER (a member of endoribonuclease III family) to a double-strand miRNA (figure 2) (Bartel, 2004, Lam et al. , 2015). This miR is loaded into the AGO component of RISC (RNA-induced silencing complex), where the passenger strand of miR gets dissociated. The remaining silencer complex targets the mRNA at its 3'UTR region (the three prime untranslated regions of mRNA) and suppresses its translation. In this way, these biologic molecules act as gene regulatory agents by partially pairing with complementary sequences on mRNA, making silencing complex and suppressing the protein-coding genes in a post-transcriptionally manner. It is also suggested that miRs directly interact with DNA to make a silenced DNA complex (Bartel, 2004, Lam et al., 2015). Thus it is now recognized that the main effect of miRs is lowering the protein synthesis, including enzymes, receptors, structural proteins, hormones and other intrinsic biologic substances (Bartel, 2004, Lam et al., 2015).

Notably, a novel mechanism for the action of miRs has been proposed by the Brandenstein and colleagues. The miRs are capable of binding to the non-coding DNA strand in the nucleus, leading to the inhibition of transcription. This process will result in production of proteins with truncated C-termini (von Brandenstein et al. , 2018). This mechanism may open a novel paradigm about the putative truncated isoforms which affect a variety of disorders.

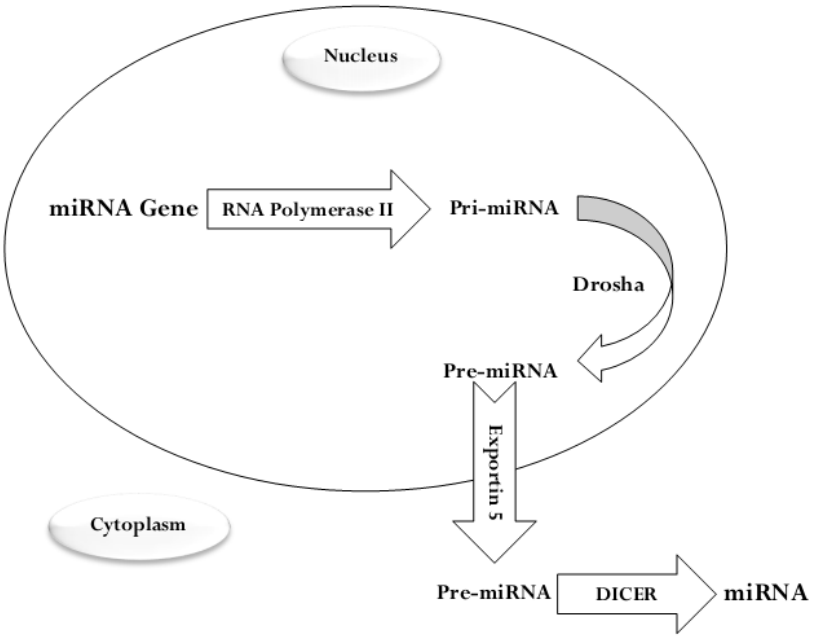

Figure 2: A simple schematic diagram of miRNA synthesis, RNA polymerase II transcripts pri-miRNA from DNA, then pri-miRNA cleaved to pre-miRNA by Drosha and exported out of the nucleus into the cytosol by exportin-5 activity, where it processed by DICER to miRNA (Lam et al., 2015).

3. MiRs-based therapies under diminished antioxidant defense systems

Based on the role of oxidative stress in the development of various disorders and due to the modulatory impact of miRs on various oxidative pathways, miRs can be considered as promising candidates in improving the antioxidant defense system and protection against oxidative stress. Doxorubicin (DOX) is one of the potent chemotherapeutic agents commonly used in treatment of cancers (Burridge et al. , 2016). Treatment with DOX is associated with a number of adverse effects. Cardiotoxicity is one of the most serious side effects of DOX treatment and patients exposed to DOX therapy could develop cardiac dysfunction, heart failure and a reduction in left ventricle ejection fraction (Asselin et al. , 2016, Levis et al. , 2017, Lipshultz et al. , 2012, Lipshultz et al. , 2004). The ROS contribute to the side effects of DOX on the heart and are responsible for the induction of cardiac hypertrophy and failure (Giorgio et al. , 2005, Graiani et al. , 2005, Münzel et al. , 2015, Spescha et al. , 2012, Yan et al. , 2014). These studies

demonstrates that oxidative stress and diminished antioxidant defense system in patients exposed to DOX are mainly responsible for the side effects on heart. Enhancing the expression of miR-124 can ameliorate the DOX-mediated cardiac injury. miR-124 overexpression reduces the expression of p66shc, which is one of the key players in the generation of ROS and triggering apoptosis, leading to the improvement in the cardiac function (Liu et al. , 2020b). Selenium also uses a similar mechanism to reduce oxidative stress. Administration of selenium activates miR-128-3p which in turn diminishes the oxidative stress and promotes antioxidant defense system (Liu et al. , 2020a).

miR therapy is also beneficial in the treatment and prevention of neurological disorders. The oxidative stress has a role in the development of various neurological disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Bello-Medina et al. , 2019, Simon et al. , 2020). Besides, oxidative stress deteriorates the prognosis of spinal cord injury (SCI) (Yang et al. , 2019c). Overexpression of miR-371-5p is beneficial in the amelioration of SCI and stimulates the neuronal repair via suppressing the oxidative stress (Dai et al. , 2019). Overall, these studies demonstrate that miRs are potential mediators in the regulation of oxidative stress. By understand the underlying molecular pathways of the miRs involved in the modulation of oxidative stress and antioxidant defense system, we will be able to identify further targets in the treatment of various pathological conditions (Ge and Gao, 2020, Ke et al. , 2019, Li et al. , 2019b).

4. Nrf2 signaling pathway

Nrf2 signaling pathway acts as the center for the regulation of the antioxidant defense system and responds to oxidative stress (Hegazy et al. , 2019, Vargas-Mendoza et al. , 2019, Wang et al. , 2019a). Notably, a key member of the bZIP transcription factor, NFE2L2, accounts for

encoding Nrf2 (Tebay et al. , 2015). During physiological conditions, Keltch-like ECH-associated protein 1 (Keap1)/Cullin-3 (Cul3) complex has a negative effect on Nrf2. Cul3 binds to the BTB/POZ domain of Keap1. Next, Keap 1 suppresses the nuclear translocation of Nrf2 by binding to the Nrf2-ECH homology domain 2 (Neh2). Then, Keap1 stimulates the proteosomal degradation by ubiquitination of Nrf2 through Cul3 containing E3 ubiquitin ligase (Kobayashi et al. , 2004). However, any interruption in this basal condition leads to stress. In conditions of stress, such as oxidative stress, Keap1 fails to interact with Nrf2, resulting in its dissociation from Nrf2. As a consequence, a high level of Nrf2 accumulates in the cytoplasm. Nrf2 then translocates to the nucleus where it targets antioxidant response element (ARE) and subsequently, triggers the expression of antioxidant genes such as heme oxygenase-1 (HO-1), NADPH quinone reductase-1 (NQO1), superoxide dismutase (SOD) and glutathione-s-transferase (GST) (Batliwala et al. , 2017, Zhang et al. , 2013). These antioxidant enzymes effectively diminish a load of oxidative stress, thereby reducing the damages to lipids, proteins, cell membrane and the genetic material.

5. The role of Nrf2 pathway in pathological states

Since the Nrf2 signaling pathway is vital in maintaining the redox balance, any perturbation in this molecular pathway leads to various pathological states (Papp et al. , 2012). AD is one of the most common neurological disorders that is partly contributed by oxidative damage. Some research studies have tried to stimulate Nrf2 to scavenge ROS, thereby reducing the amount of amyloid-β protein (Li et al. , 2019a). The Nrf2 signaling pathway can also be considered as a potential target in the management of diabetes. It has been shown that β-cells have high sensitivity to oxidative damage (Ramkumar et al. , 2014), hence induction of Nrf2 signaling pathway can reduce the risk of developing diabetes mellitus by reducing the level of oxidative

stress. It has been shown that the enhanced concentration of ROS results in an interruption in the bone metabolism by inhibition of proliferation and differentiation of osteoblasts (Kim et al. , 2014). Nrf2 has a crucial role in the development and management of various cancers. There is growing evidence suggesting that the Nrf2 can exert anti-tumor activity by preserving the cell homeostasis and by generating an anti-inflammation effect. The wider discussion of the Nrf2 pathway in various pathological conditions is out of the scope of this study but has been reviewed extensively in other reviews (Francisqueti-Ferron et al. , 2019b, Wu et al. , 2019c).

6. Regulation of Nrf2 signaling pathway

6.1 Pharmacological regulation

A variety of drugs target Nrf2 signaling pathway to exert their therapeutic effects. Among them, naturally occurring antioxidants are the commonest ones. These agents are able to affect the Nrf2 signaling pathway in various phases. The final goal is to reduce the level of ROS and improve the antioxidant defense system. Based on their impact on Nrf2 signaling pathway, these naturally occurring compounds have been applied in the treatment of various pathological states. Curcumin is a plant-derived chemical and is well-known due to its great therapeutic potential (Abdollahi et al. , 2018, Momtazi et al. , 2016, Panahi et al. , 2017, Rezaee et al. , 2017). Studies have demonstrated that curcumin is able to alleviate oxidative stress and prevent the development of oxidative stress-related disorders by regulation of Nrf2 signaling pathway. These compounds affect the expression of Nrf2, inhibit keap1, and induce the expression of target genes of Nrf2. The table 1 provides a summary of a number of naturally occurring antioxidants targeting Nrf2 signaling pathway.

Table 1: The antioxidant agents and their impact on Nrf2 signaling pathway.

Agent	Effect on Nrf2	Results	Ref
Saffron	Induction	Inhibition of myocardial infarction and reducing myocardial ischemic/reperfusion injury	(Efentakis et al. , 2017)
Ginsenoside Rg1	Induction	Alleviation of nephritis	(Guo et al. , 2019)
Ginsenoside Re	Induction	Suppressing the apoptosis caused by amyloid-beta	(Liu et al. , 2019c)
Thymoquinone	Induction	Protection of cardiac muscles against oxidative stress	(Atta et al. , 2018)
Curcumin	Induction	Reducing the cytotoxicity of methylmercury on primary rat astrocytes	(Yang et al. , 2019a)
Emodin	Induction	Increasing antioxidant capacity	(Song et al. , 2019)

Emodin	Induction	Neuroprotection against oxygen-glucose deprivation/reperfusion injury	(Park et al. , 2018)
Emodin	Induction	Exerting inhibitory effect on the replication of influenza virus pneumonia	(Dai et al. , 2017)
Thymoquinone	Induction	Amelioration of hyperuricemia-mediated renal oxidative stress and mitochondrial abnormalities	(Dera et al. , 2019)
Curcumin	Induction	Improving antioxidant and consequently, alleviation of jejunum damage	(Yan et al. , 2020)
Curcumin	Induction	Increasing hepatic antioxidant capacity	(Niu et al. , 2019)
Curcumin	Induction	Preventing testicular injury by reducing oxidative stress	(Yang et al. , 2019b)

6.2 Genetic regulation

A number of molecular pathways are involved in regulation of Nrf2 signaling pathway. In this section, we discuss some of these pathways. Long non-coding RNAs (lncRNAs) have demonstrated great potential in modulating Nrf2 signaling pathway. LncRNA Blnc1 undergoes upregulation in diabetic nephropathy and alleviates the oxidative stress, inflammation and renal fibrosis by activation of Nrf2/HO-1 pathway (Feng et al. , 2019). Besides, lncRNA AK094457 exerts an inhibitory effect on the Nrf2 signaling pathway, leading to an increased level of ROS in the oxidized-low density lipoprotein (OX-LDL) induced vascular smooth muscle cells (Liu et al. , 2019d). These studies demonstrate that lncRNAs have both positive and negative impacts on the Nrf2 signaling pathway and manipulation of lncRNAs may be potentially beneficial in the treatment of diseases.

Mitogen-activated protein kinase (MAPK) (Liu et al. , 2019a, Ola-Davies et al. , 2019) and mammalian target of rapamycin (mTOR) (Qiao et al. , 2019, Yuan et al. , 2019) can act as upstream mediators of the Nrf2 signaling pathway. Based on these studies, we can conclude that Nrf2 pathway may be a down-stream mediator of the miRs (Chi et al. , 2019, Du et al. , 2019, Qin et al. , 2019, Wu et al. , 2019a).

7. Regulation of microRNAs by Nrf2 signaling pathway

It is worth mentioning that Nrf2 is also capable of regulation of the miRs. In this section, we provide some of the recently published articles to shed some light on the modulatory impact of Nrf2 signaling pathway on the miRs. Histone deacetylase inhibitors (HDACis) are extensively applied in the treatment of cancer (Minucci and Pelicci, 2006, Nikolova et al. , 2017). However, one of the most important problems associated with the application of HDACis is the development of resistance of the cancer cells (Zhang et al. , 2015). This issue is frequently

observed in treatment of cancer with other chemotherapeutic agents and there have been attempts to understand the molecular signaling pathways involved in this resistance (Pabla et al. , 2019, Rodriguez-Ruiz et al. , 2019). It seems that the effect of Nrf2 on miRs plays a significant role in the development of resistance to HDACis. During chemotherapy with HDACis, an upregulation occurs in the expression of Nrf2. As an upstream mediator, Nrf2 signaling pathway increases the expression of miR-129-3p to trigger the mTOR pathway (Sun et al. , 2019). The resistance of cancer cells to HDACis is due to the activation of a process, known as "autophagy". The autophagy process is responsible for alleviation of stress and ensuring the survival of cells (Galluzzi and Green, 2019, Yang and Klionsky, 2020). This process also accounts for the degradation of aged or damaged components and macromolecules at physiological conditions to suppress the oxidative stress (Gatica et al. , 2019, Liu et al. , 2019b). Increasing evidence demonstrates that autophagy activation contributes to the resistance of tumor cells into chemotherapy (Wen and Klionsky, 2019). In the case of HDACis, Nrf2 signaling pathway activates miR-129-3p to stimulate autophagy, leading to chemo-resistance of the cancer cells (Sun et al., 2019). This demonstrates Nrf2 can regulates miRNA in cancer therapy.

Another study clarifies the role of Nrf2 signaling pathway in multiple myeloma (Yaribeygi et al.). It has been shown that a reduction in the expression of ferroportin (FPN1), an iron-exporter protein, predisposes to the development of cancer (Cairo et al. , 2006, Lattuada et al. , 2015). Hence, understand the underlying pathway is of interest in cancer therapy. It has been shown that Nrf2 signaling pathway inhibits the expression of miR-17-5p to down-regulate FPN1. This impact results in the aggregation of iron and ROS. The FPN1 down-regulation contribute the survival and growth of MM (Kong et al. , 2019). Besides, regulation of miR-380-3p by Nrf2 is involved in the paraquat (PQ) toxicity (Cai et al. , 2019). These studies demonstrate that Nrf2

signaling pathway has the capability of regulating miRs. This understanding of the relationship between Nrf2 and miR is advantageous for delineating the underlying molecular pathways and consequently, the treatment of various pathological conditions.

8. Nrf2 regulation by microRNAs

8.1 miR-200a

The miR-200a mediates the ameliorative impact of thymosin β-4 (Tβ-4) in cardiac microvascular endothelial cells after hypoxia-reoxygenation injury (Li et al. , 2017). Tβ-4 exerts a stimulatory effect on the expression of miR-200a. The up-regulation of miR-200a induces the nuclear translocation of the Nrf2 signaling pathway, leading to a reduction in cell apoptosis, ROS generation and adhesion molecules.

MiR-200a can also function in a keap1-dependent manner. This miR suppresses the keap1 to stimulate the Nrf2 signaling pathway. During dexamethasone (Dex) therapy, osteoblasts undergo injuries (den Uyl et al. , 2011, Kerachian et al. , 2009). In order to ameliorate the damages, miRs are potential candidates. It has been shown that miR-200a induces Nrf2 signaling pathway by inhibition of Keap1 to reduce the concentration of ROS, leading to the inhibition of apoptosis in osteoblasts (Zhao et al. , 2017).

8.2 miR-144

Oxidative stress is responsible for the induction of potentially toxic damages in erythroid cells and predisposes them to thalassemia. Hence providing a genetic control towards oxidative stress can be advantageous in the treatment of thalassemia. The miR-144 is involved in the modulation of oxidative stress in the erythrocytes (Srinoun et al. , 2019). The up-regulation of miR-144 diminishes the expression of the Nrf2 signaling pathway, resulting in increased sensitivity of erythrocytes to oxidative stress. Hence reducing the expression of miR-144 can be beneficial in the treatment of thalassemia. Furthermore, miR-144 disrupts the integrity of alveolar epithelial

cells in HIV-1 transgenic rats (Kukoyi et al. , 2019). This adverse effect on epithelial cells is mediated by suppressing the expression and activation of the Nrf2 signaling pathway. Besides, miR-144 ameliorates the impact of ischemia/reperfusion (I/R) injury in neurons by enhancing the expression of the Nrf2/ARE signaling pathway and, consequently, improving the antioxidant defense system (enhancing the expression of HO-1 and NQO1) (Chu et al. , 2019). The miR-144-3p mediates the antioxidant activity of some compounds isolated from Patrinia Villosa by improving the expression of Nrf2 and downstream mediators, HO-1, and NQO1 (Feng et al. , 2018).

Lung cancer is one of the most malignant tumors worldwide (Chen et al. , 2016, Jones and Baldwin, 2018). Cisplatin is a potent chemotherapeutic agent in treatment of lung cancer (Barr et al. , 2013). This agent suppresses the DNA synthesis to stimulate apoptotic cell death in lung cancer cells (Dasari and Tchounwou, 2014, Rudolph et al. , 2017). Cisplatin resistance is a common phenomenon in lung cancer therapy. miR-144-3p prevents cisplatin resistance in lung cancer cells by inhibition of the Nrf2 (Yin et al. , 2018).

8.3 MiR-601

Retinal pigment epithelium cells are sensitive to oxidative damage. It has been reported that the Nrf2 signaling pathway can inhibit the oxidative damage in PRE cells by reinforcing the antioxidant defense system (Wang et al. , 2019b). However, the molecular pathway underlying the activation of the Nrf2 signaling pathway is of importance in term of pharmacological targeting of this pathway. An increase in the expression of miR-601 leads to the inhibition of Cul3 and enhanced nuclear translocation of Nrf2. As a consequence, the antioxidant defense system is reinforced by increased expression of the ARE-dependent genes such as HO-1 and

NQO1. Hence, miR-601 can be considered as a potential candidate in the pharmacological or genetic targeting for the protection of PRE cells against oxidative stress.

8.4 miR-19b

Drug-mediated organ damage occurs after taking a particular drug and much effort has been made to diminish the toxicity of drugs by targeting the underlying mechanisms. Acetaminophen (APAP) overdose causes hepatotoxicity by regulation of the miR-19b (Liu et al. , 2018). It has been shown that upon APAP administration, miR-19b undergoes down-regulation. This phase is vital for the stimulation of sirtuin-1 (SIRT1), which in turn, triggers Nrf2 cascade and various downstream mediators, including antioxidant enzymes. These events result in the inhibition of APAP-mediated hepatoxicity.

8.5 miR-320

One of the most important factors in the management of I/R injury is the inhibition of oxidative damage. It has been shown that the Nrf2 signaling pathway has high efficiency in the prevention of oxidative damage upon I/R injury. Concerning the modulatory effect of miRs on the Nrf2 signaling pathway, regulation of miR targeting Nrf2 pathway appears to be beneficial. In line with this strategy, a reduction in the expression of miR-320 has been made after I/R injury (Zhu et al. , 2019b). The down-regulation of miR-320 remarkably accelerates the activation and expression of the Nrf2 signaling pathway and its downstream mediator, HO-1. As a consequence of Nrf2 stimulation, the concentrations of ROS were reduced, leading to the attenuation of I/R injury.

8.6 miR-181

The incidence of various neurological disorders, particularly PD and AD are increasing and there is an unmet need for novel targets for managing them (Cookson, 2017). It has been demonstrated

that exposure to insecticides is one of the risk factors for developing neurological disorders. Hence, expanding our knowledge towards the mechanism of action of these agents is of interest. Chlorpyrifos (CPF) is an insecticide and has the potential to stimulate various neurological disorders (Zhao et al. , 2019b). Exposure to CPF is associated with cell pyroptosis and high sensitivity to oxidative stress. These harmful impacts on the SH-SY5Y cells are mediated partially via the up-regulation of miR-181 by CPF. As a result, miR-181 suppresses the molecular pathway involved in cell protection and inhibition of ROS generation, known as the SIRT1/PGC-1α/Nrf2 signaling pathway. This inhibition predisposes to the development of PD.

8.7 miR-125b

Although much progress has been made in the field of cancer therapy, it is still one of the leading causes of death around the world (Ahmadi et al. , 2019, Ashrafizadeh et al. , Ashrafizadeh et al. , 2019a, Mohammadinejad et al. , 2019a, Mohammadinejad et al. , 2019b). Oral squamous cell carcinoma (OSCC) is one of the common types of cancer. It has been reported that gene therapy can be advantageous in OSCC treatment. On the other hand, based on the role of oxidative stress in cell and genetic material damage, targeting oxidative stress is an option in OSCC therapy. In agreement with this strategy, Chen and colleagues have studied the effect of miR-125b in OSCC therapy (Guo et al., 2019). The miR-125b is involved in the regulation of a protein, known as peroxiredoxin, like 2A (PRXL2A). PRXL2A has various important roles, but it is mainly associated with the protection of the cells against oxidative damage. The up-regulation of PRXL2A by miR-125b inhibits the oxidative damage in cells by positively affecting the Nrf2 signaling pathway. Overall, miR-125b prevents OSCC by therapeutic targeting of the PRXL2A/Nrf2 pathway.

8.8 miR-24-3p

Cardiomyocytes are vulnerable to I/R injury (Liao et al. , 2012). This vulnerability can be reduced by targeting the molecular pathways involved in antioxidant defense system (Xiao et al. , 2018). miR-24-3p effectively triggers the Nrf2 signaling pathway by inhibition of Keap1, leading to the protection of cardiomyocytes against I/R injury (Xiao et al., 2018).

8.9 miR-34

Ischemic stroke carries significant morbidity and mortality worldwide. An effort has been made to reduce the cerebral I/R injury by miR-34b after ischemic stroke (Huang et al. , 2019). The findings confirmed that miR-34b significantly attenuates infarction volume, the neurological severity scores and the level of nitric oxide (NO), whereas it enhances the activities of SOD and manganese SOD (MnSOD). It was found that these protective impacts of miR-34b are mediated by the inhibition of Keap1, so that Keap1 inhibition activates the Nrf2 signaling pathway and, consequently, stimulates the antioxidant enzymes. Furthermore, crocin targets miR-34a thereby attenuating myocardial I/R injury (Li et al., 2019b). MiR-34a was inhibited after treatment with crocin. Consequently, there was an up-regulation of the SIRT1/Nrf2 axis. This axis diminished the expression of Bax, caspase 3, glucose-regulated protein 78 kDa (GRP78) and C/EBP homologous protein (CHOP), while the SIRT1/Nrf2 axis enhanced the expression of Bcl-2, an anti-apoptotic factor. These protective effects attenuated the I/R injury.

8.10 miR-223

Diabetes mellitus is a chronic metabolic disorder that can lead to complications in various organs (Yaribeygi et al., 2019a). Insulin resistance and oxidative stress are the most challenging barriers in the management of type 2 diabetes mellitus (T2DM) (Ashrafizadeh et al. , 2019b). miR-223 has this capability to modulate oxidative stress associated with T2DM (Ding et al. , 2019). Investigation of the underlying molecular pathways revealed that miR-223 could exert a

therapeutic impact in the HepG2 cells exposed to a high glucose condition by reducing the oxidative stress and by improving insulin resistance. By doing so, miR-223 suppresses the Keap1 to stimulate the Nrf2 signaling pathway, resulting in an improvement in the expression of HO-1, SOD1 and SOD2, and consequently, the promotion of the antioxidant defense system.

8.11 miR-27a

It has demonstrated that adipokine modulators are beneficial in the management of diabetic nephropathy (Yaribeygi et al. , 2019c). For example, omentin-1, an adipokine modulator, has shown to have great potential in the amelioration of diabetic nephropathy (Song et al. , 2018). Omentin-1 can exert its inhibitory effect on the concentrations of inflammatory cytokines (interferon-γ, tumor necrosis factor-α and interleukin-8) and oxidative stress levels by improving the activities of antioxidant enzymes such as catalase and SOD, and by reducing malondialdehyde (MDA). miR-27a has a negative effect on the expression of the Nrf2 signaling pathway by binding to its 3′UTR. Notably, miR-27a undergoes down-regulation under omentin-1 administration, resulting in the activation of the Nrf2 signaling pathway and inhibition of oxidative and inflammatory damages.

8.12 miR-101

Regulation of the cell cycle is of interest in terms of the prevention of various pathological states, especially cancer (Kastan and Bartek, 2004). miRs can control the proliferation of cells by influencing various molecular pathways (Johnnidis et al. , 2008). Nrf2 signaling pathway is a potential target of miRs in the regulation of gastric mucosal epithelial cells (Dong et al. , 2019). It has been shown that miR-101 inhibits proliferation and stimulates the apoptotic cell death in the gastric mucosal epithelial cells by inhibiting the Nrf2/ARE pathway. MiR-101 suppresses the activity of Nrf2 by binding to the UTR of Nrf2.

8.13 miR-340-5p

One of the most challenging barriers in chemotherapy is the resistance of tumor cells to various chemotherapeutic agents (Li et al. , 2008). Investigation of various molecular pathways contributing to this can be beneficial in decreasing the chance of resistance (Stavrovskaya, 2000). In a recent study conducted by Wu and colleagues in 2019, it was found that NRAL, a long non-coding RNA, contributes to cisplatin resistance (Wu et al. , 2019b). Also, there was a reverse relationship between NRAL and miR-340-5p, where NRAL negatively affects the miR-340-5p to trigger the Nrf2-dependent antioxidant enzymes, demonstrating the critical role of the NRAL/miR-340-5p/Nrf2 axis in the cisplatin resistance in hepatocellular carcinoma cells (Wu et al., 2019b).

8.14 miR-365

There are concerns about the spread of heavy metals in the environment (Bradl, 2005). The half-life of heavy metals, particularly lead and cadmium is high (Bradl, 2005). Hence, exposure to heavy metals results in long term carriers of these metals (Bradl, 2005). Many efforts have been performed to find the molecular pathways of their action (Bradl, 2005). Induction of oxidative damage is the most common way that cadmium and other heavy metals cause damage (Bradl, 2005). There is evidence demonstrating that long non-coding RNAs such as MT1DP may accelerate the oxidative damage caused by cadmium (Gao et al. , 2018). MT1DP enhances the expression of miR-365 to inhibit the Nrf2 signaling pathway, leading to the aggravation of oxidative stress. It appears that miR-365 binds to the UTR of Nrf2 to suppress its activity (Gao et al., 2018).

8.15 miR-29

Reinforcing the antioxidant defense system is considered to be beneficial in the inhibition of cell death caused by oxygen and glucose deprivation/reperfusion (OGD/R) in neurons (Wei et al. , 2018). miR-29 family (miR-29a/b/c) is involved in improving the activity of antioxidant enzymes under OGD/R (Wei et al., 2018). Upon OGD/R, the miR-29 family undergoes down-regulation. However, enhancing the expression of the miR-29 family is associated with a reduction in ROS generation and mitochondrial membrane potential (MMP). Examination of the molecular pathways demonstrated that up-regulated miR-29 suppresses the Keap1, leading to the activation of the Nrf2 signaling pathway and, consequently, promoting the antioxidant defense system (Wei et al., 2018).

8.16 miR-495

Epilepsy and seizure-mediated damages can be reduced by the regulation of genes (Geng et al. , 2018). It appears that during epilepsy and seizure, the Nrf2 signaling pathway undergoes down-regulation by the activity of miR-495, leading to apoptosis. It has been shown that a long non-coding RNA, known as UCA1, suppresses the miR-495 to stimulate the Nrf2 pathway, leading to the inhibition of apoptosis in neurons and epileptiform hippocampal tissues (Geng et al., 2018).

8.17 miR-141-3p

The lung is one of the potential targets of PQ and the effect of transplantation of endothelial progenitor cells (EPC) in amelioration of PQ-induced lung toxicity has been studied (Jin et al. , 2018). This study revealed a novel pathway for the action of EPCs in the attenuation of lung injury. During the PQ toxicity, there is an increase in the expression of miR-141-3p that, in turn, exerts harmful effects in the lung by Nrf2 pathway inactivation. After transplantation of EPCs, the lung injury was reduced and the infiltration of neutrophils and leukocytes was reduced. Examination of the molecular pathways revealed that EPCs suppress miR-141-3p to stimulate

the Notch/Nrf2 axis, leading to its therapeutic impacts in the lungs exposed to the PQ (Jin et al., 2018).

8.18 miR-148b

Enhancing the generation and concentration of ROS induces cell death, which is a strategy extensively applied in cancer therapy. miR-148b, as a tumor suppressor, provides a condition with a high concentration of ROS to suppress the tumor cells (Qu et al. , 2018). miR-148b exerts its inhibitory effect on the expression of endoplasmic reticulum metalloprotease 1 (ERMP1). As a consequence, the Nrf2 undergoes down-regulation that, in turn, enhances the level of ROS, leading to the inhibition of cell proliferation in human endometrial cancer RL95-2 cells (Qu et al., 2018).

8.19 miR-503

The phase II enzyme inducer (CPDT) complex functions as an upstream mediator of miR-503 in the regulation of the antioxidant defense system (Miao et al. , 2017). miR-503 reduces the expression of the Nrf2 by binding to UTR to exert adverse effects in diabetic cardiomyopathy rats by enhancing myocardial cell size and myocardial apoptosis. Treatment with CPDT is associated with a reduction in expression of the miR-503. As a result, the Nrf2/ARE signaling pathway is activated and subsequently, this pathway improves the activity of antioxidant enzymes (Miao et al., 2017).

8.20 miR-136

MiR-136 is considered as a potential target in attenuation of non-alcoholic fatty liver disease (NAFLD) (Wang and Wang, 2018). High-content hydrogen water (HHW) administration exerts a therapeutic effect in NAFLD. Evaluation of molecular pathways revealed that miR-136 functions as an upstream mediator of MEG-3, so that enhanced expression of miR-136 is

associated with a down-regulation of MEG3, leading to the impairment in Nrf2 activity. HHW negatively affects miR-136 to elevate the expression of MEG3. As a consequence, Nrf2 is stimulated, resulting in a reduction in serum lipid level and amelioration of NAFLD (Wang and Wang, 2018).

8.21 miR-93

Inhibition of apoptotic cell death has been at the center of focus for diminishing the adverse effects of OGD/R. Gene therapy has been aimed at the prevention of apoptosis in cells exposed to the OGD/R (Yan et al. , 2017). It has been reported that upon OGD/R, miR-93 suppresses the Nrf2 activity to induce apoptosis. Application of antagonist of miR-93 remarkably enhances the activity of Nrf2 to inhibit the apoptotic cell death and caspase-3 (Yan et al., 2017).

8.22 miR-101

There have been efforts to use naturally occurring compounds with synthetic anti-tumor drugs to reduce the chance of chemo-resistance. Apigenin as a key member of the flavonoid family with anti-tumor activity and has been applied to enhance the efficacy of chemotherapy (Gao et al. , 2017). A large body of studies demonstrates the vital role of miR-101 in the malignancy and chemo-resistance (Liu et al. , 2016, Xu et al. , 2013). Cancer cells obtain chemo-resistance by down-regulation of miR-101. miR-101 diminishes the activity of Nrf2 by binding to the UTR. It appears that apigenin enhances the sensitivity of human hepatocellular carcinoma cells by up-regulation of miR-101. As a consequence, the inhibition of Nrf2 occurs and a high level of ROS sensitizes the cancer cells to apoptotic cell death (Liu et al., 2016, Xu et al., 2013).

8.23 miR-455

Bone metabolism is negatively affected by oxidative stress and miR-455-3p has this capability to modulate oxidative damage (Zhang et al. , 2018). Exposure to the ferric ammonium citrate

(FAC) is associated with the induction of apoptosis and a decrease in cell proliferation (Kang et al. , 2005). These adverse effects are a result of the high level of oxidative stress (Kang et al., 2005). Enhancing the expression of miR-455-3p reversed the harmful impacts of FAC so that after the overexpression of miR-455-3p, bone metabolism was restored and apoptosis was inhibited (Zhang et al., 2018). The miR-455-3p stimulates the activation of Nrf2 by its upstream mediator, HDAC2, leading to the alleviation of oxidative damage (Zhang et al., 2018).

Accumulating data shows that increased concentration of ROS has a deleterious effect on osteoblasts and increases the risk of development of osteoporosis and osteonecrosis (Baek et al. , 2010, Himburg et al. , 2010, Souttou et al. , 2001, Tare et al. , 2002). Hydrogen peroxide (H_2O_2) can elevate the level of ROS and stimulate oxidative stress. Studies have shown that the relationship between H_2O_2 exposure and induction of osteoporosis and osteonecrosis (Herbst, 2004, Liang et al. , 2013, Rigel et al. , 1996, Salopek et al. , 1995, Talasila et al. , 2013). Hence, protection of osteoblasts against the adverse impacts of H_2O_2 is of importance. MiR-455 stabilizes and enhances the level of Nrf2 by degradation of the cul3 that in turn, activates the ARE-related genes such as NQO1, HO-1 and GCLC. This improves the antioxidant defense system, leading to the protection of osteoblasts against adverse effects of H_2O_2 (Xu et al. , 2017).

8.24 miR-155

Arsenic trioxide (ATO) is a potential anti-tumor agent with high application in chemotherapy (Wang, 2001). As mentioned earlier; one of the difficulties faced in chemotherapy is the development of resistance to chemotherapeutic agents (Li et al., 2008). It appears that miR-155 is involved in the resistance of tumor cells into ATO (Gu et al. , 2017). It has been shown that miR-155 makes lung cancer cells resistant to ATO by the activation of the Nrf2 signaling

pathway. As a result, the downstream mediators of Nrf2 such as HO-1 and NQO1 are induced and the level of apoptosis reduced by enhancing the ratio of bcl-2/Bax (Gu et al., 2017).

8.25 MiR-153

During OGD/R, miR-153 level increases that in turn, mediates the generation of ROS, resulting in the induction of apoptosis in cardiomyocytes. The Nrf2 signaling pathway is a target of miR-153 in these adverse effects on the heart. By down-regulation of miR-153, the activation of Nrf2 signaling pathway happens which diminishes the level of ROS and consequently, inhibits the apoptosis in cardiomyocytes (Zhu et al. , 2019a).

Another study demonstrated the effect of miR-153 on Nrf2 and its stimulatory impact on the development of cancer. In breast cancer cells, miR-153 undergoes upregulation. This miR inhibits the activation of Nrf2 signaling pathway to decrease apoptosis and enhance the colonization of cancer cells. So, miR-153 functions as an oncogenesis miR in breast cancer via suppressing the Nrf2 (Wang et al. , 2016). Besides, miR-153/miR-27a/miR-142-5p/miR-144 axis is involved in regulation of Nrf2 and redox homeostasis in neuronal cells, so that this axis is capable of inhibiting the expression of Nrf2 signaling pathway and protecting against oxidative damage (Narasimhan et al. , 2012). Another study also demonstrates the inhibitory effect of miR-153 on Nrf2 signaling pathway. As it was mentioned, increased level of oxidative stress increases the risk of development of PD. The miR-153 can deteriorate the PD via suppressing Nrf2/HO-1 signaling pathway and consequently, increasing the concentration of ROS (Zhu et al. , 2018).

Table 2: The stimulatory effect of miRs on Nrf2 signaling pathway.

Experimental model	MiR	Interaction	Major outcomes	Refs
Cardiac microvascular endothelial cells	MiR-200a	Enhancing the nuclear translocation of Nrf2	Decreasing cell apoptosis, ROS generation and adhesion molecules	(Li et al., 2017)
PRE cells	MiR-601	Enhancing the nuclear translocation of Nrf2	Protection against oxidative damage	(Li et al., 2019b)
Hepatocytes	MiR-19b	Enhancing the expression of Nrf2 and downstream mediators such as antioxidant enzymes	A decrease in miR-19b activates SIRT1, resulting in activation of Nrf2 cascade	(Liu et al., 2018)
OSCC tumor	MiR-125b	Positively affecting upstream mediator of Nrf2	Stimulation of PRXL2A, resulting in Nrf2 activation and protection against oxidative stress	(Guo et al., 2019)
Cardiomyocytes	MiR-24-3p	Inhibition of Keap1	Improving the antioxidant defense system and reducing I/R injury by stimulation of the Nrf2 signaling pathway	(Xiao et al., 2018)
Cerebral I/R injury	MiR-34b	Inhibition of Keap1	Decreasing NO level, infarction volume and neurological severity scores and improving SOD and MnSOD activities by Nrf2 stimulation	(Huang et al., 2019)
HepG2 cells	MiR-223	Inhibition of Keap1	Diminishing oxidative stress and improving insulin resistance by Nrg2 pathway stimulation	(Ding et al., 2019)
PC12 cells	MiR-144	Enhancing the expression of Nrf2	Reducing I/R injury in neurons by promoting Nrf2/ARE signaling pathway and subsequently, induction of antioxidant enzymes	(Chu et al., 2019)
Neuronal HT-22 cells	MiR-29a/b/c	Inhibition of Keap1	Reducing the level of ROS and MMP by activation of Nrf2 signaling pathway	(Wei et al., 2018)
Osteoblast cell lines MC3T3-E1 Osteoporosis mice	MiR-455-3p	Stimulation of HDAC2/Nrf2 pathway	Overexpression of miR-455-3p is associated with stimulation of Nrf2 through HDAC2 and attenuation of oxidative damage	(Zhang et al., 2018)
Human lung adenocarcinoma A549R cell line	MiR-155	Enhancing the expression of Nrf2	Activation of Nrf2 and downstream mediators, HO-1 and NQO1, enhanced the ratio of bcl-2/Bax and suppressed apoptosis in cancer cells	(Gu et al., 2017)
Esophageal squamous cell carcinoma	MiR-432	Inhibition of Keap1	Enhanced expression of miR-432 diminished the sensitivity of cancer cells to chemotherapy by	(Akdemir et al. ,

			upregulation of Nrf2	2017)

Table 3: The inhibitory effect of miRs on Nrf2 signaling pathway.

Experimental model	MiR	Interaction	Major outcomes	Refs
Thalassemic erythroid cell	MiR-144	Decreasing the mRNA expression of Nrf2	Sensitizing thalassemic erythroid cells to oxidative stress and providing the conditions for thalassemia	(Srinoun et al., 2019)
Alveolar epithelial cell	MiR-144	Decreasing the expression and activity of Nrf2	Stimulation of alveolar epithelial cell dysfunction	(Kukoyi et al., 2019)
Myocardial I/R injury	MiR-320	Decreasing the expression of Nrf2 signaling pathway	MiR-320 inhibits Nrf2 signaling pathway, so down-regulation of miR-320 is beneficial in activation of the Nrf2 pathway and amelioration of I/R injury	(Zhu et al., 2019b)
SH-SY5Y cells	MiR-181	Negatively affecting upstream mediators of Nrf2	Preventing the activation of SIRT1/PGC-1□/Nrf2 pathway, leading to PD	(Zhao et al., 2019b)
Type 2 diabetic db/db mice	MiR-27a	Decreasing the expression of Nrf2 by directly binding to its UTR	Inhibition of oxidative and inflammation damages by omentin-1 through Nrf2 activation and miR-27a inhibition	(Song et al., 2018)
Gastric mucosal epithelial cells	MiR-101	Decreasing the expression of Nrf2 by directly binding to its UTR	Stimulation of apoptosis in gastric mucosal epithelial cells	(Dong et al., 2019)
SMMC-7721 and HepG2 cell lines	MiR-340-5p	Decreasing the expression of Nrf2 by directly binding to its UTR	NRAL suppresses miR-340-5p to activate Nrf2-dependent enzymes, resulting in cisplatin resistance	(Wu et al., 2019b)
Human hepatocellular carcinoma cell line HepG2	MiR-365	Decreasing the expression of Nrf2 by directly binding to its UTR	MT1DP inhibits Nrf2 through elevation of miR-365, resulting in aggravation of oxidative stress	(Gao et al., 2018)
HEK-293 cells	MiR-495	Decreasing the expression of Nrf2 by directly binding to its UTR	UCA1 down-regulates miR-495 to activate the Nrf2 pathway, resulting in inhibition of apoptosis in neurons and hippocampal tissue	(Geng et al., 2018)
Endothelial progenitor cells	MiR-141-3p	Inhibition Notch/Nrf2 axis	EPCs suppress miR-141-3p, resulting in improvement in Notch/Nrf2 axis and therapeutic effect in lung	(Jin et al.,

				2018)
Human endometrial cancer RL95-2 cells	MiR-148b	Inhibition of ERMP1/Nrf2 axis	Enhancing ROS level and inhibition of cell proliferation in cancer cells	(Qu et al., 2018)
Cardiomyocyte Mouse model	MiR-34a	Inhibition of SIRT1/Nrf2 axis	Crocin activates SIRT1/Nrf2 axis by miR-34a inhibition, leading to the alleviation of myocardial I/R injury	(Li et al., 2019b)
Primary myocardial cells	MiR-503	Decreasing the expression of Nrf2 by directly binding to its UTR	CPDT decreases the expression of miR-503 to activate Nrf2/ARE signaling pathway and improve the antioxidant defense system	(Miao et al., 2017)
High-fat diet (HFD)-induced NAFLD mice model and cellular model	MiR-136	Inhibition of MEG3/Nrf2 axis	HHW down-regulates miR-136 to activate MEG3, resulting in Nrf2 induction and reducing serum lipid levels	(Wang and Wang, 2018)
Primary cardiomyocytes	MiR-93	Reducing the expression of Nrf2	Inhibition of miR-93 activates Nrf2, leading to the prevention of apoptotic cell death and caspase-3	(Yan et al., 2017)
Human HCC cells line BEL-7402 and ADM-resistant HCC cell line BEL-7402/ADM	MiR-101	Decreasing the expression of Nrf2 by directly binding to its UTR	Apigenin sensitizes cancer cells to chemotherapy by inhibition of Nrf2 through miR-101 and subsequently, enhancing ROS levels	(Gao et al., 2017)
Hepatic ischemia-reperfusion (Kobayashi et al.) mice model	MiR-34a	Decreasing the expression of Nrf2	MEG3 down-regulates miR-34a to induce Nrf2 pathway, leading to the decreased level of ROS and serum concentrations of ALT and AST and subsequently, protection against HIR	(Huang et al. , 2018)
Cultured human umbilical vein endothelial cells (HUVECs)	MiR-92a	Activation of Keap1	Down-regulation of miR-92a enhances the level of Nrf2 and decreases the level of Keap1, leading to the facilitation of cell proliferation and decreased level of caspase-3 and ROS	(Liu et al. , 2017)
Renal I/R injury in mice	MiR-126	Increased expression of Nrf2 and HO-1s	Inhibition of injury by reducing oxidative stress	(Zhao et al. , 2019a)

9. How miRs affect the Nrf2 signaling pathway?

In short, miRs are the potential upstream modulators of the Nrf2 signaling pathway with high capability to regulate the Nrf2 pathway in multiple phases (Cheng et al. , 2013, Kabaria et al. , 2015). Overall, miRs regulate the Nrf2 pathway via four significant pathways: a) affecting the nuclear translocation of Nrf2, b) influencing the expression of Nrf2, c) regulating the upstream mediators of Nrf2 and d) modulation of Keap1 (Table 2 and 3). Figures 3 and 4 demonstrate that which miR with what strategy affects the Nrf2 signaling pathway.

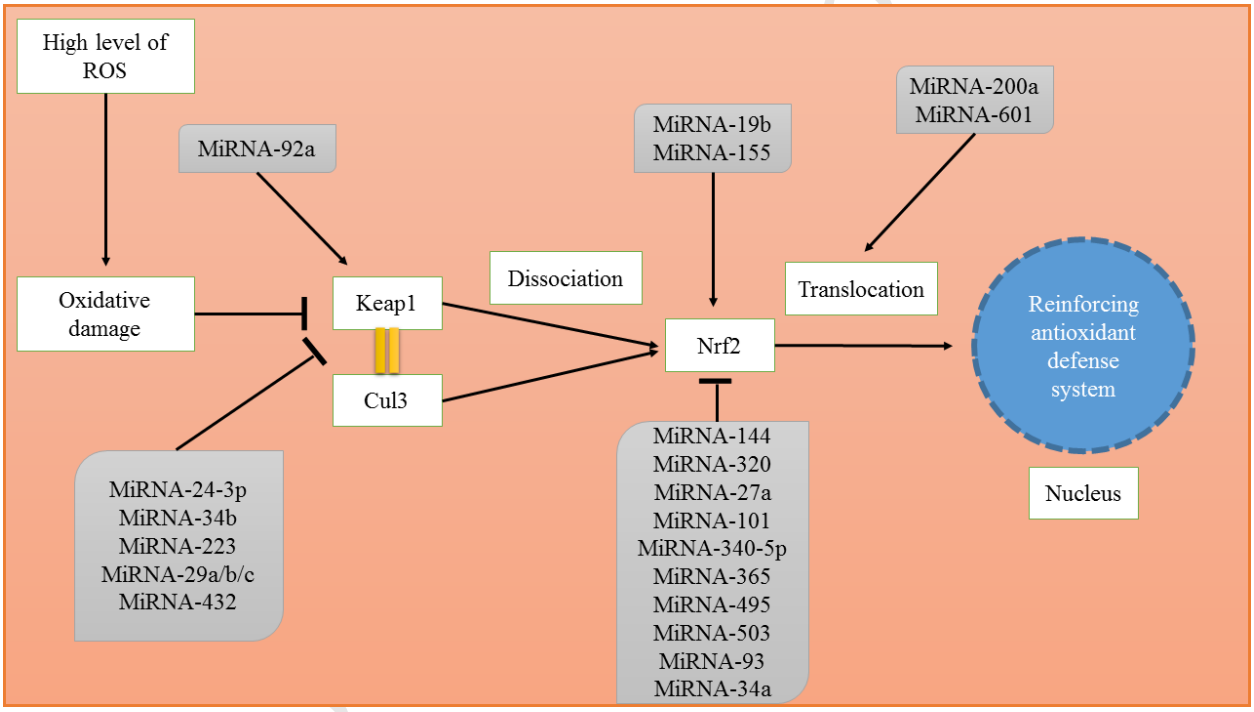

Figure 3: Modulation of the Nrf2 signaling pathway in various steps.

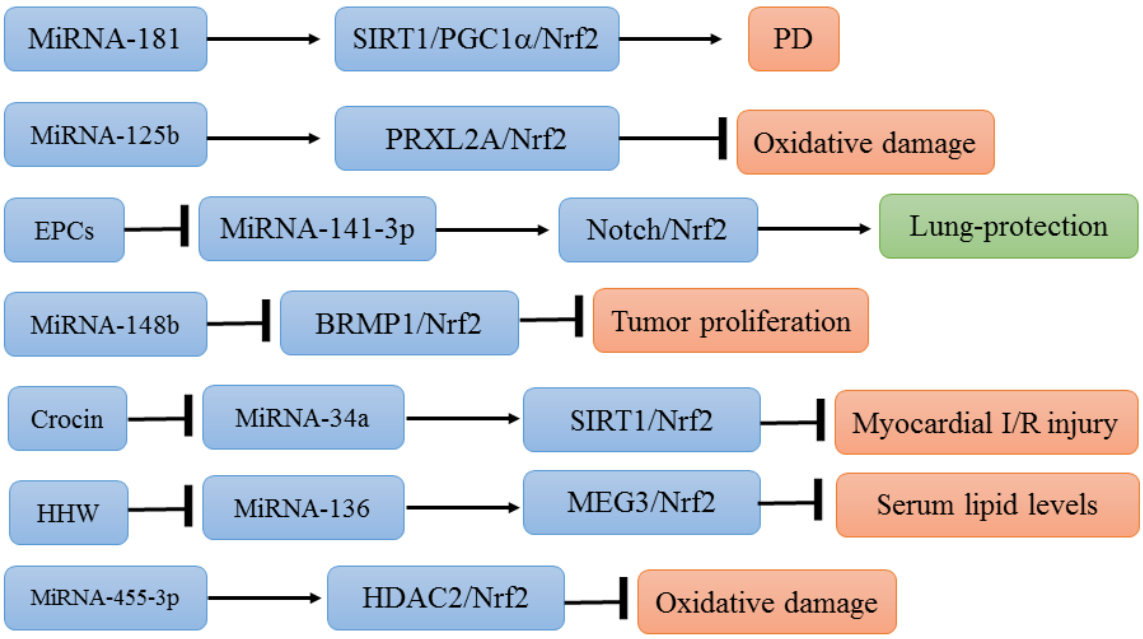

Figure 4: Regulation of upstream mediators of the Nrf2 signaling pathway using miRs.

10. Conclusion

Regulation of oxidative stress is of importance for the prevention of various pathological disorders. Nrf2 signaling pathway plays a significant role in preserving the redox balance through potentiating the antioxidative defense system. However, this crucial molecular pathway undergoes alteration in particular conditions resulting in various disorders such as cancer, diabetes mellitus and neurological complications. Many attempts have been made to influence the Nrf2 signaling pathway in the prevention and treatment of these pathological conditions. miRs could potentially help in this regard by acting as novel therapeutic targets against oxidative stress-induced complications. The miRs can modulate the Nrf2 signaling pathway by its effects on Keap1, by regulating the expression of Nrf2, by influencing the nuclear translocation of Nrf2 and by modulating the upstream mediators of Nrf2 pathway including SIRT1/PGC1α, PRXL2A,

Notch, BRMP1, HDAC2 and MEG3. By targeting the regulation of the Nrf2 signaling pathway by miRs can potentially lead to the development of new therapeutic agents for the management of various conditions, including diabetes and cancer.

Conflict of interest

The authors declare that they have no conflict of interest.

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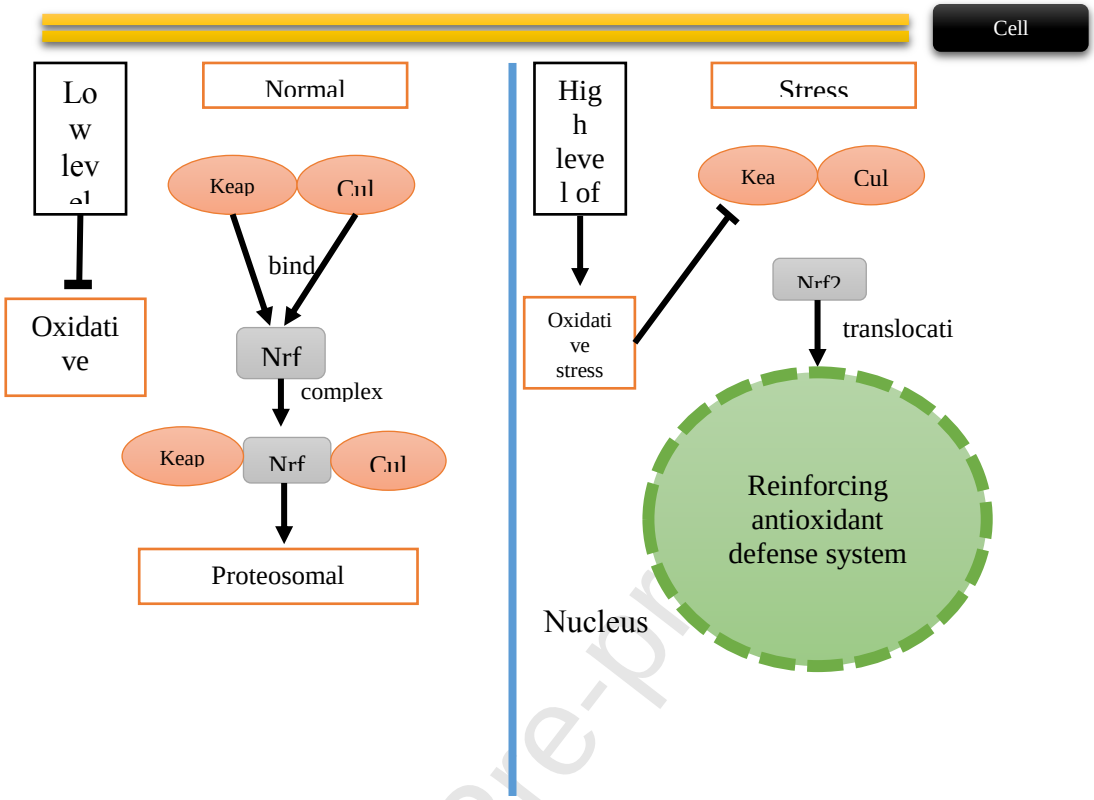

Graphical abstract