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An insight into the role of microRNAs in reactive oxygen species activity

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Abstract
MicroRNAs (miRNAs) are non-coding RNAs and have a pivotal role in a range of mechanisms related to physiological and pathological conditions in humans. Reactive oxygen species (ROS) are unstable molecules derived from oxygen ions and initially produced during mitochondrial oxidative phosphorylation. These levels are tightly related to several diseases, such as cancer pathogenesis, neurodegenerative, cardiovascular, inflammatory, and apoptosis-related diseases. In recent years, ROS-related specific miRNA expression levels have gained attraction in the fields of pathology, molecular biology, physiology, pharmacology, and tissue engineering. Interestingly, both increases and decreases in miRNA expression have dual effects on ROS production. Variable changes occur during a ROS-related disease in the expression levels of miRNAs. The main point is the clarification of whether the increase or decrease of the related miRNAs has a suppressive, scavenger, or therapeutic effect on ROS. There is still a lack of substantial evidence about the relationship between ROS. Here we summarized the relationship between ROS production and miRNAs from a narrative perspective.
Keywords: *Reactive Oxygen Species, Oxidative Stress, MicroRNA, Oxidative Damage, Primary MicroRNA*

1. Introduction

1.1. MicroRNAs

MicroRNAs (miRNA) were first identified at Caenorhabditis elegans (C. elegans) in the 1990s as a type of non-coding RNA. Until now, miRbase classified approximately thousands of miRNAs related to 271 organisms. Moreover, 2000 of them have been placed in humans.[1,2] miRNAs have various roles in multiple mechanisms in the body including cell proliferation, cell death, metabolism, apoptosis, neuronal patterns, hematopoietic differences, differentiation organogenesis, stem cell, and germline proliferation, growth, controlling of growth, immunity.[1,3]

miRNAs family inherited evolution and have a single chained structure. This formation can be produced in canonical and non-canonical ways. Canonically, the first step is the synthesis of primer miRNA (pri-miRNA) from DNA in the nucleus. pri-miRNA has hairpin or bear fragments which must be cropped for activation of the miRNAs. The process occurs in two phases: the first takes place in the nucleus and the other in the cytoplasm. The identification of miRNA is achieved by a complex meaned microprocessor complex in the nucleus. The complex consists of unique RNase III Drosha and two DiGeorge Syndrome Critical Region 8 (DGCR8) that are cofactors of RNase III Drosha. pri-miRNA is cropped by this complex and precursor miRNA (pre-miRNA) is released. Following that, exportin-5/Ras-related nuclear protein-GTPase (XPO5/Ran-GTP) transports pre-miRNA from the nucleus to the cytoplasm. RNase III Dicer is responsible for cleavage and miRNA duplex is acquired. One of the duplex strips is linked with Argonaute 2 (AGO2) which is a member of Argonaute. It results in a complex identified as a mature RNA-induced silencing complex (miRISC). The final structure binds the DNA and completes the process (Figure 1).[1,4–9] Also, some of the miRNAs could be produced by non-canonical pathways that classify two categories as Drosha-/DGCR8-independent ways and Dicer-independent ways. Both these ways, use different molecules for two-staged cleavage or transport from the nucleus to the cytoplasm. Regardless of which molecules were used, the last product is the miRISC complex which triggers intracellular changes.[9]

The main function of miRNAs is the regulation of gene expression through making changes in messenger RNA (mRNA) activities. The result of the gene expression regulation depends on coadaptation between the miRNA and mRNA. miRNAs especially target the 3' UTR zone in mRNAs and link that part of the substance. Following that, if the coadaptation is weaker, it leads to a suppressed translation of protein. Whether the coadaptation is stronger, miRNAs begin to degrade the related mRNA.[4,7,10,11] It is clear from this issue that miRNA regulates protein levels in all living cells.

Under physiological conditions, miRNAs regulate plenty of genes and functions due to the affectable capacity that a unique miRNA can target hundreds of mRNA.[12] This clarifies that miRNAs have a pivotal role in complex genetic interactions and cell connections.[13] In addition, there is substantial evidence points out that the changes in miRNA levels could be the basic reason for several diseases. In contrast, a specific miRNA may be the alleviating factor of a disease either. Considering, miRNAs have been suggested as new approaches for the treatment of various pathophysiological conditions.[3]

Current studies indicated that there is a mutual relationship between miRNA and reactive oxygen species (ROS). Functional properties such as transcription, and translocation of miRNAs are highly correlated with ROS activity. Based on this, some miRNAs are identified as

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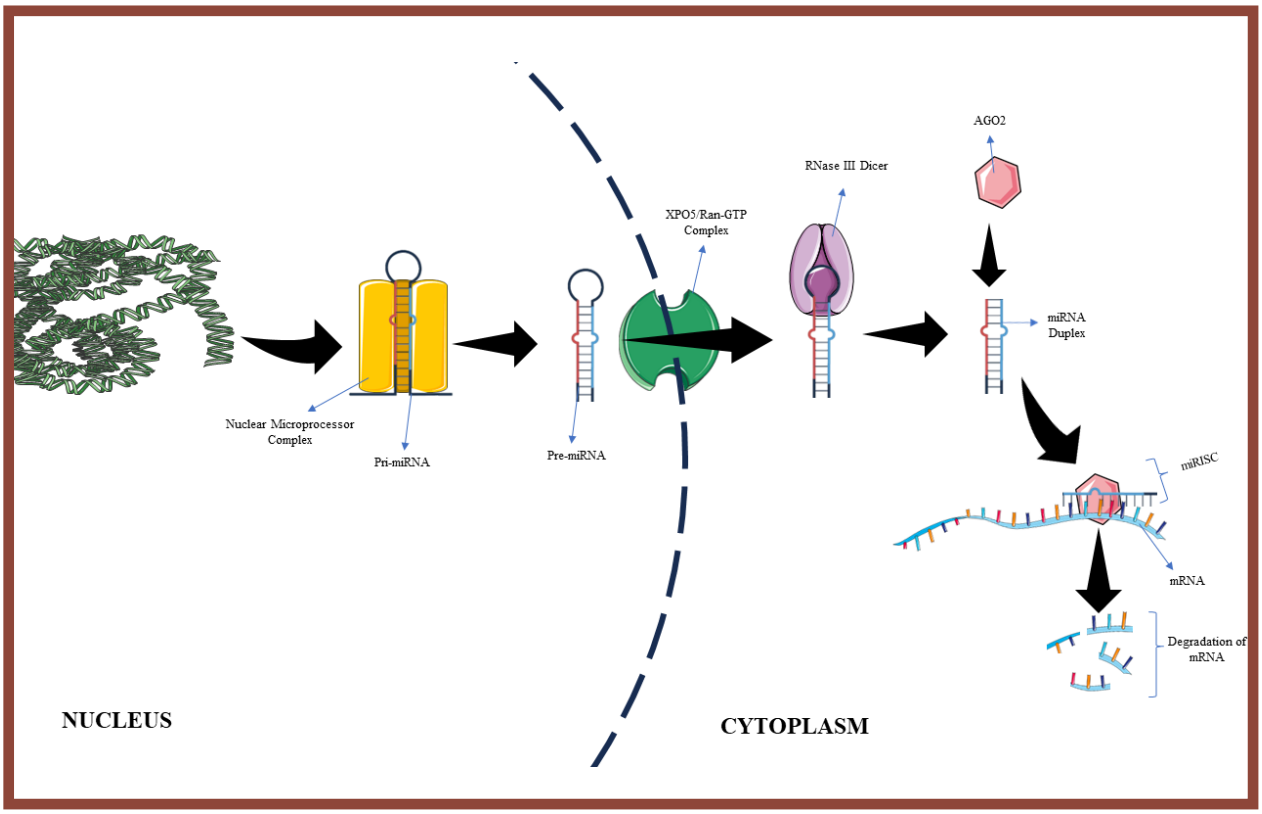

Figure 1. miRNA production in a canonical way.

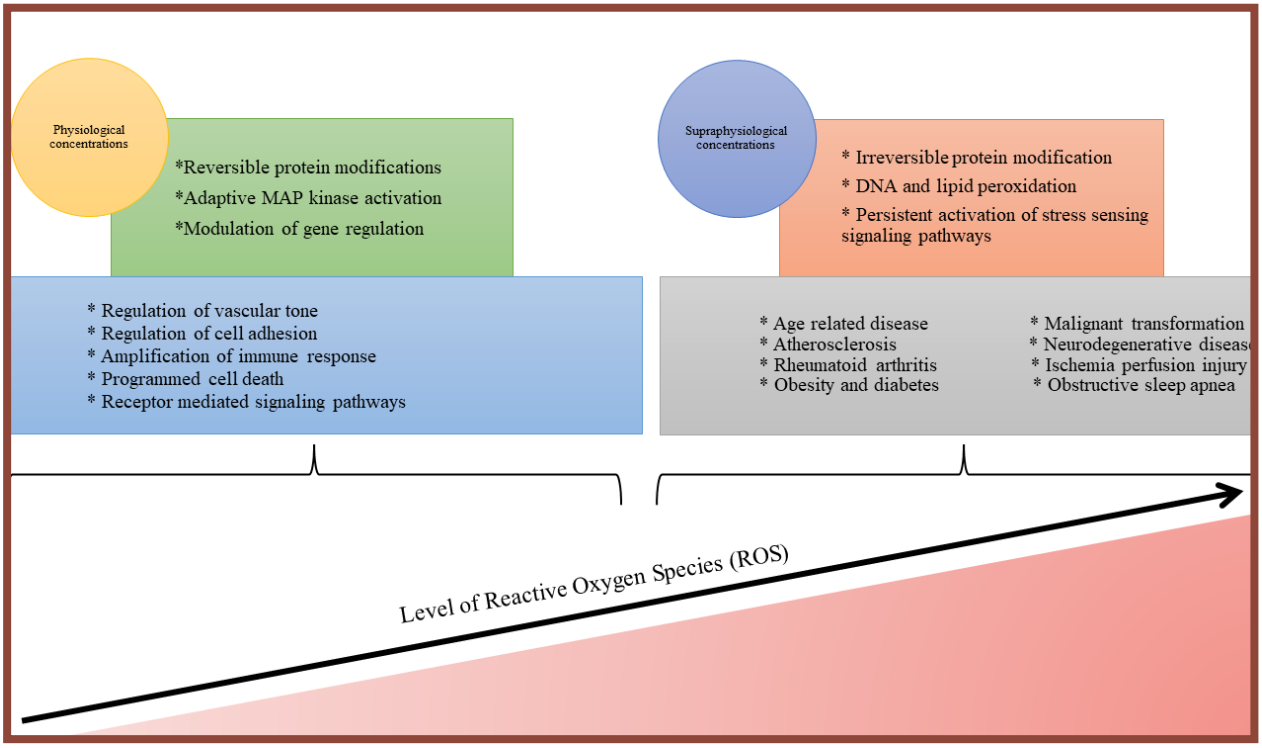

Figure 2. Physiologic and supraphysiologic effects of ROS.

ROS-miR or redoksmiR. Over the past decade, a bunch of specific miRNAs were identified in the regulation of transcription factors that modulate oxidative stress.[11] It is clear that the association between miRNAs and ROS gained attraction in the field of pathophysiology.

1.2. Reactive oxygen species

ROS is generated from oxygen molecules in numerous pathways, including oxidants such as Hydroxyl radical ($^{\cdot}OH$), Superoxide radical anion ($O_2^{\cdot-}$), Peroxyl radical ($ROO^{\cdot}$), Alkoxyl radical ($RO^{\cdot}$), hydrogen peroxide (H_2O_2), perhydroxyl radical ($HOO^{\cdot}$), Singlet oxygen ($^1O_2$). Depending on accumulative concentration in the human body, these molecules have different properties and biological functions.

Interestingly, it was previously reported that ROS may cause beneficial stress termed eustress in physiological concentrations. ROS levels improve the antioxidant systems of the cells and improve homeostasis. In addition, it is indicated that physiologically increased levels of ROS promoted the expression levels of growth factors. On the other hand, the supraphysiological concentration of ROS results in distress. ROS reacts with proteins, lipids, nucleic acids, and carbohydrates non-specifically. Consequently, cell signalization is ruined, and cell survival is hit by ROS.[14–17] The general effects of physiologic and supraphysiologic levels of ROS are represented in Figure 2.

Intracellular inducible factors and/or pathways might trigger ROS production (Table 1).[14] Endogen ROS is produced mainly from mitochondria, membrane-depended NADPH oxidases (NOXs), and peroxisomes (Figure 3). In addition, peroxisomal β-oxidation of fatty acids, microsomal cytochrome P450, xenobiotic compounds metabolism, induced phagocytosis by pathogens or lipopolysaccharides, arginine metabolism, and cellular-specific enzymes are other factors of ROS production. Not only endogen but also exogen sources could result in ROS release. Ultraviolet radiation, some kinds of medicines used for cancer, smoking, and consuming alcohol could be referred as exogen sources of ROS.[15,16]

Table 1. The main source of ROS[14]

Source of ROS	Main ROS	Response stimuli	Pathway complexes
Mitochondria	$O_2^{\bullet-}$	Oxidative metabolism	Electron transport chain, NADH
NADPH oxidase	$O_2^{\bullet-}$	Inflammation	NAPDH
Xanthine oxidase	$O_2^{\bullet-}$	Purine catabolism	O_2
Nitric oxide synthase	NO, OONO	Synaptic activity, inflammation, hypoxia	NAPDH
Peroxisomes	H_2O_2, $O_2^{\bullet-}$	Lipid metabolism (β-oxidation)	NADH, NADPH, $FADH_2$
Cytochrome P450	$O_2^{\bullet-}$	Clearance of various compounds (hormones, lipids, xenobiotics)	NAPDH
Lipoxygenases	$O_2^{\bullet-}$	Arachidonic Acid (PUFA) metabolism	O_2
Exogenous stress	$O_2^{\bullet-}$, $ONOO^{\bullet-}$, H_2O_2	Direct peroxidation, increased NOS, DNA damage	Ultraviolet radiation, environmental toxins, drugs

2. Conclusion

A growing number of studies have indicated that there is a correlation between miRNAs and various diseases targeting ROS generators, antioxidant pathways, and selected antioxidant effectors. Numerous experimental studies exhibited that changes in miRNA profile are crucial in various diseases such as cancer, neurological disorders, and cardiovascular diseases.[18–20]

The relationship between miRNAs and ROS has been largely examined as underlying mechanisms of neurodegenerative diseases such as Parkinson's (PD), Huntington's (HD), Alzheimer's (AD) disease, and amyotrophic lateral sclerosis (ALS). Konovalova et al. (2019) revealed that miR-34, miR-124, miR-132, miR-26, and mir-7 have been the most effective miRNAs in neurodegenerative diseases. In addition, it was also recommended that targeting the mentioned miRNAs could be a potential remedy for the diseases.[19] Not only neurodegenerative diseases but also conditions such as traumatic brain damage, characterized by high-level ROS accumulation and leading the neuronal damage, exhibit the linkage between the ROS and miRNAs.[19,21] In a previous study, the effects of miRNA-743a on the hippocampal cell line were examined. Results indicated that miRNA-743a diminished oxidative stress by reducing the activity of malate dehydrogenase which is a mitochondrial enzyme.[22] An in vitro study established in superior cervical ganglion culture examined the activity of miR-338, a brain-specific miRNA. According to the results of the study, it was presented that miR-338 affected two mitochondrial enzymes called ATP5G1 and COXIV. miR-338 reduced ROS levels and induced axonal growth.[23]

Ischemia-reperfusion (I/R) damage, where ROS has a crucial role, is another process involving the activity of miRNAs. Thereby some miRNAs are identified as hypoxamiRs. Especially known as the master of hypoxamiRs, miR-210, has a pivotal role in mitochondrial respiration. Under normal conditions, it functions as an inhibitor of mitochondrial energy production, corruption of oxygen consumption, induction of lactate accumulation, alteration of mitochondrial membrane potential, and ob-

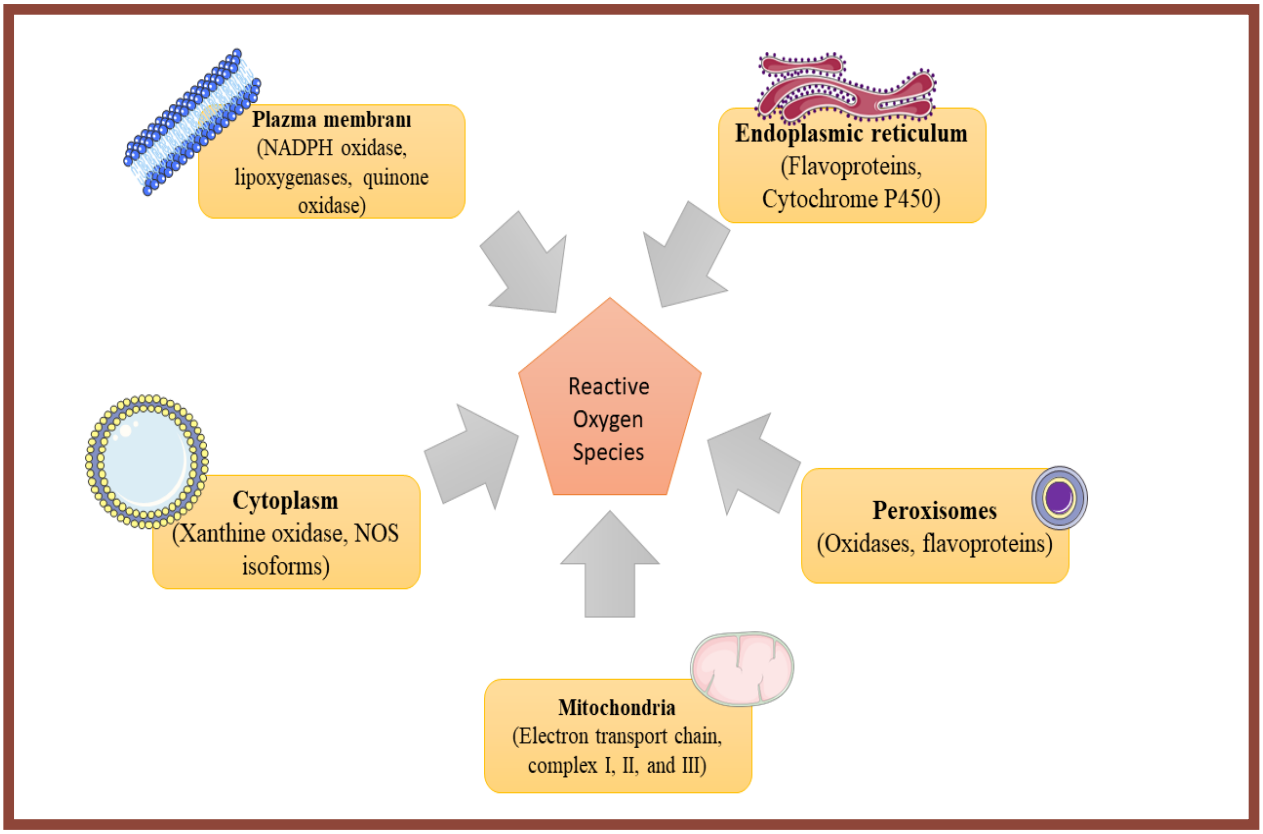

Figure 3. Endogen ROS production.

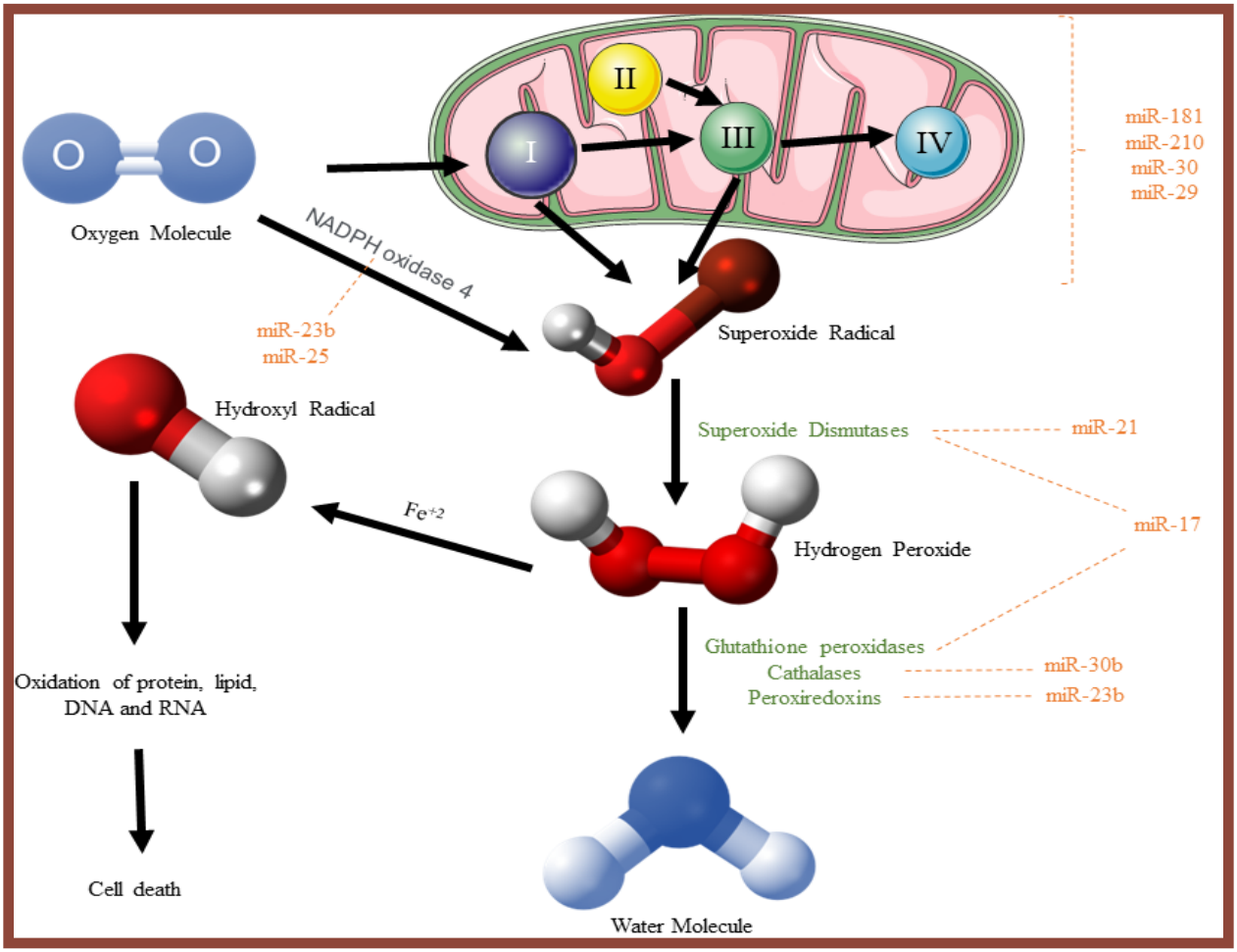

Figure 4. The relative mechanism of miRNAs and ROS.

taining mitochondrial structure. In hypoxia, an increase of miR-210 was suggested as a potential molecule for treatment.[24,25]

ROS production is one of the underlying mechanisms of cardiovascular diseases such as hypertension, so the miRNAs-ROS relation becomes considerable. Based on this, there is excessive research on cardiovascular system cells about the interaction of miRNAs and ROS. One of them presented that miR-145 diminished ROS caused by hypercholesterolemia.[26,27] In another study, Li et al.[28] examined primer cardiomyocytes after I/R damage. They also reported that miRNA-145 has a protective role on cardiomyocytes following oxidative stress.[28]

Accumulative studies clarified the association between ROS and miRNAs in various kinds of cancers. He et al.[29] performed a study on human prostate cancer cells. Results showed that miR-23b reduced mitochondrial enzyme peroxiredoxin III which is related to the antioxidant system.[29] Babu et al.[10] examined ROS and miRNA in the cancer at a review. It was determined that targeting crosstalk between miRNA and ROS could open new horizons to the treatment of cancer.[20] As outlined above, ROS levels are tightly related to miRNA changes as represented in Figure 4. In various conditions, ROS could be a result or a cause of a disease-related increase or decrease of tissue-specific miRNAs. Similarly, miRNAs could be a reason for ROS production or a suppressing factor of ROS release. The main point is to identify tissue and pathological condition-related miRNA during ROS production. Further studies are required to explain and highlight the main tissue and ROS-specific miRNAs. At this point, the identification of the expression level of the related miRNA could be a therapeutic factor for ROS-related diseases. This aim would provide new approaches in various clinical applications.

Ethical approval

This study does not require approval from the Ethics Committee for Animal Experiments.

Conflict of interest

There are no conflicts of interest associated with this research publication, according to the authors.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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This situation does not exist.

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