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FREE RADICALS MEDICINE (X SHI, SECTION EDITOR)

Interplay Between Reactive Oxygen Species and MicroRNAs in Cancer

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Abstract As both reactive oxygen species (ROS) production and microRNA expression signature have been associated with tumor development, progression, metastasis, and therapeutic response, it is important to understand the crosstalk between ROS and microRNAs. Indeed, growing evidence suggests a reciprocal connection between ROS signaling and microRNA pathway, resulting in diverse biological effects in cancer cells. In this mini review, we discussed the ROS-responsive microRNAs that have implications in cancer and the possible mechanisms in which ROS regulate microRNAs. We also highlighted the microRNAs which are able to modify cellular ROS homeostasis during tumorigenesis, their biological targets and subsequent functions. As the use of antioxidants is limited due to the diverse or even opposing roles of ROS signaling in cancer, the discovery of ROS-responsive microRNAs provides a potential new strategy to specifically overcome ROS-mediated tumor progression or benefit from ROS-induced apoptosis.

Keywords Reactive oxygen species · miRNAs · Carcinogenesis

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Introduction

Reactive oxygen species (ROS) are oxygen-containing and chemically reactive species formed by incomplete one-electron reduction of oxygen, which include superoxide ($O2^{-}$), hydroxyl radical (OH^{-}), hydrogen peroxide (H_2O_2), nitric oxide (NO), peroxynitrite (ONOO−), and nitrogen dioxide radical (NO_2) [1]. ROS are naturally produced by cells through aerobic metabolism and are known to play a dual role in biological systems—with potentially beneficial or harmful effect [2]. Mitochondria respiratory chain, NADPH oxidase, and peroxisomes are the major endogenous sources of ROS, while environmental agents, ionized radiation, UV light, and chemical drugs contribute to the induction of exogenous sources of ROS. Low levels of ROS facilitate cell survival as a second messenger and mediate a plethora of intracellular signal transduction events, whereas high levels of ROS induce cell apoptosis and necrosis. ROS has been implicated in a number of pathologies, especially in cancer. Excessive and sustained ROS production has been found in a variety of cancer cells, which is strongly correlated with the tumorigenic potential of cancer cells [3]. However, ROS-mediated signaling pathways not only promote cell survival, oncogenic transformation, and metastasis, but also render cancer cells resistant to anticancer drugs [4]. Still, the mechanisms of ROS signaling and underlined redox adaptation in cancer cells remain elusive.

The past decade has witnessed a great progress on microRNA research. MicroRNAs are a small class of endogenous 18 ~ 25 nucleotide long, non-coding RNA molecules that regulate gene expression at the posttranscriptional levels [5]. They can induce either mRNA degradation or translational suppression by binding to their target messenger RNAs, especially 3′untranslated region (UTR) based on the sequence complementarities. Alternatively, they can also cause the translational activation of their respective targets [6]. Up to

one third of human mRNAs are potential microRNA targets. The observation that the frequent deletion of chromosome 13q14 causes the loss of *miR-15a* and *miR-16-1* in chronic lymphocytic leukemia (CLL) is the first evidence of the involvement of microRNAs in human cancer [7]. It was further revealed that these non-coding genes are frequently located within cancer-associated genomic regions. Since that, increasing number of studies demonstrate that microRNAs may function as potential tumor suppressors or oncogenes in all stages of cancer development. Deregulations of microRNA expression have been associated with tumor development, progression, metastasis, and therapeutic responses, and have recently been known as one of the hallmarks of cancer [8].

Since both ROS and microRNAs are dysregulated in cancers, it is important to understand the crosstalk between ROS and microRNAs. Accumulative evidence suggests a reciprocal connection between ROS signaling and microRNA pathways. Some microRNAs, so-called ROSmirs, are regulated by oxidative stress to mediate the expression levels of their direct targets in response to ROS. For example, ionizing radiation, as a standard way to treat malignancy, causes severe DNA damage to kill cells, resulting in ROS accumulation and altered microRNA expression levels [9]. The addition of free radical scavenger cysteine can abrogate the microRNA response induced by radiation, suggesting ROS production is an upstream event of the microRNAs in response to exogenous genotoxic stress. On the other hand, as microRNAs may directly regulate 30 % of genes in a cell, it is not surprising that microRNAs are involved in all major cellular functions including modification of cellular redox homeostasis such as ROS production. In this review, we will highlight literatures regarding how ROS exert biological effects through microRNAs, and how microRNAs regulate cellular redox homeostasis in different types of cancers.

ROS-Responsive MicroRNAs

Cancer cells normally adapt to persistent oxidative stress in the cells. A global microRNA profiling analysis revealed that exposure to hydrogen peroxide (H_2O_2) causes changes of a set of microRNA contents, suggesting that the ROS-sensitive microRNAs may be important in cancer cells in response to ROS [9, 10]. Accumulative studies show that intracellular ROS can either inhibit or induce microRNA expression level, which generates subsequent biological effects through the regulation of their direct target genes. For example, macrophages are known to produce ROS during phagocytosis in response to stimuli [11]. Macrophage-derived ROS are not only critical for microbial killing but also may act as a carcinogen causing tumor initiation and promotion. Exposure to exogenous H_2O_2 in macrophage cell line RAW 246.7 alters the microRNA expression levels, including downregulation of *miR-27a**, *miR-27b**, *miR-29b**, and *miR-24-2*, and upregulation of *miR-21* [12]. In a context of cancer microenvironment, increased infiltrated macrophages in tumor stroma are found to suppress *miR-328* expression level through ROS production, and then induced CD44 expression in gastric cancer cells for regulating tumor progression [13]. Our group previously showed that ROS are involved in insulin-regulated aerobic glycolysis in hepatocellular carcinoma cells [14]. Insulin-induced ROS inhibit *miR-145* and *miR-128* expression levels and upregulate the key enzyme M2 isoform of pyruvate kinase 2 (PKM2) to promote insulin-induced glucose consumption and lactate production. Although the cause-effect relationship between ROS and microRNAs has been proved through experiments by cell exposure to H_2O_2 or ROS scavengers, the mechanism underlying ROS-regulated microRNA expression is complicated and poorly understood. The major proposed mechanisms so far are showed in Fig. 1.

ROS Regulate MicroRNA Biogenesis Enzymes

ROS can affect microRNA expression through the components of microRNA processing machinery. The biogenesis of miRNAs is controlled by two RNase-dependent processing steps.

MicroRNA genes are transcribed by RNA polymerase II into longer molecules (pri-microRNAs) which are further cleaved by RNA-specific RNAse III type ribonuclease Drosha into hairpin intermediates (pre-microRNAs). The pre-microRNAs then transport through nuclear pores into the cytoplasm with the aid of Exportin 5 and are cleaved by another ribonuclease Dicer into double-stranded mature microRNAs [15]. A study showed that aging-related oxidative stress is associated with downregulation of Dicer in cerebromicrovascular endothelial cells (CMVECs) [16]. Exogenous H_2O_2 exposure in endothelial cells causes significant decrease of Dicer expression resulting in downregulation of 89 % of microRNAs that are normally expressed in CMVECs. Interestingly, Dicer expression level can also affect ROS production as a negative feedback loop to maintain cellular homeostasis. Knockdown of Dicer in human microvascular endothelial cells (HMECs) decreased ROS production in the cells [17]. Further mechanism study showed that microRNA-deficient HMECs due to Dicer knockdown show higher levels of nuclear HBP1, a suppressor transcription factor of p47phox. The inhibition of p47phox by HBP1, a key subunit of NADPH oxidase, abolished ROS induction and impaired angiogenesis property of endothelial cells [17].

ROS Regulate MicroRNA Expression Through Transcription Factors

ROS function as intermediates in the activation of stress-related transcription factors such as p53, nuclear factor (NF)-κB, c-jun, FOXO, and HIF in response to stress agents [18, 19]. Therefore, it is plausible to speculate that ROS can

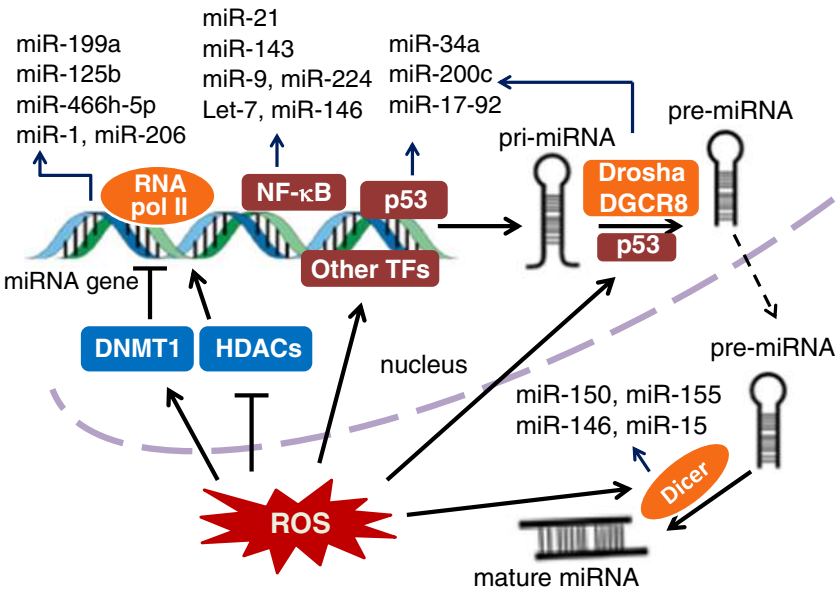

Fig. 1 Schematic model showing mechanisms in which ROS regulate microRNA expression. ROS are involved in every step of miRNA biogenesis. ROS can induce epigenetic alterations of miRNA genes. For example, ROS inhibit and enhance expression of certain miRNA genes through DNMT1 and HDACs, respectively. ROS can also activate transcription factors to induce miRNA expression. Moreover, Drosha and Dicer, which are two essential enzymes for miRNA biogenesis, can be directly or indirectly regulated by ROS

regulate certain microRNAs through these transcription factors. Tumor suppressor protein p53 is a central molecule in maintaining genomic integrity by inducing cell cycle arrest, senescence, and apoptosis via differential activation of target genes [20]. There are broad interactions between ROS and p53 pathway. As a cellular stress-related transcription factor, p53 expression can be induced by ROS to selectively activate p53 target genes for protecting the genome stability [21]. In addition, p53 is involved in microRNA processing pathway such as Drosha-mediated pri-microRNA processing and in directly transactivating some microRNA genes to promote the transcription of microRNAs such as *miR-34a*, *miR-200c*, and *miR-17-92* clusters. p53 interacts with the Drosha processing complex through the association with DEAD-box RNA helicase p68 (also known as DDX5) and facilitates the processing of primary microRNAs to precursor microRNAs [22]. A number of stress-induced microRNAs are induced in a p53-dependent manner such as *let-7s*, *miR-34s*, and *miR-200s*. The *miR-200* family has been implicated as a tumor suppressor by inhibition of epithelial-mesenchymal transition (EMT) process, an initial event for cancer metastasis [23]. Overexpression of the *miR-200* family leads to a reversal of EMT in various cancers including bladder cancer, gastric cancer, ovarian cancer, pancreatic cancer, prostate cancer, and others [24]. It is reported that *miR-200c* is upregulated upon H_2O_2 exposure in vascular endothelial cells, which leads to cellular apoptosis and senescence through ZEB1 inhibition [25]. Knockdown of p53 remarkably reverses H_2O_2-induced *miR-200c* expression, an indicative of p53 regulation.

In addition to its pivotal role in the canonical Wnt pathway, β-catenin has been found to be involved in transcription regulation induced by ROS through interaction with the transcription factor FOXO [26, 27]. A recent study indicated that ROS-induced *miR-182* is not regulated by p53 but by β-catenin in high-grade serous ovarian carcinoma [28]. They found that ROS greatly upregulate β-catenin resulting in its nucleus translocation. In p53 intact fallopian tube secretory epithelial (FTSE) cells, overexpression of *miR-182* triggers cellular senescence by p53-mediated p21 upregulation. However, in cells with p53 mutations, *miR-182* acts as an oncogene to promote tumorigenesis by impairing DNA damage responses mediated by ROS and β-catenin [28].

ROS are often generated within inflammatory environment to activate NF-κB in cells by various mechanisms [29]. Several microRNAs such as *miR-9*, *miR-21*, *miR-143*, and *miR-146* and *miR-224* have been validated to be directly transcriptionally regulated by NF-κB [30–35]. Among them, *miR-21* is one of the most investigated oncogenic microRNAs, which is generally upregulated in cancer cells [36]. *miR-21* possesses pro-survival and antiapoptotic properties by directly targeting tumor suppressor proteins PTEN, PDCD4, IGFBP3, and MKK3 [37–40]. It was reported that ROS induce *miR-21* expression and functions, which contributes to the highly invasive and metastatic phenotype of prostate cancer cells [41]. NF-κB activation might be one of the mechanisms for ROS-mediated *miR-21* induction. Environmental agents are one of the exogenous sources of ROS in the body. ROS-induced *miR-21* is involved in arsenic-induced cell malignant transformation, and NF-κB mediates *miR-21* induction upon ROS exposure by binding directly to the promoter of *miR-21* gene [42]. In addition, NF-κB can also indirectly regulate microRNA expression through the synthesis of proteins that are responsible for microRNA biogenesis. For example, Lin28, a microRNA processing inhibitor, can be activated by NF-κB activation, resulting in rapid reduction of *let-7* microRNA levels, which contributes to Src-induced cellular transformation [43].

ROS Regulate MicroRNA Expression Through Epigenetic Modification

Altered epigenomic patterns as major features of cancer are associated with aberrant microRNA expression profiles in cancer. The main epigenetic changes in mammals, particularly in humans, are DNA methylation and posttranslational histone modifications including acetylation, methylation, and phosphorylation [44]. Like protein-coding DNA sequences, microRNA genes in non-coding regions may undergo DNA methylation and histone modification.

We previously described that endogenous ROS inhibit *miR-199a* and *miR-125b* expression in ovarian cancer cells, and overexpression of these microRNAs inhibit tumor-induced angiogenesis associated with the decreased expression of HIF-1α and VEGF [45]. We further found that the promoter regions of both *miR-199a* and *miR-125b* genes are hypermethylated upon H_2O_2 exposure analyzed through methylation-specific PCR and bisulphite sequencing assays, which is mediated by DNMT1 upregulation [46]. DNMT1 functions in a way of DNMT1/transcription factor-including complex, which is recruited to the oxidative stress-damaged DNA in order to silence gene transcription temporarily for the DNA repair and/or microRNA expression [47]. Redox-sensitive transcription factors in the DNMT1 complex such as NF-κB may act as cofactors to promote direct binding of DNMT1 into certain microRNA promoters.

Histone acetylation refers to the acetylation of lysine residues, and the levels of histone acetylation play a crucial role in chromatin remodeling to regulate gene transcription. The deacetylation of lysine residues by histone deacetylases (HDACs) is associated with a more condensed chromatin state and transcriptional gene silencing [48]. Several studies show the reduced activities of HDACs under oxidative stress may cause alteration of microRNA expression levels [49, 50]. For example, *miR-466h-5p* is shown to have a pro-apoptotic role through targeting several antiapoptotic genes including *bcl2l2*, *birc6*, *dad1*, *smo*, and *stat5a* [51]. Accumulation of ROS caused by glucose deprivation increases *miR-466h-5p* expression levels through inhibition of HDAC2, a direct target of *miR-466h-5p*, which increases acetylation and induction of the microRNA expression, resulting in increased apoptosis [49].

MicroRNAs Regulate ROS Production

In addition to as essential regulators of the ROS-mediated stress response across multiple species, microRNAs are capable of regulating redox homeostasis by modulating genes that are either ROS activators or scavengers. MicroRNAs that are associated with ROS levels and related signaling pathways in cancer cells are listed in Table 1.

Inhibition of ROS Production

Certain microRNAs may inhibit ROS levels through targeting genes that are responsible for ROS synthesis. NADPH oxidases are considered as the major source of ROS production in epithelial cells [66]. NADPH oxidase-derived ROS may elevate the risk for genomic instability and cancer [67]. NOX2 subunit is the catalytic core of NADPH oxidase complex. A study showed that NOX2 is the direct target of *miR-34a*, and restoration of *miR-34a* in glioma cells induces apoptosis through NOX2-derived ROS generation [52]. Proline oxidase (POX), as a mitochondria suppressor, is a p53-induced redox gene that can generate ROS and mediate apoptosis in tumor cells [68]. Upregulation of *miR-23b** is found in renal cancer [53]. As a negative regulator of POX, *miR-23b** knockdown increases apoptosis through induction of mitochondria-derived ROS and inhibition of HIF signaling, thus suppresses kidney tumor growth.

Enhancement of ROS Production

The enzymatic and non-enzymatic antioxidant defense systems including superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase, ascorbic acid (vitamin C), and α-, glutathione (GSH) act against ROS accumulation in cells in order to maintain cellular oxygen radical homeostasis [69]. Several microRNAs increase cellular ROS levels through targeting antioxidants. SOD is the antioxidant enzyme that catalyzes the dismutation of the highly reactive superoxide anion to O_2 and to the less reactive species H_2O_2. In humans, there are three forms of SOD: cytosolic Cu/Zn-SOD (SOD1), mitochondrial Mn-SOD (SOD2), and extracellular SOD (SOD3) [70]. A study showed that *miR-21* potentiates ionizing irradiation (IR)-induced ROS production by its direct target SOD2 and an indirect target SOD3 through TNFα, resulting in an increase of IR-induced cell transformation [54]. Hydrogen peroxide (H_2O_2) is eliminated by antioxidant enzyme catalase and GPX. *miR-551b* expression level is high in apoptosis-resistant lung cancer cells. Further study indicates that higher *miR-551b* expression levels inhibit catalase expression and enhance ROS accumulation, which activates a redox-active oncogene Mucin-1 (MUC1) for survival and chemoresistance in cancer cells [55]. Upregulation of *miR-155* is involved in *K-Ras*-induced oncogenic transformation in pancreatic cancer through redox regulation [56]. The study suggests that *miR-155* promotes ROS levels through directly targeting a transcription factor Foxo3a that induces SOD2 and catalase transcription [56]. Like *miR-21*, the *miR-200* family not only responds to oxidative stress as a downstream effector of ROS, but also regulates intracellular ROS levels through antioxidants. For instance, *miR-200c* negatively regulates three redox proteins, PRDX2, GABPA/Nrf2, and SESN1, all of which contribute to antioxidant defense system in cancer

Table 1 MicroRNAs affect ROS levels in cancer cells

microRNAs	ROS level	Target gene	Type of cancer	Outcome	Ref
miR-34	Down	NOX2	Glioma	↑Apoptosis	[52]
miR-23b*	Down	POX	Kidney	↑Tumor growth	[53]
miR-21	Up	SOD2, SOD3		↑Oncogenic transformation	[54]
miR-551b	Up	Catalase	Lung	↑Survival and chemoresistance	[55]
miR-155	Up	Foxo3a	Pancreas	↑Oncogenic transformation	[56]
miR-200c	Up	PRDX2	Lung	↑Radiosensitivity	[57]
miR-28	NA	Nrf2	Breast	↑Tumor progression	[58]
miR-210	Up	ISCU, COX10	Colon, breast, esophagus	↑Glycolysis	[59–61]
miR-128a	Up	Bim1	Medulloblastoma	↓Cell proliferation	[62]
miR-141, 200a	Up	p38α	Ovary	↑Tumor growth ↑chemosensitivity	[63]
miR-506	Up	NF-κB	Lung	↑Apoptosis	[64]
miR-193a-3p	Up	Mcl-1	Glioma	↑Apoptosis	[65]

NA not applicable

cells. Overexpression of *miR-200c* augments ROS and p21 expression levels, leading to increased radiosensitivity in lung cancer cells [57].

Nuclear factor erythroid2-related factor2 (Nrf2) is a redox-sensitive transcription factor serving as a "master regulator" of cell survival through the coordinated induction of antioxidants and phase II detoxification enzymes via antioxidant-response element (ARE) in the promoter of target genes [71]. Activation of Nrf2 will increase the transcription of antioxidant defense genes such as catalase and SOD. As a result, microRNAs that are capable of regulating Nrf2 would have an impact on intracellular ROS levels. Nrf2 pathway seems to play dual roles in cancer cell biology, which depends on the activation of Nrf2-dependent pro-survival genes or antioxidant genes [72]. A study reported a role of *miR-28* in regulation of Nrf2 expression in breast cancer. *miR-28* not only targets the 3′UTR region of Nrf2 mRNA but also reduces the stability of *Nrf2* mRNA and protein. As a result, loss of Nrf2 increases colony formation in breast cancer cells [58].

Mitochondria respiratory complex is the major source of free radicals, and compromised mitochondria function can augment ROS production. The hypoxia-inducible *miR-210* is known to regulate cancer cell metabolism by reducing mitochondria respiratory activity and activating superoxide production [73]. The possible mechanism involves inhibition of mitochondrial iron-sulfur cluster scaffold homologue (ISCU), a target gene of *miR-210*. ISCU is essential for the assembly of Fe-S cluster, and loss of function of ISCU can decrease mitochondria activity and disrupt iron homeostasis [59]. *miR-210* increases ROS generation by downregulation of ISCU [60]. In addition, inhibition of ISCU by *miR-210* causes ROS induction in hypoxia, resulting in a shift to glycolysis in normoxia and enhanced cell survival [61]. Another group also found that *miR-210* increases ROS levels in colon cancer cells under hypoxia condition, but argued that the upregulation of ROS caused by *miR-210* may be due to other identified targets because knockdown of ISCU does not show a significant change of ROS levels [74]. The polycomb gene Bim1 has functions in maintaining mitochondrial activities and redox homeostasis. Cells derived from Bmi1-/- mice show impaired mitochondrial activities, a marked increase in the intracellular levels of reactive oxygen species and subsequent engagement of DNA damage response pathway [75]. It is reported that *miR-128a* increases ROS levels via the specific inhibition of Bim1, thus represses medulloblastoma cancer cell growth [62].

MicroRNAs can regulate ROS levels not only through ROS synthesis, but also by redox-active signaling pathways such as p38α MAPK and NF-κB. The p38α MAPK usually acts as a sensor of oxidative stress and suppresses tumorigenesis by promoting apoptosis [76]. Inactivation of p38α is associated with ROS accumulation and the subsequent activation of antioxidant defense system [77]. Two members of the *miR-200* family, *miR-141* and *miR-200a*, are identified to directly target p38α and modulate the oxidative stress response in ovarian cancer [63]. Interestingly, p38α deficiency achieved by upregulation of *miR-141* and *miR-200a* potentiates tumor growth, but at the same time, sensitizes cancer cells in response to chemotherapy evidenced by the improved survival in patients. It further indicates the diverse and even opposing effects of ROS on cell behavior. NF-κB activity can inhibit ROS by activation of antioxidant enzymes. Upregulation of *miR-506* occurs in 83 % lung cancer; however, *miR-506* is considered as a tumor suppressor instead of an oncomir. It is known that *miR-506* negatively regulates NF-κB p65 expression and thus increases ROS production,

which, in turn, activates p53 to kill cancer cells through increased apoptosis [64].

ROS and miRNAs in Carcinogenesis

Cancer development is a complex and multiphase process with three major stages: initiation, promotion, and progression. Oxidative stress inducing the accumulation of DNA damage or mutation is the critical step in cancer initiation [78]. In addition, the endogenous elevated ROS production found in many tumor cells activates oncogenic signaling pathways, which results in cancer promotion and progression [78, 79]. As for miRNAs, it contributes to carcinogenesis through functional interactions with oncogenes or tumor suppressor genes. Overexpression, deletion, epigenetic silencing, or mutation of mature miRNAs may inhibit or stimulate oncogenic activity through regulation of the expression level of the target protein [80]. Therefore, ROS may affect carcinogenesis through miRNAs by alteration of methylation status of miRNA genes, miRNA biogenesis, and oxidative DNA damage-induced mutation of miRNA genes or mature miRNA sequences. Similarly, miRNAs are capable of regulation of intracellular ROS levels by targeting proteins responsible for ROS generation and elimination, thus indirectly are involved in ROS-mediated carcinogenesis. It is worth noting that ROS and miRNAs can act either synergistically or antagonistically to influence cancer development. A few targets or pathways cannot fully explain the biological effect; it depends on the net result of multiple pathways and the dominant molecules in the specific context.

Therapeutic Implications and Challenges

Growing studies have demonstrated a dual role of ROS in cancer. Excessive and sustained ROS production promotes carcinogenesis by inducing DNA damage causing genomic instability. ROS can positively respond to mitogenic stimulation such as growth factors to active receptor tyrosine kinases, which are necessary in cancer progression and maintenance. On the contrary, intracellular ROS are also critical to activate apoptosis in response to exogenous agents such as chemical drugs and ionized radiation through activation of pro-apoptotic signaling molecules including p53 and p38 MAPK, which sensitize tumor cells to the treatment. Therefore, the use of antioxidants in cancer treatment has a limited effect [81–83]. In some cases, antioxidant treatments such as *N*-acetylcysteine (NAC) and vitamin E even speed cancer progression in an animal model [84]. The discovery of ROS-responsive microRNAs provides a potential new strategy to specifically overcome ROS-mediated tumor progression or benefit from ROS-induced apoptosis. As discussed in the majority of studies in this review, the roles of microRNAs in cellular adaptation to ROS are different in cells based on cell types or tumors. This raises the possibilities to apply specific microRNAs as therapeutic target(s) in different contexts. Theoretically, microRNA-target therapy has several potential advantages. First, microRNAs are short and much conserved across multiple species with known sequences. Secondly, an individual microRNA is able to target multiple genes within defined pathways; it would be possible to regulate the entire oncogenic or tumor suppressor network via pharmacological modulation of cancer-associated microRNAs [85]. Several clinical trials based on microRNA-based therapy have been on the way [86]. The locked nucleic acid (LNA)-modified anti-miR inhibitor against *miR-122* called *miravirsen* is the first miRNA-targeted drug to enter human clinical trials to treat HCV [85, 87]. Clinical data from the phase IIa trial show that *miravirsen* is well-tolerated and generally provides antivirus activity in HCV patients. Although the great progress has been made, challenges are remaining in several aspects. Firstly, new techniques are needed to design molecules with appropriate modifications to specifically inhibit or "mimic" mature microRNAs in vivo. Second, the application of microRNAs in humans is also hindered by lack of approaches to achieve high efficiency in vivo delivery for microRNA mimic or anti-miR inhibitor. In the context of ROS signaling, further understanding of ROS-microRNA network is of importance for the application of microRNAs to ameliorate ROS-mediated oxidative stress or enhance ROS-stimulated apoptosis in response to cancer therapy.

Compliance with Ethical Standards

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Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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