ROS

REVIEW ARTICLES

Reactive Oxygen Species Signaling in Cancer Development

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ABSTRACT | Cancer cells exist in chronic condition of metabolic oxidative stress compared to normal cells mainly due to inherent mitochondrial dysfunction and NADPH oxidases activation. DNA damage, mutation, and altered gene expression induced by reactive oxygen species (ROS) are all required participants in the process of carcinogenesis. The modification of gene expression by ROS has direct effects on cancer development such as tumor growth, survival, invasion and angiogenesis through the manipulation of signaling pathways, thus promoting metastasis. Meanwhile, some ROS-regulated miRNAs are also involved in mediating tumor progress. Although a precise mechanism of signal transduction remains to be elucidated, in this review we outline the probable role of these signaling cascades and ROS-regulated miRNAs in mediating tumor metastasis. Understanding of the molecular functions of ROS as one of key mediators in cancer development may provide widely opportunities for pharmacological intervention and anticancer therapy.

KEYWORDS | Cancer development; miRNA; Reactive oxygen species; Signal transduction

ABBREVIATIONS | AP-1, activating protein-1; DDR1, discoidin domain receptor 1; DNMT, DNA methyltransferase; ECM, extracellular matrix; EMT; epithelial-to-mesenchymal transition; ERK1/2, extracellular-regulated kinase ½; Ets, E twenty-six; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FAK, focal adhesion kinase; GSH, glutathione; GST, glutathione S-transferase; HIF-1, hypoxia inducible factor-1; IKK, IκB kinase; IL, interleukin; JNK, c-Jun N-terminal kinase; 5-LOX, 5-lipoxygenase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; MEKK, mitogen-activated protein kinase kinase kinase; MKP3, mitogen-activated protein kinase phosphatase 3; MMP, matrix metalloproteinase; NAC, N-acetyl-L-cysteine; NF-κB, nuclear factor κ-B; NIK, NF-κB-inducing kinase; PDGF, platelet-derived growth factor; PKC, protein kinase C; ROS, reactive oxygen species; RTK, receptor tyrosine kinase; SFK, Src family of protein tyrosine kinase; SOD, superoxide dismutase; TGFβ, transforming growth factor β; TLR, toll-like receptor; TIMP, tissue inhibitor of metalloproteinase; TNFα, tumor necrosis factor α; TRAF, TNF receptor-associated factor; VEGF, vascular endothelial growth factor

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1. REACTIVE OXYGEN SPECIES (ROS) IN CANCER

ROS are oxygen-derived small molecules that are produced as normal byproducts of cellular metabolism. ROS are generally categorized as free oxygen radicals and non-radicals. The free oxygen radicals contain one or more unpaired electrons in their outermost shell such as superoxide ($O_2^{\bullet-}$) and hydroxyl radical ($OH^{\bullet}$). In contrast, non-radical ROS including hydrogen peroxide (H_2O_2), single oxygen ($^1O_2$) and ozone/trioxygen (O_3) do not have unpaired electron. In aerobic organism, the balance of oxidation and antioxidation is mainly controlled by ROS level which is regulated via a wide variety of mechanisms such as superoxide dismutase (SOD), catalase, glutathione (GSH) and thioredoxin (TRX) [1, 2]. ROS generation is a cascade of reactions that begins with the production of superoxide [3]. Briefly, intracellular superoxide radicals are abundantly produced by electrons leaked from aerobic respiration at the inner membrane of the mitochondria [2, 4], or by the oxidation of NADPH by NADPH oxidase enzymes (NOX) in the cytosol [5, 6]. The majority of superoxide is rapidly dismutated to H_2O_2 by superoxide dismutase 2 (SOD2) in the mitochondrial matrix, whereas some of the superoxide is converted to H_2O_2 by SOD1 in the cytosol. H_2O_2 is capable of oxidizing cysteine residues on proteins to initiate redox biology, or H_2O_2 may be converted to H_2O by cellular antioxidants such as catalase, peroxiredoxins (PRx) and glutathione peroxidase (GPx). Other sources of ROS generation include peroxynitrite formation by the reaction of superoxide with nitric oxide, the peroxidase-catalyzed formation of hypochlorous acid from hydrogen peroxide, and the generation of hydroxyl radical from the metal cations (Fe^{2+})-catalyzed Fenton reaction [7, 8]. This process is highly reactive and can cause damage to cellular macromolecules, which contributes to the irreversible damages to proteins, lipids and dominantly DNA, leading to mutations and cell death [9].

Depending on the concentration of individual ROS species and the location of ROS products, ROS play a dual role during tumorigenesis and cancer development [10, 11]. ROS act as double-edged swords, low-dose of ROS induces the activation of cell signaling which is involved in promoting events, whereas high-dose of ROS induces apoptotic signaling to kill the cells. ROS are generated by cell-extracellular matrix (ECM) interaction, growth factors and integrin, and redox signaling plays an essential role in anchorage-dependent growth of non-transformed cells [12, 13]. Cancer cells are different from normal cells by constitutively activating growth factor pathways to sustain cell proliferation and growth. This renders cancer cells to take up abundant nutrients, exhibit survival stress and continuous proliferation, leading to abundant ROS production due to the hyper-metabolism from mitochondria, endoplasmic reticulum and the activation of NADPH oxidases [14]. Elevated rate of ROS generation is one of the characteristics of cancer cells, which promotes many aspects of tumor progression [13]. To maintain the delicate balance of intracellular ROS levels required for cancer cell function, tumor cells display an adaptive response to oxidative stress by expressing increased levels of antioxidant proteins for ROS detoxification [15]. Under intrinsic metabolic oxidative stress condition, excessive ROS production induces damage to cellular proteins, lipids, and DNA to promote cancer malignancy [16, 17]. On the other hand, high level of ROS or their products generated from radiation and chemotherapy exerts anti-tumorigenic function to trigger apoptotic process [18]. The mechanisms of adaptation to high-dose ROS generation have in fact contributed to resistance to cancer therapy, and the interruption of these mechanisms will increase ROS-mediated cancer cell apoptosis [19]. Therefore, ROS influence signaling pathways that

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are critical for determining beneficial or detrimental outcomes, and the modulators of redox signaling pathways to prevent early events in tumor development or to promote ROS-induced apoptotic signaling are potential targets in cancer therapy.

2. THE SIGNALING CASCADES INDUCED BY ROS IN PROMOTING CANCER DEVELOPMENT

ROS cause DNA damage, gene modification and further carcinogenesis through both genotoxic and non-genotoxic effects [20–22]. The genotoxic effects of ROS usually occur in a dose-dependent manner, leading to point mutations [20], deletions and chromosomal translocations [17]. In this case, ROS contribute to the initiation of carcinogenesis by directly attacking DNA strands, as well as generating the breakdown products of lipid peroxidation to implement mutagenesis. Meanwhile, endogenous ROS via the non-genotoxic effects are mainly involved in tumorigenesis and metastasis [14, 22]. Tumor metastasis formation is a multi-step process where tumor cells already show additional genetic alterations or mutations that allow primary tumor cell detachment from surroundings, invasion and growth at distant site [23]. ROS act as second messengers to affect tumor metastasis through modulating signal transduction pathways to regulate downstream molecules which are important for cancer cell growth, survival, invasion and angiogenesis [14, 22].

2.1. Regulation of Src Kinases by ROS

Src is the prototypic member of a family of non-receptor membrane-associated tyrosine kinases (Src family of protein tyrosine kinases, or SFKs), which are redox-regulated proteins and play important roles in carcinogenesis [24, 25]. The increased ROS cause oxidation-dependent Src activation and recruitment of Src-associated proteins into the signal transduction complex. After contact with ECM, Src displays a slight activation during focal adhesion formation in early phase, and a strong activation associated with ROS production, cell spreading, and integrin-elicited kinase oxidation in late phase [26]. The activation of Src kinases can not only alter ECM components via the activation of extracellular proteases, but also promote tumor cell growth and migration through induction of sustained phosphatidylinositol 3-kinase (PI3K), protein kinase C (PKC) and extracellular-regulated kinase (ERK) activation (**Figure 1**). For example, it has been demonstrated that ROS activated ERK1/2 affects the gene expression of integrins [27, 28], the essential receptors of ECM proteins, as well as decreases the gene expression of E-cadherin in a PKC-dependent manner, leading to the remodel of surrounding tissues and thereby the promotion of epithelial mesenchymal transition (EMT). Src induces EMT through phosphorylation, degradation of E-cadherin [29], and upregulation of mesenchymal markers vimentin and N-cadherin [30]. Redox sensitive Src, which is recruited to and activated in cell-ECM adhesion, plays a key role in the resistance to apoptosis induced by ECM detachment, a phenomenon termed anoikis. It has been reported that transiently increased Src activity triggers PI3K and ERK survival signal to protect epithelial cells from anoikis [27, 30]. Src also transactivates epidermal growth factor receptor (EGFR) and receptor tyrosine kinases (RTKs) signaling to promote carcinogenesis and tumor metastasis. Recent studies also confirmed that mitochondrial DNA mutations generated by ROS enhance the breast cancer metastasis via increased transcription of hypoxia inducible factor 1 (HIF-1α) and the activation of PKC pathways [23]. HIF-1 is a heterodimeric transcription factor composed of two subunits: HIF-1α and HIF-1β. HIF-1β protein is constitutively expressed, whereas HIF-1α expression is induced in human cells by hypoxia, growth factors, and oncogenes. HIF-1α subunit is a rate-limiting factor for HIF-1 activity. HIF-1 activation is important for tumorigenesis and angiogenesis, and HIF-1α expression is frequently increased in many human cancers and is also associated with survival and angiogenesis. In addition to playing a vital role in microenvironment adaption, tumor growth, metastasis and drug resistance in cancer cells, HIF-1α also functions as an important pro-angiogenic factor by regulating its target genes, among which vascular endothelial growth factor (VEGF) has the strongest angiogenic effect in tumor angiogenesis [31, 32]. Our extensive previous studies have shown that PI3K/AKT/HIF-1/VEGF and MAPK/ERK/HIF-1/VEGF pathways are critical for tumor growth and angiogenesis [23, 31, 33, 34]. Therefore, Src redox regulation plays a key role in mediating tumor progression, cell survival and anoikis, receptor cross talk, and angiogenesis.

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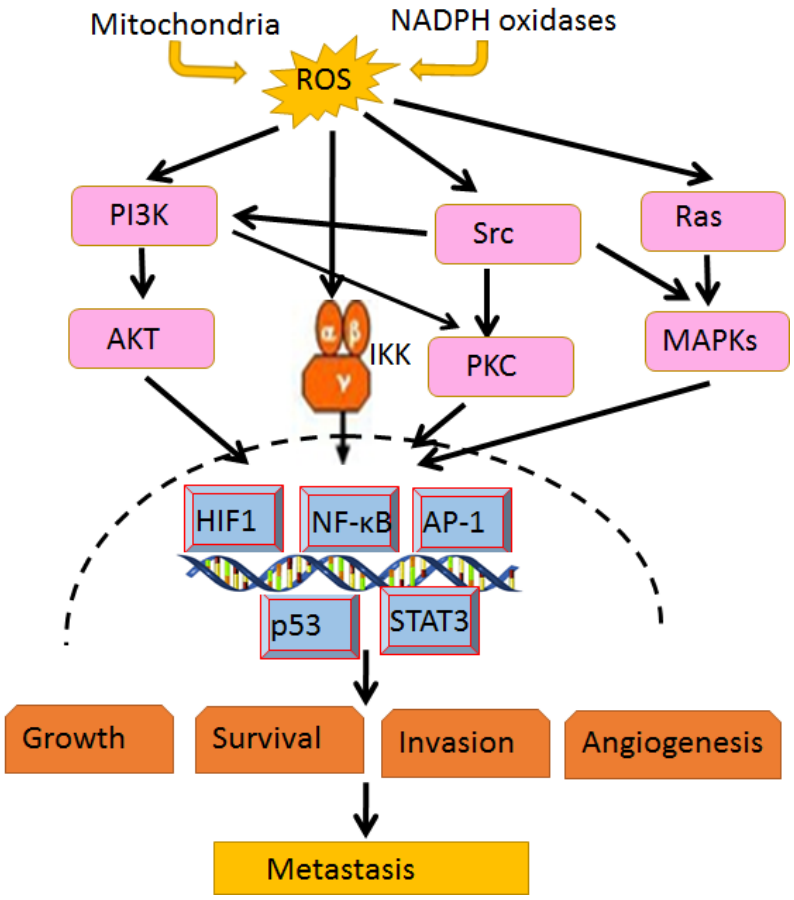

FIGURE 1. The ROS-regulated signaling in tumor metastasis. ROS can be generated via NADPH oxidases or by electron leak in mitochondria. The excessive intracellular ROS in cancer cells can activate Src/PKC, PI3K/AKT and Ras/MAPKs pathways to affect many transcription factors such as NF-κB, HIF-1, AP-1, p53 and STAT3 that contribute to cancer metastasis by promoting cell growth, survival, invasion and angiogenesis by controlling their target genes and downstream effectors. ROS also directly activate NF-κB signaling for cancer development.

2.2. Regulation of PI3K/AKT Pathway by ROS

The PI3K/AKT pathway is involved in many critical cellular functions including protein synthesis, cell cycle progression, proliferation, anti-apoptosis, invasion, autophagy, angiogenesis and drug resistance in response to the stimulation of growth factors such as VEGF, epidermal growth factor (EGF) and platelet-derived growth factor (PDGF), hormones such as prostaglandin (PGE2), and cytokines such as IL-6 and IL-8 [35–37]. Once activated by the binding of growth factor to its receptor(s), PI3K catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-triphosphate (PIP3), which is a second messenger, and recruits and activates proteins that contain the pleckstrin homology (PH) domain such as AKT, subsequently promotes the activation and transcription of the downstream targets including mTOR/p70S6K1, GSK3, FOXO, p53, nuclear factor κ-B (NF-κB) and HIF-1 [32, 37, 38]. ROS directly activate PI3K to amplify its downstream signaling, or indirectly activate PI3K by inactivating phosphatase and tensin homolog deleted on chromosome 10 (PTEN), which

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hydrolyzes the 3' phosphate on PIP3 to generate PIP2 and negatively regulates PIP3 mediated signaling pathways [39, 40]. In addition, ROS is able to promote the phosphorylation by casein kinase II of PTEN, which urges PTEN to enter the proteolytic degradation pathway [40, 41].

2.3. Regulation of Mitogen-Activated Protein Kinases (MAPKs) Pathway by ROS

The MAPKs family consists of ERK1/2, the c-Jun N-terminal kinase (JNK), the p38 MAPK and the big MAP kinase 1 (BMK1/ERK5), which are the major and important intracellular signal transduction pathways in mediating various cellular processes such as cell growth, differentiation, development, cell cycle, survival and cell death [42, 43]. The MAPKs transfer intracellular signals from the cell membrane to the nucleus and are activated in response to a wide range of stimuli such as growth factors (EGF and PDGF), cytokines (IL-1β and TNF-α) and environmental stress (particularly, oxidative stress). ROS have been shown to activate the receptors of EGF and PDGF without corresponding ligands, which stimulates Ras and subsequently activates MAPKs pathway [25]. Hydrogen peroxide (H_2O_2) treatment leads to the generation of inositol trisphosphate (IP3) and diacylglycerol (DAG) by phospholipase C phosphorylation and activation. IP3 increases the intracellular calcium to mediate ERK activation, whereas DAG and increased intracellular calcium activate PKC, leading to Ras and Raf activation [44]. In addition, oxidative stress directly or indirectly affects MAP kinase kinase kinase (MEKK) and subsequently activates p38 and JNK pathways [45]. MAPK cascades are important to cancer progression, and increased level of ROS usually enhances MAPK activities that eventually promote tumor metastasis by promoting EMT and cell migration [46]. For example, ROS stimulate EMT in normal human epidermal keratinocytes via ERK1/2 and JNK activation and transforming growth factor β (TGF-β) secretion. Treatment of highly metastatic breast cancer cells with ROS scavengers or inhibitors that target ERK1/2 or its upstream kinase mitogen-activated protein kinase kinase (MEK) attenuates cell migration and invasion [47]. In addition, the research of our lab and others has demonstrated that ROS activated PI3K/AKT and MAPK/ERK pathways play important roles in regulating tumorigenesis, angiogenesis, and metastasis.

2.4. Regulation of Nuclear Factor κ-B (NF-κB) Pathway by ROS

The transcription factor NF-κB is crucial in mediating a series of cellular processes including cellular adhesion, differentiation, proliferation, senescence, apoptosis, immune and inflammatory responses. The NF-κB family members include Rel (c-Rel), RelA (p65), RelB, p50/p105 (NF-κB1), and p52/p100 (NF-κB2). In physiological conditions, NF-κB binds to inhibitors of NF-κB (IκBs) and is sequestered in the cytoplasm. Upon stimulation, IκB kinase (IKK) complexes including IKKα, IKKβ, and NF-κB essential modulator (NEMO, also called IKKγ) are rapidly activated, leading to phosphorylation and proteasome-mediated degradation of IκBs, and the free NF-κB translocates into the nucleus, binds to its consensus sequence, and induces transcription of its target genes [48]. Interestingly, ROS can both positively and negatively regulate NF-κB cascade. Oxidative stress has the potential to activate NF-κB in the early phase, whereas oxidative stress also inhibits basal or inducible activation of NF-κB in the late phase. Accumulating evidence has demonstrated that ROS activates NF-κB pathway by various manners. Typically, ROS induce activation of NF-κB cascade mainly through stimulating the phosphorylation of IκBα. H_2O_2 treatment affects the phosphorylation of IκBα, leading to the subsequent degradation of IκBα and activation of NF-κB pathway [49, 50]. Moreover, IKK and its kinases upstream MEKK1 are also the primary targets for ROS, and ROS cause the inactivation of MEKK1 and IKKβ through S-glutathionylation to influence NF-κB activity [51, 52]. ROS also disturb IκB ubiquitination and degradation, therefore activating NF-κB via the inactivation of Ubc12 [48]. Finally, ROS activate NF-κB inducing kinase (NIK), the upstream kinase in the noncanonical NF-κB pathway, through inhibition of phosphatases and oxidation of cysteine residues.

The activation of Src/PKC, PI3K/AKT and Ras/MAPKs pathways by endogenous ROS in cancer cells results in the changes of transcription factors such as induction of NF-κB, HIF-1α, AP-1 and STAT3, and inhibition of tumor suppressor p53. As mentioned above, ROS also directly activate NF-κB which has been demonstrated as a key regulator in cancer development by modulating metastasis-associated genes including matrix metalloproteinases (MMPs) [53, 54]. AP-1 induces the expression of

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genes that function as invasion effectors including MMP9, CD44 and EGFR [55], and represses other genes that function as invasion suppressors such as TSC-36, fibronectin and PCDHGC3 [56]. STAT3 is constitutively activated in many different types of cancer and regulates the expression of numerous oncogenic genes controlling the growth and metastasis of tumor cells [57]. The activated redox-sensitive signaling cascades and related transcription factors promote cancer metastasis by inducing cell growth, survival, invasion and angiogenesis (**Figure 1**).

3. THE INTERPLAY OF ROS AND MICRORNAS (MIRNAS) IN TUMOR METASTASIS

miRNAs are a group of small endogenous (usually 18–25 nucleotide-long) noncoding, single stranded RNA species that normally bind to the 3′-untranslated region (UTR) and regulate gene expression through hybridizing to their target messenger RNAs (mRNAs) in a sequence-specific manner, typically leading to mRNA cleavage or suppression of its translation. miRNA expression can be altered by several mechanisms including chromosomal abnormalities, epigenetic changes and oxidative stress.

Compared to normal cells, cancer cells always have a greater capacity to adapt to a hostile and hypoxic environment for survival, which contributes to their malignant and aggressive behavior [10, 58]. This adaptation is controlled by many factors, including the transcriptional and post-transcriptional changes in gene expression in cells [12, 22, 59]. As mentioned, a variety of human genes are responsive to ROS at their transcriptional levels during tumor metastasis. The global microRNA profiling analysis revealed that exposure to hydrogen peroxide caused changes of various microRNA contents [60, 61], suggesting that these ROS-sensitive miRNAs may play important roles in cells, particularly in cancer cells in response to oxidative stress. Up to date, increasing evidence has demonstrated that some miRNAs are redox sensitive and respond to the aberrant cellular oxygen levels, and these ROS-associated miRNAs specifically regulate gene transcription under the oxidative stress. On the other hand, miRNAs are also reported to target mitochondrial protective proteins and antioxidative enzymes to modulate ROS production [62, 63]. In this review, we will focus on ROS-regulated miRNAs in mediating tumorigenesis and cancer development (**Table 1**). All the references related to the targets of these miRNAs are listed in Supplemental Table 1.

3.1. ROS-Upregulated miRNAs in Carcinogenesis and Cancer Development

Human cancers display an aberrant expression profile of miRNAs which either act as oncogenic molecules (e.g., miR-21) or tumor-suppressors (e.g., miR-34a), and some of these miRNAs are redox sensitive [60, 64]. Among all the ROS-upregulated miRNAs, miR-21 and miR-155 are well characterized as oncomiRs. For example, ROS-dependent activation of miR-21-programmed cell death 4 protein (PDCD4) signaling mediates arsenic- and chromium-induced malignant transformation of human lung bronchial epithelial cell [65, 66]. PDCD4 is a suppressor of tumorigenesis, tumor progression, and invasion by interacting with translation initiation factors eIF4A and eIF4G to inhibit translation in an mRNA-specific manner, which leads to inhibition of pro-oncogenic factors [67]. A recent study also showed that miR-21 affects toll-like receptor (TLR) pathway by directly targeting TLR-4, myeloid differentiation primary response protein (MYD88) and chemokine CXCL10 [68]. MYD88 is a co-activator of TLR4 signaling for the activation of transcription factors and production of pro-inflammatory cytokines. It has been reported that TLR4 is required for protective immune response and killing of cancer cells [68]. CXCL10 mediates its effects to modulate innate and adaptive immune response by activating T lymphocytes, NK cells, inflammatory dentritic cells, most macrophages and B cells. In addition to the targets above, miR-21 also targets some other tumor suppressor genes such as tissue inhibitor of metalloproteinase 3, tropomyosin 1, ras homolog gene family member B and maspin to promote cancer development [69]. On the other hand, miR-21 also targets SOD3 and downregulates SOD2 by targeting TNF-α, thus forming a feedback loop to modulate the levels of ROS generation [63]. Thus, these findings clearly suggest that miR-21 has a strict functional interplay with ROS during tumor development.

A recent study has shown that H_2O_2 scavenger catalase treatment significantly decreases miR-155 expression, demonstrating that miR-155 can be regulated by ROS [70]. miR-155 has been consid-

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TABLE 1. miRNAs regulated by ROS and their targets in cancer development

Name	Response to ROS	Targets	Effect in Cancer
miR-21	↑	PTEN, PDCD4, TLR-4, MYD88, CXCL10	Apoptosis, tumorigenesis and cancer development, immune response to cancer cells, therapeutic resistance
miR-23	↑	BCL2, SMAD3, Keap-1	Apoptosis, migration, invasion, response to oxidative stress
miR-210	↑	E2F3, MNT, Cdc25b, Ccnf, EFNA3, Ptp1b, BCL2, COX10, SDHD	Cell cycle, apoptosis, mitochondrial metabolism, DNA damage, angiogenesis, metastasis
miR-200	↑	VEGF, IL8, CXCL1, ZEB1, ZEB2, CDH, MMP3, FN1, FAP1	Tumor growth, angiogenesis, migration, invasion, metastasis and therapeutic resistance
miR-25	↑	PTEN, CCNE1, CDKN1C, MOAP1, FBXW7, RECK, CDC42, Bim, cyclin E2	Cell cycle, apoptosis, proliferation, metastasis
miR-155	↑	FADD, BCL2, FOXO3a, TP53INP1, RHOA	Apoptosis, EMT, proliferation, migration, invasion, metastasis, immune response, therapeutic resistance
miR-125b	↓	ERBB3, cadherin, MMP13, c-Jun, Mcl-1, BCL2, IL-6R, SMAD, MAPK2K7,	Cell proliferation, apoptosis, invasion, EMT, angiogenesis, metastasis, therapeutic resistance
miR-199a	↓	ERBB2, ERBB3, IKKB, DDR1, CD44, GRP78, ApoE, HIF-1α, COX-2, SNAI1, N-cadherin, FZD7, FZD6, Bcam, Wnt7a, Podxl, HK2, PKM2, MAP3K11, CCR7, Beclin1	Cell proliferation, invasion, angiogenesis, glycolysis, metastasis, therapeutic resistance
miR-192	↓	TCF7, SERPINE1, EGR1, HOXB9, BCL2, ZEB2, VEGFA, RB1, ERCC3, ERCC4	Angiogenesis, proliferation, apoptosis, DNA repair, metastasis, therapeutic resistance
miR-124	↓	R-Ras, N-Ras, CDK4, PI3KCA, AKT2, ROCK1, Slug, SNAI2, STAT3, ZEB1, EZH2, Src, DNMT3B, DNMT1	Cell cycle, apoptosis, angiogenesis, cell growth, migration, invasion, metastasis, EMT, DNA methylation, therapeutic resistance
miR-34a	↓	CD44, CDK4, CDK6, E2F3, Cyclin E2, BCL2, Myc, c-Met, Notch-1, Notch-2, SIRT1, DLL1	Cell cycle, apoptosis, EMT, metastasis, cancer stem cell phenotype, therapeutic resistance
let-7	↓	Bach1, c-Myc, RAS, HMGA1, HMGA2, IL6, TLR4, CCND2	Angiogenesis, proliferation, apoptosis, EMT, metastasis, response to oxidative stress

ered to act as an oncogene or a tumor suppressor, depending on tumor system. MiR-155 has been strongly implicated in promoting cancer development of various solid tumors including breast, lung, liver cancers, lymphoma and leukemia since its discovery [71]. A lot of direct targets of miR-155 have been verified. A mini-review by Mattiske S et al. published in 2012 has shown a total of 147 validated miR-155 target genes were identified from the literature in the context of breast cancer [72], indicating the complex effect of miR-155. For instance, oncogenic miR-155 is involved in mediating apoptosis,

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EMT, cell proliferation, migration, invasion and metastasis by targeting BCL2, FOXO3a, and RhoA (Table 1). However, several studies have shown the tumor suppressor effect of miR-155 [73, 74]. miR-155 deletion mice show a greater number of polyps/adenomas, a higher grade of epithelial dysplasia and a decrease in survival with activation of the TGF-β/SMAD pathway, which is correlated with the increased tumorigenesis using a chemically induced (azoxymethane-dextran sulfate sodium) mouse model of colitis-associated colon cancer, suggesting that careful evaluation of the role of miR-155 in tumorigenesis is necessary prior to any consideration of its potential as a biomarker and/or therapeutic target [75].

Some other miRNAs are also upregulated upon ROS stimulation, including miR-210, miR-200 family members (e.g., miR-141, miR-200a/200b/200c), miR-23 and miR-25. These miRNAs exhibit their role in regulating cell growth, angiogenesis, migration, invasion, cell cycle, apoptosis, EMT, tumor metastasis and drug resistance through targeting their targets, suggesting the important role of oxidative stress-upregulated miRNAs in cancer development (**Table 1**).

3.2. ROS-Downregulated miRNAs in Carcinogenesis and Cancer Development

miR-34a is a member of the miR-34 family with two other members: miR-34b and miR-34c. It is identified as one of the p53-regulated miRNAs to induce a G1 cell cycle arrest, senescence and apoptosis in response to DNA damage [76, 77]. It has been recently reported that H_2O_2 promotes miR-34a induction, which is associated with PI3Kα activation and PTEN reduction [78]. miR-34 is an important tumor suppressor in inducing cell cycle arrest, apoptosis, senescence, suppression of EMT and cell proliferation of cancer stem cells [79, 80]. miR-34a targets many oncogenes and cancer stem cell markers including CD44, cyclin-dependent kinases 4, 6 (CDK4, CDK6), Cyclin E2, BCL2, Myc, c-Met, Notch-1, Notch-2, Sirtuin SIRT1 and Delta-like1 (DLL1) to induce tumor suppression by inhibiting cancer regeneration, migration and metastasis (**Table 1**). Other p53-regulated miRNAs, let-7a and let-7b, can also be downregulated upon H_2O_2 treatment in colon cancer cells in a p53-dependent manner [81]. H_2O_2 treatment also decreases let-7g expression in gastric cancer cells, suggesting that these let-7 family members are redox sensitive [82]. Let-7 family is composed of let-7a/b/c/d/e/f/g/i and miR-98. Let-7 miRNAs were originally discovered to play crucial roles in the temporal regulation of *Caenorhabditis elegans* and the maintenance of normal differentiation and development of living organisms [83, 84]. The evidence for the tumor suppressor role of let-7 in cancer came from early research showing that overexpression of let-7 inhibited colon cancer cell proliferation [85], and let-7 miRNAs in human lung cancers are reduced, which is associated with a shortened postoperative survival [86]. In 2005, the 3′-UTRs of the human RAS genes containing multiple let-7 complementary sites (LCSs) were found to be regulated by let-7 miRNA family [87]. Since then, many oncogenes have been identified as direct targets of let-7, including c-Myc, high mobility group AT-hook 1, 2 (HMGA1, HMGA2), IL6, TLR4, central compartment node dissection 2 (CCND2) (**Table 1**), demonstrating that let-7 miRNA family is involved in inhibiting oncogenesis through regulating cell apoptosis, angiogenesis, malignant transformation, EMT and tumor progression. In addition, let-7 also targets Bach1 to enhance heme oxygenase-1 and attenuates oxidant injury in human hepatocytes [88].

A recent publication indicates that low concentration of H_2O_2 treatment decreases the expression levels of miR-124 in a dose-dependent manner [89]. Growing evidence has demonstrated that miR-124 acts as a tumor suppressor. For example, miR-124 is involved in regulating tumor cell proliferation, migration, radiosensitivity and drug resistance by targeting some oncogenic molecules such as R-Ras, N-Ras, CDK4, PI3KCA, AKT2, Rho-associated kinase1 (ROCK1), STAT3, Src, and CD164 (**Table 1**). More importantly, some well-known oncogenes such as Slug, Snai2 and zinc finger E box binding homeobox 1 (ZEB1) which are EMT-associate genes, are direct targets of miR-124 (**Table 1**). Finally, miR-124 also targets DNA methyltransferases 3B (DNMT3B) and DNMT1, the key enzymes in regulating DNA methylation [90]. Another ROS-decreased miRNA is miR-192 since mouse liver hepatoma cells Hepa 1-6 show significant decrease on miR-192 expression upon H_2O_2 treatment [91]. miR-192 targets many genes such as T-cell specific transcription factor (TCF7), plasminogen activator inhibitor-1 (PAI-1) gene (SERPINE1), EGR1, BCL2, ZEB2, VEGFA, retinoblastoma (Rb1), DNA exci-

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sion repair cross complementing gene (ERCC3, and ERCC4), thereby mediating cell proliferation, apoptosis, DNA repair, tumor angiogenesis, metastasis and therapeutic resistance (**Table 1**).

Our previous study has identified that miR-199a and miR-125b are downregulated by ROS generation. Furthermore, ERBB2 and ERBB3 are direct targets of miR-199a, whereas ERBB3 is a direct target of miR-125b. ROS inhibit miR-199a and miR-125b expression through increasing the promoter methylation of these two miRNAs by DNMT1. Meanwhile, overexpression of miR-199a and miR-125b is associated with the decrease of HIF-1α and VEGF expression that regulates tumor angiogenesis [92, 93], suggesting that redox-sensitive miR-199a and miR-125b act as tumor suppressors in ovarian cancer development. In addition to ERBB2 and ERBB3, it is known that miR-199a targets IKKB, discoidin domain receptor 1 (DDR1), apolipoprotein E (ApoE), the heat shock factor DNAJA4, SNAI1, N-cadherin, Frizzled type 7 receptor (FZD7), FZD6, Bcam, Wnt7a, Podxl, hexokinase 2 (HK2), pyruvate kinase M2 (PKM2), mitogen-activated protein kinase kinase kinase 11 (MAP3K11), chemokine receptor 7 (CCR7), Beclin1, to mediate cell proliferation, angiogenesis, EMT, glycolysis, metastasis, and therapeutic resistance (**Table 1**).

The role of miR-125b in carcinogenesis is controversial. miR-125b acts as a tumor suppressor to suppress cell malignant transformation, cell proliferation, invasion, angiogenesis, cancer development and increase therapeutic effect by targeting ERBB3, c-Raf, E2F3, BCL3, mucin 1(MUC1), LIN28B2, ETS1, STAT3, BCL2, AT-rich interactive domain 3B (ARID3B), vascular endothelial (VE)-cadherin, myc-associated zinc finger protein (MAZ), matrix metallopeptidase 13 (MMP13), Mcl-1, BCL-w, IL-6R, sirtuin 7 (SIRT7), MAD1, phosphoinositide 3-kinase catalytic subunit delta (PIK3CD), ENPEP, CK2-α, CCNJ, MEGF-9, ER alpha-1, 2-mannosidase (ERManI), small mothers against decapentaplegic (SMAD2, SMAD3), Interferon regulatory factor 4 (IRF4), and Sphingosine Kinase 1 (SphK1) (**Table 1**). On the other hand, miR-125b is an important oncomiR in hematopoietic malignancies. For example, overexpression of miR-125b is sufficient both to shorten the latency of BCR-ABL-induced leukemia and to independently induce leukemia in a mouse model [94]. The Emu/miR-125b transgenic mice develop lethal B-cell malignancies [95]. Meanwhile, miR-125b also regulates hematopoiesis by targeting Lin28A [96]. miR-125b has also been reported to act as an oncomiR by targeting TP53INP1, Bcl-2 antagonist killer 1 (Bak1), p53, Puma, StAR-related lipid transfer domain containing 13 (STARD13) and Connexin43 to promote tumor cell growth, invasion, cell renewal and resistance to apoptosis (**Table 1**). miR-125b constitutively activates NF-κB pathway by targeting the tumor necrosis factor alpha-induced protein 3 (TNFAIP3) [97], and TNFAIP3 and NF-κB inhibitor interacting RAS-like 2 (NKIRAS2), another target of miR-125b, are involved in temozolomide resistance in glioblastomas [98]. Finally, miR-125b functions as a key mediator for Snail-induced stem cell propogation and chemoresistance. Overexpression of Snail dramatically increases the expression of miR-125b through the Snail-activated Wnt/β-catenin/TCF4 axis. Snail confers chemoresistance to taxol by repressing Bak1 through miR-125b upregulation. Moreover, overexpression of miR-125b significantly increases the cancer stem cell population ($CD24^-$ $CD44^+$), while depletion of miR-125b or rescue of the expression of Bak1 increases the non-stem cell population ($CD24^+$ $CD44^+$) in Snail-overexpressing cells [99]. Overall, miR-125b plays a dual role in tumorigenesis.

4. SUMMARY

The intracellular production of ROS plays an important role in both cancer initiation and development. ROS emerge on the signaling transduction and miRNAs regulation relevant to tumor metastasis. The activation of PI3K/AKT, PKC, Ras/MAPKs cascades and the downstream transcription factors such as NF-κB, HIF-1, AP-1, p53 and STAT3 are involved in promoting tumor metastasis. Moreover, some miRNAs can be upregulated (miR-21, miR-155, miR-23, miR-210, miR-200 and miR-25) or downregulated (miR-125b, miR-199a, miR-192, miR-124, miR-34a and let-7) by ROS generation, which takes part in mediating malignant transformation, cell proliferation, apoptosis, angiogenesis, migration, invasion, metastasis, glycolysis, EMT, cancer stem cell phenotype, immune surveillance, and therapeutic resistance through their direct targets. On the other hand, some miRNAs such as miR-21 and let-7 are also involved in regulating ROS production by targeting their targets SOD3 and

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Bach1, or by controlling the expression levels of ROS-related enzymes. In this review, we outline the possible roles of these signaling cascades and ROS-regulated miRNAs in mediating tumor metastasis, which may be helpful for providing potential therapeutic targets for cancer treatment in the future.

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