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Targeting CSCs in Tumor Microenvironment: The Potential Role of ROS-Associated miRNAs in Tumor Aggressiveness

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Abstract

Reactive oxygen species (ROS) have been widely considered as critical cellular signaling molecules involving in various biological processes such as cell growth, differentiation, proliferation, apoptosis, and angiogenesis. The homeostasis of ROS is critical to maintain normal biological processes. Increased production of ROS, namely oxidative stress, due to either endogenous or exogenous sources causes irreversible damage of bio-molecules such as DNA, proteins, lipids, and sugars, leading to genomic instability, genetic mutation, and altered gene expression, eventually contributing to tumorigenesis. A great amount of experimental studies *in vitro* and *in vivo* have produced solid evidence supporting that oxidative stress is strongly associated with increased tumor cell growth, treatment resistance, and metastasis, and all of which contribute to tumor aggressiveness. More recently, the data have indicated that altered production of ROS is also associated with cancer stem cells (CSCs), epithelial-to-mesenchymal transition (EMT), and hypoxia, the most common features or phenomena in tumorigenesis and tumor progression. However, the exact mechanism by which ROS is involved in the regulation of CSC and EMT characteristics as well as hypoxia- and, especially, HIF-mediated pathways is not well known. Emerging evidence suggests the role of miRNAs in tumorigenesis and progression of human tumors. Recently, the data have indicated that altered productions of ROS are associated with deregulated expression of miRNAs, suggesting their potential roles in the regulation of ROS production. Therefore, targeting ROS mediated through the deregulation of miRNAs by novel approaches or by naturally occurring anti-oxidant agents such as genistein could provide a new therapeutic approach for the prevention and/or treatment of human malignancies. In this article, we will discuss the potential role of miRNAs in the regulation of ROS production during

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CONFLICT OF INTEREST

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DISCLOSURE

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tumorigenesis. Finally, we will discuss the role of genistein, as a potent anti-tumor agent in the regulation of ROS production during tumorigenesis and tumor development.

Keywords

ROS; CSCs; EMT; hypoxia; miRNAs; genistein

1. INTRODUCTION

Reactive oxygen species (ROS) have been widely recognized as critical cellular signaling molecules that are involved in a variety of biological processes. The term of ROS encompasses a range of oxygen molecules which mainly contain one or more unpaired, unstable electrons. ROS can be generated mainly through endogenous sources such as mitochondria, peroxisomes, and inflammatory cells as well as exogenous sources such as environmental agents, pharmaceuticals, and irradiation [1]. The homeostasis of ROS is very important in maintaining normal physiological and biological functions. Increased production of ROS, called as oxidative stress, may cause irreversible damages of bio-molecules such as DNA, proteins, sugars, and lipids, leading to genomic instability, genetic mutations, and altered gene expression, thereby contributing to chronic diseases such as carcinogenesis. A large number of evidence has suggested the important role of ROS in the tumorigenesis and tumor progression. Moreover, the concept of cancer stem cells (CSCs) has been accepted in the field of cancer research, due to its increased capacity of self-renewal, high potential of differentiation to multiple cell lineages, and their ability in tumor initiation. Great numbers of experimental studies have produced solid evidence supporting that CSCs are associated with cell growth and proliferation, invasion and metastasis, and drug resistance, leading to poor clinical prognosis of cancer patients. In this article, we will describe the role of ROS in the regulation of CSC characteristics. We will also describe the role of ROS in the regulation of epithelial-to-mesenchymal transition (EMT) and hypoxia, key factors in the regulation of CSC characteristics. Furthermore, we will describe the potential role of microRNAs (miRNAs) in the regulation of ROS production during tumorigenesis. Finally, we will describe the role of genistein, which is both a class of isoflavone and a naturally occurring agent, as a potent anti-tumor agent in the regulation of ROS production during tumorigenesis and progression of human tumors.

2. REACTIVE OXYGEN SPECIES (ROS) AND ITS PHYSIOLOGICAL ROLE

Chemically, ROS are created as endogenous by-products in reduction-oxidation (redox) processes during the reactions of oxygen to water in the body [2, 3]. In the presence of a free electron, the univalent reduction of oxygen generates superoxide ($^{\cdot}O_2^-$), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH), all of which are classified as ROS. Superoxide contains an unpaired electron, which confers itself highly reactive, extremely unstable, and very short-lived [4, 5]. ROS are produced continuously in the body mostly under aerobic conditions; however, the production of ROS and its elimination is a well-balanced process for free radical homeostasis to maintain normal physiological and biological functions in the body. In eukaryotic cells, the most significant endogenous sources of ROS include the mitochondrial respiratory chain, phagocytosis, microsomal cytochrome p450 enzymes,

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flavoprotein oxidases, peroxisomal fatty acid metabolism, inflammatory cell oxidation, and non-enzymatic reactions of oxygen [6–9]. Environmental agents, pharmaceuticals, pollutant chemicals, ionizing radiation contribute to exogenous source of ROS in the body. The NADPH oxidases are a group of plasma membrane-associated enzymes, which catalyze the production of superoxide from oxygen by using an anti-oxidant molecule NADPH as the electron donor [10]. Therefore, NADPH oxidase is one of the major endogenous enzymes contributing to the production of ROS. ROS have been widely considered as second messengers and have been implicated as important cellular signaling molecules involving in a variety of biological processes such as cell proliferation and differentiation, cell death/apoptosis, DNA damage repair, and angiogenesis in the body [2]. Similar to second messengers, production of ROS is closely regulated by extra-cellular stimuli such as hypoxia/oxygenation, growth factors, and inflammatory cytokines. ROS-mediated redox signaling pathways usually involve in the oxidation of a signaling molecule induced by ROS. Such oxidation of bio-molecules might be reversible in the presence of endogenous anti-oxidants in the body [11].

Under normal physiological conditions, the homeostasis of ROS has been involved in wide variety of biological processes such as gene transcriptional activation, cell differentiation and proliferation, cell cycle, apoptosis, and DNA repair pathway. Thus, the homeostasis of ROS has been considered as a critical factor in the extension of lifespan in humans. The defense systems that evolve to minimize ROS-induced bio-molecule damage include endogenous anti-oxidants (such as GSH, tocopherols, and carotenes), heme-containing peroxidases (such as catalase and heme oxygenase-1), glutathione peroxidase, superoxide dismutase (SOD), and DNA damage repair mechanisms in the body [1, 9, 12].

Under abnormal conditions, either due to endogenous or exogenous sources, disequilibrium between ROS production and antioxidant protection results in an increase in the bio-availability of ROS or high level of ROS activity namely a state of oxidative stress [9, 12]. The pathogenic consequence of ROS-induced oxidative stress is oxidative damage of cells or tissues [5], which is a major cause of DNA damage that ultimately leads to genomic instability, genetic mutation, and altered gene expression, eventually resulting in malignant transformation during the development of many chronic diseases including cancers as discussed below.

3. ROS, CELL/TISSUE DAMAGE, AND TUMORIGENESIS

It has been well known that ROS react with many bio-molecules including DNA, proteins, lipids, and carbohydrates by oxygenation of these molecules, and modify the structures and functions of these molecules, which cause cellular stresses, leading to cellular injury or damage. Increased levels of oxidative DNA damage have been widely recognized to be one of the major etiologic factors in carcinogenesis induced by cigarette smoking and chronic inflammatory diseases. ROS-mediated DNA damages include adducts of both base and sugar group modifications, single and double strand breaks in the DNA “backbone”, and cross-links between DNA and other bio-molecules [7, 8]. Proteins also represent a diverse spectrum of molecular targets by ROS for oxidative damage. Oxidizable prosthetic groups such as metal-sulfur clusters contribute to increased sensitivity of proteins to ROS-induced

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damage. A primary target of ROS is sulfhydryl (SH) group of amino acids such as cysteine, arginine, histidine, methionine, proline, tyrosine and tryptophan in the proteins [7, 13, 14]. These modifications of proteins are believed to be in part responsible for the development of chronic diseases such as cancers [15]. For example, hydroxyl radicals react with pyrimidines, purines, and chromatin protein, resulting in base modifications, genomic instability, genetic mutation, and altered gene expression, thereby contributing to carcinogenesis [15].

Sufficient evidence has shown that tumor cells or tissues have high level of ROS, compared to normal cells or tissues [16]. In normal cells or tissues, increased levels of ROS can damage DNA, proteins, lipids, leading to apoptosis or genomic instability, genetic mutation, and altered gene expression, if these tissues experience sustained exposure to high levels of ROS. However, in tumor cells, ROS-induced DNA damage can trigger the expression of anti-apoptotic proteins by activation NF-κB, a major anti-apoptotic mediator, which contributes to its tolerance of high level of ROS, leading to drug resistance [15–17]. It has also been noted that H_2O_2 treatment to tumor cells can inhibit PTEN, an AKT inhibitor, leading to AKT activation, resulting in increased BAD activity which leads to the inhibition of apoptosis [15–17]. Furthermore, a great amount of experimental studies *in vitro* and *in vivo* have revealed that the high levels of ROS in cancer cells are strongly associated with cell growth, therapy resistance, and metastasis [16]. These findings suggest that ROS have a critical role in tumorigenesis and progression of tumor which is further discussed in the following sections.

4. THE ROLE OF ROS IN CSCs

The existence of cancer stem cells (CSCs) or tumor-initiating cells (TICs) was first recognized over few decades ago; however, only in the past decade, the CSCs were identified and characterized from hematological malignancies especially from leukemia [18]. Since then, the CSCs have attracted remarkable attentions due to their potential role in tumor aggressive phenotypes such as treatment resistance, and their capacity in causing tumor recurrence or relapse and metastasis. Similar to the common features of normal pluripotent stem cells such as self-renewal and differentiation to multiple lineage cells in various tissues, the CSCs have several distinct properties such as long-lived and quiescent potentials with high resistance to apoptosis, a selective capacity to initiate tumor formation and drive neoplastic proliferation, a strong ability to unlimitedly create copies of themselves through self-renewal, and a high potential to amplify more mature non-stem cell cancer progeny through differentiation [19, 20]. These characteristics suggest the role of CSCs in tumorigenesis and tumor progression. However, the pathogenesis of CSCs is still poorly characterized. It has been widely believed that intrinsic and extrinsic alterations in the tumor microenvironment of stem cells niche within a tumor tissue as well as mutations and epigenetic regulations are mainly responsible for the development of CSCs [21].

It has been documented that the CSCs are only comprised of a very small percentage (0.05–1%) of sub-sets of tumor cells within a tumor mass or within the tumor microenvironment. These cells are capable of self-renewal, giving rise to uncontrolled amplification of differentiated cell populations with alterations in molecular and cellular phenotypes that

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eventually leads to the heterogeneous primary and metastatic tumors with potential of therapeutic resistance, contributing to tumor recurrence or relapse [22–25]. This concept of CSCs provides important clinical implications in the prognosis of many different tumors, especially because of the identifications of sub-populations of CSCs in the majority of malignant tumor tissues such as brain, lung, breast ovary, gastrointestinal, prostate tumors, and thus these sub-populations of CSCs are broadly considered to be responsible for resistance to chemo-radiation therapy relative to their differentiated mature progenies, due to many distinct properties [26–29]. This reasonably explains for the clinical observations that treatment-causing reduction of tumor size alone may not correlate with the overall disease-free survival rate of cancer patients [26] because of tumor recurrence/relapse due to the existence and sustenance of CSC sub-populations within the tumor microenvironment after conventional therapy.

A great amount of clinical and experimental studies have produced convincing evidence in support of the role of CSCs that participate in the regulation of the chemotherapy resistance and metastasis, which leads to poor clinical outcome of patients diagnosed with many common types of tumors [30–33]. It has been noted that at the invading areas of human pancreatic tumor, the CD133+ pancreatic CSC cells co-express CXC chemokine receptor (CXCR4), a well-known mediator of cell migration and invasion [28, 34, 35]. Both the CD133+CXCR4− and CD133+CXCR4+ cells isolated from human pancreatic cancer are able to generate primary tumor in mouse xenograft tumor model. However, only the CD133+CXCR4+ cancer cells show an increased capacity of metastasis in this animal model, compared to the CD133+CXCR4− cancer cells. The blockage of CXCR4 in these pancreatic CSCs prevents metastasis in the same xenograft mouse model [36], suggesting a critical role of CSCs in tumor metastasis. Moreover, the CSCs also contribute to resistance to radio-therapy through preferential activation of the DNA damage response pathway, and an increase in DNA repair capacity [37]. Overwhelming evidence indicates that only a subset of rare CSC population is responsible for maintaining and sustaining malignant diseases, which clearly suggests that the CSCs would exert a pivotal role in the regulation of chemo-radiation therapy resistance, tumor metastasis and recurrence/relapse after currently available conventional therapy, and these biological events are mediated through deregulations of multi-cellular mechanisms and networks, as recently reviewed elsewhere [33, 38, 39]. Therefore, targeting CSCs would provide an effective therapeutic approach for the prevention and/or treatment of malignant diseases.

The role of ROS in the regulation of CSC characteristics has not yet been fully elucidated. It has been documented that normal stem cells have low level of ROS [40, 41]. Similar to normal stem cells, CSCs have been considered to have low level of ROS, potentially due to its enhanced ROS defense system against DNA damage [42]. One experimental study has demonstrated that human and mouse breast CSC-like cells have low levels of ROS. Lower levels of ROS in these CSC-like cells are associated with increased expression of free radical scavenging systems. The depletion of ROS scavengers by a pharmacological inhibitor in mouse breast Thy-1+CD24+Lin- CSC-enriched cells markedly decreased clonogenicity and resulted in radio-sensitization [43]. Therefore, low levels of ROS and enhanced ROS defense may contribute to tumor radio-resistance, compared to non-tumorigenic progeny. Another study has found that the CSC cells derived from uterine

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cervical CD133+/CD49f+/CD34+ CSC sphere cells, exhibit increased expression of genes involving in ROS metabolism and EMT markers as well as increased drug resistance [44]. These findings suggest that ROS may play an important role in the pathogenesis of CSCs. More investigations are required to understand the potential role of ROS in the regulation of CSC characteristics.

5. THE ROLE OF ROS IN EMT PHENOTYPE DURING TUMORIGENESIS

The acquisition of EMT phenotype is a fundamental biological process that has been recognized to exert a critical role during embryogenesis in which cell migration and tissue remodeling display a primary role in the regulation of morphogenesis in multi-cellular organisms [38, 45]. The EMT process also takes place in the placenta formation and fibroblast formation during inflammation and wound healing after birth [38, 45]. During the EMT process, epithelial or epithelial-like cells with a cobblestone structure lose their polarization and specialized junctional structures for cytoskeleton re-organization, acquire motile mesenchymal-like phenotypes with a spindle-shaped fibroblast-like morphology, and detach from the epithelial sheet by increasing matrix degradation. This complex process is closely associated with a dismantlement of cell-cell junctions by the down-regulation of E-cadherin and zonula occludens-1 (ZO-1), epithelial-like phenotype markers, re-organization of actin cytoskeleton, and up-regulation of mesenchymal-like phenotype markers such as Vimentin, fibronectin, α-smooth muscle actin (α-SMA), and N-cadherin. This process renders mesenchymal-like cells to have lower capacity of cell adhesion by up-regulation of MMPs, which leads to an increase in cell migration/invasion [46–49].

During the induction of EMT process, some gene transcription factors such as zinc-finger E-box binding homeobox 1 (ZEB1) and ZEB2/SIP2, and Snail/Snail1, Snail2/Slug, Twist/Twist1, and E47/TCF3 (T cell factor 3) have been identified to be central mediators of EMT phenotype induced by various stimuli such as TGF, FGF, and PDGF in many different cell lines including tumor cells [49, 50]. ZEB1 has been well identified to regulate the gene expression by its binding to ZEB-type E-boxes (CACCTG) within the promoter/enhancer regions of target genes such as E-cadherin, which induces chromatin condensation and gene inactivation, leading to the inhibition of E-cadherin expression [49, 51]. The inhibition of the gene expression of E-cadherin is essential for the induction of EMT phenotype process [52]. Although the induction of the EMT process has been originally observed during embryogenesis, a large number of experimental and clinical data have produced convincing evidence supporting that EMT exerts an important role in the induction of cancer cell invasion/migration, and metastasis, thereby leading to the acquisition of resistance to chemo-radiation therapy, contributing to tumor recurrence/relapse [53].

Because both CSC and EMT phenotypes have been believed to be the cause for the resistance to chemo-radiation therapy and tumor metastasis, leading to poor clinical prognosis/outcome of cancer patients, there should be an inter-relationship between CSC and EMT characteristics in tumorigenesis and progression of tumor. Accumulating numbers of experimental studies have produced solid evidence suggesting that the EMT process also generates the EMT phenotypic cells with stem cell properties such as the self-renewal capacity and drug resistance [26, 54, 55]. Additionally, several lines of evidence reveals that

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CSC cells in tumor tissues undergo an EMT process to gain migratory, mesenchymal phenotype characteristics that drive CSC cells to migrate from the primary tumor to colonize to distant sites where these cells then undergo a mesenchymal-to-epithelial transition (MET) process to form a metastatic tumor of the same character as its prototype tumor [56, 57]. These findings have clearly suggested an inter-relationship between the inductions of metastasis, drug resistance, and CSC self-renewal capacity in the cancer cells undergoing the acquisition of EMT process. It has been found that several molecular signaling pathways such as Notch, Hedgehog (Hh), Wnt/β-catenin, Akt/mTOR, NF-κB, as well as epigenetic regulators EZH2 and Bmil1 exert a pivotal role in the regulation of both CSC and EMT characteristics [26, 54, 55, 58, 59]. It is also reported that forced over-expression of Snail2 by its cDNA transfection in breast epithelial MCF-10A CD44−/CD24+ non-CSC-like tumor cells gives rise to an increase in the sub-population of CD44+/CD24− CSC-like cells [60]. These findings suggest that the EMT process plays a key role in the regulation of CSC characteristics.

The relationship between ROS and EMT processes has been well established as reviewed recently [61, 62]. Emerging evidence suggests that ROS may play a pivotal role in the induction of the EMT process during tumorigenesis and tumor progression. Limited evidence has suggested that ROS production is associated with EMT process. One early study revealed that repeated treatments with low doses of H_2O_2 result in EMT like morphological changes of mouse mammary epithelial cells in the matrigel invasion chamber [63]. H_2O_2 treatment also up-regulates Snail expression in breast cancer cells [64]. Further experimental studies have indicated that EMT stimuli such as TGF-β, FGF, and cytokines induce the production of ROS in a NADPH oxidase-dependent mechanism [61]. It has been documented that ROS increase PKC/MAPK activation which regulates the Snail2 activity/signaling. It has been well known that ROS can activate NF-κB signaling, which up-regulates Twist, a known EMT inducing gene [61]. ROS have also been found to activate Wnt/β-catenin signaling pathway, which closely participates in the regulation of EMT and CSC characteristics [61].

Other experimental reports have indicated that increased levels of ROS can contribute to angiotensin II-induced EMT by up-regulation of α-SMA and down-regulation of E-cadherin in rat peritoneal mesothelial cells [65]. The data also show that matrix metalloproteinase 3 (MMP3, an enzyme which is involved in the breakdown of extracellular matrix and used as a tumor metastatic marker) induces EMT phenotype by the increased production of ROS *via* Rac1b (RAC1 ras-related C3 botulinum toxin substrate 1b, a key mediator of EMT) [66]. These findings clearly suggest that ROS play a pivotal role in the induction of EMT processes, by the regulation of multi-cellular signaling pathways. Interestingly, Snail has been found to increase the ROS production in human prostate cancer cells. High levels of Snail-induced ROS increase the expression of Vimentin and suppresses the expression of E-cadherin *via* the activation of ERK/MAPK [67], suggesting the existence of a crosslink between ROS and EMT. The detailed mechanism(s) of how ROS exert a critical role in the induction of EMT phenotype requires further investigation.

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6. THE ROLE OF ROS IN HYPOXIA AND HYPOXIA-MEDIATED PATHWAY DURING TUMORIGENESIS

6.1. The Role of Hypoxia and HIF in Tumors

It has been well documented that hypoxia is one of the most common biological features that is closely related to many aspects of biological processes such as cell survival, apoptosis, invasion, angiogenesis, drug resistance, and cellular metabolic alterations during the tumorigenesis and tumor progression. Hypoxia-inducible factors (HIF), a central transcription factor regulating the expression of a variety of hypoxia-induced genes, have been considered to exert an essential role in the regulation of tumor invasion, metastasis, angiogenesis, and chemo-radiation resistance, leading to tumor aggressive phenotype. Clinically, tumor hypoxia along with alterations in the expressions of HIF and its downstream targets have been documented to be associated with poorer clinical prognosis of the patients diagnosed with a wide variety of solid tumors.

6.2. The Role of Hypoxia and HIF in the Regulation of CSCs

Hypoxia has been more and more accepted as a key factor that modulates the sub-population of normal stem cells or stem cell niches and sustains the normal tissues or non-stem cell tissues in a stemness state during embryogenesis and adult development after birth [68–70]. The evidence from many experimental studies has revealed that hypoxia also exerts a pivotal role in the regulation of CSC characteristics by enriching the CSC self-renewal capacity and maintaining its undifferentiated state [71–75]. Hypoxia has been shown to be capable of sustaining the stem cell-like state of neuroblastoma cells and stimulate cellular signaling pathways that are related to undifferentiated states of normal stem cells, such as sex determining region Y (sRY) box 2 (Sox2), Oct4 and Notch-1, which are well-known stem cell signature genes [76]. The hypoxia-mediated activation of the CSC signature genes may be one of the main reasons why hypoxia is related to an increase in tumor aggressive phenotypes, contributing to poorer clinical prognosis of tumor patients.

Accumulating evidence has suggested that the areas of tumor tissues experiencing hypoxia or the areas of necrotic tumor tissues are widely considered as a niche where small sub-sets of CSC cells reside, namely CSC niches [77]. Such hypoxic CSC niches may exert a pivotal role in tumorigenesis and progression of tumors. Therefore, it is possible that tumorigenesis may be associated with the evolution and development from mutations in normal stem cells such as mesenchymal stem cells or from small sub-populations of non-stemness tumor cells exposing to hypoxic scenario. The detailed mechanism(s) by which hypoxic conditions modulate the CSC characteristics has not been completely elucidated. It has been identified that hypoxia-mediated CSC characteristics is modulated by HIF proteins, specifically HIF-1α and 2α, which participate in the regulation of HIF targeting genes, such as Oct4, CD44, and other CSC signatures, as recently reviewed elsewhere [78–80].

Increased numbers of *in vitro* and *in vivo* studies have produced solid evidence revealing that both HIF-1α and 2α exert a pivotal role in the regulation of CSC characteristics, in a cell-specific fashion. For instance, hypoxia-induced HIF-1α and 2α or forced over-expression of HIF-1α or 2α by its cDNAs enhances the CSC characteristics, in agreement

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with the up-regulation of HIF-1α, and HIF downstream target genes such as Oct4, Nanog, c-Myc, Notch-1, CD44, and CD133, which are the typical CSC signature genes, in a variety of tumor cells including CSCs [72, 75, 81–87]. Functional loss of HIF-1α or 2α by its siRNAs inhibits the expansion and functions of hypoxia-induced CSCs [88–91]. These findings clearly suggest that HIF-1α and 2α are essential for the regulation of CSC characteristics in certain cancers, as reviewed elsewhere [21].

6.3. The Cross-Link of Hypoxia and ROS in Tumor Aggressive Phenotypes

The data from many experimental studies have produced solid evidence suggesting that hypoxia can trigger the induction of the EMT process, resulting in tumor aggressive phenotypes such as metastasis and drug resistance [92]. One recent experiment demonstrates that moderate hypoxic (3% O_2) condition-induced ROS can induce EMT phenotype by up-regulation of Snail and HIF-1α in variety of tumor cells such as breast, colon, and pancreatic cancers, giving rise of increased invasion [93]. Therefore, hypoxia may exert a pivotal role in the regulation of CSC and EMT characteristics during tumorigenesis and tumor progression. The role of ROS in the regulation of hypoxia and hypoxia-mediated signaling pathways has been received great attentions, as reviewed elsewhere [94, 95]. It is noted that hypoxia triggers the induction of gene responsive for ROS and NO metabolism [96]. Although few studies have reported that hypoxia led to decreased production of ROS, potentially due to the low specificity of the ROS measurements used [95], the majority of the reports show that hypoxia induces the higher production of ROS in variety of cells including tumor cells. It has been noted that hypoxia can induce the release of ROS into the cytosol. Furthermore, hypoxia is able to induce the accumulation of DNA and lipid oxidation products, suggesting that hypoxia increases cellular oxidant production [97, 98]. Moreover, it has been identified that ROS are required for hypoxic activation of HIF proteins [95]. For instance, the treatments of cells with H_2O_2 and Gfs, H_2O_2 inducers, or cellular mutation-induced H_2O_2 accumulation are found to be essential for the stabilization of HIF-1α [99, 100]. It has also been documented that ROS increases HIF-1α activity by multiple mechanisms such as increasing HIF stabilization, inhibiting PHD, an endogenous HIF inhibitor, and activating Akt/MAPK cellular signaling pathways [94, 95, 101]. These findings collectively suggest that ROS exert a pivotal role in the stimulation of HIF signaling pathway.

7. THE ROLE OF MIRNAS IN THE REGULATION OF ROS PRODUCTION

It has been widely recognized that microRNAs (miRNAs), a group of small non-protein-coding RNAs, act as post-transcriptional regulators of mRNAs by binding to their specific binding sites in the 3′ un-translated region (3′-UTR) of their target mRNAs, resulting in either the degradation of mRNAs or inhibition of protein synthesis [102, 103]. Numerous clinical and experimental studies have produced clear evidence supporting that miRNAs have an important role in tumorigenesis. The altered expressions of miRNAs are clearly related to poorer clinical prognosis of tumor patients, therapy resistance and tumor recurrence/relapse. Importantly, increasing numbers of miRNAs have been shown to function as regulators of CSC and EMT characteristics as well as hypoxia mediated events through the regulation of multiple signaling pathways. More importantly, some miR-NAs

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are reportedly associated with the ROS production in various cells including tumor cells. In the following sections, we will provide example of some well-characterized miR-NAs that are potentially involved in the regulation of ROS production during tumorigenesis and tumor progression.

7.1. The Role of Let-7

A great amount of clinical and experimental studies have demonstrated that let-7 exerts a key regulatory role during tumorigenesis by targeting multi-cellular signaling pathways. The low levels of let-7 expression have been revealed to be related to poorer clinical prognosis of the patients diagnosed with many different tumors. Several let-7 family members such as let-7b, c have been displayed as negative regulators of EMT and CSCs characteristics mediated through the differential regulation of tumor suppressor gene PTEN and CSC signature gene Lin28b in pancreatic and prostate cancer cells [54, 104–107]. Therefore, let-7 has been widely considered as a potential tumor suppressor molecule. Recently, the expression of several let-7 family members, especially let-7a-g has been reported to be associated with hypoxic conditions in several human cancer cells [108]. The data supports that hypoxia can induce the down-regulation of let-7a-g in human nasopharyngeal cancer cells. Moreover, let-7b has been identified to be a putative VEGF target miRNA [108], which suggests the potential regulatory role of let-7 within a tumor microenvironment by targeting VEGF-mediated angiogenesis; however, the detailed role and exact mechanism of hypoxia-mediated let-7 expression within the tumor hypoxic microenvironment is not fully understood.

Emerging evidence suggests that oxidative stress decreases the expression of let-7 family in variety of cells including tumor cells. One previous study demonstrated that irradiation treatment resulted in the down-regulation of the majority of tested let-7 family members such as let-7a-f at different time points in human lung cancer cells. Only one let-7 family member, let-7g was up-regulated [109]. More recently, the data suggests that irradiation- and agents-induced oxidative stress decreases the let-7 expression in wide variety of cells including cancer cells and fibroblasts [110–113]. Oxidative stress inhibits the expression of let-7 which has been found to be dependent on p53, a known tumor suppressor [111]. Moreover, the treatment of anti-oxidant cysteine has a protective role in the irradiation-inhibited expression of let-7a/b in human fibroblasts [112]. These findings suggest that ROS may exert a pivotal role in the regulation of tumor-associated let-7 family members. However, the detailed molecular mechanisms are not fully understood.

7.2. The Role of miR-21

It has been widely accepted that miR-21 appears to act as an oncogenic miRNA by targeting multiple signaling pathways. A great amount of clinical and experimental studies have revealed a high level of miR-21 expression in many different types of tumors, and it is strongly related to poorer clinical prognosis of cancer patients [114, 115]. It has been noted that the high levels of miR-21 expression cause the suppression of PTEN expression in various tumors [116, 117]. The miR-21 has been shown to have anti-apoptotic, proliferative, invasive and angiogenic potentials in a wide variety of tumor cells [115, 118–120]. Several experimental studies *in vitro* and *in vivo* have revealed that the expression of miR-21 was

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found to be significantly increased in the CSC sub-populations, compared to non-CSC cancer cells [121, 122]. Moreover, the forced over-expression of miR-21 by its precursor was able to enhance the survival of the bone marrow mesenchymal stem cells. The functional loss of miR-21 by its siRNA increased apoptosis of mesenchymal stem cells [123]. One additional study demonstrates that the functional loss of miR-21 reverses the EMT phenotype and inhibits HIF-1α in breast CSC-like sphere cells, consistent with decreased capacity of cell migration and invasion [124]. These findings strongly suggest that miR-21 plays a critical role in the regulation of CSC and EMT characteristics mediated by the modulation of multi-cellular signaling pathways, and further it might be useful as a therapeutic target for the prevention and/or treatment of tumors.

Emerging evidence indicates that ROS are closely associated with the levels of miR-21 expression. Several experimental studies *in vitro* and *in vitro* have demonstrated that oxidative stress, either induced by H_2O_2 treatment or irradiation, or inflammation increases the expression of miR-21 in variety of cells including tumor cells [112, 125, 126]. The supplementation of anti-oxidant to bacteria-infected mice attenuates the expression of ROS-induced miR-21 [125]. We demonstrate that hypoxia-induced oxidative stress induces the miR-21 expression, which is in agreement with an increase in tumor cell migration and the self-renewal capacity of CSCs in human prostate and pancreatic cancer cells [127, 128]. These findings clearly suggest that ROS may have a pivotal function in the regulation of the expression of miR-21 during tumorigenesis and tumor progression. Moreover, a new study reveals that miR-21 stimulates MAPK-mediated ROS production by down-regulation of SOD2/SOD3 and sprouty homolog 2 (SPRY-2, a negative regulator of Ras-Raf-Erk signaling) as well as up-regulation of TNF-α, leading to the promotion of tumorigenesis [129, 130]. These findings clearly suggest that miR-21 may have key function in the regulation of ROS homeostasis. However, further investigations are required to elucidate a detailed relationship between ROS and miR-21 during tumorigenesis.

7.3. The Role of miR-34

Increased numbers of clinical and experimental studies have revealed that miR-34 family members such as miR-34a are under-expressed in a variety of human tumors such as breast, ovarian, pancreatic, brain, and lung tumors [131–133], which is also consistent with our recent findings in prostate and colon cancers [134, 135]. Low levels of miR-34a, b, and c have been reportedly found to be related to poorer clinical outcome of cancer patients [134, 136]. The miR-34 has been proposed as a potential tumor suppressor molecule which contributes to the inhibition of cell survival, proliferation, invasion, and metastasis mediated, in part, through the activation of p53 and inactivation of cyclin D1, E2F1/2, and CDK6 in tumor cells [132, 137–140]. Recently, miR-34a has been found to suppress the expression of CSC signature genes such as CD44 as well as EMT markers, which is consistent with the attenuation of tumor invasion and metastasis, and the CSC self-renewal capacity in various tumor cells [103, 134, 141, 142]. Our published data has indicated that re-expression of miR-34a by its mimics decreases the expression of androgen receptor, PSA, and Notch-1 in prostate cancer cells [134]. Our unpublished data also demonstrates that forced over-expression of Notch-1 decreases the miR-34a expression in human pancreatic cancer cells. Re-expression of miR-34a by its precursor results in the inhibition of the CSC self-renewal

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capacity of human pancreatic cancer as assessed by sphere formation assay, consistent with the suppression of the protein expression of CSC cell surface proteins CD44 and EpCAM in CSC-like sphere cells of pancreatic cancer cells. Moreover, the miR-34a expression has been found to be significantly decreased in CD133+ glioma CSC-like cells [143]. These findings suggest that miR-34a plays a key role as a potential tumor suppressor in the regulation of CSC characteristics.

The interaction between ROS and miR-34 has recently received much more attentions. One animal study reveals that bacteria-infected mice have significantly increased expression of miR-34a, b, and c [125]. Other *in vitro* experimental studies demonstrate that oxidative stress increases the expression of miR-34a,b,c in a variety of cells such as lymphocytes, fibroblasts and stem cells, and tumor cells and stromal cells [144, 145]. The miR-34a has been found to promote renal cell senescence by inhibition of mitochondrial anti-oxidant enzymes [146]. However, it has been reported that p53−/− genotoxic stress decreases the expression of miR-34a in variety cells including cancer cells [147]. The exact mechanism(s) by which miR-34 family is involved in the regulation of ROS homeostasis during tumorigenesis needs further in-depth studies.

7.4. The Role of miR-146a

Decreased levels of miR-146a expression have been identified to be closely related to poorer clinical prognosis of prostate cancer and pancreatic cancer [148, 149]. A great amount of experimental studies *in vitro* and *in vivo* have suggested that miR-146a may act as a potent tumor suppressor molecule *via* regulation of multiple signaling pathways in many different cancers such as pancreatic cancer and prostate cancer. The data shows that miR-146a decreases NF-κB activity, consistent with decreased expression of NF-κB target genes such as IL-1β, IL-6, IL-8, and TNF-α mediated by the regulation in the expression of IL-1 receptor associated kinase 1 (IRAK1) and TNF receptor associated factor 6 (TRAF6) [150]. The activation of NF-κB signaling has been reported to be involved in the enrichment of CSC and EMT characteristic by the regulation of CSC genes such as Nanog, Sox2, and Lin28 as well as EMT marker Snail [151]. Recently, we have revealed that the miR-146a expression was lost in pancreatic cancer cells while re-expression of miR-146a resulted in the low capacity of tumor cell invasion, consistent with inactivation of EGFR and NF-κB, which led to the down-regulation of NF-κB targets [148]. However, one study showed that oral squamous cell carcinoma tissue samples had high levels of miR-146a and increased expression of miR-146a enhanced the oncogenicity of oral squamous cell carcinoma cells [152]. These results suggest that the role of miR-146a in tumorigenesis and tumor progression appears to be cell lineage specific, suggesting that further investigations are needed to understand the role of miR-146 in the regulation of CSC and EMT characteristics.

Limited evidence suggests that ROS may exert a key role in tumorigenesis mediated through the regulation of miR-146. It was noted that oxidative stress could induce oxLDL, and increased the expression of miR-146a, b in human primary monocytes [153]. Metal-sulfate-induced oxidative stress is also found to increase the expression of miR-146a in human astroglial cells. Treatment of metal-sulfate-stressed astroglial cells with anti-oxidants such as phenyl butyl nitrone, curcumin, or pyrollidine dithiocarbamate inhibited the induction of

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oxidative stress-induced miR-146a expression [154]. It has been documented that miR-146a and b inhibit TLR/NF-κB downstream pro-inflammatory proteins/molecules IRAK-1 and TRAF6 [155], suggesting a potential role of miR-164a and b as anti-inflammatory regulators. However, further investigations are needed to understand the exact functions of miR-146 in the regulation of ROS homeostasis during tumorigenesis.

7.5. The Role of miR-200

It has been well document that miR-200 family members play very important roles in tumorigenesis by targeting multiple cellular signaling pathways. It has been shown that the miR-200 expression is decreased in a wide variety of tumors such as prostate, pancreatic, lung, brain, GI, and breast tumors. The alterations in the miR-200 expression have been shown to be closely related to poor clinical prognosis of cancer patients [107, 118, 156]. We have reported that drug-resistant human cancer cells have decreased expression of miR-200a, b, c, and displayed more mesenchymal-like phenotype, along with EMT characteristics. Re-expressions of miR-200a,b,c by its precursor miRNAs in drug-resistant pancreatic cancer cells or PDGF-D-induced EMT prostate cancer cells decreased the expression of ZEB1, ZEB2, Slug, and increased the expression of E-cadherin, which was consistent with the findings of other experimental studies [106, 107, 136]. It is also noted that miR-200 decreases the expression of Bmil-1, Suz12, and Notch-1, known regulators of CSC and EMT phenotypes that are known to function in various cancer cells, consistent with the inhibition of CSC self-renewal capacity [157–159]. More importantly, the down-regulation of miR-200a, b, and c has been observed in CSC-like (CD44+/CD24−) cells of breast cancer [160]. These data clearly suggest that miR-200 family may work as potential tumor suppressor molecules by targeting multi-cellular signaling pathways.

The role of miR-200 in the regulation of ROS homeostasis during tumorigenesis has not been fully elucidated. Several recent studies have identified a new function for miR-200 in the regulation of oxidative stress response. It has been found that accumulation of oxidative stress induced by oxidant agents significantly increased the expression of miR-200a, c in a variety of cells including cancer cells [113, 161–163]. One study demonstrates that H_2O_2- and oxidant agents-induced oxidative stress increases the expression of miR-200c, induces growth arrest, apoptosis and senescence in HUVEC cells *via* targeting negatively ZEB1 [163]. These findings suggest a potential role of miR-200 in the regulation of ROS homeostasis. However, more studies are needed to understand the role of miR-200 in the regulation of ROS production during tumorigenesis.

7.6. The Role of miR-210

Several lines of clinical studies have indicated that increased levels of miR-210 are related to poor clinical prognosis of breast and pancreatic cancers [164, 165]. The high levels of miR-210 are also identified in lymphoma and lung cancer patients [166–168]. It has been documented that hypoxia highly induces the miR-210 expression in all the cells tested including cancer cells [169–178], suggesting a close relationship of miR-210 with hypoxia-mediated ROS production. However, the role of ROS-mediated miR-210 in tumorigenesis is still not characterized and understood. The hypoxia-induced expression of miR-210 is known to promote the expression of hypoxia responsive targets VEGF and CAIX in human

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pancreatic cancer cells by a HIF-1α-dependent mechanism [171, 178], which clearly suggests a regulatory role of miR-210 in tumor angiogenesis [108, 176, 179–182], resulting in tumor aggressive phonotypes. Hypoxia-induced expression of miR-210 has been found to participate in the modulation of DNA damage repair pathway. Over-expression of miR-210 by its mimics was shown to decrease the expression of radiation sensitive 52 (RAD52), a key mediator in homology-dependent repair (HDR) system, contributing to defective DNA repair and genetic instability [183]. These findings suggest that hypoxia-induced expression of miR-210 may have a pivotal role within a tumor microenvironment, further suggesting that a new therapeutic approach could be designed for the prevention and/or treatment of cancer by targeting miR-210.

The role of miR-210 in the regulation of ROS homeostasis has received increased attentions supported by novel investigations. Emerging evidence suggests that miR-210 is strongly associated with ROS production. It has been noted that hypoxia-induced oxidative stress induces the miR-210 expression in several different cells including cancer cells. The miR-210 has also been found to promote cell proliferation and survival in hypoxic region within tumors [184], which in part could be due to the regulation of HIF-1α that is responsible for hypoxic response in cancer cells [184]. Over-expression of miR-210 by its mimics causes mitochondrial dysfunction, enhancing the ROS production in cancer cells [185]. Moreover, the miR-210 has been found to regulate hypoxia-induced free radical response in mitochondria of cancer cells by targeting iron sulfur cluster protein ISCU [172]. These findings suggest that miR-210 may exert a key role in the regulation of ROS homeostasis although the detailed mechanism is still not clear.

7.7. The Role of miR-221/miR-222

Increased evidence suggests that miR-221/miR-222 are strongly related to tumorigenesis and tumor progression. The clinical data revealed that altered expression of these miR-NAs correlates with poor clinical prognosis of the patients diagnosed with different tumors. The miR-221/miR-222 have been considered as either oncogenic molecules or tumor suppressor molecules, depending on specific cell type or tumors [186]. In the majority of tumors such as GI tumors, breast tumors, prostate tumors, brain tumors, NSCLC, and thyroid papillary carcinoma, miR-221/miR-222 act as oncogenic molecules by targeting tumor suppressor genes such as PTEN, TIMP3, BIM, FOXO3A, p27/p57, and ER-α, contributing to cell invasion and proliferation, and tumorigenesis. In the erythropoietic cell lineages and oral tongue squamous cells, these miRNAs act as tumor suppressor molecules by targeting c-Kit, MMP1, and SOD1 [186]. It has been noted that TNF-α has been found to induce the up-regulation of miR-221/miR-222 in adipocytes [187]; however, several experimental studies have shown that oxidative stress induced by either irradiation or ROS-based ER stress decreases the expression of miR-221/miR-222 in various cells including cancer cells [112, 188]. Forced over-expression of miR-221/miR-222 enhances ER-stress-induced apoptosis in human hepatocellular carcinoma (HCC) cells. Functional loss of miR-221/miR-222 by its siRNAs attenuates oxidative stress-induced apoptosis, suggesting that these miRNAs may have a protective function against oxidative stress-induced apoptosis in HCC cells [188].

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7.8. Functional and Therapeutic Role of miRNAs

The findings reported above suggest that miRNAs could be targeted for cancer therapy. Although miRNAs could be up-regulated or down-regulated by experimental approaches, such strategies are currently not applicable in humans, suggesting that novel agents must be developed which will selectively target miRNAs and thus will deregulate the expression of genes that are related with tumorigenesis and tumor progression. To that end, limited studies have shown that natural agents could function as deregulators of miRNAs, which are briefly discussed in the following section relevant to one such natural agent.

8. GENISTEIN, A SOY ISOFLAVONE AS A POTENT ANTI-OXIDANT AGENT SHOWING ANTI-TUMOR ACTIVITY

Isoflavones are one group of flavanoid compounds, the largest class of polyphenolic compounds and are primarily existed in the Leguminosae family plants such as soybean, lentil bean, and chickpea. However, soybeans are the most common foods that contain greatest amounts of isoflavones. Genistein, daidzein, and glycitein are three main components of isoflavones that exist in soybeans and soy protein-rich products such as tofu, soy milk, and soy sauce. Genistein has been known as phytoestrogen, due to its structural similarity to estrogen, exerting a weak estrogenic activity by its binding to estrogen receptor, thereby inhibiting estrogen receptor signaling pathway. Therefore, genistein is perhaps the most studied of these bioactive compounds. Several lines of epidemiological and clinical studies have indicated that isoflavone-rich soy products could exert protective roles against prostate cancer in Japan and USA [189–192].

Sufficient data from *in vitro* and *in vivo* experimental studies have produced solid evidence supporting the role of genistein as a potent anti-tumor agent by targeting multiple signaling pathways such as NF-κB, Wnt, Notch-1, and Akt/mTOR in many different types of cancers [193–199]. Accumulating evidence from multiple *in vitro* and *in vivo* studies has also indicated that genistein exerts an anti-oxidant activity by inhibition of ROS production, DNA oxidation, lipid peroxidation, and NF-κB-mediated inflammatory cytokines in various cells including cancer cells [200–207]. However, two studies have reported that genistein increases the production of ROS along with exerting an anti-tumor activity *in vitro* in cancer cells by using DCF dye-fluorescence method. None of the studies reported the findings on oxidative stress markers such as lipid peroxidation and DNA oxidation by-products. However, one of the studies reported that genistein could enhance irradiation-induced ROS production, along with the inhibition of irradiation-induced COX2 expression and PGE2 production. Both COX2 and PGE2 are inflammatory cytokines, which increase the production of ROS. These limited studies suggest that more the well-designed studies are needed to classify the role of genistein in the regulation of ROS production in the future. Recently, we have demonstrated that genistein up-regulates the expression of let-7b-e, miR-146a, and miR-200, and down-regulates the miR-21 expression, CSC cell surface markers CD44 and EpCAM, and CSC self-renewal capacity along with exerting its anti-tumor activity of human pancreatic cancer AsPC-1 and MIaPaCa-2 cells [106, 157, 208, 209]. These findings, collectively, suggest that genistein, a potential anti-oxidant agent that also shows strong anti-tumor activity, which in part could be due to deregulation of tumor-

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related miRNAs during tumorigenesis and tumor progression. Although there are many other natural agents that could also function as deregulators of miRNAs but due to space limitations, those agents are not discussed in this article for which the authors sincerely apologize to those authors whose work could not be discussed and cited.

CONCLUSION

ROS are critical cellular signaling molecules that are involved in a wide array of biological processes such as cell growth, proliferation, apoptosis, and angiogenesis. Increased production of ROS, namely a state of oxidative stress, is clearly associated with tumor cell growth, drug resistance, and metastasis, leading to increased tumor aggressiveness. Emerging evidence suggests that altered production of ROS is associated with CSCs, EMT, and hypoxia, the most common features or phenomena associated with tumorigenesis and tumor progression. Sufficient evidence suggests that miRNAs play a very important role in tumorigenesis mediated *via* the regulation in the expression of genes that are involved in cell growth, proliferation, apoptosis, and angiogenesis. The altered expressions of miRNAs have been documented to be associated with tumor aggressive phenotypes such as CSCs, EMT, and hypoxia-mediated cellular signaling pathways. Emerging evidence suggests that miRNAs also play pivotal role in the regulation of ROS homeostasis. Therefore, targeting ROS-associated miRNAs by novel agents or naturally occurring agents such as genistein could provide newer therapeutic strategies for the prevention and/or treatment of human malignancies.

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LIST OF ABBREVIATIONS

α-SMA	α-smooth muscle actin
Akt	Protein kinase B
APE	Apurinic/apyrimidinic endonuclease
AR	Androgen receptor
Bad	BCL2-associated agonist of cell death
BIM	Bcl2-like 11
CAIX	Carbonic anhydrase 9
c-Kit	Cellular v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
CD44	The cluster of differentiation 44

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CDK	Cyclin-dependent kinase
CDKN1A	Cyclin-dependent kinase inhibitor 1A
COX2	Cyclooxygenase 2
CSC/CSCs	Cancer stem cell/cancer stem cells
CXCR4	CXC chemokine receptor
DCF	2′,7′-dichlorofluorescein
EMT	Epithelial-to-mesenchymal transition
EZH2	Enhancer of zeste homolog 2
EpCAM	Epithelial cell adhesion molecule
EGFR	Epithelial growth factor receptor
ER	Estrogen receptor
ERK	Extracellular signal-regulated kinase
FGF	Fibroblast growth factor
GI	Gastrointestinal
Gfs	growth factors
H_2O_2	Hydrogen peroxide
HCC	Hepatocellular carcinoma
HDR	Homology-dependent repair
Hh	Hedgehog
HIF	Hypoxia-inducible factors (HIF)
HUVEC	Human umbilical vein endothelial cells
$^{\cdot}OH$	Hydroxyl radical
IGF-1	Insulin-like growth factor 1
IL-6	Interleukin 6
IRAK1	IL-1 receptor associated kinase 1
LEF	Lymphoid-enhancing factor
Lin-28	A conserved regulator of cell fate succession in animals
MAPK	MAP kinase
miRNAs	microRNAs
MMP	Matrix metalloproteinases
TIMP3	Metalloproteinase inhibitor 3
mTOR	Mammalian target of rapamycin

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NF-κB	Nuclear factor of κB
Notch1	Notch homolog 1
NSCLC	Non-small cell lung cancer
Oct4	Octamer-binding transcription factor 4
oxLDL	Oxidized LDL
PTEN	Phosphatase and tensin homolog deleted on chromosome 10
PDGF	Platelet-derived growth factor
PHD	Prolyl hydroxylase
Raf	Proto-oncogene serine/threonine-protein kinase
PGE2	Prostaglandin E2
PKC	Protein kinase C
PSA	Prostate-specific antigen
PDK1	Pyruvate dehydrogenase kinase 1
RAD52	Radiation sensitive 52, a DNA damage repair protein
Rac1b	RAC1 ras-related C3 botulinum toxin substrate 1b
Ref^1	Redox factor 1
ROS	Reactive oxygen species
S6K1	Ribosomal protein S6 kinase
SCID	Severe combined immunodeficiency
SH	Sulfhydryl
SPRY-2	Sprouty homolog 2
$\cdot O_2^-$	Superoxide
SOD	Superoxide dismutase
Sox2	Sex determining region Y box 2
STAT	Signal transducer and activator of transcription
TGF-α	Transforming growth factor-α
TCF	T cell factors
TIC	Tumor initiating cells
TNF-α	Tumor necrosis factor α
TRAF6	TNF receptor associated factor 6
uPA	Urokinase-type plasminogen activator
3′-UTR	3′-untranslated region

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VEGF	Vascular endothelial growth factor
ZEB1	Zinc-finger E-box binding homeobox 1
ZO-1	Zonula occludens-1

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