

## Apoptotic signaling through reactive oxygen species in cancer cells

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**Core tip:** Reactive oxygen species originally used to induce injurious cellular effects are now recognized as key physiological molecules for the induction of host defense genes, activation of transcription factors, and regulation of signal transduction. Tumorigenic cells can induce a new redox balance, resulting in cellular adaptation and proliferation. Here, we review the role of oxidative stress in cancer cells using a pathophysiological view.

### Abstract

Reactive oxygen species (ROS) take part in diverse biological processes like cell growth, programmed cell death, cell senescence, and maintenance of the transformed state through regulation of signal transduction. Cancer cells adapt to new higher ROS circumstance. Sometimes, ROS induce cancer cell proliferation. Meanwhile, elevated ROS render cancer cells vulnerable to oxidative stress-induced cell death. However, this prominent character of cancer cells allows acquiring a resistance to oxidative stress conditions relative to normal cells. Activated signaling pathways that increase the level of intracellular ROS in cancer cells not only render up-regulation of several genes involved in cellular proliferation and evasion of apoptosis but also cause cancer cells and cancer stem cells to develop a high metabolic rate. In over the past several decades, many studies have indicated that ROS play a critical role as the secondary messenger of tumorigenesis and metastasis in cancer from both *in vitro* and *in vivo*. Here we summarize the role of ROS and anti-oxidants in contributing to or preventing cancer. In addition, we review the activated signaling pathways that make cancer cells susceptible to death.

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### INTRODUCTION

The high intracellular ROS levels are related to various human diseases, including neurodegenerative disease<sup>[1-7]</sup>, inflammatory disease<sup>[8,9]</sup>, cardiovascular disease<sup>[10,11]</sup>, immune system dysfunctions<sup>[12]</sup>, obesity<sup>[13]</sup>, and diabetes<sup>[14,15]</sup>. Survival of tumor cells is greatly dependent on their capacity to control expression of endogenous antioxidants to maintain the upper standard level of ROS below the threshold that will induce tumor cell death<sup>[16,17]</sup>. ROS could contribute to the initiation of cancer by accelerating tumorigenic signaling pathways, increasing DNA mutations and changing the activity of the tyrosine phosphatases superfamily<sup>[18-21]</sup>. For example, cancer inactivates the tumor suppressor phosphatase and tensin homolog (PTEN) by oxidation<sup>[22,23]</sup> and inhibits the

mitogen-activated protein kinase (MAPK) phosphatase by ROS, which in turn induces activation of extracellular signal-regulated kinases (ERK). Although greater oxidative stresses activate nuclear factor-kappa B (NF- $\kappa$ B) for growth or survival, high intracellular ROS levels also lead to activation of c-Jun N-terminal kinase (JNK) and p38 kinases, and their activities often facilitate cell apoptosis<sup>[24,25]</sup>. Normally, the inhibition of PTEN by ROS activates the phosphoinositide-3 kinase (PI3K)/Akt signaling pathway and blocks cell apoptosis<sup>[26,27]</sup>. In contrast to the apoptotic death, necrosis induces *via* mitochondrial production of ROS after signaling from tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) or death receptor<sup>[28,29]</sup>. Interestingly, apoptotic cells inhibit ERK1/2 but induce p38 and JNK inside macrophage, while necrotic cells induce macrophage ERK1/2<sup>[30-32]</sup>. ROS-mediated signaling has received more attention in oncological studies than ROS-mediated cellular stress and damage of cancer cells. In this article, we present and summarize the interaction between redox status or redox signaling systems and apoptosis in tumor cell death and anti-cancer treatments.

## ROS CELLULAR SOURCES AND DETOXIFICATION

ROS are mainly generated from mitochondrial electron transfer complex (ETC) during the reduction of oxygen. Superoxide anion ( $\cdot\text{O}_2^-$ ) generated by  $\text{O}_2$  from the mitochondrial electron transport chain, which is usually changed into hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) by several cytoprotective enzymes, including superoxide dismutase (SOD)<sup>[33,34]</sup>. Although scientists are now considering the consequences of different levels of oxidative stress, ROS formation in cells can inflict serious hazards and was originally known for their ability to induce injurious cellular effects.

### Sources of oxidative stress (internal and external)

Reactive oxygen species (ROS) are the most abundantly produced oxygen species in mitochondria. Reactive nitrogen species (RNS) are also produced during intracellular metabolic processes in mitochondrial ETC. Extracellular ROS can be also found in a variety of natural or acquired environment. NAD(P)H oxidase (NOX) can be found in cell membrane phagosomes in neutrophil. The NOX complex is composed of seven members, NOX1-5, and two dual oxidases (Duox), Duox1 and Duox2<sup>[35]</sup>. Although activation mechanisms and tissue distribution are significantly different, all these enzymes, including cytochrome c oxidase and cyclo-oxygenase (COX) are able to generate superoxide anion<sup>[36,37]</sup>. Nitric oxide ( $\text{NO}\cdot$ ) is produced from arginine catalyzed by a nitric oxide synthase (NOS). Fast reaction between  $\cdot\text{O}_2^-$  and  $\text{NO}\cdot$  gives rise to peroxynitrite ( $\text{ONOO}^-$ ) and  $\text{ONOO}^-$  is oxidizing molecule that connected to cancer.  $\text{NO}\cdot$  is finally converted into a hydroxyl radical and nitrite anion ( $\text{NO}_2^-$ )<sup>[38,39]</sup>. Numerous agents, including anti-cancer drugs, have been shown to induce proliferation or apoptosis through ROS

production in various cancer types. Low sodium arsenite induces MCF-7 epithelial breast cancer cell proliferation by ROS production, activation of NF- $\kappa$ B, and increases in c-Myc and heme oxygenase-1 (HO-1)<sup>[40]</sup>. ROS-enhancing compound, such as piperlongumine, is insufficient to induce death of cancer cell lines including osteosarcoma cells, breast, and glioblastoma cancer cells, but not in normal cells<sup>[41-43]</sup>.

### Natural defense mechanisms of antioxidants

Although the ROS levels modestly increases in tumorigenic cells, intracellular ROS is maintained below a toxic level in normal cells by various scavengers and antioxidative enzymes. Besides mitochondrial superoxide dismutases (SODs), catalase, glutathione (GSH), peroxidase (GPx), and peroxiredoxin also modulate oxidative status<sup>[44]</sup>. SODs are metalloenzymes which catalyze the dismutation of  $\cdot\text{O}_2^-$  to  $\text{O}_2$  and  $\text{H}_2\text{O}_2$ . They ubiquitously exist in eukaryotes and prokaryotes. SODs also play a critical role in inhibiting oxidative inactivation of NO, thereby preventing  $\text{ONOO}^-$  formation and mitochondrial dysfunction<sup>[45]</sup>. SODs utilize metal ions such as copper ( $\text{Cu}^{2+}$ ), zinc ( $\text{Zn}^{2+}$ ), manganese ( $\text{Mn}^{2+}$ ) or iron ( $\text{Fe}^{2+}$ ) as cofactors. Ferric ions catalyze hydrogen peroxide, which is the Fenton reaction<sup>[46]</sup>. Catalase, which is located in peroxisomes, facilitates the decomposition of  $\text{H}_2\text{O}_2$  to water and oxygen and protects cells from  $\text{H}_2\text{O}_2$  produced within the cell<sup>[46]</sup>. GPx catalyzes the reduction of hydrogen peroxide using cellular GSH as the reducing reagent. GPx converts  $\text{H}_2\text{O}_2$  to  $\text{H}_2\text{O}$  +  $\text{O}_2$ <sup>[47]</sup>. Peroxiredoxins are thioredoxin peroxidases that catalyze the reduction of hydrogen peroxide, organic hydroperoxides and peroxynitrite<sup>[48]</sup>. In neutrophil, many species of bacteria are killed readily by a myeloperoxidase/hydrogen peroxide/chloride system. HOCl, oxidizing chloride ions, is the most bactericidal oxidant produced by myeloperoxidase<sup>[49]</sup>.

## THE ROLE OF ROS IN CANCER CELLS

Besides, genetic factors have important roles in the transforming events that lead to carcinogenesis. The enhanced oxidative stress is generally associated with cancer promotion and progression. Meanwhile, high levels of ROS are less harmful in cancer cells than they would be in normal cells because cancer cells have developed mechanisms to keep themselves from intrinsic oxidative stress through regulation of antioxidant functions and pro-survival molecules<sup>[16,17]</sup>; however, oxidative stress still has a negative impact on various types of cancer cells as well<sup>[50,51]</sup>. The identification of specific alterations in critical cellular components by ROS can provide evidences for early detection, prevention of cancer.

### ROS in chronic inflammation associated with cancer

Over the several years' studies about the cytokine, inflammatory cells and cytokines found in neoplastic tissues seems to contribute to tumor growth, progression, and immunosuppression. ROS induced by these cells and

cytokines facilitate cancer growth, invasion, and metastasis through DNA damage or inhibition of DNA repair. Chronic inflammation predisposes cells for an oncogenic transformation through overproduction of ROS, increased COX-2, and aberrant NF- $\kappa$ B expression<sup>[52,53]</sup>. Defective mitochondria have also been characterized by excessive ROS production in several chronic human diseases associated with inflammation. ROS derived from mitochondria (mtROS) enhance signaling pathways to produce pro-inflammatory cytokine subsets. mtROS activates NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome-dependent pro-inflammatory cytokine production<sup>[18,54]</sup>.

Oxidative stress can activate various transcription factors including NF- $\kappa$ B, activating protein-1 (AP-1), p53, and hypoxia inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ). Activation of these transcription factors can result in the expression of numerous different genes, including cytokines and chemokines<sup>[55,56]</sup>. Nuclear factor erythroid-related factor 2 (Nrf2) is one of the master transcription regulators in controlling antioxidant responses. Nrf2 controls the expression of hundreds of genes, including NAD(P)H:quinone oxidoreductase 1 (NQO1), Glutathione S-transferase (GST), GPx and oxidoreductases for inflammatory responses, tissue remodeling and fibrosis, carcinogenesis, and metastasis<sup>[57-59]</sup>. Kelch-like protein 1 (Keap1), a suppressor protein anchored in the cytoplasm that physically binds Nrf2, controls the access of Nrf2 to promoters of Antioxidant Response Element (ARE)-regulated antioxidant enzymes<sup>[60,61]</sup>. MAPK, PI3K, atypical protein kinase C (PKC), and other pathways are also found as alternative pathways for Nrf2 activation<sup>[62,63]</sup>. Importantly, somatic mutations that disrupt the Nrf2-Keap1 interaction are identified in cancer patients. In non-small-cell lung cancer (NSCLC) cells with Keap1 gene mutations, Nrf2 is constitutively activated and cells proliferate independently of epidermal growth factor receptor (EGFR) signaling<sup>[64-66]</sup>. Although the above-mentioned studies show the effects of ROS-mediated inflammation in carcinogenesis, It is contrast with blockade of NF- $\kappa$ B predisposes murine skin to squamous cell carcinoma. RelA subunit of NF- $\kappa$ B has tumor suppressing activity under some circumstances<sup>[67-71]</sup>. Because NF- $\kappa$ B is modulated by ROS, the effects of ROS on carcinogenesis may be unfavorable to certain type of cells and conditions.

### Role of ROS in mitochondrial DNA mutations

Although the significance of ROS and antioxidant systems in carcinogenesis is still controversial, substantial evidence suggests that an increase of intracellular ROS might contribute to carcinogenesis<sup>[72-74]</sup>. ROS also might stimulate the expansion of initiated cell clones through stimulation of cell proliferation and suppression of apoptosis<sup>[72]</sup>. The involvement of mitochondria in disease has been largely recognized to their essential role in production of ROS and to the damaging effect of chemical agents or pathological conditions on these organelles<sup>[33,52]</sup>. Recently, several studies have reported that tumorigenic

mitochondrial DNA (mtDNA) mutations affect respiratory chain complexes. Decreased mitochondrial activity is considered to be tumorigenic, mainly because of the enhanced ROS production. H<sub>2</sub>O<sub>2</sub> exported to the nucleus enhances the transcription of selected genes that favor tumor progression<sup>[75,76]</sup>. Depletion of mtDNA, especially encoded OXPHOS genes, plays a key role in transformation of breast epithelial cells. Breast epithelial cells results in *in vitro* tumorigenic phenotype as well as breast tumorigenesis in a xenograft model<sup>[77]</sup>. Claudin-1 and 7 in p53 network of breast epithelial cells are down-regulated in tumorigenesis<sup>[77]</sup>. In humans, mtDNA mutations coding (ND1, ND4, ND5, and cytochrome b genes) or noncoding regions are frequently detected in breast cancer tissue<sup>[78,79]</sup>. However, the pathological relevance of mtDNA mutations in cancer cells is still controversial<sup>[80]</sup>. Nonetheless, a clear-cut correlation between the occurrence of pathogenic mtDNA mutations and mitochondrial energetic impairment is a well-demonstrated feature of oncocyomas, characterized by disruptive mutations of mtDNA, especially in complex I subunits<sup>[81]</sup>. Initial enhanced ROS generation may induce supercomplex disorganization, eventually leading to a possible decrease of complex I assembly<sup>[82]</sup>. Dissociation of the supercomplex might further induce ROS generation and have harmful consequences, such as disassembly of complex I and III<sup>[83,84]</sup>. However, ROS measurements in tumor biopsies are not practicable currently in oncocyoma. Further studies are needed to understand whether ROS may influence the proliferative potential and accumulation of mutations in oncocyoma. Because elevated ROS have been proposed to induce apoptosis, additional studies are required to determine the role of apoptosis in regulating the survival and proliferation of oncocyotic cells. It has been reported that the cell line carrying the heteroplasmic ND5 mtDNA mutation showed progressively decline of respiratory function and significantly enhancement of dependence on glucose in tumor growth, while cells with homoplasmic ND5 mutation inhibited tumor formation<sup>[85,86]</sup>.

## SIGNALING PATHWAYS REGULATED BY ROS IN CANCER

ROS-related pathways are considerably activated in many types of cancers. In particular, transient formation of H<sub>2</sub>O<sub>2</sub>, as second messengers, participates in growth, proliferation, and metabolism<sup>[87]</sup>. The level of intracellular ROS has a considerable influence on various signal pathways, including MAPK signaling cascades<sup>[88,89]</sup>, PI3K/Akt signaling cascades<sup>[90,91]</sup>, and I $\kappa$ B kinase/NF- $\kappa$ B signaling pathway<sup>[40,92]</sup>. Oxidative stress-mediated signaling involves all characters of cancer cell behaviors, such as cell survival, apoptosis, energy metabolism, angiogenesis, metastasis, and cancer stem cell generation. Researchers have noticed that some cancer cells show death or arrested growth when exposed to increased ROS, whereas others are able to eliminate even high levels of ROS for survival<sup>[93,94]</sup>. Emerging research indicates that modest in-



creases in ROS are oncogenic, whereas dramatic increases in ROS seem to suppress tumors<sup>[95]</sup>. GTPase Rac1 in the cytoplasm activates NF- $\kappa$ B and markedly blocks the activity of caspase-3 and TNF-induced apoptosis, whereas mitochondria-derived ROS promote TNF-induced apoptosis<sup>[96]</sup>. ROS generated by the newly described NOX5 are essential for prostate cancer growth<sup>[97]</sup>. NOX4-mediated ROS generation in extracellular matrix of cancer partially transfers cell survival signals through the Akt/apoptosis signal-regulating kinase 1 (ASK1) pathway in pancreatic cancer cells<sup>[98]</sup>. Inhibiting ROS with the antioxidants, NOX4 antisense, or MnSOD overexpression efficiently stimulates apoptosis in pancreatic cancer cells<sup>[99]</sup>. ROS produced by NADPH oxidase also inhibit protein tyrosine phosphatases (PTPs) and sustain the activation of Janus kinase 2 (Jak2)<sup>[91,100]</sup>.

### Proliferation and survival

The high intracellular ROS levels in cancer cells are largely the byproducts of the highly metabolic nature of these cells. These ROS levels could be protumorigenic, but also increase the susceptibility of cancer cells to cell death. High levels of ROS in cancer cells indicate hyperactive PI3K/Akt signaling generated by increased mitochondrial metabolism and by the suppression of antioxidant gene expression, through the inhibition of forkhead box O (FOXO) transcription factor<sup>[101]</sup>. In addition to elevating SOD2 and catalase, FOXO induces the expression of Sestrin3<sup>[102,103]</sup>. Sestrin3 is a member of a family of proteins that includes Sestrin1 and Sestrin2, which were originally identified as antioxidants induced by the tumor suppressor p53<sup>[104,105]</sup>. Thus, the suppression of Sestrins expression in cancer cells could increase intracellular ROS and activate mammalian target of rapamycin complex 1 (mTORC1). ROS produced by reactive oxygen species modulator 1 (Romo1), a mitochondria-localized protein<sup>[106-108]</sup>, are necessary to the ERK-dependent proliferation of lung cancer cells<sup>[108]</sup>. Similarly, high intracellular ROS levels generated by inactivation of antioxidant mechanisms has been connected with increased proliferation of breast<sup>[109]</sup> and ovarian<sup>[110]</sup> cancer cells.

Methionine sulfoxide reductase A (MsrA), a ROS scavenger, is down-regulated in a number of breast cancers. Moreover, reduction of MsrA levels results in increased ROS levels, which reduces the PTEN activity and activates PI3K pathway and leads to increased cell proliferation and a more aggressive cellular phenotype consequently<sup>[109]</sup>. Cancer cells adopt alternative mechanisms of antioxidation in order to maintain the intracellular level of ROS below a toxic threshold level<sup>[109-111]</sup>. Forkhead box M1 (FOXO1) is expressed at low levels in normal cells, but its expression is markedly elevated in cancer cells<sup>[111]</sup>. FOXO1 controls multiple pro-tumorigenic activities, but also reduces ROS levels through the transcriptional induction of SOD2, catalase, and mitochondrial-dependent peroxide reductase<sup>[112]</sup>. In addition, the expression of detoxifying enzymes such as GST and NQO1 are elevated in cancer cells<sup>[113,114]</sup>. The high intracellular ROS levels

generated by exogenous administration of ROS enhance the proliferation of several cancer types. Akt activity and cell growth are significantly stimulated by treating hepatoma cells with low concentration of ROS, which could be abolished by adding antioxidants. PI3K inhibitor, wortmannin, inhibits Akt phosphorylation induced by ROS<sup>[115]</sup>. In another study, monomethylarsonous acid (MMAIII), ROS inducer, induces proliferation and activation of MAPK pathway as well as up-regulation of COX-2 and EGFR in human urothelium cells<sup>[116]</sup>. Generally, COX-2 expression is induced by NF- $\kappa$ B, not CCAAT/enhancer binding protein (C/EBP) in chronic gastritis and gastric cancer. Sphingosine kinase 1 and Sphingosine-1-phosphate are required for TNF-induced COX-2 induction in lung cancer<sup>[117,118]</sup>.

### Apoptosis and necroptosis

Elevated intracellular ROS levels in cancer cells render these cells more vulnerable to oxidative stress-induced cell death. Therefore, cancer cells can be selectively killed without harming normal cells. Intracellular ROS levels in tumor cells are more likely to reach a threshold that triggers death after exposing to exogenous ROS-producing or -stimulating agents<sup>[119-121]</sup>. Apoptosis is prompted through extrinsic and intrinsic pathways<sup>[122]</sup>. In the extrinsic pathway, ROS are generated by ligation of cell surface death receptors [CD95(Fas), TNFR1, death receptor 3 (DR3), and DR5]. In turn, death receptor-ligand interaction leads to the subsequently activation of Fas-associated protein with death domain (FADD) and caspase-8<sup>[123-126]</sup>. In the intrinsic pathway, apoptosis is induced by mitochondria membrane disruption without involving death receptors. Subsequently, ROS activated by Bcl-2 family members, which are located in the outer mitochondrial membrane make pore. That results in cytochrome c release, apoptosome formation, and activation of caspases-3 and -7<sup>[127]</sup>. Exogenous administration of H<sub>2</sub>O<sub>2</sub> induces apoptosis in various cancer cells, including lymphoma cells<sup>[128]</sup>, leukemia cells<sup>[129,130]</sup>, hepatoma cells<sup>[42,131]</sup>, and bladder cancer cells<sup>[132]</sup> through the activation of MAPK signaling pathways.

ROS have been paid little attention in adaptive immunity because ROS production by the transformed and primary human B cells is very low compared to the levels of ROS are released by phagocytes<sup>[133,134]</sup>. However, later studies showed T cell receptor (TCR) or B cell receptor (BCR) engagement elicits ROS production transiently and superoxide controls pro-apoptotic and proliferative signal transduction, respectively<sup>[135,136]</sup>. In previous reports, we have shown that ROS might regulate apoptosis of lymphocytes directly or indirectly using EBV-transformed B cells as lymphoma or using an activated B cell model. Engagement of B7-H4, a negative regulator of T-cell mediated responses, induces the high levels of intracellular ROS and the expression of FasL. B7-H4 ligation induces Fas/FasL-mediated apoptosis through activation of caspase. Subsequently, cytochrome c, apoptosis-inducing factor (AIF), and endonuclease G (EndoG) are

released from the mitochondria on EBV-transformed B cells after stimulation of B7-H4<sup>[137]</sup>. B7-H1 stimulation in EBV-transformed B cells also induces both transcription and translation of FasL. B7-H1 stimulation activated the phosphorylation of JNK and down-regulated ERK1/2 and p-Akt. N-acetylcysteine (NAC), ROS scavenger, and SP600125 completely blocked the induction of FasL and activation of JNK. B7-H1-mediated apoptosis on EBV-transformed B cells may be involved in the induction of FasL, which is evoked by ROS generation and JNK activation after cross-linking of B7-H1<sup>[138]</sup>. Ligation of CD70, the ligand for CD27, expressed on EBV-transformed B cells induced production of ROS and triggered ER stress-mediated apoptosis *via* ROS generation and MAPK pathway activation. These reports suggest that ROS-mediated alternate signaling pathways induce apoptosis and provide information supporting ROS as a target against EBV-related tumors<sup>[139,140]</sup>. The present paradigm of cell death is caspase-dependent apoptosis, whereas necroptosis is a regulated through caspase-independent manner<sup>[141-143]</sup>. TNF $\alpha$ , FasL, and Trail, the same ligands that can initiate apoptosis also trigger the necroptosis. Receptor-interacting protein-1 (RIP-1) and RIP-3 play a critical role in TNF-induced necroptosis<sup>[144]</sup>. TNF-mediated ROS generation and their lethal action are confined to the inner mitochondrial membrane in L929 cells<sup>[145,146]</sup>. ROS scavenger butylated hydroxyanisole (BHA) efficiently blocks TNF-induced necroptosis. Interestingly, inhibitors of NF- $\kappa$ B facilitate TNF-induced necrotic cell death, suggesting that NF- $\kappa$ B suppresses the necrotic cell death pathway<sup>[147]</sup>. However, antioxidant treatment against ROS is unable to protect all cell lines from necroptosis<sup>[141,148]</sup>. Recent work revealed the critical role of RIP-3 kinase activity in linking TNFR1/RIP-1-associated events. RIP-3 binds RIP-1 through this unique C-terminal segment to inhibit RIP- and TNF receptor-1-mediated NF- $\kappa$ B activation and necrostatin-1, RIP-1 kinase inhibitor, prevents RIP-1/RIP-3 interaction from necroptosis<sup>[149,150]</sup>.

### Role of ROS in tumor cell dissemination

ROS mediate induction of matrix metalloproteinases (MMPs) involved in cancer invasion and metastasis. ROS have been reported to cause a significant increase in the production and expression of MMP-7. MMP-7 expression after H<sub>2</sub>O<sub>2</sub> exposure is mediated by AP-1-dependent MAPKs in colorectal cancer cells<sup>[151]</sup>. ROS also up-regulate Akt and CXCR4 expression as well as inactivating PTEN. ROS mediate CXCR4-dependent cell migration cancer progression in prostate cancer cells<sup>[152]</sup>. Meanwhile, Hydrogen peroxide and hydroxyl radical prevent migration of non-small cell lung cancer cell from inhibiting Caveolin-1 down-regulation<sup>[153]</sup>. TNF or ROS can induce p38 MAPK- and MMP-9-dependent angiogenesis of endothelial cells<sup>[154,155]</sup>. Furthermore, oxidative stress induced by H<sub>2</sub>O<sub>2</sub> stimulates angiogenesis and tumor progression by altering the gene expression of CXC chemokine ligand 14 (CXCL14) and IL-8 through the EGFR/MAPK signaling pathway<sup>[156]</sup>. EGF treatment induces

H<sub>2</sub>O<sub>2</sub> production, leading to activation of the Akt and vascular endothelial growth factor (VEGF) expression for angiogenesis in ovarian cancer cells<sup>[90]</sup>. Stimulation of tumor angiogenesis is connected with intracellular level of ROS. ROS regulate HIF-1 $\alpha$  and VEGF expression<sup>[157]</sup>. Antioxidant N-acetyl-L-aspartate (NAC) decreased vessels number *via* suppressing HIF-1 $\alpha$  expression in colon<sup>[158]</sup>, liver<sup>[159]</sup> cancer cells. Conditions of energetic stress could lead to oxidative stress. Cancer cells that consume high levels of glucose create energetic stress during the formation of solid tumors. Higher levels of stress may occur when cells detach from the matrix and translocate to the lumen or during metastasis<sup>[160]</sup>. Decreased glucose uptake during these processes suppresses ATP production and activates AMP-activated protein kinase (AMPK), but also inhibits the generation of NADPH *via* the pentose phosphate pathway. Reduced levels of NADPH result in increased intracellular ROS, which could eventually cause cell death<sup>[161,162]</sup>. However, the concomitant activation of AMPK elicits alternative mechanisms that maintain intracellular NADPH levels.

Several studies have reported that cancer-associated fibroblasts (CAFs) play a critical role in the metastatic spread of cancer cells<sup>[163,164]</sup>. ROS-controlled signaling mechanisms involved in myofibroblast differentiation have diverse cellular effects. Recent data from human breast cancers and animal models established that myofibroblasts are derived from bone marrow derived cells such as fibrocytes or mesenchymal stem cells<sup>[165,166]</sup>. Moreover, various mesenchymal cell types including endothelial cells, pericytes, or pre-adipocytes can also be converted into myofibroblasts in breast carcinomas as well as local resident fibroblasts<sup>[167-169]</sup>. Mitochondrial ROS generation results in expression of NOX4, an enzyme that is required for TGF- $\beta$ -driven conversion of fibroblasts into myofibroblasts<sup>[170]</sup>. In addition, fibroblasts suffering from chronic oxidative stress exhibit properties normally found in myofibroblasts<sup>[171]</sup>. Indeed, fibroblasts derived from mouse models exhibiting chronic oxidative stress (such as JunD<sup>-/-</sup> or NRF-2<sup>-/-</sup> mice, depleted for key anti-oxidant transcription factors) are converted into myofibroblasts<sup>[172]</sup>. Cancer cells themselves produce H<sub>2</sub>O<sub>2</sub>, which is a highly diffusible species. NOX enzymes, located at the plasma membrane in various carcinomas, might contribute to the production of H<sub>2</sub>O<sub>2</sub> and the conversion of surrounding fibroblasts into myofibroblasts<sup>[173]</sup>. The increase of ROS in the stromal fibroblasts results in the promotion of tumor cell motility and neo-angiogenesis, further increasing metastatic dissemination<sup>[174,175]</sup>. CAFs, similar to fibroblasts exposed to chronic oxidative stress, express genes that encode for proteases involved in extracellular matrix (ECM) remodeling, including collagens, cell adhesion molecules, and MMPs<sup>[171,173]</sup>. ROS remodel the ECM and create tracks for collective migration of tumor cells through the activation of Rho-dependent pathways<sup>[176]</sup>. Improved understanding of ROS functions in cancer progression or metastasis could therefore help pave the way for new concepts in therapy.

### ROS in hypoxia and tumor metabolism

As a cancerous tumor grows, the cancer cells repeatedly face limited oxygen supply due to the imbalance between growth rate and neovascularization. Cancer cells are able to adapt to oxidative stress and switch to glycolysis. Tumors utilize the Warburg effect, relying on glycolysis to supply energy for cancer cell survival<sup>[177]</sup>. The ROS released from mitochondria during the hypoxia act as signaling molecules that initiate diverse functional responses<sup>[178]</sup>. The increased ROS under low oxygen conditions, HIF-1 $\alpha$  becomes transcriptionally active and accumulates at low levels of manganese (Mn)-containing SOD (Mn-SOD) activity. However, at moderate levels of MnSOD activity, hypoxic induction of VEGF and HIF-1 $\alpha$  protein are suppressed in human breast carcinoma cells. This suggests that superoxide may contribute to accumulation of HIF-1 $\alpha$ <sup>[179]</sup>.

HIF-1 $\alpha$  expression has been correlated with poor prognosis and increased cancer cell invasiveness and recent studies have also shown that the antitumorigenic effect of antioxidants is HIF-dependent<sup>[180]</sup>. HIF-1 $\alpha$  regulates glycolysis-related genes in response to hypoxia and leads to glycolytic ATP generation<sup>[181,182]</sup>. However, it is not yet clear why tumor cells rely on glycolysis in the presence of oxygen and whether cellular ROS involved in regulation of glucose metabolism. ROS Accumulation and HIF-1 stabilization in CAFs results from the down-regulation of sirtuin-3 (SIRT3), a mitochondrial NAD-dependent deacetylase. HIF-1 $\alpha$  can work with SIRT3 to regulate CAF metabolism, driving to metabolic reprogramming towards glycolysis<sup>[183]</sup>. In addition, hydrogen peroxide stabilizes HIF-1 $\alpha$  thus leading to transcription of genes that code for signaling stromal cells such as macrophages and fibroblasts to support an invasive tumor cell phenotype. ROS-mediated HIF-1 $\alpha$  helps the tumor cell convert energy production from OXPHOS to glycolysis, a metabolic switch that has been associated with increased metastatic potential<sup>[184]</sup>.

### Generation of cancer stem cells using ROS

Stem cells can be difficult to obtain, which makes it challenging to directly evaluate the role of ROS and the regulatory mechanism in stem cells<sup>[185]</sup>. However, interesting research has been conducted using Hematopoietic stem cells (HSCs) in the bone marrow. HSCs are principally located in a low-oxygen environment, which allows long-term protection from ROS-related oxidative stress. The ROS<sup>low</sup> population has a higher self-renewal potential. In contrast, ROS<sup>high</sup> population expresses high levels of the activated p38 MAPK and mammalian target of rapamycin (mTOR)<sup>[186]</sup>. ROS production and NF- $\kappa$ B activation triggered by GTPase Rac 1 are critical events for facilitating tumorigenesis after APC loss<sup>[187]</sup>. In comparison with cancer cells, cancer stem cells (CSCs) also have a lower intracellular ROS content than non-CSCs, which is similar to HSCs and may be caused by the increased expression of antioxidant systems<sup>[38,188]</sup>.

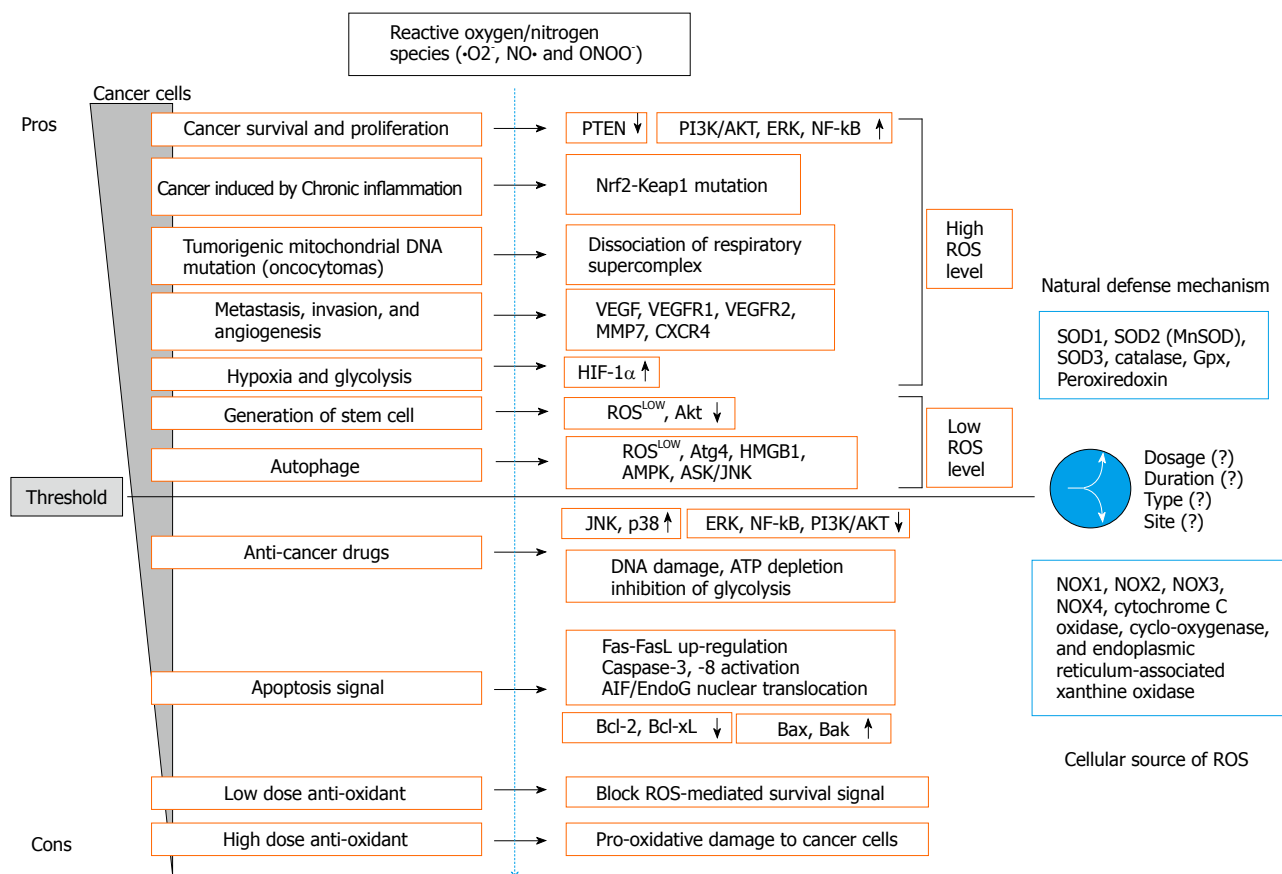
ROS<sup>low</sup> breast cancer cells are predominantly in quiescent phase of the cell cycle compared with ROS<sup>high</sup>

cells. The expression of ESR1 or MYC, which are both necessary for MCF7 proliferation in ROS<sup>low</sup> breast cancer cells do not change<sup>[189]</sup>. Since ROS are critical mediators of ionizing radiation induced-therapy and chemotherapy, the expression of antioxidants in CSCs prevented DNA damage and protected cells from irradiation- or drug-induced cell death<sup>[38]</sup>. Due to high levels of antioxidant signaling, cancer stem cells also may not be responsive to other (chemotherapeutic) treatments that target cancer cells by increasing intracellular ROS levels<sup>[52]</sup>. Niclosamide, antihelminthic agent, increases induces apoptosis through up-regulation of ROS in progenitor/stem cells from acute myelogenous leukemia (AML) patients as well as Niclosamide inhibits the transcription and DNA binding of NF- $\kappa$ B<sup>[190]</sup>. Niclosamide is synergistic with the frontline chemotherapeutic agents, such as cytarabine, etoposide, and daunorubicin<sup>[190]</sup>. The peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) is a ligand-dependent transcription factor belonging to the nuclear hormone receptor superfamily<sup>[191]</sup>. PPAR $\gamma$  agonists inhibit the stem cell-like features and repress tumor growth of human hepatocellular carcinoma (HCC) cells through NOX2-mediated ROS generation<sup>[192]</sup>. To date, it is unclear how ROS kill CSCs, although it does appear that ROS levels in normal or cancer environment may influence development and differentiation of stem cells<sup>[193]</sup>.

### ROS in autophagy

Autophagy is activated under stress conditions as protective process for the cell and in various pathological conditions, including cancer and neurodegenerative diseases<sup>[194-196]</sup>. One major breakthrough in both the understanding of autophagy regulation and its implication in cancer was the discovery of Beclin-1. Mutation of Beclin-1 is detected in human breast, ovarian, and prostate cancer<sup>[197]</sup>. Beclin-1<sup>(-/-)</sup> mutant mice die in early embryonic stage and Beclin-1<sup>(+/-)</sup> mutant mice have shown the decreased autophagy formation and suffer from a high incidence of spontaneous tumors<sup>[198]</sup>. Beclin-1 is the first identified tumor suppressor protein that functions in the lysosomal degradation pathway of autophagy. Bcl-2, a specific inhibitor for apoptosis, inhibits starvation-induced autophagy in cancer cells and mice through interacting with Beclin-1<sup>[199,200]</sup>. In addition, oncogenic signaling molecules, including class I PI3K, Akt, and mTOR suppress the macroautophagic pathway. However, PTEN and p53 stimulate autophagy<sup>[201-203]</sup>. Autophagy-related genes (Atg) 4, a direct target for oxidation by Intracellular H<sub>2</sub>O<sub>2</sub> generated during starvation, is regulated by conjugating Atg8 at the site of autophagosome formation via the lipidation of Atg8<sup>[204]</sup>. Low levels of ROS modify Atg4 and HMGB1 proteins, which activate AMPK and ASK1/JNK pathways or transactivate various proteins that could up-regulate autophagy, leading to reductions in apoptosis<sup>[205]</sup>. MAPKs, such as JNK and p38 MAPK, play a critical role in ROS-mediated autophagy events<sup>[206,207]</sup>. Meanwhile, activated ERK and JNK are also upstream





**Figure 1** The role of reactive oxygen species on cancer cells to explain the different effects at each condition. Reactive oxygen species (ROS) level inside cancer cell appears varied even within a given type of cancer cells. A so-called “double-edged sword strategy” uses to manipulate the opposite role of ROS sequentially to kill cancer cells more effectively. VEGF: Vascular endothelial growth factor; PI3K: Phosphoinositide-3 kinase; PTEN: Phosphatase and tensin homolog; HIF-1 $\alpha$ : Hypoxia inducible factor-1 $\alpha$ ; JNK: C-Jun N-terminal kinase; AMPK: AMP-activated protein kinase; SOD: superoxide dismutase; NOX: NAD(P)H oxidase.

effectors controlling both autophagy and apoptosis in response to elevated intracellular ROS<sup>[208]</sup>. Antioxidant, N-acetyl-L-cysteine (NAC), clearly reduces K-Ras-induced Atg5 and Atg7 induction, autophagy, and malignant cell transformation<sup>[209]</sup>. Starvation-induced production of  $\cdot\text{O}_2^-$  induces autophagy and cell death. Exogenous  $\text{H}_2\text{O}_2$  is effectively converted to intracellular  $\cdot\text{O}_2^-$  leading to autophagy-induced cell death. Overexpression of SOD2 and 3-methyladenine, autophagy inhibitor, attenuate starvation-induced autophagy<sup>[210]</sup>. 2-Methoxyestradiol inhibits SODs and induces autophagy-mediated cell death in the transformed or cancer cell lines, but not in astrocytes<sup>[210]</sup>. From these results, understanding the mechanisms that regulate the crosstalk between ROS and autophagy regulation is important for various disorders, including neurodegenerative diseases and cancer.

## ROS AS A THERAPEUTIC TARGET FOR CANCER TREATMENT AND PREVENTION

Many chemotherapeutic drugs are designed to increase cellular ROS levels with the goal of inducing irreversible damage, consequently resulting in tumor cell apoptosis. For example, intracellular ROS levels increase in a dose-dependent manner in A549 human lung cancer cells after

treatment with paclitaxel. Addition of NAC or GSH, two  $\text{H}_2\text{O}_2$  scavengers, induces a four-times increase in paclitaxel IC<sub>50</sub><sup>[211]</sup>. Combined treatment with trichostatin A and gemcitabine synergistically inhibits growth of pancreatic adenocarcinoma cell lines and induces apoptosis through the induction of ROS by gemcitabine<sup>[212]</sup>. Wogonin, a flavonoid isolated from *Scutellaria baicalensis*, synergistically sensitizes cancer cells to TNF-induced apoptosis through inhibition of catalase activity and an increase of cellular  $\text{H}_2\text{O}_2$ . Wogonin-induced ROS inhibit TNF-induced phosphorylation on the NF- $\kappa\text{B}$  p65 subunit<sup>[213]</sup>. Mutations in mitochondrial genes (mtDNA), such as the gene encoding cytochrome c oxidase II, are associated with increased ROS generation and involved in cancer initiation and progression<sup>[74-76]</sup>. However, the susceptibility of mitochondrial DNA to ROS-induced mutation may also be utilized for therapy<sup>[214]</sup>. Low levels of exogenous  $\text{H}_2\text{O}_2$  or  $\text{H}_2\text{O}_2$  produced by mitochondria induce a modest drop in ATP level, delayed toxicity, and G<sub>2</sub>/M arrest without affecting cell viability. Concomitant inhibition of glycolysis was found to markedly sensitize cells to death in the presence of nontoxic concentrations of  $\text{H}_2\text{O}_2$ <sup>[215]</sup>. Another approach to regulating intracellular ROS levels is the use of antioxidants to prevent tumor cells from entering the ROS-mediated survival signaling pathway. ROS, as sec-

ond messengers in signaling pathways, regulate not only kinase phosphorylation (MAPK, Rho kinase) but also transcription factors (NF- $\kappa$ B, AP-1, and HIF-1). ROS also up-regulate proto-oncogene and pro-inflammatory gene expression and activity<sup>[216,217]</sup>. The protective effects of antioxidants have generated significant interest in developing synthetic and natural antioxidants as therapeutic agents to prevent and/or treat patients with cancer.

Several clinical trials have been published regarding the effects of antioxidant vitamins on the risk of cardiovascular disease. However, clinical trial data has been inconsistent and inconclusive, until now<sup>[218]</sup>. Although oxidative stress against cancer cells induces apoptosis, several exogenous antioxidants also produce favorable effects in various cancer patients<sup>[219]</sup>. The major antioxidant vitamin systems include vitamin E, vitamin C, and GSH<sup>[220]</sup>. Vitamin C (ascorbic acid) is a water-soluble antioxidant involved in the reduction of radicals by recycling radicals produced by oxidation of vitamin E. A 20  $\mu$ mol/L rise in plasma ascorbic acid concentration is associated with an approximately 20% reduction in the risk of all-cause mortality. Ascorbic acid was inversely related to cancer mortality in men but not women<sup>[221]</sup>. In a study conducted in Japan, Vitamin C was found to reduce oxidative stress among subjects with atrophic gastritis<sup>[222]</sup>. However, Vitamins E and C, at high concentrations, also function as pro-oxidants causing cell damage<sup>[223]</sup>. Unfortunately, one report showed Vitamin E supplement significantly increased the risk of prostate cancer compared with placebo group and selenium combination group<sup>[224]</sup>. There is possibility that the bioavailability of anti-oxidants may be insufficient after oral administration, or that they may be inaccessible to the source of free radicals, particularly if ROS are generated in specific cellular compartments and organelles<sup>[225]</sup>. In addition, antioxidants do not inhibit the production of ROS; rather, they scavenge ROS after ROS has been generated. Selenium supplementation has been shown to reduce total and prostate cancer incidence but was not significantly associated with lung and colorectal cancer incidence<sup>[226]</sup>. In addition, selenium shows the most prominent protective effect on former male smokers<sup>[226]</sup>. However, the benefits of selenium were only observed in those patients with the lowest baseline blood selenium levels<sup>[226]</sup>. A phase II clinical trial about the effect of pomegranate for men reveals that prostate-specific antigen (PSA) doubling time is significantly extended after treatment with pomegranate juice in patients received surgery or radiotherapy. Further, a decrease in cell proliferation and an increase in apoptosis is observed in patients who consumed pomegranate<sup>[227]</sup>. Green tea is popular because it contains epigallocatechin gallate, a polyphenolic compound that provides potential benefits for prostate cancer control<sup>[228,229]</sup>.

Lycopene in tomato decreases serum prostate-specific antigen levels and oxidative DNA damage and increases apoptotic cells in carcinomas<sup>[230]</sup>. In another study, tomato sauce consumption suppresses the progression of prostate carcinoma<sup>[231]</sup>. Curcumin is also demonstrated

the inhibitory effects in colon carcinogenesis<sup>[232]</sup>.

## CONCLUSION

Daily fruits and vegetables intake has been inversely correlated to the risk of the development of chronic diseases, including cancer. Cancer is caused by both internal factors and environmental factors<sup>[233]</sup>. The link between diet and cancer indicates that cancer is a disease which can be prevented largely by lifestyle changes. In addition, ROS have plenty roles in carcinogenesis or anti-tumor effects though numerous pathways (Figure 1). Since ROS are involved in the transformation of nonmalignant cells to malignant cells, regulation of ROS can be a critical approach to prevent cancer development. ROS act as the second messenger for generating further intracellular events. ROS play a crucial role in tumorigenesis and cancer cell survival as well as apoptotic signaling in cancer cells. In biological systems, enzymatic and nonenzymatic systems have evolved to protect against oxidative damage. The potential of pro-oxidants or antioxidants in treating cancer associated with oxidative stress is reinforced by experimental researches, several clinical studies, and epidemiological data. Therefore, future studies should continue to clarify the different roles of ROS in cancer cells.

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