Cancer Letters 387 (2017) 95–105

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Reactive oxygen species (ROS) and cancer: Role of antioxidative nutraceuticals

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ARTICLE INFO

Keywords:
Cancer
ROS
Antioxidant
Transcription factors
Nutraceuticals

ABSTRACT

Extensive research over the past half a century indicates that reactive oxygen species (ROS) play an important role in cancer. Although low levels of ROS can be beneficial, excessive accumulation can promote cancer. One characteristic of cancer cells that distinguishes them from normal cells is their ability to produce increased numbers of ROS and their increased dependence on an antioxidant defense system. ROS are produced as a byproduct intracellularly by mitochondria and other cellular elements and exogenously by pollutants, tobacco, smoke, drugs, xenobiotics, and radiation. ROS modulate various cell signaling pathways, which are primarily mediated through the transcription factors NF-κB and STAT3, hypoxia-inducible factor-1α, kinases, growth factors, cytokines and other proteins, and enzymes; these pathways have been linked to cellular transformation, inflammation, tumor survival, proliferation, invasion, angiogenesis, and metastasis of cancer. ROS are also associated with epigenetic changes in genes, which is helpful in diagnosing diseases. This review considers the role of ROS in the various stages of cancer development. Finally, we provide evidence that nutraceuticals derived from Mother Nature are highly effective in eliminating cancer cells.

Introduction

Cancer is a major public health problem in the United States and in many other parts of the world. Recent reports indicate that 1 in 3 women and 1 in 2 men in the United States will develop cancer during their lifetime. It is the second leading cause of death in the United States and is expected to surpass heart diseases in the next few years. The American Cancer Society estimated that 1,685,210 new cases of cancer will be diagnosed and 595,690 individuals will die of cancer in 2016 in the United States [1]. According to the World Cancer Report (2014; http://www.who.int/mediacentre/factsheets/fs297/en/), more than 60% of the world's new cancer cases occur in Africa, Asia, and Central and South America; 70% of the world's cancer deaths also occur in these regions. In 2010, U.S. expenditures for cancer care were about $125 billion, and this cost could reach $156 billion by 2020. Several therapeutic modalities are available for cancer, which include chemotherapy, radiotherapy, and/or surgery. Because of improved care, better prevention options, and earlier diagnosis, death rates for many cancer types have also declined. However, rates for several other cancers have stabilized or have even increased.

Cancer is a genetic disease caused by both internal factors (such as inherited mutations, hormones, and immune conditions) and environmental/acquired factors (such as tobacco, diet, radiation, and infectious organisms). These factors modulate some important cellular elements including genes such as proto-oncogenes, tumor suppressor genes, and DNA repair genes through cellular intermediates [2]. Cellular intermediates are comparatively unstable but influence the cellular signaling pathways, which are primarily mediated through the following transcription factors: nuclear factor-κB (NF-κB), signal transducer and activator of transcription (STAT)-3, hypoxia-inducible factor (HIF)-1α, kinases, various growth factors, cytokines, and other proteins. One of the major cellular intermediates is reactive oxygen species (ROS), which are produced in all aerobic organisms. In low levels, ROS exhibit beneficial effects, whereas in excessive accumulation, ROS cause several disorders including carcinogenesis [3] (Fig. 1). In this review, we discuss the role of ROS in modulating various stages of tumor development and further consider how an antioxidative lifestyle could reduce the incidence of cancer.

Molecular basis of ROS production

ROS, produced by various biochemical and physiological oxidative processes in the body, are also associated with numerous physiological and pathophysiological processes. ROS play a major role in the pathogenesis of various human diseases. At low concentrations, ROS exhibit beneficial effects by regulating intracellular

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http://dx.doi.org/10.1016/j.canlet.2016.03.042
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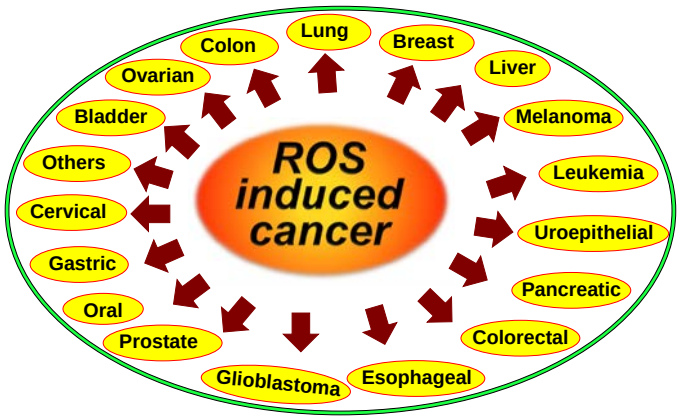

Fig. 1. Excessive production of reactive oxygen species (ROS) causes progression of multiple cancers.

signaling and homeostasis; at high levels, however, ROS play a major role in the damage of proteins, lipids, and DNA [3]. Antioxidant defense systems in the human body maintain the balance between the production and neutralization of ROS and include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione S-transferase (GST), and glutathione (GSH) [4]. However, imbalances between ROS and antioxidant defense systems lead to oxidative stress, which initiates carcinogenesis [5]. ROS have also been implicated in the mediation of apoptosis in cancer cells [6,7].

ROS are oxygen-derived small molecules that include oxygen radicals [superoxide ($O_2^{\bullet-}$), hydroxyl (•OH), peroxyl ($RO_2^{\bullet}$), and alkoxyl ($RO^{\bullet}$)] and certain nonradicals that are either oxidizing agents or are easily converted into radicals, such as hypochlorous acid (HOCl), ozone (O_3), singlet oxygen ($^1O_2$), and hydrogen peroxide (H_2O_2). ROS are produced inside the cells both by endogenous and exogenous sources. Endogenous ROS are produced as a byproduct in subcellular organelles such as mitochondria, peroxisomes, and cytochrome P-450. Exogenous sources of ROS are pollutants, tobacco, smoke, drugs, xenobiotics, radiation, and other mediators (Fig. 2). Ionizing radiation produces ROS through interaction with water. Upon interaction, water loses an electron and is sequentially converted into a hydroxyl radical ($^{\bullet}OH$), hydrogen peroxide (H_2O_2), a superoxide radical ($O_2^{\bullet-}$), and ultimately oxygen (O_2) [8]. However, intracellular ROS are produced through multiple mechanisms, depending on the cell and tissue types. One of the major sources of intracellular ROS is NADPH oxidase (NOX), the enzyme system that primarily generates ROS instead of generating ROS as a byproduct.

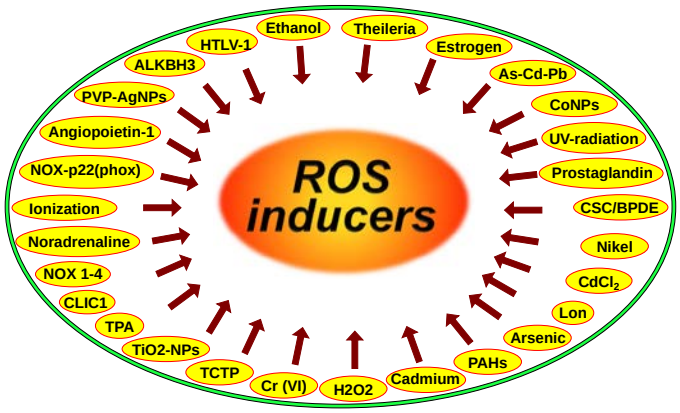

Fig. 2. Various factors contributing to the generation of reactive oxygen species (ROS).

NOX complexes are found in 7 distinct isoforms, including NOX1, NOX2 ($gp91^{phox}$), NOX3, NOX4, NOX5, DUOX1, and DUOX2, in cell membranes, mitochondria, peroxisomes, and endoplasmic reticulum [9]. A high level of ROS in any normal cell can convert it into a malignant cell and thus plays an important role in the various stages of cancer (Table 1). The development of cancer mediated by ROS involves various signaling molecules (Table 2).

Role of ROS in transformation

Transformation is the process in which the cellular and molecular makeup of a cell is altered as it becomes malignant. Numerous reports have described the role of ROS in the transformation of nonmalignant to malignant cells. ROS, generated exogenously or endogenously, first counteract cellular defense mechanisms such as antioxidants. Under the dynamic nonequilibrium of ROS, an antioxidant usually induces DNA damage. The accumulation of DNA damage through misrepair or incomplete repair may lead to mutagenesis and consequently transformation, particularly if combined with a deficient apoptotic pathway [10]. Furthermore, ROS generated by different metals such as arsenic, cadmium, and lead can result in cell transformation. In a recent study, subchronic exposure to arsenic induced BEAS-2B cell transformation that was accompanied by increased ROS generation [11]. Another study showed that arsenite-induced cell transformation by ROS is mediated through activation of AKT, ERK1/2, and p70S6K1 [12]. Zhang et al. [13] also observed that arsenic enhanced both transformation and tumorigenesis of DLD1 cells, possibly through a ROS-mediated Wnt/β-catenin pathway. These findings are further supported by the fact that antioxidants can inhibit arsenite-induced cell transformation [14].

ROS are implicated in cellular transformation induced by other metals as well. For example, cadmium was shown to induce malignant transformation of human bronchial epithelial cells by increased expression of HIF-1α and VEGF through ROS, ERK, and AKT signaling pathways [15]. Chronic exposure to low doses of chromium (0.125, 0.25, and 0.5 μM) promoted ROS generation and NOX subunit expression, such as p47 (phox) and p67 (phox), and inhibited the expression of antioxidant enzymes, which resulted in the transformation of BEAS-2B cells [16]. A mixture of metals (arsenic, cadmium, and lead) was shown to induce morphological cell transformation only when these metals acted as initiator stimuli, probably through the production of ROS [17].

Short-term exposure to cobalt nanoparticles induced ROS in MEF cells. However long-term exposures induced cell transformation of MEF cells, probably through higher production of ROS [18]. Another nanoparticle, nano-TiO_2, also disturbed cell cycle progression and duplicated genome segregation, leading to chromosomal instability and cell transformation [19]. In addition, cigarette smoke condensate and $CdCl_2$ treatment in MCF-10A cells increased ROS. Thus, the heavy metals present in cigarettes of Indian origin may substantially contribute to transformation and tumorigenesis by inducing intercellular ROS accumulation and increased expression of PI3K, AKT, and NF-κB proteins [20]. Long-term carcinogen exposure has been shown to lead to malignant transformation of nontumorigenic lung epithelial cells by NO-mediated S-nitrosylation and stabilization of Bcl-2 protein [21]. Another carcinogen, BPDE, also induced transformation of human bronchial epithelial cells, and this transformation was significantly reduced by suppression of RIP1 expression. Thus, RIP1 promotes malignant transformation by protecting DNA-damaged cells against carcinogen-induced cytotoxicity associated with excessive ROS production [22].

Besides heavy metals, oncogenes induce ROS production, which subsequently contributes to cellular transformation. It has been shown that oncogene K-Ras induced ROS generation by activation of NADPH oxidase 1 (NOX1), which is a critical regulator for K-Ras–induced cellular transformation. Moreover, translationally controlled

Table 1
Involvement of ROS at various stages of tumorigenesis.

ROS inducer/mediator	Cancer type	Reference	ROS inducer/mediator	Cancer type	Reference
Transformation			Cl-intracellular channel 1	Colon cancer	[53]
Chromium (VI)	Lung cancer	[10]	Pancreatic stellate cells	Pancreatic cancer	[54]
As–Cd–Pb metals	Fibroblast	[11]	Epidermal growth factor	Prostate cancer	[55]
Cobalt nanoparticles	Embryonic fibroblast	[12]	Mitochondrial dysfunction	Breast cancer	[56]
Oxidant therapy	Melanoma	[13]			
Cigarette smoke	Breast cancer	[14]	Tumorigenic macrophage	Melanoma	[57]
Theileria	Several cancer	[15]	Ionizing radiation	Breast cancer	[58]
Benzo[a]pyrene	Lung cancer	[16]	Ethanol	Breast cancer	[59]
Nickel	Mesenchymal stem cells	[17]	Caveolin-1	Lung cancer	[60]
Prostaglandins	Gastric cancer	[18]	BLT2	Bladder cancer	[41]
Arsenic	Lung cancer	[19]	Obg-like ATPase 1	Breast cancer	[61]
4-Hydroxy estradiol	Breast cancer	[20]	Tks – adaptor proteins	Multiple cancer	[62]
Arsenic	Lung cancer	[21]	Ethanol	Breast cancer	[56]
FMS-like tyrosine kinase 3	Acute myeloid leukemia	[22]	***Cancer cell metastasis***		
Cadmium	Lung cancer	[23]	Monoamine oxidase A	Prostate cancer	[63]
Sodium arsenite	Multiple cancers	[24]	TGF-β	Breast cancer	[64]
Arsenic	Colorectal adenocarcinoma	[25]	BLT-2	Ovarian cancer	[65]
Chromium (VI)	Lung cancer	[26]	Low-dose of capsaicin	Colorectal cancer	[66]
Arsenite	Lung cancer	[27]	Thioredoxin-like-2	Breast cancer	[67]
TCTP	Breast epithelial cells	[28]	BLT2	Bladder cancer	[68]
NO-S-nitrosylation	Several cancer	[29]	***Angiogenesis***		
HTLV-1 Tax	T-cell leukemia	[30]	Cyclosporin A	Endothelial cells	[69]
Ionizing radiation	Embryonic fibroblasts	[31]	Arsenic	Bronchial epithelial cells	[70]
TiO2 nanoparticles	Multiple cancers	[32]	Arsenic	Uroepithelial carcinoma	[71]
Methylarsonous acid	Bladder urothelial cells	[33]	RRM2 up-regulation	Cervical cancer	[72]
UVB radiation/Cd	JB6P+ cancer cells	[34]	Ethanol	Colon cancer	[73]
v-Rel	Macrophage cell	[35]	ALKBH3	Uroepithelial carcinoma	[74]
Cancer cell survival			NADPH oxidases	Several cancer	[75]
Lithium chloride	Colorectal cancer cells	[36]	PVP-AgNps	Skin cancer	[76]
BRCA	Breast cancer	[37]	Arsenic	Several cancer	[77]
Dickkopf1	Lung cancer	[38]	PKCδ activator	Prostate cancer	[78]
Lon protease	Multiple cancers	[39]	Hypoxia-inducible factor	Colon cancer	[79]
BLT2	Bladder cancer	[40]	VDUP1	Endothelial cells	[80]
BLT2	Breast cancer	[41]	Angiopoietin-1	Vein endothelial cells	[81]
Extracellular matrix	Pancreatic cancer	[42]	JunD-deficiency	Several cancer	[82]
Cancer cell proliferation			VEGF, TGF-α, β-FGF	Vascular diseases	[83]
Lon expression	Bladder cancer	[43]	Hydrogen peroxide	Several cancers	[84]
p66Shc protein	Ovarian cancer	[44]	***Epigenetics of cancer cell***		
Cancer-derived IgG	Breast cancer	[45]	Ionizing radiation	Several cancer	[85]
Peroxiredoxin	Breast cancer	[46]	DNA methylation	Several cancer	[86]
Rac1/APC loss	Colorectal cancer	[47]	Histone H3K9 trimethylation	Breast cancer	[87]
LGR5 induction	Colon cancer	[48]			
GRP94 upregulation	Breast cancer	[49]	Caudal type homeobox-1	Colorectal cancer	[88]
Sodium arsenite	Breast cancer	[50]	RUNX3 methylation	Colorectal cancer	[89]
Hemoglobin	Colon cancer	[51]	DNA methyltransferases	Several cancer	[90]
Cancer cell invasion			Histone deacetylases	Lung cancer	[91]
Adrenaline/noradrenaline	Breast cancer	[52]	E-cadherin methylation	Hepatocellular carcinoma	[92]

APC, adenomatous polyposis coli gene; BLT2, a receptor for leukotriene B(4) LTB(4) and 12(S); HETE, hydroxyeicosatetraenoic acid; HTLV-1 Tax, human T-cell leukemia virus type I; LGR5, leucine-rich repeat G; PKCδ, protein-coupled receptor 5 activator; ψδRACK, ψδ receptor for active C kinase; PVP-AgNps, polyvinylpyrrolidone-coated silver nanoparticles; TCTP, translationally controlled tumor protein; Tks, tyrosine kinase substrate; VDUP1, vitamin D3 up-regulated protein 1.

tumor protein was implicated in cell growth and malignant transformation through enhanced NOX-dependent ROS generation [23]. Conversely, Bach1, a gene associated with ROS metabolism, has been found to be a repressor of the oxidative stress response. Thus, Bach1 is critical for the transformation of mouse embryonic fibroblasts by Ras (V12) and ERK signaling [24]. Another oncogenic catechol estrogen, 4-hydroxyestradiol (4-OHE_2), has been shown to produce ROS, which further leads to activation of IKKβ–NF-κB signaling and induction of COX-2 expression in MCF-10A cells [25]. The HTLV-1 proto-oncogene Tax mediates DNA damage, which is believed to be essential in initiating the transformation process [26]. Besides these, v-Rel, the oncogenic member of the Rel/NF-κB family of transcription factors, transformed lymphoid cells and fibroblasts and activated telomerase. The expression of v-Rel in a macrophage cell line resulted in elevated levels of ROS that were involved in cellular transformation [27].

The modulation of transcription factors is another mechanism by which ROS induce transformation. In one study, it was found that hypoxia modulated the activity of three critical transcription factors (c-MYC, p53, and HIF-1α), resulting in ROS accumulation and causing hMSCs to undergo cellular transformation [28]. HIF-1α activation is also essential for host leukocyte transformation, since inhibition of HIF-1α, or treatment with antioxidants, led to a marked reduction in transformed phenotype. Thus, stabilization of HIF-1α, after increased ROS production, modulated cell transformation [29]. Besides HIF-1α, HIF-2α also drives the malignant transformation process in hypoxic cells and in cells affected by low glucose [30]. Activating protein-1 (AP-1) is one of the transcription factors rapidly activated by elevated intracellular ROS levels. AP-1 has been shown to be important in cellular transformation and in tumor progression [31]. Yang et al. [32] also reported a significant increase of ROS during JB6P+ cell transformation. These researchers found that an increase in ROS production contributed to Ref-1 reduction and to a decrease in AP-1 transcription activities in JB6P+ cells [32]. Prostaglandin reductase 2 is also known to modulate ROS-mediated transformation of gastric cancer cells [33]. MAPK activation has been found to be crucial in phenotypic changes associated with transformation in MSC52 cells, where ROS play a role in maintaining the

Table 2
Molecular targets of ROS inducers involved in tumorigenesis.

ROS inducer(s)	Molecular mechanism/targets	Reference
As–Cd–Pb mixture	Acts as promoter and stimulant to avoid the senescence	[11]
Cobalt nanoparticles	Induce acute toxicity and oxidative DNA damage	[12]
UV radiations	Upregulate RAS/RAF/ERK1/2, PI3K/AKT pathway, RAC1 and NF-κB	[13]
$CdCl_2$ and CSC	Increase in the expression of PI3K-AKT-NF-κB	[14]
Theileria	Stabilizes HIF-1α, increase ROS, and modulates glucose metabolism	[15]
CSC/BPDE	Activates MAPKs, including JNK, ERK and p38	[16]
Nickel and hypoxia	Increase the expression of c-MYC, p53, and HIF-1α	[17]
Prostaglandin reductase 2	Activates ERK1/2, caspase 3, Bcl-2 and suppressed Bax expression	[18]
Arsenic	Increases ROS generation and autophagy activation	[19]
4-Hydroxyestradiol	Induces activation of IKKβ, NF-κB signaling and COX-2 expression	[20]
Cadmium	Increases HIF-1α/VEGF expression through ROS/ERK/AKT signaling	[23]
Arsenite	Activates ROS, AKT, ERK1/2, and p70S6K1	[24]
Arsenic	Activates β-catenin and Wnt signaling pathway	[25]
Hexavalent chromium	Increases NOX activity and expression of subunits (p22(phox), p47(phox), p40(phox), and p67(phox))	[26]
Arsenite	Induces ROS-mediated Ras/Erk pathway	[27]
TCTP	Involves Src-dependent EGFR transactivation	[28]
HTLV-1 Tax	Induces ROS, chromosomal instability and DNA damage	[30]
TiO_2 nanoparticle	disturbs cell cycle progression and chromosomal stability	[31]
Monomethylarsonous acid	Activates MAPK signaling and upregulation of COX-2 and EGFR	[33]
UVB radiation/H_2O_2/Cd	Induces JunB and Fra-1 in AP-1 DNA binding complexes	[34]
UVB radiation/H_2O_2/Cd	Reduces the Ref-1 and AP-1 transcription activities	[93]
Lon protease	Induces ROS, MAPK and Ras-ERK signaling pathway	[39]
H_2O_2	Activates c-Met-PI3K-AKT and c-Met-Grb2/SOS-Ras-p38 pathways	[94]
Lon suppression	Suppresses JNK phosphorylation	[43]
Estrogen	Elevates p66Shc protein with ROS, ErbB-2 and ERK/MAPK activation	[44]
Cancer-derived IgG	Induces the production of ROS	[45]
Sodium arsenite	Induces DNA oxidative damage, HO-1, c-Myc protein expression and NF-κB activation	[50]
Noradrenaline	Induces the gene expression of HMOX1, MMP-2, and MMP9	[52]
CLIC1	Upregulates ROS/ERK pathway under hypoxia-reoxygenation	[53]
Ionizing radiation	Activation of ErbB2-dependent signaling, FoxM1, and MMP2	[58]
Ethanol	Expresses high levels of ErbB2	[59]
Ethanol	Activates JNKs, p38 MAPK and ROS in ErbB2 overexpressing cells	[56]
Arsenic	Induces COX-2 expression through HIF-1α regulation	[70]
Arsenic	Induces HIF-1α, VEGF and COX-2 expressions	[71]
Ethanol	Induces ROS generation, NADPH oxidase activation, and upregulation of PI3K/AKT and hypoxia-inducible factor 1 alpha (HIF-1α) signaling	[73]
ALKBH3	Activates NADPH oxidase and tweak/Fn14/VEGF signaling pathway	[74]
PVP-AgNPs	Activation of FAK, AKT, ERK1/2, and p38MAPK	[76]
Arsenic	Activates AKT, ERK1/2 and increases HIF-1α and VEGF expression	[77]
Angiopoietin-1	Activation of p44/42 MAPK, AKT signaling pathway	[81]
Monoamine oxidase A	Induces epithelial-to-mesenchymal transition and stabilize HIF-1α	[63]

BPDE, benzo[a]pyrene diol epoxide; CLIC1, chloride intracellular channel 1; CSC, cigarette smoke condensate; HTLV-1 Tax, human T-cell leukemia virus type I; PVP-AgNPs, polyvinylpyrrolidone-coated silver nanoparticles; TCTP, translationally controlled tumor protein; TPA, 12-O-tetradecanoylphorbol-13-acetate.

phenotypic characteristic [34]. p38-MAPK has been shown to play a role in p47 (phox)-NOX1–dependent ROS generation and consequent transformation of cells [35].

Role of ROS in tumor survival

Numerous findings in the past several years have indicated that ROS play a crucial role in the survival of cancer cells. Edderkaoui et al. [36] showed that ROS produced by an extracellular matrix increased pancreatic cancer cell survival through 5-lipoxygenase and NOX. These authors found that fibronectin stimulated ROS production through activation of NOX [36]. Another study showed that ROS produced by NOX4 mediated the antiapoptotic effect of growth factors. ROS inhibited protein tyrosine phosphatases and thus sustained the activation of kinases mediating antiapoptotic pathways in pancreatic cancer cells. Finally, NOX promoted pancreatic cancer cell survival by inhibiting JAK2 dephosphorylation by tyrosine phosphatases [37].

Survival of cells by elevated ROS has also been associated with expression of leukotriene B_4 receptor, BLT2, which is evident by the knockdown of NOX1 or by treatment with a ROS scavenging agent, which caused dramatic apoptotic death in these breast cancer cells. Thus, the BLT2-NOX1/NOX4-ROS cascade is linked to the pro-survival signaling of cells [38,39]. In non–small cell lung cancer (NSCLC), NOX4 has been shown to interplay with IL-6 to promote cell proliferation and survival. Thus, IL-6/STAT3 and NOX4/AKT signaling reciprocally and positively regulated each other, leading to enhanced NSCLC cell proliferation and survival [40].

The increased level of mitochondrial ROS was shown to promote cell proliferation, cell survival, cell migration, and epithelial–mesenchymal transition through mitogen-activated protein kinase (MAPK) and Ras-ERK activation [41]. It has also been reported that activated O_2 ($\bullet^-$) and H_2O_2 mediated cell survival in NSCLC A549 cells via c-Met-PI3K-AKT and c-Met-Grb2/SOS-Ras-p38 pathways [42]. ROMO1 is another molecule that enhanced ROS production and cell survival through the strict modulation of DKK1 expression [43].

Some hereditary cancers associated with key mutations, such as the BRCA mutation in breast cancer, generally lead to increased ROS and ultimately to repression of mitochondrial activities and other ROS-associated signaling and to continuous cell division for survival [44]. Overexpression of ROS quencher manganese superoxide dismutase has been shown to promote the survival of prostate cancer cells [45]. However, depending on the source, the site of production, the specific species, concentration, and time, ROS may also induce cell death in some cell types [46]. In fact, most of the currently available cancer therapeutics are based on their ability to induce ROS production [7].

Role of ROS in tumor cell proliferation

The role of ROS in tumor cell proliferation has been reported in a number of experimental systems. In one study, exogenous H_2O_2 at a low concentration promoted cell proliferation by increasing intracellular ROS levels [47]. H_2O_2 treatment induced LGR5 expression and caused cell proliferation via the JNK signaling pathway in colon cancer cells. In addition, β-catenin was increased in H_2O_2-treated colon cancer cells [48]. Cancer-derived IgG also enhanced the growth and proliferation of cancer cells by inducing the production of ROS at a low level [47]. Other molecules such as hemoglobin have been shown to induce colon cancer cell proliferation by release of ROS [49]. It has also been observed that estrogen (E2) treatment in CaOV-3 cells caused increased ROS level and enhanced cell proliferation [50]. Furthermore, the use of ROS scavengers can suppress cancer cell transformation. Suppression of Mn-SOD expression by small interfering RNA caused an increase of superoxide in ovarian cancer cells, which leads to stimulation of cell proliferation *in vitro* and more aggressive tumor growth *in vivo* [51]. Suppression of the Lon molecule, an inducer of ROS, in bladder cancer cells also blocked cancer cell proliferation by suppressing JNK activation, since expression of Lon in bladder cancer tissues is significantly higher than expression in noncancerous tissues [52].

Numerous signaling molecules have been shown to be involved in ROS-induced proliferation of cells. Muniyan et al. [50] observed that increased ROS elevated the p66Shc protein level, ErbB-2 level, and ERK/MAPK activation for cell proliferation. Moreover, overexpression of GRP94 in breast cancer cells also promoted high levels of cancer cell proliferation and migration, whereas silencing of this protein inhibited cell proliferation and migration activities [53]. ROS have been shown to regulate the proinflammatory transcription factor, NF-κB, which in turn controls the expression of signaling molecules associated with tumor cell survival. In one study, RAC1 triggered ROS production, and NF-κB activation was found to facilitate WNT-driven intestinal stem cell proliferation and colorectal cancer initiation [54]. In another study using human breast cancer MCF-7 cells, sodium arsenite induced ROS generation, DNA oxidative damage, HO-1 and c-MYC proteins, NF-κB activation, and further proliferation of cells. This study suggested that these factors play a relevant role in arsenite-induced MCF-7 cell recruitment into the S-phase of the cell cycle and in cell proliferation [55].

Role of ROS in tumor cell invasion

ROS targets several major signaling molecules, including kinases and transcription factors, which are known to be involved in migration and invasion of cancer cells. Studies have shown that cells exhibiting ROS had higher migration and invasive behaviors [56]. Ethanol was shown to induce ROS generation and to promote migration/invasion of breast cancer cells [57]. Endogenous catecholamines such as adrenaline and noradrenaline also produced ROS and promoted invasion of MDA-MB-231 human breast cancer cells through β_2-adrenergic signaling. In addition, noradrenaline treatment induced gene expression of heme oxygenase-1 (HO-1), matrix metalloproteinase (MMP)-2, and MMP-9 [58]. High levels of ROS have also been implicated in the invasiveness of primary melanoma cells. Furthermore, increased secretion of tumor necrosis factor α, translocation of peroxisome proliferator-activated receptor γ (PPARγ), and activation of MAPK/ERK kinase 1 were found to be ROS-dependent [59].

The inhibition of ROS with antioxidants was shown to prevent radiation-induced invasion [60]. Catalase, an antioxidant, inhibited the migration and invasion ability of lung cancer cells by controlling the production of ROS, thereby regulating cathepsin activity [61]. Polyphenol treatment also inhibited invasion of tumor cells into embryonic stem cell–derived vascularized tissues through decreased ROS generation and down-regulated MMP-9 expression [62]. ROS induced Src and ERK in A549 human NSCLC cells. Suppression of ROS by maclurin led to suppression of Src/FAK and ERK signaling and activated GSK3-β, thus inhibiting nuclear accumulation of β-catenin and further attenuating the migration and invasion of A549 cells [63]. Expression of Obg-like ATPase 1 (OLA1) has also been associated with production of ROS and migration and invasion in breast cancer cell line MDA-MB-231. Knockdown of OLA1 decreased the ROS level and further inhibited cell migration and invasion [64]. STMN1 expression and the PI3K-AKT-mTOR pathway were also found to be involved in ROS-induced and ITGB3-mediated migration and in the invasion of colorectal cancer cells. Thus, ITGB3 plays an important role in ROS-induced migration and invasion in colon cancer cells [65].

In addition to these tumor cell inhibitors, chloride intracellular channel 1 (CLIC1) regulated colon cancer cell migration and invasion through the ROS/ERK pathway. Furthermore, ROS production increased the expression of MMP-2 and MMP-9, which is regulated by CLIC1-mediated invasion of cells [66]. Hypoxia can induce ROS that can lead to HIF-1α stabilization and GLI1 up-regulation [67]. HIF-1α along with TWIST1 is a known modulator of cancer cell invasion and metastasis. The ROS scavenger N-acetyl-L-cysteine (NAC) significantly reduced EGF-induced HIF-1α expression and further cancer cell invasion and metastasis [68]. Another molecule, Cav-1, plays an important role in the migration and invasion of human lung carcinoma H460 cells and is regulated by cellular ROS. It has been shown that the hydroxyl radical up-regulated Cav-1 expression and promoted cell migration and invasion [69]. BLT2 also mediated invasiveness through a signaling pathway dependent on NOX1- and NOX4-induced generation of ROS and subsequent NF-κB stimulation [70].

ROS also regulated urokinase-type plasminogen activator (uPA) expression and cell invasion via MAPK pathways after treatment with hepatocyte growth factor in stomach cancer cells. Treatment with NAC decreased the enhancement of uPA production and tumor invasion in cells. HGF regulated Rac-1–induced ROS production through the AKT pathway, and ROS regulated uPA production and invasion via MAP kinase, which provides novel insight into the mechanisms underlying the progression of gastric cancer [71].

Role of ROS in tumor cell angiogenesis

High levels of ROS such as superoxide and H_2O_2 are observed in various cancer cells. Accumulating evidence suggests that ROS function as signaling molecules to mediate various growth-related responses including angiogenesis. Wartenberg et al. [72] showed that increased levels of ROS in confrontation cultures resulted in high expression of MMPs [72]. In ischemic reperfused hearts, ROS have been found to stimulate angiogenic response. Short exposure to hypoxia/reoxygenation produced ROS, which further increased angiogenesis or neovascularization [73]. The role of ROS in angiogenesis can be further confirmed by using ROS quenchers. Moriyama et al. [74] showed that antioxidant micelles can inhibit angiogenesis by scavenging ROS. ROS scavenger vitamin E also inhibited angiogenesis by suppressing MMP expression [72]. Rosmarinic acid exhibited antiangiogenic potential by reducing intracellular ROS levels, H_2O_2-dependent VEGF expression, and IL-8 release of endothelial cells. These findings suggested that ROS has an important role in tumor angiogenesis [75].

Numerous inducers of ROS have been reported to be involved in angiogenesis. Cyclosporin A treatment of endothelial cells *in vitro* increased mitochondrial ROS that promotes tumor angiogenesis in a calcineurin-independent manner. Also in the *in vivo* model of skin carcinogenesis, prolonged treatment with cyclosporin A promoted tumor growth and angiogenesis, probably by increasing ROS [76]. ROS production by chronic arsenic exposure has been revealed

to cause angiogenesis in human bronchial epithelial cells by regulating the angiogenic factors miR-199a-5p, HIF-1α, and COX-2 [77]. Arsenic also induced the expression of other angiogenesis-related factors such as PI3K and MAPK in SV-HUC-1 human uroepithelial cells by increasing ROS [78]. Moreover, ethanol markedly enhanced arsenic-induced tumor angiogenesis *in vitro*. These responses have been shown to be related to intracellular ROS generation, NOX activation, up-regulation of PI3K/AKT, and hypoxia-inducible factor 1 alpha (HIF-1α) signaling. Antioxidant enzymes inhibited arsenic/ethanol-induced tumor angiogenesis, demonstrating the role of ROS in arsenic- and ethanol-induced angiogenesis [78,79].

The major source of ROS is NADPH oxidase, which consists of NOX1, NOX2, NOX4, NOX5, p22phox, p47phox, and the small G-protein Rac1 [80]. ROS derived from NOX are critically important for angiogenesis both *in vitro* and *in vivo* by regulating VEGF and other signaling molecules [81]. This is evident by the fact that NOX4 knockdown reduced ROS production and suppressed glioblastoma cell angiogenesis and increased their radiosensitivity *in vitro* [82]. NOX4 knockdown also decreased the levels of VEGF and HIF-1α and tumor angiogenesis in ovarian cancer cells. These studies provide strong evidence that endogenous ROS play an important role in cancer cells to induce angiogenesis and tumor growth [83]. In prostate cancer cells, NOX subunit p22 (phox) mediated ROS generation that contributed to angiogenesis and tumor growth through AKT and ERK1/2 signaling pathways [84]. Moreover, superoxide and H_2O_2 caused blood vessels to thicken, leading to inflammation in the vessel wall, which is important in inducing angiogenesis. Another *in vitro* study revealed that ROS produced by an RRM2 molecule activated the ERK1/2 pathway. RRM2 also enhanced capillary tube formation and angiogenesis that was dependent on VEGF expression [85]. Besides these factors that lead to angiogenesis, tumor angiogenesis by melanoma cells was shown to be dependent on activated levels of NF-κB, which is activated by ROS [86].

It has also been found that silver nanoparticle–induced generation of ROS is associated with induced endothelial cell tube formation and with production of angiogenic factors, such as vascular endothelial growth factor (VEGF) and nitric oxide (NO) in SVEC4-10 cells [87]. One study showed that treatment with a specific protein kinase (protein kinase C-δ) increased the growth and angiogenesis of PC-3 xenografts by increasing the levels of HIF-1α, VEGF-, and CD31-positive cells. Mechanistically, protein kinase C-δ activation increased the levels of ROS and HIF-1α by binding to and phosphorylating NOX [88]. Since ROS are critical for angiogenesis, the role of vitamin D3 up-regulated protein 1 in angiogenesis and endothelial proliferation has also been observed. Vitamin D3 up-regulated protein 1 increased ROS production and angiogenesis of Ras-overexpressing endothelial cells [89]. Angiopoietin-1 (Ang1) also mediated angiogenesis by enhancing ROS production. Human umbilical vein endothelial cells treated with Ang1 produced ROS transiently, which further activated p44/42 MAPK and delayed the deactivation of AKT phosphorylation involved in *in vitro* endothelial cell migration, *in vivo* tubule formation, and angiogenesis [90].

Role of ROS in metastasis

Cancer metastasis is the major cause of cancer-related mortality. Accumulated evidence has suggested that highly metastatic cancer cells contain high levels of ROS. The role of ROS in metastasis is also supported by the fact that ROS attenuation by antioxidants suppressed hypoxia-induced metastasis of human pancreatic cancer cells in a xenograft nude mouse model [91]. ROS function as second messengers to regulate multiple cancer metastasis-related signaling pathways [92]. In NSCLC cells, ROS modulate the TLR4 signaling pathway. This modulation of TLR4 signaling causes metastasis of cells treated with lipopolysaccharide. Inhibition of either NOX1 or ROS was found to suppress lung tumor metastasis induced by lipopolysaccharide [93]. ROS also play important roles in transforming growth factor (TGF) β signaling, an important inducer of cancer metastasis. TGF-β induced ROS production in breast cancer 4T1 cells and enhanced cell migration [94]. In addition, redox protein thioredoxin-like 2 (TXNL2) regulated the growth and metastasis of human breast cancer cells through a redox signaling mechanism [95].

BLT2 is another signaling molecule that can promote the survival, invasion, and metastasis of aggressive cancer cells through a ROS-linked pathway. Metastasis of 253J-BV cells and SKOV-3 cells in mice was also dramatically suppressed by inhibition of ROS-linked BLT2 signaling [70,96]. Capsaicin, an active component of chili, is known to be an antimetastatic compound. However, at a low concentration, capsaicin promotes colorectal cancer metastasis by triggering ROS production and modulating the Akt/mTOR and STAT-3 pathways [97].

Production of ROS in inflammatory conditions

High levels of ROS have been implicated in the inflammatory microenvironment. The interaction between ROS and inflammation plays an important role in the pathogenesis of various chronic diseases including cancer. However, the relationship between ROS and inflammation is complicated. Wu et al. [98] have shown that inflammatory mediators, including cytokines and growth factors, regulated the production of ROS through induction of NOX family proteins. Inflammatory molecule IL-20 has been reported to produce TNF-α, IL-1β, MCP-1, CCR4, CXCR4, and ROS in oral cancer cells via activated STAT3 and AKT/JNK/ERK signals [99]. Numerous other studies have found that inflammation induced ROS generation. A recent study found that ROS generated through inflammation or mitochondrial dysfunction accelerated endoplasmic reticulum malfunction [100]. Ohnishi et al. [101] also showed that ROS produced under inflammatory conditions from inflammatory and epithelial cells resulted in DNA damage, an important factor in carcinogenesis. Because ROS serve as effector molecules, they participate in host defense or as chemoattractants that recruit leukocytes to wounds, thereby influencing the inflammatory reaction in damaged tissues [98]. In addition, sustained inflammation has been shown to elicit stem cell insult by inducing chronic oxidative stress with elevated levels of ROS in the bone marrow. This inflammatory microenvironment can cause DNA damage in hematopoietic cells [102].

Numerous other studies have revealed that ROS activate inflammatory mediators and subsequently the inflammatory microenvironment, which is followed by carcinogenesis. Wang et al. [103] showed that ROS produced by the fungal component zymosan induced inflammatory responses in Kupffer cells through the activation of p38 MAPK and NF-κB. Several other studies have reported that ROS mediated inflammation in various conditions. Valavanidis et al. [104] showed that ROS and oxidative stress mediated an increase in pulmonary inflammation and initiated or promoted mechanisms of carcinogenesis in the respiratory system.

ROS generated by tobacco lead to oxidative stress and inflammation with high DNA damage, a potential cause of lung cancer in smokers. In animals, ethanol exposure induced high levels of ROS, which further induced inflammatory mediators including TNF-α, NF-κB, and p65 and decreased IκBα [105]. ROS also trigger the inflammatory process in the cochlea (an auditory portion of the inner ear) by activating STAT1 through activation of NOX3. Because knockdown of NOX3 by siRNA reduced STAT1 activation, ROS have an important role in STAT1-mediated inflammation [106].

It has also been reported that activation of Ras, MYC, and p53 caused mitochondrial dysfunction, resulting in ROS production and downstream inflammatory signaling (e.g., NF-κB and STAT3). A recent murine transgenic study established that mitochondrial metabolism

and ROS production are necessary for K-Ras–induced tumorigenicity [107]. Compelling evidence highlights that ROS and inflammation are closely linked, which may contribute to further DNA damage. In recent years, DNA damage repair has emerged to contribute to the development of innate and acquired immunity [108]. However, further studies are required to improve our understanding of the involvement of DNA repair pathways in immune and inflammatory responses.

Role of ROS in epigenetics

Epigenetics refers to heritable changes in gene expression that do not cause any direct changes to the DNA sequence itself; disruption of epigenetic mechanisms has important implications in the control of disease. ROS play an important role in the etiology and progression of several human diseases through genetic and epigenetic alterations. In a state of oxidative stress, excessively accumulated ROS overwhelm cellular defenses, and in such a state, ROS regulated both genetic and epigenetic cascades underlying altered gene expression in human disease including cancer [109]. ROS have been shown to regulate major epigenetic processes such as DNA methylation and histone acetylation. In cancer cells, ROS enhanced DNA methylation, causing the silencing of tumor suppressor and antioxidant genes and enhancing the proliferation of cancer cells under oxidative stress conditions. Mechanistically, it has been shown that during DNA methylation, superoxide deprotonated the cytosine molecule at the C-5 position and in doing so, accelerated the reaction of DNA with the positively-charged intermediate S-adenosyl-L-methionine. Superoxide also deprotonated histone N-terminal tail lysines and accelerated the formation of their complexes with acetyl-coenzyme A [110]. High intra-mitochondrial ROS levels also damaged mitochondrial DNA, and its mutations affect the epigenetic control mechanisms of the nuclear DNA by decreasing the activity of methyltransferases [111].

Oxidative stress causes epigenetic alteration in several types of cancer cells. In colorectal cancer cells, expression of CDX1 has been altered by ROS. H_2O_2 treatment in these cells increased CDX1 promoter methylation, DNA methyltransferase 1 (DNMT1), and histone deacetylase 1 (HDAC1) expression and activity [94]. ROS also induced silencing of RUNX3 by epigenetic alteration. It has been shown that H_2O_2 treatment increased RUNX3 promoter methylation and NAC and that the cytosine methylation inhibitor 5-aza-2-deoxycytidine (5-Aza-dC) inhibited it [112]. These results suggest that ROS silence the tumor suppressors CDX1 and RUNX3 through epigenetic regulation, and thus promote the progression of colorectal cancer. ROS also promote hypermethylation of the promoter region of E-cadherin protein by increasing Snail expression in hepatocellular carcinoma. It has been shown that Snail induced DNA methylation of the E-cadherin promoter by recruiting histone deacetylase 1 and DNA methyltransferase 1. Thus, epigenetic modulation induced by ROS contributes in the process of carcinogenesis [113].

ROS as a diagnostic marker

ROS generation via NOX4 has also been shown to be important in the cytological diagnosis of cancers. In urothelial carcinoma of the urinary bladder, the pathobiological role of NOX4-mediated ROS generation has been demonstrated in urine cytology. As NOX4 was overexpressed in several urinary bladder cancer cell lines, a study disease condition has been analyzed in urine samples obtained from urinary bladder cancer cases. Urine samples were treated with fluorescent reagents, which labeled the hydrogen peroxide/superoxide anion and cytological atypia of ROS-positive cells, and different grades of diseases were detected. Thus this study indicates that ROS labeling could be a useful diagnostic tool in human bladder cancer [114]. Moreover, salivary ROS are also being considered as a parameter for saliva-linked disease [115]. Since ROS damage DNA, 5-methylcytosine DNA in patients may also be useful as a primary diagnostic tool or as a marker for early detection of relapse of disease [116,117].

Antioxidative lifestyle

Numerous studies from preclinical to clinical models have indicated that antioxidants are helpful in reducing cancer risk. Epidemiologic data suggest that persons with antioxidative diets rich in fruits and vegetables have a lower risk of several chronic diseases and mortality than do those eating fewer fruits and vegetables. In a cohort study, Agudo et al. [118] showed that high intake of fresh fruit, root vegetables, and fruiting vegetables rich in antioxidants was associated with reduced mortality. In a clinical study with 77,446 participants, intake of antioxidants from diet and supplements in relation to pancreatic cancer risk was examined. An inverse association between dietary selenium and pancreatic cancer risk was observed, indicating that antioxidants protect cells from initiation of cancer [119]. Another study of male smokers revealed that a combination of dietary antioxidants in their lifestyle reduced lung cancer risk [120]. Moreover, many other studies revealed that adding antioxidants in the daily diet could be helpful in preventing cancer risk.

Studies have suggested that nutraceuticals rich in antioxidants provide a protective effect in the development of cancer. Quercetin, a member of the flavone family, exhibits antioxidant characteristics by quenching lipid peroxides and enhancing the production of the endogenous antioxidant glutathione, thus protecting against ethanol-induced oxidative stress in mice [121]. High intake of tomatoes, rich in the antioxidant carotenoid lycopene, is associated with decreased risk of chronic disease. High intake of tomatoes has also been shown to protect against carcinogen (diethyl nitrosamine, DEN)-initiated alcohol-promoted alcoholic liver disease in a mouse model. In addition, tomato powder reduced steatosis and inflammatory foci and abolished the presence of preneoplastic foci of altered hepatocytes in DEN-injected mice that were fed alcohol [122].

In another study, when mice were treated with azoxymethane (AOM)/dextran sulfate sodium (DSS), increased levels of malondialdehyde (MDA) were observed; however, subsequent administration of cocoa decreased the MDA. Enzymatic and nonenzymatic antioxidants, such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase, were also restored in mice treated with cocoa and AOM/DSS. Another study revealed that cocoa increased NF-E2-related factor 2 and its downstream targets, such as NQO1 and UDP-GT [123]. Thus, these nutraceuticals exhibit a chemopreventive property that helps to prevent various types of cancer.

Wushen, a food mixture containing 55 different natural ingredients, also demonstrated antitumor activity in a mice model. It decreased tumor growth in Kunming mice implanted subcutaneously with murine sarcoma S180 cells. This antitumor potential of wushen was associated with its antioxidant properties [124]. β-carotene, a vitamin A precursor, has been shown to exert anticancer effects because of its antioxidant nature. Furthermore, in animal study, β-carotene has exhibited antimetastatic effects as it attenuated the migratory and invasive capabilities of highly malignant SK-N-BE(2)C neuroblastoma cells in animals [125]. Another antioxidant nutraceutical, maesil (*Prunus mume* Siebold and Zucc.), has been reported to have antioxidative effects, as well as anticancer effects in 7,12-dimethylbenz[a]anthracene (DMBA), 12-O-tetradecanoyl phorbol-13-acetate (TPA)-induced mouse skin carcinogenesis via its antioxidative potential [126]. Grape antioxidant dietary fiber, rich in proanthocyanidin, has been shown to decrease spontaneous intestinal tumorigenesis in the Apc (Min/+) mouse model, suggesting the potential of this fiber in the prevention

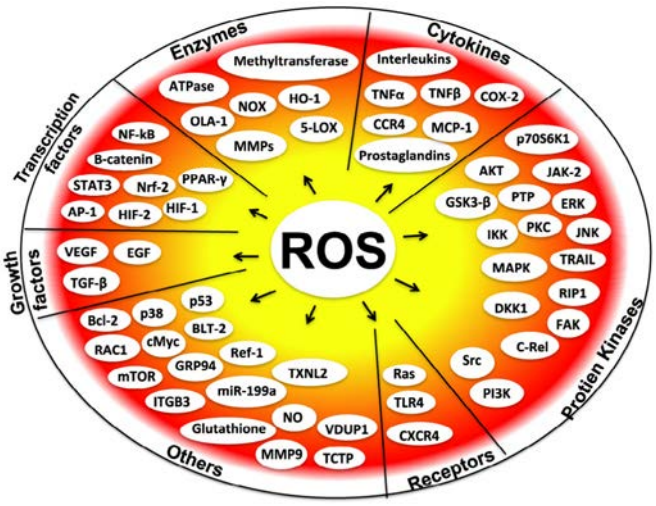

Fig. 3. Excessive levels of reactive oxygen species (ROS) cause progression of cancer, mediated through modulation of various signaling molecules.

of colorectal cancer [127]. These studies indicate that nutraceuticals rich in antioxidants have the potential to decrease the incidence of cancer.

Numerous studies have revealed that some antioxidant nutraceuticals exhibit pro-oxidative properties that kill cancer cells. Previously, we showed that ursolic acid found in various fruits induces the death receptor pathway through production of ROS and causes apoptosis of cancer cells [128]. In ovarian cancer cells, quercetin demonstrated pro-oxidant activity rather than antioxidant activity. It induced the production of ROS, followed by activation of the death receptor signaling pathway, and further increased the sensitivity of the cells to tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) treatment [129]. Similarly, a component of garlic diallyl sulfide increased the production of ROS in colon cancer cells, causing cell cycle arrest, decreasing cell proliferation, and inducing apoptosis [130]. In normal cells, diallyl sulfide restores the level of antioxidant enzymes and lipid peroxidation modulated by carcinogens, thus protecting the cells from oxidative damage [131,132]. These studies conclusively indicate that nutraceuticals are beneficial as an antioxidant in both the prevention and treatment of cancer. However, antioxidant treatments alone or in combination with chemotherapy or radiotherapy are still considered controversial [133].

Conclusions

It is becoming increasingly evident that ROS play an important role in carcinogenesis. It is also clear that numerous chemotherapeutics mediate their effects by inducing ROS generation. Such dual roles of ROS indicate their critical importance in cellular homeostasis. Antioxidants can suppress ROS to prevent activation of protumorigenic signaling pathways. The generation of ROS, either by disabling cellular antioxidants or specific inducers to cause cell death, could be a promising approach for cancer therapeutics. However, it is very critical to carefully implement these strategies because the level of ROS varies from cell to cell and because ROS mediate carcinogenesis through the modulation of several cell signaling molecules and pathways (Fig. 3). Therefore, targeting ROS could be another approach in preventing cancer. In this regard, nutraceuticals are a better option because of their safety, efficacy, and ROS-scavenging properties. Unfortunately, no nutraceuticals have been approved for human use. Future attempts in this direction will help to place them in front of novel therapeutics.

Acknowledgments

The authors thank Tamara Locke from the Department of Scientific Publications for carefully proofreading the manuscript.

Conflict of interest

The authors have no conflict of interest.

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