An Overview of Antioxidative Anticancer Therapies with Reference to the Cancer Stem Cells

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Abstract

Reactive species comprise a group of molecules that are generated as byproducts of various eukaryotic metabolic reactions. They are known to regulate several signal transduction pathways and gene expressions. Cells are constantly exposed to oxidative stress arising from several endogenous and exogenous factors. However, excessive oxidative stress leads to chronic inflammation, which could

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turn into several pathological conditions like cardiovascular diseases, diabetes, neurological disorders, and even cancer. Reactive species mainly reactive oxygen species (ROS) are closely linked with all facets of carcinogenesis and its prevention as well as treatment. Cancer cells exhibit an increased metabolic and proliferation rate and hence demand a higher redox level. Moderate elevation in the manifestation of ROS contributes to cancer stemness by promoting epithelial-to-mesenchymal transition, invasion, proliferation, and angiogenesis. ROS alter several cellular signaling pathways and deregulate many proto-oncogenes and tumor suppressor genes. Nevertheless, majority of the chemotherapeutic agents and even radiotherapy significantly increase the levels of ROS in the tumor microenvironment. Pro-oxidants induce programmed cell death, and this effect is harnessed in anticancer therapy; however, antioxidants improve the quality of life of patients undergoing chemotherapy. This chapter highlights the implications of oxidative stress in the process of carcinogenesis and resistance of cancer to chemotherapy with respect to the cancer stem cells. Oxidative stress triggers the stem cell-likeness of cancer cells and renders them resistant to anticancer therapies. Hence, targeting the oxidative stress may provide novel druggable molecules to alter the stem cell-likeness cancer cells and to sensitize them to the anticancer therapies.

Keywords

Oxidative stress · Reactive oxygen species (ROS) · Cancer stem cells (CSCs) · Antioxidants · Pro-oxidants · Cancer therapy

Introduction

Cancer is the second most common non-communicable disease globally, having a morbidity and mortality rate just second to the cardiovascular diseases (Ferlay et al. 2015; Jemal et al. 2007). According to WHO (World Health Organization), cancer causes more causalities than all cardiovascular diseases, and the American Cancer Society has declared cancer to be the second most death-causing disease in the USA (Siegel et al. 2020).

Cancer cells incapacitate the ability of the normal cells to prevent overgrowth and invasion in the surrounding tissues and alter their intercellular molecular signaling. This altered milieu induces cancer cells to rapidly proliferate by establishing cellular changes like inhibition of growth suppressors, high nucleus-to-cytoplasm ratio, inhibition of apoptosis, activation of angiogenesis, metastasis, and invasiveness (Fouad and Aanei 2017). These alternations in the cancer cells are caused by mutations in the cell cycle regulator genes and subsequent mutations of other genes over a time (Collins et al. 1997). These mutative traits further translocate to the daughter cells. If these mutated and aggressively proliferating cells endure their indigenous site, they are termed as “benign,” and if they become invasive and metastasize, they are termed as “malignant” (Fouad and Aanei 2017). Cancers

originating at different sites in the human body have distinct patterns of growth and spread. Dependent upon the organ of origin, approximately 200 different types of cancer have been documented (Potash and Anderson 2013). However, dependent upon their tissue origins, all cancers can be classified into three categories: ***carcinomas*** (derived in the epithelium), ***sarcomas*** (developed in the supportive and connective tissues of all kind), and ***leukemias*** (originated in the blood-generating tissues like the bone marrow).

The etiopathogenesis of cancer is well delineated, and exhaustive information has been accumulated on the factors contributing to carcinogenesis like irreversible and persistent cellular mutations and physical and chemical triggers like tobacco, alcohol, ionizing radiation, ultraviolet radiation, pesticides, metals, and pollutants. The biological triggers like bacterial/viral infections also contribute to carcinogenesis along with aging, inappropriate diet, obesity, and lack of physical activity as predisposing factors. The mechanisms underlying carcinogenesis include genetic mutations, DNA lesions, chromosomal breaks, deregulation of cell cycle checkpoint proteins, and proinflammatory states (Ames et al. 1995).

In the twentieth century, the cancer research mainly aimed to elucidate the cancer signaling and target the cancer cells with cytotoxic agents. However, in the late 1990s, a breakthrough discovery of the cancer stem cells (CSCs) by a Canadian scientist, John Edgar Dick, opened up a new horizon for cancer research. During the last two decades, direct correlations have been established between the oxidative stress and all the stages and facets of carcinogenesis including stem cell-likeness. Oxidative stress is an imbalance between the production of redox species and innate antioxidative mechanisms to quench them. It leads to structural alterations in the vital biomolecules and initiates the vicious cycle of carcinogenesis and resistance to cancer chemotherapy.

Oxidative Stress and Onset of Carcinogenesis

Mitochondria are the powerhouse of eukaryotic cells, and aerobic respiration is the process by which energy is generated. The byproducts of the energy metabolism are required in lower concentrations for multiple gene expressions, enzyme activation, disulfide bond formation, caspase activity, and several other signal transductions. However, in higher concentrations, these byproducts may prove to be toxic to the cells. The reactive species derived from mitochondrial, microsomal, and peroxisomal activities in the electron transport chain (ETC) are the major sources of endogenous oxidative stress (Sosa et al. 2013). The reactive species are of four different types: ROS (reactive oxygen species), RNS (reactive nitrogen species), RSS (reactive sulfur species), and RCS (reactive chlorine species) (Sosa et al. 2013). The sources of reactive species and involvement in oxidative stress are documented in Table 1. Apart from these innate reactive species, the exogenous triggers of cancer pollutants, UV radiation, and smoking and drinking habits also contribute to oxidative stress.

Table 1 Different types of Reactive species, their source and involvement in Oxidative stress

Reactive species	Source	Involvement in oxidative stress
ROS	Intracellular metabolic processes like ETC	It is the amplest of all kinds of reactive species. Half-life of ROS ranges from nanoseconds to hours. It includes O_2^- (superoxide anion), $^1O_2$ (singlet oxygen), H_2O_2 (hydrogen peroxide), OH^- (hydroxyl ion) and O_3 (ozone).
RNS	Intracellular metabolic processes like ETC	Widely available RNS is NO^- (nitric oxide) that reacts with O_2^- (superoxide anion) and produce $ONOO^-$. Later, peroxynitrous acid is formed from NO^- and finally into hydroxyl radical and NO_2^- (nitrite anion).
RSS	Oxidation of disulfides and thiols in greater oxidation states	RS• (Thiyl radical), RSSR (Disulfide), RS(O)SR′ [Disulfide-S-monoxide (thiosulfinate)], RS $(O)_2$SR′ [Disulfide-S-dioxide (thiosulfonate)], RSOH (Sulfenic acid), RSO_2H (Sulfinic acid) are the main forms of RSS. They are involved in oxidation and inhibition of thiol-proteins and enzymes.
RCS	Immune cells	They are mainly natural antimicrobials in nature. Cl, Cl_2^- and ClO are the main kinds of RCS that cause oxidative stress.

Anti-oxidants control the cellular oxidation-reduction reactions, thereby balancing the pro-oxidant/antioxidant equilibrium. Oxidative stress is generated when the number of reactive species, especially ROS, exceeds, and this leads to the deregulation of many important molecular compounds like DNA, RNA, proteins, lipids, etc. (Sosa et al. 2013). ROS causes gene mutations and thereby induces DNA lesions, nick or damaged DNA, deregulation in DNA repair mechanisms, and generations of mutagens like 8-Oxo-2′-deoxyguanosine (Matsui et al. 2000). Continued generation of ROS for a very long time leads to sustainable damage to cell structure and functions. The ROS induce excessive lipid peroxidation ultimately enhancing the cell membrane's permeability (Sosa et al. 2013). Under oxidative stress, carbonyl and thiol groups of certain proteins get converted into sulfur reactive radicals leading to the loss of protein function (Levine 2002). Collectively, all these derangements lead to somatic mutation, neoplastic transformation, cell death, and eventually cancer initiation and progression (Sosa et al. 2013) as depicted in Fig. 1.

The most authentic ROS-induced DNA damage marker is 8-oxo-7,8-dihydroguanine (8-oxodG) which is invariably elevated in most of the cancer cells (Ziech et al. 2011). Upregulation of 8-oxodG indicates a strong connection between ROS and the onset of tumorigenesis (Ziech et al. 2011). The 8-oxodG assay is widely used to detect the oxidized DNA. Direct measurements of other parameters like ROS, RNS oxidized DNA, and product of lipolysis are also used to determine the severity of oxidative stress. In addition to these, estimations of reduced levels of antioxidants (SOD, catalase, vitamins C and E, β-carotene etc.) are also used to estimate the oxidative stress.

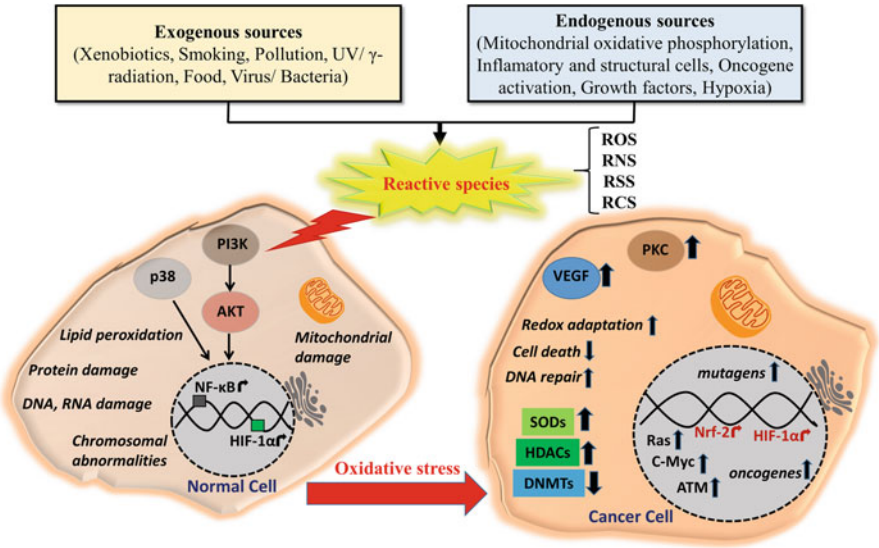

Fig. 1 Oxidative stress and the onset of tumorigenesis. Several exogenous and endogenous factors contributing to the oxidative stress transform the normal cells to cancerous cells by modulating intercellular signaling pathways

Oxidative Stress and Cancer Stem Cells

Cancer stem cells (CSCs) are a very little population of cells situated in the cancer microenvironment responsible for the chemoresistance and cancer relapse (Reya et al. 2001). CSCs are pluripotent in nature and possess higher DNA repair and drug efflux capabilities. These are thought to be involved in the cancer initiation, progression, and metastasis (Reya et al. 2001). CSCs are reported to have self-renewal properties, and by differentiation, they are responsible for cancer heterogeneity. Till date, CSCs have been found in all solid cancers like lung cancer, prostate cancer, ovarian cancer, brain cancer, colon cancer, melanoma, and so on (Sosa et al. 2013). ROS are considered to be major mutagens to stem cells. Nevertheless, when the ROS level is elevated, several signaling molecules are upregulated, which play a significant role in the progression not only of cancer cells but also of CSCs. Unlike normal cells, cancer cells usually have a high redox level. However, CSCs are reported to contain less ROS and high scavenging molecules than the cancer cells, which help CSCs to promote chemoresistance. For example, chemoresistance of liver $CD13^{+}$ CSCs was found to be due to elevated expression of ROS scavenging enzyme, aminopeptidase N (Sosa et al. 2013). ROS upregulated MAPK/ERK pathway and VEGF/Flt1 signaling (Sosa et al. 2013). These two pathways play a crucial role in the augmentation of CSC population (Dayem et al. 2010). NF-κB was reported to be an important gene that regulates many signaling pathways, especially those controlling cell proliferation and inflammation. Hence, ROS or hypoxia-mediated

activation of NF-κB can further accelerate CSC proliferation (Dayem et al. 2010). Hypoxic environment helps both cancer cells and CSCs to proliferate rapidly. Increased expression of HIF-2α has been reported in the glioblastoma CSCs (Sosa et al. 2013), and under hypoxic condition only, HIF-2α expression was easily detectable in glioma stem cells (Li et al. 2009). The stemness of human glioblastoma cells is enhanced in hypoxia-mediated activation of Sox2 and Oct-4 (Sosa et al. 2013). Studies using ovarian cancer and hepatocellular carcinoma cells also show that CSCs ($CD133^{+}$) became resistant to chemotherapeutic ROS producers, cisplatin and doxorubicin (Baba et al. 2009; Ma et al. 2008). These findings indicate a strong relation between ROS and various aspects of CSCs. These characteristics of CSCs are as follows:

Oxidative Stress and Cancer Epithelial-to-Mesenchymal Transition

Epithelial-to-mesenchymal transition (EMT) is the onset of metastatic cancer, and it determines the aggressive and invasive characteristic of that particular cancer. This process loosens the cell-cell adhesion and alters the polarity of epithelial cells rendering the cells more invasive and migratory (Dayem et al. 2010). EMT induces the CSCs and enables them to sustain metastasis. This suggests a strong reciprocal relationship between CSCs and EMT in tumor progression (Dayem et al. 2010).

ROS play a crucial role in the EMT and survival of the CSCs. Multiple signaling molecules are involved in the EMT. TGF-β (tumor growth factor-beta) signaling plays a key role and links the ROS with the EMT. TGF-β activation is associated with EMT signaling molecules like phosphorylation of p38α, Smad2, and ERK1/2 (Sosa et al. 2013). Apart from these, ROS and EMT-associated signaling proteins also include Smad, Snail, integrin, MMPs, E-cadherin, β-catenin, TGF-β, AP1, HGFR/c-Met, NF-κB, HIF-1α, COX-2, TAK1, Ets-1, etc. (Sosa et al. 2013). Extracellular matrix (ECM) is the barrier that inhibits the EMT process, and in many metastatic cancers, the hyperactivity of matrix metalloproteinases (MMPs) degrades the ECM. Similar alterations are also observed during oxidative stress. An upregulation of the MMP-3 (stromelysin-1) in association with the ROS activation is reported in certain types of cancers. Raised MMP3 expression is associated with an enhanced expression of the Snail, downregulation of E-cadherin, and nuclear translocation of β-catenin ultimately triggering cancer cell proliferation and metastasis. Apart from MMP-3, MMP-9 and MMP-2 also stimulate oncogenic protein Rac1b during oxidative stress (Sosa et al. 2013). Along with this, Wnt signaling, MAPK pathway, PKC, PAK-1 cascades, and Rac signaling pivotally play roles in metastasis. All these signaling pathways are also triggered by ROS (Sosa et al. 2013; Dayem et al. 2010). All these evidences unequivocally project ROS as a major stimulus for the EMT of cancer cells.

Oxidative Stress and Tumor Cell Invasion

CSCs resemble the normal stem cells and exist during almost every stage of carcinogenesis including initiation, progression, metastasis, and reoccurrence. In

an invasive cancer, the morphological alteration of epithelial cells makes them more motile and invasive. ROS performs a vital role in metastasis by triggering tumor invasiveness. The expression of ICAM-1 (intercellular adhesion protein-1) is regulated by ROS (Reuter et al. 2010). Similar to EMT, MMPs also play prime roles in tumor invasiveness and metastasis. MMP-9 and MMP-2 are associated with highly invasive cancers, and activation of these MMPs is considered to involve reaction of ROS with the thiol groups in the protease catalytic domain (Reuter et al. 2010). Moreover, expressions of MMP-1, MMP-3, MMP-9, MMP-10, and MMP-13 are stimulated by H_2O_2 and NO donors (Reuter et al. 2010). In addition, MMP expressions is modulated by several signaling molecules like iNOS, Ras, ERK1/2, p38, JNK, etc. and chemokine like CXCR-4 (Reuter et al. 2010). Collectively, it is evident that these MMPs play a crucial role in ROS-mediated invasive carcinoma.

ROS and Cancer Angiogenesis

Cancer cells continuously need very high amount of blood supply for their growth and as a strategy to eliminate the byproducts of cellular metabolism. This is achieved by the cancer cells through stimulating angiogenesis, a process of new blood vessel formation. Angiogenesis is required in normal physiological conditions like during embryo development and wound healing. However, the unusually accelerated pathological angiogenesis is linked to the cancer growth and metastasis (Nishida et al. 2006). Similar to the cancer cells, CSCs also need nourishment through increased blood circulation. Certain growth factors like VEGF, FGF, PDGF, angiopoietin, and cytokines like IL-8 are known to trigger and support the process of angiogenesis (Nishida et al. 2006). Under the hypoxic conditions, ROS upregulates the VEGF expression and plays a cardinal role in the angiogenesis (Sosa et al. 2013). Similarly, in response to ROS-mediated stimuli, the angiogenic factors like FGF and PDGF are elevated (Longo et al. 2002). As mentioned above, the ROS-mediated activation of MMPs, TGF-β, and Nectin-4 plays pivotal roles in the cancer angiogenesis through the activation of several angiogenic cascades (Nishida et al. 2006; Chatterjee et al. 2021). NADPH oxidases are some ROS-causing enzymes and are involved in the activation of redox signaling and ultimately the process of angiogenesis (Sosa et al. 2013). Among these NADPH oxidases, Nox1 is hyperactivated in colon and prostate cancers, and Nox4 and Nox5 are overexpressed in melanoma and prostate cancer, respectively. These factors raise the levels of VEGF and MMPs and increase angiogenesis (Sosa et al. 2013).

Oxidative Stress and Cancer Cell Proliferation

Tumor cells grow rapidly, aggressively, and in an uncontrolled manner through the deregulation of different cellular signaling cascades, such as alterations in cell cycle, cell survival, apoptosis, etc. CSCs constitute a very small population in the niche of cancer, and they perform a very significant role in the cancer proliferation. Redox status significantly impacts on cancer cell proliferation. Different signaling

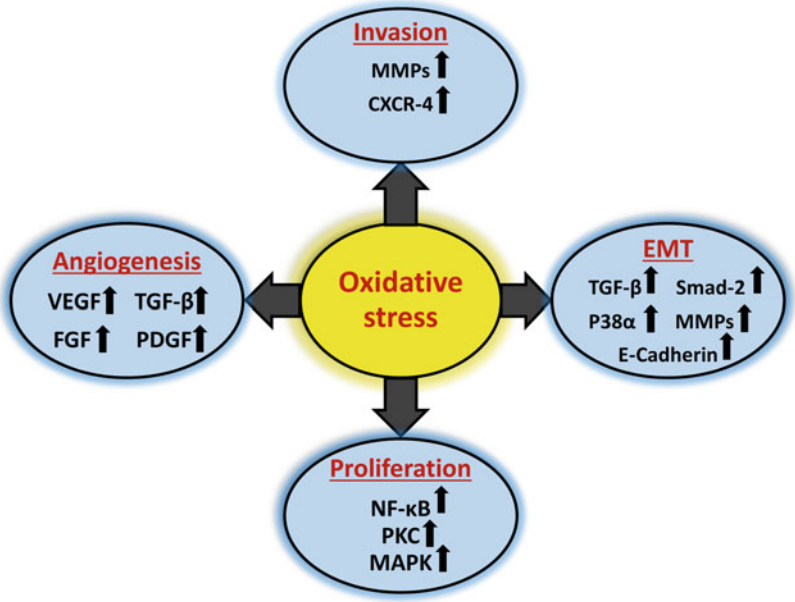

Fig. 2 Oxidative stress induces cancer stemness. Redox imbalance leads to the upregulation of tumor proliferation, invasiveness, and angiogenesis and epithelial-to-mesenchymal transition, which ultimately enhance the stemness properties of cancer cells

molecules like NF-κB, MAPK, ERK, JNK, etc. play pivotal roles in cancer cell proliferation, and report suggested that the alterations of these signaling molecules were found in oxidative stress (Reuter et al. 2010). Different extracellular stimuli like UV radiation and alcohol activate NF-κB and thereby promote cell proliferation (Reuter et al. 2010). Again, JNK and MAPK pathways are mainly regulated by H_2O_2 (Reuter et al. 2010). In addition, PKB/Akt (protein kinase B/Akt) and PKC (protein kinase C) are activated by different redox signaling molecules (Reuter et al. 2010). All these proteins are upregulated in ROS-mediated oxidative stress condition and induce cell proliferation. Apart from activating specific cellular signaling pathways, ROS also alters physiological milieu supporting the cancer growth as shown in Fig. 2.

Hypoxia and Oxidative Stress

Hypoxia provides an ideal condition for tumor vascularization and enables survival, angiogenesis, metastasis, aggressiveness, and drug resistance. Hypoxia also nurtures CSCs in their stemness (Najafi et al. 2020). Hypoxia-inducible factors 1α and 2α (HIF-1α and HIF-2α) are two prime proteins that are upregulated in the hypoxic condition due to the inhibition of 26S proteasomal complex, and hence they translocate into the nucleus and activate different genes. Both HIF-1α and HIF-2α are

indispensable for the survival, proliferation, and stemness of cancer stem cells (Najafi et al. 2020). Activated HIF in many ways induces cancer progression. It has been proved that the enzymes involved in oxidative stress also can induce HIF-1α through Akt/PI3K or MEK/ERK signaling cascade (Sosa et al. 2013). Activated HIF-1α can induce nitric oxide (NO) through iNOS pathway, which will promote cancer vascularization and vasodilation-mediated cancer angiogenesis (Sosa et al. 2013; Olson and Van Der Vliet 2011). Hypoxia induces ADAM-17, proteasomal cleavage of Nectin-4, or Notch and can promote cancer proliferation, metastasis, angiogenesis, and even cancer relapse (Chatterjee and Kundu 2020; Chatterjee et al. 2021; Najafi et al. 2020). HIF-1α upregulation can also be associated with the activation of VEGF (Najafi et al. 2020). VEGF, a well-studied angiogenic factor, enhances angiogenesis through several pathways like iNOS-mediated NO production, Akt signaling cascade, and PKD1 signaling cascade (Sosa et al. 2013). Nevertheless, hypoxia has great impacts on cellular plasticity, maintenance of cancer stemness, oxidative modulation, enhanced activities of ABC transporter proteins, cytokines present in cancer microenvironment, and different CSCs associated with cellular signaling – TGF-β, COX-2, WNT/β-catenin, NF-κB, STAT-3, etc. (Najafi et al. 2020).

ROS-Modulated MicroRNA in Cancer

MicroRNA or miRNA are small (typically 18–25 nucleotides), non-coding RNA, which play important roles in RNA silencing and regulate post-translational modification of many genes. Alteration of miRNA leads to cancer metastasis, angiogenesis, and tumor growth (Khan et al. 2019). miRNAs regulate the stemness of cancer by controlling different cellular signaling pathways like Notch, WNT/β-catenin, JAK/STAT, PI3K/AKT, NF-κB, etc. (Khan et al. 2019). ROS deregulates global miRNA scenario. For example, miR-210 is a hypoxia-induced miRNA, which is upregulated in breast cancer and hepatocellular carcinoma, enhancing their metastasis and invasiveness (Sosa et al. 2013). ROS also modifies miR-21 in the metastatic breast cancer cells in vitro (Khan et al. 2019). Thus, ROS and miRNAs synergistically orchestrate the cancer stemness, proliferation, and metastasis.

Oncogene, Tumor Suppressor Gene, and Oxidative Stress

Proto-oncogenes are necessary for normal cell division; however, under certain circumstances when they are permanently switched on (oncogenes), uncontrolled cell division ensues. Chromosomal rearrangements and gene duplications are major oncogenic activators. Tumor suppressor genes inhibit excessive cell divisions, repair damaged DNA, and decide the apoptotic fate of the cells. Alterations of tumor suppressor genes lead to unregulated cell division. The synergistic activities of proto-oncogenes and tumor suppressor genes maintain normal cellular phenomenon. These genes regulate multiple proteins important for cell division, cell cycle

regulation, and cell growth and proliferation. Their alterations result in ontogenesis (Sosa et al. 2013). Nrf2 gene also works as a tumor suppressor gene because of its cytoprotective effects like defensive property against oxidative stress and xenobiotics. It regulates a number of genes implied in oxidative stress, carcinogenesis, metastasis, and inflammatory responses. ROS-mediated alteration in Nrf2 resulted in the deregulation of PI3K, MAPK, and other kinase-dependent signaling pathways (Sosa et al. 2013). Nevertheless, BRCA1, a tumor suppressor gene, also regulates the activities of Nrf2 and NF-κB. In breast cancer, BRCA1 mutation leads to the modulation of many important cellular signaling cascades. Moreover, the antioxidative enzymes like GPx, GST, and oxidoreductases encoded by Nrf2 exert cytoprotective and quench the ROS (Sosa et al. 2013). Ref1/APE1 can act as potential therapeutics because they take part in lowering the ROS level (Seo and Kinsella 2009). Similarly, Ras GTPase also participates in the carcinogenesis and ROS. Ras mutations have been found in approximately 30% of all human cancers, and mutant Ras resulted in the elevated expression of ROS (Sosa et al. 2013). Moreover, Ras-overexpressed cells usually have higher mitochondrial mass and ROS level. Nox proteins are reported as oncogenic proteins due to their ROS generation capabilities in the cytoplasm. In addition to this, Myc, Mos, Raf, MEK, cyclin E, and hTERT are some oncogenes, and p53, p21, and pTEN are some tumor suppressor genes that are involved in ROS-mediated cancer initiation, proliferation, and metastasis (Sosa et al. 2013).

Oxidative Stress and Epigenetic Modification in Cancer

It is known that cancer initiation, progression, metastasis, and even invasion are also epigenetically regulated events. Epigenetic modification is the alteration of gene expression without any change in the DNA sequence, and it can potentially contribute to neoplastic development and cancer progression. Moreover, abnormal epigenetic modification could lead to transformation of stem cells to cancer stem cells (Toh et al. 2017). ROS may also be regulated through epigenetic modification in cancer cells. Mahalingaiah et al. recently demonstrated that ROS influenced histone modifications (HDAC1, HMT1, and HAT1) and DNA methylation (MBD4, DNMT1, and DNMT3a) in HK-2 cells to facilitate its malignant transformation to renal cell carcinoma (Mahalingaiah et al. 2017). ROS-mediated DNA oxidation can alter epigenetic events which will inactivate the expressions of various tumor suppressor genes, resulting in the progression of carcinogenesis (Toh et al. 2017).

Tumor Microenvironment and Oxidative Stress

Tumor microenvironment is consisting of various kinds of cells, like cancer-associated fibroblasts (CAFs), myofibroblasts, vascular cells, natural killer cells, and tumor-associated macrophages. Eventually, by the effect of reactive species especially ROS, normal fibroblast cells also get converted into CAFs, and these

cells detect the ROS, which are secreted into the tumor microenvironment by cancer cells. This triggers the activation of various transcription factors like NF-κB, HIF-1α, etc., generation of ROS, promotion of cancer angiogenesis, etc. (Sosa et al. 2013). CAFs are also reported to uplift the ROS level and help in cancer growth and invasiveness (Chan et al. 2018; Sosa et al. 2013). The growth hormones promote EMT and enhance DNA damage in order to induce chemoresistance. Estrogen is a gonadocorticoid that plays important roles in the onset of breast cancer. By the effect of cytochrome P450 1B1, estrogens can be transformed into metabolite 4-hydroxyestradiol (4-OHE2 and 2-OHE2), which is carcinogenic in nature. Again, the oxidized form of 4-OHE2 and 2-OHE2 can interact with DNA and induce ROS (Sosa et al. 2013). However, ROS is also reported to be involved in the structural and functional modification of estrogen receptors in order to enhance the poor diagnosis of ER-positive breast cancer patients (Yau and Benz 2008).

ROS as Cancer Therapeutics

Oxidative stress plays two different roles in tumorigenesis. During the onset of carcinogenesis, imbalance of redox levels promotes cancer. A different nature of homeostasis of oxidative stress is present in the cancer microenvironment, where lower level of ROS promotes cancer and enhancement of ROS leads to toxicity in cancer cells. So, ROS helps in cancer cell survival, proliferation, and metastasis, but if it remains uncontrolled, cell death takes place. There are several drugs (quinine, chloroquine, primaquine, artemisinin, ciprofloxacin, mefloquine, etc.) that can induce ROS and can be used in cancer therapy. Hence, ROS can be used as a potent cancer therapeutic in order to make it an innovative target for cancer therapy.

Antioxidants as Preventives and Cancer Therapeutics

Antioxidants are protective agents that save our cells from the toxic load of free radicals, as they interact and scavenge the free radicals. Natural compounds like β-catenin, vitamins (A, C, E etc.), lycopene, glutathione, polyphenol metabolites, etc.; endogenous antioxidants including GSH, α-lipoic acid, glutathione, ferritin, coenzyme Q, uric acid, metallothionein, bilirubin, L-carnitine, superoxide dismutase (SOD), melatonin, catalase (CAT), thioredoxins (TRX), glutathione peroxidases (GPXs), peroxiredoxins (PRXs), etc.; and synthetic antioxidants like tiron, N-acetylcysteine (NAC), butylated hydroxytoluene, pyruvate, propyl gallate, butylated hydroxyanisole, selenium, etc. are some of the well-studied antioxidants that have been used as protective agents against cancer (Yoshida et al. 2003). These molecules act as double-edged swords in cancer. Antioxidants not only prevent the oncogenesis, but they also reduce the chemotherapy-induced high-dose-limiting toxicity (Singh et al. 2018). Many of the anticancerous drugs act by enhancing the redox level inside the tumor microenvironment which ultimately helps in the killing of cancer cells. However, cancer cells tackle the situation through some particular

type of redox-controlling agent. Thioredoxin is one of these controversial antioxidants (scavenger) which helps tumor cells to survive in oxidative stress and ultimately acts as a tumor growth enhancer (Perillo et al. 2020). Enhanced level of thioredoxin was reported in many cancers as well (Miyazaki et al. 1998). Moreover, in cancer therapy, antioxidants are used in two dosages: preventive dose (low dose of antioxidants) and therapeutic dose (high dose of antioxidants). The preventive dose is used to uplift the health status of patients who are undergoing chemotherapy. Though ROS leads to tumorigenesis, excessive ROS is also toxic to the cancer cells. Hence, in some cases, the therapeutic dose is given to potentiate the cytotoxic effect of anticancer therapeutics. Figure 3 shows the schematic representation and involvements of antioxidants (in both preventive dose and therapeutic dose) in cancer therapy.

Antioxidants usually do not hinder the actions of chemotherapy. They act as a shield to normal cells and increase chemotherapeutic efficacy in terms of enhancing chemotherapy-induced toxicity and patient survivability. As a result, various antioxidants were clinically used along with other chemotherapeutic agents to evaluate their combined efficacy. Increasing evidences support the fact that antioxidants show beneficiary results when administered along with traditional chemotherapeutic agents. A population-based cohort study reported that vitamin supplementation is linked with low risk of cancer-associated mortality and recurrence. Researchers have concluded this by supplementing vitamin in the first 6 months of 4877 breast cancer-diagnosed women (Singh et al. 2018). Moreover, supplementation of antioxidants also boosts the health status of cancer patients undergoing chemotherapy, because deprivation of antioxidants is very normal in chemotherapy due to the lipid

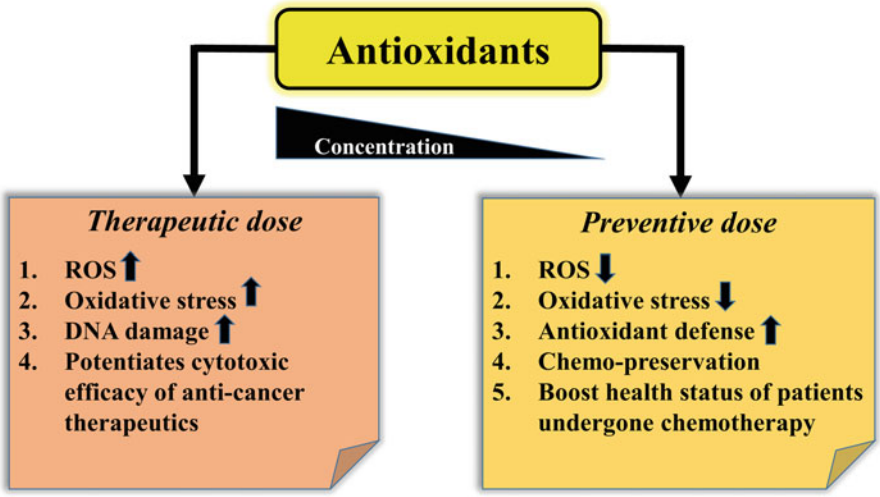

Fig. 3 Implication of antioxidants in cancer therapeutics. Antioxidants can be used as therapeutic dose (higher concentration) and preventive dose (lower concentration), and in both the doses' condition, it can be used in cancer therapy

peroxidation and high ROS. Due to the abovementioned reasons, supplementing antioxidants during chemotherapy is a modern trend in patients newly diagnosed with ovarian cancer (Singh et al. 2018). Another population-based study also showed that antioxidants are used during adjuvant treatment in breast cancer therapy (Singh et al. 2018). Moreover, frequent administration of vitamin E and vitamin C is linked with low risk of breast cancer-associated mortality and recurrence (Singh et al. 2018). A brief summarization of antioxidants in chemotherapeutic combination is listed in Table 2 (Singh et al. 2018).

Pro-oxidants in Cancer Therapeutics

Though ROS are involved in the onset of oncogenesis, their accumulation is found to be toxic to cancer cells. Pro-oxidants enhance cellular redox level, and high load of ROS may kill cancer cells selectively. In the year 1981, Nathan and Cohn for the first time reported the use of glucose oxidase as pro-oxidants in order to decrease tumor growth (Nathan et al. 1981). Along with cancer cells, pro-oxidants are also effective on cancer stem cells. As we discussed earlier, CSCs are known to be involved in developing chemotherapeutic resistance. Similar observation was found in mouse xenograft model system, where CD-13-positive cells were found to decrease the reactive species-mediated DNA damage after chemoradiotherapy. But the combination of CD-13 inhibitor and pro-oxidant, 5-FU, was found to be more effective than their individual treatment to reduce tumor volume (Haraguchi et al. 2010). Apart from these, Carmen et al. reported that some natural products also have shown significant effect as pro-oxidants and some of the major pro-oxidants are enlisted in Table 3 (Martin-Cordero et al. 2012).

The therapeutic implications of the pro-oxidants are mainly due to the ROS-mediated killing of cells, which eventually activates the programmed cell death through caspase activity. ROS-mediated type I programmed cell death (apoptosis) can be induced by either extrinsic or intrinsic pathway. Apoptotic extrinsic pathway involves the attachment of death-inducing ligands (TNF-α, TRAIL, Fas, etc.) to death receptors which are then involved in the requirement of adaptor proteins, pro-caspases. This, in turn, forms the DISC (death-inducing signaling complex), and apoptosis takes place due to the activation of caspase-8, caspase-3, caspase-6, and caspase-7 (Wang et al. 2008). On the other hand, intrinsic pathway is related to the discharge of pro-apoptotic factors (i.e., cytochrome c) from the cytoplasm by the mitochondrial permeability transition pores, which leads to the activation of apoptosome (Zuo et al. 2009). In addition to this, ROS can induce apoptosis by triggering the ubiquitination of Bcl-2 (pro-apoptotic protein) by down-regulating Bad and Bax (Luanpitpong et al. 2013; Li et al. 2004). ROS-mediated apoptosis is the key mechanism of major potent anticancer therapeutics including tyrosine kinase inhibitors, monoclonal antibodies, and other therapeutics (Dimitrov and Marks 2009; Hartmann et al. 2009; Shen et al. 2013; Brenneisen and Reichert 2018). A brief list of these cancer therapeutics and their mechanisms of action are described in Table 4 (Perillo et al. 2020; Sosa et al. 2013).

Table 2 Clinical, in vitro/in vivo supplementation of vitamins (alone/mixture of vitamins/vitamin analogs and other compounds) with different chemotherapeutics

Antioxidants	Chemotherapeutic agent	Greater therapeutic response	Enhanced survivability
Vitamin A	Cyclophosphamide	Yes	Yes
	Bleomycin, Doxorubicin, Methotrexate, 5-fluorouracil,	Yes	Yes
	Doxorubicin and Etoposide	Yes	–
	Doxorubicin, Cisplatin and Vincristine	Yes	–
	Methotrexate	–	–
	Etoposide, Cisplatin	–	–
	Vincristine	Yes	–
	Tamoxifen	Yes	–
	5-fluorouracil	Yes	–
	5-fluorouracil, Doxorubicin, Bleomycin, Mitomycin-C	Yes	Yes
	Cisplatin, Vindesine, 5-fluorouracil, Interferon	Yes	Yes
	5-fluorouracil, Cisplatin	Yes	Yes
	Cyclophosphamide, Tamoxifen, 5-fluorouracil, Prednisone, Vincristine, Methotrexate, Mitoxantrone, Mitomycin-C	Yes	Yes
Vitamin B	3-ethoxy-2-oxobutyraldehyde Bis (thiosemicarbazone)	Yes	–
Vitamin C	Doxorubicin, Cisplatin, Paclitaxel	Yes	–
	Vincristine	Yes	–
	Doxorubicin	Yes	Yes
	5-fluorouracil, Bleomycin	Yes	–
	Cyclophosphamide, Methotrexate, 5-fluorouracil	Yes	–
Vitamin D3	Cisplatin	Yes	–
Vitamin E	Cyclophosphamide	Yes	–
	Doxorubicin	Yes	–
	Doxorubicin, 5-fluorouracil	Yes	–
	Doxorubicin, Methotrexate, Vincristine	Yes	–
	Cisplatin	Yes	–
	13-Cis retinoic acid	Yes	Yes
	Cyclophosphamide, Adrianmycin, 5-fluorouracil	Yes	–
	Doxorubicin, Nifedipine	Yes	–
	5-fluorouracil, Cisplatin, Doxorubicin, Arabinosyl cytosine	Yes	–
	Adrianmycin	Yes	–
	Camptothecin	Yes	–
	Bleomycin, Chlorozotocin, 5-fluorouracil, Cisplatin, Adrianmycin, Mutamycin, DTIC, CCNU	Yes	–

(continued)

Table 2 (continued)

Antioxidants	Chemotherapeutic agent	Greater therapeutic response	Enhanced survivability
Vitamin K2	Cisplatin	Yes	–
Vitamin K3	Adrianmycin	Yes	–
β-carotene	Cyclophosphamide	Yes	–
Menadione (Vitamin D analogue)	Mitomycin-C	Yes	–
Vitamin D analogues	Irinotecan	Yes	Yes
	Oxaliplatin	Yes	–
	Imatinib mesylate	Yes	–
	Cyclophosphamide	Yes	–
Vitamin A, β-carotene	5-fluorouracil, Melphalan 4-Hydroperoxycyclophosphamide, Cyclophosphamide	Yes	–
Vitamin C and K3	Cyclophosphamide, Doxorubicin 5-fluorouracil	Yes	–
β-carotene, Vitamin A, C and E	Cisplatin, Tamoxifen, Interferon	Yes	–
Vitamin A, E, C, B12, D, β-carotene, Thiamine, Riboflavin, Pyridoxine, Calcium and Biotin	Cyclophosphamide, Doxorubicin, Vincristine	Yes	Yes
Vitamin C, E and GSH	5-fluorouracil, Peplomycin	Yes	–
Vitamin A and E	5-fluorouracil, Epirubicin, Leucovorin, Methotrexate,	–	Yes
	5-fluorouracil, Methotrexate, Epidoxorubicin	–	Yes
Vitamin A, E, β-carotene, and Selenium	Cyclophosphamide, Doxorubicin- HCl, Vincristine	Yes	Yes
Vitamin C, E, and Glutathione	5-fluorouracil, Peplomycin	Yes	–
Vitamin C and K	Cyclophosphamide, Vinblastine, Doxorubicin, 5-fluorouracil, Procarbazine, Asparginse	Yes	–
Vitamin A, C, E, coenzyme Q10 and β- carotene	Carboplatin and paclitaxel	Yes	–
Vitamin C and E	5-fluorouracil, Cyclophosphamide, Doxorubicin	Yes	–
	Doxorubicin	Yes	–
Vitamin D3 and 13-cis-retinoic acid	5-fluorouracil	Yes	–
Riboflavin, Niacin and Co-enzyme Q10	Tamoxifen	Yes	–

(continued)

Table 2 (continued)

Antioxidants	Chemotherapeutic agent	Greater therapeutic response	Enhanced survivability
Glutathione (GSH)	Cisplatin	Yes	–
	Cisplatin, Cyclophosphamide	Yes	–
	Cisplatin, Carboplatin	Yes	Yes
	Cisplatin, Bleomycin	Yes	–
	Cisplatin, Epirubicin 5-fluorouracil	Yes	–
	Mitomycin-C, 5-fluorouracil and Phenobarbital	Yes	–
Melatonin	Cisplatin, Etoposide	–	Yes
	Tamoxifen	Yes	Yes
	Cisplatin, Gemcitabine and Etoposide	Yes	Yes
	Doxorubicin, Paclitaxel and Mitoxantrone	Yes	Yes
	5 FU & Folinic acid	Yes	Yes
	5-fluorouracil and Cisplatin	Yes	Yes
	Vincristine/Isophosphamide	Yes	–
Quercetin	Cisplatin	Yes	–
	Busulfan, Cisplatin	Yes	–
	Doxorubicin, Daunorubicin	Yes	–
Coenzyme Q10	Doxorubicin	Yes	–
	Tamoxifen	Yes	–
	Cyclophosphamide + Doxorubicin + 5-fluorouracil	Yes	–
	Cyclophosphamide + OK432	Yes	–
Selenium	Doxorubicin	Yes	–
	Melphalan	–	Yes
	Methotrexate	Yes	–
	Cisplatin	Yes	–
	Cyclophosphamide	Yes	–

Apart from apoptosis, autophagy (type II programmed cell death) is one of the cell death mechanisms by which some pro-oxidants can be therapeutically explored. Enhancement of LC3-associated autophagosomes (positive regulator of autophagy) and downregulation of mammalian target of rapamycin 1 (TORC1, a negative regulator of autophagy) are involved in the ROS-mediated cell death (Perillo et al. 2020). Sanguinarine (polycyclic ammonium ion) and rapamycin cause cell death in autophagic manner. Sanguinarine induces H_2O_2-mediated autophagy, and rapamycin causes RAS-mediated reduction in tumor growth and ROS-mediated autophagy (Perillo et al. 2020). In addition to this, the bioactive compounds curcumin and quinacrine also induce ROS-mediated autophagy along with apoptosis (Araveti and Srivastava 2019; Das et al. 2017). In association with apoptosis and

Table 3 List of natural pro-oxidants used in cancer therapeutics

Natural products used in Pro-oxidant therapy				
Primary metabolites and derivatives	Phenolic compounds	Terpenoids	Alkaloids	Other natural products
Abrin	2′-Hydroxycinnamaldehyde	18β-Glycyrrhetinic acid	6-Methoxydihydrosanguinarine	Vitamin A
Ajoene	3,7,4′-trihydroxyflavone	Andrographolide	Berberine	Vitamin C
Allicin	4′-Hydroxycinnamaldehyde	Artemisinin	Boldine	Vitamin D2
Benzyl isothiocyanate	4-Hydroxycinnamic acid	Asiatic acid	Caffeine	Vitamin D3
Diallyl disulfide	6-Dehydrogingerdione	Astilbotriterpenic acid	Camptothecin	Docosahexaenoic acid (DHA)
Dimethyl disulfide	6-Gingerol	Betulinic acid	Cepharanthine	Eicosapentaenoic acid (EPA)
Jasmonic acid	6-Shogaol	Bixin	Chelerythrine	Bleomycin
Linoleic acid	8-Shogaol	Bufalin	Ellipticine	Boningmycin
Linolenic acid	Acacetin	Cannabidiol	Homoharringtonine	Deoxycholic acid
L-Mimosine	Aesculetin	Costunolide	Indole acetic acid	Capsaicin
Melatonin	Aloe-emodin	Cucurbitacin B	Indole-3-carbinol	Doxorubicin
Methyl jasmonate	Apigenin	Dioscin	Lycopodine	Cholic acid
Phenylethylisothiocyanate	Baicalein	Diosgenin	Morphine	Arachidonic acid
Sorbitol	Baicalin	Erythrodiol	Oxymatrine	Cribrostatin 6
Sulforaphane	Benzaldehyde	Farnesol	Pancratistatin	Daunomycin

Table 4 List of important cancer therapeutic drugs that induce apoptosis by several ways

Drug	Uses in chemotherapy	Mode of action
Imatinib	PDGFR inhibitor	Induction of ROS-mediated apoptosis in melanoma cells by disrupting membrane potential of mitochondria.
Erlotinib	EGFR inhibitor	Induce reactive-species mediated cell death in lung cancer cells by JNK and p38 phosphorylation.
Vemurafenib	BRAF inhibitor	Uplift superoxide anions in order to induce mitochondria mediated cell death.
Rituximab	Monoclonal antibody (anti-CD-20)	Inhibit ROS mediated downregulation of Bcl-2 and p38 in order to induce apoptosis in B cells lymphomas.
Procarbazine	Chemotherapeutic agent	Trigger unrepairable oxidative DNA damage in brain cancers and Hodgkin's lymphoma.
Doxorubicin	Chemotherapeutic drug	Induce cytotoxicity by generating hydroxyl radicals in several cancers.
Arabinocytosine	Chemotherapeutic drug	Hinder DNA replication and induce ROS in order to kill acute myeloid leukemia cells.
Arsenic trioxide	Chemotherapeutic drug	Trigger the leakage of electron in order to induce apoptosis in different cancer cells.
5-fluorouracil	Chemotherapeutic drug (pyrimidine analog)	Induces p53 dependant ROS mediated apoptosis in different cancer cells.
2-methoxyestradiol	17β-estradiolmetabolite	Induce apoptosis in neuroblastoma cells
N-(4-hydroxyphenyl) retinamide	Analog of retinoic acid	Induce program cell death in lung cancer cells
Gamitrinib	HSP-90 inhibitor	Trigger mitochondrial damage in order to induce apoptosis in prostate cancer cells.
ARQ 501	Quinone derivative	Enhance ROS through leakage in the mitochondrial ETC in order to induce apoptosis in solid tumors and pancreatic adenocarcinoma.
STA-4783	Copper chelator	Induce ROS mediated apoptosis in adenocarcinoma through manipulating ETC.
Celecoxib	Nonsteroidal anti-inflammatory drug	Enhance redox level, increase Bax/Bcl-2 ratio and induce stress to endoplasmic reticulum in order to kill prostate cancer cells.
Paclitaxel	Chemotherapeutic drug (Mitotic inhibitor)	Increase Nox (NADPH oxidase) activity in order to induce ROS mediated cell killing.
Bortezomib	Chemotherapeutic agent	Induce ROS that has been generated from endoplasmic reticulum stress in order to kill HNSCC cells.
Platinum drugs	Chemotherapeutic agents	Induce ROS mediated DNA damage in several line of cancers.
Curcumin	Bioactive compound	Induce ROS mediated apoptosis.
Quinacrine	Bioactive compound	Induce ROS activation (endoplasmic reticulum stress- mediated) in order to kill cancer cells.

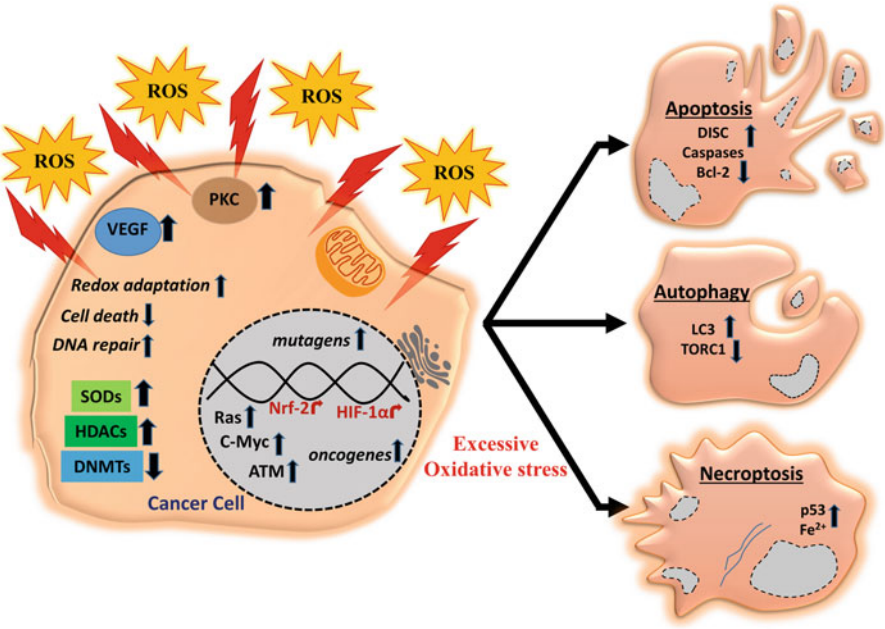

Fig. 4 ROS-mediated programmed cell deaths (apoptosis, autophagy, and necroptosis) implicated in cancer therapy

autophagy, ROS can also induce necrosis or necroptosis – the type III programmed cell death (Perillo et al. 2020). Recently, an unusual type of ROS-mediated cell death was observed, and it was termed as ferroptosis, which is also linked with the upregulation of tumor suppressor protein p53 (Jiang et al. 2015). A synthetic drug, erastin, is reported to induce ferroptosis by enhancing the ROS level in order to alter mitochondrial permeability (Dolma et al. 2003). The oxidative stress-mediated cell death is depicted in Fig. 4.

Conclusion

Reactive species (mainly ROS) are produced as a result of mitochondrial metabolic reactions, and physiological redox level is regulated by different enzymes maintaining redox homeostasis. If the redox balance is disturbed due to exogenous or endogenous factors, then the oxidative stress ensues. For the last couple of decades, extensive research has been carried out in redox biology, mainly to identify biomarkers involved in oxidative stress, implication of dietary antioxidants, and their involvement in different health problems including cancer. As summarized in this topic, the ROS also imparts tumor initiation, progression, and metastasis. For

judicious therapeutic management of the cancers, the understanding of molecular cascades associated with ROS needs to be systematically explored.

Cancer cells are known to have an elevated level of redox species, and generation of different reactive species (especially ROS) transforms the normal cells into the cancer cells (Fig. 1). Though ROS helps in the malignant transformation of normal cells, excessive redox level may prove toxic to the cancer cells as well. Traditional chemotherapy targets cancer cells by mainly causing DNA damage. However, recurrence of cancer has been reported in almost all type of cancers. Recent discoveries have highlighted the role of CSCs in the cancer recurrence. CSCs contribute to the resistance to chemotherapy, drug efflux, and deregulation of the DNA-damaging effects of chemotherapy. They have lesser amount of redox species as compared to the cancer cells, and this helps them to survive the cytotoxicity of ROS. In order to enhance the cancer stemness, ROS plays several pivotal roles in the niche of tumor microenvironment. ROS-mediated alterations of several cellular signaling lead to the epithelial-to-mesenchymal transition, enhanced invasion, proliferation, and angiogenesis (Fig. 2). In addition, elevated level of ROS is linked with the hypoxia-mediated upregulation of cancer stemness markers, which resulted in the downregulation of redox level in CSCs in order to facilitate the survivability of CSCs and cancer progression. Moreover, ROS is also involved in the modulation of several microRNAs, oncogenes, tumor suppressor genes, and even epigenetic modifications. Eventually, these modifications lead to tumor initiation, tumor progression, and tumor metastasis, establishing a strong relation between ROS and carcinogenesis.

Oxidative stress is having several important roles in cancer, which makes redox biology a whole new era, and it can be used as cancer therapeutics. Apart from the fact that ROS plays a prime role in the onset of carcinogenesis, it acts as a double-edged sword in cancer therapy. Firstly, it is well established that each and every chemotherapeutic agent has its own adverse reaction inside the body, which causes plethora of side effects, complications, and deterioration of patient's quality of life. In order to improve the health status of patient's life, a preventive dose of antioxidants is being used in adjuvant chemotherapy (Fig. 3). Secondly, it is well known that several cancer therapeutics, radiation, and chemotherapy generate ROS, which are key mediators for programmed cell death (Fig. 3). Pro-oxidants or therapeutic dose of antioxidants induce more oxidative load in cancer cells, which lead to the activation of several factors involved in apoptosis, necrosis, autophagy, and ultimately death of cancer cells (Fig. 4). Even though cancer cells ought to have a strong antioxidant defense mechanism in order to tackle elevated redox level, cancer cells are also found to be more sensitive to it. Hence, ROS can be used as a novel therapy to kill cancer cells through all three mechanisms of programmed cell death.

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