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Review Article

Reactive Oxygen Species: Synthesis and Their Relationship with Cancer-A Review

Ayesha Noreen[1], Dilara A. Bukhari[2] and Abdul Rehman[1,*]

[1]*Department of Microbiology and Molecular Genetics, University of the Punjab, New Campus, Lahore 54590*
[2]*Department of Zoology, GC University Lahore, Lahore 54590*

ABSTRACT

The reactive oxygen species (ROS) can be generated by intake of environmental pollutants, smoke, tobacco, xenobiotic, drugs, medical materials, radiations, pesticides, industrial solvents and ozone. The processes running in the cell membranes, peroxisomes, mitochondria and endoplasmic reticulum also generate ROS. ROS can be activated by numerous external factors, and play an important role in cancer growth and metastasis. ROS and tumor cell interaction could activate the signalling pathways, promoting cell proliferation, invasion, inducing angiogenesis, inflammation and cellular transformation in cancer. A better understanding into the mechanism of ROS in cancer progression might be useful for the development of biomarkers and therapeutic strategies. The objective of this review was to summarize the roles of ROS in different stages of cancer, cell invasion, angiogenesis and metastasis.

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AN collected information and wrote the manuscript. DAB helped in manuscript preparation. AR conceived the idea and wrote and edited the manuscript.

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ROS, Cancer, Cell signaling, Cancer prevention.

INTRODUCTION

Sources of reactive oxygen species (ROS)

Oxygen is an essential survival component of human life; however, it is also an alarming sign for human life due to the production of toxic agents (Pramanik and Pandey, 2013). During ATP synthesis in mitochondria electrons transfer from NADPH and succinate to molecular oxygen and may leak out of the electron transport pathway. These electrons react with O_2 to form reactive oxygen species (ROS) (Fig. 1) which are highly reactive (Gogvadze *et al*., 2008; Murphy, 2009; Andrea and Chandel, 2014), move through mitochondrial pore into the cytoplasm (Storz, 2006; Andrea and Chandel, 2014) and converted into H_2O_2 by superoxide dismutase (SOD_2, SOD_3) of mitochondrial matrix or of cytosol (SOD_1) (Brown and Bicknell, 2001; Rhee, 2006; Gupta *et al*., 2012; Andrea and Chandel, 2014; Costaa *et al*., 2014). Under normal circumstances, cellular antioxidants defense mechanisms minimize any damage. ROS are also formed during non-enzymatic processes. For example, exposure to UV light and ionizing radiation causes ROS formation.

Mitochondria are not only generator of ROS while the neutrophils and macrophages also generate ROS by oxidase enzyme bounded in the plasma membrane (NADPH-oxidase) controlled by the GTPase Rac1 downstream of the proto-oncogene *Ras* (Sundaresan *et al*., 1996; Brown and Bicknell, 2001; Ishimoto *et al*., 2014).

ROS can be divided into major two types; first form carrying one or two unpaired electron while the second form having no unpaired electron is also highly reactive due to its conversion into radical form. ROS can be generated by the intake of extracellular agents *i.e.,* all types of environmental pollutants such as smoke, tobacco, xenobiotics, drugs, medical materials, radiations, pesticides, industrial solvents, ozone *etc*. (Ebadi, 2001; Choudhari *et al*., 2014) and also generated from the mechanisms working in various organelles of the body *i.e.,* NADPH oxidase complex in the cell membranes, peroxisomes, mitochondria, endoplasmic reticulum (Inoue *et al*., 2003; Gupta *et al*., 2012; Choudhari *et al*., 2014; Zhou *et al*., 2014), phagocytosis, arachidonate pathways, exercise, ischemia/reperfusion injury by oxygen metabolism, immune responses and inflammation (Miguel and Cordero, 2012; Salman and Ashraf, 2013; Choudhari *et al*., 2014; Okon and Zou, 2015).

Peroxisomes contain xanthine oxidase enzyme for the generation of superoxide and H_2O_2 (Bonekamp, 2009; Misra and Reddy, 2014). The former reacts with nitric oxide and produces highly reacted peroxynitrite while the later in the presence of catalase converted into harmless product *i.e.,* water, while in the presence of metallic catalyst, it transformed itself into more reacted hydroxyl radicals (Szabo *et al*., 2007). Similarly, cell membrane synthesizes and retains various reactive oxygen species from various organelles *i.e.,* endoplasmic reticulum (Geiszt *et al*., 2000;

* Corresponding author: rehman_mmg@yahoo.com
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Lambeth, 2004; Bedard and Krause, 2007; Gupta *et al*., 2012; Zhou *et al*., 2014).

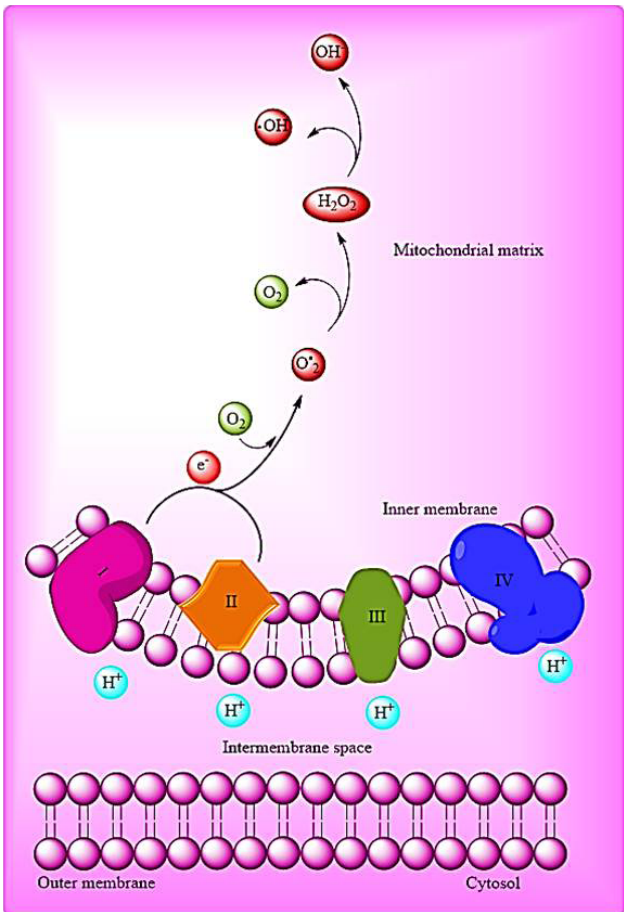

Fig. 1. ROS formation in the mitochondrion. Electrons inadvertently leak from the electron transport chain and react with O_2 to form superoxide. Superoxide is converted to hydrogen peroxide and H_2O_2 eventually converted into hydroxyl radical.

Role of mitochondria in reactive oxygen species production

According to Haas *et al*. (2008), the level of CoQ in mitochondria can be used as biological marker; its deficiency reduces activity of mitochondrial respiratory enzymes, low expression of oxidative phosphorylated protein, lower mitochondrial membrane potential, enhances the ROS production, mitochondrial permeabilization, mitophagy of dysfunctional mitochondria, reduced growth rates and cell death (Rodriguez-Hernandez *et al*., 2009; Cotan *et al*., 2011; Miguel and Cordero, 2012). During respiratory damage in the cancerous cells, at the inner membrane of the mitochondria, electron having low coupling capacity causes more release of electron to form superoxide radicals that move into the cytosol, thus stimulating neighboring mitochondria for further ROS production. This phenomenon is known as "ROS-induced ROS-release", working as positive feedback mechanism for ROS generation to damage mitochondria (Pelicano *et al*., 2003; Zorov *et al*., 2006; Miguel and Cordero, 2012).

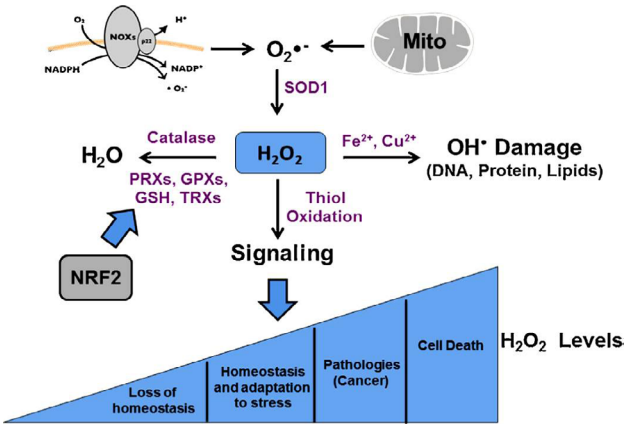

Fig. 2. ROS regulation and cellular effects. H_2O_2 and superoxide (O_2^{-}) from mitochondria and cytosolic NADPH oxidases converted to H_2O_2 by cytosolic SOD_1 later on converted to water by catalase, GPXs and PRXs. H_2O_2 causes damages to DNA, proteins and lipids and cell signaling via OH- radicals and oxidation of protein's thiol. H_2O_2 at different ranges have different cellular effects; very low range is beneficial to cell 's homeostasis and optimum level used to cope with cellular stresses and its level above this range can cause disease (cancer) and very high range leads to cell death.

Relationship between cancer and ROS

Oxidative stress is the condition when an unbalance of oxidants and antioxidants (which remove oxidants) occur which consequently enhanced the production and accumulation of oxidants within the body (Salman and Ashraf, 2013) *i.e.,* hydroxyl radical, superoxide radical, nitric oxide radical, lipid peroxyl radical, peroxy and alkoxy radicals, oxygen derived non-radical species like hydrogen peroxide and singlet oxygen (Circu and Aw, 2010; Stojnev *et al*., 2013; Choudhari *et al*., 2014). Mammalian cells utilize oxygen during aerobic respiration normally generated the oxygen radicals continuously for bactericidal and other cell defending activities, and their level maintained by the cell scavenging system to stop alteration in protein, lipids and DNA (Klaunig and Kamendulis, 2004; Choudhari *et al*., 2014; Ma *et al*., 2014). During aerobic respiration 4-5% of molecular oxygen is converted to reactive oxygen species (Salman and Ashraf, 2013) and over production of these radicals may cause various type of diseases *i.e.,* cancer (Brown and Bicknell, 2001; Benhar *et al*., 2002; D'Autreaux, and

Toledano, 2007; Fruehauf and Meyskens, 2007; Veal *et al*., 2007; Winterbourn, 2008; Alexander *et al*., 2010; Gupta *et al*., 2012; Choudhari *et al*., 2014). Carcinogenesis is known as the cell cycle disease consisting of various steps *i.e.,* a healthy cell intake non genotoxic and genotoxic agents that cause various mutation. If the damage occurred, due to mutation, within DNA molecules is not high then move on to newly dividing cell by malfunction of the cell cycle machinery producing neoplastic, if it's to high then stimulate the cell death (Fig. 2) machinery by triggering p53 for apoptosis and cell necrosis (Sandhu *et al*., 2000; Miguel and Cordero, 2012; Choudhari *et al*., 2014; Ma *et al*., 2014).

Damages caused by ROS in carcinogenesis

Mitochondria are the major source of the generation of ROS, mainly superoxide due to malfunctioning of electron transport chain, later on reduced to hydrogen peroxide and hydroxyl radicals. These ROS cause the DNA mutations which can induce guanine to thymine trans versions or vice versa (Lunec *et al*., 2002), alkali labile sites, oxidized purines and pyrimidine's, instability formed directly or by repair processes (Dizdaroglu *et al*., 2002; Cooke *et al*., 2003; Jaruga *et al*., 2004; Choudhari *et al*., 2014). These mutations mostly affect GC base pairs *i.e.,* base pair substitutions, deletions and insertions are less occurring, while AT base pair cause rare mutations; single or double strand breaks and exchanges of sister chromatid, and all these genetic instability results the inactivation of tumor suppressor genes or enhance the expression of proto oncogenes strengthen the cancer (Szatrowski and Nathan, 1991; Retel *et al*., 1993; Brown and Bicknell, 2001). The 8-hydroxy-2'-deoxyguanosine in case of invasive ductal cancer is 10 times highly occurring as compared to the noninvasive (Wiseman and Halliwell, 1996; Brown and Bicknell, 2001). Brain cells are highly susceptible to harmful effect of ROS due to their low ability for cellular regeneration and enhanced metabolic rate (Waris and Ahsan, 2006; Choudhari *et al*., 2014).

Effect of ROS on different stages of cancer

The oxidative damage has been linked to at least 100 human diseases because each and every tissue of the body can undergo malignant state by activation of proto oncogenes into carcinogenic oncogenes, and having various type of cancer (Sugimura, 1998; Waris and Ahsan, 2006; Choudhari *et al*., 2014). Cell cycle normally controlled by set of proteins *i.e.,* cyclins and cyclin-dependent kinases (CDKs) which regulate cell-cycle growth that are under the control of cyclins and CDK inhibitors *i.e.,* p21 and p27 inhibit the further progression of the cell cycle whereas they also activate CDKs of G1 phase (Gupta *et al*., 2012). Broadly, cancer contains three major stages; firstly, initiation that includes non-lethal DNA damage; to remove this error cell stops its cell cycle for further growth and later on resumes its activity (Yano *et al*., 2009); secondly, the promotion stage that expands the initial stage by cell growth, suppressing the apoptosis, reducing antioxidants function, promoting free radicals generation that cause the loss of cell homeostasis and construct nodules, polyp or the papilloma and thirdly, the progression of chronic DNA damage, causes genomic instability which leads to malignant transformations by failures in metabolic activity and provoking a high ROS generation (Waris and Ahsan, 2006; Kryston *et al*., 2011; Miguel and Cordero, 2012).

ROS induces signaling cascades

Receptor tyrosine kinases (RTKs) cascade phosphorylation, initiated by ROS that were activated by various growth factors (*i.e.,* epidermal growth factor, platelet derived growth factor, fibroblast growth factor as well as cytokines, tumor necrosis factor, γ-interferon and interleukins) in no phagocytic cells (Waris and Ahsan, 2006; Behrend *et al*., 2003; Ahn *et al*., 2014). The two protein families which control signal transduction pathways by ROS activation are; firstly, the mitogen activated protein kinase (MAPK) that phosphorylates serine or threonine residue to transduce message (in the form of gene expression, mitosis, proliferation, motility, metabolism, and programmed cell death) from cell membrane to nucleus of the cell, and further divided into three major groups, the extracellular signal-regulated kinase, the c-Jun NH2-terminal kinase, and the p38 MAPK that control proliferation, differentiation, and apoptosis, respectively (Wada and Penninger, 2004). Secondly, the redox sensitive kinases which contain cysteine motifs i.e., thioredoxin, nuclear signaling factors such as Ref-1 and transcription factors *i.e.,* AP-1, NF-κB, Nfr-1, Egr-1, all are plying critical role for DNA synthesis, and cell growth. The retardation in these factors arrests the cell cycle to proceed (Cook *et al*., 2004; Waris and Ahsan, 2006; Ahn *et al*., 2014).

Cell promotes mitosis by enhancing the expression of cyclin D1 and cyclin dependent kinase by increasing the activation of AP-1 (Salman and Ashraf, 2013; Ahn *et al*., 2014). In carcinogenesis, NF-κB plays a very important role for the cell survival and its proliferation during activated state by extracellular stimulating agents for the cell growth and retard apoptotic pathways activation (Klaunig and Kamendulis, 2004; Waris and Ahsan, 2006; Ahn *et al*., 2014).

ROS and cancer cell proliferation

Abnormal cells increase oxidative stress within the

cell by catabolizing the thymidine to thymine and 2-deoxy-D-ribose-1-phosphate (that quickly bind with proteins to form glycated proteins) by thymidine phosphorylase (Brown *et al*., 2000; Brown and Bicknell, 2001). For cancer cell proliferation, more energy and building material of biological mass construction is required to fulfill their needs. Tumor cells undergo glycolysis and complex I and complex III of the respiratory chain, do not move into oxidative phosphorylation by stopping the movement of glycolytic product *i.e.,* pyruvate by pyruvate dehydrogenase kinase 1. It also inhibits pyruvate dehydrogenase synthesis required to run Krebs cycle and enhances the lactate production. This ultimately inhibited the production of antioxidant agent generated during Krebs cycle and induces ROS generation through electron leakage by disturbing membrane potential although it's have more energy demand for quickly growing cell. This is called as Warburg effect which is a hallmark of cancerous cells (Puntel *et al*., 2007; Lu *et al*., 2012; Costa *et al*., 2014).

Hypoxia is another characteristic of rapidly growing cancerous cells having more oxygen demand for massive cell growth which lack proper supply of oxygen to these cell growth, generating more oxidative stress (Chandel *et al*., 1998) and their survival maintained by activating hypoxia inducible factor (HIF) that increases the glucose uptake by activating glucose transporters (GLUT1 and GLUT3) for ATP synthesis. New blood vessels are constructed through the angiogenesis for more oxygen supply but these vessels are disorganized and leaky; cause the periods of hypoxia, reperfusion and ROS release (Gerald *et al*., 2004; Pouyssegur and Mechta-Grigoriou, 2006; Laurent *et al*., 2008; Costa *et al*., 2014).

ROS in cancer cell invasion, angiogenesis and metastasis

In tumor, there is a rapid outgrowth of tumor cells that increases blood supply by vasodilation that activates cGMP by carbon monoxide (CO) whose level increased by oxidative stress which transforms heme to biliverdin and CO by heme oxygenase-1 (Brown *et al*., 2000). The angiogenesis formation for energy in the form of glucose consequently enhances the levels of hypoxia inducible factor-1 (HIF-1) and causes the hypoxia (glucose deprivation) which results in more oxidative stress within cell and produces the more vascular endothelial growth factor (VEGF) (Spitz *et al*., 2000; Brown and Bicknell, 2001).

The last stage of cancer leads to cell invasion, angiogenesis, and metastasis by activating various factors i.e., serine proteases and its receptors, VEGF and its receptors, platelet-derived growth factor, fibroblast growth factors, epidermal growth factor (EGF), ephrins, angiopoietins, endothelins, integrins, cadherins, and transcription factors (Wang, 2001; Aggarwal *et al*., 2009; Gordon *et al*., 2010). These factors are involved in cell attachment, growth, migration by breaking the barriers between tissue through dissolving it by proteolytic enzymes *i.e.,* matrix metalloproteinases and blood vessels formation known as angiogenesis (Jiang *et al*., 2001; Sternlicht and Werb, 2001; Fan *et al*., 2006). The high rate production of ROS, reverses its function by inhibiting the expression of genes and transcription factors participating in malignancy (Ushio-Fukai and Alexander, 2004; Ushio-Fukai, 2006; Ushio-Fukai and Nakamura, 2008; Gupta *et al*., 2012).

ROS role in cancer inflammation

In body defense system inflammation plays an important role for providing security to the cells, acute inflammation, is very beneficial to body, however, chronic inflammation is the alarming sign of various chronic diseases, top of which is cancer, as first time reported by Virchow (Balkwill and Mantovani, 2001; Schetter *et al*., 2010). Thus there is a strong relationship between chronic concentration of ROS induces COX-2, inflammatory cytokines (TNF-a, interleukin), chemokine, and pro-inflammatory transcription factors (*e.g.,* NF-jB activation for chronic inflammation and cancer (Hussain *et al*., 2003; Mantovani, 2005; Mantovani *et al*., 2008; Colotta *et al*., 2009; Reuter *et al*., 2010; Schetter *et al*., 2010; Grivennikov *et al*., 2010; Grivennikov and Karin, 2010; Gupta *et al*., 2012).

ROS role in cellular transformation

There are two types of mutations for transformation of normal cell into cancerous cell; first one is gain of functional mutations of oncogenes and second one is the loss off functional mutation of tumor suppressor genes (Wang, 2010). A variety of genes mutate their function to reach malignancy state *e.g.,* p53, Raf, retinoblastoma (Rb), protein phosphatase 2A, telomerase, Ral-GEFs, phosphatidylinositol 3-kinase (PI3K), Ras, Rac, cellular v-myc myelocytomatosis viral oncogene homolog (c-Myc), STAT3, NF-jB, and HIF-1a. Chemicals, viruses, radiation, hypoxia, and nutrient deprivation all contribute in this process (Ralph *et al*., 2010; Gupta *et al*., 2012).

Role of ROS in cancer treatment

For the cancer treatment two main strategies are applied. In ROS elevated strategy, ROS generation increases within cell, decreases the antioxidant activity while in ROS elimination strategy, ROS eaters (antioxidants) reduce ROS level and promoted the antioxidant system for cellular defense (Schumacker, 2006; Fruehauf and Meyskens,

2007; Wang and Yi, 2008; Trachootham *et al*., 2009; Gupta *et al*., 2012). ROS elevated level by radiotherapy, photodynamic or any other way from threshold limit helps in cancer therapy by apoptosis (Brown and Bicknell, 2001). Sub-lethal oxidative stress stimulates cell proliferation by activation of MAPK pathways (Wang *et al*., 1998; Brown and Bicknell, 2001). According to Wang *et al*. (2011), normal cells are exposed to Cr^{6+} that induces ROS generation and cellular transformation. Its production can be reduced by overexpression of antioxidants *i.e.,* SOD1, SOD2, or CAT (Gupta *et al*., 2012). A combined therapy has been proved more successful.

Dual role of ROS in cancer

There is a strong relationship between ROS and cancer due to multiple reasons such as ROS promote the initiation of cancer. In cancerous cell, more ROS concentration helps in continuous expression of oncogenes and enhances the chances of error occurring in powerhouse of the cell (mitochondria). This evokes glycolytic energy generation mechanism which leads to cancer progression by activating growth factors and receptors, causes angiogenesis, inflammation, and cell transformation. ROS invasion causes mutation in tumor suppressor gene and inhibits it to perform its function and help in tumor progression and metastasis (Chandel *et al*., 2000; Schafer and Buettner, 2001; Seo *et al*., 2002; Behrend *et al*., 2003; Hussain *et al*., 2003; Boonstra and Post, 2004; Hileman *et al*., 2004; Ramsey and Sharpless, 2006; Takahashi *et al*., 2006; Wu, 2006; Liu *et al*., 2008; Reuter *et al*., 2010; Gupta *et al*., 2012). ROS and cancer (like as lock and key relationship), can be treated by enhancing or eliminating the level of ROS within cancerous cells. Such disturbance in optimum level of cancer causing ROS leads to death of cancerous cells (Hyoudou *et al*., 2006, 2008; Ozben, 2007; Seifried *et al*., 2007; Gupta *et al*., 2012). According to US Food and Drug Administration, few drugs have been used as antioxidants for pro-oxidant activity *i.e.,* procarbazine, motexafin gadolinium, elesclomol, 2-methoxyestradiol, imexon, minodronate and histamine (Gupta *et al*., 2012).

In cancerous cells, ROS dosage, duration, type, and site of action help in promoting cancer cells growth or suppress their growth by cell death. Although medium concentration of ROS supply helps in cell survival and elevated concentration inhibit cell growth and kill them (Kong *et al*., 2000; Schafer and Buettner, 2001; Gupta *et al*., 2012). A low concentration of arsenite increases the expression of c-Myc, heme oxygenase-1, and NF-jB activity in breast cancer by producing ROS and promoted its growth from G1 to S phase of cell cycle (Ruiz-Ramos *et al*., 2009). According to Qu *et al*. (2011), higher the level of ROS within breast cancer cells lower the NF-JB activity, thus suppressing the cell progression (Gupta *et al.,* 2012).

In short, in living systems ROS induces beneficial effect (*i.e.,* responses to noxia, involve in cellular signaling systems, defense against pathogenic and induce mitogenic response at low level of ROS); or harmful effect (Valko *et al.,* 2004*,* 2006). ROS causes various type of cellular damage at high level (lipids and membranes, proteins and nucleic acid) (Poli *et al.,* 2004; Valko *et al.,* 2006; Ma *et al.,* 2014).

Hurdles in cancer treatment by ROS

In cancerous cell, there is a high level of ROS, and the persistent ROS concentration in it, made it resistant to external ROS stress by activating antioxidant system of cell by various transcription factors i.e., nuclear factor kappa-light-chain enhancer of activated B cells (NF-jB), nuclear factor (erythroid- derived 2)-like factor 2, cellular Ju-nanna (c-Jun), and hypoxia-inducible factor-1a (HIF-1a) (Pervaiz and Clement, 2004; Tiligada, 2006; Sullivan and Graham, 2008) e.g., resistance to H_2O_2, arsenic trioxide (As_2O_3), by enhancing the level of catalase, SOD and GSH antioxidant (Lenehan *et al.,* 1995; Hour *et al.,* 2004; Gupta *et al.,* 2012). Continued oxidative stress causes resistance to apoptosis by the production of antioxidant thiol thioredoxin, metallothionein, malondialdehyde, superoxide dismutase, glutathione peroxidase and catalase (Lazo *et al.,* 1998) and it also causes resistance to therapy (Brown and Bicknell, 2001). Our focus should be on mutual generation of ROS and harm signaling molecules associated with antioxidant system to treat cancer (Gupta *et al.,* 2012).

ROS in cancer cell death

Cancerous cell has survival ability as inheritable character. Apoptosis, necrosis, and autophagy are the three ways used for treatment of cancer cell without harming the normal cells (Simon *et al*., 2000; Wochna *et al*., 2007; Gupta *et al*., 2012).

ROS and apoptosis

Apoptosis is defined as programmed cell death and is tightly controlled by cellular machinery. It is classified into extrinsic and intrinsic pathway and both are regulated by ROS (Brown and Bicknell, 2001; Ozben, 2007; Ma *et al*., 2014). In the extrinsic pathway, ROS required for phosphorylation of Fas ligand for its stimulation to activate death domain and caspase 8 to induce apoptosis (Denning *et al*., 2002; Uchikura *et al*., 2004; Medan *et al*., 2005; Reinehr *et al*., 2005) via ubiquitination and destruction of the FLICE inhibitory protein to retain Fas in activated state (Brown and Bicknell, 2001; Wang *et al*., 2007). ROS induces the activation of destabilizing proteins *i.e.,* Bcl-

2-associated X protein, Bcl-2 homologous antagonist/killer and suppresses the pore-stabilizing proteins activity *i.e.,* Bcl-2 and Bcl-xL (Martindale and Holbrook, 2002) stimulate the cytochrome c to move out from mitochondria, construct apoptosom and activate caspase (Gupta *et al*., 2012; Zou *et al*., 2015). According to Choudhary *et al*. (2011), apoptosis can be induced by ROS via without caspase activity in human bladder cancer cells. It was also stimulated by administration of H_2O_2 to enhance the activation of caspase-3 (Gupta *et al*., 2012; Zou *et al*., 2015).

ROS and necrosis

However, a huge amount of ROS production can induce necrotic cell death. A cancerous cell can die by apoptosis and necrosis (Hampton and Orrenius, 1997). A small level of H_2O_2 induces the cells to caspase activation leading to apoptosis while no caspase activation occurred in case of necrosis. As a result, high ROS are produced at higher H_2O_2 concentration induction (Gupta *et al*., 2012).

ROS and autophagy

Self-eating by lysosome of distressed cellular organelles sequestrates and cytoplasmic protein aggregates help in cell survival and cell death pathways (Hippert *et al*., 2006; Gupta *et al*., 2012).

According to US Food and Drug Administration, drugs are classified into two major groups. First one is non-targeted drugs that are further classified into two classes; first those non targeted drugs that function at specific phases of cell-cycle while cell-cycle nonspecific function at any targeted point. The second is targeted drugs that are attached at targeted growth factors to stop cell growth *e.g.,* monoclonal antibodies (rituximab, ibritumomabtiuxetan, ofatumumab, and alemtuzumab (Renschler, 2004; Gupta *et al*., 2012). In cancerous cells, there is over production of H_2O_2 that can be prevented by diphenyleneiodonium, which is an inhibitor of the flavoprotein component of the NADPH-oxidase (Brown and Bicknell, 2001).

Cancerous cells suppress antioxidant enzymes production, contact directly to ROS generating agents, and reduce buffering capacity of the cellular oxidants. Normally, cells contain less ROS stress and more activated antioxidant system to reduce oxidative damage within cell as compared to the cancerous cells (Salman and Ashraf, 2013). *In vitro* and *in vivo* combination therapy is more beneficial to kill the cancerous cells by promoting the ROS and suppressing the antioxidants (Salman and Ashraf, 2013).

Mutagenesis is one of the causing agents of chronic inflammation by activating the expression of JAK-STAT activation and JAK2. The inhibitory agents, those targeted the JAK 1-2, are very useful for suppressing the tumor progression (Verstovsek *et al*., 2010; Salman and Ashraf, 2013). For the therapeutic purpose electron transport chain is a good target to enhance the ROS generation within the cancerous cells and suppress antioxidant system to improve the susceptibility of ROS to induce apoptosis (Pramanik and Pandey, 2013).

Cancer prevention

Anand *et al*. (2008) reported that 90–95% of cancers caused by external environment *i.e.,* advancement in life style and only 5%–10% caused by genetic defects. To overcome this disorder we have to change our lifestyle to simplest form. ROS production can be reduced by more intake of antioxidant producing fruits and vegetables (Gupta *et al*., 2012; Belcaid *et al*., 2014).

ROS and resistance therapy

Various cancerous cells develop multidrug resistance proteins in them to resist chemotherapy and radiotherapy. To overcome this problem, several researchers proposed oxidation therapy by ROS-generating anticancer agents to treat cancer (Gupta *et al*., 2012). According to Tsai *et al*. (1996), cancerous cells showed resistance against cytotoxic drugs by expressing higher level of Her-2/neu. The suppression of signaling pathways retarded the expression of Her-2/neu and cell became sensitive against these drugs; likewise mutated EGFR overexpression suppress apoptosis and retardation in EGFR signaling stop the cell growth and cell became sensitive against this drug (Nagane *et al*., 1998). Murillo *et al*. (2001) reported that the suppression in the expression of HER-2/neu stimulates p38 activity for initiation of apoptosis. So such combined strategies are very helpful to eradicate the tumor (Benhar *et al*., 2002; Stojnev *et al*., 2013; Phillips *et al*., 2014).

CONCLUSIONS

Oxidative stress arising from the ubiquitous production of reactive oxygen species has been implicated in the pathogenesis of various diseases including cancer. Literature review has provided some evidence of the important physiological role of ROS in normal cell function, diseases may arise where the concentration of ROS exceeds and overwhelms the body's natural defense against them. Additionally, ROS may induce genomic alterations which affect cellular homoeostasis and may result in disease. Apoptosis, necrosis, and autophagy are the three ways used for cancer treatment of the cell without harming the normal cells in ROS presence. This disease can also be minimized by simplified life style and oxidation therapy by utilizing ROS to generate anticancer

agents to treat cancer. The need is particularly pressing in developing treatments for conditions which remain difficult to treat different stages of cancer.

Statement of conflict of interest

The authors declare that they have no conflict of interest.

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