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A Review of Reactive Oxygen Species and the Antioxidant System

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ABSTRACT

Reactive oxygen species (ROS) are the oxygen derivatives that are produced by the cells during their metabolic processes. These are reactive, unstable, or partially reduced oxygen derivatives that include the superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), hypochlorous acid (HOCl), and hydroxyl radical (·OH). ROS also function as second messengers in signaling pathways that are crucial for several normal and cancer cell pathways. Nevertheless, ROS production can incite damage to cellular components thereby disturbing the normal cell physiology. The unevenness in the ROS production and the antioxidant defenses lead to a variety of diseases including cancer. Several studies have shown that ROS can act either as cancer promoter or suppressor by virtue of its cell location, molecular interactions etc. Antioxidant enzymes, like Glutathione (GSH) and Thioredoxin (Txn) etc. act as the key players in maintaining the intracellular balance mechanisms along with other antioxidants that work in co-ordination to get rid of the ROS and keeping the system integrity intact. Paradoxically, ROS is also generated as an effect of chemo- and radiotherapy (RT) to kill the cancer cells. This review will focus on how a normal cell can combat ROS in contrast to ROS generated by RT in cancer patients.

KEYWORDS

ROS; Oxidative stress; Antioxidant system; Radiotherapy

INTRODUCTION

Cancer continues to be a global burden despite the fact that a noteworthy advancement has been made in the understanding of cancer-associated molecular mechanism and its related treatment modalities. The International Agency for Research on Cancer (IARC) has forecasted that by 2030, ~26 million fresh cancer cases and 17 million cancer deaths will occur every year globally [1]. Radiotherapy is still the core component of cancer treatment management which bestows survival benefits to a larger extent, therefore, around 50% localized malignant cancers receive radiotherapy as a part of the treatment [2,3]. For some patients who cannot undergo surgery, radiotherapy seems to be an option of choice [4]. In addition, patients who are partly resected or recurrent of cancers after surgery are also frequently treated by radiotherapy [4]. Although, RT works by imparting high-energy radiation on the cancer tissues, the biological effectiveness of radiation depends on many parameters like the linear energy transfer (LET), total dose, and number of fractions and radiosensitivity of the targeted cells or

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tissues. Radiation can damage the cells nuclear or genetic material either directly or indirectly by producing free radicals. The elevated levels of free radicals induce oxidative stress in the cancer cell. A little boost in ROS levels stimulate various signaling pathways to initiate several biological processes, whereas oxidative stress indicates an elevated levels of ROS that results in damaging the DNA, protein or lipids [5]. Cells also produce the ROS as a metabolic byproduct under normal circumstances. However, under adverse stressful conditions, cell will not only produce ROS, but gradually evolve in their responses to adjust to the ROS exposure [6]. Cells also utilize ROS as a signaling molecule that would elicit oxidative stress leading to initiation of cell death processes like autophagy, apoptosis and necrosis. Hence, ROS is known to play a significant role in the cell death pathways. To counterbalance the excessive ROS, cells have developed a system to balance the oxidative stress with the help if the antioxidant system which includes the enzymatic (superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidases (GPxs), thioredoxin (Trx)) and non-enzymatic antioxidants. However, there are also certain plant-based compounds that exhibit the antioxidant property and are used in several diseases including cancer [6].

CANCER CELL RADIORESISTANCE

Radiotherapy is known to work by generating ROS that typically cause the radiation-induced DNA DSBs. However, during the course of RT and even later that evolve to develop the mechanisms that can overcome the therapy-induced cell death which are emerging as a consequence of direct or indirect effect of radiation of generating free radicals, e.g., reactive oxygen species (ROS) [7,8]. This is done at the cost of a delayed cell cycle which utilizes time to fix up the DNA [9]. However, the severity of the DNA would decide whether the cell would survive. Apart from DNA being accurately repaired under the normal circumstances, it might also lead to mis repair or inability to repair due to severe damage which consequently leads to genomic instability and cell death (refRB book). Most tumor cells typically have a p53 mutation which leads to a faulty G1 checkpoint due to which they rely on the G2/M checkpoint and tend to stack up in the G2-phase [10]. Nevertheless, the cell also has its own antioxidant scavenging system to avoid the ROS increase. Superoxide dismutases (SOD), glutathione peroxidase, peroxiredoxin, glutaredoxin, thioredoxin, and catalase are the antioxidants which are a part of the cells scavenging system [11]. Hence, radiation-induced ROS levels can be reduced if there is an increased level of these antioxidants. As a result, the decline in DNA damage may contribute to imparting radio resistance to the cancer cells. What determines the radiotherapy success is the balance between the ROS-induced DNA damage and DDR [12]. Besides, ROS enriching anticancer drugs have revealed promising results in vitro and in vivo [13,14].

REACTIVE OXYGEN SPECIES AND THE SCAVENGING SYSTEM

Cells contain an exclusive molecular structure of oxygen because of which it can accept free electrons that are produced from the cells own oxidative mechanism. Aerobic organisms utilize this molecular oxygen and subsequently, forms oxygen containing reactive species, which are commonly called as reactive oxygen species. ROS is a collective term used for hydrogen peroxide (H_2O_2), superoxide ($O_2^{\bullet-}$), hydroxyl radical ($OH^{\bullet}$), singlet oxygen ($^1O_2$), alkoxyl radical ($LO^{\bullet}$), peroxyl radical ($LOO^{\bullet}$), lipid hydroperoxide (LOOH), peroxynitrite ($ONOO^-$), and hypochlorous acid (HOCl) [15]. The unpaired electron of superoxide anion makes it highly reactive and later alters it to H_2O_2 with the antioxidant enzyme SOD [16]. H_2O_2 can be further reduced to H_2O and O_2 by various other cellular enzymes and antioxidants. ROS levels can be maintained by removing substrates away from oxidative phosphorylation resulting in

decreased mitochondrial respiration. With mitochondria being a major source of ROS, cellular mechanisms leading to uncoupling of electron transport can enhance the production of ROS [17]. There are also other cells components that contribute to ROS production like the cell surface plasma membrane, enzymes in the cytoplasm and enzymes bound to the ER [18,19].

In addition, ROS is also generated by the membrane-bound protein NADPH oxidase, which uses the NADPH to produce O_2^- and later, H_2O_2. Other enzymes that can enhance ROS production are the xanthine oxidoreductase, cytochrome P_{450} monoxygenase system, nitric oxide synthases, nitric oxide synthases etc. Cellular production of $O_2^{\cdot-}$ and H_2O_2 can aid the development of lethal and reactive $HO^{\cdot}$ in the presence of reduced transition metals such as iron. Prominently, $O_2^{\cdot-}$ react rapidly with nitric oxide to form peroxynitrite ($ONOO^-$), a strong nitrating and oxidizing compound [7]. Such highly reactive species, such as $HO^{\cdot}$ or $ONOO^-$, can also react with membrane lipids to cause more complex radicals by instigating the lipid peroxidation process.

Exogenous sources include some xenobiotics, air pollutants and radiation which are known to undergo the redox cycling. In a cell, the levels of ROS are determined by their production rates and by the existence and actions of cellular antioxidant defenses. Similar to ROS, there are reactive nitrogen species (RNS) and reactive chlorine species (RCS). The RNS comprise of the nitric oxide ($NO^{\bullet}$), peroxynitrite, nitrogen dioxide radical ($NO_2^{\bullet}$), and other oxides of nitrogen or nitrogen-containing reactive species, whereas the RCS comprises of the chlorine containing reactive species like the hypochlorous acid (HOCl) [20]. The ROS scavenging system tightly regulated the ROS production in the normal physiology. The antioxidant enzymes that act as the ROS scavengers work by counterbalancing the ROS by reacting with and/or accepting electrons from ROS. During OS, the cell utilizes its various antioxidants that are ROS-species specific. Due to this the cell can repair the oxidative damage induced on the cellular components. This scavenging system includes the superoxide dismutase (SOD), peroxiredoxins, catalase, thioredoxin (TRX), glutathione reductase (GR), and glutathione peroxidase (GPX). The most abundant antioxidant synthesized by the cell is the Glutathione (GSH). The glutaredoxin and TRX system reduces the H_2O_2 and oxidizes proteins. Other antioxidants like the SOD and catalase reduce the O_2^- and H_2O_2, respectively. Antioxidants are also localized within the mitochondria as well which enhances the efficacy of the scavenging system. Endogenous sources forming ROS are the mitochondria electron transport chain of respiration and the NAD (P)H oxidases. The secondary oxidative stress is exhibited by the electrophiles that deplete cellular GSH [20].

ROS MEDIATED OXIDATIVE STRESS

Reactive oxygen species (ROS), such as $O_2^{\cdot-}$, H_2O_2, and $OH^{\cdot}$ are the by-products of aerobic metabolism and are found to be augmented in several cancer cells. This pool of increased endogenous ROS leads to adaptive changes and may play pivotal roles in tumorogenisis, metastasis, and resistance to radiation and chemotherapy. However, OS is the outcome of imbalance occurring due to the surplus accumulation of ROS or reduction in cellular antioxidants or both. Such conditions are at times beyond the cells defense capability; and therefore, unfavorable consequences of oxidative stress are observed. Such condition can overpower in a biological system under stressful unfavorable environments or physiologic conditions. In such scenarios the increase in the endogenous ROS or generation of antioxidant defenses are quick biological indicators of the oxidative stress. A range of stressful environmental conditions like the high light intensities, UV-radiation, extreme temperatures, toxins etc. hasten the ROS production. ROS production and its buildup is a general denominator in numerous diseases and environmental insults and can direct to rigorous cellular

damage leading to physiological dysfunction and cell death. The cell work against the oxidants effects and also tries to resetting vital homeostatic factor by balancing and restoring redox balancing whenever it encounters the oxidative stress. Cellular actions like these either activate or silence the genes that are involved in encoding the transcription factors, and structural proteins and defensive enzymes [21,22]. The action of IR generates the ROS inside the cell which is known to induce cancers as well as treat them. Hence, it is also considered as the double-edged sword in the cellular biochemical processes. Many known mutagens and carcinogens are known as the oxidative stress inducers.

ROS AND CELLULAR TARGETS

Reactive oxygen species causes oxidative damage to the cell components that includes the nucleic acids, proteins and lipids. In case of proteins, ROS can cause the protein oxidation and nitrosylation that can lead to the cell undermining as the damage caused to growth factors and their associated enzymatic processes [23]. Lipid peroxidation caused by the ROS can lead to apoptosis as it has an effect on the phospholipids of the cell membrane where it stimulates the sphingomyelinase and discharge of ceramide [24]. Similarly, there are DNA strand breaks that can push the cell to apoptosis or necrosis due to Nucleic acid oxidation [25]. Whether these modifications can be adaptive or not is dependent on the cells capability to restore [26]. The cell is very well equipped to shield themselves from the ROS induced damages due to the presence of a variety of antioxidants. Under normal physiological conditions ROS can interact with the redox signaling proteins and contribute to a cell signal transduction, a progression known as redox signaling. Hence ROS can also work as a second messenger to mediate reaction that are obligatory for accurate functioning and continued existence of the cell [20]. However, surplus amount of ROS can also induce apoptosis, necrosis and autophagy as depicted in Figure 1.

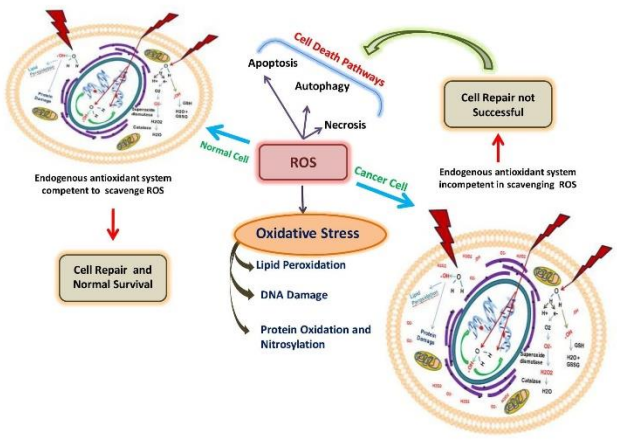

Figure 1: Surplus amount of ROS induces apoptosis, necrosis and autophagy.

ROS induced oxidative stress can suppress the mTOR activity. It can set in motion AMP-activated protein kinase (AMPK) to kindle vacuolar protein sorting 34 (Vps34) complex activity which is essential for commencement of autophagy [6]. The C-Jun-N-terminal kinase (JNK)/P53 pathway can also be activated by ROS. Apart from that, ROS can injure the mitochondria and aid in the release of the apoptotic factors. The downstream ROS production is critically controlled by the stable RIP1-RIP3 complex.

ROS IN RADIOTHERAPY

Cancer therapeutic approached aim in selectively killing cancer cells while sparing the normal cells. One of the strategies is to kill cancer cells by radiotherapy induced ROS production. OS stress destabilizes the cellular integrity due to the augmented levels of ROS due to radiation. Cancer cells experience a constant OS which sensitizes them to the therapy thereby pushing them to undergo apoptosis. Cancer cells are vulnerable to the therapy generated ROS as they already have a threshold for enduring ROS [27]. Radiation induced reactive species develop a lesion cluster on the DNA which are usually challenging to repair and restore and hence undergo a subsequent cell death [28,29]. Other targets of radiation induced ROS are the cell membrane and its organelles. ROS can easily peroxide the member lipids which lead to

the functional as well structural impairment and finally to arrest the cell cycle and lead to apoptosis [28,30]. Apoptosis can also be an outcome of the indirect effects associated with the altered signaling pathways and modified cell homeostasis [29]. ROS mediated upregulation of the mitogen-activated protein kinases like the ERK, JNK and p38 MAPK might decide the fate of cancer cells if they would proliferate, undergo cell cycle arrest or apoptosis [27]. Sometimes cell also exhibit radio resistance at optimal doses and therefore radiosensitizers are looked for enhancing the cancer cell radiosensitivity which is antioxidant mediated. When RT alone is not effective for the radioresistant cancer cells, it can be combined with an antioxidant to impart them sensitivity.

CONCLUSION

ROS production is a biological process that is conserved evolutionarily and can be generated by multiple cellular pathways. It not only serves as a cell defense mechanism but also participates in the signal transduction pathways. However, oxidative stress; an outcome of excessive ROS triggers many biological processes like that of the necrosis, autophagy and apoptosis. Killing cancer cells with radiotherapy induced ROS in a direct or indirect manner is considered to be a choice of therapeutic approaches in patients who cannot undergo surgery. RT enhances the ROS pool in the cancer cells which is contrast to that of normal cells. This subsequently leads to cancer cell death sparing the normal cells. This can be attributed that to the weakening of the antioxidant system of the cancer cells which cannot bear the load of the excessive ROS. However, in normal cells ROS is taken care by the antioxidant systems which can influence the ROS levels by controlling the gene expression pathway and the associated signaling pathways that aid on maintaining the redox balance and cell integrity. Therefore, RT is the choice of treatment in patients who cannot undergo surgery, and who are partly resected or recurrent of tumors.

CONFLICT OF INTEREST

There is no conflict of interest between the authors.

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