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Review Article

Reactive oxygen species and cancer paradox: To promote or to suppress?

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ABSTRACT

Reactive oxygen species (ROS), a group of highly reactive ions and molecules, are increasingly being appreciated as powerful signaling molecules involved in the regulation of a variety of biological processes. Indeed, their role is continuously being delineated in a variety of pathophysiological conditions. For instance, cancer cells are shown to have increased ROS levels in comparison to their normal counterparts. This is partly due to an enhanced metabolism and mitochondrial dysfunction in cancer cells. The escalated ROS generation in cancer cells contributes to the biochemical and molecular changes necessary for the tumor initiation, promotion and progression, as well as, tumor resistance to chemotherapy. Therefore, increased ROS in cancer cells may provide a unique opportunity to eliminate cancer cells via elevating ROS to highly toxic levels intracellularly, thereby, activating various ROS-induced cell death pathways, or inhibiting cancer cell resistance to chemotherapy. Such results can be achieved by using agents that either increase ROS generation, or inhibit antioxidant defense, or even a combination of both. In fact, a large variety of anticancer drugs, and some of those currently under clinical trials, effectively kill cancer cells and overcome drug resistance via enhancing ROS generation and/or impeding the antioxidant defense mechanism. This review focuses on our current understanding of the tumor promoting (tumorigenesis, angiogenesis, invasion and metastasis, and chemoresistance) and the tumor suppressive (apoptosis, autophagy, and necroptosis) functions of ROS, and highlights the potential mechanism(s) involved. It also sheds light on a very novel and an actively growing field of ROS-dependent cell death mechanism referred to as ferroptosis.

1. Introduction

Reactive oxygen species (ROS) are a heterogeneous group of highly reactive ions and molecules derived from molecular oxygen (O_2) [1]. Some of the most important ROS with physiological significance are free radicals such as hydroxyl radical (•OH), superoxide anion ($O_2^{\bullet -}$),

Abbreviations: •OH, hydroxyl radical; 2,2-BP, 2,2-bipyridyl; ABC, ATP-binding cassette; AIF, apoptosis-inducing factor; AMPK, AMP-activated protein kinase; AMPKK, AMPK kinase; ANT, adenine nucleotide translocase; AP-1, activator protein 1; Apaf-1, protease activating factor 1; ASK1, apoptosis signal-regulating kinase 1; ATG, autophagy-related gene; ATM, ataxia-telangiectasia mutated; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma-2; BHT, butylated hydroxytoluene; BNIP3, Bcl-2/adenovirus E1B 19 kDa interacting protein 3; BRCA1, breast cancer 1; BSO, buthioninesulfoxamine; CDKN2A, cyclin dependent kinase inhibitor 2A; CDX1, caudal type homeobox 1; c-FLIP, cellular FLICE-inhibitory protein; CHOP, C/EBP homologous protein; COX-2, cyclooxygenase-2; CSC, cancer stem cells; Cyt-c, cytochrome-c; DISC, death-inducing signaling complex; DNMT1, DNA methyltransferase 1; DR, death receptor; Drp1, dynamin-related protein 1; DUOX1, dual oxidase 1; EC, endothelial cells; ECM, extracellular matrix; EGCG, epigallocatechin gallate; ER, endoplasmic reticulum; ERK1/2, extracellular signal-regulated kinase 1/2; ETC, electron transport chain; FAK, focal adhesion kinase; FasL, Fas ligand; FasR, Fas receptor; GAG, glycosaminoglycan; GLUD1, glutamate dehydrogenase 1; GLUL, glutamate-ammonia ligase; GPx, glutathione peroxidase; GR, glutathione reductase; GRX, glutaredoxin; GSH, glutathione; H_2O_2, hydrogen peroxide; HDAC1, histone deacetylase 1; HGF, hepatocyte growth factor; HIF-1α, hypoxia-inducible factor-1α; HSPB1, heat shock protein B1; HX-XO, hypoxanthine-xanthine oxidase; JNK, c-Jun N-terminal kinase; KEAP1, Kelch-like ECH-associated protein 1; LKB1, liver kinase B1; LOX, lipoxygenase; MAPK, mitogen activated protein kinase; Mcl-1, myeloid cell leukemia 1; MMP, matrix metalloproteinase; MPTP, mitochondrial permeability transition pore; mTOR, mammalian target of rapamycin; NAC, N-acetylcysteine; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-κB; NOX, NADPH oxidase; Nrf2, nuclear factor erythroid 2–related factor 2; O_2, molecular oxygen; $O_2^{\bullet -}$, superoxide anion; Par-4, prostate apoptosis response-4; PDGF, platelet derived growth factors; PGAM5, phosphoglycerate mutase family member 5; P-gp, P-glycoprotein; PI3K, phosphoinositide 3-kinase; PKB/Akt, protein kinase B; PKC, protein kinase C; Prx, peroxiredoxin; PTEN, phosphatase and tensin homolog; PTP, phosphotyrosine phosphatase; PTP1B, protein tyrosine phosphatase 1B; PYGL, glycogen phosphorylase; Rb, retinoblastoma; Ref-1, redox factor-1; RFK, riboflavin kinase; RIP1, receptor-interacting protein kinase 1; RNS, reactive nitrogen species; ROS, reactive oxygen species; RSL, Ras-selective lethal; RUNX3, runt related transcription factor 3; Smac/DIABLO, second mitochondria-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low pI; SMase, sphingomyelinase; SOD, superoxide dismutase; SQSTM1, sequestosome 1; SSH1L, slingshot 1L; TGF-β1, transforming growth factor beta 1; TIMP, tissue inhibitor of metalloproteinase; TNFR, TNF receptor; TNF-α, tumor necrosis factor-α; TPA, tetradecanoyl phorbol acetate; TRAIL, TNF-related apoptosis-inducing ligand; TRX, thioredoxin; TrxR, thioredoxin reductase; TSC2, tuberous sclerosis complex 2; uPA, urokinase plasminogen activator; VDAC, voltage-dependent anion-selective channel; VEGF, vascular endothelial growth factor; VHL, Von Hippel–Lindau; XO, xanthine oxidase; X-XO, xanthine-xanthine oxidase

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as well as, non-radical molecules like hydrogen peroxide (H_2O_2) [1,2]. When introduced for the first time, ROS were thought to be very toxic and associated only with various pathological conditions. Since then, a tremendous amount of research have been published linking ROS to various physiological processes as well [3,4]. In this context, the biological role of ROS is rather complex and paradoxical [3,5,6]. Primarily, ROS is involved in numerous biological processes that are important for cellular homeostasis. However, ROS is also implicated in various disease states such as cancer, diabetes mellitus, atherosclerosis, and cardiovascular diseases to name few [1,2]. This role of ROS is being delineated continuously and becoming pronounced, adding complexity to our understanding of these radicals in pathophysiology. This review discusses the relationship between ROS and cancer from both tumor promotive and tumor suppressive perspectives.

2. Sources and activation of ROS

Reactive oxygen species, as byproducts of oxygen metabolism, are constantly produced in and removed from the cells via a variety of complex synthesis and degradative pathways. $O_2^{\bullet -}$ is generally considered as the primary ROS, which can be rapidly dismuted by superoxide dismutase (SOD) yielding H_2O_2. In the presence of Fe^{2+} or Cu^{2+} ions, H_2O_2 can be further converted into •OH in a process called the Fenton reaction (Fig. 1). Simultaneously, $O_2^{\bullet -}$ itself can also react with H_2O_2 and generate •OH [7]. Different types of ROS have different diffusion capabilities and reactivity towards their targets. For example, •OH is extremely reactive and does not diffuse outside its site of formation, while $O_2^{\bullet -}$ is highly active and has limited diffusion capacity, especially through certain channels. In contrast, H_2O_2 readily diffuses through membranes making it an ideal candidate for intracellular signaling [8].

Reactive oxygen species generation can be triggered by several exogenous and endogenous factors (Fig. 1). Mitochondrial electron transport chain (ETC) is the major endogenous source of ROS in most mammalian tissues [9]. In the ETC, mainly at complex I and III, $O_2^{\bullet -}$ is formed in the mitochondrial matrix by the single electron reduction of O_2 [10,11]. Simultaneously, complex III can also release $O_2^{\bullet -}$ into the mitochondrial intermembrane space [11]. $O_2^{\bullet -}$ may also be generated at the ETC complex II [12–14]. $O_2^{\bullet -}$ formed in the mitochondria can be diffused into the cytosol via voltage-dependent anion channels (VDAC; also known as porin). Other important endogenous sources of ROS are enzymes such as NADPH oxidases (NOX), xanthine oxidase (XO), lipoxygenases (LOX), and cytochrome P450 [15] (Fig. 1).

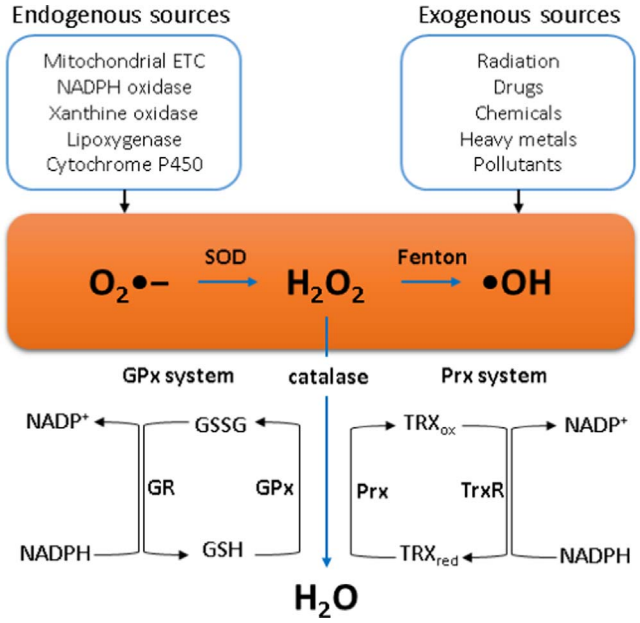

Fig. 1. Sources and conversion of ROS. Details of these processes and abbreviations are described in the text. Briefly, this figure shows major endogenous and exogenous sources of ROS molecules and the antioxidant systems that catalyze the reduction of different ROS molecules. It also depicts Fenton reaction leading to the formation of •OH.

The seven membered NOX family enzymes, namely NOX1-5, dual oxidase 1 (DUOX1), and dual oxidase 2 (DUOX2) have dedicated function of generating ROS [16]. When activated, all of the NOX1-3 mainly generate $O_2^{\bullet -}$, while NOX4, DUOX1, and DUOX2 are capable of producing H_2O_2 directly [16,17]. Depending on the specific subcellular distribution, NOX family of proteins execute a wide range of ROS-mediated biological functions [17]. Unlike NOX, which has sole function of producing ROS, XO is a uric acid forming enzymes which produce both $O_2^{\bullet -}$ and H_2O_2 as a byproduct of its enzymatic reaction [18]. XO also generate $O_2^{\bullet -}$ in the peroxisomes, where H_2O_2 is the major type of ROS produced by XO and number of other enzymes [19]. $O_2^{\bullet -}$ can also be formed in the endoplasmic reticulum (ER) as a result of oxidative protein folding [20]. In addition, as mentioned earlier, ROS generation can be facilitated by a multitude of exogenous factors such as radiation, drugs and chemicals, heavy metals, pollutants, etc. (Fig. 1) [21].

3. Conversion and clearance of ROS

The balance between production and scavenging of ROS is of critical importance as ROS have been linked to numerous biological processes and disease conditions. Cellular redox balance is typically maintained by a powerful battery of antioxidant system that is present in different subcellular compartments [22]. These antioxidant systems can be divided into (1) enzymatic: such as SOD, catalase, peroxiredoxin (Prx; also known as thioredoxin peroxidase) system, glutathione peroxidase (GPx) system, etc., and (2) non-enzymatic: such as ascorbic acid, lipoic acid, α-tocopherol, etc.

As mentioned earlier, SOD catalyzes the dismutation of $O_2^{\bullet -}$ into H_2O_2, which can then be further reduced to water by Prx system, GPx system, and catalase (Fig. 1). Based on the metal co-factor they harbor and site of action, human SOD can be classified into three groups: Copper/Zinc (CuZn)-SOD (SOD1), Manganese (Mn)-SOD (SOD2), and extracellular CuZn-SOD (EC-SOD or SOD3) [23]. The Prx system consists of two electron donors and two types of antioxidant enzymes: Prx itself, thioredoxin reductase (TrxR), thioredoxin (TRX), and nicotinamide adenine dinucleotide phosphate (NADPH). During the metabolism of H_2O_2, Prx gets oxidized and is inactivated. TRX acts as an immediate electron donor and reduces Prx back to the active form. TRX is subsequently reduced by TrxR which receives its electrons from NADPH (Fig. 1). In the GPx system, GPx catalyzes the reduction of H_2O_2 leading to the oxidation of glutathione (GSH), which can be reduced back by glutathione reductase (GR), using NADPH [24] (Fig. 1).

4. Tumor promoting functions of ROS

Cancer cells have an inherent elevated ROS level compared to their normal counterparts. This may partly be due to defective mitochondrial oxidative metabolism [25]. Elevated oxidative signaling may be implicated in the promotion and progression of a number of different cancers including melanoma, hepatoma, leukemia, glioma, and cancers of breast, pancreas, bladder, colon, lung, and prostate [26]. In addition, increased ROS levels have been linked to cancer initiation, malignant transformation, and resistance to chemotherapy. Some of the important tumor promoting functions of ROS are discussed in the following sections.

4.1. Tumorigenesis

ROS, depending on the concentration and duration of exposure, can effect cellular proteins, lipids, and DNA, leading to genomic instability and activation of various signaling cascades related to tumorigenesis