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Reactive Oxygen Species

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Reactive oxygen species (ROS) is a diverse group of small molecules with different reactivity, sources of production, and, ultimately, biological functions. Some of these molecules are important contributors to pathogenesis of major chronic diseases including cancer, diabetes, and atherosclerosis. Others play major roles in environmental, radiation and space biology. In normal state, specific ROS carry out homeostatic functions such as innate immunity and signaling. However, the word "ROS" is still often used in the literature as a generic term synonymous to oxidative stress. This review provides a brief description of ROS diversity, interrelations and main biological functions.

Generation of ROS: There are several major ROS important in normal and pathological physiology: superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), hydroxyl radical (HO•), and hypochlorous acid (HOCl) (Figure 1). These species originate from superoxide anion, which is most often formed during the reduction of oxygen by cellular mitochondrial electron transport chain or in the reactions catalyzed by NADPH oxidase [1,2]. Two superoxide molecules are converted to hydrogen peroxide either spontaneously or by the action of enzyme superoxide dismutase (Figure 1). In the presence of catalytic transition metal ions such as Fe^{2+} or Cu^{+}, H_2O_2can be converted further to hydroxyl radical [3]. Although this reaction is non-enzymatic, it can be modulated by metal chaperones and antioxidant defense proteins, including transferrin, ceruloplasmin, catalase and others [3]. Hydrogen peroxide can also be converted to HOCl by myeloperoxidase (MPO) and other peroxidases in the presence of chloride ions (Figure 1). Superoxide can react with nitric oxide (NO•) produced by nitric oxide synthase to form peroxynitrite ($ONOO^-$), a major reactive nitrogen specie [3] (Figure 1).

ROS in normal physiology: In normal physiology, when their levels are tightly controlled by antioxidant defenses, specific ROS carry out important homeostatic functions such as signaling by H_2O_2 and innate immunity by HOCl.

Among different ROS, only H_2O_2 fulfills the requirements for intracellular second messenger in cell signaling, i.e. specificity and ability to reach different cell compartments. Specificity of H_2O_2 is achieved by its relatively low reactivity (see standard reduction potentials of major ROS in Figure 1, inset table). It reacts almost exclusively with a subset of highly reactive protein thiol groups in acidic microenvironment (pK<6). Only few proteins possess such groups, including peroxiredoxin 2, which is considered a primary sensor of H_2O_2[4]. Peroxiredoxin thiol groups, oxidized by H_2O_2 to sulfenic acid, can further oxidize other proteins such as protein tyrosine phosphatases via disulfide formation. Oxidation of peroxiredoxins affects their direct binding to a number of regulatory proteins such as c-Myc and JNK [5]. H_2O_2 is a non-polar molecule, which can diffuse relatively readily across biological membranes and excerpt its effect in multiple cellular compartments. Due to its low reactivity, H_2O_2 also has a relatively long half-life, a feature necessary to carry out long-distance effects across the cell.

HOCl produced by MPO at the sites of inflammation is an important molecule of anti-bacterial innate immunity in normal physiology [6]. HOCl is produced in the neutrophil phagosome and reacts either directly with ingested bacteria or through generation of chloramines on phagosomal proteins which contribute to bacterial killing. It has been suggested that HOCl provides a frontline response that kills majority of the microorganisms in high-level infections thus modulating immune response [7].

ROS in pathophysiology: Under the conditions of oxidative stress, when ROS concentrations exceed threshold levels of cellular antioxidant defenses, ROS may become pathogenic. For example, in diabetes hyperglycemia causes leakage of electrons from mitochondrial electron transport chain which results in the increased reduction of molecular oxygen and production of superoxide [1]. Another intracellular process contributing to the increase of superoxide in diabetes is depletion of NADPH, an important cofactor in cellular antioxidant defenses. In diabetes, this depletion is caused by the activation of the enzymes NADPH oxidase [8] and aldose reductase [9]. In addition, hyperglycemia-induced increase in circulating advanced glycation end products (AGE) can activate AGE receptor (RAGE)-dependent pro-inflammatory signaling giving rise to intracellular superoxide [10]. Moreover, oxidative stress can damage metal chaperones, thus causing the release of catalytic metals and the enhancement of oxidative reactions such as formation of hydroxyl radical from hydrogen peroxide [11]. As a result, oxidative tissue damage consistent with hydroxyl radical or peroxynitrite reactivity can accumulate in diabetes [12,13].

Hypohalous acids are produced by a family of peroxidase enzymes, most prominently MPO and peroxidasin [14,15]. MPO is a critical part of the innate immunity while peroxidasin catalyzes reinforcement of collagen IV networks with sulfilimine crosslinks [15]. However, in the disease states, overproduction of hypohalous acids by these enzymes may have pathogenic consequences. Indeed, activation of MPO and overproduction of HOCl has been reported in diabetes [16] and peroxidasin has been shown to mediate oxidative vascular damage and renal fibrosis [17-20]. Increase in HOCl-derived protein oxidation has been reported in renal tissues of patients with chronic kidney disease [14,21]. Also, MPO-derived HOCl has been shown to damage HDL and to uncouple and inhibit endothelial nitric oxide synthase in atherosclerotic lesions [22-24].

Ionizing radiation-induced ROS: In biological tissues, ROS can

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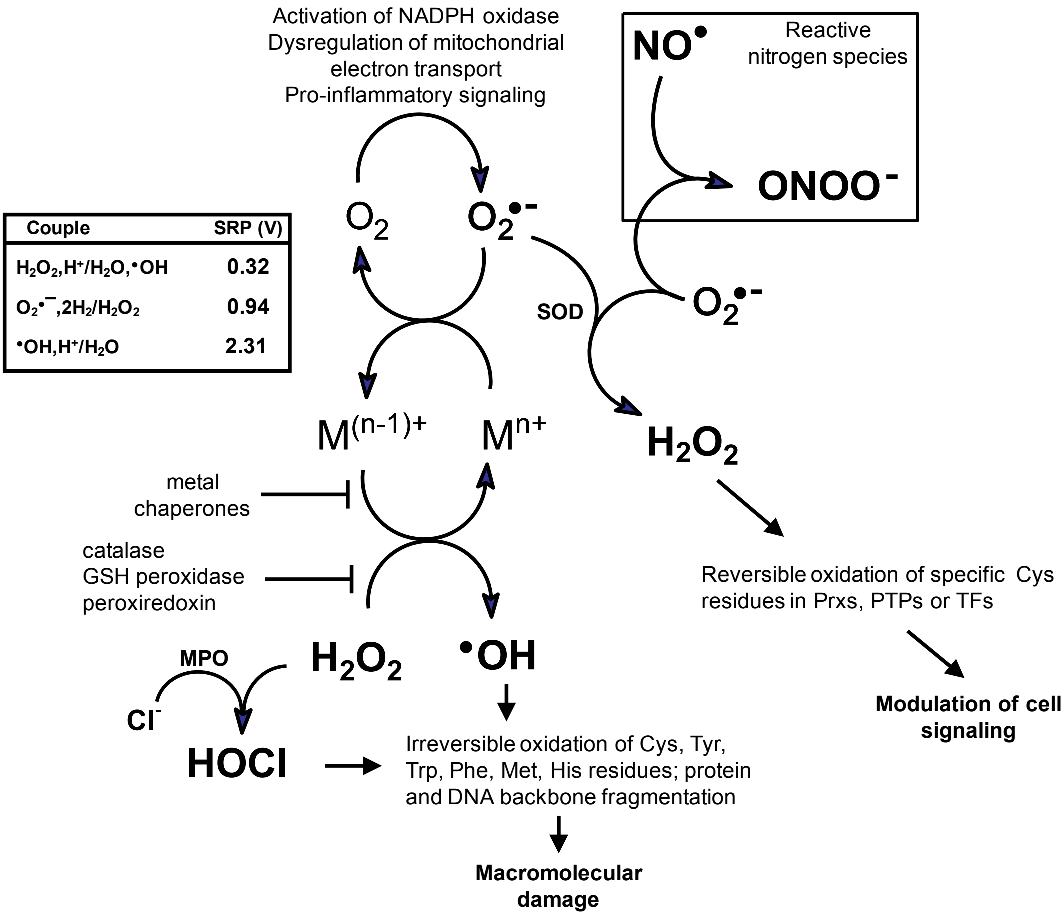

Figure 1: Interrelations and biological functions of major physiological ROS. NADPH, nicotinamide adenine dinucleotide phosphate (reduced form); SOD, superoxide dismutase; NO•, nitric oxide; $ONOO^-$, peroxynitrite; SRP, standard reduction potential; $O_2^{\bullet -}$, superoxide; H_2O_2, hydrogen peroxide; M^{n+}, redox active metal ion; •OH, hydroxyl radical; MPO, myeloperoxidase; HOCl, hypochlorous acid; Prx, peroxiredoxin; PTP, protein tyrosine phosphatase; TF, transcription factor. See the text for details.

also arise from exposure to ionizing radiation (IR). Water radiolysis results in generation of specific ROS: e^-_{aq}, •OH, H•, and H_2O_2. In the presence of oxygen, e^-_{aq} and H•atoms are rapidly converted to superoxide/perhydroxyl ($O_2^{\bullet -}$/$HO_2^{\bullet}$) radicals [25].

IR is classified as either electromagnetic or particulate. Whereas X and γ rays belong to electromagnetic radiation, energetic electrons, protons, neutrons, α particles and heavy charged particles are different forms of particulate radiation. Many of the damaging effects of water radiolysis are due to specific feature of IR, liniar energy transfer (LET) [25]. High LET radiations (e.g. α particles, high charge and high energy (HZE) particles), which are predominant in space, cause greater increase in locally multiply damaged sites in DNA as compared to low LET radiations (X and γ rays) [26].

IR-induced ROS cause pathogenic oxidative changes of biological molecules resulting in protein carbonylation, lipid peroxidation, and enhanced rates of spontaneous gene mutations and neoplastic transformation [27,28]. Because of continuous ROS generation, these changes may arise for days and months after the initial exposure and occur not only in the irradiated cells but also in bystander cells through intercellular communication mechanisms, in their own progeny and in progeny of bystander cells. The persistence of such stressful effects has profound implications for long-term health risks. Increasing evidence also supports the role of chronic oxidative stress caused by IR-induced ROS in the progression of degenerative diseases, formation of secondary malignancy following radiotherapy treatments and radiation-induced late tissue injury [29,30].

In conclusion, ROS is a diverse group of molecules that carry out distinct biological functions in normal state and in disease.

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