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Review article

Studies on oxidants and antioxidants with a brief glance at their relevance to the immune system

Banafsheh Amir Aslani [a], Sirous Ghobadi [b,*]

[a] Department of Biology, Faculty of Science, Payame Noor University, 19395-3697 Tehran, Iran
[b] Department of Biology, Faculty of Science, Razi University, 67149-67346 Kermanshah, Iran

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ABSTRACT

Free radical generation occurs continuously within cells as a consequence of common metabolic processes. However, in high concentrations, whether from endogenous or exogenous sources, free radicals can lead to oxidative stress; a harmful process that cause serious damages to all biomolecules in our body hence impairs cell functions and even results in cell death and diseased states. Oxidative injuries accumulate over time and participate in cancer development, cardiovascular and neurodegenerative disorders as well as aging. Nature has bestowed the human body with a complex web of antioxidant defense system including enzymatic antioxidants like glutathione peroxidase and glutathione reductase, catalase and superoxide dismutase as well as non-enzymatic antioxidants such as thiol antioxidants, melatonin, coenzyme Q, and metal chelating proteins, which are efficient enough to fight against excessive free radicals. Also, nutrient antioxidants such as vitamin C, vitamin E, carotenoids, polyphenols, and trace elements are known to have high antioxidant potency to assist in minimizing harmful effects of reactive species. The immune system is also extremely vulnerable to oxidant and antioxidant balance as uncontrolled free radical production can impair its function and defense mechanism. The present paper reviews the ways by which free radicals form in the body and promote tissue damage, as well as the role of the antioxidants defense mechanisms. Finally, we will have a brief glance at oxidants and antioxidants relevance to the immune system.

Contents

* Corresponding author.
E-mail addresses: sirousghobadi@yahoo.com, ghobadi@razi.ac.ir (S. Ghobadi).

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1. Introduction

Free radicals can be described as highly reactive molecules that contain one or more unpaired electrons in their outer orbit [1–5]. Free radicals are generally unsteady and originate from oxygen (Reactive Oxygen Species: ROS), nitrogen (Reactive Nitrogen Species: RNS), and sulfur (Reactive Sulfur Species: RSS) [2,4]. Examples of ROS and RNS are superoxide ($O_2^{\bullet-}$), hydroxyl ($^{\bullet}OH$), peroxyl ($ROO^{\bullet}$), alkoxyl ($RO^{\bullet}$), hydroperoxyl ($HO_2^{\bullet}$) and lipid peroxyl ($LOO^{\bullet}$) radicals, nitric oxide ($NO^{\bullet}$), and nitrogen dioxide ($NO_2^{\bullet}$) [1,2,4–6]. RSS are easily obtained as a result of the reaction between ROS and thiols [2]. There are also other non-radical reactive species that generated from oxygen and nitrogen free radicals such as hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), hypobromous acid (HOBr), and peroxynitrite ($ONOO^-$) [4,6]. Generation of ROS and RNS (radical and non-radical species) can be occurred in animal and human cells under normal physiologic and pathologic states as well [4]. ROS-induced oxidation appears to be the main cause of cellular damage and death and also has been implicated in cancer, neurodegenerative, and cardiovascular diseases [7].

Reduction of O_2 results in formation of considerably reactive superoxide radical (Reaction 1) [7].

$$O_2 + e^- \rightarrow O_2^{\bullet-} \quad (1)$$

In the lack of scavengers, $O_2^{\bullet-}$ has a long half-life (5×10^{-2} s), so it can inactivate a number of enzymes such as catalase (CAT) and glutathione peroxidase (GPx) and cause glutathione (GSH) oxidation as well [7]. Due to inability of $O_2^{\bullet-}$ to pass lipid membranes, it is encompassed within the compartment of formation [8]. The activity of some enzymes like xanthine oxidase, cyclooxygenase, lipoxygenase, NADPH oxidase and peroxidases can generate $O_2^{\bullet-}$ [6,8]. Additionally, oxidation of specific molecules such as adrenaline, flavin nucleotides, thiol compounds and glucose in the presence of oxygen, can generate $O_2^{\bullet-}$ [9]. Presence of transition metals like iron and copper can extremely accelerate these reactions [9]. During the reduction of O_2 to water in the electron transport chain, free radical intermediates are produced which are usually strictly bound to the elements of the electron transport chain [9]. However, a few electrons can penetrate into the mitochondrial matrix, react with oxygen and generate $O_2^{\bullet-}$ [9–11]. Also, the activity of other enzymes such as hepatic cytochrome P450 oxidase and the enzymes participate in adrenal hormones synthesis may cause the electrons to percolate into the cytoplasm and participate in $O_2^{\bullet-}$ formation [9]. It seems that single $O_2^{\bullet-}$ is unable to cause direct damage to DNA [7].

In specific circumstances such as inflammation, cells can produce $O_2^{\bullet-}$ and nitric oxide, that in turn react with each other to generate highly toxic peroxynitrite (Reaction 2) [7,8,12].

$$2O_2^{\bullet-} + NO^{\bullet} \rightarrow ONOO^- \quad (2)$$

$ONOO^-$ may cause LDL oxidation and release of copper ions by breaking down ceruloplasmin, and attacking tyrosine residues in various proteins, as observed in numerous inflammatory disorders [8]. Peroxynitrite-mediated nitration of tyrosine results in formation of 3-nitrotyrosine, a product which may harm some cellular functions [12]. Moreover, $ONOO^-$ is able to cause DNA damage and lipid oxidation and also has a role in aging due to its ability to harm guanine repeats in telomeres [7].

Hydrogen peroxide, a non-radical species, is highly reactive and relatively stable [3,7]. H_2O_2 can be generated through the activity of superoxide dismutase (SOD) which reduces $O_2^{\bullet-}$ to H_2O_2 and O_2 (Reaction 3) [7].

$$2O_2^{\bullet-} + 2H^+ \rightarrow H_2O_2 + O_2 \quad (3)$$

Also other enzymes such as glycolate oxidase, amino acid oxidase, and urate oxidase are further sources of H_2O_2 production [7]. In contrast to $O_2^{\bullet-}$, H_2O_2 is able to cross cell membranes freely [9]. Therefore, H_2O_2 may travel long distances far from the site of its generation before breaking down to form the harmful hydroxyl radical, which probably mediates most of the noxious effects of H_2O_2 [9]. Hence, H_2O_2 may act as a channel to transfer free radical induced damages among cells and across cellular compartments as well [9]. The interest in H_2O_2 comes from its ability to produce ROS especially $^{\bullet}OH$, which believed to be the most reactive and destructive ROS [6–8]. It mainly originates from Fenton or Fenton type reactions in which Fe^{2+} and Cu^+ react with H_2O_2 (Reactions 4 and 5) [7,8,13].

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + OH^- \quad (4)$$

$$Cu^+ + H_2O_2 \rightarrow Cu^{2+} + {}^{\bullet}OH + OH^- \quad (5)$$

Since $^{\bullet}OH$ lifetime is diffusion limited (10^{-9} s), it reacts with molecules instantly after its generation and release [7]. Lipids, proteins, and nucleic acids are at risk of being oxidized by $^{\bullet}OH$, and lesions such as DNA strand breaks, base modifications and DNA cross linking have been reported due to the oxidation reaction [7,9]. Furthermore, H_2O_2 has a role in generation of hypochlorous acid by the activity of myeloperoxidase, a key reaction occurs in phagocytes in order to kill bacteria (Reaction 6) [8,9].

$$H^+ + Cl^- + H_2O_2 \rightarrow HOCl + H_2O \quad (6)$$

Oxygen derivatives, especially $O_2^{\bullet-}$ and $^{\bullet}OH$ are the most important free radicals in various disorders [9].

2. Biological roles of free radicals

Act at low or moderate levels, ROS and RNS are biologically important, which serve as signaling and regulatory molecules [1,4,6]. For example, nitric oxide is an important neurotransmitter generated by neurons as well as being a key mediator of the immune response produced by activated macrophages [4]. Another example is oxygen radicals which not only participate in signal transduction and gene transcription but also in regulation of soluble guanylate cyclase activity in cells [4]. As a part of their physiological function, ROS molecules have also a role in defense against infection [8]. Upon activation, phagocytes produce sufficient amounts of ROS to kill invading bacteria [8]. In this system, NADPH oxidase produces $O_2^{\bullet-}$ which is then reduced in phagosome by SOD to H_2O_2 [8]. The resultant H_2O_2 is then converted to HOCl (Reaction 6) which may ultimately generate $^{\bullet}OH$ spontaneously through reaction with either $O_2^{\bullet-}$ or Cu^+/Fe^{2+} (Reactions 7 and 8) [8]. The produced HOCl and $^{\bullet}OH$ in phagosome are poisonous enough for bacteria swallowed by the phagocyte and exert the direct antimicrobial effects of ROS [8].

$$HOCl + O_2^{\bullet-} \rightarrow {}^{\bullet}OH + O_2 + Cl^- \quad (7)$$

$$HOCl + Cu^+/Fe^{2+} \rightarrow {}^{\bullet}OH + Cl^- + Cu^{2+}/Fe^{3+} \quad (8)$$

3. Sources of free radicals

Sources of free radicals can be intracellular or extracellular [9,13]. Mitochondria are the main site of ROS generation mostly due to the presence of electron transport chain (ETC) in these organelles [3,13–15]. Furthermore, the activity of some enzymes including certain oxidases, cyclooxygenase, lipoxygenases, dehydrogenases, and peroxidases can result in production of free radicals [3]. Cytochrome P450 metabolism, lysosomes, peroxisomes, and inflammatory cell activation are the other endogenous sources of ROS [3,13]. Extracellular sources of free radicals are ionizing radiation, cigarette, some pollutants, pesticides, and certain medications that can penetrate into the body and