Chapter

Introductory Chapter: Free Radicals and Lipid Peroxidation

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1. Introduction

During cellular metabolism, a potentially dangerous by-product named free radicals is liberated. They have several effects on cell survival, growth, and development and have remarkable effects in the pathogenesis of atherosclerosis, aging, development of cancer, and several other conditions including inflammatory diseases [1]. A free radical is characterized by containing in its outer orbit an unpaired electron [2]. During the process of adenosine triphosphate (ATP) production in the mitochondria, free radicals are generated by aerobic organisms. During the electron- transport steps of ATP production, due to the leakage of electrons from mitochondria, reactive oxygen species (ROS), superoxide anion ($\mathbf{O_2^{-\bullet}}$) and hydroxyl ($\mathbf{OH^{\bullet}}$) radicals, are generated. These free radicals through chemical reactions can lead to the production of hydrogen peroxide ($\mathbf{H_2O_2}$). Based on the presence of Fe^{2+} ions, hydroxyl radicals are produced [3].

Free radicals are involved in several beneficial and harmful actions. Free radicals are involved in the signal transduction pathways that regulate cell growth [4] and reduction-oxidation (redox) status [3] and have a vital role in the defense polymorph nuclear leukocytes against infections as it acts as the first line of defense [5]. However, free radicals in excessive amounts can induce lethal chain reactions, leading to inhibition and inactivation of vital enzymes and many other proteins which are important subcellular elements needed for cell survival and leading to apoptosis [6]. Thus, functionally free radicals are considered a double-edged sword (**Figure 1**).

Reactive oxygen species include radicals such as superoxide ($\mathbf{O_2^{-\bullet}}$), hydroxyl radical ($\mathbf{HO^{\bullet}}$), nitric oxide ($\mathbf{^{\bullet}NO}$), and non-radical species such as hydrogen peroxide ($\mathbf{H_2O_2}$) and peroxynitrite ($\mathbf{ONOO^-}$) [7].

Reactive oxygen species is produced both enzymatically and nonenzymatically. Enzymatic sources include NADPH oxidase located on the cell membrane of polymorphonuclear cells, macrophages and endothelial cells [8], and cytochrome P_{450}-dependent oxygenases [9]. Irreversible conversion of xanthine dehydrogenase to xanthine oxidase by mitochondrial protease uses molecular oxygen as electron acceptor and produces remarkable amounts of both $O_2^{-\bullet}$ and H_2O_2. Therefore it can provide another enzymatic source of both free radicals and also constitutes a source of $OH^{\bullet}$. The production of $O_2^{-\bullet}$ occurs nonenzymatically too via transfer of a single electrons to oxygen reduced coenzymes or prosthetic groups (e.g., flavins or iron sulfur clusters). Furthermore, previously reduced xenobiotics by certain enzymes (e.g., the anticancer agent Adriamycin or the herbicide paraquat) can also produce free radicals.

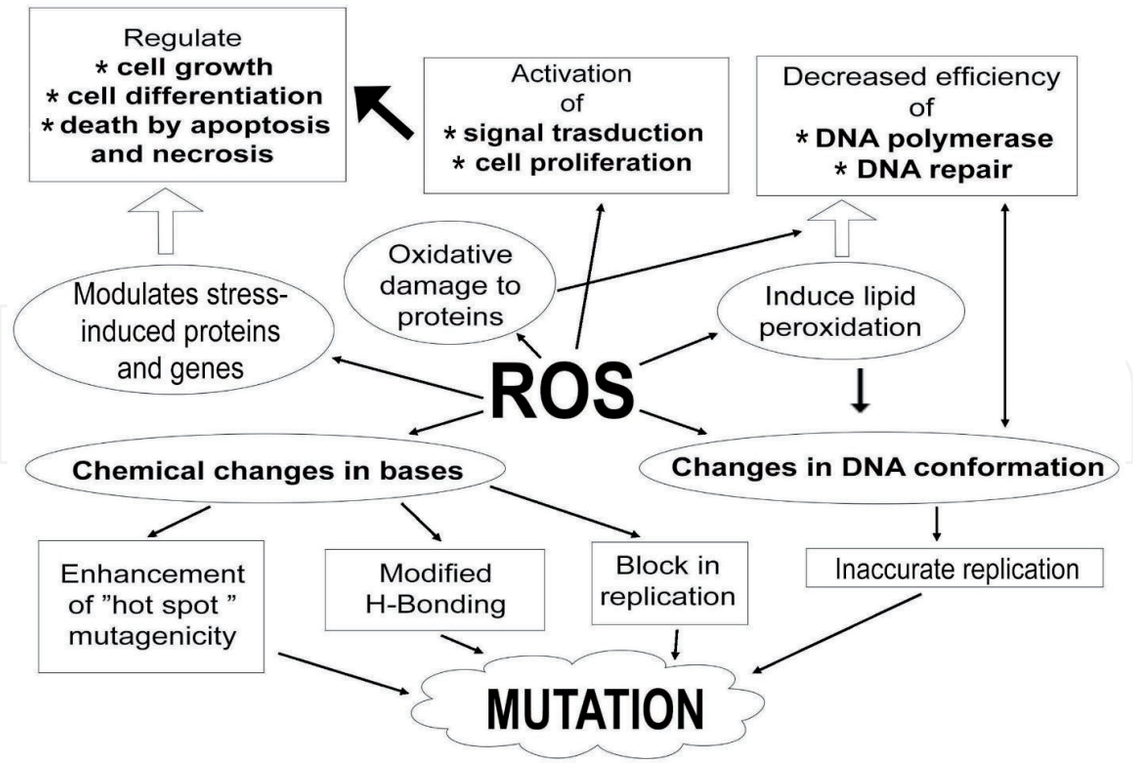

Figure 1.
ROS, oxidative damage, and human diseases. Interrelationship between the effect of imbalance in the reactive oxygen species (ROS) and their consequences on the cellular growth and the cellular function leads to DNA damage and mutation.

2. Role of oxidative stress in different diseases

The oxidative stress plays a role in the pathogenesis of different clinical conditions. Cancer diseases, diabetes mellitus, atherosclerosis, chronic inflammatory diseases, human immunodeficiency virus (HIV) infection (AIDS), ischemia–reperfusion injury, and sleep apnea are important examples. The previously mentioned disease can be classified into two categories [10]. In the first category, a pro-oxidative shift in the systemic thiol/disulfide redox state is in parallel with impaired glucose clearance, suggesting that the mitochondria of the skeletal muscle may be the primary site of elevated ROS production; these conditions may be referred to as "mitochondrial oxidative stress" which is clearly in diabetes mellitus and cancer [11]. The second category is based on excessive stimulation of NADPH oxidase activity by cytokines or other agents and therefore refers to "inflammatory oxidative conditions." In this case, elevated free radical levels or alteration of intracellular glutathione levels is often associated with pathological changes indicative of a dysregulation of signal transduction and/or gene expression, represented by a change in the expression of cell adhesion molecules [12].

3. Lipid peroxidation and incidence of cancers

There is clear evidence supporting the role of lipid peroxidation in the induction of selected human cancers, including the kidney, liver, and skin. Estrogen treatment induces lipid peroxidation and subsequently increases the incidence of renal cell cancer in experimental models [13, 14]. Based on this mechanism, it has been hypothesized that estrogen increases breast cancer risk as lipid peroxidation may

be one mechanism [15]. But estrogen induces renal cancer or liver cancer in this experimental model, not breast cancer.

In contrast, there is evidence favoring lipid peroxidation as an anticarcinogenic mechanism in breast cancer. It has been confirmed that higher level of lipid peroxidation is usually associated with lower rate of cell proliferation. Therefore, there is an inverse relationship between the concentrations of lipid peroxides and the rate of the cell proliferation [16]. This is supported by the observation that tumor cells are more resistant to lipid peroxidation than normal cells [17]; indeed, it was shown that in hepatomas, the higher the growth rate of the tumor, the lower the microsomal phospholipid content and the degree of fatty acid unsaturation [16]. Hosmark and Lystad [18] have also reported that low levels of polyunsaturated fatty acids and cytochrome P_{450} and elevated levels of lipid-soluble antioxidant alpha-tocopherol in the hepatoma cells are the main causes behind lower rate of lipid peroxidation.

It has been reported that lipid peroxidation represents a protective mechanism in breast cancer. Decreased plasma malondialdehyde (MDA), which is a marker for lipid peroxidation, has been significantly associated with severity of prognosis factors for breast cancer. A significant lower plasma level of MDA was detected in patients with large tumors or in whom nodes and/or metastasis was present [19, 20].

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