Chapter 10

Oxidative Stress and Disease

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Abstract

Typically in aerobic metabolism, organic compounds such as nucleic acids, proteins and lipids can undergo structural damage by oxidative reactions. This damage caused by reactive oxygen/nitrogen species has been recognized as "oxidative stress". Despite the biological systems present efficient enzymatic and nonenzymatic antioxidant systems, oxidative stress indicates a pro-oxidant/antioxidant imbalance in favor of excessive generation of free radicals or decrease in the removal rate. Various diseases such as cancer, diabetes, cardiovascular diseases and neurodegenerative clearly exemplify the chronic oxidative stress. Therefore, it is important to consider that at low and moderate ROS levels, it can, for example, act as signaling molecules that support cell proliferation and differentiation and activate survival pathways in response to stress. Correlations between oxidative stress and disease should be carefully investigated in order to understand whether oxidative stress actually increases susceptibility to a particular disease or opposite.

Keywords: oxidative stress, free radicals, oxidative damage, antioxidants, diseases

1. Introduction

The generation of free radicals is a continuous physiological process, fulfilling relevant biological functions. The mechanisms of generation of free radicals occur mostly in the mitochondria, cell membranes and cytoplasm. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are formed as unavoidable by-products of metabolism. During the metabolic processes, these radicals act as mediators for the transfer of electrons in various

biochemical reactions. Its production, in appropriate proportions, is possible to generate adenosine triphosphate (ATP) through the electron transport chain; fertilization of the ovum; activation of genes and participation of defense mechanisms during the infection process [1]. The continuous production of free radicals during the metabolic processes culminated in the development of antioxidant defense mechanisms (enzymes and substances such as glutathione, metallothionein, vitamin A, vitamin C and vitamin E). These are intended to limit the intracellular levels of these reactive species and control the occurrence of damage caused by them. However, excessive production can lead to oxidative damage. The structural modifications in the molecules of nucleic acids, proteins and lipids caused by increased concentration of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) lead to various metabolic changes that may contribute to the development of neurological diseases, cardiovascular diseases, cancer, among others [2].

2. Oxidative stress and molecular damage

The installation process of oxidative stress arises from an imbalance between oxidants and antioxidants in favor of excessive generation of free radicals or removal speed thereof. This process leads to the oxidation of biomolecules with consequent loss of its biological functions and/or homeostatic imbalances, whose manifestation is the potential oxidative damage to cells and tissues. Accumulation of ROS/RNS can result in a number of deleterious effects such as lipid peroxidation, protein oxidation and DNA damage [3].

2.1. Nucleic acids damage

DNA and RNA are chemically unstable and vulnerable to hydrolysis, nonenzymatic methylation and oxidation, due to its susceptibility to endogenous and exogenous damage. The endogenous genotoxic agents are mainly produced by cellular metabolism and composed of ROS and RNS, estrogen metabolites and aldehydes produced by lipid peroxidation [4, 5].

There are two major endogenous oxidants causing nucleic acids damage: hydroxyl radicals ($HO^{\bullet}$) and peroxynitrite (ONO_2^-). One major source of ROS is the mitochondrial respiration because up to 5% of oxygen undergoes single electron transfer and generates superoxide anion radical (O_2^-). The superoxide dismutase (SOD) converts O_2^- to hydrogen peroxide that should be reduced by catalase (CAT) or glutathione peroxidase (GPx), however when transition metals are present, it is reduced to hydroxyl radicals ($HO^{\bullet}$). These radicals have a high reactivity, so it must be generated close to DNA or RNA in order to oxidize them. The generation of peroxynitrite (ONO_2^-) occurs by the reaction of nitric oxide (NO) and superoxide, both produced simultaneously in macrophages. Although these specimens can directly oxidize the nucleic acids, there is a secondary synergic mechanism of RNS to break the oxidative balance: the RNS are able to inhibit the enzyme FAPY glycosylase, a DNA repair mechanism to oxidation [6].

Oxidative stress can lead to different lesions in DNA, including direct modification of nucleotide bases, training sites apurinic/apyrimidinic, single strand break and much less frequently,

breaking double strands. Considering all the bases of the nucleotides, guanine is most susceptible to oxidative changes because it has lower reduction potential and hydroxyl radicals interact with the imidazole ring of this nitrogenous base at positions C4, C5 and C8 [7].

The most studied marker for DNA oxidation is 8-hydroxydeoxyguanosine, a product of guanosine oxidation by $HO^{\bullet}$ [6, 8]. This product is able to pair with adenine, generating a GC/TA mutation upon replication [6]. It is also known that oxidative stress regulates DNA methylation, playing a role in epigenetics regulation. Epigenetics constitutes several mechanisms of controlling gene expression without changing DNA sequence, but responding fast and precisely to environmental changes. One of the most characterized methods of epigenetic regulation is DNA methylation. The methylation of DNA CpG islands is mediated by DNA methyltransferases (DNMTs), but when the ROS or RNS interacts with cytosine, it is chemically modified from 5-methylcytosine to 5-hydroxymethylcytosine, which prevents DNMT binding and alters methylation patterns [9].

For RNA oxidation, the most relevant marker is the homologue 8-hydroxyguanosine. It has been made clear that RNA is more often oxidized than DNA, due to its cellular location closer to ROS and RNS occurrence. The major consequences of RNA oxidization are the breakage of the strand and ribosomal dysfunction, preventing correct protein production [8].

2.2. Protein damage

The effects of oxidation in proteins can be observed in impaired protein folding, side-chain oxidation and backbone fragmentation, resulting in loss of function and stop a variety of biochemical processes. Among the amino acids, the cysteines and methionines are more easily oxidizable, but this reaction is reversible through disulfite reductases activity. However, the cysteine can also suffer irreversible oxidation reactions leading to the formation of S-carboxymethylcysteine and S-(2-Succinyl)cysteine, which implies the formation of fumarate and dicarbonyl groups covalently bound to cysteine residues. When the amino acids lysine, proline, arginine and threonine are oxidized, occurs the production of carbonyl derivatives, which are used as markers for oxidative stress. In the oxidation of aromatic amino acids, such as tyrosine, different products are formed due to interaction with ROS – dityrosine or RNS – 3-nitrotyrosine [8].

These oxidized-modified proteins are usually recognized and degraded in the cells, but some of them can accumulate over time and lead to cellular dysfunction. A physiological example is the lipofuscin, a brown-yellow pigment that is a product of iron-catalyzed oxidation (polymerization) of proteins and lipids, as it is extremely resistant to proteolysis, it accumulates and it is used as an aging marker [10].

2.3. Lipid damage

In biological systems, lipid peroxidation occurs in two forms, one enzymatically, involving the participation of cyclooxygenase and lipoxygenase in the oxidation of fatty acids and other nonenzyme medium, involving transition metal, the reactive species oxygen, nitrogen and others [11]. Excess peroxidation results are very damaging to the cell, despite contribute to the