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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

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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

inflammatory response, due to its importance in the cascade reaction from arachidonic acid to prostaglandin formation. The action of free radicals on lipids leads to the formation of lipid hydroperoxides and aldehydes, such as malondialdehyde, 4-hydroxynonenal and isoprostanes that contribute further to increased cellular toxicity and can be detected in biological samples to measure oxidative stress. Lipid peroxidation disrupts the normal structure and function of lipid bilayers surrounding both the cell itself and in the membranes of organelles. In particular, the lipid peroxidation can alter membrane permeability, transportation and fluidity [12]. The chronicity of the process in question has important implications for the etiologic process of many chronic diseases, including atherosclerosis, diabetes, obesity, neurodegenerative disorders and cancer [1].

3. Antioxidant defense system

The antioxidant defense system has the primary objective to maintain the oxidative process within physiological limits and subject to regulation by preventing oxidative damage from spreading, culminating in systemic irreparable damage. The enzymatic defense system includes enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). These enzymes act through mechanisms of preventing and/or controlling the formation of free radicals and species nonradical, involved with the initiation of chain reactions that culminate in propagation and process amplification and, consequently, the occurrence of oxidative damage. CAT and GPx enzymes act with the same purpose, to prevent the hydrogen peroxide accumulation. Such integrated action is of great importance, since this reactive species through the reactions of Fenton and Haber-Weiss, with the participation of iron and copper metals, culminates in the generation of $OH^{\bullet}$ radical against which there is no enzyme system defense [13, 14].

The human organism is constantly exposed to a vast number of molecules that can lead to oxidative stress, such as drugs and alcohol. However, there is a conserved cellular component to oxidative stress response, which is constituted by over 100 genes responsible for detoxification and antioxidant protein production. The first line of the antioxidant defense to exogenous toxins includes the enzymes involved in phase I and II metabolism. The phase I metabolism is responsible for increased compound polarity through oxidation, reduction or hydrolysis reactions. The phase II metabolism, in the other hand, is responsible for facilitating the cellular export of those compounds; its reactions are mainly glucuronidation, acetylation and sulfation [15].

The enzymes that compose the cytochrome P450 are the most responsible for oxidation of drugs, chemicals and various endogenous substrates, such as eicosanoids, cholesterol, vitamin D3 and arachidonic acid [16]. The P450 is a superfamily of heme-thiolated enzymes with over 2000 members [17]. In humans, 57 functional genes and 58 pseudogenes are grouped according to the sequence similarity in 18 families and 44 subfamilies. The CYP-enzymes that belong to the families 1, 2 and 3 are responsible for metabolizing up to 90% of the drugs, this phase I drug oxidation system is frequently redundant, but many drugs are metabolized to a clinical concentration by one or few CYPs only [18].

In steroidogenic tissues (converts cholesterol into pregnenolone via the P450 side chain cleavage enzyme) there is a prevalence of CYP450 enzymes located in mitochondria and the electron transport system is very susceptible to oxidative stress. During the electron transport, a leakage of electron to the ultimate acceptor leads to their binding to oxygen, being considered a primary source of ROS, this may result in acceleration of ROS production in mitochondria. In this context, it is considered the effectiveness of electron transfer from NADPH to CYP enzymes for monooxygenation of substrates as a source of ROS because during the uncoupling reaction, without the presence of any substrates, the electron-transfer chain oxidizes NADPH and yields ROS. During CYP2E1 metabolism is frequently observed this kind of uncoupling reactions, thus this enzyme is strongly associated to ROS production and oxidative stress [16]. The enzyme CYP2E1 is associated with the metabolism of small molecules, and can be induced by ethanol, obesity, diabetes and polyunsaturated fatty acids; this induction is related to toxicity and oxidative stress. Another mechanism of CYP2E1 activation is the reduction of glutathione levels, upon acetaminophen administration, for example. Besides, this drug increases lipid peroxidation and protein carbonylation, enhancing the ROS production due to higher activity of CYP2E1 and being associated to hepatotoxicity mediated by MAP-kinase pathway [16, 19].

Glutathione S-transferase (GST) is a family of intracellular enzymes that prevent the action of endogenous and exogenous toxins on the cells. GSTs are multifunctional enzymes that participate in the phase II of the xenobiotic metabolism and catalyze the nucleophilic attack of the reduced form of glutathione (GSH) to potentially hazardous compounds. How are involved in the metabolism of many carcinogens, environmental pollutants and cancer-fighting drugs, it is therefore reasonable to assume that the lack of specific isoenzymes has a significant effect on the tolerance of an organism to carcinogens [20]. Human GSTs are categorized into cytosolic/nuclear, mitochondrial and microsomal. Based on their amino acid sequences and/or nucleotide substrate specificity and immunological properties, seven classes of cytosolic GSTs are described: Alpha, Mu, Pi, Sigma, Theta, Omega and Zeta. Microsomal GSTs are designated MAPEG (membrane-associated proteins in eicosanoid and glutathione metabolism) and the only mitochondrial GST confirmed in humans is GST-kappa, which is also present in peroxisomes. GSTs are normally found in biological medium as homo or heterodimers and these dimers have two active sites whose activities are independent. After combining with reduced glutathione (GSH), these enzymes have higher specificity for a second substrate (the electrophilic). GST enzymes participate in the metabolism of endogenous and exogenous compounds, for example, polycyclic aromatic hydrocarbons, phenylalanine and tyrosine amino acids, testosterone and progesterone. These enzymes target endogenous compounds, maybe derived from peroxidation of polyunsaturated fatty acids present in cell membranes and the activity of reactive oxygen species [21–23].

4. Oxidative stress and neurological disorders

Conclusive evidence suggests that oxidative stress is a major contributor to the pathophysiology of a variety of neurodegenerative diseases, including Alzheimer's, Parkinson's, Hunting-

ton's, tardive dyskinesia (TD), epilepsy and acute diseases of the central nervous system, such as spinal cord injuries and/or brain traumatic. The human brain is vulnerable to oxidative stress due to many facts such as (i) metabolism of catecholamines; (ii) decrease in antioxidants; (iii) presence of transition metals; (iv) occurrence of brain trauma/injury; and also (v) the brain is a organ that proportionally requires more oxygen and (vi) expresses low levels of antioxidant enzymes, which contribute to formation of ROS. As a consequence of redox unbalance in brain, one of the most affected structures is the lipid membrane [24].

Parkinson's disease (PD) is characterized by loss of dopaminergic neurons in the substantia nigra pars compacta of the brain, leading to rigidity or slowing movements and postural instability. Most of the cases of PD are idiopathic and some cases are genetic-related, but in general context, aging is a determinant factor. In both idiopathic and genetic cases of PD, the oxidative stress plays a critical role in pathogenesis, being a common underlying mechanism. There is an elevated level of oxidized lipids, proteins and DNA associated with decreased glutathione level in the brain of PD patients. This increased susceptibility to oxidative damage in the dopaminergic neurons is due to (i) the presence of ROS generating enzymes, such as tyrosine hydroxylase and monoamine oxidase and (ii) these neurons contain iron, a catalyser of Fenton reaction ($Fe(II) + H_2O_2 \rightarrow Fe(III) + OH^{\bullet} + OH^{-}$) that leads to superoxide radicals and hydrogen peroxide production [25].

A fact of Alzheimer's disease is the dysregulation of iron and copper homeostasis and various evidence of oxidative stress, mainly RNA oxidation. Neurons usually do not store big amounts of iron, but with aging there is an accumulation of iron in the brain, especially in microglia, astrocytes and neurons from cortex and hippocampus. If iron levels increase much more than ferritin, an iron-storage protein, it becomes free to catalyze Fenton's reaction [26].

The tardive dyskinesia (TD) is an adverse effect of antipsychotic use, it affects up to 25% of schizophrenic patients. However, as the majority of patients do not develop TD, it is considered that genetics factors may define its occurrence but TD pathophysiology remains unclear. One of the strongest hypotheses suggests that it is caused by oxidative stress originated from neurotoxic free-radical production upon antipsychotic medication. This affirmation is supported by genetic polymorphisms evaluated in genes that encode a mitochondrial enzyme that prevents oxidative damage due to energetic metabolism (manganese superoxide dismutase) and a cytosolic flavoenzyme that prevents quinone reduction (NADPH quinone oxidoreductase), playing a role in antioxidant defense [27].

5. Oxidative stress and metabolic syndrome

Metabolic syndrome is a term that designates a cluster of health problems often associated to modern life style, including obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and high blood pressure. The metabolic syndrome is diagnosed when at least three of the following alterations are present: visceral obesity (waist circumference >102 cm in men or >88 cm in women); raised arterial blood pressure (>130/85 mm Hg); dysglycemia (fasting

plasma glucose >100 mg dL); raised triglyceride concentrations (>150 mg dL) and low high-density lipoprotein (HDL) cholesterol (<40 mg dL in men or < 50 mg dL in women) [28].

The oxidative stress is related to metabolic syndrome in several ways: (i) H_2O_2 promotes insulin signaling, being associated with increased insulin resistance; (ii) superoxide anion is generated by angiotensin stimulation of NADPH and angiotensin II/angiotensin II type I receptor (AT1R), which plays a critical role in blood pressure control; (iii) hyperglycaemia leads to overproduction of superoxide by mitochondrial electron transfer chain, activating oxidative stress; (iv) elevated low-density lipoprotein (LDL) and low high-density lipoprotein (HDL) are correlated with oxidative stress and the dyslipidemia treatment with rosuvastatin is known to reduce oxidative stress through raise of antioxidant enzymes [28].

Due to oxidative DNA damage there is a direct correlation between diabetes and cancer. Diabetic patients present high levels of ROS because of elevated glucose, fatty acids and insulin blood levels; combined to lower antioxidative capacity derived from reduced glutathione synthesis. To support those findings, it has been proved that polymorphisms in peroxisome proliferator-activated receptor-γ coactivator-1α (PPARGC1A) – a protein that regulates mitochondrial electron transport, leads to decontrolled redox activity [29].

6. Oxidative stress and atherosclerosis

Atherosclerosis is defined as an arterial disease characterized by fibrous and cholesterol rich plaques. Atherosclerosis progression causes blood flow obstruction, hemorrhage due to rupture and thrombosis leading to strokes or myocardial infarctions. Many risk factors are associated with atherosclerosis development, the most widely known are serum low-density lipoprotein (LDL) cholesterol, low serum high-density lipoprotein (HDL) cholesterol, diabetes, hypertension, smoking, aging and oxidative stress [30].

During LDL oxidation, a progressive process and very important for the beginning of the formation of atheromatous plaque, the cholesterol is target of oxidants, which generate a variety of oxysterols. On the other hand, lipid peroxidation products (MDA and 4-HNE) can react with histidine, cysteine or lysine residues of proteins, leading to formation of stable Michael adducts with a hemiacetal structure or to Schiff bases that undergo a rearrangement generating the Amadori products. These aldehydes can derivatize Lys residues of apoB, which decreases the number of positive charges and interferes on LDL binding to LDLR and scavenger receptors [31].

In endothelial cells, besides stimulating the antioxidant defense (mainly by glutathione), Nrf2 (nuclear factor (erythroid-derived 2)-like 2) suppresses inflammation-associated expression of adhesion molecules and cytokines, which are associated with the early stage of atherogenesis [29]. NAD(P)H oxidases (NOXs) are major sources of ROS in the vasculature, producing superoxide from molecular oxygen using NAD(P)H as the electron donor and endothelial NO synthase (eNOS) produce NO which represents a key element in the vasoprotective function of the endothelium. However, pathological conditions associated with oxidative stress may become eNOS inefficient and promote the rapid inactivation of NO by excess superoxide [32].

There is growing evidence that reversal of oxidative stress with antioxidants can reduce the degree of myocardial ischemic injury and heart dysfunction [33].

7. Oxidative stress and infection

The pathological effects of NO and O_2^- in virus infection are in clear contrast to their beneficial antimicrobial effects in bacterial and fungal infections. In virus infections, NO and $ONOO^-$, which are primitive host-defense molecules, cause nonspecific oxidative damage in virus-infected tissue, leading to various pathological events. Virus-induced oxidative stress has been reported during HIV, influenza virus, HBV, hepatitis C virus, encephalomyocarditis virus (EMCV), respiratory syncytial virus (RSV), dengue virus (DENV) and others [34].

Studies including rotavirus-infected patients showed that viral infection stimulates NO production, decreases superoxide dismutase and glutathione peroxidase activities and increases inducible nitric oxide synthase (iNOS) mRNA and iNOS expression in murine ileum [35].

Influenza virus is probably the best characterized pathogen modulating redox homeostasis. Influenza-induced ROS production has been associated with host immune and inflammatory responses, as well as modulation of viral replication. Oxygen radicals and their derivatives are recognized as principal mediators of influenza virus-induced lung injury [36].

Within the Flaviviridae family, hepatitis C virus infection promotes oxidative stress and manipulates antioxidant systems, leading to liver damage and chronic disease. Elevated levels of reactive oxygen species (ROS) are considered as a major factor contributing to HCV-associated pathogenesis. HCV core protein is considered as a major regulator affecting the release of ROS from mitochondria. In this context, mitochondria play a crucial role for the production of ROS in HCV-infected cells. Several pathways are affected upon HCV infection to result in an induction of autophagy that interferes with various steps of the viral life cycle to promote a permanent viral infection. The assembly and release of viral particles are closely linked to the VLDL synthesis and occur via the secretory pathway. Elevated glucose production, enhanced fatty acid uptake or upregulation of genes involved in lipid and cholesterol synthesis may contribute to oxidative stress-induced insulin resistance linked to HCV infection [36].

Induction of iNOS and production of NO, accumulation of ROS and RNS, as well as perturbation of the reduced glutathione (GSH) content are all signatures of Dengue virus (DENV) infection in different human cells and animal models. DENV infection resulted in an intracellular accumulation of NAD(P)H oxidase (NOX2)-derived ROS in monocyte-derived dendritic cells (Mo-DCs). Alteration in the redox status of DENV-infected patients has been associated with increased inflammatory responses, cell death and correlated with different parameters associated with dengue disease [37].

The HPV infection, although necessary, is not sufficient to cause cancer and several studies have been devoted to the search for concurrent carcinogenic factors. Among these cofactors,

many evidence support the role of ROS. It is clear that viral infection induces ROS that in turn causes damage to all types of biological macromolecules. Two different types of cooperative mechanisms are presumed to occur between ROS and HPV: (i) the ROS genotoxic activity and the HPV-induced genomic instability concur independently to the generation of the molecular damage necessary for the emergence of neoplastic clones. This first mode is merely a particular form of cocarcinogenesis and (ii) ROS specifically interacts with one or more molecular stages of neoplastic initiation and/or progression induced by the HPV infection [38, 39].

Therefore, it seems reasonable to hypothesize that, while in most cases the cells react to HPV infection and can overcome the virus-induced ROS by activating apoptosis leading to termination of viral replication and lesion regression, in some of the infected cells a steady state balance between ROS generation and detoxification is established, partly due to viral-induced antioxidant response. Thus, infected cells can aberrantly proliferate, paving the way to neoplastic progression HPV, exploit host cell survival mechanisms, through modulation of redox homeostasis, increasing the activity of catalase, SOD among other, as an adaptive response to the high ROS conditions of preneoplastic lesions. Elevated GST and GSH provide the HPV hosting cell with improved oxidative damage detoxifying systems, but suppression of p53 and iNOS together with induction of vascular endothelial growth factor (VEGF) and resistance to ROS leads to the suppression of apoptosis and generates an oxidant fitting cell phenotype. Therefore, the tumor cell adapts their metabolism in order to support their growth and survival, creating a paradox of high ROS production in the presence of high antioxidant levels [38, 39].

8. Oxidative stress and cancer

Many signaling pathways that regulate the metabolism of ROS are also linked to tumorigenesis [40, 41]. However, ROS can also promote tumor formation by inducing DNA mutations and pro-oncogenic signaling pathways. The production of low level of ROS is required for homeostatic signaling events. It can be driven by NAD(P)H and NAD(P)H oxidase (NOX), leading to the increase of cell proliferation and survival through the posttranslational modification of kinases and phosphatases. At moderate levels, ROS induce the expression of stress-responsive genes such as *HIF1A*, which in turn trigger the expression of proteins providing prosurvival signals, such as the glucose transporter GLUT1 (also known as SLC2A1) and vascular endothelial growth factor (VEGF). At low and moderate levels ROS can act as signaling molecules that sustain cellular proliferation and differentiation and activate stress-responsive survival pathways, stimulating the phosphorylation of protein kinase C (PKC), p38 mitogen-activated protein kinase (p38 MAPK), extracellular signal-regulated kinase (ERK)1/2, phosphoinositide 3-kinase/serine-threonine kinase (PI3K/Akt), protein kinase B (PKB) and JUN N-terminal kinase (JNK) [40, 42].

The regulation of oxidative stress is an important factor not only for tumor development but also for the responses to anticancer therapies. As high ROS levels are harmful to cells, oxidative stress can have a tumor-suppressive effect. This imparts pressure on cancer cells to adapt by developing strong antioxidant mechanisms. But despite having an enhanced antioxidant system, cancer cells maintain higher ROS levels than normal cells. At high levels, ROS can

cause damage to macromolecules, including DNA; induce the activation of protein kinase Cδ (PKCδ), triggering senescence; and/or cause permeabilization of the mitochondria, leading to the release of cytochrome *c* and apoptosis. ROS are also involved in the increased expression of antioxidant genes related to the activation of transcription factors such as the Nrf2, activator protein 1 (AP-1), nuclear factor kB (NF-kB) and p53 [40–42].

The role of ROS in carcinogenic process can be either pro or anti oncogenic, and it can be summarized as follows: (i) regulating tumor development and signaling pathways for cell progression through ERK1/2 activation and ligand-independent RTK activation; (ii) regulating chronic inflammation for example through NF-kB activation; (iii) controlling tumor suppressor expression and cell cycle inhibitors; (iv) mediating angiogenesis by the release of vascular endothelial growth factor (VEGF) and angiopoietin; (v) favoring metastasis and tissue invasion due to metalloproteinase secretion; (vi) avoiding cellular death by activating SRC and PI3K/AKT pathway. Additionally, generating ROS is the mechanism of attack used by most of chemotherapies and radiotherapy [43, 44].

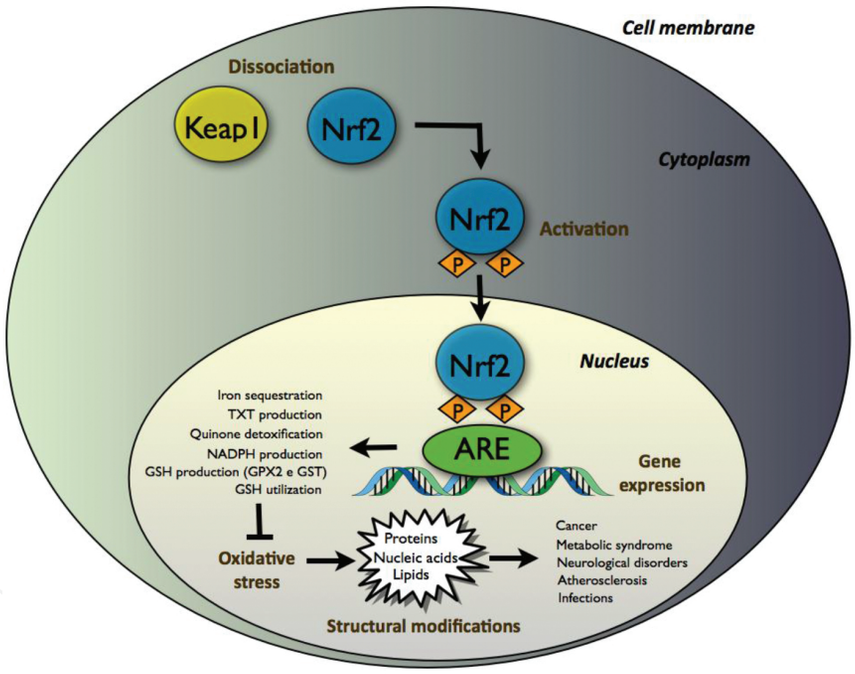


Figure 1. Keap1 (Kelch-like ECH-associated protein 1) sequesters Nrf2 (nuclear factor erythroid-derived 2) in the cytoplasm by binding to its aminoterminal regulatory domain. Keap1 is a sulfhydryl (S)-rich protein, and several cysteine residues mediate the Keap1–inducer interaction. When the interaction between Keap1 and Nrf2 disrupts, it allows Nrf2 to translocate to the nucleus. In the nucleus, Nrf2 controls several different antioxidant pathways by activating the expression of GSTs and other genes. This control is important to avoid cellular wear caused by oxidative stress, thus hindering the onset of various diseases.

The interindividual variation of the activity of antioxidant enzymes, for example, GST, considered by both environmental factors (e.g., diet and exposure to toxins such as cigarette) and genetic, is directly related to the etiology of cancer. Cytosolic GST present polymorphisms in humans and, this is probably the cause for differences in interindividual response to

xenobiotics. The first studies in this area have addressed the correlation between GSTM1 null and/or GSTT1 null genotypes and a higher incidence of lung cancer, bladder, breast, colorectal head/neck. The discovery of allelic variants of GSTP1, encoding enzymes with reduced catalytic activity, led many researchers to examine the hypothesis that the combinations of polymorphisms of the Mu class, Pi and Theta of GST contribute to disorders with environmental factors [45, 46]. Studies with mice that exhibited a homozygous deletion of Nrf2 showed that Nrf2 is critical for inducing hepatic glutathione S-transferase (GST), NAD(P)H: quinone oxidoreductase (NQO1) and regulating levels of glutathione (**Figure 1**) [47].

Besides genetic variants of GST, changes in phase I enzyme activity as encoded by the cytochrome P450 family can also have implications for the metabolism of specific nitrosamines from the tobacco, alcohol and other carcinogenic substances [48].

The GST enzymes are part of an integrated protection system, so it is important to note that the efficiency of this system depends on the combined action of other enzymes, such as γ-glutamylcysteine synthase γGluCysS) and glutathione synthase, in order to provide glutathione as well as carriers to facilitate the elimination of glutathione conjugates [21].

9. Conclusion

The modulation of intracellular ROS levels is crucial for cellular homeostasis, and different ROS levels can induce different biological responses. It can occur due to the accumulation of intrinsic and/or environmental factors, such as hypoxia, enhanced cellular metabolic activity, mitochondrial dysfunction, increased activity of oxidases, lipoxygenases and cyclooxygenases. The accumulation of free radicals can lead to important changes in the structure of nucleic acids, proteins and lipids, altering their functions with consequent impact on cellular metabolism. These changes create conditions favorable to the onset of different diseases. The determination of oxidative stress markers and plasma antioxidants can suggest a targeted therapy against deficiencies in cell protection systems and it could be useful in an attempt to minimize complications caused by increased oxidative stress, leading to a better prognosis of various diseases.

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