Chapter

Endogenous Enzymatic Antioxidant Defense and Pathologies

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Abstract

Oxidative stress is an important component of various diseases. It manifests as an imbalance caused by an excessive production of reactive oxygen species (ROS) which are associated with a deficit of antioxidant activity. This deficit can be the consequence of genetic factors, environmental ones, metabolic imbalance, toxicity or direct attacks by the accumulation of free radicals. These can induce metabolic dysfunction affecting biological macromolecules in their structures or activities. From a physiological perspective, the neutralization of free radicals is ensured by enzymatic, antioxidant and non-enzymatic defense systems. In the present chapter, we will focus on the endogenous enzymatic antioxidant defense system such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPxs), thioredoxin (Trx) and paraxonase which play an important role in homeostatic redox balance. Also, we will review this set of antioxidants enzymes within different pathological states such as diabetes, cancer, autoimmune diseases, cardiovascular, Alzheimer's, Parkinson's or parasitic diseases such as Leishmaniasis and Malaria.

Keywords: oxidative stress, antioxidant defense, ROS, enzymatic antioxidant, pathology

1. Introduction

Oxidative stress is defined as an imbalance between the production of reactive oxygen species (ROS) and cellular antioxidant capacities. ROS have long been considered toxic by-products of normal oxygen metabolisms and they are implicated in various pathologies. Yet, their controlled production is an essential mechanism of cell signaling that participates in the maintenance of cell homeostasis [1].

As a concept in redox biology and medicine, Oxidative stress was formulated in 1985 [2]. Currently, as of late 2020, approximately 14,216 publications are presented for the term oxidative stress and 3,775 are associated with the term antioxidant defense in PubMed. An important component of various diseases, oxidative stress can also be said to be the result of a biological inability to detoxify reactive intermediates [3]. A large number of methods, such as DNA oxidation, have been developed and used in almost all diseases to measure its extent and nature. Findings confirm the fact that the paradox of ROS, as these are both toxic products of metabolism, and molecules essential for cell signaling and regulation. A moderate and controlled production of ROS can lead to a reversible oxidation of the surrounding molecules.

In such a case, ROS act as correct second messengers. Conversely, an overproduction of ROS or a deficit in defense mechanisms can lead to the appearance of stress which causes non-specific and irreversible oxidation of biological molecules, engendering dysfunction [1, 4]. The production of free radicals occurs continuously in cells as a result of common metabolic processes. However, at high concentrations, whether from endogenous pathological stimuli (hyper-LDLemia, hypertension, diabetes, etc.) or exogenous sources (environmental pollutants, smoking, etc.), they can lead to cell death and disease states via the deterioration of molecular and cellular constituents of the arterial wall [5]. Such a stress can be limited by antioxidant systems, followed by a rapid return to a physiological redox state. It can also be prolonged, resulting in the creation of a new redox balance of a higher and permanent oxidizing level, similar to the one that can be found in chronic pathologies [6].

It is well established that oxidative stress is the main pathophysiological component of many human or animal. It participates in pathogenesis as well as the inflammation with which it is often associated. In several serious diseases, especially those related to aging, oxidative stress is often the original triggering factor. This is the case for cancers, eye pathologies (cataracts and macular degeneration), neurodegenerative diseases (ataxias, lateral sclerosis, Alzheimer's disease). Familial amyotrophic lateral sclerosis is the most illustrative example, since it is caused by a defect in the antioxidant enzyme superoxide dismutase gene. In other diseases, oxidative stress plays only a secondary role in the onset of the pathology, but participates nonetheless in immune or vascular complications. This is the case for infectious diseases such as AIDS, septic shock, diabetes, Parkinson's disease or kidney failure [7]. This is also the case with parasitic diseases. Studies suggest the hypothesis that cellular environments, lifestyle, genetic factors (genetic polymorphism) and metabolic state such as hyperglycemia are stimulants that trigger stress. They have shown that when the antioxidant defense is diminished or absent, the biological environment can no longer counter or adapt to the new physiological situation, and a cascade of ROS production reaction is triggered inducing both immune and metabolic imbalance, as well as structural and functional altercations of proteins involved in antioxidant defense. In the present chapter, we are interested in elements of the endogenous enzymatic antioxidant defense system, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPxs), thioredoxin (Trx) and paraxonase which play a role important in the homeostatic redox balance. We will discuss the association of endogenous enzymatic defense with certain pathologies such as neurodegenerative diseases, autoimmune diseases such as diabetes, cancer, cardiovascular diseases, parasitic diseases.

2. Antioxidant defense mecanisms

The production of free radicals in living systems is continuous [8]. Oxygen (or dioxygen, O_2) is an essential gas to life. It can become reactive, forming superoxide ($O_2^{\bullet -}$). It is likely to cause damaging effects in the human body via the formation of free radicals and reactive oxygen species (ROS) [9]. These are much more toxic than oxygen itself [10]. However, O_2 toxicity and "free radical theory" has already been proposed in the literature to explain the aging process [11].

Antioxidant enzymes play a key role in detoxifying free radicals and reducing oxidative stress. They are the basis of the scavenging of reactive oxygen species (ROS) [12].

Electrons released by the mitochondrial electron transport chain (Mito-ETC) and produced by NADPH oxidases (NOX) are the main source of endogenous

reactive oxygen species. Coupled with molecular oxygen, they give rise to the primary free radical and the precursor of the remaining species - superoxide ($O_2^{\bullet -}$). When in reaction with a short-lived nitric oxide ($NO^{\bullet}$), the superoxide forms a highly reactive peroxynitrate ($ONOO^-$) capable of modifying the structure and function of proteins. Superoxide dismutase (SOD) converts superoxide to hydrogen peroxide (H_2O_2), which can be converted in several ways. In the presence of transition metal ions like Fe^{2+} (Fenton reaction) or in the context of a reaction with superoxide, H_2O_2 forms a highly reactive hydroxyl radical ($OH^{\bullet}$) which damages lipids, proteins. DNAHydrogen peroxide (H_2O_2) can also be implicated in the oxidation reaction of monomeric glutathione (GSH) to glutathione disulfide (GSSG), or that of reduced thioredoxin (Trx red) to oxidized thioredoxin (Trx ox) catalyzed by glutathione peroxidase (GPX) or peroxidases involved in the renewal of thioredoxin (Trx). The reduced glutathione pool is restored by glutathione reductase (GR) which reduces oxidized glutathione via the use of NADPH. Thanks to the thiol groups in the cysteine (Cys) residues, glutathione and thioredoxin participate in the reduction of oxidized proteins. Their synthesis and renewal take place under tight homeostatic control creating a system responsible for the reduction of proteins sensitive to oxidation–reduction in the event of oxidative stress (**Figure 1**). Permeable H_2O_2 is involved in the signaling process and is degraded by catalase, glutathione peroxidase and peroxiredoxin3. Efficient regulation of mitochondrial H_2O_2 via endogenous antioxidant pathways is therefore an essential mechanism for maintaining physiological redox signaling and homeostasis [13, 14].

The mitochondria is not only one of the main sources of intracellular ROS, it is above all the main target. ROS can have a direct effect on mitochondrial activity. An induced alteration of mtDNA can alter the functioning of the respiratory chain and

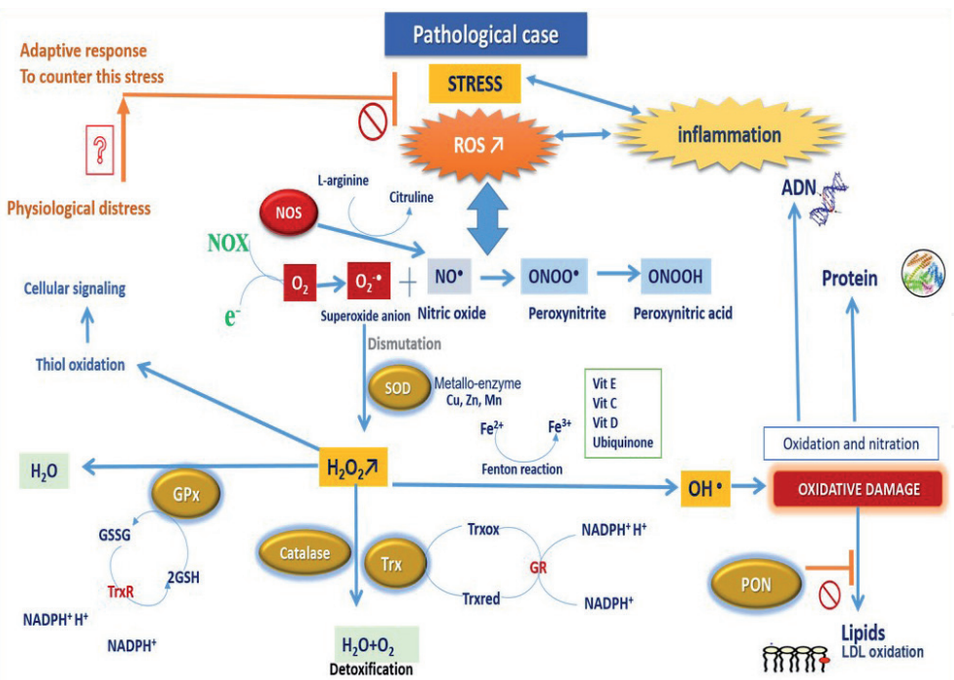

Figure 1.
Defense mechanisms of antioxidants. e-: electron; GPxs: glutathione peroxidase, GR: Glutathione reductase, GSH: Glutathione, GSSG: Glutathione disulfide ; H_2O_2 : Hydrogen peroxide, iNOS: nitric oxide synthase; LDL: low density lipoprotein; $NO^{\bullet}$: Nitric oxide ; NOS : nitricoxide synthase ; NOX: NADPH oxidases; NADP: Nicotinamide Adenine Dinucleotide Phosphate; O_2: Dioxygen; $O_2^{\bullet -}$: Superoxide anion; $OH^{\bullet}$: Hydroxyl radical; $ONOO^{\bullet}$: Peroxynitrite; ONOOH: Peroxynitrite acid; PON: Paraxonase; ROS: reactive oxygenated species; SOD: superoxide dismutase; Trx ox: oxidized thioredoxin ; Trx red: reduced Thioredoxin ; Trx: thioredoxin; Cu: copper Fe: iron; Zn: zinc; Mn: manganese;Vit: vitamin.

trigger a vicious cycle that increases ROS production and oxidative mitochondrial damage. Likewise, increased oxidation of mitochondrial membrane phospholipids could alter mitochondrial function [15].

3. Endogenous antioxidant enzymes

3.1 Superoxide dismutases

Superoxide dismutase (SOD) is a metalloprotein, representing one of the first lines of defense against the deleterious effects of free radicals. Thus, SODs are able to eliminate the superoxide anion $O_2^{\bullet -}$ by a disproportionation reaction, forming, with two superoxides, one molecule of oxygen and one molecule of hydrogen peroxide H_2O_2. In humans, 3 isoenzymes are described: cytosolic SOD1 (Cu/Zn-SOD), mitochondrial SOD2 (Mn-SOD) and extracellular SOD3 (Cu/Zn-SOD) [9, 16, 17]. These different forms of SOD elicit similar functions, but the characteristics of their quaternary protein structures, their chromosomal locations, their requirements for metal cofactors, their gene distributions and their cellular compartmentalisation are different from one another [18, 19].

SOD1, or CuZn-SOD (EC 1.15.1.1) was the first enzyme to be characterized. It consists of a copper and zinc-containing homodimer found almost exclusively in intracellular cytoplasmic spaces [20]. The SOD2, or Mn-SOD (EC 1.15.1.1), exists in the form of a tetramer containing manganese. It is a 222 amino acid protein with an N-terminal signal sequence of 24 amino acids. This enzyme is found exclusively in the mitochondrial matrix [21]. SOD3, or EC-SOD (EC 1.15.1.1), is a tetramer containing copper and zinc. It is found exclusively in the extracellular spaces. It is secreted by smooth muscle cells and constitutes the major antioxidant system of the arterial wall: its expression and secretion are increased by vasoactive factors (histamine, endothelin 1, angiotensin II) and decreased by homocysteine [9].

3.2 Catalase

Human catalase [CAT; EC 1.11.1.6] is an endogenous antioxidant enzyme of approximately 60 kDa. Its protein structure takes the form of a tetramer composed of a complex of 4 identical subunits, each containing 527 amino acid residues and a heme group with Fe_3^+ [22, 23]. Catalase has been mapped on chromosome 11p13. It converts the hydrogen peroxide "H_2O_2" of reactive oxygen species into water "H_2O" and oxygen "O_2" thus reducing the toxic effects of hydrogen peroxide [24].

3.3 Glutathion peroxydase

Glutathione peroxidases (GPx; EC 1.11.1.19) are a family of phylogenetically related oxidoreductases distributed in all living domains. GPx is a tetrameric selenoprotein, containing seleno-cysteine (Sec) in the active site [25]. It catalyzes the reduction of organic hydroperoxides (-ROOH) into alcohol and water groups using reduced glutathione (GSH) as a cosubstrate. It can also catalyze the reduction of hydrogen peroxide (H_2O_2) to H_2O and oxygen by oxidation of GSH reduced to its disulfide (GSSG). Oxidized glutathione (GSSG) can be reduced to GSH by the enzyme GSH reductase (GR), via the use of NADPH as a reducing substrate [26, 27]. Thus, GPxs protect against oxidative damage and are involved in the detoxification of hydrogen peroxide [28].

3.4 Paraxonase

The paraoxonase (PON) (EC:3.1.1.2) gene family includes three proteins, PON1, PON2 and PON3. PON1 and PON3 are both associated with high density lipoprotein (HDL) particles and exert anti-oxidant and anti-inflammatory properties [29]. The PON gene is located on the long arm of chromosome 7 in humans [30, 31]. PON proteins are all associated with high density lipoprotein (HDL) particles and exert anti-oxidant, anti-inflammatory and lipo-lactonase activities [29]. All PON proteins are involved in the pathogenesis of several inflammatory diseases including atherosclerosis, Alzheimer's disease, Parkinson's disease, diabetes and cancer. PON1 is found exclusively extracellular and associated only with high density lipoprotein (HDL) particles in the circulation, and partly confers the anti-oxidant and anti-inflammatory properties associated with HDL. Studies have shown that intracellular PON proteins; PON2 and PON3 are associated with mitochondria and membranes associated with mitochondria, modulate mitochondria-dependent superoxide production and prevent apoptosis. In addition, it has been shown that the overexpression of the PON2 and PON3 genes protects the mitochondria from mitochondrial dysfunction [31].

3.5 Thioredoxine

The thioredoxin (Trx) system is one of the central antioxidant systems in mammalian cells, maintaining a reducing environment by catalyzing the flow of electrons from nicotinamide adenine dinucleotide phosphate to Trx reductase in Trx, which reduces its target proteins using highly conserved thiol groups. Thioredoxin (Trx) is a 12 kD oxidoreductase enzyme containing a dithiol-disulfide active site. It is ubiquitous and found in many organisms, from plants and bacteria to mammals. It is located on chromosome 9 in the cytogenic position 9q31.3[32]. The redox cascade of the Trx system is initiated by $NADPH^{+}$. H^{+} is generated by the pentose phosphate pathway. $NADPH^{+}H^{+}$ reduces oxidized Trx reductase (TrxR), which regenerates the pool of reduced Trx. Reduced Trx helps maintain a reducing environment for a number of different proteins [33]. In mammalian cells, there are two isoforms of Trx, a cytosolic Trx1 isoform which under certain circumstances can be transferred into the nucleus and secreted out of the cell, and the mitochondrial isoform Trx2. Unless explicitly stated otherwise. There is also a truncated form of Trx (Trx80) which has no redox properties and is not reduced by Trx reductase [33]. Trx, as an antioxidant, maintains the balance of redox status bound to thiol and also plays a central role in the regulation of redox signaling. Trx detects and responds to environmental oxidative stress1. The ROS generated by cellular respiration, metabolism and immune response, then modulates the redox status, function and activity of its target signaling proteins. Deregulation of such a Trx system affects various cellular functions and outcomes such as cell survival and death, leading to human diseases including cancer and inflammation.[34]. Thioredoxin reductase (rxRs) are oxidoreductases necessary for the reduction of the active disulfide site in Trx and responsible for maintaining the pool of reduced and active Trx. Additionally, TrxR is a selenoprotein, and selenium is required for its expression and activity [33].

4. Pathologies

4.1 Neurodegenerative diseases

Aging is a major risk factor for several common neurodegenerative diseases, including Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS),

Alzheimer's disease (AD) and Huntington's disease (HD). Recent studies have implicated mitochondrial dysfunction and oxidative stress in the aging process and also in the pathogenesis of neurodegenerative diseases. In the brain and other tissues, aging is associated with progressive impairment of mitochondrial function and increased oxidative damage. Three phenomena leading to oxidative stress in the brain, and implicated in neurodegenerative diseases, include inhibition of mitochondrial metabolism, neuronal excitotoxicity, and neuroinflammation [35].

4.1.1 Parkinson disease

Oxidative stress is an important factor in the Parkinson's disease (PD) pathogenesis. The main source of oxidative stress in the genesis of PD is the activation of glial cells and dopaminergic neuronal death of the substantia nigra [36, 37]. The oxidative imbalance involved in the neurodegenerative processes of PD appears to be a multifactorial phenomenon triggered by factors such as aging of the brain, genetic predisposition, mitochondrial dysfunction, free radical production and environmental toxins [37, 38]. Some studies suggest that although the accumulation of ROS plays a key role in the initiation and acceleration of cell death in PD, it is not the only cause of cell death in this disorder [39].

The activities of SOD, CAT, glutathione peroxidase (GSH-Px) and glucose-6-phosphate dehydrogenase (G6PD) have been reported to be significantly lower in patients with PD [36, 37]. The production of superoxide has also been found to increase considerably when the flow of electrons is inhibited at the level of the mitochondrial complex I or III complex [35, 40, 41].

4.1.2 Alzheimer's disease

Oxidative stress plays a role in Alzheimer's disease (AD), an age-related multifactorial disease leading to loss of cognitive functions [42]. It is characterized by a loss of synapses, an increase in the number of senile plaques (SP) and extracellular amyloid rich in beta-peptide (Aβ). Metal ions can bind to beta amyloid peptide (Aβ) to produce ROS. Thus, the damaged Aβ during the production of ROS, causes cellular toxicity and oxidation of neuronal membrane biomolecules and leads to disruption of membrane integrity [43]. It has been reported that oxidative stress may play a role in the pathogenesis of dementia AD and cerebral ischemia that causes vascular dementia (DV) [43]. The presence of early oxidative damage in mild cognitive impairment in amnesia (aMCI) has been shown to exist before clinical dementia in AD develops [44].

It has been reported that the neurodegenerative process of this disease is linked to a cyclical process between impaired energy metabolism, associated with lactate production and oxidative stress. Indeed, a decrease in complex IV activity and mitochondrial DNA mutations has been identified in patients with AD [40]. In addition, oxidative stress may be an early event in AD etiology, since markers of oxidation appear in mild cognitive impaired regions of the brain [42]. A strong association between low serum CAT, SOD, GPx and PON1 activity and the risk of AD has been reported.

4.2 Cardiovascular diseases

Cardiovascular disease is a group of disorders affecting heart and blood vessels. In a physiological state, ROS are modulators of signal transduction pathways and

gene expression involved in vascular homeostasis. The cells of the vascular wall exhibit a physiological redox state that can be disrupted under many pathophysiological circumstances, causing oxidative stress that is deleterious to the cells concerned and their vascular functions. The causes of this imbalance are multiple, and overlap at least partially the classic cardiovascular risk factors: arterial hypertension, hypercholesterolemia, diabetes, etc. These risk factors are at the origin of stimuli responsible for an abnormal production of ROS, in particular by activation of NADPH oxidases and of the mitochondrial respiratory chain, a decrease in the bioavailability of NO to vasodilator effects. The pro-oxidant imbalance leads to the formation of oxidized LDL and multiple cell dysfunctions: release of pro-inflammatory factors and factors promoting cell proliferation, process of apoptosis and/or necrosis [6].

Several causes can produce an oxidative alteration which ultimately affects gene expression. Extracellular signals (cytokines emitted during inflammation, for example) are transmitted at the membrane level by receptors. These activate oxidases, thus generating H_2O_2, which acts as a second messenger. Likewise, an influx of xenobiotics can activate oxidative metabolism and lead to an overproduction of H_2O_2. The resulting modification of the "intracellular redox potential" will modulate the activity of certain transcription factors, and lead to a modification of gene expression [45] which as a result is partly responsible for the lowering of the defense of antioxidant enzymes.

4.3 Auto-immune diseases

Autoimmune disease is a pathological condition characterized by the breakdown of the self-tolerance of the immune system in the body in which genetic and environmental factors are involved. Immunological processes against tissues and organs lead to increased oxidative stress, and in turn, an imbalance of oxidative stress worsens the pathobiology of the disease. This is for example the case in type1 diabetes, multiple sclerosis or rheumatoid arthritis, systemic lupus erythematosus (SLE) and Sjögren syndrome (SS) [46]. Here, we will look at the oxidative stress and antioxidant defense relationship in type 1 diabetes (T1D).

T1D is a multifactorial disease and results from the destruction of insulin-secreting beta cells induced by an autoimmune process [47] with a strong inflammatory component [48]. Usually T1D is triggered by individuals with a specific genetic predisposition [49]. It is now clear that environmental factors play an important role in the development of this disease [50]. T1D involves the generation of pro-inflammatory cytokines and reactive oxygen species (ROS) [1]. The generation of free radicals potentiates the pathogenesis by promoting the destruction of cellular components, tissue damage and inflammation [51].

There is an inherent association with stress and the synthesis of reactive oxygen species (ROS) by immune cells to directly induce the destruction of B cells in the pancreas. However, recent evidence has shown that ROS can not only function as effector molecules involved in the pathogenesis of pancreatic β cells, but can also promote activation of innate and adaptive immune pathways in T1D [52]. Several previous studies have shown that hyperglycemia is associated with a decrease in oxidative defense. This confirms the hypothesis that hyperglycemia is at the origin of the production of reactive species and the decline in antioxidant defense [53, 54]. On the other hand, another study, carried out on endothelial cells of human origin, shows that high concentrations of glucose increase the activities of anti-oxidant enzymes (SOD, catalase, glutathione-peroxidase) as well as their cellular overexpression. This is evidence of an oxidative stress response resulting

from high glucose levels [55]. It has been reported in poorly balanced diabetic patients that erythrocyte SOD is often reduced when the glycation level is high. This results in a reduction of enzyme's activity. Experimental evidence has shown that exposure to high concentrations of hydrogen peroxide can damage beta cells in the pancreas [56].

4.4 Cancer

It is becoming increasingly evident that ROS play an important role in the biology of tumorigenesis. Cancer cells increase ROS production to activate localized pro-tumorigenic signaling, and balance the increase in ROS with high antioxidant activity to maintain redox balance. Nevertheless, mutations associated with different types of cancer are often cited as the cause in the increased production of ROS. Hypoxia, activation of oncogenes, mutations in mitochondrial DNA, and loss of tumor suppressors have all been shown to lead to increased mitochondrial ROS-dependent tumorigenesis. Several tumor suppressors such as the "guardian of the genome" P53 have been shown to have ROS inhibitory functions. In about 50% of cancers, the tumor suppressor p53 is lost or mutated [57].

Several studies have shown that there is a strong relationship between inflammation, oxidative stress and cancer. The evolution of tumor metastases depends on an oxidative environment and inflammation, thus contributing to long-term cell damage and promoting carcinogenesis. Alterations in PON status encompassing genotype, activity and/or expression have been demonstrated in cancer patients, as well as in various cancer cells in vitro [58]. In recent years, overexpression of PON2 and PON3 has been observed in cancer cells and it has been proposed that both enzymes may be involved in tumor survival and resistance to stress. In addition, a lower activity of serum PON1 has been reported in cancer patients [58, 59]. Huang et al. found that PON3 is involved in multi-drug resistance in esophageal cancer (CE). Drug resistance prevents effective treatment of cancers [60]. As a result, blocking the antioxidant defense in tumors decreases their ability to balance oxidative stress and results in cell death [61]. Indeed, several clinical studies on several types of cancer have reported low levels of activity of antioxidant enzymes such as SOD, GSH and CAT in groups of patients with prostate cancer [62], breast cancer [63] et malignant lymphoma in children [64]. Also, another study showed that MCF-7 breast cancer cells chronically exposed to ascorbate/menadione become resistant (Resox cells) by primarily increasing catalase activity. These data suggest that chromatin remodeling is a major regulatory process controlling the expression of catalase in breast cancer cells when developing resistance to oxidative stress [65].

4.5 Parasitic diseases

Infectious diseases are often associated with oxidative stress and an inflammatory response. Infection and inflammation trigger a cascade of reactions in the host, known as the acute-phase response. Neglected diseases due to the parasitic protozoa *Leishmania*, *Trypanosoma* and *Plasmodium* affect millions of people worldwide, and the lack of suitable treatments has promoted an ongoing drug discovery effort to identify novel nontoxic and cost-effective chemotherapies. Leishmaniasis and Malaria are the most important neglected tropical diseases, with a disease burden of 0.2 to 0.4 million cases with a mortality rate of 20,000 to 40,000 reported per year for visceral leishmaniasis [66] and 214 million cases for malaria in 2015 and mortality of 1 to 2 million every year [67].

4.5.1 Oxidative stress and malaria

In response to infection caused by *Plasmodium* parasites, the natural host defense mechanism is activated with involvement of phagocytes (macrophages and neutrophils). These, in turn, generate large amounts of ROS and RNS, causing an imbalance between the formation of oxidizing species and the activity of antioxidants. This imbalance is what triggers oxidative stress, which is an important mechanism of human hosts in response to infections and, in the case of Malaria, can lead to the death of the parasites [68]. *Plasmodium* spp. are global pathogens with a complex life cycle alternating between female Anopheles mosquitoes and vertebrate hosts that require the formation of unique zoite forms to invade different cell types at specific stages. Once sporozoites enter the host, they infect hepatocytes, and this is followed by the asexual cycle in the blood. Sexual forms that develop during the blood stage are ingested by a feeding mosquito, completing the cycle [69].

Plasmodium digests hemoglobin within its acidic food vacuole and releases toxic ferriprotoporphyrin IX (FP) and ROS [70]. Normally FP polymerizes to hemozoin but can also react with O_2 to form ROS, superoxide radical ($O_2^{\bullet -}$) that can be reduced to H_2O_2 by SOD. H_2O_2 can further be reduced to H_2O by either thioredoxin-dependent peroxidase (TPx) or GST in the parasite or by GST, TPx, GPx, and CAT in the host cell. ROS can react with lipids and proteins forming oxidized lipids or proteins. During the redox reactions, GSH and TrxSH become oxidized to GSSG and thioredoxin disulfide (TrxS2). Both GSSG and TrxS2 are reduced back by GR and TrxR, respectively. GSH is also synthesized in a pathway involving c-glutamyl-cysteinyl ligase (cGCL) and glutathione synthetase (GSH synt). NADPH is recycled by the pentose phosphate pathway under enzymes glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (6PGD) [71].

4.5.2 Leishmania implementation and oxidative stress

Leishmaniosis are group of parasitic of neglected tropical diseases endemic in 98 countries. *Leishmania* spp. are intracellular parasitic protozoa with a complex digenetic life cycle requiring a susceptible vertebrate host and a permissive *phlebotomus* insect vector, which allow their transmission. The disease manifestations are from self-healing cutaneous lesion to visceral pathology depending on complex interactions between the parasite and the host immune system. The parasite *Leishmania* use Trojan horse strategy when it is transmitted into the circulation system of the mammals after the vector sandfly blood meal. The promastigote motile form is phagocytized by macrophages and subsequently transform into the nonmotile amastigote form. The obligatory intracellular amastigotes reside within phagolysosomal vacuoles and adopt sophisticated mechanisms that enable them to avoid the hostile defense system of their host organism. The interplay between the parasite and its host is a complex process, in which the paramount interest of the parasite is to restrict the immune and microbicidal activities of the macrophage, while keeping it alive as a nutritional Source [72].

Phagocytosis of microbes leads to a burst of $O_2^{\bullet -}$ production through activation of NADPH oxidase [73, 74]. Once inside the host cell, ROS and RNS are the cellular major arms against *Leishmania*. NO is synthesized by nitricoxide synthase (NOS) during the conversion of l-arginine to l-citrulline, while $O_2^{\bullet -}$ and other ROS are generated by the membrane-bound NADPH-dependent oxidases (NOX) [75].

To deal with this avalanche of oxidative stress molecules and host immune response, *Leishmania* has developed several immune evasion strategies to avoid a certain death by oxidative stress. NO production by nitric oxide synthase iNOS is

disturbed by highlighting the efficiency of this effect or mechanism. *Leishmania* parasites are particularly efficient at disrupting signals that lead to the activation and differentiation of CD4+ Th1cells, such as IL-12 and CD40 signaling [76, 77]. *Leishmania* does not express GSH/GR, but its redox metabolism relies on the glutathione conjugate N1,N8-bis(L-γ-glutamyl-L-hemicystinylglycyl) spermidine, also known as trypanothione (T(SH)2). Trypanothione disulfide (TS2) is generated when T(SH)2 reduces ROS [78]. Trypanothione reductase (TRs) have structural analogies with GRs and are also members of the NADPH-dependent flavoprotein oxidoreductase family. TR uses NADPH as an electron donor for the reduction of $T(S)_2$ [77, 79].

Leishmania does not express catalase and classical selenium-containing glutathione peroxidases, two major hydroperoxide-eliminating enzymes generally present in eukaryotes (Krauth-Siegel & comini, 2008). Instead, these organisms' hydroperoxide metabolism was found to depend on tryparedoxin (TXN) and peroxiredoxin (PRX) belonging to the peroxiredoxin family of enzymes and are pivotal for $T(SH)_2$ to reduce H_2O_2 [80, 81]. Overexpression of peroxidases in *Leishmania* demonstrated its protective action against oxidative stress, ROS-induced programmed cell death, and protein damage [82, 83]. The combined hydroperoxide and ONOO- metabolizing activities of 2-Cys peroxiredoxins are also likely to account for the increased infectivity of Leishmania mutants overexpressing a cytosolic peroxiredoxin, in an ex vivo model of infection [84].

5. Conclusion

The moderate and controlled production of ROS can lead to a reversible oxidation of the surrounding molecules: the ROS then act as true second messengers. Conversely, an overproduction of ROS or a deficit in defense systems leads to the appearance of stress which causes a non-specific and irreversible oxidation of biological molecules, leading to a loss of function [4]. In addition, it is obvious to emphasize that individuals do not have the same antioxidant potential depending on their eating habits, their lifestyle, their genetic characteristics or the environment in which they live. As a result, the antioxidant defense may be different from one individual to another. In order to counter the ROS attack and adjust the redox balance, a repair process is set up for each pathological situation. As a result, endogenous defense induces several signaling mechanisms to adapt to the new physiological situation.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

6PGD	6-phosphogluconate dehydrogenase
AD	Alzheimer's disease
ALS	Amyotrophic Lateral Sclerosis
aMCI	cognitive impairment in amnesia
Aβ	beta-peptide
CAT	catalase
cGCL	c-glutamyl-cysteinyl ligase

FP	ferriprotoporphyrin IX
G6PD	glucose-6-phosphate dehydrogenase
GPxs	glutathione peroxidase
GR	Glutathione reductase
GSH synt	glutathione synthetase
GSH	Glutathione
GSSG	Glutathione disulfide
H_2O_2	Hydrogen peroxide
HD	Huntington's disease
HDL	High Density Lipoprotein
iNOS	nitric oxide synthase
LDL	low density lipoprotein
Mito-ETC	Mitochondrial- Electron Transport Chain
mtDNA	mitochondrial DNA
$NO^{\bullet}$	Nitric oxide
NOS	nitricoxide synthase
NOX	NADPH oxidases
$O_2^{\bullet -}$	Superoxide
O_2	Dioxygen
$OH^{\bullet}$	Hydroxyl radical
$ONOO^{\bullet}$	Peroxynitrate
PD	Parkinson's disease
PON	paraxonase
$ROOH^{-}$	Hydroperoxides
ROS	reactive oxygenated species
SLE	Systemic lupus erythematosus
SOD	superoxide dismutase
SS	Sjögren syndrome
T(SH)2	trypanothione
$T(SH)_2$	trypanothione.
T1D	Type 1 diabetes
TP53	tumor protein 53
TRs	trypanothione reductase
TRs	trypanothione reductase
Trx ox	oxidized thioredoxin
Trx red	reduced Thioredoxin
Trx	thioredoxin
TrxR	Trx Reductase
TS2	Trypanothione disulfide
TS_2	Trypanothione disulfide
β cells	beta cells

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