Chapter

Subcellular Localization of Glutathione Peroxidase, Change in Glutathione System during Ageing and Effects on Cardiometabolic Risks and Associated Diseases

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Abstract

Glutathione peroxidase (GPx) is a selenoprotein with biological properties that allow the detoxification of endogenous or exogenous reactive oxygen species as well as the elimination of xenobiotic compounds in the cells. Due to its isoform activities and pathophysiological functions, GPx holds the status of a redox system (GSH/GSSG) in the glutathione (GSH) system to prevent oxidative damage of cellular constituents. As such, the GPx is the first line of defense against free radicals. Its deficiency causes oxidative stress that not only promotes the oxidation of proteins and deoxyribonucleic acid (DNA) but also leads to insulin resistance, dyslipidemia, inflammation, and metabolic alterations, which expose to high risk for cardiometabolic disorders due to cardiovascular and degenerative diseases especially when associated with aging. This work presents a review of different studies done on the localization of GPx in subcellular organelles, activity changes during cellular aging, their effects on cardiometabolic risks, and associated diseases.

Keywords: aging, antioxidants, cardiometabolic risks, disease, free radicals, glutathione, glutathione peroxidase, selenium, traditional foods

1. Introduction

Cardiometabolic risks (CMR), the main causes of the onset of cardiovascular diseases (CVDs), insulin resistance (IR), dyslipidemia, and systemic inflammation are among the major metabolic alterations caused largely by oxidative stress. The oxidative stress is the result of the imbalance of the antioxidant system in favor of prooxidants, which interferes with the GSH/GSSG system in the antioxidant defense and the regulation of gene expression, the synthesis of DNA and proteins, cell proliferation and apoptosis, and cytokine production and protein glutathionylation, due to alteration of certain cellular functions. In this system, the deficiency of GPx, as a first line of defense against free radicals, stimulates oxidative stress, which

promotes the development of chronic noncommunicable diseases (NCDs), such as CVDs, as well as early aging and cancer [1]. Having sufficient knowledge of the GSH system and the regulation and functions of GPx is essential to prevent metabolic alterations and to develop effective strategies for treating these diseases. This chapter reviews (i) the main scientific information on GPxs and the GSH system and their location in subcellular organelles and changes during aging; (ii) the link between oxidative stress, GPxs, and the metabolic syndrome; and (iii) the effects of GPxs in chronic pathogenesis and CVDs in particular and the role of dietary selenium (Se) in GPx activities.

2. Glutathione system

2.1 Structure and functions of the glutathione system

Glutathione, γ-glutamyl-cysteinyl-glycine (GSH), is a ubiquitous intracellular tripeptide present in all mammalian tissues, especially in the liver. This thiol-containing molecule is an important antioxidant in cell compartments with high concentrations in cytosol (1–11 mM), nuclei (3–15 mM), and mitochondria (5–11 mM). GSH represents a significant part of the redox status of thiol mammalian systems [2, 3]. It should be noted that the research on GSH metabolites was done in vivo more than a century before [4].

GSH has several biological functions including the detoxification of electrophiles, the antioxidant defense, the maintenance of the thiol status of proteins, and the modulation of DNA synthesis and the immune system [4]. Additionally, GSH serves as a cysteine reservoir with a proton-donating sulfhydryl function, which allows GSH to act as an antioxidant. In its role as an antioxidant, GSH effectively removes free radicals and other reactive oxygen species through the GPx activity [5], which oxidizes GSH to GSSG, and the action of NADPH-dependent glutathione reductase, which generates GSH [3]. In the presence of GSH, glutathione-S-transferase activity detoxifies xenobiotics and various physiological metabolites to form mercapturates and reactivated glucose-6-phosphate dehydrogenase [6]. With NO, GSH is necessary for the hepatic action of insulin sensitizing agents and plays a crucial role in regulating the redox state of the cell with lipids, glucose, and amino acids. Besides to its antioxidant nature, GSH is involved in the transfer of amino acids by the gamma-glutamyl cycle as well as in the hormonal metabolism of estrogen, leukotrienes, prostaglandins and as a transduction signal for transcription [3]. In the central nervous system (CNS), GSH functions include maintenance of neurotransmitters, membrane protection, detoxification, metabolic regulation, and modulation of signal transduction. The depletion of GSH in the brain is implicated in both Parkinson's disease and neuronal damage after stroke [7].

2.2 Regulation of glutathione metabolism

Glutathione is synthesized in the cytosol of all animal cells by the regulated action of gamma-glutamate cysteine ligase (γ-GCL), glutathione synthetase, glutathione reductase (GSR), and gamma-glutamyl transpeptidase (γ-GGT) and from which it is distributed to the other cellular compartments [8]. The key transcription factors that regulate gene expression are NF-E2-related factor 2 (Nrf2) via the antioxidant response element (ARE), AP-1, and nuclear factor kappa B (NF-κB). The alteration of the GSH concentration affects the dysregulation of cell proliferation and the transcription of detoxification enzymes and apoptosis [9]. Therefore, de novo synthesis of GSH is essential for the adaptive response to oxidative stress.

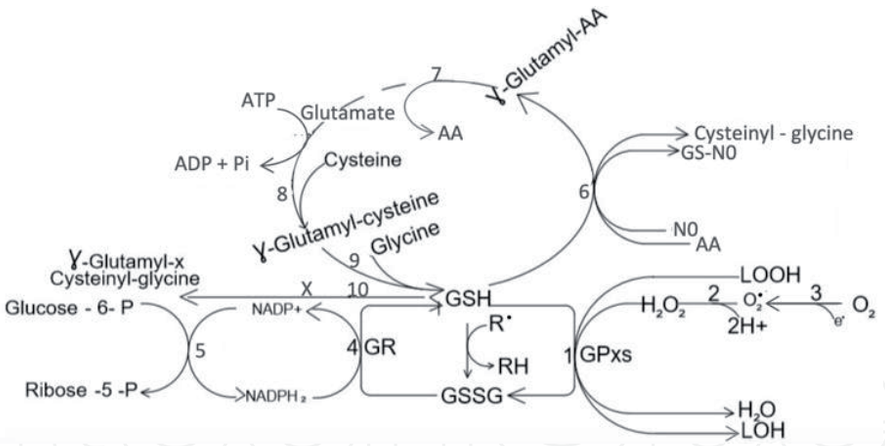

Figure 1.
Glutathione system with synthesis routes and pentose phosphates: the enzymes that catalyze the reactions are (1) GPxs, (2) superoxide dismutase, (3) NADPH oxidase and mitochondrial respiratory complexes, (4) glutathione reductase, (5) gluco-6-phosphate dehydrogenase, (6) γ-glutamyl transpeptidase, (7) γ-glutamyl cyclotransferase, (8) γ-glutamylcysteine synthetase, (9) glutathione synthetase, (10) γ-glutamyl transpeptidase. Abbreviations: AA, amino acid; O_2^-, radical superoxide; H_2O_2: hydrogen peroxide; GS-NO, glutathione-nitric oxide adduct; LOH, alcohol lipid; LOOH, hydroperoxide lipid, $R^\cdot$, radical; RH, nonradical; X, electrophilic xenobiotics.

Intracellular GSH homeostasis is regulated not only by de novo synthesis but also by several factors, including its use and recycling in cells [3]. A disruption of GSH homeostasis could induce oxidative stress and lead to neurodegenerative diseases, including amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, and dementia, with impaired motor and cognitive functions [7]. There is also increasing evidence that deregulation of GSH synthesis contributes to the pathogenesis of diseases such as diabetes mellitus, pulmonary and hepatic fibrosis, alcoholic liver disease, cholestatic liver injury, endotoxemia, and drug-resistant tumors cells [10]. GSH also modulates cell death whether it is apoptosis or necrosis. In both cases, GSH levels influence the expression/activity of caspases and other important signaling molecules in cell death. The regulation of GSH is well reported by Lu [11], and its role is illustrated in **Figure 1**.

3. GPx, oxidative stress and cardiometabolic risk

GPx is the most powerful biological antioxidant reducer. The GSH/GSSG ratio of GSH, as well as other active redox couples, including NADP/NADPH and FAD/FADH2, regulates and maintains cellular redox status. Under normal conditions, antioxidant systems neutralize ROS. However, when the ROS level is high metabolic alterations of cellular constituents occurs related to oxidative damage to the cells [6, 10]. When there is a prolonged increase in oxygen reactive species (ROS) levels that the existing antioxidant potential cannot eliminate, cell enters in the state of chronic oxidative stress. This leads to insulin resistance (IR), atherogenic dyslipidemia, visceral obesity, and pro-inflammatory and pro-thrombotic status. These are potential factors that increase cardiometabolic risks (CMRSs) and may lead to or accompany some pathologies, such as diabetes mellitus, cardiovascular disease, neurodegenerative, cancer, and aging diseases [12].

The GSH redox cycle is a major source of protection against mild oxidative stress with the GPx, antioxidant enzyme that oxidizes GSH to GSSG to protect cells against the proliferation of reactive oxygen species (ROS) or reactive nitrogen species (RNS), sparing them from oxidative damage, while catalase is becoming increasingly important in protecting against severe oxidative stress [3, 6, 10]. The

variation in the erythrocyte GSH system without nuclear capacity to restore homeostasis may be an early biomarker of chronic oxidative stress that could be a first step in the development of cardiometabolic complications. If the cells are overwhelmed by the intensity of the oxidative stress, they die by necrosis or apoptosis [13].

It has also been reported that obese women with high GPx activity have an altered cardiometabolic profile, evidenced by insulin resistance predominantly affecting the liver, altered carbohydrate and lipid metabolisms, and a larger wall thickness of blood vessels than those with lower GPx activity. This suggests that GPx blood activity may be a parameter contributing to the identification of subclinical asymptomatic cardiometabolic disorders [14].

4. Subcellular localization of GPx and change of the glutathione system during aging

In view of its role in the regulation of the cellular redox status, GSH has specific vital functions within the intracellular organelles where it is located. GSH is generally in the greatly reduced state in the different cellular compartments. The integrity of cell and subcellular membranes is highly dependent on the presence of GSH and GPx [15]. Decreased GSH levels in some organelles and tissues during aging expose cells to an increased risk of succumbing to stress. Moderate stress increases glutathione levels to protect cells against more severe stress. In the cytoplasm, the oxidized form (GSSG) is usually in the order of at least about 1% of the total. In the nucleus, GSH maintains the redox status of the sulfhydryl groups of the proteins involved in nucleic acid biosynthesis and DNA repair. It is also used in the reduction of ribonucleotides to produce deoxyribonucleotides by ribonucleotide reductase [16]. A significant portion of ER glutathione is oxidized, with a [GSH]/[GSSG] ratio that can reach 3:1. This relatively oxidative thiol-disulfide medium is essential for the oxidative folding of nascent proteins in ER. Mitochondria contain 10–15% of cellular GSH, but being of a very small volume, the local concentration of GSH in these organelles is generally great and 85–90% in the cytosol. Studies have shown that there is a close relationship between the survival of the mitochondrial GSH pool (mGSH) and that of the cells due to the central role of mitochondria in programmed cell death (apoptosis) as well as important involvement of ROS produced at 90% in mitochondria [17]. High levels of ROS and calcium, acting together, can trigger the mechanism of cell death via apoptosis or necrosis. Thus, the decrease in mGSH levels is closely associated with certain pathologies in both humans and animals. Differential centrifugation and isopycnic equilibration in WI-38 fibroblast density gradients allowed for GSH localization in all subcellular fractions, whereas glutathione peroxidase and reductase activities were restricted to cytoplasm and mitochondrial fractions. The evolution of GSH in aging fibroblasts showed a sudden increase in its concentration just before cell death, whereas GPx activity was already decreasing at the beginning of passages, and that of glutathione reductase was constant and reaching a very low level at the end of the cell culture, suggesting that the GSH system was probably involved in cell degeneration associated with aging [18].

Glutathione peroxidase (EC 1.11.1.9 and EC 1.11.1.12) is a superfamily of proteins found in many living organisms. It consists of four subunits generally containing a Se atom incorporated in the form of selenocysteine (Sec), which is recognized today as the twenty-first amino acid, the first major enzyme identified as an intracellular antioxidant. In animal cells, and in particular in human erythrocytes, GPx is the main antioxidant enzyme for detoxification hydrogen peroxide (H_2O_2) [17]. It is dependent on Se; the deficiency of which is associated with the

risk of contracting several diseases, notably cancer. GPxs that use GSH to catalyze the reduction of H_2O_2 and lipid peroxides have been identified. Some GPxs are therefore dependent on Se and use GSH as a reducing agent, while others, called TGPx, do not contain Se (NS-GPx) and reduce ROS using thioredoxin, which acts as ROS sensors in various pathways and signal transduction. Catalysis of GPx is essentially following three distinct redox modifications of the Se at the center of the active site, in a triad of selenocysteine, glutamine, and tryptophan, which reduces GSH to GSSG [14, 19].

The study on the evolution of the gene family of GPxs suggests that classes of basal peroxidase glutathione originate from independent evolutionary events such as gene duplication, gene loss, and lateral transfer of genes between invertebrates and vertebrates or plants. This evolution of the family of the GPx gene as a whole has been described by Deponte and Margis et al. [20, 21]. The mammalian GPx family is divided into six clades according to their amino acid sequence, substrate, specificity, and subcellular localization. Other studies have revealed other GPx containing as peroxidic site the residue of cysteine. These include the GPx7 and GPx8, which are isoforms of endoplasmic reticulum sulfhydryl peroxidases.

As a reminder, in humans, eight different isoforms of GPx (GPx1–8), which use GSH to catalyze the reduction of hydrogen peroxide and lipid peroxides, have been identified [19, 20]: GPx1, GPx2, GPx3, GPx4, and GPx6, which contain a selenocysteine residue (SeCys) and the GPx5, GPx7, and GPx8 that do not contain SeCys but contain a Cys residue. Noteworthy, GPx1, GPx2, GPx4, GPx5, GPx6, and GPx7 are tetramers, while GPx3 is monomeric and GPx8 is dimeric [20, 22, 23]. The following paragraphs briefly provide an overview of each of the eight types of GPx.

- Glutathione peroxidase 1 (glutathione: H_2O_2 oxidoreductase, EC 1.11.1.9, GPx1 or cGPx) is abundant in the cytoplasm of almost all mammalian tissues. Its gene is characterized by the Pro198Leu polymorphism and a number of leucine-repeated alanine (A7L) codons, which are associated with the risk of cancer and type 2 diabetes. GPx1 prevents oxidative damage, lipid peroxidation, and protein degradation induced by cytotoxic peroxides. GSH cytosolic and mitochondrial peroxidases only reduce soluble hydroperoxides, such as H_2O_2 and some organic hydroperoxides, such as hydroperoxy fatty acids, cumenehydro peroxide, or t-butyl hydroperoxide. Increased activity of GPx1 inhibits hydroperoxide-induced apoptosis. GPx1 and phospholipid hydroperoxide glutathione peroxidase GPx4 (or PHGPx) are found in most tissues [17, 19]. A study of the subcellular localization of GPx1 variants to appreciate the molecular consequences associated with diseases demonstrated that the primary sequence of GPx1 affects subcellular localization and that the sequence and cell location can be important to understand the impact of GPx1 on human diseases, including cancer [24].

- Glutathione peroxidase 2 (GPx2 or GI-GPx) is extracellular and important as a barrier against the absorption of hydroperoxide in the gastrointestinal tract. GPx2 could be an anti-inflammatory and anticarcinogenic enzyme [25].

- Glutathione peroxidase 3 (GPx3 or pGPx) is excreted from various tissues in contact with body fluids and is particularly abundant in plasma. It reduces hydroperoxides of phospholipids and contributes to extracellular antioxidant status in humans. Low levels of GPx3 increase the risk of cardiovascular events in patients with a trial fibrillation and in the elderly. GPx3 is directed to extracellular compartments [23].

- GPx4 or PHGPx is located in the cytosol and membrane fraction. It reduces more complex lipids such as phosphatidylcholine hydroperoxides, fatty acid hydroperoxides, and cholesterol [26]. GPx4 shares the amino acid motif of selenocysteine, glutamine, and tryptophan (catalytic triad) with other GPxs. Its inactivation causes an accumulation of lipid peroxides, resulting in the death of ferroptotic cells and mutations causing spondylometaphyseal dysplasia [27]. In mice and rats, three distinct GPx4 isoforms, cytosolic GPx4, mitochondrial GPx4 (mGPx4), and nuclear GPx4 (nGPx4), were identified with different functions. Cytosolic GPx4 is essential for embryonic development and cell survival. Both mGPx4 and nGPx4 are involved in spermatogenesis and male fertility. GPx4 has been shown to be a more attractive candidate for silencing lipooxygenases and influencing cytokine signaling [27].

- Glutathione peroxidase (GPx5) does not contain Sec or Se; it is specifically expressed in the epididymis of the male reproductive tract in mammals and is regulated by androgens. It plays a role in the protection of sperm membranes against the harmful effects of lipid peroxidation and/or in preventing the premature reaction of the acrosome [21].

- Glutathione peroxidase 6 (GPx6) is a selenocysteine close to GPx3 whose expression of its gene is limited to embryos and adult olfactory epithelium [19, 21].

- Glutathione peroxidase 7 (GPx7) is an endoplasmic reticulum (ER) monomer containing a Cys redox center (CysGPx). It catalyzes the peroxidase cycle through a Cys mechanism in which GSH and protein disulfide isomerases,are alternative substrates, allowing rapid reactivity with thioredoxin (Trx) or proteins related to most other CysGPx. It protects esophageal epithelia and breast cancer cells from oxidative stress [19].

- Glutathione peroxidase 8 (GPx8) is a resident endoplasmic reticulum (ER) protein that introduces disulfide bonds into nascent proteins via protein disulfide isomerase (PDI); it is a PDI peroxidase that reduces the H_2O_2 content and oxidative stress in emergency rooms [21]. In the presence of peroxide, GPx7 and GPx8 interact by oxidation for the folding of disulfide-forming proteins.

5. Metabolic regulation of glutathione peroxidase

Many studies on the metabolic regulation of GPx have been focused on GPx1, a selenocysteine-dependent enzyme (Sec). The latter is encoded by UGA and directed by the selenocysteine insertion sequence, SECIS element [28, 29], which serves as a platform for the recruitment of elongation factors of selenocysteine-tRNA$^{[Ser]Sec}$ (Sec-tRNA $^{[Ser]\ Sec}$) translation that decodes the UGA codon for the whole family of selenoproteins. The exogenous Se supply controls the enzymatic activity of human GPx1 without affecting the level of GPx1 mRNA, suggesting that the human GPx1 gene is posttranscriptionally regulated by Se [30].

GPx1 is induced by etoposide, topoisomerase II inhibitor, apoptosis inducer, and p53 activator, which positively regulates a promoter element upstream of the GPx1 gene. This transactivation of GPx1 by p53 bonds is the p53 signaling pathway to the antioxidant pathway. In addition, analysis of p53-induced apoptosis in a human colon cancer cell line showed that elevated p53 expression was associated with an elevation of GPx1 [31, 32]. Studies have shown that in the skeletal muscle of severely dyslipidemic transgenic mice and in a pro-oxidative and pro-inflammatory

state, GPx1 is hypermethylated, which decreases GPx1 expression and weakens the endogenous antioxidant defense. The chronic physical exercise allowed increasing the expression of GPx1 in connection with a transient hypomethylation of its gene. The epigenetic regulation of the expression of GPx1 is therefore a function of the methylation of its coding gene [32]. As part of this review, we report knowledge on regulatory factors, the link between the regulation of the mRNA and the expression of GPx activity, the relationship between abnormal expression of GPx1 and the ethology of diseases, and finally the roles of GPx in different diseases especially in chronic diseases.

In addition to Se as the main regulator of GPx1 expression, the factors associating the selenocysteine insertion sequence (SECIS), adenosine [33], c-Abl and Arg tyrosine kinase receptors, and epidermal growth factor influence gene expression of GPx1 and affect the functional coordination between GPx1 and other selenoproteins or antioxidant enzymes in various metabolic circumstances. It will also be interesting to know how these regulators affect the functional coordination between GPx1 and other selenoproteins or antioxidant enzymes in various metabolic circumstances [34]. Se is the main regulator of GPx1 expression. Lower levels of Se cause a decrease in GPx activity [35], increasing the damage caused by free radicals, which contribute to aging and mortality in adults over 65 [36, 37]. In the cells, Se deficiency results in a 60% reduction in GPx1 mRNA and a 93% loss of GPx1 activity. The injection of dietary Se allows rapid recovery of a saturable activity of GPx1. Of these facts, GPx1 was used as a biomarker for assessing body status in Se or Se nutritional status requirement; it is also considered a place of storage of Se for the regulation of the expression of selenoprotein [38, 39]. Se reduces the incidence of aberrant preneoplastic colon cancer and crypt foci in animal models [40]. He has also been involved in the possible chemoprevention of certain cancers [41]. Using a mouse TGFα/c-Myc model of cancer, Novoselov et al. suggested that selenoproteins and Se compounds contributed to the inhibition of liver carcinogenesis. Although GPx1 is unlikely to be the only selenoprotein involved, these results have suggested the involvement of GPx1 in chemotherapy prevention conferred by the food Se [42].

The SECIS selenocysteine (sec) insertion sequence represents mRNA and serves as a platform for the recruitment of Sec -ARNt translation stretching factors that decode the UGA codon for the incorporation of Se into selenoproteins [43]. The SECIS association factors regulate the expression of selenoprotein by displacement of SECIS-binding protein 2 (SBP2), which specifically binds SECIS to dry EF elongation factor with specificity for selenocysteyl-tRNA (Sec-tRNA$^{[Ser]\ Sec}$). TRNA (Ser) SECIS is aminoacylated with serine which is then converted to intracellular Sec [44] from cytoplasm to nucleus in case of exposure to ROS or depending on Se status that modulates Sec-tRNA$^{[Ser]\ Sec}$ with methylation of Sec in position [45], which modifies the secondary and tertiary structure of Sec-tRNA $^{[Ser]\ Sec}$. It is for this reason that the expression of GPx1 and GPx3 is highly reactive to the deficiency in Se. The basic mechanisms of the synthesis and insertion of Sec in proteins, their characterization, the molecular and physiological functions of selenoproteins, and their roles in human health were reviewed by Vyacheslav [46].

Adenosine is a powerful and independent regulator of GPx expression; it attenuates damaging effects of ROS in the cells and improves the stability of the mRNA [47]. The non-receptor c-Abl and Arg tyrosine kinases represent another Se-independent regulator for GPx1 expression. They are activated in the response to ROS and involved in the apoptotic response to oxidative stress. C-Abl and Arg combine, and their interaction is regulated by the intracellular level of oxidants. GPx1 functions as a substrate for c-Abl- and Arg-mediated phosphorylations in Tyr-96, which induces its activity. Loss of GPx1 regulation by c-Abl and Arg

increases the susceptibility to ROS induced by apoptosis [48]. NF-κB is a transcription factor involved in the regulation of cellular responses to a variety of environmental stressors [49]. Recent evidence has suggested that GPx1 and c-Src tyrosine kinases participate in the phosphorylation of IκBα which, in response to hypoxia, leads to the activation of NF-κB elevated in hydrogen peroxide-treated embryonic fibroblasts [50]. GPxs modulate the activation of NF-κB inhibitors by cyclooxygenases and lipooxygenases, the activation which depends on hydroperoxide. It also neutralizes hydroperoxide effects, such as cytokine signal and apoptosis, and also has an important role in the human immunodeficiency virus (HIV) infection. The mitogen-activated protein kinase p38 (MAPK) and c-Jun N-terminal kinase (JNK) transmit essential information in ROS-induced apoptosis [51]. GPx1 (−/−) mouse fibroblasts showed a decrease in protein kinase B (Akt) phosphorylation at Ser-473 during stimulation with hydrogen peroxide, while GPx1-under-expressed MCF-7 cells did not affect the expression and phosphorylation of p38 MAPK [52]. Homocysteine, a risk factor for cardiovascular disease, interferes with the translational reading of SECIS in the expression of GPx1 [53] and, therefore, inhibits the expression of GPx1 promoting the increase of oxygen species reagents that inactivate nitric oxide and cause endothelial dysfunction.

6. Physiopathological functions of GPx and associated diseases

The increase of ROS has been associated with the appearance and progression of aging and related diseases including arthritis, diabetes, dementia, cancer, atherosclerosis, and vascular diseases, which are inflammatory disorders, a consequence of oxidative stress [54, 55]. In reproductive medicine, free radicals cause fragmentation of spermatozoa in humans or the occurrence of ovarian failure in women, thus reducing the mobility of spermatozoa and their ability to fertilize especially in the elderly [56]. Deficiency of GPx results in direct tissue damage and activation of age-related NF-κB inflammatory pathways [57]. The application of over-expressing or knock-out and transgenic GPx1 mouse models overwhelming in vivo evidence for the protective role of GPx1 against oxidative injury and death induced by ROS and RNS. Also, the impairment of GPx1 expression is associated with the etiology of a number of chronic diseases, including cancer, cardiovascular diseases, autoimmune diseases, and diabetes [19, 27].

6.1 Diabetes

Type I diabetes, Type II DM, and gestational diabetes are characterized by hyperglycemia, dyslipidemia, and insulin resistance, which increase oxidative stress and activate the protein kinase C (PKC) as well as the receptor for advanced product glycation (AGE) and low levels of antioxidants and GPx in diabetic patients. GSH is a constituent of blood plasma. It has been found that in normal subjects, GSH plays an important role in controlling the production of free radicals, but in the case of diabetes mellitus, there is abnormal generation and elimination of plasma GSH [58]. In fact, diabetes induces an alteration in the activity of glutathione peroxidase and reductase to maintain a normal GSH level in order to avoid the increase of nitric oxide and the risk of thrombosis. However, the free radicals may play a pathogenic role in the pathophysiology of the response of glucose in β-cells and in the genesis of chronic complications. Mitochondria, the main source of ROS production, contribute to the complications of diabetes [19]. Insulin resistance, associated with mitochondrial dysfunction and increased production of ROS, alters the cardiovascular, renal, and neural functions of insulin and is a risk factor

for microvascular disease. It should also be noted that ROS generates a metabolic syndrome due to changes in energy metabolism, activation of RNS, xanthine oxidase, increased expression of inflammatory mediators, and low levels of GPx and other antioxidant enzymes. Their increase induces endothelial lesions and the oxidation of LDL and redox-sensitive genes, reaching the monocyte-1 chemo attracting protein and the vascular cell adhesion molecules, molecular mechanisms that are involved in the development of the atherosclerosis. Under these conditions, it is likely that ROS and RNS contribute to the destruction of pancreatic β-cells during type diabetes. Increased levels of saturated fatty acids (FFA) and glucose in the blood are considered to be major mediators of signals that bind β-cells to apoptosis and death for T2 DM. The ER-resident GPx7 or GPx8 isoforms protect β-cells of insulin-secreting INS against lipotoxicity by enhancing the antioxidant capacity of ER without compromising insulin production and oxidative protein folding mechanisms [19, 59]. Presumably, oxidative stress is involved in the pathogenesis and complications associated with all three types of DM, and GPx1 plays a critical role in the regulation of oxidative stress [60].

6.2 GPx and obesity

Obesity promotes the storage of triglycerides in adipose tissue. Firstly, adipose tissue produces interleukin-6 (IL-6) that stimulates the absorption of dopamine creating a feeling of satiety, which has a direct effect on weight control. Tumor necrosis factor-α (NF-α) activates the NF-κB, which promotes the adhesion to the surface of endothelial and vascular smooth muscle cells of molecules causing an inflammatory state of adipose tissue, dysfunction of the endothelium, and finally, atherogenesis [61]. With the production of adipokines and decreased activity of GPx and antioxidant capacity, the endothelium becomes deficient in nitric oxide (NO), a vasodilator, and thus promotes atherosclerotic diseases. Secondly, the low level of serum GPx in obese patients and the low-serum Se concentrations, associated with the onset of signs of metabolic syndrome, may be related to the presence of a predisposing state to atherosclerosis manifested by increased consumption of antioxidants by radical interaction [19, 62].

6.3 Cardiovascular diseases

Cardiovascular diseases (CVDs) are also characterized by insulin resistance, a pro-oxidative and pro-inflammatory state, as well as a dysregulation of the expression of various factors responsible for the homeostasis of redox and inflammatory environment [62]. This is a result of oxidative stress, because plasma total GSH content is low in patients with cardiovascular disease.

High levels of homocysteine, with the slowing of GPx1 blood vessel activity, promote a higher concentration of intracellular peroxides that enhances oxidative stress and causes damage to endothelial cells in the pathogenesis of atherogenesis. Homocysteine probably interrupts UGA reading so that GPx1 expression is down-regulated [53].

Studies on the evaluation of the association between GPx1 and atherosclerosis variants in Japanese patients with type 2 diabetes, with four polymorphisms, reported that functional variants of the GPx1 gene are associated with increased mean intima-media (IMT) thickness of carotid arteries and cardiovascular risk and peripheral vascular disease in type 2 diabetics [63]. These results suggest that GPx1 protects against atherogenesis in blood vessels and virus-induced myocarditis by reducing ROS levels. Disturbances in GSH metabolism may explain an increase in blood pressure related to age [64]. Selenoprotein polymorphisms are a risk factor

for the development of systolic heart failure (HF) and peripheral atherosclerosis but prevent the development of abdominal aortic aneurysm (AAA). Excess weight can reduce the effectiveness of antioxidant stores in AAAs.

6.4 Neurodegenerative diseases

Neurodegenerative disorders are characterized by ROS activation of microglia that act as macrophages in the brain. The latter generate, in these glial cells, reactive nitrogenous species including inducible nitric oxide synthase (iNOS) and NADPH oxydase (NOX2); the activation of which can lead to a respiratory explosion of superoxide flooding the mitochondria and contributing more to neurodegeneration [65, 66]. GPx1 has a 10-fold higher activity in glial cells than in any other region of the brain. The in vivo administration of GPx1 to dopaminergic neurons decreases the toxicity of 6-hydroxydopamine in Parkinson's disease. By employing a lentivirus-based system to provide GPx1 to neuroblastoma cells in vitro, Ridet et al. witnessed a doubled GPx1 expression that protected the neuroblastoma cells against 6-hydroxy-dopamine-induced neurotoxicity. Other studies have shown that selenocysteine in GPx significantly delays human amyloid-Î²-induced paralysis, which is positively correlated with the incidence of Alzheimer's disease and recovers β-amyloid-induced toxicity and reduces the cellular level of EOS, by positively affecting life span and age-related pathophysiological alterations [67, 68]. Kainic acid is a neurodegenerative drug that induces PN formation in the brain. GPx1 knock-out mice are more resistant to kainic acid-induced mortality and seizures than wild-type mice. It is likely that the roles of GPx1 in neurodegenerative diseases are specific as appropriate [66, 69].

6.5 Autoimmune diseases

Generally, people infected with HIV have low levels of Se and GPx1 activity. Analysis of 75S labeling of Jurkat human T cells revealed four 75S proteins including GPx1, GPx4, TR1, and Sep15. Taking into account the function of these selenoproteins, we can think that Se influences the pathogenesis of acquired immune deficiency syndrome (AIDS) via redox regulation. The possible mechanism is that GPx1 protects HIV-infected individuals from the loss of helper T cells by preventing oxidative-induced apoptosis. HIV replication depends on the activation of NF-κB [70].

6.6 Cancers

GPx1 has an impact on signal transmission related to cell death, protein kinase phosphorylation, and activation of NF-κB via an oxidant; the anomaly of the expression of its activity would be at the base of several diseases notably cancer and chronic diseases [71]. It is known that the single nucleotide polymorphism (SNP) that alters the sequences of a particular amino acid of 201 amino acids, GPx1, is associated with certain diseases including lung, bladder, and breast cancers [72]. The cells of cancer patients often have defects in the regulation of proliferation, apoptosis, and senescence. DNA analysis of breast and colorectal cancers revealed that 36–42% of GPX1 genes lose heterozygosity during tumor formation [73]. Azoxymethane treatment of Sec-tRNA$^{[Ser]\ Sec}$ i6A transgenic mice with reduced expression of GPx1 resulted in aberrant crypts in their colon compared to wild-type mice. It appears that the SNP of the GPx1 Pro198Leu would be influenced by modulation of ROS levels and the regulation of carcinogenesis. Additional identification of GPx tagSNPs and systematic evaluation of their associations with cancer will help to expand the ability to diagnose and treat GPx1-related cancers. The GPx1

allelic loss of pathologically normal tissue adjacent to tumors would be an early event in cancer progression. Chu et al. suggested a possible protective role of GPx2 against colon cancer. GPx3 has an antioxidant protective role for proximal kidney epithelial cells in patients with kidney disease [74].

6.7 Chronic hepatopathy

Patients with chronic liver diseases have shown that disturbances of antioxidant parameters in their blood may be the cause of peroxidative damage to hepatocytes. Elevated serum carbonyl protein levels, glutathione, GPx, and glutathione reductase activities significantly decreased following increased oxidative stress in patients with pulmonary and extra pulmonary tuberculosis [75].

7. Heath benefits of traditional foods as source of precursors of glutathione and glutathione peroxidase

Hepatic GSH level is closely related to nutritional conditions, especially the cysteine content of the diet. One of the major determinants of the rate of GSH synthesis is the availability of cysteine. Cysteine is derived normally from the diet, by protein breakdown and in the liver from methionine via transulfuration [3, 11]. Se, incorporated as selenocysteine in GPx, acts in antioxidant defense and thyroid hormone formation as a protective agent against cancer, muscle diseases, coronary heart disease, and HIV [76]. In the immune system, Se stimulates the formation and activity of antibodies to helper T cells, cytotoxic T lymphocytes, and natural killer (NK) cells. The Se level drops during oxidative stress. High Se intake may be associated with a reduced risk of cancer. The recommended daily intake of Se ranges from 60 μg/day for women to 70 μg/day for men. The requirements are estimated at 100 μg/kg dry matter and 200 μg/kg for pregnant or lactating women. Generally, the dietary intake of Se ranges from 7 to 499 μg/day, with average values ranging from 40 to 134 μg/day depending on the country [70, 76, 77]. The reasons for the variability of consumption are related in particular to factors that determine the availability of selenium in the food chain, including soil pH, organic matter content, as well as the presence of ions that can form a complex with Se. Se deficiency can cause several diseases and even cause reproductive disorders in humans and animals [77]. The health benefits of Se have increased considerably since the discovery of diseases associated with polymorphisms in selenoprotein genes. Low Se status has been associated with impaired immune function with cognitive decline and increased risk of death, while Se supplementation with deficient individuals reduces the risk of prostate cancer, lung cancer, colorectal cancer, and bladder [76, 77]. Daily supplementation with Se at a supra-nutritional dose (200 μg) results in significant reductions in mortality associated with total carcinomas of lung, prostate, and colon cancers without knowing how Se reduces the risk of cancer and if the GPx1 is involved in the action [42]. Several cross-sectional studies have demonstrated the correlation between high Se status and plasma cholesterol. Indeed, Se supplementation increases the ratio of total cholesterol to significant HDL cholesterol in the plasma, suggesting a potentially beneficial effect on cardiovascular risk supplementation [77]. Prospective studies have provided some evidence of beneficial effects of Se on the risk of lung, bladder, colorectal, liver, esophagus, cardio-gastric, thyroid, and prostate cancers, but these results are sometimes disparate [77]. High Se status was associated with decreased risk of hyperglycemia and type 2 diabetes, while other studies also reported that high serum Se concentration favored increased prevalence of diabetes male participants followed over

9 years. Discrepant Se status in cancer and diabetes is thought to be associated with systemic inflammatory status and insulin resistance [77, 78]. The effects of Se on human health are multiple and complex, requiring additional research to maximize the benefits and reduce the risks of this powerful trace element. The controversial results of studies on Se supplementation based on the plasma concentrations of the individuals studied require that selenoprotein polymorphisms may be taken into account. At this stage, it should be remembered that supplemental Se intake from fortification of foods or supplements would be beneficial to people with low status, while those with adequate or high status could be negatively affected and no Se supplements would be required [77]. Tissue concentration of GSH is controlled by the availability of substrate supplied by the diet, the nutritional effects on GSH synthetic enzymes, and nutritional influences on the uptake and efflux mechanisms for GSH. Sulfur amino acid and Se contents of the diet regulate tissue GSH concentration [79]. Forms of Se in foods are essentially selenomethionine from plant sources and selenocysteine from animal sources [47].

Traditional and ethnic foods have already existed for a long time and have cultural and traditional values. Ethnic foods are defined as those edibles that are eaten and prepared by groups of people who share a common religion, language, culture, or heritage. Of course, many ethnic foods are prepared using traditional foods and vice versa [80]. Traditional foods consist of vegetables, fruits, nuts, seeds, yams, mushrooms, herbal teas, meat, fish, insects, etc. The flora of the Democratic Republic of Congo is rich in plant resources with high nutritional values and powerful medicinal properties [81, 82]. Some of traditional foods could be considered as a source of precursors of GSH and GPx by their amino acid and Se contents. Mbemba et al. studied traditional foods from Bandundu areas of DRC and listed some edible vegetables, mushrooms, nuts, and roots that showed high nutritional value [83]. Amino acid content of certain traditional foods was interesting about the presence of considerable quantity of cysteine and methionine considered such as precursor amino acids of glutathione. *Salacia pynaerti, Gouania longipetala*, *Dewevrea bilabiata*, *Phytolacca dodecandra* and *Solanum macrocarpon* were the traditional vegetables identified which are rich in methionine and *Alternanthera sessilis*, *Gnetum africanum*, *Justicia* sp., *Olax subscorpioides*, and *Salacia pynaerti* and rich in cysteine. Some mushrooms were equally identified which are rich in cysteine: *Auricularia delicate*, *Cookeina sulcipes*, *Gymnopilus* sp., *Lentinus squarrosulus*, *Pilocratera engleriana*, *Pleutorus tuber-regium*, *Shizophyllum commune*, and *Oudemansiella canarii* [83]. Regarding Se, the literature indicates that the animal-derived foods tend to be a better dietary of these micronutrients. Seafoods and organ meats are the richest food sources of selenium [84]. Preliminary studies on mineral composition of Congolese traditional foods showed that edible insects are the excellent sources of Se (unpublished data). Edible insects are known to be excellent sources of mineral micronutrients [85, 86]. Other sources of Se include cereals, grains, and dairy products [84]. Selenium concentrations in plant-based foods vary widely by geographic location. For this, Brazil nuts (*Bertholletia excelsa*, H.B.K.) have the highest selenium concentration of all edible nuts and are considered one of the most selenium concentrated food sources [87, 88].

8. Conclusion

The glutathione system plays important biological roles, including the defense of cellular tissues against reactive oxygen and nitrogen species, as well as maintaining the redox status and detoxification of cells. GPx, the main enzyme in the antioxidant line, is characterized by eight isomorphs whose activities are localized in the various subcellular organelles. During aging, the GSH system in general and

the GPx family in particular undergo modifications that promote the production of oxidative stress resulting in disturbances in metabolic regulation, damage of cellular constituents accompanied by cardiovascular follow-up, neurodegeneration, and cancers. In this evolution, GPx may be a parameter contributing to the identification of subclinical asymptomatic cardiometabolic disorders and their repair, since its decrease favors atherosclerotic diseases. GPx deficiency results in direct tissue damage and activation of age-related NF-κB inflammatory pathways, which is associated with aging. Data accumulates to bind alteration or abnormality of GPx1 expression toward the etiology of cancer, cardiovascular diseases, neurodegeneration, autoimmune disease, and diabetes. The involvement of the GSH system and GPxs in various diseases, especially those of the elderly, is obvious. However, at this stage, there is a need for a thorough study to better elucidate the mechanism of GPx1 in the pathogenesis and potential applications of GPx1 manipulation in the treatment of these disorders.

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Conflict of interest

The authors declare that they have no conflict of interest.

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