Chapter

Glutathione Peroxidase in Health and Diseases

Eren Sarıkaya and Selami Doğan

Abstract

The aim of this study is to give information to readers about the importance of glutathione peroxidase. The physiopathology of most diseases is not fully elucidated currently; however, in many epidemiological studies, there are limited studies indicating the relationship between low levels of glutathione peroxidase status and the rise of cancer risk in many types of cancer. Anytime, situations in case of the distortion due to imbalance between enzymatic and nonenzymatic antioxidants and oxidants which lost one of paired electrons in the atomic level mean reactive oxygen species (ROS) withal reactive nitrogen species (RNS) in favor of oxidants that are related to oxidative stress. The possible mechanisms of glutathione peroxidase have been reviewed using the major findings of more than 1000 papers related to the ROS, glutathione peroxidase, and oxidative stress. Oxidative stress plays an important role in the occurrence and development of most diseases in both animal and human studies. Moreover, antioxidants have protective effects against nearly 50 disease pathogenesis. Oxidative stress, which occurs as an outcome of lipid peroxidation, concurrently may have a key importance in the phase of carcinogenesis occurring with a multistage course devoted to environmental toxicity and in cancer pathogenesis.

Keywords: glutathione peroxidase, oxidative stress, antioxidant, free radical

1. Introduction

1.1 Reactive oxygen species

Reactive oxygen species (ROS), superoxide radicals (O_2-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH-), and singlet oxygen are formed in normal oxygen metabolism. Free radicals can initiate free radical sequence reactions that shape various free radicals [1]. Reactive oxygen species have been associated with many disease categories, including cancer. In addition, ROSs have been reported to increase tumor cell migration and increase the risk of metastasis and metastasis. It is known that the harmful effects of ROS are controlled by various cellular defense systems consisting of enzymatic components (catalase, glutathione peroxidase and superoxide dismutase, etc.). Epidemiological literature studies have found a relationship between low levels of antioxidants and an increased risk of cancer [2].

Although many definitions are made for free radicals, in the general definition, free radical is a chemical product that is in molecular or atomic orbit and is generally highly reactive and contains unpaired electrons. The electrons in atoms move in spaces called orbit. Each orbit has up to two electrons moving in opposite

directions. Free radicals can be positively charged, negatively charged, or neutral. In biological systems, they occur mostly by electron transfer. Although free radical reactions are necessary for the defense mechanism of cells such as neutrophils and macrophages from immune system cells, overproduction of free radicals results in tissue damage and cell death [3].

Electrons are orbital in atoms and are present in pairs in the spatial region. Bonds are formed as a result of the interaction between atoms and molecular structure is formed due to these bonds. Free oxygen radicals, atomic or molecular structures in the single electron, are the name given to uncommon parts. These molecules that easily exchange electrons with other molecules are also called free oxygen radicals (FOR) or reactive oxygen radicals (ROR) [4].

As a result of oxidation which is a natural process during the process of metabolism, the formation of free radicals, which cause various damages in the organism and initiator of some vital chronic diseases such as cancer and heart diseases, increased the interest in antioxidant compounds that combat them, and studies on this subject mostly focused on the determination of antioxidant activities. This interest is directed mainly to reactive oxygen species (ROS) damage in the aging process and in the etiopathogenesis of many diseases. Aging and chronic diseases in humans occur as a result of some complex biological processes. To understand these complex processes, various hypotheses have been proposed and tested experimentally. The theories about aging have been explained in recent years by some advances in molecular genetics and experimental techniques. Increasing damage caused by ROS in the cell mainly involves telomere erosion, genome instability, DNA mutations, and changes in gene profiles in senescent cells [5, 6].

The formation of free radicals occurs during the use of oxygen in the organism. Unmapped electron-containing atoms or molecules initiate a sequence of reactions in which cells are damaged. The formation of free radicals in the body begins and increases with catabolic reactions as well as factors such as fatty diets, unhealthy nutrition, smoking, drug treatments, alcohol consumption, radiation, pesticides, and environmental pollution. Free radicals weaken the immune system, leading to various diseases and premature aging. In this respect, antioxidants are important in cell-protective treatment and protection from degenerative diseases. Research has shown that antioxidants neutralize free radicals and prevent damage to cells. In the context of antioxidant compounds, microalgae species have an important place besides terrestrial foods. When some microalgae species are grown under various stress conditions (nitrogen deficiency, high light intensity, high salinity, etc.), it is possible to accumulate in the cell pigment substances with strong antioxidant properties such as beta-carotene, astaxanthin, zeaxanthin, and lutein. Thus, in the context of biotechnology, microalgalas can be manipulated with various parameters in culture conditions to create various physiological stresses on cells. Thus, it can be ensured that the cultured cells produce more of the desired product [6].

The form of lipid peroxidation with the result of molecular oxygen conversion to reactive oxygen species (ROS) with various environmental factors, particularly cigarette smoke, alcohol, UV rays, and other oxidants, leads to oxidative stress. As a result of this, a multistage carcinogenesis process is favored by ROS in the body.

1.2 Oxidative stress

Oxidative stress is an important component in binding environmental toxicity to a multistage carcinogenic process. In addition, oxidative stress is characterized by the cumulative effect of more than one activity, such as a multistage process (three stages in a single cell; onset, elevation, and progression), such as cancer development. Reactive oxygen species (ROS) are produced in response to endogenous and

exogenous stimulation. ROS can affect all these stages of carcinogenesis [7]. For this reason, the term oxidative stress is used to describe the imbalance between cellular levels of oxidants and antioxidants [8].

Cell damage caused by free radicals is believed to play an important role in the progression of aging process and aging-related degenerative diseases (especially atherosclerosis, cataract, diabetes, neurodegenerative diseases, immunosystem disorders, and cancer formation). Oxidative stress has been associated with almost 50 disease pathogenesis [9].

Catalase (CAT), peroxidase (POD), glutathione reductase (GR), and superoxide dismutase (SOD) are enzymes that have antioxidant effects in biological and biochemical systems. The antioxidant defense system protects the cell against oxidative damage of free radicals or other reactive molecules. Therefore, antioxidant enzymes such as CAT, POD, GSSG-Rx, and SOD are of great importance in this defense system. The harmful effects of free radicals are controlled by antioxidant defense systems in cells [10].

1.3 Glutathione peroxidase

Antioxidants are substances that prevent, reduce, or delay the oxidation of materials that may be exposed to oxidation such as proteins, lipids, carbohydrates, and DNA in living cells, and this is called antioxidant defense. Antioxidants are substances that prevent or delay the damage of free oxygen radicals on target tissues. Antioxidants are classified into two categories, enzymatic and nonenzymatic. Enzymatic antioxidants are superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), and nonenzymatic antioxidants are vitamin E, vitamin C, vitamin A, selenium (Se), transferrin, and lactoferrin. Antioxidants are often intracellular and sometimes extracellular [4]. Reduction in circulating antioxidant may be due to sequestration by tumor cells as well as sweeping lipid peroxides by tumor cells [2].

The negative aspect of ROS production is that ROS constitutes various types of cancer that can be resistant to exogenous growth in itself [11, 12]. For example, HL-60, multidrug-resistant, is resistant to growth of ROS due to the endogenous height of antioxidants which are detoxifying and which are ROS scavenger such as leukemia and CAT [11, 12]. Several oncogene-induced cancer cells enhance the antioxidant activity by activating nuclear factor erythroid 2-related factor 2 (NRF2) and maintaining the effect [12–16]. ROS levels allow the activation of pro-tumorigenic signaling pathways without induced cell death [12, 17]. Also, in the event of an increase in GSH levels, which play an active role in protecting cells from cell death, also appears to play an active role in protection from ROS-inducing therapy [12, 17]. The antioxidant defense system is a large network of molecules which eliminate free radicals and production of ROS [18, 19]. Endogenous antioxidant defense systems are available to compensate the ROS welded damage [7, 20]. These systems function their form by maintaining intracellular ROS activity and redox balance with chelating [7, 20].

Glutathione peroxidase catalyzed by the reaction catalyzed by the reduced form of glutathione (GSH) by reacting with hydrogen peroxide or lipid peroxides while playing a role in the detoxification of these molecules by creating a glutathione bridge with another glutathione molecule (GSSG) form [21]. H_2O_2 is detoxified by catalase and glutathione peroxidase [22].

The glutathione redox cycle plays a key role in the reduction of intracellular hydroperoxides. GPx belongs to the class of selenocysteine compound because it binds four atoms of selenium and provides the catalytic activity of glutathione peroxidase. It needs glutathione as a co-substrate [23].

Glutathione is a tripeptide which is composed of cysteine, glutamic acid, and glycine. GSH has two structural characteristic: γ-glutamyl linkage and sulfhydryl (-SH) group. GSH is known for its multiple physiological functions as an antioxidant against ROS and free radicals in detoxification of xenobiotic compounds [24–28]. When the cell fails to protect GSH content no longer, certain cell death may be followed [28, 29]. GSH, which is the most important antioxidant molecule of intracellular environment, has many physiological functions such as detoxification of xenobiotics, transport of amino acids, keeping sulfhydryl groups in proteins in the reduced state, and acting as a coenzyme in some enzymatic reactions other than involving antioxidant defense system [21, 30–32]. Glutathione, in reduced form (GSH), turns itself into oxidized glutathione (GSSG) form with creating disulfide bridge with another glutathione molecule while playing role in detoxification of these molecules by reacting with hydrogen peroxides or lipid peroxides, with the reaction catalyzed by the GPx enzyme. In order for the maintenance of free radical detoxification in cell, GSSG needs to be converted back to the reduced form. GSSG is converted to reduced glutathione form with GR enzyme by a reaction in which NADPH is used [21, 30, 33].

Glutathione peroxidase (GSH-Px; E.C. 1.11.1.9) is a cytosolic enzyme responsible for the reduction of hydroperoxides. In erythrocytes, GSH-Px is the most effective antioxidant against oxidant stress and has some important functions in phagocytic cells [34]:

$$H_2O_2 + 2GSH \xrightarrow{GP_x} 2H_2O + GSSG \quad (1)$$

$$ROOH + 2GSH \xrightarrow{GP_x} ROH + GSSG + H_2O \quad (2)$$

GPx is an enzyme responsible for the removal of hydroperoxides formed in cells. Since its subunits contain a Se atom, it is thought to be a selenoenzyme that protects cells against various damages. The presence of this enzyme was first found by Mills in 1957 in mammalian erythrocytes. It is the most effective enzyme in endothelial cells and especially in the lung. About 60–75% of enzyme activity is found in the eukaryotic cell cytoplasm and 25–40% is found in mitochondria. The most common enzyme activity is clear in erythrocytes and liver. GPx is the most important enzyme that protects lipids from peroxidation at intracellular distance. For this reason, this enzyme, especially in the cytosolic compartment of the cell, maintains the structure and function of the cell. The phospholipid hydroperoxide glutathione peroxidase (PLGSH-Px), which reduces membrane phospholipid hydroperoxides to alcohol, also contains the Se atom and is monomeric. It is also a cytosolic enzyme. PLGSH-Px provides protection against peroxidation of the membrane in cases where vitamin E, a membrane-bound antioxidant, is insufficient [35–37].

Glutathione peroxidase catalyzes detoxification of H_2O_2 and lipid peroxides by reduced glutathione. Thus, it protects membrane lipids and hemoglobin from oxidation of peroxides. GSH-Px is also involved in the detoxification of xenobiotics. It is the antioxidant enzyme system that provides the most vital defense against the peroxidative damage of biological membranes in mammalian cells. From these enzymes, glutathione peroxidase, catalase, and superoxide dismutase together form a common system aimed at protecting the cell from peroxidant molecules [38].

In a study, when the serum GPx ($p < 0.001$) levels were compared, the coronary artery ectasia (CAE) patient group was significantly lower compared to the control group [39]. In a literature study, there was no significant difference

($p > 0.05$) between GPx activities in both groups of patients with malignant tumors in the head and neck region [40]. An increase in the level of free oxygen radicals may cause mutagenicity, cytotoxicity, and changes in gene expression, leading to the development of malignant tumors, and this mutagenicity may contribute to the transformation of benign development into malignant [41]. In conclusion, high GPx activity in the blood can be considered as a factor reducing cancer risk. Comparison of oxidative parameters in Parkinson's disease groups and control groups showed that GSH-Px was significantly higher in the patient group [42]. Decreased levels of GPx activities were observed in progressive hypothyroidism in the postnatal period [43]. Reduced activities of GPx, one of the most important antioxidant defense systems in the body, either reported increased or decreased intracellularly in different tissues antioxidant enzymes [44, 45]. Increased GPx activity experimental colitis was reported in the parotid glands of mice; decreased enzyme activity was found in submandibular glands [46]. The results of GPx activities in plasma in both Crohn's disease (CD) groups as well as controls did not reveal any statistically significant differences [47]. Results of GPx and SOD activities measured in CD patients have been demonstrated to be diverse when analyzing plasma samples [48]. Previous studies focusing on the role of GPX1 single nucleotide polymorphisms (SNPs) included GPX1 SNP rs1050450, which often caused the C to T mutation [49]. GPX1 SNP was found to affect the risk of lung cancer and bladder cancer of r1010450 [50]. The risk of vascular calcification and atherosclerosis is also affected by the Leu allele of GPX1 SNPs [51, 52]. However, available evidence did not acknowledge that GPX1 SNP rs1050450 plays an important role in chronic kidney disease (CKD) progression or renal allograft dysfunction [53, 54]. Significant influences of GPX1 Pro197Leu SNPs on the risk of ESRD in Han Chinese population have not been detected [55]. It is suggested that individuals with low GPx activity are prone to intact antioxidant protection leading to oxidative damage to membrane fatty acid and functional proteins and consequently to neurotoxic damage [56]. Forgione and colleagues previously hypothesized that GPX1 deficiency caused an increase in vascular oxidative stress with endothelial dysfunction directly involved [57]. Inhibition of ferroptosis by GPx4 provides protective mechanisms against neurodegeneration. In addition, we suggest that selenium deficiency increases susceptibility to ferroptotic processes and other programmed cell death pathways due to a decrease in GPx activity [58]. GPX1 affects the effects of the major factors involved in both macro and micronutrient metabolism by regulating gene expression, protein function, and enzyme activities [59–61]. Some studies [62, 63] underline the importance of maintaining an appropriate expression and activity of this selenoperoxidase to control redox balance and glucose and lipid metabolism. GPX1 polymorphism with risk of diabetes and obesity in different populations [64–68]. Oxidative stress-induced intestinal injury has been reduced by the addition of SOD, glutathione peroxidase, and N-acetylcysteine, which reduces intestinal tissue tumor necrosis factor-a concentrations with anti-inflammatory and antioxidant properties [69, 70]. A significant increase in GPx activity in the inflamed mucosa was found in either active or remission stage in ulcerative colitis (UC) patients. Other studies confirmed significantly higher plasma GPx levels in the UC and CD groups than in the control group [71]. Children with inflammatory bowel diseases (IBDs) had increased GPx activity and GSH content compared with control children [72]. Selenium supplementation in patients with autoimmune thyroiditis is associated with decreased antithyroperoxidase antibody levels, improved thyroid ultrasound characteristics, and improved quality of life [73]. ROS has been incorporated into cellular signaling, which may activate mitogenic cellular

pathways and proinflammatory processes leading to disruption of renal fibrosis and GPx, which support progressive impairment of renal function [74]. Total glutathione, decreased/oxidized glutathione, and ubiquinone were significantly decreased in patients with susceptibility-related diseases, while DNA fragmentation was significantly increased in patients. However, these differences were not associated with the GPx1 genetic background [75]. It has been reported a linear relationship between estrogen and GPx in erythrocytes of postmenopausal women [76]. Serviddio et al. [77] showed a positive correlation between the activity of GPx and luteinizing hormone (LH) concentrations in healthy women. They also observed a significant positive correlation between estradiol and GPx. Significant increase in GPx activity was found in abdominal obesity in postmenopausal women [78]. Glutathione peroxidase (GPx) has important functions in the reduction of peroxides that are reported to inactivate vasodilating NO and the decomposition of S-nitrosoglutathione (GSNO), which plays an important role in vascular homeostasis [79]. Seleno-glutathione peroxidase mimic ebselen (PZ51)-protected endothelial and vascular system of spontaneous hypertensive rats (SHRsp) prone to stroke during pregnancy chronic hypertension [80]. It showed a significant relationship between low GPx level and vitiligo. Asian vitiligo patients showed lower levels of GPx than the controls, Caucasian populations, and healthy controls [81]. GPx polymorphism may contribute to the reduced GPx activity and the prevalence of vitiligo in Gujarat population [82]. In experimental models, GPx1 deficiency led to endothelial dysfunction, impaired angiogenesis, and increased infarction size and vascular permeability following ischemia/reperfusion injury [57, 83]. Furthermore, recent data [84] and others [85] showed that GPx1 deficiency provides atherosclerosis sensitivity in diabetic and hyperlipidemic environments, respectively. A recent study by Lubos et al. [86] showed that the reduction of GPx-1 activity in silenced human endothelial cells for GPx1 expression accelerated oxidative stress and increased nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and c-Jun-N-terminal kinase (JNK) activation. GPx activity is associated with an increased risk of major adverse cardiovascular events at 1 year following an acute coronary syndrome. Serum GSHPx and arylesterase activity levels increased significantly after laryngectomy [87]. In a study [88], a decrease in GSH-Px activity was observed in patients with colon cancer. In another study [89], there was no difference in GPX or CAT activities in hypoxic and non-hypoxic patients. In one OSAS study [90], patients had lower GPX levels than healthy controls.

It is known that ROS have detrimental effects, which are controlled by various cellular defense system, consisting of enzymatic (catalase, glutathione peroxidase and superoxide dismutase, etc.) compounds [2, 91]. H_2O_2 is detoxified by catalase and glutathione peroxidase [22, 92]. Selenium is a trace element which is located in selenoenzymes, comprising thioredoxin reductase (TrxR) that is an enzyme which is related to the reduction of proteins and disulfides and glutathione peroxidase (GPx) for the detoxification of H_2O_2 [93–95].

Many studies show that the effect of organic and inorganic Se supplements on physiological functions and human health has been researched, but the most appropriate usage form of Se addition to dietary has not been specified [95–97].

2. Conclusion

The form of lipid peroxidation with the result of molecular oxygen conversion to ROS with various environmental factors particularly smoking cigarette, alcohol, UV rays, and other oxidants leads to oxidative stress. As a result of this, a

multistage carcinogenesis process starts, and cells with diseases may occur by the degradation of the balance between both lipophilic and enzymatic antioxidants that form the antioxidant capacity of skin and ROS. Glutathione peroxidase activity is a primary antioxidant defense system that plays a key and fundamental role in the overall defense mechanisms and strategies in biological systems. There are at least eight GPx enzymes in humans, GPx1–GPx8. The GPx 1–8 genes are mapped to chromosomes 3, 14, 5, 19, 6, 6, 1, and 5, respectively. Glutathione peroxidases have also been implicated in the development and prevention of many common and complex diseases, including cancer and cardiovascular disease. Optimization of the nutritional status of selenium may result in higher GPx4 activity and thus delay or even prevent neuronal loss. Increasing selenium levels may reduce the risk of developing neurodegenerative disease in populations with low selenium exposure. The brain is vulnerable to increased ROS due to its high metabolic rate and relatively low antioxidant defense ability. Se deficiency has been associated with increased oxidative stress and neurodegenerative diseases. The role of Se proteins in the neurodegeneration of oxidative stress and ferropose can provide a unique insight into the mechanisms of cellular death in neurodegeneration. Optimization of nutritional status of Se may result in higher GPx activity. In a population with low selenium uptake, the toxic effects of mercury may be more pronounced because the metal forms an insoluble complex with selenium, thereby reducing bioavailability in various antioxidant systems (e.g., glutathione peroxidase). Recent developments in the new field of selenium biology and GPX1 have been shown to attempt to suggest the signaling and molecular mechanisms involved in glucose and lipid metabolism-related diseases. It mimics the requirements and opportunities of mimicking applications of various antioxidant enzymes in the treatment of insulin-dependent diseases. GPX enzyme is the main regulator of insulin physiology and energy metabolism. Hyperbaric oxygen, medical ozone, and enteral glutamine, alone or in combination with arginine, have shown positive effects on necrotizing enterocolitis (NEC) by modulating antioxidant defense mechanisms. Maintaining the physiological concentration of selenium is a prerequisite for preventing thyroid disease and maintaining general health. Supplementation with organic form is more effective and appears to be beneficial in immunological mechanisms in patients with autoimmune thyroiditis. Selenium supplementation has proven clinically beneficial in patients with mild to moderate Graves' orbitopathy. Decreased GPx activity causes hepatocellular degeneration and premature death of mice. Since many harmful conditions are known to directly disrupt the GPx, inhibition of ferroptosis may represent a suitable therapeutic approach to improve hepatocyte cell death. GPx is particularly vulnerable to the oxidative stress associated with hypertension. Low GPx levels may contribute to the pathogenesis of vitiligo in the Asian population as opposed to the White population. GPx1 plays a major role in vascular homeostasis. Specifically upregulating the activity of this isoform or designing functionally active mimetics may provide cardiovascular protection. GPx1 deficiency causes endothelial cell dysfunction and activation supporting atherogenesis. It can be concluded that serum GPx activity is low in patients compared to healthy control groups, and the balance between antioxidant and prooxidants is deteriorated in favor of prooxidants, and the deficiency of antioxidant enzymes in diseases may be a symptom in the explanation of cancer pathophysiology. The result could not be fully confirmed as there are some limitations. Limited numbers, small sample sizes, and methodological diversity may weaken statistical power. Higher quality studies with larger samples should be performed to confirm the results. Further studies are needed on this subject. We believe that this study will shed light on future studies.

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