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Glutathione system in animal model of solid tumors: From regulation to therapeutic target

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ABSTRACT

Glutathione (GSH) is one of the most important defenses against oxidative stress through the fine-tuned regulation of redox homeostasis. Glutathione is also involved in many metabolic processes and is important for the regulation of cell survival, proliferation, and death. Furthermore, GSH and the enzymes that are involved in its biosynthesis, catabolism, and detoxification (e.g., disulfide-oxidized glutathione, glutathione *S*-transferase, glutathione peroxidase, glutathione reductase, and γ-glutamyltranspetidase) play an important role in several diseases, including cancer. In cancer cells, these enzymes protect the tumor microenvironment against oxidative stress and cell death and are important for tumor growth and development. Thus, the GSH system is an important tool for investigating new pharmacological approaches for cancer treatment. Several preclinical models of solid tumors are available for this purpose. This review summarizes and discusses the regulation and dysregulation of GSH and its related enzymes in different models of solid tumors, and potential treatments that target the GSH system.

1. Introduction

Glutathione (GSH) is involved in scavenging reactive oxygen species (ROS) to maintain antioxidant defenses and regulate redox-dependent cell signaling (Masella et al., 2005). GSH is also involved in several metabolic processes, including the synthesis of proteins and DNA, enzyme activity, metabolism, gene expression, signal transduction, and the intensification of cytoplasmic and transmembrane transport (Meister and Anderson, 1983; Zmorzyński et al., 2015). The detoxification of xenobiotics and endogenous compounds is another relevant function of GSH (Ballatori et al., 2009).

Considering the complex physiological function of the GSH system, its disequilibrium is involved in several pathological pathways and thus plays an important role in cancer and regulation of the progression through the cell cycle and cell survival, growth, and death (Lu, 2014). The levels of GSH and enzymes that are related to GSH biosynthesis are high in cancer cells, thus leading cancer cells to become resistant to cell death through oxidative stress mechanisms. Glutathione can also regulate apoptosis by binding to Bcl-2 and regulating tumor necrosis factor α (TNF-α) levels (Matsumaru et al., 2003; Zimmermann et al., 2007). The present review discusses the influence of the GSH system in several models of solid tumors in vivo to clarify its pathological and pharmacological relevance to cancer.

2. Glutathione synthesis and hydrolysis

Glutathione (γ-L-glutamyl-L-cysteinylglycine) is a tripeptide that is synthesized in the cytosol from glutamic acid, cysteine, and glycine in two adenosine triphosphate-dependent steps. The first reaction, which is catalyzed by the enzyme γ-glutamylcysteine ligase (GCL), produces γ-glutamyl cysteine (γ-EC). In the second step, glycine is added and catalyzed by glutathione synthetase (GSH_2) to form GSH (Kaplowitz et al., 1985). A schematic representation of glutathione biosynthesis and its main roles are presented in Fig. 1.

Intracellular levels of GSH (0.5–10 mM) are controlled by γ-glutamyltranspetidase (GGT), which is only present on the external surface

Abbreviations: 20-MC, 20-Methylcholanthrene; 3-MC, 3-Methylcholanthrene; ALDH, aldehyde dehydrogenase A1; AsA, ascorbate; APx, ascosbate peroxidase; As_2O_3, arsenic trioxide; BSO, L-buthionine-(S,R)-sulfoximine; CNS, Central Nervous System; DMBA, 7,12-Dimethylbenz[a]anthracene; DSF, disulfiram; FDA, Food and Drug Administration; GCL, γ-glutamylcysteine ligase; GGT, γ-glutamyltranspetidase; GPx, glutathione peroxidase; GR, glutathione reductase; GRx, oxidoreductase glutaredoxin; GSH, reduced glutathione; GSSG, oxidized glutathione; GST, glutathione (S)-transferase; GST-P1-1, glutathione (S)-transferase pi-1-gene; H_2O_2, hydrogen peroxide; MAPEG, membrane-associated proteins in eicosanoid and glutathione metabolism; NAC, *N*-acetyl cysteine; MDA, malondialdehyde; NF-ƙB, nuclear factor ƙB; NQO1, NAD(P)H dehydrogenase quinone 1; PABA/NO, O^2-[2,4-dinitro-5-(N-methyl-N-4-carboxyphenylamino)phenyl]1-N,N-dimethylamino)diazen-1-ium-1,2-diolate; PARP, poly-(ADP-ribose); PRx, peroxiredoxin; PSSGs, glutathionylation proteins; ROS, reactive oxygen species; S180, sarcoma 180; SEC, Solid Ehrlich Carcinoma; SRx, sulfiredoxin; TNF-α, tumor necrosis factor α; TRx, thioredoxin; γ-EC, γ-glutamyl cysteine

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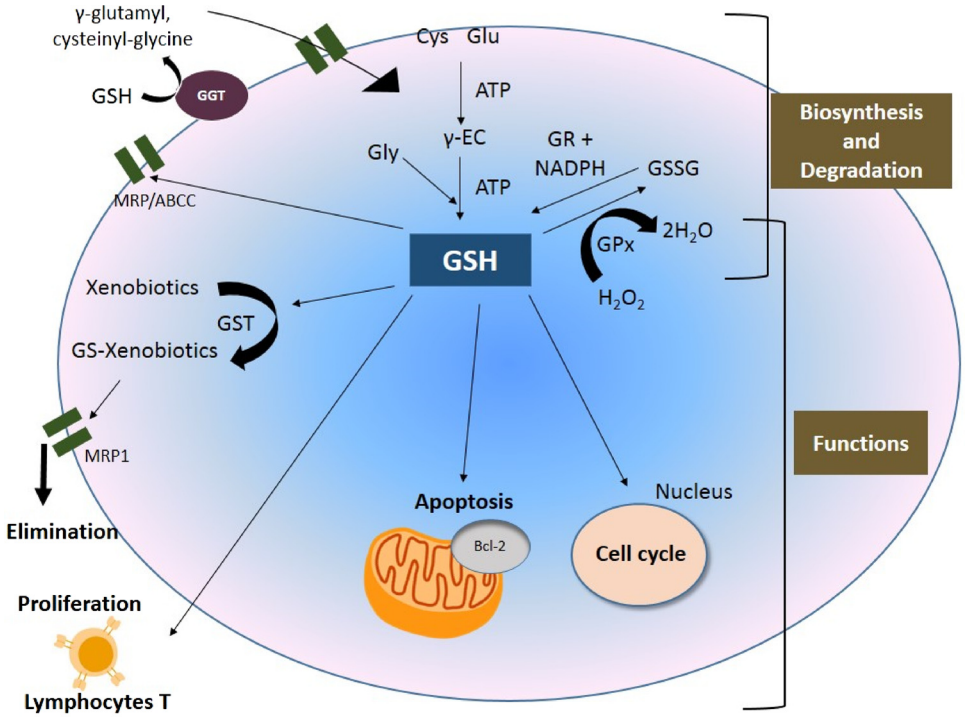

Fig. 1. Glutathione biosynthesis and its main roles. Glutathione is synthesized from Cys, Glu, and Gly amino acids in the presence of ATP. Its degradation involves GSH export to the cell surface through MRP/ABCC transporters and hydrolysis by the GGT enzyme to produce γ-glutamyl and cysteinylglycine. These amino acids can be further broken down into Cys, Glu, and Gly and reincorporated by the cell for *de novo* GSH biosynthesis, thus constituting the γ-glutamyl cycle. The main function of GSH is the detoxification of peroxide through GPx, which prevents oxidative stress in the cellular environment. Moreover, glutathione *S*-transferase (GST) and GSH play an important role in the detoxification of xenobiotics. Glutathione modulates the cell cycle in the nucleus and the onset of cell proliferation. A shift in redox status and imbalance of GSH levels can induce cell cycle arrest and alter DNA synthesis and consequently many cellular functions. Glutathione also controls apoptosis by modulating Bcl2. In a high oxidative environment, high levels of GSH can bind to Bcl-2 and prevent apoptosis and cell death.

of certain cell types. This enzyme is responsible for GSH hydrolysis (Meister and Anderson, 1983). Because GGT is present only in the extracellular space, GSH is resistant to intracellular degradation. Thus, GSH must be released from the cell to be metabolized and for constituent amino acids to be taken up by cells and reincorporated into GSH (referred to as the γ-glutamyl cycle) (Fig. 1) (Meister and Tate, 1976). This is an important function of GSH as a continuous source of cysteine because cysteine can auto-oxidize and generate potentially unstable oxygen free radicals. Once outside the cell, GGT catalyzes GSH into γ-glutamyl amino acid and cysteinylglycine. γ-Glutamyl amino acid can be transported back into the cell and metabolized to release the amino acid and 5-oxoproline, which can be converted to glutamate. Cysteinylglycine is broken down by dipeptidase to generate cysteine and glycine. This amino acid can then be reincorporated to further synthesize GSH (Meister and Anderson, 1983). This cycle is important for GSH homeostasis and maintenance of the thiol-redox status of cells. Moreover, the presence of dipeptidase cysteine is essential for mercapturic acid biosynthesis and metal transport and excretion (Ballatori et al., 2009; Jozefczak et al., 2012).

Glutathione exists in thiol-reduced (GSH) and disulfide-oxidized (GSSG) forms (Kaplowitz et al., 1985; Lu, 2014). Under physiological conditions, ~98% of intracellular glutathione is in the thiol-reduced form (GSH), except in the endoplasmic reticulum where GSSG is found at higher concentrations (Hwang et al., 1992). The lower concentration of GSSG is attributable to its potential toxicity to cells. During oxidative stress, GSSG can react with a thiol group of the proteins generating proteins with disulfide bonds in a reaction that is catalyzed by disulfide isomerase. This enzyme is abundant in the endoplasmic reticulum, which is the only part of the cell with a relatively high GSSG/GSH ratio (Huang and Huang, 2002). Nevertheless, GSSG can also regenerate GSH through the action of glutathione reductase (GR) in an NADPH-dependent step (Jozefczak et al., 2012). The importance of GR activity for GSH metabolism has been recognized, whereas exposure to agents that increase oxidative stress also leads to an increase in GR mRNA content. Furthermore, mutations that affect GR activity have been reported and may have deleterious consequences with regard to cellular redox homeostasis (Masella et al., 2005). Thus, the GSSG/GSH redox balance plays an important role in fine-tuning cellular signaling pathways (Jozefczak et al., 2012).

Glutathione is present in many cellular compartments, including the endoplasmic reticulum, the nucleus, and mitochondria and is found at higher concentrations in the liver (Kaplowitz et al., 1985; Marí et al., 2009). Glutathione is also found in the extracellular space, such as in bile and plasma to supply other cells and tissues and in lung fluid to protect epithelial cells against ROS (Aquilano et al., 2014; Forman et al., 2010; Venglarik et al., 2003). The bulk of plasma and bile GSH that originates from the liver plays a central role in inter-organ GSH homeostasis (Lauterburg et al., 1984).

3. Glutathione regulates oxidative status, the immune system, cell proliferation, and cell death

The key function of GSH is to reduce hydrogen peroxide (H_2O_2) and other organic peroxides through glutathione peroxidase (GPx), resulting in its corresponding hydroxyl compounds. GPx constitutes a family of enzymes that have tissue-specific functions, through reduction of GSH and/or other substrate (Masella et al., 2005). The thiol group of cysteine that is present in GSH is able to donate a reducing electron to unstable molecules, such as ROS, and becomes reactive. This reactive GSH connects with another reactive GSH to form GSSG (Jozefczak et al., 2012), which serves as a substrate for GR to regenerate GSH. Another important step in redox balance involves the ascorbate (AsA)-GSH cycle. Ascorbate and GSH are oxidized and reduced through the action of dehydroascorbate reductase to allow AsA peroxidase (APx) to neutralize H_2O_2 (Jozefczak et al., 2012).

A notable amount of GSH can bind reversibly to –SH of protein cysteinyl residues (Prot-SH). This mechanism is called *S*-glutathionylation, which generates glutathionylation proteins (PSSGs) in the presence of NADPH (Dalle-Donne et al., 2009; Lu, 2014). This process can proceed under physiological conditions, but for the majority of proteins, these reactions occur only under conditions of oxidative stress. *S*-glutathionylation protects protein cysteines from irreversible oxidation and may prevent the loss of GSH under oxidative conditions. *S*-glutathionylation also serves to transduce a redox signal by changing the structure/function of target proteins (Aquilano et al., 2014; Lu, 2014). *S*-glutathionylation can be reversed by the thiol-disulfide oxidoreductase glutaredoxin (GRx) or sulfiredoxin (SRx). The opposite