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Review

# Regulation of glutathione synthesis

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ABSTRACT

Glutathione (GSH) is a ubiquitous intracellular peptide with diverse functions that include detoxification, antioxidant defense, maintenance of thiol status, and modulation of cell proliferation. GSH is synthesized in the cytosol of all mammalian cells in a tightly regulated manner. The major determinants of GSH synthesis are the availability of cysteine, the sulfur amino acid precursor, and the activity of the rate-limiting enzyme, glutamate cysteine ligase (GCL). GCL is composed for a catalytic (GCLC) and modifier (GCLM) subunit and they are regulated at multiple levels and at times differentially. The second enzyme of GSH synthesis, GSH synthase (GS) is also regulated in a coordinated manner as GCL subunits and its up-regulation can further enhance the capacity of the cell to synthesize GSH. Oxidative stress is well known to induce the expression of GSH synthetic enzymes. Key transcription factors identified thus far include Nrf2/Nrf1 via the antioxidant response element (ARE), activator protein-1 (AP-1) and nuclear factor κ B (NFκB). Dysregulation of GSH synthesis is increasingly being recognized as contributing to the pathogenesis of many pathological conditions. These include diabetes mellitus, pulmonary fibrosis, cholestatic liver injury, endotoxemia and drug-resistant tumor cells. Manipulation of the GSH synthetic capacity is an important target in the treatment of many of these disorders.



**Contents**



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## 1. Structure and Functions of GSH

Glutathione is a tripeptide, γ-L-glutamyl-L-cysteinyl-glycine, found in all mammalian tissues and especially highly concentrated in the liver. Glutathione exists in the thiol-reduced (GSH) and disulfide-oxidized (GSSG) forms (Kaplowitz et al., 1985). GSH is the predominant form, existing in millimolar concentrations in most cells (liver 5–10 mM). The GSSG content is less than 1% of GSH (Akerboom et al., 1982). Eucaryotic cells have three major reservoirs of GSH. Almost 90% of cellular GSH are in the cytosol, 10% is in the mitochondria and a small percentage is in the endoplasmic reticulum (Meredith and Reed, 1982; Hwang et al., 1992). Cytosolic GSH in the rat liver turns over rapidly with a half-life of 2–3 h. The peptide bond linking glutamate and cysteine of GSH is through the γ-carboxyl group of glutamate rather than the conventional α-carboxyl group (Fig. 1). This unusual arrangement is subject to hydrolysis by only one known enzyme, namely γ-glutamyltranspeptidase (GGT), which is only present on the external surfaces of certain cell types (Meister and Anderson, 1983). As a consequence, GSH is resistant to intracelluar degradation and is only metabolized extracellularly by organs with GGT.

GSH serves several vital functions including (1) detoxifying electrophiles; (2) scavenging free radicals; (3) maintaining the essential thiol status of proteins; (4) providing a reservoir for cysteine; and (5) modulating critical cellular processes such as DNA synthesis, microtubular-related processes, and immune function (Kaplowitz et al., 1985; Meister and Anderson, 1983; DeLeve and Kaplowitz, 1990; Suthanthiran et al., 1990). In addition, GSH has been shown to regulate nitric oxide homeostasis (Hogg, 2002), modulate the activity of proteins by post-translational modification (protein S-glutathionylation) (Pompella et al., 2003), and modulate the activity of neurotransmitter receptors (Oja et al., 2000). Clearly GSH is a multifunctional molecule with diverse and still emerging functions that affect critical cellular processes. This review summarizes how GSH synthesis is regulated in health and dysregulated in certain diseases, with an emphasis on the liver. This is because the liver plays a central role in the interorgan GSH homeostasis as plasma GSH and cysteine levels are largely determined by the sinusoidal efflux of hepatic GSH (Ookhtens and Kaplowitz, 1998). Some of the key functions of GSH are described in more detail before turning the attention to GSH synthesis.

### 1.1. Detoxifying functions of GSH

A major function of GSH is detoxification of xenobiotics and/or their metabolites. These compounds are electrophiles or electron-loving substances (Fig. 2, indicated as X) and form conjugates with GSH either spontaneously or enzymatically in reactions catalyzed by GSH-S-transferase (Meister, 1988). The conjugates formed are usually excreted from the cell or into bile as in the case of hepatocytes. GSH conjugates can undergo GGT-mediated cleavage of the γ-glutamyl moiety, leaving a cysteinyl-glycine conjugate. The cysteinyl-glycine bond is then cleaved by dipeptidase, resulting in a cysteinyl conjugate. This is followed by *N*-acetylation of the cysteine conjugate, forming a mercapturic acid (Fig. 2). The metabolism of GSH conjugates to mercapturic acid begins either in the biliary tree, intestine or kidney, but the formation of the *N*-acetylcysteine conjugate usually occurs in the kidney (DeLeve and Kaplowitz, 1990). In addition to exogenous compounds, many endogenously formed compounds also follow similar metabolic pathways. Although the majority of the conjugation reactions to

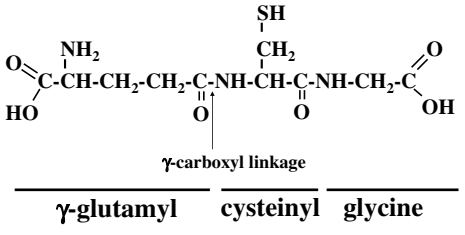


**Fig. 1.** Structure of GSH or γ-glutamylcysteinyl glycine, where the *N*-terminal glutamate and cysteine are linked by the γ-carboxyl group of glutamate.