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Review Article

Glutathione Homeostasis and Functions: Potential Targets for Medical Interventions

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Glutathione (GSH) is a tripeptide, which has many biological roles including protection against reactive oxygen and nitrogen species. The primary goal of this paper is to characterize the principal mechanisms of the protective role of GSH against reactive species and electrophiles. The ancillary goals are to provide up-to-date knowledge of GSH biosynthesis, hydrolysis, and utilization; intracellular compartmentalization and interorgan transfer; elimination of endogenously produced toxicants; involvement in metal homeostasis; glutathione-related enzymes and their regulation; glutathionylation of sulfhydryls. Individual sections are devoted to the relationships between GSH homeostasis and pathologies as well as to developed research tools and pharmacological approaches to manipulating GSH levels. Special attention is paid to compounds mainly of a natural origin (phytochemicals) which affect GSH-related processes. The paper provides starting points for development of novel tools and provides a hypothesis for investigation of the physiology and biochemistry of glutathione with a focus on human and animal health.

1. Introduction

Glutathione (GSH) is a tripeptide (L-γ-glutamyl-L-cysteinyl-glycine) with multiple functions in living organisms [1–4]. As a carrier of an active thiol group in the form of a cysteine residue, it acts as an antioxidant either directly by interacting with reactive oxygen/nitrogen species (ROS and RNS, resp.) and electrophiles or by operating as a cofactor for various enzymes [5–8]. Glutathione is moderately stable in the intracellular milieus because intracellular peptidases can cleave peptide bonds formed by the α-carboxyl groups of amino acids, but typically not the γ-carboxyl groups.

The reduced and oxidized forms of glutathione (GSH and GSSG) act in concert with other redox-active compounds (e.g., NAD(P)H) to regulate and maintain cellular redox status [9]. The former is quantitatively described by the redox potential, calculated according to the Nernst equation. In most cells and tissues, the estimated redox potential for the GSH/GSSG couple ranges from −260 mV to −150 mV (cited after [10]).

GSH is synthesized in a two-step process catalyzed by L-glutamate: L-cysteine γ-ligase, (γGLCL, EC 6.3.2.2) (also called γ-glutamyl-L-cysteine ligase or γ-glutamylcysteine synthase), and glutathione synthase (GLS, EC 6.3.2.3). GSH is consumed in many ways, such as by oxidation, conjugation, and hydrolysis [11]. GSH can be directly oxidized by ROS and RNS or indirectly during GSH-dependent peroxidase-catalyzed reactions. Conjugation with endogenous and exogenous electrophiles consumes a substantial portion of cellular GSH. In addition, cells may lose GSH due to export of its reduced, oxidized or conjugated forms. Extracellularly, GSH can be hydrolyzed by γ-L-glutamyl transpeptidase (GGT, EC 2.3.2.2) transferring the γ-glutamyl functional group to water during hydrolysis to form free glutamate [12]. The enzyme may also transfer the γ-glutamyl moiety of GSH to amino acids and peptides. Frequently, products of GSH hydrolysis are taken up by cells either as individual amino acids, or as dipeptides. The intra- and extracellular GSH levels are determined by the balance between its production, consumption, and transportation. Due to important physiological functions of GSH, these processes are tightly regulated. The activities of the enzymes involved in GSH metabolism are controlled