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Chapter 1

Introductory Chapter: A General Overview of Glutathione, Glutathione Transport, and Glutathione Applications

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1. Introduction

Reduced glutathione (GSH) is a water-soluble tripeptide with the structure of γ-glutamyl-cysteinyl-glycine. The gamma bond between glutamic acid and cysteine provides stability to GSH as there are lower amounts of γ-peptidases in biological systems when compared to α-peptidases [1].

GSH is the most important thiol in living organisms. GSH is a catalyst, reductant, and reactant. This molecule is found in large quantities (millimolar concentrations) in organs exposed to toxins such as liver, kidney, lungs, and intestines. However, in body fluids, GSH concentrations are at micromolar concentrations [2].

GSH is synthesized in the cell cytosol. In a reaction catalyzed by "γ-glutamylcysteine synthetase," L-cysteine and L-glutamate form "γ-glutamylcysteine." By the addition of glycine, GSH is formed in a reaction catalyzed by "glutathione synthetase." The catabolism of GSH is mainly catalyzed by "γ-glutamyl transpeptidase" (forming glutamate and cysteinylglycine) and "dipeptidases" (forming cysteine and glycine). Cysteine is then catabolized to mercapturic acid [3].

GSH plays a role in amino acid transport, protein synthesis, DNA synthesis and protection, and more generally, in cellular detoxification. The main source of plasma GSH is liver. As part of their physiological functions, viable cells such as hepatocytes and macrophages extrude this particular thiol. This phenomenon supplies antioxidant protection for the extracellular environment as well [4].

GSH acts essentially as an intracellular key component of antioxidant system, serves as a free radical scavenger and can be effective against the attacks of many reactive species, including electrophilic substances and epoxides. Upon contact with reactive species, GSH is converted to oxidized glutathione (GSSG, dimeric glutathione) by glutathione peroxidases (GPxs) and later can be reduced to GSH again by glutathione reductase (GR). Therefore, there is a cycle of GSH and this cycle provides higher intracellular levels of GSH. On the other hand, glutathione S-transferases (GSTs) can form conjugates between GSH and endogenous (e.g., estrogens) or exogenous substances (e.g., electrophiles like arene oxides, organic halides, or unsaturated carbonyls). The decrease in the activities of GSTs may increase risk for disease; however, some GSH conjugates can also be toxic, paradoxically [5].

The transport of GSH through plasma membrane is regulated by a switch mechanism orchestrated by open/closed configuration of the transporters. This transfer from the cell to the extracellular environment occurs according to a concentration gradient. The transport is uniport and cells usually export GSH rather than import as intracellular GSH levels are higher than extracellular fractions [6].

The molecular nature of GSH transporters is still elusive though these transports are functionally identified as sinusoidal or canalicular type due to their position in the hepatic anatomy and their responsiveness to specific inhibitors [7, 8]. Data from different reports show that GSH transporters coincide with the multi-drug resistance-associated proteins (MRPs) [6, 9]. The regulatory mechanism/s behind the activity of GSH transporters is/are still ambiguous. These transports are possibly being controlled by the differential concentration of GSH on the internal vs. external side of the cellular membranes. Thereby, their control may mainly rely on the zonal control of GSH levels by intracellular trafficking [4]. A different regulation mechanism operates in the export of GSSG when cells are subject to oxidative stress or when GSSG cannot be reduced to GSH by GR. Even though GSSG was shown to be target of MRP [6], in conditions of oxidative stress GSSG crosses the plasma membrane and passively exits from cells. This is a balancing mechanism which helps to avoid a dangerous drop in the redox (GSH/GSSG) ratio due to the accumulation of GSSG, and the consequent redox imbalance [6, 10].

It is still a question mark whether GSH depletion is a cause or an outcome of different pathological conditions and exposure to certain environmental chemicals. Several diseases may cause depletion of intracellular GSH levels. On the other hand, environmental chemicals and drugs may also lead to GSH repression. In addition, GSH levels are depleted at different degrees if the cellular death mechanisms are triggered by different chemicals or conditions. GSH depletion and apparent oxidative stress may also cause cytotoxicity [10–12].

Reduced glutathione was shown to be preventive against aging, cancer, heart disease, and dementia. Moreover, GSH supplementation (mainly as cysteine) can help to reduce the symptoms of many diseases and can be beneficial in different conditions like autism, Alzheimer's disease, Parkinson's disease, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), hepatitis, type 2 diabetes, cystic fibrosis, and certain infections [13–16].

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Plasma and liver GSH levels were shown to decrease dramatically in certain liver disease patients (i.e., viral hepatitis, chronic hepatitis, chronic liver injury, and liver cirrhosis) [17]. GSH also plays an important role in the activation of T-lymphocytes [18]. In HIV infection, a systemic drop in intracellular/extracellular GSH is linked to an increase of virus replication. Moreover, cysteine deficiency may also lead to decrease in GSH levels which also leads to high viral load [18, 19].

In Parkinson's disease, the level of glutathione in *substantia nigra* was found to be lower in Parkinsonian patients compared to controls. This decrease may be related to the increased degradation of GSH by γ-glutamyltranspeptidase [20–23]. GSH levels were also found to be depleted in certain lung diseases, like acute respiratory disease (ARDS), and in neonatal lung damage [24–26].

A reduction of GSH levels was determined in the ischemic tissue during myocardial ischemia and reperfusion and myocardial injury was found to be negatively associated with the myocardial concentration of GSH. The administration of γ-glutamylcysteine or N-acetyl cysteine (NAC) markedly reduced the infarct size and myocyte death [27–30]. GSH levels were reported to be significantly reduced in renal ischemia and in cyclosporin intoxication as both conditions induce lipid peroxidation in microsomes [31–34].

Studies on the interaction between GSH levels and aging are still contradictory. Therefore, large-scale epidemiological studies are needed in order to reach conclusions [35–37]. On the other hand, GSH was shown to protect against several types of cancer [35–37]. For instance, administration of GSH can provide decrease in the rate of different types of cancers [38, 39]. However, GSH treatment should be reconsidered in some types of cancer as GSH is a double-edged knife in cancer treatment and may lead to the development of resistance to chemotherapy [38, 39].

GSH has poor bioavailability. This phenomenon restricts its direct use in clinics [30]. Hydrophobic forms such as monoethylester of GSH have been synthesized to overcome this restriction. These synthetic forms are cleaved by cellular esterases to form GSH. After such forms are administered to after GSH-deprived rats by oral route, an increase in GSH concentrations was observed in both plasma and liver [40]. Due to the oxidation of cystine, cysteine may cause toxicity. Therefore, N-acetyl cysteine (NAC) has been used as an exogenous source of cysteine to provide intracellular glutathione in GSH-deficient patients. After hydrolysis, NAC can be a source of cysteine, the major amino acid in synthesis of GSH [41]. The administration of NAC to HIV positive patients provides increases in GSH levels of CD4+ lymphocytes, inhibits the activity of nuclear factor kappa B (NFkB), and arrests viral replication [42].

In conclusion, GSH continues to be investigated in diverse pathological conditions. Cancer, liver diseases, neuropathological diseases, acute respiratory distress syndrome, HIV/AIDS, and aging are the main research fields for studies on GSH. However, there is a long road ahead in order to use GSH or its different forms in clinics for certain conditions. GSH will continue to be the subject of new studies and hopefully GSH or its different forms will be used as a drug or adjunct therapy for certain pathological conditions in the future.

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