Published in final edited form as:
Biol Chem. 2009 March ; 390(3): 191–214. doi:10.1515/BC.2009.033.

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Glutathione dysregulation and the etiology and progression of human diseases

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Conjugation IS phase 2 liver detoxification

Abstract

Glutathione (GSH) plays an important role in a multitude of cellular processes, including cell differentiation, proliferation, and apoptosis, and as a result, disturbances in GSH homeostasis are implicated in the etiology and/or progression of a number of human diseases, including cancer, diseases of aging, cystic fibrosis, and cardiovascular, inflammatory, immune, metabolic, and neurodegenerative diseases. Because of GSH's pleiotropic effects on cell functions, it has been quite difficult to define the role of GSH in the onset and/or the expression of human diseases, although significant progress is being made. GSH levels, turnover rates and/or oxidation state can be compromised by inherited or aquired defects in the enzymes, transporters, signaling molecules, or transcription factors that are involved in its homeostasis, or from exposure to reactive chemicals or metabolic intermediates. GSH deficiency or a decrease in the GSH/glutathione disulfide (GSSG) ratio manifests itself largely through an increased susceptibility to oxidative stress, and the resulting damage is thought to be involved in diseases such as cancer, Parkinson's disease, and Alzheimer's disease. In addition, imbalances in GSH levels affect immune system function, and are thought to play a role in the aging process. Just as low intracellular GSH levels decrease cellular antioxidant capacity, elevated GSH levels generally increase antioxidant capacity and resistance to oxidative stress, and this is observed in many cancer cells. The higher GSH levels in some tumor cells are also typically associated with higher levels of GSH-related enzymes and transporters. Although neither the mechanism nor the implications of these changes are well defined, the high GSH content makes cancer cells chemoresistant, which is a major factor that limits drug treatment. The present report highlights and integrates the growing connections between imbalances in GSH homeostasis and a multitude of human diseases.

Keywords

Glutathione; neurodegenerative diseases; aging; cancer; cardiovascular diseases; metabolic diseases

Introduction

GSH is required for many critical cell processes, buy plays a particularly important role in the maintenance and regulation of the thiol-redox status of the cell (Meister and Anderson, 1983; Meister, 1984; Deleve and Kaplowitz, 1990; Wang and Ballatori, 1998; Sies, 1999; Hammond et al., 2001; Ballatori et al., 2005; Schafer and Buettner, 2001). The redox state of the GSH/glutathione disulfide couple (GSH/GSSG) can serve as an important indicator of redox environment (Jones, 2006; Kemp et al., 2008; Schafer and Buettner, 2001), and changes in this

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Table 1

Endogenous glutathione *S*-conjugates and complexes

Thioethers:
Acetoacetyl
Acetyl
Acyl-adenylated bile acids*
Acyl-CoA thioesters of bile acids*
β-Alanyl-dopa
Anthocyanins*
Auxins*
Catechol estrogen quinones*
Cholesterol-5,6-oxide
Cytokinins*
Dicarboxyethyl
Dopa
Dopamine
17-β-Estradiol
Ethyl
Flavonoids*
Hepoxilin A_3
Hydroxyethyl
4-Hydroxyhexenal
4-Hydroxynonenal
5-Hydroxytryptamine
5-Hydroxytryptophan
Indoles*
Leukotriene C_4
Linoleic acid oxidation products*
Menadione
Methyl
α-Methyldopamine
Methylglyoxal
Nitric oxide
Nitrolinoleic acid
13-Oxooctadecadienoic acid
Palmityl
Porphyrins*
PGJ_2, PGD_2, PGA_1, PGA_2
Quinones*
Tetrapyrroles*
Trans-urocanic acid
Thioesters:
Coenzyme A

conjugation of glutathione with L-dopa and dopamine may deplete glutathione