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Regulation of Glutathione Synthesis as The Response to Oxidative and Chemical Stress

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Editorial

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Reduced glutathione (GSH) plays an important role in the detoxification of electrophiles and reactive oxygen species (ROS) generated during the biotransformation of some xenobiotics. Many toxicologically important compounds undergo metabolic activation catalyzed by cytochrome P450 (CYP) enzymes, mainly isoenzyme CYP 2E1, to electrophilic reactive intermediates such as: epoxides, quinones, aldehydes and carbocations, and additionally ROS as a by-product. The electrophilicity of the metabolites dictates covalent adduction with nucleophilic sites on nucleic acid or nucleophilic amino acid residues on proteins. Reduced glutathione offers cellular protection since it can react with electrophilic or oxidizing species before they damage critical cellular macromolecules [1,2]. The increase in the cellular GSH level has been reported to serve as an adaptive response to withstand oxidative and chemical stresses that would otherwise have been lethal. The up-regulation of GSH content is achieved mostly through transcriptional mechanism [3,4].

Glutathione is a tripeptide, L-γ-glutamyl-L-cysteinyl-glycine. The sulfhydryl group of cysteine serves as a proton donor and is completely responsible for the high capacity of GSH to scavenge radicals and makes glutathione particularly suitable for the formation of conjugates with electrophilic species [5,6]. However, a number of xenobiotic metabolites are strong electrophiles, such as carbocations, and their conjugation with GSH requires enzymatic catalysis of glutathione S-transferases (GSTs) [7]. GSH is biosynthesized in the cytosol in a two-step ATP-dependent pathway catalyzed by glutamate-cysteine ligase (GCL) and glutathione synthetase (GS) [3]. Nonetheless, the rate of GSH biosynthesis is largely determined by cysteine availability and GCL activity [5]. Mammalian GCL consists of two subunits: heavy or catalytic (GCLC, 73 kDa), exhibiting feedback inhibition by GSH, and the light or modifier subunit (GCLM, 31 kDa) [8]. It has been shown that ROS and electrophiles are able to induce the transcription of *Gclc* and *Gclm* through the Keap1/Nrf2/ARE and NF-κB signalling pathways [4,9].

Exposure to electrophilic compounds such as 4-hydroxy-2-nonenal and *tert*-butyl hydroquinone has been proved to increase the rate of GSH biosynthesis in human bronchial epithelial cells. Both of the treatments caused an increase in the two GCL mRNAs that has been correlated with the raise in the GCL proteins [10]. It is clear, since electrophiles can activate the Keap1/Nrf2/ARE pathway, either directly or indirectly through the generation of ROS [4]. CYP2E1-dependent oxidative stress has been reported that also affects GSH homeostasis. Pyrazole-mediated induction of CYP2E1 up-regulated the expression and activity of GCL in wild type mice, but to a lesser extent, or not at all in Nrf2 knockout mice. Likewise, in CYP2E1-overexpressed HepG2 cells, demonstrating an increased generation of ROS, the total GSH level, the GSH synthetic rate and GCL mRNA were concomitantly elevated [11,12].

The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway has been also demonstrated to be involved in the cellular defence against chemical and oxidative insult. NF-κB binds and directly activates the *Gclc* promoter, whereas it indirectly regulates the *Gclm* promoter by activator protein1. Hence, it has been postulated that the basal levels of GCLC and GCLM expression and GSH homeostasis in unstressed cells is the consequence of IκB kinase (IKKβ) signals required to maintain a basal level of NF-κB activity. Inactivation of this IKKβ signalling pathway markedly reduces basal NF-κB activity, decreases its binding to the promoters of *Gclc* and *Gclm* leading to a reduction of GCLC and GCLM expression and consequently

reduces cellular GSH [13]. In cells deficient in the (IKKβ) it has been reported that loss of IKKβ signalling decreased binding of NF-κB to the promoters of *Gclc* and *Gclm*, leading to the reduction of GCLC and GCLM expression and finally to GSH depletion [9,13]. *In vivo*, hepatocyte-specific IKKβ deficient mice showed a reduced expression of major cellular antioxidants including GSH and excessive ROS level in the liver in response to N-nitrosodiethylamine, generating carbocation and ROS during its biotransformation [14]. Chia *et al*. [9] evaluated a putative simultaneous regulation of Nrf2 and NF-κB in a hepatocyte cell line during redox perturbation caused by N-acetyl-p-benzoquinineimine (NAPQI), an electrophilic metabolite of acetaminophen. The results of their study showed a nuclear accumulation of Nrf2, which elevated with increasing concentration of NAPQI and, in contrast to Nrf2 expression, NF-κB DNA binding decreased with increasing concentrations of the xenobiotics [9]. Nrf2 has been suggested to be regulated hormetically. Electrophiles at low to moderate levels cause the activation of Nrf2 with a cell survival-promoting effect, while high doses oppositely affect - diminish Nrf2 and ARE-responsive genes and upregulate NFκB [15].

The regulation of GSH biosynthesis under oxidative or chemical stress entails a transcription-based mechanism involving Keap1/Nrf2/ARE and NF-κB transcriptional pathways and the consequent enhancement of GSH synthesis capacity through greater GCL content. The cellular response is a multifaceted and complex phenomenon which depends on the level of stress.

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