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Research Article

# The Glutathione S-Transferase Supergene Family: Regulation of GST and the Contribution of the Isoenzymes to Cancer Chemoprotection and Drug Resistance Part I

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## Abstract

The glutathione S-transferases (GST) represent a major group of detoxification enzymes. All eukaryotic species possess multiple cytosolic and membrane-bound GST isoenzymes, each of which displays distinct catalytic as well as noncatalytic binding properties: the cytosolic enzymes are encoded by at least five distantly related gene families (designated class alpha, mu, pi, sigma, and theta GST), whereas the membrane-bound enzymes, microsomal GST and leukotriene C, synthetase, are encoded by single genes and both have arisen separately from the soluble GST. Evidence suggests that the level of expression of GST is a crucial factor in determining the sensitivity of cells to a broad spectrum of toxic chemicals. In this article the biochemical functions of GST are described to show how individual isoenzymes contribute to resistance to carcinogens, antitumor drugs, environmental pollutants, and products of oxidative stress.

A description of the mechanisms of transcriptional and posttranscriptional regulation of GST isoenzymes is provided to allow identification of factors that may modulate resistance to specific noxious chemicals. The most abundant mammalian GST are the class alpha, mu, and pi enzymes and their regulation has been studied in detail. The biological control of these families is complex as they exhibit sex-, age-, tissue-, species-, and tumor-specific patterns of expression. In addition, GST are regulated by a structurally diverse range of xenobiotics and, to date, at least 100 chemicals have been identified that induce GST; a significant number of these chemical inducers occur naturally and, as they are found as nonnutrient components in vegetables and citrus fruits, it is apparent that humans are likely to be exposed regularly to such compounds. Many inducers, but not all, effect transcriptional activation of GST genes through either the antioxidant-responsive element (ARE), the xenobiotic-responsive element (XRE), the GST P enhancer I(GPE), or the glucocorticoid-responsive element (GRE).

Barbiturates may transcriptionally activate GST through a Barbie box element. The involvement of the Ah-receptor, Maf, Nrl, Jun, Fos, and NF- $\kappa$ B in GST induction is discussed. Many of the compounds that induce GST are themselves substrates for these enzymes, or are metabolized (by cytochrome P-450 monooxygenases) to compounds that can serve as GST substrates, suggesting that GST induction represents part of an adaptive response mechanism to chemical stress caused by electrophiles. It also appears probable that GST are regulated in vivo by reactive oxygen species (ROS), because not only are some of the most potent inducers capable of generating free radicals by redox-cycling, but  $H_2O_2$  has been shown to induce GST in plant and mammalian cells: induction of GST by ROS would appear to represent an adaptive response as these enzymes detoxify some of the toxic carbonyl-, peroxide-, and epoxide-containing metabolites produced within the cell by oxidative stress.

Class alpha, mu, and pi GST isoenzymes are overexpressed in rat hepatic preneoplastic nodules and the increased levels of these enzymes are believed to contribute to the multidrug-resistant phenotype observed in these lesions. The majority of human tumors and human tumor cell lines express significant amounts of class pi GST. Cell lines selected in vitro for resistance to anticancer drugs frequently overexpress class pi GST, although overexpression of class alpha and mu isoenzymes is also often observed. The mechanisms responsible for overexpression of GST include transcriptional activation, stabilization of either mRNA or protein, and gene amplification.

In humans, marked interindividual differences exist in the expression of class alpha, mu, and theta GST. The molecular basis for the variation in class alpha GST is not

known. Absence of certain class mu and theta GST can be attributed to deletion of the GSTMIgene in 50% of the population and deletion of the GSTTIgene in 16% of the population. The biological consequences of failure to express hGSTMI or hGSTTI protein can include susceptibility to bladder, colon, skin, and possibly lung cancer.

Key Words:

glutathione S-transferases

chemoprotection

enzyme induction

adaptive response

antioxidants

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