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The quantitatively important relationship between homocysteine metabolism and glutathione synthesis by the transsulfuration pathway and its regulation by redox changes

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Abstract

Homocysteine is a key junction metabolite in methionine metabolism. It suffers two major metabolic fates: transmethylation catalyzed by methionine synthase or betaine homocysteine methyl transferase and transsulfuration catalyzed by cystathionine beta-synthase leading to cystathionine. The latter is subsequently converted to cysteine, a precursor of glutathione. Studies with purified mammalian methionine synthase and cystathionine beta-synthase have revealed the oxidative sensitivity of both junction enzymes, suggesting the hypothesis that redox regulation of this pathway may be physiologically significant. This hypothesis has been tested in a human hepatoma cell line in culture in which the flux of homocysteine through transsulfuration under normoxic and oxidative conditions has been examined. Addition of 100 microM H(2)O(2) or tertiary butyl hydroperoxide increased cystathionine production 1.6- and 2.1-fold from 82 +/- 7 micromol h(-)(1) (L of cells)(-)(1) to 136 +/- 15 and 172 +/- 23 micromol h(-)(1) (L of cells)(-)(1), respectively. The increase in homocysteine flux through the transsulfuration pathway exhibited a linear dose dependence on the concentrations of

both oxidants (50-200 microM H(2)O(2) and 10-200 microM tertiary butyl hydroperoxide). Furthermore, our results reveal that approximately half of the intracellular glutathione pool in human liver cells is derived from homocysteine via the transsulfuration pathway. The redox sensitivity of the transsulfuration pathway can be rationalized as an autocorrective response that leads to an increased level of glutathione synthesis in cells challenged by oxidative stress. In summary, this study demonstrates the importance of the homocysteine-dependent transsulfuration pathway in the maintenance of the intracellular glutathione pool, and the regulation of this pathway under oxidative stress conditions. Aberrations in this pathway could compromise the redox buffering capacity of cells, which may in turn be related to the pathophysiology of the different homocysteine-related diseases.

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- Cystathionine / metabolism
- Cystathionine beta-Synthase / metabolism
- Glutathione / biosynthesis*

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