Benzo[a]pyrene and glycine N-methyltransferse Interactions: Gene expression profiles of the liver detoxification pa

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Abstract

Benzo[a]pyrene (BaP) is one of many polycyclic aromatic hydrocarbons that have been identified as major risk factors for developing various cancers. We previously demonstrated that the liver cancer susceptibility gene glycine N-methyltransferase (GNMT) is capable of binding with BaP and protecting cells from BaP-7,8-diol 9,10-epoxide-DNA adduct formation. In this study, we used a cytotoxicity assay to demonstrate that the higher expression level of GNMT, the lower cytotoxicity occurred in the cells treated with BaP. In addition, a cDNA microarray containing 7,597 human genes was used to examine gene expression patterns in BaP-treated HepG2 (a liver cancer cell line that expresses very low levels of GNMT) and SCG2-1-1 (a stable HepG2 clone that expresses high levels of GNMT) cells. The results showed that among 6,018 readable HepG2 genes, 359 (6.0%) were up-regulated more than 1.5-fold and 768 (12.8%) were down-regulated. Overexpression of GNMT in SCG2-1-1 cells resulted in the down-regulation of genes related to the detoxification, kinase/phosphatase pathways, and oncogenes. Furthermore, real-time PCR was used to validate microarray data from 21 genes belonging to the detoxification pathway. Combining both microarray and real-time PCR data, the results showed that among 89 detoxification pathway genes analyzed, 22 (24.7%) were up-regulated and 6 (6.7%) were down-regulated in BaP-treated HepG2 cells, while in the BaP-treated SCG2-1-1 cells, 12 (13.5%) were up-regulated and 26 (29.2%) were down-regulated ($P < 0.001$). Therefore, GNMT sequesters BaP, diminishes BaP's effects to the liver detoxification pathway and prevents subsequent cytotoxicity.