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Gene Expression Patterns Induced by Acetaminophen on Mice Hepatocytes Using Toxicogenomic Technique

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Acetaminophen (APAP) is one of most popular analgesic and antipyretic, which exhibits hepatotoxicity at high dose. Cytochrome P450 2E1 (CYP2E1) metabolizes APAP to toxic N-acetyl-p-benzoquinonimine (NAPQI), which induces disruption of energy homeostasis in hepatocytes by mitochondrial respiratory chain dysfunction, finally leading to hepatotoxicity. APAP-induced hepatic injury is associated with reactive oxigen species (ROS), which might cause mtDNA damage and apoptosis, following to cytochrome-c release and caspase activation. ROS also induces mitochondrial damage characterized by membrane permeability transit (MPT) by collapse of mitochondrial transmembrane potential, which is caused by loss of phosphatitylglycerol /cardiolipin. APAP hepatotoxicity might progressed with ROS through NAPQI from CYP2E1. It has been reported that APAP-mediated hepatotoxicity might be relieved by exogenously overexpressed antioxidant genes, of which products are glutathione (GSH), glutathione-s-transferase (GST), glutathione peroxidase (GPX), catalase, Cu/Zn superoxide dismutase (SOD1), and MnSOD for antioxidant system. In this study, we investigated that gene expression profile of mice hepatocytes exposed to APAP at subtoxic level, using a low-density cDNA microarray containing mice 380 genes selected for prospective response genes. In our result of DNA microarray analysis, most of antioxidant genes and xenobiotic metabolic genes are highly up-regulated. We suggest that MTF1/ MT1(Metal-responsive transcription factor-1, Metallothionein-1) could be a new candidate for APAP-mediated hepatotoxicity

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