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Gene Expression Profiles on Acetaminophen-induced Liver Toxicity in Rat Using Microarray Technology

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Microarray analysis of RNA from acetaminophen (APAP)-administered rat livers was performed at various time points to establish a global gene expression profile. A single dose of 1g/kg of APAP was given by ip injection, and the liver samples were obtained after 0h, 24h, 48h, and 2wk. Histopathologic studies of liver tissues enabled the classification of the APAP effect into early (24 h and 48 h) and late (2 wk) stages. The expression levels of 5,184 clones on a custom rat gene microarray were analyzed and the results were confirmed by semi-quantitative RT-PCR. The greatest changes, hepatocellular degeneration and necrosis, were observed at 24h and 48h. By 2wk, severity of lesions had significantly decreased. Significant alterations in gene expression, both positive and negative, were noted within the livers of APAP-treated rat. Genes related to liver functions such as glycogen metabolism, cholesterol biosynthesis, fatty acid synthesis and gluconeogenesis were repressed by APAP in both early and late stages. Moreover, we observed a repression in mitochondrial-specific genes such asacyl-CoA dehydrogenases and 2,4 dienoyl-CoA recdutase at 24h. In contrast, a number of oxidative response genes and cytoplasmic ribosomal proteins were increased in APAP-treated livers at 24h and 48h. These results suggest that mitochondrial damage and oxidative stress are identified as the principle mechanisms in APAP-mediated hepatotoxicity. In conclusion, these data provide new directions for mechanistic studies that may lead to a better understanding of the molecular basis of APAP-induced liver injury. This work was supported by the grant from the National Institute of Toxicology Research, Korea(to Gu Kong).

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