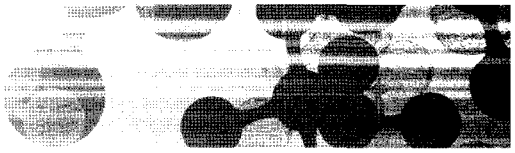

S10-3

Time and Dose-based Gene Expression Profiles Produced by a Bile Duct-damaging Chemical, 4,4'-Methylene Dianiline, in an Acute Phase in the Mouse Liver

Byung-IL Yoon

School of Veterinary Medicine and Institute of Veterinary Science, Kangwon National University, Chuncheon, Republic of Korea

Toxicogenomics study was performed to clarify unique gene expression profile produced by a bile duct-damaging chemical, **4,4'**-methylene dianiline (MDA),in the mouse liver across multiple doses and time points in an acute phase, using Applied Biosystems Expression Array System. ICR mice were given single oral administration of control vehicle corn oil, low (10 mg/kg b.w.) and high dose (100 mg/kg b.w.) of MDA. The mice were respectively sacrificed at 6, 24 and 72 hours after the treatment and liver samples were then prepared for mRNA isolation. Serum chemistry and histopathological examination were also carried out to compare the results with the altered gene expression profile at each time point of the select doses. Single treatment of MDA increased the hepatic and bile duct cell injury-related enzymes in blood, and histopathologically induced bile duct cell injury characterized by degeneration, necrosis and periductal inflammation, followed by the recovery responses including fibrosis. Hundreds of genes associated with transport, transcription factor, signal transduction, receptor, protein and lipid metabolism, oxidative stress, oncogenesis, immunity, developmental processes and cell cycle/proliferation created differential genetic signatures depending on time and dose. At the low dose, the most numerous genes gave rise to altered gene expressions at 24 hour after MDA treatment, while, at the higher dose, at 72 hour. As early responsive genes, the altered genes were very differential depending on dose, but we could point out nineteen commonly altered genes independent of dose including up-regulated (Gpx6, Emid2, Dio1, etc) and down-regulated genes (Prss22, Wgscr16, Nupl1, Havcr1, Cox10, etc). At the low dose, Egr1, Nmyc1 and Cxcl1 were noteworthy as potential markers at the early phase. As delayed responsive genes, differential altered genes depending on dose (160 genes for low dose, 703 genes for high dose) and commonly altered genes independent of dose (16 genes) were respectively pointed out. Thus, our microarray data represented time and dose-based unique gene expression profiles produced by MDA in an acute phase. In addition, several candidate genes of which expression patterns are distinguishable from those of other hepatotoxicants had been pointed out as potential biomarkers to discern the toxic endpoints of certain of chemicals in bile duct cell population.