Toxicogenomics approaches in Toxicological Pathology

Tomoyuki Shirai
Nagoya City University Graduate of Medical Sciences, Nagoya Japan

It is believed that cell and/or tissue toxicity is resulted from alterations in expression of many genes in response to environmental stresses or toxicants. New technology, such as DNA microarray analysis, can measure the expression of thousands of genes at a time providing the potential to accelerate discovery of toxicant pathways and specific gene targets. Toxicogenomics is a new scientific field that expected to overcome many difficulties present in conventional toxicological examinations. For example, a standardized long-term rodent carcinogenicity assay for predicting carcinogenic hazard of chemical substances to human beings is very expensive in terms of financial and human resources and a time-consuming. Many potential short-assays have been developed but none of them can predict carcinogenicity of chemicals particularly non-mutagenic compounds that generate tumors only after long-term administration to rodents. Global gene expression profiles obtained from toxicogenomics analysis are expected to predict carcinogenic potentials of environmental chemicals in a relatively short period, because each chemical with different mode-of –action will possess a specific gene expressions. The lack of available test systems for non-genotoxic carcinogens becomes a significant problem for risk assessment in recent years. To address this, the Ministry of Economy, Trade and Industry in Japan have undertaken a toxicogenomics project that aims at developing a novel testing approach based on combination of animal toxicology studies and gene expression monitoring. This project is a consortium which cooperated by 8 laboratories together with 3 academic supports. In the present study, male Fischer 344 rats aged 5-week old were treated by daily oral gavages with known carcinogenic and non-carcinogenic compounds at two dose levels for 28 days. The liver, kidney, spleen and colon were sampled at the following 6 timepoints: Day 1, 3, 7, 14, 21 and 28. Physical signs, organ/body weight ratios and histological changes including serum liver function enzymes were measured. For monitoring the gene expression levels, the in-house microarray containing approximately 9,000 genes and ESTs from the liver, kidney, spleen and colon of rats was prepared and GeneChip (Affymetrix) was also applied for comparison. In this symposium, I will present recent preliminary data obtained in this project as well as some data from toxicogenomic analysis performed in my laboratory.