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The potentials and limitations of microarray-based gene expression profiles for predicting genotoxicity and carcinogenicity in L5178Y mouse lymphoma cells

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Recently we reported gene expression profiling of genotoxic compounds with differing tumorigenicity results (Environ. Mol. Mutagen. 2003, 42:91-97). In the present study, cDNA microarray analyses were performed with mouse cDNA chips (~7400 cDNAs) to identify similarity and difference in gene expression profiles between each class with eight test substances including two genotoxic carcinogen (1,2-dibromoethane and glycidol), and genotoxic non-carcinogen (8-hydroxyquinolineand emodin), two non-genotoxic carcinogen (methyl carbamate and o-nitrotoluene), two non-genotoxic non-carcinogen(o-mannitol and 1,2-dichlorobenzene). Cells were exposed for 24 h to nontoxic concentrations for four non-genotoxic substances or genotoxicity-inducing concentrations for four genotoxic substances. The results from the quadruplicate hybridizations were averaged. SAM was performed for identifying a set of genes for 4 classes with significant expression changes. Twelve genes including unknown genes were identified whose expression was consistently altered by the two genotoxic non-carcinogen, 8-hydroxyduinoline and emodin. Four genes were consistently down-regulated and eight genes were up-regulated more than 2-fold. Also, four genes were consistently regulated by non-genotoxic carcinogen, methyl carbamate and o-nitrotoluene. One gene was identified whose expression was consistently up-regulated by the four genotoxic chemicals. Real-time RT-PCR was utilized to attempt confirmation of the microarray results for selected genes showing significant changes in the microarray analysis. Among the genes consistently regulated by genotoxic non-carcinogen, 8-hydroxyquinoline and emodin, RT-PCR results for one of four down-regulated genes and six of eight up-regulated genes were relatively consistent with

the array results. The RT-PCR results also confirmed the microarray for two genes regulated by non-genotoxic carcinogen, methyl carbamate and o-nitrotoluene. In order to identify groups with a similar pattern of expression, the genes showing more than 2-fold change in expression level by at least one chemical were analyzed with hierarchical clustering after category assignment of each gene according to its main cellular function. The difference between genotoxic and non-genotoxic substances was apparent in the category of cell cycle, response to stress, and immune response. However, the clustering specific to four carcinogenic substances was not detected in any functional categories. Taken together, these results suggest that gene expression profiling can provide valuable information in evaluation of potential genotoxicity but may have limitations in predicting carcinogenicity.

Keyword : cDNA array, genotoxicity, carcinogenicity, gene expression, real-time PCR