【P-1】

cDNA Microarray gene expression profiling of hydroxyurea, paclitaxel and p-anisidine that are genotoxic compounds with differing tumorigenicity results

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The potential application of toxicogenomics to predictive toxicology has been discussed widely, but the utility of the approach remains largely unproven. Using cDNA microarrays, we have compared the gene expression profiles produced in mouse lymphoma cells by three genotoxic compounds, hydroxyurea (a carcino- gen), p-anisidine (a noncarcinogen) and paclitaxel (carcinogenicity unknown). To minimize the effect of biological variability and technological limitations, quadruplicate observations were made for each compound, and a subset of genes yielding reproducible induction/repression was selected for comparison. A method was applied to attach normalized expression data to genes with a low false- discovery rate (< 0.1) to yield more confidence regarding differential expression. This analysis identified genotoxicity-specific gene ex- pression. Seven genes were consistently up-regulated and twelve down-regulated more than 2-fold by the three genotoxic compounds. Using additional genes, the expression pattern in- duced by the genotoxic non- carcinogen, p-anisidine, was readily distinguished from that associated with the genotoxic carcinogen, hydroxyurea. Comparison of paclitaxel-induced expression data to data of p-anisidine and hydroxyurea, suggested that paclitaxel is a genotoxic non-

carcinogen. With further supporting evidence it may be possible to perform large-scale monitoring of gene expression during drug and chemical development that can provide an early warning of potential toxicological responses.