Application of an integrated bioinformatics system for pathway-based analysis of toxicity data

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The ebTrack system is being developed as an integrated bioinformatics system for toxicological research and consistent analysis of environmental and toxicological data from diverse sources. It is a modular “multi-tool” platform based on enhancements to US FDA’s ArrayTrack system. Enhancements include additional modules for pathway-based analysis of gene expression data; linkages to external systems for analysis of toxicity pathways; and modules for the analysis of proteomic and metabolomic/metabonomic data. An application of ebTrack is presented focusing on pathway analysis of gene expression after exposure to sulfur mustard (HD, SM), a chemical warfare agent. In the first phase [Gerecke et al., 2009; Toxicology and Applied Pharmacology 234 (2): 156-165], ebTrack was applied to study the progression of SM-induced blistering through differential pathway analysis of the time course data that spanned time periods up to 172 hours. Pathway analysis employing the KEGG library as well as Ingenuity Pathway Analysis (IPA) indicated that cytokine-cytokine receptor interaction, cell adhesion molecules (CAMs), and hematopoietic cell lineage are common pathways affected at different time points. Gene ontology analysis identified the most significantly altered biological processes as the immune response, inflammatory response, and chemotaxis; these findings are consistent with other reported results for shorter time periods. A second phase of analysis, that is reported here, focuses on additional microarray experiments that were conducted to assess the impact of different inhibitors (MMP-2/MMP-9 inhibitor and ilomastat) on the response to SM exposure. In case of MMP-2/MM-9 inhibitor pre-treatment, subtle, but clearly identifiable differences in gene expression were noted, whereas substantial differences were noted in the case of ilomastat pre-treatment. Furthermore, significant variability in gene expression profiles were noted in different mice that are of same sex, age, and body weight. Ongoing analysis focuses on characterizing inter-individual variability in time-course profiles of pathway activities in the presence of different candidate countermeasures.

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