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Pharmacology 2019: Toxicogenomics in the Evolution of Toxicology: A Review Article- Fang Liu, National Center for Toxicological Research

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New molecular technologies have promoted the rapid development of toxicogenomics, which aims at understanding the response of the entire genome of an organism to toxicants/toxins. The primary goals of toxicogenomics are to understand the relationship between environmental stress and human disease susceptibility; to explore the molecular mechanisms of toxicants/toxins, and to identify biomarkers for predicting the onset of toxicity. It is important to note that not all changes in gene expression can be explained as responses to a toxicant/toxin; altered gene expressions can result from homeostatic adjustments and other mechanisms in biological settings. Additionally, the use of different platforms and different analysis approaches also impact data interpretation. Thus, it is a challenge to identify accurately the real changes and minimize false positive and false negative results. The microarray is an efficient tool for examining the effects of toxicants/toxins at the transcription level; unfortunately, mRNA levels do not always parallel protein levels and protein function. Post-translational modifications of protein can change protein function, which is not necessarily reflected at the mRNA level. In addition, there are toxicants/toxins whose toxicities are due to their protein binding properties; genes may not be the direct targets. Thus, simple investigations of gene expression may miss certain important information. The emergence of proteomics offers a way to analyze protein sequence, structure, and modifications, providing more functional understandings of toxic effects. It is viewed as a complementary approach to genomics, and understanding the relationship between mRNA and protein may guide the identification of more accurate, sensitive, and specific biomarkers. Alterations of mRNA and protein will result in changes of metabolite levels, but neither the genomic nor the proteomic approach can indicate what those changes are. Metabonomics, combining the application of analytical technologies, such as Nuclear Magnetic Resonance (NMR), with statistics, quantitatively measures the changes of endogenous metabolites in tissues and biofluids. Metabolites are the endpoints of the response an organism makes to a stimulus. Metabonomic measurements directly reflect the metabolism and physiology of an organism after toxicant/toxin exposure. Genomics, proteomics, and metabonomics have shown the ability to identify biomarkers and provide information for toxic mechanism elucidation at the molecular level. It is anticipated that the integration of these “omics” methods will work in concert, or even synergistically, to provide a better understanding of toxic responses. More in-depth integration will rely on the development of toxicogenomics data repositories and more advanced technologies, such as next-generation sequencing.

Studying alterations in mRNA, proteins, and metabolites are critical in identifying molecular signatures, traditional methods, such as molecular biological, biochemical, and histological methods, are still indispensible for studying and verifying the changes of the molecules.

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