

Toxicogenomics in the Evolution of Toxicology

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The Advent and Development of Toxicogenomics

Advances in 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 [1].

Toxicogenomics is defined as a combination of conventional toxicology with high-throughput technology. The term toxicogenomics was popularized in the literature in the late 1990s [2], when microarray technology emerged to display the capability of simultaneously monitoring the expression of thousands of genes. In this aspect, it is also referred as “transcriptomics”. Toxicogenomics extended its scope to include metabolomics and proteomics when efficient detection methods for proteins and metabolites arose through high-throughput techniques. The use of the methods of “omics” offers opportunities of discovering biomarkers, revealing pathways, and learning how organisms respond to toxicant/toxin challenges. Since then, more than a decade of research has witnessed the evolution of toxicogenomics from isolated toxicant/toxin-induced gene-expression studies to full-scale studies with the integration of several “omics” strategies in toxicology [3-8].

Transcriptomics in Toxicogenomic Study

Microarray technology has proved to be a powerful tool in toxicological studies because it provides a platform for studying genome-wide gene expression patterns after toxicant/toxin exposure, which usually causes alterations of gene expression. It is generally believed that changes in gene expression are sensitive indicators of toxicity and thus are expected to be useful biomarkers of that toxicity. Moreover, gene expression profiles obtained from microarray analysis can improve our understanding the mechanisms of toxicity. For instance, Shi et al. [9] investigated the gene expression profile of ketamine (an *N*-methyl-D-aspartate (NMDA) receptor antagonist)-treated developing rat brain. They observed a significantly increased expression of the NMDA receptor in ketamine-treated brain. In addition, a series of studies from the same group investigated the neurotoxic effects of ketamine on developing brain. Higher expression of the NMDA receptor has been observed consistently and is closely related to the toxic effects of ketamine [10-12]. If ketamine's effect on the NMDA receptor during early development can be verified for other NMDA receptor antagonists, this common change in gene expression can indicate a unique mechanism by which NMDA receptor antagonists cause damage to the developing brain.

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 Quality Control (MAQC) project, a community-wide effort led by the U.S. Food and Drug Administration, was established with the goals of assessing the performance of microarrays, searching for ways to minimize the poor concordance of gene expression data generated by various platforms and laboratories, and reaching consensus on methods of data analysis [13]. The findings from MAQC project demonstrated that reproducible measurement of differentially expressed genes across different platforms and laboratories for the same toxicants could be achieved, if microarray experiments were performed with strict quality control and adequate criteria are applied for data analysis [14].

Proteomics and Metabonomics in Toxicogenomic Study

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 [8,15].

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 [16]. This is a promising and feasible method since body fluids, such as urine,

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Received July 30, 2012; Accepted August 24, 2012; Published August 26, 2012

Citation: Liu F, Guo L (2012) Toxicogenomics in the Evolution of Toxicology. J Pharmacogenom Pharmacoproteomics 3: e123. doi:10.4172/2153-0645.1000e123

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blood, or cerebrospinal fluids are more readily available from human subjects. Furthermore, the continuous availability of these samples during toxicant/toxin exposure or during toxicant/toxin elimination makes it possible to search for biomarkers under a variety of treatment conditions [17].

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.

It is worth mentioning that it is critical for scientists to choose carefully an appropriate platform and perform such high-throughput experiments with strict quality control. Alternative methods should be always considered to validate the results generated from “omics” before drawing conclusions. For example, changes of RNA or microRNA expression detected by a high-throughput technology should be validated using different gene expression platforms such as “TaqMan”. Finally, although “omics” approaches for 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 indispensable for studying and verifying the changes of the molecules.

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