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*Review*

# Toxicogenomics

**S. Amala**

Department of Biotechnology and Bioinformatics, Dhanalakshmi Srinivasan, College of Arts and Science for Women, Perambalur-621212, Tamil Nadu, India. E-mail:amala.santhanam@gmail.com.

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**The field of toxicology is defined as the study of stressors and their adverse effects. One discipline should deals with hazard identification, mechanistic toxicology, and risk assessment. Thus emerge a new field called toxicogenomics. Toxicogenomics is a rapidly developing discipline that promises to aid scientists in understanding the molecular and cellular effects of chemicals in biological systems. This is a comparatively new field of biological inquiry now providing insights into the toxic effects of chemicals on biological systems and helping investigators to predict risks associated with exposure to these agents. This field encompasses global assessment of biological effects using technologies such as DNA micro arrays or high throughput NMR and protein expression analysis.**

**Key words:** Genomics, toxicogenomics, toxicology.

## INTRODUCTION

The rapid evolution of genome-based technologies has greatly accelerated the application of gene expression profiling in toxicology studies. These technological advances have led to the development of the field of toxicogenomics, which proposes to apply mRNA expression technologies to study effects of hazards in biological sys-tems. Application of genomics to toxicology, toxicogeno-mics, yield a number of substantial dividends, including assisting predevelopment toxicology by facilitating more rapid screens for compound toxicity, allowing compound selection decisions to be based on safety as well as efficacy, the provision of new research leads; a more detailed appreciation of molecular mecha-nisms of toxicity, and an enhanced ability to extrapolate accurately between experimental animals and humans in the context of risk assessment.

Toxicogenomics combines traditional toxicology using appropriate pharmacological and toxicological models with global “omics” technologies to provide a comprehensive view of the functioning of the genetic and biochemical machinery in organisms under stress. Applications of these technologies help in predicting the potential toxicity of a drug or chemical be-fore functional damages are recognized, in classification of toxicants, and in screening human susceptibility to diseases, drugs or environmental hazards.

## WHAT IS TOXICOGENOMICS?

Toxicogenomics is a field of science that deals with the collection, interpretation, and storage of information about gene and protein activity within particular cell or tissue of an organism in response to toxic substances. Toxicogenomics combines toxicology with genomics or other high throughput molecular profiling technologies such as transcriptomics, proteomics and metabolomics. Toxicogenomics endeavors to elucidate molecular mechanisms evolved in the expression of toxicity, and to derive molecular expression patterns that predict toxicity or the genetic susceptibility to it. Toxicogenomics is a rapidly developing discipline that promises to aid scien-tists in understanding the molecular and cellular effects of chemicals in biological systems. This field encompasses global assessment of biological effects using technologies such as DNA micro arrays or high throughput NMR and protein expression analysis.

Toxicogenomics represents the merging of toxicology with technologies that have been developed, together with bioinformatics, to identify and quantify global gene expression changes. It represents a new paradigm in drug development and risk assessment, which promises to generate a wealth of information towards an increased understanding of the molecular mechanisms that lead to

drug toxicity and efficacy, and of DNA polymorphisms responsible for individual susceptibility to toxicity. Gene expression profiling, through the use of DNA micro array and proteomic technologies will aid in establishing links between expression profiles, mode of action and traditional toxic endpoints. Such patterns of gene expression, or 'molecular fingerprints' could be used as diagnostic or predictive markers of exposure that is characteristic of a specific mechanism of induction of that toxic or efficacious effect. It is anticipated that toxicogenomics will be increasingly integrated into all phases of the drug development process particularly in mechanistic and predictive toxicology, and biomarker discovery.

## DEFINITION OF TOXICOGENOMICS

United States environmental protection agency stating that "the term "genomics" encompasses a broader scope of scientific inquiry and associated technologies than when genomics was initially considered. A genome is the sum total of all an individual organism's genes. Thus, genomics is the study of all the genes of a cell, or tissue, at the DNA (genotype), mRNA (transcriptome), or protein (proteome) levels. Genomics methodologies are expected to provide valuable insights for evaluating how environmental stressors affect cellular/tissue function and how changes in gene expression may relate to adverse effects. However, the relationships between changes in gene expression and adverse effects are unclear at this time and may likely be difficult to elucidate.

In pharmaceutical research, toxicogenomics is more narrowly defined as the study of the structure and function of the genome as it responds to adverse xenobiotic exposure. It is the toxicological sub discipline of pharmacogenomics, which is broadly defined as the study of inter-individual variations in whole-genome or candidate gene single-nucleotide polymorphism maps, haplotype markers, and alterations in gene expression that might correlate with drug responses.

## TECHNOLOGIES IN TOXICOGENOMICS

### Gene expression profiling

Gene expression changes are associated with signal pathway. Activation can provide compound-specific information on the pharmacological or toxicological effects of a chemical. An advantage of this traditional molecular technique is that it definitively shows the expression level of all transcripts for a particular gene.

Alternate technologies, including DNA microarrays, can measure the expression of tens of thousands of genes in an equivalent amount of time.

There are two basic types of micro arrays used in gene expression analyses:

#### *Oligonucleotide-based arrays and cDNA arrays*

For example, one can compare tissue extracted from toxicant treated organism versus that of vehicle exposed animals. In addition, other scenarios may include the analysis of healthy versus diseased tissue or susceptible versus resistant tissue. One can combine micro arrays with quantitative polymerase chain reaction (QPCR) or Taqman and other technologies in development to monitor the expression of hundreds of genes in a high throughput fashion.

#### *Protein expression*

Gene expression alone is not adequate to serve the understanding of toxicant action and the disease outcomes they induce. Abnormalities in protein production or function are expected in response to toxicant exposure and the onset of disease states. To understand the complete mechanism of toxicant action, it is necessary to identify the protein alterations associated with that exposure and to understand how these changes affect protein/cellular function. Unlike classical genomic approaches that discover genes related to toxicant induced disease, proteomics can aid to characterize the disease process directly by capturing proteins that participate in the disease. The lack of a direct functional correlation between gene transcripts and their corresponding proteins necessitates the use of proteomics as a tool in toxicology. Proteomics, under the umbrella of toxicogenomics, involves the comprehensive functional annotation and validation of proteins in response to toxicant exposure. Understanding the functional characteristics of proteins and their activity requires a determination of cellular localization and quantization, tissue distribution, post-translational modification state, domain modules and their effect on protein interactions, protein complexes, ligand binding sites and structural representation. Currently, the most commonly used technologies for proteomics research are 2-dimensional (2D) gel electrophoresis for protein separation followed by mass spectrometry analysis of proteins of interest. Matrix-assisted laser desorption mass spectrometry (MALDI-MS) has become a widely used method for determination of biomolecules including peptides.

### Metabolite analysis by NMR

Genomic and proteomic methods do not offer the information needed to gain understanding of the resulting output function in a living system. Neither approach addresses the dynamic metabolic status of the whole animal. The metabonomic approach is based on the premise that toxicant-induced pathological or physiological alterations result in changes in relative concentrations of endogenous biochemical. Metabolites in body fluids such

as urine, blood, or cerebrospinal fluid (CSF), are in dynamic equilibrium with those inside cells and tissues, thus toxicant-induced cellular abnormalities in tissues should be reflected in altered biofluid compositions.

## TOXICOGENOMIC COMPONENTS

### Comparative/predictive toxicogenomics

Comparative genomic, proteomic, or metabonomic studies measure the number and types of genes, protein, and metabolites, respectively, that is present in normal and toxicant-exposed cells, tissues, or biofluids. This approach is useful in defining the composition of the assayed samples in terms of genetic, proteomic or metabolic variables. Thus a biological sample derived from toxicant, or sham treated animals can be regarded as an n-dimensional vector in gene expression space with genes as variables along each dimension.

The possibility that a specific group or class of compounds (grouped by toxic endpoint, mechanism, structure, target organ etc.) may induce signature patterns of gene expression changes is the basis for the application of toxicogenomics to predictive toxicology. The use of these technologies to analyze genome-wide changes in mRNA expression following treatment of *in vitro* systems with known reference toxicants may permit the identification of diagnostic gene expression patterns. Pattern recognition allows the design and construction of mini-arrays, customized to detect specific toxicity endpoints or pathways.

### Functional toxicogenomics

Functional toxicogenomics is the study of genes and proteins biological activities in the context of compound effects on an organism. Gene and protein expression profiles are analyzed for information that might provide insight into specific mechanistic pathways. Mechanistic inference is complex when the sequence of events following toxicant exposure is viewed in both dose and time space. Gene and protein expression patterns can indeed be highly dependent on the toxicant concentrations furnished at the assessed tissue and the time of exposure to the agent. Expression patterns are only a snapshot in time and dose space. Thus, a comprehensive understanding of potential mechanisms of action of a compound requires establishing patterns at various combinations of time and dose. Studies that target temporal expression of specific genes and protein in response to toxicant exposure will lead to a better under-standing of the sequence of events in complex regulatory networks. An area of study which is of great interest to toxicologists is the mechanistic understanding of toxicant induced pathological endpoints. The premise that perturbations in gene, protein, or metabolite levels are reflective of adverse phenotypic effects of toxicants offers an opportunity to phenotypically anchor these perturbations.

This is quite challenging due to the fact that phenotypic effects often vary in the time-dose space of the studied agent and may have regional variations in the tissue. Furthermore, very few compounds exist that result in only one phenotypic alteration at a given coordinate in dose and time. Thus, objective assignment of measured variables to multiple phenotypic events is not possible under these circumstances.

## APPLICATIONS OF TOXICOGENOMICS

### Toxicogenomics in drug safety

New drugs are screened for adverse reactions using a laborious, costly process and still some promising therapeutics is withdrawn from the marketplace because of unforeseen human toxicity. Novel higher throughput methods in toxicology need to be developed. These new approaches should provide more insight into potential human toxicity than current methods. Toxicogenomics, the examination of changes in gene expression following exposure to a toxicant, offers the potential to identify a human toxicant earlier in drug development and to detect human-specific toxicants that cause no adverse reaction in rats.

### To understand the mechanisms of drug-induced hepatotoxicity during drug discovery and development

Hepatotoxicity is a common cause of failure in drug discovery and development and is also frequently the source of adverse drug reactions. Therefore, a better prediction, characterization and understanding of drug-induced hepatotoxicity could result in safer drugs and a more efficient drug discovery and development process. Toxicogenomics represents an attractive approach to predict toxicity and to gain a mechanistic understanding of toxic changes.

### Ecotoxicogenomics

Rapid progress in the field of genomics (the study of how an individual's entire genetic make-up, the genome, translates into biological functions) is beginning to provide tools that may assist our understanding of how chemicals can impact on human and ecosystem health. Given the parallel implications for ecological (environmental) risk assessment, a term ‘ecotoxicoge-nomics’ is there to describe the integration of genomics (transcriptomics, proteomics and metabolomics) into ecotoxicology. Ecotoxicogenomics is defined as the study of gene and protein expression in non-target organisms that is important

in responses to environmental toxicant exposures.

The potential of ecotoxicogenomic tools in ecological risk assessment seems great. Many phenomenological approaches that are useful for identifying chemicals of potential concern provide little understanding of the mechanism of chemical toxicity. Without this understanding, it will be difficult to address some of the key challenges that currently face aquatic ecotoxicology. Ecotoxicogenomic tools may provide us with a better mechanistic understanding of aquatic ecotoxico-logy (Snape et al., 2004).

In endocrine disruption Toxicogenomics can be expected to be a useful method for detecting the carcino-genic potential of endocrine active substances (EASs) in the short term with the generation of understanding of mode-of-action and mechanisms when a reliable database with information about proteomics and informatics is established. At present, there are no concrete epidemiological data supporting any exogenous EAS contribution to hormone-related organ carcinogene-sis in humans. However, with the establishment of appropriate animal models and analysis of genomic-scale gene expression, risk identification and evaluation should be facilitated within a relatively short period, and this approach eventually promises to contribute a great deal of risk management regarding EASs (Tomoyuki and Makoto, 2003).

### In assessment of immunotoxicity

Microarray analysis is used for simultaneous measurement of expression of thousands of genes in a given sample and as such extends and deepens our understanding of biological processes. Application of the technique in toxicology is referred to as toxicogenomics. The assessment of immunotoxicity by gene expression profiling show that micro array analysis is able to detect known and novel effects of a wide range of immunomodulating agents. Besides the elucidation of mechanisms of action, toxicogenomics is also applied to predict consequences of exposing biological systems to toxic agents. Successful attempts to classify compounds using signature gene expression profiles have been reported. The application of toxicogenomics in evaluation of immunotoxicity contributes to the understanding of immunotoxic processes and the development of *in vitro* screening assays, though, and is therefore expected to be of value for mechanistic insight into immunotoxicity and hazard identification of existing and novel com-pounds (Baken et al., 2007).

## TOXICOGENOMICS DATABASE AND RESOURCES

Toxicogenomics studies are generally built on standard toxicology studies generating biological end point data, and as such, one goal of toxicogenomics is to detect relationships between changes in gene expression and in those biological parameters. These challenges are best addressed through data collection into a well-designed toxicogenomics database (Mattes et al., 2004).

### The chemical effects in biological systems (CEBS) knowledge base

The CEBS knowledge base (http://www.niehs.nih.gov/nct/cebs.htm) is under development by the NIEHS NCT as a public toxicogenomics information resource combining data sets from tran-scri-ptomics, proteomics, metabonomics, and conventional toxicology with pathway and network information relevant to environmental toxicology and human disease. The overall goal of CEBS is to support hypothesis-driven and discovery research in environmental toxicology and the research needs of risk assessment. Specific objectives are a) to compare toxico-genomic effects of chemicals/stressors across species yielding signatures of altered molecular expression; b) to phenotypically anchor these changes with conventional toxicology data classifying biological effects as well as disease phenotypes; and c) to delineate global changes as adaptive, pharmacologic, or toxic outcomes defining early biomarkers, the sequence of key events, and mechanisms of toxicant action. CEBS is designed to meet the information needs of systems toxicology and involves study of chemical or stressor perturbations, monitoring changes in molecular expression, and iteratively integrating biological response data to describe the functioning organism.

### Comparative toxicogenomics database (CTD)

The NIEHS DERT supports an international public database devoted primarily to comparative toxicogenomics in aquatic and mammalian species, the CTD (http://www.mdibl.org/). The Mount Desert Island Biological Laboratory is developing CTD as a community-supported genomic resource devoted to genes of human toxicological significance. CTD will be the first publicly available database to a) provide annotated associations between genes, references, and toxic agents; b) include nucleotide and protein sequences from diverse species with a focus on aquatic and mammalian organisms; c) offer a range of analytical tools for customized compara-tive studies; and d) provide information to investigators on available molecular reagents. The primary goals of CTD are to advance the understanding of the effects of environmental chemicals on human health.

### DbZach

The Molecular and Genomic Toxicology Laboratory, Michigan State University (East Lansing, MI) has developed the dbZach System (http://dbzach.fst.msu.edu/), a multifacteted toxicogenomics

bioinformatics infrastructure. The goal of the dbZach System is to provide a) facilities for the modeling of toxicogenomics data; b) a centralized source of biological knowledge to facilitate data mining and allow full knowledge-based understanding of the toxicological mechanisms; and c) an environment for bioinformatics algorithmic and analysis tools development. DbZach, designed in a modular structure to handle multispecies array-based toxicogen-omics information, is the core database implemented in Oracle.

## Array track

The NCTR (http://www.fda.gov/nctr/science/centers/toxicoinformatics/tools.htm) is developing TIS to integrate genomics, proteomics, and metabonomics data with conventional *in vivo* and *in vitro* toxicology data. TIS is designed to meet the challenge of data management, analysis, and inter-pretation through the integration of toxicogenomics data, gene function, and pathways to enable hypothesis generation.

## EDGE

The EDGE database (http://genome.oncology.wisc.edu/edge2/edge.php) was developed at the McArdle Laboratory for Cancer Research, University of Wisconsin (Madison, WI) as a resource for toxicology-related gene expression information. It is based on experiments conducted using custom cDNA micro arrays that include unique ESTs identified as regulated under conditions of toxicity.

## Public toxicogenomics projects

- Chemical Effects in Biological Systems (CEBS) - Project hosted by the National Institute of Environmental Health Sciences (NIEHS) is building a knowledgebase of toxicology studies including study design, clinical pathology, and histopathology and toxicogenomics data.
- InnoMed PredTox for assessing the value of combining results from omics technologies together with the results from more conventional toxicology methods in more informed decision making in preclinical safety evaluation.
- Predictive Safety Testing Consortium aimed at identifying and clinically qualifying safety biomarkers for regulatory use as part of the FDA's Critical Path Initiative
- ToxCast program for Predicting Hazard, Characterizing Toxicity Pathways, and Prioritizing the Toxicity Testing of Environmental Chemicals at the United States Environmental Protection Agency

## Conclusion

Toxicogenomics is an information- and informatics-intensive field. An important aspect of toxicogenomics research is the development and application of bioinformatics tools and databases in order to facilitate the analysis, mining, visualizing and sharing of the vast amount of biological information being generated in this field. This rapidly growing research area will have a large impact on many other scientific and medical disciplines, including systems biology, as researchers strive to generate complete descriptions of how components of biological systems work together and across organisms to respond to specific stresses, drugs, or toxicants. By establishing associations between the unique genetic makeup of individuals and their responsiveness to specific drugs, we expect to discover better therapies and improve prospects for providing individuals with personalized medicine. And by combining this knowledge with technology for high-throughput screening of candidate drugs early on, we also expect to streamline and enhance the process of drug discovery

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