

**TOXICOGENOMICS AND ITS APPLICATIONS****¹Dr. Sanjay B. Nandedkar and ²Dr. Yadunath C. Waykole**

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ABSTRACT

Toxicogenomics is a new scientific discipline describing the combination of a systematic and comprehensive study of gene expression in response to a nutrient/drug interaction in a biological system. High expectations are set on this new discipline to fundamentally change the process of drug development, especially in toxicity assessment. The use of expression profiling technologies to mechanistic and predictive toxicology, and biomarker discovery, will enable us to ask detailed questions and generate hypotheses. Ideally, such toxicology research will improve the quality of drug candidates and reduce the overall costs due to attrition during drug development. The integration of data from different toxicogenomic technologies has been explored to some extent but these approaches need to be integrated fully.

KEYWORDS: Toxicogenomics, genomics, toxicology.**INTRODUCTION**

Toxicology has classically been viewed as the science of poisons. In the modern world, however it has evolved into a composite of related, but distinct, disciplines that together seek to understand how chemicals of all kinds that both man made and natural that affect human health and environment. So toxicogenomics can be defined simply as a combination of toxicology and genomics. Toxic is any substance,

artificial or natural, or any substance that produces a harmful effect on living beings in contact with them & the study of toxic called toxicology. 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.

Toxicogenomics is define as, a field of sciences 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 the toxic substances.

Application of genomics to toxicology that mean toxicogenomics, provide 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 mechanisms of toxicity, and an enhanced ability to extrapolate accurately between experimental animals and humans in the context of risk assessment.

Risk assessment, it is the process that scientists and officials use to estimate the increased risk of health problems in humans and animals expressed to difference amounts of toxic substances. It includes-

- 1) Hazard identification – What problems are caused by toxicant?
- 2) Exposure assessment – How many people are exposed & how much of the toxicant do they receive.
- 3) Dose response - The health problems at different dose of toxicant.
- 4) Risk characterization – The extra risk of health problem in exposed population.

The key questions that should be addressed for improved risk assessment such as,

- 1) Which animal's models are the best predictors for humans?
- 2) What are the overlaps in human and animal's ranges of sensitivity?
- 3) How much variability exists in human populations?

The answers of these questions are obtained by toxicogenomics.

TECHNOLOGIES IN TOXICOGENOMICS

Gene expression profiling(GEP)

Indeed this is a currently dominant technique used in toxicogenomics studies. Gene expression changes are associated with signal pathway. It can provide compound-specific information on the pharmacological or toxicological effects of a chemical. An advantage of this molecular technique is that it definitively shows the expression level of all transcripts for a particular gene. Alternate technologies, including DNA microarrays -A DNA microarray is a collection of microscopic DNA spots attached to a solid surface. Scientists use DNA microarrays to measure the expression levels of large numbers of genes simultaneously or to genotype multiple regions of a genome.

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. Also include the analysis of healthy versus diseased tissue or susceptible versus resistant tissue.

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. The lack of a direct functional correlation between gene transcripts and their corresponding proteins necessitates the use of proteomics as a tool in toxicology. 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 Nuclear Magnetic Resonance Spectroscopy (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 metabolomics 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 blood, urine,

orcerebrospinal fluid (CSF), are in dynamic equilibrium with those inside cells and tissues, thus toxicant-induced cellular abnormalities in tissues should be reflected in altered bio fluid compositions. An advantage of measuring changes in body fluids is that these samples are much more readily available from human subjects. High resolution NMR spectroscopy has been used in a high-throughput fashion to simultaneously detect many cellular biochemicals in urine, bile, blood plasma, milk, saliva, sweat, gastric juice, seminal, amniotic, synovial fluids and cerebrospinal fluids.

TOXICOGENOMICCOMPONENTS

There are two main applications for a toxicogenomic approach, comparative/predictive and functional.

Comparative/Predictive Toxicogenomics

Comparative genomic, proteomic, or metabolomics studies measure the number and types of genes, protein, and metabolites respectively that are present in normal and toxicant-exposed cells, tissues, or bio-fluids. 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 same analogy can be applied for protein expression or NMR analysis data thereby providing n- dimensional fingerprints or profiles of the biological sample under investigation.

The data profiles reflect the pharmacological or toxicological effects, such as disease outcome, of the drug or toxicant being utilized. The underlying goal is that a sample from an animal exposed to an unknown chemical, or displaying a certain pathological endpoint, can then be compared to a database of profiles corresponding to exposure conditions with well-characterized chemicals, or to well define pathological effects, in order to predict some properties regarding the studied sample. These predictions, divided into two major categories, first is classification of samples based on the class of compound to which animals were exposed to, and another is classification of samples based on the histopathology and clinical chemistry that the treated animals displayed.

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

analysed 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.

These analyses might suggest relationships in the expression of some genes or proteins depending on the concerted modulation of these variables.

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. It is significant to mention that, stand-alone, gene and protein expression, or metabolite fluctuation analyses are not expected to produce decisive inferences on the role of genes or proteins in certain pathways or regulatory networks.

APPLICATION OF TOXICOGENOMICS

1) 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. 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.

2) In hepatotoxicity

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, 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.

3) In ecotoxicogenomics

In many ways, if scientific and regulatory efforts in the 20th century have sought to establish which chemicals cause damage to ecosystems, then the challenge in ecotoxicology for the 21st century is to understand the mechanisms of toxicity to different wildlife species. Ecotoxicogenomics is defined as the study of gene and protein expression in non-target organisms that is important in responses to environmental toxicant exposures. (Integration of genomics into ecotoxicology) This approach is of critical importance to identify major and minor pathways of toxic action and decipher what drives the interaction between environment and the organism (and vice versa). By doing so, the molecular biological approach will undoubtedly provide a long-lasting platform for legislative and administrative purposes. Ecotoxicogenomics tools may provide us with a better mechanistic understanding of aquatic ecotoxicology. For ecotoxicogenomics to fulfil its potential, collaborative efforts are necessary through the parallel use of model microorganisms together with aquatic and terrestrial plants, animals and microorganisms.

4) In immunotoxicity

The immune system is a complex set of cellular, chemical, and soluble protein component that interact with each other with sequential, regulated manner to protect the body against foreign substance. The deleterious effect of xenobiotic on the immune system, immunotoxicity can be result as

- A) Immunosuppression- it can lead to reduced resistance against infectious diseases or to increased susceptibility non-genotoxic carcinogens and development of cancer.
- B) Immunostimulation- elicitation of an immune response –such as Hypersensitivity & Autoimmune disease.

Assessment of immunotoxicity by gene expression profiling presented and discussed here, show that microarray analysis is able to detect known and novel effects of a wide range of immunomodulating agents. The application of toxicogenomics in evaluation of immunotoxicity is thus not yet without challenges. It already contributes to the understanding of immunotoxicity 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 compounds.

5) In reproductive and developmental toxicology

Reproductive toxicology demonstrates the effects of chemicals on the reproductive and neuroendocrine systems. Application of genomic technology to study the reproductive and developmental toxicology overcomes the limitations of conventional or classical toxicological methods. Current developments in genomics and new developments in genetic technologies, such as DNA microarrays, have encouraged the transition of nutrition and drug research from epidemiology and physiology to molecular biology and genetics.

TOXICOGENOMICS: SCOPE

Toxicogenomics has three principal goals

- 1) To understand the relationship between environmental stress and human disease susceptibility
- 2) To identify useful BIOMARKERS of disease and exposure to toxic substances
- 3) To elucidate the molecular mechanisms of toxicity.

A typical toxicogenomics study might involve an animal experiment with three treatment groups: high dose and low dose treatment groups and a vehicle control group that has received only the solvent used with the test agent. These groups will be observed at two or three points in time, with three to five animal subjects per group. In this respect, a toxicogenomics investigation resembles a simple, acute-toxicity study. The two approaches differ in the scope of the response they aim to detect, and in the methods used. The highest-dose regimen is intended to produce an overtly toxic response that can be detected in a toxicogenomics study.

LIMITATIONS

- 1) Difficulty in analysis of high density data.
- 2) Difficulty in integration of data obtained by different technologies.
- 3) Difficulty in linking “omics” data to specific adverse effects.
- 4) Difficulty in translation statistical assessments into biological understanding.
- 5) Limitations of incomplete functional annotation of genome data bases.
- 6) Incomplete knowledge of functional pathways and networks, particularly trans-genome relationship.

CONCLUSION

The field of toxicogenomics is a sub discipline that combines genomics with toxicology, and the expression of thousands of genes simultaneously in response to chemical exposure to better understand the underlying mechanism of chemical toxicity. 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. However, toxicogenomic technologies are assuming an increasing role as adjuncts to, and extensions of, existing technologies for predictive toxicology. Toxicogenomics can provide molecular level information and tests that add to the “weight of the evidence” for or against the safety of specific environmental toxicants and drugs. Ultimately, toxicogenomic technologies are envisioned to be more sensitive and more informative than existing technologies and may supplant some approaches currently in use, or at least be a component of batteries that will replace certain tests.

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