TOXICOGENOMICS TECHNOLOGY FOR PREDICTIVE TOXICOLOGY AND SAFETY ASSESSMENT

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ABSTRACT

Background: To recognize and measure the worldwide changes in gene expression that are occurring in cells, new methods and technologies have been created as human genetics and genomics. Virtually all areas of biological study in the field of toxicology are being transformed by these new technologies, which are enabling researchers to improve their understanding of the function and control of genes at the systems level. **Objective:** The aim of toxicogenomics research is to uncover molecular patterns that can be utilized as biomarkers to anticipate toxicity or a person's vulnerability to it, as well as to clarify the molecular mechanisms underlying the expression of toxicity. There are many chemical compounds found in the environment with no toxicity data because the number of chemicals that can be analyzed by current toxicity testing techniques is restricted. Toxicogenomics, which study of the interaction between the genome, proteome, or metabolome and severe biological endpoints brought on by exposure to toxicants, offers a quick way to produce toxicity data for a lot of different substances. Additionally, toxicogenomic investigations can identify susceptibility and exposure biomarkers and provide a more accurate evaluation of the hazardous potential of an untested substance. To uncover and define the molecular processes that result in toxicity, toxicogenomics has evolved. **Conclusion:** This review focuses on recent studies in toxicogenomics and discusses the promises and future challenges in this field.

Keywords: *Toxicogenomics, Genomics, Proteomic, Metabonomic, Bioinformatics*.

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INTRODUCTION

While the climate emergency, the global biodiversity crisis, and the coronavirus disease (COVID-19) pandemic garner headlines, pollution and hazardous substances continue to be largely disregarded for their terrible effects on human health and environmental integrity ***(Piqueras and Vizenor, 2016)***.

However, each year at least 9 million premature fatalities result from pollution and harmful substances, which is twice as many deaths as the COVID-19 pandemic caused in its first 18 months. Diseases caused by pollution account for one in six fatalities worldwide, three times more than deaths from AIDS, malaria, and tuberculosis put together, and fifteen times more than deaths from all wars, homicides, and other acts of violence combined. With an estimated 7 million deaths each year, air pollution is the leading environmental cause of early deaths. Low- and middle-income countries bear the brunt of pollution-related illnesses, with nearly 92 percent of pollution-related deaths. Every year, over 750,000 workers lose their lives as a result of being exposed to hazardous materials at work, such as diesel exhaust, asbestos, particulate matter, and arsenic ***(Boyd and Orellana, 2022)***.

Environmental toxicity leads to neurodegenerative diseases (e.g Alzheimer's disease and Parkinson's disease) ***(Nabi and Tabassum, 2022)***, Chronic obstructive pulmonary disease (COPD), asthma, acute lower respiratory illness (ALRI), ischemic heart diseases, hepatotoxicity, nephrotoxicity, birth defects and cancer ***(Mitra et al., 2022)***.

By increasing the number of new chemicals that being produced every year, it is crucial to evaluate them for toxicity before placing them on the market. Rats and mice are typically used in the lifetime bioassay for this. However, this test has clearly developed

several problems over time, including the usage of several animals and the lengthy, expensive, and insensitive tests. In addition, there is considerable scientific doubt about the reliability of the assay, because there have been far too many instances of false positive results. Alternative techniques to anticipate chemicals' hazardous properties are therefore needed. In this regard, emerging technologies like toxicogenomics may help to enhance the existing test strategy ***(Kennedy, 2000)***.

It was anticipated that the development of new innovative technologies will revolutionize toxicological studies by enabling significant advancements in the comprehension and prediction of the toxicity. This will happen in conjunction with the recent dramatic increases in genomic knowledge ***(Kennedy, 2002)***. In classic toxicology, potential hazards from toxicant exposure were assessed using endpoints such as body weight changes, biochemical alterations, and histological findings. However, these findings didn`t reveal anything about how toxicity occurs ***(Waters and Fostel, 2004)***.

Toxic substances were anticipated to cause a wide range of complicated molecular perturbations, involving differential gene expression at the transcript and functional protein level, in a wide number of pathways, resulting in beneficial and/or harmful effects. These alterations in gene expression had the potential to reveal toxicity already at lower doses or at earlier time periods since they were frequently more sensitive and typical of the toxic response or process than used pathological endpoints ***(Guerreiro et al., 2003)***.

The transcriptional and translational activities of individual genes and even the entire genome are now possible because of technological advancements resulting from genomic research. Toxicogenomics is a new field of study that emerged from the application of genome-wide expression profiling technologies to toxicology, and it has the potential to provide a more thorough understanding the mechanisms of underlying pharmacology and toxicity than has previously been possible using classical toxicology methods **(Figure 1)** ***(O'Brien et al., 2012)***.

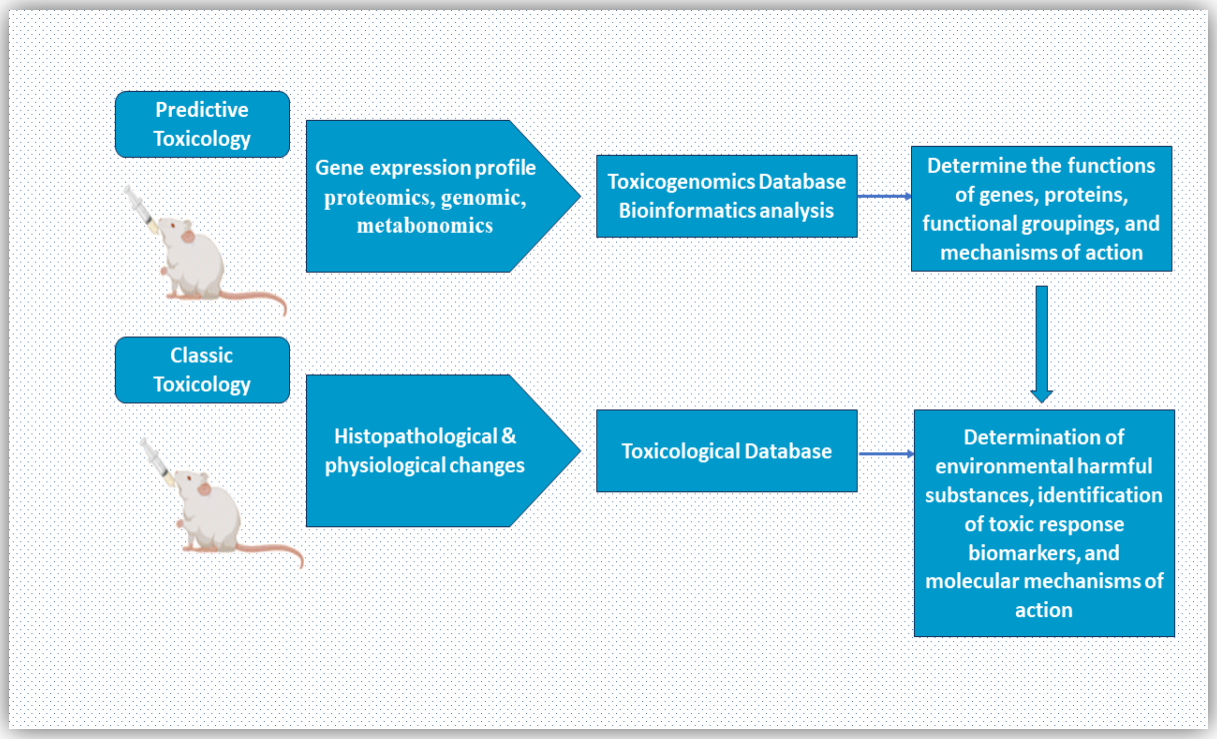

Figure (1): Toxicogenomics' applications and the advancement of predictive toxicology (Aristizábal et al., 2014).

THE AIM OF THE WORK

Toxogenomics study aims to clarify the molecular mechanisms underlying the expression of toxicity and identify molecular patterns that can be used as biomarkers to predict toxicity or an individual's susceptibility to it.

Definition of toxicogenomics

The scientific subject of toxicogenomics is concerned with gathering, analyzing, and storing data regarding gene and protein activity in specific cells or tissues of an organism in response to toxic substances. Genomic analysis and other high throughput molecular profiling methods, including as transcriptomics, proteomics, and metabonomics, are combined with toxicology to form toxicogenomics. The goal of toxicogenomics is to identify molecular expression patterns, or molecular biomarkers, that indicate a person's hereditary predisposition to toxicity or to clarify the molecular mechanisms that have developed in the manifestation of toxicity ***(Liu et al., 2019)***.

In fact, the use of genomic technologies in toxicology has led to an era in which genotypes and toxicant-induced changes in genome expression protein and metabolite patterns, can be used to identify hazards, track exposure to toxicants in individuals, monitor cellular responses to various doses, determine the mechanisms of action, and predict individual differences in sensitivity to toxicants ***(Aristizábal et al., 2014)***.

Because it provides information on the genotypic alterations in an individual who is exposed to exogenous agents, toxicogenomics has the advantage of helping people to understand the hazardous reaction to a chemical at a very early stage. To correlate and determine the phenotypic response that relates to changes in an individual's genotype, the data from various researches can be compared with toxicogenomic databases ***(Kolla et al, 2011)***.

Additionally, toxicogenomics not only examine genetic variation affects the pharmacokinetic and pharmacodynamic profiles of drugs, but they can also be used to look into how individuals differ in their susceptibility to the emergence of drug dependence and/or addiction. The analysis of the impacts of genetic variability on drug disposition, including absorption, distribution, metabolism, and secretion, is the area of toxicogenomics that forensic toxicologists are most interested in. It is well established that individual variances in response to several commonly abused drugs are caused by sequence variation within the genes encoding for a range of proteins ***(Kolla et al., 2011; Lappas and Lappas, 2021)***.

As opposed to conventional toxicological endpoints including morphological abnormalities, carcinogenicity, and reproductive toxicity, gene expression alterations detected by DNA microarrays can offer a more sensitive and distinctive marker of toxicity ***(Suter et al., 2004)***. Moreover, changed gene expression might take place immediately following exposure, whereas clinical toxicity manifestations may take days, months, or even years to develop ***(Perera and Herbstman, 2011)***. Based on their gene expression profiles, preliminary "proof-of-concept investigations had been successfully discovered and categorized toxicological pathways and dangerous substances" ***(Julie et al., 2015)***.

Regarding the amount of data generated by array technology, manual processing is not practical. To effectively process and analyze huge amounts of data and to make it easier to recognize patterns across different time points or dose levels, sophisticated data management are required. For this application, various academic and commercial software packages have been created. Spot quantitation, data storage and retrieval, and higher-level analysis is often included ***(Xia, 2017)***.

1.Analytical technologies of toxicogenomics

1.1. Transcriptomics:

Transcriptomics is the study of the transcriptome, which is the collection of all RNAs in a cell. The studies of general and genetic toxicology place particular emphasis on the tools that enable worldwide investigation of cellular components. Among these worldwide techniques, the toxicology community is now paying the most attention to nucleic acid microarrays. These methods allow for the simultaneous monitoring of thousands of nucleic acid sequences,

including DNA polymorphisms or expressed RNAs ***(Canon et al., 2022)***.

Microarray study of expressed mRNAs is comparable to simultaneous northern blot analysis, which provides the ability to track the expression of particular genes over the entire genome. Thus, a microarray technology provides a means of studying multiple pathways and mechanisms at the same time. Since toxicity involves a cascade of gene interactions rather than just changes in one or a few genes, worldwide examinations of gene expression may provide a more thorough understanding of toxicity than currently is achievable. This objective method of investigation will undoubtedly produce a more complete picture of toxicological pathways and cause many of preconceived ideas to be re-evaluated ***(Lowe et al., 2017)***.

1.2. Proteomics:

The study of all the proteins expressed in a cell, tissue, or individual is known as proteomics. Since proteomics offers useful information on the identification, expression levels, and alteration of proteins, it has grown in importance within the molecular sciences. Since proteins serve as the final functional mediators of gene expression rather than the intermediary function represented by gene transcripts, the examination of proteins has a distinct advantage over gene expression approaches. Because proteins have additional characteristics including secondary structures and post translational modification, the methodologies for protein characterization and quantification are typically far more sophisticated than the technology used to assess gene expression. Numerous procedures are involved in proteomics, including protein expression profiling, protein changes, interactions between proteins, protein structure, and protein function ***(Yung and Ruotolo, 2012)***.

The information gathered from such tasks can be utilized to identify and predict illnesses, understand the mechanisms underlying diseases, assist in developing of new drugs, and give the basis for biological discovery. The science of proteomics is appealing due to its capacity to identify new disease biomarkers. For instance, modifications to protein distribution and profiles as cancer advances ***(Lill et al., 2021)***.

The development in molecular biology has brought various technologies for global analysis of proteins and peptides. Among these advances are improvements in classical 2-dimensional (2D) gel electrophoresis, the introduction of multidimensional liquid chromatography, western blotting, tandem mass spectrometry, and database searching technologies (termed multidimensional protein identification technology, or MudPIT), and improved mass spectroscopic identification of protein sequences using matrix- or surface- enhanced laser desorption/ionization (MALDI, SELDI) a method that results in the isolation of tens of thousands to hundreds of thousands of low molecular weight fragments that represent a proteome. These proteomic methods allow for the analysis of functional and structural proteins in a sample ***(Shah et al., 2020)***.

1.3. Metabonomics:

Metabonomics is the study of the connections between tiny compounds found in intermediary metabolic processes and genetic information. The metabonomic method is founded on the idea that changes in the relative quantities of endogenous biochemicals are a consequence of pathological or physiological changes brought on by toxicants. Because the metabolites in bodily fluids including blood, urine, and cerebrospinal fluid (CSF) are in a constant state of equilibrium with those in tissues and cells, changes in the composition of biofluids should be indicative of cellular abnormalities brought on by toxicants. To understand toxicity better, tiny molecules' simultaneous monitoring is also beneficial ***(Zhan et al., 2021)***.

In order to conduct human research that would not be feasible at obviously hazardous exposures, it is crucial to be able to track defense responses by proteome or metabonomics in humans at sub-pathological dosages. These innovations supplement gene expression data with additional information. Clearly, post-translational modifications of proteins, such as phosphorylation, wouldn`t be evident as changes in gene expression. Also, nucleic acids might not be available for

analysis in all cases (e. g invasive procedures would be needed to obtain samples from many human tissues), although proteins would be secreted or diffuse into accessible compartments or be amenable to imaging techniques ***(Martı´nez et al., 2013)***.

Metabonomics is mainly based on Nuclear magnetic resonance spectroscopy (NMR spectroscopy), which carry information regarding the structure of the metabolites. Characterizing biofluids for byproducts and intermediates of drug metabolism and other physiological processes is a part of this procedure. In-depth time-course data for hazardous responses can be captured using metabonomic techniques, and the resulting data can be used to calculate the cumulative impact of several organ responses in whole animal models ***(Zhong et al., 2022)***.

Metabonomic sampling can be carried out repeatedly, this contrasts with gene and protein technologies, which are frequently restricted to examining changes in a small number of organs over a limited number of time points due to sample size, the intrusive nature of sampling, and expense. Furthermore, metabonomics' techniques for drug response characterization are easily transferable to human clinical investigations since typical biofluid samples are more easily accessible from human populations than solid tissue samples ***(Carrera, 2021)***.

2. Bioinformatics

For the purpose of analyzing and interpreting genomes and proteomics data, the computer-based scientific field of bioinformatics combines computer science, biology, and mathematics. The two primary facets of bioinformatics are (a) database gathering and analysis and (b) software tool and algorithm development for biological data interpretation **(Figure 2)** ***(Tan et al., 2022)***.

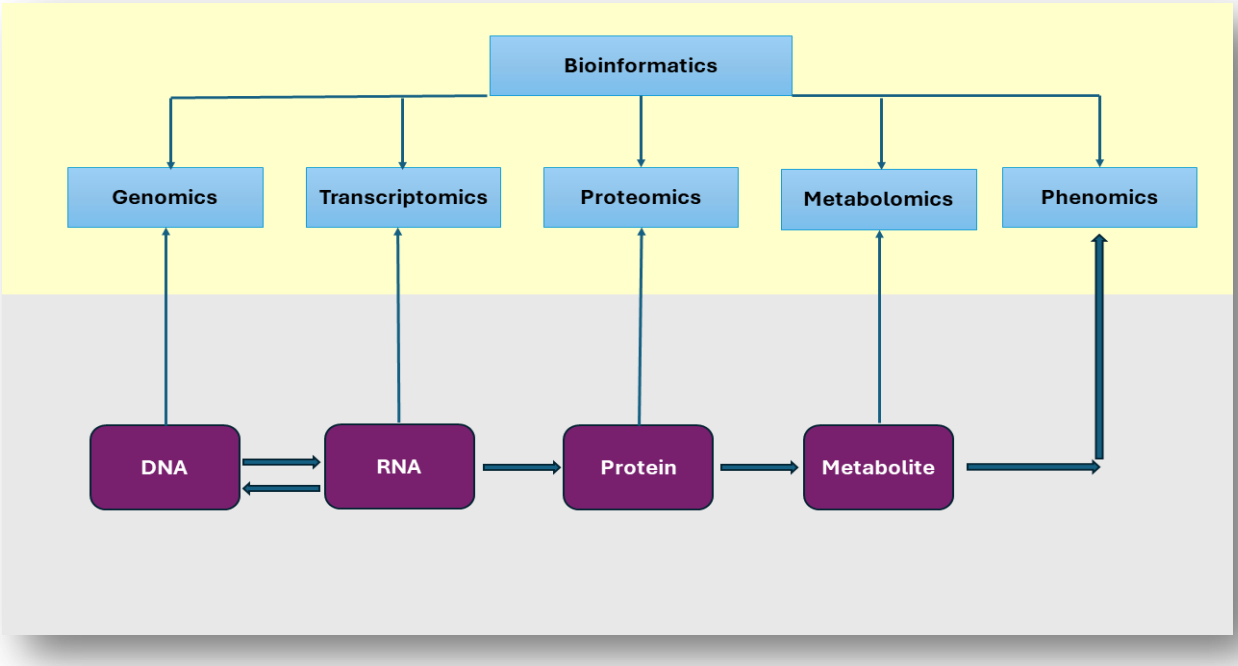

Figure (2): Relationship of biological "-omics" with bioinformatics (Facchiano, 2015).
Profiles corresponding to gene, protein, or metabolite measurements should be housed in a relational database that will facilitate the query of data depending on different criteria. From a biological point of view, the ideal database would have not only the mentioned data but also extra toxicological information outlining numerous parameters of the biological systems that were treated to the stressor. The parameters might include body and organ weights, mortality, histopathological results, and clinical chemistry measurements in animal studies or cell viability, cell cycle analyses, cell density, culture conditions and cell morphology reports in the case of in vitro studies (Orlov et al., 2022).

3.Applications of Toxicogenomics

3.1.Use of toxicogenomics to predict toxic responses:

By identifying substances with the potential to cause toxicity, modern toxicology aims to protect the human population from exposure to dangerous substances. Toxicogenomics focus on identifying gene expression alterations linked to chemical exposure; this will aid in the development of techniques that use short-term testing to predict long-term effects of chemicals. The basic premise is that chemicals with similar methods of toxicity induction will alter gene expression similarly; as a result, alterations in expression carried on by a toxin will serve as sensitive and precise indications of a harmful mechanism. Gene expression "fingerprints" for various systems can be found in this method, and they can be added to a database. It is possible to compare the gene expression profiles of an unknown toxin to the expression fingerprints of known toxin. The clinical scenario has offered the most convincing evidence of gene expression profiling's predictive power. Gene expression variations may help with the selection of substances for advanced phases of toxicity assessment in commercial settings and the prioritization of chemicals to be tested in a high throughput manner ***(Nabi and Tabassum 2022)***.

The toxicogenomic studies were conducted to address whether compounds with similar toxic mechanisms produced similar transcriptional alterations. By creating gene expression profiles for recognized hepatotoxicants in vitro (rat hepatocytes) and in vivo (liver of male Sprague-Dawley rats), microarray technology was used to test this notion. The outcomes of in vitro experiments demonstrated that substances with comparable toxic mechanisms produced comparable but distinct gene expression profiles. The scientists examined a variety of hepatocellular injuries brought on by the chemicals (necrosis, DNA damage, cirrhosis, hypertrophy, hepatic cancer), and they compared the pathology endpoints to the clustering result of the gene expression profiles of the chemicals. The investigation revealed a significant association between the gene expression profiles caused by diverse drugs, clinical chemistry, and histology ***(Hamadeh et al., 2002)***.

3.2.Use of toxicogenomics as a mechanistic tool:

Numerous applications of the global analysis of gene expression levels can be explored in modern biology. The holistic nature of this method, which offers an unbiased picture of changes in cellular processes brought on by chemical injury, makes it particularly effective when used in toxicology. Global gene expression profiling, when used in the context of mechanistic toxicology, is the perfect technique for developing hypotheses in this regard. Using more traditional methods, specific genes or entire pathways implicated in a mechanism of toxicity by this technology could be furtherly examined ***(Dadannagari et al., 2014)***.

The identification of gene regulatory elements directly related to the mode of toxicity under research is a significant problem in the application of gene expression technology to mechanistic toxicology. Understanding the relationship between phenotype and alterations in gene expression is necessary for the successful implementation of toxicogenomics in this situation. It is now common practice to measure changes in tens of thousands of genes at once ***(Tennant, 2002)***.

Any given toxicant is likely to induce changes in expression levels of many different genes, and only some of these genes would play a role in mechanism of toxicity. Appropriate experimental design could facilitate the identification of relevant gene expression changes directly linked to the molecular mechanism of a toxicant ***(Kultima et al., 2004)***.

Valproic Acid is avoided in pregnancy due to birth defects. Kultima et al., used toxicogenomics and DNA microarrays to show that the expression of a number of mouse fetal genes increased following a Valproic Acid exposure. It was found that one of the genes with increased expression is for a cofactor metallothionein which leads to fetal Zn+ deficiency. Thus, the teratogenic activity of Valproic Acid was understood using toxicogenomics ***(Kultima et al., 2004; Tennant, 2002)***.

Furthermore, the gene expression patterns of cisplatin-induced nephrotoxicity was done using cDNA microarrays. In these trials, rats were given daily Cisplatin treatments for 1 to 7 days at a dose that caused renal proximal tubular epithelial cell necrosis but no hepatotoxicity on day 7. The authors suggested a possible mechanism for Cisplatin nephrotoxicity by looking at the gene expression patterns for transplantin, an inactive isomer, which showed little change in the expression of genes associated to cellular remodeling, apoptosis, and modification of calcium homeostasis in the kidney ***(Orlov et al., 2022)***.

3.3.Use of toxicogenomics to study biomarkers:

The use of genomic technology in toxicology is a growing field, with emphasis on the application of such data for biomarker development. The hepatic gene expression profiles in rats following a treatment with various chemicals showed clear chemical-specific changes in the transcriptome profile which led to changes in the proteome profile, the profile of the metabolome and ultimately the phenotypes at the tissue level. Therefore, it makes sense that the transcriptome profile would include a substantial amount of information about current biological conditions, which could result in a deeper comprehension of molecular perturbations caused by chemicals. However, such chemical-specific gene expression data contain mixed molecular events that reflect complicated interactions among biological pathways such as xenobiotic metabolism, stress response, energy metabolism, protein synthesis/degradation, mRNA transcription/ degradation, DNA repair/replication, cell proliferation/cell death control, etc. Numerous gene sets, or toxicogenomics biomarker gene sets, such as cell damage, carcinogenicity, phospholipids, and glutathione depletion, have been revealed to have close relationships with certain toxicological endpoints and their expression levels. These toxicogenomics biomarkers could be then utilized for evaluation, diagnosis or prediction of toxicity based on their gene expression changes ***(Kultima et al., 2004)***.

There are certain genes that are expressed during certain diseases as the genes BRCA1 and BRCA2 are expressed in a patient suffering from breast cancer. The level of expression of these genes increase in the diseased state of a person hence those genes serve as biomarkers **(Table 1)** ***(Van"t Veer et al., 2002)***.

Gene categories	Types of Genes in category
Apoptosis	Caspases, BAK, Bax, Fas, Cyclins, TNFs
Cell cycle Cell proliferation	Cyclins, DNA Binding Protein, Waf 1 Kinases, Transcription Factors, Growth Factors and Receptors, Connexins
DNA Damage/repair	DNA Repair genes, ERCC`s, GADDs, Helicases, Topoisomerase
Inflammation	Serum amyloids, Interleukines, Adhesion molecules, Chemokines
Metabolism	P450s, Glucuronidation Enzymes, Glutathione Enzymes, Methyltrasferases, Redox Enzymes
Oxidative stress	O2 Response Genes, Superoxide Dimutase, Redox Enzymes
Peroxime proliferators transport	Peroxisomal Enzymes, Multi-drug Resistance proteins, Organic Anion and Cation Transporters

Table (1): Types of different genes in category ***(Van"t Veer et al., 2002)***.

Use of toxicogenomics to study variations in individual response to toxic substances:

The knowledge of toxicogenomics is useful to understand the variation in individual's response to toxic substances. This variation is due to genetic polymorphism. Single nucleotide polymorphisms, or SNPs, occur very frequently in the human genome (one SNP occurs every 100–300 base pairs of DNA), making them extremely useful as markers for identifying or mapping the genes involved in complex genetic diseases and responses to environmental factors. Significant effort has been put into developing technologies that can identify these small variations in genes ***(Sitinjak et al., 2023)***.

Within various racial and ethnic groupings, there are often variances in population response depending on genetic variation. The rate at which ethanol is metabolized varies by race. Acetaldehyde accumulates more in eastern races than it does in Caucasians, particularly among Japanese people. They experience face flushing and palpitations following a moderate alcohol intake. This is a result of the slower rate of acetaldehyde oxidation caused by genetic variation ***(Yook et al., 2024)***.

Frequent corticosteroid use might cause elevated intraocular pressure in 5% of people. It is a recessive autosomal characteristic. Even without corticosteroids, these people have a 100-fold higher risk of getting glaucoma ***(Fini et al., 2016)***.

Use of toxicogenomics in risk assessment:

The gene expression profiling has been suggested to have the potential of reducing number of experimental animals and time needed for toxicological investigation of compounds compared to the established procedures of hazard identification. When compared to traditional toxicity studies, toxicological effects could be detected earlier, and when similarities to classes of recognized toxins are discovered, substances could be prioritized for future investigation ***(Mattes, 2006)***.

The role of toxicogenomic technologies as supplements and extensions of current technology for prediction toxicology is growing ***(NRC, 2007)***.

The "weight of the evidence" for making decisions about the hazards presented by environmental toxicants could be strengthened with the use of additional molecular level data and tests that are provided by toxicogenomics. They would, however, replace some already employed methods since they are anticipated to be more sensitive and informative than existing technologies ***(Dadannagari et al, 2014)***.

Standardized toxicogenomics' platforms are suitablefor detecting signs of exposure to ces in target and environmental toxic substan substitute tissues and fluids. The individual differences in how they react to environmental exposure and the durability of a toxicogenomic signal following exposure present a technological difficulty. By creating o particular chemicals signatures of exposure t and even chemical mixtures, toxicogenomic could be adopted and employed technologies for the research of exposure assessment. To facilitate the development of exposure assessment tools based on toxicogenomics, studies should large human population include a collection of samples suitable for transcriptomic, proteomic, metabolomic, or other toxicogenomic analysis in addition to traditional epidemiological measures of exposure ***(Koedrith et al., 2004)***.

Proteomics were used to identify early markers of hepatic steatosis. The findings that several proteins showed significant changes in abundance before the onset of over toxicity in response to drug treatment, combined with the finding that these proteins played a role in relevant functions such as cell death, cellular organization and fatty acid biosynthesis, suggested that these proteins could serve as predictive biomarkers of compounds with a propensity to induce liver steatosis ***(Govaere et al., 2023)***.

Genetic variants influencing chemical sensitivity should be identified through genome-wide human investigations and animal models. Toxicogenomics is a valuable tool in the identification, comprehension, and characterization of the mechanisms underlying the impact of genetic and epigenetic factors on individual differences in the toxicity of substances ***(Mattes, 2006)***.

A study of Cleveland clinic identified a set of non-synonymous SNPs that might be associated with the severity of sunitinib-induced toxicity in patients with metastatic clear cell renal carcinoma. These nsSNPs clusterd into a functional network around IFNγ, TNFα and TGFβ. Interestingly, no differences in the 3 nsSNPs for CYP4503A4 (involved in sunitinib metabolism) was observed between patient groups (patients with or without significant toxicity***) (NRC, 2005)***.

A team from the FDA's Divisions of Systems Toxicology and Genetic and Reproductive Toxicology used toxicogenomics to examine the changes in gene expression caused by comfrey in rat liver and was able to identify the underlying mechanisms for comfrey-

induced hepatic toxicity. A molecular model for comfrey-induced liver damage and tumor genesis through mutation induction was developed by integrating gene expression alterations with recognized pathophysiological abnormalities ***(NRC, 2005)***.

To better communicate the results of animal testing to human health, genotyped and genetically modified animal model strains should be employed as experimental tools. Toxicogenomics ought to be employed to investigate variations in human and animal toxicant responses. Algorithms must be developed in order to correctly identify orthologous genes and proteins, which are utilized in toxicologic research and have the same function in a variety of animals and species ***(Soufan et al., 2019)***.

Particularly at low doses, toxicogenomics has the potential to advance our understanding of dosage response interactions. Future toxicological evaluations should include the proper dose-response and time course analysis. An intellectual framework from research investigations could be provided by analysis of toxic compounds that are adequately defined ***(Trivedi et al., 2013)***.

Toxicogenomic technologies had been expected to reveal important molecules involved in development and molecular events that can be impacted by toxicants due to their sensitivity. Additionally, toxicogenomics could make it possible to search for substances that alter gene expression and have detrimental developmental effects. To put it briefly, toxicogenomic technologies could be used to research how exposure during early development affects a person's sensitivity to toxins from drugs and chemicals ***(Pedrete et al., 2016)***.

Humans are routinely exposed to many chemicals, despite the fact that toxicology focuses primarily on the study of individual substances. It is challenging to determine how exposure to several chemicals will affect the effects of individual compounds. Although it is unlikely that toxicogenomic signatures able to identify every interaction among complex mixtures, it should be possible to use mechanism-of-action data to design insightful toxicogenomic experiments. These studies could involve identifying and investigating potential interactions more thoroughly, screening chemicals for potential biologic conversion points (overlap), such as shared activation and detoxification pathways, and extending beyond empirical tests. To assess the applicability of techniques for the ongoing problem of predicting possible dangers associated with mixtures of environmental chemicals, toxicogenomic approaches should be applied ***(Portugal et al., 2022)***.

Application of toxicogenomics is only possible when data are examined in the context of extensive knowledge about pathways, gene annotations, functions, and regulatory networks that effectively bridge the gap between molecular profiles and toxicological responses and phenotypes identified through traditional toxicology approaches. One of the most notable and distinctive advantages of a toxicogenomics approach to predictive toxicology and safety assessment has emerged as the enhancement in mechanistic knowledge produced by toxicogenomic techniques. This improved insight leads to what may be the ultimate practical benefit to incorporating a toxicogenomics approach into research programs: a significant reduction in decision making time that comes from gaining insight from gene expression models rather than relying solely on lengthy, expensive animal studies. Toxicogenomics' distinctive advantages include the highest potential for mechanistic understanding, better interpretation of vast, complicated volumes of data with many variables, the ability to identify toxicity earlier in the drug discovery process, and the ability to make project faster decisions ***(Liebler and Guengerich, 2005)***.

Validation of toxicogenomic technologies

In the end, the usefulness of toxicogenomic technologies hinges on how reliable, reproducible, and broadly applicable the findings are from a specific research project or analytical technique. Validation, which is the process of making sure a test measures and reports the identified end point(s) accurately, is necessary before moving beyond laboratory assays and into more widely used applications. There must be

multiple stages of validation. Technology platforms must first demonstrate that they can produce consistent, dependable findings. This includes evaluating the stability of the device, determining the analytical sensitivity, and determining the assay limits for detection, interference, and precision. Second, the data collection and analysis software for an application ought to yield reliable findings. Third, testing and validation of the application which includes both software and hardware is required. Fourth, the relevant application that is displayed needs to be extremely precise for a smaller target market or broadly applicable to a larger population. Lastly, it is important to think about how these technologies and the applications that employ them can be approved for usage in regulatory contexts ***(Kinaret et al., 2020)***.

Ethical, legal, and social issues

It is crucial to make sure that toxicogenomic data in medical records and data utilized in research are adequately protected in terms of privacy, confidentiality, and security as these data are related to clinical and epidemiologic data. Important individual and social interests would be better advanced by protecting this information. Additionally, it could stop people from being discouraged from taking part in research or genetic testing, which is the initial stage of a personalized risk assessment and risk mitigation ***(NRC, 2007)***.

Challenges and technical considerations

The ability to predict potential risks to human health from chemical stressors is complicated by three main factors: the many different properties of the tens of thousands of chemicals and other environmental stressors; the time and dose parameters that define the link between exposure to a chemical and disease; and the diversity of genetic and life experiences among human and animal populations as well as among organisms used as surrogates to assess the harmful effects of a toxicant ***(McHale et al., 2018)***.

Limitations of toxicogenomics

Despite the process of development and implementation of toxicogenomics is continuously grow up, several obstacles have limited the interpretation of gene expression data and extraction of meaningful and useful information from it. For example, compounds' methods of action may be influenced by dose, timing, and duration of exposure, as well as cell phenotype. In addition, unlike other toxicological endpoints, gene expression responses are dynamic and reversible ***(Pain et al., 2020)***.

For accurate hazard characterization, insight into the relationship between genomics- based endpoints and known health outcomes is needed. It is not always possible to determine that a considerable change in gene expression has a negative impact until results are placed in an appropriate biological context and natural range of physiological variability of gene expression is known. Moreover, the collection of epidemiologic data and samples is expensive. One of the main obstacles is that many studies have either not collected the proper forms of specimens or the specimens that have been obtained are in a form that makes toxicogenomic research difficult. Lastly informed consent can limit the extension of toxicogenomics ***(Pain et al., 2020)***.

CONCLUSION

Toxicogenomic tools are inevitably improving the way data is extracted from classical toxicology studies.

Ultimately, environmental hazard identification can be done quickly and effectively by utilizing the computational methods included in the comparative branch of toxicogenomics.

The establishment of gene, protein, or metabolite markers whose concentrations can be evaluated in samples taken from exposed populations will facilitate these accomplishments.

By revealing details about the underlying molecular pathways involved in the response to compound exposure, compound profiling will help enhance our understanding of toxicant-induced unfavourable endpoints in biological systems (pathological lesions, cell cycle changes).

This knowledge will lead to a more informed and precise classification of compounds for their safety evaluation.

Conflict of interest: The Author declares that they have no conflicts of interest to disclose.

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