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Short communication

Toxicogenomics: opportunities and challenges of application in drug development, toxicity prediction and human health risk assessment

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Introduction

Long experimental durations and associated high costs of long-term toxicity studies, as well as reliance on animal studies to measure adverse effects, which are often not sufficient for predicting toxicity in humans, make defining the toxicity profile of a new chemical entity in humans a difficult task. Recently, there has been a lot of effort to improve the current situation. Advances in predicting toxicity would lessen the need for animal testing and improve the attrition rate in drug development and chemical risk assessment. To connect hazard identification, mechanistic toxicology, and risk assessment, a new rapidly developing field of toxicology called toxicogenomics has emerged (Alexander-Dannet al., 2018).

Therefore, the aim of this paper was to introduce this new field of toxicology, toxicogenomics, as well as prospects for its application in drug development, toxicity prediction, and human health risk assessment.

Toxicogenomics

Toxicogenomics investigates the role of the complete genome in biological responses of organisms exposed to environmental toxicants/stressors. It represents the combination of toxicological research with developing new technologies which widely investigate the functional genome (RNA, protein, metabolite profiling, and polymorphisms/functional DNA mutations) (Alexander-Dannet al., 2018; Amala, 2010). Additionally, there has been a rapid increase in publicly available toxicological and 'omics' data, particularly gene expression data, and a corresponding development of methods for its analysis. This allows us to begin reaping the benefits of years of effort in terms of technology, time, and cost (Wilsona et al., 2013).

Toxicogenomics aims to: 1) understand the link between environmental stress and human disease susceptibility, 2) find relevant biomarkers of disease and toxic chemical exposure, and 3) unravel the molecular processes of toxicity. These issues are best addressed by collecting data in well-designed toxicogenomics databases (Amala, 2010).

Applications of toxicogenomics

Toxicogenomics offers an outstanding opportunity to uncover the biological pathways and processes influenced by pharmaceutical compounds and/or environmental toxicants. It combines traditional toxicology with information-dense genomic technologies, to integrate toxicant-specific alterations in gene, protein, and metabolite expression patterns with phenotypic responses of cells, tissues, and organisms (Wilsona et al., 2013). This is particularly helpful in predicting the potential drug/chemical toxicity before functional damages are recognized, in classification of toxicants, as well as in screening human susceptibility to diseases, drugs or environmental chemical hazards (Amala, 2010; Wilsona et al., 2013).

Drug development

Compound toxicity is a key contributor to the high clinical dropout rates of novel drug candidates, with a

quarter of failures attributed to a lack of safety. Hence, novel higher throughput methods should provide more insight into potential human toxicity than the existing ones. Such patterns of gene expression, or 'molecular fingerprints', could be used as diagnostic or predictive markers of exposure (Amala, 2010; Wilsona et al., 2013). Toxicogenomics is anticipated to be increasingly integrated into all phases of the drug development process, particular mechanistic and predictive toxicology, as well as biomarker discovery. This discipline offers the potential to identify a human toxicant earlier in the drug development process and detect human-specific toxicants that cause no adverse reaction in experimental animals. Furthermore, understanding the mechanisms of drug-induced hepatotoxicity during drug discovery and development is of a great importance. 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 and characterization of drug induced hepatotoxicity could result in safer drugs and more efficient drug discovery/development process (Amala, 2010).

Predicting toxicity

Toxicogenomics represents an attractive approach to predict toxicity and gain a mechanistic understanding of toxic changes. It can be a useful method for detecting the carcinogenic potential of endocrine disruptors (EDCs) in the short period of time (Alexander-Dann et al., 2018; Wilsona et al., 2010). At present, there are no concrete epidemiological data supporting any exogenous EDCs contribution to hormone-related organ carcinogenesis 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 of time. In the light of this, toxicogenomic approach promises to contribute a great deal of risk management regarding EDCs (Wilsona et al., 2010). Immunotoxicity assessment by gene expression profiling shows 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 (Alexander-Dann et al., 2013). Toxicogenomics in immunotoxicity evaluation adds to the knowledge of immunotoxic processes and the development of *in vitro* screening tests, and is thus likely to be useful for mechanistic insight into immunotoxicity and hazard identification (Amala, 2010).

Human health risk assessment

In hazard identification step toxicogenomics might help determine types of hazards a chemical might poses (i.e., cancer or non cancer risks), as well as connected modes and mechanisms through which it exerts its harmful effects (Amala, 2010; Wilsona et al., 2013). Information on the mode of action is also a component in deciding the appropriate approach to dose-response assessment. Toxicogenomic approaches could support exposure assessment by indicating cellular exposure to toxicants. It could also aid in better understanding variability in the human population, extrapolation of data from one species to another, and identification of susceptible subpopulations (Wilsona et al., 2013).

Conclusion

Toxicogenomics assists in understanding molecular/cellular effects of chemicals in biological systems and, thus, enhances drug discovery, toxicity prediction and chemical risk assessment processes. The creation and deployment of bioinformatics tools and databases is a key part of toxicogenomic research in order to enable the analysis, mining, visualization, and sharing of the huge quantity of biological data generated in this field.

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