REVIEW ARTICLE

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Potentiation of Toxicology with Proteomics: Toxicoproteomics

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Abstract

Proteomics, which is called the identification phase of the proteome identifying all the proteins encoded by the genome, has an important place in solving the difficulties experienced in toxicology. Proteomics refers to the study of interactions with other proteins and macromolecules, structure, location, amount, post-translational modifications (PTM), function in tissues/cells of the proteome. With proteomic studies, new relationships between proteins and toxicopathological effects can be determined and it is revealed the information on the toxic action mechanisms of various substances, from metals to peroxisome proliferators. On the other hand, toxicoproteomics seeks to identify critical proteins and pathways in biological systems that respond to it and adversely affected by chemical and environmental exposures using protein expression technologies. Toxicoproteomics combines 3 discipline areas. These are 1) traditional toxicology and pathology 2) differential protein and gene expression analysis 3) systems biology. Toxicoproteomic studies are an important area that can provide critical tools for identification of biomarkers associated with exposure to toxic substances, assessing their reliability and designing appropriate measures that can minimize adverse effects. In this statement, it is aimed to emphasize the importance of proteomics in toxicology.

Keywords: Toxicoproteomics, ecotoxicoproteomics, toxicology, proteomics.

INTRODUCTION

The mechanism of action of toxic substances on living organisms is one of the most difficult parts to elucidate in terms of toxicology. Toxicology provides information on how toxic substances diffuse (their movement on molecular targets) into cells and cause adverse effects. The information obtained from biochemical and physiological studies (both organismal and cellular) helps toxicologists to analyze the mechanisms of toxicity. Toxicology follows the paths that have been resolved, but has difficulty deciphering new mechanisms and shaping different assumptions. Due to advantages like being a broad field and working with biased hypotheses; proteomics takes an important place in overcoming these difficulties in toxicology (Rabilloud and Lescuyer, 2015). "Toxicoproteomics" seeks to identify critical proteins and pathways in biological systems that are adversely affected by and respond to chemical and environmental exposures using protein expression technologies (Wetmore and Merrick, 2004). Proteomics identifies protein markers of toxicity. Therefore, it can increase the speed and sensitivity of toxicological screening. With proteomic studies, new relationships between proteins and toxicopathological effects can be determined. The information on the toxic action mechanisms of various substances, from metals to peroxisome proliferators, is revealed. Thus, a great progress towards the post-genomic era has been seen. In addition, the inclusion of proteomics in drug development studies has revealed a new field, "Pharmacoproteomics" (Kennedy, 2002).

The term "proteome" was coined at a meeting in 1994 on two-way electrophoresis. This term describes the total set of proteins expressed by a genome in a cell, tissue or organism at a given time (Wilkins et al. 1996; Başaran et al. 2010). The first technique of proto-proteomics, attempts to screen a wide-ranging protein in toxicology has began shortly after publications of two-dimensional electrophoresis (Rabilloud and Lescuyer, 2015). Analytical tools used for proteomic analysis; proteome and sample complexity, two-dimensional gel electrophoresis, high performance liquid chromatography, protein and peptide microarrays, mass spectrometry, bioinformatics tools (Wilson and Hooser, 2018).

The expression phase of the proteome, which identifies all the proteins encoded by the genome, is called proteomics. Proteomics is all of the proteins found or expressed in an organism at a certain time and place. Proteomics helps define the structures, locations, and amounts of all proteins. In addition, it helps to describe the post-translational modifications of all proteins, their functions in tissues and cells, and their interactions with other proteins and macromolecules (Başaran et al. 2010). The term "space" describes the expression of different proteins in different cell types and different cell compartments. The term "time", on the other hand, defines processes such as different developmental stages, environmental conditions, various diseases, and old age. That is, the proteome is a dynamic structure that differs in some situations (to tissues and cells, phases of the cell cycle, internal-external stimuli, environmental conditions, etc.). Although proteomics is a dynamic concept unlike genomics, it can also be defined as a quantitative analysis technology of proteins in cells, tissues or body fluids under different conditions (Bal and Budak, 2013). On the other hand, comparative proteomics, is based on the comparison of expression between two different states (normal and disease, old and young) (Marko-Varga, 2004; Başaran et

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al. 2010). In this review, it is aimed to emphasize the importance and potential of proteomics in toxicology.

Objectives of proteomics studies: mRNA expression levels do not correlate well with protein expression levels; mRNA levels do not reflect the activity of the encoded protein, information on post-translational modifications of proteins cannot be provided at the mRNA level, Genome and Proteome = provide complementary data (Başaran et al. 2010).

Proteomics is more than identifying proteins that result from pathology that increase or decrease their expression. There are cells that communicate with the extracellular microenvironment and then the serum-plasma macroenvironment. The aim in proteomics should be to characterize the flow of information through the intercellular protein circuit. Serum proteomic model diagnosis consists of high-dimensional mass spectrometry data and is a new type of proteomic platform in which proteomic models are used as diagnostic classifiers. This approach shows promise in the early detection of cancers. Detection of drug-related toxicity may also be possible with the same technology. As a result of an experimental rat study to prove these, a serum proteomic model seems to reflect treatment history and serum c TnT (serum cardiac troponin T) levels. In addition, it was observed that the serum proteomic model has a classification accuracy that reflects the histology underlying heart damage quite well. Studies are underway to determine whether a serum proteomic model can detect early cardiotoxicity, which is irreversible and occurs before heart damage has progressed (Petricoin et al. 2004).

Analysis of a proteome requires both qualitative and quantitative analysis. Only the amount of protein or a change in its amount is important for the state of a biological system. This change in the amount of protein is an important indicator of if the deterioration is stated by chemicals or physical. For example, "toxicoproteomics" reflects the effect of toxic substances. The search for biomarkers that indicate cancer, tumors and other diseases and disorders in the early stages of development should include robust and reliable quantitative data (Linscheid, 2005).

Proteomics is associated with many different fields of application, including drug development. It has recently been used in both animal models and humans. In addition to tissues, biofuels, subcellular components and enzymatic pathways, proteomic analyzes have been performed on various disease and toxicological conditions. The greatest challenge of proteomic technology and bioinformatics tools is their translation into clinical specimens such as disease and toxicity biomarkers (Elrick et al. 2006).

Toxicoproteomics which expressing the identification of marker proteins that respond to toxic substances by expression, combines the 3 discipline fields. 1) conventional toxicology and pathology, 2) differential protein and gene expression analysis, and 3) systems biology. In the seventeenth century, the invention of the microscope, the development of modern histology and pathology, and the ongoing technological developments were followed by the understanding of the complexity of systems in cellular tissues and organs with the light microscope. After, the electron microscope and, more recently, the atomic force microscope were developed. These events were followed by successes in sequencing whole genomes, the search for the transcriptome, the development of proteomics, and gene expression technologies that allowed other Omic technologies to emerge. Toxicogenomics evolved from the need to determine how genomes respond to environmental stressors or toxicants by combining genome-wide mRNA expression profiling (transcriptomics) with global protein expression patterns (proteomic) interpreted with the use of bioinformatics to understand the role of gene-environment interactions in disease and dysfunction (Wetmore and Merrick, 2004). Historically, toxicoproteomic analyzes have been developed for virtually all possible domains and biological systems, from bacteria to plants, including all animal classes (Rabilloud and Lescuyer, 2015).

The aim of ecotoxicology is to understand the effects of toxic chemicals on ecologically exposed species. (Lam and Gray, 2001; Lemos et al. 2010). The explanation of the effects of these stressors on the molecular mechanism of the cell contributes to the understanding of events occurring at both the cellular and organismal level. It also contributes to understanding of known and predicted events with toxicological approaches (Iguchi et al. 2007). (Proteomics methodologies can be used not only to unravel the mechanisms underlying the toxicological effects of stressors but also to identify new biomarkers (Dowling and Sheehan, 2006; López-Barea and Gómez-Ariza, 2006; Lemos et al. 2010).

With the importance of proteomic technologies in ecotoxicology, the term "ecotoxicoproteomics" has emerged. The emergence of ecotoxicoproteomics began with the use of proteomic technology to solve emerging problems in toxicology. In this way, early warning indicators can be developed. It can also be used in "in situ" bioanalysis and environmental risk assessment (Lemos et al. 2010).

Environmental proteomics or ecotoxicproteomics was developed mainly from human toxicoproteomics or clinical proteomics (Jung et al. 2005; Cho and Kim, 2006). There have been some studies using invertebrates as models to investigate the effects of toxic substances in the proteome. They mostly focused on rainbow trout (*Oncorhynchus mykiss*) zebrafish (*Danio rerio*), hake (*Merluccius merluccius*), and other aquatic vertebrates (Piñeirove et al. 2001, Shrader et al. 2003, Hogstrand et al. 2002, Wang et al. 2007, Ling et al. 2009, Martyniuk et al. 2009). However, invertebrates were not included in ecotoxicoproteomics studies due to the lack of sequenced genomes (Lemos et al. 2010).

In a study, the response of *Bacillus subtilis* to existing and newly developed antibiotic groups was examined. Proteomic technology was used to study complex cellular actions against selected antimicrobial compounds in the study. It was emphasized that proteome analysis can be used for identification targets and validation. As a result of this study, it has been suggested that proteomics can broaden the perspective of known antibiotics and contribute to the discovery of new antibiotics (Bandow et al. 2003).

Living things face the risk of disease as a result of exposure to different environmental toxic substances and their combinations. The field of toxicoproteomics is supported by quantitative and qualitative proteomic technologies and their applications in toxicology research. It also finds application in periods of acute and chronic exposure to toxic substances. It focuses on proteomic studies of toxicity occurring in response to toxic chemicals and their environmental exposure (George et al. 2010). Toxicoproteomics includes technologies for determine total protein in biological fluids and tissues applied after the host is exposed to harmful agents. Thus,

toxicoproteomics exploits the exploratory potential of proteomics in toxicology research (Merrick, 2008). Toxicoproteomic studies; Identification of biomarkers associated with exposure to toxic substances is an important area that can provide critical tools for assessing their reliability and designing appropriate measures to minimize their adverse effects (George et al. 2010).

CONCLUSION

Proteomics, associated with many different applications, including drug development, has recently been used in both animal models and humans. In addition to tissues, biofuels, subcellular components, and enzymatic pathways, proteomic analyzes are performed on various diseases and toxicological conditions. The field of toxicoproteomics is supported by quantitative and qualitative proteomic technologies and its applications in toxicology research, and it finds application in acute and chronic exposure periods to toxic substances. The working mechanism of toxicoproteomics focuses on proteomic studies of toxic chemicals and toxicity that occurs in response to their environmental exposure. Toxicoproteomics has the advantage of better identifying molecular targets or molecular mechanisms of toxicity. Due to this advantage, proteomics has an important place in the field of toxicology, and its use in drug development studies creates new application areas.

Conflict of Interest

The authors declared that there is no conflict of interest.

Authorship contributions

Concept: M.Y. Design: M.Y. Processing: M.Y., A.I., Interpretation: M.Y., A.I., Literature Search: M.Y., A.I., Writing: M.Y., A.I.

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