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Approaches and perspectives to toxicogenetics and toxicogenomics

Aproximaciones y perspectivas en toxicogenética y toxicogenómica

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| Summary |

Toxicology is one of the scientific disciplines that has most evolved in recent years due to scientific and technological advances that have created a deeper understanding of the genetic and molecular basis for appreciative variability in toxic response from one person to another. The application of this knowledge in toxicology is known as toxicogenetics and toxicogenomics. The latter is the discipline that studies the genomic response of organisms exposed to chemical agents, including drugs, environmental pollutants, food additives, and other commonly used chemical products. The use of emerging omic technologies, such as genomics, transcriptomics, proteomics, metabolomics and bioinformatics techniques, permits the analysis of many variants of genes simultaneously in an organism exposed to toxic agents in order to search for genes susceptible to damage, to detect patterns and mechanisms of toxicity, and determine specific profiles of gene expression that give origin to biomarkers of exposure and risk. This constitutes predictive toxicology.

Keywords: Toxicogenetics; Toxicology; Genome (MeSH).

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Resumen

La toxicología es una de las disciplinas científicas que más ha evolucionado en los últimos años; esto se ha dado gracias a los avances científicos y tecnológicos que han generado un conocimiento cada vez más profundo de las bases genéticas y moleculares de la variabilidad en la respuesta tóxica de unas personas a otras. La aplicación de estos conocimientos a la toxicología se conoce como toxicogenética y toxicogenómica; esta última es la disciplina que estudia la respuesta genómica de los organismos expuestos a agentes químicos, dentro de los que se incluyen fármacos, contaminantes ambientales, aditivos alimentarios y otros productos químicos de uso común. Dichos estudios se adelantan mediante el empleo de las tecnologías ómicas emergentes, como genómica, trascriptómica, proteómica, metabolómica y las técnicas bioinformáticas, las cuales permiten analizar múltiples variantes de genes simultáneamente de un organismo expuesto a agentes tóxicos, con el propósito de buscar los relacionados con susceptibilidad al daño, detectar de patrones y mecanismos de toxicidad, determinar moléculas endógenas susceptibles al ataque de agentes tóxicos y determinar perfiles específicos de expresión de genes que pueden originar biomarcadores de exposición y riesgo, constituyendo la toxicología predictiva.

Palabras clave: Toxicogenética; Toxicología; Genoma (DeCS).

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Introduction

The advent of molecular biology and bioinformatics gave us novel technologies based on the genome that allow the analysis on a large scale of the biological responses to external stimuli. This has led to progress in several different scientific disciplines, toxicology among them.

Traditional methods focus on determining toxic potential and evaluating the risk of chemical substances mainly through the examination of the different biochemical pathways connected to responses observed in the clinic together with the analysis of the hematological and histopathological parameters that are indicative of damage to organs and tissues (1).

On the one hand, toxicogenomics —which refers to the combination of "toxicology" and "genomics— is an approach that combines the "omic" technologies (genomics, transcriptomics, proteomics, and metabolomics) to better understand the response of cells or organisms to pharmaceuticals and xenobiotic compounds in the environment and their toxicological evaluation.

The basis of the methodology is that the particular properties of the xenobiotics can cause, on the one hand, direct toxic effects or alteration to the expression of genes that are required for the cell to respond to the toxic aggression and, on the other hand, that they can or not be biotransformed by enzymes, forming metabolites that generate diverse favorable and/or unfavorable responses for the organism (2,3).

The profiles of gene expression that are obtained contribute to the elucidation of the mechanisms of toxicity of the compounds, something that can give rise to the discovery and development of biomarkers, specific genes and their variants, as well as the design of new targets and their corresponding therapeutic options. These profiles also facilitate the prediction of the potential toxicity of new chemical entities (xenobiotic entities), and with this, at some point in the future, we may be able to detect susceptibilities to a toxicological effect due to an environmental, occupational, or food-based xenobiotic agent based on genotyping and in a timely fashion (2,4). This approach is known as toxicogenetics.

It is necessary to understand that the genetic and metabolic dynamics of an organism —understood as the ability of genes, enzymes, proteins, and peptides to participate in processes involving the transformation of xenobiotics— is determined not only by genetic factors but also by inter-individual and intra-individual genetic characteristics. This is seen, for example, in the fact that two populations respond in different ways to a xenobiotic agent and that, within a single population, different individuals can evidence different processes of biotransformation (2).

An approach to the principles of toxicogenetics and toxicogenomics will allow us to develop predictive toxicology, with which susceptibility to xenobiotics would be detectable. Thus, not only would it impact the development of safer and more effective medications; it would also open up possibilities of estimating environmental influences on health according to evaluations of the chemical risks present in the patients' food and work environments, among other things. Below, we will take a look at the changes in toxicology that have been generated by toxicogenomics and toxicogenetics.

Traditional Toxicology

The term "toxic agent" makes reference to any substance that causes damaging effects to living organisms. Generally, these effects are dependent on the level of exposure to the chemical substance (5).

Classic toxicology is the discipline that studies chemical substances and the physical phenomena that are capable of producing pathological alterations to living beings and their action mechanisms. It is also interested in strategies for counteracting them, detecting them, identifying them, and mitigating their effects (6).

Currently, thousands of chemical substances are used in diverse applications of interest to everyday human life, and industry in general. The majority of the toxicological data that is associated with them is obtained from biochemical pathways, which are related to the responses observed and identified using points of pathological, histological, and blood/chemical assessment, as well as observations of behavior in tests carried out on laboratory animals.

In the case of pharmaceuticals particularly, the studies go further, implying pre-clinical studies in diverse biological models and clinical trials in humans before commercialization. In this way, traditional toxicology is mainly focused on the individual study of the adverse effects produced in the organism from exposure to a given chemical compound (7-11).

However, the traditional standpoints of toxicity tests are not enough to face the challenge of the current requirements of toxicological assessment. This is the case, fundamentally, because biological systems are complex and can generate

responses to xenobiotics that vary from generic stress responses to very specific changes that are closely associated with the toxicity mechanism.

Up to the present, it was common to assert that this variability was associated with age, sex, weight, state of health, and racial characteristics. However, despite the fact that this is often the case, there is evidence that individuals with the same weight and exposed to the same concentration of a xenobiotic can show variations in their response. This case can even occur with things like racial aspects, where the variation is significant and should be approached in terms of interindividual variation. This brings us to the differentiation between toxicokinetics and toxicodynamics.

The former takes into account the fact that the majority of the biomolecules implicated in kinetic and dynamic processes are proteins whose structure, function, and degree of expression are conditioned by the corresponding collection of genes that codify them and their regulation. These genes may present allelomorphic variants that codify the proteins with different degrees of functionality or that change their expression due to the effect of the regulating proteins that are stimulated or repressed by certain substances (12,13).

Toxicology has undergone a significant evolution with respect to the times of Paracelsus thanks to the coming of genetics. This has been especially useful for clinical toxicology, the branch of toxicology charged with studying the toxic effects of chemical substances on human beings, that has been limited by the extrapolation of data in the experimental field (12).

The preclinical models cannot predict many toxicities induced by pharmaceuticals in humans, particularly those with a low incidence of toxicity or the reactions measured immunologically or by idiosyncrasy. Furthermore, the animal models take a large amount of time, are costly, and unfeasible for many compounds. Also, currently, it has been established that they may be limited in terms of their ability to detect toxicity or variation in human responses to pharmaceuticals and other xenobiotics. In addition, there is the ethical imperative to minimize the quantity of animal trials with the three Rs, "reduce, refine, replace" (14).

All of the above makes the use of alternative high-yielding standpoints or tools necessary to enable the overall and simultaneous analysis of the molecular events that occur in the cell so that we might better understand the phenomenon of toxicity (2,10,11,15).

Toxicogenetics and toxicogenomics

The advance into the era of genomics is the most significant achievement of the last 50 years of scientific research. Basic science has discovered the genetic code and the fundamental pillars of molecular activity that hold up biological structure and function (16,17).

As it is known, biological systems respond to the exposure to xenobiotics by activating compensation mechanisms that are directly or indirectly regulated at the levels of transcription, transduction, and even at the level of protein modification. This leads to an increase or decrease in the activities of specific networks of genes. When these mechanisms are not effective, the organisms suffer from toxic effects (2,12).

Due to the sequencing of the human genome and the rapid advances in sequencing technology that allows us to sequence a human genome quickly and at an increasingly lower cost, we have moved from the first studies of gene expression that described the response of a biological system to a particular toxin and made possible the explorations of simple and complex networks of genes related to proteins that directly intervene in the modulation of the toxic response.

The new genomic tools allow for the analysis of the chemical that affects the expression of thousands of genes simultaneously or sequentially along the regulation pathways. This cascade of genomic information and related technologies makes an effort to establish genomic function in response to a pharmaceutical, toxic agent, toxin or other external stimulus, giving rise to a new field called toxicogenomics (15,18-20).

Toxicogenomics consists of the application of genomic technology to the study of toxicology. In other words, it is the study of the effects of chemical substances, including pharmaceuticals, environmentally present contaminants, food additives, and common chemical products, in the genes. In this way, it is possible to understand the role of the interactions between genes and the environment for the development of diseases of abiotic origin. This field of science has developed over the last 15 years, mainly due to advances in toxicology, cellular biology, genomics, and bioinformatics (11,18,21-24).

Toxicogenomics should not be confused with toxicogenetics, which is related to specific genetic characteristics (genotyping) of individual genes that produce different responses to toxic substances through the presence of production of isoforms of the target protein or the proteins associated with the primary biotransformation of the xenobiotic agents (Figure 1) (12,23).

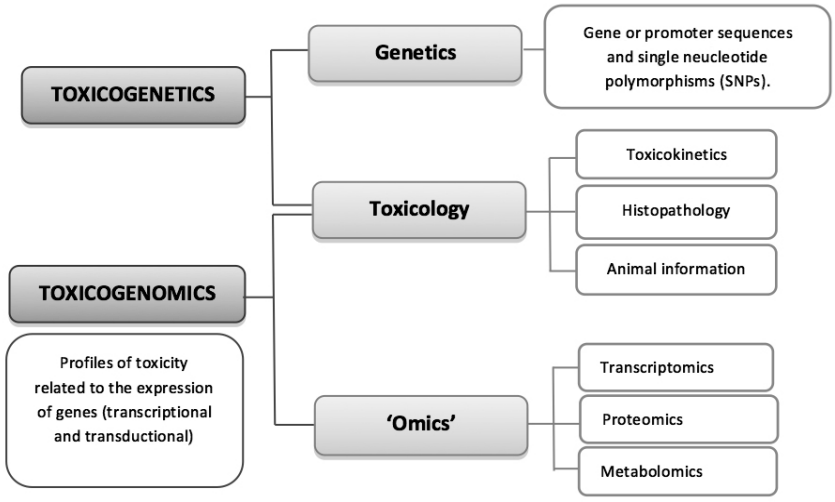

Figure 1. Relationship between traditional toxicology with genetics and omic technologies. Source: adapted from (25,26).

From the toxicogenomic standpoint, profiles of gene expression of the biological systems exposed to the chemical products are made. The analysis of the data of these gene expressions provides important information about the states of the cells and their responses to chemical and environmental stimuli. This information can be used to predict the potential toxicity of xenobiotic agents —new chemical entities in particular— and can lead to the elucidation of the mechanisms of toxicity (2,18,20).

The underlying premise of toxicogenomics is that an overall assessment of the biology of exposure to chemical products can lead to a deeper understanding of the mechanisms of action of the toxic agents (10). The main focus of this field is to identify and study changes in gene expression "signatures or fingerprints" (based on biomarker genes) for a group of known prototype compounds (factors of oxidative stress, polycyclic aromatic hydrocarbons, etc) with the goal of learning to manage, and even induce, a particular toxic response that later could be used to better understand the mechanism of action of unknown compounds. The intention behind using these signatures is, on the one hand, to better understand the biology that underlies toxic response, and, on the other hand, to develop strategies for testing new compounds, thereby determining potential toxicity on the basis of profiles of gene expression (2,10,20).

Classification in toxicogenomics

With a basis in genomics, toxicogenomics is classified according under the categories of structural and functional. Structural genomics is concerned with the physical characterization of complete genomes. In other words, it aims to decipher the number, order, and sequence of the nucleotides of the DNA molecule (7).

In this process, genotyping is performed. The analysis of the individual variations in the DNA sequence of an organism is known as genotyping. By performing laboratory techniques, the genetic information of an organism or genotype is found, thereby determining alleles that correspond to each genetic variant. Some of the methods that are currently available for this process are: conventional or real-time PCR, DNA sequencing, ASO probes, and hybridization in DNA microarrays or microspheres (27).

Similarly, the term epigenetics describes the study of the alterations in gene expression that arise during cell development and multiplication through processes that do not change the information (the sequence) contained in the genetic material, but that modulate the gene expression through specific modifications related to the remodeling of chromatin. This is mediated by chemical variations in the histone and the DNA (28). The main modifications include DNA methylation, covalent modification of cytosines, and post-transductional modifications of histones (including methylation, acetylation, and phosphorylation) (29). These changes in the DNA can be stable and pass through mitotic and meiotic divisions of the cells —that is, they can be inherited— (28).

The main pathway in which epigenetic information is stored and propagated is through the methylation of DNA in cytosine residues in order to form the modified base 5-methylcytosine and the post-transductional modification of the proteins that wrap genomic DNA in chromatin. The methylation of the cytosines generally occurs in sites of the genome known as CpG islands, and is usually associated with the silencing of adjacent genes. As such, the perturbation of the state of DNA methylation alters the spectrum of genes and the expression of proteins in a cell. At the same time, it may lead to alterations in the cell phenotype (30).

Epigenetic alterations predispose individuals to the development of diseases. A wide variety of types of human cancers show aberrations in the patterns of DNA methylation.

This suggests that the changes in the state of DNA methylation of certain genes can contribute to the transformed phenotype. However, the epigenome is dynamic, and it is thought that it is influenced by ambient factors over the subject's lifetime. Epigenetic perturbation, like the methylation of DNA and histone modification, may be implicated in the adverse effects associated with some xenobiotic agents, including certain non-genotoxic chemical carcinogens. As such, they may represent more stable exposure fingerprints for genes altered or implicated in protein expression. Furthermore, the inter-individual differences in the epigenetic state could also affect susceptibility to xenobiotics and the risk of associated disease (30,31).

On the other hand, functional genomics is defined as the development and overall application (the entire genome or systems) of experimental focusses for evaluating the function of genes by making use of genome information and sequencing. Functional genomics in the context of toxicology is known as functional toxicogenomics. In other words, it refers to the study of the biological activities of genes and proteins in an organism in their response to the effects of a toxic agent. Functional genomics directly measures phenotype. As a result, it provides a direct link between specific or networks of genes, their variants (polymorphisms), and their products with the variation of cell responses to a xenobiotic (10).

Omic technologies

Up until a short time ago, the complexity of toxic response remained incomprehensible due to the simplicity of the analytical tools available. Indeed, they allowed for the determination of only a few genes in any study (2). The development of new technological tools associated with the identification and characterization of the human genome has led to the construction of a new sub-discipline of toxicology that involves the knowledge of the effects associated with different xenobiotics and the interindividual response of the organisms (32,33).

In conventional toxicology, a great quantity of data from histopathological trials, toxicokinetic trials of xenobiotic metabolizing enzymes, toxicodynamic trials from biological toxicity targets, and information from animal models. However, the most exceptional and complicated data are generated by emergent omic technologies, such as genomics, transcriptomics, proteomics, and metabolomics, that provide new perspectives for understanding toxicological mechanisms at the molecular level and, as a whole, help to better delineate the physiological events that underlie toxicity (25).

Toxicogenomics initially arose from the combination of experiments on DNA microarrays and the study of classic toxicology in 1999 to evaluate global gene regulation (measured by the relative abundance of messenger RNA) after treatment with different stress factors (10). When the cells of the body are exposed to a certain pressure or xenobiotic, they respond by altering the pattern of expression of the genes within their chromosomes, then the genes are transcribed into messenger RNA. The chemical information codified in the genes is translated into proteins, which leads to functional proteins that develop a variety of cell functions as a response to the exposure (Figure 2). The production of the protein codified by a given gene can increase, decrease, or remain the same, depending on the type of exposure and the needs of the cell (18).

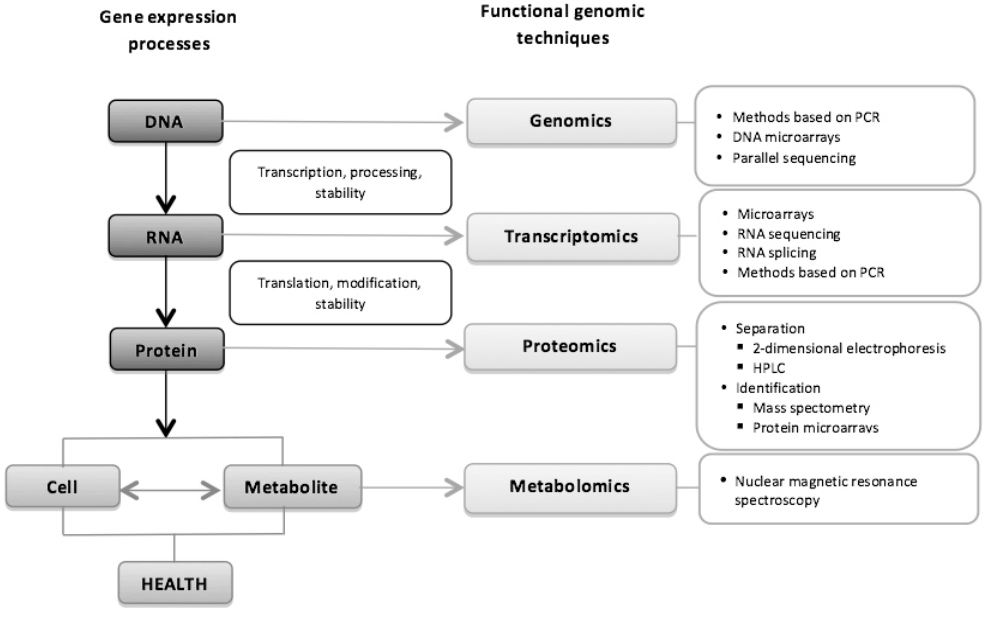

Figure 2. Functional genomics techniques relating to the gene expression process. Source: adapted from (7).

Transcriptomics

It is possible to approach functional genomics at the transcription level —that is, at the level of the formation of messenger RNA from DNA— since the changes in level of expression of a great number of organized genes regulate biological processes, as well as specific biological functions, pathways and networks. Upon entering the body, toxic agents can cause alterations in the expression of one or several genes, later leading to the interruption of the corresponding biological functions, networks, and pathways that are of vital importance for the normal operation of the cells/tissues/organs. Therefore, the alterations in the levels of expression of these genes can be the reflection of the toxicity.

There is substantial evidence that suggests that the changes in gene expression in the target organs of the intoxication present before the appearance of classic indicators of toxicity like biochemical and histological changes. As such, the determination of changes in gene expression in the target organs in response to the exposure to toxic agents, can provide a window of opportunity for the pre-clinical diagnosis of toxic endpoints and the application of effective intervention strategies for preventing adverse effects for health that result (34).

The transcriptome is measured by the global profile of the gene expression using analysis of DNA microarrays or microplate. This allows the simultaneous analysis of thousands of genes and, most recently, through studies of RNA-Seq using next generation sequencing (NGS) and high-throughput generation sequencing (HTGS) (7,31).

The base of the microarray technology lies in that a large number of known genes are stuck to the surface of a matrix with tiny micro-spaces (generally a fine sheet of glass), on which sequences of marked cDNA obtained from messenger DNA taken from a cell of interest are placed. This cDNA hybridizes with the matrix. The quantity of marked cDNA that attaches to the DNA stuck to the matrix can later be measured. Experiments with microarrays are always run comparing two or more samples and measure genetic expression. That is to say that the relative quantity mRNA at the time of the study may or may not correlate with the transcription levels, and, as such, they are highly related with the levels of protein in the cell (35).

This technology helps to define the complex regulatory circuit within a cell, tissue, or organ, and gives a global perspective on how the organ responds to xenobiotics, including pharmaceuticals, foods, or toxic substances. The data generated provides information about the cellular gene networks that respond and define important molecules associated with the mechanism of toxicity and provide biomarkers that measure the biological susceptibility that results from exposure or as an effect of an environmental agent. Lastly, this information allows us to identify ways of reducing or preventing damage or disease through the localization of the biochemical and molecular functions that have been disrupted by the environmental chemical products (18). An advantage of this molecular technique is that it allows us to approach an awareness of toxic effects through the study of the modulations of the levels of expression of the transcripts. However, it is important to remember that in peripheral human blood, the transcriptome is dynamic, modulating itself in response to environmental factors like stress, exercise, diet, and lifestyle (18,31).

Proteomics

It is also widely known that proteins are the final mediators in all biological processes. For this reason, compared to the transcriptome, the proteome may better reflect the molecular and cellular process due to the fact that transcriptional changes cannot be used to predict changes at the level of active proteins since protein expression must be analyzed separately (26,31,36).

The proteome is defined as the totality of the proteins expressed by a genome at a given time and under determined conditions of time and environment. Each cell in an organism contains the same genome, though different cell types express several thousand different proteins, and each one of them may experience numerous modifications in response to a determined microenvironment. Proteomics is defined as the part of functional genomics that is responsible for the study of proteomes and takes into account the overall analysis of quantitative changes in levels of proteic expression and of modifications after the translation of the proteins in the cell.

Proteomic analysis provides important information on the intra-cellular microenvironment, including the identification of the proteins involved (cell map), the quantification of proteins (protein profiles), the localization of proteins, their 3-D structure (structural proteomics), and later modifications to the translation and protein-protein interactions. In this way, proteomic research contributes to increase our knowledge of the behavior of biological systems, making possible the identification of biochemical changes through the control of collections of proteins that may be associated with toxicity (7,36-38).

The main challenge of proteomics consists in approaching the enormous and dynamic variety of proteins. There are several different perspectives for studying the proteome of a tissue or cell type. Currently, diverse practical standpoints are applied, each of them with their strong points and technical limitations. The identification of specific proteins is generally performed using a combination of separation techniques. For example, two-dimensional electrophoresis and high-efficiency liquid

chromatography, followed by tandem mass spectrometry for the quantification of proteins in complex mixes. Nevertheless, the analysis of the total production of proteins codified by the genome using proteomic techniques is more complex and less susceptible to application on a large scale due to differences in protein properties, location, and abundance (7,26,31).

Metabolomics

The metabolome can be defined as the sum total of the substrates, metabolites, and other small molecules that have a population within cells and have to do with the last level of gene expression. Metabolomics is defined as the global and impartial study of the structure and distribution of the amount of these tiny molecules (<1 kDa). It is concerned with the complete measurement of the final products of the cellular metabolism, of the metabolites of the endogenous and exogenous substrates in a biofluid, tissue, organ, or organism (26,39).

Different quantitative analytical methods have been developed for identifying the metabolites. Largely, this has been done with nuclear magnetic resonance spectroscopy and mass spectrometry. These techniques provide structural and quantitative information about small endogenous molecules such as peptides, amino acids, sugars, lipids, and final products of degradation. The signals detected in the nuclear magnetic resonance spectrums offer information about the structure of the metabolites. Meanwhile, the m/z fragments obtained from mass spectrometry is associated with molecular weights (40,41).

Metabolomics has a certain attraction over the other omic technologies due to the ease of preparation of the samples, of the acquisition of data, and the use of biofluids collected through minimally invasive procedures in preclinical (animal) and clinical studies (40).

Applications of toxicogenomics

The applications of toxicogenomics can be described loosely by the two classes that are superimposed on them: the mechanistic or research class, and the predictive toxicology. These studies are related to the adverse toxicological effects in clinical trial for the development of appropriate diagnostic markers (18).

One of the main objectives of toxicogenomics is to understand the relationship between gene-environment interaction and susceptibility to human disease by satisfactorily identifying the genes responsible for susceptibility to harm, the expression profiles that constitute exposure biomarkers, and the early effect biomarkers that can prematurely identify the development of a disease without clinical evidence, in addition to elucidating the molecular mechanisms of toxicity (11,41).

A challenge to the interpretation of toxicogenomic data is the fact that a gene change does not necessarily man a change in the expression of the protein or indicate an adverse event. Here, it should be related with other physiological events in order to understand the mechanisms of action, the pathways, and the toxicological effects (22), as seen in Figure 3.

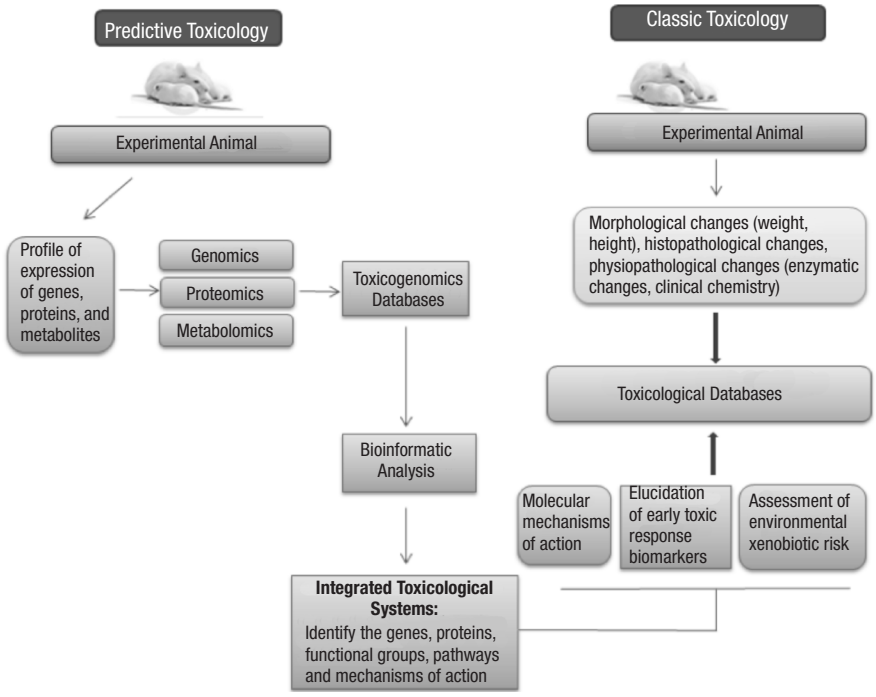

Figure 3. Applications of toxicogenomics and the development of predictive toxicology. Source: adapted from (22,41).

Gene expression and toxic response

In human beings, approximately 0.1% of the 3 billion DNA base pairs that make up their genome varies between individuals. This small variation can have profound effects on biology, resulting in serious disease and, in some cases, premature death (33). These polymorphisms can involve large segments of the genome, producing deletions, conversions, and duplications of genes. However, the biggest part of variability of the genome is due to "single nucleotide polymorphisms" (SNPs), which can affect biological function in many ways, including for example polymorphisms that can increase or decrease enzymatic activity (Figure 4).

The SNPs that are located in the coding region of a gene can give rise to a protein that has an amino acid substitution or that is split, causing a change in the activity, localization, or stability. The polymorphisms that induce changes in the translational reading frames lead to synthesis of proteins with alterations to the amino acid sequence, which, with the production of different proteins, undoubtedly leads to the loss of protein activity.

The alterations of nucleotides in the regulatory regions of a gene can also have an significant impact on the integrity of the function of proteins by influencing the quantities of proteins expressed in the different moments in which they are required. The polymorphisms in promoter regions can change the regulation and the level of expression of a protein, while polymorphisms localized close to the intron-exon interface may cause alterations in the processing of mRNA.

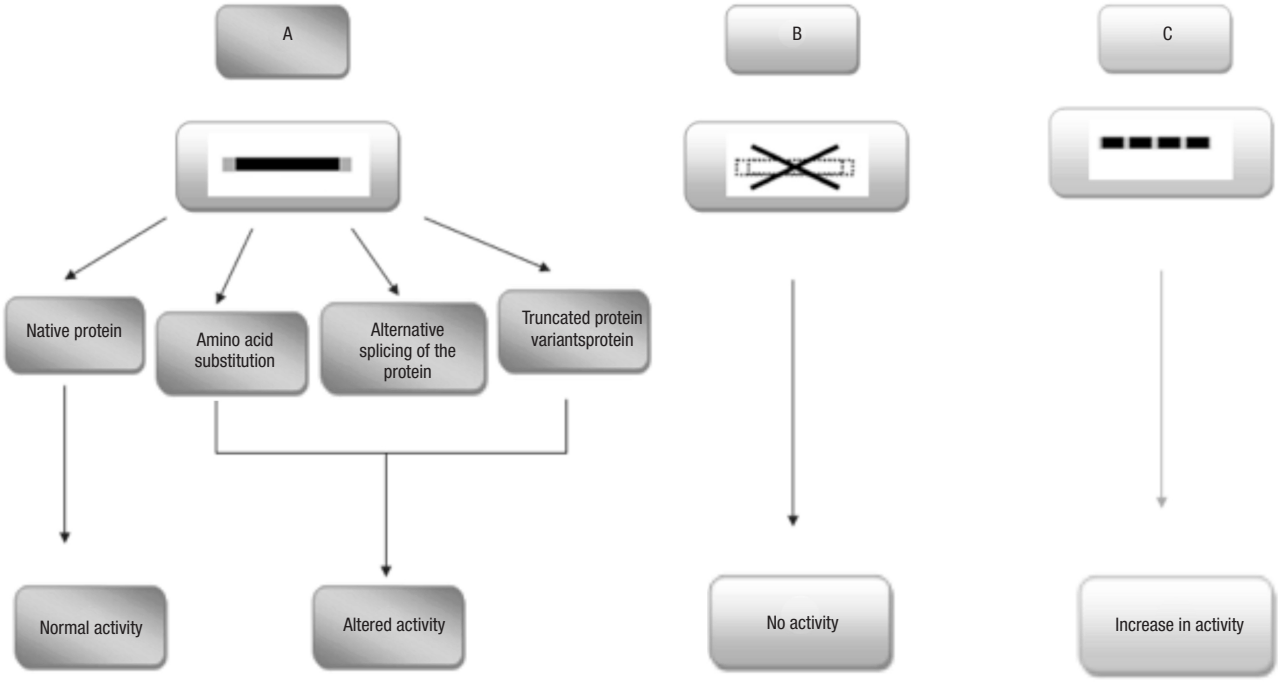

Figure 4. Effect of polymorphisms in relation to enzymatic activity. Source: adapted from (33).

The above shows that, when polymorphisms exist in the genes implicated in biological and metabolic processes like absorption, metabolism and excretion of pharmaceuticals and xenobiotics from the environment, the reparation of the DNA, in cell cycle control, and in membrane signaling, they occasion some sort of genetic susceptibility in certain individuals (23).

Genetic diversity has also been recognized as an important factor in how individuals react to the exposure to chemicals (42). For this reason, it is normal to find variations in the activity or expression of the metabolizing enzymes, which finally leads to an alteration in the metabolization of the xenobiotic (13).

The metabolization of xenobiotics is carried out by phase I and phase II enzymes. The majority of the genes that codify for these enzymes are structural and functionally polymorphic, especially those of the cytochrome P450 superfamily that metabolizes an estimated 56% of existing chemical products (23). The genetic polymorphisms of these enzymes have demonstrated that they cause frequent interindividual variation in the ability to metabolize pharmaceuticals and chemical

products, either in the process of deactivation (disintoxication) or activation (intoxication), differing markedly in the relative distribution of the variant alleles between ethnic groups. Such variations are probably very important factors in the determination of the clinical efficacy and safety of a variety of pharmaceuticals and in the appearance of possible adverse effects on health resulting from the environmental or occupational exposure to diverse chemical substances (23,42).

The use of biomarkers as tools for understanding the interaction of environmental chemical compounds and living organisms has again put forward experimentation on animal models, just as it has also had a large incidence in the pharmaceutical industry, since it contributes to the development of safer therapeutic alternatives (13). In the case of the development of new therapeutic alternatives, the identification and functional analysis of the genes is revolutionizing the research and development areas of the pharmaceutical industry, favoring rational use and development of pharmaceuticals that are ever safer and more effective (42).

The development of a new pharmaceutical implies a complex, costly, and prolonged research process that can end in failure due to adverse effects that can transform a promising study into a disaster (43-46). An early and reliable prediction of toxicity induced by an active principle represents one of the main challenges in pharmaceutical development. Toxic effects are the main cause, due to 44% of abandonment in the continuity of studies of a promising molecule. In phases I, II, and III, effectiveness becomes the main cause of failure (approximately 75%). As a result, recognition of the toxic effects at the molecular level is a more appropriate tool for evaluating the most promising candidates so that they may be developed in a more efficient way and at a reasonable cost (44,46).

The deficiency in the evaluation of the toxicological effects of promising molecules is gradually being remedied by toxicogenomic approaches. This, based on the application of differential gene expression, has become the focal point for the development of new therapeutic agents. This has occurred with the advantage that is can identify and evaluate adverse reactions to the new molecules or medications earlier and more quickly and precisely. This permits decisions regarding molecule selection that are based on safety and effectiveness (44,47,48).

Toxicogenomics and environment

The environment is everything that surrounds human life: the air we breathe, the water we drink, and the food that we consume. It contains tens of thousands of synthetic and natural chemical products, micro-organisms, radiation, pesticides, industrial byproducts, viruses, and physical factors with which individuals interact in their daily lives (23).

The interactions between people and their environment are complex. In some scenarios, they lead to disease, disability, and death. The identification of the causes of diseases is the first step in their prevention. We know very little about the effects of toxic substances in the environment, and it is a tremendous challenge to determine which compounds contribute to the appearance of —or susceptibility to— diseases in human beings. People living in urban areas are exposed to environmental contaminants, some of which are toxic for human beings (this list includes arsenic, polycyclic aromatic hydrocarbons, nitrosamines, and heavy metals) (23).

Risk assessment

Assessing risk is the process through which scientific data related to the toxicity of a chemical agent are assessed in order to make practical decisions about the liberation of this chemical agent into the environment (49). Toxicogenomics opens the door to the generation of this information, thereby improving the stages of the assessment processes of chemical risk at multiple levels (toxicokinetics and toxicodynamics) through the construction of predictive models for identifying risks for human health. These models replace the traditional way that involved performing toxicological studies with animal models as subjects, something that generated ethical conflicts (7,50).

Furthermore, by proving that inter- and intraindividual variation exists, the animal model should be rethought, for studies of chemical risk, through studies in a single population to establish criteria or standards related to responses to xenobiotics, improving the reliability of dosis-response extrapolation (22). On the other hand, the study of the chronic effects of environmental xenobiotic agents has been a complex task, with the development of predictive models favoring the strengthening of health promotion and prevention programs (23).

Another expectation is that, through the characterization of the molecular fingerprint and typical mechanisms of action, the classification of chemical products and mixes of products would be viable. This factor would contribute to the design of environmental management and industrial safety policies (26).

Conclusions

Without a doubt, it is worth addressing questions from the ethical and legal point of view related to what the information

and interpretations generated from toxicogenetics and toxicogenomics are, what types of technologies should be applied in the different population studies, and, lastly, how this information should be managed, whether publicly, privately, or in a mixed fashion.

Other aspects that should be defined are the ethical criteria for establishing study priorities that can be addressed through epidemiological analyses. This includes, for example, studies that define the policies and strategies of promotion and prevention, the studies that aim to develop new treatments, or studies that determine the toxic effects from xenobiotics through the search for markers of susceptibility in vulnerable populations (populations exposed occupationally, addicted populations) in order to take the appropriate measures.

Also, the ethical mechanisms for the collection and management of information should be unified, guaranteeing their confidentiality, and that they are being used for what was intended. Finally, there should be a tendency towards equitable access to these new technologies that favor the development of emergent disciplines (such as toxicogenetics and toxicogenomics) that offer refined information on the relationships between living organisms and their surroundings.

Conflict of interest

None declared by the authors.

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