Chapter 5

Pharmaco-Metabolomics: Drug Effects on Metabolites

Eda Sonmez Gurer*, PhD
Department of Pharmacognosy, Faculty of Pharmacy,
Sivas Cumhuriyet University, Sivas, Turkey

Abstract

The development and advancements in technology, artificial intelligence, and fields of bioinformatics, enabled the use of enormous data coming from genes, transcripts, and proteins processed by the omics in medicine as biomarkers. Scientists are improving different methods, such as stem-cell therapies, applications of regenerative medicine, and enhanced drug interactions in personalized medicine, using omics technologies in a broad scope of biology. Thus, the omics can discern functions of individual genes, proteins, and metabolites; to evaluate drug effects of drugs made or derived from such substances; and analyze differences in cellular pathways that occur from these drugs. The combined use of omics with system biology in regenerative medicine research, and pharmacology fields increases the information regarding concealed molecular mechanisms of diseases, their potential therapies, and personalized applications of stem-cell applications. Improved characterization of living systems along with a detailed evaluation of clinical and pharmacological data are required aspects for the further development of studies containing multiple omics methodologies. The application of data mining on the present data from the literature would enable to obtain experimental evidence in a cost-effective manner by reducing the prior experimental research. Metabolomics in

* Corresponding Author's Email: edagurer@cumhuriyet.edu.tr.

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pharmacology serves to attain personalization in medicinal treatments to preserve health and prevent diseases. Different branches of omics, such as metabolomics, transcriptomics, proteomics, and toxicogenomics, would lead to improved and easier use of pharmacometabolites in treatment protocols.

Keywords: biomarkers, diagnosis, individual therapy, pharmacology, metabolomics, pharmaco-metabolomics

Introduction

Changes in the amount of messenger RNA do not always respond to variations in protein levels and/or protein activities in the cell. Therefore, metabolites better represent actual outcomes of gene expression than proteomics information. Therefore, changes in the concentrations of metabolites may be more relevant for describing the physiological regulatory processes of organisms, diagnosing diseases, and treating the individual. Likewise, the biological effects that occur with the use of a drug cannot be decreased to the effect of just one compound. Metabolomics studies involve the sequential and combined use of many analytical techniques to create metabolite profiling and create relevant bioinformatics equipment. Currently, NMR technology is the generally used tool for metabolomics. Another important instrumental tool for pharmaco-metabolomics is MS-based proteomics technology. With MS instruments, all organic soluble components can be profiled quantitatively and with high precision (Zhang et al., 2010; Fiehn et al., 2000; Watkins and German, 2002). In addition, HPLC and UPLC technologies are also included in the field of metabolomics. Compared to conventional HPLC-TOF-MS systems, UPLC-TOF-MS systems appear to have a significant reduction in time with peak capacity and sensitivity. For metabolomic studies, it is a noteworthy problem that the experimental profile is affected by gender, genotype, age, nutritional status, drugs, lifestyle, and stress (Zhang et al., 2010). Individual metabolic fingerprinting creates new perspectives for metabolomics studies in determining personalised therapies and drug interaction profiles. Existing statistical studies of morbidity and mortality from the use of drugs reveal the urgent need for individual pharmaco-genomic and pharmaco-metabolomic profiling studies (Chadwick, 2010). Metabonomics/metabolomics and pharmaco-metabolomics technologies also provide a possibility for quality control (Wang and Tang, 2010).

Metabonomics involves metabolic responses from the multivariate analysis of organisms to physiological or pathological stimuli (Nicholson et al., 1999; 2002; 2004; Nicholson and Wilson, 2003). Metabonomics analyses NMR or mass data. In the target organism, all chemical components within a process under investigation are revealed as a "metabolic fingerprint" visualised by applying statistical data to identify the pattern of change of environmental or genetically induced variations in metabolite composition (Wang and Tang, 2010). The science of metabolomics has begun to create striking effects on biological, biomedical, and pharmacological studies. Researchers also use metabolomic approaches to elucidate xenobiotic toxicity mechanisms, pathophysiological processes, diagnosis and improvement of disease states, and the discovery of herbal or synthetic drugs (Whitfield and Kirwan, 2010; Lindon et al., 2005; Kaddurah-Daouk et al., 2008; Griffin ve Shockor 2004; Denkert et al., 2006; Whitfield et al., 2005; Marchesi et al., 2007; Kenny et al., 2008). Metabolomics studies on the determination of metabolic pathways related to normal physiology and pathophysiological conditions, including cancer (Trujillo et al., 2006; Barnes, 2008; Kim et al., 2008). The metabolome is the most comprehensive evaluation process for internally or produced low molecular weight metabolites externally such as vitamins, small peptides, amino acids, lipids, and carbohydrates, which are the most common metabolites in biological systems. At the same time, these metabolites can be sensitive indicators of various states of the disease and drug use (Jenab et al., 2009; Barnes, 2008; Kim et al., 2008; Emenaker and Milner, 2010). With the developments from many fields such as transcriptomics, genomics, metabolomics, and proteomics, it has been possible to benefit from all kinds of data from different sources in every field of biological sciences, and advances have been seen with bioinformatic analyses on the discovery of drug targets and understanding of pathways (Chen et al., 2005). More than 80% of current pharmaceutical drugs target enzymes such as G-protein coupled receptors (GPCR), kinases, and pathways belonging to several gene classes, such as proteases, nuclear hormone receptors, and ion channels. Studies on the development of new therapeutic drugs for these target genes for therapeutic use have gained weight. Regarding drug metabolism and drug transport, it can be said that the in-vivo response to a chemical component or drug treatment taken by the organism is very complex. As a matter of fact, the changes that occur within the cell and within the organism after the drugs are taken by the organism are an extremely dynamic process and consist of many sub-steps. For example, a large number of molecules consisting of at least 50 proteins participate in the pharmacodynamic process for metabolized drugs. Also,

various genes contain different polymorphisms to encode such proteins, control activity, or alter expression level (Pirmohamed and Park, 2001). Thus, the individual response to a drug reflects the interaction of multiple genetic variations involving multiple pathways, such as drug metabolism, toxicity, and drug delivery. Additionally, metabolic changes occur rapidly. When necessary or due to a physiological or pathological stimulus, there is the formation of target metabolites in the cell within seconds or minutes, with the expression of the messenger RNA changing, directing the focus on metabolomics research (Fanos, 2016). Liver metabolism is an essential center for drug elimination of (Rushmore and Kong, 2001). These metabolisms are generally dependent on the cytochrome P450 isoenzyme, which is presented in the biotransformation of drugs. More than 100 isoforms for P450 have been identified in humans (Nelson, 1998; Chen et al., 2005; Sensen, 2005).

Pharmaceutical Metabolomics

The field of pharmaco-metabolomics and pharmaco-metabonomics is an approach that aims to provide predictions of drug effects such as efficacy, toxicity, and drug metabolism using mathematical models created from pre-dose metabolic profiles. As a matter of fact, urine profiles determined before the administration of the toxin are used to estimate the toxicity profiles resulting from the administration of toxins in rats (Clayton et al., 2006). There is an important relationship between the metabolic profile before the application of an active substance and the metabolic profile that may occur after the application. Similarly, a strong correlation was determined between post-dose outcomes and pre-dose urinary metabolite profiles, both in terms of toxicity and metabolic aspects. Such pharmacometabolomic profiling to screen patients in drug trials is an extremely important area, but significant efforts are required to obtain knowledge of the metabolic profiling and outcomes of drug metabolism. The potential of metabonomics and pharmaco-metabolomics to illuminate systems-level responses is currently under investigation in a variety of complex multicellular and multiorgan animals such as rodents and humans. Combined with data at other levels, integrating biomolecular organization with metabolomic changes at the proteome and genome level appears promising for producing new pharmacometabolomic insights. Identification of better biomarkers in areas such as toxicity and disease detection will certainly bring about a fundamental understanding of monitoring disease processes and a better understanding of molecular

organization (Wilson and Nicholson, 2008). Together with pharmaco-metabolomics, it will be possible to diagnose diseases and monitor drug therapy for humans on pharmaceutical metabolomics. However, research is intense and clinical applications will change rapidly in the future with pharmacometabolomic profiling and monitoring studies compared to many preclinical samples. One of the factors that will positively affect this is the emergence of huge biological bank capacity to comparison (Dumas et al., 2006; Everett, 2007; Lindon et al., 2007).

Pharmaco-Metabolomics and Cancer Drugs

The genetic and metabolic pathways used as drug targets. The interconversion of metabolites is expressed as extreme pathways of the metabolic network, and these pathways are used for drug screening. In the current century of genomic studies, scientists are keen to apply genomic knowledge from molecular engineering research in medicinal trials. In the field of pharmacogenomics, a genetic signal is thought to act as an on-off switch in metabolic control. However, the genotype-phenotype correlation must be established in drug screening to successfully implement genetic switches. Gene expression and peptides are signaling switches for metabolism. So, the effect of drugs on metabolic regulation is related to genetic translation. Cancer cells generally have different metabolic properties from normal cells and synthesize macromolecules for cell growth and proliferation. The deficiency of the tumor suppressor gene or the overexpression of an oncogene is sufficient to generate the genetic signals to modulate metabolic pathways in the formation of the cancer phenotype (Lee et al., 2012; Roessner, 2012).

Overall, pharmacometabolomic approaches have been observed to be quite successful in cancer studies. It is expected that ‘personalized medicine’ studies will benefit greatly from pharmaco-metabolomics, along with data from all omics sciences. The goal of chemotherapy is to both cure the disease and reduce symptoms. Chemotherapeutic-induced cytotoxicities may occur in the patient shortly after administration or chronically. The aim of pharmaco-metabolomic approaches is to conduct profiling studies on the metabolite differentiations that occur at the onset of the disease, in the diagnosis, treatment stages and depending on drug use, by providing small amounts of samples that can be taken from all body fluids, or by the samples that can be obtained quickly without harming the patient, and, accordingly, directing the treatment (Chiang et al., 2018).

The Dynamic Nature of Metabolism

There is increasing interest in drug transport, spatial distribution, and analysis of drug metabolites in a target cell or in various cell cultures. The imaging, monitoring, and analysis of drug metabolisms are generally based on the LC-MS method. The LC-MS method makes it possible to detect trace amounts of molecules and to determine the localization of drugs within a cell. Primary cultures of human hepatocyte cells are used as a basis for estimating drug-related metabolism pathways. Therefore, hepatocytes are preferred as suitable cell line systems for metabolomics. In addition, LC-MS techniques are quite successful even in determining the heterogeneity of drugs even in a single cell. This approach has the potential to identify correlations between drug metabolism in cells cultured from a single cell and at subcellular levels, and between pharmacological studies, pharmacometabolomic analyses, and even toxicological effects (Fukano et al., 2012; Emara et al., 2017). However, more detailed studies are required with very large sample groups. In the preclinical phase of biomarker discovery, several technical challenges need to be overcome, and mass spectrometry data needs to be analyzed very carefully. In fact, there may be a high degree of correlation between metabolites in LC-MS data, making it difficult to distinguish between metabolites with similar chemical properties or significant correlations based on shared metabolic pathways. On the other hand, the identification of informative and specific biomarkers is an important limitation of pharmaco-metabolomics as a health technology. Identifying which metabolites could be potentially useful biomarkers is a much more difficult process than previously thought. The dynamic nature of metabolism, which can be significantly affected by genetic differences and environmental exposure, is quite complex. Furthermore, prior to inclusion in clinical practice, clinical validation is required to determine whether a particular metabolic test is sensitive enough to identify those at risk or affected by a disease and whether it is specific enough to a particular disease process.

Conclusion

Metabolomics research plays an increasingly important role in the sciences, in the diagnosis and treatment of nutritional-related chronic and systemic diseases, and in the profiling of physiological processes. Additionally, studies

that search for metabolite clues that can express the symptoms or treatment processes of the disease in all body tissues or fluids of individuals in the diagnosis or treatment processes of common or rare diseases occupy a large place in the field of pharmaco-metabolomics. Pharmaco-metabolic strategies that have the ability to describe pharmaco-metabolomics create a great opportunity to obtain knowledge of the molecular basis of metabolic processes. It is likely that with future technological developments studies on the effects of drugs on physiological processes and the profiling of formed metabolites in various diseases will be sought in the field of pharmaco-metabolomics. On the other hand, with the effect of the drugs or herbal or synthetic active substances used, metabolite changes that occur in individuals before or after their use seem to be the focus of research for all diseases or pathological processes. However, with the increased capacity to determine metabolite profiles and technologies to develop them, it will support a more detailed understanding of direct control mechanisms and improve our understanding of the effects of different environmental or internal stimuli on individuals. Similarly, pharmaco-metabolomics makes it possible to help develop functional nutrients and follow and classify the effects of drugs or active substances to be used before and after treatment. This may ultimately improve personalized medicine and individualized therapeutic approaches where pharmaco-metabolomics exists.

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