

Pharmacometabolomics: Current Applications and Future Perspectives

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Metabolomics, a novel “omics” platform, is a powerful tool for the discovery of clinically useful biomarkers and biochemical processes to improve diagnosis and therapy. Through the use of advanced analytical technologies, metabolomics enables the assessment of comprehensive metabolic profiles that are affected by both genotype and environmental factors. Recently, attention has been focused on the concept of pharmacometabolomics, an emerging field that is derived from metabolomics. Pharmacometabolomics is focused on the use of individual metabolic signatures for the prediction and evaluation of drug efficacy and safety, eventually accelerating clinical pharmacology toward personalized drug therapy.

Introduction

Metabolomics is the study of all of the small molecular metabolites present in cells, tissues, or organs. These small molecules are intermediates and/or end products of cellular processes and may reflect the metabolic phenotype, which is regulated by interactions between genotype and other environmental factors, including diet, lifestyle, and the gut microbiome. In this regard, the metabolomic approach provides a complete overview of an individual's metabolic state, which cannot be obtained from transcriptomics and proteomics.[1]

Pharmacometabolomics is a rapidly emerging discipline that involves the direct measurement of metabolites in an individual's body fluids to understand mechanisms of drug action and to identify novel biomarkers of the cellular response to drug intervention (Fig. 1). This approach further allows the identification of the metabolic pathways implicated in individual variations in response to drug treatment. This review addresses the current state of pharmacometabolomics, its applications, and its future potential in drug development.

Pharmacokinetics and predose metabolic profiling to evaluate the response phenotype

The metabolic phenotype is a result of the overall influences of an individual's physiological status and environmental fac-

tors. Metabolic profiling can provide useful information for predicting individual drug response and variation. Recently, using liquid chromatography/mass spectrometry (LC/MS)-based metabolomics, we evaluated urinary metabolic profiles from healthy volunteers before and after oral administration of tacrolimus to identify a metabolic phenotype that would be predictive of individual variation in the response to tacrolimus.[2] Although tacrolimus is a commonly used immunosuppressive drug during organ transplantation, its efficacy is influenced by its narrow therapeutic index and the large variability in tacroli-

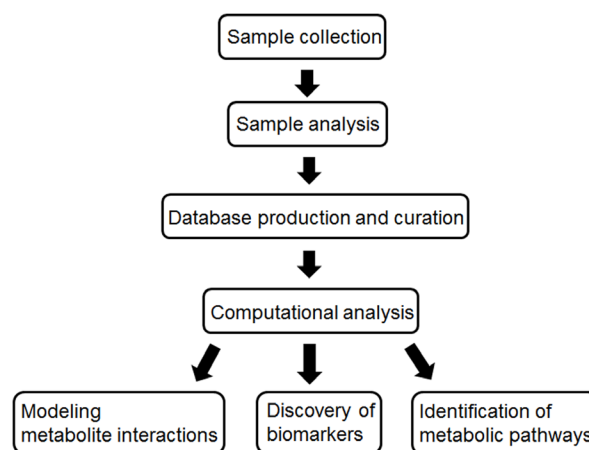


Figure 1. Overview of the pharmacometabolomics process.

mus blood concentrations among individuals who receive the drug.[3] Therefore, it would be interesting to predict individual variation in the pharmacokinetics (PK) of tacrolimus to avoid adverse drug effects and therapeutic failures. In our study, partial least squares modeling was performed to predict the PK of tacrolimus after drug administration. Based on this model, we identified key metabolites that eventually allowed us to predict the individualized PK of tacrolimus. This pharmacometabolomic approach, combined with metabolic profiling, could be extended to evaluate the PK of other drugs that show interindividual variability. Overall, our study demonstrates the potential for pharmacometabolomics as a useful tool in individualized drug therapy.

Pharmacometabolomics for predicting individual drug response

Several studies have demonstrated the practical value of pharmacometabolomics in predicting individual drug response and variation.[4–6] A recent study employed a lipidomics platform to develop metabolite signatures that predict individual response to statin treatment.[4] Statins are used to reduce cardiovascular disease risk by lowering low-density lipoprotein cholesterol (LDL-C). However, there is considerable variation in the individual response to statins as well as in their mechanism of action. Through a targeted lipidomics approach, Kaddurah-Daouk et al. evaluated blood samples from good and poor responders (based on the percentage change in LDL-C) to simvastatin treatment. These authors showed that there were large changes in the blood levels of cholesterol esters and free cholesterol in the good responders, while there were fewer changes in the poor responders. They also demonstrated that baseline cholesterol ester and phospholipid metabolite concentrations were positively correlated with LDL-C levels in response to statin treatment. Thus, this pharmacometabolomics study showed the potential for predicting drug efficacy in an individual.

In addition to the lipidomics study, a targeted gas chromatography/mass spectrometry (GC/MS) study evaluated metabolites implicated in cholesterol synthesis, dietary sterol absorption, and bile acid formation to determine metabolite signatures that may predict variation in the efficacy of statins for lowering LDL-C.[5] The study showed that plasma levels of simvastatin were positively correlated with levels of several secondary bile acids, which may be produced by the gut microbiome. In addition to this metabolomics approach, a pharmacogenetic study was performed. The genetic analysis revealed that one single-nucleotide polymorphism (SNP) in the gene encoding the organic anion transporter was associated with the plasma levels of seven bile acids. Together, this study indicated that the gut microbiome has an important role in cardiovascular disease and that both genetic and environmental factors can lead to variation in the statin response.

Recently, a follow-up study was conducted by Trupp et al.[6] Using a non-targeted GC time-of-flight MS-based metabolo-

mics platform, these authors evaluated the global metabolic effects of simvastatin. Plasma from a broad sample of the full range of LDL-C responders was analyzed before and after simvastatin treatment. Pathway enrichment analysis revealed that the metabolites generated from simvastatin exposure were enriched for the pathway class “amino acid degradation”. Simvastatin responders in the full-range group contained urea cycle intermediates and a group of dibasic amino acids that are related based on shared transporters. In addition, through orthogonal partial least square discriminant analysis, the study showed that baseline metabolic profiling could clearly discriminate between good and poor response groups based on a select group of metabolites, including xanthine, 2-hydroxyvaleric acid, succinic acid, stearic acid, and fructose. Overall, these results indicated that groups of metabolites from multiple biochemical pathways that are not directly associated with cholesterol metabolism may be important for regulating the response to simvastatin treatment.

Integrating pharmacometabolomic and pharmacogenomic approaches in clinical studies

Pharmacometabolomic analyses are often coupled or followed up with pharmacogenetics studies. The so-called “pharmacometabolomics-informed pharmacogenomic approach” might make it possible to consider the roles of both nongenetic and genetic factors that can affect drug outcomes. Recently, Yerges-Armstrong et al. applied this approach to gain insights into aspirin response variability and defined novel genetic determinants of drug response.[7] Using this approach, they identified multiple SNPs in the adenosine kinase gene associated with platelet aggregation in response to aspirin. When combined with the pharmacogenomics approach, pharmacometabolomics will allow for a more comprehensive understanding of the mechanisms affecting variability in drug response.

Pharmacometabolomics and biomarkers

The main application of metabolomics lies in the identification of biomarkers that may be useful as diagnostic tools. Shin et al. recently employed a targeted metabolomics approach to evaluate endogenous biomarkers of cytochrome P450 (CYP)-mediated drug metabolism in healthy subjects.[8] Although the plasma level of 4 β -hydroxycholesterol is known as an endogenous marker that is correlated with CYP3A activity,[9] this metabolite might not be a good marker for predicting basal levels of (or the inhibition of) CYP3A activity.[8] The study employed a GC/MS method to investigate the relationship of 47 steroid metabolites with CYP3A activity, as mirrored by midazolam clearance. They identified several endogenous metabolites that were better correlated with midazolam clearance than traditional markers of CYP3A activity. This study revealed the ability of the pharmacometabolomics approach to generate predictive markers of CYP3A activity and further provided insights into variations in CYP-mediated drug metabolism.

Pharmacometabolomics and the future

Pharmacometabolomics has been successfully applied in pre-clinical animal studies and human clinical studies to evaluate the effects of drugs. Although pharmacometabolomics is now widely used as a powerful tool for understanding biological changes after a drug intervention, there are several challenges surrounding the pharmacometabolomics field. These challenges include the need for accurate quantification of metabolites as well as the need for appropriate maintenance and calibration of the analytical and computational equipment. However, with the advancements in instrumentation and various computational methods, pharmacometabolomics will play a critical role in future drug discovery and development. Furthermore, the pharmacometabolomic approach will provide individual-specific information about drug efficacy and facilitate the development of processes to identify novel therapeutic targets, ultimately enhancing the movement toward personalized medicine.

Conflict of Interest

Nothing to declare

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