

Metabolomics in Drug-induced Toxicity and Drug Metabolism

Jinchun Sun*

Division of Systems Biology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA

Editorial

New drugs might be approved by the Food and Drug Administration (FDA) if the chemicals can demonstrate therapeutic efficacy and lack of serious adverse effects by a series of rigorous preclinical tests and clinical trials. Toxicology assessments are routinely used in preclinical animal studies to evaluate the harmful effects of a potential new drug candidate and its major drug metabolites. Despite the rigorous testing of new drug candidates in the screening and preclinical developmental phases, there are still some drugs that have toxic side effects that arise in the clinical testing phase and/or post-market. The failure of a drug candidate due to safety concerns at the end stages of testing or pulling it off the market after approval, is a public safety concern and results in an enormous loss to the pharmaceutical company in terms of both time spent (average 8-10 years from the drug development to ultimate approval by US FDA) in development and overall costs (estimated cost of developing a new drug candidate was over 1 billion dollars in 2006) [1]. The current set of clinical chemistry biomarkers used to diagnose liver injuries include serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels while blood urea nitrogen (BUN) and serum creatinine are used to monitor kidney injury. The kidney injury markers BUN and creatinine only increase after significant organ damage has occurred. ALT is usually considered as a liver damage biomarker but can also increase due to muscle injury. Therefore, significant energy and monetary efforts have been invested by the pharmaceutical industry and regulatory agencies to discover novel, more specific and/or sensitive biomarkers. Currently, the high-throughput omics technologies, which comprise transcriptomics, proteomics and metabolomics, are promising platforms in terms of finding new translational biomarkers of drug-induced toxicity.

Global metabolic profiling, including both metabolomics and metabonomics studies, evaluates downstream changes in small molecules resulting from changes in transcription and proteomics. Metabolomics is defined as “the measurement of the metabolite pool that exists within a cell under a particular set of conditions” [2] while metabonomics is described as “the quantitative measurement of the dynamic multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification” [3]. Metabolic profiling is an emerging technology, which has the potential to identify early toxicity biomarkers that are indicators of drug-induced organ injury. Two major analytical platforms employed in metabolic profiling are proton nuclear magnetic resonance spectroscopy (¹H NMR) [4,5] and mass spectrometry (MS) [6,7] coupled with a separation technique such as liquid chromatography (LC), gas chromatography (GC) or capillary electrophoresis (CE). Metabolic profiling has been and will continue to impact the investigation of drug toxicity in terms of identification of novel biomarkers or patterns of biomarker changes related to drug toxicity in biofluid samples (such as urine and blood), which is expected to differentiate the origin of the toxicity, specifically the organ that is targeted by a particular drug compound [4,6,8]. Metabolic profiling methods have been widely employed in various drug-induced toxicity studies, including hepatotoxicity [8], nephrotoxicity [9] and vasculitis [10]. It must be noted that careful experimental design is required for a successful metabolomics experiment. It is important to consider the factors which can influence the metabolic profiling such

as animal gender and age, diet, drug efficacy, gut microflora status, sample collection, sample storage, and sample processing, etc. By doing so, metabolic profiling has the potential to identify translational biomarkers which can differentiate effects that arise solely from drug-induced toxicity. Metabolic profiling may also provide clues about the mechanisms of drug-induced toxicity. If this information is obtained early in the drug development pipeline, it will protect public safety and improve the productivity of the drug development process.

In addition to applications in the investigation of drug-induced toxicity, metabolic profiling has been proven as a powerful tool in rapidly identifying drug metabolites from global profiling combined with multivariate statistics tools [11-13]. Identification and characterization of drug metabolites, whose nonclinical toxicity needs to be evaluated, has been a topic of both pharmaceutical and regulatory interest. Early identification of disproportionate drug metabolites can provide clear justification for additional testing in animals, assist in interpreting and planning clinical studies, and prevent delays in drug development. Metabolic profiling can provide a more thorough understanding of the drug's metabolic fate. Drug metabolism information is very important for prediction of the safety and efficacy of investigational medical products since the route(s) of drug metabolism (through which a drug can be transformed to one or more active or inactive metabolites) can significantly affect the drug's safety and efficacy. Therefore, the importance of pharmacokinetic and metabolic profiling approaches should be highly recognized in the risk assessment of drugs. For example [6], both LC/MS- and NMR-based metabolic profiling were utilized to evaluate the excretion kinetics of acetaminophen (APAP) and its major metabolites in urine at 0, 24, 48, 72 and 96 h after a single dose of APAP. Results showed that the urinary levels of its major metabolite, *N*-acetyl-*L*-cysteine acetaminophen (APAP-NAC, a metabolite from deactivation of the reactive electrophilic intermediate *N*-acetyl-*p*-benzoquinone imine), was correlated to a statistically significant extent with clinical chemistry data, endogenous oxidative stress-related metabolites and histopathology data. The toxicity of APAP can be understood through monitoring the excretion kinetics of APAP-NAC. This metabolic profiling approach combined with multivariate statistical analysis could be extended to detect a drug candidate metabolite profile in biofluids to accelerate drug safety and screening processes.

Drug toxicity and efficacy can be affected by an individual's genotype, the chemical and physical properties of a drug, and by other environment factors like the gut microbiome, nutrition, medications, etc. Metabolic phenotype data encodes the physiological phenotype information of an

*Corresponding author: Jinchun Sun, Division of Systems Biology, National Center for Toxicological Research, US FDA, 3900 NCTR Road, Jefferson, AR, 72079, USA, Tel: +1 870-543-7556; Fax: +1 870-543-7686; E-mail: Jinchun.Sun@fda.hhs.gov

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individual, which is a critical component for predicting an individual's physiological response following a therapeutic intervention. Since the metabolic phenotype is generally downstream of alterations in gene and protein expression, understanding the metabolic phenotype can provide more useful information about patients' current physiological status that could be used for predicting the outcome following a therapeutic intervention. Global metabolic profiling has been playing important roles in determining the metabolic phenotype, which can be linked to disease, therapeutic interventions or overall health status of the individual. An individual's susceptibility to drug toxicity can be predicted from the metabolomic analysis of urine or serum samples of the individual before drug exposure. Recently, Clayton *et al.* [14] employed NMR-based metabolomics approaches to profile predose and postdose urinary metabolites and discovered that human subjects with high pre-dose levels of *p*-cresol (one of the metabolites related to gut microbiome) had lower concentrations of sulfonate APAP (a major of APAP metabolite), which is due to the competition of the binding site to the sulfotransferase enzyme. The individual with lower urinary concentrations of sulfonate APAP might be more susceptible to APAP-induced toxicity since less APAP was detoxified through urine by sulfate conjugation to produce sulfonate APAP. The findings indicated that each individual colonized by a unique assortment of trillions of microbes could respond to a drug differently, either beneficially or adversely. Therefore, evaluation of metabolic phenotype by metabolic profiling could play an important role in drug toxicity and metabolism as well as in personalized health care.

In summary, metabolic profiling will have an increasing and major impact on drug development and personalized medicine to improve public health. However, multiple analytical platforms are needed to provide complementary information due to the wide dynamic ranges and the diversity of metabolites making it impossible to analyze all of the biomolecules with a single analytical platform. Further, although advances in metabolic profiling are obvious in terms of stability, robustness and a higher degree of reproducibility of the analytical procedures, a set of broadly accepted quality control standards is needed to ensure the quality of metabolic profiling data and to validate the potential metabolomics biomarkers of drug toxicity. In all, metabolomics combined with transcriptomics and proteomics will offer a better understanding of the metabolism pathways of a drug molecule itself and its potential toxicity.

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