Journal of Chromatography
Separation Techniques

Li, J Chromat Separation Techniq 2012, 3:7
DOI: 10.4172/2157-7064.1000e106

Editorial Open Access

Xenobiotic Metabolomics: An Ideal Tool for Drug Metabolism

Fei Li*

Laboratory of Metabolism, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA

Xenobiotics are chemicals which include not only drugs but also dietary supplement, natural compounds, and environmental pollutants. Human exposure to xenobiotics is pervasive, and one might be exposed to 1-3 million xenobiotics in a human life time [1]. These chemicals can be toxic or harmful for the organism when they dramatically disrupt the metabolism and transport of endogenous compounds in the body, such as amino acid, bile acid, lipids, and hormone. Xenobiotics can be eliminated unchanged or metabolized by metabolism enzymes *in vivo*. Metabolomics, one high-throughput analytical technology, can systematically profile the endogenous metabolites in biofluid, cell, and tissue, which has been widely used to identify the biomarkers for clinical disease [2,3]. It also represents an ideal tool for understanding the impact of xenobiotic exposure on the body [4], especially for drugs. Multivariate data analysis and LC-MS were first combined for detection of xenobiotic metabolites in 2003 [5]. Since then, mass spectrometry-based on metabolomics has become a powerful tool to identify drug metabolites *in vivo*, especially for minor metabolites with the potential biological functions [6,7]. Recently, metabolomics has shown its advantage in the prediction of drug efficacy and drug induced side effects as well as personalizes medicine [8,9]. It is apparent that xenobiotic metabolomics has expanded the knowledge of drug and become a leading strategy to understand their metabolism, pharmacological activities, and side effects.

As one high-throughput analytical technology, the wide application of metabolomics is attributing to the development of analytical techniques and data analysis model. The ultra-performance liquid chromatography coupled with electrospray ionization quadrupole time-of-flight mass spectrometry (UPLC-ESI-QTOFMS), gas chromatography mass spectrometry (GC-MS), and nuclear magnetic resonance (NMR) are the major analytical techniques for xenobiotic metabolomics. Multivariate data analysis, including principal components analysis (PCA), partial least squares discriminant analysis (PLS-DA), and orthogonal projection to latent structures discriminant analysis (OPLS-DA), has been widely applied in xenobiotic metabolomics. UPLC–ESI-QTOFMS coupled with OPLS-DA model are one ideal strategy for drug metabolism to identify drug metabolites and candidate endogenous metabolites. In this method, the drug treatment group and vehicle group are specifically separated in scores plot of an OPLS-DA model. The drug metabolites and increased endogenous metabolites are shown in the top of first quadrant (p(corr)>0.75) in OPLS-DA loadings *S* plot, whereas the decreased endogenous metabolites occur in the bottom of third quadrant (p(corr)<-0.75). These metabolites can be initially determined to be drug metabolites or endogenous metabolites based on their trending plots. The further identification of these metabolites will be performed through their MS/MS spectrum and comparison with authentic compound.

There are a number of publications reporting the application of UPLC-ESIQTOFMS coupled with OPLS-DA-based metabolomics in drug metabolism. One example is ifosfamide and cyclophosphamide, which are common chemotherapeutic agents [10]. Interestingly, while the two drugs are isomers, only ifosfamide treatment is known to cause nephrotoxicity and neurotoxicity. Metabolomics profiling ifosfamide and cyclophosphamide metabolites (identification 23 metabolites with 5 novel metabolites) revealed that ifosfamide preferentially underwent *N*-dechloroethylation, the pathway yielding 2-chloroacetaldehyde, while cyclophosphamide preferentially underwent ringopening, the pathway yielding acrolein. Another example is pocainamide, a type I antiarrhythmic agent, which can cause lupus erythematosus in 25-30% of patients in clinic [11]. Interestingly, procainamide does not induce lupus erythematosus in animal. To explore this difference, metabolomics is conducted on the urinary metabolites from procainamide-treated humans and mice. Thirteen urinary procainamide metabolites, including nine novel metabolites, are derived from procainamide through oxidations and acylation reactions. Significant differences in *N*-acylation and *N*-oxidation of the drug between humans and mice largely account for the interspecies differences in procainamide metabolism. Significant levels of the novel N-oxide metabolites in humans might be associated with the development of procainamide-induced systemic lupus erythematosus. It is evident that observations based on the UPLC-ESI-QTOFMS coupled with OPLS-DA-based metabolomics can offer clues to understanding drug metabolism and side effects.

These observations have provided compelling evidence that xenobiotic metabolomics is an ideal analytical tool that can aid in understanding and revealing mechanism involved in drug metabolism. Through analysis of metabolomics, drug metabolites can be systematically determined and the potential toxic metabolites can be identified. More importantly, the biomarkers induced by drug exposure can be used to predict drug action or toxicity. In addition, inter-individual variation revealed by metabolomics can provide the import information for personalized medicine in the clinic.

References

1. Idle JR, Gonzalez FJ (2007) Metabolomics. Cell Metab 6: 348-351.
2. Patterson AD, Bonzo JA, Li F, Krausz KW, Eichler GS, et al. (2011) Metabolomics reveals attenuation of the SLC6A20 kidney transporter in nonhuman primate and mouse models of type 2 diabetes mellitus. J Biol Chem 286: 19511-19522.
3. Zhang Y, Li F, Patterson AD, Wang Y, Krausz KW, et al. (2012) Abcb11 deficiency induces cholestasis coupled to impaired beta-fatty acid oxidation in mice. J Biol Chem 287: 24784-24794.
4. Patterson AD, Gonzalez FJ, Idle JR (2010) Xenobiotic metabolism: a view through the metabolometer. Chem Res Toxicol 23: 851-860.
5. Plumb RS, Stumpf CL, Granger JH, Castro-Perez J, Haselden JN, et al. (2003) Use of liquid chromatography/time-of-flight mass spectrometry and multivariate

***Corresponding author:** Dr. Fei Li, Laboratory of Metabolism and Center for Cancer, Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA, Tel: (301)402-2499; E-mail: lif3@mail.nih.gov

Received October 19, 2012; **Accepted** October 21, 2012; **Published** October 24, 2012

Citation: Li F (2012) Xenobiotic Metabolomics: An Ideal Tool for Drug Metabolism. J Chromat Separation Techniq 3:e106. doi:10.4172/2157-7064.1000e106

statistical analysis shows promise for the detection of drug metabolites in biological fluids. Rapid Commun Mass Spectrom 17: 2632-2638.

6. Li F, Patterson AD, Hofer CC, Krausz KW, Gonzalez FJ, et al. (2011) A comprehensive understanding of thioTEPA metabolism in the mouse using UPLC-ESI-QTOFMS-based metabolomics. Biochem Pharmacol 81: 1043-1053.
7. Fang ZZ, Krausz KW, Li F, Cheng J, Tanaka N, et al. (2012) Metabolic map and bioactivation of the anti-tumor drug noscapine. Br J Pharmacol.
8. Johnson CH, Patterson AD, Idle JR, Gonzalez FJ (2012) Xenobiotic metabolomics: major impact on the metabolome. Annu Rev Pharmacol Toxicol 52: 37-56.
9. Patterson AD, Slanar O, Krausz KW, Li F, Hofer CC, et al. (2009) Human urinary metabolomic profile of PPARalpha induced fatty acid beta-oxidation. J Proteome Res 8: 4293-4300.
10. Li F, Patterson AD, Hofer CC, Krausz KW, Gonzalez FJ, et al. (2010) Comparative metabolism of cyclophosphamide and ifosfamide in the mouse using UPLC-ESIQTOFMS- based metabolomics. Biochem Pharmacol 80: 1063-1074.
11. Li F, Patterson AD, Krausz KW, Dick B, Frey FJ, et al. (2012) Metabolomics reveals the metabolic map of procainamide in humans and mice. Biochem Pharmacol 83: 1435-1444.