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Metabolomics: One Powerful Tool for the Understanding of Xenobiotic Receptors

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Xenobiotic receptors including members of the nuclear and soluble transcription factor superfamilies, can mediate the metabolic response of organism to the chemical environment. Upon activation, these receptors function to regulate numerous physiological processes, including the metabolism of xenobiotic pharmaceuticals and carcinogens as well as the control of endogenous lipid, cholesterol, energy and inflammatory pathways. For example, the peroxisome proliferator activated receptor (PPAR) α involves in the metabolism and transport of fatty acid; the farnesoid X receptor (FXR) is responsible for control of bile acid metabolism and transport; the pregnane X receptor (PXR) is a key regulator of drug transport and metabolism. A number of clinical drugs can perform their efficacy through the activation of xenobiotic receptors, including hypolipidemic fibrate drugs, ursodeoxycholic acid (UCDA), and rifaximin. However, in many cases, activation of xenobiotic receptors can lead to toxic and carcinogenic responses. Over past 20 years, the transgenic mouse model, including knockout and humanized mice, was widely used to explore the function of xenobiotic receptors. Despite numerous studies are conducted in xenobiotic receptors, the mechanism about how these receptors perform their function in response to xenobiotic challenge and their roles in the development of various diseases, such as cancer and diabetes, still remains unclear.

Metabolomics, one high-throughput analytical technology, can systematically profile the endogenous metabolites in biofluid, cell, and tissue. Currently, 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 metabolomics. Several data analysis models are widely applied to metabolomics analysis, including principal components analysis (PCA), partial least squares-discriminant analysis (PLS-DA), and orthogonal projection to latent structures- discriminant analysis (OPLS-DA). By the combination of advanced instrumental and data analysis models, metabolomics has become a powerful tool to identify the biomarker for clinical diseases, drug action, and drug toxicity, profile the metabolic maps of drugs, and reveal the toxic reason of environmental pollutants [1-6]. Recently, metabolomics analysis of the biomarker for xenobiotic receptor expression and activation greatly contributes to the understanding of the physiological function of xenobiotic receptors *in vivo*.

Peroxisome proliferator-activated receptor α (PPARα) is a nuclear receptor that plays an important role in the regulation of lipid metabolism, glucose homeostasis, and inflammation. To define the urinary biomarkers for PPARα, UPLC-ESI-QTOFMS-based metabolomics was conducted to analyze the altered metabolite in *Ppara*-null mice fed for 2 week PPARα ligand Wy-14,643. PPARα urinary biomarkers significantly elevated byWy-14,643 treatment included HDOPA, DHOPA, nicotinamide, nicotinamide 1-oxide, 1-methylnicotinamide, hippuric acid, and 2,8-dihydroxyquinoline-β-D-glucuronide. PPARα urinary biomarkers significantly attenuated by Wy-14,643 treatment included xanthurenic acid, hexanoylglycine, phenylpropionylglycine, and cinnamoylglycine [7]. These biomarkers indicate that PPARα shows its effects on tryptophan, corticosterone, and fatty acid metabolism and on glucuronidation. Another metabolomics study showed that the severe liver injury was induced in *Ppara*-null mice following cholic acid challenge revealed by the disruption of bile acid metabolism, phospholipid metabolism, and hormone metabolism, suggesting that PPARα is an essential regulator of bile acid biosynthesis, transport, and secretion [8]. Further study revealed that the decrease in the transporters of bile acid, phospholipid, and cholesterol was responsible for liver injury during PPARα mutation. Farnesoid X receptor (FXR) is a nuclear receptor that regulates genes involved in synthesis, metabolism, and transport of bile acids. To further evaluate its effect on bile acid homeostasis, metabolomic responses were investigated in urine of wild-type and *Fxr*-null mice fed cholic acid, an FXR ligand, using metabolomics. Multivariate data analysis between wild-type and *Fxr*-null mice on a cholic acid diet revealed that the most increased ions were metabolites of p-cresol (4-methylphenol), corticosterone, and cholic acid in *Fxr*-null mice [9]. These activated adaptive metabolic pathways upon bile acid challenge strengthen the effect of FXR on bile acid.

These studies have demonstrated the power of mass spectrometry-based metablomics in combination with transgenic mouse model and nuclear receptor ligand to determine the physiological function of xenobiotic receptors. The metabolic pathways correlated with xenobiotic receptors can be identified based on the results of metabolomics analysis. I believe that metabolomics will play more important role in elucidation of the function of xenobiotic receptors in the future.

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