Discovery of early urinary biomarkers on cisplatin nephrotoxicity by UPLC-TOF-based non-target metabolomics in rats

Cheng-Lung CHEN¹, Li-Heng PAO²,³,⁴

¹Graduate Institute of Life Sciences, National Defense Medical Center, Taiwan,
²School of Pharmacy, National Defense Medical Center, Taiwan,
³Department of Nutrition and Health Sciences, Chang Gung University of Science and Technology, Taiwan,
⁴Research Center for Industry of Human Ecology, Chang Gung University of Science and Technology, Taiwan

Cisplatin, a platinum-containing anticancer drug, is widely used as the chemotherapeutic agent for solid tumors. Unfortunately, the dose-limiting factor is cisplatin nephrotoxicity. The emerging “metabolomics” is a reproducible method reflecting the biological events, which provides the robust tool, fast examination, and holistic view to discover novel biomarkers. Recently, three articles have used three different metabolomics approaches including NMR, GC/MS and LC/MS (linear ion trap) to find out novel biomarkers and to investigate the metabolic mechanisms on cisplatin nephrotoxicity. However, the high sensitivity, high resolution and high mass accuracy, UPLC-TOF-based metabolomics platform, is never used to be studied. The aim of this study is to discover the early urinary biomarkers on cisplatin nephrotoxicity by the UPLC-TOF-based non-target metabolomics in rats. Serum biochemistry, BUN and creatinine, showed the significant nephrotoxicity in 3, 5, and 7 days after cisplatin administration. Histopathological findings of kidneys showed moderate to moderate/severe injury in the cisplatin-treated rats. For urinary metabolomics, the cisplatin-treated group showed significant separating from control group in the scores plot of PLS-DA in 3, 5, and 7 days after cisplatin administration. In order to find out the early urinary biomarkers, we used OPLS-DA to compare cisplatin-treated and control group in the 1, 3, or 5 days after administration, respectively. The results showed that 12 metabolites significantly change between cisplatin-treated and control group in the 1, 3, and 5 days after administration. These metabolites may be the early urinary biomarkers of cisplatin nephrotoxicity.