DOCTORAL THESIS

Mass Spectrometry-based Metabolomics and Imaging for Studying Cadmium Exposure and Its Toxicity

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ABSTRACT

Cadmium (Cd) is a toxic environmental pollutant that is readily absorbed by rice grains and poses serious threats to human health. Mass spectrometry (MS)-based metabolomics and imaging are useful analytic tools that have excellent sensitivity, fast speed and robust visualization for characterizing Cd toxicity. In this thesis, efficient MS-based methodology was applied and proved to be a new avenue for health risk assessment.

The thesis research content included three parts. In the first and second parts, metabolomics was executed to investigate the two different indica rice grains and a total of 403 human urine samples under Cd exposure, respectively. In the third part, the integration of omics analysis and atmospheric pressure matrix-assisted laser desorption/ionization mass spectrometry imaging (AP MALDI MSI) on the Institute of Cancer Research (ICR) female mice with acute Cd toxicity were conducted to explore the multi-system organ failure and uncover its acute toxicological mechanism.

There is a compelling need for the biomarker determination and characterization of metabolic pathways for the low-Cd-accumulating rice. The obtained results indicated that when the Cd concentration increased in rice grains, most carbohydrates and amino acids were down-regulated, except myoinositol which can prevent Cd toxicity was up-regulated. D-mannitol and L-cysteine were up-regulated with the increase of Cd concentration in low-Cd-accumulating rice. Also, organic acids were activated,

especially 13-(S)-hydroperoxy-9(Z), 11(E), 15(Z)-octadecatrienoic acid, which is related to the alpha-linolenic acid metabolism and jasmonic acid production.

Early urine metabolic detection using MS and machine learning (ML) algorithms is advantageous to predict the adverse health effects. After the comparison of seven ML algorithms based on the 403 urinary metabolic datasets, the extreme gradient boosting (XGBoost) and random forest (RF) classifiers showed better accuracy and predictive performance than others. Then, the MS-based metabolomics investigation of a cohort of 144 volunteers was conducted to explore sex-specific metabolic alteration and to screen biomarkers related to Cd-induced nephrotoxicity. The results indicated that when the concentration of urinary Cd increased, the creatine pathway, amino acid metabolism especially the tryptophan metabolism, aminoacyl-tRNA biosynthesis, and purine metabolism were primarily influenced regardless of gender. Also, the most specific biomarkers linked with nephrotoxicity based on the statistical analysis were detected including creatine, creatinine, L-tryptophan, adenine and uric acid.

The obtained results demonstrated that exposure to Cd caused significant metabolic alterations in the liver and kidney among all mouse tissues associated with acute Cd toxicity. The representative lipids on the mouse liver and kidney were visualized by AP MALDI MSI. Diglycerides (DG) and triglycerides (TG) were found down-regulated in the exposure group of mouse liver. Accordingly, phosphatidylcholines (PC), phosphatidylglycerol (PG), lysophosphatidylcholine (LPC), sphingomyelin (SM), phosphatidic acid (PA), and TG were down-regulated while phosphatidylethanolamine (PE) and phosphatidylinositol (PI) were up-regulated

in the renal cortex or medulla regions in kidney tissues of the mouse with acute cadmium toxicity. These insights could help discover tissue-specific biomarkers, enhance knowledge of its toxicological mechanism and guide risk assessment in the future.

Keywords: Cadmium, metabolomics, mass spectrometry, AP MALDI MSI, toxicity