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Multi-sample mass spectrometry-based approach for discovering injury markers in chronic kidney disease

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Objectives: Urinary proteomics studies have primarily focused on identifying markers of chronic kidney disease (CKD) progression. Here, we aimed to specify CKD-related injury markers through proteomics analysis in animal kidney tissues and cells, along with urine of patients with CKD.

Methods: Label-free quantitative proteomics analysis based on liquid chromatography-tandem mass spectrometry was performed on urine samples obtained from 9, 11, and 10 patients in CKD stage 1, 3 and 5, respectively, and kidney tissue samples from a rat CKD model by 5/6 nephrectomy. Tandem mass tag-based quantitative proteomics analysis was performed for primary cultured glomerular endothelial cells (GECs) before and after inducing 24-h hypoxia injury. Proteins commonly identified across the three sample types were validated.

Results: Upon hierarchical clustering, 264 among 2577 proteins in CKD urine increased sequentially according to CKD stage. Between rat 5/6 nephrectomized and sham-operated kidney tissue, 2497 proteins differed significantly; 4032 significantly differed between human GECs under normoxic and hypoxic conditions. Overall, five proteins (galectin-1, protein S, thymosin beta-4, gelsolin, and vimentin) increased with chronic injury in all types of samples. Among the five proteins, the validation analyses for protein S and galectin-1 were performed and galectin-1 showed significant inverse correlation with renal function as well as higher expression in glomerulus with chronic injury compared to protein S. After blocking Galectin-1, anti-fibrotic and anti-apoptotic effect was discovered in hypoxia induced fibrosis injury.

Conclusions: This constitutes the first multi-sample proteomics study for identifying key renal-expressed proteins associated CKD progression. The discovered proteins represent potential markers of chronic renal cell and tissue damage, and candidates for contributing to CKD pathophysiology.