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Mitochondrial structural and ROS system are down-regulated under renal fibrosis process

Soie Kwon[1], Dohyun Han[3], Areum Seo[2], Jong Joo Moon[2], Dong Ki Kim[1], Yonsu Kim[1], Seung Hee Yang[2]
[1]Department of Internal Medicine-Nephrology, Seoul National University Hospital, Korea, Republic of
[2]Department of Department of Kidney Research Institute, Seoul National University College of Medicine, Korea, Republic of
[3]Department of Department of Proteomics Core Facility, Seoul National University Hospital, Korea, Republic of

Objectives: Fibrosis is a common pathway of chronic kidney disease (CKD) progression. As a reflection of cellular response to environment, proteomics is widely applied in kidney disease. Though, most of previous proteomics are confounded to disease specific scheme and human samples. To understand renal cell response by fibrosis stress, we did untargeted proteomics in cellular and animal CKD models.

Methods: A primary cultured human tubular epithelial cell (hTEC) with 48 hours induction of recombinant TGF-β (2ng/ml) and 5/6 nephrectomy model were selected. hTEC cultured without any stimulation were used as control. 5/6 nephrectomy rat and shame were sacrificed at 8 weeks after operation and kidney tissue was obtained. Tandem mass spectrometry based label-free quantitative proteomic analysis was performed with hTEC and kidney tissue.

Results: In hTEC, total 10,324 proteins were quantified and 2,100 differentially expressed protein (DEP) were found. In 5/6 nephrectomy model, total 7,245 proteins and 2,889 DEP were identified. Among those affirmed proteins, 138 DEPs were up-regulated and 213 DEPs were down-regulated concurrently.

Gene ontology (GO) enrichment analysis was done and presented by adjusted false discovery rate (FRD) on each group to gain insights into the cellular functions and biological processes. The up-regulated proteins in fibrotic condition were significantly enriched with GO categories linking to cell adhesion, extracellular matrix organization and cytoskeleton organization (maximal –log FDR=24.1). On the other hand, down-regulated proteins were over-represented with GO terms associated with mitochondria structure and function (including matrix, inner membrane, protein complex and organization), oxidation-reduction process and small molecule catabolic process (maximal –log FDR=96.1). We finally identified that mitochondria structural and ROS proteins (BCKDHB, AK2, VDAC3 and GLDC) are down regulated under renal fibrotic process.

Conclusions: Mitochondria can be a clue and a new treatment target of CKD progression. Further validation study of discovered proteins in human samples and chronic renal cell are needed.

Figure 1. Gene ontology enrichment analysis of cellular and animal CKD model