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Change of peritoneal proteomes in response of fibrotic injury and Cyclo His-Pro treatment

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Objectives: Peritoneal fibrosis is the main cause of dialysis failure in peritoneal dialysis patients. We conducted an in-depth proteome analysis of peritoneal fibrosis and cyclo Histidine-Proline (Cyclo His-Pro, CHP) administration to determine whether peritoneal fibrosis could be changed through administration of CHP which showed a protective effect on fibrosis of kidneys and other organs in previous studies.

Methods: Quantitative proteomics analysis based on liquid chromatography-tandem mass spectrometry was performed for three groups of mice; sham, peritoneal fibrosis, and peritoneal fibrosis+CHP. Peritoneal fibrosis model of mice was developed by daily injection of chlorhexidine gluconate for 4 weeks. Mice were treated with intraperitoneal CHP(35mg/kg) or intraperitoneal normal saline 3 times a week for 4 weeks. To analyze the significance of CHP in human peritoneum, we measured CHP levels in peritoneal fluid of 31 peritoneal dialysis patients.

Results: The peritoneal proteomes in each mouse group were measured and they showed significant difference between sham, peritoneal fibrosis and peritoneal fibrosis + CHP groups. The number of differentially expressed proteins (DEPs) compared to sham were 1100 and 826 in peritoneal fibrosis and fibrosis with CHP groups, respectively. In the clustering analysis, among the DEPs, 33 proteins including Hp, Tmed5, G6pdx, Hdac2 and Ckap5 showed an increase in expression after fibrosis and then decreased according to CHP injection, whereas 25 proteins including Clip2, Ppic and Dnajb5 showed a decrease in expression with fibrosis and then increased by following CHP injection. In peritoneal dialysis patients, measured endogeneous CHP levels in peritoneal fluid showed significant association with dialysate/plasma creatinine ratio (R2=0.295, p=0.001). Also, the patients with high or high-average type of peritoneum in peritoneal equilibrium test showed elevated levels of CHP compared to the others(p=0.015).

Conclusions: We found significant alteration and restoration of peritoneal proteomes in fibrosis and oxidative stress related pathways by fibrotic injury and subsequent injection of CHP.