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Cystamine inhibits TGFβ induced changes in podocytes using metabolomic analysis

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Objectives: Transglutaminase 2 (TG2) is activated by TGFβ. The activity of TG2 in kidney is associated with several pathologic changes including fibrosis and cell death in kidney. Because of these features, TG2 is considered as a potential therapeutic target for kidney diseases. The purpose of this study is to elucidate the effect of TG2 inhibition on TGFβ induced pathologic changes in kidney cells using the metabolomic analysis.

Methods: The primary cultured podocytes were cultured with 2ng/mL of recombinant TGFβ for 48 hours, then cystamine was administered. The podocytes were harvested after 48 hours from administration of cystamine. Metabolites were extracted using 80% methanol and Methyl t-butyl ether. LC-MS analysis for metabolomics was performed using a liquid chromatography-tandem mass spectrometry (LC-MS/MS). MS/MS data were analyzed for identification and quantification using Compound Discoverer software. Statistical data analyses were performed using the Perseus software and MetaboAnalyst.

Results: In podocytes, a separation among control, TGFβ and TGFβ + cystamine groups was observed in principal component analysis. Comparing the TGFβ and TGFβ + cystamine groups, the level of 13 metabolites such as L-Tyrosine (61.2 folds), and coronaric acid (2.61 folds) were higher and the level of 22 metabolites were evaluated in lower level including L-Phenylalanine (0.93 folds), melatonin (0.03 folds), L-Kynurenine (0.35 folds) and 5-Hydroxy-DL-tryptophan (0.02 folds) in TGFβ + cystamine group. And the pathway analysis revealed the metabolisms that implicated with cystamine, including phenylalamine, tyrosine and tryptophan biosynthesis (L-phenylalanine, L-Tyrosine), linoleic acid metabolism (coronaric acid), tryptophan metamolism (melatonin, L-Kynureinine, 5-Hydroxy-DL-tryptophan), and phenylalanine (L-Phenylalanine, L-Tyrosine) metabolism.

Conclusions: The inhibition of TG2 using cystamine showed its activity via several metabolism that associated with phenylalanine, tyrosine, tryptophan and linoleic acid metabolism in TGFβ treated podocytes.