KSN 2021
FULLY VIRTUAL MEETING
September 02 (Thu) - 05 (Sun)

Abstract Submission No. : 2568

Human kidney organoids revealed the therapeutic efficacy of glutathione for renal Fabry disease

Jinwon Kim[1], Sun Ah Nam[1], Jong Young Lee[1], Hyung Wook Kim[2], Hae Jin Cho[3], Tae-Min Kim[3], Yong Kyun Kim[2]
[1]Department of Cell Death Disease Reserch Center, School of Medicine, The Catholic University of Korea, Korea, Republic of
[2]Department of Internal Medicine-Nephrology, The Catholic University of Korea, St. Vincent's Hospital, Korea, Republic of
[3]Department of Cancer Research Institute, School of Medicine, The Catholic University of Korea, Korea, Republic of

Objectives: Renal Fabry disease is a rare X-linked inherited disorder that causes defects in the glycosphingolipid metabolic pathway that result from deficient or absent activity of the lysosomal enzyme, α-galactosidase A and result in end-stage renal disease. Recombinant enzyme replacement therapy (ERT) has become the major therapeutic approach for patients with renal Fabry disease. However, ERT has lower therapeutic efficacy when started in advanced stages of renal Fabry disease. Herein, we modeled renal Fabry disease using human inducible pluripotent stem cell-derived kidney organoids and the CRISPR-Cas9 genome-editing system and investigated the potential therapy for renal Fabry disease.

Methods: CRISPR-Cas9 genome-editing system was carried out to generate GLA knock-out human inducible pluripotent stem cells (GLA KO hiPSCs). GLA KO hiPSCs were differentiated into kidney organoids (GLA-mutant kidney organoids). We determined whether human kidney organoid phenocopy renal Fabry disease. To investigate the mechanisms as well as the therapeutic target, we performed transcriptomic analysis of GLA-mutant kidney organoids.

Results: GLA-mutant human kidney organoids revealed deformed podocytes and tubular cells with the accumulation of Gb3. Ultrastructural analysis showed abundant electron-dense granular deposits and electron-dense lamellate lipid-like deposits that formed concentric bodies (zebra bodies) in the cytoplasm of podocytes and tubules. The oxidative stress level was increased in GLA-mutant kidney organoids accompanied by cellular apoptosis. Enzyme replacement treatment with recombinant human α-Gal A decreased the accumulation of Gb3 and oxidative stress. Transcription profile analyses showed decreased glutathione metabolism in GLA-mutant kidney organoids. GSH replacement treatment decreased oxidative stress and improved structural deformity of GLA-mutant kidney organoids. GSH treatment also increased the expression of podocytes and tubular markers and decreased apoptosis.

Conclusions: GLA-mutant kidney organoids derived from human iPSCs represent a valuable tool for studying the mechanisms and therapeutic target for renal Fabry disease. Our data support that GSH treatment may be one of therapeutic alternatives for renal Fabry disease.