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Humanized experimental model of renal Fabry disease using iPSCs- derived kidney organoids

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Objectives: Fabry disease is an X-linked lysosomal storage disease caused by a mutation in the galactosidase alpha (GLA) gene. Despite the advances in therapeutic technologies, lack of humanized experimental model of Fabry disease have limited the development of new therapy for cure the disease. Here, we modeled Fabry disease using human iPSCs-derived kidney organoids.

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 , which were examined their recapitulating efficacy of Fabry disease.

Results: The deformed podocytes and tubular cells with the accumulation of Globotriaosylceramide (Gb3) were observed in GLA-KO kidney organoids. Ultrastructural analysis revealed Zebra body in cells of GLA-KO kidney organoids. Oxidative stress and apoptosis were increased in GLA-KO kidney organoids. Enzyme replacement treatment (ERT) with recombinant human α Gal A (rhα-GLA) decreased the accumulation of Gb3 and restored the deformed cellular structure of GLA-KO kidney organoids. Gene therapy using rAAV was also decreased the accumulation of Gb3 although its clearance was lesser than ERT.

Conclusions: GLA-KO human kidney organoids represents a valuable tool for studying the mechanisms and development of novel therapeutic alternatives for Fabry disease.