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Generation of The Functional Proximal Tubular Cells from human iPSC-derived Kidney Organoids

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Objectives : Human renal proximal tubular epithelial cells are crucial for exploring the molecular and cellular mechanisms that underlie the pathophysiology of kidney injuries. From a clinical application perspective, the more functionally and morphologically mature human proximal tubular cells, the more useful they will be. Kidney organoids derived from human induced pluripotent stem cells (iPSCs) are an attractive source of proximal tubular epithelial cells. In this study, we generated the functionally enhanced kidney organoid-derived proximal tubule cells (KOPTCs) and determined their clinical applications.
Methods : We generated KOPTCs by the development of the protocols for enhancing the maturation proximal tubules isolated from functionally matured-kidney organoids-derived from human iPSCs.
Results : KOPTC showed significantly enhanced barrier function, polarization state, and transporter function on microfluidic conditions, which leads to improved drug uptake compared to primary human renal proximal tubular epithelial cells (RPTECs). We demonstrated that 3D KOPTCs-on-chip is a more sensitive predictor for the nephrotoxicity test compared with RPTEC in static conditions as well as microfluidic conditions. KOPTCs can be cryopreserved and serially passaged without loss of identity, unlike kidney organoids. By using CRIPSR-Cas9 genetic mutation of alpha-galactosidase A (GLA), the causative gene of Fabry disease, KOPTCs can recapitulate the phenotype of Fabry kidney disease, which allow to investigate the pathophysiological implications of globotriaosylceramide (Gb3) accumulation in renal proximal tubular cells. The transplantation of KOPTSs into the kidneys of NOD-SCID mouse revealed the transplanted KOPTCs reassembled in the kidney of the host mouse and regenerated the proximal tubular structures with intact lumens and transporters, which indicated that KOPTCs might be an attractive cell source for the regenerative medicine.
Conclusions : Taken together, we showed that KOPTCs are more functionally mature than RPTECs and can be applicable for the nephrotoxicity testing, disease modeling, and regenerative medicine.