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Disease modeling of karyomegalic interstitial nephritis using patient derived induced pluripotent stem cells

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Objectives: Karymegalic interstitial nephritis (KIN) is a genetic kidney disease that is associated with mutations in the FANCD2/FANCI-Asociated Nuclease 1 (FAN1) gene on 15q13.3, resulting in nucleation and fibrosis of kidney cells due to DNA damage. In this study, we explored the possibility of kidney organoid-based in vitro model to study genetic alternations in KIN-derived from patient-specific iPSCs.

Methods: The human-induced pluripotent stem cell (KIN-hiPSCs) line, derived from peripheral blood mononuclear cells of a 42-year-old woman with KIN caused by the mutation of FAN1 gene, was generated using Sendai virus. KIN-hiPSC was differentiated into kidney organoids, treated with 20 nM of mitomycin A (MMC) for 24 or 48 hr and analyzed with expression of PI or Ki67 to detect DNA damage, compared with WTC-11 hiPSC-derived kidney organoid as control.

Results: KIN-hiPSCs showed typical human embryonic stem cell-like morphology. They expressed all analyzed pluripotency-associated markers. They could be differentiated into cells from all three germ layers. They demonstrated a normal female karyotype and retained the same mutation (Gly663Ilefs*54 mutation) in FAN1 gene. KIN-hiPSCs differentiated into kidney organoids containing nephron-like structures with glomerular epithelial cells, proximal tubules, and distal tubules. Compared with WTC-11-derived kidney organoid, expression of PI or Ki67 did not differ with KIN-hiPSC-derived kidney organoid. However, MMC treatment for 24 hr significantly induced the expression of PI or Ki67 in KIN-hiPSC-derived kidney organoid compared to those of WTC-11 hiPSC-derived kidney organoid, and furtherly increased in 48 hr incubation.

Conclusions: We generated a novel KIN patient-specific hiPSC line and produced in vitro kidney organoid using this cell line and showed the importance of FAN1 gene disorder as in vitro disease modeling of chronic kidney disease.