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Modeling and drug discovery for ADPKD using iPSC-derived kidney organoids

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In autosomal dominant polycystic kidney disease (ADPKD), renal cyst lesions predominantly arise from collecting ducts (CDs). However, relevant CD cyst models using human cells are lacking. Although previous reports have generated in vitro renal tubule cyst models from human induced pluripotent stem cells (hiPSCs), therapeutic drug candidates for ADPKD have not been fully identified. Here, we succeeded in advancing the developmental stage of hiPSC-derived CD organoids and showed that all CD organoids derived from $PKD1^{-/-}$ hiPSCs spontaneously develop multiple cysts. The cyst formation was inhibited by the arginine vasopressin V2 receptor antagonist, tolvaptan, which is the only clinically approved drug for ADPKD. We also reduced cystogenesis by identifying several biochemical signals that activate cyst formation, including lipid metabolism-related signals. Then, by developing a mass production method for CD cysts using the passage culture, we established a high-throughput screening (HTS) platform that explores therapeutic drug candidates for ADPKD. Furthermore, we successfully identified retinoic acid receptor (RAR) agonists as candidate drugs that significantly suppress in vitro cystogenesis and confirm the therapeutic effects on an ADPKD mouse model in vivo. We have started phase IIa clinical trial of the RAR agonist, tamibarotene, which is the clinically approved drug for treatment of acute promyelocytic leukemia (APL) in Japan, to examine the safety and efficacy for ADPKD. In parallel, we are currently conducting HTS of chemical compounds in an unbiased manner to identify novel therapeutic drug candidates. Therefore, our in vitro CD cyst model contributes to understanding disease mechanisms and drug discovery for ADPKD.

Keywords: ADPKD, iPS cell, collecting duct cyst model, drug discovery, RAR agonist