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Establishment of a Drug Screening Platform for Polycystic Kidney Disease using Human Urine Tubuloids

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Objectives : Autosomal dominant polycystic kidney disease (ADPKD), a hereditary kidney disorder caused by mutations in the PKD1 or PKD2 genes, is characterized by fluid-filled cysts growing in the glomeruli. Tolvaptan, a vasopressin receptor 2 antagonist, is the approved drug, but its limited efficacy and side effects side effects necessitate the need for new drugs.
Methods : In this study, we utilized kidney tubuloids to establish the dual drug screening platform for ADPKD. Healthy control and ADPKD patient tubuloid strains were generated from urine-derived adult stem cells, with ADPKD tubuloids showing increased susceptibility to cisplatin-induced nephrotoxicity and larger size compared to healthy controls.
Results : Stimulation of cystogenesis by forskolin or desmopressin resulted in a 2-fold increase in ADPKD tubuloids compared to the controls. Our platform integrated imaging-based and multiplex single-cell RNA sequencing, providing insights into the pharmacologic mechanisms of drugs at the molecular level. We evaluated 15 drugs related to cystogenesis using this platform. We performed single-cell transcriptomics on 26,132 cells collected from tubuloids of 1 control and 2 ADPKD patients that expressed various renal markers including distal convoluted tubules, loop of henle, and collecting duct. Comparative analysis of each cluster revealed upregulation in cell cycle, proliferation, mTOR, and cAMP-related response pathways in ADPKD tubuloids compared to controls. Furthermore, drugs associated with the MEK/ERK and CDK pathways exhibited efficacy in reducing cystogenesis.
Conclusions : Our drug screening platform contributes to understanding the pathogenesis of ADPKD and developing therapeutic agents.