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Generation of Functionally Matured Human Ureteric Bud Organoids with Enhanced Branching Morphogenesis

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Objectives : Branching morphogenesis is essential for kidney organogenesis, where the ureteric bud (UB) repeatedly branches to form the entire collecting system. UB organoids differentiated from human pluripotent stem cells (hPSCs) can recapitulate the branched epithelial structure of embryonic UBs. Despite advances in UB organoid differentiation, recent protocols for differentiating hPSCs into UB organoids have several technical and functional limitations. In this study, we generated the functionally matured UB organoids from hPSCs with the enhanced branching morphogenesis.

Methods : We hypothesized that kidney decellularized extracellular matrix (kdECM) would be crucial for the differentiation of kidney organoids, enhancing the maturity of UB differentiation and developed the culture system for the de novo direct differentiation of UB organoids from hPSCs based on kdECM.

Results : This culture system upregulated the gene expression of anterior intermediate mesoderm. This culture system enhanced the branching morphogenesis and the maturation of the tip-stalk organization in UB organoids. Single-cell RNA transcriptomics revealed that kdECM not only promoted UB tip enrichment and specification but also enhanced the acquisition of transcriptional programs associated with downstream epithelial maturation. This culture system enhanced the differentiation of AQP2/ENaC-expressing principal cells and substantially improved their functional capacity for electrogenic sodium transport and response to aldosterone and amiloride. This culture system dramatically decreased the population of off-target cells from 13% to 2.5% in UB organoids. This culture system has led to novel and effective advancements in disease modeling for autosomal dominant polycystic kidney disease, which enabled spontaneous cyst formation in patient-derived UB organoids without c-AMP stimulation.

Conclusions : Taken together, these data suggest that this culture methods are an advanced protocol to develop structurally and functionally matured UB organoids, which can be applied to studies for kidney development, disease modeling, and regenerative medicine.