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Human kidney organoids: Re-creating development and disease

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Kidneys cannot naturally regenerate lost tissue, and few preventive medications exist, limiting treatment options to temporary salves of dialysis or transplant with substantial side effects. We have developed a simple method to differentiate human pluripotent stem cells into intricately patterned, multi-segment organoids that resemble kidney tissues. These organoids form via a developmental pathway that induces the nephron progenitor cell, which gives rise to the epithelial lineages of the proximal nephron such as podocytes, proximal tubules, and distal tubules along a proximal-to-distal axis.

While beautiful, how to translate organoids into innovative therapies for organs as complex as human kidneys remains a critical question. To address this challenge, we have applied CRISPR gene editing and high throughput automation to reveal disease mechanisms in organoids and test therapeutic interventions. Mutations associated with polycystic kidney disease or cilia cause organoid tubules to swell thousands of times in size, producing large, fluid-filled cysts of centimeter diameters. In contrast, mutations associated with podocytes, the filtering cells of the kidney, do not affect tubules but cause junctional deformities that explain urinary defects in vivo.

Harnessing the power of automation, scRNA-seq analysis of organoids reveals sixteen different cell types, and identifies a novel three-gene signature of glomerular disease that appears in human patients. Microdissection of tubular organoids from non-kidney stroma greatly simplifies scRNA-seq cell types and produces purified kidney grafts suitable for transplantation into pre-clinical animal models.

To improve organoid function and seek therapies, thousands of organoids can be manufactured simultaneously in high throughput screening formats, and analyzed for multi-dimensional phenotypes of differentiation, toxicity, and disease. Screening reveals treatments that dramatically increase the vascular endothelium, and a surprising role for non-muscle myosin in cystogenesis, which can be targeted pharmacologically to modulate cystogenesis. Organoids with live fluorescence reporters and in microfluidic kidney-on-a-chip formats provide next-generation platforms for phenotypic screening and illumination of intracellular mechanisms at the tissue scale.

Collectively, our findings delineate key strategies and focus areas for advancement of kidney therapeutics using human organoids as surrogates for drug discovery, gene therapy, and regeneration.