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# New Challenges of Kidney Organoids

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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, commercially available 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 podocytes, parietal cells, proximal tubules, and distal tubules along a proximal-to-distal axis. This developmental trajectory requires modulation of hedgehog signaling through primary cilia, thus cilia knockout stem cells fail to efficiently differentiate into organoids. Organoid tubules accumulate dyes and solutes from the surrounding media, and swell in response to adenyl cyclase stimulation. When implanted in mice beneath the kidney capsule, human podocytes recruit murine endothelial cells to form chimeric, glomerulus-like structures.

While beautiful, organoids still have limitations and there are several current challenges. The grafts that arise from organoids remain immature and become overgrown by stromal cells, which would make them unsafe for use in humans. Because organoids are complex and heterocellular, experiments require multiple cell lines and tight experimental and quality controls, in order to draw accurate conclusions. The longevity of organoids in vitro and their maturation state also remain understudied, and could be improved by deeper investigation of their culture conditions. How to translate organoid technology into innovative therapies for organs as complex as human kidneys remains a critical challenge. Mutations associated with polycystic kidney disease or cilia knockout cause organoid tubules to swell thousands of times in size, producing large, fluid-filled cysts of centimeter diameters. Surprisingly, these cysts arise inside-out, via an absorptive process rather than a secretory one. Organoids are also susceptible to infection with SARS-CoV-2, through the ACE2 receptor. These disease models are currently being used to test innovative therapeutics and disease-specific mechanisms. Organoids with live fluorescence reporters, high throughput formats, and microfluidic kidney-on-a-chip devices provide next-generation platforms for phenotypic screening and illumination of intracellular mechanisms at the tissue scale. Collectively, these findings delineate strategies and focus areas for advancement of kidney therapeutics using human organoids as surrogates for patients, and as a source of regenerative grafts.