Patterning a Ureter Is All in the Stroma

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Substantial progress has been made over the past few years in the development of methods for generating human fetal kidney tissue via the directed differentiation of pluripotent stem cells. Several groups initially reported a capacity to recapitulate the stepwise differentiation of both embryonic stem cells and induced pluripotent stem cells through sequential commitment to mesoderm, intermediate mesoderm, and ultimately, to the formation of organoids composed of nephrons, surrounding stroma, and vascular elements. Although the interconnection of nephrons via a GATA3-expressing epithelium was initially interpreted as collecting duct, more recent analysis suggests that this is more likely to represent distal nephron/connecting segment as RET+ ureteric tips supporting a nephron progenitor niche are not observed.

The need for such ureteric tips to support nephron progenitors, arborize to expand organ size, and provide a unified exit path for urine is understood from developmental biology. The generation of epithelium competent to support this role is also a key requirement for the cellular engineering of the complete organ. To this end, Taguchi and Nishinakamura returned to the mouse and developed a distinct differentiation protocol to re-create a ureteric epithelium. The branching ureteric tree arises in vivo as a side branch of the Wolfian duct or nephric duct, itself the distal epithelial element of the pronephros. Although the leading tip of the ureteric epithelium grows into the metanephric mesenchyme to create the collecting ducts, the epithelium between the forming kidney and the Wolfian duct forms the watertight, peristaltic ureter through which the urine will pass to reach the bladder. Hence, the ureter arises within the peri-Wolfian mesenchyme, which is known to express Tbx18 and shows no capacity to give rise to nephrons.

In JASN, Sallam et al. show that the identity of mouse pluripotent stem cell–derived ureteric epithelium is influenced by the surrounding mesenchyme. Using the protocol previously defined by Taguchi and Nishinakamura, these authors placed epithelial tips adjacent to either the metanephric mesenchyme or the peri-Wolfian mesenchyme of a dissected 11.5 days post coitum mouse urinary tract. When placed near the nephron progenitor mesenchyme population, the ureteric epithelium branched, became surrounded by an SIX2-expressing mesenchyme, then induced, and apparently fused to nephrons arising from this mouse nephron progenitor mesenchyme. This suggests a ureteric tip identity. However, dissected tips from the same culture when placed within the peri-Wolfian mesenchyme displayed a distinct morphology, began to produce uroplakins suggestive of umbrella cell differentiation, and became surrounded by an αSMA-positive muscularis. Indeed, after 7 days of culture, this epithelium showed initiation of peristalsis as is anticipated of the ureter. The fact that the same starting epithelium can adopt a ureteric tip and a ureter morphology would suggest that epithelial identity is being driven by the surrounding stroma. Previous studies have shown that stromal populations can maintain or even instruct epithelial identity, with the latter able to be shifted even across germ lineage by coculture with ectopic tissue stroma. The ability to instruct ureter patterning is perhaps less surprising given the common origin of collecting duct and ureter, but the clear reciprocal induction of a surrounding muscular layer and the initiation of peristalsis shows that the epithelium, having committed to ureter, can also instruct the stroma. Of note, in studies in which mammalian epithelium was induced to adopt a prostatic identity, this was shown to require hedgehog and Wnt signaling. Manipulation of these same signaling pathways within the medullary stroma has previously been shown to disrupt maturation of medullary collecting duct and ureter, showing a clear role for stromal-epithelial signaling.

Although generation of a peristaltic ureter will be required for kidney engineering, this obviously cannot be achieved via coculture with ex ovo mouse embryo. Indeed, this study still provides proof of concept only for “mouse on mouse” and not “human on mouse,” or indeed “human on mouse.”
human.” Hence, a capacity to generate an appropriate stromal population from human pluripotent stem cells or the elucidation of the signaling pathways required for the appropriate response in human ureteric epithelium is clearly required. Reinvestigating what we know already around ureter patterning in mouse will likely once again provide solutions, although profiling of the human fetal kidney stroma will also provide important information. In the meantime, if proven to work for human stem cell–derived ureteric epithelial cultures, the classic anatomic coculture approach adopted in Sallam et al.\textsuperscript{8} may become a standard functional assay of ureteric competence with which to assess the growing number of protocols for differentiation to this epithelial end point.

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REFERENCES


Do-Not-Resuscitate Orders among Patients with ESKD Admitted to the Intensive Care Unit: A Bird’s Eye View

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The goal of advance care planning (ACP) is to help elucidate, clarify, and communicate patients’ values, goals, and care preferences.\textsuperscript{1} Engaging patients and their families in an iterative and ongoing process of ACP can help to ensure that they receive care that is congruent with their core values in situations where they may be unable to speak or advocate for themselves.\textsuperscript{1–3} During ACP, patients’ preferences related to cardiopulmonary resuscitation and other treatments along with their preferred surrogate decision maker(s) are typically documented in their medical record (e.g., advance directive, do-not-resuscitate [DNR] order, Provider Orders for Life Sustaining Treatment, and Medical Orders for Life Sustaining Treatment). To uphold personhood throughout the course of illness and across the continuum of care, ACP should ideally