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Improving our resolution of kidney morphogenesis across time and space

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As with many mammalian organs, size and cellular complexity represent considerable challenges to the comprehensive analysis of kidney organogenesis. Traditional analyses in the mouse have revealed early patterning events and spatial cellular relationships. However, an understanding of later events is lacking. The generation of a comprehensive temporospatial atlas of gene expression during kidney development has facilitated advances in lineage definition, as well as selective compartment ablation. Advances in quantitative and dynamic imaging have allowed comprehensive analyses at the level of organ, component tissue and cell across kidney organogenesis. Such approaches will enhance our understanding of the links between kidney development and final postnatal organ function. The final frontier will be translating this understanding to outcomes for renal disease in humans.

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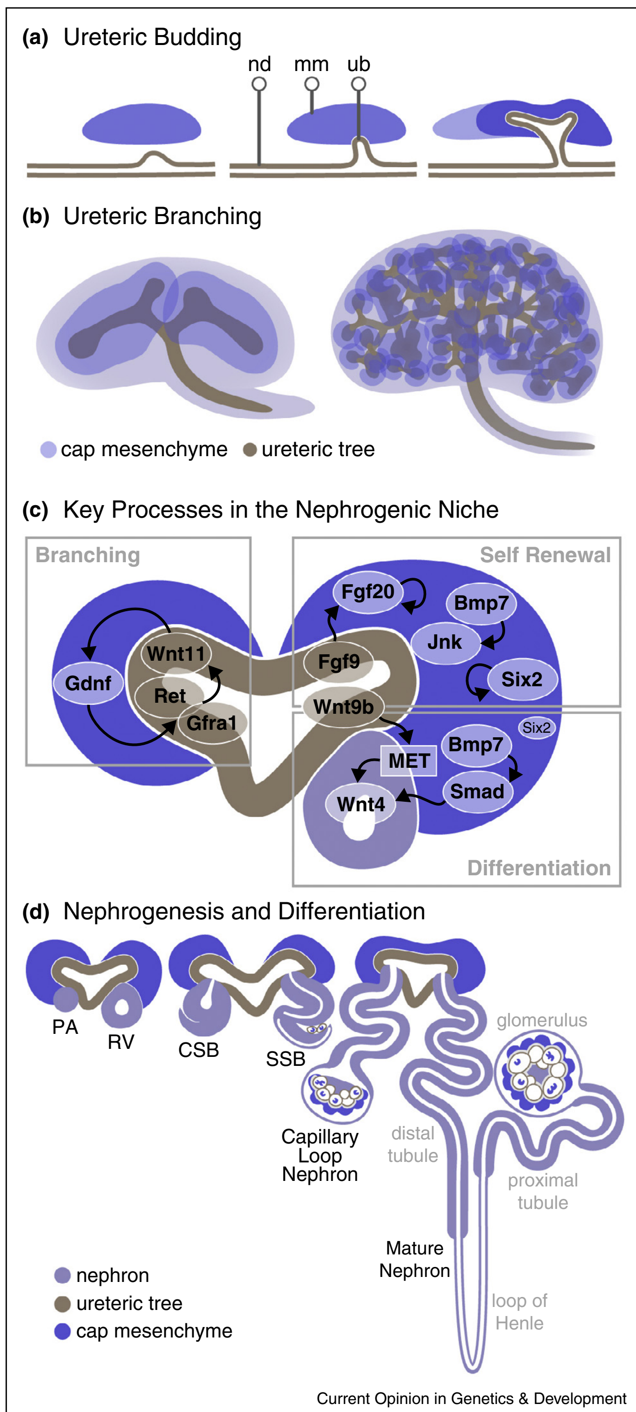
Introduction

The mammalian kidney is a complex organ comprising over 25 functionally and morphologically distinct cell types anatomically placed to deliver the filtration, reabsorption and secretion capacities essential for the maintenance of fluid homeostasis, nitrogenous waste regulation, blood pressure, red cell count and bone density. As congenital anomalies of the kidney and urinary tract are present in 40–50% of children with chronic kidney disease [1], the development of this organ has been the subject of extensive attention. The last 15 years have seen a revolution in our understanding of the molecular basis of kidney morphogenesis in the mouse, with the capacity to tag specific cells facilitating temporospatial profiling of individual cellular subcompartments, the dissection of lineage relationships across development and the conditional alteration of gene expression. Coupled with advances in imaging across time and space the possibility of probing the nature of kidney organogenesis is improving. This article will focus on how these advances have changed our understanding of kidney development and the pertinence of these findings to the human kidney.

Fundamental events in kidney morphogenesis

The final kidney in mammals, the metanephros, is mesodermal in origin and arises through reciprocal signalling between the nephric duct (ND) and the adjacent metanephric mesenchyme (MM) (Figure 1). Kidney morphogenesis can be divided into two key tubulogenetic events; the formation of a branching ureteric tree and nephron formation at the tips of this tree [2] (Figure 1). The first evidence of metanephros formation (gestational week 5 in humans, 10.5 dpc in mice) occurs as the ureteric bud (UB) branches from the ND, extending towards the MM in response to GDNF secretion. By 11.5 dpc, the UB begins to branch dichotomously to form the ureteric tree, which will become the collecting ducts through which urinary filtrate will exit. Exquisite timelapse imaging of UB branching in explant cultures has identified the requirement for ongoing expression of the GDNF receptor, RET, in the UB tips and the contribution of cells from the tips to subsequent tips as well as trailing and elongating branches [3]. RET signalling in the ureteric tips, in response to GDNF from the surrounding mesenchyme, upregulates *RET* and *WNT11*, the latter resulting in an upregulation of *GDNF* [7] (Figure 1c). Around this ureteric tree, the nephrons arise via a mesenchyme to epithelial transition triggered via Wnt9b from the adjacent ureteric tip [4] (Figure 1c). Grobstein identified the requirement for a ureteric signal to induce this event from the mesenchymal population [5]. It is now appreciated that the only the cap mesenchyme (CM) closely associated with each branching ureteric tip responds to form the nephrons. CM cells first condense to form a pretubular aggregate that, after a second Wnt4-mediated non-canonical signal [6], polarises to form the renal vesicle (RV) (Figure 1d). This structure is immediately patterned such that the side closest to the adjacent tip (distal RV) fuses with it [7]. After subsequent proliferation, elongation, segmentation and patterning, distinct functional domains form such that each nephron has a vascularised glomerulus, proximal tubule, loop of Henle

Figure 1



Key inductive events in mammalian kidney morphogenesis. **(a)** *Ureteric budding*. Diagram showing the formation of the ureteric bud (UB) as a swelling of the nephric duct (ND) which grows towards the metanephric mesenchyme (mm) before undergoing initial bifurcation. **(b)** *Ureteric branching.* Diagrammatic view of the branching ureteric epithelium of the developing mouse kidney from 11.5 dpc (left) to 15.5 dpc (right) showing the ureteric tree and surrounding cap mesenchyme. **(c)** *Key processes in the nephrogenic niche.* Diagram of a nephrogenic niche illustrating the signalling pathways critical for branching (left) versus cap mesenchyme self renewal (top right) and differentiation (bottom right). **(d)** *Nephrogenesis and differentiation.* Diagram showing the stages of nephron maturation from pretubular aggregate (PA) through renal vesicle (RV), comma-shaped body (CSB), S-shaped body (SSB), capillary loop nephron and mature nephron. The RV represents the point of transition from mesenchyme to a polarised epithelial state [7]. The formation of a connection between the forming nephron and the lumen of the adjacent ureteric epithelium occurs at late RV stage and is shown here at comma-shaped body.

and distal tubule all connected back to the tips of the ureteric tree (Figure 1d). Regulation of this complex specialisation remains poorly investigated, although a growing number of compartment markers and key signalling pathways are being identified [2].

A global molecular atlas of the developing mouse kidney

Elucidation of the molecular basis of these foundational morphogenetic events has largely been gene-by-gene, using knockout or overexpression studies in transgenic mice together with explant culture. The advent of microarrays for global transcriptional profiling represented a major change. Beginning with the separation of cellular compartments based on microdissection or laser capture, a global atlas of gene expression across time and space in the developing mouse kidney was generated [8]. In a process of iterative re-evaluation, gene expression was validated using RNA section *in situ* hybridisation with compartment specific markers then used to more specifically enrich via FACS [9–12] (Figure 2a). This led to the identification of smaller and smaller anatomical subdomains. The capacity to analyse all genes expressed at a given time and/or cell type facilitated network and pathway analyses previously not possible (Figure 2a,b). The advent of Next Generation sequencing allowed the identification of novel transcripts not necessarily present on microarrays and the capacity to sequence from single cells [13•]. This has begun to reveal the transcriptional complexity present during kidney development, including the temporal and spatial variation in miRNA and non-coding RNA species. Within the CM/ureteric tip niche alone, almost all previously described genes show evidence for alternative exon splicing, 5′ and 3′ sequences and antisense transcripts [14] (Figure 2c). The comprehensive analysis of specific types of genes across kidney development has also been performed. The temporospatial expression of all transcription factors (TFs) across kidney development identified a subset of TFs enriched in key cellular compartments. Identifying other genes with comparable temporospatial expression patterns allowed the prediction of specific TF targets and gene-regulatory networks [15•]. RNA sequencing is now being applied post chromatin immunoprecipitation (ChIP) to directly examine the action of specific TFs. For example, self-renewal of the CM requires *Six2* expression, with β-catenin mediated canonical Wnt-signalling required for both CM survival and differentiation into nephron [4,16]. Six2 and β-catenin

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