Down the tube of obstructive nephropathies: The importance of tissue interactions during ureter development

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Congenital obstructive malformations of the ureter are amongst the most common human birth defects. To date, the etiology of these diseases has remained largely unexplored, which has preempted any rational approach for therapeutic intervention. Here, we describe that obstructive ureter defects can arise from genetic insults affecting various subprograms of ureter development including formation and patterning of the ureteric bud, differentiation of tissue compartments of the ureter, and junction formation with the bladder and pelvis. New experimental findings have highlighted the importance of epithelial–mesenchymal tissue interactions in all of these subprograms and provided unique insights into the molecular nature of the transcriptional regulators and signaling pathways involved.

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The urinary system is a multicomponent entity, whose primary functions are (1) the maintenance of body homoeostasis by controlling the water and ionic balance of the blood, and (2) the excretion of excess water, solutes, and waste products. Anatomically, these functions are served by the composite design of an upper unit comprised of the kidneys, which filter and modify the blood, and a lower unit consisting of the ureters, the bladder, and the urethra, which drain the urine to the outside. The epithelial lining of the kidney is functionally adapted to ensure the selective secretion and resorption of solutes and water from the primary urine in renal tubules and collecting ducts, while the urothelium constitutes a specialized permeability barrier to urinary toxicity in the lower urinary tract. The urothelium of the ureter and bladder is heavily invested with smooth-muscle layers that provide structural rigidity, flexibility, and contractility.

Rather than being a simple, passive tubular outlet of the pelvis, the ureter represents a pivotal connection between the upper and lower urinary systems. After filling the renal pelvis with urine, the upper portion of the ureter undergoes unidirectional peristaltic contractions, triggered by pacemaker cells, to propel the urine down to the bladder, while preventing any reflux or efflux at the same time. The specialized anatomical design of the ureter interfaces with the pelvis and the bladder as well as the two-layered tissue architecture of the ureter tube itself ensure that these tasks are met.

The crucial importance of the ureter for renal function is dramatically reflected by acquired and inherited defects that interfere with the efficient removal of the urine from the renal pelvis. Any kind of anatomical or functional obstruction along the ureter or at its junctions will result in fluid pressure-mediated dilation of the tubular system proximal to the side of constriction. Obstruction may originate from physical barriers or compromised structural integrity and peristaltic activity of the ureter. Dilation of the ureter (hydroureter) will lead to dilation of the pelvis and collecting duct system of the kidney (hydronephrosis). This condition may progress to pressure-mediated destruction of the renal parenchyme and culminate in end-stage renal disease.

Since congenital obstructive malformations of the ureter are a leading cause of renal failure in children and young adults,[1–3] analysis of the molecular pathways regulating normal ureter

development are prerequisite to the identification of the genetic aberrations underlying hydroureter/hydronephrosis and exploration of the disease etiology. In contrast to other organs such as the kidneys, our knowledge of the genetic control of ureterogenesis has been limited. However, recent experimental findings from gene expression studies, embryological manipulations, and particularly the phenotypic analysis of mouse mutants (see Table 1 for an overview) have resulted in the emergence of a more comprehensive picture of the genetic circuits acting during ureter development. Here, we will review the current status of ureter development by focusing on recent molecular studies that highlight the importance of tissue interactions for early ureter development and the etiology of obstructive nephropathies.

URETER DEVELOPMENT

Although the ureter is structurally and functionally part of the drainage system of the lower urinary tract, its ontogenetic origin is clearly distinct from that of the bladder and the urethra (see Figure 1, first four columns, for the embryonic development of the ureter and its tissue compartments in the mouse). While the latter two arise from the endodermal urogenital sinus, ureters derive with the kidneys from the Wolffian duct in the intermediate mesoderm. At embryonic day (E)10.5 in mouse, an epithelial diverticulum called ureteric bud (UB) evaginates from the distally elongating Wolffian duct at the level of the hind limb buds and starts to grow toward an adjacent group of mesenchymal cells. After intrusion into this metanephric blastema, the tip of the UB acquires a drastically different fate from the 'stalk'—the portion remaining outside of the metanephros. The tip engages in repetitive rounds of elongation and branching and ultimately generates the collecting duct system of the kidney, whereas the stalk merely elongates to form the epithelial component of the ureter. From E12.5 on, the distal end of the stalk separates from the Wolffian duct and integrates into the developing bladder wall, which establishes continuity of the urinary tract. Starting at E15.5, the epithelium of the ureter stalk differentiates into the urothelium, which is then able to resist the toxicity of the urine being produced from E16.5 onwards. In parallel with the dichotomy of epithelial development, mesenchymal cells covering either region of the UB epithelium take completely different developmental routes. The metanephric mesenchyme surrounding the proximal tip regions undergoes a mesenchymal–epithelial transition to form nephrons and differentiates into interstitial mesenchyme or stroma, respectively. In contrast, the mesenchyme surrounding the ureter stalk differentiates into smooth-muscle cells that will form layers with longitudinal and transverse orientation. Finally, the establishment of the peristaltic machinery at the ureter–pelvis junction, the pyeloureteric region, ensures full functionality of the ureter at birth.

TAKING OFF: MESENCHYMAL CONTROL OF URETER BUDDING

Since formation of both ureter and metanephric kidney depend on ureter budding from the Wolffian duct, any disruption of this process will certainly have dramatic effects on either structure. Both embryological manipulations and genetic analyses have shown that the emergence of the ureteric bud is not determined by positional information intrinsic to the epithelial Wolffian duct, but that signals from the adjacent mesenchyme direct the outgrowth, setting a first paradigm for the importance of mesenchymal–epithelial interaction for ureter (and kidney) development. Since the regulation of ureter budding has been extensively reviewed in recent years,[36,37] we will summarize the key findings that are relevant for ureter development. Temporal and spatial control of ureter budding is achieved by establishment of a mesenchymal signaling center at the posterior end of the intermediate mesoderm at around E10.0, shortly before the Wolffian duct has reached this position. Glial-derived neurotrophic factor (Gdnf) released from the metanephric blastema induces ureter budding and outgrowth from the Wolffian duct. Loss of any of the components of the network establishing and interpreting the Gdnf signal or the simple experimental separation of the Wolffian duct from the metanephric blastema disrupts or delays ureter budding and outgrowth, leading to ureter and kidney agenesis in the extreme and renal hypoplasia, or dysplasia in less severe cases.

Spatial restriction of Gdnf signaling is tightly controlled to ensure the localized appearance of a single UB (Figure 1e). Genetic ablation of the genes encoding the transcription factors Foxc1 and Foxc2,[7] and the signaling system of the large secreted protein Slit2 and its receptor roundabout homolog2 (Robo2)[10] in the mesenchyme surrounding the Wolffian duct results in the expansion of the metanephric blastema and the region of Gdnf signaling. Ectopic activation of the Gdnf signal transduction pathway is likely to be caused by deletion of the signaling molecule bone morphogenetic protein 4 (Bmp4)[5,6] and the angiotensin type II receptor[4] in the mesenchyme surrounding the Wolffian duct, the cytosolic factor Sprouty1,[11] the adhesion molecule L1cam,[8] and the transcription factor Nfia[9] in the Wolffian duct epithelium (see Table 1, first section for a summary of mouse mutants with obstructive ureter malformations caused by ectopic ureter budding). Although it is still unclear how these transcriptional activities and signaling pathways are precisely interwoven to restrict Gdnf signaling spatially, phenotypic analyses of some of these mouse mutants have established that ectopic Gdnf signaling induces supernumerary ureteric buds. These will give rise to additional kidneys and ureters with improper connections to the bladder, leading to hydroureter and subsequent hydronephrotic lesions due to physical obstruction.[4,6–8,10,11]

PROXIMAL–DISTAL REGIONALIZATION OF THE URETERIC BUD IS UNDER MESENCHYMAL CONTROL

Shortly after emerging from the Wolffian duct, the development of the epithelium and its surrounding mesenchyme at the two ends of the UB diverges. Which mechanisms direct the proximal–distal segmentation of the UB into the kidney and ureter? First, regionalization may rely on positional