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Review

Ureter growth and differentiation

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ABSTRACT

The mammalian ureter is a slender tube that connects the renal pelvis with the bladder. It allows the unidirectional movement of urine by means of a peristaltically active smooth muscle layer that together with fibroelastic material ensheathes a water-impermeable multilayered urothelium. The ureteric urothelium as well as the outer mesenchymal coat arise from undifferentiated precursor tissues, the distal ureteric bud and its surrounding mesenchyme, respectively. Specification, growth and differentiation of these ureteric precursor tissues are tightly linked to each other, and are highly integrated with those of the adjacent rudiments of kidney and bladder. Here, we review the current knowledge on the cellular mechanisms as well as the molecular players that guide development of the tissue architecture of the ureter and its peristalsis.

Contents

1. Introduction

The ureters are a pair of muscular tubes that convey urine from the renal pelvis to the bladder. They are located in fibrous tissue behind the peritoneum to which they tightly adhere. The upper aspect of the ureter is thin-walled and funnel-shaped and emanates within the sinus of the kidney in close association with the renal vessels. The thick-walled rest of the ureter passes unbranched through the abdomen to enter the bladder in a rather oblique angle and end with a slit-like opening of valvular nature [1].

Each ureter consists of two tissue compartments. The tubular lumen is lined by a specialized epithelium that is tightly sealing yet highly distensible. This urothelium consists of a layer of basal cells, one or several layers of intermediate cells and a luminal layer of superficial cells. An outer mesenchymal coat further supports rigidity and flexibility of the tube. It is organized in an inner ring of fibroelastic material, the lamina propria, multiple layers of smooth muscle cells (SMCs), and an outer ring of connective tissue, the tunica adventitia. The tunica adventitia contains long ascending and descending blood and lymph vessels, and nerves that subdivide and ramify to serve the SM layers and the urothelium [1]. Ureters are not simply passive tubular outlets of the renal pelvis but undergo unidirectional peristaltic contractions to actively propel the urine down to the bladder. Contractions are triggered by pacemaker cells in the pelvic-kidney junction (PKJ), the auto-rhythmic depolarization of which drives electrically silent SMCs [2,3].

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Changes in the functional integrity of the SM layer and the urothelium as well as the connections with the pelvis (the ureteropelvic junction, UPJ) and bladder (the vesico-ureteric junction, VUJ) are incompatible with an efficient drainage of the urine from the renal pelvis and result in urinary efflux or reflux. Depending on the level and intensity of the functional or physical obstruction, widening of the ureter (hydroureter) and the pelvis (hydronephrosis) occurs that may culminate in destruction of the renal parenchyma. Congenital forms of these anomalies represent a prominent subgroup of CAKUT, congenital anomalies of the kidney and the urinary tract, that belong to the most frequent human birth defects [4,5]. Deciphering the etiology of CAKUT as well as the underlying genetic defects has been a major driving force in efforts to better understand the cellular processes and the molecular circuits that regulate normal growth and differentiation of the urinary system in the mouse [6–8]. Although analysis of kidney and bladder development has been pushed forward with greater efforts, a basic understanding of the cellular and molecular mechanisms that control normal and pathological development of the ureter has recently been gained from engineered mouse models and *ex vivo* culture systems (for older reviews on ureter development see [9–11].

2. Growth and differentiation of the ureter

2.1. Ureter development: a brief overview

Ureters arise together with the kidneys from the nephric duct (ND, also known as Wolffian duct), an epithelial tube that extends within the intermediate mesoderm from the fore limb level to the cloaca, the rudiment of the bladder and urethra. At E10.5, an epithelial diverticulum called ureteric bud (UB) evaginates from the ND slightly anterior to the cloaca and invades the surrounding mesenchyme, the metanephric blastema. The tip of the UB subsequently engages in repetitive rounds of elongation and branching and ultimately generates the collecting duct system of the kidney. The stalk region merely elongates to form the epithelial component of the ureter. From E12.5 on, the distal end of the stalk separates from the ND and integrates into the developing bladder wall. Around E13.5 to E14.5, the epithelium of the ureter stalk starts to thicken and differentiates into the urothelium slightly preceding the onset of urine production at E16.5. Parallel to the dichotomy of epithelial development, mesenchymal cells covering the tips and the stalk of the UB, respectively, follow different developmental avenues. The bulk of the mesenchyme surrounding the tip region undergoes a mesenchymal-epithelial transition to form nephrons whereas a minor part differentiates into stroma. In contrast, the mesenchyme surrounding the ureter stalk (and the bladder epithelium) differentiates into SMCs and fibroblasts. At E12.5, the mesenchymal cells adjacent to the ureteric epithelium change from a slender to a more cuboidal shape and become more densely organized. Around E14.5-15.5, these cells start to express SMC markers in a proximal to distal wave, indicating terminal differentiation of this cell type. The more peripheral and an innermost layer of mesenchymal cells remain loosely organized and differentiate into fibrocytes of the tunica adventitia and the lamina propria, respectively. Finally, the establishment of the peristaltic machinery at the PKJ ensures full functionality of the ureter from around E16.5 onwards [9,12] (see Fig. 1 for a graphic summary of ureter development).

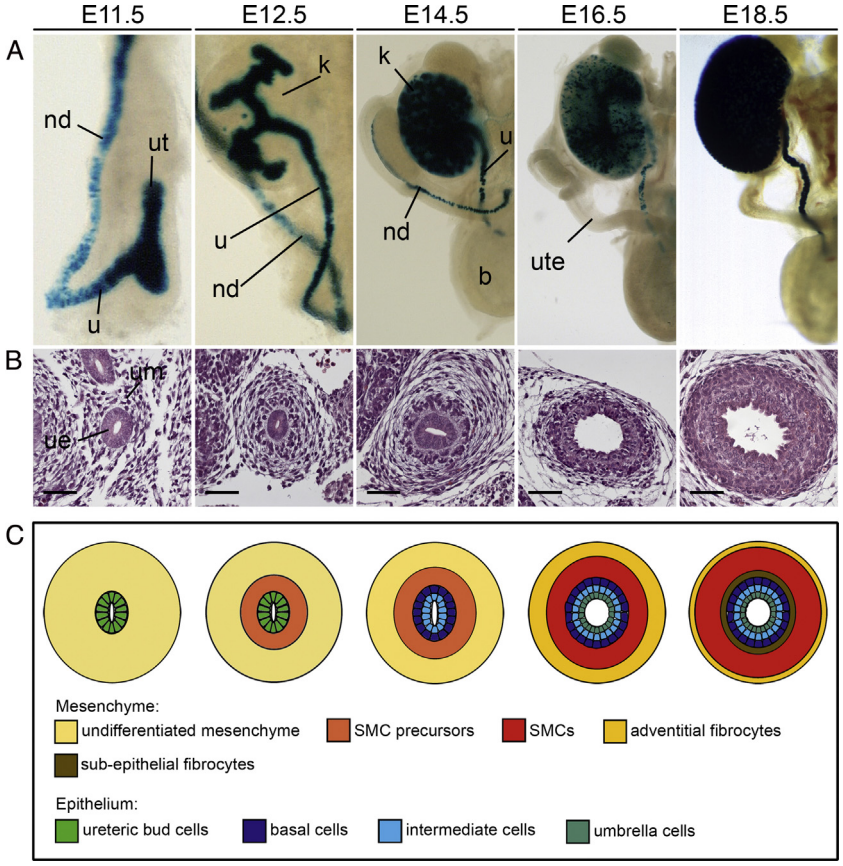

Fig. 1. Ureter morphogenesis and differentiation. (A) Visualization of the ureteric epithelium by b-gal activity from a *Pax2*(*8.5*)-*lacZ* transgenic line. (B) Hematoxylin and eosin stainings on transverse 5 μm proximal ureter sections. Scale bars represent 50 μm. (C) Scheme of mesenchymal and epithelial differentiation in ureter development. Stages are as indicated. b, bladder; k, kidney; nd, nephric duct; u, ureter; ue, ureteric epithelium; ureteric mesenchyme; ut, ureter tip; ute, uterus.

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