The development of kidney tubules involves reciprocal induction by the ureteric bud and surrounding mesenchyme

The mammalian kidney is mainly composed of a many thousands of functional units, which consist of a series of convoluted tubules that receive fluid and salts from the blood, balance its composition, and then convey the final product—urine—to the ureter, which carries it out of the body. One end of each tubule ends in a glomerulus; this is the site at which blood capillaries release fluid and salts that are then taken up by the tubule. The other end of the tubule connects to the ureter. The kidney is formed from two regions of intermediate mesoderm (see Section 3.4, the ureteric bud and the metanephric mesenchyme (another name for the mammalian kidney is the metanephros). The ureteric bud branches off the Wolffian duct, a tube of epithelial cells, which develops in association with a primitive form of kidney, the **pronephros**. The pronephros is the first "kidney" that arises from the intermediate mesoderm in the embryo, followed by the mesonephros and finally the metanephros in an anterior-to–posterior sequence. In mammals, the pronephros and the mesonephros degenerate in the fetus but they function as the adult kidney in some amphibians and fish. In mammals, the Wolffian ducts develop into the vas deferens in males (see Section 9.13).

The epithelial ureteric bud is induced to form at the posterior region of the Wolffian duct by the adjacent metanephric mesenchyme. Under the influence of the mesenchyme, the ureteric bud grows and undergoes extensive branching morphogenesis to form the proximal portions of the urine-carrying tubules, which are known as the collecting ducts. The tips of the branches of the ureteric bud induce the mesenchymal cells to condense around them and undergo a mesenchymal-to epithelial transition (see Section 7.4) to form epithelial structures that develop into renal tubules or nephrons. Each tubule elongates to form a glomerulus at one end, where filtration of the blood will occur, while the other end fuses to the ureteric collecting duct connecting to the ureter (Fig S10.1). The intermediate portion of the tubule is convoluted and its epithelial cells become specialized for the resorption of ions from urine. The mammalian kidney is a good developmental system to study as it can develop in organ culture; explanted metanephric mesenchyme will form many glomeruli and tubules over a period of about 6 days, even though a blood supply is absent.

The development of the ureteric bud and the mesenchyme depends on mutual inductive interactions, neither being able to develop in the absence of the other.

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The establishment of the Wolffian duct requires activity of the transcription factor, Pax2. The metanephric mesenchyme induces the initial formation of the ureteric bud from the Wolffian duct by secreting glial-cell-derived neurotrophic factor (GDNF) and FGF10. The secretion of these factors is critical for positioning ureteric bud development.. The positional information that specifies the metanephric mesenchyme is encoded along the antero-posterior axis of the intermediate mesoderm by the combined activity of genes of the Hox11 paralogous subgroup. These Hox proteins together with other transcription factors activate *Gdnf* expression. The restriction of ureteric bud formation to a single site also involves repression of *Gdnf* expression in more anterior intermediate mesenchyme by the secreted protein Slit2 via its receptor Robo2. As we shall see in Chapter 11, these proteins are also involved in the guidance of axons in nervous-system development. Mutations in the Slit2 or Robo2 genes lead to *Gdnf* expression extending more anteriorly and hence the formation of multiple ureteric buds. Continued signaling by GDNF in the mesenchyme is the main controller of subsequent ureteric bud branching, and its receptor, Ret, is present in the bud. Both FGF10 and FGF7 are also involved. The cellular basis for branching is similar to that described earlier for lung development (see Section 10.27). Activation of Ret activates the expression of *sprouty*, which, as in the lung, inhibits branching in the region behind the tip of the tubule. Knock-out of the gene for either GDNF or Ret results in the absence of ureteric bud outgrowth.

As the bud branches it induces the overlying mesenchyme at its tips to condense and to form epithelium that then forms the nephrons. The key regulatory primary signal from the ureteric bud that induces this mesenchyme-to-epithelial transition is

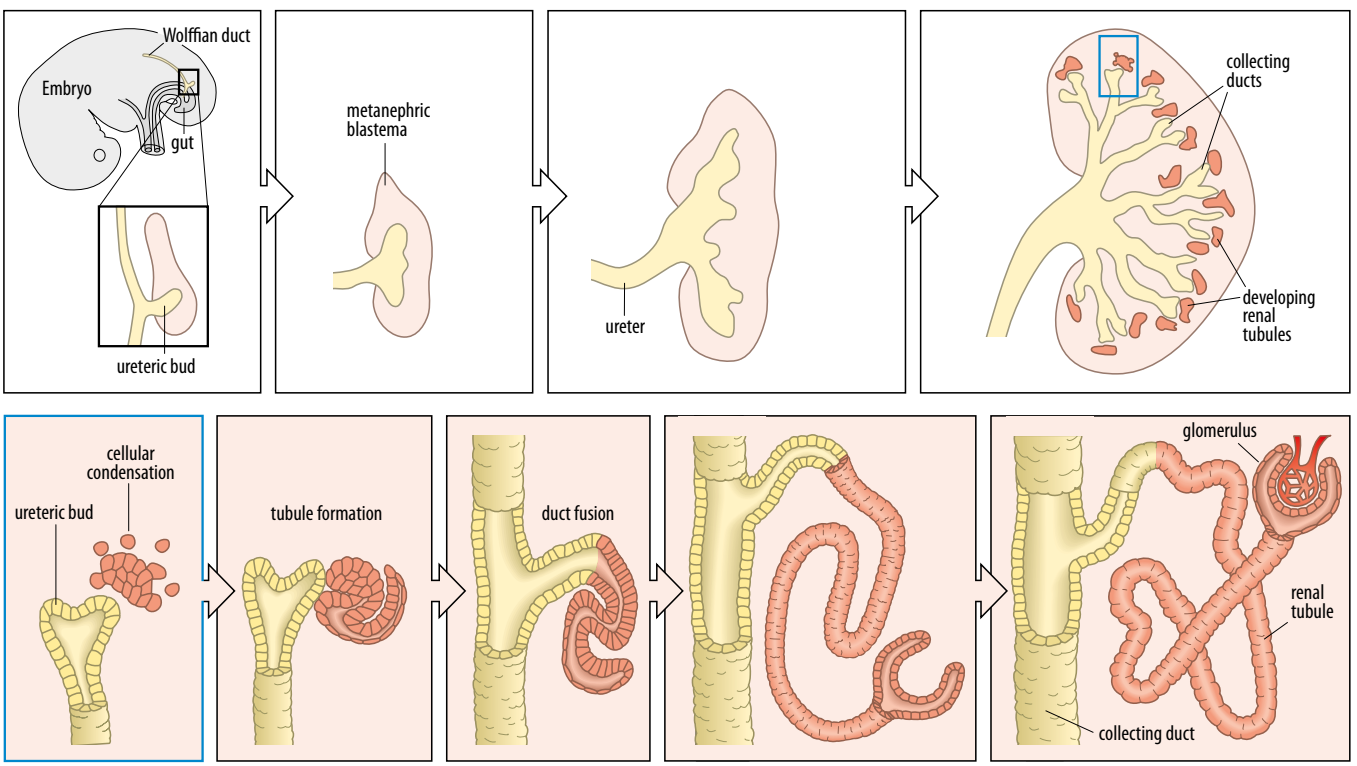

Fig. S10.1 Kidney development involves branching morphogenesis and a mesenchymal-to-epithelial transition. The kidney develops from a loose mass of mesenchyme, the metanephric blastema, which is induced to form tubules by the ureteric bud. The ureteric bud is itself induced by the mesenchyme to grow and branch to form the collecting ducts of the kidney that connect to the ureter. The mesenchyme cells form cellular condensations that become epithelial tubules, which open into the collecting system formed from the ureteric bud. Each tubule develops a glomerulus, through which waste products are filtered out of the blood.

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Wnt9b. As the mesenchyme cells start to condense, they express a matrix glycoprotein, syndecan, on their surface. This condensing stage is followed by the formation of distinct cellular aggregates, in which the mesenchymal cells become polarized and acquire an epithelial character. Production of the signaling molecules, Wnt4 and Fgf8 by the cells in these aggregates is essential for further development. Each aggregate then forms an S-shaped tube, which elongates and differentiates to form the functional unit of a renal tubule and glomerulus. During this transition, the composition of the extracellular matrix secreted by the cells changes: mesenchymal collagen I is replaced by basal lamina proteins, such as collagen IV and laminin, that are typically secreted by epithelial cells. The adhesion molecules (see Box 7A) expressed by the cells also change; for example, the N-CAM expressed by the mesenchymal cells is replaced by E-cadherin in the epithelial cells. Integrins are also involved in the epithelial–mesenchyme interactions. A key protein that must be expressed for tubule formation to occur is the zinc-finger transcription factor WT1. Loss-of-function mutations in the *WT1* gene are associated with Wilm's tumor, a cancer of the kidney in children, and the gene is therefore known as the Wilm's tumor suppressor gene.

The number of nephrons per kidney varies widely, in human kidneys, for example, from around 200,000 to 1,800,000. Nephron number is determined by the number of bud branches but how is accomplished and branching is terminated is not well understood. These issues have clinical importance as nephron number is inversely related to timing of the onset of renal disease in post-natal life.

Further reading

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