

Development of Rat Kidney: Pre- and Post-natal Study

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ABSTRACT

Background: The mammalian kidney arises through three successive stages in cranio-caudal sequence, the pronephros, the mesonephros and the metanephros. The last stage, the metanephros, persists as the definitive kidney. The pronephros and mesonephros regress, but both contribute essential inductive signals and cellular precursors to later stages of urogenital development. Formation of the metanephros depends on reciprocal molecular signaling between the ureteric bud and the metanephric mesenchyme, which drives nephron induction, patterning of the nephrogenic zone, branching morphogenesis of the collecting system, differentiation of the renal stroma, and coordinated growth of the renal vasculature. A distinguishing feature of the rat, compared to the mouse and the human, is that nephrogenesis continues after birth during the early neonatal period, making the rat a useful and experimentally accessible model for studying environmental, dietary, or pharmacological impacts on post-natal kidney development. This review describes the sequence and molecular control of rat renal organogenesis, from the pronephros to postnatal maturation, and highlights the comparative timing of these events across rat, mouse and human.

Keywords: kidney development; nephrogenesis; pronephros; mesonephros; metanephros; ureteric bud; renal stroma; renal vasculature

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INTRODUCTION

The kidney is the organ chiefly responsible for the excretion of metabolic waste, regulation of fluid and electrolyte balance and maintenance of acid-base homeostasis. Its development is one of the most intricate examples of organogenesis in the mammalian embryo, proceeding through three successive, partly overlapping stages; the pronephros, the mesonephros and the metanephros. The renal structures arise in sequence from the intermediate mesoderm within the urogenital ridge⁽¹⁾.

The pronephros and mesonephros are transient stages that regress during development. Despite their transient nature, the earlier stages contribute to subsequent urogenital development and establish developmental signaling systems that are relevant to metanephric organogenesis. Only the metanephros persists as the functional kidney of the adult animal⁽²⁾.

Developmental Stages of the Rat:

I. The Pronephros:

The pronephros represents the earliest renal stage. In rats it appears early during embryogenesis and rapidly regresses.

They arise from the cranial part of the urogenital ridge^(3,4). It consists of a pronephric duct and pronephric tubules. Unlike the functional pronephros of some lower vertebrates, the mammalian pronephros is transient and nonfunctional⁽³⁾. Its importance lies partly in the persistence of the caudal portion of the pronephric duct, which contributes to formation of the mesonephric duct and then supports subsequent mesonephric development⁽¹⁾.

II. The Mesonephros:

The mesonephros develops caudal to the pronephros. Each mesonephric nephron develops as the ventral end of a mesonephric tubule which is invaginated and invaded by a capillary tuft arising from the dorsal aorta, forming a glomerulus enclosed within a Bowman's capsule. The lateral end of each mesonephric tubule connects to the mesonephric duct⁽²⁾.

Unlike the amphibian mesonephros, which remains the definitive kidney throughout life, the mammalian mesonephros filters blood only transiently before degenerating. Mesonephric tubules do not all appear at the

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same time; as proximal tubules regress, more distal tubules continue to form and mature ⁽²⁾.

Before the mesonephros regresses, they induce several cell populations to migrate into the adjacent Adreno gonadal primordium, including endothelial cells. Endothelial cells with signaling molecules such as vascular endothelial growth factor (VEGF), help organize the vascular supply of the developing urogenital system ^(5,6).

The mesonephros also plays an important role in steroidogenesis. Cells that will populate the adrenal cortex and, depending on sex, the Leydig cells of the testis or the theca cells of the ovary, originate within or migrate through the mesonephros. In addition, WT1 and steroidogenic factor 1 are transcriptional regulators involved in the development of steroidogenic tissues. ^(5,6).

The fate of the mesonephric structures differs by sex. In the male, the Wolffian duct gives rise to the seminal vesicles, the epididymal tubules, portions of the vas deferens and the ejaculatory duct. While caudal mesonephric tubules form the vasa efferentia and the paradidymis. In the female, most mesonephric tubules regress although remnants may persist as the epoophoron and paroophoron. Remnants of the mesonephric duct may persist as Gartner duct remnants. ^(1,2,7).

III. The Metanephros:

Metanephros is the final and only permanent nephric organ in mammals. Its formation begins with the outgrowth of the ureteric bud, an epithelial outpouching that arises from the distal Wolffian duct close to its junction with the cloaca, at approximately GD 12 in the rat, GD 10.5–11 in the mouse, and the fifth gestational week in the human ^(3,4,8).

The metanephric mesenchyme secretes glial-derived neurotrophic factor (GDNF), which acts primarily through RET/GFR α 1 signaling in the ureteric bud epithelium which drives the ureteric bud to branch, first into a T-shaped tubule and then through repeated dichotomous divisions that ultimately generate the collecting ducts and the collecting system as a whole ^(1,2).

In turn, signals from the ureteric bud induce the surrounding metanephric mesenchyme to condense along the surface of each branch tip. These condensates, known as pre-tubular aggregates, undergo a mesenchymal-to-epithelial transition to form the renal vesicle, the structure from which each nephron subsequently develops ^(1,2).

Nephrogenesis:

Nephron formation begins in fetal life. In humans, nephrogenesis is completed before birth, but in mice and rats it extends into the early postnatal period. In rats, there is reported completion around the second postnatal week depending on the developmental criteria and strain. This feature makes postnatal nephrogenesis in the rat a valuable and readily accessible model for the study of renal developmental toxicity ⁽¹⁾.

Nephron formation is directed by a tightly regulated program of genetic and molecular signaling that converts the metanephric mesenchyme into a series of epithelial-lined structures, which then undergo further growth and morphological remodeling to form the mature nephron ⁽¹⁾. The earliest recognizable event is the aggregation of metanephric mesenchymal cells around the tip of each

branching ureteric bud, forming a “cap” of condensed mesenchyme. These cap cells begin to epithelialize and coalesce into small renal vesicles, each renal vesicle gives rise to a single nephron ^(1,2,3,4).

Each renal vesicle then undergoes a stereotyped sequence of shape changes, first forming a comma-shaped body and then an S-shaped body. The proximal portion of the S-shaped body develops a glomerular cleft, which is invaded by ingrowing capillary loops to form the glomerulus. The distal end fuses with an adjacent branch of the collecting duct system, establishing a continuous luminal connection. The intervening segment of the S-shaped body differentiates into the remaining components of the nephron; the proximal convoluted tubule, the loop of Henle, and the distal convoluted tubule ^(1,2,3,4).

The Nephrogenic Zone:

As ureteric bud branching proceeds and new nephrons are progressively induced, the developing kidney exhibits a peripheral nephrogenic zone containing ureteric tips, nephron progenitors and cortical stromal cells. While more centrally located structures undergo progressive differentiation and maturation ⁽²⁾.

Because new nephrons are continuously added at the periphery, a centrifugal gradient of maturity is established within the developing cortex: the most mature nephrons lie closest to the medulla, and the least mature, most recently induced nephrons lie at the outer margin of the cortex ⁽²⁾.

The Collecting System:

The entire collecting duct system including; collecting ducts, calyces, renal pelvis and ureter is derived from the ureteric bud. Its mature architecture is generated through repeated rounds of branching morphogenesis. Ureteric bud branching and tip number are major determinants of nephron endowment, since each new branch tip induces further nephrogenesis in the adjacent mesenchyme ⁽²⁾.

The earliest rounds of ureteric bud branching are broadly symmetrical, but later rounds become asymmetrical. The main ductal trunk extends outward toward the nephrogenic zone while lateral side branches form to induce new nephrons. The resulting duct system converges on a renal papilla, which sits within a funnel-shaped calyx connected to the ureter. Species differ markedly in the resulting gross anatomy: the rat kidney has a single papilla draining into a single calyx, whereas the human kidney is multipapillate, with eight to ten papillae draining into minor and then major calyces ^(9,10).

Development of The Renal Stroma and Interstitial Cell Populations:

Not all cells derived from the metanephric mesenchyme contribute to nephron formation. A separate lineage, the renal stromal cells, arises from the same mesenchymal source but does not condense around the ureteric bud tips; instead, these cells populate two broad compartments; a cortical stroma beneath the renal capsule and surrounding the developing nephrons, and a medullary stroma occupying the interstitial space between tubules and collecting ducts ^(2,9).

Cortical stromal cells provide signals that are essential for normal ureteric bud branching and overall patterning of the kidney. Their loss or dysfunction markedly impairs

branching, reduces the eventual nephron number, and disrupts formation of a normal cortico-medullary boundary^(2,9).

This relationship is reciprocal: the ureteric bud, in turn, sends signals that constrain stromal cell patterning, and loss of these signals allows stromal cells to accumulate abnormally beneath the renal capsule. As the kidney matures, stromal cells differentiate further into peritubular interstitial cells and pericytes. Both cell populations are required for vascular remodeling and for the deposition of extracellular matrix necessary for normal nephron architecture^(2,9).

Forkhead Box D1 (Foxd1+) and T-box 18 (Tbx18) are the primary master regulators of mammalian renal stroma development⁽¹¹⁾.

Foxd1+ cells constitute an important stromal cell lineage progenitor. They are predominantly localized in the cortical stroma, with lower expression in the medullary stroma surrounding the collecting system. Foxd1+ expression is regulated by the transcription factors Wt1, Ets-1 and Wnt11 together with the p53 protein, while the homeobox factor Hox10 governs the correct positioning of Foxd1+ expressing cells. On the other hand, additional factors such as Tcf21, Ecm1, Fat4, Alcam, and Rarb participate in ureteric-bud branching and stromal differentiation⁽¹²⁾.

Foxd1+ cells are multipotent progenitors that give rise to nearly all non-epithelial, non-endothelial cell types in the mature kidney, including interstitial fibroblasts, pericytes, vascular smooth muscle cells (VSMCs), and glomerular mesangial cells⁽¹³⁾.

Foxd1+ deficiency leads to renal hypoplasia accompanied by ureteric bud (UB) epithelial abnormalities, caused by the absence of Raldh29 (retinaldehyde dehydrogenase 2) and metanephric mesenchyme Sfrp1 (secreted frizzled-related protein 1) expression. Also, this loss leads to an expansion of endothelial and non-capsular (Bmp4+) stromal cells, with Ret overexpression in the UB. Ectopic overexpression of Dcn (decorin) further dysregulates Bmp/Smad signaling cascades, while the downregulation of renin-angiotensin system genes (Agt, Ren, Ace, and At1) demonstrates that Foxd1 is essential for maintaining local intrarenal renin-angiotensin system activity⁽¹²⁾.

T-box 18 (Tbx18) operates alongside Foxd1+. T-box 18 marks a distinct stromal lineage originating near the ureteric stalk and intermediate mesoderm. T-box 18 progenitors migrate inwardly along renal arterial trees, giving rise to ureteral smooth muscle, perivascular mural cells, and inner cortical pericytes without passing through a transient Foxd1+ cap state⁽¹⁴⁾.

Because TBX18 regulates mesenchymal proliferation, condensation, and smooth muscle specification, its absence severely disrupts urinary, cardiovascular, skeletal, and reproductive system morphogenesis⁽¹⁴⁾.

Renal Vascular Development:

The metanephric mesenchyme is entirely avascular at the time the ureteric bud first invades it (around GD 10.5–11 in the mouse), but a dense capillary network is established within a day (GD 11.5–12), and vascularized glomeruli are already present by GD 12.5–14 in the mouse^(2,9).

Renal vascularization arises from two overlapping processes:

1. Vasculogenesis: the de novo assembly of vessels from endothelial precursor cells resident within the metanephric mesenchyme and
2. Angiogenesis: the sprouting and branching of new vessels from pre-existing ones that grow into the kidney from the main renal artery^(9,15,16).

Notably, essentially all the mural cell precursors of the kidney vasculature; vascular smooth muscle cells, renin-producing cells, mesangial cells and interstitial pericytes are derived from the Foxd1+ expressing stromal lineage described above⁽¹⁶⁾.

Within the developing glomerulus, endothelial precursors differentiate and proliferate to form a single primordial capillary loop in response to vascular endothelial growth factor A (VEGFA) secreted by the adjacent developing podocytes. This primitive loop then matures into the elaborate glomerular capillary tuft through cycles of intussusceptive growth and branching remodeling. Signaling through VEGFA and its endothelial receptors VEGFR1 (Flt1) and VEGFR2 (Flk1/Kdr) is essential for normal development of the glomerulus and the glomerular filtration barrier⁽¹⁶⁾.

Angiopoietin (Ang)–Tie pathway has an essential role in angiogenesis and vascular stabilization during both fetal and postnatal life. The angiopoietin family comprises Ang1, Ang2, Ang3, and Ang4, which act through the endothelial tyrosine kinase receptor Tie2. Ang1 and Ang2 are the principal, well-characterized ligands^(17,18).

Ang1 and Ang2 compete for binding to Tie2. Ang2 has context-dependent activity at Tie2, functioning as a partial agonist in some settings and antagonizing Ang1-mediated Tie2 signaling in others^(17,18).

Ang-3 (mouse) and Ang-4 (human) are species-specific angiopoietin. Ang-3 acts as a natural Tie2 antagonist in mouse models, inhibiting Tie2 phosphorylation similarly to Ang-2, while Ang-4 acts as an agonist for the human Tie2 receptor, inducing receptor autophosphorylation and promoting survival signaling⁽¹⁹⁾.

Deletion of Ang1 during fetal life produces abnormal glomerular capillary development. Although its deletion later in life does not disturb glomerular morphology, it increases the kidney's vulnerability to subsequent injury. Ang2 acts as a “remodeler”; in the presence of VEGF, it destabilizes existing vessels to permit new growth. But in the absence of VEGF, it can lead to regression of vessels^(17,18).

Postnatal Maturation of Rat Kidney:

Although the metanephros is morphologically recognizable well before birth, full maturation of the kidney extends considerably beyond the completion of nephrogenesis⁽¹⁾.

Day 1-2 post-natal: The subcapsular nephrogenic band contains the branching (ampullary) tips of the collecting ducts, undifferentiated nephrogenic mesenchyme, renal vesicles, and S-shaped bodies — the structures from which Bowman's capsule and every nephron segment will eventually arise⁽²⁰⁾.

The cortex is subdivided into two regions; the subcortical region having immature glomeruli and the juxtamedullary

region having more mature glomeruli. Both have immature tubules. Medullary rays can be seen by light microscope extending from medulla to cortex. The youngest Bowman's capsules have no open lumen yet, and the primitive tubules are lined by columnar cells with basally located nuclei around a narrow lumen ^(20,21).

From Day 5 to 10 post-natal: development of new nephrons takes place ⁽²⁰⁾. At approximately day 10, there is no immature glomeruli. The final nephron anlagen is now functioning. The developing medulla initially resembles the outer zone, particularly the region that later becomes the inner stripe. A clear distinction between the medullary zones cannot yet be established yet. By approximately day 10, the inner zone becomes recognizable ^(20,21).

Day 15 post-natal: the outer strip of outer medulla is now identifiable ⁽²⁰⁾.

Day 21 post-natal: The renal corpuscles are composed of lobulated glomeruli surrounded by partial and visceral layers of Bowman's capsule enclosing Bowman's space. The parietal layer was lined by flattened cells, and the visceral layer lies close to glomerular capillaries ⁽²¹⁾.

By Day 36 post-natal: The medulla appears to reach full structural maturation. The renal corpuscles increase in diameter with advancing age. Differentiated proximal tubules increase in number. They are lined by epithelial cells resting on a distinct basement membrane. These cells exhibited numerous closely packed apical microvilli and euchromatic nuclei. The distal convoluted tubules are similarly lined by epithelial cells resting on a basement membrane and contain oval, euchromatic nuclei ⁽²¹⁾.

Final, adult-like organization (near the renal pelvis): Vascular bundles become embedded within the collecting ducts and the thick ascending limbs of Henle's loops; the thin descending limbs separate from the thick ascending limbs; the loose connective tissue of the primitive outer zone disappears; and the medullary ray bundles thicken and fuse at their margins, so that the medulla's ray-bundle subdivisions are no longer visible ⁽²⁰⁾.

Through a gradual, distally progressing process, the primitive squamous epithelium of the oldest Henle loops converts into straight proximal-tubule epithelium. Interstitial lengthening of the tubules increases cortical volume, the cortex thickens overall, and the tubule loops shift to lie above the apices of the medullary rays. Because the transition from straight proximal-tubule epithelium to the thin descending-limb epithelium becomes abrupt rather than gradual, the inner and outer stripes become more sharply defined ⁽²⁰⁾.

Molecular Regulation of Post-natal Kidney Development:

Gene-expression profiling of the developing rodent kidney has shown that postnatal maturation proceeds as sequential transcriptional waves: an early wave of genes governing proliferation and morphogenesis, followed by a later wave encoding extracellular-matrix proteins and drivers of terminal differentiation ⁽²²⁾.

Within this landscape, Dissanayake et al., (2024) ⁽²²⁾ identified *Xdh* as a gene whose cortical expression rises specifically over PND 5–15, coinciding with the period of most active nephron formation. Loss of *Xdh* reduces

nephron number and leaves the kidney less structurally differentiated, with a marked surge in several signaling pathways at PND 15–21 and evidence linking this dysregulated maturation to nephrotoxicity and inflammation ⁽²²⁾.

A second, complementary line of evidence comes from work on *Gas1*, a pleiotropic, growth-arrest-associated protein already known to help preserve renal progenitor cells (RPCs) during embryonic kidney development. Because RPCs remain active into postnatal life and persist, in reduced form, into adulthood, Cetina-Palma et al., (2023) ⁽²³⁾ found *Gas1* expressed throughout the nephron; in Bowman's capsule, the glomerulus, the proximal convoluted tubule and the distal nephron with an expression pattern that changes dynamically as the kidney matures. Across every region examined, *Gas1* expression rose as maturation progressed, while expression of RPC markers such as NCAM and CD24 fell in an inverse pattern, suggesting that *Gas1* may act as a negative regulator of RPC activity, progressively restraining progenitor proliferation as each nephron segment reaches its mature, differentiated state.

In Bowman's capsule, *Gas1* was detectable from PND 10 and remained constant into adulthood, leading to propose it as a candidate marker of parietal-cell differentiation. In the glomerulus, *Gas1* was present from PND 1, absent from the slit diaphragm at every stage examined, and appeared as two protein isoforms on Western blot, plausibly reflecting distinct *Gas1* species with potentially distinct signaling roles in mesangial cells and podocytes ^(23,24).

In the proximal convoluted tubule; the nephron segment with the highest baseline proliferative capacity and the greatest susceptibility to tubular injury, *Gas1* was present from PND 1, increased with maturation, and was found in a cytosolic, plausibly soluble form consistent with its status as a GPI-anchored protein capable of paracrine or endocrine signaling; the authors propose *Gas1* as a candidate cell-cycle checkpoint that helps arrest fully differentiated tubular cells once renal maturity is reached ⁽²³⁾.

In the distal nephron, *Gas1* was present from PND 1 but not uniformly across all distal segments until after PND 21, when its expression became homogeneous — coinciding with completion of distal-segment maturation and again suggesting a role as a differentiation marker ⁽²³⁾.

Segment-specific markers; nephrin (glomerulus), *Cln2/SGLT1/DppIV* (proximal tubule) and *Cln4/Cln8* (distal nephron) all increased over the same postnatal period, corroborating that the structural immaturity present at birth resolves through a coordinated program of segment-specific cellular maturation ⁽²³⁾.

The *Xdh*-linked network appears to act largely through oxidative and inflammatory signaling; via COX-2 and the EGF-STAT3 axis, with its principal consequence being a reduction in nephron number and increased susceptibility to nephrotoxic and fibrotic injury when disrupted. The *Gas1*-linked program, by contrast, appears to act more directly at the level of the cell cycle, restraining RPC proliferation and driving fully differentiated cells into a quiescent, mature state once each nephron segment has completed its structural development ^(22,23,24).

Mahmoud et al., (2023) ⁽²⁵⁾ used the immunohistochemical staining of calbindin (a protein which regulates Ca^{2+} reabsorption from the kidney), proliferating cell nuclear antigen (PCNA), and apoptotic single-stranded DNA (ssDNA) to track the postnatal kidney maturation in rats. They found that in the first week of rat life, calbindin reactivity appeared in the distal convoluted tubule (DCT), the immature nephrons and surrounding mesenchyme. Over the same period, PCNA staining was moderately positive in developing podocytes but absent from other tubular segments, while ssDNA reactivity was moderately present in undeveloped nephrons.

By the 3rd to 6th week of rat life, calbindin staining in the DCT had intensified, whereas PCNA and ssDNA reactivity in podocytes was moderate. By the 2nd to 3rd month of rat life, calbindin expression became particularly intense in the DCTs and collecting tubules. Overall, the distribution of calbindin demonstrated an inverse pattern in relation to PCNA and ssDNA immunoreactivity across the developing nephron compartments ⁽²⁵⁾.

Ding et al., (2021) ⁽²⁶⁾ claimed that cellular composition changed substantially across development. Podocytes, collecting-duct principal cells, and DCTs declined in relative proportion over the postnatal period, while collecting duct intercalated cells increased steadily. The loop of Henle declined through postnatal day 10 before rising again, and proximal tubules showed the inverse pattern, expanding through day 10 before declining. Pseudotime trajectory analysis placed podocytes as the first cell type to exit the progenitor state and mature, followed by the LOH and collecting-duct principal cells, then DCTs and intercalated cells, with proximal tubules maturing last ⁽²⁶⁾.

Genes that changed most across pseudotime were dominated by ribosomal-protein transcripts, which were highly expressed early and declined with maturation, implying elevated protein-synthetic demand during active morphogenesis ⁽²⁷⁾. RPS12 was the single most dynamically expressed gene; while its role in kidney development is untested, Drosophila data indicate it regulates organ growth and size ⁽²⁸⁾, raising the possibility that ribosomal protein dosage contributes to the reduced nephron numbers seen in preterm infants ^(26, 27).

Gene Ontology analysis of the remaining differentially expressed genes similarly pointed to translational and post-

translational processes, consistent with cell types completing lineage-specific functional maturation. Among transcription factors, TCF21, FOXD1, WT1, MAFB, and JUN were the top five dynamically expressed regulators, and all were most enriched in podocytes; each has independent, established roles in stromal patterning, glomerular differentiation, or renal disease pathogenesis ⁽²⁶⁾.

Known glomerular disease genes curated from OMIM were examined across podocytes, endothelial cells, and stromal cells, the majority of these genes were most highly expressed in podocytes, reinforcing the centrality of podocyte biology to glomerular disease susceptibility during kidney maturation ⁽²⁶⁾.

Conclusion:

Development of the mammalian kidney proceeds through the sequential formation of the pronephros, mesonephros and metanephros, coordinated by reciprocal signaling between the ureteric bud, the metanephric mesenchyme, and the renal stromal and vascular lineages that arise alongside it. Although the general program of kidney organogenesis is conserved across mammals, its timing differs substantially between species, with nephrogenesis continuing into the postnatal life in rats and mice but it is completed before birth in humans. This prolonged, experimentally accessible window of postnatal nephrogenesis is central to the rat's continued use as a model organism for studying both the normal maturation of the kidney and its vulnerability to developmental and reproductive toxicants.

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