AJKD
Core Curriculum in Nephrology

Kidney Development: Core Curriculum 2011

Kenneth A. Walker, BSc (Hons), PhD, and John F. Bertram, BSc (Hons), PhD

INTRODUCTION

The morphologic stages of kidney development, including nephron development, have been well understood for decades. In recent years, numerous studies in mutant mouse models as well as a growing number of studies in humans have yielded new insights into the genetic regulation of these developmental processes. Moreover, the effects of perturbation of the fetal environment on kidney development, especially nephron endowment, are being increasingly understood, together with consequences for adult kidney and cardiovascular health. Remarkably, nephron number in normal human kidneys varies more than 10-fold, indicating extreme variation in kidney development and likely kidney robustness in the face of postnatal challenges.

KIDNEY DEVELOPMENT

- Three pairs of excretory organs develop in mammals
  - All are derived from mesoderm
    - Predominantly from intermediate mesoderm, but also some contribution from paraxial mesoderm
  - They develop in a temporal and craniocaudal sequence
    - Pronephroi "primitive kidneys"
    - Mesonephroi "middle kidneys"
    - Metanephroi "permanent kidneys"
- Pronephroi and mesonephroi are largely transient structures
  - In females, the mesonephroi completely regress
  - In males, some mesonephric tubules contribute to ducts draining the testes, epididymal ducts, and vas deferens
- The nephric duct is an epithelial tube formed from cells derived from the intermediate mesoderm
  - Formed during development of the pronephros
  - Gives rise to the mesonephric duct (mesonephric development) and subsequently the Wolffian duct (metanephric development)
- Metanephric development
  - Begins in humans in week 5 of gestation
  - Begins in mice at embryonic day 10.5
  - When nephrogenesis ceases (gestation week 36 in humans; around postnatal day 5 in mice), no new nephrons can form
  - Nephrogenesis appears to continue for some weeks after premature birth in humans, but it is unclear whether a full complement of nephrons is achieved
  - Metanephric development continues after termination of nephrogenesis, with significant growth, differentiation, and remodeling of kidney tissue

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METANEPHRIC INDUCTION

- The epithelial ureteric bud emerges from the Wolffian duct and invades the metanephric mesenchyme (also known as metanephric blastema or metanephrogenic mesenchyme; Figs 1 and 2)
- Specification of metanephric mesenchyme from the intermediate mesoderm is determined by localized EYA1, PAX2, ODD1, and WT1 expression (see Table 1 for expansions of genes and gene products described here)

From the Department of Anatomy and Developmental Biology, School of Biomedical Sciences, Monash University, Clayton, Victoria, Australia.
Originally published online April 25, 2011.
Address correspondence to John F. Bertram, BSc (Hons), PhD, Department of Anatomy and Developmental Biology, School of Biomedical Sciences, Monash University, Clayton, Victoria 3800, Australia. E-mail: john.bertram@monash.edu

0272-6386/$36.00
doi:10.1053/j.ajkd.2011.03.009

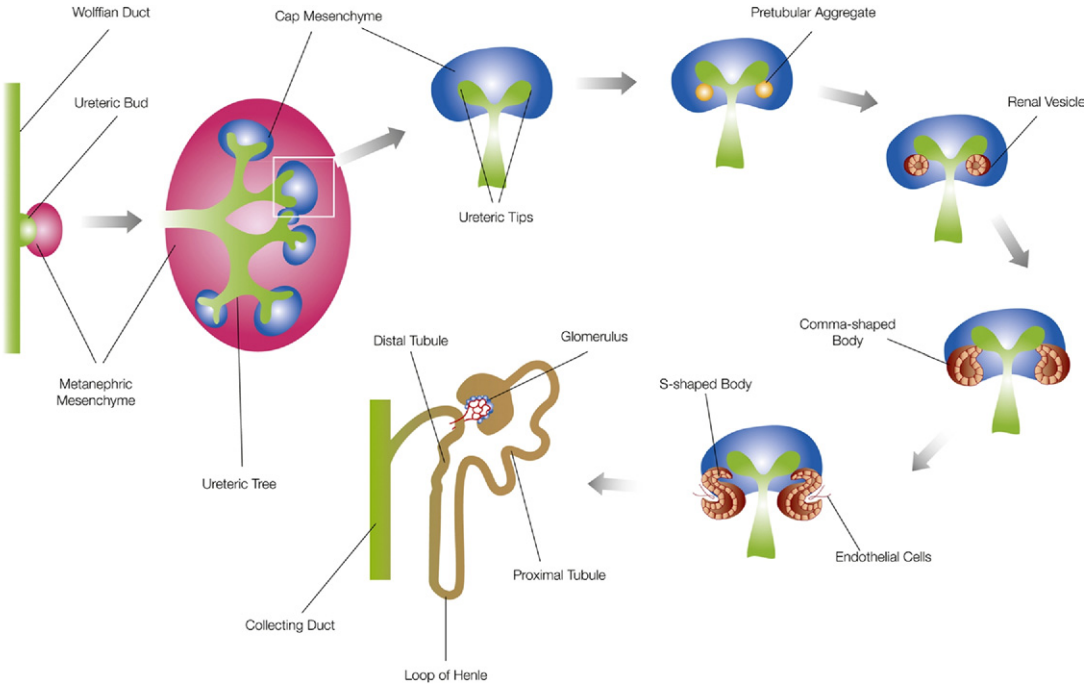

Figure 1. Schematic diagram of morphologic stages of metanephric kidney development.

- Ureteric budding is driven by metanephric mesenchyme-secreted GDNF interacting with ureteric bud–expressed receptors c-RET and GFRα1 (see Fig 2)
  - Ectopic GDNF is capable of inducing ectopic ureteric bud formation
- The site of ureteric budding is regulated tightly by BMP4
  - BMP4 is expressed by a subpopulation of mesenchymal cells adjacent to the Wolffian duct and acts to inhibit ureteric budding
  - GREM1 (gremlin 1) expression at the site of ureteric budding antagonizes the inhibitory actions of BMP4 (Fig 2)
- The site of metanephric induction is critical for normal kidney development and development of the urinary tract
  - Ectopic ureteric budding is associated with congenital anomalies of the kidney and urinary tract (CAKUT)

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URETERIC BRANCHING MORPHOGENESIS

- Branching (mostly dichotomous) of the ureteric bud gives rise to the ureteric tree, precursor to the collecting duct system of the mature metanephros
- Reciprocal physical and molecular interactions occur between the ureteric epithelium and metanephric mesenchyme
- Similar to metanephric induction, ureteric branching morphogenesis is driven by metanephric mesenchyme–secreted GDNF acting through c-RET and GFRα1 receptors localized at the tips of ureteric branches (Figs 2 and 3)
  - This localized signaling prevents ectopic branching events
- The ureteric tree is divided into trunk, ureteric branches, and ureteric tips (Fig 3); classification determined by differential gene expression
- Ureteric branching occurs at only the periphery of the kidney in the so-called nephrogenic zone

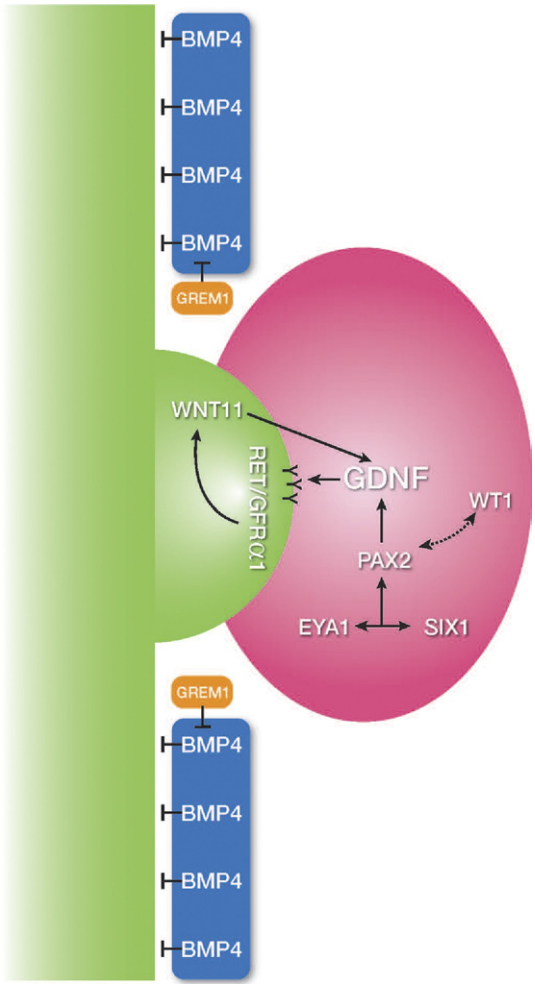

Figure 2. Molecular regulation of ureteric budding. Emergence of the ureteric bud involves reciprocal interactions between ureteric epithelium (green) and the metanephric mesenchyme (pink). The site of ureteric budding is regulated negatively by BMP4, which is expressed in a sleeve of mesenchymal cells adjacent to the ureteric epithelium. BMP4 is antagonized by GREM1. EYA1 and SIX1 interact directly to upregulate the developmental transcription factor PAX2, which in turn induces the expression and secretion of GDNF (a key inductive molecule in kidney development) by the metanephric mesenchyme. PAX2 is believed to interact directly with WT1 to maintain uninduced metanephric mesenchyme and propagate GNDF expression; however, this interaction is still unclear. Secreted GDNF binds to the epithelially expressed c-RET-GFRα1 receptor complex (Y) and activates WNT11, initiating a positive-feedback loop maintaining GDNF expression and secretion. (solid arrows) indicate direct interaction between factors; (broken arrows) indicate unclear interaction between factors; (blocked arrows) indicates inhibitory action of factor. Expansions of abbreviations for gene products are listed in Table 1.

- ◦ As the kidney continues to grow, the nephrogenic zone is located farther and farther from the center of the kidney
- ◦ As kidney growth continues, the radial proximity of the nephrogenic zone to the medulla and kidney pelvis is increased

- In vitro (whole metanephric culture) and in vivo (optical projection tomography) imaging approaches have added greatly to our knowledge of this process
- The ureteric bud ultimately gives rise to not only the collecting duct system, but also the kidney calyces and sinus and the ureter

Table 1. Important Genes in Kidney Development

Gene Symbol	Gene Name (alias)
ALDH1A2	Aldehyde dehydrogenase family 1, member A2
BMP4/BMP7	Bone morphogenetic protein 4/7
CD2AP	CD2-associated protein
CITED1	Cbp/p300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain 1
EMX2	Empty spiracles homolog 2
EYA1	Eyes absent 1
FAT1/FAT2	FAT tumor suppressor 1/2
FGF2/FGF7	Fibroblast growth factor 2/7 (FGF-2/FGF-7)
FOXD1	Forkhead box protein D1
FRAS1	Fraser syndrome 1
FREM2	Fras1-related extracellular matrix protein 2
FRS2α	Fibroblast growth factor receptor substrate 2α
GDNF	Glial cell line–derived neurotrophic factor
GFRA1	Glial cell line–derived neurotrophic factor receptor α1 (GFRα1)
GLI3	GLI-Kruppel family member 3
GREM1	Gremlin 1
IRX3	Iroquois-related homeobox 3
KDR	Kinase insert domain receptor (also known as FLK-1 [fetal liver kinase 1] or vascular endothelial growth factor [VEGF] receptor 2]
KIRREL	Kin of IRRE like (also known as NEPH1 [nephrin-like protein 1])
LHX1	LIM homeobox protein 1 (also known as LIM-1)
LIF	Leukemia inhibitory factor
MET	Met proto-oncogene; c-Met
NOTCH2	Notch gene 2
NPHP1-NPHP9	Nephronophthisis 1-9 (also known as nephrocystin)
NPHS1	Nephrosis 1 (also known as nephrin)
NPHS2	Nephrosis 2 (also known as podocin)
OSR1	Odd-skipped related 1 (also known as ODD1)
PAX2/PAX8	Paired box gene 2/8
PKD1-PKD2	Polycystic kidney disease 1-2 (also known as polycystin 1-2)
PKHD1	Polycystic kidney and hepatic disease 1 (also known as fibrocystin or polyductin)
POU3F3	POU domain, class 3, transcription factor 3 (also known as brain-1 [BRN1])
RET	Ret proto-oncogene (also known as c-Ret)
SALL1	Sal-like 1
SIX2	Sine oculis-related homeobox 2
TGFB2	Transforming growth factor β2 (TGFβ2)
TP53	Tumor protein p53 (also known as transformation-related protein 53)
VEGFA	Vascular endothelial growth factor
WNT4/WNT9B/WNT11	Wingless-type MMTV integration site family member 4/9b/11
WT1	Wilms tumor 1

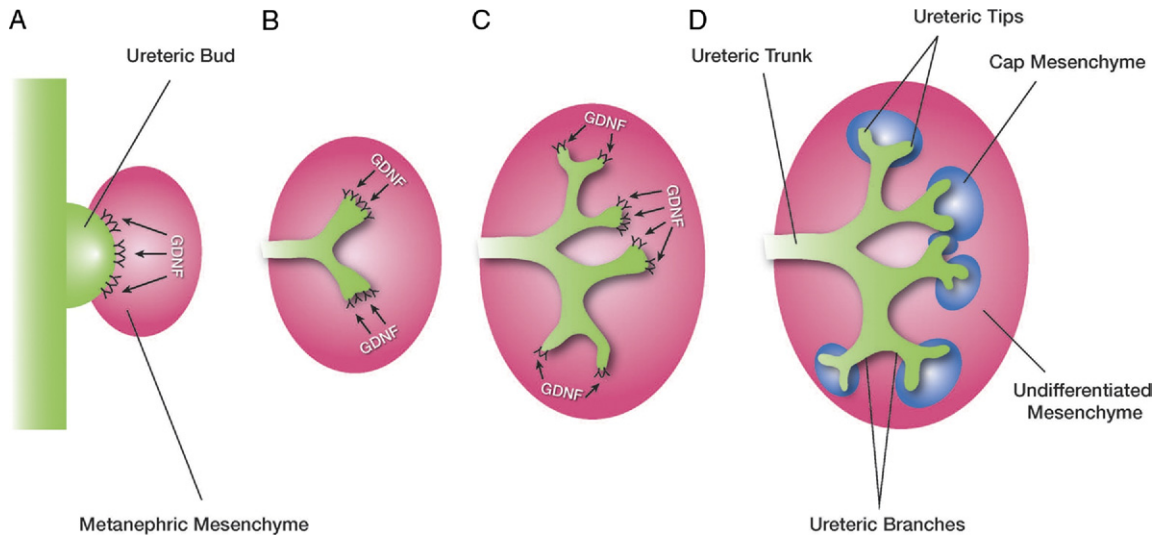

Figure 3. Ureteric branching morphogenesis. (A) Metanephric mesenchyme-secreted GDNF acts directly on epithelially expressed c-RET-GFRα1 receptor complex (Y) to initiate invasion of the metanephric mesenchyme (pink) by the ureteric bud (green). (B) After invasion, the ureteric bud undergoes a dichotomous branching event termed T-stage. (C) c-RET-GFRα1 expression becomes localized to the tips of ureteric branches, in turn restricting branching events to the tips of developing ureteric branches. (D) Subsequent dichotomous branching events give rise to the ureteric tree, with mesenchymal cells induced to condense and form cap mesenchyme at the ureteric tips. Expansions of abbreviations for gene products are listed in Table 1.

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NEPHROGENESIS

- Nephrogenesis is the process whereby new nephrons are generated
- Induction of new nephrons occurs adjacent to the tips of the ureteric tree, the precursor structure for the collecting duct system
- Nephrogenesis occurs in only the nephrogenic zone
- Total nephron endowment is the number of nephrons present at the end of nephrogenesis
  - Believed to correlate strongly with the extent of ureteric branching morphogenesis
  - However, total number of ureteric tips does not equal total nephron number
- During early branching morphogenesis in mice, fewer than 1 nephron is induced per ureteric tip
  - However, during later stages, ~4 nephrons are induced by a single ureteric tip, increasing nephron endowment exponentially
  - Multiple nephrons associated with a single collecting duct constitute a kidney arcade
- Cells of the metanephric mesenchyme condense at the ureteric tips to form cap mesenchyme, structures responsible for the formation of all epithelial components of the nephron (Fig 3)
- Cap mesenchyme differentiates in the following sequence: pretubular aggregates → epithelial renal vesicles → comma- and S-shaped bodies → kidney corpuscles and tubules (Fig 1)

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CAP MESENCHYME AND PRETUBULAR AGGREGATES

- Cap mesenchyme cells form caps of induced metanephric mesenchyme cells over the tips of the ureteric branches (Fig 1)
- Induced cap mesenchyme cells express GDNF, PAX2, and WT1, supporting and promoting ureteric branching
- Cap mesenchymes are highly dynamic and important structures for metanephric development (Fig 4)
  - They can be classified further into distinct subpopulations due to genetic marker expression
  - All subpopulations express SIX2, which has been hypothesized to be a "kidney stem cell" marker
  - CITED1, EYA1, FLK-1, and WNT4 also are distinct genetic markers of cap mesenchyme subpopulations, whereas FOXD1 expression is present in interstitial metanephric mesenchyme
- Gradual loss of SIX2 expression is believed to be associated with the cessation of nephrogenesis
- Genetic ablation of *SIX2* rapidly depletes cap mesenchyme after induction and nephrogenesis ceases long before the normal complement of nephrons has formed
- SIX2 is required to maintain a nephron progenitor population
- Cap mesenchyme cells proximal to the ureteric tip and immediately adjacent to its basement membrane condense to form a ball of cells called pretubular aggregates (Fig 4)
  - SIX2-positive cells renew cap mesenchyme after differentiation events
- Cap mesenchyme requires 3 basic signals
  - Survival: BMP7 and BMP4 prevent an autoapoptotic pathway from being initiated
  - Proliferation: SIX2, as discussed
  - Recruitment of metanephric mesenchyme to the tip of the ureteric tree: EMX2 (empty spiracles homeobox 2 protein)
- Exposure of cap mesenchyme to epithelially derived WNT9B, TGFβ2, FGF-2, and LIF results in loss of SIX2 expression and is responsible for induction of pretubular aggregates

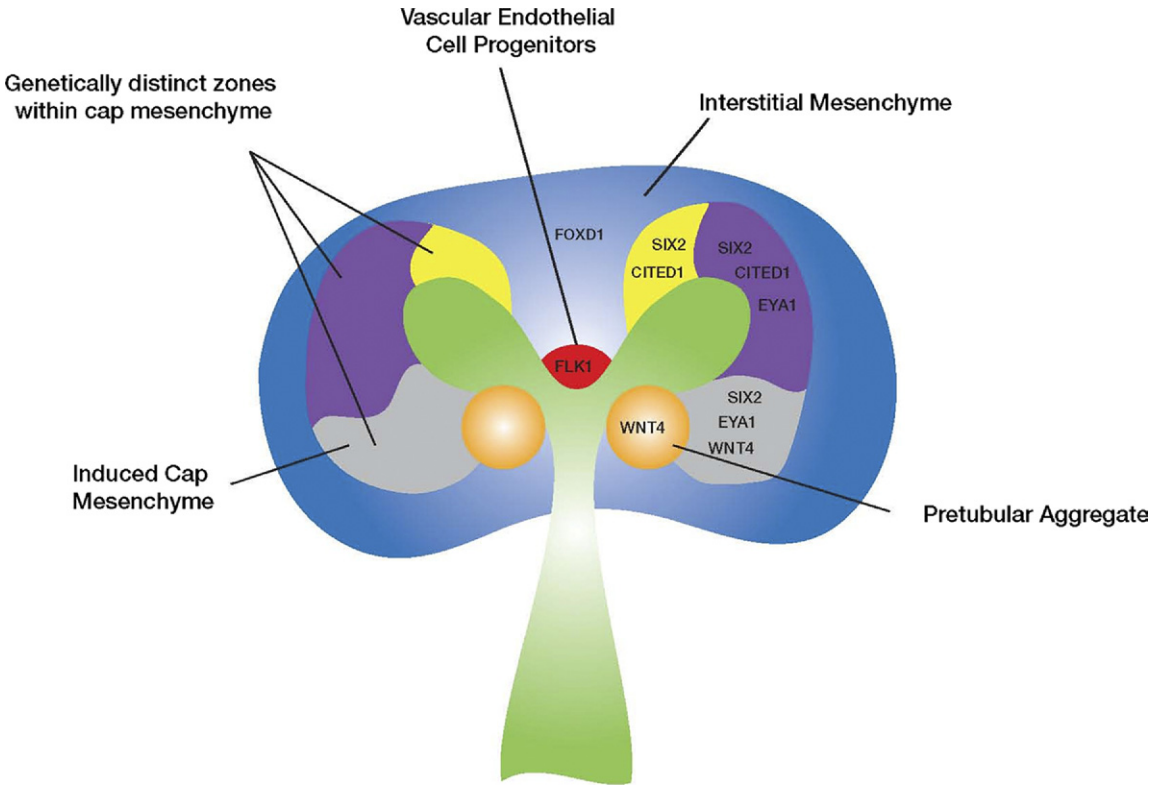

Figure 4. Subcompartments of the cap mesenchyme. Induced cap mesenchyme can be classified into subcompartments based on the expression of genetically distinct markers. Shown are key factors for the determination of each compartment. SIX2 is a definitive marker of all compartments of the induced cap mesenchyme. FLK1 expression defines vascular endothelial cell progenitors. Strong WNT4 expression is observed in pretubular aggregates. Finally, interstitial mesenchymal cells express FOXD1. Expansions of abbreviations for gene products are listed in Table 1.

- Pretubular aggregates initially consist of 4 cells, which proliferate to ~30 cells
- LIM1 and WNT4 are definitive markers of pretubular aggregates

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EPITHELIALIZATION OF METANEPHRIC MESENCHYME

- Pretubular aggregates epithelialize and thereby give rise to all epithelial cells of the nephrons
- The first sign of epithelialization involves conversion from a mesenchymal cell phenotype to a columnar phenotype
- Continual exposure to epithelial factors activates pretubular aggregates to undergo mesenchymal-to-epithelial transition to form renal vesicles → comma-shaped bodies → S-shaped bodies → kidney corpuscles → kidney tubules → all epithelial cell types of nephrons (Fig 1)

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SEGMENTATION OF THE NEPHRON TUBULE

- Segmentation is the process whereby the undifferentiated cells of the early nephron tubule differentiate into the structurally and functionally specialized tubule segments of the adult nephron
- Molecular regulation of tubule segmentation is poorly understood, but some new insights recently have been reported
  - Gamma secretase is required for overall nephron segmentation, with different segments showing different levels of sensitivity to the enzyme
  - PAX2 expression in the distal portion of the renal vesicle denotes where it will fuse with the ureteric tip
  - High WT1 and NOTCH2 expression in the distal region of the renal vesicle is required for specification of glomerular podocytes and proximal tubules
  - BRN1 and IRX3 are associated with specification of the loop of Henle

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KIDNEY STROMA

- The kidney stroma is arranged in layers adjacent to ureteric branches and contains a variety of extracellular matrix molecules, including collagens (including type IV collagen), fibronectin, and laminin
- Development of the stroma begins with condensation of mesenchymal cells peripheral to the induced cap mesenchyme
- Kidney stroma cells are FOXD1 positive, unlike other metanephric mesenchyme populations
- Kidney stroma originally was viewed as a relatively inert supportive structure for developing nephrons, but recently has been suggested to be integral for ureteric branching
- Kidney stroma expresses retinoic acid receptors α and $\beta 2$, suggesting that retinoic acid signaling through the stroma may be important for the maintenance and propagation of downstream epithelial c-RET expression
- Secretion of cytokines from the kidney stroma simultaneously inhibits glomerulogenesis and stimulates tubulogenesis
- Kidney stromal cells are required for formation of the kidney capsule and delineation of zones within the developing kidney

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KIDNEY VASCULATURE

- We do not yet have a full understanding of how glomeruli and the developing kidney become vascularized
- Initially, vascular cells were believed to be derived from an extrakidney source
  - Subsequent studies suggested that an endogenous population of FLK-1–expressing endothelial progenitor cells arranged in a large cluster in the metanephric mesenchyme was responsible for all kidney vasculature
  - However, recent studies hypothesize that local FLK-1–positive cell populations are associated with each ureteric tip and provide for more regionally coordinated vascularization
- Vascularization of glomeruli
  - Developing podocytes in the S-shaped body secrete VEGF, the ligand for FLK-1
  - VEGF acts to recruit endothelial cells into the distal cleft of the S-shaped body and form the glomerular capillary network
- Much less is known about the vascularization of the remainder of the kidney
  - The renal artery develops in close proximity to the Wolffian duct, invades the developing mouse metanephros at approximately embryonic day 12.0
  - Renal artery → interlobar arteries → arcuate arteries → interlobular arteries → afferent arterioles → connections formed with glomerular capillary network (derived from induced endothelial cells as mentioned)
- Maturation of kidney vasculature continues after birth

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NEPHRON ENDOWMENT

Introduction

- Nephron endowment can be considered to be an overall measure or index of the success of kidney development
- Much research attention in the past 20-25 years has focused on the environmental and genetic regulation of nephron endowment, as well as the adult health consequences of low nephron endowment
- The catalysts for this research were the Brenner hypothesis and Barker hypothesis
  - Brenner and colleagues proposed that a reduction in nephron endowment at birth likely confers an increased risk of developing hypertension in adulthood
  - Barker and colleagues proposed that a suboptimal intrauterine environment caused the fetus to make adaptations during development that increased its chance of short-term survival, but resulted in an increased likelihood of developing diseases in later life
    - This more recently has been termed the "developmental origins of adult health and disease" hypothesis

Variation in Nephron Number in Normal Human Kidneys

- Nephron endowment is defined as the number of nephrons present at or shortly after the cessation of nephrogenesis
- Nephron number reflects the number of nephrons formed during development minus the number of nephrons subsequently lost during the life course
- Large variations in nephron number in normal human kidneys have been reported by several studies in the past 20 years
- In the largest study to date (the Monash series), nephron number was estimated in 420 kidneys obtained at autopsy from 5 populations (white Americans and African Americans, white Australians and Aboriginal Australians, and Senegalese)
  - Mean nephron number was 901,902

  - Nephron number ranged almost 13-fold from 210,332-2,702,079
  - A large range in nephron number also is observed in children
  - In a study of 15 infants younger than 3 months, nephron number ranged from ~250,000-1.1 million
    - Nephron number correlated with kidney volume
    - The regression predicts an additional 24,000 nephrons/1 g of kidney mass
- Australian Aborigines have very high rates of chronic and end-stage kidney disease
  - Nephron number is lower in Australian Aborigines than white Australians from the same geographic region
- Human nephron number has correlated with risk factors for chronic kidney disease, including
  - Birth weight (directly)
  - Age (inversely)
  - Race (lower in Aboriginal Australians than white Australians)
  - Hypertension (indirectly in several studies)

Nephron Number in Animal Models

- There is overwhelming evidence from animal studies that a nephron deficit frequently, but not always, is associated with increased blood pressure in adult life
- Fewer studies have examined kidney structure and physiology; the observed phenotype depends on
  - Timing of the perturbation (environmental or genetic) relative to stage of kidney development
  - Nature, duration, and severity of the perturbation
  - Sex of offspring
  - Timing of the phenotypic analysis
  - Lactational and postweaning diets
- A "second hit" perturbation often is required to show a physiologic deficit in animals born with a nephron deficit

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CAKUT AND KIDNEY DEVELOPMENT MALFORMATIONS

- Prevalence of CAKUT
  - Detected in ~1:500 fetal ultrasound examinations
  - Represent ~20%-30% of all anomalies identified during the prenatal period
- Importantly, 50% of childhood kidney failure worldwide is attributed to CAKUT (Table 2)
- The primary insults believed to be associated with the development of CAKUT, in particular, kidney hypoplasia/dysgenesis/agenesis, are environmental factors and genetic mechanisms

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Table 2. Definition of CAKUT

Abnormality	Description
Kidney hypoplasia	Small kidneys presumably containing fewer intact nephrons
Kidney dysplasia	Kidney contains immature/maldeveloped components
Kidney agenesis	Absent kidney
Multicystic kidney	Presence of multiple cysts in the kidney
Horseshoe kidney	Both kidneys are fused together, also known as kidney fusion
Duplex kidney	1 ureter with a duplicated collecting system due to bifurcation of the ureter or 2 ureters
Vesicoureteric reflux (VUR)	Backward flow of urine into the kidney
Hydroureter	Dilated ureter
Hydronephrosis	Dilation of the kidney pelvis
Obstruction at the vesicoureteric junction (VUJ)	Obstruction at ureter-bladder junction
Obstruction at the ureteropelvic junction (UPJ)	Obstruction at the ureter-kidney pelvis junction

Abbreviation: CAKUT, congenital anomalies of the kidney and urinary tract.

GENETIC REGULATION OF NEPHRON ENDOWMENT

- Polymorphisms in 2 human genes (*PAX2, RET*) have been linked to small kidney size in neonates and presumably low nephron endowment
- In contrast, a common variant in the *ALDH1A2* gene is associated with a 20% increase in newborn kidney size
- Other genes with polymorphisms associated with human kidney hypoplasia have been identified through analyses of rare syndromes and include
  - *EYA1*, *SIX1*, and *SIX5*: branchio-oto-renal syndrome (also known as Melnick-Fraser syndrome)
    - 1:40,000 live births
    - A dominant genetic syndrome that can result in hearing loss, ear pits, pharyngeal cysts or fistulas, and kidney anomalies, such as kidney hypoplasia and/or kidney agenesis
  - *FRAS1* and *FREM2*: Fraser syndrome
    - ~1:200,000 live births
    - A recessive genetic syndrome primarily associated with cryptophthalmos and maldevelopment of genitalia
    - Syndactyly, as well as malformations of the kidneys, ears, nose, and larynx, also have been observed in patients with Fraser syndrome
  - *GLI3*: Pallister-Hall syndrome
    - ~1:200,000 live births
    - A rare syndrome characterized by hypothalamic hamartoma, central and postaxial polydactyly, and kidney abnormalities, including cystic malformations, kidney hypoplasia, and ectopic ureteral implantation
    - Also presents with bifid epiglottis, which is a key diagnostic feature, because this is very rare in other syndromes or as an isolated malformation
  - *PAX2*: renal-coloboma syndrome (also known as papillorenal syndrome)
    - Prevalence currently is unknown
    - An autosomal dominant genetic syndrome characterized by kidney hypoplasia and colobomas of the optic nerve
    - Almost 100% of patients develop end-stage kidney disease
  - *SALL1*: Townes-Brock syndrome
    - 1:250,000 live births
    - Characterized by thumb malformations and dysplastic ear development, which is commonly associated with conductive hearing impairment
    - ~30% of patients develop end-stage kidney disease with or without the presence of a number of structural and functional kidney malformations, including horseshoe kidney, kidney hypoplasia, polycystic kidneys, and vesicoureteral reflux
- In mice, full or partial deletion of more than 25 genes has resulted in kidney hypoplasia
  - Deletion of several of these genes results in low nephron endowment, including *Wnt11, Met, Pax2, p53, Gli3R, GDNF, Fgf7, Frs2α,* and *Six2*
  - Mice heterozygous for TGFβ2 have 60% more nephrons than wild-type mice

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ENVIRONMENTAL REGULATION OF NEPHRON ENDOWMENT

- We know very little about the effects of the human fetal environment on nephron endowment
  - Kidney volumes in newborns of women with vitamin A deficiency are smaller than in children born to mothers with normal vitamin A levels
- Animal studies have shown that a variety of perturbations to the fetal environment can result in reduced nephron endowment, including
  - Maternal global food restriction
  - Maternal low-protein diet
  - Placental insufficiency
  - Maternal vitamin A deficiency
  - Maternal exposure to
    - Natural and synthetic glucocorticoids
    - Alcohol
    - Certain antibiotics
- Early postnatal overfeeding of rats results in kidneys with more nephrons than control kidneys

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CYSTIC KIDNEY DISEASES

- Cystic kidney disease is characterized by the development of fluid-filled cysts within the kidney parenchyma, resulting in distortion and degeneration of kidney structure accompanied by progressive impairment in kidney function
  - Can be inherited or acquired (primarily associated with kidney carcinoma)
  - Can manifest at any age from the neonatal period to much later in adult life
  - Can consist of singular or multiple cysts
  - Can be functionally benign or result in kidney insufficiency
- A major factor involved in the development of cystic kidney disease is structural and/or functional defects in primary cilia and/or the associated centrosome
  - Primary cilia generally are immobile structures built upon a centrosome
  - They extend from the apical membrane of a cell
  - Consist of a 9+0 arrangement of microtubules, which differs from motile cilia, which have a 9+2 arrangement
- Cilia detect tubular flow (mechanosensory), stimulating intracellular calcium ion release, which is transmitted through gap junctions to neighboring cells
  - In conjunction with arginine vasopressin (AVP; antidiuretic hormone), this process is important for the regulation of cell membrane composition
- Primary cilia have been implicated as participants in multiple signaling pathways, including PDGF (platelet-derived growth factor) and Hedgehog and WNT signaling pathways
  - For example, dysfunctional WNT signaling can alter apical-basolateral cell polarity and induce cyst formation
- Inherited cystic conditions include
  - Autosomal dominant polycystic kidney disease (ADPKD): ~1:600
  - Autosomal recessive polycystic kidney disease (ARPKD): 1:20,000
  - Nephronophthisis (NPHP): 1:50,000
  - Joubert syndrome (JBTS): 1:100,000
  - Bardet-Biedl syndrome (BBS): ~1:140,000
  - Meckel-Gruber syndrome (MKS): ~1:140,000
  - Orofacial digital syndrome type 1 (OFD1): 1:250,000

Autosomal Dominant Polycystic Kidney Disease

- Most prevalent cystic kidney disease
  - Kidney failure observed in ~50% of patients with ADPKD by age 60
  - Bimodal expression of disease, first during childhood and subsequently in adulthood
- 85% of ADPKD associated with a polymorphism in *PKD1*; however, the pathologic phenotype also is observed in the presence of polymorphism in *PKD2*
  - Polycystin 1 (product of *PKD1* gene) is a transmembrane glycoprotein that detects environmental signals and is implicated in intracellular signaling
  - Polycystin 2 (product of *PKD2* gene) acts in a regulated ion channel complex and is important for intracellular calcium ion release from the endoplasmic reticulum

Autosomal Recessive Polycystic Kidney Disease

- Kidney cysts are associated with cystic development of the biliary tract
- Condition predominantly seen in neonates, but can manifest later
- ~50% of affected neonates die shortly after birth due to systemic hypertension and kidney insuffi-

ciency with accompanying hepatic fibrosis and portal tract hypertension
- Development attributed to a polymorphism in *PKHD1*, which encodes fibrocystin (also known as polyductin)
  - Fibrocystin is involved in differentiation of collecting duct epithelium
  - Fibrocystin is localized to the primary cilium and centrosome; however, exact function of the protein is unknown

Nephronophthisis

- Recessively inherited condition that is classified further into infantile, juvenile, and adolescent onset
- 9 subtypes attributed to 9 different genes (*NPHP1-NPHP9*), all of which predominantly affect the nephron tubule
- Characterized by thickening of the tubular basement membrane and diffuse tubular fibrosis
  - These features are considered precursors to tubular atrophy and kidney cyst development
  - Cysts commonly are small and result from tissue distortion and atrophy, not aberrant cellular proliferation
- *NPHP* genes encode nephrocystins
  - Nephrocystins are localized at adherence junctions and focal adhesions
  - They are critical for cell polarity and cell-cell communication

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ABNORMAL DEVELOPMENT OF THE GLOMERULAR FILTRATION BARRIER

- The glomerular filtration barrier consists of glomerular endothelium, the glomerular basement membrane (GBM), and podocytic epithelium; the barrier filters molecules from plasma based on molecular size and charge
  - Glomerular endothelial cells adhere to the GBM and contain numerous openings (fenestrae) ~70-100 nm in diameter; endothelial cells are covered with a glycocalyx believed to assist in size and charge selective filtration
  - The main components of the GBM are type IV collagen, laminin, proteoglycans, and nidogen
  - Podocytes are distinctly shaped cells with a prominent cell body and cytoplasmic projections that are divided further into foot processes that cover the exterior of glomerular capillaries
    - Foot processes adhere to the external aspect (urinary space side) of the GBM
    - Foot processes from adjacent podocytes interdigitate with one another
    - Filtration slits are located between adjacent foot processes and contain a diaphragm (slit diaphragm)
- The slit diaphragm is a specialized cell-cell junction
  - Structurally, the slit diaphragm appears similar to a zipper, with extracellular protein domains expressed by adjacent foot processes cross-talking and interacting
  - A number of proteins have been identified as critical for the structural and functional integrity of the slit diaphragm
  - Nephrin, Neph1, Fat1, Fat2, Podocin, and CD2AP are components of the slit diaphragm and are required for normal diaphragm function
  - Polymorphisms in slit diaphragm proteins have been associated with congenital and familial nephrotic syndromes
  - Nephrin (*NPHS1*): Finnish-type nephrotic syndrome
  - Podocin (*NPHS2*): ~20% of steroid-resistant nephrotic syndromes

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ACKNOWLEDGEMENTS

The authors acknowledge Monash University's Multimedia group in the Faculty of Medicine, Nursing, and Health Sciences for preparation of the figures.

Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.