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REVIEW ARTICLE

Embryology of the urinary tract: At a glance

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Abstract

The urinary tract's embryonic development is a fascinating process that begins early in human embryogenesis. The review explores the developmental stages of kidney formation, ureter development, and bladder formation, which are all essential components of the urinary tract. The process is guided by intricate interactions between various embryonic tissues, forming a complex network of signaling pathways that ensure proper formation. Any disruptions to these pathways can lead to congenital anomalies of the kidney and urinary tract (CAKUT), which are prevalent in approximately 1 out of every 500 live births and account for 40 to 50% of childhood cases of end-stage kidney disease. The review discusses the clinical significance of CAKUT, including the prevalence, genetic factors, and environmental influences that contribute to these complex conditions. The review also highlights three types of CAKUT: renal agenesis, multicystic dysplastic kidney disease, and polycystic kidney disease. Renal agenesis refers to the inborn absence of one or both kidneys, while multicystic dysplastic kidney disease is marked by compromised kidney function due to the presence of irregular cysts in the affected kidney(s). Polycystic kidney disease is a genetic disorder that results in the formation of fluid-filled cysts on the kidneys, gradually impairing renal function. Significant progress has been made in understanding the genetics and environmental influences contributing to CAKUT. However, further research is still necessary to fully comprehend these complex conditions. With a better understanding, healthcare professionals can provide more targeted care to patients with CAKUT and improve their long-term outcomes.

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Introduction

The fascinating journey of urinary tract development begins at the very early stages of human embryogenesis, specifically around the fourth week, with the emergence of the nephrogenic cord. This cord is the embryonic structure from which the primitive kidneys, namely the pronephros, mesonephros, and metanephros, develop sequentially. Interestingly, the metanephric kidneys start functioning as primitive excretory units by the eleventh week, but the complete formation of the urinary tract, characterized by the development of one to three million collecting tubules through multiple branching events, extends until the thirty-second week (1).

This complex developmental process is coordinated by a series of intricate interactions between various embryonic tissues, including the mesonephric duct, ureteric bud, and metanephric blastema. These interactions form an elaborate network of signaling pathways that guide the proper formation of the urinary tract. However, any disruptions to these pathways, whether genetic or environmental, can lead to a range of congenital abnormalities known as congenital anomalies of the kidney and urinary tract (CAKUT). These anomalies encompass a wide spectrum of conditions, such as renal agenesis and dysplasia, multicystic dysplastic kidney disease, and polycystic kidney disease (2).

Kidney development

The genesis of the urinary tract commences during the fourth week of embryonic development with the process of embryonic folding, leading to the formation of a longitudinal structure, the urogenital ridge. This ridge bifurcates into two parts: the nephrogenic cord, which gives rise to the urinary tract, and the gonadal ridge, which develops into the reproductive system. The nephrogenic cord sequentially forms three distinct types of kidneys: the pronephros, mesonephros, and metanephros, progressing from the rostral end to the caudal end (3).

Development of the pronephros begins around the fourth week, with the formation of pronephric ducts in the cervical region of the nephrogenic cord. These ducts extend and eventually fuse with the cloaca, and adjacent intermediate mesoderm condenses to form non-functional nephron units, the pronephroi. By day 25, these primitive kidneys regress completely. Following this, the mesonephric duct, or Wolffian duct, initiates development in the more caudal region of the nephrogenic cord. Here, the neighboring intermediate mesoderm also condenses to form mesonephroi. Although around 40 pairs of mesonephroi form, only those positioned between the L1-L3 vertebrae progress to form functional excretory units. These units are capable of excreting small volumes of fluid into the amnion between the sixth and tenth week of development. The mesonephros and its duct later degenerate in females, but persist and evolve into components of the male reproductive system, such as the epididymis, vas deferens, seminal vesicles, and the ejaculatory duct (4).

The metanephric kidney, the final and permanent kidney, starts its development in the fifth week. The mesonephric duct fuses with the cloaca, thereby prompting the sacral intermediate mesoderm to form a mass known as the metanephric blastema. In the early fifth week, the metanephric blastema releases a protein called glial-cell derived neurotropic Factor (Gdnf), which induces the formation of the ureteric bud in the mesonephric duct. This protein acts as a ligand for the cell surface receptor RET and its co-receptor, Gdnf Family Receptor alpha 1 (Gfr-alpha1), both of which are predominantly expressed in the mesonephric duct (5).

The ureteric bud starts a branching cascade in the sixth week, forming the basic renal architecture and the collecting tubules. The first bifurcation forms the renal pelvis and the kidney's cranial and caudal lobes. The subsequent four bifurcations form the major calyces, and the next four, occurring in the seventh week, form the minor calyces. This branching process is stimulated by Gdnf acting on the RET expressing cells at the tips of the ureteric bud, with each branch acquiring a blastemal cap from which Gdnf is secreted. This cascade continues until week 32, resulting in approximately 1 million to 3 million collecting tubules (4-6).

The formation of functional nephrons begins when each collecting tubule's tip triggers the blastemal caps to form nephric vesicles. These vesicles then evolve into nephric tubules, which consist of an S-shaped Bowman's capsule, proximal and distal tubules, and the loop of Henle. The development of the glomerulus begins when podocyte precursors within the S-shaped body release VEGF2, attracting endothelial cells to form a primitive vascular tuft. This process gives rise to the glomerulus' afferent and efferent arterioles. Interaction between the podocyte precursors and the endothelial cells stimulates the differentiation of podocytes, with the glomerular basement membrane forming at the interface between these two cells. The distal convoluted tubule, which is the distal end of the nephric tubule, merges with the collecting duct to form a uriniferous tubule (7).

During early embryonic development, the kidneys are positioned close together in the embryo's sacral region. However, as the abdomen expands, the kidneys move apart and ascend to their definitive location in the lumbar region between the sixth and ninth weeks. Blood supply to the kidneys is provided by the renal arteries, which are branches of the dorsal aorta. As the kidneys ascend, the lower branches degenerate, and the kidneys begin to receive blood from progressively higher branches (8).

Bladder and ureter development

The formation of the bladder commences in the fourth week of embryonic development when the urogenital septum segregates the cloaca into two distinct parts. The posterior part evolves into the rectum, while the anterior part, known as the urogenital sinus, expands to create the bladder. The lowermost part of the urogenital sinus shapes the urethra (9). Simultaneously, the mesonephric duct integrates with the cloaca, with a portion of the duct becoming part of the bladder's posterior wall. It's important to note that while the ureteric bud sprouts from the mesonephric duct, it establishes a separate entrance into the urinary bladder (9).

As the kidneys rise, the ureters stretch and make an opening into the bladder from above. The roots of the mesonephric ducts shift downward and merge, culminating in the formation of the trigone region. As the final step, the trigone region's mesodermal cell epithelium gets replaced by endodermal cells from the urogenital sinus, marking the completion of the bladder's development (10).

Clinical significance

Congenital anomalies of the kidney and urinary tract (CAKUT) are prevalent in approximately 1 out of every 500 live births, accounting for 40 to 50% of childhood cases of end-stage kidney disease. Studies have recognized genetic factors contributing to CAKUT, including Pax2 and BMP4 mutations, while also spotlighting environmental influences such as maternal diabetes and in-utero exposure to ACE-inhibitors. CAKUT represents a wide range of disorders resulting in abnormal development, discussed further below (11).

Renal agenesis refers to the inborn absence of one (unilateral) or, less often, both (bilateral) kidneys. This condition frequently coincides with irregularities in the heart, male reproductive system, and gastrointestinal tract. Bilateral renal agenesis hinders the generation of adequate amniotic fluid, leading to a condition called oligohydramnios, which in turn results in Potter's Syndrome. Affected fetuses may exhibit various physical abnormalities, notably Potter's facies, characterized by low-set ears, a flat nose, a recessed chin, and infraorbital creases. Babies born with bilateral renal agenesis typically do not survive past a few days post-birth. In contrast, children with unilateral renal agenesis can live a normal life as the remaining kidney compensates by hypertrophying. Several genes, such as ANOS1, EYA1, and RET, have been associated with bilateral renal agenesis, although more research is needed (12).

Multicystic dysplastic kidney disease (MCDK) is marked by compromised kidney function due to the presence of irregular cysts in the affected kidney(s). It impacts approximately 1 in every 4300 live births globally, with a higher prevalence in males. Most cases are diagnosed through prenatal ultrasounds. Fetuses with bilateral MCDK, unfortunately, do not survive, while those with unilateral MCDK are typically healthy but require routine imaging to monitor any changes in the affected kidney size. In some cases, a nephrectomy may be performed to remove the diseased kidney. The causes of MCDK remain unclear, though it's suspected to arise from a defect in the Gdnf-RET signaling pathway between the ureteric bud and the metanephric blastema (13).

Polycystic kidney disease (PKD) is a genetic disorder that results in the formation of fluid-filled cysts on the kidneys, gradually impairing renal function. PKD can be of two types: autosomal dominant PKD and autosomal recessive PKD. Autosomal dominant PKD is the most common inherited kidney disease, believed to be caused by PKD1 mutations in 85% of cases and by PKD2 mutations in the remaining 15%. Symptoms can include abdominal discomfort, high blood pressure, and blood in urine. However, symptoms typically manifest only after the cysts have grown large enough to disrupt normal kidney function, usually after the age of thirty. Conversely, autosomal recessive PKD, caused by PKHD1 mutations, presents symptoms soon after birth (14). Up to half of affected newborns succumb to pulmonary hypoplasia due to oligohydramnios; those who survive have a shorter lifespan and face other comorbidities, such as systemic hypertension and end-stage renal disease as they age. Besides structural anomalies in the kidney, malformation can also occur if the kidneys fail to ascend. The two most common malformations are an ectopic kidney and a horseshoe

kidney (13). An ectopic kidney, also known as a pelvic kidney, happens when a kidney doesn't ascend or complete its ascent to its final location in the lumbar region. A horseshoe kidney forms when both kidneys fuse at their lower ends to form a U-shaped structure, reminiscent of a horseshoe, situated just below the inferior mesenteric artery. In both circumstances, the individual typically remains asymptomatic, and the condition is usually discovered during investigations for unrelated health issues (14,15).

Conclusions

The development of the urinary tract is a complex and fascinating process that begins early in human embryogenesis. The formation of the three types of kidneys, the pronephros, mesonephros, and metanephros, is sequential and progresses from the rostral end to the caudal end. The metanephric kidney is the final and permanent kidney and starts its development in the fifth week. The ureteric bud induces the formation of collecting tubules through a branching cascade process, resulting in approximately 1 to 3 million collecting tubules by week 32. Any disruptions to the intricate signaling pathways involved in the urinary tract's development can lead to a range of congenital anomalies of the kidney and urinary tract (CAKUT), which account for 40 to 50% of childhood cases of end-stage kidney disease. The three types of CAKUT discussed are renal agenesis, multicystic dysplastic kidney disease, and polycystic kidney disease. CAKUT encompasses a wide spectrum of disorders that can lead to abnormal development, affecting not only the urinary tract but also other systems such as the heart, male reproductive system, and gastrointestinal tract. Although significant progress has been made in understanding the genetics and environmental influences contributing to CAKUT, further research is still necessary to fully comprehend these complex conditions.

Conflict of interest

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