ACTA FAC. MED. NAISS. **UDC 611.61**

Review article

ACTA FAC. MED. NAISS. 2004; 21 (3): 163-170

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HUMAN KIDNEY DEVELOPMENT

SUMMARY

The kidney is one of the main excretory and homeostatic organs of the body. It excretes most of the final products of metabolism, and controls the concentration of certain constituents of the body fluids. Organogenesis of the kidney is complex and stepwise process with the successive appearance of pronephros, mesonephros, and metanephros. Pronephros and mesonephros are the transient structures with little excretory capacity, which precede the formation of the adult (metanephric) kidney. Metanephros grow as the result of the reciprocal inductive interactions between the two primordial mesodermal derivates: ureteric bud, an epithelial outgrowth of the Wolffian duct, and metanephric blastema, a group of mesenchymal cells. The ureteric bud causes the metanephric mesenchyme to differentiate and form nephrons, whilst the metanephric mesenchyme causes the ureteric bud to grow and bifurcate to form collecting ducts. The nephron progresses through four developmental stages, which are described as 1) vesicle, 2) comma-shaped and S-shaped stages, 3) developing capillary loop, and finally 4) maturing glomerulus stage.

Despite its importance, the origin of the kidney vasculature is not completely elucidated. As the renal vesicle invaginates, signals, presumably elaborated by the cells of the vascular cleft, recruit angioblasts or endothelial cells into the forming glomerulus. Once within the vascular cleft, the endothelial cells undergo mitosis and assemble into a capillary as the glomerulus expands. The glomerular basement membrane is assembled from extracellular matrix components produced by both the endothelium and podocytes. Finally, mesangial cells or "glomerular pericytes" are also recruited into the glomerulus and they contribute to the stabilization of the glomerular capillary tuft.

The fetal kidney produces dilute urine which is a major input into the amniotic fluid. Any factor preventing urine production by the kidneys could thus induce fetal abnormalities. Recently, several studies emphasized the relation of kidney development and adult renal diseases.

Key words: **kidney, development, nephron**

INTRODUCTION

The kidney is one of the main excretory and homeostatic organs of the body that evolved as protovertebrates migrated into fresh water to keep their internal environment of high osmolarity from surrounding freshwater (1). It excretes most of the final products of metabolism, removing them from the blood and controls the concentration of certain constituents of the body fluids, such as salt and uric acid, managing their excretion and reabsorption (2).

The knowledge of human fetal kidney development is still limited. Several studies emphasized the relation of fetal kidney development, especially nephrogenesis, to adult renal diseases. It has been proposed that kidney disease may be determined by events that occurred during fetal development (3,4). Brenner et al. (5) suggested that congenital nephron deficits predispose individuals to hypertension later in life. It has been also documented that any disturbance of the ureteric bud outgrowth during renal organogenesis and/or its branching pattern may lead to renal malformation and various degree of oligonephronia (6).

The human kidney is constituted of blood vessels, connective tissue, and epithelial cells. How all of these elements get there?

HUMAN KIDNEY DEVELOPMENT

Two processes are responsible for the organ growth and development: organogenesis, the process of specific induction and differentiation of cells, and maturation, the process during which an organ achieves its complete functional maturity (7).

Organogenesis of the kidney is a complex and stepwise process with the successive appearance of pronephros, mesonephros, and metanephros (8). Organogenesis involves many cellular processes, such as cell proliferation, cell adhesion, apoptosis, cell differentiation, changes in cell shape and cell migration, all of which require molecules from different classes and families (2).

Two embryonic kidneys (the pronephros and mesonephros) precede the formation of the adult (metanephric) kidney in reptiles and humans, whereas the mesonephros is the adult kidney in fish and amphibians (9). In mammals, pronephros and mesonephros are transient structures with little excretory capacity. However, they are important for the appropriate development of the metanephros, the definitive mammal kidney (10).

THE PRONEPHROS

In mammals, the pronephros is non-functional, but in some lower vertebrates, such as amphibia and fish, the pronephros acts as the embryonic kidney and is essential for survival (11). In the pronephros, after filtration through the glomus, fluid enters the coelomic cavity, also known as the nephrocoel. From there the filtrate is collected via ciliated funnels (nephrostomes) connected to the pronephric tubules. Surrounding these tubules is a blood sinus into which reabsorbed fluid passes, whilst unabsorbed fluid is excreted via the pronephric (Wolffian) ducts (12).

THE MESONEPHROS

The mammalian mesonephros develops from a mesodermal region called the AGM zone (aorta–gonad–mesonephros). The AGM region apparently contributes to the development of the aorta and gonads, but it is also the source of hematopoietic stem cells (13). Organogenesis of the mesonephros is initiated when the pronephric duct reaches the presumptive mesonephric mesenchyme and induces adjacent mesenchymal cells to condense. Thereafter the condensate will contribute to the formation of the mesonephric tubules that develop into nephrons (8). In the human embryo at day 24–26, mesonephric ducts form on the lateral and ventral sides of the nephrogenic ridge and induce formation of the mesonephros (14). By day 28, these ducts join the cloaca and by 8 weeks post conception, the human mesonephros has reached its maximal size and starts to regress. Complete regression occurs by week 16 (15). Mesonephric development and complexity varies significantly between species, whilst in some species the mesonephros appears to have an excretory capacity, in others it is clearly non-functional. Generally, the glomeruli of the mesonephros are relatively large compared to those of the metanephros but there are many smaller among them too (between 10 and 50 per kidney) (12). In principle, nephrogenesis is very similar in the meso- and metanephros. However, it should be noted that in the mesonephros the tubules are formed along the Wolffian duct whereas in the metanephric kidney they are organized around the ureter tree and are apparently regulated by differential epithelial morphogenesis. Mammalian mesonephric nephrons consist of glomeruli like structures and proximal and distal ducts. The size, distribution, functional maturity and developmental fate of these nephrons differ significantly between species. Eventually, mesonephric tubules start to regress, leading to the complete disappearance of the organ in the female. In male embryos, some caudal tubules and duct remain and develop further as part of the male genitals. The factors that regulate these events in the mesonephros may be involved in setting the primary sex as well (16) (fig. 1).

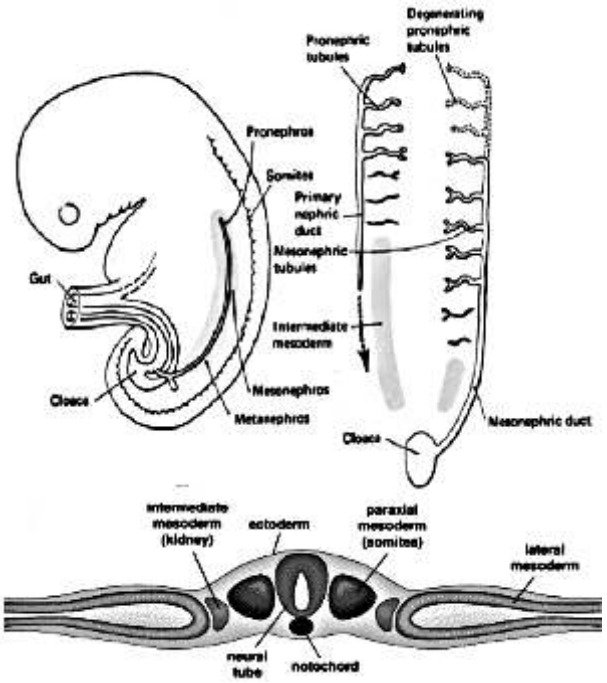

Figure 1. Kidneys in mammal development. Embryonic precursors of metanephros, pronephros and mesonephros are sequentially induced and formed. (Adapted from Perantoni AO. Seminars in Cell & Developmental Biology 2003;14:201–08.)

THE METANEPHROS

Human fetal kidney development runs through series of dependent changes during which it achieve its morphological and functional maturity (7). In humans, metanephros grow as the result of the reciprocal inductive interactions between the two primordial mesodermal derivates: ureteric bud, an epithelial outgrowth of the Wolffian duct, and metanephric blastema, a group of mesenchymal cells. The metanephric kidney begins to develop after the Wolffian duct has extended caudally along the body axis and has produced an outgrowth called the ureteric bud. The ureteric bud is an epithelial tissue that invades the metanephric blastema at around embryonic day (E)10.5–E11 in mouse and E35–E37 in humans (2). After the ureteric bud has formed, reciprocal inductive interactions occurs. The ureteric bud causes the metanephric mesenchyme to differentiate and form nephrons, whilst the metanephric mesenchyme causes the ureteric bud to grow and bifurcate to form collecting ducts. It is not known whether the metanephric mesenchyme initiates organogenesis by inducing the formation of the ureteric bud, which then invades the mesenchyme and starts to branch repeatedly (a process termed branching morphogenesis), or whether the initial signals derive from the Wolffian duct before budding of the ureteric bud.

Around the fifth week of gestation in humans, the ureteric bud induces the mesenchyma to form tubular and glomerular epithelia. The nephron arises from the metanephric mesoderm, while the collecting ducts, calyces and renal pelvis arise from the ureteric bud (8). Metanephros, the definitive human kidney is first visible at about the 5th week of intrauterine life (7). From the 8th throughout the 32nd to 36th weeks, nephrogenesis is continuously induced by ureteral bud ramifications (10,17). The nephron progresses through four developmental stages, which are described as 1) vesicle, 2) comma-shaped (or lipped) and S-shaped stages, 3) developing capillary loop, and finally 4) maturing glomerulus stage (8,18,19, 20).

During human nephrogenesis, branching is repeated 15 times to give rise to approximately 65000 collecting ducts (21). During the latter stages of renal embryogenesis, the first five generations of the ureteric bud undergo transformation into the pelvis and calyces by increased growth and dilatation of these tubules. The ureteric bud induces the mesenchyme to undergo mesenchymal–epithelial transformation, leading to the formation of the glomerulus, proximal tubule, loop of Henle, and distal tubule. Each tip of the branch is capable of inducing about 100 mesenchymal cells to survive, proliferate and to undergo mesenchymal to epithelial transformation leading to the generation of the epithelial cells of the nephron (22).

It is interesting that among large numbers of undifferentiated (stem) cells, only a few are selected to enter the developmental pathway because they have been rescued from apoptosis. The conversion from induced mesenchymal cell to epithelial cell phenotype is complex (22,23,24). The first step, after rescue from apoptosis, is cell to cell adhesion that directs mesenchymal cells to condense and to form globular aggregates. Within the aggregates, mesenchymal cells begin to express the polarized epithelia (18,25). Polarity does not mean positive and negative charges, but implies that certain membrane proteins, especially receptors, are localized to a specific side of the cell. Mesenchymal cells are not polarized. They are characterized by random distribution of cell membrane receptors over the whole cell surface. For the conversion of mesenchymal into epithelial cells to occur, specific cellular adhesion molecules are required to bind cells one t another and to the underlying basal lamina. These adhesion molecules have a role in cell orientation and polarity (26).

Each branch of the ureteric bud and its daughter collecting duct induces the formation of one nephron. Thus, formation of 15 generations of ureteric buds: collecting ducts induces an identical

number of nephrons. This number is lower than the number of nephrons in one human kidney (approximately 1000000). The remaining nephrons develop by induction of approximately ten nephrons around the stem of each elongating branch. The connecting tubules of each of these nephrons then attach to the stem of the collecting duct branch in series to form an arcade. After the arcades form, the terminal branch of the 15th generation begins to elongate and develop a succession of ampullae that induce nephrons on each side of the terminal branch (20, 27,28). As the ureteric bud branches in the metanephric mesenchyme, it induced the mesenchymal cells to condense around the tip of the bud forming a cap-like structure (fig. 2). Shortly after aggregation, each mesenchymal condensate undergoes a phenotypic switch to become a hallow sphere or vesicle of epithelial cells. Following these phenotypic changes, the epithelial cells at the lower pole of the vesicle, opposite to the ureteric bud, then change their shape and a cleft appears, forming a comma--shaped body. Next, a second cleft forms at the opposite pole of the comma-shaped body, which is termed an S-shaped body. The lower cleft of the S-shaped body is invaded by endothelial cells and presumably also by precursors of mesangial cells. These cells eventually give rise to the glomerular capillary loops and mesangium. These events seem to occur concomitantly with the development of the glomerular arterioles. The glomerular cells continue their maturation and achieve their adult features. In humans, nephrogenesis is completed at about 34 to 35 weeks of gestation. The permanent mammalian kidney is derived from nephrogenic cord mesoderm. The nephron arises from the metanephric mesoderm, and the collecting ducts, calyces and renal pelvis arise from the ureteric bud that branches off the mesonephric duct (8,20) (fig. 3).

The cells lining these vessels are the source of glomerular vasculature (11,12). At the onset of the comma shaped stage and continuing into the S-shaped stage, morphological segmentation of the developing nephron in to glomerular and tubular regions can be recognised. The S-shaped body begins to elongate and it fuses with the ureteric bud (29,30). The tubules continue to elongate and become more convoluted. Glomerular cells continue to differentiate until they acquire their adult features (forming maturing stage glomeruli in the developing kidneys). The morphogenesis of individual nephrons takes place in a temporal and centripetal manner, so that the entire range of structures found during nephrogenesis can be observed in a single kidney section. The number, shape, size, and distribution of nephrons contain important information about the

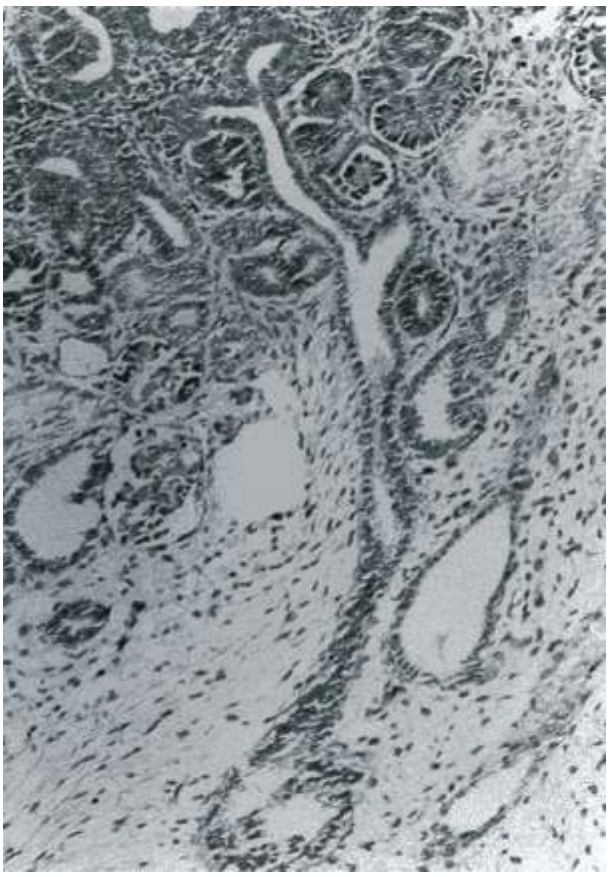

Figure 2. Ureteric bud (human fetal kidney in IV lunar month). Haematoxylin–eosin X 200

organization of the studied kidney (31). Fetal glomerular features change during development (32).

The kidney mesenchyme also gives rise to cell types other than those that contribute to the nephron. One such cell type is the stromal cell, which does not differentiate into nephrons or into the collecting-duct system. The role of the stromal compartment in kidney development has been overlooked in past years, but studies in mice have shown that the stroma is an important source of signaling in kidney organogenesis, in addition to the ureteric bud and the nephrogenic mesenchyme signalling centers (27).

There are many reasons why the study of kidney development is important. Human developing kidney has not been quantified. It has been proposed that many renal disease in adult may be determined by events that occurred during fetal development (33). The fetal metanephric kidney produces dilute urine which is a major input into the amniotic fluid which is essential as an aqueous environment, for the symmetrical growth of the fetus, and correct lung development. Any factor that prevents urine being produced by the kidneys could result in fetal abnormalities (34,35).

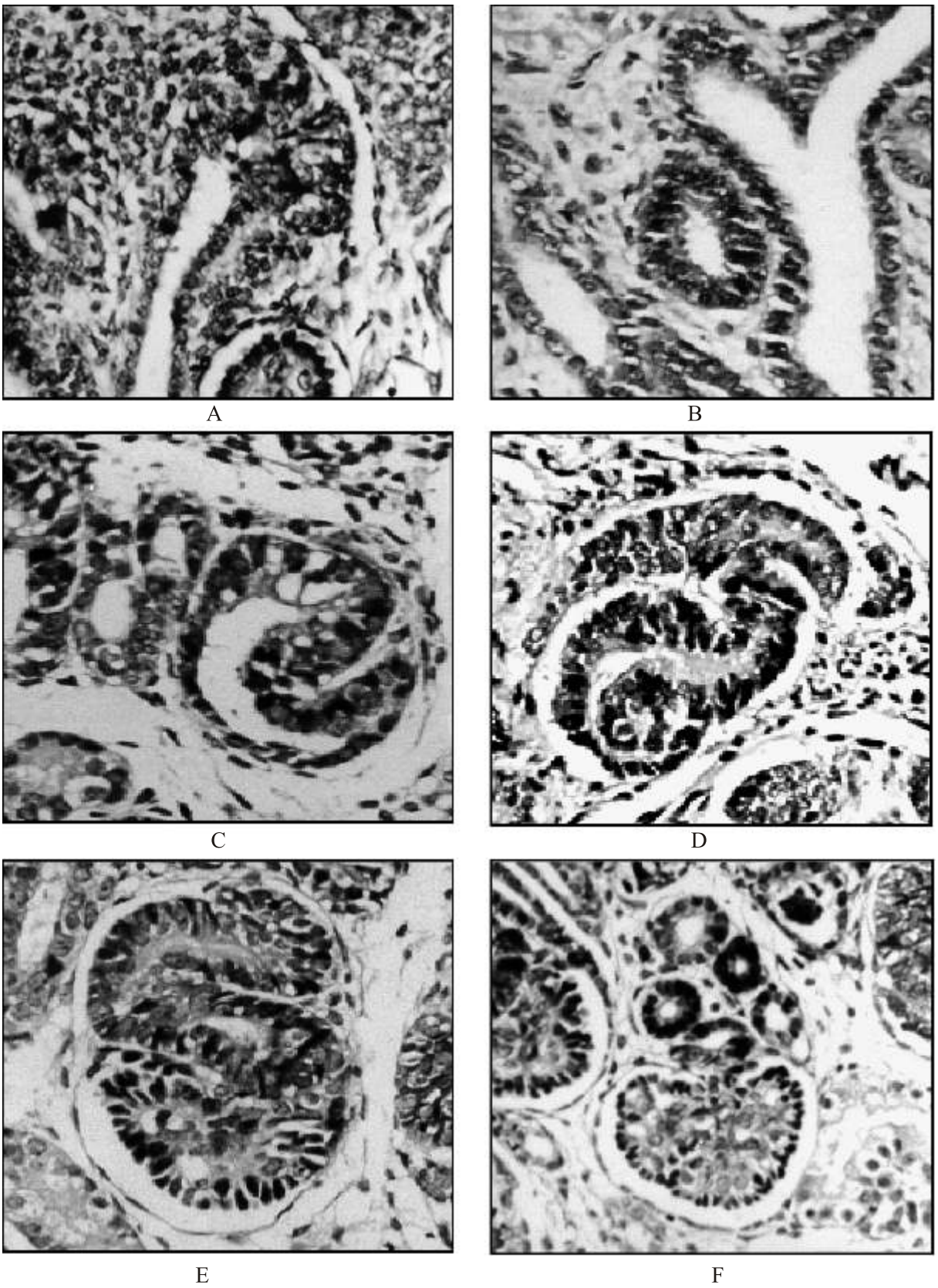

Figure 3. Different stages of nephron development (A–condensation of metanephric mesenchyma around the tip of ureteric bud; B–vesicle; C–comma shaped; D–S shaped; E–developing glomerulus; F–maturing glomerulus). Haematoxylin–eosin X 400

VASCULAR DEVELOPMENT

Microvessel assembly in the developing kidney may occur through vasculogenic, angiogenic, or both processes(36). Angiogenesis refers to the assembly of a new blood vessel from pre-existing vasculature. First, a tissue in need of a vascular supply must signal vicinal endothelial cells that a new vessel is required. Second, the responding vascular endothelial cells form a sprout, undergo mitosis, and migrate toward the source of the angiogenic signal. Finally, the migrating endothelial cells aggregate tightly one the another, a basement membrane is produced by the endothelial cells and pericyte envelope, and the new endothelial tube is stabilized. A second process of blood vessel formation is termed vasculogenesis, and this occurs predominately in the embryo (37). The overall sequence is similar to what occurs with angiogenesis, but here the endothelial cells are not derived from existing vessels but instead originate from distinct endothelial precursor cells called angioblasts. Upon appropriate stimulation, these angioblasts divide, migrate, aggregate to assemble a tube and, finally, differentiate into vascular endothelial cells (38).

In spite of its importance, the origin of the kidney vasculature is not completely clear. Until recently, it was accepted that the renal vessels originated by branching off preexisting (angiogenesis) extrarenal vessels (8). From those experiments, it was concluded that endothelial and mesangial cells derived from angiogenic sprouts originating outside the kidney (*eg*, aorta or its branches) (39). However, recent experiments challenge the exclusive, angiogenic, extrarenal origin of the kidney vasculature. Using specific markers, several laboratories have identified vascular precursors in the embryonic kidney, before vessels could be detected morphologically (18).

There are two probable embryonic sources for the glomerular endothelium (8). Metanephric mesenchymal cells may migrate into the vascular cleft and, by vasculogenesis, establish the glomeruli. The possibility that glomerular endothelium stems from from metanephric vasculogenic angioblasts is still without direct experimental support (36). Another possible source for embryonic kidney endothelial cells is from the ingrowth of tubelike angiogenic sprouts derived from external vessels. The formation of arterioles is insufficiently understood, particularly regarding their acquisition of smooth muscle and juxtaglomerular cells.

For appropriate glomerular capillary development, glomerular vascularization must coincide with podocyte development (19).

As the renal vesicle invaginates, signals, presumably elaborated by the cells of the vascular cleft, recruit angioblasts or endothelial cells into the forming glomerulus. Once within the vascular cleft, the endothelial cells undergo mitosis and assemble into a capillary as the glomerulus expands. The glomerular basement membrane is assembled from extracellular matrix components produced by both the endothelium and podocytes. Finally, mesangial cells or "glomerular pericytes" are also recruited into the glomerulus and contribute to stabilization of the glomerular capillary tuft (fig. 4).

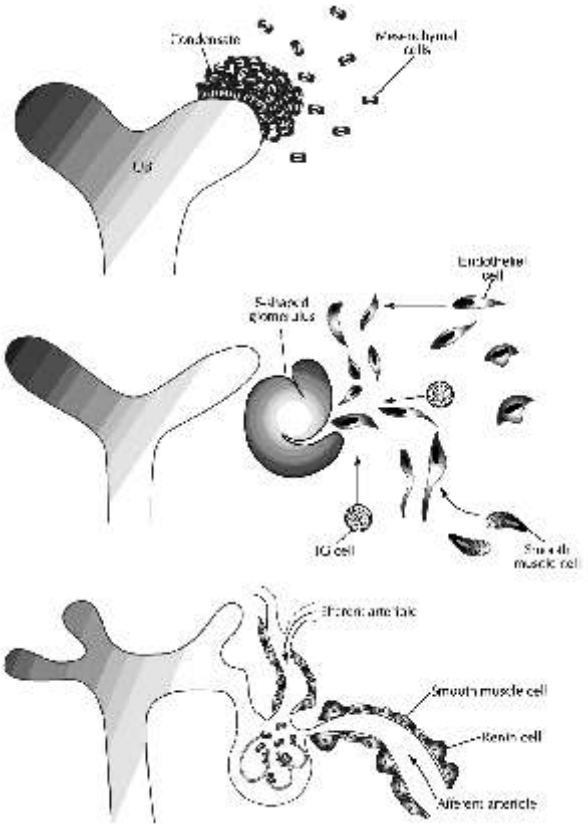

Figure 4. Major events in vascularisation of the nephron. Mesenchymal cells are precursors for endothelial, smooth muscle/mesangial, or renin producing cells. JG–juxtaglomerular UB–ureteric bud. (Adapted from Gomez RA et al. Microsc Res Tech 1997;39: 254–60.)

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RAZVOJ HUMANOG BUBREGA

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SA@ETAK

Bubreg je jedan od glavnih ekskretornih i homeostatskih organa u telu. On ekskretuje krajnje produkte metabolizma, i kontroli{e koncentraciju odre|enih sastojaka telesnih te~nosti. Organogeneza bubrega je kompleksan i postepen proces sa sukcesivnom pojavom pronefroza, mezonefroza i metanefroza. Pronefroz i mezonefroz su prolazne strukture sa malim ekskretornim kapacitetom koje prethode nastanku zrelog (metanefri~kog) bubrega. Metanefros nastaje kao rezultat recipro~nog induktivnog delovanja ureteralnog pupoljka, epitelnog izra{taja Wolfovog kanala, i metanefri~ke blasteme, grupe mezenhimnih }elija. Ureteralni pupoljak uti~e na diferencijaciju metanefri~kog mezenhima i nastanak nefrona, dok metanefri~ki mezenhim dovodi do rasta i grananja ureteralnog pupoljka od koga nastaju sabirni kanali}i. Nefron prolazi kroz ~etiri stadijuma razvoja, koji su opisani kao 1) vezikula, 2) zapeta- oblik i S- oblik 3) glomerul u razvoju i 4) zreo glomerul.

Uprkos njenom zna~aju, poreklo vaskulature bubrega nije u potpunosti jasno. Nakon invaginacije renalne vezikule signali nastali u }elijama vaskularnog `leba dovode do privla~enja angioblasta ili endotelijalnih }elija u glomerul u razvoju. Kada se jednom na|u u vaskularnom `lebu, endotelijalne ælije podle`u mitozi i organizuju se u kapilare paralelno sa {irenjem glomerula. Glomerularna bazalna membrana izgra|ena je od komponenti ekstra-}elijskog matriksa produkovanih od strane endotela i podocita. Najzad, mezangijalne }elije ili “glomerularni periciti” se tako|e regrutuju u glomerul doprinose}i stabilizaciji glomerularnog klup~eta.

Fetalni bubrezi stvaraju razbla`eni urin koji daje glavni doprinos nastanku amnionske te~nosti. Bilo koji faktor koji uti~e na prestanak stvaranja mokra}e mo`e dovesti do fetalnog poreme}aja. Nekoliko novijih studija istaklo je povezanost razvoja bubrega i bubre`nih bolesti kod odraslih.

Klju~ne re~i: **bubreg, razvoj, nefron**