Development of the Renal Arterioles

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ABSTRACT
The kidney is a highly vascularized organ that normally receives a fifth of the cardiac output. The unique spatial arrangement of the kidney vasculature with each nephron is crucial for the regulation of renal blood flow, GFR, urine concentration, and other specialized kidney functions. Thus, the proper and timely assembly of kidney vessels with their respective nephrons is a crucial morphogenetic event leading to the formation of a functioning kidney necessary for independent extrauterine life. Mechanisms that govern the development of the kidney vasculature are poorly understood. In this review, we discuss the anatomical development, embryological origin, lineage relationships, and key regulators of the kidney arterioles and postglomerular circulation. Because renal disease is associated with deterioration of the kidney microvasculature and/or the reenactment of embryonic pathways, understanding the morphogenetic events and processes that maintain the renal vasculature may open new avenues for the preservation of renal structure and function and prevent the progression of renal disease.


The mechanisms that govern the development of the kidney vasculature are poorly understood. In this brief review, we discuss the anatomical development, embryological origin, lineage relationships, and key regulators of the kidney arterioles and postglomerular circulation. For other important regulatory molecules and mechanisms already demonstrated for nonrenal vessels, as well as for the development of the glomerular capillaries, the reader is referred to some excellent reviews.1–14

In vivo, vascularization of the kidney is synchronized with epithelial nephrogenesis. Nephrogenesis of the definitive kidney results from the reciprocal inductive interaction between the primitive ureteric bud and the metanephric mesenchyme (Figure 1). The ureteric bud induces the mesenchyme to form tubular and glomerular epithelia. In turn, the surrounding mesenchyme induces the ureter to continue to grow and branch into the renal mesenchyme. As the ureter branches, the mesenchymal cells condense around each ureteric tip. The condensate develops into a vesicle, followed by a comma-shaped body that subsequently develops into an S-shaped body. Simultaneously, the glomerular cells differentiate until they acquire their adult features. In humans, nephrogenesis is complete by 34 to 35 weeks of gestation. In mice and rats, however, nephrogenesis continues after birth for about 3 to 7 days, respectively.

Anatomical Development of the Renal Arterial Tree
Using microdissection techniques combined with histologic assessment, we studied the anatomical development of the renal arterial tree in mice and rats throughout embryonic and postnatal life, including adulthood (unpublished observations and Figure 2). Those studies reveal that in the mouse kidney, the first arterioles are seen around 15 to 16 days of gestation. By 18 to 19 days of gestation, there is a basic blueprint of arterial and arteriolar development.15 This is followed in the ensuing days by a burst of branching and elongation of new arterioles that repeat the basic pattern for about a week after birth, resulting in a remarkable increase in the complexity and surface area of the vasculature. These orchestrated series of events require that progenitor cells differentiate, acquire positional information, assemble in the right location within the vessel, and segregate those cells that participate in branching. When this process fails, the consequences are devastating as exemplified by the serious developmental defects described below, which occur (particularly in the newborn period when branching is at its peak) in animals and humans with ablation of renin cell precursors, mutations of the renin-angiotensin system, and lack of microRNAs in the renal vasculature, resulting in early arterial and arteriolar abnormalities that are followed by deterioration of kidney structure and function.15–23 In spite of its importance, very little is known about the fate of the vascular precursors and the mechanisms that lead them to differentiate and assemble into the kidney arterioles.

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Vascular Progenitors and Arteriolar Development

As mentioned above, for nephrons to function properly, each glomerulus must establish its own circulation. Blood enters the glomerulus through an afferent arteriole that is continued by glomerular capillaries where filtration occurs and leaves the glomerulus through an efferent arteriole (Figure 3). The establishment of these nephrovascular units is a remarkable morphogenetic event requiring spatial and temporal coordination of the cells destined to form these structures. Despite the critical relevance of this process, the actual events and molecules that control the formation of the kidney arterioles are unclear. At the time of the first division of the ureteric bud, within the metanephric mesenchyme (E11 mouse, E14 rat), the embryonic kidneys do not have arteriolar vessels. Whereas renal and extrarenal origins have been suggested for the renal vasculature, it is clear that progenitors are present in the metanephric kidney very early, well before vessels can be discerned. It is also clear that those progenitors differentiate into all of the cell types necessary for the development of the kidney arterioles, including endothelial cells (ECs), smooth muscle cells (SMCs), and renin cells. Furthermore, cross-transplantation studies of those embryonic prevascular kidneys under the kidney capsule of a host mouse allowed us and others to demonstrate that precursor cells have the capacity to differentiate, acquire the right positional information, and fully assemble to form the kidney arterioles. The origin, lineage relationships, and morphogenesis of the kidney vasculature are also not well understood. Within the stromal compartment, we identified two putative and distinct early progenitor cells that give rise to all cells of the kidney arterioles and their perivascular compartment. Those progenitors are a precursor of hemogenic endothelium—provisionally called renal hemangioblasts—capable of giving rise to erythroid and ECs of the renal arteriole and a Foxd1+ cell from which all other arterial and perivascular/adventitial cells originate (Figure 3).

Hemogenic Progenitors.

It is now accepted that hematopoietic stem cells (HSCs) and ECs originate during embryogenesis from a common progenitor, the hemangioblast. These cells consist of a subpopulation of the primitive streak mesoderm that migrates to the yolk sac where they establish the primitive hematopoietic system. Primitive erythroid progenitors expand within the yolk sac and at embryonic day (E)8.5 enter the newly developing circulation and continue to mature. As soon as the liver starts to form, they home to it, where they complete their maturation and enucleate. On the other hand, definitive hematopoiesis is established within the embryo proper in the para-aortic splanchnopleural region by regional hemangioblasts or hemogenic endothelium, which supports the development of HSCs. Primitive hematopoiesis generates mainly nucleated primitive erythrocytes, whereas definitive hematopoiesis generates all hematopoietic lineages, including nucleated and enucleated definitive erythrocytes and HSCs with a long-term repopulating activity. Using multiple techniques including Tie2.Cre; R26R lineage tracing, electron microscopy, laser capture microdissection, organ culture, and cross-transplantation experiments, we showed there is a lineage relationship between ECs and HSCs during embryonic development and the presence of HSCs budding from the en-
Figure 3. Two main progenitors give rise to the renal arteriole: the hemangioblast and the Foxd1+ progenitor cell. Solid arrows indicate current knowledge from others and our lab. Dashed arrows indicate possible lineage relationships. Phenotypic markers are indicated in gray. The renin cell precursor gives rise to a subset of vascular SMCs.

Progenitors of Mural Cells, Pericytes, and Interstitial Cells.
Foxd1 is a winged-helix transcription factor expressed in developing ventral diencephalon and in stromal cells of the developing kidney. Recently, we traced the lineage of Foxd1 cells within the kidney using a FoxD1.GFP.Cre knock-in mouse and found that Foxd1+ cells differentiate into renin cells, which in turn differentiate into a subset of vascular SMCs and mesangial cells, and the rest of SMCs, not originating from renin cells, mural/interstitial pericytes, and adventitial fibroblasts (unpublished, Figure 3). Whereas the lineage relationship among all of these cell types still needs to be examined in detail, those studies suggest that Foxd1+ cells are upstream in the differentiation pathway of mural cells of the arteriole.

Embryonic Origin of the Renal Vasculature: Renal, Extrarenal, or Both?
Whether the renal vessels originate from outside or within the kidney has been a long-standing controversial issue. Inter-species cross transplantation experiments of prevascular embryonic kidneys were originally performed into quail chorioallantoic membrane because of the presence of a characteristic quail nuclear marker that could easily track the contribution of the host tissue. Those experiments show the presence of host-derived ECs and mesangial cells within the embryonic kidney and suggest an extrarenal source for ECs and mesangial cells. The development of genetically-labeled mice with traceable reporters allowed further experiments in mice. When embryonic kidneys are transplanted into the anterior chamber of the eye or under the kidney capsule of adult hosts, the embryonic kidneys develop a proper vasculature with all of the vascular cell types (ECs, SMCs, and renin cells) originating from within the donor embryonic kidney (Figure 4). However, when prevascular embryonic kidneys are transplanted under the kidney capsule of newborn mice, cells derived from the host, still undergoing nephrogenesis, contribute to the ECs of developing vessels and glomeruli. Those studies suggest that when the embryonic kidney is transplanted into sites actively undergoing vascular development (such as the avian chorioallantoic membrane or the nephrogenic cortex of the newborn mouse), vascular precursors from the host respond to cues from the transplanted, developing metanephric mesenchyme, migrate, and differentiate into ECs and form part of the transplanted kidney vasculature. Thus, the presence, stage of development, and location of vascular progenitors determines where the vasculature originates. Within the embryo proper, the embryonic kidney is surrounded by a loose developing mesenchyme that also contains vascular precursors. It may be possible that some extrarenal vascular precursors originate from outside the embryonic kidney and migrate to form renal vessels. Therefore, renal vessels may have a dual, chimeric origin as discussed below.

Angiogenesis versus Vasculogenesis
Both angiogenesis and vasculogenesis have been described as major processes for vessel formation, and both are likely to occur during normal development as well as in pathologic conditions. Vasculogenesis consists in the local differentiation and assembly of endothelial precursors into endothelial tubes followed by recruitment of local mesenchymal cells that differentiate into SMCs, which coat the growing endothelial tube and provide stability to the newly formed arteriole. Angiogenesis is the formation of new
vessels from preexisting ones and involves the sprouting, migration, and proliferation of already differentiated ECs followed by recruitment of perivascular cells along the way. Whereas both processes are markedly different, some studies support the notion that the kidney arterioles actually form by a combination of vasculogenesis and angiogenesis.37 We generated chimeric mice by injecting either ROSA26 ES cells (all cells are blue upon X-gal reaction) into wild-type blastocysts or vice versa and examined their kidneys at different stages of development. By assessing the contribution of labeled versus unlabeled cells to a particular vessels or nephron segment, the technique permits us to infer its clonality or lack thereof. Our unpublished experiments suggest that the renal vasculature develops by a combination of both processes, with a prominence of vasculogenesis in the early embryonic kidney and a strong angiogenic component during the elongation of the vasculature at later stages. Interestingly, whereas the endothelial layer of the vessels appears to be clonal, the smooth muscle layer of the arterial tree is usually chimeric, indicating that differentiation of the smooth muscle wall occurs by vasculogenesis (Figure 5).

Although vasculogenesis and angiogenesis were originally thought to occur in the developing embryo, there now is evidence that these processes also occur during physiologic (endometrial angiogenesis) and pathologic (tumor vascularization) stresses of adult life. It is possible therefore that vasculogenesis and angiogenesis are activated during remodeling of the vasculature after pathologic conditions including ischemic renal injury.38

**Regulation of Vascular Development**

The major mechanisms that control vascular development in other systems have been the subject of excellent reviews1–14 and in the case of arteriolar development involve an active cross-talk between pericytes and ECs. Pericytes coat endothelial tubes, providing mechanical stability for the mature vessel, but they also partici-
precursor cell population. In turn, ECs activate the pericyte, stimulating EC proliferation and migration. In embryonic lethality caused by angiogenesis. S1P1–S1P5. The S1P pathway is also a key regulator of EC cell migration and growth. S1P is a bioactive sphingolipid metabolite crucial in many biologic processes, including angiogenesis. S1P generated by two sphingosine kinases, SphK1 and SphK2, activates a family of five G-protein–coupled receptors, S1P1–S1P5. The variety of responses mediated by S1P receptors depends on the type of receptor and its coupled downstream effectors expressed in a given cell. Deletion of S1P1 in mice results in embryonic lethality at E12.5 to 14.5 caused by abnormal formation of blood vessels, possibly because of failure of migration and/or differentiation of vascular SMCs and pericytes, demonstrating the critical role of S1P1 in vascular maturation. However, the role of this pathway in the development of the renal vasculature has not yet been investigated.

**Renin-Angiotensin in Kidney Vascular Development.**

We have previously shown the association of renin-expressing cells with branching and elongation of the renal arterial tree. Development of a new arterial branch is preceded by the appearance of renin-expressing cells at the point of branching, followed by outpouching and elongation of a new arteriole covered almost exclusively with renin cell progenitors. As the vessels mature, renin cells differentiate into SMCs and mesangial cells. Finally when elongation is complete, a few renin cells remain near the glomerulus, the juxtaplomerular cells usually found in the adult animal. These experiments suggest that renin cells either directly or indirectly regulate the branching and elongation of the renal arterial tree through local generation of angiotensin. Support for this hypothesis is derived from separate experiments described below.

Treatment of rats during the first 12 days of postnatal life, when arteriolar branching is at its peak, with the AT1 blocker losartan results in marked impairment of kidney vascular development characterized by fewer, shorter, and thicker radial and afferent arterioles. This is accompanied by reduced glomerular size and tubular atrophy with attendant reduction in overall kidney growth. Interestingly, inhibition of angiotensin generation in *rana catesbiana* tadpoles undergoing metamorphosis results in even more marked renal abnormalities with persistence of pronephric tubes and areas of undifferentiated mesenchyme.

These experiments, as well as those of other investigators, indicate that not only is angiotensin II necessary for nephrovascular development but also its vascular growth actions are conserved across the phylogenetic scale.

In agreement with those findings, deletion of any of the genes of the renin-angiotensin system (angiotensin-converting enzyme, renin, angiotensinogen, and AT1A + B) results in similar abnormalities (Figure 6). The growth effects of angiotensin II are not limited to the renal arterioles and extend to the postglomerular circulation. Recent work from Madsen et al., indicate that treatment with candesartan for 2 weeks reduces the length, volume, and surface area of capillaries in both the cortex and the medulla and inhibits the proper organization of vasa recta bundles. These findings are accompanied by inhibition of VEGF, angiopoietin-1 and -2, and the angiopoietin receptor Tie-2. As a result, medullary abnormalities en-
sue, encompassing hypoplasia of the papilla, thickening of vessels, and accumulation of αSMCs in the outer medullary interstitium. Functionally, this is reflected by a marked reduction in renal blood flow. As the authors suggest, it seems that postnatal development of the kidney depends on appropriate regulation of angiogenesis.

**Role of the cAMP Pathway.**

We have previously shown that cAMP signaling is necessary for renin cell identity and is also linked to development of kidney arterioles. Ligand binding of G-protein–coupled receptors results in activation of adenyl cyclases, which in turn generate cAMP from ATP. cAMP activates protein kinase A, which in turn phosphorylates cAMP response element–binding (CREB) protein, a transcription factor that regulates the promoter activity of many genes, including the renin gene. Recently, in vitro and in vivo studies demonstrate the crucial role of the cAMP pathway on the acquisition and maintenance of the renin cell identity.51,52

Activation of the cAMP pathway was proven to be of importance not only for the well known stimulation of renin release but also for vascular development early in fetal life. Conditional deletion of Goα in cells from the renin lineage such as arteriolar SMCs and mesangial cells results in almost complete absence of renin-expressing cells in the fetal kidney accompanied by blunted development of the glomerular arterial tree.53 Thus, the cAMP pathway is an early regulator of the development and maturation of mural cells of the kidney. Whether the effect is direct in the SMC or as a result of diminished expression of renin and/or the presence of renin cells remains unclear. Interestingly, studies performed on β1/β2-adrenergic receptor–deficient mice show a marked reduction of renin expression in the vasculature in the embryo without changes in the number of juxtaglomerular cells in the adult, suggesting a distinct responsiveness to β-adrenergic stimulation between these two cell populations. The vasculature in those mice appears normal.54 Given that deletion of a more downstream element of the cAMP pathway, as in the case of Goα, does impair vascular development, it seems that other mechanisms may compensate for the absence of the β receptors, whereas deletion of more proximal elements (with respect to the renin gene) of the cAMP pathway have a more profound phenotypic consequence. In fact, deletion of CBP and p300, two well known coactivators of CREB possessing histone acetyl transferase activity, results in severe vascular and nephron alterations accompanying a nearly complete depletion of renin cells. Overall, the aforementioned studies indicate that the cAMP pathway is fundamental in the differentiation of mural cells (renin and SMCs) of the renal arterioles.

**Role of MicroRNAs in Vascular Development.**

Endogenous miRNAs are small, noncoding RNAs of about 18 to 22 nucleotides in length. miRNAs exhibit tissue and cell specificity, and some are regulated developmentally. They control a myriad of cellular processes and are involved in cell differentiation and morphogenetic events. The generation of mature miRNAs requires the sequential processing of a looped primary transcript (pri-miR, 100-1000 nucleotides) to a single-stranded miR by two RNase III endonuclease complexes: Drosha-DGCR8 in the nucleus and Dicer in the cytoplasm. miRNAs mediate posttranscriptional events including mRNA degradation and translational repression. They may also have chromatin effects that ultimately influence gene expression.

Deletion of Dicer in renin cells results in a severe reduction in the number of renin-expressing cells accompanied by decreased circulating renin, hypotension, and striking nephrovascular abnormalities characterized by a unique type of striped corticomedullary fibrosis.23 Within the fibrotic stripes, renal arterioles are unusually formed, replaced by interstitial cells in different states of development, phenotypic conversion, and /or degeneration. The mechanisms for the peculiar striped fibrosis remain to be studied, but it is likely to result from the combination of abnormal vessel architecture, which together with arterial hypotension leads to localized tissue hypoperfusion and ischemia along the path where the renal vessels traverse from the juxtamedullary area through the renal cortex (Figure 7).23 Contrary to the phenotype encoun-

Figure 6. Gene deletion of any component of the renin angiotensin system results in renal arteriolar abnormalities. Representative Masson’s Trichrome staining showing a marked increase in the size of the vascular wall and diminished lumen.
Deletion of Dicer in renin cells

↓Renin cells

Abnormal vessel architecture

Hypotension

Hypoperfusion

Localized ischemia

Striped fibrosis

Figure 7. Schematic of possible mechanisms for the pathogenesis of striped renal fibrosis in mice with deletion of Dicer in the renin cell lineage (from reference 1).

cluded in mice with targeted deletions of the renin angiotensin system genes, in which SMCs proliferate around the blood vessel (Figure 6), Dicer-/- animals do not have arteriolar thickening, displaying instead adventitial fibroplasia. The reasons for the apparent decrease in SMCs is unlikely to be due to decreased renin because mice with homozygous deletion of the renin gene also have arteriolar thickening. The answer to this question is suggested from experiments in which the renin cells were ablated using diphtheria toxin targeted to the renin locus. Mice expressing diphtheria toxin A in renin cells have thin vessels and do not show hyperplasia of SMCs surrounding the arterioles (Figure 8). These experiments suggest that renin cells produce factors that stimulate the abnormal concentric growth of the kidney interlobular and different arterioles. In fact, recent gene profiling indicates that renin cells are capable of producing more than 14 different well known angiogenic and trophic factors, including VEGF, angiopoietin, IGF2, and autotaxin, among others (Figure 9). These factors may contribute in health to the branching and elongation of the renal arterial tree and in pathologic conditions to aberrant, circumferential growth of the renal arterioles as demonstrated in situations where there is an absence of angiotensin II actions in the presence of renin cell hyperplasia, ischemia, or exogenous activation of renal vasoconstrictors as described above.

Vascular Development and Renal Disease

In adults, the incidence of chronic renal disease is about 16%. The number
of patients with end-stage renal disease continues to increase by 8 to 14% per year and is expected to double during the next 15 years. Many kidney diseases have either primary or secondary vascular lesions. Renal disease is associated with alterations in vascular remodeling, and progression of renal disease is accompanied by deterioration of kidney microvessels and development of glomerular and tubulointerstitial fibrosis. Thus, understanding the contribution of the pre- and postglomerular circulation to the progression of renal disease may help identify potential therapeutic targets. Alterations in the fate of vascular cells is a cause of renal interstitial fibrosis resulting from ureteral obstruction, a situation where pericytes and ECs phenotypically switch from ureteral obstruction, a situation where pericytes and ECs phenotypically switch from ureteral obstruction, a situation where pericytes and ECs phenotypically switch from ureteral obstruction, a situation where pericytes and ECs phenotypically switch from ureteral obstruction, a situation where pericytes and ECs phenotypically switch from ureteral obstruction, a situation where pericytes and ECs phenotypically switch from ureteral obstruction, a situation where pericytes and ECs phenotypically switch.

Vascular rarefaction and dysfunction in both small renal and systemic arteries also precedes renal end-organ damage in spontaneous models of hypertension-associated renal damage. It is unknown what mechanisms establish phenotypic variability in the vascular beds and how these might function for the maintenance of a healthy vascular system. When formation of the kidney vasculature is altered, the consequences are devastating, as exemplified by the serious developmental defects described above, occurring in animals and humans with ablation of renin cell precursors, mutations of the renin-angiotensin system, and a lack of miRNAs in the renal vasculature, resulting in early arterial and arteriolar abnormalities that are followed by the deterioration of kidney structure and function.

Generation of new vessels in the kidney is not confined to embryonic development but seems to be a mechanism also activated in response to injury. Given the fact that a variety of renal diseases have abnormalities in the renal vasculature, understanding the mechanisms underlying the formation and maintenance of the renal vasculature is a logical step in developing strategies to preserve renal structure and function.

Future Opportunities

It is now more accepted that both ECs and HSCs derive from a common precursor cell, the hemangioblast. However, the mechanisms by which the early ECs and blood cells subsequently develop further diversity remain unknown. Some of these mechanisms are important for the maintenance of healthy blood and vascular systems and for injury repair in adult life. Thus, defining the mechanisms that regulate differentiation of this population of progenitor cells could lead to the discovery of new treatments for congenital and acquired blood and blood vessel diseases, including those related to the kidney and the systemic circulation. Thus, understanding the molecular cues for progenitor differentiation, vascular maturation, and branching are fundamental biologic questions with applicability to multiple renal and extrarenal disease processes. By providing new and fundamental knowledge regarding the mechanisms whereby progenitor cells contribute to the endowment of renal vascular cells and how those cells differentiate and assemble to form and maintain the renal arterioles, a frontier basally unexplored has the potential to benefit children and adults with congenital and acquired kidney diseases, vascular diseases, and hypertension.

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DISCLOSURES

None.

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