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Peritubular capillary rarefaction: a new therapeutic target in chronic kidney disease

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Abstract

Chronic kidney disease (CKD) is epidemic around the world and desperately needs new therapies. Peritubular capillary (PTC) rarefaction, along with interstitial fibrosis and tubular atrophy, is one of the major hallmarks of CKD and predicts renal outcome in patients with CKD. PTC endothelial cells (ECs) undergo apoptosis during CKD, leading to capillary loss, tissue hypoxia, and oxidant stress. Although the mechanisms of PTC rarefaction are not well understood, the process of PTC rarefaction depends on multiple events that happen during CKD. These events, which lead to an antiangiogenic environment, include deprivation of EC survival factors, increased production of vascular growth inhibitors, malfunction of ECs, dysfunction of endothelial progenitor cells, and loss of EC integrity via pericyte detachment from vasculature. In this review, we focus on major factors regulating angiogenesis and EC survival and describe roles of these factors in PTC rarefaction during CKD and possible therapeutic applications.

Keywords

endothelial cell; angiogenesis; angiogenic growth factors; CKD; pericytes

Introduction

Chronic kidney disease (CKD) affects one in every seven adults in the United States, and its prevalence appears to be 10–13% around the world. CKD is a leading cause of death due to premature cardiovascular diseases [1–3]. While a variety of conditions can lead to CKD, the final common pathway of renal destruction involves interstitial fibrosis, tubular atrophy, and peritubular capillary (PTC) rarefaction. Although numerous published studies have investigated the mechanisms of renal fibrosis, the mechanisms of PTC rarefaction are not well understood. Therefore, in this review we focus on PTC rarefaction. Based on several studies in human CKD and animal models of CKD, it is known that PTCs disappear in association with progressive interstitial fibrosis and tubular atrophy. Although the sequence of events connecting PTC loss to fibrosis and impaired tubular function is poorly characterized, it has been suggested that interstitial hypoxia due to arteriolar vasoconstriction and/or PTC regression is a primary event in CKD [4]. In this review, we describe (1) the contribution of PTC rarefaction to CKD progression, (2) the mechanisms of PTC rarefaction, (3) major factors regulating EC survival and angiogenesis in CKD, and (4) putative therapeutic targets for PTC rarefaction.

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Disclosures

None

Contribution of peritubular capillary rarefaction to CKD progression

Loss of renal PTCs is correlated with the severity of fibrosis in human patients during CKD [5–7] and chronic allograft rejection [8]. The extent of PTC loss predicted both interstitial damage and glomerular filtration rate (GFR) in human subjects [6]. Rodent CKD models such as experimental glomerulonephritis [9], the remnant kidney model [10], unilateral ureteral obstruction (UUO, obstructive nephropathy model) [11–14], and the aging kidney [15] also showed a negative correlation between capillary density and the severity of fibrosis. Furthermore, damage to PTCs influenced the long-term outcome after ischemia-reperfusion injury (IRI) [16]. In treated rats, GFR returned to the normal range 1–2 weeks after bilateral IRI. However, over 40 weeks the animals developed prominent fibrosis, which was accompanied by a 30–50% reduction in PTC density [16]. Similar results were obtained in mice [17]. These experimental results were similar to outcomes of clinical studies, in which acute kidney injury dramatically increased the risk of developing end-stage renal disease (ESRD) [18, 19]. Taken together, these findings strongly suggest that PTC rarefaction contributes to the progression of CKD. Currently it is speculated that PTC rarefaction is both a cause and a result of CKD progression.

Mechanisms of PTC rarefaction

In healthy kidneys, there is a tightly controlled balance between the expression of proangiogenic and antiangiogenic molecules. However, this balance is disrupted in CKD, leading to an antiangiogenic environment that favors loss of PTCs.

Angiogenesis has been investigated in several models of CKD [10, 11, 20, 21]. In the rat UUO model, Ohashi et al. [11] observed early angiogenesis (EC proliferation) in PTCs, accompanied by intense expression of vascular endothelial growth factor (VEGF), a major proangiogenic factor, within the tubular epithelium. This was followed by EC apoptosis in PTCs, a decrease in VEGF and its major angiogenic receptor VEGF receptor 2 (VEGFR-2), and capillary regression. Vascular growth inhibitors may also modulate angiogenesis and tissue damage during chronic injury [22]. Thrombospondin-1 (TSP-1) was up-regulated in the rat remnant kidney at the time when early EC proliferation declined [10]. In the mouse UUO and IRI models, another anti-angiogenic factor, endostatin, was elevated after kidney injury [23, 24].

In response to kidney injury, ECs of PTCs may initially proliferate and subsequently disappear due to apoptosis. Endothelial apoptosis is induced by deprivation of survival growth factors such as VEGF and by increased proapoptotic stimuli such as FasL, interleukin-1, and tumor necrosis factor α (TNF- α) [25, 26]. Apoptotic ECs become pro-coagulant and pro-adhesive, leading to capillary occlusion by thrombosis and enhanced inflammation by extravasation of leukocytes. Impairment of blood flow decreases laminar shear stress on ECs, resulting in further endothelial apoptosis [27]. Furthermore, following kidney injury, vascular pericytes, which structurally and functionally stabilize PTC ECs, promptly migrate away and differentiate into myofibroblasts [28]. In the absence of pericytes, PTCs are destabilized, resulting in further PTC loss [28].

It has been reported that PTC density was positively correlated with proximal tubular density in patients with CKD [5]. Renal tubular epithelial cells make up the bulk of the renal mass, and these cells disappear during the progression of CKD. Without any additional insults, genetic ablation of proximal tubules caused PTC loss and fibrosis *in vivo* [29]. However, how reduction of tubular mass induces PTC loss is still poorly understood.

Major factors regulating angiogenesis and EC survival in CKD

(1) Vascular endothelial growth factor (VEGF)

Despite its complexity, angiogenesis is predominantly regulated by a single growth factor, VEGF-A [30]. VEGF-A is expressed in podocytes and renal tubular epithelial cells in the developing kidneys and continues to be expressed in the adult kidneys. VEGFR-1 (Flt1) and VEGFR-2 (Flk1/KDR) are expressed predominantly in ECs. VEGFR-1 is thought to act as a decoy receptor that sequesters VEGF-A from VEGFR-2 binding. Recently, VEGF-A was identified as a risk locus related to CKD by a genome-wide association study [31], indicating that VEGF-A has a pivotal role in the development of CKD. The dose-dependent deletion or overexpression of VEGF-A in podocytes led to a variety of glomerular capillary diseases including mesangiolysis and endotheliosis, suggesting that VEGF-A is an essential growth factor for development and maintenance of glomerular capillaries [32–34]. VEGF-A is also found to be important for tubular development [35]. VEGF expression continuously increased in tubular epithelial cells in neonatal rats between 14 and 28 days after birth, but was reduced after UUO [36]. VEGFR-2 was expressed strongly in the microvasculature in neonatal kidneys in both sham and UUO groups, whereas in adult rat kidneys VEGFR-2 expression was low in sham operated kidneys but was increased after UUO [36]. These results suggest that the vascular response to kidney injury differs between developing kidneys and mature kidneys. In human kidney biopsies, VEGF was dominantly expressed in podocytes in normal adult kidneys; however, a marked increase of VEGF expression in the renal tubules was observed in CKD [5].

(2) Angiopoietins

Angiopoietins are another critical family of angiogenic factors that play a significant role in renal vascular development as well as renal vascular homeostasis. Angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), and the receptor tyrosine kinases Tie-2 (also known as TEK) and Tie-1 (a homolog to Tie-2 that we know relatively little about) are all highly expressed in developing kidneys. Their expression peaks at birth, and they continue to be expressed in the mature kidneys. In the adult kidney, Ang-1 is expressed in tubular epithelial cells, podocytes, and pericytes, whereas Ang-2 is detected in ECs, with lower levels in tubular epithelial cells. Tie-2 is expressed in glomerular and peritubular ECs in addition to hematopoietic cells [37–39]. In general, Ang-1 binds to Tie-2, enhancing EC survival, reducing vascular permeability, and stabilizing capillaries, whereas Ang-2 competitively inhibits the binding of Ang-1 to Tie-2. The biological effects of Ang/Tie signaling may depend on an interaction with VEGF. It was demonstrated in the eye that Ang-2 induced angiogenesis in the presence of VEGF, but led to vascular regression in the absence of VEGF [40]. Recent studies suggest that Ang-1 and Ang-2 can affect an inflammatory process [38]. It is possible that Ang-1 and Ang-2 affect leukocyte transmigration stimulated by TNF- α [41]. Overexpression of Ang-2 in podocytes in mice produced a similar phenotype in diabetic nephropathy, where glomerular endothelial apoptosis is prominent [42]. Ang-2 is also strongly expressed in tubules surrounding mature *vasa recta*, which express Tie-2 [43], suggesting that Ang/Tie-2 signaling contributes to the maintenance of *vasa recta*. In patients with CKD, the serum level of Ang-1 was decreased and that of Ang-2 was elevated [44], generating an anti-angiogenic environment. The renal Ang-1 level was also decreased in the UUO model [45]. In contrast, other renal injury models (folic acid nephropathy, IRI, and angiotensin II infusion) showed increased Ang-1 expression in the kidneys [44]. This difference in Ang-1 expression indicates a unique profile in each animal model of CKD. Studies using inducible Ang-1 deletion after E13.5 produced no immediate vascular phenotype [46]. However, Ang-1 deficiency after E13.5 resulted in profound renal damage including affected vasculature after kidney insult, indicating a protective role of Ang-1 in kidney injury [46].

(3) Fibroblast growth factor-2 (FGF-2, basic FGF)

FGF-2 is another potent angiogenic growth factor, which binds to four high-affinity FGF receptors (FGFR-1, 2, 3 and 4). In the normal human kidney, FGF-2 is expressed in glomerular parietal cells, podocytes, distal tubular epithelial cells, ECs, and vascular smooth muscle cells [47]. In mouse cornea, FGF-2 stimulated VEGF-A expression in ECs and stromal cells, which was required for its angiogenic activity [48]. Furthermore, ECs lacking FGF signaling were found to be unresponsive to VEGF-A, because disruption of FGF signaling down-regulated VEGFR2 expression [49]. These results indicate that FGF signaling and VEGF signaling work together for angiogenesis. Blocking FGF signaling in mice using an adenovirus encoding soluble FGFR resulted in loss of arteriogenic response and vascular integrity [49, 50]. Although FGF-2 expression was reported to correlate with the degree of interstitial fibrosis in human kidney samples [51], the role of FGF-2 in PTC rarefaction has not been investigated.

(4) Nitric oxide (NO) and endothelial nitric oxide synthase (eNOS, NOS3)

NO is synthesized from L-arginine by eNOS and functions to maintain ECs in a quiescent state, as opposed to a stressed/damaged (“activated”) state that promotes vasoconstriction as well as coagulation and inflammation (“endothelial activation”). Reduced availability of NO and concurrent endothelial dysfunction have been documented in patients with CKD [52]. Moreover, circulating levels of asymmetric dimethylarginine (ADMA), an endogenous NOS inhibitor, were elevated in CKD patients [53]. Recently, ADMA accumulation was found to reduce eNOS phosphorylation and inhibit eNOS activity in the remnant kidney model of CKD [54]. One recent study showed that administration of L-arginine increased NO synthesis, eNOS expression, and PTC density, and attenuated fibrosis in the rat UUO model, while PTC loss and fibrosis were more severe after treatment with the NOS inhibitor N-nitro-L-arginine methyl ester (L-NAME) [55]. In another study using the remnant kidney model, eNOS-deficient mice showed accelerated PTC rarefaction due to decreased EC proliferation and increased EC apoptosis, accompanied by enhanced macrophage infiltration and fibrosis [56]. These results suggest that NO protects against PTC rarefaction in CKD.

NO is also involved in the renoprotective effects of angiotensin converting enzyme (ACE) inhibitors in CKD. Angiotensin II uncouples the eNOS-catalyzed oxidation of NADPH from the reduction of L-arginine, leading to the production of superoxide (harmful for ECs) rather than NO (beneficial to ECs) [57]. Therefore, treatment of CKD patients with ACE inhibitors or angiotensin receptor blockers (ARBs) can shift the balance back toward NO production and reduce endothelial activation; this action is independent of the blood pressure lowering effect of these agents.

(5) Hypoxia-inducible factor (HIF)

One of the most obvious consequences of PTC rarefaction is a decreased oxygen supply to the tubulointerstitial compartment. Various response pathways are activated during hypoxia in the kidney. On the molecular level, the most important adaptations to hypoxia are mediated by HIF. Mammalian HIFs function as heterodimeric transcription factors composed of either HIF-1 α or HIF-2 α bound to HIF-1 β (also known as aryl hydrocarbon nuclear translocator) [58]. In the hypoxic kidney, HIF-1 α is expressed in tubular and glomerular epithelial cells, whereas HIF-2 α is detected in glomerular and peritubular ECs and fibroblasts [59]. The primary mechanism of regulating HIF activity is oxygen-dependent proteasomal degradation of the α subunit. In normoxia, the α subunit is rapidly subjected to prolyl hydroxylation, binds to the von Hippel-Lindau tumor suppressor protein, and undergoes proteasomal degradation. In hypoxia, however, the α subunit escapes prolyl hydroxylation and binds to the β subunit. The functional heterodimeric HIF then translocates to the nucleus and promotes angiogenesis, erythropoiesis, and energy metabolism [58].

Increased HIF expression has been reported in kidney biopsies of patients with diabetic nephropathy, IgA nephropathy, polycystic kidney disease, and chronic allograft nephropathy [4]. However, the role of increased HIF in CKD is controversial. Several studies using genetically altered mice demonstrated that HIF-1 α expression promoted kidney fibrosis in the UUO model [60] and the remnant kidney [61]. In agreement with these results, one clinical study confirmed a negative effect of HIF-1 α activation on renal and patient survival in patients with acute kidney injury [62]. In contrast, the activation of HIFs appears to be protective from interstitial fibrosis and preserves PTC area in various different experimental renal diseases (the remnant kidney, IRI, cisplatin nephropathy, and diabetic nephropathy) [63–65]. Although HIF-1 α null or HIF-2 α null ECs constituted dysfunctional vasculature in other organs [66, 67], no study has been performed to investigate the role of HIF-1 α or HIF-2 α specifically in kidney ECs during CKD. For regeneration of PTCs in CKD, strategies involving HIF need to be directed to specific cell types in the kidney to avoid adverse effects.

(6) Other factors

Several other factors have been reported to affect angiogenesis following kidney injury. Thrombospondin-1 (TSP-1) is a 450 kDa homotrimeric extracellular matrix protein and a potent anti-angiogenic factor. TSP-1 expression in the normal kidney is limited to Bowman's capsule, whereas in the damaged kidney TSP-1 is expressed in all glomerular cell types as well as in tubular epithelial cells, myofibroblasts, and infiltrating macrophages [68]. In UUO models, TSP-1 null mice displayed less inflammation and had better PTC preservation than wild-type controls [68], indicating that TSP-1 has a deleterious role in PTC rarefaction during CKD. However, another study demonstrated that TSP-1 deficient ECs exhibited decreased phosphorylation of VEGFR-2 in response to VEGF-A stimulation compared with wild-type ECs [69]. This result suggests that TSP-1 promotes the inflammatory response and inhibits angiogenesis via its pro-inflammatory activity rather than via impairment of VEGF signaling after kidney injury. Although previous studies reported that TSP-1 enhanced apoptosis of ECs [70] and inhibited EC responses to NO [71], the mechanisms by which TSP-1 inhibits angiogenesis in CKD are still not clear.

CD44 is a glycoprotein that binds to hyaluronic acid (HA). After UUO treatment, CD44 expression was increased in ECs located in PTCs, and CD44-deficient mice preserved more PTC area than wild-type mice and showed decreased endothelial apoptosis [12]. An interaction between CD44 and HA enhanced the pro-apoptotic effect of transforming growth factor- β 1 on ECs [12].

ADAMTS-1 (a disintegrin and metalloproteinase with thrombospondin motif-1), a secreted VEGF inhibitor, appears to be an anti-angiogenic factor [72] and destabilizes vessels after IRI [73].

In addition to VEGF-A and FGF-2, hepatocyte growth factor (HGF) was shown to function as an angiogenic factor through binding to its receptor, c-Met [74]. In the remnant kidney model, infusion of HGF remarkably ameliorated macrophage adhesion to ECs, whereas neutralizing endogenous HGF worsened macrophage adhesion [75, 76]. These results suggest that HGF may preserve PTCs through an anti-inflammatory action.

Considerations for therapy to limit PTC rarefaction in CKD

(1) Treatment with angiogenic growth factors

Multiple studies have demonstrated that VEGF-A may help to preserve PTCs in CKD. In the remnant kidney model, administration of recombinant VEGF-A₁₂₁ improved renal function, lowered mortality, decreased PTC rarefaction, and reduced fibrosis [77]. Similarly, in a pig

model of renal artery stenosis, intrarenal infusion of VEGF-A attenuated microvascular rarefaction, prevented fibrosis, and improved renal blood flow [78]. However, other results did not support the beneficial effects of VEGF-A in CKD. In kidney injury induced by angiotensin II infusion followed by a high-salt diet, administration of VEGF-A₁₂₁ did not improve PTC rarefaction [79]. In addition, VEGF-A₁₂₁ treatment did not improve PTC rarefaction in neonatal mouse kidneys subjected to UUO [80], and systemic overexpression of a mutant form of VEGF-A that can bind only to VEGFR-2 but not to VEGFR-1 enhanced glomerular injury as well as interstitial fibrosis in mice with uninephrectomy [81]. Furthermore, the timing of angiogenic treatment is crucial. In the rat remnant kidney model, VEGF-A₁₂₁ delivered 4–8 weeks after surgery ameliorated CKD, perhaps because VEGF-A levels in the kidney are very low during this period and PTC rarefaction is severe [77]. By contrast, the first 4 weeks after surgery in the remnant kidney model were characterized by glomerular hypertrophy and increased VEGF-A levels [82]. During this initial period, neutralizing VEGF-A, but not VEGF-A injection, could improve renal function and glomerular hypertrophy [82]. In contrast, secondary CKD induced by a salt-rich diet following recovery from IRI was ameliorated by VEGF-A₁₂₁ only when it was injected immediately (within 3 days) after IRI [83]. These discrepancies in the effect of VEGF-A on CKD raise important considerations for future therapeutic strategies that target angiogenesis in CKD.

A soluble, stable, and more potent form of Ang-1 (COMP-Ang-1) was successfully used in the mouse UUO and IRI models to preserve PTC area and renal blood flow and to decrease inflammation and fibrosis [45, 84], suggesting the possible use of Ang-1 as a novel treatment for patients with CKD. However, Long et al. reported contradictory findings [38]. In mice with folic acid-induced kidney injury, these authors systemically delivered a recombinant form of Ang-1 (Ang-1*) using adenoviruses, which improved PTC rarefaction but enhanced inflammation and fibrosis [38]. Further studies are necessary to reveal the relationship between angiogenesis and inflammation in CKD. Combination therapy with VEGF-A and Ang-1 could potentially overcome this problem, as Ang-1 stabilizes blood vessels and prevents VEGF-induced endothelial leakiness [85].

Finally, there is one caveat against inhibition of VEGF signaling. As reported in clinical settings such as cancer therapy, blockade of VEGF signaling causes proteinuria, hypertension and renal thrombotic microangiopathy due to disruption of the glomerular filtration barrier [86, 87].

(2) Endothelial progenitor cells (EPCs)

EPCs have been suggested to be useful for maintaining the integrity of ECs and for repairing ECs after injury [88]. EPCs are identified by a consensus combination of markers and characteristics (individually not unique to EPCs) including CD34, VEGFR-2, Tie-2, CD133, Ulex Europaeus lectin binding, uptake of acetylated LDL, and the ability to form colonies (colony-forming units) [88]. Chade et al. demonstrated that intra-renal infusion of autologous EPCs attenuated PTC rarefaction and fibrosis, improving renal function by stimulating angiogenesis [89]. The adoptive transfer of EPCs could be one option to promote *de novo* angiogenesis and renal regeneration.

One may wonder why resident EPCs are insufficient to trigger neo-angiogenesis after kidney injury. This deficiency may arise from disease-related changes in EPC function. EPCs taken from pigs with unilateral renal artery stenosis in the early and later phases of disease progression had different characteristics [90]. EPCs isolated from peripheral blood in the early phase exhibited increased proliferation, tube formation, VEGF-A and eNOS expression, and augmented expression of C-X-C chemokine receptor type 4 (CXCR4) [90]. Homing of EPCs expressing CXCR4 is regulated by the ligand of CXCR4, α -chemokine

stromal cell-derived factor 1 (SDF-1) [91]. However, these enhanced functions were not maintained in EPCs isolated in the later phase of this disease [90]. Furthermore, EPCs from patients with CKD displayed functional impairments (i.e. hampered adherence, reduced endothelial outgrowth potential, and reduced anti-thrombotic function) [92]. These impairments became more apparent when CKD progressed [92]. These results provide evidence that endogenous EPCs become dysfunctional as CKD advances, which leads to an impairment of the repair process by endogenous EPCs. One way to overcome this deficiency is the adoptive transfer of exogenous EPCs isolated from healthy donors. It should be noted that the role of EPCs in endothelial repair remains controversial. Although EPCs could form vascular structures, these may not be stable. Alternatively, EPCs may orchestrate angiogenic processes, while proliferation of existing ECs is quantitatively more significant for vessel formation or repair following kidney injury [93, 94].

(3) Endothelial-pericyte interactions

Interactions between ECs and intimately associated pericytes were recently demonstrated to be important to preserve PTCs and to alleviate fibrosis [28, 95]. Endothelial-pericyte cross-talk has been shown to be critical for angiogenesis and vascular stabilization, and involves multiple ligand/receptor interactions including platelet-derived growth factor (PDGF)-B/PDGF receptor- β (PDGFR β) and Ang-1/Tie-2 [96]. PDGF-B/PDGFR β signaling was essential for recruitment of pericytes to vasculature, and ECs were not integrated properly into vessels without this signaling, leading to endothelial hyperplasia, abnormal EC junctions, microaneurysms, hemorrhages, and capillary rarefaction [96]. Endothelial-pericyte interactions were disrupted in IRI and UUO models of CKD, and pericytes detached and migrated away from microvasculature and finally differentiated into myofibroblasts [95]. When either PDGFR signaling in pericytes or VEGFR-2 signaling in ECs was blocked by circulating soluble receptor ectodomains, both PTC rarefaction and fibrosis were markedly attenuated during CKD progression [95]. The important findings of this study were that (1) bidirectional signaling between pericytes and ECs was necessary to prevent pericyte detachment from vessels, and (2) pericyte detachment was responsible for both PTC rarefaction and fibrosis. Thus, targeting the cross-talk between these two types of cells may provide a novel therapeutic opportunity to treat PTC rarefaction and fibrosis in CKD.

In the clinical setting, patients with idiopathic pulmonary fibrosis (IPF) were treated for 1 year with BIBF 1120, which can block signaling by multiple tyrosine kinase receptors including PDGFR β and VEGFR-2 [97]. BIBF 1120 significantly prevented exacerbation of IPF, suggesting a beneficial effect of the drug on organofibrosis. The most frequent adverse effect of the drug was gastrointestinal issues such as diarrhea and vomiting, although no information was shown about capillary density in any organ [97].

The concept of pericyte detachment suggests a connection between PTC rarefaction and kidney fibrosis. Zeisberg et al. also suggested another concept of endothelial-to-mesenchymal transition (EndMT) based on studies of fate-mapped ECs using *Tie2-Cre;Rosa26 Reporter-stop-EYFP* bigenic mice [98]. Further studies are required to evaluate the roles of pericytes as well as EndMT in capillary rarefaction in CKD.

Conclusion

The collective data from both clinical and experimental studies support the concept that PTC rarefaction is not only a prominent histological characteristic of CKD but also a central driving force that contributes to the progression of CKD. As multiple factors contribute to PTC rarefaction in each phase of the disease process, we need to tailor the treatment according to the stage of CKD.

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Figure 1. Immunofluorescence staining for CD31 (green) to visualize peritubular capillaries (PTCs) in the mouse kidney cortex. Control (left) and day 7 after UUO surgery (right). Note that the CD31+ PTC density is profoundly reduced in the UUO kidney compared with the control kidney. g: glomerulus. Bar: 50 μ m.

Figure 2.

Schematic of mechanisms of peritubular capillary (PTC) rarefaction following kidney injury. (A) In the healthy kidney, pericytes (PC) are embedded into the capillary basement membrane (BSM) and attached to capillary endothelial cells (EC). This close relationship between PCs and ECs supports capillary integrity. (B) Subsequent to an initial insult, angiogenic factors (e.g. VEGF) are up-regulated and ECs are proliferative. PCs promptly start to migrate away from the capillary area. Simultaneously, inflammatory cells infiltrate into the interstitium. (C) In response to continuous insults, (1) angiogenic factors are down-regulated, (2) anti-angiogenic factors (e.g. thrombospondin-1) are up-regulated, (3) endothelial progenitor cells (EPCs) do not promote neoangiogenesis, (4) PC detachment from vasculature destabilizes ECs, and (5) EC dysfunction and EC apoptosis progress. All of these mechanisms contribute to an anti-angiogenic environment, resulting in PTC rarefaction. The capillary BSM is also degraded. Additionally, a large number of inflammatory cells migrate from the capillary lumen into the extracapillary space. Note that some of the angiogenic factors (e.g. angiopoietin-1) and anti-angiogenic factors (e.g. thrombospondin-1) induce infiltration of inflammatory cells, which impairs the angiogenic response.

Table

Roles of major factors that regulate angiogenesis and capillary regression in CKD.

	Factor	Major mechanisms of action	Other biological effects
Proangiogenic factors	Angiopoietin-1	<ul style="list-style-type: none"> EC proliferation and migration 	<ul style="list-style-type: none"> enhancement of inflammation proangiogenic effect (model-dependent)
	Fibroblast growth factor-2	<ul style="list-style-type: none"> activation of VEGF-VEGFR-2 signaling 	<ul style="list-style-type: none"> enhancement of fibrogenesis
	Hepatocyte growth factor	<ul style="list-style-type: none"> EC proliferation and migration inhibition of leukocyte adhesion to ECs 	
	Hypoxia-inducible factor	<ul style="list-style-type: none"> upregulation of VEGF level 	<ul style="list-style-type: none"> enhancement of fibrogenesis
	Nitric oxide	<ul style="list-style-type: none"> maintenance of quiescent phenotype of ECs 	
	PIGF	<ul style="list-style-type: none"> EC proliferation and migration 	<ul style="list-style-type: none"> enhancement of inflammation
	Platelet-derived growth factor B	<ul style="list-style-type: none"> PC recruitment to vasculature 	<ul style="list-style-type: none"> enhancement of fibrogenesis
	VEGF-A	<ul style="list-style-type: none"> EC proliferation and migration 	<ul style="list-style-type: none"> proangiogenic effect (disease phase dependent) excessive amount causes vascular instability
Antiangiogenic factors	ADAMTS-1	<ul style="list-style-type: none"> inhibition of VEGF-VEGFR-2 signaling induction of vascular instability 	
	Angiopoietin-2	<ul style="list-style-type: none"> competitive inhibition of angiopoietin-1 	<ul style="list-style-type: none"> proangiogenic effect under the presence of VEGF-A
	Angiostatin	<ul style="list-style-type: none"> induction of EC apoptosis 	<ul style="list-style-type: none"> alleviation of inflammation

	Factor	Major mechanisms of action	Other biological effects
	Asymmetric dimethylarginine (ADMA)	<ul style="list-style-type: none"> inhibition of nitric oxide synthesis 	
	CD44	<ul style="list-style-type: none"> induction of EC apoptosis 	
	Endostatin	<ul style="list-style-type: none"> inhibition of VEGF-VEGFR-2 signaling 	
	Soluble fms-like tyrosine kinase-1 (sFlt-1)	<ul style="list-style-type: none"> trapping of circulating VEGF-A and PlGF 	
	Thrombospondin-1	<ul style="list-style-type: none"> inhibition of VEGF-VEGFR-2 signaling 	<ul style="list-style-type: none"> enhancement of inflammation

Abbreviations: CKD, chronic kidney disease; ADAMTS-1, a disintegrin and metalloproteinase with thrombospondin motif-1; EC, endothelial cell; PC, pericyte; PlGF, placental growth factor; VEGF: vascular endothelial growth factor; VEGFR-2, VEGF receptor-2