Vascular Permeability: Regulation Pathways and Role in Kidney Diseases

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Short Title: Vascular Permeability and Kidney Diseases

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Keywords:

Vascular permeability; Vascular endothelial cadherin; Acute kidney injury; Chronic kidney disease; Diabetic kidney disease.

Abstract

Background: Vascular permeability (VP) is a fundamental aspect of vascular biology. A growing number of studies have revealed that many signalling pathways govern VP in both physiological and pathophysiological conditions. Furthermore, emerging evidence identifies VP alteration as a pivotal pathogenic factor in acute kidney injury (AKI), chronic kidney disease (CKD), diabetic kidney disease (DKD) and other proteinuric diseases. Therefore, perceiving the connections between these pathways and the aetiology of kidney disease is an important task as such knowledge may trigger the development of novel therapeutic or preventive medical approaches. In this regard, the discussion summarizing VP-regulating pathways and associating them with kidney diseases is highly warranted.

Summary: Major pathways of VP regulation comprise angiogenic factors including vascular endothelial growth factor (VEGF)/VEGFR, angiopoietin/Tie and class 3 semaphorin/neuropilin; and inflammatory factors including histamine, platelet-activating factor (PAF) and leukocyte extravasation. These pathways mainly act on vascular endothelial cadherin (VE-cadherin) to modulate adherens junctions (AJs) of endothelial cells (ECs), thereby augmenting VP via the paracellular pathway. Elevated VP in diverse kidney diseases involves EC apoptosis, imbalanced regulatory factors and many other pathophysiological events, which in turn exacerbates renal structural and functional disorders. Measures improving VP effectively ameliorate diseased kidney in terms of tissue injury, endothelial dysfunction, kidney function and long-term prognosis.

Key Messages: 1. Angiogenic factors, inflammatory factors and adhesion molecules represent major pathways that regulate VP. 2. Vascular hyperpermeability links various pathophysiological processes and plays detrimental roles in multiple kidney diseases.

Introduction

For vertebrates, the vascular system plays indispensable roles in storing blood, nourishing tissues with oxygen and nutrients, transporting metabolites and offering gateways to the immune system. To accomplish these missions, it provides adequate interfaces and sufficient permeability for the material exchange between the circulation and different tissues. [1]

Vascular permeability (VP) is generally defined as blood vessels' ability to control the bidirectional passage of molecules and immune cells with a certain range of size and to restrict the extravasation of larger molecules. Under physiological conditions, molecules smaller than 40 kDa can pass through mature vessels, whereas larger proteins, such as albumin (66 kDa) and transferrin (80 kDa), are retained. However, under pathophysiological conditions, for instance, inflammation and allergy, even molecules of 2000 kDa may extravasate. In addition to size and physiological status, VP is also affected by the type of microvessels involved (venules or capillaries), other characteristics of the molecule (shape, charge and hydrophilicity) and the histological pathway (transcellular, paracellular or via fenestrae). [2]

Kidney vasculature is unique and complex: the renal artery enters the kidney at the renal hilum and further branches into the interlobular and arcuate arteries that eventually form the glomerular capillaries and postglomerular capillaries. This specific vasculature ensures the kidney's function of blood ultrafiltration, urine production and the maintenance of the liquid, electrolyte and acid-base equilibrium [3]. As a vital property of the kidney vasculature, VP of both glomerular and postglomerular capillaries plays crucial roles in kidney homeostasis. The glomerular permeability of the filtration barrier determines the types of molecules to be filtered from serum to Bowman's capsule. Moreover, VP of the post glomerular capillaries, including peritubular capillary network and the vasa recta, is essential to the ultrafiltrate reabsorption and the medullary osmotic gradient maintenance [4].

VP alteration is closely related to various kidney diseases. In acute kidney injury (AKI), capillary hyperpermeability contributes to microvascular hypoperfusion, oedema, hypoxia and inflammation, further aggravating tissue injury and dysfunction [5]. Alterations of systemic and glomerular permeability are associated with albuminuria and oedema in multiple proteinuric diseases such as diabetic kidney diseases (DKD), idiopathic nephrotic syndrome (INS) and hypertension [6, 7, 8]. For chronic kidney disease (CKD), particularly end-stage renal disease (ESRD), microvascular leakage accompanied by capillary rarefaction and tubulointerstitial fibrosis was reported both in animals and patients, associated with poor prognosis [9, 10]

Considering the pivotal role of VP in kidney homeostasis under both physiological and pathological conditions, further investigation of its regulation mechanism and its relation to kidney diseases is highly warranted. This review will discuss the current research progress of VP regulation by major signalling pathways, VP alteration in various kidney diseases, their correlation, and translation of such molecular mechanisms to preclinical and clinical practice.

The elements and pathways of VP in renal capillaries are summarized in Figure 1.

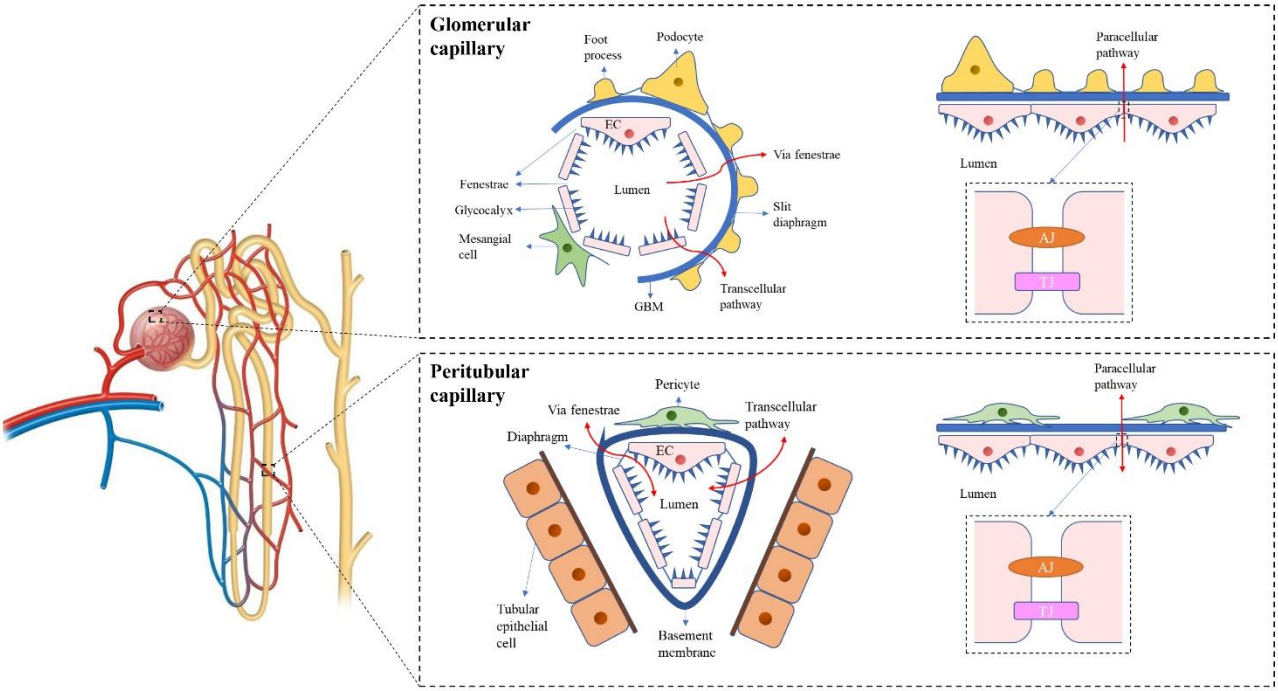

Figure 1. Renal capillary beds and permeability pathways.

Schematic summary of the elements and pathways of VP in renal capillaries. The kidney has two types of capillary beds, the glomerular capillary and the postglomerular capillary (peritubular capillary), which have different elements that impact their permeability. Both of them comprise endothelial surface glycocalyx and EC monolayer for transcellular pathway, EC junctions (TJs and AJs) for paracellular pathway, EC fenestrae (peritubular capillary fenestrae has a thin diaphragm), pericytes (mesangial cells as glomerular pericytes) and basement membrane (GBM as glomerular basement membrane). Furthermore, the glomerular permeability barrier includes the podocytes with the slit diaphragm between their foot processes.

Regulation of Vascular Permeability

VEGF/VEGFR Signaling Pathway

Vascular endothelial growth factor (VEGF) was initially named vascular permeability factor (VPF), indicating its key roles in permeability regulation. VEGF family members comprise VEGF-A to VEGF-E and placental growth factor (PlGF), which act via their receptors VEGFR1, VEGFR2, VEGFR3 and co-receptors Neuropilin-1 (NRP-1) and Neuropilin-2 (NRP-2). [11]

VEGF-A/VEGFR2 with co-receptor NRP1 is the main pathway to modulate angiogenesis and VP [11]. In the kidney, VEGF is produced primarily by podocytes and tubular epithelial cells, and VEGFR2 is expressed on endothelial cells (ECs), where it forms a mechanosensory complex with vascular endothelial cadherin (VE-cadherin), the major adhesive protein at adherens junctions (AJ). VEGF stimulation triggers VEGFR2 phosphorylation at tyrosine Y949 that binds T cell-specific adaptor (TSAd), further eliciting downstream Src/Vav2/Rac1/PAK1 signal, leading to VE-cadherin phosphorylation at Y658 and Y685, then endocytosis followed by degradation or recycling, thus augmenting VP [12, 13]. Another VEGFR2 phosphorylation site responsible for VP is Y1173, which may, through PLC-dependent calcium influx or PI3K/Akt pathway-induced endothelial nitric oxide synthase (eNOS) phosphorylation at serine S1177, activate eNOS to produce NO [12]. NO induces vasodilation and local blood flow increase, thus resulting in altered shear stress to modulate VE-cadherin phosphorylation and hydrostatic pressure change to promote intravascular components extravasation [14, 15]. Besides, NO mediates S-nitrosylation of β-catenin at Cys619, promoting its dissociation from VE-cadherin and AJs disassembly [16]. Also, VEGF/VEGFR2 pathway may mediate VP via disrupting tight junctions (TJs) [17].

Interestingly, VEGFR3 with co-receptor NRP2 was formerly considered to control lymphangiogenesis, but VEGFR3 may also modulate VP via suppressing VEGFR2 expression and VEGF/VEGFR2 pathway activity in quiescent, angiogenic ECs [18]. Such phenomenon implies the interaction between VEGFRs and emphasizes their synthetic effect when focusing on any of these pathways, even though the VEGFRs present discrepant affinity for different ligands. Of note, the data discussed above are generated by using murine models [12-18]and ECs cultured *in vitro*, including human [14, 15, 17] and mouse EC lines [14-16, 18], which may not perfectly reflect the signalling transduction process in the human body. Moreover, it should be emphasized that the internalization of VE-cadherin as the common pathway of VEGF-induced VP leads to the disruption of AJs, and finally mediates VP via the paracellular pathway.

Angiopoietin/Tie and VE-PTP

Angiopoietins (Angpts) are secreted growth factors that regulate angiogenesis and inflammation via endothelial receptor tyrosine kinase Tie. Angpt1 and Angpt2 act antagonistically in VP modulation: Angpt1 is constitutively expressed in non-endothelial cells, it phosphorylates Tie2 on ECs, promotes its redistribution and further elicits Rap1/Rac1 pathway to deactivate RhoA/ROCK pathway-mediated phosphorylation of myosin light chain (MLC), rearrangement of VE-cadherin and vascular leakage [19, 20]. Conversely, Angpt2 expression by ECs is usually controlled at low levels but upregulated under pathological conditions, and competitively binds to Tie2 to inactivate it [20]. Also, Angpt2 decreases claudin-5 expression in TJs, increases caveolin-1 expression to support the transcellular pathway and stimulates pericyte detachment and migration to mediate VP [21]. Another possible mechanism of Angpt2-induced VP may involve the damage of the endothelial surface glycocalyx that is important to endothelial dysfunction, as a clinical trial suggests that increased Angpt2 may mediate the association between low-density lipoprotein-cholesterol and glycocalyx injury marked by the biomarker syndecan-1 in patients with nephrotic syndrome [22].Tie1 is less characterized than Tie2, which might directly interact with Tie2 to regulate Angpt/Tie2 pathway and its deletion tightens the AJs by upregulating VE-cadherin expression [23]. Vascular endothelial protein tyrosine phosphatase (VE-PTP) is an endothelial-specific phosphatase associated with both VE-cadherin and Tie2, it stabilizes VE-cadherin in quiescent endothelium via inhibiting GEF-H1-mediated RhoA activation and in activated endothelium via dephosphorylating VE-cadherin at Y658/Y685 [24]. Controversially, it might play dual roles in challenged endothelium, where its inhibition activates Tie2 to stabilize AJs. However, in the absence of Tie-2, VE-PTP inhibition augments VP, consistent with its effect on VE-cadherin dephosphorylation. [19, 24] Furthermore, VE-PTP dephosphorylates VEGFR2 in Ang1/Tie2-dependent manner, which inhibits VE-cadherin phosphorylation [25]. In turn, during VEGF stimulation or leukocyte extravasation, VE-PTP is dissociated from VE-cadherin to open AJs [26]. In conclusion, VE-PTP regulates VP through its combined action on VE-cadherin dephosphorylation, Tie2 suppression and VEGFR2 regulation. Simultaneous targeting VEGF, Angpt2 and VE-PTP could be a promising therapeutic strategy for microangiopathy [27].

Similar to researches on VEGF, these data are obtained mainly from mouse models [19-21, 23, 27], human EC lines [19, 21, 23, 27] and mouse EC lines [21, 24-26], demonstrating the effects of Angpt/Tie signal via the transcellular [21] and paracellular pathway [19, 20, 24, 25]. The clinical trial [22] provides evidence of how Angpt2 modulates VP via glycocalyx damage in patients, and more clinical studies are required to add

to the reliability of current conclusions.

Class 3 Semaphorin and Neuropilin1

Class 3 semaphorins are secreted soluble molecules initially identified as axonal guidance proteins. Neuropilin1 (NRP1) is a membrane-anchored receptor for class 3 semaphorins in vertebrates, which can non-competitively bind VEGF and trigger corresponding downstream pathways. [28].

NRP1 as co-receptor of VEGF /VEGFR2 can add to ligand-receptor affinity and participate in signal transmission [11, 28]. Furthermore, NRP1 and VEGFR2 can either mediate VP independent of each other [29]. For example, SEMA3A/NRP1 pathway inhibits PP2A activity through Src/Set signal that leads to VE-cadherin phosphorylation at serine S665 and internalization, or triggers PI3K/Akt pathway [30, 31]. Also, SEMA3A may interact with VEGFR1/NRP2 complex to elicit Mical2 activation, F-actin disorganization and cytoskeleton disruption [32]. Moreover, our investigation identified SEMA3C as a pro-permeable factor that contributes to tissue injury during AKI. Of interest, SEMA3A is anti-angiogenic and to some degree antagonizes VEGF-A, whereas it does promote VP [31]; SEMA3C functions are similar to VEGF, as it promotes angiogenesis and VP in mice (Cai A et al., data in revision). These results indicate that SEMA3A (SEMA3C)/NRP1 pathway may participate in various diseases by modulating VP, which involves not only the pathway itself but its interaction with VEGFR. As for possible therapy, we may inhibit specifically class 3 semaphorin binding site on NRP1 to block the permeability response, while VEGF binding left intact to maintain EC proliferation and survival.

Collectively, the source of these data is the combination of both *in vivo* experiments using murine models [28-32] and *in vitro* cell culture using human EC lines [29-31] or murine EC lines [32]. It is suggested that class 3 semaphorins binding to NRP1 to induce VP via the paracellular pathway, but how to translate it into clinical practice needs further investigation.

Inflammatory Factors and Leukocyte Extravasation

Vascular hyperpermeability caused by various inflammatory factors plays critical parts in inflammation and anaphylaxis. Histamine, a prominent inflammatory factor, has four cognate G protein-coupled receptors (GPCRs), designated H1R to H4R. Histamine increases VP through H1R, which can also be activated by platelet-activating factor (PAF). H1R activation promotes PLC-mediated mobilization of calcium and RhoA/ROCK pathway, which together induce MLC phosphorylation and VE-cadherin redistribution,

followed by gap formation [33]. Besides, the aforementioned eNOS pathway, involving hemodynamic changes and NO-induced S-nitrosylation of β-catenin, p120 and VE-cadherin, represents another major pro-permeable mechanism of these inflammatory factors [34, 35]. Additionally, tumour necrosis factor-α (TNF-α), another famous proinflammatory cytokine, strongly promotes permeability via triggering RhoA/ROCK signal, activating Rac/ROS pathway to dissociate VE-PTP from VE-cadherin, and modulating TJ molecules, including ZO-1, occludin and claudin [36, 37].

Leukocyte extravasation, a key event in inflammation, is closely associated with VP through VE-cadherin, since anti-permeability via VE-cadherin–α-catenin complex strongly reduced leukocyte infiltration in certain tissues without affecting VEGFR2 signal, VE-PTP association or cytoskeletal organization [13, 38]. Intriguingly, VP and leukocyte extravasation are regulated by different tyrosines of VE-cadherin, as phosphorylation at Y685 enables VP, and leukocyte dephosphorylates Y731 to extravasate [39]. Notwithstanding VE-PTP functions selectively on Y685, it's critical in leukocyte transmigration, because VEGF stimulation or lymphocyte binding to vascular cell adhesion molecule-1 (VCAM-1) activates Rac1/NOX/ROS/Pyk2 pathway that mediates VE-PTP detachment from VE-cadherin, required for VP and leukocyte diapedesis *in vivo* [26]. Furthermore, VE-cadherin Y685 phosphorylation supports chemokine diffusion from inflamed interstitium to vascular lumen, thereby promoting the reverse transendothelial migration (rTEM) of activated neutrophil to induce remote organ damage [40].

These preclinical researches on inflammatory cytokines and cells are all based on murine models [33-40], with the help of human EC lines [33, 35, 38, 39] or isolated primary cells [36, 39]. Taking together, these inflammatory factors share several common mechanisms amid not only themselves but angiogenic factors, and modification of VE-cadherin to facilitate the paracellular pathway seems to play central roles.

The pathways regulating VP are summarized in Figure 2.

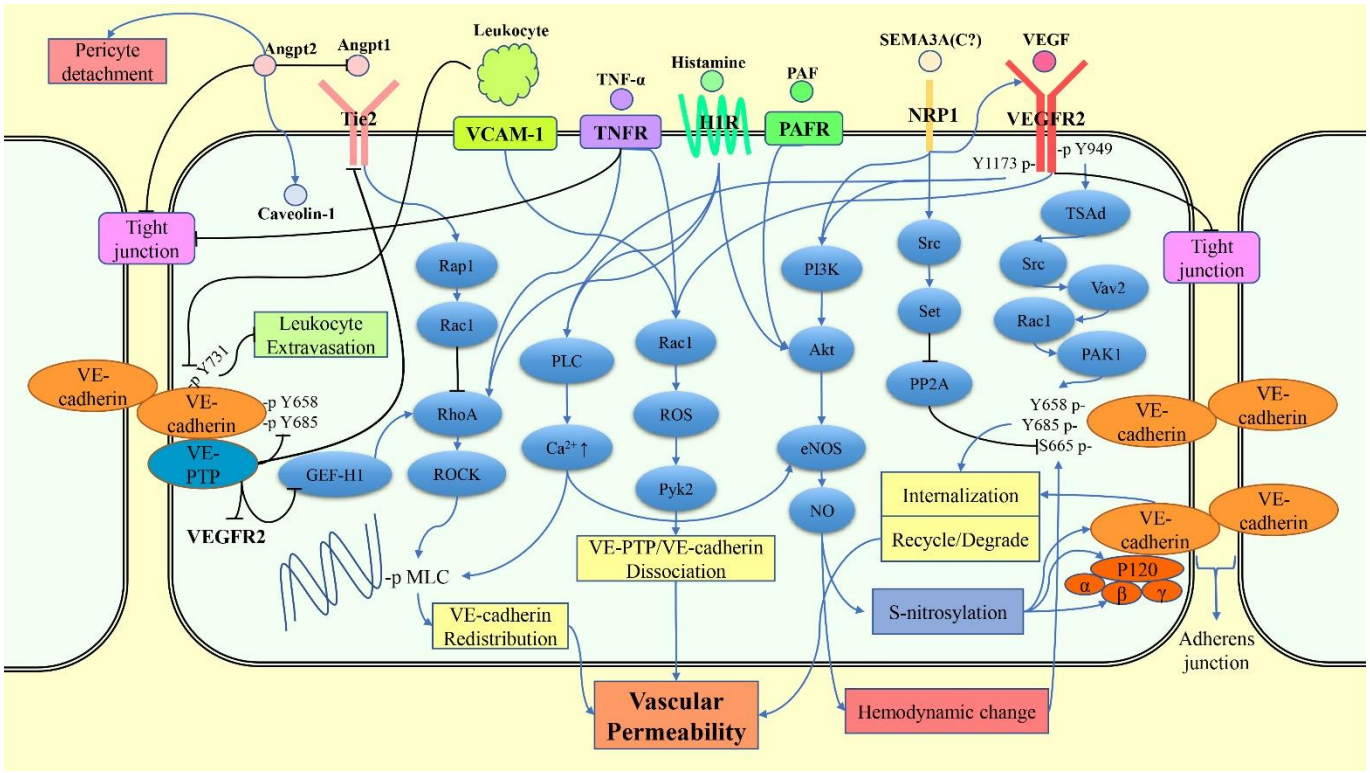

Figure 2. Major signalling pathways regulating vascular permeability.

These pathways mainly involve the angiogenic signalling pathway (VEGF/VEGFR2, Angpt/Tie2 and SEMA3A/NRP1) and inflammatory signalling pathway (Histamine/H1R, PAF/PAFR, TNF-α/TNFR and leukocyte/VCAM-1). Regardless of the precise process of signal transduction, they modulate the common substrate, VE-cadherin in the AJ. VE-cadherin phosphorylation at Y658, Y685 and S665 leads to internalization followed by degradation or recycling, thereby increasing VP. VE-PTP inhibits VE-cadherin and VEGFR2 phosphorylation to stabilize endothelial junctions, therefore its dissociation from VE-cadherin increases VP. S-nitrosylation of VE-cadherin, β-catenin and p120 mediates the disruption of AJs and VE-cadherin endocytosis. The phosphorylation of MLC, the stress fibre, promotes VE-cadherin rearrangement and redistribution to open the endothelial contact. Leukocyte dephosphorylates VE-cadherin Y731 to induce extravasation. VP is also modulated by TJs, caveolin-1 expression (transcellular transportation), pericyte detachment and hemodynamic factors.

Vascular Permeability in Kidney Diseases

Endothelial Cell Apoptosis in Kidney Diseases

The capillary endothelium consists of an EC monolayer, whose massive death disrupts endothelial integrity

and increases VP. Extreme physical, chemical and biological stimuli may lead to unregulated EC death, named necrosis. Nevertheless, recent studies focus more on EC apoptosis, a form of programmed cell death inducible by various factors including nephrotoxin, hemodynamic change and metabolic disorders, which represent respectively major pathogenic factors in AKI, CKD and DKD. The widely-used chemotherapeutic drug cisplatin as a nephrotoxin induces EC apoptosis at low concentrations and necrosis at high concentrations, thus contributing to AKI in both patients and animal models [41]. Indoxyl sulfate (IS), a typical uremic toxin in CKD, stimulates monocytes to express TNF-α that promotes ECs to recruit $CD4^+CD28^-$ T cells via CX3CL1/CX3CR1 binding, thereby provoking endothelial damage in ESRD patients [42]. Moreover, during hypovolemic shock the hypoxia and hemodynamic changes support the generation of reactive oxygen species (ROS), which induces the apoptosis of human umbilical vein endothelial cells (HUVECs) and may contribute to prerenal AKI [43]. Of note, there may be crosstalk between dyslipidaemia and hyperglycaemia, in which protein kinase B (PKB, also called Akt) activation plays a central role. In high-fat diet-induced mouse aortic EC (MAEC) and human aortic EC (HAEC) apoptosis, PI3K/PDK1/Akt/mTOR pathway activation is inhibited, whereas activation of PI3K/Akt/eNOS pathway attenuates inflammation and endothelial dysfunction in MAECs induced by oxidized low-density lipoprotein (ox-LDL), suggesting protective effects of Akt and downstream pathways in dyslipidaemia [44, 45]. Conversely, activation of ROS/Akt/NF-κB pathway acts detrimentally in hyperglycaemia-induced HUVEC apoptosis[46]. Dyslipidaemia is identified as an independent risk factor of DKD, but the mechanism linking dyslipidaemia and hyperglycaemia remains largely unclear. Further investigation should elucidate their underlying relationship during EC apoptosis, which would contribute to the prevention and treatment of DKD and other vascular complications.

The factors leading to EC apoptosis in kidney diseases are summarized in Figure 3.

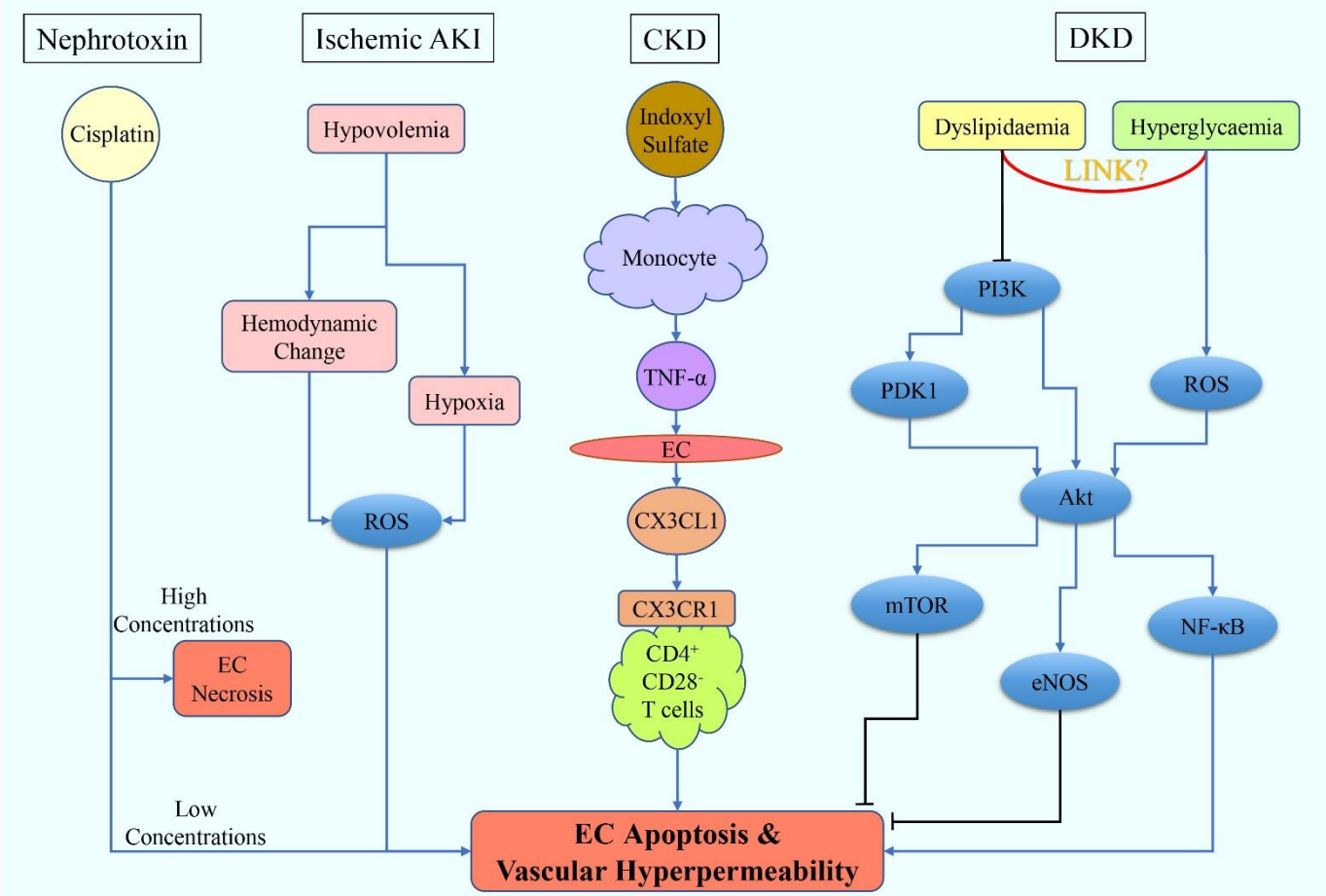

Figure 3. Factors leading to EC apoptosis in kidney diseases.

The chemotherapeutic drug cisplatin results in EC apoptosis at low concentration. In ischemic AKI, hypovolemia causes hypoxia and hemodynamic changes, which promotes ROS generation to induce EC apoptosis. During CKD, the uremic toxin IS stimulates monocytes to produce TNF-α, thereby promoting cytotoxic T cells recruitment and EC apoptosis. Dyslipidaemia contributes to EC apoptosis via inhibiting PI3K/PDK1/Akt/mTOR pathway and PI3K/Akt/eNOS pathway. Hyperglycaemia elicits ROS/Akt/NF-κB pathway to mediate EC apoptosis. These two metabolic disorders synergize to induce endothelial damage in DKD.

Vascular permeability and AKI

AKI is defined as a sharp loss of kidney excretory function, characterized by rapid declined glomerular filtration rate (GFR), increased plasma nitrogenous wastes and variably diminished urinary output. Tubular epithelial cell perturbation contributes greatly to AKI, whereas emerging evidence has unveiled the essential role of endothelial dysfunction. [5]

Capillary hyperpermeability in AKI involves multiple factors. First, the endothelial monolayer is directly

disrupted during AKI, as there exists a relative late-phase EC apoptosis in ischemic AKI mice [47], and the modification of endothelial barrier molecules such as glycocalyx and VE-cadherin occurs in post-cardiac surgery AKI pigs [48]; septic AKI also contributes to EC apoptosis via endotoxin and overactivated immune system [5]. Moreover, in ischemic AKI murine models, pericytes show an increased expression of matrix metalloproteinases (MMPs, a family of zinc-dependent endopeptidases that degrade various proteins in the extracellular matrix), especially MMP7 and MMP9; while pericytes downregulate the tissue inhibitor of metalloproteinase 3 (TIMP3) to degrade extracellular matrix, and promotes αvβ5 integrin-induced pericyte detachment and migration [49, 50]. Third, infiltrated neutrophils in interstitium release cytokines, chemokines, proteases and ROS to activate the complement system, upregulate inflammatory factors and induce adhesion molecules, thereby aggravating tissue damage and endothelial dysfunction in ischemic AKI mice [51]. Furthermore, while both tubuloglomerular feedback and imbalanced vasomotor factors contribute to renal vasoconstriction [5], the consequent altered hemodynamic force exacerbates VP [15]. These effects involve EC apoptosis [5, 47], endothelial surface glycocalyx [48], cell-cell contacts and paracellular pathway [15, 48, 51], pericytes and extracellular matrix [49, 50]. They synchronize to disrupt vascular integrity and result in microvascular hypoperfusion, interstitial oedema, hypoxia, increased tubular pressure and tubular obstruction, finally contributing to GFR decrease and tissue injury [5].

VP-regulating molecules alter significantly in AKI. During sepsis, VE-cadherin shedding and plasma soluble VE-cadherin levels are associated with severe AKI and organ dysfunctions in sepsis patients, implying endothelial AJs disruption and leukocyte rTEM [40, 52]. Besides, the disbalance of Angpts, including decreased Angpt1 and elevated Angpt2, is associated with AKI in critically ill patients independently of inflammation [53]. Especially, although VEGF/VEGFR2 pathway mediates VP, it might play beneficial roles in AKI. Higher levels of plasma VEGF and PlGF are associated with lower risks for AKI and mortality in post-cardiac surgery patients, whereas higher VEGFR1 levels with higher risks, probably due to the effect of VEGF on EC survival and angiogenesis [54]. Moreover, our studies identified SEMA3C as a pro-angiogenic and pro-permeable factor that acts deleterious roles in ischemic and nephrotoxic AKI mouse models through aggravating VP (Cai A et al., data in revision).

Undoubtedly, vascular integrity restoration treatment alleviates AKI. Adenosine 2A agonists can reduce neutrophil infiltration to inhibit renal VP and preserve renal function in ischemic AKI mice [51]. Erythropoietin (EPO) may attenuate septic AKI in mice via enhancing EPO/EPOR and VEGF/VEGFR2 signal and inhibiting HIF-1α, iNOS and NF−κB expressions, linking tissue hypoxia, endothelial dysfunction and inflammation [55]. Furthermore, adhesion molecules and pericytes act pivotal parts, as

inhibiting pericyte activation and stabilize microvasculature through blocking αvβ5 integrin can attenuate VP and protect against ischemic AKI in mice [50]. However, activated pericytes and unresolved VP may render kidney revascularization strategy futile, and failed kidney recovery lead to AKI to CKD transition [56].

Vascular permeability and CKD

CKD is defined as abnormalities of kidney structure or function of at least 3 months duration with health implications, which severely burdens public health. Irrespective of the aetiology, peritubular capillaries undergo similar ultrastructural and functional changes during progressive renal disease in both mice and humans, including capillary rarefaction and microvascular hyperpermeability [9].

Causes of vascular hyperpermeability in CKD differ from those in AKI while sharing some common features. First, a rat model shows that endothelial surface layer glycocalyx encounters a similar loss in CKD, associating proteinuria with systemic endothelial dysfunction [57]. Second, studies using patients biopsies and mouse models have unravelled that fibroblasts in renal fibrosis principally derive from pericytes, whose activation is both pro-permeable and profibrotic, linking AKI to CKD [56]. Also, mouse models indicate that pericytes deficiency and imbalanced VEGF expression impact both existing vessels and neovascularization, resulting in leaky and immature new vessels [11, 58]. Besides, specific rheological changes at microvascular branches make them major sites of vascular leakage in both AKI and CKD mouse models (Cai A et al., data in revision) [9]. . Moreover, a study using HUVECs suggests that chronic inflammation in CKD triggers the activation of NF-κB and downstream proinflammatory factors in CKD and ESRD patients [59]. Moreover, serum uremic toxins of CKD patients elicit VE-cadherin disruption and F-actin reorganization, thus opening up AJs in HUVECs [60]. The toxins may also come from normal proteins, as HDL becomes noxious particles in CKD patients which inhibit endothelial NO production, destabilize endothelial barrier and promote vascular dysfunction of HAECs [61]. In turn, vascular hyperpermeability contributes to CKD progression. Glomerular endothelial leakage results in abnormal passage of plasma protein into renal tubules and interstitium to elicit the inflammatory and fibrotic response, associated with systemic vascular dysfunction and cardiovascular complications in CKD patients [62]. Extravasated serum proteins such as fibrinogen may also disrupt TJs of rat cardiac microvascular ECs [9]. As for the permeability elements, VP in CKD involves glycocalyx [57], pericytes [56], EC junctions and paracellular pathways [9, 59-61]. As a result, the disrupt endothelial barrier participates in hemodynamic

changes including hypoperfusion, hemoconcentration and interstitial oedema, which promote hypoxia, cell swelling, inflammation and platelet activation within the kidney, leading to augmented interstitial profibrotic cytokines and impaired cell functions of degrading collagen. Altogether, these pathophysiological processes contribute to protein malnutrition, body fluid overload, renal fibrogenesis and worse survival in CKD patients [9, 10].

It's worth emphasising that vascular hyperpermeability belongs to endothelial dysfunction, an important endothelial alteration in CKD, characterised by impaired NO bioavailability [63]. NO is generated from L-arginine via eNOS catalysis, which not only regulates VP but shows vasorelaxant, anti-inflammatory and antithrombotic properties. In CKD patients, eNOS is inhibited by multiple pathophysiological events, such as oxidative stress (OS), inflammation, hyperphosphatemia, dyslipidaemia, and endogenous inhibitor of eNOS, including asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) [63, 64]. In consequence, disordered endothelium presents abnormal activation, reduced proliferation and elevated apoptosis, and disrupt endothelial barrier function [63, 64]. These alterations contribute to renal fibrosis and systemic atherosclerosis, associated with poor clinical outcomes [63].

Among the major components of endothelial dysfunction, OS represents a pivotal point correlated with VP. In OS, oxidative molecules, most commonly ROS, overwhelm antioxidant defense mechanisms [65]. Such a status is present even in the early stages of CKD, caused by chronic inflammation, mitochondrial dysfunction and excessive ROS generation [65]. During CKD progression, OS exacerbates along with reduced kidney function and severely burdens ESRD patients requiring haemodialysis (HD) and peritoneal dialysis (PD) [66][67]. As aforementioned, ROS participates in inflammatory factors-induced VP and EC apoptosis to destabilise both renal and systemic vascular integrity, contributing to body overhydration; OS can also promote leukocyte recruitment, inhibit eNOS and suppress angiogenesis, thereby aggravating both local and systemic endothelial dysfunction, renal fibrogenesis and atherogenesis in CKD and especially in ESRD patients in need of dialysis [65]. The key event of OS is the formation of oxidative products, which is impacted by lifestyle and diet habits, and by different factors in HD and PD: HD-related factors include dialyser membranes, anticoagulant usage, dialysate, medication administration and HD duration [66]. In contrast, OS status in PD mainly depends on the composition of the PD solution, in which high glucose and acidic pH are considered as the culprit. Rodent models and clinical studies have revealed that such PD fluids promote the generation of the advanced glycation end-products (AGEs) and ROS to induce oxidative stress and break redox homeostasis, thereby contributing to increased systemic and local inflammation, peritoneal cell apoptosis and peritoneal fibrosis [67-69]. In consequence, the microvascular density of

peritoneum is decreased while the microvessels undergo hyperpermeability, resulting in loss of peritoneal integrity and its transport function [67, 68]. As for treatment, antioxidant supplementation may represent possible therapeutic strategies [67, 68]; neutral-pH, low-GDP PD fluids can induce early inflammation, epithelial-mesenchymal transition and angiogenesis of the peritoneum to impact its transport function in child patients, but their long-term effect requires further investigation [70].

Similar to AKI, there exists severe dysregulation of permeability regulatory factors in CKD. Reduced VEGF levels in different renal fibrosis rodent models might account for capillary rarefaction and loss of EC fenestrations [9]. Nevertheless, VP was still elevated with more formation of caveolae and cytoplasmic vesicles in HUVECs treated with uraemic patient serum, implying the involvement of other factors such as imbalanced Angpts [71]. Indeed, Angpt2-mediated VP aggravates fluid overload, facilitates inflammatory response and implies adverse renal outcomes in CKD patients [72]. Moreover, VE-cadherin, opposite to its shedding in AKI, is upregulated in CKD mice but might be disrupted by uremic toxins [60, 73].

Considering its important roles in CKD, targeting VP represents potential therapeutics. Vitamin D supplementation enforces HUVEC integrity via strengthening VE-cadherin, stabilizing cortical F-actin ring formation and reducing MMP9, thereby attenuating endothelial dysfunction in CKD [60]. Overexpression of vasoprotective VEGF-A_{165}b isoform protects against glomerular hyperpermeability, ultrastructural abnormalities and proteinuria in CKD mouse [58]. Targeting impaired Angpt/Tie pathway, Angpt1 administration preserves pericyte coverage and enhances EC junctions to attenuate peritoneal VP and inflammation, thus ameliorating peritoneal transport function in PD rats [74]. To improve peritoneal permeability and transport function, antioxidant such as N-acetylcysteine (NAC) can protect against OS, and dipeptide alanyl-glutamine (AlaGln) may activate pathways associated with the protection of the PM integrity in mice [67-69].

The clinical-related studies of VP in CKD are summarized in Table 1.

Study (ref.)	Year	Methodology	Results
Serradell M. et al. [70]	2002	Patient serum: 10 HD Paired controls HUVECs	Endothelial dysfunction and inflammation marked by expression, redistribution and shedding of adhesion molecules: HD > control

Yu Z. et al. [10]	2012	Patients: 41 PD	1. Systemic albumin leak measured by transcapillary escape rate of albumin: PD > non-uraemic 2.Complex relationship between endothelial barrier, inflammation and hypoalbuminemia
Caballo C. et al. [58]	2012	Patient serum: 15 controls 15 CKD 15 HD & 9 PD HUVECs	Endothelial activation and damage marked by activation of p38 MAPK and NFκB in HUVECs: PD > HD ≈ pre-dialysis > control
Shroff R. et al. [60]	2014	Child patient serum: 12 controls 39 CKD (stage 2-5) 20 dialysis 23 transplants HAECs	Endothelial dysfunction marked by 1. NO production ↓, superoxide production ↑ and VCAM-1 expression ↑ in CKD-HDL treated cells; 2. urate, Angpt2, IL-6 and SDMA ↑ in patient serum: dialysis > CKD 4-5 > CKD 2-3 > control, partial recovery in transplant group
Seliger S. L. et al. [61]	2016	Older hypertensive patient: 30 non-CKD 36 CKD (stage 1-4) (11 albuminuria)	Microvascular endothelial function marked by microvascular reactivity: albuminuria < normoalbuminuria CKD < non-CKD
Tsai YC. et al. [71]	2017	Patients: 290 CKD (stage 3-5)	1. Angpt2 positively, significantly correlated with fluid overload 2. Risks for commencing dialysis and rapid renal function decline: fluid overload, high circulating Angpt 2 > low overhydration, low circulating Angpt 2
Schaefer B. et al. [69]	2018	Child patient peritoneal and omental specimens: 56 controls 90 ESRD 82 PD Follow-up biopsies: 24 PD (13 months)	Neutral pH and low–glucose degradation product dialysis fluids induce peritoneal inflammation, fibroblast activation, EMT and angiogenesis to impact peritoneal permeability and transport function.
Vila Cuenca M. et al. [59]	2019	Patient plasma : 6 non-CKD 6 CKD HUVECs	1. Endothelial barrier function marked by transendothelial electrical resistance: CKD < non-CKD 2. Disrupt cell-cell junctions in CKD group. 3. Rescuable by VD supplementation.

Table 1. Clinical-related studies of vascular permeability in CKD.

Abbreviations: CKD, chronic kidney disease; HD, haemodialysis; HUVECs, human umbilical vein endothelial cells;

PD, peritoneal dialysis; MAPK, mitogen-activated protein kinase; NFκB, nuclear factor kappa-B; HAECs, human aortic endothelial cells; VCAM-1, vascular cell adhesion molecule-1; HDL, high-density lipoprotein; Angpt2, angiopoietin 2; IL-6, interleukin-6; SDMA, symmetric dimethylarginine; ESRD, end stage renal disease; EMT, epithelial-mesenchymal transition; VD, vitamin D.

Vascular Permeability and DKD

DKD refers to chronic renal dysfunction in patients with diabetes, belonging to diabetic microvascular complications. Albeit enormous efforts taken to control diabetes, DKD remains the leading cause of ESRD [6].

Diabetes-mediated glomerular leakage is closely linked to metabolic disorders. First, hyperglycaemia can induce HUVEC apoptosis probably via ROS production [46]. Second, studies using mouse models and human renal glomerular EC lines reported that hyperglycaemia activates protein kinase C (PKC) system to facilitate glomerular EC (GEC) apoptosis and contributes to renal matrix production [75, 76]. Third, elevated circulating platelet microparticles (PMPs) in DKD impairs ROS and NO system and causes GEC injury in rats and isolated primary rat GECs [77]. Furthermore, dyslipidaemia as an independent risk factor of diabetes participates in endothelial dysfunction. Both patient biopsies and rodent models showed that lipids may stimulate TGF-β to induce ROS production and GEC damage, while triglyceride-rich lipoproteins can degrade glycocalyx [78]. The mechanisms of VP in DKD are mainly caused by the toxicity of hyperglycaemia and dyslipidaemia, involving GEC apoptosis [46, 75-78] and glycocalyx degradation [78]. Resultantly, endothelial hyperpermeability impairs filtration barrier function and contributes to albuminuria, the key event of DKD and subsequent complications [6].

As a supplement to classic diabetes therapy, treatment targeting aberrant angiogenic factors levels to inhibit VP has broad prospects. First, proper VEGF-A levels are necessary for renal microvasculature maintenance in diabetes, whereas excessive VEGF-A contributes to glomerular leakage accompanied by nodular glomerulosclerosis and massive proteinuria. More precisely, vasoactive isoform VEGF-A_{165}a is the culprit, whereas VEGF-A_{165}b normalizes glomerular permeability of both human and rodents via VEGFR2 phosphorylation and glycocalyx restoration in GECs, whose upregulation implies well-preserved kidney function [58]. Besides, using mouse models and human GEC lines, researchers found that VEGF-C counteracts VEGF-A effect via preventing VEGFR alteration and maintaining endothelial glycocalyx to protect diabetic glomerulus and inhibit DKD development [79]. Furthermore, C-peptide may inhibit VEGF-induced ROS generation, stress fibre formation and VE-cadherin disassembly, thereby preventing VEGF-mediated VP and improving renal microvascular flow in diabetic mice [80]. Second, Angpt/Tie system also

participates, as Angpt1 levels decrease in diabetes accompanied by albuminuria and renal morphologic alterations. Its glomerular repletion in diabetic mice significantly reduces albuminuria and GEC proliferation, probably through increased Tie-2 phosphorylation, elevated soluble VEGFR1 levels, decreased VEGFR2 phosphorylation and increased eNOS activity [81]. Moreover, VE-PTP is robustly upregulated in diabetic mice renal microvasculature, whose inhibition enhances Tie2 activity, activates eNOS and reduces the expression of proinflammatory and profibrotic genes, thus decreasing VP and inflammation to preserve microvasculature and kidney function in DKD [82].

Other etiologies of vascular hyperpermeability may also provide possible targets. PKC-β inhibitor LY333531 attenuates GEC apoptosis, while PKC-α and PKC-β-dual inhibitor CGP41252 prevents albuminuria development and reduces existing albuminuria in diabetic mice [75, 76]. Aspirin can reduce PMPs formation to ameliorate GEC injury, albuminuria, glomerular hypertrophy and mesangial matrix expansion in early DKD mice without affecting blood glucose levels [77].

Other Kidney Diseases

Idiopathic nephrotic syndrome (INS), characterized by massive proteinuria, hypoalbuminemia and oedema, mainly consists of minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). In INS, researchers have identified, via utilising patient specimens and murine models, multiple circulating permeability factors, including hemopexin in MCD; soluble urokinase receptor (suPAR), cardiotrophin-like cytokine factor 1 (CLCF-1), apolipoprotein A-I (APOL1), calcium/calmodulin-serine protein kinase (CASK) and CD40 agonist in FSGS [7]. These factors target GEC surface glycocalyx, glomerular basement membrane and podocytes to disrupt the integrity of glomerular filtration barrier [7]. In consequence, abnormal glomerular leakage results in proteinuria, while capillary hyperpermeability contributes to oedema formation which might be significantly reduced by steroid treatment [83].

Hypertension remains a leading cause of morbidity and mortality worldwide, with hypertensive nephropathy being its interdependent part. The disordered renin-angiotensin system (RAS) plays key roles in hypertension, whose inhibition effectively delays and reduces albuminuria. Independent of hemodynamic effects, Angiotensin II (Ang II) acts on podocyte AT1-receptor to increase nephrin-β-arrestin2 binding and nephrin endocytosis, thus augmenting glomerular permeability and contributing to albuminuria in mice, therefore AT1-receptor blockers may prevent albuminuria even in normotensives [8]. Moreover, endothelial sirtuin 6 can ameliorate Ang II-induced VP and increase vascular NO bioavailability

to alleviate endothelial dysfunction in hypertensive mice, thereby protecting against hypertension and associated cardiorenal injury [84]. Furthermore, clinical trials have revealed that inhibition of VEGF/VEGFR2 signal often accompanies proteinuria and hypertension, which probably involves the eNOS pathway [85]. The association between hypertension and dysregulated VEGF family complicates this promising chemotherapeutic strategy and requires further investigations.

The linkage between VP and kidney diseases is summarized in Figure 4.

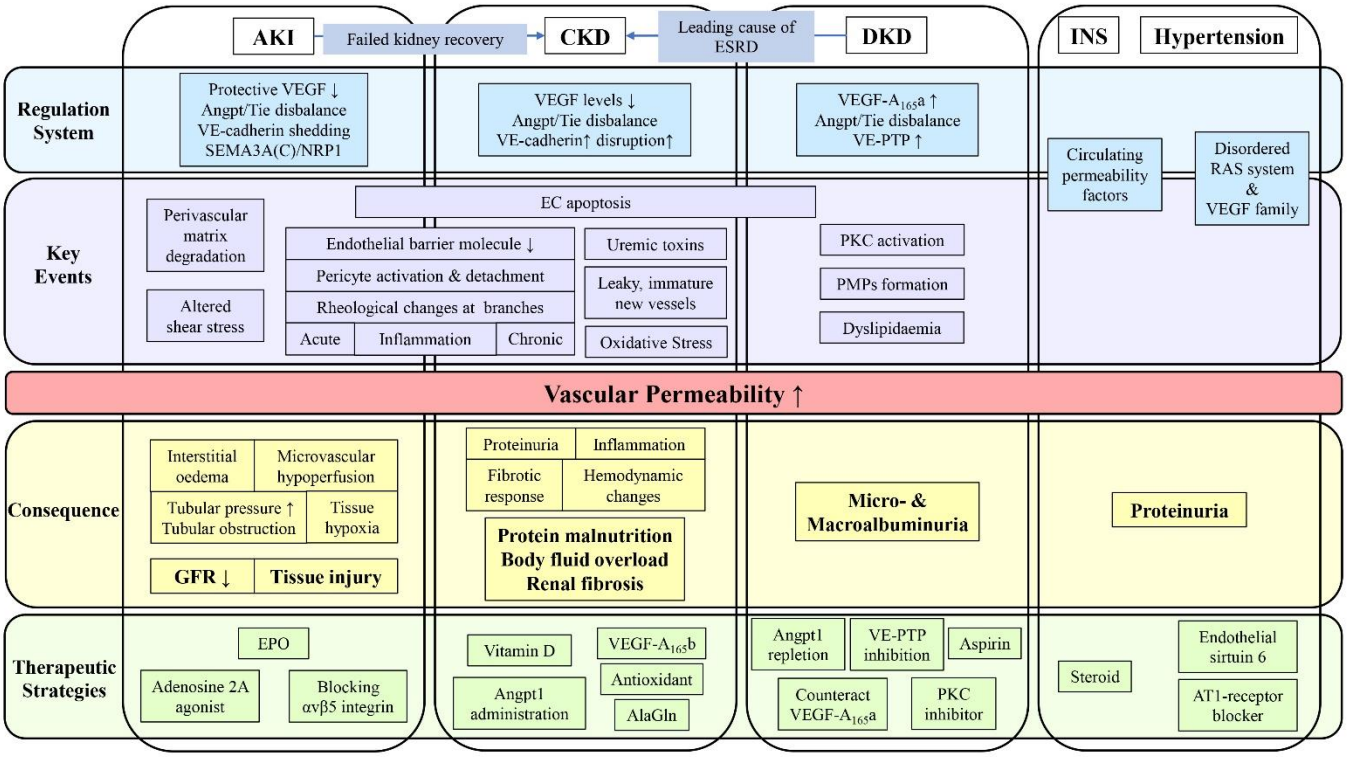

Figure 4. Vascular permeability in kidney diseases.

Schematic summary linking permeability regulation and kidney diseases. Briefly, in different kidney diseases, disordered regulatory molecules participate in the key pathophysiological events that increase permeability. Consequently, vascular hyperpermeability further contributes to the development and progression of these diseases. Treatments targeting the regulation system and key events may represent promising therapeutic strategies for these kidney diseases.

Conclusive remarks

Over the past decades, increasing clinical and preclinical investigations have unravelled the deleterious roles of vascular hyperpermeability in various kidney diseases. Extensive research has identified major

pathways regulating VP, which provides potential biomarkers to predict the severity and prognosis of diseases such as AKI and CKD. Furthermore, targeting these pathways may have broad prospects for the intervention of renal diseases. However, despite encouraging results obtained from mouse models, clinical trials focusing on VP in kidney disease remain rare, probably owing to a lack of practical methods to target specifically VP. To translate these findings into clinical practice, future investigations should further test the efficacity of such biomarkers and develop credible tools to normalize VP in kidney diseases.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was supported by an Academy de Medicine fellowships to A. Cai, and a Marie Curie Personal Fellowship [704450, Horizon2020] to A. Calmont.

Author Contributions

ACalmont and ACai designed the study. ACai wrote the manuscript and prepared the figures with inputs from all the authors.

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