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REVIEW

Exploring Angiopoietin-2: Clinical Insights and Experimental Perspectives in Kidney Diseases

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Angiopoietin-2, an important contributor to angiogenesis and vascular remodeling, is increasingly recognized in kidney research. This review explores clinical insights and experimental perspectives on angiopoietin-2 in kidney diseases. Traditionally seen as an antagonist of the Tie-2, which is a receptor tyrosine kinase of endothelial cells and some hematopoietic stem cells, angiopoietin-2 exerts both proangiogenic and antiangiogenic effects, making it a versatile and context-dependent player in kidney pathophysiology. Elevated circulating angiopoietin-2 levels in clinical scenarios are associated with sepsis and acute kidney injury (AKI), emphasizing its role as a biomarker of disease severity. In diabetic kidney disease, circulating angiopoietin-2 correlates with albuminuria, a crucial indicator of disease progression, and may serve as a treatment target in protecting the endothelium. Angiopoietin-2 is implicated in chronic kidney diseases (CKDs), where its elevated circulating levels correlate with kidney outcomes and cardiovascular complications, suggesting its potential impact on kidney function and overall health. In experimental settings, angiopoietin-2 plays a pivotal role in angiogenesis and lymphangiogenesis, influencing vascular stability and endothelial integrity. The context-dependent agonist and antagonist role of angiopoietin-2 is regulated by a Tie-2 phosphatase, vascular endothelial protein tyrosine phosphatase (VEPTP), further underscoring its complexity. Angiopoietin-2 is also involved in regulating cellular integrity, inflammation, and endothelial permeability, making it a promising therapeutic target for conditions characterized by disrupted endothelial junctions and vascular dysfunction. This review provides a comprehensive overview of the diverse roles of angiopoietin-2 in kidney research, offering insights into potential therapeutic targets and advancements in managing kidney diseases.

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Kidney diseases span from AKI and acute kidney disease to CKD, posing significant global health challenges. Although there are emerging mechanism-specific therapies for immune-mediated glomerular diseases and the application of sodium-glucose cotransporter-2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists, and glucagon-like peptide-1 receptor agonist, fibrosis-targeting therapies remain inconclusive in CKD.[1] Moreover, the reversible nature of AKI and acute kidney disease has attracted research interest. Studies have delved into mechanisms and investigated therapies targeting immune dysregulation, oxidative injury, cell-cycle arrest, and impaired microcirculation from AKI to CKD. Microvascular endothelial injury in septic and ischemic AKI leads to compromised renal perfusion, increased vascular permeability, exaggerated leukocyte recruitment, and aggravated tubular injury, ultimately contributing to CKD progression if repair mechanisms fail.[2–5] Microvascular rarefaction is extensively studied in CKD, where patients commonly exhibit endothelial dysfunction and disrupted vascular homeostasis. Animal models of CKD have revealed significant decreases in vascular density, a cardinal histologic feature closely associated with disrupted angiogenesis.[6]

Angiogenesis, crucial in both physiological and pathologic states, is regulated by angiopoietin-1 and angiopoietin-2, ligands for the Tie-2 receptor tyrosine kinase, expressed by endothelial cells and some hematopoietic stem cells. Physiologically, angiopoietin-1 and angiopoietin-2 collaboratively regulate vascular system homeostasis in the embryonic vascular system

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and the lymphatic system. Angiopoietin-1, an endogenous ligand of Tie-2 and secreted from pericytes, maintains vascular permeability and stability, inhibits inflammatory signaling, and maintains endothelial junctions.[7,8] In contrast, angiopoietin-2 functions as a context-dependent Tie-2 antagonist or weak agonist.[9,10] Stored angiopoietin-2 can be rapidly released from endothelial Weibel-Palade bodies upon stimulation from hypoxia, vascular endothelial growth factor (VEGF), basic fibroblast growth factor, thrombin, and histamine, triggering new angiogenesis and some inflammatory response.[11,12]

Microvasculature instability and inflammation are intertwined features in both AKI and CKD, necessitating therapeutic approaches targeting the microvascular endothelium. Kidneys, being highly perfused organs, rely on renal microvasculature to maintain blood flow homeostasis, nutrients and oxygen delivery, vascular integrity and permeability, coagulation balance, and leukocyte recruitment. In the setting of kidney injury, activated and compromised vasculature leads to leukocyte recruitment, tubular atrophy, and kidney fibrosis.[13] The delicate regulation of endothelial Tie-2 signaling by angiopoietin-1 and angiopoietin-2 has drawn attention, with angiopoietin-2 acting as a marker of activated endothelium and an effector molecule in various pathologies, contributing to the landscape of kidney diseases.[14-16] This review outlines the physiology and pathophysiology of angiopoietin-2 in clinical and experimental settings related to kidney diseases (Figure 1), aiming to provide insights into therapeutic opportunities and advancements.

Clinical Implication of Angiopoietin-2 in Kidney Diseases

Although most clinical studies demonstrate only disturbed circulating angiopoietin-2 levels across different kidney diseases, the association between angiopoietin-2 and clinical outcomes suggests possible causality (Table 1). Emerging mechanism-specific therapies and anti-angiopoietin-2 monoclonal antibody may exert protective effects by inhibiting angiopoietin-2 both indirectly and directly (Figure 1). We summarize the literature on disturbed angiopoietin-2 in AKI, CKD, and albuminuria, and provide current evidence about possible casual mechanisms through preclinical models.

AKI: Implications for Disease Severity and Causal Factor

Systemic angiopoietin-2 levels play a crucial role in the development and severity of AKI across conditions, such as acute myocardial infarction, post cardiac surgery, COVID-19, and liver cirrhosis.[23-27] In liver cirrhosis, vascular destabilization and endothelial dysfunction reduce vasodilatory factors such as nitric oxide, leading to increased hepatic vascular resistance and portal hypertension.[43,44] Conversely, systemic vasodilation activates the renin-angiotensin-aldosterone system and the sympathetic nervous system, thereby decreasing renal blood flow.[45] Elevated serum angiopoietin-2 levels are linked to higher mortality rates in patients with decompensated liver cirrhosis and AKI.[27] In a murine model of sepsis-induced acute-on-chronic liver failure, an increased angiopoietin-2-to-angiopoietin-1 ratio in liver sinusoidal endothelial cells contributes to endothelial dysfunction via the transcription factor CCAAT enhancer binding protein β.[46] The implications of disturbed angiopoietin-s/Tie-2 signaling in the vasculature of the cirrhotic livers remain unexplored but present an intriguing area for future research.

AKI commonly complicates critical illnesses, with dysregulated circulating angiopoietin-2 and angiopoietin-1 levels indicating increased vascular permeability, inflammation, and endothelial injury, all of which are important in the onset and progression of AKI. Studies reveal a strong association between circulating angiopoietin-2 levels and angiopoietin-2-to-angiopoietin-1 ratios with disease severity in patients with sepsis and acute respiratory distress syndrome.[47-50] Elevated plasma angiopoietin-2 levels and angiopoietin-2-to-angiopoietin-1 ratios correlate with AKI severity in sepsis and acute respiratory distress syndrome, suggesting their potential as biomarkers for assessing the degree of kidney injury.[19-22] Genetic variants near ANGPT2 have been linked to the risk of acute respiratory distress syndrome and acute lung injury, with evidence suggesting a causal relationship between plasma angiopoietin-2 and AKI risk.[51-53] Interventions targeting angiopoietin-2 in animal models with sepsis demonstrate improvements in vascular leakage, tissue inflammation, organ function, and overall survival.[54,55] Although a clinical trial evaluating anti-angiopoietin-2 monoclonal antibody therapy in patients with COVID-19 yielded suboptimal results, personalized medicine focusing on the disturbed angiopoietin-s/Tie-2 system among selected patients with AKI may represent a promising direction for intervention.[56]

CKD: Implications for Kidney Function and Cardiovascular Outcome

The relationship between angiopoietin-2 and CKD involves its role in inflammation, endothelial dysfunction, and vascular remodeling. This connection is of great interest due to its potential impact on cardiovascular complications. In patients with CKD, higher serum

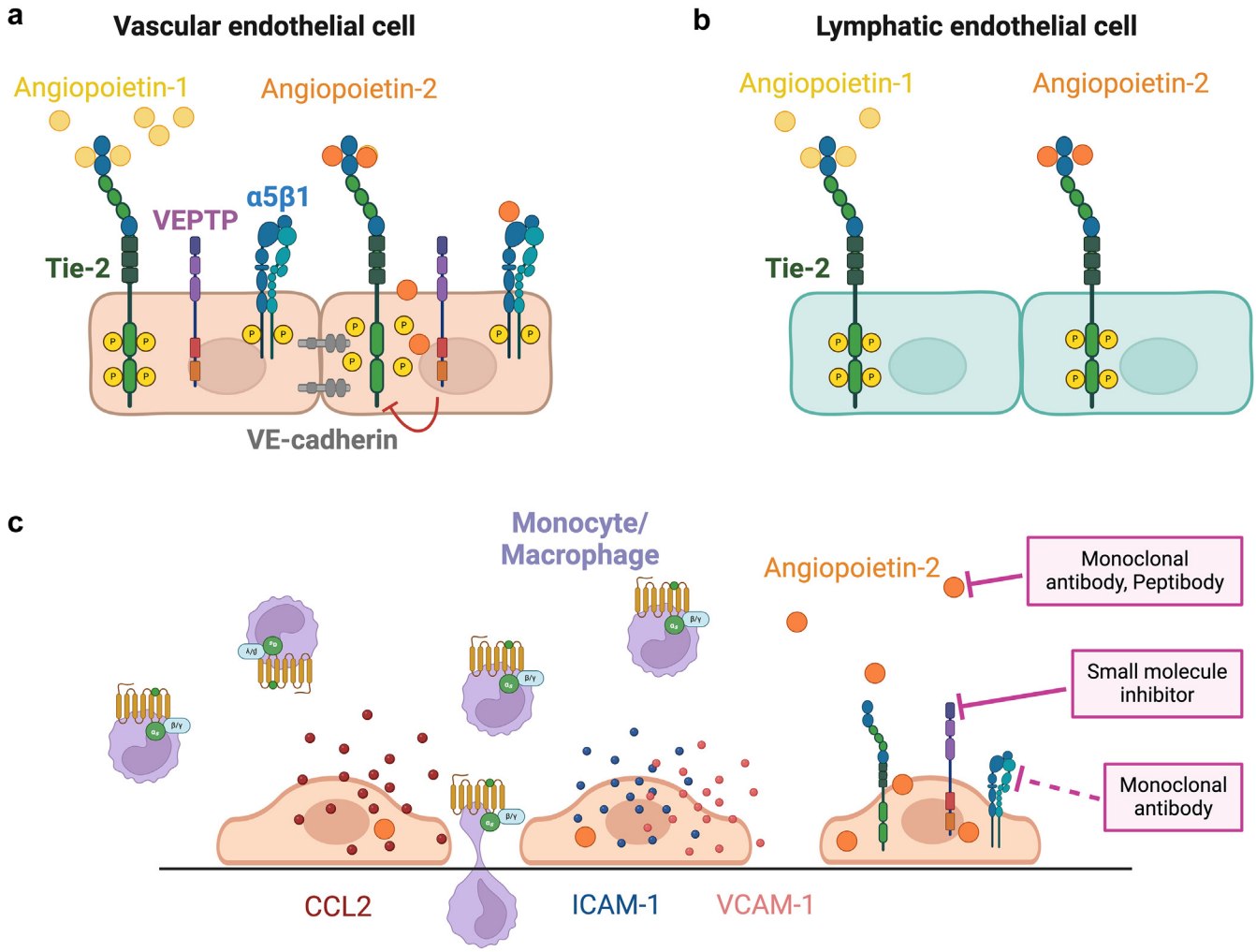

Figure 1. Scheme of angiopoietin-2 signaling and potential therapeutic targets in kidney diseases. Dysregulated angiopoietin-2 signaling is implicated in the pathogenesis of clinical scenarios, including acute kidney injury, acute kidney disease, chronic kidney disease, and other systemic conditions, such as sepsis, acute respiratory distress syndrome, cardiovascular disease, hepatic failure, and diabetes mellitus. This figure illustrates the relevant signaling pathways and potential therapeutic interventions targeting angiopoietin-2, vascular endothelial protein tyrosine phosphatase (VEPTP), and β1 integrin in kidney diseases. (a) Angiopoietin-2 signaling in vascular endothelial cells. Tie-2 is a receptor tyrosine kinase found in endothelial cells and some hematopoietic stem cells, consists of an extracellular domain for ligand binding, a transmembrane domain, and a cytoplasmic carboxy-terminal tyrosine kinase domain.[17,18] The ectodomain contains 3 Ig domains, 3 epidermal growth factor (EGF) repeats, and 3 fibronectin type III repeats, mediating angiopoietins binding. In vascular endothelial cells, angiopoietin-1 induces Tie-2 phosphorylation, which is antagonized by angiopoietin-2. This antagonistic activity is regulated by the Tie-2 phosphatase, VEPTP. In addition, angiopoietin-2 influences cell-cell junctions and endothelial cell integrity through Tie-2-independent mechanisms. Integrins are αβ heterodimeric receptors, and angiopoietin-2 has been shown to activate β1 integrin, leading to endothelial destabilization. (b) Angiopoietin-2 signaling in lymphatic endothelial cells. In the absence of VEPTP, angiopoietin-2 functions as an agonist of the Tie-2 receptor in lymphatic endothelial cells. (c) Endothelial cell activation and inflammation mediated by angiopoietin-2. The proinflammatory effects of angiopoietin-2 depend on the presence of various cytokines, such as vascular endothelial growth factor and tumor necrosis factor-α. Under the influence of these cytokines, angiopoietin-2 mediates the expression of adhesion molecules intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells, promoting monocyte/macrophage infiltration. In addition, angiopoietin-2-sensitized endothelial cells increase the expression of chemokines, such as chemokine C-C motif ligand 2 (CCL2), further facilitating monocyte/macrophage infiltration. Clinical trials targeting angiopoietin-2, through direct inhibition of angiopoietin-2 or indirect inhibition of VEPTP or β1 integrin, represent a promising approach for therapeutic intervention. VE-cadherin, vascular endothelial cadherin.

angiopoietin-2 levels correlate with higher left ventricular mass index and left ventricular hypertrophy, indicators of cardiac dysfunction.[31] Increased circulating angiopoietin-2 levels are also associated with coronary artery disease, peripheral arterial disease, and arterial stiffness in patients with CKD and kidney failure.[32,33,57] In addition, patients with kidney failure and concurrent atrial fibrillation exhibit elevated plasma angiopoietin-2 levels, linked to underlying inflammation, oxidative stress, thromboembolic events, and endothelial

Table 1. Diseases associated with disturbed angiopoietins/Tie-2 signaling

	angiopietin-1[a]	angiopietin-2	angiopietin-2/1 ratio	soluble Tie-2
Acute kidney injury in associated clinical conditions				
Critical illness	Lower[19,20]	Higher[19-22]	Higher[19-21]	Lower[20]
AMI	No difference[23]	Higher[23]		No difference[23]
Post-cardiac surgery	No difference[24]	Higher[24,25]		No difference[24]
COVID-19	No difference[26]	Higher[26]	No difference[26]	
Liver cirrhosis		Higher (mortality, AKIN stage, need for RRT)[27]		
Chronic kidney disease and outcomes				
Kidney outcome		Higher[13,28-30]	Higher[13]	
CV disease	Lower[31]	Higher[31-35]	Higher[31]	
mortality		Higher[13,35-37]		
Albuminuria				
		Higher[38-42]		

AKIN, Acute Kidney Injury Network; AMI, acute myocardial infarction; COVID-19, coronavirus disease 2019; CV, cardiovascular; RRT, renal replacement therapy.
[a]Plasma or serum angiogenic growth factors were measured by enzyme-linked immunosorbent assay.

dysfunction.[34] In patients with CKD, especially those with an estimated glomerular filtration rate < 60 ml/min per 1.73 m^2, cardiovascular disease is the leading cause of morbidity and mortality.[58] The multifactorial pathogenesis of cardiovascular disease in CKD, with endothelial dysfunction playing a cardinal role in the mechanisms of atherosclerosis, inflammation, and proteinuria, is well-established.[59] Numerous studies propose an association between circulating angiopoietin-2 levels and angiopoietin-2-to-angiopoietin-1 ratios, and their independent impact on CKD progression, cardiovascular outcomes, and mortality in CKD after adjusting for kidney function, age, and other endothelial biomarkers.[13,28,29,33,35-37] In preclinical models, angiopoietin-2 inhibition attenuates arterial stiffness and kidney fibrosis, suggesting that clinical trials of angiopoietin-2 neutralization should be the next step in CKD.[33,60]

Albuminuria: Implications for Molecular Mechanisms

Albuminuria is the primary clinical indicator of diabetic kidney disease and is pivotal in both its initiation and progression. Notably, albuminuria also predicts cardiovascular prognosis in the general population.[38,61] Endothelial dysfunction leads to increased vascular permeability and glomerular albumin leakage, defining the clinical hallmark of albuminuria. Research links circulating angiopoietin-2 with albuminuria and inflammation in CKD, with elevated serum angiopoietin-2 independently associated with new-onset microalbuminuria in type 1 and type 2 diabetes.[38-40] A murine model of immune-mediated glomerulonephritis showed upregulation of glomerular angiopoietin-2 and angiopoietin-2-to-angiopoietin-1 ratios accompanying the loss of glomerular capillaries. In addition, podocyte-specific overexpression of *Angpt2* induces albuminuria and glomerular endothelial apoptosis.[62,63] Diminished podocyte protein nephrin and VEGF-A expression within this model highlight the molecular mechanism in proteinuric diseases, emphasizing the significance of angiopoietins/Tie-2 signaling in maintaining the glomerular filtration barrier.

A *post hoc* analysis of the CREDENCE trial revealed higher plasma angiopoietin-2 levels in diabetic kidney disease associated with adverse outcomes, including primary composite outcomes, kidney composite outcomes, and all-cause mortality. Interestingly, treatment with the sodium-glucose cotransporter-2 inhibitor, canagliflozin, seemed to lower angiopoietin-2 levels, contributing to the 10% protective effect on the primary composite outcome.[41] Beyond activating tubuloglomerular feedback, proposed mechanisms contributing to the protective effects of sodium-glucose cotransporter-2 inhibitors include optimization of energy utilization, promotion of cellular renewal, attenuation of sympathetic tone, and improvement of vascular function.[64] Endothelial protection through inhibition of angiopoietin-2 by canagliflozin may explain the beneficial effects on endothelial dysfunction from sodium-glucose cotransporter-2 inhibitors, suggesting that angiopoietin-2 might be a mediator and reinforcing the promising potential of angiopoietin-2-targeting therapy.

The Pathophysiological Roles of Angiopoietin-2 Learnt from the Laboratory

Angiopoietin-2 and Endothelial Activation

The vascular structure comprises diverse cell types, including endothelial cells, perivascular pericytes, and surrounding connective tissue. Endothelial cells serve as a physical barrier that regulates vascular permeability and angiogenesis. Angiopoietin-1 induces Tie-2 phosphorylation, activating downstream Akt/phosphoinositide 3-kinase and endothelial nitric oxide

synthase, ensuring endothelial survival and vascular stability. In addition, Tie-2 activation inhibits nuclear factor kappa B signaling, thereby reducing leukocyte recruitment and mitigating inflammation.

In situations of inflammation and hypoxia, activated endothelial cells release angiopoietin-2, thereby mediating endothelial cell migration, inflammation, and increased cell permeability.[16] In the presence of endotheliotropic cytokines such as VEGF and tumor necrosis factor-α, activated endothelial cells proliferate and migrate, initiating the angiogenic cascade.[65,66] This is demonstrated by increased placental angiopoietin-2 expression in the first trimester of normal pregnancy, facilitating vascular remodeling to meet the heightened metabolic demands of the placenta.[67,68] Endothelial activation and proliferation are also observed in the early phase of kidney fibrosis, potentially mediated by angiopoietin-2.[69,70]

In the absence of survival signals and endotheliotropic cytokines, angiopoietin-2-activated endothelial cells undergo apoptosis and vascular disintegration.[9,66,71] A previous study demonstrated that angiopoietin-2 promotes apoptosis of hyaloid vascular endothelial cells in the presence of Wnt ligands from resident macrophages. Angiopoietin-2 stimulates macrophage Wnt7b signaling, which induces cell cycle entry of endothelial cells, while simultaneously inhibiting endothelial survival signals, leading to endothelial apoptosis and vascular regression.[72] In advanced kidney fibrosis, activated Wnt and angiopoietin-2 signaling in fibrotic kidneys causes endothelial apoptosis without the survival signal from angiopoietin-1.[13] Dysregulated angiopoietin-2 may autocrinally drive endothelial phenotype from quiescent to activated, leading to the perspective of targeting activated endothelium by angiopoietin-2 inhibition in kidney diseases.

Context-Dependent Agonist and Antagonist Role of Angiopoietin-2

Angiopoietin-2 plays a significant role in both angiogenesis and lymphatic vascular development. During the early stages of mouse fetal and neonatal development, angiopoietin-2 is expressed in endothelial cells of lymphatic sacs and vessels, which express lymphatic vessel endothelial hyaluronan receptor 1 or prospero homeobox 1. The absence of angiopoietin-2 results in impaired embryonic lymphangiogenesis, leading to conditions such as lymphedema and chylous ascites.[73] Mice lacking angiopoietin-2 display dysfunction in both large and small lymphatic vessels, which can be rescued by angiopoietin-1 replacement. These findings suggest that angiopoietin-2 acts as an agonist, rather than an antagonist, of lymphatic endothelial Tie-2 receptors.[74] This indicates a potential therapeutic application for angiopoietin-2 inhibition in inflammatory lymphangiogenesis, such as cancer metastases and transplant rejection.[75]

The context-dependent role of angiopoietin-2 is also influenced by the presence of a Tie-2 phosphatase, VEPTP (also known as PTPRβ), which downregulates Tie-2 by dephosphorylating the intracellular domain (Figure 1a). VEPTP is expressed in $CD31^+$ cells but not in prospero homeobox 1^+ cells, indicating its absence in the lymphatic endothelium. A strategy that combines VEPTP inhibition with angiopoietin-2 stimulation can restore the agonistic function of angiopoietin-2 on Tie-2 receptors in vascular endothelial cells.[76] In the presence of VEPTP, increased angiopoietin-2-to-angiopoietin-1 ratios cause Tie-2 inactivation and vascular destabilization, resulting in increased vascular permeability and inflammation. Paradoxically, in the absence of VEPTP in the lymphatic endothelium, angiopoietin-2 acts as a potent agonist of Tie-2 (Figure 1b). A randomized trial in diabetic macular edema evaluating the effects of AKB-9778, a small molecule inhibitor of VEPTP, showed benefits when combined with VEGF suppression, possibly through Tie-2 activation and enhanced vascular stability.[77] Although preclinical models have shown renal protective effects from the genetic deletion of VEPTP in ischemic and diabetic injury, VEPTP inhibition provides another therapeutic strategy by manipulating angiopoietins/Tie-2 signaling in kidney diseases.[78,79]

Angiopoietin-2, Integrin and Cellular Integrity

Endothelial barrier function relies on cell-cell junctions and intracellular signaling pathways, with Tie-2 phosphorylation and activation being crucial elements (Figure 1a). Dysfunction in these mechanisms can result in vascular leakage, inflammatory diseases, and abnormal angiogenesis. Notably, transgenic overexpression of angiopoietin-2 disrupts vascular formation more significantly than Tie-2 or angiopoietin-1 inhibition, suggesting that angiopoietin-2 involves additional signaling pathways.[9] Angiopoietin-2 influences cell-cell junctions through both Tie-2-dependent and Tie-2-independent mechanisms. Integrins, αβ heterodimeric receptors, anchor endothelial cells to the extracellular matrix and are essential for maintaining endothelial barrier function.[80,81] Heterodimers of integrin α5 and β1, abundant in activated and angiogenic endothelial cells, serve as major receptors for fibronectin, regulating cell adhesion and extracellular matrix deposition. Models of tumor metastases have revealed that blocking angiopoietin-2 improves endothelial cell-cell junctions, enhances endothelial integrity, and reduces metastatic

dissemination.[82] Unlike angiopoietin-1, angiopoietin-2 activates β1 integrin, leading to cytoskeletal rearrangement and endothelial destabilization (Figure 1a and c).[83] Angiopoietin-2 can directly compromise endothelial cell integrity by activating the β1 integrin pathway independent of Tie-2 receptor signaling. Inhibiting β1 integrin improves endothelial integrity in lipopolysaccharide-induced endotoxemia through angiopoietin-2-mediated β1 integrin activation.[83,84] Nevertheless, *in vitro* studies showed that *TIE-2* knockdown reduces endothelial *CCL2* expression, not integrin knockdown.[13] Further research is necessary to comprehensively elucidate the interplay between these pathways and explore their therapeutic implications in kidney diseases characterized by disrupted endothelial cell junctions and vascular dysfunction.

Angiopoietin-2 and Inflammation

Angiopoietin-2 levels are elevated in several inflammatory diseases, including sepsis, diabetes mellitus, atherosclerosis, metabolic syndrome, and autoimmune vasculitis.[22,32,38,49,85-88] The proinflammatory effect of angiopoietin-2 is context-dependent, influenced by cytokines, including VEGF, tumor necrosis factor-α, histamine, and bradykinin.[65,89] Under inflammatory stimuli, angiopoietin-2 mediates the expression of adhesion molecules such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in sensitized endothelial cells, highlighting its role in modulating endothelial phenotype and responsiveness (Figure 1c).[66]

In acute inflammation and chronic phase post myocardial infarction, angiopoietin-2 elicits myeloid cell infiltration through β2 and α5β1 integrins.[90,91] Phosphorylation of the vascular endothelial (VE)-cadherin/β-catenin complex, induced by VEGF/VEGF receptor 2 and Src signaling, compromises endothelial integrity, promotes vascular leakage, and facilitates leukocyte migration and extravasation. Conversely, angiopoietin-1 rescues VEGF-induced vascular permeability and plasma leakage by reducing serine 665 phosphorylation of VE-cadherin, preventing Src activation, and maintaining endothelial integrity.[8,92-95] In addition, the association between VEPTP and the Tie-2 receptor stabilizes VE-cadherin and endothelial barrier integrity in vascular endothelial cells.[96] It is reasonable to speculate that angiopoietin-2 contributes to increased vascular permeability and plasma leakage by antagonizing angiopoietin-1 in vascular endothelial cells. However, angiopoietin-2 inhibition blocks tyrosine residue phosphorylation of VE-cadherin and causes defective junctions in lymphatic endothelial cells.[97] Investigating the mechanisms involving angiopoietin-2 and endothelial adherens junction VE-cadherin in vascular permeability and inflammation is essential.

Our studies show that angiopoietin-2 stimulates endothelial chemokines and adhesion molecules, increasing macrophage infiltration in the aorta of mice after subtotal nephrectomy (Figure 1c).[33] Angiopoietin-2 inhibition, through angiopoietin-1 overexpression or a peptide-Fc fusion inhibitor L1-10, attenuates kidney fibrosis in murine models of unilateral ureteral obstruction and unilateral ischemia–reperfusion injury. Angiopoietin-2 inhibition also leads to reduced macrophage infiltration, microvascular rarefaction, and vascular endothelial cell apoptosis in injured kidneys. By inhibiting angiopoietin-2, the expression of chemokine C-C motif ligand 2 is reduced in kidney endothelial cells, indicating a shift toward an antiinflammatory endothelial phenotype (Figure 1c).[13] Another factor is the involvement of Tie-2-expressing monocytes/macrophages, a subpopulation of tumor-associated macrophages critical in tumor-associated inflammation. Endothelial angiopoietin-2 stimulates proangiogenic growth factors from Tie-2-expressing monocytes/macrophages, enhancing angiogenesis in tumor progression.[98] Research on Tie-2-expressing monocytes/macrophages in kidney diseases and inflammation is still lacking. These findings underscore the therapeutic potential of angiopoietin-2 inhibition in various inflammatory kidney diseases.

Angiopoietin-2 and Angiotensin II (Ang II)

Ang II, a primary effector of the renin-angiotensin-aldosterone system, critically influences vascular remodeling and angiogenesis. Acting through not only its type 1 receptor but also through the type 2 receptor, Ang II induces angiogenic growth factors, including VEGF and angiopoietin-2, in various experimental models.[99-103] Ang II stimulates VEGF release from glomeruli and retina, exacerbating conditions such as diabetic nephropathy and diabetic retinopathy.[104-108] In bovine retinal endothelial cells, Ang II induces angiopoietin-2 expression independently of VEGF via protein kinase C and mitogen-activated protein kinase pathways, contributing to angiogenesis.[100] These effects may lead to glomerular cell proliferation, potentially playing a role in the progression of kidney diseases. Aside from the widely used AT1 receptor antagonists, the Reno protective effects of renin-angiotensin-aldosterone system inhibition should involve nonhemodynamic mechanisms, engaging separate angiopoietin-2/Tie-2 and VEGF receptor signaling pathways.

Conclusions and Perspectives

Angiopoietin-2 has emerged as a significant biomarker and therapeutic target in kidney diseases. Laboratory experiments have elucidated its involvement in angiogenesis, context-dependent agonist and antagonist functions, cellular integrity, and inflammation, thereby highlighting its complexity in kidney pathology. Understanding the interactions between angiopoietin-2 and endothelial factors, including integrins, VE-cadherin, and VEGF, is essential for addressing vascular permeability and inflammation in kidney diseases.

Elevated angiopoietin-2 levels are consistently linked to endothelial dysfunction, inflammation, and vascular instability, contributing to the progression and severity of AKI, CKD, and albuminuria. The therapeutic potential of angiopoietin-2 inhibition offers a promising avenue for improving kidney health and outcomes. Future research should focus on clinical trials to validate the efficacy of anti–angiopoietin-2 therapies, explore personalized medicine approaches, and further elucidate the molecular mechanisms underlying angiopoietin-2's role in kidney disease pathogenesis. These efforts could lead to innovative treatments targeting the vascular dysfunction and inflammatory components of kidney diseases, ultimately enhancing patient care and prognosis.

DISCLOSURE

All the authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

AJL and SLL collected the references and drafted the manuscript. FCC and SLL provided the funding for the study. FCC contributed to the general improvement of the writing, and critically revised the manuscript. All the authors have seen and approved the final version of the manuscript being submitted.

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