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The role of CD146 in renal disease: from experimental nephropathy to clinics

Louis Boutin^{1,2,3} · Elena Roger^{3,4} · Etienne Gayat^{1,2} · François Depret^{1,2} · Marcel Blot-Chabaud⁵ · Christos E. Chadjichristos^{3,4}

Abstract

Vascular endothelial dysfunction is a major risk factor in the development of renal diseases. Recent studies pointed out a major interest for the inter-endothelial junction protein CD146, as its expression is modulated during renal injury. Indeed, some complex mechanisms involving this adhesion molecule and its multiple ligands are observed in a large number of renal diseases in fundamental or clinical research. The purpose of this review is to summarize the most recent literature on the role of CD146 in renal pathophysiology, from experimental nephropathy to clinical trials.

Keywords CD146/MCAM · Clinical studies · Experimental nephropathy

Introduction

Renal injury is a complex pathological process involving all renal compartments (endothelial, glomerular, tubule-interstitial), leading to cell remodeling and further tissue fibrosis. During this process, endothelium plays a major role in facilitating interactions between bloodstream content and damaged tissue. Indeed, renal endothelium becomes dysfunctional contributing thus to renal structural and functional alterations. CD146 is an immunoglobulin protein expressed mainly in the vascular system and may interact with several ligands during injury. Furthermore, after

renal impairment, CD146 appears to be involved in renal endothelial activation, thus promoting tissue alterations. The aim of this review is to summarize the literature content focusing on endothelial activation and CD146 implication during renal damage.

The renal endothelium: structure and functions

Oxygen and nutriment delivery to each organ are key elements in human physiology and they are regulated by the vascular system, which is composed of multiple types of cells supporting a specific function [1]. The complexity of kidney function relies on multiple anatomical and/or functional entities [2], composed by among others, of specific endothelial cells (from glomerular endothelium, microvascular peritubular endothelium, or large vessels endothelium) with a metabolic diversity to respond to aggression or modification of the local environment [3, 4]. During renal structural or functional damages, kidney endothelial cells are implicated in vaso-modulation, inflammatory response, cell adhesion, and coagulation [5, 6] until a breakpoint where endothelial cells are failing, causing dissociation of mural pericyte creating oedema and tissue hypoxia [7]. Furthermore, endothelial activation promotes endothelial-to-mesenchymal transition (endoMT) contributing to kidney fibrosis [8, 9].

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The kidney is composed of multiple anatomical entities associated with specific endothelial cell phenotypes exposed to different microenvironments (vascular pressure, osmolarity, hypoxia) [10–12].

The vasculature of the kidney is shown in Fig. 1 and is composed of:

- Afferent and efferent arterioles regulating the glomerular blood flow and glomerular filtration rate (GFR) [13]
- Highly fenestrated glomerular capillaries, enabling ultrafiltration of low molecular weight solutes composing the glomerular tuft [14]
- Cortical peritubular capillary network, implicated in tubular reabsorption (water, ions and nutrients, drug metabolites, urine acidification) [15–19]
- Descending vasa recta, interconnected with ascending vasa recta via capillaries involved in osmolarity regulation via cortico-papillary gradient [20]
- A venous network draining into vena cava

In pathological conditions, endothelial cells play a key role in response to aggression and are associated with phenotypic changes [21] leading to various functions:

- Regulation of vascular constriction via vasoactive factors such as endothelin-1, prostacyclin or nitric oxide (NO) [22]

- Regulation of vascular coagulation via thrombotic regulators (von Willebrand factor (vWF), tissue factor (TF), plasminogen activators and plasminogen activator inhibitor 1 (PAI1)) [23]
- Regulation of cell infiltration via impairing endothelial permeability shedding of the glycocalyx, resulting in increased exposure of cell adhesion molecules (CAMs) such as platelet endothelial cell adhesion molecule (PECAM1), intercellular cell adhesion molecules 1 and 2 (ICAM1 and ICAM2) and Vascular cell adhesion molecule-1 (VCAM1) [24]
- Regulation of inflammation via secretion of proinflammatory modulators (chemokines, activation of P-Selectin or E-selectin facilitating diapedesis) [25]
- Tissue remodeling, mesangial proliferation, renal fibrosis induction via specific protease-activated receptor [26–29]

CD146: isoforms and functions

Endothelium requires intercellular junctions to induce regulation mechanisms via adherent junctions (cells adherence to endothelium) and tight junctions (interactions with cytoskeleton, implicated in permeability and cell polarity [30–33]. CD146 is a 113-KDa transmembrane glycoprotein expressed mainly in the vascular system [34]. It is also known

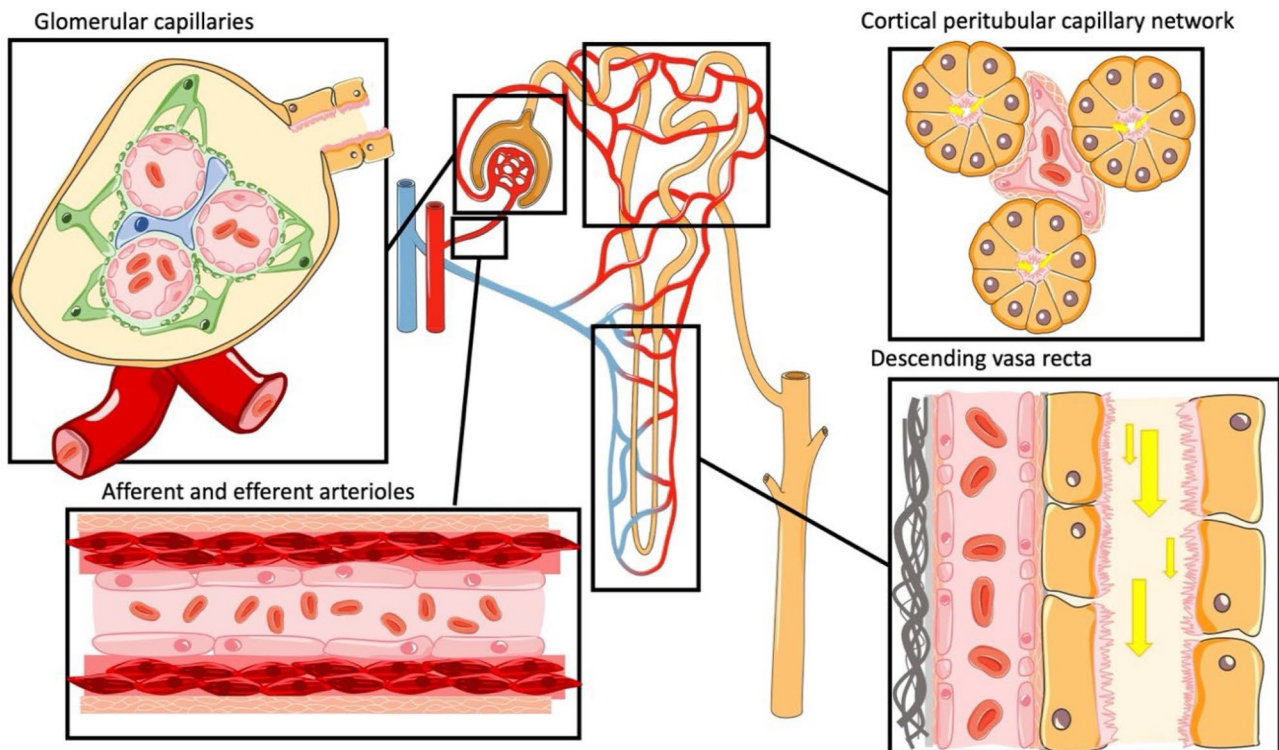


Fig. 1 Variability of endothelial cells implicated in kidney physiology

as MUC18, melanoma cell adhesion molecule (MCAM or MelCAM), and HEMCAM. CD146 belongs to the immunoglobulin superfamily and is highly glycosylated, that depends on the pathophysiological context and modifies its stability, and shares similarities with adhesion molecules [35].

CD146 structure

To date, three different forms of CD146 have been reported (Fig. 2):

-Two transmembrane isoforms, composed of an Ig-like extracellular domain, a hydrophobic transmembrane region, and cytoplasmic tail [36] with a long cytoplasmic tail (long isoform) and a short cytoplasmic tail (short isoform) [35–37]. For the long isoform, which is the more expressed; the cytoplasmic domain is composed of protein kinase C (PKC) site recognition, an ERM binding site allowing interaction with the plasma membrane via actin protein and ERM binding proteins (Erzin, Raxidin, and Moesin), a motif with microvilli extension, and a motif for basolateral targeting [36]. The cytoplasmic domain of the short isoform is composed of protein kinase C (PKC) site recognition and a PDZ binding domain. CD146 can be observed as monomer or dimers interacting via a disulfide bond with cysteine residue next to the membrane [38, 39]. CD146 has been described as an intercellular junction protein due to its

high presence at the inter-endothelia junctions, but outside tight and adherent junctions. However, later studies reported that it can act both as an adherent protein, once located on the surface of endothelial cells (adhesion and interaction mechanisms), and as a junctional endothelial intercellular protein (endothelial cell interaction and vascular permeability) [40].

-The soluble form of CD146 (sCD146), generated by the proteolytic cleavage of the membrane isoforms, [41–43] which is detected in cell culture supernatants, serum, and interstitial fluids [44–46]. This soluble form does not seem to be involved in adhesion in the absence of a transmembrane or cytoplasmic motif [35, 37].

Localization and partners

Even if CD146 has been mainly described as an endothelial-specific marker, few studies reported its expression in other cell types such as pericytes, smooth muscle cells, epithelia, fibroblasts, mesenchymal stem cells, and lymphocytes [36]. In physiological conditions, CD146 has few adhesive implications compared to other CAMs [47] but its expression increases during development or in proliferating conditions. In pathological conditions, CD146 is upregulated and has been identified as a reliable marker for specific tumors

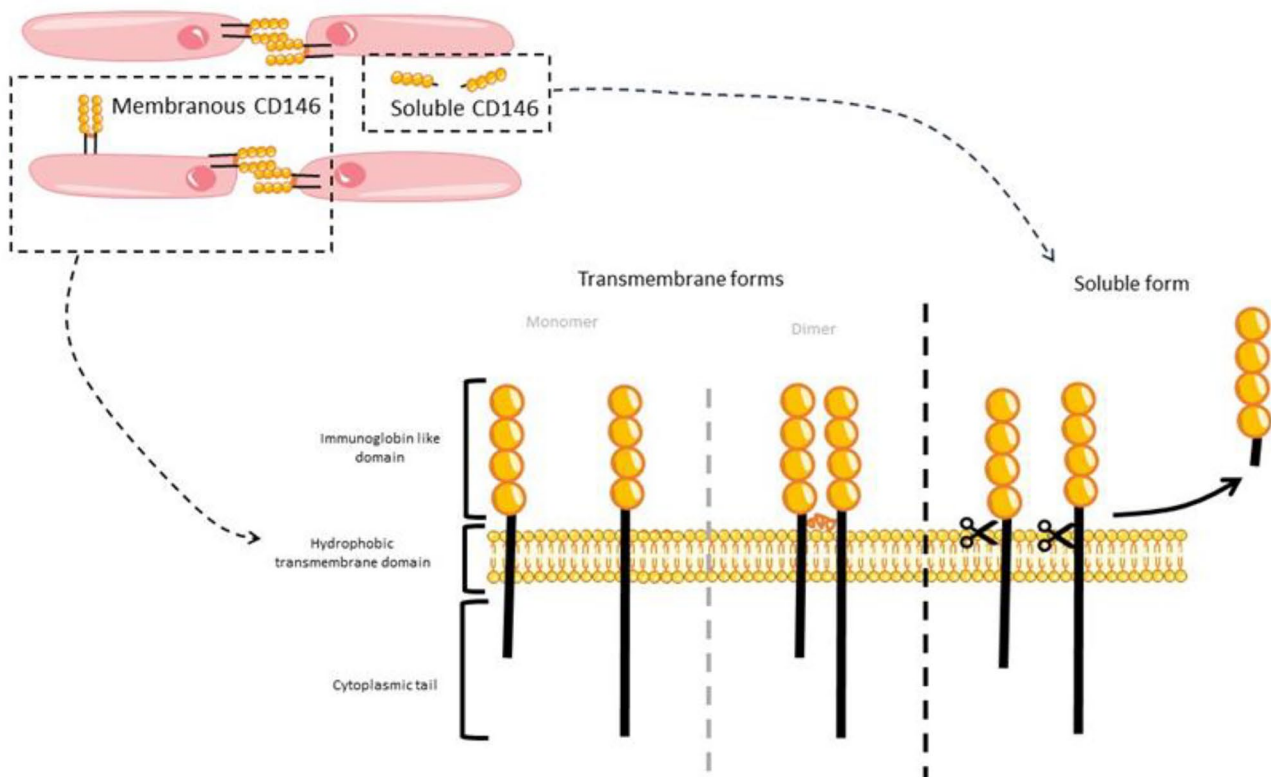


Fig. 2 The three CD146 forms

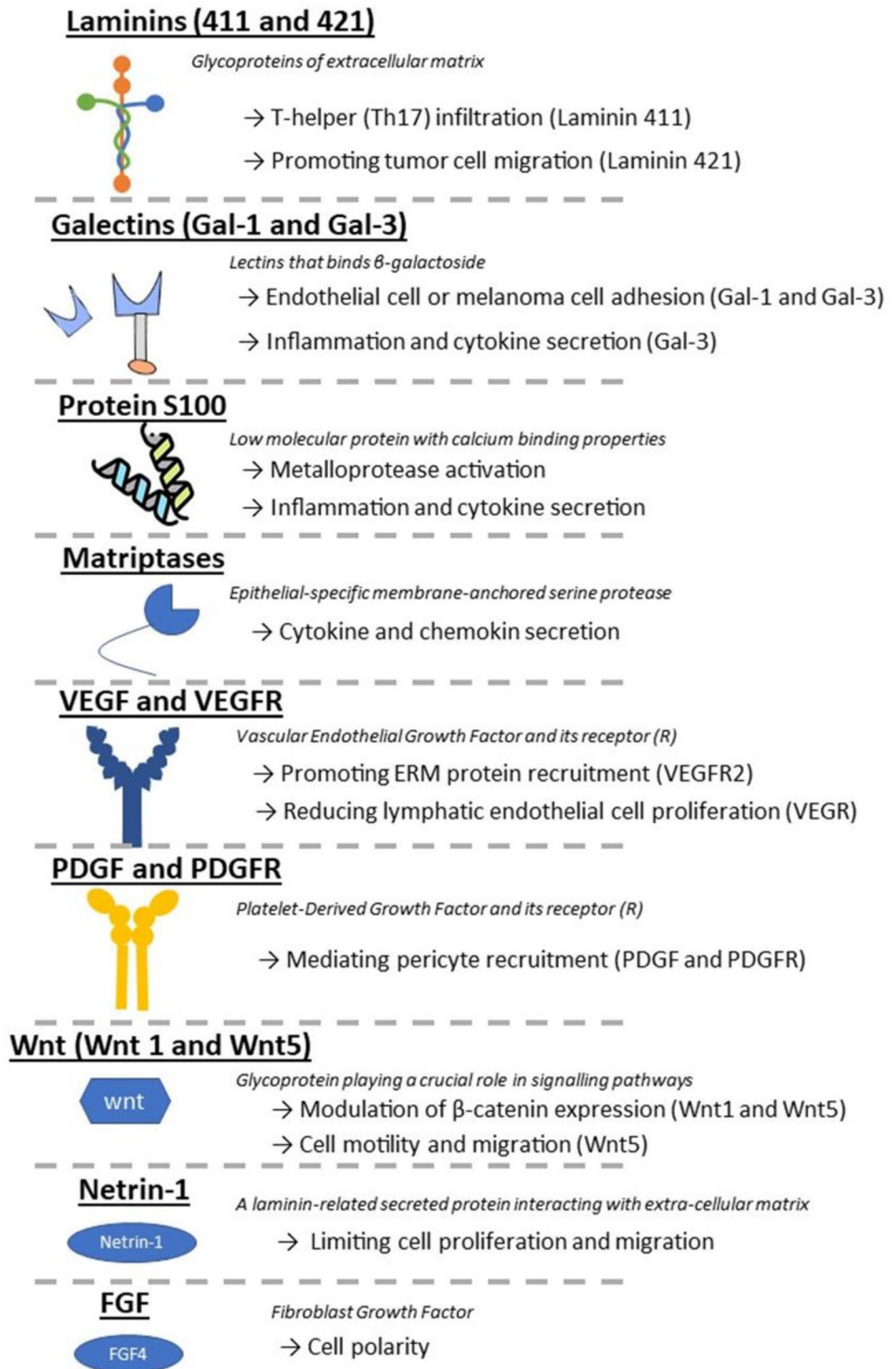
or specific organ pathology via multiple ligands (Fig. 3). The most important are listed below:

- Laminins 411 and 421: membranous heterodimer [48, 49] implicated in remodeling of the extracellular matrix and expressed along the vascular endothelium [50, 51].

Laminin 411 has been identified as a ligand for CD146 on T-helper 17 (Th17) cells [52], promoting Th17 lymphocyte infiltration. Laminin 421 is a ligand for CD146 in melanoma promoting tumor cell migration [53, 54].

- Galectins 1 and 3: As CD146 is a highly glycosylated junctional CAM [36], the galactose residues bind

Fig. 3 Ligands of CD146



with galectins, a soluble carbohydrate-binding lectins family, modulating cell-to-cell, cell-to-extracellular membrane adhesions, angiogenesis, and tumoral proliferation [55–59]. Some studies identified that Gal-1 interacts with CD146 expressed by endothelial [60] or melanoma cells [61]. Regarding interactions of CD146 with Gal-3, the pathophysiology is more complex as this galectin is involved in various processes, from cell adhesion and migration to cell activation [62, 63]. Recent studies reported that CD146 binds and co-localizes with Gal-3 to N-linked glycans, inducing CD146 dimerization and activation of protein kinase B (AKT) signaling, leading to secretion of metastasis-promoting cytokines from the endothelial cells [64–66].

- S100 proteins: they are secreted and bind with CD146 [67–71] during lung metastasis of melanoma cells, inducing reactive oxygen species formation, via NF- κ B mediated pathway, activating metalloprotease, and cytokine promoting tissue fibrosis [72, 73].
- Matriptase: this epithelial-specific membrane-anchored serine protease [74, 75] was identified as a ligand of CD146 in the brain [76]. These interactions are leading to the secretion of cytokines and chemokines via p38 and canonical Wnt/ β -catenin pathways, which were prevented when CD146 was deleted.
- VEGFR2: a class IV receptor tyrosine kinase family expressed by endothelial cells, macrophages, hematopoietic cells, and smooth muscle cells, implicated in tumor angiogenesis, and cell proliferation [77–81]. This protein interacts directly with the extracellular protein domain of CD146, promoting ERM proteins recruitment via CD146 cytoplasmic tail, leading to a specific transduction signal. Inhibition of CD146 prevented phosphorylation of VEGFR2 in human umbilical vein endothelial cells (HUVECs) [82].
- VEGF-C is implicated in lymphangiogenesis and its inhibition impairs vasculature development [83, 84]. This factor interacts with the extracellular domain of CD146, reducing the sprouting of lymphatic endothelial cells during lympho-angiogenesis [85]
- PDGF is implicated in tumor angiogenesis and lympho-angiogenesis; the interaction between CD146 with PDGF receptor mediates pericyte recruitment by secreting TGFB [86–88].
- The Wnt family: Wnt5a binds CD146 during embryogenesis, [89] leading to a downregulation of β -catenin expression mediating cell migration during development. In pathological conditions, Wnt5 and CD146 are thought to directly affect cell motility and metastasis. Wnt1 is associated with proliferative genes by the canonical β -catenin pathway. CD146 interacts with Wnt1 in fibroblasts, inducing extra-cellular membrane component production via canonical Wnt/ β -catenin pathway [90]

- Netrin-1 is implicated in cellular migration during the development of the nervous system, and its dysregulation is involved in pathological processes such as cancer and cardiovascular and kidney disease [91–95]. Netrin-1 interaction with CD146 seems to limit proliferation and migration [94].
- FGFs: the members of the fibroblast growth family are involved in several processes such as cell proliferation, survival, migration, angiogenesis, wound healing, differentiation, and endocrine secretion [96–99]. Interaction with CD146 leads to cell polarity and angiogenesis [100].

CD146 in the kidney

As mentioned above, due to its interactions with various partners, CD146 remains a significant player in organ physiopathology. The role of this junctional protein in renal disease has been reported in the last few decades. Some preclinical experimental models have been studied for this purpose. There is ample evidence in the literature that CD146 is present along the entire vascular tree (endothelial and smooth muscle cells and pericytes), regardless of vessel size or anatomical location. Under pathological conditions, tubular cells may also express CD146 at later stages of renal disease in humans and rodents.

CD146 in experimental nephropathy

CD146-positive cells are essential for kidney vasculature development. Indeed, Sefanska et al. demonstrated that CD146-positive cells will convert to endothelial cells expressing CD31 during the development of renal vasculature. In embryonic kidney organ culture, inhibiting CD146 expression prevented endothelial progenitor cells to proliferate and to differentiate into endothelial cells expressing CD31 in the development of normal vasculature [101].

In a model of renal ischemia–reperfusion (rIR), bone marrow-derived endothelial progenitor cells (EPC) and endothelial cells (EC) both contributed to endothelial repair in the kidney immediately after rIR. The numbers of circulating CD34-positive EPCs and CD146-positive ECs, decreased 1 h after rIR and increased at 35 and 73 days. This increase contributed to endothelial repair after rIR [102].

In another study, Bruno et al. observed that human glomeruli deprived of the Bowman’s capsule contained a population of CD133-positive/CD146-positive cells and a population of CD133-negative/CD146-positive cells, expressing mesenchymal stem cell markers. The CD133-positive/CD146-positive cells co-expressed endothelial markers, such as CD31/PECAM1 and von Willebrand factor (vWF), but were CD24-negative, suggesting an

endothelial commitment. The glomerular mesenchymal CD133 negative/CD146 positive population exhibited self-renewal capacity and was able to differentiate into endothelial cells and epithelial cells, expressing podocyte markers such as nephrin, podocin, and synaptopodin. This study revealed that CD146 was associated with endothelial and epithelial differentiation [103]. Moreover, CD146 modulates intercellular permeability as a junctional endothelial protein, as its overexpression correlates with a more cohesive vessel monolayer. Indeed, CD146-deficient mice showed reduced permeability, which was associated with decreased expression of VEGFR2, CD31/PECAM-1, and VE-cadherin [40].

In experimental focal segmental glomerulosclerosis, native renin lineage cells decreased, whereas newly marked renin lineage cells were increasing and surrounded by vessels expressing CD146 suggesting a role of this junctional protein in the modulation of renin pericyte regeneration after kidney damage [104]. CD146-expressing pericytes were also identified to be localized next to renin-expressing pericytes, surrounded by juxtaglomerular and afferent arterioles. CD146 + /CD34 - /CD45 - /CD56 - renal fetal pericytes, exhibited mesodermal differentiation *in vitro* confirming the potential role of CD146 in glomerular endothelial regeneration [101].

In another experimental model of nephrotoxic serum-induced glomerulonephritis (NTS-GN), CD146 expression was highly increased within glomerular endothelium and tubulointerstitial capillaries, since the early stages of the disease. CD146 increased expression in glomerular capillaries promoted monocyte adhesion and damage and was associated with the decline of renal function. The deletion of CD146 protected mice from glomerular and further renal inflammation, but vascular permeability after NTS injection was similar between WT and CD146 knockout mice (CD146^{-/-}). Interestingly, similar to CD146^{-/-} mice, endothelial-specific deletion of CD146, improved renal function and limited glomerular crescents and tubular dilatation, which are typical structural damages described of the NTS-GN, illustrating the major role of endothelial cells in controlling glomerular damage but also interstitial inflammation [105].

Regarding the role of CD146 in experimental diabetic nephropathy, Li et al. identified in 2021 that Wnt5a signaling was associated with the progression of the disease. In Db/Db mice and high glucose-treated HK-2 cells, the inhibition of CD146 or Wnt5a significantly reduced the inflammatory process. The authors identified direct interactions of Wnt5a with CD146 to activate noncanonical Wnt signaling in HK-2 cells [106]. Furthermore, in previous studies using these cells, both membrane and intracellular expression of CD146 were significantly increased upon high glucose treatment. More precisely, a soluble form of CD146, sCD146,

was detected in the supernatant of HK-2 cells in the no glucose group, which was significantly elevated in the high glucose group, suggesting that high glucose upregulates both CD146 expression and sCD146 secretion in tubular epithelial cells [107]. Finally, Bueno et al., found that IGFBP-4 activated the Wnt/ β -catenin signaling pathway and induced CD146 expression in human renal cell carcinoma [108].

Tissue fibrosis is one of the major issues of chronic kidney disease. CD146 was associated with endothelial-to-mesenchymal transition (endoMT), a complex biological process in which endothelial cells lose their specific markers and acquire a mesenchymal or myofibroblast phenotype expression with α -smooth muscle actin (α -SMA) and type I collagen [109]. Roeder et al. identified in mouse kidneys with advanced age (27 months old) an increased CD146 expression associated with fibrosis markers such as type IV collagen and heparan sulfate proteoglycan in Bowman's capsules of aged glomeruli. In addition, Stasi et al. observed that the positive pericyte-to-myofibroblast transdifferentiating early markers of fibrosis PDGFR- β and α -SMA were associated with increased expression of CD146 after rIR [110]. Finally, Zhao et al. also described the potential interaction between endothelial cells and tubular cells involving CD146, suggesting that peritubular endothelial cells could contribute to kidney fibrosis through endoMT. After 2 days of cultures with VEGF and co-cultured with mouse proximal tubule, 95% of cells expressed CD146 [111].

CD146 in clinical studies

As summarized above, preclinical experimental models identified an important role of CD146 in renal pathophysiology, suggesting that this junctional protein is a potential marker and actor of the renal response to injury. Consequently, some clinical studies evaluated CD146 at the patient's bedside.

In diabetic nephropathy (DN), Wang et al. identified in 2012 that sCD146 and P-selectin were significantly increased in the plasma of patients with type 2 diabetes and were both associated with microalbuminuria compared with healthy controls. Moreover, sCD146 and P-selectin plasma levels progressively rise, with significant renal failure and severity [107]. This was confirmed by Fan et al., showing that sCD146 was upregulated and associated with renal dysfunction in DN; moreover, it was a better marker than urine albumin creatinine ratio to evaluate disease severity in these patients. Concerning tissue CD146, its expression was co-localized with the endothelial marker CD31 within injured kidneys, was increased in DN, and was correlated with the severity of the disease. Both soluble and tissue CD146 were correlated with renal outcome and mortality [112]. In 2021, in a translational study, both the expression of Wnt5a and CD146 in the kidney and sCD146 levels in

plasma and urines increased in patients with DN and were correlated with the inflammatory process and progression of renal impairment [106].

In biopsies from patients with IgA nephropathy, Ji et al. identified that CD146 was mainly expressed in renal tubular epithelial cells, in the endothelial cells of peritubular capillaries and smooth muscle cells, and this expression was correlated with 24-h proteinuria, serum creatinine, index of glomerulosclerosis, and the degree of interstitial fibrosis [113]. CD146 expression appears to switch from endothelial cells to epithelial cells in glomeruli and proximal tubules in these clinical studies. This underlying mechanism may be triggered by inflammatory mediators, growth factors, and signaling pathways associated with kidney injury and inflammation.

In patients with metastatic renal cell cancer (RCC), Feng et al. identified that the mean value of CD146 expression in the renal tumor was significantly higher than in those with localized RCC or in controls. Among patients with localized RCC, CD146 expression was higher in patients with recurrences [114]. A panel of genes consistently upregulated by renal cell cancer tumor blood vessels was screened by Wragg et al. CD146 and Laminin- α 4 were highly expressed in an immunological analysis and were both predictors of poor survival outcomes. These data were confirmed by immunohistochemical analysis of CD146 and Laminin- α 4, showing their expression to be highly specific to RCC and colorectal carcinoma blood vessels [115].

In a population of patients with kidney transplants and coronary artery disease, Malyszko et al. identified that CD146 was correlated with endothelial immune cell adhesion, renal dysfunction, and inflammation processes. Moreover, CD146 tended to be associated with elevated plasma creatinine after transplantation [116]. Karbowska et al. also showed that sCD146 was increased in kidney transplanted patients [117]. Similar studies by Boratynska et al., in 100 patients with allograft and a stable renal function (estimated glomerular filtration rate (eGFR)), confirmed that plasma sCD146 was increased and was correlated with hyperuricemia and serum creatinine concentrations [118]. Finally, Liao et al. reported that the prediction performance of sCD146 was better than eGFR for acute rejection in kidney transplantation [119].

Concerning patients with chronic kidney disease (CKD), Bardin et al. identify that sCD146 plasma levels were higher in subjects with chronic renal failure. This increase was associated with an increase in endothelial expression of CD146 in kidney biopsies from these patients. Modifications of its basal levels could reflect alterations of junctional functions such as vascular permeability [41]. Daniel et al. confirmed the CD146 staining on endothelial cells in normal kidneys, but also on smooth muscle cells and mesangial cells, but not in tubular cells. When endocapillary proliferation was observed, the mesangial CD146 expression was higher and was correlated with proteinuria. A de novo expression of CD146 on tubular cells was found in 53 patients and this

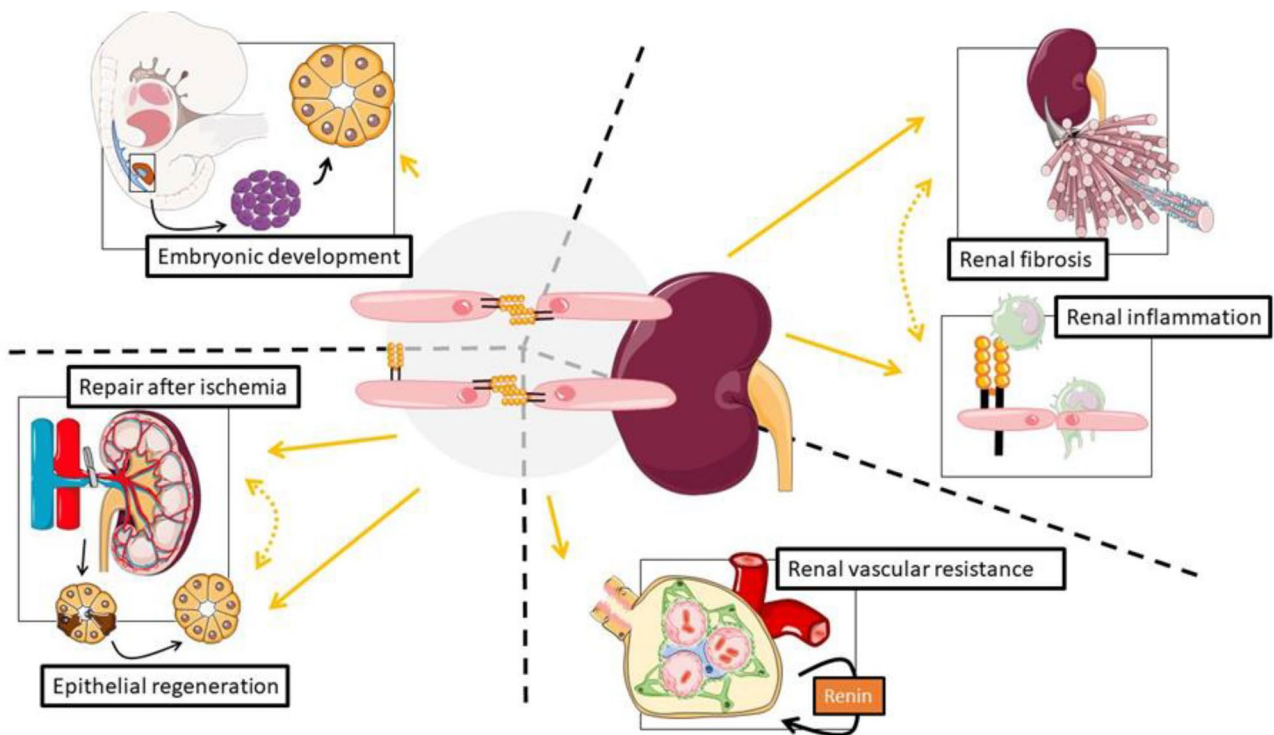


Fig. 4 Summary of CD146 implication in renal physiology and pathophysiology

expression was correlated with the severity of the injury, with glomerulosclerosis, interstitial fibrosis, and renal failure [120]. Finally, Dursun et al. evaluated the relationship between endothelial microparticles and arterial stiffness in atherosclerosis in children with CKD. The levels of CD146-positive endothelial microparticles in patients with dialysis were significantly higher than in those with no need for dialysis and control groups [121].

All specific implications of CD146 are detailed in Fig. 4.

Perspectives

All the above-mentioned studies pointed out the role of CD146 in renal damage, via its overexpression in endothelial cells, glomerular cells, and possibly epithelial cells during injury. First, as CD146 interacts with multiple ligands, leading to inflammation and remodeling processes, it is of major interest to explore in the near future mechanistic insights triggered by endothelial cells. For instance, the interaction of Gal3, S100 proteins, or matriptase with CD146 promotes specific cytokine secretion from endothelial cells, in a tumoral model modulating immune cells infiltration within injured organs [64, 65, 68, 76]. Such a mechanism could be explored in other models of acute or chronic kidney injury to understand how endothelial and epithelial cells promote post-injury mechanisms. Second, multiple cross-interactions between renal endothelium and the cardiovascular system seem to be an important point in the pathophysiology involving CD146 and its ligands. As CD146 is associated with endothelium and could be detectable as a soluble form in plasma, this could be a key point of crosstalk between different organs.

For example, it has been recently reported in an experimental model of type 3 cardiorenal syndrome that CD146 was increased in both cardiac and renal tissue after rIR [122]. We could thus hypothesize that this junctional protein can transmit different messages through the vascular endothelium in the crosstalk between the heart and kidneys. Finally, understanding the different specific roles of membranous CD146 (short or long isoform) and sCD146 would enhance the biomarker-based analysis of this protein in clinical data, to precise if it is specific to pathophysiology or to organ dysfunction.

Conclusion

CD146 is an intercellular junction protein belonging to the immunoglobulin family, involved in multiple pathways. As a soluble form in the plasma, or as a membranous form in the tissue, CD146 interacts with multiple partners. These interactions were observed mainly within the vascular endothelium during the progression of renal disease. Few data have

been reported in acute and chronic experimental nephropathy, but also in clinical studies. CD146 may be a key mediator of the understanding of the crosstalks between organs, and the transition from acute to chronic injury, through interactions with endothelial cells mediating complex molecular patterns that further trigger specific pathways.

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Availability of data and material No data availability.

Declarations

Ethics approval and consent to participate Not applicable. This study does not involve experiments.

Conflict of interest The authors declare no competing interests.

Consent for publication All authors approved the final version of the manuscript.

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