CD147 (EMMPRIN/Basigin) in kidney diseases: from an inflammation and immune system viewpoint

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ABSTRACT

The glycosylated transmembrane protein CD147/basigin, also known as extracellular matrix metalloprotease (MMP) inducer (EMMPRIN), contributes to cell survival, migration and cancer invasion. In normal kidneys, high expression of CD147 is detected only in the basolateral side of tubular epithelial cells (TECs). The pathophysiological roles of CD147 in the kidneys are diverse, ranging from involvement in the occurrence of acute kidney injury (AKI) that is frequently accompanied by ischemia, inflammation and a loss of self-tolerance to the progression of chronic kidney disease (CKD) that is caused by an imbalance in extracellular matrix protein turnover. In AKI induced by ischemia, it is the CD147 on neutrophils, rather than that on TECs, that coordinate participation in massive neutrophil recruitment via acting as a physiological ligand for E-selectin, which is specifically enhanced in the endothelium upon inflammatory stimulation. In the CKD that follows AKI, a molecular circuit involving CD147, MMPs and transforming growth factor-β may be involved in the pathogenesis of progressive fibrosis through hyaluronan production and macrophage infiltration. Whereas CD147 thus plays deleterious roles in ischemic and fibrotic kidney injuries, CD147 expression on lymphocytes might decrease the disease activity of lupus nephritis (LN) by functioning as a potential negative regulator of the extraordinary proliferation of lymphocytes that occurs in this disease. In line with these basic studies, our clinical data indicate the potential of plasma CD147 to function as a critical biomarker for both ischemic AKI and LN. CD147 is also involved in crosstalk between the kidneys and distant organs, which may be mediated by chemotactic cytokines that are derived from circulating inflammatory cells and damaged organs. Disruption of such a vicious chain reaction...
Systemic inflammation triggered by ischemia and a loss of self-tolerance induces leukocyte trafficking and recruitment to target organs through the activation of chemotactic cytokines and adhesion molecules [1, 2]. The kidneys are highly susceptible to intrinsic oxidative stress resulting from systemic ischemia and to an excessive inflammatory response of systemic autoimmunity [3]. In particular, renal tubular epithelial cells (TECs), which play critical roles as antigen-presenting cells, interact directly with neutrophils, monocytes and T lymphocytes through the activation of cell adhesion molecules that is caused by tubular injuries. Furthermore, following kidney injury there is often a vicious cycle of injury spread to the distant organs, including the heart, liver and lungs [2, 4]. Crosstalk between the kidneys and these organs may be mediated by a variety of cytokines derived from circulating inflammatory cells and from damaged organs. Indeed, several studies have demonstrated biological alterations in distant organs following ischemia-induced acute kidney injury (AKI) [5, 6]. Prevention of renal inflammation is therefore essential for improvement of mortality and morbidity rates following kidney injury. Regardless of the primary disease process, persistent kidney injury causes irreversible pathological changes such as glomerular obsolescence and interstitial fibrosis, eventually leading to the development of chronic kidney disease (CKD). The ideal approaches to identification of appropriate therapeutics for such diseases include early identification of at-risk patients and elucidation of the various underlying mechanisms that induce the involvement of inflammation and the immune system.

CD147/Basigin, which is also known as extracellular matrix metalloproteinase (MMP) inducer (EMMPRIN), is a highly glycosylated transmembrane protein belonging to the immunoglobulin superfamily [7, 8]. Its major biological roles can be categorized into three areas: cancer, the immune system and inflammation. The ability of CD147 to promote the development of carcinoma invasion and metastasis through the regulation of MMPs and monocarboxylate transporter (MCT) is well documented [9]. The immunological roles of CD147 include that of a potential negative regulatory of T cell activation [10] as well as that of a co-receptor for viral entry into host cells in human immunodeficiency virus (HIV)-1 and malaria parasitic infections [11, 12]. In addition, in vivo studies have shown that CD147 is involved in inflammation in diseases such as cardiac infarction, atherosclerosis, acute asthmatic disease and rheumatoid arthritis (RA) [13–17]. In a series of previous studies, we generated Basigin-gene-knockout mice (Bsg-/-), which display several abnormalities including amphoteric sterility, abnormalities in lymphocyte responsiveness, abnormal migration of inflammatory cells in AKI and renal fibrosis [10, 18–20]. In particular, studies with these mice have shown that the pathophysiological roles of CD147 in kidney diseases are diverse, ranging from involvement with the occurrence of AKI that is accompanied by renal ischemia and autoimmune diseases to the progression of CKD.

This review highlights various inflammatory and immunological issues in kidney diseases with an emphasis on the interactions between CD147, inflammatory cells and several inflammation-related cytokines. We further discuss the potential clinical application of CD147 to kidney diseases.

**INTRODUCTION**

**CHARACTERISTICS OF CD147**

The multifunctional transmembrane glycoprotein CD147 contributes to cell survival and the migration of various cells. CD147 is widely distributed in a variety of organs, including the brain, liver, spleen, testis, small intestine and kidney, and is expressed in many cell types including hematopoietic, epithelial, endothelial and germ cells [7]. CD147 is highly expressed in normal kidneys, especially in the basolateral side of TECs (Figure 1A). This expression is very weak in glomerular components or in vascular endothelial cells, which may be the reason why many antibody clones fail to detect low levels of CD147 by western blotting or immunohistochemistry. Indeed, CD147 induction can be detected by immunohistochemistry in inflammation-related injured glomeruli and vessels, including in glomerular adhesions to Bowman’s capsule, endocapillary proliferations and crescent formation (Figure 1B–D) [21]. Interestingly, inflammatory cells with CD147 induction show marked infiltration into injured areas. In contrast, a striking reduction of CD147 expression is observed in injured tubulointerstitium in patients with AKI and diabetic nephropathy (Figure 1A and E). This expression is not found in nodular glomerulosclerosis in patients with diabetic nephropathy (Figure 1F).

CD147 was first discovered in embryonal carcinoma cells as a receptor for *Lotus tetragonolobus* agglutinin and was determined to have the structure Galβ1→4(Fucα1→3) GlcNAc, which is known as the Lewis X structure [22]. The CD147 gene in mice is denoted as *Bsg* and in humans as *BSG*. CD147 consists of a 185 amino acid extracellular region with two immunoglobulin domains, a 24 amino acid residue transmembrane domain and a 39 amino acid cytoplasmic domain [23, 24]. The extracellular domain contains three N-linked glycosylation sites, and glycosylation of these sites varies depending on the organ. These glycosylation differences may be the reason why CD147 plays a variety of physiological roles. A wide range of CD147 binding partners, including caveolin, cyclophilin, MCT and CD147 itself, have been described to date [8, 25]. The extracellular domain of CD147 interacts with caveolin-1, β1 integrin, cyclophilin and CD147 itself, and the transmembrane domain is required for its association with MCT, CD43 and syndecan [26–30]. The downstream signaling pathway of CD147 includes mitogen-activated protein kinase and phosphatidylinositol 3-kinase [30, 31].

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AKI develops due to complex interactions between acute insults such as ischemia and kidney-specific auto-antigens, and subsequent activation of the immune system, occurring over a period of minutes to days. In this setting, inflammatory cell infiltration initially amplifies the disease activity of AKI through the release of chemotactic cytokines and reactive oxygen species [3]. Enhanced leukocyte–endothelial cell interaction due to
enhanced cell-to-cell adhesion strongly reduces peritubular capillary blood flow, leading to the induction of oxidative injury to renal tubules with depletion of adenosine triphosphate (ATP) [2, 32]. These phenomena further cause disruption of the cytoskeleton and cell polarity, and ultimately cell death, subsequently resulting in a vicious cycle that involves various cytokines and adhesion molecules. CD147 is very highly expressed in the tubules of normal kidneys, compared with its expression in other organs, suggesting that it plays important roles in these phenomena [21]. Consistent with the above concepts, CD147 deficiency causes ATP depletion in AKI induced by ischemia and hypoxia causes ATP depletion in primary cultured Bsg−/− TECs (T. Kosugi, unpublished data). These results suggest that under physiological conditions CD147 might activate the lactate metabolism cycle through interaction with MCT, resulting in ATP induction in renal tubules (Table 1).

Our understanding of the functions of CD147 is obtained from verification of in vitro studies using in vivo studies of Bsg−/− mice. In renal ischemic reperfusion in vivo, Bsg−/− mice exhibited a marked reduction in neutrophil and macrophage recruitment, leading to the amelioration of tubulointerstitial injuries [19]. These results indicate that CD147 plays a pivotal role in inflammatory cell recruitment in such injuries. CXC chemokines such as keratinocyte-derived chemokine (KC) and macrophage inflammatory protein (MIP)-2 are also known to attract neutrophils in ischemic injury. However, no obvious differences in the expression levels of these molecules are observed between wild-type and Bsg−/− mice. The question remains as to how CD147 is involved in the pathogenesis of ischemia-induced AKI. Seizer et al. [14] have demonstrated that pharmacological inhibition of CD147 can prevent the migration of neutrophils and monocytes/macrophages after myocardial ischemia and reperfusion, eventually leading to the protection of left ventricular function and myocardial tissues. In particular, the interaction between CD147 and its ligand Bsg is critical in the regulation of leukocyte recruitment in inflammation. The results of several in vivo experiments, including sepsis-induced AKI, bronchial asthma and lipopolysaccharide-induced lung injury and collagen-induced arthritis, further support this concept [16, 33,35,36]. However, no obvious differences were found in CyPA expression between wild-type and Bsg−/− mice. Thus, the interaction between CD147 and CyPA may not be responsible for the development of ischemic AKI, although further experimentation is needed to fully understand this interaction.

More interestingly, in terms of the role of CD147 in leukocyte recruitment in inflammation, the massive neutrophil infiltration that occurs into injured areas was attributed to CD147 on neutrophils, rather than CD147 on other cells such as TECs (Table 1). It is further noteworthy that CD147 on neutrophils plays an indispensable role as a physiological ligand for E-selectin in adhesion to vascular endothelial cells. Selectin is specifically induced in adhesion to vascular endothelial cells upon inflammatory stimulation [37, 38]. Indeed, E-selectin gene-knockout mice show a striking reduction in myeloperoxidase activity which is a marker of active neutrophils. The structure of CD147 contains sialyl Lewis X which is a minimal recognition motif for E-selectin [22]. Besides CD147, several other glycoproteins such as P-selectin glycoprotein ligand (PSGL)-1 and CD44 bind to E-selectin. The primary interaction between neutrophils and the endothelium is accompanied by PSGL-1 expression in the tip of neutrophil microvilli and the steady slow rolling of leukocytes is mediated by CD44 on the planar surface of neutrophils [39, 40]. Adhesion-related molecules, similar to chemotactic cytokines, might be essential for leukocyte recruitment. Thus, highly glycosylated CD147 molecules on the planar surfaces and the microvilli of neutrophils coordinately participate as a ligand for E-selectin in the early steps of leukocyte–endothelial contact formation, resulting in the enhancement of neutrophil recruitment in the ischemic kidney.

**Table 1. Role of CD147/Basigin in kidney diseases**

<table>
<thead>
<tr>
<th>Disease</th>
<th>CD147-expressing cell</th>
<th>Interacting partner</th>
<th>Molecular/cellular function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic AKI [19, 32]</td>
<td>Neutrophil, TEC</td>
<td>E-selectin on EC</td>
<td>Leukocyte–EC contact formation</td>
</tr>
<tr>
<td>Septic AKI [33]</td>
<td>Leukocyte, TEC</td>
<td>Cyclophilin on injured tissues</td>
<td>Chemotactic cytokines induction (TNF-α, IL-10, IL-6)</td>
</tr>
<tr>
<td>Fibrosis [20]</td>
<td>Monocyte, TEC</td>
<td>E-selectin on EC</td>
<td>Infiltration into injured tissues</td>
</tr>
<tr>
<td></td>
<td>Fibroblast</td>
<td>Fibroblasts</td>
<td>MMPs-2, -9 induction (MMPs-regulated TGF-β induction)</td>
</tr>
<tr>
<td>SLE [21, 34]</td>
<td>Activated CD3+ T cell, Regulatory T cell</td>
<td>Unknown</td>
<td>Hyaluronan synthase α-SMA induction</td>
</tr>
</tbody>
</table>

EC, endothelial cell; TNF-α, tumor necrosis factor-α; α-SMA, α-smooth muscle actin.
TECs is a strong inducer of MMPs [9]. Since MMPs are a key factor in the disruption of tubular basement membranes, their overexpression leads to the acquisition of contractile motility and loss of polarity. Indeed, an in vivo study using Bsg−/− mice showed that, after renal injury induced by unilateral ureteral obstruction (UUO), the Bsg−/− mice have less tubulointerstitial fibrosis than wild-type mice and display suppression of macrophage recruitment [20]. Furthermore, our in vitro experiments demonstrated that CD147 on fibroblasts participates along with MMPs on TECs in the induction of hyaluronan, which is responsible for fibroblast differentiation and maintenance of the myofibroblast phenotype in response to TGF-β. Hyaluronan promotes α-smooth muscle actin expression in fibroblasts. Thus, a molecular circuit involving CD147, MMPs and TGF-β may be involved in the pathogenesis of renal fibrosis (Table 1). Macrophages also express CD147, which acts as a ligand of E-selectin [35]. We confirmed that CD147 expressed on a human monocyte cell line bound to E-selectin. E-selectin induction was comparable between wild-type and Bsg−/− mice after UUO surgery, indicating the importance of this finding. The combined data suggest that the presence of CD147 on macrophages might play a critical role in macrophage infiltration into the interstitium via E-selectin binding (Table 1). Indeed, mice with a triple knockout of E-, P- and L-selectin show a striking reduction in macrophage recruitment after UUO treatment [44]. The above-described results, combined with previous reports and our data, suggest that CD147 orchestrates renal fibrosis through the regulation of MMPs, hyaluronan production and macrophage infiltration with the responsiveness of TGF-β.

CD147 AND AUTOIMMUNITY

As stated earlier, CD147 is a multifunctional glycoprotein. Thus, apart from its involvement in the processes described above, it is also involved in various other pathophysiological and immunological processes. Coste et al. [45] demonstrate that inhibition of CD147 expressed on the surface of erythrocytes causes disruption of the circulation of erythrocytes by selectively trapping erythrocytes with attenuated CD147 expression in the spleen. Consistent with this finding, some Bsg−/− mice show splenomegaly, indicating that Bsg−/− erythrocytes might be destroyed as immature erythrocytes in the spleen (data not shown). This phenomenon may be associated with renal anemia and senescence of erythrocytes.

In addition to its function in inflammation-associated cyclophilin signaling, recent studies indicate that CD147 may also act as a potential negative regulator of extraordinary proliferation of T lymphocytes through the activation of regulatory T cells [46]. In particular, the finding of hyperproliferation of lymphocytes in a mixed lymphocyte reaction of Bsg−/− mice prompted later studies on the role of CD147 in T-cell activation and development [10]. The overexpression in CD3+ T lymphocytes in patients with active systemic lupus erythematosus (SLE) activates regulatory T cells, which maintain tolerance to self-antigens and abrogate autoimmune disease (Table 1) [34]. Aberrations in immune mechanisms involving CD147-mediated T lymphocyte function may be a crucial determinant in active SLE. In contrast to its potential inhibitory role in SLE, CD147 exacerbates the disease activity of RA by inducing vascular endothelial growth factor (VEGF) and hypoxia inducible factor-1α, thereby promoting angiogenesis [17]. VEGF induction is also observed in carcinoma invasion regulated by CD147. The predominant role of CD147 in the pathophysiological mechanism of RA may be a role in inflammation, rather than a role in regulation of the immune system. The diverse mechanisms by which CD147 is involved in autoimmune diseases need to be further elucidated by in vivo studies in the near future.

POTENTIAL OF CD147 AS A BIOMARKER

The current outcomes of the treatment of severe kidney injuries are unsatisfactory, despite the development of new diagnostic techniques and aggressive therapeutic management. In particular, the lack of early biomarkers of AKI impairs the ability to intervene in a time-dependent manner [47]. Therefore, novel molecular biomarkers that can be easily detected and that are suitable for a clinical setting need to be developed. In this respect it is interesting that the levels of both plasma and urinary CD147 are strikingly increased in patients with established AKI [32]. Both of these increases in CD147 levels clearly correlate with serum creatinine (Cr) and show a high ability to detect AKI compared with the 'golden standard' of serum Cr. Based on previous evidence, plasma CD147 is derived from soluble CD147 on leukocytes that is shed by the action of membrane-associated type I transmembrane MMP. Urinary CD147 might be a result of the degeneration of injured TECs. The potential utility of CD147 as a biomarker for early AKI has been evaluated by comparison with that of urinary t-fatty acid-binding protein (t-FABP). Urinary t-FABP is excreted from injured proximal TECs and is elevated within a short time of AKI [48]. The sensitivity and specificity of plasma CD147 for established AKI are actually higher than those of t-FABP. In addition, a time-dependent evaluation of CD147 and t-FABP levels has been performed in patients undergoing open surgery to treat abdominal aortic aneurysm. Neither parameter changed immediately after aortic declamping, but the plasma level of both parameters was significantly increased on postoperative day 1 in the AKI patient group, prior to elevation of serum Cr. Thus, basic and clinical research supports the possibility that plasma CD147 might be a prime candidate biomarker for the diagnosis of early AKI [19, 32].

With regard to SLE, early identification of at-risk patients would be extremely helpful in avoiding higher drug toxicity and poor toleration. Therefore, new biomarkers that can function as noninvasive diagnostic tools and that accurately reflect the disease activity of LN are required. Candidate biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) and MCP-1 have already been reported that might reflect histological features of LN and that might allow the prediction of impending flares and selection of future therapies [21, 49, 50]. However, the diagnostic accuracy of LN biomarkers, including the above molecules and the traditional parameters, remains...
unsatisfactory. Previous evidence indicates that CD147 might be involved in the pathogenesis of LN through induction of the polarization of T lymphocytes [10]. Indeed, in kidney tissues of patients with LN, CD147 is strongly induced in infiltrating inflammatory cells and injured glomeruli, including in endocapillary proliferation in glomerular adhesions to Bowman's capsule and also in cellular crescent formations [21]. In addition, plasma CD147 levels accurately reflect the histological disease activity of LN and significantly correlate with renal function including with Cr levels. Of note, lower values of plasma CD147 are observed in inactive LN patients that have undergone immunosuppressive treatment and in SLE patients without renal involvement. However, based on the best knowledge of basic and clinical research, like NGAL and MCP-1, CD147 expression might not be specific for LN. Furthermore, due to the intricate pathogenesis of LN, prediction using a single molecule is quite difficult and multiplex markers would therefore be required to achieve high diagnostic accuracy for LN [50]. In our study, the combinations of plasma CD147 and component C3 levels showed a more reliable accuracy for estimating pathological LN activity than either factor alone or the combinations of either factor. These data indicate that plasma CD147 levels might act as an important biomarker for, and offer useful insights into disease activity of LN.

CONCLUSION

Analysis of the underlying mechanisms of diverse kidney diseases ranging from the occurrence of AKI to the progression of CKD provides key insights for the development of new therapeutic strategies. As described in the various studies reviewed above, CD147 is involved in pathophysiological processes that are associated with increased leukocyte recruitment. In particular, CD147 may cause distant organ dysfunction associated with a systemic inflammatory response following kidney injury through the activation of CD147 itself on leukocytes. Disruption of a vicious chain reaction that is regulated by CD147 and its interacting molecules is essential in order to overcome kidney diseases. In addition to the contribution of CD147 to the mechanistic details of disease processes, plasma CD147 levels might act as a critical biomarker in patients with AKI and LN, thereby allowing the start of preemptive medication for these diseases. In-depth research targeted toward elucidation of these points will open a new avenue for targeting therapeutics for kidney diseases and distant organ damage.

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CONFLICT OF INTEREST STATEMENT

None declared.

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