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ORIGINAL ARTICLE

CD147/basigin reflects renal dysfunction in patients with acute kidney injury

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Abstract
Background Acute tubular necrosis (ATN) describes a form of intrinsic acute kidney injury (AKI) that results from persistent hypoperfusion and subsequent activation of the immune system. A glycosylated transmembrane protein, CD147/basigin, is involved in the pathogenesis of renal ischemia and fibrosis. The present study investigated whether CD147 can reflect pathological features and renal dysfunction in patients with AKI.
Methods Plasma and spot urine samples were collected from 24 patients (12 controls and 12 with ATN) who underwent renal biopsy between 2008 and 2012. In another study, patients undergoing open surgery to treat abdominal aortic aneurysms (AAAs) were enrolled in 2004. We collected urine and plasma samples from seven patients with AKI and 33 patients without AKI, respectively. In these experiments, plasma and urinary CD147, and urinary L-fatty acid-binding protein (L-FABP) levels were measured, and the former expression in kidneys was examined by immunostaining.
Results In biopsy tissues of ATN with severe histological features, CD147 induction was strikingly present in inflammatory cells such as macrophages and lymphocytes in the injured interstitium, but not in damaged tubules representing atrophy. Both plasma and urinary CD147 levels were strikingly increased in ATN patients; both values showed greater correlations with renal dysfunction compared to urinary L-FABP. In patients who had undergone open AAA surgery, urinary and plasma CD147 values in AKI patients were significantly higher than in non-AKI patients at postoperative day 1, similar to the profile of urinary L-FABP.
Conclusion CD147 was prominent in its ability to detect AKI and may allow the start of preemptive medication.

Keywords CD147 · Acute tubular necrosis · Acute kidney injury · L-FABP

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Introduction

Acute tubular injury develops due to complex interactions between acute insults such as ischemia and subsequent activation of the immune system, occurring over a period of minutes to days [1–3]. Acute tubular necrosis (ATN) describes a form of intrinsic acute kidney injury (AKI) that results from persistent hypoperfusion and subsequent inflammation [1]. The mechanism whereby ischemia and focal oxygen depletion injure tubular cells starts with depletion of adenosine triphosphate (ATP). This activates harmful proteases and phospholipases, eventually resulting in oxidative injury to tubular epithelial cells (TECs) and endothelial cells in peritubular capillaries by reperfusion. In this setting, inflammatory cell infiltration is closely involved in the pathogenesis of AKI through the release of cytotoxic cytokines, reactive oxygen species and proteolytic enzymes.

In the present investigation, mortality and morbidity rates associated with AKI remain high despite advanced interventions and the development of new diagnostic techniques [4–6]. The lack of early biomarkers for AKI has impaired the ability to intervene in a time-dependent manner [7]. The identification of various underlying mechanisms for AKI would be extremely helpful for improving these rates.

CD147/basigin, a glycosylated transmembrane protein, belongs to the immunoglobulin superfamily and is distributed in various types of cells, including hematopoietic, epithelial, and endothelial cells [8, 9]. CD147 is well documented for its ability to function as an extracellular matrix metalloproteinase (MMP) inducer [10] and is thought to contribute to cell survival, apoptosis, monocarboxylate transporter (MCT) induction, carcinoma metastasis and spermatogenesis [11, 12]. Relationships with a wide range of binding partners have already been found, including caveolin, cyclophilin, MCT, and CD147 itself. Indeed, CD147 plays a vital role in lactate metabolism through interaction with the MCT, leading to ATP production [12]. Interestingly, CD147 is upregulated on circulating monocytes in patients with acute myocardial infarction [13], and CD147/cyclophilin interactions are crucially involved in the pathophysiology of ischemic myocardium by mediating monocyte chemotaxis and MMP-9 activity [14]. We have also demonstrated that CD147 gene-deficient mice exhibited less tubular damage by preventing neutrophil migration after renal ischemia/reperfusion [15]. This phenotype is attributable to highly glycosylated CD147 on neutrophils bound to E-selectin on endothelial cells, rather than CD147 on other cells in the inflammation area. We have further investigated the potential roles of CD147 on monocytes in the development of renal fibrosis via MMP activation, using CD147 gene-deficient mice [16].

Elucidation of the molecular mechanisms underlying AKI from a variety of perspectives is essential for improving mortality and morbidity rates. To the best of our knowledge, the clinical relevance of CD147 in AKI has not yet been elucidated. Based on our evidence, CD147 may be a prime candidate for developing a new procedure for the evaluation of AKI. The present study examined whether CD147 can reflect the pathological features and renal dysfunction of AKI caused by ischemia compared to novel parameters such as L-fatty acid-binding protein (L-FABP) and serum creatinine (Cr).

Patients and methods

Patients and procedures

This study proceeded according to the principles of the Declaration of Helsinki, the Japanese National Ethical Guidelines (approval number; 1135), and the institutional review boards of Nagoya University Hospital and affiliated hospitals. All patients provided written informed consent.

In the first study, we examined the relationship between CD147 expression and renal dysfunction. Among adult patients clinically diagnosed with AKI, 12 patients with ATN who underwent renal biopsy as part of standard-of-care therapy in Nagoya University and affiliated hospitals between 2008 and 2012 were registered. Diagnosis was made clinically according to the Acute Kidney Injury Network (AKIN) criteria [17, 18], and made pathologically using light, immunofluorescence and electron microscopy. Cases complicated with the other kidney diseases were excluded. In the same period, 12 patients with only microhematuria or a subtle amount of proteinuria were regarded as pathological controls. These individuals did not show the kidney diseases clinically and pathologically. To further confirm the utility of CD147 value as a control, nine healthy individuals were enrolled. Except for healthy individuals, plasma and spot urine samples were collected on the day prior to renal biopsy. Urinary samples were centrifuged at $2000\times g$ for 5 min to remove cellular components and debris, then equal volumes of supernatants were stored at -80 °C. Clinical parameters such as levels of serum Cr, proteinuria and C-reactive protein (CRP) were measured as described previously [19, 20].

We further verified the time course of CD147 expression with regard to AKI development associated with abdominal aortic aneurysm (AAA) surgery. In this examination, we registered 40 patients undergoing open surgery to treat AAA between January and November 2004 at Nagoya University Hospital. Exclusion criteria included the use of nephrotoxic drugs before or during the study period. Urinary samples were obtained from all patients at the start of anesthesia, attaching the aortic clamp, opening the aortic clamp, at the end of the surgery and on post-operative day 1. Plasma samples were collected except for the time point of opening the aortic clamp. Serum Cr levels of all patients were measured at baseline before surgery and monitored daily until post-operative day 3 to confirm the onset of AKI. The diagnostic criteria for post-operative AKI were defined using the AKIN criteria [17, 18]. Finally, we collected urine and plasma samples from seven and 33 patients with and without AKI, respectively.

Renal histology

Kidney tissues were fixed in 10 % formalin, embedded in paraffin and then cut into 4-μm sections for periodic acid-Schiff reagent (PAS) staining and immunohistochemical staining. A mouse monoclonal anti-human CD5 antibody (Novocastra, Newcastle upon Tyne, UK) to lymphocyte marker, mouse monoclonal anti-human CD68 antibody

(Dako) and mouse monoclonal anti-human CD147 antibody (Abcam, Cambridge, MA, USA) were used for immunohistochemical staining. The staining was visualized with 3,3′-diaminobenzidine (Nichirei), a brown color being produced.

Measurement for CD147 and L-FABP

Plasma and urinary CD147, and urinary L-FABP values were measured using commercial enzyme-linked immunosorbent assay kits according to the respective instructions from the manufacturers (R&D Systems, Minneapolis, MN, USA; Mitsubishi Chemical Medience Corporation, Tokyo, Japan). Measured levels in urine were then normalized to urinary Cr levels.

Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables as numbers and ratios (%). Continuous variables were compared using Student's *t* test, the non-parametric Mann–Whitney *U* test or Kruskal–Wallis test followed by Steel–Dwass post hoc multiple comparisons as appropriate. We used Spearman correlation coefficients to examine the strength of association between two variables. Receiver-operating characteristics (ROC) curves were constructed to compare the accuracy of diagnosing AKI and diagnostic performance was quantified as areas under the curve (AUC) [21]. We explored the longitudinal effects of urinary CD147 and L-FABP over open repair of AAA using repeated-measures analysis of variance. Two-tailed *P* values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS and STATA version 9, commercial software.

Results

Patient characteristics with ATN

Table 1 summarizes the characteristics of the 12 patients with ATN included in the present study. All participants were Japanese, with a mean age of 57.4 years (range 24–76), and the majority (75 %) were male. As expected, patients with ATN showed more renal dysfunction in parameters such as serum Cr level and proteinuria than control patients. Hypertension, anemia and inflammation were also observed in patients with ATN. No obvious abnormalities were found in healthy individuals (data not shown).

CD147 expression in the kidney

Control patients showed strong expressions of CD147 in the basolateral side and intercellular junction of both proximal and distal tubules (Fig. 1A). In biopsy tissues of patients with ATN, CD147 expression was strikingly reduced in lesions representing tubular damage (Fig. 1A–C). Interestingly, tubules with degeneration of TECs exhibited striking declines in CD147 expression, whereas inflammatory cells with CD147 induction showed marked infiltration into these areas. Most CD147-positive cells infiltrating around damaged tubules and blood vessels were consistently detected with CD68 antibody to macrophages and CD5 antibody to lymphocytes, using serial sections (Fig. 1D). Small proportions of cells were neutrophils and fibroblasts with CD147 expression (data not shown). Of note is the fact that CD147 induction was suppressed in injured interstitium at the recovery period in which acute or chronic inflammation subsided.

Table 1 Patient characteristics

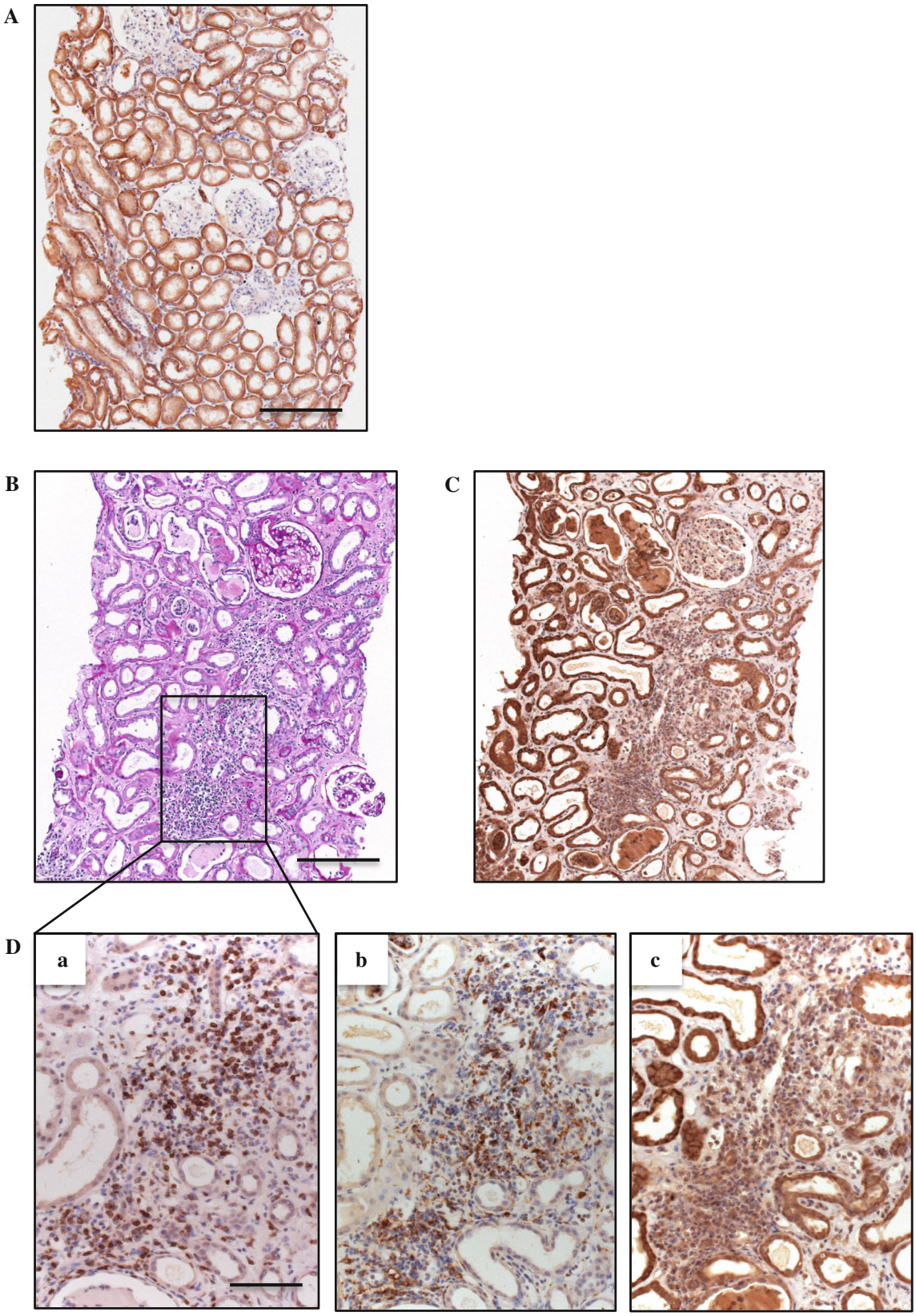
	ATN ($n = 12$)	Pathological control ($n = 12$)
Sex (%) female	25	58
Age (years)	57.4 ± 17.1 (24–76)	31.5 ± 15.3 (17–70)
Weight (kg)	58.1 ± 12.1 (39.6–81.0)	59.0 ± 17.0 (32.8–90.0)
Systolic BP (mmHg)	141 ± 24.7 (114–192)	115 ± 15.0 (92–140)
Diastolic BP (mmHg)	78 ± 16.5 (62–105)	70 ± 10.9 (50–90)
Serum Cr (mg/dl)	7.0 ± 3.5 (2.67–15.2)	0.74 ± 0.24 (0.44–1.29)
UP/urine Cr	2.05 ± 2.42 (0.14–6.53)	0.24 ± 0.23 (0–0.71)
Ht (%)	30.2 ± 6.42 (21–37.4)	42.2 ± 4.5 (36.7–50.9)
CRP (mg/dl)	4.51 ± 8.24 (0.01–29.8)	0.07 ± 0.10 (0–0.23)

Data are expressed as mean ± SD (range)

ATN acute tubular necrosis, *BP* blood pressure, *Cr* creatinine, *UP* urine protein, *Ht* hematocrit, *CRP* C-reactive protein

Plasma and urinary CD147 levels

No significant differences in plasma and urinary CD147 values were apparent between control patients (plasma 2,717 ± 530 pg/ml; urine 11,844 ± 5,984 pg/mg Cr) and healthy individuals (plasma 2,676 ± 452 pg/ml; urine 12,473 ± 4,194 pg/mg Cr) (Fig. 2A, B). In contrast, both plasma and urinary CD147 levels (plasma 8,574 ± 3,742 pg/ml; urine 52,575 ± 29,841 pg/mg Cr) in patients with ATN were approximately 3- and 4-fold higher than those in control groups, respectively (Fig. 2A, B). Plasma and urinary CD147 levels markedly correlated with markers of renal function, such as levels of serum Cr (Fig. 2C, D) and blood urea nitrogen (BUN), but to a lesser extent in proteinuria (data not shown). Interestingly, no significant correlations existed between plasma CD147 expression and CRP, indicating that CD147 induction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◀ **Fig. 1** Renal histology in patients with ATN. **A** Immunohistochemical staining of CD147 expression in pathological control patients. *Bar* 200 μm. **B** Representative photograph of PAS staining in a patient with ATN. *Bar* 200 μm. **C** Immunohistochemical staining for CD147 expression. **D** *a*, CD5 expression in infiltrating cells into injured tubulointerstitium. *Bar* 100 μm. *b* CD68 expression. *c* CD147 expression. **B–D** Serial sections were used

might not be associated with systemic inflammation (data not shown). A striking association was evident between plasma and urinary CD147 levels (Fig. 2E).

Comparison with urinary L-FABP in patients with ATN

To investigate the reliability and benefit of CD147 as a hallmark for ATN, we next compared levels with urinary

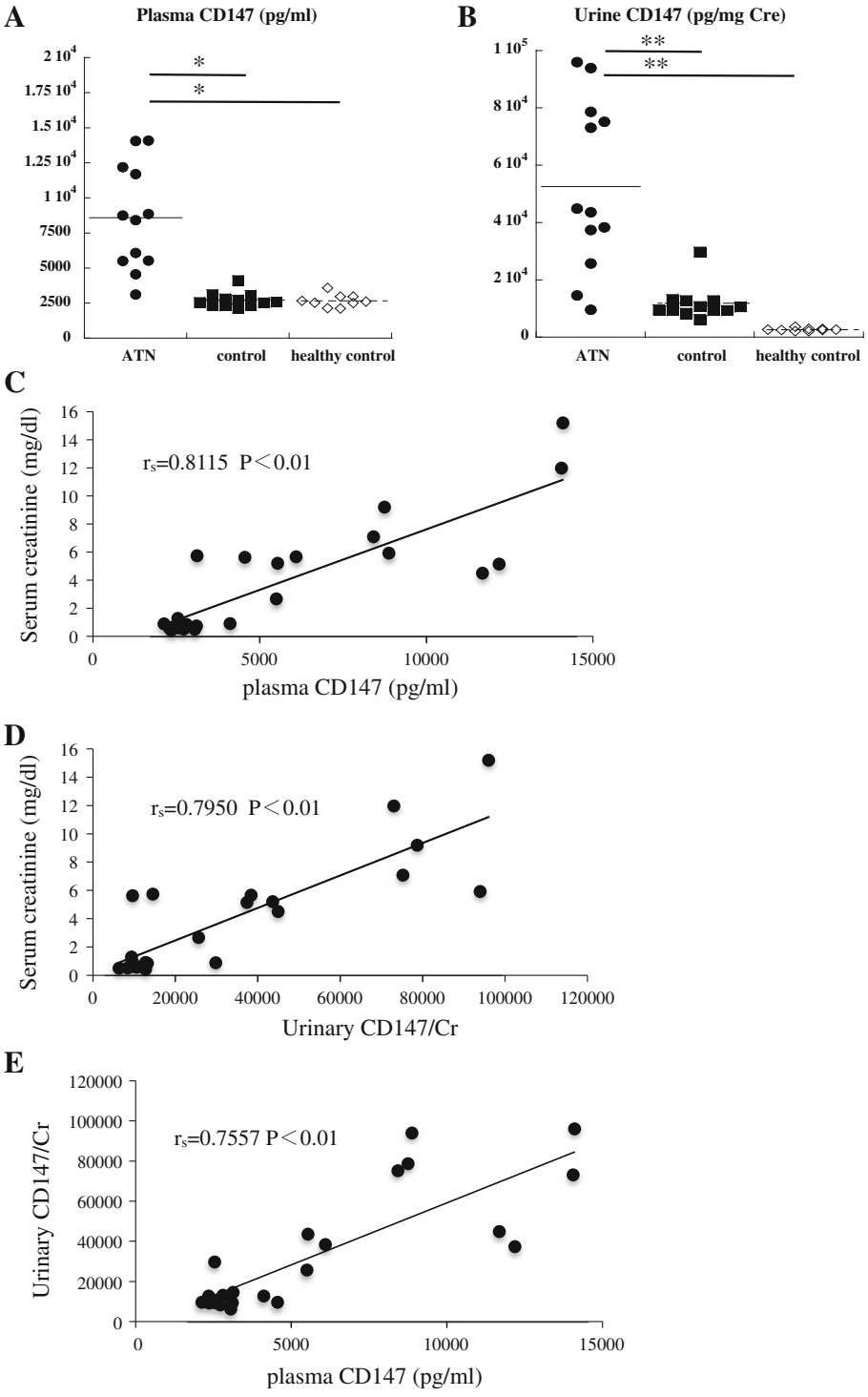

Fig. 2 Plasma and urinary CD147 values in patients with ATN. **A** Plasma CD147 levels (pg/ml). **B** Urinary CD147 values (pg/mg Cr). $*p < 0.0001$; $**p < 0.0005$. **C–D** Correlation between serum Cr and plasma CD147 or urinary CD147 levels. **E** Correlation between plasma and urinary CD147 levels

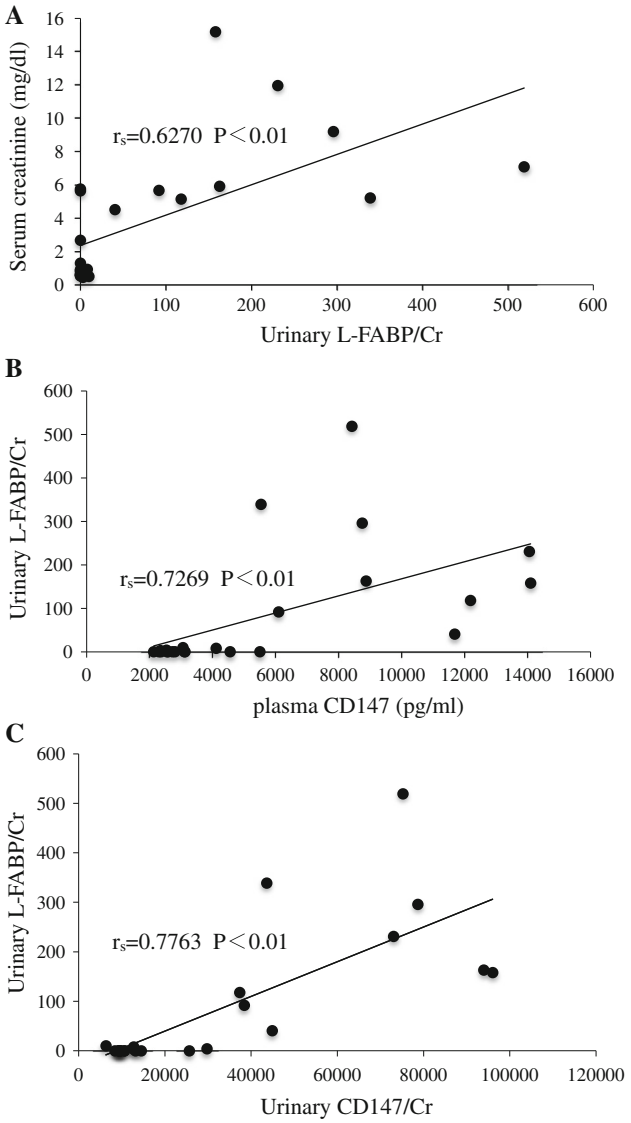

Fig. 3 Correlation with urinary L-FABP in patients with ATN. **A** Correlation between serum Cr levels and urinary L-FABP. **B** Correlation between plasma CD147 levels and urinary L-FABP. **C** Correlation between urinary CD147 levels and urinary L-FABP

concentrations of L-FABP, as a novel biomarker for tubulointerstitial injury. Urinary L-FABP levels did not show a higher correlation with serum Cr values compared with plasma and urinary CD147 levels (Figs. 2C, D, 3A). Urinary CD147 levels showed a closer correlation with urinary L-FABP values, compared to plasma CD147 levels (Fig. 3B, C).

We examined the sensitivity and specificity of these parameters for ATN by constructing ROC curves (Fig. 4). AUCs were 0.993, 0.938 and 0.833 for plasma CD147, urinary CD147 and urinary L-FABP, respectively. These findings suggest that CD147 would be more reliable for diagnosing ATN, similar to urinary L-FABP.

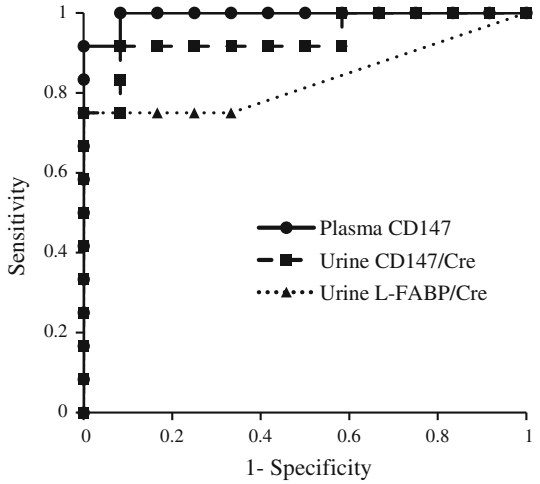

Fig. 4 Comparison of ROC curve for plasma and urinary CD147, and urinary L-FABP among patients with ATN. ROC curve analysis of each biomarker indicates ability to diagnose ATN. *ROC* receiver-operating characteristics

Urinary and plasma CD147 in patients with AKI caused by renal ischemia

With regard to characteristics of patients undergoing AAA surgery, no obvious differences in serum Cr levels before surgery and aortic cross-clamp duration were found in patients with/without AKI. Urinary CD147 levels were consistently lower in patients with and without AKI until the time of aortic declamping during the operative duration, and then gradually increased in both groups (Fig. 5A). This value in patients with AKI was higher on post-operative day 1 compared to that of patients without AKI. Serum Cr, typically used to diagnose AKI, gradually increased after the experimental duration and peaked at post-operative day 2 or 3 in patients with AKI (data not shown). Urinary L-FABP, already termed as a novel biomarker for tubulointerstitial damage, was transiently increased in patients with AKI at the time of aortic declamping, but not significantly compared with patients without AKI (Fig. 5B). Consistent with urinary CD147 values at post-operative day 1, urinary L-FABP was significantly increased in patients with AKI. Consistent with the profiles of urinary CD147 and L-FABP, plasma CD147 levels in patients with AKI significantly increased on post-operative day 1 compared with patients without AKI (Fig. 5C). In contrast to the profile of urinary CD147, interestingly, plasma CD147 levels in patients without AKI did not show the rise during the observation period. Urinary CD147 and L-FABP, and plasma CD147 surpassed serum Cr for detecting early AKI among patients with AKI.

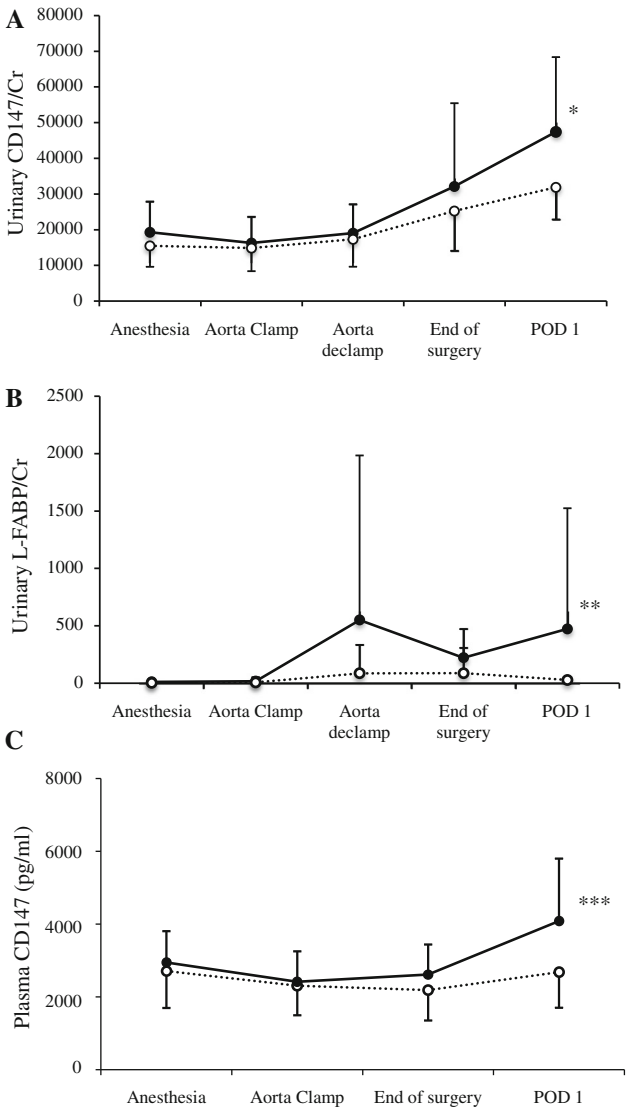

Fig. 5 Detection of CD147 and L-FABP in patients undergoing open surgery for AAA. **A** Urinary CD147. **B** Urinary L-FABP. **C** Plasma CD147. *Solid line* AKI patient: *broken line* non-AKI patient. *$p < 0.005$ vs non-AKI groups at the same time point; **$p < 0.05$; ***$p < 0.01$

Discussion

The present study demonstrated that both plasma and urinary CD147 levels specifically reflect renal dysfunction, including serum Cr and BUN, when caused by renal ischemia. Based on previous evidence, plasma CD147 would be derived from soluble CD147 on leukocytes shed by membrane-associated type 1 transmembrane MMP and in itself further provokes an inflammatory response in the kidney [11, 15, 22]. Conversely, most urinary CD147 might be caused by degeneration of injured TECs rich in CD147. In biopsy tissues of ATN with severe histological features, CD147 induction was strikingly present in inflammatory cells that had infiltrated into the injured interstitium, but not in injured tubules representing atrophy. More interestingly, urinary and plasma CD147 values, clearly correlated with serum Cr, showed a prominent ability to detect AKI compared to the 'golden standard' of serum Cr.

In the setting of ATN, tubular injury is a direct consequence of the metabolic pathway with ATP depletion and oxidative stress, but is potentiated by inflammation and microvascular compromise [1]. Leukocyte infiltration is augmented by proinflammatory and chemotactic cytokines generated by ischemic TECs. According to our unpublished data, CD147 induction was promoted in primary cultured TECs from mouse kidneys and the immortalized proximal HK2 TEC line derived from normal adult human kidney exposed to hypoxia. Lack of CD147 strikingly ameliorated tubulointerstitial injury and the infiltration of inflammatory cells, including neutrophils and macrophages [15, 16]. In the present study, CD147 expression was found to co-localize on inflammatory cells. In particular, massive CD5-positive cells with CD147 expressions were closely clustered in the injured tubulointerstitium. In line with our data and previous evidence, CD147 might represent a critical component for leukocyte trafficking and recruitment in inflammation-mediated pathologies, including ATN and AKI. In addition, mitochondria cannot produce ATP in oxidative phosphorylation to aid in electron transport under the influence of hypoxia in ATN [1]. Lactate accumulation often occurs within areas of hypoxia/necrosis [12]. Instead, CD147 in TECs may contribute to yielding ATP via lactate metabolism in glycolysis as a chaperone to some MCT subtypes. CD147 expression was strikingly induced in TECs immediately after tubular injury, but showed a precipitous decline with detachment of TECs. This phenomenon may suggest a protective role of CD147 in the preservation of tubules with regard to energy metabolism.

Whereas biomarker candidates can increase our understanding of the pathophysiology of AKI, promising new molecules need to be elucidated in the clinical settings of detection ability and suitability [5, 17, 23]. We therefore evaluated the potential utility of CD147 in AKI through comparison with urinary L-FABP, which is elevated within a short time in established AKI resulting from various etiologies such as ATN, sepsis and cardiac vascular surgery [3]. In addition, tubulointerstitial injury caused the up-regulation of L-FABP expression, leading to increased urinary excretion of L-FABP from proximal tubules. These characteristics appear to be similar to those of CD147. In patients with ATN, the sensitivity and specificity of plasma and urinary CD147 were higher than those of urinary L-FABP. Interestingly, urinary L-FABP levels were more associated with urinary CD147 values, compared to plasma CD147. Contrary to the profiles of urinary CD147 and L-FABP levels, plasma CD147 values exhibited mild increases in the recovery phase of patients with

ATN; these phenomena may be attributed to the origin of plasma and urinary CD147, respectively. We further elucidated the changes of urinary CD147 and L-FABP values, and plasma CD147 levels in patients undergoing open surgery to treat AAA. Neither parameter changed immediately after aortic declamping, but these were all significantly increased on post-operative day 1 prior to serum Cr. Presumably, the performance of AAA surgery would also induce oxidative stress in patients without AKI, leading to the slight increase of urinary CD147 expression. Indeed, exposure to hydrogen peroxide induced CD147 expression in a proximal HK2 TEC line (unpublished data). More interestingly, plasma CD147 hardly changed during the observation duration, indicating that plasma CD147 might be more suitable as an AKI biomarker. Our basic and clinical research also supports the notion that plasma and urinary CD147 values are responsive to the pathophysiology of AKI and might be one of the prime candidates for diagnosing early AKI, similar to other critical biomarkers such as urinary L-FABP and neutrophil gelatinase-associated lipocalin.

In order to take advantage of advanced interventions and improve mortality and morbidity rates, AKI should be identified as soon as possible [2, 5]. The development of earlier diagnostic tools and identification of prognostic factors will be required for the future. In AKI representing a variety of aspects and caused by multiple complex pathogeneses, vital diagnosis and prediction using a single molecule would be quite difficult. Combining reliable parameters would therefore be needed to achieve high diagnostic accuracy for an important diagnosis at a variety of stages of AKI. We propose that both plasma and urinary CD147 might provide key insights to understanding the disease activity of AKI and allow the start of pre-emptive medication as a crucial biomarker in patients with AKI.

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Conflict of interest None.

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