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Research Article

CD133 Staining Detects Acute Kidney Injury and Differentiates Clear Cell Papillary Renal Cell Carcinoma from Other Renal Tumors

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CD133 has recently been characterized as a progenitor cell marker in the kidney. However, the expression of this marker has not been thoroughly investigated in kidney injury and variants of renal tumors for pathology practice. We quantified CD133 expression in kidney biopsies from patients with acute renal failure and compared staining intensity with serum creatinine levels. CD133 expression levels were also evaluated in several subtypes of renal neoplasms. Normal adult renal parenchyma showed CD133 expression in parietal epithelium and in less than 5% of the epithelial cells in proximal and distal nephron tubules. However, CD133 was diffusely upregulated in the injured proximal and distal tubular epithelium and the CD133 expression scores in renal tubules were significantly correlated with serum creatinine levels. Amongst the renal tumors, CD133 was diffusely expressed in clear cell papillary renal cell carcinoma but was only focally present in other types of renal tumors. In summary, CD133 is a useful marker to detect renal tubular injury and to differentiate clear cell papillary renal cell carcinoma from other tumor types.

1. Introduction

The kidney possesses a remarkable capacity for repair of the tubular epithelium in response to various forms of acute injury. Following a reversible injury, residual tubular cells proliferate and rebuild the renal epithelium [1, 2]. When injury is severe, damaged proximal tubules may dedifferentiate into a mesenchymal fibroblastic phenotype and produce the filament vimentin, a process observed in animal models [3]. Vimentin expression has also been described in injured tubular epithelium of human kidneys, supporting the notion that a similar dedifferentiation process also occurs in humans [4]. Epithelial dedifferentiation in renal tubules is known as the epithelial-to-mesenchymal transition (EMT), in contrast to its reversed process, the mesenchymal-to-epithelial transition, which occurs during normal embryogenesis [5]. EMT is a critical step of injury response during which transformed cells may be rendered vulnerable to malignant transformation via downregulation of critical tumor suppressor mechanisms. Additionally, an EMT-like process is thought to enhance the proliferative and metastatic potential of established tumors [5, 6].

CD133 is a pentaspan membrane protein that has been investigated for its potential utility as a stem cell marker in different adult organs and tumors [7]. It has been used to identify progenitor cells in the glomerular parietal epithelium [8–11] and undifferentiated cells in the interstitium of adult kidneys [12]. Some recent studies also report an upregulation of CD133 in proximal tubules undergoing repair and regeneration [13–15]. However, CD133 expression in different etiologies of renal tubular injury occurring in native kidneys has not been well described in terms of the tubular distribution,

correlation with renal function, and potential function during tubular repair. One study shows that CD133+ renal progenitor cells may contribute to tumor angiogenesis [16], and another study reports expression of CD133 in papillary renal cell carcinoma (RCC) [4]. Otherwise, expression of CD133 in different categories of renal tumors is not well established. This is particularly true in more recently described tumor types, such as clear cell papillary RCC, a relatively new variant that was initially described in patients with end-stage renal disease [17].

The specific aim of this study was to determine firstly, if CD133 upregulation can be used to confirm acute tubular injury and secondly, if CD133 expression can be used to differentiate clear cell papillary renal cell carcinoma from other types of renal tumors in pathology practice. We confirmed the upregulation of CD133 in injured glomerular epithelium. There was extensive membranous expression in all injured proximal and distal nephron tubules. CD133 expression scores in renal tubules correlated significantly with serum creatinine levels. Finally, we found that CD133 showed diffuse expression in clear cell papillary RCC but not in other types of renal tumors.

2. Materials and Methods

2.1. Groups of Human Kidneys

2.1.1. Human Adult Kidneys. Sixteen cases of morphologically normal renal parenchyma, obtained from nephrectomies performed for tumor removal, were used as the control group (group 1). Groups 2 to 5 comprised cases of acute kidney injury (AKI) from native kidney biopsies, grouped with respect to etiology (Table 1). The groups are assigned as follows: group 2—thrombotic microangiopathy, mostly due to atypical HUS type ($n = 13$), group 3—crescentic glomerulonephritis ($n = 13$), group 4—collapsing glomerulopathy (total $n = 9$) (collapsing glomerulopathy ($n = 4$) and other forms of HIV related nephropathy such as IgA and lupus-like nephropathy ($n = 5$)), and group 5—tubulointerstitial diseases (total $n = 14$) (native acute tubular injury ($n = 8$), oxalate calcium nephropathy ($n = 4$), and acute interstitial nephritis ($n = 2$)). All cases were stained for CD133 to compare with the staining for kidney injury molecule-1 (KIM-1), a well-known marker for acute tubular injury in proximal tubules [18].

2.1.2. Renal Tumors. A total of 20 clear cell RCC, 15 papillary RCC, 7 chromophobe RCC, and 5 oncocytoma cases from the past 5 years were randomly selected from our archives. We also included all cases of clear cell papillary RCC ($n = 11$, with typical morphology for this variant and stained positively for CK7 positive but negatively for P504S) and Wilms' tumor ($n = 14$) from the past 10 years. At least 4 patients with clear cell papillary RCC were known to have end stage of renal disease. All tumor sections were stained for CD133 and another stem cell marker OCT3/4.

Table 1: Clinical indices and expression scores of CD133 in adult renal biopsies.

	sCr (mg/dL)	CD133 in PT	CD133 in DT
Controls $n = 16$	0.93 ± 0.07	0.50 ± 0.00	0.96 ± 0.03
TMA $n = 13$	3.06 ± 0.54*	1.84 ± 0.22*	1.69 ± 0.17*
Crescent GN $n = 13$	5.61 ± 1.23*#	2.16 ± 0.24*#	2.00 ± 0.24*
Collapsing GN $n = 9$	5.83 ± 1.11*#	2.66 ± 0.16*#	2.33 ± 0.23*#
TI disease $n = 14$	6.14 ± 0.73*#	2.35 ± 0.19*#	2.25 ± 0.25*

*$P < 0.05$ versus control; #$P < 0.05$ versus thrombotic microangiopathy (TMA); sCr: serum creatinine; TI disease: tubulointerstitial disease; PT: proximal tubules; DT: distal tubules; GN: glomerulopathy. Note: all biomarker scores have arbitrary units.

2.2. Antibodies and Immunohistochemical Stains

2.2.1. Antibodies and Dilutions. Monoclonal anti-CD133 (AC133, 1 : 50) was purchased from Miltenyi Biotec GmbH (Auburn, CA). Polyclonal anti-CD133 (1 : 500) and polyclonal cytokeratin 7 (CK7, for marking distal nephron tubules) (1 : 200) were purchased from Biocare Medical (Concord, CA). Monoclonal OCT3/4 (1 : 100) was purchased from Novocastra (Buffalo Grove, IL). AKG7 monoclonal antibody against kidney injury molecule (KIM-1) (1 : 8) was kindly provided by Dr. Joseph V. Bonventre, from the Renal Division of Brigham and Women's Hospital, Boston, MA [18].

2.2.2. Immunohistochemical Stains Using One Antibody. Renal tissue was fixed in formalin for 6–24 hours, processed according to our standard laboratory procedure, embedded in paraffin, sectioned at 3 μm thickness, and mounted on glass slides. The slides were dried at 60°C for 60 minutes. Slides were then dewaxed in 3 xylene baths for 3 minutes each, dehydrated in 3 100% alcohol baths for 3 minutes each followed by a 30-second rinse under running water. Antigen retrieval was carried out in a Tris EDTA buffer at pH 8.0 and 99°C for 20 minutes followed by a 20-minute cooldown at room temperature and a brief water rinse. Slides were then placed in 3% hydrogen peroxide for 15 minutes followed by a quick water rinse and then placed in Tris buffer pH 7.6. Finally, slides were placed into a programmed Dako Autostainer (DakoCytomation, Carpinteria, CA) using a Thermo Scientific Ultra Vision LP detection system (Kalamazoo, MI). The program consisted of 5-minute Ultra V block, 30 minutes incubation with a primary antibody, 8-minute primary antibody enhancer, 10-minute HRP polymer (equivalent to secondary antibody), and 5 minutes of the chromagen DAB to develop a brown colored stain.

2.2.3. Double Immunohistochemical Stains. To compare the segment of renal tubules expressing CD133 to that showing signs of acute injury, several double stains were performed. Cytokeratin 7 was used to identify distal nephron tubules;

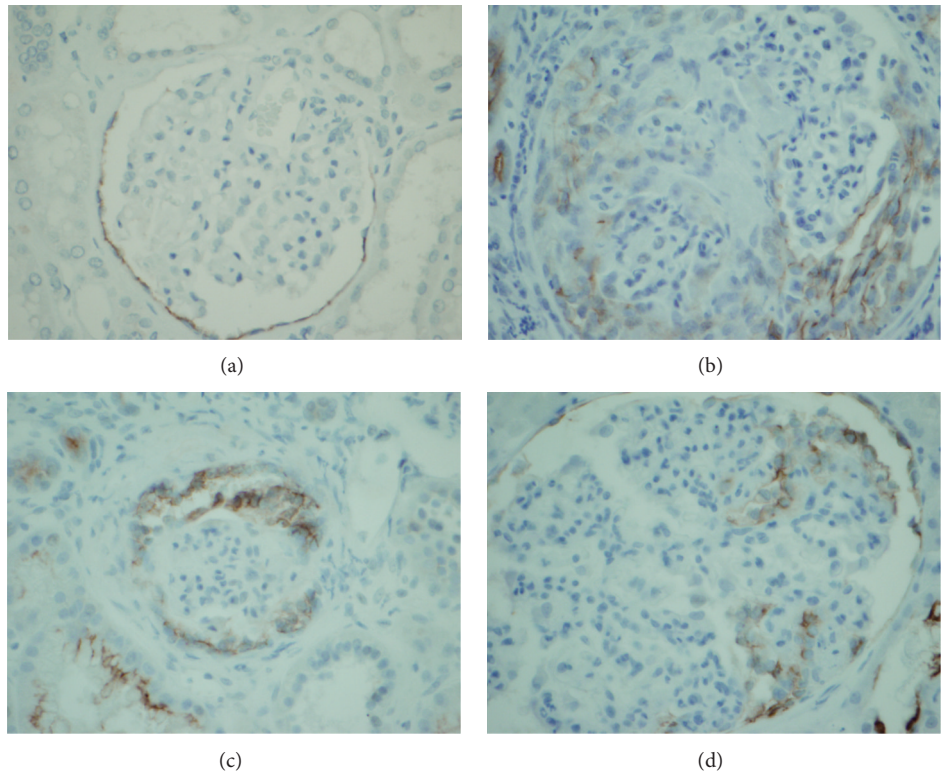


Figure 1: CD133 expression in the glomeruli of adult kidneys. CD133 is expressed weakly (1+) in the parietal epithelium of normal adult glomeruli but not in the podocytes, endothelium, or mesangium (a). In cases of glomerulonephritis, CD133 is expressed in cellular crescents (b), the proliferative epithelial component of collapsing glomerulopathy (c), and bridging tissue between parietal epithelium and visceral epithelial areas in the membranoproliferative pattern of glomerulopathy (d) (magnification ×600, (a)–(d)).

KIM-1 was used to evaluate tubular injury in proximal tubules. These dual stains included the following combinations: (1) polyclonal CD133 with monoclonal KIM-1, (2) polyclonal cytokeratin 7 with monoclonal CD133, and (3) polyclonal CD133 with monoclonal OCT 3/4. After applying the monoclonal antibody as described above, the slides were double incubated with the polyclonal antibody (Biocare Medical, Concord, CA) for 1 hour. The slides were then rinsed with TBST and incubated for 30 minutes with MACH-2, a goat anti-mouse alkaline phosphatase secondary antibody (Biocare Medical, Concord, CA). Slides were then rinsed with TBST and the chromogen substrate Vulcan Fast Red (Biocare Medical, Concord, MA) was applied for 15 minutes to develop a pink colored stain. The tissue was then counterstained with Gill-II Hematoxylin (Thermo Shandon, Pittsburgh, PA) and coverslips were applied.

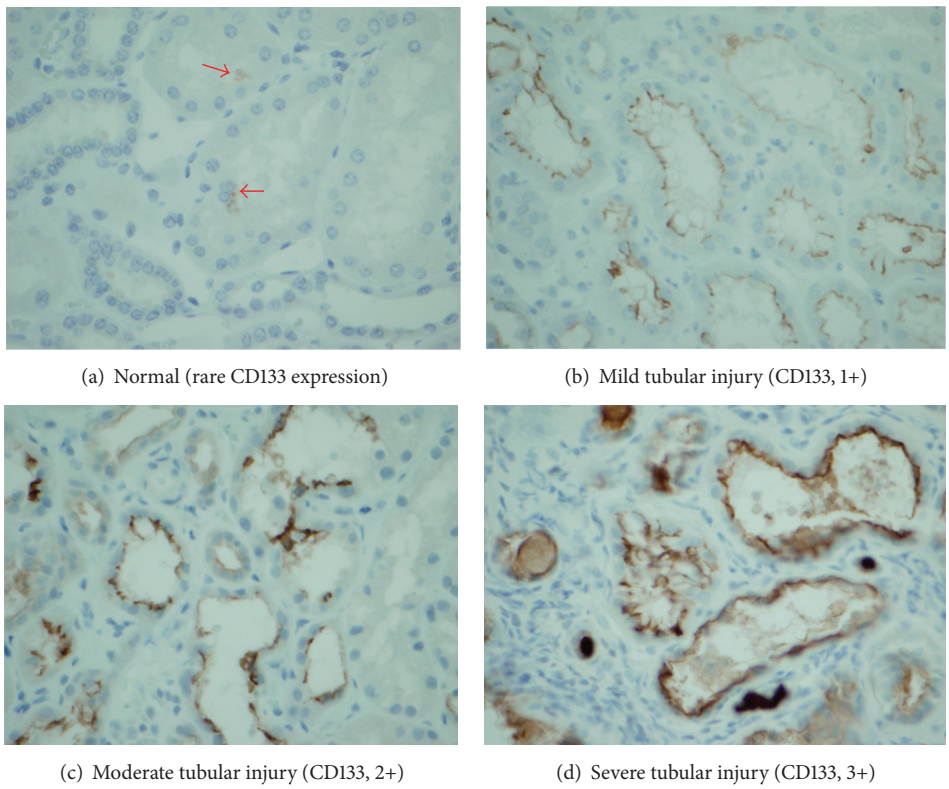
2.2.4. Quantitation of Immunohistochemical Staining and Identification of Renal Function. Granular staining intensity of CD133 along the cell membranes was graded from 0 to 3+ as follows: 0, no staining; +/− (0.50), focal weak fine granular staining; 1+, weak fine granular staining along complete luminal surface; 2+, moderate complete granular staining; 3+, strong coarse and complete granular staining. Serum creatinine levels measured in the clinical laboratory were retrospectively identified by chart review.

2.3. Statistics. Results were expressed as the mean ± SEM. The groups were compared using the ANOVA test (Statview, SAS, NC). Correlation between KIM-1 staining scores and either renal function indices or autolysis was assessed using simple regression analysis (Statview, SAS, NC). A P value less than 0.05 was considered statistically significant.

3. Results

3.1. CD133 Expression in Glomeruli with or without Disease. CD133 stained sections demonstrated 1+ staining along the cell membranes of the parietal epithelial cells. The staining was stronger near the urinary pole but weaker near the vascular pole (Figure 1(a)). There was no staining in podocytes, endothelial cells, or mesangial cells. Interstitial cells, including the endothelial and smooth muscle cells of vessels, also were negative for CD133.

In crescentic glomeruli, CD133 expression was present in 5–30% of cells in the crescents at 1+ intensity. The same proportion and intensity were seen whether crescents were of the pauci-immune or antiglomerular basement membrane type. In the crescents, CD133 positive spindle-shaped cells, mixed with some inflammatory cells, piled up in the Bowman's capsule, causing collapse of the glomerular capillary loops (Figure 1(b)). In collapsing glomerulopathy, CD133 expression was also noted in the proliferating glomerular epithelial



(a) Normal (rare CD133 expression)

(b) Mild tubular injury (CD133, 1+)

(c) Moderate tubular injury (CD133, 2+)

(d) Severe tubular injury (CD133, 3+)

Figure 2: CD133 expression in varying degrees of renal tubular injury. Under normal circumstances, only focal CD133 positive cells were noted in renal tubules (a). With injury, tubular expression of CD133 can demonstrate mild to severe upregulation (mild, (b); moderate, (c); severe, (d)) (magnification ×400, (a)–(d)).

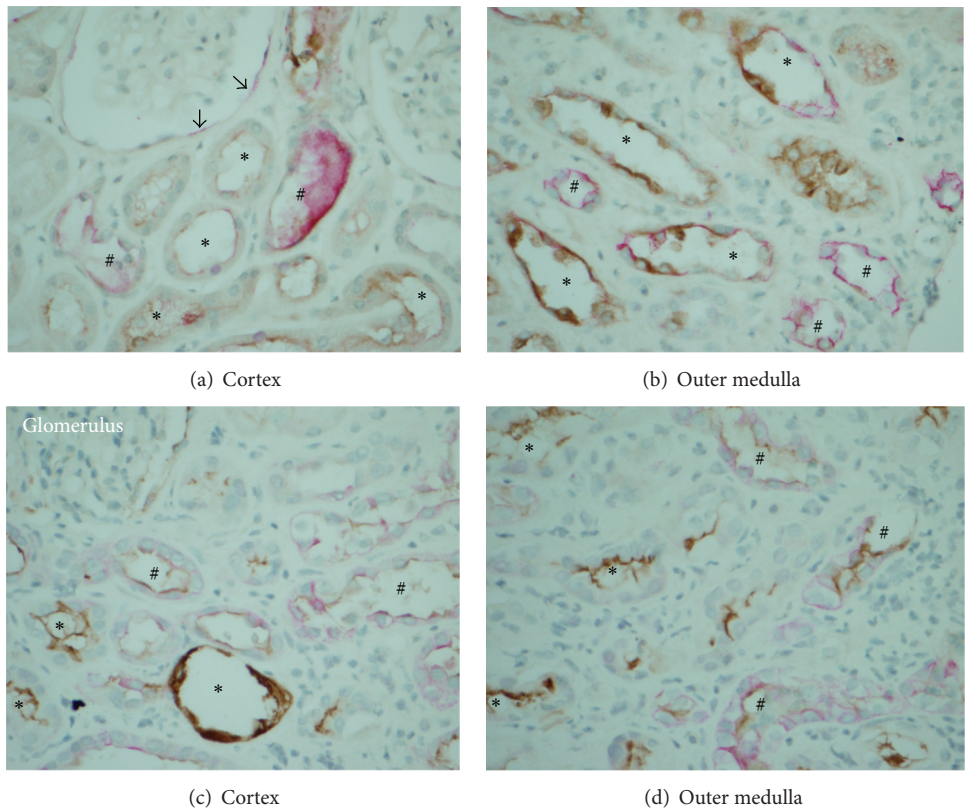
cells, suggestive of a parietal epithelial origin for these cells (Figure 1(c)). In membranoproliferative patterns of glomerulopathy such as thrombotic microangiopathy, CD133 expression was present in the parietal epithelial cells and the sclerotic junction bridging to podocytes in approximately 20% of glomeruli (Figure 1(d)).

3.2. CD133 Expression in Renal Tubules with or without Injury. In unremarkable renal parenchyma with negative staining for KIM-1, very scattered staining of CD133 along luminal membranes was seen in less than 5% of proximal tubules either around glomeruli, in the medullary rays, or in the outer stripes (Figure 2(a)). This pattern of patchy CD133 membranous staining was also noted in the distal nephron tubules including the loop of Henle and collecting ducts, particularly in the deep medulla.

Acute tubular injury cases included either primary acute tubular injury in native kidneys or secondary acute tubular injury due to tubulointerstitial or glomerular diseases. Depending on the magnitude of damage, the injured proximal tubules had a gradient of CD133 expression along the luminal membranes, in a pattern almost identical to positive membranous KIM-1 expression. With mild injury, a 1+ granular expression of CD133 was present in majority of luminal surface membranes and the cytoplasm of proximal tubules remained abundant (Figure 2(b)). With moderate injury, the tubular cell cytoplasm became more noticeably atrophic and 2+ expression of CD133 was seen not only along luminal membranes but also in the basolateral membranes (Figure 2(c)). When severe injury occurred many tubular epithelial cells had sloughed off, leaving positive CD133 staining along the naked basement membrane. The attached but injured epithelial cells showed an attenuated cytoplasm with nearly the entire cell membrane staining positively for CD133 (Figure 2(d)).

Injured proximal tubule cells coexpressed CD133 and KIM-1 in the same distribution (Figures 3(a) and 3(b)). Injured distal nephron tubules showed coexpression of CK 7 and CD133 (Figures 3(c) and 3(d)). Thus there was an upregulated CD133 expression in both injured proximal and distal tubules. Despite an upregulated CD133 expression in injured tubules, endothelial and smooth muscle cells of interstitial vessels and interstitial fibroblasts remained negative for CD133 staining.

3.3. Correlation between Tubular CD133 Expression and Serum Creatinine in Adult Cases. Serum creatinine levels and CD133 intensity scores in renal tubules for all groups are summarized in Table 1. AKI groups (groups 2–5) had significantly higher serum creatinine levels and CD133 straining scores when compared to control group 1 (Table 1). There was a significant correlation between CD133 expression in proximal tubules and serum creatinine levels ($n = 67$, R value = 0.57, and $P = 0.0001$), taking the control (group 1) and AKI (group 2–5) groups together (Figure 4). In addition, the expression of



(a) Cortex (b) Outer medulla

(c) Cortex (d) Outer medulla

Figure 3: Confirming CD133 upregulation in the injured renal proximal and distal tubules. KIM-1 is an injury marker, only positive in the injured proximal tubules [18]. With tubular injury, proximal tubules were diffusely positive for both CD133 (pink) and KIM-1 (brown) in the proximal tubules (*) of both cortex (a) and outer medulla (b), whereas CD133 (pink) was also positive in distal tubules (#) of both cortex (a) and outer medulla (b). To confirm CD133 positivity in the injured distal nephron tubules, we used cytokeratin 7 (CK7) staining as a distal tubular marker in (c) and (d). In addition to positive CD133 (brown) in the injured proximal tubules (*) from both cortex (c) and outer medulla (d), CD133 (brown) coexpressed with CK7 (pink) in the distal tubules (#) from both cortex (c) and outer medulla (d) (Magnification ×600, (a)–(d)).

CD133 in distal nephron tubules was also significantly related to serum creatinine levels ($n = 67$, $R = 0.49$, and $P = 0.0001$).

3.4. Expression of CD133 in Renal Epithelial Tumors. An example of negative CD133 in clear cell RCC is presented in Figure 5(a). There was strong and diffuse expression of CD133 in all 11 cases of clear cell papillary renal cell carcinoma (Figure 5(b)). The expression of CD133 was seen in other types of renal tumors as well but with low intensity and frequency (Table 2). Another stem cell marker, OCT3/4, was also expressed in the nuclei of 10/11 clear cell papillary renal cell carcinoma. Coexpression of CD133 and OCT3/4 is present in clear cell papillary renal cell carcinoma (Figure 5(c)). OCT3/4 was entirely negative in the remaining renal tumors studied. When we evaluated the injured peritumoral renal tubules, we found that the regenerative tubules near the various types of tumor also showed CD133 expression along tubular membranes (Figure 5(d) and Table 2).

4. Discussion

Using both monoclonal (AC133 clone) and polyclonal antibodies against CD133, our data confirmed that in unremarkable adult kidneys, CD133 expression was present in the majority of glomerular parietal epithelial cells, particularly near the urinary pole, but was absent in podocytes, endothelial cells, and mesangium as shown by the same group of investigators [8]. Second, our data revealed positive CD133 in the cellular crescents of crescentic glomerulonephritis and the proliferative epithelium in collapsing glomerulopathy as shown previously [10], supporting the view that glomerular crescents are most likely derived from the progenitor cells of parietal epithelium. However, the expression of CD133 in these glomerular epithelial lesions could range from 5 to 30% of cells and was mainly weakly staining. We feel that part of this inconsistent staining of CD133 in glomerular epithelial lesions resulted from the fact that glomerular epithelial lesions had a large inflammatory components and crescents may range from cellular type to fibrocellular types.

We identified patchy CD133 expression along the luminal membranes of both proximal and distal nephron tubules in unremarkable adult kidneys. Morphologically, the CD133 positive cells were indistinguishable from the surrounding tubular epithelium. In cases of primary and secondary acute tubular injury, there was consistent membranous CD133 expression in injured proximal and distal nephron tubules, similar to other recent reports [4, 13, 14]. As a transmembrane

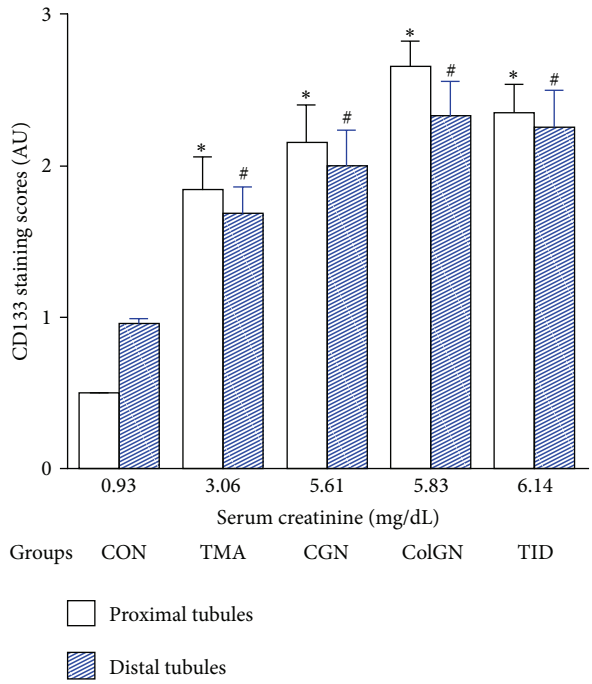
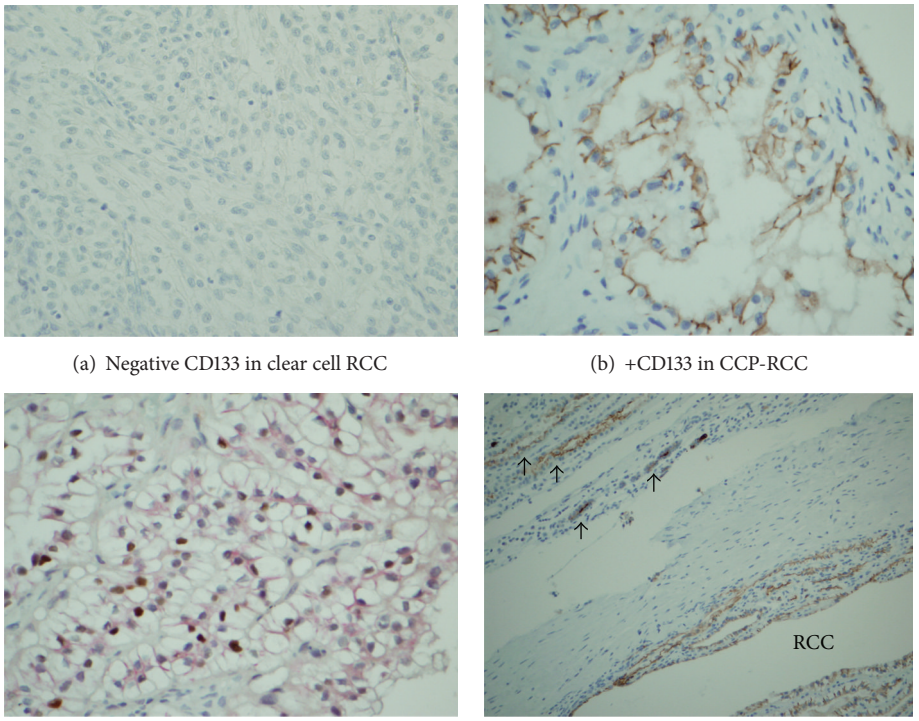


Figure 4: CD133 expression in proximal tubules and distal tubules with a range of serum creatinine. $^{*}P < 0.05$ versus control proximal tubules and $^{\#}P < 0.05$ versus control distal tubules. Con: control, TMA: thrombotic microangiopathy, ColGN: collapsing glomerulopathy, CGN: crescentic glomerulopathy, and TID: tubulointerstitial disease.



(a) Negative CD133 in clear cell RCC

(b) +CD133 in CCP-RCC

(c) + CD133 and OCT3/4 in CCP-RCC

(d) CD133 in peritumoral tubules (arrows)

Figure 5: CD133 expression in clear cell papillary renal cell carcinoma (RCC). CD133 stained negatively in a clear cell RCC (a) but showed diffuse cellular membrane expression of CD133 (monoclonal) in clear cell papillary RCC (b). The clear cell papillary RCC cells also demonstrated coexpression of CD133 (polyclonal) and OCT3/4 (monoclonal), another stem cell marker in the same tumor cells (c). CD133 was expressed in clear cell papillary RCC and regenerative tubules at the peritumoral area (d) (magnification ×400, (a)–(c); ×200, (d)).

Table 2: CD133 expression in renal Epithelial tumors.

	Positive/total (%)	Score 0	Score 1+	Score 2+	Score 3+	Peritumor tubules
Clear cell papillary RCC	11/11 (100%)	0	0	2	9	11/11
Clear cell RCC	2/20 (10%)	18	2	0	0	16/16
Papillary RCC	8/15 (53%)	7	5	1	2	13/13
Chromophobe RCC	1/7 (14%)	6	1	0	0	5/5
Oncocytomas	1/5 (20%)	4	1	0	0	4/4
Wilms' tumor	4/14 (28%)	0	4	0	0	13/13

RCC: renal cell carcinoma.

glycosylated protein, CD133 seems to play a functional role as an "organizer" of plasma membranes, since several studies have reported its interaction with membrane components [7]. In proximal tubules, we found that the intensity of CD133 membranous expression, ranging from weak to strong, correlated with the severity of tubular injury and the staining intensity of KIM-1, a specific injury marker for proximal tubules [18]. Because KIM-1 repairs injured proximal tubules primarily by mediating phagocytosis of cellular debris [19], one can argue that the membrane "organizer" CD133 may also be involved in tubular epithelial repair in addition to serving as a marker for progenitor cells. We think that CD133-positive regenerative tubular epithelial cells must possess some properties of progenitor cells which enable them to reconstitute the renal tubules following an injury. Although there is no other specific injury marker available for distal nephron tubules, the widely distributed positivity for CD133 along the distal tubular membranes during injury suggests that CD133 upregulation serves as an injury marker in this location as well when compared to the patchy CD133 expression in noninjured distal tubules. Under normal circumstances, patchy CD133 positive cells may represent "surveillance" cells that monitor the tubular environment for signs of injury. With tubular injury, it is unclear whether the "surveillance" cells would stimulate the surrounding cells to upregulate CD133 or the injury itself would induce CD133 expression in these cells. If the activated CD133-positive cells are truly "progenitor-like" during injury repair, as opposed to simply being activated mature cells, they could be described as "silent" or "stealth" progenitor cells under noninjured conditions. Many questions remain to be answered in future investigations.

There is a growing body of evidence which suggests that cancer stem cells are a force which drives the rapid growth and metastasis of malignant tumors [6]. Previous studies demonstrate that cells induced to undergo epithelial mesenchymal transformation (EMT) acquire stem-cell-like qualities [5]. This would explain why patients with end-stage kidney disease have a higher risk of developing renal cell carcinoma [20–22] as the regenerative tubules partially undergo an EMT. One leading kidney cancer stem cell research group has provided base evidence that various RCCs contain some cancer stem cells [16, 23]. The authors isolated CD133-positive stem/progenitor cells from interstitial or peritubular cell populations [12]. They then isolated CD133-positive cancer stem cells from cases of clear cell RCC and papillary RCC; these cells represented 1% of the total population [15]. The CD133-positive cancer stem cells can support other existing RCC cells in tumors that are transplanted into mice but cannot reconstitute the tumor by themselves, indicating that CD133 cancer stem cells may provide the support system for the tumor to grow [16].

In our current study, we identified CD133 expression in peritumoral regenerative tubules from all renal tumor cases, but we are uncertain for the association between the CD133 staining in regenerative tubules and the renal tumors. Clear cell papillary RCC is a low grade RCC that is commonly found in patients with end-stage renal disease [17, 24]. Clear cell papillary RCC demonstrated strong, diffuse membranous CD133 expression in all 11 cases. CD133 expression varied from 14% to 50% of cells in the other tumor types. From this study, it appears that cancer cells, with stem-cell-like properties, may be present in renal tumors although their prevalence varies remarkably. Clear cell papillary RCC appears diffusely positive for two stem/progenitor cell markers (CD133 and OCT3/4). Additional studies are warranted to determine the possible link between EMT in injured kidneys, the expression of progenitor-like cells, and the initiation of tumorigenesis.

In conclusion, glomerular and tubular epithelial cells showed upregulation of CD133 with various degrees of kidney injury. In other words, a subpopulation of glomerular and tubular epithelial cells retains properties of progenitor cells; this subpopulation markedly expands in response to renal injury. This supports the concept that the surviving glomerular and tubular epithelium are the reservoir that reconstitutes the damaged parenchyma. Finally, the extensive presence of CD133 expression in clear cell papillary RCC helps differentiate this renal tumor from other renal tumors.

Conflict of Interests

The authors declare that they have no financial or nonfinancial conflict of interests to disclose.

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