Pericyte CD248 promotes fibrosis through induction of pro-fibrotic macrophages during kidney injury

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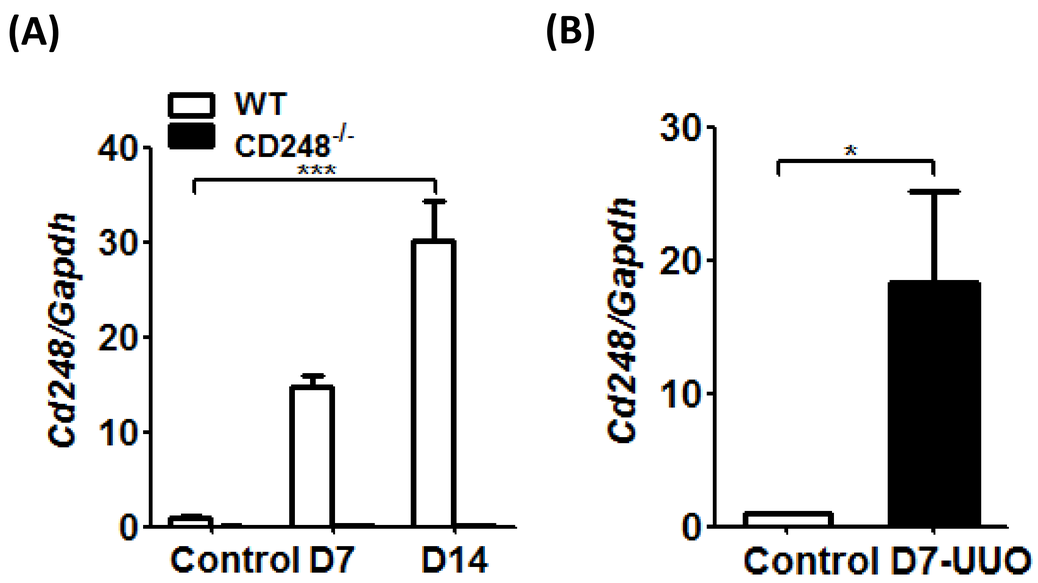
Introduction

CD248, also known as endosialin or tumor endothelial marker 1, is a type I transmembrane glycoprotein that is expressed in stromal cells of normal kidneys and uterus after birth. Using lacZ knock-in (KI/+) mice we have shown that *Cd248* expression decreases in most organs but increases and persists in postnatal kidneys, specifically in glomerular mesangial cells and pericytes/perivascular fibroblasts. In human chronic kidney disease, upregulated expression of CD248 is shown in myofibroblasts, which is negatively associated with renal survival. Although limited experimental data suggest that CD248 is involved in the cross-talk with the post-receptor signalling and cell proliferation of fibroblasts activated by platelet-derived growth factors, the role of CD248 in kidney fibrosis is still unclear. Many studies including ours have identified $CD248^{+}$ pericytes as the major source of precursors of scar-producing myofibroblasts during progressive kidney fibrosis.

Method

Unilateral ureteral obstruction (UUO) was used as a kidney fibrosis models. Fibrosis and cell number of macrophages were quantified by Picosirius Red stain and immunohistochemistry respectively. The expression of fibrotic genes was check by qPCR.

Fig. 1: CD248 were up-regulated after kidney injury

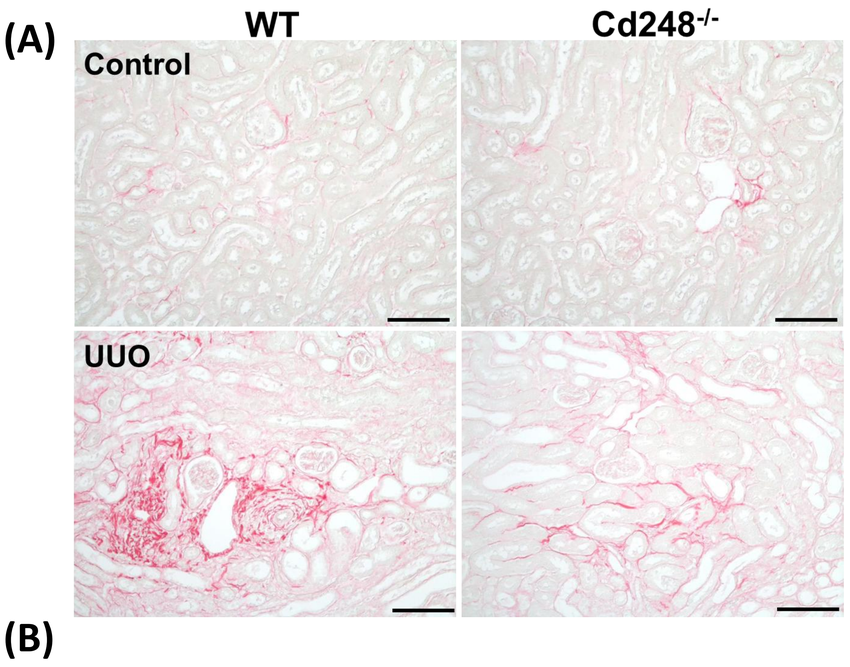


(A) Quantitative polymerase chain reaction (QPCR) of renal *Cd248* in mice of wild type (WT) and CD248 knockout ($Cd248^{-/-}$) before (control) and after unilateral ureteral obstruction (UUO) surgery. The expression was normalized by glyceraldehyde 3-phosphate dehydrogenase (Gapdh) first and then compared with that of WT control. **(B)** QPCR of *Cd248* in pericytes and myofibroblasts isolated from control and day 7 UUO kidneys of Co1a1-GFPTg mice respectively.

Results

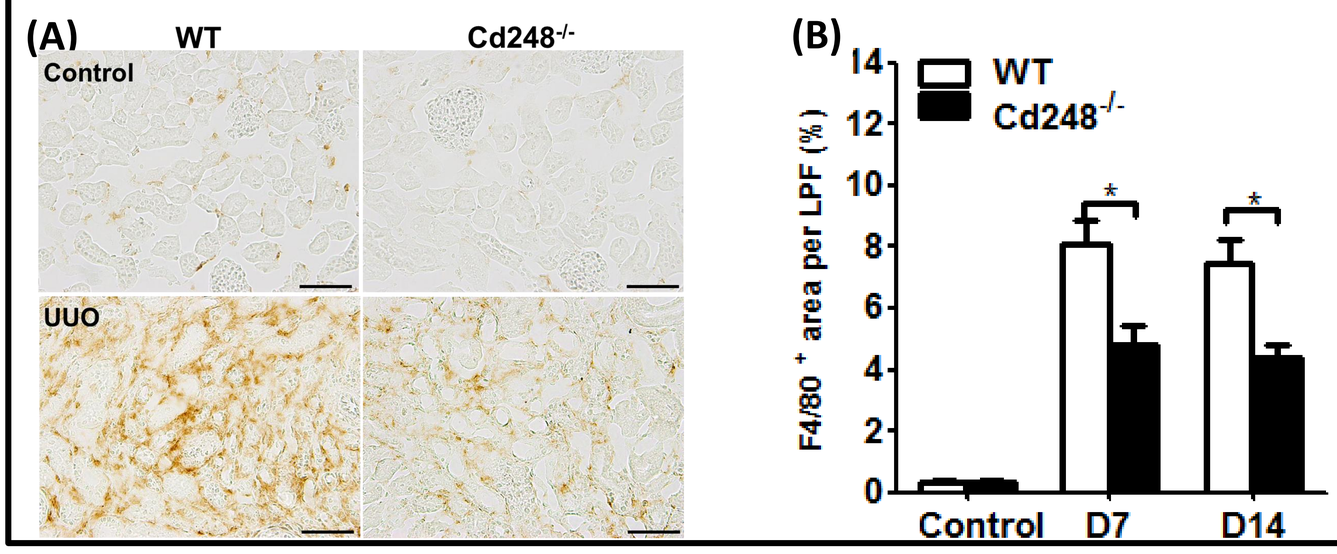
To study the role of CD248 in kidney fibrosis, we first compared the kidney fibrosis between wild type (WT) and $Cd248^{-/-}$ mice subjected to unilateral ureteral obstruction (UUO) surgery. The expression of Cd248 increased in kidneys of WT mice after UUO surgery (Figure 1A). However, Cd248 was not detected in kidneys of Cd248-/- mice (Figure 1A). *Cd248* was detected in pericytes and markedly increased in myofibroblasts who were isolated from control and day 7 UUO kidneys of Col1a1-GFPTg mice respectively (Figure 1B). Using Sirius red staining for collagen fibril, $Cd248^{-/-}$ mice showed attenuated kidney fibrosis (Figure 2A, B). The increased expression of *Col1a1* in UUO kidneys and myofibroblasts was also attenuated by CD248 disruption (Figure 2C, D). Moreover, the cell numbers of macrophages were also decreased in $Cd248^{-/-}$ UUO kidneys (Figure 3).

Fig. 2: Targeted disruption of Cd248 gene attenuates kidney fibrosis



(A) Representative images of Sirius red staining in kidneys before (control) and day 14 after UUO surgery. Original magnification X200. Scale bar, 100 μm. **(B)** Quantification of Sirius red+ collagen fibril in low-powered field (LPF) images of kidney section taken at magnification X100. * : $p<0.05$.

Fig. 3: *Cd248* disruption reduces infiltration of macrophages during kidney fibrosis



(A) Representative images of F4/80 immunostaining for macrophages in control and day 14 UUO kidneys. Original magnification X200. Scale bar, 100 μm. **(B)** Quantification of $F4/80^{+}$ area in LPF images of kidney section taken at magnification X100. **(C)** QPCR of *Ccl17* in macrophages isolated from UUO kidneys.
* : $p<0.05$.

Conclusion

Our data showed that expression of *Cd248* was upregulated in the fibrotic kidney myofibroblasts of mouse model induced by unilateral ureteral obstruction (UUO). $Cd248^{-/-}$ showed less fibrosis and cell numbers of macrophages in the UUO kidneys. Moreover, UUO kidney macrophages expressed lower levels of chemokinde (C-C motif) ligand 17 (Ccl17) in Cd248KI/KI mice, suggesting CD248 deficiency led to a decrease of pro-fibrotic macrophages.

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