CD248/Endosialin: A Novel Pericyte Target in Renal Fibrosis

Monica Chang-Panesso Benjamin D. Humphreys

Renal Division, Washington University School of Medicine, St. Louis, Mo., USA

Fibrotic diseases such as chronic kidney disease (CKD) are estimated to account for up to 45% of deaths in the industrialized world. Until recently, there have been no therapies for these diseases that include cirrhosis, idiopathic pulmonary fibrosis, systemic sclerosis, dilated cardiomyopathy and others. In October 2014, however, the FDA approved 2 new therapies for idiopathic pulmonary fibrosis based upon convincing phase 3 trial results [1, 2]. As a consequence, there is reason for optimism that new therapies for other fibrotic diseases – like CKD – may be on the horizon.

The last 10 years have witnessed substantial progress in our understanding of the pathophysiology of CKD, including the important role of interstitial pericytes and perivascular fibroblasts as the cell of origin for myofibroblasts [3–5]. Under conditions of chronic injury, damage to tubular epithelial cells triggers dedifferentiation leading to cell cycle arrest and secretion of profibrotic mediators [6]. These act on interstitial cells, predominantly pericytes, which proliferate and differentiate into myofibroblasts leading to the accumulation of matrix proteins and fibrosis. The process of pericyte differentiation causes migration away from capillary endothelial cells, triggering their destabilization and capillary rarefaction with chronic hypoxia. Identifying molecular regulators of this transition from pericyte to myofibroblast is thus a priority in order to develop new therapies for CKD.

It is in this context that the Buckley group [7] has investigated the role of CD248, also known as endosialin, in

pericyte to myofibroblast transition and CKD. CD248 was first identified as a tumor vascular endothelial antigen in the early 1990s [8]; however, it was later reported to be a marker of stromal fibroblasts and a subset of pericytes associated with tumor vessels as well as human mesenchymal stem cells, but not tumor endothelium [9, 10]. CD248 is known to bind to extracellular matrix proteins and also modulates transmembrane signaling pathways, including the platelet-derived growth factor (PDGF) receptor pathway.

A previous study from this group showed that CD248 is expressed in the mesangium and a subset of interstitial cells in healthy kidney. CD248 expression was upregulated during fibrosis, and expression correlated with progression of human renal disease [11]. This expression pattern was consistent with a pericyte identity of CD248-positive cells and provided an encouraging basis on which to investigate the functional role of CD248 in fibrosis. In this study, Smith et al. [11] used a panel of pericyte markers including PDGFR- β , NG2, α -smooth muscle actin (α SMA) and desmin, and find CD248 present in a majority but not all of these pericytes. This result itself points to heterogeneity within the stromal compartment of kidney – an underinvestigated area. Indeed, the authors conclude that CD248 serves as a marker of a stromal subset, which is not identified by commonly used pericyte markers. In the unilateral ureteral obstruction (UUO) model of renal fibrosis, CD248 expression increased progressively with high CD248 expression in vascular pericytes

and stromal fibroblasts/myofibroblasts in UUO samples, but low in sham samples with expression limited to a small group of pericytes and mesangial cells of the glomerulus. Bone marrow transplantation studies confirmed that none of the CD248+ kidney cells originated from a hematopoietic stem cell precursor.

To define the function of CD248, the authors subjected CD248^{-/-} versus wild-type mice to UUO. CD248^{-/-} mice were protected from renal fibrosis, with less collagen deposition by Sirius red staining and also less collagen-1 α 1 mRNA expression as compared to wild-type mice. There was no significant difference in the leukocyte response by immunofluorescence staining for CD45, CD3 and F4/80; therefore, the protection from renal fibrosis was not related to a change in the inflammatory response. This important result bolsters the authors' conclusion that CD248 regulates pericyte fate in kidney fibrosis – rather than modulating the global inflammatory response. The authors also found substantially reduced numbers of α SMA+ interstitial myofibroblasts in knockout mice, with increased numbers of NG2+ pericytes remaining in close contact with endothelium even at day 14 of UUO. This suggested the possibility of a reduction in fibrosis-induced capillary rarefaction in knockout mice, which was confirmed by CD31 staining and quantitation.

Although the precise mechanism for the profibrotic effect of CD248 remains unclear, there are several intriguing possibilities raised by this work. The authors show that primary renal fibroblasts isolated from CD248 knockout versus wild-type mice had differences in proliferation rates, with knockout mice exhibiting slower basal proliferation as well as reduced collagen secretion in vitro. Thus, CD248 may be promoting the proliferation of pericytes after injury, as they differentiate into collagen-secreting myofibroblasts. Whether this proliferative sig-

nal is mediated by the matrix-binding properties of CD248 or by its known ability to potentiate PDGF signaling is unclear. Recent studies in hepatic fibrosis, however, have provided evidence that CD248 does promote fibrosis by enhancing a PDGF pro-proliferative signal to hepatic stellate cells [12]. Combined with established roles for the PDGF signaling axis in renal fibrosis [13], a role for CD248 in enhancing PDGF signaling in kidney pericytes during fibrosis appears likely.

These studies confirm CD248 as a promising new therapeutic target in renal fibrosis. It will be important to establish the mechanism by which CD248 loss ameliorates kidney fibrosis because this knowledge would set the stage for translational studies in humans. A humanized monoclonal anti-CD248 antibody, ontuxizumab, has recently completed a first-in-human phase I dose-escalation study in patients with advanced solid tumors [14]. Most recently, a proof-of-concept study reported on the effective use of a monoclonal anti-CD248 antibody conjugated to a potent cytotoxic small molecule (antibody-drug conjugate) in endosialin(+) tumors [15]. This growing armamentarium of therapeutics targeting CD248 might be repurposed to treat human CKD. The convergence of expanding knowledge concerning novel therapeutic targets in renal fibrosis, new targeted therapies and the recent emergence of the first FDA-approved anti-fibrotic therapies make these exciting times in fibrosis research.

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