

The Role of Bone Marrow-Derived Fibroblasts in Renal Fibrosis

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Abstract

Renal fibrosis is a salient pathological feature of chronic kidney disease, which leads to destruction of renal parenchyma and progressive loss of kidney function. Although activated fibroblasts are the effector cells that are responsible for the excessive production and deposition of extracellular matrix, the cellular origin of these cells has been of intense debate. It was traditionally thought that resident fibroblasts are the source of increased extracellular matrix. Recently, a novel paradigm for the pathogenesis of renal fibrosis has emerged – bone marrow-derived fibroblast precursors migrate into kidney and contribute significantly to the pathogenesis of renal fibrosis. This review focuses on recent advance in our understanding of the role of bone marrow-derived fibroblasts in renal fibrosis.

Keywords: Chemokine; Bone marrow-derived cells; Fibroblasts; Fibrocytes; Renal Fibrosis; Extracellular matrix; Chronic kidney disease

Background

Chronic kidney disease is a growing public health problem. Renal fibrosis is a hallmark of chronic kidney disease and the degree of interstitial fibrosis correlates well with the progression of kidney disease, regardless of the underlying etiology [1,2]. Renal interstitial fibrosis is characterized by fibroblast activation and excessive production and deposition of extracellular matrix (ECM), which leads to the destruction and collapse of renal parenchyma and progressive loss of kidney function. Because fibroblasts are the principal effector cells that are responsible for ECM production in the fibrotic kidney, their activation is regarded as a key event in the pathogenesis of renal fibrosis [3,4]. However, the origin of these fibroblasts remains controversial.

Activated fibroblasts are traditionally thought to arise from resident renal fibroblasts. Recent evidence indicates that they may originate from bone marrow-derived progenitor cells [5-9]. A study of mismatched kidney transplantation in humans has shown that the proportion of host-derived SMA-positive cells is approximately 30% in allografts undergoing chronic rejection compared with 10% in those without rejection [7]. In rodent models of renal fibrosis, several studies using bone marrow transplantation have shown that bone marrow-derived fibroblasts migrate into the kidney in response to injury [5,8-12]. For example, one study using bone marrow transplantation of transgenic mice that express enhanced green fluorescence protein (GFP) under the control of the fibroblast specific protein 1 (FSP1) promoter has demonstrated that 15% of bone marrow-derived fibroblasts are present in the kidney 10 days after obstructive injury [5]. Another study using bone marrow transplantation of transgenic rats that express human placental alkaline phosphatase has shown that more than 30% α -SMA positive myofibroblasts are derived from bone marrow 7 days after ischemia-reperfusion injury [8].

The bone marrow-derived fibroblast precursors termed fibrocytes were first identified in the peripheral circulation in 1994 [13]. These cells arise from a subset of bone marrow-derived monocytes with fibroblast-like features. They express mesenchymal markers such as collagen I and vimentin and hematopoietic markers such as CD45, CD11b, and CD34 [13-16]. These cells in culture display an adherent, spindle-shape morphology and express α -SMA that is enhanced when cells are treated with TGF- β 1, consistent with the concept that they

can differentiate into myofibroblasts [14-16]. The differentiation of fibrocytes is regulated by other inflammatory cells, such as CD4⁺ T cells, via secretion of cytokines [17]. Profibrotic cytokines IL-4 and IL-13 promote fibrocyte differentiation, where as antifibrotic cytokines IFN- γ and IL-12 inhibit its differentiation, suggesting a complex interplay among the inflammatory cells in the inflamed milieu determines the fate of bone marrow-derived fibroblasts [18,19].

We have recently provided unequivocal evidence that bone marrow-derived fibroblasts accumulate in the kidney in response to obstructive injury [9]. We demonstrate that CD45 and vimentin dual positive fibroblasts or CD11b and vimentin dual positive fibroblasts accumulate in the kidney in response to obstructive injury using confocal microscope. To confirm the bone marrow origin of these cells, we have generated chimeric mice using bone marrow transplantation. The donor mice express GFP under the control of collagen α 1(I) promoter [20]. Our results demonstrate that bone marrow-derived CoI-GFP cells are present in the obstructed kidney, but not in the normal kidney.

The signaling mechanisms underlying the recruitment of bone marrow-derived fibroblast precursors into kidney are incompletely understood. Chemokines play an important role in the regulation of fibroblast precursor infiltration in response to injury. Chemokines are classified based on the relative position of cysteine residues near the NH2 terminus into four major families: CC, CXC, C, and CX3C [21,22]. Chemokines activate their seven-transmembrane G protein-coupled receptors and play primary roles in mediating the trafficking of circulating cells during inflammation [23]. Recently it has been reported that CCL21 and its receptor-CCR7 are involved in the infiltration of circulating fibroblast precursors in the kidney in a murine model of renal fibrosis induced by obstructive injury [6].

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CXCL16 is a recently discovered cytokine belonging to the CXC chemokine family [24]. There are two forms of CXCL16. The soluble form generated by its cleavage at the cell surface functions as a chemoattractant to recruit circulating cells. The transmembrane form has a transmembrane structure which functions as an adhesion molecule for CXCR6 expressing cells and scavenger receptor for oxidized low-density lipoprotein. We have recently found that CXCL16 is induced in response to obstructive injury [9]. Specifically, we demonstrate that CXCL16 mRNA is induced in the kidney in response to obstructive injury in a time-dependent manner and CXCL16 protein is upregulated mainly in the kidney epithelial cells in the obstructed kidney. Furthermore, we show for the first time that CXCL16 is pathologically important because targeted disruption of CXCL16 causes a significant decrease in the number of bone marrow-derived fibroblast precursors in the kidney in response to obstructive injury. These data indicate CXCL16 plays a critical role in recruiting bone marrow-derived fibroblast precursors into the kidney.

Fibrocytes express certain chemokine receptors such as CCR2, CXCR4, and CCR7 and inhibition of these chemokine receptors has been shown to suppress fibrosis through suppression of fibroblast precursor infiltration into injured tissues [20,25,26]. Recently, we demonstrate for the first time that bone marrow-derived fibroblast precursors express CXCR6, the receptor for CXCL16 [9]. CXCR6 was first cloned as an orphan receptor in 1997 [27-29] and was termed STRL33, BONZO, or TYMSTR. We then show that targeted disruption of CXCL16 suppresses the infiltration of CD45, CXCR6 and collagen I triple positive fibroblast precursors into the kidney, suggesting that CXCL16 regulates fibroblast precursor trafficking by an interaction with its receptor - CXCR6 [9].

Myofibroblasts are a population of smooth muscle-like fibroblasts that play a central role in wound healing and fibrosis [30]. Their activation is generally considered a key event in the pathogenesis of renal fibrosis [3,4]. Furthermore, experimental and clinical studies have shown that the number of interstitial myofibroblasts correlates closely with the severity of tubulointerstitial fibrosis and the progression of kidney disease [31-33]. We have recently demonstrated that bone marrow-derived myofibroblasts identified as CD45 and α -SMA dual positive cells accumulate in the injured kidney of WT mice, whereas their accumulation is significantly reduced in the injured kidney of CXCL16-KO mice [9]. This finding strongly indicates that bone marrow-derived fibroblast precursors are activated in the kidney and contribute to the population of renal myofibroblasts.

A salient pathological feature of renal fibrosis is a striking increase and deposition of extracellular matrix proteins including collagen and fibronectin. Morphometric analysis of picrosirius red staining of kidney sections at day 14 after obstructive injury demonstrates the presence of interstitial collagen deposition. This collagen deposition is significantly attenuated in the obstructed kidneys of CXCL16-KO mice [9]. Consistent with these findings, we further illustrate that the mRNA and protein levels of collagen I and fibronectin are markedly increased in the injured kidneys of WT mice, whereas these responses are significantly inhibited in the injured kidney of CXCL16-KO mice.

In summary, recent studies have demonstrated that bone marrow-derived fibroblasts migrate into kidney and contribute significantly to

the pathogenesis of renal fibrosis in response to injury. Furthermore, our study defines a novel mechanism by which CXCL16 participates in renal fibrosis. In response to injury, the upregulated CXCL16 recruits circulating fibroblast precursors into the kidney, which play a critical role in the pathogenesis of renal fibrosis. These data suggest that inhibition of CXCL16 could represent a novel therapeutic approach for fibrotic kidney disease.

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