Renal fibrosis and the origin of the renal fibroblast

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Many studies have determined that the extent of tubulointerstitial involvement, particularly fibrosis, correlates better with renal function than glomerular changes do, thus, the extent of tubulointerstitial damage in any given renal biopsy has important implications for the renal prognosis of the patient (summarized in [1]). Tubulointerstitial fibrosis is characterized by the accumulation of extracellular matrix components including collagen types I, III, IV, proteoglycans and fibronectin. In recent years, much controversy has been created in the nephrology community regarding the origin of matrix-producing cells in the kidney. Several possibilities exist, including activation of resident interstitial fibroblasts, migrating haematopoietic or mesenchymal stem cells from the bone marrow, periadventitial cells and epithelial-mesenchymal transition (EMT) of tubular epithelial cells. This review summarizes recent data indicating the possible origin of matrix-producing cells in the kidney, and illustrates from a clinical point of view why this may be important.

Traditionally, resident interstitial fibroblasts have been thought to be the sole source of extracellular matrix. In 1867, Cohnheim published a classical article on mechanisms of inflammation, stating that fibroblasts (called contractile cellular elements at that time) are descendents of migrating leucocytes [2]. This theory was widely believed for over a century, until Ross and coworkers [3] demonstrated, in a very elegant set of experiments with the use of parabiotic rats, that fibroblasts were of local origin. Nevertheless, recent controversy exists regarding the origin of matrix-producing cells in the kidney, and illustrates from a clinical point of view why this may be important.

As outlined above, activated resident interstitial fibroblasts are not the only cells participating in extracellular matrix production. A number of studies have confirmed the existence of bone marrow-derived cells within the interstitium [10] and the EMT of bone marrow cells to tubular epithelium [11]. Preliminary evidence using genetically tagged fibroblast and tubular epithelial cells indicates that fibroblasts derived from bone marrow comprise about 12% of the resident interstitial population in normal murine kidneys [12]. In that study, this percentage did not change when an experimental model of progressive renal disease [the rapidly progressive model of unilateral ureteral obstruction (UUO)] was induced. Conversely, up to 36% of the additional extracellular matrix-producing cells are derived from tubular epithelial cells by EMT in that model. EMT is a variant of transdifferentiation.
and a well-recognized mechanism for dispersing cells in vertebrate embryos [13] and forming fibroblasts in injured tissues [14]. EMT is a dynamic process which involves the gradual loss of epithelial cell markers paired with a gain of mesenchymal markers and has been described mainly in models of rapidly progressive chronic failure. Disruption of the integrity of the tubular basement membrane is a prerequisite for EMT to occur and the composition of the extracellular matrix is known to influence the differentiation state of tubular epithelial cells [15]. Very recently, Yamashita and colleagues [16] determined that renal progenitor tubular cells may undergo EMT and suggested these cells as typical source of interstitial myofibroblasts.

Is the origin of the renal fibroblast comparable in different forms of progressive renal disease?

Recently, Faulkner and colleagues [17] analysed the origin of $\alpha$-smooth muscle actin positive cells in an accelerated model of angiotensin II-induced renal fibrosis after habu venom injury. The combination of angiotensin II and habu venom injections induce an accelerated model of renal fibrosis and glomerulonephritis after 14 days. Using that model, the authors determined that most, if not all, of the tubulointerstitial $\alpha$-smooth muscle actin expressing cells were of local origin. No disruption of tubular basement integrity could be detected and no traffic of proximal tubular epithelial cells into the interstitial compartment was seen by labelling with Texan Red dextran [17]. Interestingly, early expansion of $\alpha$-smooth actin positive myofibroblasts was seen in perivascular regions, corroborating similar observations by Wiggins et al. [5] in an anti-glomerular basement membrane antibody-induced nephritis and in periglomerular areas, in a study by the same group [18]. Does this mean that activation of resident interstitial fibroblasts is the sole source of myofibroblasts in the angiotensin II/Habu venom model? No, it does not. Firstly, as the authors themselves admit, EMT may still occur, since they focused on the exclusion of proximal tubular epithelial cells as the source of EMT. However, EMT may also occur in distal tubular cells. Secondly, infiltration of marrow-derived haematopoietic or mesenchymal stem cells was not excluded in the study and remains a possibility. Thirdly, as indicated before, using $\alpha$-smooth muscle actin expression alone as a marker for matrix-producing cells may not sample all these cells, as was well shown by Okada et al. [19] in a model of murine polycystic kidney disease. Finally, and perhaps most importantly, the origin of matrix-producing cells may vary according to the model used.

Therapeutic implications

Are these findings of relevance for the clinician? Not as yet, but they may prove to be of clinical importance very soon with the advent of novel anti-fibrotic therapeutics. The origin of matrix-producing cells may vary according to the underlying disease and/or the time course of renal fibrogenesis. The predominant origin of matrix-producing cells may have therapeutic implications. For example, despite their anatomic location, interstitial fibroblasts may be excellent targets for gene transfer [20]. On the other hand, the proliferation and stimulation of resident fibroblasts may be less important in other forms of chronic progressive renal disease, such as the experimental UUO model. In that model, as well as the
model of nephrotoxic serum nephritis, the formation of activated fibroblasts via EMT may be more important. Blocking EMT by bone morphogenetic protein (BMP)-7 or hepatocyte growth factor inhibit progression and, in the case of BMP-7, may even revert matrix deposition in these models [21]. Conversely, BMP-7 as an anti-fibrotic agent may not work in models where there is no or little EMT, such as the overload proteinuria model [22]. Unfortunately, the relative contribution of cellular sources to the formation of activated fibroblasts in human studies is an area of research that has just begun. Thus, it will be very interesting to see how this information gathered from experimental models will be transferred to clinical studies.

Conclusion

The renal fibroblast remains a (partial) mystery. The lack of clear-cut markers to describe this cell has hampered in vivo research of these cells. At the same time, this lack of markers may indicate the heterogeneity of this cell type. Even the myofibroblast, which is easily defined and detected in vivo due to the expression of α-smooth muscle actin, is probably only one of the several activation states of fibroblasts in the sense of matrix-producing cells. These cells may be derived from resident interstitial cells, mesenchymal and/or haematopoietic stem cells, periadventitial cells derived from resident interstitial cells, mesenchymal cell and/or haematopoietic stem cells, periadventitial cells derived from resident interstitial cells, mesenchymal and/or haematopoietic stem cells, periadventitial cells, adventitial cells, and by the process of EMT. The relative contribution of these cellular elements may vary according to the model of progressive renal disease applied. Even more interestingly, this contribution may have therapeutic implications. However, at the same time it must be stressed that almost all of these data have been generated in animal models and their significance for human renal fibrogenesis remains to be determined.

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References


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