Unexpected news in renal fibrosis

Juan A. Oliver

Commentary

A striking characteristic of many diseases of the kidney is their ability to induce decreases in function that may initially be modest but that inexorably progress until all function is lost. The anatomical correlate of this evolution is a relentless substitution of renal parenchymal cells by fibrotic tissue. Fibrosis had long been recognized as a prominent feature of diseased kidneys, but nephrology's intellectual landscape had long focused on the widely variable and aesthetically alluring glomerular changes caused by disease. A seismic change was initiated by two important discoveries that initially concerned glomerular diseases but have proven to have much wider implications in our understanding of the mechanisms responsible for the inexorable evolution of many renal diseases. First, the hypothesis by Brenner and collaborators that increases in glomerular pressures and flows initiate progressive loss of renal function led to the discovery that inhibitors of the renin-angio-tensin system retard renal-function loss and ameliorate renal fibrosis (1, 2). Second, Border and colleagues discovered that TGF-β1 is a key mediator of renal fibrogenesis (3, 4). This work not only resulted in substantial advances in patient care (2) but also initiated a veritable explosion of research aimed at elucidating the mechanisms regulating renal fibrogenesis. Elegant experimental design has attracted many research-ers to a model of fibrosis resulting from unilateral ureteral obstruction (UUO), but many other […]

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Macrophages and renal fibrosis

Macrophages have critical roles in wound healing, and a vast amount of literature suggests that they promote atherogenesis. Perhaps for these reasons, and because in many conditions the extent of renal fibrotic tissue and the number of infiltrating macrophages change in parallel, these cells have long been suspected to contribute to loss of renal function and renal fibrosis. Support for this hypothesis has been found in renal diseases of animals depleted of macrophages (7) and in animals lacking genes that encode proteins important in macrophage recruitment (8–10). The mechanism(s) whereby macrophages may facilitate renal fibrogenesis is undefined, and the myriad functions of which macrophages appear to be capable suggest that their role in this process may well be very complex. Indeed, in this issue of the *JCI*, Nishida et al. (11) present evidence that infiltrating macrophages in the kidney may play a beneficial antifibrotic role that, surprisingly, requires the action of angiotensin.

Angiotensin regulation of macrophage function

It has previously been shown that mice lacking the gene for the angiotensin receptor type 1a (Agtr1a, the predominant isoform in mice) develop less renal fibrosis with lower macrophage infiltration than wild-type mice during UUO (12), findings consistent with the well-known antifibrotic effect of inhibitors of the renin-angiotensin system and with work done with other genetic models with deficiencies in this system (13). However, the consequences of disrupting angiotensin II activity, given its vast array of cell targets, are likely to be many, and evidence exists that the renin-angiotensin system can directly regulate macrophage function (14, 15). To more precisely examine the role of infiltrating macrophages in renal fibrogenesis, Nishida et al. (11) used wild-type mice that were transplanted, after lethal irradiation, with bone marrow from mice lacking the Agtr1a gene. Unexpectedly, 2 weeks after UUO, kidneys from mice with Agtr1–deficient bone marrow showed more renal fibrosis and less infiltrating macrophages than did those from wild-type mice. Agtr1a–deficient mice also had less circulating monocytes and less macrophage precursors in the bone marrow.

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Nonstandard abbreviations used: unilateral ureteral obstruction (UUO); angiotensin receptor type 1a (Agtr1a); green fluorescent protein (GFP).

Two exciting conclusions can be drawn from this work. First, it suggests that, much indirect evidence notwithstanding, infiltrating macrophages activated by angiotensin can have antifibrotic action in the kidney; and second, it highlights the potentially important interaction between bone marrow cells and the kidney. How could infiltrating macrophages have antifibrotic action? Given the myriad actions described for these cells, the possibilities are many, but it could simply be due to their ability to phagocytize dead cells and cellular debris. Indeed, analysis of macrophage function by Nishida et al. (11) revealed that macrophages lacking Agtr1a have reduced migratory capacity and decreased phagocytic activity, a characteristic that could also be elicited in wild-type macrophages by the angiotensin II receptor antagonist losartan. Since inhibitors of the renin-angiotensin system are widely used in clinical medicine, it is urgently important to determine whether they block beneficial effects of invading macrophages. Experiments that reverse the model of Nishida et al. (11), i.e., UUO in mice that lack Agtr1a but contain wild-type bone marrow, should answer this question.

Nishida et al. (11) consider other possibilities by which invading macrophages could inhibit renal fibrosis. Macrophages can be a source of HGF (16), recently found to block the conversion of renal epithelia to mesenchymal cells (17, 18). However, because the presence of smooth muscle actin (a marker for renal interstitial fibroblasts) in the chimeras was similar to that in wild-type mice, the authors suggest that this conversion was unchanged in the chimeras. Another intriguing possibility they consider is that generation of reparative capillaries depends on invading macrophages, well known to secrete angiogenic factors. Capillary density quantified by CD31 was, surprisingly, no different between the two sets of animals. However, because newly generated endothelial cells may be negative for this marker (19), and Agtr1 appears to be involved in ischemia-induced angiogenesis (20), this possibility needs to be kept in mind.

Other, more speculative possibilities may be considered. Because pathological changes in the kidney can be self-repaired and not result in renal fibrosis, adult kidneys may contain organ-specific stem cells, and invading macrophages (or other cells from the bone marrow) may provide critical signaling for their activation. Needless to say, quite independently of macrophages, the bone marrow could also be a source of cells that directly contribute to kidney repair. A variety of exciting reports have suggested that bone marrow may function as a reservoir of stem cells for adult organs (21, 22) suggesting that hematopoietic stem cells possess broad developmental plasticity that may be important for tissue repair. While recent work indicates that under normal conditions the developmental potential of the hematopoietic stem cell may be more restricted than originally believed (23), it may be different in diseases where selective pressure may amplify rare stochastic events. Furthermore, bone marrow also contains mesenchymal stem cells that might migrate to disease organs and participate in tissue repair (24). Regardless of the mechanism whereby invading macrophages (and/or other bone marrow cells) exert their antifibrotic effect, Nishida et al. (11) cast a new light on the role of macrophages in renal fibrosis and, more importantly, call attention to possible interactions between bone marrow cells and the kidney. Indeed, the kidneys of rats transplanted with bone marrow expressing green fluorescent protein (GFP) show a surprising abundance of interstitial GFP-positive cells (25), further supporting the notion that bone marrow cells play important and unexpected roles in renal regulation and disease.

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