A blast from the mast?

The accumulation of chronic inflammatory cells in the cortical interstitial space plays a pivotal role in the formation of tubulointerstitial fibrosis (TIF) in progressive chronic renal diseases. Inflammatory cells secrete fibrotic mediators, which incite matrix-producing cells to deposit extracellular matrix proteins in the interstitium. Contemporary research has concentrated on delineating the functions of T lymphocytes and monocytes/macrophages in this pathologic process [1]. Until recently, the contribution of the mast cell to TIF has largely been overlooked [2–3]. In this issue of Kidney International, Jones et al [4] provide the first evidence to suggest that mast cell accumulation could, in part, mediate TIF in the remnant kidney rat model of progressive non–immune-mediated chronic renal disease.

To begin generating a tangible hypothesis that mast cells are one of the key cellular participants in TIF, it is pertinent to appreciate their basic biology. Mast cells are bone marrow–derived blood-borne precursor cells that mysteriously enter the mucosal surfaces and connective tissue compartments of organs [5–6]. Here, they differentiate, proliferate, and evolve into a group of durable sentinel cells, trained to monitor the local microenvironment fornoxious stimuli for weeks to months. Mast cells exhibit considerable tissue-specific functional heterogeneity, and this is a consequence of the paracrine influence of the resident organ. In humans there are at least three different phenotypes (positive for tryptase only, positive for chymase only, and positive for tryptase and chymase), whose physiologic roles remain to be defined. While the habitual role of the mast cell was once thought to be restricted to mediating type I allergic reactions via immunoglobulin E (IgE)-dependent mechanisms, they are now recognized to be important cellular transducers of not only innate immunity, but also chronic inflammation, angiogenesis, tissue remodeling, and fibrosis. These multifunctional capabilities are evidenced by the possession of cell-surface receptors for the Fc portion of IgE, cytokines/growth factors [c-kit, the ligand for stem-cell factor (SCF), which induces mast cell migration, differentiation, and degranulation], cell adhesion molecules (ICAM-1, CD44), and microbes (Toll-like receptors). Upon receptor engagement, mast cells transform into aggressive and highly versatile effector cells. Depending on the inciting stimuli, mast cells extrude from their secretory granules a plethora of preformed (most notably histamine, but also heparin, neutral proteases—tryptase, chymase, acid hydrolases, cathepsin G, carboxypeptidase) and formed inflammatory substances, including lipid mediators [prostaglandin D2, leukotriene C4, thromboxane A2, polyclonal antibody (PAF)], cytokines [tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-3–6, IL-13, granulocyte macrophage colony stimulating factor (GM-CSF), interferon-gamma (IFN-γ)], chemokines [macrophage inflammatory protein-1 (MIP-1), trichloroacetic acid-3 (TCA-3), monocyte chemotactant protein-1 (MCP-1), endothelin], growth factors [platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor-β1 (TGF-β1)], matrix metalloproteinases, and matrix proteins. Mast cells secrete active TGF-β1 by simultaneously releasing latent TGF-β1 together with the activating enzyme, chymase 1. In coculture in vitro studies mast cell products caused the activation and proliferation of fibroblasts [7].

In the normal kidney, mast cells are constitutively expressed in small numbers [3]. However, in a variety of human renal diseases, the number of mast cells in the renal interstitium is increased. These include glomerular diseases (IgA nephropathy, membranous nephropathy, crescentic glomerulonephritis, diabetic nephropathy), tubulointerstitial diseases (chronic pyelonephritis, cyclosporin nephrotoxicity), and allograft rejection. In IgA nephropathy and chronic allograft disease, interstitial mast cell number is correlated with renal function and TIF [3]. In animal models, interstitial mast cell accumulation is increased in rats fed a magnesium-deficient diet and in IL-9 transgenic mice, whereas mast cells do not appear to be present in serum sickness nephritis rat, Masugi nephritis, or rat Thy-1 nephritis [3].

In the remnant kidney rat model, Jones et al [5] found that renal injury correlated positively with interstitial mast cell accumulation (as determined by toluidine blue staining and chymase/tryptase immunohistochemistry). Although the tubular cell protein expression of the mast cell chemokine, SCF, was increased, it is notable that whole kidney mRNA levels of SCF and the other mast cell chemokines (IL-8, TGF-β1) did not correlate precisely with mast cell numbers. Mast cells being profibrotic in this model was suggested by the following: (1) mast cells expressed TGF-β1; (2) mast cells were localized to regions of tubular injury and peritubular fibrosis; and (3) renoprotection with angiotensin blockade was associated with a reduction in interstitial mast cell accumulation.

Key words: mast cell, tubulointerstitial fibrosis.

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The protective effect of angiotensin blockade may hold particular relevance because chymase is a potent producer of angiotensin II.

However, the data by Jones et al [4] provide only indirect proof of the importance of mast cell activation in TIF, and further studies are needed to strengthen the hypothesis, as well as elucidate the relative importance of mast cells in comparison to other inflammatory cells. Potential experimental strategies for the future include the induction of renal disease models in mast cell–deficient mice (such as W/Wv, c-kit mutant; Sl/Sl d, c-kit ligand mutant) combined with reconstitution studies [2, 8–9]; the in vivo administration of pharmacologic inhibitors of chymase and mast-cell stabilizing agents, particularly in established disease models; and co-culture in vitro studies of mast cells and their paracrine interactions with tubular epithelial and renal fibroblast cells. Bearing in mind the limitations of these latter approaches, such studies have been performed in non-renal disease models. These data suggest that mast cells either have a major, partial, or insignificant role in non-renal fibrosis, depending on the disease model examined. In addition, other basic questions about mast cell biology in renal disease remain unanswered; for example, is mast cell accumulation dependent on local proliferation and differentiation, rather than recruitment? What regulates mast cell survival, and do they undergo apoptosis, when there is resolution of injury?

More than 100 years ago, Erlich, who was the first to recognize the mast cell in tissues, named them ‘Mastzellen’ to signify the chunky and well-nourished appearance of these cells with huge cytoplasmic granules [3]. This simple histologic observation perhaps predicts the enormous paracrine potential of the mast cell and its postulated role as an important cellular mediator of fibrosis. If mast cells do indeed turn out to be one of the pathologic players in TIF, then this will provide an additional therapeutic approach for established human chronic renal diseases, possibly using the new generation of mast-cell stabilizing drugs which are currently in development [10].

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