Role of Mast Cells in Progressive Renal Diseases

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ABSTRACT

Advances in understanding mast cell biology reveal their diverse functional capacity well beyond already established roles in host defense against parasites and allergic disease. Mast cells can initiate, amplify, and direct innate and adaptive immune responses. They also modulate inflammation and regulate immunity. Mast cells potentially induce tissue repair and direct fibrosis; however, they also play other roles in tissue remodeling and repair. Various activation and differentiating signals result in a diverse range of functional phenotypes called “mast cell heterogeneity.” Mast cells are significant participants in chronic progressive kidney disease, and their presence is associated with function loss and fibrosis. This suggests a potential role in the fibrotic process, which may involve mast cell activation of local renin-angiotensin systems. Experimental animal studies suggest, however, they do not directly cause renal fibrosis but rather spark inflammation. Evidence for both pro- and anti-inflammatory roles in nephritis is emerging.

The mast cell, originally named “fattened or well-fed cell” (Mastzellen) by Ehrlich,1 is a sentinel for host defense.2 After recent discoveries demonstrated an expanded role for mast cells in both systemic and local host immune responses, Galli3 suggested the name “master” cell would be more appropriate. Mast cells are present in low numbers in all vascular organs, including the kidney. In chronic progressive kidney diseases, mast cell proliferation in tubulointerstitial injury is prominent regardless of the initiating disease and correlates with progressive loss of function and poor outcome.

Outside the kidney, mast cell biology is a rapidly advancing field. Mast cells have diverse functional capacities well beyond those associated with allergy and IgE. Rodents genetically deficient in mast cells are required for optimal innate immune responses conferring survival benefit.6,7 Complement also activates mast cells, and complement-dependant microbial killing is at least partially dependent on mast cell function for full expression.8 The pattern recognition receptors, TLR, serve as an important link between

MAST CELL BIOLOGY

Mast cells derive from hematopoietic progenitor cells. They migrate through vascularized tissue to complete their maturation.4 Mast cells are tissue-specific multifunctional cells, with diverse phenotypes in different anatomic sites in various species, collectively referred to as “mast cell heterogeneity.”2,4 They locate close to blood vessels, epithelia, and nerves in connective tissues, allowing their participation in homeostatic functions as well as being strategic sentinels at primary immune barriers where their density is increased. Their anatomic distribution and structural relationships allow mast cells to modulate innate immune and adaptive effector responses; however, this role requires mast cell activation to stimulate cell degranulation together with synthetic molecule release.

The best known, classical pathway of mast cell activation is through IgE-Fce cross-linking.5 The role mast cells serve in expulsion of parasites from their host is well known.2 More recent studies recognized additional, alternative, activating pathways including complement and signaling through microbial pattern recognition receptors, toll-like receptors (TLR). This work has expanded our understanding of a role for mast cells in host defense in other diseases.

In animal models of bacterial infection, including bacterial peritonitis, mast cells are required for optimal innate immune responses conferring survival benefit.6,7 Complement also activates mast cells, and complement-dependant microbial killing is at least partially dependent on mast cell function for full expression.8 The pattern recognition receptors, TLR, serve as an important link between

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innate and adaptive immunity. Both mouse⁹,¹⁰ and human mast cells¹¹ express TLR. In animal models, the important synergistic interaction between TLR in mast cells demonstrates upregulated cytokine production¹² and increased survival from bacterial infection.¹³ In addition to complement and TLR activation, stress hormones, in particular corticotrophin-releasing hormone, enhances mast cell activation and degranulation, facilitating further mediator release.¹⁴

As well as these novel pathways, several other molecules can initiate mast cell activation. These include growth factors such as stem cell factor, co-stimulatory molecules CD28 (and ligands CD80/86), the integrins, and CCR1.¹⁵ The close proximity of mast cells to neurons facilitates neuropetide activation of mast cells.¹⁶ Mast cells are also important in chronic inflammation with the capacity to produce a range of bioactive amines, proteoglycans, growth hormones, chemokines, and cytokines, which mediate a diverse range of mast cell function (Figure 1). This breadth of activity has been reviewed extensively.²,¹⁷,¹⁸

**MAST CELLS IN RENAL INFLAMMATION AND FIBROSIS**

Although mast cells are found infrequently in normal kidney tissue, their numbers increase significantly in the setting of renal disease. Mast cells are prominent in tubulointerstitial nephritis associated with progressive fibrosis and renal failure. These include almost all of the primary and secondary forms of glomerulonephritis, nineteen to thirty diabetic nephropathy, thirty-one, thirty-two and allograft rejection, thirty-three to thirty-eight as well as amyloid, thirty-nine renovascular ischemia, forty reflux nephropathy, forty-one polycystic kidney disease, forty-two and drug-induced nephropathy.¹⁹ Mast cell presence is correlated semiquantitatively with fibrosis, progressive decline in glomerular filtration, and poor outcome.²⁰–²²,²⁴,²⁵,²⁷,²⁹ The intensity and extent of tubulointerstitial damage is one of the strongest determinants of progressive functional decline.⁴³,⁴⁴

Interstitial inflammation and fibrosis involve a common sequence of events requiring the interaction of tubular and interstitial cells with infiltrating leukocytes. Early events in this process involve leukocyte (including mast cell) recruitment and epithelial-mesenchymal transition forming fibroblasts. Profibrotic stimuli include key growth factors, TGF-β⁴⁵ and fibroblast growth factor, as well as inflammatory cytokines and chemokines facilitating leukocyte recruitment and activation. Tubular epithelial cells play an important role in these processes, and the release of proteolytic enzymes, including matrix metalloproteases (MMP), mediates fibrogenic injury. The balance of overall activators and inhibitors is altered in a manner favoring net matrix deposition and scarring.

Mast cells have the potential to support this process actively. They elaborate cytokines,⁴⁶ chemokines,⁴⁷ and leukotrienes⁴⁸ recruiting and activating leukocytes. They also indirectly support leukocyte recruitment by affecting vascular endothelial expression of selectins and adhesion molecules.⁴⁹,⁵⁰ Mast cell degranulation leads to the release of histamine, heparin, and cytokines, in particular IL-4⁵¹ and TNF-α⁵² which can influence fibroblast function. Furthermore, the release of TGF-β,⁵³ MMP-9,⁵⁴ and a variety of proteases, principally tryptase and chymase, contributes to progressive fibrogenesis.⁵⁵,⁵⁶ In addition to direct injury, some proteases are capable of activating latent MMP and other proteases. They also serve as chemottractants and mitogens for fibroblasts. Growth factors are mediators of mast cell–associated histologic and functional kidney injury,⁵⁷ although their mechanism of action is complex.

**RAS IN MAST CELL–INDUCED FIBROSIS**

Current understanding of the systemic RAS suggests it is rate limited by renin release from juxtaglomerular cells in response to renal baroreceptors or sodium chloride delivery to the macula densa.⁵⁸ There is growing interest in the local role of the RAS in specific tissues.

The kidney provides all of the necessary molecular components for a functional RAS, and there is increasing evi-
dence of the participation of the intrarenal RAS in the pathophysiology of chronic renal injury.59 RAS activity predictably plays a profibrotic role in chronic renal disease. Angiotensin II (AngII) stimulates TGF-β production60 and suppresses matrix degradation,61 favoring increased extracellular matrix deposition.62 Mounting evidence supports the role of the local RAS through AngII in regulating cell proliferation, apoptosis, and fibrosis.63,64

There is immunohistochemical evidence of increased expression of the local RAS in human proliferative glomerulonephritis65,66 and experimental evidence to support a functional role in injury through AT1 receptors in anti–glomerular basement membrane (anti-GBM) disease.67 In anti–Thy-1 antibody–induced glomerulonephritis, infusion of AngII receptor blocker attenuates injury and reduces matrix expansion and sclerosis.68 In diabetic nephropathy, there is evidence of increased expression of the local RAS.69,70 RAS activity precedes the development of increased expression of the local RAS. One alternative AngII-generating pathway is through the enzyme chymase. This is a major pathway for AngII generation in renal artery clipping–induced hypertension.77 Furthermore, chymase inhibitors prevented AngII and TGF-β generation in a model of cardiac failure.78 Mast cells are the major tissue source of chymase.79

Huang et al.80 demonstrated marked upregulation of chymase in human diabetic nephropathy where ACE was also upregulated. Whereas no difference in ACE expression was seen in normal versus hypertensive patients, chymase expression was significantly higher in patients with hypertension, suggesting that chymase may be an important therapeutic target in addition to ACE.81 The importance of chymase is also confirmed by studies in polycystic kidney disease, where mast cells are associated with tubulointerstitial damage. Strong AngII-generating capacity, as a result of chymase, was found in 13 of 14 patients with polycystic disease, and mast cells were found to be the source of chymase.82

It has been known for some time that there are alternative pathways for converting AngI to AngII that do not require ACE. This has provided support for the argument that therapeutic combinations of angiotensin receptor blockers (ARB) and ACE inhibitors are theoretically superior to ACE inhibitors alone in blocking local RAS. One alternative AngII-generating pathway is through the enzyme chymase. This is a major pathway for AngII generation in renal artery clipping–induced hypertension.77 Furthermore, chymase inhibitors prevented AngII and TGF-β generation in a model of cardiac failure.78 Mast cells are the major tissue source of chymase.79

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In streptozotocin-induced diabetes, fibrosis in mesenteric vessel is associated with mast cell infiltration. Mast cells stain for chymase, TGF-β, and tryptase. Administration of a mast cell stabilizer reduces fibrosis and the number of chymase-positive mast cells, without affecting TGF-β expression, consistent with a role for fibrosis-induced by chymase-generated AngII.31 A further link between AngII and mast cells comes from a rodent study of fibrosis after five-sixths nephrectomy. TGF-β staining, chymase-positive mast cells infiltrate areas of fibrosis in association with increased expression of stem cell factor and IL-8, known mast cell attractants. This fibrosis was prevented by treatment with ACE inhibitors, suggesting a feedback link between AngII-induced mast cell chemoattractants and ACE-independent generation of AngII by mast cells.81 These studies collectively provide evidence for mast cell–induced renal fibrosis by newly discovered pathways leading to mast cell activation of local RAS.

EXPERIMENTAL STUDIES

EXPLORING THE ROLE OF MAST CELLS IN RENAL FIBROSIS

Mast cells have been associated with fibrosis in other organs besides the kidney, including skin,82 experimental models of lung fibrosis,83 and scleroderma.84 The availability of mast cell–deficient and mast cell–“knock-in” (bone marrow reconstituted) mice confirm a role for mast cells in some forms of tissue fibrosis in vivo. The models include homocysteine-induced cardiac remodeling85 and pancreatic fibrosis,86 where the unexpected outcomes suggest mast cells protect against the development of fibrosis. In several other models, including bleomycin-induced pulmonary fibrosis,87,88 carbon tetrachloride–induced liver fibrosis,89,90 and murine scleroderma,91 mast cell–deficient mice showed no reduction in fibrosis.

Models of renal injury producing fibrosis in mast cell–deficient mice have not been as extensively studied, but preliminary data do not show a functional role for mast cells in this fibrogenesis. In puromycin aminonucleoside–induced nephropathy, mast cell–deficient mice had enhanced fibrosis. These KitW-sh/KitW-sh null mice surprisingly had increased levels of mRNA encoding TGF-β, suggesting an unexpected role for mast cells in modulating TGF-β expression in this model. In vitro experiments showed that heparin inhibited the expression of mRNA encoding TGF-β in cultured rat fibroblasts.91 Preliminary studies in a murine model of ureteral obstruction also suggested that mast cells protect against fibrosis.92 Thus, data from experimental mast cell–deficient mice do not support the attractive hypothesis that mast cells play a profibrotic role in chronic renal disease. In fact, the data
suggest that the net outcome of mast cell involvement is either mitigation of fibrosis or facilitation of repair.

ROLE OF MAST CELLS IN INFLAMMATORY AND AUTOIMMUNE KIDNEY DISEASE

The central role of mast cells in asthma, allergy, hypersensitivity, and anaphylactic reactions has been extensively studied and recently reviewed.93–95 As outlined already, mast cells now feature much broader roles in immunity and inflammation. The predominant sense surrounding mast cells in these settings is they facilitate, among other facilitators, the development of immune responses and inflammation at multiple levels, and this inflammation can be fibrogenic. There are data, albeit more limited, that suggest that mast cells can also act as modulators of inflammation.

In addition to their role in host defense through activation of the innate immune system, mast cells confer resistance to endogenous and exogenous toxins and venoms by interactions with adaptive immunity through IgE-Fcε receptors.96 Exaggerated IgE/mast cell responses are widely known to cause anaphylactic and allergic disease.97 These latter responses have limited relevance to kidney injury except for some drug-induced nephropathies.

Mast cells also have close adjacencies to T cells in secondary lymphoid organs and in the periphery.98 They present antigens to naive T cells in an MHC-restricted manner.99,100 Mast cells stimulate the migration of antigen-presenting cells to nodes through the release of IL-1, -3, and -6 and TNF.101 They also influence T cell differentiation: IL-4 and histamine direct Th2 responses as well as modulate the differentiation of Th17+ CD4 cells.102 It is in the generation of effector responses, however, where mast cells may have the greatest impact. Mast cells in the periphery enhance effector T cell recruitment directly by the production of chemoattractants. LTB4 from mast cells recruits CD8 cells,104 and IL-16 recruits CD4 cells.46 Mast cells also recruit effector T cells indirectly by their cytokine activation of local vascular endothelia enhancing the expression of intercellular adhesion molecule 1 and vascular cellular adhesion molecule, leukocyte adherence, and transmigration.105 T cell/mast cell activation is also bidirectional. T cell cytokines activate mast cells106 and enhance their proliferation through IL-3.107

Mast cells also have the potential to act as immunoregulators of adaptive immunity because of their potential to produce TGF-β, IL-4 and -10, and histamine. There have been only limited examples of this in vivo induction of contact hypersensitivity by ultraviolet irradiation leading to mast cell histamine release in vivo.108 Recent work on transplant tolerance (mediated by local graft T regulatory cells) showed a new role for mast cells as immune modulators. Transplanted skin allografts into class II mismatched (KitW-sh/KitW-sh) mast cell–deficient recipients were rejected but this did not happen in mast cell–reconstituted recipients. Other evidence suggests that T regulatory cells recruit mast cells by their production of IL-9.109 IL-9 is a cytokine that enhances mast cell growth and functionality.110 Mast cell–deficient mice have been used in a number of animal models of human autoimmune disease. They include experimental allergic encephalomyelitis,111 delayed-type hypersensitivity (DTH),112 the Arthus response,113 Bullous pemphigoid,114 experimental vasculitis,115 atherosclerosis,116 antigen-induced arthritis,117 anti-GPI antibody–induced arthritis in KBxN mice,118 and dermal contact hypersensitivity.119 These studies provide increasing evidence for a functional role of mast cells in disease.

The mechanisms of facilitation by mast cells in these models are variable and speculative in some. In models induced by antibody (pemphigoid, K/BxN arthritis), complement anaphylatoxins and FcR cross-linking are likely mast cell activators. The resulting mast cell activation enhances pathologic immunity. Most of the other models are dependant on T cell–directed immune responses. As discussed, the bidirectional T cell–mast cell interaction supporting the development of T cell responses is the likely explanation for the injurious role of mast cells in these models. In some of these T cell models, mast cell IgE–Fcε linking may also be necessary to prime mast cells for subsequent T cell activation and injury.120,121 Mast cell priming by IgE is necessary to facilitate T effector cell responses causing contact hypersensitivity.120 Interestingly, such priming occurs with antigen-independent IgE.

A number of studies have also analyzed the facilitative injury of mast cells in anti-GBM nephritis. Timoshanko et al.122 demonstrated a role for mast cells in inducing functional renal injury by the mechanism of infiltrating mast cells that recruit DTH effector leukocytes. These local effects were comparable to studies showing a role for mast cells in dermal DTH.112 Two other studies demonstrated a potential protective role for mast cells in this model. This was not attributable to local effects, because mast cells were not visible in renal sections. With the association of mast cells and T regulatory cells already established,109 one study suggested that systemic mast cells infiltrate local lymphoid organs and activate regulatory T cells to confer protection.123 Kanamaru et al.124 attributed the beneficial outcome of mast cell–competent mice to improved repair function in the kidney. In a model of autoimmune immune complex disease, the absence of mast cells facilitated an altered pattern of disease but did not alter the severity of injury.125 A recent study using anti-GBM nephritis in rats showed that histamine and histamine agonists can significantly attenuate renal inflammation. In this Th1-driven, DTH-mediated model, histamine reduced the expression of the Th1–inducing cytokine IL-12.126

CONCLUSIONS

There is a role for mast cells in immune homeostasis beyond simple allergy. Mast cells participate in many inflammatory kidney diseases, particularly those associated with fibrosis. Mast cells have very diverse roles ranging from proinflammatory to immunomodulatory. Currently,
the mechanisms determining the specific, functional phenotype of involvement are not fully understood. Mast cells also have the potential to induce injury and fibrosis, possibly by mast cell activation of the local RAS; however, current evidence, although insufficient to draw firm conclusions, does not support a functional role for mast cells in renal fibrosis. Studies in experimental inflammatory renal disease are also limited but show diverse, active roles for mast cells, ranging from protection from disease to enhancement. Further work is required to determine which factors drive their pathologic participation. Other approaches are also needed to identify potential therapeutic targets as well as define potential protective regulatory pathways induced by mast cells.

DISCLOSURES
None.

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