Mast cells in autoimmune disease

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Mast cells are known to be the primary responders in allergic reactions, orchestrating strong responses to minute amounts of allergens. Several recent observations indicate that they may also have a key role in coordinating the early phases of autoimmune diseases, particularly those involving auto-antibodies.

In imperial times, the Great Wall of China was easily breached and was not in itself a very effective defence against resolute adversaries. Rather, it was a communication route and housed, far from the imperial centre, a string of lonely guards who quickly engaged invaders and slowed their progress, while alerting and beckoning more substantial back-up forces.

Mast cells, which are scattered in skin and mucosa, have been considered in a similar outward-looking perspective[1,2]. They are the lead effector cells in the immediate responses that can occur when sensitized individuals contact allergen through outer body surfaces. On a more beneficial note, their importance in early responses to bacterial or parasitic pathogens has become recognized in recent years. In both situations, mast cells also follow up by recruiting larger cohorts of neutrophils and lymphocytes. Recent studies suggest, however, that this picture may be incomplete and illustrate how mast cells are important in the complex cellular chains that lead to autoimmune disease.

Ehrlich's "gorged cells"

Mast cells, whose differentiation pathways and heterogeneity are still poorly understood, originate from precursors of the haematopoietic lineage and circulate in blood and the lymphatic system before homing to tissues and acquiring their final effector characteristics. The expansion, homing and maturation of mast cell precursors are influenced by several cytokines including interleukin 4 (IL-4), IL-9 and nerve growth factor (NGF)[2], but stem-cell factor (SCF) binding to its receptor c-Kit seems to be the main drive for their differentiation and survival: SCF-deficient (Sl/Sl^d) and c-Kit-deficient (W/W^v) mice are largely, albeit not completely, devoid of mast cells (for review, see refs 2, 3).

Mast cell produce an impressively broad array of mediators and cell–cell signalling molecules, and it may be this very breadth that confers on the mast cell its individuality in the immune system. Many of these mediators, including histamine, numerous specific proteases (members of the tryptase and chymase families) and tumour-necrosis factor-α (TNF-α), are released by triggered exocytosis from rich intracellular stores. The fast release of TNF-α is noteworthy because of the pleitropic pro-inflammatory effects of this cytokine, and because mast cell granules are a plentiful source of rapidly mobilizable TNF-α (ref. 4), whose usually slower induction is the result of activated synthesis in other cell systems.

On activation, mast cells also rapidly synthesize bioactive metabolites of arachidonic acid, prostaglandins and leukotrienes. A specific program of gene expression is also activated, leading to *de novo* synthesis of several cytokines (IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, IL-14 and NGF), chemokines (macrophage inflammatory protein 1α, monocyte chemoattractant protein 1 (MCP-1) and lymphotactin) and, again, TNF-α. This second-wave response comes after the immediate hypersensitivity reactions, which it amplifies. It may also bias the type of secondary events, for example, by moulding the anti-inflammatory T helper 2 (T_H2) bias of T cells in the local response to airway allergens in asthma[5]. Thus, activated mast cells signal to the vascular system through the potent vasoactivity of histamine and arachidonic metabolites, to monocytes and lymphocytes through the chemotactic and differential properties of cytokines and chemokines, and to the connective substratum through the extracellular proteases. (This is an oversimplification, however, because there is crosstalk between the different mediators and pathways, for example, in the immunomodulatory properties of prostaglandins.)

Several triggers can elicit these responses. The best characterized are allergens complexed to immunoglobulin-ε (IgE) molecules[6]. Because of the unusually high affinity (10^{-10} M) of the Fc receptor (FcR) for IgE (FcεR), mast cells are constantly coated with antigen-specific IgE and are, in essence, masquerading as cells of the adaptive immune system. The crosslinking of these surface-bound IgE by antigen leads to activation and degranulation. Other members of the FcR family are also active, in particular the FcγRIII receptor (refs 7–9). Anaphylatoxins generated by activation of the complement pathway are also potent activators of some mast cells[10,11]. Bacterial microbes can trigger mast cells through Toll-like receptors (TLRs), endowing them with the broad 'pattern recognition' capability of the TLR system, which is probably an important element of their antibacterial responses[12,13]. Some cytokines and chemokines activate mast cells, in particular TNF-α and MCP-1, which are themselves released by mast cells, thus raising the potential for a positive feedback loop. Finally, activation of mast cells by co-culture with activated T cells has been described, but it is not clear what molecular mediators may be involved[14,15]. Direct crosstalk by surface molecules on T cells and mast cells may be important in this context.

Autoimmune disease in the brain

The recent spark of interest in a role for mast cells in initiating or propagating autoimmune disease was prompted by studies on multiple sclerosis and its animal model, experimental allergic encephalomyelitis (EAE)[16]. Multiple sclerosis is a chronic inflammatory disorder of the central nervous system (CNS), which is characterized by a breach of the blood–brain barrier, mononuclear cell infiltration of white matter and eventual demyelinization. A similar autoimmune disease can be induced in susceptible rodent strains by injecting different myelin components, including myelin basic protein (MBP), proteolipid protein and myelin oligodendrocyte glycoprotein (MOG).

Both multiple sclerosis and EAE depend critically on pro-inflammatory T helper 1 (T_H1) $CD4^+$ T cells. B cells, and more specifically the antibodies that they produce, may also be important, although this is still under debate. Numerous studies, dating as far back as 100 years, have reported a correlation between the number and/or distribution of mast cells and the development of multiple sclerosis or EAE (reviewed in ref. 17). Evidence of mast cell activation in the course of the disease came from the demonstration of increasing degranulation[18] and increased amounts of proteolytic enzymes such as tryptase in cerebrospinal fluid[19]. In addition, drugs considered to 'stabilize' mast cells (for example, cromolyn sodium) have been shown to ameliorate the severity of EAE[20–22].

Although these observations were highly suggestive of an essential role for mast cells in these CNS autoimmune diseases, the association remained indirect until the recent studies of Brown and colleagues[23]. These researchers showed that mice lacking mast cells (W/W^v mice) develop EAE later and less severely than do control mice in response to injection of MOG. Complementation of W/W^v mice with immature mast cells derived *in vitro* restores typical EAE susceptibility. Mast cell function seems to be the result of binding antibodies, as it was found to be dependent on expression, by the mast cells, of the FcγR[17]. Notably, Brown and colleagues[17] subsequently showed that their procedure does not result in reconstitution of mast cells in CNS tissues, suggesting that mast cells might be exerting their crucial influence outside the inflammatory lesion.

Another line of evidence has independently piqued interest in a role for mast cells in multiple sclerosis and EAE. Gene expression profiling of multiple sclerosis brain lesions detected an unexpectedly high contribution of transcripts either derived from mast cells or otherwise associated with the allergic response, including transcripts encoding histamine receptors, proteases and other inflammatory mediators[24,25]. These findings rekindle interest in the perplexing finding that the transfer of MBP-specific T_H2 cells to healthy recipients unexpectedly provoked a variant form of EAE characterized by eosinophilic infiltrates into the CNS[26].

Autoimmune disease in the joint

A potential role for mast cells in rheumatoid arthritis has also been highlighted recently. Rheumatoid arthritis is a chronic inflammatory disease of the diarthrodial joints. K/BxN mice spontaneously develop a joint disorder that has many similarities to rheumatoid arthritis[27]. Although the development of disease in this model is initiated by T cells, it also requires B cells, and immunoglobulin-γ (IgG) antibodies from an arthritic donor can induce disease in a healthy host. The target of both the pathogenic T cells and arthritogenic antibodies is the ubiquitous cytoplasmic enzyme glucose-6-phosphate isomerase (GPI)[28]. This enzyme and antibodies against it aggregate as immune complexes at the surface of the articular cavity, where they initiate an inflammatory cascade involving the alternative pathway of complement (acting through C5a), FcRs (in particular, FcγRIII), neutrophils and cytokines such as IL-1 and TNF-α (refs 29–31).

Now it seems that mast cells are also important in this disease process[32]. Both Sl/Sl^d and W/W^v mice are resistant to the induction of arthritis by antibodies against GPI. More definitively, reconstitution of these mice with mast cell precursors restores sensitivity to disease induction. Notably, one of the first events detected after injection of arthritogenic antibodies into wild-type mice is mast cell degranulation in the joint but not in other tissues. This very early event is already apparent an hour after antibody administration, before the recruitment of neutrophils. These results prompted the conclusion that mast cells might have an early, coordinating role in this model of rheumatoid arthritis.

The generality of this conclusion is supported by observations from other murine models of rheumatoid arthritis and from individuals affected with rheumatoid arthritis. Mast cells accumulate in the swollen paws of mice suffering from collagen-induced arthritis, and they degranulate during the disease process[33]. Salbutamol is a β2-adrenergic agonist that prevents mast cell degranulation, and this drug had a strong therapeutic effect on the progression of collagen-induced arthritis[33]. Mast cell deficiency was also found to inhibit the course of antigen-induced arthritis in mice, although the effect was rather mild[34]. Mast cells also accumulate in the synovial tissues and fluids of humans suffering from rheumatoid arthritis[35,36], reflecting the presence of mast cell chemotactic or survival activities such as SCF and transforming growth factor-β in the synovial fluid[37]. The invading mast cells produce several inflammatory mediators, notably TNF-α, IL-1β and vascular endothelial growth factor (VEGF)[35,38]. Notably, TNF-α can induce further production of SCF by synovial fibroblasts, potentially augmenting mast cell recruitment and thereby creating an amplification loop.

Autoimmune disease in the skin

Bullous pemphigoid seems to present a situation that is highly similar to the one that unfolds in K/BxN mice. This autoimmune skin disease is characterized by subepidermal blisters resulting from auto-antibodies against two hemidesmosomal antigens, BP230 and BP180 (ref. 39). The key features of the human disease can be mimicked by injecting neonatal mice intradermally with IgG antibodies directed against murine BP180 (ref. 40). The antibody-induced disease has been known for some time to require activation of the complement pathway[41] and the accumulation of neutrophils[42]. Recently, it has been also shown to depend critically on mast cells[43].

Mast cell degranulation was one of the first responses detected after the injection of antibodies against BP180, occurring only 1 h after administration and preceding neutrophil accumulation and skin blistering[43]. Injection of antibodies against BP180 into mice lacking mast cells (W/W^v or Sl/Sl^d) did not induce bullous pemphigoid, nor did their injection into wild-type mice pre-treated with cromolyn sodium. But mice lacking mast cells that were reconstituted intradermally with mast cells derived *in vitro* showed typical features of disease. In the absence of mast cells, IgG still accumulated in the skin and the complement pathway was activated to yield C3a and C5a, but neutrophils were no longer recruited to the dermal lesion. Bullous pemphigoid could be induced in mast-cell-deficient mice injected with antibodies against BP180 if neutrophils or the potent neutrophil attractant IL-8 were injected intradermally. Thus, it was concluded that the crucial role of mast cells in murine bullous pemphigoid is to recruit neutrophils to the developing lesion. A similar process might also occur in the human disease, because degranulated mast cells are a prominent feature of the skin blisters of individuals affected with bullous pemphigoid[44], and mast-cell-derived chemoattractants are present at high concentrations in blister fluids[45,46].

There are several other examples of autoimmune disorders in which mast cells have been implicated, although often only by 'guilt by association'. These include Sjogren's syndrome[47], chronic idiopathic urticaria[48], thyroid eye disease[49] and experimental vasculitis[50]. For these disorders it will be important to provide evidence, as in the three diseases highlighted here, that mast cells are more than bystanders that become activated in the inflammatory maelstrom and are involved directly in the complex chain of cellular events that lead to autoimmune damage.

The role of mast cells

Where, however, are mast cells positioned in this chain? What triggers them into action, and which are the important relay molecules (Fig. 1)? For the antibody-mediated models (pemphigoid and K/BxN arthritis), there is no dearth of candidates that might activate mast cells: the two main consequences of immune complex formation — the production of complement-derived anaphylatoxins and FcγR crosslinking — can both trigger mast cells efficiently[7–11]. It will be important to pinpoint which of these pathways is involved by analysing mast cell degranulation in knockout animals and by reconstituting W/W^v mice with mast cells derived from complement- or FcR-deficient mice.

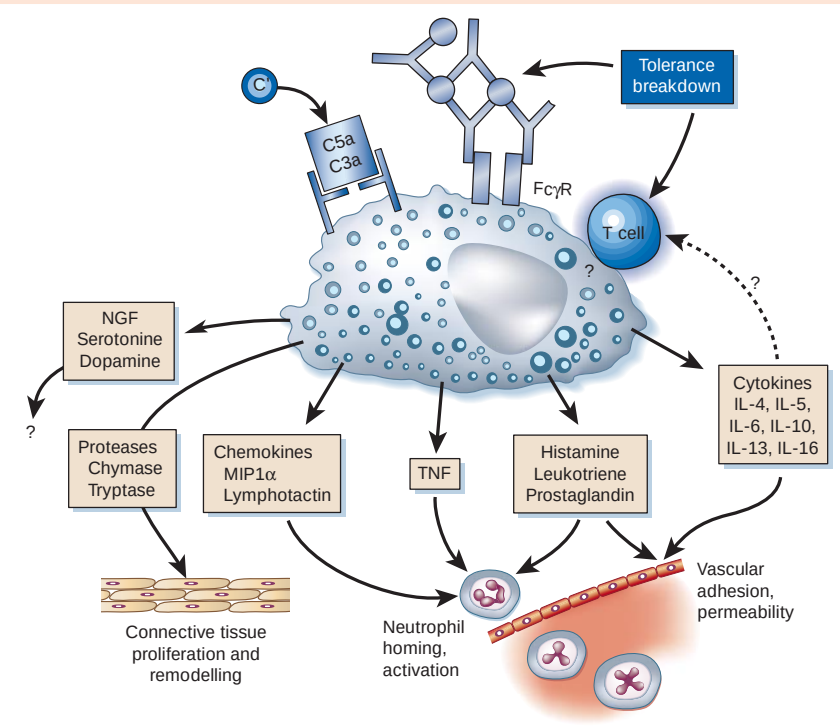

Figure 1 The mast cell as an integrator or amplifier of autoimmune responses. The breakdown of tolerance and/or immunoregulatory mechanisms leads to autoimmune activation and recognition in the tissues. These responses, which are 'adaptative' in their anti-self specificity, generate primary 'innate' inputs into mast cells, such as immune complex binding to FcRs, and C3a and C5a anaphylatoxins of the complement pathway binding to specific receptors. The molecular route for direct 'bystander' activation of mast cells by T cells remains conjectural. The mast cell, owing to the abundance and diversity of secondary mediators in its granules, responds by activating a host of pathways, thus amplifying the local response. Vascular permeability is increased, allowing influx of additional molecules (antibody, complement). The adhesiveness of the vascular endothelium is increased, facilitating the homing of leukocytes (and in particular neutrophils) provoked by chemokine and TNF-α release. These leukocytes are also activated by the same cytokines. Mast cell mediators may be also involved in remodelling connective tissue, or in biasing secondary T-cell responses. Mast cell activation may also signal to local neuronal constituents by the release of NGF, serotonin or dopamine. Thus, the mast cell takes in what may be a low pro-inflammatory input and amplifies it to bring about a much wider response.

For the EAE models, in which T cells are classically thought to be the effectors, one might have invoked the effect that activated T cells have on mast cells[14,15]. But the effectiveness of mast cell reconstitution seems to be dependent on the presence of FcγR[17], pointing to an involvement of antibodies against MOG in this disease. Notably, MOG-induced EAE is the model that is thought to be most dependent on antibodies for lesion development; thus, here again the mast cell contribution may be antibody-dependent. These data do not rule out a direct interaction between T cells and mast cells, and it will be interesting to examine the role of mast cells in 'pure' T-cell-mediated autoimmune diseases, such as diabetes.

The heterogeneity of mast cell populations, their variations in different tissue environments and how they may differentially integrate input from different stimuli are incompletely understood facets of their biology. Is the response of an airway mast cell to an allergen that crosslinks IgE receptors the same as that of a joint mast cell to deposited IgG? Complex interactions take place between the intracellular signals elicited when FcγR and FcεR are both engaged, and these influence the mediators that are released or induced[7,9]. It will be important to determine how concomitant triggering of mast cells through the FcγR, C5a and other secondary byproducts of immune complexes may be integrated differentially by mast cells, thereby leading to consequences as different as a pemphigus blister or an EAE plaque.

Downstream of mast cell activation, all of the events described in IgE-induced allergic responses[1,2] have the potential to fan the autoimmune flames. For example, there will be increased permeability of the local vasculature, which will recruit even more immune complexes into the lesion; notably, local oedema is one of the earliest events in the unfolding of antibody-induced arthritis. There will be modifications of vascular adhesive properties contributing to the recruitment of leukocytes by chemokines, comparable to the mast-cell-mediated influx of neutrophils in models of peritonitis[11,51,52]. In the arthritis model, neutrophils are also essential[30], and it may be that the sequential mast cell/neutrophil tandem will constitute a frequently recurring theme. The very early timing of mast cell degranulation in both the bullous pemphigoid and rheumatoid arthritis mouse models are consistent with that view. In the peritonitis models, TNF-α seems to be the essential mediator for neutrophil recruitment[51,52]. Given the central role that TNF-α seems to have in arthritis, it will be interesting to see whether it is also the principal contribution of the mast cell.

In both asthma and arthritis, the worst damage lies not so much in the immediate inflammation as in the subsequent tissue reorganization and chronic inflammation. Connective tissue proliferation leads to loss of organ function, whether as an eroding pannus in the joint or as thickened and hyperreactive bronchi. Arthritis, in particular, has been described as a tumour-like anarchic proliferation of synoviocytes. Several mast cell products have strong trophic effects, including classical growth factors (NGF, epidermal growth factor, VEGF), but some of the mast cell proteases also have mitogenic properties[2]. One might propose that mast cells are important contributors in the anarchic joint reconstruction triggered by the autoimmune attack. Last, as suggested by Brown and colleagues[17,23], there is the intriguing possibility that mast cell activation also feeds back to the initiating autoimmune responses in lymphocytes. The release of tissue neo-antigens through proteolysis might contribute to the epitope spreading observed in EAE. Or, as in asthma, the locally released cytokines might bias T-cell phenotypes, enhancing a T_H2 response that would bolster the dangerous production of autoantibodies.

Autoimmune diseases such as multiple sclerosis or rheumatoid arthritis are complex and involve long and convoluted molecular and cellular chains, with many possible points for therapeutic intervention. Yet the demonstration of an obligate passage through mast cells in these animal models opens the perspective of harnessing agents that modulate mast cell homeostasis or function to treat human disease.

Mast cells have been positioned historically in the private domain of allergists and have been largely ignored by the autoimmunity field. This ignorance can no longer be sustained as the demarcation between autoimmunity and allergy becomes fuzzy. This is illustrated by the anaphylactic reactions induced, under certain conditions, by

injecting myelin proteins or peptides into mice or individuals with multiple sclerosis[53–55]. And the view of mast cells as a ring of outward-looking sentinels can no longer hold. Their scope clearly includes the inner realm as well. □

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