

The role of mast cells in allergy and autoimmunity

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Two potential outcomes of dysregulated immunity are allergy and autoimmunity. Both are characterized by localized inflammation that leads to the injury and/or destruction of target tissues. Until recently, it was generally accepted that the mechanisms that govern these disease processes are quite disparate; however, new discoveries suggest that the mast cell may underlie much of the pathology in both these disease syndromes. Amongst these discoveries is the observation that mast cell-deficient mice exhibit significantly reduced disease severity compared to wild-type littermates in a murine model of multiple sclerosis (MS) and drugs that block mast cell function can improve clinical symptoms in this model. In addition, gene microarray analysis has revealed that the expression of several mast cell-specific genes is increased in the central nervous system plaques of MS patients. Although well established as effector cells in allergic inflammation, the location of mast cells and the wealth of inflammatory mediators they express make it likely that they have profound effects on many other autoimmune processes.

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Abbreviations

CNS	central nervous system
DC	dendritic cell
EAE	experimental allergic or autoimmune encephalomyelitis
IL	interleukin
MOG	myelin oligodendrocyte glycoprotein
MS	multiple sclerosis
RA	rheumatoid arthritis
TLR	Toll-like receptor

Introduction

There is a well-established paradigm of mast cell development and function. Mast cells are derived from CD34⁺ hematopoietic progenitor cells and initiate their differentiation in the bone marrow under the influence of c-kit ligand (stem cell factor) and IL-3 [1]. Similar to dendritic cells (DCs) and tissue macrophages, mast cells do not circulate in the blood. High affinity IgE receptor positive (FcεRI⁺), c-kit⁺ bone marrow-derived mast cell precursors migrate to vascularized regions of the body and exist as fixed cells where they complete their differentiation under the influence of a unique array of differentiation and growth factors present at each tissue site [2]. Mast cells are often

associated with blood vessels and found within mucosal surfaces of the gastrointestinal and respiratory tracts, in the skin and in close proximity to peripheral nerves. Less appreciated is their prevalence in the central nervous system (CNS), where they are concentrated in the leptomeninges, hypothalamus, thalamus and habenula of the brain as well as in the spinal cord dura mater [3,4]. There are well-defined differences in the array of mediators expressed by distinct mast cell populations found in connective tissue versus mucosal sites [2,5].

It has long been recognized that mast cells play a direct and pathologic role in the inflammatory processes associated with allergic disease (for a review, see [6]). These include effects on acute local and systemic responses, such as allergic rhinitis and anaphylaxis, as well as on late phase responses and chronic asthma. These pathologic responses are dominated by Th2 cells and are dependent on the ability of antigen-specific IgE to bind to FcεRI expressed on mast cells. Cross-linkage of FcεRI results in activation of the mast cell and the initiation of a signal transduction cascade that leads to the release of two general classes of mediators upon subsequent antigen exposure. Hallmark mast cell molecules, such as TNF-α, IL-4, histamine, heparin, serotonin, kinins and proteases, are preformed and are released immediately upon activation of the mast cell. A second class of newly synthesized mediators includes the interleukins 1–8, TNF-α, IL-12, IL-13, IL-15 and IL-16, chemokines, and growth and angiogenesis factors, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), as well as prostaglandins and leukotrienes. Together these molecules have profound effects on inflammatory cell activation and recruitment (through effects on endothelium adhesion molecule expression, chemokine production or vascular permeability) as well as smooth muscle contraction associated with allergic disease.

Mast cells also provide immune protection in some settings. IgE-mediated mast cell responses are thought to have evolved as the major defense mechanism against parasites. Protective Th2-dominated immune responses which result in IgE production dominate in parasitic infections, a situation best characterized in the setting of *Nippostrongylus brasiliensis* infections [7]. In addition, TNF-α production by mast cells is essential for protective immunity to certain bacterial infections of the respiratory and gastrointestinal tracts [8,9]. Th2 cytokine production by mast cells, notably IL-4, might downregulate the development or effector function of Th1 cells, thus playing an important immunoregulatory role.

Despite the well-characterized role of FcεRI-mediated mast cell activation, there are a variety of other agonists

that lead to the activation of mast cells. Cross-linking of IgG can activate mast cells [10]. In addition, studies have shown that several Ig-independent activation pathways exist. Toll-like receptors (TLRs) that recognize specific molecular patterns associated with microbes are expressed on mast cells and activate pro-inflammatory cytokine production and migratory function [11••,12••]. *Helicobacter pylori*, *Staphylococcus aureus*, lipopolysaccharide, Fim H (a bacterial adhesion molecule; [13]) and *Salmonella typhimurium* (M Sherman, personal communication), are among the microbial products that stimulate mast cells; presumably through the TLRs. Mast cells are also activated by complement [14–16], neuropeptides [17] and components of the myelin sheath such as myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG) (V Secor, personal communication; [18]). The identification of Ig-independent stimulators of mast cell activation is significant for at least two reasons: first, these data indicate that mast cells can act at the earliest stages of an immune response, before the development of adaptive immune responses that are necessary for B cell isotype switching and subsequent Fc receptor-mediated activation; second, mast cells are located at the interfaces of the host with its external environment, and they probably make a major contribution to the first line of host defense via their direct activation by pathogens.

Autoimmunity as an inflammatory disease

The term autoimmunity refers to a wide spectrum of diseases that vary in aetiology, target organ involvement and symptomology [19]. However, all of these diseases are characterized by the presence of clonally expanded populations of self-reactive lymphocytes; cells that have escaped negative selection during development. Self-reactive T and B cells are activated to express their effector function upon encounter with their target self-antigens only under fairly restricted conditions. Because most autoreactive responses are self limiting, several criteria must be met for these self-reactive lymphocytes to be pathologic: mechanisms must exist to effectively expand the autoreactive lymphocyte population and limit the activity of regulatory cells; the antigen must persist and be accessible to the T and B cells; and co-stimulatory signals that allow full activation of reactive T cells to initiate the response must be present.

There is emerging evidence that infection-associated inflammation is a major contributor to all of these processes [20,21]. It has been proposed that molecular mimicry (i.e. the sharing of antigenic epitopes between the host and the pathogen) can result in the initial expansion of pathogen-specific T cells that cross-react with self during an infection [22]. For example, there is a correlation between infection with coxsackie B virus and the development of Type 1 diabetes [23]. Multiple sclerosis (MS) is associated with Epstein Barr virus infection [24,25] and there is speculation that the relapsing-remitting form of the disease reflects new infections, and thus new

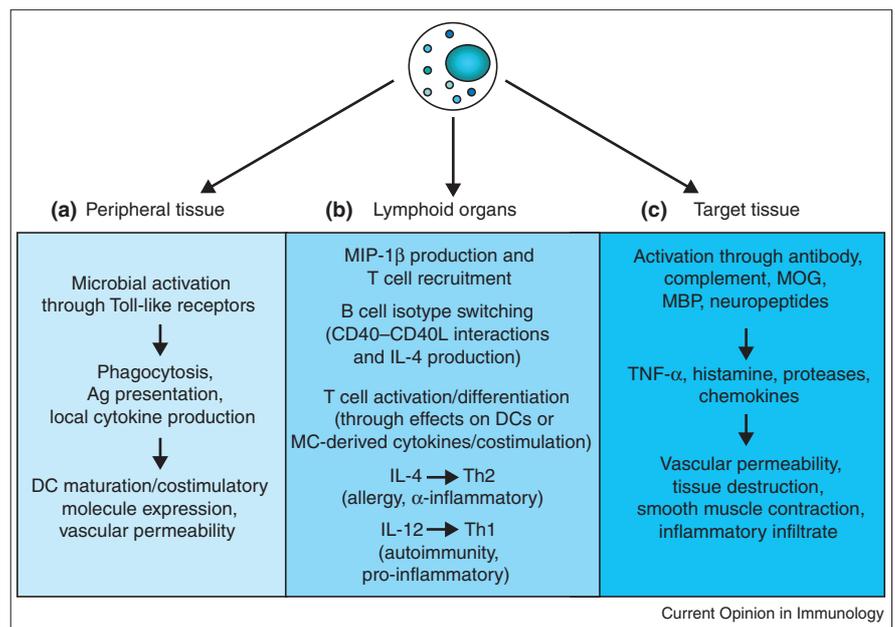
inflammatory episodes. Subsequent infections with the same organism may boost the cross-reactive lymphocyte pool and this may be a key factor in the reactivation and/or maintenance of autoimmune responses. Alternatively, there may be bystander expansion and activation of self-reactive lymphocytes when innate immune cells sensitized by TLR activation release a myriad of pro-inflammatory cytokines and chemokines in response to infection [26]. TLR-mediated activation of innate cells may occur in rodent models of autoimmunity, such as experimental autoimmune encephalomyelitis (EAE), where disease induction requires immunization not only with self-antigen but also with complete Freund's adjuvant (CFA); the adjuvant (often *Mycobacterium tuberculosis*) provides the boost to the innate immune system to achieve a sufficient inflammatory response. The mediators expressed in the course of an inflammatory response can induce co-stimulatory molecules on antigen presenting cells and can cause tissue damage either directly or through the recruitment of other inflammatory cells. It is clear that cells of the innate immune system, including macrophages, neutrophils and DCs, are essential players in this process. What has not been studied in detail is the contribution of mast cells.

Mast cells: a role in autoimmune disease?

The existing evidence that mast cells play a role in autoimmune diseases is largely indirect and relatively scant. Mast cell infiltrates have been found in the salivary glands of patients with Sjogren's syndrome [27]. A variety of studies have documented the presence of mast cells or mast cell mediators in the synovial fluid of patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [28–32]. The best correlative evidence comes from studies of mast cells and the neuroinflammatory disease MS and its rodent model EAE (perhaps not by coincidence, interchangeably designated experimental 'allergic' or 'autoimmune' encephalomyelitis). EAE shares many of the clinical features of MS although it does not occur spontaneously and must be induced by immunization with myelin components. In both the human and murine disease, mast cells are associated with sites of demyelination and CNS inflammation [33–35]. Trypsin, a mast cell-specific protease, is elevated in the cerebrospinal fluid of MS patients [36] and mast cell proteases generate encephalogenic myelin fragments *in vitro* [34,37]. There is a correlation between genetically determined mast cell numbers and disease susceptibility in inbred mouse strains [38]. Drugs that inhibit mast cell degranulation are often effective in treating disease symptoms in both humans and mice [39,40]. Finally, microarray analysis of genes expressed in multiple sclerosis lesions isolated from patients with both acute and silent disease revealed several mast cell-specific genes are significantly increased when compared to normal controls [41••]. These genes include FcεRI (18-fold increase in plaques from patients with chronic disease where no acute inflammation is detected at the time of analysis) and trypsin (>20-fold increase in chronic disease).

Figure 1

Mast cells have many potential effects on inflammatory processes associated with the development of autoimmune responses. **(a)** In the peripheral tissues at early stages of disease, microbial infection may activate mast cells locally through TLRs, initiating mast cell phagocytosis, antigen presentation and local cytokine production. Cytokines such as IL-4 can affect DC differentiation which can ultimately influence the development of Th cell phenotypes in local secondary lymphoid organs. **(b)** Although formerly considered 'fixed tissue cells', mast cells are known to migrate to the spleen and lymph nodes when activated. At these sites, cytokine and histamine production can contribute to bystander activation of autoreactive T cells or can directly promote Th differentiation and expansion. Co-stimulatory molecules expressed by mast cells may influence these processes as well. It has been demonstrated that Th1-dominated and, in some cases, Th2-dominated immune responses can initiate or exacerbate disease. In some settings, Th2 responses may also be anti (α)-inflammatory and protective. **(c)** During later stages of disease, mast cells located in proximity to tissues targeted for autoimmune destruction may be activated through Ig- and complement-mediated mechanisms, as well as



via neuropeptides. The resulting release of mast cell mediators can contribute to the recruitment of inflammatory cells (through increases in local vascular permeability or

chemokine production) or directly damage tissues. Tissue damage can result in the release of more target antigen and play a role in promoting 'antigen persistence'.

The most direct evidence implicating mast cells in this demyelinating disease syndrome comes from studies using mast cell-deficient mice (designated WBB6F1-W/W^v; for a review, see [42]). W/W^v mice are heterozygous for two distinct, naturally occurring mutations at the white spotting locus, a region that encodes the c-kit receptor. The net effect of these mutant genes is a 90% reduction in signaling through this receptor in comparison to the wild-type receptor. Because mast cells are exquisitely dependent on c-kit ligand for normal development, W/W^v mice virtually lack mast cells. These mice have been used in several experimental settings to define a role for mast cells *in vivo* [8,9,43]. Mast cell populations can be selectively restored to W/W^v mice (so called 'mast cell knock-in mice') by intravenous or local injection of committed mast cell precursors, obtained through *in vitro* differentiation of wild-type bone marrow (c-kit^{+/+}) with IL-3. Secor *et al.* [44] used this system to demonstrate that a mast cell deficiency significantly reduces the severity of MOG-induced EAE. Restoration of the mast cell populations with normal mast cells restored the ability to induce severe disease.

Mast cells as modulators of inflammation associated with autoimmunity

The widespread distribution of mast cells and the recent appreciation of the myriad of immunologically important molecules expressed by these cells strongly suggest the potential for mast cells to exert both parallel and unique effects in the inflammatory processes that accompany

autoimmune diseases when compared to DCs and other cells of the innate immune system (see Figure 1). At early stages in the generation of an infection-associated autoreactive response, mast cells may be directly activated through TLRs in the peripheral tissues through microbial interaction. The release of cytokines (for example, IL-4) locally may influence DC maturation, which in turn can dictate Th cell differentiation fates [21]. Mast cell-derived chemokines may recruit inflammatory cells to local tissue sites, amplifying the local immune response. We speculate that the lack of local activation of mast cells during EAE disease induction with MOG in CFA contributes to the reduced disease severity observed in the W/W^v mice [44]. Activated mast cells can also migrate to secondary lymphoid organs [45-47] placing them at sites where they may directly influence the development of Th cell responses through the local release of immunomodulatory cytokines and expression of co-stimulatory molecules. Mast cell-derived chemokines (MIP-1 β and others, as yet undefined) may help to recruit more T cells into the spleen or lymph nodes [48]. It has been proposed that mast cells, the major producer of histamine and other vasoactive amines, have a role in altering the blood-brain barrier and facilitating the entry of T cells into the CNS in MS [49]. Similar effects on other vasculature may also be of importance. Histamine also regulates T cell and antibody responses and may skew the local Th responses to favor autoimmune reactions [50**]. Secreted proteases may contribute to the destruction of the myelin sheath or cause

direct axonal damage in MS and may act on the specific target organs in other diseases. These events may contribute to the release of self-antigens, thereby maintaining 'antigen persistence'.

IgG receptor and complement-mediated mast cell activation may be important in autoimmune inflammatory processes in later stages of the disease process. IgG auto-antibodies contribute to the pathology manifested in several autoimmune diseases [19]. These include SLE, MS and RA. We speculate that these antibodies may act to initiate the complement cascade generating agonists for mast cell activation (C3 and C5a) or they may act by complexing with self-antigens and directly activating, through Fc γ RIII, an IgG-activating receptor that is expressed on mast cells. Evidence to support the second idea comes from recent studies by Robbie-Ryan and co-workers (M Robbie-Ryan, MB Tanzola, VH Secor, MA Brown, unpublished data) that demonstrate reconstitution of W/W^v mice with Fc γ RIII-deficient mast cells fails to restore EAE disease to wild-type levels. Thus, in addition to the proposed local TLR-mediated activation of mast cells at the site of MOG immunization during disease induction, these data demonstrate the potential for IgG-mediated activation that could occur at distal tissue sites and cause more widespread inflammation and possible tissue damage during disease progression. Mast cell activation subsequent to disease onset may contribute to relapses in disease severity using many of the same mechanisms that are operational during disease induction.

Autoimmunity, an 'allergic' disease?

Many autoimmune diseases including MS, RA and diabetes are defined by a pathogenic CD4⁺ Th1 type response and a protective immune deviation towards a Th2 response. However, it is becoming increasingly apparent that we can no longer consider the destructive phase of these diseases to be strictly Th1 mediated, as there is an emerging role for Th2 cytokines in disease pathogenesis. Recent clinical trials focused on treating MS with an altered peptide ligand regime aimed at skewing the Th cell response to the more 'protective' anti-inflammatory Th2 response [51]. Because of hypersensitivity reactions in 9% of the patients, the trial was halted. Immediate hypersensitivity reactions and anaphylactic shock developed in 71% mice with EAE that were re-challenged with specific myelin antigens during the recovery phase of the disease [52*]. In addition, if Th2 MBP-specific T cells are injected into immunodeficient mice, these mice develop severe clinical EAE disease that correlates with a large mast cell infiltrate in the meninges [35]. Although the importance of mast cells in disease onset has been demonstrated [44], these studies further implicate mast cells in later stages of EAE. Thus, although mast cells produce IL-4, a cytokine associated with remission of MS and EAE, there may be situations where mast cells and mast cell-derived IL-4 act to amplify a hypersensitivity response through their effects on mast cell growth and IgG and IgE production, causing pathology rather than protection.

Conclusions

Although mast cells have been well characterized in the context of Th2-type allergic responses, it is important to consider the often-overlooked impact that mast cells may play in autoimmune diseases. The variety of potent pro-inflammatory mediators expressed by mast cells and the widespread tissue distribution of these cells make them excellent candidates for modulating autoimmune responses, especially those that are associated with infection and modulated by inflammation. We propose that mast cells, activated through a variety of mechanisms, including activation by microbial products, antibody, complement components and cytokines, can initiate and sustain both Th1 and Th2-type responses. Under some conditions, both types of response can amplify the self-reactive lymphocyte responses associated with autoimmunity. Because they exist primarily as fixed tissue cells, it is a formidable but necessary challenge to define the multiple ways that mast cells act *in vivo*. An understanding of their relative contribution will provide new therapeutic avenues for autoimmunity as well as for a variety of other diseases in which mast cells have been implicated.

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