

BRIEF REVIEWS

The Multitasking Mast Cell: Positive and Negative Roles in the Progression of Autoimmunity

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Among the potential outcomes of an aberrantly functioning immune system are allergic disease and autoimmunity. Although it has been assumed that the underlying mechanisms mediating these conditions are completely different, recent evidence shows that mast cells provide a common link. Mast cells reside in most tissues, are particularly prevalent at sites of Ag entry, and act as sentinel cells of the immune system. They express many inflammatory mediators that affect both innate and adaptive cellular function. They contribute to pathologic allergic inflammation but also serve an important protective role in bacterial and parasite infections. Given the proinflammatory nature of autoimmune responses, it is not surprising that studies using murine models of autoimmunity clearly implicate mast cells in the initiation and/or progression of autoimmune disease. In this review, we discuss the defined and hypothesized mechanisms of mast cell influence on autoimmune diseases, including their surprising and newly discovered role as anti-inflammatory cells. The Journal of Immunology, 2007, 179: 2673–2679.

Mast cells usually get their obligatory 15 min of fame in basic immunology classes during the description of immediate-type hypersensitivity responses. As the story goes, these cells come into play only after T cells respond to allergen, generating a Th2-type adaptive immune response and producing IL-4. IL-4 in turn acts on B cells to elicit IgE isotype switching (1). Allergen-specific IgE Abs bind to the high affinity IgE receptor (FcεRI), poisoning the mast cell for activation and degranulation upon subsequent exposure to Ag. However, the understanding of the profound effects of these cells on a variety of allergy-independent responses has undergone a revolution that has not yet made it to the textbooks.

Mast cells (named Mastzellen by Paul Ehrlich in the late 1800s because of their appearance as “fattened well-fed cells”) (2) have been ignored as major players in conventional, nonallergic immune responses until recently for a number of reasons. First, despite their widespread distribution in many tissues, particularly at the interface of the host and its environment, their

numbers are relatively limited and their detection in vivo most often relies on histological staining. Second, it was not evident until fairly recently that alternative activation pathways in addition to those elicited by FcεRI cross-linking were available to mast cells. We now know that these cells can be stimulated by complement components, neuropeptides, and stress hormones and by both viral and bacterial pathogens through TLRs, resulting in the increased expression of cell surface molecules that can modulate T cell and dendritic cell (DC)² function (reviewed in Ref. 3). Mast cells are characterized by the presence of numerous cytoplasmic granules containing a plethora of preformed proinflammatory mediators that are released immediately upon activation. Although histamine is perhaps the most famous, this group of first line responders includes leukotrienes (e.g., LTB₄), prostaglandins (e.g., PGE₂ and PGD₂), proteases (e.g., tryptase), and some cytokines (e.g., TNF-α and IL-4). These factors can also be induced de novo along with many other cytokines and chemokines (4). The pattern of mediator and cell surface molecule expression is both agonist- and strain-specific in mice, suggesting that mast cells have adapted to respond differentially to distinct immunological insults (4–7).

Most in vitro studies of mast cell function rely on bone marrow-derived mast cells generated by culture with IL-3 and stem cell factor. These cells exhibit some (but not all) characteristics of terminally differentiated tissue mast cells, including high expression of FcεRI and *c-kit*, the stem cell factor receptor, and the production of many mediators. The peritoneum also provides adequate numbers of mature mast cells to study ex vivo in normal animals. Mice with defects in *c-kit* expression, including WBB6kit^{W/W^v} or C57BL/6kit^{W^{sh}/W^{sh}}, are mast cell-deficient and have been useful in defining an in vivo role for mast cells in many infection and autoimmune settings (8, 9).

Autoimmunity: a failure to “tolerate” self

To be effective in protecting an organism from harmful pathogens, the immune system must do the following: 1) distinguish between “self” (one’s own molecules) and “non-self” (pathogens); and 2) determine what constitutes a danger to an organism. When the system is unable to make these distinctions, self-reactive T and B cells can be activated and, with help from

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² Abbreviations used in this paper: DC, dendritic cell; CRH, corticotropin-releasing hormone; EAE, experimental allergic/autoimmune encephalomyelitis; MS, multiple sclerosis; NGF, nerve growth factor; PAR-2, protease activated receptor 2; RA, rheumatoid arthritis; Tr1, T regulatory type 1 cell; Treg, regulatory T cell.

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innate immune cells, orchestrate an inflammatory response directed to self-tissues. The checkpoints in the progression to autoimmune disease are dependent on the presence of a proinflammatory microenvironment. It is our contention that the mast cell plays multiple roles in this progression.

Mast cell associations with autoimmune disease

Although this review will focus mainly on the role of mast cells in experimental allergic/autoimmune encephalomyelitis (EAE), the murine model of multiple sclerosis, mast cells have been directly implicated in models of several other autoimmune diseases. Mast cell-deficient mice do not get disease in models of rheumatoid arthritis (RA) (10) or bullous pemphigoid (11), indicating an essential role in these Ab-mediated, organ-specific autoimmune diseases. However, in Ab-mediated systemic lupus erythematosus (12) mast cell-deficient mice have normal or enhanced disease progression, illustrating a possible role of mast cells in protection against multiorgan autoimmunity.

The role of mast cells in insulin-dependent diabetes is similarly complex. Mast cells are normal residents within the pancreatic ducts in close proximity to the pancreatic islets (13–17) and are associated with inflammatory conditions of the pancreas, including chronic pancreatitis and pancreatic cancer. However, mast cell production of TNF- α and TGF β appears to regulate T cell tolerance to autoantigens in some models of diabetes (18–20). Mast cells also express PD-L1 (B7-H1) (Ref. 4 and B. A. Sayed, G. D. Gregory, and M. A. Brown, unpublished observations), an inhibitory molecule implicated in protection from disease (21).

Multiple sclerosis (MS)

MS is a “spontaneous” autoimmune disease whose etiology is still unknown and is characterized by distinct episodes of myelin destruction within the CNS (22). The rodent model of MS, EAE, employs immunization with a myelin peptide in the context of complete Freund’s adjuvant to generate disease. Although EAE is not the same disease as MS, featuring different locations of demyelination and a different makeup of cellular infiltrate into pathological plaques (23), EAE has long been considered a useful model for the understanding of MS pathology and the identification of therapeutic targets (24–26). In both diseases, blood-brain barrier permeability is a checkpoint in disease development that allows the massive infiltrate of inflammatory cells, including T cells, into the CNS. Autoreactive T cells are restimulated by myelin epitopes in the brain and spinal cord and orchestrate a local inflammatory response that profoundly damages CNS tissues and leads to functional neurological deficits, often including paralysis. For many years both EAE and MS were thought to be Th1-mediated diseases despite the finding that mice experience increased disease when deficient in IFN- γ , a Th1-derived cytokine (25, 27). This apparent paradox was explained by the discovery that CD4⁺ IL-17-producing T cells, termed Th17 cells, are the critical effector cells in EAE. In the absence of strong inhibition from IFN- γ , a pathologic Th17 response can proceed relatively unchecked (28).

There is a large body of evidence suggestive of mast cell involvement in EAE (for review see Ref. 29). Mast cells reside in the CNS, proximal to nerves and blood vessels. In acute EAE, the percentage of degranulated mast cells increases with the clinical onset of disease symptoms (30). A correlation between the numbers of mast cells and disease susceptibility in various mouse strains also

exists. For example, the classic EAE-susceptible strain SJL/J has at least 4-fold higher numbers of mast cells than the resistant C3H mouse (31). Finally, mast cell-stabilizing drugs such as cromolyn sodium can alter the severity of EAE (32).

The first *in vivo* proof of mast cell involvement in an autoimmune disease came in 2000 with the report that mast cell-deficient *c-kit*^{W/W^v} (W/W^v) mice experience delayed onset of disease and decreased disease severity in the EAE model (33). Reconstitution of W/W^v animals with mast cells restores disease without restoring mast cells directly to the CNS, implying a role for mast cells in the periphery (34). Subsequently, it was observed that both CD4⁺ and CD8⁺ T cells are less activated following EAE immunization in W/W^v mice than in wild-type littermates, although W/W^v-derived T cells are fully functional and cause equivalent disease when cultured *ex vivo* and adoptively transferred (35).

Evidence indicates that mast cells play a role in human disease as well. Over 100 years ago, mast cells were observed in the CNS lesions of patients with MS (36), a finding subsequently corroborated by others (37, 38). Importantly, gene expression profiling demonstrated that many transcripts associated with the allergic response, including a number of mast cell-specific genes, are highly expressed in MS brain lesions (39). Mast cell activation in disease is also suggested by the high levels of tryptase in the cerebrospinal fluid of MS patients (40).

How might mast cells become activated and aggravate the disease course in EAE? During induction of EAE, mast cells can be directly activated through TLRs by exposure to mycobacterium contained in CFA, leading to expression of a variety of cytokines but not degranulation (41). Myelin peptide can itself activate mast cells, promoting release of the enzyme β -hexosaminidase and cytokines, including IL-4 and TNF- α (Ref. 42 and M. A. Sherman and M. A. Brown, unpublished data). In addition, mast cells are likely to respond to the inflammatory cytokines expressed by other immune cells that have encountered myelin peptide or mycobacterial Ags.

It has been hypothesized that human MS is elicited by an infection (43) that provides a danger signal analogous to that provided by CFA, and this signal could activate mast cells directly. Once the inflammatory processes damage the myelin sheath, released myelin peptides might further activate mast cells. Activation of mast cells by inflammatory cytokines produced by T cells and other cells can also aggravate established disease.

Mast cell-stabilizers like cromolyn sodium have been shown to decrease the severity of EAE ((32, 44, 45). In humans, the tyrosine kinase inhibitor imatinib mesylate, which has effects on mast cell viability, is currently being tested for the treatment of autoimmune diseases like RA (46) and lupus nephritis (47). The mast cell stabilizer hydroxyzine has been tested as an adjuvant in clinical MS treatment (48).

The path to a fully activated effector Th cell and adaptive immune responses

The pivotal cell in the mast cell-dependent autoimmune diseases defined to date is the Th cell, a cell that directs the character and effector function of other innate and adaptive immune cells including DCs, neutrophils, CD8⁺ T cells, and Ab-producing B cells. During the development of CD4⁺ T cells in

the thymus, most cells that respond strongly to local self-peptides are deleted. T cells not eliminated in the thymus, including some self-reactive cells, move to the periphery and recirculate through the secondary lymphoid organs where they first encounter Ag. Recent evidence suggests that naive cells may also traffic to nonlymphoid organs at a much lower frequency where they could play a role in immunosurveillance and tolerance induction (49). For a naive $CD4^+$ T cell to become fully activated it must receive at least two signals (50). "Signal one" results from cross-linking of the Ag receptor and "signal two," a so-called "costimulatory" signal, is delivered by the APC. The DC plays a vital role in this scenario via its capacity to integrate other environmental signals, leading to its maturation as defined by the expression of costimulatory molecules, cytokines, and chemokines, migration to the lymphoid organs, and the ability to acquire, process, and present antigenic peptides on the cell surface in the context of MHC class II molecules.

The cytokines and costimulatory molecules expressed by DCs can also be modulated by the microenvironment and will ultimately contribute to specific $CD4^+$ Th cell fate decisions (27). DC-derived IL-12 elicits Th1 IFN- γ -producing cells and blocks the differentiation of IL-4-producing cells. DCs are also sources of TGF β , IL-6, and IL-23, cytokines that can influence the development or survival of either IL-17-producing Th17 cells or FoxP3 $^+$ regulatory T cells (Tregs) (discussed below).

Mast cell interactions with T cells and DCs

So how do mast cells fit into this picture? As shown in Fig. 1, both positive and negative effects could potentially result from mast cell activation in the context of disease. Mast cells colocalize with DCs in most tissues, particularly at sites of Ag entry, and express many molecules that regulate DC function. Because of their constitutive expression of many cell surface molecules including CD28, PD-L1 and PD-L2, CD40L and OX40, 41BB, GITR, and CD70 and their ability to immediately release preformed inflammatory mediators upon activation (4), mast cells are in a position to have strong modulatory effects on DCs. Indeed, it has been demonstrated that a coculture of activated mast cells with DCs results in their maturation as assessed by increased expression of CD80 and CD86 (51). In vivo, the migration of Langerhans cells (skin-derived DCs) to the lymph node in response to peptidoglycan is mast cell dependent (52). Similar results were observed using a contact hypersensitivity model of inflammatory disease (53). Mediators including histamine, PGD $_2$, thymic stromal lymphopoietin (TSLP), TNF- α , IL-4, and chemokines have been shown to regulate maturation, migration, or cytokine production of DCs (54–57). Histamine and PGD $_2$ in particular inhibit IL-12 and enhance IL-10 release from human DCs, altering the balance of Th differentiation to one that is Th2 skewed (58–60).

Mast cells can also directly influence T cell differentiation and function. The lymph nodes and spleen are normally sparsely populated with mast cells, but mast cells can migrate to these tissues under inflammatory conditions (34). Thus, they are in close proximity to T cells and are poised to influence their activation. T cell-mast cell coculture experiments demonstrate that mast cells significantly enhance T cell proliferation and cytokine production and that this effect is mediated in part by mast cell-derived TNF- α (4, 61). DCs and macrophages are most often considered the source of T cell-polarizing cytokines, yet mast cells are prolific producers of TGF β , IL-6 and IL-1 β ,

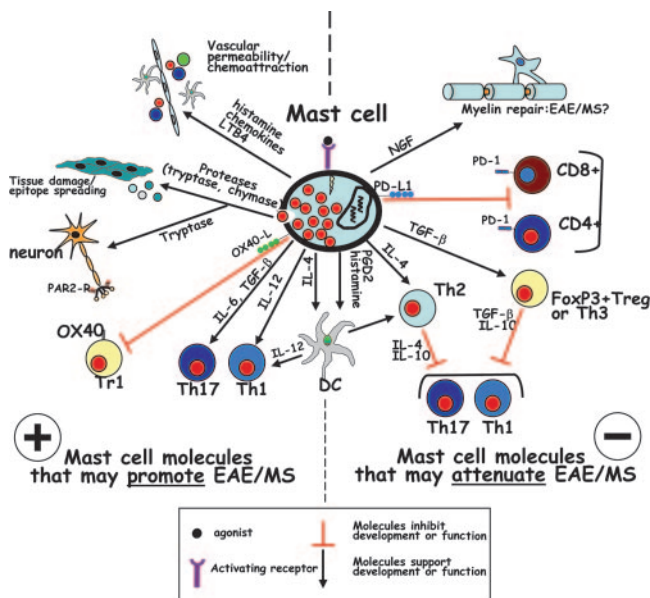


FIGURE 1. Mast cells can exert both positive and negative influences on the course of EAE/MS. Several variables can dictate the dominant influence mast cells can exert on immune cell function and ultimate tissue damage in EAE/MS (this is not meant to be a comprehensive list). Selective expression of mediators or cell surface immunomodulatory molecules, site variability of expression, and genetically determined heterogeneity in mast cell phenotypes all contribute to the quality of mast cell response in a given individual. From *top left and counter clockwise*: mast cell histamine, chemokines, and leukotrienes may enhance cellular trafficking into the CNS and permeation of the blood-brain barrier. Mast cell proteases can directly degrade tissue, causing direct damage, and may promote epitope spreading. The mast cell-specific protease trypase has been shown to act directly on neuronal PAR-2 receptors to cause nerve excitability. Activation of PAR-2 receptors on other cells induces the production of proinflammatory mediators. The costimulatory molecule OX40L on mast cells could bind OX40 on T cells and reduce the numbers of Tr1 regulatory cells. Mast cells express cytokines that can directly promote Th1 (IL-12) and Th17 (IL-6 and TGF- β) cell differentiation or indirectly act on DCs through IL-4 to enhance IL12 production and promote Th1 development. In contrast, mast cells may inhibit inflammation by enhancing Treg and Th3 cell development via the release of TGF- β (in the absence of IL-6) and skewing $CD4^+$ cells toward a Th2 (via IL-4 release). Cytokine released by Treg cells block the development of a Th1 or Th17 response. Mast cell expression of PD-L1 may inhibit $CD4^+$ and $CD8^+$ cell responses, and the release of NGF could lead to repair in inflammatory CNS conditions like MS.

and production of IL-2, IL-12, and IL-23 has also been detected (for review, see Ref. 62). Yet, a direct role for mast cell-derived cytokines in Th polarization in the lymph node is still largely speculative. Mast cell costimulatory/inhibitory molecules such as B7-1, B7-2, OX40, or PD-L1 may also be relevant in regulating the ultimate T cell response.

One might imagine that mast cells could aggravate disease in EAE by limiting the production of IFN- γ by skewing naive T cells to a Th2-like response and directly enhancing Th17 responses via the production of TGF β , IL-6, and IL-1. Studies in mast cell-deficient mice show that the development of a strong Th response in the periphery is mast cell dependent. Myelin oligodendrocyte glycoprotein peptide (MOG $_{35-55}$)-specific Th1 responses are attenuated after EAE disease induction in W/W ^{v} mice when compared with wild-type littermates (35). Studies are underway to characterize the balance of Th1, Th2, and Th17 responses elicited during EAE in mast cell-deficient mice.

Even in the face of a fully activated effector T cell population, mechanisms are in place to prevent pathologic responses. As the critical cells in allergy and autoimmunity, two disorders involving an inappropriate inflammatory response to harmless molecules, it has been assumed that mast cells play a role in overriding these suppressive mechanisms and breaking tolerance. However, as discussed previously, mast cells express molecules implicated in tolerance such as IL-10, TGF β , and PD-L1. Recent studies have even demonstrated a role for mast cells in creating and maintaining tolerance in a skin transplant model (63). Can these two opposing roles for mast cells be reconciled?

Several distinct regulatory T cell populations play an important role in the generation of peripheral tolerance and are functionally defined by their ability to inhibit T cell proliferation and IL-2 production. T regulatory type 1 (Tr1) cells are induced from naive CD4⁺ T cells in vivo and in vitro by priming with Ag in the presence of IL-10 (64) or by culture with immature or tolerogenic DCs (65, 66). Th3 cells are induced in vivo by priming in the presence of TGF- β and are associated with the generation of oral tolerance (67). As both Tr1 and Th3 cells produce IL-10 and TGF- β and mediate Ag-specific suppression of effector cells, it is not clear whether there is truly a difference between these two types of cells. There are some reports that Th3 cells express the transcription factor FoxP3 (68) whereas Tr1 cells are distinguished by the expression of the repressor of GATA-3 (ROG), the mast cell growth factor IL-9, and IFN- γ (69). However, because these proteins are expressed in other cell types, it is difficult to identify and distinguish Tr1 and Th3 regulatory cells in vivo.

Naturally occurring Tregs develop in the thymus and can suppress the proliferation of T cells specific for self-peptide. These CD4⁺CD25⁺FoxP3⁺ cells are crucial for avoiding an autoimmune response. Mutations in the gene for the transcription factor FoxP3 produce fatal multiorgan autoimmunity, both in mice (*scurfy*) (70) and humans (IPEX) (71). IL-2 (72) and TGF- β (73) are necessary for in vivo and ex vivo expansion of Tregs, which may then suppress the proliferation of effector T cells through direct cell contact, the release of cytokines such as TGF- β and IL-10, or the release of other factors like prostaglandin E₂ (74–76). It is tempting to speculate that thymic mast cells, through their production of TGF β , influence the development of this population. Ag-specific CD4⁺CD25⁺FoxP3⁺ Tregs can also be induced in vivo from CD4⁺CD25[−] naive T cells by continuous low doses of peptide (77) and have been found to arise de novo during the EAE disease course (78).

The importance of CD4⁺CD25⁺FoxP3⁺ Tregs in specific autoimmune diseases has been demonstrated by their ability to prevent and reverse disease in animal models of diabetes (79) and MS (80). However, recent studies of the Treg compartment in these models (78, 81, 82) and in human systemic lupus erythematosus (83) suggest that the pathology of autoimmunity is not due to a simple deficiency in Ag-specific Tregs. A study of CNS-trafficking Tregs in an EAE model suggests that Ag-specific effector cells may actually become resistant to Treg suppression, leading to the inflammation associated with autoimmunity (78). Mast cells, known to augment the severity of disease in EAE, could potentially modify the activation of effector T cells, either directly or through DC Ag presentation, and increase their resistance to Tregs in the CNS.

The relationship between mast cells and Tr1/Th3 cells is unknown. The presence of the OX-40 ligand has been shown to inhibit the generation of IL-10-producing Tr1 cells in vitro (84). However, mast cells could also act to promote the generation of Tr1 and Th3 cells as producers of TGF- β and, to a lesser extent, IL-10.

A recent study using a murine skin transplant model demonstrated that the presence of mast cells increased allograft tolerance and increased numbers of Tregs in the skin, an effect that was decreased in absence of the mast cell growth factor IL-9 (63). In addition, it has often been observed that W/W^v mice develop a spontaneous dermatitis, possibly due to defective tolerance induction in mast cell-deficient skin (8). The idea that mast cells could actually enhance tolerance is fascinating given their long-standing role as mediators of allergy, which is essentially a lack of tolerance to nonpathogenic substances.

There are several ways that mast cells could positively influence regulatory T cell activity. Mast cell PD-L1 can bind PD-1, a molecule that is highly expressed on Tregs (as well as conventional CD8⁺ and CD4⁺ cells) and is crucial for tolerance in the NOD mouse model (85). Several mast cell-released factors have been identified as promoters of immune suppression, including TGF- β and IL-10. The cytokine IL-4 acts as a growth factor for Th3 and Tr1 cells (86) and enhances Treg proliferation (while decreasing Treg suppression) in vitro (87).

The opposing roles displayed by IL-4, which can promote either Th1 or Th2 responses (6, 55, 88) or activate or inhibit Treg responses, highlight the finding that both the timing and the location of a stimulus critically influence the corresponding T cell response. This is particularly important in a discussion of mast cells, which possess an exquisite sensitivity to environmental cues and an ability to produce a wide breadth of factors. It is thus possible that mast cells could contribute, in different circumstances, to both the generation of tolerance and the breaking of tolerance in autoimmunity (Fig. 1).

Homing of inflammatory cells to the CNS and other target tissues

Mast cells play a crucial role in the trafficking of T cells to inflamed organs, possibly generating or perpetuating an autoimmune reaction. The inability to fully activate T cells in W/W^v mice correlates with both decreased cytokine production and decreased expression of homing molecules like CD44 and CD11a (6, 35). Correspondingly, there is a remarkable difference in the trafficking of immune cells to the inflamed CNS in wild-type and W/W^v mice, including Th1 CD4⁺ cells, CD8⁺ cells, and macrophages.

Mast cells also increase the migration of other cells, including myeloid DCs, through the release of factors like leukotriene B₄ (LTB₄) and TNF- α (54, 89, 90). Thus, mast cells could attract pathologic cells to the CNS and then influence the penetration of these cells into the immunologically privileged area (91). Mast cells are clearly important in regulating blood vessel permeability in allergic reactions and they have been shown to provide the critical chemokines required for entry into the brain and spinal cord, including MCP-1 for macrophages and MIP-1 α (CCL3), IP-10 (CXCL10) (92), and LTB₄ for T cell recruitment (93). As we learn more about requirements for immune cell trafficking, it will be important to carefully examine the contribution of mast cells to these events.

Mast cells in the CNS and other target tissues

The lack of CNS mast cells in reconstituted mice does not preclude a role for these cells *in vivo*. Hypothetically, mast cell proteases expressed in the CNS could cause direct local tissue destruction, and their presence in areas prone to autoimmune damage, including joints, the CNS and the pancreas, is consistent with this idea (94). Perhaps more importantly, tissue destruction by proteases may release Ags that can contribute to the epitope spreading that is characteristic of some forms of EAE and in the NOD murine model of diabetes. Thus, mast cells may amplify the immune response by allowing the priming of T cells to new epitopes.

The finding that sensory innervation of tissue is altered in human autoimmunity, particularly in the mast cell-dependent disease of RA (95), leads to the hypothesis that mast cells could influence disease by mediating neuronal changes. A mast cell-specific protease, tryptase, is a ligand for protease-activated receptor-2 (PAR-2) expressed on spinal afferent nerve fibers and dorsal root ganglion neurons as well as some immune cells (96). Tryptase can cleave this receptor, exposing a tethered ligand that activates the cell and leads to neurogenic inflammation via the release of proinflammatory neuropeptides such as substance P and calcitonin gene-related peptide (CGRP). Prostaglandins also directly induce release of these neuropeptides and sensitize local sensory neurons (97).

Mast cells also express nerve growth factor (NGF), a molecule that can act on neurons and myelin-producing oligodendrocytes and promote myelin repair. This was shown to protect against full EAE development in marmosets (98). Together with the anti-inflammatory effects of TGF- β and IL-10, it is conceivable that under some conditions mast cells could play a direct protective role within the CNS. However, the release of NGF in peripheral tissues could actually promote inflammation by inducing the neuronal production of substance P (99, 100).

Other sites of mast cell action on autoimmunity

One unexplored aspect of mast cells is their role in the stress response, a factor that exacerbates many disease states including autoimmune diseases. Corticotropin-releasing hormone (CRH), produced by the paraventricular nucleus of the hypothalamus during stress, initiates a hormonal cascade that results in activation of the sympathetic system and the release of epinephrine and norepinephrine. Although the stress response generally suppresses the function of immune cells, CRH has also been localized in inflamed tissues where it appears to increase inflammation locally (101–103). Mast cells possess both receptors for CRH (104) and the ability to release CRH *de novo* (105). Although the relationship between hypothalamic CRH and the CRH located in inflamed tissues is not yet determined, it has been hypothesized that the proinflammatory response of mast cells to CRH could account for the aggravation of RA and other inflammatory conditions during periods of stress. The normal increase in serum IL-6 following restraint stress is not observed in mast cell-deficient animals (106); however, *in vitro* human mast cells release only vascular endothelial growth factor when stimulated with CRH and not IL-6 or other proinflammatory factors (107). It is thus still unclear exactly how local or systemic CRH might contribute to the inflammatory role of mast cells.

Reproductive hormones, particularly estrogen and progesterone, may also influence mast cell activation in autoimmunity. Most autoimmune diseases, including MS, are more prevalent in females, and fluctuations in hormonal levels during ovulation or pregnancy can aggravate or diminish disease (108). Estrogens, including environmental estrogenic pollutants, can induce mast cell degranulation *in vitro* (109, 110), whereas progesterone appears to inhibit histamine secretion (111). A greater understanding of the relationships between hormone levels, stress, and mast cell activation will likely open doors to therapeutic measures in human autoimmunity.

Conclusions

Despite the numerous studies on mast cells, they remain enigmatic. The molecules expressed by these cells are largely redundant with other cells, making the assignment of a mast cell contribution difficult. It is clear that mast cells are not required for the development of some autoimmune diseases, including EAE. EAE disease can develop in W/W^v mice, although it is delayed and less severe, and in time many W/W^v mice will progress to frank EAE. It is our contention that mast cells play a critical amplifying role in the inflammatory events that lead to disease. During the initiation of disease mast cells are one factor that can contribute to the priming of the autoreactive T cell response and the homing of cells to their target organ. Perhaps the proinflammatory environment contributed by the mast cell lowers the threshold for T cell activation. Once a T cell response is established, mast cells in the CNS may act in concert with the T cells to promote tissue damage. Yet, in the face of a strong T cell response the contribution of mast cells may be less important.

There is strong but still relatively scant evidence of heterogeneity in mast cell responses. This diversity is observed in mast cells derived from different strains of mice and from within the same strain in response to various activators. In addition, it has long been appreciated that there are tissue-specific differences in mast cells. Therefore, the specific contribution of a mast cell may depend on its location and the proximal target cells, the activating signals it receives, and the genetic background of the individual. Such differences must be considered when evaluating disease models and in devising therapies to treat human diseases that are influenced by mast cells.

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