

Mast cells in allergy and infection: Versatile effector and regulatory cells in innate and adaptive immunity

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Mast cells are widely distributed in tissues, particularly near surfaces exposed to the environment. Mast cells can be activated to secrete diverse mediators and cytokines by IgE and specific Ag and many other stimuli, including products derived from either pathogens or the host during innate immune responses. Although mast cells are best known for their role in IgE-associated allergic disorders, mast cells can also exacerbate models of autoimmunity, enhance the sensitization and/or effector phases of certain cutaneous contact hypersensitivity responses, and increase inflammation and mortality during some severe bacterial infections. In other settings, however, mast cells can limit inflammation and tissue injury: mast cells promote host resistance in certain models of bacterial or parasite infection, limit pathology during some acquired immune responses to environmental Ag, including examples of severe contact hypersensitivity, and have adjuvant-like properties that can enhance the development of protective immunity against pathogens. These and other findings suggest that mast cells occupy a critical niche at the interface of innate and acquired immunity, where, depending on circumstances that remain to be fully understood, mast cells may function to perturb or help to restore homeostasis (or both), with consequences that can either promote health or contribute to disease.

Key words: Allergy · Infection · Mast cells

Introduction

Long regarded as critical effector cells in IgE-associated allergic disorders and responses to certain parasites, mast cells have also been found to promote host defense against bacteria. This has suggested that mast cells have opposite roles in allergy and in host defense against infection: mast cells drive pathology in the context of allergic diseases, but contribute to health by enhancing resistance to parasites and bacteria; however, recent data indicate that mast cells can exacerbate mortality in mice subjected to certain models of severe infection and can limit the pathology associated with some models of chronic allergic inflammation, innate immune responses to chronic irradiation

with UV B (UVB) light, and severe cutaneous contact hypersensitivity (CHS). These findings suggest a more nuanced view of mast cell function, *i.e.* depending on the context, mast cells can either positively or negatively regulate innate or adaptive immune responses to pathogens or allergens. In this review, we provide a brief introduction to mast cell biology, describe experimental approaches for defining the contributions of mast cells to biological responses *in vivo*, and then discuss some of the evidence supporting the view that mast cells can function as both effector cells and positive or negative immunoregulatory cells in allergic disorders and in host responses to pathogens.

Basic biology of mast cells

Mast cells are derived from haematopoietic stem cells; cells in this lineage ordinarily circulate as immature progenitors that enter

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peripheral sites and then mature locally [1, 2]. In vertebrates, mast cells are widely distributed throughout vascularized tissues, particularly near surfaces exposed to the external environment, including the skin, airways, and gastrointestinal tract [1, 2]. Along with DC, mast cells are well positioned to be one of the first cells of the immune system to interact with environmental Ag, environmentally derived toxins, or invading pathogens.

Mast cells are potentially long-lived cells that can re-enter the cell cycle and proliferate after appropriate stimulation [1–3]. Depending on the setting, local expansion of mast cell populations may occur by several processes in addition to proliferation, including increased recruitment, survival, and/or local maturation of mast cell progenitors [1–3]. Increases in the number of mast cells, and changes in their tissue distribution and/or phenotypic characteristics, can occur during Th2 responses and other settings associated with persistent inflammation and/or tissue remodeling [1–4]. For example, in subjects with birch pollen allergy, the number of mast cells in the epithelium of the nasal mucosa increases during the birch pollen season in Northern Europe [5]. In mice, Th2 responses to intestinal nematodes can result in striking increases in the numbers of mast cells in the gut and spleen [1–4]. Th2 responses are also often associated with increased numbers of circulating basophils, hematopoietic cells that are developmentally distinct from mast cells but that can secrete mediators, including histamine, which are also produced by mast cells [6, 7].

Environmental and genetic factors can finely control or “tune” many key features of mast cell populations. These features include cell proliferation, survival, and phenotype, such as the mast cells’ susceptibility to activation by various stimuli generated during innate or acquired immune responses, ability to store and/or produce various secreted products, and the magnitude and nature of the secretory responses to specific stimuli of activation [2]. Stem cell factor (also known as Kit ligand) is the main survival and developmental factor for mast cells but many other growth factors, cytokines, and chemokines can also influence mast cell numbers and phenotype, including IL-3, which is especially important in mice, Th2-associated cytokines (e.g. IL-4 and IL-9), and TGF- β_1 [1–4].

Important aspects of mast cell phenotype can vary depending on many factors. These include species of animal, specific anatomical location, individual genetics (e.g. strain background in mice), systemic or local changes in the levels of factors that can alter various properties of the cell, and whether the cell is analyzed *in vivo* or *in vitro*. It is especially important to remember that while mouse and human mast cells share many similarities, they also have some interesting differences [2, 4, 8]. Given that there may be substantial differences between aspects of mast cell phenotype and function *in vitro* and *in vivo*, it is particularly important to attempt to define the roles of mast cells during biological responses *in vivo*.

Analyzing mast cell function *in vivo*

Mice that specifically lack only mast cells have not been reported/generated; however, WBB6F₁-Kit^{W/W-v} mice and the more

recently characterized C57BL/6-Kit^{W-sh/W-sh} mice, which are profoundly deficient in mast cells but have other phenotypic abnormalities, can be used to analyze the *in vivo* functions of engrafted WT or genetically modified mast cells (reviewed in [2, 9]). Kit^W is a point mutation that produces a truncated Kit that is not expressed on the cell surface; Kit^{W-v} is a (Thr660Met) mutation in the c-kit tyrosine kinase domain that substantially reduces Kit-kinase activity; and Kit^{W-sh} is an inversion mutation that affects transcriptional regulatory elements upstream of the c-kit transcription start site on mouse chromosome 5 (reviewed in [2, 10]).

Adult WBB6F₁-Kit^{W/W-v} and C57BL/6-Kit^{W-sh/W-sh} mice are profoundly deficient in mast cells and melanocytes (reviewed in [2, 9, 10]). WBB6F₁-Kit^{W/W-v} mice exhibit several other abnormalities, including macrocytic anaemia, reduced numbers of bone marrow and blood neutrophils, sterility, and markedly reduced numbers of interstitial cells of Cajal (reviewed in [2]). C57BL/6-Kit^{W-sh/W-sh} mice are neither anaemic nor sterile, but have increased numbers of bone marrow and blood neutrophils, enlarged spleens, and mild cardiomegaly [9–11].

Differences in biological responses in WBB6F₁-Kit^{W/W-v} and C57BL/6-Kit^{W-sh/W-sh} mice and WT mice may be due to any of their abnormalities, and not necessarily their mast cell deficiency. The lack of mast cells in these mutant mice can be selectively repaired by the intravenous, i.p., or intradermal adoptive transfer of genetically compatible, *in-vitro*-derived, WT, or mutant mast cells, to create so-called “mast cell knock-in mice” [2, 9]. These mast cell knock-in mice can then be used to assess the extent to which differences in the expression of biological responses observed in WBB6F₁-Kit^{W/W-v} and C57BL/6-Kit^{W-sh/W-sh} mice, compared with those in WT mice, are due to the lack of mast cells or mast-cell products in the mutant mice.

The role of specific mast cell-associated mediators can be investigated *in vivo* by testing animals in which that mediator has been knocked out. To the extent that the mediator is selectively expressed by mast cells, and if its deletion does not significantly influence the expression of other mast cell products, then one can draw conclusions about the role of that mast cell mediator *in vivo*. For example, mice that lack mast cell protease-1 (MCPT1) [12], MCPT4 [13], tryptase β -2 (TPSB2; also known as MCPT6) [14], or mouse mast cell-carboxypeptidase A3 (CPA3; also known as MC-CPA) [15], or that have a mutated form of CPA3 that essentially lacks enzymatic activity [16]. Such mice have been used to analyze whether the absence of these proteases (or their enzymatic activity) influences other aspects of mast cell phenotype, such as content of other stored mediators, and to define the functions of such proteases *in vivo*.

Other promising approaches to investigate the specific functions of mast cells and their products are currently in development, such as “mast cell-specific Cre” mice that can be crossed with other strains in which the genes of interest are “floxed” [17]. As discussed elsewhere, it can be problematic to attempt to use pharmacological approaches to discern the roles of mast cells *in vivo* [18].

Mast cells in allergy

Mast cells, similar to basophils, constitutively express on their surface substantial numbers of FcεRI, the high-affinity receptor for IgE, and the number of surface FcεRI is positively regulated by ambient concentrations of IgE [19]. Ag- and IgE-dependent activation of mast cells, *via* aggregation of FcεRI when bi- or multi-valent Ag is recognized by the cells' surface-FcεRI-bound IgE, initiates a complex secretory response. This FcεRI-dependent mast cell activation response includes the rapid release (in minutes) of cytoplasmic granule-associated mediators such as histamine, heparin, and other proteoglycans, several proteases, and certain cytoplasmic-granule-associated cytokines, the secretion of *de novo*-synthesized lipid mediators (including cysteinyl leukotrienes and prostaglandins) and the production, with a prolonged kinetics, of many cytokines, chemokines, and growth factors [2, 18, 19]. Aggregation of only a small fraction of the mast cell's FcεRI is sufficient to trigger mast cell activation and mediator secretion; as a result, individual mast cells can be simultaneously sensitized to respond to many different specific Ag [19]. The extent to which mast cells secrete various types of mediators can vary according to the strength of the activation signal, with release of some cytokines occurring at lower Ag concentrations than the concentration required to induce substantial degranulation and release of stored mediators [20]. The magnitude of mast cell activation in response to Ag and IgE can also be positively or negatively regulated by exposure to ligands for many other receptors expressed by this cell type [2, 18, 20].

Ag- and IgE-dependent mast cell activation is widely regarded to be a, if not *the*, major initiator of the clinical signs and symptoms that are induced rapidly after the exposure of sensitized, *i.e.* "allergic", individuals to small amounts of specific Ag. Anaphylaxis, a catastrophic and sometimes fatal systemic reaction to an otherwise innocuous Ag (such as components of foods), which can begin in a sensitized subject within moments of exposure to small amounts of Ag, arguably represents the most striking imbalance between the cost and the benefit of an immune response [19]. It is likely that basophils contribute importantly to certain types of anaphylaxis, particularly that mediated by IgG₁ antibodies in the mouse [7]. In contrast, abundant evidence from both mice and humans indicates that Ag- and IgE-dependent activation of mast cells *via* aggregation of FcεRI is critical for the pathophysiological manifestations and mortality associated with IgE-dependent anaphylaxis [2, 19].

Findings from human studies and work in mast cell knock-in mice indicate that mast cells can also contribute to later consequences of allergen exposure, by promoting local inflammation and by directly or indirectly enhancing certain aspects of tissue remodeling. Depending on the model system, mast cells can contribute to the migration, local accumulation, and activation of T cells, DC, and cells of innate immunity (neutrophils, eosinophils, and monocytes) [21]. Moreover, in a mouse model of chronic allergic inflammation of the airways, mast cells are required for the full development of several features of tissue

remodeling, including increased numbers of mucus-producing goblet cells in the airway epithelium and increased lung collagen deposition, changes accompanied by a mast cell-dependent exacerbation of airway hyperreactivity to methacholine [22].

Mast cells may even have roles in allergic disorders beyond that of pro-inflammatory effector cells. IL-4 and IL-13, which promote Ig class switching and IgE production, and, coincidentally, bear the traditionally "unlucky numbers" of the Eastern and Western worlds, respectively, are among the cytokines that can be produced by mast cells (and basophils) stimulated with IgE and Ag (reviewed in [2, 6, 7, 23]). Mast cells and basophils also can express CD40L (reviewed in [2, 6, 7, 23]). This raises the possibility that mast cells (and/or basophils) can drive further IgE production, and epitope spreading, during IgE-associated responses in allergic disorders, or in responses to parasites. Finally, in a model of allergic inflammation of the airways, mice lacking the mast cell chymase, MCPT4, compared with the corresponding WT mice, exhibited more substantial increases in airway hyperreactivity to methacholine, increased airway inflammation, and thickening of bronchial smooth muscle [24]. These findings indicate that at least one mast cell product may help to limit the pathology associated with allergic inflammation.

Mast cells in immune responses to parasites

It is often suggested that IgE-associated allergic disorders represent consequences of "misdirected" Th2 responses, which originally evolved as a host-defense mechanism against parasites, particularly nematodes. It is true that many parasite infections are associated with: (i) high levels of parasite-Ag-specific and nonspecific IgE; (ii) changes (typically, increases) in the numbers and distribution of mast cells at sites of infection; and (iii) evidence of mast cell activation in the vicinity of the parasites [25]. Nevertheless, perhaps because host-defense strategies often employ redundant or partially overlapping components, it has been challenging to identify conclusive evidence that mast cells, and particularly IgE-dependent mast cell activation, confer benefit during parasite infection.

In mice, the most convincing evidence that mast cells and IgE can enhance host resistance to parasites is the demonstration that both mast cells and intact IgE are required for optimal expression of resistance to a secondary infestation of the skin of WBB6F₁-Kit^{W/W^{-v}} mice with larval Ixodid *Haemaphysalis longicornis* ticks [26]. However, there is evidence that basophils, more than mast cells, confer protection against secondary infestations with larval Ixodid *Dermacentor variabilis* ticks [27]. In guinea pigs, treatment with an anti-basophil antibody essentially abrogated the ability of animals subjected to a primary infestation with larval Ixodid *Amblyomma americanum* ticks to exhibit resistance to the feeding of such larval ticks during a secondary infestation [28].

Taken together, such work suggests that basophils and mast cells may have overlapping or complementary functions as effectors of adaptive immune responses that interfere with tick feeding. Evidence from WBB6F₁-Kit^{W/W^{-v}} mast cell knock-in mice

indicates that mast cells can contribute to host defense against primary cutaneous infections with *Leishmania major* [29], and also, in part via mast cell-derived TNF, to host resistance to *Plasmodium berghei* ANKA in a mouse model of malaria [30].

Studies employing genetically mast cell-deficient or mast cell-protease-deficient mice support the conclusion that mast cells can also contribute to resistance to infections with certain nematodes, including *Strongyloides ratti* [31], *S. venezuelensis* [32], and *Trichinella spiralis* [12]; however, short-term engraftment of adoptively transferred mast cells did not correct the impaired host response to a primary infection with *S. ratti* in WBB6F₁-Kit^{W/W-v} mice [32]. Studies in WBB6F₁-Kit^{W/W-v} mice indicate that mast cells make little or no contribution to the expulsion of *Nippostrongylus brasiliensis* during primary infections with this nematode (reviewed in [33]), whereas a modest defect in expulsion of *N. brasiliensis* was observed in C57BL/6-Kit^{W-sh/W-sh} mice during primary but not secondary infections [34]. Finally, treatment of rats with a neutralizing antibody to stem cell factor, that resulted in depletion of intestinal mast cells, also resulted in substantially decreased parasite egg production during primary infection with the nematode *N. brasiliensis* [33].

One hypothesis that is consistent with the divergent findings from studies investigating whether mast cells (or IgE) influence parasite immunity is that, depending on the setting, mast cells either can have net effects favoring the host (as in the case of certain ticks and certain intestinal nematodes) or can have net effects that favor the parasite (as in the case of *N. brasiliensis* in rats, perhaps by enhancing parasite nutrition by increasing local vascular permeability) (Fig. 1). In light of the long-term co-evolution of parasites and their hosts, with each attempting to probe weaknesses in or to co-opt the defense mechanisms of the other, it should not be surprising that the engagement of mast cells and IgE during host/parasite interactions may not always produce results that favor the host.

Mast cells in bacterial and viral infections: A double-edged sword?

Work by many groups, using both mast cell knock-in and mast cell-associated protease-deficient mice, has shown that mast cells can enhance host resistance and survival during several examples of bacterial infections [9, 14, 18, 35–45]. This has been demonstrated in models such as cecal ligation and puncture (CLP, considered by some investigators to be the “gold standard” mouse model of sepsis (reviewed in [9]) [9, 35, 37–40, 43, 44], and in mice subjected to i.p. [14, 36, 44], intranasal [36], or intracutaneous [42] injection of pathogenic bacteria. Indeed, activation of mast cells by many different mechanisms can contribute to the ability of mast cells to enhance resistance to bacterial infection. Such mechanisms include mast cell activation via TLR4 [38], products of complement activation [37], or endothelin-1 [40]). Moreover, several mast cell functions can contribute to host defense against bacteria including phagocy-

tosis of bacteria (reviewed in [45]), enhancement of the recruitment or function of granulocytes [9, 14, 35, 36, 41–44], and the proteolytic degradation of endogenous mediators which would otherwise be elevated to toxic levels, such as endothelin-1 [40] and neurotensin [43].

These findings support the conclusion that mast cells have important sentinel and effector roles during bacterial infection that help to promote clearance of the bacteria, protect the host from pathology, and enhance survival. Yet evidence from mast cell-engrafted C57BL/6-Kit^{W-sh/W-sh} mice shows that mast cell dipeptidyl peptidase-I can have effects during a severe model of CLP that reduce levels of IL-6 and increase mortality [39]. Moreover, in mast cell-engrafted C57BL/6-Kit^{W-sh/W-sh} mice subjected to a model of severe CLP, mast cell production of TNF (and perhaps other mast cell functions) can exacerbate inflammation and mortality [9]. Another setting in which mast cell responses to bacteria may contribute to pathology is in atopic dermatitis, an allergic disorder in which the majority of patients have colonization of the skin with *Staphylococcus aureus*, a source of peptidoglycan that could mediate TLR2-dependent activation of mast cell cytokine production [45, 46]. A conclusion that can be drawn from these experiments is that, depending on the setting, including the severity and/or type of infection or the presence of another disorder, mast cells can either promote health or increase pathology during host responses to bacteria (Fig. 1). Intrinsic properties of the mast cell, such as genetic predispositions to produce larger or smaller amounts of TNF and other cytokines, or the presence of other abnormalities in the host (e.g. C57BL/6-Kit^{W-sh/W-sh} mice have increased numbers of neutrophils [9–11]), may also influence whether the role of mast cells, in particular bacterial infections, is beneficial or harmful.

There is evidence that mast cells participate in host responses to certain viruses, but their precise roles in such settings are not yet clear. Rats infected with Sendai virus exhibit increased numbers of both bronchiolar mast cells and airway hyperresponsiveness [47]. Rodent [41, 42, 45, 48] and human [8, 41, 49] mast cells express TLR (e.g. TLR3), which can be activated by viral double-stranded RNA to release various chemokines and cytokines, including IFN- α and IFN- β [49]. Some of these mast cell-derived products may contribute to host defense against viruses [41, 45, 49, 50]. In other settings, viral activation of mast cell cytokine production might also result in effects on the airways that contribute to pathology, such as the exacerbations of asthma symptoms and hospitalizations that occur in conjunction with seasonal respiratory virus infections [50]. Co-stimulation of rodent and human mast cell populations *in vitro* via the Fc ϵ RI and certain TLR can enhance mast cell secretion of various pro-inflammatory mediators, suggesting another mechanism through which bacterial or viral infections might exacerbate atopic asthma and other IgE- and mast cell-associated disorders *in vivo* [45].

Some viruses, including HIV [51] and dengue virus [41], can infect mast cells. The biological significance of this is not yet clear, but the interaction between mast cells, TLR, IgE, and HIV is of particular interest. There is evidence that human mast cells can

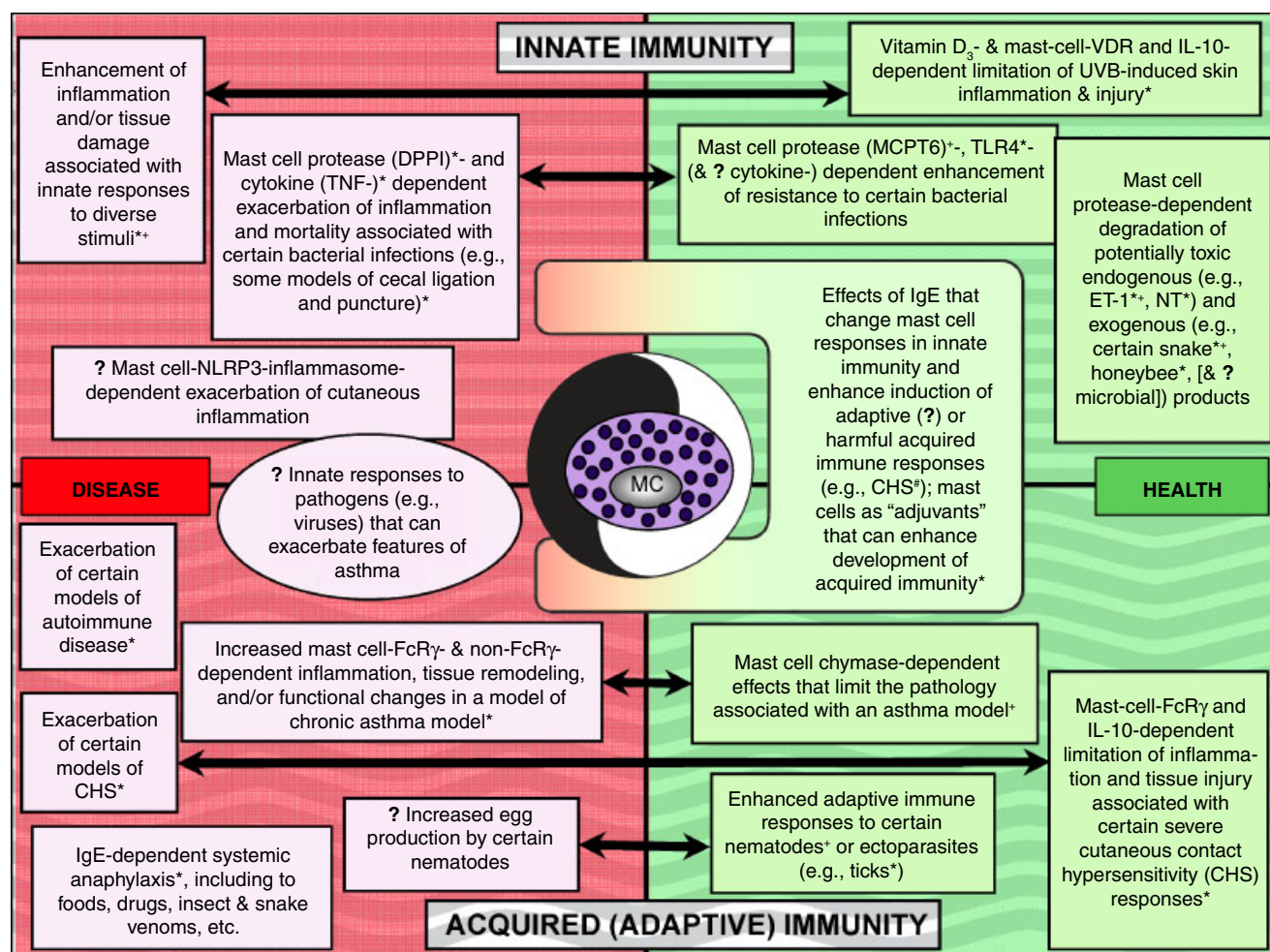


Figure 1. Diverse roles of mast cells in innate or acquired (adaptive) immune responses that contribute to health or disease. This figure highlights some of the roles of mast cells that are thought to promote health (green, right) or exacerbate disease (red, left). These functions either have been demonstrated using mast cell-engrafted genetically mast cell-deficient mice (*), or mice that lack certain mast cell-associated products (+) or IgE[±], or represent speculation (?) based on the known properties of mast cells. Arrows link examples of settings in which, depending on the circumstances, mast cells may either promote health or exacerbate pathology. ET-1, endothelin-1; MC, mast cell; NLRP3, nucleotide-binding oligomerization domain-leucine-rich repeats containing pyrin domain 3; NT, neurotensin; VDR, vitamin D receptor.

represent a reservoir of persistent HIV infection, that mast cell exposure to TLR2, -4, or -9 ligands can trigger HIV-1 virus replication in latently infected cells, and that IgE-FcεRI interactions may influence HIV-1 co-receptor expression by mast cells, and their susceptibility to infection with CXCR4-tropic and R5X4-tropic variants (reviewed in [51]). Moreover, many subjects infected with HIV have increased blood levels of IgE, and HIV-1 gp120 and Tat proteins have effects on human mast cells and/or basophils that promote their migration and functional activation *in vitro* (including the release of IL-4 and IL-13 from human basophils) [52]. In human basophils, Tat protein also can upregulate the β-chemokine receptor CCR3, which is expressed on human basophils and lung mast cells and is also a co-receptor of HIV-1 infection [52].

The evidence that mast cells can have effects during host response to pathogens that favor either the host or the pathogen may reflect a basic principle of mast cell biology:

that, depending on the circumstances, mast cells have the potential to function either as positive or as negative immunoregulatory cells, both during innate and acquired immune responses.

Mast cells as positive and negative immunoregulatory cells

Mast cells can perform many functions, such as Ag presentation and interactions with other immune cells *via* co-stimulatory molecules or secreted mediators, that have the potential to enhance or suppress either the development or the tissue manifestations of innate or adaptive immune responses [21, 53]. Some of these functions, and the distinction between effector and immunoregulatory roles of mast cells, are summarized in Table 1. We would like to focus here on certain mast cell

Table 1. Effector and immunomodulatory functions of mast cells^{a)}*Effector functions^{b)}*

Promote clearance of pathogens by phagocytosis and/or secretion of anti-microbial peptides
 Degrade potentially toxic endogenous peptides and components of venoms
 Increase vascular permeability (e.g. by histamine)
 Stimulate bronchial smooth muscle–cell contraction (e.g. by leukotriene C₄)
 Promote fibroblast collagen synthesis (e.g. by tryptase)

*Immunomodulatory functions^{c)}**Examples of positive immunomodulatory functions*

Promote the migration, maturation, differentiation, and function of immune cells via secretion of factors such as TNF, chemokines, histamine, LTB₄, and proteases
 Present Ag to T cells (via MHC class I or II molecules) or enhance Ag presentation by capturing IgE-bound-Ag via FcεRI and then undergoing apoptosis
 Promote B-cell IgE production (through IL-4, IL-13, and CD40L)
 Promote expression of TSLP on epithelial cells (for example, by TNF, IL-4, and IL-13)
 Promote recruitment of immune cells by production of TNF and other mediators that upregulate adhesion molecule expression on vascular endothelial cells
 Promote Th2 responses via effects of prostaglandin D₂ on DC maturation
 Promote airway smooth muscle production of chemokines and cytokines (via TNF, IL-4, and IL-13)
 In the presence of physiological levels of IgE, promote sensitization in certain models of CHS (via increased migration of skin DC and perhaps other functions)
 In response to certain activators of mast cells used in conjunction with vaccines, enhance development of protective adaptive immune responses to pathogens

Examples of negative immunomodulatory functions

Suppress sensitization for CHS (via UVB-induced production of histamine)
 Promote peripheral tolerance to skin allografts (via mechanisms that remain to be defined)
 Mediate *Anopheles* mosquito-bite-induced suppression of development of certain T-cell-dependent responses (via effects of mast cells that remain to be defined)
 Suppress many features of certain models of severe CHS, in part via effects of IgG₁/mast cell-FcγR-dependent production of IL-10
 Suppress many features of the pathology of chronic low-dose UVB irradiation of the skin, in part via effects of vitamin D₃-mast cell-VDR-dependent production of IL-10
 Suppress cytokine production by T cells and monocytes (via IL-10)
 Suppress production of pro-inflammatory cytokines and chemokines by keratinocytes (via IL-10)
 Enhance ability of DC to reduce T-cell proliferation and cytokine production (via IL-10)

^{a)} This table is a modified version of Box 1 in ref. [21], which is reproduced with the permission of the publisher. Please see the original source for relevant references.

^{b)} Effector functions include the non-immunomodulatory physiological or pathological functions of mast cells or the direct regulation of “nonimmune” cells, such as vascular endothelial cells, epithelial cells, fibroblasts, nerve cells, and muscle cells.

^{c)} These are effects on other immune cells (such as DC, T cells, B cells, monocytes/macrophages, and granulocytes) and effects on structural cells (such as vascular endothelial cells, epithelial cells, and smooth muscle cells) that alter their ability to influence immune cells.

immunoregulatory functions that are supported by findings derived from *in vivo* models and which may be particularly relevant to the roles of mast cells in infections or allergic disorders.

Studies in mast cell knock-in mice suggest that it may be possible to exploit a positive immunoregulatory function of mast cells to improve vaccination strategies [54]. This study [54] indicates that, in mice, small molecules that induce innate activation of mast cells can enhance the development of protective Ag-specific immune responses to pathogens by inducing mast cells to secrete TNF and other products at sites of vaccination [54] (Fig. 1). By contrast, in models of allergic inflammation of the airways, there is so far no convincing evidence that mast cells

are required for either Ag sensitization or the development of Ag-specific IgE or IgG₁ responses *in vivo* [22].

There is evidence, however, that IgE can influence the mast cell's ability to perform innate functions that in turn enhance Ag sensitization. Studies in IgE-deficient and mast cell-deficient mice show that the binding of IgE to skin mast cells, independently of the Ag specificity of that IgE, can “prime” mast cells in a way that enhances their ability to promote the sensitization phase of certain cutaneous CHS responses [55] (Fig. 1). In addition to supporting other evidence indicating that the binding of IgE to FcεRI *per se* can activate certain mast cell functions [19], this finding represents an example of how adaptive immunity (specifically, the generation of “physiological” levels of IgE) can alter the mast cell's ability to

function during an innate immune response (*i.e.* to respond to happen challenge of the epidermis in a way that promotes migration of cutaneous DC to draining lymph nodes). It remains to be determined whether mast cell binding of IgE also has any effect on the cell's ability to participate in the development of adaptive immune responses to microbial pathogens, either in the vaccine protocols or in the context of actual infections.

A possible therapeutic exploitation of a negative immunoregulatory function of mast cells would be to harness the cell's ability to suppress, *via* IL-10 production and probably other mechanisms, the cutaneous inflammation and tissue damage associated with certain severe CHS responses or with chronic UVB irradiation [56] (Fig. 1). Mast cell IL-10 production in these settings appears to be regulated by distinct mechanisms, with mast cells being activated *via* receptors containing the FcR γ -chain (presumably, by immune complexes of IgG₁ and Ag interacting with Fc γ RIII) in severe CHS responses [56] but *via* the receptor for physiologically active vitamin D₃ in the innate response to chronic UVB [57]. Although mast cells can limit tissue damage in innate responses to chronic UVB, mast cells have been implicated as initiators and amplifiers of inflammation in many other innate immune responses [2, 4, 18, 41, 42, 45]. Moreover, studies in mice indicate that activation of mast cells *via* the NLRP3 inflammasome can contribute to IL-1 β over-production and chronic urticarial rash in subjects with cryopyrin-associated periodic syndrome, a disorder associated with NLRP3 mutations [58].

Concluding remarks

Mast cells have long been regarded as exceptionally efficient initiators and amplifiers of certain innate and acquired immune responses, especially IgE-dependent acute responses to challenge with specific Ag; however, as shown in Fig. 1, there is evidence that, depending on the circumstances, mast cells can either enhance innate responses that help to clear bacterial infections or exacerbate pathology associated with infections. In addition, mast cells can either exacerbate or suppress the features of various cutaneous CHS responses and either enhance or suppress the inflammation and pathology associated with certain innate immune responses. Although mast cells can enhance host responses to certain parasites, it is possible that in other settings mast cells have effects that favor parasite fecundity. There is even recent evidence that some mast cell functions may limit the pathology associated with allergic inflammation of the airways [24].

Indeed, mast cells appear to be able to help limit or “turn off” the inflammation and tissue injury associated with examples of both innate and acquired immune responses. We do not yet have sufficient evidence to decide whether the models in which mast cells limit pathology represent unusual settings that have uncovered an interesting but minor facet of the mast cell's functional repertoire, or instead have revealed a fundamentally important property of this enigmatic cell. But one thing is certain: evolution did not give us mast cells so that we can eat a

peanut and die. It is even possible that the mast cell's fundamental role is to contribute to an outcome that is the polar opposite of anaphylaxis, *i.e.* to initiate and then finely regulate perturbations of homeostasis that restore health, rather than to incite catastrophic perturbations of homeostasis that result in death.

The importance of the mast cell as a regulator of homeostasis during particular innate or adaptive immune responses, and the identification of factors that recruit mast cells to the dark side in interactions between the host and its environment, represent just some of the many questions about mast cell function in health and disease that remain to be addressed. For example, can mast cell interactions with pathogenic or endogenous, nonpathogenic microbes contribute to immunological changes that *reduce* an individual's propensity to develop allergic disorders? There is evidence that the Th2 cell and regulatory T-cell responses associated with some helminth infections can both suppress allergic and autoimmune disorders and also diminish responses to vaccines (reviewed in [59]); do mast cells have any role in those findings? Under which circumstances, in addition to peripheral tolerance to skin allografts [60], can mast cells contribute significantly to the development of immunological tolerance, and can such mast cell functions be manipulated therapeutically? Will a better understanding of mast cell biology yield new insights for improving strategies to induce protective immune responses to pathogenic organisms [54], while avoiding effects that may increase the mast cell's propensity to induce pathology? What is the biological significance of the infection of mast cells with HIV [51] and dengue [41] viruses, and can HIV-1 infection of cells in the mast cell lineage be influenced by TLR ligands or IgE and Fc ϵ RI *in vivo* as well as *in vitro* [51]?

Answering these questions will take time. It is already clear, however, that mast cells have a much larger spectrum of potential roles in health and disease than was thought only a short time ago, when interest focused mainly on their role as effector cells in IgE-associated responses. Indeed, mast cells are increasingly viewed as versatile effector and immunoregulatory cells that occupy a critical position at the interface of innate and acquired immunity, where, depending on circumstances that remain to be fully understood, mast cells may either help to sustain and restore health or contribute to disease.

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Abbreviations: CHS: contact hypersensitivity · CLP: cecal ligation and puncture · CPA: carboxypeptidase A · MCPT: mast cell protease · UVB: UV B radiation

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