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Mast Cells in Inflammation and Disease: Recent Progress and Ongoing Concerns

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Abstract

Mast cells have existed long before the development of adaptive immunity, although they have been given different names. Thus, in the marine urochordate *Styela plicata*, they have been designated as test cells. However, based on their morphological characteristics (including prominent cytoplasmic granules) and mediator content (including heparin, histamine, and neutral proteases), test cells are thought to represent members of the lineage known in vertebrates as mast cells. So this lineage presumably had important functions that preceded the development of antibodies, including IgE. Yet mast cells are best known, in humans, as key sources of mediators responsible for acute allergic reactions, notably including anaphylaxis, a severe and potentially fatal IgE-dependent immediate hypersensitivity reaction to apparently harmless antigens, including many found in foods and medicines. In this review, we briefly describe the origins of tissue mast cells and outline evidence that

these cells can have beneficial as well as detrimental functions, both innately and as participants in adaptive immune responses. We also discuss aspects of mast cell heterogeneity and comment on how the plasticity of this lineage may provide insight into its roles in health and disease. Finally, we consider some currently open questions that are yet unresolved.

INTRODUCTION

Mast cells are derived from progenitors that migrate into and complete their maturation in most vascularized tissues (1–5). Mature mammalian mast cells ordinarily reside near blood vessels or nerves and beneath or in epithelia, and, within the airways and the gastrointestinal and genitourinary tracts, near or within smooth muscle and mucus-producing glands (2, 6, 7). Mast cells can remain for long periods of time in the same locations or can both expand locally and migrate into different sites, in both epithelial tissues and other settings (2, 6, 7). Some species, including murine rodents, have mast cells within mesothelium-lined cavities, such as the peritoneal or pulmonary cavities (8, 9).

In early development in mice, yolk sac–derived mast cell progenitors migrate into diverse connective tissues, such as the skin (10–13). Tissue mast cells in mice also arise from classical hematopoietic tissues (such as the bone marrow), with precursors traveling through the circulation before they acquire more mature characteristics in peripheral tissues (10–13). Thus, based on work in the mouse, at least two different mast cell maturation pathways have been described. The extent to which this applies to other mammals, including humans, is not yet fully elucidated.

However, considerable work has been done attempting to identify distinct mast cell populations, both in murine rodents and in humans. Perhaps the best known system is that which has identified connective-tissue mast cells (CTMCs) and mucosal mast cells (MMCs) in murine rodents (14). CTMCs populate the skin, peritoneal cavity, and muscularis propria of the gastrointestinal tract (among other sites), and their cytoplasmic granules contain heparin proteoglycan and relatively high concentrations of histamine (15). MMCs populate the mucosa of the gastrointestinal tract, contain little or no heparin proteoglycans in their granules, and have lower amounts of histamine (15). The two populations also differ in which of the mast cell–associated proteases they ordinarily express (3, 16) and in which stimuli of activation they can respond to (6, 16). While each population can expand in certain settings, the most remarkable expansion generally has been reported for MMCs, whose numbers can increase to over 100 times baseline levels during infections with certain intestinal parasites (17, 18). Such expanded MMC populations can diminish markedly once the parasite has been rejected (17, 18).

As attempts have been made to characterize the phenotype of mast cell subpopulations in other species, it is clear that work with mouse mast cells is not recapitulated exactly in humans. For example, mast cell proteases have been used to define distinct mast cell populations in humans (separating mast cells with chymase in their granules in addition to tryptase, from those with tryptase but no detectable chymase) (19). However, expansions of mast cell populations in humans, while they certainly occur (20), are not as robust as have been reported in the mouse. Moreover, newer and more comprehensive approaches for examining the phenotype of various mouse mast cell populations [including assessment of gene expression (11, 12, 21)] have revealed that mouse mast cells have more complexity than had previously been widely appreciated. Indeed, it has become clear not only that phenotypically distinct mast cells comprise more than two subsets in mice but also that certain aspects of mast cells' phenotype/gene expression can vary during inflammatory responses associated with mast cell participation (22).

Although mammalian mast cells have been studied extensively in the context of IgE-associated diseases or host defense processes, it is clear that mast cells can be found even in creatures that lack immunoglobulins. Indeed, cells with many of the morphological, biochemical, and functional characteristics that we associate with mammalian mast cells (including the ability to be activated to degranulate by compound 48/80) have been described in urochordates, i.e., in organisms that developed before the acquisition of immunoglobulins as components of adaptive immunity (23–28). Cavalcante et al. (23, 24) have speculated that the mast cells of the urochordate *Styela plicata*, which are called test cells, might play an important role in host defense. This is logical, given the abundance of heparin-containing cells beneath the surface of the developing organism and in close proximity to the digestive system of mature animals (23, 24). However, this proposed protective role of test cells (and/or heparin-containing cells in other parts of the anatomy) in host defense in urochordates has not yet been experimentally verified.

Whatever the functional repertoire of urochordate test cells, it is clear that, in mammals, mast cells have acquired the ability to bind large quantities of IgE to their surface (28). In certain mammals, including mice (29, 30) and humans (31–34), at least some mast cell populations can also bind immune complexes of IgG and antigen. While it appears that the expression of high-affinity receptors for IgE (i.e., FcεRI) is a feature of most if not all mature mast cells, their ability to bind IgG-antigen immune complexes may vary according to the cell's adaptation to immune responses or diseases (30, 35, 36). Besides the ability to be activated by IgE and specific antigen or by IgG-antigen immune complexes, certain mouse and human mast cells can also respond to products of complement activation (37, 38) (e.g., C3a and C5a), diverse agonists of Toll-like receptors (39–41), adenosine (42), stem cell factor (43, 44), a variety of endogenous peptides [including substance P (45–47) and VIP (46, 48)], and diverse components of reptile or insect venoms (48–51), among many other factors (41).

In addition to mast cells, which normally reside in the tissues, often for long periods of time, there is a granulocyte that shares multiple features with mast cells. This is the basophil, ordinarily by far the least abundant of the circulating leukocytes but one that shares a number of biochemical and functional features with the mast cell (52–55). Thus, basophils bear large numbers of FcεRI and can produce preformed mediators (histamine and nonheparin proteoglycans), cytokines (IL-4, IL-13, TNF, etc.), and products of arachidonic acid (e.g., LTC_4) upon activation with antigen or by other mechanisms (52, 53, 55–57). However, in contrast to mast cells, basophils are circulating granulocytes that mature in the bone marrow, circulate in the blood as mature cells, and can be recruited into the tissues during inflammatory or immune responses (52, 54, 56). Like other granulocytes, basophils appear to lack the ability to proliferate and are thought to undergo apoptosis after participating in tissue responses (58). By contrast, tissue or peritoneal mast cells can be long-lived [and some can proliferate (59–62)] and can undergo multiple rounds of activation by IgE and antigen or other stimuli (63). The exact relationship of mast cells and basophils during hematopoiesis has been studied by several groups, but the data are not entirely consistent (64–71). However, there is no convincing evidence that mature basophils can give rise to mast cells (or vice versa), and it seems best to regard them as distinct hematopoietic lineages with many overlapping functional features.

MAST CELLS AS ANCIENT COMPONENTS OF INFLAMMATION

Urochordate test cells have been proposed to have a critical role in host defense, and their anatomical distribution supports this notion (23, 24). Test cells can be induced to degranulate in response to compound 48/80 (23, 27), which also can elicit degranulation of mouse and human mast cells (72, 73). However, to our knowledge, a specific role for test cells in host defense has not yet been demonstrated.

Numerous studies have investigated the participation of mast cells in inflammation and other pathology in a variety of vertebrates (74). Such work has been useful, for example, in documenting changes in the numbers of mast cells at various anatomical sites that also exhibit specific pathology. However, until recently, the inability to specifically delete mast cells in such settings has left the importance, and exact nature, of their roles unclear.

In mammals, it has been possible to identify roles of mast cells during a variety of inflammatory responses based on the utilization of mast cell–deficient mice. A perfect mast cell–deficient mouse, that is, a mouse that selectively lacks all mast cell populations but that is otherwise fully identical to a normal mouse, has not yet been described. However, several mutant mice have now been reported to be largely devoid of tissue mast cells, with limited additional (presumably mast cell–unrelated) abnormalities (see below). Work with such mast cell–deficient mice has strongly supported the roles of mast cells in promoting, and in some cases limiting, the extent of inflammation.

MAST CELL–DEFICIENT MICE

When we last reviewed mast cell function herein (in 2005) (7), most work conducted with mast cell–deficient mice was done with WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ or C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice and the corresponding wild-type mice (**Table 1**). However, such *Kit* mutant mice have long been known to have a variety of non–mast cell abnormalities attributable to their *Kit* mutations (in WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice) and, in C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice (which have a large deletion affecting *Kit* and other genes), also attributable to deficiencies in genes besides *Kit* (**Table 1**). Consequently, we recommended the adoptive transfer of in vitro–derived mast cells into such WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ or C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice (75, 76). This approach permitted comparison of results in three groups of mice: *Kit* mutant (mast cell–deficient) mice, the corresponding wild-type mice, and *Kit* mutant mice that had adoptively transferred populations of wild-type (or genetically altered) mast cells. If any difference in expression of a biological response in *Kit* mutant and wild-type mice was corrected by the adoptive transfer of mast cells into the *Kit* mutant mouse (producing a mast cell knock-in mouse), this was taken as evidence of an important role for mast cells in the response under investigation.

However, this approach was limited by several considerations. First, the adoptive transfer of in vitro–derived mast cells had to be monitored for the anatomical location of the transferred mast cells. In some cases, such as the direct intradermal injection of in vitro–derived mast cells, the transferred mast cells had what appeared to be the same relationship to other cutaneous structures and cells as did the mast cells in the corresponding wild-type mouse (76). But the intravenous transfer of in vitro–derived mast cells did not fully reconstitute a normal distribution of mast cells. For example, it produced very low transfer of mast cells into the skin but higher than normal concentrations of mast cells into other sites, such as the muscularis propria of the stomach (76–78). We therefore advised that the anatomical distribution and numbers of such adoptively transferred mast cells always be documented when using this approach (79).

Second, we pointed out that the adoptively transferred mast cells would have some aspects of phenotype different than those in the corresponding population of native mast cells in wild-type mice (7, 79, 80). An obvious difference was the content of cytoplasmic-granule-associated mediators, as these progressively increase with the age of the mast cell (81). The longer one waits, the higher the concentration of such mediators in the transferred cells (75). We routinely wait 4–8 weeks after transfer of the in vitro–derived mast cells, but such transferred mast cells still would be expected to contain smaller amounts of the granule-associated mediators than the

Table 1 Characteristics of mast cell–deficient mice

Mice[a]	Production	MC numbers	Known or potential limitations for MC studies	Ref.
Kit-dependent, constitutive MC deficiency				
WBB6F$_1$-*Kit*$^{W/W\text{-}v}$	Cross between WB/Re-*Kit*^{W} and C57BL/6-*Kit*$^{W\text{-}v}$	**Steady state:** 1% of normal MC numbers in skin and no MCs in other tissues **Inflammatory conditions:** MCs developed in idiopathic dermatitis and following PMA application or IL-3 perfusion	■ Lack melanocytes, interstitial cells of Cajal, germ cells ■ Reduced γδ T cells ■ Moderate neutropenia ■ Anemia ■ 75–90% reductions in basophils in blood and spleen	89, 179–181
C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$	These can be produced by mating C57BL/6-*Kit*$^{W\text{-}sh/+}$ and selecting the white progeny or by breeding the C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice	**Steady state:** born with MCs, but adult mice lack MCs **Inflammatory conditions:** slight increases in MC numbers in jejunal mucosa and peritoneal cavity after *Strongyloides venezuelensis* infection	■ Enhanced myelopoiesis with increased myeloid-derived suppressor cells ■ Cardiac hypertrophy ■ Lack interstitial cells of Cajal and melanocytes, with normal germ cells, γδ T cells ■ Neutrophilia, megakaryocytosis, thrombocytosis ■ Increased basophils in blood	76, 88, 182–184
Kit-dependent, inducible MC deficiency				
***Kit*$^{CreERT2/+}$R26-GFPStop^{F}DTA**	Cross between *R26-GFPStop^{F}DTA* mice, in which expression of DTA is inducible upon the removal of a loxP-flanked STOP cassette, and transgenic *Kit*$^{CreERT2/+}$ mice expressing a tamoxifen-inducible Cre recombinase (CreER) under the control of one allele of the endogenous c-*kit* locus	**Steady state:** 14 days following treatment with a tamoxifen-containing diet (400 mg/kg tamoxifen citrate), deficient in peritoneal, ear skin, back skin, and glandular stomach MCs **Inflammatory conditions:** following tamoxifen regimen and upon IL-3 injection, no increase in Mcpt1 and Mcpt2 expression in the small intestine, as well as no detectable mMCP-1^{+} cells in the large intestine **Repopulation:** ear skin and peritoneal MCs undetectable 4 weeks after tamoxifen treatment	■ Splenic basophil number slightly reduced 14 days following tamoxifen regimen; restored when analyzed 4 weeks after the cessation of the treatment	96

(*Continued*)

Table 1 (*Continued*)

Mice[a]	Production	MC numbers	Known or potential limitations for MC studies	Ref.
Kit-independent, constitutive MC deficiency				
Mcpt5-Cre; R-DTA Tg(Cma1-cre) ARoer; B6.129P2-*Gt(ROSA)26Sor*$^{tm1(DTA)Lky}$/J	Cross between *R-DTA* floxed mice and transgenic mice expressing *Cre* under the *Mcpt5* promoter	**Steady state:** marked reductions in peritoneal (98%) and skin (89–96.5%) MCs; MMCs unlikely to be depleted	■ Presence of MMCs ■ Are there cell-intrinsic defects of NK cells or other cell types? ■ Basophil numbers and function not assessed	92, 98
Cre-Master *Cpa3*$^{Cre/+}$ Cpa3$^{tm3(icre)Hrr}$ (now produced on both C57BL/6 and BALB/c strains)	Gene targeting *Cre* expression under the control of the *Cpa3* promoter while deleting 28 nucleotides of the first exon of *Cpa3* locus	**Steady state:** absence of connective-tissue MCs and MMCs (in skin, peritoneum, intestine) **Inflammatory conditions:** remain deficient in skin MCs after PMA-induced dermatitis and in intestinal MMCs following helminth infection	■ 60% reduction in numbers of spleen basophils (basophil status in blood and bone marrow not reported) ■ Cpa3 expressed in other cell types ■ Are there functional abnormalities of basophils or cell-intrinsic defects in other cell types?	89
Hello *Kitty* ***Cpa3-Cre; Mcl-1*$^{fl/fl}$** Tg(Cpa3-cre)3Glli; B6;129-Mcl1^{tm3sjk}J	Cross between *Mcl-1* floxed mice and transgenic mice expressing *Cre* under a *Cpa3* promoter fragment	**Steady state:** marked reductions (92–100%) in connective-tissue MCs and MMCs in the skin, trachea, lung, peritoneum, digestive tract, etc., but no reduction in small numbers of splenic MCs **Inflammatory conditions:** slight increases in MC numbers in jejunal mucosa and peritoneal cavity after *S. venezuelensis* infection	■ Reductions in basophil numbers in spleen (58%), blood (74%), and bone marrow (75%) ■ Markedly reduced IgE- and basophil-dependent chronic allergic inflammation of skin ■ Cpa3 expressed in other cell types ■ Are there cell-intrinsic defects in other cell types?	88, 91
***Mcpt5-Cre; Dicer*$^{fl/fl}$** Tg(Cma1-cre) ARoer; Dicer1^{tm1Tara}	Cross between *Dicer1* floxed mice and transgenic mice expressing *Cre* under the *Mcpt5* promoter	**Steady state:** marked reductions in peritoneal (85.8%) and skin, mesentery, muscularis of the glandular stomach, tongue, and heart (89–96.5%) MCs	■ Presence of MMCs ■ Basophil numbers in blood and spleen not affected, but function not assessed ■ Are there cell-intrinsic defects of NK cells or other cell types?	97

(*Continued*)

Table 1 (*Continued*)

Mice[a]	Production	MC numbers	Known or potential limitations for MC studies	Ref.
Kit-independent, inducible MC deficiency				
Mcpt5-Cre; iDTR Tg(Cma1-cre) ARoer; C57BL/6-*Gt(ROSA)* $26Sor^{tm1(HBEGF)Awai}$/J	Cross between inducible *DTR* floxed mice and transgenic mice expressing *Cre* under the *Mcpt5* promoter	**Steady state:** 1 week after 4 weekly i.p. and 2 s.c. DT treatments, deficient in peritoneal and skin MCs (97.5%); stomach and intestinal MMCs present. **Repopulation:** 10% of pretreatment skin and peritoneal MC numbers 3 weeks after the last DT treatment	■ Bone marrow basophils not affected 1 week after 4 weekly i.p. treatments with DT ■ Basophil function not assessed ■ Presence of MMCs ■ Are there off-target or other side effects of repeated treatment with DT?	92
Mas-TRECK	Transgenic mice expressing human DTR under an intronic enhancer of the *Il4* gene	**Steady state:** 3 days after 5 daily i.p. DT treatments: deficient in peritoneal, skin, stomach, and mesenteric window MCs **Repopulation:** skin MCs undetectable 12 days after the last DT treatment	■ Transient >95% reduction in blood basophil numbers 5 days after start of DT treatment with recovery 12 days after the last DT treatment ■ Markedly reduced features of IgE- and basophil-dependent chronic allergic inflammation of skin (induced 2 days after 5 daily i.p. treatments with DT) ■ Are there off-target or other side effects of repeated treatment with DT?	93, 94
Cpa3-Cre; iDTR Tg(Cpa3-cre)3Glli; C57BL/6-*Gt(ROSA)* $26Sor^{tm1(HBEGF)Awai}$/J	Cross between inducible *DTR* floxed mice and transgenic mice expressing *Cre* under the control of a *Cpa3* promoter fragment	**Steady state:** 1 week after 2 weekly intra-articular injections of low-dose DT (50 ng): deficient in synovial MCs in the ankle joints. No effect on blood basophils 48 h after i.p. injection of 500 ng DT; deficient in peritoneal MCs, but no effect on ear skin MCs **Repopulation:** Not assessed	■ Reduced blood basophils after i.p. treatments with DT, but basophils are not affected after intra-articular DT injection	185

[a]The common name of the mutant mouse is given in bold font; in some cases, the full name of the mutant is given beneath in plain font.
Abbreviations: DT, diphtheria toxin; i.p., intraperitoneal; MC, mast cell; MMC, mucosal MC; NK, natural killer; PMA, phorbol myristate acetate; s.c., subcutaneous.

corresponding native mast cell population in wild-type mice (7, 79, 80). Finally, at least some adoptively transferred mast cells (such as peritoneal mast cells) may undergo a change in aspects of their phenotype (e.g., pattern of mast cell protease expression) that is not fully appropriate for the new anatomic site (82).

Accordingly, it is best to interpret cautiously work in which one attempts to transfer mast cells into *Kit* mutant mice. Having said that, it is interesting that, depending on the model being analyzed, mast cell knock-in mice may exhibit biological responses that are statistically indistinguishable from those in the corresponding wild-type mice (83, 84). This may reflect the fact that, for the response being investigated, the mast cells present in mast cell knock-in mice are sufficient to produce the types, amounts, and distribution of biologically active mediators needed for the production of the measured tissue response (83, 84). However, in other responses, mast cell activation that is sufficient to fully repair some aspects of the reaction (e.g., tissue swelling) may not be adequate to restore completely other features of the response (e.g., deposition of cross-linked fibrinogen) (85).

Now, several types of mutant mice with more selective deficiencies in mast cells (not involving mutations affecting *Kit*) have been reported (79, 80). These have been particularly useful for studies of the roles of mast cells in anatomical sites where mast cell deficiency is difficult to repair by intravenous injection of mast cells, e.g., the gastrointestinal tract (86–88) and central nervous system (89, 90). While the list of newer models of mast cell deficiency is relatively long (79, 80, 89, 91–97), and each model is useful, a few cautionary points about these models should be kept in mind.

First, except for the mice rendered deficient in mast cells that express the protease Mcpt5 (92), each of the mutant mast cell–deficient mice that does not have abnormalities in c-kit is rendered relatively deficient in mast cells by a genetic change that could affect other lineages. Indeed, the mice in which Cpa3 is used to generate mast cell deficiency also express numerical (89, 91) and, if appropriately tested, functional abnormalities in basophils (91). Thus, Hello *Kit*ty mice (*Cpa3-Cre*, *Mcl-1*$^{fl/fl}$ mice) have an ~75% deficiency of circulating basophils (and an ~60% reduction in splenic basophils) in addition to a profound reduction in tissue mast cells (91). Despite what might be considered to be a relatively modest deficiency in the number of circulating basophils, a cutaneous chronic allergic inflammation reaction that is basophil- but not mast cell–dependent is markedly impaired in Hello *Kit*ty mice (91). This illustrates that at least one function of basophils can be markedly impaired in such mice, despite the persistence of some basophils in the circulation. The same caution probably also should be considered for the mast cell–deficient *Cpa3*$^{Cre/+}$ mice (89), as these mice, like the Hello *Kit*ty mice, have an ~60% reduction in the numbers of spleen basophils. However, to our knowledge, basophil functions have not yet been specifically examined in the *Cpa3*$^{Cre/+}$ mice. So while these mutant mice have a more selective deficiency in mast cells than do the mice with abnormalities affecting c-kit, they cannot be considered purely mast cell deficient. Moreover, in the case of Mcpt5-deficient mice, the animals still retain mast cells that do not express sufficient amounts of Mcpt5 (92, 98).

Second, most of the work has been done on the C57BL/6 background, and work in *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice developed on the C57BL/6 versus BALB/c background shows that for particular biological responses (e.g., allergic airway responses), the mast cell deficiency on the C57BL/6 background is associated with a substantial defect in the response, whereas the same response is apparently unaffected by an equivalent mast cell deficiency on a BALB/c background (99, 99a). By contrast, both the C57BL/6- and the BALB/c-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice exhibited markedly impaired acute IgE-dependent responses in the skin (99, 99a). This work suggests that an individual functional effect of a deficiency in mast cells, in a particular biological response, may only be revealed in a host with

a suitable genetic background. This point has also been made in studies of Cpa3-deficient mice on the C57BL/6 vs. BALB/c background (86, 98).

Third, in some cases, the genetic abnormality induced can affect both basophils and mast cells, at least at certain times after induction of the deficiency (93, 94). In such cases, the timing of the experiment will determine whether one is dealing with a pure mast cell deficiency or a mixed deficiency of basophils and mast cells.

Finally, it should be noted that several mice have been described in which mast cells can express various fluorescent tags, whether because of the genetically determined expression of a particular fluorescent protein (47, 92, 100–102) or because of the marking in vivo of existing mast cell populations with a fluorescent dye (47, 101). The latter approach is particularly attractive because the method can be employed in mice of any strain. Moreover, if one examines the mouse 15 min after the intradermal injection of fluorochrome-labeled avidin [e.g., sulforhodamine 101-labeled avidin (Av.SRho), which strongly binds to the highly anionic heparin-containing proteoglycans of the mast cell granules], one can visualize solely those granule structures that have been exteriorized (101, 103) (**Figure 1*a***). By contrast, by examining the mouse 1 week after injection of Av.SRho, one can label the granules retained within mast cells and then follow these Av.SRho-labeled granules for a prolonged period of time, until they are exteriorized in response to mast cell–activation stimuli (101, 103) (**Figure 1*b*,*c***).

INNATE MAST CELL ACTIVATION

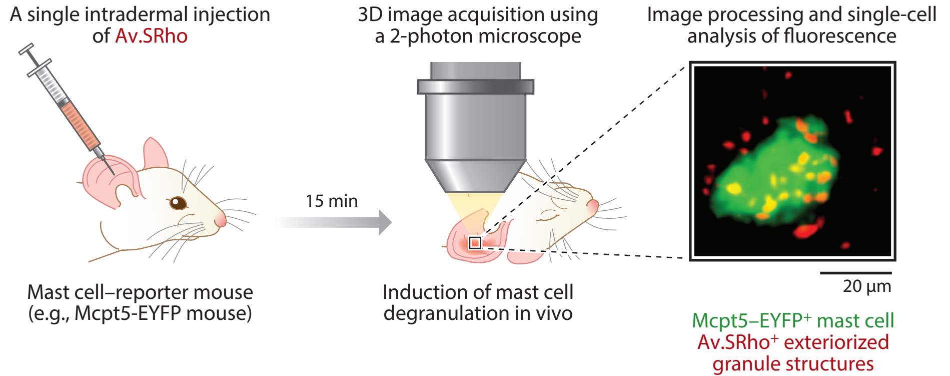
Urochordates lack conventionally defined adaptive immunity. Therefore, the roles of mast cell–like test cells in urochordates may include participation in innate, but not adaptive, immune responses (23, 24, 27). Yet there is evidence that some of such innate roles have been retained by mammalian mast cells. Thus, both urochordate test cells (23, 27) and certain mouse and human mast cells (72, 73) can undergo activation with compound 48/80. And a variety of signals that can be generated during innate responses can induce (or, in some cases, suppress) activation of mammalian mast cells.

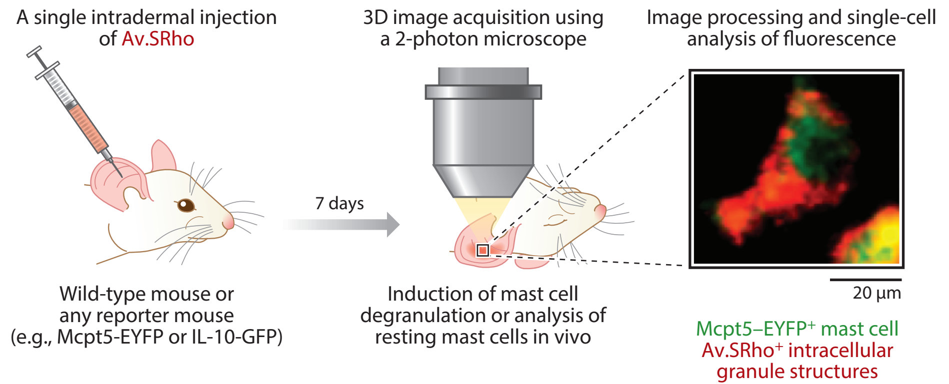
Activating signals include components of complement activation (that can occur independently of antibodies) (37, 38, 41); agonists of Toll-like receptors (these may have different distributions among anatomically distinct mast cell populations) (39–41); adenosine (42); corticotropin-releasing factor receptors (of subtype 1) (104); a variety of endogenous peptides, including VIP (46, 48) and substance P (46, 47); and many, many other stimuli (41). Fewer signals that suppress mast cell activation have been reported (41, 105), but these include corticotropin-releasing factor receptors (of subtype 2) (106) and inhibitory CD300 receptors (105).

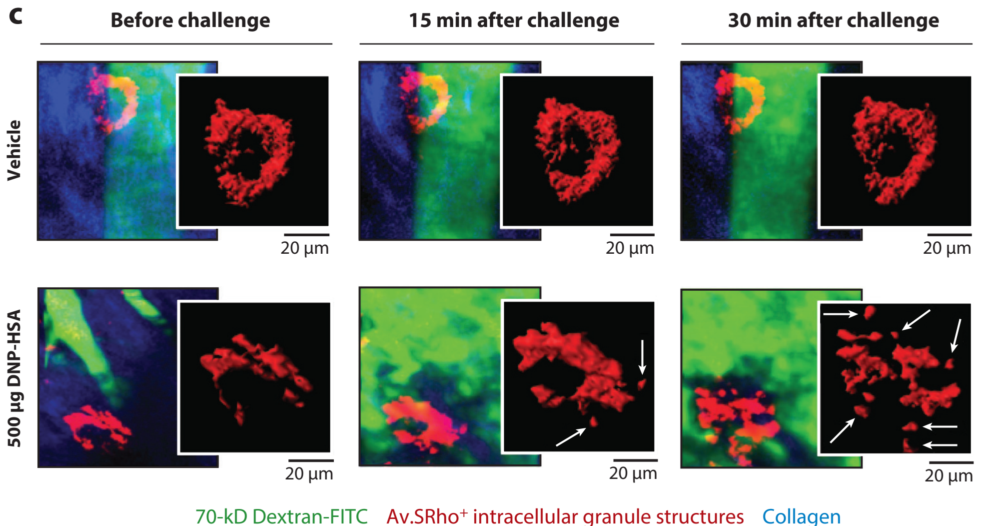
Mast Cell Activation via Members of the MRGPR Family

Recent work has emphasized the role of the Mas-related G protein–coupled receptor (MRGPR) family, specifically, Mrgprb2, in mast cell activation (**Figure 2**). Mrgprb2 is the mouse receptor for several cationic molecules and the ortholog of the human receptor MRGPRX2. To date, Mrgprb2 and MRGPRX2 have been reported to be expressed only on certain populations of mast cells (107–109). Natural endogenous ligands of Mrgprb2/MRGPRX2 have been reported, such as the neuropeptide substance P, β-defensin, cathelicidin, and PAMP9–20 (107–109).

The Mrgprb2/MRGPRX2 receptor has been primarily analyzed for its participation in IgE-independent, drug-induced allergic reactions (i.e., pseudoallergic reactions) (109–111). McNeil et al. (110) reported that most classes of US Food and Drug Administration (FDA)-approved peptidergic drugs associated with allergic-type injection-site reactions have the capacity to







(Caption appears on following page)

Figure 1 (*Figure appears on preceding page*)

Fluorochrome-labeled avidin can be used to identify either exteriorized or intracellular mast cell granule structures in living mice. (*a*) Five micrograms of sulforhodamine 101–coupled avidin (Av.SRho) are injected intradermally into the ear pinna of a mast cell–reporter mouse (e.g., Mcpt5-EYFP). The mouse is anesthetized 15 min later and placed under a 2-photon microscope, mast cell degranulation is induced by intradermal injection of stimulus, 3D high-resolution images of single cells are taken, and Av.SRho fluorescence signal is assessed. The photograph shows a single dermal EYFP^{+} mast cell, activated upon intradermal injection of substance P, exhibiting Av.SRho^{+} exteriorized small granule structures. (*b*) Five micrograms of Av.SRho are injected intradermally into the ear pinna of a mouse. The mouse is anesthetized 7 days later and placed under a 2-photon microscope; 3D high-resolution single-cell images are taken, and Av.SRho fluorescence signal is assessed. The photograph shows a single EYFP+ mast cell exhibiting Av.SRho^{+} intracellular granule structures. (*c*) Five micrograms of Av.SRho were injected intradermally into the ear pinnae of C57BL/6 mice. One week later, mice were sensitized by intradermal injection of 20 ng of mouse anti-2,4-dinitrophenyl (anti-DNP) IgE into the ear pinnae. Sixteen hours later, 250 µg of 70-kD dextran-FITC (dextran-fluorescein isothiocyanate) were injected retro-orbitally and the anesthetized mice were positioned under the 2-photon microscope. Anti-DNP IgE-sensitized mice were injected intraperitoneally with 500 µg of DNP-conjugated human serum albumin (DNP-HSA) or with vehicle (control). Image sequences were acquired in 3D at a rate of 1 picture per min over 30 min using a 2-photon microscope. The photographs show representative 3D time-lapse sequences of merged Av.SRho (*red*), dextran-FITC (*green*), and collagen structure (*blue*) fluorescence. Insets identify the magnified area in which Av.SRho fluorescence was modeled. Arrows indicate exteriorized Av.SRho^{+} granule structures. Images in panels *a* and *b* are adapted from Reference 103 with permission, and images in panel *c* are adapted from Reference 101 with permission.

activate both Mrgprb2 in vivo and MRGPRX2 in vitro. They engineered *Mrgprb2^{mut}* mice (in which the numbers of mast cells are normal but Mrgprb2 is genetically inactivated by mutation) and demonstrated that such mice are protected from cationic injection-site reactions induced by cationic drugs. They also identified a common chemical motif in these FDA-approved molecules to help predict any potential side effects of other compounds possibly linked to mast cell activation in patients.

A better understanding of how mast cells regulate their secretion dynamics under different conditions of stimulation will be important for understanding many mast cell–dependent inflammatory reactions, notably including pseudoallergic reactions. In 2016, Gaudenzio et al. (47) reported

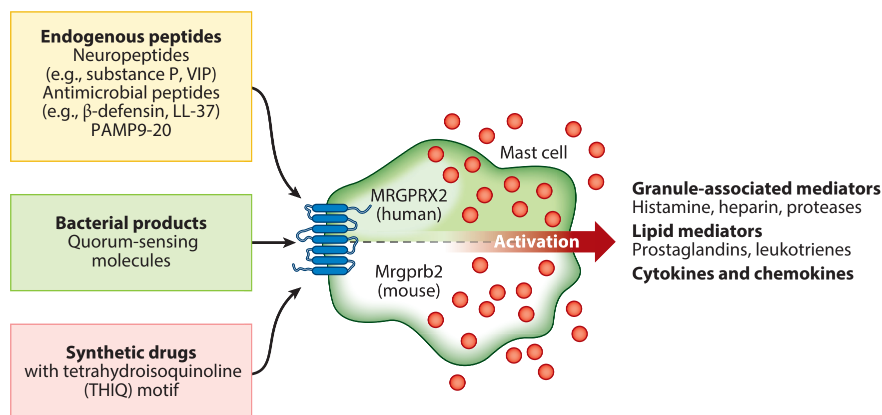


Figure 2

Mast cell activation via MRGPRX2 (in humans) or Mrgprb2 (in mice). The receptors can be activated by members of at least three classes of stimuli (endogenous peptides, bacterial products, and synthetic drugs), and the activated mast cells can release diverse mediators.

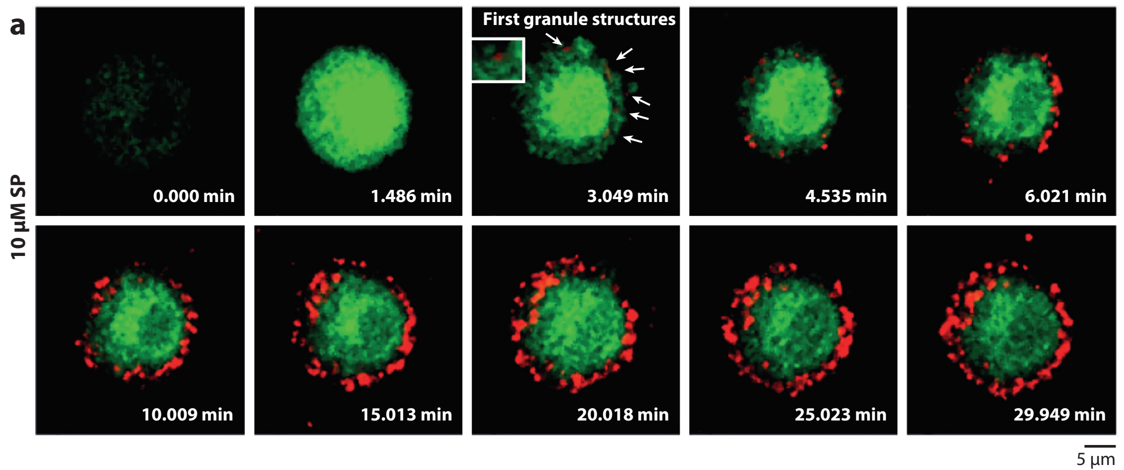
that mast cells can decode different activation signals into spatially and temporally distinct patterns of granule secretion. Certain innate signals, including the cationic neuropeptide substance P (via MRGPRX2), the complement anaphylatoxins C3a (via C3R) and C5a (via C5R), and endothelin 1 (via ET_A), rapidly induced human mast cells to secrete small and, primarily, roughly spherical individual granule structures (**Figure 3*a*,*c***). Conversely, activating mast cells with adaptive signals, including anti-IgE (via FcεRI) or IgG-antigen (IgG/Ag) immune complexes (via FcγR), increased the time between initial signaling and secretion, a delay associated with a period of sustained elevation of intracellular calcium and the ultimate exteriorization of larger and heterogeneously shaped granule aggregates (47) (**Figure 3*b*,*c***). Notably, innate signaling with substance P (at 10 μM) and adaptive signaling with anti-IgE (at 2 μg/mL) produced roughly similar amounts of degranulation (assessed by release of β-hexosaminidase at 60 min after stimulation), but anti-IgE activation resulted in substantially more production of PGE_2 and PGD_2 (at 60 min) and more release of several cytokines at 90 min or 12 h after stimulation.

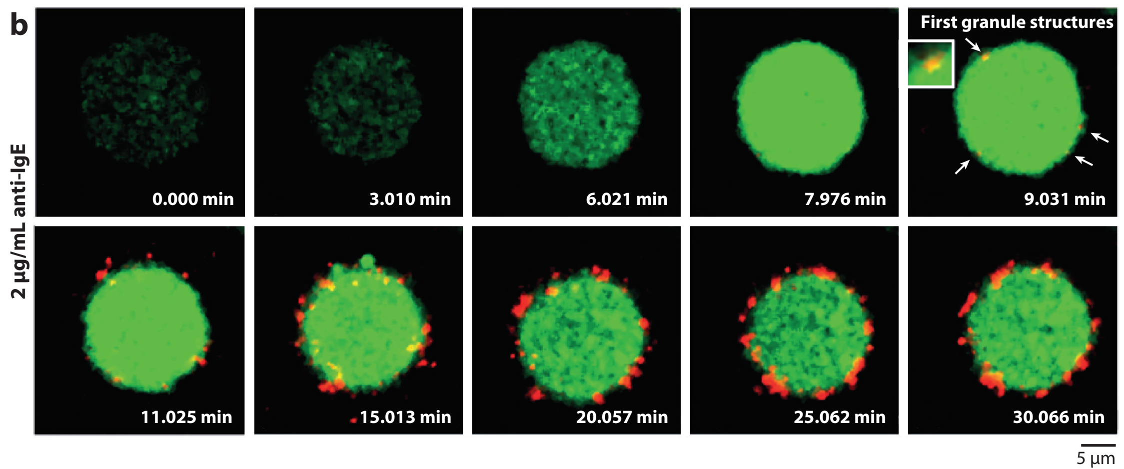
Substance P– versus IgE-dependent activation in vivo also induced different patterns of mouse mast cell degranulation that were associated with distinct local and systemic inflammatory reactions (47). The larger granule aggregates induced upon IgE-dependent activation appeared to be stable enough to traffic to the draining lymph node and activate its hypertrophy, while the relatively small granules released upon substance P challenge were associated with more local and transient inflammation (47). These findings highlighted how specific cellular activation patterns can affect the phenotype of mast cell–dependent responses and also provided important information about how mast cells can differentially process various stimuli into distinct degranulation programs. One can speculate that these findings provide insights into a long-standing clinical observation: IgE-independent pseudoallergic responses (i.e., reactions now thought to be MRGPRX2 mediated) are often rapid but transient, while IgE-dependent reactions are more prolonged and involve additional inflammatory components (112, 113).

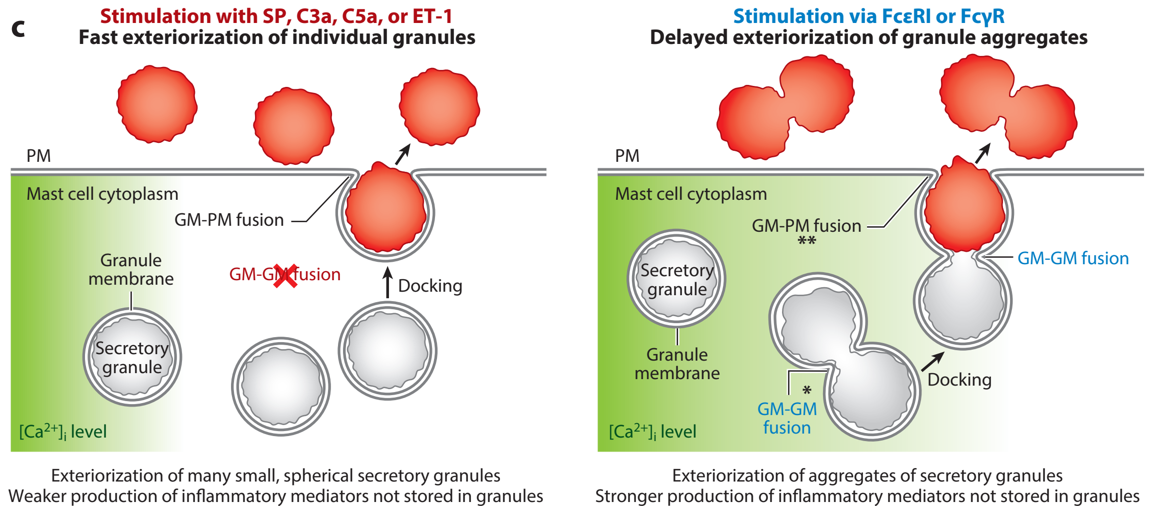
Antibacterial Functions Mediated by Mrgprb2/MRGPRX2

Growing evidence shows that in addition to mediating certain drug-induced responses, mast cells often can play important roles in immune surveillance, and modulation of early inflammation, in response to infection by different pathogens (40). For example, Arifuzzaman et al. (114) have reported that topical treatment with the mast cell activator mastoparan (i.e., a peptide toxin from wasp venom that can bind to MRGPRX2) enhanced the clearance of *Staphylococcus aureus* and accelerated the healing of lesions in infected mice. This net beneficial effect of mastoparan on resistance to bacterial infection was shown to be dependent on activation of connective-tissue mast cells in vivo.

Of particular relevance to mast cell antibacterial function, Pundir et al. (115) have recently identified Mrgprb2 and MRGPRX2 as mammalian receptors for gram-positive bacterial quorum-sensing molecules (QSMs). QSMs are usually secreted by bacteria as a signal of population density. Pundir et al. showed that a subclass of QSMs named competence-stimulating peptides (CSPs) (with a particular focus on CSP1) triggered Mrgprb2- and MRGPRX2-dependent mast cell degranulation, which could, in turn, directly kill bacteria and prevent biofilm formation. The observed antibacterial functions were significantly reduced in Mrgprb2- or MRGPRX2-deficient mast cells or when CSP-deficient bacterial strains were used. Also, *Mrgprb2^{mut}* mice exhibited a severe deficiency in bacterial clearance, while in vivo pharmacological activation of Mrgprb2 favored bacterial clearance. These results showed how mast cells, via specific expression of Mrgprb2/MRGPRX2, can represent a first line of host defense (before the initiation of specific adaptive immunity) by sensing bacteria-associated QSMs and secreting antibacterial mediators.







(Caption appears on following page)

Figure 3 (*Figure appears on preceding page*)

Human mast cell activation by substance P (SP) or anti-IgE induces distinct Ca^{2+} signaling and degranulation dynamics. IgE-sensitized or nonsensitized human PBCMCs were loaded with Fluo-4 and stimulated with anti-IgE antibodies or SP in the presence of Av.SRho. Fluo-4 (*green*, $[Ca^{2+}]$) and Av.SRho (*red*, identifying exteriorized granule structures) and fluorescence were measured, at the single-cell level, using time-lapse confocal microscopy in a controlled atmosphere (37°C and 5% CO_2). (*a*) Representative time-lapse of a single PBCMC stimulated with substance P. (*b*) Representative time-lapse of a single IgE-sensitized PBCMC stimulated with anti-IgE. (*a*,*b*) White boxed insets show a budding granule structure at higher magnification. Arrows indicate first budding granule structures. Time scale reflects the kinetics of the responses induced by the two stimuli. (*c*) Models of distinct patterns of mast cell degranulation in response to substance P, C3a, C5a, or ET-1 (*left*) versus anti-IgE or IgG immune complexes (*right*). Activation with SP, C3a, C5a, or ET-1 (*left*) induces rapid docking of discrete intracellular cytoplasmic granules with the plasma membrane, a process associated with the relatively transient elevation of levels of intracellular $[Ca^{2+}]$ (indicated by a *narrow green gradient*) and resulting in the fast secretion of small spherical Av.SRho^{+} secretory granule structures that are likely to represent primarily single granules. Activation via FcεRI or FcγR (*right*) results in a longer time partition between signaling and secretion, associated with a period of sustained elevation of $[Ca^{2+}]$ levels (indicated by a *wide green gradient*). During this period, and before granule matrix material can be detected on the cell surface by binding of Av.SRho, some granules undergo deacidification, perhaps reflecting transient fusion of the granule membrane with the plasma membrane (not shown), favoring what may appear to represent, in static images, intracellular granule-granule fusion (*asterisk*, *right*). The fusion of granules with each other and the plasma membrane that occurs during the process of compound exocytosis (*double asterisks*, *right*) results in the formation of heterogeneously shaped granule structures, likely representing aggregates of the matrices of multiple individual granules, that undergo exteriorization (as reflected by the binding of Av.SRho) over a more prolonged period than is seen with substance P activation. Abbreviations: GM, granule membrane; PBCMC, peripheral blood–derived cultured mast cell; PM, plasma membrane; SP, substance P. Adapted from figures 2 and 9 of Reference 47 with permission.

Effect of Mrgprb2/MRGPRX2 on Itch and Pain Sensations

Several groups have reported biopsy evidence of nerve fiber–mast cell proximity or contact in animals and humans (116–121) or have shown that mouse and human mast cells can be directly activated by neuropeptides in vitro or in vivo (45–47, 121, 122). Studies have also suggested the existence of important bidirectional activation processes between mast cells and submucosal neurons in mouse small intestines (123) and cultured human gut biopsies (124). However, fully convincing in vivo evidence of functional nerve cell–mast cell cross talk and assessment of the role of such nerve cell–mast cell interactions in the regulation of inflammatory reactions and associated sensations of itch or pain remain to be clearly demonstrated.

Recently, a few reports have shown evidence of neuron–mast cell communication in vivo and the functional consequences of such communication on physiological and pathological processes. Members of the MRGPR family are widely expressed by peripheral sensory neurons and have been classically involved in mediating itch sensations (108). In their study, Green et al. (125) have shown that expression of Mrgprb2 by mast cells can modulate neurogenic inflammation and pain. Using a postoperative model of inflammatory pain and *Mrgprb2*^{mut} mice, they showed that both substance P and Mrgprb2 were involved in inflammatory mechanical and thermal hyperalgesia, and in the recruitment of innate immune cells at the site of injury. These findings identified Mrgprb2 as an important modulator of pain and imply that it could be potentially targeted for the treatment and/or prevention of inflammatory pain.

Mast cells also are well known to be involved in FcεRI-IgE-mediated histaminergic itch. Meixiong et al. (126) recently reported that, compared to classical FcεRI activation, mast cell activation via Mrgprb2 induced itch that was distinct from classical histaminergic itch. They found that Mrgprb2-mediated mast cell activation resulted in differential release of granule-associated mediators (including some with known pruritogen function). Thus, while FcεRI-mediated activation was associated with greater release of histamine and serotonin, Mrgprb2-mediated activation triggered the release of more tryptase beta 2. Using *Mrgprb2*^{mut} mice, they also showed that an Mrgprb2 deficiency significantly decreased itch in different models of allergic contact dermatitis, a pruritic skin inflammatory disorder in which treatment with antihistamines is usually ineffective.

Interestingly, Gaudenzio et al. (47) reported that, compared to classical IgE/Ag-mediated FcεRI activation, Mrgprb2 agonists triggered more rapid degranulation of smaller granules associated with a fast and transient form of inflammation. Meixiong et al. (126) also reported that calcium imaging of mast cell–activated sensory neurons was consistent with this model, as PAMP9–20 (i.e., an Mrgprb2 agonist)-activated neurons displayed earlier and reduced amplitude of excitation compared to anti-IgE-associated calcium traces in neurons. These results reveal new information about how Mrgprb2-mediated mast cell secretion can trigger nonhistaminergic itch by activating different subtypes of itch-sensory neurons.

Space does not permit a full analysis of all disorders in which some role for mast cells has been proposed. However, it should be noted that complement activation, which is thought to be involved in the manifestations of several human disorders (127), can result in significant mast cell activation via receptors for C3a and C5a (37, 38). Whether such complement-dependent mast cell activation results in net harmful as opposed to adaptive consequences in these settings largely remains to be determined.

ROLES IN ADAPTIVE IMMUNITY

IgE-Associated Immunity

Studies in mast cell–deficient mice indicate that certain manifestations of IgE-dependent adaptive immune responses seem clearly to be dependent on mast cells, the major cell type that is resident in tissues and expresses FcεRI. Examples include cutaneous reactions elicited after intradermal injection of IgE followed by specific antigen, in that essentially no detectable reaction can be elicited in mice that are profoundly deficient in mast cells (89, 91, 94, 128). Yet such reactions can be considered to be unnatural in that they test solely the ability of antigen-specific IgE to elicit a mast cell–dependent biological response.

Mast cells also appear to have major roles in certain active immune responses associated with IgE responses, e.g., those characterized by the development of airway inflammation and functional changes in response to antigen challenge (83, 94, 129–133). The same is true of the mast cells' roles in models of food allergy, in that reactions elicited in mice devoid of mast cells are greatly attenuated but generally not absent (95, 134). While it is clear in the case of such active, IgE-associated reactions that a lack of mast cells significantly weakens several aspects of the elicited response, reactions can continue to occur in many such settings in mast cell–deficient mice, albeit weakly (95, 130, 132, 134). The same is true in a mouse model of osteoarthritis, in which at least some, but not all, of the cartilage destruction appears to depend on IgE and mast cells (135). However, it should be kept in mind that, in some of these models, the importance of the mast cells' role can exhibit variation that may at least in part reflect the strain background in which the reaction is elicited (99, 99a, 136).

However, basophils represent the second hematopoietic cell that constituently expresses FcεRI, and at least one model of an IgE-associated immune response, cutaneous chronic allergic inflammation, requires the participation of basophils, rather than mast cells (137). In this setting, basophils are a numerically minor component of the elicited reaction (generally, $\leq$2% of infiltrating cells), but they are critical for the overall expression of the reaction (137).

Now that mice have been described that selectively lack basophils but retain mast cells (67, 94, 138–140), the relative importance of mast cells versus basophils in specific examples of IgE-associated (and other) immune responses should be more amenable to analysis. It seems reasonable to consider that the acute IgE-dependent responses that can be elicited rapidly in tissues in which no basophils are present will be largely mast cell dependent. By contrast, in IgE-associated responses that require days to develop and that feature the infiltration of basophils into the affected tissues, the basophil's role is more likely to be important.

Finally, it is known that allergic skin diseases, such as atopic dermatitis, are clinically characterized by severe itching and type 2 immunity–associated hypersensitivity to widely distributed domestic allergens, including those derived from house dust mites (HDMs). Serhan, Basso, et al. have recently shown that Mrgprb2$^+$ mast cells established functional clusters in the dermis with a subpopulation of peptidergic nociceptors expressing the transient receptor potential cation channel subfamily V number 1 (TRPV1) and *Tac1*, the gene encoding the precursor for the cationic neuropeptide substance P (141). They found that domestic HDM strains with cysteine protease activity were direct activators of TRPV1$^+$*Tac1*$^+$ nociceptors in the skin. Activated nociceptors then drove the development of allergic skin inflammation by inducing degranulation of contiguous mast cells via release of substance P and activation of Mrgprb2.

Moreover, using a new intravital imaging approach, Serhan, Basso, et al. (141) also found that the majority of TRPV1$^+$ neuron endings were in very close proximity (less than 25 μm) or formed actual physical contacts with skin mast cells and that specific activation of neurons led to the degranulation of contiguous mast cells. Their results suggest that functional knots between TRPV1$^+$*Tac1*$^+$ nociceptors and Mrgprb2$^+$ mast cells might represent tissue-resident sensory systems capable of detecting allergens with cysteine-like protease activity in the skin and then initiating type 2 immunity–associated allergic skin disease. Mast cells and sensory neurons are present in virtually all organs in contact with the microenvironment. However, additional work is needed to investigate the precise role played by neuroimmune sensory clusters in the development of other allergic disorders, such as asthma, and in protection against pathogens, such as certain parasites that are associated with the development of protective type 2 immune responses.

Additional Immune Responses

Mast cells have been noted to change in numbers and/or distribution during a variety of immune responses in which IgE is thought to have a less important or no role. Several of these settings have been investigated using older varieties of mast cell–deficient mice, but in some instances reports of critical roles for mast cells have not been supported by studies in more modern types of mast cell–deficient mice. For example, early work conducted with C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice suggested that mast cells were important drivers in models of diet-induced changes resulting in atherosclerosis (142) or obesity and diabetes (143). However, subsequent work in *Cpa3*$^{Cre/+}$ mice provided no evidence that mast cell deficiency influenced the development of either diabetes in NOD mice (144) or diet-induced or genetic (i.e., *Lep*$^{Ob/Ob}$) models of obesity and insulin resistance (145).

Work in older models of mast cell deficiency indicated that mast cells could participate in immune responses to certain nematodes, notably those in the genus *Strongyloides*. For example, with infections with *Strongyloides venezuelensis*, work in mast cell–deficient WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice showed that mast cells represented one important component of host resistance to primary infections (146–148). This finding supported the conclusions of earlier studies of WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice, which also suggested an important role for mast cells in resistance to a primary infection with *Strongyloides ratti* (149, 150).

Two groups now have studied resistance to infection with *Strongyloides* species in mice with a more restrictive genetically determined mast cell deficiency than WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ mice (88, 98). In both of their studies, conducted with different numbers of parasites of different *Strongyloides* species, an important role for mast cells in the primary host response to *Strongyloides* was confirmed. Based on comparison of *Cpa3*$^{Cre/+}$ mast cell–deficient mice (which essentially lack both connective-tissue and mucosal mast cells) and *Mcpt5-Cre*; *R-DTA* mice (which lack only connective-tissue mast cells), Reitz et al. (98) concluded that mucosal mast cells were especially critical for the timely termination of infection with parasitic adults of *S. ratti*. And both studies

showed that the mast cell–deficient mice examined were significantly impaired in their expulsion of parasitic adults of the *Strongyloides* species tested (and exhibited a much stronger deficiency than did basophil-deficient mice) (88, 98). However, the deficit in host response to *S. venezuelensis* still was not as great as in mice deficient in T and B cells and type 2 innate lymphoid cells (ILC2s) (88). Indeed, during responses to primary infection with *S. venezuelensis*, the hierarchy of effector cells/molecules appeared to be $CD4^+$ T cells/ILC2s, IgG and FcRγ > mast cells > IgE and FcεRI > basophils (88).

Nevertheless, it appears that a mast cell–dependent contribution to resistance to primary infection with *Strongyloides* species in mice has been confirmed (88, 98). By contrast, in secondary *S. venezuelensis* infection, the presence of $CD4^+$ T cells is of critical importance, but mast cells, antibodies, and basophils have few or no nonredundant roles (88). *Cpa3*$^{Cre/+}$ mast cell–deficient mice also exhibited intact Th2 polarization after vaccination with *S. ratti* and efficiently developed protective immunity (98).

Another important role for mast cells in host defense, i.e., promoting resistance to certain venoms, has also been supported both by work in mast cell–engrafted WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ and C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice and by work in mice selectively deficient in mast cell–associated proteases. Thus, a role for mast cells in promoting resistance to sarafotoxin (in the venom of *Atractaspis engaddensis*) that was initially identified by studies in mast cell–engrafted WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ and C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice (49) was subsequently also shown by experiments conducted in *MC-Cpa*^{Y356L,E378A} mice, which lack active mast cell carboxypeptidase (151). Similarly, impairment of the survival of mice injected with the venom of the Gila monster (*Heloderma suspectum*) that was demonstrated using mast cell-engrafted WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ and C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice was also confirmed using mice with a selective defect in mast cell protease 4 (mMCP-4) (48).

It should be noted that the death of hosts that have been envenomated typically occurs within hours. This is generally thought to be too soon for the establishment of an adaptive immune response. Therefore, the innate roles of tissue-based effector cells, such as mast cells, in these responses are thought to be especially critical. This does not exclude the possibility that mast cells also play an important role in providing enhanced resistance to a second envenomation, and this does occur in mice receiving a second challenge with honeybee venom (50) or Russell viper venom (50, 51).

Suppression of Severe Immune Responses

Mast cells are so often regarded as critical initiators of pathogenic adaptive immune responses that their potential role in limiting the expression of these, and other, immune responses can be overlooked. Work with WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ and C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice provided evidence that mast cells can limit the development of cutaneous swelling and necrosis elicited by either severe contact hypersensitivity reactions to urushiol or reactions to UVB irradiation (152). Studies with mast cell–deficient mice engrafted with normal versus IL-10-deficient mast cells showed that at least some of the mast cells' ability to have such a regulatory effect was dependent on their ability to produce IL-10 (152).

This negative regulatory effect was recently reexamined using mice whose mast cell deficiency is due to more restricted genetic abnormalities (i.e., *Cpa3-Cre;Mcl-1*$^{fl/fl}$ and *Mcpt5-Cre; DTA* mice), and employing dinitrofluorobenzene as the hapten for contact hypersensitivity (101). This work supported the earlier findings obtained with mast cell–engrafted WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ and C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice, including the role of mast cell–derived IL-10 in mediating the regulatory function of mast cells in such a setting (101).

However, while we found that the *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice exhibited an ~200% increase in ear swelling on day 5 of the reaction (compared to littermate controls), this difference was less pronounced in the *Kit*-independent, mast cell–deficient mice examined at the same time point (~120% increase in *Cpa3-Cre;Mcl-1*$^{fl/fl}$ mice and ~50% increase in *Mcpt5-Cre;DTA* mice) (101). We think that the simplest interpretation is that mast cells can have effects that can significantly limit the assessed features of this model of severe contact hypersensitivity in each of the three examined mouse strains, but that additional phenotypic abnormalities in the *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice (beside their mast cell deficiency) probably also contribute to the exacerbation of severe contact hypersensitivity responses in this strain.

We also tested mice in which the *il10* gene was floxed out specifically in connective-tissue mast cells, by generating *Mcpt5-Cre*$^{+}$*;il10*$^{fl/fl}$ mice (101). Dermal mast cells were present in the same numbers in the ear pinnae of *Mcpt5-Cre*$^{+}$*;il10*$^{fl/fl}$ mice (in which connective-tissue mast cells are deficient for IL-10) and littermate control *Mcpt5-Cre*$^{-}$*;il10*$^{fl/fl}$ mice. However, the *Mcpt5-Cre*$^{+}$*;il10*$^{fl/fl}$ mice exhibited significantly enhanced ear swelling and epidermal hyperplasia compared to the littermate controls. Notably, enhancement of both the tissue swelling and the epidermal thickness associated with reactions in *Mcpt5-Cre*$^{+}$*;il10*$^{fl/fl}$ mice was less pronounced than that observed in *Kit*-independent mast cell–deficient mice, suggesting that mast cells might help to limit these features of this acute model of severe contact hypersensitivity by both IL-10-dependent and IL-10-independent mechanisms.

However, beyond reconfirming a negative regulatory role of mast cells (and mast cell IL-10) in examples of severe contact hypersensitivity, this study emphasized the importance of analyzing suitably severe reactions (101). Notably, we found, in support of many prior studies (92, 153–155), that mast cells did not exert a net negative role in cutaneous inflammation when the reaction in normal mice was of low or moderate intensity (101). It remains to be determined what signals are responsible for switching mast cell function from net proinflammatory to anti-inflammatory in such settings. A related issue that may have clinical relevance in humans is the extent to which such anti-inflammatory mast cell function(s) can be regulated, either genetically or environmentally.

PARTICIPATION IN DISEASE

Mast cells can be activated to produce such a variety of mediators, in so many different settings, that it has been tempting to suggest that they are involved in the pathogenesis of many diseases beside those involving IgE. However, except in the case of mast cell–deficient mice, it can be difficult to know whether the net effect of such mast cell activation is to promote or retard the development of disease. An example is the role of mast cells in cutaneous hypersensitivity induced by certain haptens. In some settings, notably those producing relatively weak responses, mast cells can enhance expression of local pathology (92, 101, 154–156), and in others, mast cell–deficient mice may have responses that are not statistically different than those induced in the corresponding wild-type mice (153). In other settings, particularly in severe examples of cutaneous hypersensitivity, mast cells may have net effects that suppress manifestation of the process, in part by producing IL-10 (101, 152). Mast cell production of IL-10 may also be important in inflammatory reactions elicited at other anatomical sites, such as the urinary bladder (157).

While the reason the mast cell's role switches from proinflammatory to anti-inflammatory, even in cutaneous reactions elicited by different concentrations of the same hapten, remains to be fully elucidated, one thing is certain: Histological evidence that a reaction involves alterations in mast cells (whether activation or changes in their numbers or phenotype) simply indicates that they may have a role in the response; it does not reveal what that role is.

To give one example, it had long been known that the envenomation of mammals is often associated with the local, and at times systemic, activation of mast cells, by both innate and adaptive mechanisms, and this was thought to produce pathology associated with envenomation (158, 159). However, for several venoms, while the innate response to the venom does induce pathology associated with mast cell degranulation, the net effect of this is to enhance the survival of the envenomated mouse (48, 49, 51). And for two venoms, of honeybees (*Apis mellifera*) (50) and Russell viper (50, 51) (*Daboia russelii*), mice that survived an initial envenomation developed an IgE-associated adaptive immune response that enhanced their ability to survive a subsequent venom injection. Thus, for these examples, the net effect of the innate or adaptive mast cell degranulation induced by the envenomation of the host is to favor survival.

However, in humans who develop IgE to otherwise innocuous antigens (e.g., those contained in foods, pollens, HDM excretions, etc.), IgE-driven mast cell activation clearly is both unwanted and disease inducing (160–163). However, the extent to which such IgE-associated human pathology is dependent on mast cells may vary. Unlike inbred mice, humans are genetically diverse, and extensive programs are underway to discern the basis for variation in disease manifestations, and causality, in disorders that are associated (at least in some sufferers) with mast cell activation.

Asthma is an example of a group of disorders in which IgE-dependent mast cell activation can occur, but that may encompass individuals in which this may not be the main underlying mechanism (164). Notably, a recent study suggests that, among those with relatively severe asthma, the mast cell may represent one source of mediators contributing to the disease (165, 166). However, in other asthma patients, mast cells may play a less important role (167). By contrast, food allergy so far appears to be largely both an IgE-mediated and mast cell–dependent disorder (163). Yet other mechanisms may also have a role in this setting, including IgE-dependent basophil activation (56, 95).

UNANSWERED QUESTIONS (A PARTIAL LIST)

Despite the tremendous progress in elucidating mast cell development and functions, several important questions remain unanswered. In part, this reflects the fact that definitive information about mast cell functions requires understanding how biological responses are affected when these cells are absent. While there is no perfect mast cell–deficient mouse, much progress has been made recently in generating mice that have a relatively selective, as well as relatively severe, mast cell deficiency.

This has already been beneficial, in that some reactions shown to be abnormal in certain mast cell–deficient *Kit*-mutant mice have been demonstrated to be due to not the absence of mast cells in these mice, but instead probably other consequences of their underlying mutations (87, 89, 144, 145, 168–173). Indeed, the fact that c-*Kit* mutations (and, especially, the large genetic deletion in $Kit^{W\text{-}sh/W\text{-}sh}$ mice) can influence lineages other than the mast cell was one reason we recommended that two different *Kit*-mutant mast cell–deficient mice (and also, importantly, tests of mast cell–engrafted *Kit*-mutant mice) be used to evaluate the role of mast cells in individual biological responses (7, 79, 80).

The fact that it is now possible to use mice whose mast cell deficiency is reflective of more selective genetic changes rather than mutations affecting c-*Kit* represents real progress. However, such work still is being conducted primarily with mice on the C57BL/6 background and, to a lesser extent, the BALB/c background. The good news is that C57BL/6 mice have been selected by the US National Institutes of Health as the mice in which all genetic changes can eventually be tested (174, 175). The bad news is that it is not clear whether this strain is most appropriate

for discerning which mast cell functions are relevant to humans. More importantly, humans are genetically outbred, and it is reasonable to assume that the mast cell dependence of particular biological responses will vary among different individuals.

Under the circumstances, it seems reasonable to propose that even if it were possible to render humans selectively deficient in mast cells, the effect of this maneuver on the expression of disease, or on any beneficial mast cell roles, would exhibit variation based on the person's overall genotype. This general caution should be kept in mind when assessing the roles of mast cells in those individuals (such as patients with chronic myeloid leukemia) who have virtually lost this population as a result of treatment with agents active on c-*Kit*–bearing lineages (176). First, the effects of chemotherapy would be broader than the mast cell deficiency it induces, and a change in biological responses in such patients could reflect effects of the treatment on mast cells and/or other affected cell types. Second, the challenges to survival faced by such patients generally would not include exposure to poisonous reptiles, nor could such exposure be properly controlled by testing matched subjects with normal mast cell populations. Therefore, the possible effects of a mast cell deficiency on responses to this type of challenge cannot be properly evaluated experimentally.

CONCLUSIONS

In 2005, we focused on evidence that mast cells were tunable initiators, amplifiers, and regulators of acquired immune responses (7). We stated that, while in some immune responses (e.g., those associated with an important role for antigen-specific IgE) the mast cell's role may be essential, in many other immune responses the mast cell may play net positive or negative roles. We proposed that "in certain circumstances, the mast cell's immunomodulatory functions not only can influence the magnitude or time course of the acquired immune response, but may even be essential for its occurrence." (7, p. 772) However, we noted that only a few studies provided compelling evidence (e.g., derived from studies in the then available mast cell–deficient mice) that such roles could actually be expressed in vivo.

It now appears from studies involving the newer, more genetically restrictive, models of mast cell deficiency that, in some circumstances, mast cells indeed can regulate the intensity of adaptive immune responses, either positively (92–94) or negatively (101, 157), depending in part on the intensity of the response. For example, in suppressing the intensity of contact hypersensitivity, the mast cell acquires the ability to secrete IL-10 (101, 152), but how this immunosuppressive role is regulated at the molecular level remains to be determined. However, an IL-10-dependent mechanism of mast cell suppression of an immune response has also been detected in the urinary bladder (157), suggesting that the phenomenon is not restricted to cutaneous mast cells.

As useful as studies of mast cell–deficient mice are in elucidating mast cell functions, it must be noted that, so far, such work has been conducted primarily in mice on the C57BL/6 (or WB/ReBxC57BL/6) background, with many fewer studies with mast cell–deficient BALB/c mice. And in work on asthma models, very different results were obtained with C57BL/6- or BALB/c-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mast cell–deficient mice (99, 99a). So, given the many obvious differences between mice and humans, it remains to be determined which strain of mouse is able to provide the most useful information about the roles of mast cells in humans.

Finally, in 2005, we proposed that "the type, intensity, kinetics, and pattern of mast cell secretory responses can be 'tuned,' not only genetically but also environmentally, over a wide range" (7, p. 773). Now we have two additional phenomena influencing the release of mast cell products to consider. First, it has recently been shown that perivascular dendritic cells can help to mediate IgE-dependent anaphylaxis by the very rapid transfer of allergens to mast cells via microvesicles (177). Second, it also has been shown that normal, and particularly neoplastic,

mast cells can release products contained in extracellular vesicles (178). Will each of these newly appreciated, and potentially important, aspects of mast cell activation exhibit significant genetic variation among different people and represent yet additional factors to consider in explaining the occurrence or intensity of mast cell–associated disorders? Time will tell.

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