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Potential effector and immunoregulatory functions of mast cells in mucosal immunity

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Abstract

Mast cells (MCs) are cells of hematopoietic origin that normally reside in mucosal tissues, often near epithelial cells, glands, smooth muscle cells, and nerves. Best known for their contributions to pathology during IgE-associated disorders such as food allergy, asthma, and anaphylaxis, MCs are also thought to mediate IgE-associated effector functions during certain parasite infections. However, various MC populations also can be activated to express functional programs – such as secreting pre-formed and/or newly synthesized biologically active products – in response to encounters with products derived from diverse pathogens, other host cells (including leukocytes and structural cells), damaged tissue, or the activation of the complement or coagulation systems, as well as by signals derived from the external environment (including animal toxins, plant products, and physical agents). In this review, we will discuss evidence suggesting that MCs can perform diverse effector and immunoregulatory roles that contribute to homeostasis or pathology in mucosal tissues.

Keywords

Anaphylaxis; asthma; basophils; complement system; food allergy; innate immunity; infection; parasites; pattern recognition receptors; pathogen-associated molecular patterns; Toll-like receptors; IgE; immunoglobulin E

Introduction

Mast cells (MCs) are normal residents of mucosal tissues, but their numbers and anatomical location can change markedly during immune responses, infections, and other disorders affecting such sites, in humans, mice, and other species[1–5]. MCs stimulated via the high affinity receptor for IgE (FcεRI) or by any of multiple other mechanisms can release a diverse spectrum of biologically active mediators, and such products, individually or in aggregate, can have many different effects on immune or structural cells present in mucosal

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tissues[4, 6–8]. As a result, there is no lack of ideas about the *potential* effector or immunoregulatory functions MCs might have during mucosal immune responses[3, 4, 8].

However, it can be quite challenging to *prove* that MCs can perform such proposed functions *in vivo*, and even more difficult, in light of the potential redundancy of effector and immunoregulatory mechanisms, to assess the biological importance of such MC functions in particular settings. In this review, we will outline some basic principles of MC biology and then consider evidence that implicates MCs in physiological, immunological and pathologic processes affecting mucosal sites. We will particularly focus on findings derived from studies in mice, a species in which biological responses can be analyzed in animals that lack MCs or specific MC-associated products.

Mast cell development, phenotype, tissue distribution and plasticity

MCs are tissue-resident cells that arise from hematopoietic progenitors[9]. Unlike other immune cells, MCs normally do not mature before leaving the bone marrow but circulate through the vascular system as immature progenitors that complete their development peripherally within connective or mucosal tissues, or in serosal cavities, in a process potentially regulated by multiple local factors[3–5, 10, 11].

The KIT ligand stem cell factor (SCF) plays a critical role in MC biology by regulating the development, migration, growth, survival and local activation of MCs[12–14]. Various other factors also can modulate MC growth and survival, including IL-3[15], IL-4[16–19], IL-9[20, 21], IL-10[22–24], IL-33[25–27], CXCL12[28, 29,] TGF-β[30] and NGF[31].

MCs reside in almost all vascularized tissues, and can be especially numerous in those exposed to the external environment, such as the skin and mucosal sites[3]. MCs are therefore well positioned to respond to various allergens, pathogens, and other agents which can be ingested, inhaled or encountered after disruption of the epithelial barrier[8]. Moreover, many phenotypic and functional characteristics of MCs, such as their proliferation, survival, and ability to store and/or secrete various products, can be modulated or “tuned” by many genetic and environmental factors, including changes in the cytokine milieu associated with inflammatory or immune responses[8].

Despite their potential phenotypic “plasticity”, MCs are often sub-classified based on certain of their “baseline” phenotypic characteristics and their anatomic locations (Table 1). In mice, two types of MCs have been described: “connective tissue-type” MCs (CTMCs) and mucosal MCs (MMCs)[4, 5, 8]. CTMCs are often located around venules and near nerves, and reside in serosal cavities, while MMCs occupy the mucosae of the gut and respiratory mucosa[5]. MMCs are found at relatively low numbers in most mucosal tissues (in mice, they are normally present in higher numbers in the glandular stomach mucosa than in the intestines), but expansion of MMC populations can be induced in a T cell-dependent manner[5, 32]. CTMCs and MMCs often are distinguished based on their protease content (Table 1). Mouse intestinal MMCs elicited during parasite infection express the chymase mouse MC protease-1 (MCPT1) but not the elastase MCPT5, whereas CTMCs do not express MCPT1 but express MCPT5, the chymase MCPT4, and the tryptases MCPT6 and MCPT7[5, 33, 34] (notably, C57BL/6 mice don’t express MCPT7 because of a point mutation

in the exon/intron 2 splice of the *Mcpt7* gene[35]). However, the plasticity of MC phenotype can make such classification challenging, as features of the cells, including their protease content, may vary during the course of immune responses[5, 8, 33, 36, 37].

In humans, MCs can be subcategorized into MC_T, which express high levels of the MC-specific protease tryptase but little or no chymase (these therefore are thought to resemble rodent MMCs), and MC_{TC}, which express both tryptase and chymase (and in that respect resemble rodent CTMCs)[38, 39] (Table 1). MC_C (which express chymase but little or no tryptase) also have been described, but they appear to be infrequent[40]. Clinical evidence suggests that human MC_T (like mouse MMCs) may be dependent on T-cells, at least in part, to maintain normal numbers in mucosal sites[41]. The majority of human lung MCs ordinarily are MC_T (~ 90%), and these cells are found in the bronchial/bronchiolar lamina propria and alveoli[42]. MC_{TC} typically are located beneath the epithelium in the lamina propria and submocosa, in close proximity to submucosal glands, and some MC_{TC} are found within and around the airway smooth muscle layers of major bronchi[43]. The lamina propria of the human intestinal mucosa normally contains ~1.5–3% MCs[44, 45]. In the human small intestine, MC_T represent about 98% of all MCs in the mucosa and ~13% of MCs in the submucosa are MC_T[42]. In naïve mice, relatively low numbers of MCs are found in the lung, and these cells are located around the larger airways and blood vessels. As noted above, in naïve mice few MCs are found in the mucosa of the gastrointestinal tract except for the glandular stomach, and small numbers can be found in the submucosa and muscularis propria.

However, MC numbers at mucosal sites can increase in both humans and mice in pathological settings such as inflammatory bowel disease (IBD)[46, 47], food allergy[48, 49], parasite infections[50, 51], asthma[52–56] or various types of lung fibrosis[57–60]. Such increases in MC numbers could reflect, at least in part, the division of mature MCs at mucosal sites. Although MCs are often considered terminally differentiated cells which can't divide, we and others have provided evidence that at least certain "mature" mast cells, i.e., those which can be identified morphologically based on their abundant cytoplasmic granules, retain some proliferative ability[61–64]. Increased MC numbers in such settings also may reflect the maturation of increased numbers of MC progenitors, whose numbers in tissues may increase due to their increased recruitment and/or survival in such tissues, and/or via the local proliferation of such progenitors[5, 65]. While it is not yet clear to what extent MC progenitors can proliferate in tissues, increased numbers of such progenitors have been observed at mucosal sites under various pathological conditions. For example, Arinobu *et al*. observed a four-fold expansion of MC progenitors in the intestine following sensitization and challenge of mice with the antigen ovalbumin[66]. Antigen-dependent expansion of MC progenitors also was observed in mouse lung following sensitization and challenge with aerosolized ovalbumin, and IL-9 and $CD4^+$ T cells were found to contribute to such expansion[67]. Finally, it has been reported that certain MC progenitors can proliferate *in vitro*[66], however, whether they can also proliferate within mucosal tissues remains to be proven.

Mast cell activation

MCs ordinarily express on their surface large numbers of the high affinity IgE receptor, FcεRI. During IgE-dependent immune responses, the antigen-dependent cross-linking of antigen-specific IgE bound to FcεRI induces the aggregation of FcεRI, promoting the activation of downstream signaling events that lead to the secretion of biologically active products implicated in allergic reactions[6, 68, 69]. The IgE-dependent stimulation of MCs has been extensively reviewed[6, 69–72]. It was recently reported that perivascular MCs can "sample" circulating IgE directly in the blood by extending cell processes across the vessel wall[73]. Moreover, MC FcεRI were shown to be able to distinguish between high- or low-affinity stimuli, permitting the MCs to respond differentially to such signals by releasing distinct spectra of secretory products *in vitro* and by orchestrating distinct *in vivo* outcomes[74].

Our group recently reported a beneficial role for IgE, FcεRIα, and FcεRIγ in defense against honeybee venom-induced mortality in mice[75]. Together with evidence that expression of the FcεRIα chain is important for full expression of acquired resistance to the hypothermia-inducing effect of honeybee venom-derived phospholipase A_2[76], these findings support the hypothesis that IgE, which contributes to allergic disorders, also has an important function in protection of the host against noxious substances[77, 78].

MCs can respond to many stimuli beside IgE. MCs can respond to various pathogens though activation of TLRs, including TLR-2 and TLR-4[79, 80] and, *via* GPCRs, to certain peptides found in venoms[81–83], or can be activated by various complement peptides[84, 85] and platelet-activation factor[86]. There is evidence that MCs also can be directly or indirectly activated by some plant products, including aqueous pollen extracts from birch[87], and by products of the coagulation system, including Factor Xa[88] and thrombin receptor activating peptide (TRAP)[89]. MCs also can respond to certain chemokines and cytokines (including IL-33[25–27, 90, 91] and TSLP[92]), or be activated through the aryl hydrocarbon receptor[93, 94], the CD40 ligand[95] or the OX40 ligand[96–98] or by immune complexes of IgG[99, 100]. MC activation (e.g., *via* the FcεRI) can also be modulated by various mechanisms, including interactions with other cells such as granulocytes[101], regulatory T cells[102] and other lymphocytes[103], *via* a variety of negative regulatory receptors expressed on their surface[8, 104–106], or by exposure to certain cytokines, including the KIT ligand SCF[8, 12–14, 107, 108], IL-33[25–27, 109] and IFN-γ[56, 110].

Mast cell-derived mediators

MCs store preformed mediators in their granules and can release some of them almost instantly upon degranulation. These stored mediators include vasoactive amines such as histamine[111, 112] (although MCs are considered the main source of histamine outside of the CNS, other cells also can produce histamine, including basophils[113] and neutrophils[114, 115]), and, in rodents, serotonin[112]. MC granules also contain many neutral proteases (tryptases, chymases, and carboxypeptidase A3 [CPA3])[42, 116–122] (Table 1). As noted above, MC protease content can vary depending on the cells' tissue location and microenvironment. Only one chymase is expressed in human MCs but there are 13 known mouse chymase

genes[123]. Among those, the β-chymase MC protease 4 (MCPT4) appears to be the most functionally similar to human chymase[124, 125]. MC granules also contain some preformed cytokines and growth factors, including TNF in both humans[126, 127] and mice[128, 129]. MCs can also synthesize and secrete certain lipid mediators, such as prostaglandins and leukotrienes[130, 131]. Finally, MCs are also able to synthesize and secrete a large number of cytokines, chemokines, and growth factors, including TNF[128, 132–134], IL-1[135–137], IL-6[135, 138, 139], IL-10[140–142], IL-17[143–145], VEGF and other vascular growth factors[146–148], SCF[149, 150] and many others. Release of lipid mediators typically occurs within 1–2 hours after MC activation and is associated with immediate responses, whereas synthesis and secretion of cytokines and chemokines characteristically occurs over a longer time frame, associated with the development of late phase or more chronic responses[8, 151].

Mouse models to study mast cell functions *in vivo*

Pharmacological agents thought to target MC activation or MC proteases have been used *in vivo* to assess the functions of MCs. However, none of the drugs or antibodies described to date is fully specific for MCs or for particular MC proteases[70, 152, 153]. Therefore, we favor using genetic approaches to gain insights into MCs functions *in vivo*.

c-*kit* mutant mast cell-deficient mice and the ‘mast cell knock-in model’

For many years, c-*kit* mutant MC-deficient mice, such as WBB6F$_1$-*Kit*$^{W/W\text{-}v}$ and C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice, have been used to analyze the functions of MCs *in vivo*[7, 8, 141, 154–158]. These two types of mice are profoundly MC-deficient but also have several other phenotypic abnormalities[155, 157–163], including a marked reduction in intestinal cells of Cajal (ICCs), which results in abnormal electrical pacemaker activity in the small intestine[155, 164]. Abnormalities in biological responses in c-*kit* mutant mice may reflect their MC deficiency and/or one or more of their other phenotypic abnormalities. However, at many anatomical sites, the deficiency in MCs can be selectively “repaired” by the adoptive transfer of genetically-compatible, *in vitro*-derived MCs such as bone-marrow-derived cultured MCs (BMCMCs), to create so-called ‘MC knock-in mice’[8, 10, 60, 155, 156, 165, 166].

c-*kit*-independent mast cell-deficient mice and mice deficient for mast cell-associated products

More recently, several groups have generated new strains of mice permitting the constitutive or inducible deletion of MCs independently of mutations affecting c-*kit* structure or expression[60, 167–172]. Most of these groups used a strategy consisting of generating transgenic mice expressing the Cre recombinase under the control of promoters for MC proteases, such as those for carboxypeptidase A3 (*Cpa3*) or MC protease 5 (*Mcpt5*)[167, 168, 172]. Such mice then were crossed with mice in which genes of interest have been “floxed” to delete expression of these gene products in the MCs[168, 173]. Our group mated *Cpa3*-Cre mice with mice expressing the floxed survival factor *Mcl-1*: the resulting *Cpa3-Cre; Mcl-1*$^{fl/fl}$ mice were severely deficient in MCs but had also markedly reduced basophil levels[167]. Feyerabend et al. reported a severe MC deficiency (and a more modest deficiency in basophils) in another line of *Cpa3-Cre* mice due to Cre-mediated cytotoxicity[172]. *Mcpt5-Cre* mice, which express Cre in connective tissue-type MCs but not

mucosal MCs[168, 169], were mated with transgenic mice expressing Cre inducible diphtheria toxin A (DT-A) or diphtheria toxin receptor (iDTR) genes to achieve constitutive (in *Mcpt5-Cre; DTA*$^{+}$ mice) or inducible (after DT injection in *Mcpt5-Cre; iDTR*$^{+}$ mice) ablation of CTMCs[168]. All of these mice and some additional new types of MC-deficient mice have been recently reviewed in detail[152, 174, 175].

Several strains of mice that are deficient for one or multiple MC-associated proteases, or are unable to synthetize histamine (due to a deficiency in histidine decarboxylase) or heparin (due to a deficiency in N-deacetylase/N-sulfotransferase-2) also have been developed. While each of these strains of mice can provide important information concerning the roles of particular products released by MCs, some of them have a complex phenotype and there are a number of considerations that should be kept in mind when interpreting findings obtained with these animals, as reviewed in[152, 175, 176].

Role of mast cells in the regulation of intestinal epithelial permeability

The intestinal epithelium forms a selectively permeable barrier against the external environment[177]. Disruption or dysregulation of this barrier is associated with many intestinal disorders, including bacterial, viral and parasitic infections, inflammatory bowel disease (IBD), and food allergies[177, 178]. Groschwitz *et al*. demonstrated that naïve c-*kit* mutant MC-deficient *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice and mice deficient for the chymase MCPT4 have altered intestinal barrier structure and function, with decreased intestinal epithelial cell migration along the villus/crypt axis of jejunum, increased crypt depth in the jejunum (without differences in villus length) and increased intestinal permeability as compared to WT mice[177]. Engraftment of *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice with WT BMCMCs but not *Mcpt4*$^{-/-}$ BMCMCs restored these features to levels observed in WT mice, evidence that MCs can contribute to the homeostatic regulation of the intestinal barrier through MCPT4-dependent mechanisms[177].

Other studies have provided evidence that MCs can control intestinal epithelial ion transport or permeability during effector phases of inflammatory responses[179–181], including during anaphylaxis[179]. Isolated intestinal preparations from ovalbumin (OVA)-sensitized WT mice displayed increases in short-circuit current (Isc) following *ex vivo* stimulation with OVA or following electrical transmural stimulation of intestinal neurons. Such responses were significantly diminished in MC-deficient *Kit*$^{W/W\text{-}v}$ or WCB6F$_1$-*Mgf*$^{Sl/Sl\text{-}d}$ mice (*Sl-d* is a deletion in the transmembrane domain of the *Scf* gene[182] and *Mgf*$^{Sl/Sl\text{-}d}$ mice don't express the membrane form of SCF[183]). Moreover, transfer of BM cells from WT mice to *Kit*$^{W/W\text{-}v}$ mice "normalized" the Isc responses to both antigen and transmural stimulation, indicating a role for MCs and/or other BM-derived cell type in this process[179]. A role for MCs in this setting also was suggested by tests of pharmacological agents which antagonize the factions of certain MC-derived mediators[179].

Infection with the parasite *T. spiralis* increases paracellular permeability of the jejunum and decreases the expression of occludin in the tight junctions of enterocytes[181]. Treatment of WT mice with a c-*kit* blocking antibody abrogated MC hyperplasia during *T. spiralis* infection and blocked parasite-induced increases in intestinal permeability[181]. Mice deficient

in the chymase MCPT1 also exhibited diminished intestinal permeability during *T. spiralis* infection, even though numbers of intestinal MMCs were higher during infection in *Mcpt1*$^{-/-}$ mice than in WT mice[181].

Injection of the neuropeptide substance P induces intestinal ion secretion with increase in Isc responses. In intestinal preparations from MC-deficient *Kit*$^{W/W\text{-}v}$ mice, substance P-induced Isc responses were diminished to about 50% of those observed in WT mice and were normalized by the adoptive transfer of WT BM cells, suggesting that MCs can contribute to substance P-induced changes in intestinal ion secretion[184]. By contrast, our group demonstrated that MCs can *limit* the toxicity associated with high concentrations of another neuropeptide, vasoactive intestinal polypeptide (VIP)[82]. In that setting, our evidence indicated that VIP induced MC degranulation, releasing the chymase MCPT4 which then degraded VIP[82].

Roles of mast cells in allergic responses at mucosal sites

Asthma

Asthma is a multifaceted disorder characterized by reversible airway narrowing (in many patients in response to particular allergens), immunologically non-specific airway hyper-responsiveness (AHR), chronic inflammation of the airways, and airway remodeling, including fibrosis, goblet cell hyperplasia/metaplasia, increased mucus production, smooth muscle thickening and increased vascularity[185–187]. Early manifestations of the disorder can appear in childhood, and both genetic[188] and environmental factors[189] contribute to the development and progression of asthma. Rather than being a single “disease”, the disorder called asthma is likely comprised of distinct subphenotypes with different clinical characteristics and underlying mechanisms[190–192]. Analysis of lung epithelial brushes, bronchoalveolar lavage (BAL) fluids, lung biopsies, and autopsies have shown increased numbers of MCs in the airways of some asthmatic subjects[54, 193–195] but not others[194, 196, 197]. One feature more often seen in asthmatic subjects than in those without the disease is the presence of MCs within the bronchial epithelium[198–200].

In subjects with asthma, B cell class switching to IgE occurs in the lymph nodes[201], as well as locally in the respiratory mucosa[202]. IgE binds to FcεRI, highly expressed on MCs and basophils, but also, in certain settings by eosinophils and neutrophils; evidence has been reported that FcεRI also can be expressed by airway epithelial and smooth muscle cells and by certain nerves (reviewed in[69]). IgE not only permits allergen-dependent MC activation, but also enhances the stability of FcεRI on the MC surface, thus increasing the levels of receptor expression of FcεRI, contributing to the maintenance of a positive amplification loop (reviewed in[6]).

Several mouse models of allergic airway inflammation have been developed to recapitulate many aspects of asthma. Studies using the MC knock-in model in c-*kit* mutant mice sensitized with an antigen in the absence of artificial adjuvant[55, 56, 203–206], or employing relatively low doses of antigen for sensitization or challenge[207, 208], have provided evidence that MCs and MC-derived TNF can amplify multiple features of allergic airway inflammation, including airway responsiveness, inflammation, and tissue

remodeling[55, 56, 203–205, 207, 208]. However, contributions of MCs to various features of allergic asthma are not observed (perhaps because they are redundant) in some models of allergic airway inflammation employing strong artificial adjuvants (such as alum) and relatively high doses of antigen for sensitization and challenge[203, 209–212].

Genetic background also can influence the contribution of MCs to allergic airway inflammation. Becker *et al.* confirmed that *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice on the C57BL/6 background have reduced airway inflammation and AHR in an adjuvant-free model of asthma, but found no significant differences between BALB/c-*Kit*$^{W\text{-}sh/W\text{-}sh}$ and BALB/c-WT mice in their model[213]. These findings clearly indicate that roles of MCs in this asthma model that are important in one strain background (the "Th1-biased" C57BL/6 background) may not be important (or may be redundant) in the more "Th2-biased" BALB/c background. These findings are of substantial interest, given the strong evidence that genetic factors have an important role in human asthma.

In a mouse model of chronic allergic airway inflammation, studies in MC knock-in mice indicated that MC expression of the IFN-γR contributes to the development of many features of the model that also require MCs and FcεRIγ for optimal expression, including AHR, neutrophil and eosinophil infiltration in the lung, lung collagen deposition, and increased expression of lung IL-6, IL-13, IL-33, multiple chemokines, arginase-1, and the acute-phase protein serum amyloid A3. However, expression of IFN-γR also contributes to some features of the model which require MCs for optimal expression but that occur relatively independently of FcεRIγ, such as elevations of levels of integrin α7 and the macrophage receptor with collagenous structure (MARCO) in the affected lungs[56]. In a passive model of OVA-induced allergic airway inflammation, transfer of $OVA_{323–339}$-peptide-specific, IFN-γ-producing Th1 cells to naive mice primed them to develop airway neutrophilia and AHR that was most prominent in mice challenged with LPS as well as antigen[214]. It also has been reported that co-stimulation of mouse pulmonary macrophages with LPS and IFN-γ induces the production of IL-27[215], that in turn can enhance production of IL-1 and TNF by MCs[216]. Such studies provide support for the hypothesis that bacterial infections can sustain or enhance inflammation driven by Th1 responses in asthma.

Some patients with severe asthma exhibit enhanced sputum neutrophilia (but not eosinophilia) and enhanced serum and sputum levels of IL-17[217]. In diseases with a prominent Th17 signature such as atopic dermatitis[218], chronic exposure to antigens, such as *via* epicutaneous sensitization[219], can enhance airway inflammation and "local" Th17 inflammation in the lung[220]. Evidence from our mouse models[55, 56] and those of others[221] show that chronic airway exposure to OVA can increase BAL neutrophils and lung levels of IL-17 (in addition to Th2 cytokines), and that the presence of MCs is essential for the development of such features. Some mouse or human MCs can produce IL-17 upon non-IgE-dependent stimulation (e.g., with 6-formylindolo(3,2-*b*)carbazole [FICZ]) or when exposed FICZ in combination with IgE/antigen and, based on immunohistochemical findings, MCs appear to represent a major *in vivo* source of IL-17 in the chronically inflamed bronchial lamina propria of patients with chronic obstructive pulmonary disease[94], and in other settings[145, 222, 223].

IL-33 is also thought to contribute to the pathology of asthma[100, 224–228]. The IL-33 receptor, ST2, is expressed by MCs and basophils[229], but not by airway smooth muscle cells or lung fibroblasts[230]. In mice, IL-33-induced enhanced airway inflammation is partly dependent on IL-33-dependent MC production of IL-13[231]. IL-33 is considered an alarmin or a pro-inflammatory cytokine[232], but its biology might be more complex since it has been reported that chronic exposure of human and mouse MCs to IL-33 *in vitro* can induce a hypo-responsive MC phenotype, raising the intriguing possibility that IL-33 might actually have certain protective roles in chronic airway inflammation[233].

In summary, evidence from studies of human asthma and mouse models of the disorder support the general conclusion that MCs can have critical roles in amplifying acute immunological responses to antigen and in helping to orchestrate the later development of multiple features of the disorder, but also suggest that the roles of MCs in particular sub-phenotypes of asthma may vary, in part due to differences in the cytokines present in those settings (Figure 1). Moreover, recent data raise the interesting possibility that some individual MC mediators may have effects that can *restrain* the development of certain features of the pathology. For example, Waern and collaborators reported that mice deficient for the chymase MCPT4 exhibit *increased* pathology (i.e., airway inflammation, AHR and smooth muscle thickening) in two different models of allergic lung inflammation, and that such protective effects might reflect, at least in part, degradation of IL-33 by the chymase[234, 235].

Food allergy and anaphylaxis

Food allergies are caused by adverse acquired immune responses to food components, primarily proteins[236]. Their prevalence has recently increased and food allergies now affect ~6% of children and 3–4% of adults in developed countries[236]. The manifestations of food allergy can range from mild to severe, with the most severe form being anaphylaxis, an acute and potentially life-threatening multisystem reaction to allergen exposure. In the U.S., the majority of cases of food-induced fatal or near-fatal anaphylaxis are caused by peanuts or tree nuts[237, 238]. Studies in mice indicate that MCs are critical effector cells of both food-induced intestinal inflammation and anaphylaxis (Figure 2).

Multiple mouse models of anaphylaxis have been developed to investigate the contribution of MCs and other effector cells. Two main pathways of active anaphylaxis have been described in mice: a “classical” pathway consisting of antigens, IgE, FcεRI, MCs, and histamine, and an “alternative” pathway involving IgG-antigen immune complexes, FcγRIII, platelet-activating factor (PAF), and, depending on the exact model used, macrophages, basophils and/or neutrophils[239–245]. Several studies using $Kit^{W/W\text{-}v}$ and/or $Kit^{W\text{-}sh/W\text{-}sh}$ MC-deficient mice have provided evidence that MCs can contribute significantly to peanut-induced active anaphylaxis[242, 244, 245]. We recently confirmed these findings using c-*kit*-independent MC-deficient mice, by showing that selective ablation of CTMCs (induced by repeated injections of diphtheria toxin in *Mcpt5-Cre; iDTR* mice[168]) significantly diminished the hypothermia induced by peanut challenge in mice sensitized orally with peanut together with the mucosal adjuvant cholera toxin[243]. However, antigen challenge induced significant hypothermia (albeit less than that in the corresponding WT mice) in

Cpa3-Cre^{+}*; Mcl-1*$^{fl/fl}$ mice, which have a marked MC deficiency and a substantial reduction in basophils[243]. Antigen-induced elevations in serum histamine were abolished in MC- and basophil-deficient *Cpa3-Cre*$^{+}$*; Mcl-1*$^{fl/fl}$ mice, whereas small but significant increases in PAF levels were still detected in spleen specimens from these mice[243]. Together, these findings implicate the involvement of both the classical and alternative pathways of anaphylaxis in this mouse model of peanut-induced active anaphylaxis.

The reaction to peanut in some mouse models might be even more complex, since Khodoun *et al*. found that peanut, but not milk or egg proteins, can induce shock reactions through an innate immune mechanism in mice[246]. The authors found that this response was almost absent in mice lacking the complement factor C3 or the receptor C3aR, but developed fully in antibody-deficient Rag1 mice (which lack mature T and B cells) and μMT mice (in which the development of conventional B cells is arrested at the pro-B cell stage)[246]. However, some reports indicate that μMT mice have B1 B cells and can produce IgE and IgG[247–249]. Macrophages, basophils and PAF contributed to this shock reaction to a greater extent than did MCs and histamine[246]. Therefore, depending on the model used, innate components might also participate importantly in peanut-induced anaphylaxis, which perhaps accounts for the fact that peanut allergy is more likely than most other forms of food allergy to cause lethal anaphylaxis. However, it is important to recognize that Khodoun *et al*. increased the sensitivity of the mice to develop shock reactions in these experiments by pretreating the animals i.v. with a long-acting form of IL-4 (consisting on IL-4/anti–IL-4 mAb complexes, which slowly dissociate *in vivo* to release free IL-4) and with the β-adrenergic antagonist propranolol[246].

Although IgE-dependent activation of MCs is widely thought to contribute importantly to anaphylaxis in humans, subjects with food allergy-associated anaphylaxis, unlike those with insect venom-induced anaphylaxis, typically exhibit little or no elevations in blood levels of the MC-associated protease, tryptase[250]. By contrast, levels of PAF in the serum have been directly correlated with the severity of organ system involvement in patients with acute allergic reactions triggered by foods, medications, or insect stings[251, 252]. Moreover, the serum activity of PAF acetylhydrolase (an enzyme that converts PAF to the biologically inactive lyso-PAF) was significantly lower in peanut allergic patients with fatal peanut anaphylaxis than in those with mild allergic reactions to peanuts or in control groups[251]. Although they do not constitute proof, these results are consistent with the possibility that activation of both the “classical” pathway and the “alternative” pathway might be involved in at least some examples of anaphylaxis in humans. The existence of IgG-mediated anaphylaxis in humans is perhaps best supported by the occurrence of anaphylaxis in patients infused with monoclonal antibodies (mAbs), such as the chimeric mouse/human anti-TNF mAb infliximab[239, 253]. One study showed that 11 out of 165 patients with Crohn disease treated with infliximab developed signs of anaphylaxis. All these patients had IgG antibodies to the mouse immunoglobulin determinants on infliximab. While none of the patients had detectably increased serum levels of total IgE, the authors did not report whether they attempt to measure levels of infliximab-specific IgE. However, none of these patients had increased tryptase levels in blood 20 minutes after the onset of the reaction[239, 253].

Anaphylaxis represents the extreme end of a spectrum of responses to food allergens in allergic patients. In most patients, reactions are manifested mainly by local signs and symptoms, and the skin is affected in ~80% of subjects[254]. Up to 50% of patients also develop gastrointestinal symptoms (abdominal pain, vomiting, diarrhea) and a significant portion of patients also experience respiratory symptoms (cough, chest tightness, wheezing)[255, 256]. Multiple lines of evidence suggest that IgE-dependent MC activation can play an important role in these local manifestations of food allergy. Cafarelli *et al*. found elevated numbers of IgE-positive cells (plasma cells, and 2.7% MCs) in duodenal biopsies from children with food allergies, whereas MCs were virtually absent in the control biopsies[256, 257]. Moreover, when stimulated *ex vivo* with anti-IgE, intestinal MCs obtained from enzymatically dispersed duodenal biopsies from food allergic patients released more histamine in comparison to cells from non-allergic individuals[256, 258].

Brandt *et al*. developed a mouse model of allergen-induced gastrointestinal inflammation consisting of sensitization with OVA together with alum and repeated oral challenges with OVA[48]. In this model, sensitized and challenged BALB/c mice (but not C57BL/6 mice) developed large increases in numbers of MMCs in the jejunum, ileum, and colon and increased levels of MCPT1 in the plasma. These mice also exhibited a strong Th2 response in the intestine, with signs of allergy such as diarrhea and increased intestinal permeability, but without hypothermia[48]. However, systemic (i.v.) OVA challenge of OVA/alum-sensitized mice induced hypothermia that was significantly more severe in animals which had been previously challenged with OVA intra-gastrically compared with those mock-challenged with saline. Notably, lethal anaphylactic shock occurred only in mice that previously had developed gastrointestinal allergy, suggesting that gastrointestinal allergic inflammation can prime mice for more severe anaphylaxis following systemic antigen challenge[48]. The authors showed that treatment with an anti-KIT antibody (ACK2) abrogated the diarrhea, diminished intestinal permeability, and eliminated MMCs in the jejunum[48]. These features were also diminished in mice treated with an anti-IgE antibody and in mice deficient for the high affinity IgE receptor FcεRI (but not in mice treated with a blocking antibody against the IgG receptors FcγRII/III). Finally, they demonstrated that treatment with a combination of pharmacological inhibitors of PAF and serotonin blocked diarrhea, while blockade of histamine had no effect on diarrhea[48]. Wang *et al*. reported that, in a model of peanut allergy in BALB/c mice, allergen-induced diarrhea and other features of the response were also partially diminished in mice deficient for the FcεRIα chain. Adoptive transfer of WT BMCMCs, but not *FcεRIα*$^{-/-}$ or *Il-13*$^{-/-}$ BMCMCs, restored diarrhea in FcεRIα-deficient mice, suggesting that this feature is dependent on IgE-mediated activation of MCs and on the release of IL-13 by MCs[259].

Little is known about the mechanism(s) leading to sensitization with food allergens. Forbes *et al*. showed that transgenic mice which overexpress IL-9 have increased numbers of intestinal MMCs, associated with increased intestinal permeability which can enhance oral sensitization to OVA administered without an adjuvant[260]. Epidemiologic studies have demonstrated that cutaneous inflammation associated with atopic dermatitis (AD) is a significant risk factor for the development of food allergies[261–263]. Recently, Noti *et al*. reported that epicutaneous sensitization of mice to food antigens (OVA or peanut extract)

applied to an AD-like skin lesion (which lead to increased levels of TSLP in the skin) followed by oral challenge with the antigen promoted intestinal Th2-driven inflammation and increased numbers of intestinal MMCs[263]. Such features are much diminished in mice deficient for the TLSP receptor (TSLPR) or IgE, or in mice in which basophils have been depleted (but the authors did not assess responses of MC-deficient mice in this model). These results indicate that a "TSLP-basophil axis" can contribute to the development of IgE-mediated intestinal MMCs expansion and food allergy in mice sensitized epicutaneously with food allergens[263].

Burton *et al*. recently developed an adjuvant-free model of peanut allergy using mice with a disinhibiting mutation in the IL-4 receptor α chain (*il4raF709* mice), which results in amplified signaling upon interaction of the receptor with the Th2 cytokines IL-4 or IL-13 but not constitutive activation[264]. Oral sensitization of *il4raF709* mice with peanut, followed by oral challenge with peanut, led to expansion and activation of intestinal MMCs, and the development of diarrhea, intestinal inflammation and hypothermia. The authors used MC-deficient *Mcpt5-Cre;DTA* mice and IgE-deficient mice to demonstrate that, in this model, both MCs and IgE were required for induction of antibody and Th2-cell-mediated responses to peanut ingestion, as well as for suppression of expansion of regulatory T (Treg) cells. MC-targeted genetic deletion of the FcεRI signaling kinase *Syk* in *Mcpt5-Cre;Syk*$^{fl/fl}$ mice also prevented peanut sensitization. Therefore, in addition to their key effector role during many allergic reactions, under certain circumstances MCs and IgE also appear to be able to amplify sensitization to certain food allergens such as peanut, as well as participate in the suppression of tolerance.

Roles of mast cells in defense against mucosal pathogens

MCs are located at sites exposed to invading pathogens, such as the skin, the gut, and the lung and genitourinary mucosa. MCs are therefore likely to be among the first innate cells (together with macrophages and dendritic cells [DCs]) to respond to such pathogens. Studies in mice indicate that MCs can contribute to multiple defense strategies against various pathogens, including parasites (Figure 2), bacteria, and viruses[79, 265–268], but that, in certain settings, MCs can contribute to the pathology associated with such infections.

Parasite infections

Parasite infections that involve the intestines and provoke the development of Th2 responses are often associated with a large expansion in MMCs in rodents[269–271], and with expansion of mucosal MC populations in monkeys[272] and humans[273]. Space does not permit a comprehensive discussion of the complex innate and adaptive immune mechanisms which are thought to contribute to helminth clearance[274–277]. Instead, we will review briefly some of the evidence indicating that MCs can influence aspects of these responses. Woodbury *et al*. demonstrated that, in rats infected with *Trichinella spiralis* or *Nippostrongylus brasiliensis*, systemic secretion of the rat MC-associated chymase rMCP-2 coincides with the immune expulsion of these nematodes[269]. Many groups have assessed the responses of *Kit*$^{W/W\text{-}v}$ and/or *Kit*$^{Wsh/Wsh}$ mice to primary infection with various parasites, including *Nippostrongylus brasiliensis*[278, 279], *Strongyloides ratti*[280], *Strongyloides venezuelensis*[51, 281, 282], *Trichinella spiralis*[283, 284], and *Trichinella muris*[285, 286]. Most of

these studies show that such c-*kit* mutant MC-deficient mice have a delay in intestinal worm clearance during the primary infection. However, due to the inability to engraft intestinal MMCs in such c-*kit* mutant mice by the systemic adoptive transfer of MCs[155, 177, 287, 288], it is not possible to know to what extent the delays in parasite clearance detected in these MC-deficient mice reflect their lack of MMCs vs. one or more of their other phenotypic abnormalities (including their deficiency on intestinal cells of Cajal, which results in abnormal gut motility[164]).

However, other lines of evidence support an important contribution for MCs in intestinal worm clearance. Ha *et al*. showed that engraftment with total BM cells accelerated expulsion of *T. spiralis* in $Kit^{W/W\text{-}v}$ mice[283]. Expulsion of *T. spiralis* was significantly delayed in mice lacking the chymase MCPT1, which suggests an important contribution of intestinal MMCs and MCPT1 in the clearance of this infection[271]. Although the kinetics of *T. spiralis* expulsion from the small intestine were similar between MCPT6-deficient and WT mice, the MCPT6-deficient mice had diminished levels of eosinophils in infected skeletal muscle[289]. Recently, Blankenhaus *et al*. showed that c-*kit*-independent MC-deficient BALB/c-$Cpa3^{Cre/+}$ mice (which, beside their MC deficiency, also have reduced basophil numbers[172]) exhibited increased parasite burden in the small intestine following infection with *S. ratti*[290].

While results described above suggest potentially important roles for MMCs and some of their associated chymases in worm expulsion, it is possible that in some parasite infections effects of MCs might actually favor the parasite. For example, anti-SCF treatment diminished intestinal MMC hyperplasia in rats infected with *N. brasiliensis* or *T. spiralis*, but such anti-SCF treatment *decreased* parasite egg production during *N. brasiliensis* infection[291]. Similarly, during a primary infection with *N. brasiliensis*, c-*kit* mutant MC-deficient *Ws/Ws* rats exhibited *reduced* numbers of eggs in the feces at day 8 of infection than did the corresponding WT rats[292]. Neither study proved that MCs were responsible for the observed effects, but the results are intriguing in suggesting that some parasites may have learned how to exploit MC-associated effector mechanisms to their own advantage.

IL-3 can promote expansion of intestinal MMCs in mice[51, 283] and treatment with IL-3 accelerates expulsion of *S. ratti*[283]. Both $Kit^{W/W\text{-}v}$ mice and mice lacking IL-3 exhibited a delay in *S. venezuelensis* expulsion, and this delay was greatly enhanced when these deficiencies were combined (i.e., in $Il\text{-}3^{-/-}$; $Kit^{W/W\text{-}v}$ mice, in which infection provoked little or no expansion of basophil or MMC populations)[51]. These findings indicate that one of the functions of IL-3 in this setting is to expand populations of hematopoietic effector cells, and are consistent with the possibility that both MCs and basophils contribute to expulsion of *S. venezuelensis* during the primary infection.

IL-9 also plays an important role in expansion of intestinal MMCs during parasite infection and transgenic mice which overexpress IL-9 have increased intestinal MMCs and increased efficiency of worm expulsion during infection with *T. spilaris*[181]. There is evidence that IL-9-mediated MC activation is also a key mechanism mediating *S. ratti* expulsion in mice[290]. This mechanism can't be generalized to all parasites, since in the case of infection

with *N. brasiliensis*, it appears that neither IL-9 nor MCPT1 influences worm expulsion[271, 293].

Most studies of the roles of MCs in parasite infection have focused on the primary responses to the infection (Figure 2). Many parasites induce strong antibody responses, including high levels of antigen non-specific IgE as well as antigen-specific IgE and IgG antibodies, and secondary infections are often associated with a more rapid expulsion of the parasites than occurs in the primary infection[294–296]. However, it is not yet clear to what extent interactions of such antibodies with MCs importantly contribute to such secondary responses. While there have been few studies of secondary parasite infections in genetically MC-deficient mice, numbers of MMCs and serum MCPT1 levels were significantly higher in BALB/c WT mice at day 3 after secondary vs. primary infections with *T. spiralis*, and worm burden at that time was significantly less in the secondary than in the primary infection[181]. Given that co-engagement of FcγRIIB with FcεRI can diminish antigen-dependent MC activation[297, 298], it will be important to investigate whether this or other mechanisms can down-regulate or otherwise alter MC responses during secondary parasite infections, as well as to determine whether MCs can confer benefits to the host or the parasite in such settings.

Bacterial infections

Several studies have indicated that MCs can have an important role in enhancing survival during models of experimental bacterial sepsis in mice. Many of these data were obtained using the cecal ligation and puncture (CLP) model in which commensal bacteria are allowed to escape from the cecum into the peritoneum, and most of the studies employing MC-deficient mice have used $Kit^{W/W\text{-}v}$ and/or $Kit^{W\text{-}sh/W\text{-}sh}$ mice, which have multiple defects in immune responses other than their MC deficiency[80, 158, 299–305]. Experiments assessing responses of MC-deficient $Kit^{W/W\text{-}v}$ mice engrafted with WT or various mutant BMCMCs have demonstrated that such MCs are mainly activated through TLR4 (but not TLR2) during polymicrobial sepsis[80], and that MC-derived IL-12[306], as well as MC expression of the cysteinyl protease dipeptidyl peptidase I (DPPI)[302] and the transcription factor Smad3[307], are also required for optimal survival during the CLP model.

MCs also can be activated by the endogenous peptide endothelin-1 (ET-1), primarily through the ET(A) receptor. Activation by ET-1 promotes MC degranulation and the release of proteases which in turn can degrade ET-1. MC protease-dependent degradation of ET-1 can contribute to optimal survival during CLP, which is associated with markedly elevated levels of ET-1[301], and carboxypeptidase A3 (CPA3) is the critical protease which mediates degradation of ET-1[81, 83]. Other MC-associated proteases also have been implicated in defense against bacteria. Studies in $Mcpt4^{-/-}$ mice indicate that the chymase MCPT4 has effects that can enhance survival in a moderately severe model of CLP, perhaps in part through degradation of TNF[305]. Orinska *et al*. reported evidence that intra-cellular IL-15 expression in MCs can transcriptionally limit the amount of the chymase MCPT2 in the cells, resulting in decreased MC antibacterial properties and reduced survival of the mice after CLP[308].

MCs can mediate neutrophil recruitment after intraperitoneal injection of *Klebsiella pneumoniae*, probably via multiple mechanisms including the release of TNF[133], IL-6[304], and the tryptase MCPT6[309, 310]. There is evidence that MCs can enhance resistance to pulmonary infection with *Mycoplasma pneumonia*[311]. Histamine plays an important role in this model, but neutrophils, rather than MCs, were the major source of histamine in the lungs of the infected mice[115]. MCs also can contribute to *Clostridium difficile* toxin A-induced intestinal fluid secretion and neutrophil infiltration[312]. Malaviya *et al.* reported that, during infection with *E. coli*, neutrophil recruitment and bacterial clearance is controlled by JAK3 activation in MCs; this effect was attributed to the diminished ability of *Jak3*$^{-/-}$ MCs to produce TNF[313]. By contrast, there is evidence from work in MC knock-in mice that MC-derived TNF can enhance bacterial growth and hasten death after intraperitoneal inoculation of *Salmonella typhimurium*[158].

Urinary tract infections (UTIs), mainly caused by uropathogenic *E. coli*, represent one of the most common bacterial infections in humans[314]. Using the MC knock-in approach in c-*kit* mutant mice, Shelburne and collaborators demonstrated that MCs and MC-derived TNF can amplify the protective adaptive immune response to infection with uropathogenic *E. coli* by promoting: 1) recruitment of DCs at the site of infection (in this case the footpad), 2) migration of DCs into the draining lymph nodes (DLNs), and 3) production of *E. coli*-specific IgG and IgM antibodies[315]. Increased numbers of surviving bacteria were found in the urinary bladder of c-*kit* mutant MC-deficient *Kit*$^{W/W\text{-}v}$ mice as compared to *Kit*$^{+/+}$ mice following experimental infection with *E. coli*[316]. Chan *et al*. compared the kinetics of *E. coli* clearance in the bladder and kidneys of infected mice and found that, while all bacteria were cleared within five days in the kidneys, significant numbers of bacteria were still found in the bladder as late as one month after infection[317]. They demonstrated that this prolonged bacterial survival was due to production of IL-10, and the absence of significant levels of *E. coli* specific antibodies, in the bladder[317]. There is evidence that mouse MCs can represent an important source of IL-10 during inflammation[141, 317] and that MC-derived IL-10 can: 1) limit inflammation during contact hypersensitivity[141] (although these findings have been recently challenged by Dudeck *et al*.[168]), as well as 2) diminish the severity of experimental graft-versus-host disease (GVHD)[318]. In line with these findings, Chan *et al*. demonstrated that MC-derived IL-10 contributed importantly to the suppression of *E. coli*-specific antibody production during experimental UTI in mice and accounted, at least in part, for the persistence of *E. coli* in the bladder[317]. Therefore, MCs appear to be able to play a dual role during *E. coli* infections in the bladder, first promoting the initial innate response to infection and later limiting the antibody response to *E. coli* by producing IL-10[317].

Because c-*kit* mutant MC-deficient mice have many c-*kit*-related phenotypic abnormalities that may influence the responses of such animals to infection (including those which do or do not affect MC numbers or functions)[152, 158, 175], it will be of great interest to continue to evaluate the roles of MCs in infection models using some of the newer, c-*kit*-independent, models of MC deficiency. For example, Rönnberg *et al*. recently reported that peritoneal MCs are activated by *Staphylococcus aureus in vitro*, however, the authors used c-*kit*-independent MC-deficient *Mcpt5-Cre; DTA*$^{+}$ mice to demonstrate that MCs do not influence the *in vivo* manifestations of one model of intraperitoneal *S. aureus* infection[319].

Such work will help to clarify which roles of MCs are variably redundant with those of other cell types (including neutrophils or macrophages, among others) and which MC roles – whether to enhance and/or suppress aspects of these innate or acquired immune responses – may be non-redundant.

Viral infections

MCs have been implicated in the defense against certain viruses, although there have been relatively few studies in this area[79]. Sendai virus can induce histamine release from rat peritoneal MCs *ex vivo*[320] and infection of rats with Sendai virus results in increased numbers of MCs in the lung[321, 322]. Kulka *et al*. showed that human peripheral blood-derived cultured MCs (HCMCs) and two lines of human MCs (LAD and HMC-1), as well as mouse BMCMCs, can respond to stimulation with dsRNA (poly[I:C]) by producing type I interferon (IFN-α) through TLR3. They also found that HCMCs can produce IFN-α when stimulated with live respiratory syncytial virus (RSV), reovirus type 1, or UV-inactivated influenza virus[323]. It has been reported, based on studies in MC knock-in $Kit^{W/W\text{-}v}$ mice, that MCs can promote the recruitment of CD8+ T cells following i.p. injection of poly(I:C)[324].

Several reports suggest that MCs can contribute to the pathology induced by some viruses *in vivo*. Both MC-deficient $Kit^{W/W\text{-}v}$ mice and $Kitl^{Sl/Sl\text{-}d}$ mice exhibited reduced myocardial inflammation and necrosis as well as increased survival as compared to the respective littermate WT mice after i.p. infection with encephalomyocarditis virus[325]. Furthermore, adoptive transfer of BMCMCs into $Kit^{W/W\text{-}v}$ mice or repeated subcutaneous treatment of $Kitl^{Sl/Sl\text{-}d}$ mice with recombinant SCF (which can induce the appearance of both CTMCs and MMCs in these mice[63, 326]) significantly increased the histopathological severity of the myocardial lesions induced by the virus (albeit not to levels observed in WT mice)[325]. By contrast, studies in $Kit^{W\text{-}sh/W\text{-}sh}$ mice, including engraftment of these mice with BMCMCs, showed that MCs can participate in host defense against vaccinia virus, and MC production of the antimicrobial peptide cathelicidin was implicated as a key defense mechanism against this virus[327, 328].

In humans, infection with Dengue Virus leads to increased levels of MC chymase in the serum[329], and chymase levels are significantly higher in patients with severe dengue fever (also known as dengue hemorrhagic fever) as compared to patients with dengue fever[329, 330]. Using the MC knock-in model in $Kit^{W\text{-}sh/W\text{-}sh}$ mice, St John and collaborators demonstrated that MCs can promote the recruitment of natural killer (NK) and NK T cells during Dengue Virus infection in mice[329–331]. Ebert *et al*. recently used a similar approach to demonstrate that MCs can contribute to clearance of Pulmonary Murine Cytomegalovirus in the lung by enhancing the recruitment of $CD8^+$ T cells to the infection site[332].

There is evidence that MCs may have roles in HIV infection. *In vitro* experiments show that the HIV gp120 envelope protein can promote production of Th2 cytokines (IL-4 and IL-5) in human MCs[323]. MCs and their progenitors might also serve as a reservoir for latent virus, a role which would be detrimental to the host[333–336].

In line with the potential of MCs to help to orchestrate protective adaptive responses at mucosal sites, McLachlan *et al*. demonstrated that certain small molecules (‘MC activators’)

are potent mucosal adjuvants, and provided evidence that these agents mediate such functions in a largely MC-dependent manner[337]. So-called 'MC activators' comprise a family of structurally diverse cationic peptides and polymeric compounds that can induce strong MC degranulation[338, 339]; such agents include compound 48/80 (c48/80)[340–342], and a variety of peptide toxins, such as MC-degranulating peptide (MCD), which is found in honeybee and bumblebee venoms[343]. Using the MC knock-in system in c-*kit* mutant mice, McLachlan *et al*. demonstrated that compound 48/80 (which promotes MC degranulation, but also has other effects) can act as a potent mucosal adjuvant when co-administered in the footpad with recombinant anthrax protective antigen, and that this adjuvant effect largely depends on MCs and MC-derived TNF. Importantly, vaccination with c48/80 co-administered with the vaccinia virus antigen B5R intranasally conferred protection against intranasal challenge with a normally lethal dose of vaccinia virus[337].

Conclusions

We are in the midst of an interesting period in MC research. For many years, an increasing understanding of the diversity of MC products, signaling mechanisms, and interactions with other cell types has led to the generation of many attractive hypotheses about the diverse *potential* effector and immunoregulatory roles of MCs in the biology and pathology of mucosal tissues (and in other settings). Increasingly, these hypotheses are being tested in ways that permit us to accrue definitive evidence regarding the nature, and the importance, of such proposed MC roles. In addition to long-established mouse model systems, including "MC knock-in c-*kit* mutant mice" and various MC protease-deficient mice, there are now many promising new models of constitutive or inducible MC deficiency, as well as many new models for achieving the targeted deletion of individual products in MCs. Based on the results obtained so far with both the older and newer models for MC research, we think that the most robust conclusions about the nature and importance of the roles of MCs in various biological responses *in vivo*, in mucosal tissues and other sites, probably will be derived from studies employing multiple informative model systems[152]. Taken together, such approaches offer many opportunities to obtain increasingly solid evidence to support (or discard) notions about how MCs might influence the development, physiology, homeostasis, immunology and pathology of mucosal tissues.

It hardly needs mentioning that findings in mice do not prove that the same processes occur in humans, and there are likely to be multiple differences in the details of immune responses and disease pathogenesis in the two species, not just differences in the roles of MCs in such settings. However, pre-clinical studies using models in which individual cells or products can be manipulated offer the promise of revealing pathways that, with luck, might be exploited to provide benefit to those suffering from any of the diverse mucosal pathologies in which MCs have been implicated. Time will tell to what extent this hope will be realized.

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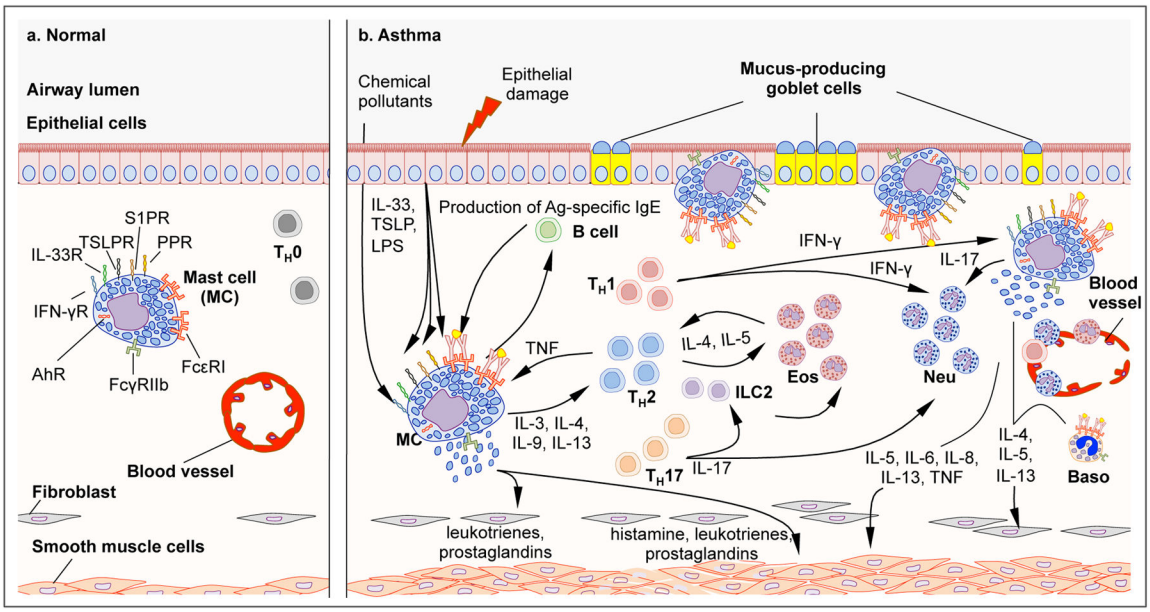

Figure 1. Schematic, highly simplified representation of the potential roles of MCs in airway chronic allergic inflammation and remodeling

Individuals not yet sensitized to environmental allergens do not have specific IgE to such allergens, and few MCs are present within the epithelium (left panel). During allergic sensitization, environmental antigens (Ag) are captured by APCs in the airway lumen or in the epithelium of the airway mucosa, and Ag-activated APCs mature and migrate to regional lymph nodes, where priming of T cells occurs (not shown). The presence of IL-4 or IL-13, which may be derived from a variety of potential cellular sources, induces T cells to become T_H2 cells (right panel). In some cases, allergens also can reach APCs in the submucosa through damaged epithelium. Cytokines induced by epithelial damage (such as IL-33 and TSLP) can activate ILC2 cells, which secrete type 2 cytokines, such as IL-4 and IL-13. The Th2 environment promotes heavy-chain class switching from IgM or IgG to IgE for Ag-specific IgE production in B cells. IgE binds to FcεRI on MCs (and basophils) and sensitizes these cells to respond to subsequent Ag exposures. Ag-induced aggregation of IgE-bound FcεRI causes the prompt release of pre-stored MC mediators, including histamine and TNF, which can promote bronchoconstriction and, more slowly, fibroblast proliferation. FcεRI activation also induces the production and the release of *de novo* synthesized compounds, such as leukotrienes, prostaglandins, and pro-inflammatory cytokines (e.g., IL-5, IL-6, IL-8, IL-13, and TNF) and chemokines (not shown), that contribute to the development of local inflammation.

Both soluble factors, such as IFN-γ, TSLP, IL-33, S1P, LPS (through PRRs) and cells present at the site, such as T_H cells and various T_{reg} cells (not shown), which can interact with OX40L on MCs, modulating IgE-dependent MC activation, or B cells, which can interact with CD40L on MCs, which may enhance B cell IgE production. At least one MC-secreted product, MCPT4 (not shown), can negatively regulate the inflammatory environment, in part through the degradation of IL-33.

Repetitive exposure to specific Ag favors persistent inflammation (with large numbers of eosinophils, and with MCs appearing within the epithelium), goblet cell hyperplasia and

increased mucus secretion, smooth muscle cell proliferation, increased vascular permeability (and increased numbers of blood vessels) and airway edema, thickening and remodeling. In some asthma subtypes, genetic or environmental factors, including pathogen-derived products, tissue damage, airway pollutants, and oxidative stress, may confer strong T_H1 and/or T_H17 signatures associated with large numbers of neutrophils at the site of inflammation. Studies in MC–knockin mice have indicated that some actions of MCs, such as increasing the number of epithelial goblet cells, can occur in a model of chronic allergic inflammation by MC–dependent mechanisms that do not require MC signaling through the FcεRIγ chain, whereas MCs must express both the FcεRIγ chain and the IFN-γ receptor 1 (IFN-γR1) to mediate substantial increases in lung eosinophils and neutrophils. Note: down-regulatory mechanisms that can be engaged in this setting, such as co-engagement by multivalent Ag of both FcεRI and FcγRIIb, or effects of regulatory T cell populations, are not shown.

AhR, Aryl hydrocarbon receptor; Baso, basophils; Eos, eosinophils; FcεRI, high affinity receptor for IgE; ILC2, innate lymphoid cells type 2; Neu, neutrophils; PRR, pattern recognition receptor; TH, T helper; TSLP, thymic stromal lymphopoietin.

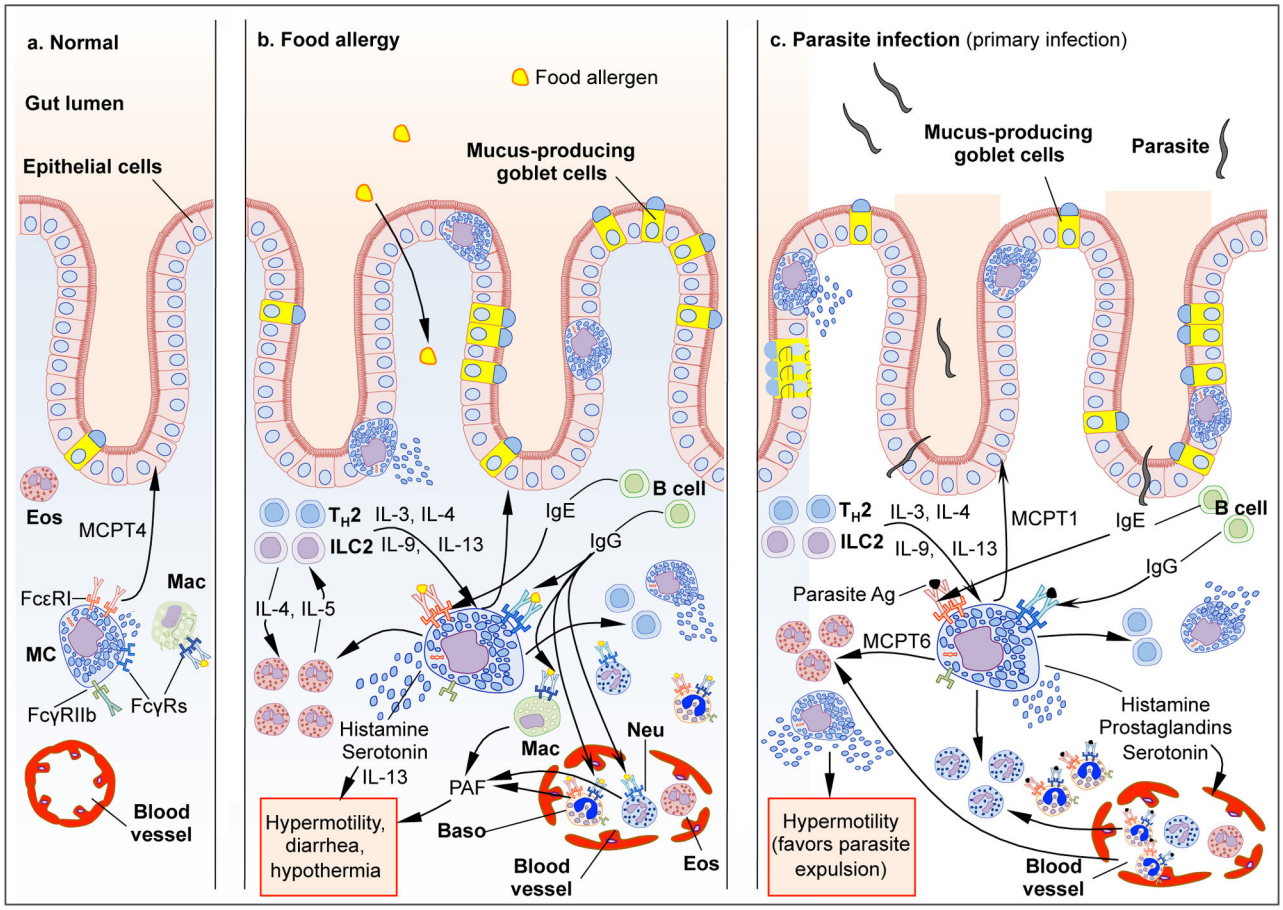

Figure 2. Schematic, highly simplified representation of the potential roles of MCs in food allergy and parasite infections

In the normal intestine, MCs can contribute to the homeostatic regulation of the epithelial barrier through chymase- (MCPT4-) dependent mechanisms and few MCs are present within the epithelium (left panel). During sensitization with food allergens (middle panel) or primary infections with parasites (right panel), antigens (Ag) are captured by APCs and Ag-activated APCs mature and migrate to regional lymph nodes, where priming of T cells occurs (not shown). The presence of IL-4 or IL-13, which may be derived from a variety of potential cellular sources, induces T cells to become T_H2 cells. T_H2 cells and ILC2 cells release IL-3 and IL-9 which promote expansion of mucosal MCs (MMCs), and some of these MMCs are found in the intestinal epithelium. IgE binds to FcεRI on MCs (and basophils) and sensitizes these cells to respond to subsequent Ag exposures. Ag-induced aggregation of IgE-bound FcεRI causes the prompt release of pre-stored MC mediators, including histamine which can promote vasodilatation and increased vascular permeability. FcεRI activation also induces the production and release of *de novo* synthesized compounds, such as leukotrienes, prostaglandins, and pro-inflammatory cytokines (such as IL-13) and chemokines (not shown). Such MC-derived products contribute to intestinal inflammation (including the recruitment and activation of neutrophils, basophils and eosinophils and other leukocytes), increased intestinal permeability and motility, and, in the case of parasite infections, worm expulsion. During food allergy, the activation of MCs also can promote

diarrhea and, in some unfortunate individuals, anaphylaxis (not shown). IgG-Ag immune complexes can potentially modulate MC activation through Fcγ receptors (MCs express the activating receptor FcγRIII and the inhibitory receptor FcγRIIb). Macrophages, basophils and neutrophils are also activated by IgG-Ag immune complexes and release PAF, which is thought to contribute to diarrhea and anaphylaxis in food allergy. Note: down-regulatory mechanisms that can be engaged in these settings, such as co-engagement by multivalent Ag of both FcεRI and FcγRIIb, or effects of regulatory T cell populations, are not shown. Baso, basophils; Eos, eosinophils; FcεRI, high affinity receptor for IgE; FcγRs: receptors for IgGs; ILC2, innate lymphoid cells type 2; Neu, neutrophils; PAF, platelet-activating factor; PRR, pattern recognition receptor; T_H2, T helper 2.

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Table 1

Major mast cell "subtypes", and some of their phenotypic features, in mice and humans

Many aspects of the phenotype of MC populations can vary based on whether the MCs are present at sites of inflammatory or immune responses, their exposure to various growth factors and other cytokines, and/or the history of their activation for secretion[175]. Accordingly, the features listed in the table are primarily those of MC populations at "baseline" in the tissues mentioned. These MC subpopulations can vary in features not covered in the table, such as in their sensitivity to pathogen-associated molecular patterns and in the spectrum of cytokines, chemokines and growth factors that they can secrete or respond to. However, much of the evidence for such differences is based on *in vitro* rather than *in vivo* studies, and these features also may be subject to variation *in vivo* depending on the biological setting.

CTMC, connective tissue-type mast cell; FcγR, receptor for IgG; FcεRI, high affinity receptor for IgE; MCPT, mast cell protease; MMC, mucosal mast cell; MC_T, tryptase-expressing mast cell, MC_{TC}, tryptase and chymase-expressing mast cell.

	Mouse		**Human**	
Classic "subtypes"*	**MMCs**	**CTMCs**	**MC_T**	**MC_{TC}**
T cell dependence	T cells required for baseline populations and for expansion (e.g., in response to parasites)[32]	Do not require T cells for baseline populations or for expansion	Reduced numbers in subjects with congenital or acquired deficiencies in T cells[41]	Normal numbers in subjects with congenital or acquired deficiencies in T cells[41].
Anatomical distribution (at baseline)	Glandular stomach mucosa (many at baseline), small intestinal and colonic mucosae (very few at baseline), and respiratory mucosa[344–346]	Skin, serosal cavities, tongue, submucosa and muscularis of the stomach, trachea & around large airways[155, 346]	Preponderance of MCs in nasal and bronchial mucosae, lung alveoli, conjunctiva, gastric, small intestinal and colonic mucosae[40, 42]	Preponderance of MCs in skin, gastric, small intestinal and colonic submucosa and muscularis, bronchial submucosa, smooth muscle of major bronchi, conjunctiva, breast parenchyma and axillary lymph nodes[40, 42]
Proteoglycan content	Little or no heparin[347, 348]; Chondroitin sulfate di-B, A, E[349, 350]	Heparin[347, 348]; Chondroitin sulfate E[349, 350]	Heparin[351]; Chondroitin sulfate A, E[349, 350]	Heparin[351]; Chondroitin sulfate A, E[349, 350]
Protease content	Express predominantly the chymases MCPT-1 and 2[5, 118, 175, 352]	Express predominantly the chymase MCPT-4, the elastase MCPT-5, the tryptases MCPT-6 and 7 and Carboxypeptidase A3[5, 118, 175, 352]	Tryptase (α, β[I–III], and γ)[353–355]**; Little or no chymase, carboxypeptidase A3 and cathepsin G[38, 356, 357]	Tryptase (α, β[I–III], and γ)[353, 354, 358]**; Chymase[38]; Carboxypeptidase A3[357]; Cathepsin G[356]
Bioactive amine content	Low levels of histamine[359] ; Serotonin[360]	High levels of histamine[359]; Serotonin[361]	Histamine; No evidence of serotonin	Histamine; Low level of serotonin detected in MCs derived from $CD34^+$ peripheral blood progenitors[362]
Response to cationic compounds	Little or none (?)***	Yes	Little or none[363]	Yes[363]
Adenosine receptors[364]	A2a[365]; A2b[365]; A3[365]	A3[366]	A2a[367]; A3[368]	Skin-derived cultured MCs express low levels of A3 receptor[368]
Ig receptors[100]	FcεRI; FcγRIIb[369]; FcγRIII (?)****	FcεRI; FcγRIIb[370]; FcγRIII[371, 372]	FcεRI[373]; Human intestinal MCs express FcγRI, FcγRIIa, FcγRIIb but not FcγRIII[374]	FcεRI[375]; MCs derived from $CD34^+$ peripheral blood progenitors[110] and some skin MCs in patients with psoriasis[376] express FcγRI; skin-

	Mouse		Human	
Classic "subtypes"*	**MMCs**	**CTMCs**	**MC_T**	**MC_{TC}**
				derived MCs express FcγRIIa but not Fc γRIIb[377]

*Not all features listed have been reported for MCs in each anatomic site.

**In humans, α tryptases have no or minimal catalytic activity and are absent in many people, whereas β tryptases are active (βI and βII) or are predicted to be active (βIII); tryptase deficiency alleles are common, and different populations of humans differ in whether they inherit 2 versus 4 active alleles[378]. The more recently described γ-tryptases are expressed at the mRNA level in multiple MC populations but less is known about the distribution of the protein in various MC populations[353, 355].

***This point is well established in the rat, based on studies of purified MMCs[379]. However, much less is known about the responsiveness of mouse MMCs to such compounds.

****BMCMCs (which have been used by some groups as a "model" for MMCs) express functional FcγRIII when stimulated with SCF[380]. However these cells only resemble MMCs in some respects and, to our knowledge, FcγRIII expression on mouse MMCs has not been reported *in vivo*.