REVIEW

Recent advances in mast cell activation and regulation [version 1; peer review: 2 approved]

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Abstract

Mast cells are innate immune cells that intersect with the adaptive immunity and play a crucial role in the initiation of allergic reactions and the host defense against certain parasites and venoms. When activated in an allergen- and immunoglobulin E (IgE)-dependent manner, these cells secrete a large variety of allergenic mediators that are pre-stored in secretory granules or de novo-synthesized. Traditionally, studies have predominantly focused on understanding this mechanism of mast cell activation and regulation. Along this line of study, recent studies have shed light on what structural features are required for allergens and how IgE, particularly anaphylactic IgE, is produced. However, the last few years have seen a flurry of new studies on IgE-independent mast cell activation, particularly via Mrgprb2 (mouse) and MRGPRX2 (human). These studies have greatly advanced our understanding of how mast cells exert non-histaminergic itch, pain, and drug-induced pseudoallergy by interacting with sensory neurons. Recent studies have also characterized mast cell activation and regulation by interleukin-33 (IL-33) and other cytokines and by non-coding RNAs. These newly identified mechanisms for mast cell activation and regulation will further stimulate the allergy/immunology community to develop novel therapeutic strategies for treatment of allergic and non-allergic diseases.

Keywords

Allergy, mast cells, allergen, IgE, FceRI, MRGPRX2, IL-33, miRNA
Introduction

Mast cells (MCs) play a crucial role in allergic reactions and the host defense against certain parasites, bacteria, and venoms. Morphologically, MCs are featured by a large number of secretory granules containing various bioactive molecules, including histamine, serotonin, proteoglycans, and proteases. Upon encounter with multivalent antigen (or allergen), antigen-specific immunoglobulin E (IgE)-bound high-affinity IgE receptors (FceRI) on the surface of MCs are cross-linked or aggregated. Consequently, activation of the FceRI signaling system is triggered, leading to the release of granular contents (degranulation) and de novo synthesis and secretion of lipid mediators, cytokines, and chemokines. Activation of MCs entails immediate hypersensitivity and late-phase allergic inflammation. With regard to the IgE-mediated MC activation, recent years have seen a deeper understanding of IgE synthesis, structural features of allergens, FceRI signaling mechanisms, and counter-mechanisms. Non-IgE-dependent MC activation mechanisms have been studied at a slow pace for many years. However, we have witnessed significant progress in this area more recently.

Murine MCs are classified as connective tissue MCs (CTMCs) and mucosal MCs (MMCs) on the basis of their tissue distribution. CTMCs and MMCs are also characterized by the heparin content of their granules: CTMCs contain a large amount of heparin in their granules, whereas MMCs have very little or no heparin. Human MC proteases include tryptases (mMCP-6 and -7 in mouse), chymases (mMCP-1, -2, and -4), an elastase (mMCP-5), and a carboxypeptidase-A3 (CPA3). Human MCs are categorized by expression of MC tryptase (MC\textsubscript{\textalpha}) or MC chymase (MC\textsubscript{\textgamma}) or both (MC\textsubscript{\textalpha\textgamma}). A recent transcriptional analysis demonstrated that the MC is one of the most transcriptionally variable cell types of the immune system. Murine MCs that were purified from different tissues shared an “MC-specific” transcriptional signature of at least 100 genes. Also, these MCs showed a tissue-specific regulation of their transcriptomes.

Substantial progress has recently been made in several areas of MC research, such as degranulation machinery, cancer, microbiota, and food allergy. Readers interested in these topics are referred to recent review articles.

Allergen, immunoglobulin E, and FceRI

A comprehensive understanding of the IgE-mediated MC activation requires a better knowledge of allergens, IgE synthesis and structure, and FceRI structure and signaling pathways. Here, we highlight recent advances in this area, particularly allergens and IgE synthesis. We certainly know three-dimensional structures of many parts of IgE and FceRI (composed of an IgE-binding α and receptor-stabilizing and signal-amplifying β and activation signal-triggering γ subunits) and important principles in signaling, such as tyrosine phosphorylation of β and γ subunits at the immunoreceptor tyrosine-based activation motif (ITAM) by Src family kinases, the essential functions of Syk, Ca\textsuperscript{2+} flux, several adaptor molecules, mitogen-activated protein kinases (MAPKs), and several transcription factors.

However, we feel obliged to note that our understanding of FceRI signaling pathways is still in the early stages in light of an incomplete understanding of degranulation processes and a large number of genes regulated by MC activation.

One of the most important hypotheses on structural features of allergens stemmed from the requirement of cross-linking of cell surface IgE molecules by various allergens for MC activation and IgE synthesis. This line of thinking led Jensen-Jarolim et al. to recognize that allergens display repetitive motifs, which they designate allergen-associated molecular patterns (AAMP). Indeed, many allergenic molecules occur as dimers or multimers. Some allergens—small proteins, in particular—have just a single immunodominant B-cell epitope and thus do not fulfill the requirement for cross-linking as a single molecular unit. Oligomerization provides the necessary means for efficient IgE cross-linking. Examples where only single dominant epitopes have been found are the allergens Der p 1 from house dust mite (HDM) and Bet v 1 from birch. Also, the occurrence of repetitive epitopes on single native allergen molecules has been shown on high-molecular-weight proteins of wheat and for HDMs and insects, cockroach Bla g 1, latex Hvb 5, and tropomyosin from shrimp.

IgE concentrations in serum are kept to the lowest level among immunoglobulin subtypes by several layers of regulation: in addition to the high rate of turnover, low efficiency of class-switch recombination to IgE, and lower surface expression of membrane IgE than that of IgG1 on germinal center (GC) B cells, IgE\textsuperscript{+} B cells are predisposed to swiftly exit GCs and differentiate into plasma cells (PCs) and IgE-producing GC B cells die by apoptosis. Therefore, IgE\textsuperscript{+} memory B cells are scarce. Class switching of antigen-specific IgG1\textsuperscript{+} cells to become IgE\textsuperscript{+} cells, via the so-called sequential switching, was proposed as the mechanism involved in the production of affinity-matured IgE antibodies in memory responses.

Using a culture system of induced GC B cells, Haniuda et al. showed that the CD19-phosphatidylinositol 3-kinase (PI3K)-Akt-IRF4 axis is the essential pathway for PC differentiation and the BLNK-JNK-p38 axis serves an enhancing role in PC differentiation. They also showed that BLNK is essential for B-cell apoptosis and that CD19 is rather anti-apoptotic.

Recent studies have shown that T follicular helper (Tfh) cells are the primary T-cell subset responsible for IgE responses. Interleukin-4 (IL-4) is required to generate and sustain IgE production in mice. In response to allergens, T helper type 2 (Th2) and Tfh cells show unique cytokine responses, tissue localization, and phenotypes. In vivo, Tfh cells assist the sustained production of IgE antibody. But conditional deficiency of Bcl6, the master regulator of Tfh, in CD4\textsuperscript{+} T cells results in a significant decrease in IgE antibody levels and Tfh cell numbers. However, eosinophilic inflammation and type 2 cytokine responses in the airways are not affected. Thus, Th2-derived IL-4, but not Th2-derived IL-4, is necessary for IgE production. Gouthaman et al. recently discovered a new Tfh subset in mice with T cell–specific Dock8 deficiency. These mice made allergen-specific anaphylactic IgE with the help
of an IL-4– and IL-13–producing Th2 cell population called Th13 cells. Th13 cells have an unusual cytokine profile (IL-13^+IL-4^+IL-5^+IL-21^+) and co-express the transcription factors Bcl6 and GATA3. These cells are required for production of high- but not low-affinity IgE and subsequent allergen-induced anaphylaxis. Single-cell RNA sequencing analysis confirmed that Th13 cells are distinct from related Th2 or IL-4–expressing Th2 cells. Conditional ablation of Th13 cells or isolated loss of IL-13 in Th cells resulted in impaired anaphylactic IgE responses to allergens. Thus, blocking Th2 cells might represent a therapeutic means to ameliorate anaphylaxis.

We have known effects of monomeric IgE on FcεRI surface levels and on survival of MCs in the absence of allergen for a long time. A recent study showed that IL-3 but not monomeric IgE regulates FcεRI expression and cell survival in primary human basophils, in contrast to human and murine MCs.

**Mast cell activation by interleukin-33**

IL-33 belongs to the IL-1 family and is expressed by several cell types, including epithelial cells. IL-33 binds to a specific receptor called T1/ST2 (ST2) that belongs to the Toll-like receptor/IL1R family. ST2 forms homodimers with the IL-1 receptor accessory protein (IL-1RACp), namely a transmembrane form (ST2 or ST2L) and a soluble form (sST2). ST2L isoform is expressed on MCs, basophils, Th2 cells, and natural killer cells and coordinates spatially and temporally with IL-33 signaling, which might trigger a key regulatory amplification loop involved in immune homeostasis. IL-33 is considered an alarmin as it is released after necrosis or tissue damage. However, apoptosis leads to the inactivation of IL-33 by cleavage of IL-33 by caspases. In contrast, MC serine proteases cleave the full-length IL-33 (IL-33^full^) and liberate active forms: IL-33^IL-1^, IL-33^IL-20^, and IL-33^IL-20^−. These cleaved forms have 10 times greater potency than the full-length protein. MC chymase also degrades IL-33 that leads to higher bioactivity. Downstream of ST2, the IL-33–mediated signaling pathway involves MyD88, IRAK1, IRAK4, and TRAF6 as well as activation of MAPKs (ERK1/2, p38, and JNK1/2) and nuclear factor-kappa B (NF-kB).

IL-33 can induce full activation of MCs, including degranulation and production of several cytokines and chemokines, and elicits systemic MC-dependent anaphylaxis. Several studies have shown that IL-33 plays a significant role in severe asthma and refractory nasal polyposis. Earlier studies have been summarized in excellent reviews. Here, we touch on newer reports that showed a possible role of IL-33 in various allergic conditions: IL-33–mediated airway constriction was exacerbated through increased secretion of serotonin from MCs. *Staphylococcus aureus*–derived serine protease–like protein (Sph) D is a potent allergen and induces a Th2-biased inflammatory response in the airways in an IL-33–dependent manner. Aspirin-exacerbated respiratory disease (AERD) is a severe eosinophilic disorder of the airways and is characterized by overproduction of cysteinyl leukotrienes, activation of airway MCs, and bronchoconstriction in response to non-selective cyclooxygenase inhibitors that deplete prostaglandin E (PGE) synthase (a model of AERD). A study using clinical samples and mice deficient in PGE synthase (a model of AERD) found up-regulation of IL-33 in airway epithelium. Deletion of leukotriene C4 synthase in the AERD model mice eliminates the increased IL-33, lung eosinophilia, and aspirin-induced MC activation and bronchoconstriction. MCs have been shown to play a crucial role in a model of skin inflammation by IL-33–mediated recruitment of leukocytes and resulting inflammation in an MK2/3 (MAPK-activated protein kinases 2 and 3)–dependent manner. In a murine model of food allergy, IL-33 and MCs promote inflammation in the gastrointestinal tract through IL-4 production by IL-33–stimulated ILC2s, as IL-4 blocks the generation of allergen-specific regulatory T (Treg) cells. However, on the positive side, IL-33 and MCs play a protective role in intestinal helminth infections by activating ILC2, leading to helminth expulsion. MCs can ameliorate IL-33–mediated inflammatory effects under certain circumstances. Stimulation of MCs with IL-33 in the absence of IgE cross-linking can induce Treg cell expansion by producing IL-2 and reduce the inflammation in a papain-induced innate-type airway inflammation model.

**Mast cell activation via Mrgprb2/MRGPRX2**

Mas-related G protein–coupled receptor-X2 (MRGPRX2) has been the hottest receptor in MC research over the last few years. Mrgprb2 is the murine ortholog of MRGPRX2. Under homeostatic conditions, CTMCs in the skin and peritoneum of mice express Mrgprb2, whereas MMCs do not express Mrgprb2. Mrgprb2/MRGPRX2 recognizes a wide range of cationic molecules, including substance P (SP), basic secretagogues (for example, compound 48/80), numerous US Food and Drug Administration–approved drugs, and endogenous protein fragments. Mrgprb2/MRGPRX2-mediated activation of MCs by these ligands results in their rapid degranulation of individual granules and MC-dependent local inflammation, whereas FcεRI–elicited secretion is delayed but progressive and is characterized by granule-to-granule fusions.

MRGPRX2 has been implicated in allergic and chronic inflammatory diseases. LL-37, the cathelicidin peptide and MRGPRX2 agonist, is up-regulated in rosacea and MCs play a key role as the primary source of LL-37 in a murine model of rosacea. The pathology in asthma and urticaria correlates with MC-specific expression of MRGPRX2. Mrgprb2 inactive mutant Mrgprb2^mutant^ mice show reduced itch in multiple models of allergic contact dermatitis (ACD), a pruritic inflammatory skin disorder. MC numbers and PAMP1-20 (MRGPRX2 agonist) concentrations are increased in human ACD skin biopsies, which is associated with pathogenic CD8 T-cell responses. MRGPRX2 is found in close proximity to peripheral nerve endings and Atopic dermatitis, another pruritic skin disease, has been studied by using a mouse model sensitized and challenged with HDMs in the presence of staphylococcal enterotoxin B. Using this model, a recent study shows that HDMs with cysteine protease activity directly activate peptidergic nociceptors on sensory neurons expressing the ion channel TRPV1 and...
Tac1 (gene encoding the precursor for SP) [71]. HDM-activated nociceptors drive the development of allergic skin inflammation by SP/Mrgprb2-mediated activation of MCs [71]. Another study indicates that activation of the natriuretic polypeptide b (Nppb)-expressing class of sensory neurons elicits scratching responses in mice [72]. Interestingly, however, Nppb+ neurons express receptors for leukotrienes, serotonin and sphingosine-1-phosphate, and these receptors induce itch by the direct activation of Nppb+ neurons and neurotransmission through the canonical gastrin-releasing peptide-dependent spinal cord itch pathway [72]. Mrgprb2/MRGPRX2 is also involved in inflammatory mechanical and thermal hyperalgesia [73]. In this case, SP activates MCs via Mrgprb2/MRGPRX2 to release multiple pro-inflammatory cytokines and chemokines, which facilitate the migration of immune cells. It is noteworthy that SP-mediated activation of MCs does not involve its canonical receptor, neurokinin 1 receptor (NK-1R). However, activation of NK-1R by hemokinin-1 likely contributes to allergic airway inflammation in mice, whereas activation of the human MC line LAD-2 by hemokinin-1 requires MRGPRX2. MRGPRX2 expression is upregulated in lung MCs from patients with lethal asthma [63].

Studies of Mrgprb2/MRGPRX2-mediated MC activation have been extended to their new ligands, signal transduction, effects of other MC modulators, and so on. For example, compound 48/80, AG-30/5C (angiogenic defense peptide), and icatibant (bradykinin B2 receptor antagonist) all activate pertussis toxin-sensitive G proteins, but only compound 48/80 activates β-arrestin [74]. The same study also found resveratrol (polyphenolic compound in peanuts, grapes, red wine, and some berries) as an inhibitor of MRGPRX2. As the FceRII signaling is initiated by tyrosine phosphorylation with Src, Syk, and Tec family kinases while Mrgprb2 and MRGPRX2 are G protein–coupled receptors, FceRI- and MRGPRX2-stimulated pathways are completely independent of each other [75]. Stem cell factor (SCF) and IL-4, which are the two main MC differentiation and growth factors, negatively regulate MRGPRX2 expression in human skin MCs, whereas SCF promotes allergic stimulation via FceRI [66]. In contrast, pre-incubation (20 minutes) of human MCs with IL-33 or IL-6 or both does not affect their activation with SP, whereas such priming, particularly that with both IL-33 and IL-6, enhances IgE/allergen-mediated MC activation [76]. Another study shows that chronic exposure (5 weeks) of human MCs to IL-33 reduces FceRII expression and responsiveness to its aggregation [69]. Short-term (30 minutes) pre-incubation with IL-33 enhances MRGPRX2-mediated degranulation by SP or compound 48/80 without changing MRGPRX2 expression, whereas chronic (5 weeks) pre-treatment with IL-33 reduces...
mRNA and protein expression of MRGPRX2 and its function. MCs are also required for cardiac fibrosis in multiple animal models. Interestingly, NK-1R expression in MCs is not required in cardiac fibrosis. It should be tested whether MrgrpB2 is involved in this process.

**MicroRNA and mast cell biology**

MicroRNA (miRNA), a small non-coding RNA molecule that is 19 to 25 nucleotides in length, functions in post-transcriptional regulation and RNA silencing of gene expression. miRNAs work by base pairing with complementary sequences inside of mRNA molecules. Because of the broad regulatory mechanisms, miRNAs regulate differentiation, proliferation, survival, apoptosis, stress response, and the effector function as well as the resolution of an immune response.

Numerous studies have examined the role of miRNAs in MC biology. Silencing of Dicer, a key enzyme of miRNA biogenesis, attenuates degranulation, indicating that miRNAs are involved in MC activation. Overexpression of miR-142-3p, which rescues Dicer expression, enhances FcεRI-mediated degranulation in MCs. IgE/antigen stimulation of bone marrow–derived MCs induces up- or down-regulation of several miRNAs, which affects mRNA expression of some key signaling molecules, including Lyn, Vav3, and Csf2. miR-155 plays a critical role in FcεRI-mediated MC responses by modulating components of the PI3K pathway, and miR-155–deficient mice show enhanced anaphylaxis. Down-regulation of miR-155 in MCs is also involved in suppression of IL-33–induced inflammation by lactic acid or of IL-33–induced IL-6 production in MCs. As a basis of IL-10–mediated MC regulation, IL-10–induced miR-155 expression enhances protease and cytokine production in MCs by suppressing SOCS1, a suppressor of cytokine signaling. A novel miRNA let-7i inhibits MC degranulation by suppressing expression of Exoc8, which is an exocytosis-related gene. MiR-126 accelerates IgE-mediated MC degranulation, which is associated with PI3K/Akt activation and increased Ca2+ influx. MiR-223 reduces IL-6 secretion in MCs by inhibiting the IGF1R/PI3K signaling pathway. Expression of miR-210 and miRNA-132/212 cluster is increased by IgE-mediated MC activation. MiR-21 inhibits MC degranulation by inhibiting the p38 pathway in a murine model of ACD. MiR-221-222 is up-regulated in MC stimulation and regulates the cell cycle by

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inhibiting p27Kip1 expression\textsuperscript{55,97}. MiR-221-3p, which is markedly increased in asthmatics, up-regulates IL-4 secretin from MCs by targeting phosphatase and tensin homolog (PTEN) as well as activation of p38 and NF-κB\textsuperscript{98}. MiR-302e negatively regulates RelA/p65 expression in MCs and ameliorates allergic inflammation through inhibition of the NF-κB signaling pathway\textsuperscript{99}. MiR-143 and miR-146 reduce MC activation by targeting IL-13Rx1 and TRAF/IRAK, respectively, leading to a reduced allergic response\textsuperscript{100–103}

\textsuperscript{104}. miR-20a inhibits expression of tumor necrosis factor (TNF), IL-1β, and interferon gamma (IFN-γ) while promoting IL-10 in HMC-1 human MCs. miR-20a also targets histone deacetylase 4 (HDAC4), which contributes to the epigenetic regulation of IL-10 expression\textsuperscript{104}.

Shefler \textit{et al.} showed that MCs are activated by interaction with activated T cells or their microvesicles (mVT\textsuperscript{s})\textsuperscript{105,106}. The physical contact of MCs with activated T cells or with mVT\textsuperscript{s} induces Ras activation and ERK phosphorylation, leading to degranulation and release of several cytokines in MCs\textsuperscript{106–110}. The same group later found that miR-4443 in mVT\textsuperscript{s} targets the expression of protein tyrosine phosphatase receptor type J (PTPRJ), a known ERK inhibitor\textsuperscript{111}. Several miRNAs that play a role in cancer have recently been discovered: miR-9 increases the invasion of neoplastic MCs\textsuperscript{112}. miR-122 targets SOCS1 mRNA and regulates cellular interactions involving cancer cells, MCs, and macrophages during allergic inflammation\textsuperscript{113}. Exosomal miRNAs have emerged as mediators of the interaction between MCs and tumor cells. MCs can inhibit hepatocellular carcinoma cell metastasis by inhibiting the ERK1/2 pathway by transferring the exosomal shuttle microRNAs, including miR-490, into hepatocellular carcinoma cells\textsuperscript{114}.

**Perspectives on mast cells in diseases**

Traditionally, MCs have been implicated in allergic diseases. Efficacy of omalizumab—humanized anti-IgE monoclonal antibody (mAb)—and mAbs targeting Th2 cytokines or Th2 cytokine receptors for the treatment of asthma and other allergic diseases supports crucial pathogenic roles for MCs in these diseases\textsuperscript{115–117}. Among the mAbs targeting cytokine/receptors, the most illustrative example is dupilumab (mAb for IL4Rα, the subunit shared by IL-4 and IL-13 receptors). This mAb blocks the functions of both IL-4 and IL-13 and is highly efficacious for the treatment of atopic dermatitis\textsuperscript{118} and asthma\textsuperscript{119,120}. However, effects of dupilumab likely reflect pleiotropic functions of IL-4 and IL-13 in immune and non-immune cells.

MCs are considered an important player in inflammation-associated diseases in general, as recent studies have extended their potential role in other diseases. For example, MCs seem to be involved in gastrointestinal diseases such as inflammatory bowel disease, celiac disease, and irritable bowel syndrome\textsuperscript{121}. The phenotype and the activation status of MCs rather than the absolute numbers in the intestinal mucosa are important for the development and progression of the diseases\textsuperscript{122}. MCs might also play a role in atherosclerosis. Immunohistochemical studies in autopsied human subjects and studies in murine atherosclerotic models have collectively provided evidence that the compounds released by activated MCs might promote atherogenesis at various stages during the development of atherosclerotic lesions\textsuperscript{123}. MCs can be pro-tumorigenic and anti-tumorigenic\textsuperscript{4,124}. A recent study found that immune cells such as MCs, tumor-associated neutrophils, tumor-infiltrating macrophages, and myeloid-derived suppressor cells promote prostate cancer via various types of intercellular signaling\textsuperscript{125}. With regard to neural diseases, MCs might contribute to modulate the intensity of the associated depressive and anxiogenic component on the neuronal and microglial biological front\textsuperscript{126}. Preclinical evidence suggests that the intestinal microbiota contributes significantly to behavioral and mood disorders. Microbiotic conditions have been linked to pain, anxiety, stress, and depression in humans\textsuperscript{127}. Far from being substantiated by other studies, symptoms of autism spectrum disorder might also be caused by the mediators derived from MCs which could activate microglia, causing localized inflammation\textsuperscript{128}. MCs might play a significant role as a neuroimmune connection between these components. The next decade might see unexpected developments in MC research and their clinical translations.

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