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Human eosinophils and mast cells: birds of a feather flock together

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Summary

While the origin of the phrase “birds of a feather flock together” is unclear, it has been in use for centuries and is typically employed to describe the phenomenon that people with similar tastes or interests tend to seek each other out and congregate together. In this review, we have co-opted this phrase to compare innate immune cells of related origin, the eosinophil and mast cell, because they very often accumulate together in tissue sites under both homeostatic and inflammatory conditions. To highlight overlapping yet distinct features, their hematopoietic development, cell surface phenotype, mediator release profiles and roles in diseases have been compared and contrasted. What emerges is a sense that these two cell types often interact with each other and their tissue environment to provide synergistic contributions to a variety of normal and pathologic immune responses.

Keywords

Eosinophils; mast cells; receptors; mediators; cytokines; lineage; inflammation; homeostasis

1 Introduction

Mast cells (MCs) and eosinophils are immune cells well known for their roles in initiating allergic responses. These cells are developmentally and functionally similar and participate in many of the same diseases, often in a synergistic manner. They have been described as

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Conflict of Interest:

B.S.B. has current or recent consulting or scientific advisory board arrangements with or has received honoraria from Sanofi-Aventis, TEVA, GlaxoSmithKline, AstraZeneca and Allakos, and owns stock in Allakos and Glycomimetics. He receives publication-related royalty payments from Elsevier and UpToDate™ and is a co-inventor on existing Siglec-8-related patents and thus may be entitled to a share of royalties received by Johns Hopkins University on the potential sales of such products. B.S.B. is also a co-founder of Allakos, which makes him subject to certain restrictions under University policy. The terms of this arrangement are being managed by the Johns Hopkins University and Northwestern University in accordance with their conflict of interest policies. The authors have no additional competing financial interests.

key players in atopic dermatitis, food allergies, asthma and rhinitis, all of which have increased in prevalence in recent decades. Since the late 1980's, MCs and eosinophils have been the subject of many human and animal research studies that consistently demonstrate their important contributions to disease pathogenesis. It is therefore not surprising that the majority of approved biologicals for the treatment of these diseases target MCs and eosinophils, for example through IgE and IL-5.

This review will focus on MC and eosinophil similarities during differentiation and maturation and their response to external stimuli. While they do have a comparable repertoire of surface receptors, their responses and reactions often vary. Replete with granules, both MCs and eosinophils harbor a unique collection of pre-stored mediators to be released upon their activation. They also have overlapping but distinct patterns of newly formed lipid and protein mediators. Thus, key similarities and differences will be highlighted while summarizing what is known about their paired roles in allergies and other relevant disorders.

2 Origin and development

2.1 Hematopoietic lineage

MCs and eosinophils both arise from $CD34^+$ hematopoietic stem cells in the bone marrow. Hematopoietic stem cells can exist as long-term self-renewing cells or as cells capable of differentiating into multiple cell lineages, i.e. multipotent progenitors. Classic models of hematopoiesis highlight a bifurcation downstream of multipotent progenitors where commitment towards a myeloid or lymphoid lineage occurs. In humans, eosinophil-committed progenitors branch directly from common myeloid progenitors [1]. However, the origin of human MC-committed progenitors is still controversial. Studies in mice suggest they come from granulocyte/monocyte progenitors downstream of common myeloid progenitors [2]. To make matters more complicated distinct developmental pathways and tissue microenvironments govern MC phenotypes, i.e. tryptase-positive (MC_T) and tryptase/chymase-positive (MC_{TC}) [3].

2.2 Differentiation and maturation

Differentiation of progenitors, towards a terminal MC or eosinophil fate, is a complex process regulated by transcription factors and extrinsic signals such as cytokines. The most pertinent transcription factors in eosinophil differentiation are GATA-1 and C/EBPα, because their forced expression in human myeloid progenitors results in eosinophil formation [4,5]. In addition, PU.1 and FOG-1 indirectly contribute to the emergence of eosinophils because augmentation of either one shifts progenitors towards an alternate fate [6–9]. Recent studies in mice have identified additional transcription factors important for eosinophil differentiation; Helios and Aelios, which regulate gene expression during development [10] and Xbp1, critical for eosinophil differentiation and granulogenesis [11]. Another protein necessary for eosinophil granularity and survival in mice is cystatin F [12]. In MCs, GATA-1 and GATA-2 drive differentiation and regulate transcription of FcεRI and kit genes [3]. PU.1 also promotes MC development, but expression becomes weaker as MCs

mature [9]. Similar to eosinophils, FOG-1 inhibits MC differentiation redirecting progenitors towards other cell lineages [9,13].

MCs and eosinophils both originate in the bone marrow, however eosinophils enter the circulation as mature cells while MCs circulate as progenitors and become mature once they reach the tissues where they ultimately reside (as reviewed in [13,14]). Growth factors are important for regulating a variety of cellular processes including differentiation and proliferation. Eosinophil maturation and proliferation is dependent on cytokines IL-3, IL-5 and GM-CSF, for which receptors are expressed on eosinophil precursors and feature a common β chain. While different combinations of these cytokines generally can promote eosinophilic differentiation and proliferation, the three together greatly enhance both [15]. It is well established that IL-5 is selective for eosinophil production and also mediates their release from the bone marrow [16]. The importance of IL-5 to eosinophil development has been further demonstrated in recent trials of now approved anti-IL-5 monoclonal antibodies that attenuated eosinophil numbers [17]. Of note, it was recently reported in mice that IL-33 can expand eosinophil progenitors upstream of IL-5 and promote upregulation of IL-5Rα [18]. IL-5R is a critical component of eosinophil lineage commitment and is responsible for the occurrence of increased eosinophil numbers observed in allergic inflammation (e.g. increased blood and sputum eosinophils in asthmatic patients following allergen challenge) [19]. Interestingly, IL-4Rα supports IL-5 mediated maturation of eosinophils, but in the absence of IL-5 CCL3 (from eosinophil precursors) can promote cell differentiation through CCR1 [20]. In homeostatic conditions, eosinophils are most commonly found in the circulation. However, eosinophils also home to tissues where eotaxin-1 (CCL11) is constitutively expressed, such as the GI tract, thymus, mammary glands and uterus [21].

Bone marrow and blood MC precursors are $CD13^+$, $CD34^+$and $CD117^+$ (c-Kit, receptor for SCF discussed below) and express low levels of FcεRIα [13,22,23]. Other cytokines, including IL-4, IL-9, IL-10, TGFβ and nerve growth factor, can also contribute to the maturation and proliferation of human MCs. Interestingly, a key growth factor for bone marrow-derived mouse MCs, IL-3 [24], promotes survival of human cord blood-derived MCs [25] but not human lung MCs [26], suggesting that differences in developmental pathways are species-specific and governed by MC phenotype. During an inflammatory or allergic event, tissue-resident MC numbers increase due to recruitment of precursors [27], which is chemokine-driven[22]. MC precursors also respond to other chemotactic factors, including histamine leukotriene B_4 (LTB_4), [28] TGF-β1 and fractalkine, the latter produced by endothelial cells and by smooth muscle cells in human airways during asthma [27,29].

3 Cell Surface Receptors

3.1 Immunoglobulin and immunoglobulin-like receptors

Immunoglobulin or immunoglobulin-like receptors are a family of receptors that feature extracellular immunoglobulin domains comprised of 2 antiparallel β sheets. The most common types are Fc receptors that exist on a variety of cells, including MCs and eosinophils, and serve a protective role by recognizing pathogen-associated antibodies and virally-infected cells. Different classes of Fc receptors exist, named for the antibody to which they bind. Fc gamma (Fcγ) receptors recognizing IgG make up the largest family of

Fc receptors. Human MCs express both FcγRI (CD64) and FcγRII (CD32). FcγRI expression can be upregulated by IFNγ [30] and engagement triggers the release of inflammatory mediators such as histamine, prostaglandins, leukotrienes and type 1 cytokines [31]. FcγRII is constitutively expressed on human skin MCs [32] and its aggregation is known to inhibit histamine release [33]. Human eosinophils lack FcγRI, but do express FcγRII [34]. However, unlike MCs, internalization of FcγRII on eosinophils results in activation [35,36] and promotes survival [37]. Of note, there are several different isoforms of FcγRII, including FcγRIIa and FcγRIIb [38]. Human MCs and eosinophils express FcγRIIa, which features an activating immunoreceptor tyrosine-based activation motifs (ITAM) domain and has been shown to play a role in allergic responses [32,39]. ITIM-bearing FcγRIIb is expressed by some but not all MCs and when present and co-engaged can inhibit IgE-dependent activation and proliferation in mice [40,41]. The other IgG receptor, FcγRIII (CD16), is normally internally expressed in eosinophils, but can translocate to the surface during allergic inflammation [42] or in the presence of mediators such as IFNγ, C5a or platelet activating factor [43,44]. In humans there are two Fc receptors to which IgE can bind. The high-affinity IgE receptor, FcεRI, features an immunoglobulin-binding α chain, while the low-affinity receptor, FcεRII (CD23), does not and is instead characterized as a C-type lectin. Canonical activation of MCs occurs upon antigen cross-linking of FcεRI-bound IgE. MC-expression of FcεRI is upregulated in the presence of IgE, IL-4 and IL-13 [45–47] and downregulated by granulocyte macrophage colony-stimulating factor (GM-CSF) and TGFβ1 [48,49]. In addition, a monoclonal antibody that targets the high-affinity binding site on IgE, called omalizumab, reduces FcεRI expression [50]. Human MCs express FcεRI (which consists of α, β, and γ subunits) either as tetrameric $\alpha\beta\gamma_2$ or trimeric $\alpha\gamma_2$ [51]. Expression of FcεRI is γ chain-dependent, while the β chain enhances MC signaling through ITAM located within the cytoplasmic tails of both the γ and β chains [51,52]. Interestingly, when ITAM-containing FcεRI is cross-linked with the ITIM-bearing FcγRII receptor on MCs, IgE-mediated activation is inhibited [53]. Expression of FcεRI on the surface of human eosinophils is still controversial, but the majority of studies suggest that surface expression, if present at all, is low and unaffected by IgE levels [54]. There may also be an intracellular pool of α chain albeit with unknown function [55]. Like for MCs, IL-4 can stimulate FcεRI expression on human eosinophils, however receptor engagement does not induce degranulation [56]. Eosinophils also express the low-affinity IgE receptor FcεRII (CD23) intracellularly at homeostasis. Upon activation, FcεRII is translocated to the cell surface, followed quickly by reinternalization [57]. There is one IgA-binding receptor, FcαR, which features 2 immunoglobulin domains that are homologous to FcγR and FcεRI [58]. IL-4, IL-5 and corticosteroids have been shown to enhance IgA/ FcαR binding on eosinophils, triggering release of peroxidase [59,60]. A study by Bracke *et al.* found that human eosinophil priming with GM-CSF, IL-4 or IL-5 is necessary for IgA binding to occur [59].

Sialic acid-binding immunoglobulin-like lectins (Siglecs) also feature extracellular domains that resemble immunoglobulins. Siglecs are expressed by a variety of immune cells, including MCs and eosinophils. It has been reported that $CD34^+$ MC progenitors express a variety of Siglecs during differentiation and maturation, including Siglec-2, -3, -5, -6, -8 and -10. We found that as MCs mature, expression of Siglec-5 and Siglec-10 decrease, while Siglec-6 and Siglec-8 appear *de novo* around the same time as FcεRIα, perhaps indicating a

more functional role for these Siglecs in MCs [61]. Another study reported that Siglec-7 is expressed by human MCs [62]. Siglec-8 exists as two distinct isoforms with differing cytoplasmic regions, dependent on splicing [62], while its extracellular domains preferentially bind 6′-sulfo-sialyl Lewis X [63]. In humans, Siglec-8 engagement has profound functional consequences on both MCs and eosinophils [64]. For example, IL-5 priming in human eosinophils leaves them much more susceptible to Siglec-8 mediated apoptosis [65,66], whereas in MCs Siglec-8 ligation inhibits FcεRIα-dependent MC activation and calcium flux in an ITIM-dependent manner [67]. Other studies have highlighted the contribution of IL-33 priming to Siglec-8 mediated eosinophil apoptosis and demonstrated how Siglec-8 ligation promoted eosinophil adhesion via β2 integrins that was necessary for apoptosis [66,68]. In addition to Siglec-8, Siglec-10 expression has also been detected on human eosinophils [69], however further studies are needed to determine its functional relevance.

CD300 receptors are transmembrane proteins which feature IgV-like extracellular domains. These receptors are expressed on many different immune cells, including MCs and eosinophils, and can be activating or inhibitory. CD300a features several ITIM domains and, once activated by endogenous ligands (i.e. phosphatidylserine and phosphatidylethanolamine), can inhibit IgE- and SCF-mediated functions in cord blood-derived MCs [70]. A bispecific antibody targeting both CD300a and c-Kit inhibits activation in cord blood-derived MCs and in human MC leukaemia cell line (HMC-1) [70]. The inhibitory effects of CD300a was also highlighted in CD300a KO mice, where IgE activation of MCs triggered an increased release of cytokines and chemokines compared to MCs in WT control mice [71]. In human peripheral blood eosinophils, activation of CD300a inhibits chemotactic responses to eotaxin-1 and IL-5 and GM-CSF-associated survival and cytokine release [72]. CD300c is also expressed on human MCs [73] and is characterized by the presence of a cytoplasmic ITAM-bearing FcRγ chain [74] and its ligation results in MC activation [73]. Lastly, MCs and eosinophils both express inhibitory CD300f [75]. Increased expression of CD300f has been detected on eosinophils from allergic rhinitis patients [76]. The primary ligands for CD300f are sphingolipids, such as sphingomyelin and ceramide [77,78]. Activated CD300f can inhibit FcεRI-driven MC activation [77]. Of note, CD300f can also display an activating phenotype when cross-linked with mutated ITIM-expressing receptors [75].

Leukocyte immunoglobulin-like receptors (LILRs) are another group of cell surface proteins with both activating and inhibitory properties. Human eosinophils express activating LILRA2 and inhibitory LILRB1, B2 and B3 on their surface [79]. MC precursors express LILRB1, B2, B3, B4 and A1 [80], while mature MCs express LILRB5 on their granules. In MCs, it is suggested that LILRs play a role in down-regulating inflammatory responses [80]. However, studies suggest they promote activation in eosinophils [79]. To date, therapeutics targeting LILRs have yet to be developed, but theoretically targeting of these receptors might be useful in treating cancer and autoimmune diseases.

3.2 Cytokine receptors

One important form of cell communication is governed by cytokine receptors that trigger cellular responses to external stimuli. When cytokines bind to their receptor, transduced signals lead to changes in gene expression, release of inflammatory mediators and other

reactions. Type 2 inflammatory responses prominently feature MCs and eosinophils and are defined by production of the cytokines IL-4, IL-5 and IL-13. The IL-4 receptor is constitutively expressed on eosinophils. A study by Wedi *et al.* reported that IL-4 may participate in inflammatory resolution by inhibiting eosinophil survival by promoting apoptosis [81]. In MCs, IL-4 priming enhances IL-13 and histamine production following IgE-dependent activation [82,83]. A study by Oskeritzian *et al.* found that MCs cultured with recombinant IL-4 experienced increased apoptosis [84]. The receptor for IL-5 is a heterodimer complex which consists in a unique α subunit, required for signaling, and a common β subunit shared with IL-3 and GM-CSF receptors, that regulates binding affinity [85]. Human eosinophils express IL-5R throughout development and maturation [86] and both IL-5 and its receptor have been successfully targeted in several clinical trials utilizing anti-IL-5 antibodies i.e. reslizumab [87], mepolizumab [88] and benralizumab, the latter unique since it specifically targets the IL-5 receptor α subunit with an antibody engineered to have enhanced antibody-dependent cellular cytotoxicity (ADCC) activity [89]. There have been reports that human MCs also express IL-5R; however, its functional role is not yet understood [90]. Of note, Otani *et al.* demonstrated that MCs numbers were reduced in pediatric EoE patients undergoing mepolizumab therapy [91], an effect not observed in mepolizumab-treated adult patients [92]. The most common IL-13 receptor contains α chain 1 and has weak binding capacity that is strengthened upon formation of a heterodimer complex with IL-4Rα [93]. Human eosinophils express low levels of IL-13Rα1, which can be upregulated by TGFβ or IFNγ [94]. Human lung MCs and the immature MC line HMC 1.1 also express IL-13Rα1. MCs primed with IL-13 display increased FcεRI expression and proliferation [45,95].

Together with FcεRI, c-kit is a particularly important receptor on MCs playing a central role in their differentiation, regulation of cell growth, priming and chemotaxis. It is a type 3 tyrosine kinase receptor, which in humans exists in four different isoforms [96]. It is expressed by a variety of cells including mature MCs during homeostasis and inflammation. SCF is the high-affinity ligand of c-kit. Interestingly, SCF can be released by eosinophils via a mechanism involving MC-derived chymase [97], highlighting the importance of MC-eosinophil crosstalk (i.e. the allergy effector unit, AEU [98,99], discussed in detail below). Eosinophils have also been shown to express c-kit, where it is suggested to have a role in promoting cellular adhesion [100]. In disease, c-kit is involved in cancer and asthma. Activating mutations in c-kit, especially the D816V mutation, is the main cause of systemic mastocytosis, which involves widespread proliferation and accumulation of MCs in numerous organs [101,102]. Of note, mutations of c-kit have also been found in patients with hypereosinophilic syndromes [103]. Additionally, imatinib, a tyrosine kinase inhibitor mostly used to treat leukemias and some forms of hypereosinophilic syndromes, has recently been shown to modestly decrease MC numbers and airway hyperresponsiveness in patients with severe asthma [104].TSLP signaling is associated with many MC and eosinophil prominent diseases. Receptors for TSLP are heterodimeric complexes that consist in TSLPRα chain and IL-7 receptor α chain [105]. TSLP is released from stimulated epithelium and mediates MC-driven type 2 inflammation in response to physical trauma or allergen exposure [106,107]. Of note, activated MCs can also produce TSLP [108]. In eosinophils, expression of TSLPR is elevated in the presence of IL-3 or TNFα [109]. TSLP promotes eosinophil survival, adhesion

and release of eosinophil-derived neurotoxin (EDN), IL-6 and several chemokines [110]. Tezepelumab (AMG-157), an anti-TSLP monoclonal antibody, has been successful in improving lung function in mild asthmatic patients [111] and decreasing the number of asthma exacerbations, blood eosinophil levels and total serum IgE in subjects with moderate-to-severe asthma [112]. Additionally, the finding that Tezepelumab attenuated both the early and late phase response to inhalational allergen challenge in humans implies potential effects of TSLP antagonism on both eosinophils and MCs [111].

Another important cytokine receptor expressed by both MCs and eosinophils is the IL-33 receptor, interleukin-1 receptor-like 1 (IL1R1, commonly called ST2). This receptor also exists as soluble ST2 (sST2) upon differential splicing of the ST2-encoding gene [113,114]. ST2 is expressed by MCs, independent of maturation status, and IgE/allergen activation or IL-33 stimulation induces sST2 production [115,116]. In mice, IL-33-dependent MC activation triggers release of many pro-inflammatory mediators including IL-1β, IL-6, IL-13, TNFα, CCL2 and PGD2 [117,118]. IL-33 can induce secretion of IL-5, IL-6, IL-13 and TNFα from human MCs, an effect that can be enhanced by TSLP [119]. MCs do not only respond to IL-33, but can produce it upon IgE/allergen activation in a calcium-dependent manner [120,121]. Eosinophils also express ST2 and respond to IL-33, but by producing superoxide anion [122]. IL-33 is necessary for eosinophil hematopoiesis, homeostasis and promotes cell survival via the MyD88 pathway [18,123]. IL-33 promotes eosinophil-mediated inflammation and our lab has recently demonstrated that Siglec-8 engagement on IL-33-primed eosinophils results in apoptosis [68,124]. Lately it has been shown that eosinophil progenitors express a functional IL-33 receptor capable of producing pro-inflammatory cytokines at levels that far surpass those observed in mature eosinophils [125].

3.3 Cell migration

Integrins are a family of heterodimeric transmembrane cell adhesion receptors composed of α and β subunits. In humans, 18 α subunits and 8 β subunits can differentially combine to form at least 24 receptors [126,127]. Ligation of integrin receptors modulates a variety of cellular responses including proliferation, degranulation, survival and cell motility. Integrin actions via the cytoskeleton drive vascular adhesion, endothelial transmigration and other aspects of cell trafficking and extravasation. Inflammatory pathways often feature α4 integrins. For example, the α4β1 integrin, or very late antigen-4 (VLA-4), is expressed by MCs and eosinophils [128,129] and binds VCAM-1 and fibronectin [130] to promote eosinophil migration and extravascular accumulation, and contributes to the perivascular localization of MCs [131–133]. Another α4 integrin expressed by eosinophils and MCs is α4β7, which binds mucosal addressin cell adhesion molecule 1 (MAdCAM-1) and VCAM-1 and is important for homing of cells to mucosal tissues such as the intestine [134–137]. Recent studies have shown that β2 integrins are necessary for release of granule proteins and cell death [66,138] and can mediate eosinophil-MC crosstalk through their activation on MCs by eosinophil-produced major basic protein-1 (MBP-1) [139].

Prostaglandin D2 (as described below) is a pro-inflammatory mediator with a role in allergic responses. Its high affinity G-protein coupled receptor, CRTH2, is expressed by eosinophils. Activated MCs are a major producer of PGD2, which promotes eosinophil recruitment and

activation [140–142]. Eosinophils can also produce PGD2 but at much lower levels per cell [143]. Recent studies have reported that MC CRTH2 expression is internal [144] so its function is still unknown. It is worth noting that small molecule CRTH2 antagonists are showing some promising efficacy in early clinical trials [145–148].

Anaphylatoxins C3a and C5a are produced following activation of the complement system, and both eosinophils and MCs can respond to these proteins via expression of C3aR and C5aR. In eosinophils, C3a and C5a can trigger an increase in intracellular Ca^{2+} and release of reactive oxygen species (ROS) [149]. Furthermore, they promote eosinophil rolling and adhesion and C5a influences eosinophil transmigration, integrin expression and superoxide anion production [150,151]. Complement proteins C3a and C5a are also MC chemotaxins. Interestingly, C3a is more effective than C5a at recruiting MCs and can also stimulate production of CCL2 and CCL5, which have been shown to be important for early inflammatory responses [152–155]. Recently another receptor for C5a was described in MCs, called C5aR2, which can stimulate release of certain cytokines, namely TNF, GM-CSF, CCL2 and CXCL10, and can mediate chemoattractant functions [156]. While C5aR2 is expressed by mouse eosinophils, its expression in humans is unknown [157].

Sphingosine-1-phosphate (S1P) is important for cell trafficking, proliferation and survival responses. Crosslinking of high affinity FcεRI on MCs by IgE activates sphingosine kinases (SphK) that produce S1P, whose pleiotropic properties can be attributed to the fact that S1P binds to 5 different G-protein coupled receptors [158]. MCs express S1PR1 and when activated it promotes MC movement. S1PR2 activation halts MC movement and initiates degranulation and release of pro-inflammatory mediators [159,160]. The MC/S1P/S1PR2 axis was recently shown to be crucial for propagating early inflammatory responses in murine models of pulmonary and cutaneous allergic responses [154,155]. Additionally, S1PR2 ligation leads to production of tissue remodeling matrix metalloproteinase-2 (MMP2) and vascular endothelial growth factor (VEGF)-α from human MCs [161]. Eosinophils express S1PR1, 3, 4 and 5 and can therefore be recruited to inflamed tissues by MCs and other S1P-producing cells. Eosinophil chemotaxis towards S1P can be abrogated in the presence of the S1P receptor antagonist FTY-720, which has pharmacologically significant affinity for all S1PR except S1PR2 [162].

Histamine is another MC-produced mediator that stimulates eosinophil recruitment through G-protein coupled histamine receptors [163]. For eosinophils, histamine can act as a chemoattractant through H1R [164] and inhibit chemotaxis through H2R (when histamine concentration is high) [165]. Histamine influences eosinophil adhesion, Ca^{2+} mobilization and cytoskeleton rearrangement via H4R [166,167]. MC-expressed H4R regulates calcium mobilization and release of inflammatory mediators [168]. Studies in mice found that antagonism of H4R resulted in inhibition of IgE-induced upregulation of FcεRI, suggesting H4R regulates FcεRI expression and function [163] andH4R antagonists have been shown to reduce histamine-mediated pruritus [169] in AD patients [170]. In addition to H4R, human skin MCs express H2R, which negatively regulates histamine production, while H1R is expressed on HMC-1 cells [171].

Cannabinoid receptors exist as part of the endocannabinoid system and respond to endogenous ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG). There are 2 distinct cannabinoid receptors CB1 and CB2, and while AEA can bind to both, 2-AG is a specific agonist of CB1 expressed by cells of the nervous system. MCs express both CB1 and CB2 (Samson, 2003), while eosinophils and most immune cells express CB2 alone (Oka, 2004). Studies have shown that 2-AG acts as a chemoattractant for peripheral blood eosinophils [172], increasing their migration towards inflamed tissues [173].

3.4 Toll-like Receptors and others

Toll like receptors (TLRs) are important for pathogen recognition for innate and adaptive immunity [174,175]. Both human MCs and eosinophils express TLRs 1–10, except TLR 8. Studies show contradicting evidence of TLR expression on both MCs and eosinophils as sometimes mRNA is expressed that does not translate to protein production (reviewed in [176,177]). MCs and eosinophils respond to different TLR ligands, such as LPS and flaggelin which bind TLR-4 and TLR-5 respectively (reviewed in [176,177]). Levels of TLR2 and TLR3 are elevated in the epithelium in fatal asthma specimens, suggesting that they may contribute to disease severity. Moreover, in asthma eosinophil density has been negatively correlated with TLR2 and TLR4 levels, while TLR3 seems to promote eosinophil numbers [178].

CD48 and 2B4 are receptors belonging to the CD2 family that are expressed on MCs and eosinophils. They are rather unique because they are high-affinity ligands for each other. CD48 is a GPI-anchored activating receptor, present in two forms: membrane associate (mCD48) and soluble (sCD48). 2B4 (CD244) is a SLAM family receptor and a CD2-like cell surface protein. CD244 is not expressed on human MCs, but is expressed on murine MCs where it has inhibitory activity. It was shown to have an activating effect on both murine and human eosinophils [179]. Triggering of the CD48 on MCs and eosinophils induces activation (186, 188). *S. aureus* can activate MCs through CD48, causing bacterial uptake and TNF-α release [180], and on eosinophils, causing increasing of CD48 expression,the release of granular proteins, and of cytokines (188). CD48 expression is increased on both peripheral blood and bronchial eosinophils in asthma patients [181]. CD48 on eosinophils from the skin of atopic dermatitis patients is upregulated as well [182]. Activation of CD244 on eosinophils contributes to cell adhesion and migration [183] and induces degranulation [72]. I*n vivo* activation of human eosinophils by the *S. aureus* endotoxin B (SEB) leads to the formation of sCD48 and upregulates transcription of CD48 [182,184]. Interactions between CD48 on MCs and CD244 on eosinophils are an important part of the physical formation of the AEU and its pro-inflammatory properties. The AEU comprises physical and soluble interactions between MCs and eosinophils that promotes their survival and activation and can augment the intensity and duration of allergic inflammation (reviewed in [185]). The importance of CD48 and CD244 in the AEU and in the interactions of MCs and eosinophils with *S. aureus* highlight the potential importance of these receptors in allergic inflammatory diseases in which there is superinfection with *S. aureus* [186].

4 Mediators released upon activation

4.1 Cytokines and chemokines

MCs and eosinophils can both store and synthesize *de novo* a wide array of cytokines, chemokines, eicosanoids, lipids and other inflammatory mediators. Cytokines and chemokines are most often released upon cell activation during the process of degranulation. The main mechanism for the release of these mediators from MCs is via antigen/allergen cross-linking of IgE receptors [144]. Eosinophils on the other hand can release GM-CSF, IL-2, IL-10, IL-12, IL-13, RANTES (CCL5) and eotaxin (CCL11) among others [187], upon their activation [187] by Th2 cytokines such as IL-5 [188]. Notably, some mediators are produced by both MCs and eosinophils, such as SCF, IL-4, IL-5, IL-6 and TNFα, although quantities released per cell vary and can often be quite small [187,189,190]. The evidence that MCs and eosinophils release some common cytokines and chemokines points out their shared capacity to influence similar pathophysiological processes and even each other via paracrine mechanisms. MCs store and release preformed TNFα [191]. Eosinophils, on the other hand, do not store TNFα, but can synthesize it once activated [192]. Moreover, since both MCs and eosinophils produce TNFα, they can potentially be important regulators of carcinogenesis since TNFα has cytotoxic and cytostatic effects against tumour cell lines [193]. IL-4 is another key cytokine of Th2-driven immune responses that, together with SCF, can regulate MC proliferation and cytokine production [194]. Eosinophil-derived IL-4 may therefore be important for MC regulation. Interestingly, recent studies have highlighted the importance of the eosinophil/IL-4 axis in limiting obesity in mice by promoting adipocyte beiging (i.e. a healthy and lean phenotype) through activation of M2 macrophages [195–197]. IL-5, the main cytokine regulating eosinophils [198], can be produced by MCs, and it has been reported that PrMCs express IL-5R [90], suggesting that this mediator could be involved in the mutual regulation of these two cells.

4.2 Eicosanoids

Prostaglandins are arachidonic acid derivatives produced by the activity of phospholipase A2 and cyclooxygenase enzymes (COX 1 and 2) from membrane phospholipids. MCs and eosinophils have both COX 1 and 2 and release prostaglandins within seconds following their activation. MCs are the main producer of PGD2 involved in allergic reactions [199]. It is produced from PGH_2, synthesized by COX 1 or 2, which is converted into PGD_2 via PGD_2 synthase [200]. Moreover, since activated MCs are the primary source of PGD_2, this mediator and its metabolites are used as biomarkers for those pathologies characterized by activation of MCs, such as mastocytosis [201] and asthma, in which there is enhancement of the PGD_2 pathway [202]. Eosinophils can also produce PGD_2, but in quantities that are much lower than for MCs [143], thus their contribution of PGD_2 in disease seems less likely. PGD_2 exerts its biological effect via DP1 and DP2/CRTH2, both G-protein coupled receptors (GPCRs) [144]. On MCs, PGD_2 triggers the synthesis of Th2 mediators through DP1 [203], while the functions of CRTH2 receptor on MCs are controversial [144]. On eosinophils, DP1 and CRTH2 have some overlapping and cooperative functions, since both receptors are able to induce the egress of eosinophils from bone marrow, and mediate chemotactic activity and production of leukotriene C4 (LTC4) [204]. In asthma models, PGD_2 activation of eosinophils increases their

degranulation, mobilization and recruitment in the lungs through CRTH2. Currently, a CRTH2 antagonist, fevipiprant, is being tested in advanced clinical asthma trials [205,206].

Leukotrienes (LTs) are also rapidly synthesized and released following MC and eosinophil activation [207]. The main leukotrienes produced by MCs and eosinophils are products of lipoxygenase 5 activity on arachidonic acid and they comprise the cysteinyl leukotriene (CysLT) LTC_4 and LTB_4. LTC_4 is formed via the addition of a molecule of glutathione to LTA_4. LTC_4 is then transported outside of the cell where it can be converted to LTD_4 and then to LTE_4 by specific enzymes [208]. Receptors for CysLTs are GPCRs called $CysLT_1R$ and $CysLT_2R$. These receptors are expressed on eosinophils and MCs [209]. Recently it was found that an ADP receptor, $P2Y_{12}$, on LAD-2 MCs can also function as a receptor for LTE_4, with powerful pro-inflammatory effects [210]. On MCs, CysLTs trigger activation and induce proliferation and cytokine secretion [209]. LTC_4 and LTD_4 have been shown to increase Ca^{2+} influx in MCs [211], enhance cytokine production [212] and, together with LTE_4, increase MC proliferation [213]. On eosinophils, CysLTs induce chemotaxis, migration and secretion of mediators; moreover, binding of $CysLT_1R$ can increase survival of eosinophils. While MCs and eosinophils are important sources of CysLTs, LTB_4 is mainly produced by neutrophils and macrophages, with MCs and eosinophils producing only modest quantities [214]. The effects of LTB_4 are mediated by two GPCRs, BLT1 and BLT2, expressed on human HMC-1 and perhaps normal MCs, while human eosinophils express only BLT1 [209]. On eosinophils, binding of LTB_4 to BLT1 induces their recruitment and chemotaxis; on MCs, both receptors induce chemotaxis and migration in a dose-dependent fashion [215]. Given the relevance of leukotrienes and their receptors in inflammation, antagonists of CysLT1R have been developed for treatment of asthma [210] as well as drugs that target 5-lipoxygenase and thereby inhibit the synthesis of multiple leukotrienes [216].

4.3 Reactive oxygen species

Reactive oxygen species (ROS) include hydrogen peroxide (H_2O_2), nitric oxide (NO) and others [217,218]. The primary role of ROS in inflammation is probably to eradicate invaders through their toxic effects [218,219]. Both human MCs and eosinophils can produce ROS upon IgE-dependent activation and by activation of FcγR, Siglec-8 or other receptors, respectively [66,149,220,221]. ROS plays a role in the regulation of airway inflammation and remodeling by MCs, through their involvement in the VEGF production cascade [222]. Unlike MCs, ROS production in eosinophils is involved in the resolution of inflammation. In a preclinical model of asthma, mice with decreased ability to produce ROS showed no resolution compared to WT mice where resolution was observed regularly after 72h [218]. Mice treated with H_2O_2 showed decreased allergic inflammation [218], and death induced by Siglec-8 activation in cytokine-primed eosinophils is completely dependent on internal ROS generation [66]. The opposite effects of ROS production by MCs and eosinophils are interesting and raise questions about the possible effect of treatment with ROS scavengers.

4.4 Histamine

MCs, together with basophils, are the only eukaryotic cell sources of preformed histamine that they release promptly upon activation [223]. Histamine is involved not only in allergy and anaphylaxis, but it is also important for immunomodulation, cell proliferation, wound

healing, neurotransmission, stimulation of gastric secretion, regulation of blood pressure and perception of pain [224]. There are four receptors for histamine, H1-4R, some of which are expressed on MCs and eosinophils (discussed above and in another review of this series).

5 Mast cells and eosinophils in allergic disease

5.1 Atopic dermatitis

Atopic dermatitis (AD) is a chronic eczematous disease characterized by itchy, dry and inflamed skin, which affects 10–20% of the world's population including both adults and children [225]. MC and eosinophil activation is a main characteristic of this disease. AD is often the first manifestation of allergies and is considered the first step in the atopic march because affected individuals are likely to develop other allergies such as asthma or rhinitis [226]. Mutations in *FLG*, the gene encoding human filaggrin, are the most known and accepted risk factor for genetic predisposition of AD. Filaggrin is a protein involved in maintenance of the epidermal architecture and keratinocyte development. Thus, mutations in this gene can disrupt the structure of the skin barrier, resulting in increased sensitivity to allergens [226]. Interestingly, skin barrier impairment correlates with infections from *S. aureus* [227], a main player in AD, by producing toxins such as enterotoxin A, B, C, D, etc., which can act like superantigens [224,228,229]. Activated MCs are found in AD lesions and eosinophils can be activated by *S. aureus* directly via TLRs or CD48 [180,182]. MCs are in part responsible for the itching and skin dryness experienced by AD patients due to their release of histamine, tryptase and other pro-inflammatory mediators [230]. Moreover, MCs produce IL-4 and IL-13, which promote eosinophil recruitment, via stimulation of chemokine production from keratinocytes and fibroblasts. Eosinophils recruited to AD lesional skin by MCs, once activated discharge several mediators that contribute to AD symptoms. For example, ECP, EDN and MBP have the ability to increase permeability of blood vessels and neurotoxic properties, while chemokines such as CCL11 can increase eosinophil recruitment [226].

5.2 Asthma

Atopic asthma is characterized by allergic, eosinophilic inflammation (reviewed in [231]). One of the main players in the development of atopic asthma are MCs, which have a central role in eliciting the early asthmatic reaction and also contribute to the late phase, likely due to production of substances such as cytokines, chemokines and arachidonic acid metabolites. Even though the number of airway MCs of atopic and non-atopic patients is similar to what is observed in healthy controls, the density of FcεRI on MCs is increased, probably due to the presence of higher levels of serum IgE. The fact that omalizumab can effectively reduce exacerbations further supports the role of MCs in late-phase responses (reviewed in [232]). Moreover, MC-derived substances contribute to the recruitment of other immune cells such as lymphocytes, macrophages and eosinophils [190]. The release of mediators such as histamine, PGD_2, LTC_4, cytokines and others by MCs contribute to bronchoconstriction, mucus secretion and mucosal edema [232]. The role of eosinophils in asthma, via release of granule proteins and other substances, is probably multifactorial (reviewed by [198]). Based on clinical trials employing eosinophil targeting agents anti-IL-5 and anti-IL-5R, the most consistent finding is that of ≈50% reduction in asthma exacerbations, with little to no effect on lung function or airways hyperreactivity [233]. The notable role of MCs and eosinophils in

asthma makes them useful as biomarkers for diagnosis and treatment. For example different eosinophil and MC products, including Charcot-Leyden crystal protein and carboxypeptidase A3 respectively, have the potential to predict patient responses to oral corticosteroids treatment [234]. Patients who successfully respond to treatment have high levels of these proteins initially, which decrease following treatment [234]. Another possible marker for asthma is CD48 expressed by MCs and eosinophils. Moderate asthma patients exhibit increased CD48 compared to healthy controls, while CD48 levels in patients with severe asthma are decreased compared to moderate asthma patients. In contrast, sCD48 levels were higher in patients with mild asthma compared to control and decreased levels were detected in moderate patients compared to mild and even lower levels in patients with severe asthma [181]. More studies are needed to provide the ideal combination of biomarkers to direct asthma care.

5.3 Rhinitis

Allergic rhinitis, or hay fever, manifests as inflammatory conditions that affect the nasal mucosa, usually accompanied by sneezing, itching, watery discharge and/or blockage [235]. Approximately 10–40% of the population within industrialized countries, including 8–15% of children, experiences these symptoms. Episodes usually occur seasonally or perennially in geographical regions with defined seasons, but inflammation and symptoms can exist year-round in situations where continual exposure to allergens such as dust mites and pet dander are relevant. The nasal cavity is lined with epithelium that forms a barrier between the environment and underlying tissues. This epithelial layer comprises basal cells, ciliated cells, and mucus-producing goblet cells and is protective against external allergens (e.g. pollens, molds and others) [236]. Epithelial cells play a key role in the pathogenesis of rhinitis, initiating type-2 inflammatory responses through secretion of TSLP, IL-25 and IL-33 [237,238]. Release of these inflammatory mediators can trigger production of IL-5 and IL-13 from ILC2s, directly and indirectly affecting eosinophils and MCs. Human studies have identified MCs as major effector cells driving early inflammatory responses following activation through their high-affinity IgE receptor, FcεRI [239]. Eosinophils, however, are among the initial cells recruited to the nasal mucosa during the late or chronic phase of inflammation [240,241]. Eosinophil activation following nasal allergen challenge was reported by Bascom *et al.* through the detection of eosinophil-derived proteins (MBP and ECP) in nasal fluids [242]. Kountakis *et al.* found that the presence of nasal polyps, often a feature of chronic rhinitis, correlates with increased eosinophil activation and more severe clinical features [243]. In some patients, eosinophils can make up 20% or more of total cell counts in nasal smears [244].

5.4 Food allergy and eosinophilic gastrointestinal disorders

Food allergies have recently gained a great deal of attention as the leading cause of anaphylaxis in the United States. Approximately 8% of children and 2–3% of adults are affected by food allergies [245,246]. Common allergens include wheat, egg, shellfish, peanuts, tree nuts, soy and cow’s milk. Adverse reactions to food can be classified as food intolerance, a reaction that may not be reproducible and is usually dose-dependent, or food allergy that is reproducible. Patients with food allergies can be further classified into 3 sub-categories: 1) IgE-mediated, 2) cell-mediated, or 3) IgE and cell-mediated. There has been a steady increase in the number of individuals affected by food allergies, particularly in the

last 20 years. Generally, symptoms of food allergy and anaphylaxis appear very soon after food consumption and can include urticaria, wheezing or coughing, nausea, vomiting and/or diarrhea, and in extreme cases, hypotension and even death. Whether such immediate reactions are due to MCs activation in tissues, as opposed to basophil activation in the circulation, cannot be easily determined, but in mouse models these are primarily MC-dependent reactions.

Histamine and tryptase levels in the blood can both increase during food-induced anaphylaxis, directly implicating MCs in food allergy [247]. Furthermore, platelet activating factor, which has been linked to disease severity, can also be produced and released by MCs [247]. MC activation through IgE had been linked to IL-9 and IL-33 production, both of which have been shown to play a role in disease pathogenesis. Eosinophils are more predominantly featured within the inflamed GI tract of patients with non-IgE mediated food allergies (e.g. eosinophilic esophagitis, EoE) [245]. EoE features include painful swallowing (dysphagia) and sometimes food impaction. More common in males, EoE is predominantly associated with non-IgE-mediated hypersensitivity to foods [245]. Inflammation is primarily driven by eosinophils but also MCs and is defined by presence of at least 15 eosinophils/HPF in biopsy sections [248]. The EoE transcriptome was described, with CCL26 (eotaxin-3), an eosinophil chemoattractant, being the most highly induced gene [249]. Of note, CD11c, CRTH2, ICAM-1 and the low affinity IgE receptor FcεRII (CD23) are also upregulated on eosinophils in EoE [250,251]. As mentioned, MC_T are elevated in esophageal tissue of EoE patients compared to healthy controls [252]. Surprisingly, MCs may also drive the pathophysiology of EoE as Omani *et al.* demonstrated that MC numbers were attenuated within a group of pediatric EoE patients undergoing anti-IL-5 treatment [91]. They also discovered that both eosinophils and MCs were producing the MC growth factor IL-9 and that MC numbers correlated with disease severity [91].

5.5 Urticaria

Urticaria, or hives, occurs in 15–25% of the population sometime during their lifetime and is characterized by pruritic lesions containing a pale center also known as a wheal with surrounding redness known as a flare [253]. Associated inflammation can be acute, but nearly 30% of urticaria patients experience chronic lesions defined by recurrent episodes for at least 6 weeks [253]. While urticaria can result from physical stimuli (i.e. temperature or direct stroking of the skin), non-physical cases are often categorized as autoimmune or most commonly idiopathic [254]. MCs are considered a primary effector cell responsible for initiation of inflammation, in part due to release of histamine and cell-recruiting chemokines. While the exact contribution and trigger of MCs in urticaria remains controversial [255,256], it has been shown that histamine release correlates with an autoimmune phenotype [254]. Recent guidelines agree that anti-histamines are the mainstay of initial treatment for chronic urticaria, even though responses can vary [257]. Omalizumab, an anti-IgE monoclonal antibody, is another approved treatment option that is effective in over 60% of antihistamine-refractory patients [258]. Eosinophils also participate in chronic urticaria, primarily in patients lacking an autoimmune component, and accumulate in urticarial lesions where MBP and ECP can also be detected [259]. Marques *et al.* recently conducted a study

where they found that tissue eosinophilia was linked to disease severity in patients with chronic urticaria [260].

6 Mast cells and eosinophils during bacterial, viral and parasitic infections

Beyond their involvement in allergic inflammation, MCs and eosinophils also serve a protective role during infection and host defense against viruses, bacteria and parasites. MCs and eosinophils are uniquely placed at the interface between the outer environment and tissues, allowing for their response to penetrating pathogens via production of immunoregulatory mediators. Eosinophils can also be recruited by activated MCs in inflamed tissues.

The role of MCs in viral infections is still poorly understood. However, it is known that some viruses, such as HIV, respiratory syncytial virus (RSV) and Dengue virus, can infect MCs [261–263] and remain latent. Troupin *et al.* recently demonstrated that Dengue virus can directly induce degranulation in human skin MCs. Furthermore, they found that the virus localized to MC secretory granules rendering them infectious, suggesting that MCs are key players in the systemic spread of Dengue [263]. Eosinophils can recognize viruses via TLRs and release their mediators after activation. The mechanisms through which eosinophils promote antiviral effects are still unclear, but it is known that eosinophils cannot propagate viruses after being infected and eosinophil-derived nitrous oxide can inhibit viral proteases and alter host cell functions by promoting nitrosylation of thiol and tyrosine groups, which can impair the protein and RNA synthesis [264]. Ribonuclease activity in certain eosinophil granules may also be antiviral [187,264]. The role of MCs and eosinophils in viral defense still needs clarification, but the finding that reductions of eosinophils via biological therapies do not appear to increase risk of infections is reassuring.

MCs and eosinophils are also participants in fungus-associated inflammation. For example, MCs express PRRs specific for fungi, including *Aspergillus* and *Fusarium* species, highlighting their capacity to mediate antifungal responses [265]. Some fungi can also infect MCs. *Candida albicans* can induce MCs degranulation, triggering production of pro-inflammatory cytokines. Interestingly, *C. albicans* can also be internalized by MCs, where it is able to grow and germinate leading to disruption of MC membranes and ultimately cell death [266]. Eosinophils can directly interact with β-glucans, a component of fungal cell walls, via CD11b integrin [267]. This interaction leads to eosinophil activation and release of granule proteins resulting in fungal cell death [267]. Alternatively, eosinophils can be activated via proteinase-activated receptors (PARs) [268], or by products released by fungal cells [269].

Besides allergies, MCs and eosinophils are most well known for their roles in parasitic infections. When MCs recognize parasites, they form clusters around them and become activated [270], leading to release of parasite-killing mediators and tissue damage [271]. For example, histamine released by activated MCs during *P. falciparum* infection, initiates inflammatory responses and increases vascular permeability and associated damage, driving the pathogenesis of malaria [271]. During infections from *T. cruzi,* the number of MCs, and levels of MC-derived mediators such as chymase, is increased in the myocardium of patients with Chagas disease, resulting in myocardial fibrosis [271]. During helminth infections, MCs

accumulate at sites of infestation where they are involved in initiating Th2 responses, contributing to helminth expulsion [270]. However, the majority of studies focusing on the role of MCs in helminthic infections are conducted in rodents, thus more studies should aim to focus on human infections to better understand the specific contribution of MCs. Helminthic infections are also characterized by high IgE production and marked blood and tissue eosinophilia [272]. Comparable to MCs, eosinophils can form aggregates around parasites and kill them by ADCC [273] or through the release of granule proteins and ROS production [272]. In contrast, there may be situations where eosinophils may instead benefit parasitosis and be detrimental to host cells and tissues [274], since their granule proteins and other mediators have strong cytotoxic activity [272].

In addition to viral, fungal and parasitic infections, MCs and eosinophils may be involved in bacterial immune responses. Eosinophils granule proteins EPO, ECP and MBP-1 are toxic to microorganisms. For example, ECP can reduce bacterial survival following recognition of LPS and/or peptidoglycans. EPO can generate ROS, leading to the production of hypohalous acids, with bactericidal activity [275]. Both MCs and eosinophils are capable of direct and indirect killing of microbes via phagocytosis or enzymes or by recruiting other immune cells. Bacteria can trigger MC degranulation and/or selective cytokine release via pattern recognition receptors (PRRs), such as TLRs, Fc receptors, Nod-like receptors, C-type lectins, and CD48, [276]. Furthermore, MC granules contain tryptase and chymase proteases that contribute to microbial killing [277]. Eosinophils exhibit phagocytic activity, and both MCs and eosinophils can release their DNA to create traps [187,278,279]. Whether the successful targeting of MCs and eosinophils will result in increased risks of developing parasitic or other infections remains to be seen.

7 Conclusions

MCs and eosinophils are complex immune cells that develop and function similarly in many ways. They can be beneficial when protecting us from pathogens, but they can also be detrimental in when activated inappropriately. They have overlapping immunomodulatory roles in both acute and chronic inflammation and can help orchestrate recruitment of other cells through release of pre-stored mediators, with the added capacity to synthesize additional mediators *de novo*. Within recent decades, the percentage of individuals affected by allergies has steadily increased and several MC/eosinophil-targeting biologics have been approved for use in allergic individuals in the last five years. These drugs are quite effective in select patient cohorts, but they are quite expensive, do not work in everyone and can have undesirable side effects. Thus, it is important to continue studying these cells, especially in humans, because they do vary in important ways from their rodent counterparts. Ultimately, an improved understanding of these closely related cells and their roles in homeostasis, and in both favorable and unfavorable immune responses, should allow us to best determine when targeting of these cells is warranted or best avoided to maintain optimal health.

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Table 1

Comparison of a broad selection of cell surface molecules expressed by mast cells and eosinophils.

		Mast Cells	Eosinophils
Fc Receptors	FcγRI (CD64)	+ [30,31]	—
	FcγRII (CD32)	+ [32,33]	+ [34–37]
	FcγRIIa	+ [32,39]	+ [39]
	FcγRIIb	+ [40,41]	—
	FcγRIII (CD16)	—	+ [42–44]
	FcεRI	+ [45–49,51–53,280]	—
	FcεRII (CD23)	—	+ [57]
	FcαRI	—	+ [59,60]
Siglecs	Siglec-2	+ [61]	—
	Siglec-3	+ [61]	+ [281]
	Siglec-5	+ [61]	—
	Siglec-6	+ [61]	—
	Siglec-7	+ [62]	+ [281]
	Siglec-8	+ [61,64,67]	+ [64–66,68]
	Siglec-10	+ [61]	+ [69]
CD300 Receptors	CD300a	+ [70,71]	+ [72]
	CD300c	+ [73]	—
	CD300f	+ [75,77]	+ [75,76]
Leukocyte Ig-like Receptors (LILR)	LILRA1	+ [80]	—
	LILRA2	—	+ [79]
	LILRB1	+ [80]	+ [79]
	LILRB2	+ [80]	+ [79]
	LILRB3	+ [80]	+ [79]
	LILRB4	+ [80]	—
	LILRB5	+ [80]	—
Cytokine Receptors	IL-4R	+ [82–84]	+ [20,81]
	IL-5R	± [90]	+ [19,86]
	IL-13Rα1	+ [45,95]	+ [94]
	c-kit (CD117)	+ [96,101,102]	+ [100]
	TSLPR	+ [106,107]	+ [109,110]
	IL1RL1 (ST2)	+ [115–119]	+ [18,68,122–125]
Migratory Receptors and Others	α4β1 integrin (VLA-4)	+ [129,131]	+ [128,132,133]
	α4β7 integrin	+ [131,134,135,139]	+ [66,136–138]
	CRTH2	± [144]	+ [140–142]
	C3aR	+ [152,153]	+ [149,150]

		Mast Cells	Eosinophils
	C5aR	+ [152]	+ [150,151]
	C5aR2	+ [156]	± [157]
	S1PR1	+ [159]	+ [162]
	S1PR2	+ [154,155,159–161]	—
	S1PR3	—	+ [162]
	S1PR4	—	+ [162]
	S1PR5	—	+ [162]
	H1R	+ [171]	+ [164]
	H2R	+ [171]	+ [165]
	H4R	+ [163,168]	+ [166,167]
	CB1	+ [282–284]	—
	CB2	+ [283]	+ [172,173]
	TLRs	± [176,177]	± [176,177]
	CD48	+ [180]	+ [181,182,184]
	2B4 (CD244)	± [98]	+ [72,179,183]

Abbreviations: Immunoglobulin (Ig) G receptor (FcγR), IgE receptor (FcεR), IgA receptor (FcαR), (Sialic acid-binding Ig-type lectin (Siglec), Leukocyte Ig-like receptor (LILR), Interleukin 1 receptor-like 1 (IL1RL1), Prostaglandin D2 receptor 2 (CRTH2), Sphingosine-1-phosphate receptor (S1PR), Histamine receptor (HR), Cannabinoid receptor (CB), Toll-like receptor (TLR), Natural killer cell receptor (2B4).