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Emerging Role of Human Basophil Biology in Health and Disease

Jessica L. Cromheecke, **Kathleen T. Nguyen**, and **David P. Huston**
Departments of Microbial Pathogenesis & Immunology and Medicine, Texas A&M College of Medicine; Clinical Science and Translational Research Institute, Texas A&M Health Science Center; 2121 West Holcombe Boulevard, Houston, TX 77030, USA

Abstract

Basophils have emerged in recent years as a small but potent subpopulation of leukocytes capable of bridging innate and adaptive immunity. They can be activated through IgE-dependent and IgE-independent mechanisms to release preformed mediators and to produce Th2 cytokines. In addition to their role in protective immunity to helminths, basophils are major participants in allergic reactions as diverse as anaphylaxis and immediate hypersensitivity reactions, late-phase hypersensitivity reactions, and delayed hypersensitivity reactions. Additionally, basophils have been implicated in the pathophysiology of autoimmune diseases such as lupus nephritis and rheumatoid arthritis, and the modulation of immune responses to bacterial infections, as well as being a feature of myelogenous leukemias. Distinct signals for activation, degranulation, transendothelial migration, and immune regulation are being defined, and demonstrate the important role of basophils in promoting a Th2 microenvironment. These mechanistic insights are driving innovative approaches for diagnostic testing and therapeutic targeting of basophils.

Keywords

Basophil; Allergy; Anaphylaxis; Autoimmunity; Infection; Malignancy

Introduction

Although basophils comprise less than 1 % of peripheral blood leukocytes, emerging insight into basophil biology demonstrates how potent they are for both effector functions and immune regulation. Historically, basophils were primarily associated with immediate hypersensitivity reactions, based on their cell surface expression of the high-affinity IgE receptor (FcЄ RI) and the release of histamine and other atopy mediators upon FcЄ RI crosslinking [1–3]. However, this perception of limited basophil functionality is changing dramatically, with evidence for their expression of numerous cell surface receptors that, when ligated, are capable of transcriptionally activating basophils to produce cytokines that promote and regulate Th2 adaptive immune responses, making them mechanistically important in late-phase hypersensitivity reactions and delayed hypersensitivity reactions, as

Corresponding author: David P. Huston, M.D.; Vice Dean and Professor, Texas A&M College of Medicine; Director, Clinical Science and Translational Research Institute, Texas A&M Health Science Center, 2121 West Holcombe Boulevard, Houston, TX 77030, USA, dhuston@medicine.tamhsc.edu.

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well as in immediate hypersensitivity reactions [4–28]. There is also evidence that basophils may be important in the pathogenesis of autoimmune diseases [•29–•31], physiologic immune responses to infections [32, 33], and myeloid leukemias [34–38]. Thus, basophils are becoming recognized as a potential target to harness in the therapy of atopy, autoimmunity, and myeloid leukemia [39–42]. Although murine studies have helped elucidate basophil biology, this review will focus on human basophil biology.

Basophil Biology: Origin, Phenotype, and Function

Derived from CD34+ myeloid hematopoietic progenitors in the bone marrow, basophils are phenotypically and functionally distinct from other leukocytes, including mast cells. Although basophils and mast cells do share many characteristics, mast cells reside in tissues whereas basophils reside in the circulation and can be recruited to tissues [11, 17, 43–45]. A key distinction from mast cells is the lack of CD117 (c-kit) expression by basophils and high expression of CD123 (IL-3Rα) by basophils [46]. In vitro derivation of mast cells occurs when CD34+ cells are cultured with stem cell factor (SCF, the ligand for CD117) and IL-6 [47], whereas in vitro derivation of basophils occurs when CD34+ cells are cultured with IL-3 in the absence of SCF [46–•49]. In vivo, basophils enter the circulation with a mature phenotype and survive approximately 5 days [1, •10]. Therefore, the turnover rate is high, with precursor cells constantly being signaled to differentiate into basophils to maintain homeostatic surveillance in the periphery.

Basophils can be morphologically distinguished from other circulating leukocytes by the metachromatic staining of their cytoplasmic granules with Wright Giemsa or Toluidine Blue [7, 50]. Basophils can be phenotypically identified by multi-parameter flow cytometry or immunohistochemistry as FCε RI+, CD 123+, and CD303– (to exclude plasmacytoid dendritic cells) [1, 50–52]. Basophils also express a low level of CD203c, which is increased with basophil activation and may correspond to piecemeal degranulation [9]. CD203c is a glycosylated type II transmembrane molecule that belongs to the family of ecto-nucleotide pyrophosphatase/phosphodiesterase (E-NPP3) enzymes [53]. Basophil activation also induces expression of CD69, while basophil degranulation correlates with expression of CD63 as a consequence of the fusion of the cytoplasmic granule membrane with the cell surface plasma membrane which is termed anaphylactic degranulation [7, 9, 53–56]. CD69 is a member of the C-type animal lectin superfamily that functions as a signal-transmitting receptor, and is expressed on virtually all activated hematopoietic cells [53]. CD63 is a 53-kd tetraspanin family glycoprotein expressed in the membranes of cytoplasmic granules in basophils as well as other granulocytes [16, 55]. Exocytosis leads to fusion of the granule membrane to the cell membrane and hence cell surface CD63 expression where it functions to engage integrins.

Initially, basophils were recognized for their rapid release of histamine and synthesis of leukotriene C4 (LTC4) following crosslinking of IgE bound to their Fcε RI, and subsequently for their synthesis of IL-4 and IL-13 in response to Fcε RI crosslinking [13, 55, 56]. Basophils contain approximately 1 pg of histamine/cell, and can synthesize more IL-4 and IL-13/cell than other leukocytes [•10, 13–16]. Thus, basophils have the ability to bridge innate and adaptive immunity, including the capacity to induce and propagate Th2 immune responses [13–28]. The complexity of basophil activation is further evidenced by their responsiveness to IgE-independent mechanisms involving ligation of toll-like receptors (TLR) 2 and 4, IL-3R, IL-5R, IL-18R, IL33R (ST2), C5aR, leukocyte inhibitory receptors (LIR), chemokine receptor (CCR) 2, CCR3, chemoattractant receptor homologous Th2 (CRTH2), granulocyte macrophage colony stimulating factor receptor (GM-CSFR, CD116), CD32 (FcγRII), CD62L, and CD40L [11, 16, 19, 44, 48, 53, 57–65]. Basophil degranulation is largely restricted to signals induced by Fcε RI crosslinking, or the anaphylatoxin C5a, and

to a lesser extent IL-3 [59–62]. Other IgE-independent stimuli promote production of predominantly Th2 cytokines (IL-4, IL-13, and to a lesser extent IL-5), but these stimuli alone do not induce basophil degranulation [9, 32, 48, 59, 66]. A summary of the functional effects of ligands that can stimulate human basophils is shown in Table 1.

In addition to its role in promoting basophil differentiation, IL-3 is a physiologically important enhancer of basophil responsiveness to agonistic factors and of basophil effector functions [11, 67–69]. In particular, basophil degranulation and Th2 cytokine synthesis in response to FcЄ RI crosslinking is enhanced in the presence of IL-3 [70]. The role of IL-3 in basophil biology cannot be overstated. It is essential for many functions throughout the lifecycle of basophils and serves to promote signaling, growth, and mediator release, and often has enhanced effects when combined with other stimuli. For example, IL-3 is synergistic with IL-33 stimulation of basophil synthesis of Th2 cytokines [71]. The only cytokines reported to negatively regulate basophils are the type 1 interferons which limit IL-3-induced cytokine production, but not FcЄ RI crosslinking-induced degranulation [43]. IgG binding to CD32 can also downregulate basophil responsiveness to FcЄ RI signaling, which has led to novel therapeutic approaches using chimeric molecules that can simultaneously crosslink the FcЄ RI and engage CD32 [72]. Additional stimuli reported capable of activating basophil synthesis of Th2 cytokines include: allergens with endogenous protease activity (i.e., Der p 1), HIV gp120, helminthes (Necator americanus), ligands for TLR 2 and 4, and IgD immune complexes (which also induces basophil secretion of antimicrobial peptides and B cell activating factor) [19, 28, 48, 58, 63, 65, 73, 74].

Recent murine studies have suggested the potential for hematopoietic precursors to differentiate into basophils via an IL-3-dependent pathway and an IL-3-independent, thymic stromal lymphopoietin (TSLP)-dependent pathway [11]. The IL-3-derived basophils have conventional responses to FcЄ RI crosslinking, while TSLP-derived basophils are functionally independent of IgE by virtue of not degranulating in response to FcЄ RI crosslinking, but are able to produce Th2 cytokines in response to IL-3 or IL-33. However, such heterogeneity of basophil development and function has not yet been demonstrated for human basophils. Likewise, murine, but not human, basophils have been reported to produce Th2 cytokines in response to IL-18 [64, 75]. Furthermore, there are conflicting reports as to whether human basophils have the potential to serve as antigen-presenting cells, as has been reported for murine basophils [17–20]. Therefore, the murine data, in the absence of confirmatory human data, should be interpreted cautiously, since genomic responses in mouse models are known to poorly mimic human inflammatory diseases. [•76].

The recruitment of basophils in response to injury, assault, or infection is dependent on both activation and chemotactic factors. IL-3 activation increases basophil expression of CD11b and CD18, thereby potentiating adherence to endothelium [77, 78]. Chemotaxis is mediated predominantly by the CCR3 ligands eotaxin (CCL11) and RANTES (CCL5) [58, 79]. In addition to the constitutively expressed CCR3, basophils also express CCR2 and migrate in response to MCP-1 [79]. Further, basophils can produce chemotactic factors in their microenvironment and further modulate the inflammatory response. Basophils can also release platelet activating factor (PAF) in response to stimulation by IL-3 [78, 80], which then stimulates endothelial cells to increase vascular permeability and allows further migration of immune cells. Activation of TLR 2 and 4 can lead to production of B cell activating factor (BAFF) and IL-13 [63, 65], indicating that the microbiota might modulate immunity by interacting with basophils.

Overall, despite being a minor population of leukocytes, basophils have potent and diverse roles in orchestrating immune responses. Greater elucidation of the mechanisms regulating

basophil function should provide insight for developing novel strategies for therapeutic modulation of basophils and hence basophil-mediated disorders (2–8, •10, 39–42, 81).

Basophil Activation Test

Delineation of molecules which can identify basophils and determine their activation state with high sensitivity and specificity has led to use of an in vitro assay, termed the basophil activation test (BAT), with which to investigate the potential role of basophils in disease states [55, 82–•87]. The BAT is a microfluoremetry-based assay that can be performed on peripheral blood. Basophils can be gated as CD123+, FcЄ RI+, and CD303– cells. The basophil activation state is determined by basophil expression of CD69, and the degranulation state is determined by expression of CD203c (piecemeal degranulation) and CD63 (anaphylactic degranulation). Figure 1 experimentally illustrates the microfluoremetry analysis of purified resting basophils before and after in vitro activation by FcЄ RI crosslinking with anti-FcЄ RI mAb. Clinically, the BAT analysis of peripheral blood samples is used largely as a surrogate for basophil involvement in an immune reaction, as was recently reviewed [•84]. However, the clinical value of BAT in patient management will require further investigation.

Role of Basophils in Allergic Diseases

Based on increasing understanding of basophil biology, basophils may prove to be pathophysiologically important in many if not all allergic diseases, including anaphylaxis, allergic rhinitis, asthma, urticaria, and food allergies. The potential for basophils to degranulate for immediate release of histamine, rapidly generate LTC4, and produce Th2 cytokines provides the mechanistic basis whereby basophils can cause immediate hypersensitivity clinical symptoms, as well promote late-phase hypersensitivity reactions, and contribute to delayed hypersensitivity reactions (Fig. 2).

Immediate Hypersensitivity Reactions

Anaphylaxis is clinically characterized by cardiovascular, cutaneous, respiratory, and gastrointestinal manifestations consequent to basophil and mast cell degranulation, and is usually IgE-dependent [1, 3, 11, 16, 33, •49, 52, 55, 82– •84]. Although specific triggers of anaphylaxis in a given patient may be elusive at the time of presentation, the most common defined causes include allergy to foods, drugs, and insect stings and bites [52, 82–88], as well as non-IgE-mediated inducers of basophil or mast cell degranulation, such as exercise, physical factors, opiates, and the anaphylatoxin C5a that is generated by immune complex activation of the complement cascade [62, 83, 85]. Efforts to determine the relative roles of basophils and mast cells in an anaphylactic episode have included measurements of histamine, tryptase, and prostaglandin D2 (PGD2), as well as BAT [55, 82–•87]. Elevated tryptase and PGD2 levels suggest mast cell involvement and a positive BAT suggests basophil involvement [16, 33]. A recent study evaluating the kinetics of mast cell, basophil, and oral food challenge responses in omalizumab-treated adults with peanut allergy suggested that acute clinical reactions were basophil-dependent [•87]. Whether autoantibodies to IgE or FcЄ RI are etiologies for systemic anaphylaxsis, in addition to their role in urticaria, is not clear [•89]. Nonetheless, as a circulating pool of leukocytes, basophils are ideally poised to mediate anaphylaxsis in response to blood-borne triggers.

Late-Phase Hypersensitivity Reactions

Late-phase hypersensitivity reactions (LPR) occur approximately 6–12 h after an immediate hypersensitivity reaction, and can be observed in allergic rhinitis and severe asthma, and perhaps occur in the context of some urticarias and atopic dermatitis [4–9, •89–91]. The potential contribution of basophils to LPR is based on their presence in target tissues within

hours following experimental allergen challenge [6–8, 11, •87, 88, 91]. In cutaneous allergen challenges, the LPR may be comprised of up to 50 % basophils [7, 8, •89]. In nasal allergen challenges and lung segmental allergen challenges, basophils appear within hours, consistent with a LPR [•89, 92, 93]. Basophils detected in bronchoalveolar lavage fluid in individuals with lung inflammation are correlated with increased IL-4 levels, which is consistent with basophil promotion of a Th2 microenvironment [44]. Additionally, in post mortem assessment, lungs of patients with fatal asthma were found to have significantly more basophils than those who died from other causes [93]. The increase in IL-4 in LPR, and the demonstrated capacity for activated basophils to produce large quantities of IL-4, provide correlative evidence for basophils playing an important role in the pathophysiology of LPR with propagation of Th2 immune responses [1, 4, 72, •89–91, •94, -95].

Delayed Hypersensitivity Reactions

Although delayed hypersensitivity reactions are predominantly characterized by mononuclear leukocytes and peak reaction at the site of allergen challenge at 2–3 days, the predominant granulocyte in the reaction is the basophil [6– 8, 33, 93, 96]. Ultrastructural studies of those basophils suggest piecemeal necrosis, rather than anaphylaxis degranulation. Such characteristic basophils have also been found in skin lesions of poison ivy (rhus toxoid)-sensitive patients, as well as other contact dermatoses, skin allograft, and tumor rejection reactions, and gut mucosa of Crohn disease [6–8, 12, 48, 96]. The likely role of basophils in these delayed hypersensitivity reactions is production of IL-4 and IL-13, with enhancement of a Th2 polarizing microenvironment [6, 7, 97].

Role of Basophils in Other Clinical Conditions

Autoimmunity

In addition to the potential role of basophil activation and degranulation by anti-FcЄ RI autoantibodies in the pathogenesis of autoimmune urticaria, basophils have also been implicated in the pathogenesis of lupus nephritis [•29, 30]. This is based largely on correlations between the presence of elevated serum levels of IgE autoantibodies, especially IgE anti-dsDNA, and activated basophils with severity of lupus nephritis [•29]. The proposed model is that IgE anti-dsDNA/dsDNA immune complexes bind to the basophils FcЄ RI, causing basophil activation with homing to lymphoid organs, where the activated basophils produce IL-4 and promote a Th2 adaptive immune response that enhances autoantibody production. Although this scenario is supported in the lyn-/- murine model of lupus nephritis, evidence in humans remains associative. Nonetheless, strategies to include omalizumab as part of other treatment strategies, such as belimumab (a mAb against BAFF), have been proposed as a means of inhibiting basophil participation in the pathogenesis of lupus nephritis [•29, 30].

Basophils are also being implicated in the pathogenesis of rheumatoid arthritis, wherein citrullinated proteins can activate basophils due to IgE anti-citrullinated protein [•31]. This has led to speculation that basophil activation may contribute to the pathogenesis of autoimmune diseases as diverse as anti-glomerular basement membrane disease, membranous nephropathy, or anti-neutrophil cytoplasmic antibody-associated vasculitis [50, •89]. Should evidence solidify around a role for basophils in the pathogenesis of these disorders, it is likely that consideration of indirect therapeutic modulation of basophil activation, such as omalizumab, will be extended to direct therapeutic targeting of basophils to inhibit their activation and promotion of a pathogenic Th2 microenvironment.

Infections

The physiologic role of basophils in protective immunity to helminths is well established [15, 17, 67]. More recently, basophils have also been implicated in the initiation of Th2 immune responses within lymph nodes [17, 20, 27] and enhancing B cell responses to respiratory bacteria, when the basophils are activated by immune complexes consisting of bacterial antigens and IgD bound to the basophil via a putative IgD receptor [28, 74]. These IgD-activated basophils promoted B cell class switching to IgA and IgD and could prevent the replication of H. influenza and *Moraxella catarrahalis*. Crosslinking of IgD on basophils stimulated the release of immunoactivating, proinflammatory, and antimicrobial mediators [28, 74]. This proinflammatory relationship between IgD and basophils was further implicated in autoinflammatory syndromes with periodic fevers, which are characterized by increased isotype switch to IgD and increased IgD-armed basophils [28]. Also, as discussed previously, activation of TLR 2 and 4 may play a potential role with gut microbiota interactions and could be enhanced upon exogenous bacterial infection [63, 65, 98].

Malignancy

There is a strong association of basophils with some malignancies, particularly acute and chronic myeloid leukemia (AML, CML) [34–36]. Increased numbers of circulating basophils and dysplastic basophils are common features of AML and the accelerated phase of CML [36], and basophil transformation can rarely occur. It is not uncommon in patients with CML to have 70 % blood basophils [37]. In a cohort study of 1,008 patients with myelodysplastic syndromes, basophilia, defined as basophils greater than 250/ul, was associated with reduced survival [38]. Myeloproliferative disorders are also linked to hypersensitivity to IL-3 signaling, with a link of BCR-ABL growth dependence on IL-3 as shown in a murine model [99]. These associations of basophils with myeloid leukemias and poor outcomes have led to the proposal for a clinical trial with an anti-CD123 mAb in patients with CD123+ acute myeloid leukemia in remission with standard chemotherapy, in an effort to delay or prevent recurrence [•40].

Conclusions

Historically, basophils were known for their role in IgE-mediated effector responses manifest as allergic diseases, and their physiologic role in immune responses to helminths. However, it is now evident that basophils are dynamic and can interact with their local environment by responding to various stimuli mediated by both IgE-dependent and IgE-independent mechanisms, and can participate in a broad spectrum of immune-mediated diseases. The multitasking capability of basophils enables them to serve a unique role in bridging innate and adaptive immune responses. A recent provocative study in mice suggested that basophils may differentiate via either an IL-3-dependent or a TSLP-dependent pathway, leading to distinct functional phenotypes, and that TSLP-dependent basophils may be important in the pathogenesis of eosinophilic esophagitis [11, •49, 100–102]. However, verification of such alternative differentiation pathways in humans has not been confirmed. Further understanding of basophil activation mechanisms will help advance development of diagnostics, such as the BAT, for evaluation and management of patients. Understanding the precise mechanisms by which basophils are activated for diverse effector functions will also be important for the development of targeted therapeutics of diseases linked to basophils. Leading therapeutic candidates targeting basophils include omalizumab and anti-CD123 mAb [•29, •40, •84, •87].

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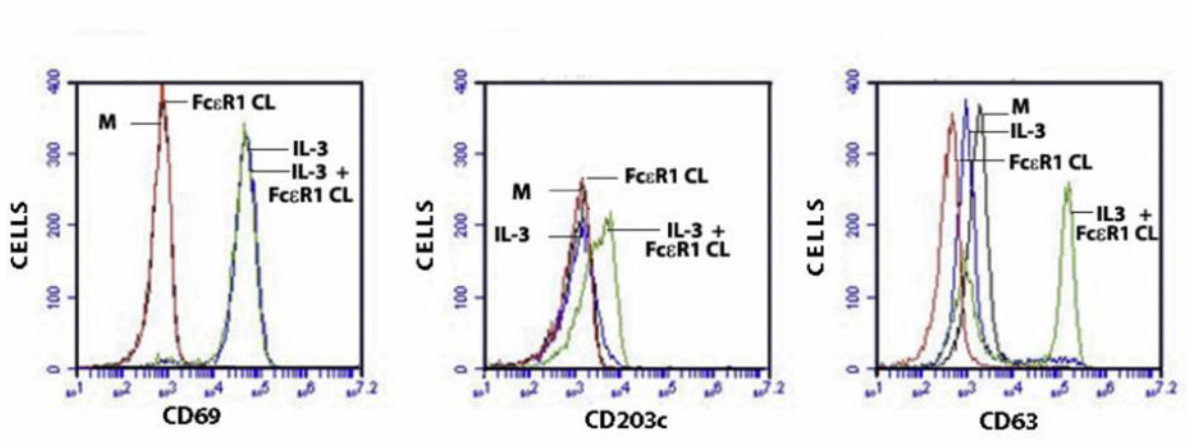

Figure 1.

Basophil activation. Human basophils purified from leukopacks from healthy individuals were analyzed by microfluorimetry. The effects of IL-3, alone (*blue*) or Fcε R1 crosslinking (CL) alone (*red*), or in combination (*green*), on the expression of CD69, CD203c, and CD63 are shown as flow cytometry histograms. Unstimulated control basophils in media only (*M*) are in *black*

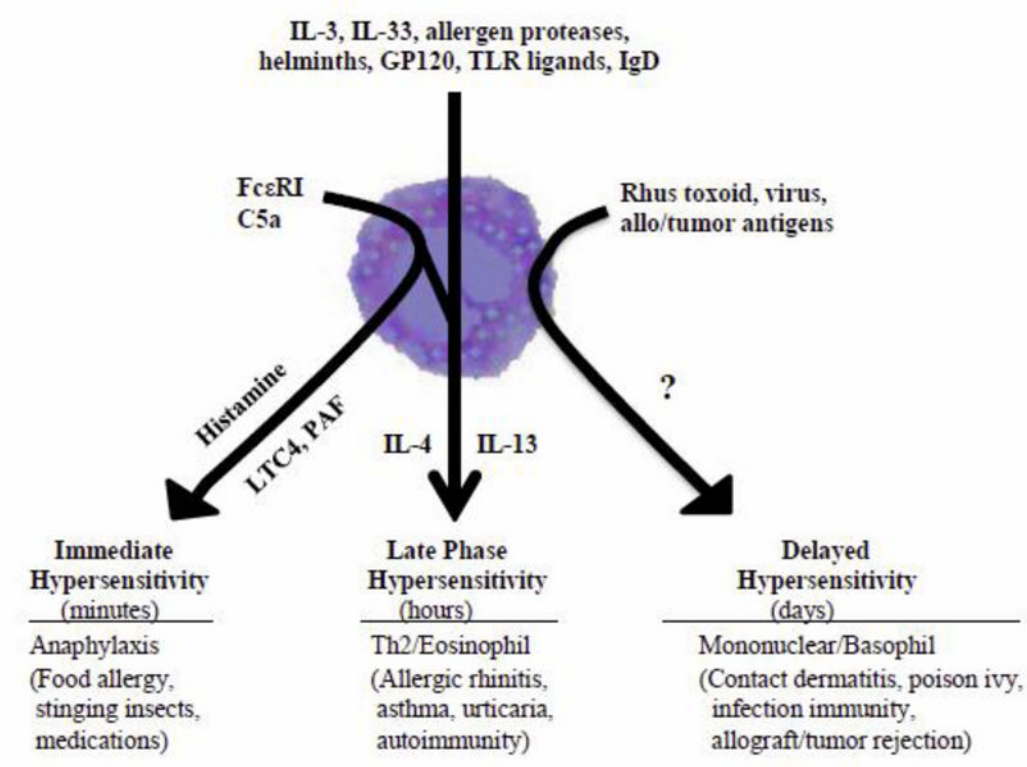

Figure 2. Heterogeneity of human basophil responses in clinical disease

Table 1

Functional effects of stimulating human basophils

Stimulus	Effects				References
	Degranulation	Leukotriene synthesis	Cytokine sSynthesis	Other	
Fcε RI CL	Histamine	LTC4	IL-4, IL-13	PAF	10, 50
C5a	Histamine				62, 66, 80
IL-3	Histamine	LTC4	IL-4, IL-13	PAF, CD11b, CD18	70, 78-80
IL-33			IL-4, IL-5, IL-6, IL-13		64, 71, 75
Proteases			IL-4, IL-5, IL-13		15, 20, 41
Helminths			IL-4, IL-5, IL-13		15, 17, 67
HIVgp120			IL-4, IL-13		73
TLR ligands			IL-4, IL-13		63, 65, 98
IgD R			IL-1, IL-4	BAFF, AMP	28, 74
Eotaxins				TEM (CCR3)	58, 79
RANTES				TEM (CCR3)	79
MCP-1				TEM (CCR2)	79

FcεR1 CL Fcε R1 crosslinking; *LTC4* leukotriene C4; *PAF* platelet activation factor; *BAFF* B cell activating factor;

TLR toll-like receptor; *AMP* antimicrobial peptide; *RANTES*: CCL5; *CCR* chemokine receptor; *MCP-1* monocyte chemotactic protein-1; *TEM* transendothelial migration