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# Basophils and allergic inflammation

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## Abstract

Basophils were discovered by Paul Ehrlich in 1879 and represent the least abundant granulocyte population in mammals. The relative rarity of basophils and their phenotypic similarities with mast cells resulted in this cell lineage being historically overlooked, both clinically and experimentally. However, recent studies in humans and murine systems have shown that basophils perform non-redundant effector functions and significantly contribute to the development and progression of $T_H2$ cytokine-mediated inflammation. Although the potential functions of murine and human basophils have provoked some controversy, recent genetic approaches indicate that basophils can migrate into lymphoid tissues and, in some circumstances, cooperate with other immune cells to promote optimal $T_H2$ cytokine responses *in vivo*. This article provides a brief historical perspective on basophil-related research and discusses recent studies that have identified previously unappreciated molecules and pathways that regulate basophil development, activation and function in the context of allergic inflammation. Further, we highlight the unique effector functions of basophils and discuss their contributions to the development and pathogenesis of allergic inflammation in human disease. Finally, we discuss the therapeutic potential of targeting basophils in preventing or alleviating the development and progression of allergic inflammation.

## Introduction

Despite being the least frequent granulocyte population in the mammalian body, the accumulation of basophils have been reported in a number of human diseases states including allergic disease, organ rejection, autoimmunity and cancer. For example, basophils are thought to contribute to the pathogenesis of allergic contact dermatitis[1], atopic dermatitis[2], allergic drug reactions[3], immediate hypersensitivity reactions (eg, anaphylaxis)[3], asthma[4–6], bullous pemphigoid[2], lupus nephritis[7], Crohn's disease[3], skin and kidney allograft responses[8, 9] and acute and chronic myelogenous leukemia[10, 11] (Fig. 1).

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Further, the basophil activation test (BAT) has been used experimentally to detect allergic reactions to drugs, food and venom in patients[12, 13]. Although basophil responses are associated with a number of diseases, the focus of this review will be to examine the current understanding of the function of basophils within the context of allergic inflammation.

The development of new murine genetic tools and models of inflammation, coupled with the development of more selective reagents to detect and manipulate basophils, has resulted in novel insights into the potential contribution of basophils to human disease. In this review, we provide a brief historical perspective on basophil-related research. Next, we focus on the current understanding of the role basophils play in promoting $T_H2$ cytokine-mediated inflammation and allergic disease. We discuss how heterogeneity in basophil responses may contribute to the complexity of allergic disease states and how a better understanding of basophil biology may lead to the development of new therapeutic strategies to alleviate allergic inflammation.

## Basophils: a historical perspective

The German physician-scientist Paul Ehrlich identified basophils in 1879 based on their unique microscopic appearance after being exposed to basic stains[14]. Basophils are the least abundant granulocyte population in the peripheral blood, comprising less that one percent of all leukocytes[15, 16]. This fact made early research on basophils difficult and promoted the notion that their lack of abundance equated to a lack of biological importance. Subsequent studies that occurred almost a century later determined that basophils contain histamine and express the high affinity IgE receptor FcεRIα[16–18]. However, due to their relative lack of abundance and phenotypic and functional similarities to mast cells, basophils were regarded as a redundant granulocyte population lacking unique functions. In addition, the presence of basophils in the peripheral blood allowed them to be more easily obtained than tissue-resident mast cells and as a result, basophils began to be employed as surrogates for mast cells in functional assays to better understand granulocyte biology[16]. However, subsequent studies directly comparing mast cell and basophil populations began to elucidate that basophils exhibit unique developmental, phenotypic and functional features[19–23] (see below). Several seminal studies in the 1970s and 1980s employing both rats and guinea pigs demonstrated that basophil populations expand dramatically in response to various helminth parasites and parasite-derived antigens, suggesting that basophils may play a role in protective $T_H2$ cytokine-mediated immunity to some parasites[24–28]. Despite these observations, the unique contribution of basophils to the development of allergic inflammation could not be studied at the time due to the lack of a mouse model and tools to selectively manipulate basophil responses *in vivo*.

In 1981, a histamine-containing cell population termed the “persisting cell” or P cell was identified in mice and was the first identification of a basophil-like cell population in mice[29]. Subsequent studies the following year by Dvorak *et al.* elaborated on these original observations and identified a granular cell population in the bone marrow of mice that resembled basophils in rats. This study was the first to officially report the identification of basophil populations in mice[30]. The identification of basophils in mice enabled technologic advancements to directly test the pathways that regulate their development and contribution to immunity, inflammation and disease.

Since the identification of murine basophils in 1982, significant advances in basophil biology have been made. For example, the development of two mouse models by the laboratories of Paul and colleagues[31] and Locksley and colleagues[32] that expressed green fluorescent protein (eGFP) under the control of the interleukin (IL)-4 promoter allowed for a series of studies that significantly enhanced our understanding of basophil biology. These

murine models facilitated the discovery that mature eosinophils, mast cells and basophils constitutively express IL-4/eGFP and allowed basophils to be identified *in vivo*, systematically phenotyped and easily tracked by flow cytometric techniques[31–33]. Research from the laboratories of Karasuyama and colleagues and Kubo and colleagues extended these studies to develop novel techniques to deplete murine basophils, thereby allowing the *in vivo* functions of basophils to be tested by targeting the membrane glycoprotein CD200R or by engineering basophils to express the diphtheria toxin receptor (DTR) under the control of basophil-specific IL-4 enhancer elements or proteases[34–36]. In addition, Voehringer and colleagues developed a mouse that expressed toxic levels of Cre recombinase under the basophil-specific protease Mcpt8, resulting in a loss of greater than 90 percent of mature basophil populations[37]. Further, Locksley and colleagues developed Basoph8 mice that have the Mcpt8 gene replaced with yellow fluorescent protein (YFP), allowing for two-photon imaging of basophil responses *in vivo*[38]. Employing these mice, research from Locksley and colleagues allowed tracking of basophil populations *in vivo* and identified them in both secondary lymphoid tissues and in inflamed tissues[38]. Collectively, the ability to ablate, temporally deplete and track basophil populations *in vivo* have facilitated a series of studies that have directly interrogated the ability of basophils to contribute to the development of $T_H2$ cytokine-mediated inflammation in murine model systems[35, 37–45]. As discussed below, studies employing these new mouse models have revealed that basophils function as important contributors to the development of protective immunity to *Trichinella spiralis*[43], secondary *Nippostrongylus brasiliensis*[46] infection and immunity to ectoparasites[34]. Further, similar studies demonstrated an important role for basophils in the induction of optimal $T_H2$ cytokine-mediated inflammation in the context of acute atopic dermatitis, chronic IgE-mediated dermatitis, airway inflammation and eosinophilic esophagitis-like disease[35, 37, 42, 45, 47]. Collectively, these new tools and approaches are revealing previously unappreciated roles of basophils in regulating immunity and inflammation.

## Basophil development

Murine basophils are myeloid in origin and are thought to develop primarily from hematopoietic stem cell (HSC) populations that reside in the bone marrow. However, many of the cellular and molecular events that promote basophil commitment from HCSs remain unknown. This section will describe the known mechanisms that regulate the basophil cell lineage commitment and will discuss how these pathways result in phenotypically and functionally distinct basophil populations that may contribute to allergic disease.

### Stem cell populations

Basophils are reported to develop from common HCS-derived granulocyte-monocyte progenitor cells (GMPs) that reside in the bone marrow (Fig. 2)[48]. GMPs maintain the capacity to develop into multiple cell lineages including macrophages, eosinophils, mast cells and basophils[48]. Critically, as GMPs mature, they are known to enter intermediate commitment steps and can become mast cell precursors (MCPs), basophil-mast cell precursors (BMCPs) or basophil precursors (BaPs) (Fig. 2)[20, 48]. Both BMCPs and BaPs possess the capacity to develop into mature basophil populations[48, 49]. Unlike mast cells, which are known to exit the bone marrow with an immature phenotype and complete their maturation in peripheral tissues, basophils are reported to exit the bone marrow once they have fully matured (Fig. 2)[48, 49]. However, recent studies have identified that multiple bone marrow-resident progenitor cell populations, including GMPs, exit the bone marrow in the context of inflammation and undergo extramedullary hematopoiesis (EMH) in the periphery[50, 51]. Although this process remains to be fully defined, it is likely that the peripheral basophilia observed in the context of $T_H2$ cytokine-mediated inflammation is supported by the development of basophils from both bone marrow-resident cells and

through EMH. However, additional studies are needed to further determine the contributions of EMH and basophil development in promoting inflammation.

## Transcription factors

While the commitment of progenitor cells to the basophil cell lineage remains to be fully defined, several binding proteins and transcription factors are known to play critical roles in the process. For example, mature basophil development is reported to be dependent on the expression of C/EBPα and GATA2[49]. In addition, recent studies by Mukai *et al.* demonstrated that mice deficient in the transcription factor distal-promoter Runt-related transcription factor 1 (P1-Runx1) have a 90 percent reduction in mature basophil populations in the periphery, but exhibit normal numbers of neutrophils, eosinophils and mast cells[52]. Collectively, these studies identify P1-Runx1 as a selective regulator of basophil development in mice.

## Environmental factors

Recent studies have also identified that beneficial microbial communities, including commensal bacteria can have significant effects on basophil development and activation[53, 54]. For example, eliminating or experimentally altering commensal bacteria-derived signals resulted in increased serum IgE levels in germ-free mice (GF) or antibiotic-treated mice compared to conventionally housed mice[53, 54]. Increases in IgE promoted the development of mature basophil populations by enhancing the responsiveness of progenitor cell populations to growth factors[53]. Consistent with murine studies, it was also shown that increased IgE levels in immunodeficient patients with atopic disorders was associated with elevated frequencies of circulating basophils[53]. Collectively, these data indicate that commensal microbial-derived signals and IgE regulate basophil development. Given the established association between repeated exposure to antibiotics during childhood and the development of allergic inflammation[55, 56], it is tempting to speculate that dysregulated basophil responses may contribute to these processes.

## Cytokines

Unlike the lifespan of other granulocyte populations, the lifespan of mature basophils is relatively short and is estimated to be between 1 and 2 days[49, 57, 58]. Therefore, the constant presence of basophils in the periphery is thought to be a result of continuing development and replenishment of cells from bone marrow-resident progenitors[57]. In the context of $T_H2$ cytokine-mediated inflammatory responses, increased basophil development and peripheral basophilia is often observed[35, 42, 43, 59–61] suggesting that basophil development can be positively regulated by proinflammatory factors. Seminal studies by Lantz *et al.*, Shen *et al.* and Ohmori *et al.*, demonstrated that peripheral basophilia following *N. brasiliensis* or *Strongyloides venezuelensis* infection is critically-dependent on IL-3-IL-3R signaling[59–62]. These studies provoked the hypothesis that peripheral basophilia was predominately regulated by IL-3 signaling (Fig. 2). This hypothesis was further supported by subsequent reports demonstrating that basophil recruitment to the draining lymph nodes following *N. brasiliensis* infection was IL-3-dependent[63].

Although it is clear that IL-3 is a key regulator of basophil development in the context of some stimuli, recent studies have identified that the predominantly epithelial cell-derived cytokine thymic stromal lymphopoietin (TSLP) also regulates basophil development and peripheral basophilia (Fig. 2)[42, 43]. For example, it was demonstrated that peripheral basophilia following *Trichuris muris* infection, *T. spiralis* infection or the induction of atopic dermatitis (AD)-like inflammation is critically dependent on TSLP-TSLPR signaling[42, 43]. In addition, it was determined that TSLP was capable of cooperating with IL-3 to promote optimal basophil responses, but also maintained the capacity to promote

basophil development and peripheral basophilia in the absence of IL-3-IL-3R signaling[42]. Critically, TSLP-elicited basophils exhibited distinct phenotypic and functional characteristics from classical IL-3-elicited basophils. Most notably, they lacked the ability to degranulate in response to IgE-mediated FcεRIα signaling but were potent producers of IL-4 in response to IL-3, IL-18 or IL-33 stimulation[42]. Collectively, these studies demonstrate that basophil responses can be regulated by IL-3/IgE-dependent mechanisms, or by TSLP-dependent mechanisms (Fig. 2) (see below).

As described above, recent data suggest that there is an IL-3-elicited basophil population that is activated by IgE and a distinct TSLP-elicited basophil population that appears to function independently of IgE (Fig. 2)[42]. In this review, we will focus on how these distinct pathways and cell types may contribute to various allergic disease states. The recent identification of functionally distinct basophil populations is of particular interest to our understanding of human allergic disease states such as food allergy and eosinophilic esophagitis (EoE), asthma, urticaria, allergic rhinitis, and AD. Some conditions, such as food allergy[64], urticaria[65, 66] and asthma[67] can be predominately IgE-mediated and responsive to anti-IgE therapy, while others such as AD[68] and EoE[69] have shown mixed results in response to anti-IgE therapy, indicating that IgE-independent processes may be critical for the pathogenesis of these diseases (Fig. 3). Further, AD and EoE have been directly associated with polymorphisms in *TSLP* and elevated TSLP protein production at the site of inflammation[70–73]. These observations provoke the hypothesis that there may be IgE-dependent basophil responses that contribute to inflammation in some diseases states (eg, food allergy, urticaria and asthma) and TSLP-elicited, IgE-independent basophil responses that contribute to inflammation in other disease states (eg, AD and EoE) (Fig. 3). Whether these pathways represent heterogeneous mechanisms across allergic disease states or within one disease remains an active area of investigation. In the sections below, we will discuss in more detail the potential interplay between IgE, TSLP and basophil function in human disease.

In summary, there are a variety of developmental, transcriptional and cytokine-mediated pathways that may influence the function of basophils. The following sections will put these different aspects into the context of potential basophil heterogeneity as it pertains to human allergic disease.

## Basophil activation and effector functions

Basophils can be activated by an array of signals including those mediated by cytokines, antibodies, proteases and directly by antigens themselves. The following section will highlight the known mediators of basophil activation and will describe the effector processes they initiate. We will then describe how these distinct methods of activation and effector function are associated with human allergic disease states and may promote the development of allergic inflammation.

### Antibody-mediated activation

Perhaps the best-studied and most well recognized mode of basophil activation is initiated via FcεRIα and IgE-mediated crosslinking (Table 1). Basophils have been shown to produce effector molecules such as histamines and leukotrienes in response to IgE-mediated activation[16]. The ability of basophils to produce histamines and leukotrienes in response to IgE-antigen complexes has implicated these cells in the induction of smooth muscle contraction and as contributors to systemic anaphylaxis (Table 1)[74]. Although basophils have never been directly shown to contribute to IgE-mediated anaphylaxis in experimental systems, it has been reported that basophils promote an alternative pathway of anaphylaxis in response to IgG-antigen complexes in C57BL/6 mice[75]. Specifically, basophils have been

shown to produce platelet-activating factor (PAF) and significantly contribute to anaphylaxis in response to penicillin-IgG antibody complexes[75]. In addition to IgE- and IgG-mediated activation, basophils have also been shown to be activated in an IgD-dependent manner. For example, IgD-antigen complexes can induce the production of antimicrobial peptides from basophils, and supernatants from IgD-activated basophils were capable of inhibiting the growth of certain bacteria[76]. Collectively, these findings demonstrate distinct pathways by which the humoral immune system influences basophil function. However, further studies are needed to better understand the kinetics of IgG-, IgD and IgE-mediated basophil activation and the specific mediators that are released by both IL-3-elicited and TSLP-elicited basophils in response to these distinct stimuli.

## Cytokines

As discussed above, IL-3 is capable of promoting basophil development both *in vitro* and *in vivo*; however, in addition to its effects on basophil development, IL-3 is capable of promoting aspects of basophil activation. For example, IL-3 can directly promote the release of cytokines (IL-4, IL-6) and chemokines (CCL3, CCL4, CCL12, Cxcl2) from TSLP-elicited basophil populations in an IgE-independent manner in mice (Table 1)[16, 42] and can also enhance the production of IL-4 and IL-13 production from human basophils following IgE-mediated activation[77, 78]. In addition to IL-3, the IL-1 cytokine family members IL-18 and IL-33 can also directly activate basophils and enhance their effector functions[42, 79–83]. In both mice and humans, IL-33 has been shown to activate basophils, but IL-18 has only been demonstrated to activate murine basophils (Table 1). For example, IL-18 treatment promotes the production of IL-4 from basophil populations in a MyD88-dependent manner[80]. Similar to IL-18, IL-33 also promotes IL-4 and IL-13 production from basophil populations in a MyD88-dependent manner[80]. Critically, while IL-3-elicited basophils degranulate in response to IgE-mediated crosslinking[42], they did not respond robustly to IL-3, IL-18 or IL-33 stimulation[42]. In contrast, while TSLP-elicited basophils exhibit a limited ability to degranulate in response to IgE-mediated crosslinking, they respond robustly to stimulation with IL-3, IL-18 or IL-33[42]. Collectively, these studies highlight that IL-3-elicited and TSLP-elicited basophils differentially respond to IgE-mediated activation and are further distinguished by their response to a variety of cytokines.

## Direct activation by protease allergens

In addition to antibody- and cytokine-mediated activation, basophils respond directly to protease activity. For example, the house dust mite (HDM) protease Derp1 can promote the production of IL-4, IL-5 and IL-13 from human basophil cell lines[84] (Table 1). Further, parasite-derived proteases and the cysteine protease papain have been shown to promote the production of type 2 cytokines from murine basophils[40, 84]. These studies also demonstrated that rendering the proteases inactive by exposure to heat inactivation or treatment with protease inhibitors eliminated their ability to promote basophil activation, suggesting that basophils are sensing the protease activity directly. Collectively, these data suggest that basophils are capable of sensing and responding to active proteases, but the mechanisms through which this occurs remain unknown. Moreover, the ability of basophils to detect proteases may allow them to respond robustly to common allergens, many of which possess protease activity.

## Additional mediators of activation

Basophils are known to respond to a variety of environmental stimuli such as drugs, venoms and pollens, and their reactivity can be assessed by the basophil activation test (BAT)[12]. Additionally, human peripheral blood basophils have been shown to spontaneously release histamine in response to a histamine-releasing factor from other mononuclear cell

populations in patients with food allergy and AD[85, 86]. A less well-understood method of basophil activation is initiated by a series of "super antigens" which are capable of promoting basophil activation independently of antigen-specific antibodies or protease activity (Table 1). For example, the gp120 glycoprotein of the human immunodeficiency virus (HIV) is capable of non-specifically interacting with surface bound IgE on human basophils and promoting IL-4 and IL-13 production[87, 88]. Similarly, the *Schistosome*-derived glycoprotein IPSE/alpha-1 also promotes IL-4 production by basophils in the absence of antigen-specific IgE[89]. However, whether common allergens can also act as super antigens and promote type 2 cytokine production by basophils remains unknown. Collectively, these findings demonstrate that a variety of naturally occurring and pathogen-associated stimuli can directly influence basophil function.

### Additional effector mechanisms

Additional studies have also shown that MHC class $II^+$ basophils may promote Th2 cytokine-associated inflammation via antigen-presentation to T cells[39, 41, 44]. While murine basophils have been reported to function as APCs, subsequent studies investigating the role of basophils as APCs in humans have been less clear[90–93]. Therefore, future studies are required to determine the clinical significance of basophils functioning as APCs, as therapies targeting dendritic cells is an active area of investigation in patients across multiple diseases.

## Basophils and allergic inflammation: pathogenesis and implications for clinical management

Classically, allergic or atopic diseases are driven by $T_H2$ cytokine responses and therefore are associated with the production of IL-4, IL-5, IL-9 and IL-13. Furthermore, the inflammatory responses underlying these conditions are associated with peripheral eosinophilia, IgE production and tissue-resident mast cell responses[94]. In recent years, basophils have emerged as a contributor to the pathogenesis of multiple models of allergic disease[35, 37, 42, 95]. In the following sections we will discuss experimental evidence obtained by employing murine model systems of human allergic diseases to illustrate the potential of targeting basophil populations as a therapeutic strategy. In addition, we will highlight the potential role of basophils in the development and progression of human allergic diseases and discuss how current treatment strategies may unintentionally target basophil-specific pathways. Finally, we will illustrate how employing more specific methods to target functionally distinct basophils in the context of allergic inflammation may result in increased therapeutic potency.

### Food Allergy

Adverse reactions to food remain the leading cause of anaphylaxis that results in emergency room visits[96]. Although anaphylaxis has a much lower incidence (0.03–2%) than other allergic conditions such as AD, it is a life-threatening condition[97]. Anaphylaxis in the context of food allergy is mediated by antigen-specific IgE responses to ingested food allergens[97]. Although food allergy can be prevented by avoiding known food allergens, immunomodulatory therapeutics to prevent the onset of symptoms are limited. Recent clinical studies indicate that anti-IgE therapy using omalizumab may be a useful therapeutic approach in the treatment of food allergy and anaphylaxis by targeting IgE-mediated release of various pro-inflammatory factors[64, 98]. Although the precise contribution of the IgE-basophil axis in anaphylaxis and food allergy remains poorly defined, a recent study employing omalizumab in patients with peanut allergy identified that early clinical responses to therapy correlated with basophil suppression rather than mast cell suppression[98]. Furthermore, the basophil activation test (BAT) is a clinical tool employed to test the IgE-mediated reactivity of basophils to food allergens[99]. These studies indicate that

targeting IgE-FcεRIα interactions on basophils may represent a promising new method to treat food allergy and anaphylaxis. Clinical trials are currently underway to determine whether anti-IgE therapy prior to desensitization results in faster or safer reductions in allergic reactions.

Although the role of TSLP in classical IgE-mediated food allergy remains unclear, its potential role in the food allergy-associated disease eosinophilic esophagitis (EoE) has emerged as an active area of investigation. EoE is characterized by chronic inflammation of the esophagus associated with ingested or inhaled allergens, and in contrast to classical food allergy associated with anaphylaxis, anti-IgE therapy has demonstrated poor efficacy in ameliorating EoE symptoms[64, 69]. Although swallowed topical steroid therapy is effective in treating EoE, side effects with regard to long-term steroid use in children are a significant concern and additional therapeutic approaches would greatly aid in the treatment of EoE [100]. Strikingly, gain-of-function polymorphisms in *TSLP* have been strongly associated with the development of EoE in patients[70, 73]. Although the role of basophils remains poorly defined in EoE, recent findings have shown that patients with EoE and a gain-of-function polymorphism in *TSLP* present with basophil populations that exhibit the phenotype of TSLP-elicited basophils in mice[42]. Further, patients with a gain-of-function polymorphism in *TSLP* present with elevated peripheral basophilia[47]. These data, along with the ability of TSLP-elicited basophils to promote IgE-independent inflammation, provoke the hypothesis that TSLP-elicited basophils may contribute the pathogenesis of EoE via a distinct mechanism from the IgE-dependent pathways that contribute to classical food allergy. Further differentiating the role of IgE-activated versus TSLP-elicited basophils in classical food allergy and EoE may provide significant insight into the pathogenesis of these conditions.

These concepts are supported by recent studies employing a new murine model of EoE-like disease. Specifically, studies in our laboratory identified that TSLP promotes IgE-independent murine EoE-like disease characterized by eosinophilic inflammation and food impaction following repeated challenges with food antigens[47]. Critically, EoE-like disease was associated with a significant population expansion of TSLP-elicited basophils and $T_H2$ cytokine responses. Further, depletion of TSLP-elicited basophils prior to the initiation or after the onset of inflammation in the esophagus was established resulted in a loss of EoE-like disease[47]. Translational studies revealed that patients suffering from EoE had increased expression levels of *TSLP* and significantly increased basophil populations in esophageal biopsies[47]. Collectively, these findings provoke the hypothesis that TSLP elicits a functionally distinct population of IgE-independent basophils in the context of EoE. Understanding the mechanisms by which TSLP-elicited basophils contribute to the pathogenesis of EoE and how these mechanisms differ from the IgE-dependent mechanisms that promote classical food allergy may provide significant insight towards new therapeutic strategies for these conditions.

## Urticaria

Urticaria is a very common skin condition that results in the development of itchy wheals or hives. When this condition lasts longer than six weeks, it is referred to as chronic urticaria. Many cases of chronic urticaria lack an identifiable cause and are referred to as chronic idiopathic urticaria (CIU). A significant portion of CIU patients have recently been shown to develop urticaria in response to anti-IgE-FcεRIα antibodies that may activate mast cells or basophils[101]. Further, basophil activation has been associated with urticaria in patients in response to IL-3, demonstrated by upregulation of CD203[102, 103]. Consistent with previous findings that IL-3 elicited basophils are responsive to IgE-mediated activation, murine studies have shown that basophils critically orchestrate IgE-mediated chronic allergic

inflammation in the skin[95]. Although CIU is thought to be mediated by both IgE-dependent and IgE-independent mechanisms, a recent study revealed that omalizumab is effective in treating the symptoms of CIU[66]. It is widely appreciated that many patients with CIU do not respond to aggressive first-line therapies with antihistamines. However, Maurer *et al.* demonstrated that patients who were unresponsive to treatment with $H_1$-antihistamine therapy responded to omalizumab, which is now currently awaiting FDA approval for CIU as a new indication[66]. Further, recent studies indicate that omalizumab may be influencing basophil function[104, 105], but future studies will be required to determine the precise contribution of basophils to urticaria. Although the role of IgE in promoting urticaria is widely appreciated, the role of TSLP and TSLP-elicited basophils in the development of urticaria remains to be determined.

## Allergic Rhinitis

Allergic rhinitis (AR) affects 40 million people in the US across all ethnic, socioeconomic and age groups[106]. Classically, AR is thought to be mediated by IgE responses to allergenic proteins in the environment and subsequent cross-linking of mast cells. Activation of mast cells results in the release of a variety of inflammatory mediators such as histamines, leukotrienes (eg, LTC4) and prostaglandin D2 to promote clinical rhinorrhea[107]. Based on these pathophysiologic features, therapies to treat AR include antihistamines, inhaled corticosteroids, lipoxygenase inhibitors (zileuton), leukotriene antagonists (zafirlukast and montelukast) and mast cell stabilizers (cromolyn sodium)[108]. Furthermore, given that this condition is thought to be mediated by antigen-specific IgE, omalizumab has been proposed as a potential therapeutic[109]. Basophils have been identified in the nasal washes of patients with AR and are thought to be the dominant source of histamine in late phase responses (LPR) to allergen challenge in patients[110, 111]. Furthermore, as noted above, basophils are a significant source of LTC4. Thus, therapeutics that are thought to target mast cell activation in the context of AR may partially be deriving their efficacy based on their effect on basophil-derived histamine and leukotrienes.

Despite these advances, the role of IgE-activated basophils in AR is an active area of research. For example, recent studies indicate that patients with AR can demonstrate local IgE-responsiveness to allergens in the absence of systemic IgE-based reactions[112]. Therefore, whether basophils act locally or systemically in AR remains an area that can yield significant insight. In addition to IgE-based studies, a recent genome-wide association meta-analysis of AR subjects demonstrated an association with *TSLP* variants[113], and subsequent studies identified increased expression of *TSLP* in nasal polyps, which are strongly associated with AR[114, 115]. While these findings are supportive of a causative role for TSLP in the sequelae of AR, future studies are required to determine whether IgE-activated basophils or TSLP–elicited basophils contribute to the pathogenesis of AR.

## Asthma

Asthma affects 300 million people worldwide and is the most common chronic disease of childhood[116]. Currently, therapeutics in asthma include beta-agonists, oral and inhaled corticosteroids, anticholinergics, phosphodiesterase inhibitors, molecules that inhibit leukotriene production (zileuton, zafirlukast and montelukast) and anti-IgE monoclonal antibody (omalizumab)[117, 118]. Omalizumab is the first anti-IgE therapy to demonstrate efficacy and to be approved by the FDA for asthma[67]. Basophils activated by IgE are known to release histamine and LTC4 to promote inflammation[18]. Despite the fact that basophil-associated pathways are targeted by some of these therapeutics, the precise role of basophils in the pathogenesis of asthma remains poorly understood.

Animal model systems have provided some insights into potential roles for basophils in contributing to the development or propagation of allergic airway inflammation. For example, in a recent study employing a murine model of HDM-induced airway inflammation, basophils were found to play a direct role in promoting optimal $T_H2$ cytokine responses[53]. Although it was demonstrated that a rare populations of FcεRI-expressing inflammatory DCs were found to be both necessary and sufficient for the development of airway inflammation, specific depletion of basophils following the induction of airway inflammation resulted in significantly reduced $T_H2$ cytokine-associated inflammation[45]. Collectively, these studies suggest that basophils might operate with DC populations to contribute to pathologic airway inflammation[45]. Although the contribution of basophils to the pathogenesis of asthma in humans remains poorly understood, studies have identified that basophils are highly enriched in post-mortem lung tissue of patients who have died from asthma as well as in bronchial biopsies of patients with asthma[5, 6]. Furthermore, a recent study identified that T cell-derived IL-3 induces the expression of amphiregulin from human basophils[119]. Although amphiregulin has recently been shown to be a critical growth factor for the orchestration of epithelial repair and remodeling in the airway, the role of basophil-derived amphiregulin in asthma remains poorly defined[120]. These findings suggest that basophils may contribute to the pathogenesis of asthma in humans, but future studies will be required to directly address this hypothesis.

Classically, histamine and other inflammatory factors derived from IgE-activated mast are thought to be the primary mediators of asthma-associated inflammation[121]. Further, elevated FcεRIα expression has been shown to reduce innate immunity to rhinovirus, the most common trigger of asthma flares[122]. The role of IgE in the pathogenesis of asthma was further reinforced by the finding that anti-IgE therapy has demonstrated efficacy in patients with high levels of serum IgE[67]. While we are only starting to understand the cellular and molecular mechanisms by which anti-IgE therapy mediates its beneficial effects, one possibility is that blocking IgE disrupts IgE-mediated activation of basophils and the release of basophil-derived histamine, LTC4 and other inflammatory mediators. Indeed, omalizumab therapy has been shown to correlate with reduced basophil FceRI expression[123–126] and reduced allergen-mediated basophil activation [104, 123, 126–128]. Despite these advances, the specific role of the IgE-basophil axis in asthma remains to be determined.

In addition to IgE-mediated basophil responses, recent murine studies have demonstrated a critical role for TSLP-TSLPR interactions in promoting inflammation in different animal models of airway hyperresponsiveness[129, 130]. For example, a recent study employing a murine model of HDM-induced allergic inflammation in the lung demonstrated that TSLP blockade ameliorates disease[129]. In support of its role in human asthma, gain-of-function polymorphisms in *TSLP* have been associated with asthma and allergic airway disease in patients[131]. Further, TSLP signaling was shown to promote asthmatic airway remodeling pathways in human lung fibroblasts, and its expression was found to be significantly elevated in bronchial biopsies from patients with severe asthma[132, 133]. Despite these developments, the cellular mechanisms by which TSLP promotes allergic inflammation in the lung, and whether TSLP-elicited basophils play a role in asthma pathogenesis remain to be determined.

Asthma is a disease that is phenotypically and pathophysiologically heterogeneous in its clinical presentation and response to treatments[134]. Prior studies have shown that asthmatic patients exhibit phenotypically distinct basophil populations in the peripheral blood, some of which respond robustly to IgE-mediated activation, while others are minimally responsive[135]. As such, uncovering the precise roles of IgE-activated versus TSLP-activated basophils may help to clarify the complex inflammatory mechanisms that underlie asthma.

## Atopic Dermatitis

AD is a chronic, relapsing skin disease that is associated with the development of food allergies, asthma, AR and urticaria. It often begins in the first year of life and affects as many as 20% of children and 2–9% of adults[94]. AD has classically been associated with $T_H2$ cytokine responses as well as elevated serum IgE levels in patients. However, the precise role of these pathways in AD remains poorly defined. It has been observed that, early in infancy, IgE responses are not present due to an immature adaptive immune system, but subsequent sensitization to food and environmental allergens results in the development of allergen-specific IgE[94]. Further, a recent study showed that antigen-specific IgE-mediated activation of basophils occurs in the peripheral blood of AD patients[136]. In a similar context, IgE-dependent basophils were also found to be critical for the pathogenesis of chronic AD in mice in an IgE-dependent manner[37]. Although basophils only accounted for a small proportion of the cellular infiltrate found in the lesional skin, depletion of basophils resulted in a significant reduction in infiltrating eosinophils and neutrophils and also resulted in a dramatic loss in skin thickness[37]. Whether these mouse models are more representative of AD or urticaria remains to be determined. Collectively, these studies provoke the hypothesis that IgE-activated basophils may play a role in AD.

Although basophils have recently been implicated in the pathogenesis of murine AD-like disease, their precise role in human disease remains to be defined. The development of novel monoclonal antibodies (mAbs) (J175-7D4, BB1 and 2D7) that specifically stain human basophils has allowed for the identification of basophils in the lesional skin of AD patients by immunohistochemical techniques[2, 137] (Kim *et al.*, unpublished). Employing anti-human basophil-specific mAb (2D7) and flow cytometric techniques, we have also identified enrichment of human basophils in lesional skin of AD patients but not in healthy control subjects or control psoriatic skin (Kim *et al.*, unpublished). Although these studies provoke the hypothesis that basophils may contribute to human AD, whether IgE-activated or TSLP-elicited basophils predominate in human AD remains unclear.

In recent years, TSLP has been associated with human AD and identified as an early promoter of $T_H2$ cell-associated cytokine responses[72]. Further, TSLP has been found to be a key hematopoietic cytokine in the elicitation of functionally distinct basophil populations that are potent producers of IL-4 and are activated independently of IgE[42]. In a murine model of AD associated with elevated TSLP production, significant TSLP-dependent basophilia was observed in lesional AD-like skin[42]. Critically, specifically targeting and eliminating TSLP-elicited basophil populations reduced $T_H2$ cytokine responses in the skin-draining lymph nodes, suggesting that TSLP-elicited basophils contribute the pathogenesis of AD-like inflammation. These findings are consistent with the finding that many patients with AD, particularly infants, may have disease that is promoted primarily by TSLP and its direct effects on the innate immune response as opposed to antigen-specific IgE and adaptive immune responses. However, the precise role of TSLP-elicited basophils in human AD remains to be determined.

Topical steroids remain the first-line agents in the treatment of AD. However, these treatments are associated with a wide range of both local and systemic side effects of particular concern in children[138]. Although there are no therapies designed to specifically target basophils, there are a number of therapeutics that target pathways common to both basophils and other hematopoietic cells. For example, the only nonsteroidal anti-inflammatory FDA-approved agents in AD are topical calcineurin inhibitors, tacrolimus and pimecrolimus. Although these agents are thought to act on T cells by inhibiting nuclear factor of activated T cell (NFAT) family-mediated transcriptional activation of IL-2, previous studies have shown that calcineurin inhibitors prevent IgE-mediated activation of

IL-4 production through NFAT pathways in human basophils[139, 140]. These findings suggest that existing therapeutics in AD may actually modulate basophil-specific pathways.

Although omalizumab blocks IgE-FcεRIα interactions on both mast cells and basophils, clinical studies employing omalizumab have yielded mixed results in AD[68]. AD is a disease with complex diagnostic criteria in which the role of IgE remains poorly understood. Therefore, future studies with well-defined stratification of disease may be required to address the role of IgE and basophils in AD. Additionally, recent studies implicating TSLP as a key mediator of basophil hematopoiesis offer a new avenue of investigation[42]. Future studies specifically targeting TSLP and/or basophils may provide new therapeutic targets for novel biologics to treat AD. Elucidating whether IgE-activated basophils and/or TSLP-elicited basophils contribute to the pathogenesis of AD will help to direct future therapeutics.

## The influence of anti-IgE therapy on basophils

The growing number of clinical trials employing anti-IgE therapy has resulted in the emergence of a better understanding of the role of IgE in regulating basophil responses. For example, a number of studies have shown that anti-IgE therapy results in the down-regulation of FcεRIα expression basophils[123, 124, 141] as well as a reduction in basophil effector responses during anti-IgE therapy[127, 128]. However, the precise mechanisms by which anti-IgE therapy result in reduced basophil responses, and whether these effects contribute to the clinical improvement observed with anti-IgE therapy, remain to be determined. Nonetheless, a better understanding of these pathways may identify biomarkers of disease severity or allow for the development of new targeted approaches for the treatment of allergic disease.

## Concluding remarks

Basophils are implicated in multiple human diseases including autoimmune disorders, inflammatory disorders, cancer and allergies and asthma. However, the contributions of basophils to the development of human disease states remain poorly defined. Recent murine and human studies suggest that developmental and functional heterogeneity exists within basophil populations and that basophils can be divided into at least two categories, IL-3-elicited basophils and TSLP-elicited basophils (Fig. 3). Moreover, these studies suggest that IL-3-elicited basophils operate in an IgE-dependent manner while TSLP-elicited basophils operate in an IgE-independent manner. It is also becoming more apparent that allergic conditions can also be stratified into two categories, those mediated by IgE and those that appear to be IgE-independent. Critically, allergic diseases that are thought to be predominately IgE-independent are highly associated with gain-of-function polymorphisms in the gene encoding *TSLP* and elevated TSLP expression (Fig. 4). Therefore, it is likely that the contributions of basophils to human allergic disorders will differ depending on the allergen, the disease state and whether the disease is IgE-dependent or TSLP-dependent. These recent studies may also provide insight into varied efficacy of anti-IgE therapy and other biologics across different allergic disease states. Although anti-IgE-treatment may be beneficial in preventing the activation of IL-3-elicited basophils populations, this strategy may prove ineffective in targeting TSLP-elicited basophils. Thus, it is likely that directly targeting basophil populations or simultaneously targeting both TSLP and IgE may prove beneficial in the treatment of allergic disease states. Currently, clinical trials are underway employing anti-TSLP monoclonal antibodies in patients, and multiple studies are investigating the influence of anti-IgE therapy on basophil populations in patients (see www.clinicaltrials.gov). Future studies of basophil phenotype, activation and function in

patients undergoing anti-TSLP and anti-IgE treatment would yield significant insight into the clinical relevance of basophil heterogeneity in the context of human allergic disease.

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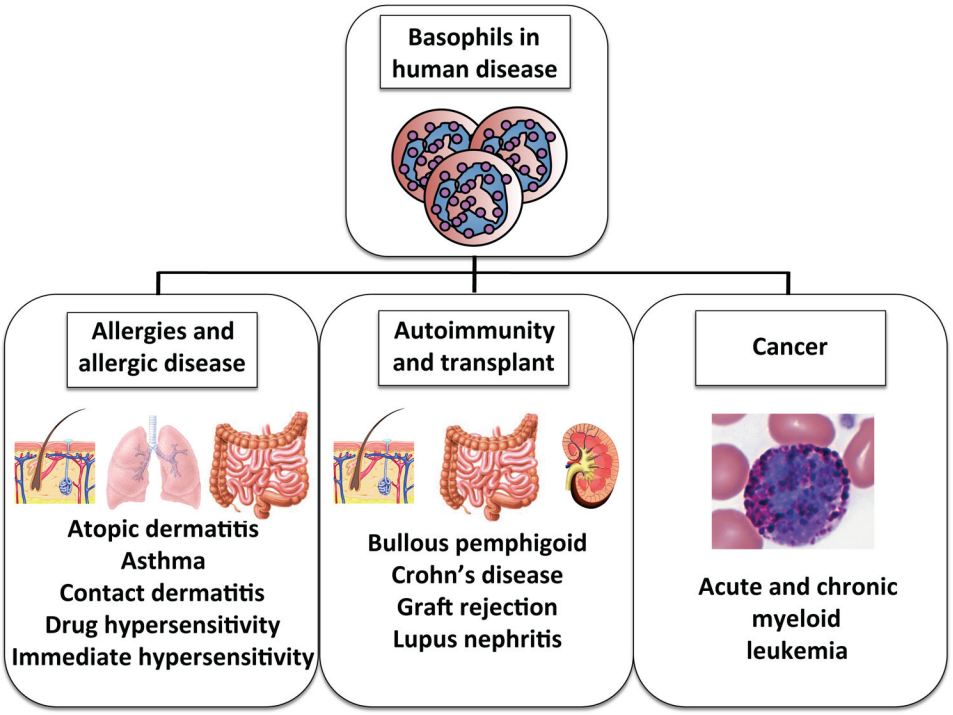


**Figure 1. The clinical relevance of basophils**

Basophils have been shown to contribute to many human disease states. Including allergic disease (contact dermatitis, atopic dermatitis, hypersensitivity responses and asthma), autoimmunity (bullous pemphigoid and lupus nephritis), inflammatory disorders (Crohn's disease) and cancer (acute and chronic myelogenous leukemia). This article will focus on the contribution of basophils to allergic disease.

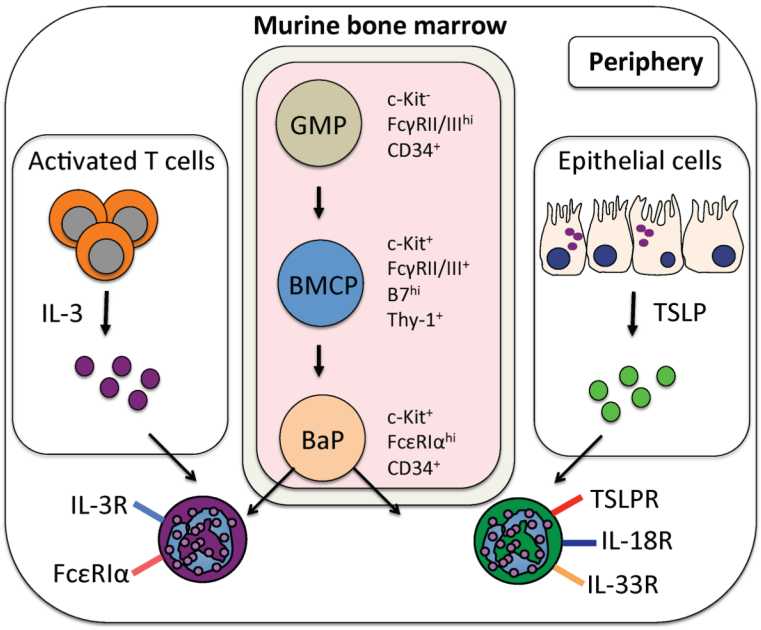


**Figure 2. Basophil development**

Murine basophils develop from hematopoietic stem cell (HSC) populations that reside in the bone marrow. As HSCs mature, they become granulocyte monocyte precursors (GMPs), basophils mast cell precursors (BMCPs) and basophil precursors (BaPs). To date 2 cytokines, T cell-derived IL-3 and epithelial cell-derived TSLP, have been shown to promote distinct phases of basophil development. After fully maturing in the bone marrow, basophils can enter the periphery and contribute to inflammation.

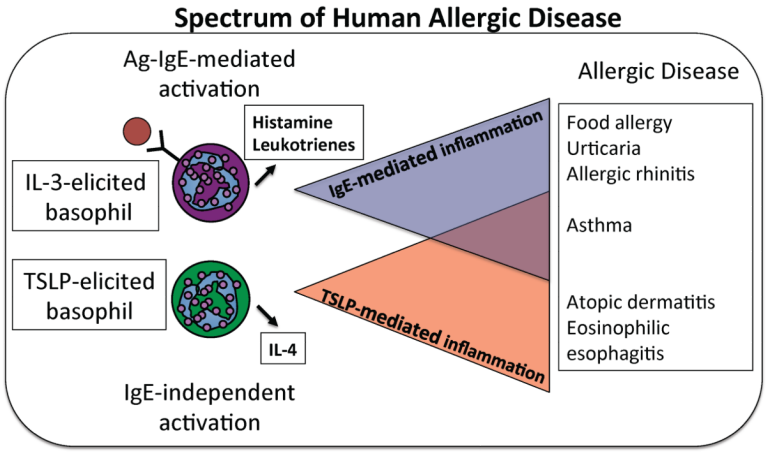


**Figure 3. Heterogeneous effector functions of basophil populations**

Recent studies have demonstrated that IL-3-elicited basophils are highly responsive to FcεRI crosslinking via IgE-antigen complexes. After encountering antigen, IL-3-elicited basophils release multiple effector molecules that can contribute to allergic inflammation. TSLP-elicited basophils are non-responsive to IgE-antigen complexes but produce multiple effector molecules following stimulation with cytokines such as IL-33 and IL-18. The observed functional heterogeneity between IL-3-elicited and TSLP-elicited basophils may allow IL-3-elciteid basophils and TSLP-elicited basophils to contribute to various allergic disorders that are associated with IgE responses and/or TSLP production.

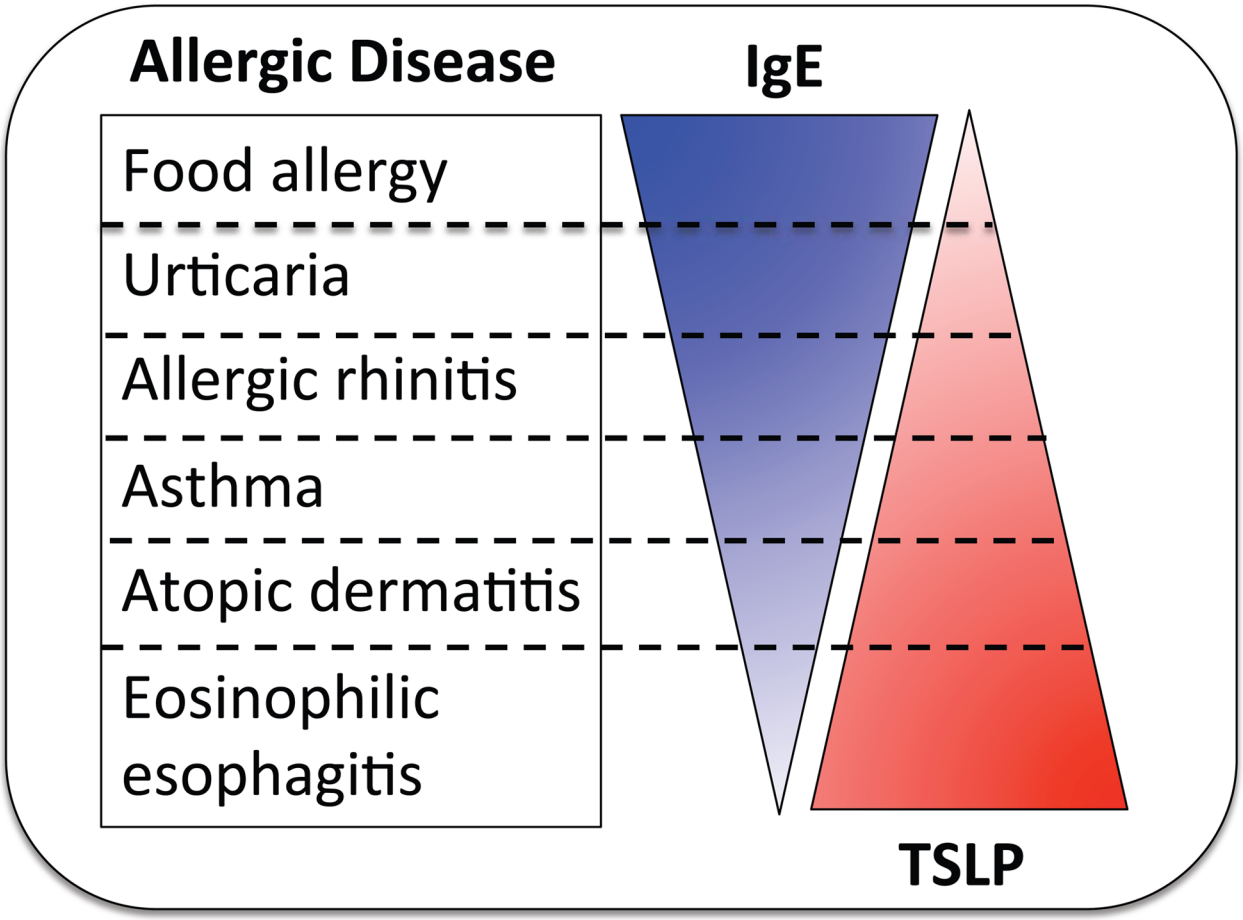


**Figure 4. The contributions of IgE and TSLP to allergic disease**

Allergic disease states appear to separate into three separate categories, those that are highly IgE-dependent (urticarial and food allergy), those that are partially IgE-dependent (asthma and atopic dermatitis) and those that are IgE-independent (eosinophil esophagitis). Critically, allergic diseases that are only partially dependent on IgE, or independent of IgE are highly associated with TSLP production. Therefore, it is likely that IL-3-elicited basophils that are highly responsive to IgE-antigen complexes contribute to IgE-mediated allergic disorders, while TSLP-elicited basophils contribute to IgE-independent disorders.

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**Table 1**

Summary of the activating factors and effector molecules of murine and human basophils.

| | Mouse | | | Human | | |
|---|---|---|---|---|---|---|
| **Stimulus** | **Response** | **Effector Molecules** | **Ref.** | **Response** | **Effector Molecules** | **Ref.** |
| ***Immunoglobulin*** | | | | | | |
| IgD | ? | | | Yes | IL-1, IL-4, antimicrobial peptides, B cell activating factor | 76 |
| IgE | Yes | IL-4, histamine | 142, 143 | Yes | IL-4, IL-13, histamine, leukotriene, platelet-activating factor | 144,77,78 |
| IgG | Yes | Platelet-activating factor | 75 | No | | |
| ***Cytokine*** | | | | | | |
| IL-3 | Yes | IL-4, IL-13 | 145 | Yes | IL-13, histamine, leukotriene, amphiregulin | 146–148 |
| IL-18 | Yes | IL-4, Il-13, histamine | 80 | ? | | |
| IL-33 | Yes | IL4, IL-13 | 80145 | Yes | IL4, IL-5, IL-6, IL-13 | 79 |
| TSLP | Yes | IL-4, IL-6, CCL3, CCL4, CCL12 Cxcl12 | 42 | ? | | |
| ***Complement*** | | | | | | |
| C5a | ? | | | Yes | Histamine | 149, 150 |
| ***Allergen*** | | | | | | |
| Derp1 | ? | | | Yes | IL-4, IL-5, IL-13 | 84 |
| Papain | Yes | IL-4 | 40 | ? | | |
| ***Microbial*** | | | | | | |
| *Necatur americanus* | ? | | | Yes | IL-4, IL-5, IL-13 | 84 |
| *Nippostrongylus brasilielensis* | Yes | IL-4 | 31 | ? | | |
| *Strongyloides venezuelensis* | Yes | IL-4 | 60 | ? | | |
| Schistotome-derived IPSE-alpha-1 | Yes | IL-4 | 89 | ? | | |
| HIV-derived GP120 | ? | | | Yes | IL-4, IL-13 | 88 |
| TLR ligands | ? | | | Yes | IL-4, IL-13 | 151 |

?, represents unknown or untested areas of research.