



Antibody mediated regulation of basophils: emerging views and clinical implications

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Abstract

An increasing number of human diseases, such as allergies, infections, inflammation, and cancer, involve roles for basophils. Traditionally viewed as the rarest leukocytes present only in circulation, basophils have recently emerged as important players in systemic as well as tissue-specific immune responses. Their functions are regulated by immunoglobulins (Igs), which enable basophils to integrate diverse adaptive and innate immunity signals. IgE is well known to regulate basophil responses in the context of type 2 immunity and allergic inflammation; however, growing evidence shows that IgG, IgA and IgD also shape specific aspects of basophil functions relevant to many human diseases. Here, we discuss recent mechanistic advances underpinning antibody-mediated basophil responses and propose strategies for the treatment of basophil-associated disorders.

The basophil-antibody partnership

Human basophils represent the least abundant leukocyte population and are traditionally viewed as the circulating counterpart of tissue-based mast cells. These two circumstances have somewhat limited our understanding of the fundamental biology of basophils and its relevance to disease. Recent advances show that basophils participate in immune responses

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that go well beyond allergen-induced IgE-driven degranulation (see Clinician's corner). Indeed, basophils can home to lymphoid or non-lymphoid tissues after sensing antigen [1]. These antigen-activated basophils implement a large spectrum of effector functions which promote the amplification of physiological or pathological immune responses, mainly **type 2 immunity** [2]. Of note, basophil-mediated type 2 responses largely depend on the ability of basophils to bind antigen-specific IgE through the high-affinity Fc epsilon receptor (FcεRI), which basophils express at high density [2].

Aside from IgE, basophils bind other antibody classes, including IgG, IgA, IgD and possibly IgM, which can enhance or mitigate IgE-dependent and IgE-independent basophil responses. Such responses are under the additional control of a large array of effector molecules other than Igs, including cytokines and chemokines. Some of these regulatory molecules derive from the same basophils following their activation by IgE-driven signals emanating from FcεRI. In general, the fine composition of basophil-regulating molecules released during an immune response depends on the immunological and anatomical context associated with that response.

Antibody-activated basophils have recently been found to play a pathogenetic role in a growing number of disorders, including allergy, autoimmunity, and cancer. Here, we discuss the impact that distinct antibody responses have on basophil functions and how antibodies may interact with other immune effector molecules to regulate these functions positively or negatively. We also discuss potential therapeutic strategies to attenuate the pathological functions of basophils in disease.

Basophils and IgE responses

IgE binds to two cell surface receptors, the high-affinity IgE receptor FcεRI and the low-affinity IgE receptor CD23, also known as FcεRII in humans and mice [3]. Of note, basophils express FcεRI, but not CD23 which is instead expressed by B cells and dendritic cells (DCs) among other cell types in humans [3] [Human Protein Atlas, <https://www.proteinatlas.org/>]. Aside from FcεRI and CD23, IgE has been reported by some groups to bind to Fc gamma receptors (FcγRs), including FcγRIIB, FcγRIII and FcγRIV [4–6]. Little is known about these interactions, but IgE immune complexes seem to bind FcγRIIB on the C57.1 mouse mast cell line and J774 macrophage cell line with low affinity through an interaction that occurs at high IgE concentrations [4].

The high-affinity IgE receptor

FcεRI consists of three subunits, an α subunit that binds the Fc portion of IgE, an accessory β subunit that amplifies signaling, and a γ subunit that drives signaling and is shared by other Fc receptors, including FcγRI, FcγRIIIA and FcαRI [7]. Of note, basophils and mast cells express FcεRI as an αβγ₂ tetramer at high density [8]. Human circulating basophils do not appear to endocytose and clear FcεRI-bound IgE as circulating **BDCA1⁺ dendritic cells (DCs)** and monocytes do [9]. Together with the extremely high affinity of human IgE for FcεRI receptors that saturates these receptors at physiological IgE concentrations, IgE can persist on the surface of basophils for weeks or months despite its short half-life of only

2–3 days in the fluid phase [10], making the functional pool of IgE much bigger and more persistent than the circulating free IgE that can be measured.

By binding to FcεRI, IgE regulates multiple aspects of basophil differentiation, survival, and function (Figure 1). Of note, serum IgE can increase the expression of FcεRI on basophils in a concentration-dependent manner, thereby providing positive feedback to IgE-dependent basophil responses [11,12]. Moreover, crosslinking of FcεRI-bound IgE by multivalent antigens or an anti-IgE antibody, signals an immediate inflammatory response dominated by degranulation, which consists in the release of preformed mediators such as histamine, heparin, and tryptases, as well as *de novo* synthesized compounds such as leukotriene C4 (LTC₄) by secretory granule exocytosis [13]. These mediators promote a **type I hypersensitivity** reaction, which includes acute vasodilation, vascular permeability, airway smooth muscle constriction, mucus secretion, itching, and anaphylaxis [13].

As recently shown, the magnitude of basophil degranulation depends on the sialic acid content of IgE [14]. Furthermore, by showing that the induction of basophil degranulation by an anti-IgE antibody *ex vivo* varies at different times of a day, additional studies point to the involvement of a circadian component in the regulation of FcεRI signaling in basophils, at least in patients with asthma [15]. Aside from the immediate inflammatory response that takes place within a few minutes following crosslinking of FcεRI-bound IgE, basophils mount a delayed inflammatory response hours later [13]. Such late response reproduces many of the symptoms of the early response and involves basophil secretion of cytokines and chemokines that leads to the accumulation and activation of various pro-inflammatory leukocytes in tissues [13].

Effects of IgE-induced signaling

Although mostly patrolling the general circulation, some basophils home to draining lymph nodes following immunization [16]. Here, they express MHC-II that may present antigens to specific CD4⁺ T cells [16–19]. Following IgE crosslinking, basophils also enhance the release of cytokines such as interleukin-4 (IL-4) and IL-13, which promote **T_H2 polarization** of antigen-activated T cells [18–20]. Furthermore, IgE-activated basophils express CD40 ligand (CD40L) and B cell-activating factor of the TNF family (BAFF) [16,17], which elicit IgE and IgG1 **class switching** in B cells by signaling in concert with IL-4 and/or IL-13 [19,21]. Finally, IL-4 and IL-6 from IgE-induced basophils enhance B cell survival and memory responses [18]. Last but not least, cytokines and chemokines from tissue-based IgE-activated basophils promote the recruitment and activation of eosinophils, group 2 **innate lymphoid cells** (ILC2s), and macrophages [22–24]. This process contributes to the development and amplification of type 2 responses and allergic inflammation [25,26].

Modulation of IgE-induced signaling

IgE-mediated basophil responses can be modulated by a variety of signals (Figure 1). IL-3, a cytokine from T cells, macrophages, and stromal cells, is required for the development of basophil precursors in the bone marrow and potentiates IgE-induced histamine as well as IgE-induced IL-4 and IL-13 production by basophils [27,28]. Also, members of the IL-1 family of cytokines, including IL-1β, IL-18, and IL-33 from innate immune cells, enhance

IgE-mediated basophil activation. Indeed, IL-1 β may increase IgE-induced basophil release of histamine [29,30], although this finding remains controversial because other studies have not observed such an enhancing effect [31,32]. Furthermore, IL-18 enhances IgE-induced IL-4 and IL-13 release by IL-3-stimulated bone marrow basophils in vitro [33]. In addition, IL-33 enhances IgE-induced secretion of histamine, LTC₄, and cytokines such as IL-4, IL-13 and IL-8 by circulating basophils [34]. Similarly, GM-CSF and IL-5 increase IgE-induced basophil release of histamine and LTC₄ [32].

Of note, blood basophils from patients with seasonal allergic rhinitis express high amounts of IL-17RB, a subunit of the IL-25 receptor [35]. Engagement of this receptor by IL-25 from allergen-sensing mucosal epithelial cells, including chemosensory **tuft cells**, enhances IgE-mediated basophil survival, activation, IL-4 secretion, and degranulation in vitro [35]. Together with the IL-25-dependent activation of ILC2s secreting IL-5 and IL-13 [36], the IL-25-dependent activation of basophils releasing IL-4 and IL-13 may lead to the amplification of T_H2 responses in vivo. Of note, microbial signals from **Toll-like receptor 2** (TLR2), TLR4, or TLR9, also enhance IgE-induced basophil production of IL-4, IL-13, and RANTES, as well as the ensuing T_H2 polarization of naïve CD4⁺ T cells [37,38], enabling basophils to link microbial infection with type 2 immunity.

Human basophils also express receptors of the CD300 family, including the inhibitory receptors CD300a and CD300f as well as the activating receptor CD300c [39,40]. In addition to binding to the phospholipids phosphatidylserine (PS) and phosphatidylethanolamine (PE) on the outer leaflet of the plasma membranes of apoptotic and activated cells, these CD300 family members modulate IgE-mediated basophil activation [39,40]. Remarkably, the membrane density of CD300a is lower on basophils from patients with birch pollen allergy compared to basophils from healthy controls [39]. Accordingly, apoptotic cells expressing PS and PE inhibit anti-IgE-mediated basophil degranulation more efficiently in healthy donors than in allergic patients [41]. Conversely, the density of surface CD300c is increased on basophils from children with cow's milk allergy and correlates with the severity of hypersensitivity symptoms [40]. Unlike signals emanating from CD300a, signals generated by CD300c enhance IgE-induced degranulation and IL-4 expression [40]. These findings highlight the importance of the modulation of IgE-mediated basophil responses in allergic diseases and may support therapeutic strategies against allergies, by aiming to activate CD300a or inhibiting CD300c. Thus, basophils integrate multiple innate and adaptive environmental signals to shape IgE-induced Fc ϵ RI-mediated immune responses. However, many of these signals also modulate basophil responses independently of Fc ϵ RI, which highlights the importance of targeting molecules beyond IgE or Fc ϵ RI in therapies against allergy. This approach may be especially important for those allergic disorders that are independent of IgE but dependent on basophils, including **eosinophilic esophagitis** [42,43].

IgE signaling in health and diseases

In addition to being involved in the pathogenesis of various ailments, including allergy, IgE modulates physiological basophil responses and enhances immune homeostasis and immune protection. The homeostatic nature of some IgE responses is exemplified by the

detection of abundant IgE on circulating basophils and tissue mast cells from healthy individuals. Growing evidence indicates that this IgE mostly derives from extrafollicular B cells, including mesenteric lymph node B cells exposed to local **glucocorticoids** [44]. Unlike pathological IgE from allergic patients, which typically has high affinity for allergen, this natural IgE from healthy individuals has low affinity for antigen [45].

Accordingly, natural IgE generally lacks extensive **somatic hypermutation** in its antigen-binding variable region, possibly because the production of natural IgE does not require cognate B cell interaction with CD4⁺ T cells in the context of the **germinal center** reaction [46]. Unlike high-affinity IgE from allergic patients, low-affinity IgE from healthy individuals does not induce massive oligomerization of the FcεRI receptor and thus, does not trigger extensive basophil (or mast cell) degranulation. Rather, low-affinity IgE may enhance host resistance against noxious antigens by promoting limited basophil degranulation, which causes proteolytic degradation and clearance of IgE-bound antigens [47,48]. Low-affinity IgE may also compete with high-affinity IgE for both antigen and FcεRI binding to limit any exuberant activation of basophils and mast cells [44].

Furthermore, natural IgE-mediated basophil responses support skin barrier defense [49] and can protect against skin carcinogenesis following skin exposure to carcinogens [50]. In helminth infections, basophil activation by IgE-worm antigen complexes contributes to worm clearance and is essential for **granuloma** formation upon repeated worm exposure to limit tissue damage in mice [51,52]. IgE-induced immunity has also been proposed to play a role in the control of food quality by mounting allergic defenses against foods associated with noxious substances, the exaggeration of which can result in pathological food allergy [53]. In summary, natural IgE contributes to systemic and tissue immune surveillance against common environmental antigens, noxious substances or worms by working in partnership with basophils and mast cells.

In **atopic dermatitis** (AD), an inflammatory skin disorder, a large proportion of patients show increased propensity to developing itchy flare-ups and allergy [54]. These patients harbor pathogenic allergen-specific IgE [54], possibly due to their exposure in early life to common environmental antigens, including food antigens, through the inflamed skin, rather than via tolerance-inducing mucosal surfaces such as the gut which harbor myriad tolerogenic mechanisms [55–58]. In a mouse model of AD, skin basophils but not mast cells released leukotrienes in response to IgE, which triggered acute itching through a mechanism involving leukotriene-responsive skin sensory neurons [54]. Moreover, in AD neonates or young children, antigen penetration through the inflamed skin may predispose them to allergy by stimulating the production of high-affinity IgE by B cells already expressing high-affinity IgA or IgG [55,56,59]. These B cells would first undergo sequential class switching from IgA or IgG to IgE in draining lymph nodes to subsequently differentiate into plasma cells secreting high-affinity IgE [59].

IgE-mediated basophil responses are also dysregulated in certain autoimmune conditions, having an impact on pathogenesis. For instance, aside from producing autoreactive IgE, patients with **systemic lupus erythematosus** (SLE) harbor circulating basophils at a heightened activation state, with increased expression of CD203c and HLA-DR [17].

These activated basophils exhibit enhanced migration to the spleen and lymph nodes [17], which has been associated with increased SLE severity. Accordingly, in the *Lyn*^{-/-} mouse model of SLE, basophils promote autoantibody production and nephritis in an IL-4- and IgE-dependent manner [17].

Chronic spontaneous urticaria (CSU) is another autoimmune condition in which IgE-activated basophils, including skin basophils, express IL-31, a key pathogenicity factor in CSU [60]. In this regard, an anti-IgE monoclonal antibody, omalizumab, shows efficacy in the treatment of CSU [61]. **Mixed connective tissue disease** (MCTD) is an overlap disease characterized by a combination of autoimmune disorders, including SLE, **systemic sclerosis**, and **polymyositis**. Similar to SLE patients, MCTD patients can display IgE dysregulation, including increased IgE reactivity against small nuclear ribonucleoprotein U1, which is a nuclear self-antigen. Moreover, MCTD patients exhibit basopenia together with basophil overexpression of CCR3, a chemokine receptor that promotes lung homing [62,63]. In mice, basophil depletion dampens MCTD-associated lung pathology and IgE deficiency prevents MCTD development [64], which suggests a key pathogenic role for IgE-activated basophils in this autoimmune disorder.

Finally, basophils can also be found in tissues and/or draining lymph nodes from patients with certain cancers, such as ovarian cancer or pancreatic ductal adenocarcinoma; their presence has been associated with either pro- or anti-tumorigenic functions [1]. In a mouse model of chronic skin inflammation, IgE-induced histamine from skin-infiltrating basophils acted via the histamine receptors H1R and H4R to promote hyperplasia of epithelial cells harboring oncogenic mutations, which can potentially lead to cancer development [49]. In summary, the available evidence suggests that IgE, FcεRI, and basophils may represent promising therapeutic targets not only in allergic disorders, but also in various autoimmune diseases and cancers, although this still warrants further and robust investigation.

Basophils and IgG responses

IgG has long been reported to bind to human basophils [65], where two low-affinity receptors, FcγRIIA and FcγRIIB, were subsequently identified [66,67]. However, additional IgG receptors may also exist.

Activating and inhibitory IgG receptors

In humans, basophils also express a small amount of the GPI-anchored low-affinity IgG receptor FcγRIIB [68], the biological function of which is not well understood. For instance, FcγRIIA but not FcγRIIB crosslinking triggers basophil upregulation of CD203c, a hallmark of degranulation [67]. Yet, IgG immune complexes cannot activate basophils, which indicates that the inhibitory IgG receptor FcγRIIB might exert a dominant effect over the activating IgG receptor FcγRIIA, although this warrants further investigation [65]. Additional studies show that co-ligation of all FcγRs and FcεRI does not cause basophil activation in vitro [67], which supports the notion that the inhibitory IgG receptor FcγRIIB might also have a dominant effect over the activating IgE receptor FcεRI (Figure 2).

In mice, basophils co-express the activating Fc γ RIIA receptor and the inhibitory Fc γ RIIB receptor [67]. In agreement with results from studies with human basophils, Fc γ RIIB deploys a dominant inhibitory function on the activation of mouse basophils triggered by Fc γ RIIA in vitro [67]. Nevertheless, Fc γ RIIA-mediated basophil activation, such as that mediating histamine release in response to asparaginase-specific IgG, contributes to asparaginase hypersensitivity in mice [69]. In addition, Fc γ RIIA on mouse basophils can capture antigen-specific IgG1 after passive or active sensitization, eliciting basophil release of **platelet-activating factor** to cause **anaphylaxis** following systemic exposure to antigen [70].

Interaction between IgG and IgE

Aside from engaging the inhibitory receptor Fc γ RIIB, allergen-specific IgG competes with basophil-bound IgE for allergen binding, thereby interfering with Fc ϵ RI activation by allergen-specific IgE and the ensuing amplification of T_H2 responses [71] (Figure 2). These effects of allergen-reactive IgG contribute to the induction of allergen-specific protection by **allergen immunotherapy** (AIT), which triggers the production of allergen-specific IgG [72]. Among various IgG subclasses, IgG4 best correlates with the induction of protection by AIT in clinical studies [73], although experimental evidence suggests that the efficacy of IgG4 in interfering with basophil activation via Fc γ RIIB is comparable to that of IgG1, based on the expression of basophil surface CD63 [74].

A further mechanism by which IgG regulates basophil function involves the production of IgG autoantibodies to autologous IgE, which can be detected in both healthy individuals and atopic patients [75,76]. These autoantibodies can either elicit or inhibit basophil activation by crosslinking Fc ϵ RI-bound IgE [75,77–79] or blocking the binding of IgE to Fc ϵ RI [75], respectively. In the latter case, IgG binding by IgE also reduces the concentration of free IgE available for interaction with Fc ϵ RI, which renders basophils more resistant to allergen sensitization by causing Fc ϵ RI downregulation [80]. Last but not least, IgE-specific IgG antibodies can interfere with the activation and plasma cell differentiation of IgE class-switched B cells by targeting the IgE-B cell receptor as well as the inhibitory receptor Fc γ RIIB [81]. All these inhibitory effects of IgE-specific IgG account for the clinical efficacy of monoclonal antibodies such as omalizumab that is currently used in the therapeutic management of allergic disorders [82].

Remarkably, IgE-reactive IgG antibodies can also promote basophil-dependent allergic and inflammatory responses. In pregnant women, circulating IgE-specific autoantibodies can facilitate the passage of maternal allergen-specific IgE to the fetus across the placenta via the neonatal Fc receptor [83]. Accordingly, most IgE from cord blood is complexed with IgG [83]. In mice, this pathway sensitizes fetal mast cells against allergens and mediates allergic responses in newborns following their initial exposure to allergen [84]. In SLE patients, IgE-specific IgG is detectable in circulation and significantly increases during active disease [17]. By crosslinking Fc ϵ RI-bound IgE, this autoantibody potentiates the antigen-presenting and T cell-activating functions of basophils and enhances basophil expression of B cell-activating cytokines such as IL-4 and BAFF that can aggravate the production of pathogenic autoantibodies [17].

Basophils and IgA responses

IgA is the most abundant antibody in most mucosal secretions in humans and mice, which acquire secretory IgA (SIgA) following the interaction of mucosal plasma cells secreting IgA dimers with mucosal epithelial cells expressing the polymeric Ig receptor (pIgR) [85]. However, IgA is also relatively abundant in the general circulation, which harbors monomeric IgA from bone marrow-based IgA-secreting plasma cells.

Receptors for mucosal and circulating IgA

Mucosal SIgA is comprised of an IgA dimer produced by mucosal plasma cells that is covalently bound to a J-chain protein from plasma cells and secretory component (SC) protein that corresponds to a fragment of the pIgR from epithelial cells [85]. Of note, SC is a highly glycosylated protein that derives from the proteolytic processing of pIgR during endosome-mediated basolateral-to-apical translocation of dimeric IgA across mucosal epithelial cells, a process referred to as transcytosis [85].

Unlike dimeric IgA or SIgA from mucosal tissues, human but not mouse IgA from the circulation is largely monomeric [85]. Of note, neither human nor mouse basophils express common receptors for monomeric or dimeric IgA, including Fc α RI (CD89), pIgR, Fc μ R, Fc α / μ R, asialoglycoprotein receptor (ASGPR), FcRL4 and SIGNR1 [86] [Human Protein Atlas: <https://www.proteinatlas.org/>]. Therefore, in principle, IgA should have no effect on basophils. Yet, human basophils show some expression of the less common IgA receptors, including the transferrin receptor CD71, which binds IgA monomers, as well as DC-SIGN and dectin-1, two carbohydrate-binding C-type lectin receptors that bind SIgA [87] [Human Protein Atlas: <https://www.proteinatlas.org/>]. Consistent with this expression, early studies show that SIgA could induce histamine and LTC₄ release by IL-3-primed basophils in vitro [88]. This effect was independent of signals from Fc α RI and may have involved the SC component of SIgA [88]. By showing that the SIgA-induced basophil release of histamine was inhibited by pertussis toxin, one study pointed towards the possible involvement of a G-protein coupled receptor in SIgA signaling to basophils [89].

Complex interactions between IgA and IgE

Monomeric IgA binds to human basophils and negatively modulates their IgE-induced responses as evidenced from reduced cell surface CD63 expression [90], suggesting that basophil receptors for monomeric IgA have an inhibitory impact on IgE-induced signals from Fc ϵ RI (Figure 3). Indeed, monomeric IgA from peanut-allergic patients inhibited basophil degranulation by IgE-sensitized basophils exposed to peanut extract in a dose-dependent manner [90]. Similarly, monomeric IgA has bound to peritoneal or bone marrow-derived mast cells from mice in a calcium- and sialic acid-dependent manner, inhibiting IgE-induced degranulation [90]. However, it remains unclear whether the inhibitory effects of monomeric IgA on IgE-sensitized basophils require Fc α RI. This species-specific IgA receptor is only expressed by human immune cells and delivers immune inhibitory signals upon interacting with monomeric but not dimeric IgA [91,92].

Unlike Fc α RI ligation by monomeric IgA, crosslinking of Fc α RI by dimeric IgA, SIgA, or an agonistic antibody to Fc α RI triggers degranulation of the rat basophilic cell line RBL-2H3 [93]. These data suggest that Fc α RI delivers basophil-activating signals upon its extensive engagement by multivalent IgA-antigen complexes [91,93]. The opposing effects of monomeric IgA and anti-Fc α RI might result from differential phosphorylation patterns of the FcR γ -chain from Fc α RI. Specifically, engagement of Fc α RI by a monovalent ligand such as monomeric IgA may induce partial phosphorylation of the immunoreceptor tyrosine-based activation motif (ITAM) from the FcR γ -chain, which thereafter recruits the SHP-1 phosphatase to inhibit signaling from Fc ϵ RI [94]. In contrast, crosslinking of Fc α RI by a multivalent ligand such as IgA-bound antigen complexes likely triggers extensive phosphorylation of the ITAM from the FcR γ -chain, which thereafter recruits the kinase Syk, the activation of which is key for Fc ϵ RI to initiate degranulation [91].

IgA and IgE in diseases

Further insights into the function of IgA in basophils have come from some epidemiological studies showing an increased incidence of various allergic diseases in some patients with **selective IgA deficiency** (SIgAD) [95]. Since these patients have markedly reduced concentrations of serum IgA, the association of SIgAD with allergy is consistent with diminished inhibition of pro-allergy basophil functions by circulating monomeric IgA, which predominantly corresponds to the IgA1 subclass. Besides SIgAD, some allergic or atopic subjects harbor reduced concentrations of allergen-specific IgA in serum compared to healthy controls [96,97]. Conversely, allergic patients treated with AIT show increased serum concentrations of allergen-specific IgA, which correlates with protection against allergy [98].

Despite these findings, the protective role of serum IgA in allergy is not conclusive, as additional studies found no increased frequency of allergy in SIgAD [95] and no negative correlation of circulating allergen-specific IgA with allergy [99]. These seemingly conflicting findings likely reflect the heterogeneity of study populations and the complex symptoms and pathogenic mechanisms of SIgAD and allergic disorders. One possibility is that allergen-specific IgA confers protection against allergy in some but not all SIgAD patients, although this remains conjectural and future studies should clarify these discrepancies.

In addition to circulating monomeric IgA, some findings indicate that mucosal dimeric SIgA has a protective role against allergy [100,101], although this conclusion needs further validation [102]. The possible protective role of SIgA against allergy may seem at odds with the ability of SIgA to induce basophil degranulation [88]. However, by limiting the penetration of allergens across the mucosal surface, SIgA might reduce host sensitization and/or subsequent allergen stimulation. Furthermore, SIgA might induce tolerogenic responses in other immune cells, including antigen-presenting dendritic cells. In agreement with this possibility, mucosal SIgA positively correlates with protection against allergy, including AIT-induced protection [98]. Finally, SIgA may further protect against allergy by shaping the composition and immunometabolic functions of the gut microbiota [55,56].

Basophils and IgD responses

IgD is an ancient antibody that is highly conserved in jawed vertebrates, but the function of its secreted component has long remained mysterious [103]. Besides serving as a signal-transducing antigen receptor on B cells, IgD is secreted in circulation and some mucosal fluids by IgD-secreting plasma cells clonally derived from IgM-to-IgD class-switched B cells [104]. In humans, IgD-secreting plasma cells mostly emerge from tonsillar inductive sites and predominantly home to effector sites from the nasopharyngeal mucosa. Pioneering studies found that basophils increase in both spleen and bone marrow following injection of an agonistic anti-IgD antibody in mice [105,106]. These early findings raise the possibility that basophils are equipped with an IgD receptor that delivers activating and/or survival signals. Accordingly, secreted IgD can bind circulating basophils, tissue-based mast cells as well as basophil and mast cell lines [107–110].

IgD receptor and T_H2 responses

IgD binding to basophils involves a protein complex containing the tandem-repeat galactose-binding lectin galectin-9 and the transmembrane proteoglycan CD44, which serves as a galectin-9 receptor [109]. Upon crosslinking of surface IgD, human basophils produce pro-inflammatory mediators such as IL-6, IL-8, and CXCL10, B cell-activating molecules such as IL-4, IL-13, and BAFF, as well as anti-microbial molecules such as LL-37 and β -defensins [104,107,110]. Some of the cytokines such as IL-6 and BAFF from IgD-activated basophils cooperatively induce plasma cell differentiation and/or survival, highlighting the possible involvement of basophils in mucosal homeostasis.

In mice, IgD-activated basophils migrate to draining lymph nodes and release IL-4 and IL-13, which amplify T_H2 cell polarization and T_H2 cell-driven B cell production of antigen-specific IgG₁ and IgE [109] (Figure 3). Human mast cells mount similar responses following crosslinking of cell-bound IgD [108]. Collectively, these findings indicate that IgD secreted by IgD class-switched plasma cells amplify T_H2 immunity by linking the innate and adaptive arms of the immune system. This process might occur early during T_H2 responses and contribute to the clearance of common environmental antigens from highly exposed mucosal regions such as the nasopharyngeal cavities where IgD is abundantly produced [109].

Perturbations in the mechanisms underpinning the production of allergy-protective IgD responses might lead to the exacerbation of certain pro-inflammatory functions of basophils. For instance, such perturbations might occur in patients with **hyper-IgD syndrome (HIDS)** or **periodic fever-aphthous stomatitis-pharyngitis-adenitis (PFAPA) syndrome**, two **inflammatory syndromes** involving increased serum IgD titers and IgD class-switched B cells in some patients [110,111]. Patients with such inflammatory disorders suffer from dysregulated inflammation, which might increase IgD production as a compensatory effect aimed at attenuating inflammation [104]. During their typical periodic attacks of intense fever, some patients with these inflammatory disorders show decreased circulating basophils [110]. Such basopenia suggests that increased circulating IgD may promote tissue infiltration of basophils, which might participate in the inflammatory process, although this remains to be further investigated.

Interaction between IgD and IgE

Aside from eliciting basophil release of cytokines, chemokines and anti-microbial peptides, crosslinking of basophil-bound IgD mitigates IgE-induced FcεRI-driven basophil release of allergic mediators, including histamine [109,110] (Figure 3). This effect likely results from the stabilization of the cytoskeleton and suppression of degranulation by the IgD receptor complex through its ability to interfere with key basophil signaling events downstream of FcεRI [109]. Thus, unlike signals from the FcεRI receptor, which trigger basophil degranulation and increase T_H2 cytokine expression [2], signals from the IgD receptor segregate the T_H2-inducing functions of basophils from degranulation. This property might help explain why increased allergen-specific IgD correlates with a reduced risk of anaphylaxis in some patients with food allergy [112,113].

Of note, the T_H2-amplifying function of basophil-bound IgD does not contradict the protective effect that allergen-specific IgD seems to have against allergy, as indicated by various recent studies [109]. Specifically, a large fraction of human secreted IgD has low-affinity for multiple common antigens, at least in humans [114]. Besides deploying degranulation-inhibiting signals to IgE-sensitized basophils [109], this low-affinity IgD would enhance allergen clearance and compete with both circulating and FcεRI-bound IgE for allergen binding. In addition, basophil-bound IgD may mostly amplify T_H2 cell-driven B cell production of natural low-affinity IgE, which mediates immune protection against common environmental antigens, rather than enhancing B cell production of pathological high-affinity IgE, which mediates allergic reactions against these antigens [109].

Aside from IgE, IgD-enhanced T_H2 responses yield antigen-specific IgG, including IgG4, an IgG subclass typically associated with AIT-induced tolerance [73]. Consistent with this, beekeepers that are completely tolerant to the major bee venom allergen phospholipase A2 (PLA2) show increased circulating IgD to PLA2 compared to non-beekeepers, along with increased circulating IgE and IgG4 to PLA2, the latter being a T_H2-type antibody that is typically associated with protection against allergy [109]. Moreover, in egg-allergic children, circulating ovomucoid-specific IgD titers correlate with a reduced risk of anaphylactic reaction [112] and are increased in subjects who naturally outgrow egg allergy [113]. In a different cohort, egg-allergic children that were successfully desensitized after oral immunotherapy exhibited increased circulating ovalbumin-specific IgD, whereas egg-allergic children unresponsive to oral immunotherapy did not [109]. These clinical findings are in line with experimental data showing the active role of IgD in attenuating IgE-mediated basophil degranulation and suggest that allergen-specific IgD might serve as a tolerance biomarker [109] and/or have direct protective functions; it could thus represent a candidate therapeutic agent to prevent or treat IgE-mediated allergies.

Basophils and IgM responses

Few studies have examined the impact of IgM on basophils. In the fugu fish *Takifugu rubripes*, basophils bind IgM, possibly through an inducible receptor, and crosslinking of this IgM induces basophil degranulation [115]. However, human and mouse basophils do not seem to express any known IgM receptors, including Fcα/μR, FcμR, and pIgR. Thus, any effect of IgM on basophils might occur through an indirect mechanism involving a

different receptor(s) and/or a cell(s) different from basophils. However, IgM autoantibodies that are specific to the α chain of the Fc ϵ RI receptor are frequently detected in CSU patients, often in association with markers of active disease such as a positive autologous serum skin test and basopenia [116]. This finding suggests that activation of Fc ϵ RI by IgM might trigger basophil activation and tissue infiltration which merits further investigation into the regulation of basophil function by IgM.

Concluding remarks

Many aspects of basophil function are intimately linked to basophil interactions with antibodies and their regulation. Of note, basophil-modifying antibodies are not confined to IgE, but further extend to IgG, including IgG1 and IgG4 subclasses, as well as IgA, IgD, and possibly IgM. This is important because growing evidence is changing the long-held view that basophils are merely short-lived granulocytes heavily involved in the pathogenesis of allergy. Indeed, we now know that, during an immune response, basophils can get recruited to lymphoid and/or non-lymphoid tissues where they release a vast array of immune mediators that enhance T_H2 immune responses. In addition to causing allergy and contributing to other immune disorders, basophil-amplified T_H2 immune responses may increase protection against some infectious agents and clearance of common environmental antigens. They might also facilitate tissue repair and tumor surveillance. Distinct antibody classes or subclasses enhance or inhibit specific facets of basophil responses by means of elusive mechanisms that may change based on the specificity, antigen affinity, and/or glycosylation patterns of the basophil-binding antibody involved. Of note, it remains unclear how basophils respond to diverse innocuous or noxious antigens. One possibility is that antibodies interact with dynamic tissue-specific cues to shape distinct basophil responses tailored to each of the above antigenic categories (see Outstanding questions). Future studies involving high-resolution experimental approaches will likely yield unprecedented mechanistic insights into the functional crosstalk between antibodies and basophils. A better understanding of this crosstalk can inform new therapies for old as well as emerging disorders.

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Glossary

Type 2 immunity

Immune response characterized by the production of cytokines such as IL-4, IL-5, IL-9, IL-13, IL-25, IL-33, and TSLP. Type 2 immunity is essential for defense against helminths infections, metabolic homeostasis, suppression of excessive type 1 inflammation, maintenance of barrier defense, and regulation of tissue regeneration, but has a pathological role in allergic diseases and fibrosis.

BDCA1⁺ dendritic cells (DCs)

subset of human DCs, also called CD1c⁺ DCs or classical type 2 DCs (cDC2), that engage in the general functions of DCs, such as priming of CD4⁺ T cells and co-stimulation, in contrast to CD141⁺ cDC1 that perform cross-presentation of exogenous antigens to activate CD8⁺ T cells.

Type I hypersensitivity

also known as an immediate hypersensitivity reaction, involves IgE-mediated mast cell and basophil degranulation and release of vasoactive and inflammatory mediators to cause vasodilation, vascular permeability, smooth muscle constriction, mucus secretion, itching, and/or anaphylaxis.

T_H2 polarization

The differentiation of activated CD4⁺ T helper cells into effector T cells that secrete type 2 cytokines.

Class switching

process whereby a B cell changes the expression of its antibody isotype to diversify its antibody effector functions. It involves DNA recombination and requires the enzyme activation-induced cytidine deaminase (AID).

Innate lymphoid cells

Innate lymphocytes that mirror the phenotype and functions of T cells without expressing the TCR. They encompass cytotoxic ILCs (also called natural killer cells), group 1 ILCs (ILC1s; enhance TH1 responses against viruses, certain bacteria and tumors), group 2 ILCs (ILC2s; enhance TH2 responses against macroparasites, noxious chemicals, toxins, and common environmental antigens), group 3 ILCs (ILC3s; enhance TH17 responses to ensure epithelium integrity and mucosal homeostasis), and lymphoid tissue-inducer (LTi; promote lymphoid organogenesis).

Tuft cells

Chemosensory cells from intestinal and respiratory epithelia engaged in immunometabolic and regulatory networks at the interface of the host and the environment; harbor brush-like microvilli that project from the apical membrane; cells are equipped with taste and succinate receptors.

Toll-like receptor

family of transmembrane receptors that recognize conserved molecular patterns derived from microbes or stressed tissues to instruct or amplify innate and adaptive immune responses.

Eosinophilic esophagitis

allergic inflammatory condition of the esophagus that involves eosinophils migrating to the esophagus in large numbers and contributing to tissue damage and inflammation when triggered by food. Symptoms include swallowing difficulty, food impaction, vomiting, and heartburn.

Glucocorticoids

Endogenous steroid hormones mediating the general stress response; used as immunosuppressive drugs; attenuate lymphocyte survival. Their production by a rare subset of B cells from mesenteric lymph nodes induces natural IgE in the absence of allergen by promoting IgM-to-IgE class switching in cooperation with IL-4. This natural IgE probably has broad reactivity, low affinity, and protects against allergy.

Somatic hypermutation

B cell process that introduces point mutations within the antigen-binding variable (V) region gene of an antibody to generate antibody diversity; requires the enzyme AID; enables antigen-mediated selection of antibodies in the germinal centers of secondary lymphoid organs.

Germinal center

Specialized areas of secondary lymphoid organs inhabited by antigen-activated B cells that undergo somatic hypermutation and class switching to increase their antibody affinity and diversify their antibody effector functions.

Granuloma

aggregation of immune cells, mainly macrophages, in response to chronic inflammation; forms when the immune system attempts to isolate foreign substances that it is otherwise unable to eliminate (e.g. infectious organisms such as bacteria, fungi, parasites, as well as other materials such as foreign objects, keratin, and suture fragments).

Atopic dermatitis

chronic disease, often referred to as eczema; causes inflammation, redness, and irritation of the skin.

Systemic lupus erythematosus

systemic autoimmune disorder that progressively damages multiple organs through the activation and clonal expansion of pathogenic autoreactive B cells expressing immunoglobulins against a large spectrum of self-antigens.

Chronic spontaneous urticarial

inflammatory skin condition that lasts for more than 6 weeks without an identifiable provoking factor; usually starts as an itchy patch of skin that turns into swollen red welts.

Mixed connective tissue disease

complex overlap disease with features of different autoimmune connective tissue diseases; namely, systemic sclerosis, poly/dermatomyositis, and systemic lupus erythematosus in patients with antibodies targeting the U1 small nuclear ribonucleoprotein particle.

Systemic sclerosis

group of rare diseases, also known as scleroderma, involving the hardening and tightening of the skin, a buildup of scar tissues, and damage to the internal organs.

Polymyositis

rare disease involving chronic muscle inflammation and weakness, and in some cases, pain.

Platelet-activating factor

phospholipid with multiple immune functions: e.g. platelet aggregation, basophil and mast cell degranulation, increasing vascular permeability, inflammation, and anaphylaxis.

Anaphylaxis

potentially fatal allergic reaction in individuals sensitized against a foreign substance, such as food allergens and toxins from stinging or biting insects; requires immediate medical attention.

Allergen immunotherapy

involves the exposure of patients with allergies to gradually increasing amounts of allergen administered through the oral, sublingual, subcutaneous, or transdermal routes, and aimed at desensitizing the patient.

Selective IgA deficiency

Primary immunodeficiency characterized by IgA deficiency but normal IgM, IgG, and IgE production. About half the patients have respiratory and, less frequently, gastrointestinal symptoms. The other half are asymptomatic, likely due to compensatory mechanisms that include increased IgM production.

Hyper-IgD syndrome

rare, autosomal-recessive genetic disorder caused by mevalonate kinase deficiency due to mutations in the mevalonate kinase (*MVK*) gene; characterized by recurrent febrile episodes typically associated with lymphadenopathy, abdominal pain, and an elevated serum IgD titers.

Periodic fever-aphthous stomatitis-pharyngitis-adenitis (PFAPA) syndrome

pediatric syndrome with unknown etiology; manifests as repeated episodes of fever, mouth sores, sore throat, and swollen lymph nodes in the neck.

Inflammatory syndromes

group of inherited disorders characterized by dysfunction of the innate immune system where bouts of sterile (i.e., non-infectious) inflammation are associated with periodic fever.

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Clinician's corner

Both immune protection against helminth infections and the immunopathogenesis of allergy crucially involve basophils. These innate immune cells bind IgE, an antibody involved in T_H2 immunity. IgE with high affinity for antigen is central to pathological T_H2 immune responses, which typically develop in individuals predisposed to allergy by a favorable genetic background and/or unfavorable environmental conditions such as those causing skin eczema. In contrast, IgE with low affinity for antigen deploys protective functions against potential allergens as well as venoms from insects or snakes.

Other antibodies, such as IgA, IgG, and IgD, may enhance immune homeostasis and protection by limiting basophil sensitization by IgE and/or constraining basophil responses to IgE. A better understanding of the mechanisms underpinning antibody-dependent basophil responses may help identifying new targets for the treatment of a broad spectrum of diseases, ranging from allergy to infections, inflammation, autoimmunity, and cancer.

Outstanding questions

- Do basophils include subpopulations with distinct antibody-binding profiles and unique functions under homeostatic or pathological conditions and in various tissue or disease contexts?
- How do basophils with distinct antibody-binding profiles initiate and instruct the development of type 2 immunity in different antigenic and environmental contexts?
- Do basophils with distinct antibody-binding profiles interact with other innate cell types central to type 2 immunity such as ILC2s and conventional type 2 dendritic (cDC2) cells?
- Do basophils contribute to metabolic and autoimmune disorders developing in patients with primary or secondary antibody deficiencies?
- What signals regulate the trafficking of basophils with distinct antibody-binding profiles into or out of different anatomic locations?
- Do specific tissue environments differentially shape the response of basophils with distinct antibody-binding profiles?
- How do basophils with distinct antibody-binding profiles differentially contribute to immune homeostasis, disease pathogenesis, or disease protection?
- Can specific biologicals target basophils with distinct antibody-binding profiles to restore immune homeostasis, interfere with disease pathogenesis, or enhance disease protection?
- How do low-affinity antibodies to common environmental antigens constrain pathological basophil responses in healthy individuals or allergic patients, including patients treated with allergen immunotherapy?
- How do basophils with distinct antibody-binding profiles interact with ILC2s and cDC2s in allergy, infections, inflammation, autoimmunity, and cancer?

Highlights

- Basophils are important to systemic and tissue immune defense against helminth infections and noxious environmental substances. They can participate in a wide spectrum of diseases beyond allergies, including infection, inflammation, and cancer.
- Antibodies regulate various aspects of basophil functions, enabling basophils to integrate adaptive signals with innate signals in immune defense or disease pathogenesis.
- Recent studies have revealed new mechanisms underlying antibody-mediated basophil regulation and identified antibody-dependent basophil responses that are either protective or pathogenic in allergic and non-allergic diseases.
- Active or passive antibody-based therapies capable of stimulating protective basophil effector functions or mitigating pathogenic basophil responses may help in the management of diseases that significantly involve basophil functions.

Significance

Basophils are important innate regulators of immune responses which can also contribute to the pathogenesis of various disorders, including allergy, autoimmunity, inflammation, infection, and cancer. Basophil functions are shaped by antibodies, allowing basophils to integrate antigenic and environmental cues at the intersection of innate and adaptive immunity. Further knowledge of the mechanisms by which antibody classes achieve their effects might inform on new basophil-targeting therapeutic strategies to prevent and/or treat certain allergic and non-allergic disorders.

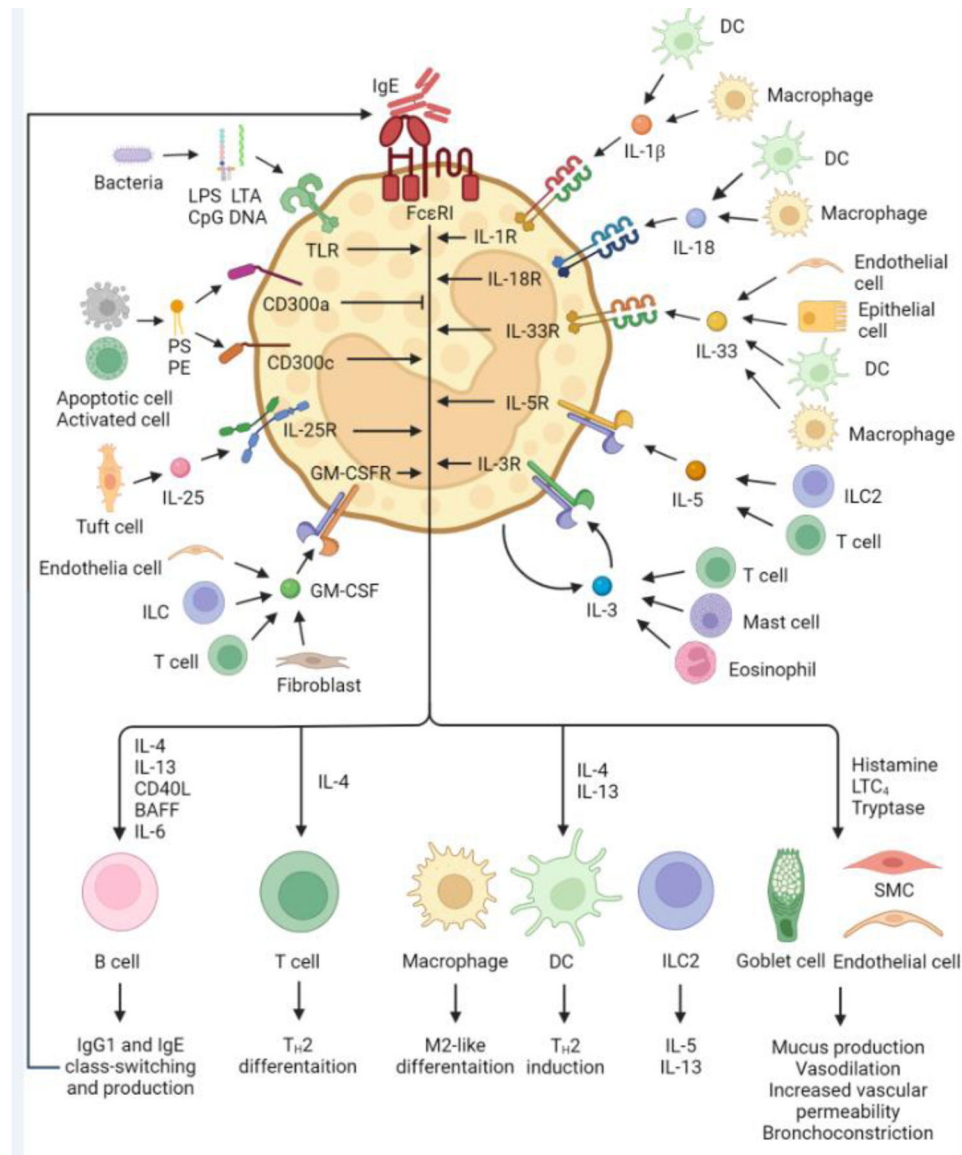


Figure 1. The functions and modulation of IgE-mediated basophil responses.

Basophils express the high-affinity IgE receptor termed FcεRI [8]. Following cross-linking of FcεRI-bound IgE by antigen, basophils release pre-formed vasoactive peptides such as histamine, pleiotropic lipid mediators such as LTC₄, and proteases such as tryptases [13]. These mediators act on goblet cells, smooth muscle cells, and endothelial cells to promote a type I hypersensitivity reaction featuring vasodilation, bronchoconstriction, increased mucus production, and enhanced vascular permeability, leading to leukocyte recruitment and tissue swelling [13]. IgE-activated basophils also express cytokines and chemokines to enhance type 2 immunity by acting on various innate and adaptive immune cells [18–20]. IgE-induced IL-4, IL-13, CD40L, BAFF and IL-6 target B cells to enhance IgG1 and IgE class-switching and production [19,21]. Activated basophils can express MHC-II, and together with IgE-induced IL-4, promote antigen-mediated differentiation of naïve CD4⁺ T cells to T_H2 effector cells [18–20]. IL-4 and IL-13 further elicit “M2-like” differentiation

of macrophages, T_H2-inducing DC differentiation, and group 2 innate lymphoid cell (ILC2) activation, resulting in the amplification of type 2 immune responses. Basophils further integrate multiple innate and adaptive immune signals that represent various antigenic and immunological contexts and positively or negatively modulate specific aspects of IgE-induced basophil responses, based on the expression of specific receptors for these respective signals. These responses contribute to humoral and cellular immunity, defense against helminths, as well as tissue homeostasis and repair. When improperly regulated, basophil responses participate in the pathogenesis of a variety of allergic, fibrogenic, inflammatory, and even malignant disorders. Hence, IgE, FcεRI and the signaling pathways underpinning IgE and FcεRI functions in basophils might serve as candidate therapeutic targets for such diseases. This figure was created using [Biorender.com](https://biorender.com)

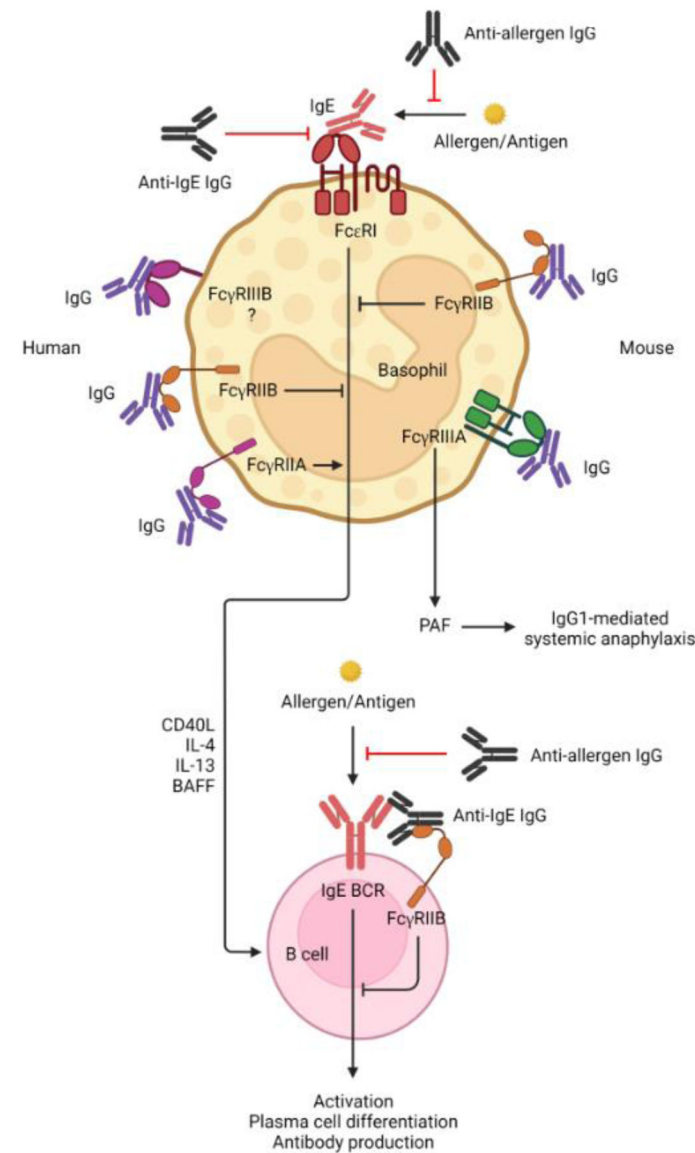


Figure 2. The functions and modulation of IgG-mediated basophil responses.

Basophils express various IgG receptors, including activating Fcγ receptors (FcγRIIA in humans, FcγRIIA in mice) as well as the inhibitory Fcγ receptor FcγRIIB [66,67]. Upon binding and activation by IgG immune complexes or anti-IgG crosslinking antibodies, these Fcγ receptors modulate IgE-induced basophil degranulation and cytokine production, with FcγRIIB inhibiting, and FcγRIIA activating, IgE-induced degranulation [67]. In mice, IgG1 immune complexes can activate basophils via FcγRIIA to produce platelet-activating factor (PAF) and cause systemic anaphylaxis [70]. The function of the GPI-anchored FcγRIIB on basophils is unknown. Therapeutic strategies such as passive administration of allergen-specific IgG antibodies or allergen immunotherapy (AIT) aimed at inducing such antibodies, including IgG4, confer protection by interfering with the recognition of allergen by FcεRI-bound IgE on basophils and by the IgE-BCR (B cell receptor) on B cells. IgE-targeting agents, called IgE antagonists, such as omalizumab, ligelizumab, and XmAb7195, can offer

clinical efficacy in allergy treatment by blocking IgE-induced FcεRI-mediated basophil and mast cell activation and/or by inhibiting IgE-BCR-induced B cell differentiation and IgE production [82]. This figure was created using [Biorender.com](https://biorender.com)

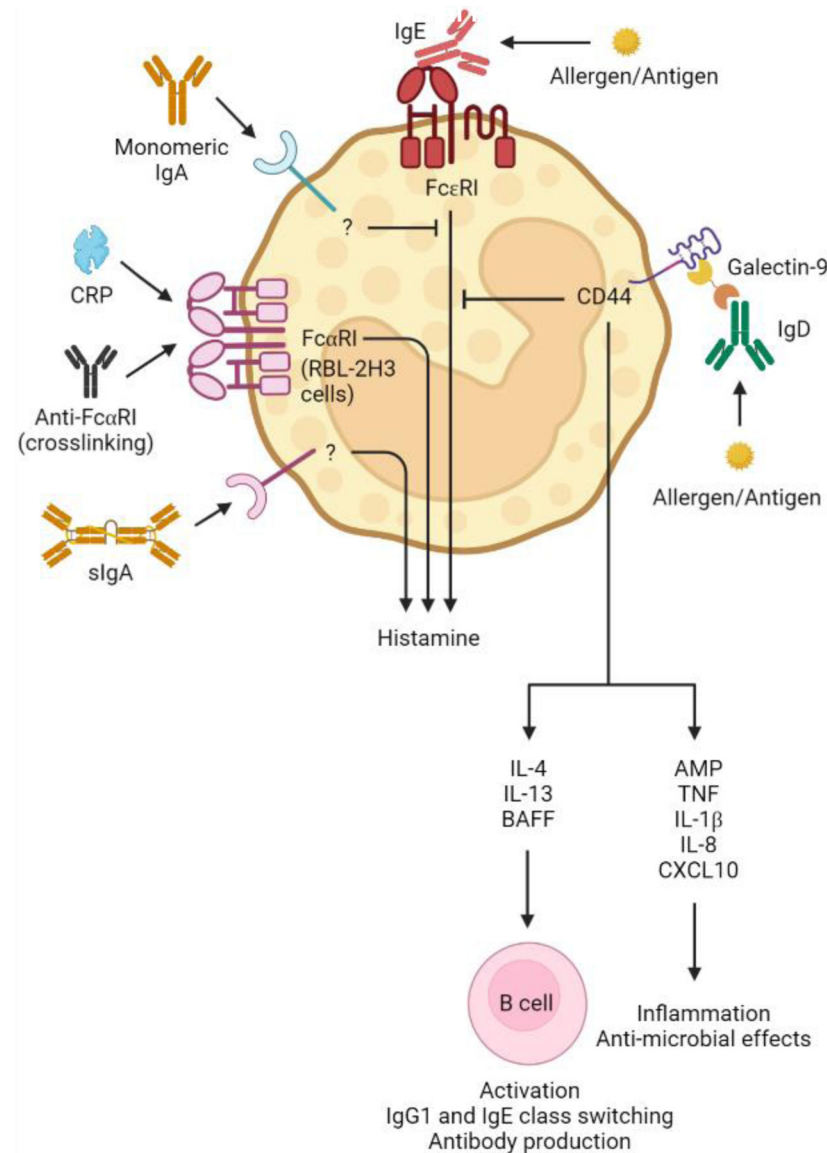


Figure 3. The functions and modulation of IgA- and IgD-mediated basophil responses.

Basophils can bind monomeric or polymeric SIgA which regulates basophil responses, although the receptor(s) to which monomeric and SIgA bind is not clear [87,88]. In the rat basophilic cell line RBL-2H3, crosslinking of FcαRI by antibodies or the alternative ligand C-reactive protein (CRP) induces degranulation and histamine release [93]. Polymeric IgA, including SIgA, induces a similar effect but does so through an FcαRI-independent mechanism involving the secretory component (SC) polypeptide. Unlike polymeric IgA, monomeric IgA does not induce degranulation but can interfere with the allergen-induced degranulation [90]. Unlike IgA, IgD only exists as a monomer and binds to basophils by means of a receptor complex that includes galectin-9, CD44, and possibly other proteins [109]. Cross-linking of basophil-bound IgD by anti-IgD antibodies or antigen complexes does not trigger degranulation but can interfere with the degranulation induced by IgE [109,110]. Cross-linking of basophil-bound IgD activates the release of anti-microbial

molecules such as PTX3, pro-inflammatory cytokines such as IL-1 β , as well as immune-activating cytokines such as IL-4, IL-5, IL-13, and BAFF [109,110]. In addition to amplifying T_H2 cell differentiation, these basophil-derived cytokines enhance antibody production by directly stimulating B cells to produce antibodies, including IgG1 and IgE [109,110]. This figure was created using [Biorender.com](https://biorender.com)