

EXPERT
REVIEWS

Basophils as critical orchestrators of Th2-type immune responses

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Basophils are relatively rare leukocytes that potentially play a role in both systemic anaphylaxis and, owing to their ability to migrate from the blood into various other tissues, in more localized aspects of allergic inflammation. Given their greater sensitivities to allergen provocation compared with their tissue-fixed mast cell counterparts, and by virtue of their capacity to more readily generate Th2-type cytokines, basophils have been considered to play more than a bystander role in initiating and maintaining allergic disorders. However, only very recently has clearer evidence shed light on the abilities of this cell type to orchestrate chronic allergic inflammation and promote Th2 immunity in the early induction stages of allergy. This review summarizes these recent advances in understanding the role of basophils in orchestrating and maintaining allergic responses.

KEYWORDS: allergy • basophil • histamine • IgE • IL-4 • mast cell • Th2 • VEGF

Basophils are the least common cell type found within human peripheral blood leukocytes, of which they comprise less than 1%. They are classified as granulocytes and contain cytoplasmic secretory granules that undergo metachromatic staining with certain dyes such as toluidine blue. Their ontology is, however, poorly understood, given that progenitors for both basophil/eosinophil, basophil/mast cell and basophil/eosinophil/megakaryocyte lineages have been reported (reviewed in [1,2]), with some indication of distinct mast cell and basophil lineages [3].

Although basophils usually circulate within the bloodstream, they are recruited to peripheral tissues under certain pathological conditions, such as during parasitic infections or in allergic disorders (reviewed in [4]). High-affinity IgE receptors (FcεR1s) are expressed on their surface and cross-linking of receptor-bound IgE by specific allergens triggers a complex cascade of signal transduction events, resulting in the release of a number of chemical mediators, including histamine, eicosanoids and cytokines.

History of basophil research

Basophils share many characteristics with tissue-fixed mast cells, such as expression of FcεR1s and a high granule-associated histamine content, and this has often led to the assumption that they

may simply be a redundant circulating mast cell type. However, differences in their lineage, life cycle, ability to react to various stimuli and in the mediators they release suggest that basophils have a distinct role in immune responses. The discovery that basophils secrete Th2-type cytokines (especially IL-4 and IL-13) and that their cytokine profile differs from that of mast cells was a turning point in the way researchers viewed the basophil [5]. Mast cells release an array of inflammatory cytokines, including TNF-α and IL-8, but, in contrast to mice, human mast cells from healthy individuals are poor sources of IL-4. Basophils, however, are comparatively constrained to generate IL-4 and IL-13 (reviewed in [6]), as well as VEGF [7] and small amounts of IL-3 [8]. This finding in the 1990s led to the original suggestion that basophils could be involved in mediating allergic diseases and immunity to certain pathogens such as helminths by supporting Th2 responses [9–14].

Another observation during this time that increased the interest in basophils as allergic effector cells was their presence in organs affected by allergic inflammation. Their presence was difficult to demonstrate before the emergence of basophil-specific markers, but was implied during late-phase reactions owing to the release of histamine without the accompanying

PGD₂ or tryptase, which are mast cell-associated mediators [15,16]. Basophils were found at sites of nasal and cutaneous late-phase reactions, and late-phase secretions contained a cell population identified morphologically as basophils [17–20]. Although increasing circumstantial evidence indicated a potentially integral role for the basophil in allergy and immune function, definitive proof-of-principle derived from animal – especially mouse – models was lacking.

Originally, mice were believed to lack basophils owing to the reduced number of basophilic granules compared with human basophils [21,22], but tools for identifying murine basophils were eventually available so that their presence was confirmed [5]. However, in various studies, the method of identifying them is still a point of discussion [5]. There is wide variation in mast cells and basophils between species, including in cell number and type of mediators released, so that a murine model, for example, would not completely mirror the human situation. Human mast cells from the lung or skin have a limited ability to produce Th2-type cytokines, especially IL-4, whereas rodent mast cells can produce much larger quantities (reviewed in [23]). By contrast, human basophils rapidly synthesize and secrete IL-4, some of which is from preformed stores and released within 30 min [10–13], which suggests they may be the missing link by providing the initial IL-4 required by Th2 cells to differentiate down the Th2 pathway, and further study confirmed this view [5].

The lack of suitable animal models has continually limited basophil research, especially the absence of mutant or genetically engineered mice deficient only in basophils. Mast cell-deficient mice have been generated by virtue of their dependence on stem cell factor, but a similar approach for basophils failed to produce basophil-deficient mice. IL-3 is an important growth factor for the *in vitro* cultivation of human basophils, but the fact that IL-3 knock-out mice still have basophils [24] suggests that it is not the only basophil growth factor in these animals. A recent study by Shen *et al.* also supports the notion that IL-3 is not majorly involved in murine basophil survival and proliferation *in vivo* [25].

Experimentally, another problem was the lack of a reliable method of basophil purification, since a high degree of basophil purity is required to exclude mediator secretions from contaminating cells. The advent of a number of commercially available methods, using both positive and negative selection techniques, has made it possible to purify a cell population to near homogeneity [6]. Currently, there are no cell lines available that fully reflect the morphological and functional characteristics of primary basophils [4].

Improved tools for basophil research

Recently, tools for basophil studies have improved, and animal models have been created either by the *in vivo* transfer of basophils from normal mice to FcεRI-deficient mice, or basophil-deficient mice have been established using basophil-depleting antibodies [4]. Different research groups have achieved this in different ways; using either of the monoclonal antibodies, Ba103 [26], specific for the CD200 receptor 3 (CD200R3), or MAR-1, which is specific for FcεRIα [27,28]. Both antibodies preferentially deplete circulating basophils *in vivo*, and their success had contributed significantly to the recent increase in basophil research.

The ability to measure basophil activation by flow cytometry using CD203c and CD63 as activation markers has also facilitated basophil activation tests (BATs) for diagnostic purposes [29]. While CD63 was first described as a constituent of granules of platelets [30] and later also described in granules of basophils [31], CD203c occurs exclusively on basophils in peripheral blood [32]. Several articles have described and compared the relative merits of using CD63 or CD203c for the diagnosis of allergy to food [33,34], classical inhalatory allergens such as cat dander allergens [35], drugs (reviewed in [36]) or hymenoptera venom (reviewed in [37]).

The main advantage of using a BAT in comparison to techniques measuring the levels of allergen-specific IgE is its biological readout – that is, its ability to discriminate clinically significant sensitization from tolerance, a distinction that is particularly important in food hypersensitivity, such as in the case of peanut or egg allergy [35]. Furthermore, BATs allow the diagnosis of pseudo-allergies to drugs, which cannot be tested by methods based on IgE measurements. The downside of BATs is the occurrence of nonresponders (as described elsewhere in this review), which will not respond to IgE-mediated stimulation (including positive-control stimulation) in these tests, and thus could be wrongly diagnosed as negative [29].

Combining the numeric power of protein arrays with the advantage of using a biological readout such as basophil activation, a recently described technology also uses CD63 upregulation for the detection of the activation of lactic acid-stripped peripheral blood basophils or a humanized rat basophil-like cell line resensitized with allergic patients' serum [38]. Interestingly, although human IgE is species specific, human basophils (and mast cells) may also be sensitized with IgE antibodies from other mammals.

Implications of the role of basophils in allergy

Basophil recruitment to tissues

Basophils are rarely present in normal tissues [39], but are recruited into inflamed sites during allergic reactions, where they are thought to carry out effector functions through the release of mediators and cytokines [40]. A wide variety of chemokine receptors are expressed on basophils, and they also respond to many chemokines and cytokines that aid their migration [39,41]. Their presence in various tissues affected by allergic disease, including in the airways of asthmatic patients and in the skin of atopic dermatitis patients, has been successfully demonstrated using the basophil-specific BB1 and 2D7 antibodies (reviewed in [42,43]).

Basophils have been shown to be responsible for the presence of IL-4 during allergen-induced asthmatic reactions; 72% of IL-4 protein-positive cells in the bronchial mucosa were basophils [44] and they are the main IL-4-producing cells in the bronchoalveolar lavage [45]. These cells also exclusively express IL-4 and IL-13 in the peripheral blood within the first 2 h after antigen challenge [46]. A real-time quantitative PCR-based assay in whole blood after stimulation with the cat allergen Fel d1 also identified basophils to be the primary early source of IL-4 and IL-13 [47]. These cytokines increase both the expression of vascular cell-adhesion molecule-1 on the microvascular endothelium and eotaxin synthesis

Modulation of local IgE production

Correlations between disease severity and serum IgE levels in patients with asthma or atopic dermatitis have been observed in a number of studies [55,56]. In addition, treatment with the humanized anti-IgE monoclonal antibody (mAb), omalizumab, has shown in clinical trials that the resulting decrease in serum IgE correlates with an improvement in symptoms in some patients with poorly controlled asthma [57,58].

Basophils have been shown *in vitro* to induce class-switching of the B-cell isotype to IgE [59,60], and IL-4 production is crucial, as the neutralization of IL-4 abolishes IgE synthesis [42]. Surface expression of the CD40 ligand is upregulated on activated basophils, and this interacts with CD40 on B cells to aid in class-switching [42]. However, it remains unclear whether this occurs in the same manner *in vivo*.

By administering the mAb Ba103, Obata *et al.* created transiently basophil-deficient mice, and showed that basophils play a pivotal role in the initiation and maintenance of a novel type of chronic allergic inflammation – that which is dependent on IgE and the FcεRI receptor, but is independent of mast cells, T cells and natural killer cells [26]. When administered after ear swelling, Ba103 demonstrated a therapeutic effect, and resulted

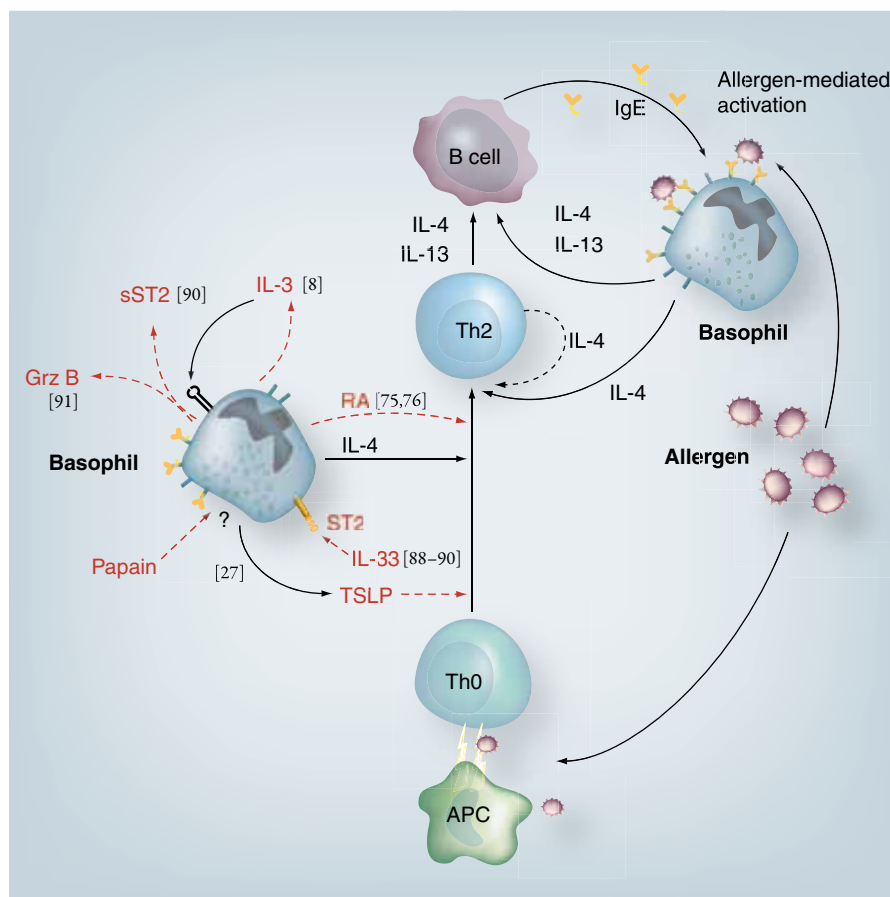


Figure 1. Summary of recent advances in the understanding of basophil immunobiology (dashed arrows). Several authors have demonstrated high expression of ST2 on human peripheral blood basophils [88–90]. Its ligand, IL-33, is reported to exert priming effects on basophils (similarly to IL-3) and interacts synergistically with IL-3 to release Th2 cytokines [89,90]. Basophils have also been shown to be an important source of retinoic acid [75], which can promote the differentiation of Th0 cells into Th2 cells. Papain has been shown to induce TSLP, which can also promote Th2 cell differentiation, but the production of TSLP still needs to be confirmed for human basophils. IL-3, the main growth and survival factor for basophils, has been shown to be released by basophils themselves and act in an autocrine manner. The anti-apoptotic effects of IL-3 have been partially elucidated (not shown) [98]. IL-3 also results in increased expression of ST2, and sorting of sST2 and GrzB to the granules [91].

APC: Antigen-presenting cell; GrzB: granzyme B; RA: Retinoic acid; sST2: Soluble ST2; ST2: ; TSLP: Thymic stromal lymphopoietin;

in a huge reduction in infiltrating eosinophils and neutrophils, which suggests they are not recruited independently of basophils and implies a role for basophils in the maintenance of allergic inflammation. Treatment with Ba103 did not produce any significant effect on type I hypersensitivity, for which mast cells are responsible, showing that basophils have little contribution to the IgE-mediated immediate-type allergic reaction in this setting [26,61].

The results of this study strongly suggest that basophils might act as initiators, as well as effectors, of allergic inflammation by recruiting other proinflammatory cells such as eosinophils and neutrophils. In response to allergens, possibly via chemokines, IgE-bound basophils are recruited to the peripheral tissues where they are activated to secrete various soluble factors, including

cytokines and proteases. These released factors then act on tissue-resident cells, causing them to secrete a range of chemokines, and it is these that recruit more proinflammatory cells, leading to the chronic allergic inflammation [58].

Role of basophils in IgG-mediated anaphylaxis

Anaphylaxis is a rapid-onset, severe and potentially fatal systemic allergic reaction, usually associated with IgE, mast cells and histamine. However, an alternative IgG-mediated pathway has been suggested, since not all cases of anaphylaxis can be explained by the IgE-mediated route [4,62]. It was recently shown by Tsujimura *et al.* that basophils are the most important cells in IgG-mediated but not IgE-mediated systemic anaphylaxis [63]. In this study, the *in vivo* depletion of basophils in mice, using the mAb Ba103, improved IgG-mediated passive anaphylaxis and protected mast cell-deficient mice from death due to active anaphylaxis. After stimulation with allergen–IgG immune complexes, peripheral blood basophils were shown to induce systemic anaphylaxis through the release of platelet-activating factor (PAF), which acted to increase vascular permeability with a much greater efficacy than histamine [4,63]. This showed that even low levels of basophils in the blood can induce anaphylaxis, and suggests that they might be suitable therapeutic targets, despite their small numbers.

While the existence of this IgG-mediated alternative pathway has not yet been determined in humans, it has been reported that PAF levels in human sera correlate with the severity of anaphylaxis [64]. Allergen-specific IgG antibodies have been detected in patients who displayed anaphylactic reactions to certain medical reagents [65–67]. However, human basophils are inhibited by IgG via the FcγRIIb receptor, and cannot be activated through an IgG receptor [5].

Basophils drive Th2-cell differentiation

In vitro, basophils can affect lymphocyte responses; naive Th cells stimulated in the presence of basophils differentiate into Th2 effector cells, whereas those without basophils present do not [27,42]. This adds weight to the claim that basophils provide the initial IL-4 required by naive Th cells to promote the Th2 response. *In vivo*, this has been supported in interferon-regulatory factor (IRF)2-deficient mice, which have more basophils and spontaneous Th2 immunity; when a mutation in the *Kit* gene was introduced into these mice, the basophil number was decreased, leading to a reduction in the prominence of Th2 polarization [68]. However, the *Kit* gene mutation has also been shown to reduce mast cell numbers [24], so any observed effect cannot be entirely attributable to basophils. Further evidence comes from studies into stimulation with a *Schistosoma mansoni* egg antigen, which causes the release of IL-4 from basophils [69,70]. However, it has not yet been established whether this IL-4 is actually involved in the *in vivo* development of *S. mansoni*-specific Th2 immunity.

A study by Sokol *et al.* actually showed that basophils were activated and specifically recruited to the lymph nodes in mice in response to challenge with a Th2-inducing protease allergen, papain, which induces Th2 responses without dendritic cell involvement [28]. These authors also showed that basophils produced Th2 cytokines, including IL-4 and thymic stromal

lymphopoietin (TSLP), which drive the differentiation of Th2 cells *in vivo*. The basophil was shown to be the accessory cell type required for Th2 induction by this allergen. Therefore, this showed that murine basophils play a critical role in innate immune recognition leading to Th2 responses by secreting IL-4 and TSLP. However, the production of TSLP by human basophils has not yet been reported. In mice, recent studies have clearly demonstrated that basophils may even act as antigen-presenting cells and initiate Th2-type immune responses to allergens and helminth infections [71–74]. Again, however, these findings have not been verified using human basophils, which, as mentioned earlier, differ substantially in morphology to these murine cells.

In addition to the aforementioned, Spiegl *et al.* have recently shown that basophils are a new source of retinoic acid (RA), since they express high levels of retinaldehyde dehydrogenase (RALDH)2 [75]. RA is known to be an important regulator of immune cell functions, including defence against infections and inflammation [76]. Basophil-derived RA was shown to act on both the basophils themselves and on neighboring cells, including T cells, which then became polarized to release Th2 cytokines. It has been suggested that this generation of RA might be an important link in the communication between basophils, mast cells and T cells during polarization towards a Th2 response [75,76]. The ‘vitamin hypothesis’ suggests that basophils act as ‘agent cells’ between the food environment and the immune system, whereby Th2 responses are downregulated in case of vitamin A deficiency, but the risk of allergy is increased in response to an excess of vitamin A [76]. This may play some part in explaining the rapid increase in allergy seen in the developed world.

Basophils as targets for anti-allergic therapy

Given the aforementioned role of basophils in directing allergic responses, these cells are increasingly recognized as an attractive target for anti-allergic therapy. Some existing anti-allergic agents, including glucocorticoids, methylxanthines and calcineurin inhibitors, inhibit the ability of basophils to release mediators, and this may partially explain their clinical effectiveness. The well-known limitations of these agents have prompted renewed attempts to block allergen-mediated FcεRI activation of mast cells and basophils. The humanized anti-IgE mAb, omalizumab, is a promising treatment as it prevents free IgE antibodies from binding to FcεRI, and reduces both effector cell sensitization and FcεRI expression. Treatment with omalizumab in allergic rhinitis patients has been shown to markedly reduce basophil reactivity and lead to rapid decline in FcεRI expression, faster in comparison to mast cells [77]. In allergic asthma patients, a similar decline in basophil reactivity has been observed, but this does not always correspond with clinical improvement [78]. Any therapy that aims to reduce free IgE levels would need to be highly effective, as mast cells and basophils are extremely sensitive to IgE-mediated stimulation; it has been shown that histamine release could be initiated by less than 100 molecules of antigen [79].

Basophils may be directly affected by rush desensitization regimes, which has been attributed to loss of Syk expression [80], but their signal transduction machinery includes a range of inhibitory signals, which may contribute to their functional

desensitization. One possible signalling target is the src homology 2 domain-containing inositol 5' phosphatase (SHIP), an inhibitory enzyme that is centrally involved in IgE-mediated signalling in basophils and mast cells [81–83]. Upon the activation of inhibitory receptors such as IRp60 (CD300a), SHIP has been shown to be mobilized, leading to a dramatic reduction in mast cell effector function [84]. CD300a, as well as CD200R3 [85], Siglec-8 [86] and FcγRIIb, which only blocks basophil responses in conjunction with FcεRI co-cross-linking [87], upregulate SHIP expression and may be exploited in the future for anti-allergic therapies.

New insights into the regulation of basophil reactivity & survival

The effect of a recently discovered cytokine, IL-33, on human basophils has been studied by Suzukawa *et al.*, who found that basophils express the transcript and protein for ST2, an IL-33 receptor [88]. IL-33 was found to have a range of effects on basophils, and although it did not directly induce degranulation, it did exert priming effects. Degranulation in response to IgE cross-linking was enhanced, as was eotaxin-directed chemotaxis and basophil adhesion [88]. Therefore, this suggests that IL-33 potentially regulates the migration and activation of human basophils, and may be a key cytokine in Th2-mediated allergic inflammation. Smithgall *et al.* also confirm a high level of ST2 expression in human peripheral blood basophils as well as activation by IL-33, resulting in the production of IL-4, IL-5, IL-6, IL-8, IL-13 and other cytokines, particularly after priming with IL-3 [89]. The secretion of IL-5 by human basophils has not been reported before, and thus needs further confirmation [90]. Strong synergistic effects of IL-3 and IL-33 on basophil Th2 cytokine production were also described by Pecaric-Petkovic and coauthors [90]. These authors also found that IL-3 induces an increase in both soluble ST2 (sST2) and IL-33 receptor (ST2). sST2 was shown to be directed to the basophil granules and released upon degranulation [90]. A similar induction and sorting to the granules in response to IL-3 of another putative mediator of allergic inflammation, granzyme B, had previously been shown by Tschopp *et al.* [91].

It has long been known that IL-3 acts as a growth factor for basophils *in vitro* and considerably increases their responsiveness by way of increased release of mediators. The effects of IL-3 are mediated through CD123 receptors, which are highly expressed on basophils [8]. Since IL-3 appears to regulate many aspects of basophil biology, it seems likely that this cytokine plays a significant role in chronic allergic inflammation. It was thought that IL-3 required by basophils was produced by activated T cells, but a very recent study by Schroeder *et al.* shows that basophils themselves rapidly secrete IL-3 when activated through the FcεRI receptor [8]. The secretion of IL-3 only became evident after blocking absorption using the IL-3R antibody, showing that basophils rapidly bind and utilize the IL-3 they produce. This explains why previous attempts to test whether basophils produced IL-3 proved negative. The generation of IL-3 appears to mirror IL-4 production, in that it was only produced after IgE–FcεRI activation, and increases in IL-3 mRNA were also observed as early as 15 min after stimulation with anti-IgE antibody [8].

This autocrine IL-3 produced by basophils was shown to modulate IL-13 secretion and CD69 expression, suggesting that basophils may regulate their own priming *in vivo* [92]. This may be of clinical relevance, since evidence from many studies over the years has shown that basophils from allergic subjects are both functionally and phenotypically primed when compared with basophils from normal subjects. Constitutive expression of CD69 on basophils has been reported in patients suffering with asthma [92], allergic rhinitis and chronic idiopathic urticaria [93]. The hyper-reactive nature of basophils observed in allergic disease may thus be due to the cells having come into contact with IL-3, quite possibly from the basophil itself [8].

IL-3 has been shown to regulate Syk expressions in basophils and may also play an important role in governing the ability of these cells to respond to IgE-dependent activation [94]. Indeed, low Syk expressions have been linked to nonresponding basophil phenotypes [94,95], which fail to degranulate following allergen-mediated or anti-IgE stimulation, despite adequate sensitization of FcεRI. Interestingly, basophils from these donors revert to a releaser phenotype upon culture with IL-3 [94], which increases Syk expression. SHIP also appears to play a role in governing constitutive basophil reactivity, and several studies have now shown that changes in the expression levels of SHIP and Syk modulate human basophil responsiveness [83,95,96], also from donors with allergies or urticaria [97].

One of the most under-researched areas in terms of basophil immunobiology is the regulation of apoptosis. While much is known about the apoptotic mechanisms in neutrophils and eosinophils, very few studies have been published regarding primary basophils. A recent study by Didichenko *et al.* has now provided the first insights into several key questions [98]. The authors of this study have compared the relative *in vitro* survival of *ex vivo*-derived purified neutrophils, eosinophils and basophils. While in the absence of a stimulus most neutrophils and eosinophils underwent spontaneous apoptosis within 24 h, close to 60% of basophils were still alive after 3 days of incubation. At this time point, most neutrophils and eosinophils had died. The authors found that basophils express constitutively high levels (26 kDa) of Bcl-2, while this anti-apoptotic factor was not expressed in neutrophils and was barely detectable in eosinophils.

IL-3 is a major survival factor for basophils and suppresses spontaneous basophil apoptosis, in contrast to the actions of IL-5 or granulocyte–macrophage colony-stimulating factor, which enhance basophil mediator release but do not affect basophil survival [99]. It has been shown that spontaneous apoptosis involves caspase 3 activation and that the 17-kDa cleaved active caspase 3 is a sensitive and reliable indicator of early basophil apoptosis [99]. IL-3 induced strong activation of Stat 5 and Stat 3. Transfection of primary cells, and in particular granulocytes, is very inefficient [100]. Didichenko *et al.* were able to overcome these limitations using an elegant protein transduction approach [98]. The proteins of interest (wild-type Pim1, or a functional mutant Pim1 kinase dead [KD]) were fused to a peptide derived from the HIV-1 TAT protein which is able to cross the cytosolic membrane via its cell-penetrating

peptide-like properties. Tat–Pim1, but not the KD mutant, was able to induce the survival of basophils in the presence of wortmannin and in the absence of IL-3. This was independent of phosphoinositide 3 kinase signaling. The authors also suggest the pharmacological inhibition of Pim kinase activity as a possible novel target for the resolution of allergic inflammation [98].

Expert commentary & five-year view

The tools for basophil analysis may have improved considerably over the last few years; however, they still need to be further refined to provide increased research options. While transiently basophil-deficient mice have been utilized successfully in research, the establishment of a genetically engineered mouse that is deficient only in basophils would be a major breakthrough. This should be aided by identifying those genes that are selectively expressed in basophils. However, there would still be problems in that murine and human basophils are not identical, and roles identified in mice may not be relevant in humans *in vivo*.

There are many areas that have yet to be fully elucidated in the field of basophil research, including the pathways leading to basophil lineage differentiation, the molecular mechanisms underlying the initiation and maintenance of chronic allergic inflammation, and whether or not the many *in vitro* observations are in fact comparable *in vivo*.

With regards to basophils being initiators rather than effectors of IgE-mediated chronic allergic inflammation, this suggests that they could be potential therapeutic targets for this type of inflammation, at least in the skin. Since the infiltrating cells comprise such a small percentage of basophils when compared with other granulocytes, this means that there is a much smaller number of initiator cells to target, which is likely to be more effective than targeting a much larger number of effector cells [26].

Basophil research has also led to the possibility of a treatment for a certain type of anaphylaxis. Although most cases of human

anaphylaxis appear to be IgE-mediated, some patients have elevated serum PAF and allergen-specific IgG in addition to IgE [64]. Further research into the possible involvement of basophils and PAF, especially in anaphylaxis due to allergy to medication, could be beneficial in creating an adjunct therapy for those patients at high risk, possibly with PAF antagonists [58].

While basophils may migrate to the lymph nodes in rodents, it is crucial to verify whether this also occurs in humans and, if so, determine the mechanisms involved. Moreover, it would also be of interest to elucidate whether basophil migration into the lymph nodes is an absolute requirement, or whether basophil production of Th2 cytokines in other locations is sufficient [4].

The recent years in basophil research have proven that just because a subpopulation of cells is small, it does not necessarily imply that their biological role is also small. There is overwhelming evidence to suggest that basophils contribute to the symptoms of allergic disease and play a pivotal role in supporting underlying Th2 immunity, especially in chronic allergy (summarized in FIGURE 1). Therefore, the basophil and its mediators are promising therapeutic targets, with the identification of ligands for inhibitory receptor engagement being one possible approach. Since there is huge potential for basophil research to yield effective allergy therapies in the future, it is very important to delve further into every aspect of basophil development and function in an attempt to fully understand this cell type, including its physiological purpose, which also remains unknown.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Key issues

- Basophil-depleting monoclonal antibodies allow for *in vivo* models demonstrating role for basophils in chronic allergic inflammation.
- However, possible heterogeneous aspects of the morphology and function between murine and human basophils have yet to be elucidated.
- Basophil-derived IL-4 and IL-13, as well as retinoic acid, support Th2 immunity.
- New insights into the control of basophil reactivity caused by IL-33 and autocrine actions of IL-3.
- Targeting inhibitory signaling (e.g., src homology 2 domain-containing inositol 5' phosphatase) may lead to new therapeutic approaches.

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