

The role of basophils in allergic inflammation

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Summary

In recent years there has been growing evidence to suggest a major role for basophils in allergy despite being one of the rarest leukocytes. These blood-borne cells have clearly been observed to invade other tissues such as skin or lung affected by allergic inflammation. More recent studies have shown that basophil responses – typified by degranulation – correlate with the severity of allergic reactions in food allergy. However, despite studies suggesting major input in governing allergy symptoms their immunomodulatory roles are less clearly defined. While basophils are an important early source for pro-allergic Th2-type cytokines, interleukins 4 and 13 (IL-4 and IL-13), it is unclear whether they play a role in initiating allergic immunity or merely enhance existing allergy. In this regard, mouse models of allergy are more supportive of a key innate

immune function of basophils in orchestrating Th2-type immunity and allergy, and potentially acting as antigen presenting cells. However, these important roles have not been observed in primary human basophils although there is clear evidence to suggest that they crucially promote group 2 innate lymphoid cells (ILC2s) in atopic dermatitis. Shedding more light on these immunomodulatory roles of human basophils, and differentiating them from their rodent counterparts, will provide much needed greater understanding of this elusive cell type, especially in view of developing new therapeutic strategies against allergy.

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Introduction

There has been much debate about whether or not basophils play an important role in allergy. On the one hand, their relative scarcity compared to other leukocytes and their functionally-related mast cells counterparts could, at a first glance, suggest that their input into allergic inflammation is at best dwarfed by that from other allergic effector cells. On the other hand, in the past decade this opinion has changed to a large extent given increasing evidence to suggest that this cell type performs critical immunomodulatory roles as well as contributing majorly in certain inflammatory settings. However, differences in basic biological functions between primary human basophils and those derived from mouse models of allergy continue to hamper a clearer definition of their ultimate roles in allergic inflammation. See a summary of the possible roles of basophils in allergy in **fig. 1**. Most of the current breakthroughs in basophil biology have come from animal studies and, until recently, it was not even clear whether mouse basophils even remotely re-

Abbreviations

alpha-gal	Galactose-alpha-1,3-galactose
ATP	Adenosine triphosphate
BAT	Basophil activation tests
FcεRI	Immunoglobulin E receptor
HIF-1	Hypoxia-inducible factor-1
Ig	Immunoglobulin
IL	Interleukin
ILC2	Group 2 innate lymphoid cell
MHC	Major histocompatibility complex
PGD ₂	Prostaglandin D ₂
Th	T helper
VEGF	Vascular endothelial growth factor

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seem their human counterparts e.g., whether they can produce, store, and release histamine [1, 2]. Thankfully, some of these issues are being resolved and indicate that basophils are pivotal to human allergic disease.

Basophils in acute allergy and anaphylaxis?

Basophils are the rarest type of granulocyte that mature in the bone marrow from CD34+ myeloid stem cells and are then released into the circulation. Like mast cells, basophils express high affinity immunoglobulin E (IgE) receptors (*FcεRI*) and synthesize histamine from histidine due to the actions of histidine decarboxylase. This archetypal pro-allergic mediator is stored within intracellular granules bound to proteoglycans but is readily released from the cells following stimulation. The release of this biogenic amine is one of the most important pro-allergic mediators that governs the classical hallmarks of acute allergic inflammation. Although, in humans, mast cells are more numerous than basophils the latter are at least one order of magnitude more sensitive to IgE-mediated provocation than mast cells [3]. This, along with their usual location in the blood, places basophils as potentially important contributors to systemic anaphylaxis. Recent advances in the use of basophil activation tests (BAT), which utilize flow cytometry to assess the expression of degranulation markers (e.g., CD63), have suggested that these cells contribute to the clinical symptoms of severe food allergic reactions, including anaphylaxis [4, 5, 6, 7, 8, 9]. The symptoms of delayed anaphylaxis to red meat due to IgE directed against galactose-α-1,3-galactose (α-gal) were also clearly shown to correlate with the activation of basophils as concentrations of this antigen rose [10]. At the very least, these observations lend support to basophils acting as good predictors of clinical symptoms of allergy but they do not rule out a bystander effect of these cells.

Further signs to the participation of basophils in allergic reactions are also given by studies investigating the effects of anti-IgE therapy using omalizumab, a monoclonal antibody which prevents unbound IgE from sensitizing basophils and mast cells. Given the relative longevity of mast cells compared to basophils, and the substantial time required before omalizumab reduces mast cell-bound IgE levels, the early benefits of this monoclonal antibody therapy has been ascribed to the rapid prevention of basophil sensitization and subsequent lack of response to allergen challenge from basophils [11, 12, 13]. This indicates a partial input from basophils in the symptoms of acute allergy, a role which has previously been mainly ascribed to mast cells. Mouse models of allergy also support a role of basophils in acute allergic reactions, especially anaphylaxis [14].

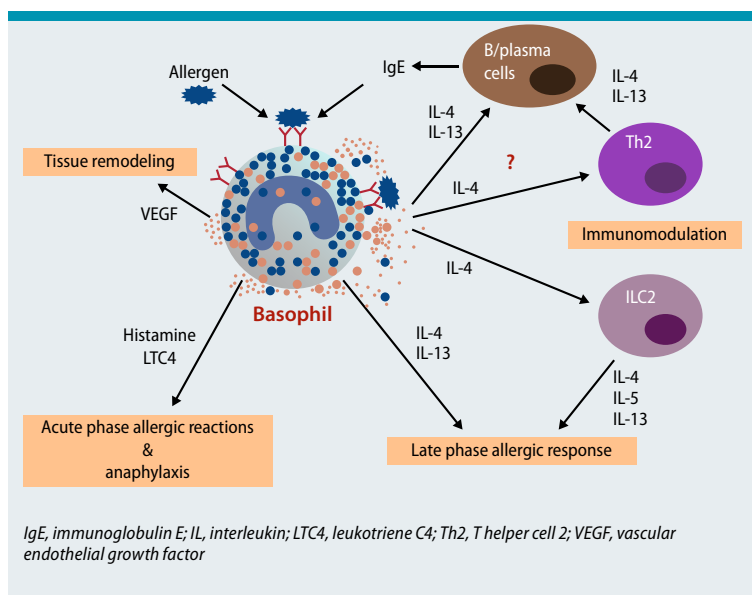


Fig. 1: Summary of the possible roles of basophils in allergy.

However, basophil-associated anaphylaxis has been reported to be IgG-mediated rather than due to IgE [15], a mechanism which is unlikely to reflect human allergy [16, 17] and may even involve macrophage input [18]. This is because of differences in the types of IgG receptors that predominate in basophils from these different species. In terms of stimulatory IgG receptors, mouse basophils express FcγRIIA whereas human basophils express FcγRIIA, of which only the former provides sufficient activation. Countering the effects of these receptors are FcγRIIB, inhibitory IgG receptors which, although present in both mouse and human basophils, predominate in human basophils. The net contribution of IgG-mediated responses is therefore inhibitory in human basophils but stimulatory in mouse basophils, one of many examples of heterogeneous responses that stifle a simple extrapolation of allergic mouse models to human allergy.

Basophil recruitment and activation in various tissues affected by allergic inflammation

While there may be growing evidence to suggest a possible role for basophils in acute allergic reactions, their role in late-phase reactions is less disputed. Although basophils are most commonly found in the circulation, numerous reports have shown their ability to invade tissues other than the blood, such as the skin and airways, affected by allergic inflammation (reviewed in [19]). The use of basophil-specific BB1 and 2D7 antibodies [20, 21] has greatly facilitated their identification in these tissues and some of these studies additionally show an associa-

tion between disease severity and basophil influx, especially in severe and fatal asthma [22, 23]. This is further corroborated by studies showing increased CD203c expressions on basophils positively correlating with clinical symptom severity [24]. Several older studies provide indirect evidence of basophil participation in late-phase reactions by virtue of the detection of histamine release in either suction blister fluid or nasal secretions following allergen provocation of allergic volunteers (reviewed in [19]). In these cases, histamine release during late-phase reactions was not accompanied by mast cell mediators, such as prostaglandin D_2 (PGD_2) or tryptase. Since basophils and mast cells are considered as the main source of histamine, the above strongly indicates major basophil involvement in the local release of this mediator during these responses.

In addition to differential histamine and tryptase/ PGD_2 release, the participation of basophils in contributing to allergic inflammation during late-phase reactions is further supported by studies showing their ability to migrate into affected tissue sites within the timeframe in which these reactions occur (reviewed in [25]); this is also the case with regard to mouse models of allergy [26]. Moreover, basophils are almost uniquely capable of rapidly releasing the archetypal Th2-type cytokine IL-4 and it has also been demonstrated that levels of this cytokine in airway tissue is almost entirely basophil derived following allergen challenge [27, 28]. IgE-mediated IL-4 release from basophils is complete within 4 hours of stimulation and occurs almost continuously over this period due to the release of preformed IL-4 during the first hour of stimulation [29]. IL-13 is also readily released by basophils, although the kinetics are longer than for IL-4 [29], and both cytokines contribute to increased adhesion molecule expressions that potentiate further inflammatory cell influx into the inflamed tissues. Therefore, basophils are well placed to support late-phase allergic reactions and ongoing, chronic, allergic inflammation.

These cells also express CD40 ligand, which in conjunction with IL-4 and IL-13 causes class switching in B cells (at least *in vitro*) to favor IgE synthesis from plasma B cells [30]. Human mast cells, in contrast (especially to their rodent counterparts), produce little or no IL-4 and at present it seems unlikely that they can fulfil the above immunomodulatory roles as effectively as basophils. There is some evidence to support the local production of allergen-specific IgE in allergically inflamed tissues which potentially places the basophil in a position of masterminding the perpetuation of ongoing allergic responses [31, 32]. However, there is still a lack of definitive data from human allergy to prove that basophils are key to this.

Mouse models of basophils: a breakthrough in understanding their biological roles?

In the last decade, mouse models of allergy have conclusively demonstrated that basophils are essential for chronic allergic inflammation. Studies by Mukai et al. described a form of delayed onset allergic reaction in mice which was dependent on IgE and basophils, whereas mast cells and T cells did not play an essential role in these responses [33]. Two years later, Obata et al. used a mouse basophil-depleting antibody and described that this cell type is indispensable for the development of signs of inflammation associated with chronic mouse allergy as well as the migration of other granulocytes into allergen-stimulated tissues [34]. These studies set the scene for a resurgence of interest into basophils since they appeared to support our earlier claims that these cells are best placed to impact on ongoing allergic inflammation. Given the rarity of human diseases associated with basophilia or basopenia for genetic reasons, it has proved difficult to deduct a major role for basophils without resorting to mouse models. But it is questionable whether these mouse models truly resemble human allergy since the delayed-type of chronic allergic reactions described above are not a feature of human allergy. In spite of this, animal models do clearly highlight that basophils have important and conserved biological functions in the animal kingdom, such as combating parasitic infections where similar roles of basophils causing chronic inflammation were observed [35].

Sustained functions of basophils by use of hypoxic signaling

Whatever the differences in clinical manifestations of allergic inflammation caused by basophils may be, their ability to rapidly secrete Th2-type cytokines (e.g., IL-4, IL-13) seems to be a key common biological response to all basophils. Interestingly, FcεRI triggering in basophils is associated with so called hypoxic signaling (a network of intracellular pathways taking place at low oxygen availability, which could also act as stress adaptation mechanisms under normal oxygen conditions). This supports the ability of these cells to produce cytokines over long periods in potentially hostile inflammatory environments [36, 37, 38]. Hypoxic signaling also controls vascular endothelial growth factor (VEGF) production, which plays a role in tissue remodeling (particularly in asthma), and is under direct control of hypoxia-inducible factor-1 (HIF-1) activity. Signal transduction pathways leading to histamine release and eicosanoid production rapidly sequesters adenosine triphosphate (ATP) levels [36]. In inflammatory environments, where oxygen consumption by activated

cells is high, this is known to lead to hypoxia which can rapidly cause cell death by apoptosis unless mitochondrial-derived energy production is switched to obtaining ATP from glycolysis. By switching on hypoxic signaling pathways following IgE-dependent triggering alone, basophils are crucially adapted to inflammatory and hypoxic stress, which further supports an important role in allergic inflammation and their well-known input in defence against parasites. Important questions on the role of basophils in ongoing allergic inflammation remain however, including how they (and other allergic effector cells) actually respond within inflamed tissues, potentially affected by low tissue pH and oxygen tension and whether HIF-1 activity can prolong the survival of this relatively short-lived cell.

Basophil and ILC2 cell interactions: further evidence for a pro-inflammatory role?

Another vital issue pertinent to explaining the role of basophils in allergic inflammation is delineating the importance of cell-cell interactions between basophils and other immune cells within inflamed tissues. Recently, it has been reported that basophil-derived IL-4 promotes group 2 innate lymphoid cells (ILC2) *in vivo* and *ex vivo* in mouse models of cutaneous and lung inflammation [39] and, importantly, ILC2 have been shown to co-accumulate with basophils in inflamed human skin [40]. ILC2 are associated with eosinophilic inflammation, which is common to most tissues affected by allergic inflammation, by contributing to IL-5 release and other Th2-type cytokines. Both ILC2 and basophils are activated by the epithelial-derived cytokine IL-33 (in the case of basophils this leads to a strong potentiation of IgE-responses [41]) and the interaction of basophils and ILC2 has been shown to control IL-33 mediated allergic responses [39]. Unraveling the cooperative cell-cell interactions between these cells may provide new insights into the nature of inflammatory processes and new therapeutic applications. In contrast to the close interactions of basophils with ILC2 cells, neutrophilic inflammation which is also present in certain allergic diseases, such as asthma, and regulated by Th17 cells does not appear to be regulated by basophils [42].

Basophils and Th2 immunity

A potentially game-changing aspect of basophils is whether they participate in the early orchestration of allergic diseases, either by acting as antigen presenting cells or directing Th2 cell development to their unique ability to rapidly supply IL-4, even after innate triggering, or both. Most of these crucial questions have largely been investigated in mouse

models of either allergy or parasitic infections. In 2009, Sokol et al. demonstrated that the absence of major antigen presenting cells did not affect the Th2 immunity whereas basophils expressed major histocompatibility complex (MHC)-II molecules and were able to process and present antigens to T cells by migrating to the lymph nodes [43]. Similar functions were discovered at the same time by Perrigoue et al. and Yoshimoto et al. who both showed that basophils crucially initiated Th2-type immune responses to nematodes [44, 45]. Sokol et al. also reported that mouse basophils respond to innate triggering by protease allergens, such as papain, which results in the crucial early supply of IL-4 required for Th2 development [43]. This was further supported, in part, by Tang et al., although the authors showed that input from dendritic cells was necessary to facilitate basophil-mediated Th2 development [46].

Regarding the antigen-presenting abilities of basophils, Hammad et al. convincingly demonstrated that dendritic cells, but not basophils, presented antigens in mice exposed to inhaled house dust mite allergens [47], although basophils were majorly involved in supporting Th2 differentiation. These discrepancies have yet to be fully resolved and underline the caution from extrapolating these animal models to human allergy. Regarding the latter, there is currently no clear evidence to suggest that human basophils are capable of processing allergens for presentation on HLA-DR (MHC-II) even though MHC-II expression can be induced in a subpopulation of basophils by various cytokines [48]. Moreover, we demonstrated over a decade ago that primary human basophils do not express protease activated receptors and do not respond to protease allergens [49]. Furthermore, they also do not appear to promote secondary immune responses to allergens in allergic patients [50].

Concluding remarks

At this time, we can conclude that basophils seem more likely to participate in acute allergic reactions than previously thought and their activation status serves as a useful diagnostic marker of clinical symptoms of allergy. However, their role as antigen presenting cells or major contributors to early conditioning of Th2 immunity in allergy is unresolved. In contrast, recent studies do tend to support an essential role in perpetuating ongoing allergic disease, both at the level of directly increasing inflammation and maintaining immunomodulatory mechanisms responsible for underlying allergic inflammation and Th2 immunity. The heterogeneity between mouse and human basophils remains however a serious complication in

providing more definitive answers to their role in allergy.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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