Basophils as Key Regulators of Allergic Inflammation and Th2-type Immunity

Bernhard F. Gibbs

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Key Words: basophils, mast cells, Th2 immunity, allergy

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expression on the microvascular endothelium and eotaxin synthesis from airway epithelial cells, supporting leukocyte influx into affected tissues during late-phase responses. They also play a key role in B-cell immunoglobulin class switching to favor IgE synthesis, and IL-4 is a vital factor for the early differentiation of CD4+ lymphocytes to a Th2 type (reviewed in Haas et al.29).

Given that basophils are major producers of these cytokines, an immunomodulatory role in supporting the previously mentioned events by these cells seems highly plausible (Fig. 2). However, direct in vivo evidence for this has been, until very recently, scarce, owing largely to a lack of basophil knockout animal models because a basophil-specific growth factor has not yet been identified. Although growth factors such as IL-3, in particular, promote basophil development from CD34+ progenitors (and controversially, murine mast cells, but not human mast cells), basophils are still present in IL-3-deficient mice.30 This has stifled the development of basophil-knockout models analogous to mast cell-deficient mice (lacking c-kit receptors or c-kit ligand/stem cell factor, mandatory for mast cell maturation). To circumvent this problem, basophil-specific monoclonal antibodies have been used to deplete circulating murine basophils,31 a technique that could potentially revolutionize future investigations into unraveling their biological roles.

**BASOPHILS REGULATE LATE-PHASE REACTIONS AND CHRONIC ALLERGIC INFLAMMATION**

Although murine mast cells can readily produce the Th2-type cytokines ascribed to human basophils, implying a redundancy in function for the latter, it is remarkable that some of the strongest evidence for a major role of basophils in allergic inflammation comes from murine allergy models. One such model uses transgenic mice generating 2,4,6-trinitrophenol (TNP)-specific IgE that gives rise to a variety of allergic responses after subcutaneous TNP injection.32 This consists of early- and late-phase allergic responses, chronic allergic inflammation, and anaphylaxis after intravenous TNP injection. It was demonstrated that these mice fail to display signs of chronic allergic inflammation after prior depletion of circulating basophils.33 Furthermore, a combinational approach, using a range of mice genetically defective in various lymphocytes and mast cells and reconstitution experiments, showed that mast cells, T cells, and natural...
killer cells (NK) and natural killer T cells (NKT) were not necessary for the late-phase allergic reactions, in stark contrast to basophils.33

**BASOPHILS AS POTENTIAL MODULATORS OF LOCAL IgE SYNTHESIS**

Recently, it has been shown that B cells residing in the bronchial mucosa of asthmatic patients undergo class switching to IgE synthesis, supporting earlier observations regarding their local generation of allergen-specific IgE in the nasal mucosa.34 Gould et al35 calculated that this local IgE production may account for a substantial portion of IgE saturating allergic effector cells within these sites. The fact that IgE synthesis occurs not only in the lymph nodes but locally within organs affected by allergic inflammation permits immunomodulatory input from resident allergic effector cells such as basophils.

Immunoglobulin E class switching is controlled by IL-4, IL-13, and CD40 ligand (CD40L) binding to its counterpart receptor on B cells. Yanagihara et al36 showed that basophils can indeed direct polyclonal IgE synthesis in vitro by virtue of their ability to produce the previously mentioned stimuli, the effects of which were inhibited by the addition of neutralizing antibodies against IL-4, IL-13, and other Th2-type cytokines themselves (reviewed in Haas et al29). The importance of IL-4 in initiating Th2 development was confirmed by studies showing that mice lacking either IL-4Rα or Stat6 (which controls IL-4-directed signaling) do not generate Th2 immune responses.38,39 In addition to governing chronic allergic inflammation and perhaps also IgE synthesis, basophil-derived IL-4 may thus play a role in controlling Th2 immunity too. At the very least, basophils may exacerbate existing Th2 polarization in ongoing allergic disease. Further evidence for an association between basophils and Th2 lymphocytes is given by clinical studies showing that specific allergen immunotherapy reduces basophil reactivity and numbers as well as Th2 immunity.40

Although there is strong evidence to show that basophils are capable of supporting local Th2 immune responses at sites of allergic inflammation and possibly regulating local B-cell IgE class switching, several important issues remain. First, do basophils migrate to the lymph nodes, which are the prime tissue sites for developing immune responses? Second, do basophils participate in the induction phase of Th2 immunity? The latter would require basophils to be activated by mechanisms that do not require the presence of surface-bound antigen-specific IgE.

**DO BASOPHILS CONTROL Th2 IMMUNITY?**

As already discussed, it is increasingly clear that basophils are the main early source of IL-4 after allergen exposure in peripheral blood and asthmatic airways. Unlike IL-13, IL-4 is unique in driving CD4+ T cells to a Th2 phenotype, which subsequently produce IL-4, IL-13, and other Th2-type cytokines themselves (reviewed in Haas et al29). The liaison between tissue-associated basophils and B cells certainly represents a plausible circulus vitiosus of increasing IgE and effector cell sensitization central to the pathophysiology of allergic disease.
Basophils are not usually attributed to being present in the lymph nodes. However, a recent study has clearly demonstrated that they transiently migrate into the draining lymph nodes of mice after immunization with the protease allergen, papain.41 Interestingly, these investigations also showed that basophils were activated by protease allergen by innate triggering and released Th2 cytokines that were essential for initiating Th2 differentiation. A considerable proportion of activated basophils within the lymph nodes also released thymic stromal lymphopoietin (TSLP), in addition to IL-4, and were the only cell type within the lymph nodes that produced this Th2-driving factor. The TSLP-neutralizing antibodies indeed diminished Th2 differentiation without affecting either dendritic cell maturation and migration or basophil accumulation within the draining lymph nodes. This report clearly suggests that mouse basophils play a vital role in innate immune recognition leading to Th2 responses by secreting IL-4 and TSLP.

Although the previously mentioned data add further credence to the immunomodulatory capabilities of basophils, there are a number of unresolved issues. For example, TSLP production in human basophils has not yet been reported, and there is contradictory evidence regarding their ability to react to specific protease-activated receptor agonists42 versus protease allergens (eg, Der p1).43 Elucidating the mechanisms of basophil migration into the lymph nodes after protease allergen challenge and whether this migration takes place in other settings also need addressing. For instance, although basophils have been shown to be critical in recruiting Th2 cells into affected tissues after Nippostrongylus brasiliensis infection (which also causes a substantial Th2-type response),44 their innate activation was not necessary for Th2 differentiation in the lymph nodes.45 Thus, although the evidence for basophil-directed immunomodulation within organs such as the lung is strong, their ability to control Th2 immunity, as well as IgE class switching, within lymphatic tissues is by no means fully resolved. This applies both to their ability to participate in early (innate) events of conditioning Th2 responses and to ongoing allergic disease, where their role in the lymphatic tissues is also not known.

**INNATE ACTIVATORS OF BASOPHIL CYTOKINE SYNTHESIS**

There is now a wealth of literature showing that human basophils produce IL-4 and IL-13 in nonsensitized individuals by various innate triggers, some of which cause activation of FceRI by binding to IgE in a non-antigen-specific manner (reviewed in Falcone et al45). These include parasite antigens (eg, Schistosoma mansoni, Echinococcus multilocularis), lectins (eg, concanavalin A), and viral superantigens (eg, human immunodeficiency virus 1 gp120) that activate basophils by binding to non–antigen-specific IgE antibodies. Furthermore, basophil cytokine release is also caused by engagement of certain leukocyte immunoglobulinlike receptors (eg, LIR7), toll-like receptors (eg, TLR2), and to a more limited extent, by C5a/C3a and formyl-methionyl-leucylphenylalanine (iMLP).

In addition to the previously mentioned innate stimuli, basophil growth factors such as IL-3 and nerve growth factor (NGF) can also induce considerable levels of Th2-type cytokine synthesis.47,48 Although this usually occurs only at relatively high concentrations of either IL-3 or NGF (above 10 ng/mL), lower amounts (1 ng/mL) substantially enhance IgE-dependent basophil mediator release to both specific allergens and innate activators. Regarding NGF, there is compelling evidence to suggest that this neurotrophin participates in both animal models of allergy and in human allergic asthma, where it correlates with disease severity and IgE levels.49,50 Because basophils from asthmatic donors display a hyperreleaser phenotype,51 factors such as NGF may have an important function in enhancing the synthesis of basophil-derived Th2-type cytokines and thereby their proallergic immunomodulatory roles (Fig. 2).

**BASOPHILS AS TARGETS FOR ANTIALLERGIC THERAPY**

Given their potential in supporting both allergic inflammation and underlying Th2 immunity, basophils are an attractive target for antiallergic therapy. Their abilities to release mediators are inhibited by certain existing antiallergic agents such as glucocorticoids, methylxanthines, and calcineurin inhibitors, and this may partially explain their clinical effectiveness. Other traditional therapeutic agents, such as cromoglycate, have no known effects on basophils and highly variable actions on various mast cell subtypes.

The well-known limitations of these agents, including their heterogeneous actions on basophils and mast cells, have prompted renewed attempts to block allergen-mediated FceRI activation of these cells. One promising approach is to prevent free IgE antibodies from binding to FceRII using monoclonal anti-IgE (omalizumab), which reduces both effector cell sensitization and FceRII expressions. Treatment with omalizumab in allergic rhinitis patients has been shown to strikingly reduce basophil reactivity and lead to a rapid decline in FceRII expression, which was faster in comparison to mast cells.52 In parallel, these authors also observed a reduction in allergen-induced wheat size. A similar decline in basophil reactivity after omalizumab therapy is seen in allergic asthma, although in these settings, this was not always matched by clinical improvement.53 Basophils may also be directly affected by rush desensitization regimens, which has been ascribed to a loss of Syk expression,54 a crucial stimulatory signal associated with FceRI activation. But their signal transduction machinery additionally encompasses a range of inhibitory signals that may contribute to their functional desensitization. One such signaling target is the src homology 2 domain–containing inositol 5phosphatase (SHIP), an inhibitory enzyme that is centrally involved in IgE-mediated signaling in both basophils and mast cells.55,56 The SHIP has been shown to be mobilized upon the activation of inhibitory receptors, such as IRp60 (CD300a), leading to a dramatic reduction in allergic effector cell function.57 CD300a, CD200R,58 Siglec-8,59 and FcγRIIB (the latter only blocks basophil responses in conjunction with FceRI co-cross-linking)60 up-regulate SHIP expressions and may in the future be exploited for antiallergic therapies.
CONCLUSIONS
Recent in vivo investigations have provided exciting new inroads that support earlier in vitro studies showing that basophils are far from mere bystander cells of allergy and Th2 immunity. Their propensity to rapidly deliver Th2 cytokines under a variety of conditions and their necessity in eliciting chronic allergic inflammation underscores their immunomodulatory potential. However, the details concerning these actions still need to be elucidated, also in view of input from regulatory T cells that may down-regulate proallergic responses after parasitic helminth infections. The physiological purpose of basophils also remains elusive, as well as their interactions with other effector cells of the allergic inflammatory response. Nonetheless, there is overwhelming evidence to show that basophils contribute to the symptoms of allergic disease and support underlying Th2 immunity, especially in ongoing allergy. This cell therefore poses an obvious therapeutic target, and identifying ligands for inhibitory receptor engagement may be a promising approach to generate new antiallergic therapies.

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