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Do basophils play a role in immunity against parasites?

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The link between parasites and eosinophilia has been known for more than a century, although the role of eosinophils in host protection is still an open issue. Much less appreciated, however, is the concurrent systemic induction of a related cell type, the basophil, in parasitized hosts. To date, little is known about the role of basophils in immunity against parasites, but recent evidence points to a possible crucial role in the initiation of T-helper type 2 responses in the host. In this article, we review the current understanding of parasitic infections and basophils and discuss their putative role in immunity.

Granulocytes are leukocytes and are part of the innate immune system, which is a first line of defence against invading pathogens. They are further differentiated into neutrophilic, eosinophilic or basophilic granulocytes, according to the differential staining properties of their cytoplasmic granules with

particular dyes. Currently, the predominating concept is that neutrophils are crucial in immunity against bacterial and other unicellular pathogens, whereas eosinophils are important effectors of immunity to pathogens that are too large to phagocytose, particularly against tissue-dwelling larval stages of several nematode infections¹.

A pivotal role of neutrophils is well established and convincingly shown in humans with inherited diseases such as chronic granulomatous disease (CGD), in which a defect in the leukocyte oxidase gene severely impairs immunity to several bacterial pathogens². In addition, peripheral blood eosinophilia, together with a marked elevation of serum IgE and intestinal mastocytosis, have long been known as hallmarks of infection with parasitic helminths, although it is difficult to show that eosinophils have a host-protective function¹. It is widely accepted that these responses reflect a T-helper type 2 (Th2)-skewed immune response, characterized by an increased production of the cytokines interleukin-4 (IL-4), IL-5 and IL-13. Much less appreciated, however, is the concurrent systemic induction of the third granulocyte type, the basophil (basophilia). In animals experimentally infected with nematodes, basophils have been shown to proliferate in the bone marrow^{3–5}, to increase up to 50-fold in the circulation^{3–7} and to accumulate and degranulate at the site of infection^{3–4}. In rats infected with *Nippostrongylus brasiliensis*, the period of expulsion coincides with the peak of blood basophilia⁶,

suggesting a possible involvement of basophils in expression of immunity. In humans infected with the hookworm *Necator americanus*, basophil levels are strongly increased in peripheral blood and are the only cell population responsive to worm removal after treatment with anthelmintics (E.A. Walsh, PhD thesis, University of Nottingham, 1994). This finding, apart from suggesting that basophils be used as indicators of successful treatment and worm removal, also suggests that hookworms might directly drive host basophilia.

The powerful induction of basophilia by parasitic worms might suggest a role in host protection, but there is currently no direct evidence for this assumption. Can basophils be attributed a specific function in immunity against parasites? It has become increasingly clear that basophils play a role in allergic diseases such as asthma⁸. However, it is difficult to accept the idea that basophils (or mast cells) have been widely preserved in the animal kingdom without a specific and/or host-beneficial biological function. The analysis of gene-deficient mice has shown clearly that mast cells can play a host-protective role, at least against some intestinal helminths^{9–10}. Unfortunately, this technology cannot yet be applied to the study of basophils because basophil-specific developmental pathways are still unknown¹¹. Mast cells are now increasingly being considered as important cells of innate immunity against bacterial pathogens¹². Can anything comparable be said about the biological function of basophils?

Basophils in tick immunity

The only examples suggesting a host-protective function for this cell type have come from the study of the local immune response to ectoparasites (e.g. ticks). Work performed ~20–30 years ago^{13–15} indicated that basophils are important effectors of tick rejection. Although the relationship between the feeding tick and the host immune response is now known to be complex and bidirectional^{16–17}, earlier research, which was based on a paper by Trager published in 1939 (Ref. 18), nevertheless showed the importance of basophils as a major component of acquired resistance to ticks in the phenomenon of cutaneous basophil hypersensitivity (CBH)^{19–21}. In an experimental model using guinea pigs that have acquired immunity to *Amblyomma americanum*, basophils are quickly recruited to the feeding site where they degranulate, thus leading to the rejection of the tick²¹. In this model, treatment with a specific anti-basophil serum before challenge ablated immunity²², whereas a specific anti-eosinophil serum had only a partial effect. Detailed analyses of the cell types recruited to the feeding site showed that in sensitized guinea-pigs infested with *Rhipicephalus appendiculatus*, basophils were the dominant cell type accounting for up to 90% of all infiltrating cells¹⁵. The local recruitment of basophils was accompanied

by a systemic basophilia: peripheral blood basophils peaked in *A. americanum*-infested guinea pigs (threefold increase) at the peak of tick drop-off²³. A similar recruitment of basophils to the feeding site, as well as a marked systemic increase (up to 12-fold) of blood basophils, has also been reported in guinea pigs infested with the tsetse fly *Glossina morsitans*²⁴.

Basophils, mast cells and eosinophils

Taken together, the current parasitological literature supports the idea that basophils have an important role in immunity to ticks and perhaps also to other ectoparasites, but is this the only *raison d'être* of this cell type? We will answer this question by summarizing the main similarities and differences between basophils and two related cell types: mast cells and eosinophils.

Mast cells, eosinophils and basophils are all generated in the bone marrow from CD34⁺ haematopoietic precursor cells⁸. Basophils and eosinophils are normally released from the bone marrow as mature cells, whereas mast cells undergo their final maturation in the tissues. Mast cells can proliferate and persist in tissues, for example during infection with intestinal helminths, whereas eosinophils and basophils have relatively short lifespans and have to be replenished from the bone marrow. Eosinophils are mainly tissue-dwelling cells, and therefore make up only 1–5% of leukocytes circulating in peripheral blood. In contrast to mast cells and eosinophils, basophils are not found in healthy tissues but can infiltrate them rapidly during an inflammatory reaction. This is facilitated by the expression of a variety of receptors for chemoattractants such as complement 3a (C3a), C5a, platelet activating factor (PAF), leukotriene B₄ (LTB₄), *N*-formyl-methionyl-leucyl-phenylalanine (fMLP), eotaxin, eotaxin-2, monocyte chemoattractant protein-1 (MCP-1), MCP-4, granulocyte macrophage-colony stimulating factor (GM-CSF), IL-3 and IL-8, as well as the expression of β -integrins, which facilitate adhesion to the endothelium.

The similarity between mast cells and basophils in terms of morphology and stored mediators (e.g. histamine), as well as the classical activation mechanism itself (crosslinking of specific high-affinity receptor-bound IgE by allergens), has sometimes led researchers to consider basophils as the equivalent of circulating mast cells. Despite the evident similarities, however, there are several fundamental differences that might point to the biological significance of basophils. These differences, as well as those between human histaminocytes and their rodent counterparts, including tissue-specific heterogeneity, have been reviewed extensively^{11,25}. Here, we shall highlight only the aspects that might be relevant to the putative role of basophils in immunity against parasites. For example, some stimuli that are strong activators of basophils do not have an effect on mast cells (e.g. the bacterial peptide

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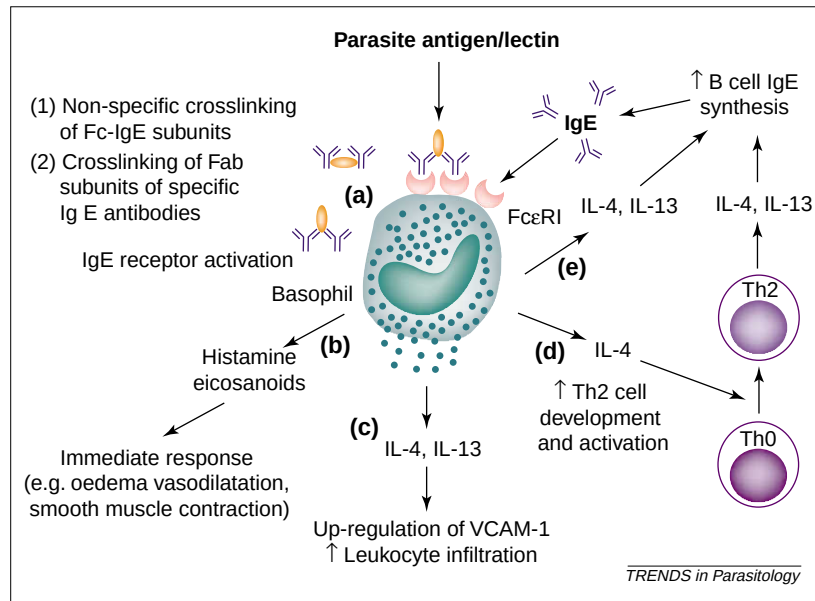


Fig. 1. Basophils can influence immune responses. (a) Antigen specific (e.g. parasite antigens or allergens) and non-antigen specific stimuli (e.g. lectins specific for IgE carbohydrate side chains, superallergens) crosslink the high-affinity receptor for IgE (FcεRI), resulting in basophil degranulation. (b) Release of preformed (histamine) or *de novo* synthesized substances (eicosanoids) induces immediate effects such as vasodilatation and smooth muscle constriction. Within hours of degranulation, the basophils release large amounts of IL-4 and IL-13, which might play a pivotal role in biasing the emerging immune response to the Th2 phenotype. (c) Increased expression of the adhesion molecule VCAM-1 on the endothelial cell surface by the basophil-derived cytokines IL-4 and IL-13 augments inflammatory cell extravasation and infiltration into the tissues. Basophil-derived cytokines can also play a central role in skewing T-cell differentiation to the Th2 phenotype (d) as well as directly switch ongoing antibody production to the IgE isotype (e).

fMLP), and a variety of cytokines and growth factors, such as IL-1, IL-3, IL-5, nerve growth factor-β (NGF-β) and GM-CSF, are known to enhance releasability of basophils (of which IL-3 is the most potent) but have little effect on mast cells. Therefore, it appears that basophils are indeed a particularly flexible cell type, with the ability to respond to a wide range of chemotactic, priming or activating stimuli. However, basophils are much more restricted, with respect to the mediators stored in their granules, relative to other granulocytes or mast cells and/or their ability to kill invading pathogens. Neutrophils can kill by phagocytosing, generating reactive oxygen species and releasing antimicrobial peptides such as defensins. Eosinophils have granules containing extremely toxic basic proteins, such as major basic protein (MBP), eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin (EDN), that have been shown to kill parasitic worms *in vitro*²⁶. Mast cells are a major source of proteases (tryptase, chymase and cathepsin G) and can phagocytose microorganisms via CD48 (Ref. 27), whereas basophils have not been shown to be phagocytic, and contain only small quantities of preformed proteases or toxic proteins (with the notable exception of MBP and lysophospholipase). But the most distinctive (and perhaps most revealing) feature of basophils has come from the recent analysis of the cytokines produced by activated basophils: these are strikingly restricted to a Th2-like profile.

Basophils as key initiators of the Th2-response?

It has long been known that basophils release preformed histamine and other mediators upon crosslinking of high-affinity receptor-bound IgE, but only recently has it been appreciated that this stimulus also leads to the production and release of large quantities of IL-4 and IL-13 (Ref. 28). The kinetics of release is rapid (within 4 h for IL-4 and 16 h for IL-13)²⁸, and, in terms of all circulating

leukocytes, this early production is exclusively basophil-derived²⁹. IL-4 and IL-13 share many biological activities that skew the immunological response towards a Th2 type. First, both IL-4 and IL-13 derived from basophils promote IgE production from B cells³⁰. Second, IL-4 directly or indirectly orchestrates the development of Th2 cells, which eventually become capable of producing IL-4 and IL-13 themselves³¹. Thus, the rapid release of large amounts of basophil-derived IL-4 might be crucial for the support of Th0 cell-subset differentiation to Th2. This cellular source of IL-4 might therefore be a pivotal factor influencing the overall impact of infection with parasitic nematodes by skewing the immune response to the Th2 phenotype.

The evidence indicating that basophils might have such a critical early function is not restricted to the rapidity of Th2 cytokine generation. Further support comes from data showing that the release of Th2 cytokines might also occur in the absence of a developed specific immune response. It has been shown that antigens derived from *Schistosoma mansoni* eggs induce the release of IL-4 from basophils of non-immune donors, but in the presence of receptor-bound IgE³². Furthermore, various plant lectins also induce IL-4 and IL-13 from basophils, possibly by binding to IgE carbohydrate side-chain residues³³. Similarly, HIV-1 glycoprotein gp120, has been shown recently to induce IL-4 and IL-13 production from basophils and mast cells by binding to the V_H3 region of IgE (Ref. 34). *Necator americanus* produces a strong allergen, which is a putative homologue of calreticulin³⁵, a lectin with a carbohydrate affinity that also matches the glycosylation pattern of human IgE. Thus, several pathogenic organisms may induce the activation of basophils by the release of 'superallergens' [molecules with the ability to crosslink the high-affinity receptor for IgE (FcεRI), either directly or via receptor-bound IgE in a non antigen-specific manner] (Fig. 1). Together, these data clearly show that IgE-dependent basophil-activation is possible without the classical interaction of processed antigens with Fab subunits. In this context, it is important to note that several parasitic nematodes are known to secrete large amounts of calcium-dependent (C-type) lectins³⁶, indicating a class of molecules that might be instrumental in skewing the immune response. A prominent member of the C-type lectin family is CD23, the low-affinity receptor for IgE. Soluble, proteolytic fragments of membrane-bound CD23 activate basophils by interacting with CD21 (also known as C3 complement receptor), which is present on their surface³⁷. Therefore, other hypothetical scenarios leading to the non-antigen-specific activation of basophils and subsequent release of IL-4 and or IL-13 are (1) the interaction of soluble homologues of CD23 secreted by the parasites and (2) the cleavage of host-derived membrane CD23 by parasitic proteases³⁸, where both stimulatory effects would be mediated via CD21 on the basophils. This, and histological evidence

showing the presence of basophils in tissues infected by parasites, makes it increasingly apparent that basophils might be key initiators of the early stages of the Th2-type response to helminth infection.

As already discussed, basophils are largely restricted to a Th2 cytokine profile, and there have been no reports of a significant production of pro-inflammatory factors, such as tumour necrosis factor (TNF- α), IL-5, IL-6, IL-8 or GM-CSF, all of which are released from rodent mast cells³⁹. Human mast cells have differential abilities to release these cytokines and it is not clear to what extent they can produce IL-4 and IL-13 by an IgE-dependent route. In contrast with human mast cells, those from rodents are clearly capable of secreting Th2- as well as Th1-type cytokines. However, it appears that, in humans, the basophil might have adopted the role of the main Th2-cytokine producing cell type.

Conclusions

A possible function of basophils could be the rapid, non antigen-specific production of large amounts of IL-4 and IL-13, skewing the emerging immune response to the Th2-phenotype and thereby linking the innate and the adaptive immune response to infection with parasitic helminths. Further investigations are needed to elucidate the relative roles of mast cells, basophils and eosinophils as a source of Th2 cytokines in other animal species as well as their interplay during infection. A better understanding of the specific developmental pathways underlying basophil differentiation should enable the application of gene deletion strategies to the study of their putative roles in immunity against parasites.

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