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Basophils: Are they only shadow dancers in allergy or more…?

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INTRODUCTION

Although basophils are one of the rarest types of leukocyte they are remarkably endowed with an abundance of receptors and mediators relevant to allergic disease. Some of these are shared with their tissue-fixed counterparts, the mast cells, including expression of high affinity IgE receptors (FcεRI), the release of histamine and leukotriene-C_4 following allergen provocation as well as their ability to undergo metachromatic staining. However, far from being blood-born mast cell impersonators, human basophils posses certain unique abilities that in some circumstances surpass other allergic effector cell types. These include their capacity for rapid synthesis of IL-4 and IL-13 (in the case of IL-4 even release of preformed stores) and expression of CD40 ligand, which enables these cells, at least in theory, and incidentally *in vitro*, to support Th2 immunity and the production of IgE antibodies. Although these abilities potentially place the basophil at the forefront of any allergic scenario their relative low numbers and awkwardness to purify has all too often discouraged much needed research into unravelling their biological purpose. This short article redresses some of the basophil's previously disguised roles in allergic inflammation, highlighting not only problems regarding basophil research but also several recent breakthroughs which favour a more prominent position for basophils in allergy than previously thought.

PROBLEMS ASSOCIATED WITH BASOPHIL RESEARCH

We still know little concerning the origins of basophils and even less about their fate after entering tissues affected by allergic inflammation. Furthermore, in certain rodent species mast cells are quite capable of generating the Th2-type cytokines ascribed to human basophils. Couple to that the increased overall mast cell numbers in rodents compared to humans, and the fact that certain mast cell knockout mice models fail to undergo anaphylactic shock, and one could easily jump to the conclusion that basophils are obscure cellular remnants of the animal kingdom.

However, it is perhaps worth considering that humans are far more sensitive to the effects of histamine than mice and human basophils are generally 50-100 fold more sensitive to IgE-mediated triggering than their mast cell counterparts. Thus one could envisage that, in man, basophils may still be capable of eliciting systemic anaphylactic reactions though, apart from sparse case/conference reports, not much attention has been given to this possibility to date. A lack of basophil knockout animal models has not helped clarify their role. This is because we still haven't identified a basophil-specific growth factor. While IL-3 is important for increasing basophil development from CD34+ progenitors, to our frustration IL-3 deficient mice still express these cells. Despite this, alternative approaches have recently led to the successful depletion of basophils in mice and, together with new staining techniques, are beginning to shed light on this elusive cell.

BASOPHILS IN HUMAN ALLERGY: NEW STAINING TECHNIQUES DEMONSTRATE BASOPHIL INVOLVEMENT

Significant inroads have been made regarding the migration of basophils into various organs affected by allergic inflammation, especially their detection. Basophils express a striking variety of chemokine receptors (e.g. CCR1, CCR2, CCR3, CXCR1, CXCR3 and CXCR4) and respond to many different chemokines, cytokines and chemokinetic factors that facilitate their migration [1, 2]. The basophil-specific BB1 and 2D7 antibodies have greatly assisted the staining of these cells in various tissues, with a wealth of literature [reviewed in 3] clearly showing their presence in the allergic asthmatic lung, with high basophil numbers associated with fatal cases [4]. Similar evidence has been reported for allergic diseases of the skin and nose too [3].

What is the evidence that basophils are activated at these sites of allergic inflammation? Unlike mast cells, which store and release tryptase, a specific marker for degranulation, no basophil-specific mediators are known, as yet, that enable a quantitative assessment of their activation *in vivo* (e.g. in serum). Despite this, older (but remarkably elegant) studies demonstrated histamine release during late-phase reactions in asthma without accompanying mast cell-specific mediators such as PGD_2 or tryptase [5]. And similar observations have been published regarding antigen-induced mediator secretion in the skin [6]. While basophil-specific inflammatory mediators are lacking, flow cytometric techniques assessing CD63 and CD203c expressions have been successfully used as a marker of *ex vivo* basophil activation in insect venom allergy [7] and may be considered as a diagnostic tool [reviewed in 8].

NEW EVIDENCE USING RODENT MODELS OF ALLERGY: BASOPHILS ARE CRUCIAL FOR INITIATING CHRONIC ALLERGIC INFLAMMATION

Currently the strongest evidence for a major role of basophils in allergic disease surprisingly comes from a murine allergy model with transgenic mice that generate 2,4,6-trinitrophenol (TNP)-specific IgE [9]. Intravenous injection of TNP in these mice leads to anaphylaxis, and a subcutaneous injection gives rise to an allergic response consisting of early phase, late phase and very late phase responses (the latter reach a maximum at 4 days after challenge). Combining the use of range of gene knockout mice defective in various lymphocytes and mast cells, and by performing reconstitution experiments, Karasuyama's group found that mast cells, T cells, NK and NKT cells were dispensable for the late-phase allergic reaction. In stark contrast, basophils, though present in small numbers (2% at day 4), were indispensable to the generation of chronic allergic inflammation [9].

Although basophil knockout mice do not yet exist (for reasons given earlier) the above researchers recently generated monoclonal antibodies against murine basophils that can effectively deplete their numbers in the blood [10]. Using these antibodies in their TNP-specific IgE animal model to eliminate circulating basophils, the authors clearly demonstrated that a range of allergic inflammatory parameters were almost completely abolished upon antigen challenge compared to controls. This strongly suggests that basophils are indeed not only effector cells but play a pivotal role as initiators of chronic allergic inflammation.

BASOPHILS AS MAJOR SUPPORTERS OF TH2-TYPE IMMUNITY

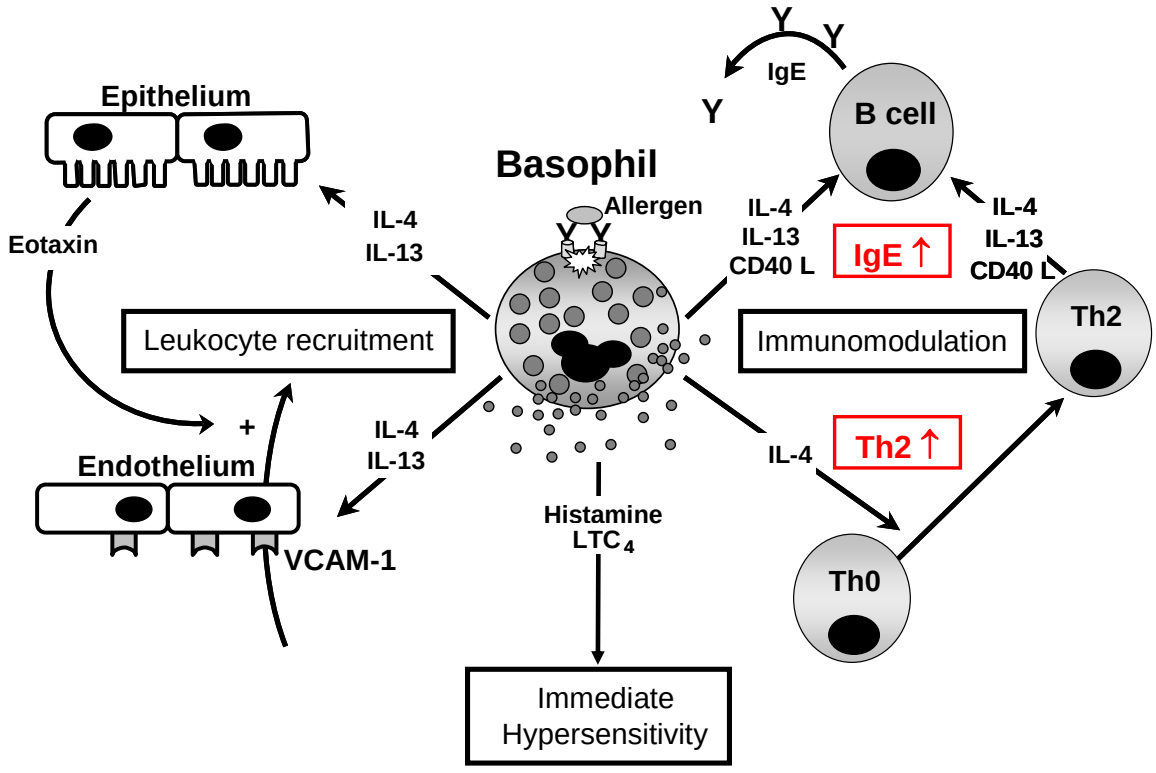
We have known for some time now that, in contrast to most human mast cell types, basophils are extremely capable of generating the Th2-cytokines IL-4 and IL-13 [reviewed in 3 and 11]. It is now also increasingly clear that basophils are the main IL-4-expressing cell type shortly after allergen exposure in peripheral blood and asthmatic airways [12-14], observations which are also mirrored in murine asthma models [15]. Based on this evidence, basophil-derived IL-4 may indeed play a crucial role in controlling Th2 development, at least by exacerbating the existing Th2 polarization and, therefore, a tendency for atopic disease. That basophils and Th2 lymphocytes are intricately linked is supported further by a study showing that specific allergen immunotherapy reduces both Th2 responses and the number of basophils, as well as their reactivity [16].

The release of these cytokines and other basophil mediators is not restricted to antigen-specific IgE crosslinking, but can also be caused in non-sensitized individuals by a growing list of parasitic antigens, lectins and viral superantigens, binding to non-specific IgE antibodies [reviewed in 3 and 11]. This, together with novel IgE-independent routes of activation, suggests a potential role of basophils in innate immunity too, especially in terms of supporting developing Th2-responses.

OUTLOOK

There is now compelling evidence to promote basophil research so that we can truly unravel its physiological/pathophysiological function, its uses in diagnostics and as a target for anti-allergic therapy. In terms of the latter, we know that basophils are one of the key cells affected by anti-IgE therapy and that rush desensitization regimes often lead to a loss of basophil activation, which has been ascribed to a loss of Syk expression [17]. However, basophils are also endowed with a range of inhibitory signals which may also contribute to their functional desensitization. One example is SHIP, an inhibitory phosphatase involved in IgE-mediated signalling [18]. Recent reports show that it is mobilized upon the activation of inhibitory receptors such as IRp60 (CD300a) leading to a dramatic reduction in allergic effector cell function [19]. These inhibitory receptors and their natural ligands may in future be exploited for anti-allergic therapies.

Figure:
Major roles of basophils in supporting allergic inflammation and underlying Th2-type immunity



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