

Review Article

The 21st century renaissance of the basophil? Current insights into its role in allergic responses and innate immunity

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Abstract: Basophils and mast cells express all the three subchains of the high-affinity immunoglobulin E (IgE) receptor FcεRI and contain preformed histamine in the cytoplasmic granules. However, it is increasingly clear that these cells play distinct roles in allergic inflammatory disease. Despite their presence throughout much of the animal kingdom, the physiological function of basophils remains obscure. As rodent mast cells are more numerous than basophils, and generate an assortment of inflammatory cytokines, basophils have often been regarded as minor players in allergic inflammation. In humans, however, basophils are the prime early producers of interleukin (IL)-4 and IL-13, T helper (Th)2-type cytokines crucial for initiating and maintaining allergic responses. Basophils also express CD40 ligand which, in combination with IL-4 and IL-13, facilitates IgE class switching in B cells. They are the main cellular source for early IL-4 production, which is vital for the development of Th2 responses. The localization of basophils in various tissues affected by allergic inflammation has now been clearly demonstrated by using specific staining techniques and the new research is shedding light on their selective recruitment to the tissues. Finally, recent studies have shown that basophil activation is not restricted to antigen-specific IgE crosslinking, but can be caused in non-sensitized individuals by a growing list of parasitic antigens, lectins and viral superantigens, binding to non-specific IgE antibodies. This, together with novel IgE-independent routes of activation, imparts important new insights into the potential role of basophils in both adaptive and innate immunity.

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Introduction

Despite the discovery by Ehrlich in 1879 (1), basophil granulocytes (basophils), are still one of the least studied and understood types of leucocytes. Basophils usually comprise less than 1% of nucleated blood cells in humans. Although their number and morphology vary throughout the animal kingdom, basophils are found in most vertebrates, such as mammals, birds, reptiles and amphibians, as well as fish (2). This conservation in a wide section of the animal kingdom suggests a non-redundant role in immunity.

Human basophils originate and develop in the bone marrow from haematopoietic pluripotent CD34+ stem cells and, like other granulocytes, are generally released into the circulation as mature cells [reviewed in Refs (3,4)]. The exact lineage, however, is not well understood given the observations pointing to the existence of progenitors for basophil/eosinophil, basophil/mast cell and basophil/eosinophil/megakaryocyte lineages (3), with some indications of early and distinct branching points between mast cells and basophils (5). Despite this, basophils can be generated in

vitro from cord blood cells under the influence of interleukin (IL)-3 (6), which also prevents apoptosis (7) and potentiates mediator release caused by allergens [reviewed in Ref. (4)]. Although human basophils require IL-3 during the early stages of maturation (3,6), mice deficient in IL-3 display remarkably normal numbers of basophils (8), which has greatly hindered attempts of producing a basophil-depleted model.

Factors that have negatively affected the acquisition of knowledge regarding the functions of basophils in the past were the unavailability of research tools such as basophil-specific antibodies, the difficulties in purifying large numbers of basophils, as well as the lack of specific surface markers (see Table 1). As new tools for basophil purification, detection in tissues and monitoring activation by fluorescence-activated cell sorting have been developed and marketed, there is now a new surge of interest in this cell type, documented by the increasing number of publications and laboratories addressing the immunobiology of basophils.

Thus basophils are now much more amenable to research, and as a result the perception of their role in the immune system has shifted from mere effector cells, involved in allergic reactions by virtue of their high-affinity immunoglobulin E (IgE) receptor (FcεRI) activation-dependent release of leucotrienes and histamine, to a cell which is potentially deeply implicated in modulating the immune responses to parasites and allergens. Much of this is accomplished by their ability to rapidly generate the two archetypal cytokines involved in T helper (Th)2 responses, namely IL-4 and IL-13. A summary of these actions is shown in Fig. 1.

However, it remains difficult to ascertain the role of basophils owing to the lack of animal models to test their ultimate importance (i.e. basophil 'knockouts'). Also, except for two anecdotal reports of complex immunological syndromes with a combined lack of eosinophils and basophils (9,10), there does not appear to be any genetic deficiency leading to the selective loss of basophils in humans. This review will address the

Table 1. Tools useful for basophil research. In the recent years, kits for immunomagnetic negative selection have been marketed. Several monoclonal antibodies are now available for detection of basophils in IHC, and diagnosis of IgE-dependent allergy in whole blood or purified basophils. There are controversies regarding the relative merits e.g. of CD203c vs. CD63

Tool	Reference	Remarks
<i>Basophil purification</i>		
Basophil purification kits (negative selection using magnetic cell sorting)	(79)	Currently available from at least two companies
<i>Targets and tools for basophil detection</i>		
Antibody designation	Identity of target	
WS-80274, Clone A8	CD13	(80) Rapidly upregulated upon activation
— ¹	CD63	(81) Useful as degranulation marker. Not present on unactivated basophils, but also found in other granulocytes and platelets
WS-80280, clone E63-880	CD107a	(80) Upregulated on activated basophils with a similar time-course to CD63
— ¹	CD123	(80) IL-3 receptor alpha chain, highly expressed on basophils (but not exclusively)
WS-80160, clone N6B6, WS-0162, clone 67D2	CD164	(80) Rapidly upregulated upon activation
— ¹	CD203c ectonucleotide pyrophosphatase/ phosphodiesterase 3 (ENPP3)	(82) Useful as a specific activation marker; low expression on resting basophils; only found on basophils and mast cells; rapidly upregulated on basophils upon activation
BB1	Basogranulin	(30) Recognizes basogranulin, a basophil-specific granular component. Suitable for IHC
Bsp-1	?	(83) Recognizes a 45 kDa surface protein found on basophils and the cell line KU-812. Not suitable for IHC
97A6	CD203c (ENPP3)	(82,84) Recognizes a surface antigen present on basophils and mast cells (lung, skin) and their CD34+ progenitors
2D7	granular protein	(31) Recognizes granular protein (76 150 and 72 260 Da in WB). Suitable for IHC
J175-7D4	proMBP-1	(85) Recognizes pro-form of major basic protein 1 not present in neutrophils, eosinophils, lymphocytes, monocytes and skin mast cells. Suitable for IHC

¹Available from several commercial sources.

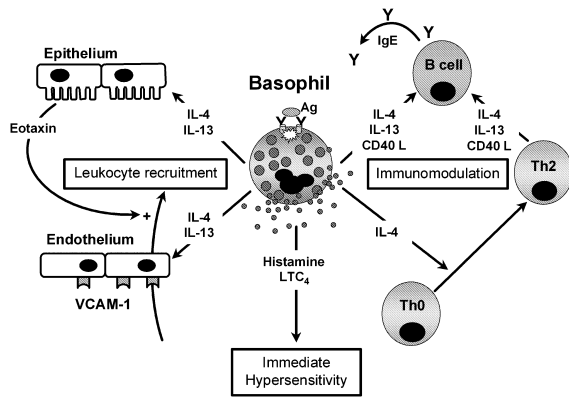


Figure 1. Pro-inflammatory and immunomodulatory activities of basophils following FcεRI-triggering by allergen (Ag) binding. Alongside the release of histamine and LTC₄, the rapid generation of IL-4 and IL-13 potentially facilitates further leucocyte recruitment in affected tissues and supports Th2 immune responses leading to enhanced IgE synthesis.

potential roles of basophils in allergic inflammation and innate immunity in the light of recent findings.

Basophils are recruited to the tissues from peripheral blood

During inflammation, factors are released from resident cells that cause basophils to migrate into tissues. This multistep process involves adhesion to the microvascular endothelium, trans-endothelial migration and finally locomotion through the tissues. Endothelial cells express several adhesion molecules during allergic inflammatory responses that cause basophil recruitment including P- and E-selectin, VCAM-1 and ICAM-1 (11,12). Migration of basophils through the endothelium is promoted by endogenous cytokines such as IL-1 β , IL-3 and several chemokines (13). Basophils respond strongly to the chemokine eotaxin (CCL11), via the CCR3 receptor, which is shared with eosinophils and Th2 cells (14). Eotaxin is produced by epithelial and smooth muscle cells and plays a major role in leucocyte recruitment, particularly in the asthmatic lung [reviewed in Ref. (15)]. Basophil migration can be further enhanced by PGD₂ and thromboxane B₂ which are released by resident mast cells during allergic reactions and bind to basophil CRTH2 receptors (16–18).

Following their passage through the endothelium, locomotion of basophils through the tissues is directed by factors that cause either chemokinesis, increasing their random movement, or chemotaxis, facilitating directional movement. Basophils express a large number of

chemokine receptors including CCR1, CCR2, CCR3, CXCR1, CXCR3 and CXCR4 [reviewed in Ref. (19)]. CCR3 and eotaxin seem to play a prominent role in basophil chemotaxis (13,14), and it is well-established that this chemokine is upregulated in allergic disease and a major cause for eosinophil invasion of the tissues (15). In addition, RANTES (CCL5), MCP-8 (CCL7) and MCP-4 (CCL13) likewise cause basophil migration via CCR3 binding and, as for eotaxin, potentiate allergen-induced mediator release from the cells. IL-8 (CXCL8) and MCP-1 (CCL2) are also known to induce a weak *in vitro* migration of basophils via CXCR1/CXCR2 and CCR2, respectively (20), but the former cytokine failed to induce transendothelial migration in a system that uses HUVEC cells (13).

Despite the above, basophils paradoxically display different kinetics of recruitment to sites of allergic inflammation compared with eosinophils, which also respond to CCR3 ligands, and because of this the involvement of basophil selective agents has been proposed (21,22). Alternatively, Heinemann et al. suggest that basophil-selective chemotaxis may be achieved by the collective, sequential action of chemokines resulting in a different pattern of chemokine receptor usage, rather than the use of distinct basophil-specific chemokines/receptors (23). Candidates for the latter may include insulin-like growth factors (IGF)-1 and IGF-2, non-CC-chemokines that have been recently described to selectively cause basophil chemokinesis, potentiate the chemotactic effects of eotaxin-1 (24) and to enhance IgE-dependent mediator release (25). These proteins represent the first chemotactic factors which act selectively on basophils, without having an effect on eosinophils, neutrophils or monocytes. Another mechanism underlying the selective basophil recruitment recently suggested is based on the finding that prolonged *in vitro* incubation of basophils with IL-3 (up to 48 h) upregulates c-kit, the receptor for stem cell factor (SCF, c-kit ligand) (26). SCF alone is not chemotactic for basophils as expression of c-kit is low compared with mast cells, but in the presence of IL-3, chemotaxis is selectively enhanced in basophils together with the upregulation of β 2 integrin CD11b/CD18 (26).

Elevated levels of these factors in inflamed tissue locations have a dual role in attracting basophils as well as enhancing their reactivity to allergen provocation. This is the case with IGF, but also occurs with many other chemokines (e.g. RANTES, Eotaxin) and cytokines

(e.g. IL-3). A recent *in vitro* study has shown that IL-3 promotes selective adhesion of basophils to HUVEC under physiological shear flow conditions in a process involving the $\beta 1$ integrins CD49d and CD49e, as well as P-selectin and P-selectin glycoprotein ligand 1 (27). Altogether, these data therefore provide a novel insight into the interplay between basophils and the tissue in the context of an inflammatory response in which IL-3 is prominent, resulting in the preferential recruitment of basophils.

A final tier of control of basophil recruitment and activation is given by various bacterial and viral peptides that are recognized by formyl peptide receptors as well as by the anaphylatoxins C3a and C5a [reviewed in Ref. (19)], demonstrating a role for basophils in IgE-independent immune responses. An overview of receptors expressed on basophils that are associated with their migration is shown in Fig. 2.

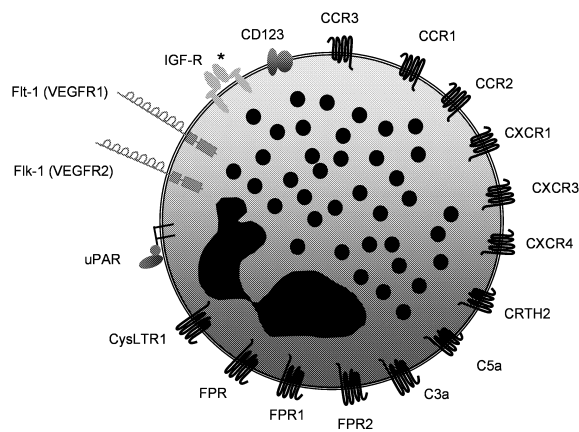


Figure 2. Schematic diagram of receptors involved in basophil chemotaxis and chemokinesis. Basophils express a wide variety of G-protein-coupled, seven transmembrane-type chemotactic receptors for chemokines (CCR1, CCR2, CCR3, CXCR1, CXCR3, CXCR4) or other chemotactic factors (CRTH2, C5a, C3a, FPR, FPR1, FPR2, CysLTR1). Basophils also express non-G-protein-coupled receptors such as Flt-1, Flk-1 and the urokinase receptor. The presence of the IGF-R on basophils as the receptor for IGF-1 and IGF-2 remains to be demonstrated (*). Overall, the chemotactic receptor pattern found on basophils is distinct from that found on eosinophils or mast cells. Whether selective recruitment of basophils to tissues during allergic inflammatory responses is achieved by the use of basophil-selective chemoattractants such as IGF-1 and IGF-2, or by the collective, sequential action of chemokines, resulting in a different pattern of chemokine receptor usage, is still open for debate. The SCF receptor c-kit, recently identified as upregulated on basophils *in vitro* by IL-3 treatment, indirectly increases the selective chemotactic response of basophils by enhancing eotaxin- and IL-8-induced expression of CD11b on basophils but not on neutrophils or eosinophils, and by increasing the basophil chemotactic response to eotaxin, MIP-1 α , MCP-2 and C5a (26). SCF, however, is not directly chemotactic for basophils (26).

Detection of basophils in skin and other organs affected by allergic reactions

Basophil recruitment to the skin has long been known to occur in contact dermatitis (28,29) in a reaction formerly known as Jones-Mote reaction, where basophils are the major infiltrating cell type. Using the recently developed basophil-specific monoclonal antibodies BB-1 (30) and 2D7 (31), basophils have also been demonstrated in bronchial biopsies from patients with asthma (21,32–34), including high numbers associated with fatal asthma (35,36). Similarly, basophils have been detected in nasal lavage fluids after allergen provocation from patients with allergic rhinitis (37) and in skin biopsies from patients with atopic dermatitis (21,38). Importantly, there is evidence showing that basophils are indeed activated at these sites of allergic inflammation as seen by the release of histamine during late-phase reactions in asthma without accompanying mast cell-specific mediators such as PGD₂ or tryptase (39). Similar observations have also been reported regarding antigen-induced mediator secretion in the skin (40). Therefore, despite their relatively low numbers in peripheral blood, basophils are not only recruited to the tissues, but their mediators appear to be released in sufficient quantities to contribute to allergic symptoms. In this context, it may be argued that tight control of basophil numbers in peripheral blood is necessary in view of the potentially lethal consequences of uncontrolled histamine release as seen in anaphylactic shock. The currently strongest evidence for a pivotal role of basophils in the establishment of chronic allergic inflammation (although this is still within the boundaries set by available animal models of allergy) comes from an allergy model using mice transgenic for 2,4,6-trinitrophenol (TNP)-specific IgE (41). In this model, intravenous injection of TNP leads to anaphylaxis, and subcutaneous injection without prior sensitization leads to an allergic inflammatory response with three distinct phases, comprising of an early (1 h after challenge), late (6–10 h after challenge) and very late response (48 h after challenge, peaking at 4 days). The authors found, combining the use of gene knockout mice (RAG-2 $-/-$ defective in B and T cells, RAG-2 $-/-$ plus γc double knockouts, with additional deficiency in NK and NKT cells, CD23 $-/-$, WBB6F1-W/W^v mast cell deficient mice) with cell reconstitution experiments, that mast cells, T cells, NK and NKT cells were dispensable for the late-phase

allergic reaction, whereas basophils, although present in small numbers (2% at day 4), were indispensable. Basophils were identified by their surface phenotype (c-kit⁺, NK1.1⁺, CD3⁺, B220⁺, Gr-1⁺, CD11c⁺, CD11b^{dim}, 2B4⁺ and Thy-1.2⁺) and electron microscopic features.

Basophils rapidly synthesize IL-4 and IL-13 of which they are a prominent source

In contrast to their mast cell counterparts, which release inflammatory cytokines such as tumor necrosis factor α and IL-8, cytokine synthesis from human basophils is primarily restricted to the production of IL-4 and IL-13 (42–47), key regulators of Th2-(allergic)-type immune responses. IL-4 is released from basophils rapidly, with maximum levels being reached within 4 h of Fc ϵ RI triggering. Basophils from some individuals also contain preformed IL-4, which is secreted within minutes from the cells during degranulation (45). In contrast, IL-13 appears to be released more slowly but in a sustained fashion and is not stored preformed in basophil granules (45). Despite this, there is some evidence to suggest that basophils from allergic donors are capable of spontaneous IL-13 production owing to priming factors, arising from local allergic inflammatory sites, having a distal effect on circulating basophils (48).

IL-4 and IL-13 are the key cytokines responsible in conditioning the immune response to a Th2 type as well as orchestrating allergic late-phase reactions (49). Both factors increase VCAM-1 expression in microvascular endothelial cells and eotaxin synthesis by airway epithelial cells, which supports the influx of leucocytes into affected tissues (50–52). Both factors also synergistically cause B cells to proliferate and change to IgE as well as IgG4 production [reviewed in Ref. (53)], a process which is further facilitated by the ability of basophils to express CD40 ligand upon IgE-dependent stimulation (54). Basophils are indeed capable of orchestrating IgE synthesis, as shown by Yanagihara et al., who demonstrated that allergen-stimulated cultured human basophils, but not mast cells, cause B-cell IgE production as a result of the above factors (55). These effects were inhibited by addition of neutralizing antibodies against IL-4, IL-13 and CD40L and are in line with the earlier report that used mast cell and basophil cell lines (54).

A special feature of IL-4 (not shared by IL-13) is in driving CD4⁺ T cells to a Th2

type, which then generate IL-4, IL-13 and other 'Th2-type' cytokines themselves [reviewed in Ref. (53)]. IL-4 is necessary to induce Th2 responses as clearly demonstrated in mice lacking either IL-4R α or Stat6 (which mediates IL-4-derived signalling); both knockouts display an impaired Th2 immunity (56,57). It is also increasingly clear that human basophils are the main IL-4-expressing cell type shortly after allergen exposure in peripheral blood and asthmatic airways (34,58), an observation also mirrored in a murine asthma model (59). A recently described real-time qPCR-based assay in whole blood also identifies basophils as the most prominent source of IL-4 and IL-13 after stimulation with cat allergen *Fel d1* (60). Based on the above 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 observations showing that specific allergen immunotherapy reduces both Th2 responses and decreases the number and reactivity of basophils (61). A role for basophils in biasing the early immune response to a pathogen or allergen to the Th2 phenotype however critically hinges on the activation mechanisms, which do not require the presence of surface-bound antigen-specific IgE. Such mechanisms have been described and reviewed in the next section.

Basophils as key regulators of innate immunity?

Numerous stimuli can cause basophil cytokine release without the need for sensitization with antigen-specific IgE. For example, various lectins have been shown to induce activation of basophils (62), probably via cross-linking of specific carbohydrate side chains on IgE or alternatively direct cross-linking of Fc ϵ RI. Thus basophils can be involved in generating Th2 responses from the onset of initial contact with pathogens. These may also cause basophil migration as seen by *Helicobacter pylori* antigens – which activate N-formyl-peptide receptor (FPR)-like 1 and -2 (63) [as do urokinase (64)]- and HIV-1 envelope gp41 peptides (65). Furthermore, HIV-1 gp120, which serves as a superantigen by interacting with VH3 domains of IgE, and viral Tat have been reported to stimulate IL-4 and IL-13 release from basophils (66,67). It has been proposed that increased serum IgE levels and a Th2 predominance

indicate HIV disease progression (68), which potentially could be explained by basophil involvement.

In addition to the above, basophils have been shown to release IL-4 and IL-13 to bacterial peptidoglycans via TLR2 receptor stimulation, which can also enhance basophil mediator release caused by IgE-dependent triggering (69). Altogether, these observations may be taken to suggest that basophils may contribute to exacerbation of chronic allergic diseases caused by viral and bacterial infections (19). Another tier of IgE-independent basophil activation is represented by the recently identified leucocyte immunoglobulin-like receptors LIR7 and LIR3, which are shared with neutrophils and eosinophils (70). Crosslinking of LIR7 leads to histamine release and de novo synthesis of IL-4 and cysteinyl-leucotrienes, whereas engagement of LIR3, which carries several intracellular inhibitory motifs, results in basophil inhibition (70).

While there is an increasing evidence suggesting a role for basophils in bacterial and viral infections, it is their involvement in parasitic infections which gives the clearest indication that these cells have a major defence function [reviewed in Ref. (71)]. Nematode infections give rise to a striking elevation of serum IgE and a prominent Th2 cytokine response which, in animal models, accompanies basophilia as well as accumulation and activation of basophils in infected tissues, especially during the expulsion period (72). In an elegant experiment in which the *egfp* gene replaced the first exon and part of the first intron of the IL-4 gene in so-called G4 mice, Min et al. tracked the production of IL-4 in mice infected with *N. brasiliensis* to basophils, and obtained a similar result in infected Stat6^{-/-} G4 mice. Interestingly, IL-4 producing basophils were found in the lung and unexpectedly in the liver, but not in the lymph nodes. This study also showed that upon restimulation with parasitic antigens, basophils from the liver of the infected animals were the main IL-4-producing cell population (73). Importantly, in humans, similar observations showing that basophils are the main IL-4 secreting cell type during filarial infections have been demonstrated (74). Although systemic basophilia appears to be less clear-cut in humans, basophils are triggered by a large number of antigens in *Schistosoma*-, *Toxocara*-, *Wuchereria*-, *Strongyloides*-, *Onchocerca*- and *Ascaris*-infected patients (75). Crucial to the possible innate role of basophils are the reports showing that basophils from non-immunized donors

strongly react to *Schistosoma mansoni* egg antigen and *Echinococcus multicularis* metacestode extract (76–78). The mode of action for basophil triggering is IgE-dependent but does not require antigen-specific IgE, showing the existence of a further class of novel FcεRI activators along with viral immunoglobulin superantigens and lectins.

Conclusions and perspectives

A mere decade ago, basophils were considered by many as rare effector cells of allergic disease, taking a back-seat to their mast cell counterparts. Since then, much evidence has accumulated to suggest that this view needs to be revised. The discovery that basophils readily release IL-4 and IL-13 to IgE-mediated provocation, unlike most human mast cells, first not only pointed to their potential role in enhancing the recruitment of inflammatory cells to affected organs but also in sustaining – and maybe even initiating – Th2 immune responses. The detection of basophils in various tissues using novel specific antibodies clearly confirmed their presence in organs affected by allergic disease and other disorders. Receptors for a large number of chemotactic agents have been reported too, highlighting a multitude of mechanisms of how basophils migrate to these tissue sites and become involved not only in allergic reactions but also reacting against bacterial, viral and helminthic parasitic assault. The fact that so many antigens have been found to bypass the necessity of IgE-specificity, eliciting a response from basophils immediately after first contact, shows a clear role for these cells in innate immunity. All these advances have truly awakened interest in the basophil, although many challenges remain such as pinpointing the specific growth factors in order to develop basophil-depleted animal models. Only with yet-to-be-delivered animal models and the new available tools for detection and purification can we definitively test the ultimate importance of this cell and confirm its potential as a major regulator of immune responses.

However, there are many other issues still open for exploration such as the potential role of basophils in wound healing and tissue remodelling, and their role in cancer. Little is also known regarding the regulation of apoptosis in basophils, compared with a plethora of studies using neutrophils and eosinophils. Circumstantial evidence points to a relatively long lifespan of basophils compared with these other

granulocytes, but we have not yet even begun to address how long basophils can survive in the tissues and whether they are recycled back into the peripheral blood. Indeed, the phenotypic plasticity of basophils upon migration into various organs remains largely unexplored. It is now well established that basophils in peripheral blood express relatively few cytokines (mainly IL-4 and IL-13). However, the interactions and changes undergone by these cells after recruitment to the tissues, e.g. in the course of an allergic reaction, are not sufficiently known. It is an open question whether basophils that have migrated into the tissues still display a limited cytokine repertoire or whether, by interacting with locally produced cytokines, growth factors, as well as contact-dependent signals with local or other recruited cells, display phenotypic changes.

The possibility that basophils display phenotypic heterogeneity, at least in terms of their cytokine spectrum, needs to be explored with modern immunogenomic approaches. This would require screening not only the effect of cytokines for which basophils are known to express receptors (e.g. IL-3, IL-4 and IL-5) on gene expression, but also the effects of growth factors such as NGF, known to modulate basophil functionality, in combination with signal transduction pathways induced, e.g. by integrin engagement on basophils. These interactions could be studied under different conditions representative of various tissues (e.g. skin, lung) and/or different inflammatory conditions (e.g. allergic or antimicrobial responses) to investigate the synergistic signals underlying possible phenotypic changes of basophils in the tissues. As these signals are likely to be complex, involving soluble mediators and contact-dependent signals, it will be necessary to increase the complexity stepwise, first by the use of single cytokines, growth or other factors such as chemokines and defensins, then using combinations of these factors known to occur during inflammation, and finally by studying the cross-talk between basophils and other cells such as eosinophils, neutrophils and mast cells. In other words, a full picture likely to increase our understanding of the functions of basophils in tissues will likely involve a systems biology approach, integrating the information about gene regulatory networks, cellular cross-talk and cell signalling, a task which is unlikely to be achieved by any single research group, thus requiring a concerted action by a dedicated research network.

Finally, the perception of the basophil is shifting from a largely redundant cell type (with known effector functions in some pathological settings such as asthma), to a specialized, non-redundant role as the central orchestrators of the immune response. From this perspective, basophils have more in common with, e.g. NKT cells, T helper or dendritic cells than with effector cells such as neutrophils and eosinophils. The tight regulation of basophil cell number at a low level in humans reflects the necessity to effectively limit the potential damage and threat posed by basophil-derived mediators and cytokines.

We firmly believe that a 21st century immunogenomic approach, combined with the availability of reliable tools for detection and purification, should favourably impact on our knowledge of this cell type in the years to come.

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