REVIEW

Recent advances in understanding basophil functions *in vivo*

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Abstract

Basophils are mainly known as pro-inflammatory effector cells associated with allergy and helminth infections. Although they were identified over 130 years ago, their *in vivo* functions are still poorly understood. New insights into basophil development and function have been gained by the development of various transgenic mouse lines and staining techniques to detect and purify these cells from different organs. Several studies over the past few years have identified unexpected functions for basophils, including immunomodulatory properties and interactions with other immune cells. Here, I summarize and discuss the main findings.

Keywords

basophil, transcription factors, antigen-presentation, inflammatory response, allergy

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Introduction

Basophils belong to the group of granulocytes which constitute rather short-lived effector cells of the innate immune system. They usually represent less than 1% of all leukocytes in the peripheral blood, but they have potent effector functions. In contrast to many other cell types of the immune system, it is poorly understood how basophils develop and execute their effector functions. Not too long ago, it was even questioned whether mice contain a bona fide basophil population mainly because mouse basophils contain fewer granules as compared to human basophils¹. After establishing staining protocols and genetically engineered mouse strains basophils could be identified, isolated, and functionally characterized in various settings of immune responses. Basophils and mast cells share the expression of the high-affinity receptor for IgE (FcεRI), histamine, and a few other effector molecules, yet basophils do not represent a subset or precursor population of mast cells; rather, they constitute a distinct cell lineage with a very different gene expression profile². Basophils can be efficiently depleted *in vivo* with the monoclonal antibody MAR-1 directed against FcεRI or Ba103 which binds to another activating receptor named CD200R3. However, since the recognized antigens of both antibodies are not exclusively expressed on basophils, this approach can cause bystander effects that interfere with clear interpretations of such depletion experiments. Transgenic mice expressing the Cre recombinase, GFP, or human diphtheria-toxin receptor under control of regulatory elements of the *Mcpt8* gene have been developed by several groups over the past few years (reviewed in 3). *Mcpt8* encodes the mouse mast cell protease 8 (mMCP-8), a serine protease which is highly expressed in basophils but not mast cells⁴. The genetically modified mouse strains facilitate the functional characterization of basophils *in vivo*. However, it is important to keep in mind that mouse and human basophils differ in many respects, and it remains to be determined to what extent findings in mouse models can be translated to the human immune system. In the following paragraphs, I summarize some major new findings regarding the *in vivo* functions of basophils published during the past few years.

Basophil development and critical transcription factors

Interleukin (IL)-3 is the most potent cytokine to promote basophil proliferation, but high concentrations of thymic stromal lymphopoietin (TSLP) can have similar effects⁵. IL-3 and TSLP-elicited basophils differ in terms of their gene expression profiles and may resemble different states of activation rather than representing stable subpopulations of basophils. The receptors for IL-3 and TSLP are linked to the STAT5 signaling pathway, and it was recently shown that STAT5 binds to regulatory elements of Gata2, which is another critical transcription factor for basophil development⁶. In addition, it was found that IRF8 can also promote Gata2 expression in precursor cells and thereby drive basophil differentiation⁷. Other transcription factors including Gata1, P1-Runx1, c/EBPα, and MITF also play an important role in basophil development and maintenance (reviewed in 8).

Relevance of antigen-presentation by basophils

Basophils were found to display low levels of major histocompatibility complex class II (MHC-II) on the cell surface, and antibody-mediated depletion of basophils resulted in poor Th2 polarization^{9–11}. However, genetically basophil-depleted *Mcpt8Cre* mice showed normal expansion of Th2 cells during primary infection with the helminths *Nippostrongylus brasiliensis*¹², *Heligmosomoides polygyrus*¹³, and *Schistosoma mansoni*¹⁴. Ovalbumin (OVA)-alum immunized and challenged *Mcpt8Cre* mice also showed an unimpaired Th2 response and eosinophilia in the lung¹². Furthermore, papain+OVA-induced T-cell proliferation and Th2 polarization in draining lymph nodes was normal in *Mcpt8Cre* mice while genetically dendritic cell (DC)-depleted mice showed a severely impaired response¹². With another genetically basophil-depleted mouse model (*Basoph8* x *Rosa-DTa* mice), it was shown that footpad immunization with *S. mansoni* eggs results in normal Th2 priming in the absence of basophils¹⁵. In contrast, diphtheria toxin (DT)-mediated depletion of DCs causes impaired Th2 priming upon *S. mansoni* egg immunization and diminished Th2 cell accumulation in the liver of *S. mansoni*-infected mice¹⁶. It was further shown that DCs are required and sufficient for the Th2 response to house dust mite antigens¹⁷. This study also demonstrated that a subset of monocyte-derived DCs express FcεRI. These cells will therefore also be depleted with the anti-FcεRI antibody MAR-1 frequently used to deplete basophils *in vivo*.

Basophils lack the machinery for antigen uptake and processing, although they can contain MHC-II molecules on the cell surface which may be loaded with exogenous peptides and are then capable of stimulating T cells^{9,18,19}. Two other studies provide evidence that basophils and DCs cooperate to promote Th2 polarization. It was shown that subcutaneous papain injection induced reactive oxygen species that indirectly activated DCs to promote basophil recruitment into lymph nodes and subsequent Th2 polarization²⁰. Another study showed that TSLP-elicited dermal DCs express OX40L to induce IL-3 secretion from T cells leading to the recruitment of basophils which then promote Th2 polarization²¹. The Th2-promoting activity of basophils in both studies might be explained by basophil-derived IL-4 rather than direct antigen recognition on basophils.

Recent evidence shows that basophils can in fact acquire MHC-II from DCs by the uptake of plasma membrane patches, a process termed trogocytosis¹⁹. Clearly, further studies are needed to determine whether MHC-II trogocytosis by basophils has functional consequences for T-cell activation or memory formation or other processes that are regulated by antigen recognition.

Basophil functions in type 2 immune responses

Lung inflammation

In a mouse model of allergic lung inflammation induced by the administration of the cysteine protease papain, it was found that basophil-derived IL-4 promotes the secretion of IL-5, IL-9, and

IL-13 from type 2 innate lymphoid cells (ILC2s) in the lung and thereby induces lung eosinophilia²². Another type 2 immunity-inducing property of basophils was observed in a commonly used model for allergic lung inflammation which is based on alum adjuvant-mediated priming of the Th2 response. It was recently reported that alum enhanced the ability of basophils to induce Th2 polarization by the release of TSLP and IL-25 but independently of IL-4 secretion²³. However, we and others observed no impairment in lung Th2 responses with *N. brasiliensis* infection or OVA/alum immunization in genetically basophil-depleted mice^{12,15}.

Local inflammatory responses in the skin

Similar to reports from papain-induced lung inflammation, it was reported that basophil-derived IL-4 induces ILC2 accumulation and proliferation in the skin after topical application of MC903, a vitamin D analog²⁴. MC903 elicits high levels of TSLP expression in the skin and causes pathology reminiscent of skin lesions of atopic dermatitis patients. Anti-TSLP antibodies can block the accumulation of basophils in the skin²⁵ but also inhibit peripheral TSLP-induced basophilia during *Trichinella spiralis* infection²⁶. Experiments with mixed bone marrow chimeras revealed that basophil accumulation in the MC903-treated ear does not require direct recognition of TSLP by basophils⁵. Basophils were further found to cooperate with fibroblasts to promote the recruitment of eosinophils in a murine model of irritant contact dermatitis²⁷. Related to this, it was reported that basophils regulate the entry of eosinophils into the skin by the induction of VCAM-1 expression on endothelial cells²⁸.

Local activation of basophils in the ear skin via FcεRI causes an ear swelling response termed “chronic allergic inflammation” or IgE-CAI, which peaks at day 2–3 and resolves by day 6. This IgE-CAI response is strictly dependent on basophils²⁹. Using this model, Egawa *et al.* reported that the release of IL-4 from basophils promotes the differentiation of alternatively activated or “M2” macrophages which have anti-inflammatory and tissue repair properties, arguing for a role of basophils in the resolution of inflammation³⁰. Others observed that α(1,3) fucosyltransferases IV and VII are essential for the initial recruitment of basophils in the IgE-CAI model³¹. Basophils express various proteases including mMCP-8 and mMCP-11. By analyzing mMCP-11-deficient mice, Iki *et al.* showed that mMCP-11 promotes the ear swelling response in IgE-CAI³². However, basophils can also have anti-inflammatory properties, as shown in a model of skin contact hypersensitivity where UVB irradiation reduced the hapten-induced ear swelling response. In this model, it could be demonstrated that basophil-restricted expression of amphiregulin, a cytokine with tissue repair activities, was required for the suppressive effect of UVB irradiation³³. Increased numbers of basophils were also found in skin biopsies from patients with various skin disorders, indicating that these cells also regulate inflammatory responses in human skin³⁴.

Protection against parasites in the skin and intestine

The presence of basophils in the skin indicates that they could be involved in protective immunity against helminths that enter

their hosts via the skin or against ectoparasites like ticks. Using basophil-depleted mice, Wada *et al.* showed that basophils impair tick feeding upon secondary engorgement³⁵. Furthermore, basophils promote the trapping of larvae in the skin upon secondary *N. brasiliensis* infection³⁶. In addition, basophils accumulate in the small intestine and induce rapid expansion of Th2 cells and protection against *N. brasiliensis* or *H. polygyrus* during secondary infection by IgE-induced secretion of IL-4/IL-13¹³. Basophils further promote a Th2 response in a TSLP-dependent manner during *T. spiralis* and *Trichuris muris* infections^{25,26}. In contrast, basophils play only a minor role in the control of *Strongyloides ratti* infection³⁷. Anti-CD200R3-mediated depletion of basophils resulted in smaller granulomas around *S. mansoni* eggs in the liver³⁸, while this effect was not observed in genetically basophil-depleted *Mcpt8Cre* mice¹⁴. This difference might be explained by secondary effects caused by the injected antibody, including mast cell activation and Fc receptor-mediated modulation of phagocytes.

Basophils in food allergy and eosinophilic esophagitis

An interesting role for basophils during skin sensitization followed by oral challenge to elicit a food allergic response has been described. Mice developed a severe food allergic response when chicken OVA was first applied in combination with MC903 to the ear skin and later given intragastrically by oral gavage³⁹. The authors further showed that basophils and TSLP are required for this effect. In a subsequent study, it was further revealed that basophil-derived IL-4 promoted the IgE-mediated food allergic response and eosinophils were dispensable for this effect⁴⁰. A role for basophils, TSLP, and IL-33 to elicit an anaphylactic response to oral antigens was also shown in another model where OVA was applied to skin pretreated with 4% SDS instead of MC903⁴¹.

The impaired skin barrier function in atopic dermatitis may facilitate allergic sensitization that can lead to eosinophilic esophagitis (EoE). Pathology reminiscent of EoE can be elicited by intranasal OVA challenge of MC903+OVA skin-sensitized mice⁴². Using this model, Noti *et al.* showed that IgE is dispensable for EoE while basophils and TSLP are required⁴². Furthermore, IL-33 was identified as a critical cytokine to promote the accumulation of basophils in the esophagus and the recruitment of eosinophils⁴³.

Basophils in other inflammatory settings, allograft transplantation, and tumor control

Intravenous immunoglobulin (IVIG) therapy, the intravenous administration of high doses of purified IgG, is used as a therapeutic approach to treat antibody-mediated inflammation in various clinical settings. The anti-inflammatory mechanism of IVIG therapy is incompletely understood. Using a mouse model of serum-induced arthritis, researchers showed that IVIG elicits IL-33 secretion, which in turn promotes IL-4 release from basophils. Basophil-derived IL-4 then upregulates the inhibitory Fc receptor FcγRIIB on macrophages and thereby ameliorates pathology⁴⁴. However, others found no role for basophils in IVIG-induced suppression of serum-induced arthritis⁴⁵. The apparent discrepancies between these observations remain to be resolved.

Systemic lupus erythematosus (SLE) is another autoantibody-mediated disease. SLE patients were found to have higher serum levels of IgE and activated basophils⁴⁶. Another study showed that basophils from SLE patients promoted Th17 differentiation *in vitro*, probably by the secretion of IL-6⁴⁷. Depletion of basophils from SLE-prone MRL-lpr/lpr mice resulted in ameliorated pathology and an extended lifespan, while adoptive transfer of basophils had the opposite effect⁴⁷. Further evidence for an important role of basophil-derived IL-6 in Th17 differentiation is based on a cholera toxin-induced lung inflammation model. Here it was shown that Th17-associated lung inflammation was reduced in the absence of basophils and could be restored by the transfer of wild-type but not IL-6-deficient basophils⁴⁸.

Basophils were also found to regulate the rejection of allogeneic transplants. In a mouse model of pancreatic islet allotransplantation, it was reported that the depletion of basophils results in improved graft survival⁴⁹. Furthermore, basophil-derived IL-4 was found to act on myofibroblasts and promote fibrosis in a cardiac allotransplantation model⁵⁰. *In vitro* studies with human basophils further revealed their potential to inhibit TLR4-induced monocyte activation⁵¹ and to induce the differentiation of alternatively activated macrophages⁵².

Recently, basophils were further found to modulate immune responses against solid tumors. One study described the recruitment of basophils into tumor-draining lymph nodes in correlation with a Th2-biased immune response and poor survival of pancreatic cancer patients⁵³. In contrast, basophils were also shown to promote tumor rejection by recruiting CD8⁺ T cells.

Future perspective

Our current understanding of basophil development and effector functions has improved considerably over the past few years. We realize now that basophils not only function as pro-inflammatory cells during allergic responses and helminth infections but also modulate the immune system in many ways. Most of our knowledge is still based on mouse models. It will be important to translate these findings to the human immune system in order to develop new therapeutic approaches for the treatment of inflammatory diseases where basophils may play an important role.

Abbreviations

DC, dendritic cell; EoE, eosinophilic esophagitis; FcεRI, high-affinity IgE receptor; IL, interleukin; ILC2, type 2 innate lymphoid cells; IVIG, intravenous immunoglobulin; MHC-II, major histocompatibility complex class II; mMCP-8, mouse mast cell protease 8; OVA, ovalbumin; SLE, systemic lupus erythematosus; TSLP, thymic stromal lymphopoietin.

Competing interests

The author declares that he has no competing interests.

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