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Basophils in allergic immune responses

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Basophils are rare effector cells of the innate immune system. They are generally associated with type 2 immune responses that develop during helminth infections and allergic reactions. The role of basophils for initiation and execution of allergic immune responses is not well understood. Over the past few years new tools have been generated to study the function of basophils in mouse models. Depending on the experimental systems used conflicting results were obtained with regard to the role of basophils for initiation and execution of immune responses against allergens and helminths. This review highlights the current knowledge about basophil *in vivo* functions with a focus on the role of basophils for allergic responses like asthma, allergic skin diseases and anaphylaxis.

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Introduction

Basophils are the least abundant type of granulocytes after neutrophils and eosinophils. They mature in the bone marrow and have a lifespan of about 60 h under steady-state conditions in mice [1]. Basophils are morphologically and functionally very similar to tissue-resident mast cells. Both cell types contain granules that can be stained with basophilic aniline dyes. They both express the $\alpha\beta\gamma 2$ form of the high-affinity receptor for IgE (Fc ϵ RI). Interestingly, Fc ϵ RI can also be expressed as signaling competent $\alpha\gamma 2$ form by subsets of dendritic cells [2,3[•],4], monocytes [5] and eosinophils [6]. Effector molecules produced by mast cells and basophils include vasodilators like histamine and platelet-activating factor (PAF), leukotriene C4 and the Th2-associated cytokines IL-4 and IL-13 [7]. However, basophils represent a distinct cell lineage and are not a population of immature circulating mast cells.

The early type 2 immune response – are basophils crucial for Th2 polarization?

In analogy to Th1 polarization where early secretion of IL-12 by DCs initiates the Th1 differentiation program it was proposed that an innate source of IL-4 is required for Th2 polarization. Several reports pointed toward an important role for basophils as inducers of Th2 polarization. Mice deficient for interferon response factor 2 (IRF2) or the tyrosine kinase Lyn show increased levels of circulating basophils and a spontaneously Th2-biased phenotype [8,9]. Furthermore, basophils are recruited to draining lymph nodes of helminth-infected or allergen-treated mice a few hours before the first Th2-polarized CD4 T cells can be observed [3[•],10[•],11[•],12,13[•]]. DC-derived reactive oxygen species were shown to be required for basophil recruitment to lymph nodes in response to injection of the proallergic cysteine protease papain [14]. Basophils were further reported to express low levels of MHCII and serve as antigen-presenting cells when exposed to IgE-immune complexes or ovalbumin (OVA) [13[•],15[•],16[•]]. Direct contacts between basophils and T cells could be observed in lymph nodes by immunofluorescence microscopy [15[•]]. The finding that Th2-polarization induced by footpad injection of papain was normal in DC-depleted mice but significantly reduced when basophils were depleted by anti-Fc ϵ RI antibody (MAR-1) led to the conclusion that DCs are not required and basophils are indeed essential for Th2 polarization [15[•]].

However, the proposed role of basophils as crucial Th2-polarizing antigen-presenting cells was recently challenged by other studies. Time-lapse microscopy revealed that CD4 T cells and basophils form stable contacts in the lung but not in lymph nodes [17[•]]. We observed a normal Th2 response induced by papain injection, OVA/alum immunization or *Nippostrongylus brasiliensis* infection in genetically basophil-deficient Mcpt8Cre mice (Box 1) [10[•]]. Basophil depletion by MAR-1 treatment before *S. mansoni* egg (SEA) immunization did not affect Th2 polarization in draining lymph nodes while fewer Th2 cells were observed in DC-depleted mice [18[•]]. A normal Th2 response to SEA was also reported with another genetically basophil-deficient mouse strain (Basoph8 $\times$ Rosa-DT α ; see Box 1). In a murine model of allergic airway inflammation it could be shown that inhalation of house dust mite extracts resulted in antigen presentation by Fc ϵ RI⁺ DCs but not by basophils that apparently lack important components of the antigen-presentation machinery [3[•]]. In the same study MAR-1 injection was found to not only deplete basophils but also Fc ϵ RI⁺ DCs. In addition, injection of MAR-1 can cause side effects including mast cell

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Box 1 Newly developed mouse strains to study the role of basophils *in vivo*

All three currently developed basophil-targeted mouse strains are based on expression of the granzyme B-related serine protease mouse mast cell protease 8 (mMCP-8) that is encoded by the *Mcpt8* gene on chromosome 14 at 28.14 cM. This protease is expressed mainly by basophils but not by mature mast cell or other major cell populations [1,50–51]. Therefore, this gene was independently chosen by us and two other groups to express the Cre-recombinase or the human diphtheria toxin receptor specifically in basophils.

Mcpt8DTR mice

They were developed by homologous recombination of an IRES-huDTR-EGFP cassette behind the stop-codon of the endogenous *Mcpt8* gene. In these mice, basophils can be detected via eGFP expression analysis in histological sections or flow cytometry. Basophils can also be transiently depleted by injection of diphtheria toxin that binds to the human diphtheria toxin receptor (huDTR) on basophils.

Mcpt8Cre mice

These are BAC-transgenic mice that express the Cre recombinase under control of regulatory elements of the *Mcpt8* gene [10]. The Cre cassette was placed behind the start-codon of *Mcpt8*. The BACtransgenic mouse line carries 5 copies of the construct per haploid genome. Basophils but no other major cell types are constitutively reduced by more than 90% owing to high expression level of Cre in developing basophils that results in Cre-toxicity, a previously described phenomenon based on recognition of cryptic loxP sites in the genome [52].

Basoph8 mice

These mice were generated by homologous recombination of a YFP-IRES-Cre cassette behind the start-codon of the endogenous *Mcpt8* gene so that YFP and Cre are specifically expressed in basophils [17]. Unlike Mcpt8Cre mice, basophil numbers are normal in this strain. Basoph8 mice might be useful to specifically delete conditional alleles of genes of interest in basophils. Furthermore, YFP expression in basophils allows the identification of basophils in histology, intravital microscopy and flow cytometry.

activation, anaphylaxis and neutrophilia that may partly explain the impaired Th2 response in MAR-1 treated mice.

Basophil mobilization and activation by cytokines

Basophils respond to different cytokines that modulate their survival, effector functions and tissue recruitment. IL-3 from T cells is important for basophilia during helminth infection, although IL-3 is not essential for basophil development under steady-state conditions [19,20]. Basophils also express IL-3 and may thereby regulate their survival in an autocrine manner [21]. In addition, IL-3 exerts an important co-stimulatory function for mediator release. IL-3, IL-18 or IL-33 are potent inducers of Th2 cytokines in basophils [22,23]. Basophils express the thymic stroma derived lymphopoietin (TSLP) receptor and TSLP has been reported to promote basophilia [13^{••}]. Basophil survival, migration and activation are further regulated by the adipokine Leptin that directly binds to the Leptin receptor on basophils [24,25].

Tissue recruitment of basophils can also be induced by Insulin-like growth factors 1 and 2 that were found to act as chemoattractants for human basophils in nasal polyps [26].

Basophils in allergic skin reactions

The recruitment of basophils during allergic skin reactions has been observed in early studies with guinea pigs that developed a ‘cutaneous basophil hypersensitivity’ reaction upon injection of protein antigen with incomplete Freund’s adjuvant [27]. Basophils were also identified in human skin of allergic contact dermatitis patients [28] and in allergen-induced patch test sites of atopic dermatitis patients [29]. Basophils are found in skin biopsies and blister fluid of cutaneous late-phase reactions in response to ragweed extracts [30]. The detection of basophils in human tissue samples is difficult since they are usually present in low numbers and activated basophils are often degranulated. However, mAbs that recognize basogranulin (BB1), pro-major basic protein 1 (J175-7D4) or a basophil-associated cytoplasmic protein (2D7) can be used to stain basophils in human tissue sections [31–33]. In murine tissues basophils can be identified with the mAbs TUG8 or TUG11 that recognize mouse mast cell protease 8 (mMCP-8) or mMCP-11, respectively [34]. Both proteases are expressed in basophils but not in mast cells. Histological analysis of basophil infiltration in 136 biopsies of 24 inflammatory skin diseases revealed that basophils were present in skin lesions of patients suffering from atopic dermatitis, prurigo, urticaria, bullus pemphigoid, drug eruptions, eosinophilic pustular folliculitis, insect bites, scabies, Henoch-Schönlein purpura and dermatomyositis while basophils were not found in biopsies of psoriasis vulgaris, mastocytosis, tumoral lesions, systemic sclerosis and systemic lupus erythematosus [35]. Future work should clarify whether and how basophils contribute to pathology. Basophils may indeed promote the inflammatory response in the skin especially during chronic allergic reactions. Supporting evidence comes from mouse models where it could be shown that basophils are required for IgE-mediated chronic allergic inflammation (IgE-CAI) of the skin independently of mast cells and T cells [10^{••},36^{••},37]. Basophils are also recruited to the skin in response to tick bites in different animals [38–39]. Basophil depletion with anti-basophil serum results in reduced tick resistance upon secondary exposure [40]. These results could recently be confirmed with Mcpt8DTR mice (Box 1) where basophils were transiently depleted by injection of diphtheria toxin [41^{••}].

Basophils in asthma and allergic rhinitis

Basophils were found in large numbers in post-mortem biopsies of fatal asthma [42,43]. Accumulation of basophils was also observed in bronchial biopsies of atopic asthma patients [44] and nasal washes of allergic rhinitis patients [45]. Basophils probably contribute to pathology

since they are the main source of histamine during the late phase response (LPR) after nasal challenge of seasonal allergic rhinitis patients [46]. However, a short-term allergic inflammation model of the murine lung induced by intraperitoneal OVA/alum sensitization followed by intranasal OVA challenge revealed that recruitment of eosinophils and Th2 cells was normal in basophil-depleted Mcpt8Cre mice [10^{••}]. Basophils also appeared dispensable for the acute phase of allergic lung inflammation induced by house dust mite extracts [3^{••}]. However, it remains to be determined whether basophils are involved in regulation of chronic allergic inflammation of the lung.

Basophils and anaphylaxis

Anaphylaxis is a severe systemic allergic response characterized by rapid drop of blood pressure, shortness of breath, reduced body temperature and loss of consciousness. The classical form of anaphylaxis is mediated by histamine released from mast cells that are activated by allergens via crosslinking of surface-bound IgE molecules. Basophils were reported to be responsible for an alternative form of anaphylaxis that is mediated by platelet activating factor (PAF) released from basophils after IgG1-induced crosslinking of Fc γ RIII [47]. This observation was based on the finding that mice could be rescued from IgG1-induced passive and active systemic anaphylaxis by depletion of basophils via injection of Ba103, a mAb specific for CD200R3 that is an activating receptor expressed by basophils and mast cells. However, we observed a normal active anaphylactic response to OVA in Mcpt8Cre/c-Kit^{sh/sh} mice that constitutively lack both basophils and mast cells. Furthermore, passive IgE-mediated or IgG1-mediated systemic anaphylaxis was normal in Mcpt8Cre mice [10^{••}]. The apparent discrepancy might be explained by side-effects of the Ba103 antibody or the different antigens used to elicit the anaphylactic response. There is also evidence from other groups that basophils play a minor role and macrophages [48] and neutrophils [49] are the crucial source of PAF during IgG1 anaphylaxis.

Conclusion

Basophil *in vivo* functions were ignored for a long time owing to their low frequency and lack of specific markers. The observation that basophils can be depleted with antibodies that bind to activating receptors on basophils and mast cells enabled researchers to address the role of basophils in mouse models. Some of these studies proposed that basophils act early during type 2 immune responses as crucial antigen-presenting cells for polarization of Th2 cells. More recent studies with different genetically basophil-depleted mice could not confirm these findings. However, murine basophils clearly act as important effector cells against gastrointestinal helminths and chronic allergic inflammation of the skin. Whether these findings from mouse models can be

translated to the human immune system remains to be determined.

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