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Invited review article

Emerging roles of basophils in allergic inflammation

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Abbreviations:
5-LOX, 5-lipoxygenase; AD, atopic dermatitis; APC, antigen-presenting cell; APRIL, a proliferation-inducing ligand; BAFF, B cell-activating factor; CIU, chronic idiopathic urticaria; COX, cyclooxygenase; DC, dendritic cell; DT, diphtheria toxin; EGF, epidermal growth factor; EoE, eosinophilic esophagitis; EMA, European Medicines Agency; FcRγ, Fc receptor common γ-chain; FDA, Food and Drug Administration; GFP, green fluorescence protein; GPCR, G protein-coupled receptor; IgE-CAI, IgE-mediated chronic allergic inflammation; ILC2, group 2 innate lymphoid cell; Lm, *Listeria monocytogenes*; LPS, lipopolysaccharide; MHC-II, major histocompatibility complex class II; mMCP-11, mouse mast cell protease 11; Nb, *Nippostrongylus brasiliensis*; OVA, ovalbumin; PAF, platelet-activating factor; PGN, peptidoglycan; PspA, pneumococcal surface protein A; SLE, systemic lupus erythematosus; TLR, Toll-like receptor; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin; VCAM-1, vascular cell adhesion molecule-1; WT, wild-type

ABSTRACT

Basophils have long been neglected in immunological studies because they were regarded as only minor relatives of mast cells. However, recent advances in analytical tools for basophils have clarified the non-redundant roles of basophils in allergic inflammation. Basophils play crucial roles in both IgE-dependent and -independent allergic inflammation, through their migration to the site of inflammation and secretion of various mediators, including cytokines, chemokines, and proteases. Basophils are known to produce large amounts of IL-4 in response to various stimuli. Basophil-derived IL-4 has recently been shown to play versatile roles in allergic inflammation by acting on various cell types, including macrophages, innate lymphoid cells, fibroblasts, and endothelial cells. Basophil-derived serine proteases are also crucial for the aggravation of allergic inflammation. Moreover, recent reports suggest the roles of basophils in modulating adaptive immune responses, particularly in the induction of Th2 differentiation and enhancement of humoral memory responses. In this review, we will discuss recent advances in understanding the roles of basophils in allergic inflammation.

Introduction

Basophils are the least common granulocytes, representing less than 1% of peripheral blood leukocytes in both mice and humans. Basophils share some features with tissue-resident mast cells,

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including basophilic granules in their cytoplasms and expression of the high-affinity IgE receptor FcεRI on their cell surfaces.[1] Therefore, basophils have long and erroneously been considered to serve redundant roles with mast cells. Nevertheless, basophils and mast cells differ in several aspects, including their localization and life span.[1,2] Basophils circulate in the peripheral blood and migrate to sites of inflammation, whereas mast cells reside in the peripheral tissues and are rarely detected in blood. Moreover, the life span of basophils (~60 h) is much shorter than that of mast cells (2–3 weeks). Despite these differences that suggest functional differences between basophils and mast cells, the non-redundant roles of basophils have not been identified until recently, partly because of the rarity of basophils and lack of tools for basophil research. The recent development of novel analytical tools, including basophil-depleting antibodies and genetically-engineered mice deficient for basophils, have revealed non-redundant functions of basophils in various immune responses such as chronic allergic inflammation and protective immunity against parasites.[3–5] Moreover, a recent report showed that expression profiles of basophils are much different from those of mast cells,[6] indicating their distinct roles in immune responses. In this review, we focus on recent advances in our understanding of basophils in allergic inflammation.

Roles of basophils in allergic inflammation

IgE-dependent allergic inflammation

IgE-mediated chronic allergic inflammation(IgE-CAI) in the skin

Infiltration of basophils into inflammatory sites has been reported in various types of allergic inflammation, including atopic dermatitis, allergic rhinitis, and asthma.[7–9] However, until recently, the contribution of basophils in allergic reactions has remained obscure. Our group has identified non-redundant roles of basophils in a mouse model of IgE-CAI.[10–12]

In this model, mice were passively sensitized with antigen-specific IgE and then their ears were subcutaneously injected with antigens. Consequently, mice exhibited mast cell-dependent biphasic ear swelling (comprising immediate-phase and late-phase ear swelling), followed by severe ear swelling that peaked on days 3–4 after challenge. This delayed-onset ear swelling accompanied massive infiltration of inflammatory cells, including eosinophils, neutrophils, and macrophages, and hyperplastic epidermis with hyperkeratosis. We designated this delayed-onset response IgE-CAI. IgE-CAI can be elicited even in the absence of mast cells or T cells, suggesting that neither mast cells nor T cells are essential for the development of IgE-CAI. Importantly, adoptive transfer of basophils into FcεRI-deficient mice can reconstitute IgE-CAI, even though basophils account for only ~2% of skin-infiltrating cells, demonstrating the pivotal role of basophils in this reaction. Later studies further confirmed the indispensable role of basophils in IgE-CAI by using basophil-specific depletion antibody (anti-CD200R3 antibody (Ba103)) or genetically engineered-mice that specifically lack basophils (*Mcpt8Cre* mice, diphtheria toxin (DT)-treated *Mcpt8*^{DTR} mice, and DT-treated Bas-TRECK mice).[11–14] Notably, depletion of basophils even during the progress of inflammation resulted in the suppression of ear swelling and a drastic reduction in inflammatory cell infiltration, suggesting the effectiveness of basophil-targeted therapy.[11] Therefore, basophils appear to act as initiators of inflammation, recruiting other inflammatory cells such as eosinophils and neutrophils. We postulate the following scenario in IgE-CAI pathogenesis (Fig. 1); First, a small number of basophils are recruited to skin lesions by unknown mechanisms. IgE-bound basophils are activated by antigens, causing the release of various inflammatory mediators, including

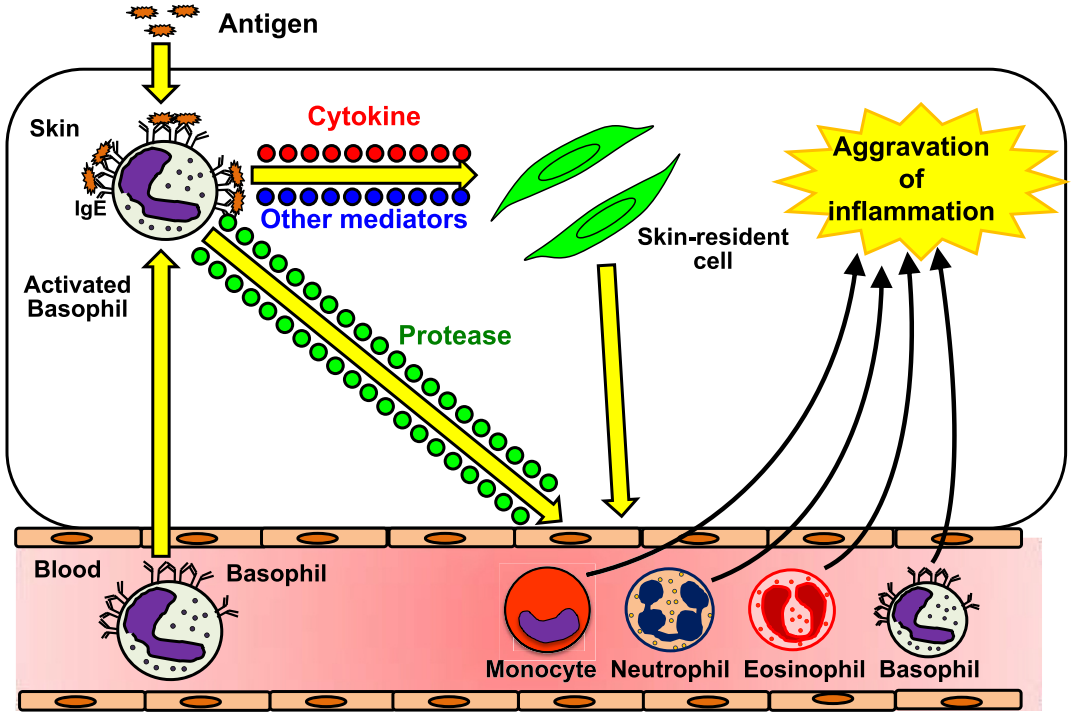

Fig. 1. Roles of basophils as initiator of chronic allergic inflammation. In antigen-sensitized mice, circulating basophils are armed with antigen-specific IgE. After administration of antigens into ear skin, a small number of basophils infiltrate into skin lesions and activated by antigens, leading to the release of a variety of mediators. Cytokines and other mediators produced by activated basophils acts on skin-resident cells, including fibroblasts, endothelial cells, and ILCs. Stimulated skin-resident cells secrete substantial amount of chemokines, promoting the migration of inflammatory cells, including neutrophils, eosinophils, monocytes and basophils. On the other hand, basophil-derived serine proteases such as mMCP-11 act on serum proteins to generate chemotactic factors, leading to the recruitment of inflammatory cells. Thus basophil-derived inflammatory mediators induce further recruitment of inflammatory cells, leading to chronic allergic inflammation.