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REVIEW ARTICLE

# New Insights into the Roles for Basophils in Acute and Chronic Allergy

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## ABSTRACT

Basophils represent less than 1% of peripheral blood leukocytes. They are often recruited to the site of allergic inflammation, albeit in small numbers. However, it remained uncertain whether basophils play any significant role in allergic reactions or act as minor and redundant 'circulating mast cells'. We have recently demonstrated that basophils play critical roles in systemic anaphylaxis and chronic allergic inflammation, distinctively from mast cells. Basophils are one of the major players in the IgG- but not IgE-mediated systemic anaphylaxis, in contrast to mast cells. In response to the allergen-IgG immune complexes, basophils release the platelet-activating factor rather than histamine as the major chemical mediator to induce the systemic anaphylaxis. The depletion of basophils protects mice from death due to anaphylactic shock. Basophils also play a crucial role in the development of the IgE-mediated chronic allergic inflammation with massive eosinophil infiltration in the skin, independently of T cells and mast cells, even though basophils account for only ~2% of the infiltrates. The basophil depletion shows a therapeutic effect on on-going allergic inflammation. Accumulating evidence suggests that basophils function as initiators rather than effectors of the chronic allergic inflammation. Thus, basophils and their products seem to be promising therapeutic targets for allergic disorders.

## KEY WORDS

allergic inflammation, anaphylaxis, basophils, IgE, IgG

## *INTRODUCTION*

Circulating basophils share several features with tissue-resident mast cells, including the presence of basophilic granules in the cytoplasm, the surface expression of high-affinity IgE receptor FcεRI, and the release of chemical mediators such as histamine upon stimulation.[1,2] Because of these similarities and their small numbers, basophils have often been neglected or considered as minor and possibly redundant 'circulating mast cells'.[3] Moreover, mice, a useful laboratory animal species, were erroneously thought to lack basophils for a long time, because mouse basophils have far fewer basophilic granules stained with conventional methods such as Giemsa stain, as compared with human basophils.[4,5] The discovery that basophils rapidly secrete large quantities of Th2 cytokines such as IL-4 in both humans and mice[3,6-10] has changed the traditional image of basophils that they release only preformed histamine and newly synthesized leukotriene C4 after stimulation. This has also provided insight into a possible role for basophils in allergic diseases and immunity to pathogens such as parasites. Nevertheless, the functional studies of basophils have long been hampered by the lack of suitable animal models, including mice deficient only in basophils.

Recent studies have solved this bottleneck by using the adoptive transfer of basophils from normal to FcεRI-deficient mice or establishing basophil-depleting antibodies.[11-15] These studies have defined previously-unrecognized roles for basophils, and have markedly changed our view of basophils from a neglected minority to key players in immune regulation and allergic responses. Basophils have been shown to drive the differentiation of T cells in lymph nodes

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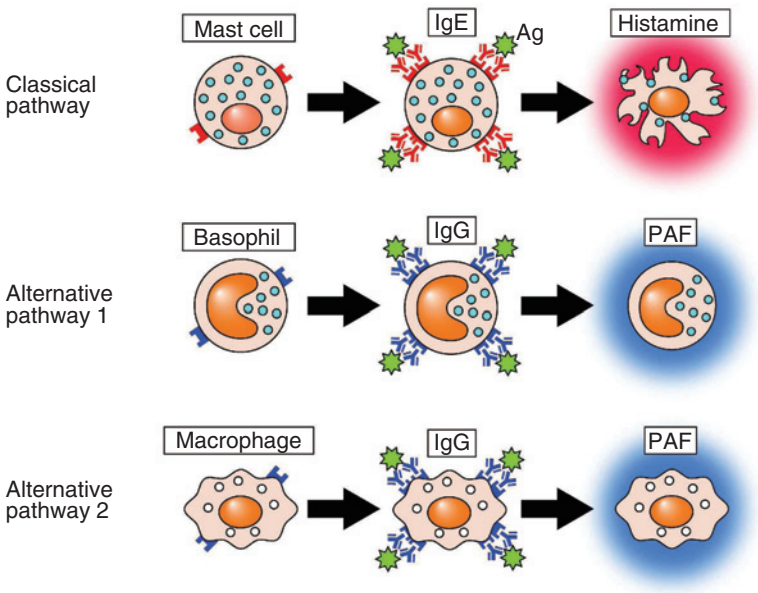


**Fig. 1** Classical and alternative pathways toward systemic anaphylaxis. The classical pathway utilizes mast cells, IgE, and histamine while the alternative pathway utilizes basophils and/or macrophages, IgG, and PAF.

from naïve to Th2-type cells through the secretion of IL-4 and thymic stormal lymphopoietin (TSLP) in response to protease allergens such as papain.[13] Basophils also play an important role in the augmentation of humoral memory responses in that upon the re-exposure to the antigen basophils secrete IL-4 and IL-6 which in turn stimulate memory B cells and T cells for their proliferation and antibody production.[14] In this review, we focus on the newly-defined roles for basophils in allergic responses, including IgG-mediated systemic anaphylaxis and IgE-mediated chronic allergic inflammation in mice,[11,12,15] and discuss the possible involvement of basophils in human allergic disorders.

## *THE ROLE FOR BASOPHILS IN SYSTEMIC ANAPHYLAXIS*

Anaphylaxis is an acute-onset, potentially fatal systemic allergic reaction.[16,17] The term anaphylaxis was created by Dr. Charles Robert Richet, the French physiologist, who received the Nobel Prize in Physiology or Medicine in 1913.[18] He and his colleague Paul Portier reported in 1902 the unexpected experimental result using dogs that were immunized with venom from sea anemones. They intended to make dogs tolerant to the venom by injecting them with non-lethal dose of venom. Shibasaburo Kitasato and Emil von Behring had already demonstrated that animals immunized with bacterial toxins produced antitoxin, which we now know as neutralizing antibodies. In contrast to the original intention of Richet and Portier, the immunized dogs displayed fatal reactions to the second injection of the venom even in a small dose. To describe this curious phenomenon, they created the novel word, anaphylaxis, that was derived from the Greek words a- (against) and -phylaxis (protection).

## IgE- VERSUS IgG-MEDIATED SYSTEMIC ANAPHYLAXIS

Anaphylaxis is commonly triggered by exposure to allergens including foods, insect venoms, and medications through immunological mechanisms, although non-immunological reactions such as those triggered by exercise and cold are involved in some cases.[16,17] It is well documented that IgE and mast cells play pivotal roles in the induction of anaphylaxis (Fig.1 top).[19] When IgE antibodies against a given allergen are produced by B cells in individuals sensitized with the allergen, they circulate in the peripheral blood and bind to FcεRI expressed on the surface of tissue-resident mast cells. The re-exposure to the same allergen triggers the mast cell activation through cross-linking of IgE-Fcε RI complexes by the allergen, leading to the release of chemical mediators, such as histamine, that are pre-formed and stored in secretory granules of mast cells.[19-21] The chemical mediators act on many types of cells in the body, including vascular endothelial cells and bronchial smooth muscle, and induce anaphylactic manifestations such as hypotension and dyspnea.[22]

It is not essential to distinguish the molecular mechanisms underlying different types of systemic anaphylaxis with regard to clinical diagnosis and

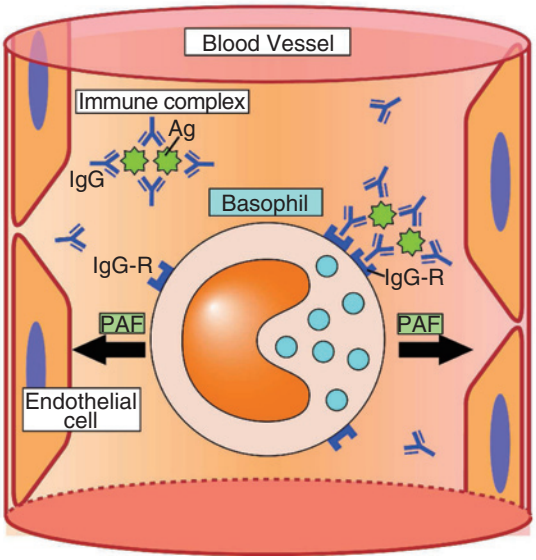


**Fig. 2** Basophils are one of the major players in the IgG-mediated systemic anaphylaxis. When allergens enter the blood stream, they form immune complexes with specific IgG antibodies that circulate in the blood. Circulating basophils efficiently capture the immune complexes through their receptors for IgG (IgG-R), and are activated to release PAF, that in turn stimulates vascular endothelial cells, resulting in the increased vascular permeability leading to hypotension.

acute treatment.[17] The prompt intramuscular injection of epinephrine is needed to treat the anaphylactic shock regardless of the underlying mechanism. However, it is very important to understand the molecular basis of anaphylaxis for the development of risk reduction strategies and the prevention of recurrence.[17] There are few prospective studies of induced anaphylaxis in human subjects because of the potentially rapid, life-threatening outcome. Therefore, many efforts have been made to develop and analyze the modes of anaphylaxis in laboratory animals, particularly mice. Such studies indicated that the classical pathway utilizing IgE and mast cells does not account for all anaphylactic responses. Mice deficient for mast cells, IgE or FcεRIα chain could develop active systemic anaphylaxis whereas FcRγ$^{-/-}$ mice that lack the expression of FcεRI and stimulatory IgG receptors displayed no apparent sign of active systemic anaphylaxis.[23-27] These results suggested that not only IgE but also IgG played a critical role in the induction of systemic anaphylaxis. Indeed, mice that were passively sensitized with allergen-specific monoclonal IgG, particularly IgG1 subclass, developed systemic anaphylaxis upon exposure to the corresponding allergen.[25,26] When the mice were pre-treated with anti-FcγRII/III mAb, the IgG-mediated systemic anaphylaxis was inhibited,[27] indicating the involvement of the low affinity IgG receptor FcγRIII. These results implied that in addition to the classical pathway of anaphylaxis, an alternative pathway is operative in mice, in which non-mast cells, IgG, and FcγRIII are involved in place of mast cells, IgE, and FcεRI.[28]

## BASOPHIL IS ONE OF THE MAJOR PLAYERS IN THE IgG- BUT NOT IgE-MEDIATED SYSTEMIC ANAPHYLAXIS

In order to identify cells responsible for the IgG-mediated systemic anaphylaxis, we first screened candidate cells by examining their ability to capture the allergen-IgG immune complexes in the mouse model of penicillin allergy.[15] Mice were passively sensitized with intravenous injection of penicillin V (PenV)-specific monoclonal IgG1, and subsequently challenged with intravenous injection of PenV-conjugated bovine serum albumin (PenV-BSA) as the allergen. This induced typical signs of systemic anaphylaxis, including the drastic drop (−6℃) in the body temperature within 30 min after the challenge, in both mast cell-sufficient and deficient mice. Flow cytometric analysis of cells isolated from mice immediately after the allergen challenge revealed that various types of cells captured the allergen-IgG immune complexes on the cell surfaces, including NK cells, macrophages, monocytes, dendritic cells, neutrophils, eosinophils, basophils and mast cells. Among them, basophils bound the greatest amount of the allergen per cell (Fig.2), and the binding was strongly inhibited when the mice were treated with anti-FcRII/III mAb before the sensitization with IgG1.[15] Thus, basophils were thought to be a good candidate of the cell responsible for IgG-mediated systemic anaphylaxis. No study has explored the possible involvement of basophils in the IgG-mediated systemic anaphylaxis, most likely due to the lack of analytical tools such as mice deficient for only basophils

We have recently developed a mAb Ba103 specific to mouse CD200R3, a CD200 receptor-like glycoprotein,[12,29] and found that Ba103 selectively depletes basophils when administered *in vivo*.[12] Thus, we have succeeded in establishing mice that are transiently deficient for only basophils. The basophil depletion with Ba103 efficiently ameliorated the PenV-specific, IgG1-mediated systemic anaphylaxis.[15] In contrast, the depletion of macrophages, NK cells, neutrophils, or eosinophils showed no significant effect on the anaphylaxis under our experimental conditions. Of note, the IgE-mediated systemic anaphylaxis was not significantly affected by the basophil depletion, in accord with the fact that mast cell-deficient mice cannot develop the IgE-mediated anaphylaxis. These results demonstrated that basophil is a major player in IgG-mediated systemic anaphylaxis but not IgE-mediated one (Fig.1 middle row and Fig.2).

We next examined the contribution of basophils to anaphylaxis under conditions closer to the real life, that is, active systemic anaphylaxis, in that mice were immunized with PenV-conjugated ovalbumin (PenV-

OVA) and 14 days later challenged with intravenous injection of PenV-BSA. This protocol induced severe anaphylaxis, and all mice analyzed, including mast cell-deficient mice, died from anaphylactic shock. The basophil depletion with Ba103 before the allergen challenge protected mast cell-deficient mice, but not wild-type mice, from anaphylactic death.[15] These results demonstrated that both basophils and mast cells make the critical contribution to active systemic anaphylaxis, most likely through distinct mechanisms: IgG-mediated one utilized by basophils and IgE-mediated one by mast cells.

## BASOPHILS RELEASE PAF RATHER THAN HISTAMINE TO INDUCE IgG-MEDIATED ANAPHYLAXIS

Anti-histamine showed little or no inhibitory effect on the IgG1-mediated passive anaphylaxis even though it efficiently ameliorated the IgE-mediated one. In contrast, antagonists of platelet-activating factor (PAF) almost completely inhibited the IgG1-mediated anaphylaxis, indicating that PAF rather than histamine is the major chemical mediator in the IgG1-mediated anaphylaxis,[15] unlike in the IgE-mediated one. Basophils released much higher amounts of PAF as compared to other types of cells when stimulated with the allergen-IgG immune complexes. The intravenous injection of PAF or histamine alone induced the drastic drop in the body temperature as observed in the IgG1-mediated anaphylaxis. However, the amounts necessary for inducing the same extent ($-5$℃) of drop in the body temperature differed between two reagents: 3 mg of histamine was needed while as little as 100 ng of PAF was sufficient. Based on the *in vitro* measurement, 100 ng of PAF can be released from $3 \times 10^5$ basophils, which is close to the total number of basophils in peripheral blood, spleen and bone marrow. Thus, basophils can elicit system anaphylaxis through the release of PAF that has 30,000-times higher potency than histamine (Fig.1 middle row and Fig.2), even though basophils account for less than 1% of leukocytes in the body.

## MACROPHAGE IS ANOTHER MAJOR PLAYER IN THE IgG-MEDIATED SYSTEMIC ANAPHYLAXIS

Finkelman and his colleagues previously reported that macrophages played a critical role in the distinct model of active systemic anaphylaxis.[27] In their model, mice were first immunized with goat anti-mouse IgD antiserum. This induced the secretion of IL-3 and IL-4 from T cells, and these cytokines in turn promoted the production of large amounts of IgE and IgG antibodies specific to goat IgG. The intravenous injection of goat IgG induced systemic anaphylaxis, which was inhibited by the treatment of mice with anti-FcγR II/III mAb before the allergen challenge. Moreover, the anaphylaxis could be induced even in mast cell-deficient or FcεRIα-deficient mice although some decrease in the severity of anaphylaxis was observed in the latter mice compared to wild-type mice. The PAF antagonist completely inhibited this type of anaphylaxis. These results demonstrated that the allergen-induced anaphylaxis in this system is mast cell-independent but depends on FcγR III and PAF. Of note, intravenous injection of gadolinium chloride before the allergen challenge almost completely abolished the allergen-induced anaphylaxis.[27] Gadolinium chloride is known to inactivate or deplete macrophages. Therefore, it was concluded that macrophages play the major role in the IgG-mediated systemic anaphylaxis through release of PAF (Fig.1 bottom).[27]

It remains to be clarified what makes the difference in the cell types responsible for the IgG-mediated anaphylaxis between this model and our model. Beside the allergens and immunization protocols, the mouse strains utilized in two studies were different. We mainly performed the experiments using mouse strains with the C57BL/6 background as many genetically-engineered mice have this genetic background.[15] In contrast, Finkelman's group mainly utilized mouse strains with the BALB/c background.[27] If the difference is indeed attributed to the genetic background, it is important to explore the molecular basis of the difference. This might help understanding the possible difference in the susceptibility to and the severity of anaphylaxis among individual human subjects with different genetic backgrounds.

## POSSIBLE ROLES FOR BASOPHILS IN HUMAN ANAPHYLAXIS

It remains uncertain whether the alternative anaphylaxis pathway utilizing IgG, PAF and basophils or macrophage is operative in humans. The studies in the mouse models revealed that higher amounts of antigens and antibodies are needed to induce the IgG-mediated anaphylaxis compared to the IgE-mediated one.[15,30] If this is also the case in humans, it would be rare to find the case of the IgG-mediated anaphylaxis in patients with allergy against foods or insect venoms. However, in certain situations such as medication, relatively large amounts of antigens including therapeutic antibodies are introduced into the body, which might trigger the production of large amounts of IgG against such antigens. Several case studies reported that anaphylaxis occurred in the apparent absence of detectable allergen-specific IgE in serum or in the absence of increase in serum tryptase levels as an indication of mast cell degranulation.[31,32] Allergen-specific IgG antibodies instead of IgE were detected in individuals who manifested systemic anaphylaxis against medical reagents such as protamine, dextran, and recombinant IgG including anti-TNFα.[31,33-35] Human basophils have been shown to release PAF in response to various stimuli,[36] al-

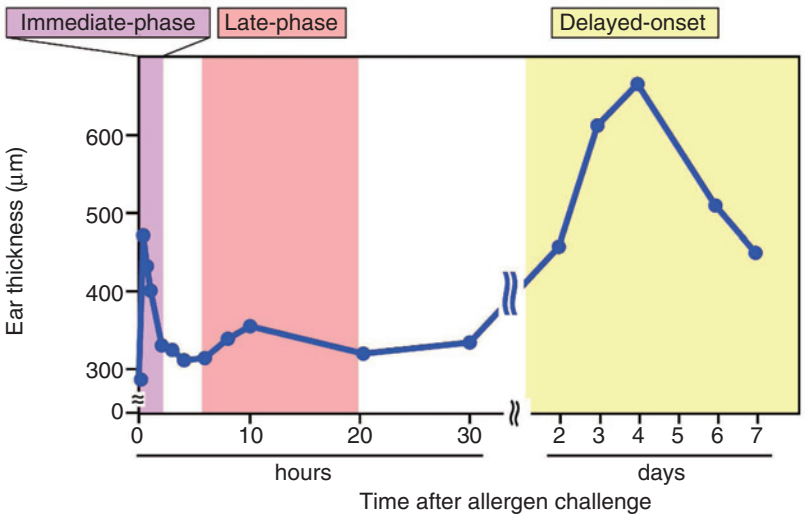


**Fig. 3** The development of tri-phasic ear swelling in the IgE transgenic mice after the allergen challenge. TNP-specific IgE transgenic mice were challenged with subcutaneous injection of TNP-OVA. The time course of ear thickness is shown. The immediate-phase ear swelling was observed within 1 hr after the allergen challenge, followed by the late-phase ear swelling 6–10 hr later. The delayed-onset ear swelling started on day 2, and peaked on day 4.

though it remains to be determined whether allergen-IgG immune complexes stimulate human basophils to release PAF. It has been recently reported that serum PAF levels are correlated with the severity of anaphylaxis in patients.[37] Therefore, it would be worthwhile to reassess the possible involvement of basophils and PAF in human cases of anaphylaxis, particularly in those with high levels of serum IgG but not IgE specific to a relevant allergen. The pretreatment of high-risk patients with PAF antagonists together with anti-histamine before medications might be beneficial for the prevention of anaphylaxis.

## *THE ROLE FOR BASOPHILS IN CHRONIC ALLERGIC INFLAMMATION*

### JONES-MOTE HYPERSENSITIVITY AND CUTANEOUS BASOPHIL HYPERSENSITIVITY

In 1970s, the cutaneous delayed-type hypersensitivity reaction containing large basophil infiltrate was extensively studies.[38] It was termed Jones-Mote hypersensitivity (JMH) in humans[39] or cutaneous basophil hypersensitivity (CBH) in guinea pigs.[40] CBH is distinct from the classical delayed-type (tuberculin test-type) hypersensitivity in several aspects.[38] In general, CBH is elicited by immunization of proteins in incomplete Freund's adjuvant (without mycobacterial components) whereas the immunization using complete Freund's adjuvant (with mycobacterial components) is usually needed to elicit the classical hypersensitivity. CBH is characterized by erythema and slight thickening, peaks at 18–24 hr after the antigen challenge and fades by 48 hr. The classical delayed-type hypersensitivity is characterized by erythema and induration, reaches its maximal intensity within 24 to 30 hr, and remains indurated after 48 to 72 hr. Basophils constitute as much as 80% of the dermal infiltrates in guinea pig CBH whereas basophils are poorly recruited into the skin lesions of the classical hypersensitivity. It was originally reported that CBH could be transferred passively with lymphocytes (most likely T cells) from sensitized animals to naïve animals, but not with the serum from sensitized animals, as observed in the classical delayed-type hypersensitivity.[41] Later studies demonstrated that IgG1 or IgE from sensitized guinea pigs could also transfer CBH.[42,43] The studies on JMH and CBH peaked in 1970s and promptly faded out thereafter, as judged from the numbers of publication regarding these reactions. This may stem from the fact that mice, a powerful experimental model animal, hardly developed CBH. At that time, this failure was thought to be owing to the lack of circulating basophils in mice. Thus, the pathogenesis and molecular mechanism underlying the JMH and CBH reactions remain to be clarified.

### ALLERGEN-SPECIFIC, IgE-MEDIATED CHRONIC ALLERGIC INFLAMMATION

We have established a panel of IgE transgenic mice that constitutively produce monoclonal IgE specific to allergens such as OVA and the hapten 2, 4, 6-trinitrophenol (TNP).[44,45] Intravenous injection of the allergen elicited the typical systemic anaphylaxis in these mice,[44] as expected. Subcutaneous injection of

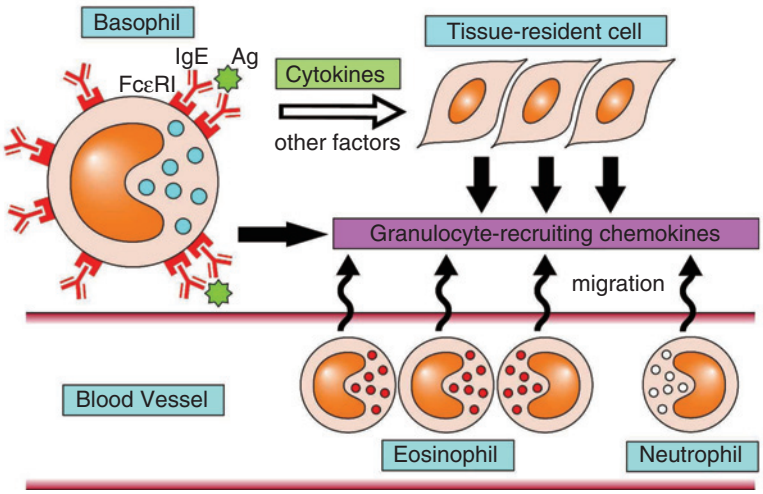


**Fig. 4** A proposed mode of IgE-mediated chronic allergic inflammation. When IgE-bearing basophils are recruited into the peripheral tissue and encounter the relevant allergens, basophils are activated to secrete soluble factors including cytokines. These factors act on surrounding tissue-resident cells to induce the production of chemokines that in turn recruit large numbers of proinflammatory cells such as eosinophils and neutrophils, resulting in chronic allergic inflammation.

TNP-conjugated OVA (TNP-OVA) induced the typical immediate-type skin reactions, that is, the early-phase ear swelling within 1 hr after the allergen challenge followed by the late-phase ear swelling 6–10 hr later (Fig.3). Importantly, after the late-phase swelling subsided, the ear swelling started again on day 2 and peaked on day 4 (Fig.3).[45] This delayed-onset swelling was much more intense than the first and second ones, and the ear thickness became twice the basal level or that of ears challenged with control OVA. Histopathological examination revealed the massive infiltration of eosinophils in the skin lesions as well as hyperplastic epidermis with hyperkeratosis. This IgE-mediated chronic allergic inflammation (IgE-CAI) was elicited not only in the TNP-specific IgE transgenic mice but also in mice that had been passively sensitized with exogenous TNP-specific IgE one day before the challenge with TNP-OVA.[11] These observations indicated that IgE was involved in both immediate and chronic allergic reactions in the skin.

The delayed-onset ear swelling with inflammation was ameliorated by the treatment of mice with immunosuppressants such as cyclosporine A and steroids, suggested that T cells might be involved in the development of IgE-CAI.[45] However, T cell-deficient mice could develop the allergic inflammation with massive eosinophil infiltration to the same extent as did wild-type mice. Furthermore, mast cell-deficient mice also elicited IgE-CAI even though they failed to develop the early- and late-phase ear swelling. Thus, T cells and mast cells were dispensable for the development of IgE-CAI.[11]. The absence of IgE-CAI in FcεRI-deficient mice suggested that FcεRI-expressing cells other than mast cells might be responsible for the development of IgE-CAI.

## BASOPHIL FUNCTIONS AS AN INITIATOR RATHER THAN AN EFFECTOR IN IgE-MEDIATED CHRONIC ALLERGIC INFLAMMATION

The cell transfer of various types of cells in the bone marrow from wild-type mice to FcεRI-deficient mice demonstrated that IgE-CAI could be reconstituted in FcεRI-deficient mice only when CD49b (DX5)-positive cells were transferred.[11] Approximately 20% of the CD49b$^+$ cells expressed FcεRI on their cell surfaces, and possessed lobulated nuclei. These phenotypes and the characterization of secretory granules by the electron microscopic examination defined the CD49b$^+$FcεRI$^+$ cells as basophils.[11] Taken together, it was concluded that basophils were responsible for the development of IgE-CAI. Flow cytometric analysis demonstrated that basophils were indeed recruited into the skin lesions. However, they accounted for only ~2% of the infiltrates whereas eosinophils and neutrophils were abundant, raising the big question how such a small number of basophils could induce the allergic inflammation.

The treatment of mice with the basophil-depleting mAb Ba103 before the allergen challenge prevented the development of IgE-CAI,[12] confirming the critical role for basophils in IgE-CAI. The administration of Ba103 during the progress of the dermatitis showed a therapeutic effect, resulting in suppression of ear

swelling and inflammation in the skin lesions.[12] Of note, the numbers of eosinophils and neutrophils infiltrated in the skin lesions were drastically reduced by the treatment, concomitantly with the elimination of basophils from the inflammation sites. This cannot be expected if basophils, eosinophils and neutrophils were independently recruited to the skin lesions. These results strongly suggested that basophils might function as initiators rather than effectors of the allergic inflammation, and recruit other proinflammatory cells such as eosinophils and neutrophils.[12] Our preliminary experiments support the following scenario (Fig.4). When IgE-bound basophils are recruited to the peripheral tissue such as skin in response to the relevant allergens (through an unidentified mechanism, most likely via chemokines), and encounter the allergens, they are activated through the FcεRI-mediated signal to secrete soluble factors including cytokines and proteases. These factors in turn act on tissue-resident cells such as fibroblasts to secrete a variety of chemokines that recruit proinflammatory cells including eosinophils and neutrophils, resulting in the chronic allergic inflammation.

## POSSIBLE ROLES FOR BASOPHILS IN CHRONIC ALLERGIC INFLAMMATION IN HUMAN

It remains to be determined whether the IgE-CAI-type mechanism is also operative in human allergic disorders. However, there is circumstantial evidence for this. A number of cohort studies indicated the correlation between the disease severity and serum IgE levels in patients with atopic dermatitis or asthma, particularly in younger people.[46,47] Recent clinical trials with humanized anti-IgE antibody (omalizumab) demonstrated that the decrease in serum IgE achieved by the treatment is correlated with improvement of the severity of symptoms in some poorly controlled asthma patients.[48-50] These results suggest the possible involvement of IgE in the pathogenesis of chronic allergic disorders. The infiltration of basophils has often been observed in the affected tissues in chronic allergic disorders including asthma and atopic dermatitis.[51-56] However, the numbers of infiltrated basophils were usually much fewer than those of eosinophils and neutrophils, and therefore the significance of basophil infiltration in the pathogenesis remains uncertain. Given our observation that basophils played a critical role in IgE-CAI in mice even though they accounted for only ～2% of infiltrates, it would be reasonable to assume that basophils contribute to the initiation, prolongation or deterioration of chronic allergic inflammation in some allergic patients.

## *CONCLUSION AND PERSPECTIVE*

Recent advances in the basophil research have cast a new light on the *in vivo* roles of basophils, that are distinct from those played by mast cells.[11-15] Basophils are no longer regarded as redundant 'circulating mast cells'. Basophils are one of the major players in IgG-mediated anaphylaxis,[15] and function as initiators rather than effectors in IgE-mediated chronic allergic inflammation,[11] even though they account for less than 1% of leukocytes in the body. The treatment with cyclosporine A or steroids almost completely suppressed the IgE-mediated chronic allergic inflammation even in the absence of T cells,[11,45] suggesting that these immunosuppressants act on basophils besides T cells.[57-59] These findings make basophils and their products promising therapeutic targets for allergic disorders, even though it remains to be clarified whether those roles for basophils identified in mice are relevant to human counterparts. It is important to understand the *in vivo* roles for basophils not only under pathological conditions but also under physiological conditions in order to develop the therapeutic strategy targeting basophils.

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