



Contents lists available at ScienceDirect

Journal of Dermatological Science

journal homepage: www.jdsjournal.com



Invited review article

Recent advancement in the mechanism of basophil activation

Chisa Nakashima^a, Atsushi Otsuka^{a,b,*}, Kenji Kabashima^{a,c,*}

^a Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan

^b Translational Research Department for Skin and Brain Diseases, Kyoto University Graduate School of Medicine, Kyoto, Japan

^c Singapore Immunology Network (SIgN) and Institute of Medical Biology, Agency for Science, Technology and Research (A*STAR), Biopolis, Singapore

ARTICLE INFO

Article history:

Received 14 February 2018

Received in revised form 7 March 2018

Accepted 8 March 2018

Keywords:

Basophil

IgE

TSLP

ABSTRACT

Basophils have been recognized as crucial players in allergic inflammation. Basophils have the potential to initiate and expand inflammation through the production of specific cytokines and proteases, and are associated with T helper 2 (Th2) immune responses. In addition, recent studies revealed the heterogeneity in basophil populations. Basophils have been clarified important roles in not only IgE-mediated allergic inflammation but also TSLP-mediated and IgE-independent inflammation. Moreover, basophils infiltrate in many human cutaneous diseases. Basophils are responsible for recruiting other inflammatory cells such as macrophages, eosinophils, and fibroblasts. In this review, we discuss recent advances in our understanding of basophil activation and migration in allergic inflammation.

© 2018 Japanese Society for Investigative Dermatology. Published by Elsevier B.V. All rights reserved.

Contents

1. Introduction	00
2. Basophil activation	00
2.1. IgE-dependent allergic inflammation	00
2.2. The role of IL-3 on basophil activation	00
2.3. IgE-independent allergic inflammation	00
2.4. TSLP-elicited basophils	00
3. Basophil recruitment	00
3.1. Initial phase	00
3.2. Early phase	00
3.3. Late phase	00
4. Conclusion	00
Conflicts of interest	00
Funding	00
References	00

1. Introduction

Basophils comprise less than 1% of peripheral blood leukocytes in both humans and mice and were first identified by Paul Ehrlich in 1879 based on their unique microscopic appearance [1]. Because basophils have some similarities to mast cells, they were, however,

regarded as “peripheral circulating mast cells” until the early 1990s. The advent of transgenic mouse technology enabled the visualization and experimental manipulation of basophils *in vivo* [2–5].

Basophils share many features with mast cells; both have basophilic granules in their cytoplasm and express the high-affinity immunoglobulin E (IgE) receptor FcεRI on their cell surfaces. Furthermore, both basophils and mast cells are associated with T helper 2 (Th2) immune responses [6]. Basophils, however, have a distinct lineage with many unique features, and they play crucial roles in allergic inflammation, parasite infections, delayed-type allergic reactions, and anaphylaxis [7–9]. Basophils exhibit

* Corresponding authors at: Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan.

E-mail addresses: otsukamn@kuhp.kyoto-u.ac.jp (A. Otsuka), kaba@kuhp.kyoto-u.ac.jp (K. Kabashima).

rapid and potent expression of interleukin (IL)-4 and IL-13, leading to cutaneous Th2 skewing [10]. The accumulation of basophils has been reported in numerous human diseases, including allergic diseases, such as atopic dermatitis (AD), asthma, and allergic rhinitis (AR), as well as autoimmune diseases and cancer [11].

In this review, we focus on the recent studies on basophils and mainly describe basophil activation and migration.

2. Basophil activation

The basophil activation pathway is divided into two major types, IgE-dependent and IgE-independent. IgE and IL-3 are well-known classical regulators of basophil function. Recently, several studies have identified distinct basophil populations that are elicited by thymic stromal lymphopoietin (TSLP)—these are called TSLP-elicited basophils (Fig. 1).

The most studied basophil activation mechanism is the cross-linking of IgE with its high-affinity receptor FcεR. IgE cross-linking can induce the degranulation and release of several cytokines, including IL-4, IL-13, histamines, leukotriens (LTC4, LTD4, and LTE4), and platelet-activating factor [12]. C3a and C5a also activate human basophils through their receptors, and human basophils express C3a receptors (C3aR) and C5a receptors (C5aR) on their cell surface. C3aR alone does not induce mediator release, but human basophils primed by IL-3 can release histamine and LTC4 via C3aR-mediated responses. Unlike C3a, C5a induces rapid histamine release without IL-3 [13,14], and C5a of human basophils primed by IL-3 in particular has the capability to release histamine, LTC4, and the Th2 cytokines IL-4 and IL-13 induced via FcεR cross-linking. Interestingly, LTC4 synthesis induced by the stimulation of IL-3 and C5a occurs in two phases, a rapid phase (within 1 min) and a chronic phase (18–24 h of IL-3 treatment) [15,16]. Furthermore, histamine release from human basophils was observed when purified IgG and normal serum were added, but not when purified IgG and C5-depleted serum were added. IgG cross-links with the IgE receptor of basophils directly release histamine, which is augmented by complement [17]. In addition, basophils are dispensable for IgE-mediated anaphylaxis, but play a major role in IgG-mediated passive and active systemic anaphylaxis in mice [9].

2.1. IgE-dependent allergic inflammation

Basophils play crucial roles in several mouse disease models, such as skin inflammation, airway inflammation, and AR [18–20]. Mukai et al. demonstrated the pivotal roles of basophils in IgE-dependent allergic inflammation via a mouse model of delayed-onset cutaneous allergic response, designated IgE-mediated chronic allergic inflammation (IgE-CAI) [21]. In this model, mice were first passively sensitized with antigen-specific IgE and then intravenously injected with antigens. Their responses comprised three phases of ear swelling: the first and second phases mediated by mast cells were immediate-type reactions that occurred within a day, and the third phase (IgE-CAI) was a strong and relatively long-lasting reaction induced following the immediate reaction. Massive inflammatory cells, including eosinophils, neutrophils, and macrophages, infiltrated the lesional skin during delayed-onset ear swelling. The third reaction phase was not observed under the basophil-depleted condition. Therefore, basophils, but not mast cells, act as initiators in IgE-CAI.

Recently, a monoclonal anti-IgE antibody (omalizumab), which is used in the treatment of severe asthma and chronic idiopathic urticaria (CIU), provided some evidence of basophil function in human diseases. Omalizumab decreases the levels of circulating IgE by binding to the constant region (Cε3) of IgE molecules, which prevents free IgE from binding to IgE receptors, FcεRI and FcεRII. Administration of omalizumab reduced the serum IgE levels and downregulated the FcεRI density of circulating basophils in AR [22,23]. The expression of FcεRI in peripheral blood basophils was reduced by approximately 90% in one week and by 99% in a longer treatment period.

Omalizumab is effective for CIU patients. CIU is characterized by itchy wheal-and-flare skin reactions and/or angioedema present for more than 6 weeks, and is usually treated with anti-histamines. Thus far, four phase-III multicenter, randomized, placebo-controlled clinical trials have established that omalizumab is effective and safe for treating CIU. The presence of basophils in both peripheral blood and lesional skin were observed in CIU patients, and treatment of CIU with omalizumab improved the severity of itch score and the number of blood basophils observed [24]. Thus,

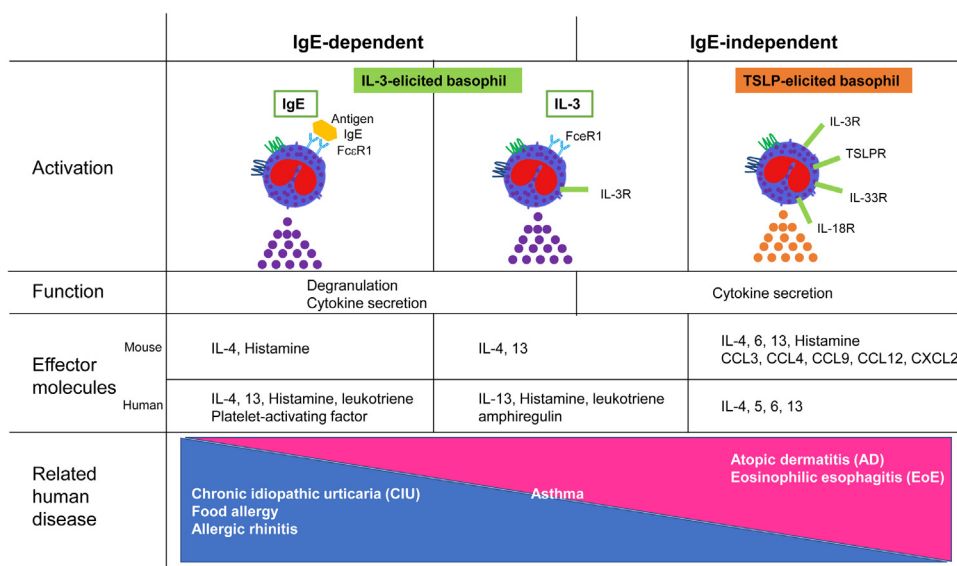


Fig. 1. Summary of basophil activation factors, effector molecules, and related human diseases.

Basophils are activated by antigen and IgE stimulation (IgE-dependent) and degranulate and secrete histamine and several cytokines. Recently, several reports have demonstrated that basophil heterogeneity can be divided into two populations, IL-3-elicited and TSLP-elicited basophils. IL-3-elicited basophils are highly responsive to FcεRI cross-linking through IgE-antigen complexes. TSLP-elicited basophils are activated by several cytokines, including IL-3, IL-18, and IL-33.

omalizumab can improve the symptoms in IgE- and basophil-mediated diseases.

2.2. The role of IL-3 on basophil activation

IL-3, which is predominantly produced by T cells, is a key cytokine for basophil survival and IL-4 induction. Numerous *in vitro* studies have shown that increased numbers of basophils arise from bone marrow precursors in response to IL-3. Furthermore, IL-3 increases basophil survival via NF- κ B induction and upregulation of the serine/threonine kinase Pim1 [25,26]. IL-3 also promotes the reactivity of basophils mediated by IgE cross-linking, and human basophils can produce more IL-4 and IL-13 with the synergistic effect of IL-3 and IgE cross-linking. Thus, IL-3 and IgE cooperate and are involved in basophil activation.

The activation profiles of basophils from atopic asthmatics challenged intranasally with human rhinovirus 16 were monitored directly either *ex vivo* or in 24 h cultures at baseline (day 0) and at days 4 and 21 post-challenge.

IL-3 can directly promote the release of cytokines and chemokines from TSLP-elicited basophils in an IgE-independent pathway. Human basophils were recently reported to have a similar capacity to respond to IL-3 and anti-IgE as TSLP. In allergic asthma patients, expression levels of the TSLP receptor (TSLPR) in bone marrow, peripheral blood, and sputum were elevated after allergen inhalation challenge compared to those at baseline. TSLP stimulation in human basophils upregulated the expression levels of TSLPR, IL-3R α , and CCR3 to magnitudes similar to that of incubating basophils with IL-3. Furthermore, TSLP-induced increases in the intracellular expression of IL-4 and IL-13 were inhibited by neutralizing antibodies of TSLPR as well as IL-3R α . Thus, the effects of TSLP are partially dependent on the IL-3-specific pathway [27].

2.3. IgE-independent allergic inflammation

Basophils play important roles in IgE-independent allergic inflammation in mouse disease models, including AD, irritant contact dermatitis, asthma induced by proteases, and eosinophilic esophagitis (EoE). Basophils are known to produce various cytokines by numerous stimuli without an antigen-specific IgE mechanism.

Both basophils and mast cells contribute to protection against helminth infection, as the production of IL-4 and IL-13 by basophils was recently shown to contribute to worm expulsion during the primary infection. *Strongyloides venezuelensis* (*S. venezuelensis*) infection induced a Th2 cell response by the primary IL-4 production of basophils in a STAT6-independent manner [28], and *Nippostrongylus brasiliensis* infection induced a Th2 response with the infiltration of IL-4+ basophils into the liver and lungs in a STAT6-independent manner [29].

Human basophils respond to a variety of innate immune-related stimuli involving Th2 responses to pathogens, such as bacterial and viral infections. For instance, the *Helicobacter pylori* antigen activates basophils via N-formyl-peptide receptor-like 1,2 and produces IL-4 and IL-13 [30]. In addition, recent studies have shown that HIV-1 gp120 acts as a superantigen via the VH3 domain of IgE and activates basophils [31]. Furthermore, human basophils express toll-like receptor (TLR) 2 and TLR4. Peptidoglycan as a TLR2 ligand, but not LPS as a TLR4 ligand, stimulated human basophils, and IL-4 and IL-13 were secreted [32].

2.4. TSLP-elicited basophils

Recent studies have suggested that basophils elicited by TSLP play crucial roles [33]. TSLP produced mainly by epithelial cells is a

master regulator of Th2 immunity and contributes to the pathogenesis of Th2 diseases, such as AD, asthma, AR, and EoE [34]. Furthermore, TSLP and basophils are required for the development of the murine EoE model.

Because the TSLPR is expressed on bone marrow basophil progenitors, TSLP regulates basophil haematopoiesis. When bone marrow cells from wild-type mice were cultured with IL-3, both basophils and mast cells were derived. In contrast to IL-3, TSLP-stimulated bone marrow cultures exhibited increased frequencies of only basophils. Furthermore, administration of TSLP (recombinant TSLP of the TSLP-cDNA plasmid) promoted systemic basophilia in mice and increased the production of Th2 cytokines [33]. Administration of a topical application of the vitamin D3 analog MC903 (calcipotriol) generates a well-known TSLP-dependent murine AD model [35]. Basophils infiltrated the skin after topical MC903 application, and MC903-induced basophil accumulation was deemed TSLP-dependent, as treating wild-type mice with anti-TSLP diminished the accumulation of basophils in lesional skin.

Regarding surface markers, differences exist between IL-3- and TSLP-elicited basophils. Specifically, although both IL-3- and TSLP-elicited basophils express CD200R and CD69, IL-3-elicited basophils express higher levels of CD11b and CD62L. On the other hand, TSLP-elicited basophils express higher levels of CD123, IL-33R, and IL-18R.

TSLP-elicited basophils produce greater amounts of IL-4, IL-6, CCL3, CCL4, and CCL12 with IL-3 stimulation than IL-3-elicited basophils. IL-18 and IL-33 stimulation increases the production of CCL3, CCL4, CCL9, CCL12, and CXCL2 in TSLP-elicited basophils (Fig. 1).

For human diseases, basophil accumulation is observed in active EoE biopsy samples. EoE is a food allergy associated with esophageal eosinophilia, and a significant association between a gain-of-function polymorphism in the gene encoding the predominantly epithelial cell-derived TSLP and EoE development has been established in children. The expression of TSLP in EoE biopsies was higher, and an infiltration of basophils was observed in EoE lesions by flow cytometry analysis. Indeed, the TSLP-basophil axis contributes to the pathogenesis of human EoE.

3. Basophil recruitment

3.1. Initial phase

As we mentioned above, basophils are responsible for initiating and recruiting other inflammatory cells, such as eosinophils and neutrophils (Fig. 2). However, how the initial basophil accumulation in peripheral tissues occurs remains largely unknown.

Human mast cells, basophils, and eosinophils share numerous recruitment pathways. The expression of adhesion molecules and chemokine receptors on the cell surface is important for leukocyte migration. Regarding chemotactic factors, human blood basophils express the chemokine receptors CCR1, CCR2, CCR3, CCR5, CXCR1, CXCR2, and CXCR4 [36,37], and an intradermal injection of eotaxin/CCL11 and eotaxin-2/CCL24 acting through CCR3 induces basophil accumulation in humans [38]. Several reports demonstrated that the serum levels of CCL5/RANTES (binds CCR1, CCR3, and CCR5) and eotaxin (binds CCR3) were increased in patients with CIU compared to those in healthy subjects [39,40]. Recently, the percentage of basophils expressing IL-17RB, ST2, and intracellular IL-25 was significantly increased 24 h post-allergen exposure in the peripheral blood of asthma patients. CCR3 expression in peripheral blood basophils from allergic donors was significantly elevated with IL-33 and IL-25 stimulation. These findings suggested that IL-25 and IL-33 increase the migratory potential of basophils in allergic asthma [41]. In addition, prostaglandin D2

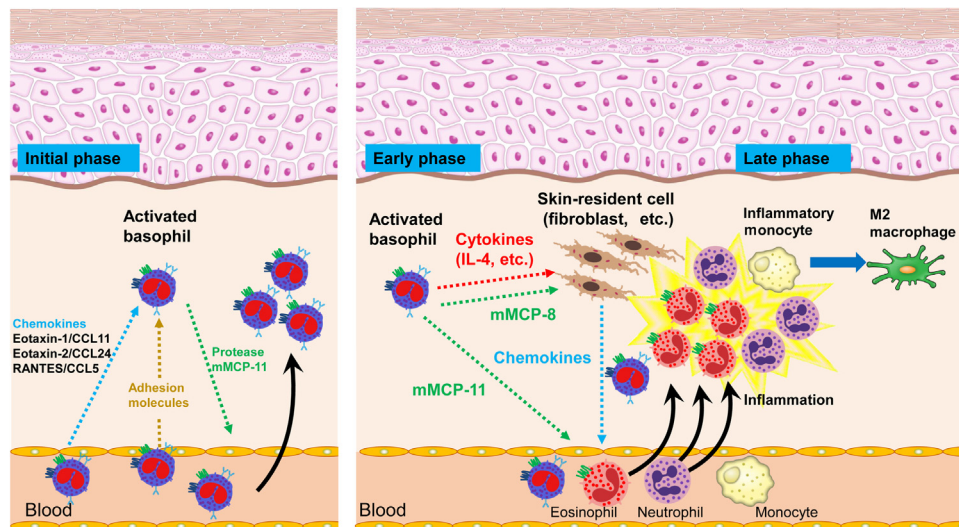


Fig. 2. Basophil recruitment.

Chemokines (e.g., eotaxin and RANTES), basophil proteases, and the expression of adhesion molecules on basophil surfaces are involved in the recruitment of basophils to peripheral tissues. Basophils rapidly infiltrate inflammatory sites and act as initiator cells. In the early phase, basophil-derived IL-4 affects resident skin cells, including fibroblasts, endothelial cells, and ILCs, leading to the accumulation of inflammatory cells. In the late phase, basophil-derived IL-4 influences the differentiation of M2 macrophages from inflammatory monocytes.

(PGD2) is known to cause the activation and chemotaxis of basophils and eosinophils through its receptor, a chemoattractant receptor-homologous molecule expressed in Th2 cells (CRTH2). Suppression of CRTH2 expression was revealed in blood basophils and eosinophils of patients with CIU compared to healthy control subjects. PGD2 stimulation induces dose-dependent CRTH2 receptor internalization in human basophils, and is involved in basophil accumulation in the lesional skin of CIU patients. But further studies are required because none of these receptors are specific for basophils.

In terms of adhesion molecules, human basophils are found on several surface structures, including VLA-4, VLA-5, $\beta 2$ integrins, $\alpha 4\beta 7$, L-selectin, and PSGL-1. The phenotype of basophil adhesion molecules, however, overlaps that of other leukocytes and is not unique. The expression of $\beta 2$ integrins is upregulated by IgE cross-linking, and IL-3 stimulation directly augments their adhesiveness for endothelium and upregulates CD11b expression.

In mice, $\alpha(1, 3)$ fucosyltransferases (FTs) IV and VII, the glycans that contribute to selectin counter-receptors, are essential for the initial recruitment of basophils in IgE-CAI, as FT-IV(-)/FT-VII(-/-) mice exhibit significantly impaired inflammation [42].

3.2. Early phase

Next, we describe how basophils acting as initiator cells are involved in the recruitment of inflammatory cells to peripheral tissues. As mentioned above, basophils act as initiators by recruiting other inflammatory cells, such as eosinophils and neutrophils. Activated basophils secrete various inflammatory mediators, including cytokines, chemokines, and proteases, and basophil-derived mediators may influence resident skin cells, such as fibroblasts.

Along with other groups, we previously reported that basophil-derived IL-4 plays a role in the recruitment of other immune cells, such as eosinophils. Basophils enhanced eosinophil recruitment to the skin in a murine irritant contact dermatitis model. Bone marrow-derived basophils (BMBs) promote the migration and activation of eosinophils *in vitro*. In addition, basophil-derived IL-4 and TNF α increased the amounts of CCL11/eotaxin and CCL5/RANTES by the co-cultivation of murine embryonic fibroblasts and

promoted eosinophil migration [43]. Basophil-derived IL-4 modulates induction of the endothelial vascular cell adhesion molecule-1 (VCAM-1) in IgE-dependent dermatitis [44]. IL-4 from basophils, which upregulate the expression of VCAM-1 in the vascular endothelium, is required for eosinophil entry.

Basophils store serine proteases in their granules, and the mouse mast cell protease (mMCP) family comprises six chymases (mMCP-1, 2, 4, 5, 9, and 10), four tryptases (mMCP-6, 7, 11, and mTMT), and a granzyme B-like protease mMCP-8 [45]. mMCP-8 and mMCP-11 are featured in basophils rather than mast cells [46,47].

Recently, mMCP-11 was demonstrated to play significant roles in IgE-CAI responses [48]. IgE-CAI responses were improved in mMCP-11-deficient mice compared to wild-type mice, and the improvements included reduction of ear swelling, microvascular permeability, and leukocyte infiltration in skin lesions. Basophil infiltration in IgE-CAI skin lesions remained even in mMCP-11-deficient mice, although to a lesser extent than that in wild-type mice. Therefore, although mMCP-11 is not essential for basophil infiltration, it is responsible for basophil infiltration. Furthermore, repeated injection of recombinant mMCP-11 intradermally induced the infiltration of leukocytes, including basophils, in a tryptase activity-dependent manner. Furthermore, mMCP-11-mediated proteolytic products of serum proteins promoted the migration of basophils, eosinophils, and macrophages via a G protein-coupled receptor, as determined using a transwell migration assay. Thus, basophil-derived mMCP-11 can recruit basophils to the lesional skin, and recruited basophils are activated and release mMCP-11, which induces the accumulation of other immune cells. mMCP-11 plays a pivotal role in the development of allergic cutaneous inflammation.

Basophil-derived mMCP-8 reportedly induces the recruitment of leukocytes. In particular, mMCP-8 is specifically expressed by basophils, but not by mast cells, and the repeated administration of recombinant mMCP-8 protein promotes ear swelling, microvascular permeability, and the skin infiltration of leukocytes, including neutrophils, monocytes, and eosinophils [49]. mMCP-8 does not, however, exhibit chemotactic capacity *in vitro*. Thus, both MCP-11 and MCP-8 promote the infiltration of immune cells and are involved in the development of allergic inflammation.

3.3. Late phase

Inflammatory monocytes generally differentiate into classically activated macrophages (known as M1) and alternatively activated macrophages (known as M2), and IL-4 produced by basophils is important for M2 macrophage differentiation [50]. Inflammatory monocytes are recruited to the lesional skin in IgE-CAI and differentiate into M2-like macrophages in the presence of basophil-derived IL-4.

4. Conclusion

Recent establishment tools have accelerated functional research on basophils. Basophils are recognized an important key player in various type of allergic inflammation. Moreover, basophils have also shown heterogeneous populations such as IgE-mediated, IL-3 elicited, and TSLP-elicited type. However, there remains a compelling need to determine whether these findings in mouse models are relevant to humans. Most of the current knowledge *in vivo* is based on the murine model. Further elucidations are needed to investigate the counterpart in human skin diseases. It will help for the development of newly therapeutic target for allergic diseases.

Conflicts of interest

None declared.

Funding

This work was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare of Japan.

References

- [1] P. Ehrlich, Beiträge zur Theorie und Praxis der histologischen Färbung. Thesis, Leipzig University, 1878.
- [2] C. Ohnmacht, C. Schwartz, M. Panzer, I. Schiedewitz, R. Naumann, D. Voehringer, Basophils orchestrate chronic allergic dermatitis and protective immunity against helminths, *Immunity* 33 (2010) 364–374.
- [3] M. Sawaguchi, S. Tanaka, Y. Nakatani, Y. Harada, K. Mukai, Y. Matsunaga, et al., Role of mast cells and basophils in IgE responses and in allergic airway hyperresponsiveness, *J. Immunol.* 188 (2012) 1809–1818.
- [4] T. Wada, K. Ishiwata, H. Koseki, T. Ishikura, T. Ugajin, N. Ohnuma, et al., Selective ablation of basophils in mice reveals their nonredundant role in acquired immunity against ticks, *J. Clin. Invest.* 120 (2867) (2010).
- [5] B.M. Sullivan, H.-E. Liang, J.K. Bando, D. Wu, L.E. Cheng, J.K. McKerrow, et al., Genetic analysis of basophil function in vivo, *Nat. Immunol.* 12 (2011) 527–535.
- [6] D. Voehringer, Protective and pathological roles of mast cells and basophils, *Nat. Rev. Immunol.* 13 (362) (2013).
- [7] C. Sokol, R. Medzhitov, Emerging functions of basophils in protective and allergic immune responses, *Mucosal. Immunol.* 3 (129) (2010).
- [8] H. Karasuyama, K. Mukai, K. Obata, Y. Tsujimura, T. Wada, Nonredundant roles of basophils in immunity, *Annu. Rev. Immunol.* 29 (2011) 45–69.
- [9] Y. Tsujimura, K. Obata, K. Mukai, H. Shindou, M. Yoshida, H. Nishikado, et al., Basophils play a pivotal role in immunoglobulin-G-mediated but not immunoglobulin-E-mediated systemic anaphylaxis, *Immunity* 28 (2008) 581–589.
- [10] A. Otsuka, S. Nakajima, M. Kubo, G. Egawa, T. Honda, A. Kitoh, et al., Basophils are required for the induction of Th2 immunity to haptens and peptide antigens, *Nat. Commun.* 4 (1738) (2013).
- [11] Y. Ito, T. Satoh, K. Takayama, C. Miyagishi, A. Walls, H. Yokozeki, Basophil recruitment and activation in inflammatory skin diseases, *Allergy* 66 (2011) 1107–1113.
- [12] K.D. Stone, C. Prussin, D.D. Metcalfe, IgE, mast cells, basophils, and eosinophils, *J. Allergy Clin. Immunol.* 125 (2010) S73–S80.
- [13] S.C. Bischoff, A.L. De Weck, C.A. Dahinden, Interleukin 3 and granulocyte/macrophage-colony-stimulating factor render human basophils responsive to low concentrations of complement component C3a, *Proc. Nat. Acad. Sci. U. S. A.* 87 (1990) 6813–6817.
- [14] Y. Kurimoto, A. De Weck, C. Dahinden, Interleukin 3-dependent mediator release in basophils triggered by C5a, *J. Exp. Med.* 170 (1989) 467–479.
- [15] D.W. MacGlashan, W.C. Hubbard, IL-3 alters free arachidonic acid generation in C5a-stimulated human basophils, *J. Immunol.* 151 (1993) 6358–6369.
- [16] D. MacGlashan, J. Warner, Stimulus-dependent leukotriene release from human basophils: a comparative study of C5a and Fmet-leu-phe, *J. Leukoc. Biol.* 49 (1991) 29–40.
- [17] Y. Kikuchi, A.P. Kaplan, A role for C5a in augmenting IgG-dependent histamine release from basophils in chronic urticaria, *J. Allergy Clin. Immunol.* 109 (2002) 114–118.
- [18] K. Wakahara, V. Van, N. Baba, P. Begin, M. Rubio, G. Delespesse, et al., Basophils are recruited to inflamed lungs and exacerbate memory Th2 responses in mice and humans, *Allergy* 68 (2013) 180–189.
- [19] Y. Shiraishi, Y. Jia, J. Domenico, A. Joetham, H. Karasuyama, K. Takeda, et al., Sequential engagement of FcεRI on mast cells and basophil histamine H4 receptor and FcεRI in allergic rhinitis, *J. Immunol.* 190 (2013) 539–548.
- [20] Y. Haenueki, K. Matsushita, S. Futatsugi-Yumikura, K.J. Ishii, T. Kawagoe, Y. Imoto, et al., A critical role of IL-33 in experimental allergic rhinitis, *J. Allergy Clin. Immunol.* 130 (e111) (2012) 184–194.
- [21] K. Mukai, K. Matsuoaka, C. Taya, H. Suzuki, H. Yokozeki, K. Nishioka, et al., Basophils play a critical role in the development of IgE-mediated chronic allergic inflammation independently of T cells and mast cells, *Immunity* 23 (2005) 191–202.
- [22] S. Holgate, T. Casale, S. Wenzel, J. Bousquet, Y. Deniz, C. Reisner, The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation, *J. Allergy Clin. Immunol.* 115 (2005) 459–465.
- [23] H. Lin, K.M. Boesel, D.T. Griffith, C. Prussin, B. Foster, F. Romero, et al., Omalizumab rapidly decreases nasal allergic response and FcεRI on basophils, *J. Allergy Clin. Immunol.* 113 (2004) 297–302.
- [24] S.S. Saini, T.A. Omachi, B. Trzaskoma, H.N. Hultner, K. Rosén, P.M. Sterba, et al., Effect of omalizumab on blood basophil counts in patients with chronic idiopathic/spontaneous urticaria, *J. Invest. Dermatol.* 137 (2017) 958–961.
- [25] X. Zheng, A. Karsan, V. Duronio, F. Chu, D.C. Walker, T.R. Bai, et al., Interleukin-3, but not granulocyte-macrophage colony-stimulating factor and interleukin-5, inhibits apoptosis of human basophils through phosphatidylinositol 3-kinase: requirement of NF-κB-dependent and-independent pathways, *Immunology* 107 (2002) 306–315.
- [26] S.A. Didichenko, N. Spiegel, T. Brunner, C.A. Dahinden, IL-3 induces a Pim1-dependent antiapoptotic pathway in primary human basophils, *Blood* 112 (2008) 3949–3958.
- [27] B.M. Salter, J.P. Oliveria, G. Nusca, S.G. Smith, R.M. Watson, M. Comeau, et al., Thymic stromal lymphopoietin activation of basophils in patients with allergic asthma is IL-3 dependent, *J. Allergy Clin. Immunol.* 136 (2015) 1636–1644.
- [28] T. Yoshimoto, K. Nakanishi, Roles of IL-18 in basophils and mast cells, *Allergol. Int.* 55 (2006) 105–113.
- [29] B. Min, M. Prout, J. Hu-Li, J. Zhu, D. Jankovic, E.S. Morgan, et al., Basophils produce IL-4 and accumulate in tissues after infection with a Th2-inducing parasite, *J. Exp. Med.* 200 (2004) 507–517.
- [30] A. de Paulis, N. Prevete, I. Fiorentino, A.F. Walls, M. Curto, A. Petraroli, et al., Basophils infiltrate human gastric mucosa at sites of *Helicobacter pylori* infection, and exhibit chemotaxis in response to H. pylori-derived peptide Hp (2–20), *J. Immunol.* 172 (2004) 7734–7743.
- [31] G. Florio, A. Petraroli, V. Patella, M. Triggiani, Marone G: The immunoglobulin superantigen-binding site of HIV-1 gp120 activates human basophils, *AIDS* 14 (2000) 931–938.
- [32] A.P. Bieneman, K.L. Chichester, Y.-H. Chen, J.T. Schroeder, Toll-like receptor 2 ligands activate human basophils for both IgE-dependent and IgE-independent secretion, *J. Allergy Clin. Immunol.* 115 (2005) 295–301.
- [33] M.C. Siracusa, S.A. Saenz, D.A. Hill, B.S. Kim, M.B. Headley, T.A. Doering, et al., TSLP promotes interleukin-3-independent basophil haematopoiesis and type 2 inflammation, *Nature* 477 (2011) 229–233.
- [34] M. Noti, E.D.T. Wojno, B.S. Kim, M.C. Siracusa, P.R. Giacomini, M.G. Nair, et al., Thymic stromal lymphopoietin-elicited basophil responses promote eosinophilic esophagitis, *Nat. Med.* 19 (2013) 1005–1013.
- [35] M. Li, P. Hener, Z. Zhang, S. Kato, D. Metzger, P. Chambon, opical vitamin D3 and low-calcemic analogs induce thymic stromal lymphopoietin in mouse keratinocytes and trigger an atopic dermatitis, *Proc. Natl. Acad. Sci. U. S. A.* 103 (2006) 11736–11741.
- [36] B.S. Bochner, R.P. Schleimer, Mast cells, basophils, and eosinophils: distinct but overlapping pathways for recruitment, *Immunol. Rev.* 179 (2001) 5–15.
- [37] E.T. Oliver, P.M. Sterba, K. Devine, B.M. Vonakis, S.S. Saini, Altered expression of chemotactant receptor-homologous molecule expressed on T cells on blood basophils and eosinophils in patients with chronic spontaneous urticaria, *J. Allergy Clin. Immunol.* 137 (e301) (2016) 304–306.
- [38] A. Menzies-Gow, S. Ying, I. Sabroe, V.L. Stubbs, D. Soler, T.J. Williams, et al., Eotaxin (CCL11) and eotaxin-2 (CCL24) induce recruitment of eosinophils, basophils, neutrophils, and macrophages as well as features of early- and late-phase allergic reactions following cutaneous injection in human atopic and nonatopic volunteers, *J. Immunol.* 169 (2002) 2712–2718.
- [39] A. Tedeschi, R. Asero, M. Lorini, A. Marzano, M. Cugno, Serum eotaxin levels in patients with chronic spontaneous urticaria, *Eur. Ann. Allergy Clin. Immunol.* 44 (88) (2012).
- [40] I. Puxeddu, F. Panza, F. Pratesi, D. Bartaloni, S.C. Rabl, V. Rocchi, et al., CCL5/RANTES, sVCAM-1, and sICAM-1 in chronic spontaneous urticaria, *Int. Arch. Allergy Immunol.* 162 (2013) 330–334.
- [41] B.M. Salter, J.P. Oliveria, G. Nusca, S.G. Smith, D. Tworek, P.D. Mitchell, et al., IL-25 and IL-33 induce Type 2 inflammation in basophils from subjects with allergic asthma, *Respir. Res.* 17 (5) (2016).

- [42] K. Saeki, T. Satoh, H. Yokozeki, α (1, 3) Fucosyltransferases IV and VII are essential for the initial recruitment of basophils in chronic allergic inflammation, *J. Invest. Dermatol.* 133 (2013) 2161–2169.
- [43] C. Nakashima, A. Otsuka, A. Kitoh, T. Honda, G. Egawa, S. Nakajima, et al., Basophils regulate the recruitment of eosinophils in a murine model of irritant contact dermatitis, *J. Allergy Clin. Immunol.* 134 (e112) (2014) 100–107.
- [44] L.E. Cheng, B.M. Sullivan, L.E. Retana, C.D. Allen, H.-E. Liang, R.M. Locksley, IgE-activated basophils regulate eosinophil tissue entry by modulating endothelial function, *J. Exp. Med.* 20141671 (2015).
- [45] H.P. McNeil, R. Adachi, R.L. Stevens, Mast cell-restricted tryptases: structure and function in inflammation and pathogen defense, *J. Biol. Chem.* 282 (2007) 20785–20789.
- [46] T. Ugajin, T. Kojima, K. Mukai, K. Obata, Y. Kawano, Y. Minegishi, et al., Basophils preferentially express mouse Mast Cell Protease 11 among the mast cell tryptase family in contrast to mast cells, *J. Leukoc. Biol.* 86 (2009) 1417–1425.
- [47] M. Poorafshar, H. Helmbj, M. Troye-Blomberg, L. Hellman, MMCP-8, the first lineage-specific differentiation marker for mouse basophils. Elevated numbers of potent IL-4-producing and MMCP-8-positive cells in spleens of malaria-infected mice, *Eur. J. Immunol.* 30 (2000) 2660–2668.
- [48] M. Iki, K. Tanaka, H. Deki, M. Fujimaki, S. Sato, S. Yoshikawa, et al., Basophil tryptase mMCP-11 plays a crucial role in IgE-mediated, delayed-onset allergic inflammation in mice, *Blood* 128 (25) (2016) 2909–2918 blood-2016-2007-729392.
- [49] H. Tsutsui, Y. Yamanishi, H. Ohtsuka, S. Sato, S. Yoshikawa, H. Karasuyama, The basophil-specific protease mMCP-8 provokes an inflammatory response in the

skin with microvascular hyperpermeability and leukocyte infiltration, *J. Biol. Chem.* 292 (2017) 1061–1067.

- [50] M. Egawa, K. Mukai, S. Yoshikawa, M. Iki, N. Mukaida, Y. Kawano, et al., Inflammatory monocytes recruited to allergic skin acquire an anti-inflammatory M2 phenotype via basophil-derived interleukin-4, *Immunity* 38 (2013) 570–580.



Chisa Nakashima received the MD from Osaka City University in 2005. After the residency at Kyoto and Hyogo, she received the PhD from Kyoto University in 2014. She was assigned as an assistant professor at the Department of Dermatology, Kyoto University (2014–2017). Now she is working as the Research Fellowship (Japan Society for the promotion of Science: JSPS) at Kyoto University. Her interests are cutaneous immunology, basophils and eosinophils.