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Differentiation of innate type-2 effector cells

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Abstract

Type-2 immune responses are the underlying cause of many allergic diseases and provide protection against parasitic infection. Effective type-2 immune responses are generated by type-2 helper $CD4^+$ T cells (Th2) as well as type-2 innate effector cells. While we have learned a great deal about how $CD4^+$ Th2 cells regulate their Th2 cytokine gene transcription, we still do not know how type-2 innate effector cells acquire their capacity to express Th2 cytokine genes. Furthermore, it remains poorly understood how Th2 cytokines regulate the differentiation of innate type-2 progenitor cells. In this review, we will focus on (1) the long distance interaction between the sites of allergic inflammation and the site of hematopoiesis in the bone marrow, (2) the characteristics of innate type-2 progenitors, and (3) the molecular mechanisms by which innate type-2 effector cells acquire the capacity to produce type-2 cytokines.

Keywords

Type-2 immunity; Innate type-2 progenitors; Th2; Developmental regulation

Introduction

The incidence of allergic diseases, such as anaphylaxis, allergic rhinitis, atopic dermatitis, and asthma, has tripled in Western countries since the 1980s. Meanwhile, hundreds of millions of people in the developing world are infected with helminth parasites. Together, these two types of disease affect a large population of people worldwide. Type-2 immunity is the underlying cause of many allergic diseases and provides protection against parasitic infection. Type-2 immunity is characterized by the production of T helper type-2 (Th2) cytokines, such as interleukin (IL)-4, IL-5, and IL-13. This type of immune response is mounted by effector cells, including Th2 cells, eosinophils, basophils, and mast cells. Basophils play a non-redundant role in both causing allergic inflammation and expelling worms by releasing IL-4 and IL-13, whereas mast cells contribute to type-2 immunity by releasing histamine, leukotrienes, and cytokines, such as IL-13. However, the mechanism by which eosinophils, basophils, and mast cells develop into defined effector cells with specialized functions is not known. In this review, we will focus on (1) the long distance interaction between the sites of allergic inflammation and the site of hematopoiesis in the

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bone marrow, (2) the differentiation of allergic progenitors, and (3) the molecular mechanisms by which allergic progenitors acquire the capacity to produce type-2 cytokines.

Long distance interaction between the sites of allergic inflammation and the site of hematopoiesis

The bone marrow is an organ where hematopoietic stem cells and progenitors self-renew and differentiate. It also provides an environment for interaction between T cells and hematopoietic cells. Hematopoietic stem cells respond directly and immediately to infections and inflammatory signals [1]. For example, the number of hematopoietic stem cells increases in response to *Escherichia coli* infection in the lung [2, 3]. An accumulation of evidence supports a long distance interaction between the sites of allergic inflammation and the site of hematopoiesis. Denburg et al. [4] reported increased numbers of circulating basophil and eosinophil progenitors in atopic asthmatic patients. O'Byrne et al. further demonstrated that allergen challenge of the lungs of asthmatic patients resulted in increased expression of the IL-5 receptor in $CD34^+$ progenitors that resided in the bone marrow [5, 6], indicating that eosinophil progenitors found in bone marrow can sense the changes that occur in the lung. More recently, $CD34^+$ progenitors have been shown to be potent effector cells in the airway of asthmatic patients [7]. Studies from the Lambrecht group showed that increased numbers of dendritic cell progenitors were found in the bone marrow of allergen-sensitized and challenged rats [8]. Together, these studies demonstrate that progenitor cells that reside in the bone marrow can sense signals generated in the lungs of allergic subjects. Because mature basophils and eosinophils lose or have a limited capacity to proliferate, recruitment of allergic bone marrow progenitors can be an effective way to expand the number of allergic effector cells rapidly. It is still not clear, however, whether allergic inflammation in the lung would lead to the formation of a favorable local lung environment for the recruited allergic progenitors to proliferate.

The exact mechanisms by which allergic progenitors sense signals from the lung remain to be elucidated. Memory Th2 cells have been shown to enter the blood stream and reside in the bone marrow [9-11]. It is reasonable to speculate that allergic-specific memory $CD4^+$ T cells can reside in the bone marrow. Allergen or dendritic cells with processed allergen can enter the blood stream and stimulate and activate allergic memory $CD4^+$ T cells in the bone marrow. The activated $CD4^+$ T cells can produce IL-3 and IL-5, which then stimulate allergic progenitors. These activated allergic progenitors enter the blood stream to find the distal sites of allergic inflammation. It is also possible that circulating Th2 cytokines can enter the bone marrow to exert their biological activities directly on various hematopoietic progenitors. However, because cytokines turnover rapidly, this latter route of communication is less likely.

The characteristics of innate type-2 progenitors

Basophils and mast cells share many common characteristics with mast cells—such as the expression of a high affinity immunoglobulin (IgE) receptor (FceRI)—and basophils contain many of the same granules found in mast cells [12, 13]. But basophils are unique in tissue distribution and lifespan. Basophils become circulating cells after maturation in the bone marrow, whereas mast cell precursors leave the bone marrow before undergoing maturation in connective tissue and submucosal areas. Basophils exist for approximately 72 h, while mast cells can survive for 3 months. Functionally, basophils have been shown to play non-redundant roles in IgE-mediated chronic allergic inflammation. It remains controversial whether basophils play regulatory roles beyond their roles in allergic inflammation. Medzhitov et al. reported that upon protease allergen sensitization, basophils are activated and recruited into draining lymph nodes where they direct Th2 effector cell differentiation

[14]. More recently, Medzhitov's group, along with two other groups, demonstrated that basophils promote Th2 effector cell differentiation through the function of antigen presenting cells [15-17]; they found that treatment with papain, an occupational allergen, resulted in the upregulation of class II expression. However, by using mice that are deficient in basophils, three other groups do not support the conjecture that basophils are essential in initiating Th2 immune responses [18-20]. The newer approach confirms the role of basophils in mediating IgE-mediated chronic allergic inflammation. Mast cells are essential in IgE-mediated anaphylaxis, food allergies, and certain models of airway hypersensitivity [18-20].

The origin of and developmental relationships between basophils and mast cells have been a long-standing, unsolved issue in hematology. By using colony formation assays, several groups have claimed that basophils develop from a common basophil and eosinophil progenitor [21, 22]. Using multicolor cell sorting, Akashi et al. prospectively isolated a population of spleen cells (defined as $Lin^{-}c\text{-}kit^{+}\beta7^{hi}Fc\gamma RII/III^{hi}$ cells) that can give rise to both basophils and mast cells [23]. However, whether or not the spleen basophil and mast cell common progenitors are truly bi-potential has been challenged by a recent report [24]. Akashi et al. also demonstrated that eosinophil lineage-restricted progenitors were enriched in a population of bone marrow cells defined as Lin^{-} $Sca\text{-}1^{-}CD34^{+}c\text{-}kit^{lo}IL\text{-}5R\alpha^{+}$ cells [25]. There is no evidence to support that enriched basophil-mast cell progenitors can give rise to eosinophils or enriched eosinophil progenitors can give rise to basophils.

Molecular mechanisms by which innate type-2 effector cells acquire the capacity to produce type-2 cytokines

Despite the remarkable progress made in understanding transcription factors and repressors that regulate the *Il4* gene in Th2 cells, little is known about which transcription factors and repressors regulate the *Il4* gene in eosinophils and basophils. Here, we review and discuss how Th2 cytokines promote the development of Th2 cytokine-producing capacity in eosinophils and basophils.

Regulation of Th2 cytokine gene expression in Th2 cells and mast cells

In the past decade, we have learned a great deal about how $CD4^{+}$ Th2 cells regulate their *Il4* gene transcription. Both transcription factors and transcription repressors play critical roles in regulating the *Il4* gene. The activation of STAT6 by IL-4 upregulates GATA3, c-Maf, and Jun B expression as naive $CD4^{+}$ T cells differentiate into Th2 cells [26-28]. The upregulated GATA3, c-Maf, and Jun B, together with NFAT and AP-1, are essential for Th2 cells to transcribe the *Il4* gene. Recently, an IL-4-independent transcriptional pathway triggered by Notch ligand and Jegged1 has been described. Interaction of Jegged1 with Notch activates RBPJκ and directly upregulates GATA3 expression [29, 30]. Equally important, for *Il4* gene transcription to occur, $CD4^{+}$ T cells must also suppress transcription repressors, such as T-bet and RUNX3 [31-33]. IL-4, the key Th2-priming factor, has been shown to be a potent factor in suppressing T-bet and Runx3 expression [31, 33]. Remarkably, mast cells use the same transcription factors and regulatory regions as Th2 cells with one exception: mast cells do not use CNS1 [34]. $CNS1^{-/-}$ bone marrow-derived mast cells do not show any impairment in IL-4 or IL-13 production [35].

Regulation of Th2 cytokine gene expression in basophils

Virtually, the transcription factors and regulatory regions that confer basophil-specific IL-4 expression are not known. Using the transgenic approach, Kubo et al. tested the regulatory regions known to regulate *Il4* gene expression in Th2 cells and demonstrated that a 4-kb-long HS4 element together with a 5′ enhancer [− 863 to −5,448 base pair (bp)] and the *Il4*

promoter (−64 to −827 bp) conferred basophil-specific GFP expression [36]. Paradoxically, this study, which shows that HS4—a recognized silencer of *Il4* gene transcription in Th2 cells [37]—is an enhancer for *Il4* gene transcription in basophils, also reveals that basophils might use a different set of regulatory regions to confer basophilspecific *Il4* gene expression [36], implying that basophils might also use a different set of transcription factors.

Using a candidate gene approach, we analyzed mRNA expression of known Th2 transcription factors and transcription factors that are pivotal for basophil development, such as GATA3, RBPJκ, c-Maf, JunB, C/EBPα, GATA1, and GATA2. The major myeloid transcription factor, C/EBPα was highly expressed in basophils, not in Th2 cells [38]. Our results showed that C/EBPα selectively activated *Il4* promoter-luciferase reporter gene transcription in response to IgE cross-linking, but C/EBPα did not activate other known Th2 or mast cell enhancers. Our mutation analyses revealed that C/EBPα drove *Il4* promoter-luciferase activity depending on its DNA binding domain, and two C/EBPα binding sites (−44 to −36, and −87 to −79) in the *Il4* promoter. PI3K pathway and calcineurin were essential in C/EBPα-driven *Il4* promoter-luciferase gene transcription. Our results further showed that a mutation in nuclear factor of activated T cells (NFAT)-binding sites in the *Il4* promoter also negated C/EBPα-driven *Il4* promoter-luciferase activity. Our study demonstrates that C/EBPα, in cooperation with NFAT, directly regulates *Il4* gene transcription [38].

IL-3 is a cytokine produced primarily by $CD4^+$ T cells [39-41] and has been shown to expand basophils. In vitro, IL-3 has been demonstrated to induce basophil differentiation and to enhance acute IL-4 production in mouse basophils [42, 43]. It has been reported that mice lacking IL-3 fail to show increased numbers of basophils and ultimately fail to expel the nematode *Stronglyoides* [44]. However, mechanisms underlying basophil expansion remain unclear. Mature basophils have a short half-life and respond to IL-3 stimulation with a limited proliferation capacity [40, 45]. Thus, it is likely that IL-3 induces basophil expansion by enhancing basophil lineage commitment. We demonstrate that the injection of IL-3 greatly increased the number of basophil lineage-restricted progenitors (BaPs) and the number of basophil/mast cell progenitors (BMCPs) in the spleen measured directly ex vivo. We found that granulocyte–macrophage progenitors, but not common myeloid progenitors, expressed low levels of IL-3 receptor. IL-3 receptor expression was dramatically upregulated in BaPs, but not in eosinophil lineage-restricted progenitors. We showed that about 38 % of BMCPs expressed the IL-3 receptor. The IL-3 receptor expression patterns might explain why IL-3 specifically expanded basophils in vivo [46]. We demonstrated that signal transducer and activator of transcription 5 (STAT5) signaling is required for IL-3-driven basophil expansion. We also found that in vivo administration of IL-3 can enhance the Th2-cytokine-producing capacity of basophils (unpublished data).

Regulation of Th2 cytokine gene expression in eosinophils

Eosinophils are known to produce Th2 cytokines when they are activated by inflammatory conditions and ligation of receptors to cytokines and immunoglobulin [47]. Our studies demonstrated that IL-4 and IL-5, but not IL-13 or IL-25, drive allergic progenitors to differentiate into effector cells that produce Th2 cytokines [48]. We further demonstrated that IL-5 primarily drives bone marrow progenitor cells to differentiate into Th2 cytokine-producing eosinophils dependent upon STAT5 [48]. In addition to STAT5, we found that Erk1 and the transcription factor GATA1 are critical in regulating *Il4* gene expression in eosinophils (unpublished data).

Regulation of Th2 cytokine gene expression in innate helper type-2 cells

Recently, a novel type of innate cells that can produce a large amount of IL-13 in response to IL-25, IL-33, and parasitic infection has been identified [49, 50]. This type of innate IL-13-producing cells has been named nuocytes, natural helper, and innate helper type-2 (ih2) [51]. They can be identified by flow cytometry as Lin-Sca-1$^+$, c-Kit$^+$, $^{-\text{ or lo}}$, ST2$^+$, IL-7R$^+$, IL17BR$^+$, CD25$^+$, CD44$^+$ [49, 50, 52]. These cells fail to develop in the absence of common-γ chain [49-51], which is shared by IL-2 and IL-7 receptor. Since the initial discovery, ih2 cells have been found to be critical in mediating the virus-induced airway hypersensitivity [53], in allergen-induced airway inflammation [54, 55]. However, it has not been defined that bone marrow progenitors give rise to ih2 cells. Furthermore, it remains to be determined the mechanisms by which ih2 acquire the capacity to express IL-13.

Concluding remarks

Th2 cells, once differentiated in the draining lymph nodes, can migrate into sites of inflammation where they exert a broad influence on many cell types. Th2 cells can provide signals to distal bone marrow progenitor cells; Th2 cells can orchestrate type-2 inflammation by recruiting various types of type-2 innate effectors to the sites of inflammation. Injured epithelial cells at the site of inflammation can release TSLP, IL-25, and IL-33, which activate innate lymphoid cells. Together, Th2 cells and innate type-2 effector cells form a powerful positive feedback loop, leading to an exacerbated type-2 inflammation. A greater understanding of how Th2 cells signal innate type-2 progenitors in the bone marrow, how innate type-2 progenitors differentiate into various type-2 innate effectors, how TSLP, IL-25, and IL-33 productions by epithelial cells are regulated at molecular levels, and how innate type-2 effectors transcribe their Th2 cytokine genes will lead to more effective interventions and more successful strategies in developing preventions.

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