Published in final edited form as:

Trends Immunol. 2010 January ; 31(1): 39–44. doi:10.1016/j.it.2009.10.001.

Eosinophils and allergic airway disease: there is more to the story

Elizabeth R. Walsh^{1,2} and Avery August^{1,3}

¹ Center for Molecular Immunology & Infectious Disease and Department of Veterinary & Biomedical Sciences, The Pennsylvania State University, University Park, PA 16802

² Pathobiology Graduate Program, The Pennsylvania State University, University Park, PA 16802

Abstract

The eosinophil has been perceived as a terminal effector cell in allergic airway diseases. However, recent work has shown that this multifunctional cell could be more involved in the initial stages of allergic disease development than was previously thought, particularly with regard to the ability of the eosinophil to modulate T-cell responses. In this review, we discuss recent advances that suggest that eosinophils can present antigen to naïve as well as to antigen experienced T cells, induce T helper 2 cell development, cytokine production or both, and affect T-cell migration to sites of inflammation. These findings are changing the way that eosinophil function in disease is perceived, and represent a shift in the dogma of allergic disease development.

Eosinophil interactions in allergic disease

Eosinophils have long been regarded as one of the most puzzling and enigmatic cells in the immune system with regard to their function in disease. This long-standing controversy is likely to continue for some time; however, the advent of eosinophil-deficient mouse models has provided the tools to start dissecting the vagaries of this complex cell. New, potentially paradigm-shifting findings have been reported, many focused on the relationship between eosinophils and T cells in allergic airway diseases. The requirements for these two types of cell in the development of allergic asthma have been studied and discussed extensively, but many aspects, including how they potentially influence each other in the pathogenesis of this disease, remain ambiguous. In this review, we provide an update on the relationship between eosinophils and T cells and discuss how they provide new insight into the ways in which they interact in allergic airway disease (Figure 1).

Th2 cells and allergic inflammation

T cells are one of the main purveyors of disease in allergic asthma, and mice deficient in T cells, and more specifically CD4⁺ T cells, have been shown to be defective in their ability to develop allergic responses, highlighting the importance of these cells in allergic disease [1–3]. Upon activation by interactions with antigen-presenting cells (APCs) in an antigen draining lymph node, naïve CD4⁺ T cells can differentiate into either Th1 cells that produce interferon- γ (IFN- γ) and IL-2, Th17 cells that produce IL-17, or in the case of allergic asthma, Th2 cells that secrete IL-4, IL-5 and IL-13 (although there may be some plasticity in these responses [4]). T cell secretion of IL-4 can induce B cell class switch to IgE, the primary antibody involved

³Corresponding author: Avery August (avery@psu.edu).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

in exacerbating allergic diseases, and can also induce goblet cell metaplasia and mucus hypersecretion in prolonged cases of allergic asthma [5,6]. IL-5 production leads to the development of eosinophils from the bone marrow, and their activation and survival [7,8]. T cells are also largely responsible for IL-13 production (although not solely, since eosinophils can also secrete this cytokine) and in the absence of this cytokine many studies indicate that allergic asthma cannot develop [9]. IL-13 can upregulate chemokines important for immune cell infiltration into the lung tissue, such as CCL11, CCL24, CCL17, and CCL22 (reviewed in [6]). While dendritic cells have traditionally been thought of as the professional APC for T cell responses, there is now significant evidence that eosinophils can function in this capacity as well during Th2 responses.

Eosinophils and antigen presentation

One perspective that has been gathering momentum in recent studies of mouse models of allergic inflammation is that eosinophils play a larger role in the development of allergic disease than has been suggested previously. Surprisingly, many of these studies indicate that the actions of eosinophils propel T-cell responses rather than being solely driven by them. It is becoming increasingly recognized that after airway exposure to allergen, eosinophils can upregulate major histocompatibility complex (MHC) class II molecules and the co-stimulatory molecules CD40, CD80, and CD86 [10]. Eosinophils process antigen and migrate to lymph nodes that drain the lungs, where they present antigenic peptides to T cells, and are thus able to present antigen in Th2 responses [11–16]. Indeed a comparison of eosinophil exposure to ammonium chloride or to hypotonic saline during lysis of erythrocytes demonstrated that ammonium chloride-exposed eosinophils failed to function optimally as antigen-presenting cells [14,16]. On the other hand, eosinophils not exposed to ammonium chloride were fully functional as “professional” antigen-presenting cells in activating antigen naïve T cells, thus confirming the obligate lysosomal processing of antigen within eosinophils [16,17]. In addition, in a model of threadworm infection, eosinophils were able to present *Strongyloides stercoralis* antigens and induce Th2 differentiation of naïve T cells while MHC class II null eosinophils were unable to do so [15]. These results provide evidence that contests the argument made in an earlier study showing that eosinophils play no role in antigen presentation and activation of naïve T cells in the draining lymph nodes, despite eosinophils trafficking there during an allergic response in the lung [14]. Taken together, these findings indicate that the ability of eosinophils to process and present antigens has been generally underestimated and that this function can be added to the ever-growing list of mechanisms by which eosinophils regulate the immune system.

Eosinophils in Th2 responses and allergic inflammation in the lung

In humans with asthma as well as in animal models of allergic asthma, eosinophilia of the lung and airways has been observed together with other symptoms, and has been regarded as a cardinal feature of the asthmatic response. Eosinophils develop from CD34⁺ progenitors in the bone marrow under the impetus of IL-5 that can be produced by a number of cell types, including CD4⁺ Th2 cells, basophils, mast cells, and CD8⁺ T cells [7,18–21]. They then migrate into the bloodstream, circulate through the lymphoid tissue and commonly home to the gut and uterus, although they can be found to circulate through the lung in low numbers as well [22, 23]. During an allergic asthma response, significantly more eosinophils are recruited to the lung by chemokines, including chemokine ligand 11 (CCL11) (also known as eotaxin-1) and CCL24 (also known as eotaxin-2), that are produced by the airway epithelium, as well as by cytokines such as IL-13 [24,25]. Once in the lung, eosinophils can perform and participate in a variety of functions including: antigen presentation, cytokine production, chemokine production, secretion of granule mediators, and leukotriene secretion [10,22]. Indeed, eosinophils in some cases have preformed stores of a number of cytokines that allow them to

be rapidly released without *de novo* protein synthesis (e.g. see [10,22,26]. They can also produce their own unique products (e.g. eosinophil peroxidase [EPO]) [22]. Mouse models lacking eosinophils have been recently used in allergic airway inflammation experiments in an attempt to better understand the role of these cells in this disease.

Classically, eosinophils have been considered to be terminal effector cells in allergic diseases and to be mobilized *en masse* by IL-5 produced by T cells to sites of inflammation, where they can produce products such as cytokines (IL-4, IL-13), chemokines (CCL11, CCL22) and leukotrienes (LTC₄, LTB₄) [27–29]. However, early evidence implicated these cells in the regulation of Th2 cytokines in the lung, mucous production and airways hyperresponsiveness. As reported by Lee and colleagues, intratracheal transfer of eosinophils into IL-5 null mice (which have significantly reduced numbers of eosinophils) exposed to antigen resulted in restoration of Th2 cytokines, mucous production and airways hyperresponsiveness, the latter of which were dependent on CD4⁺ T cells, strongly implicating eosinophils in the elevated levels of Th2 cytokines and allergic inflammation in this model [30]. However, this evidence has been considerably strengthened, suggesting that eosinophils play a more central role in Th2 responses (Table 1). In experiments performed using mice specifically lacking eosinophils (C57Bl/6 Tg^{PHIL}), one group found defects in the development of airway inflammation and airway hyperresponsiveness, indicating that these cells might be more integral to the development of allergic asthma [31]. Yet a second group in parallel studies using Balb/c ΔdblGATA mice (also lacking eosinophils), found that eosinophils were not required for the development of allergic inflammation and airway hyper-responsiveness, but rather were required for long-term remodeling in a chronic model of allergic airway inflammation [32]. Both groups used the classical model of ovalbumin (OVA) sensitization to induce allergic airway inflammation, while a long-term chronic model was also performed on the Balb/c ΔdblGATA mice. Closer analyses of these strains and other eosinophil-deficient mice have revealed defects in different aspects of generation of Th2-type responses (Table 1, Box 1). Further studies using the Balb/c ΔdblGATA mice in an model of allergic airway inflammation induced by the fungus *Aspergillus fumigatus* showed that there is a significant reduction in bronchoalveolar lavage (BAL) levels of Th2 cytokines IL-4 and IL-13, as well as mucus hypersecretion in the lungs of these mice, although these mice could generate IgE responses, suggesting intact systemic Th2 responses [33].

Box 1

Strain-specific requirements for eosinophils in ΔdblGATA mice

As with other murine models of human disease, there are strain-specific variations in models of allergic asthma. For example, spontaneous development of airway inflammation occurs in T-bet deficient mice on the C57Bl/6 background, but not on the Balb/c background [54,55]. Eosinophil deficient strains have proven to be no exception to the rule (see Table 1). Humbles et al showed that on the Balb/c background that eosinophils are not required for the development of allergic asthma, although eosinophils were found to be necessary for airway remodeling [32]. In contrast, using the same genetically modified mice, or other approaches to remove eosinophils on the C57Bl/6 background, these cells have been shown to be important for recruitment of T cells to the lung as well as subsequent cytokine production therein, leading to the development of allergic asthma [42,43].

There are many potential reasons for this strain-specific difference. Balb/c mice might have a greater predisposition for the development of allergic asthma by differential expression of genes that regulate this disease, either through genetic polymorphisms or as yet unidentified regulatory elements. In humans, single nucleotide polymorphisms (SNPs) in IL-13 as well as IL-4 have been identified that are associated with a higher prevalence of asthma (e.g. [56]). Indeed, similar types of polymorphisms have been found in strains of

mice that are highly predisposed to developing airway hyperresponsiveness (e.g. complement factor C5 [57]). Downstream, the effects of changes in genes or gene expression levels might result in Balb/c mice having higher basal levels of circulating Th2 cytokines compared to C57Bl/6 mice as well as higher levels of IgE antibodies, priming the immune system for Th2 asthmatic responses and decreasing the threshold necessary to initiate an allergic response. Alternatively, these mice might be more sensitive to the effects of these cytokines. To determine the explanation for differing requirements for eosinophils in allergic responses between these two strains in-depth genetic mapping would have to be conducted. It is also possible that the difference in eosinophil dependence for disease development between the two strains results from epistatic gene effects (i.e. dominance of one gene over another), in which case pinpointing the causative genes will become even more difficult. Regardless, performing duplicate experiments in more than one strain of mouse may give us information that better reflects what we can expect to see in diverse human populations.

The different backgrounds (C57Bl/6 vs. Balb/c) used in these mouse models of allergic asthma could contribute to the observed differences in the development of characteristics of allergic disease. Indeed, discrepancies between mouse models and strains in the generation of allergic disease have been reported. For instance, on the C57Bl/6 background (which have markedly reduced numbers of eosinophils), many of the symptoms of allergic airway disease in an OVA-induced model in IL-5 null mice are abolished, whereas blockade of IL-5 in Balb/c mice does not appear to have a significant effect on the disease, indicating that this cytokine might not be crucial in this strain [34,35]. However, in related experiments using Balb/c IL-5/Eotaxin-1 double-deficient mice (which have significantly reduced eosinophils), it was found that Th2 cells lacked the ability to produce IL-13 when rechallenged *in vitro* with antigen [36]. This suggests that eosinophils may be important for the generation of localized Th2 responses. It is possible that eosinophils are either stimulated through IL-5 or Eotaxin-1 to produce a factor which then stimulates local T cell cytokine production, or perhaps that these factors act directly on T cells to promote cytokine secretion.

Other published evidence demonstrates a role for eosinophils in the development of allergic inflammation. Less conclusive but nonetheless intriguing, mice deficient in βc IL-3R, the common β receptor for IL-3, IL-5 and granulocyte-macrophage-colony-stimulating factor (GM-CSF) which is required for development of eosinophils, basophils and mast cells, exhibit a reduction in airway hyperresponsiveness (AHR) and fail to develop OVA-specific IgE responses. In addition, T cells from these mice produce lower amounts of the Th2-type cytokines IL-4, IL-5, and IL-13, along with a reduction in proliferation upon antigen restimulation *ex vivo*, suggesting a defect in T cell activation [37]. T cells from the peribronchial lymph nodes of allergic $\beta c^{-/-}$ mice were also attenuated in their ability to migrate to the lung upon allergic provocation [37]. The caveat in these experiments is that the lack of T cell function cannot definitively be attributed to the absence of signal-competent granulocytes since βc signaling is also important in myeloid dendritic cell development. In addition, basophils have also recently been reported to be important for the development of memory and Th2 responses [38–41]. Thus, direct and indirect evidence suggest that eosinophils might regulate the generation of Th2 cytokines during allergic responses in the lung, and that they play a greater role in this process than was previously suspected.

Eosinophils in the regulation of T-cell migration to the lung

Results of two more recent studies support the idea that eosinophils might play a regulatory role in the generation of allergic responses in the lung (Table 1). In one set of studies, Lee and colleagues, demonstrated that C57Bl/6 TgPHIL eosinophil null mice exhibit reduced T cell

recruitment and Th2 cytokine production in the lung in an OVA model of allergic airway inflammation [42]. In addition, migration of Th2 differentiated OT-II OVA specific T cells (delivered intravenously into the C57Bl/6 Tg*PHIL*), required eosinophils (instilled intratracheally) [42]. Similar studies using Δ dblGATA mice on the C57Bl/6 background showed that eosinophils are required for the development of allergic airway responses and recruitment of T cells to the lung [43]. This was in contrast to the Δ dblGATA mice on a Balb/c background, where neither AHR nor recruitment of T cells to lungs were significantly impaired [32,43]. In the C57BL/6 models, eosinophils do not seem to be required to initiate the immune response since transfer of eosinophils into mice one day prior to lung antigen exposure was able to rescue the defects in T cell recruitment to the lung, Th2 cytokine production and airway hyperresponsiveness showing that eosinophils are required for these functions (Table 1).

These two reports support the view that that eosinophils are required to provide a signal or interact with T cells in order to promote Th2 responses and migration into the lung. The particular signal required for these responses remains to be determined. Both groups suggest a role for chemokine dependent migration in their analyses, however; the particular chemokine required differs somewhat between the two reports. In experiments performed on the Tg*PHIL* mice, CCL22 and CCL17 were significantly reduced (but not CCL11 and 24), and neutralizing antibodies to these chemokines could prevent T cell recruitment to the lung. In addition, transfer of eosinophils and OT-II T cells recovered the levels of CCL22 and CCL17 in these mice [42]. In experiments using the Δ dblGATA C57Bl/6 however, CCL11, CCL17 and CCL24 were reduced, and delivery of CCL11 to the lung in combination with OVA was sufficient to rescue T cell influx and Th2 cytokine production [43]. However CCL22 was not statistically reduced compared to wild type levels in the allergic lung [43]. The CCL11-CCR3 axis can contribute to the recruitment of Th2 cells to the lung during allergic airway inflammation, dependent on the timing of the response [44]. In addition, this chemokine can induce migration of Th2 cells toward a source of this chemokine, including in the lung [43, 44]. However, the majority of allergic asthma studies (including those using a “humanized” mouse model) show that CCR4 (via CCL17 and CCL22) is largely responsible for recruiting Th2 cells to the lung during allergic airway inflammation, and these chemokines are clearly critical for this response [44,45].

The reason for the discrepancy in observed production of CCL11, 22 and 24 expression in these two model systems is unclear, and while minor, could be due to several factors. While the Δ dblGATA mice lack mature eosinophils and there is a cell intrinsic defect in their development *in vivo* [46], eosinophils can apparently be generated from bone marrow from these mice cultured *ex vivo* in the presence of IL-3, IL-5, and GM-CSF [47]. As such, other defects in these Δ dblGATA mice (which may be affected by strain background) cannot be ruled out at this time. By contrast, the Tg*PHIL* mice completely lack eosinophils due to the eosinophil peroxidase promoter driven expression of diphtheria toxin A, which specifically ablates eosinophils while other lineages are still able to develop [31]. There is a non-specific but statistically significant increase in the white blood cell compartment in the blood of the Tg*PHIL* mice [31], and while T cells derived from these mice are able to produce cytokines in response to nonspecific CD3/CD28 stimulation *ex vivo*, Th2 responses in these mice are impaired in the allergic asthma model, and it is not clear if they are able to develop such responses *in vivo* [42]. While there is some question regarding the consequences of expressing diphtheria toxin in mice (e.g. potentially low level leakiness and/or expression in other tissues, see for example the case of Foxp3 [48] and discussed for CD11c⁺ dendritic cell model in reference [49]), other cell types have been efficiently ablated using this approach with little apparent side effects (including dendritic cells and neurons [50,51]). Thus, both model systems have potential caveats, but the effect of eosinophil deletion on the induction of allergic airway

responses in two independently derived C56Bl/6 eosinophil deficient mouse strains suggest that these cells are important in the recruitment of T cells to the lung.

Concluding remarks

Evidence that eosinophils play a larger part in allergic responses than was previously thought has been rapidly accumulating with the advent of transgenic or gene deficient eosinophil models. New studies have now shown that these cells have not been getting the credit they deserve, and their role could potentially be multifunctional in influencing T cells in the development of allergic airway disease. It should come as no surprise that these versatile cells can be involved in induction of immune responses as well as acting as terminal effector cells. Their ability to store pre-formed cytokines, and to secrete virtually any cytokine or chemokine, as well as present antigen and produce effector molecule containing granules, makes them a formidable weapon in pathogen defense and a frustrating adversary in allergic disease. Future work on the specific effectors used by these cells in allergic airway disease will allow clarification of their functions, as well as change the way we look at how allergic airway responses are driven, and will likely show that eosinophils are a significant driving force in immune responses (see Box 2).

Box 2

What eosinophil functions are important in the development of allergic asthma?

Whether eosinophils are required for the development of allergic asthma has been so controversial that most researchers have glossed over what eosinophil functions might be important in this disease. The multi-functional nature of these cells makes it difficult to home in on any one essential activity, and it is likely that eosinophils have multiple roles in the generation of allergic asthma. Eosinophils are present in the thymus during T cell development and selection [52,53], and it is possible that they present selecting ligands during T cell maturation that could predispose certain individuals to developing allergic asthma later in life. Antigen presentation by eosinophils could potentially play a role at disease onset as well, presenting peptides from benign environmental proteins to T cells to induce activation and proliferation and/or cytokine production.

Secretion of specific cytokines or chemokines by eosinophils could also have direct and indirect effects on the development of allergic asthma. Eosinophils store preformed cytokines in granules that can be rapidly released upon antigenic provocation [22]. These cytokines can be Th2 cytokines such as IL-4 and IL-13 that act directly on T cells, as well as other inflammatory cytokines that can prime antigen presenting cells and the vascular endothelium to secrete chemokines and cytokines that recruit and activate T cells. Eosinophils can also secrete granule mediators and leukotrienes that are capable of changing the environmental milieu to an inflammatory phenotype [22]. Finally, eosinophils express pattern recognition receptors such as Toll like receptors, as well as Fc receptors that can sense and enrich for antigens to potentially be presented [22].

Acknowledgments

We thank the members of the August lab, and the Center for Molecular Immunology & Infectious Disease at Penn State for their helpful comments. Supported by NIH grants AI51626, AI065566 & AI073955 to AA. EW is the recipient of a Penn State College of Agricultural Sciences Graduate Fellowship and a NASA Space Grant Fellowship. We apologize to those workers in the field whom we could not directly reference their work due to space limitations.

References

1. Corry D, et al. Requirements for allergen-induced airway hyperreactivity in T and B cell-deficient mice. *Molecular Medicine* 1998;4 (5):344–355. [PubMed: 9642684]
2. Hogan SP, et al. A Novel T Cell-Regulated Mechanism Modulating Allergen-Induced Airways Hyperreactivity in BALB/c Mice Independently of IL-4 and IL-5. *J Immunol* 1998;161 (3):1501–1509. [PubMed: 9686617]
3. Hogan S, et al. Interleukin-5-producing CD4+ T cells play a pivotal role in aeroallergen-induced eosinophilia, bronchial hyperreactivity, and lung damage in mice. *Am J Respir Crit Care Med* 1998;157:210–218. [PubMed: 9445302]
4. Locksley R. Nine lives: plasticity among T helper cell subsets. *J Exp Med* 2009;206:1643–1646. [PubMed: 19635860]
5. Snapper CM, et al. IgE class switching is critically dependent upon the nature of the B cell activator, in addition to the presence of IL-4. *J Immunol* 1991;147 (4):1163–1170. [PubMed: 1714474]
6. Kuperman D, Schleimer R. Interleukin-4, interleukin-13, signal transducer and activator of transcription factor 6, and allergic asthma. *Curr Mol Med* 2008;8:384–392. [PubMed: 18691065]
7. Campbell H, et al. Molecular cloning, nucleotide sequence, and expression of the gene encoding human eosinophil differentiation factor (interleukin 5). *Proc Natl Acad Sci U S A* 1987;84:6629–6633. [PubMed: 3498940]
8. Takatsu K, Nakajima H. IL-5 and eosinophilia. *Curr Opin Immunol* 2008;20:288–294. [PubMed: 18511250]
9. Wills-Karp M. Interleukin-13 in asthma pathogenesis. *Immunol Rev* 2004;202:175–190. [PubMed: 15546393]
10. Akuthota P, et al. Immunoregulatory roles of eosinophils: a new look at a familiar cell. *Clinical & Experimental Allergy* 2008;38 (8):1254–1263. [PubMed: 18727793]
11. MacKenzie J, et al. Eosinophils promote allergic disease of the lung by regulating CD4(+) Th2 lymphocyte function. *J Immunol* 2001;167:3146–3155. [PubMed: 11544300]
12. Shi H, et al. Lymph node trafficking and antigen presentation by endobronchial eosinophils. *Journal of Clinical Investigation* 2000;105 (7):945–953. [PubMed: 10749574]
13. Lucey D, et al. Mature human eosinophils have the capacity to express HLA-DR. *Proc Natl Acad Sci* 1989;86:1348–1351. [PubMed: 2919183]
14. van Rijt L, et al. Airway Eosinophils Accumulate in the Mediastinal Lymph Nodes but Lack Antigen-Presenting Potential for Naive T Cells. *J Immunol* 2003;171 (7):3372–3378. [PubMed: 14500630]
15. Padigel U, et al. Eosinophils act as antigen-presenting cells to induce immunity to *Strongyloides stercoralis* in mice. *J Infect Dis* 2007;196:1844–1851. [PubMed: 18190266]
16. Wang HB, et al. Airway Eosinophils: Allergic Inflammation Recruited Professional Antigen-Presenting Cells. *The Journal of Immunology* 2007;179:7585–7592. [PubMed: 18025204]
17. Ziegler H, Unanue E. Decrease in macrophage antigen catabolism caused by ammonia and chloroquine is associated with inhibition of antigen presentation to T cells. *Proceedings of the National Academy of Sciences of the United States of America* 1982;79 (1):175–178. [PubMed: 6798568]
18. Ohnmacht C, Voehringer D. Basophil effector function and homeostasis during helminth infection. *Blood* 2009;113:2816–2825. [PubMed: 18941115]
19. Hamelmann E, et al. Requirement for CD8+ T cells in the development of airway hyperresponsiveness in a murine model of airway sensitization. *J Exp Med* 1996;183:1719–1729. [PubMed: 8666929]
20. Rådinger M, et al. Regulation of allergen-induced bone marrow eosinophilopoiesis: role of CD4+ and CD8+ T cells. *Allergy* 2007;62:1410–1418. [PubMed: 17983375]
21. Rådinger M, et al. Regulatory role of CD8+ T lymphocytes in bone marrow eosinophilopoiesis. *Respir Res* 2006;7:83. [PubMed: 16740158]
22. Rothenberg M, Hogan S. The eosinophil. *Annu Rev Immunol* 2006;24:147–174. [PubMed: 16551246]

23. Ohnmacht C, et al. Analysis of Eosinophil Turnover In Vivo Reveals Their Active Recruitment to and Prolonged Survival in the Peritoneal Cavity. *J Immunol* 2007;179 (7):4766–4774. [PubMed: 17878375]
24. Zimmermann N, et al. Chemokines in asthma: Cooperative interaction between chemokines and IL-13. *Journal of Allergy and Clinical Immunology* 2003;111 (2):227–242. [PubMed: 12589338]
25. Horie S, et al. Interleukin-13 but not interleukin-4 prolongs eosinophil survival and induces eosinophil chemotaxis. *Internal Medicine* 1997;36 (3):179. [PubMed: 9144009]
26. Spencer L, et al. Human eosinophils constitutively express multiple Th1, Th2, and immunoregulatory cytokines that are secreted rapidly and differentially. *J Leukocyte Biol* 2009;85:117–123. [PubMed: 18840671]
27. Han S, et al. Interleukin (IL)-5 Downregulates Tumor Necrosis Factor (TNF)-Induced Eotaxin Messenger RNA (mRNA) Expression in Eosinophils: Induction of Eotaxin mRNA by TNF and IL-5 in Eosinophils. *Am J Respir Cell Mol Biol* 1999;21:303–310. [PubMed: 10460747]
28. Nakajima T, et al. Intracellular localization and release of eotaxin from normal eosinophils. *FEBS Lett* 1998;434:226–230. [PubMed: 9742928]
29. Hogan S, et al. Eosinophils: biological properties and role in health and disease. *Clin Exp Allergy* 2008;38:709–750. [PubMed: 18384431]
30. Shen H, et al. A causative relationship exists between eosinophils and the development of allergic pulmonary pathologies in the mouse. *J Immunol* 2003;170:3296–3305. [PubMed: 12626589]
31. Lee JJ, et al. Defining a Link with Asthma in Mice Congenitally Deficient in Eosinophils. *Science* 2004;305 (5691):1773–1776. [PubMed: 15375267]
32. Humbles AA, et al. A Critical Role for Eosinophils in Allergic Airways Remodeling. *Science* 2004;305 (5691):1776–1779. [PubMed: 15375268]
33. Fulkerson P, et al. A central regulatory role for eosinophils and the eotaxin/CCR3 axis in chronic experimental allergic airway inflammation. *Proceedings of the National Academy of Sciences USA* 2006;103 (44):16418–16423.
34. Foster P, et al. Interleukin 5 deficiency abolishes eosinophilia, airways hyperreactivity, and lung damage in a mouse asthma model. *J Exp Med* 1996;183(1):195–201. [PubMed: 8551223]
35. Corry D, et al. Interleukin 4, but not interleukin 5 or eosinophils, is required in a murine model of acute airway hyperreactivity. *J Exp Med* 1996;183:109–117. [published erratum appears in *J Exp Med* 1997 1185:1715]. [PubMed: 8551213]
36. Mattes J, et al. Intrinsic Defect in T Cell Production of Interleukin (IL)-13 in the Absence of Both IL-5 and Eotaxin Precludes the Development of Eosinophilia and Airways Hyperreactivity in Experimental Asthma. *J Exp Med* 2002;195:1433–1444. [PubMed: 12045241]
37. Asquith K, et al. The IL-3/IL-5/GM-CSF Common Receptor Plays a Pivotal Role in the Regulation of Th2 Immunity and Allergic Airway Inflammation. *J Immunol* 2008;180 (2):1199–1206. [PubMed: 18178860]
38. Denzel A, et al. Basophils enhance immunological memory responses. *Nat Immunol* 2008;9:733–742. [PubMed: 18516038]
39. Perrigoue J, et al. MHC class II-dependent basophil-CD4+ T cell interactions promote T(H)2 cytokine-dependent immunity. *Nat Immunol* 2009;10:697–705. [PubMed: 19465906]
40. Yoshimoto T, et al. Basophils contribute to TH2-IgE responses in vivo via IL-4 production and presentation of peptide-MHC class II complexes to CD4+ T cells. *Nat Immunol* 2009;10:706–712. [PubMed: 19465908]
41. Sokol C, et al. Basophils function as antigen-presenting cells for an allergen-induced T helper type 2 response. *Nat Immunol* 2009;10:713–720. [PubMed: 19465907]
42. Jacobsen EA, et al. Allergic pulmonary inflammation in mice is dependent on eosinophil-induced recruitment of effector T cells. *J Exp Med* 2008;205(3):699–710. [PubMed: 18316417]
43. Walsh E, et al. Strain-specific requirement for eosinophils in the recruitment of T cells to the lung during the development of allergic asthma. *J Exp Med* 2008;205(6):1285–1292. [PubMed: 18490489]
44. Lloyd C. CC chemokine receptor (CCR)3/eotaxin is followed by CCR4/monocyte-derived chemokine in mediating pulmonary T helper lymphocyte type 2 recruitment after serial antigen challenge in vivo. *J Exp Med* 2000;191:265–274. [PubMed: 10637271]

45. Perros F, et al. Blockade of CCR4 in a humanized model of asthma reveals a critical role for DC-derived CCL17 and CCL22 in attracting Th2 cells and inducing airway inflammation. *Allergy* 2009;64:995–1002. [PubMed: 19630858]
46. Yu C, et al. Targeted deletion of a high-affinity GATA-binding site in the GATA-1 promoter leads to selective loss of the eosinophil lineage in vivo. *J Exp Med* 2002;195:1387–1395. [PubMed: 12045237]
47. Dyer KD, et al. Eosinophils from Lineage-Ablated {Delta}dblGATA Bone Marrow Progenitors: The dblGATA Enhancer in the Promoter of GATA-1 Is Not Essential for Differentiation Ex Vivo. *J Immunol* 2007;179 (3):1693–1699. [PubMed: 17641035]
48. Chen G, et al. Cutting edge: Broad expression of the FoxP3 locus in epithelial cells: a caution against early interpretation of fatal inflammatory diseases following in vivo depletion of FoxP3-expressing cells. *J Immunol* 2008;180:5163–5166. [PubMed: 18390696]
49. Bennett C, Clausen B. DC ablation in mice: promises, pitfalls, and challenges. *Trends Immunol* 2007;28:525–531. [PubMed: 17964853]
50. Jung S, et al. In vivo depletion of CD11c+ dendritic cells abrogates priming of CD8+ T cells by exogenous cell-associated antigens. *Immunity* 2002;17:211–220. [PubMed: 12196292]
51. Lem J, et al. Tissue-specific and developmental regulation of rod opsin chimeric genes in transgenic mice. *Neuron* 1991;6:201–210. [PubMed: 1825171]
52. Müller E. Localization of eosinophils in the thymus by the peroxidase reaction. *Histochemistry* 1977;52:273–279. [PubMed: 885739]
53. Throsby M, et al. CD11c+ eosinophils in the murine thymus: developmental regulation and recruitment upon MHC class I-restricted thymocyte deletion. *J Immunol* 2000;165:1965–1975. [PubMed: 10925279]
54. Fujiwara M, et al. T-bet inhibits both TH2 cell-mediated eosinophil recruitment and TH17 cell-mediated neutrophil recruitment into the airways. *J Allergy Clin Immunol* 2007;662–670. [PubMed: 17336616]
55. Finotto S, et al. Development of spontaneous airway changes consistent with human asthma in mice lacking T-bet. *Science* 2002;295:336–338. [PubMed: 11786643]
56. Vercelli D. Advances in asthma and allergy genetics in 2007. *J Allergy Clin Immunol* 2008;122:267–271. [PubMed: 18619666]
57. Karp C, et al. Identification of complement factor 5 as a susceptibility locus for experimental allergic asthma. *Nat Immunol* 2000;1:221–226. [PubMed: 10973279]

Figure 1. Eosinophil functions in lung and draining lymph node during allergic airway inflammation

(1) Airway epithelial cells detect the presence of antigen and secrete chemotactic factors, which can recruit eosinophils to the lung. Alternatively, a small number of eosinophils circulating through the lungs may be affected by airway epithelial cells, or directly by allergen, and are induced to secrete Th2 attracting chemokines directly or indirectly. Secreted chemokines aid in the migration of T cells into the lung. (2) T cells can then secrete Th2-type cytokines such as IL-4, IL-5, and IL-13, which further enhance the recruitment of eosinophils. (3) Eosinophils can also secrete cytokines such as IL-4 and IL-13 that amplify or modulate Th2 responses in the lung. (4) Eosinophils endocytose antigen in the lung airway or tissue, migrate to the draining lymph node and, (5) present it in the context of MHC Class II to Th0 cells to induce proliferation/activation along with the generation of a Th2 milieu of IL-4 and IL-13. (6) Dendritic cells and basophils are also able to present antigen to drive the proliferation, activation and differentiation of T cells.

Table 1

Eosinophil deficient mouse strain-specific variation in development of allergic asthma symptoms

	Δ dblGATA/C57Bl/6	Δ dblGATA/Balb/c	C57Bl/6 Tg $PHIL$	Reference
Airway Inflammation (Acute OVA model)	–	+	–	[31] [42] [43]
Airway Inflammation (Chronic OVA model)	ND	+	ND	[32]
Airway Inflammation (<i>A. fumigatus</i> model)	ND	–*	ND	[33]
Airway hyperresponsiveness (AHR)	–	+	–	[31] [32,43]
Chemokine secretion	–	ND	–	[42] [43]
T cell recruitment to the lung	–	+	–	[42] [43]
Lung Th2 cytokines	–	+	–	[32] [42] [43]
Mucous secretion	–	+/-**	–	[33] [31] [32, 42] [43]
Increase in IgE	+	+	ND	[32,33,43]
AHR rescue with eosinophil add back	+	NA	ND	[43]
AHR rescue with chemokine add back	+	NA	ND	[43]
Long term airways remodeling	ND	–	ND	[32]

NA=Not Applicable; ND= Not Determined;

* reduction in leukocyte infiltration;

** mucous observed in OVA model, but reduced in *A. fumigatus* model.