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Eosinophil Progenitors in Airway Diseases*

Clinical Implications

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Asthma, allergic rhinitis, nasal polyposis, chronic rhinosinusitis, and related forms of upper and lower airway diseases are often characterized by eosinophilic and basophilic inflammation, involving systemic processes. Eosinophil/basophil (Eo/B) lineage-committed progenitor cells in cord blood, peripheral blood, bone marrow, lung tissue, and sputum are up-regulated in the above conditions, and respond to allergen and other stimuli with increased differentiative and migratory capacity. A considerable body of evidence now exists showing that activation of such Eo/B-selective hemopoietic processes is not only associated with the onset and maintenance of allergic inflammation in atopic adults, but also with the development of the allergic diathesis. Moreover, eosinophilopoietic processes within hemopoietic compartments and, importantly, at mucosal tissue sites during an allergic inflammatory response provide novel targets for the treatment of allergy as a systemic process and disease. (CHEST 2008; 134:1037–1043)

Key words: allergic rhinitis; asthma; basophils; eosinophils; hemopoiesis; nasal polyposis; progenitors

Abbreviations: BM = bone marrow; CS = corticosteroids; CysLT = cysteinyl leukotriene; CysLT1-R = cysteinyl leukotriene-1 receptor; ECP = eosinophilic cationic protein; Eo/B = eosinophil/basophil; Eo/B-CFU = eosinophil/basophil colony-forming unit; IL = interleukin; IL-5R α = interleukin-5 receptor α ; LTRA = leukotriene receptor antagonist; SDF = stromal cell-derived factor; Th2 = T-helper type 2

Atopic and atopy-related diseases such as asthma, allergic rhinitis, and atopic dermatitis have until now primarily been conceived as occurring in specific local tissues, for example the lung, nose, and skin, respectively. Recently, however, the notion of the systemic nature of allergy has been proposed, based on numerous clinical, neurophysiologic, and

epidemiologic findings. Although the exact nature of these relationships is still not fully understood, an important mechanism to consider is the active participation of the bone marrow (BM) and related systemic hemopoietic events in the development and maintenance of local tissue allergic inflammation.

In response to allergen provocation, a systemic response is activated in subjects with allergic diseases that involves the initiation of BM production of specific inflammatory cell (eosinophil/basophil [Eo/B]) progenitors, leading to early initiation of Eo/B differentiation and release of both progenitors and their progeny from the BM compartment; these cells are then typically recruited to the respiratory mucosa and other tissues in atopic individuals. Understanding the cellular and molecular signaling involved in these systemic responses, *ie*, between the tissue (especially the airways) and the BM, may open up new avenues of therapy for allergic inflammation, as well help in the optimization of dosage and routes of therapy.

This review will examine how the BM supplies hemopoietic progenitors to sites of allergic inflam-

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mation and what modulates these progenitors physiologically and, potentially, therapeutically. Evidence concerning the “systemic effects” of current and experimental allergy therapies will also be discussed.

HEMOPOIETIC PROCESSES IN ALLERGIC INFLAMMATION

In adults, hemopoietic stem-cell differentiation and maturation have traditionally been thought to be restricted to the BM microenvironment. However, a novel view has emerged in recent years according to which at least some hemopoietic (and nonhemopoietic) stem cells present in adult tissue may be recruited from the BM, through the peripheral circulation, into tissues, becoming part of a regenerative and/or inflammatory process at these “distal” sites. This process has been referred to as the *plasticity* of stem cells.¹ More specifically, hemopoietic progenitor cells have the potential not only to give rise to mature cells within the BM compartment that can then egress into the circulation, but may also egress from the BM as immature progenitors, and home to various organs and tissues under the orchestrated control of specific chemokines and cytokines. Once within the tissue, the fate of these primitive hemopoietic progenitor cells is determined by locally elaborated growth factors that permit a process termed “*in situ hemopoiesis*.”^{2,3}

CD34 is a stage-specific hemopoietic cell antigen that can aid in accurately enumerating progenitor cells in cord blood, peripheral blood, BM and, more recently, lung tissue and sputum, using flow cytometric methodologies.^{4,5} Studies⁴ in adults have shown that a circulating, common progenitor of eosinophils and basophils, measured as *in vitro* colony-forming units (Eo/B colony-forming units [Eo/B-CFU]), is detectable in greater numbers in the peripheral blood of asymptomatic atopic patients, compared with nonatopic control subjects; these Eo/B-CFU are responsive to activated T-(especially T-helper type 2 [Th2]) cell-derived cytokines and chemokines, and specifically to interleukin (IL)-5. Additional studies⁶ extended these findings by showing relevant fluctuations in blood and BM Eo/B-CFU in response to allergen-induced allergic inflammatory responses. The finding that, following natural allergen exposure, the numbers of circulating Eo/B-CFU are greatly reduced in symptomatic allergic rhinitis at the peak of a pollen season is an indication that during the inflammatory process, progenitor cells may home to tissue site(s) of inflammation. Previous seasonal allergic rhinitis studies^{7–9} found that Eo/B-CFU fell twofold to sixfold in mid-season ($p < 0.02$); this is equivalent to a reduction in potential mature Eo/B generation and availability in tissues of several

orders of magnitude, even assuming a conservative estimate of 100 to 500 nascent Eo/B from each progenitor.

In addition, the detection of locally elaborated hemopoietic growth factors and Eo/B-CFU within nasal polyps further supports the concept of *in situ* hemopoiesis. This view is strengthened by the following findings: (1) CD34-immunopositive/IL-5 receptor α (IL-5R α) messenger RNA⁺ cells are detected in lung biopsy samples from atopic asthmatic patients¹⁰; (2) *ex vivo* allergen challenge of nasal explant tissue from allergic rhinitis demonstrates IL-5-driven eosinophil differentiation¹¹; and (3) in mouse models of allergen-induced airway eosinophilia, increased numbers of IL-5-responsive Eo/B-CFU can be grown from lung-extracted progenitors following allergen challenge, compared with saline solution challenge.⁵

Mouse models of allergic rhinitis have highlighted the multifactorial nature of this inflammatory disease, and directly implicate the role of hemopoietic processes in allergic airways disease, specifically in allergic rhinitis and allergic asthma. The upregulation of myeloid progenitors in the BM after airway allergen inhalation, and their trafficking to the airways from the BM in several animal models of either upper or lower airways inflammation, have been demonstrated.¹² The resultant blood, nasal, and/or pulmonary eosinophilia in these models can be blocked by antibodies to IL-5, or by deletion of the gene encoding IL-5¹³; eotaxin is also critical in this process.¹⁴ Rather than demonstrating a complete ablation of the allergic inflammatory response in the nose, IL-5-deficient mice have delayed nasal symptoms and basophilic, rather than eosinophilic, inflammation within the nasal mucosa. Hemopoietic cytokine redundancy among IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor is thought to ensure adequate production of inflammatory cell progenitors even in the absence of one of these cytokines, *eg*, IL-5. This may partially explain the results of the effects of anti-IL-5 therapy in asthma, for which it has been shown to cause a maturational arrest of Eo/B progenitors.¹⁵ Likewise, as proof of concept, anti-IL-5 has now proven to be useful in managing hypereosinophilic syndrome,¹⁶ and may also be beneficial in clinical trials in patients with asthma with airway eosinophilia associated with poor control when corticosteroids (CS) are reduced.

These data support the concept that systemic, hemopoietic mechanisms are involved in rhinitis as well as asthma. It is quite possible that similar mechanisms contribute to eosinophilic esophagitis, atopic dermatitis, and bronchitis in patients with increased sputum eosinophils.^{16,17}

Phenotypic analyses of progenitor cells using CD34, together with antibodies to cytokine and chemokine

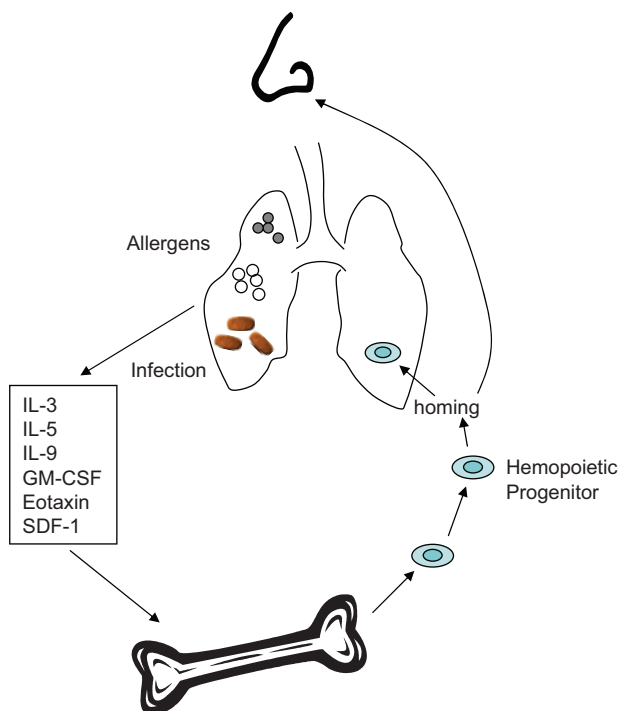


FIGURE 1. Systemic hemopoietic processes involving active communication among upper and lower airways tissue sites, the BM, and the bloodstream are depicted schematically, highlighting key cytokines and chemokines. Both differentiative and migratory events are critical in the participation of hemopoietic and, specifically, eosinophilopoietic progenitors in allergic diseases and asthma.

receptors, has provided insight into the contribution of systemic and tissue related-hemopoietic processes in the development of allergic inflammatory responses. We have shown that, whereas upregulation of IL-5R α on CD34 $^{+}$ cells within the BM promotes increased eosinophilopoiesis,⁴ the upregulation of the chemokine receptor CCR3 on CD34 $^{+}$ cells may favor increased traffic of progenitor cells from the BM to the peripheral circulation in response to eotaxin.¹⁸ Chemokines may therefore orchestrate the egress of progenitor cells from the BM microenvironment and the homing of progenitor cells to tissue sites of inflammation, such as the upper and lower airways. An important candidate may be stromal cell-derived factor (SDF)-1, a potent progenitor cell chemoattractant that plays a role in stem-cell homing during embryogenesis¹⁹ (Fig 1).

INFLAMMATION IN ASTHMA AND RELATED AIRWAY DISEASES

Eosinophilic and basophilic inflammation is present in a large number of allergic and nonallergic airway diseases. These conditions include, but are not limited to, allergic rhinitis, nonallergic rhinitis and rhinosinus-

itis, nasal polyposis, allergic and nonallergic asthma, and some forms of COPD. Eosinophils are pivotal in the pathophysiology of most forms of chronic respiratory mucosal inflammation. There is strong evidence for the crucial role of eosinophils in ongoing inflammation and tissue damage. Granules of eosinophils contain toxic basic proteins, the major protein being eosinophilic cationic protein (ECP). Experimental studies²⁰ on eosinophil function have shown cytotoxic effects on airway epithelium resulting in ciliostasis and lysis of the epithelium. ECP constitutes a well-described and standardized marker for tissue eosinophilia and activation.²¹ In addition, it has been demonstrated that recruited luminal airway eosinophils are distinct allergic "inflammatory" professional antigen-presenting cells able to activate primary CD4(+) T-cell responses in regional lymph nodes.²²

Links Between Upper and Lower Airway Inflammation

Allergic rhinitis is often associated with an increased prevalence of asthma: 20 to 50% of patients with allergic rhinitis will eventually have asthma.²³ Airway inflammation and remodeling can be present in the lower airways of patients with allergic rhinitis, although it is less intense than in patients with asthma.²⁴ During natural exposure, both the nose and lung come into contact with airborne allergens. Nasal inflammation may influence lower airway inflammatory processes by the release of inflammatory mediators into the circulation or through an effect on BM progenitors or inflammatory cells.²⁵

As most clinical trials have been performed during natural allergen exposure, studies evaluating the influence of upper airway disease on lower airways cannot properly assess the influence of nasal inflammation on lower airways. Provocative nasal allergen challenge has been used to help sort out the influences of allergic rhinitis on lower airways and specifically determine the influence of the upper airways on lower airway inflammation.²⁶ Braunstahl et al²⁷ performed nasal allergen provocations in allergic rhinitic patients without asthma and in normal control subjects. An increase of eosinophils as well as increased expression of intercellular adhesion molecule-1 was observed in the nasal and bronchial biopsies of allergic rhinitic patients compared with control subjects. However, Beeh et al²⁸ observed no significant difference in sputum eosinophils following nasal allergen provocation, although sputum ECP and intercellular adhesion molecule were increased. In addition, Braunstahl et al²⁹ have shown that segmental bronchial allergen challenge can produce nasal eosinophilic inflammation.

Nasal Allergen Challenge: Systemic Effects

In this regard, we recently performed a study using repeated nasal challenges to determine if this can induce lower airway inflammation and to obtain a more accurate model of allergen exposure. Our preliminary results show that a large number of patients with allergic rhinitis with or without asthma can have significant lower airway inflammation after repeated nasal challenge. Our observations expand those from Wilson et al,³⁰ who showed that despite a significant increase in nasal symptoms and lavage eosinophil counts, a single nasal allergen challenge was not sufficient to elicit a measurable hemopoietic response in circulation, or an increase in sputum eosinophil counts. However, based on animal models (below) and the bulk of evidence from human studies, Eo/B progenitor differentiation and/or migration may be a critical process underlying the inflammatory changes in the lung following allergen provocation in the nose.

Chronic Rhinosinusitis: Local or Systemic Disease?

As was noted, most of the studies performed over the past few decades on BM progenitors in lower airways inflammation have been in atopic, usually asthmatic individuals, with the inclusion, however, of all pertinent control groups (nonatopic, nonasthmatic). We also have gathered a body of evidence on the role of the BM and Eo/B progenitors in allergic rhinitis and nasal polyposis (with or without allergy). Although the “systemic” nature of allergy (*ie*, its involvement of IgE-producing cells throughout the immune system as well as locally in tissues) is essential to the diagnosis of inhalant allergy, allergic Th2 inflammation can exist as a localized condition in the presence of negative skin-prick test findings. This phenomenon of Th2-mediated Eo/B progenitor mobilization and differentiation has also been established to occur *in vitro/ex vivo* and as a correlate *in vivo*,^{11,31} lending even more credence to the clinical relevance of progenitor changes and resultant eosinophilic inflammation in Th2-driven disease.

For example, in the nasal mucosa of some subjects with persistent rhinitis, Powe et al³² found specific pollen allergen binding similar to that found in individuals with symptoms and positive skin-prick test results, but not in control subjects. Their findings support the concept of localized nasal allergy in “nonatopic” rhinitis patients.³² Huggins and Brostoff³³ also showed positive nasal allergen challenge results in skin-prick test-negative patients. Finally, a study by Carney et al³⁴ found that a significant proportion (62%) of patients with idiopathic rhinitis have positive results on nasal challenge, the vast majority to house dust mite allergen. Their findings

add to the weight of evidence that suggests “localized allergy” may exist in the absence of systemic atopic “biomarkers.” Thus, the diagnosis of nasal allergy is no longer simple and skin-prick test-negative patients with nasal eosinophilia may require allergen challenge before they can be said to be nonallergic.³⁵ A parallel finding has been previously reviewed in nasal polyposis with local IgE production in nasal tissue in the absence of positive skin-prick test results.³⁶ Similar findings have been found in nonallergic asthma. However, the existence of localized allergic inflammation without a systemic IgE response does not at all preclude the active involvement of hemopoietic processes in the development and maintenance of tissue Eo/B responses, as evidenced by the presence of hemopoietic progenitors within nasal polyp and other airway tissues.

DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS

Systemic vs Local Therapy

The knowledge that systemic inflammation occurs in conditions where the inflammation is primarily localized to the respiratory tract has led to debate as to whether it is necessary to treat these conditions systemically or whether local treatment is sufficient; in this discussion, it is not precluded that local treatment may have some beneficial (direct or indirect) systemic effects. The type of inflammation locally also may determine choice of therapy. The development of induced sputum and nasal lavage to measure the type of inflammation locally present has helped to better understand the type of treatment necessary both at the time of exacerbation and during long term treatment.

It is possible that optimal treatment of allergic rhinitis not only may improve coexisting asthma but also potentially postpone or prevent its development, although this remains to be examined. Up to now, inhaled and nasal CS are widely recognized to be effective antiinflammatory treatments for both asthma and rhinitis.³⁷ Inhaled CS act at various sites of the inflammatory process, particularly in reducing inflammatory cells and release of mediators.³⁸

While intranasal steroids can improve lower airway hyperresponsiveness, a greater benefit is seen in patients with both allergic rhinitis and asthma if topical steroids are delivered to both sites of inflammation.³⁹ Of less remarkable but still significant clinical benefit, working through a different pathway, montelukast, a specific leukotriene receptor antagonist (LTRA), has been shown to reduce allergic rhinitis and asthma symptoms.^{40,41} Cysteinyl leukotrienes (CysLTs) are potent receptor agonist mediators capable of inducing cell recruitment and bron-

Table 1—Effects of Several Antiallergic Treatment Options on Hemopoietic Processes and Eosinophils*

Treatment	Sputum Eosinophils	Nasal Eosinophils	Eo/B Progenitors
Antihistamine	Uncertain	Reduce/no effect	Reduce
LTRA	Reduce	Reduce	Reduce
Topical steroid	Reduce	Reduce	Reduce
Systemic steroid	Reduce	Reduce	Uncertain

chospasm, increased vascular permeability, and nasal airway resistance.⁴² Montelukast antagonizes these effects and thus attenuates the allergen-induced early and late asthmatic responses.⁴³ It also reduces sputum eosinophilia following allergen challenge.⁴⁴ Since CysLT receptors are expressed on hemopoietic progenitors, antagonism with montelukast may attenuate tissue eosinophilia via a systemic antiinflammatory effect (see below).

HEMOPOIETIC PROCESSES AS TARGETS OF THERAPY

Modulation of Eosinophil Differentiation by CS

Hemopoietic mechanisms can be targeted by antiallergic therapies (Table 1). For example, topical treatment with CS can affect the hemopoietic response by abrogation of cytokine production by

airways tissues, reduction in peripheral blood Eo/B progenitors, and decreases in BM myeloid progenitors (in a canine asthma model). Most likely, inhaled CS in these models exert their effects on the marrow progenitor response indirectly by interfering with cytokines elaborated from the inflamed tissue, which can then act systemically on the BM. However, a direct effect on progenitors cannot be excluded because there is evidence that, both *in vitro* and *in vivo*, low systemic levels of CS (10^{-9} mol/L) can block differentiation of the Eo/B progenitor in humans and of the myeloid progenitor in dogs.⁴⁵ Studies^{46–48} of the apparently paradoxical stimulation by budesonide, a topically active CS that suppresses allergic inflammation *in vivo*, of IL-5-induced eosinophilopoiesis *in vitro* have revealed that one possible mechanism of action of CS is the early upregulation of an eosinophil lineage-specific transcription factor, GATA-1, followed by later suppression. These studies support the concept that topical CS alone might represent an insufficient therapeutic option in long-term management of rhinitis and asthma because of a lack of control of the progenitor-marrow contribution to allergic inflammation.

Modulation of Eosinophil Differentiation by Other Antiallergic Compounds

We have provided evidence for the blockade of eosinophil differentiation by CysLT receptor antagonists.

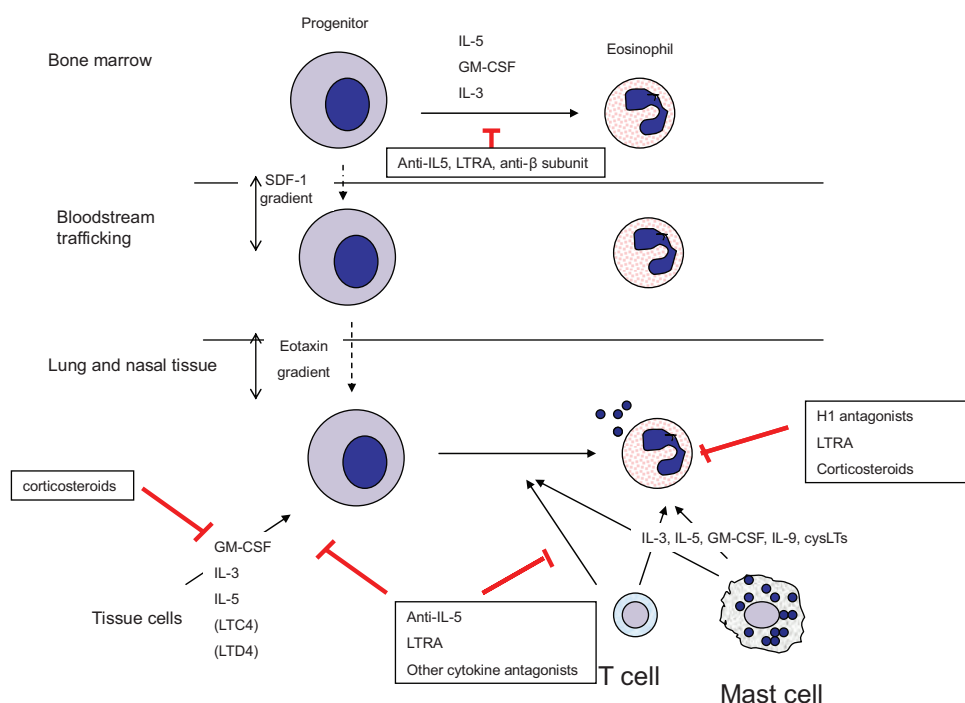


FIGURE 2. Progenitors differentiate to mature eosinophils within the BM but also traffic as progenitors through the bloodstream and into airway tissue sites where they can differentiate into mature eosinophils. The effects of some treatments on eosinophil differentiation and survival are illustrated. Parentheses indicate a cofactor. H1 = histamine type 1; LTC4 = leukotriene C₄; LTD4 = leukotriene D₄.

onists,⁴⁸ antibodies to IL-5,¹⁵ and nonsedating, histamine type 1 antihistamines,⁴⁹ both *in vivo* and *ex vivo/in vitro*, in human cells and animal models of airways inflammation. In murine experimental allergic rhinitis, CysLT-1 receptor (CysLT1-R) antagonism *in vivo* limits IL-5-responsive eosinophilopoiesis, acting at several stages of eosinophil differentiation and maturation. The antiallergic effects of CysLT1-R antagonists are consistent with the concept that CysLTs and IL-5 act together in the recruitment of eosinophils and eosinophil progenitors from the marrow during upper airway allergic inflammation, targeting both IL-5R α and CysLT1-R on progenitors. Thus, a potential therapeutic target in eosinophilic airways disease is the Eo/B progenitor (Fig 2).

Implications for Other Diseases

A brisk BM response that includes the release of immature cells has been documented during the course of a variety of nonatopic inflammatory events in the lung, such as pneumonia, endotoxemia, cigarette smoking, asthma, and exposure to air pollutants.⁵⁰ This suggests that BM progenitors contribute to lung repair following infection or may determine inflammation and/or disease severity in COPD⁵¹; a defective BM response could underlie the pathogenesis of COPD and related chronic upper and lower airway conditions.

CONCLUSIONS

This review has examined how the BM supplies and delivers hemopoietic progenitors to sites of allergic inflammation, and discussed factors that can modulate these progenitors physiologically and, potentially, therapeutically. Evidence that current and experimental therapies have a systemic effect may change the way we treat these increasing global health concerns.

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