

# Viewpoint

## Eosinophils in asthma

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The contribution of eosinophils to host-defense and inflammatory responses has undergone periodic reevaluations. Thirty years ago, eosinophil was considered as a principal effector cell in host-defense against parasites.<sup>1</sup> Furthermore, the actions of eosinophil enzymes, like histaminase, were thought to suppress mast cell-released allergic mediators. Asthma is a chronic inflammatory condition of the airways that is characterized by a prominent eosinophilic inflammatory infiltration into the bronchial mucosa. Activated eosinophils secrete granular basic proteins that damage the bronchial epithelium and membrane-derived lipid mediators, which contract smooth muscle, increase mucous secretion, and cause vasodilation. The correlation between eosinophil numbers and disease severity supports the hypothesis that the eosinophil is the central effector cell in ongoing airway inflammation in asthma.<sup>2</sup> However, it would be unwise to totally overestimate eosinophil's potential in the development of asthma unless we have effective and selective methods of depleting the cells from the tissues.

Wenzel and coworkers<sup>3</sup> suggest that the phenotype of asthma is composed of at least two subtypes based on the presence or absence of eosinophils in the airways. Eosinophilic and non-eosinophilic asthmatics are two distinct groups with different pathologic, physiologic, and clinical features. Douwes et al<sup>4</sup> selected from Medline studies from 1995 onwards with data on eosinophil levels in biopsy specimens, bronchoalveolar lavage fluid, or sputum of asthmatic subjects where the subjects were not clearly selected on the basis of atopic characteristics, and where data were presented so that the subjects could be classified as eosinophilic or non-eosinophilic asthmatics. Cut off values used to define eosinophilic and non-eosinophilic asthma were the same as those reported in the original studies (2% - 4%). The weighed mean proportion of subjects with eosinophilic asthma was 51%, so 49% had non-eosinophilic asthma. These studies, from a variety of different laboratories, clearly demonstrate the existence of non-eosinophilic asthma.

This raises the question as to the role of eosinophilic inflammatory mechanisms in the pathophysiology of asthma, and that other inflammatory mechanisms may be involved in producing the final common pathway of enhanced bronchial reactivity and reversible airflow obstruction that characterises asthma.

If eosinophils are the principal inflammatory cells in the pathogenesis of asthma, treatment targeted toward eosinophils should have an impact on symptoms as a result of suppression of alternating cycles of tissue damage and repair. Our previous data have provided direct evidence that interleukin-5 (IL-5) increases airway responsiveness and infiltration of activated eosinophils into the airway in patients with allergic asthma.<sup>5</sup> Leckie and coworkers<sup>6</sup> evaluated the effect of anti-IL-5 monoclonal antibody (mAb) administration on the airway response to inhaled antigen, and found that the usual increase in peripheral blood and sputum eosinophils to inhaled antigen was nearly abolished by anti-IL-5 mAb treatment; on the other hand, anti-IL-5 mAb in human asthma did not affect either the immediate- or late-phase response to antigen or the expected increase in post-allergen-induced airway hyperresponsiveness. In order to determine whether anti-IL-5 mAb depletes airway tissue eosinophils and their products, Patrick and coworkers<sup>7</sup> treated 24 patients with mild asthma with intravenous doses of either 750 mg of anti-IL-5 mAb or placebo in a randomized, double-blind, parallel-group fashion over 20 weeks. Anti-IL-5 mAb produced a median decrease by 55% for airway eosinophils, 52% for bone marrow eosinophils, and 100% for blood eosinophils. There were no significant changes in airway hyperresponsiveness,

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forced expiratory volume in 1 second ( FEV<sub>1</sub> ), and peak flow recordings between the anti-IL-5 mAb and placebo-treated groups. Based upon these observations , the authors questioned the “ prerequisite ” role of eosinophils in the late asthmatic response to inhaled antigens and its “ relevance to the pathogenesis and treatment of asthma ”. One explanation for these findings was that these patients ’ asthma was too mild to show an appreciable clinical effect of eosinophil depletion and that this form of treatment would only be effective in subjects with more severe disease.

More recently , Kips et al<sup>8</sup> described the effects of a second humanized anti-IL-5 mAb ( SCH55700 ). Their patients had severe asthma with persistent symptoms despite high-dose inhaled corticosteroids and/or oral prednisolone. Volunteers received a single infusion of SCH55700 or placebo in a double-blind fashion. Blood and sputum eosinophils , spirometry , peak flow recordings , and symptoms were monitored for up to 30 days. In agreement with previous data <sup>6,7</sup> SCH55700 produced a significant decrease in blood eosinophil counts at the two highest doses used. A 0.3 mg/kg dose of SCH55700 produced a significant increase in FEV<sub>1</sub> at 24 hours , which persisted at subsequent time points. This improvement did not parallel changes in symptom scores or peak flow recordings. Therefore , the rapid improvement in FEV<sub>1</sub> was difficult to interpret , and the fact that it was not sustained and only observed with the submaximal dose was disappointing. This finding may have been related to more acute bronchoconstricting effect of eosinophil-derived cysteinyl leukotrienes or even to an eosinophil-independent property as airway smooth muscle cells express the IL-5 receptor and *in vitro* incubation with IL-5 selectively primes for hyperresponsiveness. <sup>9</sup> Thus , the rapid improvement in FEV<sub>1</sub> may have been due to direct blockade of the actions of IL-5 on airway smooth muscle , which in turn improves airway caliber.

Overall , the finding that a reduction in the number of blood and airway eosinophils was not associated with a reduction in allergen-induced bronchoconstriction or hyperreactivity challenges the hypothesis that eosinophil is a central effector cell in asthma. The eosinophilic response and the physiological responses to allergen challenge seem to be separable. Blocking eosinophil production or migration may thus be of little benefit for asthma.

This is not to say that eosinophil has no role in the pathophysiology of asthma. There is evidence that the eosinophil is involved in cough , airway remodeling , and asthma exacerbations. <sup>10</sup> The role in exacerbations may

be particularly important because an asthma management strategy directed at normalizing the sputum eosinophil count reduced the number of severe exacerbations compared with standard management. <sup>11</sup> The potential of anti-IL-5 mAb as a therapy for asthma and the role of the eosinophil in asthma could be better realized by studying the effect of this treatment on these other outcomes rather than clinging to the concept that eosinophilic airway inflammation and airway hyperresponsiveness are causally associated.

In comparison with other cell types of antigen-presenting cells such as dendritic cells , the antigen-presenting function of eosinophils is presumably marginal , however , several properties of eosinophils likely combine to endow them with distinct roles as antigen-presenting cells. <sup>12</sup> The first property would be their tissue localization. The normal localization of eosinophils within the mucosal tissues of the respiratory , gastrointestinal and lower genitourinary tracts would position them to encounter foreign antigens at these mucosal surfaces. Moreover , in allergic airway diseases , eosinophils are found within the lumen and secretions of the airways and could directly interact with inhaled allergens within the airways. Second , eosinophils have the capacity to transmigrate from the luminal surface of the mucosa into regional lymph nodes. <sup>13</sup> Both alveolar macrophages and dendritic cells can also migrate from the airways into the tissues , but *in vivo* antigen-pulsed macrophages do not transfer processed peptides to dendritic cells<sup>14</sup> and alveolar macrophages do not function as antigen-presenting cells *in vivo*. <sup>15</sup> A third feature of eosinophils might be that as antigen-presenting cells at airway surfaces they are capable of interacting with particulate antigens. While dendritic cells and B cells effectively present soluble protein antigens , they are unable to handle particulate antigens. <sup>16</sup> In the respiratory tract , inhaled allergens are particulate. The principal cells recognized to ingest particulate antigens are phagocytic macrophages ; but alveolar macrophages are not effective antigen-presenting cells and even antagonize antigen-presenting cell function of dendritic cells. <sup>17</sup> Alternatively , eosinophils would be well suited to handle particulate antigens , since eosinophils are phagocytic , characteristically engage large , even non-phagocytosable multicellular targets and accumulate early at tissue sites of particulate antigens. Therefore , eosinophil might also be involved in the pathogenesis of asthma by presenting antigens to T lymphocytes.

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