

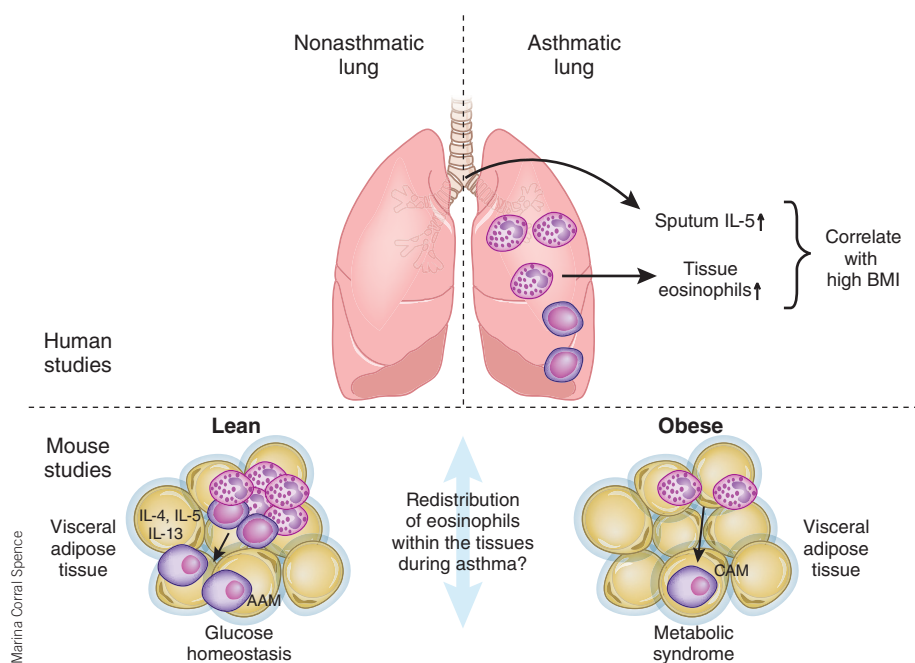


Figure 1 Is redistribution of eosinophils a factor in asthmatic pathology? In individuals without asthma, eosinophils are absent from the lungs, but they maintain metabolic homeostasis within visceral adipose tissue. Eosinophils and other innate immune players secrete T_H2 cytokines, such as IL-4, IL-5 and IL-13, to sustain alternatively activated macrophages (AAMs) and maintain glucose homeostasis. In obese individuals, there are fewer eosinophils in the fat tissue and there is a lack of T_H2 -type cytokines, resulting in macrophages with a classical activated phenotype that promotes metabolic disease. T_H2 disease increases eosinophil numbers in the fat and increases insulin sensitivity. Although eosinophils can be found in the lungs of asthmatics, only the number of eosinophils in airway tissue directly correlates with BMI. Perhaps redistribution of eosinophils from fat to lungs is a factor in determining severity of disease. CAM, classically activated macrophages.

in vivo? The recent DREAM study reported that subcutaneous injection with IL-5-specific antibody reduced asthma exacerbations in subjects with severe asthma. As the study did not stratify patients according to BMI and only measured reduction of eosinophil numbers in sputum¹⁰, associations between drug efficacy and BMI were not reported; however, this may be an

important association to consider in future trials.

In the developed world, where parasitic infections are relatively uncommon, circulating eosinophils are rare, but the incidences of the metabolic syndrome and asthma are increasing. In contrast, in developing countries, where people commonly have intestinal parasites and concomitantly high levels of circulating eosino-

phils and plasma IL-5, metabolic syndrome and obesity are rare, as is the incidence of asthma. Perhaps this may be partly explained by the function of eosinophils being directly related to their distribution within visceral tissues—either adipose tissue or the airway wall, as shown in mice (Fig. 1). The fact that lung tissue eosinophil numbers directly correlate with BMI indicates that the interaction with local stromal cells might determine their function. It would be very interesting to further understand whether the visceral fat of patients with asthma harbors eosinophils in numbers comparable to that of individuals without asthma, independent of their BMI. It is also conceivable that there may be a distinct population of tissue eosinophils that reside within the visceral fat and perform a homeostatic role, whereas bone marrow-derived eosinophils are important during inflammation.

Given that the incidence of both asthma and obesity is increasing at an alarming rate, a greater understanding of the role of eosinophils in glucose homeostasis and in patients with asthma is now warranted to provide more accurate phenotype-driven therapy.

COMPETING FINANCIAL INTERESTS

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■ BEDSIDE TO BENCH

Eosinophilic airway inflammation in nonallergic asthma

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Asthma is defined as a chronic inflammatory disorder of the lower airways that is associated

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with airway hyperresponsiveness and variable airflow obstruction, which leads to episodic symptoms of shortness of breath, wheezing and cough. It is a heterogeneous syndrome that affects more than 300 million people worldwide and can be categorized into multiple phenotypes on the basis of the inflammatory cell profile, the presence of allergy and the age at onset of disease¹. For one particular asthma phenotype, the predominant type of granulocyte underlying the chronic airway inflammation is the eosinophil. Eosinophilic

asthma can occur in both allergic and non-allergic patients, but whereas the origin of eosinophilia in allergic asthma is largely understood, the triggers for eosinophilia in nonallergic eosinophilic asthma remain to be elucidated.

In allergic eosinophilic asthma, type 2 helper T (T_H2) lymphocytes are believed to drive asthma pathobiology (Fig. 1)¹. In genetically susceptible individuals, inhalation of aeroallergens activates specialized antigen-presenting cells that steer the

differentiation of naive T lymphocytes toward T_H2 cells, which produce cytokines such as interleukin-4 (IL-4), IL-5, IL-9 and IL-13 (ref. 2). Allergic T_H2 -associated asthma, which starts most frequently during childhood (also called early-onset asthma), is associated with other allergic diseases such as atopic dermatitis and allergic rhinitis¹.

Although this asthma phenotype is usually responsive to treatment with inhaled corticosteroids, molecular insights into allergic asthma have led to specific treatment approaches. The crucial role of IL-5 in eosinophil activation, maturation and survival makes it an interesting drug target, as elevated eosinophil numbers and activation have been associated with severe asthma exacerbation³. This evidence has spurred the clinical development of two humanized monoclonal antibodies against IL-5, mepolizumab and reslizumab, and their use in patients with asthma. However, specific inhibition of the IL-5 pathway in nonphenotyped patients with persistent asthma who were already treated with inhaled corticosteroids has been ineffective. In the recent dose-ranging efficacy and safety study with mepolizumab in severe asthma (DREAM) trial, Pavord *et al.*⁴ showed that add-on treatment with mepolizumab significantly reduced the number of asthma exacerbations and the eosinophilic inflammation characteristic of the enrolled patients, which indicates that phenotypic characterization and appropriate patient selection are important in asthma trials.

Intriguingly, half of the severe eosinophilic asthmatics in the DREAM study were not allergic, which challenges the idea that allergy is important in the pathogenesis of (severe) asthma and raises the question as to which cellular and molecular mechanisms drive airway eosinophilia in nonallergic asthma. Indeed, late-onset eosinophilic asthma that develops at adulthood and is frequently associated with chronic rhinosinusitis and nasal polyps¹ is often severe and nonallergic. The lung and blood eosinophilia in this asthma phenotype persist despite treatment with inhaled corticosteroids, and high doses of systemic corticosteroids are generally required to overcome the lack of drug response. Recently, increased numbers of type 2 innate lymphoid cells (ILC2s), key nonspecific innate immune effectors, have been detected in nasal polyps of chronic rhinosinusitis, which is characterized by large numbers of eosinophils⁵. Upon stimulation with the epithelial cytokines thymic stromal lymphopoietin (TSLP) and IL-33, ILC2s produce T_H2 -associated cytokines, including

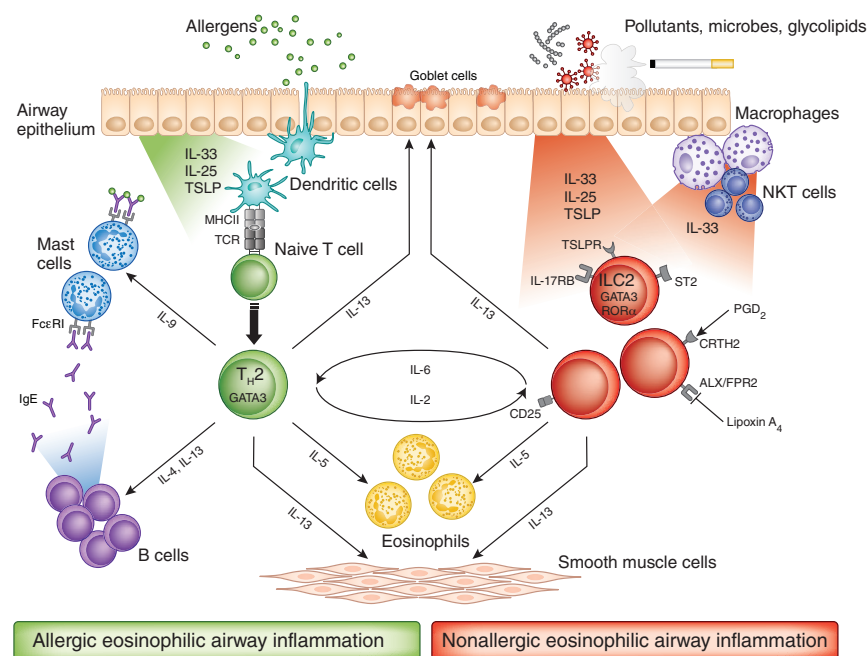


Figure 1 Two different pathways lead to eosinophilic airway inflammation in asthma. In allergic asthma, dendritic cells present allergens to $CD4^+$ T cells, inducing T_H2 cells, which produce IL-4, IL-5 and IL-13, and leading to IgE switching in B cells, airway eosinophilia and mucous hypersecretion. In nonallergic eosinophilic asthma, air pollutants, microbes and glycolipids induce the release of epithelium-derived cytokines, including IL-33, IL-25 and TSLP, which activate ILC2s in an antigen-independent manner via their respective receptors (IL-17RB, ST2 and TSLPR). Activated ILC2s produce high amounts of IL-5 and IL-13, leading to eosinophilia, mucous hypersecretion and airway hyperreactivity. CRTH2, chemoattractant receptor-homologous molecule expressed on T_H2 cells. ALX/FPR2, receptor for lipoxin A4; FcεRI, high-affinity receptor for IgE; GATA3, GATA-binding protein 3; PGD₂, prostaglandin D₂; RORα, retinoic acid receptor-related orphan receptor α.

high amounts of IL-5 and IL-13 and, to a lesser extent, IL-4 (Fig. 1)^{6,7}. This elevated IL-5 production might explain severe eosinophilic inflammation in the absence of classical T_H2 -mediated allergy (allergen-specific IgE) in late-onset eosinophilic asthma.

Different lines of evidence support a role for ILC2s in airway eosinophilia in nonallergic eosinophilic asthma. First, high numbers of ILC2s have been detected in eosinophilic nasal polyps of patients with chronic sinusitis and in lung and peripheral blood of humans with asthma⁵. As airway expression of the epithelial cytokine TSLP is increased and expression of lipoxin A₄, which decreases IL-13 release by ILC2s⁸, is decreased in a subset of patients with severe asthma, unrestrained activation of ILC2s might drive refractory eosinophilia in these individuals with severe asthma. Second, genes discovered in genome-wide association studies of asthma have key roles in the development and activation of ILC2s: the gene encoding ROR-α is crucial for ILC2 differentiation; and the genes encoding IL-33 and IL-1 receptor-like 1, which is part of the IL-33 receptor complex

(also known as ST2), mediate IL-33 signaling and activate ILC2s⁹. Finally, in a mouse asthma model induced by exposure to the fungus *Alternaria alternata*, characterized by airway eosinophilia and high bronchoalveolar amounts of IL-33, IL-5 and IL-13, ILC2s were required and sufficient to drive eosinophilia and airway hyperresponsiveness¹⁰. Similarly, mice exposed to glycolipid antigens, which activate natural killer T cells and ILC2s, rapidly developed airway hyperresponsiveness (even in the absence of conventional $CD4^+$ T cells) that required IL-13 and IL-33 signaling¹¹. Respiratory tract infections by viruses can increase the risk of developing asthma and induce asthma exacerbations, as shown in a mouse model of influenza infection that acutely induced airway hyperresponsiveness through ILC2s via the IL-33–IL-13 axis¹², but independently of T_H2 cells.

In asthma, two different non-mutually exclusive pathways driven by either allergen-specific adaptive T_H2 cells or allergen-independent innate ILC2s may lead to production of IL-5, which induces eosinophilic airway inflammation. In experimental allergic asthma, adoptive transfer of ILC2s into

Il13-deficient mice has been shown to restore airway hyperresponsiveness and eosinophilic infiltration. In subjects with asthma, ILC2s generate IL-13 in response to the mast cell product prostaglandin D₂, and inhibitors of its receptor, such as QAW039, are therefore in clinical development for the treatment of allergic and nonallergic asthma. It remains unknown whether the number or activation status of ILC2s in blood or lower airways correlates with specific asthma phenotypes. From a therapeutic perspective, it would be interesting to address whether ILC2s are more corticosteroid-resistant than T_H2 cells and, more important, whether interfering with

ILC2s will improve outcomes in asthmatic patients.

The DREAM trial has taught us that phenotyping patients with asthma on the basis of molecular and cellular mechanisms, in addition to clinical data, improves responses to targeted therapies. A thorough understanding of the role of ILC2s in different asthma phenotypes will lead to more specific and effective treatments of this heterogeneous syndrome.

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