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The role of eosinophil and asthma airway remodelling

What is asthma?

Asthma is an inflammatory disease of the small airways of the lung. Asthma has now reached epidemic proportions, with more than 10% of children being affected in many westernized societies. Asthma is a complex and heterogeneous disease characterized by reversible airflow obstruction, bronchial inflammation and tissue remodelling of the airway wall. Detailed histologic and physiologic analyses of asthmatic subjects have demonstrated that both the structure and function of the airways are altered in asthma. Airway remodeling in asthma includes not only structural changes but also fundamental changes in the relationships between and among various airway constituents. Inflammatory and structural cells are important because they release pro-inflammatory mediators and thus induce an acute inflammatory response that includes increased mucus secretion, epithelial shedding and airway narrowing. At the same time, the release of chemokines and growth factors causes airway inflammatory infiltrate to persist in asthmatic airways and thus induces structural changes within the airway wall.

Airway remodelling

Asthmatic airway biopsies, autopsy studies, and animal models all show that the epithelium is remodeled in asthma. Epithelial cells are found in increased amounts in asthmatic sputum, and epithelial detachment from the basement membrane is frequently observed in the various models of asthma.

In the last decades, it has been suggested that the apparent progressive loss of lung function in more severe forms of asthma is due to structural or remodelling changes in the airways and perhaps parenchyma. The remodelled phenotype in asthma, which might be the consequence of excessive repair processes following repeated airway injury, includes increased deposition of several extracellular matrix (ECM) proteins in the reticular basement membrane (RBM) and bronchial mucosa, as well as increases in airway smooth muscle mass, goblet-cell hyperplasia and new blood vessel formation.

These ECM proteins include pro-collagen III (the mature precursor for collagen III) and the proteoglycans, tenascin and lumican. Apart from the effects on airway structure, these ECM proteins might also influence cellular function, including adhesion, differentiation and survival.

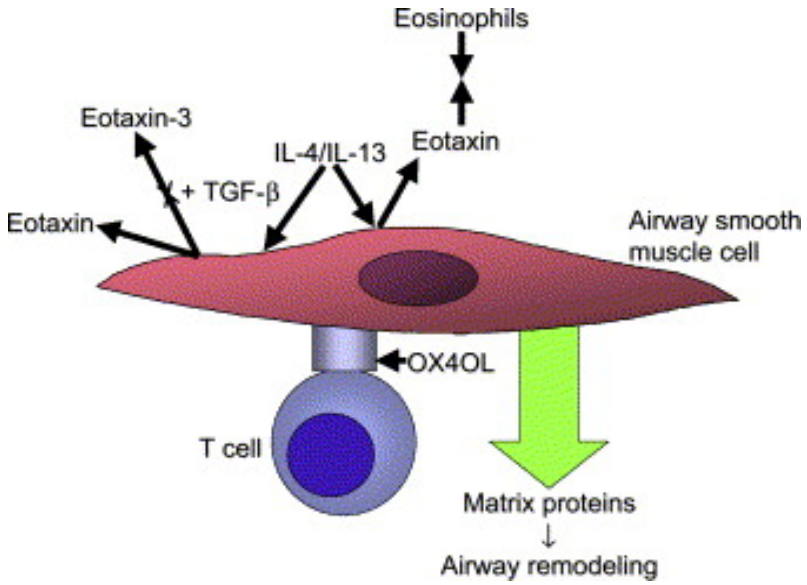

Fig 1. Airway smooth muscle generation of inflammation

Significant abnormalities in the bronchial wall in asthma are known to contribute to increased mural thickness. Remodelling is the result of persistent inflammation in the bronchial wall, associated with the production of proinflammatory cytokines and growth factors. Increased thickness is due to con tributions from each of cellular influx, collagen and matrix deposition and smooth muscle hypertrophyperplasia. The consequences of remodelling may include: bronchial hyperreactivity reduced lung function with fixed airflow obstruction, lack of responsiveness to bronchodilator medication and an increased risk of asthma mortality. The remodelling process in the airway wall in asthma relies on the production of growth factors by stimulated cellular elements. Many airway cells are capable producing a multitude of cytokines.

Association with eosinophils

The key inflammatory cells involved in asthma are lymphocytes, eosinophils, mast cells, antigen presenting cells and, in a percentage of asthmatic patients, neutrophils. The Th2

cytokines IL-4 and IL-13 are able to increase the expression of VCAM-1 by endothelial cells which will facilitate eosinophil attachment to the surface of the endothelium. The appearance of T helper (Th)2-like lymphocytes in respiratory airway tissues is concomitant with the availability of interleukin (IL)-5, a cytokine essential for the maturation, terminal differentiation, survival and function of eosinophils. IL-5 stimulates the expansion and differentiation of eosinophil precursors and upregulates the expression of its own specific receptor α chain during human eosinophil development. IL-5 is also able to induce the release of mature eosinophils into the blood by stimulating their migration across the marrow sinus endothelium. Increases in IL-5 correlate with blood eosinophilia and an increase in the number of BAL eosinophils in the late asthmatic response. When asthmatics were given three infusions of anti-IL-5 antibody (mepolizumab), this produced a ~90% reduction in blood and bronchial-lavage eosinophils (1). A study in IL-5-deficient transgenic mice also showed the importance of eosinophils, as these animals failed to develop airway hyperresponsiveness and eosinophilia after allergen challenge.

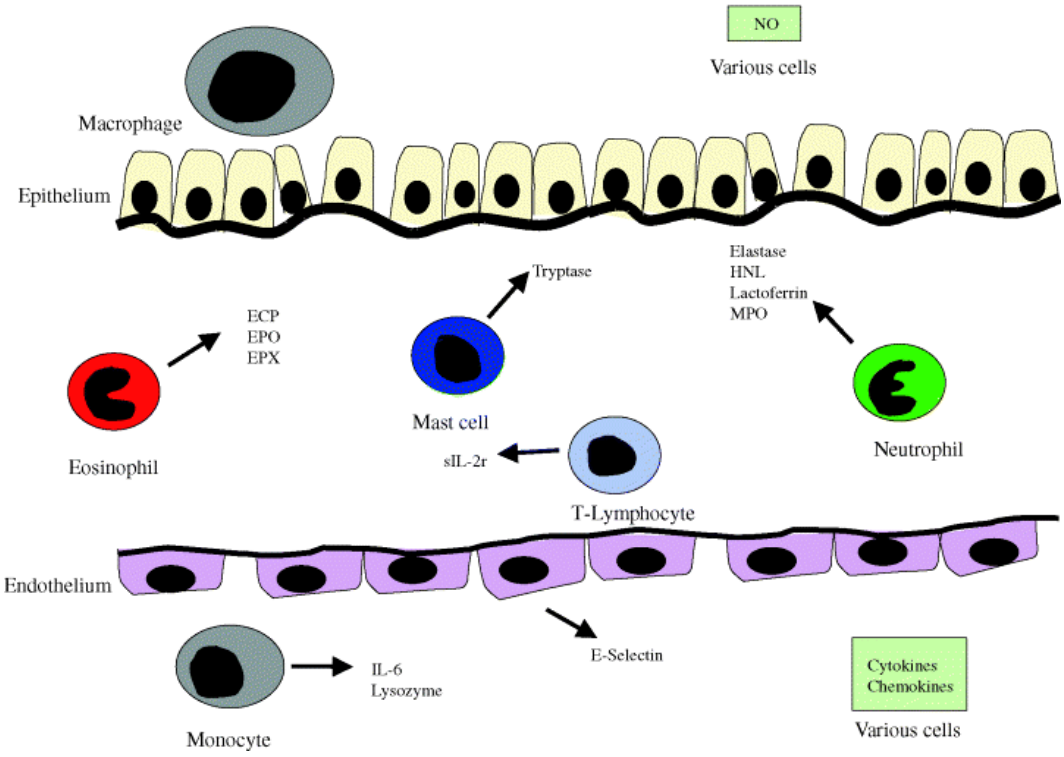

Fig 2. Cells involved in airway inflammation

In most asthma phenotypes, there are increases in eosinophils in the tissues, blood and bone marrow and, in general, raised numbers correlate with disease severity (although non-eosinophilic or neutrophilic asthma is characteristic of bacterial, viral and pollutant triggers. This has led to the hypothesis that the eosinophil is the central effector cell that is responsible for ongoing airway inflammation.

In histopathological samples of patients with asthma, eosinophils can be found clustered around the vagal nerve ganglia in the lung. Eosinophils are characteristic of the cellular infiltrate in asthma. Derived from myeloid progenitors in the bone marrow, mature eosinophils circulate in the peripheral blood and sites of inflammation, particularly parasitic or allergic sites. Eosinophils have been described in large numbers, infiltrating the walls of airways in fatal asthma, as well as mild asthma. Eosinophils normally circulate in the blood in low numbers (1-4% of blood leukocytes). Eosinophilia described in peripheral blood and bronchial lavage has been related to airway hyperreactivity. Airway and lung eosinophilia is highly regulated by the T_H2 cytokines IL-4, IL-5, and IL-13. As effector cells, eosinophils are capable of producing T_H2 and other cytokines, chemokines, lipid mediators, and growth factors and are also capable of causing an increase in mucus production, causing subepithelial fibrosis, and altering ASM contractility.

Activated eosinophils release toxic proteins capable of causing airway tissue damage, including major basic protein (MBP), (which damage nerves and epithelial cells), eosinophil-derived neurotoxin (EDN), eosinophil cationic protein (ECP), (which damage nerves and epithelial cells), eosinophil peroxidase, and lipid mediators (which cause bronchoconstriction, vasodilatation and mucus hypersecretion).

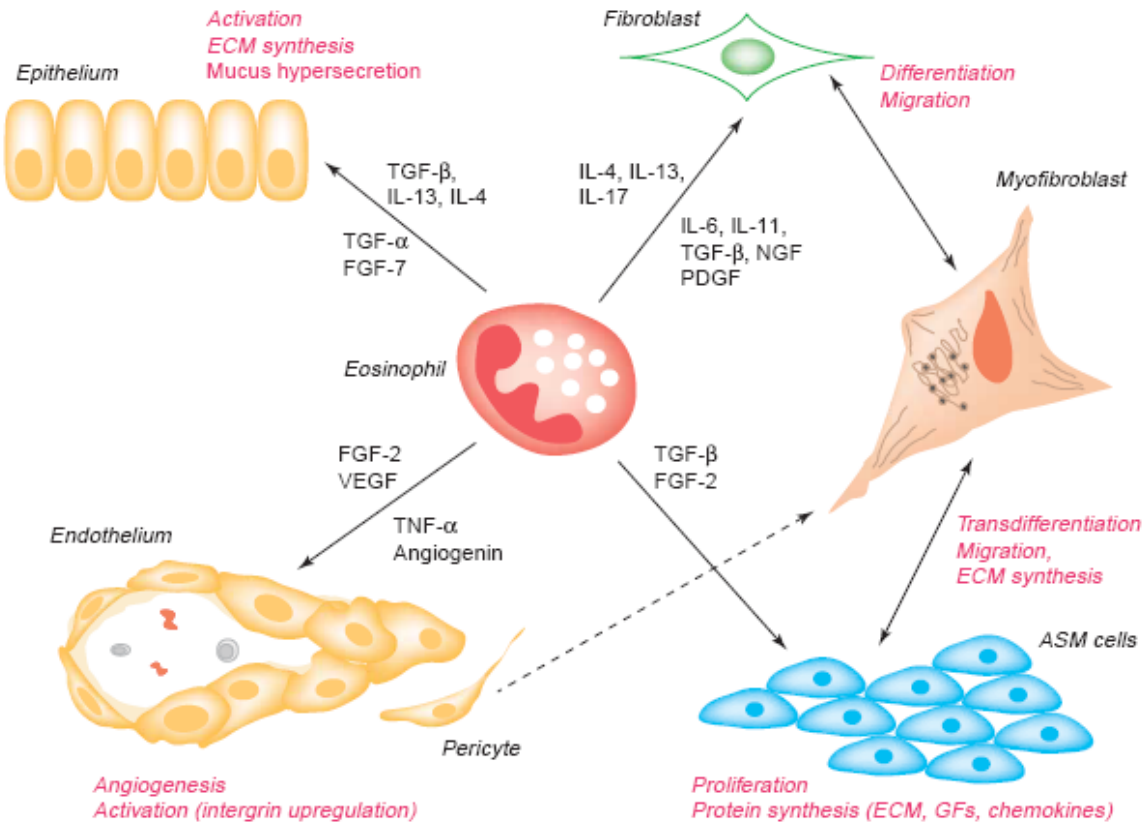

Fig 3. Potential involvement of eosinophils in airway remodeling

Airway inflammation has been known to be a prominent feature of asthma for decades, it still is not known whether inflammation drives the remodeling response in the airway wall or whether an intrinsic abnormality of airway structure or function drives inflammation. It has been widely assumed that allergic inflammation is the initiating event. Chemokines are a crucial facet of the interaction between eosinophils and the airway epithelium in asthmatic inflammation. Eosinophils produce a wide range of proteins involved in fibrogenesis and angiogenesis, as well as cytokines, which activate various mesenchymal cells and induce the synthesis of ECM proteins. Activation of fibroblasts is a property of IL-4, IL-6, IL-11, IL-13, IL-17, TGF-β, NGF and PDGF. This, in turn, can lead to fibroblast migration and differentiation to the myofibroblast phenotype, trans-differentiation of myofibroblasts to ASM cells, as well as the migration of various mesenchymal cells and ECM synthesis. Thus, there is considerable plasticity between fibroblasts, myofibroblasts and ASM cells. The pericyte is also involved in these

trans-differentiation processes. TGF-β and FGF-2 have direct effects on airway smooth muscle (ASM), such as proliferation and protein synthesis. Eosinophils also produce angiogenic factors, including VEGF and angiogenin. Endothelial cells can also be activated by FGF-2 and TNF-α. Epithelial-cell activation, ECM synthesis and mucus hypersecretion might be the result of the release of eosinophil-derived TGF-β, IL-4, IL-13 and TGF-α.

Protein	Properties relevant to remodelling
Angiogenin	Angiogenesis
FGF-2	Fibroblast proliferation; endothelial-cell proliferation and migration; angiogenesis
HB-EGF	Fibroblast and smooth muscle-cell proliferation
IL-4	Fibroblast activation
IL-11	*In vivo* fibroblast activation
IL-13	Increased fibroblast activity mediated through upregulation of epithelial and fibroblast TGF-β
IL-17	Inducer of fibroblast cytokine and chemokine production
MBP	Act synergistically with IL-1 and TGF-β to increase IL-6 production by fibroblasts
MMP-9	Matrix protein degradation
NGF	Fibroblast ECM production; endothelial-cell proliferation and migration
PDGF	Myofibroblast development
TGF-α	Epithelial proliferation
TGF-β	Myofibroblast formation; ECM production and collagen contraction
TIMP-1 and TIMP-2	Inhibitor of MMPs
TNF-α	Inducer of angiogenic and fibrogenic growth factors
VEGF	Angiogenic factor; induces vascular hyperpermeability

Table 1. Inflammatory mediators derived from eosinophils.

Other histopathological features of asthma include sub-basal membrane thickening, hypertrophy and hyperplasia of both smooth muscle cells and subepithelial glands, events thought to result directly from the activity of matrix metalloproteinases (MMP) in airway interstitial tissue. Significant quantities of mRNA transcripts for MMP−9 (gelatinase-B) have been detected in bronchial biopsies from asthmatic subjects, the majority of which were expressed by eosinophils, and eosinophil stimulation with TNF-α markedly upregulates their ability to release MMP-9 *in vitro*. Furthermore, MMP-9 has been reported to play an important role in eosinophil migration through the basement membrane underlying the endothelium. Thus, the significant quantities of MMP-9 secreted by eosinophils might contribute to asthma pathogenesis by instigating pathological changes; they may also weaken epithelial cell-cell junctions through their capacity to cleave the adhesion molecules responsible for maintaining the integrity of the

lung epithelium, thereby contributing to the loss of epithelial integrity that is characteristic of asthma.

Animal models

A key goal when studying asthma and the role of eosinophils is to develop realistic models of this disease. The mouse model of eosinophil-related asthma has been questioned because the mouse eosinophil does not degranulate in the same way as the human eosinophil (2). A recent study by Justice *et al*. (3) specifically depleted airway, tissue and blood eosinophils using a monoclonal antibody against CCR3, a chemokine receptor specific for eosinophils. The ablation of virtually all pulmonary eosinophils in ovalbumin-treated mice led to a significant reduction of AHR following allergen challenge, but did not affect other components of allergic inflammation characteristically seen in murine asthma.

Two recent papers in Science addressed the role of eosinophils in asthma. Lee *et al.* (4) targeted eosinophils through the transgenic expression of the diphtheria-toxin A chain under the control of the eosinophil peroxidase promoter (*PHIL*) and showed that eosinophils were required for both airway hyperresponsiveness and mucus accumulation. Humbles *et al.* (5) deleted the high affinity GATA-1 binding site on the GATA-1 promoter (Δbdl) and found that AHR and mucus accumulation were unaffected by eosinophil depletion, although the cell appeared to be essential for producing the phenotypic changes that are associated with airway remodelling.

Conclusion

The airway epithelium is composed primarily of ciliated, non-ciliated and basal cells which, under normal circumstances, provide a protective barrier against the external environment. Eosinophil–epithelial interactions are thought to make a major contribution to asthmatic airway inflammation. Firstly, lung tissue damage can manifest itself as a consequence of an inappropriate accumulation of eosinophils and the subsequent release of their highly toxic granule proteins. In particular, deposition of eosinophil major basic protein has been heavily implicated in epithelial damage and loss, an event thought to be important in the development of airway hyperresponsiveness. In addition, release of

eosinophil granule-associated products such as chemokines and cytokines at local sites of inflammation is likely to be of significant relevance to both paracrine and autocrine functions. Secondly, a large number of studies have demonstrated that airway epithelial cells are potent sources of pro-inflammatory substances including GM-CSF, IL-1β, IL-6, IL-11, IL-16 and IL-18, together with the chemokines RANTES, eotaxin, macrophage inflammatory protein-1α and IL-8. The profound effects exerted by GM-CSF on eosinophil function include inducing their prolonged survival through the inhibition of apoptosis. Additionally, chemokines such as eotaxin, RANTES and MIP-1α can attract eosinophils to sites of ongoing asthmatic inflammation.

Animal and human studies point to an important function of eosinophils in airway remodelling in asthma, but many questions remain. The cell probably also has a crucial role in natural exacerbations of the disease. Studies on the role of the cell in AHR and mucus production, using eosinophil-lineage depletion in mice, have given conflicting results, although the bulk of evidence still supports a role for eosinophils in acute airway pathology, possibly through the participation of IL-13. The eosinophil-lineage depletion approach might provide a valuable tool for studying the interrelationships between acute and chronic inflammation, in addition to the various components of remodelling and the genes that control these events.

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