

New evidence of inflammation in asthma

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The inflammation of chronic asthma appears to be far more complex than a simple eosinophilic inflammation. All cells of the airways—inflammatory and structural—are involved and become activated including T cells, eosinophils, mast cells, macrophages, epithelial cells, fibroblasts, and even bronchial smooth muscle cells. All these cells play an effector role by the release of pro-inflammatory mediators,¹ cytotoxic mediators, and cytokines resulting in vascular leakage, hypersecretion of mucus, smooth muscle contraction, epithelial shedding, and bronchial hyperresponsiveness. These cells are also involved in the regulation of inflammation of the airways and initiation of the process of remodelling by the release of cytokines and growth factors.

The cellular network in asthma

T lymphocytes play a central role in the development of airway inflammation.² They are present in increased numbers in the airways of patients with fatal asthma³ or in patients with asthma of variable aetiology including occupational asthma.⁴ Most bear CD4 receptors while CD8 positive cells are more rarely identified, even during exacerbations of asthma.⁵ T cells are likely to play a role in controlling the chronic inflammation of asthma. Using *in situ* hybridisation, the Th2 phenotype of T cells has been observed in cells recovered by bronchoalveolar lavage (BAL) from patients with asthma. After allergen challenge, many allergen specific T cells in bronchial biopsy specimens or BAL fluid are of the Th2 phenotype.⁶ Eosinophils are a major target of Th2 cytokines and their number is increased in the airways of asthmatic subjects. In asthma these cells are also activated and release high levels of several mediators such as eosinophilic cationic protein, growth factors,⁷ and metalloproteases. These cells are therefore able to play an important part in both airway inflammation and remodelling. A recent study has suggested that the presence of eosinophilic inflammation is associated with markers of airway remodelling such as increased levels of transforming growth factor (TGF) β expression and a thickened basement membrane.⁸

Bronchial epithelial cells also have an important role in asthma. These cells are functionally activated and release large amounts of 15-HETE, prostaglandin E₂ (PGE₂), fibronectin, and endothelin spontaneously or after stimulation.⁹ In asthma, epithelial cells can express membrane markers such as adhesion molecules,¹⁰ endothelin,¹¹ nitric oxide synthase, cytokines,¹² or chemokines, directly contributing to the development of airway inflammation. Among structural cells, fibroblasts and myofibroblasts also have a fundamental role; their

number can be increased in the airways following allergen challenge¹³ and this has been correlated with the thickness of the basement membrane.^{7 14}

Cell survival in airway tissues

It is now increasingly accepted that inflammation in asthma is caused by increased recruitment of inflammatory cells from the bloodstream to the bronchial mucosa and also by enhanced survival of these cells in the inflamed airways. The survival of inflammatory cells in airway tissues depends on survival factors. Apoptosis, a dynamic process involved in the control of the “tissue load” of cells at inflamed sites, tends to limit inflammatory tissue injury and to promote resolution rather than progression of inflammation.¹⁵ We have recently found that the number of apoptotic eosinophils and macrophages is significantly reduced in the bronchial mucosa of asthmatic subjects compared with normal subjects. Interestingly, the number of apoptotic eosinophils and macrophages was inversely correlated with the clinical severity of asthma, suggesting that reduced apoptosis can influence the clinical severity of the disease.¹⁶

Remodelling of the airways

Asthma is characterised by remodelling of the airways.¹⁷ A typical feature of airway remodelling is the increased thickness of the reticular layer of the basement membrane. Increased expression of growth factors such as TGF β ⁷ and endothelin,¹⁸ together with active involvement of mesenchymal cells,¹⁴ seem to play an important part in the development of the structural alteration of the airways. Another feature of airway remodelling in asthma is the disruption of elastic fibres.¹⁹ It is likely that these alterations are caused by enhanced elastolysis, possibly resulting from the increased levels of elastase activity in the airways of asthmatic patients.²⁰ The development of airway remodelling in asthma is also characterised by synthesis and deposition of the extracellular membrane. In this regard, recent evidence suggests that an imbalance between metalloproteases (MMPs) and tissue inhibitor metalloproteases (TIMPs) may have a crucial role in the increased deposition of the extracellular membrane in the airways leading to thickening of the airway wall.²¹

Two other prominent features of airway remodelling in asthma are smooth muscle and mucous gland hypertrophy and hyperplasia.²² In patients who have died from an asthma exacerbation, the increase in smooth muscle is far greater than in those who died from other causes.²³ Mucous glands are considerably

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enlarged in the segmental bronchi of asthmatic subjects, and Dunhill *et al*²⁴ showed that their volume is twice as high as in normal subjects.

Conclusions

Bronchial inflammation has been demonstrated in asthma and appears to be far more complex than a simple eosinophilic inflammation. There is evidence that the persistent inflammation of the airways is almost always associated with airway remodelling.

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