Mechanisms of asthma

Chris Corrigan

Abstract

Asthma is a syndrome of variable airflow obstruction. It is characterized pathologically by bronchial inflammation with prominent eosinophil infiltration and remodelling changes, physiologically by bronchial hyperresponsiveness, and clinically by cough, chest tightness and wheeze. Cytokines secreted by CD4+ Th2 type T cells play a major role in coordinating asthmatic bronchial inflammation and remodelling, while other effector cells, particularly eosinophils and myofibroblasts, play an intermediary role in airways damage and remodelling. Although the pathological changes in the airways in association with asthma are now well described, there is a gap in our understanding of precisely how these changes cause clinical symptoms. A key aetiological factor for asthma is exposure to inhaled allergens, including occupational allergens, which are probably a major drive to T cell activation in asthma. Genetic factors governing the production of T cell cytokines and their actions on target cells, as well as variability in the structure and development of the mesenchymal elements of the bronchial mucosa, influence the risk of developing asthma. Many other environmental agents exacerbate asthma but the evidence that they cause disease is much less clear.

Keywords asthma; atopy; cytokine; eosinophil; pathogenesis; remodelling; T cell

Clinical pathology

The diagnosis of asthma is made on the basis of typical symptoms and abnormalities in lung function. The key clinical features of asthma include the following.

Variable airways obstruction – airways obstruction in asthma, as measured by spirometry, may vary spontaneously from none to severe in the course of hours to minutes, and improves after suitable therapy. Obstruction, particularly of the smaller airways, in asthmatics causes shortness of breath, impaired exercise tolerance, tightness in the chest which may be perceived as wheeze, and chest hyperinflation (small airways obstruction prevents complete emptying of the alveoli, causing gas trapping).

Non-specific bronchial hyperreactivity – this refers to the tendency of asthmatic airways to constrict in response to a whole host of non-specific (that is, non-immunological) stimuli (including for example strong smells, cold air, fog, smoke, exercise, aerosol sprays, dust) that would not cause clinically significant bronchoconstriction in non-asthmatics. Bronchial hyperreactivity causes excessive cough and contributes to bronchospasm, which may have different triggers in different patients.

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Histopathology

Asthma is characterized by inflammatory changes throughout the airways, but not the alveoli or lung parenchyma. The inflammation is characterized by the activation of CD4+ helper T lymphocytes,[1] as well as a selective accumulation of eosinophil leukocytes in the bronchial mucosa (Figures 1 and 2),[2] although these changes do not allow a definitive diagnosis on histopathological grounds. Some chronic, severe asthmatics show a paucity of mucosal eosinophils, but a more prominent neutrophil leukocyte infiltrate.[3] Mast cells are present in the bronchial mucosa, as they are at all mucosal surfaces, but their numbers are not particularly elevated in asthmatics. It has so far not been possible to associate aetiological subdivisions of asthma with reproducible and discernible variability in histopathology.

Asthma is also associated with structural changes in the airways collectively termed 'airways remodelling' (Figure 3).[4,5] These include hypertrophy and hyperplasia of airways smooth muscle cells, increased numbers of mucous goblet cells in the airways epithelium, laying down of fibrous proteins (including collagen, fibronectin and tenascin) beneath the epithelial basement membrane and in the submucosa, and neovascularization (proliferation of vascular capillary beds within the submucosa).

Pathophysiology

Asthmatic inflammation appears to be coordinated principally by activated CD4+ T lymphocytes of the Th2 type phenotype, characterized particularly by the production of the cytokines interleukin (IL)-4, IL-13 and IL-5 (Figure 2).[1] The cytokine IL-5 acts on eosinophils, while IL-4 and IL-13 up-regulate adhesion molecules in the capillary endothelium of the bronchial mucosa,

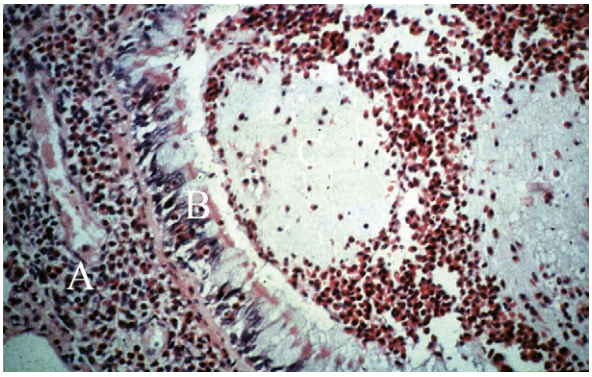
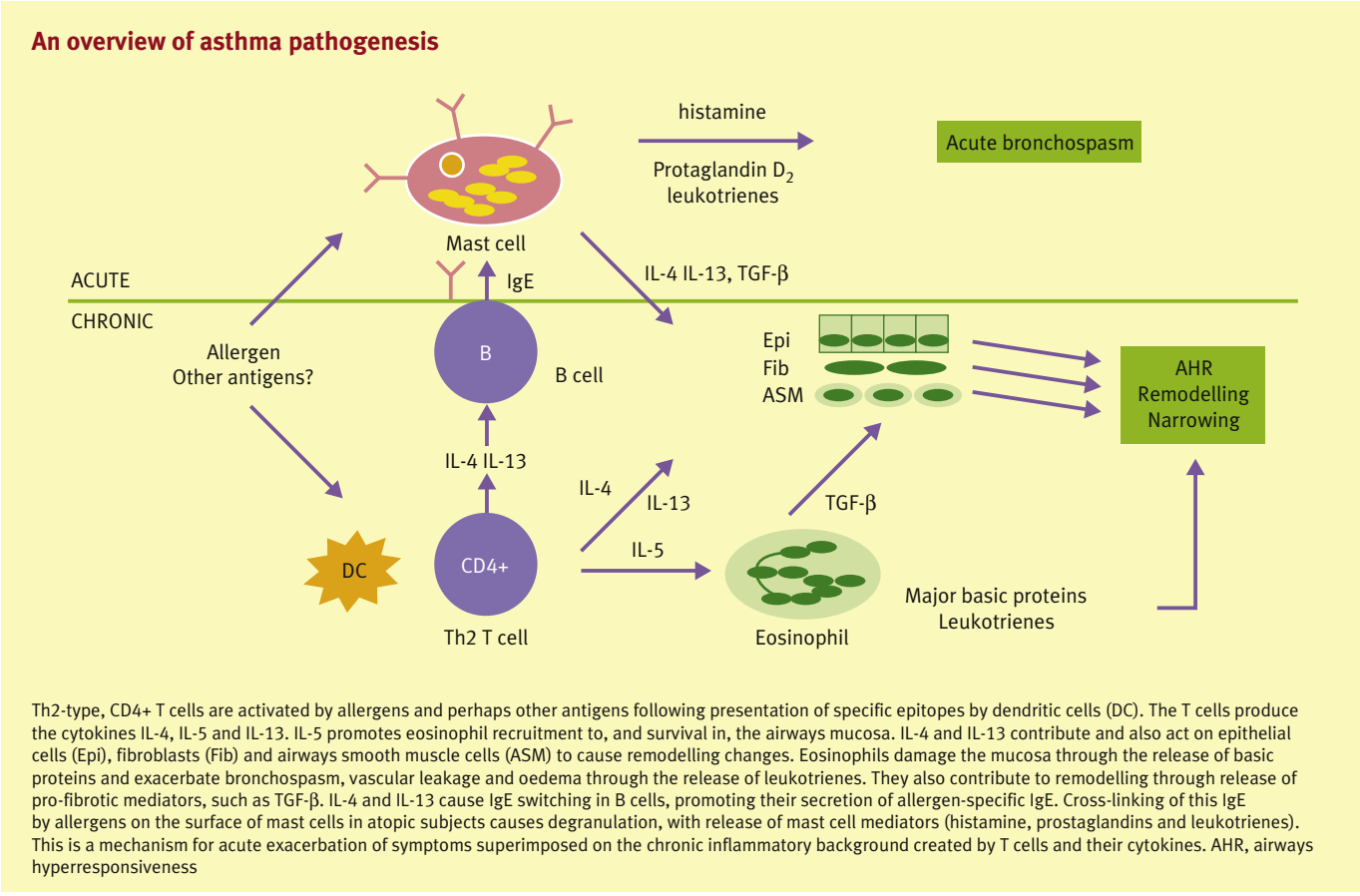


Figure 1 Section of an airway from a patient who died of acute asthma stained with haematoxylin and eosin. Eosinophils ('eosin loving') cells stain pink because of their basic proteins. Note the intense eosinophil infiltrate in the submucosa **A** the bronchial epithelium **B** and surrounding the large mucus plug which is occluding the lumen of the bronchiole **C**.



Th2-type, CD4+ T cells are activated by allergens and perhaps other antigens following presentation of specific epitopes by dendritic cells (DC). The T cells produce the cytokines IL-4, IL-5 and IL-13. IL-5 promotes eosinophil recruitment to, and survival in, the airways mucosa. IL-4 and IL-13 contribute and also act on epithelial cells (Epi), fibroblasts (Fib) and airways smooth muscle cells (ASM) to cause remodelling changes. Eosinophils damage the mucosa through the release of basic proteins and exacerbate bronchospasm, vascular leakage and oedema through the release of leukotrienes. They also contribute to remodelling through release of pro-fibrotic mediators, such as TGF-β. IL-4 and IL-13 cause IgE switching in B cells, promoting their secretion of allergen-specific IgE. Cross-linking of this IgE by allergens on the surface of mast cells in atopic subjects causes degranulation, with release of mast cell mediators (histamine, prostaglandins and leukotrienes). This is a mechanism for acute exacerbation of symptoms superimposed on the chronic inflammatory background created by T cells and their cytokines. AHR, airways hyperresponsiveness

Figure 2

resulting in increased adhesion of eosinophils to the endothelium whereby they are recruited into the tissues. Once in the tissues, IL-5 prolongs the survival of eosinophils and activates the release of their granule proteins. These proteins carry a high negative charge and are cytotoxic. Mucosal epithelial damage is thought to be one cause of hyperresponsive airways in asthma, although the precise mechanism is unknown. Other eosinophil mediators, such as cysteinyl leukotrienes, promote vascular leakage and thus oedema of the lining of the airways, and are also very potent constrictors of bronchial smooth muscle. All of these effects probably contribute to airways obstruction.[6]

These same cytokines, as well as tumour necrosis factor (TNF)-α, have been implicated in causing remodelling changes in the airways as described above. Some cytokines, such as IL-13, act directly on target cells, such as mucous glands, while others act through intermediary cells, such as eosinophils. For example, activated eosinophils produce a growth factor called transforming growth factor (TGF)-β which acts on fibroblasts, causing them to transform into myofibroblasts, a cross between fibroblasts and smooth muscle cells which are responsible for the laying down of fibrous proteins in the bronchial mucosa. TGF-β and other growth-regulating cytokines also cause increased proliferation of airways smooth muscle cells. Injured epithelial cells also release TGF-β forming the so-called 'epithelial mesenchymal trophic unit' which may also contribute to remodelling changes in asthmatic airways.[7]

Finally, IL-4 and IL-13 are the only human cytokines which induce B lymphocytes to switch to IgE synthesis following activation by interaction with antigen-specific T cells (Figure 2). These cytokines are therefore implicated in the pathogenesis of atopy (a propensity for inappropriate production of IgE antibodies against antigens or 'allergens' encountered at mucosal surfaces detected by skin prick or laboratory tests).

Cytokines derived largely from T cells are thought to drive most of the inflammatory and airways structural changes characteristic of asthma, regardless of its aetiology, and also play an important role in the development of atopy (Figure 4). Airways structural cells, as well as other infiltrating leukocytes, including eosinophils and mast cells, are likely to also contribute to the production of cytokines and growth factors causing airways remodelling.

The antigenic drive to T cell activation in asthma is unknown. There is a tacit assumption that inflammation in asthma is driven largely by T cells which recognize inhaled allergens, some of which may also interact with allergen-specific B cells resulting in IgE production and the atopic phenotype. All individuals, however, have allergen-specific T cells, and a major facet of current research in asthma and atopy is to attempt to understand why allergens produce a particularly exuberant Th2-type T cell response in patients with asthma and atopy, leading to inflammation of the bronchial mucosa and the atopic phenotype on the one hand, with inappropriate production of IgE against allergens on the other. It is quite possible that other antigens, such as viral antigens, also drive T cell activation in asthma in particular circumstances. T cell activation may become self-perpetuating with time in the manner of an autoimmune disease.