Asthma mechanisms

Peter J Barnes

Abstract

Asthma is characterized by a chronic allergic inflammatory response in all airways that results in bronchoconstriction, vasodilatation, airway oedema and activation of sensory nerve endings. In asthmatic airways, several inflammatory cells are activated, including mast cells and dendritic cells, and there is infiltration of activated lymphocytes and eosinophils. The predominant lymphocytes in allergic asthma are helper T cells (Th2) and in non-allergic asthma innate lymphoid cells. In severe asthma, Th17 cells may also be involved and linked to neutrophilic inflammation. Structural cells, especially airway epithelial cells and airway smooth muscle cells, can also release inflammatory mediators to drive inflammation. Many (>100) mediators have been implicated in asthma, including lipid mediators, such as cysteinyl leukotrienes, prostaglandin D_2, cytokines, particularly T2 cytokines, interleukins 4, 5 and 13, and chemokines that attract inflammatory cells such as Th2 cells and eosinophils into the airways. Chronic inflammation can lead to structural changes, with friability of airway epithelial cells, increased bulk of airway smooth muscle, fibrosis under the epithelium, airway smooth muscle hyperplasia and hypertrophy, increased blood vessels and mucus hyperplasia. Superimposed on the chronic persistent inflammation are acute increases linked to exacerbations and loss of asthma control.

Keywords Airway epithelium; airway smooth muscle; cytokines; eosinophil; inflammation; inflammatory mediators; lymphocyte; mast cell

Key points

- Asthma involved chronic inflammation of the airways, with activation and infiltration of inflammatory cells
- Mast cell activation causes bronchoconstriction due to the release of inflammatory mediators that contract airway smooth muscle cells
- Several types of lymphocyte are involved in orchestrating inflammation of the airways, particularly Th2 and ILC2 cells which result in eosinophilic inflammation
- Chronic inflammation leads to structural changes with subepithelial fibrosis, increased airway smooth muscle, mucus secreting cells and blood vessels

Introduction

Asthma is associated with chronic inflammation of the lower airways mucosa and is usually controlled when the inflammation is effectively suppressed by corticosteroids.

Pathology

The pathology of asthma has been elucidated from bronchial biopsies and by studying the lungs of patients who have died of asthma. The airway mucosa is infiltrated by activated eosinophils and T lymphocytes, and mucosal mast cells are activated.[1] However, inflammation is not closely related to disease severity, being seen even in atopic patients without asthma symptoms. The inflammation is usually reduced by inhaled corticosteroids.

There are also characteristic structural changes in the airways (remodelling). Characteristic thickening of the basement membrane under the airway epithelium due to subepithelial deposition of collagen is likely to be caused by eosinophilic release of fibrogenic mediators. The epithelium is often friable and often shed. The airway wall can be thickened and oedematous. In fatal asthma, the airway lumen can be occluded by mucous plugs, which are composed of mucous glycoproteins secreted from goblet cells and plasma proteins exuded from leaky bronchial vessels (Figure 1). The airways appear reddened as a result of vasodilatation and increased numbers of blood vessels (angiogenesis). Different phenotypes of asthma, including atopic (extrinsic), non-atopic (intrinsic), occupational, aspirin-sensitive and paediatric, have similar pathology. The inflammatory changes are found in all airways from trachea to terminal bronchioles, but do not extend to the lung parenchyma as in chronic obstructive pulmonary disease. Small airway inflammation is particularly a feature in patients with severe asthma.

Airway inflammation

Although airway inflammation is critical to the mechanisms underlying asthma, it is not certain how inflammatory cells interact and how this leads to the symptoms and clinical features of asthma (Figure 2). Airway inflammation in asthma is associated with airway hyperresponsiveness (AHR), the physiological abnormality that underlies variable airflow obstruction. The pattern of inflammation in asthma is characteristic of allergic diseases, with similar inflammatory cells seen in the nasal mucosa in rhinitis (Figure 3).[2] An indistinguishable pattern of inflammation is found in intrinsic asthma, perhaps reflecting local rather than systemic IgE production. Acute-on-chronic inflammatory episodes, corresponding to exacerbations of asthma, are usually triggered by upper respiratory tract virus infections or allergen exposure. Although the common pattern of

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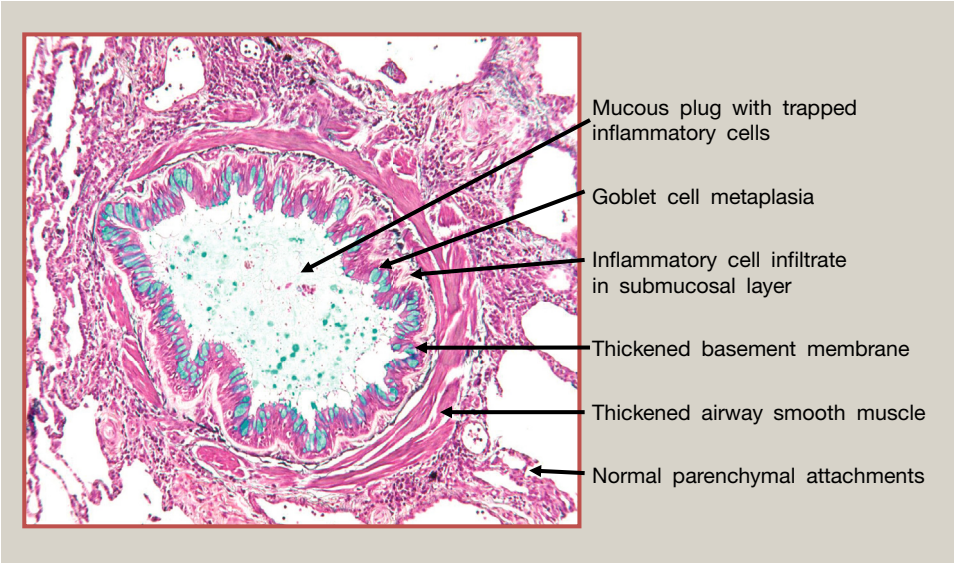

Figure 1 Pathology of fatal asthma. The lumen of a small airway is occluded with a mucous plug, and there is goblet cell metaplasia. The airway wall is thickened, with an increase in basement membrane thickness and airway smooth muscle. Courtesy of Dr. J. Hogg, University of British Colombia, USA.

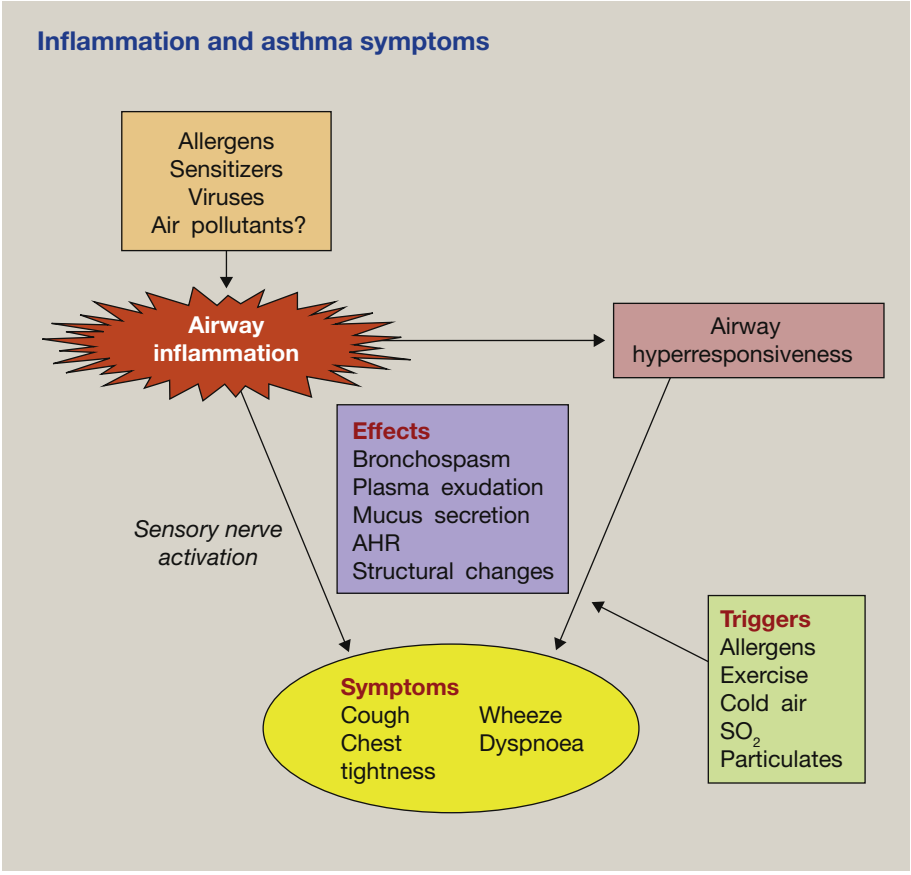

Figure 2 Inflammation in asthmatic airways results in airway hyperresponsiveness (AHR), which allows triggers such as exercise or sulphur dioxide (SO_2) to cause symptoms. However, inflammation can directly lead to symptoms through the activation of airway sensory nerves.