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

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

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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

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 sub-epithelial fibrosis, increased airway smooth muscle, mucus secreting cells and blood vessels

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 (SO₂) to cause symptoms. However, inflammation can directly lead to symptoms through the activation of airway sensory nerves.

Figure 3 Several inflammatory cells interact through the release of inflammatory mediators, which cause bronchoconstriction, vasodilatation, plasma exudation, mucus secretion, epithelial shedding, sensory nerve activation and cholinergic reflex effects. Over time there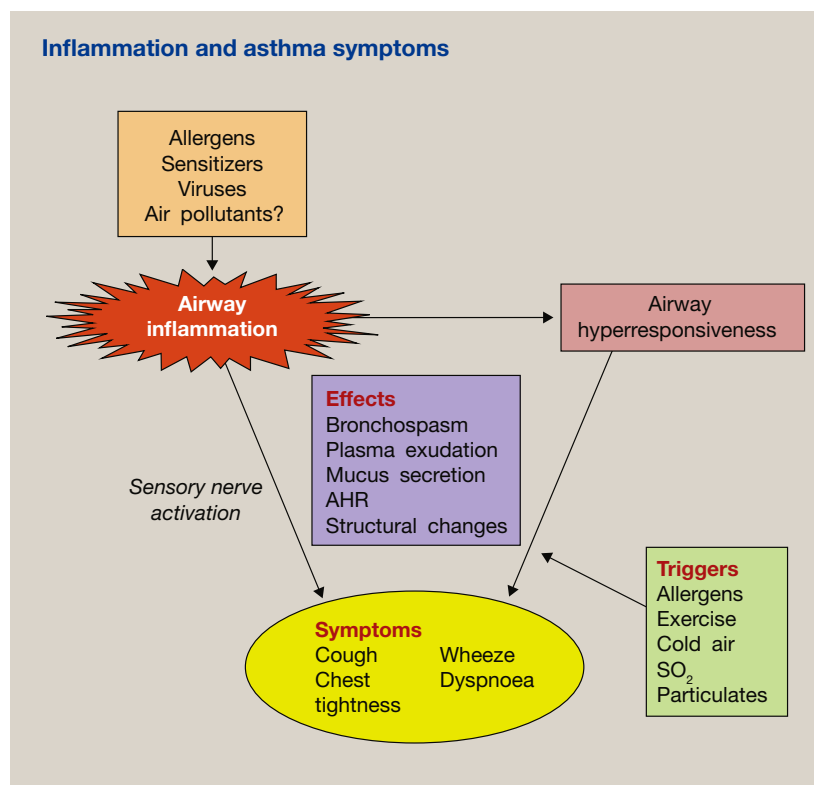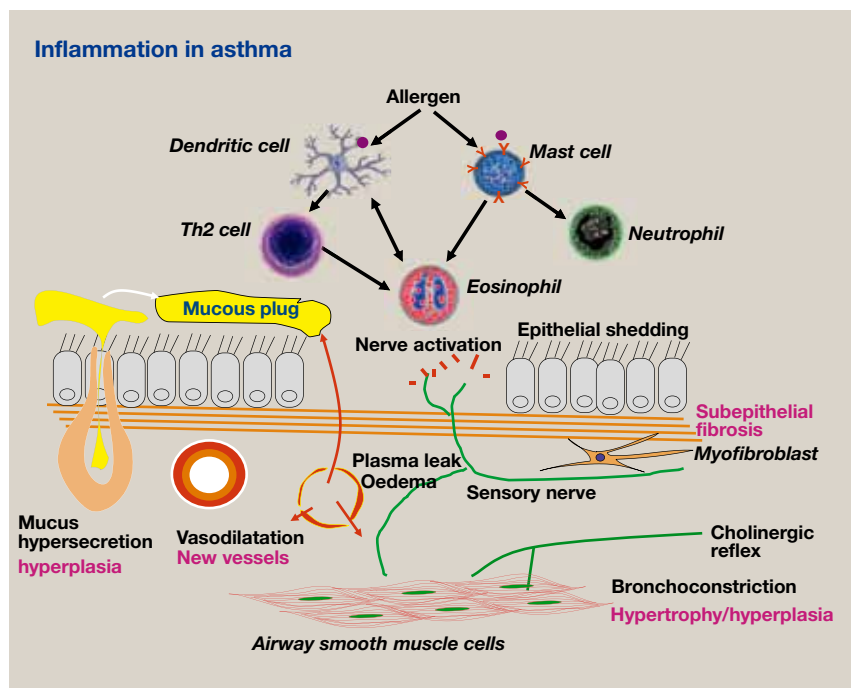 are structural changes including increases in airway smooth muscle and blood vessels and mucus cell hyperplasia. Subepithelial fibrosis is found even in early disease.

inflammation is eosinophilic, some patients with severe asthma and asthmatics who smoke show a predominantly neutrophilic pattern that is less sensitive to corticosteroids. Several inflammatory cells are involved in asthma.

Mast cells

These play a key role in producing asthma symptoms as their mediators cause bronchoconstriction. Mast cells are activated by allergen through binding to IgE bound to high-affinity IgE receptors on mast cells (Fc_eRI), and also by other triggers such as exercise and hyperventilation (via increased fluid osmolality in airway linings). Activated mucosal mast cells occur at the airway surface and in the airway smooth muscle layer in patients with asthma, but not healthy individuals. Mast cells release bronchoconstrictor mediators including histamine, prostaglandin (PG) D_2 and cysteinyl leukotrienes, as well as several cytokines, chemokines, growth factors, neurotrophins and proteases. The role of mast cells in chronic allergic inflammation is uncertain.
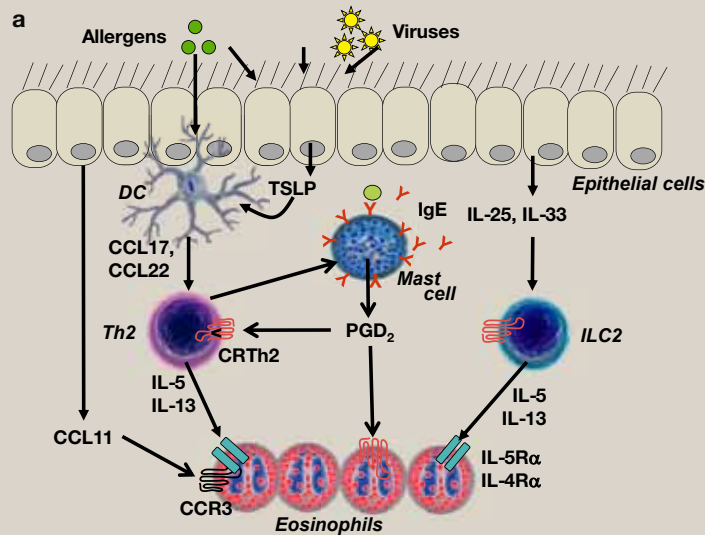
Macrophages and dendritic cells

Macrophages are derived from blood monocytes, traffic into the airways in asthma and can be activated by allergens via low-affinity IgE receptors (Fc_eRII). Macrophages produce proinflammatory cytokines and also anti-inflammatory mediators such as interleukin (IL)-10; their role in asthma is therefore uncertain. Dendritic cells are specialized macrophage-like cells that lie in the airway epithelium; they are the major antigen-presenting

cells in the airways. They take up allergens, process them to peptides and migrate to local lymph nodes where they present the allergenic peptides to uncommitted T lymphocytes to programme the production of allergen-specific T cells. Immature dendritic cells in the respiratory tract promote helper T cell (Th2) differentiation. The cytokine thymic stromal lymphopoietin (TSLP) released from epithelial cells in asthmatic patients programmes dendritic cells to release chemokines that attract Th2 cells into the airways.[3]

Eosinophils

Eosinophilic inflammation is a characteristic feature of asthmatic airways (Figure 4a). Eosinophils are linked to the development of AHR through the release of basic proteins and oxygen-derived free radicals. Eosinophil recruitment involves several stages: adhesion of eosinophils to vascular endothelial cells in the airway circulation by interaction between adhesion molecules; migration into the submucosa under the direction of chemokines; and subsequent activation and prolonged survival in the airways. IL-5 plays a critical role in the generation of eosinophils in bone marrow and their survival in the airways. Antibodies blocking IL-5 cause a profound and prolonged reduction in circulating and sputum eosinophils. This is not associated with reduced AHR or asthma symptoms, but selected patients with corticosteroid-resistant airway eosinophils show a reduction in exacerbations. Eosinophils may be important in release of the growth factors involved in airway remodelling and in exacerbations, but probably not in AHR.

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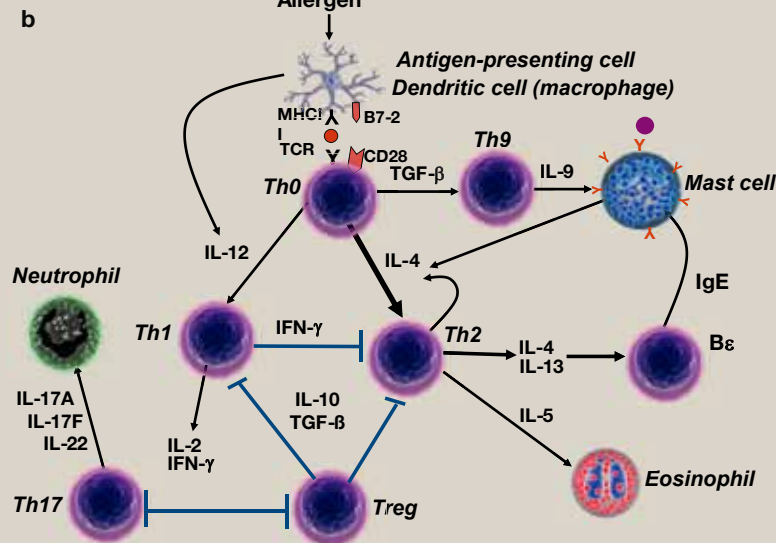
Figure 4 (**a**) Eosinophilic inflammation in asthma. Allergens are taken up by dendritic cells (DCs), which attract Th2 lymphocytes. These secrete T2 cytokines that are involved in mast cell and eosinophil recruitment and survival. Mast cells also attract Th2 cells and eosinophils through the release of PGD$_2$ through chemotactic receptors on Th2 cells (CRTh2). Epithelial cells release IL-25 and IL-33 to recruit type 2 innate lymphoid cells (ILC2s); these also attract eosinophils. (**b**) Lymphocytes in asthma. Several types of T cell participate in the pathogens of asthma. Allergen processed by dendritic cells lead to differentiation of Th2 cells rather than the normally predominant Th1 cells. IL-4 and IL-3 from Th2 cells cause switching of B cells to produce IgE (Bϵ). Th9 cells may play a role in mast cell regulation and Th17 cells in neutrophilic inflammation Regulatory T cells (Treg) may be defective leading to increased Th1, Th2 and Th17 activation.

Neutrophils

Increased numbers of activated neutrophils are found in the sputum and airways of some patients with severe asthma, in asthmatics who smoke and during exacerbations, although some patients with milder asthma have predominant neutrophils. The mechanisms of neutrophilic inflammation are uncertain and could be related to the use of high dosages of corticosteroids prolonging neutrophil survival in the airways, or to bacterial infection. The role of neutrophils in asthma is also unclear, and anti-neutrophilic therapies have so far been ineffective.

Lymphocytes

B lymphocytes are important in producing IgE, and B cells producing IgE locally in the airways have been identified even in non-atopic asthmatic individuals. T lymphocytes play an important role in coordinating the inflammatory response through the release of specific patterns of cytokines (T2 cytokines), resulting in the recruitment and survival of eosinophils and in the maintenance of a mast cell population in the airways (Figure 4b). The naive immune system and immune system in asthma are skewed to express the Th2 phenotype, whereas Th1 cells predominate in healthy airways. Th2 cells release IL-5, which drives eosinophilic inflammation, and IL-4 and IL-13, which stimulate IgE formation. Regulatory T cells suppress Th2 cells and can be reduced in asthma. Type 2 innate lymphoid cells (ILC2s) without T cell receptors also release Th2 cytokines and have been identified in the airways of asthmatic patients. ILC2s are regulated by epithelial cytokines, such as IL-25 and IL-33, and may be important in non-allergic asthma.

Structural cells

Structural cells in the airways, including epithelial cells, fibroblasts and airway smooth muscle cells, are also important sources of inflammatory mediators such as cytokines and lipid mediators.[3] Epithelial cells play a key role in translating inhaled environmental signals into an airway inflammatory response and are probably major targets for inhaled corticosteroids.

Inflammatory mediators

Over 100 inflammatory mediators have been implicated in asthma. These can have a variety of effects on the airways, accounting for the pathological features of asthma. Mediators such as histamine, PGD_2 and cysteinyl leukotrienes contract airway smooth muscle, increase microvascular leakage and airway mucus secretion, and attract other inflammatory cells. Because each mediator has many effects, the role of individual mediators in the pathophysiology of asthma is not always clear. Furthermore, targeting single mediators is unlikely to have a major impact in clinical asthma. However, clinical studies with anti-leukotrienes suggest that cysteinyl leukotrienes play some role in bronchoconstriction.

Cytokines

Multiple cytokines orchestrate chronic inflammation in asthma. The T2 cytokines (IL-4, IL-5, IL-9, IL-13) mediate allergic inflammation, whereas proinflammatory cytokines such as tumour necrosis factor alpha and IL-1β amplify the inflammatory response and play a role in more severe disease. TSLP is an upstream cytokine released from epithelial cells in asthma that orchestrates the release of chemokines that selectively attract T2 cells. Th17 cells release IL-17 and IL-22, which are increased in severe asthma and may regulate neutrophilic inflammation.[4] Some anti-inflammatory cytokines (IL-10, IL-12) can be deficient in asthma.

Chemokines

Chemokines are involved in attracting inflammatory cells from the bronchial circulation into the airways. Eotaxin (CCL11) is selectively attractant to eosinophils via CCR3 and is expressed by epithelial cells in asthma, whereas CCL17 (TARC) and CCL22 (MDC) from epithelial cells attract Th2 cells via CCR4 (Figure 4).

Oxidative stress

Activated inflammatory cells such as macrophages and eosinophils produce reactive oxygen species. Evidence for increased oxidative stress in asthma is provided by increased concentrations of 8-isoprostane (a product of oxidized arachidonic acid) in exhaled breath condensates and increased ethane (a product of lipid peroxidation) in the expired air of asthmatic patients. Increased oxidative stress is related to disease severity, can amplify the inflammatory response and can reduce responsiveness to corticosteroids.

Nitric oxide (NO)

NO is produced by NO synthases in several airway cells, particularly epithelial cells and macrophages. The fractional exhaled NO in asthmatic patients is higher than in healthy individuals and is related to the eosinophilic inflammation. Increased NO can contribute to the bronchial vasodilatation observed in asthma. Fractional exhaled NO is increasingly used in the diagnosis and monitoring of asthmatic inflammation, although it is not yet used routinely in clinical practice.

Transcription factors

Proinflammatory transcription factors such as nuclear factor kappa B and activator protein-1 are activated in asthmatic airways and orchestrate the expression of multiple inflammatory genes. More specific transcription factors that are involved include nuclear factor of activated T cells and GATA-3, which regulate the expression of T2 cytokines in Th2 and ILC2 cells.

Effects of inflammation

The chronic inflammatory response in asthma has several effects on the target cells in the airways, with characteristic pathophysiological and remodelling changes. Continuous inflammation and repair proceeds simultaneously.

Airway epithelium

Airway epithelial shedding may be important in contributing to AHR and explain how several mechanisms, such as ozone exposure, virus infections, chemical sensitizers and allergens (usually proteases), can lead to its development, as all of these can cause epithelial disruption. Epithelial damage may contribute to AHR by several mechanisms: loss of barrier function to allow penetration of allergens; loss of enzymes (such as neutral endopeptidase) that degrade certain peptide inflammatory mediators; loss of a relaxant factor (epithelial-derived relaxant factor); and exposure of sensory nerves, which may lead to reflex neural effects on the airway.

Fibrosis

In asthmatic patients, the basement membrane is apparently thickened because of subepithelial fibrosis with deposition of types III and V collagen below the true basement membrane. This is associated with eosinophil infiltration, presumably through the release of profibrotic mediators such as transforming growth factor beta. Mechanical manipulations can alter the phenotype of airway epithelial cells in a profibrotic fashion. In more severe disease, fibrosis within the airway wall can contribute to irreversible narrowing of the airways.

Airway smooth muscle

In vitro airway smooth muscle from asthmatic patients usually shows no increased contractility, although there may be reduced bronchodilator responses. In asthmatic airways, there is characteristic hypertrophy and hyperplasia of airway smooth muscle, presumably because of stimulation of airway smooth muscle cells by growth factors such as platelet-derived growth factor or endothelin-1 released from inflammatory or epithelial cells.[5] Airway smooth muscle also releases several inflammatory mediators, maintaining inflammation in the airway. Bronchial thermoplasty selectively ablates airway smooth muscle and provides some clinical benefit in highly selected patients.

Blood vessels

There is increased airway mucosal blood flow in asthma, which can contribute to airway narrowing. An increase in the number of blood vessels in asthmatic airways results from angiogenesis in response to growth factors, particularly vascular endothelial growth factor. Microvascular leakage from postcapillary venules in response to inflammatory mediators is observed in asthma, resulting in airway oedema and plasma exudation into the airway lumen.

Mucus hypersecretion

Increased mucus secretion contributes to the viscid mucous plugs that occlude asthmatic airways, particularly in fatal asthma. There is hyperplasia of submucosal glands that are confined to large airways, and increased numbers of epithelial goblet cells. IL-13 induces mucus hypersecretion in experimental models of asthma.

Neural regulation

Cholinergic pathways (i.e. acetylcholine acting on muscarinic receptors) cause bronchoconstriction and can be activated via a neural reflex by triggers of airway sensory nerves. Inflammatory mediators can activate sensory nerves, resulting in reflex cholinergic bronchoconstriction or release of inflammatory neuropeptides. Long-acting muscarinic antagonists have a beneficial effect in some patients with severe asthma. Inflammatory products can also sensitize sensory nerve endings in the airway epithelium such that the nerves become hyperalgesic. Various ion channels on sensory nerves, including transient receptor potential channels, may be important in mediating the coughing of asthma. Neurotrophins, such as nerve growth factor, can be released from various airway cell types, including epithelial cells and mast cells, and can cause proliferation and sensitization of airway sensory nerves. Airway nerves can also release neurotransmitters, such as substance P, which have inflammatory effects. ◆

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