Pathogenesis of asthma

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Asthma is a chronic inflammatory airway disease that typically manifests itself as chest tightness, wheezing, cough, and dyspnea, all symptoms that are associated with airway obstruction. They can occur spontaneously, often during the night or the early morning hours, following exercise, or after exposure to an allergen. These symptoms and airflow limitation are associated with an exacerbation of the underlying airway inflammation. The cells and mediators involved in these exacerbations are probably different depending on the stimulus (eg, nocturnal, exercise-induced, allergen-induced, or virus-induced); however, the end results probably include smooth muscle contraction and inflammation that resolve spontaneously or with appropriate therapy.

Improvement in airflow limitation often parallels the resolution of asthma symptoms. Although asthma has been historically viewed as a reversible disease, more recent evidence indicates that permanent structural changes in the airway are typically seen in asthma and include subbasement membrane fibrosis, smooth muscle hyperplasia, new vessel formation, and glandular hyperplasia [1]. These changes are collectively referred to as airway remodeling and contribute to asthma pathogenesis, disease severity, progression, and lack of reversibility. Furthermore, there is recent evidence that, over the long term, asthma is associated with an accelerated decline in lung function [2–5]. This decline, though relatively smaller than the decline seen in smokers and those with chronic obstructive lung disease, is also an indication of structural and probably permanent changes in the airways of patients with persistent asthma.

Despite a greatly enhanced understanding of the pathogenesis of asthma over the past 2 decades, there has been an alarming trend of increased incidence and morbidity of asthma, especially in westernized countries. The
etiology of that increase remains under intense investigation. Asthma is believed to affect more than 15 million people in the United States, and although most patients have a mild, well-controlled version of the disease, it still accounts for more than 10 billion dollars of direct medical and indirect costs to the economy [6].

**Cellular inflammation in asthma**

Although the mast cell has received attention as the principal effector cell of allergic reaction in asthma, other cells have also been acknowledged as playing an important role in the inflammatory airway process; these include eosinophils, lymphocytes, macrophages, dendritic cells, and neutrophils. Furthermore, structural cells (e.g., epithelial cells, fibroblasts, and smooth muscle cells) have also been recognized as potential contributors to ongoing inflammation and injury [7]. Although most of the earlier information stems from autopsy studies of fatal asthma, more recent evidence has been gathered using fibro-optic bronchoscopy, bronchoalveolar lavage (BAL), and endobronchial biopsy [8]. Furthermore, noninvasive studies, such as sputum induction and exhaled breath condensate, have been added recently to the tools of investigating airway inflammation in asthma and have been used to gather further evidence of the contribution of various inflammatory cells and mediators to airway inflammation in asthma [9].

**Mast cells**

The mast cell is a key player in the early allergic response that typically starts within minutes of exposure to an appropriate antigen. When exposed to an adequate dose of antigen, allergic asthma patients develop acute symptoms (coughing, wheezing, and dyspnea). These symptoms peak within 10 to 15 minutes and typically resolve within 60 minutes of the exposure [10]. The mast cell surface-bound IgE is cross-linked by the antigen, leading to mast cell activation and release of potent mediators such as histamine, leukotrienes, prostaglandin D2, thromboxane B2, and platelet-activating factors (Fig. 1) [11,12]. These mediators result in airway smooth muscle contraction, edema, and enhanced mucous secretions that lead to airflow limitation and the manifestation of acute asthma symptoms.

There is evidence that the mast cell may also contribute to ongoing airway inflammation through the release of cytokines (IFN-γ, IL-1, IL-4, IL-5, IL-6, IL-8, IL-16) and chemokines (MIP-1α, MIP-1β, MCP, and RANTES) [11]. Through the release of these factors, the mast cells could conceivably contribute not only to the acute allergic response but also to the persistence of airway inflammation and occurrence of the late phase response. The role of mast cells in the acute allergic response is well established and has been recently substantiated in studies using monoclonal anti-IgE antibodies that
have demonstrated significant down-regulation of the early allergic asthmatic response [13–15]; however, there is also evidence of ongoing release of histamine that is associated with increased airway responsiveness and obstruction in asthma [16]. The exact source of histamine in the airway of patients with chronic stable asthma is not well established, because the level of BAL histamine did not correlate with levels of other mast cell mediators (eg, tryptase) [16]; therefore, the basophil, another cell capable of generating histamine, has been proposed as a potential source for ongoing release of histamine and a contributor to allergic airway disease [17].

**Eosinophils**

Eosinophils are closely linked to allergic diseases. They are often present in airways of allergic asthmatics and correlate with parameters of disease
severity. These cells contain potent mediators in their granules, including major basic protein, eosinophil cationic protein, eosinophil derived neurotoxin, and eosinophil peroxidase (Fig. 1) [18]. These proteins—major basic protein, in particular—can induce airway damage and contribute to airway hyperresponsiveness [19]; therefore, the eosinophil has been proposed as a principal effector cell in asthma pathogenesis. In addition, these cells, which include leukotrienes, cytokines, matrix metalloproteinase, and reactive oxygen species, have the capacity of generating other important factors that could contribute to airway obstruction and injury.

Further evidence supporting the contribution of eosinophils to airway disease in asthma comes from studies of allergen challenge in which enhanced eosinophil numbers and activation have been demonstrated during and following the late allergic response. Typically the eosinophils are recruited to the airway a few hours after an allergen is inhaled [20–22], peak 2 to 4 days following the locally instilled allergen [23–27], and can persist for 2 to 4 weeks thereafter [28]. Their maturation activation and recruitment to the airway is strongly influenced by IL-5 [29]. Levels of IL-5 are increased in blood [30] and BAL fluid of allergic asthma subjects [31,32], especially following allergen challenge [23,33,34]. Corticosteroids, which are the cornerstone of asthma therapy, led to dramatic reduction in the number of circulating and airway eosinophils in association with improvement in asthma symptoms and airway obstruction [35]. Despite the strong evidence for their contribution to asthma, recent clinical trials, using a monoclonal antibody against IL-5, found that this compound succeeded in dramatically reducing circulating and sputum eosinophils while the symptoms of asthma showed no improvement [36]. Although this is only preliminary evidence, it has certainly raised questions regarding the significance of eosinophils in the pathogenesis of asthma.

**Neutrophils**

Studies of asthmatic patients that used bronchoscopy techniques over the past 2 decades have, for the most part, focused on the role of the eosinophil in the pathogenesis of asthma; however, recent studies that have evaluated acute asthma exacerbations (infectious [37,38] as well as noninfectious [39,40]) and severe nonsteroid responsive asthma [41–43] have demonstrated that, in these patients, the airway has an increased number of neutrophils. These cells can presumably contribute to the pathogenesis of asthma through production of lipid mediators, reactive oxygen species, and proteases (myeloperoxidase and matrix metalloproteinase; Fig. 1) [44].

Even in the antigen challenge model, in which eosinophils are predominant cells, the neutrophils are recruited to the airways before the eosinophils, and they are a predominant cell within 6 hours after the challenge [45,46]. Leukotriene B₄, IL-8, GM-CSF, and TNF-α attract and activate
neutrophils and reduce their apoptosis (programmed cell death). Interestingly, the numbers of neutrophils seen 6 hours after local allergen challenge correlate with the level of IL-8 in BAL fluid [45,46], suggesting that this cytokine plays an important role in neutrophil recruitment to the airway. Paradoxically, corticosteroid therapy, which is very effective in reducing eosinophil numbers, leads to up-regulation of neutrophil activity and numbers by suppressing neutrophil apoptosis [47]. In addition to their well-known contribution to asthma induced by viral infections or occupation exposure, there has been increased focus on the role of neutrophil in other asthma manifestations, particularly in patients with severe, persistent asthma [48].

Lymphocytes

Lymphocytes—T cells, in particular—play a key role in the pathogenesis of asthma. There has been special emphasis on a T cell subset, the Th2 type, that secrete cytokines such as IL-4, IL-5, IL-9, and IL-13 [49], because these cells are increased in bronchoalveolar lavage fluid of atopic asthmatics [30,50–52] and increase further following the introduction of an allergen (Fig. 1) [33,34,53]. Through the generation of these cytokines, Th2 cells can contribute to eosinophil recruitment and activation, IgE production, mucous secretion, and expression of adhesion molecules such as VCAM-1, the latter of which is essential for selective recruitment of eosinophils [49]. One of the important cytokines in allergic response is IL-5, which regulates the terminal differentiation of eosinophil in the bone marrow, primes the eosinophil for activation, and enhances its survival [18]. Levels of IL-5 correlate with the number of BAL eosinophils obtained after antigen challenge in allergic and asthmatic subjects [16,24,33,34,54]. Giving this cytokine by inhalation to allergic asthma subjects leads to increased numbers of eosinophils in the sputum and enhanced airway responsiveness [55]. The T cell is also capable of producing numerous chemokines and cytokines that contribute to up-regulation of other inflammatory cells and worsening of acute and chronic inflammation.

Macrophages

Macrophages are predominant resident cells in the lower airway and represent more than 90% of cells recovered by bronchoalveolar lavage in normal and stable asthmatic subjects. They are key contributors to normal host defense by phagocytosis, generation of enzymes, and reactive oxygen species. They can also up-regulate the inflammatory response by generations of cytokines such as GM-CSF, IL-1, IL-6, lipid mediators (LTB4, C4, D4, PGD2, and thromboxane A2), and generations of matrix metalloproteinase (Fig. 1) [56–59]. There has been increased interest in the ability of
macrophages to generate anti-inflammatory cytokines such as IL-10, IL-12, and TGF-β. A decrease in production of these cytokines has been proposed as a potential mechanism for up-regulated airway inflammation in asthma [60,61]. Finally, alveolar macrophages can function as antigen-presenting cells in the airway [62,63]; however, dendritic cells are the “professional” antigen-presenting cells in the lung [64,65] and serve to take up an antigen and present it to T lymphocytes with subsequent development of a Th2 cell type that can contribute to eosinophil maturation (through generation of IL-5) and IgE production (through generation of IL-4).

**Epithelial cells and fibroblasts**

While epithelial cells and fibroblasts are traditionally viewed as structural cells, they are being increasingly recognized for their ability to contribute to airway inflammation and injury by release of cytokines and chemokines, in addition to matrix proteins (elastin, fibronectin, laminin, and collagen) [66,67].

**Airway remodeling**

It is now well recognized that structural airway changes are present not only in severe fatal asthma, but also in mild to moderate versions of the disease. These changes include increased smooth muscle mass, mucous gland hyperplasia, angiogenesis, and subbasement membrane fibrosis [1]. Subbasement fibrosis has received most of the attention because of the relative ease of evaluation on airway samples obtained by endobronchial biopsy (Fig. 2). Although initially viewed as a result of longstanding disease and a correlate of its severity [68], recent studies have shown fibrosis to be present in mild asymptomatic asthma [69]. It has been proposed that chronic airway inflammation leads to remodeling; however, its detection in young children with mild asthma [70] raised doubts about the role of chronic inflammation in promoting airway remodeling.

The association of fibrosis with disease severity has also been questioned in recent studies [71]. It has been shown that allergic airway inflammation is associated with enhanced generation of fibronectin [72] and TGF-β1 [73]. The latter is particularly important in subepithelial fibrosis because it stimulates fibroblast function, including the generation of fibronectin [74]. Expression of TGF-β in airway mucosa correlates with disease severity and the degree of subepithelial fibrosis [75,76]. Finally, expression of another cytokine, I-11, is increased in the airway mucosa of patients with moderate to severe compared with mild asthma [77]. This suggests that it may play a role in the development of airway remodeling. Angiogenesis has also been reported in chronic asthma [78]. Although its mechanism is not completely clear, there is evidence for increased expression of vascular endothelial
growth factor (VEGF) that correlates with the area of vascularity in airway mucosa of asthmatics [79,80]. Treatment with inhaled corticosteroids has been shown to decrease the area of vascularity and number of vessels in asthma patients [81].

**Summary**

There is now strong evidence that airway inflammation is a predominant underlying problem in patients with asthma, and it has been suggested that ongoing inflammation may lead to airway injury and remodeling. There is
also recent evidence that longstanding asthma could be associated with loss of elastic recoil, which can enhance airway obstruction and worsen asthma control [82,83]. Therefore, the use of anti-inflammatory therapy has been advocated in all guidelines, including the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report [84] and its recent update [85] that recommended inhaled steroids as a first mode of therapy for patients with mild, moderate, or severe, persistent asthma.

There is preliminary evidence that early institution of anti-inflammatory therapy might lead to disease modification and limit the progression of subepithelial fibrosis and airway remodeling. The pathogenesis of asthma clearly involves many cells and mediators, although the contribution of each individual factor is probably different from patient to patient depending on the setting and stimulus. Although currently available therapies are highly effective in controlling asthma symptoms and limiting exacerbations in the majority of patients, there is still a subset of patients that proceed to develop severe asthma with decreased lung function, lack of responsiveness to therapy, or frequent exacerbations.

It is hoped that rapid progress in the area of asthma genetics and pharmacogenetics will yield a more precise and patient-specific understanding of asthma pathogenesis and allow practitioners to prescribe therapies that are designed for a particular patient or exacerbation. That will undoubtedly help to improve the care of asthma, limit its morbidity, and reduce the side effect of medications.

References


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