

Asthma: an inflammatory mediator soup

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Reversible or partially reversible airway obstruction, inflammation, and bronchial hyperresponsiveness to various stimuli are the defining characteristics of asthma. Airway obstruction in asthma is a complex event that is due to bronchospasm, inflammation, and mucus formation. Inflammation has assumed a more central role in the pathogenesis of the disease, as it contributes not only to airflow obstruction, but also to bronchial hyperresponsiveness. The inciting trigger, or inhaled allergen, in asthma induces the activation of mast cells and macrophages with the subsequent release of several proinflammatory mediators, including leukotrienes, chemotactic factors, and cytokines. Antigen processed by macrophages is presented to undifferentiated T helper cells, inducing differentiation to the Th2 phenotype, with the subsequent release of IL-4 and IL-5, causing IgE synthesis and eosinophil infiltration, respectively. Macrophage-derived cytokines, such as IL-1, TNF- α , and IFN- γ , activate endothelial cells, upregulating the expression of adhesion molecules such as ICAM-1 and VCAM-1, which permit egression of leukocytes from the vasculature to the airway mucosa. Several inflammatory cells, such as eosinophils, mast cells, and macrophages, not only cause airway damage, but also synthesize cytokines that perpetuate the inflammatory process. This complex interplay of inflammatory cells and mediators causes the classic histopathophysiologic features in the airways of both symptomatic and asymptomatic individuals with asthma, emphasizing the importance of early recognition and anti-inflammatory treatment.

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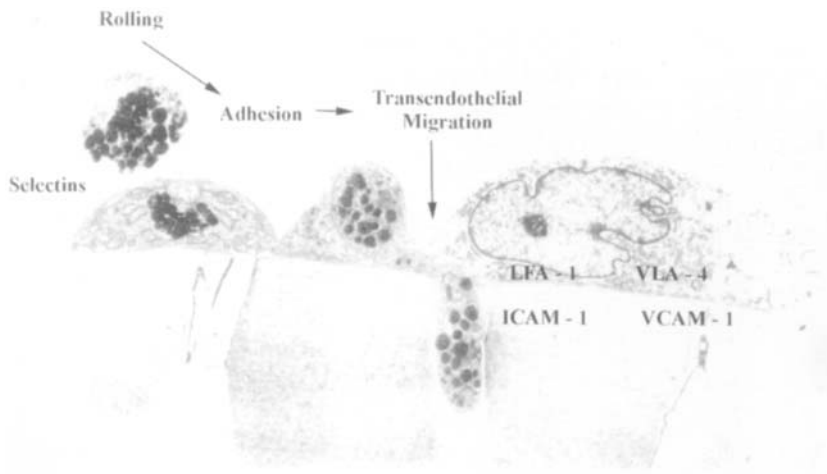


Figure 1. Potential mechanisms of eosinophil recruitment to lung during allergic inflammation. Circulating eosinophils passing through area of activated endothelium bind loosely to expressed selectins. This class of adhesion molecules act to reduce eosinophil movement, permitting them to “roll” effectively along endothelium. Eosinophil integrins subsequently bind to ICAM-1 and VCAM-1, firmly anchoring cell within vasculature. Cellular pseudopods are formed, and transendothelial and interstitial migration of eosinophils follows.

Introduction: asthma is a complex interplay of inflammatory cells and mediator

Reversible or partially reversible airway obstruction, inflammation, and bronchial hyperresponsiveness to various stimuli are the defining characteristics of asthma (1). In the past, airflow obstruction was felt to represent the end result of bronchospasm, and the cornerstone of asthma therapy rested primarily on bronchodilators. Over the past several years, however, numerous basic and clinical studies have demonstrated the central role of inflammation, by itself and via its effects on bronchial smooth muscle, in determining airflow obstruction in asthma. Airway inflammation, found in virtually all individuals with asthma, is now viewed as the critical factor in determining disease severity (2, 3).

The inciting trigger or inhaled allergen in asthma induces the activation of mast cells and macrophages with the subsequent release of several proinflammatory mediators, including leukotrienes, chemotactic factors, and cytokines (4). Antigen processed by macrophages is presented to T helper lymphocytes, stimulating the release of IL-4 and IL-5, which, in turn, cause B-cell IgE synthesis (5, 6) and eosinophilia, respectively. Macrophage-derived cytokines, such as IL-1, TNF- α , and IFN- γ , activate endothelial cells, upregulating the expression of adhesion molecules such as ICAM-1 (7) and VCAM-1. Furthermore, T-cell-derived IL-4 selectively upregulates VCAM-1 expression (8). This permits egression of leukocytes from the vasculature to the airway mucosa. The consequences of this inflammatory cell infiltrate include disruption of the airway epithelium (9), abnormalities in autonomic neural control of airway tone (10), changes in mucociliary function, and increased bronchial smooth-muscle responsiveness (4). A self-perpetuating inflammatory cycle ensues, in that some effector cells, such as eosinophils

and mast cells, are capable of synthesizing cytokines that further promote and upregulate the inflammatory process.

The importance of the eosinophil

Several lines of evidence implicate eosinophils as active and major participants in the pathogenesis of asthma (11). First, eosinophils and their granule constituents, MBP, ECP, EDN, and EPO, are found in increased numbers in the peripheral blood, sputum, bronchoalveolar lavage (BAL) fluid, and bronchial tissues of patients with active asthma (12). In addition, there is a distinct correlation between the presence of eosinophils, their products, and asthma severity (13). Patients with mild asthma (14) and those that die of status asthmaticus (15) have significant eosinophilic infiltration of the bronchi, in the latter situation involving the entire thickness of the bronchial wall, the adjacent parenchyma as well as the bronchial lumen. Second, eosinophils and their granule contents have the capability to cause the characteristic histopathologic changes (desquamation and destruction of epithelial morphology) seen in the bronchial mucosa (16) in asthma, and can induce many of the pathologic (17, 18) and physiologic (19) features of the disease. Third, eosinophils and/or their products are a consistent and characteristic feature in the airway mucosa and BAL fluid, following the development of late-phase asthmatic responses (LAR) to inhaled allergens (20, 21), probably due to activation of Th2 lymphocytes and the release of IL-3, IL-5, and GM-CSF (22–24). Furthermore, these cytokines prolong eosinophil survival and augment eosinophil function. Studies have demonstrated that activated airway eosinophils survive 4–5 times longer than those obtained from the peripheral circulation (25), and that peripheral blood eosinophils survive longer when incubated in the presence of IL-5 (26).

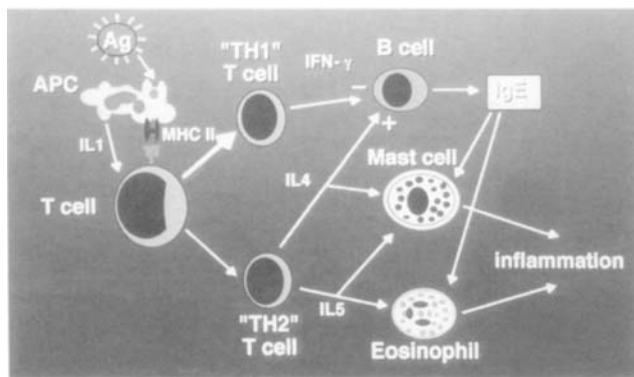


Figure 2. Hypothetic scheme of cytokine interactions leading to allergen-specific Th2 responses. Central to atopic allergy are T-cell/B-cell interactions, which ultimately lead to IgE responses. Macrophage processing of antigen induces release of cytokines such as IL-1. Activated T cells need to recognize same peptide-MHC class II complexes to which they were first sensitized. In presence of allergen, this interaction can induce T-cell activation, with preference for Th2 cells. Cytokines for Th2 clones are associated with allergic inflammation and include IL-4 and IL-5. IL-4 is centrally involved in propagation of allergic reactions. It is one of major cytokines involved in T-B-cell interactions, and plays important role in isotype switching from IgG to IgE. IL-5 has proinflammatory effects on eosinophil, including activation, adhesion, prolonged survival, chemotaxis, and enhanced maturation. Th1 clones mediate delayed-type hypersensitivity and are associated with the production of IFN- γ .

Interestingly, eosinophils can synthesize IL-3, IL-5, and GM-CSF in an autocrine fashion (27), effectively generating their own “survival kit”, and thereby perpetuating the inflammatory response. In addition to the release of granule contents, eosinophils also generate lipid mediators, such as leukotrienes (28) and PAF (29), which can further mediate bronchoconstriction and increased vascular permeability. Therefore, it is not surprising that a significant correlation exists between the degree of eosinophilia (30), the number of activated (or hypodense) eosinophils (31), and bronchial hyperresponsiveness.

Epithelial denudation

Critical to the development of bronchial hyperresponsiveness is injury to the airway epithelium, which may be mediated by both immunologic and nonimmunologic mechanisms. The bronchial epithelium normally functions as a protective barrier against external stimuli. In the asthmatic airway, however, much of the epithelium is denuded (9), and this protective role is thus lost. This effect may in part be due to the release of eosinophil MBP (32). Afferent nerve endings, which are normally covered by epithelium, are exposed and vulnerable to inflammatory

mediators in the airway lumen, as well as mechanical and chemical stimuli (i.e., cold air, sulfur dioxide), resulting in cholinergic bronchoconstriction (33) and the release of neuropeptides which generate mucus secretion, smooth-muscle contraction, plasma extravasation, and neutrophil adhesion (i.e., “neurogenic inflammation”) (34, 35). Epithelial injury also permits increased permeability and sensitivity to inhaled allergens, irritants, and phlogistic mediators.

The asthmatic epithelium is an active metabolic organ and is in a constant state of destruction and repair (36). Recurrent inflammatory insults to the airway are followed by repeated attempts to “heal” the epithelial damage. As with other “healing” processes, cells at the site of injury lay down collagen and fibrous tissue, the secondary scarring resulting in airway remodeling. Selected inflammatory cells may orchestrate this response, as mast-cell tryptase (37) stimulates fibroblast replication and eosinophil-derived TGF- β (38) induces collagen secretion by fibroblasts, potentially further thickening the reticular basement membrane. This cycle of repeated denudation/restitution, and the net balance of these two processes, determines whether chronic inflammatory insults to the airway result in fixed disease with symptoms of severe, persistent asthma.

Migration of cells from the bloodstream to the airway

To cause damage in the airway, inflammatory cells must travel from the bloodstream to the airway mucosa. This is mediated by a complex molecular system of endothelial adhesion molecules which serve as a ligand for leukocyte cell-surface receptors, thereby enabling cell migration from the vasculature to specific sites of inflammation (39, 40). Macrophage processing of antigen in the airway results in the release of cytokines, such as IL-1, TNF- α , and IFN- γ , which activate the endothelium by upregulating the expression of adhesion molecules (7) such as ICAM-1, VCAM-1, and E-selectin. Furthermore, the expression of VCAM-1, but not ICAM-1 (41), appears to be regulated by the release of IL-4 from T cells. IL-4 is centrally involved in the propagation of allergic reactions (42). During an allergic inflammatory response, circulating eosinophils passing through an area of activated endothelium transiently bind to expressed selectins, which act to reduce eosinophil movement, permitting them to “roll” effectively along the endothelium (43). The subsequent binding of eosinophil integrins to ICAM-1 and VCAM-1 firmly anchors the cell within the vasculature. Transendothelial and interstitial migration of the eosinophil

(44) then follows (Fig. 1). There the eosinophil comes into contact with proteins in the extracellular matrix. This complex network of fibrillar proteins has a profound influence on cellular function. Through adhesive interaction with extracellular matrix integrins, the eosinophil is altered to a primed or activated phenotype (45). Upon arrival in the airway, the cytokine milieu further primes the eosinophil, enhancing its capacity as a proinflammatory cell (46).

The role of adhesion molecules in granulocyte recruitment

Important roles for the adhesion molecules have recently emerged. ICAM-1 plays a pivotal role not only in the cell migration during the inflammatory response, but also in respiratory infections. For example, ICAM-1 has been shown to be the receptor for more than 90% of rhinovirus infections (47), a common clinical trigger of asthma. Experimental attempts have been made selectively to block this receptor. In one study (48), asthmatic monkeys given monoclonal antibody to ICAM-1 demonstrated both reduction in eosinophil infiltration into the lung and attenuation in allergen-induced airway hyperresponsiveness, further revealing the critical role of adhesion molecules in modulating leukocyte recruitment and the subsequent physiologic effects. Similar studies have been performed in a sheep model (49) with monoclonal antibodies to VLA-4, an adhesion protein found selectively on eosinophils. In sheep treated with anti-VLA-4, the immediate response to inhaled allergen was unchanged, whereas the late reaction and increase in airway hyperresponsiveness were significantly diminished. These findings have obvious clinical implications for future asthma therapy.

T-helper cell polarization (Fig. 2)

T cells play a central role in the initiation and regulation of immune responses, as they are the only cells capable of recognizing foreign proteins processed by antigen-presenting cells. Upon activation, T helper cells differentiate into one of two distinct subsets, termed Th1 and Th2 (50), in part dependent on the cytokine milieu present at the time of activation. These subsets have distinct patterns of cytokine secretion conferring differential function. Th1 lymphocyte clones are characterized by the production of IL-2, IFN- γ , and TNF- β and mediate delayed-type hypersensitivity (DTH) reactions (51), whereas Th2 lymphocytes secrete IL-4, IL-5,

IL-6, IL-10, and IL-13 and mediate allergic inflammatory responses (52). In addition, IFN- γ produced by Th1 cells inhibits the proliferation of Th2 clones (53), whereas IL-10 from Th2 cells inhibits Th1 lymphocyte proliferation (54, 55), further modulating a preferential Th1 or Th2 inflammatory response. A recently described IFN- γ -inducing cytokine, IL-12, inhibits the production of IL-4 and IL-10 in allergen-specific human CD4⁺ T cells (56). However, whereas the distinction between Th1 and Th2 cells is clear-cut in mice, this may not be the case in man.

The atopic state is characterized by Th2 predominance. Th2-derived IL-4 (58) and IL-13 (59, 60) play a critical role not only in the differentiation of T helper cells to the Th2 phenotype, but also in IgE isotype switching. Both IL-4 and IL-13 inhibit secretion of IFN- γ and IL-12 by monocytes and thus promote the development of Th2-like CD4 lymphocytes. In contrast, IFN- γ , a Th1 cytokine, inhibits B-cell IgE synthesis, thereby downregulating the allergic inflammatory response (61). The BAL fluid of patients with asthma has shown increased levels of IL-4 and decreased levels of IFN- γ , consistent with the Th2 phenotype (62). Indeed, low levels of umbilical cord-blood IFN- γ may represent a marker for the development of atopy later in life (63). IL-5, another Th2 cytokine, plays a critical role in eosinophil differentiation, survival, chemotaxis, vascular adhesion, and activation of various effector responses (64, 65). Similar effects have been demonstrated by IL-3 (66) and GM-CSF (67), although these lymphokines are not as eosinophil-specific as IL-5. In addition, a recent study has shown that both IL-4 and IL-13 can upregulate endothelial VCAM-1 expression, thereby enhancing eosinophil infiltration (68, 69).

If allergic disease and asthma are characterized by overproduction of Th2 cytokines, conversion of allergen-specific Th2 clones to the Th1 phenotype may represent an important strategy for prevention and treatment. Several lines of evidence support this hypothesis. First, conventional immunotherapy effectively ameliorates allergic rhinoconjunctivitis by increasing the development of allergen-specific Th1 clones while reducing that of Th2 cells (70). Second, the incidence of atopic diseases is reduced in individuals afflicted with conditions characterized by Th1 cytokine excess, such as multiple sclerosis (71). Third, an inverse relationship exists between the prevalence of atopic disorders and DTH responses to *Mycobacterium tuberculosis* (72). Finally, the administration of IL-12 and IL-18 as potent stimulants of IFN- γ production (73) causes parallel reductions in IL-4 and IL-5 levels, and attenuation in airway hyperresponsiveness and pulmonary eosinophilia (74).

Conclusion

The inflammatory component of asthma is characterized by a complex interplay of leukocytes, epithelial and endothelial cells, mediators, and adhesion molecules that creates the classic histopathophysiologic findings of asthma: denudation

of airway epithelium, subepithelial fibrosis, mast-cell degranulation, and mucosal infiltration of eosinophils and lymphocytes. These findings are seen in the airways of both symptomatic and asymptomatic individuals with asthma and emphasize the importance of early recognition and treatment of the disease with anti-inflammatory medications.

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