Pathophysiology of the inflammatory response

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Airway allergic reactions enlist diverse cells and a multitude of chemical mediators that are responsible for the clinical symptoms of allergic rhinitis and asthma. Experiments in vitro and in animal models, as well as increasingly numerous studies in atopic human subjects, are revealing that an orchestrated continuum of cellular activities leading to airway allergic inflammation is set in motion in genetically predisposed individuals at the first exposure to a novel antigen. This sensitization step likely depends on differentiation of and cytokine release by T_H2 lymphocytes. Among T_H2-derived cytokines, IL-4 potently enhances B-lymphocyte generation of immunoglobulin E antibodies. The attachment of these antibodies to specific receptors on airway mast cells sets the stage for an acute inflammatory response on subsequent antigen exposure because IgE cross-linking by a bound antigen activates mast cells to release numerous inflammatory mediators. These mast cell–derived mediators collectively produce acute-phase clinical symptoms by enhancing vascular leak, bronchospasm, and activation of nociceptive neurons linked to parasympathetic reflexes. Simultaneously, some mast cell mediators up-regulate expression on endothelial cells of adhesion molecules for leukocytes (eosinophils, but also basophils and lymphocytes), which are key elements in the late-phase allergic response. Chemoattractant molecules released during the acute phase draw these leukocytes to airways during a relatively symptom-free recruitment phase, where they later release a plethora of cytokines and tissue-damaging proteases that herald a second wave of airway inflammatory trauma (late-phase response). The repetition of these processes, with the possible establishment in airway mucosa of memory T lymphocytes and eosinophils that are maintained by paracrine and autocrine cytokine stimulation, may account for airway hypersensitivity and chronic airway symptoms. (J Allergy Clin Immunol 1999;104:S132-7.)

Key words: *Allergy, atopy, asthma, allergic rhinitis, mast cells, interleukins*

Abbreviations used
APC: Antigen-presenting cell
VCAM: Vascular cell adhesion molecule

In spite of a mortality rate associated with asthma that has stabilized in the United States in the 1990s, this rate is more than 50% higher than in 1979.[1] Similarly in a Swedish study the prevalence of allergic rhinitis increased almost 2-fold between 1971 and 1981.[2] It is also noteworthy and it is responsible for diminished quality of life in 20% to 25% of the US population.[3] Although socioeconomic and environmental factors behind these trends are being elucidated, so are the biologic underpinnings of atopic disorders.[1] Never before has there been such a convergence of research addressing the mechanisms of airway disease, delving into the multitude of cellular interactions that generate inflammatory and immune responses. Numerous cell types are involved, including not only those with well-established roles (eg, mast cells, eosinophils, airway smooth muscle cells) but newly acknowledged participants (eg, airway epithelial cells, submucosal fibroblasts, endothelial cells, nociceptive neurons). The chemical conversations of which these cells appear capable through cytokines, enzymes, and neuropeptides are of astonishing complexity. Further, their influence appears to reach beyond airway tissue into bone marrow and, very likely, lymphoid tissue. Because, however, of the complexity of this response, there are opportunities to intervene in a variety of ways.

This article will review the data on the pathogenesis of allergic rhinitis and asthma—much of it from in vitro and animal studies—into a model of human airway atopic disease that is relevant to the clinician. The intent here is to define the involvement of inflammatory and immune cells and their chemical communications in acute- and late-phase responses in airway atopy. A basic model for airway inflammation in early and late phases is presented, highlighting cellular and chemical events associated with each phase. It is emphasized at the outset, however, that the entire process is seen as a continuum. It is hoped that from this summary the rationales behind both traditional and novel pharmacologic interventions can be better appreciated by the clinician.

AIRWAY ATOPY: A CONTINUUM OF CELLULAR RESPONSES

It is believed that individuals who express allergic symptoms are subject to an orchestration of cellular responses that commences with exposure to a specific antigen. The current model proposes that the potential for these responses is established with the first exposure to the antigen (sensitization), particularly in people with certain MHC alleles and other genetic predispositions.[4] During this exposure several cellular players are recruited, both in terms of differentiation from inactive or pre-

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0091-6749/99 $8.00 + 0 **1/0/101682**

cursor cells and possibly by signaling accumulation of cells at the site of exposure. At second and subsequent exposures to the same antigen, these primed cellular players respond through the release of chemicals directly responsible for rapid (within minutes) inflammatory changes. In the case of airway atopy, this early-phase response is evidenced clinically by nasal itch, sneezing, rhinorrhea, and congestion (allergic rhinitis) or by congestion, wheezing, and reduced airflow (asthma). A clinical late-phase response (3 to 11 hours) is seen in many individuals, consisting principally of congestion (allergic rhinitis) and a resurgence of bronchoconstriction (asthma). The late phase represents the longer-term outcome of cellular activities that were set in motion during the early phase: the last movement of a sweeping symphony.

Each of these stages in atopic airway disease is outlined below. Features common to both allergic rhinitis and allergic asthma, which are numerous and reflect a fundamentally similar pathogenesis, form the basis of this review.

Sensitization

Inhalation of a novel antigen and its entrapment in airway mucus exposes underlying naive airway epithelial cells and resident Langerhans' (dendritic) cells.[5] Antigen likely also penetrates the underlying submucosa, where it may contact phagocytes (eg, tissue macrophages, granulocytes) and enter lymphatics. It is believed that all of these cells can internalize, enzymatically degrade, and superficially display pieces of the antigen. In doing so, such antigen-presenting cells (APCs) are key in activating lymphocytes responsible for setting the stage for subsequent atopic responses.

An emerging awareness of the role of lymphocytes in airway allergy posits a key role for naive $CD4^+$ T thymocytes (T_H0 cells) during the sensitization phase.[4,6,7] T_H0 cells that bear receptors for an antigen (allergen) become activated if they contact that antigen on an APC in association with MHC class II and B7 (as well as other) proteins. Binding with the antigen triggers their differentiation, with the aid of cytokines, into an active ($CD4^+/CD25^+$) state.[6]

A specific subclass of T_H0 cells that differentiates in response to IL-4 and is particularly associated with allergy is designated T_H2 (Fig 1).[8,9] In humans, these cells are capable of releasing a unique combination of ILs and other cytokines that includes IL-2, IL-3, IL-4, IL-5, IL-9, IL-10, IL-13, and GM-CSF.[10] Of these cytokines, IL-4, IL-5, and IL-9 distinguish T_H2 cells from a T_H1 subclass, which is associated instead with delayed hypersensitivity. The precise location of T_H0 cells when they encounter antigen-bearing APCs (airways, thymus, lymph nodes) in an unsensitized individual has yet to be elucidated, but T_H2 cells have the ability to accumulate in airway tissue through surface interactions with specific endothelial adhesion molecules and to clonally expand in affected tissue.[4]

The T_H2 subclass likely is responsible, through cytokine release, for setting up cellular and molecular conditions for both episodic and chronic allergic reactions. Of particular significance in the sensitization stage is their release of IL-4, which enhances synthesis of IgE class immunoglobulins by antigen-stimulated B lymphocytes (plasma cells).[10] Such antibody production requires that these B lymphocytes previously have encountered, and made specific surface-receptor recognition of, the same antigen (Fig 1). Thus binding of antigen to specific surface receptors on B lymphocytes, in an IL-4 environment, stimulates the generation of IgE antibodies that enter the circulation and infiltrate tissues, including airways. The antibodies become affixed, through specific amino acid sequences in their Fc region, to cells bearing surface IgE receptors. High-affinity IgE receptors (FcεRI), in particular, are most relevant to atopic responses because they are present on mast cells/basophils and dendritic cells in airway epithelium.[11-14] The placement of these antigen-specific antibodies on airway mast cells sets the stage for an acute-phase allergic response during subsequent exposures to that antigen.

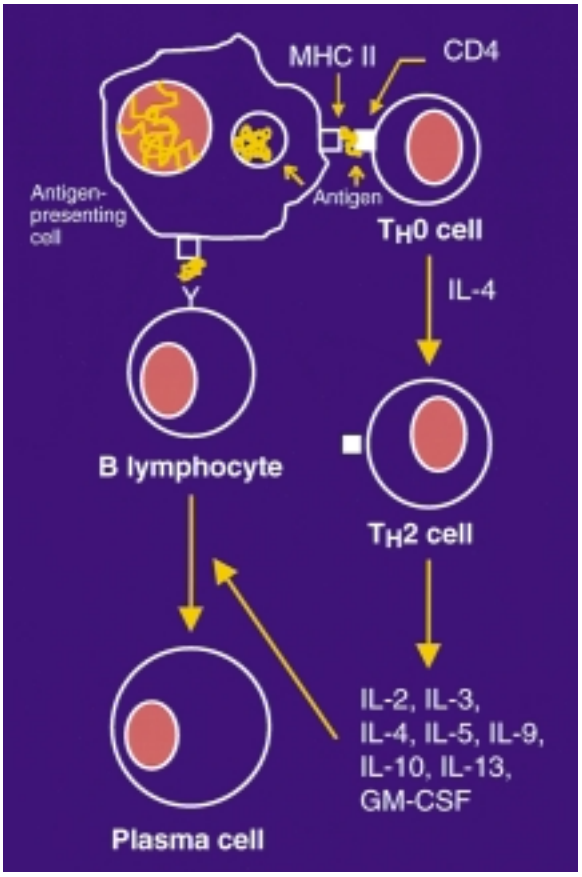

FIG 1. Simplified schema of the differentiation of T_H2 cells and activation of B lymphocytes in the establishment of sensitization to airway allergens.

Acute-phase response: mast cell activation

Antigen penetration of the epithelium in previously sensitized individuals activates IgE-studded mast cells resident in the airway tissue. Evidence suggests that dual

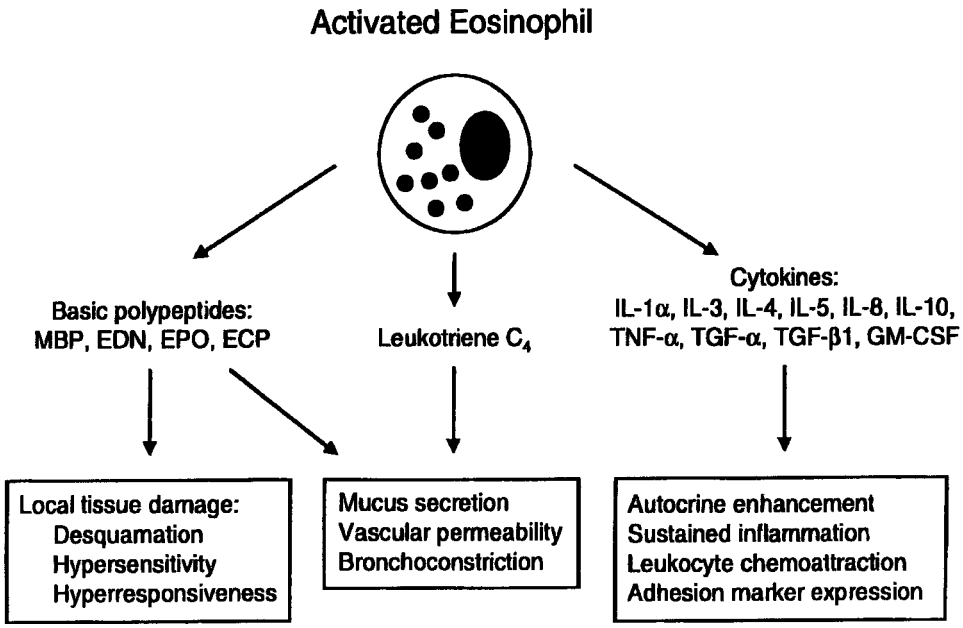

FIG 2. Several eosinophil products implicated in establishing late-phase allergic response. *MBP,* Major basic protein; *EDN,* eosinophil-derived neurotoxin; *EPO,* eosinophil peroxidase; *ECP,* eosinophil cationic protein; *TGF,* transforming growth factor.

TABLE I. Mast cell mediators and their proposed roles in inflammatory response

Mediator	Actions
Histamine*	↑Vascular permeability, vasodilation, ↑mucus production, bronchoconstriction, activation of nociceptive neurons
Proteases (tryptase, chymotryptase, carboxypeptidase, kininogenase)*	Degradation of tissue, activation of protein precursors, ↑mucus production, generation of bradykinin
Arachidonic acid derivatives†	
Leukotrienes (B_4, C_4, D_4)	↑Vascular permeability, ↑mucus production, bronchoconstriction, neutrophil/eosinophil chemoattractant (B_4), ↑leukocyte adhesion molecule expression (B_4)
PGD_2	↑Vascular permeability, bronchoconstriction (↑transient airway hyperresponsivity)
Thromboxane A_2	Bronchoconstriction
Cytokines†	
IL-3	Hematopoietic growth factor, chemoattractant for basophils
IL-4	↑IgE antibody formation by B lymphocytes, ↑differentiation of T_H2 from T_H0 thymocytes
IL-5	↑Eosinophil proliferation and differentiation, chemoattractant for eosinophils and basophils
TNF-α	Potent stimulator of inflammatory cascade, up-regulation of leukocyte adhesion molecules on endothelium
GM-CSF	↑Proliferation of granulocytes
Platelet-activating factor†	Eosinophil/neutrophil chemoattractant, ↑vascular permeability

*Preformed in granules.
†Synthesized de novo on allergen exposure.

populations of mast cells reside in airway tissue ("connective tissue mast cells" in the submucosa and "mucosal cells" in the epithelium), with different profiles of chemical release, and that their numbers increase after allergen exposure.[15-17]

Antigen cross-linking of mast cell IgE antibodies has been well documented to trigger mast cell degranulation and synthesis of proinflammatory molecules. A consideration of mast cell–derived chemicals and their actions (Table I) supports the central role for airway mast cells in initiating vascular, bronchotonic, and cellular changes typical of an acute-phase allergic response. These

include several mediators that increase venule permeability: histamine, leukotriene C_4, platelet-activating factor, and bradykinin (indirectly through mast cell kininogenase action on plasma kininogens).[15,18,19] Airway edema is attributed largely to these chemicals, leading to clinical symptoms of congestion and rhinorrhea. Several mast cell products (histamine, leukotriene C_4, PGD_2) are smooth muscle constrictors and may induce bronchoconstriction. Increased mucus secretion is attributed to leukotrienes and possibly chymase. Other mast cell proteases likely contribute to activation of protein cascades and inflict local tissue damage.

Of particular significance to the evolution of a clinical late-phase response is the attraction to the inflamed site, after abatement of acute-phase signs, of cells that will extend the proinflammatory actions initiated by mast cell mediators. And, indeed, IL-5 is a chemoattractant for eosinophils, whereas IL-3 and IL-5 are chemoattractants for basophils.[15] Leukotriene B_4 appears to attract neutrophils and, to a lesser degree, eosinophils.[19] Further, adhesion molecules on endothelial cells that enhance attachment of leukocytes and facilitate their infiltration of tissues are increased after exposure to TNF-α.[20]

Acute phase response: neuronal responses

Histamine appears to induct local nociceptive type C neurons into the inflammatory response through binding to neuronal H_1 receptors. Depolarization of these neurons leads to local release of several potential inflammatory mediators, including substance P, a calcitonin gene-related peptide, and neurokinin A, a gastrin-releasing peptide.[21] Although the significance of neuronal release of these chemicals in human airway allergy is unclear, a role for substance P is suggested by its ability to increase vascular permeability and exudate formation and prompt eosinophil influx in patients with allergic rhinitis on repeated application to the nasal mucosa.[15,22] Further, a statistically significant elevation ($P < .01$) in ILs (IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6) and other inflammatory mediators (TNF-α and IFN-γ) is stimulated by treatment of nasal mucosal explants in vitro with substance P.[23]

In addition to a possible local impact of nociceptive neuronal depolarization, such neurons recruit parasympathetic reflexes that have an impact on airway physiologic features within minutes.[23,24] Specifically, postganglionic parasympathetic fibers in the nasal mucosa rapidly release acetylcholine and neurotransmitters that include vasoactive intestinal peptides, vasoactive intestinal–like peptides, and nitric oxide synthase. Cholinergically mediated enhancement of airway glandular secretion, which can be inhibited by muscarinic antagonists, may account more for increased mucus production in allergic rhinitis than do mast cell–derived mediators.[25]

Late-phase response

Some of the mast cell–generated chemicals are chemoattractants (leukotriene B_4, platelet-activating factor) that stimulate an influx of inflammatory and immune cells over the several hours after allergen challenge.[26] Eosinophils in large numbers, as well as neutrophils, basophils, and lymphocytes, are increased in airway tissue, including the submucosa, epithelium, and airway lumen, several hours after allergen challenge.[7,11,26,27] A burgeoning host of cellular adhesion molecules identified through in vitro and animal studies is associated with escorting these cells from the bloodstream across endothelia into tissues. In humans the mechanisms appear no less complex.[28] Endothelial cells can express several adhesion molecules of the immunoglobulin superfamily (intercellular adhesion molecules 1 and 2, platelet endothelial cell adhesion molecule-1, and vascular cell adhesion molecule-1 [VCAM-1]) and the selectin superfamily (E-selectin, P-selectin). Corresponding ligands on leukocytes include more than a dozen integrins and L-selectin. Expression of some of the endothelial adhesion molecules is up-regulated by certain cytokines, including TNF-α and IL-4, which are released during the acute phase, suggesting that endothelial changes enhance late-phase leukocyte infiltration of airway tissue.[28]

In spite of extensive data about the existence of endothelial cell/leukocyte adhesion molecule pairs, the extent to which their expression has an impact on the course of asthma and allergic rhinitis awaits confirmation. Currently, expression of VCAM-1 appears to be up-regulated in those with allergic inflammation after allergen challenge.[11,28-30] The affinity of VCAM-1 for very late activation antigen-4, which is an integrin on eosinophils, basophils, and lymphocytes, provides a theoretic mechanism explaining eosinophil influx in the late-phase response and an increase in basophils that might be responsible for a late-phase histamine release. Indeed, blocking the association of these molecules with antibodies prevented eosinophil accumulation in guinea pig nasal mucosa and eosinophil and T-cell infiltration in mouse trachea.[31,32]

The accumulation, predominantly of eosinophils, in airway tissue is credited with inducing, through release of eosinophil products, the late-phase clinical responses of congestion and increased mucus production in airway allergic responses and possibly airway hypersensitivity and bronchial hyperresponsiveness.[33] Eosinophils, like mast cells, appear to generate a variety of proinflammatory chemicals as well as cytolytic enzymes that disrupt airway epithelial integrity (Fig 2). In the latter category are several basic, highly charged polypeptides, including major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase.[15,26] Together, this quartet could inflict substantial damage to airway endothelial cells, extracellular matrix, and neurons; exposure of nerve endings to airway lumina may account for bronchial hyperresponsiveness or airway hyperreactivity on subsequent exposures to specific antigens or generalized irritants.[26,34] Eosinophils also generate leukotriene C_4, a potent proinflammatory mediator, bronchoconstrictor, and glandular secretagogue.

Several cytokines are released by eosinophils, including some (IL-3, IL-5, GM-CSF) that are stimulatory to

eosinophil proliferation and enhance their adhesion to endothelium and hence may promote eosinophil recruitment and activation through autocrine mechanisms. Animal models of asthma with use of mAbs against IL-5 demonstrate the importance of this cytokine in airway eosinophil accumulation, late-phase symptoms, and bronchial hyperresponsiveness because these parameters were significantly reduced ($P < .05$) among antibody-treated animals.[35-37] Leukocyte chemoattractants (IL-5, IL-8) also are among eosinophil products. TNF-α and IL-1α up-regulate the expression of endothelial cell adhesion molecules, as well as being proinflammatory. Additional eosinophil products are recognized, such as transforming growth factors α and β, which may mediate local tissue repair.[33]

Other granulocytes (basophils, neutrophils) and T lymphocytes are elevated in number in airway inflammation after several hours of allergen challenge.[38,39] Memory T cells ($CD4^+$) are among a suite of lymphocyte subsets that are selectively increased in nasal mucosa and distinct from the subset profile of peripheral blood in patients with perennial allergic rhinitis, suggesting that the nasal mucosa becomes a complex and specialized compartment of interacting cells and secretions.[38] In some patients the recruitment of cells after the immediate mast cell and local neuronal responses appears to generate not only a late-phase response but also chronic allergic inflammation.

CONCLUSION

This brief consideration of the most well-documented cellular events that underlie atopic airway diseases illustrates the complexity and interrelatedness of several lines of response. Temporally, the immediate clinical symptoms of airway edema, constriction, and glandular secretion rapidly follow the allergen-triggered release of potent chemical mediators from mast cells in situ, whereas the late-phase responses of mucus secretion, bronchoconstriction, and airway hypersensitivity are conducted predominantly by cells drawn to the affected site. Undoubtedly, intensive research will continue to reveal additional functions for cells already implicated in this current model of allergic inflammation as well as uncover roles for historically less-conspicuous performers. For example, nasal epithelial cells of subjects with allergic rhinitis express substantially elevated IL-8 and GM-CSF, and bronchial epithelial cells, on exposure to a component of air pollution (nitric oxide), release substantially increased levels of TNF-α and GM-CSF, which places them within the arena of inflammatory-enhancing agents.[33,40,41] The accumulating wealth of data derived from in vitro experiments and animal models presage a future confirmation of the processes we currently envision behind allergic airway disease in humans. Additionally, we hope that this information will provide a framework for the targeted pharmacotherapy leading to the alleviation or elimination of allergic airway disease.

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