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Continuous Medical Education

Inflammation in asthma.

Ashraf Abdel Baky, MD
Assistant Professor of Pediatrics, Ain Shams University

Today asthma experts consider airway inflammation to be a central feature of asthma pathogenesis and its clinical manifestations. In fact, airway inflammation plays a critical role in airway obstruction and hyper-responsiveness.

Evidence of inflammation may appear very soon after the onset of symptoms in newly diagnosed asthmatic patients. Accordingly, treatment algorithms for asthma have emphasized treatment of the underlying inflammation, as well as the bronchoconstrictive symptoms. By acquiring a better understanding and appreciation of the inflammatory process, physicians can employ treatments to inhibit specific steps in the process and improve the control of asthma and its symptoms.

INFLAMMATORY CASCADE

Inflammatory disorders involve a potentially wide range of cell types and cellular mediators. Asthma-associated inflammation cascade occurs as a seven-step process:

1. Sensitization
2. Stimulation
3. Cell signaling
4. Inflammatory cell migration
5. Activation of inflammatory cells
6. Airway remodeling
7. Resolution

Sensitization

Sensitization occurs as a result of presentation of an antigen to a T-lymphocyte. Several candidate cells have been postulated, including monocytes, macrophages, B-lymphocytes and dendritic cells. T-lymphocyte, which responds by changing from a naive lymphocyte to an allergic type of cell (T-Helper 2, or T-H2), emits signals through the cytokine networks. The cytokines find their way to B-lymphocytes, which react by producing IgE specific for the antigen. The IgE then attaches to mast cells, thereby completing the sensitization or antigen presentation phase, the first step in the inflammatory cascade.

Stimulation

Genetically predisposed individuals exposed at an early age to indoor aeroallergens, occupational antigens and respiratory viral infections become sensitized to certain allergens. Any number of factors may stimulate an exacerbation of the disease, including allergens and environmental agents, through triggering of mast cells.

Allergens are the most extensively studied of the asthma stimuli. Most, if not all, asthma does have an allergic basis that may revolve around IgE. High prevalence of asthma is associated with early-age exposure to specific allergens.

Cell signaling

Stimulation activates a complex communication network. Signaling cells issue biological commands that lead to recruitment of inflammatory cells into the airways.

T-lymphocytes, macrophages and monocytes are activated in symptomatic asthma, as indicated by the expression activation markers. An intracellular molecule critical for expression of both cytokines and adhesion molecules is nuclear factor (NF-kappa-B), a DNA-binding protein that functions as a transcription factor controlling the "readout" of genes. The list of genes activated by such binding is extensive. It includes genes for the cytokines granulocyte-monocyte colony stimulating factor (GM-CSF), interleukin (IL-1-beta), and tumour necrosis factor (TNF-alpha), the chemokines like eotaxin, the adhesion molecules VCAM-1 and ICAM-1, and enzymes such as inducible nitric oxide synthase. Expression of these markers appears to correlate with disease activity, and, perhaps more importantly, steroid therapy decreases expression of the markers.

Migration

During the triggering and signaling processes, substances are produced that induce leukocyte migration into the airways. At various times after allergen challenge, migration may involve eosinophils, neutrophils, lymphocytes and monocytes. The migration begins within two hours and may continue for up to 48hours.

One possible explanation for migration of inflammatory cells is the release of chemoattractant mediators by signaling cells. Alternatively, signaling cells may release cytokines that up regulate adhesion molecules that stimulate cellular migration into a focus of inflammation. Tumor necrosis factor-alpha (TNF-alpha) of mast cell or macrophage origin upregulates endothelial expression of intercellular adhesion molecules (ICAMs) 1 and 2, while IL-4 and IL-13

upregulate endothelial expression of vascular cell adhesion molecule 1 (VCAM-1). These interact with their ligands, lymphocyte function associated antigen-1 (LFA-1) and very late activating antigen-4 (VLA-4), on T cells and eosinophils, allowing cell migration from the vasculature. Subsequent infiltration of these cells into the airways is associated with many of the pathologic changes seen in asthma.

Activation of inflammatory cells

Following migration into the airways, inflammatory cells require activation to produce the pathophysiologic changes associated with asthma symptomatology. Activation probably occurs after the cells' exposure to cytokines and other potential activators found in inflamed lungs. Potential activating substances include IL-1, IL-5, TNF-alpha and GM-CSF.

Considerable evidence exists to indicate that eosinophils are activated in the lungs of asthmatic patients. A limited amount of data suggests that monocyte-macrophage activation occurs during the late asthmatic response (LAR) to allergen exposure or other challenges. The data include evidence of increased expression of low-affinity IgE receptor and increased macrophage production of IL-6 and TNF-alpha following allergen exposure.

Airway Remodeling

Evidence continues to accumulate to suggest that the inflammatory processes of asthma lead to tissue alterations (including stimulation and damage) at the level of the epithelium, basement membrane, smooth muscle and nerves. Vascular changes imply that angiogenesis may be an accompanying feature.

Various cytokines and growth factors contribute to the remodeling process. These appear to include transforming growth factor (TGF-beta-1), GM-CSF, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), endothelin (ET), and insulin-like growth factor 1 (IGF-1). Although many are products of eosinophils infiltrating the airway, they appear to be elaborated by both infiltrating and constituent cells. Metalloproteinases such as MMP-2 and MMP-9, produced by eosinophils or epithelial cells, also contribute. Mast cells contribute, too, by secreting the serine proteases tryptase and chymase.

Epithelium. The airways of asthmatic patients exhibit abnormal epithelium, possibly a result of exposure to enzymes, growth factors and other proteins released by inflammatory cells. The damage may intensify the effects of bronchoconstricting stimuli to transform the stimuli into major factors in airway reactivity. Studies in animal models of asthma suggest a possible role for the nonadrenergic, noncholinergic system in the airway epithelial damage. A number of neuropeptides have been linked to bronchoconstriction and response to allergen challenge.

Basement membrane. Evidence suggests that the basement membrane or associated connective tissue is altered in asthmatic patients. Deposition of such matrix proteins as laminin, tenascin, fibrin, fibronectin, and type III and V collagen is contributing to subepithelial fibrosis, and hyperplasia of smooth muscle and goblet cells.

Smooth muscles and nerves. Pathologic studies indicate that asthmatic smooth muscles may be both hyperplastic and hypertrophied. In vivo, a thickened airway structure could be more reactive or exhibit more constriction.

Resolution

The discovery that asthma involves chronic underlying inflammation has given rise to the hypothesis that abnormal or incomplete resolution of inflammation may play a role in the disease and its exacerbations. Reasons for the abnormal (or absent) resolution remain largely unknown. Inhibition of resolution signaling processes in association with a prolonged, severe late allergen response (LAR) and probably impairment of alveolar macrophages' suppressor activity on lymphocytes, possibly leading to uncontrolled lymphocyte proliferation and inflammatory response. Better understanding of the resolution process could help explain the differences among mild, moderate and severe asthma and lead to the development of more effective therapies.

INFLAMMATORY CELLS AND MEDIATORS

Ongoing research has identified numerous cells and mediators that may be involved in the airway inflammation associated with asthma. Key inflammatory cells and mediators identified thus far include:

Cells

- Mast cells. Possibly a primary triggering mechanism for the immediate asthmatic response (IAR).
- Macrophages. Implicated in the IAR and in the antigen processing and presentation associated with later stages of the asthmatic response.
- Eosinophils. Eosinophils are considered pivotal cellular mediators of asthma. Eosinophils produce immunoregulatory cytokines (IL-3, 4, 5, 6, and 8, GM-CSF, TNF-alpha), growth factors TGF-alpha, and proteins toxic to cells (major basic protein [MBP], eosinophil peroxidase [EPO], and eosinophil-derived neurotoxin [EDN]), thereby contributing to airway inflammation and, over the long term, remodeling.
- Lymphocytes. Possibly the overall cellular coordinator of the varied processes and interactions that constitute the inflammatory response in asthma.

- Epithelial cells and myofibroblasts, may also contribute to the pool of inflammatory cytokines and chemokines.

Mediators

- Products of the arachidonic acid cascade: leukotrienes, prostaglandins and thromboxane, all of which are known mediators of inflammation.
- Cytokines and growth factors, including the interleukins and GM-CSF, implicated in activities ranging from mast cell production and growth to inflammation-associated eosinophil migration to activation of various inflammatory cells and proteins. IL-5 mediates eosinophil recruitment and infiltration, acting in tandem with members of the beta-chemokine family, especially eotaxin, macrophage inflammatory protein-1-alpha (MIP-1-alpha) and monocyte chemoattractant protein-1 (MCP-1). IL-4 and IL-13 regulate IgE synthesis.
- Preformed inflammatory mediators, such as histamine, proteases and eosinophil major basic protein.

IMPLICATIONS FOR THERAPY

Controlling inflammation has become a central objective of asthma therapy. Better control of inflammation is essential to better control of the disease and may open the door to alteration of the disease course. Control of inflammation can occur at several levels.

Environmental control:

In allergy-driven asthma, environmental measures are very important, as they eliminate disease "triggers." Specifically, in humid regions, removing all unnecessary carpeting and upholstery (especially in bedrooms) diminishes dust mites' ability to thrive. The allergen burden can be further minimized by encasing pillows and mattresses in plastic and washing all bedding in very hot water. Individuals allergic to animal dander should keep pets out of the house.

Pharmacological control:

Inflammation control has been accomplished primarily by the use of corticosteroids. Inhaled or oral steroids have been shown to decrease populations of inflammatory cells and cytokines in the airways of asthmatics. Improvement in inflammation is associated with improvement in pulmonary symptoms. The effect likely relates to an interruption in the inflammatory cascade. Certain other drugs (such as nedocromil, cromolyn and theophylline) may have anti-inflammatory effects as well, but the effects are milder.

Improvement in the understanding of asthmatic inflammation has enhanced the ability to design drugs that target specific components of the inflammatory process. Examples include drugs that modulate leukotrienes, such as LTD 4 receptor antagonist, and the 5-lipoxygenase inhibitor. Ongoing studies are evaluating drugs that inhibit cytokine activity, including IL-4 and IL-5, as well as drugs that prevent IgE binding to mast cells. These specific drugs should improve our understanding of inflammation and hopefully lead to its improved treatment.

SOURCES AND FURTHER READINGS

Djukanovic R. Asthma: A disease of inflammation and repair. J Allergy Clin Immunol 2000; 105(2Pt2): S522-6.

Goldstein RA, Paul WE, Metcalfe DD, Busse WW, Reece ER. NIH conference. Asthma. Ann Intern Med 1994; 121(9): 698-708.

Hamid Q, Tulic' MK, Liu MC, Moqbel R. Inflammatory cells in asthma: mechanisms and implications for therapy. J Allergy Clin Immunol 2003; 111(1Suppl): S5-S12; discussion S12-7.

Jarjour NN, Kelly EA. Pathogenesis of asthma. Med Clin North Am 2002; 86(5): 925-36.

Larche M, Robinson DS, Kay AB. The role of T lymphocytes in the pathogenesis of asthma. J Allergy Clin Immunol 2003; 111(3): 450-63.

National Asthma Education and Prevention Program Expert Panel Report. Guidelines for the Diagnosis and Management of Asthma, Update on Selected Topics. J Allergy Clin Immunol 2002; 110(5): 145-7.

Oettgen HC, Geha RS. IgE regulation and roles in asthma pathogenesis. J Allergy Clin Immunol 2001; 107(3): 429-40.

Vignola AM, Mirabella F, Costanzo G, Di Giorgi R, Gjomarkaj M, Bellia V, et al. Airway remodeling in asthma. Chest 2003; 123(3Suppl): 417S-22S.

Wenzel S. Inflammation in asthma. Medical scientific update of National Jewish Medical and Research Center 1996; 14(3): 1-10.