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EDITORIAL

The New Gestalt: Asthma as a Chronic Inflammatory Disease

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A general appreciation of the role of chronic inflammation in the immunopathogenesis of bronchial asthma is long overdue. The consequence of this new gestalt will be a renaissance in basic research, drug development, and treatment, the focus of which will be aimed at understanding and ameliorating the causes rather than just the symptoms of chronic asthma. The recent "rediscovery" and "reinterpretation" of the histopathologic features of chronic asthma, the careful definition of the tissue, cellular, and humoral events integral to the development of chronic bronchopulmonary inflammation, and the demonstration that chronic asthma possesses many features of recurrent late-phase reactions, has provided the basis for models and testable hypotheses of the complex cellular and humoral networks involved. The model proposed by Professor A. B. Kay, in this issue of the *Journal of Asthma*, provides just such a framework for further elucidation of the role of inflammatory cells and their soluble mediators in bronchial asthma, specifically focusing on the possibility of a central role for "chronically activated" T helper cells, T-cell-derived lymphokines, and eosinophils in the chronic pathology of this disorder.

Asthma is clearly a multifactorial disease; as pointed out by Dr. Kay, "it is very unlikely that one cell, or one mediator, will totally explain the mechanisms of asthma," nor will one cell, or one mediator provide the elusive key for development of a single, totally effective therapeutic agent capable of blocking all aspects of the complex inflammatory cascade responsible for its morbidity and mortality. Nevertheless, the reductionist approach to understanding the functions of individual, but prominent proinflammatory effector cells such as the eosinophil, has and continues to provide novel insights into the importance of chronic inflammation, tissue damage, and hyperreactivity in the pathogenesis of

ongoing asthma. Since "it is more likely that the *combined* effects of cells and mediators are required for the observed effects," future research needs to focus on the dynamic interactions of the regulatory and effector cells involved in the development and maintenance of ongoing "chronic" inflammation in the lung. To this end, Dr. Kay's review and synthesis of current knowledge of the likely inflammatory players, both cellular and humoral, poses numerous questions and avenues for further investigation; it also suggests potential points of attack for the development of more specific and effective anti-inflammatory agents.

In this asthma model, the interactions between mediators of hypersensitivity and inflammatory cells are functionally distinguished by their specific roles in a vicious inflammatory cycle that includes the early phase immediate reactions, late-phase reactions, and the ongoing chronic reactions of asthma. For the early phase, it is generally accepted that the mast cell is central to the development of bronchoconstriction through IgE-dependent or IgE-independent release of potent soluble mediators that include histamine, prostaglandins (PGD_2), leukotrienes (LTC_4/LTD_4), and probably platelet-activating factor (PAF). Whether other cells possessing low affinity IgE receptors (Fc Epsilon IIR) such as monocytes/macrophages, eosinophils, and possibly platelets are functionally involved in these reactions is unclear and requires further investigation.

The late-phase component is clearly characterized by an influx of macrophages, some neutrophils, and large numbers of eosinophils; while the specific factors involved in vivo in both the recruitment and activation of these cells remain uncertain, especially those responsible for the preferential recruitment and activation of the eosinophil, numerous chemotactic and activating factors have now been identified and characterized in vitro including mast cell-derived (LTB_4, PAF, high-molecular weight neutrophil chemotactic factor), T-cell-derived [lymphokines, granulocyte/macrophage colony-stimulating factor (GM-CSF), interleukin-5 (IL-5), interferon-γ (INF-γ)], and monocyte/macrophage-derived [monokines, tumor necrosis factor (TNF)] products. The activation of eosinophils infiltrating the lung, with the consequent release of potent preformed granule cationic proteins (MBP, ECP, EPO) and newly synthesized lipid mediators (PAF, LTC_4) is likely responsible for the ensuing submucosal edema, enhanced mucus secretion, and nonspecific airway hyperreactivity, all prominent features of late-phase pulmonary reactions. Additionally, the secretion of eosinophil-derived cationic proteins may further stimulate mast cells or basophils to release mediators of inflammation and bronchoconstriction, further exacerbating this cycle (1). Of particular interest are recent findings that the same T-cell-derived hematopoietic factors (IL-3, IL-5, and GM-CSF) that play a role in eosinophil differentiation also prime or directly enhance eosinophil cytotoxicity, generation of oxidative products, production of lipid mediators, cell survival, and possibly adhesive interactions with vascular endothelium (2). This immediate-phase/late-phase scenario is further complicated by recent findings that the same hematopoietic growth factors and lymphokines that modulate eosinophil differentiation and function (IL-3, IL-5, GM-CSF), or play a role in the regulation of IgE synthesis and immunoglobulin secretion (IL-4, IL-6), are produced by mast cells in response to IgE receptor (Fc-epsilon RI)-mediated activation (3,4). Thus, the consequences of IgE-dependent activation of mast cells may not be limited exclusively to the pathogenesis of immediate bronchoconstriction as portrayed in the model proposed by Dr. Kay.

The ongoing "chronic" phase of asthma in this model is characterized by a sustained cycle of eosinophilopoiesis in the bone marrow, prolonged tissue and peripheral eosinophilia, and continued eosinophil activation and secretion of protein and lipid mediators (MBP, ECP, EPO, PAF, LTC_4, lymphokines) which are likely responsible for the focal epithelial cell damage, microvascular leakage, augmentation of airways hyperreactivity, mucus hypersecretion, impairment of mucociliary clearance, and mucus plug

formation, all features of the chronic pathology of asthma. Indeed, the accumulated evidence for the eosinophil as the primary proinflammatory effector of mucosal cell damage in the ongoing chronic phase of asthma is quite persuasive (5), with clear support for "the hypothesis that bronchial hyperresponsiveness is secondary to the epithelial cell damage mediated through eosinophil-derived granule products." It has become apparent that eosinophils, which also participate as effector cells in host immune responses to certain parasitic helminths, likely function in the etiology of inflammation and tissue damage in a variety of eosinophil-associated hypersensitivity and other diseases (5). As a prominent cellular component, their role may be critical to either the regulation or expression of the allergic, inflammatory or related immunologic responses in chronic asthma. Thus, pharmacologic intervention aimed at modulating eosinophilopoiesis, or eosinophil recruitment, activation, and secretion could have significant therapeutic consequences in the treatment of eosinophil-associated disorders such as asthma.

Finally, as outlined in Dr. Kay's review, evidence has accumulated from clinical studies and examination of postmortem biopsy specimens to suggest that CD4 T-lymphocyte activation may play a prominent role in the pathology of asthma; these cells have been identified in and around bronchi as components of the inflammatory infiltrate in ongoing chronic asthma. In Dr. Kay's model, T cells "chronically activated" in the lung, perhaps by viral or as yet unidentified antigens, produce a panel of lymphokines such as IL-5, thus regulating or perpetuating the inflammatory cycle depending upon the relative contribution and/or availability of helper (CD4) versus suppressor (CD8) T-cell subsets. This intriguing hypothesis of a central regulatory role for the T cell in the immunopathogenesis of asthma requires further investigation.

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