

Asthma as a Paradigm for Autoimmune Disease

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Abstract

Allergy and autoimmunity result from dysregulation of the immune system. Until recently, it was generally accepted that the mechanisms that govern these disease processes are quite disparate; however, new discoveries suggest possible common pathogenetic effector pathways. This review illustrates the concomitant presentation of these conditions and the potential relationship or common mechanisms in some cases, by looking at the key elements that regulate the immune response in both asthma and autoimmune conditions: mast cells, antibodies, T cells, cytokines, and genetic determinants. The parallel appearance of asthma and autoimmune conditions in the same patients may reveal that such aberrations of the immune system have a common pathophysiologic mechanism. Mast cells, which play a key role in asthma, and the wealth of inflammatory mediators they express, make it likely that they have profound effects on many autoimmune processes. Activation of protein kinases by inflammatory cytokines and environmental

stressors may contribute to both allergic and autoimmune diseases. The presence of autoantibodies in some allergic diseases suggests an autoimmune basis for these conditions. Because of the central role T cells play in immune reactivity, the T cell receptor loci have long been considered important candidates for a common disease susceptibility within the immune system such as asthma, atopy, and autoimmunity. Immunomodulation is the key to successful treatment of asthma and autoimmune conditions.

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Asthma as an Autoimmune Disease

The allergic response to common environmental allergens has been regarded as an important mechanism in the development of airway inflammation of patients with asthma. The idea of a possible involvement of autoimmunity in the pathogenesis of a nonallergic asthma has been proposed by few studies [1]. Atopic individuals with asthma, allergic rhinitis or atopic eczema have impaired sensitivity to β -adrenergic agents. Antibodies directed toward the β -adrenergic receptor were found in sera of some patients with asthma [2] suggesting that autoantibodies to β -receptors play a pathogenetic role in asthma and related disorders. The serum γ -globulin fraction from patients with allergic bronchial asthma was found to inhibit the positive chronotropic action of the β_2 -selective adrenergic

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agonist, but not of β_1 -adrenergic agonist [3]. The inhibitory immunoglobulins of the patients with asthma were mainly autoantibodies of the IgG isotype, capable of cross-reacting with chronotropic β_2 -adrenergic receptors on the cultured rat cardiomyocytes. These findings provide support for the notion that autoimmunity plays a role in the impairment of β -adrenergic responsiveness in patients with allergic bronchial asthma. Similar studies were performed to reveal the role of antibodies on bronchial epithelium. Initially, circulating IgG autoantibodies, directed against a common 55-kD antigen shared by platelets and cultured endothelial cells, who were mainly non-allergic patients and corticosteroid-dependent asthma. These antibodies were also detected in a few patients with autoimmune disorders like systemic lupus erythematosus or rheumatoid arthritis. T cell reactivity has also been observed in 3 out of 17 patients without detectable serum anti-55-kD antigen antibodies. Moreover, a significant correlation was found between T cell reactivity and FEV1. The data indicated that the detection of such antibodies allows to distinguish a subgroup of asthmatics in terms of severity and to suggest a relationship between clinical severity and T and B cell autoreactivity to the 55-kD platelet/endothelial cell antigen [4]. Serum samples from healthy controls, patients with atopic asthma, patients with nonatopic asthma, and patients with systemic lupus erythematosus were studied for the presence of circulating autoantibodies to cultured human bronchial epithelial cells using enzyme-linked immunosorbent assay [5]. Levels of IgG autoantibodies to bronchial epithelial cells were significantly higher in patients with nonatopic asthma and systemic lupus erythematosus than in healthy controls and patients with atopic asthma. These circulating IgG autoantibodies were further studied by immunoblot analysis [6]. IgG autoantibodies to the 49-kD bronchial epithelial cell antigen were detected in 43% of patients with nonallergic asthma, 11% of patients with allergic asthma, 10% of patients with systemic lupus erythematosus, and 9% of healthy volunteers. The 49-kD autoantigen was purified and identified as 18 by amino acid sequencing. In this study cytokeratin 18 was identified as a bronchial epithelial autoantigen associated with nonallergic asthma.

A search for the presence of IgE autoantibodies in sera from patients with various manifestations of atopy and other autoimmune disorders indicated that IgE reactivity against a variety of autoantigens occurred most frequently in atopic dermatitis (AD) patients [7]. The majority of sera from patients with severe AD contain IgE antibodies directed against human proteins Hom s 1–5 and DFS70

[8, 9]. These IgE-reactive autoantigens have been cloned from a human epithelial cDNA expression library and found to represent primarily intracellular proteins [7]. Such antibodies were not detected in patients with chronic urticaria, systemic lupus erythematosus, graft versus host disease, or healthy controls. While the autoantigens were mainly intracellular proteins, they were detected in IgE immune complexes in the sera of AD patients, suggesting that the release of these autoantigens from damaged tissues could trigger IgE or T cell-mediated responses. Thirty percent of sera from patients with AD have been found to have autoantibodies that react with tissue culture cells to display a characteristic pattern of nuclear distribution of dense fine particles [8]. These sera react with a 70-kD protein on Western immunoblots, so the antigen has been termed dense fine speckles 70 kD (DFS70). Both IgG and IgE antibodies to DFS70 are present in AD sera. Recently, it was demonstrated that some patients with asthmatics also have antibodies to DFS70, as patients with AD. A cDNA isolated from an expression library encoding DFS70 has been found to be identical to a transcription coactivator called p75, which has been shown to be required for RNA polymerase II-dependent transcription [9]. Taken together, the presence of autoantibodies to β -adrenergic receptors and bronchial epithelium in patients with atopic and nonatopic asthma, respectively, demonstrates autoimmune phenomena in these conditions.

Common Pathogenic Mechanisms

Allergy and autoimmunity are two potential outcomes of a dysregulated immunity [10].

While the role of mast cells in asthma and allergic diseases is well recognized, it was not until recently that knowledge has been gathered on their physiological role and their role in nonallergic diseases and non-IgE-mediated stimuli. Mast cells play a pivotal role in asthma allergy and inflammation. There is a predominance of lesional mast cells in multiple sclerosis [11], cardiomyopathy [12], congestive heart failure [13], rheumatoid arthritis [14, 15], liver disease [16] and fibrotic lung conditions [17]. Mast cell-deficient mice exhibit significantly reduced disease severity compared to wild-type littermates in a murine model of multiple sclerosis and drugs that block mast cell function can improve clinical symptoms in this model. In addition, gene microarray analysis has revealed that the expression of several mast cell-specific genes is increased in the central nervous system

plaques of multiple sclerosis patients. Although well established as effector cells in allergic inflammation, the location of mast cells and the wealth of inflammatory mediators they express make it likely that they have profound effects on many other autoimmune processes [18].

Autoantibodies are the hallmark of autoimmunity. The allergic response to common environmental allergens has been regarded as an important mechanism in the development of airway inflammation of patients with asthma. The idea of a possible involvement of autoimmunity in the pathogenesis of asthma has been proposed by few studies as already reviewed above. Szczeklik et al. [19] assessed the autoimmune status of 185 adult patients with bronchial asthma and 46 healthy subjects of similar sex and age. The patients were divided into groups with aspirin-induced asthma, intrinsic asthma with good aspirin tolerance, and atopic asthma. Antinuclear antibodies (ANA) at a titer of $\geq 1:40$ were present in the sera of 55% of the patients with aspirin-induced asthma, 41% of those with intrinsic asthma, 39% of those with atopic asthma, and 11% of the healthy subjects, with the difference between each patient group and the healthy subjects being statistically significant ($p < 0.05$). Positive ANA were associated with signs of complement activation, the presence of rheumatoid factor, and circulating immune complexes. Clinical signs of autoimmunity, evidenced by rheumatic symptoms, cold sensitivity, and Raynaud's phenomenon, were more common among the patients who harbored the ANA. Autoantibodies have also been found in other allergic autoimmune conditions such as AD and chronic idiopathic urticaria [20, 21]

T cell dysregulation is another important mechanism in asthma and autoimmune diseases. Regulatory T cells (also referred to as suppressor T cells) are important components of the homeostasis of the immune system, as impaired regulatory T cell activity can cause autoimmune diseases and atopy. CD8⁺ T cells are known to mediate delayed-type hypersensitivity (DTH) responses in allergic contact dermatitis, drug eruptions, asthma, and autoimmune diseases. DTH is defined as the recruitment of T cells into tissues to be activated by antigen-presenting cells to produce cytokines that mediate local inflammation. This inflammatory effector capability of CD8⁺ cytotoxic T cells was previously poorly recognized, but there is now considerable evidence that inflammatory diseases may be mediated by CD8⁺ DTH [22]. The cause of asthma, which has been linked to a chronic, T-cell-mediated bronchial inflammation, remains unclear. A number of other T-lymphocyte-mediated, chronic inflammatory disorders have been associated with autoimmunity and there

are data indicating that autoimmune phenomena might also be present in asthma. Arnold et al. [23] tested the hypothesis that allergic and intrinsic asthma might be associated with an increase in lymphocytes producing perforin, a cytotoxic molecule produced by lymphocytes that has been implicated in the pathogenesis of autoimmune diseases, by comparing the expression of intracellular perforin in peripheral blood lymphocytes of patients with extrinsic asthma compared to patients with intrinsic asthma and healthy control subjects. The percentage of perforin-positive total lymphocytes was significantly elevated in patients with allergic as well as intrinsic asthma compared with normal control subjects. Analysis of lymphocyte subpopulations also revealed a significant increase in the percentage of CD3⁺, CD4⁺, CD8⁺, and CD56⁺ cells expressing perforin in allergic asthma and a significant increase in the percentage of CD4⁺ and CD56⁺ cells in intrinsic asthma when compared with healthy control subjects. Perforin expression in CD4⁺ cells in intrinsic asthma was also significantly elevated compared with allergic asthma. Thus, allergic and intrinsic asthma is associated with increased expression of perforin in T lymphocyte subsets. Suppressor T cells play important roles in the regulation of immune responses and the mediation of dominant immunologic tolerance. Suppressor T cell function has recently been identified as a minor fraction (approximately 10%) of CD4⁺ T cells that coexpress CD25. CD4⁺CD25⁺ T cells have been shown to play a critical role in the prevention of organ-specific autoimmunity and allograft rejection. Because tumor antigens are self-antigens, it is not surprising that CD4⁺CD25⁺ T cells also inhibit the induction of tumor immunity. Although CD4⁺CD25⁺ T cells are capable of inhibiting TH2 responses, their role in the suppression of allergic responses has not been firmly established. Depending on the desired immune response, enhancement or restraint suppressor T cell function might be required.

Because of the central role T cells play in immune reactivity, the T cell receptor (TCR) loci have long been considered important candidates for a common disease susceptibility within the immune system such as asthma, atopy, and autoimmunity.

Over the past two decades, hundreds of sequence variations known as single nucleotide polymorphism (SNPs) in the TCR loci have been identified. Most studies have focused on defining SNPs in the variable gene segments which are involved in antigenic recognition. On average, the coding sequence of each TCR variable gene segment contains two SNPs, with many more found in the 5', 3'

and intronic sequences of these segments [24]. Meaningful association studies in the TCR loci will require the analysis and typing of large marker sets to fully evaluate the role of TCR loci in common disease susceptibility in human populations. Inherited abnormalities in either coding or regulatory regions of TCR genes may predispose to aberrant T cell function and autoimmune disease [25].

Cytokine dysregulation has been proposed as a contributory element in asthma and autoimmunity. Multicellular organisms have three well-characterized subfamilies of mitogen-activated protein kinases (MAPKs) that control a vast array of physiological processes [26]. These enzymes are regulated by a characteristic phosphorelay system in which a series of three protein kinases phosphorylate and activate one another. The extracellular signal-regulated kinases (ERKs) function in the control of cell division, and inhibitors of these enzymes are being explored as anticancer agents. The c-Jun amino-terminal kinases (JNKs) are critical regulators of transcription, and JNK inhibitors may be effective in the control of rheumatoid arthritis. The p38 MAPKs are activated by inflammatory cytokines and environmental stresses and may contribute to diseases like asthma and autoimmunity.

The genetic basis of atopic diseases is represented by a complex network of interacting genes or common genetic variants rather than a few disease-causing mutations. Polymorphism within IL-4R α , which is associated with asthma and atopy, is also associated with autoimmune diseases such as systemic lupus erythematosus and Crohn's disease [27].

Common Therapies

Treatment of mast cell disease usually involves antihistamines and local application of glucocorticoids. Future therapy may potentially include anti-SCF antibodies, directed against the main cytokine which controls mast cell viability and survival. Induction of long-term, antigen-specific immunologic unresponsiveness holds great promise for the treatment of many immune system-mediated diseases, including asthma, allergies, autoimmune diseases, and transplant rejection. Unlike current immunosuppressive treatments, immunologic tolerance therapies affect only the undesired immune responses, leaving protective immunity intact [28]. A variety of approaches to immunological tolerance induction are being taken, reflecting the molecular and cellular complexity of immune system activation and regulation. Possible approaches include the following: interference with costimulatory signals in T cell induction, TCR antagonism by altered peptides, exploitation of antigen-induced apoptosis to eliminate undesired T cells, opposition of inflammation by the induction of regulatory cytokines, induction of transplant tolerance by mixed chimerism, and deviation from deleterious allergic antibody responses by use of immunostimulatory DNA sequences. These multifaceted approaches are strongly supported by knowledge of basic immune mechanisms, which should facilitate the rational development of these therapies for controlling immune-mediated diseases. Therefore immunologic or pharmacologic manipulation of regulatory T cell populations represents an important future approach to immunotherapy of a wide range of immune responses.

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