The Association Between Immunodeficiency and the Development of Autoimmune Disease

J.W. Sleasman

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THE ASSOCIATION BETWEEN IMMUNODEFICIENCY AND THE DEVELOPMENT OF AUTOIMMUNE DISEASE

J.W. SLEASMAN

Division of Pediatric Immunology and Allergy
University of Florida College of Medicine
Box 100296, 1600 SW Archer Road
Gainesville, Florida 32610-0296

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Abstract—There is a paradoxical relationship between immunodeficiency diseases and autoimmunity. While not all individuals with immunodeficiency develop autoimmunity, nor are all individuals with autoimmunity immunodeficient, defects within certain components of the immune system carry a high risk for the development of autoimmune disease. Inherited deficiencies of the complement system have a high incidence of systemic lupus erythematosus (SLE), glomerulonephritis, and vasculitis. Carrier mothers of children with chronic granulomatous disease, an X-linked defect of phagocytosis, often develop discoid lupus. Several antibody deficiencies are associated with autoimmune disease. Autoimmune cytopenias are commonly observed in individuals with selective IgA deficiency and common variable immune deficiency. Polyarticular arthritis can be seen in children with X-linked agammaglobulinemia. Combined cellular and antibody deficiencies, such as Wiskott-Aldrich syndrome, carry an increased risk for juvenile rheumatoid arthritis and autoimmune hemolytic anemia. Several hypothetical mechanisms have been proposed to explain the associations between autoimmunity and immunodeficiency. Immunologic defects may result in a failure to exclude microbial antigens, resulting in chronic immunologic activation and autoimmune symptoms. There may be shared genetic factors, such as common HLA alleles, which predispose an individual to both autoimmunity and immunodeficiency. Defects within one component of the immune system may alter the way a pathogen induces an immune response and lead to an inflammatory response directed at self-antigens. An understanding of the immunologic defects that contribute to the development of autoimmunity will provide an insight into the pathogenesis of the autoimmune process.

Key words: Autoimmunity, immunodeficiency, T-cells, antibody, complement.

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Paradoxically, individuals with primary or acquired immunodeficiency disease have an increased incidence of autoimmunity. Human primary immunodeficiency disease can be classified as disorders of cell-mediated immunity, humoral immunity, phagocytic cell function, and the complement system (Barrett and Sleasman, 1990). Cell-mediated and humoral immunity comprise the adaptive arm of the immune response, which is antigen-specific and confers immunologic memory. The innate immune response, which is antigen-nonspecific, is composed of phagocytic cells and the inflammatory peptides. Not all individuals with inherited immunodeficiency develop autoimmunity, nor are all individuals with autoimmune disease immunodeficient. Defects within particular components of the immune response carry a higher risk for autoimmune disease than others. An understanding of the immune defects that may contribute to the development of autoimmune disease provides an insight into the nature of the autoimmune process.

SPECIFIC IMMUNODEFICIENCY DISORDERS ASSOCIATED WITH AUTOIMMUNITY

The most commonly observed association between disorders of innate immunity and an increased risk for the development of autoimmunity is in individuals with inherited defects in the complement cascade (Frank, 1995). Low serum complement levels found in patients with autoimmune disease generally reflect increased consumption of complement proteins as a result of immune complex-mediated inflammation. Clinical manifestations of the inherited deficiencies of complement components include both an increased incidence of infection and autoimmunity. The complement cascade can be organized into three components: the classical pathway, initiated by the binding of C1 to immunoglobulin Fc receptor; the alternative pathway, initiated by microbial proteins binding to C3 and the membrane attack complex; and the final common pathway, consisting of C5 through C9, leading to cytolysis (Fig. 1).

Inherited deficiencies in the components of the classic cascade carry with them a risk for the development of systemic lupus erythematosus (SLE), anaphylactoid purpura, and juvenile arthritis. Though rare, nearly 85% of patients reported to have homozygous C4 deficiency have clinical manifestations of autoimmunity. Approximately one-half of the individuals with symptomatic C2 deficiency have autoimmune disease (Hauptmann *et al.*, 1988). Recurrent infections are uncommon in C2 deficiency compared with other complement disorders, but an increased incidence of bacterial pneumonia, meningitis, and sepsis has been

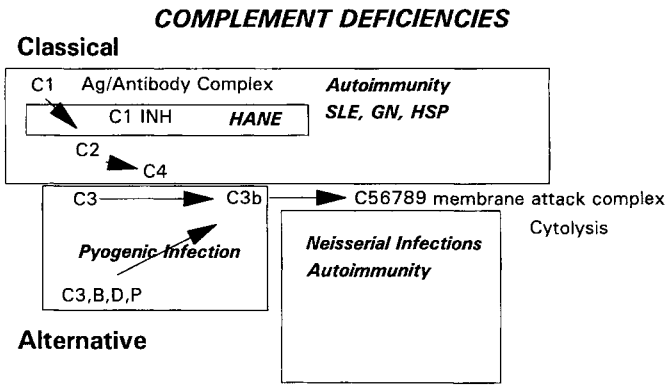

Fig. 1—Complement deficiencies and their association with infection and autoimmunity. The classic pathway is activated by antigen/antibody complexes binding to C1. Loss of C1 inhibitor (C1 INH) leads to Hereditary Angioneurotic Edema (HANE). Defects in components of the classic pathway carry an increased risk of SLE, glomerulonephritis, and HSP. Deficiencies in the alternative pathway are generally associated with recurrent infections with pyogenic bacteria. Defects within the components of the membrane attack complex carry a risk of neisserial infections and autoimmune nephritis

reported. A deficiency of C1 inhibitor results in uncontrolled activation of the classic pathway components and consumption of C2 and C4. This deficiency leads to recurrent episodes of angioedema of the viscera, soft tissues, and airway, and a high risk of SLE, Crohn's disease, and Sjögren's syndrome (Brickman *et al.*, 1986a,b).

Defects in the alternative complement pathway are more commonly associated with recurrent pyogenic infections, particularly infections with *Neisseria meningitidis* and *Streptococcus pneumoniae*; SLE, systemic vasculitis, and glomerulonephritis have been reported in 15 to 20% of patients with C3 deficiency (Borzy *et al.*, 1988). Cytolysis by terminal complement components (C5 through C9) are important in host defense against Gram-negative organisms, particularly *Neisseria* species, but also brucella and toxoplasmosis. Chronic pyelonephritis and recurrent pneumonia are sometimes seen in these patients. Autoimmune symptoms, such as Raynaud's phenomena and lupus-like syndromes, have been reported in 11% of patients with defects in terminal complement components (Ross and Densen, 1984).Disorders of leukocyte function are less commonly associated with autoimmune disorders than with defects in the complement system. Chronic granulomatous disease (CGD), an inherited inability of polymorphonuclear leukocytes to kill bacteria following phagocytosis, is an X-linked recessive condition characterized by recurrent infections with catalase-positive organisms such as *Staphylococcus aureus* (Galin and Malech, 1990). The disorder results from an abnormality of the cytochrome b_{245} subunit of the metabolic pathway, which generates superoxide free radicals (Segal *et al.*, 1983). The failure of leukocytes to achieve intracellular killing of catalase-positive organisms results in granuloma formation. In this way, the immune response compensates for the defect in leukocyte function. While autoimmunity has not been reported in affected male children, the genetic defect is associated with a high incidence of discoid lupus erythematosus (DLE) in carrier mothers (Humbert *et al.*, 1976). Superoxide generation in carrier mothers is reduced but not absent. Studies of women with DLE who are not CGD carriers indicate that leukocyte bactericidal activity is generally normal (Humbert *et al.*, 1976). Defects of adaptive immunity consist primarily of disorders of T-cell and B-cell function. Autoimmunity is uncommon in patients with pure T-cell immunodeficiency (Rosen, 1987). Children with X-linked severe combined immunodeficiency exhibit T-cell maturation arrest within the thymus (Sleasman *et al.*, 1994). B-cell numbers are normal, and immunoglobulin secretion can occur in the presence of normal T-cell help. Although this is the most common form of human SCID, autoimmunity has not been reported in these patients, perhaps a result of early treatment with bone marrow transplantation or death in early infancy due to infection. While opportunistic infections are a prominant feature of both adults and children with idiopathic or congenital $CD4^+$ T lymphocytopenia, autoimmune disease has not been associated with this newly described immunodeficiency of $CD4^+$ T lymphocytes (Sleasman *et al.*, 1990; Duncan *et al.*, 1993; Ho *et al.*, 1993; Smith *et al.*, 1993; Spira *et al.*, 1993). In contrast to purely T-cell deficiencies, defects in immunoregulatory peptides involved in cell-to-cell interactions are commonly associated with autoimmune disease. Children with Wiskott-Aldrich Syndrome, an X-linked immunodeficiency characterized by low expression of sialophorin (CD43), demonstrated a high incidence of Coombs-positive hemolytic anemia, juvenile rheumatoid arthritis, and severe eczema (Amman and Hong, 1989).

Unlike T-cell defects, humoral immunodeficiencies carry a high risk of autoimmunity. Children with X-linked agammaglobulinemia have little detectable immunoglobulin production due to a maturation defect in B-cell development (Conley, 1985). Children with this disorder have a high incidence of polyarticular arthritis and inflammatory bowel disease (Barnett *et al.*, 1970). X-linked hyper-IgM syndrome results from a mutation within the gene encoding the ligand for CD40 (Aruffo *et al.*, 1993). This defect results in ineffective immunoglobulin isotype class-switching from IgM to IgG or IgA. In addition to antibody deficiency and recurrent infections, affected boys have a high incidence of autoimmune thrombocytopenia and autoimmune hemolytic anemia (Cairns and Rosen, 1986).

Selective IgA deficiency is the most common antibody deficiency seen in humans (Barrett *et al*, 1995). It occurs as commonly as one in every 400 Caucasians. While most individuals with selective IgA deficiency are asymptomatic, there is a high incidence of recurrent sinopulmonary infections, allergic disease, and autoimmune disease. Organ-specific autoimmune conditions are seen at much higher incidence in patients who have IgA deficiency (Liblau and

TABLE 1

DEFECTS OF INNATE IMMUNITY ASSOCIATED WITH AN AUTOIMMUNE DISEASE

Phagocytic Defects	Autoimmune Association
Chronic granulomatosis disease	Discoid SLE[a] in mothers
Complement Deficiencies	
C1	SLE
C1 inhibitor	SLE, GN[a], angioedema
C2	SLE, GN[a], HSP[a]
C3	SLE, GN[a], vasculitis

[a] SLE, systemic lupus erythematosis; GN, glomerulonephritis; HSP, Henoch-Schonlein purpura.

TABLE 2

DEFECTS OF ADAPTIVE IMMUNITY ASSOCIATED WITH AUTOIMMUNE DISEASE

Humoral Immunodeficiencies	Autoimmune Association
IgA deficiency	JRA[a], IDDM[a], SLE[a], RA[a], others
X-linked agammaglobulinemia	Polyarticular arthritis
Common variable immunodeficiency	ITP[a], AHA[a] RA, polymyositis, SLE
X-linked hyper-IgM syndrome	ITP[a], AHA[a]
Combined and T-cell Immunodeficiencies	
Wiskott-Aldrich Syndrome	JRA, AHA

[a] Abbreviations: JRA, juvenile rheumatoid arthritis; IDDM, insulin-dependent diabetes mellitus; SLE, systemic lupus erythematosis; RA, rheumatoid arthritis; ITP, idiopathic thrombocytopenia purpura; and AHA, autoimmune hemolytic anemia.

Bach, 1992). Insulin-dependent diabetes mellitus (IDDM), myasthenia gravis, and Crohn's disease have all been reported to be several times higher in these individuals compared with the unaffected population. Systemic autoimmune diseases observed to occur at a high frequency include SLE, juvenile rheumatoid arthritis (JRA), and adult rheumatoid arthritis. Common variable immunodeficiency (CVID) includes a heterogeneous group of disorders of antibody production. It occurs in males and females of all ages (Cunningham-Rundles, 1989). CVID and IgA deficiency frequently occur in members of the same family, suggesting a possible HLA association or other genetic linkage between these two immunologic disorders Conley *et al.*, 1986). One-fourth of individuals with CVID develop autoimmune disease, including autoimmune hemolytic anemia, ITP, autoimmune endocrinopathy, rheumatoid arthritis, SLE, and dermatomyositis (Cunningham-Rundles, 1986). Similar autoimmune diseases have been reported at a high incidence among first-degree relatives.

HYPOTHETICAL ORIGINS FOR THE ASSOCIATION BETWEEN AUTOIMMUNITY AND IMMUNODEFICIENCY

Immunologic failure to exclude antigens

Linkages between infection and autoimmunity have been recognized for many years in both human and animal systems (Shoenfeld and Isenberg, 1989). Examples of viral, bacterial, and parasitic infections associated with autoimmune disorders include Coxsackie virus infection and Type I diabetes, Group A streptococcal pharyngitis and rheumatic fever, and *Shigella* enteritis and Reiter's Syndrome. Animal retroviral infections that have been shown to result in autoimmune conditions are equine infections, anemia virus, and caprine arthritis. In humans, HIV infection results in laboratory and clinical manifestations similar to those in patients with collagen vascular disease (Katz, 1993). Because immunodeficiency most commonly precedes the development of autoimmunity, it is possible that immunodeficient states render individuals more susceptible to infectious agents, which then trigger an autoimmune condition. This hypothesis could be applied to the association of autoimmunity with hypogammaglobulinemia or selective IgA deficiency. Infection may lead to increased expressions of MHC antigens or trigger the immune response through molecular mimicry and cross-reactivity against endogenous and microbial peptides (Barnett and Fujimani, 1992). Another possibility is that chronic infection may result in failure to clear circulating immune complexes, leading to autoimmunity through immune complex deposition in the tissues. These mechanisms may play a role in the development of autoimmune disease in patients with complement deficiencies.

Common genetic factors

Many autoimmune diseases have an established HLA association. Particular HLA class I and class II alleles have been linked with IDDM, SLE myasthenia gravis, Graves' disease, and rheumatoid arthritis (French and Dawkins, 1990). Many of the same haplotypes are commonly found, frequently in patients with selective IgA deficiency and CVID (Conley *et al.*, 1986). Many of the complement component genes including C2 and C4 are located within the MHC locus on chromosome 6. Extended haplotypes are inherited and expressed in an autosomal co-dominant fashion; thus, linkage between genes regulating complement or immunoglobulin production could be inherited with HLA genes that predispose to autoimmunity. A susceptibility gene for these disorders within the HLA locus has not been identified. Although the linkage of complement genes to HLA haplotypes provides an attractive explanation for the association between autoimmunity and complement deficiencies, it is equally plausible that the complement deficiency itself is the primary risk factor for autoimmune

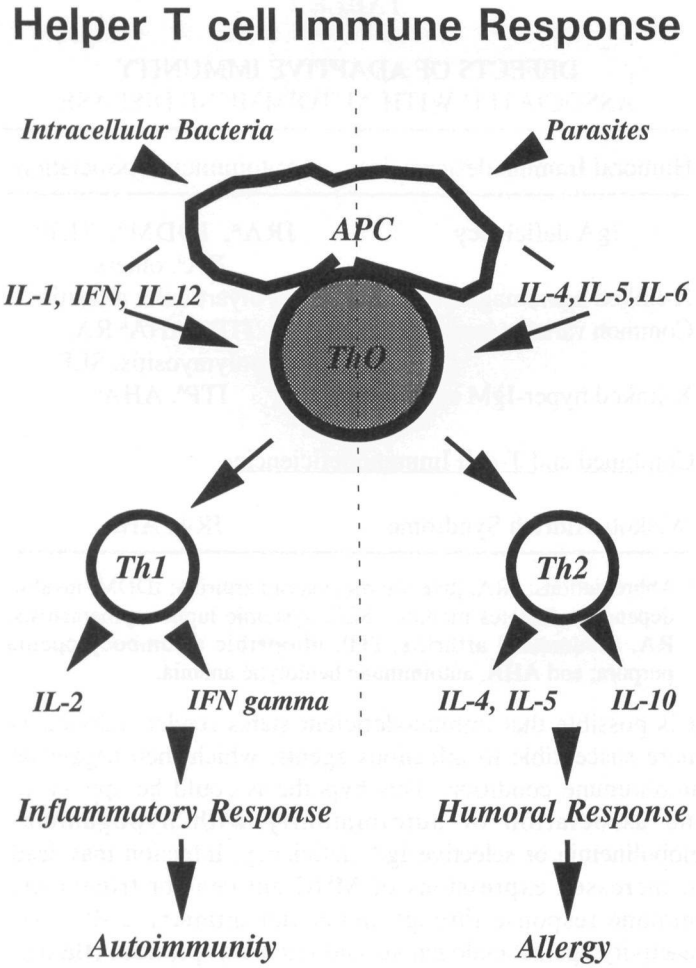

Fig. 2—Modulation of the T helper immune response. Intracellular bacteria stimulate antigen-presenting cells (APC) to elaborate IL-1, interferon, and IL-12. These cytokines activate ThO T lymphocytes to commit to a Thl-activated T-cell clone which produces IL-2 and gamma interferon. These T-cells induce a local inflammatory response and have been associated with autoimmunity. Parasitic infections stimulate APC to produce IL-4, IL-5, and IL-6. ThO T helper cells activated by these cytokines become Th2 T-cell clones and secrete IL-4, IL-5, and IL-10. These cytokines evoke a humoral immune response characterized by the production of IgA, IgE, and eosinophilia. This immune response has been associated with allergy.

disease. Individuals who have deficiency of C1 esterase inhibitor, which leads to hereditary angioneurotic edema, have low or undetectable levels of C4 and C2 as a result of chronic consumption of complement proteins. This disorder carries a risk of recurrent infections and a high incidence of autoimmune disease, but no known HLA association (Frank, 1993).

Altered pathogen-induced immune response

The microbial properties of most pathogens dictate the nature of the immune response against them. Encapsulated bacterial pathogens such as *Pneumococcus* or *Haemophilus influenzae* stimulate antibody production and microbial clearance through a T-cell independent pathway. *Staphylococcus* is cleared primarily by intracellular killing by polymorphonuclear neutrophils. Parasites induce eosinophilia and IgE production. A defect within a particular component of the immune system will result in an alteration in the way the pathogen activates the immune response. For example, in chronic granulomatous disease, the immune response compensates for the defect in neutrophil microbial killing by the formation of giant cells and granuloma in response to infections with catalase-positive organisms (Galin and Malech, 1990).

New insight into the pathogenesis of autoimmunity has come as a result of our expanded understanding of the activation of $CD4^+$ T lymphocytes by antigen-presenting cells (APC). Following phagocytosis, microbial antigens are processed and presented to a $CD4^+$ T helper cell within the MHC class II molecular complex. Binding of the MHC class II complex to the CD3/T cell receptor complex results in T-cell activation and clonal proliferation. In this way, the T-cell immune response maintains its antigen specificity. When processed by an APC, intracellular bacteria such as *Listeria monocytogenes* or *Salmonella* stimulate an uncommitted ThO $CD4^+$ T helper cell toward an immune response characterized by the production of IL-2 and gamma interferon (Fig. 2). ThO activated through this pathway are termed Thl-type T-cells and evoke a localized inflammatory response. Alternatively, parasitic infections result in a different array of cytokine production by APC. ThO cells activated by this pathway are termed Th2 and predominantly produce IL-4, IL-5, and IL-10. These cytokines result in shifting the immune response toward the production of IgA, IgE, and eosinophilia.

It has been postulated that some organ-specific autoimmune diseases are predominantly characterized by a Thl-type immune response (Romagnani, 1994). Allergic diseases and autoimmune diseases associated with B-cell dysfunction, such as SLE, are characterized by a Th2 type of immune response. It is possible that immunologic defects alter the common mechanisms in which a pathogen is cleared by the host. Examples would include deficiencies involving the complement cascade or antibody production. This results in a shift toward a cellular immune response with predominance toward activation of either the Thl or Th2 T-cells. Though highly speculative, this model might also explain why some T-cell immunodeficiency states are rarely associated with autoimmune disease.

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