

AUTOIMMUNE BULLOUS DISEASES

Epidemiology and Immunogenetics of Autoimmune Bullous Diseases

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Most cases of autoimmune diseases occur sporadically, without evidence of geographic or familial clustering. However, numerous exceptions to this tendency have been uncovered that may offer insight into potential triggers to the autoimmune response. Schmidt (1926) described the coincidence of idiopathic hypothyroidism and Addison's disease in two patients, a coincidence that has since been reported in over 100 patients now recognized as having Schmidt's syndrome (autoimmune polyendocrine syndrome, type 2). This observation prompted others to seek out potential genetic and/or environmental factors that may predispose one individual to develop multiple autoimmune diseases. Multiple additional diseases of presumed autoimmune pathogenic etiology have since been shown to occur with increased frequency both within individual patients and among members of the same family.

Lilly *et al.* (1964) demonstrated a genetic linkage between the murine major transplantation (H-2) antigen complex and viral leukemogenesis, stimulating other investigators to contemplate the role of histocompatibility antigens in human disease. Given this initial observation, early work predictably focused on HLA associations with hematologic malignancy. However, Grumet *et al.* (1971) observed an increased frequency of histocompatibility antigens HL-A8 and W15 (LND) in a group of 40 unrelated patients with systemic lupus erythematosus, marking the first observed HLA association with

an autoimmune disease. Increased frequencies of certain genetically determined MHC antigens, especially HLA class II antigens, have since been observed in several autoimmune bullous disorders, including dermatitis herpetiformis, pemphigus vulgaris (PV), and endemic pemphigus foliaceus (PF) (also known as fogo selvagem (FS)). Additionally, the epidemiologic features of dermatitis herpetiformis, PV, and FS are unique and have provided investigators a valuable tool for eliciting potential pathogenetic mechanisms of autoimmunity. This section emphasizes these features in these diseases.

Katz *et al.* (1972) noted an increased prevalence of the same histocompatibility antigen associated with gluten-sensitive enteropathy (HL-A8) among patients with dermatitis herpetiformis, providing a genetic basis for the association between these two diseases. A year later, Fry *et al.* (1973) reported improvement in both the cutaneous and gastrointestinal manifestations of dermatitis herpetiformis in patients on a gluten-free diet, marking the first instance where controlling exposure to an environmental trigger was shown to block the development of the clinical manifestations of an autoimmune disease.

Despite an apparent lack of geographic or familial clustering of cases, the immunogenetics of PV are unique. Eller and Kest (1941) were the first to report increased percentages of PV among individuals of Jewish descent. Krain *et al.* (1973) noted increased frequency of HLA-A10 among nonre-

lated Jewish patients with PV when compared with Jewish controls as well as non-Jewish patients and controls. The same year, Katz *et al.* (1973) reported an increased frequency of HLA-A13 among PV patients. In more recent years, extensive reports have documented the strong association of PV with HLA class II alleles HLA DRB1*0402 and HLADQ*0503, with over 95% of PV patients exhibiting one or both alleles (Sinha *et al.*, 1988; Szafer *et al.*, 1988). Recently, Brazilian investigators have described an endemic form of PV in endemic areas of FS (Rocha-Alvarez *et al.*, 2007), suggesting that rare individuals exposed to environmental desmoglein cross-reactive antigen(s) may develop FS or endemic PV.

Fogo selvagem is a fascinating model of a human organ-specific autoimmune disease mediated by pathogenic IgG autoantibodies where the immune response is linked to an environmental etiology. Unique epidemiological features of FS include geographic and temporal clustering of cases, increased incidence among young adults and children, increased frequency of familial cases, and an association with certain distinct HLA alleles such as the DRB1*0102, 0404, 1402, or 1406 (RR:14; Moraes *et al.*, 1997). Hans-Filho *et al.* (1996) reported an approximately 3% prevalence of disease in the Amerindian reservation of Limao Verde, located in the state of Mato Grosso do Sul, Brazil. Intriguing subsequent seroepidemiological observations from

Limao Verde, including the clinical and serological conversion from normal-to-disease state in several individuals, suggest that the immune response in FS patients likely arises from recurrent and persistent antigenic exposure to an as yet unknown environmental cross-reactive antigen(s) harbored in endemic areas (Warren *et al.*, 2000). Efforts to uncover the specific environmental trigger(s) are ongoing. Future studies will be aimed at better understanding of the interplay of genetic, environmental, and immunologic factors in the pathogenesis of this disease.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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