Our goal was to review the hypotheses in evolution that promise to elucidate the genetic bases of autoimmune hepatitis. DRB1*0301 and DRB1*0401 are the principal risk factors in Britain and the United States. Other susceptibility alleles in different ethnic groups commonly share the same or a similar motif at the critical DRβ71 position of the HLA class II molecule. Disease severity may be determined by the number of alleles encoding lysine at the DRβ71 position, the density of dimers presenting antigen, and the avidity of T-cell receptors for the displayed antigen. Concurrence on the same or different chromosomes of other nonspecific autoimmune promoters may also contribute. A negatively charged residue at the P4 position of antigenic peptides is preferred for binding to the disease-susceptibility alleles, and this complex may be recognized by promiscuous T cells. We conclude that autoimmune hepatitis is a model by which to study the genetic bases of autoimmunity.

Key Words: autoimmune hepatitis; autoimmunity; autoantigens; HLA.

Autoimmune hepatitis is a hepatocellular inflammation of unknown cause that is characterized by interface hepatitis and portal lymphocytic infiltration on histological examination, hypergammaglobulinemia, and autoantibodies (1). The demonstration of an immune response to host antigens is sufficient to suggest an autoimmune pathogenesis, but the reasons for impaired self-tolerance and the mechanisms by which this impairment causes liver disease remain unclear (2).

The long-recognized predilection of women for autoimmune diseases and the association of many of these diseases with human leukocyte antigens (HLA) have emphasized the importance of host predisposition for autoreactivity (3, 4). Recent studies have identified strong genetic bases for both disease susceptibility and behavior. Autoantigen presentation, immunocyte activation, effector cell differentiation, and liver cell injury can be influenced by genetic factors (5), and characterization of these factors may result in better diagnostic and management algorithms (6, 7).

The goal of this report is to review the hypotheses in evolution that promise to elucidate the genetic bases of autoimmune hepatitis and direct future investigations.

Female Predisposition for Autoimmune Hepatitis

Autoimmune hepatitis has a strong female predilection, but it is uncertain if this gender effect is due to immunomodulatory mechanisms controlled by sex-linked genes or sex hormones that act on the immunocytes and/or the susceptibility alleles (8). An immunomodulatory gene on the X chromosome has been proposed, and the increased immunoreactivity in women may reflect a “double dose” of this gene (9–11). Alternatively, estrogens and other gender-related hormones may influence the vigor of the immune response by facilitating antigen processing and recognition (12, 13). The heightened immunoreactivity in women is manifested by higher serum levels of immunoglobulin after exposure to a fixed antigen load (10, 14), more common expression of natural
autoantibodies (15, 16), increased cell-mediated immunity after immunization (8), and greater occurrence of autoimmune phenomena and disease than in men (3, 4, 8).

Women are more likely to develop a type 1 cytokine response after exposure to an infectious agent or antigen than men (8). During pregnancy, however, they have mainly a type 2 response. This shift may, in part, explain the observed differences in the activity of certain autoimmune diseases during pregnancy. Changes in estrogen levels and the expression of certain autoimmune diseases during pregnancy. Part, explain the observed differences in the activity of certain autoimmune diseases during pregnancy. Changes in estrogen levels and the expression of estrogen receptors on immunocytes during pregnancy may contribute to these responses.

Estrogen has biphasic dose effects and two different receptors on immune cells. High estrogen levels, as in pregnancy, inhibit the proinflammatory type 1 cytokine response and promote a type 2 cytokine response that favors antibody production and antibody-dependent pathogenic pathways (8). Conversely, low estrogen levels favor a type 1 cytokine response and promote cell-mediated pathogenic pathways. Pituitary hormones, such as prolactin and growth hormone, and sex hormones, such as progesterone and testosterone, counterregulate the immune response, probably by altering the cytokine milieu and/or estrogen receptor expression (8). Lastly, microchimerism can persist for years after pregnancy, and fetal cells in the maternal circulation have been associated with the initiation and exacerbation of autoimmune disease (17–19). Mechanisms by which microchimerism affects postpartum immunoreactivity are unknown, but it may compromise self-tolerance by promoting cross-reactivity.

Recognition that gender differences exist in the immune response does not translate into a coherent hypothesis of pathogenesis in autoimmune hepatitis. If there is a genetic basis for gender differences in this disease, it most likely relates to disparate modulations of the susceptibility genes by the sex hormones alone or in conjunction with secretions from the hypothalamic–pituitary–adrenal axis. Women with type 1 autoimmune hepatitis more commonly have HLA DR4 than men with the disease, and they have a greater diversity of HLA DR4 alleles (20, 21). This diversity of HLA DR4 alleles in women implies that they are able to present a greater variety of autoantigens to CD4 T helper cells than men. This propensity may in turn enhance their potential to trigger an autoimmune response. The mechanisms by which the female gender enables different HLA DR4 molecules to generate the disease is unclear. Synergisms between the sex hormones, immunoregulatory cytokine profiles, and polymorphisms of various autoimmune promoters, such as Fas (CD95/APO-1), cytotoxic T lymphocyte antigen-4, and tumor necrosis factor-α, may enhance immunocyte activation by different complexes of antigenic peptide and class II molecules of the major histocompatibility complex (MHC) (6–8).

HLA RISK FACTORS FOR AUTOIMMUNE HEPATITIS

Type 1 autoimmune hepatitis is characterized by the presence of smooth muscle antibodies and/or antinuclear antibodies in serum (22), and the principal HLA susceptibility allele among caucasoid northern Europeans and North Americans is DRB1*0301, which encodes the HLA DR3 antigen (23, 24). A secondary, independent risk factor is DRB1*0401, which encodes the HLA DR4 antigen. Eighty-four percent of caucasoid adult patients from Britain or the United States have either or both of these alleles (23, 24). In contrast, the principal susceptibility allele for type 1 autoimmune hepatitis in Japan is DRB1*0405 (25, 26). Among Argentine adults, it is DRB1*0405 (27, 28), and among Argentine children, it is DRB1*1301 (27, 28). DRB1*0404 confers susceptibility in Mestizo Mexicans (29), and DRB1*13 and DRB1*03 are associated with the disease in Brazil (30) (Table 1).

Type 2 autoimmune hepatitis is characterized by the presence of antibodies to liver/kidney microsome type 1 in serum (22, 31), and it has susceptibility alleles that distinguish it from type 1 disease (30, 32, 33). In Brazilian and white German patients, DRB1*07 is the principal risk factor (30, 32). Other studies have implicated HLA B14, DR3, and C4A-QO as contributors to susceptibility (33). These associations imply that the target antigen of type 2 autoimmune hepatitis and the genetic risk factors for the disease are different between type 1 and type 2 autoimmune hepatitis. The identification of the cytochrome monoxygenase, P450 IID6 (CYP2D6), as a type-specific autoantigen for type 2 disease has supported this hypothesis (34–36). Differences in the clinical expression and behavior of type 1 and type 2 autoimmune hepatitis may reflect distinctions in the peptide–MHC complex and the lack of plasticity in TCR recognition of each disease-associated unit (37, 38). Conversely, clinical similarities between type 1 and type 2 autoimmune hepatitis may reflect promiscuous interactions between CD4 T helper cells and the peptide–MHC complex of each disease (39).