5

Autoimmune Disorders

HLA, Genetic Predisposition, and the Immune System

Many diseases with autoaggressive immune components appear to have predisposing genetic factors. Such a contention is supported by the observation of an increased prevalence of many autoimmune diseases among family members and among ethnic or racial groups (1). Moreover, autoimmune diseases are more often shared among monozygotic twins than among dizygotic twins or nonrelated individuals (1,2). Ultimately, disease association with genetic factors has often been defined in terms of human leukocyte antigens (HLA), particularly those for the highly polymorphic class I and class II genes. Yet most HLA-associated diseases (which include infectious diseases and some forms of cancer) do not reveal a simple Mendelian mode of inheritance, either recessive or dominant, are only partially penetrant, and may involve a number of different HLA alleles in addition to non-HLA loci (3). Taken together, these observations indicate that autoimmune diseases have a genetic basis, but that they also have environmental components and that multiple genetic loci are probably critical to disease onset.

Although there are no unequivocal explanations why class I and class II alleles associate with disease, there are a number of diseases, particularly those with autoimmune components, that are worth discussing in terms of their associations with class I or class II HLA (3–6). Class I and class II HLA genes are encoded in a region that spans about 3500 kb (about 0.03% of the total human genome) and incorporates more than 100 known genes, clustered on the distal portion of chromosome 6 (6p21.3) (7,8) (see Chapter 1). Because there is great expectation that the role of class I and class II molecules in disease may reveal itself in part from studies in mice, it is important to note that the three class I HLA categories HLA-A, HLA-B, and HLA-C roughly correspond to murine MHC class I groups H-2K, H-2D and H-2L, respectively, and that the human class II HLA groupings HLA-DQ and HLA-DR show considerable molecular, genetic, and serological identity with murine I-A and I-E, respectively (Figure 5.1). The functional similarities between human and murine class I or class II can indeed be striking: For example, a comparison of class II molecules associated with insulin-dependent diabetes mellitus (IDDM) and murine nonobese diabetes (NOD) reveals that in both cases susceptibility to disease involves the amino acid residue at position 57 of the class II molecule, which is a residue involved in peptide binding (4,10).

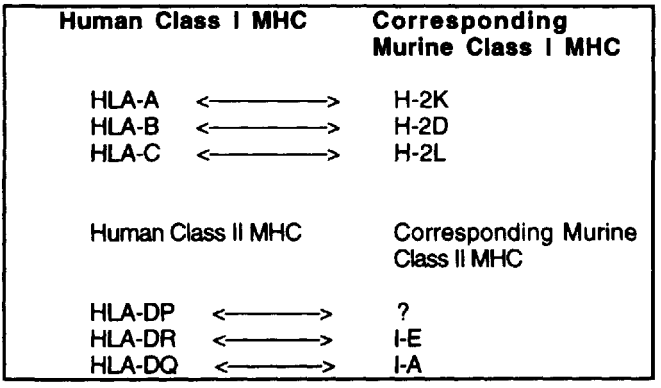

Figure 5.1. Molecular and genetic similarities exist between mouse and human class I and class II MHC.

Because it is the function of HLA class I and class II molecules to display peptides in their polymorphic peptide-binding grooves, the observation that certain HLA haplotypes were associated with specific autoimmune diseases clearly hinted that certain peptide binding characteristics may ultimately reflect disease susceptibility (Table 5.1). What is perhaps a logical extension of this thinking has become known as the molecular "mimicry" hypothesis (11–13). Each class I and class II allele displays a unique affinity for a set of peptides, which are derived from either invading pathogens or from endogenous pro-

Table 5.1
HLA Serotypes that Segregate with Disease[a]

Disease	Associated HLA	Relative risk
Addison's disease	DR3/DQ	6.3
Ankylosing spondylitis	B27	87.4
Autoimmune liver disease		3–15
Autoimmune hepatitis		
Primary biliary cirrhosis	DP/DQ	
Primary sclerosing cholangitis	DR/Dw2	
Behcet's disease	B5	6.3
Celiac disease	DR3	
Cicatrical pemphigoid	DQ/DR	
Dermatitis herpetiformis	DR3	15.4
Insulin-dependent diabetes mellitus	DR3	5.3
Multiple sclerosis	DR2	
Myasthenia gravis	B8/DR3	2.7/2.5
Pemphigus vulgaris	DR4	14.4
Reiter's syndrome	B27	37.0
Rheumatoid arthritis	DR4	4.2
Systemic lupus erythematosus	DR3	5.8

[a]See text for a more detailed discussion of various alleles and their associations with disease.

teins. However, in the absence of infection, most peptides displayed on the surface of cells on class I or class II molecules are presumably derived from *self-proteins*, which include those derived from fragments of class I or class II molecules themselves (see discussion on antigen processing, Chapter 2). Problems may arise after an infectious organism is processed into peptides and displayed on class I or class II molecules. If these peptides are a close match, or even identical, to any one of the *self-peptides* normally displayed on the cell surface (derived from endogenous proteins), the ensuing antigen-specific immune response may attack not only these foreign peptides but also may target those displaying self-peptides. As HLA class I and class II polymorphisms largely involve residues that determine peptide binding characteristics, the result is an association between autoimmune disease and the HLA allele involved in presenting the "mimicking" peptide. The model is further validated by the reasoning that if self-peptides described are largely derived from endogenous proteins that are expressed in a tissue-specific manner, these antigens would not be involved in negative selection (tolerance induction) in the thymus and thus potentially autoreactive T cells might indeed be part of the normal peripheral T-cell repertoire. Although teleological in design, transgenic murine models of autoimmunity are not inconsistent with a molecular mimicry hypothesis. Such a model exists for T-cell-mediated autoimmune destruction of pancreatic β-islet cells, where mice transgenically express a viral protein exclusively on β-islet cells, and where islet destruction is induced by infection with the intact virus (14). There are a number of reports that reveal much of the current thinking on the subject of how mimicry might arise (15–17).

Another intriguing role for class I and class II HLA in autoimmune disease involves their possible function in positive and negative selection of thymocytes. Certain HLA alleles might facilitate positive selection of an αβ TCR repertoire prone to self-reactive T cells. Conversely, disease-related HLA alleles may not function properly to induce negative selection of potentially autoreactive T cells (18), resulting in a mature T-cell compartment predisposed to attacking self-epitopes. Explanations for autoaggressive diseases that point to "mimicry" and "selection" may both be correct: HLA association may result from involvement of class I and II molecules at both levels of central and peripheral tolerance.

Mimicry between self- and foreign antigens has been thought of in terms of primary sequence collinearity between different antigens. Nonetheless, T cells that are cross-reactive with epitopes contained in self- and foreign antigens have been difficult to demonstrate (12,19,20). Interestingly, in one report, using synthetic peptides from myelin basic protein (MBP), seven viral and a single bacterial peptide were all able to stimulate cross-reactive MBP-specific T-cell clones, whereas only one of the foreign peptides showed collinear sequence alignment with those from MBP (11). Thus, it appears that "mimicry" of self-epitopes by foreign antigens may occur despite a lack of primary sequence coidentity. This may suggest that TCR "read" antigenic surfaces of peptide–MHC complexes that are only partially defined by the sequence of the bound peptide (21–24). The exact role of the class I and class II MHC molecules in determining antigenicity and cross-reactivity of these antigens is still forthcoming.

5.1. HLA CLASS I

A compilation and nomenclature for HLA antigens has been established by the World Health Organization (WHO) (see Section 1.2). There are at present at least 50 HLA-A, 97 HLA-B, and 34 HLA-C alleles known (25). Originally defined through

serological methods, the alleles are now additionally defined based on nucleotide sequencing, restriction fragment length polymorphism (RFLP), and other means, such as cytotoxic T-cell reactivity (25). Although the class I HLA molecules consist of both α and β chains (β_2-microglobulin), polymorphism is only a feature of the α chain, particularly the α1 and α2 domains of the peptide-binding groove. Among the three broad groups of class I HLA molecules, it has been determined that the HLA-B molecules contain the largest number of positions with high variability, HLA-A is intermediate, and HLA-C molecules have the least variability (26). HLA-A, -B, and -C have highly variable positions in the α1 domain at amino acid positions 9 and 116 and in the α2 domain at position 156. X-ray crystallographic analyses have been performed for class I molecules (i.e., HLA-B27) (27,28) and the basic principles governing class I peptide binding have been relatively well defined (see Section 1.3).

5.2. HLA CLASS II

The class II HLA molecule is a heterodimer, with each α and β subunit containing two external domains of about 90 amino acids each. The α1 and β1 domains form a β-pleated sheet that is believed to create the floor of the peptide-binding groove (29). Typical regions or sites with high degrees of polymorphism vary between different HLA-DP, -DQ, and -DR molecules. In class II nomenclature the first uppercase letter to appear after DR, DQ, and DP designations refers to either α or β chains: For example, DRB refers to the β chain of HLA-DR and DQA, the α chain of HLA-DQ.

5.2.1. HLA-DP

Both α and β chains of DP are polymorphic. Polymorphic residues, clustered around five locations on the β chain, are known as hypervariable regions (HVRs). These regions form part of the β-pleated sheet and include amino acids at positions 8–11, 35–36, 55–57, 65–69, and 84–88 (30). Additional diversity arises from the ability of α and β chains to mix and match with chains expressed from both parental alleles, permitting the production of four different DP heterodimers in individuals heterozygous at DP loci (which is almost always the case in an outbred, i.e., human, population).

5.2.2. HLA-DQ

Both α and β chains of DQ contain polymorphism. Variability has been detected at numerous amino acid positions spanning the entire length of the α1 domain, and an HVR in the DQ α chain occurs at positions 40–56. For DQB1, HVRs have been identified at positions 26–37, 52–57, and 70–74. Identical DQ serological specificity can occur for DQ dimers composed of different α- (DQA) and β-chain (DQB) alleles: Thus, DQ serological designations suggest a much lower diversity than actually exists for DQ molecules. In addition, as with the DP class II molecules, α and β chains can mix and match with those expressed from both parental loci. Although the peptide-binding pockets and peptide motifs for HLA-DR have been well characterized, those for HLA-DQ remain relatively uncharted (31–33). DQ polymorphisms in the peptide-binding cleft have been documented as they associate with different autoimmune disorders, such as IDDM (10,34), and may involve an Ala→Asp polymorphism at codon 57 (23,35).

5.2.3. HLA-DR

Polymorphic residues are clustered around three HVRs on the β chain, which accounts for virtually all of the observed allelic variation in the DR group (36). The α chain essentially lacks polymorphism. DR molecules have highly conserved peptide-binding grooves, formed predominately by the α chain, although a critical Val/Gly dimorphism exists at position 86 in the β chain which regulates peptide specificity (37). Of the nine genomic DRB loci, only six are known to be expressed (B1, B3, B4, B5, B6, and B7), and 85% of all DRB polymorphism is found at DRB1. It has been suggested that hypervariable coding regions might exist as intact cassettes, such that HVRs could be mixed and matched to form various class II HLA allelic variants (38). On DRB1, polymorphism predominates at positions 9–13, 25–28, and 67–74. The HLA-DR molecules have been studied by X-ray crystallography; peptide-binding motifs have been generated for several important disease-related alleles (23,29,39). In addition to expression on APC, HLA-DR has been detected under normal conditions in tissues from salivary (40) and mammary glands (40,41), kidney tubules (42), small intestine (43,44), endometrium and fallopian tubes (43), and adrenal cortex (45).

5.3. CALCULATING RELATIVE RISK VALUES FOR HLA DISEASE ASSOCIATIONS

The relative risk calculations that appear with many of the HLA associations reflect the frequency that a particular allele or haplotype occurs with a disease relative to its occurrence in normal healthy individuals. That is, relative risk compares the frequency of disease in a group of randomly selected persons (who have the allele of interest) with that in persons who do not carry the allele (Figure 5.2). For example, if 20% of a population carries a specific allele, and half of persons with disease carry the same allele while the other half with disease do not carry the allele, the allele has a relative disease risk of about 4.

5.4. ADDISON'S DISEASE

Addison's disease (AD) is an organ-specific disease of the adrenal cortex characterized by circulating cortex-specific autoantibodies (46) and lymphocyte infiltration into areas where adrenocortical destruction occurs (47,48). Autoantibodies to adrenocortical

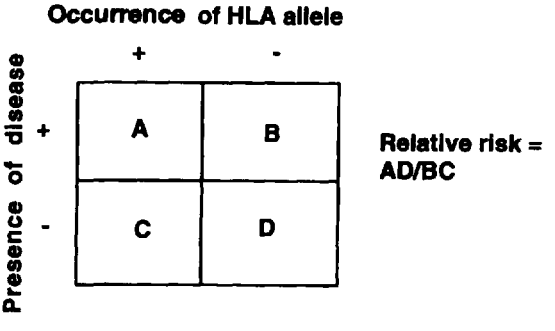

Figure 5.2. The simple relationship illustrated can be used to calculate relative disease risks for HLA class I and II association.

microsomal and plasma membrane antigens are detected in about two thirds of patients with the disease (46,49–51). The major target of autoantibodies is the p450 steroidogenic enzyme 21-hydroxylase (21-OH) (52,53). Autoantibodies from patient sera have been shown to bind a conserved epitope at the 21-OH hormonal binding site, inhibiting its enzyme activity (54).

In autoimmune AD there is class II expression on about 50–100% of adrenocortical cells (55). Interestingly, under normal conditions a portion (~10%) of adrenocortical cells express class II molecules (45); moreover, there is some degree of lymphocytic infiltration in normal adrenal glands by $CD4^+$ T cells, particularly in persons over 60 years of age (56). Thus, it would appear that factors besides upregulated class II expression play a role in disease. The disease has been associated with DR3 and DR4 subgroups (57,58). Expression of the HLA DQA1*0501 allele is associated with AD and a variety of other endocrine autoimmune diseases, such as IDDM and Grave's disease (59). AD has also been associated with HLA-DR3 class II molecules, as have a number of other endocrinopathies (60), and almost half of AD patients have one or more concurrent autoimmune diseases (61).

5.5. ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is an inflammatory condition that affects joints of the spine (62,63). HLA-B27 alleles B*2702 and B*2705 have long been associated with AS (64,65) and the peptide binding characteristics of these alleles have been studied in detail (66). Mimicry involving bacterium-derived peptides has been suggested in disease etiology (67), and may involve an epitope on the disease-related HLA-B27 molecule itself (68). Interestingly, five HLA alleles (B*2701, B*2702, B*2704, B*2705, and B*2706) associated with AS have been shown capable of presenting the same immunodominant peptide derived from Epstein–Barr virus (EBV) (69), indicating conserved antigen presentation function among various disease-associated alleles. A line of rats doubly transgenic for the HLA-B27 molecule and β_2- microglobulin spontaneously develop disease similar to AS seen in humans (70). However, some murine lines expressing the transgenes did not develop disease. Because AS-associated alleles are also found in healthy subjects, other genes located in class I and class II regions, such as TNFα, LMP2, and TAP, have been investigated for polymorphisms that might predispose to disease, although conflicting results have been reported (71–75).

5.6. AUTOIMMUNE LIVER DISEASE

Autoimmune hepatitis (AIH), primary biliary sclerosis (PBS), and primary sclerosing cholangitis (PSC) are major liver diseases with autoaggressive immune components. All three diseases are characterized by circulating autoantibodies and an association with class II genotypes (76,77). Interestingly, there are a number of concurrent immunological diseases that present with these liver conditions (Table 5.2). Nonetheless, as with all other autoimmune diseases, the HLA associations are not complete, and it is unclear whether the HLA linkage to the disease is a direct one. In addition, for the liver diseases discussed below, all can have complement abnormalities associated with them (78–80).

Table 5.2
Immunological Diseases that Present with Liver Disease[a]

	Liver disease		
Concurrent autoimmune disease	Chronic viral hepatitis	PBC[b]	PSC[c]
Asthma			1
Crohn's			1
Dermatitis herpetiformis	1		
Diabetes type I		1	
Graves'	1		
Idiopathic thrombocytopenic purpura	1		
Keratoconjunctivitis sicca		3	
Lichen planus		1	
Nephritis	1		
Rheumatoid arthritis	2		
Sjogren's syndrome		1	
Synovitis	4	1	
Thyroiditis	8	1	
Ulcerative colitis	1		7
Vasculitis	6		
Total	25	8	9

[a]Patients with chronic liver diseases and concurrent immunological disease are more commonly HLA-DR4 (51 versus 30%, $p = 0.02$) and are more likely to be heterozygous for HLA-DR3 and DR4 (13 versus 2%, $p = 0.04$) compared with normal subjects [Ref. 368].
[b]PBC, primary biliary cholangitis.
[c]PSC, primary sclerosing cholangitis.

5.6.1. Autoimmune Hepatitis

AIH also referred to as chronic active hepatitis, is characterized by hypergammaglobulinemia, circulating autoantibodies against liver-specific antigen, inflammatory infiltrate in periportal regions of the liver, and in most forms of the disease, treatment response to immunosuppressive agents such as corticosteroids (81,82). In AIH, these symptoms occur in the absence of viral infection, which is seen in other forms of liver disease. Spontaneous remission in AIH has been reported to be associated with generalized autoimmunosuppression in AIH patients (83). Over 50% of AIH patients express a DR3 subtype, compared with about 20% of healthy persons, and most patients express one of either DR3 or DR4 subgroups (84). The DR4 subtypes have been found to have a high frequency of DRB1*0401 and DRB3*0101 alleles, which share a common string of residues at positions 67–72 (85). Arg or Lys at position 71, which points from the α-helical domain toward the peptide-binding groove, interacting with both peptide and TCR (86), correlates with reduced or elevated risk (77,87) for AIH, respectively. In one study, 94% of AIH patients had the motif LLEQKR at positions 67–72 with lysine at position 71, which translated into a ninefold increased risk for the disease (77). The HLA associations for AIH are similar to those for PSC (88,89).

5.6.2. Primary Biliary Cirrhosis

PBC is a chronic granulomatous inflammatory disease that affects small bile ducts of the liver, resulting in scarring, progressive liver damage, and organ failure (90,91). Antimitochondrial antibodies (AMA) are present in about 90% of patients with PBC (92,93). Both IgM and IgG AMA-specific antibodies are present, with highly elevated levels of IgG3 (94,95). The target autoantigens include subunits of the pyruvate dehydrogenase complex (PDC), 2-oxo-acid dehydrogenase and 2-oxo-glutarate dehydrogenase complexes, Eα1, and protein X (96–103). Both $CD4^+$ and $CD8^+$ T cells are involved in bile duct pathogenesis (104–109). T-cell clones specific for pyruvate dehydrogenase antigens have been cloned from liver of PBC patients (110). On the other hand, there are reduced numbers of γδ T cells in the peripheral blood of PBC patients (111).

Elevated levels of class II HLA molecules are detected on PBC bile duct epithelium (112–114). However, abnormal PDC-E2 expression on luminal surfaces of biliary epithelium has been reported to occur prior to class II or BB1/B7 expression (115). HLA-DR8 and DPB1*0301 have been associated with PBC and the concurrent immunological disease manifestations (116–119). In a study in Japan, PBC patients were found to have a significantly higher frequency of DPB1*0501 and DQ3 alleles (120). A Leu residue at position 35 of the peptide-binding groove of the DP β subunit was found in 91.4% of PBC patients and appeared to be important in disease susceptibility. A more recent study in Britain, however, has failed to find a significant association between DPB1 and PBC (121). Other studies have found a DRB1*08 association with disease (77).

5.6.3. Primary Sclerosing Cholangitis

Sclerosis, inflammation, destruction, and fibrosis of intra- and extrahepatic bile ducts are characteristic features of PSC, a disease that largely (70%) afflicts men (122,123). There is a frequent concurrence with inflammatory bowel disease, which occurs in about 70% of PSC patients (124,125). HLA-DR3 may be associated with PSC (88,89,126). A recent report indicated that compared with normal subjects, frequencies of HLA-DR3 (B1*0304), DR2 (B1*1606), Dw2 (B1*1501), and DR52a (B3*0101) were all significantly increased in PSC patients, and that DR52a was associated with those ultimately requiring liver transplants (89). HLA-DR4 association corresponds with accelerated disease progression (89), and the DRB3*0101 allele in this group was most often associated with both disease and poor prognosis. A second allele, DRB5*0101, also conferred susceptibility. Both of these alleles contain a leucine residue at position 38 of the DR β chain. The DRB4*0101 allele, which correlates with a lower risk for PSC, contains alanine at position 38. The highest relative risk for PSC has been reported for two DR molecules with Leu38 in the β chain, and lowest risk was observed for two molecules with alanine at this position (127,128).

5.7. BEHCET'S DISEASE

BD is a multisystemic inflammatory disorder that involves lesions in the eyes, mouth, skin, vasculature, and genitals characterized by marked infiltration with functionally abnormal neutrophils (129). T cells from patients with BD have been found to respond to four synthetic peptides corresponding to mycobacterial heat shock proteins (HSP), and to peptides from homologous human HSP (130). Sera from patients also contain antibodies

against epitopes that overlap with previously defined HSP T-cell epitopes (131). $CD4^+$ T cells from BD patients show abnormally low levels of the apoptosis-inducing Fas antigen (132). HSP-reactive γδ T cells have also been reported in patients with BD (133). The disease has been associated with HLA-B51 (134,135) and HLA-B52 expression (134,136,137), particularly the B*5101 allele, which was found, without exception, in all patients in a Japanese cohort with BD (138). Recent findings have shown that HLA-B51 expression correlates with neutrophil hyper activity regardless of whether BD is present or absent; and that HLA-B51 transgenic mice show elevated superoxide production by neutrophils (129). Individuals with B*5102 and B*5103 do not have elevated risk for BD, whereas these alleles differ from the risk-associated molecule B*1501 only by single amino acid substitutions at residues 171 and 167, respectively (138,139). Interestingly, allelic polymorphism in transporters associated with antigen processing (TAP) and low-molecular-weight polypeptide (LMP) have been found to associate with disease (140,141).

5.8. CELIAC DISEASE

Autoimmune celiac disease (CD) is a gut disorder precipitated by the ingestion of gluten (142–144). CD manifests with chronic diarrhea, weight loss, edema, and other findings suggestive of gastrointestinal malabsorption; histologically, it is characterized by crypt hyperplasia and villous atrophy. There is about 70% concordance for the disease in identical twins (145), suggesting a strong genetic element in disease susceptibility. Serum antigliadin, antireticulin, and antiendomysial antibodies are often present (146–148) as are highly elevated numbers of intraepithelial γδ cells (149). Most CD patients (~90%) carry the class II HLA alleles DQA1*0501 and DQB1*020 (DQ2), which are present in about 20% of the general population, and thus the gene pair appears to confer significant disease risk (150–153). The two genes may appear in *cis* or in *trans*, as in each case expression results in the formation of a functional class II heterodimer (see Section 1.2). As a corollary, there appear to be gene dosage effects for the disease-related DQ alleles (154); more recently, elevated expression levels, which reflect promoter polymorphisms, have been suggested to increase susceptibility (155). There may also be involvement of another class II MHC locus, HLA-DPB1, located about 400 kb centromeric of DQ (156,157), although this relationship may merely reflect linkage disequilibrium between DQ and DP loci (153,158).

CD may also be associated with DQ-restricted gliadin-specific T cells (159,160). The N-terminal portion of α-gliadin has been proposed as a potential autoantigen, as T cells from CD patients recognize peptides mimicking this region when presented in the context of DR7 and DQ2 (161,162). A more recent study has found that α-gliadin peptides do not efficiently bind DQ2 (163). Patients with CD have increased risk for a number of other diseases (150) such as asthma (164), atopy (165), arthritis (166), diabetes (167), and malignancies such as non-Hodgkin's lymphoma (168,169).

5.9. CICATRICIAL PEMPHIGOID

CP is a chronic disease affecting mucous membranes such as the mouth and eyes, characterized by subepidermal and mucosal blistering (170). Immunoglobulin deposition

at basement membrane zones (BMZ) (171,172) has been suggested as the pathogenic mechanism by which the disease progresses. However, BMZ antibodies are not detected in all cases of CP and the cause of tissue destruction is not entirely clear (170). The occurrence of CP has been noted in patients with rheumatoid arthritis treated with D-penicillamine, and it has been suggested that the antibiotic might induce BMZ antibodies in genetically susceptible individuals (170). A genetic link for class II loci has been found for ocular and oral forms of the disease, involving the DQB1*0301 allele (173,174) and the DRB1*04-DRB4*0101-DQA1*03-DQB0301 haplotype (175). Amino acid sequence analysis of DQB1 alleles from patients with CP suggested that positions 57 and 71–77 may be critical to disease association (175).

5.10. DERMATITIS HERPETIFORMIS

Immunopathological lesions afflict both the skin and small intestine in dermatitis herpetiformis (DH) (176). The disease is characterized by IgA deposits in the upper dermis of uninvolved skin, about two thirds of patients have intestinal disorders with villous atrophy similar to those seen in DC, and gluten sensitivity and lymphocytic infiltration of gut epithelium (177). DH is also complicated by a high incidence of malignancies, particularly lymphomas that appear to originate in the gastrointestinal tract (177,178). The presence of antibodies against the cereal-derived protein gliadin (179), and resolution of disease in gliadin-free diets, implicates this protein in disease pathogenesis. This is similar for CD and the two diseases have been considered to possibly reflect a common genetic lesion, although genetic linkage for DH and CD has been reported to reflect different regions of the MHC (180). T-cell infiltrates in lesions are mainly $CD4^+CD45RO^+$ memory cells, but significant numbers of $CD8^+$ T cells are also present (181). Positive associations with class I and II HLA haplotypes have been reported, but the strongest correlations are with DR3 and DQw2, carried by almost 100% of patients with DH (182).

5.11. INSULIN-DEPENDENT DIABETES MELLITUS

IDDM occurs as a consequence of destruction of the insulin-producing β-islet cells of the pancreas (183,184). Circulating islet autoantibodies and lymphocytic infiltration into islets suggest an immune component to islet destruction. Low concordance among identical twins also indicates the importance of environmental factors in the disease (185). There also appear to be multiple genetic loci involved in the disease, although linkage analyses indicate that the MHC loci are probably the most critical for disease susceptibility (186). $CD8^+$ T cells likely play an important role in islet destruction, as they infiltrate affected tissue early in disease onset, show restricted Vβ usage, and appear to be capable of attacking β islets, which display upregulated class I expression in IDDM (187–189). Moreover, negative selection in the thymus against β-islet antigens appears to protect susceptible animals from diabetes (190). $IL\text{-}2R^+$ oligoclonal T-cell populations are present in the peripheral blood (191). T cells from peripheral blood of patients or those at risk for IDDM (i.e., first-degree relatives) were reported to proliferate in coculture with either islet cells or purified insulin (192,193), or glutamic acid decarboxylase (GAD65) (194,195).

Coxsackievirus has been implicated as a candidate etiological agent in IDDM (196–200). The enzyme carboxypeptidase H expressed in the β-islet cells of the pancreas, has possible antigenic sequence homology with a peptide processed from the β chain of the class II allele HLA-Dq3.2, which is displayed on the HLA-DR4 subgroup (185,201,202). It is of interest that carboxypeptidase H can be processed into peptides with sequence alignments similar to the coat protein of coxsackievirus and the nucleoprotein of influenza A. Islet cell antigen 512 (ICA512) is a CD45-related molecule, found from an islet cDNA expression library screened with human IDDM sera (203). Antibodies against ICA512, expressed in insulin-producing pancreatic β islets and other cells (204), are prevalent in IDDM individuals (205,206) and the protein contains sequences shared with HLA-DQB alleles. Similarity between a GAD65 and proinsulin peptide sequences has been noted, and representative synthetic peptides have been shown to stimulate T cells from patients at risk for IDDM (207). A retrovirus component behaving like a superantigen has been isolated and may represent an autoantigen involved in type I diabetes (208).

The DR3 (B1*0301,B1*0302) and DR4 (B*0401,B*0402) class II alleles are associated with IDDM; when DR3/DR4 molecules are found together, the relative risk is significantly increased (209). DQβ chains are also associated with IDDM susceptibility (DQw3.2, DQw2, DQQw1.1, DQw1.19), and these alleles share a common Val or Ser residue at position 57 (4). The actual charge of the amino acid at position 57 has been correlated with disease susceptibility (210), and modeling studies have predicted that the negative correlation observed with Asp at position 57 may result from the formation of a salt bridge at one end of the peptide-binding groove (10). IDDM is also frequently associated with autoimmune thyroid disease (ATD), in which case it segregates with the DQB1*0201 allele (211). A TAP1 allele has been associated with IDDM albeit with low relative risk (212). Another report has shown an IDDM-protective effect for a TAP allele (213).

NOD mice serve as a murine model for IDDM (214). The NOD phenotype involves over a dozen loci (215) including, in an obligatory way, genes of the MHC (216). The disease can be transferred from NOD mice to healthy recipients using NOD-derived $CD4^+$ or $CD8^+$ T cells (217–219) and athymic nude mice are resistant to NOD (220). Monoclonal T cells expressing Vβ TCR have also been identified in young prediabetic NOD mice, suggesting a possible role for T cells in disease onset (221).

5.12. MULTIPLE SCLEROSIS

Chronic inflammatory reactions of the central nervous system with concomitant degeneration of myelinated cells are the hallmark of MS (222–224). A concordance rate of 26–31% for MS is observed in monozygotic twins versus about 3% in dizygotic pairs, indicating a genetic predisposition for the disease but also a critical environmental component (2,225,226). Recent evidence also supports the involvement of multiple genetic loci in disease susceptibility (227). The role of T cells in disease pathogenesis has been widely investigated and restricted TCR usage in patients with MS has been observed (228,230). Analysis of mRNA from T cells of patients with MS revealed restricted V-region usage in brain tissues (231,232), oligoclonal αβ T-cell populations in cerebrospinal fluid (233, 234), and preferential usage in blood (235–237). Nevertheless, myelin basic protein (MBP)-specific T-cells precursors are reported to occur with similar frequency in individuals with MS and healthy subjects (238,239).

T- and B-cell IgG responses in MS patients possessing the HLA-DR2 subgroup, which represents about two thirds of patients, are targeted at MBP epitopes, involving residues 84–103 (240). Retroviral infections have been suggested as a trigger for MS, but definitive evidence remains to be presented (11,241), HLA-DR-restricted T cells cross-reactive with coronavirus and MBP have been proposed as a possible immune mediator of disease (242). Association of MS with the haplotype DRB1*1501-DQA1*0102-DQB1*0602 has been reported (243–246). Detailed analysis of this haplotype has established the importance of the DRB1*1501 allele in the positive association with MS, and the highest correlation with disease is observed when both DRB1*1501 and DRB1*0400 appear together (247). Other HLA associations have been made when both DRB1*1501 and DRB1*0400 appear together (247). Other HLA associations have been made with MS but these vary according to populations studied (247,248). Murine experimental autoimmune encephalomyelitis, which involves immunization with MBP, has been used as a model to study the possible pathogenic role of T cells in MS (249,250), which can be blocked using T-cell TCR antagonist peptides (251).

5.13. MYASTHENIA GRAVIS

Circulating IgG specific for the acetylcholine receptor (AChR) is a common feature of myasthenia gravis (MG) (252–254), accompanied by progressive deterioration of striated muscle fiber. However, anti-AChR antibody levels do not correlate with disease manifestations and some patients with MG have no demonstrable AChR antibodies (255). Hyperplasia of the thymus and risk of thymoma are common features of MG, suggesting a role for the thymus and T cells in the disease (256,257). MG associations have been found with both class I and class II MHC, although correlation varies for different alleles depending on age of onset, sex, and accompanying clinical symptoms (258–262). Patients with MG frequently demonstrate B and T lymphocytes with reactivity against AChR (263–265), including $CD4^+$ T cells specific for embryonic forms of the AChR complex (eAChR) (266,267), which is also expressed in the thymus (268,269). Also, $CD4^+$ T cells reactive against epitopes of the γ subunit of AChR (270,271) have been identified from patients (266,267), some with different HLA haplotypes. However, AChR-specific T cells are also present in the normal immune repertoire (272). $CD4^+$ T cells from MG patients are largely restricted by HLA-DR molecules (273–276). Natural peptide ligands binding MG-associated HLA-DR3 molecules have been identified (277).

The class II HLA-DQ alleles DQB*0301, B*0302, B*0303, and DPB1*0201 have been observed with elevated frequency in female patients with early onset disease, and association was especially high for carriers of both of the (unlinked) DQB1*03 and DPB1*0201 alleles (278). Another study has shown susceptibility when the heterodimers DQA1*01-DQB1*0201 or DQA1*01-DQB1*0301 are present (relative risk 6.2) (279). DQA1*01 alleles DQA1*0101, 0102, and 0103 have glycine and arginine residues at positions 55 and 64, respectively, while DQB1*0301 and DQB1*0201 contain a negatively charged glutamic acid at positions 45 and 46, respectively. In MG patients with thymic hyperplasia, DQA1*0501 was in linkage disequilibrium with DQB1*0201 and DQB1*0301 (relative risk 17.2) (279).

An experimental MG can be induced in rats by immunization with AChR protein. Rats depleted of $CD8^+$ T cells have significantly reduced disease severity, as is antibody

against the AChR (280); however, these results are in conflict with an earlier study in class I-deficient mice (281). Treatment of animals with IFNα, which downregulates class II expression, reduces disease in experimental autoimmune MG (282).

5.14. PEMPHIGUS VULGARIS

PV is a chronic blistering disease of the skin characterized by high levels of circulating autoantibodies specific for desmogleins (Dsg), a member of the cadherin family of molecules (283–285). Antibodies and immune complexes appear to mediate breakdown of epidermal cell adhesion; and sera from PV patients, affinity purified using Dsg-fusion proteins, induce blistering in mice (286). This disease is associated with the class II DR4 subtype among others. Interestingly, the DR4 subtypes involved in PV and rheumatoid arthritis show differences only for amino acids in the DR β chain at positions 67–71 (287–289). PV has been associated with several different haplotypes, including HLA-DQ5, DQ8, DR4, and DR6 class II subgroups (290–293).

5.15. REITER'S SYNDROME

RS, a form of reactive arthritis that attacks peripheral joints, is a classic spondylarthropathy that includes other inflammatory diseases such as AS (63,294,295). Bacterial antigens have been detected in the synovial joints and membranes of patients with RS (296,297). Specific T cells have been isolated from synovium that respond to bacterial antigens associated with disease (298–305). Although RS shows a strong association with the class I alleles HLA-B27, the specific T cells isolated from patients have been $CD4^+$ and presumably class II restricted. It has been suggested that the HLA-B27 correlation with disease may reflect the inability of the molecule to adequately present disease-causative bacterial antigens, prolonging infection and resulting in autoimmune disease (306–308). Interestingly, although transgenic lineages of rats expressing cDNA of human HLA-B27 develop reactive arthritis, disease is dependent on the copy number of HLA-B27 genes expressed in the animals (309,310).

5.16. RHEUMATOID ARTHRITIS

Inflammation of the synovial membrane, cartilage destruction, and bone erosion are characteristic features of rheumatoid arthritis (RA), which, in a subset of individuals, is also accompanied by vasculitis (311). Autoantibodies against type II collagen (CII) are found in serum and joints of RA patients (312,313). Extensive somatic mutations of autoantibodies, or RF factors (314), also suggest an antigen-driven immune response (315,316). CII-specific T cells have been reported in the synovial membrane of an RA patient (317) and there are numerous reports of preferential usage of T-cell V-region genes in patients with RA (318–325), although $CD4^+$ T-cell depletion in RA patients provides little relief from disease (326). There is a strong association between RA and expression of the MHC class II DR1 and DR4 molecules B1*0101, and B1*0401, B1*0404, and B1*0405, respectively (4,327–330). Homozygosity for DR4 molecules has been found to

significantly increase risk for disease and may be linked to severity and vasculitis (331,332). The DRB1*0404 allele associated with RA and the DRB1*0402 allele, which correlates with less risk of disease, differ only in residues found at positions 67–71 of the β chain (327). Collinear sequence identity at positions 67–71 of the DR β chain, shared by HLA-DR disease-associated molecules (333–336), is likely involved in peptide binding (23,29,37). The peptide binding characteristics of disease-associated alleles have been studied in detail and may lead to identification of the autoantigens involved (39,328). Molecular mimicry has been suggested in the etiology of RA and may involve sequences in Epstein–Barr virus glycoprotein B (201), or in heat shock proteins from *E. coli* (337).

A murine model of arthritis involves immunization with CII and is associated with class II I-A^q (338). The I-A^q CII epitope involved in strong activation of specific T cells is an octamer (IAG*FKGEQ*) (339), which overlaps with the DRB1*0401-restricted epitope 263–270 (*FKGEQ*GPK) (340). Mice transgenic for HLA-DRB1*0401 have also been used to determine the T-cell epitope involved in CII reactivity, which appears to involve CII 261–273, a conserved region of CII involved in I-A^q-restricted T-cell responses in experimental RA in mice (340). A recent report of changing patterns of dominant T-cell clones in synovial tissue, however, suggests a growing use of different antigenic determinants over the course of RA (341).

5.17. SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is characterized by immunologogical abnormalities such as autoantibodies to DNA and nuclear proteins (342–345). Concordance among monozygotic twins has been reported at 70% (346) and 24% (347). The disease predominately afflicts females (348). Alleles from the HLA-DR2 and DR3 group have for some time been considered associated with SLE, although the relative risk for these alleles has never been shown to be high (349,350). Persistent B-lymphocyte activation has been suggested to have a pathogenic role in SLE, supported by the finding that B cells isolated from patients with quiescent disease spontaneously secrete DNA autoantibodies *in vitro* (351). Blocking cognate T–B-cell interactions can ameliorate disease exacerbation in SLE patients (352–354), underpinning a critical role for T-cell-driven B-cell autoimmunity in the disease. There are reports of hyperactive T-cell compartments in SLE, as evidenced by increased levels of soluble IL-2R and class II HLA-DR on T cells (355,356). An HLA-DR-restricted T-cell clone has been found that induces anti-dsDNA antibody secretion by SLE-derived B cells (357), and both $CD4^+$ and $CD8^+$ T cells appear to support polyclonal antibody synthesis *in vitro* (358). Paradoxically, lymphocytes from SLE patients show higher rates of apoptosis *in vitro* compared with normal lymphocytes (359). Restricted junctional diversity has also been reported in γδ T cells from SLE patients (360).

There have been demonstrations of SLE associations with DRQ genes (361,362). HLA-DP associations have been made, although a more recent study suggests no link exists (363). A relative risk of 2.0 has also been found for the class I molecule HLA-B*08 (364,365). More recently, the occurrence of an HLA-DR3-B8 haplotype with a TNF-α polymorphism was found to have increased relative risk of SLE (364). Deficiencies at the class III region complement genes may also have a role in disease (350,366). A recent report found that all of 22 SLE patients investigated, and 12 of 15 normal subjects who had C4A and CYP21A gene deletions (the most common cause of C4A null alleles in SLE), had an allele from the HLA-DR3 group (367).

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