abacavir, an antiretroviral therapeutic, is directly linked to binding of abacavir in the antigen-binding pockets of HLA-B*57:01, where it is buried underneath antigenic peptides and distorts the landscape, changing T cell recognition specificity; an adverse drug reaction to abacavir is more than 500 times more likely to occur in persons with HLA-B*57:01 than in individuals without this HLA allele. Another example is chronic beryllium toxicity, which is linked to binding of beryllium by HLA-DP molecules with a specific glutamic acid polymorphic residue on the class II beta chain. Even in the case of more complex diseases, particular HLA alleles are strongly associated with certain inappropriate immune-mediated disease states, particularly for some common autoimmune disorders (Chap. 377e). By comparing allele frequencies in patients with any particular disease and in control populations, >100 such associations have been identified, some of which are listed in Table 373e-1. The strength of genetic association is reflected in the term *relative risk*, which is a statistical odds ratio representing the risk of disease for an individual carrying a particular genetic marker compared with the risk for individuals in that population without that marker. The nomenclature shown in Table 373e-1 reflects both the HLA serotype (e.g., DR3, DR4) and the HLA genotype (e.g., *DRB1*03:01*, *DRB1*04:01*). It very likely the class I and class II alleles themselves are the true susceptibility alleles for most of these associations. However, because of the extremely strong linkage disequilibrium between the DR and DQ loci, in some cases it has been difficult to determine the specific locus or combination of class II loci involved. In some cases, the susceptibility gene may be one of the HLA-linked genes located near the class I or class II region, but not the HLA gene itself, and in other cases, the susceptibility gene may be a non-HLA gene such as TNF-α, which is nearby. Indeed, since linkage disequilibrium of some haplotypes extends across large segments of the MHC region, it is quite possible that combinations of genes may account for the particular associations of HLA haplotypes with disease. For example, on some haplotypes associated with rheumatoid arthritis, both HLA-DRB1 alleles and a particular polymorphism associated with the TNF locus may be contributory to disease risk. Other candidates for similar epistatic effects include the IKBL gene and the MICA locus, potentially in combination with classic HLA class II risk alleles.

As might be predicted from the known function of the class I and class II gene products, almost all of the diseases associated with specific HLA alleles have an immunologic component to their pathogenesis. The recent development of soluble HLA-peptide recombinant molecules as biological probes of T cell function, often in multivalent complexes referred to as "MHC tetramers," represents an opportunity to use HLA genetic associations to develop biomarkers for detection of early disease progression. However, it should be stressed that even the strong HLA associations with disease (those associations with relative risk of ≥10) implicate normal, rather than defective, alleles. Most individuals who carry these susceptibility genes do not express the associated disease; in this way, the particular HLA gene is permissive for disease but requires other environmental (e.g., the presence of specific antigens) or genetic factors for full penetrance. In each case studied, even in diseases with very strong HLA associations, the concordance of disease in monozygotic twins is higher than in HLA-identical dizygotic twins or other sibling pairs, indicating that non-HLA genes contribute to susceptibility and can significantly modify the risk attributable to HLA.

Another group of diseases is genetically linked to HLA, not because of the immunologic function of HLA alleles but rather because they are caused by autosomal dominant or recessive abnormal alleles at loci that happen to reside in or near the HLA region. Examples of these are 21-hydroxylase deficiency (Chap. 406), hemochromatosis (Chap. 428), and spinocerebellar ataxia (Chap. 452).

CLASS I ASSOCIATIONS WITH DISEASE

Although the associations of human disease with particular HLA alleles or haplotypes predominantly involve the class II region, there are also several prominent disease associations with class I alleles. These include the association of Behçet's disease (Chap. 387) with HLA-B51, psoriasis vulgaris (Chap. 71) with HLA-Cw6, and, most notably, the spondyloarthritides (Chap. 384) with HLA-B27. Twenty-five HLA-B locus alleles, designated *HLA-B*27:01–B*27:25*, encode the family of B27 class I molecules. All of the subtypes share a common B pocket in the peptide-binding groove—a deep, negatively charged pocket that shows a strong preference for binding the arginine side chain. In addition, B27 is among the most negatively charged of HLA class I heavy chains, and the overall preference is for positively charged peptides. *HLA-B*27:05* is the predominant subtype in whites and most other non-Asian populations, and this subtype is very highly associated with ankylosing spondylitis (AS) (Chap. 384), both in its idiopathic form and in association with chronic inflammatory bowel disease or psoriasis vulgaris. It is also associated with reactive arthritis (ReA) (Chap. 384), with other idiopathic forms of peripheral arthritis (undifferentiated spondyloarthropathy), and with recurrent acute anterior uveitis. B27 is found in 50–90% of individuals with these conditions, compared with a prevalence of ~7% in North American whites.

It can be concluded that the B27 molecule itself is involved in disease pathogenesis, based on strong evidence from clinical epidemiology and on the occurrence of a spondyloarthropathy-like disease in HLA-B27 transgenic rats. The association of B27 with these diseases may derive from the specificity of a particular peptide or family of peptides bound to B27 or through another mechanism that is independent of the peptide specificity of B27. In particular, HLA-B27 has been shown to form heavy chain homodimers, utilizing the cysteine residue at position 67 of the B57 α chain, in the absence of β_2-microglobulin. These homodimers are expressed on the surface of lymphocytes and monocytes from patients with AS, and receptors including KIR3DL1, KIR3DL2, and ILT4 (LILRB2) are capable of binding to them, promoting the activation and survival of cells expressing these receptors. Alternatively, this dimerization "misfolding" of B27 may initiate an intracellular stress signaling response, called the unfolded protein response (UPR), capable of modulating immune cell function, possibly in enthesial-resident T cells that act as sensors of damage and environmental stress.

CLASS II DISEASE ASSOCIATIONS

As can be seen in Table 373e-1, the majority of associations of HLA and disease are with class II alleles. Several diseases have complex HLA genetic associations.

Celiac Disease In the case of celiac disease (Chap. 349), it is probable that the HLA-DQ genes are the primary basis for the disease association. HLA-DQ genes present on both the celiac-associated DR3 and DR7 haplotypes include the *DQB1*02:01* gene, and further detailed studies have documented a specific class II αβ dimer encoded by the *DQA1*05:01* and *DQB1*02:01* genes, which appears to account for most of the HLA genetic contribution to celiac disease susceptibility. This specific HLA association with celiac disease may have a straightforward explanation: Peptides derived from the wheat gluten component gliaden are bound to the molecule encoded by *DQA1*05:01* and *DQB1*02:01* and presented to T cells. Gliaden-derived peptides that are implicated in this immune activation bind the DQ class II dimer best when the peptide contains a glutamine to glutamic acid substitution. It has been proposed that tissue transglutaminase, an enzyme present at increased levels in the intestinal cells of celiac patients, converts glutamine to glutamic acid in gliadin, creating peptides that are capable of being bound by the DQ2 molecule and presented to T cells.

Pemphigus Vulgaris In the case of pemphigus vulgaris (Chap. 73), there are two HLA genes associated with disease, *DRB1*04:02* and *DQB1*05:03*. Peptides derived from desmoglein-3, an epidermal autoantigen, bind to the *DRB1*04:02*- and *DQB1*05:03*-encoded HLA molecules, and this combination of specific peptide binding and disease-associated class II molecule is sufficient to stimulate desmoglein-specific T cells. A bullous pemphigoid clinical variant, not involving desmoglein recognition, has been found to be associated with *HLA-DQB1*03:01*.

Juvenile Arthritis Pauciarticular juvenile arthritis (Chap. 380) is an autoimmune disease associated with genes at the DRB1 locus and also with genes at the DPB1 locus. Patients with both *DPB1*02:01* and a