

Special Topics in Ocular Immunology

Highlights

- Experimental autoimmune uveoretinitis is an animal model of human uveitis that can be induced by immunization with ocular-specific antigens such as S-antigen and interphotoreceptor retinoid-binding protein. One of the most important observations from animal models is the dominant role of T lymphocytes in ocular inflammation.
- A family of cell surface glycoproteins called *major histocompatibility complex (MHC) proteins* is expressed in all animals with white blood cells. In humans, MHC proteins are called *human leukocyte antigen (HLA) molecules*.
- The presence of many different HLA alleles within a population should ensure that the collective adaptive immune system will be able to respond to a wide range of potential pathogens. However, some individuals might be at increased risk for immunologic diseases.

Animal Models of Human Uveitis

Our understanding of the pathogenesis of inflammatory eye disease has been significantly influenced by research involving animals. Animal models of human uveitis use a variety of species, antigens, adjuvants, and protocols to produce disease ranging from transient to persistent and mild to severe. Although none of these models are an exact corollary to human disease, they have contributed substantially to our understanding of ocular immunology. One of the most important observations is the dominant role of T lymphocytes in ocular inflammation.

The most widely used and well-studied animal model of human uveitis is *experimental autoimmune uveoretinitis (EAU)*, which can be induced in experimental animals of several different species that are immunized with ocular-specific antigens such as purified arrestin (also called *S-antigen*). EAU is most commonly induced in mice by immunization with interphotoreceptor retinoid-binding protein (IRBP), a molecule whose role is to transport vitamin A derivatives between the photoreceptors and the retinal pigment epithelium. Within 2 weeks of immunization, clinical and histologic evidence of anterior segment, vitreous, and choroidal inflammation develops. Of note, there is similarity between

the histologic changes in mouse EAU and those in human ocular sarcoidosis, specifically, subretinal exudate and retinal detachment.

Other concepts elucidated by various uveitis animal models (noted in parentheses) include the following:

- the dynamics of leukocyte function in the anterior chamber (endotoxin-induced uveitis)
- the presence of autoantibodies and autoreactive T lymphocytes (equine recurrent uveitis)
- the role of the transcription factor *autoimmune regulator (AIRE)* in the development of self tolerance in the thymus (AIRE-deficient mice)
- the promotion of inflammation by ocular resident cells with increased expression of class II antigens (EAU)
- the presence of retina-specific regulatory T lymphocytes that resolve inflammation and maintain remission (EAU)

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Forrester JV, Klaska IP, Yu T, Kuffova L. Uveitis in mouse and man. *Int Rev Immunol.* 2013;32(1):76–96.

Sen HN. Elements of the immune system and concepts of intraocular inflammatory disease pathogenesis. In: Whitcup SM, Sen HN, eds. *Whitcup and Nussenblatt's Uveitis*. 5th ed. Elsevier Health Sciences; 2022:1–28.

Human Leukocyte Antigen Associations and Disease

Major Histocompatibility Complex and Human Leukocyte Antigen Molecules

The major histocompatibility complex (MHC) is a genomic region that includes many genes responsible for coordinating the immune response via cell surface glycoproteins. MHC proteins are expressed in all animals with white blood cells. In humans, the MHC genes are located on chromosome 6; the proteins encoded by these genes are called *human leukocyte antigen (HLA) molecules*. These molecules play a crucial role in the ability of the antigen-presenting cell to bind and present peptide fragments, thus determining T-lymphocyte immune responsiveness. See Chapter 2 for further discussion of the important role that HLA molecules play in immunologic function.

The MHC is divided into 3 genomic regions termed *classes*. Initially, 6 gene families comprising classes I and II were identified:

- MHC class I: *HLA-A, -B, -C*
- MHC class II: *HLA-DR, -DP, -DQ*

The original 6 gene families are called “classic genes” because additional genes with distinctly different gene products, as well as pseudogenes, were subsequently identified in each class. For example, in the class II region, a nonclassic gene encodes HLA-DM, a molecule

that serves as a peptide editor and plays a critical role in peptide loading of HLA class II molecules. Class III, located between classes I and II, contains immune and non-immune-related genes, including some that encode complement components and other proteins that play a role in inflammation (ie, tumor necrosis factor).

Allelic Variation

Within the human population, many alleles exist for each of the HLA genes. An individual has 2 alleles for every HLA gene. One set of alleles (called a *haplotype*) is inherited from the mother, and the other haplotype is from the father. Siblings have a 50% chance of sharing a haplotype. Thus, except for identical twins, it is rare for all potential haplotypes to match between 2 individuals. See Figure 4-1.

Allelic diversity provides protection through *population-wide immunity*. Each HLA haplotype covers a theoretical set of antigens that an individual's immune system may recognize. The presence of many different HLA alleles within a population, therefore, should ensure that the collective adaptive immune system can respond to a wide range of potential pathogens. The converse also holds true: some individuals may be at increased risk for immunologic diseases due to an aberrantly strong immune response to a benign pathogen or inappropriate recognition of host peptides if an HLA molecule is misidentified as foreign. See Clinical Example 4-1.

Clinical detection and classification of different alleles

Initially, the HLA haplotype was determined by antisera reactions. Current methods utilize molecular techniques to identify the nucleic acid sequence of the HLA gene alleles. HLA molecules are composed of 2 chains: the α chain and the β_2 -microglobulin chain for class I,

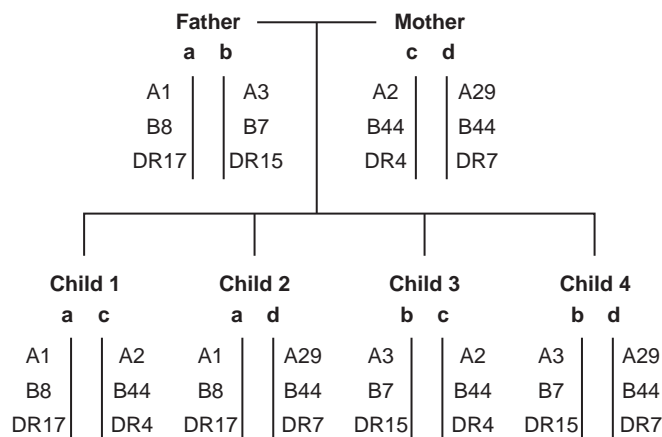


Figure 4-1 Human leukocyte antigen (HLA) inheritance. Each child inherits 1 haplotype from each parent. There are 4 possible HLA haplotype combinations in offspring. A sibling has a 50% chance of sharing 1 haplotype with another sibling. Two siblings have a 25% chance of having the same HLA haplotypes and a 25% chance of sharing no HLA haplotypes. (Redrawn with permission from Choo SY. *The HLA system: genetics, immunology, clinical testing, and clinical implications*. Yonsei Med J. 2007;48(1):11–23, Figure 2.)

CLINICAL EXAMPLE 4-1**HLA-B27–Associated Acute Anterior Uveitis**

Depending on the ethnic population, the prevalence of HLA-B27 ranges from 19% to 88% in patients with acute anterior uveitis. Many of these patients also have other immunologic disorders, such as reactive arthritis, ankylosing spondylitis, inflammatory bowel disease–related arthritis, and psoriatic arthritis (see Chapter 8). Although the immunopathogenesis of HLA-B27–associated acute anterior uveitis remains unknown, various animal models permit informed speculation. Many cases of uveitis or reactive arthritis in humans follow gram-negative gastroenteritis or chlamydial infection. (Chapter 1 discusses the possible role of bacterial lipopolysaccharide and innate mechanisms.) Experiments in rats and mice genetically altered to express human HLA-B27 molecules suggest that bacterial infection of the gut predisposes rats to arthritis and a reactive arthritis–like syndrome, although uveitis is uncommon.

Wakefield D, Clarke D, McCluskey P. Recent developments in HLA B27 anterior uveitis. *Front Immunol.* 2021;11:608134. doi:10.3389/fimmu.2020.608134

and the α chain and β chain for class II. Genotyping specifies the chain, major genetic type, and specific minor molecular variant subtype. For example, genotype DRB1*04:08 refers to the HLA-DR4 molecule β chain with the “–08” minor variant subtype. Haplotypes currently recognized as a single group will continue to be subdivided into new categories or new subtypes as research progresses.

Disease Associations

In 1973, the first association between an HLA haplotype and a disease—ankylosing spondylitis—was identified. Since then, more than 100 other disease associations have been established, including several for ocular inflammatory diseases (Table 4-1). An HLA–disease association is established when there is a statistically significant increase in frequency of an HLA haplotype in persons with that disease compared with the frequency in a disease-free population. The ratio of the probability of the disease occurring in individuals with the HLA haplotype to individuals without the haplotype is termed *relative risk*. A relative risk of 1 denotes no difference in risk, <1 indicates a reduced risk, and >1 indicates an increased risk. Several points are important when considering HLA–disease associations:

- The HLA association identifies individuals at risk, but it is not a diagnostic marker. The associated haplotype is not necessarily present in all people with the disease, nor does its presence in a person ensure the associated diagnosis.
- The association depends on the validity of the haplotyping. Older literature often reflects associations based on HLA classifications (some provisional) that might have changed.
- The association is only as strong as the clinical diagnosis. Diseases that are difficult to diagnose on the basis of clinical features may obscure real associations.

Table 4-1 HLA Associations and Ocular Inflammatory Disease

Disease	HLA Association	Relative Risk (RR), Other Associations
Uveitic diseases with strong HLA associations		
Tubulointerstitial nephritis and uveitis syndrome	HLA-DRB1*01:02	RR = 167
Birdshot chorioretinopathy	HLA-A29, A29.2	RR up to 224 for North American and European individuals
Reactive arthritis	HLA-B27	RR = 60
Acute anterior uveitis	HLA-B27	RR = 8
Uveitic diseases with weaker HLA associations		
Juvenile idiopathic arthritis	HLA-A2, DR5, DR8, DR11, DP2.1	Acute systemic disease
Behçet disease	HLA-B51, A26	RR = 4–6; Japanese and Middle Eastern individuals HLA-A26 associated with ocular disease
Intermediate uveitis	HLA-B8, B51, DR2, DRB1*15 (part of DR15 haplotype)	RR = 6, possibly the DRB1*15:01 allele
Sympathetic ophthalmia	HLA-DR4	Unknown
Vogt-Koyanagi-Harada syndrome	HLA-DR4, DRB1*04	RR = 2, Japanese and North American individuals RR = 5.3, Mexican Mestizo individuals
Sarcoidosis	HLA-B8 HLA-B13	Acute systemic disease Chronic systemic disease but not for eye
Multiple sclerosis	HLA-B7, DR2, DRB1*15 (part of DR15 haplotype), DQB1*06:02	RR = 3 (DR15)
Retinal vasculitis	HLA-B44	British individuals

HLA = human leukocyte antigen.

- The concept of *linkage disequilibrium* proposes that if 2 genes are physically close together on a chromosome, they are likely to be inherited together rather than undergo genetic randomization in a population. Thus, HLA genes may be coinherited with a separate gene that confers the actual risk. Sometimes 2 HLA haplotypes can occur together more frequently than predicted by their independent frequencies in the population.

The ocular inflammatory disease with the strongest HLA association is birdshot chorioretinopathy (BCR); nearly all patients with BCR are HLA-A29 positive. However, although approximately 8% of the White population in the United States has the HLA-A29 allele, fewer than 1 in 10,000 US residents have this ocular disease. Thus, most individuals who are HLA-A29 positive will never develop BCR, indicating the likely involvement of additional genetic and environmental factors in the pathogenesis of this disease. For example, genome-wide association studies of BCR have identified endoplasmic reticulum

aminopeptidase (ERAP) genes, which encode aminopeptidases involved in the processing of HLA class I ligands. See Chapter 5, Tables 5-10 and 5-11, for examples of how HLA haplotyping may be used in the clinical workup of uveitis.

Several mechanisms have been proposed for HLA–disease associations. The most direct theory postulates that HLA molecules act as peptide-binding molecules for pathogenic antigens or infectious agents. Thus, individuals bearing a specific HLA molecule may show a predisposition to processing certain antigens, such as an infectious agent that cross-reacts with an autoantigen (also called *self antigen*). Specific variations or mutations in the peptide-binding region would greatly influence this mechanism; only molecular typing can detect these variations. Preliminary data supporting this theory are available for type 1 diabetes.

A second theory proposes molecular mimicry between bacterial antigens and an epitope on the HLA molecule (ie, an antigenic site on the molecule itself). An appropriate antibacterial effector response might inappropriately initiate a cross-reactive effector response with an epitope of the HLA molecule.

A third theory suggests that the T-lymphocyte antigen receptor (gene) might be the true susceptibility factor. Because each T-lymphocyte receptor uses a specific HLA haplotype, a strong correlation would exist between an HLA molecule and the T-lymphocyte antigen receptor repertoire. See Chapter 2 for further discussion about HLA molecules and T-lymphocyte antigen receptors.

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Takeuchi M, Mizuki N, Ohno S. Pathogenesis of non-infectious uveitis elucidated by recent genetic findings. *Front Immunol.* 2021;12:640473. doi:10.3389/fimmu.2021.640473