

REVIEW ARTICLE

Immunogenetics of ocular inflammatory disease

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Abstract

Ocular inflammatory disease comprises of a diverse group of clinical entities that may result from autoimmune processes, infections, or both. While many individual ocular inflammatory diseases are quite rare, ocular inflammation is one of the more common causes of visual disability, including blindness, in the developed world. Better understanding of ocular inflammatory disease is an important step in designing more sophisticated therapies that may help prevent loss of visual function for these patients.

Introduction

Ocular inflammatory disease is comprised of a diverse group of clinical entities that may result from autoimmune processes, infections, or both. These are not common; the incidence of uveitis in a community-based population of 731,898 patients in the Kaiser Permanente health care system was 52.4/100,000 person-years and the prevalence was 115.3/100,000 (1). While many individual ocular inflammatory diseases are quite rare, ocular inflammation is one of the more common causes of visual disability, including blindness, in the developed world. It has been estimated that 5%–20% of blindness in the United States is due to the complications of ocular inflammation. Better understanding of ocular inflammatory disease is an important step in designing more sophisticated therapies that may help prevent loss of visual function for these patients; this review discusses what we have tried to learn by exploring the immunogenetics of these diseases.

Ocular inflammation – terminology

Before proceeding, it is important to be clear on the terminology used. The term most commonly used is ‘uveitis’,

but uveitis is a subset of ocular inflammation, and in addition, there are subsets of uveitis. The uvea is the pigmented, vascular middle coat inside the eye, consisting of the iris, ciliary body, and choroid. Any one of these structures can be involved, and the terms used are iritis, cyclitis, and choroiditis, respectively. Many uveitis specialists believe that it is difficult if not impossible to discriminate which tissue is primarily involved (for example the ciliary body or the iris) and consider it is more appropriate to classify patients as having anterior, intermediate, posterior, or panuveitis depending on the anatomic distribution of the primary site of inflammation (the anterior chamber, vitreous cavity and anterior retina, posterior retina or choroid, or multiple sites concurrently, respectively) (2). In addition, ocular inflammatory disease is not limited to uveitis. Any tissue of the eye can be involved in inflammatory processes, resulting in terms such as conjunctivitis (inflammation of the superficial epithelial tissue, the conjunctiva), episcleritis (inflammation of the vascular connective tissue deep to the conjunctiva), keratitis (inflammation of the cornea), scleritis (inflammation of the sclera, the collagenous white wall of the eye), vitritis (inflammation of the gel that fills the posterior portion of

the eye), retinitis (inflammation of the retina), retinal vasculitis, and optic neuritis (inflammation of the optic nerve). Each has different implications regarding likely etiologies, treatment, and prognosis, some of which will be indicated when relevant to the discussion of the immunogenetics of disease.

The role of immunogenetics in ocular inflammation

Genetic studies in medicine are often pursued in order to develop diagnostic tests or to allow the identification of individuals at risk for disease. In fact, human leukocyte antigen (HLA) testing can play an important role in the diagnosis of ocular inflammatory disease. However, the predictive positivity of genetic testing in such rare diseases that are likely to be polygenic (and are also likely to have environmental contributions to disease pathogenesis) is too low to be useful in any practical way for screening populations at risk.

Immunogenetic studies have been used to better understand the pathogenesis and nosology of ocular inflammatory disease, as well as the interactions of nature and nurture in ocular inflammation. There are large gaps in our understanding of the pathophysiology of ocular inflammation, in part because it is very difficult to obtain tissue to study. While we can often observe the results of intraocular inflammation by clinical examination and adjunctive clinical testing, the risks to the eye of obtaining intraocular tissue for research purposes are considered too great to pursue and is rarely done in the United States. Intraocular specimens are sometimes available for research purposes, but these are often from eyes that have received treatment, and may be obtained late in the course of the disease, limiting the ability to perform systematic studies. Animal models have been helpful (3), but they involve artificial experimental protocols such as sensitizing a susceptible animal with retinal antigens and adjuvant so may not be directly applicable to human disease. In addition, some aspects of the immune response differ between animals commonly used in the laboratory and humans. For example, we are interested in the role of natural killer (NK) cells and killer immunoglobulin-like receptor (KIR) genes in the pathogenesis of uveitis. This is a very rapidly evolving system, and KIR genes are not found in rodents, so our usual animal models cannot be used to answer questions about these receptors (4). Our preliminary results (manuscript in preparation) indicate that there may be a predominance of activating KIR genes in uveitis patients compared with controls. Based on these results, we will also be looking at the expression of these genes in peripheral blood lymphocytes. We do not know yet whether our techniques will be sensitive enough to find such changes; after all, very few cells are involved, and the activated cells are presumably in the intraocular fluids or relevant tissues of the immune

system rather than in transit most of the time. This does illustrate, however, the importance of immunogenetics in uveitis for suggesting pathophysiologic mechanisms and avenues for further research in ocular inflammation.

Most of the literature on the immunogenetics of uveitis consists of studies with relatively small numbers of subjects, looking for associations of disease with specific genes. More sophisticated genome scans and population and family studies are difficult mostly because these diseases are so rare and involvement of multiple family members is very rare for most of these diseases. The most common uveitis in clinical practice is anterior uveitis, comprising as much as 90% of patients with uveitis in community-based practice, but that suggests a prevalence of only about 1:1000 in the population (5). It has been possible to do a study looking at families with siblings with acute anterior uveitis (6). Most other forms of uveitis only rarely involve multiple family members. One of the most interesting diseases from the point of view of HLA associations is birdshot chorioretinopathy. Birdshot choroidopathy is a bilateral, chronic posterior uveitis characterized by hypopigmented choroidal infiltrates consisting primarily of CD8 lymphocytes and retinal vasculitis (7). Birdshot choroidopathy is a rare disease (we have estimated that there are about 0.14 cases per 100,000 people; 95% confidence interval 0.0035–0.76 cases per 100,000 people) (DC Gritz, unpublished data, Francis I. Proctor Foundation for Research in Ophthalmology, University of California, San Francisco, CA, and Kaiser Permanente Medical Group, Northern California Region; presented at 'Birdshot Retinochoroidopathy: An International Workshop', UCLA Conference Center, Lake Arrowhead, 15–17 October 2002). Of about 130 patients with birdshot chorioretinopathy seen in two referral practices (Hopital Cochin, Paris, France, and UCLA, Los Angeles, CA, USA), we have three families with two siblings with the disease. One difficulty is that the disease is diagnosed at an average age of over 50 years; therefore, we cannot say uninvolved family members will not develop the disease over time (8). Clearly doing family studies would be very difficult.

The most common and the strongest genetic associations with ocular inflammatory disease have been with HLA genes on the major histocompatibility complex (MHC) of chromosome 6. Other genes in the MHC that have been suspected of playing a role in conferring risk for uveitis include nonclassical HLA genes and non-HLA genes.

HLA associations

Associations between HLA serotypes with uveitis were among the first such HLA associations with human disease described. In the more than three decades since the association of the HLA-B27 serotype and acute anterior uveitis was first made, both class I and class II HLA genes

Table 1 Human leukocyte antigen (HLA) associations with uveitis^a

Disease/syndrome	HLA	Uveitis ^b
Acute anterior uveitis	B27	Anterior, unilateral, sudden onset
Behcet's disease	B51, B52	Anterior, acute, posterior acute, or chronic
Birdshot chorioretinopathy	A29	Chronic bilateral posterior uveitis
Idiopathic intermediate uveitis/pars planitis	DR15	Chronic/recurrent, bilateral intermediate uveitis
Juvenile rheumatoid (or chronic) arthritis	DPB1*0202	Chronic bilateral anterior uveitis
Tubulointerstitial nephritis and uveitis	DRB1*0102, DQA*01	Chronic/recurrent bilateral anterior uveitis or sudden onset
Vogt-Koyanagi-Harada syndrome	DR1, DR4 (DRB1*0405 in Asians)	Bilateral panuveitis of acute onset followed by chronic anterior uveitis

^a Uveitis syndromes and diseases discussed in the text.

^b Most common manifestations.

have been implicated in conferring risk for uveitis (Table 1). They have been among the strongest HLA class I [birdshot chorioretinopathy with HLA-A29, with a relative risk estimated to be 50–220 (8)] and class II [tubulointerstitial nephritis and uveitis [TINU] syndrome with HLA-DRB1*0102, estimated to be 167 (9)] associations with any human disease.

HLA, uveitis, and systemic disease

Some forms of uveitis with either class I or class II HLA associations have systemic manifestations of inflammation, while others do not. The HLA-B27 gene is very strongly associated with ankylosing spondylitis less so with reactive arthritis. The HLA-B27 gene is found in half to two thirds of patients with acute anterior uveitis, with a relative risk estimated at about 10, a much lower relative risk than for ankylosing spondylitis. There is a lifetime incidence of acute anterior uveitis of about 1% in HLA-B27–positive individuals (10). Acute anterior uveitis is a distinct clinical entity that is characterized clinically by the sudden onset of anterior uveitis (iritis or iridocyclitis), most commonly in one eye at a time (though recurrent episodes can be in either eye and bilateral disease can occur), with each episode lasting an average of 4–6 weeks. The reasons for these characteristic features are not known. Patients with HLA-B27–associated uveitis do have a high prevalence of HLA-B27 arthritides (11–13).

Table 2 Non-human leukocyte antigen immunogenetic associations

Disease/syndrome	Suspected genes/loci
Acute anterior uveitis	MIC; D95137 (9p21p24), 1q23-1-q31, TNF-857T; TNFSRF1A-201T, TNFSRF1A-1135T; CCL2/MCP-2518G
Behcet's disease	MIC, interleukin-1, tumor necrosis factor promoter region, Factor V Leiden
Birdshot	Myelin oligodendrocyte glycoprotein
Blau syndrome	CARD/NOD
Intermediate uveitis	Cytokine gene polymorphisms

Another systemic inflammatory disease in which uveitis may be seen is Behcet's disease. Behcet's disease is a multi-system inflammatory disease that is associated with the HLA-B*51 and HLA-B*52 alleles. This is a somewhat weak association, with a relative risk of about 5 (14, 15).

Patients with TINU syndrome most commonly have bilateral anterior uveitis of sudden onset, with half or more of patients developing chronic or recurrent anterior uveitis, with evidence of systemic inflammation, primarily the kidneys (acute interstitial nephritis, which is most commonly self-limited). Other organs may be involved, although not usually with clinically apparent disease, with granulomata having been demonstrated in the liver and bone marrow in some patients (16). The TINU syndrome is strongly associated with HLA-DRB1*0102 and DQA1*01, and in particular with the HLA-DQA*01/DQB1*05/DRB1*01 haplotype (9). It is not known whether any HLA gene confers risk for acute interstitial nephritis without uveitis. Currently, studies are planned to see whether patients with the typical bilateral anterior uveitis of acute onset seen in TINU syndrome share the same HLA associations as patients with TINU syndrome.

Chronic bilateral anterior uveitis associated with juvenile rheumatoid arthritis is associated with HLA-DR5, HLA-DP2.1, and HLA-DPW8 as well as with the lack of HLA-DR1 (17). In Greek children, HLA-DPB1*0202 was associated with disease (18). The class II association of HLA-DR15 with multiple sclerosis overlaps with the association of a form of chronic bilateral intermediate uveitis, pars planitis (19–21). Individuals with pars planitis can later develop multiple sclerosis, and family members can have one or the other disease or both. Vogt-Koyanagi-Harada (VKH) disease, a bilateral panuveitis of acute onset that often results in chronic bilateral anterior uveitis, does have systemic findings, with meningismus during the early stage of the disease and later vitiligo and hearing difficulty in some patients. However, many patients have few systemic findings. The HLA associations are primarily with HLA-DR1 and DR4 (22).

Conversely, some forms of uveitis with strong HLA associations appear to be limited to ocular manifestations without systemic disease. Birdshot chorioretinopathy has no clear systemic manifestations, although based on anecdotal observations, a study is now being conducted to explore the possibility of autoimmune diseases being more common in close relatives of patients with birdshot chorioretinopathy. I have suspected that my patients had an unusually high likelihood of having autoimmune thyroid disease but have not been able to demonstrate this conclusively. We found that a large number of patients with birdshot chorioretinopathy in an ongoing longitudinal clinical study had a history of allergies (23), but there was no age-matched local control group to ascertain whether this was truly significant. Similarly, another group suspected a high prevalence of cardiovascular disease in patients with birdshot chorioretinopathy (24), which is intriguing as retinal vasculitis is seen in birdshot chorioretinopathy, and there is much interest in the role of inflammation in atherosclerotic cardiovascular disease. Again, there was no age-matched local control group, making these observations difficult to assess.

HLA genotype and disease phenotype

Researchers have also asked whether HLA associations correlate with ocular disease phenotype. This is not the case, at least for most entities. Class I associations confer risk for anterior uveitis (HLA-B27-associated acute anterior uveitis), chronic posterior uveitis (HLA-A29 and birdshot chorioretinopathy), and either posterior or anterior, acute or chronic uveitis (patients with Behcet's disease can have an acute iris, but unlike HLA-B27-associated ocular inflammation, individuals with Behcet's disease can also have a blinding, progressive, chronic posterior uveitis.). Class II associations similarly can be associated with panuveitis (HLA-DRB1*01 and 04 with VKH disease), intermediate uveitis (HLA-DR15 and pars planitis), or anterior uveitis (HLA-DR and DQ and TINU syndrome, HLA-DPB1*0202 in juvenile rheumatoid arthritis). There is evidence, on the other hand, that the disease phenotype may differ between HLA-B27-positive and HLA-B27-negative patients with acute anterior uveitis, with worse ocular manifestations and greater prevalence of systemic disease in HLA-B27-positive patients (25).

On the other hand, sympathetic ophthalmia is clinically and pathologically very similar to VKH disease, although the former is believed to be due to antigens released from immunologically privileged sites after surgery or injury and the latter has no known inciting event. Both are associated with HLA-DR1*0405 in Asians and other HLA-DR4 subtypes in Caucasians (22, 26, 27), implying that diseases with similar phenotypes but differing precipitating events can have the same HLA genotypes that confer risks for developing disease.

HLA associations in different populations and HLA subtypes

Different populations can have different HLA associations with the same forms of uveitis depending on the prevalence of the relevant genes in the population. A related question is whether specific HLA subtypes confer higher risk for disease than others. Different HLA-DR associations have been reported for different populations with VKH disease. In Asian patients, the HLA-DRB1*0405 allele is very strongly associated with disease (29–32), but this is not true for mestizo patients (22, 32, 33). Mestizo patients in fact have quite weak associations with HLA-DR1 and DR4. There have been putative autoantigens described for VKH disease. *In silico* studies that predict binding of antigens using computer algorithms appeared to correlate with risk, and as may be expected, this was similar for both HLA-DR1 and DR4, which share some critical motifs, as has also been described for rheumatoid arthritis (34). These results did vary with the algorithm used, however (34). In VKH disease, there are both HLA-DR and DQ associations (28–31); these are tightly linked, making it difficult to know which is primary in conferring risk. There has been speculation that specific HLA-DQ alleles may confer risk and HLA-DR alleles influence phenotype. This is based in part on the differences between HLA-DR associations in Asian and mestizo patients and the impression of clinicians that Asians may have less severe and chronic disease, but this is not established.

The HLA-B*5101 subtype was found in 56 of 57 Japanese patients with Behcet's disease (35) and 33 of 36 Iranian patients (36), but 18 Japanese control subjects who were HLA-B*51 positive had the B*0501 allele, and in the Iranian population, no particular subtype was believed to predominate compared with controls. In Greek patients with Behcet's disease, HLA-B*5101 was found, but so was HLA-B*5108 (37). In Israeli patients, both HLA-B*51 and 52 alleles were found, with no individual subtype being increased compared with controls.

Similarly, while some reports suggested that HLA-29.1 was less common than HLA-A29.2 in patients with birdshot chorioretinopathy, when examining patients genotype with DNA-based techniques, neither HLA-A*2901 nor A*2902 predominated (38). In general, it does not seem that particular subtypes are critical and that similar disease phenotypes may have somewhat different subtype associations (and even different HLA-DR genes in the case of VKH disease). Conversely, it does appear that HLA-B*2705 may confer increased risk in HLA-B27-associated inflammatory disease.

Nonclassical HLA genes, class III MHC genes, and non-MHC genes

It is not clear how HLA genes or their products play a role in the pathogenesis of ocular inflammatory disease. There is

some evidence for a direct role of HLA molecules in the pathogenesis of disease, but indeed, such associations could be due to linkage disequilibrium with other genes in the MHC. Animals transgenic for HLA-B27 do not get inflammatory disease until they are taken from germ-free facilities, and it is believed that gut colonization with bacteria plays a role, a favored theory being through 'molecular mimicry'. This is consistent with the evidence that mucosal bacteria may play a role in human diseases, albeit often with 'subclinical' mucosal inflammation (that is the patient often does not have gastrointestinal or urinary symptoms). Nonetheless, just as with systemic HLA-B27 disease, the role of antigen presentation and 'molecular mimicry' remains unproven. A mouse transgenic for HLA-A*29 did develop spontaneous uveitis that did have features similar to human disease (birdshot chorioretinopathy), which is very rare in animal models. Even in HLA-B27 transgenic animals that develop spondylosis, skin lesions, or arthritis, uveitis is uncommon, and when present, often mild. It did not appear that surface expression of the HLA-A29 molecule was necessary in the HLA-A*29 transgenic animal for disease to develop, implying that antigen presentation by the HLA-A29 molecule was not a critical step in disease pathogenesis. Unfortunately, the group involved has been unable to pursue this murine model. New HLA-A*29 transgenic mice are being developed from the same HLA-A*29 construct, with tissue-specific promoters. Although the HLA-A*29 transgenic mice should not have had any other human genomic material, it does remain possible that the HLA-A29 gene or its product interact with other genes on the MHC (or are in linkage equilibrium with them), resulting in the strong association with disease. A recent study from the laboratory that did prepare the HLA-A*29 constructs used for the transgenic mice explored the MHC in patients with birdshot chorioretinopathy to look for evidence of genetic risk in addition to the HLA-A*29 allele (39). In fact, the study did find such evidence. The study is particularly interested in the gene for myelin oligodendrocyte glycoprotein (MOG). However, myelin is not normally found in the retina, and the choroidal infiltrates (the birdshot lesions) are unlikely to be correlated with areas of myelin (the distribution of lesions appears to have more to do with choroidal blood vessels). It is, of course, possible that MOG is expressed in ocular blood vessels or other tissues, perhaps being used for functions other than myelin formation, but this is speculative.

Clearly, specific HLA genotypes are not necessary or sufficient for any form of uveitis. Investigators have searched for additional genes that may confer risk (Table 2). Nonclassical HLA associations with acute anterior uveitis include possible associations with the MHC class I-like molecules (MIC) genes. As the products of these genes interact with gamma delta T cells, which are important in gut mucosal immunity, and mucosal inflammation and

infections have been implicated in the pathogenesis of acute anterior uveitis, this has generated some excitement. It has not been clear, however, whether these associations are due to linkage disequilibrium with HLA-B27 gene. There is evidence of interactions between T lymphocytes and cells expressing NK antigens, perhaps through MICA on the cell surface (40). The immunogenetics of MICA and MICB in Behcet's disease has also been explored. While evidence of both positive and negative associations have been described, these again may have been due to linkage disequilibrium with HLA-B51 (41). In addition, many of these studies have involved a very small number of patients. While a consistent picture has not emerged, the tantalizing suggestion that there may be subgroups with particular disease phenotypes with specific MIC alleles remains an interesting observation, and several groups continue to examine this issue.

Class III MHC genes, in particular genes for tumor necrosis factor (TNF), may be important in the pathogenesis of uveitis. As these genes are part of the MHC, it is possible that some of the weaker HLA associations, for example HLA-B51 and Behcet's disease, could be in part due to linkage disequilibrium with such genes. Studies of non-MHC genetic associations have either concentrated on targeted examinations of gene polymorphisms in selected genes such as genes for cytokines or on genomic scans, as has been done for HLA-B27-associated uveitis. Early animal studies implied that TNF either does not play a role in the pathogenesis of uveitis or in fact if it does, inhibition may make uveitis worse (42, 43). Animal models were clearly misleading in this case as there is little question currently whether TNF plays a role in human uveitis as the TNF inhibitor infliximab (Remicade) can be very effective for many forms of noninfectious uveitis (44). This again is one of the reasons to pursue immunogenetic studies in humans rather than relying on animal studies alone. One goal would ultimately be to try to understand whether genetic polymorphisms in the critical genes (including the promoter and other regulatory regions) would predict therapeutic response. There have been suggestions of allelic variations of the TNF gene, including in the promoter region, in Behcet's disease (45). Other investigators could not find associations with TNF gene polymorphism in Behcet's disease (46), but this was in Korean patients, and the genetics may vary for different populations. A very interesting recent article reported an increase in a single-nucleotide polymorphism (SNP) (TNF-857T) in acute anterior uveitis, as this has been associated with Crohn's disease (which can have an associated anterior uveitis) and rheumatoid arthritis (which rarely if ever has an associated anterior uveitis, unless there is also a scleritis) (47). There was also a trend toward increased complications in HLA-B27-positive subjects who were carriers of the TNFSRF1A-201T or TNFSRF1A-1135T alleles, although clinical details are not given in the article (47). An odds ratio of 2.1 was

found for the CCL2/MCP-2518G in HLA-B27-positive patients with acute anterior uveitis compared with HLA-B27-positive control subjects (48). In perhaps the most ambitious genome-wide search for uveitis, linkage was found at marker D9S157 on chromosome 9p21-p24 (Logarithm of the odds (LOD) score 3.72) (6). This was not described as an association with ankylosing spondylitis but with iritis alone. Linkage with another region on chromosome 1q23-1q31 was suggested (LOD score 2.05). Linkage with HLA-B was also found, which was expected, of course, due to the strong association with HLA-B27.

Genetic associations have been pursued for other chemical mediators of the inflammatory response. Cytokine gene polymorphisms may confer risk for idiopathic intermediate uveitis (49). Single nucleotide polymorphisms in the interleukin-1 gene cluster on chromosome 2 have been found in individuals with Behcet's disease (50, 51). Gender-specific difference in chemokine genes has been suggested (52). These data are difficult to interpret, as there was no SNP associated with disease, although the gender differences in specific SNPs were found. Cytotoxic T lymphocyte-associated antigen-4 polymorphisms may contribute to the development of erythema nodosum and ocular inflammation in Behcet's disease (51). The authors give few clinical details about the ocular involvement. A small study suggested that Factor V Leiden polymorphisms may be a risk factor for Behcet's disease, which is intriguing as the most severe manifestations include retinal vascular occlusive disease (53).

The CARD/NOD gene family had attracted attention because it was found to be associated with a rare form of pediatric uveitis, Blau syndrome, which shares some clinical features in common with granulomatous inflammatory processes including sarcoidosis (54, 55). Additional studies failed to show any association with sarcoidosis or Behcet's disease (56), so despite enthusiasm for this new genetic association, it may be limited to Blau syndrome (57).

Conclusion

Studies of the immunogenetics of uveitis have revealed that there are not only HLA associations with many forms of ocular inflammation, but also that they are among the strongest associations of HLA genes with any human disease. Immunogenetic studies hold promise for revealing additional pathologic mechanisms, monitoring or predicting the response to treatment, and are currently used in the diagnosis of uveitis.

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