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GENETIC CONTROL OF SUSCEPTIBILITY IN CLINICAL AND EXPERIMENTAL UVEITIS

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Genetic association of some immune-mediated human uveitic diseases with histocompatibility antigens, ethnic origin, familial background, or gender have suggested the presence of a hereditary component in susceptibility to uveitis. Uveitis is a genetically complex disease, in which genes and environment contribute to the phenotype appearance. In complex traits, genotypes of particular sets of genes, together with environmental factors, alter the probability that an individual will express the characteristic, although each individual factor is typically insufficient to cause the disease. The main susceptibility genes for clinical and experimental uveitis seem to be located within the major histocompatibility complex (MHC) region, but genes possibly regulating responses to lymphokines, hypothalamic-adrenal-pituitary axis hormones, vascular effects, and possibly T cell repertoire and other pathways play a role to determine "permissiveness" or "nonpermissiveness" to the disease.

Keywords: Uveitis, multigenic disease, autoimmunity, genetic analysis

INTRODUCTION

There appears to be a genetic predisposition to uveitis that is apparent in humans as well as in animal models. Uveitis is considered a multifactorial, polygenic disease. The types of studies that have addressed this issue include: 1) the analysis of disease prevalence in identical versus nonidentical twins; 2) the determination of disease prevalence and segregation model within families; 3) the investigation of karyotype modifications in patients' cells; and 4) the association studies,

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in which the probability of an individual bearing a particular allele at a particular locus to express the disease is determined. Once it was clear that there was a genetic predisposition to development of uveitis, the search for candidate genes and alleles that might underlie this genetic susceptibility began. The major histocompatibility complex (MHC) has been, and still is, the main target for intensive scrutiny as regards the genetic basis of uveitis and autoimmune disease in general. The reason is that molecules encoded by genes within the MHC have a powerful role in regulating the immune response. However, the MHC accounts for only a part of the genetic predisposition to immune-mediated uveitis and autoimmunity in general, since both human and animal studies have shown that there are multiple genes not linked with the MHC that contribute to immune-mediated disease [1–3].

The determination of the molecular lesions in polygenic disorders, where multiple genes are involved, is more difficult than in monogenic diseases that are predominantly influenced by a single gene. The slower progress in polygenic disease is due to a number of factors. Perhaps most important is that in polygenic diseases the penetrance of each gene, which is the probability of disease expression in an individual bearing a particular allele, is usually low. In single-gene disorders the penetrance of the mutated gene is high, and one copy of a dominant mutation or two copies of a recessive mutation will usually result in disease. The incomplete risk conferred by any single allele is the main reason why complex diseases are not inherited in a simple Mendelian manner, as are the monogenic diseases. Genes in complex traits together determine susceptibility, and no particular gene is necessary or sufficient for disease expression. Even in the presence of a full set of susceptibility alleles at multiple loci, disease does not always result, a phenomenon termed “incomplete penetrance.” Genetic complexity is also determined by genetic heterogeneity, in which the same phenotype can be the result of the collective effect of different gene combinations. The susceptibility alleles that generate these diseases appear to be common in the general population. Natural selection does not operate efficiently against the alleles that contribute to polygenic disorders, unlike in the case of monogenic diseases, where a mutation often seriously or completely compromises the function of a gene. Finally, in polygenic diseases, the complexity of the genetic analysis is further increased by the fact that susceptibility alleles may interact with one another (epistasis), or act independently (additivity) to result in the phenotype [4]. Studies using several animal models have contributed greatly to the elucidation pathogenesis of complex traits. The study of animal models offers the opportunity to eliminate the effects of the environment. Under environmentally controlled

conditions, expression of disease in experimental animal crosses appears to be solely a reflection of the genes inherited, their penetrances, and how the products of these genes interact. Even if the actual genes involved in human disease and their animal models are not identical, it is likely that the general immunologic pathways will be similar in animal models and in humans [5].

The definition of uveitis includes a number of different diseases having in common an injury, possibly immune-mediated, of the uveal tract of the eye. This phenomenon is called "clinical heterogeneity". In some of these diseases the ocular lesions are primary, and in others uveitis is secondary to and part of a systemic or more complex syndrome. This clinical heterogeneity is reflected in the genetic heterogeneity of the disease and can explain the sometime discordant results of the studies conducted thus far. The low incidence of certain uveitic diseases adds complexity to the study of the genetic basis of uveitis. For these reasons, the study of the genetic basis of experimental autoimmune uveitis (EAU), the corresponding animal model induced in different species and strains, greatly contributes to elucidate the genetic influences in human uveitis.

CLINICAL UVEITIS

Twin Studies

Twin concordance studies are frequently being used for estimating the role of genetic factors in the pathogenesis of multifactorial diseases. Monozygotic (MZ), or identical twins share 100 percent of their genetic material, while dizygotic (DZ), or fraternal twins share, on average, 50 percent of their genes. In the twin study design, the concordance (defined as the proportion of twin pairs that both have the trait) in MZ twins is compared with the concordance between DZ twins. In general, a higher concordance in MZ than DZ twins is considered as evidence for a genetic etiology of the considered trait.

Because of the already mentioned clinical heterogeneity and relative rarity of uveitic diseases, only a few twin pairs have been studied thus far, and a clear estimation of concordance is not possible. The largest twin study on uveitis included 58 pairs of Finnish twins with ophthalmic diseases, five of which were concordant for the presence of iritis [6]. Twin pairs concordant for Behçet's disease, birdshot chorioretinopathy, Vogt-Koyanagi-Harada syndrome, and intermediate uveitis have been described [7–12]. They were concordant for the presence of disease and for the MHC allele HLA-B51, HLA-A29, and HLA-DR4, respectively [8,9,11]. One twin pair discordant for Behçet's

disease and for the presence of the predisposing MHC allele HLA-B51 has been described [13], supporting a strong role of MHC in susceptibility to the disease. Interestingly, some of the twin pairs showed a time lag of 7–16 years between the onset of disease [8–10]. Monozygotic twins were reported with discordance for Fuchs' heterochromic uveitis [14]. Further and more accurate twin studies are needed to estimate the heritability of immune-mediated uveitis.

Familial Aggregation and Segregation Studies

The first evidence that genetic factors may be involved in the etiology of a disease or trait is the observation that the disease clusters in families. This clustering is known as "familial aggregation." The identification of a recurrence pattern (segregation) of the trait through the generation helps to clarify the model of inheritance and can be helpful in understanding whether common genetic factors underlie distinct clinical phenotypes and in identifying the risk and the clinical prognosis of individuals in familial cases of the disease.

Aggregation has been described for primary uveitic diseases and in uveitis secondary to other immune-mediated diseases in families of different ethnic origin [12,15–38]. In all of these studies a specific pattern of inheritance was unrecognizable. A cosegregation of uveitis and specific MHC alleles was, however, identifiable, meaning that the affected individuals in a family carried the same MHC allele. Acute anterior uveitis was associated with HLA-B27 [19], chronic iridocyclitis with juvenile rheumatoid arthritis and HLA-DR5 [25], Behçet's disease with HLA-B51 [27,36,39]. These results led to the conclusion that uveitic syndromes behave according to a multifactorial, polygenic model of inheritance, in which an MHC allele, or a gene closely linked to it, acts as main susceptibility gene [40–43]. An autosomal recessive model of inheritance for Behçet's disease was tested but was found not to suit the data [44].

Sibling recurrence rate (λs), defined as the ratio of the risk of being affected among the siblings of the patients and the risk of being affected in the general population, can be considered an estimation value of the magnitude of genetic factors in the pathogenesis of a disease. Among uveitic diseases, sibling recurrence rate has been calculated only in families of different ethnic origin in which Behçet disease was segregating, and varied between 2.1 in United Kingdom and up to 52.5 in Turkey [45].

In families with Behçet disease, genetic anticipation was observed [46,47]. Genetic anticipation is an epidemiological phenomenon with a molecular basis characterized by earlier disease onset or increase in

disease severity, or both, in successive generations. It has been observed in monogenic diseases, such as myotonic dystrophy, and in multifactorial diseases, such as rheumatoid arthritis. In monogenic diseases, anticipation appears to be related to an expansion of unstable trinucleotide repeats [46]. The molecular basis of this phenomenon in multifactorial diseases is unknown.

The risk of relatives of uveitis patients to develop an autoimmune disease is greater than the risk of a nonrelated individual from an ethnically matched general population [20,48]. The risk of relatives of patients with another autoimmune disease of developing a uveitic disease is also greater than the risk of a nonrelated individual from the ethnically matched general population [17,19,25,26,29,49]. This is interpreted to mean that there are common predisposing genes to autoimmunity segregating in families, and the presence of disease-specific or tissue-specific genes determines the phenotype of the pathologic manifestations [3].

Besides, the uveitic diseases of possible autoimmune origin following a multifactorial model of inheritance, there are syndromes in which uveitis is present that segregate in a Mendelian manner. Elucidation of the molecular pathogenesis of these diseases has the potential to provide insight into the mechanism of the sheared features. Among them are neovascular inflammatory vitreoretinopathy, autosomal dominant, mapping on chromosome 11q13 [50]; Blau's syndrome, autosomal dominant with variable expressivity, mapped on chromosome 16p12-q21[51–56]; familial exudative vitreoretinopathy, an X-linked disease [57]; familial Mediterranean fever, autosomal recessive, mapped on chromosome 16p13.3 [58]; and a new possibly autosomal dominant disease characterized by retinal breaks and uveitis [59]. The products of the genes associated with pathology of these diseases might have a more general role in the etiology of immune-mediated, multifactorial, polygenic uveitis.

Cytogenetic Studies

The karyotype analysis and the study of chromosomal aberration are generally useful to determine the genetic cause of a disease and to map possible susceptibility genes. In uveitis, however, karyotype modifications do not seem to be a predisposing factor. Peripheral lymphocytes from patients with Behçet's disease were examined for frequencies of chromosomal aberration, and no numerical abnormality, in terms of an abnormally high frequency of gaps and breaks, was observed [60], although in another study a high sister chromatid exchange rate was identified [61]. The frequency of dicentrics was

increased in patients treated with anticancer medicines [62], but the effect of treatment was probably one of the causes of the chromosome aberration observed [63]. Also, cytogenetic high-resolution analysis of patients with iritis did not reveal any chromosomal abnormalities [12].

Association Studies

Association studies, whereby allele frequencies are compared between affected and unaffected individuals, are the primary method to study the role of a candidate susceptibility gene. As mentioned above, the major uveitis susceptibility genes seem to be located within the major histocompatibility complex, called human leukocyte antigens (HLA) in humans, and located on chromosome 6p21.31 [64]. In general, primary uveitic diseases, such as birdshot chorioretinopathy, Behçet disease, or Vogt-Koyanagi-Harada syndrome, are associated with specific HLA class I or class II alleles. On the other hand, uveitis secondary to other autoimmune diseases, such as acute anterior uveitis secondary to ankylosing spondylitis or pars planitis secondary to multiple sclerosis, shares an association with the HLA class I or class II allele associated with the primary disease. This is a reflection of the clinical and genetic heterogeneity of immune-mediated uveitis.

Since the dawn of HLA and disease association studies, when the number of loci constituting the major histocompatibility complex was still unknown, the association with the different uveitic diseases was one of the first to be ascertained in different populations [65–71]. Uveitic diseases are associated either with HLA class I loci (HLA-A, -B, -C), or class II loci (HLA-DR, -DQ, -DP), and the associated allele may vary depending on the ethnic origin of the population studied. The association between HLA-A29 and birdshot chorioretinopathy is the strongest association between HLA and disease ever described. The relative risk of an individual bearing the HLA-A29 allele developing birdshot chorioretinopathy in some populations can reach the value of 157, meaning that an HLA-A29–positive subject has a 157 times higher probability of developing the disease than an HLA-A29–negative person. Thus, the determination of HLA assumes diagnostic significance [72,73].

In a study report, HLA-A28 was found to be associated with intermediate uveitis characterized by an increased prevalence of arthralgia and hypocomplementemia [74]. No other reports have confirmed this observation.

Behçet's disease is primarily associated with the HLA-B51 antigen, molecular subtype B*5101 [75]. Given the geographic distribution of the disease and the frequency of this allele in different populations, it

seems likely that the susceptibility genes to Behçet's disease may have been spread by the old nomadic tribes or the Turks via the Silk Route [75–79]. The relative risk of HLA-B51–positive individuals developing Behçet's disease ranges from 6.3 to 11.5 [75,77,78], being higher in the population from the Mediterranean area and lower in North Europeans. For this reason, the determination of HLA-B51 is of limited but still significant value for the diagnosis of Behçet's disease in countries around the Mediterranean Sea or Japan. In Northern Europe, HLA-B51 determination will not give much practical information [72]. It is also still debatable whether HLA typing is of prognostic value to identify individuals at risk for Behçet's [78,80].

It must be remembered that the MHC loci are a cluster of genes involved in regulation of immune responses. Therefore, susceptibility to an HLA-associated disease might involve other genes encoded in the region, whose alleles are inherited together as a haplotype and are described as being in linkage disequilibrium. It seems that in an Italian population the susceptibility genes for Behçet's disease reside in the B51;DR5;DQw3 haplotype [81]. Linkage disequilibrium with HLA-B51 could be the reason why the study of other polymorphisms of the region has given contrasting or negative results. For example, there is a report of involvement of the HLA-Cw2 antigen in a population from southern Spain [82] that was not confirmed in other populations. Analyses of the polymorphisms of HLA-class II revealed unconfirmed or no significant association of the disease with DR, DQ, or DP types [75, 79, 83]. HLA-DMA and HLA-DMB genes have also been studied [86], but no association with alleles at these loci has been confirmed in different populations. Polymorphism of transporter associated with antigen processing (TAP) and large multifunctional protease (LMP) genes, whose products are involved in the pathways of peptide loading and presentation by HLA class I molecules, have been investigated without clear-cut results, indicating that the involvement of these genes might be due to linkage disequilibrium with the HLA-B51 allele [83, 85]. No significant associations were seen from the analysis of the polymorphisms included in the HLA class III, such as tumor necrosis factor (TNF), complement factors and heat shock protein 70 (Hsp70) [88–90]. Attention has recently been paid to the microsatellite polymorphisms of the MHC class I chain-related A and B (MICA and MICB) genes, located in centromeric position in respect to the HLA-B locus [64]. Behçet disease showed significant association with the MICA*009 and A6 alleles, and with variants of the transmembrane region of MICA (MICA-TM) polymorphism in some populations [91–93]. Further studies, however, concluded that the association with alleles of the MICA and MICB genes was due to linkage disequilibrium with HLA-B51 [94–97].

Acute anterior uveitis shows association with the HLA-B27 antigen [98]. Acute anterior uveitis can be one of the clinical features of ankylosing spondylitis, with which it shares the same predisposing HLA allele [48]. The association between HLA-B27 and acute anterior uveitis is relatively weak. It is nevertheless evident that B27-positive acute anterior uveitis is clinically different from B27-negative acute anterior uveitis. In a prognostic perspective, about half of the B27-positive acute anterior uveitis patients have or will have ankylosing spondylitis or Reiter's syndrome [72]. Generally the prognosis of anterior uveitis associated with the HLA-B27 haplotype, either with or without associated systemic disease, is less favorable when compared to that of HLA-B27-negative patients with idiopathic anterior uveitis [99]. In a Japanese population, HLA-DR8 was reported to be important for the development of B27-positive acute anterior uveitis [100], but this was not seen in Mexican Mestizo [101]. Association with alleles of the TAP and LMP alleles is again probably due to linkage disequilibrium with HLA-B27 [102–106]. The C4B2 allele of the C4 gene of the complement cascade, located within the HLA class III region, has been shown to be prevalent in HLA-B27 positive acute anterior uveitis [107], but others have not confirmed the result.

In contrast to these HLA class I-associated uveitides, a series of other uveitic diseases show a prevalent association with alleles of class II genes. The reason for this differential association is unknown but could nevertheless underline differences in pathogenesis of these diseases. The HLA-DRB1*0405 allele, encoding for a variant of the HLA-DR4 antigen, was found to be significantly increased in a Japanese population of Vogt-Koyanagi-Harada patients, with a relative risk of 46.7 [108]; this was also confirmed in other populations [109–110]. As for the DQB1 locus, all the patients carried DQB1*0401 or DQB1*0402, which is in strong linkage disequilibrium with DRB1*0405 or DRB1*0410, respectively, in the Japanese population, but only DQB1*0401 showed a statistically significant increase, compared with the healthy controls, with a relative risk of 41.3 [111]. These results were confirmed in a Korean population [110]. Comparison of the amino acid sequences of these HLA-DRB1 and HLA-DQB1 alleles indicates that some amino acids play a crucial role in determining the susceptibility to Vogt-Koyanagi-Harada disease, possibly affecting the presentation of disease-specific antigenic peptides. These include serine at position 57 of DRB1 and/or glutamic acid at position 70 of the β chain of the DQ molecule, or amino acid motifs such as the motif LLEQRRAAG located at positions 67–74 and 86 of the β chain of the DR4 antigen [109, 111]. Clinically similar to Vogt-Koyanagi-Harada syndrome, sympathetic ophthalmia is also

associated with HLA-DRB1*04 and DQA1*03 genotypes in Japanese, British, and Irish populations [112–113]. Differences in DRB1*04 allelic variant associations (DRB1*0405 in Japan and DRB1*0404 in Britain and Ireland) may have implications for HLA peptide binding in disease initiation [113]. The association with the HLA-DPB1*0501, found in a Japanese population of Vogt-Koyanagi-Harada syndrome, patients may have been due to linkage disequilibrium of this allele with DRB1*0405 [108].

A common immunogenetic predisposition to multiple sclerosis and pars planitis may be associated with the HLA-DR15 subtype of the HLA specificity DR2 [114–115]. The strong association of pars planitis with HLA-DR2 and the temporal codevelopment of multiple sclerosis in some patients with pars planitis further supports the clinical association between these two diseases [116]. Similarly to pars planitis, patients who are HLA-DR15−positive and have intermediate uveitis may have systemic findings of other HLA-DR15−related disorders, which include multiple sclerosis, optic neuritis, and narcolepsy [117]. In contrast, intermediate uveitis not correlated to multiple sclerosis was associated to the HLA-DR3 antigen, while panuveitis showed association to HLA-DR4 in an Italian population [118].

Chronic iridocyclitis secondary to juvenile rheumatoid arthritis seems to be associated with the HLA-DRB1*1104 allele, a variant of the DR5 specificity [119–120], while the presence of the DRB1*01 allele appears to convey some protective effect [121]. HLA-DQA1*0501 and HLA-DQB1*0301, both in linkage disequilibrium with HLA-DRB1*1104, also were significantly associated with eye disease [120].

This long list of HLA alleles associated to different uveitic diseases testifies to the extreme genetic heterogeneity of uveitis, but it underscores a common pathogenetic mechanism that involves the role of MHC molecules in antigen presentation and T cell receptor repertoire shaping. Different MHC molecules have the ability to present different antigenic peptides, possibly triggering the pathogenic immune response. The origin of the disease-relevant peptides presented by the HLA molecules associated with specific diseases is still unclear. It is generally thought that viral or bacterial antigens that mimic self-antigens are presented in the context of disease-associated HLA molecules and can activate autoreactive cells in the periphery, thus eliciting an autoimmune response [122]. Such viral and bacterial mimics bearing sequence similarity to autoantigens and capable of eliciting autoaggressive responses have been identified for various autoimmune diseases. Another hypothesis, for which some support exists as well, postulates that the origin of these peptides is the HLA molecule(s) itself. In this case, peptides derived from the processed

HLA molecules would be mimics of autoantigen(s) and elicit the autoimmune reaction [123]. Such a mechanism has been proposed to underlie the association of HLA B-27 with uveitis [123].

The MHC/peptide complex counterpart in the process of antigen recognition is the T cell receptor (TCR). There is a tight relationship between the MHC haplotype and the TCR repertoire of an individual, since the gamut of peptides presented by the MHC molecules serves as the basis for positive and negative selection of T cells during thymic development [124]. The role of the TCR in susceptibility to uveitis is suggested by detectable expansions of particular T cell clones, such as the presence of an oligoclonal TCR repertoire detected in Behçet disease patients [125].

Other genes involved in the immune response, besides MHC and TCR, have also been investigated. Among them the loci encoding for immunoglobulin allotypes have been investigated, but no strong association with any uveitic disease was found [126–129]. On the same chromosome 14q as some immunoglobulin loci, the gene encoding α1-antitrypsin is located, and a possible association with uveitis has been postulated for a long time [49, 130–132]. However, no clear association was found [133]. Interleukins and adhesion molecules have been studied and it appears that a polymorphism within the gene of the IL1α chain might contribute to ocular complications in juvenile rheumatoid arthritis [134] independently of MHC. Similarly, a polymorphism within the ICAM-1 gene might contribute to the susceptibility toward Behçet disease [135]. In addition, in Behçet disease patients the presence of certain alleles of the coagulation factor V and prothrombin genes might increase the risk of developing venous thrombosis [136–141]. Additional susceptibility risk in Behçet disease can be conferred by the presence of some mutations of the MEFV gene, on chromosome 16p13.3, also responsible for the familial Mediterranean fever [142]. Familial Mediterranean fever and Behçet disease share clinical and epidemiological features, suggesting the existence of common pathogenetic mechanisms.

ANIMAL MODELS

Experimental autoimmune uveitis or uveoretinitis (EAU) is a disease of the neural retina and related tissues that can be induced by immunization of experimental animals with preparations of purified retinal antigens, such as intraphotoreceptor retinoid-binding protein (IRBP) or retinal-soluble antigen (S-Ag). EAU is thought to represent various human ocular inflammatory diseases of possible autoimmune origin that are accompanied by immunologic responses to ocular

antigens. As in clinical uveitis, susceptibility to EAU in rodents is genetically controlled and it appears to be a complex trait following a multifactorial, polygenic pattern of inheritance. There are species-specific differences in sensitivity to uveitogenic proteins, e.g., IRBP is a more potent uveitogen than S-Ag for mice, while the reverse is true in guinea pigs, and both proteins are strongly uveitogenic in Lewis rat [143]. Within each species, strain dependence of susceptibility is apparent, and high-, intermediate-, and non-responder strains exist. The responsiveness to EAU induction is determined by the effect of MHC (H-2 in mouse, RT1 in rat) and non-MHC genes [144].

MHC gene control is, at least on the face of it, relatively straightforward, being determined largely by epitope recognition. In the mouse, some H-2 haplotypes, which when present on the appropriate background are conducive to induction of disease, are H-2 b, d, k, and r. These haplotypes have been termed as susceptible. MHC control of susceptibility to EAU in the H-2k haplotype was tentatively mapped to the I-A molecules of the class II MHC region, corresponding to human HLA-DQ antigens [1, 143], with I-E molecules (HLA-DR equivalent) exerting a modifying influence. However, this "division of labor" among the I-A and I-E class II molecules may well be different in other MHC haplotypes.

Non-MHC control is shown when a susceptible MHC haplotype is present on a background that does not permit expression of disease. Thus, the AKR mouse, which has the same MHC haplotype as the susceptible B10.BR strain, is resistant. Thus, the B10 background is permissive and the AKR background is nonpermissive. In rats a similar situation exists. The susceptible Lewis and resistant F344 strains share an almost identical MHC haplotype but differ in multiple background genes. Thus the Lewis background is susceptible, whereas the F344 background is permissive. A number of studies have been published in mouse and in rat pointing to cytokine responses and the control of hypothalamic-adrenal-pituitary axis as some of the genes that might make the background nonpermissive to EAU induction [145–147]. However, due to the complex and multigenic nature of this control, in-depth identification of non-MHC genes that affect EAU expression requires genome-wide linkage studies. A genome scan of EAU in the F2 intercross progeny of resistant (F344/N) and susceptible (LEW/N) rats identified regions of the rat chromosome 2, 4, 10, and 12 in which EAU-susceptibility genes seem to map [2]. In these intervals there are many immunologically relevant genes, including genes encoding for the TCR, lymphokines, hormones, and neurotransmitters. More precise mapping across much smaller intervals, which can be achieved by careful breeding and selection, is required to

identify among these candidate genes the ones that can be shown to differentially affect susceptibility. Similar studies in other autoimmune diseases in animal models and in humans revealed that complex interactions among multiple genes underlie the susceptible phenotype [3,148–149].

Importantly, by chromosome conserved synteny and gene linkage groups it appears that common susceptibility loci are shared by different autoimmune diseases. Furthermore, the susceptibility loci cross species barriers, with many of the same loci identified in human disease and in animal models [3,144]. It is thus likely that the pathways involved in genetic predisposition to autoimmune disease are similar in animals and in humans, validating the use of experimental animals to model human disease. The genetic factors that influence disease predisposition are under intense scrutiny. An answer will be possible when the molecular interactions of these gene products are elucidated.

To dissect the role of a single gene or a few genes, genetically manipulated animals have served an important role. Gene knockout or transgenic mice and rats have provided important insights into the role of MHC genes as well as genes affecting immune function in general in susceptibility and resistance to autoimmune disease [150–152]. Humanized rodent models of uveitis are particularly worth mentioning in this connection. HLA transgenic mice have been proven of great interest in substantiating the association between uveitis and HLA antigens as not only a statistical, epidemiological observation, but a functional observation as well. Although HLA B-27 transgenic rats do not develop anterior uveitis [153], HLA-A29 transgenic mice develop spontaneous uveitis [154]. In this model, aging HLA-A29 transgenic mice develop retinopathy, showing a striking resemblance to the HLA-A29–associated chorioretinopathy [154]. HLA-B27 and HLA-DR3, -DR4, -DQ6, and -DQ8 transgenic mice develop uveitis as a result of immunization with IRBP [155–157]. These observations show that human MHC molecules are able to present uveitogenic peptides of retinal antigens, triggering the autoimmune response leading to tissue destruction. Importantly, unlike wild type mice, HLA-DR3 transgenic mice are susceptible to EAU induced with S-Ag (arrestin) [157]. Because human uveitis patients frequently exhibit strong responses to S-Ag but not to IRBP, this observation is of significance and can provide new insights into the role of HLA molecules in uveitis.

CONCLUSIONS

Identification of genes involved in susceptibility to uveitic disease is still an ongoing process in experimental models and in patients.

The results of these studies will open the door to new diagnostic and therapeutic applications. The prediction for individual risk and recurrence risk of primary familial uveitis and uveitis associated with other autoimmune diseases will become more accurate. With the help of new technologies, the expression patterns and interactions among the susceptibility genes and their products will be clarified, and functional studies in vitro and in vivo will validate the role of these gene products in the pathogenesis of disease. At the end of this process, translating the result from bench to bedside and tailoring the therapy over the genetic makeup of the patient will become a reality.

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