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Infection and Autoimmunity
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Infections Associated with Retinal Autoimmunity

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1. INFECTIONS & AUTOIMMUNITY IN THE RETINA

The topic of immune-mediated vision loss, with an emphasis on autoimmune reactivity and autoimmune disease in the eye, is a rapidly expanding area of research and therapy. Numerous studies in other body sites have clearly identified links between infections and autoimmunity and autoimmune disease [4, 5]. Only a limited number of studies have been reported in which retinal disorders have been evaluated to study this relationship. We will begin this chapter with a brief overview of infection and autoimmunity in the eye. This will be followed by specific examples of infections and autoimmunity in the retina. We will highlight two human diseases triggered by Onchocerca volvulus or Toxoplasma gondii and an experimental model referred to as experimental coronavirus retinopathy (ECOR), triggered by the murine coronavirus, mouse hepatitis virus (MHV).

2. THE EYE: INFECTION AND AUTOIMMUNITY

The visual axis is a precious sense. The eye is an organ that is known to have immunologic processes that are both infectious and non-infectiously driven. The eye is unique in that it lacks lymphatics and still enjoys an intimate relationship with the immune system. An inflammatory process in the eye is termed an uveitis, and it in no way reflects the origin of the inflammatory process nor where it is located in the eye. While there are many descriptions of inflammatory processes in the eye, there are three major presentations of these conditions. If the inflammatory condition is centered in the front of the eye, the process is termed an anterior uveitis. If upon examination the dominant part of the inflammation is centered in the vitreous of the eye, it is termed an intermediate uveitis. Finally, if inflammation occurs in the back of the eye, that is centered in the retina or the choroid of the eye, it is termed a posterior uveitis. Clearly inflammatory conditions may involve several parts of the eye, and if all anatomic of the eye are involved it is termed a panuveitis. Most of the comments of this chapter will address disorders of the back of the eye, i.e., those involving the retina.

Eye specialists have the great advantage of being able to visualize directly the parts of the eye that can be involved in an inflammatory process. In addition to simple visualization, many additional tools can be readily applied. Electrophysiologic testing is easily and frequently performed, This is an excellent way to evaluate the retina's ability to react to a light stimulus. Fluorescein angiography, the use of dye injected into an arm vein and then rapid photographs are taken of the back of the eye. This approach helps to visualize the vascular system and the integrity of the retina. The severity of the inflammatory response can be graded by direct visualization of the inflammatory response in the eye. Most inflammatory process that we recognize will have a cellular response associated with it. We also know that antibody mediated pathology, as seen in such entities as cancer associated retinopathy, can occur, but appears to be the distinct minority of cases.

The eye is a complex organ from the point of

view of the immune system. It is known that antigen placed into the anterior chamber of the eye will induce a deviated immune response, with a marked decrease in cell mediated responses, but an intact cytotoxic and B-cell response is seen [1]. Addtionally, the retina is a complex structure with several layers needed to turn the light stimulus into a chemical signal ultimately sent to the brain. At the photoreceptor level and the single layer just below it, the retinal pigment epithelium, a number of uveitogenic antigens have been identified and characterized [2]. Two antigens in particular, the retinal S-antigen and the interphotoreceptor retinal binding protein (IRBP), have been used to develop a model of autoimmune ocular disease which is termed experimental autoimmune uveoretinitis (EAU) [3]. This model has many qualities of the disease seen in humans and has helped to better understand the underlying mechanisms that lead to disease. One major difference between this model and the human disease is of course that it is not spontaneous. It is not clear what triggers the human disease. This chapter will explore one such trigger, that of ocular infection. Several entities, some based on animal models, other seen in the clinic, will be discussed to elucidate the possible role between infection and autoimmunity.

3. EXPERIMENTAL CORONAVIRUS RETINOPATHY

Experimental coronavirus retinopathy (ECOR) is an animal model system that we generated in the 1990's to demonstrate that a virus can trigger a progressive retinal degenerative disease [6]. Studies during the past 12 years have identified that this degenerative eye disease is composed of three basic components; a virus component, a genetic component and an immunologic component [7, 8]. In our system, we selected a naturally occurring neurotrophic strain (JHM) of a mouse hepatitis virus that infects and persists within the retina. The virus causes an acute infection, marked by virus replication in distinct retinal cells, neutralizing antibody and the production of cytokines, namely IFN-gamma. This disease also has a genetic component. That is, different strains of mice behave differently after virus infection. Two strains of mice, BABL/c and CD-1, were extensively studied after coronavirus infection. During the early phase of the disease (day 1–8) the virus infects and replicates within the retina of both BALB/c and CD-1 mouse stains [9]. However, on days 10 to 140, only the BALB/c mice experience a late phase of the disease which is marked by a retinal degeneration. The CD-1 mouse does not undergo the retinal degenerative phase but rather, the retina returns to a normal architecture within 20 days.

Finally, the immune component of this disease is characterized by the presence of autoantibodies, specifically, anti-retinal and anti-RPE auto-antibodies. The presence of these antibodies are observed only in the retinal degenerative susceptible BALB/c mice. These auto-antibodies are absent in the retinal degeneration resistant CD-1 mice. In summary, ECOR is a virus triggered retinal degenerative disease that is influenced by both genetics and the immune response. In this session we will discuss in detail the virologic, pathologic, immunologic, genetic and autoimmune factors involved in this model system.

3.1. Virologic Component of ECOR

Coronaviruses are large, enveloped, positive strand RNA viruses that cause significant diseases in a number of animal species and humans. In animals, coronaviruses are responsible for important diseases of livestock, poultry and laboratory rodents. Until recently, man was known to be infected with two strains of coronavirus. Either of these strains are responsible for approximately 50% of the common colds. A new human coronavirus has been identified as the causative agent for severe acute respiratory syndrome (SARS) [12]. One of the closest relatives to the human SARS-Coronavirus is the murine coronavirus, mouse hepatitis virus (MHV). The JHM strain of MHV is the most thoroughly studied neurotropic coronavirus. It causes both acute and chronic central nervous system effects in mice and rats. Acute encephalomyelitis and chronic CNS disease have been observed in mice. In rats an autoimmune disease known as subacute demyelinating encephalomyelitis, has been described.

Initial studies in the ECOR system, showed that inoculation of this JHM strain into the vitreous or anterior chamber of BALB/c mice resulted in retinal tissue damage [7, 8]. Infectious virus could be

detected within the retina between 1 and 6 days post inoculation (PI), reaching a peak level of $10^{4.5}$ pfu/ml at day 3 [13]. Virus antigen was also identified within the retina between day 2 and 6 PI [8]. Virus antigen was first detected within the RPE cell and the ciliary body epithelial cell at day 2 and this virus replication intensified at day 3 and 4. Between day 3 and 6 virus antigen was also detected in Muller-like cells that span the multiple layers of the neural retina. Occasionly, virus antigen was also observed within the ganglion cells. After day 7, infectious virus and viral antigen could not be detected within the retina. However, *in situ* hybridization studies identified that the viral RNA persisted within the retina until 60 days PI [14]. Anti-virus neutralizing antibodies were first noted at day 7 PI [13] and coincided with the disappearance of infectious virus and viral antigen.

3.2. Retinal Pathology in ECOR

After inoculation with JHM virus, two distinct patterns of retinal pathology were noted in the BALB/c mice [8]. The early phase of the disease, day 1 to 8, was characterized by retinal vasculitis and perivasculitis. The late phase of the disease, after day 10, was characterized by retinal degenerative changes. The retinal layers revealed disorganization with large areas of outer and inner segment loss. In addition, the RPE cells were morphologically abnormal with focal RPE cell swelling or proliferation, or with focal RPE cell atrophy or loss. Analysis of retinal cell function also revealed dramatic changes [15, 16]. There was a significant decrease of complete loss of electroretinogram (ERG) patterns and the disappearance of an important transport protein in the retina, the interphotoreceptor retinoid-binding protein (IRBP).

3.3. Host Response in ECOR

The host immune response to this virus infection was evaluated by tracking the cellular infiltrate and identifying the cytokine profile within the retina [10]. The most prominent infiltrating cell was the macrophage. MAC-1 staining was detected in 100% of the eyes at day 6 and 10 PI, and was occasionally seen on day 20 and beyond. The second most prominent cell was the T cell. CD4 T cells were present in the retina at days 3 and 6. This was followed by a shift to CD8 T cells which were observed at day 6 and 10 PI. A low number of CD8 T cells were still noted at day 20 PI. B cells and NK cells were not detected.

During the course of the disease, cytokine profiles were studied by evaluating retina tissue and sera [10]. Analysis of pooled retinal mRNAs from untreated, mock-injected and virus infected BALB/c mice revealed the presence of IL-6, IFN-γ and TNF-α mRNAs in virus infected retinas isolated during the acute disease, day 4 and day 8 PI. Gene expression for these cytokines was not detected in retinas from untreated or mock-injected mice. EIA analysis of sera identified the presence of these same cytokine proteins in virus infected mice and not in untreated or mock injected mice. The presence of retinal mRNA for IFN-γ was also associated with the upregulation of MHC Class I and II molecules within the retina. MHC class I and II molecules were not identified within the normal or mock injected retinas. It was noted that the first cell to express these MHC molecules was the RPE cell. This cell is also the first cell to express new viral antigens during the infection *in vivo* and is persistently infected *in vitro* [17]. It is critically important to point out that this RPE cell has been shown to process and present retinal and non-retinal antigens to sensitized T cells and is upregulated to express MHC class II molecules during retinal autoimmune and degenerative processes [18, 19].

3.4. Genetic Factors in ECOR

The genetic constitution of the host can be a critical factor in determining the outcome of a virus infection [9]. We therefore evaluated the possible role of host genetics in ECOR. We inoculated selected strains of mice and evaluated the retinal disease. BABL/c, C57Bl, A/J and CD-1 mice were studied. When C57Bl and A/J mice were evaluated, we observed a disease pattern similar to that seen in BALB/c mice. However, retinal changes were less severe than those seen in BALB/c mice. Retinal tissue damage induced by JHM virus in CD-1 mice was very different (Table 1). Only the early phase of the disease, consisting of retinal vasculitis, was observed. These CD-1 mice did not develop the retinal degenerative disease. In fact, by day 20 PI,

Table 1. Retinal inflammation and retinal degenertation in mice inoculated with murine coronavirus (JHM strain)

Retinal Disease	Day	BALB/c Mice		CD-1 Mice	
		Positive / tested	(%)	Positive / tested	(%)
Inflammation (Vasculitis)	0	0 / 30	0	0 / 20	0
	1–7	26 / 26	100	20 / 20	100
	10–45	0 / 30	0	0 / 20	0
Degeneration	0	0 / 30	0	0 / 20	0
	1–7	0 / 26	0	0 / 20	0
	10–45	30 / 30	100	0 / 20	0

Table 2. Anti-retinal antibody production and retinal degeneration in coronavirus inoculated mice

Mouse	Treatment	Autoantibody in Retinal Tissue Positive / Number tested	Retinal Degeneration
BALB/c	untreated	0 / 20	0 / 20
	Mock injected	0 / 15	0 / 15
	JHM Virus	22 / 22	22 / 22
CD-1	untreated	0 / 15	0 / 15
	Mock injected	0 / 15	0 / 15
	JHM Virus	0 / 20	0 / 20

the retina had a normal appearance. These studies underscored the role of genetics in ECOR and showed that the genetics of the host profoundly affected the nature of retinal tissue damage.

Since the CD-1 mice did not exhibit the late retinal degenerative phase of the disease, we evaluated a variety of parameters and compared the findings with the data obtained in BALB/c mice. For example, during the acute phase of the disease (days 3–10), virus load in the retina, production of anti-virus antibody, blood–retina barrier breakdown, lymphoid trafficking and MHC Class I and II staining were similar in both mouse strains. Moreover, gene expression for IFN-γ in pooled retinas from CD-1 mice was positive at PI day 4 and 8. Again, this is similar to the pattern observed in BALB/c mice. The disease pattern in the late phase was clearly different in the two mouse strains. BALB/c mice displayed a retinal degeneration with blood-retina barrier breakdown, and CD-1 mice showed a normal retinal architecture. Immuno-staining observed at day 20 in CD-1 mice was clearly different from that observed in BALB/c mice, in that CD-1 mice were negative for MHC class I and II expression and CD8 T cells were absent from the retina.

3.5. Autoimmune Component of ECOR

In ECOR, the late phase of the disease was associated with the lack of direct evidence for viral replication within the retina. This observation suggested that the continued degenerative process may be associated with alterations directly induced by virus replication during the first few days after infection or it may be associated with additional factors. Inasmuch as viruses are know to trigger an autoimmune phenomena and some human retinopathies may be associated with autoantibody formation, we studied the possible production of antiretinal autoantibodies [11]. We found that the retinal degenerative process in BALB/c mice was associated with the presence of antiretinal autoantibodies (Table 2). These

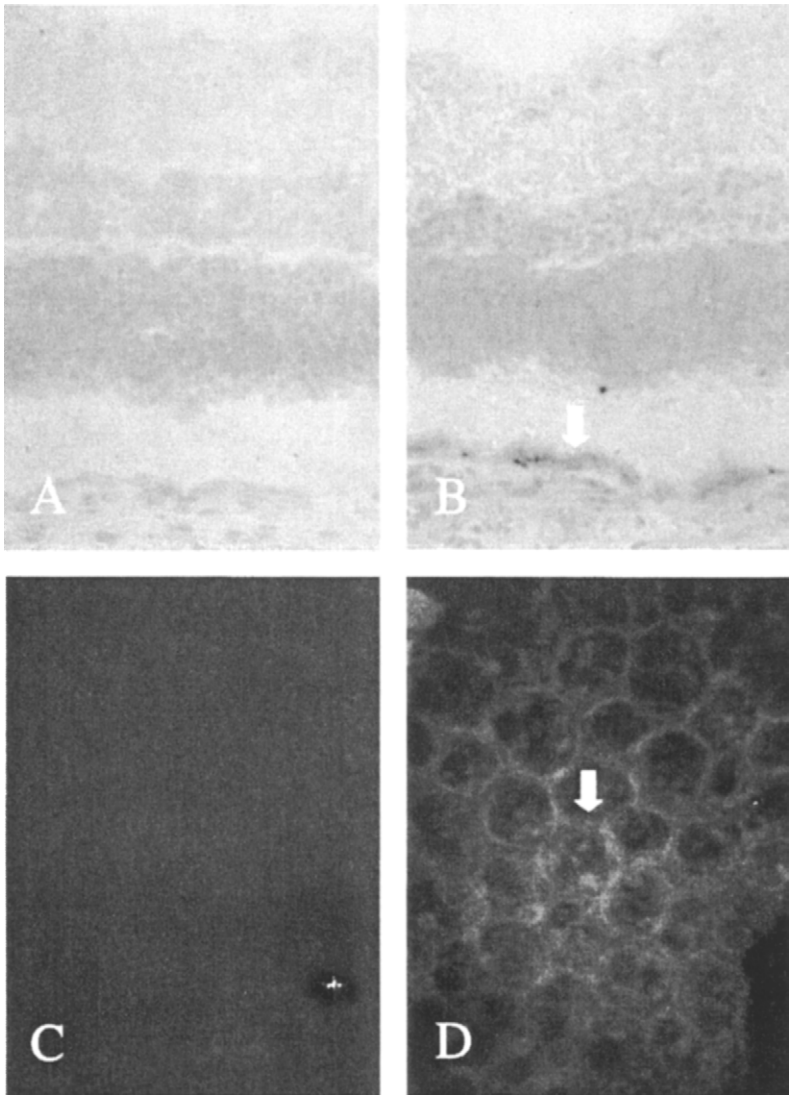

Figure 1. Anti RPE cell autoantibodies. A & B are immunoperoxidase staining showing anti RPE cell autoantibodies. Frozen sections of normal rat eyes were incubated with (A) normal mouse sera or with (B) sera from JHM virus-infected mice (day 15) (1:40 dilution). C & D are immunofluorescent staining showing RPE cell autoantibodies. Cytospin preparations of freshly isolated rat RPE cells were incubated with (C) sera from mock-injected BALB/c mouse (day 10) (1:40 dilution) or with (D) sera from JHM virus infected BALB/c mouse (day 10) (1:40 dilution). Arrows indicate areas of positive staining.

autoantibodies were not found in sera from normal or mock-injected mice. The presence of antibodies to retinal tissue was evaluated by immunoperoxidase staining on frozen sections of normal rat eyes. Two patterns of staining were observed, reactivity in the neural retinal and reactivity in the retinal pigment epithelium (RPE) (Fig. 1). The antiretinal autoantibodies first appeared as IgM class antibodies. This was later replaced by IgG class autoantibodies. The anti-RPE cell autoantiboedies were predominantly of the IgG class.

As stated above, JHM virus infected CD-1 mice developed a retinal disease that is different than the retinal disease observed in BALB/c mice. In CD-1 mice, only the early stage, consisting of retinal vasculitis was seen. The CD-1 mice recovered and were not susceptible to the later phase of the disease, the retinal degenerative disease. We therefore, evaluated

the development of a retinal degenerative disease and the development of antiretinal autoantibodies in these two strains of mice after inoculation with JHM virus [11]. The data summarized in Table 2 shows that all of the BABL/c mice developed antiretinal antibodies and developed pathologic changes consistent with retinal degenerative processes. In contrast, none of the CD-1 mice developed antiretinal autoantibodies. That is, in those mice that failed to develop antiretinal autoantibodies, they also failed to develop a retinal degeneration. These findings suggest a role for autoimmunity in the pathogenesis of ECOR.

4. TOXOPLASMOSIS (T. GONDII)

Toxoplasmosis is a disorder that has a worldwide distribution. It is caused by the obligate intracellular parasite, Toxoplasma gondii. Over 500 million people are believed to have the disease. In 1908, the organism was first described in the brain of the North African rodent, the gondii, by Nicolle and Manceaux [20] and by Splendore in a rabbit [21]. The first connection between this organism and human disease was made by Janku [22]who described the presence of the organism in a child who died of disseminated toxoplasmosis. While suspected for a long period, it was not till the early 1950's that the parasite was shown to cause ocular disease. Helenor Campbell Wilder, working at the Armed Forces Institute of Pathology in Washington, DC, identified the organism in eyes that were believed to have other types of inflammatory processes, particularly tuberculosis [23]. It is interesting to note that a similar observation has been made more recently in Nepal, where many cases of ocular tuberculosis have now been rediagnosed as toxoplasmosis of the eye.

The cat (and perhaps related species) appears to be the definitive host. The sexual cycle is one of schizogony and gametogony leading to the the development of toxoplasma oocysts, which are 10–12 μm in size and are found uniquely in the intestinal mucosa of cats. Two forms of the organism can be found in man, cysts and tachyzoites. The tachyzoites (the proliferative intracellar form) are believed to be the cause of most of the tissue damage in human, though often it is very difficult to demonstrate the presence of the stage of the organism. The bradyzoites (the latent form of the organism found in cysts) are found in host cells. Hundreds of bradyzoites (with very slow metabolic rates) have a propensity towards neural tissue such as the eye and brain, but are also found in skeletal muscle and heart. It is assumed that attacks occur with rupture of the cyst, leading to a pouring out of bradyzoites and then the conversion of bradyzoites to tachyzoites. The mechanisms that lead to cyst rupture are still unknown.

4.1. Clinical Features

While the hallmark of the disease is changes in the posterior portion of the eye, changes in the front of the eye are also noted. An anterior uveitis can be seen in many patients with this disorder. This is an interesting finding since the organism is not seen in the anterior segment of the eye except possibly in immunocompromised individuals. Additionally, there is a loss of pigment in the iris that can be seen and is associated with changes in the back of the eye [24]. This finding, termed Fuch's heterochromia, is thought to be an autoimmune phenomenon.

The classic finding in ocular toxoplasmosis is that of a retinal lesion, which is destructive. It is typically an oval lesion where all layers of the retina and frequently many layers of the choroid have been infected. It is the result of an immune response believed to have occurred against the toxoplasma organism. While there may be only one lesion, often there are multiple lesions surrounding an old large scar, and these are called satellite lesions. In addition to the lesion itself, during the active stage of the disease, evidence of retinal vascular leakage is seen. It has been hypothesized that this vasculitis is due to an immune complex related phenomenon.

Typically while stigmata of the disease may be present in both eyes, recurrences of the disorder occur only in one eye. Additionally, while reactivation of the disease is believed due to the breakage of cysts and the presence of tachyzoites, it is rare to see this stage of the organism in the retina. Patients who are immunocompromised, such as those with AIDS, will often have bilateral disease and multiple lesions, suggesting a different mechanism in these patients as compared to the immunocompetant patient.

4.2. Evidence for Autoimmunity

Abrahams and Gregerson [25] evaluated five patients with ocular toxoplasmosis. This longitudinal study measured serum antibody responses to the retinal S-antigen, a "P" antigen (thought to contain rhodopsin), and new antigen designated $p59^{ag}$, all isolated from bovine retina. They reported that all the patients initially tested showed antibody responses to all three antigens. The anti-S-antigen responses tended to decrease with clinical improvement, while the anti-P antibodies remained high even after the acute attack was over. A more recent report by Whittle and colleagues [26] looked at a larger number of toxoplasmosis patients. In this study a total of 36 patients with toxoplasma retinochoroiditis were evaluated for evidence of anti-retinal antibodies. Thirty-four of these sera showed antibodies directed against the photoreceptor layer of the retina when tested with indirect immunofluorescence. Six of 16 controls showed a similar staining pattern with the p value as reported as < 0.001. Interestingly, using an EIA to measure the presence of anti-S-antigen antibodies, the researchers observed that 27 of 36 sera from toxoplasmosis retinochoroiditis patients were positive, but so were 10 of 16 normals, with a calculated p value of greater than 0.05. The antibodies seen in the two assays did not appear to run in parallel. The author's interpretation of their data was that the extent of anti-retinal antibodies could not be explained by anti-S-antigen findings alone. They argued that these findings probably did not reflect an epiphenomenon since patients with idiopathic retinal vasculitis were also evaluated. In that study the number of sera positive from patients with idiopathic retinal vasculitis was considerably lower than that found in the toxoplasmosis group.

Our group has had the chance to evaluate cell mediated responses of lymphocytes from patients with ocular toxoplasmosis. In a very early study [27] in which we looked at proliferative responses from patients with all kinds of uveitic conditions, we reported that a small number of ocular toxoplasmosis patients' lymphocytes did respond to the uveitogenic retinal S-antigen. In a later study, we evaluated the proliferative cell mediated responses in 40 patients with ocular toxoplasmosis. In addition to the retinal S-antigen, we also evaluated the response to crude toxoplasma antigen and to purified antigens from the parasite [28]. In addition, we performed an EIA to look for anti-S-antigen antibodies and HLA phenotyping to see if a specific HLA type was associated with S-antigen responsiveness. Of the 40 patient's lymphocytes tested, 16 (40%) had proliferative responses with a stimulation index above 2.5 (see Fig. 2). There appeared to be no correlation with this responsiveness and any HLA phenotype. Additionally, we were unable to demonstrate anti-S-antigen antibodies using EIA. The ocular toxoplasmosis patients could be divided by their lymphocytes responsiveness to the various toxoplasma antigens tested. However, no correlation was seen in S-antigen responsiveness and the stimulation index to toxoplasmosis antigens.

5. ONCHOCERCIASIS

Infection with the nematode parasite Onchocerca volvulus can result in severe eye disease, often referred to as river blindness. It is estimated that approximately 18 million people in tropical Africa, the Arabian peninsula and Latin America are infected with the organism and of these, approximately one to two million are blind or have severe visual impairment. Humans are infected with the helminth larvae by the bite of a black fly of the Simulium genus and approximately one year after infection, the adult female worms produce microfilariae. In fact, the adult worm can live for up to 15 years, producing 900 to 1900 microfilariae per day. It is the microfilariae that are able to move through subcutaneous and ocular tissues. When these microfilariae die, they incite an immune response that is associated with clinical symptoms.

5.1. Clinical Features

Onchocerciasis is one of the leading causes of blindness in the developing world. Ocular disease occurring in the anterior segment of the eye consists of corneal opacification and sclerosing keratitis, whereas, ocular disease occurring in the posterior pole is characterized by retinal degeneration [29]. Clinical disease activity in the anterior segment is associated with microfilarial load and it is generally believed that ocular pathology is a result of host directed inflammatory responses to the nematode.

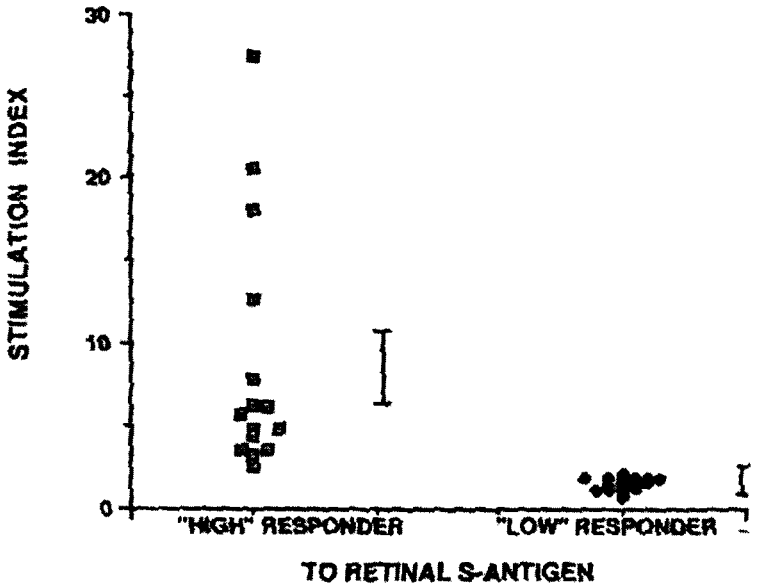

Figure 2. Proliferative responses of peripheral lymphocytes from 40 ocular toxoplasmosis patients to the retinal S-antigen. Sixteen of these had stimulation indices above 2.5 and were designated as "high responders". This responsiveness was not correlated to either a specific HLA phenotype nor the vigor of the cell mediated response to toxoplasma antigens. (Reprinted with permission.)

In contrast, pathology associated with the retina and optic nerve has not been directly linked to microfilarial load.

5.2. Evidence for Autoimmunity

Posterior ocular onchocerciasis is characterized by atrophy of the retinal pigment epithelium and as lesions advance, subretinal fibrosis occurs [30]. A number of studies indicate that this retinal disease process may involve autoimmune responses. In 1987, Chan and associates identified that a majority of onchocerciasis patients had anti-retinal antibodies in their sera and vitreous [31]. Using FA assays on human retina tissue, they observed reactivity in the inner retina and photoreceptor layers. During the 1990's, Braun, McKechnie and associates performed a number of studies to elucidate the nature of the autoimmune reactivity [32–35]. They identified a recombinant antigen in O. volvulus that showed immunologic cross-reactivity with a component of the RPE [32, 33]. By western blot analysis, an antibody to a 22,000 mw antigen (OV39) of O. volvulus recognized a 44,000 mw component of the RPE cell. Subsequent studies have shown that hr 44 Ag is present in the optic nerve, epithelial layers of iris, ciliary body and RPE. Although OV39 and the hr 44 proteins are not homologus, they did show limited amino acid sequence identity [36]. Immunization of Lewis rats with either OV39 from O. volvulus or hr 44 from human retinal tissue, induced ocular pathology [35]. The retinal disease in the rat was characterized by extensive breakdown of the posterior blood-ocular barrier, iridocyclitis and retinitis and the activation of retinal microglia. These studies indicate that, molecular mimicry between O. volvulus and human RPE protein may contribute to the retinopathy found in patients with onchoceriacis.

6. RETINOPATHIES THAT MAY HAVE INFECTIOUS/AUTOIMMUNE ETIOLOGIES (WHITE-DOT SYNDROMES)

A large group of clinical entities have been grouped under the title, White dot syndromes. As the name infers, they are all characterized by whitish lesions of varying sizes that are found strewn throughout the fundus. Some have a significant inflammatory

reaction associated with them while others do not. The natural history of some may lead to significant visual handicap while others may not. Some of these disorders seem to progress while others fade away. The disorders that are included in this list include such entities as acute multifocal placoid posterior pigment epitheliopathy (AMPPE), serpiginous choroiditis, the multifocal evanescent white dot syndrome (MEWDS), and multifocal choroiditis. The underlying cause of these diseases is unknown. Many of these disorders seem to be preceded by a viral illness, and one disorder, AMPPE, was hypothesized to be due to the an Epstein-Barr infection [37]. This concept is no longer thought to be the case [38]. However, a few patients have been treated with anti-viral medications, with unclear responses. The most common therapy for all of these conditions is that of immunosuppression and therapy is directed against what is believed to be an autoimmune, or least non-infectious, process in the back of the eye.

7. SUMMARY

In summary, we have reviewed the evidence that three distinct classes of infectious agents have been implicated in the development of autoimmune processes within the retina. These data also indicate that distinct pathogenic mechanisms are involved in the induction of autoimmunity triggered by these three organisms. In T. gondii infections, the persistence and chronic reactivation of the organism is probably responsible for introduction and presentation of sequestered retinal epitopes to the immune system. In O. volvulus infections, molecular mimicry between the organism and human RPE protein may contribute to the retinal pathology. In ECOR, similar processes are induced in coronavirus-infected mice displaying either retinal degeneration susceptibility or retina degeneration resistance. However, recent evidence indicates that differences in time of induction, in duration and intensity of immune reactivity may contribute to autoimmune reactivity in BALB/c mice.

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