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CHAPTER 57

Infections Associated with Retinal Autoimmunity

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1 INFECTIONS AND AUTOIMMUNITY IN THE RETINA

Autoimmune reactivity and autoimmune disease in the eye is a rapidly expanding area of research and therapy.[1–5] Numerous studies of other body sites revealed clear links between infections and autoimmunity and autoimmune disease.[6,7] However, only a limited number of studies in which retinal disorders were evaluated to study this relationship have been reported. This chapter begins with a brief overview of infection and autoimmunity in the eye, focusing on some of the unique features of the ocular microenvironment. This is followed by specific examples of infections and autoimmunity in the retina. We highlight two human diseases triggered by *Onchocerca volvulus* or *Toxoplasma gondii* and discuss an experimental model of retinal degenerative disease, referred to as experimental coronavirus retinopathy (ECOR). This degeneration is triggered by the murine coronavirus, the mouse hepatitis virus (MHV), and is characterized by genetic predisposition and autoimmune reactivity. Finally, we explore mechanisms by which different infectious agents trigger autoimmune reactivity.

2 THE EYE: INFECTION AND AUTOIMMUNITY

The visual axis is a precious sense. The eye is an organ with known immunologic processes that are driven by both infectious and non-infectious factors. The eye is unique in that it lacks lymphatics and still enjoys an intimate relationship with the immune system. An inflammatory process nor where in the eye is called uveitis, but this term does not reflect the origin of the inflammatory process nor where in the eye it is located. While there are many descriptions of inflammatory processes in the eye, there are three major presentations

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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 and is centered in the retina or the choroid, it is termed a posterior uveitis. Clearly, inflammatory conditions may involve several parts of the eye, and if all anatomic components of the eye are involved, it is termed a panuveitis.

Eye specialists have the distinct 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, which uses a dye injected into a vein in the arm, allows photographs of the retina to be printed. 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 ocular inflammatory response. Most inflammatory processes that we recognize have associated cellular responses. We also know that antibody-mediated pathology, as seen in such entities as cancer-associated retinopathy, can occur but seem to do so in the distinct minority of cases.

The eye is a complex organ from the point of view of the immune system. It is known that an antigen placed into the anterior chamber of the eye induces a deviated immune response, with a marked decrease in cell-mediated responses, but intact cytotoxic and B-cell responses are maintained (1). In addition, the retina is a complicated structure; several layers are needed to turn a light stimulus into a chemical signal that is ultimately sent to the brain. A number of uveitogenic antigens have been identified and characterized at the photoreceptor level and the single layer just below it, that is, the retinal pigment epithelium (RPE) (2). Two antigens in particular, the retinal S-antigen and the inter-photoreceptor binding protein (IRBP), have been used to develop a model of autoimmune ocular disease, called experimental autoimmune uveoretinitis (3). This model has many qualities of the disease observed in humans, and it has enhanced our understanding of the underlying mechanisms that lead to disease. One major difference between this model and human disease is, of course, that it is not spontaneous. It is not clear what triggers the human disease. This chapter explores one such trigger–ocular infection. Several entities, some based on animal models, others seen in the clinic, are discussed to elucidate the possible role between infection and autoimmunity.

3 EXPERIMENTAL CORONAVIRUS RETINOPATHY

ECOR is an animal model system that we generated in the 1990s to demonstrate that a virus can trigger a progressive retinal degenerative disease.[8] Studies during the past 20 years have identified that this degenerative eye disease is composed of three basic components: a virus component, a genetic component, and a immunologic component.[9,10] In our system, we selected a naturally occurring neurotrophic strain (JHM) of MHV that infects and persists within the retina. The virus causes an acute infection marked by virus replication in distinct retinal cells, and the production of both neutralizing antibody and cytokines. This disease also has a genetic component. Different strains of mice, such as BABL/c and CD-1, were extensively studied after coronavirus infection. During the early phase of the disease (days 1–8) the virus infects and replicates within the retina of both BALB/c and CD-1 mouse strains.[11] However, only the BALB/c mice experience a late phase of the disease (days 10–140) that is marked by a retinal degeneration. CD-1 mice do not undergo the retinal degenerative phase; rather, the retina returns to a normal architecture within 20 days.

Finally, this disease is characterized by the presence of autoantibodies, specifically anti-retinal and anti-RPE antibodies. The presence of these antibodies is observed only in the BALB/c mice susceptible to retinal degeneration. These autoantibodies are absent in the CD-1 mice resistant to retinal degeneration. In summary, ECOR is a virus-triggered retinal degenerative disease that is influenced by both genetics and immune response. In the following sections we 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 among livestock, poultry, and laboratory rodents. Until recently, man was known to be infected with two strains of coronavirus. Either of these strains is responsible for approximately 50% of the incidence of the common cold. A new human coronavirus was discovered 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 MHV. The JHM strain of MHV is the most thoroughly studied neurotrophic coronavirus. It causes both acute and chronic central nervous system (CNS) effects in mice and rats. Acute

encephalomyelitis and chronic CNS disease have been observed in mice, whereas an autoimmune disease known as subacute demyelinating encephalomyelitis has been described in rats.

Initial studies of 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.[9,10] Infectious virus could be detected within the retina between 1 and 6 days post-inoculation (PI), reaching a peak level of $10^{4.5}$ plaque-forming units/mL at day 3.[13] Virus antigen also was identified within the retina between days 2 and 6 PI.[10] On day 2, virus antigen was first detected within the RPE cells and the ciliary body epithelial cells, and this virus replication intensified at days 3 and 4. Between days 3 and 6, virus antigen also was detected in Müller-like cells that span the multiple layers of the neural retina. Virus antigen was occasionally observed within the ganglion cells. After day 7, infectious virus and viral antigen could not be detected anywhere within the retina. However, in situ hybridization studies identified that the viral RNA persisted within the retina until 60 days PI.[14] Antivirus 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 the JHM virus, two distinct patterns of retinal pathology were noted in the BALB/c mice.[10] The early phase of the disease was characterized by retinal vasculitis and perivasculitis. The late phase of the disease was marked 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. Analysis of retinal cell function also revealed dramatic changes.[15,16] There was a significant decrease in or complete loss of electroretinogram patterns and the disappearance of an important transport protein in the retina, 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.[17] Macrophages were the most prominent infiltrating cells, followed by T cells (CD4 and CD8). During the course of the disease, cytokine profiles were studied by assessing retina tissue and sera.[17] On day 4, cytokine retinal gene expression and serum protein expression revealed the presence of

IL-6, interferon (IFN-γ), and tumor necrosis factor (TNF-α) in retinas infected with the virus. The presence of IFN-γ also was associated with an up-regulation of MHC class I and II molecules on a variety of retinal cells. In contrast, 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 infection in vivo and is persistently infected in vitro.[18] 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 it is up-regulated to express MHC class II molecules during retinal autoimmune and degenerative processes.[19,20]

3.4 Innate Immunity is a Key Factor

We next examined very early cytokine and chemokine profiles as a measure of the intensity of immune reactivity in mice infected with coronavirus. These studies identified a distinct difference in the early innate immune response between the susceptible and resistant mouse strains.[21] These differences are noted in the production of IFN-γ and the two chemokines triggered by IFN-γ: *CXCL9* and *CXCL10*. For example, on day 2 and 3 PI, the BALB/c mice have high levels of IFN-γ, *CXCL9* and *CXCL10* in their sera. At the same time, significantly lower levels of these molecules are detected in the sera from CD-1 mice. Moreover, real-time PCR analysis of retinas confirmed that *CXCL9* and *CXCL10* gene expression is significantly greater in the BALB/c mice retinas compared with CD-1 mice retinas. *CXCL9* and *CXCL10* interact with *CXCR3*, which is present on activated T cells and natural killer (NK) cells, and they direct the migration of these cells to specific targets, such as the retina.[22] These studies underscore an important concept: that innate immunity directs and sets the stage for adaptive immunity. In this model system, we describe how the robust immune response in the BALB/c mouse could trigger an autoimmune component.

3.5 Genetic Factors in ECOR

The genetic constitution of the host can be a critical factor in determining the outcome of a virus infection.[11] We therefore evaluated the possible role of host genetics in ECOR. We inoculated selected strains of mice (BABL/c, C57B1, A/J, and CD-1) and examined the retinal disease. When C57B1 and A/J mice were evaluated, we observed a disease pattern similar to that

Table 1 Retinal Inflammation and Retinal Degeneration in Mice Inoculated with Coronavirus (JHM Strain)

		BALB/c Mice		CD-1 Mice	
Retinal Disease	**Days**	**Positive/ Tested (*n*)**	**%**	**Positive/ Tested (*n*)**	**%**
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

observed in the BALB/c mice. However, retinal tissue damage induced by the JHM virus in the 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 retinal degenerative disease. In fact, by day 20 PI, the retina had a normal appearance. These studies underscore the role of genetics in ECOR and showed that the genetics of the host profoundly affects the nature of retinal tissue damage.

Since the CD-1 mice did not exhibit the late retinal degenerative phase of the disease, we studied a variety of parameters and compared these findings with the data obtained from BALB/c mice. For example, during the acute phase of the disease, viral load in the retina, production of anti-virus antibody, breakdown of the blood–retina barrier, lymphoid trafficking and MHC class I and II staining were similar in both mouse strains. Only in the late phase of the disease did the two mouse strains show significant differences: one group (BALB/c mice) displayed a retinal degeneration with blood–retina barrier breakdown, and the other (CD-1 mice) showed a normal retinal architecture.

3.6 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 known to trigger autoimmune phenomena and some human retinopathies may be associated with autoantibody formation, we studied the possible production

Table 2 Anti-Retinal Antibody Production and Retinal Degeneration in Coronavirus-Inoculated Mice

Mouse	Treatment	Autoantibody in Retinal Tissue Positive/Tested (*n*)	Retinal Degeneration Positive/Tested (*n*)
BALB/c	Untreated	0/20	0/20
	Mock injection	0/15	0/15
	JHM virus	22/22	22/22
CD-1	Untreated	0/15	0/15
	Mock injection	0/15	0/15
	JHM virus	0/20	0/20

of anti-retinal autoantibodies.[23] We found that the degenerative process in the BALB/c mice was associated with the presence of anti-retinal autoantibodies (Table 2). These autoantibodies were not found in sera from normal or mock-injected mice. Furthermore, the CD-1 mice that developed an immune response in the acute disease did not develop autoantibodies.

The presence of antibodies to retinal tissue was evaluated by immunoperoxidase staining of frozen sections of normal rat eyes. Two patterns of staining were observed in the BALB/c mice: reactivity in the neural retinal and reactivity in the RPE. The anti-retinal autoantibodies first appeared as IgM class antibodies. This was later replaced by IgG class autoantibodies. The anti-RPE cell autoantibodies were predominantly of the IgG class. Therefore, those mice that failed to develop anti-retinal autoantibodies also failed to develop retinal degeneration (Table 2). These findings suggest a role for autoimmunity in the pathogenesis of ECOR.

Our latest approach towards better understand this disease process was the development of an autoantigen discovery programme. Using a mouse RPE cDNA library, we identified two retinal autoantigens, α-fodrin and villin 2, in ECOR. α-Fodrin is found in the cytoplasm of cell bodies in inner nuclear layer (INL) and retinal ganglion cell (RGC) and on the apical surface of the RPE. Villin-2 is found in both RPE cells and Müller cells. A truncated form of α-fodrin was expressed and purified. This purified α-fodrin reacted only with sera from virus-infected BALB/c mice. Moreover, CD4 T cells from virus-infected BALB/c mice specifically responded to α-fodrin peptide. These data suggest that both antibodies to α-fodrin and CD4 T cells specifically sensitized to α-fodrin may contribute to the retinal degeneration seen in the ECOR susceptible mice. It is of interest to note that autoantibodies to α-fodrin have been observed in three human diseases: glaucoma, Alzheimer's disease, and Sjögren's syndrome.

4 TOXOPLASMOSIS (*T. GONDII*)

Toxoplasmosis is a disorder that has a worldwide distribution. It is caused by the obligate intracellular parasite *T. gondii*. Over 500 million people are believed to have the disease. The organism was first described in the brain of gondii, a North African rodent, by Nicolle and Manceaux[24] in 1908 and in a rabbit by Splendore.[25] The first connection between this organism and human disease was made by Janku,[26] who described the presence of the organism in a child who died of disseminated toxoplasmosis. While suspected for a long period, it was not until the early 1950s 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.[27] It is interesting to note that a similar observation has been made more recently in Nepal, where many cases of ocular tuberculosis have been re-diagnosed as toxoplasmosis of the eye.

The cat (and perhaps related species) seems to be the definitive host of *T. gondii*. The sexual cycle is one of schizogony and gametogony, leading to 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 organisms can be found in man: cysts and tachyzoites. The tachyzoites (the proliferative intracellular form) are believed to be the cause of most tissue damage in humans, although often it is very difficult to demonstrate the presence of this 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 also are found in skeletal muscle and heart. It is assumed that attacks occur with rupture of the cysts, leading to a release of bradyzoites and then the conversion of the brayzoites to tachyzoites. The mechanisms that lead to cyst rupture are still unknown.

4.1 Clinical Features

While the hallmark of the disease is distinct, changes in the posterior portion and the front of the eye also are noted. 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. In addition, there is a loss of pigment in the iris that can be observed, and this is associated with changes in the back of

the eye.[28] This finding, termed Fuchs 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 infecting all the layers of the retina and frequently many layers of the choroid. 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; these are called satellite lesions. In addition to the lesion itself, evidence of retinal vascular leakage is seen during the active stage of the disease. It has been hypothesized that this vasculitis is caused by an immune complex-related phenomenon.

While stigmata of the disease may be present in both eyes, recurrences of the disorder typically occur only in one eye. In addition, while reactivation of the disease is believed to be 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 acquired immunodeficiency virus, often have bilateral disease and multiple lesions, suggesting a different mechanism in these patients compared to immunocompetent patients.

4.2 Evidence for Autoimmunity

A longitudinal study of patients with ocular toxoplasmosis by Abrahams and Gregerson[28] evaluated serum antibody responses to three retinal antigens. They tested the retinal S-antigen, a "P" antigen (thought to contain rhodopsin) and a new antigen designated p59ag. 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, whereas the anti-P antibodies remained high even after resolution of the acute attack. A more recent report by Whittle and colleagues[29] looked at a larger number of patients with toxoplasmic retinochoroiditis. Using indirect immunofluorescence, they reported that 34 of 36 sera samples showed antibodies directed against the photoreceptor later of the retina. However, 6 of 16 controls showed a similar staining pattern ($p < 0.001$). Interestingly, using an enzyme immunoassay (EIA) to measure the presence of anti-S-antigen antibodies, the researchers observed that 27 of 36 sera samples from patients with toxoplasmosis retinochoroiditis were positive, but so were those from 10 of 16 normal individuals ($p > 0.05$). The antibodies seen in the two assays did not seem to run in parallel.

Our group and others have had the chance to evaluate cell-mediated responses of lymphocytes from patients with ocular toxoplasmosis. In an

early study in which we examined proliferative responses from patients with various uveitic conditions, we reported that a small number of lymphocytes from patients with ocular toxoplasmosis did respond to the uveitogenic retinal S-antigen.[30] 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.[31] We also used EIA to look for anti-S-antigen antibodies and investigated HLA phenotyping to determine whether 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 (Figure 1). There seemed to be no correlation with this responsiveness and any HLA phenotype. In addition, we were unable to demonstrate anti-S-antigen antibodies using EIA. The patients with ocular toxoplasmosis 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.

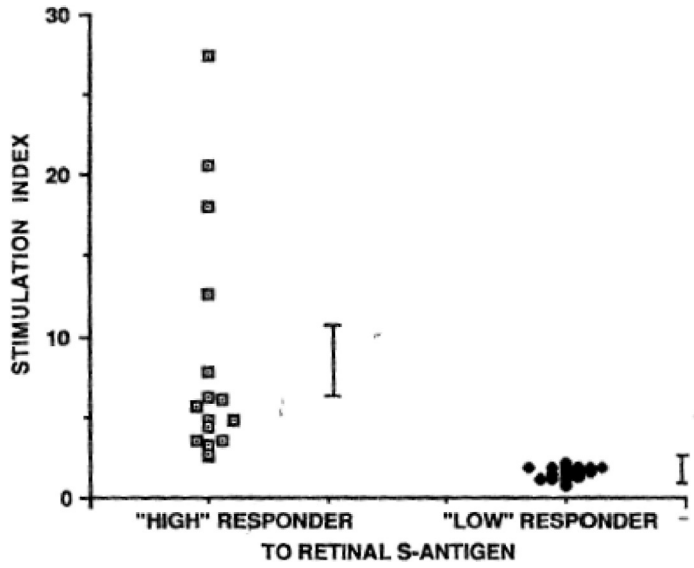

Figure 1 Proliferative responses of peripheral lymphocytes from 40 patients with ocular toxoplasmosis to the retinal S-antigen. Sixteen of these had stimulation indices above 2.5 and were designated as "high responders". This responsiveness was not correlated to either a specific HLA phenotype nor the vigor of the cell-mediated response to *Toxoplasma* antigens. *Reprinted with permission.*

A study by Vallochi et al.[32] in Brazil introduced an interesting interpretation of autoimmune reactivity in *Toxoplasma* infections. Three different retinal antigens were used to stimulate peripheral blood leukocytes (PBLs) from normal individuals, patients with mild ocular disease and patients with severe ocular disease. They found that patients with mild disease responded to one or more retinal antigens with a significantly higher frequency than patients without disease or with severe disease. Based on these findings, they suggested that the presence of cellular immune response towards retinal autoantigens is not protective against the development of ocular lesions induced by *T. gondii*, but it may protect against the development of severe disease. Autoimmune responses may protect the neural retina against the damage caused by infection with *T. gondii*. This protective effect may occur by providing the local cells with cytokines and growth factors that protect retinal cells and limit *T. gondii* replication.

5 ONCHOCERCIASIS

Infection with the nematode parasite *O. 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 1–2 million are blind or have severe visual impairment. Humans are infected with the helminth larvae by the bite of a black fly from the *Simulium* genus; approximately 1 year after infection, the adult female worms produce microfilariae. In fact, the adult worm can live for up to 15 years, producing 900–1900 microfilariae per day. It is the microfilariae that are able to move through subcutaneous and ocular tissues. When these microfilaria 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.[33] 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. 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 RPE, and as lesions advance, subretinal fibrosis occurs.[34] A number of studies indicate that this retinal disease process may involve autoimmune responses. In 1987, Chan and associates[35] identified that a majority of patients with onchocerciasis had anti-retinal antibodies in their sera and vitreous. Using an immunofluorescent assay of human retina tissue, they observed reactivity in the inner retina and photoreceptor layers. During the 1990s, researchers performed a number of studies to elucidate the nature of autoimmune reactivity.[36–39] They identified a recombinant antigen in *O. volvulus* that showed immunologic cross-reactivity with a component of the RPE.[36,37] Using Western blot analysis, an antibody to a 22,000-molecular weight antigen (OV39) of *O. volvulus* recognized a 44,000-molecular weight component of the RPE cell. Subsequent studies showed that hr44 antigen is present in the optic nerve, epithelial layers of iris, ciliary body, and RPE. Although OV39 and the hr44 proteins are not homologous, they did show limited amino acid sequence identity.[40] Immunization of Lewis rats with either OV39 from *O. volvulus* of hr44 from human retinal tissue induced ocular pathology.[39] 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 onchocerciasis.

Saint André and colleagues[41] recently proposed that the predominant inflammatory response seen in the cornea of *Onchocerca*-infected animals is really directed against the endosymbiont of *Onchocerca*, *Wolbachia*. Parasite antigens and *Wolbachia* endotoxin or endotoxin-like molecules are released into the ocular microenvironment and bind to Toll-like receptor (TLR4) on stromal fibroblasts. TLR4 activation stimulates the production of neutrophil chemokines and pro-inflammatory cytokines, leading to enhanced inflammation.[42]

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 scattered throughout the fundus. Some patients have a significant associated inflammatory reaction, whereas others do not. The natural history of some may lead to significant visual handicap,

whereas others may not. Some of these disorders seem to progress, yet others fade away. These disorders include such entities as acute multifocal placoid posterior pigment epitheliopathy (AMPPE), serpiginous choroiditis, the multifocal evanescent white dot syndrome, and multifocal choroiditis. The underlying cause of these diseases is unknown. Many of these disorders seem to be preceded by a viral illness, and AMPPE, was hypothesized to be due to Epstein–Barr virus infection;[43] however, this concept is no longer thought to be the case.[44] A few patients have been treated with anti-viral medications, with unclear responses. The most common therapy for all of these conditions is 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

We have reviewed the evidence implicating three distinct classes of infectious agents in the development of an autoimmune process 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 the 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 susceptibility or resistance to retinal degeneration. However, recent evidence indicates that differences in time of induction, duration, and intensity of innate immune reactivity may contribute to autoimmune reactivity in BALB/c mice.

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REFERENCES

1. Stein-Streilein J, Streilein JW. Anterior chamber associated immune deviation (ACAID): regulation, biological relevance, and implications for therapy. *Int Rev Immunol* 2002;**21**(2–3):123–52.
2. Nussenblatt RB, Whitcup S. *Fundamentals. Uveitis. Fundamentals and clinical practice.* Philadelphia, PA: W.B. Saunders; 2004, pp. 1–46.
3. Caspi RR. Understanding autoimmune uveitis through animal models. The Friedenwald Lecture. *Invest Ophthalmol Vis Sci* 2011;**52**:1872–9.

4. Forooghian F, MacDonald IM, Heckenlively JR, Heon E, Gordon LK, Hooks JJ, et al. The need for standardization of antiretinal antibody detection and measurement. *Am J Ophthalmol* 2008;**146**(4):489–95.
5. Hooks JJ, Tso MOM, Detrick B. Retinopathies associated with antiretinal antibodies. *Clin Diagn Lab Immunol* 2001;**8**(5):853–8.
6. Fujinami RS, Oldstone MB. Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity. *Science* 1985;**230** (4729):1043–5.
7. Rose NR. The role of infection in the pathogenesis of autoimmune disease. *Semin Immunol* 1998;**10**(1):5–13.
8. Detrick B, Hooks JJ. Immune regulation in the retina. *Immunol Res* 2010;**47** (1–3):153–61.
9. Robbins SG, Detrick B, Hooks JJ. Ocular tropisms of murine coronavirus (strain JHM) after inoculation by various routes. *Invest Ophthalmol Vis Sci* 1991;**32**(6):1883–93.
10. Robbins SG, Hamel CP, Detrick B, Hooks JJ. Murine coronavirus induces an acute and long-lasting disease of the retina. *Lab Invest* 1990;**62**(4):417–26.
11. Wang Y, Burnier M, Detrick B, Hooks JJ. Genetic predisposition to coronavirus-induced retinal disease. *Invest Ophthalmol Vis Sci* 1996;**37**(1):250–4.
12. Holmes KV. SARS-associated coronavirus. *N Engl J Med* 2003;**348**(20):1948–51.
13. Wang Y, Detrick B, Yu ZX, Zhang J, Chesky L, Hooks JJ. The role of apoptosis within the retina of coronavirus-infected mice. *Invest Ophthalmol Vis Sci* 2000;**41**(10):3011–18.
14. Komurasaki Y, Nagineni CN, Wang Y, Hooks JJ. Virus RNA persists within the retina in coronavirus-induced retinopathy. *Virology* 1996;**222**(2):446–50.
15. Robbins SG, Wiggert B, Kutty G, Chader GJ, Detrick B, Hooks JJ. Redistribution and reduction of interphotoreceptor retinoid-binding protein during ocular coronavirus infection. *Invest Ophthalmol Vis Sci* 1992;**33**(1):60–7.
16. Vinores SA, Wang Y, Vinores MA, Derevjanik NL, Shi A, Klein DA, et al. Blood-retinal barrier breakdown in experimental coronavirus retinopathy: association with viral antigen, inflammation, and VEGF in sensitive and resistant strains. *J Neuroimmunol* 2001;**119** (2):175–82.
17. Hooks JJ, Wang Y, Detrick B. The critical role of IFN-gamma in experimental coronavirus retinopathy. *Invest Ophthalmol Vis Sci* 2003;**44**(8):3402–8.
18. Wang Y, Detrick B, Hooks JJ. Coronavirus (JHM) replication within the retina: analysis of cell tropism in mouse retinal cell cultures. *Virology* 1993;**193**(1):124–37.
19. Detrick B, Rodrigues M, Chan CC, Tso MO, Hooks JJ. Expression of HLA-DR antigen on retinal pigment epithelial cells in retinitis pigmentosa. *Am J Ophthalmol* 1986;**101** (5):584–90.
20. Percopo CM, Hooks JJ, Shinohara T, Caspi R, Detrick B. Cytokine-mediated activation of a neuronal retinal resident cell provokes antigen presentation. *J Immunol* 1990;**145** (12):4101–7.
21. Detrick B, Lee MT, Chin MS, Hooper LC, Chan C-C, Hooks JJ. Experimental coronavirus retinopathy (ECOR): retinal degeneration susceptible mice have an augmented interferon and chemokine (CXCL9, CXCL10) response early after virus infection. *J Neuroimmunol* 2008;**193**(1–2):28–37.
22. Hooks JJ, Nagineni CN, Hooper LC, Hayashi K, Detrick B. IFN-beta provides immuno-protection in the retina by inhibiting ICAM-1 and CXCL9 in retinal pigment epithelial cells. *J Immunol* 2008;**180**(6):3789–96.
23. Hooks JJ, Percopo C, Wang Y, Detrick B. Retina and retinal pigment epithelial cell autoantibodies are produced during murine coronavirus retinopathy. *J Immunol* 1993;**151**(6):3381–9.
24. Nicolle C, Manceaux L. Sur Une infection a corps de Leishman (ou organismes voisins) due Gondii. *C R Biol* 1908;**147**:763–6.

25. Splendore A. Un nuovo protozoa parassita dei conigli: incontrato nell lesioni anatomiche d'une malattia che ricorda in molti punti kala-azar dell'uomo. *Rev Soc Sci* 1908;**3**:109–12.
26. Janku J. Pathogenesis and pathologic anatomy of coloboma of macula lutea in eye of normal dimensions, and in microphthalmic eye, with parasites in the retina. *Cas Lek Cesk* 1923;**62**:1021–7.
27. Holland GN, Lewis KG, O'Connor GR. Ocular toxoplasmosis: a 50th anniversary tribute to the contributions of Helenor Campbell Wilder Foerster. *Arch Ophthalmol* 2002;**120**(8):1081–4.
28. Abrahams IW, Gregerson DS. Longitudinal study of serum antibody responses to retinal antigens in acute ocular toxoplasmosis. *Am J Ophthalmol* 1982;**93**:224–31.
29. Whittle RM, Wallace GR, Whiston RA, Dumonde DC, Stanford MR. Human antiretinal antibodies in toxoplasma retinochoroiditis. *Br J Ophthalmol* 1998;**82**(9):1017–21.
30. Nussenblatt RB, Gery I, Ballintine EJ, Wacker WB. Cellular immune responsiveness of uveitis patients to retinal S-antigen. *Am J Ophthalmol* 1980;**89**(2):173–9.
31. Nussenblatt RB, Mittal KK, Fuhrman S, Sharma SD, Palestine AG. Lymphocyte proliferative responses of patients with ocular toxoplasmosis to parasite and retinal antigens. *Am J Ophthalmol* 1989;**107**(6):632–41.
32. Vallochi AL, da Silva Rios L, Nakamura MV, Silveira C, Muccioli C, Martins MC, et al. The involvement of autoimmunity against retinal antigens in determining disease severity in toxoplasmosis. *J Autoimmun* 2005;**24**(1):25–32.
33. Hall LR, Pearlman E. Pathogenesis of onchocercal keratitis (river blindness). *Clin Microbiol Rev* 1999;**12**(3):445–53.
34. Abiose A. Onchocercal eye disease and the impact of Mectizan treatment. *Ann Trop Med Parasitol* 1998;**92**(Suppl. 1):S11–22.
35. Chan CC, Ottesen EA, Awadzi K, Badu R, Nussenblatt RB. Immunopathology of ocular onchocerciasis. I. Inflammatory cells infiltrating the anterior segment. *Clin Exp Immunol* 1989;**77**(3):367–72.
36. Braun G, McKechnie NM, Connor V. Immunological crossreactivity between a cloned antigen of *Onchocerca volvulus* and a component of the retinal pigment epithelium. *J Exp Med* 1991;**174**(1):169–77.
37. McKechnie NM, Braun G, Kläger S, Connor V, Kasp E, Wallace G, et al. Cross-reactive antigens in the pathogenesis of onchocerciasis. *Ann Trop Med Parasitol* 1993;**87**(6):649–52.
38. McKechnie NM, Braun G, Connor V, Kläger S, Taylor DW, Alexander RA, et al. Immunologic cross-reactivity in the pathogenesis of ocular onchocerciasis. *Invest Ophthalmol Vis Sci* 1993;**34**(10):2888–902.
39. McKechnie NM, Gürr W, Braun G. Immunization with the cross-reactive antigens Ov39 from *Onchocerca volvulus* and hr44 from human retinal tissue induces ocular pathology and activates retinal microglia. *J Infect Dis* 1997;**176**(5):1334–43.
40. Braun G, McKechnie NM, Gürr W. Molecular and immunological characterization of hr44, a human ocular component immunologically cross-reactive with antigen Ov39 of *Onchocerca volvulus*. *J Exp Med* 1995;**182**(4):1121–31.
41. Saint André A, Blackwell NM, Hall LR, Hoerauf A, Brattig NW, Volkmann L, et al. The role of endosymbiotic Wolbachia bacteria in the pathogenesis of river blindness. *Science* 2002;**295**(5561):1892–5.
42. Hise AG, Gillette-Ferguson I, Pearlman E. Immunopathogenesis of *Onchocerca volvulus keratitis* (river blindness): a novel role for TLR4 and endosymbiotic Wolbachia bacteria. *J Endotoxin Res* 2003;**9**(6):390–4.
43. Tiedeman JS. Epstein-Barr viral antibodies in multifocal choroiditis and panuveitis. *Am J Ophthalmol* 1987;**103**(5):659–63.
44. Spaide RF, Sugin S, Yannuzzi LA, DeRosa JT. Epstein–Barr virus antibodies in multifocal choroiditis and panuveitis. *Am J Ophthalmol* 1991;**112**(4):410–13.