Retinopathies Associated with Antiretinal Antibodies

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Retinopathies Associated with Antiretinal Antibodies

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MINIREVIEWS

The identification of autoantibodies during the course of a disease has been shown to be useful in making a diagnosis, understanding mechanisms of pathogenesis, identifying therapeutic strategies, and monitoring treatments. Numerous examples of the utility of autoantibody detection are seen in both systemic and organ-specific diseases. 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. The maintenance of self-tolerance within the retina may be overcome by a combination of factors, including both genetic and environmental factors. In this review we highlight retinopathies that are associated with the presence of antiretinal antibodies.

We should stress that we are not inferring that all of the antiretinal antibodies described in this review are actually inducing ocular disease. Rather, we wish to highlight the concept that one may utilize sera to identify immune reactivity in the posterior segment of the eye. The detection of autoantibodies may allow one to subtype the disease according to its autoantibody profile. This process may help to define specific subgroups of retinopathies in terms of pathogenesis and therapy. When there is immune-mediated retinal damage, it may result from a combination of factors, such as antibodies, activation of T cells and macrophages, and cytokine production. In fact, cytokines, chemokines, and adhesion molecules produced by infiltrating and ocular resident cells may contribute significantly to ocular tissue damage.

A variety of human and experimental retinopathies are associated with the production of antiretinal antibodies. As is shown in Table 1, these retinopathies can be categorized into three groups: (i) visual paraneoplastic disorders, frequently referred to as cancer-associated retinopathies (CAR), (ii) infection-associated retinopathies and (iii) retinal degenerative disorders.

**VISUAL PARANEOPlastic DISORDERS**

Visual paraneoplastic disorders are observed in several malignancies (Table 2). The CAR syndrome is a retinal paraneoplastic disorder most commonly associated with small-cell carcinoma of the lung. Melanoma-associated retinopathy (MAR) can occur in patients with cutaneous melanoma.

**CAR.** CAR is most commonly associated with small-cell carcinoma of the lung, but it has also been less frequently reported in patients with breast, endometrial, and other cancers (26, 42, 49, 52). In these patients, antibodies develop with reactivity to the retina, and this response is associated with rod and cone dysfunction. Visual loss occurs over months and may even precede the identification of the malignancy. This association between progressive blindness as a remote effect of cancer was first reported in 1976 (48). Subsequent studies have shown that autoimmune mechanisms in cancer-induced blindness may be operative since patients with antiretinal, anti-photoreceptor cell antibodies responded to corticosteroids (22, 28).

During the past two decades, Thirkill and Keltner have been on the forefront of identifying antiretinal antibodies in CAR (J. L. Keltner and C. E. Thirkill, Editorial, Am. J. Ophthalmol. 126:296–302 [Erratum 126:866], 1998). Analysis of autoantibodies by immunofluorescent antibody (FA) assays using retinal sections demonstrates reactivity to the photoreceptor outer segments and ganglion cells of the retina. Analysis of retinal antigens has revealed that a variety of antigens may be involved in this process. The primary antigens identified are a 23-kDa antigen (recoverin), a retinal enolase (46 kDa), and a group of reactivities with retinal antigens identified as a 40-, 43-, and 60-kDa molecules. A recent study has identified a Tubby-like protein 1 (TULP1) as an autoantigen in CAR (24). Although over 15 retinal antigens have been described in the CAR syndrome, the most common antigen linked to CAR is the 23-kDa recoverin, a calcium-binding protein found in both rods and cones (2, 44, 53, 54).

The identification of antiretinal reactivity in CAR syndrome is important both in terms of therapy and the ability to monitor disease progression. Treatments for CAR syndrome include anticancer therapy, prednisone, plasmapheresis, and intravenous immunoglobulin (17). We should point out that spontaneous recovery of vision in this disease has not been reported. In some instances the administration of steroids and antilymphocytic serum has resulted in improvement in visual function (17, 23). A review of the literature has shown that, following corticosteroid treatment, 10 of 16 patients (62%) recovered visual function (17). It is generally believed that if immunosuppressive treatment is begun early in the course of the degenerative process, visual improvement or stabilization may be achieved. However, therapy is not likely to be beneficial once widespread retinal degeneration has occurred (Keltner and Thirkill, Editorial).
Antiretinal antibodies are initially identified with an immunofluorescence assay on retinal tissue. This can be followed by a confirmatory assay such as Western blot and enzyme-linked immunosorbent assay. Monitoring the level of antiretinal antibodies during immunosuppressive therapy has been tested. At least five case reports have demonstrated a decrease in antiretinal autoantibodies in patients with CAR who recovered visual function following various forms of immunosuppressive treatment (13, 17, 23, 35, 52). Clearly, additional studies are needed to carefully evaluate fluctuations of the antibody titer during the course of the disease and during treatment. Multicenter studies should be initiated to share sera and clinical information in order to determine if antibody profiles can be used as a marker to start, continue, and discontinue treatment.

The CAR syndrome is probably the most extensively studied blinding disease that is associated with antiretinal antibodies. The most common, but not the only antigen, is the 23-kDa recoverin. It has been reported that the malignant cells in small-cell carcinoma are induced to express recoverin (51, 55). McGinnis et al. suggested that a mutational event inactivating the murine coronavirus, mouse hepatitis virus (MHV) (Table 3). Experimental coronavirus retinopathy (ECOR), triggered by Toxoplasma gondii and an experimental model referred to as 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 Africa and in Central and South America are infected with the organism and, of these, approximately one million are blind or have severe visual impairment. Ocular disease occurring in the anterior segment of the eye consists of receptors and bipolar cells was observed (3). Both in vitro and in vivo studies demonstrated that anti-recoverin antibody triggered apoptosis only in recoverin-positive cells. These studies suggest that antibody-mediated degeneration of photoreceptors can occur through apoptotic mechanisms (60).

MAR. A second paraneoplastic syndrome identified as MAR occurs in patients with cutaneous melanoma. Progressive visual loss develops over months and is frequently associated with metastatic melanoma. The electroretinogram (ERG) in these patients is characterized by a reduction of the photopic b-wave and scotopic b-wave. These ERG changes correspond to a functional defect in retinal ON-pathway responses involving depolarizing bipolar cells. Patients with MAR do not develop antibody reactivity to recoverin as was seen in the CAR syndrome (6, 25, 57). Antibodies in MAR patients react with bipolar cells and their dendrites in the outer plexiform layer of the retina (34). A recent work by Lei et al. demonstrated that the intravitreal injection of MAR immunoglobulin G into monkey eyes resulted in the alteration of monkey ERG patterns consistent with changes observed in bipolar cells (29).

Clinical and experimental observations in CAR and MAR probably provide the best evidence for a pathologic role of self-reactive antibodies in human retinopathies. First, CAR and MAR patients suffer from a retinopathy which is characterized by retinal tissue damage and the presence of antiretinal antibodies. Second, some of these patients respond to plasma exchange and immunosuppressive therapy. Third, retinal cell damage can be induced by the self-reactive antibodies in vitro, and there is evidence of passive transfer of disease to animals.

### Infection-Associated Retinopathies

The second group of retinopathies associated with antiretinal antibodies is retinal disorders that are triggered by an infectious agent. Numerous studies in other body sites have clearly identified links between infections and autoimmunity and autoimmune disease (14, 47). Only a limited number of studies of retinal disorders have been performed. 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) (Table 3).

**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 Africa and in Central and South America are infected with the organism and, of these, approximately one million are blind or have severe visual impairment. Ocular disease occurring in the anterior segment of the eye consists of

### Table 1. Retinopathies associated with antiretinal antibodies

| Retinopathy                                      | Malignancy                                      |
|-------------------------------------------------|------------------------------------------------|
| Visual paraneoplastic disorders                 | Small-cell carcinoma of the lung; less frequently in breast and endometrial cancer |
| Infection-associated retinopathies              | Toxoplasmosis (*T. gondii*)                     |
| Retinal degenerative disorders                  | Marburg neuroretinopathy                        |
| Idiopathic retinopathies                        | Idiopathic retinopathy                          |
| Neurological diseases (Stiff-man syndrome)       | Small-cell carcinoma of the lung; less frequently in breast and endometrial cancer |

### Table 2. Characterization of antiretinal antibodies detected in patients with visual paraneoplastic disorders

| Visual paraneoplastic disorder | Malignancy                                      | Antibody detection                                      |
|--------------------------------|-------------------------------------------------|---------------------------------------------------------|
| CAR                            | Small-cell carcinoma of the lung; less frequently in breast and endometrial cancer | Immunoblot: recoverin (23 kDa), retinal enolase, other (40, 45, and 60 kDa), TULP1 |
| MAR                            | Cutaneous melanoma                              | FA: photoreceptor outer segment; TULP1 (40, 45, and 60 kDa) |

The above tables summarize the characteristics of antiretinal antibodies detected in patients with visual paraneoplastic disorders.
TABLE 3. Characterization of antiretinal antibodies detected in patients with infection-associated retinopathies

| Disease       | Infectious agent | Antibody detection                                      |
|---------------|------------------|---------------------------------------------------------|
| Toxoplasmosis | *T. gondii*      | FA: photoreceptor layer                                 |
| Onchoderciasis| *O. volvulus*    | FA: RPE, neural retina                                  |
| ECOR          | MHV              | Cross-reaction between onchocercal antigen (OV39) and human retinal antigen (hr44) |

Corneal opacification and sclerosing keratitis, whereas ocular disease occurring in the posterior pole is characterized by retinal degeneration (18). It is generally believed that ocular pathology is a result of host-directed inflammatory responses to the nematode.

Posterior ocular onchoderciasis is characterized by atrophy of the retinal pigment epithelium (RPE) and, as lesions advance, subretinal fibrosis occurs (1). A number of studies indicate that this retinal disease process may involve autoimmune responses. In 1987, Chan et al. found that a majority of onchoderciasis patients had antiretinal antibodies in their sera and vitreous (10). Using FA assays on human retinal tissue, Chan et al. observed reactivity in the inner retina and photoreceptor layers. During the 1990s, Braun and associates performed a number of studies to elucidate the nature of the autoimmune reactivity (7, 31–33). These authors identified a recombinant antigen in *O. volvulus* that shows immunologic cross-reactivity with a component of the RPE (7, 31). By Western blot analysis, an antibody to a 22,000-molecular-weight (MW) antigen (OV39) of *O. volvulus* recognizes a 44,000-MW component of the RPE cell. Subsequent studies have shown 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 (8). Immunization of rats with either OV39 from *O. volvulus* or hr44 from human retinal tissue induced ocular pathology and activation of retinal microglia (33). This was also associated with extensive breakdown of the posterior blood-ocular barrier. These studies indicate that molecular mimicry between *O. volvulus* and the human RPE protein may contribute to the retinopathy found in patients with onchoderciasis.

**Toxoplasmosis.** It is estimated that the protozoan parasite, *T. gondii*, infects 500 million humans worldwide. *T. gondii* is also the most frequently identified etiologic agent in posterior uveitis, and toxoplasma retinochoroiditis is an important cause of blindness in young adults. Historically, ocular manifestations were thought to be the result of congenital infections. However, recent evidence accumulated over the past 10 years indicates that infection via ingestion of the parasite from contaminated soil or meat may also result in ocular disease.

In patients with toxoplasma retinochoroiditis, *T. gondii* cysts can be identified within the retina and the RPE cell. Several mechanisms of retinal tissue damage have been identified, including direct parasite-induced cell lysis, production of a parasite toxin, and immunopathology from reactivity to the parasite. In the 1980s, a number of reports identified antiretinal and anti-S antigen reactivity in *T. gondii*-infected individuals (40). A recent study has identified that antiretinal antibodies are also generated in patients with *Toxoplasma* retinochoriditis (59). Using FA analysis on human retinal tissue section, Whittle et al. (59) identified antiretinal antibodies in 94% of patients with *Toxoplasma* retinochoriditis. These antibodies were directed against photoreceptors. In these studies, a screening dilution of 1:10 identified positive reactions in 34 of 36 (90%) *Toxoplasma* retinochoriditis patients. In contrast, 6 of 16 normal subjects and 3 of 12 idiopathic uveitis patients were positive. We feel that this screening dilution is probably inappropriately low. Fortunately, the sera were also tested at higher dilutions. At a 1:40 dilution, antiphotorceptor antibody was detected in 50% of the *Toxoplasma* retinochoriditis patients, 6% of the normal subjects, and 1% of the uveitis patients. Twenty-five percent of the *Toxoplasma* retinochoriditis patients showed a positive reactivity at a 1:80 dilution. Taken together, these reports suggest a high prevalence of antiretinal antibodies directed against the photoreceptor layer in *T. gondii*-infected patients.

There is no evidence that these antibodies are acting alone to induce retinal tissue damage. However, we do know from in vitro studies that *T. gondii* infections of human RPE cells result in the upregulation of a variety of cytokines (36, 37). Interleukin-6 (IL-6), IL-8, granulocyte-macrophage colony-stimulating factor, and the adhesion molecule, ICAM-1, are produced when *T. gondii* replicates in human RPE. As suggested by Rose, the cytokine profile initiated during the infection may drive the progression from benign autoimmunity to pathogenic autoimmune disease (47).

**Experimental coronavirus retinopathy.** The murine coronavirus, MHV, is a naturally occurring hepatitis virus. Neurotropic strains have been identified. Ocular infection of susceptible mouse strains leads to a biphasic disease that is first manifested as an acute retinal inflammation, followed by a chronic, immune-associated retinal degeneration (45, 46). During the degenerative phase of the disease, virus nucleic acid persists within the retina (27). However, infectious virus cannot be found. Target cells for early infection are RPE cells, ciliary body epithelial cells and Muller-like cells, and some photoreceptors (56). The role of the immune system in the degenerative phase is supported by the identification of antiretinal and anti-RPE cell antibodies in retinal degeneration-susceptible mice (21). These autoantibodies are absent in retinal degeneration-resistant mice (CD-1), which demonstrate only the acute phase of the disease. We are presently evaluating the retinal and RPE cell epitopes that are identified in ECOR.

Virus infections in man have frequently been associated with the development of autoimmune reactivity. ECOR is an animal model system, which was established to delineate the possible mechanisms operative in virus-triggered retinal degeneration. Thus, ECOR provides a model which suggests that some human retinal degenerative diseases with genetic predisposition and autoimmune components may be triggered by viruses.
Thousands of humans are diagnosed with retinal degenerations. However, our ability to determine which of these have a viral trigger and which do not has been hampered by difficulty obtaining ocular samples at the initial stages of the disease. An alternative approach may consist of correlative studies to determine if certain retinal degenerative processes are associated with specific antiretinal antibodies that may have a viral etiology.

**RETINAL DEGENERATIVE DISORDERS**

The third group of retinopathies associated with antiretinal antibodies is classified as the retinal degenerative disorders (Table 4). We have subdivided these disorders into five classes: retinitis pigmentosa (RP) with cystoid macular edema, recoverin-associated retinopathy (RAR), age-related macular degeneration, idiopathic retinopathies, and retinopathies associated with autoimmune neurologic diseases.

**RP.** RP is considered a hereditary degenerative process, often leading to blindness. However, up to 60% of patients do not have a family history of retinal degeneration. Screening of patient sera by FA assays on human retinal tissues has shown that approximately 37% of these patients have antiretinal antibodies. Galbraith et al. showed that these antiretinal antibodies can be directed against a neurofilament protein (15). Moreover, RPE cells within the retinas of these patients have been upregulated to express major histocompatibility complex class I and II molecules (12).

Patients with RP have been shown to have a breakdown in the retinal-blood barrier, and it has been difficult to associate the development of antiretinal antibodies with specific retinal tissue damage. Recently, Heckenlively et al. attempted to identify subpopulations of RP patients and to determine if antiretinal antibodies are associated with selected disease processes (19, 20). Fortified with the knowledge that macular edema is seen in CAR, these investigators initiated a prospective study evaluating antiretinal antibody in patients with bilateral cystoid edema or cysts and panretinal degeneration. They found a significant association between cystoid macular edema and antiretinal antibodies in RP patients (20). Ninety percent (27 of 30) of RP patients with macular edema contained antiretinal antibodies in their sera. In contrast, only 4 of 30 RP patients without macular edema and only 3 of 50 normal subjects had antiretinal antibody reactivity. The most common retinal proteins were carbonic anhydrase II (30 kDa) and enolase (46 kDa).

**Recoverin-associated retinopathy.** Recently, Whitcup et al. proposed the use of the term recoverin-associated retinopathy to describe a condition in patients with a clinical and immunologic disease similar to CAR but without a detectable underlying malignancy (58). These investigators described a patient with a rapidly progressive loss of vision, retinal degeneration, and an extinguished ERG. Moreover, the patient had elevated levels of antibodies in serum against recoverin and displayed a strong cellular immune response to recoverin. Thus, clinical, electrophysiological, and immunological data were all present despite the absence of an underlying malignancy.

Anti-recoverin antibodies have also been identified in 10 patients with clinical findings consistent with RP (19). These studies indicate that recoverin-associated retinopathy in the absence of cancer may be a more widespread phenomena than was previously recognized.

**ARMD.** Age-related macular degeneration (ARMD) is the most common cause of blindness in the United States and yet the etiology of this disease is still not defined. Gurne et al. studied antiretinal autoimmunity as one of the pathogenetic factors in 30 patients with this disease (16). Sera from 14 of these patients demonstrated positive binding, predominantly to a doublet protein of between 58 and 62 kDa. The serum antibodies also reacted with proteins from isolated photoreceptor outer segments of human, bovine, and monkey origin. The cross-reactivity of the serum antibodies with a protein of 58 to 62 kDa, the lower band present in a bovine purified neurofilament–68-kDa protein preparation, suggests that this protein may be a component of the neuronal cytoskeleton. It is unclear whether these autoantibodies play a direct role in the etiology of ARMD or simply represent a response to retinal damage.

**Idiopathic retinopathy.** A variety of idiopathic retinopathies and retinal degenerative diseases have been associated with the presence of antiretinal antibodies. For example, Whittle et al. (59) demonstrated that antibodies to the photoreceptor layer and outer plexiform layer are detected more frequently in patients with retinal vasculitis than in patients with systemic vasculitis. Antiretinal Muller cell-specific autoantibodies have also been described in a patient with progressive loss of vision (43). Chan et al. (10) found antiretinal reactivity to photoreceptors and Muller cells in Vogt-Koyanagi-Harada syndrome. Here, the presence of antibodies correlated with disease activity. It is also possible that antiretinal antibodies play a role in the retinal white dot syndromes (9). More extensive evaluation of the development of antiretinal antibodies is needed. In these diseases, it is not clear if the antibodies preceded the retinal disease or if the immune reactivity is a consequence of the retinal degenerative process. In either case, the autoantibodies may contribute to the disease process. Ideally, further study and characterization of autoreactivity may allow the subclassification of retinopathies. This analysis may then be instrumental in the design of treatment strategies.

A number of retinal antigens have been evaluated and implicated in uveitis. S antigen and IRBP are two such antigens. Both of these retinal antigens appear to play a role in T-cell-mediated disease processes within the eye (39, 41). It is beyond
the scope of this brief review to give a detailed description of these studies (for a review, see reference 38).

**Neurological disease with associated retinopathy.** Finally, recent studies have identified that a neurological disease may also present with immune-mediated retinopathy. The concept of a pathogenetic role of autoantibodies in neurological diseases has recently been reviewed (50). Stiff-man syndrome is a rare neurological disorder which is characterized by rigid axial and proximal limb muscles. An autoimmune pathogenesis is suggested due to the presence of autoantibodies directed against glutamic acid decarboxylase (GAD) in these patients. Recently, Steffen et al. identified a patient with Stiff-man syndrome who developed severe bilateral visual deterioration (50). The patient sera contained anti-GAD antibodies, which reacted with GABA-ergic retinal structures, suggesting that this reactivity may be associated with the ophthalmic manifestations.

**SENSITIVITY, SPECIFICITY, AND STANDARDIZATION**

This review highlights the fact that patients with some retinal degenerative diseases develop antiretinal autoantibodies. However, these antibodies are directed against a variety of different antigens. To date, there is insufficient data to accurately identify the specificity and sensitivity of these assay systems. It is obvious that standardization of antiretinal reactivity is critical to both research studies and to the development of diagnostic assay systems. In the future it will be important to establish a dialog to encourage the exchange of serum among investigators to standardize antiretinal autoantibodies. In addition, it will be advantageous to develop a proficiency testing program to monitor assay performance in different laboratories.

**SUMMARY AND CONCLUSION**

The pathogenetic involvement of antibodies or cellular immunity to retinal proteins in humans is not clear. In this brief review, we have presented evidence that selected retinopathies are associated with the development of antiretinal antibodies. The initiating factors that contribute to the generation of these autoantibodies may vary with the different clinicopathological settings. In CAR, antibodies are directed against tumor-induced antigens that also recognize proteins within the retina. In infection-associated retinopathies, antibodies directed against an infectious agent may cross-react with retinal proteins or the antibodies react with retinal antigens released during the infection. In the retinal degenerative diseases, antibodies have been identified that react to a variety of retinal antigens. In these diseases it is difficult to determine if the antiretinal antibodies initiated the disease process or if the retinal degeneration occurred first and an immune response was later triggered against selected released retinal antigens. Irrespective of the initiating event, the presence of antiretinal antibodies may contribute to the pathologic processes involved in selected retinopathies.

Presently, the identification of antiretinal antibodies is neither specific nor sensitive for the diagnosis of retinopathies. Nevertheless, demonstration of these antibodies may be helpful as diagnostic and prognostic markers in patients with retinal diseases. Analysis of immune-mediated vision loss is in its infancy, and a careful analysis and characterization of antiretinal antibody specificities will help in our understanding of the mechanisms and the diagnosis of patients with this form of vision loss.

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