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Autoantibody Targets and their Cancer Relationship in the Pathogenicity of Paraneoplastic Retinopathy

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Abstract

Paraneoplastic retinopathies (PR), including cancer-associated retinopathy (CAR) or the closely related melanoma-associated retinopathy (MAR) occur in a small subset of patients with retinal degeneration and systemic cancer. This autoimmune syndrome is characterized by sudden, progressive loss of vision in association with circulating anti-retinal autoantibodies. The PR syndromes are heterogeneous, may produce a number of ocular symptoms, and may be associated with several different neoplasms, including lung, breast, prostate, gynecological, and colon cancer, melanoma, and hematologic malignancies. We examined the onset of retinopathy in correlation to the diagnosis of cancer and the presence of specific anti-retinal autoantibodies in PR patients. In some patients without diagnosed malignant tumors, the onset of ocular symptoms and the presence of autoantibodies preceded the diagnosis of cancer by months to years, including anti-recoverin, anti-transducin- α , and anti-carbonic anhydrase II antibodies. Although anti-retinal autoantibodies may not be a good predictor of a specific neoplasm, they can be used as biomarkers for different subtypes of retinopathy. Identification of autoantibodies involved in autoimmune-mediated PR will help elucidate the mechanisms underlying the PR syndromes and develop targeted therapies for these sight-threatening disorders.

Keywords

Cancer-associated retinopathy; anti-retinal autoantibodies; recoverin; enolase; autoimmune retinopathy

Take home message

- Retinal autoantigens can be used as biomarkers for different subtypes of CAR.
- Autoantibodies to retinal antigens that also recognize tumor autoantigens may be useful biomarkers for the cause and origin of paraneoplastic disease.
- In some patients, the onset of ocular symptoms and the detection of anti-retinal autoantibodies may precede the diagnosis of systemic cancer.
- The recognition of retinopathy as part of a paraneoplastic syndrome should prompt an immediate search for an occult neoplasm.

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- Early detection of anti-retinal autoantibodies may serve to identify those who are at risk of retinal deterioration and blindness.

1. Paraneoplastic retinopathy

Retinal degeneration is one of the leading causes of blindness in the world. There are multiple causes of retinal photoreceptor cell death, including genetic, infectious, ischemic, inflammatory, drug toxicity, and autoimmune factors. Paraneoplastic retinopathies (PR) such as cancer-associated retinopathy (CAR) or closely related melanoma-associated retinopathy (MAR) represent retinal disorders mediated by autoimmune mechanism and are associated with serum anti-retinal autoantibodies. These uncommon syndromes are defined as remote effects of cancer outside of the eye, independent of either the primary tumor or a metastatic lesion. The syndromes are highly heterogeneous and may produce different ocular symptoms or be associated with a number of different cancers.

CAR is characterized by sudden, progressive loss of vision associated with photosensitivity, ring scotoma, attenuated retinal arteriole, visual field defects, abnormal electroretinogram (ERG), and the presence of circulating serum autoantibodies specific to retinal antigens [1]. Although the syndrome has been associated with different systemic malignant tumors, including carcinomas, lymphomas, and hematopoietic malignancies, the presence of anti-recoverin antibodies has been found in individuals with benign breast and thymus tumors, suggesting that aberrant expression of retinal antigens in tumors may lead to PR. MAR is defined by night-blindness, light sensations or visual field defects, reduction of the b-waves in the ERG, and the presence of antibodies reactive with retinal bipolar cells in association with skin melanoma [2]. Retinopathy may develop either before or after the diagnosis of cancer. CAR has been studied more intensively than MAR over the years and it is believed that the syndrome is autoimmune-mediated by autoantibodies directed against proteins present in retinal neurons [3]. However, autoantibody production may be triggered by immune responses to antigens aberrantly expressed in tumor cells of affected individuals, such as lung cancer cells or melanoma cells [4–7]. Such antibodies then may cross-react with the identical or similar antigens in the retina and cause retinal cell death through the mitochondrial-mediated apoptotic process [3,8]. Autoantibodies can cross the blood-ocular barrier and can be also found in patients' intraocular fluids. Consequently, an autoimmune mechanism contributes to the destruction of retinal cells and retinal degeneration.

There is a high degree of correlation between the presence of serum autoantibodies, the development of visual symptoms, and the presence of retinal degeneration. In this review, we examined whether the onset of retinopathy and the presence of specific autoantibodies can precede the diagnosis of cancer, and whether autoantibodies may be predictive markers for different subtypes of retinopathy as well as markers of underlying neoplasia.

2. Association of retinopathy with cancer

Our recent examination of 209 patients with cancer in our laboratory revealed that major cancers associated with the syndrome were lung (16%), breast (31%), colon (6%), prostate (7%), melanoma (16%) and gynecological neoplasms (9%) as well as hematological malignancies (15%) including lymphomas, leukemias, and myelomas. In majority of patients, CAR develops after the age of 45 years old; the average age is 65 and ranges from 24 (leukemia) - to 85 (lung) years old. The disease affects women more than men at a ratio of about 2:1. The time from the diagnosis of cancer to the onset of retinopathy varies from weeks to months (lung and lymphoma) to years (breast or prostate). Interestingly, eight out of the 209 patients in our cohort presented with visual symptoms and anti-retinal autoantibodies prior to being diagnosed with cancer. We speculate that the delay in tumor detection is most likely related to tumor kinetics, while patients' clinical presentation with visual loss reflects retinal damage

attributable to anti-retinal immune responses. The successful anti-tumor response would be expected to go clinically unnoticed by the patient, but the autoantibodies mediating retinal damage somehow traverse into the retina, resulting in an autoimmune attack on retinal neurons and eventually produced visual symptoms. In our study group, the latency period of various cancers to the recognition of PR was greater than a year, although about 15% these patients developed visual symptoms within the first year of cancer diagnosis. It is also possible that visual deterioration developed within the time of cancer diagnosis but visual loss was slowly progressive, unnoticeable to the patient. The longest reported time preceding diagnosis of carcinoma was 11 years in a patient with bronchioloalveolar carcinoma associated with anti-recoverin antibodies [9]. The prognosis of CAR varied depending on the level of visual impairment and the degree of retinal degeneration and may be important in determining medical intervention. Bilateral visual loss of sudden onset varied from slowly progressive (breast, colon, prostate, melanoma) to rapidly progressive (lung and lymphomas).

MAR development varied from months to 11 years after the initial diagnosis of cutaneous melanoma. The latter observation was similar to previously published findings, indicating that the average latency from melanoma diagnosis to the recognition of MAR was 3.6 years from 2 months to 19 years [10]. Moreover, MAR development often corresponds to the discovery of metastases [10]. Since the cancer latency period may last years, and because PR may develop before cancer becomes clinically evident, it is important that the patient manifesting retinopathy be referred for anti-retinal antibody testing as part of their diagnostic workup. If paraneoplastic anti-retinal antibodies are detected in the absence of known cancer, workup for an occult neoplasm may be appropriate.

3. Association of CAR and MAR with anti-retinal autoantibodies

Autoantibodies frequently precede the onset of clinical symptoms by several years in a number of autoimmune diseases, such as systemic lupus erythematosus [11]. Recognition of paraneoplastic syndromes is important, as it may lead to an early diagnosis of cancer. Some rheumatologic disorders such as myopathies, rheumatoid arthritis, scleroderma or dermatomyositis, and some atypical vasculitides, can precede the clinical manifestations of a variety of solid and hematological tumors [12,13]. In neurological paraneoplastic syndromes, autoantibodies have been frequently detected in the sera of patients with breast and other neoplasms prior to the clinical diagnosis of cancer [14–17]. Even though these syndromes are rare, they provide clear examples of autoantibodies preceding the clinical diagnosis of cancer. Despite this well-described temporal association in several other autoimmune diseases, the association of autoantibodies and CAR has not been well established, both because of the rarity of these syndromes and the length of patient follow-up required to make a comprehensive conclusion on the subsequent course of cancerous disease. Patients are usually tested for anti-retinal antibodies when they present with visual symptoms (Table 1). Importantly, some autoantibodies such as anti-recoverin, anti- α -enolase, anti-CAII, and anti-transducin- α autoantibodies have been found months to years before cancer was found (Figure 1). Other antibodies might have also been detected before cancer diagnosis in patients with retinopathy but often a lack of follow up data does not allow us to make definitive conclusions about which antibodies have cancer connections.

For years, it has been believed that recoverin, a calcium-binding protein often referred to as CAR antigen, is the sole autoantigen involved in the development of CAR [18]. The role of this antigen in autoimmune-retinal degeneration has been intensively studied by several groups [19–21]. However, results from the current cohort of cancer patients indicate that anti-recoverin antibodies can be detected in only about 10% of patients with visual symptoms [22]. Nevertheless, anti-recoverin autoantibodies can be predictive of cancer, in particular small cell carcinoma of the lung (SCCL) since almost all reported patients with anti-recoverin antibodies

have been diagnosed with cancer. In fact, in our patient cohort of nine SCCL patients, 4 had anti-recoverin autoantibodies, 3 were negative (follow-up data not available) and 2 patients had other anti-retinal antibodies at the time of initial testing. In addition, low levels of anti-recoverin autoantibodies have been also reported in individuals with lung and other cancers without visual symptoms but not in normal subjects [23], indicating their connection to initial anti-tumor responses. Interestingly, SCCL patients with anti-recoverin antibodies have better survival without SCCL recurrence than SCCL patients who lack anti-recoverin antibodies [24], suggesting that these antibodies play a double role, a positive as a part of the anti-tumor immune response, and a negative in the induction of retinal degeneration.

It is clear from evaluation of published case reports that the syndrome is immunologically heterogeneous. In our cohort of patients with clinical PR, about 65% of patients had various anti-retinal autoantibodies, although not always directed against well-characterized autoantigens (Table 1). Autoantibodies directed against a glycolytic enzyme, α -enolase, were the most frequent and were detected in about 30% of seropositive CAR patients, followed by autoantibodies specific to transducin in ~17%, carbonic anhydrase II (CAII) in 14%, and recoverin in about 10% of seropositive patients.

Clinically, there are no strong clues that predict the presence of an underlying cancer in patients with presumed autoimmune CAR syndrome. The detection of anti-retinal autoantibodies thereby provides important laboratory evidence supporting the diagnosis of PR. Anti-retinal autoantibodies can be associated with unique clinical presentations, symptoms, phenotypic findings, and ERG patterns. Based on correlation of specific serum autoantibodies such as anti-recoverin or anti-enolase with ocular symptoms and findings, we have started discriminating unique phenotypes that differ in both symptomatic presentation and retinal findings [25].

Anti-recoverin CAR is associated with cancer in almost 100% cases and leads to an almost equal loss of both rods and cones, indicating widespread retinal dysfunction [26]. In contrast, anti- α -enolase CAR is less predictive of an associated neoplasm, is equally associated with or without cancer [25], and usually develops months to years after the discovery of the malignancy [27]. Anti- α -enolase retinopathy is typically related to cone dysfunction [25]. Epitope mapping for anti- α -enolase antibodies revealed a CAR-associated epitope, sequence 56–63, which was recognized by 70% of CAR patients. Moreover, this epitope was strongly associated with breast and bladder cancers [28,29]. Autoantibodies against transducin- α are typically found in patients who present with defects in rod (scotopic) photoreceptor function and did not have cancers at the initial examination [30].

Autoantibodies that recognize retinal antigens also recognize antigens expressed in tumors of affected individuals, suggesting that these tumors may be the original source of antigens for autoimmunization. The four most common autoantigens associated with PR are present in the retinal and cancer cells. Recoverin, photoreceptor specific antigen, has been found in many tumors, including lung cancer [4,23]. Transducin- α and other photoreceptor-specific antigens are expressed in carcinoma and melanoma cells [5,31]. Although α -enolase is a ubiquitous enzyme its expression depends of cell physiology, and it was found to be highly expressed in neoplasms. Enolase can escape when the tumor is resected or during regular tumor cellular turnover, and can thus induce an anti-enolase response [32,33]. Anti-CAII autoantibodies have also been found in some retinopathy patients with cancer. CAII expression is increased during carcinogenesis, which may consequently contribute to the immune response to cancer CAII [34]. Together, these findings strongly suggest that the development of anti-retinal antibodies is originally provoked by the aberrant expression of these autoantigens by tumor cells rather than antigens “leaking” from the degenerating retina.

Historically, anti-bipolar cell autoantibodies have been recognized as markers of MAR syndrome although the specific bipolar cell antigen has not been identified [35]. However, antibodies with other specificities have also been detected in MAR patients with different stages of melanoma and these antibodies reacted with the both retinal and melanoma cells of affected individuals [10,36]. Since visual rhodopsin, transducin, recoverin, arrestin, and other phototransduction proteins are expressed in melanoma it is not surprising that autoantibodies against three photoreceptor proteins, transducin- β [37], rhodopsin [38], and arrestin [39] were found in MAR. From our current pool of MAR patients, five patients had anti-transducin- α antibodies (manuscript in submission). Moreover, the aberrant expression of mRNA for rhodopsin, PDE6, CGC, guanylyl cyclase 1, recoverin and arrestin was detected in some normal tissues, but never transducin or rhodopsin kinase. These findings not only indicate heterogeneity of this paraneoplastic disorder but also the involvement of photoreceptor cells in MAR as seen in CAR.

4. Concluding remarks

Autoantibodies to retinal antigens that also recognize tumor autoantigens may be useful biomarkers for the origin of paraneoplastic disease. At least some autoantibodies found in patients with presumed PR can predict the presence of an underlying neoplasm (i.e. anti-recoverin autoantibodies) but their diagnostic value is not fully determined. In some patients without diagnosed cancer the onset of ocular symptoms and autoantibodies preceded the cancer diagnosis by months to years. Although anti-retinal autoantibodies are not good predictors of specific neoplasms in patients with presumed CAR, they can be used as biomarkers for different subtypes of retinopathy. This is in contrast to neuronal paraneoplastic syndromes, where the autoantibody profiles observed in patients, indicate the targeting of multiple oncoantigens and predict the patient's neoplasm, but not a specific neurological syndrome [40]. A more complete understanding of the relationship between the cancer and the specific retinal pathology observed may lead to better understanding of the cellular and molecular mechanisms of retinal degeneration and inform the development of rational therapies. The early detection of anti-retinal autoantibodies may serve to identify those who are at risk of developing immune-mediated CAR and MAR and may provide the best protection against loss of vision in susceptible patients.

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Figure 1.

A diagram showing a relationship between the detection of specific autoantibodies and the time of cancer diagnosis in patients with visual symptoms. Autoantibodies specific against recoverin, transducin- α , α -enolase and carbonic anhydrase II (CAII) can be found months to years before cancer is clinically detected

Table 1

Major Autoantigens Detected in Patients with Paraneoplastic Syndrome

Cancer	Seropositive Patients	Antigens (molecular weight)	Major antigens	Time of Cancer Diagnosis to AAb Detection
Breast	40/65	23k, 30k, 40k, 46k	Enolase, transducin	
Gynecological	14/18	23k , 35k, 46k , 75k, 84k	Recoverin (endometrial) Enolase (cervical)	
Lung	15/32	23k, 30k , 35k, 40k, 46k, 68k, 100k	Recoverin (SCCL) CAII, PDE	Can precede
Colon	13/13	30k, 40k , 46k	Transducin CAII	Can precede
Prostate	9/15	30k, 46k , 23k, 40k	Enolase, CAII	Can precede
Hematological	15/15	46k , 67k, 62k, 23k	Enolase	
Cutaneous Melanoma	19/34	40k, 46k	Transducin, enolase	