

An experimental autoimmune uveoretinitis model and intraocular inflammation

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Abstract

Intraocular inflammation is one of the leading causes of vision damage. Human uveitis is a group of conditions characterized by inflammatory lesions of intraocular structures. Many cases are idiopathic and can be classified as infectious uveitis or autoimmune-related uveitis. Compared with infectious uveitis, our knowledge of and treatment options for autoimmune-related uveitis remain very limited. In order to develop effective therapeutic strategies and agents, it is essential to explore the basic mechanisms and pathogenesis of autoimmune ocular diseases. An experimental autoimmune uveoretinitis animal model has been widely used to study the physiopathogenesis of autoimmune inflammation. The present review describes the characteristics of experimental autoimmune uveoretinitis, as well as the research on intraocular inflammation using this animal model.

Key words: Autoimmune diseases; Electoretinography; Tomography, optical coherence; Uveitis

Introduction

The uveal tract represents the vascular organ of the eye. It comprises the iris, ciliary body and choroid, and serves as the primary entry site for immune cells, particularly T cells, to migrate into the eye. Some of these T cells recognize specific antigens in the eye and secrete various cytokines

and chemokines that trigger an inflammatory cascade by recruiting additional inflammatory cells. The uveal tract is therefore involved in the progression of intraocular inflammation. The term “uveitis” refers to inflammation that affects almost any intraocular structure, and thus reflects a state of intraocular inflammation, not just inflammation of the iris, ciliary body, and choroid.

Uveitis is a sight-threatening disease. In 2010, the World Health Organization estimated that around 4 million people globally were permanently blind because of uveitis.¹ Clinically, according to the anatomical structures, uveitis is divided into 4 types²: (1) anterior uveitis, that has the typical signs of iris hyperemia and keratic precipitates, affects the cornea, iris, pars ciliaris of the ciliary body, and the anterior chamber; (2) intermediate uveitis, in which the pars plana of the ciliary body, posterior chamber, vitreous base, and periphery retina and choroid are involved, shows the snowbank symptom of posterior hypopyon; (3) posterior uveitis, where vitreous, retina and choroid are inflamed by vasculitis; and (4) panuveitis, that is observed as inflammation affecting all parts of the eye, and is a significant clinical feature of Vogt-Koyanagi-Harada syndrome and Behçet’s disease.

According to the etiology, intraocular uveitis can be infectious or non-infectious. Infectious uveitis can be due to a specific etiology, such as bacterium, virus, or fungi; whereas in patients with non-infectious uveitis, lymphocytes from peripheral blood often respond to antigenic proteins expressed in the retina. The etiology is thought to be an autoimmune disorder. For patients with infectious uveitis, treatment of the underlying infection is the primary therapy. In non-infectious uveitis, corticosteroids and

immunosuppressants are the standard therapeutic strategies. Nonetheless, such treatment is reported to show severe side-effects, such as elevated intraocular pressure and other systemic disorders.

Many studies have investigated the disease mechanisms of intraocular inflammation, and sought effective treatment for infectious and non-infectious uveitis. Animal models have been developed to compensate for the difficulties in collecting human inflamed eye tissue for research purposes.

Endotoxin-induced uveitis induced by lipopolysaccharide is a well-established model to study infectious uveitis. For autoimmune ocular inflammation, several animal models have been introduced, namely experimental autoimmune uveoretinitis (EAU), experimental melanin protein-induced uveitis, and experimental autoimmune encephalitis associated with anterior uveitis. Of these autoimmune animal models, EAU reflects the photoreceptor damage and other clinical features of uveoretinitis, and is therefore widely used to mimic human posterior uveitis and panuveitis of autoimmune etiologies, such as Behçet's disease. Our paper will focus on the characteristics of the EAU model and relevant studies.

Background of experimental autoimmune uveoretinitis model

In 1963, Aronson et al³ developed an EAU model in guinea pigs by injecting homologous uvea into the eyes; Wacker⁴ adapted the model by injecting photoreceptor extracts into rats 10 years later. The model was further refined by de Kozak et al⁵ who replaced the photoreceptor extracts with retinal soluble antigen (S-Ag). Subsequently other autoantigens, such as interphotoreceptor retinoid-binding protein (IRBP), rhodopsin, recoverin, and phosducin were used to induce EAU in rats. Further investigations in rat models revealed that the disease was mediated by T cells and thus could be included in naïve rats by transferring CD4⁺ T cells activated by retinal antigens. Furthermore, specific pathogenic regions, the so-called epitopes, of these autoantigens were shown to induce uveitis effectively.⁶⁻⁸ In 1988, Caspi et al⁹ successfully induced EAU in mice.

Although rats and mice have been widely used to study uveitis, not all strains of rats and mice are suitable. Their disease susceptibility is determined by their genetic background, especially in the chromosome regions related to the class II I-A (a peptide family that presents antigen to other immune cells) of the major histocompatibility complex (MHC) haplotype.¹⁰ These susceptible haplotypes, in terms of the order of susceptibility, can be ranked as H-2^r > H-2^k (or H-2^a) > H-2^b. Additionally, different animal species and even various genetic strains within the same species show very different susceptibilities to specific uveitogenic proteins and pathogenic epitopes. **Table 1**^{7,11-15} shows some commonly used strains of rats and mice in inducing EAU. Choice of animal should be based on the purpose of the studies and the analytical techniques. For example, there are many mice with different manipulated genetic backgrounds, thus a mouse model is more appropriate for studying the genetic pathways in uveitis.

The S-Ag, also called S-arrestin, is a photoreceptor protein mainly found in photoreceptors and pineal gland cells.⁷ Its main physiological role is to desensitize the photoactivated transduction cascade by inhibiting the coupling of rhodopsin to transducin. Peptide M of S-Ag comprises 18-amino acids and has been shown to be highly uveitopathogenic in different species, such as guinea pigs, rats, and monkeys.¹¹

The IRBP is an abundant protein presenting in the interphotoreceptor matrix that is situated between the retinal pigment epithelium (RPE) and photoreceptor cells. It plays a physiological role in the transport of vitamin A derivatives (retinoids) between the retina and RPE cells.^{16,17} It has high uveitopathogenicity in mice,⁹ rats,¹⁸ rabbits,¹⁹ and monkeys,²⁰ but is poorly uveitogenic in guinea pigs.²¹ The disease course and severity depend on the animal species or strain and the dose of antigen injected. In Lewis rats, inflammatory changes become apparent as early as 8 days after immunization and last 5 to 10 days.¹⁸ In mice, the disease has a longer incubation and duration. IRBP comprises 1264 amino acids, forming 4 repeated units of 300 amino acids each. The peptide R16 (amino acids 1177-1191, sequence ADGSSWEGVGVVDPDV)²² of bovine IRBP is a highly immunopathogenic determinant, mainly used for induction of EAU in rats. Many studies based on an EAU model have

Table 1. Susceptibility of different rat and mouse strains to EAU.

Strain	MHC	Susceptibility	Antigen	Epitope and position recognized
Lewis rats	RT1 ¹	High	S-Ag, IRBP	TSSEVATEVPFRLMHPQPED (343-362) of S-Ag ¹¹ ADGSSWEGVGVVDPDV (1177-1191) of IRBP ¹²
BN rats	RT1 ^a	Low	S-Ag	TSSEVATEVPFRLMHPQPED (343-362) of S-Ag ⁷
B10.RIII mice	H-2 ^r	High	IRBP	SGIPYIISYLHPGNTILHVD (161-180) of IRBP ¹³
B10.A mice	H-2 ^a	High	IRBP	ADKDVVVLTSRTGGV (201-216) of IRBP ¹⁴
C57BL/6J mice	H-2 ^b	Moderate	IRBP	GPTHLFQPSLVLDMAKVCLLD (1-20) of IRBP ¹⁵

Abbreviations: BN rat = brown Norway rat; EAU = experimental autoimmune uveoretinitis; IRBP = interphotoreceptor retinoid-binding protein; MHC = major histocompatibility complex; S-Ag = soluble antigen.

identified the immunogenic epitopes.^{13,15,23} Uveitogenic human IRBP epitopes for susceptible mice strains have been identified (**Table 1**).

Pathogenesis of experimental autoimmune uveoretinitis

The classic mouse EAU can be induced with IRBP. IRBP solution is emulsified in complete Freund's adjuvant (CFA) that comprises *Mycobacterium tuberculosis* bacteria (MTB) and mineral oil. The emulsion can be subcutaneously injected into animals. Additionally, intraperitoneal injection of pertussis toxin is essential for many strains to stimulate the inflammation.

After injection of the autoantigen into susceptible animals, CD4⁺ cells recognize antigens presented by the antigen-presenting cells (APC) in the context of class II MHC molecules. The differentiation of these retina-specific T cells to demonstrate pro-inflammatory phenotypes is driven by CFA that contains the heat-inactivated MTB. Although the healthy eye is protected by the blood-retinal barrier (BRB), these activated T cells circulating through the body become invasive and stick to the blood vessels. The BRB ceases to be protective against these activated T cells that can then pass through the BRB and adhere to the vascular endothelium. Consequently, the activated T cells produce matrix-degrading enzymes and metalloproteinases that enable them to break through the tight vascular junctions of the BRB and infiltrate the tissues. The infiltrated T cells recognize their specific antigens in the eye and secrete various cytokines and chemokines that trigger an inflammatory cascade: activation of the local microvasculature, recruitment of inflammatory leukocytes and APC from the circulation, breakdown of the BRB and leakage of retinal antigens into the draining lymph nodes, priming and expansion of additional autoreactive T cells and recruitment of additional inflammatory cells, and enhancement of tissue damage and antigen release.²⁴⁻²⁸

EAU can also be induced by adoptive transfer of primed uveitogenic effector cells from IRBP-immunized donors into recipient animals. Donors are immunized using classic methods described above. Their lymph node cells and spleen cells are isolated, pooled, and cultured with the autoantigen peptides, and adoptively transferred into recipient animals that will develop EAU after an abbreviated latent period. The mechanisms of how these adoptively transferred effector cells induce EAU in the recipient animals is believed to be similar to the direct injection of IRBP. Nonetheless, time of onset of EAU differs for these 2 methods. Because the injected T cells have been activated prior to isolation from the donors, onset of EAU induced by adoptive transfer usually occurs 1 week earlier than EAU induced using the classic immunization methods.

Peripheral injection of retinal antigen-pulsed (IRBP peptide 161-180) in-vitro-matured dendritic cells (DCs) and transfer into recipient animals has also been reported to successfully induce EAU.²⁹ This novel method is believed to induce

EAU by a similar mechanism to direct injection of IRBP. In addition, this new method offers some advantages over the direct IRBP injection model as it avoids the efferent phase of inflammation caused by the autoantigen and MTB.

In addition to induced EAU, several spontaneous EAU models have been established. These models contain a high frequency of retina-specific T cells, either as a result of retina-specific T cell receptor transgenes³⁰ or defective elimination of retina-specific T cells by the thymus.^{31,32}

Methodologies for characterization of experimental autoimmune uveoretinitis

To characterize the diseases, histological verification and biochemical analyses were typically performed following sacrifice of EAU animals. Nonetheless, recent advances in biomedical technologies now allow the animals to be monitored non-invasively. This allows identification of histological progression in real time and is crucial for longitudinal studies of uveitis.

Optical coherence tomography

Optical coherence tomography (OCT) is a novel method of ocular imaging. Using a coherent infrared laser to analyze the reflectance properties of the ocular structures, OCT can obtain high-resolution cross-sectional pictures.³³ As a well-established state-of-the-art imaging tool in ophthalmology, OCT has revolutionized the diagnosis, follow-up, and treatment of human eye diseases.³⁴ Recent improvements have enabled OCT to be adapted for high-resolution imaging of the retina in animals to reveal clinical features of retinal pathology *in situ* and in real time.³⁵

In 2011, Gadjanski et al³⁶ correlated the OCT images of EAU animals with retinal histology in brown Norway rats, and concluded that OCT is a reliable tool for detection and follow-up of histopathological changes during EAU in rats. Retinal thickness as an OCT parameter was proved to be a sensitive marker for distinguishing disease phases in vivo. Subsequently, Chen et al³² evaluated the application of OCT in a mouse model of EAU in 2013. In addition to the significant correlation between OCT images and histological observations, they found that OCT could visualize pathological lesions in different retinal layers. In terms of morphological changes to retinal lesions distinguished by OCT imaging of EAU in mice, cellular infiltrates around the optic nerve head and retinal edema could be observed during early phases of the disease. Nonetheless, at the peak of disease severity, retinal structures could not be clearly resolved by OCT because of partial blocking of the OCT signals by proteinaceous exudations and cellular infiltrations in the vitreous of the eye. In late stages of the disease, if blocking of the OCT signals is minimal, prominent retinal vasculitis, retinal folds, and reduced retinal thickness can be observed on OCT images (**Figure 1**). Based on these clinical observations on OCT imaging, grading systems were established to semi-quantify the severity of disease. An example of these grading systems is shown in **Table 2**.³⁷

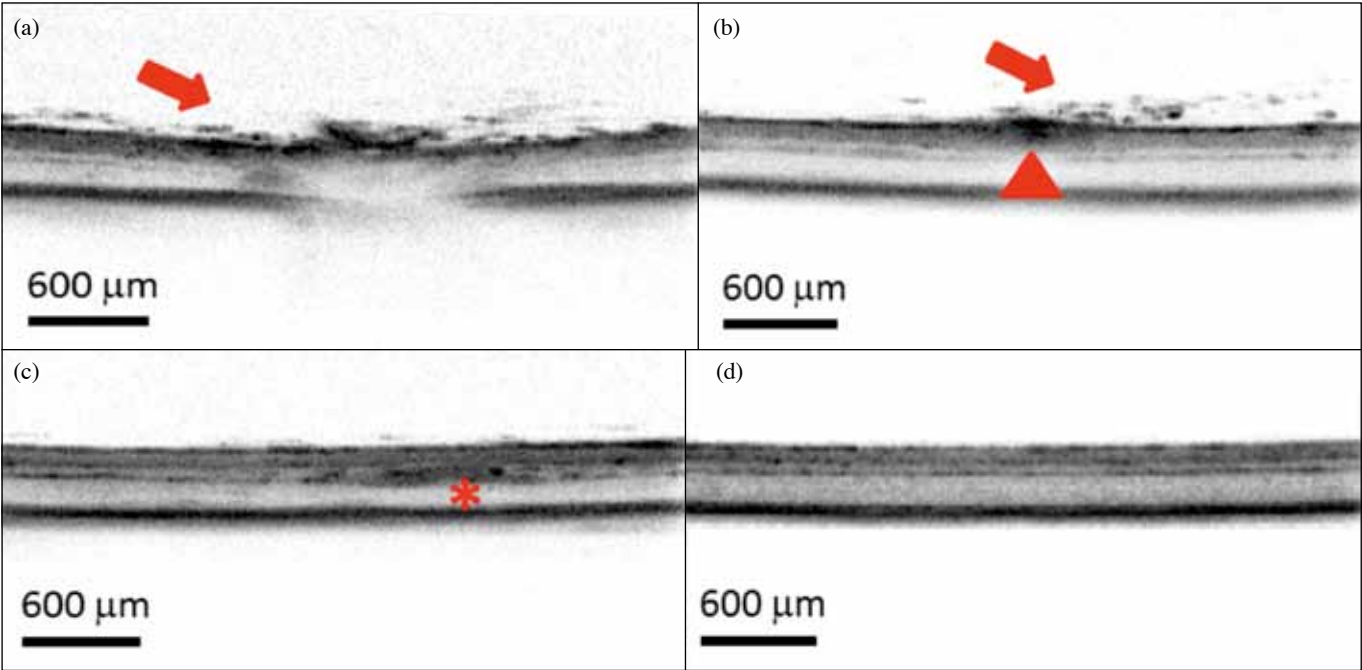


Figure 1. Spectral-domain optical coherence tomographic images of retina in (a to c) experimental autoimmune uveoretinitis mice and (d) in a normal mouse. Infiltrating cells in the vitreous (arrows), vasculitis (arrow head) and disturbance of the retinal layer structure (asterisk) are indicated.

Table 2. Scoring criteria for optical coherence tomography–based monitoring of experimental autoimmune uveoretinitis in C57BL/6J mice. ³⁷	
Grade	Criteria
0	No abnormal image
1	Few high reactive dots in the vitreous and around retinal vessels
2	High reactive dots in the vitreous and around retinal vessels more than grade 1 High reactive dots in the retinal all layers Few high reactive masses in the outer retina Partial retinal layer disruption
3	Many high reactive dots in the vitreous, around vessels, and in all retinal layers Multiple high reactive masses in the outer retina Disturbance of the total retinal layer structures Disappearance of external limiting membrane and inner segment/outer segment line
4	Disappearance of the outer retinal layers

Confocal scanning laser ophthalmoscopy

State-of-the-art imaging in animals based on conventional fundus cameras or even confocal scanning laser ophthalmoscopy (cSLO) provides predominantly retinal surface information.³⁸ The OCT+infrared reflectance channel of Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany) has been employed to capture retinal images with a 30-degree angle of view in many EAU studies.^{37,39} These 30-degree images can be manually merged into a wider-field image of the whole retina. From the cSLO-based fundus photos, swelling of vessels, perivascular exudates, retinal folds, and even vitreal hemorrhage can be observed (Figure 2). Similar to OCT images, these cSLO images can be used to grade EAU using clinical criteria shown in Table 3.⁴⁰

Retinal vasculitis results in leakage that leads to retinal swelling, exudation, and edema. Fundus fluorescein angiography (FFA) is widely adopted in diagnosis and monitoring of retinal diseases. As fluorescein sodium emits wavelengths as fluorescent light, it mainly gives information about the superficial structures of the fundus. Therefore, to assess vasculopathy in a model of EAU, FFA images of animals following fluorescein injection can also be obtained using the autofluorescent channel of the Spectralis HRA. Retinal vasculitis and optic nerve head edema can be observed by FFA examination (Figure 3).

Electroretinography

Electroretinography (ERG) is widely used to evaluate visual function in both clinical practice and basic research.⁴¹

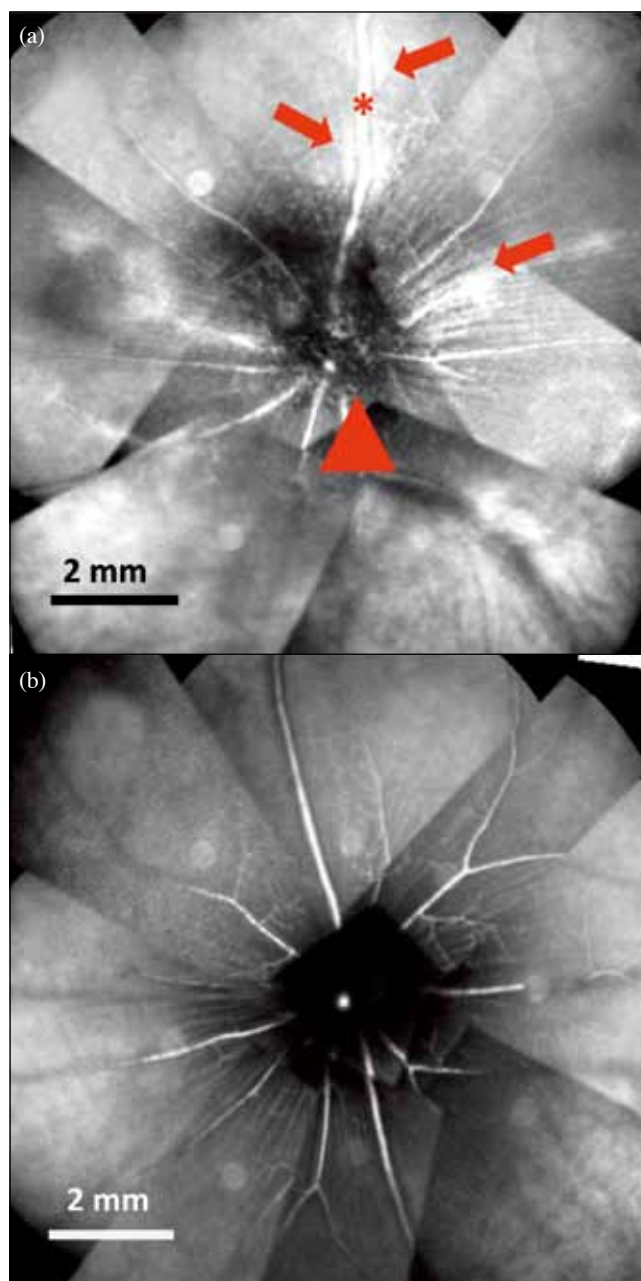


Figure 2. Confocal scanning laser ophthalmoscopy–based fundus photos of (a) experimental autoimmune uveoretinitis mouse and (b) normal mouse. Cellular infiltrates in the vitreous (arrow head), perivascular exudates (arrows) and swelling vessels (asterisk) are shown.

The retinal inflammation of EAU that leads to functional changes in vision can be assessed by recording the dark- and light-adapted ERG. Although scotopic (dark-adapted) and photopic (light-adapted) a- and b-waves reflect retinal cell activity of different signal pathways, such as rod cells, cone cells and bipolar cells, we found that EAU development led to detectable reductions in dark- and light-adapted a-wave and dark-adapted b-wave amplitudes (**Figure 4**).

Histopathological verification

The final assessment of EAU should be histopathological verification. This involves visualising the whole area of retinal tissue damage, as well as detecting autoantigens resident in the retina. After sacrificing the animals, eyeballs are sectioned onto slides and stained with different chemicals, such as hematoxylin and eosin (**Figure 5**). According to the extent of tissue damage, EAU can be scored on a scale of 0 to 4 using the criteria listed in **Table 4**.⁴⁰

Experimental autoimmune uveoretinitis and ocular immunology

Ocular immune privilege is a term coined by Peter Medawar in the middle of the 20th century and describes the ability to limit intraocular immune and inflammatory responses in order to preserve vision.⁴² The privilege system comprises 3 layers of defense. The first line is the efficient BRB that separates the immune system and the eye. The second line is the immunoinhibitory ocular microenvironment that is composed of diverse soluble and cell-bound molecules. If the BRB is destroyed (as in the case of trauma or surgery), immune cells can enter the eye but are inhibited by the immunoinhibitory ocular microenvironment. If the microenvironment is not sufficient to prevent inflammation, the third line, the systemic regulatory mechanisms, will be elicited. These systemic regulatory mechanisms, such as the anterior chamber-associated immune deviation and the post-recovery eye-dependent tolerance, can limit ocular tissue damage caused by infiltrating cells.^{43–46} In the case of animal models of EAU, the immune privilege is unable to protect the eyes from a strong adaptive response. Unlike naïve T cells, the activated T cells are able to pass through the BRB and are not inactivated to regulatory T cells (Tregs) within the eye. These activated T cells continue to express immune effector functions but also cause the loss of immune

Table 3. Scoring criteria for confocal scanning laser ophthalmoscopy–based monitoring of experimental autoimmune uveoretinitis in mice.⁴⁰

Grade	Criteria
0	No change
0.5	1 to 2 very small, peripheral focal lesions; minimal vasculitis/vitritis
1	Mild vasculitis; < 5 focal lesions; ≤ 1 linear lesion
2	Multiple (> 5) chorioretinal lesions and / or infiltrations; severe vasculitis (large size, thick wall, infiltrations); < 5 linear lesions
3	Pattern of linear lesions; large confluent lesions; subretinal neovascularization; retinal hemorrhages; papilledema
4	Large retinal detachment; retinal atrophy

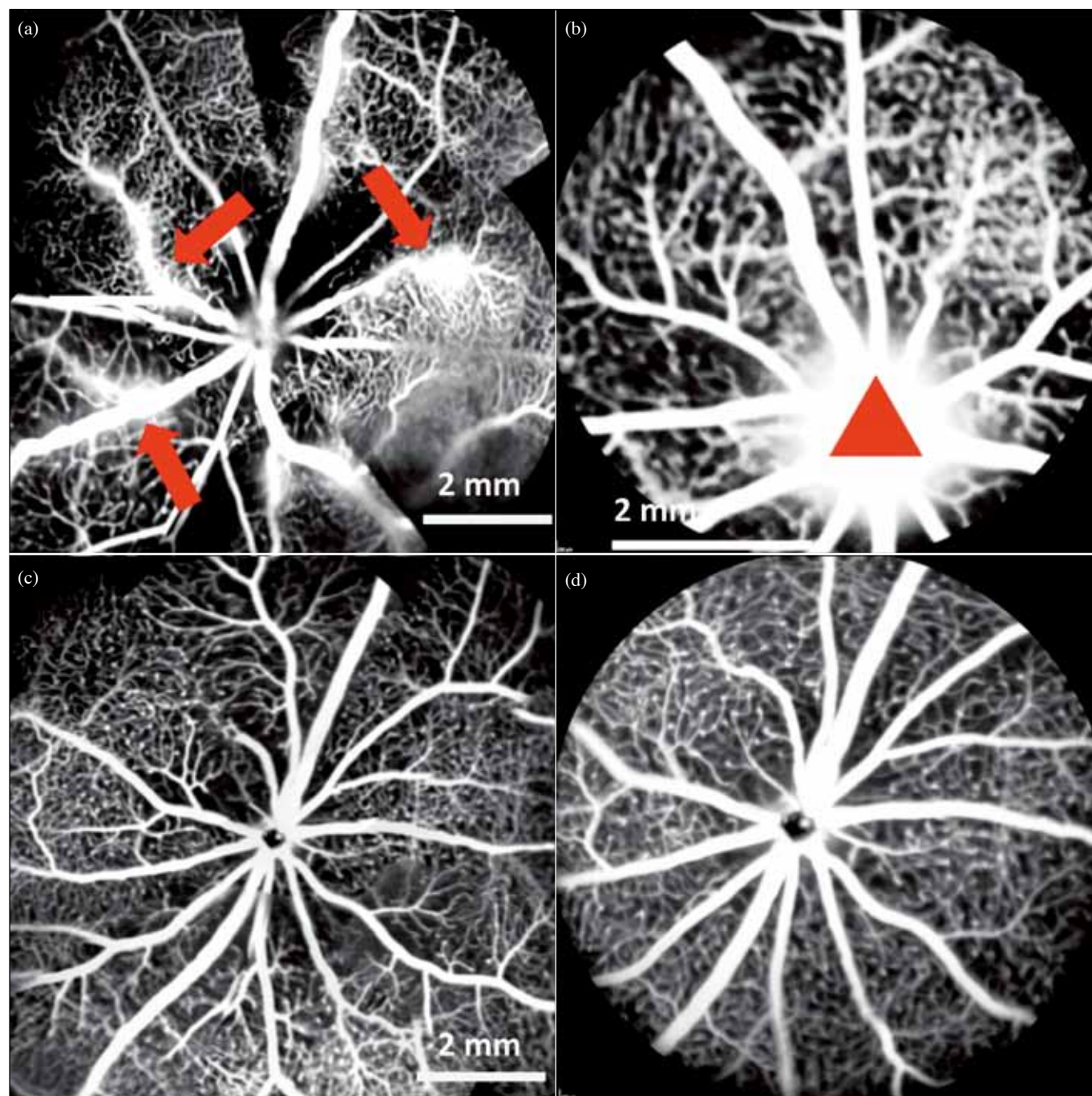


Figure 3. Fundus fluorescein angiographic images of (a and b) experimental autoimmune uveoretinitis mice and (c and d) normal mouse. Swelling vessels and vascular exudates (arrows in fig a) indicating retinal vasculitis are shown. Hyperfluorescence (arrow head in fig b) appeared on the disc indicating optic nerve head edema. Retinal blood vessels in normal mouse are shown in fig c.

privilege by compromising Tregs conversion in the inflamed eye, likely due to the loss of molecules to maintain the inhibitory ocular microenvironment.⁴⁷⁻⁴⁹

There are multiple animal models available to study uveitis. In particular, for the CD4⁺ T cell-mediated inflammatory response, EAU is an invaluable model for basic as well as clinical studies of intraocular autoimmunity.

EAU has been used to address many questions, such as

genetic control of susceptibility and resistance to intraocular inflammation, cellular and molecular mechanisms contributing to the maintenance or breakdown of organ-specific antigen tolerance, and immunological events that constitute the autoimmune amplification cascade that culminates in the expression of not only uveitis, but also other autoimmune diseases.

According to the immunological classification, antigen-specific effector T lymphocytes can be divided into several

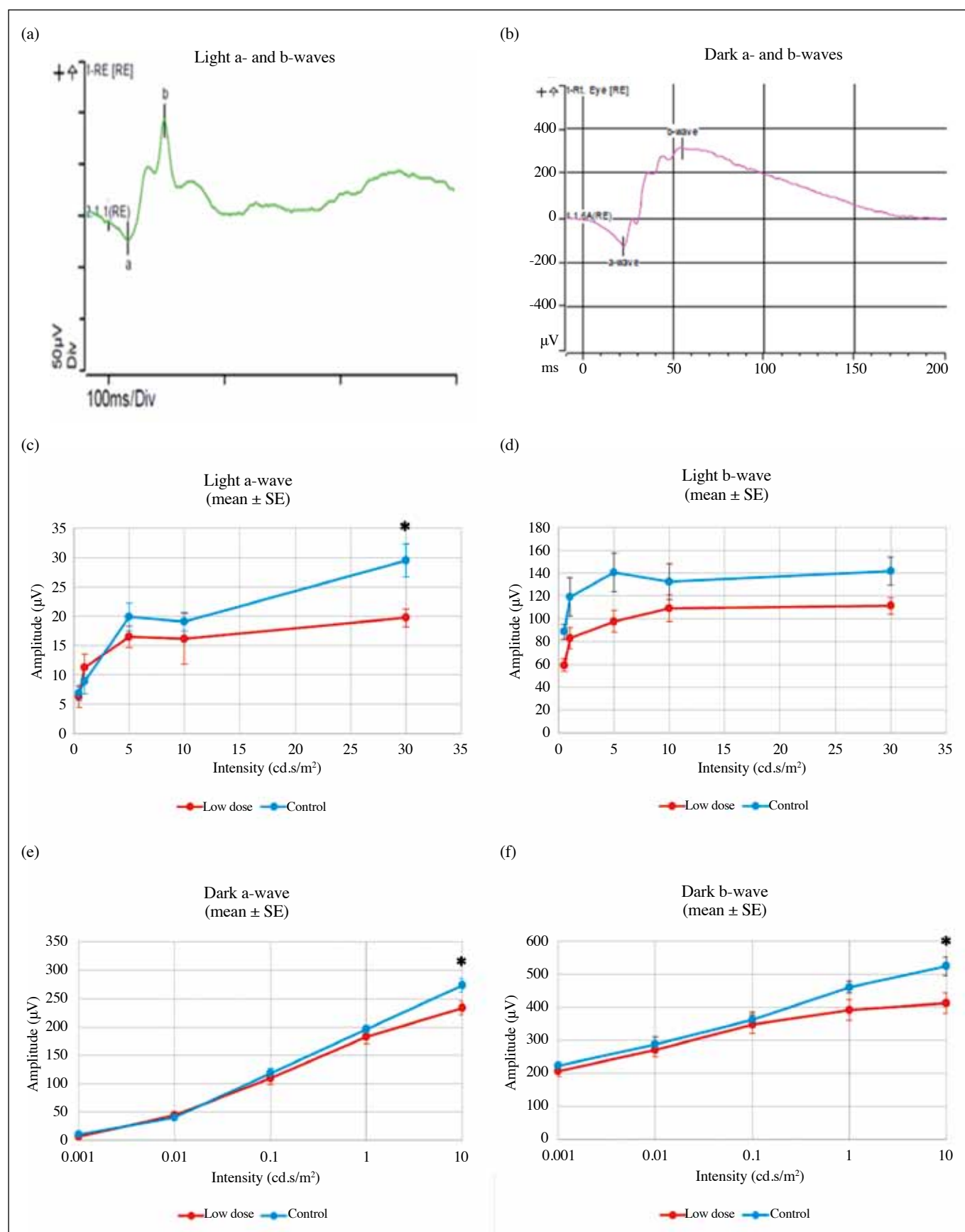


Figure 4. Electrophysiology (ERG) responses after dark and light adaptation. (a and b) Definition of a- and b-waves of ERG waveforms after dark and light adaptation. (c to f) Comparisons of dark- and light-adapted ERGs under different light intensities between experimental autoimmune uveoretinitis and normal mice. Data are presented as mean $\pm$ standard error (SE) of 4 mice. Statistical analyses are performed using the Mann-Whitney test. The asterisks (*) denote $p < 0.05$.

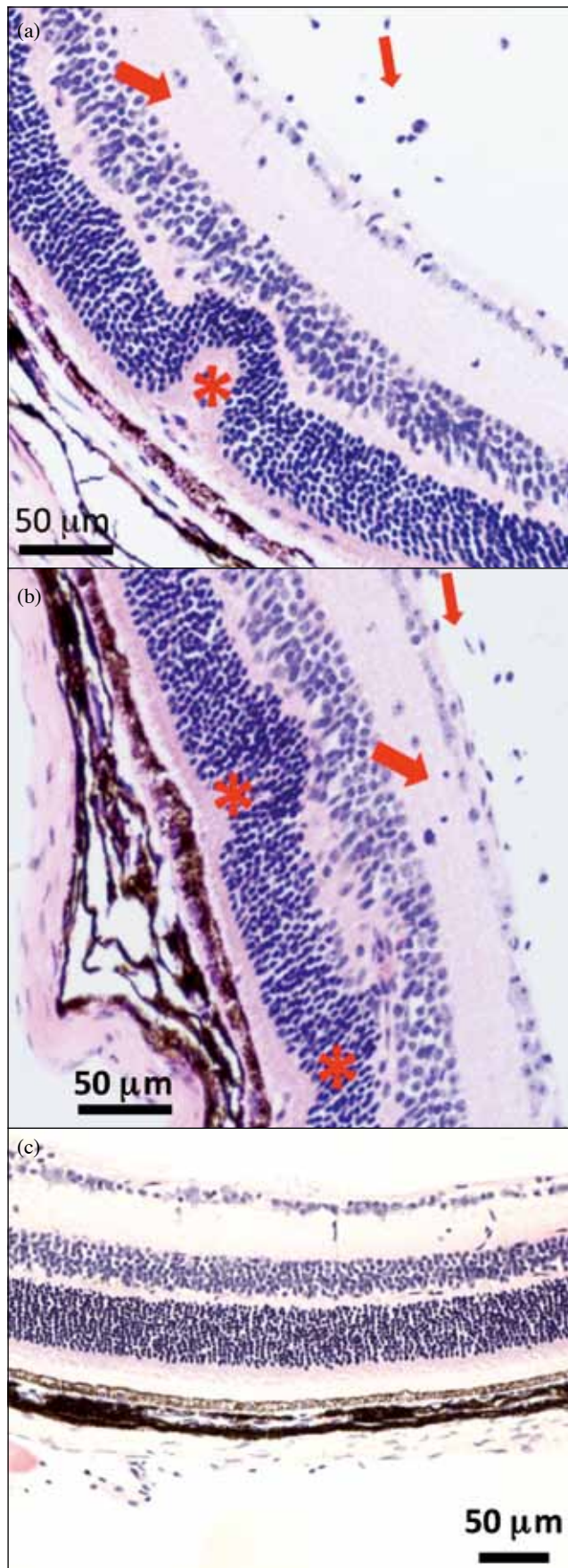


Figure 5. Histopathology of experimental autoimmune uveoretinitis in (a and b) C57BL/6J mouse (H&E stain, $\times 40$) and (c) normal mouse (H&E stain, $\times 20$). Cellular infiltrates in vitreous and retina (arrows) and retinal folds (asterisks) are shown.

major groups such as Th1, Th2, and Th17 that differ in phenotype and function. Th2 cells participate in allergic diseases and asthma, whereas Th1 and Th17 cells are involved in inflammatory and autoimmune diseases such as uveitis, multiple sclerosis and rheumatoid arthritis.^{50,51} In EAU, uveitis is driven by Th1 or Th17 cells.⁵² This result was revealed by comparing the effector cytokine dependence between the classic model induced by immunization with IRBP emulsified in CFA (CFA-EAU) and the novel model induced by injection of IRBP-pulsed, in-vitro-matured DCs (DC-EAU).²⁹ These 2 EAU models result in intraocular inflammation but differ in inflammatory features, disease duration and, importantly, involve different types of T cells: Th1 for DC-EAU and Th17 for CFA-EAU. In these experiments, neutralization of interleukin-17 (IL-17), but not interferon-gamma (IFN- γ), prevented CFA-EAU. On the contrary, DC-EAU required generation of an IFN- γ -producing effector response, while an IL-17 response by itself was insufficient to elicit inflammation phenotypes. Furthermore, genetic deficiency of IL-17 did not disturb DC-EAU susceptibility. These results demonstrated that the predominant phenotypes may be determined by conditions during the first exposure to antigens, such as the quality and / or quantity of toll-like receptor and the type of cells involved in the antigen presentation. For the classic CFA-EAU, DCs, monocytes, and $\gamma\delta$ T cells participate in or influence the antigen presentation process. Subsequently, DCs migrate into the regional lymph nodes and present the antigens to T cells. These mechanistic studies in animals have important implications for our clinical practice. Currently, it is difficult to determine the initial cause in patients with uveitis. Nonetheless, based on the comparable findings in animal and human scenarios, we can speculate the pathways relevant to the disease course and the implications for therapy.

Clinically, an EAU model serves as a useful means to investigate the mechanisms and effects of conventional therapeutic and novel immunotherapeutic strategies. To date, the US Food and Drug Administration (FDA) has approved many therapeutic approaches for clinical use based on the effective alleviation of inflammation in EAU animals, such as the topical use of cyclosporine⁵³ and anti-IL-2 receptor therapy using the humanized CD25-specific antibody daclizumab.⁵⁴ IFN- α has also been successfully used to treat uveitis patients with Behçet's disease, a rare immune-mediated small-vessel systemic vasculitis, in Europe based on studies in EAU animals.⁵⁵ Immunotolerogenic strategies such as the administration of retinal antigens is another promising approach that has been used to correct defective peripheral tolerance and to enhance the numbers and function of Tregs.⁵⁴ Additionally, the tolerogenic B cell-based therapy has been shown to modulate EAU in transgenic mice and has significant clinical potential.⁵⁶

According to the pathogenesis of EAU, inhibition or neutralization of the pathogenic effector cytokines produced by specific T cells, as well as blocking of the recruitment of inflammatory factors, may provide another therapeutic strategy for uveitis. Anti-tumour necrosis factor therapy,

Table 4. Scoring experimental autoimmune uveoretinitis histopathologically in mice.⁴⁰

Grade	Criteria
0	No change
0.5 (trace)	Mild inflammatory cell infiltration; no damage
1	Infiltration; retinal folds and focal retinal detachments; few small granulomas in choroid and retina; perivasculitis
2	Moderate infiltration; retinal folds and detachments; focal photoreceptor cell damage; small- to medium-sized granulomatous; perivasculitis and vasculitis
3	Medium to heavy infiltration; extensive retinal folding with detachments; moderate photoreceptor cell damage; medium-sized granulomatous lesions; subretinal neovascularization
4	Heavy infiltration; diffuse retinal detachment with serous exudate and subretinal bleeding; extensive photoreceptor cell damage; large granulomatous lesions; subretinal neovascularization

which was effective in EAU animals,⁵⁷ has been effective in controlling uveitis in patients with systemic autoimmune diseases, such as seronegative spondyloarthropathies and juvenile idiopathic arthritis.⁵⁸ As mentioned before, neutralization of IL-17 by monoclonal antibodies in mice aborts EAU, even when the uveitogenic effector T cells have already been generated.⁵² Meanwhile, migration and recruitment of inflammatory cells into the eye is another target for inhibition and may be achieved by disturbing adhesion molecules, chemokines, and their receptors on cell membranes. The integrin very late activation antigen 4 (VLA4)–specific monoclonal antibody has become an FDA-approved treatment for autoimmune diseases of multiple sclerosis and Crohn's disease.⁵⁹ Encouragingly, the treatment effects of blocking the VLA4 have also been observed in EAU mice.⁶⁰ Additionally, inhibition of EAU has been found in animals by blocking the chemokine receptor CXCR3 and CCR5 that are essential for migration of uveitogenic cells into the eye.^{61,62} Similarly, blockage of the integrin lymphocyte function-associated antigen 1 or its ligand

intercellular adhesion molecule 1 ameliorates EAU, as well as blocking CD44 which is the receptor for hyaluronan, osteopontin, collagens, and matrix metalloproteinases.^{63,64} Blocking these molecules can effectively prevent migration and recruitment of inflammatory cells into the eye.

Summary

Research on EAU is vital to understand the pathophysiological mechanisms involved in ocular autoimmune inflammatory diseases. After immunization with specific autoantigens, animals develop an autoimmune response mediated mainly by CD4+ T cells. The inflammatory features are used to mimic human autoimmune uveitis. Nonetheless, many questions remain unanswered, such as those relating to individual disease susceptibility and recurrence. With developments in genetic and molecular engineering, transgenic animals may help explore the pathogenesis and aid in development of specific and efficient new therapies with minimal side-effects.

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