

Experimental autoimmune uveitis and other animal models of uveitis: An update

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Over the past several decades, animal models of autoimmune uveitis directed at eye-specific antigens (Ags) have been developed. These have allowed researchers to understand the basic mechanisms that lead to these diseases and also recently helped the researchers in translational research for therapeutic interventions. Experimental autoimmune uveitis (EAU) is an animal disease model of human endogenous uveitis and can be induced in susceptible animals by immunization with retinal Ags. Ever since the first description of EAU in mice in 1988, several animal models of uveitis has been described by researchers. Disease-specific model for cytomegalovirus retinitis and tubercular uveitis has evolved our understanding of these complex entities. Endotoxin induced uveitis is another useful model for anterior uveitis, which is not an autoimmune process and is triggered by injection of bacterial endotoxin (lipopolysaccharides) resulting in a rapid short lasting uveitis. The current article will give an insight into the various EAU animal models and their current implications in translational research. The article will also highlight the different grading systems for EAU in the animal model.

Key words: Animal uveitis model, cytomegalovirus retinitis animal model, endotoxin-induced uveitis, experimental autoimmune uveitis, spontaneous, tubercular uveitis animal model

Uveitis is a general term used for the inflammation of the uveal tissue (iris, ciliary body, and choroid). Anatomically it has been classified as anterior, intermediate and posterior or as panuveitis. Noninfectious uveitis is believed to be autoimmune or immune-mediated.^[1] Although the distinction between autoimmune and immune-mediated uveitis is still indistinct, the autoimmune type is believed to be driven by aberrant immune recognition of self, whereas the immune-mediated is primarily an inflammatory reaction triggered by environmental (microbial) or autologous (tissue damage) signals. Uveitis, especially if untreated, can result in significant visual deficit and blindness. It accounts for 5–20% of blindness in the developed countries and 25% in the developing countries.^[2]

In idiopathic uveitis, the possible mechanism hypothesized is of molecular mimicry with common micro-organisms, but the etiological triggers in autoimmune uveitis are unknown. However, strong major histocompatibility complex (MHC) associations have been found to be linked with some of the different types of autoimmune uveitis [Table 1].

Patients with autoimmune uveitis frequently show immune responses targeted to ocular antigens (Ags) such as uveal

melanin and proteins involved in its metabolism like retinal arrestin (retinal soluble antigen or [S-Ag]), inter-photoreceptor retinoid-binding protein (IRBP), and recoverin.^[3,4]

The delicate nature of ocular tissues makes it difficult to obtain tissue specimens. This had greatly hampered the study of the mechanisms involved in uveitic disease. However, over the past several decades, animal models of autoimmune uveitis directed at eye-specific Ags have been developed.^[5-7] These have allowed researchers to understand the basic mechanisms that lead to these diseases. Historically the first such model was prepared in guinea pigs by injecting the retinal extracts. This resulted in very severe panuveitis. This model, over a span of several years and after various modifications in terms of animal species and usage of other Ags, has led to the development of what is now known as experimental autoimmune uveitis (EAU).

Experimental Autoimmune Uveitis

What is experimental autoimmune uveitis?

Experimental autoimmune uveitis (EAU) is an animal disease model of human endogenous uveitis. It can be induced in susceptible animals by immunization with retinal Ags. EAU resembles the key immunological characteristics of uveitis in humans as both are T-cell mediated diseases (Th1) targeting the neural retina and related tissues. EAU is induced by immunization with preparation of purified retinal Ags or their fragments.

The uveitogenic retinal proteins identified so far are as follows:

Retinal soluble antigen, arrestin

This 48-kDa intracellular photoreceptor protein is involved in the photo-transduction cascade. It binds to photo-activated phosphorylated rhodopsin, thereby apparently preventing the transducin-mediated activation of phosphodi-esterase.^[8]

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Table 1: HLA association of different ocular inflammatory conditions^[1]

Disease	Association
BRC	HLA-A29
VKH disease	HLA-DR4
Behcet's disease	HLA-B51
Intermediate uveitis (except associated with multiple sclerosis)	HLA-DR3

HLA: Human leukocyte Ag, VKH: Vogt Koyanagi Harada, BRC: Birdshot retinochoroidopathy

Inter-photoreceptor retinoid-binding protein

This 148-kDa protein is found in the inter-photoreceptor matrix, which helps in transporting Vitamin A derivatives between the photoreceptor and the retinal pigment epithelium (RPE). IRBP is composed of four evolutionary conserved homologous domains, which are thought to have arisen by gene duplication.^[9]

Rhodopsin and its illuminated form – opsin

This 40-kDa membrane protein is the rod visual pigment.^[10] Pathogenicity of this protein appears to be conformation dependent as rhodopsin is more pathogenic than opsin.^[11]

Recoverin

It is a 23-kDa calcium-binding protein. Recoverin controls the phosphorylation of the visual receptor rhodopsin by inhibiting rhodopsin kinase in photoreceptor cells.^[12]

Phosducin

It is a 33-kDa soluble cytosolic photoreceptor protein and regulates the G-protein mediated signaling in the retina.^[13] Out of all the above, the S-Ag and the IRBP are the most commonly used uveitogenic Ags for the EAU model.^[14]

Animal model for experimental autoimmune uveitis

Experimental autoimmune uveitis can be induced in a variety of species including rats, mice, monkeys, guinea pigs and rabbits.^[4,15,16] No animal model in itself represents the complete spectrum of human uveitis. Each has a unique characteristic that makes it suitable for the study of a particular disease aspect. The rat model combines the advantage of being average sized and well characterized immunologically and immuno-genetically.^[5] The Lewis rat is especially susceptible to develop diseases when challenged with retinal Ags.^[5] The Lewis strain has been hence particularly useful in studying uveitis due to its susceptibility to different Ags. The most susceptible strain of mouse is B10.R111, followed by B10.A. The C57BL/6 strain is useful to study the basic mechanism of uveitis. EAU in Lewis rats is an acute, self-limiting disease, which does not recur, however, in B10.A mouse a recurring form of the disease is seen.^[1]

Method of induction of experimental autoimmune uveitis

The classic EAU model of mice, as reported in 1988 and modified later^[14,17] was induced with IRBP. For induction of EAU, IRBP is emulsified in complete Freund's adjuvant (CFA), which consists of a suspension of tuberculosis bacteria in mineral oil. CFA is critical for inducing the disease in both mice and rats. Many mouse and rat strains also require an additional inflammatory stimulus in the form of pertussis

toxin.^[17] Following intradermal immunization with CFA the animals develop panuveitis in 1–2 weeks. The role of the adjuvant is to trigger a Th1 like response. The main features of EAU in animals are retinal and/or choroidal inflammation, retinal vasculitis, photoreceptor destruction and loss of visual function.^[11]

An alternate method of disease induction is known as the adoptive transfer.^[18] In this method, the disease is induced by injecting lymphocytes specific for retinal Ag. These Ags are taken from genetically compatible donors who had been immunized for EAU induction and are cultured *in vitro* with the Ag. The advantage of this method is that it does not require an adjuvant and the disease resembles the clinical situation in which the patient has circulating lymphocytes, which have been exposed to retinal Ags.^[18]

Genetics of experimental autoimmune uveitis susceptibility

Susceptibility to EAU is genetically controlled. It has been observed that different species and strains within species, vary in their susceptibility. Thus, rats develop EAU after immunization with either S-Ag or IRBP. Guinea pigs are susceptible to S-Ag but not to IRBP, and mice develop severe disease with IRBP, but not with S-Ag.^[19] Studies have shown that in order to develop EAU, a strain needs to have both a susceptible haplotype and a permissive background.^[19] The haplotypes that have been identified to be highly to moderately susceptible are H-2r, H-2k, and H-2b, in descending order.^[19] Some of the examples of the strains of the mice that have these haplotypes are B10.R111, B10.BR and C57BL/6 respectively. However, the disease in these strains will only develop in the presence of a permissive background. Hence, if the strain has a susceptible haplotype and a nonpermissive background, the disease will be seen in an attenuated form or will not develop at all.

Special models of experimental autoimmune uveitis

Humanized model of experimental autoimmune uveitis in human leukocyte antigen class II transgenic mice

In this model the mice lack the murine MHC class II molecule 1-A and are made transgenic (Tg) for the human leukocyte Ag (HLA) class II molecules HLA DR3, –DR4, –DQ6 or DQ8. Of these 4 strains, HLA – DR3 Tg mice develop the most severe disease when immunized with S-Ag. These mice are Tg for a single HLA molecule, however, in humans several HLA class II molecules are expressed together. It was observed that double Tg mice expressing DQ6 + DR3 or DR3 + DQ8 alleles were more susceptible than the single Tg models. This is an indicator that different HLA molecules influence each other for the development of the disease process. These humanized EAU models thus promise to help to identify the antigenic molecules responsible for human uveitis.^[20,21]

Experimental melanin induced uveitis

Antigenic extracts from melanin incite a disease that targets uvea, but not retina and presents as recurrent anterior uveitis (RAU) with choroiditis. This is seen in a very severe form in Albino Lewis rats who have promelanocytes, but no melanin pigment showing that the pigment is not the actual target of the disease. Experimental autoimmune anterior uveitis (EAAU) and Experimental melanin induced uveitis are elicited by injecting crude fractions of bovine RPE, iris and ciliary body.^[22-24] EAAU is a well-established model of acute anterior uveitis, which

resembles the human disease clinically and pathologically.^[23] It can be induced in Lewis rats with bovine melanin associated Ag from the iris and ciliary body. The resultant inflammation is present only in the anterior chamber. Collagen type 1 has also been reported as an Ag in EAAU.^[25]

A well-defined model with melanin associated Ag is experimental Vogt Koyanagi Harada (VKH) disease in rats by using recombinantly expressed tyrosinase-related proteins (TRPs).^[26] TRPs are proteins involved in the biosynthesis of melanin. The uveitis thus seen resembles VKH disease.

Endotoxin induced uveitis

Endotoxin-induced uveitis is a very useful model for anterior uveitis. It is not an autoimmune process and is triggered by the injection of bacterial endotoxin lipopolysaccharides (LPS). In this model after an injection of LPS (subcutaneous or intraperitoneal) a rapid but short-lived anterior uveitis is seen within 24 h of the injection.^[24] Endotoxin-induced uveitis in mice is typically milder than the one seen in Lewis rats. Although it is not known whether a similar type of disease exists in humans, this model has been very useful for studying the various aspects of the acute ocular inflammatory process and the different therapeutic interventions.

The models of myelin basic protein-induced RAU, uveitis induced with RPE membrane components (experimental autoimmune posterior uveitis = EAPU or RPE65 uveitis)^[27,28] and lens-induced uveitis^[1] are not in use currently.

An alternate model of experimental autoimmune uveitis induced with inter-photoreceptor retinoid-binding peptide presented by dendritic cells

Dendritic cells (DCs) are the main Ag presenting cells capable of stimulating nascent T-cells. Recently a model of EAU induced by the infusion of DC has been developed. These DC had been harvested from the spleens of mice injected with Flt3L DNA and later matured *in vitro* with LPS + anti CD40 antibody and pulsed with IRBP peptide 161–180.^[29] This EAU model differs from the classic EAU model immunologically, clinically and pathologically.

Mice with DC-EAU have a distinct appearance of the fundus, the lesions being punctate versus confluent in the conventional EAU model. The inflammatory infiltrate is neutrophilic in DC-EAU versus the monocytic infiltrate in CFA-EAU. The course of the disease is shorter, and the disease is milder in DC-EAU.

Spontaneous uveitis models

In these type of experimental models, the disease process is not triggered by the inoculation of the Ag but it develops

spontaneously over a period without any triggering agent. Some of these models are:

Human transgenic mice

Szpak *et al.*^[20] made a HLA-A29 Tg mouse that spontaneously develops a posterior uveitis that resembles birdshot choroidoretinopathy. The target Ag has not yet been identified yet.

R161H mice express a Tg T-cell receptor specific to IRBP residues 161–180 (IRBP161-180; amino acid sequence SGIPYIISYLHPGNTILHVD) and spontaneously develop ocular inflammation by 5–6 weeks of age.^[30]

Autoimmune regulator knockout mice

Autoimmune regulator (AIRE) is a transcription factor that has been shown to cause ectopic expression of many tissue Ags in the thymus.^[31] This expression has been found useful to delete or anergise the T-cells that respond with high affinity to self-Ags.

Autoimmune regulator deficient mice fail to express various self-Ags like S-Ag, IRBP and other retinal Ags in their thymus. And over a period these AIRE deficient mice develop antibodies against IRBP and spontaneous uveitis.^[32] Further, it has been seen that those AIRE deficient mice that do not express IRBP in their retina do not develop uveitis despite the fact that they express another potential target retinal Ags for uveitis.^[31]

Table 2 presents the clinicopathological differences between the spontaneous and the induced models of EAU.^[33]

Specific uveitis animal models

Some special experimental animal models have been developed over the past years which warrants a special mention.

Experimental animal model of cytomegalovirus retinitis

This model has been developed in the mice strain C5BL/6 which is susceptible to develop a retrovirus induced murine acquired immunodeficiency syndrome (AIDS) similar to AIDS.^[34] These mice develop a retinitis 8–10 days after intraperitoneal inoculation with murine CMV, which is characterized by full-thickness retinal necrosis with viral inclusions and cytomegalocytes and is quite similar to CMV retinitis in humans with AIDS. The retinitis develops in 90% of the immune-deficient mice as compared to 8% of the normal mice.

This model has been used to study the use of cytokine immunotherapy in CMV retinitis.^[35] It has been shown that treatment of immunosuppressed mice with polyethylene glycol-interleukin (IL-2) prior to inoculation with murine cytomegalovirus (MCMV) reduces the intraocular MCMV

Table 2: Clinicopathological differences between the spontaneous and the induced models of EAU

Type of model	Type of uveitis	Anterior chamber involvement	Type of lesions	Cellular infiltrates	ERG findings
IRBP induced (B10.RIII)	Monophasic and chronic posterior	Present	Diffuse retinal lesions	Extensive with exudates	Decline during acute and atrophy phase but partial recovery in the chronic phase
R161H (Tg)	Chronic posterior	Minimal	Focal retinal	Persistent cellular infiltrates	Decline during atrophy phase
AIRE knockout	Chronic posterior	Absent	Small focal retinal and choroidal	Less cellular infiltrates	Decline in atrophy phase

EAU: Experimental autoimmune uveitis, ERG: Electroretinography, IRBP: Inter-photoreceptor retinoid-binding protein, AIRE: Autoimmune regulator

replication and a decrease in the frequency of retinitis. This prospect has led to an exciting opportunity to explore the therapeutic effect of this cytokine in combination with ganciclovir to combat this potentially sight-threatening disease.

Experimental animal ocular tuberculosis model

Rao *et al.*^[36] developed an animal model of ocular tuberculosis from hematogenous spread of *mycobacterium tuberculosis* following aerosol delivery of the bacilli to the lungs of Hartley strain guinea pigs. All the exposed animals developed pulmonary tuberculosis, and 42% had ocular lesions resembling the human disease.

The animals demonstrated primarily posterior uveitis followed by intermediate and limbal inflammation. All the sites showed granulomatous inflammation and some showed the presence of acid-fast bacilli detectable by quantitative polymerase chain reaction. The animals treated with anti-tubercular therapy (ATT) showed no granulomatous inflammation indicating the importance of systemic ATT in the treatment of ocular tuberculosis.

However, the lack of retinal vasculature in the retina of guinea pigs would make it impossible to study the retinal vasculitis pathogenesis in this model. Having said this, still this animal model holds a lot of promise for understanding the pathogenesis of ocular tuberculosis and to develop further treatments for this clinical conundrum.

Cellular Mechanisms in Experimental Autoimmune Uveitis

Experimental autoimmune uveitis is a T-cell mediated autoimmune disease model. It has been proven in several studies beyond doubt that Th1 cells represent the main effector phenotype in EAU.^[37] The main evidence to this effect are: (i) There is an association in the mouse strains between susceptibility to develop EAU and genetic propensity to mount a Th1 (a high interferon [IFN γ]) response to IRBP. (ii) Immune T-cells derived from EAU models that caused EAU in normal mice when infused, were able to produce high IFN γ and low IL-4 *in vitro* when stimulated with IRBP. (iii) Immune T-cell populations that make less IFN γ are nonuveitogenic, but can be converted into uveitogenic phenotype by culture with IL-12.^[38]

All the above facts suggest a strong role of the Th1 cells as the main effector arm in the EAU.

However, a new effector T-cell phenotype was discovered recently which has been named after the cytokine IL-17. The

name of the lineage has thus been coined as Th17. This lineage has been now hypothesized to play an important role in many autoimmune diseases, and several studies indicated its uveitogenic role in EAU.^[39-42] In fact, the classical EAU model shows a mixture of Th1 and Th17 response i.e. both IFN γ and cytokine IL-17 are produced with very little IL-4. However, IFN γ predominates over IL-17 in not only the draining lymph nodes (periphery), but also in the target organ.^[41] However, studies show that the disease development can be stopped by neutralization of only IL-17 and not IFN γ , thereby indicating that the presence of IL-17 is more critical in the pathogenesis of the disease. IL-17 and Th17 effector response may also have a role in human uveitis, but additional studies are required to establish this association more concretely.

The assay of cytokines from the lymph nodes of DC-EAU models predominantly show an IFN γ dominant response with low production of IL-17.^[29] That IFN γ has a functional importance is further supported by the fact that an infusion of uveitogenic DC into IFN γ knockout mice failed to develop the disease although they developed a good Th17 response.

These findings thus show that EAU is driven by 2 effector arms, Th1 and Th17, depending on the model. The main difference lies in the manner in which the Ag is presented to the immune system. In CFA-EAU, the Ag is presented to the draining lymph nodes where the mycobacterial components of the adjuvant provide stimulation to the Ag presenting cells over a prolonged period of time. However in DC-EAU the stimulus is a more focused and limited type inciting a different type of response and disease.

Extrapolating this to human disease, it can be inferred that the dominant type of Th effector response depends on the milieu present during the initial recognition of the auto Ags by the immune system. The inciting agents leading to human uveitis are unknown, but if these EAU models are applicable to humans, the events surrounding the initial Ag exposure maybe critical to the nature of the subsequent disease. On-going trials targeting IL-17 in uveitis may soon provide answers to these questions.

Grading of Experimental Autoimmune Uveitis in Rat and Mouse

Clinical grading of EAU and histo-pathological grading has been reported by Caspi^[43] separately in mouse and rat [Tables 3 and 4]. This can be quite widely used in animal models of uveitis in different therapeutic intervention

Table 3: EAU-Clinical grading in rat and mouse (adapted from Caspi *et al.*)^[43]

Grade	Criteria of clinical grading in the rat	Criteria for clinical grading in the mouse
0	No disease; eye is translucent and reflects light (red reflex)	No change
0.5 (trace)	Dilated blood vessels in the iris	Few (1-2) very small, peripheral focal lesions; minimal vasculitis/vitritis
1	Engorged blood vessels in iris; abnormal pupil contraction	Mild vasculitis; <5 small focal lesions; 1 linear lesion
2	Hazy anterior chamber; decreased red reflex	Multiple (>5) chorioretinal lesions and/or infiltrations; severe vasculitis (large size, thick wall, infiltrations); few linear lesions (<5)
3	Moderately opaque anterior chamber, but pupil still visible; dull red reflex	Pattern of linear lesions; large confluent lesions; subretinal neovascularization; retinal hemorrhages; papilledema
4	Opaque anterior chamber and obscured pupil; red reflex absent; proptosis	Large retinal detachment; retinal atrophy

EAU: Experimental autoimmune uveitis

Table 4: Scoring of EAU histopathologically in rat and mouse (adapted from Caspi *et al.*)^[43]

Grade	Criteria in the rat	Criteria in the mouse
0	No disease; normal retinal architecture	No change
0.5 (trace)	Mild inflammatory cell infiltration of the retina with or without photoreceptor damage with <1/4 of retinal section affected	Mild inflammatory cell infiltration; no tissue damage
1	Mild inflammation and/or photoreceptor outer segment damage with $\geq 1/4$ of retinal tissue affected	Infiltration; retinal folds and focal retinal detachments; few small granulomas in choroid and retina, perivasculitis
2	Mild-to-moderate inflammation and/or lesion extending to the outer nuclear layer with $\geq 1/4$ of retinal tissue affected	Moderate infiltration; retinal folds, detachments, and focal photoreceptor cell damage; small-to-medium-size granulomas, perivasculitis, and vasculitis
3	Moderate-to-marked inflammation and/or lesion extending to the inner nuclear layer with $\geq 1/4$ of retinal tissue affected	Medium-to-heavy infiltration; extensive retinal folding with detachments, moderate photoreceptor cell damage; medium-size granulomatous lesions; subretinal neovascularization
4	Severe inflammation and/or full thickness retinal damage with $\geq 1/4$ of retinal tissue affected	Heavy infiltration; diffuse retinal detachment with serous exudate and subretinal bleeding; extensive photoreceptor cell damage; large granulomatous lesions; subretinal neovascularization

EAU: Experimental autoimmune uveitis

Table 5: Bird's eye view of the different experimental animal models

Type of model	Antigen used/method of induction	Example of model	Clinicopathological features
Induced models			
Induced rat model of EAU	Retinal antigens in CFA or adoptive transfer	Arrestin induced model in lewis rats	Very severe panuveitis which is acute and self-limiting
Induced mouse models of EAU	Ocular antigens in CFA or adoptive transfer of immune cells from immunized donors to naïve recipients	EAU induced in B10.R111, B10.A and C5BL/6 with IRBP	Uveoretinitis which is chronic Recurrences are seen in B10.A strain
Humanized Tg models (induced)	S-Ag in CFA	HLA-DR3 mice induced with S-Ag or its fragments	Posterior uveitis
DC-EAU	Infusion of antigen pulsed syngeneic DCs	B10.R111 mice are given splenic DC's elicited with Flt3L, matured <i>in vitro</i> and pulsed with IRBP p161-180	Punctate chorioretinal lesions with predominantly neutrophilic infiltrate. Disease course is milder and shorter than classic EAU
EMIU, EAAU	TRP 1 and 2	Rats inoculated with melanin components or TRP 1 and 2	VKH like illness with inflammation of anterior chamber, iris, ciliary body and choroid and fundus hypopigmentation
EIU	Bacterial LPS	Systemic injection of LPS in mice or rats or local intraocular injection in rabbits	Acute anterior uveitis. Rapid onset and short duration
Spontaneous models			
AIRE knockout mice	Deficient central tolerance	AIRE deficient mice develop antibodies directed at IRBP	Posterior uveitis
Tg mice	Tg mice deficient for human HLA class 1 antigen associated with uveitis	HLA-A29 Tg mice	BRC develops at 8-12 months of age
Double Tg mice	Double Tg mice expressing a neo self-antigen in the retina and an antigen specific TCR	R161H mice	Develop spontaneous uveitis at 5-6 weeks of age
Some specific models			
Experimental animal CMV retinitis model	MCMV inoculation in MAIDS affected mice	C5BL/6 mice with MAIDS inoculated intraperitoneally with MCMV	Full thickness retinal necrosis with viral inclusion bodies

Contd...

Table 5: Contd...

Type of model	Antigen used/method of induction	Example of model	Clinicopathological features
Experimental animal ocular tuberculosis model	Mycobacterium tuberculosis inoculation	Hartley strain guinea pigs infected with aerosol delivery of the bacilli	Primarily posterior uveitis followed by intermediate and limbal inflammation. All the sites showed granulomatous inflammation and some showed the presence of acid fast bacilli

DCs: Dendritic cells, BRC: Birdshot retinochoroidopathy, EAU: Experimental autoimmune uveitis, Tg: Transgenic, EMIU: Experimental melanin-protein induced uveitis, EAAU: Experimental autoimmune anterior uveitis, EIU: Endotoxin-induced uveitis, AIRE: Autoimmune regulator, CMV: Cytomegalovirus, MCMV: Murine cytomegalovirus, MAIDS: Murine Acquired Immunodeficiency Syndrome, CFA: Complete Freund's adjuvant, S-Ag: Retinal soluble antigen, TRP: Tyrosinase related proteins, LPS: Lipopolysaccharide, HLA: Human leukocyte antigen, TCR: T-cell receptor, IRBP: Inter-photoreceptor retinoid-binding protein, VKH: Vogt Koyanagi Harada

studies. Xu *et al.* proposed a clinical grading system for retinal inflammation in the chronic model of experimental autoimmune uveoretinitis using digital color fundus images. The authors used endoscopic imaging system to acquire digital fundus images. Fundus changes were classified as inflammatory changes, which include retinal tissue inflammation, vascular inflammation and optic disc inflammation and retinal structural damage.^[44]

With advances in spectral domain optical coherence tomography (SD-OCT), this imaging system was applied to develop an OCT-based grading system for EAU severity by Harimoto *et al.* The authors graded SD-OCT images of EAU as follows: Grade 1, a few infiltrating cells in the vitreous and retina; grade 2, increased vitreous cells, retinal vasculitis, and granulomatous lesion; grade 3, cell infiltration into the whole retina with disappearance of inner segment-outer segment line, and destruction of the retinal layer structure; and grade 4, disappearance of the outer retina.^[45]

Therapeutic Implications of Experimental Autoimmune Uveitis

The various EAU models [Table 5] have given us valuable insights into the pathogenesis of human uveitis, which has been translated into its use to develop various therapeutic agents to halt the disease process at different levels. The development of therapeutic agents has been aimed to strike the disease at all levels of its evolution.

Historically, therapeutic approaches used successfully to modulate disease in EAU models have been shown to be efficacious in clinic as well. T-Cell targeted therapies like Cyclosporine, FK506 and Rapamycin are already Food and Drug Administration approved and in clinical use.^[46] Anti-tumor necrosis factor (TNF) therapy, which has been efficacious in EAU^[47] has been used clinically with good results in sero-negative spondyloarthropathies and juvenile idiopathic arthritis.^[47] IFN- α is being used with relative success to treat uveitis in Behcet's disease.^[48]

The EAU model has given insights into the effector cytokines produced by the uveitogenic T-cells, which when neutralized lead to abortion of the disease process. Targeted therapies against TNF- α are already in clinical use.^[48] The finding that neutralization of IL-17 by monoclonal antibodies halts the development of EAU^[49] is being already investigated and clinical trials are underway to explore this as a therapeutic possibility.

Other potential targets are the adhesion molecules and the chemokines, which are responsible for migration and

recruitment of inflammatory cells. The blockage of integrin very late activation Ag-4 (VLA-4) inhibits EAU in mice.^[50] This VLA-4 specific monoclonal antibody is already in use in Crohn's disease and multiple sclerosis and is being evaluated for use in uveitis. Similarly, blocking of the integrin lymphocyte function-associated Ag 1 or its ligand intercellular adhesion molecule 1 inhibits EAU as does blockage of CD44.^[51,52] Blockage of chemokine receptors chemokine receptor type 3 (CXCR3) and CXCR5, which play a role in cell migration, also aborts EAU.^[53]

Conclusions

Uveitis is comprised of a variety of a heterogeneous group of disorders with ambiguous etiology and pathogenesis. The etiologic triggers of most types of uveitis are still unknown. Because of the limitation of ocular tissue available for studies, animal models of uveitis have been a wonderful resource to us for studying and understanding this mystifying group of diseases.

The EAU model has greatly increased our knowledge in understanding the whole mechanism of development of the human uveitis at both molecular and genetic level. The various advancements in the types of animal models like the Tg mice and the DC-EAU models have helped us further broaden our perspective about the pathogenesis of the disease [Table 3]. Numerous therapeutic agents have been developed using the EAU model, which have been put into successful clinical use. However, the search for the "wonder drug," which will target the retinal Ag specific T-cells that drive the disease is still on. There is a wide scope for further studies in this direction.

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