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Immunological disorders and autoimmunity

Animal models of autoimmune and immune-mediated uveitis

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Uveitis of putative autoimmune origin comprises a heterogeneous group of sight-threatening diseases prevalent in the US and worldwide. Several animal models, representing various forms of uveitis, have been developed. These models reproduce distinct aspects of human disease and can serve to study basic mechanisms and as templates for therapy. ‘Humanized’ models have recently become available that might help to better characterize the antigenic molecules driving human disease.

Introduction

Uveitic diseases in the US total about 150,000 cases per year and are estimated to cause about 10% of the severe visual handicaps [1]. Endogenous uveitis most probably has an autoimmune nature, driven by lymphocytes of the T lineage specific to retinal antigens (Ags) (see Glossary), that have failed to acquire self-tolerance [2,3]. The etiologic triggers are unknown, except possibly in sympathetic ophthalmia, where a trauma to one eye and release of normally sequestered ocular Ags into the draining lymph node is thought to trigger an aberrant response to these Ags. In idiopathic uveitis, MOLECULAR MIMICRY (see Outstanding issues) (see Glossary) with common microorganisms has been suggested. There are strong MHC associations with disease, patients exhibit frequent responses to retinal antigens and dramatic improvement is often seen with immunomodulatory agents such as cyclosporin, rapamycin and other treatments that target T lymphocytes. Thus, birdshot retinochoroidopathy (BRC) (see Glossary) is strongly associated with HLA-A29, Vogt-Koya-

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nagi Harada (VKH) (see Glossary) disease with HLA-DR4, Behcet’s disease with HLA-B51 and intermediate uveitis (not associated with multiple sclerosis) with HLA-DR3 among others [4]. Ags that might be involved in the etiology and progression of uveitis are increasingly being defined (see Outstanding issues). For example, BRC patients often have responses to retinal arrestin (S-Ag) (see Glossary), whereas VKH patients exhibit responses to tyrosinase-related proteins [5]. Cancer-associated retinopathy (CAR) (see Glossary) is believed to be driven at least in part by antibodies (Abs) to recoverin [6]. Immunotherapeutic approaches being developed with the help of animal models seek to understand the basic mechanisms that lead to autoimmune disease and to reprogram the immune system so as to re-establish functional tolerance to self-Ags.

Main body text

In vitro models

There is a paucity of *in vitro* models that represent aspects of ocular autoimmune or inflammatory disease. Currently, the only *in vitro* model studies cytotoxic effects of antibodies to recoverin on cultured retinal cells, such as photoreceptor and bipolar cells, which express this protein. Autoantibodies against recoverin are found in the sera of patients with CAR syndrome, and it is believed that they are causally associated with the retinopathy because retinal damage can be induced in animals by intravitreal injection of anti-recoverin Ab. If that is indeed the case, the *in vitro* model is

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Glossary

- Ab:** antibody (Abs – antibodies).
- Adjuvant:** a substance that stimulates the immune response.
- Ag:** antigen (Ags – antigens).
- AIRE:** autoimmune regulator – transcription factor that controls ectopic expression of tissue Ags in the thymus.
- Anticlonotypic Abs:** antibodies to the specific T cell receptor for Ag.
- BRC:** birdshot retinochoroidopathy.
- CAR:** cancer-associated retinopathy.
- Complete Freund's Adjuvant:** a suspension of heat-killed mycobacteria in mineral oil.
- EAAU:** experimental autoimmune anterior uveitis.
- EAPU:** experimental autoimmune posterior uveitis.
- EAU:** experimental autoimmune uveoretinitis or uveitis.
- EIU:** endotoxin-induced uveitis.
- EMIU:** experimental melanin-protein induced uveitis.
- Epitope:** minimal antigenic region of a protein recognized by T cells or antibodies.
- HEL:** hen egg lysozyme.
- IRBP:** interphotoreceptor retinoid-binding protein.
- Knockout:** made deficient in a particular gene by genetic engineering.
- LPS:** lipopolysaccharide (bacterial endotoxin).
- Molecular mimicry:** immunological similarity of unrelated protein molecules.
- RAU:** recurrent anterior uveitis.
- RPE:** retinal pigment epithelium.
- S-Ag:** retinal soluble Ag (retinal arrestin, 48 kDa protein).
- TCR:** T cell receptor.
- Tg:** transgenic, that is, expressing a foreign gene inserted by genetic engineering.
- TRP:** tyrosinase related proteins – proteins involved in biosynthesis of melanin.
- VKH:** Vogt Koyanagi Harada disease.
- Wild type (mice):** normal, genetically unmanipulated laboratory strain.

relevant to retinal pathology and can serve to study cellular and molecular mechanisms involved in retinal cell damage. In a series of studies Adamus [6] showed that these Abs are able to enter cells, and induce apoptosis through the mitochondrial pathway involving sequential activation of caspases 9 and 3. Although Abs to recoverin are the ones most extensively studied in this regard, similar cytotoxic effects against retinal cells were also seen with Abs to α -enolase and it is possible that additional studies will uncover other pathogenic Ab specificities.

In vivo models

For a small organ, the eye has a staggering number of models that represent various aspects of ocular inflammation. The models differ from each other in multiple respects, such as mode of onset (spontaneous or induced), the anatomical source and the biochemical method of the antigenic preparation, and finally the susceptible species (Table 1). The reader should note that owing to space limitations, the sources cited in most cases do not reflect the original description of the model, but rather point the reader to a useful current review and/or description of its use. Although no animal model by itself reproduces the full spectrum of human uveitis (see

Outstanding issues), each has unique characteristics that make it suitable for studying particular aspects of disease.

Within each model, the choice of species will be influenced by the particular needs of the study. Guinea pigs are particularly sensitive to developing anaphylaxis, which might make them a suitable model for testing some kinds of drugs. However, they have a nonvascular retina, which is different from that of humans and other mammals. The rabbit has a relatively large eye, which makes it an attractive model for development of local drug delivery systems such as implants. However, lack of a selection of well-characterized inbred strains make it unsuitable for basic studies of immunological mechanisms. The rat has been a useful model for many years because it combines the advantage of a reasonably sized eye and is relatively well characterized immunologically and immunogenetically. Furthermore, the rat, and in particular the Lewis strain, is susceptible to developing disease when challenged with a large variety of Ags, that result in development of distinct types of uveitis (Table 1). The reason for this high susceptibility of the Lewis strain to ocular autoimmunity (and autoimmunity in general) is unknown, but several reasons have been proposed, including low thymic expression of some retinal Ags, which would impede deletion of Ag-specific effector cells in the thymus [5]. The reason for this extremely high susceptibility is undoubtedly polygenic. An earlier study from our lab identified four chromosomal regions (quantitative trait loci) in the rat that are associated with susceptibility to experimental autoimmune uveoretinitis (EAU) (see Glossary) using F2 progeny of the susceptible Lewis and the resistant F344 strain [4]. Chromosome substitution strains for these regions are being developed, which will permit detailed study of these regions separately from the rest of the genome (Mattapallil and Caspi, unpublished). It is unclear at this point, but plausible that the same regions will also be involved in other retinal diseases for which these two strains exhibit differential susceptibility, because genes for autoimmune, inflammatory and infectious diseases were shown to be shared among different diseases and across species barriers. For basic mechanistic studies, the mouse is the most sophisticated and versatile model. Thanks to the many genetically manipulated strains, it is possible to do in the mouse what is impossible to achieve in other species.

To represent distinct types of human uveitis (e.g. anterior versus posterior), the use of different antigenic preparations will generally result in pathology that targets primarily the tissue where the Ag has originated. Historically the first model of ocular autoimmunity was induced by immunizing guinea pigs with retinal extracts, which was subsequently refined by purifying a soluble retinal Ag (S-Ag) from the photoreceptor cell layer. The resulting disease was an inflammation of the retina and choroid, developing into panuveitis in its more severe forms. This model has been extended to additional species and numerous other antigens, and is now

Table 1. Models of uveitis

Source of uveitogenic material	Antigen or mode of induction ^a	Main site of pathology	Susceptible species	Refs
Photoreceptor proteins (experimental autoimmune uveoretinitis – EAU)	Retinal arrestin (S-Ag)	Posterior pole (uveoretinitis)	Rat, rabbit, guinea pig, primate, HLA-DR3 Tg mouse	[5,7–10], Fig. 1
	IRBP		Rat, mouse, rabbit, primate	
	Recoverin, phosducin, rhodopsin/opsin Transgenic HEL or β -gal targeted to retina		Lewis rat Mouse	
Melanin components (EMIU, EAAU, experimental VKH disease)	Soluble or insoluble fractions of melanin; tyrosinase-related proteins 1 and 2	Anterior chamber, iris, ciliary body and choroid	Rat	[13–15,17]
RPE components (EAPU, RPE65 uveitis)	RPE membrane antigens (EAPU) purified RPE65 protein	Posterior pole (RPE) and choroid	Lewis rat Rat (various)	[19,20]
Lens components (experimental phacoanaphylaxis)	Lens homogenate Transgenic HEL targeted to lens	Panuveitis	Lewis rat Mouse	[5]
Nerve myelin sheath	Myelin basic protein	Anterior chamber, iris	Lewis rat	[21]
Spontaneous uveitis (EAU-like)	HLA-A29 transgene – target Ag unknown	Posterior (mimics Birdshot retino-choroidopathy)	Mouse	[11]
	HEL-HEL TCR Tg mice – HEL	Posterior	Mouse	L.V. Forrester, pers. commun. and http://www.abdn.ac.uk/ophthalmology/research.htm
	Athymic mouse implanted with neonatal rat thymus – IRBP(?) AIRE deficient mice – Ag unknown	Posterior Posterior	Mouse Mouse	[12] [22]
Non-autoimmune	Bacterial endotoxin	Anterior chamber, iris, ciliary body	Lewis rat, mouse	[15], Fig. 2

^a Uveitogenic peptide fragments have been identified that induce pathology in a given species. The pathogenic sequences and/or a reference to the original publication them, can be found in the cited bibliography.

known as experimental autoimmune uveoretinitis or uveitis (EAU) [5] (Fig. 1).

The typical method of EAU induction is by immunization of a susceptible animal with one of several Ags originating from the retina (Table 1). In order for EAU to be induced, the Ag must be emulsified in COMPLETE FREUND'S ADJUVANT (see Glossary) that contains an increased amount heat-killed mycobacteria, and in many cases an injection of heat-killed pertussis bacteria or purified pertussis toxin is required as an additional adjuvant at the time of immunization [5,7]. The adjuvant is required to trigger the type of innate immune response that will result in a Th1-like, proinflammatory adaptive response profile. In rats (usually Lewis strain) either the retinal soluble Ag (S-Ag = retinal arrestin) (see Glossary) or the interphotoreceptor retinoid-binding protein (IRBP) (see Glossary) can be used. Many uveitogenic EPITOPES (see Glossary) for the Lewis rat have been defined, which can be chemically synthesized and used in place of the whole protein to elicit disease. In mice the Ag of choice is IRBP. The most susceptible strain of mouse currently known is B10.RIII,

followed by B10.A. The C57BL/6 strain is only moderately susceptible to EAU, but because most of the available gene KNOCKOUT (see Glossary) and transgenic (Tg) (see Glossary) mice have been made or backcrossed onto the C57BL/6 background, this strain is very useful as a model for the study of basic mechanisms of uveitis. Each of these strains has had at least one peptide epitope defined that elicits EAU which can be used to induce disease in place of the whole protein [7]. EAU in Lewis rats is an acute, self-limited disease which does not recur, although the disease can take on a recurring form in the B10.A mouse [5].

An alternative way of disease induction, known as adoptive transfer, is by infusion of lymphocytes specific for a retinal Ag. These are taken from genetically compatible donors who had been immunized for EAU induction, and are cultured *in vitro* with the Ag for various periods of time. This alternative method of induction avoids the use of adjuvants in the recipient, and represents 'clean' efferent-stage disease, resembling the clinical situation where the patient has circulating lymphocytes that had already been exposed to the target Ag.

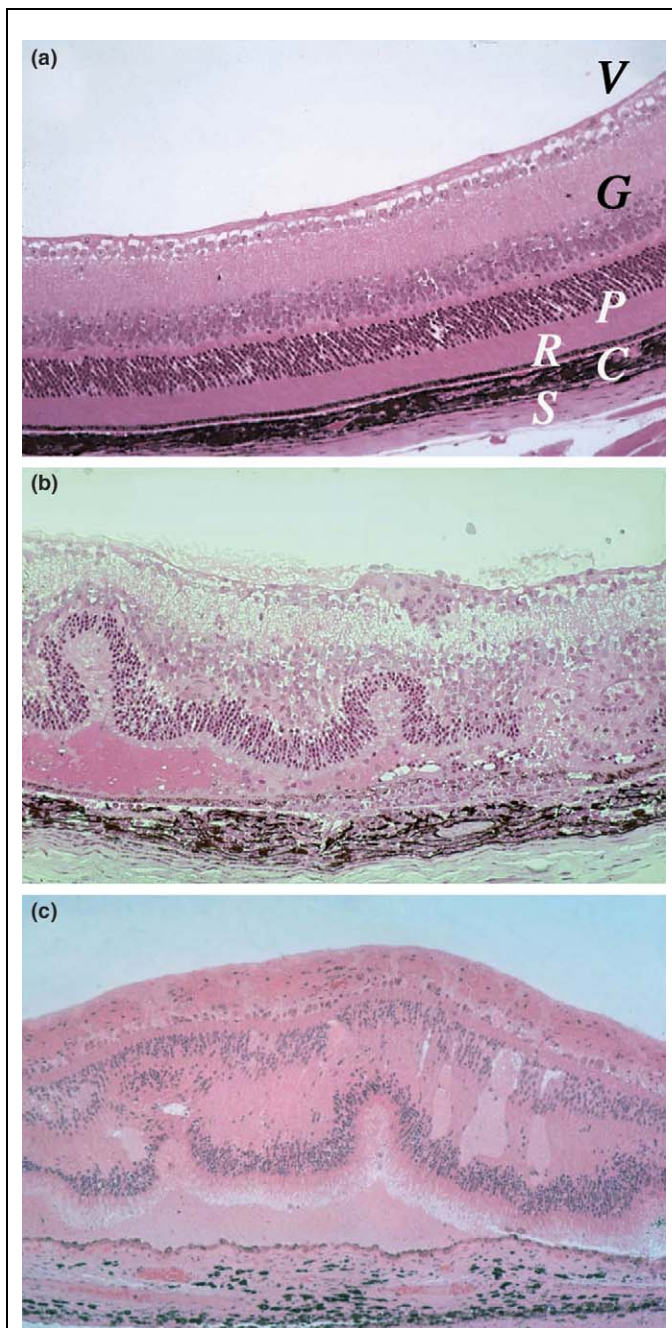


Figure 1. Histopathology of murine EAU compared with uveitis in human: (a) healthy mouse retina. A section of the posterior pole of the eye is shown. From top to bottom: V, vitreous; G, ganglion cell layer; P, photoreceptor cell layer; R, retinal pigment epithelium; C, choroid; S, sclera. (b) EAU was induced in the B10.RIII mouse by immunization with IRBP in complete Freund's adjuvant. Note disorganization and loss of nuclei in the ganglion and the photoreceptor cell layers, retinal folds, subretinal exudate, vasculitis, damage to the retinal pigment epithelium and choroid inflammation. (c) Uveitis in human (ocular sarcoidosis). Note gross similarity in pathological picture between (b) and (c). (Photographs provided by Dr Chi-Chao Chan, Laboratory of Immunology, NEI.)

Abs by themselves do not transfer disease, although they can aggravate the course of EAU when present [8].

In addition to the 'traditional' EAU model induced in WILD TYPE MICE (see Glossary) by immunization with IRBP or its fragments, several EAU variants in gene-manipulated mice have been described (Table 1). A useful model is based on expressing a well-characterized Ag, such as hen egg lysozyme (HEL) (see Glossary) in the retina under control of a retina-specific promoter, for example, rhodopsin or IRBP. Transgenic HEL or β -galactosidase expressed in the retina behaves immunologically like a native retinal Ag, and can serve as a target of uveitis upon immunization of the transgenic animals with HEL or β -galactosidase protein ([9,10] and L.V. Forrester, pers. commun.). In combination with a strain of mice expressing the complementary T cell receptor (TCR) (see Glossary) for this antigen as a transgene, a model is obtained that permits the direct tracking and study of uveitogenic cells with anticolonotypic Abs (see Glossary).

Another recently developed EAU variant worth mentioning is the 'humanized' model of uveitis in HLA-transgenic mice. In this model, mice made deficient for murine MHC class II and expressing transgenic human class II antigens, process and present retinal Ags on the human MHC molecules. Interestingly, HLA-DR3 Tg mice develop severe EAU with S-Ag, which is the retinal Ag to which human patients often exhibit lymphocyte responses, but which does not induce EAU in wild type mice. This 'humanized' EAU model promises to help identify the antigenic molecules driving human uveitis [8,11].

It is important to mention the models of spontaneous uveitis. BRC is highly associated with HLA-A29. Szpak *et al.* [11] made an HLA-A29 Tg mouse and found that it spontaneously develops a posterior uveitis that resembles BRC. The target Ag has not yet been identified. Another spontaneous model is retinitis that develops in AIRE (see Glossary) knockout mice. AIRE is a molecule that controls ectopic expression of tissue Ags in the thymus, including several retinal Ags. Although it has not been proven directly, it appears that the consequent lack of expression of retinal Ags in the thymus prevents negative selection of T cells reactive to retinal Ags, which exit into the periphery and cause the mice to develop a spontaneous EAU-like disease. This can also help us to understand an older 'spontaneous' uveitis model, which was reported to develop in athymic ('nude') mice implanted with a neonatal rat thymus [12]. It is probable that faulty negative selection of mouse effector cells in this situation permits emergence of self-reactive cells. Interestingly, these mice were reported to show immunological responses to IRBP, which is hypothesized to be the target Ag in this model.

Immunization with antigenic preparations from melanin elicits a disease that targets the uvea rather than retina, and manifest as recurrent anterior uveitis and choroiditis. Interestingly, severe pathology is induced in the albino Lewis rat,

which has promelanocytes but no mature melanin pigment, so that the actual pigment is not a necessary target of pathology. Experimental autoimmune anterior uveitis (EAAU) (see Glossary) and experimental melanin-protein induced uveitis (EMIU) (see Glossary) are elicited by immunization with rather crude fractions of melanin from bovine retinal pigment epithelium (RPE) (see Glossary) as well as from iris/ciliary body [13–15]. Because the actual melanin Ags involved in their pathogenesis are poorly defined, and because the clinical and histological manifestations are overlapping, it is difficult at this point to classify them as distinct models. Recently collagen type 1 was reported as an Ag involved in EAAU [16]. An interesting and relatively well-characterized model induced with melanin-associated Ags is experimental VKH disease, elicited in rats using recombinantly expressed tyrosinase related proteins (TRP) (see Glossary) 1 and 2. TRPs are proteins involved in biosynthesis of melanin [17]. The resultant uveitis resembles pathology seen in VKH disease, including anterior uveitis and fundus depigmentation, as well as meningitis and skin lesions.

All the induced ocular models described above, irrespective of the antigenic preparation used to elicit them and the target tissue of the pathology, appear to share essential immunological mechanisms. This includes the ability to be adoptively transferred with T cells, but not with serum, a dominant Th1 cytokine response profile and inhibition by cyclosporin treatment.

A useful model of anterior uveitis that is not autoimmune is the model of endotoxin-induced uveitis (EIU) (see Glossary), which represents an inflammatory response driven by innate immune mechanisms, elicited by systemic injection of bacterial endotoxin (lipopolysaccharide = LPS) (see Glossary) [15]. In this model, systemic injection of LPS (subcutaneous or intraperitoneal) elicits within 24 h a rapid but short-lived inflammatory response in the anterior chamber of the eye (Fig. 2). Cytokines and chemokines are involved in this response, but why would systemic injection of LPS cause a response in the eye, is still unknown. Also it is unclear whether there is a human equivalent of this response. Nevertheless, this model has been extremely useful in studying acute inflammatory processes in the eye.

In the interests of brevity, this review will not discuss the models of myelin basic protein induced recurrent anterior uveitis (RAU) (see Glossary), uveitis induced with RPE membrane components (experimental autoimmune posterior uveitis = EAPU or RPE65 uveitis) (see Glossary) and lens-induced uveitis because these are not mainstream models or no longer in current use. At this time they do not appear to offer an advantage over the models discussed above for understanding basic mechanisms of human uveitis or for developing novel therapeutic approaches. The interested reader is encouraged to consult the references cited in Table 1.

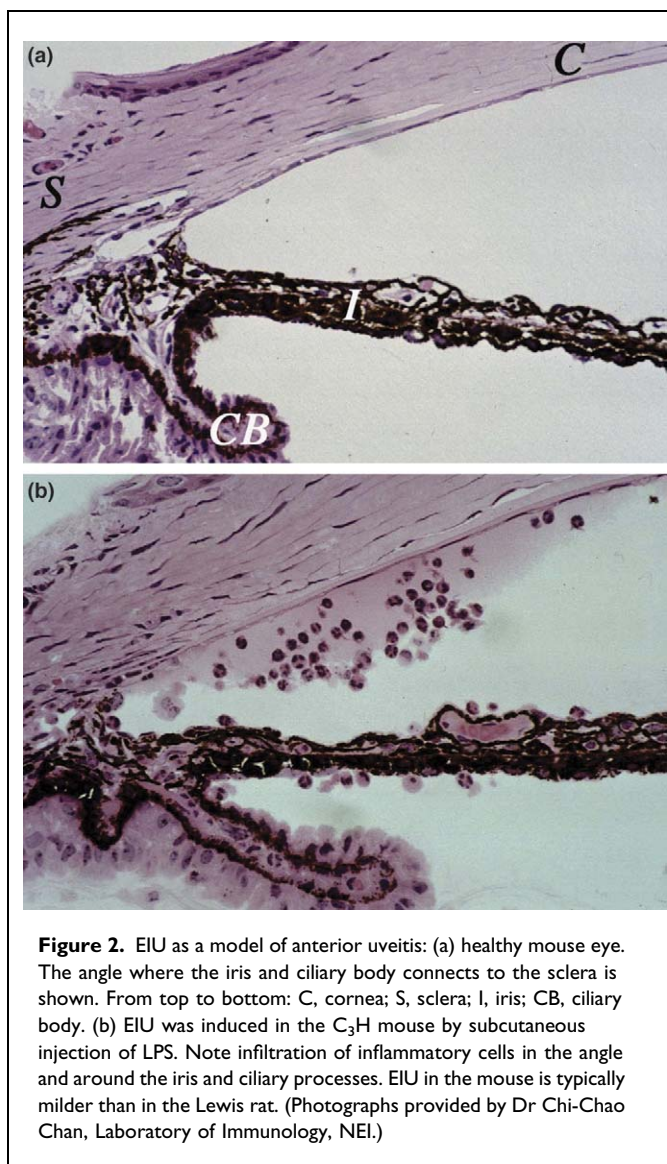


Figure 2. EIU as a model of anterior uveitis: (a) healthy mouse eye. The angle where the iris and ciliary body connects to the sclera is shown. From top to bottom: C, cornea; S, sclera; I, iris; CB, ciliary body. (b) EIU was induced in the C₃H mouse by subcutaneous injection of LPS. Note infiltration of inflammatory cells in the angle and around the iris and ciliary processes. EIU in the mouse is typically milder than in the Lewis rat. (Photographs provided by Dr Chi-Chao Chan, Laboratory of Immunology, NEI.)

In silico models

None

Model comparison

A quick Medline search reveals that by far the most widely used model for posterior uveitis is EAU, whereas EIU is the most widely used model for anterior uveitis (Table 2). Together, these two models account for the vast majority of publications on uveitis. Table 3 briefly compares these two major models of uveitis and the single *in vitro* model currently available. In this section, we shall not deal further with the *in vitro* model, owing to its limited popularity.

Some therapeutic approaches necessitate the use of models having a large eye, such as guinea pig or rabbit. However, because of the paucity of inbred strains, immunological reagents and genetic information available for these species, this comes at the expense of the ability to study the basic mechanisms involved.

Table 2. Usage of uveitis models – Medline search November 2005

Search terms	Hits
EAU, eye	392
Endotoxin-induced uveitis	209
Lens-induced uveitis ^a	29
EMIU, eye	13
EAAU, eye	11
(TRP1 or TRP2), uveitis	5
Anterior uveitis, MBP	8
EAPU, eye	5
RPE65, uveitis	3

^a Actual search term: ('lens-induced uveitis' or phacoanaphylac³) and (rabbit or rat or mouse) not EAU.

For the study of basic mechanisms of disease at the genetic and cellular and molecular level, it is necessary to use a well-characterized species. Because basic mechanisms of disease appear to be shared among the induced autoimmunity models, and largely among species, the overriding consideration might not be the species or the Ag used, but rather how much information about the species and the model itself are available. For posterior uveitis, the largest amount of information has been collected about the EAU model, including detailed knowledge of multiple uveitogenic proteins and their epitopes. For genomic and proteomic approaches, the rat and the mouse are most appropriate at this time, and their genetic code has largely been elucidated. Owing to the sheer abundance of genetically manipulated strains and immunological reagents available for the mouse, coupled with the already

available mouse strains having genetically altered expression of retinal Ags, the mouse EAU model clearly stands poised to yield most information on basic immunological mechanisms of ocular inflammation.

By contrast, EIU has been very valuable as an acute inflammatory model, with dominant involvement of innate immune system components. In addition, it serves as a model of anterior uveitis. Arguably, the various anterior uveitis models elicited with ocular melanin are a more faithful representation of human anterior uveitis, but these models have not gained anything close to the popularity enjoyed by EIU.

It should be pointed out that the eye in general has a unique advantage to study imaging of inflammatory processes owing to the transparency of the ocular media, which obviate the need to use invasive techniques to visualize the processes taking place in the tissue. Elegant studies by intravital microscopy of inflammatory cell trafficking and extravasation have been done in the models of EIU and EAU [18].

Model translation to humans

Although no animal model by itself reproduces the full complexity of human uveitis (see Outstanding issues), they nevertheless are important tools to study immunological mechanisms involved in ocular disease, and are invaluable as templates of therapeutic approaches. There is a mounting evidence that EAU in mice and rats shares many essential mechanisms with human uveitis and can thus be used as a reasonable representation of human disease. Although this is

Table 3. Comparison summary

	<i>In vitro</i> models (CAR)	<i>In vivo</i> models		<i>In silico</i> models
		Posterior uveitis (EAU)	Anterior uveitis (EIU)	
Pros	Easy, cheap	Reasonable representation of human disease. Inducible in several species. Many genetically manipulated strains permit sophisticated studies of mechanisms.	Easily and rapidly induced. A robust and well-characterized model. Inducible in several species.	
Cons	Limited in the type of information gained	Expensive. Experiments are often prolonged.	No parallel human disease.	n/a
Best use of model	Basic study of cell damage mechanisms	Studies of basic mechanisms in autoimmune disease and development of therapeutic approaches.	Study of innate inflammatory mechanisms. Imaging of inflammatory process.	n/a
How to get access to the model	Explants of rat retina are cultured in the laboratory	For mice: Jackson Labs. B10.RIII-H2 ^r H2-T18b/(71NS)Snj – Stock # 000457; C57BL/6J, H-2 ^b – Stock # 000664. Rat (Lewis and other strains): Harlan Sprague Dawley or Charles River Laboratories. Breeding stock for spontaneous and TCR Tg models of EAU can be obtained from the researcher(s) who developed the mice (see Table 2).	Lewis rat: Harlan Sprague Dawley or Charles River Laboratories. Mice: (C3H and other strains) Jackson Labs or Taconic Farms.	n/a
Relevant patents				n/a
References	[6]	[7], Fig. 1	[15], Fig. 2	n/a

a bit of circular reasoning, the similarity between EAU and human uveitis is supported by the fact that therapeutic strategies that were successful in treating the experimental disease, were often subsequently shown to have efficacy in the clinic [2]. By contrast, EIU, which is induced by a systemic injection of bacterial LPS, is not known to have a parallel condition in the human. Nevertheless, it has served as a useful model for ocular acute inflammatory processes and their effects on the tissue.

Conclusions

Animal models of ocular disease have provided an invaluable tool to study human uveitis and as templates for development of therapies. Current studies are taking advantage of state-of-the-art technologies to refine and focus the questions on development, maintenance and failure of self-tolerance to immunologically privileged retinal Ags, and how to restore immune homeostasis therapeutically. Genetically engineered mice are rapidly gaining importance for the understanding of basic mechanisms of disease. Neo-retinal Ag Tg mice, coupled with the corresponding TCR for that Ag, will help to dissect the trafficking and behavior of Ag specific effector cells. As more putative Ags are identified that might drive disease in the human, HLA-transgenic models, such as the HLA-A29 and HLA class II transgenics, will become more important to identify the pathogenic epitopes and to study HLA-related cellular and genetic mechanisms of susceptibility.

Outstanding issues

- Is all idiopathic uveitis in humans truly autoimmune?
- Is antigenic mimicry a triggering factor in human uveitis?
- What are the target Ags in human uveitis?
- How well do the animal models represent human uveitis?
 - Are 'humanized' models better than conventional models?
 - Are 'spontaneous' models better than induced models?
 - Is LPS uveitis a model in search of a disease?

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