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Understanding Autoimmunity in the Eye: From Animal Models to Novel Therapies

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Abstract

In recent years considerable headway has been made on understanding the mechanisms underlying inflammatory diseases of the eye. This includes the role of the innate vs. adaptive arms of the immune systems in disease, the concept that distinct immune pathways can drive end-organ pathology, and the role as well as limitations of immune privilege in controlling the innate and adaptive effector responses that lead to eye pathology and loss of vision. These insights have largely been derived from basic studies in established and in newly developed animal models of uveitis. The increased understanding of disease mechanisms has the potential to guide development of rational therapies for human uveitis. Many novel biologics currently in use or being evaluated have been developed, or validated, in animal models of autoimmune and inflammatory disease, including experimental uveitis. Paradoxically, and fueled in part by dwindling research budgets, a campaign has been gathering momentum against use of animal models in preclinical research, as being poorly representative of responses in humans. Given the extensive genetic similarity between humans and laboratory rodents as revealed by the Human, Mouse and Rat Genome Projects, and the finding that almost all known disease-associated genes have orthologs in mice and rats, perhaps the problem is our still-insufficient understanding of mechanisms and inadequate knowledge of species differences, resulting in poor choice of models, rather than in an inherent unsuitability of animal models to represent human disease.

Introduction

Non-infectious uveitis is an inflammatory condition within the eye that has no known infection etiology. Uveitis is a heterogeneous disease: it can be a standalone condition affecting the eye only, or can be part of a more generalized systemic syndrome (see Table 1 for examples). Patients exhibit secondary responses to retinal antigens that are involved in vision and are unique to the eye, and have strong associations with HLA. The latter are associated with induction of immune responses because they present antigens to T cells. These findings have led to the notion that uveitis is autoimmune in nature, with particular HLA molecules presenting autologous retinal antigens that are normally sequestered within

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the eye, to the immune system. Additional support for this notion came from clinical findings that uveitis tends to respond clinically to T cell targeting agents (such as CsA, rapamycin, IL-2R, Campath -- see Table 2) and that elevated inflammatory T cell responses of the Th1 and Th17 phenotypes often accompany the disease (Chi *et al.*, 2008; Wang *et al.*, 2012a). For ethical and logistic reasons, etiological agents and mechanistic associations are hard to study in humans. Nevertheless, animal models of uveitis induced by immunization with retinal antigens, or by transfer of retina-specific T cells (either Th1 or Th17) specific to these antigens, whose pathology is in many ways reminiscent of the human disease, would seem to support the notion that retina-specific T lymphocytes may be involved in driving disease pathology in humans.

Due to the heterogeneity and complexity of human uveitis, different animal models, induced and spontaneous, have been developed that permit to study various aspects of human disease. Induced models can be triggered by purely innate mechanisms, such as injection of bacterial products systemically or intravitreally. Inflammation is short-lived, and while they serve as proof of concept that innate mechanisms alone can induce an inflammatory response in the eye, it is unclear to what extent these models parallel human disease (Rosenbaum *et al.*, 2008). Alternatively, disease can be driven by the adaptive response whose T cell effector choice is instructed by innate mechanisms, i.e., immunization with ocular antigen in mycobacteria-containing complete Freund's adjuvant (CFA). Finally, infusion of polarized antigen-specific Th1 or Th17 cells represents uveitis induced by purely adaptive mechanisms (though innate immune effector cells are recruited to participate in pathology). Spontaneous uveitis models rely on initial high frequency of retina-specific cells, whether through introduction of a T cell receptor (TCR) transgene or due to compromised thymic negative selection (AIRE KO). For more detailed information about these models, the interested reader is directed to recent reviews on the subject (Caspi, 2006a; 2010; Horai and Caspi, 2011).

Major mechanistic insights into pathogenesis of uveitis, gained from recent studies using these models, are discussed in the following paragraphs.

Immune Privilege vs. Uveitis

The eye has a special relationship with the immune system known as immune privilege, which has been first recognized by Medawar in the middle of the previous century as persistence in the anterior chamber of skin grafts that would be rejected from a peripheral location (Medawar, 1948; reviewed by Niederkorn, 2006). The immune responses affecting the eye must therefore be viewed against the backdrop of its immunologically privileged status. As an example, we attribute the extraordinary rate of acceptance of (tissue unmatched) corneal grafts to ocular immune privilege. The eye is separated from the immune system by a blood-retinal barrier, which prevents free traffic of cells and even larger molecules in and out of the eye. In addition, the internal environment of the eye resists inflammation. This is due to immunoregulatory molecules present in ocular fluids and on the surface of ocular resident cells that confer upon the eye an ability to inhibit initiation and in some cases expression of immunity, and to convert naive T cells that have passively made their way into the eye, e.g., due to a vascular abnormality or microtrauma, to a

regulatory phenotype. The fact that uveitis occurs in the face of immune privilege has for a long time perplexed researchers, but we now understand that immune privilege is not a panacea and has limitations. On the one hand, the relative inaccessibility of the ocular compartment hinders induction of peripheral tolerance (Caspi, 2006b). On the other hand, the inhibitory ocular microenvironment, which is adequate to control naïve T cells, is unable to control T cells that have already acquired effector function in the periphery and are now actively able to cross the blood retinal barrier (Zhou *et al.*, 2012). Nevertheless, some aspects of privilege persist despite inflammation (Mo and Streilein, 2001) and may act to limit the amount of damage to the tissue as well as participate in induction of regulatory mechanisms and re-establishment of ocular homeostasis.

Etiology of Uveitis

We harbor in our bodies T lymphocytes that can respond to ocular antigens that have a rather high frequency. A simple calculation is based on the finding that frequency of T cells specific to S-antigen in peripheral blood lymphocytes is 4 per 10^7 lymphocytes by proliferation (de Smet *et al.*, 1998), representing at least 20− underestimation vs. methods using MHC-tetramers (Tan *et al.*, 1999). There are at least 10 antigens known to be uveitogenic in animals, including: S-antigen = retinal arrestin, interphotoreceptor retinoid binding protein (IRBP), rhodopsin, opsin, phosducin, recoverin, Rpe65 (RPE), melanin (iris, choroid), TRP1 and TRP2 (choroid), lens proteins, and undoubtedly many others. If the same is true for humans, this calculates to at least 80 eye-specific T cells per million lymphocytes in human peripheral blood. Because, as mentioned above, the relative inaccessibility of ocular antigens residing behind the blood-retinal barrier hinders establishment of peripheral tolerance, these cells are likely to be “ignorant” rather than tolerant, and are poised to be activated by a chance encounter with an antigen from the eye, or possibly a microbial mimic.

The prototypic ocular autoimmune disease, which fits this theory, is sympathetic ophthalmia (SO), an acute inflammatory condition precipitated by a penetrating trauma to one eye, followed weeks or months (and sometimes years) later by a destructive inflammation in the uninjured “sympathizing” eye. This is thought to be due to auto-immunization to ocular antigens released from the injured eye that reach the draining lymph node and activate autoreactive T cells. Indeed, presence of immune responses to eye-derived antigens (S-antigen, melanin-related proteins) has been reported in these patients (Gery *et al.*, 1986; Gery and Streilein, 1994). However, unlike SO, the etiology of most types of uveitis is obscure and the triggers are unknown. It has been speculated that infectious agents may trigger disease due to molecular mimicry, and mimics that induce uveitis upon immunization of Lewis rats have been reported (Wildner and Diedrichs-Mohring, 2004). More recently, we have obtained evidence in a new mouse model of spontaneous uveitis that commensal micro-biota may provide a trigger for development of disease (Horai, Zárate-Bladés, and Caspi, unpublished).

Autoinflammatory or Autoimmune, and Does It Make a Difference?

A frequent finding in uveitis patients is a detectable T cell memory response to retinal antigens. Most frequently, patients respond to retinal arrestin (retinal soluble antigen -- S-antigen), but responses to IRBP, and less frequently to other antigens, have been described (Gery et al., 1986; Gery and Streilein, 1994). These findings, in conjunction with the ability to reproduce critical disease manifestations in animals immunized with these antigens and strong HLA association of many uveitic diseases, have led to a strong conviction that non-infectious uveitis has an autoimmune basis. Although not all patients demonstrate such responses in vitro, in many cases this may be due to using the incorrect antigen or to the patients being on immunosuppressive therapy, which prevents expression of such responses.

Recently, a class of conditions has been recognized as autoinflammatory diseases (distinct from autoimmune), that may have strong genetic associations with innate immunity genes such as NOD2 or NLRP3 and can be clinically responsive to IL-1 inhibition (Masters *et al.*, 2009; Park *et al.*, 2012). This group of diseases prominently includes a number of conditions affecting the eye, namely, Behcet's disease, Blau syndrome, Muckle-Wells syndrome (MWS), and Chronic Infantile Neurological Cutaneous Articular Syndrome (CINCA, also known as Neonatal-Onset Multisystem Inflammatory Disease -- NOMID). The uncertainty surrounding the etiology of many uveitic diseases, and the reported (admittedly anecdotal) connection to infectious events, has raised the question whether non-infectious uveitis should be considered autoinflammatory rather than autoimmune in nature, a question that could have a bearing on therapy. Nevertheless, even in conditions now classified as autoinflammatory -- Behcet's disease prominently comes to mind, memory responses to retinal/uveal antigens have been reported. Therefore, the two concepts are not necessarily opposed -- irrespective of etiology, secondary responses to antigen released from damaged tissue may continue to drive disease, such that an autoinflammatory etiology may transition to an autoimmune progression. That said, innate immune cells are important in autoimmune tissue pathology, as they are recruited by the autoimmune effector cells and are the proximate effectors of tissue damage. Therefore, therapies directed at both adaptive immune components, namely, T cells, B cells and innate components such as monocyte-macrophages, neutrophils, as well as the cytokines elaborated by them, hold promise of efficacy (Table 2).

New Insights into Pathogenesis

We now have at our disposal categories of animal models to study both autoinflammatory and autoimmune mechanisms of ocular inflammation, which can help to examine this notion. Endotoxin-induced uveitis (EIU) and uveitis induced by muramyl dipeptide (MDP) or proteoglycan (PGN) injected systemically (EIU) or directly into the eye (all), which are driven solely by signaling through germ line-encoded receptors for microbial products, represent the former (Caspi, 2010). The different models of autoimmune uveitis (uveoretinitis), driven by antigen-specific T cells that recognize proteins found in the retina and uvea represent the latter (though innate cells and cytokines are involved both in the induction and/or effector stage). Importantly, a recent study from our lab demonstrated that a purely innate stimulus: injection of "blank" CFA containing mycobacteria but without

retinal antigen, can precipitate autoimmune uveitis in an IRBP TCR-transgenic line of mice that would not normally develop the disease, bridging the gap between innate environmental stimuli and development of adaptive autoimmunity (Horai *et al.*, 2013). Again, it is of practical relevance that even though they are very different mechanistically, innate and adaptive variants of uveitis share inflammatory mediators that may serve as therapeutic targets (Table 2).

Recent findings in animal models have demonstrated that, depending on the model, either the Th1 or the Th17 effector response can independently drive uveitis (Luger *et al.*, 2008). Elevated Th1 and/or Th17 responses have been described in different human uveitic diseases (Chi *et al.*, 2008; Furusato *et al.*, 2011; Wang *et al.*, 2012a); therefore, this finding may have a bearing on understanding of the heterogeneity of human uveitis. Notably, although in all the models of uveitis, induced and spontaneous, retina-specific Th1 and Th17 cells are both present, either one or the other can be functionally dominant. Thus, the "classical" model of experimental autoimmune uveitis (EAU) in rats and mice, induced by immunization with retinal antigen such as IRBP emulsified in CFA, is strongly dominated by the Th17 effector response. Inhibition of the IL-23/IL-17 pathway prevents or reverses development of disease (Luger *et al.*, 2008). In contrast, if the disease is induced by injection of antigen-pulsed dendritic cells (DC), the Th1 effector response predominates. This conclusion is based on the finding that wild-type DC infused into IFN-γ deficient mice fail to elicit disease, indicating that induction of an IFN-γ producing Th1 cell in the host is critical for disease induction (Tang *et al.*, 2007). In spontaneous uveitis developed by IRBP TCR transgenic mice, disease pathogenesis, as in the induced DC model, also appears to be Th1-dependent (Horai and Caspi, 2011; unpublished data) (Table 3).

In all the mouse uveitis models discussed above the target antigen (IRBP) and the genetic background (B10.RIII) are the same. This begs the question: what factors determine which of the two effector responses will predominate? This answer appears to be: the innate immune environment in which the initial antigen exposure takes place. The massive innate stimulation by the mycobacteria in CFA drives strongly towards Th17, whereas a less intense microbial stimulation in the other models may tip the balance towards dominance of the Th1 effector. It is possible that the conditions surrounding the initiating event(s) in human uveitis might have a parallel effect in determining the dominant effector T cell response associated with a particular disease. Thus, conditions surrounding an unknown initiating event might subsequently determine if, down the line, a therapeutic approach targeting the Th1 or the Th17 responses might be a good choice clinically.

That said, we should keep in mind that there is no direct evidence that the Th1 or Th17 responses recorded in uveitis patients are related to their disease, especially if it is part of a systemic syndrome. Furthermore, even if the observed response phenotype were to be related to pathology, T cell responses are plastic. This is true at the single-cell level (Th17 differentiate to Th1) and certainly at the population level, since different Th lineages are drawn from a common precursor. Thus, it is conceivable that suppressing one effector pathway could shift the response towards the other, without reducing pathology. As can be seen in Table 2, clinical trials targeting Th17 in uveitis have so far had mixed success and a recent trial of IL-17 neutralization in Crohn's disease, where Th17 cells were also thought to

have strong involvement, was stopped prematurely due to exacerbation of the symptoms (Hueber *et al*., 2012). Thus, clinical approaches targeting Th1 and Th17 lineages concurrently might have a greater chance of success, e.g., ustekinumab, which targets the p40 subunit common to both IL-12 and IL-23 that are involved in Th1 and Th17 responses, respectively (ClinicalTrials.gov identifier #NCT01647152). Another such approach, still at the preclinical stage, is targeting gp130 signaling, involved in signaling by L-27, which promotes Th1, and IL-6, which promotes Th17 response (Chong *et al.*, 2013; Wang *et al.*, 2012b).

Animal Models as Surrogates of Human Disease -- Are We Being Naïve?

The usefulness of animal models as a representation of human disease has recently come into question. In many immunological diseases, including uveitis, rodent models have been used to predict clinical outcomes of therapy, with variable success. This has led some investigators to propose that animal models are not clinically relevant. In the opinion of this author, this notion stems from insufficient understanding of the disease as well as of the model chosen to represent it, leading to unrealistic expectations and/or to use of the wrong model for the disease under study.

A major argument raised by opponents of preclinical use of animal models is that responses in animals to a particular therapy have not been able to accurately predict the responses in patients. Simple logic should tell us that this is actually more expected than surprising, given that the response of one patient does not predict the response of another patient, that each inbred mouse strain is genetically a single individual and that the vast majority of studies only use one strain (mostly C57BL/6). Examples abound throughout the literature that genetically different mouse strains, just like genetically diverse humans, can respond differently to the same physiological perturbation or immunological stimulus. The answer therefore could be to use more models, rather than no models, based on an improved mechanistic understanding of the disease in both animal and human.

As already mentioned, uveitis is heterogeneous in presentation, clinical course and in its associated immunological responses. It is therefore likely to also be heterogeneous in terms of underlying immunological mechanisms. Differential responses of uveitis patients to immunomodulatory agents, including biologics, support this contention. And yet, the vast majority of preclinical studies in animals have employed the “classical” immunization-induced EAU model in mice and rats, with its stereotypic Th17-dominated effector response, to represent uveitis in general (Table 2). It is perhaps surprising that responses to therapy in the EAU model matched the clinical effects of the various therapeutic modalities as well as they did (Table 2). Undoubtedly, using more than a single model of uveitis (Table 3) to examine the therapeutic potential of a new modality could help us not only to understand better the effector mechanisms involved in human disease, but also, down the line, to predict with greater accuracy those uveitis entities that are most likely to respond to a given therapy.

Finally, as an example of the wrong model for the disease, we seem to insist on using mice to study conditions for which they do not even possess the physical structures. Case in point:

modeling adult macular degeneration (AMD) in mice is problematic at best, because they do not have a macula -- not to speak of the difficulty of modeling diseases of aging that develop over many decades in a species as short-lived as the mouse. Granted, certain aspects of the disease can be modeled, but interpretations must recognize and take into account the relevant species differences.

The Human Genome Project, the Mouse, and the Rat Genome Projects, have revealed that 99% of mouse genes have analogues in humans (Waterston *et al.*, 2002) and 75–80% have direct equivalents (Church *et al.*, 2009). Furthermore, almost all known disease-associated genes have orthologs in mice and rats (Huang *et al.*, 2004). It therefore stands to reason that when used appropriately, animal models can provide invaluable information at the basic as well as the clinical levels.

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Table 1

Examples of Autoimmune Uveitic Diseases.

Restricted to the eye
Idiopathic uveitis
Sympathetic Ophthalmia
Birdshot retinochoroidopathy
Part of a systemic syndrome
Sarcoidosis
Behçet's disease
Vogt-Koyanagi-Harada disease

Table 2

Selected Traditional Therapies and New Biologics for Treatment of Uveitis and Their Associated Animal Models.

Targeted Pathway (Therapeutic Modality)	Biological Activity	Human Disease(s) (Refs)*	Animal Model (Refs)
Calcineurin (CsA, FK-506=tacrolimus)	Prevent T cell activation and proliferation by inhibiting the Ca2+/calmodulindependent protein phosphatase, calcineurin	Effective in various types of uveitis, often used as corticosteroid sparing agents	Rat EAU, monkey EAU
mTOR signaling (rapamycin=sirolimus, everolimus)	Interferes with mTOR signaling: inhibits T cell activation by modulating signaling pathways of IL-2, IL-4, and IL-15; promotes Treg induction	Systemic pilot study and local Tx in Phase III clinical trial indicate efficacy (Nguyen *et al*., 2013)	Rat EAU (Roberge *et al*., 1993); Mouse EAU (Hennig *et al*., 2012)
TNF-α (infliximab, adalimumab, etanercept)	Chimeric, fully humanized Abs to TNF-α (inflixi- and adalimumab, respectively) and TNFR-IgG Fc fusion protein (etanercept). The antibodies neutralize soluble and membrane bound forms of TNF-α; fusion protein binds to TNFR and prevents signaling.	Infliximab, and more recently adalimumab, show good efficacy in JIA; Etanercept appears not useful for treatment of uveitis.	Rat and mouse EAU models (Dick *et al*., 2004; Dick *et al*., 1996; Sartani *et al*., 1996)
IL-6 (tocilizumab)	Antibody to IL-6R; blockade of the receptor prevents IL-6 signaling; inhibition of direct proinflammatory effects of IL-6 and indirect such as induction of Th17 response	Effective in uveitis patients who failed anti TNF-α therapy	Mouse EAU (Haruta *et al*., 2011; Hohki *et al*., 2010)
IL-1 (anakinra, rilonacept, gevokizumab)	Recombinant IL-1RA (Anakinra) blocks binding of IL-1 to its receptor; engineered IL-1R-Fc fusion protein (Rilonacept) and monoclonal Ab Gevokizumab bind to and neutralize IL-1	Uveitis associated with resistant Behçet's disease or with CINCA syndrome respond to Anakinra. Rilonacept and Gevokizumab clinical trials pending.	Mouse EAU (Lim *et al*., 2005; Su *et al*., 2005)
IFN type 1 (IFN-α,IFN-β)	Recombinant human IFN-α and IFN-β: mechanism of action poorly defined	Extensive experience in various types of uveitis more with IFN-α than with IFN-β. Especially effective in Behçet's disease.	(Stubiger *et al*., 2003; Sun *et al*., 2011; Suzuki *et al*., 2002)
IL-2 (daclizumab)	Antibody to CD25 (IL-2Rα chain): blockade of high-affinity IL-2R; associated with emergence of suppressive CD56-bright NK cells.	Strikingly effective in several small, open-label trials in various types of uveitis, but a randomized, placebo controlled trial for Behçet's disease did not show good efficacy	Rat EAU (Higuchi *et al*., 1991; Nussenblatt, 2002)
CTLA-4 (ligand of CD80 and CD86) (abatacept)	CTLA-4-Ig fusion protein: prevents effective costimulation of T cells by antigenpresenting cells, by blocking the CD80 and CD86 molecules.	Recent reports indicate that abatacept is highly effective in JIA associated uveitis even in cases where the disease was refractory to immunosuppressive agents and TNF inhibitors	Rat EAU (Verwaerde *et al*., 2003)
IL-12/IL-23 p40 (ustekinumab)	Ab to IL-12/23 p40 subunit: inhibits Th1 and Th17 lineage commitment	Behçet's disease single case report (Baerveldt *et al*., 2013). Clinical trial pending (NCT01647152).	Mouse EAU (Tarrant *et al*., 1998; Yoshimura *et al*., 2009)
IL-17 (secukinumab= AIN457)	Monoclonal Ab to IL-17; IL-17 neutralization	An open label trial from Novartis reports efficacy in a mix of chronic intermediate, posterior, and pan uveitis (Hueber et al., 2010) but	Mouse EAU (Luger *et al*., 2008)

Targeted Pathway (Therapeutic Modality)	Biological Activity	Human Disease(s) (Refs)*	Animal Model (Refs)
		several placebo controlled trials in Behçet's disease did not meet primary efficacy criteria (Dick *et al*., 2013)	
CD-20 (rituximab)	Antibody to the CD20 molecule: depletion of B cells. Mechanisms may include reduction of B cell produced Abs and cytokines (IL-6) and elimination of antigen presentation by B cells to disease associated T lymphocytes.	Effective in uveitis and scleritis associated with different systemic syndromes, which was refractory to other treatments, e.g., Wegener's granulomatosis, Sjogren's syndrome and JIA	Mouse experimental autoimmune encephalomyelitis (Barr *et al*., 2012; Monson *et al*., 2011)
CD52 (altemtuzumab= Campath1)	Antibody to CD52: Depletion of T cells. New T cells may be "reprogrammed" for tolerance	Relatively few patients treated, but efficacy reported in various types of uveitis including Behçet's disease	Humanized SCID mice (de Kroon *et al*., 1996; Watanabe *et al*., 2006)

* If other references are not cited, the reader is referred to the following comprehensive recent reviews on biologics in uveitis: (Heiligenhaus *et al*., 2010; Heo *et al*., 2012; Larson *et al*., 2011; Leung and Thorne, 2013; Servat *et al*., 2012; Takeuchi, 2013).

Table 3

Either Th1 or Th17 Responses Can Drive Experimental Uveitis.

Model	Dominant Effector T Cell Lineage	Reference
"Classical" EAU induced by immunization with IRBP/CFA	Th17	Luger *et al*., 2008
Adoptive transfer of polarized retinaspecific effector T cells	Th1 or Th17*	Luger *et al*., 2008
DC-EAU induced by infusion of retinal antigen-pulsed mature DC	Th1	Tang *et al*., 2007
Spontaneous EAU in IRBP TCR transgenic mice	Th1	Horai *et al*., 2013 and unpublished data
Spontaneous uveitis in AIRE$^{-/-}$ mice	Not studied	Chen *et al*., 2013

* depending on the phenotype to which the cells were polarized in vitro. Th1 or Th17 cells can induce EAU independently; each one represents a fully competent effector phenotype.