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Immunological disorders and autoimmunity

Mechanisms Underlying Autoimmune Uveitis

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Autoimmune uveitis is a group of HLA-associated inflammatory diseases of the eye, which can cause blindness. Patients exhibit cellular and humoral responses to immunologically privileged antigens resident in the eye. Animal models of uveitis, induced with these retinal antigens, serve an important role in studying disease mechanisms and therapies. On the basis of animal and clinical studies, T lymphocytes are believed to play a central role in pathogenesis. T-cell-targeted therapeutic approaches are showing promising results in clinical trials.

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Introduction

Uveitis of a putative autoimmune nature has been estimated to affect 150,000 Americans annually [1]. Uveitis encompasses a group of potentially blinding inflammatory diseases, which can be limited to the eye, or can be associated with a systemic syndrome [2]. An autoimmune causality is supported by strong HLA associations and by frequent responses to one or more retinal antigens (Ags) [3]. Ocular trauma can precipitate uveitis, presumably through breach of the blood-ocular barrier and release of normally sequestered Ags. In most cases, however, the etiologic triggers are unknown and have been postulated to include antigenic mimicry by microorganisms in conjunction with a concomitant adjuvant effect, resulting in priming of T lymphocytes capable of recognizing ocular Ags. Such T lymphocytes are believed to persist in the circulation because of inefficient peripheral tolerance to Ags residing within the eye, as a consequence of their sequestration. The immune privileged status of the eye would thus be a double-edged sword, which hinders an immune attack, but also prevents potentially autoreactive lymphocytes from acquiring tolerance by encounter with ocular Ags under noninflammatory conditions.

Animal models of uveitis as a tool for the study of basic mechanisms

Experimental autoimmune uveitis (or uveoretinitis) (EAU) in mice and rats serves as an invaluable model for the study of basic mechanisms in autoimmune eye disease [4]. EAU is induced in mice or rats by immunization with a retinal protein or one of its fragments in complete Freund's adjuvant (CFA). After 9–12 days the immunized animals develop an ocular inflammation, ranging in intensity from mild inflammatory cell infiltration in the posterior pole to panuveitis and complete destruction of the retina. Alternatively, lymphoid cells from draining lymph nodes and spleen of immunized donors can be collected, cultured *in vitro* for varying periods of time with the specific Ag, and infused into genetically compatible recipients. The recipients will then develop typical EAU after a shortened latent period. The development and severity of the disease can be followed by periodic FUNDUS examination (fundoscopy) under a binocular microscope, as well as by histopathology [4]. Typical EAU histopathology is shown in Fig. 1. There exist variants of uveitis induced by immunization in CFA with Ags from other locations in the eye, such as ocular melanin and its subfractions or the RPE-65

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Glossary

ACAID: anterior chamber associated immune deviation. A deviant immune response induced as a result of injection of an antigen into the anterior chamber of the eye.
Ab: antibody.
Ag: antigen.
APC: antigen presenting cell (usually, but not always, a denderitic cell).
CD40 and CD40 ligand (CD40L): an interacting receptor (on APC and B cells) / ligand (on T lymphocytes) pair, involved in exchanging co-stimulatory signals between the cells involved in the interaction.
CFA: complete Freund's adjuvant (mineral oil supplemented with heat-killed mycobacteria).
DC: dendritic cell.
EAU: experimental autoimmune uveoretinitis (or uveitis). Autimmune inflammatory disaease targeting antigens in the neural retina.
Fundus: the part of a hollow organ farthest from its opening, in this case, the part of the eye's retina opposite the pupil and surrounding the optic nerve.
IRBP: interphotoreceptor retinoid binding protein.
Macrolides: a class of antibiotics with immunosuppressive properties that include Cyclosporin A and FK–506.
PT: pertussis toxin; the toxin produced by Bordetella pertussis bacteria.
RAU: recurrent anterior uveitis.
RPE: retinal pigment epithelium.
S-Ag: retinal soluble Ag (retinal arrestin).
TCR: T cell receptor.
4-1BB = CD137: co-stimulatory molecule that delivers a necessary 2nd singnal required us to elicit a positive response in a lymphocyte exposed to its specific Ag for the first time.

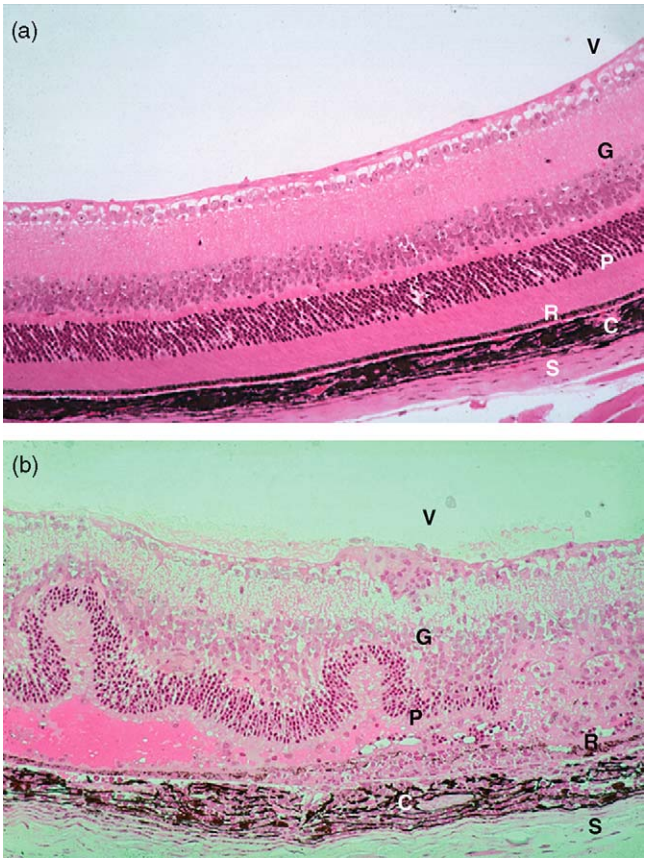

Figure 1. Typical EAU induced with IRBP in the B10.RIII mouse. (a) Healthy retina. Note ordered retinal layers *V*: vitreous; *G*: ganglion cell layer; *P*: photoreceptor cell layer; *R*: retinal pigment epithelium; *C*: choroid; *S*: sclera. (b) Uveitic retina. Note disorganized retinal architecture including loss of nuclei in the ganglion and the photoreceptor cell layers, retinal folds, subretinal exudate, vasculitis, disruption of the retinal pigment epithelium and inflammation of the choroid.

protein. These can target preferentially other compartments of the eye, such as the iris or choroid, but all indications are that they all share essential immunological mechanisms with EAU. An overview of animal models of autoimmune and immune-mediated ocular disease appears in another issue of this journal [5].

Central and Peripheral tolerance to ocular Ags

Self-tolerance is induced and maintained by a combination of central and peripheral mechanisms. The thymus expresses many tissue-specific Ags, which eliminate potentially autoreactive T cells by a process known as negative selection [6]. Studies on thymic expression of retinal Ags have indicated that they are indeed expressed in the thymus and their level of expression correlates with susceptibility [7]. Furthermore, they set the threshold of susceptibility to EAU both by negatively selecting retina-specific effector T cells and by positively selecting retina-specific 'natural' regulatory cells that protect from EAU [8,9]. Available evidence indicates that similar thymic control of repertoires specific to retinal Ags can also be true for humans [10].

However, negative selection in the thymus is never 100% efficient, and autoreactive T cells that failed to be eliminated exit the thymus into the periphery [6]. For most tissues, such lymphocytes have a 'second chance' at tolerance because they recirculate through the body and encounter tissue Ags under noninflammatory conditions (in the absence of co-stimulation). However, because Ags resident in the healthy eye are sequestered behind an efficient blood-organ barrier, they are not freely accessible to recirculating lymphocytes. Therefore, peripheral tolerance is unlikely to operate efficiently with respect to retinal Ags.

The notion of sequestration of ocular Ags has recently been questioned on the basis of the phenomenon known as anterior chamber associated immune deviation (ACAID). Ags injected into the anterior chamber of the eye are not ignored, rather, they induce a deviant type of immunity which includes generation of Ag-specific regulatory cells that suppress cell-mediated responses. However, one must be careful when extrapolating from these data to Ags residing in the healthy eye, because ACAID by necessity involves perturbation of the ocular integrity. Lack of substantial peripheral tolerance to retinal Ags has been supported by studies in rats and in mice, showing that forced peripheral expression of retinal Ag results in resistance to uveitis [11]. Thus, although once the ocular integrity is breached, 'active' privilege mechanisms such as ACAID can come into play, there is

no compelling evidence as yet that the intact eye can elicit peripheral tolerance to its resident Ags.

Processes leading to priming of potentially autoreactive T cells in uveitis

Because peripheral tolerance to retinal Ags is inefficient, autoreactive cells are present in the periphery and can become primed under the appropriate conditions. These might include, at a minimum, exposure to a retinal Ag or a microbial mimic, and probably adjuvant effect that provides 'danger' signals, which drive the adaptive response to generate the cell-mediated proinflammatory type of effector T cells. In the prototypic ocular autoimmune disease, sympathetic ophthalmia, a trauma to one eye precipitates a destructive inflammation in the fellow ('sympathizing') eye, apparently representing an autoimmune response to antigens released from the damaged eye. Microbial molecules have been described that mimic the sequence(s) derived from retinal proteins, for example S-Ag [12,13]. Studies in animals indicate that innate stimulation is crucial to drive the adaptive response towards the proinflammatory pathway [14]. This can be the IL–12/IFN-γ and/or the more recently described TGF-β-IL-6–IL-23/IL-17 effector pathway [15]. Without appropriate adjuvant stimulation EAU is not induced by administration of retinal Ag, and instead, tolerance develops.

Fig. 2 summarizes what we believe to be the important checkpoints in the pathogenesis of uveitis, starting with exposure to Ag and culminating in ocular manifestations of the disease. This sequence is based on studies from numerous laboratories over many years. Importantly, each of these stages can be targeted by therapeutic interventions directed at the particular checkpoint in the process. Examples of approaches that could be used to disrupt discrete stages in the process are shown at each checkpoint, although this is by no means an exhaustive list. Some of these are already in clinical use or clinical trials, but many have not yet progressed beyond the purely experimental stage. Immunotehrapeutic targets and approaches that have been explored to treat experimental and clinical uveitis are summarized in Table 1.

Because priming involves presentation of Ag to T cells by the MHC class II molecule in the context of co-stimulatory signals given by interaction between molecules such as B7 on the APC and CD28 on the T cell, it can be disrupted by blocking these processes. Ag presentation can be prevented by blockade of the MHC, by antibody (Ab) or by a competing Ag of high affinity to the MHC. In uveitic diseases there are some very strong MHC associations, for example, relative risk for developing Birdshot Retinochoroidopathy for HLA-A29-positive individuals can be as high as 229, whereas sympathetic ophthalmia and Vogt Koyanagi Harada disease are strongly associated with HLA-DR4 (relative risk more than 40) [16]. Although MHC blockade strategies have been reported to inhibit disease induction in some other autoimmune disease

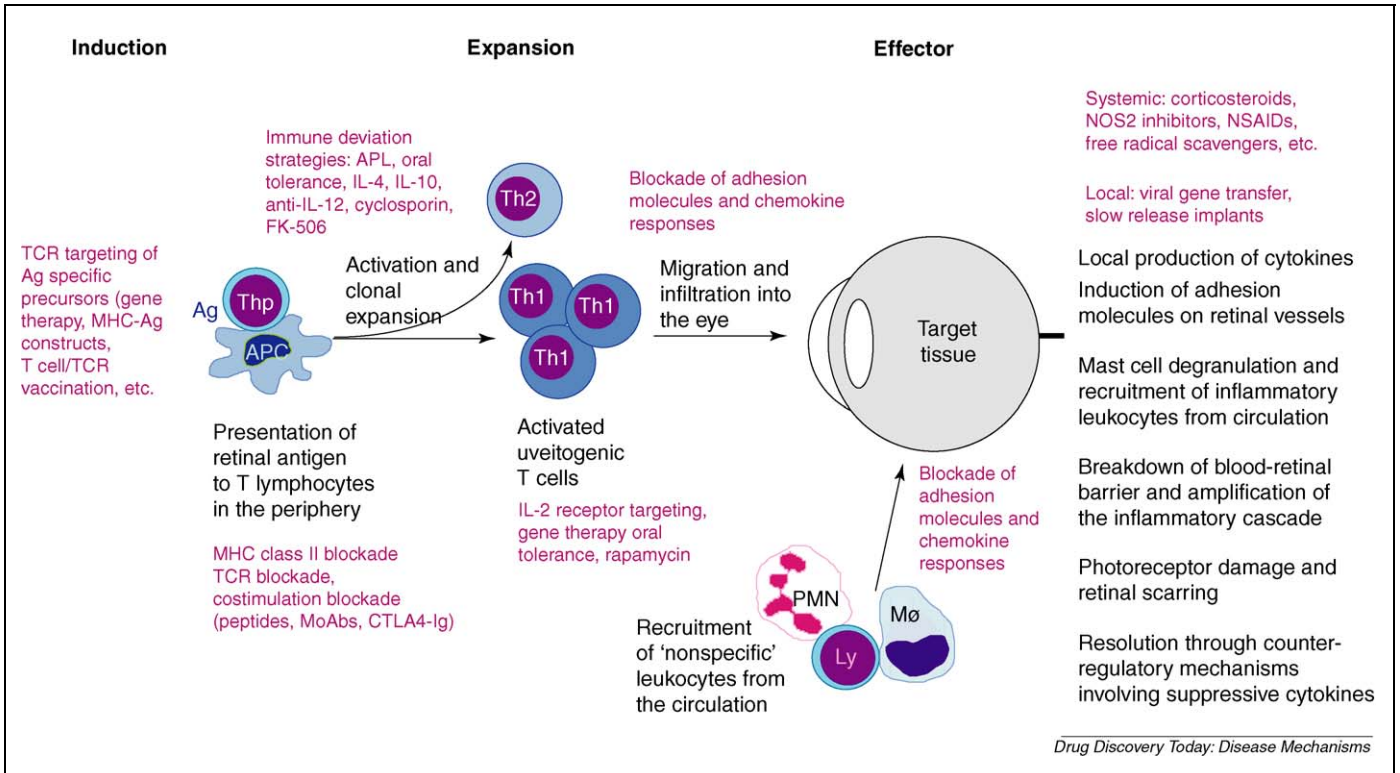

Figure 2. Crucial checkpoints in disease pathogenesis that can serve as targets for immunotherapy. The mechanisms are shown in black text, whereas targeting strategies are in purple text. Not all the strategies shown here have been examined in the uveitis model and therefore are not being discussed.

models, there are no reports of this approach being attempted in models of uveitis. Other possible targets are co-stimulatory molecules. If a T cell receives a signal through the T cell receptor (signal 1) without a cos-timulatory signal (signal 2), the result is anergy [17]. Thus, in theory, blocking co-stimulation should permit only signal 1 to be delivered and the autoreactive T cells would be anergized. Co-stimulatory blockade showed clinical promise in models of transplantation, however, its success in animal models of uveitis was limited. Whereas blockade of 2 different co-stimulatory receptor-ligand pairs, B7-CD28 or CD40-CD40L, prevented onset of the disease [18–20], long-term tolerance was not induced [18,19]. Whereas these two co-stimulation pathways act by delivering positive co-stimulatory signals, the 4-1BB CD137 pathway delivers a negative co-stimulatory signal to T cells that have already been activated. Abrogation of EAU expression was achieved by an agonistic anti-CD137 Ab [21], in line with similar effects of 4-1BB crosslinking on a series of other tissue-specific autoimmune diseases. It is unknown whether long-term tolerance was induced by this treatment.

After exposure to Ag the autoreactive T cells undergo clonal expansion and differentiate towards a pathogenic effector phenotype. This stage can be targeted as well. Already in routine clinical use to inhibit T cell expansion are corticosteroids, MACROLIDES such as cyclosporin A (CsA), FK-506 (Tacrolimus) and rapamycin, as well as the DNA synthesis inhibitor mycophenolate mofetil (MMF) [2]. FK-506 and CsA are calcineurin inhibitors that inhibit IL-2 production and IL-2R expression. Rapamycin acts later in the pathway and markedly impedes the response to IL-2. MMF through its active derivative mycophenolic acid acts to inhibit guanosine nucleotide synthesis in B and T lymphocytes and slows their proliferative response. A recent approach that has shown promise in a clinical trial is administration of humanized anti-IL-2 receptor antibodies (Daclizumab). This approach was based on the premise that effector T cells are activated and express IL-2 receptors. However, it is now known that regulatory T cells, present also in humans, express IL-2 receptors and might be eliminated by such treatment. Nevertheless, most patients treated with infusions of Daclizumab showed favorable responses [22,23]. The mechanism, however, is complex and seems to involve expansion of regulatory NK-like cells rather than depletion of effector T cells [24].

Ag-specific approaches, targeting both priming and/or clonal expansion and effector generation, could be used to either tolerize the Ag-specific T cells or deviate them into a non-pathogenic pathway of differentiation. Several Ag-specific therapies have been explored in uveitis models (Table 2). These include a wide gamut of approaches, from oral administration of retinal arrestin (S- Ag) (which has shown promise in a clinical trial) [25], through tolerogenic dendritic cells and genetic therapies designed to express the retinal Ag in the periphery – thus effectively revoking its immune privileged status [11,26,27] - to sophisticated reagents such as soluble Ag-MHC complexes that seek to deliver signal 1 without signal 2 to T cells [26,28]. Although Ag-specific interventions hold the promise of most precisely targeting the disease-relevant cells, there are several problems that have thus far prevented their development as useful clinical tools. Firstly, Ags involved in uveitic disease are not certain and are only now beginning to be identified. Secondly, there is a concern to introduce a potentially pathogenic auto-Ag into an already primed host. Thirdly, single-Ag therapies do not address the problem of epitope and Ag spreading, shown to occur in

Table 1. Targets and related therapies

Targeted process	Strategic approach to target	Expected outcome of intervention at target	Who is working on the target	Therapies in trial (if applicable)	Refs
Co-stimulation of T cell priming	Blockade of co-stimulatory molecules by non-agonistic monoclonal Abs	Reduction of T cell priming and induction of T cell anergy	Caspi *et al.*, Kaplan *et al.*	None	[18–20]
Il-2 production and signaling	Reduction of T cell expansion by macrolide antibiotics: CsA, FK-506, Rapamycin	Reduction in number or function of effector T cells	Various	Already in clinical use	[2]
Binding of IL-2 to its receptor	IL-2 receptor blockade using monoclonal abs	Reduced generation of effector T cells	Nussenblatt *et al.*, NIH	Phase I/II completed, Phase III starting	[23,24]
Generation or function of Ag-specific effector T cells	Induction of Ag-specific tolerance (see Table 2 for details)	Reduction in number and/or activity of Ag-specific effector T cells through induction of apoptosis, anergy or regulatory cells	Various (see Table 2)	Phase I/II trial on oral tolerance to S-Ag completed	See Table 2
Inflammatory cell recruitment	Adhesion molecule blockade, chemokine receptor blockade	Reduction of inflammation by prevention of leukocyte influx	Not current	none	[36–38]
Local inflammatory processes	Local production of an immunosuppressive cytokine by gene transfer	Reduction of local production of inflammatory cytokines and chemokines	De Kozak *et al.*	none	[48]

Table 2. Antigen specific therapy strategies for uveitis

Strategy	prevention	reversal	Comments	Refs
Mucosal tolerance	Yes	Yes (in relapsing EAU)	Clinical trial in oral tolerance performed with encouraging results	[25]
Retinal Ag expressed in the periphery by gene transfer (BM stem cells, autologous B cells, naked DNA vaccination)	Yes	Yes	Immunoablation required for BM stem cell approach	[4,5,11], Silver and Caspi (unpublished)
Ag-MHC class II dimers	Yes	Probably	*In vitro* data only. Tolerance induced in polarized T cell line bodes well for reversal	[28]
Ag pulsed semimature DC	Yes	Unknown		[26]
altered peptide ligands	Yes	Unknown	Alanine-substituted analogs of p161-180	Cortes and Caspi (upublished)
Inhibition of effector T cells and induction of regulatory T cells by α-MSH	Yes	Yes	Modeled after eye-derived tolerance mechanisms	[42]

animal models of autoimmunity, including uveitis [29]. Finally, because it is difficult to alter the functional program of T cells that have already differentiated into a particular effector phenotype, approaches that incorporate immune deviation tend to be more effective in prevention than in reversal of the disease process. Because the patient already has an ongoing disease process, are preventative approaches that target naive cells being exposed to Ag for the first time even relevant? The answer is 'yes'. In chronic autoimmunity new lymphocytes are continuously recruited into the effector pool (see ahead) and blocking this process can be expected to prevent progression of disease.

How do primed autoreactive cells get into the eye

The eye is a profoundly immunosuppressive environment, and it is unlikely that naive T cells can become productively primed within the eye. Current data indicate that priming takes place in the regional lymph node, on specialized APC, usually DC. Autoreactive T cells that recognize retinal Ags probably are primed in the periphery, whether as a result of exposure to retinal Ags released from a traumatized and possibly infected eye, or a crossreactive microbial mimic. Uveitogenic immunization to induce EAU attempts to replicate this hypothetical situation. The question is how do the first primed cells find and enter the retina of the eye, where their target Ags are located, because the eye is initially intact and its Ags are tightly sequestered behind the blood retinal barrier. The word 'homing' has been invoked to describe this process, but this is probably a misnomer, because it implies some sort of specific attraction to the eye. It is hard to imagine how a migrating T cell can 'sense' its Ag is on the other side of the blood-retinal barrier, nor can these T cells, which have been primed in the periphery, recognize 'addressins' that would guide them into the eye, because they did not originate there. Although low level of mRNA for certain chemokines has been detected in the healthy retina [30,31], it is open to question whether that has a role in recruitment of these first T cells into the eye. In fact, experimental data demonstrated similar kinetics for initial extravasation into the healthy eye of adoptively transferred retinal S-Ag-specific versus nonspecific T cells: out of 10 million activated cells infused into a rat, 150 cells were found in the entire retina 24 h later and had disappeared over the next 24 h. However, whereas transfer of the nonspecific T cells produced no sequel, animals receiving the specific T cells subsequently developed severe EAU [32]. These results suggest that the initial T cells enter the eye at random, and EAU is triggered if there is recognition of specific Ag *in situ*. This notion was subsequently confirmed and extended by Thurau *et al.* [33].

Local recognition of Ag and recruitment of inflammatory cells – the inflammatory cascade

Although the inflammatory events caused by the first few Ag-specific cells that enter the eye are below the resolution of our current methods to detect, the studies mentioned above indicate that these T cells must recognize their cognate Ag to initiate the inflammatory cascade [32–34], which includes local production of cytokines and chemokines by infiltrating as well as ocular resident cells [31]. The retinal vascular endothelium becomes activated through the action of these inflammatory mediators, which facilitates leukocyte adhesion and extravasation towards the chemokine gradient emanating from the inflamed tissue. These recruited cells then produce their own mediators, amplifying the inflammatory cascade. Injection of a small number of metabolically labeled uveitogenic T cells into the eye was followed by a rapid recruitment of host-derived unlabeled leukocytes, which quickly outnumbered the few Ag-specific T cells [35]. Possible

therapeutic targets at this stage of pathogenesis are adhesion molecules and chemokine receptors. The potential efficacy of targeting these molecules is indicated by the finding that treatment of animals immunized for EAU with antibodies to the lymphocyte surface adhesion molecule LFA-1, or with Ab to its receptor on the vascular endothelium, ICAM-1, reduced disease scores, and a combined treatment had an additive effect [36]. Also, mice that received an infusion of uveitogenic T-lymphocytes with pertussis toxin (PT) (known to disrupt chemokine receptor sigaling through inhibition of Gi proteins) completely aborts induction of EAU. However, the lack of selectivity of PT action makes it highly toxic. Although Ab blockade and small molecule inhibitors of particular chemokine receptors have been described, the redundancy of interactions between chemokines and their receptors limits the usefulness of blocking single receptors [37,38].

Chronicity and its mechanisms

Unlike the mouse and rat EAU models, uveitis in patients tends to be a chronic, long-term disease that requires ongoing treatment to keep it under control. This might be due at least in part to continuous priming of new autoreactive T cells that are recruited into the effector pool. In other autoimmune disease models, emergence of responses to new antigenic specificities has been described as part of this process [39]. This is known as epitope spreading and Ag spreading, where responses appear to other epitopes within the same molecule and within other molecules from the same target tissue, respectively, whereas responses to the original antigenic specificity can be downmodulated. Because rodent models of uveitis tend to be acute and monophasic, this phenomenon has thus far not been observed in the commonly used mouse and rat EAU models. However, convincing evidence for epitope and Ag spreading has recently been reported in the spontaneously occurring equine recurring uveitis (ERU) [29].

Resolution mechanisms

The natural history of the disease in humans includes relapses and remissions, and in some cases the disease can resolve spontaneously. What might be the regulatory mechanisms that could bring about remission and even complete resolution? Several mechanisms that limit immune (and autoimmune) responses have been demonstrated in animal models, but they still remain to be studied in uveitis patients: (i) precursor exhaustion – depletion of the Ag-specific effector pool; (ii) induction of active regulatory mechanisms. One such mechanism could be ACAID or an ACAID-like phenomenon. ACAID has been well studied in animal models [40]. Upon injection of a foreign Ag into the eye, it finds its way into the spleen, and there induces generation of Ag-specific CD4+ and CD8+ regulatory cells. These inhibit the acquisition and the expression, respectively, of effector function by Ag-specific T cells. Also, postrecovery regulatory cells have been described, which might, or might not, partly overlap with the ACAID-like regulators [41]. Their induction has been reported to be dependent on presence of the eye but the reason for this requirement is presently unclear [42]. (iii) Finally, 'natural' CD4+CD25+ thymic-derived regulatory T cells, which are known to raise the threshold of susceptibility to EAU and whose counterparts are also present in humans, can limit priming of new effector T cells and possibly also the function of already primed T cell effectors [9].

Some types of regulatory cells have been reported to produce inhibitory cytokines, such as TGF-β or IL-10. Although TGF-β is considered to be effective in reducing priming of new effector T cells, it has not shown promise in animal models against already primed effector T cells [43]. In contrast, IL-10 was suggested to be involved in natural resolution of EAU, on the basis of its expression in the eye during EAU resolution, its ability to inhibit already primed uveitogenic T cells, and the finding that neutralization of IL-10 delayed resolution of disease in the mouse EAU model [44]. Finally, IFN-γ itself, which is produced by the uveitogenic T cells themselves, serves as a disease-limiting mechanism and can be involved in apoptosis of newly primed Ag-specific effector T cells through a mechanism involving NO [45,46]. Whether this interesting effect of IFN–γ also involves interference with tryptophan metabolism through induction of Indoleamine 2,3-dioxygenase [47] remains to be determined.

Summary and Conclusions

Autoimmune uveitis is a potentially blinding disease caused by breakdown of self-tolerance and driven by pathogenic responses to Ags residing within the eye. It is strictly dependent on cell-mediated immunity in which T cells play a major role and, therefore, constitute the prime target for immunotherapy. Antibodies can aggravate the disease, but as long as the blood-retinal barrier is intact, they are prevented from entering the eye. Therapeutic strategies affecting primed T cells that had already been exposed to Ag as well as the priming of naive T cells being exposed to Ag for the first time are optimal. However, therapies that only target naive T cells are also useful, because chronic autoimmunity involves continuous priming and recruitment of new T cells into the effector pool. Over the years, distinct stages of pathogenesis have been defined, and increasingly specific therapies are being devised and implemented to target critical checkpoints in the disease process. The goal is to affect the specific processes relevant to disease and avoid nonspecific effects on the immune system that are the drawback of traditional nonselective immunosuppressive agents. Strategies targeting common lymphocyte activation pathways, such as cytokine or co-stimulatory receptor blockade, are more specific, but have the potential to adversely affect host defense against pathogenic microorganisms. Ag-specific approaches are the

most accurate, as they affect primarily the autoreactive lymphocytes driving the disease process. However, there are risks inherent in introducing a disease-related Ag into an already primed host. Furthermore, disease-related Ags are often unknown, or they might change during the course of disease (Ag spreading). Nevertheless, therapeutic vaccination against autoimmunity could be the therapy of the future, once we learn how to control the process and avoid side effects. Towards this end, animal models of uveitis are important tools for understanding the rules governing self-tolerance and its breakdown, dissecting the process of disease pathogenesis, and as reasonably faithful templates for devising and testing therapeutic approaches.

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