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REVIEW

Resolution of uveitis

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Abstract

Autoimmune uveitis is a sight-threatening, rare disease, potentially leading to blindness. Uveitis is a synonym for intraocular inflammation, presenting as various clinical phenotypes with different underlying immune responses in patients, whereas different animal models usually represent one certain clinical and immunological type of uveitis due to genetic uniformity and the method of disease induction. T cells recognizing intraocular antigens initiate the disease, recruiting inflammatory cells (granulocytes, monocytes/macrophages) to the eyes, which cause the damage of the tissue. The treatment of uveitis so far aims at downregulation of inflammation to protect the ocular tissues from damage, and at immunosuppression to stop fueling T cell reactivity. Uveitis is usually prevented by specific mechanisms of the ocular immune privilege and the blood-eye-barriers, but once the disease is induced, mechanisms of the immune privilege as well as a variety of novel regulatory features including new Treg cell populations and suppressive cytokines are induced to downregulate the ocular inflammation and T cell responses and to avoid relapses and chronicity. Here we describe mechanisms of regulation observed in experimental animal models as well as detected in studies with peripheral lymphocytes from patients.

Keywords Autoimmunity · Eye · Immune privilege · T cells · Cytokines · Chemokines

What is uveitis?

Uveitis is an inflammatory disease of the inner eye, leading to deteriorated vision and potentially resulting in permanent destruction of the delicate tissues of the neuroretina. The "uvea" in the anatomical sense only comprises the iris, ciliary body, and choroid, while the clinical term "uveitis" includes inflammatory involvement of any intraocular structure within the sclera and cornea. The disease course is either relapsing-remitting or chronic and can lead to blindness in the worst case [1]. Depending on the region within the eye that is mainly affected by inflammation, we differentiate between anterior (iris, anterior chamber), intermediate (ciliary body, peripheral retina, and peripheral vitreous), and posterior uveitis (vitreous, retina, retinal vessels, retinal pigment epithelium (RPE), choroidal vessels, and papilla) [2]. Uveitis can be caused by trauma or infection, but can also emerge endogenously, presenting as autoimmune uveitis. Autoimmune uveitis is an orphan disease with an incidence of about 4‰. It can also arise from ocular trauma with destruction of the blood-eye-barriers or from an immune response to a systemic infection via antigenic mimicry, as previously described and shown in animal models and human disease [3–6].

Uveitis is regarded as a T cell–mediated disease, and autoantibodies to ocular antigens have been found but obviously play no major role for the pathogenesis [7]. The role of B cells in uveitis is not well understood; they might promote T cell activity, serve as antigen-presenting cells, or as Bregs even suppress uveitis [8, 9]. The promoting role of B cells in human uveitis is indirectly shown by the therapeutic effect of the B cell specific anti-CD20 antibody rituximab in some uveitis patients (reviewed in [8]), while the suppressive effect of IL-10- and IL-35-producing regulatory B cells was described in a mouse model of experimental autoimmune uveitis [9–11]. Analysis of aqueous humor and vitreous cells revealed more T than B cells in human noninfectious uveitis [12–14]; moreover, adoptive transfer of regulatory T cell populations has been shown to ameliorate uveitis in rats [15] and mice [16] and regulatory T cells were found increased in the peripheral blood of human patients during remission of uveitis [17]. In

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addition, targeting T cells is the major aim of most therapies; therefore, we have concentrated on T cells in this review.

The treatment options so far are corticosteroids for a fast resolution of inflammation to rescue the ocular tissues from collateral damage, and immunosuppression with pharmacologics like methotrexate (MTX), cyclosporine A (CyA) or mycophenolate mofetil (MMF), or the biologic TNF-blocker adalimumab [18, 19]. The use of other biologicals like rituximab (anti-CD20) [20–22], canakinumab (anti-IL-1β) [23, 24], or tocilizumab (anti-IL-6R) [25–27] is sometimes successful, but not yet approved. Local treatment by intraocular application of corticosteroids or other drugs is an option to avoid systemic side effects; however, intraocular corticosteroid treatment also may lead to side effects like cataract and glaucoma [28]. Novel small-molecule drugs like the T cell–specific DHODH-inhibitor PP-001 were proven successful in animal models for intraocular use and are currently tested in clinical trials [29, 30]. While corticosteroids target inflammatory cells as well as T and B cells, most novel therapies aim at mainly suppressing T cells.

Induction of uveitis

Experimental autoimmune uveitis (EAU) can be induced by immunization of rats or mice with retinal autoantigens or peptides emulsified in complete Freund's adjuvant, which is additionally fortified with *Mycobacterium tuberculosis*. Mice mostly need a supplemental injection of pertussis toxin and only develop uveitis after immunization with interphotoreceptor retinoid–binding protein (IRBP) or strain-dependent peptide epitopes, while Lewis rats do not need pertussis toxin and get uveitis after immunization with many different ocular antigens [31]. The best characterized ones are IRBP and retinal soluble antigen (S-Ag). Adoptive transfer of autoantigen-activated autoreactive T cells also induces EAU, as well as peptides from foreign antigens that resemble autoantigen peptides (antigenic mimicry), like peptides from rotavirus or bovine milk casein, mimicking a peptide (PDSAg) from retinal S-Ag. Enhanced antibody and T cell responses to these mimicry peptides are also found in uveitis patients [4, 32]. Mice expressing a transgenic T cell receptor specific for IRBP peptide spontaneously develop uveitis dependent on their microbiota, suggesting a still unknown antigenic mimicry of gut microbiota and retinal autoantigens [33].

Immune reactions often lead to inflammation, which can cause irreversible destruction of intraocular tissues. Neuronal cells and photoreceptors cannot be regenerated; thus, it is necessary to prevent collateral damage by inflammation. This is in accordance with the primary corticosteroid treatment of uveitis in the clinic to achieve a quick regression of inflammation.

Prevention of intraocular inflammation

The induction of uveitis is usually prevented by natural Tregs induced via the expression of retinal autoantigens in the thymus [34–36], furthermore by the immune privilege of the eye sustained by the blood-eye-barriers [37] or active regulatory mechanisms like the anterior chamber–associated immune deviation (ACAID) [38–40].

There are three different blood-eye barriers, the inner blood-retina barrier, comprising the endothelia of the retinal blood vessels, is a "real barrier" with tight junctions, which are impermeable for large molecules like antibodies and complement factors as well as non-activated leukocytes. The other two barriers, the blood-aqueous barrier at the ciliary body in the anterior chamber and the outer blood-retina barrier, formed by the RPE between photoreceptors and choroid in the posterior eye, are "educational barriers". This means that cells of the immune system are allowed to pass these barriers by entering an "intraocular boot camp", which presses the invading cells to change from an aggressive effector to a tolerogenic (T cells) or repairing cell type (macrophages, M1 ⇒ M2), or even eliminating them via apoptotic receptor-ligand interactions [37]. In addition, the surfaces of intraocular cells express only low levels of MHC class I molecules for decreased "visibility" by cytotoxic T cells and complement regulatory proteins to hamper the activation of complement. Furthermore, iris and ciliary body epithelia produce many immunosuppressive factors like TGF-β, α-melanocyte-stimulating hormone (α-MSH), thrombospondin-2 (TSP2), macrophage migration inhibitory factor (MIF), vasoactive intestinal peptide (VIP), and others [41, 42]. These factors affect local antigen-presenting cells (APC), which migrate from the eyes to peripheral lymphoid organs where they induce regulatory T cells specific for ocular antigens. The injection of antigen into the anterior chamber of eyes induces a systemic, antigen-specific immune tolerance, called ACAID. Similar mechanisms can be found in the retina [37, 39, 40]. McPherson et al. demonstrated that the eye is protected from inflammation by locally generated, antigen-specific iTregs, and that these iTregs are induced "on demand," independently of circulating n/iTregs [43]. All together, these are the reasons why autoimmune uveitis is a rare disease. Nevertheless, despite all these preventive mechanisms, the eye can be hit by destructive immune reactions. It was shown that the immune privilege is not able to efficiently control pathogenic T cells that are activated and become Teff cells prior to entering the eye but, as addressed later, similar mechanisms are found in post-uveitis tolerance, which prevents relapses of disease in most animal models [44].

Onset of uveitis

Activated lymphocytes and leukocytes are allowed to leave the blood vessels and screen all tissues/organs of the body, even those that are immune privileged like eyes, brain, inner ear, gonads, and pregnant uterus for pathogens or tumor cells. This is very important for the integrity of the organism to avoid that dangerous events like infections or tumors can hide from the immune defense and are deleterious for the organism. Therefore, activated T cells also invade ocular tissues in search of their antigen, irrespective whether they are specific for ocular autoantigen or not. The invasion is random and only depending on the activation status of the cells and their expression of certain (not yet fully known) proteins and the presence of several receptors (e.g., ICAM/CD54 and CD11a/CD18) on the ocular blood vessels to promote the egress of the cells from the circulation [45]. The fate of the cells and their further action in the tissue depends on whether they find their respective antigen or not. Immune-privileged tissues provide a hostile environment for lymphocytes, which is deleterious for non-activated cells, as previously described. However, even activated T cells will need to acquire additional capabilities to survive the ocular environment when they pass the blood-eye barriers. When antigen-activated T cells specific for ocular autoantigen are injected intravenously or intraperitoneally into naive animals, they will induce intraocular inflammation about 4 to 7 days later. However, when the same activated cells are directly injected into the vitreous of the eye, they are not able to induce uveitis, indicating that they are missing some features for "pathogenicity," which are not yet known (Master Thesis, Michael Foehlinger, 2013).

To follow the fate of T cells in ocular tissues, we have made investigations using GFP-expressing T cells and intravital fluorescence microscopy [46]. After adoptive intravenous transfer of retina-specific T cells, the number of T cells invading the iris tissue slowly increases during the first days post transfer; however, there are no immediate signs of inflammation like influx of inflammatory cells, which are mainly monocytes/macrophages in the rat model [47]. Then, after 3 days and within a few hours, inflammatory cells like macrophages and granulocytes accumulate in ocular tissues and fluids. The recruitment of inflammatory cells follows the intraocular, antigen-specific reactivation of the infiltrating T lymphocytes, as we have demonstrated with T cells specific for ocular autoantigen or transfer of T cells specific for the foreign antigen ovalbumin (Ova) and subsequent intraocular injection of Ova to provide the antigen. In both cases, we could induce uveitis with tissue-destructive inflammation, while intraocular injection of bovine serum albumin after prior transfer of Ova-specific T cells did not induce disease, proving the antigen-dependence. T cells isolated from eyes with uveitis had upregulated activation markers like TCR-αβ, CD25, Ox40 (CD134), and MHC class II. T cells isolated from eyes without uveitis, e.g., after transfer of Ova-specific T cells without providing ocular ovalbumin, did not show upregulation of these markers [46]. These few days between the first T cell infiltration and the invasion of inflammatory cells is also known from patients with acute anterior uveitis, who often have an intraocular "sensation" without any signs of irritation or inflammation that precedes the clinically visible uveitis by about 2–3 days and is called prodrome [48].

Re-induction and spontaneously relapsing experimental uveitis

Some years ago, we have detected two types of uveitis in Lewis rats, a clinically monophasic disease with a subclinical chronic course, and a spontaneously relapsing-remitting disease. Both types of uveitis are induced in rats by immunization with two different retinal autoantigen peptides or adoptive transfer of T cells specific for these peptides. Peptide PDSAg from retinal S-Ag induces a monophasic/chronic disease, with growth of new blood vessels from the choroid into the retina (choroidal neovascularization, CNV) [29, 30, 49]. The reason for the new vessel growth was found to be the production of VEGF by PDSAg-specific T cells, which can be prevented by specifically suppressing the T lymphocytes [29, 30].

In contrast, peptide R14 from IRBP elicits a spontaneously relapsing-remitting uveitis without CNV-formation. After primary induction of uveitis by immunization with PDSAg-CFA, a secondary induction of uveitis is prevented: re-induction of EAU with either PDSAg- or R14-CFA immunization or adoptive transfer of T cell lines is efficiently suppressed. In addition, any primary immunization with CFA (even without autoantigen) severely hampers uveitis induction by a secondary PDSAg-CFA, but not R14-CFA immunization. This indicates that PDSAg-mediated EAU is highly sensitive to (1) CFA-induced regulation and (2) to an antigen-specific regulation (PDSAg-specific). Moreover, immunization with PDSAg in CFA even downregulates uveitis induced by secondary immunization with R14-CFA or adoptive transfer of R14-specific T cells, indicating a strong antigen-specific immune regulation with a bystander effect, which was confirmed by coimmunization with PDSAg and R14 as described later in the "Treg cells controlling experimental uveitis" section below [49].

We have analyzed the T cell's gene expression and found 28 genes/proteins upregulated in R14-specific T cells, while VEGF production was only detected in PDSAg-specific cells [30, 50, 51]. IFN-γ mRNA was also upregulated in R14-specific T cells causing relapsing uveitis, but no difference was observed for IL-17-mRNA. In contrast, looking at intracellular expression and secretion of the respective cytokines,

more IFN-γ was found in R14-specific cells, while IL-17 protein was upregulated in PDSAg-specific T cells inducing monophasic/chronic disease.

Further investigation of intraocular lymphocytes during the course of uveitis also revealed differences between the two types of disease. The majority of lymphocytes in rat EAU eyes are TCR-αβ+ cells, and their populations during different disease stages were highly dynamic concerning their cytokine pattern [47, 52]. T cell populations during the course of PDSAg-induced (monophasic/chronic) EAU that produced IFN-γ or IL-17 remained stable, while a population coproducing both inflammatory cytokines (Th1/Th17) increased from onset to disease resolution. In contrast, during R14-induced (relapsing) EAU, the Th1/Th17 population remained stable, while IFN-γ^+IL-17^- cells increased and IL-17^+/IFN-γ^- decreased during intraocular inflammation. This led us to speculate that IL-17+ cells are needed to initiate R14-, but not PDSAg-mediated uveitis, and IFN-γ was shown to be necessary for relapses of inflammation [52].

Resolution of experimental uveitis

Cytokines, STATs, and SOCS

As previously described, T cells remain in the eye during resolution of uveitis, shown with GFP^+ T cells in rat eyes more than 5 weeks after i.v. injection [50, 53]. Unlike earlier opinions that lymphocytes are destroyed in the eye to achieve resolution of inflammation, we believe that those tissue resident T cells remain in a quiescent stage for some time and might also be reactivated to induce relapses. We found clusters of autoreactive, GFP^+ T cells in the retina shortly after relapses of EAU, suggesting that these cells have locally expanded. Those clusters were not observed when activated GFP^+ T cells specific for a foreign antigen like ovalbumin were adoptively transferred during a spontaneous relapse caused by R14-specific, GFP^- T cells. In the latter situation, the OVA-specific T cells enter the eye and show a scattered accumulation close to retinal lesions, but no cluster formation like the tissue-remaining autoreactive GFP^+ T cells specific for retinal antigens [53].

Inflammation in the eye may be controlled either by infiltrating cells producing suppressive cytokines like IL-10 or by retinal cells and endogenously produced cytokines. The majority of early infiltrating T cells in R14-induced rat EAU (relapsing) expressed IL-17, this population declined during the course of disease, while IFN-γ-producing cells increased. A small proportion of IFN-γ producing cells coproduced IL-10 throughout the disease course, but almost half of the IL-17-producing T cells at onset of disease already coproduced IL-10. In contrast, in PDSAg-induced, monophasic uveitis, both IFN-γ^+/IL-10^+ and IL-17^+ cells, irrespective of their IL-10 production, increased from onset and were still high at resolution. Intraocular T cells coproducing IFN-γ, IL-17, and IL-10 were shown in both types of rat EAU, and these cells decreased during the course of relapsing-remitting uveitis from 29 to 12% at resolution and 4.5% during relapses, while a more than fivefold increase was observed from onset to resolution of the monophasic/chronic, PDSAg-induced disease [52]. In the late remission phase of both the monophasic/chronic and the relapsing-remitting disease in the Lewis rat (around day 30 after induction and 10 days after resolution), the majority of cells only produce IL-10, but no additional inflammatory cytokine like IL-17 or IFN-γ. In PDSAg-induced uveitis, the percentage of IL-10-producing cells was about threefold higher than in R14-induced disease. We speculate that the IL-10-producing cells have a regulatory function, irrespective of their coproduction of inflammatory cytokines like IFN-γ or IL-17 [52].

F4/80 microglia cells in the retina constitutively express IL-27, which is upregulated during uveitis in mice [54]. IL-27 is a member of the IL-12 cytokine family and a heterodimeric cytokine consisting of subunits p28 and Epstein-Barr virus–inducing gene-3 (EBI-3). It has been described as a cytokine with both pro- and anti-inflammatory potential (reviewed in [55]). EAU in mice deficient in IL-27R (WSX-1) or EBI-3 is ameliorated in the acute phase (up to day 21), accompanied by a diminished Th1 response and reduced levels of the Th1-related chemokines IP-10 (CXCL10) and RANTES (CCL5) in the eye [56–58]. On the other hand, overexpression of p28 in mice ameliorates EAU, and treatment with recombinant p28 or a p28/p40 heterodimer reduces EAU in wild-type C57/BL6 mice by inhibiting Th1 and T17 responses and promoting Tregs ($Foxp3^+$ and IL-10-secreting cells) [59, 60]. Lee et al. also showed that photoreceptors constitutively express IL-27 receptor and contribute to the control of intraocular inflammation by producing IL-10 and suppressor of cytokine signaling (SOCS)1 in an IFN-γ/STAT1-dependent way, which may explain the high expression of STAT1 and IFN-γ genes in the remission phase of EAU in mice [54, 61]. It has also been shown that IL-27 suppresses expansion of Th17 effector cells in a SOCS3/STAT1-dependent way. This implicates that IL-10, which is a potent inducer of SOCS3, controls inflammation when secreted by infiltrating T cells as well as locally by ocular cells [62, 63].

Despite its pathogenic involvement in EAU, a neuroprotective function of IL-17 has been reported [64].

Recently, IL-33, a member of the IL-1 family, which can be produced by RPE cells and cells from the inner and outer retinal layer, was found increased in diseased eyes. Furthermore, treatment with rIL-33 attenuates EAU, indicating that the RPE and other endogenous cells produce their own inhibitory and controlling cytokine by shifting effector Th1/Th17 cells to a more Th2 type and polarization of macrophages towards an M2 phenotype [65, 66].

Another cytokine of the IL-12 family, IL-35, is a heterodimer consisting of subunits p35 and EBI3 and conferred protection against ocular pathology in wild-type C57/BL6 mice by inducing the expansion of regulatory IL-35$^+$ Breg as well as Treg cells and inhibited Th17 and Th1 pathogenic T cells [9], but nothing is known about its role of controlling EAU in rats.

IL-2, originally described as a Th1 effector cytokine, is now regarded as a cytokine involved in Treg expansion and has been reported to enhance protection and controlling EAU in part by stimulating regulatory T cells to produce anti-inflammatory cytokines [67].

IL-2 and IL-21 were induced in autoreactive CD4$^+$ T cells, and cells expressing either one or both of these cytokines were present among the inflammatory cells infiltrating the retina in mice. In IL-21R-deficient mice, reduced levels of IFN-γ, IL-17, and IL-1β were observed, IL-2 was similar as in WT mice, and IL-10 was enhanced, indicating a shift from pro- to anti-inflammatory cytokines in the absence of IL-21 signaling [68].

IL-10 was shown to play a key role in regulating and controlling immune responses and tolerance [69, 70]. Neutralization of IL-10 with antibody treatment exacerbates EAU, while overexpression of IL-10 in the eye can ameliorate uveitis [71, 72]. Induction of EAU in transgenic mice expressing IL-10 either constitutively in macrophages or inducible in activated T cells revealed that IL-10 protects from EAU by inhibiting de novo priming of autoreactive T cells as well as suppressing recruitment and/or function of leukocytes involved in inflammation and tissue damage [73].

In the course of EAU, it seems that infiltrating effector cells as well as endogenous cells of the affected eye contribute to the control of inflammation and the protection of the delicate structures of the inner eye from destruction by inducing regulatory cells and regulatory and protective cytokines.

Like IL-10, the cytokine TGF-β is also controlling inflammatory processes in the eye. TGF-β is constitutively expressed in the eye by many cell types and is engaged in the ocular immune privilege [74]. Within the eye, TGF-β is converted from its latent to the active form driven by thrombospondin-alpha [75], and in combination with alpha-melanocyte-stimulating hormone (α-MSH), the active TGF-β induces ocular antigen-specific Tregs. These Tregs confer bystander suppression of T lymphocytes specific for a different ocular antigen, but not of non-ocular-specific T cells [76].

Treg cells controlling experimental uveitis

We found an increase of Foxp3$^+$ cells in eyes of PDSAg-induced rat EAU from 4% at onset to about 17% during late remission between days 30 and 35 after immunization (5–10 days after resolution). In contrast, Foxp3$^+$ cell populations from onset to late remission in eyes of R14-induced EAU were almost constant around 8% with a low of 3.5% at peak disease. Like human T cells, activated rat effector T cells also transiently express Foxp3 in their cytoplasm, while in regulatory T cells Foxp3 is found in the nuclei. Since Foxp3 expression was determined by FACS analysis, we could not distinguish between cytoplasmic and nuclear localization of the transcription factor. Thus, we cannot clearly distinguish between Tregs and effector cells from Foxp3 expression in rat eyes, but assume that the increasing Foxp3 population in the eyes of monophasic disease represents regulatory rather than effector T cells [52, 77].

The situation in mice is easier, where Foxp3-expression generally is associated with regulatory function of CD4$^+$/CD25$^+$ T cells. This enabled Kitaichi et al. [78] as well as Lee and Taylor [79–81] to define Treg populations in the spleens of mice after recovery from EAU that could prevent relapses and also transfer protection from the disease. Those Tregs are induced by specialized APCs generated in the eye by locally produced factors like TGF-β or α-MSH. The respective F4/80$^+$ APCs increased in the spleens and expressed the melanocortin 5 receptor as well as CD11b, CD39, and CD73 [79]. Among others, those factors are responsible to maintain the immune privilege of the eye (ACAID), which usually prevents induction of intraocular inflammation. Those Tregs were not induced when mice were enucleated prior to immunization with the uveitogenic antigen peptide, which proves the importance of the eye-derived factors for their generation [78].

In the rat model, the monophasic, PDSAg-induced uveitis seems to undergo a more restrictive regulation than the R14-induced, relapsing disease. Coimmunization experiments by either mixing both antigen peptides or by separate immunization with the two antigens into contralateral sides indeed revealed a stronger, even intermolecular regulation induced by PDSAg. While separate immunization with both antigens dramatically reduced the frequency of relapses from 75% (after only R14-immunization) to 12.5%, the antigen mixture completely abrogated recurrent uveitis [53]. This indicates peripheral regulation at the site of immunization, when both antigens are provided simultaneously (mixed antigens), and a local regulation in the eye where R14- as well as PDSAg-specific T cells will meet and find their antigen (antigens injected into different sides). In the latter case, the suppression is not as effective as observed after the immunization with the antigen mixture.

The contribution of peripheral as well as local, ocular Tregs to resolution of EAU and prevention of relapses was also shown in a mouse model by Silver et al. [82].

Chemokines

Only little is known about the functional contribution of chemokines and chemokine receptors to resolution of EAU/

uveitis. CXCL10/IP10, CXCR6, and CCL17 are upregulated at mRNA levels 20 days post immunization and remission [61]. Both CCR6, commonly known as surface marker of IL-17 producing cells, and CXCR5, associated with Foxp3 expression, were upregulated at the mRNA level in the retina during EAU, peaked 14 days post immunization, and stayed high in the remission phase. In draining lymph nodes, the highest expression was observed 21 days post immunization. The high level at peak and in the remission phase indicates that during the course of disease, T effector cells/pathogenic T cells as well as T cells with a regulatory phenotype might coexist at the same time, or at least cells expressing molecules of both phenotypes [83]. $Foxp3^+$/IL-17-secreting lymphocytes inhibiting $CD4^+$ cells have been described in humans [84].

Crane et al. analyzed the chemokine pattern at the blood-retina barrier and found an enhanced expression of CCL2/MCP-1 and CXCL8/IL-8 and to a lesser amount CCL3/MIP-1α and CCL4/MIP-1β by retinal endothelial cells, leading to the speculation that these chemokines might play important roles for the recruitment of leukocytes during ongoing inflammation [85, 86]. While IL-1β and TNF-α increased chemokine production, anti-inflammatory cytokines such as IL-4, IL-10, IL-13, TGF-β, and also IL-6 had little effect on chemokine production of RPE and human retinal microvascular endothelial cells. This indicates that the change in the chemokine pattern at the BRB is not a requisite for recruitment of regulatory cells and/or resolution. It rather demonstrates that the infiltrated cells, endogenous cells, and factors of the eye and retina are vitally participating in disease resolution.

Resolution of noninfectious uveitis in patients

Noninfectious uveitis in humans appears in several different clinical entities and causes chronic or relapsing-remitting inflammation. Uveitis is believed to be mediated by proinflammatory Th1 and Th17 cells, and regulatory T cell populations coexpressing CD4, CD25, and Foxp3 have been described [87, 88]. An intensive characterization of peripheral blood regulatory T cells in the remission phase of uveitis was performed by Gilbert et al. [17]. In this paper, clinical remission of uveitis was defined as a 6-month period free of intraocular inflammation without treatment in patients that had active disease of the posterior part of their eyes (only intermediate and posterior uveitis was included) and had responded to immunosuppressive therapy. In contrast to other publications, the selected patients here had no additional systemic diseases.

The Treg populations were compared with those of a healthy control group and a group with active disease. In addition to the conventionally defined $CD4^+CD25^+Foxp3^+$ Treg population, also the frequency of $TIGIT^+$ (T cell immunoreceptor with Ig and ITIM domains; ITIM, immunoreceptor tyrosine–based inhibition motif) Tregs, RORγ-t, and T-bet was investigated. An enhanced frequency of $CD4^+CD25^+FoxP3^+$Tregs, $TIGIT^+$ Tregs, and $T\text{-}bet^+$ Tregs was found in patients in remission compared with patients with active disease, and the suppressive capacity of the $CD3^+CD4^+CD25^+CD127^{lo}$ regulatory cell populations was also demonstrated in vitro.

In addition, the methylation of the Foxp3 promoter and the Treg-specific demethylated region (TSDR) within the FoxP3 gene were investigated together with the expression of CD25 and Foxp3 [89–93]. Hypomethylation of the TSDR is important for Treg function and their stability and is associated with the duration of oral immunosuppressive therapy of the patients (here: mycophenolate mofetil, cyclosporine A, azathioprine, or methotrexate), indicating that conventional immunosuppression can induce regulatory T cells leading to remission of the disease. The most significant difference between patients in remission and those with active disease is the frequency of "conventional" $CD4^+CD25^+Foxp3^+$ Tregs, $TIGIT^+$, and $T\text{-}bet^+$ Tregs. Those regulatory cell populations increase in a group of patients that experienced remission from active uveitis and was followed over 12 months thereafter. Control and active uveitis groups did not show significant differences in their Treg levels. However, in patients with remission, lower levels of Th1 transcription factor T-bet as well as higher ratios of Tregs:Th1 cells were found in comparison with patients with active disease. Patients in clinical remission have increased populations of Treg cells expressing the Th1 transcription factor T-bet, TIGIT, and Foxp3, with significant hypomethylation of the Foxp3 promoter, Foxp3 TSDR, and the TIGIT loci [17].

The levels of Th17 cells determined by RORγ-t expression did not differ between controls, active disease, and remission. Interestingly, in a small group (3 of 4 patients) with active disease and transition to resolution within the observation period of one year, Th17 levels increased. Induced by immunosuppressive therapy, $Th17^+$ cells express Foxp3 during resolution; however, $Foxp3^+RORγ\text{-}t^+$ T cells seem not to play a pivotal role for clinical remission. Neither $RORγ\text{-}t^+Th17$ nor $RORγ\text{-}t^+$Treg cell populations differed between the investigated groups, suggesting that the role of Th17 cells in uveitis is rather expressing IL-22 to facilitate the ocular invasion of inflammatory cells than driving the autoimmune response [94].

There is a paradoxical expression of effector T cell transcription factors like T-bet and RORγ-t together with Treg markers, representing stable Treg populations rather than Th effector cells [95–98]. Double-positive effector $RORγ\text{-}t^+/T\text{-}bet^+$ (Th17/Th1) cells were detected but did not differ between the groups. In contrast, the serum levels of IFN-γ, IL-17A, and IL-22 decreased in patients under remission, while TGF-β and IL-10 increased during remission compared with the patients with active disease. The same observations were made investigating intracellular cytokines of $CD4^+$ T cells.

Conclusion

Different types of uveitis may have different underlying immune mechanisms, while even similar clinical pictures may be caused by different immune responses. Th1 and Th17 cells have been described as pathogenic effector cells, together with cytokines and chemokines expressed by lymphocytes and leukocytes as well as by ocular cells. The latter might facilitate the invasion of immune cells and/or support and maintain their activation. The eye as an immune-privileged tissue has special mechanisms for protection from attacks of the immune system, and part of these mechanisms that aim at preventing uveitis are also used for downregulating intraocular inflammation or preventing relapses. A variety of regulatory T and B cells was described in rat and mouse models as well as in uveitis patients, and taking into account the immunological differences between mice and rats and humans, resolution of uveitis is suggested to be the interplay of various Treg and Breg cells and different regulatory mechanisms, depending on the respective animal model and the clinical or immunological phenotype of the uveitis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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