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Cytokines in uveitis

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Abstract

Purpose of review—Increasing evidence supports Th17 cells as key mediators of ocular inflammatory disease. Cytokines that are important for the development and pathologic function of these cells are potential therapeutic targets in patients with immune mediated uveitis. This review provides an overview of these cytokines including recent insights about their roles in ocular inflammation from laboratory and clinical studies.

Recent findings—Interleukin (IL)-6, IL-10, IL-17, IL-22, IL-23 and tumour necrosis factor-alpha (TNFα) are cytokines that have been examined for their functional role in uveitis and their relationship to pathologic Th17 cells. Studies in animal models, particularly in experimental autoimmune uveitis (EAU), have been instrumental in studying the role of these cytokines in disease pathogenesis. More recently, studies on aqueous, vitreous and serum from patients with uveitis using flow cytometry and multiplex ELISA bead-based methodologies have provided insights into the contribution of Th17 cells and the related cytokines in ocular inflammatory diseases. The central role of IL-23 in determining the pathologic Th17 fate has made it an effective therapeutic target in systemic diseases such as psoriasis and thereby an attractive potential target for patients with immune-mediated uveitis.

Summary—Th17 cells, and their related cytokines, are important inflammatory mediators in autoimmune uveitis. Animal and human studies continue to provide new information to direct development of new cytokine-targeted therapies for patients with uveitis.

Keywords

cytokines; interleukin −6; interleukin-10; interleukin-17; interleukin-22; interleukin-23; tumour necrosis factor-alpha; uveitis

INTRODUCTION

T cells expressing the surface marker cluster of differentiation 4 (CD4) are known as T helper (Th) cells and play important roles in the pathogenesis of autoimmune diseases including uveitis. Th cells can be classified into different functional categories by the small molecule cytokines they secrete, as well as by the transcription factors required for their development. After the initial discovery of Th cells and their importance in adaptive

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Conflicts of interest

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immunity, two major classes of Th cells were defined in a paradigm that shaped the approach to autoimmunity for the next two decades [1]. In this paradigm, Th1 cells, defined by the expression of the transcription factor T-bet and secretion of interferon gamma (IFNγ), were the dominant cell type 'helping' cellular immunity, while Th2 cells, defined by the transcription factor GATA binding protein 3 and secretion of interleukin (IL)-4 and IL-5, were responsible for helping humoral immunity [2]. This original paradigm maintained that additional populations of helper cells were likely to be discovered to fill additional immune-modulating roles. This prediction has subsequently been realized with the identification of regulatory T cells (Tregs) and Th17 cells, among others (Th22, Th9, Th3, Follicular helper T_{FH}). Treg cells are important in maintaining tolerance and preventing autoimmunity and can be identified by their expression of the forkhead box P3 (Foxp3) transcription factor and their ability to produce transforming growth factor beta (TGFβ), IL-10 and IL-35 [3]. In addition to their role in autoimmunity, Th17 cells are important in maintaining normal mucosal health and immunity, and can be identified by their expression of the transcription factor RAR-related orphan receptor gamma (RORγτ) and expression of IL-17, IL-21, IL-22 and tumour necrosis factor-alpha (TNFα) [4].

The mechanisms of uveitis development and maintenance were initially attributed to a Th1-dominated response, but when IFNγ deficiency was not sufficient to suppress the development of experimental autoimmune uveitis (EAU), the roles ofTh17 cells and IL-17 in uveitis were identified [5,6]. In animal models, the interplay between the Th1 and Th17 responses in driving uveitis is complex, as both can drive intraocular inflammation given the correct context [5,7]. Furthermore, Th17 cells that also express IFNγ have been identified in human uveitis [8■■] as well as other inflammatory diseases [9], suggesting that there may be overlap and plasticity between Th subtypes.

Th17 cells develop from naive $CD4^+$ T cells in the presence of IL-1β, IL-6 and TGFβ produced by antigen-presenting cells (APCs). IL-23 has a distinct role in the development of autoimmunity, as in the absence of IL-23, Th17 cells still develop, but they are not pathogenic and perform essential homeostatic functions [10]. In addition to IL-17, Th17 cells express IL-22, IL-17F, IL-21, granulocyte macrophage colony-stimulating factor (GM-CSF), IL-6 and IFNγ, which all have important inflammatory functions in autoimmunity [4].

INTERLEUKIN-17

IL-17 is part of the IL-17 family of cytokines. This family includes IL-17 (also known as IL-17A), IL-17B, IL-17C, IL-17D, IL-25and IL-17F. IL-17receptor (IL-17R) signalling uses an adaptor system that is distinct from other interleukin receptor families to activate downstream regulators of the inflammatory response such as nuclear factor kappa beta (NFkB) and c-Jun N-terminal kinases (JNK) [11]. Instead of utilizing the receptor tethered kinases of the janus kinase and signal transducer and activator of transcription (JAK-STAT) system, IL-17R family members contain an intracellular SEF/IL-17R (SEFIR) domain that provides a docking site for the Act1 adaptor protein, which activates tumour necrosis receptor associated factor 6 (TRAF6) through poly-ubiquitination [12]. In addition to driving inflammatory cytokine expression, IL-17 signalling also drives the expression of

metalloproteases that can cause tissue injury and of chemokines that recruit neutrophils to the site of inflammation. IL-17 is secreted by Th17 cells as well as natural killer (NK) cells, gamma delta ($\gamma\delta$) T cells and a subset of CD8 T cells called Tc17 cells.

Roles in uveitis

In EAU, both Th17 cells and IL-17 appear to have an important role in driving inflammation. In the adoptive transfer model of EAU, interphotoreceptor retinoid binding protein (IRBP) specific Th17 cells are sufficient to induce uveitis [13], and treatment with anti-IL-17 antibody is sufficient to block development of disease [14]. However, while Th17 cells and IL-17 were initially identified for their pro-inflammatory roles in uveitis, roles in immune regulation have also been reported. For example, IL-10 expressing, nonpathogenic Th17 cells with the ability to prevent EAU have been identified in mouse models at higher density than retina-specific pathogenic Th17 cells [15]. In addition, recombinant human IL-17 given systemically in the chronic relapsing EAU rat model paradoxically protected against inflammation [16].

In humans, elevated levels of IL-17 were identified in the eyes of patients with birdshot chorioretinopathy (BSCR) [17], Vogt–Koyanagi–Harada (VKH), as well as in HLA-B27 and Behcet's uveitis [18]. Elevated serum levels of IL-17A have also been identified in patients with immune-mediated uveitis [19], and in association with active disease in patients with Behcet's uveitis [20].

Anti-interleukin-17 therapy options and results of treatment in uveitis

Secukimumab (Consentyx, Novartis, Basel, Switzerland) is a Food and Drug Administration (FDA)-approved human antibody directed against IL-17A for the treatment of psoriasis [21,22], psoriatic arthritis [23,24] and ankylosing spondylitis [25]. Phase III dose-dependent studies for secukimumab in uveitis (INSURE, ENDURE and SHIELD) failed to demonstrate efficacy and the studies were terminated early [26]. These results were surprising, but the complex roles IL-17 plays in health and disease, and the route of drug delivery could have contributed to these findings. In the study by Letko *et al.* [27], patients with uveitis were treated with either intravenous or subcutaneous secukinumab. This trial found that patients treated via the intravenous route had a higher rate of improvement in vitreous haze score and in achieving disease remission [27]. The authors concluded that the subcutaneous route might not produce clinically effective drug levels. Due to the fact that the INSURE, ENDURE and SHIELD trials all used subcutaneous administration, this could have played a role in the failure of these trials to demonstrate efficacy. Other available anti-IL-17 therapies include ixekizumab (Taltz, Eli Lilly, Indianapolis, Indiana, USA), approved for moderate to severe plaque psoriasis [28] and active psoriatic arthritis [29▪,30▪], and brodalumab (Sidiq, Valeant, Laval, Quebec, Canada), which is approved for moderate to severe plaque psoriasis [31–33]. To date, no reports of these agents in patients with uveitis have been published.

INTERLEUKIN-23

IL-23 is a member of the IL-12 superfamily of cytokines. This family includes IL-12,IL-23,IL-27 and IL-35. IL-23 is a heterodimeric protein composed of the p19 subunit,

which is unique to IL-23, and the p40 subunit that is shared with IL-12. The IL-23 receptor is composed of the IL-12Rb1 and unique IL-23R subunits that signal through tyrosine kinase 2 (Tyk2), JAK2, STAT3 and STAT4 upon binding IL-23 [34]. IL-23 functions as a crucial checkpoint governing the development of pathologic Th17 cells [35,36]. In the absence of IL-23, Th17 cells can still develop, but do not become pathogenic. In the context of inflammation, IL-23 is primarily produced by antigen-presenting cells such as dendritic cells and macrophages. Inflammatory cells that express the IL-23R include $CD4^+$ and $CD8^+$ T cells, γδ T cells, group 3 innate lymphoid cells and invariant NK cell [37].

Roles in uveitis

Mice deficient in either IL-23p19 or IL-12p40 subunits exhibit protection from developing EAU [5]. In humans, elevated serum levels of IL-23 have been identified in patients with VKH [38] and BSCR [39]. Elevated serum IL-23 has also been identified as a risk factor for developing uveitis in spondyloarthropathy patients [40]. The data from intraocular studies are mixed. One study analysing aqueous sample did not detect elevated IL-23 in patients with VKH, Behcet"s, idiopathic, HLA-B27 or sarcoid uveitis [41]. On the contrary, a proteomic study of vitreous samples from patients with posterior uveitis identified increased IL-23 [42]. Single nucleotide polymorphisms in the *IL-23R* gene have also been associated with an increased risk of inflammatory disease, including ankylosing spondylitis associated uveitis, Behcet's disease, VKH and sarcoid uveitis [43–45].

Anti-interleukin-23 therapy options and studies in patients with uveitis

Ustekinumab (Stelara, Janssen, Beerse, Belgium) is a mAb directed against the IL-12p40 subunit of both IL-23 and IL-12. It is FDA approved for the treatment of moderate to severe Crohn's disease [46,47], moderate to severe plaque psoriasis [48–50] and active psoriatic arthritis [51,52]. It is currently being studied in two phase II clinical trials for the treatment of patient with uveitis; STELARA (NEI, NCT02911116) and STELABEC (Assistance publique – Hôpitaux de Paris, NCT02648581). Guselkumab (Tremfya, Janssen, Beerse, Belgium) and tildrakizumab (Sun Pharmaceuticals, Mumbai, Maharashtra, India) are mAbs that target the IL-23specificp19subunit. Both drugs have FDA approval for use in moderate to severe plaque psoriasis [53–56]. Other p19 specific agents include brazikumab (Amgen, Thousand Oaks, California, USA), which is in development for Crohn's disease [57], and risankizumab (Abbvie, North Chicago, Illinois, USA) in development for psoriasis [58], Crohn's disease [59], psoriatic arthritis (Abbvie, NCT02986373).

INTERLEUKIN-6

IL-6 is a well known and important mediator of autoimmune diseases including uveitis [60]. It belongs to a family of cytokines including IL-11, IL-31, ciliary neurotrophic factor (CNTF), Cardiotrophin-1 (CT-1), leukaemia inhibitory factor (LIF), osteopenia (OPN) and oncostatin M (OSM). IL-6 functions by binding either a cell surface (IL-6R) or a soluble IL-6 receptor (sIL-6R). The IL-6R consists of the IL-6Rα chain (CD-126) and a signal transducing component called gp130. Gp130 is a ubiquitous signal transducer used by all members of the IL-6-like cytokine family. The IL-6/sIL6-R complex can bind any cell expressing gp130 allowing a wide variety of cell types to respond to IL-6 [60]. The binding

of IL-6 to its receptor results in the activation of the JAK-STAT (JAK1, JAK2, STAT3) and mitogen-activated protein kinase (MAPK) pathways, ultimately leading to the expression of inflammatory cytokines, vascular endothelial growth factor (VEGF) and differentiation of naive $CD4^+$ T cells into Th17 cells [61]. Activation of STAT3 also induces the suppressor of cytokine signalling 1 (SOCS1) and SOCS3, which are negative inhibitors of IL-6 signalling [62,63].

Roles in uveitis

In experimental studies, EAU is significantly attenuated in IL-6 deficient animals [64], and intravitreal anti-IL-6 reduces inflammation [65▪]. In humans, elevated levels of IL-6 have been detectedin the aqueous humour of Behcet's disease, VKH, sarcoid, idiopathic uveitis, acute retinal necrosis and HLA-B27 mediated uveitis when compared with controls [41,66,67▪]. IL-6 also plays a role in uveitis complications such as neovascularization and macular oedema [68–70].

Anti-interleukin-6 therapy options and results of treatment in uveitis

Tociluzimab (Actemra, Genentech, South San Francisco, California, USA) was the first FDA-approved anti-IL-6 agent. It is a humanized mAb against the membrane bound IL-6R and the soluble sIL-6R and is currently approved for the treatment of rheumatoid arthritis (RA) [71], and juvenile idiopathic arthritis[72].Currently, it remains an off-label agent for use in uveitis, but the efficacy and safety of tocilizumab in noninfectious uveitis is being investigated in the on-going STOP-UVEITIS trial (University of Nebraska, NCT01717170). The early 6-month results for this study showed improvement of vision, in vitreous haze and reduction in macular central mean thickness with the use of tocilizumab [73▪▪]. Used in an off-label small case series, tocilizumab was reported to be successful in treating refractory noninfectious uveitis that has been unresponsive to TNF inhibitors [74] and to treat refractory uveitic macular oedema [75].

Sarilumab (Kevzara, Regeneron, Tarrytown, New York, USA) is another humanized mAb against the IL-6R that received FDA approval for treatment of RA in 2017 [76,77]. As an alternative to targeting the receptor, other anti-IL6 agents target the cytokine itself. Siltuximab (Sylvant, Janssen, Beerse, Belgium) is a chimeric mAb with FDA approval for treatment of multicentric Castleman's disease [78]. Olokizumab (UCB group, Brussels, Belgium) and sirukumab (Janssen, Beerse, Belgium) are humanized mAbs in development for treatment of RA, while clazakizumab (Alder, Bothell, Washington, USA) is a humanized rabbit mAb in development for psoriatic arthritis [79]. None of these therapies have been tested in patients with uveitis, so the full potential of anti-IL-6 therapy for ocular disease has yet to be discovered.

TUMOUR NECROSIS FACTOR ALPHA

TNFα is a member of the tumour necrosis factor family, which includes TNFα, lymphotoxin, B-cell activating factor (BAFF) and a proliferation inducing ligand (APRIL). TNFα has both a membrane bound form and a soluble form. TNF Receptor 1 (TNFR-1) is the main receptor for either form and it is ubiquitously expressed on all cells. TNFR-2 is

only expressed on immune cells and only responds to membrane bound TNFα. Soluble versions of these receptors exist and act as an inhibitor to TNFα and is the mechanism by which etanercept (Enbrel, Amgen/Pfizer) functions therapeutically. Binding of TNFα to its receptor elicits a complex signalling cascade that is mediated through TNF receptor associated factor (TRAF) proteins [80]. Events downstream of TRAF include translocation of NF-κB to the nucleus for production of pro-inflammatory cytokines and activation of the MAPK cascade. TNFα is produced by all immune cells; however, NK cells, activated macrophages, activated T cells, mast cells and endothelial cells produce them predominantly when there is an inflammatory stimulus.

Roles in uveitis

In the EAU model, neutralization of TNFα suppresses disease [81] and mice deficient in TNFR1 are resistant to the development of uveitis [82]. In humans, aqueous sampling has identified elevated TNFα levels in patients with HLA-B27, idiopathic uveitis, VKH and Behcet's uveitis [18,66]. However, aqueous levels do not appear to reflect the impact of disease activity or treatment with systemic adalimumab [83]. In one patient cohort with intermediate uveitis, aqueous levels of TNFα were similar to controls; however, serum TNFα was elevated [70].

Anti-tumour necrosis factor-alpha therapy options and results of treatment in uveitis

TNFα inhibitors were initially approved for treatment of patients with RA. Off-label use in patients with uveitis identified evidence of efficacy, which lead to recommendations for their use prior to FDA approval [84]. The landmark VISUAL 1 and 2 trials subsequently led to the approval of adalimumab (Humira, Abbvie, North Chicago, Illinois, USA) for treatment of patients with noninfectious uveitis in 2016 [85,86]. Infliximab (Remicade, Janssen, Beerse, Belgium) is a chimeric mAb that has been used off label as an effective treatment for patients with uveitis [84]. Golimumab (Simponi Aria, Janssen, Beerse, Belgium) is another human mAb approved for treatment of psoriatic and RA, ankylosing spondylitis and ulcerative colitis. Several retrospective case studies have reported successful use of golimumab in patients with uveitis, but no larger controlled trials have been performed [87,88▪,89]. Etanercept was the first clinically available anti-TNF agent. In contrast to other medications in this class that target the TNFα molecule itself, etanercept is a fusion protein of the TNF receptor with a human Fc molecule. Etanercept is approved for use in the treatment of several rheumatologic conditions but has not demonstrated effectiveness in patients with uveitis [90]. In addition, there is a concern that etanercept may induce ocular inflammation in certain patients, so it is not recommended for the treatment of those with a known history of uveitis [91,92].

INTERLEUKIN-22

IL-22 is a member of the IL-10 family and acts primarily on nonlymphoid tissue to potentiate inflammation in association with IL-17, TNFα and IL-1β signalling. However, IL-22 also has essential homeostatic and immunoregulatory functions, particularly at barrier surfaces [93,94]. T cells and innate lymphoid cells (ILCs) are the main sources of IL-22, but other cells such as NK T (NKT) cells, γδ T cells and CD8 T cells can also produce IL-22,

particularly in the presence of IL-23 [95]. Although IL-22 can be expressed by both Th1 and Th17 cells, there is also an IL-22 specific Th subset known as Th22 cells [96▪▪]. The IL-22 receptor (IL-22R) is a type 2 cytokine receptor composed of two heterodimeric subunits, IL-22Ra and IL-10Rb. Upon binding its receptor, downstream signalling is activated through the JAK-STAT pathway (JAK1, Tyk2 and primarily STAT3). Other pathways involved in IL-22 signal transduction include the MAPK, phosphoinositide 3-kinase (PI3K), AKT and mammalian target of rapamycin (mTOR) pathways [97].

Roles in uveitis

In EAU, while IL-22 is produced by pathogenic Th cells, small doses of IL-22 led to a reduced severity of uveitis mediated by myeloid (CD11b+) cells [98], and IL-22 deficient animals developed worse inflammation than controls [99]. In humans, IL-22 producing Th clones have been isolated from the eyes and peripheral blood of patients with Behcet's disease [100], and elevated levels of serum IL-22 have been identified in patients with uveitis [101] and scleritis [102]. In addition, IL-22 serum levels decreased in response to treatment with adalimumab and this correlated with the disease activity [103]. Genetic studies have also identified an increase in IL-22 gene expression in patients with noninfectious uveitis [104]. Taken together, the human and animal studies suggest that IL-22, like its family member IL-10, may primarily have immune regulatory rather than inflammatory functions in the eye.

Interleukin-22 therapy options and results of treatment in uveitis

Fezakinumab (Pfizer, New York, New York, USA) is a human mAb against IL-22 that was tested in a phase I trial for psoriasis (Wyeth/Pfizer, NCT00563524) and a phase II trial for RA (Pfizer, NCT00883896). The results of these studies were not published, and commercial development has not ensued. Results from an additional phase II trial in patients with moderate to severe atopic dermatitis (Rockefeller University, NCT01941537) are anticipated in 2018. No studies are being conducted in patients with uveitis.

INTERLEUKIN-10

IL-10 is the founding member of the IL-10 cytokine superfamily, which also includes IL-19, IL-20, IL-22, IL-24,IL-26, IL-28 and IL-29 [105]. IL-10 was identified by its ability to inhibit IFNγ from Th1 cells [106], and it continues to be one of the more important immunoregulatory cytokines, controlling and moderating inflammatory responses [107]. It is secreted by activated T cells, macrophages, dendritic cells, NK cells and B-cells [108]. The IL-10 receptor (IL-10R) is a tetramer consisting of two α and two β subunits, where α are responsible for binding IL-10 and β is part of signal transduction. Like many other cytokines, receptor signalling is mediated by the JAK-STAT pathway, in this case through JAK1, STAT1and STAT3 [109]. Binding of IL-10 to its receptor leads to suppression of inflammatory cytokine gene transcription, inhibition of macrophage activation, downregulation of major histocompatability complex class II expression on APCs and antiapoptotic activity.

Roles in uveitis

Animal studies demonstrate the protective role of local IL-10 in uveitis, both in EAU and endotoxin-induced uveitis (EIU) [110–114]. In patients with uveitis, elevated intraocular IL-10 levels have been identified [70,115,116], and are attributed to the presence of regulatory mechanisms activated in tandem with inflammation. In the majority of these reports, the ratio of IL-10 to IL-6 was lower than 1. In cases wherein an elevated ratio of IL-10 to IL-6 (greater than 1) is identified, it is strongly suggestive of the presence of primary intraocular lymphoma [117■■,118■,119,120].

Interleukin-10 therapy options and studies of treatment in uveitis

Recombinant human IL-10 was tested as a potential therapy for patients with ulcerative colitis in several large multicentre trials [121–123]. Although it was found to be a well tolerated medication, it was no more effective than placebo. Around 40% of the patients in the trial also had extraintestinal manifestations of ulcerative colitis including uveitis, but no separate subanalysis was performed to determine an effect of IL-10 on these manifestations. Local administration has been suggested as a possible means to overcome treatment failure in ulcerative colitis [124], and on the basis of data from EAU and EIU, this may be an option to explore for patients with uveitis [111].

CONCLUSION

The Th17 cell subtype is critical to the pathogenesis of autoimmune uveitis. Cytokines associated with the differentiation, regulation and effector functions of these cells are the cytokines IL-6, IL-10, IL-17, IL-22, IL-23 and TNFα. This association has made them attractive candidates for therapeutic targeting in inflammatory diseases including ocular inflammation. Although a TNFα inhibitor is the only FDA-approved biologic therapy to treat uveitis, agents targeting IL-6 and IL-23 are being evaluated in clinical trials and have the potential to provide benefit.

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KEY POINTS

- Th17 cells and their related cytokines are important mediators of inflammation in autoimmune diseases including uveitis.
- The anti-TNFα therapy, adalimumab, is currently the only FDA-approved biologic treatment for uveitis.
- Due to their role in the development of the pathologic Th17 fate, IL-6 and IL-23 are attractive potential therapeutic targets in ocular inflammatory disease.
- The anti-IL-6 therapy, tocilizumab and the anti-IL-23 therapy ustekinumab are actively being investigated in clinical trials for their efficacy and safety in the treatment of uveitis.