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Roles of interleukin-17 in uveitis

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Abstract

Th17 cells, a $CD4^+$ T-cell subset, produce interleukin (IL)-17, a pro-inflammatory cytokine that has been shown to be involved in several forms of infectious and noninfectious uveitis. Here, we explore the roles of this IL in uveitic disorders as well as in experimental autoimmune uveitis, the possible pathogenic implications of several cytokines associated with IL-17 and analyze the current outcomes and goals for drugs aiming for the IL-17 pathway.

Key words: Interferon-γ, interleukin-6, interleukin-17, interleukin-23, interleukin-27, secukinumab, transforming growth factor-β, uveitis

Th17 cells are a subset of $CD4^+$ T-cells responsible for the production of interleukin (IL)-17. This T-cell subset is responsible for the production of IL-17A, a pro-inflammatory cytokine involved in several autoimmune diseases.

Both IL-6 and transforming growth factor (TGF)-β are necessary for Th17 differentiation and IL-17 expression; they feature complementary roles since the sole presence of TGF-β induces T-regulatory (Treg) cell production from $CD4^+$ T-cells.[1,2,3] IL-6 needs to be present to promote the differentiation of a Th17 cell subset in addition to concurrent Treg cell inhibition.[4] Although IL-6 and TGF-β have synergistic roles in Th17 cell differentiation, IL-23 is also important for Th17 cell expansion and activation.[1] By contrast, interferon (IFN)-γ and IL-27 show a regulatory role in uveitis induction through the suppression of Th17 differentiation [Fig. 1].[5,6]

IL-17 induces the production of other inflammatory cytokines such as IL-6, granulocyte colony-stimulating factor (CSF), granulocyte-macrophage-CSF, IL-1, TGF-β, and tumor necrosis factor (TNF)-α; chemokines such as monocyte chemoattractant protein-1, cytokine-induced neutrophil chemoattractant, and macrophage inflammatory protein-2; prostaglandin E2; intercellular adhesion molecule-1; and matrix metalloproteinases. It is also involved in the recruitment of neutrophils, monocytes, and Th1 cells acting with other inflammatory cytokines to induce inflammation in target tissues.[7]

Th1 cells have been previously implicated in the induction of uveitis in experimental autoimmune uveitis (EAU), but since then, several authors have reported the crucial role of IL-17-producing Th17 cells in the genesis of experimental uveitis in mice. They have pointed that treatment with anti-IL-17 antibodies reduces the induction and severity of uveitis in EAU. Moreover, the degree of intraocular inflammation was reduced in IL-17 knockout mice,[8] and although both Th1 and Th17 cells are activated during EAU,[6,8] it has been proposed that Th17 cells are responsible for retinal inflammation in the early stages of uveitis whereas

Th1 expression is increased during the late phases and resolution of the disease.[6] It has thus been shown that Th1 and Th17 cells are implicated in the genesis of EAU and may be synergistic with each other, having definitive functions at different stages of the disease.

In addition to its obvious pro-inflammatory role in the induction of EAU, IL-17 expression is also increased in the human peripheral blood of patients suffering from autoimmune and infectious uveitis.

This review aims to explore the roles of this IL in uveitic disorders as well in EAU. The possible pathogenic implications of several cytokines associated with IL-17 induction and suppression will also be discussed, and the current outcomes and goals for drugs aiming for the IL-17 pathway are analyzed. A systematic literature search was carried out using the PubMed and EMBASE databases with the search terms, “uveitis,” “interleukin-17,” and IL-17,” until July 2015. Bibliographies of the retrieved literature were manually searched.

Experimental Autoimmune Uveitis

IL-17 is crucial in the development of EAU in mice, as well as in other models of experimental autoimmune disorders.[6,8] In EAU, the intraocular expression of IL-17 is elevated in mice with uveitis and it promotes the release of inflammatory mediators from ARPE-19 cells, disrupting the retinal pigment epithelium barrier function.[9]

There is abundant information regarding the role of Th17 cells and IL-17, its main pro-inflammatory cytokine, in the induction and clinical severity of EAU, although some studies have inconsistently determined the specific timing of increased IL-17 expression in this condition.

The Th1 cytokine, IFN-γ, has a complex role in EAU and can be protective, suggesting that IL-17 has an important inflammatory effect given that IFN-γ can inhibit IL-17 expression through Th17 suppression. In a study addressing the different functions of Th1 and Th17 cells in EAU, IL-17$^{-/-}$ mice showed no difference in terms of uveitis severity concerning the early stages of the disease, and after anti-IFN-γ and anti-IL-4 antibody treatment and concomitant increase in Th17 expression, only the late stages of the disease were affected, showing the aforementioned differential response of Th1 and Th17 cell subsets during the clinical course of EAU.[8]

In another study concerning the monophasic and relapsing phases of EAU, the authors concluded that IFN-γ-producing cells may be responsible for initiating recurrence in the relapsing form of EAU. Conversely, IL-17-producing cells might be implicated in the primary mechanisms related to intraocular inflammation, thus exhibiting different roles in the monophasic and relapsing forms of the disease.[10]

Previous data have also shown that even though a Th1- or Th17-driven response can initiate uveitis in an animal model, IL-17 plays a critical role in the induction of EAU; moreover, anti-IL-17 treatment can reduce the severity of antigen-induced autoimmune uveitis in mice. The same authors suggested that IL-23 may be a key element in the early stages of intraocular inflammation, and that its function may even surpass the expansion and activation of Th17 cells. Furthermore, there seems to be an exacerbation of the Th17 response and increased disease severity with inhibition of the IL-12-IFN-γ pathway, reinforcing the previously described regulatory activities of these Th1 cytokines in Th17 differentiation.[11]

Noninfectious Uveitis

Increased IL-17 expression has been proven in several studies measuring its aqueous humor or peripheral blood concentration in noninfectious uveitic disorders [Table 1], as well as in other autoimmune diseases such as rheumatoid arthritis,[23] ankylosing spondylitis,[24] inflammatory bowel disease,[25] systemic lupus erythematosus,[26] and psoriasis,[27] in which circulating IL-17 was accessed.

In a study measuring IL-15, IL-17, IFN-γ, TNF-α, and IL-10 levels in the aqueous humor of patients with active autoimmune uveitis from different etiologies, including Behçet's disease (BD), Vogt–Koyanagi–Harada (VKH) disease, and human leukocyte antigen-B27-associated-uveitis, IL-17 levels were found to be higher in these patients than in control subjects, and these levels correlated with disease activity.[28] These results were confirmed by another study that measured IL-17 levels in the peripheral blood of a large group of patients with autoimmune uveitis with and without associated systemic disease. IL-17 levels were elevated

in the serum of uveitis patients when compared to controls, and they also served as a marker for disease activity.[29] When comparing intraocular and serum IL-17 levels, one study used a multiplex immunoassay to determine IL-17 levels in paired aqueous humor and serum samples of birdshot retinochoroidopathy (BSRC) patients.[17] The authors not only found an increased intraocular IL-17 expression in BSRC patients when compared to age-related cataract controls but also found that IL-17 levels in aqueous humor were higher than their concurrent serum levels.

All of these studies suggest that IL-17 may be used as a possible biomarker in autoimmune uveitis. Moreover, a recent study revealed a novel association between IL-17A locus polymorphisms and panuveitis, suggesting that IL-17A may also be a possible genetic risk factor for panuveitis.[30]

Infectious Uveitis

IL-17 has been implicated in the development of toxoplasmic encephalitis in an animal model, and since then, there have been studies that have analyzed its role in the induction and maintenance of intraocular inflammation caused by an infectious agent. In a previous study, upregulation of IL-17 levels in mice chronically infected with Toxoplasma gondii that lacked the IL-27 receptor was observed, and the authors suggested a protective role of IL-27 in the inflammation that follows toxoplasmic infection.[31] Moreover, the inflammatory roles of Th1 and Th17 cytokines and the regulatory roles of IL-10, TGF-β, and IL-27 in the immunologic responses following toxoplasmic infection have been reinforced in a later study concerning cytokine regulation in T. gondii infection.[32]

One study analyzed the inflammatory cytokine and chemokine levels in the aqueous humor of patients with toxoplasmic and viral uveitis. The authors found that IL-17 was upregulated in the majority of screened patients with toxoplasmic uveitis when compared to cataract patients without uveitis or with those with noninfectious intermediate uveitis. The authors suggested that the presence of elevated levels of IL-17 in the intraocular fluids of these patients may be a clue to a possible autoimmune mechanism that contributes to ocular inflammation following infection.[33] These findings were reinforced in a study addressing various cytokine levels in the aqueous humor of patients with uveitis from various etiologies – infectious and noninfectious. Patients with toxoplasmic infection and subsequent uveitis had significantly increased intraocular levels of IL-17A, whereas patients with viral uveitis showed increased IL-1β and IL-10 expression.[34] The authors postulate that this different cytokine pattern in intraocular fluids may help understand disease pathogenesis and even be used as a specific diagnostic marker for each etiology.

Another recent study highlighted the upregulation of IL-17 expression in patients with acute ocular toxoplasmosis and demonstrated a pathogenic role for this cytokine in the development of intraocular inflammation after T. gondii infection. The authors proposed a possible *in vivo* therapeutic approach for toxoplasmic retinochoroiditis based on the use of local anti-IL-17 antibodies.[35]

Interleukin-17 Induction

Several studies have shown that TGF-β and IL-6 are important cytokines in Th17 differentiation, and that IL-23 and IL-21 may also be crucial in Th17 cell expansion and activation [Table 2 and Fig. 1].

Interleukin-17 suppression

Interferon-γ

Antigen-specific IL-17 production is exacerbated in the absence of IFN-γ increasing the severity of uveitis in a murine model of spondyloarthritis. In this model, IL-17 blocking ameliorated intraocular inflammation in IFN-γ knockout mice, suggesting the regulatory function that this cytokine plays in IL-17 production.[45] Moreover, IL-17 expression was increased in the peripheral blood of patients with uveitis and scleritis and also in an EAU model. In the animal model used in this study, IFN-γ upregulated IL-27 expression by retinal cells which, in turn, inhibited Th17 cell proliferation, reducing uveitis severity and altering its clinical course.[6] Another study involving an EAU animal model also showed that IFN-γ ameliorated uveitis through Th1 and Th17 cell inhibition and IL-10 upregulation.[46] IFN-γ may also play a key role in infectious disease pathogenesis since the presence of anti-IFN-γ autoantibodies seems to be associated with nontuberculous mycobacterial infections.[47]

Interleukin-27

IL-27 is known as a regulatory cytokine that is capable of inhibiting the differentiation of precursor cells into their Th17 phenotype. By blocking the production of Th17 cells, this cytokine has been implicated in the suppression of experimental autoimmune encephalomyelitis and EAU.[6,48] A previous investigation addressing the regulatory cytokines, IL-27 and IL-10, in the development of uveitis found that mice retinal microglia and ganglion cells constitutively expressed IL-27, and that IL-27 production was elevated during uveitis.[49]

IL-27 expression was found to be decreased in BD patients with active uveitis,[50] and another study demonstrated elevated levels of IL-27 after cataract surgery in VKH patients, indicating that the upregulation of this cytokine during the 1st month following surgery might serve a protective function in postoperative inflammation.[41] Similar results were found in BD patients after cataract surgery as increased IL-27 serum levels were also evident during the postoperative period. These IL-27 levels correlated both with uveitis severity and IFN-γ levels.[43]

Therapeutic Targets

Anti-interleukin-17

An anti-IL-17 monoclonal antibody was used in the treatment of chronic noninfectious uveitis in patients with posterior and anterior segment disease. The treatment featured effects comparable to those of historical control patients with chronic noninfectious uveitis that were treated with infliximab. Specifically, this treatment was associated with improvements in visual acuity and the reduction of intraocular inflammation.[51]

Another study conducted of an animal model of spondyloarthritis demonstrated that IL-17 blockade reduced intraocular inflammation and peripheral arthritis although there was suspicion of retinal toxicity.[45] Treatment of EAU with the anti-IL-17 antibody in rats also showed a reduction in intraocular inflammation and of T-cell proliferation during disease onset.[52]

Secukinumab

Secukinumab, a human monoclonal antibody against IL-17, was used in a Phase III trial for the treatment of chronic noninfectious uveitis associated with BD; however, the study's primary outcome was not met (SHIELD study). Some authors have since claimed that the use of secukinumab in chronic uveitis has not been correctly assessed to date, since the other two trials enrolling patients with active and inactive noninfectious uveitis not associated with BD (INSURE and ENDURE) were interrupted following the termination of SHIELD. In the SHIELD study, although there was no significant difference between the treated patients and controls, there was a reduction in the use of concomitant immunosuppressant drugs and a trend toward a reduction in recurrence.[53]

Recently, another study demonstrated good results, in terms of both efficacy and safety, using intravenous secukinumab in the treatment of 37 patients with active noninfectious intermediate, posterior, or panuveitis who required corticosteroid-sparing immunosuppressive therapy.[48] This may suggest that there is still an opportunity for Phase III clinical trials using this or other monoclonal antibodies against IL-17 (or the IL-17 receptor) for noninfectious uveitis treatment.

Interleukin-17 Pathway

In addition to IL-17, there are other possible candidates for the treatment of noninfectious uveitis.

Ustekinumab, a monoclonal antibody directed at the IL-23 and IL-12 p40 subunit, was already approved for the treatment of psoriasis and it may be a future option for the treatment of uveitis patients, since a different study addressing the therapeutic effect of STA-5326 (another IL-12/IL-23 inhibitor) showed EAU clinical improvement and suppressed IL-17 production.[54]

Tocilizumab, a monoclonal antibody directed against the IL-6 receptor, has been successfully used in the treatment of refractory uveitis[55] and was approved for the treatment of rheumatoid and systemic juvenile idiopathic arthritis. It is currently being studied for use in noninfectious and juvenile idiopathic arthritis-

associated uveitis (clinicaltrials.gov). Another monoclonal antibody against the IL-6 receptor, sarilumab, is also currently being studied in a Phase II trial accessing subcutaneous administration in patients with active noninfectious intermediate, posterior, or panuveitis (clinicaltrials.gov).

Conclusions

Various studies have highlighted the importance of the IL-17 pathway in the development of various forms of infectious and noninfectious uveitis. Although the main Phase III trial addressing the use of a human anti-IL-17 monoclonal antibody in Behçet's-associated uveitis has failed to meet its primary outcomes, it seems adequate to continue the investigation concerning neutralization of the primary IL-17 pathway cytokines in the treatment of chronic noninfectious uveitis. Furthermore, the IL-17 pathway may also serve as a therapeutic target for infectious uveitis like toxoplasmic retinochoroiditis although always in addition to infection targeted therapy.

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Conflicts of interest

There are no conflicts of interest.

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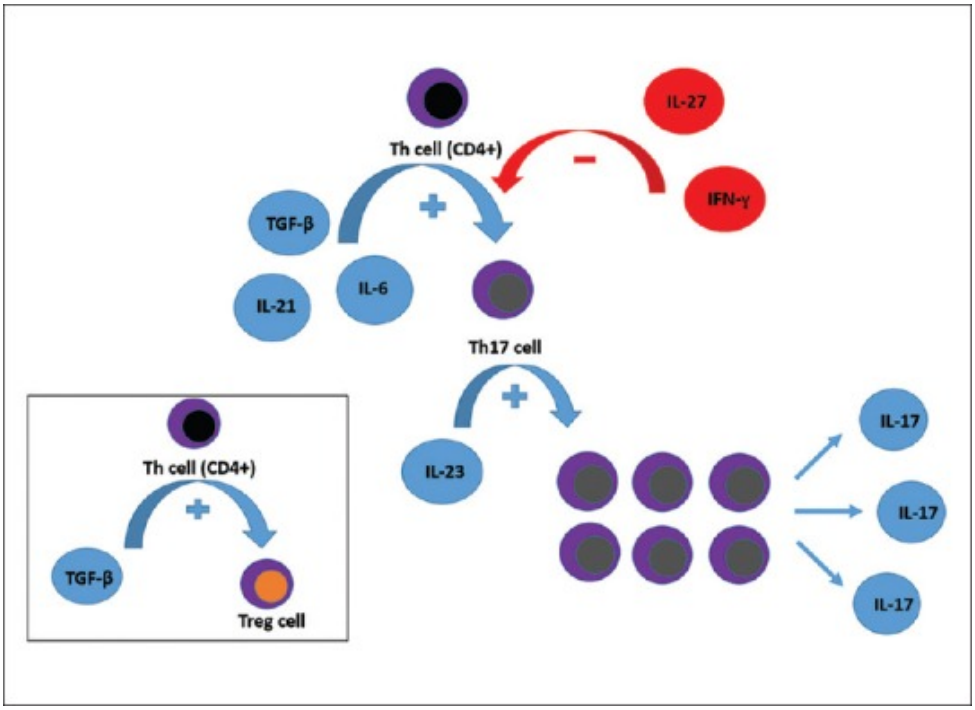
Figures and Tables

Figure 1



Both interleukin-6 and interleukin-21 can cooperate with transforming growth factor-β to promote Th17 differentiation from $CD4^+$ Th-cells while interleukin-23 is important for Th17 cell expansion and activation. Interferon-γ and interleukin-27 have regulatory roles through the suppression of Th17 differentiation. Note that the sole presence of transforming growth factor-β induces Treg cell production from $CD4^+$ Th-cells

Table 1

Systemic or intraocular autoimmune disorder associated with uveitis	Main conclusions	Authors, year of publication
VKH	Elevated IL-23 serum expression and upregulated IL-17 expression in PBMCs and CD41+ T-cells from VKH patients with active uveitis	Chi *et al.*, 2007[12]
	Decreased IL-27 expression is associated with an elevated IL-17 response in active VKH patients. Increased Th17 and IL-17 expression in PBMCs from active VKH patients	Wang *et al.*, 2012[13]
	Treatment with cyclosporine A and corticosteroids in VKH disease suppresses IFN-γ and IL-17 expression which, in turn, correlates with disease activity	Liu *et al.*, 2009[14]
	Increased IL-21 and IL-17 expression in VKH patients with the chronic or recurrent disease. Recombinant IL-21 stimulated IL-17 production via PBMCs of VKH patients	Li *et al.*, 2010[15]
BSRC	IL-21, IL-23, and TGF-β may promote differentiation and expansion of a chronic Th17 cell response in BSRC patients	Yang and Foster, 2013[16]
BSRC	Elevated IL-17 intraocular expression in BSRC	Kuiper *et al.*, 2011[17]
BD	Elevated levels of IL-23, IL-17, and IFN-γ by PBMCs and increased frequencies of IL-17- and IFN-γ-producing T-cells in BD patients with active uveitis	Chi *et al.*, 2008[18]
	Levels of IL-17 and IFN-γ-producing CD4+ T-cells are elevated in the peripheral blood of BD patients	Shimizu *et al.*, 2012[19]
	IL-17 expression is elevated in BD patients with active uveitis. Anti-TNF-α therapy inhibits Th17 cell differentiation and may ameliorate intraocular inflammation in BD	Sugita *et al.*, 2012[20]
HLA-B27-associated uveitis	Elevated IL-17 and IFN-γ expression in the peripheral blood of HLA-B27-associated uveitis patients. The increase in Th17 cells and IL-17 may correlate with disease activity	Zou *et al.*, 2014[21]
VKH, BD	Elevated IL-17F and IL-23A gene copy number variants	Hou *et al.*, 2015[22]

VKH: Vogt-Koyanagi-Harada, BSRC: Birdshot retinochoroidopathy, BD: Behçet's disease, PBMCs: Peripheral blood mononuclear cells, IFN-γ: Interferon gamma, IL: Interleukin, TGF: Transforming growth factor, HLA: Human leukocyte antigen

Studies demonstrating increased interleukin-17 expression in several autoimmune uveitic disorders that are not cited in the text

Table 2

Cytokines involved in IL-17 upregulation	Main conclusions	Authors, year of publication
TGF-β, IL-6, IL-23	IL-23 may expand the Th17 cell population, but it cannot induce this subsetxs differentiation from T-cell precursors. TGF-β induces Treg differentiation. The association between TGF-β and IL-6 induces Th17 cell differentiation	Bettelli *et al.*, 2006[3]
IL-6	IL-6 signaling blockade inhibits Th17 differentiation and induces the antigen-specific Treg formation in EAU	Haruta *et al.*, 2011[36]
	Early treatment with an anti-IL-6-receptor monoclonal antibody ameliorated mice EAU and inhibited Th17 cell differentiation	Hohki *et al.*, 2010[37]
IL-6, IL-23	EAU induction is impaired in IL-6 and IL-23 KO mice. Blocking of IL-6 and IL-23 ameliorates the clinical course of EAU through interference with Th17 cell differentiation and expansion. The anti-IL-6-receptor antibody ameliorates EAU by suppressing Th17 responses	Yoshimura *et al.*, 2009[38]
IL-21	EAU induction is impaired in IL-21 KO mice. There is decreased IL-17 expression in IL-21 KO mice. IL-21 signaling blockade inhibits IL-17 upregulation in EAU	Wang *et al.*, 2011[39]
	IL-21 and its receptor are upregulated in mouse EAU with increased IL-17 expression	Liu *et al.*, 2009[40]
IL-23	IL-23 is upregulated in the peripheral blood of VKH patients before and after cataract surgery; it is also correlated with intraocular inflammation	Jiang *et al.*, 2010[41]
	IL-23 and IL-1β induce Th17 expansion and the cytokine response	Wilson *et al.*, 2007[42]
	IL-23 serum levels are elevated before and after cataract surgery in BD patients. IFN-γ and IL-27 serum levels are elevated after cataract surgery in BD patients	Jiang *et al.*, 2011[43]
	There is increased IL-17 and IL-23 expression in patients with active BD	Na *et al.*, 2013[44]

IFN-γ: Interferon gamma, TGF: Transforming growth factor, EAU: Experimental autoimmune uveitis, KO: Knockout, VKH: Vogt-Koyanagi-Harada, BD: Behçet's disease, IL: Interleukin

Cytokines involved in interleukin-17 induction