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Mini Review

Regulation of Th1 and Th17 cell differentiation in uveitis

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Noninfectious uveitis is one of the sight-threatening disorders that are associated with systemic autoimmune diseases, such as Behçet's disease. Uveitis is often recurrent and causes subsequent tissue destruction and scarring, especially in the retina and uvea, leading to permanent loss of vision. Early studies have shown that T-helper (Th) 1 cells are the major effector cells and are critical for the development of uveitis. Recently, Th17 cells, a newly defined effector T-helper lineage that is distinct from Th1 and Th2 cell lineages, were also shown to play a pivotal role in the pathogenesis of uveitis. Furthermore, several clinical studies have reported that biological agents targeting Th17-related cytokines, such as IL-6, IL-23, and TNF-α, induced and maintained remission in human autoimmune diseases, including rheumatoid arthritis, Crohn's disease, psoriasis, and noninfectious uveitis. In this mini-review, we focus on the roles of proinflammatory cytokines in the regulation of Th1 and Th17 cell responses in uveitis, both experimentally and clinically. A deeper understanding of the underlying mechanisms will provide new insights into the development of new therapies for refractory human noninfectious uveitis.

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Introduction

Ocular inflammation, which is termed generally as uveitis, leads to vision loss as a result of the destruction and scarring of delicate tissue along the visual axis, especially in the retina and uvea. Thus, understanding the pathophysiology of uveitis, especially that of autoimmune origin, is important for therapy. Experimental autoimmune uveoretinitis (EAU) is a well-established animal disease model that resembles human uveitis and serves as a model for investigating the mechanism of human uveitis[1]. EAU is an organ-specific T cell-mediated autoimmune disease that can be induced in several susceptible animal species by immunization with retinal self-antigens, such as interphotoreceptor retinoid-binding protein (IRBP) and the retinal soluble antigen (S-Ag),

emulsified with complete Freund's adjuvant (CFA). During EAU, the integrity of the blood-retinal barrier is compromised, and infiltration of monocyte/macrophages and antigen-specific CD4+ T lymphocytes into the retina causes tissue damage. The adoptive transfer of retinal antigen-specific CD4+ T cells into naïve syngenetic recipients induces EAU[2]. In humans, several lines of evidence have revealed that activated T cells, especially CD4+ T cells, play pivotal roles in the pathogenesis of autoimmune uveitis[3-5]. In previous studies, Mossman, Coffman, and their colleagues advocated the T helper (Th) 1/Th2 paradigm to explain the immune responses involved in infection, autoimmunity, and allergy[6]. When naïve CD4+ T cells encounter antigens, effector naïve CD4+ T cells begin to differentiate into interferon (IFN)-γ-producing Th1 or Th2 cells, depending on the cytokine milieu; this is considered to be a critical process in the control of autoimmunity or allergy[7]. Recently, a third lineage of newly recognized interleukin (IL)-17-producing CD4+ T cells, called Th17 cells, were found to a crucial role in several autoimmune diseases by mediating tissue inflammation[8]. Transforming growth factor-β1 (TGF-β1) and IL-6 have been found to initiate Th17 cell differentiation, while IL-23 was found to enhance the expansion or activation of Th17 cells[9]. Th17 cells produce proinflammatory cytokines, such as IL-17A, IL-21, and tissue necrosis factor (TNF)-α. Recently, several biological agents that target proinflammatory cytokines, including IL-6, IL-17A, TNF-α, and IL-23, have been developed for the treatment of autoimmune diseases, such as rheumatoid arthritis, Crohn's disease, psoriasis, and noninfectious uveitis[10]. Anti-TNF-α therapy with infliximab, which is a chimeric monoclonal antibody against TNF-α, has been validated in patients with refractory uveoretinitis in Behçet's disease in Japan[11]. At the 12-month follow-up, uveitis improved in more than 90% of the patients and worsened in none. Thus, the elucidation of particular CD4+ T cell subsets for uveitis has been a key to understanding the pathogenesis of uveitis and developing new effective treatments. This review focuses on some roles of several proinflammatory cytokines in the differentiation of naïve CD4+ T cells into Th1 and Th17 cells in uveitis.

Th1 and uveitis

Th1 cells, which secrete IL-2, IFN-γ, and lymphotoxin, are critical for macrophage activation and nitric oxide production, which is required for eliminating intracellular pathogens and cell-mediated and delayed-type hypersensitivity

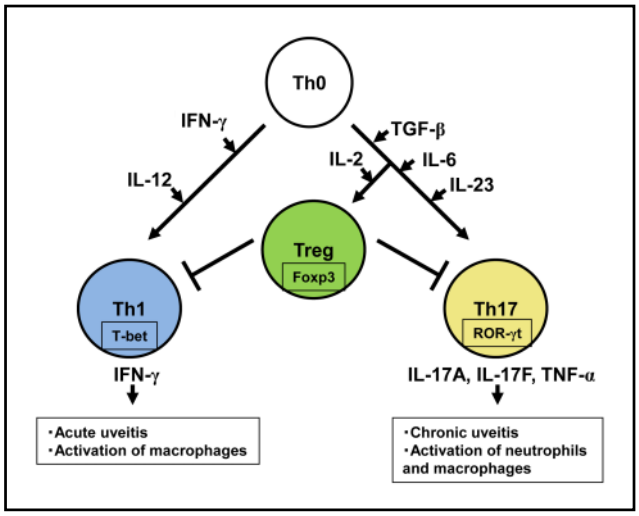

Fig. 1 Scheme of Th1 and Th17 cells differentiation

Differentiation of T helper (Th) 1, Th17, and iTreg cells from naïve CD4+ T cells. Designated cytokines promote differentiation of naïve CD4+ T cells into Th1, Th17, or iTreg cells after antigen presentation. T-bet, ROR-γt, and Foxp3 are the key transcriptional factors for the differentiation of Th1, Th17, and iTreg cells. Th1 cells play central roles in early/acute phase of uveitis, whereas Th17 cells act in the late/choronic phase of uveitis. iTreg cells suppress both Th1 and Th17 cell responses.

IFN, interferon; IL, interleukin; Foxp, forkhead box protein; ROR-γt, retinoid-related orphan receptor-γt; T-bet, T box expressed in T cells; TGF, transforming growth factor

(Fig. 1), whereas Th2 cells, which secrete IL-4, IL-5, IL-6, IL-9, and IL-13, are necessary for promoting the humoral immunity that underlies responses to helminthic infections and allergies[12]. In early studies, Th1 cell responses have been reported to play important roles in the induction of autoimmune diseases such as experimental autoimmune encephalomyelitis (EAE) and collagen-induced arthritis (CIA)[13], whereas Th2 cell responses were found to suppress these diseases. In Th1 cell differentiation, signal transducer and activator of transcription (STAT) 1, which functions downstream of IFN-γ, is an important transcriptional factor for inducing T-bet, a master transcription factor for Th1 cells, and subsequent expression of IL-12 receptor (R) β2 chain, in order to respond to IL-12 stimulation[14]. IL-12, which is a heterodimeric cytokine composed of p40 and p35, transmits signals through STAT4, leading to the expansion of Th1 cells and enhancement of IFN-γ production[15]. As in EAE, several studies have revealed that autoreactive Th1 cells mediate EAU and that their induction correlates with the production of IFN-γ by T cells[16]. Furthermore, it has been reported

that augmented Th1 cell responses result in high susceptibility to ocular autoimmunity[17]. As seen in patients with uveitis, such as Behçet's disease, Th1 cell responses are also associated with disease activity[18]. Recently, several IL-12-related cytokines have been identified, and it has been revealed that the action of these cytokines is related to the function and differentiation of $CD4^+$ T cells in autoimmunity. Among them, IL-27, which is a heterodimeric cytokine composed of Epstein-Barr virus-induced gene 3 (EBI3) and IL-27p28, engages a receptor composed of gp130 and IL-27Rα[19]. Initially, IL-27 was reported to be a proinflammatory cytokine that induces Th1 cell responses. However, IL-27 is now widely regarded as a regulatory cytokine of activated T cells, such as Th17 cells, as discussed later in this mini-review. In an analysis of IL-27Rα-deficient mice, IL-27Rα was found to be required for the normal production of IFN-γ by naïve $CD4^+$ T cells[20]. Subsequently, we and others demonstrated that IL-27 does not directly induce IFN-γ production, but rather induces IL-12-dependent IFN-γ production by the augmentation of T-bet and subsequent IL-12Rβ2 expression in naïve $CD4^+$ T cells[21-23]. Consistent with these results, we found that IL-27 participates in the development of Th1 cell responses and invasion of inflammatory cells in the eyes, especially in the early phase of EAU[24]. Taken together, these results suggest that Th1 cell responses are important for the initiation of EAU.

However, neutralization of IFN-γ, which is a hallmark cytokine for Th1 cells, is highly susceptible to EAU[25]. Similarly, mice deficient in IL-12p35 are susceptible to EAU by enhanced induction of proinflammatory cytokines other than IFN-γ, even though mice deficient in IL-12p40 protected against EAU[26, 27]. Oppmann et al. found that IL-12 shares the p40 subunit with IL-23, which activates $CD4^+$ T cells distinctly from IL-12[28]; thus, the protective role of deletion or neutralization of p40 in EAU reflects the function of IL-23, but not that of IL-12. Furthermore, when we neutralized regulated on activation, normal T cell expressed and secreted (RANTES), a Th1-related chemokine, cellular infiltration into the eyes and the disease severity of EAU were exacerbated in the late phase[29]. These results suggested that Th1 cell responses play not only a proinflammatory role, but also a protective role in EAU. Alternatively, there may be another T cell lineage that can promote autoimmunity independently of both Th1 and Th2 cell lineages, including in EAU.

Th17 and uveitis

Th17 cells constitute a Th cell lineage distinct from Th1 and Th2 cells[30]. The generation of Th17 cells is enhanced by the blockade of IL-4 and IFN-γ and is independent of Th1- or Th2-related transcriptional factors. Th17 cells produce proinflammatory cytokines, such as IL-17A, IL-17F, IL-21, IL-22, TNF-α, and granulocyte macrophage-colony stimulating factor (GM-CSF)[8]. IL-17A induces inflammation mainly through release of pro-inflammatory and neutrophil-mobilizing cytokines/chemokines, leading to neutrophil trafficking to the site of inflammation. Enhanced expression of IL-17A is also observed in human peripheral blood mononuclear cells from patients with various autoimmune diseases, including active uveitis in VKH and Behçet's disease[31, 32].

By analyzing Th17 cell responses in EAU in IL-17A-deficient mice, we and others found that mice deficient in IL-17A are susceptible to EAU because of the induction of Th1 cell responses[27, 33, 34]. In addition, we found that IL-17 deficiency is dispensable for the induction of EAU and diminishes the severity of EAU only in the late phase[33]. Furthermore, the augmentation of Th17 cell responses by the systemic administration of both anti-IFN-γ and anti-IL-4 neutralizing antibodies exacerbated EAU in the late phase. Thus, these results suggest that Th17 cell responses contribute to the disease severity, not in the initial phase, but particularly in the late/chronic phase of EAU (Fig. 1). On the other hand, analysis of mice deficient in IL-17A revealed that Th1 cell responses and subsequent invasion of inflammatory cells into the eyes occurs in the early phase of EAU. Amadi-obi et al. also demonstrated that expression of IL-17 in the retina is very low before cellular infiltration starts and that elevation of IL-17 expression in the retina is observed after cellular invasion into the eyes[35]. Thus, it is reasonable to assume that Th1 cells, rather than Th17 cells, play some roles in the initial phase of EAU. Recently, Tang et al. revealed that uveitis could not be induced in mice deficient in IFN-γ despite enhancement of Th17 cell responses in their Th1-dominant antigen-pulsed dendritic cell-induced EAU, which is different from conventional EAU, suggesting that Th17 cell responses are not essential for the induction of EAU[36]. Furthermore, we and others have shown that IFN-γ increases in the aqueous humor of acute human uveitis patients, but not in the vitreous humor of patients with chronic uveitis[37, 38]. Taken together, we speculate that Th1 cell responses may be important in the acute or initial phase, but not in the late phase of ocular inflammation in uveitis (Fig. 1).

The roles of IL-6 and IL-23 in uveitis

Initially, IL-23, a member of the IL-12-related cytokine family, which contains the p40 subunit common to IL-12 and IL-23 as well as a unique p19 subunit, was reported to be responsible for Th17 cell expansion and to be critical for the development of autoimmune diseases, such as EAE and CIA[13]. IL-23 transmits its signaling via IL-23R and STAT3[42]. However, since naïve CD4+ T cells express very low levels of IL-23R, this process produces only small fractions of IL-17-secreting T cells[39]. Subsequently, TGF-β, in combination with IL-6, IL-21, or IL-1β, initiates Th17 cell differentiation, leading to the enhanced expression of IL-23R and retinoid acid-related orphan receptor γ thymus (ROR-γt), which is a master transcriptional factor for Th17 cells, and resulting in the expansion of Th17 cells by IL-2[38]. On the other hand, TGF-β promotes the generation of inducible forkhead box protein 3 (Foxp3)-positive regulatory T (iTreg) cells, which are essential for maintaining peripheral tolerance, preventing autoimmune disease, and limiting chronic inflammatory diseases. However, IL-6 abolishes the inducible effect of TGF-β on iTreg cells[40]. Thus, the differentiation of Th17 and iTreg cells by TGF-β is reciprocally related through the action of IL-6.

In our analysis of mice deficient in IL-6 or IL-23p19, we demonstrated that lack of either IL-6 or IL-23 diminishes systemic induction of Th17 cell responses and suppression of EAU during the entire phase[38]. Several studies have provided evidence that Th17 cells promote the expression of IL-17A, IL-6, and TNF-α, resulting in the activation of fibroblasts, vascular endothelial cells, epithelial cells, and macrophages. These cells then produce chemokines to recruit neutrophils and macrophages into the retina, leading to the induction of regional inflammation[41]. We also found that the blockade of Th17 cell development reduces chemokine expression, leading to amelioration of both macrophage and neutrophil infiltration into the retina during EAU[38].

Recently, tocilizumab, a humanized anti-IL-6R monoclonal Ab, has been found to be effective for the treatment of RA patients[42]. To address the therapeutic efficacy of IL-6 in EAU, we utilized MR16-1, which is rat anti-mouse IL-6Rα neutralizing antibody, and found that systemic administration of MR16-1, but not regional treatment with this antibody, ameliorates EAU[38]. Interestingly, the blockade of IL-6 decreased Th1 cell responses as well as Th17 cell responses. Haruta et al. also showed that blockade of IL-6 signaling inhibits Th1 cell responses, but that this inhibition is abrogated by depletion of Foxp3+ Treg cells in EAU[43], suggesting that Foxp3+ Treg cells can inhibit Th1 cell responses in EAU. Thus, the targeting of IL-6 signaling is attractive for the treatment of uveitis by direct inhibition of Th17 cell development and indirect inhibition of Th1 cell responses.

Furthermore, several studies have revealed that IL-27 directly acts as a negative regulator of fully activated CD4+ T cells, including Th17 cells and that IL-27 also induces the differentiation of IL-10-producing type-1 regulatory T (Tr1) cells, which suppress Th17 cell responses[44]. In addition, we and others found that IL-27 can suppress IL-17 production by activated CD4+ T cells, thereby counteracting IL-23[35, 45]. In EAU, Amadi-Obi et al. found that IL-27 is constitutively expressed in the retina and that IL-27 can suppress IL-23-dependent production of IL-17 by uveitogenic CD4+ T cells[35]. In addition, Wang et al. reported that IL-27 was downregulated in active uveitis in patients with VKH and that an increase in IL-27 and a decrease in IL-17 were observed upon resolution of the disease by systemic administration of immunosuppressive drugs[31]. Thus, these results suggested that IL-27 is a therapeutic target for chronic inflammation in uveitis.

Anti-TNF-α therapy and uveitis

Based on the previous studies on autoimmunity in uveitis, uveitis patients are currently being treated with several immunosuppressive drugs that possess strong T-cell-suppressive effects, such as glucocorticoids, tacrolimus, and cyclosporine, to control inflammation in the eyes[10]. However, in patients with Behçet's disease, these drugs often fail to maintain remission of ocular inflammation on a long-term basis[46]. In addition, the long-term use of these drugs is unacceptable due to their severe systemic adverse side effects. Recently, several biological agents, such as monoclonal antibodies and a recombinant form of natural inhibitory molecules against proinflammatory cytokines or receptors, have been developed for the treatment of refractory immune disorders[10]. For instance, anti-TNF agents, such as infliximab, have been successfully applied to the treatment of refractory uveitis, including in Behçet's disease[10]. TNF-α is a soluble potent proinflammatory cytokine exerting pleiotrophic effects on various cell types and plays important roles in choronic inflammatory disorders[47]. It has been reported that Th17 cells as well as Th1 cells induce TNF-α in the active uveitis seen in Behçet's disease[48]. In addition, transmembrane TNF-α, the precursor form of TNF-α, also acts as a bipolar molecule that transmits signals as a ligand

as well as a receptor. Soluble TNF-α acts apart from TNF-α-bearing cells, whereas transmembrane TNF-α on TNF-α-bearing cells binds to TNF-α receptors on the target cells and transmits not only signals to the target cells as a ligand, but also reverse signals back to the TNF-α-bearing cells as a receptor, in a cell-to-cell contact manner[47]. Thus, transmembrane TNF-α is considered to play important roles in local inflammation. Since infliximab is a chimeric monoclonal antibody designed against the soluble and membrane-bound forms of TNF-α, the suppressive mechanism of infliximab involves inhibition not only of the proinflammatory roles of soluble TNF-α, but also of the action of TNF-α-producing cells, such as Th1 and Th17 cells.

Recently, Th22 cells, a Th cell lineage distinct from Th1, Th2, and Th17 cells, were found to secrete IL-22 and TNF-α and to be increased in active uveitis in Behçet's disease[49]. Th22 cell clones, which could be differentiated from $CD4^+$ T cells in patients with active Behçet's disease in the presence of IL-6 and TNF-α, secreted IL-22 and TNF-α, but not IFN-γ and IL-17. In addition, the Th22 cell clones failed to produce IL-22 after treatment with anti-TNF-α neutralizing Abs, anti-IL-6 neutralizing Abs, and infliximab[49]. Thus, an inhibitory effect of infliximab on ocular inflammation in patients with Behçet's disease may reflect the suppression of Th22 cell responses, as well as that of Th1 and Th17 cell responses. The potential mechanism of the effect of Th22 cell responses on the pathogenesis of other forms of uveitis may warrant further research in this area.

In conclusion

In the last decade, numerous studies on Th17 cells and Th17 cell responses have led to remarkable progress in the understanding of the pathophysiology of uveitis. In this review, we demonstrated that both Th1 and Th17 cell responses are responsible for the pathogenesis of uveitis, but that they act at different time points. However, in human uveitis, we cannot exclude that the relative importance of Th1 and Th17 cell responses differs depending on the circumstances, including the types of innate receptors and/or antigen-stimulating cells. A more profound understanding of the intricacies of immune responses in autoimmunity will improve innovation in approaches for the management and treatment of uveitis.

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Conflicts of interest

None

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