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The Role of Th17 Cells in the Pathogenesis of Behçet's Disease

Yuki Nanke and Shigeru Kotake

Abstract

Behçet's disease (BD) is a polysymptomatic and recurrent systemic vasculitis with a chronic course and unknown cause. BD is now categorized as both autoimmune diseases and auto inflammatory diseases. The pathogenesis of BD is still unclear; however, BD has been thought as a Th1-related disease, with elevating levels of Th1 cytokines such as IFN-γ, TNF-α, and IL-2. Some investigators found that Th17-associated cytokines were elevated in patients with BD; thus, IL-17/IL-23 pathway and Th17 cells may have crucial roles in the pathogenesis of BD. In this chapter, we review the pathogenic role of Th17 cells in BD.

Keywords: IL-17, Th17, Th1, Behçet's disease, regulatory T cells

1. Introduction

BD is a systemic vasculitis and polysymptomatic [1, 2] and characterized by recurrent aphthous stomatitis, genital ulcers, uveitis, and skin lesions. Arthritis is also a common manifestation of BD, and sometimes inflammation is involved in the gastrointestinal tract as well as vascular and central nervous systems. The cause of BD is not fully understood. BD is now categorized as both an autoimmune disease and an autoinflammatory disease.

The association between carriage of the human leukocyte antigen (HLA) B51 allele and BD has been known in different ethnic groups. Recently, the genome-wide studies showed the association of some non-histocompatibility complex (MHC) genes, including IL-23R-IL-12 RB 2 and IL-10 genes [3, 4]. The pathogenesis of BD has not been fully elucidated; in addition to genetic factors, cytokines, viral and bacterial agents, and immune dysfunction are associated with the exacerbation of BD.

CD4+ T cells and neutrophils play an important role in the pathogenesis of BD. Since IL-12 and IFN-γ from Th1 cells can mediate the inflammatory response between neutrophils and T cells, BD has been considered as a Th1-mediated disease [5, 6].

Th17 cells play an important role in immunity. Th17 cell differentiation from naïve CD4+ T cells is assisted by IL-6, IL-21, IL-1β, and IL-23. The critical feature of Th17 cells is the expression of IL-17A, IL-17F, IL-22, IL-6, IL-8, and IL-26, and TNF-α expresses RAR-related orphan receptor (ROR) γ. The current studies suggest that Th17 axis plays a pivotal role in BD pathogenesis. IL-17 has been shown to recruit neutrophils to the site of inflammation. Abnormalities in the T cell response cause the hyperreactivity of neutrophils in BD through the production of cytokines, such as IL-17 [7]. We discuss the pathogenic role of Th17 cells in BD.

2. Th17 in mouse model

In mice, the combination of IL-6 and TGF-β plays a critical role in the development of Th17 cells from naive T cells. Th17 cells play important roles in the pathogenesis of intraocular inflammation in an animal model of uveitis [8–10]. Anti-mouse IL-17 blocking antibodies are effective for intraocular inflammation in experimental models of uveitis [11].

Inhibition of the expression of TNF-α [12], and the downregulation of IL-6 [13] improved the inflammation in BD mice by the upregulation of Th17 cells. Foxp3 may inhibit Th17 differentiation by antagonizing the function of RORγt, the master transcription factor. It is reported that anti-TNF-α blockade may prevent the differentiation of Th17 cells in animal models for BD [14]. γδ T cells produce IL-17 and may play an important role in experimental uveitis in animal models [10].

3. Th17 in humans

3.1 Plasma IL-17 levels in BD

In humans, IL-23 and IL-1β are needed for the development of Th17 cells. IL-17 levels were markedly elevated in BD [15–20]. Some investigators [22, 23] reported that the ability to produce IL-17A and amount of circulating Th17 cells were increased in active BD patients. Increased levels of IL-17 may induce neutrophil activity [22].

It is reported that the ability to produce IL-17A and population of Th17 cells are enhanced in active BD despite the low expression of RORγt mRNA [21]. Chi et al. reported that elevated levels of IL-17A, IL-23, and IFN-γ in the aqueous fluid from the eyes as well as in peripheral blood of BD patients [23, 24].

3.2 Circulating Th17 cell frequencies are correlated with disease activity

It is reported that the significantly higher frequency of circulating Th17 cells are detected in active BD patients compared with the same patients in remission stages [21]. A positive correlation was seen between the plasma IL-17 level and ESR or CRP in active BD patients [21]. It has been reported that the peripheral blood Th17/Th1 ratio was markedly higher in patients with active BD than the healthy controls [25, 26] and that in BD patients with folliculitis or uveitis, the Th17/Th1 ratio was elevated [23, 24]. Thus, the balance of Th1 and Th17 cells plays an important role in the pathogenesis of BD, especially in the pathogenesis of folliculitis and uveitis. Moreover, the high expression of IL-23p19 mRNA was detected in the erythema nodosum (EN)-like lesion of BD [27].

A significant increase in IL-17- and IFN-γ-expressing CD4+ memory T cells was observed in patients with active BD compared with control groups [28]. Similarly, the levels of IL-17, IL-23, IL-12/IL-23p40, and IFN-γ in serum and supernatants were increased in active BD patients compared with control groups [28]. IFN-γ-secreting Th17 cells were elevated in BD patients [27–29]. Touzot M et al. reported that IL-17 was not inhibited by IFN-α in BD and IFN-α increased IFN-γ level in memory CD4+ T cells in BD [31]. Thus, BD is associated with a mixture of TH1/Th17 cytokine.

Patients with BD in remission expressed low Th17 levels compared to active BD [21, 24, 28]. Thus, the population of Th17 cells is correlated with BD activity [16, 22].

More recently, Lucherini et al. [32] reported that serum amyloid A (SAA) induced Th17 polarization rather than Th1 differentiation from CD4+ T cells in BD

patients. A critical regulation of Th17 may be the functional link between acute SAA increase and the induction of Th17-mediated inflammatory response in BD.

Deniz et al. [33] reported that under Th17-stimulating conditions, T cells express both IL-17 and IFN-γ in BD. In addition, they speculated that more prominent IL-17 and IFN-γ production by all lymphocyte subsets in BD may be associated with the increased innate responses, early tissue neutrophil infiltrations, and late adaptive immunity in BD.

3.3 IL-23-IL-17 axis

Recently, it is reported that IL-23R is principal for the differentiation of IL-17-producing effector T cells in vivo [34]. IL-23 was essential to preserve and to generate Th17 cells even in the absence of TGF-β [35]. The IL-23-IL-17 axis is crucial for the inflammation in BD [23]. Elevated levels of IL-23 and IL-17 [21, 28] were seen in peripheral blood mononuclear cells (PBMC) from active BD patients [23]. Recombinant IL-23 stimulated IL-17 in CD4+ T cells in BD patients [15, 23]. Recently, IL-23R, IL-12RB2, and IL-10 were identified as BD susceptibility loci by genetic surveys including GWAS [3, 4]. It is reported that the genetic variation of IL-17F and IL-23 A is associated with BD [36]. Jiang et al. [37] reported that IL-23R gene polymorphism enhanced the expression of the IL-23 R and IL-17 in BD patients.

3.4 The suppressive effect of IL-27 on Th17 cell differentiation

IL-27 is a regulator of the proinflammatory T cell response. In mouse, IL-27 plays a negative role in Th17 cell differentiation. It is reported that decreased level of IL-27 in patients with active BD [38] and decreased IL-27 expression was correlated with uveitis activity in patients with BD [38]. IL-27 inhibited human Th17 cell differentiation by upregulation of the expression of interferon regulatory factor (IRF) 8 [38]. Previous studies have shown that the presence of IL-27 limits Th17-mediated uveitis [39].

4. IL-21 and IL-26 in BD

It was reported that the expression of IL-21 was elevated in the serum of active BD patiens, and that this promoted Th17 differentiation [16]. IL-26 levels in cerebrospinal fluid and bronchoalveolar lavage fluid in BD patients showed positive correlations with IL-17 level. IL-26-stimulated CD4$^+$ T cells and monocytes promote the generation of Th17 and suppress regulatory T cell cytokines [40].

5. Uveitis in BD

Some investigators reported that IL-17 [15, 41], IL-23, and IFN-γ in the sera and aqueous humor significantly increased in BD patients with active uveitis compared with BD patients without active uveitis and HC [23]. It is also reported that IFN-γ-producing and IL-17-producing T cells in BD patients with active uveitis were increased [15, 23, 38]. Thus, the IL-23/IL-17 pathway plays an important role in active uveitis in BD patients. Activated CD4+ T cells obtained from BD patients produce TNF-α in vitro. Chi et al. demonstrated that IL-12 exerted its inhibitory effect on IL-17 through IFN-γ. They also reported that recombinant-IL-23 (rIL-23) can promote the production of IL-17 by CD4+ T cells in BD patients [23]. Jiang et al. reported an association of rs17375018 in the IL-23R gene with uveitis in BD patients [41]. Taken together, elevated levels of IL-17 may be associated with the intraocular inflammation of BD patients [15, 23].

6. Oral and genital ulcer and articular symptoms

Alpsoy et al. reported that IL-17 levels of BD patients with active stages of oral and genial ulcers and articular symptoms were higher than BD patients with inactive stages of these symptoms [42]. They also found that the percentage of CD4+ IL-17+, IL-17, and CD4− IL-17+ T cells was significantly elevated after *E. coli* and PHA stimulation in active organ involvement.

7. Skin

Hamzaoui et al. confirmed that the presence of an important population of IL-17+ cells infiltrates the erythema nodosum-like eruption in BD skin lesions using antibodies to IL-17A [21]. Shimizu et al. demonstrated that IFN-γ + IL-17 + -producing cells were dominant, and some of them were CD4+ cells in BD-EN compared with healthy controls [30]. Th17 cells are elevated in circulation and distribution over the skin lesions of BD patient. Ekinci et al. reported that serum IL-17A levels were markedly elevated in BD patients with active stages of oral ulcers or genital ulcers compared with inactive stage of these symptoms [22]. They also studied the proportion of IL-17-secreting cells in patients with active organ involvement, showing that the percentage of IL-17, CD4− IL-17+ cells, and CD4+ IL-17+ cells was significantly elevated [20, 22]. This finding indicated that Th17 and IL-17 pathway has a crucial role in the acute attack of the disease.

8. Entero-BD

Gastrointestinal involvement is an important complication of BD. Emmi et al. [43] found that T cells at the intestinal mucosal level produce a high amount of TNF-α and in the early stage of BD. Both Th17 and Th1 cells drive inflammation and mucosal damage though long-lasting cytokine production [44]. Imamura et al. reported the infiltration of CD4+ and CD8+ T cells in the intestine of BD patient, like the expression of mRNAs of proinflammatory and Th1 cytokines/chemokines [45]. Recently, IL-17A, IL-23R, and STAT4 polymorphisms may be involved in the pathogenesis of intestinal involvement in Korean BD patients [46]. On the other hand, Ferrante et al. reported that the serum and mRNA level of IL-23 and IL-17 in entero-BD were not different from those with control groups; thus a Th1 but not a Th17 response occurs with entero-BD [47]. More studies are needed to reveal the role of IL-17 in intestinal involvement of BD.

9. Neuro-BD

The expression of RAR-related orphan receptor C (RORC), which is the master transcription factor of Th17 cells, was elevated in the cerebrospinal fluid (CSF) of patients with neuro-BD [48]. In the CSF, the Th17/regulatory T cell (Treg) ratio was elevated [49]. It was reported that increased level of IL-17 secretion in the sera of BD patients and the elevated expression of transcription factors for Th17 cells were shown in the CSF were detected with neuro-BD patients [48]. It is reported that IL-17A- and IL-21-producing T cells in the CSF, brain parenchyma inflammatory infiltrates, and intra-cerebral blood vessels from patients with active BD and neuro-BD [16]. The stimulation of CD4+ T cells with IL-21 increased Th1 and Th17 differentiation and decreased the regulatory T cells [16]. Conversely, IL-21 blockade

with an IL21R-Fc restored the Th17 and regulatory T cell homeostasis in BD patients [16]. On the other hand, Saruhan-Direskeneli et al. [49] reported that, both in serum and the CSF, IL-17 was not detectable in BD patients with CNS involvement. Thus, the pathogenesis of IL-17 in neuro-BD remains controversial.

10. Polymorphisms

The signaling molecules and Th1- and Th17-related cytokines are involved in the pathogenesis of BD [50–52]. Several reports showed that polymorphisms of Th17-related cytokines and receptors, such as IL-17F, IL-23R, and IL-23 A, were related to BD susceptibility in Korean and Chinese [41, 53, 54]. STAT4 is necessary for the increase of Th17 cells activated by IL-23. Functional studies showed that the risk SNPs in the STAT4 gene took part in BD might affect the expression of STAT4 and production of IL-17 [55]. The haplotype of IL-17A had a relation to the entero-BD risk, where those of IL-23R are protected against disease expansion. The interactions of IL-23R, IL-17A, and STAT4 SNPs modify the susceptibility to intestinal BD, suggesting the crucial role of the IL-17/IL-23 axis in the pathogenesis of intestinal BD [56].

11. Plasticity

Recently, plasticity of Th17 and Th17 cells means that they can produce Th1 (IFN-γ)- or Th2 (IL-4)-type cytokines under inflammation [57, 58]. Th17 cells are able to change IFN-γ-expressing T cells in mouse Th1 disease models, which are named Th17/Th1 cells, IFN-γ-expressing Th17 cells, or Th1-like cells. The expression of RORC is not fixed in T cells, and the plasticity of Th17 cells was recognized in murine models in vivo [45]; this conception was applied to human diseases [59, 60]. Geri et al. demonstrated that the frequencies of IFN-γ CD4+ T cells and IL-17+ CD4+ T cells were increased in the CSF than in PBMC in BD patients [16]. Th1 and Th17 cells may be complicated at different steps in inflammatory process, and more Th17 cells were generated than Th1 cells during the inflammatory process. The elevated level in Th17/Treg cells and Th17/Th1 ratios is correlated with the expanse of inflammation. In BD, plasticity exists between Th1, Th17, and Treg cells during inflammation at inflammatory sites and in the peripheral circulation [61]. The low levels of Th17 in remission BD compared with active BD may be due to a conversion of Th17 cells into Treg cells. The differentiation of Treg cells into Th17 cells was involved in the downregulation of FoxP3 expression and the suppressor function. Foxp3 inhibits Th17 differentiation by antagonizing the RORγt function [62]. Sonmez et al. [63] reported that IL-17A/F levels increased parallel to IL-23 levels in BD and IL-35 levels were lower in active BD patients than the inactive BD patients, which may be a plasticity between Th17 and Treg cells according to the state of disease activity.

12. Therapy

12.1 Cyclosporine A (CsA)

CsA is effective for reducing the severity of intraocular inflammation of BD. Chi et al. reported that CsA has an effect on both IFN-γ and IL-17 productions in vitro and in vivo. In vitro, it was shown that CsA inhibited IL-17 production from PBMC of BD patients. In vivo, the improvement of intraocular inflammation in BD was

accompanied by the suppression of both IFN-γ and IL-17 productions after CsA administration [24]. Therefore, it is suggested that the efficacy of CsA on uveitis in BD is through the inhibition of IFN-γ and IL-17 production.

12.2 Antibodies to IFN-α

Type I IFNs were able to inhibit IL-17 production by PBMC. Recombinant IFN-α has been used to treat BD [57]. Liu et al. reported that significantly higher levels of IL-17 are detected in active BD patients and stimulation with IFN-α decrease IL-17 production [17]. In vitro study showed that IFN-α does not directly regulate the Th1/Th17 balance in BD but rather promotes a regulatory Th1 response through IL-10 secretion [63]. IFN-α activity was mediated via STAT2 phosphorylation [17]. IFN-α upregulates the gene expression of IL-27, a negative regulator of Th17 cells [64].

12.3 Anti-TNF-α therapy

TNF-α has been detected in patients with BD [5]. Anti-TNF-α blockade can increase Tregs [46] and prevent effector T cell differentiation in BD patients with uveitis [14, 65, 66]. It was demonstrated that the production of IL-17 by polarized Th17 cell lines exposed to infliximab in vitro or fresh CD4+ T cells from BD patients being treated with infliximab was decreased and the RORγt in T cells was also decreased. Therefore, TNF-α is needed for Th17 differentiation in BD. CD4+ T cells exposed to anti-TNF-α blockade may transform into Treg cells. Anti-TNF-α therapy-induced Treg cells from BD patients restrained the activation of target T cells [14]. Anti-TNF-α agents have efficacy for uveitis, neurological and gastrointestinal involvement, and vessel diseases in BD [66]. Taken together, the Th17/Treg cell balance may be crucial for the inflammation in BD [45, 58].

12.4 Antibodies to IL-17A

IL-17A has a crucial role in deterioration of eye disease and oral ulcers, genital ulcers, and articular symptoms [21–23]. IL-17A from active BD patients can increase the expression of adhesion molecule mRNA. Therapy with antibodies to IL-17A decreased the production of adhesion molecules [21, 67]. Some reported [68–70] that secukinumab improved active mucocutaneous manifestation refractory to previous treatment such as colchicine, conventional DMARDs, and anti-TNF-α agent [69], and refractory oral ulcers [68]. Thus, therapeutic modalities attempting to evaluate new approaches to eliminate the over activities of IL-17A and/or the IL-23/IL-17 pathway may clarify the pathological importance of Il-17A and Th17 cells in BD patients.

13. Other therapeutic strategies

It is reported that suppression of microRNA-155 reduced the amount of pathogenic IL-17-expressing T cells [71].

13.1 Prognostic biomarker

The proportion of Th17 cells was increased, which was related with the increasing levels of IL-17, IL-23, and RORγt mRNA expression in BD patients. Ahmadi

et al. [72] reported that T cell-associated miRNA expression levels, miR-25, miR-106b, miR-326, and miR-93 were significantly unregulated in PBMCs in BD patients; thus the evaluation of immune cells and related miRNA profile may serve as prognostic biomarker.

14. Conclusion

BD is predominated by Th1 and Th17 immune responses. Th17 cells are associated with the active inflammation of BD. Thus, IL-23-IL-17 axis and Th1/Th17-type immune responses are crucial for inflammation and have a pathologic role in BD.

Conflict of interest

We have no conflict of interest.

Acronyms and abbreviations

BD	Behçet's disease
IL	interleukin
TNF	tumor necrosis factor
RORC	RAR-related orphan receptor C
CRP	C-reactive protein
SAA	serum amyloid A
IFN	interferon
PBMC	peripheral blood mononuclear cells
CsA	cyclosporine A
Th	T helper
Treg	regulatory T cell

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