

Regulation of T_H17 and regulatory T cells in patients with Behçet disease

Haner Direskeneli, MD,^a Hiroyuki Fujita, MD, PhD,^{b,c} and Cezmi A. Akdis, MD^b *Istanbul, Turkey, Davos, Switzerland, and Yokohama, Japan*

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Behçet disease (BD) is a systemic inflammatory disorder with a diverse spectrum of clinical manifestations, including mucocutaneous, ocular, vascular, gastrointestinal, musculoskeletal, and central nervous system involvement.¹ Although HLA-B51 is clearly defined as the major genetic risk factor, it can account for only a part of the genetic risk. BD is currently thought to be an autoimmune/autoinflammatory syndrome that is possibly induced by infections or other environmental factors.^{2,3} There are several hypotheses to explain the pathogenesis of BD. Recurrent orogenital ulcers, mucocutaneous acneiform-like lesions, and non-deforming arthritis typically present as episodes of unprovoked, recurrent inflammatory attacks with neutrophil-dominated infiltrates and resemble the recently named autoinflammatory disorders. Autoinflammatory disorders are disorders that typically respond to IL-1 antagonist therapies (which also seem to work in patients with BD).⁴ However, several studies also showed that polarization of CD4⁺ T cells into T_H1 cells and their cytokines, such as IFN- γ and IL-12, play a central role in the pathogenesis of BD.⁵ Levels of IL-12, which drives the T_H1 response in naive T cells, are increased in sera from patients with BD in correlation with the presence of T_H1 lymphocytes. Tissue studies demonstrated T_H1-type intestinal and cutaneous lesions, possibly driven with IL-12 and IL-23. A recent study also showed that natural killer type 2 cells, which produce IL-5 and IL-13, but not natural killer type 1 cells, which produce IFN- γ and IL-10, were predominant in patients with BD in remission.⁶ However, as in the case of allergy and other autoimmune disorders, such as multiple sclerosis, only the T_H1-T_H2 paradigm cannot fully explain the full mechanism. The novel T-cell subsets T_H9, T_H17, T_H22, and regulatory T (Treg) cells and their cytokines are intricately involved in inflammatory disorders.^{7,8}

The link between innate and adaptive immunity in patients with BD is further clarified in this issue of the *Journal* by Geri et al,⁹ demonstrating the role of IL-21 in regulating T_H17/Treg cell balance in BD-associated inflammation. The authors report a marked increase in T_H17 (but not T_H1) cell numbers and a decreased frequency of CD4⁺ forkhead box protein 3–positive Treg cells in the peripheral blood of patients with active BD. T_H17 cells represent a new subset of T_H cells, which mainly produce IL-17A-F, IL-22, and TNF- α . IL-6 and TGF- β induce the differentiation of T_H17 cells from naive T cells. Geri et al demonstrated that IL-21 is the major increased cytokine in active patients' sera compared with IL-6, IL-23, and TGF- β . IL-21 is produced by central memory CD4⁺ T cells and correlated with the T_H17 response and decreased forkhead box protein 3 expression. Finally, the authors also studied local responses and demonstrated the presence of IL-21– and IL-17A–producing T cells within cerebrospinal fluid, brain parenchymal inflammatory infiltrates, and intracerebral blood vessels of patients with active BD with central nervous system involvement. CCL20, a potent chemoattractant for T_H17 cells, and CXCL8, a potent chemoattractant for inflammatory neutrophils, are strongly expressed within the choroid plexus from patients with BD, suggesting that IL-21 drives T_H17 differentiation and chemoattractants for T_H17 cells and neutrophils in central nervous system inflammatory lesions of patients with BD. Further stimulation of CD4⁺ T cells with IL-21 increased T_H17 and T_H1 differentiation and decreased Treg cell frequency.

The study has important implications for BD's pathogenesis. T_H17 cells proliferate later and stay in inflammatory tissues longer compared with T_H1 cells and are suggested to be involved both in early neutrophil chemotaxis to tissues and organ-specific autoimmunity. The study reinforces the role of T_H17 cells as a major pathogenic subset in patients with BD, which is similar to the results of other studies.^{10,11} IL-17A synergized with TNF- α induces CXCL8 and CCL20 and might allow the recruitment of neutrophils and T_H17 cells within target tissues in patients with BD. The role of IL-6 and IL-23 has not been demonstrated in the study by Geri et al⁹; however, IL-6, TGF- β , and IL-23 are accepted to have major roles in T_H17 expansion and differentiation.⁸ This mainly IL-21–driven T_H17 pathway might be unique to patients with BD and might differentiate it from other inflammatory disorders. Although an increased presence of forkhead box protein 3–positive Treg cells is reported in tissue specimens, such as those with the pathology reaction, and cerebrospinal fluid, these cells are accepted to be suppressed in patients with active BD.¹²

The study might also lead to new therapeutic approaches for BD, which is still frequently treated with broad immunosuppressives, such as corticosteroids or azathioprine. The authors demonstrated that IL-21 blockade with an IL-21 receptor Fc restores the T_H17 and Treg cell homeostasis. Anti-IL-21 receptor seems to be beneficial in a murine lupus model and might be a promising

From ^athe Department of Rheumatology, Marmara University School of Medicine, Istanbul; ^bthe Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos; and ^cthe Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Yokohama.

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Reprint requests: Cezmi A. Akdis, MD, Swiss Institute of Allergy and Asthma Research (SIAF), Obere Strasse 22, 7270 Davos, Switzerland. E-mail: akdisac@siaf.uzh.ch.

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new intervention for BD.¹³ Some of the currently used agents in the treatment of BD seem also to work through the T_H17 response, such as cyclosporin A, which is shown to inhibit IL-17 responses in patients with BD.¹⁴

In conclusion, a T_H17-dominant immune model, as suggested by Geri et al,⁹ fits well with other observations and places BD as a disorder with both innate and adaptive responses. IL-21, levels of which correlate with tissue inflammation in patients with BD, represents an important target for novel therapies. These findings result in a remarkable increase in our current knowledge and might shed light on the treatment of BD.

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