

## New Approaches in Immunotherapy of Behçet Disease

Fatemeh Zare Shahneh<sup>1,2</sup>, Mozhdeh Mohammadian<sup>2</sup>, Zohreh Babaloo<sup>1,2\*</sup>, Behzad Baradaran<sup>2,1</sup>

<sup>1</sup> Drug Applied Research Center, Tabriz, Iran, Tabriz University of Medical Sciences, Tabriz, Iran.

<sup>2</sup> Immunology Research Center (IRC), Tabriz University of Medical Sciences, Tabriz, Iran.

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### SUMMARY

Behçet Disease (BD) is an autoimmune disorder with recurrent ocular, vascular, central nervous system, articular, mucocutaneous, and gastrointestinal manifestations with unclear etiology and pathogenesis. The further characterization of inflammatory features of Behçet's disease may eventually lead to development of better treatment options. Clinical and laboratory observations suggested an important role of IL-17, IL-21 and neutrophil-mediated process in the pathogenesis of BD. New therapeutic modalities target specific and nonspecific suppression of the immune system. The various non-specific immunosuppressive drugs, used either alone or in combinations, frequently fail to control inflammation or maintain remissions. Due to encouraging clinical results (i.e. Antigenic specification, prolonged survival with acceptable levels of toxicity); antibody-based drugs could be effective for the clinical management of Behçet's disease.

### Perspective

Behçet's disease as a systemic vasculitis is mainly characterized by recurrent of remission and the exacerbation of oral, genital ulcers, and uveitis. Inflammatory symptoms may manifest as mucocutaneous lesions, arthritis, venous thrombosis, arterial aneurysms, intestinal ulcers, pulmonary lesions and central nervous system lesions.<sup>1</sup>

Behçet's disease has been reported worldwide, but has a peculiar geographic distribution with highest prevalence in countries along the ancient silk route.<sup>2</sup>

Etiology and exact mechanisms of pathogenesis remains unidentified but a boosted and dysregulated immune response has been proposed as the principal pathology. Microorganisms (viral and bacterial agent) may play a role as a trigger in genetically susceptible subjects.<sup>3</sup>

The genetic defects commonly result in a constant low-grade inflammatory activity; though intermittent inflammatory attacks at involved positions determine the clinical picture. Enhanced inflammatory response like increased neutrophil functions such as chemotaxis, phagocytosis, and excessive production of reactive oxygen species (ROS) and over-expression of proinflammatory cytokines such as IL-8, IL-17, IFN- $\gamma$ , and TNF- $\alpha$  are the prominent features responsible for damage in Behçet's disease.<sup>4,5</sup>

Traditionally, BD is regarded as a Th1-mediated inflammatory disease but prospective observational studies recommend that Th17 (a novel subset of T cells), plays a fundamental role in pathogenesis of

Behçet's disease, and genome-wide association researches confirmed it.<sup>6</sup> Furthermore, an increase of IL-17 production has been detected in rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis. These results recommend that dysregulation of Th17 cells may be involved in the pathogenesis of Behçet's diseases.<sup>7</sup>

Th17 cells predominantly produce IL-17A-F, IL-21, IL-22 and TNF-alpha. IL-6 and TGF-beta induce the differentiation of Th17 cells from naive T cells. IL-17, which is the secreted from of Th17, activate neutrophils. Hence, IL-17 might cause the symptoms resembling autoinflammatory diseases. Activated neutrophils secrete some cytokines which stimulate Th17 cytokines like IL-21 and IL 17-A. The increased production of IL-17 and IL-21 has been demonstrated in Behçet's disease.<sup>8</sup> Chi et al. stated that the production of IL-23 and IL-17 by PBMCs was upregulated in patients with BD.<sup>9</sup> On the other hand, the presence of the IL-21 and IL17-A producing T cells was demonstrated in the cerebrospinal fluid, brain parenchyma inflammatory infiltrates, and intracerebral blood vessels of patients with active BD and central nervous system involvement. IL-17A and IL-21 represents a promising target for novel therapy in BD.<sup>7</sup> Neutrophils play an essential role in innate immunity. They are the most dominant leucocytes and respond rapidly to chemotactic stimuli, phagocyte and destroy foreign particles using their oxidative and non-oxidative destroying mechanisms for pathogen

\*Corresponding author: Dr. Zohreh Babaloo, Assistant Professor of immunology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. Tel: (+98) 411 3364665, Fax: (+98) 411 3364665, Email: [dr.zohrehbabaloo@gmail.com](mailto:dr.zohrehbabaloo@gmail.com)

elimination. Functional abnormalities in any steps of these may cause following defective response in immune system.<sup>10</sup> Hyperactivity of the neutrophils is an important aspect of the immunological abnormalities in BD.

Before going directly to neutrophils function in lesions of BD, proof of concept studies relevant if perspectives are needed. Biopsy specimens from active lesions of BD display large amounts of neutrophils in the absence of infection, and neutrophils from patients with BD show increased superoxide anion production, enhanced chemotaxis, and excessive release of granular enzymes, which indicate neutrophil hyperactivity in BD.<sup>11</sup>

Several proinflammatory cytokines, such as interleukin 17 and 21 are proposed to be accounted for the priming of neutrophil activation and the enhanced cellular interactions between neutrophils and endothelial cells. Moreover, IL-17 involved in the recruitment of neutrophils to the site of inflammation.<sup>12,13</sup> Neutrophil hyperactivity and elevated inflammatory cytokine levels are hallmarks of BD. Neutrophils produce inflammatory cytokines, which promote neutrophil activity. This makes a cycle in which elevated and activated neutrophils produce more cytokines and the latter enhance neutrophil activity.<sup>14</sup>

The primary goals of BD management are symptom control, soothing the inflammation and suppression of the immune system and prevention of end-organ damage. The treatment options must be anti-inflammatory agents and immunosuppressant but in severe stages, may be resistant to all forms of immunosuppression. Conventional therapeutic approaches suppress the activity of the leucocytes and lymphocytes.<sup>15</sup> Drugs are frequently used in combination to maximize efficacy while minimizing side effects.

Conventional therapeutic approaches suppress the activity of the leucocytes (anti-inflammatory) and lymphocytes (immunosuppressive) in T-cell-mediated diseases. Now colchicine has been widely used as a basic drug for treatment of Behçet's disease and applies beneficial effects through inhibition of neutrophil functions as well as neutrophils chemotaxis.<sup>16</sup>

In this era, by the advent of Monoclonal antibodies (mAb) directed against any antigens of interest, Immunodrugs (drug immunoconjugates), Immunocytokines (Recombinant mAb-cytokine fusion proteins), immunotherapy based on mAb-therapy of human autoimmune disease have been introduced.<sup>17</sup> During the last ten-year period, Infliximab (chimeric anti-TNF- $\alpha$  monoclonal antibody), Adalimumab (humanized anti-TNF- $\alpha$  monoclonal antibody) and Etanercept (fusion protein human p75 TNF- $\alpha$  receptor IgG1) are increasingly used for patients with BD. Because clinical and laboratory observations suggested that TNF-mediated process in the pathogenesis of BD.<sup>18</sup>

The further characterization of inflammatory features of Behçet's disease may eventually lead to

development of better treatment modalities. Clinical and laboratory observations proposed a central role of IL-17 and IL-21 and neutrophil-mediated process in the pathogenesis of BD. This result indicates correlation between neutrophil biology, IL-17 and, IL-21 with Behçet's disease. Considering the fact that if in new studies, researcher focuses in these perspectives, it could be possible find better aspect in Behçet's disease therapy based on its immunopathogenesis. Due to encouraging clinical results (i.e. Antigenic specification, prolonged survival with acceptable levels of toxicity); antibody-based drugs could be effective for the clinical management of Behçet's disease.

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