



# Behçet's Syndrome Society

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## Scientific information on Behçet's Disease.

Behçet's Disease is a multisystem inflammatory disease characterised by recurrent orogenital ulceration, ocular inflammation, and skin lesions. The basis of the disease is currently unknown but evidence suggests an exaggerated response to pathogens, including increased cytokine and chemokine production and function. While such responses are certainly involved with the vasculitis associated with most manifestations of the disease, it is not clear what is responsible for the initial onset and persistence of Behçet's Disease.

The causative antigen in Behçet's Disease is unclear, and microbial, viral, and auto-antigens have been suggested as candidates. Several microbial antigens have been shown to stimulate T effector lymphocytes in Behçet's Disease patients, e.g., staphylococcal antigens, streptococcal antigens *Escherchia coli*-derived peptides and *Chlamydia pneumoniae*. Heat shock proteins (HSP) of various microbes could be involved in the pathogenesis of Behçet's Disease. A cross-reactive response to human HSP60 was suggested as causative in Behçet's Disease. Subcutaneous injection of HSP peptide 336-51 (with adjuvant), but also oral and nasal administration (without adjuvant), can induce experimental autoimmune uveitis in rats but without any other signs of Behçet's Disease. For intestinal BD, peripheral blood cells and intestinal tissue have been shown to express HSP60 in the active state of disease. Involvement of responses to HSP60 in patients with Behçet's Disease is ongoing.

Several other autoantigens that may be candidates for the initiation of the T effector lymphocytes reaction in Behçet's Disease have been identified by serum screens of protein libraries. Antibody responses to kinectin,  $\alpha$ -tropomyosin and Sip1 have been demonstrated with increased frequency in patients with Behçet's Disease compared with disease and healthy controls. One difficulty with this data is that these antigens were not detected in the every screen, suggesting that the libraries and patients sera used may give very different responses.

Cytokine are molecules secreted by cells involved in the immune response that signal between such cell types. Several studies have reported increased cytokine levels in serum and body fluids from patients with Behçet's Disease, including cytokines which are associated with the innate immune response (neutrophils and macrophages) and the adaptive immune response (T and B lymphocytes). Elevated levels of cytokines suggest a hyperactivated inflammatory response in patients with Behçet's Disease. Certain cytokines such as serum IL-8 levels, that attracts neutrophils, seem to correlate well with disease activity. Interestingly, anterior uveitis and joint lesions in patients with Behçet's Disease comprise mainly a neutrophilic infiltrate that in most cases does not lead to tissue damage and is self-limiting.

T regulatory ( $T_{reg}$ ) cells are characterized as having certain surface markers, and are capable of suppressing effector cell responses. Lack of  $T_{reg}$  cells in both humans and mice lead to extensive autoimmune cell activation and early death. It has been demonstrated that  $T_{reg}$  cells are increased in the peripheral blood of active Behçet's Disease patients; however the function of these cells has not been addressed so far. One problem is that the  $CD4^+CD25^+$  phenotype found on  $T_{reg}$  cells can also be found on a population of T effector lymphocytes and studies with more specific markers, including FoxP3, and CD27 should be carried out in patients with Behçet's Disease to determine if there is any failure/defect in  $T_{reg}$  cells. In animal models of infection, where  $T_{reg}$  are deficient or deleted, pathogens are rapidly cleared but tissue damage is more severe, and such an imbalance has been suggested for many autoimmune diseases and could explain the mucosal lesions seen in Behçet's Disease.

No convincing animal model effectively simulating Behçet's Disease has been described with only certain manifestations present in each system. Immunizing animals with HSP peptides results in iridocyclitis with certain similarities to anterior uveitis seen in patients with Behçet's Disease. The best studied model is that induced by inoculation with herpes simplex virus in which animals show several symptoms similar to Behçet's Disease. Studies have shown that depletion of macrophages alleviates the cutaneous symptoms of the model, and that driving the immune response away from a tissue damaging form also improved disease. These results suggest that certain cytokines can attenuate some symptoms of Behçet's Disease at least in these models. Animal models such as these can be used to study the effect of novel drug therapy, however, it must be stated that these models only induce aspects of Behçet's Disease-like pathology and are not a precise replica of the human disease.

A strong genetic basis for Behçet's Disease has been long supported by the association with HLA-B\*51 a molecules that interacts with cells of the immune system to present antigens. HLA-B\*51 is found on chromosome 6 in humans and in very close proximity is the gene encoding tumour necrosis factor. Mutations in the TNF gene associated with increased production of the cytokine have been linked to Behçet's Disease and HLA-B\*51, and as TNF is a potent inducer of vascular endothelium, this may explain the increased vasculitis seen in patients. A role for TNF is supported by studies with drugs such as infliximab which block the action of TNF, that are effective in some patients with Behçet's Disease. Recent studies analyzing mutations in two other genes, PTPN22 and CTLA-4, which are involved in the regulation of the immune response and have been classed as masterswitches of autoimmunity, showed no association with Behçet's Disease. This has led to the possibility that Behçet's Disease is not an autoimmune disease but rather should be classed as autoinflammatory, a distinction that should change our investigations into the causative mechanisms of Behçet's Disease.

It should be noted that as the genetic contribution to the pathogenesis of Behçet's Disease is estimated to be only 20–30%, infectious agents, heat shock proteins, abnormalities in the innate immune system, such as neutrophil hyperfunction, or the adaptive immune response such as  $T_{reg}$  activity may play a major role. Therefore the present hypothesis for the pathogenesis of Behçet's Disease is a scenario of persistent mucosal lesions, oral, genital, and gut in response to pathogen, which in turn induces a generalized vasculitis, would explain many of the complex features of Behçet's Disease.

***Dr Graham Wallace, June 2008***