

*This factsheet is also written for health professionals to use, so you may find the language more technical than in others. You may find it helpful to ask your GP or Consultant to explain this leaflet to you.*

### What is Behçet's?

Behçet's **syndrome** (or Behçet's **disease**) is a multisystem inflammatory disease characterised by recurrent orogenital ulceration, ocular inflammation and skin lesions. The basis of the condition 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.

### Possible causative antigens

The causative antigen in Behçet's disease is unclear, and microbial, viral and autoantigens have been suggested as candidates. Several microbial antigens have been shown to stimulate T effector lymphocytes in Behçet's disease patients – for example, staphylococcal antigens, streptococcal antigens *Escherichia coli*-derived peptides and *Chlamydia pneumoniae*.

Several other autoantigens that may be candidates for the initiation of the T effector lymphocyte 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 every screen, suggesting that the libraries and patients' sera used may give very different responses.

### Cytokines and the immune response

Cytokines 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 that 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. Levels of certain cytokines, such as serum interleukin (IL)-8 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.

Recently interleukin-17 (IL-17) which is produced by immune cells has been linked with BD. IL-17 is a cytokine that induces the release of neutrophils from the bone marrow. Trials to block IL-17 activity are currently under way.

T regulatory ( $T_{reg}$ ) cells are characterised as having certain surface markers, and are capable of suppressing effector cell responses. Lack of  $T_{reg}$  cells in both humans and mice leads to extensive autoimmune cell activation and early death. It has been demonstrated that  $T_{reg}$  cells are increased in the peripheral blood of patients with active Behçet's disease; 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; 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  $T_{reg}$  cells 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.

## Animal models

No convincing animal model effectively simulating Behçet's disease has been described, with only certain manifestations being present in each system. Immunising animals with HSP peptides results in iridocyclitis with certain similarities to the 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 improves 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.

## Genetics

A strong genetic basis for Behçet's disease has been long supported by the association with HLA-B\*51, a molecule 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 (TNF, a cytokine). Mutations in the TNF gene associated with increased production of the cytokine have been linked to Behçet's disease and HLA-B\*51; 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 that block the action of TNF, which are effective in some patients with Behçet's disease.

Recent studies analysing mutations in two other genes, PTPN22 and CTLA-4, which are involved in the regulation of the immune response and have been classed as master switches 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 auto-inflammatory, a distinction that should change our investigations into the causative mechanisms of Behçet's disease. Genome-wide association studies have identified several new genes linked to BD. These include mutations in endoplasmic reticulum aminopeptidase-1 which when assessed with HLA-B\*51 gives an increased risk of disease. As ERAP-1 produces peptides that fit into molecules such as HLA-B\*51 as common pathway can be suggested.

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, or 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 as a scenario of persistent mucosal lesions (oral, genital and gut) in response to pathogen, which in turn induce a generalised vasculitis, would explain many of the complex features of Behçet's disease.

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