Behçet's Factsheet 3
Scientific Information

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, α-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.

Both infliximab and adalimumab which target tumour necrosis factor (TNF) can be useful in managing patients with intestinal BD, especially severe or refractory cases, with a similar efficacy and safety profile. Anti-IL_17, secukinumab (either 150 mg and 300 mg/month) improved active mucocutaneous manifestations refractory to previous treatments, while secukinumab 300 mg/monthly was superior in treating articular manifestations in Behçet's patients. IL-23 is a cytokine involved in the generation of IL-17. Ustekinumab, which inhibits IL-23 seems to be effective in treating BD-related oral ulcers that are resistant to treatment with colchicine. Recent studies with other biologics such as anti-interleukin (IL)-1 (anakinra and canakinumab) and anti-IL-6 (tocilizumab) have shown promising results in patients with systemic, including intestinal, BD. Although both conventional IS and biologic agents are effectively used to suppress inflammation in BD, there is still an unmet need for clear therapeutic strategies in the management for different manifestations. Clustering of patients based on different organs by Japanese and Chinese colleagues may direct future drug treatment trials in BD.

Cellular responses

Increased production or responsiveness of pro-inflammatory components of the innate immune response neutrophils, natural killer cells or gamma-delta cells may be a crucial step in the pathogenesis of BD. Neutrophil extracellular traps (NETs) have been and markers of NETS levels are elevated in patients with BD and may contribute to thrombotic complications in BD. Targeting NETs may represent a potential therapeutic target for BD. In addition, is evidence of a dysregulated adaptive immune system, with a disturbed T helper-1/T helper-2 balance, expansion of T helper 17 cells and possibly a decrease in regulatory T cells, resulting in a surplus in pro-inflammatory cytokines.

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. HLA-B∗51 shows a positive interaction with a molecule called endoplasmic reticulum aminopeptidase (ERAP)1 encoding the Hap10 allotype (combination of mutations), which has the lowest trimming activity of the MHC-Class I binding peptides. Subsequent molecular studies have suggested that the disease-associated Hap10 allotype is implicated in the generation and selection of the disease protective peptides loading onto HLA-B∗51, although these pathogenic peptides have yet to be identified.

Large-scale genetic studies performed to date revealed 21 genetic susceptibility loci associated with the disease at a GWAS level of significance. These include HLA-B*%1 and ERAP-1 mentioned above and several cytokine genes, IL-17, IL-23, and TNF, now being targeted by treatment. Another gene associated with BD encodes a molecule called fucosyltransferase. This molecule is found in the gut and is involved in the generation of molecules called short chain fatty acids (SCFA) which in turn stimulate Tregulatory cells. Studies investigation the gut microbiome (populations of bacteria) have shown a decrease in bacteria involved in the generation of SCFA. Colleagues in Italy are running trials analysing the effects of diets or supplementations which increase SCFA in the gut in patients with BD. Early results suggest a positive effect in some aspects of 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, 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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