Behçet's disease

Molecular mechanisms in Behçet's disease

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T-bet may be an immunomodulatory target at which to aim

Much is still unknown about the aetiopathogenesis of Behçet's disease, although genetic, infectious, and autoimmune components are all believed to be involved.

The distribution and wide variation in relative risk of HLA-B51 is well documented and appears to support the presence of other, non-genetic risk factors for Behçet's disease.[1] The contribution of HLA-B51 to the overall genetic susceptibility to Behçet's disease is estimated to be less than 20%.[2] It is not certain if HLA-B51 has a direct role in the pathogenesis of Behçet's disease, or whether this association reflects linkage disequilibrium with a closely located gene. The association of the *009 and A6 MHC class 1 related gene A (MIC-A) alleles with Behçet's disease is due to linkage with HLA B51 and implies that HLA B51 itself is associated with the disease.[3] Analysis of the segment between the TNF and HLA-B loci revealed a strong, perhaps primary,[4] association of Behçet's disease with MIC-A, which is expressed in fibroblast, monocytes, epithelial, and endothelial cells.[5 6] This gene codes for a non-classic HLA class I protein induced by stress which probably has an important role in the destruction of cells targeted by γδT cells.[7] Bacterial infection upregulates MIC-A expression on cell surfaces, enhancing TCR dependent activation of Vγ2Vδ2 T cells by non-peptide antigens.[8]

Genetic susceptibility may lead to a primed, antigen driven immune response, which in an unbalanced state manifests itself as Behçet's disease.[9 10]

Infection has long been thought to be a contributory factor in the aetiology of Behçet's disease; some candidate antigens include those derived from streptococci,[11] staphylococci,[12] mycobacteria,[13] and herpes simplex virus.[14 15] A common denominator in the form of microbial heat shock protein (HSP), which shows significant homology with human mitochondrial HSP has been suggested.[16] HSP derived peptides which specifically stimulate T cell responses in Behçet's disease, have been used to induce uveitis in animal models.[17 18] γδT cells are essential for the maintenance of mucosal immunity. They are involved in the early response to microbial and autologous antigen and can become Th1 and Th2 type cells; they are stimulated by Behçet's disease specific HSPs and increased in active Behçet's disease.[9 19] It is suggested that the T cells taken from the Behçet's disease patients were primed to respond to bacterial antigen.[9 10] High levels of γδT cells have been detected in the intraocular fluids of Behçet's disease patients with uveitis.[20]

Lehner has postulated that microbial infection induced stress upregulates HSP 65 and MIC-A gene products which stimulate γδ and αβT cell receptor positive cells to generate effector and suppressor T cells, leading to pathological changes consistent with Behçet's disease in HLA-B51 or related subjects.[21]

Th1 cells secrete IL-2 and IFN-γ, activate macrophages, and elicit delayed hypersensitivity reactions. Th2 cells produce IL-4, IL-5, and IL-10 and suppress cell mediated immunity. These cytokines perform a cross regulatory function between the Th1 and Th2 subsets. This cross regulation and the Th1/Th2 balance is thought to be important in the regulation of autoimmune diseases such as Behçet's.[22 23] Th1 cells are autopathogenic factors, whereas Th2 cells with the same antigen specificity oppose the development and progression of disease.[23 24] A strong Th1 immune response occurs in active Behçet's disease (a useful marker of Behçet's disease activity), where IL-12 prevents spontaneous and Fas induced cell death, leading to the abnormal growth of autoreactive Th1 cells and the prolongation of the inflammatory autoimmune condition of Behçet's disease.[22]

It is interesting to note that statins may be useful in Th1 mediated autoimmune diseases. Atorvastatin was found to promote a Th2 bias in CNS autoimmune disease[25] and, more recently, simvastatin was demonstrated to suppress Th1 cellular and immune responses in an inflammatory arthritis model.[26]

T-bet is a specific T-box transcription factor that initiates Th1 development from naive Th cells by activating Th1 genetic programmes and repressing opposing Th2 programmes; additionally T-bet can reprogramme a committed population of fully polarised Th2 cells into the Th1 phenotype.[27]

Th1 cell development involves IFN-γ signalling through signal transducer and activator of transcription 1 (STAT1) and IL-12 signalling through STAT4. T-bet is induced by IFN-γ and STAT1 signalling during T cell activation; in addition T-bet mediates STAT1 dependent processes of Th1 development including the induction of IL12Rβ2,[28] and is required for the optimal production of IFN-γ and antigen specific T cell activation by dendritic cells.[29]

In this issue of the *BJO* (p 000), Li *et al* have reported that Behçet's disease is associated with an upregulation of T-bet; the presence of this transcription factor is significant in autoimmune disease. T-bet may be an immunomodulatory target at which to aim, in order to rebalance an aberrant immune system such as that found in Behçet's disease.

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Corneal wounds

Corneal fibrotic wound repair

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It may be possible to regulate corneal scarring by controlling the activity of key genes

Corneal scarring following trauma, infections, or refractive surgery can produce blinding complications, but current treatment options are limited and outcomes are typically poor. Thus, there is a need for new treatments that will prevent or reduce corneal scarring with minimal side effects. To accomplish this, however, the basic processes that regulate corneal scarring need to be understood more thoroughly. Corneal wound healing is an exceedingly complex process that is coordinated and regulated in large part by autocrine and paracrine interactions of growth factors, cytokines, and proteases produced by epithelial cells, fibroblasts, and lacrimal gland cells. Also important are the interactions of corneal epithelial cells with components of the stromal extracellular matrix. Lacking from the understanding of corneal wound healing, however, has been a simultaneous spatial localisation of growth factors, corneal cells, and extracellular matrix proteins in healing corneal wounds. In this issue of the *BJO* (p 000) Ivarsen and colleagues address this knowledge gap by combining laser confocal microscopy and immunohistochemistry to create a three dimensional relation of these components during healing of rabbit LASIK corneal wounds. They report binding of leucocytes to conjunctival vessels and their migration into the cornea at day 1 following surgery. From day 4, elongated fibroblasts migrated from the periphery to align in a circumferential band approximately 250 μm wide next to the flap edge. The lateral extensions of this stromal band were limited to the incised area in the epithelial basement membrane. Immunostaining for TGF-β isoforms, TGF-β receptor II, and CTGF, showed they were expressed in the band from day 2. Myofibroblasts were identified at week 3 in a fibrotic matrix. With time, the peripheral circumferential band became narrower and showed an increased organisation with a gradual decline in reflectivity. At all times, keratocytes within and below the flap remained quiescent and only minimal fibrosis developed at the interface. These data extend the results reported previously,[1] and show for the first time that the major region of reflectivity (haze) in LASIK corneal wounds was restricted to a narrow band peripheral to the corneal flap edge, and most importantly, was co-localised with areas of elevated growth factors (TGF-β and CTGF) and with gaps in the epithelial cell basement membrane. Furthermore, the fibrotic wound healing at the LASIK flap margin is associated with myofibroblast transformation and wound contraction and appears to involve TGF-β and CTGF signalling pathways. Extrapolation of these results to healing of other types of corneal wounds implies that it may be possible to regulate corneal scarring by controlling the activity of these key genes at the site where epithelial cells interact with the stromal matrix. This sets the stage for future research evaluating approaches to regulate activity of target genes, including neutralising antibodies, antisense oligonucleotides, RNAi, or ribozymes. If successful, it may be possible one day to control corneal scarring using gene specific approaches.

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