

*Review Article***ETIOPATHOGENESIS OF BEHÇET'S SYNDROME:
RECENT DEVELOPMENTS AND CURRENT CONTROVERSIES***Invited Paper*

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ABSTRACT

Genetic, infectious and immune dysfunctions are implicated in the etiopathogenesis of Behçet's Syndrome (BS). Histopathological studies reveal mixed cellular infiltrations consisting of mostly T lymphocytes, monocyte-macrophages and neutrophils. Although a viral etiology is also suggested, atypical streptococci (*Strep Sanguis*, *Salivarius* etc) is the most investigated. Increased pro-inflammatory and Th1 type cytokines such as TNF- α , IFN- γ , IL-2, IL-6 and IL-8 are found to be increased in the sera and in vitro culture supernatants. A controversial point is whether neutrophils are primarily defective (hyper-reactive) or activated due to the cytokine profile. Streptococcal proteins such as KTH-1 or 65 kD mycobacterial heat shock protein (HSP) and its cross-reactive human homologue are shown to cause T and B cell responses in patients with BS. Both CD4+ and $\gamma\delta$ T cells are activated with antigen-specific oligoclonal expansions and increased secretions of IFN- γ , IL-8 and TNF- α . The link with HLA-B51 which is present as a susceptibility or a severity marker of BS, is suggested to be related to neutrophil hyperreactivity with increased neutrophil burst responses also in HLA-B51 transgenic animals. T cell responses to an HLA-B51 derived peptide and its retinal-S antigen homologue in posterior uveitis patients suggest that auto-immune responses might also be relevant. The same peptides are linked to uveitis also in rats and imply that different manifestations of BS may be

related to various and possibly organ-specific antigens.

Key Words: Behçet's Syndrome, Immune response

Behçet's Syndrome (BS) is a multi-systemic disorder with muco-cutaneous, ocular, arthritic, vascular and central nervous system involvements. Recent developments in the etiopathogenesis of BS is discussed in this review.

Genetic Predisposition and HLA-B51

BS is mainly seen around Mediterranean Sea in a belt of countries extending from the Atlantic Ocean to Japan including Israel, Turkey, Iran, India, Korea and China (1). The prevalence is reported to be between 1:250 to 1:10.000 in this region whereas it is reported to be 0.3-1:100.000 in USA and North Europe. The differences are not only reflected in prevalence but also in the severity of the cases. Most of the severe spectrum of BS such as uveitis, vascular and CNS involvement are mainly reported from countries where the disease is seen more frequently. Among various genetic markers, relationship to HLA class I antigens B5 and its split B51 is the most commonly reported (2,3). The presence of this marker is reported to have

a relative risk of 3-8 in different series. An important question is whether B51 is a marker of susceptibility or severity in BS. HLA B51 is found in only 50-60 % of the cases of BS suggesting that B51 is not required for the susceptibility to the disease. B51 may be related not to a general susceptibility of BS but to certain manifestations such as uveitis or vascular involvement as reported from UK (4). In terms of disease severity, although a high prevalence is found in hospital based populations (5), a field study of BS prevalence from Turkey found HLA B5 in only 26% of the cases (6). Most of these cases were not diagnosed as BS before and had a mild disease spectrum. But in contrast with these observations, a recent report from Japan did not find higher ocular severity linked to B51(7). The spectrum of organ involvement in BS is studied mostly as the presence or absence of a certain manifestation such as uveitis or vascular involvement. As anterior and posterior uveitis have different ocular prognosis, with the latter generally causing irreversible vision loss, the role of B51 must be investigated with regard to posterior uveitis as a marker of severity.

The role of HLA class I antigens such as B51 is the presentation of endogenous antigens synthesized within the cell to CD8+ cytotoxic-suppressor T cells. The antigen specific region of B51 is analysed with the possible 8-10 amino acid length sequence of antigenic peptides reported (8). Among these peptides autoantigens such as thymidylate synthase (aa.253-61) or a yeast protein UBC5 (61-68) is present. The role of these HLA-B51 specific peptides and whether HLA B51 restricted CD8+ T cells take a role in BS etiology is currently unknown. A recent animal model is also confusing as transgenic animals with HLA B51 did not develop the disease but only have neutrophil hyperreactivity in response to neutrophil activating agents like fMLP or PMA (9). The same group also observed an increased neutrophil burst activity in patients and healthy controls carrying HLA B51 which we could not confirm in our studies (10).

In addition to being a primary risk factor itself, HLA B51 might be a marker of another gene positioned closely to B51 and is found on the same haplotype. Ohno et al. from Japan reported recently a MICA (MHC class I related-gene) between TNF- α gene and HLA B region on chromosome 6 with a higher risk factor compared to HLA-B51 (11). But whether this marker which has a low heterogeneity is the real genetic predisposition to BS requires further studies in other ethnic groups.

Neutrophil hyperreactivity

As typical BS lesions such as pustular folliculitis, pathergy reactions and hypopyon has significant numbers of neutrophils, relationship of BS to neutrophil activation is pursued for a long time (1,3).

As neutrophils are a group of very mature cells with a very short life in vitro, their research is difficult, technically, reflecting the controversy in the literature over which activity best reflects neutrophil functions and is deregulated in BS. Various studies showed increased neutrophil chemotaxis, O₂ release, enzymatic activity and phagocytosis in active BS compared to healthy controls (9, 12-14), but the results are conflicting. Mege et al have shown increased basal O₂ production, but no differences in fMLP-stimulated neutrophils (12), Pronai et al. observed increased O₂ both in stimulated or unstimulated neutrophils (13), whereas Takeno et al observed increased production only after fMLP stimulation (9). Neutrophil adhesion to endothelial cells is also reported to be both normal (14) or increased in BS with increased adhesion molecule expressions such as CD11a and CD18 (15). In addition, CD10 and CD14 two markers of neutrophil activation are also expressed higher on BS patients' neutrophils (16). An interesting point is the occurrence of Behçet's like symptoms in patients with chronic myeloid leukemia (CML) who are given interferon- α (IFN- α) treatment (17). In a controlled study, 24% of these patients also developed pathergy test positivity (18). As CML is a disease with a large number of mature neutrophils and their precursors in the blood, this effect of IFN- α may be linked to neutrophil hyperreactivity.

One of the main problems in BS research is to distinguish between whether BS neutrophils are primarily defective or whether soluble agents in BS serum or in local milieu, such as pro-inflammatory cytokines (IL-1, TNF- α , IL-6, IL-8 etc) released from activated mononuclear cells, are responsible for the neutrophil hyperreactivity (3, 19-21). As neutrophils in the active phases of BS are already activated when they are taken in vitro, this question is hard to answer. A better approach is to study the cases in complete remission but studies are very limited in this group and mostly negative.

Humoral immunity in BS

Although BS does not have the classical features of an auto-immune disease such as Sjogren's syndrome, female dominance, hypergammaglobulinemia and autoantibodies such as anti-nuclear antibodies, some B cell activity such as increased spontaneous immunoglobulin secretion is shown previously in BS (22). Some of the antibodies such as anti-endothelial cell or anti-cardiolipin antibodies are probably markers of endothelial damage and activation in BS and not specific (23). Anti-65 kD mycobacterial heat shock protein (HSP) antibodies are more interesting as these are more frequently reported in linkage with infectious etiology (24, 25). In one study from Turkey, 48% of neuro-BS patients compared to 12% of multiple

sclerosis patients had increased levels of anti-65kD HSP antibodies in the cerebro-spinal fluid (26). B cells are recently studied also in detail in our Unit and although total B cell number was normal they were found to carry increased levels of activation markers such as CD13, CD33, CD45RO and CD80 (27). The distinction of BS from auto-immune disorders was also evident in this study in the low level of CD5+CD19+ B cells which are thought to produce auto-antibodies. As the role of B cells are not limited to antibody production as previously suggested, but also include antigen-presentation, their role in BS requires further study.

T cells in BS

Various observations suggest a significant contribution of T cells in BS. Pathergy reactions are either T cell dominated or have mixed infiltrates, as oral lesions, erythema nodosum and late stages of uveitis such as enucleated eyes (28, 29). Both CD4+ and CD8+ T cells producing Th1 type pro-inflammatory cytokines such as IL-2 and interferon- γ are increased in peripheral blood (30). Recently CD4+CD16+ and CD4+CD56+ T cell subsets are also found to be increased in BS (31). An oligoclonal antigen-driven change in peripheral blood CD4 and CD8+ TCR V β repertoire in patients with BS is also supportive of T cell participation (32). In addition to TCR $\alpha\beta$ + cells, TCR $\gamma\delta$ + cells are also increased in number in various studies (33, 34).

Antigenic stimulus in BS Streptococcal antigens

T cells respond to exogenous or endogenous antigens presented by HLA class I or class II molecules on antigen presenting cells. Among the few antigens studied in detail in BS, bacterial microorganisms such as streptococci are the most implicated. KTH-1 (a crude extract or *Streptococcus sanguis* SSH-83) is shown to cause increased IL-6 and interferon- γ secretion from T cells of BS patients suggesting a role of this antigen in the pro-inflammatory response (35). KTH-1 is also shown to cause an increase of $\gamma\delta$ T cells in BS patients after 9 day T cell cultures (36). Long term $\gamma\delta$ T-cell lines produced by continuous stimulation with this antigen secrete pro-inflammatory cytokines such as IL-6, IL-8 and TNF- α but no T-helper 2 type anti-inflammatory cytokines IL-4 and IL-10, supported by the low levels of IL-4 and IL-10 in the serum (37).

65 kD Heat Shock Protein

Another important candidate antigen for BS is 65 kD HSP and its peptide derivatives. HSPs are proteins which have a scavenger role for other intracellular

proteins under denaturing stress conditions such as infections, hypoxia and toxic drugs. They are highly conserved during evolution (mycobacterial and human 65 kD HSPs have over 50% homology). Although HSPs are part of the intra-cellular protein transport mechanisms, 65 kD HSP is shown to be expressed on monocytes after interferon- γ stimulation and also on T cells going apoptosis (38). These observations suggest that 60/65 kD HSPs might be ubiquitous antigens for the immune system. As significant sequence homology exists between mammalian and microbial HSPs, human HSP-responsive T cells stimulated by microbial counterparts (cross-reactivity) might trigger a longer T cell memory, responsible for the chronicity of certain autoimmune or vasculitic disorders.

In a study by Ergun et al, in tissue specimens of pathergy reactions of BS patients, 65 kD HSP expression is found to be significantly higher compared to controls suggesting that it can also be a local antigen for BS (39). First in UK, then in Japan and in our Unit in Turkey, increased T cell responses to mycobacterial and human 60/65 kD HSP are shown in the peripheral blood lymphocytes of BS patients compared to healthy controls (40-43). Although they are reported to be specific to BS in UK and Japan, we observed a 18% positivity in our diseased controls (43).

Although $\gamma\delta$ T cell subset is reported to respond mainly to 60 kD HSP in UK, an oligoclonal increase in certain CD4+ TCR V β subsets is reported from Japan in patients with uveitis after stimulation with HSP derived peptides. These HSP responsive T cells are shown to release pro-inflammatory cytokines such as IL-6 and IL-8 and thought to participate in the inflammatory stimulus (42). Recently, by Saruhan-Direskeneli et al, PPD and 65 kD HSP specific T cell lines are also found to be reactive to human 60 kD HSP derived peptides in both BS patients and healthy controls (44). An animal model in rats where certain human HSP derived peptides cause an uveitis but no other symptom of BS is also supportive of a role of HSP in BS (45).

Retinal-S Antigen and HLA-B51-new autoantigens?

Another candidate antigen in BS is retinal-S antigen. This protein found mainly in the retina is accepted to be immune-privileged and immune responses against it are found mainly after tissue destruction due to uveitis. T cell responses against retinal-S antigen are found in various types of uveitis and are not specific to BS (46). Among various immuno-dominant epitopes of retinal-S antigen an epitope (aa 342-355) is found to share homology with a conserved region of

HLA B molecules (aa 125-138) such as HLA-B51 and B27 which are linked to uveitis (47). This epitope is shown to be recognized by CD4⁺ T cells. This observation provoked a challenging theory of class I HLA molecules becoming antigenic epitopes themselves. Indeed, a significant portion of small peptides eluded from the surface of various HLA class II molecules are found to be HLA class I originated. As T cells recognizing class I antigens are a natural part of our immune repertoire but possibly tolerized in thymus, a break-down of tolerance is hypothesized to occur after uveal inflammation by cross-reactivity of retinal-S antigen reactive T cells with HLA-reactive T cells. Development of uveitis in rats by both peptides is supportive of this observation. T cell responses to these peptides are shown in a small group of German uveitis patients and recently confirmed in a larger group of BS patients in our Unit (48). Interestingly, only T cells from patients with posterior uveitis but not with non-uveitis BS patients are responsive. This suggests that serious uvea destruction and activation of retinal-S antigen reactive T cells is required for cross-reactive memory responses.

This theory provides another explanation for HLA B51 participation in BS. Oral feeding of HLA B27/51 derived peptide is shown to prevent retinal-S antigen uveitis in animal models and is now tried in refractory human uveitis patients as a way of treatment with oral tolerance (49).

Observations from the clinical trials: different antigenic stimuli for different manifestations?

Different manifestations of BS occurring during the course of the disease unpredictably and unlinked to any previous risk factor suggests that various, possibly organ-specific antigens might be responsible for BS. Therapy studies support this observation as the effects of various popular treatments in BS seems to be organ-specific. Colchicine is especially effective for erythema-nodosum (EN) like lesions but has a limited effect on uveitis. On the other hand, in a recently published double-blind controlled trial thalidomide was effective for oral and genital ulcers, but caused a significant increase in EN lesions in the first 8 weeks (50). As an explanation for this surprising observation, Hamuryudan et al. suggest that "the cause of aphthous ulcers and EN may not have a common putative denominator in BS".

T cell responses to HLA-B and retinal-S antigen derived peptides only in posterior uveitis patients mentioned above may also support this hypothesis. Immune responses to local antigens such as dermal keratins in psoriasis or synovial antigens such as

collagen type II in rheumatoid arthritis were reported previously. Similarly, local antigens might be relevant for patient subgroups with muco-cutaneous or articular organ involvements in BS. Better characterization and immuno-modulation of these local antigens may help to develop more specific and less toxic immunotherapeutic approaches to this still unsatisfactorily treated disease.

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