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ORIGINAL INVESTIGATION

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Pathogenesis of Adamantiades-Behçet's disease

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Abstract The aetiology of Adamantiades-Behçet's disease remains unknown and its pathogenesis is not fully understood. Linked intrinsic and extrinsic factors are thought to contribute to the development of the disease, which probably occurs by environmental triggering of a genetically determined disorder. Transmission is solely vertical, indicating that the disease is not contagious. Genetic factors have been investigated and a significant link of HLA-B51, especially of HLA-B5101, has been identified. However, none of the functional correlates of the disease appear to be restricted by HLA-B51. Recently, the role of the genes encoding TNF, Tap proteins and MICA has been emphasised. Extrinsic pathogenetic candidates have been identified, including bacterial (*Streptococcus sanguis*, *Mycoplasma fermentas*) and viral (human herpes virus) antigens and environmental pollution, which may cross-react with oral mucosal antigens and induce immunological mechanisms. A common factor linking some of the possible pathogenetic agents is extrinsically induced tissue stress or heat shock proteins, which react with host tissues and elicit significant Th1 cell responses. Neutrophils may also play a role in the pathogenesis of the disease, as they are attracted by macrophages and activated endothelial cells, which release cytokines and chemokines (especially IL-8) at the site of the lesions, and thus contribute to tissue damage and self maintenance of inflammation. Endothelial activation leading to a chronic local inflammation process together with platelet and serum factors enhance coagulation and thrombosis.

Keywords Adamantiades-Behçet's disease · Environmental triggering · Genetically determined disorder · Neutrophils · HLA B51

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Introduction

Adamantiades-Behçet's disease (ABD) is a multisystemic, inflammatory disorder with a chronic recurrent course. The mucocutaneous lesions of ABD exhibit histological changes of vascular reaction or vasculitis [1]. It is characterised by the classical clinical triad of recurrent oral aphthous ulcers, genital ulcers and iritis/uveitis. The aetiology of the disease remains unknown; whereas genetic factors, infectious agents and environmental pollution, immunological mechanisms, and endothelial and clothing factors have been implicated and studied intensively. The major involvement of certain ethnic groups and the wide variation of the prevalence of the disease in the same ethnic group in association to the geographic area of residence indicate environmental triggering of a genetically determined disorder [2, 3] (Fig. 1).

Genetic factors

There is no specific mode of Mendelian transmission in ABD [4]. Familial occurrence is one of the most commonly reported epidemiological features [2, 3]; however, there are regional differences with familial occurrence being more frequent in Korea (15.4%) than in Japan or China (2.2–2.6%) and in Arab countries, Israel and Turkey (2.0–18.2%) than in Europe (0.0–4.5%; $P < 0.001$) [2]. Genetic anticipation in the form of earlier disease onset in the children compared

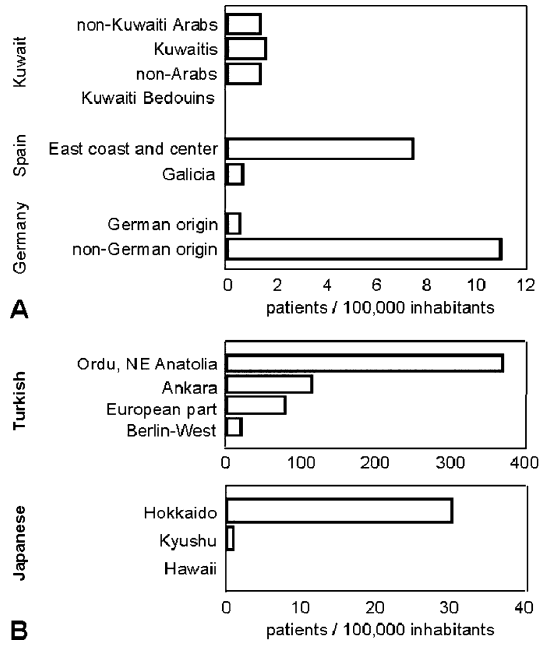

Fig. 1 Indications for Adamantiades-Behçet's disease being an environmentally triggered, genetically determined disorder. **A** Different rates of disease prevalence in a common residential area according to the ethnic origin of the patients group. **B** Different rates of disease prevalence in a single ethnic group according to the area of residence

with their parents has been identified, corroborating the higher frequency of familial cases in juveniles than in adults and the possibility of a genetic predisposition in ABD [5].

Several studies have demonstrated a significant association and an increased incidence of HLA B51 in ABD world wide, whereas there are regional differences in HLA-B51-associated risk. HLA-B5-positive individuals of German origin as well as from other northern European countries present a lower risk to develop the disease compared to southern Europeans [3] (Fig. 2). However, none of the functional correlates of the disease appear to be restricted by HLA-B51. The role of HLA-B51 has been studied extensively and current evidence is shifting towards the view that HLA-B51 is not involved directly in the aetiology of the disease but might be closely linked to disease-related gene(s) [6, 7]. On the other hand, HLA-B51 was found to be a marker for unfavourable prognosis [2, 3]. The alleles encoding the HLA-B51 antigen include HLA-B5101–5106. HLA-B5101 is the allele that is most frequently observed in the normal population and in patients with ABD [8].

Genes possibly associated with ABD have been localised on chromosome 6, in the region between TNF and HLA-B or HLA-C genes [9, 10] (Fig. 3), including the MICA, PERB, and NOB genes [11]. The MICA allele is a polymorphic major histocompatibility complex (MHC) class 1-related gene. MICA6 allele has recently been shown to be significantly associated with ABD [12]. Moreover, the Tap (transporter) genes, which encode proteins that regulate the intracellular transport of antigens to the MHC molecules, were investigated for polymorphisms, and it was determined that the Tap1C allele was absent in all 58 recruited patients with ABD [6]. In another experiment, the Tau-A microsatellite sequence localised between the HLA-B and TNF regions seemed to be a candidate gene sequence for the disease.

Infectious agents and environmental pollution

The disease is not considered to be contagious since no horizontal transmission has ever been reported, in contrast to the solely vertical one reported above. However, in addition to the genetic background, offending agent(s) may trigger an immune defence reaction. Bacterial as well as viral infections and environmental agents have

Fig. 2 HLA-B51-dependent odds ratios for the occurrence of Adamantiades-Behçet's disease

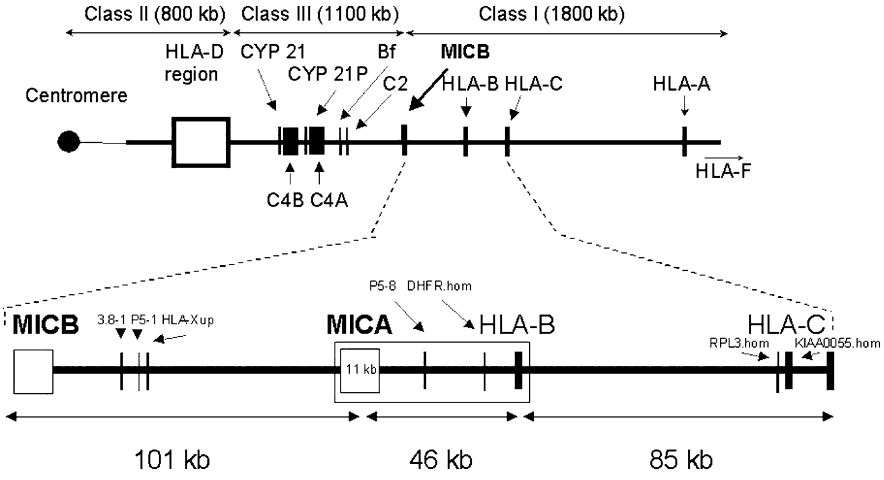

Fig. 3 The gene locus for Adamantiades-Behçet's disease (MIM 109650) is located in the area of the major histocompatibility complex, i.e. on the short arm of chromosome 6 (6p21.3)

been implicated in initiating immunopathological pathways leading to the onset of the disease.

Bacterial agents

A bacterial aetiology was suggested by Adamantiades in his first publication [13]. The Behçet's Disease Research Committee of Japan reported systemic ABD signs in patients within 1–2 weeks after controlled contact with *Streptococcus sanguis*, *S. pyogenes*, *S. faecalis* and *S. salivarius*, and with *Escherichia coli* and *Klebsiella pneumoniae* [14]. The *Streptococcus* strains *sanguis* and *oralis* dominate the flora of the oral mucosa in patients with the disease and appear to be the most relevant bacteria among those suggested as a provoking factor for the initiation of ABD [15, 16]. Streptococcal antigens and anti-streptococcal antibodies are frequently found in the oral mucosa and serum of patients with the disease [17, 18, 19]. The involvement of IgA protease-producing *S. sanguis* is proposed as factor for a chronification of the infection [20]. The BeS-1 gene encoding the immunogenic antigen of *S. sanguis* KTH-1, a 95-kDa antigen, isolated from patients with Behçet's disease has been cloned and sequenced [21]. In addition, exposure of patients to streptococcal antigens may be a major provoking factor for the activity of ABD. The proposed mechanism is through activation of neutrophils, which are elevated in patients with ABD [18].

Currently, we have detected MALP-404, a *Mycoplasma fermentas* lipoprotein, in serum of 32% of ABD patients compared to none in healthy controls [22]. Interestingly, MALP-404 contains the peptide motif -G————F, which can be presented by HLA-B51 [6]. Mycoplasmas cause infections of mucosal tissue, colonizing epithelia of the respiratory or genital tract, and especially *M. fermentans* is associated with rheumatoid disease. Most mycoplasmas contain macrophage-activating components [23], and macrophages have been shown to be strongly stimulated by factor(s) circulating in the serum of ABD patients [24].

Viral agents

A viral aetiology was suggested by Behçet in his original publication [25], based on observations of inclusion bodies in oral and genital ulcerations. A 211-bp herpes simplex virus type 1 (HSV-1) DNA fragment was identified, and partial transcription of the HSV-1 genome has been detected in patients' peripheral blood mononuclear cells [26, 27]. HSV-1 DNA was detected in 43% of saliva samples from patients ($n=91$) compared to 14% of samples from healthy controls ($n=87$) ($P<0.01$) [28], and antibodies against the virus have been found in serum of patients with ABD [29]. Increased T cells and high levels of anti-HSV antibodies have been observed in patients with CNS involvement. In contrast, no cytomegalovirus has been isolated from biopsy specimens or serum of patients with ABD [30]. Antibodies against hepatitis viruses, known to play a role in vasculitis, have been detected in serum of patients with ABD [31, 32] but no causative correlation between them and ABD has been established [33].

Environmental pollution

The experimental administration of chemical environmental compounds to swine was followed—4 to 10 months later—by oral, genital, and intestinal ulcers and cutaneous lesions [34]. On the other hand, increased levels of environmental pollutants were found in several cell types and in serum of patients [35].

Immunological mechanisms

Immunological mechanisms are considered to play a major role in the pathogenesis of ABD [36] (Fig. 4). These include the involvement of heat shock proteins (HSP), alterations of the neutrophil and macrophage

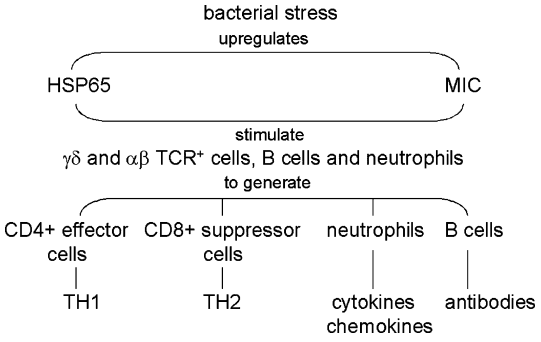

Fig. 4 The suggested immunopathogenesis of Adamantiades-Behçet's disease

activity, expression of numerous cytokines and chemokines, and autoimmune mechanisms.

Heat shock proteins

HSP are molecules that are synthesised in response to various kinds of stress in all eucaryote cells [37]. They also share antigenic epitopes with several bacterial micro-organisms which have been implicated in the pathogenesis of ABD, such as HSV, *Streptococcus* species and mycobacteria. T cell epitope mapping has identified four peptides derived from the sequence of a 65-kDa bacterial HSP which stimulate proliferation of $\gamma\delta^+$ T cell receptor lymphocytes of patients with ABD [38–40]. These peptides show significant homology with the corresponding peptides derived from the human 60-kDa mitochondrial HSP [41]. An increased level of anti-HSP antibodies was found in the cerebrospinal fluid of patients who had parenchymal neurological involvement [42]. On the other hand, IgA antibodies specific for the HSP65 of *Mycobacterium tuberculosis* could cross-react with certain serotypes of *S. sanguis* [43]. In general, cross-reactions between microbial and human 65-kDa HSP possibly link infection with autoimmunity.

The hypothesis that a 65-kDa HSP antigen determinant is involved in the aetiology and pathogenesis of ABD is supported by (1) raised serum IgA antibodies to mycobacterial 65-kDa HSP [40], (2) autoantibodies to oral epithelial antigens [43], (3) cross-reactivity between a number of monoclonal antibodies to mycobacterial HSP and *S. sanguis* [42], (4) cross-reactivity between polyclonal antibodies to mycobacterial HSP and oral epithelial antigens, and (5) significant increase of both circulating and inflammatory site infiltrating T cells during the active phase of the disease. The up-regulation of T cells observed in ABD patients suggests that the aetiological agent(s) may include 65-kDa HSP peptides shared between common bacteria and human tissues, superantigens such as bacterial toxins, or viruses [39, 44]. Interestingly, the MICA protein of the MHC region is recognised by T cells with a variable Vd1$\gamma\delta$ region in their T cell receptor and antigens presented to $\gamma\delta^+CD8^+$ T cells are assisted by the MICA molecule [45].

Neutrophil function

Neutrophil chemotaxis and phagocytosis are increased in cutaneous lesions of ABD patients [46, 47, 48]. Leucocyte adhesion molecules (L-selectin, MAC-1 and CD44) are expressed on peripheral leucocytes and may participate in the sequential cascades of leucocyte chemotaxis and adhesion. Endothelial adhesion properties are enhanced due to the increased expression of CD11a/CD18 on neutrophil surfaces and ICAM-1 on the endothelium. A higher level of superoxide production in the neutrophils of patients with ABD seems to be related to the presence of HLA-B51 [48]. In conclusion, the enhanced superoxide, excessive production of lysosomal enzymes and enhanced chemotaxis of neutrophils from patients with ABD indicate that the neutrophils are overactive, which leads to tissue injury [49, 50].

Monocyte function

The activation of monocytes may explain the production of pro-inflammatory cytokines responsible for the chronicity of inflammation [51]. Spontaneous overproduction of TNF-α, IL-6, and IL-8 by patients' monocytes is apparently related to the disease activity. Patients' serum was shown to be able to inhibit the expression of the anti-inflammatory molecule AMAC-1 on healthy monocytes induced by IL-4 and dexamethasone [24].

Cytokine and chemokine mediators

Various pro-inflammatory cytokines such as IL-1, IL-8 and TNF-α are elevated in the sera of ABD patients. Especially, IL-8 seems to play an important role, can be also released by endothelial cells, and is a sensitive marker of disease activity [52, 53]. Cytokine release may be dependent on the involved organ. Elevated levels of IL-6 in the cerebrospinal fluid were found in patients with neurological involvement [54], whereas patients with CNS involvement and oral aphthous ulcers exhibited elevated serum levels of IL-8 [52]. Patients with ocular involvement showed increased IL-2-producing $CD4^+$ cells [55]. In addition the correlation of TNF receptor-75 levels with disease activity indicates that TNF receptor-75 may serve as a biological marker of disease activity [56]. The elevation of plasma IL-12 was also shown and the correlation of IL-12 plasma levels with disease activity may suggest a pathogenetic role of a Th1 immune response in active disease [57].

Autoimmune mechanisms

Autoimmune mechanisms are involved in the pathogenesis of ABD. A number of immunological abnormalities have been identified and circulating immune complexes are compatible with the development of clinical features. The major microscopic finding at most sites of active ABD is an immune-mediated occlusive vasculitis [50, 58]. At the cellular level, CD4 T cells have been found in the perivascular inflammatory exudate and Thl cells respond to various stimuli to produce IL-2, IFN-γ, and TNF-α [46]. In addition, patients' lymphocytes express CD29 molecules and bind to endothelial cells in active disease [46, 59]. Cytokines induce B cell proliferation. On the other hand, IL-12 is generated by stimulation of CD4 T cells with the HSP peptide 336–351, and can also be secreted by neutrophils in ABD [41]. In addition, IL-8 levels are higher in patients with active disease, and this cytokine has a potent effect on the inflammatory response [52]. Natural killer (NK) cells are increased in peripheral blood of patients with active disease, but their activity was found to be relatively low at the intervals [60, 61]. Decreased NK cell activity may be correlated with increased levels of prostaglandin E_2, since the latter is known to depress NK cell activity [61, 62]. Circulating immune complexes together with enhanced neutrophil migration may be involved in the pathogenesis of systemic and mucocutaneous effects of ABD [46, 52, 63].

Endothelium and clothing factors

Endothelial cells

Recurrent vasculitis and thrombosis are key findings in ABD. The decreased levels of prostacyclin observed in serum of ABD patients and auto-antibodies against oxidatively modified low-density lipoprotein implicate a role of endothelial dysfunction in the disease [64, 65]. Lee et al. [63, 66] have detected circulating IgM complexes directed against a disease-specific 44-kDa cell membrane-bound receptor on microvascular endothelial cells. Binding of the circulating IgM complexes to their endothelial receptor does not lead to endothelial cell death but induces a type III immunological reaction, such as the synthesis and release of cytokines [52, 59, 66] (Fig. 5). Enhancement of endothelial cell E-selection expression by patients' serum and increased inflammatory cell binding to endothelial cells in the presence of infectious agents have also been detected [67, 68].

Clothing factors

Vascular changes leading to vasculitis and thrombosis are additional important pathological features of ABD. Auto-antibodies against cardiolipin have been identified

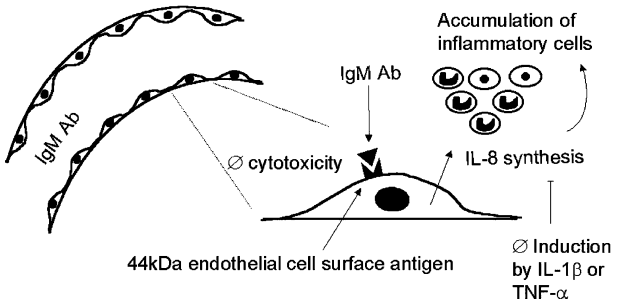

Fig. 5 The involvement of endothelial cells in Adamantiades-Behçet's disease. Circulating antibodies against a specific endothelial cell surface antigen activate vascular endothelial cells to produce cytokines, which induce accumulation of inflammatory cells

[69]. Endothelial cell damage causes auto-oxidative damage and an increase of oxygen radicals [70]. There is an increased risk of thrombosis during the course of ABD [50, 71]. Plasma endothelin-1 concentrations were found to be significantly increased, indicating vasocontraction [72] and being direct result of elevated synthesis from injured vascular endothelial cells. Thrombomodulin, a cell surface glycoprotein of vascular endothelium, which has also been shown to be increased in plasma of patients with active ABD, potentially damages the endothelial cells [71, 73].

Conclusion

Current research on the pathogenesis of ABD points to a genetically determined disorder with certain MHC genes on chromosome 6 being the most obvious candidates. Environmental factors, especially a chronic infection, are probably responsible for triggering an immunological reaction in genetically susceptible individuals. Extrinsically induced tissue stress or heat shock proteins act as a common factor linking some of the possible pathogenetic agents to cross-react with host tissues and elicit a significant Th1 cell response. Additional activation of endothelial cells leads to tissue damage and self maintenance of inflammation. The chronic local inflammation process, together with clothing factors, lead to enhanced coagulation and thrombosis.

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