An update on Behçet's disease
A Kalayciyan,*†‡ CC Zouboulis†§

†Department of Dermatology, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany, ‡Department of Dermatology, Istanbul University, Cerrahpasa Medical Faculty, Istanbul, Turkey, §Departments of Dermatology and Immunology, Dessau Medical Center, Dessau, Germany

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*Corresponding author, Istanbul University Cerrahpasa Medical Faculty, Department of Dermatology Cerrahpasa, 34098 Istanbul Turkey, tel. +90 212414 3000 (ext. 22627); fax +90 212587 0505; E-mail: drkalayciyan@yahoo.com

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Abstract

Behçet’s disease (Adamantiaides-Behçet's disease, ABD) is a multisystemic inflammatory disease, the pathogenesis of which is still a mystery. Many questions are still to be answered and the available diverse data need to be brought together to be compared and analysed. There is at least consensus on the effect of possible, but currently unknown, environmental triggering factor(s) against a background of genetic susceptibility. The possible aetiological factors form a broad spectrum, with infectious agents being the most probable ones. Whatever the stimulus is, the target tissue seems to be the small blood vessels, with various consequences of either vasculitis and/or thrombosis in many organ systems. The endothelium seems to be the primary target in this disease; however, it may just be the subject of the bizarre behaviour of the immune system. The diverse existing data could be interpreted in favour of either explanation. A similar confusion exists about the thrombotic tendency in Adamantiaides-Behçet's disease, in terms of whether a primary hypercoagulability is present or whether it is secondary to inflammation. Recent interesting immunological data promise a way out of the existing dilemma. These findings will be outlined within the context of possible hypotheses and attention will be paid to further investigations that are needed.

Introduction

Behçet’s disease (Adamantiaides-Behçet’s disease, ABD) is a multisystemic inflammatory disease, the pathogenesis of which is still a mystery. Many questions need to be answered and the available diverse data need to be inter-related. There is at least consensus on the effect of possible but currently unknown environmental triggering factor(s) against a background of genetic susceptibility. The possible aetiological factors form a broad spectrum, from infectious agents to pollution. Whatever the stimulus is, the target tissue seems to be the small blood vessels, with various consequences of either vasculitis and/or thrombosis in many organ systems.

The endothelium seems to be the primary target in this disease; however, it may just be the subject of the bizarre behaviour of the immune system. The diverse existing data may be interpreted in favour of either explanation. A similar confusion exists about the thrombotic tendency in ABD, in terms of whether a primary hypercoagulability is present or whether it is secondary to inflammation.

Recent interesting data promise a way out of the existing dilemma. These findings will be outlined within the context of possible hypotheses and attention will be paid to further investigations to be performed.

Anti-endothelial cell antibodies

Lee et al. have recently identified an IgM-type anti-endothelial cell antibody (AECA) to α-enolase in the serum of ABD patients. Enolase is an abundant enzyme in the glycolytic pathway, yet it may have alternative functions on the cell surface in addition to its enzymatic activity. Enolase is also a major structural component of turtle lens, τ-crystallin. Saccharomyces cerevisiae enolase has the ability to bind polynucleotides. Moreover, streptococcal α-enolase (streptococcal surface enolase, SEN) is a cell-surface plasminogen-binding protein. Plasminogen
receptors are involved in the activation of a mechanism that generates a targeted, localized and transient proteolytic activity. Binding of SEN to plasminogen can enhance plasminogen activation by urokinase and prevent \( \alpha_2 \)-antiplasmin from binding. The finding that plasmin bound to SEN retains its proteolytic activity even in the presence of \( \alpha_2 \)-antiplasmin indicates that SEN may be an important streptococcal virulence determinant. The fact that \( \alpha \)-enolase has recently been found to be secreted in growth medium and that increased levels of fungal-specific \( \alpha \)-enolase have been found in patients with invasive candidiasis suggest that a similar phenomenon may exist in cases of invasive streptococcal infection.\(^5\) By using anti-SEN antibodies, Fischetti et al. have identified \( \alpha \)-enolase-like molecules on the surface of both encapsulated and unencapsulated strains of *Streptococcus pneumoniae*, but not on staphylococci,\(^6\) and have suggested that surface \( \alpha \)-enolase (plasminogen binding) might be an important virulence determinant for pathogens of the respiratory mucosa. It is possible that the plasminogen/plasmin–enolase association may play a role in endothelial cell injury by causing direct damage to the extracellular matrix (ECM), possibly by enzymatic degradation of ECM proteins or other protein constituents.

Enolase is a cytoplasmic enzyme. However, several eu- karyotic studies have provided evidence that \( \alpha \)-enolase-related molecules are expressed on the surface of several cell lines such as U937 human monocyteid, human breast tumour, peripheral blood monocytes and neutrophils, and that these molecules contribute about 10% of the plasminogen-binding capacity of the cells.\(^9\)–\(^13\) Recently, \( \alpha \)-enolase has also been shown to be present as an abundant immunodominant antigen in the cell wall of *Candida albicans*.\(^5,12\) Whether endothelial enolase, like eukaryotic surface \( \alpha \)-enolases, is transported by internal signal sequences like that found with plasminogen activator inhibitor 2, needs further investigation.\(^13\)

Cell-surface enolase of *S. cerevisiae*, one of the most abundant enzymes in the cytosol, lacks the typical signal peptide sequence.\(^14\) Some alternative protein secretion pathways have been defined and proteins such as heat-shock protein (HSP) 70 species are implicated in protein trafficking and may offer a non-vesicular system for protein transport.\(^15\)–\(^16\) An alternative pathway may offer cells a method for protein export when classical secretion is arrested (e.g. by heat shock). HSP70 species, also lacking classical secretory signal sequences, have been found on the cell walls of both *S. cerevisiae* and *C. albicans*. Binding of HSPs to specific surface receptors is a prerequisite for the initiation of an immune response. To date, several cell-surface proteins have been described as the receptor for HSP70 including Toll-like receptors 2 and 4 (TLR) with their cofactor CD14. Binding of HSP70 to these surface receptors specifically activates intracellular signalling cascades, which in turn exert immunoregulatory effector functions; a process known as the chaperokine activity of HSP70.\(^17\) These findings suggest that enolase may have an alternative function on the cell wall. Following uptake of HSP-peptide complexes by antigen presenting cells (APCs) and ‘cross-presentation’ of HSP-chaperoned peptides on MHC class I molecules, a CD8-specific T-cell response is induced. HSPs per se provide activatory signals for the innate immune system. Binding of peptide-free HSP70 to APCs via TLRs initiates the secretion of pro-inflammatory cytokines and thus results in a broad non-specific immunostimulation.\(^18\) The mucosal host defence discriminates pathogens from commensals, and prevents infection while allowing the normal flora to persist. Paradoxically, TLRs control the mucosal defence against pathogens, even though the TLRs recognize conserved molecules like lipopolysaccharides, which are shared between pathogens and commensals. Pathogen-specific mucosal TLR4 activation, involving adhesive ligands and their host cell receptors, is demonstrated. TLR4 may be engaged specifically by pathogens, when the proper cell surface receptors are engaged by virulence ligands.\(^19\) Moreover polymorphisms in TLR4 have been reported to be associated with a blunted immune response to microbial pathogens. Some studies show an association between genetic polymorphism in TLR4 gene and susceptibility to infections.\(^20\),\(^21\) Many important bacterial virulence factors act as mimics of mammalian proteins to subvert normal host cell processes. Several genes identified in microbial genomes encode proteins resembling Toll/interleukin-1 receptor domain of the mammalian TLRs and their adaptor proteins.\(^22\) A significant role of HSPs in the immunopathogenesis of BD is suggested. HSP60 is regarded as an endogenous ‘danger’ signal to the immune system with rapid inflammatory cytokine release and the enhancement of adaptive Th1-type responses.\(^23\)

It is still unknown whether endothelial enolase also binds plasminogen. If it does, then a local targeted fibrinolysis, such as the one that occurs during tissue invasion of *Candida*, may interfere with local clotting. Furthermore, it is important to detect a cytoplasmic enzyme on the cell surface of prokaryotic cells, which seems to be immunotactrant. We do not know whether enolase is expressed on the endothelial cell surface of healthy individuals, whether it is externalized due to a stress factor or if it is rather a prokaryotic enzyme that is integrated into the cell surface through an insult of a microorganism. An example of the latter is enolase on the cell wall of *C. albicans*, which is an exogenously incorporated protein.\(^24\) Enolase is also found in mycoplasmas, and particularly in significant amounts in *Mycoplasma fermentans*, which has been implicated in the pathogenesis of ABD.\(^25\),\(^26\) Moreover, mycoplasmas are
known to exhibit molecular mimicry to eukaryotic structures that may modulate immune responses. Indeed, enolase has been implicated in several non-metabolic processes including various stress responses. In Streptococcus mutans, enolase was one of the proteins strongly overproduced in response to acid stress. In S. cerevisiae, HSP48 was identified as enolase 1, one of the two isoforms of enolase present in yeast. In addition, a significant portion of enolase has been reported to be located on the cell surface of several fungi and bacteria or to be exported into the medium. Enolase export has been demonstrated to be a cellular process; however, the export mechanism is unknown.

Haematopoietic cells (neutrophils, B cells, T cells, monocytes), which have been stimulated with phorbol myristate acetate and lipopolysaccharide(s), express significantly higher amounts of α-enolase on their surface. The expression of α-enolase on the surface of human haematopoietic cells has been found to be dependent on the pathophysiological conditions of these cells. In adapting to extreme environments such as high temperature or glucose deprivation, cells often secrete or express specific proteins such as HSP or glucose-regulated proteins (GRP). Vascular endothelial cells appear to respond differently to hypoxia by up-regulating the expression of hypoxia-associated proteins (HAP) in a time- and oxygen concentration-dependent manner. HAP are distinct from HSP and GRP and appear to be stress and endothelial cell-specific. In addition, while endothelial cells up-regulate HSP and GRP when exposed to a variety of stimuli, including heat shock and glucose deprivation, they do not up-regulate these traditional stress proteins when exposed to hypoxia. One of these HSP, HSP47, has been identified as α-enolase. The expression of enolase on the cell surface could result in autoantibody formation and local immune complex formation and may play a significant role in endothelial injury.

The specificity of autoantibodies directed against α-enolase in ABD is unclear. They have previously been described in some chronic inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and inflammatory bowel disease. They may just represent endothelial injury or even a vasculitic process rather than being specific for a particular disease. Moreover, these antibodies seem to bind to different isoforms of α-enolase in different diseases. Interestingly, the presence and the titre of AECA have been correlated with disease activity in systemic vasculitis. Rather than being cytotoxic to endothelial cells, AECA are able to up-regulate the expression of adhesion molecules and induce the secretion of cytokines and chemokines which, in turn, cause leucocyte recruitment and adhesion. Moreover, both haemostatic and fibrinolytic pathway markers were found to be activated in the presence of AECA, suggesting an altered endothelial cell-surface activation state. The significance of the fact that the α-chain of enolase is completely homologous with the IgM production simulator, immunoglobulin production stimulating Factor-2-β, is still not known.

Another interesting aspect of enolase is the fact that the expression of enolase-specific mRNA increases to a very high level in exponentially growing cells but remains almost at an undetectable level in the stationary/resting/quiescent phase. Zieske et al. have previously demonstrated that the glycolytic enzyme α-enolase was restricted to the limbal basal cells of the cornea and that, following wounding, the number of cells expressing α-enolase approximately doubled, suggesting that α-enolase was a marker of stem cells. These findings suggest that endothelial enolase is expressed following vessel injury. It is well known that ultraviolet (UV) light can displace autoantigens from their normal locations inside the cell to the cell surface. This would allow autoantibodies in the circulation to bind to these autoantigens that are normally sequestered from the humoral immune response inside cells. This could in turn result in tissue injury. Certain viruses are also able to induce cell-surface expression of autoantigens. External factors, infectious or not, may be involved in inducing cell-surface expression of enolase as well.

The role of microorganisms in the pathogenesis of ABD has long been investigated and there are ample data on several microorganisms, namely herpes viruses, streptococci, S. cerevisiae and M. fermentans, rather than data focusing on a single agent. Thus, it would be more reasonable to suggest that a complex immune response might be generated to a group of microorganisms that share common antigens recognized by special pattern receptors rather than to an infection due to a specific single microorganism.

γδT cells

γδT lymphocytes represent a relevant proportion of the mucosa-associated lymphoid tissue known to be deeply involved in the first-line defence against several pathogens and tumours. Among γδT cells, the Vγ2 subset represents most circulating γδ lymphocytes. In a recent study, γδT cells were detected to be higher in number in ABD patients than in healthy controls. Furthermore, an increased number of Vγ9Vδ2 subsets of T cells was demonstrated in intraocular fluid of ABD patients with uveitis. The triggering factor for this selective proliferation of T cells in ABD is still unknown.

Recent studies on this new type of defensive cells have shown that they display an activated/memory phenotype.
suggested a chronic response to environmental antigens. Moreover, γδ T cells respond to keratinocytes and stress-induced self-antigens have been observed, and it has been proposed that Vδ2 cells, which recognize phosphoantigens present on foreign pathogens, may also recognize homologous self-antigens. Various phosphoantigens that are reactive with Vδ2Vγ9 cells exist; therefore, it may be exposure to a variety of pathogens that results in the selection of these cells. An interesting aspect is that the recognition of these phosphoantigens is spontaneous and does not require MHC-presenting molecules. Vδ2Vγ9 T cells frequently express NK receptors for self-MHC or MHC-like structures, which comprise both activation and inhibition receptors. The activation receptors recognize stress-induced self-ligands, such as MIC, and upon engagement by MICA an activating signal can be delivered. MIC proteins are expressed by keratinocytes, endothelial cells, and monocyte cell lines including Th1 precursor cells. The MICA gene has been suggested to represent a genetic risk factor for ABD, in addition to HLA-B51. Thus Vδ2Vγ9 T cells may be responsible for the long debated autoimmunity and chronicity in ABD. γδ T cells were shown to proliferate in the presence of IL-12. IL-12 has recently drawn attention in ABD with the demonstration of correlation of its serum levels with disease activity. Thus, IL-12 may have a more specific role than polarizing T-cell response towards Th1 side.

Interestingly, these chemokine receptors are markers of γδ T cells associated with certain acute inflammatory and viral diseases. In addition, subversion of the immune system through the release of products exerting chemokine mimicry has been proposed to occur during viral diseases. In particular, specific herpes and lentiviruses can produce chemokine-like proteins able to block chemokine action and facilitate viral dissemination. Whether certain chemokine receptors on γδT cells in ABD are up-regulated is still unknown. The relation to a possible viral insult awaits explanation as well.

Another unanswered question is whether Vδ2Vγ9 T cells are present in ABD lesions or whether they are just increased in number in the peripheral blood. Functional studies indicate that Vδ2 T lymphocytes express CCR5 (receptor for RANTES, MIP-1α, MIP-1β) and CXCR3 (receptor for IP-10), and migrate in response to these chemokines. Penido et al. reported that the chemokine MCP-1 is generally required for the migration of γδT lymphocytes to inflammatory sites. The recent discovery of the importance of several chemokines in the pathogenesis of ABD and further studies may elucidate the relationship between this selective T-cell response and the inflamed tissues.

**Chemokines**

Chemokines are a family of small protein molecules that play an important role in the attraction and extravasation of leukocytes into and out of tissue. In leucocyte migration, chemokines control lymphocyte–endothelial interaction and tissue-specific homing. Chemokines have been carried out, IL-8 being the first identified and best known among them. Indeed, IL-8 levels in the serum of ABD patients have been shown to better correlate with disease activity than C-reactive protein. IL-8 is a potent chemoattractant for neutrophils, acting via CXCR-1 and CXCR-2 receptors. Thus, IL-8 would be expected to be relevant in a disease with enhanced neutrophil chemotaxis. Another potent chemoattractant for neutrophils is the chemokine GRO, which is functionally related to IL-8 and also binds to the same receptor, albeit with different affinity. Increased concentrations of GRO have been observed in psoriatic scales, which are also characterized by an increased infiltration of neutrophils. Indeed, GRO-α is also found to be elevated in the serum of ABD patients with uveitis. A recent study showed a persistent role of MCP-1 throughout the various stages of ABD.

Cytokines and chemokines are known to have a role in the regulation of differentiation of T-helper cells into different subtypes and to influence the ratio of Th1/Th2 cells. Th1 and Th2 lymphocytes also express different repertoires of chemokine receptors. Human Th1 cells preferentially express the chemokine receptors CXCR-3 and CCR-5, whereas Th2 cells display mostly CCR-3, CCR-4 and CCR-8. The agonists for CXCR-3, MIG, I-TAC and IP-10 have been shown to act as antagonists for the chemokine receptor CCR-3. Chemokines that attract Th1 cells by acting through the CXCR-3 receptor may enhance the polarization of T-cell recruitment and tissue homing by blocking the concomitant migration of Th2 cells. Further investigations on Th1 chemokines and their receptors may elucidate their significance in ABD, which is a Th1-mediated inflammatory disease.

Endothelial CXCR-3 expression has been detected in vessels in leucocytoclastic vasculitis. In addition, a population of infiltrating mononuclear cells, including macrophages and lymphoid cells, were found to be CXCR-3 positive. CXCR-3 is constitutively expressed on endothelial cells of certain organs as well as in different inflammatory conditions. Thus, the expression of chemokine receptors on endothelial cells would increase the specificity of leukocyte binding to endothelium, because chemokine receptor expression and availability can be tightly regulated at the transcriptional level. Leucocyte extravasation and trafficking into tissues is a tightly regulated process in which chemotactic factors play a major role.
the chemokines that interact with CXCR-3, are considered important signals for selective homing of activated/effector cells, which preferentially accumulate in inflammatory sites. High IP-10 levels have been detected in areas of chronic inflammation. In addition to chemotactic activity, IP-10 and MIG may influence adhesion of T lymphocytes on the vascular endothelium. IP-10 induces T-cell adherence to recombinant adhesion molecules and to extracellular matrix proteins. In an in vitro study, anti-CXCR-3 antibodies inhibited the adhesion of IL-2-activated T lymphocytes to stimulated endothelial cells, which express IP-10 and MIG. IP-10 and MIG have been associated with a number of clinical disorders in which Th1 cells have also been implicated. IP-10 expression was noted in delayed-type hypersensitivity responses in the skin. Future studies might establish a possible relationship between these chemokines and their receptors and the increased adherence of lymphocytes to the endothelium of ABD patients.

An enormous amount of studies on the pathogenesis of enhanced thrombotic tendency in ABD have been carried out with different, even contradictory, findings. However, the available data as a whole suggest that thrombosis is a secondary phenomenon in ABD. Indeed, several studies indicate that inflammatory processes are involved in activation of the coagulation system and may even play an important role in the occurrence of venous thrombosis. Increased cytokine and chemokine levels may lead to a procoagulant status. In vitro studies have shown that IL-6, IL-8 and MCP-1 induce the expression of tissue Factor in mononuclear cells. IL-6 is able to increase the synthesis of acute phase proteins such as procoagulant factors and fibrinogen. IL-8 and MCP-1 contribute to a procoagulant status by activating the endothelium. Furthermore, MCP-1 and IL-8 were recently shown to be powerful triggers for firm adhesion of monocytes to vascular endothelium under flow conditions. However, the coagulant process or the thrombus itself also induces inflammatory responses.

Interactions between chemokines and chemokine receptors are probably the most important mechanisms directing lymphocyte traffic and therefore determining tissue specificity in inflammatory disorders. Certain chemokine receptors are viral coreceptors. Viral infections may modulate chemokine and chemokine receptor expression or may themselves encode chemokine or chemokine-receptor-like proteins. Both pox and herpes viruses use two known strategies for interacting with the chemokine system, one via virus-encoded chemokine receptor homologues and one via virus-encoded chemokine homologues. An additional strategy, the secretion of chemokine-binding proteins with novel structures, has been demonstrated for pox viruses. Inhibition of specific aspects of chemokine signalling by Kaposi’s sarcoma-associated herpes virus, while controversial, may well be accomplished by secreting different chemokine homologues, some of which are agonists and some of which are antagonists for specific host chemokine receptors. Viruses in general may require selective activation and inhibition of specific parts of the chemokine system. It is of particular interest that human herpes virus 8 (HHV8) expresses homologous cytokines and cytokine receptors that have been evolutionarily acquired by the piracy of human genes. HHV8 encodes viral IL-6, which directly activates normal human vascular smooth muscle cells, without the need for IL-6 receptor. HHV8 also encodes other chemokines including macrophage inflammatory proteins (vMIP-I, vMIP-II and vMIP-III). Thus, a number of virus families contain genes encoding for proteins that can significantly modify pro-inflammatory cytokine networks. A proposed scenario for primary involvement of endothelia involves genetic alteration in a protein or chemokine receptor on endothelial cells, which in turn may be stimulated by a ‘virokine’ or a ‘bacteriokine’ of sequence homology to the original molecule but more potent in action. This mimicked interaction or ‘false signalling’ would attract the inflammatory cells into the field of action. This may in turn result in vasculitis.

In a recent study it has been demonstrated that chemokine responsiveness could be altered in a chronic inflammatory disease status. The selectivity of a given chemokine for certain leucocyte subsets may be altered by the up-regulation of the chemokine receptors in cells during chronic inflammation. Thus, the relevant effective concentration of an inflammatory mediator may be lower during disease stages than anticipated from previous studies. These studies highlight the importance of understanding the mechanisms that operate under chronic inflammatory conditions, because responses elicited by chemokines and other inflammatory mediators may be altered in diseased individuals.

In order to better understand cellular immunity in ABD, it is wiser to interpret a pattern of possibly involved cytokines and chemokines rather than their individual levels in the serum, as there is a complex interaction of cytokines by which they antagonize and synergize with each other in many different ways. A decrease in anti-inflammatory cytokines should also be taken into consideration along the overactivated pro-inflammatory cytokines. A disturbance in the natural balance between them may be more relevant in inflammatory conditions and could enable the generation of an inflammatory response even to commensal microorganisms.

**Conclusion**

New available data have enabled us to broaden our view and plan studies addressing the pathogenesis of such a
complex disease. A set of immune reactions to either commensal or pathogenic microorganisms, or to self-antigens may be generated, which involves complicated interactions between immune cells and the target tissues. Ancient protective mechanisms are in place, deep within our defences against infection and malignancy, often unappreciated until homologous proteins found within less phylogenetically advanced organisms are identified. Such is the case with TLRs that have high specificity, limited heterogeneity, and no plasticity; nonetheless, they play a pivotal role in rapid initial defences against pathogens. Moreover, studies of the mechanisms of TLRs show how they stand at the threshold of the adaptive immune response and help to accelerate specific immune responsiveness. Non-specific reactivity of these preprogrammed receptors may be how relatively non-pathogenic organisms magnified, if not initiated, by these innate mechanisms as drive inflammation. The inflammation of ABD may be limited heterogeneity, and no plasticity; nonetheless, they stand at the threshold of the adaptive immune response and help to accelerate specific immune responsiveness. Non-specific reactivity of these preprogrammed receptors may be how relatively non-pathogenic organisms.

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