for increased production of murine S100A15 mRNA and protein appears to require protein kinase C activity, as the calcium-dependent increase in murine S100A15 level is inhibited by protein kinase C inhibitors. Activator protein-1 transcription factors appear to be a downstream target that mediates the protein kinase C-dependent increase in murine S100A15, as the presence of a dominant-negative variant of c-Jun inhibits the increase in murine S100A15.

It is gratifying to have confirmation that S100A7 expression, regulation, and subcellular localization are similar in human and murine epidermis. Moreover, it is clear that the availability of the S100A15 sequence will provide an important new tool to identify the role of S100A7 and S100A15 in normal epidermal development and in cutaneous diseases and cancer.

CONFLICT OF INTEREST
The authors state no conflict of interest.

REFERENCES

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HLA-Independent Antibacterial Host Response toward Th1 Immunity Mediated by IL-12: a New Concept for the Pathogenesis of Adamantiades–Behçet’s Disease

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Yanagi R. et al. found an HLA-independent higher frequency of IL-12B polymorphism in Adamantiades–Behçet’s disease (ABD) patients than in controls. Stimulation with streptococcal antigens specifically increased expression of patients’ peripheral blood mononuclear cells IL-12 p40/p70. The authors provide evidence for an antibacterial host response toward T-helper type 1 immunity mediated by IL-12 in patients with ABD, which is HLA independent.


Adamantiades–Behçet’s disease (ABD) is a multisystemic, inflammatory disorder of unknown etiology with hyperergic behavior and a chronic recurrent course (Sakane et al., 1999). It is characterized by oral and genital ulcerations, various cutaneous manifestations, and ocular involvement, whereas mucocutaneous lesions exhibit histological changes of vascular reaction or vasculitis. Linked intrinsic and extrinsic factors are considered to contribute to the development of the disease, and this has led to the concept of environmental triggering.

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of a genetically determined disorder (Zouboulis and May, 2003). Genetic factors have been investigated, and a link with several HLA alleles had initially been suggested. The confirmed association with HLA-B*51, especially with HLA-B*3101, represents a prognostic marker rather than a genetic factor (Zouboulis et al., 2003a). Recently, a possible role of MICA of the major histocompatibility complex region has been emphasized.

At least four extrinsic pathogenic candidates have been identified (Lehner, 1999), including autoimmunity or crossreactivity between microbial and oral mucosal antigens, human simplex virus infection affecting the immune responses, and certain bacteria (Streptococcus sanguinis, Mycoplasma fermentans) (Zouboulis and May, 2003). A bacterial etiology was suggested in 1931 by Adamantiades. The Behçet’s Disease Research Committee of Japan reported systemic ABD signs in patients within 1–2 weeks after controlled contact with several Streptococcus strains, Escherichia coli, and Klebsiella pneumoniae. S. sanguinis dominates the flora of the oral mucosa in ABD patients and appears to be the most relevant bacterium, at least in Japanese patients, as a provoking factor for the initiation of the disease. Streptococcal antigens and anti-streptococcal antibodies are frequently found in the oral mucosa and serum of ABD patients. The BeS-1 gene encoding the immunogenic antigen of S. sanguinis KTH-1, a 95-kilodalton antigen isolated from the patients with ABD, has been cloned and sequenced. A BeS-1 DNA fragment was detected in erythema nodosum-like eruption and oral aphthous lesions in ABD (Tojo et al., 2003). The involvement of IgA protease-producing S. sanguinis species was proposed as an explanation for a chronification of the infection. On the other hand, mycoplasmas cause infections of mucosal tissue, colonizing epithelia of the respiratory or genital tract, and M. fermentans especially has been associated with rheumatic diseases. Moreover, mycoplasmas are known to exhibit molecular mimicry with eukaryotic structures that may modulate immune responses. Most mycoplasmas contain macrophage-activating components, and macrophages have been shown to be strongly stimulated by a factor(s) circulating in the serum of ABD patients (Alpsoy et al., 2003). MALP-404, the M. fermentans lipoprotein, which has been detected in serum of ABD patients, contains the peptide motif G-F----F, which can be presented by HLA-B*51 (Zouboulis et al., 2003b).

However, ABD is not considered to be contagious, as no horizontal transmission has ever been reported. Common factors linking some of the possible pathogenetic agents are microbial stress and heat shock proteins (HSPs), which crossreact with host tissues and elicit significant T-cell responses (Direskeneli and Saruhan-Direskeneli, 2003). T-cell epitope mapping has identified four peptides derived from the sequence of a 65-kilodalton bacterial HSP, which stimulate proliferation of γδ TCR lymphocytes of patients with ABD. These peptides show significant homology with the corresponding peptides derived from the human 60-kilodalton mitochondrial HSP. In the cerebrospinal fluid of patients with parenchymal neurological involvement, an increased level of anti-HSP antibodies could be found. On the other hand, IgA isotype of antibodies specific for mycobacterial tuberculosis HSP-65 could crossreact with certain serotypes of S. sanguinis. In general, crossreactions between microbial and human HSP possibly link infection with autoimmunity. The upregulation of T cells observed in ABD patients suggests that the etiological agents may include 65-kilodalton HSP peptides shared between common bacteria, superantigens such as bacterial toxins, or viruses and human tissues. Interestingly, the MICA protein is recognized by T lymphocytes with a variable Vγ6 region in their TCR, and antigens presented to Vγ6CD8+ T cells are assisted by the MICA molecule.

The endothelium seems to be the primary target in this disease; however, it may simply be subject to the complex and as-yet unexplained behavior of the immune system (Kalayciyan and Zouboulis, 2006). The diverse existing data may be interpreted in favor of either possibility. Lee et al. (2003) have identified an IgM-type anti-endothelial cell surface antibody in the serum of ABD patients and identified the antigen as endothelial α-enolase, a 47-kilodalton HSP. On the other hand, α-enolase is an abundant enzyme in the glycolytic pathway, and streptococcal α-enolase is a cell-surface plasminogen-binding protein. The finding that plasmin bound to streptococcal α-enolase retains its proteolytic activity even in the presence of α2-antiplasmin indicates that streptococcal α-enolase may be an important streptococcal virulence determinant. α-enolase is also found in mycoplasmas, especially in significant amounts in M. fermentans. α-enolase may play a role in endothelial-cell injury, either through its expression on the endothelial-cell surface, resulting in autoantibody and local immune complex formation, or through the association of plasminogen/plasmin and bacterial enolase, causing direct damage to extracellular matrix, possibly by enzymatic degradation of matrix proteins or other protein constituents. However, 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 (Kalayciyan and Zouboulis, 2006). Incceased anti-enolase antibody levels may represent endothelial injury or even vasculitis 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 titer of anti-endothelial cell antibodies have been correlated with disease activity in systemic vasculitis. Rather than being cytotoxic to endothelial cells, anti-endothelial cell antibodies are able to upregulate the expression of adhesion molecules and to induce the secretion of cytokines and chemokines that, in turn, cause leukocyte recruitment and adhesion (Zouboulis and May, 2003). Moreover, both hemostatic
and fibrinolytic pathway markers were found activated in the presence of anti-endothelial cell antibodies, suggesting an altered endothelial cell surface activation state. The significance of the fact that the α-chain of enolase is completely homologous with the enhancer of IgM production Ig production-stimulating factor-2β is yet unknown.

These findings propose that α-enolase may modify the function of the cell wall. After uptake of HSP-peptide complexes by antigen-presenting cells and "cross-presentation" of HSP-chaperoned peptides on major histocompatibility complex class I molecules, a CD8-specific T-cell response is induced. HSPs per se provide activation signals for the innate immune system. Binding of peptide-free HSP-70 to antigen-presenting cells via Toll-like receptors may initiate the secretion of proinflammatory cytokines and thus result in a broad nonspecific immunostimulation.

Various proinflammatory cytokines, such as IL-1, IL-8, and tumor necrosis factor-α, are elevated in the sera of ABD patients. IL-8 seems to play an especially important role, as it can also be released by endothelial cells and is a sensitive marker of the disease activity (Zouboulis and May, 2003). Therefore, neutrophils may also be involved in the pathogenesis of ABD, as they are attracted by macrophage- and endothelial cell-released cytokines and chemokines at the site of the lesions, especially by IL-8, and thus contribute to tissue damage and self-maintenance of inflammation. The chronic local inflammation process together with platelet and serum factors can lead to enhanced coagulation and thrombosis.

IL-12 has recently drawn attention in ABD through correlation of its serum levels with disease activity, suggested to represent a pathogenetic role of a T-helper type 1 (Th1) immune response in ABD (Frassanito et al., 1999). IL-12 is mainly produced by antigen-presenting cells and plays a crucial role in the obligatory transformation of naïve T cells into Th1 cells (Trinchieri, 1993; Alber et al., 2006). IL-12 is generated in ABD by stimulation of CD4+ T lymphocytes with HSP-336–351 and can also be secreted by neutrophils. Innate immune recognition of bacteria was recently shown to involve Toll-like receptor-2 expressed on immature dendritic cells and Vβ2 T lymphocytes expressing γδ TCR. Activated Vβ2 T cells enhance Toll-like receptor-2-induced dendritic-cell maturation, which costimulates IL-12 p70 secretion by dendritic cells (Shrestha et al., 2005). γδ T lymphocytes were shown to proliferate in the presence of IL-12 (Brown et al., 1996). On the other hand, HSP-60 is regarded as an endogenous "danger" signal to the immune system with rapid inflammatory cytokine release and the enhancement of adaptive Th1 responses (Direskeneli and Saruhan-Direskeneli, 2003).

Yanagihori et al. (2006, this issue) elucidated a characteristic gene polymorphism of IL-12 in ABD in order to approach its relevance to the immunopathogenesis of the disease. On the other hand, the authors provide additional evidence that HLA genes are not associated with ABD (Zouboulis et al., 2003a). IL-12 is composed of two heterodimeric subunits, a 35-kilodalton chain encoded by p35 and a 40-kilodalton chain encoded by p40 (IL-12B). The authors investigated IL-12B promoter polymorphism, for which the 4 bp heterozygous insertion has been shown to affect the gene transcription and subsequent protein production, by analyzing IL-12B promoter genotypes in a large cohort of 92 Japanese ABD patients and 102 normal control subjects with the use of PCR-based restriction enzyme digestion. They found that the frequency of the insertion heterozygosity was significantly higher in patients (53.3%) than in control subjects (38.2%), showing that the 4 bp insertion polymorphism within the IL-12B promoter region contributes to susceptibility to ABD. More specifically, this allelic variation is closely associated with increased production of IL-12 p40 mRNA and protein, in conjunction with IL-12 p70 induction in peripheral blood mononuclear cells from heterozygous ABD patients in response to the common bacterial antigens, as assessed by semiquantitative reverse transcription PCR and ELISA. The most pronounced reaction was obtained in the patients’ peripheral blood mononuclear cells upon stimulation with KTH-1 S. sanguinis antigen. These results indicate the involvement of a differential immune response against environmental microorganisms in ABD and provide evidence for an extrinsically pathogenic relevance of streptococcal antigens mediated by IL-12 in ABD and for antibacterial host response toward Th1 immunity. It is likely that IL-12B promoter heterozygosy contributes not only to ABD susceptibility, at least in Japanese patients, but also to loss of feedback inhibition of IL-12 p40 gene expression.

In addition, Yanagihori et al. (2006) compared the frequency of the insertion heterozygosity of the IL-12B promoter with HLA haplotype data in their patients and confirmed that the possible genetic susceptibility is independent of HLA background. Thus, identification of new ABD susceptibility genes relevant to abnormal immunobiological response against bacterial antigens still remains an important challenge.

CONFLICT OF INTEREST
The author states no conflict of interest.

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A New Wrinkle on Topical Vitamin E and Photo-inflammation: Mechanistic Studies of a Hydrophilic γ-Tocopherol Derivative Compared with α-Tocopherol

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The antioxidant function of vitamin E is thought to mediate its photo-protective effects. Cyclooxygenase-2 (COX-2) is an important mediator of early photo-inflammation. Thus, the ability of γ-tocopherol to inhibit COX-2 activity independently of its antioxidant function raises important questions regarding potential roles that this form of vitamin E plays in photo-protection and skin cancer chemoprevention.


Since Linus Pauling published his widely read and publicly debated treatise Vitamin C and the Common Cold in 1970, there has been tremendous lay interest in the potential protective effects of antioxidants in a variety of ailments. This interest did not escape the cosmetic industry. Currently, pharmacy shelves are well stocked with skin-care products, sunblocks, and sun-tanning lotions that tout the remarkable antioxidant properties of vitamin E. Given that there is good evidence that vitamin E may have protective functions within the epidermis, widespread use cannot be simply trivialized as a long-term marketing ploy. However, there is no good consensus regarding the clinical utility of the various naturally occurring forms of vitamin E, nor the widely used thermostabile esterified forms of vitamin E. This is partly because, beyond its antioxidant effect, very little is known regarding the cellular mechanisms through which the different biologically relevant forms of vitamin E work. Yoshida and colleagues (2006, this issue) demonstrate that a novel water-soluble vitamin E derivative, γ-tocopherol-N,N-dimethylglycinate hydrochloride (γ-TDMG), may be superior to the widely used α-tocopherol (α-Toc) form of vitamin E in suppressing UVB-induced photo-inflammation. Moreover, they demonstrate that γ-TDMG inhibits the production of two inflammatory mediators, prostaglandin E2 (PGE2) and nitric oxide. Finally, Yoshida et al. provide evidence that the ability of γ-TDMG to block PGE2 production may be independent of its antioxidant properties. This has important implications not only for epidermal photo-protection and chemoprevention, but also for current studies examining the chemopreventive effects of vitamin E on other epithelial malignancies, particularly prostate, colon, and lung cancer.

Historical perspective

Vitamin E was first described in 1922 by Herbert M. Evans and Katharine Bishop. In their studies, an unknown factor that they called vitamin E was found to be necessary for fetal development in rats. Fetal development was found to be aborted in female rats fed a defined diet. However, fetal development was restored by the addition of plant material, the most effective being wheat germ oil. Vitamin E was subsequently isolated in 1936 and was given the name tocopherol, or “the childbirth-producing alcohol” (Greek tokos, childbirth; pherein, to bear; ol, an alcohol). In 1938, Paul Karrer synthesized vitamin E and demonstrated its function as a lipid-soluble antioxidant. By the 1940s and 1950s, the antioxidant activity of vitamin E was well established, and it was recognized as an essential nutrient in 1968. Natural plant-derived vitamin E is composed of eight different natural derivatives (α-, β-, γ-, and δ-tocopherols and the related α-T, β-T, γ-T, and δ-tocotrienols). Whereas γ-tocopherol (γ-Toc) is the most abundant tocopherol found in the diet,