

Reply to: Behçet's disease: an MHC-I-opathy?

Sirs,

We were pleased to read the critical assessment of our manuscript entitled 'MHC-I-opathy - unified concept for spondyloarthritis and Behçet's disease' by Hatemi *et al.* (1), and we would like to comment on the issues raised by our colleagues:

1. Our perspective article mainly aimed to discuss the shared immunopathogenetic mechanisms between HLA-B*51-associated Behçet's disease (BD) and other HLA Class I associated diseases that were classified within spondyloarthritis group (2). HLA-B*51 is the strongest genetic susceptibility factor described to date for BD and we agree with Hatemi and colleagues that not all patients with BD carry HLA-B*51 allele, likewise not all of AS patients carry HLA-B*27. Therefore, other HLA Class I and ERAP1 allele combinations or MHC Class I-independent mechanisms may trigger a similar innate immune response and cytotoxic/innate lymphoid cell interactions in HLA-B*51 negative patients with BD. We think that identification of the main pathogenic mechanism would help better explain other pathways resulting in the same disease phenotype.

2. HLA-B*51 is mainly associated with classical BD phenotype originally described by Hulusi Behçet, namely mucosal, skin and ocular disease, although this association is not too strong for particular manifestations. Lack of an association with less common manifestations such as vascular or CNS disease supports further that B*51 is linked to the core elements of BD as a whole. This is supported by the observations in the other MHC-I-opathies such as psoriasis where not all skin manifestations are linked to HLA-Cw0602 and ankylosing spondylitis where gut disease has not been specifically linked to HLA-B27.

3. We disagree with Hatemi *et al.* that HLA associations point only to disease clusters in BD. We favour more of a hypothesis where less common manifestations of BD such as vascular or CNS disease possibly develop with the contribution of additional genetic and/or yet unknown environmental factors. We highlighted in our article how tissue specific differences between the different including antigenic composition and

different mechanisms of tissue specific immune homeostasis might account for their apparent differences within the disease. As a specific example of this, we would point towards the role of IL-10 that seems to be specific for bowel inflammation (3, 4).

4. Perturbation of immune system through HLA Class I and ERAP1 allele interactions is not restricted to sites of mechanical stress as discussed for ankylosing spondylitis, and it can be triggered by several different ways including infections, other environmental hazards, and emotional stress (Fig. 1 on Ref. 2). Various triggering events may affect tissue specific protein turnover, and disease expression may differ due to differences between HLA Class I allele and tissue specific peptidome interactions. The pathogenesis of posterior segment involvement with severe retinal pathology in BD may also include vascular pathologies with endothelial activation and diffuse capillary leakage as well as development of an adaptive response to retinal antigens such as retinal-S antigen or IRBP, which may amplify the inflammatory process.

5. The study by Hatemi *et al.* on acne-arthritis association actually further supports the commonalities between BD and spondyloarthritis (5). However, we did not discuss the pathogenic mechanisms of different disease subsets/clusters and tried to focus on a unifying MHC Class I-related hypothesis for BD in this article.

6. Anti-IL-17 approach for the treatment of immunological diseases is in the early days of development. We, therefore, find it preliminary to suggest that IL-17 family cytokines and the IL17 pathway are unlinked to the pathogenesis, as there is a vast literature showing increased expression of IL-17 or other activation of Th17/Tc17 pathway in BD. Further studies in different subsets of BD including ocular disease with different molecules antagonising IL-17 family cytokines activation (such as by molecules blocking JAK/STAT pathway) with different administration routes and intervals are required before concluding on the efficacy IL-17 blocking approach in BD. However, reflecting the importance of tissue specific differences in immune regulation it is already clear that anti-IL-17 works for the skin, peripheral joints and spine in the spondyloarthropathies but is not effective for gut disease.

Finally, there has been and will possi-

bly be an ongoing controversy related to classification of BD within the spectrum of 'vasculitis' or among 'spondyloarthropathies'. We think that BD is a unique entity, and current environmental, genetic, immunological and histopathological evidences point more to accept BD as a tissue-driven, innate and TH1/Th17/Tc17 mediated disease, which is in line with other MHC-I-associated disorders in spondyloarthritis group. Our article was not aimed at re-igniting the lump or splitter debate but to show how a common immunopathological basis for some categories of inflammatory disease has crystallised in the last decade (6).

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