How Much HLA-B27 Expression Is Needed for Spondyloarthritis?

Until relatively recently, quantitative effects of HLA-B27 expression have not attracted much attention in relation to explaining the allele’s association with spondyloarthritis (SpA). The classical hypothesis, that HLA-B27 presents a “spondylogenic” peptide to CD8+ T cells in order to initiate an inflammatory arthritis, does not depend critically on the amounts of B27 expressed on the cell surface. CD8+ T cells are notoriously sensitive detectors of antigen — it has even been claimed that they may be able to detect a single HLA:peptide complex on a target-cell surface, although these observations apply to antigen-specific clones already selected in vivo and in vitro for high affinity recognition of antigen. However, in viral infection the amounts of class I MHC that are expressed must have a critical bearing on generation of specific immune responses, otherwise viruses would not invest in so many strategies to downregulate host cell class I MHC expression. Intracellular bacteria have similar abilities, as demonstrated for the reactive arthritis-associated pathogen Chlamydia trachomatis.

There are additional reasons to consider in more detail the consequences of altered HLA-B27 expression in pathogenesis of SpA. First, in the B27 transgenic rat model of SpA, the requirement for multiple copies of B27 heavy-chain and/or β2m transgenes relates to a need for supranormal levels of B27 expression to produce both joint and gut pathology. Similarly, in patients with ankylosing spondylitis (AS), one group has reported statistically higher levels of B27 expression by lymphocytes of patients with AS as compared to healthy HLA-B27+ controls. These observations can be coupled with several of the more recent hypotheses put forward to explain what B27 is doing in SpA, in the absence of convincing data to clinch the concept of a spondylogenic peptide. These all have elements in which quantitative differences in B27 expression would play a part.

For instance, if the formation of B27 heavy-chain homodimers is critical to SpA pathogenesis, this would be favored by increased quantities of surface B27 molecules containing suboptimal peptides. These peptides could then dissociate from the B27 trimeric molecule producing B27:β2m dimers, which rapidly fall apart to produce free heavy chains; these are then available to form dimers. Dimers may play a role in altering T cell or antigen-presenting cell responses through their interaction with class I MHC interacting receptors other than the T cell receptor; such receptors include those of the KIR (killer cell Ig-like receptor) and LILR (leukocyte Ig-like receptor) families. These same receptors also modulate activation of classical CD8+ T cells, so even classical class I MHC-restricted responses could be influenced by quantitative changes in B27 expression.

A modification of the spondylogenic peptide hypothesis has also been proposed based on the interesting demonstration that B27 (specifically SpA-associated B*2705, but not nonassociated B*2709) is able to bind peptides in more than one configuration. Given that both configurations are not likely to be present to the same extent, the quantity of the peptides whose conformation is required to elicit pathogenic responses might depend critically on the total amount of B27 expressed.

Lastly, Colbert’s group have drawn attention to the consequences of inefficient folding of the B27 heavy chain in the endoplasmic reticulum. Misfolded heavy chains accumulate and trigger the unfolded protein response (UPR), which in turn modulates cytokine production by antigen-presenting cells. In this case the amounts of B27 expressed are clearly critical to induction of the UPR. Thus the UPR was readily detected in cells from B27 transgenic rats; in contrast, “normal” expression of B27 in a transfected monocye-like cell line, U937, did not substantially alter either gene expression at rest, or the response to lipopolysaccharide (LPS) as assessed by gene profiling. Induction of the UPR was detectable when cells were stimulated with LPS, although not in the resting state.

See: Identification of cytokines that enhance promoter activity of HLA-B27, page 862
Therefore, given that there is increasing evidence that quantitative aspects of B27 expression might be very important, it is relevant to examine factors that might modulate this. The most obvious first step is to examine factors that might alter transcription, with proinflammatory cytokines likely candidates for this role. Zhao, et al report just such an analysis in this issue of The Journal17. Their first step was an in silico examination of the 432-base pair 5′-promoter region of HLA-B*2705 and other B alleles. Interestingly, few B alleles had identical promoter sequences to B*2705, but they include B*2706, which is thought not to confer susceptibility to AS, so it is not likely that differences in this region of the gene are solely responsible for the difference in disease association seen with different B27 alleles. To determine influences on transcription, ~300 base pairs of the 5′ untranslated region of B*2705 (i.e., the promoter region) were linked to a luciferase reporter system and transacted into 2 host cell lines, HeLa and CCL6. The majority of the results reported relate to one transfectant HeLa clone that was particularly responsive to cytokines tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), but similar results (data not shown) were obtained with the polyclonal transiently transfected population, making it unlikely that those shown represent a peculiarity of one particular clone. Results using the luciferase system were corroborated using real-time quantitative polymerase chain reaction on transfected CCL6. Transfectants were then treated with a large battery of cytokines, including IL-1β, also excellent inducers of NF-κB; induced maximal and sustained responses between 72 and 96 hours, whereas TNF-α’s effect was maximal at 16 hours and being lost at 24 hours. Thus, the B27 promoter, while containing these elements, clearly has additional features that alter the response to cytokines.

Somewhat surprising was the failure of interleukin 1 (IL-

References


