HLA-B27 and spondyloarthropathies

Muhammad Asim Khan

Professor of Medicine. Case Western Reserve University. MetroHealth Medical Center. Cleveland. USA.

*A*nkylosing *s*pondylitis (AS) and related *sp*ondyloarthropathies (Sp*A*) are more common than RA in many countries. Enthesitis and subchondral inflammation is their pathologic hallmark, and the cartilage destruction seems to start from "inside out" (subchondral & enthesial bone) more than from "outside in" (synovium). The proteoglycans (aggrecan and versican) that aggregate with link protein and hyaluronan, are under study as possible autoantigen candidates.

The recurrence risk ratios (lamda values) among a set of monozygotic twins, siblings, and offspring indicate that AS results from multiple predisposing factors, both genetic and environmental. The environmental trigger for AS is still unknown, but is likely to be quite ubiquitous. There are expected to be close to five predisposing genes in AS and those have multiplicative interactions. All siblings are not at an equal risk for developing AS because the first born are at a significantly higher risk than others. Moreover, the mothers of AS patients are significantly younger at the time of their first delivery as compared with the mothers of healthy controls.

One of the disease predisposing genes is HLA-B27 itself, but how it predisposes to AS is still unknown despite 28 years of research. Whole genome-wide screenings in AS families indicate that MHC (HLA) region on chromosome 6p encodes the greatest component of susceptibility with an overall LOD score of 15.6, and the strongest non-MHC linkage lies on chromosome16q (LOD score of 4.7). One of the putative genes for psoriasis (PSORS1) is located somewhere in a 60 kb region close to HLA-C locus. This region contains three pseudogenes, and it is speculated that PSORS1 could possibly turn out to be a promoter or a long range acting enhancer sequence affecting gene regulation or expression (e.g., of the nearby gene for corneodesmosin).

A specific susceptibility gene (NOD2) for Crohn's disease has been located on chromosome 16q. The encoded NOD2 protein activates nuclear factor (NF)kappaB in response to bacterial lipopolysaccharide (LPS). A frameshift mutation in the NOD2 gene, caused by a cytosine insertion, results in a mutant-type NOD2 that does not activates NFkappaB. This provides a link between a defective innate immune response to bacterial components (LPS) and Crohn's disease.

A recently proposed novel hypothesis suggests that HLA-B27 misfolding in the endoplasmic reticulum (ER) plays a role in the pathogenesis of AS and related SpA through an ER "unfolded-protein response". This can lead to changes in gene expression profiles and subsequent signaling events to alter the cell behavior involving stress signaling and/or heavy chain (HC) dimer formation. Preliminary evidence in favor of the possibility of *in vivo* occurrence of "unfolded protein response" has been reported in the synovial fluid mononuclear cells (SFMC) of SpA patients. These cells showed higher expression of three genes encoding proteasome subunits that are known to be induced during an ER unfolded protein response. One of the expressed genes was BiP, commonly accepted as a gold standard for measuring unfolded protein response. HLA-B27 forms both folded and unfolded/misfolded dimers, and tapasin reduces the accumulation of unfolded/misfolded dimers. *In vitro* studies of HLA assembly in culture cell lines indicate that an intact peptide-loading mechanism in the ER is necessary for the formation of folded HC dimers.

HLA-B27 seems to have had an unusual cell biology as compared to most other HLA class I molecules [19, 122 - 124]; e.g., it may exist in an aberrant form (free heavy chains forming stable homodimers lacking beta(2)-microglobulin), and studies are underway to investigate if there is any recognition of such aberrant forms of HLA-B27 by antibodies, T lymphocytes, or natural killer cells [19, 123]. High level of surface expression of free heavy chains on monocytes of AS patients, and also presence of such monocytes in the synovium of a hip joint of an AS patient have been reported. HLA-B27 has a tendency to fold slowly or misfold as a consequence of its unique B pocket and the presence in the B pocket of the Cys67 residue that

Correspondencia: Dr. M. A. Khan.
Case Western Reserve University. Metro Health Medical Center. Cleveland, Ohio 44106. USA.

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leads to the formation of aberrant disulfide-linked HC complexes.

HLA-B27 encompasses 25 different alleles that encode 23 subtypes: HLA-B*2701 to B*2723, that have evolved from the most widespread subtype, B*2705. These subtypes differ from each other mostly in their exons 2 and 3, which encode the alpha 1 and alpha 2 domains of the B27 molecule, respectively. Occurrence of AS or related SpA has thus far been documented in subjects possessing any one of the first ten (B*2701 to B*2710) subtypes studied, but B*2706 in Southeast Asia and B*2709 in the Italian island population of Sardinia seem not to be associated with AS. The 13 most recent subtypes (B*2711 to B*2723) have not yet been studied for disease association, but disease occurrence has been observed in one or more patients with B*2713, B*2716, and B*2719.

One of the strongest reasons to study the HLA-B27 subtypes is to learn the effects of the sequence variations on the peptide-binding specificity of the molecule; among these peptides may be the putative arthritogenic peptide(s). These studies would be expected to provide clues as to the mechanism of disease association with HLA-B27. One needs to also know whether certain subtypes show any preferential association with some of the clinical features or forms of these diseases among the various ethnic/racial populations and geographic regions of the world. It would be of interest to study protein folding of the two rare subtypes of HLA-B27 –B*2718 and B*2723– because they do not have the Cys67 residue in their B pockets, unlike all the others.

HLA-B27 is one of the best HLA class I molecules to have for anti-viral defense. For example, the relative risk (RR) of progression of HIV infection to AIDS is lower for someone possessing HLA-B27 (RR = 0.33 [95% CI = 0.16-0.70]) than HLA-B35 (RR = 2.8 [1.7-4.0]) or the HLA phenotype A1, B8, DR3 (RR = 2.5 [1.8-3.7]). Viruses exploit different strategies to escape immune surveillance, including mutations in epitopes recognized by CTL. For example, in the immuno-dominant decamer (aa263-272) peptide (KRWIILGLNK) from HIV p24 gag protein, a substitution of Arginine (R) at residue 264 by Lysine (K) or Glycine (G) results in poor binding to HLA-B27of the resultant epitope. This is one of the documented mechanisms of the HIV "immune escape". The R264K substitution was detected in 4 of 5 HLA-B27(+) patients infected with HIV-1 virus, and R264G substitution in the other, and these coincided with HIV disease progression.

TNF blockading therapy for patients unresponsive to conventional treatment results in quick therapeutic response & significant improvement of both axial and peripheral arthritis as well as enthesitis in approximately 80% of the patients. Methotrexate (MTX) has been used for persistent severe disease, especially involving peripheral joints, but its use in AS is based on anecdotal evidence & uncontrolled studies. The first placebo controlled double blind study found no significant benefit from MTX in AS, even in the peripheral arthritis subgroup. Cyclosporine has not studied in SpA but there is a case report of an AS patient with peripheral arthritis unresponsive to conventional therapy who responded to treatment with cyclosporin. The other (novel) therapies under study include pamidronate, a bisphosphonate given by IV infusion, thalidomide and Anakirna (anti-IL-1 receptor antagonist) has just been approved for RA but has not been studied in SpA.

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