Akylosing spondylitis is a major subtype of a group of chronic inflammatory diseases known as spondyloarthropathies. It affects young adults with the peak age of onset between 20 and 30 years. Men are more often affected than women, with a ratio of approximately 3:1. About 80% of patients with AS develop the first symptoms before their third decade of life and < 5% present in the fourth decade of life. Patients with juvenile-onset AS become symptomatic at or before 16 years of age. The prevalence of AS is 0.1–1.4%, and this is dependent on the ethnicity, the prevalence of HLA-B27, the selection of patients for evaluation, and the screening criteria used for diagnosis. This condition is more common in persons of northern European heritage and least common in sub-Saharan Africans. Although it is important to recognize the strong correlation between the prevalence of HLA-B27 and AS in any given population, one must not forget that most individuals who test positive for HLA-B27 are healthy. Non–HLA-B27 genetic and environmental factors have an important role in the development and progression of this disease.

Clinical Features and Diagnosis

The primary clinical features of AS include inflammatory back pain caused by sacroiliitis, inflammation at other locations in the axial skeleton, peripheral arthritis, enthesitis, and anterior uveitis. Oligoarthritis of the hips and shoulders, enthesopathy, and anterior uveitis are common, and involvement of the heart and lungs is rare. The current understanding of the pathogenesis of this disorder is limited. Despite the strong association between human leukocyte antigen B27 (HLA-B27) and susceptibility to AS reported over the past 30 years, the exact pathogenic role of HLA-B27 in AS and other spondyloarthropathies has yet to be determined. The authors present a review of the literature pertaining to the pathogenesis of AS over the past several decades.

Ankylosing spondylitis is a polygenic disorder, with HLA-B27 playing a critical causative role in its pathogenesis. Animal studies of the immunobiology of HLA-B27 have provided significant insight into the pathogenic role of HLA-B27. The search for the antigenic peptide to support the “arthritogenic peptide” hypothesis has been disappointing. Over the past decade there has been increasing interest in the critical role of the misfolding and unfolded protein response of the heavy chain HLA-B27 in the modulation of the inflammatory response. Although there have been significant new findings in the understanding of the pathogenesis of AS, the exact mechanisms have yet to be identified. There is considerable optimism that additional susceptibility genes, predisposing factors, and regulators of the inflammatory process will be identified that will provide avenues for future treatment. (DOI: 10.3171/FOC/2008/24/1/E2)
The clinical criteria are: 1) low-back pain and stiffness of > 3 months’ duration that improves with exercise but is not relieved by rest; 2) limitation of motion of the lumbar spine in both the sagittal and frontal (coronal) planes; and 3) limitation of chest expansion relative to normal values corrected for age and sex. The radiological criteria are sacroilitis Grade 2 or higher bilaterally, or Grade 3 or higher unilaterally. The radiographic grading of sacroilitis consists of 5 grades (Fig. 1): Grade 0 is a normal spine; Grade 1 indicates suspicious changes; Grade 2 indicates sclerosis with some erosion; Grade 3 indicates severe erosions, pseudodilatation of the joint space, and partial ankylosis; and Grade 4 denotes complete ankylosis. Definite AS is present when 1 radiological criterion is associated with at least 1 clinical criterion. Probable AS is considered if there are 3 clinical criteria present or radiologic criteria exist with no signs or symptoms to satisfy the clinical criteria.40

Genetic Factors
The exact cause of AS and other spondyloarthropathies is unknown, but genetic and environmental factors play an important role in their pathogenesis. The amount of genetic contribution to the risk of these disorders is variable. Two twin studies of AS suggest a large genetic contribution to the risk of disease. The aggregate concordance of AS is 63% and 13% for monozygotic and dizygotic twins, respectively. From these concurrence rates it is estimated that approximately 90% of the risk of developing the disease is related to genetic makeup.413 A strong link between AS and the HLA-B27 gene exists and has been definitively confirmed. Despite the fact that 90–95% of patients with AS are positive for HLA-B27, it accounts for less than one third of the genetic risk for AS. More than 90% of patients with AS are positive for 1 of the alleles of HLA-B27, while the risk of developing this disease is only about 5% in HLA-B27+ individuals without seropositive relatives. This risk is increased 5-to 16-fold if there is a first degree relative with AS. Human leukocyte antigen B60 has also been implicated in the risk for AS in patients both positive and negative for HLA-B27 from Europe and Taiwan. Other MHC genes implicated in AS include MICA, HLA-DRB1/MHC Class II alleles, tumor necrosis factor–α, IL-1ra, and low molecular weight proteosome (LMP).

Role of HLA-B27
Human leukocyte antigen B27 is an HLA-B allele of the MHC Class I molecules and is the most established genetic susceptibility marker for AS. The genes of the HLA locus are located on the short arm of chromosome 6. The HLA-B27 gene designates a family of at least 31 closely related alleles, known as subtypes.24,26 Not all the subtypes are associated with AS; HLA-B*2705 is found in all populations, as is the parent HLA-B27 molecule. Most of the subtypes are a result of one or more amino acid substitutions mostly resulting from changes in exons 2 and 3 which encode the alpha-1 and alpha-2 domains of the heavy chain and along specific geographic patterns. The most common subtypes (HLA-B*2705, B*2702, B*2704, and B*2707) are associated with AS. The subtypes HLA-B*2706 and B*2709, which are found in Southeast Asia and Sardinia, respectively, are not associated with AS.

The major function of the HLA Class I molecules is to present antigenic peptides to the αβ T-cell receptors on cytotoxic (CD8+) T lymphocytes. The HLA Class I molecule is composed of a 45-kD polymorphic heavy chain, noncovalently complexed with a soluble nonpolymorphic light chain, 12-kD monomorphic unit, β2m. The heavy chain itself is composed of 3 domains, α1, α2, α3. The first 2 domains together form 2 antiparallel helices resting on a platform of an 8-stranded pleated sheet, which itself rests on 2 barrel-shaped structures derived from the third domain and β2m. Resting inside the platform is an antigenic peptide that is usually 8–11 amino acids in length. These peptides are derived from endogenous proteins and from proteins of viruses and bacteria that have invaded the cells. The antigenic peptide is in contact with the heavy chain at several locations known as “pockets.” These pockets are designated A–F along the length of the platform. The feature that distinguishes HLA-B27 from most other HLA Class I alleles is in the residues of the so-called B pocket of the heavy chain. This B pocket accommodates the second residue of the antigenic peptide. The glutamic acid residue lining this HLA-B27 B pocket is particularly important, dictating that the B pocket of HLA-B27 can accommodate only an arginine residue from the peptide. As a result, the most suitable peptide residue is arginine. Indeed, sequencing of HLA-B27 endogenous peptides shows that most antigenic peptides associated with HLA-B27 have arginine as the second residue.21,17,18,32

Fig. 1. Radiographs showing examples of Grade II (A), Grade III (B), and Grade IV sacroilitis (C).
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Fig. 2. Flow chart showing the sequence of events in antigen presentation. Self- or antigen-proteins in the cytoplasm are degraded by proteasomes, and the short peptides are transported into the ER where they meet MHC Class I molecules. The folded MHC Class I molecule with its peptide is then transported to the cell surface via the Golgi apparatus. Recognition of the MHC–peptide complex by the T-cell receptor of an antigen-specific T lymphocyte completes the antigen presentation.

In an antigen-presenting cell, the MHC molecule presents the peptide derived from the antigen to the CD8+ T cell. The peptides are formed from the degradation of proteins in the cytoplasm by proteasomes. These short peptides are transported into the ER where they meet MHC Class I molecules. The folded MHC Class I molecule with its peptide is then transported to the cell surface via the Golgi apparatus. Recognition of the MHC–peptide complex by the T-cell receptor of an antigen-specific T lymphocyte completes the antigen presentation (Fig. 2).

Animal Models

Two animal models of HLA-B27–related arthritis have verified the central role of HLA-B27 in arthritis and suggest possible mechanisms of pathogenesis. Arthritis develops in transgenic mice that express human HLA-B27 and β2m, but not in those expressing human HLA-B27 and murine β2m. Another model demonstrates that the introduction of the HLA-B27 gene plus the human β2m gene into rats results in a syndrome with features similar to those of human reactive arthritis, including inflammation of the peripheral and vertebral joints, male genital tract, gastrointestinal tract, skin, nails, and heart. In addition, the degree of susceptibility to inflammatory disease in an individual syngeneic rat line correlated with the level of HLA-B27 gene expression in that line. These models support the idea that HLA-B27 is the genetic element that predisposes to arthritis and that the presence of HLA-B27 alone is not sufficient for the development of animal spondyloarthropathy. Environmental factors also have a role since transgenic rodents do not develop arthritis if they are raised in a germ-free or a pathogen-free environment. On the other hand, these arthritis-free animals develop inflammation when switched to a regular environment.

Arthritogenic Peptide Hypothesis

Human leukocyte antigen B27–specific CD8+ T lymphocytes have been the focus of many studies. Sharing of T-cell receptors among different patients with spondyloarthropathies has been noted. This finding suggests that these different patients are responding to the same antigens. The major hypothesis is that there are certain immunodominant arthritis-causing HLA-B27–specific antigenic peptides which are shared among the arthritis-causing pathogens, and that these peptides are also cross-reactive with autoantigens. Hence, when an HLA-B27+ individual is infected with an arthritis-causing pathogen, an HLA-B27–specific, cytotoxic T-cell–mediated autoimmune response would be initiated in the joints. This is known as the “arthritogenic peptide” hypothesis.

As early as 1993, CD8+ T lymphocytes were identified in the joints of patients with reactive arthritis that could recognize both bacterially infected and uninfected target cells. These findings prompted efforts to identify and sequence the bacterial peptides responsible for the CTL reactivity. For Yersinia and Chlamydia several bacterial peptides have been identified, but it remains to be determined whether any of these are cross-reactive with self-peptides, as postulated in the “arthritogenic peptide” hypothesis.

Another self-antigen that has been investigated is derived from cartilage. At least 18 cartilage proteins have been screened for potential reactivity, first by peptide-predicting computer programs, and then by actual testing with synovial T lymphocytes from patients with AS. A peptide derived from Type VI collagen was able to stimulate T lymphocytes obtained from 4 of 7 synovial fluid samples. Other possible self and foreign antigenic peptides are those derived from human vasoactive intestinal peptide receptor-1 and the Epstein–Barr virus protein. These are the only pairs of self- and pathogen-derived HLA-B27 peptides that have been compared using x-ray crystallography. There is no conclusive evidence to prove that any of these peptides is the “arthritogenic-causing” peptide.
TABLE 1
Summary of pathological changes occurring in the joint that eventually cause AS

<table>
<thead>
<tr>
<th>Anatomical Structure</th>
<th>Pathological Changes</th>
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<tbody>
<tr>
<td>synovium</td>
<td>synovitis</td>
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<tr>
<td></td>
<td>pannus formation</td>
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<tr>
<td></td>
<td>loss of synovium</td>
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<tr>
<td>bone marrow</td>
<td>myxoid changes</td>
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<tr>
<td></td>
<td>granulation tissue formation</td>
</tr>
<tr>
<td></td>
<td>replacement with eventual trabecular bone</td>
</tr>
<tr>
<td>cartilage</td>
<td>granulation tissue</td>
</tr>
<tr>
<td></td>
<td>lysis, new cartilage formation</td>
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<td></td>
<td>endochondral bone</td>
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<td></td>
<td>replacement by trabecular bone</td>
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<td>bone</td>
<td>lysis</td>
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<td>replacement by mature trabecular bone</td>
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<td>entheses</td>
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<td>new bone formation</td>
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<td>replacement by mature trabecular bone</td>
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The HLA-B27 Folding Hypothesis

Another possible explanation for the observation that HLA-B27 heavy chains could promote arthritis has been suggested. The proposed mechanism involves a proinflammatory response to overloading of the ER with misfolded proteins. HLA molecules mature inside a compartment of the cell designated as the ER. Assembly of a stable HLA molecule (heavy chain β2m–peptide complex) in the ER is necessary before being exported to the cell surface. Following synthesis and glycosylation, free heavy chains are initially stabilized by chaperones (calreticulin and tapasin) until a conformation suitable to bind β2m and a peptide is achieved. In the absence of β2m, heavy chains ultimately misfold and are degraded. Endoplasmic reticulum–associated degradation is a quality control process of retrotranslocation of misfolded proteins from the endoplasmic reticulum to the cytosol, where there is deglycosylation and proteasomal degradation (Fig. 3). Misfolding is described as an abnormal conformation of the heavy chain, yet proteins that are stalled in the ER because they have not yet folded properly are also considered misfolded.26

The rate of folding is one of the determinants in the fate of the molecules. Human leukocyte antigen B27 is different from other HLA alleles in that it has a significantly slower rate of folding than many other proteins. In addition to its role in peptide selection, the B pocket has a dramatic effect on folding efficiency and can cause misfolding by directly influencing heavy chain folding or by altering its affinity for β2m peptide complex. When unfolded proteins overaccumulate in the ER, an unfolded protein response is signaled and leads to generation of proinflammatory arthritis–causing cytokines and chemokines.522 The unfolded protein response begins with activation of nuclear factor-κB which translocates to the nucleus and stimulates transcription of genes encoding cytokines such as tumor necrosis factor-α, interleukins (IL-1 and IL-6), and chemokines. This then leads to an inflammatory reaction in the joints.5 Indeed, an ER unfolded protein response has been demonstrated in macrophages derived from arthritic HLA-B27 transgenic rats.29 In patients with spondyloarthropathy, there is some evidence of an unfolded protein response in synovial fluid mononuclear cells.8

Conclusions

Our understanding of the pathogenesis of AS is limited. Ongoing investigation of the mechanisms of this disease process are focused on identifying initiating factors, downstream events, mediators of inflammation, and regulators of the process. It has been estimated that approximately 90% of the risk of developing AS is heritable. The most powerful of the genetic risk factors is related to the HLA-B27 molecule. Given the important role that HLA-B27 plays in risk, several possible mechanisms have been proposed. However, despite the intense interest and active investigation, there is yet no general consensus on how HLA-B27 contributes to disease susceptibility. The role of environmental factors remains elusive, as does the understanding of the propensity of AS to involve attachment of ligaments and tendons to bone (entheses) or the involvement of the sacroiliac joints.

References

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Address correspondence to: Juan S. Uribe, M.D., 2A Columbia Drive, 7th Floor, Tampa, Florida 33606. email: juribe@hsc.usf.edu.