

AUTOANTIBODIES TO HLA B27 IN THE SERA OF
HLA B27 PATIENTS WITH ANKYLOSING SPONDYLITIS
AND REITER'S SYNDROME

Molecular Mimicry with *Klebsiella Pneumoniae* as Potential Mechanism
of Autoimmune Disease

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Ankylosing spondylitis (AS)¹ and Reiter's syndrome (RS) are two major non-rheumatoid arthritic diseases of unknown etiology. Because identical twins differ in susceptibility to spondylitis (1), and because RS in particular is often preceded by a discrete episode of infection (2), an infectious etiology has been suspected. Microbes most prominently reported to be associated are Salmonella, Shigella, Yersinia, and especially *Klebsiella pneumoniae* (3). For example, the incidence of *Klebsiella* is abnormally high in the bowel flora of AS patients, and this coincides with exacerbation of the disease (4). Moreover, patients with AS have elevated titers of IgA antibodies against *Klebsiella* (5). Another marked feature of both AS and RS is their correlation with the histocompatibility antigen HLA B27. Whereas >90% of Caucasian AS and >80% of RS spondylitics are B27⁺, only 7% of healthy controls are this HLA type (6). Consequently, HLA B27⁺ individuals are at a high risk for contracting these diseases. But how HLA B27 is involved in the pathogenesis of spondylitis is unknown. Possibly, genes located within the major histocompatibility complex and linked to HLA B27 encode for an immune response that results in susceptibility to the disease (7). Alternatively, HLA B27 antigen may itself participate directly in the tissue damaging process, for example, by acting as a self antigen for a crossreacting immune response to an invading microbe. This latter possibility could occur through molecular mimicry.

Molecular mimicry is defined as the sharing of epitopes from disparate proteins (8). Although their origins may be as different as a microbe and a normal host protein, the linear amino acid sequences or the conformational fits of two such molecules may be homologous. An immune response, initiated by an invading

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¹ Abbreviations used in this paper: AS, ankylosing spondylitis; RS, Reiter's syndrome.

microbe, i.e., bacterium, virus, or parasite, many then react not only with that microbe, but also with the homologous host protein. Conceptually, molecular mimicry can occur whenever the microbial and host determinants are sufficiently similar to induce a crossreacting immune response, yet different enough to break immunologic self tolerance. Such crossreacting determinants have been shown to be limited to as few as five amino acids (9).

To learn whether molecular mimicry occurs between the HLA B27 molecule and microbes, and whether it is of significance to AS and RS, we searched for homologies between the recently published sequence of HLA B27 (10, 11) and entries of suspected bacterial pathogens listed in the Dayhoff protein sequence data bank. Our strategy was to first synthesize such homologous peptides containing hydrophilic shared sequences and test their ability to recognize antibodies from the sera of patients with AS and RS. Thereafter, we determined whether such antibodies were unique for HLA B27⁺ patients with AS and RS, but absent in healthy (nonarthritic) HLA B27⁺ individuals. Here we report that HLA B27 shares six consecutive amino acids with *Klebsiella pneumoniae* nitrogenase, and these are located in hydrophilic domains. Further, there is a highly significant correlation between B27⁺ individuals that have either AS or RS, and production of antibodies to the homologous area shared by HLA B27 and *Klebsiella pneumoniae*. In contrast, individuals with HLA B27 or other HLA haplotypes that are free of AS or RS do not possess such auto- or antiklebsiella antibodies.

Materials and Methods

Computer Search. We used the Protein Sequence Database (Dayhoff Databank) (12), containing 3,182 sequences with 694,014 residues in the release 5.0, and the database search program (13). Overlapping segments of 10 amino acids from the HLA B27 sequence were compared with all sequences in the database. For scoring, we used the Unitary Matrix, which assigns a value of 1 to residues that are identical and 0 to all the others (14). The program was run in batch mode on a VAX/VMS system. (Digital Equipment Corporation, Nashua, NH).

Hydrophobicity Plot. We used a computer program to progressively evaluate the hydrophilicity and hydrophobicity of a protein along its sequence (15). Each amino acid was assigned a hydrophobicity index, ranging from -1 for highest hydrophilicity to +1 for highest hydrophobicity, according to the properties of their side chains. We plotted the average of these indices over a stretch of six consecutive residues.

Peptide Synthesis. Selected peptides up to a length of 16 amino acids were synthesized by the solid-phase method as described by Merrifield (16), using an automated peptide synthesizer (430A; Applied Biosystems, Foster City, CA), cleaved from their insoluble polystyrene resin beads with hydrogen fluoride, extracted, and lyophilized. Peptides were checked for purity by high-performance liquid chromatography using a Vydac TPC 18 column. All peptides had a purity of at least 75%.

Patients. Patients were HLA typed as described (17) using standardized tissue typing antisera. Patients were clinically verified as to having AS or RS. None of the patients had undergone immunosuppressive therapy before the donation of sera. Controls, non-AS or RS patients, consisted of 22 healthy, HLA B27⁺ individuals and 90 non-HLA-matched individuals, of whom 20 were healthy young volunteers working in our laboratory and 70 were patients with diseases other than arthritis. All sera were stored in aliquots at -20°C until tested.

Immunochemical Analysis. The presence and specificity of antibodies to our synthesized peptides were tested by ELISA. Flexible polyvinyl 96-well microtiter plates (Becton Dickinson, Oxnard, CA) were incubated with 1 µg of peptide per well in PBS, and air dried overnight at room temperature. Remaining binding sites were blocked by incubation

TABLE I
Comparison of the Amino Acid Sequences of HLA Antigens and *Klebsiella pneumoniae* Nitrogenase

Protein	Residues	Amino acid sequence
<i>Klebsiella pneumoniae</i> nitrogenase	185-194	N S R Q T D R E D E
HLA B27.1	69-78	A K A Q T D R E D L
HLA B27.2	69-78	A K A Q T D R E N L
HLA B27.3	69-78	A K A Q T D R E S L
HLA B40	69-78	T N T Q T Y R E S L
HLA B7	69-78	A Q A Q T D R E S L
HLA A2	69-78	A H S Q T H R V D L
HLA A3	69-78	A Q S Q T D R V D L
HLA A28	69-78	A Q S Q T D R V D L

The homology between HLA B27.1 and *Klebsiella pneumoniae* nitrogenase is shown in the box.

with ELISA diluent (10% heat-inactivated FCS, 0.2% Tween 20, 0.5 mM thimerosal in PBS). An hour later the sera were added at twofold dilutions from 1:10 to 1:320. After an additional incubation of 1.5 h at room temperature, the plates were washed five times with PBS/0.2% Tween 20. Affinity-purified horseradish peroxidase-labelled goat anti-human IgG + IgA + IgM in an appropriate dilution was added for 1.5 h, and the plates were washed again. The substrate solution (0.4 mg/ml *o*-phenylenediamine, 0.01% H₂O₂ in citrate buffer, pH 5.0) was added, and the reaction was stopped with 4 M H₂SO₄ after an incubation of 30 min in the dark. For evaluation the plates were read with an automated ELISA scanner (Titertek Multiscan, Flow Laboratories), at 492 nm. Positive controls were from the pooled sera of patients with RS. All samples were tested at least twice. Seropositivity was defined as a value greater than the mean of 90 non-HLA-matched controls plus two standard deviations. The statistical evaluation was done by using Student's *t* test.

Results

Sequence Homology Between HLA B27 and Klebsiella pneumoniae. By computer search, we noted several shared sequences of different lengths between HLA B27 and microbes. The best homology consisted of six consecutive amino acids, and occurred between HLA B27.1 residues 72-77 and *Klebsiella pneumoniae* nitrogenase (18) residues 188-193. As Table I illustrates, the sharing of the residues between *Klebsiella* and HLA B27.1 is unique to this HLA haplotype and the B27.1 subtype. Additional computer searches revealed no homologies of six or more consecutive amino acids between HLA B27.2 or B27.3, or other HLA-A or -B types with microbes. Thus these results indicate that amino acid residues 72-77 of HLA B27.1 lie in a hypervariable domain for HLA-B haplotypes and yet show the strongest homology to *Klebsiella*, a microbe implicated in HLA B27-associated AS and RS.

Hydrophilicity Plots of HLA B27 and Klebsiella. The hexamers shared by HLA B27.1 and *Klebsiella* are both hydrophilic (Fig. 1). Thus, these sequences are likely expressed on the molecule's outer surface and are thereby accessible to the immune system. The homologous sequences are flanked in both residues by less hydrophilic stretches.

Presence of Autoantibody to HLA B27 in Patients with AS. By ELISA, 7 of 24

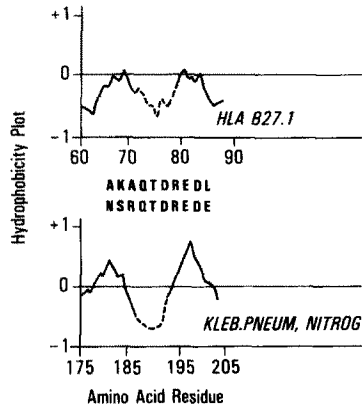


FIGURE 1. Hydrophobicity plot of HLA B27.1, residues 60-90 (top) and the *Klebsiella pneumoniae* nitrogenase, residues 175-205 (bottom). These proteins share a homologous sequence of six consecutive amino acids (dotted lines). Negative peaks indicate hydrophilic areas, whereas positive peaks represent hydrophobic sequences.

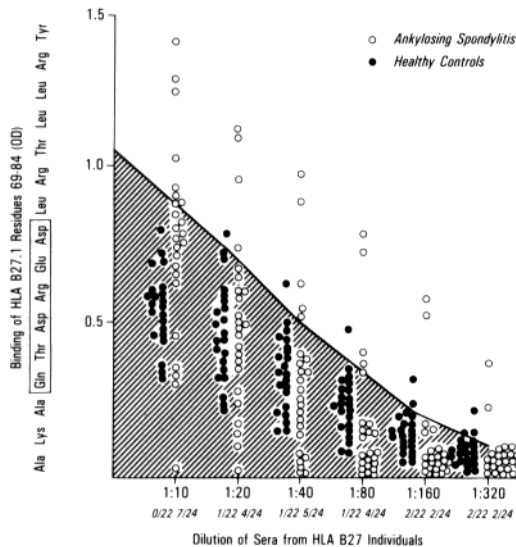


FIGURE 2. Antibodies in sera from individuals with HLA B27 bind to a synthetic peptide representing residues 69-84 of HLA B27.1. The homologous residues to the *Klebsiella pneumoniae* nitrogenase are boxed. The open circles (○) represent sera from 24 individual patients with AS, whereas the dots (●) show the values from 22 healthy individuals of the HLA B27 type. The dilutions of the sera and the number of positive sera are given on the x axis. The background (shaded areas) depicts the mean value plus two standard deviations of 90 sera from nonarthritic and non-HLA-matched controls.

sera (29%) from patients with AS contained antibodies that bound to a synthetic peptide representing the HLA B27.1 residues 69-84 and containing the homologous residues from *Klebsiella*. In contrast, none of the 22 sera from HLA B27⁺ but healthy individuals tested the same way had similar antibodies ($p < 0.01$) (Fig. 2).

Presence of Autoantibodies to HLA B27 in Sera of Patients with RS. We also tested the sera of 34 HLA B27⁺ patients with RS for antibodies that bound to a synthetic peptide representing HLA B27.1, residues 69-84. Of these 34 sera, 18 (53%) bound to the HLA B27.1 peptide, whereas none of the 22 sera from HLA B27⁺ healthy individuals reacted ($p < 0.01$) (Fig. 3). In addition, sera from three HLA B27⁻ patients who had RS did not have antibodies to the HLA B27.1 peptide (results not shown).

Presence of Antibodies to Klebsiella in Sera of HLA B27 Patients with AS and RS. As shown in Table II >40% of the sera from patients with AS (24 sera tested) and RS (34 sera tested) contained antibodies that bound to *Klebsiella*

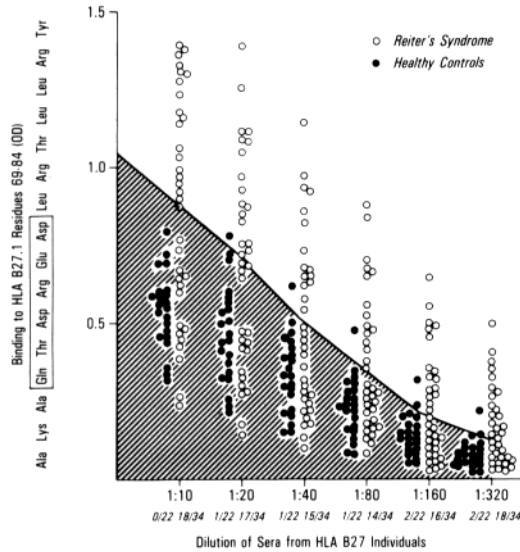


FIGURE 3. Antibodies in sera from individuals of the HLA B27 bind type to a synthetic peptide representing amino acid residues 69–84 of HLA B27.1. Amino acids of HLA B27 homologous to the *Klebsiella pneumoniae* nitrogenase are boxed. The binding of 34 sera from HLA B27⁺ patients with RS (○), and values for 22 healthy HLA B27⁺ individuals (●) are shown. The dilutions of the sera and the proportion of positive sera are given on the x axis. The background (shaded area) represents the mean value plus two standard deviations of 90 sera from donors not having RS.

TABLE II
Antibodies in Sera of Patients with AS and RS Bind to *Klebsiella pneumoniae* Nitrogenase Amino Acid Sequence 184–195 (CNSRQTDREDELI)

Serum dilution	HLA B27 ⁺ individuals			Non-HLA-typed individuals with no arthritis
	With AS	With RS	No arthritis	
1:10	11/24	15/34	0/22	1/90
1:20	9/24	14/34	0/22	1/90
1:40	8/24	16/34	0/22	1/90
1:80	8/24	15/34	0/22	1/90
1:160	6/24	14/34	0/22	1/90

Data shown are numbers of positive sera over total studied per group. Positives consisted of values greater than the mean plus two standard deviation of the 90 nonarthritis sera from non-HLA-typed individuals.

pneumoniae nitrogenase amino acid residues 184–196. In contrast, only 1 of 90 sera from nonarthritic controls contained antibodies ($p < 0.001$).

Discussion

The main finding of our study is that a substantial proportion of HLA B27.1⁺ patients with AS and RS have antibodies reactive with a peptide representing residues 69–84 of the HLA B27 molecule. Further, the antibody is directed to a hypervariable region of HLA B27 that shares sequence homology with *Klebsiella pneumoniae* nitrogenase, a microbial pathogen frequently associated with AS and RS. These results suggest that an immune response directed initially during infection with *Klebsiella* against that organism also reacts against HLA B27 sequences homologous with the *Klebsiella* region. This results in an immune response against these host self determinants. Such a scenario would explain the high incidence of HLA B27 haplotype within AS and RS patient population, as

well as antibodies in the sera of these patients that crossreact with both HLA B27 and *Klebsiella*.

The homology between Six consecutive amino acids of HLA B27.1 and *Klebsiellae pneumoniae* nitrogenase is unlikely to occur by chance. The probability that a hexamer would appear by chance in two different proteins is only 1 in 64,000,000, provided that amino acids occur at a random frequency. Indeed, <1% of the possible sequences of six residues actually occur in the Dayhoff collection of sequenced proteins (12).

There were other reasons for focusing on the shared sequence between HLA B27.1 and *Klebsiella*. First, the homology noted is unique to the HLA B27.1 subtype, thus likely explaining why patients with AS/RS have the same HLA type. Second, the *Klebsiella pneumoniae* nitrogenase is a well-characterized protein (18, 19) of a bacterium that has been shown to induce a crossreacting immune response that specifically lyses B27⁺ lymphocytes from patients with spondylitis (20–22). Third, recent experiments (D. H. Kono, J.-H. Chen, D. T. Y. Yu, P. A. McLean, P. L. Schwimbeck, and M. B. A. Oldstone, manuscript in preparation) found that an mAb to HLA B27 crossreacted with the HLA B27.1 amino acid sequences 69–84, and that rabbit antibodies to the predetermined amino acid sequence of HLA.B27.1 preferentially select HLA B27 isotypes and react with the native proteins of HLA B27 and *Klebsiella*. By using shorter peptides, it was shown that the antigenic determinant recognized by the patients' sera was identical to the six-amino-acid sequence shared between HLA B27 and the nitrogenase of *Klebsiella* (results not shown).

Why do some AS and RS patients' fail to make antibodies against the HLA B27 peptides? Our data relate only to homologies with *Klebsiella*, one of the suspected etiologic agents. While part of the *Klebsiella* genome has been sequenced and its data deposited in the Dayhoff bank, the other suspected microbes, like *Salmonella*, *Shigella*, and *Yersinia*, have either not yet been completely sequenced or are not deposited in the data bank. Alternatively, the inability to detect antibodies in some AS and RS patients may relate to stability of the disease, poor immune responses, or low-affinity response. Nevertheless our data define a subset within the AS/RS group and provide a potential etiologic agent and pathogenic mechanism for their disease.

Several factors can influence the capability of an amino acid sequence shared between two dissimilar proteins to elicit a crossreactive immune response. Two of the most critical events are the extent of the homology and the presence of an antigenic determinant. Our recent studies indicate that an antigenic determinant may consist of only four to five amino acids when conserved substitutions occur at mismatched amino acid(s) (23). Further, a large number of homologous amino acids between two proteins, in themselves, may not be sufficient to induce an immunologic crossreactivity. For example, antibodies to two predetermined peptides that differ in only 1 of 19 amino acids failed to show immune crossreactivity (24), presumably because that one mismatch was a major change in the binding site. Thus, changing one critical amino acid prevents the cross-reacting immune response, despite extensive homology between two sequences. Other examples of this are the single-amino-acid change in position 89 that discriminates Thy-1.1 from Thy-1.2 (25), and antibodies made against amino acid sequence

63–84 of HLA B27.1 that discriminate among the other HLA B27 subtypes (26), although there is only a single amino acid change at residue 77. A third factor is the location of a shared sequence in the native protein. Epitopes expressed on the surface of a protein are generally more accessible to the immune system and thus better able to induce and be recognized by immune responses than are hydrophobic sequences (27).

Molecular mimicry, or the sharing of similar sequences between two distinct proteins, as from a microbe and self antigen, has been suspected of playing a role in several diseases. For example, evidence of homology between cardiac myosin and M protein of streptococci (29), A-gliadin and adenovirus found in the gut (30), and the encephalitogenic site of myelin basic protein and several viruses (9) have been hypothesized to generate crossreactive immune responses that play a role in the pathogenesis of rheumatic heart disease, ulcerative colitis, and demyelinating diseases, respectively. The experimental evidence for this concept comes from studies showing that inoculation of a 10-amino-acid sequence from a virus that shares a 6-amino-acid homology with the encephalitogenic site of myelin basic protein generated an immune response against the native myelin basic protein and caused a histopathologic picture of injury closely resembling allergic encephalomyelitis (31). Accordingly, we suggest that infection with *Klebsiella* may induce an autoimmune response directed against the homologous epitope on HLA B27. Such an immune attack on HLA B27 antigens located on cells from synovial membranes might cause the lesions associated with AS and RS. Once begun, the autoimmune attack could be sustained by the release of autoantigen from destroyed cells, even after clearance of the infecting microbe, making it difficult to identify or recover the eliciting organism during the latter stages of disease. Studies testing this hypothesis by analysis of autoimmune response within the joint space are currently underway.

Summary

Ankylosing spondylitis (AS) and Reiter's syndrome (RS) both show a strong correlation with the HLA B27 haplotype. We studied whether sharing of homologous amino acid sequences in the HLA B27 antigen with an invading microbe might occur, and if so, what is the biological significance of such homology. In a computer search of the Dayhoff data bank, we found a homology of six consecutive amino acids between HLA B27.1 antigen residues 72–77 and *Klebsiella pneumoniae* nitrogenase residues 188–193. These shared sequences are hydrophilic, suggesting locations on molecules exposed to the cell surface. Immunochemical analysis showed that 18 of 34 sera from patients with RS (53%) and 7 of 24 sera from patients with AS (29%) contained antibodies that bound to a synthesized peptide sequence representing residues 69–84 of HLA B27.1. In contrast, only 1 of 22 sera from healthy, B27⁺ controls (5%) contained antibodies to this peptide ($p < 0.01$). Sera from three HLA B27⁻ patients with RS did not possess antibodies to the HLA B27 peptide. Additionally, >40% of HLA B27 patients with AS or RS had antibodies to *Klebsiella* residues 184–193, while none of the normal nonarthritic HLA B27 haplotype subjects did. Our results suggest that an autoimmune response(s) directed against HLA B27.1 may be a pathogenic mechanism in a subset of patients with AS and RS. Further, this

response may initially be induced against *Klebsiella pneumoniae*, a microorganism that shares sequence homology with HLA B27.

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