SERONEGATIVE SPONDYLOARTHROPATHIES - A REVIEW PART II: GENETICS AND PATHOGENESIS

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INTRODUCTION

In none of the spondyloarthropathies is the pathogenesis well understood. Much of the investigation into the aetio-pathogenesis of these diseases has focused on the association with HLA-B27 and the known triggering potential of certain infectious agents.

THE HLA LINKED GENES

The HLA linked genes are subdivided into three groups: class I, class II and class III, which are structurally and functionally distinct. The class I genes, HLA-A, B and C code for the classical transplantation antigens expressed on the surface of all nucleated cells.

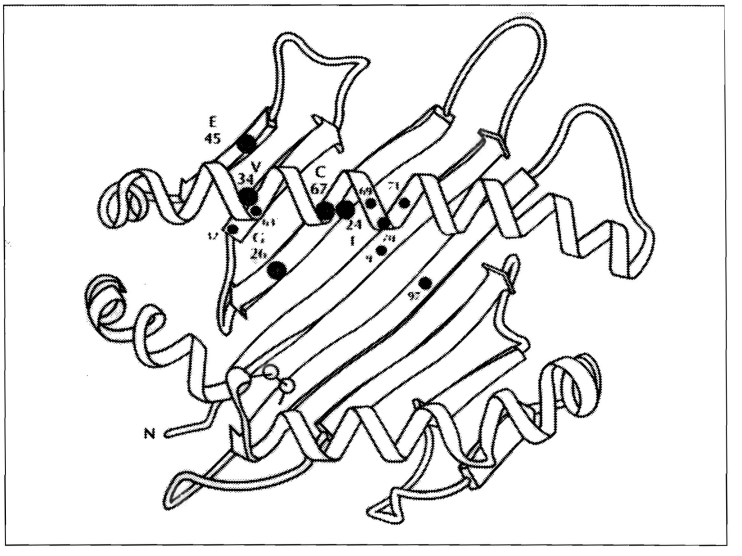

FIGURE I
Model for self-peptides bound in groove of MHC class I molecules. The backbone structures of the class I molecule are indicated by ribbons. The black circles depict the side-chains of those residues that are critical in the interaction with the bound peptide of HLA-B27.

The class I antigens are recognised in conjunction with antigen by the T-cell receptor of cytotoxicT-lymphocytes and they therefore form the target for self-recognition. The action of cytotoxic T-cells against autologous cells which are either infected or chemically modulated or which show malignant transformation, is considered to be one of the most important functions of immunological surveillance (1). The class I antigens are associated with the spondyloarthropathies.

The class II molecules are recognised in conjunction with antigens on the surface of macrophages/monocytes by the T-cell receptors. Upon cross-linking, these initiate a cascade of biochemical reactions resulting in activation of the T-cell (2).

Both class I and class II MHC-encoded molecules have distinct but related, functional requirements in immune recognition. The class I molecules primarily bind antigenic peptides available to them in their biosynthetic journey from the rough endoplasmic reticulum to the plasma membrane, while class II molecules bind proteolytic fragments derived from endocytosed extracellular proteins generated in acidic cellular compartments (Figure 1) (3). This functional distinction can be illustrated further by the mutually exclusive expression of the CD8 and CD4 'coreceptor' molecules on mature T-cells that are committed to the class I - and class II - peptide complexes respectively (4).

Certain class I or class II genotypes might provide a defect in the T-cell repertoire, which could lead to the type of autoimmunity seen in HLA-associated diseases (5). The class II site is associated with subsets of RA.

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The class III region of the HLA chromosome contains the genes for the complement components C4, Bf and C2 as well as the genes for the C21-hydroxylase. C2 and C4 are important factors in the classical pathway, while Bf is the proactivator of C3 in the alternate pathway of complement activation. Their immunological importance is best documented by the observation of severe lupuslike syndromes in the rare cases of genetic deficiency of C2 or C4 (6).

HLA-B27 AND CLINICAL SUBSETS

Since its discovery in 1973 as a genetic marker, HLA-B27 typing continues to be very useful in broadening our views of the clinical spectrum of these diseases (7). One such example is the atypical clinical presentation of patients with back inflammation who have normal sacroiliac and spinal radiographs (8).

In children, peripheral arthritis and enthesitis are the usual presenting features of a spondyloarthropathy and low back pain symptoms or sacroilitis are infrequent. The finding of HLA-B27 and/or a family history of spondylitis can be useful in diagnosing a spondyloarthropathy (9).

The structure and function of HLA-B27, its molecular sub-types (B*2701-B*2706) and other class I major histocompatibility complex (MHC) antigens has been recently established by molecular genetic studies and crystallisation (10). Most of the subtypes appear to predispose to disease development. Up to 20% of HLA-B27 positive individuals develop Ankylosing Spondylitis (AS) or develop Reiter's Syndrome (RS) (11). An offspring of an individual with HLA-B27 has a 50% chance of carrying the same antigen, thus conferring an overall 10% chance of developing AS or RS if exposed to a specific environmental trigger.

The risk for B27-positive relatives of B27-positive patients ranges from 25-50% (12-14). HLA-B27 negative relatives of patients with AS also have an increased incidence of developing a spondyloarthropathy, thus genetic factors other than HLA-B27 must be involved in the pathogenesis.

TABLE I

Frequency of HLA-B27 in different healthy populations.

POPULATION	%
Japan	<1
Black (Africa)	<1
Black (USA)	3-4
Pima Indians (USA)	18
Haida Indians (Canada)	50
Caucasians:	
London (UK)	6
Geneva (Switzerland)	7
Los Angeles (USA)	8
Edmonton (Canada)	9
Zagreb (Yugoslavia)	14
Helsinki (Finland)	14

It has long been recognised that AS occurs more rarely in non-Caucasian populations. This may be related to the different prevalence of HLA-B27 in different populations (Table I). HLA-B27 occurs in less than 1% of Japanese and black Africans. The disease is very rare in the former group and almost unknown in the latter. In the American Indian, B27 prevalence ranges from 18% to 50%, and AS is consequently more frequent (15).

There is a striking family history of different disease expressions in the Seronegative Spondyloarthropathies. In a study of first degree relatives of patients with Psoriatic Arthritis, Wright et al (16), showed a family history of Psoriasis in 21%. Psoriatic Arthritis occured in 4.4%, Ulcerative Colitis in 0.9%, AS in 5.6% and sacroiliitis in 7%.

CURRENT HYPOTHESES

Hypotheses linking the Spondyloarthropathies with HLA-B27 include (17-19):

1. B27 acting as a receptor site for an infective agent.
2. B27 being a marker for a gene close by on chromosome 6 that determines susceptibility to an unknown trigger.
3. B27 inducing tolerance to cross-reactive foreign antigens - Molecular Mimicry (20) eg. Klebsiella (21), Shigella, Chlamydia, and Yersinia (22).

The hypothesis which has received most attention is molecular mimicry between HLA B27 antigen and microbial antigens. Special attention has been focused on Klebsiella pneumoniae, which is frequently isolated in faeces of AS patients with an active disease or with acute anterior uveitis and is also increased in asymptomatic AS patients (23-24). AS patients with an active disease have an increased level of IgA anti-Klebsiella antibodies (25), and the presence of faecal Klebsiella is associated with elevation of serum C-reactive protein (26-27).

Geczy and co-workers have carried out a number of studies on the association between HLA-B27, AS and Klebsiella (28). Their studies showed that HLA B27 positive AS patients had significantly impaired in vitro lymphoproliferative responses to Klebsiella antigens when compared to HLA B27 positive or negative normal controls. They also observed that antibodies raised in rabbits against a certain Klebsiella isolate specifically lysed HLA B27 positive lymphocytes of AS patients (29).

In other experiments, Geczy and co-workers (30-31) showed that a modifying factor in the culture filtrate of a certain Klebsiella isolate was able to make HLA B27 positive lymphocytes from healthy subjects susceptible to lysis by anti-Klebsiella serum. The same result could

be reached by using virus-transformed cell lines obtained from HLA B27 positive AS patients.

This characteristic of certain Klebsiella bacteria is associated with the presence of a plasmid in the bacterium. The plasmid could be transferred to other enterobacteria, which then acquired the ability to elaborate the modifying factor (32). Some isolates of Salmonella, Shigella, Escherichia and Campylobacter strains can also elaborate this modifying factor (33).

McGuigan et al (34), have shown that cross-reactivity is shared by all enteric organisms isolated from HLA B27 positive AS patients, and that organisms with this property persist for more than one year in the bowel flora of these patients.

The observations of Geczy and his co-workers are in line with studies suggesting that HLA molecules may serve as receptors for microorganisms (35). Binding of bacteria by HLA antigens is nonspecific, since HLA A, B and C molecules bind equally well and do not distinguish one strain from another (36). A blind confirmation of the so-called Geczy factor in British (37) and Dutch (38) AS patients has been carried out, but the real nature and significance of the factor remains perplexing.

The human HLA-B27 and Beta 2 microglobulin genes have been successfully transfected and expressed into normal rats. Several strains of these animals then develop arthritis, enthesitis, psoriasiform skin lesions, onychodystrophy, urethritis or orchitis.

Diarrhoea is the first manifestation and inflammatory lesions are found in the gut resembling human inflammatory bowel disease (39). The significance of this observation is not clear in view of the similar findings in rats with adjuvant arthritis.

AS is the protoytpe of the Spondyloarthropathies (40). There is no conclusive evidence implicating a specific infectious agent as the precipitating pathogen. Extensive microbiological studies of peripheral joints have failed to detect intra-articular sepsis (21). However, a great deal of evidence both clinical and immunological has been accumulated to support the role of infectious agents through an indirect action in the pathogenesis of AS (41), possibly via the mucosal immune system.

In AS and other seronegative spondyloarthropathies there are increased serum levels of IgA (particularly of the secretory type) and circulating immune complexes (42-43). Inflammatory gut lesions have been found in

TABLE II

Some HLA associations in the Spondyloarthropathies and other rheumatic conditions.

DISEASE	HLA ANTIGEN	FREQUENCY IN PATIENTS (%)	FREQUENCY IN CONTROLS (%)
SPONDYLOARTHROPATHIES			
Ankylosing spondylitis	B27	80-100	6-8
Reiter's disease	B27	60-85	6-8
Psoriatic arthritis	B27	20-50	6-8
	B38	20-45	2-8
	B39	20-30	2-6
	DR7	30-45	15-20
	DR4	40-50	20-30
Reactive arthritis -			
Yersinia	B27	50-75	6-8
Salmonella	B27	50-70	6-8
OTHER RHEUMATIC CONDITIONS			
Behcet's disease	B5	20-85	10-25
Rheumatoid arthritis	DR4	45-75	20-30
Systemic lupus erythematosus	DR2	45-55	20-30
	DR3	40-50	15-25
Scleroderma	DR5	35-45	20-25
Sjogren's syndrome (Primary)	B8	35-60	15-25
	DR3	50-65	15-25
Giant Cell arteritis	DR3	30	15-25
	DR4	40-50	20-30

after Moll, 1987.

65% of patients with reactive arthritis and in 57% of AS patients. A good correlation was also shown between the presence of gut inflammation in biopsy specimens and the persistence of peripheral joint inflammation (44).

These findings suggest that environmental factors lead to an increase in the permeability of the intestinal wall or disturb local immunological defence mechanism allowing the entry of bacterial antigens into the circulation and induction of joint inflammation (45).

Several of the infectious agents that trigger Reiter's syndrome or Reactive arthritis are known, in sharp contrast to AS or psoriatic arthropathy. Antigens (but not viable organisms) of Chlamydia (46-47), Yersinia (48) and Salmonella (49) have been detected in the affected joints by using monoclonal antibodies and Western blotting.

This finding suggests a failure of the normal immune response to eradicate the antigens or the persistence of viable organisms shedding antigens chronically into the joints.

Although the factors leading to the location and persistence of the bacteria are not clearly known, these findings may provide a rationale for long-term antibiotic treatment.

A major advance has been the recent finding that infection with the Human Immunodeficiency Virus (HIV) can precipitate the development of Reiter's syndrome and Psoriasis (50) and should be borne in mind. In contrast to RA, there appears to be increased penetrance or expression of HLA-B27 related disease in patients with the Acquired Immune Deficiency Syndrome (AIDS). Prospective studies suggest that 5%-10% of HIV-positive patients develop Reiter's disease and most of these are HLA-B27 positive. Since HLA-B27 is only found in 8% of Caucasians (Table II) (51), it suggests that nearly all HLA-B27 patients with HIV infection are likely to develop arthritis (52). The reasons for this association may relate to the increased prevalence of other infections or the profound immunosuppression found in these patients (53).

SUMMARY

There has been great progress in our understanding of the mechanisms which underly the spondyloarthropathies, most of which involve HLA-B27. What remains unknown is why it predisposes to disease. The increased knowledge about the pathogenesis of this group of disorders will hopefully be translated into new therapeutic approaches in the future.

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