HLA–B27 and the link with rheumatic diseases: recent developments

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Introduction

The discovery that many diseases have an association with particular HLA histocompatibility antigens is one of the decade's fascinating puzzles. It is likely there are a number of mechanisms producing HLA-related disease, if only to allow for the great variety of conditions already implicated. The normal function of the histocompatibility antigens is uncertain but the suggestion made from their number and variety on the cell surface that they act as a marker of self, thus enabling micro-organisms to be recognized as foreign, is highly attractive (Snell, 1968). If such a complex system of identification does operate, then it may also be liable to breakdown due to failure on the part of the host defence system or successful evasive tactics on the part of the invading parasite. Food antigens and drugs may also produce interactions with the HLA system (Smeraldi & Scorza-Smeraldi, 1976). The results of the last few years have begun to fill in some of the pieces of the puzzle, but there is a great deal more to learn about the interactions between man, his HLA antigens and the external environment.

The association of ankylosing spondylitis with HLA–B27, although not the first reported HLA-linked disease, stands out as one of the strongest and most undisputed (Caffrey & James, 1973; Brewerton, Hart, Nicholls, Caffrey, James & Sturrock, 1973b; Schlosstein, Terasaki, Blue-stone & Pearson, 1973). The B27 antigen is found in 90–95% of patients with idiopathic ankylosing spondylitis and in about 7% of Caucasian control populations. There have been worldwide confirmatory reports establishing this association in many racial groups. For example, neither ankylosing spondylitis nor the B27 antigen have been found in full-blood central Australian Aboriginals (Cleland, Hay & Milazzo, 1975). In contrast, 50% of North American Haida Indians have the B27 antigen and sacroiliitis has been reported in 10% of the adult male Haida population (Gofton, Chalmers, Price & Reeve, 1975).

Seronegative arthropathies associated with HLA–B27

The incidence of B27 is also increased in many other forms of seronegative inflammatory arthritis, particularly those which have a predilection for sacroiliac joints and are associated with acute anterior uveitis. Reiter's syndrome has many clinical features in common with ankylosing spondylitis and tissue-typing studies show a similar high association with the B27 antigen (Brewerton, Caffrey, Nicholls, Walters, Oates & James, 1973a; Goldin & Bluestone, 1976). The association is not confined to patients having sacroiliitis or spondylitis. In both series it was noted there was a greater than 60% frequency of B27 among patients who had peripheral disease alone.

Overlapping considerably with Reiter's syndrome and particularly with incomplete forms of the disease is seronegative peripheral arthritis, an umbrella term which also includes seronegative rheumatoid arthritis. Several studies now suggest there is an overall increase of B27 in seronegative peripheral arthritis and that B27-
positive patients tend to be younger, male and have asymmetrical arthritis with sparing of the upper limb joints (Milazzo, 1977), whereas B27-negative patients have disease patterns similar to classical seropositive rheumatoid arthritis (Esdaile, Dwoch, Urowitz, Smythe & Falk, 1977; Milazzo, 1977; Nasrallah, Masi, Chandler, Feigenbaum & Kaplan, 1977; Bitter, Jeannet, de Haller & Lejeune, 1979). A high incidence of asymptomatic sacroiliitis has also been reported in the B27-positive patients (Nasrallah et al., 1977).

The B27 antigen is also found in up to 90% of patients who develop arthritis after enteric bacterial infection due to *Shigella*, *Salmonella* or *Yersinia enterocolitica* (Aho, Ahvonen, Alkio, Lassus, Saaranen, Seivers & Tiilikainen, 1975). HLA–B27 is also increased in psoriatic arthritis as are several other B and C locus antigens. Most authors, however, make the point that it is the spondylitic form of the disease in which the prevalence of B27 is high (Brewerton, Caffrey, Nicholls, Walters & James, 1974; Lambert, Wright, Rajah & Moll, 1976; Eastmond & Woodrow, 1977a).

No increase in HLA–B27 has been reported in ulcerative colitis or Crohn’s disease or in the peripheral arthritis associated with these conditions except for one report that nearly all patients with total colitis whether ulcerative colitis or Crohn’s had the antigen (Mallas, Mackintosh, Asquith & Cooke, 1976). In patients with inflammatory bowel disease who have sacroiliitis or spondylitis there is a clear association with B27 (Brewerton et al., 1974; Bluestone, Morris, Metzger & Terasaki, 1975; Mallas et al., 1976).

In juvenile chronic polyarthritis HLA–B27 is found mainly in children who have ankylosing spondylitis and in males with a pauciarthritic lower limb arthritis (Hall, Ansell, James & Zylinski, 1975; Schaller, Ochs, Thomas, Nisperos, Feigl & Wedgewood, 1976).

HLA–B27 is also associated with acute anterior uveitis, being found in 58% of unselected patients (Brewerton, 1975). Of those with associated rheumatic diseases, 89% had the B27 antigen. Even in patients without associated diseases the frequency of B27 was 43%. Similar results have been found by others (Mapstone & Woodrow, 1975; Zervas, Tsokos, Papadakis, Kabouklis & Papadopoulos, 1977).

**HLA inflammatory disease diathesis: ‘B27 disease’**

From the many reported studies it would be tempting to suggest that there is an inflammatory disease diathesis in HLA–B27-positive individuals. They appear to have an increased susceptibility to rheumatic disease particularly sacroiliitis, spinal arthritis, to a lesser degree peripheral arthritis and to ocular inflammation. Although the hypothesis of ‘B27 disease’ is attractive, there are several major problems. The association of ankylosing spondylitis and seronegative spondylarthropathies with B27 does not explain the male predominance of arthritis, it does not explain why some individuals are affected more severely than others and why most HLA–B27-positive individuals have no evidence of arthritis. Studies in B27-positive identical twins indicate that only about one-third are concordant for the disease which strongly suggests that environmental factors predominate in the production of the disease (Eastmond & Woodrow, 1977b; Hehl, Mattern, Gentz, Klemm & Hartl, 1979). The fact that a small proportion of ankylosing spondylitis patients do not carry the B27 antigen has been held as evidence that the actual disease susceptibility gene is not B27 but a closely associated gene in linkage disequilibrium with it, i.e. that two genes are found together more often than could be expected by chance (McDevitt & Bodmer, 1974).

Several more recent studies bear directly on this question. Examination of ankylosing spondylitis patients has failed to detect any increase in HLA A, C or D locus antigens (Kemple, Gatti, Bluestone & Klinenberg, 1977) except in those cases where a known linkage disequilibrium association such as A2 with B27 or Cw1/Cw2 with B27, similar to the control population, was found (Sachs, Sterioff, Robinette, Wolf, Currey & Festenstein, 1975; Arnett, Hochberg & Bias, 1978; Kozin, Duquesnoy, Rodey, Lightfoot & Ryan, 1978). Most tissue-typing studies in ankylosing spondylitis have not shown any association with B locus antigens except for B27. This may have been due to inappropriate analysis of the data. Because of the very strong association of B27 with spondylitis any link with other B locus antigens would be confined to the 5–10% of B27-negative patients. A more appropriate method of analysis is to examine the B27-negative patients separately and compare their B antigen frequencies to those in the control group or, more accurately, in a control group in whom B27-positive individuals have been deleted. By using similar methods several studies have now found an increased association of B7 cross-reacting group antigens in B27-negative patients (Arnett, Hochberg & Bias, 1977; Khan, Kushner & Braun, 1978; Säfwenberg, Domeij-Nyberg & Kjällman, 1978; Sotnik, Mackiewicz &...
& Senger-Kuczynska, 1978). The only factors linking these B7 cross-reacting group antigens, B7, B27, BW22 and BW42 are their gene products which cross-react in tissue-typing studies (Joysey & Wolf, 1978).

These fundamental observations argue strongly against a linked-gene hypothesis and suggest that a determinant of specific stereochemical configuration, expressed on the cell surface and shared by the antigens of the B7 cross-reacting group, particularly B27, predisposes to the development of the disease.

The role of infection in B27-linked diseases

Why the presence of HLA–B27 predisposes to disease is not known. The evidence for infections, particularly Gram-negative gastrointestinal infection, as an environmental factor is increasing. The association of B27 with post-dysenteric arthritis after infection with Shigella, Salmonella or Yersinia enterocolitica is well recognized. Other micro-organisms including Chlamydia (Keat, Maini, Nkwazi, Pegrum, Ridgway & Scott, 1978), Campylobacter (Urman, Zurier & Rothfield, 1977; Berden, Muytjens & Van der Putte, 1979), Brucella (Hodinka, Gomor, Meretey, Zahumenszky, Geher, Telegdy & Bozsoky, 1978) and Klebsiella (Ebringer, Cawdell, Cowling & Ebringer, 1978) have been implicated in B27-associated rheumatic diseases.

The association of ankylosing spondylitis and Klebsiella pneumoniae has now been investigated in some depth and although some of the evidence is conflicting, laboratory and clinical studies from several centres suggest that this micro-organism may play an active role in the initiation of inflammatory eye and joint disease. The studies which discovered the association were initiated to test the hypothesis that there may be stereochemical similarity between HLA cell surface antigens and structural components or products of bacteria (Ebringer, 1978).

It has been known for a long time that bacteria have antigens similar to mammalian tissue components. As early as the beginning of the century, Wasserman and others discovered immunological cross-reactions between tissue lipids and components of Treponema pallidum. The concept of cross-reactive antigens therefore is not new and has been pursued by many investigators since that time. In particular there has been active speculation suggesting that infection with micro-organisms, especially those demonstrating cross-reacting antigens, may result in the induction of autoantibodies and autoimmune disease (Jenkin, 1963; Dumonde, 1966; Asherson, 1968; Lyampert & Danilova, 1975). Interest in autoantibody formation caused by bacterial antigen-mimicking mammalian tissue components was renewed by the suggestion (Broberger & Perlmann, 1959) that the autoantibodies to colon found in ulcerative colitis were due to immunization by related antigens found in enteric micro-organisms and by the observation that Streptococci shared antigens with the human heart (Kaplan & Meyersarian, 1962).

Cross-reactions between Gram-negative bacteria and antigens of vertebrate cells have been demonstrated for Escherichia coli (Springer, Williamson & Brandes, 1961), Salmonella typhimurium (Rowley & Jenkin, 1962) and Klebsiella pneumoniae (Asherson & Holborow, 1966). HLA antigens have been shown to cross-react with bacterial antigens from Escherichia coli and Salmonella (Hirata, McIntyre, Terasaki & Mittal, 1973). One obvious explanation for the presence of these cross-reacting antigens is that parasite organisms have adopted antigens of the host in an endeavour to avoid detection or immunological destruction. The phrase ‘molecular mimicry’ (Damian, 1964) has been coined for such an adaptive mechanism.

It has been suggested that many of the immune-response gene phenomena demonstrated in inbred strains of mice, differing only at the H-2 region (the mouse equivalent of HLA), may be adequately explained by a similar molecular mimicry mechanism and evidence for this hypothesis has now been obtained in several different immune-response gene systems (Ebringer, 1979). In the HLA disease model the molecular-mimicry hypothesis proposes that determinants on the HLA complex, in this case HLA–B27, stereochemically resemble some environmental infective agents. Infection by such micro-organisms may initially lead to a compromised or delayed immune response and then possibly, due to persistence of bacterial antigen or recurrent infection, the subsequent production of antibodies which have both antimicrobial and antiself (autoimmune) activity.

Antigenic similarity was noted between B27-positive lymphocytes and several strains of Gram-negative micro-organisms, Klebsiella pneumoniae, Enterobacter aerogenes and Yersinia enterocolitica (Ebringer, Cawdell, Ngwa Suh, James & Ebringer, 1976). The data have now been reported in detail (Welsh, Avakian, Cawling, Ebringer, Wooley, Panayi & Ebringer, 1980) and there is further evidence from studies with monospecific human tissue-typing sera of cross-reactivity between B27 and Klebsiella antigens.
Other investigators have obtained evidence that rabbit antisera raised against certain strains of *Klebsiella pneumoniae* are cytotoxic for B27-positive lymphocytes from ankylosing spondylitis patients but not for B27-negative patients or healthy B27-positive controls (Seager, Bashir, Geczy, Edmonds & de Vere-Tyndall, 1979). Further studies have demonstrated that a factor from specific *Klebsiella* culture filtrates can adhere to the HLA–B27 complex and result in lysis of the cell upon exposure to the appropriate *Klebsiella* antisera (Geczy, Alexander, Bashir & Edmonds, 1980). These findings indicate that some bacterial antigens have the specific effect of modifying HLA gene products, thus making them vulnerable to immune attack. These findings, however, do not explain the observation that human B27 monospecific tissue-typing sera binds to *Klebsiella* antigens with greater affinity than non-B27-typing sera (Avakian et al., 1980). The tissue-typing data favour the concept of direct cross-reactivity between B27 and *Klebsiella* antigen whereas the former data argue for the presence of *Klebsiella* on the surface of cells in patients with the disease. Further studies are required to resolve these differences.

*Klebsiella* has also been found to be increased in the faeces of patients with clinically active ankylosing spondylitis (Ebringer et al., 1978) and in spondylitis patients with peripheral synovitis (Eastmond, Wilshaw, Burgess, Shinebaum, Cooke & Wright, 1980) or acute anterior uveitis (Ebringer, Cawdell & Ebringer, 1979; Eastmond et al., 1980), when compared with controls or patients with inactive disease. Other investigators have not been able to confirm these findings (Warren & Brewerton, 1980). Patients with faecal cultures positive for *Klebsiella* also have higher e.s.r. and C-reactive protein levels than patients with negative cultures (Cowling, Ebringer, Cawdell, Ishii & Ebringer, 1980). Studies in a rheumatoid arthritis control population indicated that male patients and those carrying the HLA–B7 cross-reacting group antigens were found to have higher faecal *Klebsiella* carriage rates. These findings suggest that carriage of these enteric micro-organisms appears to be partly determined by the sex and HLA status of the host (Ebringer, Colthorpe, Young & Corbett, 1980).

Further evidence suggesting a gastrointestinal infective aetiology comes from the findings that serum IgA levels are elevated in ankylosing spondylitis whereas the levels of IgA and IgM are relatively unchanged (Cowling, Ebringer & Ebringer, 1980). This elevated IgA occurred in patients with more active disease as measured by elevated e.s.r. and C-reactive protein levels whereas patients with normal levels of e.s.r. and C-reactive protein had normal levels of IgA. It seems likely that the elevated IgA is produced as a result of an infective trigger acting upon the gut-associated lymphoid tissue. This response may also contribute to the associated inflammatory disease.

Further evidence for an infective aetiology in ankylosing spondylitis and acute anterior uveitis comes from the finding that a T-cell lymphopenia occurs within 20 days in individuals developing acute anterior uveitis for the first time (Byrom, Campbell, Hobbs, Dean, Timlin, Webley & Brewerton, 1979). Patients with previous rheumatic disease such as ankylosing spondylitis had a relative lymphopenia even at the onset of the uveitis episode. Household contacts whether sexual or nonsexual, related or unrelated were also found to develop a concomitant T lymphopenia. This may be evidence for a viral aetiology but similar T lymphopenias occur after attacks of acute rheumatic fever (Sapru, Ganguly, Sharma, Chaudari & Gupta, 1977), suggesting that this cellular response pattern is not restricted to viral infections.

### Conclusions

There is increasing evidence that in ankylosing spondylitis it is the antigenic stereochemical configuration of some determinant on the HLA–B27 complex which is associated with the disease rather that a gene closely linked to the B27 gene. These observations favour the concept of a potential inflammatory disease diathesis in B27 or B7 cross-reacting group individuals, which amongst other factors probably requires to be triggered by arthritogenic micro-organisms present in the gastrointestinal tract.

There is evidence of antigenic cross-reactivity between B27-positive lymphocytes and antigens present on *Klebsiella pneumoniae*. This may result in disease either by production of microbial antibodies, which also have antiself activity, or the *Klebsiella* antigens may bind to the HLA complex rendering it susceptible to immune attack.

*Klebsiella* has been found more frequently in the faeces of patients with active ankylosing spondylitis, peripheral arthritis and acute anterior uveitis indicating that this micro-organism may play some role in the initiation of acute inflammatory ocular and rheumatic disease in B27-positive individuals. Other, as yet unidentified, micro-organisms may produce disease by similar mechanisms.
HLA and rheumatic diseases

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References


