HLA-B27 and disease pathogenesis: new structural and functional insights

Paul Bowness, Nathan Zaccai, Lucy Bird and E. Yvonne Jones

The human leukocyte antigen class I allele HLA-B27 is a major histocompatibility complex (MHC) antigen that is strongly associated with the spondyloarthritic group of human rheumatic diseases, the most commmon of which is ankylosing spondylitis. Although the mechanism underlying this disease association remains unknown, numerous theories have been proposed. Much more is known of the natural role of HLA-B27 in binding and presenting antigenic peptides to T cells. The 'arthritogenic peptide hypothesis' suggests that the role of HLA-B27 in disease relates to its specificity for binding certain peptides. Recently, it has also been shown that HLA-B27 has an unusual cell biology and can adopt a novel homodimeric structure. In this review, a molecular model of the HLA-B27 homodimer is presented and the possible pathogenic significance of such a structure is discussed.

The association of the HLA class I allele HLA-B27 with the rheumatic disease ankylosing spondylitis has been recognised for over 25 years (Ref. 1). Ankylosing spondylitis is a relatively common and debilitating inflammatory rheumatic disease, affecting approximately 0.1–0.5% of the UK population. A recent study found that 94% of patients with AS carry at least one HLA-B27 allele, compared with only 9.4% of controls, giving an odds ratio of 171, with a 95% confidence interval of 135–218 (Ref. 2). HLA-B27 is also associated with several other diseases, albeit less strongly (Table 1). These diseases are collectively known as the spondyloarthropathies because they are characterised by the involvement of the spine and sacroiliac joints.

Although the pathogenetic role of HLA-B27 in the spondyloarthropathies is unknown,

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numerous theories have been proposed (Table 2). Notably, all such theories should attempt to explain not only the relationship of disease with specific triggering organisms, which has been found most clearly for reactive arthritis, but also the striking tissue distribution of these diseases. This review describes the possible mechanisms by which HLA-B27 might be involved in disease pathogenesis, and discusses the data available from HLA-B27-transgenic animals, biochemical analysis of HLA-B27 function and molecular epidemiology studies.

Theories explaining the association of HLA-B27 with the spondyloarthropathies

Several different mechanisms have been put forward to explain the association of HLA-B27 with the spondyloarthropathies. Some of these theories, summarised in Table 2, may be applicable to other HLA-associated autoimmune diseases. Theories 1–4 suggest that the pathogenic role of

Table 1. Diseases associated with HLA-B27 (tab001pbo)

Ankylosing spondylitis
Reactive arthritis (follows infection with *Chlamydia*, *Salmonella*, *Shigella*, *Campylobacter* and *Yersinia* species)
Sacroileitis associated with inflammatory bowel disease
Sacroileitis associated with psoriasis
Undifferentiated oligoarthropathy
Anterior uveitis
Aortic regurgitation together with cardiac conduction abnormality
Enthesis-related juvenile idiopathic arthritis

Table 2. Theories explaining the association of HLA-B27 with the spondyloarthropathies (tab002pbo)

Theories implicating immune function	**Comments**
(1) 'Arthritogenic peptide hypothesis'; presentation of arthritogenic peptides by HLA-B27	Peptide(s) might be derived from self and/or bacterial proteins (including HLA-B27 itself)
(2) Thymic selection of T-cell repertoire	This would probably also involve peptide binding
(3) HLA-B27 has an unusual cell biology compared with other HLA molecules	Cys67 might affect the assembly of HLA-B27
(4) 'Altered-self hypothesis'; chemical modification of Cys67	Might result in immune stimulation
Theories not directly implicating immune function	**Comments**
(5) Linkage to a disease-associated gene	Unlikely because HLA-B27-transgenic rats develop a disease resembling spondyloarthritis
(6) Crossreactivity between antibodies directed at bacterial protein(s) and HLA-B27	This has difficulty explaining the tissue specificity of disease
(7) HLA-B27 is a receptor for a bacterial ligand	
(8) Interaction of HLA-B27 with a bacterial superantigen causes nonspecific T-cell stimulation	
(9) HLA-B27-derived peptides are presented by HLA class II molecules to T cells	

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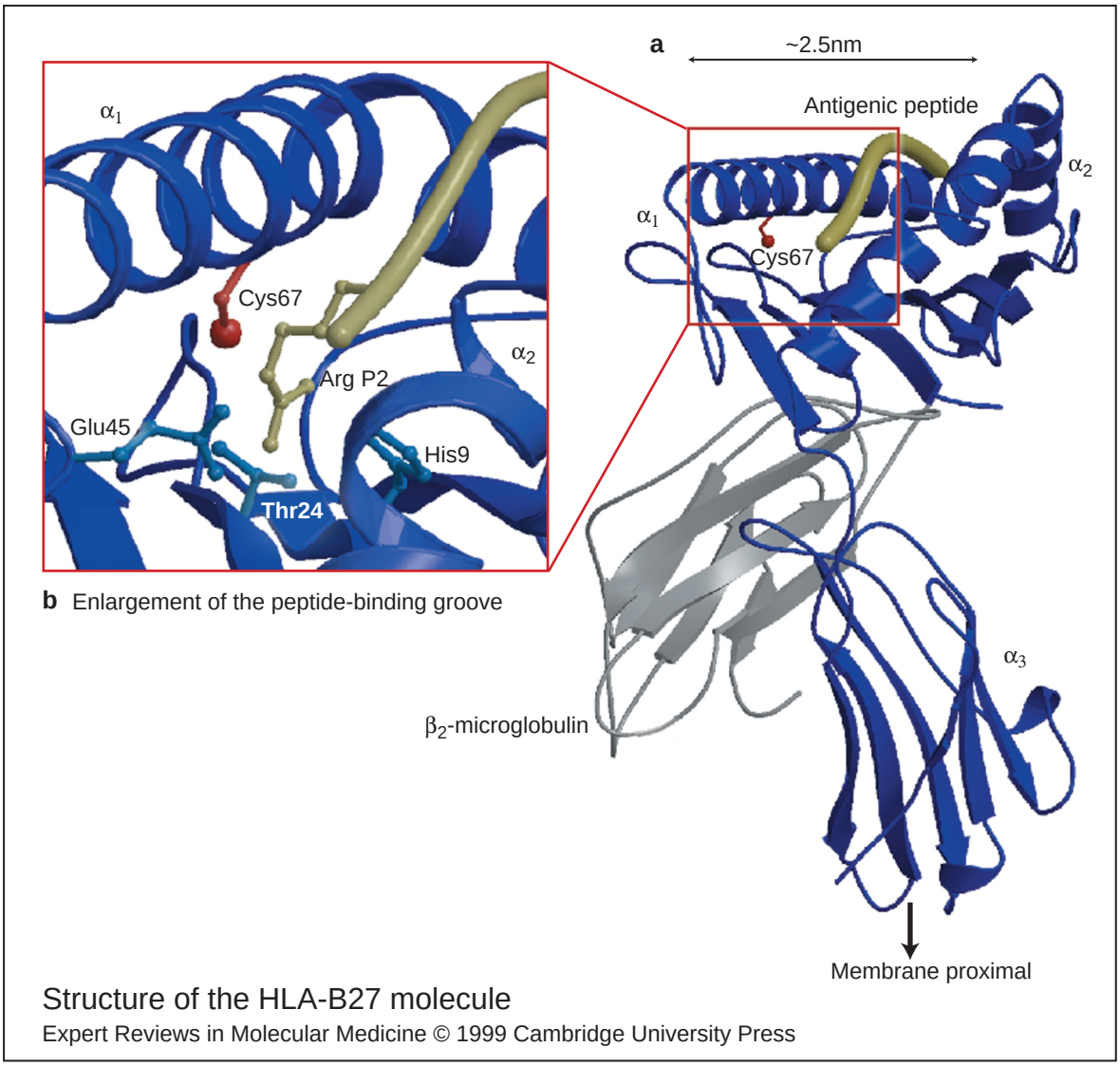

Figure 1. Structure of the HLA-B27 molecule. (a) Ribbon diagram representation of the entire extracellular domains of the HLA-B27 molecule, using the HLA-B27 crystal structure coordinates (Refs 9, 38). The HLA heavy chain (α_1, α_2 and α_3 domains) is shown in dark blue and the β_2-microglobulin in light grey (at the centre-left of the figure). The bound peptide (at the top of the figure) is shown as a yellow tube. The Cys67 side-chain of HLA-B27 is highlighted in red. (b) Close-up view of the HLA-B27 B pocket. The side-chains of particular importance for the B pocket are labelled and shown in light blue. The Arg P2 side-chain of the bound peptide is shown in yellow. The figures were produced using the programs BobScript (Ref. 42) and Raster3D (Ref. 43) **(fig001pbo)**.

HLA-B27 stems directly from its natural function in the immune system (i.e. peptide binding and presentation to T cells). Thus, HLA-B27 might be capable of specifically binding certain arthritogenic peptides, derived from either microbial or self-proteins, that are not bound by other HLA molecules (theory 1) (Ref. 3). Since the development of T cells in the thymus is also dependent on recognition of HLA–peptide complexes, HLA-B27 may also have an effect on the development of the T-cell repertoire (theory 2). HLA-B27 is unusual in possessing an unpaired cysteine residue at position 67 of the α_1 helix (Fig. 1a). Cys67, probably in combination with other residues, might affect the molecular assembly and function of HLA-B27 (theory 3). Modification of the Cys67 sulphydryl could result in immune stimulation (the 'altered-self hypothesis'; theory 4).

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A second group of theories suggests that the immune function of HLA-B27 is not directly related to its pathogenic role. The possibility that the association with HLA-B27 is due to a linked pathogenic gene (theory 5) is now considered unlikely since HLA-B27-transgenic rodents develop diseases resembling spondyloarthritis. Similarly, the tissue specificity of disease is not explained by the idea that antibodies directed at bacterial proteins can cause disease through crossreactivity with HLA-B27 (theory 6). Indeed, although anti-HLA antibodies are found in patients, controlled studies show no evidence that they are specific for HLA-B27 (Ref. 4). Alternatively, HLA-B27 might interact with ligands other than the T-cell receptor (TCR) of an HLA-B27-restricted T cell; for example, HLA-B27 might interact with a bacterial receptor (theory 7) or superantigen (theory 8). However, there is no direct evidence for either of these mechanisms and HLA class I-reactive superantigens have not been described. The final theory suggests that HLA-B27-derived peptides are capable of being bound and presented to $CD4^+$ T cells by HLA class II molecules, and could thus stimulate autoimmunity (Ref. 5). Indeed, proliferative $CD4^+$ T-cell responses to a synthetic peptide comprising residues 60–72 of HLA-B27 have been detected in some, but not all, patients with ankylosing spondylitis (Ref. 6). However, recent data from transgenic mice (see below) would appear to rule out such a mechanism, since MHC class II molecules are not required for the development of arthritis (Ref. 7).

Structure and function of HLA-B27: its role in antigen presentation

It is now known that the principle function of HLA molecules is to bind and present antigenic peptides to T cells (Ref. 8). HLA class I molecules present peptides to $CD8^+$ cytotoxic T lymphocytes (CTLs) and HLA class II molecules present peptides to $CD4^+$ T cells. These findings have led to the suggestion that the spondyloarthropathies might result from the ability of HLA-B27 to bind a unique set of peptides. This 'arthritogenic peptide hypothesis' proposes that these diseases result from a $CD8^+$, HLA-B27-restricted CTL response to a peptide(s) that is found only in joint tissues (Ref. 3).

Figure 1a shows the molecular structure of HLA-B27. Elucidation of this crystal structure (Ref. 9), together with amino acid analysis of self-peptides eluted from HLA-B27 (Refs 10, 11) and binding studies using synthetic peptides (Refs 12, 13), have shown that HLA-B27 binds a unique set of peptides. These bound peptides almost always have an 'anchor' arginine residue at their second position, known as Arg P2 (Fig. 1b). The side-chain of this Arg is bound in a B pocket, which is ringed with key amino acids that, in combination, are unique to HLA-B27: His9, Thr24, Glu45 and Cys67. The HLA-B27 D and F pockets bind 'secondary anchor' amino acid side-chains of the peptide at the third and C-terminal positions, respectively (Ref. 11). A schematic diagram showing binding of a typical peptide to HLA-B27 is shown in Figure 2.

At least 12 molecular subtypes of HLA-B27 are now recognised, all of which differ primarily at residues lining the peptide-binding groove (reviewed in Ref. 14). Interestingly, small epidemiological studies suggest that some HLA-B27 subtypes, such as B*2706 and B*2709, might not be associated with ankylosing spondylitis (Refs 15, 16). These subtypes appear to bind subtly different, but overlapping, subsets of peptides (e.g. see Ref. 17). Confirmation of such data would strengthen the arthritogenic peptide hypothesis of disease pathogenesis, and might facilitate the identification of 'pathogenic' peptides from candidate bacteria.

Transgenic models of HLA-B27-associated disease

Direct evidence for the involvement of HLA-B27 in disease pathogenesis comes from transgenic animal models. Rats made transgenic for HLA-B27, but not HLA-B7, develop a multi-system disease with many features resembling the human spondyloarthropathies (Ref. 18). Rats develop arthritis and gut inflammation only after transfer from germ-free conditions, and gut flora has been implicated as a disease trigger (Ref. 19). Arthritis is dependent on supraphysiological levels of HLA-B27 expression (Ref. 20), and requires the presence of $HLA\text{-}B27^+$ bone-marrow-derived cells (Ref. 19) and T cells (Ref. 21), suggesting a direct immune role.

Khare and colleagues have developed a murine model of HLA-B27-associated arthritis in which HLA-B27-transgenic mice lacking murine β_2-microglobulin (β_2-m) develop arthritis (Ref. 22). Disease incidence in these mice can be reduced in vivo by treatment with the monoclonal antibody (mAb) HC10, which recognises the heavy (H)

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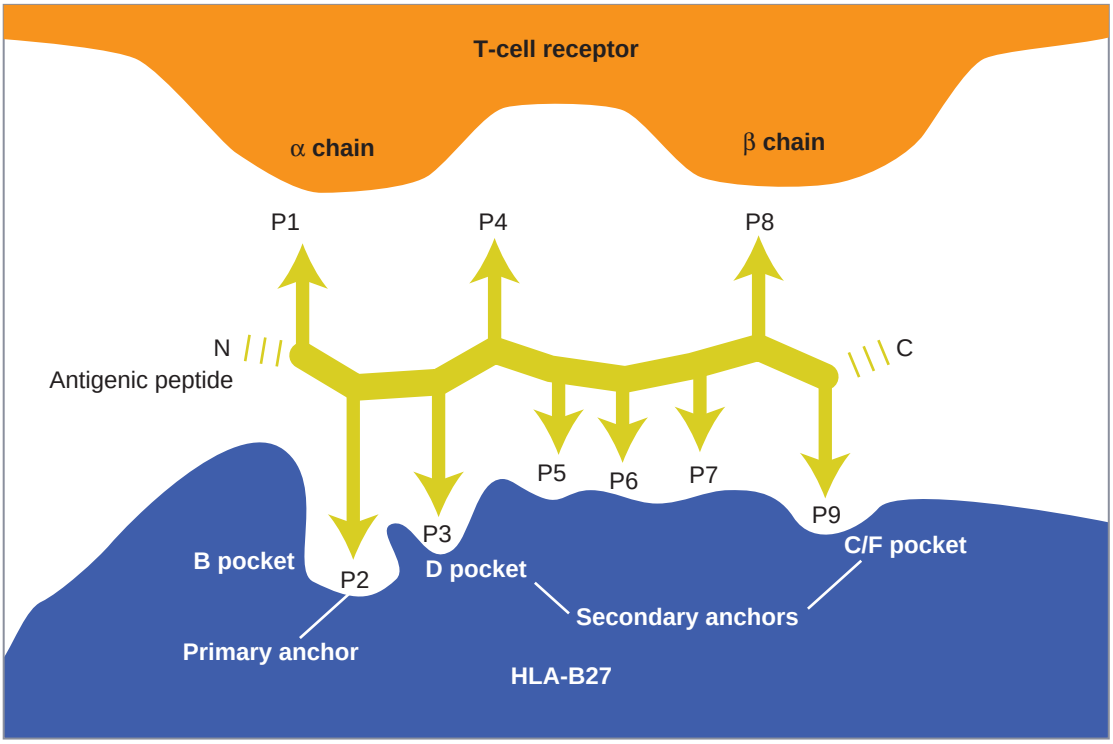

Schematic diagram showing binding of antigenic peptides to HLA-B27 and recognition by the T-cell receptor

Figure 2. Schematic diagram showing binding of antigenic peptides to HLA-B27 and recognition by the T-cell receptor. The side-chains of peptide 'anchor' residues P2, P3 and P9 (C-terminal) are bound in pockets. The side-chains of P1, P4 and P8, which extend out of the peptide-binding groove, are critical for T-cell recognition (Ref. 13) **(fig002pbo)**.

chain of HLA-B27 (Ref. 23). This suggests that cell-surface expression of HLA-B27 H chains not associated with β_2-m is directly involved in disease pathogenesis in at least these animal models.

HLA-B27-restricted T-cell responses ex vivo

It has proved relatively difficult to grow $CD8^+$ CTLs from patients with spondyloarthritis, partly because of the lack of identification of candidate self-antigen(s) that specifically drive and expand these cells. Nevertheless, Hermann and colleagues have isolated and grown CTL clones from the joint fluid of patients with reactive arthritis, and three such clones specifically recognize and kill HLA-B27 targets infected with *Yersinia* and *Salmonella* (Ref. 24). Furthermore, HLA-B27-restricted CTL responses to the 321–329 peptide from *Yersinia* heat shock protein Hsp60 have recently been identified in patients with *Yersinia*-induced reactive arthritis (Ref. 25). However, in general, $CD4^+$, rather than $CD8^+$, T-cell responses to triggering organisms have been found more widely in patients with reactive arthritis (e.g. see Ref. 26).

Evidence that HLA-B27 has an unusual cell biology

The role of HLA-B27 in disease pathogenesis might be explained by some unique feature of its biochemistry or cell biology. Indeed, several lines of evidence suggest that HLA-B27 does not behave like other MHC class I molecules. Benjamin and colleagues have detected 'empty' cell-surface HLA-B27 molecules that were

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relatively stable under physiological conditions and could present exogenously supplied peptides to T cells (Ref. 27). It was suggested that spondyloarthritis might result from the presentation by HLA-B27 of extracellular peptides that were not normally accessible to the MHC class I processing pathway (Ref. 27). Subsequently, a subset of HLA-B27 molecules has been identified that bind unusually long peptides (Ref. 28). This might reflect either an unusual flexibility in the structure of the HLA-B27 peptide-binding groove or perhaps a greater promiscuity in peptide loading. There is also evidence implying that HLA-B27 is capable of unconventional interactions with molecules involved in antigen processing. For example, HLA-B*2705, but not B*4402, is able to form peptide complexes without associating with the peptide transporter TAP. This might result in a greater degree of flexibility in the repertoire of peptides presented by HLA-B27 (Ref. 29).

Evidence that the HLA-B27 Cys67 residue might be involved in disease pathogenesis

As mentioned above, a distinctive feature of HLA-B27 is the presence of an unpaired Cys67 residue within the extracellular α_1 domain (Fig. 1). Although an unpaired Cys residue is also present at position 67 in other HLA-B alleles (such as B14, B38, B39 and B65), the chemical reactivity of Cys67 in HLA-B27 might be altered by the proximity of Lys70, a residue that is unique to HLA-B27 (Ref. 30). Direct evidence for a pathogenic role of Cys67 comes from studies of rats that have been engineered to carry a mutated HLA-B27 transgene in which Cys67 is changed to Ser67; these animals appear less susceptible to arthritis (Ref. 31).

How might Cys67 predispose to arthritis? Three mechanisms, which are not mutually exclusive, seem plausible. First, Cys67 might be chemically modified under certain conditions to alter the antigenicity of HLA-B27 (Ref. 32). Second, a similar chemical modification might alter the peptide-binding properties of HLA-B27 (Ref. 33). Last, the presence of Cys67 might be responsible for unusual features in the cell biology of HLA-B27, such as the ability to dimerise (described below). Interestingly, despite its position at the 'mouth' of the B pocket of the peptide-binding groove (Fig. 1b), Cys67 does not seem to play an essential role in the presentation of peptide to T cells (e.g. see Ref. 34).

HLA-B27 can form H-chain homodimers in vitro and in vivo

A potential pathogenic role for HLA-B27 Cys67 has been highlighted by a recent study showing that HLA-B27 can form H-chain homodimers that are not associated with β_2-m (Ref. 35). This study demonstrates that dimerisation of truncated HLA-B27 molecules in vitro is dependent on disulphide bonding through Cys67. Despite the absence of β_2-m, this novel homodimeric form (HC-B27) maintains some functional conformation of its peptide-binding groove and is capable of binding peptide. HC-B27 is recognised by the mAb W6/32, which recognises a conformation-specific epitope on HLA class I molecules, and by the HLA H-chain-specific mAb HC10 (Ref. 36), but not by the mAb ME1 that recognises a conformational epitope in the region of the HLA-B27 Cys67 (Ref. 37). The acquisition of the HC10 epitope on HC-B27 implies partial unwinding of the α_1 helix of HLA-B27 around Arg62, and the loss of ME1 antibody reactivity suggests a structural change in the region surrounding Cys67. Unwinding of the α_1 helix might enable the binding of an altered repertoire of antigenic peptides to HLA-B27, and these might be longer at their N-termini compared with most peptides bound to MHC class I. In addition, a partially unwound α_1 helix might resemble the α-chain helix of an MHC class II molecule, and provoke recognition by $CD4^+$ T cells. Although it has previously been documented that the mouse MHC class I allele $H\text{-}2D^b$ can retain its antigen-presenting function in the absence of β_2-m, HLA-B27 might be unique among human MHC class I alleles in its ability to bind peptide and remain W6/32 reactive in the absence of β_2-m.

Molecular model of HC-B27

These observations were investigated further by building a hypothetical model of the HC-B27 HLA-B27 dimer (Fig. 3; N. Zaccai and E.Y. Jones, unpublished). The model was based on the crystal structure of the extracellular region of HLA-B27 (Ref. 38). In the β_2-m-associated HLA-B27 structure (shown in Fig. 1), residue Cys67 lies buried in the wall of the B pocket of the peptide-binding groove. To form a disulphide-linked homodimer of two H chains, the conformation of Cys67 and its immediate environment had to be altered by interactive modelling – computer graphics followed by molecular dynamics – to expose the Cys67 side-chain (shown in red in

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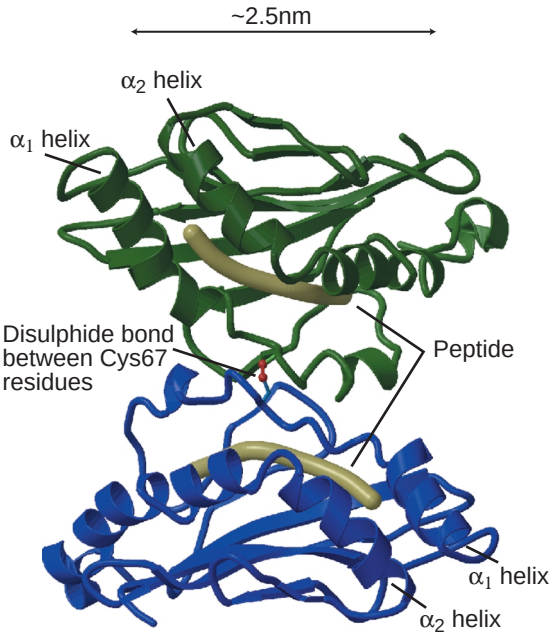

Model of the HC-B27 HLA-B27 heavy-chain homodimer

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Figure 3. Model of the HC-B27 HLA-B27 heavy-chain homodimer. The view of the HC-B27 homodimer is rotated by approximately 90° relative to Figure 1, as if looking down towards the cell surface. The α_1 and α_2 domains of the two HLA-B27 heavy chains are depicted in ribbon representation (copy 1 and copy 2 of the heavy chain in blue and green, respectively). The disulphide bond between the two Cys67 residues is coloured red and the (putative) bound peptides are depicted schematically as yellow tubes. The model was created with HLA-B27 crystal structure coordinates using the interactive computer graphics program O (Ref. 44) and the molecular dynamics program X-PLOR (Ref. 45). The most favourable relative orientation of the HLA-B27 heavy chains was assessed by rotation (in 5° increments about the disulphide bond) of one of the two heavy-chain copies. At each increment, a rigid body minimisation, followed by individual atom positional refinement, was run using standard X-PLOR protocols. The figures were produced using the programs BobScript (Ref. 42) and Raster3D (Ref. 43) **(fig003pbo)**.

Fig. 3). In its energetically most favourable form, the resulting HC-B27 model consists of the two HLA-B27 H chains aligned in parallel, in an arrangement that is compatible with both chains being 'tethered' to the cell surface. The stability of this structure is provided by the formation of a continuous β sheet between the two HLA-B27 molecules (the two copies of the β strand comprising residues 36–43 form hydrogen bonds across the dimer interface; Fig. 3).

The α-helical conformation of the α_1 helix in the region of Cys67 could not be preserved during modelling of HC-B27. This model thus concurs with the experimental evidence that a region of the α_1 helix encompassing Arg62 and Cys67 is altered in HC-B27 (Ref. 35). The HC-B27 model retains all the structural features required for both copies of the HLA-B27 to bind peptide; however, the model does display some deformation of the binding grooves. In particular, the B pocket is necessarily altered because of the displacement of the Cys67 side-chain. Clearly, such changes could alter the peptide-binding repertoire of HC-B27 and could therefore be of pathogenic relevance. Strikingly, however, the relative orientation of the two peptide-binding grooves would preclude the binding of TCRs, as currently understood for the 'footprint' mapped out in the TCR–MHC class I structures determined to date (e.g. see Ref. 39). This argues against classical TCRαβ-mediated recognition of HC-B27, and it will be important to look for evidence of recognition by γδ T cells, natural killer (NK) receptors or other ligands.

HC-B27 homodimers and disease pathogenesis: clinical implications

HC-B27 homodimers have been demonstrated in cell lines (Ref. 35), although not yet in patients or HLA-B27-transgenic animals. It is possible that HC-B27 expression in vivo might only occur under particular conditions, which might explain why not all HLA-B27$^+$ humans and animals develop disease. One possible mechanism by which expression of HC-B27 could lead to joint inflammation is by the presentation of peptides to either CD4$^+$ or CD8$^+$ T cells. Our molecular model suggests that TCRs would probably not be able to 'dock' with HC-B27 using exactly the same footprint described recently for several classical MHC class I-restricted responses (Ref. 39). Alternatively, HC-B27 might be a ligand for NK receptors (Ref. 40) or other receptors, or it might be the target of an autoantibody response. If expression of an aberrant form of HC-B27 has a pathogenic role in disease, the future development

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of a mAb that recognises HC-B27 could be valuable for research, disease diagnosis and monitoring, and therapy. Rationally designed therapy could also be directed to inhibit formation of HC-B27 (perhaps by modifying intracellular conditions in antigen-presenting cells) or against downstream effector molecules of disease such as cytokines.

Summary

Although the role of HLA-B27 in the pathogenesis of the spondyloarthropathies still remains obscure, its central role has been confirmed by studies of transgenic rodents. Structural studies have shown that particular molecular features of the HLA-B27 peptide-binding groove dictate a unique and strong preference for antigenic peptides with an Arg residue at their second position (Arg P2). HLA-B27-restricted presentation of 'arthritogenic' peptides might be involved in disease pathogenesis; however, evidence from studies using transgenic mice has implicated HLA-B27 H chains acting at the cell surface in the absence of β_2-m. HLA-B27 H chains can form homodimers that are disulphide-bonded through Cys67 and are not associated with β_2-m. Although the conditions required for HC-B27 homodimer formation in vivo have not yet been ascertained, HC-B27 formation could both explain the murine data and suggest novel pathogenic mechanisms.

Research in progress

Understanding of the role of HLA-B27 in disease pathogenesis is likely to be rapidly advanced by research in three key areas. First, HLA-B27-transgenic animal models of spondyloarthropathy are being used to dissect the pathogenic roles of various cell types in this disease (e.g. see Refs 7, 41). The types of T cells involved in disease should be determined by transducing or 'knocking out' various genes, as well as by cell-transfer experiments. Second, it is important to confirm the epidemiological studies suggesting that not all HLA-B27 subtypes are associated with spondyloarthropathy. Finally, studies are ongoing to elucidate the cell biology of HLA-B27 in antigen presentation and, in particular, the conditions leading to HC-B27 homodimer formation and its consequences. This may identify cellular targets for pharmacological or immunological intervention in these diseases.

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References

1 Brewerton, D.A. et al. (1973) Ankylosing spondylitis and HL-A 27. Lancet 1, 904-907, PubMed ID:73214579
2 Brown, M.A. et al. (1996) HLA class I associations of ankylosing spondylitis in the white population in the United Kingdom. Ann Rheum Dis 55, 268-270, PubMed ID:96297335
3 Benjamin, R. and Parham, P. (1990) Guilt by association: HLA-B27 and ankylosing spondylitis. Immunol Today 11, 137-142, PubMed ID:90253570
4 Lahesmaa, R. et al. (1992) Molecular mimicry in the pathogenesis of spondyloarthropathies. A critical appraisal of cross-reactivity between microbial antigens and HLA-B27. Br J Rheumatol 31, 221-229, PubMed ID:92208647
5 Davenport, M.P. (1995) The promiscuous B27 hypothesis. Lancet 346, 500-501, PubMed ID:95364519
6 Marker-Hermann, E., Meyer zum Buschenfelde, K.H. and Wildner, G. (1997) HLA-B27-derived peptides as autoantigens for T lymphocytes in ankylosing spondylitis. Arthritis Rheum 40, 2047-2054, PubMed ID:98030377
7 Khare, S.D. et al. (1998) Spontaneous inflammatory disease in HLA-B27 transgenic mice is independent of MHC class II molecules: a direct role for B27 heavy chains and not B27-derived peptides. J Immunol 160, 101-106, PubMed ID:98211687
8 Townsend, A.R. et al. (1986) The epitopes of influenza nucleoprotein recognized by cytotoxic T lymphocytes can be defined with short synthetic peptides. Cell 44, 959-968, PubMed ID:86161685
9 Madden, D.R. et al. (1991) The structure of HLA-B27 reveals nonamer self-peptides bound in an extended conformation. Nature 353, 321-325, PubMed ID:92018187
10 Jardetzky, T.S. et al. (1991) Identification of self peptides bound to purified HLA-B27. Nature 353, 326-329, PubMed ID:92018188
11 Rotzschke, O. et al. (1994) Dominant aromatic/aliphatic C-terminal anchor in HLA-B*2702 and

Accession information: (99)00111-8a.pdf (short code: txt001pbo); 26 October 1999
ISSN 1462-3994

B*2705 peptide motifs. Immunogenetics 39, 74-77, PubMed ID:94041470
12 Tanigaki, N. et al. (1994) The peptide binding specificity of HLA-B27 subtypes. Immunogenetics 40, 192-198, PubMed ID:94314367
13 Bowness, P., Allen, R.L. and McMichael, A.J. (1994) Identification of T cell receptor recognition residues for a viral peptide presented by HLA B27. Eur J Immunol 24, 2357-2363, PubMed ID:95010249
14 Lopez de Castro, J.A. (1998) The pathogenetic role of HLA-B27 in chronic arthritis. Curr Opin Immunol 10, 59-66, PubMed ID:98183714
15 Lopez-Larrea, C. et al. (1995) HLA-B27 subtypes in Asian patients with ankylosing spondylitis. Evidence for new associations. Tissue Antigens 45, 169-176, PubMed ID:95282144
16 D'Amato, M. et al. (1995) Relevance of residue 116 of HLA-B27 in determining susceptibility to ankylosing spondylitis. Eur J Immunol 25, 3199-3201, PubMed ID:96085198
17 Fiorillo, M.T. et al. (1997) Susceptibility to ankylosing spondylitis correlates with the C-terminal residue of peptides presented by various HLA-B27 subtypes. Eur J Immunol 27, 368-373, PubMed ID:97197610
18 Hammer, R.E. et al. (1990) Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human beta 2m: an animal model of HLA-B27-associated human disorders. Cell 63, 1099-1112, PubMed ID:91077923
19 Breban, M. et al. (1993) Transfer of the inflammatory disease of HLA-B27 transgenic rats by bone marrow engraftment. J Exp Med 178, 1607-1616, PubMed ID:94045447
20 Taurog, J.D. et al. (1993) Susceptibility to inflammatory disease in HLA-B27 transgenic rat lines correlates with the level of B27 expression. J Immunol 150, 4168-4178, PubMed ID:93232623
21 Breban, M. et al. (1996) T cells, but not thymic exposure to HLA-B27, are required for the inflammatory disease of HLA-B27 transgenic rats. J Immunol 156, 794-803, PubMed ID:96133010
22 Khare, S.D., Luthra, H.S. and David, C.S. (1995) Spontaneous inflammatory arthritis in HLA-B27 transgenic mice lacking beta 2-microglobulin: a model of human spondyloarthropathies. J Exp Med 182, 1153-1158, PubMed ID:96018814
23 Khare, S.D. et al. (1996) HLA-B27 heavy chains contribute to spontaneous inflammatory disease in B27/human beta2-microglobulin (beta2m) double transgenic mice with disrupted mouse beta2m. J Clin Invest 98, 2746-2755, PubMed ID:97136519
24 Hermann, E. et al. (1993) HLA-B27-restricted CD8 T cells derived from synovial fluids of patients with reactive arthritis and ankylosing spondylitis. Lancet 342, 646-650, PubMed ID:93368296
25 Ugrinovic, S. et al. (1997) A single nonamer from the Yersinia 60-kDa heat shock protein is the target of HLA-B27-restricted CTL response in Yersinia-induced reactive arthritis. J Immunol 159, 5715-5723, PubMed ID:98208296
26 Gaston, J.S. et al. (1996) Identification of 2 Chlamydia trachomatis antigens recognized by synovial fluid T cells from patients with Chlamydia induced reactive arthritis. J Rheumatol 23, 130-136, PubMed ID:96435635
27 Benjamin, R.J., Madrigal, J.A. and Parham, P. (1991) Peptide binding to empty HLA-B27 molecules of viable human cells. Nature 351, 74-77, PubMed ID:91226541
28 Urban, R.G. et al. (1994) A subset of HLA-B27 molecules contains peptides much longer than nonamers. Proc Natl Acad Sci U S A 91, 1534-1538, PubMed ID:94151364
29 Peh, C.A. et al. (1998) HLA-B27-restricted antigen presentation in the absence of tapasin reveals polymorphism in mechanisms of HLA class I peptide loading. Immunity 8, 531-542, PubMed ID:98281996
30 Whelan, M.A. and Archer, J.R. (1993) Chemical reactivity of an HLA-B27 thiol group. Eur J Immunol 23, 3278-3285, PubMed ID:94080894
31 Maclean, L., Hammer, R. and Taurog, J. (eds) (1997) Cytokine profiles and site-directed B27 mutation in the HLA-B27 transgenic rat. Proceedings of the 12th International Histocompatibility Workshop, EDK
32 MacLean, L. et al. (1992) Sulphydryl reactivity of the HLA-B27 epitope: accessibility of the free cysteine studied by flow cytometry. Ann Rheum Dis 51, 456-460, PubMed ID:92264822
33 Gao, X.M. et al. (1996) Homocysteine modification of HLA antigens and its immunological consequences. Eur J Immunol 26, 1443-1450, PubMed ID:96305398
34 Bowness, P. et al. (1998) Importance of a conserved TCR J alpha-encoded tyrosine for T

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ISSN 1462-3994 ©1999 Cambridge University Press

cell recognition of an HLA B27/peptide complex. Eur J Immunol 28, 2704-2713, PubMed ID:98425529
35 Allen, R.L. et al. (1999) Cutting edge: HLA-B27 can form a novel beta 2-microglobulin-free heavy chain homodimer structure. J Immunol 162, 5045-5048, PubMed ID:99244860
36 Stam, N.J., Spits, H. and Ploegh, H.L. (1986) Monoclonal antibodies raised against denatured HLA-B locus heavy chains permit biochemical characterization of certain HLA-C locus products. J Immunol 137, 2299-2306, PubMed ID:87009876
37 Ellis, S.A., Taylor, C. and McMichael, A. (1982) Recognition of HLA-B27 and related antigen by a monoclonal antibody. Hum Immunol 5, 49-59, PubMed ID:83006626
38 Madden, D.R. et al. (1992) The three-dimensional structure of HLA-B27 at 2.1 A resolution suggests a general mechanism for tight peptide binding to MHC. Cell 70, 1035-1048, PubMed ID:92405152
39 Garboczi, D.N. et al. (1996) Structure of the complex between human T-cell receptor, viral peptide and HLA-A2. Nature 384, 134-141, PubMed ID:97064169
40 Lanier, L.L. (1998) Follow the leader: NK cell receptors for classical and nonclassical MHC class I. Cell 92, 705-707, PubMed ID:98188095
41 Zhou, M. et al. (1998) The specificity of peptides bound to human histocompatibility leukocyte antigen (HLA)-B27 influences the prevalence of arthritis in HLA-B27 transgenic rats. J Exp Med 188, 877-886, PubMed ID:98401022
42 Esnouf, R.M. (1997) An extensively modified version of MolScript that includes greatly enhanced coloring capabilities. J Mol Graph Model 15, 132-134, 112-133, PubMed ID:98046670
43 Merritt, E.A. and Murphy, M.E.P. (1994) Raster 3D version 2.0. A program for photorealistic molecular graphics. Acta Crystallogr A 50, 869-873
44 Jones, T.A. et al. (1991) Improved methods for binding protein models in electron density maps and the location of errors in these models. Acta Crystallogr A 47, 110-119, PubMed ID:91222453
45 Brunger, A.T. (1992) X-PLOR Manual. Yale University, New Haven, CT, USA

Further reading, resources and contacts

Taurog, J.D. et al. (1999) Inflammatory disease in HLA-B27 transgenic rats. Immunol. Rev. 169, 209-223, PubMed ID:10450519

Calin, A. and Taurog, J.D. (eds) (1998) The Spondylarthritides, Oxford University Press, Oxford.

The Arthritis Research Campaign (ARC) is the fifth biggest medical research charity in the UK, and the only charity in the country dedicated to finding the cause of, and cure for, arthritis. Their website details the purpose and work of the ARC, cites cutting edge research funded by the ARC, and is supported by a comprehensive index to help find subjects of interest to the reader.
http://www.arc.org.uk/

The National Ankylosing Spondylitis Society (NASS), based in the UK, is a support group for individuals with ankylosing spondylitis. The society also provides an educational resource for the social and medical management of the disease, and supports and funds a modest amount of research.
http://nass.co.uk/

Features associated with this article

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