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The pathogenetic role of HLA-B27 and its subtypes

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Abstract

The strong association between HLA-B27 and ankylosing spondylitis has been known for 33 years, but the enigma of the pathogenetic role of the gene and its product has not yet been solved. Ongoing studies have produced evidence supporting different theories to explain this association, and structural and functional studies of HLA-B27 allele products at molecular level have provided information of broad and multidisciplinary value and disclosed new avenues leading to autoimmunity and immune disregulation.
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Keywords: Animal models; Ankylosing spondylitis; HLA-B27; Pathogenesis

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The remarkably strong association of ankylosing spondylitis (AS) with HLA-B27 was first described in 1973. Since then, a tremendous amount of literature has been produced, yet the issue remains as puzzling as ever. The epidemiological studies have shown that this association holds true almost worldwide, and that AS prevalence in general mirrors the HLA-B27 distribution, with peaks in those populations with highest prevalence of HLA-B27, and the disease is very rare in sub-saharian African populations where HLA-B27 is virtually absent [1].

HLA-B27 is directly involved in AS but it seems to contribute only about 16% of the total genetic risk in this

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disease [2]. There are non-B27 genes, both within and outside the major histocompatibility complex (MHC), that also seem to be involved in disease etiology. This aspect has been reviewed elsewhere [3–7].

A direct role for HLA-B27 molecules in disease pathogenesis has also emerged from animal models showing that rats transgenic for HLA-B27 develop an inflammatory arthritis reminiscent of HLA-B27 associated diseases [8,9].

The crystallographic structure of HLA-B27, solved by Madden et al. [10], has shown that this molecule is, as expected, heterodimeric, composed of the HLA-B alpha (heavy) chain (encoded in the MHC Class I region on the short arm of chromosome 6) non-covalently linked with beta 2-microglobulin (β2m). HLA-B27 has a peptide-binding cleft (formed by the alpha 1 and alpha 2 domains of the alpha chain) that has six side-pockets (designated by the letters A through F) that accommodate the side chains of the amino acids of the bound nonamer peptides. HLA-B27 binds and presents peptides to CD8+ T cells with high efficiency and is associated with comparatively better protection from viral diseases, such as influenza or AIDS [11,12], than other HLA alleles. Therefore, it seemed logical to concentrate in the antigen presenting properties of HLA-B27 in order to understand its possible role in disease pathogenesis.

1. Molecular mimicry hypothesis

Molecular mimicry between foreign and self-peptide has been proposed as the cause that could unleash a cytotoxic T cell response leading to the autoimmune destruction of self-tissues [13]. A number of bacterial species have been evoked as a source of this cross-reactivity, and "arthritogenic" peptides and bacterial-specific as well as self-reactive HLA-B27-restricted cytotoxic T lymphocytes have been described in patients with reactive arthritis (ReA) and AS [14]. HLA-B27 is not a single allele but a family of at least 31 different alleles, named HLA-B*2701 to HLA-B*2728 (Table 1), that may have evolved from the most widespread subtype, B*2705 [15,16].These subtypes, whose frequency in the worldwide population is extremely variable (Table 2), differ from each other by one or a few amino acids, and they bind overlapping peptide repertoires [17] Worldwide population-based studies indicate that, among the widely distributed subtypes, HLA-B* 2702, B*2704, and B*2705 are strongly associated with AS [16–18].

A strong support to the molecular mimicry theory has been the finding that at least two alleles, HLA-B* 2706, quite common among B27 positive individuals in Southeast Asia and HLA-B*2709, primarily observed in Sardinia, an Italian island, lack such an association with AS [18,19]. The reason for the differential disease association is not understood. This may be due to the absence of additional susceptibility genes co-inherited with B*2709 or B*2706, and/or to different antigen binding properties of these two subtypes [20,21]. B* 2705 differs from B*2709 only in residue 116 of the heavy chain (Asp in B*2705 and His in B*2709) (D116H), and B*2704 differs from B*2706 by amino acid changes at only two residues, 114 and 116 of the heavy chain [21,22]. Both these residues are known to influence peptide specificity and T cell recognition as they are located at the floor of the peptide-binding groove, forming part of the F-pocket, and they get buried as a result of binding of a peptide. The differences at residues 114 and 116 result in differential binding of antigenic peptides; B*2705 shares 79% of its peptide repertoire with B*2709 and there is 88% repertoire sharing between B*2704 and B*2706 [21,22]. In the frame of the "arthritogenic" peptide hypothesis, B*2705-positive patients with AS possess precursor T cells specific for a well-defined self-peptide pVIPR (from the vaso-active intestinal peptide receptor 1), encoded by the VPAC1 gene mapping on chromosome 3, whereas B*2709-positive individuals lack such a

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Table 1
Currently identified HLA-B27 subtypes (Ref. [17], modified)

B*2701[a]		B*2712
B*2702		B*2713
B*270[b]	B*2703[b]	B*2714[a]
B*2704		B*2715
B*2705		B*2716
	B*270502	B*2717
	B*270503	B*2718
	B*270504	B*2719[a]
	B*270505	B*2720
	B*270506	B*2721
	B*270507	B**2723
B*2706[e]		B*2724
B*2707[c]		B*2725
B*2708[d]		B*2726
B*2709[c]		B*2727
B*2710[a]		B*2728
B*2711		

B*2723

B*2702, B*2704, B*2705, B*2707 and B*2708 should be typed in bold

Note that HLA-B*2722 is not listed as this designation has been withdrawn when subsequent studies showed its identity to HLA-B*2706.

The B27 alleles shown in bold type are associated with AS.

[a] The disease occurrence in at least one patient with these alleles was shown, but needs association studies.

[b] Disease association is controversial.

[c] Suggested to be disease associated; but not in Greek Cypriots.

[d] Reported to be disease associated, but not in Venezuela.

[e] These alleles seem not to have an association with the disease.

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Table 2
HLA-B27 subtype frequencies (%) among individuals possessing HLA-B27 in different world populations (Ref. [17], modified)

Populations	*2701	*2702	*2703	*2704	*2705	*2706	*2707	*2708	*2709	*2711	*2713	*2714
Northern Europe		10			90							
Denmark		10			90							
Southern Europe		20			80							
Spain (Galicia)		18			80			3				
Northern Spain		7			91		1				1	
Azores			7		86		7					
Italy		30			65		2		3			
Sardinia		3			77				20			
Greece		34	8		50		8					
Cyprus (Greeks)		52			32		17					
Turkey	7	30			43		14	5				
Lebanon		24	12		35		30					
Jewish		48		3	38		13					
Siberia		14			84							2
Northern India				33	61		6					
Western India				34.	34		18	12				2
Japan				82	18							
Chinese		2		66	31		2					
Singapore (Chinese)				89	2	9						
Taiwan	0.05	0.5	3	87	4	7	2	0.02		0.02		
Taiwan (Han-Chinese)				94	6							
Taiwan (Aborigines)				100								
Chinese Indonesian				38		62						
Native Indonesians				6	6	89						
Malays				19	6	72	3					
Thailand				42	5	53						
Maoris				36	64							
Brazil		10	6		80		3				<1	
North Africa		50			50							
West Africans			32		68							

The numbers are rounded off for simplicity and indicate percentages in healthy controls. Only the first 14 subtypes of HLA-B27 are shown; the other subtypes are much more rare.

reactivity [23]. X-ray crystallography has then shown that the B*2705 binds the pVIPR peptide in two distinct conformations, whereas B*2709 presents the same peptide in only one of the two conformations [23]. This suggests that this dual conformation of the peptide bound to B*2705 could be responsible for a less efficient negative selection (during ontogenesis in the thymus) in B*2705 positive individuals [23].

This hypothesis was further supported by the finding that a viral peptide pLMP2 (derived from latent membrane protein 2 (residues 236–244) of Epstein–Barr virus) is presented by the B*2705 and B*2709 molecules in two drastically deviating conformations [24]. Interestingly, pLMP2, when bound to B*2705, displays a conformation very similar to that unique to the B*2705/pVIPR [23,24]. Thus molecular mimicry between a viral and a self-peptide could trigger a cross-reactive cytotoxic T cell response that activates those clonotypes which have not been eliminated during ontogenesis in the thymus (Fig. 1) [23,24].

Interestingly, another self-peptide, pGR, that is derived from glucagon receptor and shares homology with pVIPR and pLMP2, also displays a dual conformation (conformational dimorphism) when bound to B*2705 [25]. Therefore, there seems to be an array of peptides that share this property of conformational dimorphism, and they might unleash a potentially dangerous autoimmune response. Moreover, the conserved structural features of these peptides suggest that their N-terminal halves are crucial for the emergence of cytotoxic T lymphocytes and resultant autoimmunity [25]. Recent studies have also provided additional explanations for the differential disease association between B*2705 and B*2709. For example, an increased flexibility of the peptide in the binding groove of B*2709 due to weaker interactions in the F pocket, might impact T cell recognition and signaling [26]. Molecular dynamics simulations show increased flexibility of a model peptide GRFAAAIAK in the groove of the B*2709 but not of B*2705, despite the

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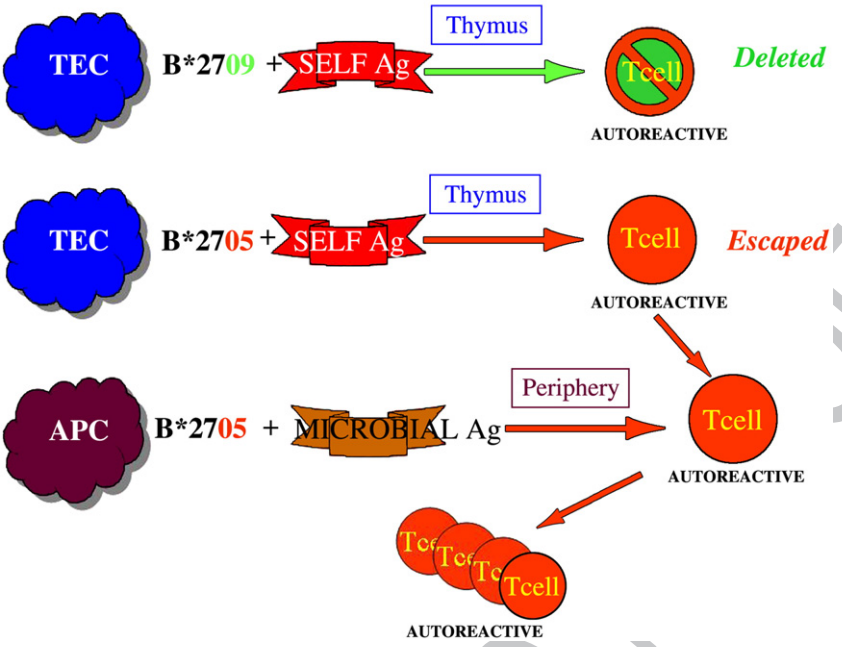

Fig. 1. Illustration of the hypothesis for the pathogenetic role of HLA-B*2705 molecules in the development of ankylosing spondylitis [Refs. 21,24]. The ''canonical'' or ''non canonical'' conformation of a self-peptide presented by B*2709 or B*2705 molecules, may be critical in determining respectively deletion or escape from negative selection of autoreactive T cells in the thymus. Persistence of autoreactive T cells in the adult in B*2705 positive subjects may lead to cross-reaction with a homologous microbial antigen. Ag: antigen; APC: antigen presenting cell; TEC: thymic epithelial cell.

essentially identical crystallographic conformation of these two subtypes.

Presentation by HLA-B27 of a peptide derived from its own molecule (from a region that is not polymorphic among HLA-B molecules) has been reported [27]. This peptide, B27-(309–320), has a strong homology to proteins from *Chlamydia trachomatis* and other arthritogenic bacteria, and is a natural ligand of 3 AS-associated subtypes, B*2705, B*2702, and B*2704, but not of the 2 subtypes, B*2706 and B*2709, not associated with this disease [27].

These studies have brought new information on how structural mimicry can lead to auto-reactivity in HLA-B*2705 positive individuals. However they do not explain the tissue specificity observed in the HLA-B27 associated diseases. Recently, HLA-B27-restricted epitopes derived from human aggrecan have been described [28,29]. It has been suggested that cartilage-directed cellular autoimmunity might play an important role in joint-specific tissue damage in patients with AS [29].

A characteristic finding in AS is inflammation of cartilage structures of the joints, and in particular at the sites of attachment of ligaments/tendons to bone (entheses), which are quite characteristic targets of inflammation (enthesitis) in AS. Aggrecan is present in such fibro-cartilaginous regions and is an interesting candidate for a potential target of autoimmunity. However, its role in the pathogenesis of AS is still uncertain and its HLA-B27 subtype-specificity has not been explored.

2. Other pathogenetic hypotheses

(unfolded protein response) should be inserted

There is also a growing interest in biological mechanisms other than those centered largely on the physiological peptide-presenting function of HLA-B27, and include ideas based on aberrant aspects of its immunobiology [30]. HLA-B27 heavy chain is unusual in that it has a tendency to misfold in the endoplasmic reticulum and to form disulfide linked heavy chain homodimers that can be expressed on the cell surface [30]. It has been hypothesized that HLA-B27 contributes to AS through an excess of misfolding, formation of heavy chain dimers, and interaction with receptors of innate immunity [31].

In a rat model of spondyloarthropathies, an activation of the UPR in macrophages has been reported to correlate with the inflammatory process [32]. The protein misfolding can be due to an excess of unpaired

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HLA-B27, such as in case of an unbalance of β2m and HLA-B27. This seems to correlate with the observation that, to develop the disease, a high level of expression of the human B27 transgene is required in rats [33]. In agreement with this observation, an increased expression of B27 molecule has been found on peripheral blood mononuclear cells of AS patients [34]. However, a new B27-transgenic rat model for spondyloarthritis has just been reported that does not support a role for B27 misfolding and resultant activation of the UPR in spondylitis [9]. These investigators speculate that gut inflammation (that occurs in many AS patients), on the other hand, may result from B27-misfolding and triggering of the UPR leading to the unusual intracellular persistence of gut bacteria [9].

The presence of non-conventional HLA-B27 homodimers on cell surface has also been evoked as a possible trigger of pathogenic immune responses [35]. MHC restriction indicates that CD8+ T cells conventionally interact with MHC class I molecules and CD4+ T cells interact with MHC class II molecules. However, CD4+ T cells have been isolated from 3 HLA-B27 positive patients with AS that interact with HLA-B27, an MHC class I molecule, but are not present in B27 positive healthy individuals, thus breaking the conventional rules of MHC restriction [36]. These T cells recognized an unconventional form of HLA-B27 in that some CD4+ T cells appear to recognize unfolded B27 heavy chain homodimers, while others recognize empty heterodimers. Therefore these authors speculate that the CD4+ T cells may be reacting to non-conventional forms of HLA-B27, specifically B27 heavy chain homodimers that might mimic MHC class II molecules and are recognized by CD4+ T cells. It is possible that continual interaction between the two could trigger off T cell effector functions that may initiate the disease process.

Another hypothesis has proposed that a helix-coil transition in a key region of the β2m-free, peptide-free B27 heavy chain predisposes this portion of the molecule to loop around [37]. This allows residues 168–181 to bind as a ligand to the sequence of the empty peptide-binding cleft, resulting in auto-displaying (within or between B27 molecules) and appearing as a foreign peptide to T cells [37]. Uchanska-Ziegler and Ziegler [38] have proposed that AS is a β2m-deposition disease, and suggest that B27 subtypes associated or not associated with AS differ for their rate of β_2m-dissociation from peptide-complexed B27 molecules expressed on the cell membrane. β2m would be trapped in the synovia where it would form amyloid substance able to induce a local inflammation; the subsequent hyperexpression of the HLA class I molecule by resident and infiltrating cells might allow the perpetuation of β2m deposition and of the inflammatory process.

Natural Killer (NK) cells possess receptors on their surface which interact with HLA-B27. In the HLA-B27 rat transgenic model, homodimers of heavy chains are ligands for immunoglobulin-like receptors expressed by lymphocytes, monocytes and dendritic cells [31] suggesting that the unusual property of HLA-B27 molecules of forming homodimers may orchestrate an inflammatory response activating different cells.

A further hypothesis proposes that HLA-B27 may modify microbial handling and impair immunity resulting in defective immune response [39]. The ability of HLA-B27 to confer susceptibility to *Salmonella*-triggered reactive arthritis may occur, at least in part, through these modulatory effects that result in an impaired capacity of monocytes to resist intracellular replication of *Salmonella enteritidis*. This effect may be due to properties of the HLA-B27 heavy chain that are dependent on glutamic acid at position 45 in the B pocket [39]. In addition to this, an impaired immune response to bacteria may be also due to a reduced ability by B27-positive AS patients to express TNFα [40].

3. Concluding remarks

The precise biological explanation for the remarkable association between HLA-B27 and AS, after more than 30 years of intense studies still remains elusive. Although, exploiting the technical advancements of the last few decades, more and more sophisticated approaches have been undertaken, no definitive results are as yet available. The more conservative hypothesis postulates that presentation of "arthritogenic" peptides shared by microbial- and self-epitopes could be responsible for the autoimmune cascade leading to AS. Such a hypothesis has found strong support from the findings that some HLA-B27 subtypes do not associate with AS and that this correlates with functional differences between these B27 molecules.

The focus of research in the past few years has shifted away from the one centered largely on the physiological peptide-presenting function of HLA-B27 to include ideas based on aberrant aspects of its immunobiology. A number of special features of the HLA-B27 molecules have been reported that could be connected with the inflammatory cascade and autoimmunity. These include: expression of free heavy chains on cell surface (that can results in heavy chain homodimer formation, increased misfolding of the heavy chains inside the endoplasmic reticulum with resultant stress response, the possibility of an exposure of self-epitope by altered HLA-B27

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molecules on the cell surface, and the recent finding of CD4+ T cell reactivity. These CD4+ T cells may be reacting to non-conventional forms of HLA-B27, specifically B27 heavy chain homodimers that might mimic MHC class II molecules and are thus recognized by CD4+ T cells. The free heavy chain homodimers can also be bound by Ig-like receptors exposed on the surface of cells of the innate immunity. There is increasing interest lately on potential pathological role of innate immunity in AS and related spondyloarthropathies.

In conclusion, the conundrum of this remarkable association of HLA-B27 with AS, that was first reported 33 years ago, still remains as puzzling as ever and it continues to challenge our minds. Meanwhile, valuable information has been uncovered that has disclosed new avenues leading to autoimmunity and immune disregulation.

Take-home messages

- World AS prevalence in general mirrors HLA-B27 distribution.
- HLA-B27 is not a single allele but a family of at least 31 different alleles, named HLA-B*2701 to HLA-B*2728.
- Worldwide population-based studies indicate that, among the widely distributed subtypes, HLA-B*2702, B*2704, and B*2705 are strongly associated with AS.
- At least two alleles, HLA-B*2706 common among in Southeast Asia and HLA-B*2709 primarily observed in Sardinia, lack such an association with AS.
- There are non-B27 genes, both within and outside the major histocompatibility complex (MHC), that also seem to be involved in disease etiology.

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