Review

Aetiology and pathogenesis of reactive arthritis: role of non-antigen-presenting effects of HLA-B27

Sanna Vähämiko, Markus A Penttinen and Kaisa Granfors

Department of Bacterial and Inflammatory Diseases, National Public Health Institute, Turku, Finland

Corresponding author: Kaisa Granfors, kaisa.granfors@ktl.fi

Published: 26 May 2005
This article is online at http://arthritis-research.com/content/7/4/136

Arthritis Research & Therapy 2005, **7**:136-141 (DOI 10.1186/ar1762)

Abstract

Spondyloarthropathies are inflammatory diseases closely associated with human leukocyte antigen (HLA)-B27 by unknown mechanisms. One of these diseases is reactive arthritis (ReA), which is typically triggered by Gram-negative bacteria, which have lipopolysaccharide as an integral component of their outer membrane. Several findings *in vivo* and *in vitro* obtained from patients with ReA and from different model systems suggest that HLA-B27 modulates the interaction between ReA-triggering bacteria and immune cells by a mechanism unrelated to the antigen presentation function of HLA-B27. In this review we piece together a jigsaw puzzle from the new information obtained from the non-antigen-presenting effects of HLA-B27.

Introduction

The association between a group of rheumatic diseases called spondyloarthropathies (SpA) and human leukocyte antigen (HLA)-B27 has been known for several decades [1,2]. Several theories have been proposed to clarify the pathogenic role of HLA-B27 [3-7], many of them based on the idea that classical function of HLA-B27, antigen presentation to T cells, is somehow abnormal and leads to the development of inflammatory diseases. However, the proposed theories about altered antigen presenting effects of HLA-B27 have not yielded a widely accepted and comprehensive explanation of the association of HLA-B27 and SpA.

Reactive arthritis (ReA) is an acute inflammatory joint disease belonging to the group of SpA. The term ReA was originally introduced to define a sterile joint inflammation during or after infection elsewhere in the body [8]. The definition was later changed because bacterial antigens and nucleic acids from the causative bacteria were found in the inflamed joints [9-11]. Today ReA is defined as an asymmetrical inflammatory oligoarthritis or monoarthritis predominantly affecting the lower limbs [12], but no established criteria for the diagnosis of ReA are available [13,14]. It is triggered by infection, most often in the gut or in the urogenital tract by various facultative or obligate intracellular Gram-negative bacteria such as *Salmonella* (different serotypes), *Yersinia enterocolitica*, *Yersinia pseudotuberculosis*, *Shigella flexneri*, *Shigella sonnei*, *Campylobacter jejuni*, *Chlamydia trachomatis* or *Chlamydia pneumoniae* [9,15,16].

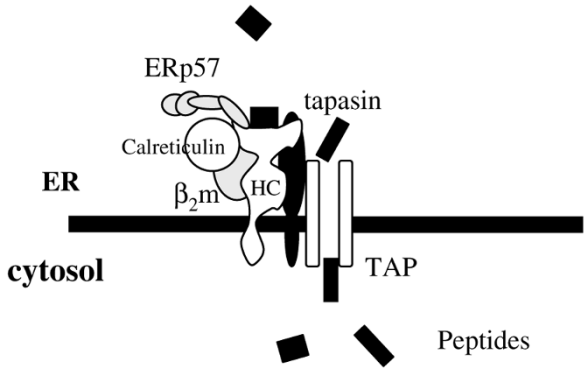
Recent studies suggest that in addition to its function as an antigen-presenting molecule, HLA-B27 might also have other functions that could modulate the inflammatory response and thus might cause susceptibility to SpA. Results from these experiments have offered new information about the abnormal host–microbe interaction between ReA-triggering bacteria and an HLA-B27-positive host [17-19]. In this review we summarize the data obtained from these non-antigen-presenting effects of HLA-B27 and their association with ReA.

Molecular characteristics of HLA-B27

HLA-B27 belongs to the major histocompatibility complex (MHC) class I molecules, which are multisubunit glycoproteins constructed in the endoplasmic reticulum (ER). MHC I complexes contain polymorphic MHC I-encoded heavy chain (HC), β_2-microglobulin (β_2m), and a small (usually 8 to 10 amino acid residues long) peptide [17]. Once newly synthesized HC is glycosylated and sufficient tertiary structure of the molecule has been achieved, it binds to β_2m with the aid of chaperone molecules and forms a heterodimer, HC–β_2m. When the heterodimer is formed, chaperone molecule calnexin is released; however, the HC–β_2m complex still interacts with the peptide loading complex, which contains the transporter-associated antigen processing molecules tapasin, calreticulin and Erp57 (oxidoreductase) (Fig. 1). The complexes formed are exported to the cell

ATF = activating transcription factor; β_2m = β_2-microglobulin; BiP = glucose-regulated protein 78; ER = endoplasmic reticulum; HC = heavy chain; HLA = human leukocyte antigen; JNK = c-Jun N-terminal kinase; LPS = lipopolysaccharide; MHC = major histocompatibility complex; ReA = reactive arthritis; SpA = spondyloarthropathies; TNF-α = tumour necrosis factor-α; UPR = unfolded protein response.

Figure 1



Several endoplasmic reticulum (ER)-resident chaperone molecules (tapasin, transporter-associated antigen processing (TAP), calreticulin and oxidoreductase ERp57) participate in the assembly of the mature major histocompatibility complex class I heavy chain (HC)/β_2-microglobulin (β_2m)/peptide complex in the ER.

surface by means of the Golgi machinery, where the carbohydrate residues of HCs are modified [17,20,21].

The formation of a stable HC–β_2m–peptide complex and the proper three-dimensional structure of the molecule in the ER are prerequisites for trafficking to the cell surface. Normally, sufficient tertiary structure of MHC class I molecules is relatively easily achieved with the aid of chaperones. However, HLA-B27 HC has two unusual features. First, the folding rate of HLA-B27 HC is unusually slow, which leads easily to the generation of misfolded HLA-B27 HCs in the ER even in the normal presence of chaperones, β_2m and peptide [17]. Second, it is capable of forming aberrant disulphide-linked dimers [22]. The B pocket is a region of the peptide-binding groove in MHC class I molecules that has an essential role in peptide selection [17]. The composition of the B pocket of the HLA-B27 HC has been shown to determine the folding efficiency and misfolding phenotype of the HLA-B27 HC, because the mutation of certain amino acid residues in the B pocket enhances the folding kinetics of the HLA-B27 HC and prevents the misfolding of the molecule [17,23].

Furthermore, the dimerization of HLA-B27 HC seems to be dependent on the composition of the B pocket, because an unpaired and reactive Cys residue (Cys 67) in the B pocket seems to form a disulphide link between two HLA-B27 HCs, allowing dimerization [22,24]. Class I HC dimerization is not a general phenomenon, but it is not unique either. It has been shown that HLA-B7 and some mouse HLA class I molecules can form aberrant dimers [22]. As well as mutating Cys 67, intermolecular disulphide bond formation can be prevented by the single substitution of methionine for glutamic acid at position 45 in the B pocket, even in the presence of Cys 67. This finding suggested that the proper folding rate of HLA-B27 HCs can prevent dimerization of the HLA-B27 molecule [17,18]. Interestingly, the amino acids in the B pocket, which markedly influence the folding rate and the dimer-forming capacity of the HLA-B27 HCs, are highly conserved in disease-associated subtypes of HLA-B27, suggesting that these non-antigen-presenting functions of HLA-B27 might have a role in the pathogenesis of SpA [18].

Translocation of protein from the ER to the cell surface requires proper folding to have occurred; unfolded and misfolded proteins accumulate in the ER, which leads to disturbances in ER function [17]. To cope with these situations, cells have evolved an ER stress-induced intracellular signal transduction pathway, the unfolded protein response (UPR). In eukaryotic cells, the UPR results in the transcriptional upregulation of several molecular chaperones and folding enzymes, which are mainly needed to improve the folding capacity of the ER [25]. Kinase IRE1, PERK kinase and the basic leucine-zipper transcription factor activating transcription factor 6 (ATF6) have been identified as proximal sensors of ER stress. The activation of these molecules depends on their dissociation from the luminal chaperone glucose-regulated protein 78 (BiP) [26]. Importantly, ER-stress induced pathways have been reported to activate nuclear factor κB (NF-κB) and c-Jun N-terminal kinases (JNKs), [17] which are critical pathways controlling inflammatory response. On the basis of those findings it has been suggested that the misfolding of HLA-B27 HCs might induce the UPR, which in turn would modulate an inflammatory response [17].

Non-antigen-presenting effects of HLA-B27 and ReA

The mechanisms by which HLA-B27 confers disease susceptibility to SpA have remained elusive despite extensive studies over the course of 30 years. However, findings obtained from ReA patients suggest that HLA-B27 modulates the interplay between ReA-triggering bacteria and immune cells, leading to abnormal host–microbe interaction. These findings *in vivo* have encouraged several scientific groups to generate model systems *in vitro* to clarify further whether HLA-B27 modulates a specific stage of host–microbe interaction such as invasion, intracellular survival or elimination of the bacteria. The significant finding obtained from patients suffering from ReA was also that bacterial antigens derived from ReA-triggering bacteria (for example lipopolysaccharide (LPS) and heat shock protein 60 (Hsp60)) were discovered from the inflamed joints. Because most of the patients suffering from chronic ReA are HLA-B27 positive, it has been proposed that inflammatory responses triggered by bacterial antigens might be altered in HLA-B27-positive patients.

Interaction between HLA-B27-expressing cells and ReA-triggering bacteria

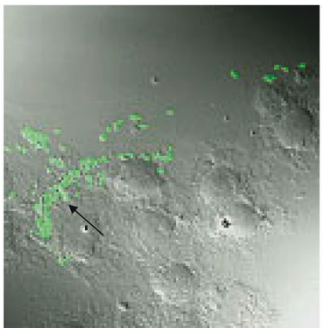
Indirect evidence suggests that the elimination of ReA-triggering bacteria might be impaired in patients suffering

from ReA. In *Salmonella*-triggered ReA, immunoglobulin M (IgM), immunoglobulin A (IgA) and immunoglobulin G (IgG) antibody concentrations – and in *Yersinia*-triggered ReA, IgA antibody concentrations – are higher and persist longer in the sera of ReA patients than in patients with the same infection but without joint complications. Prolonged persistence of IgA antibodies in the sera suggests that continuous antigenic stimulation might occur in the intestinal mucosa of ReA patients [27,28]. In addition, bacterial antigens derived from the triggering bacteria have been found in the white blood cells of patients suffering from a chronic form of ReA (most of the patients are HLA-B27 positive), even years after the onset of infection [29]. Indirect evidence therefore indicates that ReA-triggering bacteria might cause chronic infection in HLA-B27-positive patients and that the bacteria might persist at the mucosal area.

On the basis of the assumption that the interaction between ReA-triggering bacteria and HLA-B27-positive host cells is abnormal, several models have been constructed *in vitro*. The possible role of HLA-B27 in the invasion, intracellular survival or elimination of bacteria has been studied by investigators from different laboratories with different experimental settings with the use of diverse host cells and various triggering stimuli [30]. Results with *Salmonella typhimurium*, *Shigella flexneri*, *Escherichia coli* or *Yersinia enterocolitica* [31,32] suggested that invasion by these bacteria is decreased in mouse fibroblasts (L cells) by HLA-B27, but an enhanced invasion of *Salmonella enteritidis* and *S. typhimurium* was noticed in an HLA-B27-transfected epithelial cell line [33]. In contrast, several other studies indicate that HLA-B27 does not influence the invasion of ReA-triggering bacteria by various cell types [34,35]. Taken together, these studies indicate that the uptake of ReA-triggering bacteria might be modulated by HLA-B27 in some cell types with certain experimental systems. However, the evidence does not permit the conclusion that HLA-B27 would modulate the invasion of ReA-triggering bacteria, leading to the generation of chronic infection.

All ReA-triggering bacteria are able to survive intracellularly [30]. Studies have therefore been made to establish whether HLA-B27 can modulate the intracellular survival of these bacteria. Monocytes/macrophages are mobile long-lived cells that are important in limiting infection and restricting the development of systemic disease *in vivo*. For example, survival inside macrophages is essential for *Salmonella* to cause an infection [36]. For that reason the interaction between this 'first line of defence' and *Salmonella* is especially interesting. One of the major aims of our group has been to study whether HLA-B27 can modulate the interaction between monocytes/macrophages and *Salmonella*. We observed that the elimination of *S. enteritidis* is impaired in HLA-B27-transfected human monocytic cells in comparison with their HLA-A2-transfected counterparts [37]. Impaired elimination was also seen in an HLA-B27-positive fibroblast cell line [38,39], but no modulation by HLA-B27 of the survival of *Salmonella* in intestinal epithelial cells was observed [33]. In addition, the survival of *Chlamydia trachomatis* was not reported to be affected by HLA-B27 in a B cell line [40]. On the basis of the results *in vitro* from the studies about the survival of ReA-triggering bacteria inside the cells, it seems that HLA-B27 modulates the behaviour of certain host cells in response to ReA-triggering bacteria. However, several factors may contribute to contradictory or equivocal results obtained in different laboratories. These include the cell type used, the growth cycle stage of the host cells, the bacterial strain used, the growth condition of the bacteria, the growth stage of the bacteria (exponential versus stationary) and the multiplicity of infection [41].

Figure 2



Confocal microscopy image of green fluorescent protein-transformed intracellular *Salmonella enteritidis* 20 hours after infection of U937 cells transfected with human leukocyte antigen-B27. The black arrow indicates intracellular *Salmonella*.

Recently, we wished to reveal the cause of the impaired elimination of *S. enteritidis* in HLA-B27-transfected human monocytic cells and to study whether the B pocket of HLA-B27 HC contributes to these modulatory effects. Further studies revealed that the cells expressing wild-type HLA-B27 were more permissive for the intracellular replication of *S. enteritidis* than mock-transfected or HLA-A2-transfected controls. Studies with green fluorescent protein (GFP)-transformed *S. enteritidis* confirmed that the increase in the amount of intracellular bacteria was due to replication (Fig. 2) [18]. Experiments with different forms of HLA-B27 with amino acid substitutions in the B pocket suggested that the replication is dependent on glutamic acid at position 45 in the B pocket of HLA-B27. To investigate whether misfolding of HLA-B27 would induce a UPR, which in turn would modulate the regulation of genes important in the control of intracellular replication of *Salmonella* in monocytic cells, we studied whether UPR-induced genes Bip and C/EBP homologous protein-10 (CHOP) were upregulated. However, we found no induction of these genes in HLA-B27-expressing cells, suggesting that HLA-B27 HC misfolding does not induce UPR in these cells and is therefore not responsible for the permissive phenotype for the intracellular

replication of *Salmonella* in monocytic cells. Studies are now in progress to elucidate whether the dimerization of HLA-B27 HC is involved in the development of the permissive phenotype. If a similar effect also occurs in monocytes/macrophages of HLA-B27-positive individuals, this permissive phenotype might confer susceptibility to *Salmonella* infections and *Salmonella*-triggered ReA, because the ability to survive and proliferate inside macrophages is known to be crucial for the establishment of systemic disease by *Salmonella* [36].

LPS-induced tumour necrosis factor-α production and HLA-B27

Culturable bacteria are not present, and nucleic acids from triggering bacteria have been detected only occasionally, in synovial samples from patients with enterobacteria-triggered ReA [37,42]. However, bacterial antigens such as degraded LPS derived from the causative bacteria have been found in the affected joints [9,10,29]. Such processed LPS is known to be a strong antigen and capable of activating inflammatory reactions, possibly leading to the generation of arthritic symptoms [43]. It is therefore possible that LPS derived from ReA-triggering bacteria might induce ReA [30]. The main LPS-responsive cell population in the joints is monocytes/macrophages, in which LPS can trigger intracellular signalling pathways leading to the activation of several cytokines such as tumour necrosis factor-α (TNF-α) [44]. TNF-α is considered a central cytokine in the development of arthritis [45]. Furthermore, trials with anti-TNF-α therapy have proved efficient in the treatment of SpA, suggesting that TNF-α has a major role in the pathogenesis of SpA [46,47]. The central role of TNF-α is further supported by genetic studies on TNF-α polymorphism, which is associated with the development of SpA in some populations [48,49].

Because we knew that LPS is found in the inflamed joints of patients with ReA, that most of the patients with chronic ReA are HLA-B27 positive and that TNF-α is a central cytokine in the development of SpA, we sought to study whether HLA-B27 would modulate LPS-induced TNF-α production. Monocytes/macrophages are the main LPS-responding cell population in the joints; we therefore decided to discover whether HLA-B27 would influence LPS-induced TNF-α production in these cells. LPS-induced TNF-α production is controlled by the transcription factor nuclear factor κB (NF-κB) and mitogen-activated protein kinases (MAPKs; p38, JNK and extracellular regulating kinases (ERKs)) in monocytes/macrophages. For that reason we have been studying whether HLA-B27 would modulate the regulation or activation of these signalling molecules after stimulation with LPS. We found that such stimulation led to a faster degradation of the inhibitory molecule (IκB) bound to NF-κB and thus allowed faster and prolonged activation of NF-κB in HLA-B27-expressing cells than HLA-A2 and mock transfectants. The secretion of TNF-α was also found to be accelerated in HLA-B27-expressing cells after stimulation with LPS [19]. In future, our aim is to reveal whether non-antigen-presenting effects of HLA-B27 contribute to these modulatory effects, and to study whether other intracellular signalling pathways important in the control of LPS-induced TNF-α production occur in HLA-B27-expressing monocytic cells.

Our results from studies *in vitro* with cell lines do not necessarily reflect the situation in the cells of HLA-B27-positive patients *in vivo*. However, there is evidence that HLA-B27 might also modulate LPS-induced TNF-α production in monocytes/macrophages of HLA-B27-positive patients. It has been reported that monocytes/macrophages obtained from HLA-B27-positive patients produce enhanced levels of TNF-α after challenge with LPS [50]. In addition, when whole blood cultures were prepared from patients suffering from chronic iritis (most of the patients were HLA-B27 positive), it was noticed that these cells produced more TNF-α than the healthy controls after stimulation with LPS [51]. Other studies indicate that HLA-B27 does not modulate TNF-α production in various cell types [52]. However, in those studies the stimulus used was not LPS. It is therefore possible that HLA-B27 might specifically modulate LPS-induced TNF-α production in monocytes/macrophages, but more extensive studies with patient samples are required to make a definite conclusion whether HLA-B27 could interfere with LPS-induced TNF-α production *in vivo*.

Non-antigen-presenting effects of HLA-B27 and animal models

HLA-B27 transgenic rat and mice models have been generated to study the role of HLA-B27 in the pathogenesis of SpA in detail. In the rat model, which has been studied relatively extensively, a high copy number and overexpression of HLA-B27 are required for the development of an inflammatory disease closely resembling SpA [53]. Besides implicating the direct role of HLA-B27 in the pathogenesis of SpA, the rat model also provides direct evidence that commensal enteric bacteria have a crucial role in the pathogenesis of B27-associated rheumatic disease [54]. Recent studies suggest that non-antigen-presenting effects of HLA-B27 might have a role in this pathogenesis, because results indicate that disulphide-linked HC dimers are more prone to form and bind to the ER chaperone BiP in disease-susceptible HLA-B27 rats than in disease-resistant HLA-B7 rats [55]. Transgenic mice expressing HLA-B27*05 but not β_2m were reported to develop inflammatory arthritis [56]. Interestingly, HLA-B27 HC dimers have been implicated in this pathogenesis, because treatment with a specific antibody for MHC class I HC (HC10) amelioriates arthritic symptoms in these mice [57]. However, these results have been questioned by others, because β_2m-deficient mice develop spontaneous arthritis even without the expression of HLA-B27 [58]. It is therefore possible that β_2m deficiency rather than HLA-B27 expression could cause the arthritic symptoms seen in these mice.

Clinical data together with the results obtained from cell line studies support the direct role of TNF-α in the pathogenesis of HLA-B27-associated disease. However, there is no direct evidence indicating that TNF-α would have a central role in the pathogenesis of the disease in HLA-B27-transgenic rodents, although recent data show that HLA-B27 tetramers can induce TNF-α production by binding to paired Ig-like receptors [59]. The differences between animal models and differential experimental set-ups have complicated the interpretation of the results from animal studies, and no simple explanation for the association of HLA-B27 with inflammatory diseases has been suggested.

Conclusion

ReA is an acute HLA-B27-associated inflammatory joint disease triggered by certain bacteria. LPS and nucleic acids from the bacteria have been isolated from affected joints, suggesting that bacterial antigens might have a direct role in the pathogenesis of ReA. However, the exact mechanisms by which HLA-B27 causes disease susceptibility and ReA develops are still unclear. Findings *in vivo* from patients with ReA, results *in vitro* and results from animal model systems suggest that HLA-B27 expression can modulate the host–microbe interaction. Our studies with cell lines indicate that HLA-B27-expressing monocytes have a impaired capacity to resist the intracellular replication of *Salmonella*. The permissive phenotype seems to be dependent on one particular amino acid in the B pocket of HLA-B27 HC. Interestingly, the folding capacity and dimer formation of HLA-B27 HC are strictly dependent on this same amino acid, suggesting that non-antigen-presenting effects of HLA-B27 might influence the capacity of monocytes/macrophages to control the intracellular replication of *Salmonella*. In addition, results obtained by us and others suggest that HLA-B27 might enhance LPS-induced TNF-α production in monocytes/macrophages. However, the modulatory effects caused by HLA-B27 are likely to be highly dependent on the cell type studied and triggering stimulus used. Further studies are needed with patient samples and cells obtained from HLA-B27 transgenic animals to elucidate whether these modulatory effects also occur *in vivo*. It remains to be seen whether the susceptibility to SpA and ReA arises from a non-antigen-presenting effect of HLA-B27 or its altered antigen-presenting effects, or by combination of these.

Competing interests

The author(s) declare that they have no competing interests.

Acknowledgements

This work was supported financially by the Academy of Finland and Sigrid Juselius Foundation.

References

1. Brewerton DA, Hart FD, Nicholls A, Caffrey M, James DC, Sturrock RD: **Ankylosing spondylitis and HL-A 27.** *Lancet* 1973, **i:**904–907.
2. Aho K, Ahvonen P, Lassus A, Sievers K, Tiilikainen A: **HL-A 27 in reactive arthritis. A study of *Yersinia* arthritis and Reiter's disease.** *Arthritis Rheum* 1974, **17:**521-526.
3. Schwimmbeck PL, Yu DT, Oldstone MB: **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.** *J Exp Med* 1987, **166:**173-181.
4. Benjamin R, Parham P: **Guilt by association: HLA-B27 and ankylosing spondylitis.** *Immunol Today* 1990, **11:**137-142.
5. Whelan MA, Archer JR: **Chemical reactivity of an HLA-B27 thiol group.** *Eur J Immunol* 1993, **23:**3278-3285.
6. Bird LA, Peh CA, Kollnberger S, Elliott T, McMichael AJ, Bowness P: **Lymphoblastoid cells express HLA-B27 homodimers both intracellularly and at the cell surface following endosomal recycling.** *Eur J Immunol* 2003, **33:**748-759.
7. Scofield RH, Kurien B, Gross T, Warren WL, Harley JB: **HLA-B27 binding of peptide from its own sequence and similar peptides from bacteria: implications for spondyloarthropathies.** *Lancet* 1995, **345:**1542-1544.
8. Ahvonen P, Sievers K, Aho K: **Arthritis associated with *Yersinia enterocolitica* infection.** *Acta Rheumatol Scand* 1969, **15:**232-253.
9. Granfors K, Jalkanen S, Lindberg AA, Maki-Ikola O, von Essen R, Lahesmaa-Rantala R, Isomaki H, Saario R, Arnold WJ, Toivanen A: ***Salmonella* lipopolysaccharide in synovial cells from patients with reactive arthritis.** *Lancet* 1990, **335:**685-688.
10. Granfors K, Jalkanen S, von Essen R, Lahesmaa-Rantala R, Isomaki O, Pekkola-Heino K, Merilahti-Palo R, Saario R, Isomaki H, Toivanen A: ***Yersinia* antigens in synovial-fluid cells from patients with reactive arthritis.** *N Engl J Med* 1989, **320:**216-221.
11. Gerard HC, Branigan PJ, Schumacher HR Jr, Hudson AP: **Synovial *Chlamydia trachomatis* in patients with reactive arthritis/Reiter's syndrome are viable but show aberrant gene expression.** *J Rheumatol* 1998, **25:**734-742.
12. Khan MA: **Update on spondyloarthropathies.** *Ann Intern Med* 2002, **136:**896-907.
13. Colmegna I, Cuchacovich R, Espinoza LR: **HLA-B27-associated reactive arthritis: pathogenetic and clinical considerations.** *Clin Microbiol Rev* 2004, **17:**348-369.
14. Sieper J, Rudwaleit M, Braun J, van der Heijde D: **Diagnosing reactive arthritis: role of clinical setting in the value of serologic and microbiologic assays.** *Arthritis Rheum* 2002, **46:**319-327.
15. Hannu T, Puolakkainen M, Leirisalo-Repo M: ***Chlamydia pneumoniae* as a triggering infection in reactive arthritis.** *Rheumatology (Oxford)* 1999, **38:**411-414.
16. Granfors K, Marker-Hermann E, de Keyser F, Khan MA, Veys EM, Yu DT: **The cutting edge of spondylarthropathy research in the millennium.** *Arthritis Rheum* 2002, **46:**606-613.
17. Colbert RA: **The immunobiology of HLA-B27: variations on a theme.** *Curr Mol Med* 2004, **4:**21-30.
18. Penttinen MA, Heiskanen KM, Mohapatra R, DeLay ML, Colbert RA, Sistonen L, Granfors K: **Enhanced intracellular replication of *Salmonella enteritidis* in HLA-B27-expressing human monocytic cells. Dependency on glutamic acid at position 45 in the B pocket of HLA-B27.** *Arthritis Rheum* 2004, **50:** 2255-2263.
19. Penttinen MA, Holmberg CI, Sistonen L, Granfors K: **HLA-B27 modulates nuclear factor kappaB activation in human monocytic cells exposed to lipopolysaccharide.** *Arthritis Rheum* 2002, **46:**2172-2180.
20. Cresswell P, Bangia N, Dick T, Diedrich G: **The nature of the MHC class I peptide loading complex.** *Immunol Rev* 1999, **172:** 21-28.
21. Solheim JC: **Class I MHC molecules: assembly and antigen presentation.** *Immunol Rev* 1999, **172:**11-19.
22. Dangoria NS, DeLay ML, Kingsbury DJ, Mear JP, Uchanska-Ziegler B, Ziegler A, Colbert RA: **HLA-B27 misfolding is associated with aberrant intermolecular disulfide bond formation (dimerization) in the endoplasmic reticulum.** *J Biol Chem* 2002, **277:**23459-23468.
23. Mear JP, Schreiber KL, Munz C, Zhu X, Stevanovic S, Rammensee HG, Rowland-Jones SL, Colbert RA: **Misfolding of HLA-B27 as a result of its B pocket suggests a novel mechanism for its role in susceptibility to spondyloarthropathies.** *J Immunol* 1999, **163:**6665-6670.
24. Antoniou AN, Ford S, Taurog JD, Butcher GW, Powis SJ: **Formation of HLA-B27 homodimers and their relationship to assembly kinetics.** *J Biol Chem* 2004, **279:**8895-8902.

25. Mori K: **Tripartite management of unfolded proteins in the endoplasmic reticulum.** *Cell* 2000, **101:**451-454.
26. Rutkowski DT, Kaufman RJ: **A trip to the ER: coping with stress.** *Trends Cell Biol* 2004, **14:**20-28.
27. Maki-Ikola O, Leirisalo-Repo M, Kantele A, Toivanen P, Granfors K: ***Salmonella*-specific antibodies in reactive arthritis.** *J Infect Dis* 1991, **164:**1141-1148.
28. Granfors K, Toivanen A: **IgA-anti-*Yersinia* antibodies in *Yersinia* triggered reactive arthritis.** *Ann Rheum Dis* 1986, **45:**561-565.
29. Granfors K, Merilahti-Palo R, Luukkainen R, Mottonen T, Lahesmaa R, Probst P, Marker-Hermann E, Toivanen P: **Persistence of *Yersinia* antigens in peripheral blood cells from patients with *Yersinia enterocolitica* O:3 infection with or without reactive arthritis.** *Arthritis Rheum* 1998, **41:**855-862.
30. Penttinen MA, Ekman P, Granfors K: **Non-antigen presenting effects of HLA-B27.** *Curr Mol Med* 2004, **4:**41-49.
31. Kapasi K, Inman RD: **ME1 epitope of HLA-B27 confers class I-mediated modulation of Gram-negative bacterial invasion.** *J Immunol* 1994, **153:**833-840.
32. Kapasi K, Inman RD: **HLA-B27 expression modulates Gram-negative bacterial invasion into transfected L cells.** *J Immunol* 1992, **148:**3554-3559.
33. Saarinen M, Ekman P, Ikeda M, Virtala M, Gronberg A, Yu DT, Arvilommi H, Granfors K: **Invasion of *Salmonella* into human intestinal epithelial cells is modulated by HLA-B27.** *Rheumatology (Oxford)* 2002, **41:**651-657.
34. Huppertz HI, Heesemann J: **Invasion and persistence of *Salmonella* in human fibroblasts positive or negative for endogenous HLA B27.** *Ann Rheum Dis* 1997, **56:**671-676.
35. Ortiz-Alvarez O, Yu DT, Petty RE, Finlay BB: **HLA-B27 does not affect invasion of arthritogenic bacteria into human cells.** *J Rheumatol* 1998, **25:**1765-1771.
36. Mastroeni P: **Immunity to systemic *Salmonella* infections.** *Curr Mol Med* 2002, **2:**393-406.
37. Ekman P, Nikkari S, Putto-Laurila A, Toivanen P, Granfors K: **Detection of *Salmonella infantis* in synovial fluid cells of a patient with reactive arthritis.** *J Rheumatol* 1999, **26:**2485-2488.
38. Virtala M, Kirveskari J, Granfors K: **HLA-B27 modulates the survival of *Salmonella enteritidis* in transfected L cells, possibly by impaired nitric oxide production.** *Infect Immun* 1997, **65:**4236-4242.
39. Huppertz HI, Heesemann J: **The influence of HLA B27 and interferon-gamma on the invasion and persistence of *Yersinia* in primary human fibroblasts.** *Med Microbiol Immunol (Berl)* 1996, **185:**163-170.
40. Young JL, Smith L, Matyszak MK, Gaston JS: **HLA-B27 expression does not modulate intracellular *Chlamydia trachomatis* infection of cell lines.** *Infect Immun* 2001, **69:**6670-6675.
41. Granfors K: **Host–microbe interaction in reactive arthritis: does HLA-B27 have a direct effect?** *J Rheumatol* 1998, **25:**1659-1661.
42. Gaston JS, Cox C, Granfors K: **Clinical and experimental evidence for persistent *Yersinia* infection in reactive arthritis.** *Arthritis Rheum* 1999, **42:**2239-2242.
43. Duncan RL Jr, Hoffman J, Tesh VL, Morrison DC: **Immunologic activity of lipopolysaccharides released from macrophages after the uptake of intact *E. coli* in vitro.** *J Immunol* 1986, **136:**2924-2929.
44. Miyake K: **Innate recognition of lipopolysaccharide by Toll-like receptor 4-MD-2.** *Trends Microbiol* 2004, **12:**186-192.
45. Maini RN: **Current and new antitumor necrosis factor agents in perspective.** *Arthritis Res Ther* 2004, **6 Suppl 2:**S1-S2.
46. Baeten D, Kruithof E, Van den Bosch F, Demetter P, Van Damme N, Cuvelier C, De Vos M, Mielants H, Veys EM, De Keyser F: **Immunomodulatory effects of anti-tumor necrosis factor alpha therapy on synovium in spondylarthropathy: histologic findings in eight patients from an open-label pilot study.** *Arthritis Rheum* 2001, **44:**186-195.
47. De Keyser F, Baeten D, Van den Bosch F, Kruithof E, Mielants H, Veys EM: **Infliximab in patients who have spondyloarthropathy: clinical efficacy, safety, and biological immunomodulation.** *Rheum Dis Clin North Am* 2003, **29:**463-479.
48. McGarry F, Walker R, Sturrock R, Field M: **The –308.1 polymorphism in the promoter region of the tumor necrosis factor gene is associated with ankylosing spondylitis independent of HLA-B27.** *J Rheumatol* 1999, **26:**1110-1116.
49. Repo H, Anttonen K, Kilpinen SK, Palotie A, Salven P, Orpana A, Leirisalo-Repo M: **CD14 and TNFα promoter polymorphisms in patients with acute arthritis. Special reference to development of chronic spondyloarthropathy.** *Scand J Rheumatol* 2002, **31:**355-361.
50. Repo H, Jaattela M, Leirisalo-Repo M, Hurme M: **Production of tumour necrosis factor and interleukin 1 by monocytes of patients with previous *Yersinia* arthritis.** *Clin Exp Immunol* 1988, **72:**410-414.
51. Huhtinen M, Repo H, Laasila K, Jansson SE, Kautiainen H, Karma A, Leirisalo-Repo M: **Systemic inflammation and innate immune response in patients with previous anterior uveitis.** *Br J Ophthalmol* 2002, **86:**412-417.
52. Yin Z, Braun J, Neure L, Wu P, Liu L, Eggens U, Sieper J: **Crucial role of interleukin-10/interleukin-12 balance in the regulation of the type 2 T helper cytokine response in reactive arthritis.** *Arthritis Rheum* 1997, **40:**1788-1797.
53. Hammer RE, Maika SD, Richardson JA, Tang JP, Taurog JD: **Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human β_2m: an animal model of HLA-B27-associated human disorders.** *Cell* 1990, **63:**1099-1112.
54. Taurog JD, Richardson JA, Croft JT, Simmons WA, Zhou M, Fernandez-Sueiro JL, Balish E, Hammer RE: **The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats.** *J Exp Med* 1994, **180:**2359-2364.
55. Tran TM, Satumtira N, Dorris ML, May E, Wang A, Furuta E, Taurog JD: **HLA-B27 in transgenic rats forms disulfide-linked heavy chain oligomers and multimers that bind to the chaperone BiP.** *J Immunol* 2004, **172:**5110-5119.
56. Khare SD, Luthra HS, David CS: **Spontaneous inflammatory arthritis in HLA-B27 transgenic mice lacking β_2-microglobulin: a model of human spondyloarthropathies.** *J Exp Med* 1995, **182:**1153-1158.
57. Khare SD, Hansen J, Luthra HS, David CS: **HLA-B27 heavy chains contribute to spontaneous inflammatory disease in B27/human β_2-microglobulin (β_2m) double transgenic mice with disrupted mouse β_2m.** *J Clin Invest* 1996, **98:**2746-2755.
58. Kingsbury DJ, Mear JP, Witte DP, Taurog JD, Roopenian DC, Colbert RA: **Development of spontaneous arthritis in β_2-microglobulin-deficient mice without expression of HLA-B27: association with deficiency of endogenous major histocompatibility complex class I expression.** *Arthritis Rheum* 2000, **43:**2290-2296.
59. Kollnberger S, Bird LA, Roddis M, Hacquard-Bouder C, Kubagawa H, Bodmer HC, Breban M, McMichael AJ, Bowness P: **HLA-B27 heavy chain homodimers are expressed in HLA-B27 transgenic rodent models of spondyloarthritis and are ligands for paired Ig-like receptors.** *J Immunol* 2004, **173:**1699-1710.