How does HLA-B27 affect susceptibility to spondyloarthropathy?

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Human leukocyte antigen (HLA)-B27, in common with other HLA class I molecules, plays an important role in immunity to viral and bacterial infections by presenting foreign peptides to T lymphocytes. However, there are negative consequences for individuals who inherit HLA-B27, since this gene is strongly associated with susceptibility to a group of inflammatory joint diseases known as the spondyloarthropathies. A pathogenic role is suggested for the B27 molecule itself, rather than a closely linked gene, since HLA-B27 transgenic rats and mice exhibit features observed in spondyloarthropathy. This review will describe how recent research on the biology and function of the B27 molecule provides information on how B27 differs from other HLA class I molecules, and will discuss how these characteristics may lead to susceptibility to arthritis.

What clinical & pathological features are common to different forms of spondyloarthropathy?

At first glance, the clinical features of the spondyloarthropathies (SpAs) suggest that these diseases are very diverse; for example, SpAs include diseases such as reactive arthritis (ReA), a peripheral joint disease that is generally self-limiting, and ankylosing spondylitis (AS), a chronic progressive disease that mainly affects the spine. Nevertheless, there are clinical similarities among the diseases that comprise SpA; arthritis and enthesitis occur in all forms of SpA with a predilection for sacroiliac joint involvement, whilst extra-articular involvement of the skin, eyes and gut is commonly seen. This led to their recognition as forms of arthritis separate from rheumatoid arthritis. The term SpA is now applied to five different disorders: AS, psoriatic arthritis, arthritis associated with inflammatory bowel disease, ReA and undifferentiated SpA. The concept of SpA was strengthened by the discovery that each of the diseases is associated with human leukocyte antigen (HLA)-B27. The relationship of B27 with different members of the SpA family is shown in Figure 1.

In addition to synovitis affecting both peripheral and axial joints, one common pathological feature in SpA is enthesitis (i.e., inflammation at the site of attachment of a tendon, ligament or joint capsule to bone). Benjamin and colleagues have recently suggested that certain entheses consist of several distinct zones, some containing fibrocartilage, which together form an enthesis organ [1]. Different SpAs exhibit the involvement of entheses at different anatomical sites, such as flexor tendons in psoriatic dactylitis, plantar fascia in ReA, and possibly sacroiliac joints in AS. Although enthesitis does not absolutely require the presence of HLA-B27 (e.g., in psoriatic dactylitis), the relationship between HLA-B27 and the pathology in this region has been studied by focusing on enthesitis at the plantar–fascia insertion in individuals with mechanically-induced and inflammatory enthesitis. This study showed that the severity of bone edema at the site of insertion of the plantar fascia correlated with HLA-B27 expression. In mechanical and inflammatory disease, it has been proposed that the initial bone edema is due to microtrauma at a site subject to significant stresses. HLA-B27 amplifies this response in some way [2]. The mechanism of amplification is not known, but one possibility would be that microtrauma exposes a component of the enthesis such that it can become the target of an autoimmune response.

Bacterial infection & spondyloarthropathy

An alternative to microtrauma as an initiating event would be an innate immune response, perhaps triggered by bacterial components that find their way into the enthesis. It has been suggested that entheses may be sites where bacterial components may be deposited and retained, perhaps related to their physical properties. A spontaneous enthesopathy that occurs in certain mice was found not to occur when the mice were in microbe-free conditions [3]. Likewise, studies in the transgenic B27 rat demonstrated that gut inflammation precedes arthritis and that this disease requires commensal bacteria [4].
In human SpA, involvement of bacteria is self-evident in ReA, since preceding genito–urinary or gastrointestinal infection is the trigger for developing arthritis. The majority of patients with these infections do not develop arthritis, but those who are B27 positive are more likely to develop ReA. If the arthritis develops, it is more severe in B27-positive subjects and more probable to become chronic or progress to an AS-like condition. It is important to note that epidemiological studies suggest that HLA-B27 does not increase susceptibility to infection itself, but alters susceptibility to developing arthritis following infection, presumably by influencing responses to the infection [5].

Overt infection is not a feature of AS (except in those patients who progress following ReA), but subclinical gut inflammation is also detected in a proportion of AS patients, although it is not clear whether this precedes joint involvement. A recent study also suggests that subclinical intestinal inflammation occurs in first-degree relatives of AS patients [6]. Interestingly, this was not linked to HLA-B27, suggesting that certain genes confer susceptibility to gut inflammation and that these, in combination with HLA-B27, result in susceptibility to SpA.

In psoriatic arthritis, there is skin inflammation and therefore the possibility of involvement of skin bacteria in arthritis pathogenesis, since the normal barrier function of the skin is disrupted. A recent animal model of psoriatic arthritis supported this idea. This model was complex, and involved the deletion of two transcription factor genes (c-jun and JunB) in keratinocytes in adult life [7]. Shortly after the gene deletion, psoriatic lesions and inflammatory arthritis developed. Notably, a role for bacteria in the induction phase of arthritis was suggested, since broad-spectrum antibiotics appeared to delay its onset. Arthritis and psoriasis differed in their requirements for components of the immune system in this model, with only arthritis requiring T lymphocytes. Thus, in this model there was also a genetic susceptibility to develop psoriasis (in this case engineered by the investigator) and a subsequent arthritis that seems to depend on both bacteria and acquired immunity.

What additional genes are required to enable HLA-B27 to induce SpA? Although 95% of AS patients express HLA-B27, expression of B27 is not sufficient to induce disease: 7–10% of most populations express this allele and only a small percentage develop AS. Family studies investigating the genetic contributions to AS have shown that HLA-B27 is (almost always) necessary but not sufficient for susceptibility to AS. The identity of the additional genes that are required is of great interest, as are the genes that confer susceptibility to other forms of SpA. Whole-genome screening has been performed by UK, US and European groups to determine the linkage of AS with genes other than B27; several areas of the genome with suggestive linkage to AS have been identified [8–10]. These include a locus containing the interleukin (IL)-1 gene cluster, however, this region contains a significant number of IL-1 family members with different activities and regulatory capabilities so further analysis will be required to identify the exact gene(s) involved. Another gene, the enzyme cytochrome P4502D6, has been reproducibly found to be associated with disease, but its role in the etiology of AS remains obscure. The transforming growth factor (TGF)-β gene

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**Figure 1. The association of human leukocyte antigen-B27 with spondyloarthropathy.**

Human leukocyte antigen-B27 is found in approximately 95% of AS patients, 50% of patients with enteric infection-related ReA, 50% of PsA and arthritis associated with IBD-A patients when there is spinal involvement and 20–50% of undifferentiated spondyloarthropathy patients, depending on the study. AS: Ankylosing spondylitis; CARD: Caspase activation and recruitment domain; IBD: Inflammatory bowel disease; PsA: Psoriatic arthritis; ReA: Reactive arthritis.
is located in a region of the genome that showed suggestive linkage with AS in the UK and US study groups. It is an attractive candidate since it plays a role in the regulation of inflammatory processes, extracellular matrix synthesis, bone remodeling and fibrosis. Disappointingly, subsequent analysis only identified weak linkage between a rare TGF-β1 allele and AS [11]. Furthermore, van der Paardt and colleagues found no significant differences in the presence of TGF-β gene polymorphisms between controls and AS patients [12].

Mutations in the caspase activation and recruitment domain (CARD)15 gene were first identified as important factors in susceptibility to Crohn's disease [13,14], and have also been shown to be associated with sacroiliitis in patients with Crohn's disease. This gene is of particular interest since the CARD15 protein is believed to be involved as an intracellular sensor of bacterial cell wall products. An association between CARD15 mutations and AS has not generally been found, despite sacroiliitis invariably occurring in AS [15]. An association between CARD15 mutations and PsA has been found in a Newfoundland population [16], but this report must be interpreted with caution as other studies in different populations have failed to show a linkage [17].

What properties of HLA-B27 could confer susceptibility to SpA?
There are three main areas of research designed to determine how HLA-B27 confers susceptibility to SpA; these are shown in Figure 2.

Is SpA due to HLA-B27's ability to present an arthritogenic peptide?
This theory attempts to explain the association of HLA-B27 with disease, based on B27's normal function of binding antigenic peptides and presenting them to CD8+ T lymphocytes. It is suggested that one of the foreign peptides bound by HLA-B27 (e.g., from a bacterium or virus) might be sufficiently similar to a self-peptide (e.g., a peptide derived from one of the components of the enthesis) to elicit a pathogenic autoimmune response. This is often termed molecular mimicry.

Recent analysis of three further crystal structures of B27 molecules, to which particular viral peptides are bound, has contributed to our understanding of the mechanism of peptide binding to B27 and the rules that govern this interaction [18]. Although B27 binds exclusively to peptides that have an arginine at position 2 (numbered from the N terminus of the peptide), this study highlighted that B27 can accommodate peptides with diverse biochemical properties at their C terminus, while allowing a solvent-exposed region between the termini to interact with the T-cell receptor.

A number of B27 alleles, including B*2704 and B*2705, are associated with susceptibility to AS, whereas others, specifically B*2706 and B*2709, do not appear to be. The repertoire of peptides that bind disease-associated and non-associated subtypes of B27 has been analyzed extensively. Although there was a large overlap in the repertoire of peptides bound by all B27 subtypes, peptides with distinct biochemical properties were only found in particular subtypes. This work has enabled the identification of sequence motifs that would be expected to be present in potential arthritogenic peptides [19,20].

An example of molecular mimicry involving a B27 subtype associated with AS has been reported recently. CD8+ cytotoxic T cells specific for a peptide derived from the Epstein–Barr virus (EBV) protein, latent membrane protein (LMP)2 presented by B*2705, were also able to recognize a self-peptide derived from the vasoactive intestinal peptide type 1 receptor (pVIPR) [21]. Cross-reactivity was not observed when these peptides were presented by B*2709, although both peptides bound to B*2709 strongly. The lack of recognition of the peptide when presented by B*2709 was explained following x-ray crystallographic analysis of both B*2705 and B*2709 bound to the pVIPR-derived peptide. Both subtypes bound peptides in the standard conformation, exploiting all six pockets of the peptide-binding groove. However, B*2705 also exhibited a non-standard mode of peptide binding, which was not seen in B*2709. This abnormal binding was strongly dependent on the sequence of the antigenic peptide, which required an arginine at position 5 to interact with the aspartic acid at position 116 of the B*2705 heavy chain on the floor of the peptide-binding groove. This amino acid is not present in B*2709. Is this non-standard binding a unique event only applying to the pVIPR-derived peptide? Apparently not, since this mode of peptide binding to B*2705 was also identified using the LMP P2 peptide and a self-peptide derived from the glucagon receptor [22]. These studies illustrate the potential for molecular mimicry, but it is not known if these peptides can induce disease. Truly arthritogenic
peptides could be presented by B27 subtypes associated with disease, bound either conventionally or in the nonstandard configurations that disease-associated subtypes allow. If nonstandard peptide binding is required to induce disease, arthritogenic peptides will be difficult to identify, since they would be present in both disease-associated and nonassociated subtypes. It will require a radically new approach that can detect differences in peptide conformation, rather than ability to bind disease-associated subtypes (other than crystallography, which is not practical for screening).

To investigate which components of the enthesis could be the target of an autoimmune response, a number of studies have investigated T-cell reactivity to peptides derived from fibrocartilage proteins and proteoglycans that can be processed and presented by HLA-B27. A CD8+ T-cell response to the G1 domain of the proteoglycan, aggrecan, has been noted in patients with AS, while B27 transgenic mice recognized one of the peptides from aggrecan that could bind B27. Immunization with this peptide resulted in tenosynovitis [23,24]. A further study from the same group identified two HLA-B27-binding peptides derived from Type II and VI collagen, respectively, that were stimulatory for CD8+ T cells derived from the peripheral blood of only a single AS patient. By contrast, the peptide derived from type VI collagen stimulated synovial fluid-derived CD8+ T cells from four out of seven HLA-B27-positive AS patients to secrete interferon (IFN)-γ [25]. This study highlights the need to examine T cells from the site of disease rather than peripheral blood when searching for responses to autoantigens.

A novel mechanism where peptides derived from microbial infections could be arthritogenic has also been reported. This involves the recognition of HLA-B27 by natural killer (NK) receptors, which are expressed by T cells, as well as NK cells [18]. An EBV peptide was identified that prevented interaction of B27 with the inhibitory NK receptor, killer cell immunoglobulin-like receptor (KIR)3DL1. Since engagement of HLA-B27 by KIR3DL1 decreases the response of CD8+ T cells, removal of this signal would enhance T-cell responses and be potentially proinflammatory, perhaps allowing responses to autoantigens that would not otherwise be recognized with sufficient avidity to allow an immune response. However, since the peptide that showed this effect would normally occupy only a small proportion of the HLA-B27 molecules available for interaction with NK receptors, it remains doubtful whether this mechanism would be physiologically relevant.

Is susceptibility to SpA related to the abnormal properties of HLA-B27? Recently, roles for B27 other than its ability to present antigenic peptides have been proposed as explanations for its conferring susceptibility to SpA. These center on the aberrant behavior of this molecule during its synthesis. Early events in HLA class I expression require the interaction of the heavy chain with endoplasmic reticulum (ER)-resident chaperones and HLA class I-specific accessory molecules prior to association with β2-microglobulin and loading with a high-affinity peptide. The unusual features of the HLA-B27 heavy chain include a relatively slow maturation rate and increased propensity to misfold in comparison...
with other HLA class I molecules [26,27]. This behavior appears to result from unique properties of the peptide-binding groove, since mutations affecting the groove can be made that restore the maturation rate to normal.

It has been postulated that accumulation of misfolded B27 molecules could disrupt cellular homeostasis by activating a stress response within the ER. This, in turn, could initiate a cascade of signals that stimulates the unfolded protein response (UPR) (reviewed in [28]). Recently, Turner and colleagues have shown that an UPR is associated with inflammatory disease in the HLA-B27 transgenic rat. This effect was not simply due to overexpression of HLA class I molecules since the response was not seen in cells from HLA-B7 transgenic rats [29]. The study also revealed that the UPR was not constitutively active, but only detected when inflammatory disease was evident in the transgenic rats and limited to specific cell types, such as macrophages. It was reported previously that an active UPR may contribute to the defective function of dendritic cells in transgenic B27 rats [30]. It is also suggested that macrophages or dendritic cells that are disabled by an UPR would have important immunoregulatory effects since these cells have an important role in peripheral tolerance, especially in the gut (reviewed in [31]). Gut inflammation, initiated by a defect in peripheral tolerance, could lead to the activation of local innate or adaptive immune responses and a disruption of the normal relationship with gut flora. This, in turn, might lead to dissemination of bacterial components, or phagocytic cells containing bacteria to entheses or joints.

An UPR has been detected in humans cells transiently transfected with B27 [29] and overexpression of the chaperone immunoglobulin binding protein (BIP) in synovial fluid mononuclear cells has been interpreted as evidence of the UPR in vivo [32]. Future tests for the presence of an UPR in the gut or entheses in B27-positive SpA patients would be of considerable interest.

Misfolded HLA-B27 heavy chains are generally retained in the ER by ER-resident chaperones, such as BIP, but interestingly, these B27-BIP complexes have also been found on the surface of B27-positive human and transgenic rat cells [27,33]. Antoniou and colleagues argue that this form of HLA-B27 on the cell surface has evaded quality control processes, that would normally retain this complex in the ER, and has been misdirected to the cell membrane [27].

The slow maturation rate of B27, in combination with the unique biochemical properties of the molecule, may also predispose B27 to form B27 heavy-chain homodimers. These can be detected in the ER during early B27 synthesis and also on the cell surface following recycling of cell surface B27 heterodimers into an endocytic compartment [27,33,34]. Similarly to most HLA class I alleles, B*2705 benefits from an interaction with tapasin and the peptide-loading complex (PLC), thereby achieving optimization of high-affinity peptide binding. However, the SpA-associated allele B*2705 is one of a few HLA class I molecules that can achieve a high surface expression in the absence of tapasin [35]. HLA-B27's tapasin-independent behavior may be physiologically relevant; recent data suggest that tapasin function and association of HLA class I heavy chains with PLC can be compromised by viral proteins [36], thus, alleles that do not require this apparatus could be advantageous in maintaining immune responses to pathogens. Nevertheless, the peptides loaded onto B27 in the absence of tapasin will be suboptimal, perhaps allowing dissociation of the molecules at the cell surface and thus making free heavy chains available for homodimer formation [35]. An increased proportion of cell surface homodimers has in fact been observed in the absence of tapasin [34].

Other forms of HLA-B27 molecules are detected on the cell surface, including free heavy chains arising from the dissociation of unstable HLA-B27 heterodimers, a phenomenon exhibited by other HLA class alleles. By contrast, a β2-microglobulin free heavy chain that retains its ability to bind antigenic peptides has not been identified in other alleles but accounts for a significant proportion of the B27 – peptide complexes at the cell surface [37]. Dissociation of B27 heavy chains and β2-microglobulin will also result in the release of excessive amounts of β2-microglobulin from cells and it has been postulated that this might cause arthritis by its ability to form amyloid structures, which are known in other contexts to be arthritogenic [38]. However, such amyloid deposits have not been demonstrated clearly in SpA.

It may be argued that anything that decreases B27 dissociation would decrease disease, if homodimer formation is a critical event. Experiments where B27 transgenic rats coexpressed a high-affinity B27-binding peptide favored this idea since disease was decreased. However, recent results, in which excess β2-microglobulin...
was provided by crossing B27-transgenic rats with β2-microglobulin transgenic rats, spoke against the idea since arthritis was substantially exacerbated, even though expression of cell-surface free B27 heavy chains was shown to be decreased (homodimers were not examined directly) [39]. Reconciling these different findings awaits further experimentation.

The abnormal behavior of HLA-B27 was investigated initially using the AS-associated subtype, B*2705, but more recently, these aspects have been examined in other disease-associated (B*2704) and non-associated (B*2706 and B*2709) subtypes. Unexpectedly, B*2704 and B*2705 did not exhibit similar requirements for tapasin to achieve stable surface expression, suggesting that the ability to achieve optimal cell surface expression in the absence of tapasin is not a prerequisite for disease susceptibility. The non-associated allele B*2706 was the only B27 subtype tested that was truly tapasin independent as it was not detected in association with the PLC. B*2706 also exhibited a slightly faster rate of maturation than the other subtypes and a greater ratio of free heavy chains to intact B27/β2-microglobulin complexes on the cell surface. While it is tempting to speculate that these characteristics of B*2706 might abolish susceptibility to AS, it is difficult to reconcile this idea with the finding that B*2709, which is also not associated with disease, did not exhibit these properties [40].

Does an effect of HLA-B27 on intracellular infection influence susceptibility to SpA?

Whilst HLA-B27 is conventionally involved in T-cell-mediated responses to pathogens, alternative mechanisms whereby HLA-B27 influences host–cell interactions with intracellular bacteria have been suggested, particularly the effect on bacterial persistence and intracellular replication [41]. The pathogens that are associated with ReA are salmonella, campylobacter, yersinia, shigelata, and chlamydia. These organisms are either obligate or facultative intracellular Gram-negative bacteria, with a lipopolysaccharide (LPS)-containing outer membrane. Genes involved in the induction of the response to intracellular bacteria or LPS are known to be regulated by nuclear factor (NF)-κB, which orchestrates the inflammatory response. A myelo-monocytic cell line, U937, stably transfected with HLA-B27 has been reported to show altered activation of NF-κB following LPS stimulation [42]. Such an effect on NF-κB should also be evident in the expression of the diverse set of genes that are downstream of NF-κB signaling. However, a recent microarray analysis of the gene expression profile of U937 stimulated with LPS did not detect significant differences between U937 transfected with HLA-B27 or, as a control, HLA-A2 [JC Goodall, Unpublished Data].

A recent study has suggested that bacterial persistence may be modified when HLA-B27 is expressed [41]. Furthermore, HLA-B27 transfectants have also shown altered signaling responses following infection by salmonella. Thus, while an effect of HLA-B27 on the response to LPS alone has not been established, the influence of B27 may be complex and require additional factors provided by intracellular bacterial infection or the influence of exogenous cytokines, such as IFN-γ.

Does NK & T-cell recognition of abnormal forms of HLA-B27 influence susceptibility to SpA?

Despite the fact that interactions of HLA molecules with T-cell receptors have been studied for decades, the more recent discovery of additional families of class I HLA-recognizing molecules raises new possibilities with regard to HLA-B27-associated SpA. Originally described on NK cells, these receptors are also expressed on some T cells and related receptors are expressed by antigen-presenting cells. The families include the KIR, the NK group 2 C-type lectins and the leukocyte immunoglobulin-like receptor in humans, and Ly49 and paired immunoglobulin-like receptor in rodents. The effect of engagement of these receptors varies; most are inhibitory but the remaining have an activating role and the overall effect is dependent on the balance of signals transmitted through these two kinds of receptors. Interestingly, inheriting certain combinations of HLA and KIR alleles has been shown to predispose to psoriatic arthritis [43].

A subset of NK receptors bind conventional B27 heterodimers and it has been shown that cell-surface B27 homodimers also interact with these receptors and may thereby influence immune responses [44,45]. The receptors that bind conventional B27 and homodimers differ; B27 homodimers are recognized by KIR3DL2, which does not recognize conventional B27 but instead binds HLA-A2. Conversely, LILRB1 binds conventional B27 but does not interact with B27 homodimers. This suggests that there are critical differences between these different
How does HLA-B27 affect susceptibility to spondyloarthropathy? – REVIEW

forms of B27 that could enable or prevent receptor interactions that have proinflammatory consequences. The expression of the inhibitory receptor KIR3DL2 that recognizes B27 homodimers is significantly increased in patients with SpA, and this was shown to increase the survival of NK cells [46].

Abnormal forms of B27 may be involved in interactions with T-cell receptors. A curious feature of the B27-transgenic rodent models of SpA is the lack of any clear requirement for CD8+ T cells, the subset that should normally interact with a class I HLA molecule such as B27. By contrast, CD4+ T cells seem to be crucial (reviewed in [4]). Experiments with human T cells showed that it was possible to isolate CD4+ T cells, which were able to interact with HLA-B27. The observations for one subset of these cells were consistent with the recognition of free heavy chains, whereas in other cases recognition of B27-derived peptides presented by other class I HLA molecules explained the reactivity observed [47].

Future perspective

- Whole-genome screening will identify genes linked to susceptibility of SpA and provide an insight into disease mechanisms.
- Studies using microanalysis of biopsies from the site of disease in different SpAs will reveal whether an UPR is evident in SpA patients. Important differences between the different disease groups may also be identified.
- The specificity of the pathogenic T cells in the transgenic B27 rat may be discovered.

The new mouse model of psoriatic arthritis will provide an insight into why joints are targeted following psoriatic arthritis.

Executive summary

Features of the spondyloarthropathies

- Human leukocyte antigen (HLA)-B27 is associated with the spondyloarthropathies (SpAs), a group of disorders characterized by inflammation of the entheses.
- HLA-B27 cannot act alone but requires an environmental trigger, in combination with susceptible genes, to produce SpA.

Disparate theories regarding the role of B27 in susceptibility to SpA

- The presentation of arthritogenic peptide(s).
- Activation of an unfolded protein response that compromises dendritic cell function and the ability to maintain tolerance in the gut.
- The interaction of unusual forms of B27, particularly homodimers, with natural killer (NK) receptors on NK cells, T cells or dendritic cells, resulting in immunomodulatory effects.

Latest findings

- B27 subtypes associated with disease can present antigenic peptides in an unusual conformation.
- B27 homodimers have stimulatory effects on NK cells and macrophages.
- B27 subtypes have different requirements for achieving stable surface expression.
Bibliography

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.


** New psoriatic arthritis model that identifies the role of keratinocytes and bacteria in disease initiation. This study also shows that the ensuing arthritis is T-cell dependent. This is an elegant model that enables a gene to be switched off in defined cells at a time designated by the investigator.
23. A novel mode of peptide binding was identified with the disease-associated B*2705 subtype and not the disease nonassociated subtype B*2709.
27. Revealed an unusual association of B27 and an endoplasmic reticulum resident chaperone immunoglobulin binding protein on the cell surface.
30. A revealed that the unfolded protein response was detectable only in tissue derived from HLA-B27-transgenic rats with inflammatory disease.
Interesting finding that B27 transgene expression at high copy number is associated with defective dendritic cell function.

- Identified B27 homodimers on the cell surface, which suggests these unusual structures have the potential to interact with natural killer (NK) receptors.


- Reveals the unexpected finding that over expression of β2-microglobulin results in more severe arthritis.

- Suggests that NK survival is influenced by the interaction of KIR3DL2 with B27 homodimers. This is the first example that B27 homodimers can be functionally relevant to immune system cells.