This editorial refers to The arthritis-associated HLA-B*27:05 allele forms more cell surface B27 dimer and free heavy chain ligands for KIR3DL2 than HLA-B*27:09, by Alberto Cauli et al., on pages 1952-62.

We have known about the strong association between AS and the HLA-B*27 (B*27) gene for the past 40 years; however, the mechanism with which only some allomorphs of the HLA-B27 molecule, as well as some other HLA class I molecules, are involved in the occurrence of SpAs is still unclear [1]. In this issue of *Rheumatology*, Cauli et al. [2] present data that may aid our understanding of this mechanism. They show that the B*27:05 allomorph, which is strongly associated with AS, forms more free heavy chains (FHCs) and homodimers (B272) on the cell surface than the closely related B*27:09, which is not associated with this disease. These FHCs and B272 molecular species are selectively bound by KIR3DL2 receptor present on NK cells and some subpopulations of T cells. HLA-B27 belongs to the class I HLA molecules, which play two functions in our immune system. First, they bind peptides derived from the degradation of proteins produced inside the cell (both self and foreign, e.g. viral) and present them at the cell surface to antigen-specific T cell receptors of cytotoxic CD8+ T cells [3]. Second, they serve as ligands for innate immune receptors, e.g. killer immunoglobulin-like receptor (KIR) and leucocyte immunoglobulin-like receptor (LILR) families, which are not strictly specific for the bound peptide, but rather inform cells equipped with these receptors that HLA class I molecules are present or absent on target cell. Cells that have lost or reduced their HLA class I molecules because of viral infection or malignant transformation may be killed by NK cells. In contrast, normal non-infected cells would be spared [4].

Several hypotheses for the strong association of the HLA-B*27 gene with SpAs have been proposed [1, 5, 6]. One of these is based on unique molecular characteristics of the B27 molecule, i.e. an unpaired cysteine residue in position 67 (Cys67), which is involved in the formation of homodimers expressed on the cell surface. These homodimers interact with receptors of innate immunity, present on some NK and T lymphocytes and possibly contribute to AS [1]. These receptors—KIR3DL1, KIR3DL2, LILRB1 and LILRB2—exhibit differential patterns of binding to a classical B27-β2 microglobulin–peptide complex and to B27 (FHC) forms, including homodimers (Table 1). Interestingly, KIR3DL2 differs from KIR3DL1, LILRB1 and LILRB2 in binding only FHC forms of B27, including homodimers, but not B27-β2 microglobulin–peptide complex (Table 1). In addition, it differs from other KIR receptors by its structure: it forms homodimers due to a disulphide bond [7, 8], which is similar to B27 molecules.

However, the presence of Cys67 in the HLA-B*27 molecule alone cannot explain the association of B*27 with AS, because not all B*27 alleles are associated with this disease, although all contain Cys67. For example, B*27:05 allomorph is strongly associated, whereas B*27:09, differing from it by only one amino acid in position 116 (aspartate in B*27:05 and histidine in B*27:09), is not. Cauli et al. [2] give us a molecular explanation. They asked whether this difference might be caused by a stronger binding of B*27:05 than B*27:09 by immune receptors or whether the binding of B*27:05 and B*27:09 is similar, but B*27:05 forms more FHCs and homodimers on the cell surface than B*27:09. In a series of elegant experiments they show that the B272–KIR3DL2 interaction is similar for both allomorphs, but that B*27:05 forms a greater amount of FHC and B272 than B*27:09. In addition, NK and CD4+ T cells from B*27:05-positive patients with AS displayed more FHC and B272 molecular forms on their surface than cells from B*27:05-positive healthy controls. The latter cells were very similar to B*27:09 and B27-negative cells in this respect [2]. This finding needs explanation (not addressed by Cauli et al. [2]). Because B*27:05 molecules, due to negatively charged aspartate residue in position 116, bind peptides with a positively charged residue in position 9 in addition to peptides with neutral residue in this position, whereas B*27:09 molecules bind only peptides with neutral residue 9 [9], and AS may possibly be initiated by infection [6], we believe that an arthritogenic peptide derived from the pathogen and containing a positively charged residue 9 may be bound by B*27:05 but not B*27:09 (arthritogenic peptide hypothesis [1, 5, 9]).

Binding of the peptide stabilizes HLA class I molecules on the cell surface, and homodimer formation also requires peptide binding [10]. Therefore the B27 molecules in pathogen-infected B*27:05-positive AS patients may be more abundant on the cell surface than in non-infected B*27:05-positive healthy controls due to pathogen-derived peptide binding. In the study by Cauli et al. [2], KIR3DL2-positive NK and T cells survived better in AS.
patients than in healthy individuals even when both possessed B*27:05.

In conclusion, the results by Cauli et al. [2] suggest that B*27:05 could be associated with AS because it forms more FHCs on the cell surface and homodimers that interact with KIR3DL2 homodimers on NK and T cells. As these B27 molecular species are more abundant on cells from B*27:05-positive AS patients than from B*27:05-positive controls, we foresee a diagnostic test that uses KIR3DL2 tetramers to detect an elevated level of B27 FHC forms in AS patients.

Disclosure statement: The authors have declared no conflicts of interest.

Piotr Kus´nierczyk1 and Edyta Majorczyk1,2
1Laboratory of Immunogenetics and Tissue Immunology, Department of Clinical Immunology, Ludwik Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Wroclaw and 2Institute of Physiotherapy, Faculty of Physical Education and Physiotherapy, Opole University of Technology, Opole, Poland.

Accepted 27 June 2013

Correspondence to: Piotr Kus´nierczyk, Laboratory of Immunogenetics and Tissue Immunology, Ludwik Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, ul. Rudolfa Weigla 12, 53-114 Wroclaw, Poland. E-mail: pkusnier@iitd.pan.wroc.pl

References

Table 1 Interaction between HLA-B27 molecular forms and receptors of innate immunity

<table>
<thead>
<tr>
<th>HLA-B27 molecular form</th>
<th>KIR3DL1</th>
<th>KIR3DL2</th>
<th>LILRB1</th>
<th>LILRB2</th>
</tr>
</thead>
<tbody>
<tr>
<td>B27-β2 microglobulin-peptide complex</td>
<td>++</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>B27 FHC forms</td>
<td>+</td>
<td>++</td>
<td>–</td>
<td>++</td>
</tr>
</tbody>
</table>

Table based on [2, 8, 10]. B27-β2 microglobulin-peptide complex heterotrimer contains HLA-B27 heavy chain, β2 microglobulin molecule and presented peptide; B27 FHC forms, β2 microglobulin FHC forms of HLA-B27 including homodimer (B27β2); ++: stronger binding; +: weaker binding; –: no binding.