IMMUNE REGULATION

Cellular collaborations

Previous studies of protection from inflammatory bowel disease (or colitis), which is characterized by dysregulated mucosal $CD4^+$ T-cell activity to commensal gut flora, have largely focused on a key role for regulatory $CD4^+$ T-cell subsets. However, Jonathan Braun and colleagues now report that other T-cell subsets, notably $CD8\alpha^+$ T cells and natural killer T (NKT) cells, in collaboration with mesenteric lymph node (MLN) B cells, can protect mice from $CD4^+$ T-cell-induced colitis.

In their model, colitis was induced in immunodeficient mice by transfer of T cells from colitis-prone mice deficient in the G-protein subunit $G_{\alpha i2}$. However, when $G_{\alpha i2}$-deficient T cells were co-transferred with MLN B cells from wild-type mice, no disease developed. Transferred MLN B cells localized mainly in the secondary lymphoid compartments and not in the intestinal lymphoid follicles, indicating that colitis protection was not mediated locally. Compared with unprotected mice, protected mice had expanded NKT-cell populations in the spleen and MLNs, and increased numbers of $CD4^+CD8\alpha^+$ T cells in the large and small intestines, indicating that these cell populations might interact with MLN B cells to mediate protection. Consistent with this, if the $G_{\alpha i2}$-deficient T-cell inoculum was depleted of $CD8\alpha^+$ T cells before co-transfer with MLN B cells, the mice were not protected from colitis, and expansion of NKT-cell and $CD4^+CD8\alpha^+$ T-cell populations did not occur.

The authors confirmed the regulatory role for MLN B cells using another colitis model, in which colitis induced by $CD4^+CD45RB^{hi}$ T cells was similarly suppressed on co-transfer of MLN B cells and $CD8\alpha^+$ T cells.

Finally, MLN B cells from $G_{\alpha i2}$-deficient mice failed to provide protection on co-transfer, indicating that signalling through $G_{\alpha i2}$ is required for the development of this regulatory B-cell subset.

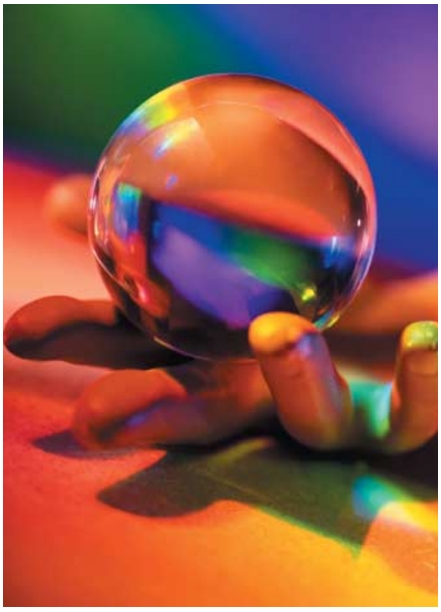
Lucy Bird

References and links

ORIGINAL RESEARCH PAPER Wei, B. *et al*. Mesenteric B cells centrally inhibit $CD4^+$ T cell colitis through interaction with regulatory T cell subsets. *Proc. Natl Acad. Sci. USA* **102**, 2010–2015 (2005).

STRUCTURE

Do crystals reveal the secrets of HLA-B27?



Crystal structures of HLA-B27 complexed with three immunodominant viral peptides, reported by Paul Bowness and colleagues, might shed light on the association of this MHC class I allele with long-term non-progression to AIDS and with the autoimmune inflammatory disease spondylitis. From the crystal structures, the authors observed that HLA-B27 can present viral peptides — derived from HIV, influenza virus and Epstein–Barr virus (EBV) — in a range of conformations, influencing interactions with the cognate T-cell receptors (TCRs) and inhibitory natural killer (NK)-cell receptors.

Consistent with previously solved structures of HLA-B27, the main 'anchor' residue (arginine at position 2, P2) of all three peptides forms hydrogen bonds with the B-pocket residues in the HLA-B27 peptide-binding groove. This anchor residue is crucial for peptide binding and for the generation of an immunodominant response, as mutation of this residue in HIV-infected patients results in viral escape and progression to AIDS. The central regions (P4–P8) of the three bound peptides show the greatest variation in structure: the HIV decamer peptide bulges out of the groove, whereas the influenza-virus and EBV nonamer peptides bind in extended conformations. Side chains of the residues in this central region are solvent exposed, so they contribute to interactions with the TCR.

Although the three peptides all contain arginine at P2, their carboxy-terminal peptide residues differ (lysine in HIV, arginine in influenza virus and leucine in EBV). The crystal structures illustrate how viral peptides with distinct residues can be accommodated in the HLA-B27 F pocket, either through formation of salt bridges, as for the influenza-virus peptide, or through hydrophobic contacts, thereby diversifying antigen presentation.

HLA-B27 binds the inhibitory NK-cell receptor KIR3DL1, which interacts with HLA-B27 residues around position 80 and with peptide residues P7 and P8. Here, the authors show that, although tetrameric complexes of HLA-B27 with the HIV and influenza-virus peptides bind KIR3DL1-expressing cells, tetramers of HLA-B27 with the EBV peptide do not. Analysis of the crystal structures revealed that glutamic acid at P8 in the EBV peptide confers a negative charge, which might interfere with binding to KIR3DL1. Consistent with this, substitution of the glutamic acid with threonine allowed binding to KIR3DL1.

So, the authors propose that the inability of HLA-B27 loaded with certain microbial peptides to interact with KIR3DL1 might have a pro-inflammatory and therefore disease-promoting effect, through increased NK-cell activation.

Lucy Bird

References and links

ORIGINAL RESEARCH PAPER Stewart-Jones, G. B. E. *et al*. Crystal structures and KIR3DL1 recognition of three immunodominant viral peptides complexed to HLA-B*2705. *Eur. J. Immunol.* **35**, 341–351 (2005).

FURTHER READING López de Castro, J. A. HLA-B27: portraying immunodominant viral epitopes. *Eur. J. Immunol.* **35**, 336–340 (2005).

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