ANTIGEN PRESENTATION

Advantages to being different

The MHC class I alleles HLA-B*4402 and HLA-B*4405 differ at only one amino acid, yet this difference markedly affects their ability to access alternative pathways of antigen presentation and their susceptibility to viral interference of conventional presentation pathways. Reporting in *The Journal of Experimental Medicine*, James McCluskey, Jamie Rossjohn and colleagues propose that such naturally occurring HLA polymorphisms might represent an evolutionary trade-off between optimal HLA class I loading and effective pathogen evasion.

Naturally occurring HLA polymorphisms in the peptide-binding groove increase the diversity of epitopes that are presented to T cells. Accordingly, analysis of the peptides eluted from the two HLA-B44 alleles indicated that the single amino-acid change at position 116 (present in the F pocket of the peptide-binding groove), from aspartic acid in HLA-B*4402 to tyrosine in HLA-B*4405, resulted in a preference for phenylalanine at position 9 of the peptide. This was due to decreased electronegativity and increased hydrophobicity of the F pocket of HLA-B*4405.

In addition to an influence on peptide-binding specificity, polymorphism at position 116 has been shown to affect allele dependency on the peptide-loading complex (PLC) for optimal peptide loading and cell-surface expression. HLA-B*4402 cell-surface expression is highly dependent on tapasin, which recruits HLA class I molecules into the PLC. By contrast, HLA-B*4405 was shown to be expressed at high levels on the surface of tapasin-deficient cells and without association with the PLC. Furthermore, compared with HLA-B*4402, HLA-B*4405 was more rapidly transported to the surface of both tapasin-deficient and tapasin-sufficient cells by circumventing PLC-mediated retention and peptide optimization in the endoplasmic reticulum (ER).

Given the ability of HLA-B*4405 to efficiently bind peptides independent of the PLC, the authors asked whether this provided resistance to TAP (transporter for antigen processing) blockade by the herpes simplex virus (HSV)-encoded TAP inhibitor ICP47. The expression of HLA-B*4402 was markedly reduced in the presence of ICP47 due to impaired peptide delivery to the ER; however, the expression of HLA-B*4405 was only marginally reduced, indicating that it can rapidly capture peptide even when in limited supply. The resistance of HLA-B*4405 to viral interference of the PLC was also confirmed using peripheral-blood mononuclear cells infected with HSV.

So, although sacrificing the optimization of peptide cargo by the PLC can come at a cost to the host, tapasin-independent alleles such as HLA-B*4405 might have been selected to provide an advantage during infection with pathogens that interfere with conventional antigen-presentation pathways.

Lucy Bird

References and links

ORIGINAL RESEARCH PAPER Zernich, D. *et al.* Natural HLA class I polymorphism controls the pathway of antigen presentation and susceptibility to viral evasion. *J. Exp. Med.* **200**, 13–24 (2004).

IN BRIEF

SIGNALLING

RabGEF1 is a negative regulator of mast cell activation and skin inflammation.

Tam, S. Y. *et al. Nature Immunol.* **5**, 844–852 (2004).

Ras signalling is required for the optimal release of lipid mediators and cytokines following IgE and antigen-induced mast-cell activation. In this study, RabGEF1 — previously identified as having guanine-nucleotide exchange factor (GEF) activity — was shown to bind Ras. Reducing RabGEF1 expression *in vitro* increased Ras activity and cytokine and lipid-mediator production on FcεRI aggregation, indicating that RabGEF1 negatively regulates these functions in mast cells. Further support for this hypothesis comes from similar results that were obtained using bone-marrow-cultured mast cells derived from RabGEF1-deficient mice. RabGEF1 mRNA is widely expressed, and RabGEF1-deficient mice have many phenotypic abnormalities; therefore, RabGEF1 might function as a negative regulator of Ras signalling in other cells as well as mast cells.

INFECTIOUS DISEASE

An efficient method to make human monoclonal antibodies from memory B cells: potent neutralization of SARS coronavirus.

Traggiai, E. *et al. Nature Med.* **10**, 871–875 (2004).

Although monoclonal antibodies could be used to prevent and treat infectious diseases, inherent difficulties in their development mean that they have had little impact. In this study, an improved method for immortalization of B cells was used to transform IgG^+ memory B cells isolated from a patient who recovered from infection with severe acute respiratory syndrome coronavirus (SARS-CoV). B-cell clones were screened for the production of SARS-CoV-specific antibodies, and 35 antibodies capable of neutralizing the virus *in vitro* were identified. One of these inhibited viral replication in the lower respiratory tract (in a mouse model of acute SARS-CoV), indicating that this improved technique of memory B-cell transformation can be used to rapidly isolate effective candidate therapeutic monoclonal antibodies.

IMMUNE EVASION

Human herpesvirus 8 K14 protein mimics CD200 in down-regulating macrophage activation through CD200 receptor.

Foster-Cuevas, M. *et al. J. Virol.* **78**, 7667–7676 (2004).

Many viruses hijack host proteins to evade immune defences. This paper describes a viral homologue of CD200 — a widely expressed host cell-surface glycoprotein — encoded by the K14 open reading frame of human herpesvirus 8. Although K14 has only 40% sequence identity with CD200, they showed that the K14 protein interacts with the CD200 receptor, which is mainly expressed by myeloid cells, with the same kinetics and low affinity as the host protein. Cells expressing CD200 or K14 inhibited the secretion of pro-inflammatory cytokines by activated macrophages, indicating that infected cells might deliver downmodulatory signals to host myeloid cells through the CD200 receptor to evade elimination.