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IMMUNE EVASION

HIV takes the indirect route

One way in which HIV can avoid detection by the immune system is to mutate the protein epitopes that are presented by infected cells on MHC class I molecules to cytotoxic T lymphocytes (CTLs). Philip Goulder and colleagues have now shown for the first time in a natural human infection that HIV can also take an indirect route to CTL escape by mutating residues outside of CTL epitopes that affect antigen processing.

This study identified a polymorphism at amino-acid residue 146 (alanine to proline; A146P) of the HIV-1 protein Gag that is more common in patients expressing the MHC class I molecule HLA-B57. The authors show that the observed variation at Gag residue 146 is the result of selection pressure mediated by HLA-B57. For example, in known examples of wild-type HIV transmission from an HLA-B57⁻ mother to an HLA-B57⁺ child, the A146P mutation arose subsequent to transmission in the child.

In HLA-B57⁺ individuals infected with HIV-1, the A146P mutation is associated with a 22-fold increase in viral load compared with wild-type virus, resulting in an increased risk of progression to AIDS. CD4⁺ T cells from an uninfected HLA-B57⁺ donor that were infected *in vitro* with a virus construct containing the A146P mutation could not be lysed by CTLs specific for the epitope ISW9, in contrast to cells infected with wild-type virus constructs. Surprisingly, however, residue 146 does not lie within

ISW9 (Gag residues 147–155), but instead is found immediately preceding the amino terminus of this epitope. The authors suggest that the mutation at residue 146 affects the pathway by which proteins become presented on MHC molecules, and therefore indirectly affects CTL recognition, because the unmutated epitope itself never reaches the surface of the cell.

In support of this, the endoplasmic-reticulum aminopeptidase ERAP1 could not cut amino-terminal-extended ISW9 peptides that contained proline, rather than alanine, at residue 146. ERAP1 is involved in antigen presentation by trimming peptide epitopes to the correct length to bind MHC class I molecules, so the failure of A146P-containing peptides to be

trimmed could result in poor presentation on the surface of HIV-infected cells and therefore poor CTL recognition and killing.

This indirect mechanism of CTL escape has been postulated by many researchers on the basis of artificial mutation studies, but this is the first time that it has been shown to occur naturally. The research has important implications for vaccine design as it indicates that the residues between epitopes are also crucial for an efficient CTL response.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPER Draenert, R. *et al.* Immune selection for altered antigen processing leads to cytotoxic T lymphocyte escape in chronic HIV-1 infection. *J. Exp. Med.* **199**, 905–915 (2004)
FURTHER READING Phillips, R. E. Immunology taught by Darwin. *Nature Immunol.* **3**, 987–989 (2002)