⤷ **HIV**

Calculating control

A new study based on computer modelling brings us a step closer to understanding why certain individuals can control HIV infection for long periods of time without therapy. The authors predict that expression of the HLA-B57 allele by these individuals generates a naive CD8+ T cell repertoire that has a larger fraction of cells that recognize the virus and that these cells are more cross-reactive to mutants of targeted viral epitopes, features that may contribute to improved control of HIV.

The relative ability to control HIV infection has been linked to the expression of certain HLA-B alleles; for example, HLA-B57 is associated with control of the virus, whereas HLA-B7 is associated with rapid progression to AIDS. Algorithms that predict the number of peptides from the human proteome that can bind to these alleles revealed that HLA-B57 binds far fewer peptides than HLA-B7 (70,000 and 180,000, respectively). This implies that HLA-B57-restricted T cells will encounter fewer self peptides during thymic development.

To explore the effect of this lower thymic peptide diversity on the mature T cell repertoire, the authors designed an *in silico* thymic selection model in which the number of self peptides varied; then they assessed cross-reactivity of the selected T cells by introducing mutations in the viral peptides that they recognize to determine the contact residues that are important for recognition. The calculations predicted that a HLA-B57-restricted T cell repertoire has more T cells that recognize viral peptides — and they do this through fewer important contacts — than a T cell repertoire restricted by HLA alleles that present a greater diversity of peptides in the thymus. These findings are consistent with previous studies of repertoire development in mice and suggest that HLA-B57-restricted T cells can recognize viral peptide epitopes with a larger number of possible point mutations, as may arise during an infection. This hypothesis is supported by experimental data showing that CD8+ T cells from HLA-B57+ patients were more cross-reactive to various mutated HIV epitopes than those from patients expressing HLA-B8 (which is associated with rapid progression to AIDS and binds a greater diversity of self peptides).

Further calculations to determine the probability with which a randomly selected T cell clone and viral peptide will interact strongly enough for recognition to occur indicated that HLA-B57-restricted T cells have a higher probability of recognizing a viral epitope than T cells restricted by other HLA molecules. This suggests that virus-specific T cells are more frequent in the HLA-B57-restricted repertoire, and this is likely to contribute to faster and more effective antiviral responses. A dynamic model of host–virus interactions also predicted that a higher frequency of virus-specific T cells and greater cross-reactivity leads to better control of viral loads during the acute phase of HIV infection. Taken together, these findings imply that patients expressing HLA alleles that bind fewer self peptides should control HIV better. This prediction was supported by analysis of samples from HLA-typed patients who were controllers and non-controllers of HIV infection.

But despite being beneficial in viral infection, T cells restricted by HLA alleles that bind fewer peptides (such as HLA-B57 and HLA-B27) are subject to less stringent negative selection in the thymus and therefore may be more prone to recognizing self peptides, providing a possible explanation for the association of these HLA alleles with autoimmune disease.

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