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**HIV vaccines: The myth of cross-reactive T cells**

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**Abstract**

The variability of HIV has raised the question of whether T cells raised against one strain can cross-react with another. This is highly pertinent to vaccine design, especially as most vaccines being prepared are B clade and more than 90% of infections worldwide are non-B clade. The clades differ by more than 20% in amino acid sequence.

The idea that virus-specific T cells are cross-reactive goes back to a misconception in the 1970s and 1980s when it was found by us and others that cytotoxic T lymphocytes could not distinguish between influenza viruses of the different A virus subtypes. It was assumed that CTLs recognized virus glycoproteins which differ by 30% between subtypes so they must be permissive in antigen recognition. Later work by us and others showed that these T cells recognized the highly conserved internal virus proteins, which are processed within the cell before presentation by MHC class I molecules at the cell surface. Thus virus-specific T cells were not widely cross-reactive, but the idea was firmly rooted and still persists.

HIV is the most variable virus known to infect humans. Besides the clade differences there are quasispecies swarms within each patient with 4-10% variation. We and others have shown that HIV can escape CTL responses by point mutations and recent data indicate that this is commonplace. This alone suggests that T cells are sensitive to mutations in the epitopes. However (nearly) all the mutations that have been shown to be selected by T-cell pressure contain mutations in the residues that anchor the peptide to the HLA molecule. Thus there was still space for T cells that cross-react broadly on epitopes that bind.

To test this, we made all 171 single amino acid changes in the immunodominant epitope in HIV gag presented by HLA-A2 in more than 70% of HLA-A2 positive patients: SLFNTVATL. Using two clones with completely different T-cell receptors that were already known to be cross-reactive between the common F3Y variants we found that more than two thirds of the altered peptides were not recognized and that most of these changes occurred in side chains involved in TCR recognition. Side chains were orientated by crystallizing SLFNTVATL + HLA-A2. When the common F3Y variant was crystallized however, it showed a 180-degree rotation in the central region of the peptide. Further analysis of recognition of amino acids changed in these positions indicated that one conformation is seen and the TCR probably triggers a rotation in the peptide so that both variants look identical. Thus the TCRs that recognize this peptide are extremely sensitive to amino acid changes in TCR interaction regions. Given that virus-specific T cells are often oligoclonal, this form of escape may be common.

The sensitivity of CTLs to peptide variation makes escape relatively easy for HIV. For the same reasons, tumors may also easily escape T-cell recognition.

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