AN HLA-C0702* RESTRICTED T-CELL RESPONSE DIRECTED AGAINST AN IMMUNE ESCAPED HIV NEF KY11 EPITOPE EXHIBITS HIGHER FUNCTIONAL AVIDITY BUT LESSER CYTOLYTIC ACTIVITY WHEN COMPARED WITH THE ANTI-WILD TYPE RESPONSE**

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HIV-1 mutational escape from a suppressive epitope-specific T-cell response has been well described. Analysis of HLA allele associated HIV polymorphism in population-based studies (n>800) suggests that HIV may also adapt to favour induction of certain epitopes that actively enhance viral replication. We therefore sought to investigate the presence and functionality of the HLA-restricted T-cell responses driving one such adaptation identified by the genetic analysis (Nef D108E in the HLA-C*0702 restricted Nef KY11 epitope).

Cryopreserved PBMC samples from 32 HIV-infected patients with HLA-C*0702 allele were assayed for IFN-γ production upon stimulation with the adapted and non-adapted ('wild type') KY11 peptides by ELISpot assay. The functional avidity of wild type and variant-specific T-cell directed responses were compared using serial peptide dilutions. Autologous epitope sequences were determined from contemporaneous plasma samples in patients with detectable HIV viral load (n=4). CTL killing of peptide-pulsed EBV transformed B-cells was determined using the Chromium release assay.

IFN-γ was detected in PBMC samples from all patients after stimulation with anti-CD3 or CEF. IFN-γ responses to the wild type or adapted KY11 epitopes were detected in 13 patients. The adapted epitope induced IFN-γ responses in 11 HLA-C*0702 patients (median-500, range 150-1110 spots/million cells). In 3 samples from 2 cases, the adapted peptide-specific response had greater functional avidity than the wild type peptide. Autologous sequence contained the D108E adaptation in 1 patient who concurrently demonstrated IFN-γ responses. In initial assessments of T-cell killing, HLA-C*0702 B-cells pulsed with wild type peptide were killed more readily by adapted peptide CTLs than wild type peptide CTLs.

Despite modest levels of epitope-specific IFN-γ responses overall in this treatment-experienced patient group, HLA-restricted responses against an HLA-adapted epitope were demonstrable, including with higher avidity than the wild type form in 3 samples, suggesting a functional basis for adaptation driving creation of epitopes. In addition, preliminary data on CTL killing suggests lesser cytolytic activity of the variant specific T-cell response would favour persistence of the adapted virus. These data support the possibility of HIV adapting to actively exploit rather than simply evade T-cell responses and have implications for epitope inclusion criteria in HIV vaccine design.