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P09-19 LB. CTL escape mutations in gag epitopes restricted by protective HLA class I alleles cause substantial reductions in viral replication capacity

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Background

CD8+ T cell responses, particularly those targeting Gag epitopes, play a critical role in the control of HIV during early infection, but the capacity of HIV to rapidly escape from such responses can undermine effective CTL-mediated control. In some cases, however, the CTL escape mutation causes a reduction in viral replication capacity. We hypothesize that such escape costs contribute to the protective effect exhibited by some HLA alleles; protective alleles restrict early, immunodominant CD8+ T cell responses from which HIV can only escape with substantial associated reductions in viral replication capacity.

Methods

Recombinant HIV-1B variants expressing one or more of 27 previously described HLA-associated polymorphisms in Gag were constructed in the NL4-3 backbone by site-directed mutagenesis. The 27 polymorphisms were associated with 15 HLA alleles and were located in, or adjacent to, 20 defined CTL epitopes. Differential replication of the variants was measured by a combination of FACS analysis in GFP-reporter cells and qRT-PCR in single and dual infection assays in PBMC. Relative replication capacity was calculated by the log relative fitness (LRF) method.

Results

The majority of mutations analyzed had little or no impact on relative replication capacity. The three mutations that caused large and statistically significant ($p < 0.05$) reductions in replication capacity, A163G, R264K, and I436L, are all located in immunodominant epitopes restricted by protective HLA alleles: A163G in B57-KF11, R264K in B27-KK10, and I436L in B13-RI9.

Conclusion

Comprehensive analysis of the impact on viral replication capacity of HLA-associated polymorphisms in Gag revealed that mutations in immunodominant CD8+ T cell epitopes restricted by protective HLA class I alleles caused the greatest reductions. These data support the hypothesis that high CTL escape costs may contribute to the protective value of these alleles and support the value of considering the viral cost of CTL escape when selecting immunogens for CTL based vaccines.