Retrovirology

BioMed Central

Poster presentation

P09-14. Emergence of b12 resistant rapidly replication HIV-1 variants during natural infection in the absence of humoral or cellular immune pressure

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from AIDS Vaccine 2009
Paris, France. 19–22 October 2009

Published: 22 October 2009

Retrovirology 2009, **6**(Suppl 3):P127 doi:10.1186/1742-4690-6-S3-P127

This abstract is available from: http://www.retrovirology.com/content/6/S3/P127

Background

Previously we identified patient H19659 who early in his progressive course of infection had HIV-1 variants that were relatively sensitive to neutralization by b12, but who later in infection developed viruses that were highly resistant to b12 neutralization. This increased b12 resistance coincided with an increase in viral replicative capacity. Here we investigated which changes in Env accounted for the differences in replication rate and sensitivity to b12 neutralization between HIV-1 variants that were isolated early and late in the course of infection from this patient and whether immune pressure *in vivo* was involved in selection of viruses.

Methods

Gp120 sequences were generated from clonal HIV-1 variants and amino acid changes that segregated with differences in b12 neutralization sensitivity and replication rate were created in the background of molecular clone LAI. LAI mutants were tested for replication rate and b12 neutralization sensitivity. CTL pressure on amino acids involved in the b12 epitope sequence was tested by ELISPOT with patient PBMC.

Results

Sequence analysis of Env mutations in clonal HIV-1 variants suggested involvement of substitutions I154M (in V1) K178T (in V2) and Q389K (in V4) in the b12 resistance of viruses from patient H19659. Indeed, any combination of these mutations in the background of LAI increased the resistance to b12 neutralization. However, in the LAI background, these mutations reduced the replicative capacity, suggesting the presence of compensatory mutations in the rapidly replicating b12 resistant primary virus variants. Interestingly, this individual had only weak autologous and heterologous neutralizing activity in serum, and no detectable CTL response against HLA-restricted epitopes that contained b12 resistance mutations.

Conclusion

In patient H19659, rapidly replicating b12 resistant HIV-1 variants emerged during the course of infection in the absence of immune pressure. In light of vaccine design, it may be important to understand how these neutralization resistant viruses were selected.