Retrovirology

Poster presentation

P09-10. Impact of CTL escape mutations in HIV-1 Nef on viral replication

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Background

HIV-1 Nef is a multifunctional protein frequently targeted by host CD8+ T cell responses in early and chronic phases of HIV-1 infection. *In vivo* reversions of CTL escape mutations within Nef have been reported, suggesting a possible impact of immune-selected mutations in Nef on viral fitness. The goal of this work was to determine whether CD8+ T cell selected mutations in regions outside of Gag, such as in Nef, also impair viral replication and may thus contribute to early immune control of HIV-1.

Methods

A set of 13 HLA class I-associated amino acid polymorphisms located in the central conserved region of Nef were engineered into HIV-1 strain NL4-3 and viral replication was assayed using a CEM-GFP reporter cell line. CD4 and MHC-I down regulation were measured by flow cytometry.

Results

While the majority of the analyzed polymorphisms had little to no effect on viral replication capacity (RC), two mutations (K94E and H116N) residing within the immunodominant CD8 epitopes B08-FL8 and B57-HW9 caused significant reductions in replication capacity of NL4-3 (RC = 0.83, P = 0.0026 and 0.85, P = 0.02, respectively using Student's t-test). These two mutations also reduced the ability of NL4-3 to down regulate CD4 surface expression but did not alter MHC-I down-regulation. Notably, both of these mutations are located adjacent to or within the well-conserved region of Nef essential for efficient down-regulation of CD4 (residues 96 to 144).

Conclusion

These data suggest that particular CTL immune-selected mutations within functional domains of Nef can impair the replication capacity of HIV-1, and thus may be contributing to the ability of particular CD8+ T cell responses to mediate early control of HIV-1 by causing reductions in viral fitness.