Retrovirology

Poster presentation

P09-17. Evolution of HLA-B*5703 HIV-1 escape mutations and their impact on HIV-1 replicative capacity

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Background

HLA-B*57 is the class I allele most consistently associated with control of HIV replication, which may be linked to the specific HIV peptides that this allele presents to cytotoxic T lymphocytes (CTL), and the resulting efficacy of these cellular immune responses. In two clade-C HIV-infected populations, we sought to elucidate the role of HLA-B*5703 in HIV disease outcome.

Methods

We sequenced HIV-1 Gag p24 (from plasma RNA and proviral DNA) from 645 South African and 178 Zambian HIV-infected individuals, analyzed cross-sectional and longitudinal viral load data, and performed viral replication assays on variants containing HLA-B*5703 escape mutations.

Results

HLA-B*5703-restricted CTL responses select for escape mutations in three Gag p24 epitopes, in a predictable order, and we show here that the accumulation of these mutations sequentially reduces viral replicative capacity *in vitro*. Despite this, *in vivo* data demonstrate that ultimately there is an increase in viral load concomitant with evasion of all three HLA-B*5703-restricted CTL responses. In HLA-B*5703-mismatched recipients, the previously described early benefit of transmitted HLA-B*5703-associated escape mutations is abrogated by the increase in viral load coincident with reversion.

Conclusion

These data demonstrate that, while costly escape from CTL responses can progressively attenuate the virus, high viral loads develop in the absence of adequate, continued CTL responses. These data underline the need for a CTL vaccine against multiple conserved epitopes.