Retrovirology

Poster presentation

P17-14. Fitness-informed HIV-1 Gag-p24 vaccine design

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Background

HIV-1's propensity to mutate is echoed in its many mutational pathways of escape from anti-retroviral, antibody and Cytotoxic T Lymphocyte (CTL) pressures. A successful vaccine must control a growing variety of strains.

Methods

We proposed a CTL-based 'Conserved Element' (CE)-vaccine exclusively composed of nearly invariant viral segments. We reason that an efficacious vaccine must elicit responses toward HIV-1 segments that cannot mutate without severely compromising viral viability, and must not elicit responses against variable, immunodominant 'decoys'. Based on known HIV-1 M-group viral sequences, we designed a Gag-p24 CE-vaccine composed of 7 segments at least 12 amino acids (AA) in length. To clarify the relationship between sequence conservation and viral fitness, we created viruses encoding AA substitutions at sites differentially conserved among HIV-1 strains, including CTL escape sites.

Results

Six mutants were engineered in the Gag-p24 'Center-Of-Tree' (COT) HIV-1-B protein of a chimeric NL4-3 virus. Mutated sites were conserved in 50 to 100% of known group M sequences. While mutations to the 2nd most-frequent AA at 5 different sites resulted in functional viruses, a substitution at a site conserved in 100% of known viruses yielded no virus production, possibly due to a defect in particle formation. Viral fitness was assessed by dual infections with the mutated and the original Gag-p24 COT HIV-1-B viruses. Growth competition assays showed varying fitness levels among mutants: some substitutions exacted a fitness cost to the virus while the HLA-associated G357S substitution at a toggle site did not impair viral fitness. Interestingly, the G357S mutation is a CTL escape mutation in the B*0702-restricted epitope GPGHKARVL and was found in 20% of HIV-1-B and 49% of HIV-1-C sequences.

Conclusion

Our data better define the interrelations between HIV-1 mutations, CTL responses and viral fitness in Gag-p24 and allow us to delineate longer HIV-1 segments for our CE-vaccine construct.