RETROVIROLOGY

POSTER PRESENTATION Open Access

HIV-1 subtype C primary isolates exhibit high sensitivity to an anti-gp120 RNA aptamer

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From AIDS Vaccine 2012
Boston, MA, USA. 9-12 September 2012

Background

Globally, HIV-1 subtype C is the most prevalent subtype, yet most antiretroviral drugs are developed against subtype B. UCLA1 RNA aptamer, which we previously showed neutralizes HIV-1 subtype C Env-pseudotyped viruses was examined for neutralization of subtype C primary isolates in PBMC and monocyte-derived macrophages (MDM). We also assessed the ability of subtype C to develop resistance to UCLA1 inhibition by propagating the isolates in increasing concentrations of the aptamer.

Methods

UCLA1 was tested against clinical isolates in PBMC (6 isolates) and MDM (4 isolates) using a p24 antigen read-out. Three viruses were grown in the presence of increasing aptamer concentrations to select for resistance. The viruses were passaged every 7 days up to 12 weeks in CD8 depleted PBMC. The gp160 was sequenced, analyzed and compared with wildtype viruses.

Results

UCLA1 neutralized 67% and 75% of viruses tested in PBMC and MDM, respectively. Overall, the aptamer neutralized one X4 and six R5 tropic viruses with IC_{80} values in the nanomolar range. Two viruses remained sensitive to the aptamer even in the presence of 4- and 12-fold increased UCLA1 concentrations. One isolate exhibited resistance after 12 weeks of propagation tolerating 12-fold the starting IC_{70}. Fifty-eight amino acid changes and two insertions along the gp160 were observed. The changes observed within the V1/V2 and V3 loops confirmed our previous data shown by truncation and single point mutational analyses to confer resistance to UCLA1.

Conclusion

UCLA1 was able to neutralize infection of primary isolates in PBMC and MDM without tropism restriction. The extensive amino acid sequence changes associated with UCLA1 resistance may indicate a high genetic barrier needed for resistance to UCLA1. This was also suggested by the low rate of resistance (only 1 of 3 isolates) observed in the study suggesting that UCLA1 is a potential anti-HIV-1 subtype C entry inhibitor drug.

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Published: 13 September 2012

doi:10.1186/1742-4690-9-S2-P215
Cite this article as: Mufhandu *et al.*: HIV-1 subtype C primary isolates exhibit high sensitivity to an anti-gp120 RNA aptamer. *Retrovirology* 2012 **9**(Suppl 2):P215.

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