

14th International HIV Drug Resistance Workshop



7-11 June 2005, Québec City, Canada

NATURAL MUTATIONS IN THE HIV-1 V3 LOOP CONFER ALTERED SENSITIVITY TO ENTRY INHIBITORS AND CORRELATE TO CO-RECEPTOR AVIDITY AND FITNESS

Antivir Ther. 10, Suppl 1:S69 (abstract no. 62)

M Lobritz, A Marozsan, D Moore, E Fraundorf, K Demers and E Arts✉

Case Western Reserve University, Cleveland, Ohio, USA

BACKGROUND: The envelope glycoprotein of HIV-1 mediates binding of the virus to host cell receptors and is a principal target of the humoral immune response. Mutations in the *env* gene must balance immune evasion with maintenance of efficient receptor binding and fusion. We have recently shown that efficiency of viral entry can vary considerably among divergent HIV-1 isolates resulting differences in replicative fitness and sensitivity to entry inhibitors. This study examines the effect of natural but specific variation within the V3 region of *env* on entry inhibitor sensitivity, CCR5 coreceptor avidity, and replicative fitness.

METHODS: We sequenced and analysed the V3 loops of primary HIV-1 isolates showing up to 100-fold variations in sensitivity to T-20, TAK-779 and PSC-RANTES. Amino acid positions 318 and 319 in the V3 loop, just downstream of the crown appeared to map with variable sensitivity to entry inhibitors. These positions were mutated in the V3 loop of an NSI/R5 subtype A primary HIV-1 isolate, 92RW009, previously identified as hypersensitive to entry inhibitors. The natural and mutated V3 region of A-92RW009 was then shuttled into *env* expression vector and pNL4-3 by a yeast recombination cloning method. The effect on these discrete mutations on drug sensitivity, fitness, and receptor avidity was tested using cell fusion assays, *env* pseudotyped viruses and infectious molecular clones.

RESULTS: Introduction of arginine at position 318 or 319 (Y318R or A319R) or arginine at position 318 in conjunction with a threonine at position 319 (Y318R/A319T) resulted in a A-92RW009 chimeric *env* protein and virus that was approximately 10-fold more sensitive than wild type to inhibition by the CCR5 inhibitors PSC-RANTES and TAK-779 and to the fusion inhibitor T20. Sensitivity differences in the envelope glycoproteins were confirmed using a luciferase-based cell fusion assay. Arginine replacement at positions 318 or 319 resulted in reduced fitness and co-receptor

binding. Growth of the double mutant was severely compromised compared to wild-type.

CONCLUSIONS: These findings suggest that natural polymorphisms at sites 318 and 319 in the V3 loop have significant effects on sensitivity to entry inhibitors, efficiency of host cell entry and fitness.

PRESENTING AUTHOR: E Arts

2005-06-07

62

Copyright © 2005 - [International Medical Press Ltd.](#) Reproduction of this abstract (other than one copy for personal reference) must be cleared through the International Medical Press Ltd. 2-4 Idol Lane, London EC3R 5DD UK.