

18th International HIV Drug Resistance Workshop



Basic Principles & Clinical Implications

June 9–13 2009, Fort Myers, Florida, USA

IDENTIFICATION OF HIV-1 MATRIX DETERMINANTS OF FITNESS COMPENSATION IN A PROTEASE INHIBITOR RESISTANT VIRUS

Antivir Ther 2009; 14 Suppl 1:A37 (abstract no. 35)

CM Parry^{1,2}, P Cane¹ and D Pillay^{1,2}

¹Virus Reference Department, Health Protection Agency, London, UK; ²UCL/MRC Centre for Medical Molecular Virology, UCL, London, UK

BACKGROUND: Mutations occur in the protease and gag genes of HIV from patients who fail therapy with protease inhibitors (PI). Protease mutations have been extensively explored while studies with *gag* have mainly been limited to cleavage sites mutations (CSM). We recently showed restoration of replication capacity (RC) for a patient plasma virus-derived (termed mutant) multidrug-resistant protease by full-length mutant Gag, as well as matrix and partial capsid. Mutant *gag*, as well as matrix and partial capsid also conferred protease inhibitor (PI) resistance with out mutations in protease.

METHODS: Using a single-cycle assay we compared the drug susceptibility of the two different regions of the mutant Gag: matrix and partial capsid, and partial capsid with the remainder of Gag. Site-directed mutagenesis identified changes in matrix and partial capsid that can restore RC to virus with the mutant protease (that alone has 5% RC of wild-type [WT]).

RESULTS: Mutant matrix and partial capsid conferred up to ninefold resistance to PIs (amprenavir 9.1×, atazanavir 5× and indinavir 9.1× the IC₅₀ of WT) without cleavage site mutations. The remainder of mutant Gag (partial capsid to the end of Gag with CSM) conferred lower levels of resistance (amprenavir 3.4×, atazanavir 2.5× and indinavir 5.8× the IC₅₀ of WT). The mutant matrix had 10 amino acid changes compared with HXB2 and an insertion (116TQ). Addition of the insertion to WT Gag had only a minor effect increasing RC of virus with the mutant protease from 5% to 10%. Changing three amino acids within the matrix from WT to those found in the mutant virus (R76K, Y79F and T81A) increased RC of the virus with mutant protease from 5% to 73% of WT.

CONCLUSIONS: We determined that the matrix and part of capsid can confer more PI resistance than regions including the p7-p1 and p1-p6 CSM. We also identified that three amino acid changes in matrix can restore the RC of a multidrug-resistant protease from 5% of WT to over 70%. The mechanism for both findings was unclear but it was independent of CSM, emphasizing that studies using full-length Gag are warranted.

2009-06-09

35

Copyright © 2009 - [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.