Retrovirology

BioMed Central

Oral presentation

Novel resistance mechanism of HIV-1 To peptide fusion inhibitors

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from 2006 International Meeting of The Institute of Human Virology
Baltimore, USA. 17–21 November, 2006

Published: 21 December 2006

Retrovirology 2006, **3**(Suppl 1):S86 doi:10.1186/1742-4690-3-S1-S86

HIV fusion is mediated by conformational changes in HIV envelope glycoprotein (Env) that involves assembly of two heptad repeats (N- and C-HR) in the gp41 ectodomain to form a six-helix bundle (6HB). Peptides corresponding to the N- and C-HR of gp41, termed as fusion inhibitors, are potent inhibitors of HIV infection. However, HIV rapidly develops resistance to such fusion inhibitors. To better understand mechanisms of resistance that will aid development of new fusion inhibitors, we generated an escape mutant virus to an N peptide inhibitor (N44). This virus, however, was also equally resistant to T20 and other C peptides. This cross-resistance to fusion inhibitors was surprising because T20 binds the N-HR, while N44 binds the C-HR. We show that two point mutations, one each in the N-HR and C-HR were responsible for the resistance, but structural modeling of these mutations indicate that the mutations would not directly impair peptide binding. Further mechanistic studies of the resistant Env demonstrated that the mutations conferred increased infection kinetics, greater sensitivity to sCD4, enhanced syncytia formation, and enhanced exposure to CD4-induced epitopes.

In summary these findings indicate a novel resistance mechanism involving improved receptor usage and faster entry kinetics. This indirect method of resistance is distinctively different from previous reports of escape from C peptide inhibitors that involve reduced peptide-binding affinity for the endogenous heptad repeat.