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HIV-1 RESISTANCE TO THE GP41-DEPENDENT FUSION INHIBITOR C-34

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BACKGROUND: During HIV-1 fusion, the N-terminal helices of gp41 lead to a trimeric coiled-coil structure onto which C-terminal helices fold. Three hydrophobic cavities have been described to form between each N-helix of the coiled-coil. C-34 is an inhibitor of gp41-mediated fusion that contains the 117-150 C-terminal residues of the gp41 ectodomain, including the three hydrophobic residues (W117, W120, I124) that are believed to project into the hydrophobic cavities. W117, W120, I124 have been described to play a major role in the inhibitory capacity of C-34. Moreover, a peptide (T-649) containing this same cavity binding region has been suggested to be much less susceptible to the evolution of resistant virus than DP178 (T-20) a compound which lacks this region.

METHODS: We developed HIV-1 resistance to C-34 by serial passage of wild-type HIV-1 NL4-3 or HXB2 in increasing concentrations of C-34. Genotypic and phenotypic analysis were done on viral stocks recovered after serial passage by DNA sequencing of the gp41 region and evaluation of the anti-HIV activity of the compound(s) by the MTT colourimetric method in MT-4 cells.

RESULTS: After seven passages for NL4-3 and 17 passages of HXB2 we obtained viruses that were able to grow at a high C-34 concentration (10 µg/ml). Viral stocks from these viruses showed reduced sensitivity (>300-fold and >1000-fold, respectively) to C-34 with respect to their corresponding wild-type strain. C-34-resistant strains were not cross resistant to reverse transcriptase (RT) inhibitors, HIV binding inhibitors or chemokine receptor antagonists suggesting that resistance is exclusively directed to gp41-dependent fusion. Genotypic analysis showed the emergence of mutations L33S for the NL4-3-derived C-34 resistant strains and mutation V38E for the HXB2-derived resistant strain. However, we did not find any amino acid changes at the residues that form the cavity of the coiled-coil structure.

CONCLUSION: We describe for the first time a mutation L33S outside of the GIV (positions 36–38) motif that generates resistance to known peptidic fusion inhibitors. Mutations at position 38 that modify sensitivity to DP178 may also affect the sensitivity of HIV-1 to inhibitory peptides that contain amino acids W117, W120, I124. HIV-1 becomes resistant to gp41 inhibitors if the peptide includes residues that are placed C-terminus from those that project into the cavity (W117, W120, I124). The design of new inhibitors of gp41-mediated fusion should be directed to the residues that form the hydrophobic cavity.

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