Retrovirology

BioMed Central

Poster presentation

P12-11. Resistance to the CD4 mimetic mini protein M48-U1 induces changes in a highly conserved region on the HIV-1 gp120 envelope protein

K Grupping*[1], L Heyndrickx[1], J Michiels[1], G Martin[2], L Martin[2] and G Vanham[1]

Address: [1]Virology, Institute of Tropical Medicine Antwerp, Antwerp, Belgium and [2]CEA Saclay, Gif sur Yvette, France
* Corresponding author

from AIDS Vaccine 2009
Paris, France. 19–22 October 2009

Published: 22 October 2009

Retrovirology 2009, **6**(Suppl 3):P177 doi:10.1186/1742-4690-6-S3-P177

This abstract is available from: http://www.retrovirology.com/content/6/S3/P177

Background

HIV-1 prevention methods, like a prophylactic vaccine and/or microbicides, are urgently needed. Since the ideal immunogen is as yet undefined and given the role of the envelope protein (Env) in the entry process, investigation of the Env structure-function relation is necessary. In this context resistance towards a promising candidate microbicide M48-U1, a CD4 mimetic mini protein, was evaluated.

Methods

Resistance to M48-U1 was obtained by culturing virus in the presence of increasing concentrations of the compound. When the degree of resistance was considered sufficient (fold change in IC50 of >10000), genotyping was performed. Additionally, phenotyping was done by testing the sensitivity towards other CD4 binding site (CD4bs) inhibitors in a TZM-bl based assay. Furthermore, the 3D structure of Env's of resistant viruses was modelled using the software application PyMol.

Results

Resistance to M48-U1 was induced in three subtype B viruses (BaL, SF162 and a biological cloned virus VI943-3). All resistant viruses differ in only one amino acid from their respective controls: S375, situated in the highly conserved Phe43 cavity of the CD4bs, is mutated into an arginine. Arginine, as a complex amino acid, is predicted to fill the Phe43 cavity, thereby abrogating the binding of M48-U1 yet still allowing binding of the CD4 receptor. Interestingly, although the viruses belong to the same subtype and exhibit the same mutation, their phenotypic outcomes are different. Cross-resistance towards some CD4bs inhibitors is observed, but with a different spectrum for the different viruses. Also, the earlier, less potent mini protein M48, is still active against some but not all of these viruses.

Conclusion

In all viruses the same mutation (S375 R) was induced by M48-U1. However, it is clear that the active site is not the sole determinant of the phenotype, as viruses with the same mutation exhibit different cross-resistance patterns.