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Abstract

Computational Approach to Structural and Conformational Characterization of Viral Surface Glycoproteins of HIV-2 †

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The efficacy of some of the available antiretroviral drugs is very limited against HIV-2 and, most importantly, none of the current drugs effectively prevents entry into the cells. HIV envelope glycoproteins mediate binding to the receptor CD4 and to CCR5 and/or CXCR4 co-receptors at the surface of the target cell, enabling fusion with the cell membrane and viral entry [1,2]. We are using computational tools to infer the structure of HIV-2 variable regions, and discover new compounds that bind to these regions and prevent cell entry. In the absence of a complete crystallographic structure of HIV-2 envelope gp125 comprising variable domains, computer aided modulation is crucial to identify structural features in the region that correlate with HIV-2 tropism and susceptibility to antibody neutralization [3].

A 3D structure of the C2V3C3 domain of HIV-2$_{ROD}$ gp125 was generated by homology modelling. HIV-2$_{ROD}$ is an X4 T-cell adapted isolate naturally resistant to antibody neutralization. To disclose the importance of the main structural features and compare with experimental results, 3D-models of six V3 mutants were also generated (H18L, H23Δ + Y24Δ, K29T, H18L+ H23Δ + Y24Δ, H18L+ K29T and H18L+ H23Δ + Y24Δ+ K29T). These mutations in V3 revealed a selective impact. The 3D structures were submitted to molecular dynamics procedures. Energy minimization and molecular dynamic simulations were performed using Gromacs 2016.01 packages.

The results were associated with higher resistance to antibody neutralization and acquisition of macrophage tropism. These new insights into the structure-function relationship will help in the design of better vaccine immunogens.

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