Mutational Analysis of the Virion Infectivity Factor (Vif) of HIV-1 subtype F2 and its influence on the interactions with APOBECs

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The Virion Infectivity Factor is a protein of HIV extremely important for viral infectivity and replication. The induction of the proteasomal degradation of antiretroviral proteins APOBECs is the most important function. The APOBEC3 family comprises cytidine deaminases which are differentially expressed in HIV-1 susceptible cells. The Vif alleles neutralize A3G and A3F efficiently, but display differences with respect to the inhibition of A3H. Two subtype F Vif variants show the highest activity against A3H; its recognition requires the residues F39 and H48 inVif structure. Alterations on this residues show to be crucial to the infectivity difference of subtype F2 against A3H protein. This work investigate possible changes in the structural stability and in the electrostatic potential of native Vif and relates it to changes in binding with A3H, A3G and A3F experimentally verified. The Vif of HIV-1 subtype F2 was modeled by homology in the Modeller software and we generated F39S, F39S/H48N and F39V/H48N variants using Fold X, to compare the free energy and electrostatics potential maps between native and mutant forms. The biologic impact of the mutations was predicted in Provean server. Then, we performed a Alanine Scanning in the motifs involved on the interaction with A3G and A3F to verify their contribution in the stability of Vif. The results showed that F39S mutant don't generate changes in the electrostatic potential and structural stability of the protein. However, the mutations F39S/H48N and F39V/H48N were classified as stabilizing (ΔΔG= +1.60 kcal and +1.56 kcal/mol, respectively). We observed inversions and other alterations in the mutants electrostatic potential maps that can influence directly the interactions with A3H protein. These two mutations induced the formation of four new hydrogen bonds between the residues R41 and E45, H42 and S46; and, V51 and H43. However, the Provean Score indicated these variants could be deleterious for Vif function. In the alanine scanning, the motifs 40YRHHY44 and 161PPLP164 (A3G binding), 14DRMR17 (A3F binding) and 21WNSLVK26 and 55VHIPLKDDSL64 (A3G/A3F binding) show to be highly important for structural stability of Vif, mainly 55VHIPLKDDSL64 (ΔΔG= +15.61 kcal/mol) and 161PPLP164 motifs (ΔΔG= 9.17 kcal/mol). According to experimentally verified, residues 39F and 48H are very important for A3H recognition and changes in their positions can alter electrostatic properties and structural stability of Vif in subtype F2.