MOLECULAR DYNAMICS STUDY OF MUTANT AND WILD-TYPE HIV-1 PROTEASE TOWARDS RITONAVIR: INSIGHTS INTO THE MECHANISMS OF DRUG RESISTANCE

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Chemotherapies against HIV-1 are limited by mutations of the viral enzymes, which are targets for many commercial drugs. To understand the basis of drug resistance, particularly of the HIV-1 protease (PR), molecular dynamics (MD) simulations of the wild-type HIV-1 protease and three model mutant structures (V82F, I84V and V82F/I84V) complexed with ritonavir, a widely used drug, were carried out in explicit aqueous solution. The mutations V82F, I84V and V82F/I84V lower the binding affinity of ritonavir by a factor of 0.8, 11.2 and 700, respectively [1]. Analysis of two nanosecond MD trajectories of the simulated systems reveals the difference in ritonavir structure and flap region of double mutant complex. Simulations show significant differences of P1' subsite and side chain of Phe82 in double mutant complexes that reduce the VdW contact between HIV-1 PR and ritonavir. In flap region, we found that V82F/I84V mutant's flap open a few Ångstroms more than the wild-type's flap for chain B during the simulation time. The flap opening in V82F/I84V complex reduces the affinity of a water molecule (WAT211) which is important for maintaining the active conformation of HIV-1 PR, because this water molecule forms four hydrogen bonds with oxygen atoms of ritonavir and with flap region in both chains [2]. In addition, these mutations decrease the stability of hydrogen bonds between HIV-1 PR and ritonavir and alter the extent of VdW interactions. These MD studies support the experimental data and clearly explain the effect of substitution of Val82 by Phe and Ile84 by Val, leading to saquinavir resistance.

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