Molecular Characterization of a New HIV-1 Protease Mutation in a Position Already Involved With Resistense to Nelfinavir

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The Human immunodeficiency virus type 1 protease (HIV-1 PR) is involved in the cleavage of Gag and Gag-Pol viral polyproteins, an important step in the viral replication cycle. This viral enzyme is also an important target for antiretroviral drugs, which improved the treatment of HIV/AIDS patients. However, the occurrence of drug resistance mutations is a frequent limitation for the clinical success of this drugs. For instance, the previously described D30N mutation causes high-level resistance to Nelfinavir, being a well established primary resistance mutation. In this work, we used bioinformatics tools to evaluate the impact of a new HIV-1 PR mutation, D30V, identified in HIV-1 subtype B sequences from infected individuals from Porto Alegre. Five PR models were generated with Modeller 9v7 and one model was selected to proceed with the Nelfinavir docking, with AutoDock 4. The modeled PR-Nelfinavir complex was then submitted to a molecular dynamics simulation, with Gromacs 4.5.1. The crystal structure of the HIV-1 PR subtype B consensus complexed with Nelfinavir, 1OHR, was also simulated. In order to assure our results, the same inputs were used to generate five independent trajectories. Both proteases (wild-type and mutated) remained in the “closed conformation” and the Asp 30 residue seem to be involved in an important hydrogen bond between the protease and the drug, which was not observed in all simulations of the mutaded complex. Therefore, the D30V mutation caused the loss of a critical interaction with the drug and might interfere with the stability of the PR-Nelfinavir complex.

Keywords: HIV-1, protease, resistance mutations
Supported by: CNPq and CAPES