Poster E-10

Structural Comparative Studies of Brazilian HIV-1 Protease Mutants: Molecular Modeling and X-Ray Data

Authors:
Paulo Ricardo Batista (*IBCCF / UFRJ*)
Pedro A. G. Lapido Loureiro (*IBCCF / UFRJ*)
Mario Sanches (*Physics Department / USP / Sao Carlos*)
Igor Polikarpov (*Physics Department / USP / Sao Carlos*)
Pedro Geraldo Pascutti (*IBCCF / UFRJ*)

Short Abstract: We exploit Molecular Modeling to perform structural comparative studies with Brazilian HIV-1 Protease mutants. Were built 3D models of each mutant and were played Molecular Dynamics simulations with the crystallographic structures in order to compare with the modeled ones, making possible analyze Molecular Modeling efficacy as structure predictor tool.

Long Abstract:
Introduction: An important question relates to effectiveness of anti-HIV therapy against different subtypes. All HIV-1 inhibitors were developed and tested for B subtype, the prevalent in developed countries but not in the world. In Brazil, B subtype is the major but F presents an important role in drug resistance. The differences between subtypes are present in many targets of anti-HIV drugs, as the protease (PR). There's no structural information of non-B PR in the Protein Data Bank and the first crystals were done by Polikarpov's group however these structures were not published yet.
TL-3 inhibits efficiently PR containing the known resistance mutations G48V and V82F against PR inhibitors (PI).
Objectives: To better understand resistance and TL-3 efficiency against different subtypes, we exploit Molecular Dynamics (MD) to perform a structural study with PR of Bwt, Fwt, B and F mutants. In addition, with the crystallographic unpublished structures we played MD simulations in order to compare with the modeled ones, making possible analyze the efficacy of Molecular Modeling as a structure predictor tool.
Methods: We applied Comparative Modeling using as template the B subtype PR structure (3THL) complexed with TL 3, obtaining Fwt, Bmut and Fmut models. The sequences utilized were based on HIV 1 drug-resistant Brazilian patients' isolates. Then we carried out MD simulations (10ns) in a periodic boundary water box, using GROMACS package. TL-3 topology was built to GROMOS96 FF, with aid of PRODRG server and ab initio calculations.
Results: The MD estimated C alpha's B-factor was in agreement with the crystallographic one. Essential Dynamics analyses reveal destabilization of active site and flaps in Fmut trajectories, confirmed by root mean square (RMS) fluctuations around the catalytic ASP 25 and ILE50. High mobility of P4 and P4' groups were observed in all the systems. Only in Fmut, P1 group presents large deviation lowering its affinity, confirmed by Delta G calculations. Now, are in progress MD analyzes with the crystallography trajectories.
Conclusions: Our MD results of Fmut PR showed a stability and affinity decrease when compared to B subtype. Analyzes of the crystallography structure's MD could provide an important contribution for validation of this modeling technique.