The impact of hinge-region mutations on the dynamics and drug interactions of the South African hiv-1 subtype c protease

Mokhantso, T.[1], Wort, R.[1], Sherry, D.[1], Achilonu, I. [1], Sayed, Y.[1]

1- Protein Structure-Function Unit, School of Molecular and Cell Biology, Faculty of Science, University of the Witwatersrand, Johannesburg 2050, South Africa.

Abstract

Introduction: HIV-1 protease is an enzyme primarily responsible for the maturation of the HI virus. The continuous emergence of amino acid mutations in HIV-1 protease can cause significant alterations in the structure and dynamics of this enzyme and may reduce the efficacy of commercially available protease inhibitors. This study aimed to highlight the impact of hinge region mutations on the molecular dynamics and drug interactions of HIV-1 protease using the wild-type South African HIV-1 subtype C protease and two hinge region variants, N37T↑V and N37T↑V^{+10}.

Method: Computational methods such as molecular dynamics simulations and induced fit docking were performed in a cubic cell universe with explicit solvent with the wild-type and variants starting in a fully closed conformation. Six FDA protease inhibitors were used for the simulations, namely; ritonavir, nelfinavir, fosamprenavir, atazanavir, tipranavir, darunavir. The trajectory of the simulation totalled 50 ns.

Results: Wild type protease has a less curled flap tip conformation of 140 degrees and this corresponds with a closed flap conformation 15 angstrom. The mutant protease has increased curling of the flap tips and this is linked to a wider flap conformation in the semi-open range. The insertion mutation variants showed increased flap and fulcrum region, while there was reduced flexibility in the cantilever region compared to the wild type. There was an increase in ICG residue tip curling seen in mutants which is understood to relate to a more open flap conformation. RMSF of protease inhibitors revealed an increase in the dynamics of the protease inhibitors about the active site, revealing that the protease inhibitors were unable to bring the variant protease to a stable and closed conformation. A decrease in overall binding interactions was also observed in the variants which relates to a decreased drug binding strength.

Discussion and conclusion: In this study we showed that hinge region insertions and non-active site polymorphisms result in an increased flap distances where the apo-mutants sample more of a semi-open conformation as compared to the apo-wild type, which samples a closed conformation. The drug bound protease revealed that the protease inhibitor were not able to bring the variant protease to a fully closed conformation when in complex, as they did the wild type. The regional RMSF for protease and PI complexes when protease was bound to ATV, DRV and TPV increased and this coincided with increased PI RMSF graphs. This indicates an increased dynamic about the active site where the PI is unable to bring the PR to a stable and closed conformation. The decreased binding interaction increased need of water bridges and solvent exposure of PIs in mutants relates to a decrease in enthalpic favourability of binding and binding strength. The information we have gathered indicates that the insertion mutation and background mutation cause less favourable binding of inhibitors both enthalpically and entropically. PIs are unable to close the flaps effectively and thus binding is minimised and less favourable.

Keywords: HIV-1 protease, molecular dynamics, induced fit docking, hinge region, protease inhibitors