HIV-2 and resistance: bioinformatic study on impacts of protease mutations

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There are two kinds of human immunodeficiency virus: the first type (HIV-1) is disseminated worldwide, while the second one (HIV-2) is less virulent and mainly distributed in West Africa [1]. Although its lower replication rate, the latter affects three million people in total. Some of the proteins involved in the virus' replication cycle include integrase, inverse transcriptase or fusion proteins—e.g. gp120 and gp41. HIV-2 protease (PR2) is one of those key enzymes and a common target to tackle both type of HIV infection [2].

One should note the lack of HIV-2 dedicated treatment in the current therapeutic arsenal. Both virus protease antiretroviral therapy are currently targeting PR1, and only three drugs (darunavir, DRV; saquinavir, SQV and lopinavir, LPV) are clinically recommended for treating HIV-2 infection [3]. Natural resistances to those molecules occur, due to the virus spontaneous mutations and, in addition many acquired resistances appear (V10I, V47A, I54M, V71I, I82F, I84V, L90M, L99F). One single mutation can lead to several protease inhibitors (IPs) resistance. For instance, the I54M variant has been associated with DRV and LPV resistance [4]. Therefore, this works aims to get a better understanding of the mechanisms underlying resistance to IPs.

Previous works discussed HIV-1 and HIV-2 structural changes [5]; and the quantification and the characterization of the structural variability of PR2, in order to apprehend the local conformational changes mechanisms in adaptation to ligand binding [6]. Only few studies address PR2 resistance by sequencing and phenotypic approaches [3,7]. Structural methods, aiming to link macromolecules structure to biological activity, are limited by the absence of mutant PR2 X-ray crystallographic data available in the Protein Data Bank (PDB).

Thus, we developed an in-house protocol combining modeling and minimization in order to build a tridimensional structure of 31 PR2 mutants extracted from the literature. Those mutants (either simple, double, or triple) are located all along the 99 residues of the homodimeric protein. Analysis were carried out by comparing the wild-type to mutant structures using multivariate methods, RMSD and distances calculations among atoms.

The first results exhibit the significance of I54M and I82F mutations in PR2 structural changes regarding to resistance mechanisms. These mutations are known to either increase darunavir resistance or sensitivity, respectively [4], making these mutation ideal subjects for the subsequent molecular dynamics analysis in the near future.

Bibliography:

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