MASTER « *In Silico* Drug Design »
1ère année

PROPOSITION DE STAGE
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Titre du stage : Identification of new binding sites in the PR2 structure

Description du sujet (quelques lignes):

HIV-2 is a retrovirus discovered a few years after HIV-1. HIV-2 infections are restricted mainly to West Africa. HIV-1 and HIV-2 are currently treated with the same therapeutic arsenal, which consists of drugs targeting integrase, reverse transcriptase, fusion protein and protease (PR). However, HIV-2 is naturally resistant to all non-nucleoside inhibitors of reverse transcriptase or fusion inhibitors. HIV-2 has also demonstrated reduced susceptibility to protease inhibitors (PIs) [1–4].
PR is an effective therapeutic target for treating HIV infection because of its essential role in hydrolysing the viral precursor polyprotein during infectious viral particle maturation. IPs bound the PR in a pocket located at the monomer interface that induces structural asymmetry in the two monomers that is important in the IP-recognition mechanism [5,6].
In the aim to study the natural resistance of PR2 against IPs, we have previously developed in silico protocols to characterize PR2 structure and flexibility [7], to compare PR1 and PR2 complexes [8] and their PI-binding pockets [9]. We showed that substitutions between PR1 and PR2 induced structural changes at some regions, particularly in an external loop (elbow), in two beta-sheets (fulcrum and cantilever), and in the α-helix [7]. In addition, sequence variations between PR1 and PR2 modify the properties of the PI-binding pocket that could impact the PI binding, the PR2 flexibility that could partially explain the PR2 resistance against PIs [8].
Another strategy, to discover new inhibitor against PR2, is to search molecules that bind other regions in the PR2 that avoids substrate binding. In PR1, several studies have shown some new inhibitor binds PR1 outside of the IP-binding pocket [10-13]. The binding of these new inhibitors alters the PR1 dynamic avoiding PR1 adopts its active form and thus the substrate binding.

The aim of this study is to search new pockets capable to bind chemical molecules that would induce inhibition of PR2. To do so, the student will use the following protocol:

1. Identification of all pockets extracted from the PR2 X-ray structure in free form.
2. Studying the deformation of these pockets after PI binding by comparing geometric properties of pockets extracted from the PR2 in free form with those extracted from PR2 complexed with PIs.
3. Studying the deformation of pockets extracted from the PR2 in free form during molecular dynamics simulations.
4. Studying the interaction of these pockets and important regions for the PI-binding and for the PR2 deformation.

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