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Binding of single walled carbon nanotube to WT and mutant HIV-1 proteases: Analysis of flap dynamics and binding mechanism

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ABSTRACT

Most of the currently treated HIV-1 protease (HIV-PR) inhibitors have been prone to suffer from the mutations associated drug resistance. Therefore, it is necessary to search for potent alternatives against the drug resistance. In the current study we have tested the single-walled carbon nanotube (SWCNT) as an inhibitor in wild type (WT) as well as in three primary mutants ($I50V_{PR}$, $V82A_{PR}$ and $I84V_{PR}$) of the HIV-1-PR through docking the SWCNT in the active site region, and then performed all-atom MD simulations for the complexes. The conformational dynamics of HIV-PR with a 20 ns trajectory reveals that the SWCNT can effectively bind to the HIV-1-PR active site and regulate the flap dynamics such as maintaining the flap-flap closed. To gain an insight into the binding affinity, we also performed the MM-PBSA based binding free energy calculations for the four HIV-PR/SWCNT complexes. It was observed that, although the binding between the SWCNT and the HIV-PR decreases due to the mutations, the SWCNTs bind to the HIV-PRs 3–5 folds stronger than the most potent HIV-1-PR inhibitor, TMC114. Remarkably, the significant interactions with binding energy higher than 1 kcal/mol focus on the flap and active regions, which favors closing flap-flap and deactivating the active residues of the HIV-PR. The flap dynamics and binding strength information for HIV-PR and SWCNTs can help design SWCNT-based HIV-1-PR inhibitors.

1. Introduction

HIV-1 protease (HIV-1-PR), an indispensable enzyme for human immunodeficiency virus (HIV) replication, is an important target for drug design strategies to combat acquired immune deficiency syndrome (AIDS). HIV-1-PR acts at the late stage of infection by cleaving the Gag and Gag-Pol polyproteins to yield mature infectious virions. Inactivation of this enzyme produces immature, noninfectious virions and hence chunks further HIV infection. Keeping that in mind, several drugs have been developed against AIDS. Up to date, the Food and Drug Administration (FDA) has approved eleven protease inhibitors for the treatment of AIDS. However, unfortunately, resistance to these approved drugs has been built up quickly due to the associated mutations in the protease leading to reduced binding affinities between inhibitors and the protease. Therefore, it is necessary to search for some other alternatives with minimal cytotoxicity and potent against the drug resistance with novel mechanisms of action.

HIV-1-PR is a C2-symmetric homodimer of 99 residues in each chain. The residues of HIV-1-PR are numbered as 1–99 and 1′–99′ for chains A and B, respectively. The active site region of the protein is formed by the dimerization of the two monomers and is covered by two glycine rich, antiparallel β-hairpins flaps. The volume of the active site and the accession of ligand to the active site are controlled by the dynamics of the two flaps [1,2]. As a member of the aspartic protease family, the protein contains the catalytic triad including the residues Asp25–Thr26–Gly27 in both chains, where the functional Asp residues (Asp25 and Asp25′) are located at the dimer interface. The residue indexes for different regions of HIV-1-PR are shown in brackets, flap (43–58 and 43′–58′), flap elbow (35–42 and 35′–42′), fulcrum (11–22 and 11′–22′), cantilever (59–75 and 59′–75′), and active site regions (23–30, 78–82 and 23′–30′, 78′–82′) for chains A and B as represented in Fig. 1. Surface view of HIV-1-PR with the single-walled carbon nanotube (SWCNT) bound inside the active site cavity is shown in Fig. 2. The docked (3,3) SWCNT has a length of 18.5 Å and a diameter of 4 Å accommodating well in the active site cavity of the HIV-PR.

Nanomaterials have several advantages over many conventionally used peptidic or non-peptidic HIV-1-PR inhibitors. Nanomaterials do not react easily with other chemical compounds, which makes it stable enough as compared to the peptidic HIV-1-PR inhibitors [3]. C_{60} and carbon nanotube (CNT) tend to retain their geometrical properties and shape making it rigid structure, which helps them in firm interaction with other non-polar biochemical motifs [4]. The investigation of the inhibition effects of fullerenes has been performed through both computational and

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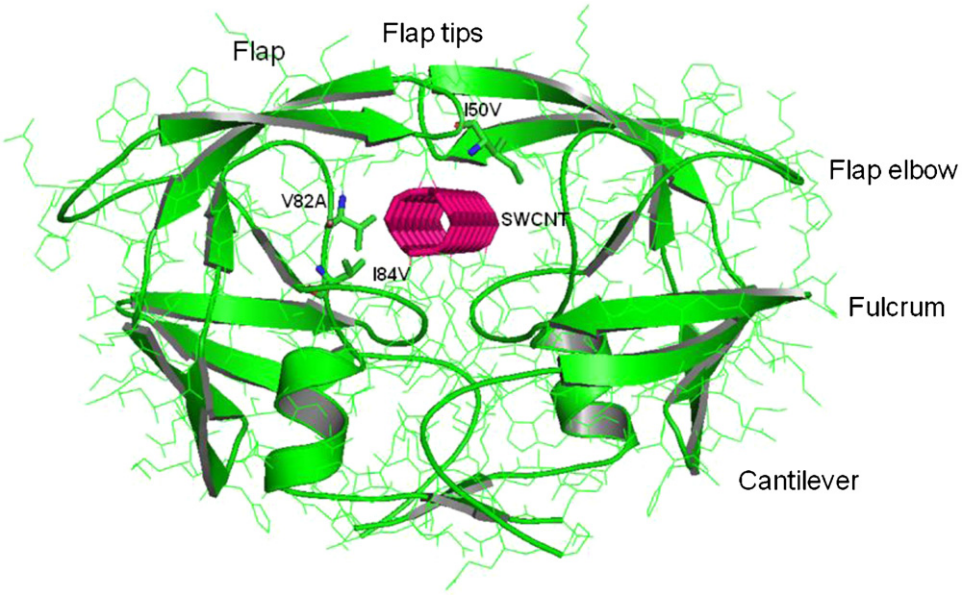

Fig. 1. Configuration of the HIV-PR/SWCNT complex. The HIV-PR is shown in green ribbons for both the chain A and the chain B. The sites of mutation for Ile50, Val82 and Ile84 are indicated by stick representation. SWCNT is bound in the active site and is labeled, which is represented by solid pink line. Important regions of the HIV-PR like flap, flap elbow, fulcrum and cantilever are also labeled.

experimental means. For example, fullerene C_{60}-derivatives have been found experimentally to be potent inhibitors with an inhibition constant K_i of ~100 nM [4–6]. Using molecular dynamics simulations and free energy calculations, Zhu et al. observed the ability of fullerene-based compounds to desolvate the cavity region that leads to a strong hydrophobic interaction between the C_{60} moiety and active site residues [7]. Zhu et al. therefore suggested that fullerene-based derivatives could be used as effective HIV-1-PR inhibitors. Moreover, the interactions of SWCNTs with human serum proteins lead to a competitive binding with different adsorption capacities and packing modes. Cellular cytotoxicity assays, with human acute monocytic leukemia cell line and human umbilical vein endothelial cells, expose that the competitive bindings of blood proteins on the SWCNT surface can greatly change their cellular interaction pathways and result in much reduced cytotoxicity for the protein-coated SWCNTs [8]. Furthermore from the virus inactivation assays of Schinazi et al., it has been found that fullerene based inhibitors are non-cytotoxic in human CEM, peripheral blood mononuclear (PBM), H9 and Vero cells with a concentration up to ~100 μM [9]. Fullerene based compounds have also inhibitory effects on a variety of enzymes like glutathione reductase [10], microsomal cytochrome P450-dependent monooxygenase and NADPH-cytochrome P450 reductase [11], carbonic anhydrase [12], M-MuLV reverse transcriptase [13], DNA polymerase [14], nitric oxide synthase [15,16], glycosidase [17], and lysozyme [18]. Based on the previously published studies and the current discussions, nanomaterial-based ligands may be used as efficient HIV-1-PR inhibitors with a great advantage compared to the conventional peptidic or non-peptidic HIV-1-PR inhibitors.

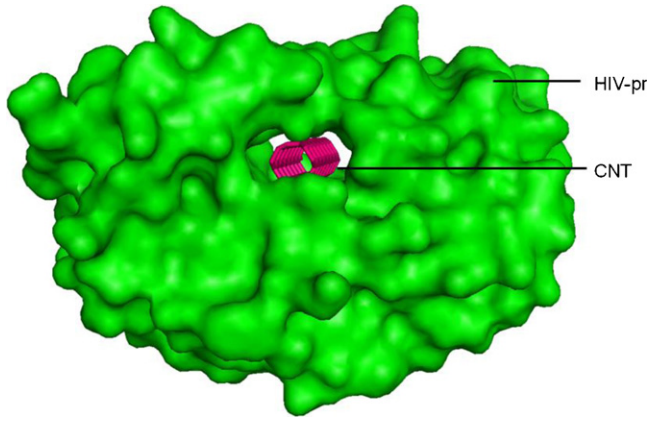

Fig. 2. Representation of the docked SWCNT inside the HIV-PR active site interior in surface view.

Nanomaterials such as fullerenes and CNT have also been tested as HIV-1-PR inhibitors in silico [3,19,20]. However, their studies were limited to wild type (WT) HIV-1-PR. In general, only the mutant HIV-1-PRs lead to drug resistance in all types of inhibitors. Thus, the more important is to investigate the flap dynamics and binding mechanism of CNT with mutant HIV-1-PRs. In the present study, we have tested the SWCNTs as inhibitors in WT as well as in three primary mutants ($I50V_{PR}$, $V82A_{PR}$ and $I84V_{PR}$) of HIV-1-PR by docking the SWCNT in the active site region, and then performed all-atom molecular dynamics (MD) simulations for the complexes. The conformational dynamics of HIV-1-PR were investigated with a 20 ns trajectory, revealing that SWCNT can bind to the HIV-PR active site and regulate the flap dynamics behavior. To gain an insight into the binding affinities, we also performed the binding free energy calculations for the four different HIV-1-PR/SWCNT complexes. Binding affinity calculations showed that the SWCNTs can bind to HIV-1-PR several folds higher than the current HIV-1-PR inhibitors, e.g., the most recent drug TMC114. With careful observations from the MD simulation results and the binding properties of SWCNT to the HIV-1-PR variants, the present study can offer SWCNTs as HIV-1-PR inhibitors with vast potential for applications against drug resistance.

2. Computational methods

2.1. Modeling CNT–protease complex through docking

The crystal structures of the wild-type and mutant HIV-1-PR bound to TMC-114 were obtained from the Protein Date Bank (PDB). The PDB entries are: 1T3R [21] for the wild type (WT), 2F8G [22] for the $I50V_{PR}$, 2QD7 [23] for the $V82A_{PR}$, and 2NNP [24] for the