Structure Analysis of Wild type HIV-I Proteases

[1]R. SreeLatha, [2]K. Ramya

Department of Physics, Bharath University, Chennai – 73,
Department of Bioinformatics, Avinashilingam University for Women, Coimbatore.

Abstract
Understanding the reactivity of the human immunodeficiency virus (HIV–1)is an emerging area in the field of drug design. The present article high lights the structure analysis of HIV-1 protease
Key words: *HIV–1, aspartylprotease,*

Introduction

Human Immunodeficiency Virus I protease (HIV-I PR) is an aspartylprotease essential for the life-cycle of the retrovirus HIV which causes AIDS. The HIV-I protease is the most important enzyme as it plays a vital role in viral maturation. The Immature, noninfectious viral particles are generally produced due to the Inactivation of this enzyme. Without effective HIV-I PR, HIV-I virions remain purely uninfectious. The enzyme therefore has become an attractive target in designing anti-AIDS drugs. Mostly thecurrent research focuses binding effect of various inhibitors on the protease structure in extenstion. This work analyze the Human Immunodeficiency Virus-I (HIV-I) interaction by looking at the following issuesHIV-1 alentivirusbelongs to the retrovirus family, causes AIDS(acquired immunodeficiency syndrome which is a condition in which the body fails to oppose the infect causing agent which leads the failure of immune system begins to fail. the progressive failure of the immune systemcauses death or malignancies to the untreated people.

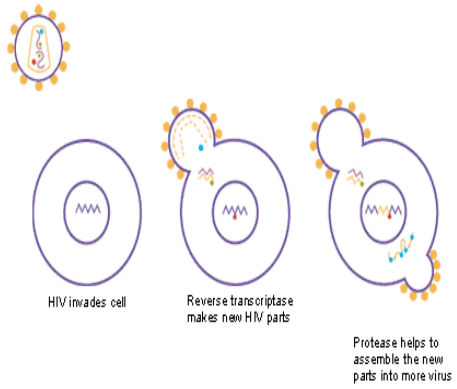

Figure 1: The mature HIV-1 virion structure

HIV-I can enter cells that express the trans membrane protein CD4 present in supporter T cells. When the HIV-I enters a carrier cell, itsRT(reverse transcriptase) molecules and and its allies are carried into the cell along with the viral RNA molecules. There conversion of the viral RNA genome into double-stranded DNAby HIV-I reverse transcriptase. The viral DNA subsequently integrated into the chromosomes of host's DNA by HIV-I integrase. Finally, after the integration, translation and post-translational proteolytic processing are done by HIV-I protease.[1-7]

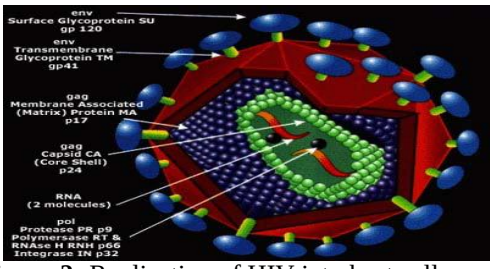

Figure 2: Replication of HIV into host cells

HIV-I protease

HIV-I protease (HIV-1 PR) , an aspartylprotease whos presence is must for the life-cycle of HIV. Figure 1 shows the mature HIV-I virion structure. In the absence of effective HIV-I PR, HIV-I virions are infectious.[8-12] HIV-1 PR cleaves the newly formulated poly proteins to make the mature protein components of an infectious HIV-1 virion. The pol and gag polypeptides (ie. Phe-Pro bonds in the Gag and Gag-Pol) is mainly caused by HIV-1 protease which thereby enervates the functional proteins in mature virions. The pol and gag(a single polypeptide) contain multiple

After they get separated, the individual parts (pol, RT, Rhase H, integrase) become functional which then facilitates thenew virus production. Thus, mutation of HIV-1 PR's active site would be enough to disrupt HIV-1's ability to duplicate and induce additional cells. This is why HIV-1 PR inhibition has become one of the important subjects of pharmaceutical research leads to structure based drug design. [13-17]

Protease cleavage mechanism

Aspartyl protease functions a "chemical scissors" that disintegrates the long chains of HIV-1 polypeptides. The inhibitors that arrest such protease functions are called as protease inhibitors. These Protease

inhibitors gums up the protease "scissors" and stops them from disintegrating resulting in the production of new viruses that can't infect other cells.

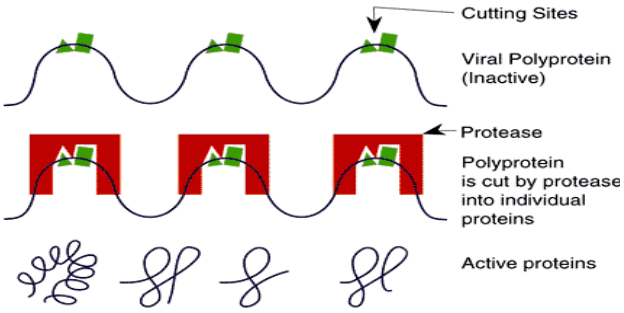

Figure 3: Protease cleavage mechanism

Structure of HIV-1 Protease

HIV-1 PR is an aspartyl protease belonging to peptidase family A2 (retropepsinendopeptidases). HIV-1 Protease is known to be highly unstable due to the effects of auto proteolysis, cysteine oxidation, and dimer instability. Unlike other monomers such as aspartyl proteases, HIV PR is a homo dimer, each of which donates one Asp-Thr-Gly triad to the pseudo-symmetric active site. Aspartyl proteases have four sites such as, oxyanion binding site, Catalytic triad, non-specific binding site for polypeptide substrate and substrate-specific pocket.

The major three domains of HIV-1 PR are flap, core and terminal domains. The Terminal /dimerization domain has the termini in the form of four stranded beta sheets (residue 1-4, 95-99 of each monomer), which plays a crucial role in formation and stabilization of dimer. The residue 10-32 along with the residue 63-85 from each monomer of the Core Domain is responsible for the stabilization of the dimmer and its catalytic site stability. At the same time the Flap domain (amino acid residue 33-43) precedes the beta hairpin (flaps residue 44-63). These cover the active site and provide the necessary interactionsfor ligand to binding. (Wlodaweret al., 1993)

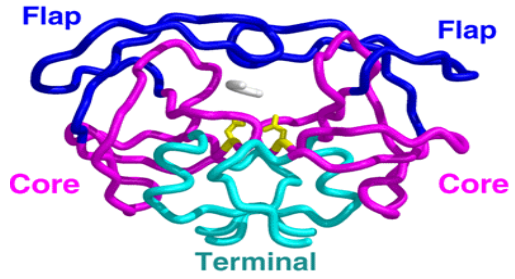

Figure 4: The 3 subdomains in HIV-1 PR

The most significant differences in the structures of viral and nonviral proteases are the symmetry of protease in the dimeric molecule. It approximately or exactly has the same single chain molecule of nonviral aspartic protease, resulted in topologically similar but not identical.

HIV Protease Inhibitors

Inhibitors are rebuilt taking into account the movement proteins emitted by regular peptide substrate .This is on account of the amino corrosive deposit contained would fit in the catalyst permitting the substrate to security with the compound all things considered. These protease inhibitor obstruct the cleavage of the viral poly peptide. Among the accessible hostile to HIV-1 drugs, protease inhibitors have been discovered produce the best concealment of viral replication. This HIV-1 protease was initially proposed by (Kramer et al., 1986) as a potential focus for AIDS treatment as it was demonstrated that poly-protein antecedent cleavage, is most crucial for the development of the HIV-1 particles(Kramer, et al.,1986).

Related studies on HIV-I protease

Designing of new inhibitors which can provide improved binding affinity has been analysed using the CoMFA and CoMSIA models. For these molecules the Pharmacokinetic along with toxicity predictions were carried out which can measure their ADME safety profile to a greater extent. Further the use of computational results that we end up may open up new directions for HIV-1 protease inhibitors synthesis. (Vijay M. Khedkar,et al.,SreeLatha. R,et al.,). Also , in addition to the internal dihedral angles .Algorithms had a wide degrees of freedom for ligand conformations. (Camila S, et al., 2004)

MD simulations Analysis has been used to allow the re-alignment of the protease side chain, specially on the active site, thereby improve the interacting complementarities of the complex. PDB (Protein Data Bank)code Crystal structures of peptidic inhibitor has two mutant HIV-1 proteases.

(Gane PJ and Dean PM ,2000) noted that "Docking approaches have been very important and useful tools in structure-based rational drug discovery and design". The problem in docking is due to the difficulties in optimization which involves with number of degrees of conformation. Effective docking algorithms and methodologies conforms the new structure as new drugs. (Marrone TJ, Briggs JM and McCammon ,1997) in Some docking programs the receptor and the ligand are treated as rigid body molecules by considering only the ligand translational and orientational degrees of freedom. (Ewing TJA and Kuntz ID, 1997) During docking analysis, the experimental crystallographic structure's

position are fixed. So most of the sophisticated docking algorithms also have a challenge when it comes to highly flexible ligands (Wang J, Kollman PA and Kuntz ID ,1999) and adding the receptor flexibility remains a primary hurdle.(Carlson HA and McCammon JA (2000)) A ligand conformation in general is represented by a chromosomewith its genes representing ligand translational, orientational and conformational degrees of freedom.(Whitley D et al (1995))

The less efficiency of the existing drugs has strongly influenced the need to search for efficient drug stimulate the development process in Drug-induced mutations of HIV-1 protease. The structural basis of a drug reaction and the methodologies for overcoming the water molecule replacement has been found tetrahedrally coordinated between the inhibitors and the enzyme. (Alexander Wlodawer and Jiri Vondrasek, 1998)

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