Systematic protein-protein docking and molecular dynamics studies of HIV-1 gp120 and CD4: insights for new drug development

Chong Teoh T., Heidelberg T., Rizman-Idid M.

Institute of Biological Sciences, Department of Chemistry, Science Faculty, University of Malaya, Kuala Lumpur, Malaysia.

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ABSTRACT

Background and the purpose of the study: The interactions between HIV-1 gp120 and mutated CD4 proteins were investigated in order to identify a lead structure for therapy based on competitive blocking of the HIV binding receptor for human T-cells. Crystal structures of HIV gp120-CD4 complexes reveal a close interaction of the virus receptor with CD4 Phe43, which is embedded in a pocket of the virus protein.

Methods: This study applies computer simulations to determine the best binding of amino acid 43 CD4 mutants to HIV gp120. Besides natural CD4, three mutants carrying alternate aromatic residues His, Trp and Tyr at position 43 were investigated. Several docking programs were applied on isolated proteins based on selected crystal structures of gp120-CD4 complexes, as well as a 5 ns molecular dynamics study on the protein complexes. The initial structures were minimized in Gromacs to avoid crystal packing effects, and then subjected to docking experiments using AutoDock4, FireDock, ChouPro and ZDock. In molecular dynamics, the Gibbs free binding energy was calculated for the gp120-CD4 complexes. The docking outputs were analyzed on energy within the respective docking software.

Results and conclusion: Visualization and hydrophobic bonding analysis were performed using the Swiss-POVViewer. Strong binding to HIV gp120 can be achieved with an extended aromatic group (Trp). However, the sterical demand of the interaction affects the binding kinetics. In conclusion, a ligand for an efficient blocking of HIV gp120 should involve an extended but conformational flexible aromatic group, i.e. a biphenyl. A docking study on biphenylalanine-43 confirms this expectation.

Keywords: HIV-1 surface-protein, Docked conformations, Free binding energy, Hydrophobic interaction.

INTRODUCTION

HIV-1 infection starts with the binding of the viral surface-protein gp120 to the human T-cell receptor CD4 via a hydrophobic pocket on gp120, which binds effectively to Phe43 in CD4 (1). This initial association is followed by membrane fusion and transfer of the viral genetic material into the cell, thus enabling the reproduction of the virus whilst destroying the host. The crucial role of the gp120-CD4 interaction has been demonstrated by an experiment leading to HIV-1 vulnerable rats after insertion of human CD4-CDR2 protein sequences (2), while the impact of Phe43 was confirmed by significant loss of binding affinity of CD4 for gp120 after mutation around the binding site (3, 4). Therefore the amino acid sequence in gp120 is highly conserved and less prone to mutations (1, 2), thus providing a promising target for the development of new drugs (5).

Blocking the cellular entry of the virus is more practical and exhibits less side effects compared to a drug operating at intracellular level, e.g. a protease inhibitor (6). BMS-378806 inhibits the gp120-CD4 binding, as shown in an enzyme-linked immunosorbent assay (ELISA), without inhibitory activity against HIV-1 reverse transcriptase, protease and integrase and it has been proposed as a good candidate against HIV-1 infection (7, 8). A clinical study of gp120 inhibition has not been conducted so far, however an oligopeptide CD4 mimic has been used to study the inhibition of the HIV-1 entry using a cell-based fusion assay (9).

Several computational studies have been performed on docking and molecular dynamics of small ligands with either gp120 (5, 10) or CD4 (11) to identify suitable inhibitor candidates. Another investigation applied molecular dynamics on the gp120-CD4 complex targeting to predict a mimic for the natural Phe43 conformation in the complex.

Correspondence: itchong@um.edu.my