One Interface – Two Perspectives
Exploration of the HIV-1 gp120 – CD4 Interaction

Kristin Kassler[1], Julia Meier[2], Jutta Eichler[2], and Heinrich Sticht[1]

[1]Bioinformatics, Institute of Biochemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg, Fahrstraße 17, 91054 Erlangen, Germany. [2]Department of Medicinal Chemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg, Schuhstrasse 19, 91052 Erlangen, Germany

The initial step of HIV-1 infection is the recognition and the binding of the cellular receptor CD4 by the viral surface protein gp120. A detailed understanding of this interaction from perspective of gp120 or CD4 can help in the rational design of HIV-1 drugs.

In order to explore the CD4 interface mediating the gp120-CD4 interaction, the differences between human and murine CD4 (hCD4 and mCD4) were investigated. Murine CD4 is not bound by HIV-1 gp120 despite a high sequence homology between hCD4 and mCD4. Strikingly, peptides derived from both human and murine CD4 bind with similar affinity and specificity. Molecular modeling indicates that mCD4 protein cannot bind gp120 due to steric clashes, while the larger conformational flexibility of mCD4 peptides allows an interaction. Molecular dynamics simulations reveal that the mCD4-peptide stably interacts with gp120 via an intermolecular β-sheet, while an important salt-bridge formed by a C-terminal lysine is lost. Fixation of the C-terminus by introducing a disulfide bridge between the N- and C-termini of the peptide significantly enhanced the affinity to gp120. [1]

The gp120-part of the interface was inspected by exploring two natural gp120 mutants (termed ALM and EM) with decreased CD4-binding affinity. In molecular dynamics simulations of wild type and mutant gp120-CD4 complexes, essential intermolecular β-sheet contacts are disrupted in the mutant gp120-CD4 complexes while stably maintained by wild type gp120. Particularly, the crucial loop anchor is totally or at least partially lost in ALM and EM, respectively. Mutant glutamates offer an explanation for disruption of those key contacts. Interestingly, though located at different sites in ALM and EM they exert a similar effect.

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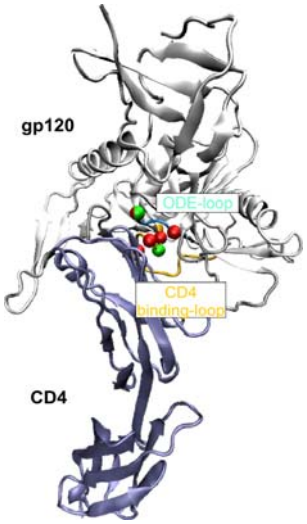

The gp120-CD4 interface. Interacting loops of the CD4-binding side are colored in yellow and cyan. Residues mutated in ALM and EM are visualized as red or green balls, respectively.

[1] K. Kassler, J. Meier, J. Eichler, H. Sticht, *Advances in Bioinformatics*, **2011**, Epub 2012 Jan 19.