[P13] CCR5 Dimer: Characterisation of Interface

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The type 5 C-C chemokine receptor (CCR5) is the major co-receptor of HIV-1. Although experimental data in the literature reveals evidences for CCR5 dimerization, the dimerization mode is not known. [1] In order to determine which residues are involved in contact between protomers, we combined biochemical crosslink and molecular modeling. [2]

Introduction of cystein and subsequent disulfure bridge formation between protomers suggest the involvement of several transmenbrane helix (TM) residues in a symmetrical organization of the dimer. The modeling of CCR5 dimer based on crystallographic structure of CXCR4 and mu opioid receptors is in agreement with two dimerization modes involving mostly TM4/TM5 and TM5/TM6, respectively. [3-4]

Dimer stability was assessed by molecular dynamics (MD) simulations of these two dimers embedded in a hydrated lipid bilayer, supporting the existence of two interfaces of dimerization. CCR5 dimerization is inhibited if a lysine residue is introduced at specific position in TM5 (as demonstrated by FRET experiments and RUSH assays). Surprisingly, the antiviral drug maraviroc restores partly the dimerization of mutants. MD simulations of monomeric CCR5, free or bound to maraviroc, indicate that the binding of maraviroc modifies the receptor dynamics and induces changes at the protein surface. Thus conformational changes may favor the formation of a new dimer interface. This dimeric organization was experimentally trapped using DSP covalent bridging of protomers.

All together, our data support at least three dimeric forms of CCR5: two interfaces involve TM5 and a third one not yet modeled.

References:

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