Coarse-grained molecular modeling of the membrane receptor CXCR4 recognition by the chemokine CXCL12

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CXCR4 belongs to the class A G-Protein-Coupled-Receptors family and its endogenous specific ligand is the chemokine CXCL12. It has been demonstrated that the CXCR4-CXCL12 axis plays, among other functions, a key role in the regulation of HIV infection and breast cancer metastasis [1]. Thus it has a great importance in pharmaceutical research.

The three-dimensional structure of the CXCR4 receptor has been recently solved by X-ray diffraction [2], but the first twenty-six amino acids of the N-terminus are missing in this structure, whereas they are one of the putative binding sites of CXCL12. In addition, NMR experiments have determined the solution structure of the chemokine CXCL12 complexed with the thirty-eight first residues of the N-terminal fragment of CXCR4 [3]. Despite this information, the interactions and recognition mechanism between the whole protein CXCR4 and its ligand CXCL12 are not completely elucidated in detail.

We report here the results of coarse-grained molecular modeling studies to gain a better insight into the CXCR4-CXCL12 interactions. First, coarse-grained protein-protein docking calculations were used to generate the most probable quaternary structures of the receptor-ligand complex. Then, coarse-grained molecular dynamics simulations were performed to assess the stability and to probe the dynamics of the CXCR4-CXCL12 conformations in a membrane environment.

References:

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