

Molecular mechanisms governing interleukin-8 binding to the chemokine receptor CXCR1

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The CXC chemokine receptor-1 (CXCR1) is a class A G protein-coupled receptor that plays an important role in mediating inflammatory responses. CXCR1 is present in the cell membrane of neutrophils and is activated upon binding of its natural ligand, interleukin-8 (IL-8). A series of experiments based on truncated constructs of CXCR1 hypothesized that binding of IL-8 to CXCR1 is a multi-step process, although the exact binding modes of IL-8 remain unknown. Here, we have analyzed the binding of IL-8 to CXCR1 using Martini coarse-grained simulations. First, we have performed microsecond timescale simulations of the full-length CXCR1 in phospholipid bilayers (POPC). We observe that the putative ligand binding N-terminal region interacts transiently with membrane, with the help of an anchoring tryptophan residue. Subsequently, we analyzed the binding of IL-8 with CXCR1 *via* multiple unbiased coarse-grained simulations. Our results show that, IL-8 initially binds the N-terminal of the receptor, such that the N-loop region of IL-8 interacts predominantly with the N-terminal of receptor. Subsequently the complex moves towards central lumen of the receptor enabling IL-8 to interact with extracellular loops. Our work is a crucial step towards understanding the molecular mechanism of IL-8-CXCR1 binding that can be exploited to design improved therapeutic strategies.