S50-2 3D-structure prediction of GPCRs with ligands using molecular modeling techniques

◯Takatsugu HIROKAWA[1]
[1]CBRC, AIST

G-protein coupled receptors (GPCRs) are the largest known family for drug targets. However, solving the 3D structures of GPCRs has proven difficult with currently available experimental techniques such as X-ray crystallography and NMR. Therefore, computational protein modeling and ligand docking fill the gaps between the GPCR sequences and structure-based drug design. We developed molecular modeling pipeline for GPCRs which is comprised of five processes: (1) sequence analysis, (2) comparative modeling, (3) MD simulation, (4) active site pocket analysis and (5) ligand docking. In sequence analysis, TM and disordered regions in a target GPCR sequence are predicted. Importance of disorder prediction in GPCR has been recently reported by Dr. Jaakola. In comparative modeling, target sequence was aligned with bovine rhodopsin or beta2- adrenergic receptor and forty sequence representation of Class A rhodopsin like family using multiple sequence alignment. And then, 3D structure was constructed using a comparative modeling approach and MD simulation with GBSA/IM model. After MD simulation, we analyzed the active site pocket candidates from MD trajectories for ligand docking. We applied this pipeline to ligand binding prediction in several GPCRs. The predicted ligand binding models were evaluated by site-directed mutagenesis experiments in collaborative research and the enrichment rate of activated ligands in virtual screening.