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Molecular modeling of GPCR dimmers

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Abstract

Dimerization or oligomerization of GPCRs is a well-established phenomenon, which has been confirmed by many experimental and molecular modeling data. Molecular modeling approaches can be classified into sequence-based and structure-based methods. The first group is based on the GPCR sequence analysis performed in order to detect evolutionary changes of the GPCR interfaces. Structure-based approaches involve protein-protein docking and molecular dynamics techniques as well as electrostatics analysis with Adaptive Poisson-Boltzmann Solver (APBS) and Normal Mode Analysis.

We first demonstrated that protein-protein docking approaches are unsuitable for the prediction of GPCR-dimer structures when applied to transmembrane proteins. Instead of that we elaborated a sophisticated protocol with subsequent docking, scoring, energy minimization and clustering procedures. The following parameters are used for consensus scoring: Rosetta score, dimer interface area, polar contribution to interface area, interface surface roughness, evolutionary conservation score, hydrogen bond interactions, shape complementarity and electrostatic complementarity. Alternatively, we also performed free energy scans on dimers with different interfaces to select the most stable interface. Furthermore, we employed APBS in order to study electrostatic interactions in GPCRs oligomerization interfaces in detail. These methods were successfully tested on dimers with available X-ray structures (opsin, kappa opioid receptor and CXCR4 dimers) and then applied to CB_1R and D_2R homodimers as well as to mGluR5-D_2R heterodimers in different conformational states. The availability of dimer models made it possible to propose the modes of interaction of bivalent ligands with these dimers.

Biography

Agnieszka Kaczor obtained her MSc in chemistry and PhD in pharmacy, both in Lublin, Poland. She made her postdoctoral training in GRIB/PRBB, Barcelona, funded by Foundation for Polish Science, and at University of Regensburg, funded by DAAD. At present she is Marie Curie fellow at University of Eastern Finland. Dr. Kaczor is author of 24 scientific articles and book chapters, 2 patents and 80 conference presentations. She has obtained several research and teaching awards, including those by the Polish Minister of Health and multiple travel grants, including Young Investigator Award by IUPAC (twice) and European Science Foundation (twice).