MBG FOCUS TALK

hosted by Section for Structural Biology

MBG Focus Talks in Molecular Biology

Tuesday 16th July 2018 from 10:15-11:00

MBG conference room (3130-303), Gustav Wieds Vej 10C, 8000 Aarhus C

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Structural insights into G protein activation

The crystal structure of beta2 adrenergic receptor (β2AR) – Gs complex provided the first high-resolution snapshot of how agonist bound GPCR activates a heterotrimeric G protein. In this nucleotide-free complex (R^*-G^{empty}), the C-terminal alpha-5 helix of Gas undergoes a large structural change to penetrate the core of the β2AR, into a space created by the outward movement of TM6. Recent single molecule experiments provide evidence for the existence of a transient complex between the β2AR and GDP bound Gs protein (R^*-G^{GDP}) that involves a smaller outward movement of TM6 and may represent an intermediate on the way to the formation of R^*-G^{empty}. R^*-G^{GDP} is not amenable to characterization by crystallography, as it appears to be a transient intermediate complex that is less stable than R^*-G^{empty}. However, we have been able to crystalize the β2AR fused to the carboxyl terminal 14 amino acids from Gαs α5 helix (GsCT). Unexpectedly, we obtained a structure of GsCT interacting with active β2AR in a different mode compare to β2AR-Gs complex. The binding mode involves interactions between conserved E392 and R389 of Gs and the D and R of the conserved DRY sequence of the β2AR. Of interest, in GDP-bound Gs, E392 and R389 are solvent exposed and accessible to the cytoplasmic surface of the β2AR. Moreover, mutations of E392 and R389 alter interactions with Gs. These observations suggest that the structure presented here may represent an intermediate state in the formation of R^*-G^{empty}.

Host: Professor Poul Nissen