Crystal structure of full-length human glucagon receptor reveals novel receptor activation mechanisms

Subject Code: C05

With the support by the National Natural Science Foundation of China, a team of scientists let by Profs. Wu Beili (吴蓓丽), Wang Mingwei and Jiang Hualiang from Shanghai Institute of Materia Medica, Chinese Academy of Sciences has determined the high-resolution atomic structure of a full-length class B G protein-coupled receptor (GPCR) that plays a key role in glucose homeostasis. The study was recently published in *Nature* (2017, 546: 259—264).

Class B GPCRs are essential to numerous physiological processes and serve as important drug targets for many human diseases such as type 2 diabetes, metabolic syndrome, osteoporosis, migraine, depression and anxiety. These receptors consist of an extracellular domain (ECD) and a transmembrane domain (TMD), both of which are required to interact with their cognate peptide ligands and to regulate downstream signal transduction. Due to difficulties in high-quality protein preparation, structures of full-length class B GPCRs remained elusive, thus limiting a comprehensive understanding of molecular mechanisms of receptor action.

The human glucagon receptor (GCGR) belongs to the class B GPCR family and has been considered as an important drug target for the treatment of type 2 diabetes. In this study, the crystal structure of the full-length human GCGR in complex with a negative modulator NNC0640 and an inhibitory antibody mAb1 was determined. The study gives many valuable insights into the structural features of GCGR. The most exciting finding is that the linker region connecting the ECD and TMD of the receptor, termed the "stalk", adopts a β-strand conformation instead of forming an α-helix as observed in the previously solved structure of the GCGR TMD. The stalk works together with an extracellular loop of the TMD to regulate peptide binding through conformational changes, serving like a modulator in receptor activation.

Based on the full-length GCGR structure, a series of functional studies were performed using hydrogen-deuterium exchange, disulfide cross-linking, competitive ligand binding and cell signaling assays as well as molecular dynamics simulations. The results are in support of the GCGR structure and confirm the interactions between different domains in modulating its functionality via conformational alterations, which further deepen our understanding about class B GPCR activity modulation.

The full-length GCGR structure not only expands our knowledge about GPCR signaling mechanisms, but also offers new opportunities in drug discovery targeting class B GPCRs.

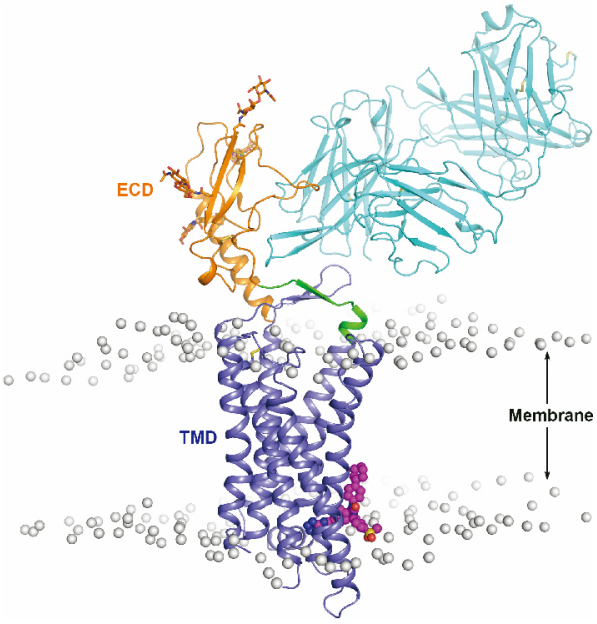

Figure Crystal structure of the full-length GCGR in complex with NNC0640 (magenta) and mAb1 (cyan).