STRUCTURAL CO-EVOLUTION OF PACAP/GCGR FROM INVERTEBRATES TO VERTEBRATES

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Statement of the Problem: G-protein coupled receptors (GPCRs), an essential molecular signaling device to connect extracellular stimulus and intracellular response, are currently one of the major targets for therapeutic drugs. Class B GPCRs are highly attractive therapeutic targets with several pathophysiological functions. In recent years, crystal structures of two full receptors (glucagon receptor and CRF receptor) and several other extracellular domains were released, enabling novel understanding of the interactions of this family of ligand-receptor at atomic level. The current knowledge base provides great opportunity to conduct comparative study and investigate the structural evolution of the receptor family by generating reliable homology model of class B1 GPCRs from various species. The comparison between primitive and advanced species provide insight into how communicating systems are built to support complicated operation of multiple tissues. Investigating these GPCRs with long evolutionary history can provide treasurable information for drug design. We intend to investigate the molecular evolution of class B1 GPCRs from structural perspective, with focus on ligand binding pocket. Comparative study of class B1 GPCRs has been a research focus of our lab for more than 10 years.

Methodology & Theoretical Orientation: We used data mining and bioinformatics analysis along with molecular cloning techniques to develop and clone ancestral PACAP/GCG receptor by using the information from the genome projects to isolate all putative ligand and receptor cDNAs from *B floridae* and *B belcheri* and further screen the receptor sequences from amphioxus. In quest to understand the pre-2WGD condition of PACAP and GCG receptor interaction with their receptor, we developed a photo-label probe analog to natural peptide, to test for the binding location on to the receptor. To understand and compare the structure of primitive receptor with the human receptors, we designed homology model of the receptor and further developed a receptor ligand complex. This complex will be validated by photoaffinity data provided by the help of photo labeled probe.

Conclusion & Significance: Investigating GPCRs with long evolutionary history by comparative approach will allow assessment of ligand binding domain of the receptor for intracellular signaling, which is a treasurable information.

Figure.1: Summary of molecular cloning of class B1 GPCRs and cognate ligands done by our group. Each red stars * indicate sequence reported in our publications.

Recent Publications

1. Ng SY (2012) Agnathan VIP, PACAP and their receptors: ancestral origins of today's highly diversified forms. PLoS One 7: e44691.
2. Ng SY (2011) Discovery of a new reproductive hormone in teleosts: pituitary adenylate cyclase-activating polypeptide-related peptide (PRP). Gen Comp Endocrinol 173: 405-410.

BIOGRAPHY

B K C Chow is a Chair Professor of the University of Hong Kong. He has his research interest in endocrinology of brain-gut peptides, pleiotropic activities of secretin in our body and evolution of GHRH/PACAP peptides and receptors.

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