Department of Biological Sciences

VISITOR'S TALK

Speaker: Prof. Amitabha Chattopadhyay

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Date/Time: Thursday, 21st June, 2018 at 03:00 pm

Venue: AB3-401

Cholesterol-induced Conformational Plasticity and Oligomerization of GPCRs: Novel Insights in Health and Disease

G protein-coupled receptors (GPCRs) are the largest class of molecules involved in signal transduction across membranes, and represent major drug targets in all clinical areas. The overall focus of our work is on the role of membrane cholesterol in GPCR organization (oligomerization), dynamics and function with implications in health and disease. The GPCR of choice is the serotonin$_{1A}$ receptor, an important neurotransmitter receptor implicated in the generation and modulation of cognitive, behavioral and developmental functions, and an important drug target. We demonstrated that membrane cholesterol is necessary for ligand binding, and G-protein coupling and signaling of serotonin$_{1A}$ receptors. Interestingly, high-resolution crystal structures of GPCRs exhibit bound cholesterol. In this context, we reported the presence of cholesterol recognition/interaction amino acid consensus (CRAC) motifs in the serotonin$_{1A}$ receptor. Recent results employing mutations in the CRAC motifs show the importance of Lys101 in transmembrane helix II in conferring cholesterol-sensitivity to signaling by the receptor. In addition, using a combination of experimental and MD simulation approaches, we demonstrated that the receptor is more stable and compact in the presence of membrane cholesterol. Further, our results provide important insights in cholesterol-dependent oligomerization of the receptor using a variety pf approaches such as photobleaching homo-FRET, photobleaching image correlation spectroscopy, and coarse grain MD simulations. We ension that progress in deciphering molecular details of the nature of GPCR-cholesterol interaction in the membrane would lead to better insight into our overall understanding of GPCR function in health and disease.

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