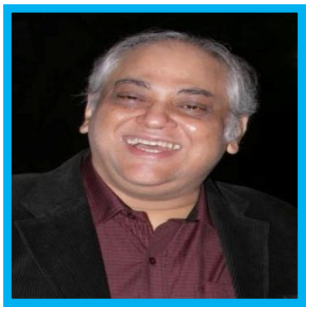
Department of Biological Sciences Seminar Series
IISER Kolkata



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Title:

"Membrane Cholesterol and the Serotonin$_{1A}$ Receptor: Recent Insights from Structural Biology"

Seminar Link: meet.google.com/efn-auik-qkf

***Seminar Host*: Prof. Jayasri Das Sarma**

Time: 4 PM, 23 June 2021

Abstract*:* 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 serotonin$_{1A}$ receptor is an important neurotransmitter receptor of the GPCR superfamily and is implicated in the generation and modulation of various cognitive, behavioral and developmental functions. In our earlier work, we demonstrated that membrane cholesterol is necessary for ligand binding, G-protein coupling and signaling of serotonin$_{1A}$ receptors. In the overall context of high-resolution structures of GPCRs showing bound cholesterol molecules, we previously reported the presence of cholesterol recognition/interaction amino acid consensus (CRAC) motifs in the serotonin$_{1A}$ receptor. In our recent work, we explored the molecular basis of cholesterol sensitivity exhibited by the serotonin$_{1A}$ receptor by generating mutants of key residues in CRAC motifs in transmembrane helices (TM) 2 and 5 of the receptor. Our results show that a lysine residue (K101) in one of the CRAC motifs is crucial for sensing altered membrane cholesterol levels. These observations are further supported from all-atom molecular dynamics simulations which reveal a tightly bound cholesterol molecule between TM1 and TM2 by establishing polar contacts with K101 that leads to stabilization of extracellular loop 1 (ECL1). Interestingly, the position of this cholesterol molecule is almost identical to a co-crystallized cholesterol molecule in the recently reported high-resolution cryo-EM structure of the serotonin$_{1A}$ receptor, thereby strongly validating the molecular mechanism for cholesterol sensitivity of the serotonin$_{1A}$ receptor proposed by us. These results constitute one of the first reports comprehensively demonstrating that cholesterol sensitivity could be knocked out by a single point mutation in a specific cholesterol binding site. We envision that progress in deciphering molecular details of the nature of GPCR-cholesterol interaction would lead to better insight into our overall understanding of GPCR function in health and disease.

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