Exploring Cholesterol Sensitivity of G Protein-Coupled Receptors: Excitements and Challenges

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G protein-coupled receptors (GPCRs) are cellular nanomachines that represent the largest group of integral membrane proteins in the human proteome involved in signal transduction across membranes. GPCRs represent major drug targets in all clinical areas and account for ~40% of current drug targets. 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. Pioneering work from our group demonstrated that membrane cholesterol is necessary for ligand binding, G-protein coupling and signaling of serotonin$_{1A}$ receptors. In our recent work, we explored the molecular basis of cholesterol sensitivity exhibited by the serotonin$_{1A}$ receptor by generating site-specific mutants of key residues in CRAC motifs in transmembrane helices (TM) 2 and 5 of the receptor supported by all-atom MD simulations. Notably, we showed that a lysine residue (K101) in one of the CRAC motifs is crucial for sensing altered membrane cholesterol levels (Kumar *et al.* (2021) *Science Advances* 7: eabh2922 (recommended in Faculty Opinions (F1000Prime)). These results constitute one of the first reports comprehensively demonstrating that cholesterol sensitivity could be knocked out by a single point mutation at a cholesterol binding site. Our 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. I will end my talk by presenting our recent exciting observations on the role of cholesterol in GPCR endocytosis (spatiotemporal regulation) and trafficking and their implications in pathophysiology and therapeutics.

References

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