REGIONAL CENTRE FOR BIOTECHNOLOGY
Seminar series

Structural basis of β-arrestin dependent regulation and signaling of G Protein-Coupled Receptors

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Abstract

G Protein-Coupled Receptors (GPCRs) represent the largest family of cell surface receptors in the human genome and they are involved in almost every physiological and pathophysiological processes in the human body. Currently, about half of the marketed medicines target this class of receptors including several blockbusters such as opiates, α- and β- blockers, antihistamines and angiotensin receptor blockers. However, the structural basis of activation and regulation of these receptors has just started to emerge and still remains in its infancy.

The functions of G-protein coupled receptors (GPCRs) are primarily mediated and modulated by the heterotrimeric G proteins, the G-protein coupled receptor kinases (GRKs), and the β-arrestins. G proteins mediate activation of second messenger generating enzymes and other effectors, GRKs phosphorylate activated receptors, and β-arrestins subsequently bind phosphorylated receptors and cause receptor desensitization. However, β-arrestins activated by their interaction with phosphorylated receptors can also mediate receptor endocytosis and G protein independent signaling. Despite their central role in regulation and signaling of GPCRs, a structural understanding of β-arrestin activation and interaction with GPCRs is still lacking.

My research has essentially focused on understanding the biophysical and structural basis of β-arrestin mediated regulation and non-canonical signaling of GPCRs. I'll present my research findings pertaining to the conformational switching in β-arrestins that underlies non-canonical GPCR signaling, activation mechanism of β-arrestin upon interaction with GPCRs as revealed by X-ray crystallography and the first snapshot of a GPCR-β-arrestin complex as visualized by cryo-EM (Electron Microscopy). I'll also discuss how these findings not only provide novel insights in to GPCR regulation and signaling but also offer unique translational opportunities.