FS CREATION Colloquium

Structural dynamics of G protein-coupled receptors revealed by NMR

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G protein-coupled receptors (GPCRs) constitute the largest membrane protein family in eukaryotes, and play fundamental roles in many physiological processes, including sensory perceptions, neurotransmissions, immunological processes, etc. Upon ligand binding on the extracellular sides, GPCRs undergo conformational changes in transmembrane regions, resulting in the signal transmission through the effectors on the intracellular sides. Interestingly, GPCRs exhibit low levels of intracellular signaling even in the absence of ligands, which is called the “basal activity”, and the signal transduction level, which is called the “efficacy”, varies depending on the bound ligands. In addition, GPCRs activate two different pathways of intracellular signaling, G protein signaling and arrestin signaling. In the G protein signaling, agonist-bound GPCRs activate intracellular G proteins, resulting in intracellular responses, such as increased or decreased cAMP levels. In the arrestin signaling, agonist-bound GPCRs are phosphorylated by GPCR kinases (GRKs), and subsequently arrestins bind to phosphorylated and agonist-bound GPCRs, resulting in multiple intracellular responses, such as the receptor internalization and the activation of MAPK pathways. These two different pathways of signaling are reportedly related to different functions. For example, in the case of μ-opioid receptor (μOR), the signaling levels of G protein and arrestin pathways are well correlated to the analgesics and the side effects, respectively. Therefore, the GPCR ligands that cause the selective activation of one pathway over the other, which is called the “biased signaling”, would be clinically beneficial drug candidates.

Recent advances in X-ray crystallography and cryo-electron microscopy revealed the high-resolution three-dimensional structures of more than 100 GPCRs, including GPCRs bound with ligands with various efficacies and biases, GPCRs bound with G proteins, arrestins, or GRKs. However, high-resolution static structures could not fully account for the GPCR functions; how GPCRs activated multiple effectors including G proteins, GRKs, and arrestins; how GPCR ligands evoke various levels of efficacies and biases; and how membrane environments affect the GPCR signaling, etc. We and other several groups recently have applied nuclear magnetic resonance (NMR) spectroscopy to investigate the dynamics of GPCRs, and now growing evidence suggests that the transmembrane structures of GPCRs are intrinsically dynamic, and ligands, effectors, and membrane environments all affect such function-related dynamics. In this colloquium, I will introduce our NMR works on GPCRs to explain how dynamical aspects of GPCRs control cellular functions.

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