The Biophysical Society of Japan (BSJ) – Miyazaki Meeting, September 2019 Session 1SHP—frontier of structure-function studies to unveil diverse GPCR signaling

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GPCR (G protein-coupled receptor) signaling utilizes an allosteric coupling between the extracellular facing ligand-binding pocket and the cytoplasmic domain of the receptor selectively interacting with a signal transducer. This allosteric effect enables one site of the receptor to regulate the function of another spatially distinct region. Therefore, it is important to understand the molecular mechanisms behind ligand-induced changes in receptor conformation and specific transducer-recognition for the development of GPCR-based drugs. This symposium is dedicated to discussing the latest trends on the structure-function studies to explore the molecular basis of GPCR signal transduction. Six presenters presented the latest GPCR research using their specialized methods (Fig. 1).

Ikuo Masuho developed a single-platform assay for profiling GPCR activity on a nearly complete set of G protein substrates.(Masuho et al. 2018)

Masataka Yanagawa analyzed the dynamic behavior of GPCRs by observing single receptor molecules in a living cell. He and his group have developed a single-molecule imaging analysis for assessing the effects of ligands on GPCRs.(Yanagawa et al. 2018)

Hideaki Kato determined the structure of the human neurotensin receptor 1 (NTSR1)-G protein complex by cryo-

electron microscopy (cryo-EM) single-particle analysis (Fig. 1). (Kato et al. 2019).

Hiroshi Kofuku measured the dynamics of GPCRs using NMR. To understand the mechanism underlying the formation of the phosphorylated GPCR-arrestin complex, they performed NMR analyses of the phosphorylated β_2 -adrenoceptor (β_2 AR) and the phosphorylated β_2 AR- β -arrestin 1 complex in the lipid bilayers of nanodisc.(Kofuku et al. 2018)

Satoshi Yasuda presented the search for thermostabilizing mutations in GPCRs on the basis of theoretical prediction. He and his group developed a theoretical prediction method for thermostabilizing mutations using their free-energy function which is focused on the translational entropy of nonpolar chains within the lipid bilayer as the entropic term and the protein intramolecular hydrogen bonding as the energetic term.(Yasuda et al. 2017)

By applying this thermostabilizing mutation, Ryoji Suno successfully determined the three-dimensional structure of S110R mutated muscarinic acetylcholine receptor 2 (M2) bound with the subtype selective antagonist (AF-DX 384).(Suno et al. 2018)

This commentary strives to provide recent advanced approaches to communicate select aspects of GPCR structure-function relationship for precise signal transduction. This latest phase of GPCR science has benefited greatly from past outstanding biochemical, biophysical, and physiological methods, and from the well-characterized information about individual proteins. Because GPCRs are of significant research interest to scientists, and continue to yield fascinating discoveries, our future work will continue to advance to fully understand the molecular mechanism of GPCR signal transduction.

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Fig. 1 The structure of NTSR-1-Gi1 complex (**a** C state, **b** NC state)

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