Shedding light on complexity of G-protein coupling by large-scale functional assays

Asuka Inoue

Grad. Sch. of Pharm. Sci., Tohoku Univ.

Signal transduction initiated from GPCRs is primarily mediated by heterotrimeric G proteins, which are grouped into four families (Gs, Gi, Gq and G12). G-protein-coupling pattern determines a cellular response unique to each GPCR and thus profiling these patterns is a critical step toward understanding GPCR biology. However, due to functional redundancy of multiple members and signal cross talk downstream of G-protein signaling, it is challenging to assess coupling signature of every G-protein member at a large scale. Over years, our lab has spent efforts to establish and standardize GPCR tools that enable measurement of individual G-protein coupling and signaling. These include a panel of GPCR effector-KO cells (G-protein, β-arrestin, GRK), TGFα shedding assay, NanoBiT-G-protein dissociation assay, etc. By combining these tools, we have recently profiled G-protein coupling of ～150 GPCRs across all G-protein members. Bioinformatics analysis of the large-scale dataset allowed us to identify generic GPCR residues that are involved in G-protein-coupling selectivity. Using the coupling-featuring residues, we generated a predictor algorithm that scores G-protein coupling based on an amino-acid sequence. Intriguingly, we successfully designed a DREADD that switched coupling from Gq to G12. In this symposium, we will explain our GPCR tools and present a recent advance in understanding where and how G-protein-coupling selectivity is encoded by "coupling determinants" in GPCRs. We will also present assays to measure G12, the least characterized G-protein family, and will discuss potential drug targets for G12-related diseases.