【Grant-in-Aid for Specially Promoted Research】

Biological Sciences

Title of Project : In situ functional analyses of membrane proteins by NMR

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Research Project Number : 17H06097 Researcher Number : 70196476
Research Area : Structural biology
Keyword : NMR, G-protein coupled receptors, ion channels, transporters

【Purpose and Background of the Research】

Over the past decade, our structural understanding of membrane proteins has dramatically progressed, owing to the growing numbers of atomic resolution crystal structures of membrane proteins, including G-protein coupled receptors (GPCRs). However, the crystal structures represent static snapshots of proteins in the crystal lattice, and the observed conformations may not be the same as those in the environment where they actually function.

In this research project, we use the solution NMR, in order to obtain dynamic structural information of the membrane proteins under physiological conditions, which are directly related to their function.

【Research Methods】

In this research project, we will analyze the relationships between the dynamical structures and the functions for biologically important membrane proteins: 1) Biased-signaling of GPCRs, 2) Gating and activation mechanisms of potassium ion channels, and 3) Synergistic regulation of multi-drug resistant (MDR) system, with dynamical structures that are responsible for their functions. For these purposes, we will also develop NMR methodologies for studying the structures and dynamics of membrane protein.

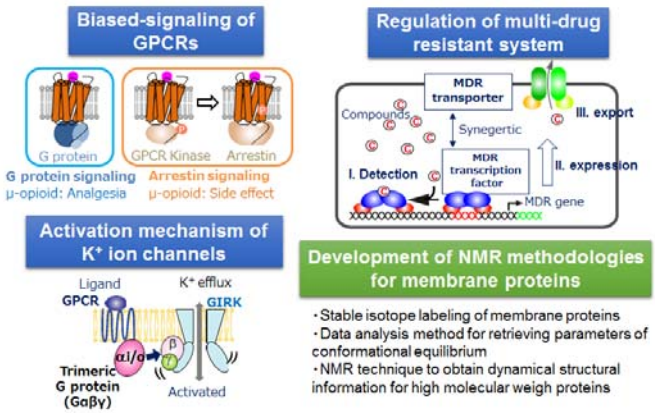

Figure 1 Overview of research project

【Expected Research Achievements and Scientific Significance】

Although the crystal structures of GPCRs bound to a G protein or arrestin are available, the mechanism underlying the biased signaling of GPCRs is still unclear. We will analyze the mechanism underlying the biased signaling of GPCRs using NMR. We expect that this NMR project will shed light on the conformational dynamics directly related to the biased-signaling, which will be valuable for the discovery of therapeutic agents targeted to GPCRs and other membrane proteins.

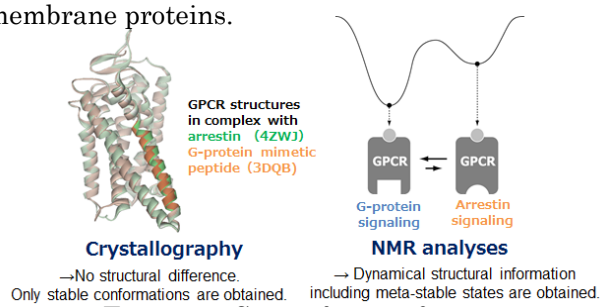

Figure 2 Scientific significance

【Publications Relevant to the Project】

・Efficacy of the β_2-adrenergic receptor is determined by conformational equilibrium in the transmembrane region, Kofuku Y, Ueda T, Okude J, Shiraishi Y, Kondo K, Maeda M, Tsujishita H, Shimada I, Nat Commun. (2012) 3, 1045
・Dynamic regulation of GDP binding to G proteins revealed by magnetic field-dependent NMR relaxation analyses. Toyama Y, Kano H, Mase Y, Yokogawa M, Osawa M, Shimada I., Nat Commun. (2017) 8, 14523

【Term of Project】 FY2017-2021

【Budget Allocation】 354,100 Thousand Yen

【Homepage Address and Other Contact Information】

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