The Role of Lipid Rafts in Trimeric G Protein-Mediated Signal Transduction

○Satoko Ohkubo (National Institute of Health Sciences)

Lipid rafts and caveolae are microdomains in the cell membranes, which contain cholesterol, glycolipids, and sphingomyelin. While caveolae are relatively stable because caveolin, an integral protein, supports the structure, lipid rafts are considered to be unstable, being dynamically produced and degraded, in which flotillin exists as a marker protein. Because these microdomains are known to be resistant to non-ionic detergents, such as Triton X-100, they are separated as the detergent-resistant membranes when the Triton X-100-treated cell lysate is subjected to sucrose gradient centrifugation. Recent studies have reported that lipid rafts contain many signaling molecules, such as glycosylphosphatidylinositol-anchored proteins, acylated proteins, G protein-coupled receptors (GPCR), trimeric and small G proteins and their effectors, suggesting that the lipid rafts have an important role in receptor-medicated signal transduction. The present study is performed to clarify the role of microdomains in GPCR-$G_{q/11}$-mediated signaling. In the study of $P2Y_2$ receptor, we found that the $G_{q/11}$-mediated phosphoinositide hydrolysis and increase in intracellular Ca^{2+} were inhibited by methyl-□-cyclodextrin (M□CD), which disrupts the structure of lipid rafts via the depletion of cholesterol. Second, we reported that although wasp toxin mastoparan inhibits phosphoinositide hydrolysis and the increase in intracellular Ca^{2+}, we found the molecular mechanism that mastoparan initially binds to gangliosides in lipid rafts and changes the localization of G□$_{q/11}$ and G□ in lipid rafts. We would like to discuss the role of lipid rafts in GPCR-mediated signal transduction.