Cell membrane localization influences Gαi protein subclass selectivity

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Abstract

G protein-coupled receptor (GPCR) signaling plays an important role in regulating cellular responses to external stimuli. GPCRs are so critical that they are a common pharmaceutical target, with 35% of available drugs targeting the receptors. But despite their importance, the mechanism underlying G protein selectivity for closely related Gαi proteins is unclear. In a recent study, researchers followed up on their previous finding that Gαi protein subunits prefer different lipid domains in the membrane. Using live-cell fluorescence microscopy techniques, they characterized the diffusion of Gαi subunits and the dopamine D2 long receptor isoform (D2R). They found that although Gαi protein subunits are very similar, the Gαi2 subunit displayed faster lateral diffusion than Gαi1. Distinct Gαi heterotrimers localized to different areas of the cell membrane, correlating with the efficiency of D2R-mediated inhibition of cAMP. These results demonstrate that even closely related subunits of Gαi differ in membrane-trafficking properties with functional implications for better understanding their signaling.