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Single-Particle Tracking Reveals Diverse Diffusion Regimes of Individual M2 Receptors and Gi Proteins in Live Cells (G)

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G protein coupled receptors (GPCRs) are a superfamily of membrane receptors known for high signal transduction efficiencies. One of the key aspects of the GPCR signaling mechanism is the coupling interaction between the receptor and the G protein in response to external stimuli. We examined the pre-stimulus receptor-G protein coupling state by single-particle tracking (SPT) of M_2 muscarinic receptors and G_i proteins in live cells. M_2 receptors and G_i proteins were genetically fused with fluorescent proteins (GFP and/or mCherry), expressed in CHO cells, and imaged on a Total Internal Reflection Fluorescence (TIRF) microscope. Single particles were identified in each frame of the TIRF movies and tracked using the TrackMate software. Mean-squared displacement (MSD) functions were computed for each single-particle trajectory. The diffusion parameters for receptors and G proteins were obtained by fitting their MSD functions to appropriate diffusion models.
Both the M_2 receptors and the G_i proteins exhibited significant fractions of confined diffusion (compatible with the membrane compartment formed by actin microfilament-based meshwork) and active transportation (compatible with the rate of myosin trafficking along actin microfilaments). The motions of the M_2 receptors and of the G_i proteins were distinctive from each other in the basal state of receptors, but they became similar when the receptors were activated by the agonist. Corroborated with dual-color fluorescence correlation spectroscopy measurements performed on the same samples, the SPT results supported a transient recruitment model without a stable pre-stimulus coupled complex.

Author: LI, Yuchong (University of Toronto Mississauga)

Co-authors: Dr WELLS, James (Dept. of Pharmacology and Pharmaceutical Sciences, University of Toronto); GRADINARU, Claudiu (University of Toronto)

Presenter: LI, Yuchong (University of Toronto Mississauga)

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