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Single-Molecule Optical Study of Cholesterol-Mediated Dimerization Process of EGFRs in Different Cell Lines

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Abstract : A growing body of data reveals that the membrane cholesterol molecules can alter the signaling pathways of living cells. However, the understanding about how membrane cholesterol modulates receptor proteins is still lacking. Single-molecule tracking can effectively probe into the microscopic environments and thermal fluctuations of receptor proteins in a living cell. In this study we applies single-molecule optical tracking on ligand-induced dimerization process of EGFRs in the plasma membranes of two cancer cell lines (HeLa and A431) and one normal endothelial cell line (MCF12A). We tracked individual EGFR and dual receptors, diffusing in a correlated manner in the plasma membranes of live cells. We developed an energetic model by integrating the generalized Langevin equation with the Cahn-Hilliard equation to help extracting important information from single-molecule trajectories. From the study, we discovered that ligand-bound EGFRs move from non-raft areas into lipid raft domains. This ligand-induced motion is a common behavior in both cancer and normal cells. By manipulating the total amount of membrane cholesterol with methyl-β-cyclodextrin and the local concentration of membrane cholesterol with nystatin, we further found that the amount of cholesterol can affect the stability of EGFR dimers. The EGFR dimers in the plasma membrane of normal cells are more sensitive to the local concentration changes of cholesterol than EGFR dimers in the cancer cells. Our method successfully captures dynamic interactions of receptors at the single-molecule level and provides insight into the functional architecture of both the diffusing EGFR molecules and their local cellular environment.

Keywords : membrane proteins, single-molecule tracking, Cahn-Hilliard equation, EGFR dimers
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