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Membrane Shape Remodeling By Lipid-Modified Ras Proteins

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Ras proteins are small GTP-hydrohydrolyzing enzymes that operate as molecular switches in signal transduction pathways and are present in a mutant, activated state in many human tumors. It has been shown that the lipid-modified C-terminus drive lateral segregation of Ras proteins into membrane sub-structure on the plasma membrane. Such transient and dynamic molecular assembly, so-called nanocluster, is emerging as a crucial mechanism by which cells achieve high-fidelity signal transmission. However, little is known about the underlying force driving the formation of nanoclusters on the plasma membrane and their influence on the membrane structure.

To investigate the interaction between nanocluster and the membrane, we carried out extensive semi-atomistic molecular dynamics simulations of the C-terminal membrane-targeting motif of H-ras (tH) in a phase separated lipid bilayer composed of 2000 DPPC, DliPC and cholesterol molecules. We found out that at ambient temperature approximately 30-40% of tH molecules assemble into clusters of 4-9 proteins, and preferentially localize at the interface between the liquid-ordered and liquid-disordered phases of the membrane. In the nanoclusters, tH backbones preferably exhibits an extended conformation and align linearly at the phase interface. With such molecular-level organization, tH molecule act as a linactant at the interface and reduce line tension of the anchor-containing monolayer and induces shape transition of the overall membrane due to the tendency of the system to minimize the free energy. The resultant geometry of the membrane is determined by the different elastic bending modulus of different phases as well as the phase boundary line tension, which is strongly affected by the localization of the nanoclusters. Our findings were explained based on the elastic membrane theory and provided new perspective on the interaction between membrane-bounded proteins and membrane domains, such as lipid rafts.