中央大學物理學系

Department of Physics, National Central University

Molecular Insights of the Interplay between SNX9 and Phosphoinositide Lipids: Implications in Endocytosis and Macropinocytosis

Dr. Feng-Ching Tsai

Institut Curie, France

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Biological membranes undergo dynamic remodeling to maintain cell homeostasis. Membrane associated proteins from the Sorting Nexin (SNX) family have been implicated in membrane remodeling through their BAR domains, which bind anionic lipids in a non-specific manner. Additionally, SNX proteins possess specific lipid-binding domains that have been proposed to facilitate their temporal membrane targeting. SNX9, known for its role in endocytosis and macropinocytosis, binds to multiple variants of phosphoinositide (PI) lipids via its PX domain. However, it remains unclear whether the PX domain of SNX9 preferentially binds a specific variant of PI lipid, and what the implications of such differential binding are for cellular functions. To address this question, we use a combination of in cellulo and in vitro assays as well as molecular dynamics simulations. We find that during macropinocytosis, membrane-bound SNX9 is spatially and temporally colocalized with PI(3,4)P2, but not with the PI(4,5)P2 and PI3P lipid populations. While in vitro assays show that the binding affinities of SNX9 to model membranes containing PI(3,4)P2 or PI(4,5)P2 are comparable, all-atom simulations indicate a specific binding between the PX domain canonical binding site and PI(3,4)P2 lipid. Our work not only provides insight into the spatial and temporal recruitment of SNX9 during macropinocytic events, but also suggests a possible mechanism by which proto-endosomal identity is retained prior to membrane scission.