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Investigating Membrane Targeting Domains & Lipid Transfer Proteins via Molecular Dynamics Simulations – Insights into their Structures, Dynamics, and Mechanisms

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Association of peripheral membrane proteins (PMPs) with cellular membranes is critical for signaling and membrane trafficking processes. Two important classes of PMPs that associate with membranes are membrane targeting domains (MTDs) and lipid transfer proteins (LTPs). PMPs interact transiently with membranes, making it arduous to determine details such as their membrane binding interface and the conformational dynamics crucial for membrane binding. Additionally, several facets of the mechanism of lipid transfer between organellar membranes via LTPs remain unknown. In this dissertation, the mechanism by which LTPs function was discerned in a high-throughput manner using Molecular Dynamics (MD) simulations.

As a first step, the accuracy with which the coarse-grained force field, MARTINI 3 (open-beta version), can be used to study peripheral-protein membrane interactions was estimated and the abilities and limitations of the model were established. Next, the binding of LTPs to membranes was investigated, demonstrating the presence of an evolutionarily conserved fold-independent mechanism of lipid transfer across LTPs that stems from the correlation between the dynamical features of the protein and its mechanistic mode of action. Furthermore, the ability of unbiased MD simulations using the coarse-grained MARTINI force field, to identify lipid binding pockets, poses, and lipid uptake pathways in LTPs, with no a priori information on the lipid binding site, was investigated. The methodologies and concepts developed in the process were also used as a proof-of-application in two experimental collaborative projects, and represent a significant step forward in the usage of computational techniques to discern several aspects of LTPs, such as their membrane binding interfaces, conformational dynamics, and lipid binding sites, in a high-throughput manner rather than via a protein-specific approach.

Jury:

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