P-2.173

Mechanism of Gate Opening and Cargo Uptake/release in Stard Lipid Transfer Proteins from Molecular Simulations

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Lipid transfer proteins (LTPs) transfer lipids between intracellular membranes through non-vesicular mechanisms and regulate lipid homeostasis. Despite a wealth of structural data, little is known about the mechanisms by which LTPs desorb lipids from well-organized membranes. We investigated 3 LTPs from the STARD family: STARD2 (phosphatidylcholine transfer domain), STARD4 (sterol transfer domain), and STARD11/CERT (ceramide transfer domain). We used a combination of multiscale molecular simulations and free energy calculations to investigate the mechanisms for extraction (or release) of their cargo lipids from (or into) their donor (or acceptor) membranes. We used multicomponent lipid bilayers modeling the plasma membrane and relevant organelle membranes.

Our simulations revealed similarities in binding orientation of the three proteins to lipid bilayers, but also striking differences in their sensitivity to lipid composition. Our work[1-4] provides detailed models for the mechanism of lipid uptake/release in START domains, and highlights striking mechanistic differences between structurally similar proteins. Experimental evidence aligns well with the proposed mechanisms for membrane selectivity and uptake/release mechanisms.

[1] Talandasthi JMB 2024; [2] Talandasthi JPCL 2024; [3] Moqadam JPCB 2024, [4] Titeca BioRxiv, 2024