

The Effect of Transmembrane Domains on the Free Energy of Stalk Formation during Membrane Fusion

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The nucleation of the stalk is the first step in membrane fusion. The overall fusion process including the stalk formation is facilitated by fusion proteins anchored in the membrane by transmembrane domains (TMDs). Although TMDs of fusion proteins have been suggested to play an active role during fusion, little quantitative or mechanistic understanding of putative TMD effects has evolved. We used molecular dynamics simulations to analyze the influence of TMDs of the SNARE complex and of viral fusion proteins on the free energy of stalk formation. The stalk free energy was computed highly efficiently via potential of mean force (PMF) calculations along a newly designed reaction coordinate together with the Martini coarse-grained force field [1][2]. The results reveal a decrease in both, the free energy barrier of stalk nucleation as well as the free energy of the final stalk structure, when TMDs are present in the membrane. However, the observed TMD effect strongly depends on the lipid composition and on the hydrophobic mismatch between the TMD and membrane core.

[1] Jochen S. Hub and Neha Awasthi, *J. Chem. Theory Comput.* 13 (5), 2352–2366 (2017).

[2] Chetan S Poojari et. al., *bioRxiv* doi:10.1101/2021.06.02.446700, (2021).