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Synergism of cell penetrating peptides in adsorbing to DOPC lipid bilayers

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Cell penetrating peptides (CPPs) represent a potential breakthrough for the cellular delivery of therapeutics. CPPs are small peptidic molecules capable of translocating through cell membranes, which generally show low cytotoxicity and high transduction efficiency. Permeation mechanisms of CPPs are not fully understood, although there is evidence for both energy dependent and energy independent (passive) pathways. In this study, we performed coarse-grained molecular dynamics simulations of CPPs in the vicinity of a dioleoylphosphatidylcholine (DOPC) lipid bilayers to investigate the free energy of passive translocation, and the synergetic effects of having multiple peptides at the bilayer surface. Four different CPPs (Penetratin, C6, Transportan, K-FGF) were used in the study in order to represent cationic, amphipathic and hydrophobic peptides. Simulations were carried out in systems containing water, lipid bilayer and a single type of peptide. The MARTINI force field was used, while simulations were run under a constant pressure (1 atm) and temperature (300 K) using Berendsen control. Umbrella sampling simulations were carried out in windows 1 nm apart, spanning the relevant separation of CPPs from the bilayer membrane. Translocation free energy curves for single peptide and multi-peptide systems were generated after simulations. In the case of the cationic peptide Penetratin, the translocation profile showed a slight tendency to adsorb onto the bilayer surface, while the insertion into the membrane was highly unfavourable. This behavior is accentuated with an increased number of peptides in the system. In the case of the hydrophobic K-FGF peptide, it shows a strong adsorption for both the singular and multiple peptide systems. Moreover, the barrier for translocation is lowered substantially for the multiple peptide system, allowing for a viable route for translocation. In the case of the two amphipathic peptides, they show different behavior, where Transportan does not show any synergy, while the C6 peptides show lowering of the barrier in the presence of other peptides. The variation in the translocation energy profiles indicate that the interactions are nuanced and cannot be generalized based on the physicochemical nature of the peptide. Moreover, the synergy shown by some peptides show the possibility of multiple peptide entry pathways.

Keywords: Free energy profiles, Molecular Dynamics simulations, membrane translocation