RESCON 2025 PS 44

ANTAGONISM IN PASSIVE TRANSLOCATION OF CELL-PENETRATING PEPTIDES

M.S.F. Musna and R.J.K.U. Ranatunga*

Department of Chemistry, University of Peradeniya, Peradeniya, Sri Lanka.
*udayana.ranatunga@sci.pdn.ac.lk

Cell-penetrating peptides (CPPs) have emerged as promising tools for the delivery of macromolecular cargo, utilising either energy-dependent (endocytic) or energy-independent (direct) translocation mechanisms. Understanding the mechanism leading to internalisation is crucial for the design and optimisation of CPPs as efficient drug delivery agents as these mechanisms reveal the extent of their impact on the cell membrane and help evaluate their safety and efficiency as delivery vectors. The study analysed the free energy profiles associated with the passive translocation of different types of CPPs, including cationic, hydrophobic, and amphipathic peptides, with a particular focus on the peptides penetratin, K-FGF, transportan, and CADY. The free energy profiles for peptide translocation across a model cell membrane were generated employing the GROMACS software, Martini 3 coarse-grained force field, and umbrella sampling molecular dynamics simulations, varying the nominal surface concentration of the peptides. The Martini 3 coarse-grained force field was chosen for accurate peptide-lipid modeling with efficient and biologically relevant time scales. The cell membrane was composed of dioleoylphosphatidylcholine, and the temperature and pressure were maintained at 300 K and 1.0 atm. The results show that the peptides investigated show unfavorable free energy profiles for direct membrane translocation, and the presence of multiple peptides does not facilitate translocation. Instead, an increase in the free energy barrier suggests the absence of a synergistic effect when multiple peptides interact with the membrane. These results provide valuable insights into the complex biophysical behavior of CPPs, as it underscores the need to consider peptide density and potentially the membrane heterogeneity when evaluating direct entry mechanisms of CPPs and highlights the importance of further studies to fully elucidate complex mechanisms underlying the process. This work contributes to the broader understanding of CPP mechanisms and offers a foundation for future research aimed at improving peptide-based drug delivery systems.

Keywords: Antagonism, Cell-penetrating peptides, Free energy profiles, Molecular dynamics, Translocation