02-1

Large-scale membrane permeability prediction of cyclic peptides crossing a lipid bilayer based on enhanced sampling molecular dynamics simulations

Masatake Sugita[1]
sugita@bi.c.titech.ac.jp

Satoshi Sugiyama[1]
sugiyama@bi.c.titech.ac.jp

Takuya Fujie[1]
fujie@bi.c.titech.ac.jp

Yasushi Yoshikawa[1]
yoshikawa@c.titech.ac.jp

Keisuke Yanagisawa[1]
yanagisawa@c.titech.ac.jp

Masahito Ohue[1]
ohue@c.titech.ac.jp

Yutaka Akiyama[1]
akiyama@c.titech.ac.jp

[1] Tokyo Inst. Tech., W8-76, 2-12-1 Ookayama, Meguro-ku, Tokyo, 152-8550, Japan

Keywords: Cyclic peptides, Membrane permeability, Molecular dynamics

Membrane permeability is a significant obstacle facing the development of cyclic peptide drugs. However, the membrane permeation mechanism of cyclic peptides with high membrane permeability is not yet understand. To investigate common features of permeable peptides, it is necessary to reproduce the membrane permeation process of cyclic peptides through the lipid bilayer for a large number of peptides. In this study, we first simulated the membrane permeation process of 100 six-residue cyclic peptides across the lipid bilayer based on steered molecular dynamics (MD) and replica-exchange umbrella sampling (REUS) simulations, and predicted membrane permeability using the inhomogeneous solubility-diffusion model (ISDM) and a modified version of it.[1] Furthermore, we confirmed the effectiveness of this protocol by predicting the membrane permeability of 56 eight-residue cyclic peptides with diverse chemical structures, including some confidential designs from a pharmaceutical company. As a result, a reasonable correlation between experimentally assessed and calculated membrane permeability was observed for the peptides, except for strongly hydrophobic peptides. Our analysis of the MD trajectory demonstrated that most peptides were stabilized in the boundary region between bulk water and membrane, and that for most peptides the process of crossing the center of the membrane is the main obstacle to membrane permeation. The height of this barrier is well correlated with the electrostatic interaction between the peptide and the surrounding media. This feature of the result emphasizes the importance of the smooth desolvation during penetration into the membrane.

[1] Sugita, M.; Sugiyama, S.; Fujie, T.; Yoshikawa, Y.; Yanagisawa, K.; Ohue, M.; Akiyama, Y. Large-Scale Membrane Permeability Prediction of Cyclic Peptides Crossing a Lipid Bilayer Based on Enhanced Sampling Molecular Dynamics Simulations. *Journal of Chemical Information and Modeling*. **2021**, *61*, 3681–3695.