Designing novel membrane active peptides and understanding their mechanism of action

ABSTRACT

Membrane active peptides (MAPs) have attracted considerable attention due to their impressive ability to interact with lipid bilayers, holding great promise for revolutionary applications in the field of medicine. This thesis conducts a comprehensive exploration of MAPs, focusing primarily on cell-penetrating peptides (CPPs) and antimicrobial peptides (AMPs). It unravels their intricate design, cellular uptake mechanisms, and potential applications in targeted drug delivery. The first section focuses on Engraulisin, a novel CPP sourced from marine origins. It effectively penetrates cells and delivers cargo without significant cytotoxicity, with notable uptake in HeLa cells. Engraulisin also shows potent antimicrobial properties against MRSA, highlighting its potential for addressing infections. The section concludes by exploring the fundamental mechanisms of CPP membrane penetration. The second section examines novel short Latarcin-derived peptides (sLtcs) as potential antimicrobial agents. sLtc 4 and 5 show broad-spectrum antimicrobial activity at micromolar concentrations. Their mechanisms include changes in membrane potential, ROS production, and membrane disruption, indicating multi-target activities. The final chapter introduces a novel predictive models for peptide cell-penetrating capabilities. Developed using large language models and machine learning techniques, our models generalize well across diverse peptide characteristics. Diligent testing and validation ensure their accuracy, offering a reliable method for predicting peptide cell-penetrating potential.

Overall, this research advances the field by introducing novel peptides such as Engraulisin and sLtcs, demonstrating their potential in drug delivery and antimicrobial applications. Additionally, the innovative predictive tool streamlines the identification of promising candidates, facilitating the rational design of peptides with enhanced cellular uptake capabilities.