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How to use lipid models to instruct the design of antimicrobial peptides

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Antimicrobial peptides (AMPs) are found in nature to selectively kill microbes by disrupting their cell membranes. Because of the rapid physical action, pathogens are less likely to develop the relative resistance mechanism to the AMPs. Therefore, AMPs are the potential candidates for the multiple-drug resistance (MDR) treatments. We have designed a series of surfactant-like AMPs based on the general formula of G(IKK)2I-NH₂ (denoted as G3). They have strong antimicrobial activity against various strain species including antimicrobial resistant strains, but have relatively mild cytotoxicity to the host mammalian cells.

In this work, we designed a series of de Novo AMPs, and studied their interactions with different lipid models as mimetics of different cell types. Small unilamellar vesicles (SUVs) as composed of specific lipids were used to mimic either the bacterial or the host mammalian cell membranes. The carboxyfluorescein (CF) leakage experiment indicated that AMPs kill bacteria by breaking their cell membranes. Lipid monolayers as constructed on the air/water interface is a simple but efficient model to study the lipid and peptide interactions. Neutron reflection (NR) is a powerful technique to determine the amount and location of the AMPs once bound to the lipid monolayers. The strongly hydrophobic AMP showed potent membrane disrupting activity to either anionic or non-charged SUVs, whilst the weakly hydrophobic AMP disrupted anionic SUVs at higher concentrations and showed little effect to the electrically neutral SUVs. These results suggest that potent AMPs could be toxic, and weak AMPs have an advantage of benign biocompatibility. All results provide a useful guideline to develop the next generations of AMPs with improved antimicrobial activity but tuned biocompatibility.

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