The difference of an amide to ester in polymers does the magic

Antibiotics kill bacteria by a specific targeting mechanism, and thereby, bacteria quickly develop resistance to antibiotics. The bacterial cell membrane is pivotal to its survival and is considered its Achille's heel. Killing bacteria by attacking their cell membrane is advantageous because bacteria find it difficult to develop resistance to such strategies. Natural antimicrobial peptides (AMPs) because of their amphiphilicity target the bacterial cell membrane. Amphiphilicity in these peptides is a balance between cationic charge and hydrophobicity and is essential for their selective interactions with the anionic lipid membranes of bacteria instead of zwitterionic mammalian cell membranes. The primary interactions between the amphiphilic compounds and bacterial lipid membranes include electrostatic and hydrophobic interactions. However, the role and importance of hydrogen bonding in these interactions have not been understood yet.

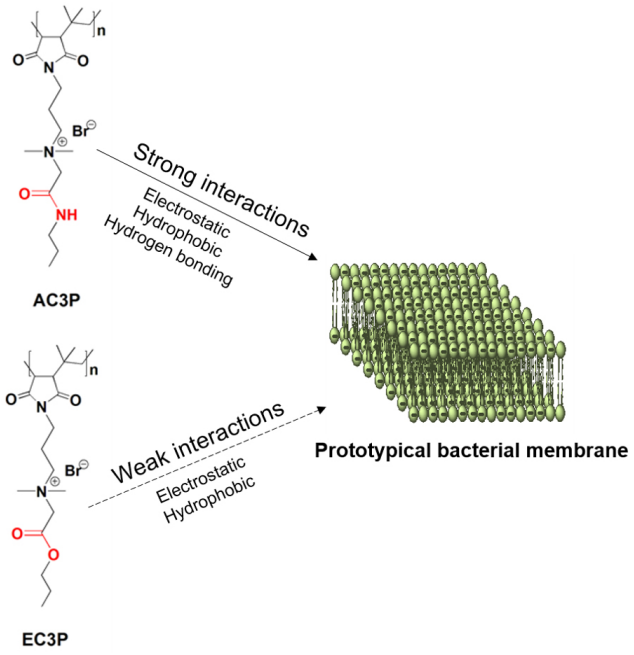

Fig. 1. Schematic representation of amide and ester bearing cationic amphiphilic polymers and their differential interactions with the prototypical bacterial membrane.

Here, using polymers that mimic the AMPs, we studied the role of hydrogen bonding in the interactions between amphiphilic polymers and bacterial lipid membranes. Such studies were possible because of the ability to tune the chemical structure of our cationic amphiphilic polymers with the ester (EC3P) and amide (AC3P) groups (Fig. 1). Ester and amide group variation in the side chains of these polymers led to drastic differences in their antibacterial activity. The difference

between an ester and amide is in their ability to form strong hydrogen bonding. Investigations using biophysical experiments like isothermal titration calorimetry and Raman spectroscopy involving bacterial model lipid bilayers revealed strong interactions of hydrogen bonding between AC3P and the lipid head groups of lipid bilayers compared to its ester counterpart, EC3P. Next, molecular dynamics simulations also revealed strong hydrogen bonding interactions of amide polymer with model lipid bilayers compared to the ester polymer. This unique chemistry of ester and amide bearing polymers, for the first time, led to understanding the importance of hydrogen bonding in bacterial membrane interactions. Overall, these findings offer unprecedented insights into the different molecular interactions between bacterial membranes and molecules that interact with them. We believe that this understanding will provide specific design principles for developing molecules to target bacterial membranes selectively.

Divakara SSM Uppu, Jayanta Haldar
Antimicrobial Research Laboratory, New Chemistry Unit and School of Advanced Materials, Jawaharlal Nehru Centre for Advanced Scientific Research, Jakkur, Bengaluru, Karnataka, India

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