The ability of synthetic antimicrobials to induce electrostatic lipid clustering and membrane permeabilization

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Natural or synthetic antimicrobial agents (AMPs or smAMPs) acting on the cell membrane are promising alternatives to classical antibiotics because they are less prone to resistance. Common to all antimicrobial treatment is the need for selectivity.

A well-known contribution to selectivity is different binding of polycationic antimicrobial agents to zwitterionic or charged lipid membranes, respectively. Another hypothesis is that electrostatic lipids clustering by antimicrobial agents, the lateral segregation of charged lipids from a mixed membrane enhances selectivity. It is assumed that both, the propensity for lipid clustering and the effect of lipid clustering on membrane integrity depend on the lipid composition of the microbial membrane or model membrane.

We examine a series of smAMPs with varying antibacterial selectivity acting on lipid vesicles of differing lipid composition. By differential scanning calorimetry, we prove the ability of the smAMPs to induce electrostatic lipid clustering. Membrane permeabilization is studied by fluorescence spectroscopy. Sophisticated analysis of vesicle leakage behaviour reveals how the combination of smAMP design and lipid mixture can determine the mode of action.

A general view on membrane permeabilization and antimicrobial activity and selectivity will aid future design of antimicrobials as well as the improvement of models for *in vitro* screening.