Antimicrobial peptide activity in a competitive lipid environment

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Mastering the structure-activity relationship and specificity of antimicrobial peptides (AMP) against bacterial lipid membranes is required for the therapeutic development of membrane-active peptides. Correlation of physiological observations with *in vitro* studies, including high resolution structural work, can provide the required understanding of the mechanism by which AMP kill bacteria. For instance, maculatin 1.1 is an antimicrobial peptide that serves as part of the innate immune defences of an Australian tree frog, and has shown promising activity against Methicillin-resistant *Staphylococcus aureus* but which also has appreciable haemolytic activity. Against that common assumption that lipid composition is often assumed to be the regulative mechanism, why does this peptide attack charged membranes mimicking the bacterial envelope almost as efficiently as neutral and cholesterol-containing membranes mimicking eukaryotic cells?

We have devised a dye release assay to investigate the affinity of maculatin 1.1 towards a particular lipid composition in a competitive environment. The use of large unilamellar vesicles loaded with calcein and mixed with non-encapsulated vesicles of a different lipid composition has allowed determination of differential affinities and/or activities of the peptide for varying lipid compositions. We also have demonstrated that a distinct secondary structure of maculatin 1.1 is not essential for its lytic activity and have data supporting a pore mechanism, the size of which is likely regulated by the lipid composition of the model membrane system.