Structure and membrane topology of the pore-forming peptide maculatin 1.1 depends on lipid composition

M.-A. Sani, S. Overall and F. Separovic, School of Chemistry, Bio21 institute, The University of Melbourne, VIC 3010, Australia.

Antimicrobial peptides (AMP) that target membranes are an attractive alternative to classic antibiotics, since they do not require internalization nor target a specific stereo-structure, thus limiting development of bacterial resistance. Their mode of action involves the disruption of lipid membranes, however, the molecular details of the killing mechanism and, more particularly, the difference in potency observed between different bacterial strains, remain unclear. We present the structural investigation of the AMP maculatin 1.1 (Mac1) in different lipid systems. Using solution and solid-state NMR with paramagnetic relaxation enhancement (PRE) agents and dye release (DR) experiments, we demonstrate the important role of the lipid composition in modulating the structure and location of Mac1. HSQC of specifically ^{15}N labeled Mac1 in buffer displayed a narrow chemical shift dispersion that is typical of random coil structures. Introduction of DPC and DHPC micelles, and DHPC/DMPC isotropic (q = 0.5) bicelles and POPE/POPG nanodiscs produced chemical shift dispersions characteristic of helical structures, with differences suggesting that Mac1 adopts a different degree of helicity dependent on the curvature. Titration of the PRE agent Gd^{3+}-(DTPA) into the Mac1–DHPC/DMPC system showed that the central core of Mac1 is mainly transmembrane. Using a spin-labelled Mac1 mixed with ^{15}N labeled Mac1, peptide-peptide interactions were mapped. In terms of activity, Mac1 induced greater leakage in neutral membranes, except for highly ordered lipid compositions, than with negatively charged membranes. However, in a competitive environment, electrostatic interactions determined the activity of Mac1, reducing the interaction with neutral membranes but these interactions are not sufficient to explain fully the specific bactericidal activity of AMP.

Live cell studies presented as a poster by S. Overall.