Interaction of antimicrobial peptides with bacteria and bacterial model membranes

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Antimicrobial peptides (AMPs) are cationic, amphipathic compounds, which are part of the innate immune system of all species. They provide the first line of defence against pathogenic microorganisms. Due to their unique mode of action AMPs have gained high interest as new drugs to overcome bacterial resistance to classical antibiotics. The primary target of AMPs is the cell membrane of bacteria. It is widely accepted that the peptides cover the bacterial membrane like a carpet and induce the formation of transient or stable pores. Their precise mode of action, however, and in particular the significance of the natural lipid composition, still is a matter of debate.

We compared the mode of membrane interaction of AMPs, which differ in origin and structure, however, exhibit similar inhibitory concentrations against certain strains of bacteria. The studied peptides were: i) NK-2 [1], an α–helical fragment of mammalian NK-lysin, ii) arenicin-1 [2], a lugworm cyclic β–sheet peptide, and iii) bee venom melittin.

We used reconstituted model membranes made of lipopolysaccharides (LPS) to mimic the outer membrane of Gram-negative bacteria, or of phospholipids (PG, PE) and lysyl-phospholipids to mimic the cytoplasmic membrane of Gram-positive bacteria. We measured (i) the binding of peptides to solid-supported bilayers on a surface-acoustic wave (SAW) biosensor, (ii) the insertion of peptides into liposome membranes by Förster resonance energy transfer (FRET) spectroscopy, and (iii) the permeabilization of Montal-Mueller planar lipid bilayers. In addition, we analyzed the bacterial ultrastructure with atomic force microscopy and transmission electron microscopy.

All peptides destroy the bacterial integrity and elicit also intracellular damages, however, the observed structural changes differ considerably. These findings are concurrent with variations of peptide-mediated changes of the viscoeleasticity of LPS bilayers measured by SAW, and with different characteristics of peptide-induced lesion/pores in planar lipid bilayers.

We conclude that the investigated peptides act on bacterial membranes by different mechanisms. Membrane interaction results either in peptide translocation and interaction with secondary, intracellular targets, or membrane permeabilization itself elicits peptide-specific intracellular events.

References

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