Bacterial Cell Wall Biosynthesis Specific Target for Antimicrobial Peptides

Hans-Georg Sahl

University of Bonn, Pharmaceutical Microbiology, 53115 Bonn, Germany

Antibiotic peptides are important effector molecules in host-parasite interactions throughout the living world. In vertebrates, they function in first line host defense by antagonizing a wide range of microbes including bacteria, fungi and enveloped viruses. The antibiotic activity is thought to be based on their cationic amphipathic nature which enables the peptides to impair vital membrane functions. Molecular details for such activities have been elaborated with model membranes, however, there is increasing evidence that these models may not reflect the complex processes involved in the killing of microbes. As an example, the overall killing activity of the bacterial peptide antibiotic nisin is composed of independent activities such as the formation of target-mediated pores, inhibition of specific biosynthesis steps and of precursor polymerization, formation of non-targeted pores and induction of autolysis. The main target for nisin and a number of related lantibiotics are the bactoprenol-bound precursors, lipid I and II which provide various binding sites for blocking different reactions. We recently reconstituted the synthesis of the staphylococcal cell wall interpeptide bridge in vitro and could show that these reactions are also prone to inhibition by peptide antibiotics. In contrast, the molecular mode of action of human defense peptides seems to be based on non-targeted mechanisms. We found that membrane depolarization contributes to rapid killing of a significant fraction of target cells within a bacterial culture. However, substantial subpopulations appear to survive the primary effects on the membrane. Depending on individual strains and species and peptide concentrations, such subpopulations may either resume growth or be killed through additional activities of the peptides. Such activities can include the activation of cell wall lytic enzymes which appears of major importance particularly for killing of staphylococcal strains.