Lipidomics based Design of Short Lipo(peptides) derived from Human Lactoferrin with Antimicrobial and Endotoxin Neutralizing Activity

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Despite the application of antibiotics in Gram-negative bacterial infection, the pathogenicity factor endotoxin or lipopolysaccharide (LPS), released from killed bacteria, can lead towards septic shock with high mortality. Thus, neutralization of endotoxin in addition to killing of bacteria by suitable compounds will protect against harmful effects of sepsis. We designed (lipo)peptides with a dual mode of action derived from a fragment of the human protein lactoferrin (aa 21-31), which is known to have multiple functions including antibacterial, antifungal and immuno-regulatory properties as well as the ability to neutralize bacterial endotoxin.

In a series of three generations, peptides were selected and modified based on 3D-determination of peptide structure, biophysical experiments on the interaction of peptides with membrane mimetic systems, and biological assays in order to improve both the antimicrobial activity and the ability to bind bacterial endotoxin, while at the same time controlling cytotoxicity. The short (8-10 residues) linear peptides are unstructured in aqueous environment, but fold into a defined conformation upon binding to their negatively charged target lipids. In case of the lipopeptides, the N-terminal acyl chain acts as a structural organizer. The acyl chain also plays a profound role in the interaction with the outer LPS layer and the less dense lipoteichoic acid network of Gram-positive bacteria, respectively. The best peptides have broad antimicrobial activity and protect mice against endotoxaemia. Improvement of peptide activity by the addition of a fatty acid chain was better in vivo as compared to in vitro, probably due to differences in its bioavailability and stability. Since the most potent (lipo)peptides showed negligible toxicity towards human cells, these compounds will be good candidates for the development of novel antimicrobial and anti-endotoxin agents.