Exploration of the Structure-Activity Relationship of Natural, Self-assembling Cyclic Lipodepsipeptides

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Cyclic lipodepsipeptides are non-ribosomal peptides produced by bacteria, mainly Pseudomonas and Bacillus spp. They consist of a short sequence of D- and L-amino acids, which forms a cyclic structure by means of an ester bond between the C-terminal and a side chain alcohol function. They exhibit antagonistic activity for several bacterial and fungal species. We are mostly interested in the CLPs of the viscosin group. These consist of 9 amino acids, of which 7 are contained in the cyclic part of the molecule. Previously, the structure and conformation of pseudodesmin A has been extensively investigated using X-ray analysis and elaborate NMR relaxation measurements [1,2].

The mechanism by which these compounds exert their antagonistic activity is as of yet unknown. One hypothesis is that they form ion pores in the bacterial cellular membrane, causing an ionic imbalance and eventually cell lysis. We propose that in hydrophobic environments such as a lipid bilayer, the lipodepsipeptides of the viscosin class self-assemble to larger supramolecular structures, only limited by the confines of the membrane. In this structure, the hydrophylic residues are directed inward and the hydrophobic residues outward. It is possible to observe this self-assembly process in non-polar organic solvent solutions such as chloroform, previously reported extensively for pseudodesmin A [2,3].

An interesting feature of the viscosin group is the unique variability of the stereogenic center at the 5-position in the peptide sequence, either featuring a D-Leu or L-Leu residue. Currently, conformations have only been reported of CLPs featuring a D-Leu5 residue. In this study, the structure and self-assembly properties of the viscosinamide (containing L-Leu5) has been investigated by NMR spectroscopy, allowing us to make a comparison with pseudodesmin A (containing D-Leu5). Using rotating frame nOe-derived distance restraints and homo- and heteronuclear coupling constants, the conformation of viscosinamide could be determined. Using PFG-NMR, the self-assembly capacity can then be characterized and compared to pseudodesmin A by observing the diffusion coefficient at various concentrations.
The analysis of the conformation of viscosinamide is an essential first step for understanding the self-assembling behavior of this molecule. Using NMR heteronuclear relaxation experiments, the diameter and length of the supramolecular structure can be determined at different concentrations. Additionally, the orientation of the monomeric units within the supramolecular structure can be calculated.