Insight into the atomic-level machinery of SAAP-148, a promising antimicrobial peptide

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Abstract:

SAAP-148 is an antimicrobial peptide derived from LL-37. It is effective against drug-resistant bacteria and biofilms, and it is stable in physiological conditions. However, the molecular mechanism of its action is not yet fully understood. To investigate the structural properties of SAAP-148 and its interaction with phospholipid membranes, we used liquid and solid-state NMR spectroscopy as well as molecular dynamic simulations. We found that SAAP-148 is partially structured in solution and that it adopts a helical conformation when it interacts with DPC micelles. The orientation of the helix within the micelles was determined by paramagnetic relaxation enhancements and was found to be similar to that obtained in oriented models of bacterial membranes (POPE/POPG), where the tilt and pitch angles of the helix were determined by solid-state NMR based on 15N chemical shifts. Molecular dynamic simulations revealed that SAAP-148 approaches the bacterial membrane by forming salt bridges between lysine and arginine side chains and lipid phosphate groups while it interacts minimally with mammalian models containing POPC and cholesterol. The simulations also showed that SAAP-148 stabilizes its helical fold onto bacterial-like membranes, placing its helix axis almost perpendicular to the surface normal. This suggests that SAAP-148 may act by forming a carpet-like layer at the bacterial membrane, rather than by forming a pore. The findings of this study provide new insights into the molecular mechanism of action of SAAP-148.