

Early Stages of Antimicrobial Peptides Binding to Resistant and Susceptible Bacterial Outer Membrane Chemotypes from Atomistic MD simulations

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Lipopolysaccharides (LPS) are the major constituent of bacterial outer membranes, acting as an effective permeability barrier against xenobiotic agents and a potent activator of the mammalian immune system in amounts as little as *fmol*. Compounds that bind Lipid-A can limit this inflammatory process. The cyclic cationic antimicrobial peptide polymyxin B (Pmx-B) is one of the simplest molecules capable of selectively bind to Lipid-A. Gram-negative bacteria resistance to Pmx-B relies on chemical modifications of the LPS structure, which lead to major changes in the physical-chemical properties of the outer membrane. We have previously developed and validated atomic parameters for classical simulations of different LPS chemotypes.^{1, 2} These parameters have been used to investigate the structural dynamics,^{3, 4} hydration⁵ and electrostatic properties⁶ of bacterial outer membranes. In this work, we have performed a systematic investigation of Pmx-B binding to outer membrane models composed of distinct LPS chemotypes experimentally shown to be either resistant or susceptible to the peptide. Molecular dynamics simulations were carried out for Pmx-B bound to the penta- and hexa-acylated forms of Lipid-A and Lipid-A modified with 4-amino-4-deoxy-L-arabinose as well as the penta-acylated form of LPS Re.⁷ Our simulations show that upon binding to the bacterial outer membrane surface, Pmx-B promotes cation displacement and structural changes in membrane curvature and integrity as function of the LPS chemotype susceptibility or resistance to the antimicrobial peptide. These findings reproduce experimental trends while providing atom-level structural information on the molecular basis of resistance and susceptibility of Gram-negative bacteria to Pmx-B.

Key words: vicinal proton-proton coupling constants, peptide-induced membrane curvature, peptide-induced cation displacement, mechanism of action, GROMOS force-field.

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