Molecular Dynamics Studies of Truncated Human Cathelicidin LL:37 Peptide Interacting with a Bacterial Model Membrane

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Abstract: In this study, we conducted a Molecular Dynamics (MD) Simulation to investigate the nature of interactions between the cationic antimicrobial peptide GF-17 and a bacterial model membrane (POPG/POPE with a ratio of 3:1). The residues 17 to 32 of human Cathelicidin peptide LL-37 was identified as the core antimicrobial region [1]. This critical region, namely, GF-17 has a significant strength in killing methicillin-resistant *Staphylococcus aureus* (MRSA) and *Escherichia coli* strains [2]. GF-17 is an amphipathic α-helical peptide with cationic residues Arg23 and Lys25 residing on the hydrophobic and hydrophilic interface and a net charge of +5 important for direct interactions with the bacterial membranes. Along with MD simulation the binding free energy was calculated using the molecular mechanics Poisson−Boltzmann surface area (MM-PBSA) method [3] to explore the structural and thermodynamic contributions of each residue to binding with the bacterial model membrane. In excellent agreement with experimental data, the simulation results revealed that the residues ARG23 and LYS25 (as numbered in LL-37) in the first layer of action favor the binding with anionic POPG lipids through electrostatic interactions and hydrogen bindings. In the second layer of action residues PHE17 and PHE27 favor the insertion of the peptide into the membrane through hydrophobic interactions. Our findings shed light on the crucial role of electrostatic attraction between cationic residues and phosphate groups in binding with bacterial membrane and yield insights useful for the design of potent antimicrobial peptides targeting multidrug resistant bacteria.

Keywords: Cathelicidin LL-37; Molecular dynamics; Antimicrobial peptide

References

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