The role of supramolecular aggregation for cationic peptide in fast bacterial killing

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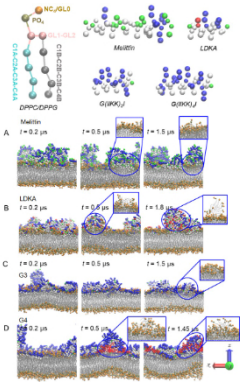
In light of the growing global threat of multidrug-resistant bacterial infections, there is an urgent need to develop novel antimicrobial agents. Short, rationally-designed antimicrobial peptides (AMPs) offer significant potential due to their tunable properties and distinct mode of action targeting bacterial membranes. This research employs an integrated multi-technique approach—combining molecular dynamics (MD) simulations, neutron reflection/scattering (NR/SANS), and stochastic optical reconstruction microscopy (STORM), to unravel the detailed mechanism of membrane disruption by designed AMPs such as G(IIKK) $_3$ I-NH $_2$ (G3) and its derivatives. Our central finding is that the formation of specific intramembrane peptide nanoaggregates is a critical determinant of bactericidal efficacy. The physicochemical properties of the peptides, particularly hydrophobicity and charge, govern the inter/intramolecular interactions and following extent, depth, and morphology of these aggregates within bacterial lipid bilayers. Optimal nanoaggregation induces membrane rigidification, hydrophobic mismatch, and peptide-aggregate-driven phase separation, leading to accelerated and catastrophic membrane disintegration. This process directly correlates with rapid dynamic killing and high potency against resistant strains like ESBL- *E. coli* , MRSA, while allowing for the fine-tuning of hemolytic cytotoxicity. By establishing intramembrane self-assembly as a core design principle, this work provides a crucial mechanistic framework for developing next-generation, aggregation-optimized peptide antibiotics.

Keywords:
AMP design, intramembrane nanoaggregates, membrane-disruption kinetics, multidrug-resistant bacteria



AMPs' intermolecular interaction with DPPG bilayers at changing simulation times (A. Melittin, B. LDKA, C. G3, D. G4). The inset graphs show the enlarged features inside the corresponding side views, and AMPs are ignored here to highlight lipid molecular restructuring caused by AMP aggregation.