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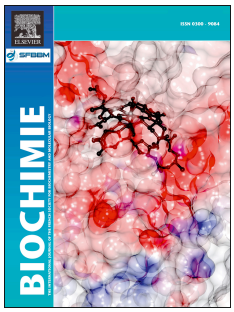

Membrane Permeabilization Design of Antimicrobial Peptides Based on Chikungunya Fusion Domain Scaffold and Its Antibacterial Activity against Gram-positive *Streptococcus Pneumoniae* in Respiratory Infection

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Membrane Permeabilization Design of Antimicrobial Peptides Based on Chikungunya Virus Fusion Domain Scaffold and Its Antibacterial Activity against Gram-positive *Streptococcus Pneumoniae* in Respiratory Infection

Abstract: The structural dynamics of membrane permeabilization are investigated systematically and compared between viral fusion peptides (VFPs) and antimicrobial peptides (AMPs). It is revealed that the permeabilization process can be divided into two phases: a fast motion phase in water (first phase) and a slow diffusion phase in lipid (second phase). Difference in peptide permeability to neutrally or weakly charged mammalian membrane and to negatively charged bacterial membrane is primarily determined by the first phase, which is dominated by the direct electrostatic interaction between peptide and the hydrophilic surface of membranes. With the harvested knowledge we attempt to rationally design anti-Gram-positive AMPs based on the VFP scaffold of Chikungunya virus fusion domain, which is an 18-mer polypeptide segment (VT18, ^{84}VYPFMWGGAYCFCDAENT^{101}) located in the structural glycoprotein E1 of viral envelope. Our simulations and previous NMR study suggest that the isolated VT18 peptide can be well structured into a double-stranded β-sheet conformation in water, but would become intrinsically disordering in lipid. Converting the negatively charged VT18 (charge = –2) to two positively charged peptides VT18-KKLV (VYPFMWGGAYCFCKAKLV-NH_2) (charge = +3) and VT18-CAKKLV (VYPFCWGGAYAFCKAKLV-NH_2) (charge = +3) by residue substitution and C-terminal amidation can largely promote peptide approaching to bacterial membrane surface, thus rendering the peptide with a substantially increased antibacterial activity against Gram-positive *Streptococcus pneumoniae* (MIC changes from >200 to 52–105 and 58–90 μg/ml, respectively). A further cyclization of linear peptide VT18-CAKKLV by adding a disulfide bond across its two strand arms, which results in a cyclic peptide cVT18-CAKKLV