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Communication

Effects of linker amino acids on the potency and selectivity of dimeric antimicrobial peptides

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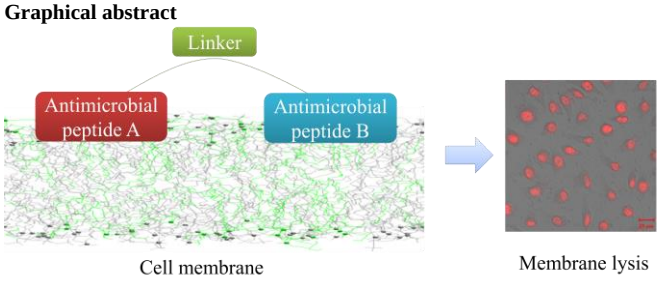
Graphical abstract



Conformational flexibility induced by proline and aminocaproic acid can increase anticancer activity and antimicrobial activity of dimeric antimicrobial peptides with reduced hemolytic activity. This study will contribute to the design of efficient antimicrobial peptides.

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ABSTRACT

Dimerization is an effective strategy for designing antimicrobial peptides that combine the advantages of different native peptides. In this study, we explored the effects of different linker amino acids, including leucine, proline and aminocaproic acid, on the anticancer, antimicrobial and hemolytic activities of the heteromeric antimicrobial peptides AM-1, AM-2, and AM-3. Proline and aminocaproic acid are ideal linkers for increasing the potency and selectivity of heteromeric antimicrobial peptides. The results of MD simulations provided a rationalization for this observation. Both AM-2, which had a proline linker, and AM-3, which had an aminocaproic acid linker, adopted a compact conformation in water and a bent conformation in membranes. This change in the flexible structures of AM-2 and AM-3 could have resulted in decreased binding of these peptides to zwitterionic lipid bilayers and increased damage to mixed lipid bilayers containing acidic phospholipids. In short, these findings obtained via assessing the effects of linker amino acids will contribute to the design of ideal heteromeric antimicrobial peptides with high selectivity and potency.

Antimicrobial peptides, which are widely distributed among microorganisms, animals and plants, form an evolutionarily conserved component of an organism's innate immune system. Despite great diversity in their primary sequences, antimicrobial peptides share certain established hallmarks, including cationicity, hydrophobicity and amphiphilicity [1, 2]. Among antimicrobial peptides, helical peptides are the most widely distributed and possess various pharmacological properties, such as antimicrobial, antiviral and anticancer activities [1, 2]. It is generally believed that the main mechanism of action of antimicrobial peptides is membrane disruption *via* a