Doubly-Stapled antimicrobial peptides

Young-Woo Kim
Dongguk University, Korea

Antimicrobial peptides (AMPs) play a critical role in the first-line defense system of various organisms. Most AMPs exhibit antimicrobial activity via membranolysis upon binding to bacterial membrane. Due to the unique mechanism of action, AMPs have been considered as promising alternative antibiotics to complement small-molecule antibiotics that are susceptible to resistance. Despite their great potential, however, the clinical application of AMPs has been hampered by their vulnerability to proteolytic degradation. Inspired by the unique architectural features of amphipathic helical AMPs, we examined the potential of Verdine's double-stapling system for the de novo design of novel antimicrobial agents. Our prototypical doubly-stapled helices of an alanine/lysine based model sequence showed potent antimicrobial activities and highly increased proteolytic stability. Through further systematic modifications, we also successfully manipulated their hemolytic activity as well as antimicrobial activity. Overall, the preliminary results obtained from this study imply that the doubly-stapled peptide helix can serve as a highly promising scaffold for the rational design of potent, selective, and metabolically stable antimicrobial peptides that can combat against the growing problems of antibiotic-resistance.