03 Building Blocks of Life: Protein-based Materials and Supramolecular Assemblies

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Hydrocarbon Stapling Converts Cell-penetrating Peptides into Potent Antibacterials

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The effectiveness of known drugs against resistant bacteria is decreasing. Antimicrobial peptides show promise as antibacterials, but its cellular instability and other limitations disqualify them as drugs. However, inactive and non-toxic cell-penetrating peptides (CPPs) offer potential for structural modification.

Our approach is to stabilize CPPs in their membrane-active form by hydrocarbon stapling to transform them into antibacterial agents. To obtain stapled CPPs, we re-examined the sequences of (KFF)3K [1] and lysine- and leucine-rich peptides [2], incorporated unnatural olefin residues, and stapled them using ring-closing metathesis.

We demonstrated that stapled CPPs exhibit bactericidal activity, remain stable in human serum, and show no hemolytic activity or toxicity to eukaryotic cells [1,2]. Molecular dynamics simulations revealed how the hydrocarbon staple stabilizes an amphipathic membrane-active helical structure that is responsible for bacterial cell envelope disruption [2].

We show that hydrocarbon stapling can transform inactive CPPs into effective antibacterials, suggesting the potential of peptide structural modification for therapeutic applications.

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[2] M. Lobka et al. Eur. J. Med. Chem. 290:117445 (2025)