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ANTIMICROBIAL DRUGS

Multifaceted approach to multidrug resistance

Multidrug-resistant (MDR) Gram-negative bacteria represent an increasing threat to public health, which is compounded by the dearth of drug candidates in the pipeline against such pathogens. Now, a study published in *Nature Microbiology* describes a new class of structurally nanoengineered antimicrobial peptide polymers (SNAPPs) as candidates to address this unmet need.

Although efforts to combat Gram-positive MDR bacteria, particularly *Staphylococcus aureus*, have intensified over the past decade, the additional outer membrane of Gram-negative bacteria, such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, has hampered progress in developing new drugs that can kill Gram-negative bacteria.

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In the current study, Lam *et al.* applied a peptide synthesis approach termed ring-opening polymerization to α-amino acid *N*-carboxyanhydrides. The authors had previously used this approach to generate star-shaped SNAPPs with complex and stable macromolecular architectures. Two SNAPPs, termed S16 and S32, with structures inspired by naturally occurring antimicrobial peptides were selected for further testing.

In vitro, S16 and S32 showed antimicrobial efficacy against a range of bacteria, with preferential activity against Gram-negative species. Importantly, the polymers were equally effective against MDR clinical isolates of *A. baumannii* and *P. aeruginosa*, and drug resistance was not detected even after 600 generations of *A. baumannii* growth in the presence of low S16 concentrations.

To test for possible effects on mammalian cells, which could limit the therapeutic utility of SNAPPs, the authors incubated S16 and S32 with red blood cells. They found that the polymers exhibited only negligible haemolytic activity.

In a mouse peritonitis model of *A. baumannii* infection, treatment with S16 or the antibiotic imipenem at 0.5, 4.0 and 8.0 h post-infection significantly reduced bacterial load and enabled survival of all mice at 24 h, whereas 80% of sham-treated mice died. When the researchers extended the mouse model studies to an MDR strain of *A. baumannii*, they found S16 treatment again enabled survival of all mice, whereas only 50% of imipenem-treated mice survived at 24 h.

Last, Lam *et al.* conducted preliminary mechanistic studies to begin to illuminate how the SNAPPs kill bacteria. Super-resolution fluorescence imaging and membrane potential measurements of the Gram-negative bacterium *Escherichia coli* in the presence of S16 indicated that the polymer causes disruption of the bacterial outer membrane, crosses the underlying peptidoglycan layer and triggers disruption of the cytoplasmic membrane, leading to unregulated transmembrane ion movement. At high SNAPP concentrations, such action is thought to rapidly lyse the bacterial cell. At lower concentrations, the authors found evidence that S16 also activates bacterial programmed cell death pathways.

SNAPPs represent a useful avenue for new drugs to target MDR Gram-negative bacteria, and their multimodal action should help to slow or prevent the development of resistance.

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ORIGINAL ARTICLE Lam, S. J. *et al.* Combating multidrug-resistant Gram-negative bacteria with structurally nanoengineered antimicrobial peptide polymers. *Nat. Microbiol.* **1**, 16162 (2016)