ANTIBACTERIAL DRUGS

Peptide power

Despite the current industry stagnation in antibiotic R&D, recent research by two industry–academic collaborative groups has resulted in the discovery of two new classes of antimicrobial peptides for treating Gram-positive bacterial infections.

Ten years after the discovery of a complex of eight closely related acyldepsipeptides (ADEPs) with *in vitro* activity against staphylococci and streptococci, Harald Labischinski and colleagues reveal in *Nature Medicine* the structure of the main peptide component of the complex, ADEP1, and report the *de novo* synthesis of optimized variants of the peptide with improved antibiotic properties.

Two of the optimized peptides, ADEP2 and ADEP4, have improved *in vitro* antibacterial potency against Gram-positive bacteria compared with the natural product ADEP1, and in rodents lethally infected with *Enterococcus faecalis* ADEP2 and ADEP4 were as effective as the clinically used antibiotic linezolid. ADEP4 also cured 80% of mice with sepsis and was superior to linezolid in rodents infected with *Streptococcus pneumoniae*. Using an ADEP1-resistant *Escherichia coli* mutant library, the authors identified the target of the ADEPs, the catalytic core of the highly conserved bacterial caseinolytic kinase (ClpP). They went on to show that ADEPs bind ClpP and confer proteolytic activities to the otherwise inactive Clp-protease complex, and that their antibacterial activity might arise from deregulating the normal mechanisms that safeguard essential bacterial proteins from proteolysis.

The second addition to the antibiotic armament comes in the form of a landmark paper published in *Nature* by Hans-Henrik Kristensen and colleagues, who report the isolation of the first defensin from fungi, a peptide they call plectasin. Defensins are a family of naturally occurring cysteine-rich peptides found in higher plants and animals that display broad activity against a wide variety of microbes, making them attractive drug candidates. Plectasin was isolated by screening cDNAs of secretory proteins from the fungus *Pseudoplectania nigrella* for significant sequence similarity to invertebrate defensins, and its identity as a fungal homologue of invertebrate defensins was confirmed by nuclear magnetic resonance spectroscopy.

Studies of plectasin in antimicrobial assays showed that it has potent activity against a wide variety of Gram-positive bacteria and killed *Streptococcus pneumoniae* at rates comparable to existing antibiotics both *in vitro* and in two mouse models of pneumococcal infection. Although its mechanism of action is not yet known, the discovery of a defensin from fungi with potent antibacterial activity could circumvent the main challenge that has hindered the development of defensin-based drugs so far — namely, the high cost of large-scale manufacture.

Both classes of peptide reported in these papers showed comparable activity to conventionally used antibiotics against the pathogens tested and also exhibited activity against drug-resistant clinical isolates. Furthermore, they showed no cross-resistance with existing antibiotics, suggesting that they could prove beneficial when used in combination with existing drugs.

Joanna Owens

References and links

ORIGINAL RESEARCH PAPERS Brötz-Oesterhelt, H. *et al.* Dysregulation of bacterial proteolytic machinery by a new class of antibiotics. *Nature Med.* **11**, 1082–1087 (2005) | Mygind, P. H. *et al.* Plectasin is a peptide antibiotic with therapeutic potential from a saprophytic fungus. *Nature* **437**, 975–980 (2005)