ANTIMICROBIALS

A ringing success

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URLs

Lactococcus lactis
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genome&prjocmd=Retrieve&dopt=Overview&list_uids=12306

Listeria monocytogenes
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genome&prjocmd=Retrieve&dopt=Overview&list_uids=12309

Clostridium botulinum
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genome&prjocmd=Retrieve&dopt=Overview&list_uids=193

NisC
<http://ca.expasy.org/uniprot/Q03202>

NisA
<http://ca.expasy.org/uniprot/P13068>

NisP
<http://ca.expasy.org/uniprot/Q07596>

In a recent issue of *Science*, Satish Nair, Wilfred van der Donk and colleagues report on an important advance in the understanding of nisin biosynthesis — a finding that could help the search for new antibiotics.

Nisin is a post-translationally modified lantibiotic that is naturally produced by *Lactococcus lactis* and is effective against a wide range of Gram-positive bacteria, including food-borne pathogens such as *Listeria monocytogenes* and *Clostridium botulinum*. It is therefore widely used in the food industry as a preservative. Nisin's microbicidal properties work through several mechanisms: by binding to lipid II — an essential intermediate in peptidoglycan biosynthesis — nisin induces pore formation in the membrane and disrupts cell-wall biosynthesis; in addition, nisin inhibits the outgrowth of bacterial spores.

Nisin contains five thioether rings of varying sizes and conformations that are required for its biological activity. Li *et al.* have now reconstituted the cyclization process of nisin *in vitro*, and report that the cyclase NisC is responsible for the formation of all of the thioether rings. NisA, the precursor peptide, is ribosomally synthesized, followed by dehydration of serine and threonine residues. NisC then catalyses five distinct cyclization reactions to generate five

cyclic thioethers: one lanthionine and four methyllanthionines. Once cyclization is complete, NisP removes the leader peptide. Leader-peptide recognition probably has a role in NisC binding, as NisC was unable to convert the dehydrated peptide into its biologically active form after cleavage of the leader peptide.

Li *et al.* also determined the X-ray crystal structure of NisC, which revealed unexpected similarities in fold and substrate activation with mammalian farnesyl transferases. Similar to farnesyl transferase, a single zinc ion is situated at the top face of the double α -barrel in NisC. These structural similarities suggest that human homologues of NisC might post-translationally modify a cysteine of a protein substrate.

Although nisin has been in use as a food preservative worldwide for decades, it has not induced the widespread biological resistance encountered by many antibiotics. This is thought to be due to its multiple modes of action and the nature of the lipid II target, which is not a protein and is not easy to modify by the bacteria. The newfound knowledge of how nisin is biosynthesized, and the enzymes involved in this process, could be useful in the search for novel antibiotics that could avoid the development of antibiotic-resistant bacteria.

Annie Tremp

ORIGINAL RESEARCH PAPER Li, B. *et al.* Structure and mechanism of the lantibiotic cyclase involved in nisin biosynthesis. *Science* **311**, 1463–1467 (2006)

FURTHER READING Christianson, D. W. Five golden rings. *Science* **311**, 1383 (2006) | Cotter, P. D., Hill, C. & Ross, R. P. Bacteriocins: developing innate immunity for food. *Nature Rev. Microbiol.* **3**, 777–788 (2005)