Scientists discover two-component lantibiotic with therapeutic potential

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The discovery and preparation of a naturally occurring antibiotic could open the door to new therapeutic drugs for treating nasty infections.

The rapid spread of drug-resistant bacterial strains poses a persistent threat to human health, and requires new sources of antibiotics to treat infections. Researchers at the University of Illinois at Urbana-Champaign are tackling this problem by discovering and preparing natural antibiotics called lantibiotics.

Lantibiotics are a class of very potent antimicrobial compounds whose antimicrobial properties are attributed to their structure. They possess unusual sulfur bridged rings that provide structural rigidity for binding their cellular targets. Lantibiotics are commonly used in the food industry to inhibit the growth of microorganisms.

"Having the ability to make analogs of these naturally occurring antibiotics gives us the flexibility to look for improvements in properties such as toxicity, biostability and bioavailability," said Wilfred van der Donk, a William H. and Janet Lycan Professor of Chemistry at the U. of I. He is a corresponding author of a paper that will be posted online this week ahead of regular publication by the *Proceedings of the National Academy of Sciences*. In previous work, van der Donk first identified the molecular activity of an enzyme (LctM) responsible for naturally turning a small protein into a lantibiotic. That discovery, reported in the journal Science in 2004, involved lacticin 481, a lantibiotic produced by several strains of Lactococcus lactis, a bacterium used in cheese production.

In March 2006, van der Donk's team reported, again in Science, the synthesis of the lantibiotic nisin. The most studied lantibiotic, nisin has been used as a food preservative for more than 40 years without the development of significant antibiotic resistance.

Then, in the Oct. 26 issue of *Chemistry and Biology*, the team demonstrated that LctM could accept substrates vastly different from its natural substrate, in vitro.

"Normally, enzymes are very selective, and will work only on their natural substrate," said van der Donk, who is also an affiliate of the university's Institute for Genomic Biology. "We showed that our enzyme could modify many synthetic substrates, and produce sulfur bridged rings of different sizes and shapes. This offered us the opportunity to control and alter the structure of lantibiotics."

In their latest work, to be published in PNAS, van der Donk and his collaborators describe a new two-component lantibiotic. These lantibiotic systems utilize two peptides that are each post-translationally modified to an active form, and act in synergy to provide antibacterial activity.

"Given the synergy observed among two-component lantibiotics, which display similar or higher activity than the best single-component lantibiotic, nisin, the possibility of engineering new lantibiotics with therapeutic potential is even greater for these systems," van der Donk said.

Using bioinformatics, the researchers found genes annotated in the fully sequenced genome of the Gram-positive bacterium Bacillus halodurans C-125 as precursors of the lantibiotics mersacidin and cytolysin. This strain had not previously been reported to produce a lantibiotic.

The new two-component lantibiotic was named haloduracin by its discoverers. "The bacterium that produces haloduracin grows at pH 9 and above, suggesting that the lantibiotic it produces will be stable in the human body, unlike nisin, which is unstable at pH 7 and above," van der Donk said. Significantly, the researchers succeeded in expressing in the bacterium Escherichia coli the machinery to produce haloduracin, thereby creating the first in vitro biosynthesis of a two-component lantibiotic.

"The in vitro biosynthesis opens the door to new, intriguing possibilities involving antimicrobial peptide design and engineering," van der Donk said. "Now we can start applying all the lessons we learned with lacticin 481."

Source: University of Illinois at Urbana-Champaign