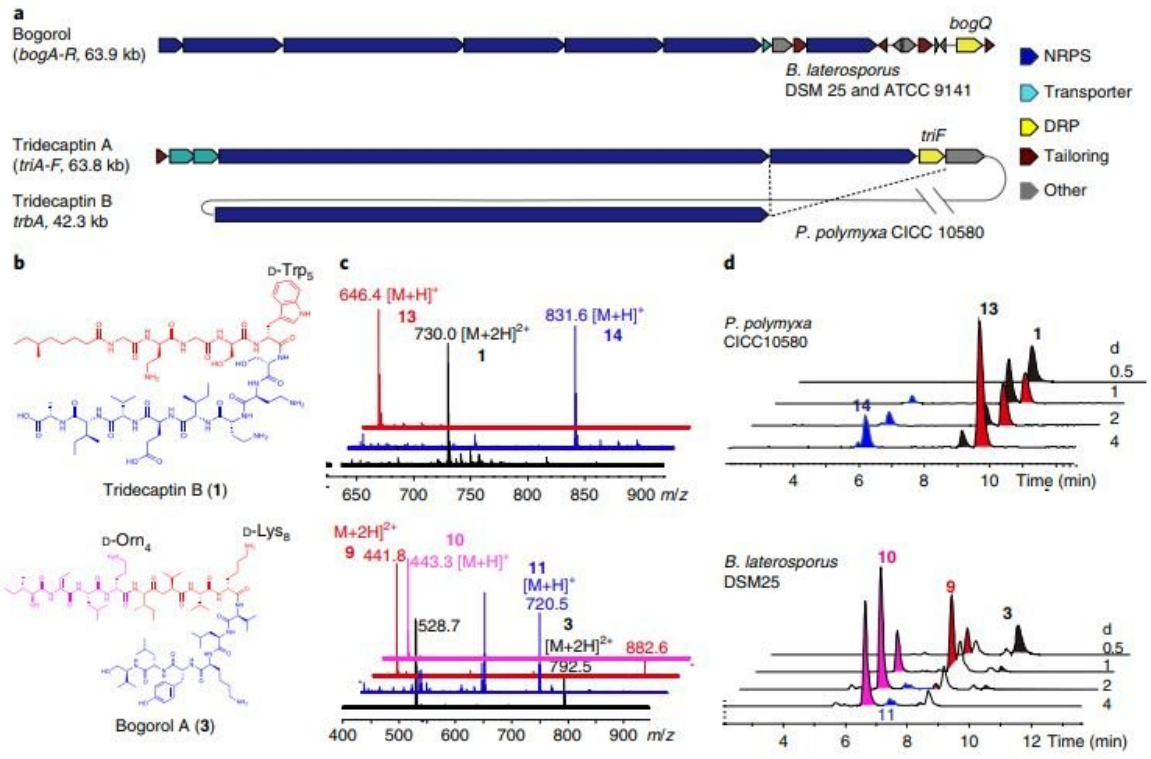
Scientists discern new bacterial resistance mechanism against peptide antibiotics

March 21 2018



a, The BGCs of bogorol from B. laterosporus DSM 25 and ATCC 9141, as well as tridecaptin A and tridecaptin B from P. polymyxa CICC 10580. BogQ from the strain DSM 25 and that from the strain ATCC 9141 share 85 percent amino acid sequence identity. The intersecting dotted lines indicate genes shared by two gene clusters within the same host (Supplementary Fig. 10). b, Structures of DNRPs tridecaptin B and bogorol A, with DRP recognition motifs highlighted. c, Stacked overlay of the mass spectra (electrospray ionization) of parent compounds (black), C-terminal fragments (blue), and N-terminal fragments

(red). Data are representative of two independent experiments. Top, tridecaptin B; bottom, bogorol A. d, Time-course analyses of corresponding compounds produced by P. polymyxa CICC 10580 (top) and B. laterosporus DSM 25 (bottom) at different fermentation times (representative of three independent experiments). Credit: Division of Life Science, HKUST

Non-ribosomal peptide antibiotics, including polymyxin, vancomycin, and teixobactin, most of which contain D-amino acids, are highly effective against multidrug-resistant bacteria. However, overusing antibiotics while ignoring the risk of resistance arising has inexorably led to widespread emergence of resistant bacteria. Elucidating the little known mechanisms of resistance to peptide antibiotics is critical when implementing peptide antibiotics and would improve effectively improve efficiency.

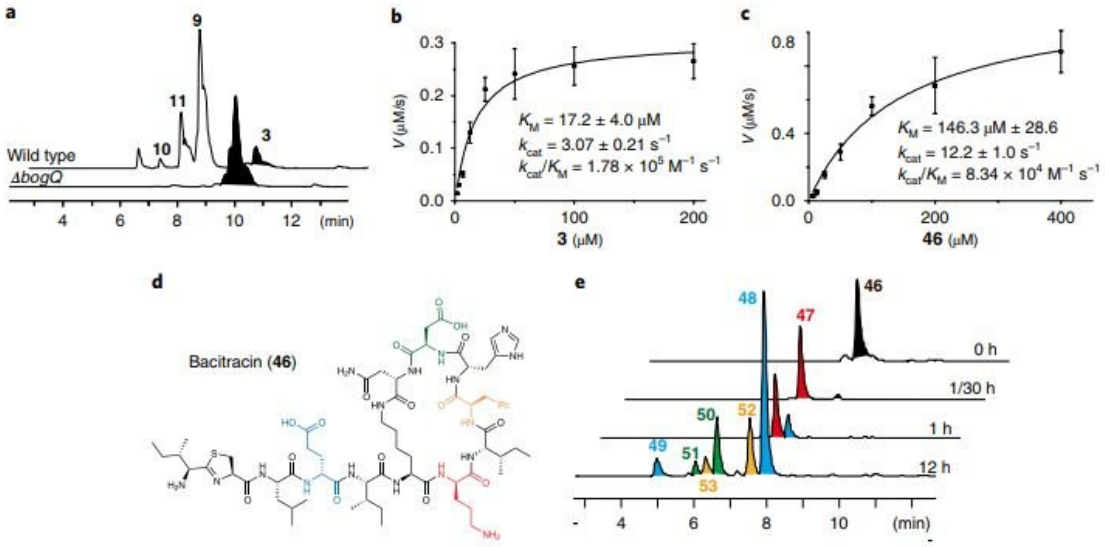
In a recent study, a group of scientists from the Hong Kong University of Science and Technology reveals both the widespread distribution and broad-spectrum resistance potential of D-stereospecific peptidases, providing a potential early indicator of antibiotic resistance to non-ribosomal peptide antibiotics.

Their findings were published in the journal *Nature Chemical Biology* on Feb 26, 2018.

"We applied an approach to 5,585 complete bacterial genomes spanning the entire domain of bacteria," said Pei-Yuan Qian, chair professor of the Division of Life Science, HKUST, and lead author of the paper. "With subsequent chemical and enzymatic analyses, we demonstrated a mechanism of resistance toward non-ribosomal peptide antibiotics that is based on hydrolytic cleavage by D-stereo specific peptidases."

The team identified a family of D-stereospecific resistance peptidases (DRPs) that are phylogenetically widely distributed in nature. The finding DRPs was found to be involved in combating widely-distributed antibiotics containing D-aa for the survival of their host, which was experimentally validated by a combination of CRISPR/Cas9 based gene editing, chemical and enzymatic analyses.

"Given the potential of DRPs for broad-spectrum resistance and their potential to target clinically important antibiotics containing D-aa, these widely distributed resistance genes are likely to be particularly dangerous if they are transferred to opportunistic pathogens," said Prof. Qian. "The finding DRPs in nature constitute only the tip of the iceberg, which will lead to intense research on the use and development of peptide antibiotics to combat antibiotic resistance."



a, LC-MS traces comparing wild-type B. laterosporus ATCC 9141 and the ΔbogQ mutant (representative of three independent experiments). b,c, Kinetic analyses of BogQ-catalyzed hydrolysis of bogorol A (b; 3) and bacitracin (c; 46) v, reaction velocit. Data are mean?±?s.d.; n=?3 independent experiments. d,

Structure of the DNRP antibiotic bacitracin; colors highlight the cleavage sites of BogQ. e, LC-MS traces of in vitro assays of BogQ (2.0?μM) against 46 (200?μM; representative of two independent experiments). Time-course cleavage products (47-53) of 46 are labeled using the same color code as their d-aa cleavage sites in d. For enzymatic cleavage patterns, see Supplementary Fig. 22. Credit: Division of Life Science, HKUST

More information: Yong-Xin Li et al, Resistance to nonribosomal peptide antibiotics mediated by d-stereospecific peptidases, *Nature Chemical Biology* (2018). DOI: 10.1038/s41589-018-0009-4