Researchers report biosynthetic pathway of mechercharmycin A

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Recently, TANG Gongli's group from the Shanghai Institute of Organic Chemistry and University of Chinese Academy of Sciences reported the biosynthetic pathway of mechercharmycin A (MCM-A), a marine natural product belonging to a family of polyazole cyclopeptides with remarkable bioactivities and unique structures.

The study was published in *Cell Chemical Biology* on Sept. 1.

Through bioinformatics analysis and structural analysis of MCM-A, the researchers presumed that the compound is a natural product of ribosomally synthesized and post-translationally modified peptides (RiPPs).

They sequenced the genome of MCM producer, Thermoactinomyces sp. YM3-251, searched the genome data with the predicted core sequence (FIVSSSCS), and identified a candidate biosynthetic gene cluster BGC (mcm) containing the possible precursor gene mcmA and a dehydratase gene mcmL.

Since the original producing strain Thermoactinomyces sp. YM3-251 is difficult to genetically manipulate, the researchers made the presumptive BGC (mcmA-mcmL) heterologously express in Bacillus subtilis 168 to investigate the biosynthetic pathway.

After activating the BGC by adding a strong promoter pLaps, they detected the target product MCM-A in the fermentation products. Based

on this heterologous expression system, two MCM-A analogs (17 and 18) with comparable antitumor activity were generated by engineering the biosynthetic pathway.

Due to the degradation of the precursor peptides in the heterologous expression host, each knockout mutant strain (inactivation of gene mcmA-mcmL) did not provide more information about intermediates or the modification of precursor peptide. The researchers carried out combinatorial co-production of the precursor peptide with different modifying enzymes in Escherichia coli, which led to the identification of a different timing of modifications, showing that a $tRNA^{Glu}$-dependent highly regioselective dehydration is the first modification step, followed by polyazole formation through heterocyclization and dehydrogenation in an N- to C-terminal direction.

More information: Zeng-Fei Pei et al, Heterologous characterization of mechercharmycin A biosynthesis reveals alternative insights into post-translational modifications for RiPPs, *Cell Chemical Biology* (2021). DOI: 10.1016/j.chembiol.2021.08.005