

Reconstitution of iterative thioamidation in closthioamide biosynthesis reveals a novel nonribosomal peptide backbone-tailoring strategy.

Dunbar KL, Dell M, Molloy EM, Kloss F, Hertweck C (2019) Reconstitution of iterative thioamidation in closthioamide biosynthesis reveals a novel nonribosomal peptide backbone-tailoring strategy. *Angew Chem Int Ed* 58(37), 13014-13018.

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Abstract

Thioamide-containing nonribosomal peptides (NRPs) are exceedingly rare. Recently the biosynthetic gene cluster for the thioamidated NRP antibiotic closthioamide (CTA) was reported; however, the enzyme responsible for and timing of thioamide formation remained enigmatic. Here, we use genome editing, biochemical assays and mutational studies to demonstrate that a Fe-S cluster-containing member of the adenine nucleotide α -hydrolase protein superfamily (CtaC) is responsible for sulfur incorporation during CTA biosynthesis. However, unlike all previously characterized members, CtaC functions in a thiotemplated manner. The reconstitution of this unusual ATP-dependent sulfur transferase facilitates a revision of the CTA biosynthetic pathway and provides the first example of a NRP thioamide synthetase. Finally, using CtaC as a

bioinformatic handle, we provide promising clues that gene clusters encoding thioamidated NRPs are more widespread than previously thought.

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Identifier

doi: 10.1002/anie.201905992

PMID: 31276268