Reconstitution of Iterative Thioamidation in Closthioamide Biosynthesis Reveals a Novel Nonribosomal Peptide Backbone-Tailoring Strategy.

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Projects

On-line modification of processes in multimodular protein systems
Details

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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