Reconstitution of polythioamide antibiotic backbone formation reveals unusual thiotemplated assembly strategy.

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Abstract

Closthioamide (CTA) is a rare example of a thioamide-containing nonribosomal peptide and is one of only a handful of secondary metabolites described from obligately anaerobic bacteria. Although the biosynthetic gene cluster responsible for CTA production and the thioamide synthetase that catalyzes sulfur incorporation were recently discovered, the logic for peptide backbone assembly has remained a mystery. Here, through the use of in vitro biochemical assays, we demonstrate that the amide backbone of CTA is assembled in an unusual thiotemplated pathway involving the cooperation of a transacylating member of the papain-like cysteine protease family and an iteratively acting ATP-grasp protein. Using the ATP-grasp protein as a bioinformatic handle, we identified hundreds of such thiotemplated yet nonribosomal peptide synthetase (NRPS)-independent biosynthetic gene clusters across diverse bacterial phyla. The data presented herein not only clarify the pathway for the biosynthesis of CTA, but also provide a foundation for the discovery of additional secondary metabolites produced by noncanonical biosynthetic pathways.

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