Genome editing reveals novel thiotemplated assembly of polythioamide antibiotics in anaerobic bacteria.

Dunbar KL, Büttner H, Molloy EM, Dell M, Kumpfmüller J, Hertweck C (2018) Genome editing reveals novel thiotemplated assembly of polythioamide antibiotics in anaerobic bacteria. *Angew Chem Int Ed* 57(43), 14080-14084.

Details

PubMed

Abstract

Closthioamide (CTA) is a unique symmetric nonribosomal peptide with six thioamide moieties that is produced by the Gram-positive obligate anaerobe Ruminiclostridium cellulolyticum. CTA displays potent inhibitory activity against important clinical pathogens, making it a promising drug candidate. Yet, the biosynthesis of this DNA gyrase-targeting antibiotic has remained enigmatic. Using a combination of genome mining, genome editing (targeted group II intron, CRISPR/Cas9), and heterologous expression, we show that CTA biosynthesis involves specialized enzymes for starter unit biosynthesis, amide bond formation, thionation, and dimerization. Surprisingly, CTA biosynthesis involves a novel thiotemplated peptide assembly line that markedly differs from known nonribosomal peptide synthetases. These findings provide the first insights into the biosynthesis of thioamide-containing nonribosomal peptides and offer a starting point for the discovery of related natural products.

Beteiligte Forschungseinheiten

Biomolekulare Chemie Christian Hertweck Mehr erfahren

Leibniz-HKI-Autor*innen



Hannah Büttner

Details



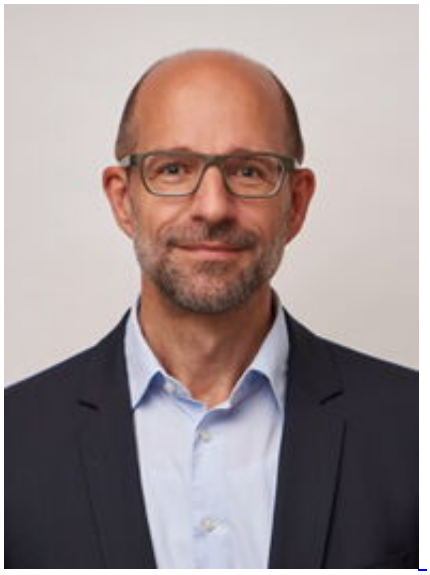
Maria Dell

Details



Kyle Dunbar

Details



Christian Hertweck

Details



Jana Krabbe

Details



Evelyn Molloy

Details

Identifier

doi: 10.1002/anie.201807970

PMID: 30193003