

Diketopiperazine formation in fungi requires dedicated cyclization and thiolation domains.

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Abstract

Cyclization of linear dipeptidyl precursors derived from nonribosomal peptide synthetases (NRPSs) into 2,5-diketopiperazines (DKPs) is a crucial step in the biosynthesis of a large number of bioactive natural products. However, the mechanism of DKP formation in fungi has remained unclear, despite extensive studies of their biosyntheses. Here we show that DKP formation en route to the fungal virulence factor gliotoxin requires a seemingly extraneous couplet of condensation (C) and thiolation (T) domains in the NRPS GliP. In vivo truncation of GliP to remove the CT couplet or just the T domain abrogated production of gliotoxin and all other gli pathway metabolites. Point mutation of conserved active sites in the C and T domains diminished cyclization activity of GliP in vitro and abolished gliotoxin biosynthesis in vivo. Verified NRPSs of other fungal DKPs terminate with similar CT domain couplets, suggesting a conserved strategy for DKP biosynthesis by fungal NRPSs.

Beteiligte Forschungseinheiten

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Leibniz-HKI-Autor*innen



Eileen Brandenburger

[Details](#)



Dirk Hoffmeister

[Details](#)

Identifizier

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