The cyclochlorotine mycotoxin is produced by the nonribosomal peptide synthetase CctN in Talaromyces islandicus ("Penicillium islandicum") - DTU Orbit (13/08/2019)

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Talaromyces islandicus ("Penicillium islandicum") is a widespread foodborne mold that produces numerous secondary metabolites, among them potent mycotoxins belonging to different chemical classes. A notable metabolite is the hepatotoxic and carcinogenic pentapeptide cyclochlorotine that contains the unusual amino acids β-phenylalanine, 2-aminobutyric acid and 3,4-dichloroproline. Although the chemical structure has been known for over five decades, nothing is known about the biosynthetic pathway of cyclochlorotine. Bioinformatic analysis of the recently sequenced genome of T. islandicus identified a wealth of gene clusters potentially coding for the synthesis of secondary metabolites. Here we show by RNA interference-mediated gene silencing that a nonribosomal peptide synthetase, CctN, is responsible for the synthesis of cyclochlorotine. Moreover, we identified novel cyclochlorotine chemical variants, whose production also depended on cctN expression. Surprisingly, the halogenase required for cyclochlorotine biosynthesis is not encoded in the cct cluster. Nonetheless, our findings enabled us to propose a detailed model for cyclochlorotine biosynthesis. In addition, comparative genomics revealed cct-like clusters are present in all of the sequenced Talaromyces strains indicating a high prevalence of cyclochlorotine production ability.

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