Reconstitution of enzymatic carbon-sulfur bond formation reveals detoxification-like strategy in fungal toxin biosynthesis.

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Abstract

Gliotoxin is a virulence factor of the human pathogen *Aspergillus fumigatus*, the leading cause of invasive aspergillosis. The activity of this metabolite is mediated by a transannular disulfide bond, a hallmark of the epipolythiodiketopiperazine (ETP) family. Through the creation of fungal gene deletion mutants, metabolic profiling and heterologous protein expression, we unveiled the critical role of the cytochrome P450 monooxygenase (CYP450) GliC for the stepwise bishydroxylation of the diketopiperazine (DKP) core. We show for the first time the formation of the C-S bond from the DKP in a combined assay of GliC and the glutathione-S-transferase (GST) GliG in vitro. Furthermore, we present experimental evidence for an intermediary imine species. The flexible substrate scope of GliC and GliG in combination parallels P450/GST pairs used in eukaryotic phase I/II detoxification pathways.

Involved units

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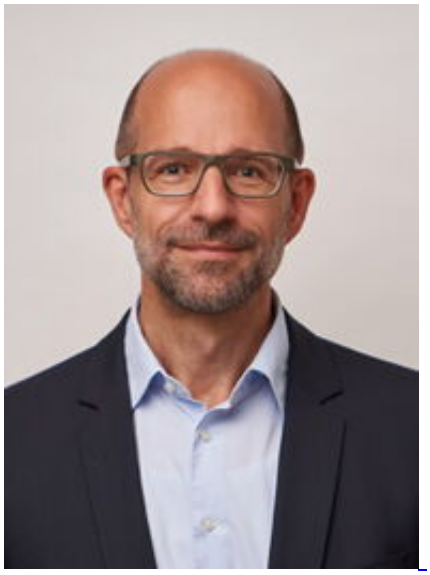
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