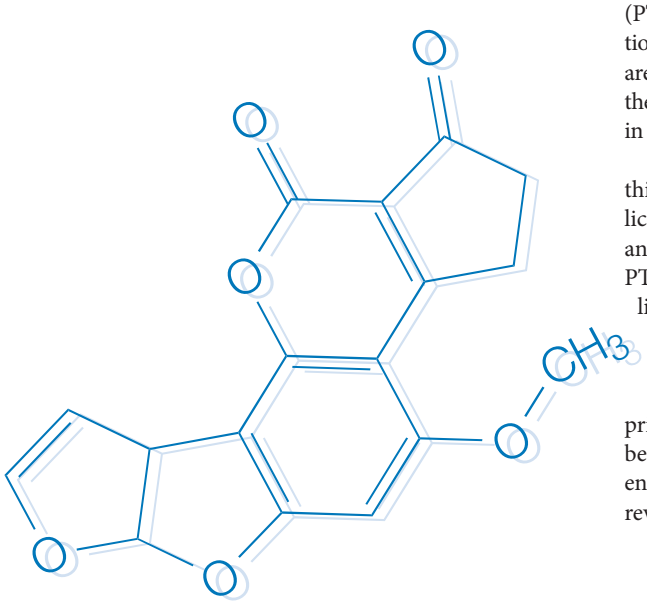
FUNGAL METABOLISM

Completing the circle

Fungi can produce an impressive variety of secondary metabolites, the most abundant of which are the polyketides. Reporting in *Nature*, Jason Crawford, Tyler Korman and colleagues present the mechanistic basis of the main cyclization reaction that is necessary for the production of the potent hepatocarcinogenic polyketide aflatoxin B_1.

In fungi, aromatic polyketides are produced by non-reducing, multi-domain iterative polyketide synthases (NR-PKSs), which cyclize linear poly-β-keto intermediates. Last year, the same group defined the domain structure of the *Aspergillus parasiticus* NR-PKS polyketide synthase A (PksA), which initiates aflatoxin B_1 biosynthesis by producing the precursor norsolorinic acid anthrone (NorA). Crawford *et al.* revealed that PksA has a complex six-domain structure and went on to assign a catalytic function to each domain, showing that the product template (PT) domain carries out the cyclization and aromatization reactions that are responsible for the formation of the penultimate bicyclic intermediate in the production of NorA.



Now, the mechanistic basis for this reaction is revealed with the publication of the 1.8 Å crystal structure and a mutational analysis of the PksA PT domain. The PT domain crystallized as a dimer, and the structure was solved in the presence of linear bound palmitate and a bicyclic substrate mimic. The primary sequence of the PT domain bears little similarity to known enzymes, but the crystal structure revealed the presence of a modified double hot dog (DHD) fold similar to that found in the dehydratase domain of animal fatty acid synthases, which carry out mechanistically related reactions. Other structural features of note include a binding pocket containing two regions that could be the docking sites of the linear β-keto substrate ends and a cyclization chamber. Taking the structural features together with the results of docking simulations and mutational analysis of the active site, the authors generated a model for the cyclization reactions that are carried out by the PksA PT domain.

The PT domain is evolutionarily conserved in a broad range of fungi, and the authors conclude that this work will 'lay a foundation for defining the molecular rules controlling NR-PKS cyclization specificity.'

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ORIGINAL RESEARCH PAPER Crawford, J. M. *et al.* Structural basis for biosynthetic programming of fungal aromatic polyketide cyclization. *Nature* **461**, 1139–1143 (2009)
FURTHER READING Crawford, J. M. *et al.* Deconstruction of iterative multidomain polyketide synthase function. *Science* **320**, 243–246 (2008)