Biosynthesis of acurin A and B in Aspergillus aculeatus

Hoof, Jakob Blæsbjerg; Nielsen, Maria Lund; Wolff, Peter Persson; Petersen, Lene Maj; Andersen, Lasse Norup; Petersen, Thomas Isbrandt; Holm, Dorte Koefoed; Mortensen, Uffe Hasbro; Nødvig, Christina Spuur; Larsen, Thomas Ostenfeld; Hoof, Jakob Blæsbjerg

Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

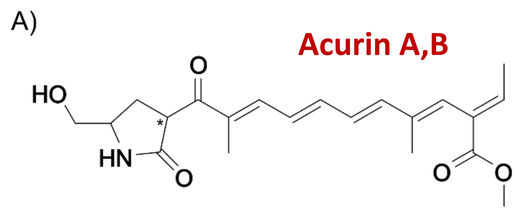
Biosynthesis of acurin A and B in *Aspergillus aculeatus*

Maria L. Nielsen†, Peter P. Wolff†, Lene M. Petersen, Lasse N. Andersen, Thomas Isbrandt, Dorte K. Holm, Uffe H. Mortensen, Christina S. Nødvig, Thomas O. Larsen, Jakob B. Hoof*

Department of Biotechnology and Biomedicine, Technical University of Denmark, Søltofts Plads, Kongens Lyngby, Denmark. *jblni@dtu.dk

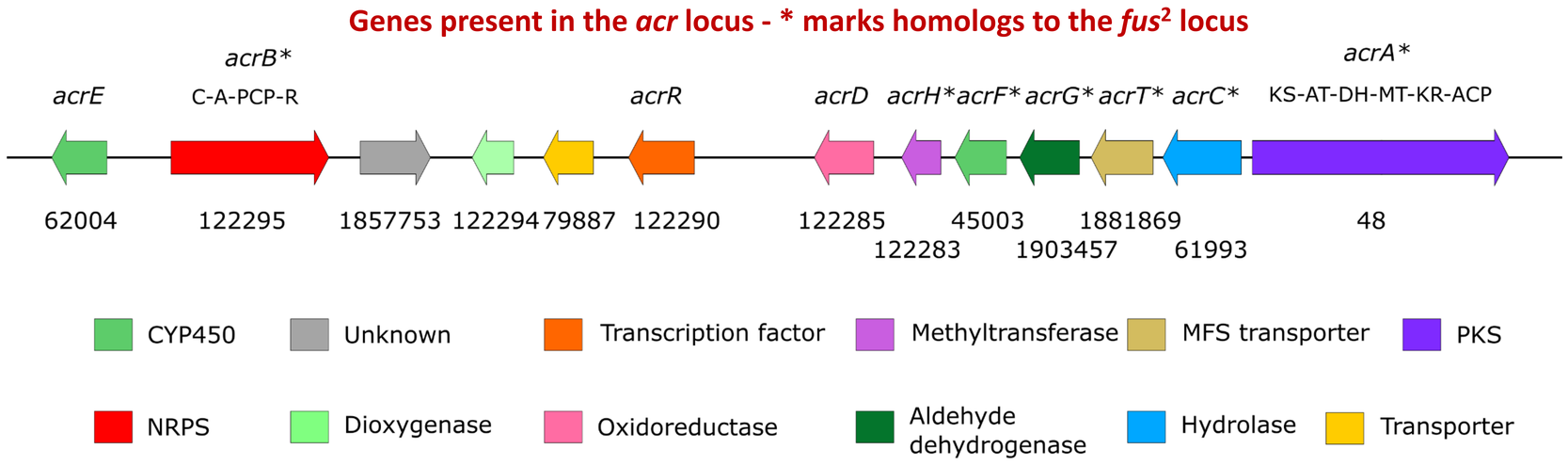
INTRODUCTION

Aspergillus aculeatus **is known for the commercial utilization in production of several enzymes. We have identified two stereoisomeric compounds of mixed polyketide-nonribosomal peptide (PK-NRP) origin in the extracts of *A. aculeatus* that we named acurin A and acurin B. Acurin resembles fusarin C, although without the epoxide. CRISPR-Cas9[1] was used to generate an *akuA*Δ strain (Ku70$^-$) facilitating strain construction.**

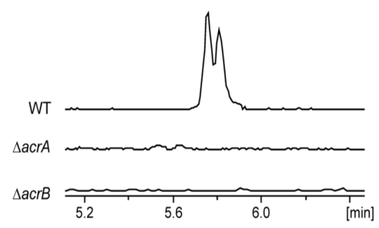


DISCOVERY OF THE ACURIN GENE CLUSTER

Genes present in the *acr* locus - * marks homologs to the *fus*[2] locus

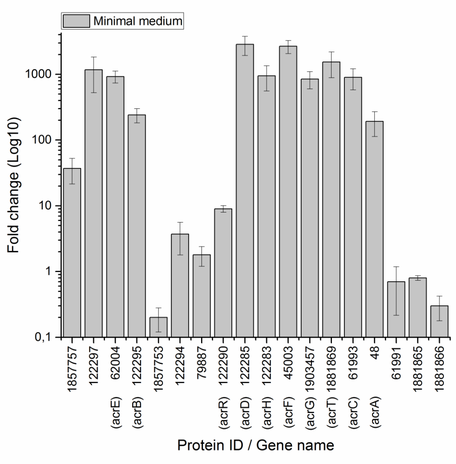


Chemical analysis of deletion strains of the PKS and NRPS in *acr* locus

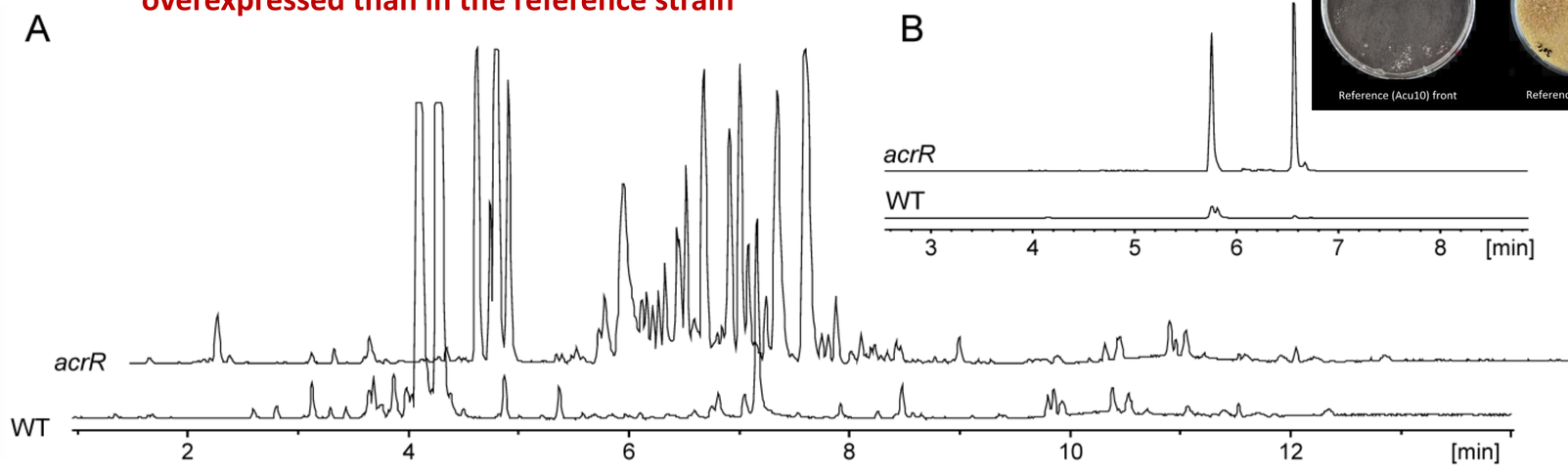


ACURIN TRANSCRIPTIONAL REGULATOR

RT-qPCR showed local *acr* regulation by AcrR

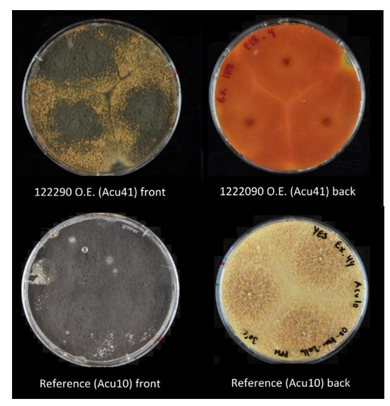


Not only local regulation -> More production of compounds in acrR overexpressed than in the reference strain



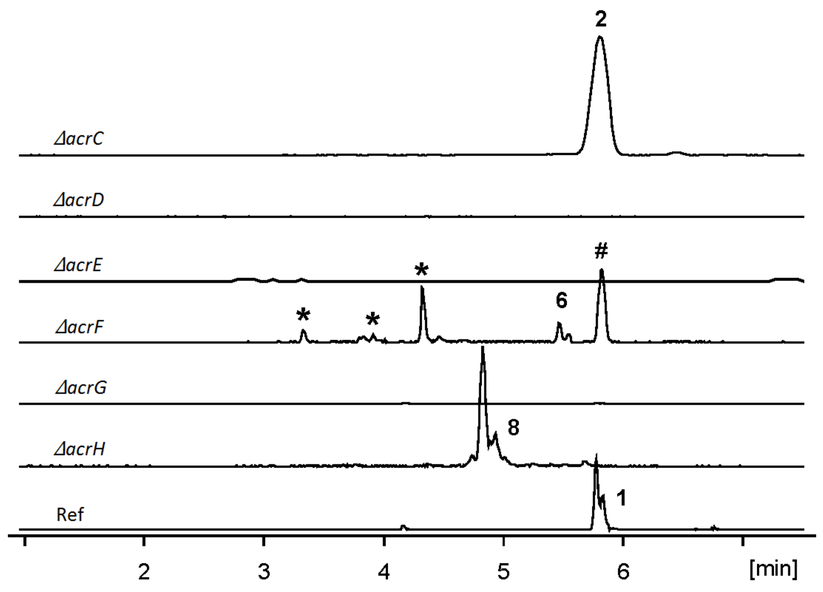
Elevated acurin production was confirmed

Global effects



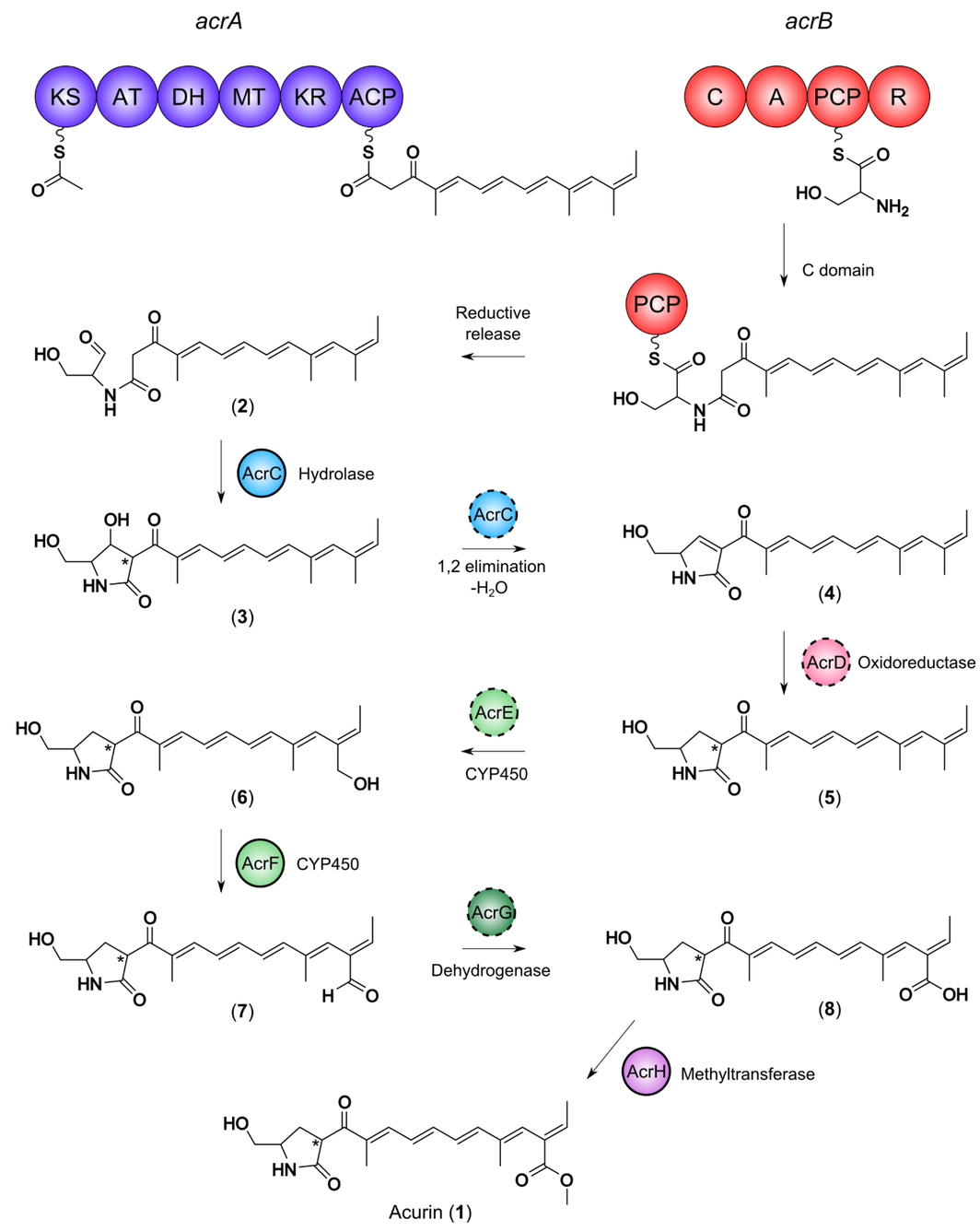
REMOVAL OF TAILORING ACTIVITIES

Deletion of all genes showing increased expression in the *acrR*↑ strain revealed that six additional genes were required for acurin production (see model for compounds)



BIOSYNTHETIC ROUTE TO ACURIN

We propose this model for biosynthesis of acurin. Not all deletion strains revealed intermediates, and in these cases enzymes will be shown with dashed lines to illustrate that the step is speculative. Other structures are verified by HPLC-MS, and acurin additionally by NMR. AcrF loss also produces compounds that we have not identified yet, and cannot couple to acurin biosynthesis



LITT.

[1]Nødvig, C.S.,…, and Mortensen, U.H. 2015. PLOS One. DOI:10.371/journal.prone.0133085

[2]Niehaus, E. … Humpf, H., 2013. Chemistry & Biology *20*, 1055-66.