A heterologous expression platform in *Aspergillus nidulans* for the elucidation of cryptic secondary metabolism in a human pathogen *Aspergillus fumigatus*

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Bridge UnderGrad Science (BUGS) *Summer Research Program*

USC University of Southern California

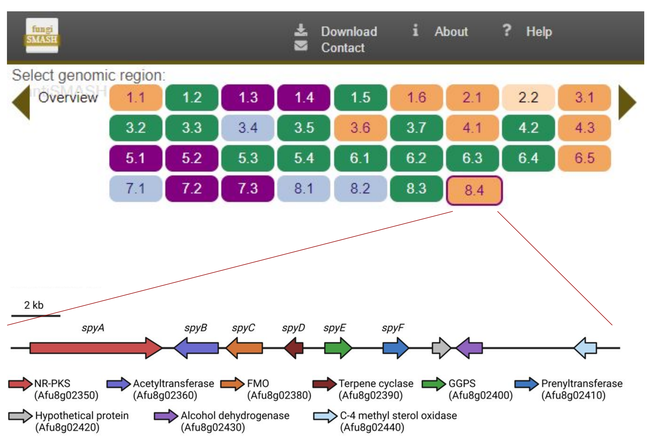
Abstract

Aspergillus fumigatus is a serious human pathogen causing life-threatening Aspergillosis in immunocompromised patients. Secondary metabolites (SMs) play an important role in pathogenesis, but the products of many SM biosynthetic gene clusters (BGCs) remain unknown. In this study, we have developed a heterologous expression platform in *Aspergillus nidulans*, using a newly created genetic dereplication strain, to express a previously unknown BGC from *A. fumigatus* and determine its products. The BGC produces sartorypyrones, and we have named it the spy BGC. Analysis of targeted gene deletions by HRESIMS, NMR, and microcrystal electron diffraction (MicroED) enabled us to identify 12 products from the *spy* BGC. Seven of the compounds have not been isolated previously. We also individually expressed the polyketide synthase (PKS) gene *spyA* and demonstrated that it produces the polyketide triacetic acid lactone (TAL), a potentially important biorenewable platform chemical. Our data have allowed us to propose a biosynthetic pathway for sartorypyrones and related natural products. This work highlights the potential of using the *A. nidulans* heterologous expression platform to uncover cryptic BGCs from *A. fumigatus* and other species, despite the complexity of their secondary metabolomes.

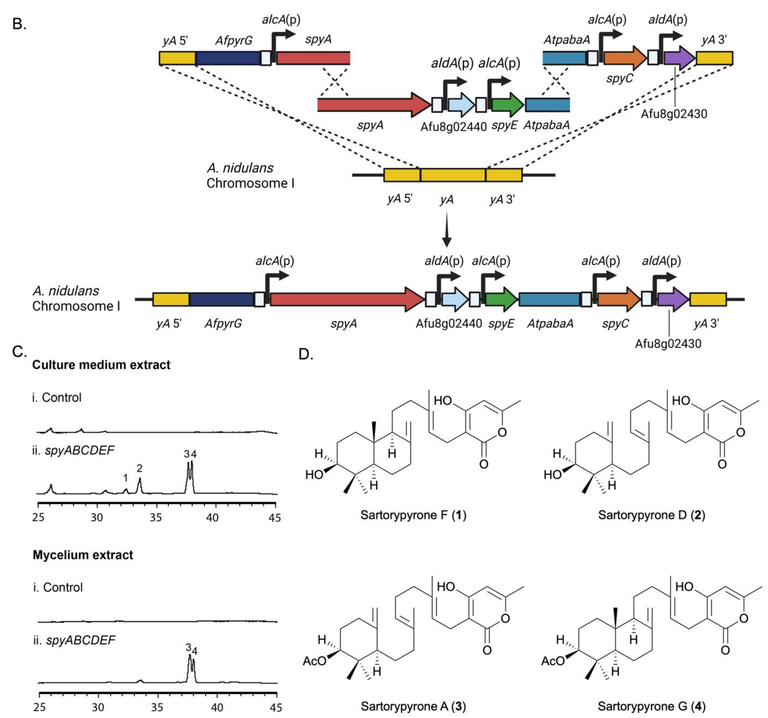
Objectives

- To express the cryptic BGCs from a human pathogen, *A. fumigatus* in the *A. nidulans* heterologous expression system.
- To identify the novel secondary metabolites produced from the unknown BGC.
- To determine the function of the biosynthetic enzymes in the BGC and propose the biosynthetic pathway.

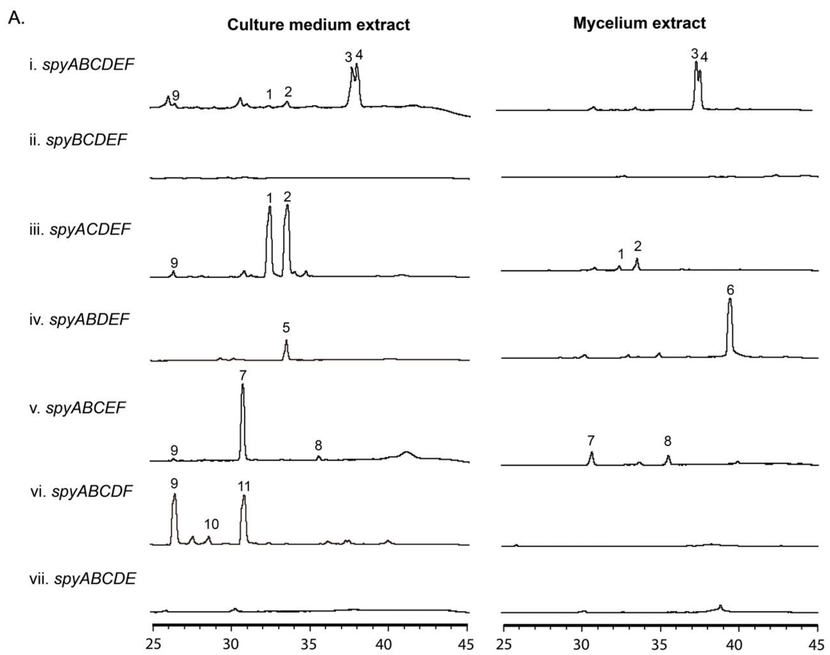
Biosynthetic gene clusters (BGCs) from *Aspergillus fumigatus*



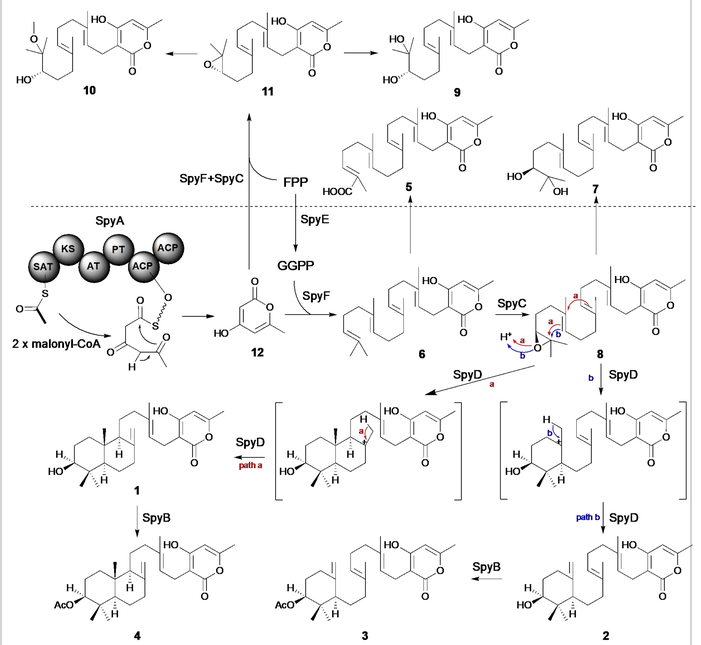
Heterologous expression of the *spy* BGC in *Aspergillus nidulans*



Individually gene deletion of the *spy* BGC



Proposed biosynthetic pathway of the *spy* BGC



Summary

- We have deciphered an unknown SM BGC in the human pathogen, *A. fumigatus* using a heterologous expression approach.
- The *spy* BGC consists of six contiguous genes involved in the biosynthesis of the sartorypyrones.
- Our approach of refactoring the entire gene cluster in the dereplicated *A. nidulans* host system provides us with a straightforward way to dissect the biosynthetic pathway.
- This work provides an appealing demonstration that the *A. nidulans* heterologous expression platform can be used for the elucidation of cryptic BGCs in *A. fumigatus* and other species.

References

1. Lin, S. Y., et al. *Chemical Science*, 2023. In press.

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