Genetic engineering activates biosynthesis of aromatic fumaric acid amides in the human pathogen *Aspergillus fumigatus*.

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Abstract

The *Aspergillus fumigatus* nonribosomal peptide synthetase FtpA is among the few of this species whose natural product has remained unknown. Both FtpA adenylation domains were characterized in vitro. Fumaric acid was identified as preferred substrate of the first and both l-tyrosine and l-phenylalanine as preferred substrates of the second adenylation domain. Genetically engineered *A. fumigatus* strains expressed either ftpA or the regulator gene ftpR, encoded in the same cluster of genes, under the control of the doxycycline-inducible tet-on cassette. These strains produced fumaryl-l-tyrosine and fumaryl-l-phenylalanine which were identified by liquid chromatography and high-resolution mass spectrometry. Modeling of the first adenylation domain in silico provided insight into the structural requirements to bind fumaric acid as peptide synthetase substrate. This work adds aromatic fumaric acid amides to the secondary metabolome of the important human pathogen *A. fumigatus* which was previously not known as a producer of these compounds.

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