

Transcriptome analysis of cAMP-dependent protein kinase A regulated genes reveals the production of the novel natural compound fumipyrrole by *Aspergillus fumigatus*

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Abstract

Aspergillus fumigatus is an opportunistic human pathogenic fungus causing life-threatening infections in immunocompromised patients. Adaptation to different habitats and also virulence of the fungus depends on signal perception and transduction by modules such as the cAMP dependent protein kinase A (PKA) pathway. Here, by transcriptome analysis 632 differentially regulated genes of this important signaling cascade were identified, including 23 putative transcriptional regulators. The highest up-regulated transcription factor gene was located in a previously unknown secondary metabolite gene cluster, which we named fmp, encoding an incomplete non-ribosomal peptide synthetase, FmpE. Overexpression of the regulatory gene fmpR using the Tet(On) system led to the specific expression of the other six genes of the fmp cluster. Metabolic profiling of wild type and fmpR overexpressing strain by HPLC-DAD and HPLC-HRESI-MS and structure elucidation by NMR led to identification of 5-benzyl-1H-pyrrole-2-carboxylic acid,

which we named fumipyrrole. Fumipyrrole was not described as natural product yet. Chemical synthesis of fumipyrrole confirmed its structure. Interestingly, deletion of fmpR or fmpE led to reduced growth and sporulation of the mutant strains. Although fmp cluster genes were transcribed in infected mouse lungs, deletion of fmpR resulted in wild-type virulence in a murine infection model.

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