Mitogen-activated protein kinase cross-talk interaction modulates the production of melanins in *Aspergillus fumigatus*.

Manfiolli AO, Siqueira FS, Dos Reis TF, Van Dijck P, Schrevens S, Hoefgen S, Föge M, Straßburger M, de Assis LJ, Heinekamp T, Rocha MC, Janevska S, Brakhage AA, Malavazi I, Goldman GH, Valiante V (2019) Mitogen-activated protein kinase cross-talk interaction modulates the production of melanins in *Aspergillus fumigatus*. *mBio* 10(2), e00215-19.

Abstract

The pathogenic fungus *Aspergillus fumigatus* is able to adapt to extremely variable environmental conditions. The *A. fumigatus* genome contains four genes coding for mitogen-activated protein kinases (MAPKs), which are important regulatory knots involved in diverse cellular responses. From a clinical perspective, MAPK activity has been connected to salvage pathways, which can determine the failure of effective treatment of invasive mycoses using antifungal drugs. Here, we report the characterization of the Saccharomyces cerevisiae Fus3 ortholog in A. fumigatus, designated MpkB. We demonstrate that MpkB is important for conidiation and that its deletion induces a copious increase of dihydroxynaphthalene (DHN)-melanin production. Simultaneous

deletion of mpkB and mpkA, the latter related to maintenance of the cell wall integrity, normalized DHN-melanin production. Localization studies revealed that MpkB translocates into the nuclei when *A. fumigatus* germlings are exposed to caspofungin stress, and this is dependent on the cross-talk interaction with MpkA. Additionally, DHN-melanin formation was also increased after deletion of genes coding for the Gα protein GpaA and for the G protein-coupled receptor GprM. Yeast two-hybrid and coimmunoprecipitation assays confirmed that GpaA and GprM interact, suggesting their role in the MpkB signaling cascade.

IMPORTANCE: *Aspergillus fumigatus* is the most important airborne human pathogenic fungus, causing thousands of deaths per year. Its lethality is due to late and often inaccurate diagnosis and the lack of efficient therapeutics. The failure of efficient prophylaxis and therapy is based on the ability of this pathogen to activate numerous salvage pathways that are capable of overcoming the different drug-derived stresses. A major role in the protection of *A. fumigatus* is played by melanins. Melanins are cell wall-associated macromolecules classified as virulence determinants. The understanding of the various signaling pathways acting in this organism can be used to elucidate the mechanism beyond melanin production and help to identify ideal drug targets.

Beteiligte Forschungseinheiten

Molekulare und Angewandte Mikrobiologie Axel Brakhage Mehr erfahren

Biobricks mikrobieller Naturstoffsynthesen Vito Valiante Mehr erfahren

Transfergruppe Antiinfektiva Axel Brakhage Mehr erfahren

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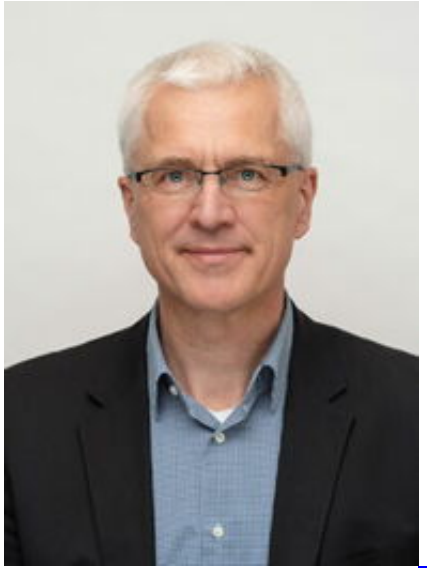

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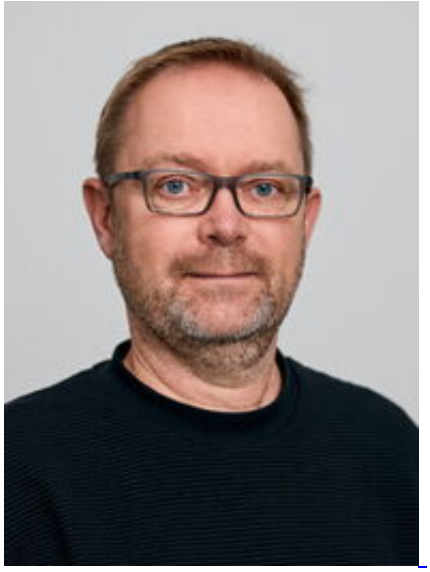

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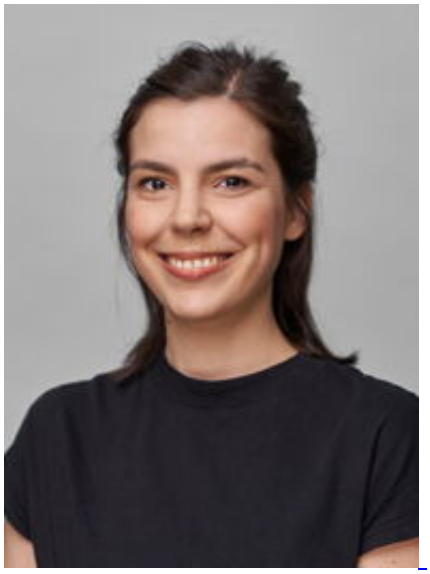

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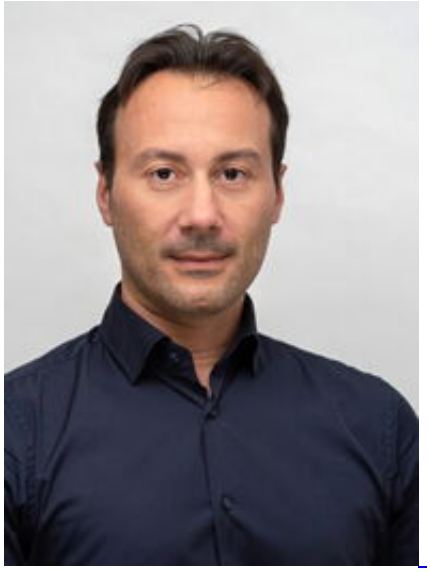

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