Pyomelanin formation in *Aspergillus fumigatus* requires HmgX and the transcriptional activator HmgR but is dispensable for virulence.

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Details

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Abstract

The opportunistic human pathogenic fungus Aspergillus fumigatus is able to produce the dark brown pigment pyomelanin by degradation of L-tyrosine. Pyomelanin was shown to protect the fungus against reactive oxygen intermediates as well as cell wall disturbing compounds and is therefore assumed to protect against immune effector cells during the infection process. Several genes for tyrosine degradation and pyomelanin formation are organized in a cluster in the genome of A. fumigatus. Here, we aimed at further analyzing tyrosine degradation and a possible role of pyomelanin in virulence. For this purpose, the function of two not yet characterized genes of the cluster, i.e., hmgX and hmgR, was analyzed. Generation of corresponding gene deletion mutants and reconstituted strains revealed that hmgX and hmgR are essential for tyrosine degradation. Both mutants, ΔhmgX and ΔhmgR, were not able to use tyrosine as sole carbon or nitrogen source and revealed impaired pyomelanin production. HmgR harbors a Zn(II)2Cys6-DNA binding domain. Analyses of the steady state mRNA levels revealed that HmgR acts as a transcriptional activator

for the genes of the tyrosine degradation cluster. Consistently, an HmgR-eGFP fusion protein was localized in the nucleus of A. fumigatus cells. By contrast, HmgX was found to be localized in the cytoplasm and does not contribute to regulation of gene transcription. HPLC analyses showed that HmgX is crucial for the conversion of p-hydroxyphenylpyruvate to homogentisic acid, the main intermediate in pyomelanin formation. Thus, HmgX is supposed to function as an accessory factor to mediate specific activity of HppD. Remarkably, the ability to degrade tyrosine and to form pyomelanin is dispensable for virulence of A. fumigatus in a murine infection model.

Beteiligte Forschungseinheiten

Molekulare und Angewandte Mikrobiologie Axel Brakhage Mehr erfahren

Mikrobielle Immunologie Ilse Jacobsen Mehr erfahren

Leibniz-HKI-Autor*innen



Axel A. Brakhage

Details



Thorsten Heinekamp

Details



Ilse Denise Jacobsen

Details



Sophia Keller

Details



Juliane Macheleidt

Details



Jeannette Schmaler-Ripcke

Details

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