The hypoxia-induced dehydrogenase HorA is required for coenzyme Q10 biosynthesis, azole sensitivity and virulence of *Aspergillus fumigatus*.

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Abstract

Aspergillus fumigatus is the predominant airborne pathogenic fungus causing invasive aspergillosis in immunocompromised patients. During infection *A. fumigatus* has to adapt to oxygen-limiting conditions in inflammatory or necrotic tissue. Previously, we identified a mitochondrial protein to be highly up-regulated during hypoxic adaptation. Here, this protein was found to represent the novel oxidoreductase HorA. In *Saccharomyces cerevisiae* a homologue was shown to play a role in biosynthesis of coenzyme Q. Consistently, reduced coenzyme Q content in the generated ΔhorA mutant indicated a respective function in *A. fumigatus*. Since coenzyme Q is involved in cellular respiration and maintaining cellular redox homeostasis, the strain ΔhorA displayed an impaired response to both oxidative and reductive stress, a delay in germination and an accumulation of NADH. Moreover, an increased resistance against antifungal drugs was observed. All phenotypes were completely reversed by the addition of the synthetic electron carrier menadione. The deletion strain ΔhorA showed significantly attenuated virulence in two murine infection models of invasive pulmonary aspergillosis. Therefore, the biosynthesis of coenzyme Q and, particularly, the fungal-specific protein HorA play a crucial role in virulence of *A. fumigatus*. Due to its absence in mammals, HorA might represent a novel therapeutic target against fungal infections.

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