Characterisation of the *Aspergillus fumigatus* detoxification systems for reactive nitrogen intermediates and impact on virulence.

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Abstract

Aspergillus fumigatus is a saprophytic mold that can cause life-threatening infections in immunocompromised patients. In the lung, inhaled conidia are confronted with immune effector cells that attack the fungus by various mechanisms such as phagocytosis, production of antimicrobial proteins or generation of reactive oxygen intermediates. Macrophages and neutrophils can also form nitric oxide (NO) and other reactive nitrogen intermediates (RNI) that potentially also contribute to killing of the fungus. However, fungi can produce several enzymes involved in RNI detoxification. Based on genome analysis of *A. fumigatus*, we identified two genes encoding flavohemoglobins, FhpA, and FhpB, which have been shown to convert NO to nitrate in other fungi, and a gene encoding S-nitrosoglutathione reductase GnoA reducing S-nitrosoglutathione to ammonium and glutathione disulphide. To elucidate the role of these enzymes in detoxification of RNI, single and double deletion mutants of FhpA, FhpB, and GnoA encoding genes were generated. The analysis of mutant strains using the NO donor DETA-NO

indicated that FhpA and GnoA play the major role in defense against RNI. By generating fusions with the green fluorescence protein, we showed that both FhpA-eGFP and GnoA-eGFP were located in the cytoplasm of all *A. fumigatus* morphotypes, from conidia to hyphae, whereas FhpB-eGFP was localized in mitochondria. Because fhpA and gnoA mRNA was also detected in the lungs of infected mice, we investigated the role of these genes in fungal pathogenicity by using a murine infection model for invasive pulmonary aspergillosis. Remarkably, all mutant strains tested displayed wild-type pathogenicity, indicating that the ability to detoxify host-derived RNI is not essential for virulence of *A. fumigatus* in the applied mouse infection model. Consistently, no significant differences in killing of ΔfhpA, ΔfhpB, or ΔgnoA conidia by cells of the macrophage cell line MH-S were observed when compared to the wild type.

Involved units

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