Conidial Melanin of the Human-Pathogenic Fungus *Aspergillus fumigatus* Disrupts Cell Autonomous Defenses in Amoebae.

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Projects

The role of virulence determinants of the human pathogenic fungus *Aspergillus fumigatus* in the defense against fungivorous amoeba
Details

Abstract

The human-pathogenic fungus *Aspergillus fumigatus* is a ubiquitous saprophyte that causes fatal lung infections in immunocompromised individuals. Following inhalation, conidia are ingested by innate immune cells and can arrest phagolysosome maturation. How this virulence trait could have been selected for in natural environments is unknown. Here, we found that surface exposure of the green pigment 1,8-dihydroxynaphthalene-(DHN)-melanin can protect conidia from phagocytic uptake and intracellular killing by the fungivorous amoeba *Protostelium aurantium* and delays its exocytosis from the nonfungivorous species *Dictyostelium discoideum* To elucidate the antiphagocytic properties of the surface pigment, we followed the antagonistic interactions of *A. fumigatus* conidia with the amoebae in real time. For both amoebae, conidia covered with DHN-melanin were internalized at far lower rates than were seen with conidia lacking the pigment, despite high rates of initial attachment to nonkilling *D. discoideum* When ingested by *D. discoideum*, the formation of nascent phagosomes was followed by transient acidification of phagolysosomes, their subsequent neutralization, and, finally, exocytosis of the conidia. While the cycle was completed in less than 1 h for unpigmented conidia, the process was significantly prolonged for conidia covered with DHN-melanin, leading to an extended intracellular residence time. At later stages of this cellular infection, pigmented conidia induced enhanced damage to phagolysosomes and infected amoebae failed to recruit the ESCRT (endosomal sorting complex required for transport) membrane repair machinery or the canonical autophagy pathway to defend against the pathogen, thus promoting prolonged intracellular persistence in the host cell and the establishment of a germination niche in this environmental phagocyte.

IMPORTANCE Infections with *Aspergillus fumigatus* are usually acquired by an inhalation of spores from environmental sources. How spores of a saprophytic fungus have acquired abilities to withstand and escape the phagocytic attacks of innate immune cells is not understood. The fungal surface pigment dihydroxynaphtalene-melanin has been shown to be a crucial factor for the delay in phagosome maturation. Here, we show that this pigment also has a protective function against environmental

phagocytes. Pigmented conidia escaped uptake and killing by the fungus-eating amoeba Protostelium aurantium When ingested by the nonfungivorous phagocyte *Dictyostelium discoideum*, the pigment attenuated the launch of cell autonomous defenses against the fungal invader, such as membrane repair and autophagy, leading to prolonged intracellular retention. Membrane damage and cytoplasmic leakage may result in an influx of nutrients and thus may further promote intracellular germination of the fungus, indicating that *A. fumigatus* has acquired some of the basic properties of intracellular pathogens.

Identifier

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