Peroxiredoxin Asp f3 Is Essential for Aspergillus fumigatus To Overcome Iron Limitation during Infection.

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Projects

Oxidative inactivation of primary metabolism pathways in the human pathogenic fungus *Aspergillus fumigatus*
Details

Abstract

Aspergillus fumigatus is an important fungal pathogen that causes allergic reactions but also life-threatening infections. One of the most abundant A. fumigatus proteins is Asp f3. This peroxiredoxin is a major fungal allergen and known for its role as a virulence factor, vaccine candidate, and scavenger of reactive oxygen species. Based on the hypothesis that Asp f3 protects A. fumigatus against killing by immune cells, we investigated the susceptibility of a conditional aspf3 mutant by employing a novel assay. Surprisingly, Asp f3-depleted hyphae were killed as efficiently as the wild type by human granulocytes. However, we identified an unexpected growth defect of mutants that lack Asp f3 under low-iron conditions, which explains the avirulence of the Δaspf3 deletion mutant in a murine infection model. A. fumigatus encodes two Asp f3 homologues which we named Af3l (Asp f3-like) 1 and Af3l2. Inactivation of Af3l1, but not of Af3l2, exacerbated the growth defect of the conditional aspf3 mutant under iron limitation, which ultimately led to death of the double mutant. Inactivation of the iron acquisition repressor SreA partially compensated for loss of Asp f3 and Af3l1. However, Asp f3 was not required for maintaining iron homeostasis or siderophore biosynthesis. Instead, we show that it compensates for a loss of iron-dependent antioxidant enzymes. Iron supplementation restored the virulence of the Δaspf3 deletion mutant in a murine infection model. Our results unveil the crucial importance of Asp f3 to overcome nutritional immunity and reveal a new biological role of peroxiredoxins in adaptation to iron limitation. IMPORTANCE Asp f3 is one of the most abundant proteins in the pathogenic mold Aspergillus fumigatus. It has an enigmatic multifaceted role as a fungal allergen, virulence factor, reactive oxygen species (ROS) scavenger, and vaccine candidate. Our study provides new insights into the cellular role of this conserved peroxiredoxin. We show that the avirulence of a Δaspf3 mutant in a murine infection model is linked to a low-iron growth defect of this mutant, which we describe for the first time. Our analyses indicated that Asp f3 is not required for maintaining iron homeostasis. Instead, we found that Asp f3 compensates for a loss of iron-dependent antioxidant enzymes. Furthermore, we identified an Asp f3-like protein which is partially functionally redundant with Asp f3. We highlight an unexpected key role of Asp

f3 and its partially redundant homologue Af3l1 in overcoming the host's nutritional immunity. In addition, we uncovered a new biological role of peroxiredoxins.

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