# Identification and characterization of a novel *Aspergillus fumigatus* rhomboid family putative protease RbdA involved in hypoxia sensing and virulence.

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## Abstract

*Aspergillus fumigatus* is the most common pathogenic mold infecting humans and a significant cause of morbidity and mortality in immunocompromised patients. In invasive pulmonary aspergillosis, *A. fumigatus* spores are inhaled into the lungs, undergoing germination and invasive hyphal growth. The fungus occludes and disrupts the blood vessels, leading to hypoxia and eventual tissue necrosis. The ability of this mold to adapt to hypoxia is regulated in part by the sterol regulatory element binding protein (SREBP) SrbA and the DscA-D Golgi E3 ligase complex critical for SREBP activation by proteolytic cleavage. Loss of the genes encoding these proteins results in avirulence. To identify novel regulators of hypoxia-sensing, we screened the Neurospora crassagene deletion library under hypoxia and identified a novel rhomboid family protease essential for hypoxic growth. Deletion of the *A. fumigatus* rhomboid homolog rbdA resulted in an inability to grow under hypoxia, hypersensitivity to CoCl2, nikkomycin Z, fluconazole and ferrozine,

abnormal swollen tip morphology and transcriptional dysregulation- accurately phenocopying deletion ofsrbA. In vivo, rbdA deletion resulted in increased sensitivity to phagocytic killing, a reduced inflammatory Th1 and Th17 response and strongly attenuated virulence. Phenotypic rescue of rbdA was achieved by expression and nuclear localization of the N-terminus of SrbA including its HLH-domain, further indicating that RbdA and SrbA act in the same signaling pathway. In summary, we have identified RbdA, a novel putative rhomboid family protease in *A. fumigatus* that mediates hypoxia adaptation and fungal virulence and that is likely linked to SrbA cleavage and activation.

**Beteiligte Forschungseinheiten**

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