

The *Aspergillus fumigatus* transcriptional regulator AfYap1 represents the major regulator for defense against reactive oxygen intermediates but is dispensable for pathogenicity in an intranasal mouse infection model.

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Abstract

Macrophages and neutrophils kill the airborne fungal pathogen *Aspergillus fumigatus*. The dependency of this killing process on reactive oxygen intermediates (ROI) has been strongly suggested. Therefore, we investigated the enzymatic ROI detoxifying system by proteome analysis of *A. fumigatus* challenged by H₂O₂. Since many of the identified proteins and genes are apparently regulated by a putative *Saccharomyces cerevisiae* Yap1 homolog, the corresponding gene of *A. fumigatus* was identified and designated Afyap1. Nuclear localization of a functional AfYap1-eGFP fusion was stress dependent. Deletion of the Afyap1 gene led to drastically increased sensitivity of the deletion mutant against H₂O₂ and menadione, but not against diamide and NO radicals. Proteome analysis of the DeltaAfyap1 mutant strain challenged with 2

mM H₂O₂ indicated that 29 proteins are controlled directly or indirectly by AfYap1, including catalase 2. Despite its importance for defense against reactive agents, the Afyap1 deletion mutant did not show attenuated virulence in a murine model of *Aspergillus* infection. These data challenge the hypothesis that ROI such as superoxide anions and peroxides play a direct role in killing of *A. fumigatus* in an immunocompromised host. This conclusion was further supported by the finding that killing of *A. fumigatus* wild-type and DeltaAfyap1 mutant germlings by human neutrophilic granulocytes worked equally well irrespective of whether the ROI scavenger glutathione or an NADPH-oxidase inhibitor was added to the cells.

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