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.

Lessing F, Kniemeyer O, Wozniok I, Loeffler J, Kurzai O, Haertl A, Brakhage AA (2007) 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. *Eukaryot Cell* 6(12), 2290-2302.

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 H(2)O(2). 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 H(2)O(2) and menadione, but not against diamide and NO radicals. Proteome analysis of the DeltaAfyap1 mutant strain challenged with 2

mM H(2)O(2) 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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