SAGA/ADA complex subunit Ada2 is required for Cap1- but not Mrr1-mediated upregulation of the *Candida albicans* multidrug efflux pump MDR1.

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Abstract

Overexpression of the multidrug efflux pump MDR1 is one mechanism by which the pathogenic yeast Candida albicans develops resistance to the antifungal drug fluconazole. The constitutive upregulation of MDR1 in fluconazole-resistant, clinical C. albicans isolates is caused by gain-of-function mutations in the zinc cluster transcription factor Mrr1. It has been suggested that Mrr1 activates MDR1 transcription by recruiting Ada2, a subunit of the SAGA/ADA coactivator complex. However, MDR1 expression is also regulated by the bZIP transcription factor Cap1, which mediates the oxidative stress response in C. albicans. Here, we show that a hyperactive Mrr1 containing a gain-of-function mutation promotes MDR1 overexpression independently of Ada2. In contrast, a C-terminally truncated, hyperactive Cap1 caused MDR1 overexpression in a wild-type strain but only weakly in mutants lacking ADA2. In the presence of benomyl or H2O2, compounds that induce MDR1 expression in an Mrr1- and Cap1-dependent fashion, MDR1 was upregulated

with the same efficiency in wild-type and ada2Δ cells. These results indicate that Cap1, but not Mrr1, recruits Ada2 to the MDR1 promoter to induce the expression of this multidrug efflux pump and that Ada2 is not required for MDR1 overexpression in fluconazole-resistant C. albicans strains containing gain-of-function mutations in Mrr1.

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