Differential requirement of the transcription factor Mcm1 for activation of the *Candida albicans* multidrug efflux pump MDR1 by its regulators Mrr1 and Cap1.

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Abstract

Overexpression of the multidrug efflux pump Mdr1 causes increased fluconazole resistance in the pathogenic yeast Candida albicans. The transcription factors Mrr1 and Cap1 mediate MDR1 upregulation in response to inducing stimuli, and gain-of-function mutations in Mrr1 or Cap1, which render the transcription factors hyperactive, result in constitutive MDR1 overexpression. The essential MADS box transcription factor Mcm1 also binds to the MDR1 promoter, but its role in inducible or constitutive MDR1 upregulation is unknown. Using a conditional mutant in which Mcm1 can be depleted from the cells, we investigated the importance of Mcm1 for MDR1 expression. We found that Mcm1 was dispensable for MDR1 upregulation by H2O2 but was required for full MDR1 induction by benomyl. A C-terminally truncated, hyperactive Cap1 could upregulate MDR1 expression both in the presence and in the absence of Mcm1. In contrast, a hyperactive Mrr1 containing a gain-of-function mutation depended on Mcm1 to cause MDR1 overexpression. These results demonstrate a differential requirement for the coregulator Mcm1 for

Cap1- and Mrr1-mediated MDR1 upregulation. When activated by oxidative stress or a gain-of-function mutation, Cap1 can induce MDR1 expression independently of Mcm1, whereas Mrr1 requires either Mcm1 or an active Cap1 to cause overexpression of the MDR1 efflux pump. Our findings provide more detailed insight into the molecular mechanisms of drug resistance in this important human fungal pathogen.

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