The transcription factor Ndt80 does not contribute to Mrr1-, Tac1-, and Upc2-mediated fluconazole resistance in *Candida albicans*.

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Abstract

The pathogenic yeast Candida albicans can develop resistance to the widely used antifungal agent fluconazole, which inhibits ergosterol biosynthesis, by the overexpression of genes encoding multidrug efflux pumps or ergosterol biosynthesis enzymes. Zinc cluster transcription factors play a central role in the transcriptional regulation of drug resistance. Mrr1 regulates the expression of the major facilitator MDR1, Tac1 controls the expression of the ABC transporters CDR1 and CDR2, and Upc2 regulates ergosterol biosynthesis (ERG) genes. Gain-of-function mutations in these transcription factors result in constitutive overexpression of their target genes and are responsible for fluconazole resistance in many clinical C. albicans isolates. The transcription factor Ndt80 contributes to the drug-induced upregulation of CDR1 and ERG genes and also binds to the MDR1 and CDR2 promoters, suggesting that it is an important component of all major transcriptional mechanisms of fluconazole resistance. However, we found that Ndt80 is not required for the induction of MDR1 and CDR2 expression by inducing chemicals. CDR2 was even partially

derepressed in ndt80Δ mutants, indicating that Ndt80 is a repressor of CDR2 expression. Hyperactive forms of Mrr1, Tac1, and Upc2 promoted overexpression of MDR1, CDR1/CDR2, and ERG11, respectively, with the same efficiency in the presence and absence of Ndt80. Mrr1- and Tac1-mediated fluconazole resistance was even slightly enhanced in ndt80Δ mutants compared to wild-type cells. These results demonstrate that Ndt80 is dispensable for the constitutive overexpression of Mrr1, Tac1, and Upc2 target genes and the increased fluconazole resistance of strains that have acquired activating mutations in these transcription factors.

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