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Unusual susceptibility of a multidrug-resistant yeast strain to peptidic antifungals.

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Abstract

The susceptibility of Saccharomyces cerevisiae JG436 multidrug transporter deletion mutant, Deltapdr5, to several antifungal agents was compared to that of JG436-derived JGCDR1 and JGCaMDR1 transformants, harboring the CDR1 and CaMDR1 genes, encoding the main drug-extruding membrane proteins of Candida albicans. The JGCDR1 and JGCaMDR1 yeasts demonstrated markedly diminished susceptibility to the azole antifungals, terbinafine and cycloheximide, while that to amphotericin B was unchanged. Surprisingly, JGCDR1 but not JGCaMDR1 cells showed enhanced susceptibility to peptidic antifungals, rationally designed compounds containing inhibitors of glucosamine-6-phosphate synthase. It was found that these antifungal oligopeptides, as well as model oligopeptides built of proteinogenic amino acids, were not effluxed from JGCDR1 cells. Moreover, they were taken up by these cells at rates two to three times higher than by JG436. The tested oligopeptides were rapidly cleaved to constitutive amino acids by cytoplasmic peptidases. Studies on the mechanism of the observed phenomenon suggested that an additive proton motive force generated by Cdr1p stimulated uptake of oligopeptides into JGCDR1 cells, thus giving rise to the higher antifungal activity of FMDP [N(3)-(4-methoxyfumaroyl)-L-2,3-diaminopropanoic acid]-peptides.

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