SIT4 is a positive modulator of multidrug resistance phenotype in *Saccharomyces cerevisiae*

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Multidrug resistance (MDR) is defined as the cell ability to survive in the presence of lethal doses of more than one drug. This phenomenom has been conserved through the evolutionary scale and in humans is associated with the failure in cancer treatment. In *S. cerevisiae*, the major determinant of MDR is *PDR5*, encoding a plasma membrane efflux pump, controlled mainly by the transcription factors Pdr1 and Pdr3. We have previously demonstrated that *PDR5*-mediated MDR phenotype in *S. cerevisiae* requires the type 2A-related serine/threonine protein phosphatase Sit4. Disrupted *S. cerevisiae* sit4 cells were sensitive to a large number of substrates including anticancer drugs, azoles and cycloheximide. Pdr5 levels in wild type cells were higher than in sit4 mutant cells, but this phenotype is not linked to differences in transcription or protein turnover. ß-galactosidase assay revealed similar *PDR5* expression in wild-type and disrupted sit4 cells, even when grown in media containing ketoconazole, a known *PDR5* substrate. A double mutant pdr5sit4 is more sensitive to all drugs tested than single pdr5 and sit4 disrupted cells, indicating that *SIT4* can also modulate the expression of MDR genes other than *PDR5*. Wild-type cells exhibited enhanced Pdr5 phosphorylation, higher Yck1 and Yck2 levels and about 75% more casein kinase activity when compared to sit4 mutant cells. This suggests that Sit4 modulates multidrug resistance in yeast through casein kinase regulation. Immunolocalization and polysome formation patterns are now under investigation.
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