PDR5-MEDIATED MULTIDRUG RESISTANCE IN *SACCHAROMYCES CEREVISIAE* REQUIRES SIT4, A TYPE 2A-RELATED SERINE/THREONINE PROTEIN PHOSPHATASE

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We have previously reported that *SIT4*, a type 2A-related serine/threonine protein phosphatase confers MDR phenotype in *S. cerevisiae*. In this organism the major determinant of this resistance is *PDR5*, encoding a plasma membrane efflux pump protein belonging to the ABC transporter superfamily, controlled mainly by the transcription factors Pdr1 and Pdr3. In this work we demonstrated that *PDR5*-mediated MDR phenotype in *S. cerevisiae* requires *SIT4* activity. Although disrupted *S. cerevisiae* sit4 cells were sensitive to known *PDR5* substrates like azoles and cycloheximide, ß-galactosidase assay revealed a small increase in *PDR5* expression in disrupted sit4 cells. However, rhodamine 6G efflux and Pdr5 levels in wild type cells were higher, indicating modulation at the post-transcriptional level. *SIT4* can also activate the *Candida albicans* MDR homologue *CDR1*, once this gene enhanced resistance to cycloheximide and fluconazole in wild type *S. cerevisiae* cells, but not in disrupted sit4 cells. These data indicate that post-transcriptional regulation of MDR genes via *SIT4* is necessary to confer MDR phenotype not only in *S. cerevisiae* but possibly in *C. albicans* and other yeasts and that Sit4 is a potential target to the development of new fungicides to control MDR phenotype.

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