A yeast cyclophilin gene essential for lactate metabolism at high temperature

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The cyclophilins are a family of ubiquitous eukaryotic proteins first identified by high affinity for cyclosporin A (CsA). The immunosuppressant and cytotoxic effects of CsA are thought to result from formation of a toxic complex between cyclophilin and CsA rather than from inhibition of cyclophilin function. The physiological role(s) of the cyclophilins is unknown. Cyclophilins have in vitro peptidylprolyl cistrans isomerase (PPIase) activity, and thus may be involved in protein folding in vivo. We have isolated a yeast cyclophilin gene, CPR3, which encodes a presumptive mitochondrial isoform. While CPR3 disruption mutants lack any phenotype at 30 degrees C, they are unable to grow on L-lactate at 37 degrees C. Disruptions of two other cyclophilin genes (CPR1, CPR2) and of FPR1, the gene encoding an FK506 binding protein with PPIase activity, do not affect growth on L-lactate at 37 degrees C. L-Lactate metabolism requires transcriptional induction of CYB2, the gene encoding flavocytochrome b2; cpr3 mutants induce transcription of this gene normally. This result demonstrates a conditional lethal phenotype for a cyclophilin mutation and presents a system for genetic and biochemical analysis of cyclophilin function.

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