Mutation in PMR1, a Ca\(^{2+}\)-ATPase in Golgi, Confers Salt Tolerance in *Saccharomyces cerevisiae* by Inducing Expression of PMR2, an Na\(^{+}\)-ATPase in Plasma Membrane*

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Sodium tolerance in yeast is enhanced by continuous activation of calcineurin, a Ca\(^{2+}\)/calmodulin-dependent protein phosphatase that is required for modulation of the Na\(^{-}\) efflux mechanism. We isolated several salt-tolerant mutants with the treatment of ethylmethane sulfonate under high salt stress. One of the mutations was mapped in the *PMR1* gene. *Pmr1p*, the P-type Ca\(^{2+}\)-ATPase in the Golgi apparatus, regulates a cytosolic Ca\(^{2+}\) level in various responses. Cytosolic Ca\(^{2+}\) concentration in the *pmr1* mutant is highly maintained, and thus calcineurin is activated continuously. The treatment of FK506, a specific inhibitor of calcineurin, abolishes the salt-tolerant phenotype of the *pmr1* mutant. Activated calcineurin induces the expression of *PMR2*, encoding the P-type Na\(^{-}\)-ATPase, through the specific transcription factor, Tcn1p/Crz1p. Also, expression of the *PMR2::lacZ* reporter gene in the *pmr1* mutant was higher than that in wild type. We propose that the *pmr1* mutation confers salt tolerance through continuous activation of calcineurin and that *Pmr1p* might act as a major Ca\(^{2+}\)-ATPase under high salt stress.

Several components of the regulatory network that controls *PMR2* expression have been identified in the last few years. Calcineurin, the Ser/Thr protein phosphatase PP2B, is required for *PMR2* expression. Mutants lacking calcineurin have a decreased ability to export Li\(^{+}\) and Na\(^{+}\) ions, suggesting a defect in the Pmr2p (8, 9), and the constitutive activation of calcineurin confers increased resistance to Na\(^{+}\) and Li\(^{+}\) ions (10). Under high salt stress, a lot of Na\(^{+}\) comes into cytosol, and the cytosolic Ca\(^{2+}\) ion level is elevated. Ca\(^{2+}\) ion-bound calmodulin activates calcineurin. Activated calcineurin induces the expression of several genes including *PMR2* (5, 6, 11–14) via a specific transcription factor, Tcn1p/Crz1p (15, 16). The intracellular Ca\(^{2+}\) ion level has been suggested to play an important role in the salt stress response. However, components regulating cytosolic Ca\(^{2+}\) ion level are not clear under high salt stress.

To study the components associated with salt adaptation mechanisms under high salt stress, we isolated several salt-tolerant mutations by using ethyl methanesulfonate (EMS) treatment. One of the mutations was mapped in the *PMR1* gene, which encodes a P-type Ca\(^{2+}\)-ATPase mainly located to the Golgi apparatus (5, 17). Under high NaCl stress conditions, the level of cytosolic Ca\(^{2+}\) ion in the *pmr1* mutant was maintained higher than wild type. The highly maintained cytosolic Ca\(^{2+}\) level in turn results in enhanced expression of *PMR2* via calcineurin. Our results indicate that the *pmr1* mutation confers salt tolerance through continuous activation of calcineurin and enhanced *PMR2* expression. Taken together, it can be concluded that the Pmr1p acts as a major Ca\(^{2+}\)-ATPase under high salt stress.

**MATERIALS AND METHODS**

**Media and Strains**— Cultures were grown in YPD (1% bacto-yeast extract, 2% bacto-peptone, and 2% glucose) or defined minimal medium containing 0.67% yeast nitrogen base without amino acid (Difco), 1% glucose, and supplements as needed. Where indicated, NaCl was added to the medium. All strains used in this study were isogenic and derived from DBY1286 (a: ade2, his3-A200, leu2-3,112, ura3-52). The following strains, with the relevant genotypes indicated, were used: DBY1286 (PMR1), YJY15 (pmr1), YJY80 (PMR1, pmr2::lacZ), YJY81 (pmr1, pmr2::lacZ), YJY93 (pRS316-PMR1), and YJY94 (pRS316).

**Plasmids and Transformations**—All recombinant DNAs were derived from pYJ117, isolated from a YCp50-based yeast genomic library containing an ~15 kilobase fragment of genomic DNA. 6.4 kilobases of a *PmII* fragment of pYJ117 was inserted into the *Smal* site of *pRS316* (named pYJ121), and 3.6 kilobases of an *Spel* fragment of pYJ121 was inserted into the *SpeI* site of pRS316 (named pYJ122). pkC201, a *pmr2::lacZ* reporter gene, was provided by Dr. Cunningham. *Escherichia coli* strain DH5α was used for the propagation of plasmids using high efficiency 5-min transformation (18). Yeast transformation was done by an improved method for the high efficiency transformation of *Saccharomyces cerevisiae* as described in the *Methods*. This paper is available on line at http://www.jbc.org.

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1 The abbreviations used are: EMS, ethyl methanesulfonate; YPD, yeast extract-peptone-dextrose; ts, temperature sensitive.
intact yeast cells as described by Daniel et al. (19).

Random Mutagenesis with EMS—Cells were grown to total saturation (~2 × 10⁶ cells) at 26 °C in YPD medium. The cells were harvested and suspended in 4 ml of 0.1 M sodium phosphate buffer (pH 7.0). 1.4 ml of the cell suspension was added to 2 ml of 0.1 M sodium phosphate buffer (pH 7.0) in a sterile 15-ml Falcon tube (~2 × 10⁶ cells/ml). A 0.2-ml aliquot was removed and added to 8 ml of freshly prepared 5% sodium thiosulfate (filter-sterilized), which should give a cell concentration of 5 × 10⁶ cells/ml. The rest of the cell suspension was treated with 0.1 ml of EMS (1.17 g/ml, Sigma) and incubated for 45 min at 30 °C in a roller drum. The 0.2-ml aliquot was removed and added to 8 ml of freshly prepared 5% sodium thiosulfate (filter-sterilized). The cells were diluted appropriately, plated on YPD containing 1 M NaCl, and incubated at 26 °C for 3–5 days.

Measurement of Cytosolic Ca²⁺ Level with a Laser Scanning Confocal Microscope—To measure cytosolic free Ca²⁺ levels in wild type and the salt-tolerant mutant, the Ca²⁺ indicator Fluoro-3/AM (Sigma) was used. Cells incubated overnight were washed three times with PBS and loaded in 40 μl Fluoro-3/AM (Sigma) at 37 °C and was named YJY15 (Fig. 1A). To localize the mutated genetic locus, YJY15 was transformed with a Ycp50-based yeast genomic library. ts⁺ transformants were selected on YPD plate at 37 °C. One clone, which complemented the ts⁻ phenotype, was recovered and named pYJ117 (Fig. 1B). Results from restriction mapping and sequencing to identify the yeast genomic DNA carried by the plasmid indicated that pYJ117 contained a 15-kilobase genomic DNA fragment harboring several genes and open reading frames such as KEM1, NUP49, ROK1, SUA5, PMR1, CUP2, YGL170w, and YGL168w in chromosome 7. The genomic DNA in the pYJ117 mutant was subcloned to identify the specific gene responsible for the phenotype, and it finally was concluded that the wild-type gene for the YJY15 mutation is PMR1, which encodes a Ca²⁺/Mn²⁺-ATPase in the Golgi apparatus.

The Salt-tolerant Mutant also Showed Manganese-sensitive Growth Phenotype, the Typical Phenotype of pmr1 Mutant—Pmr1p is known for Mn²⁺-ATPase in the Golgi apparatus and functions to influx Mn²⁺ into the Golgi apparatus. It has been reported that the pmr1 mutant showed a severe Mn²⁺-sensitive phenotype (21). Therefore, the Mn²⁺- sensitive phenotype of the pmr1 mutant was tested. The pmr1 mutant was grown in YPD medium containing different amount of MnCl₂. Although wild-type cells appeared to be sensitive to Mn²⁺ in a concentration-dependent manner, the pmr1 mutant cells were not able to

FIG. 1. Phenotypes and genetic locus of the mutation in YJY15. A, the salt-tolerant phenotype in YPD containing 0.8 M NaCl and ts⁻ phenotype at 37 °C of YJY15. Suspensions of wild type (WT) and YJY15 were spotted on a YPD plate or YPD plate containing 0.8 M NaCl and allowed to grow at 26 or 37 °C for either 2 or 5 days in the case of salt tolerance test. B, identification of the genetic locus that complements the ts⁻ phenotype of the YJY15 mutant. YJY15 cells transformed with each plasmid were tested for the complementation of the ts⁻ phenotype at 37 °C on YPD. The genetic locus of complementing clones was identified by partial DNA sequencing and comparison with the yeast genome data base.

RESULTS

Isolation of Salt-tolerant Mutants and Mapping Mutations—To isolate salt-tolerant mutants, we carried out random mutagenesis with EMS. Several salt-tolerant mutants were selected under high salt stress. One of the salt-tolerant mutants exhibited an additional phenotype that was temperature sensitive (ts⁻) at 37 °C and was named YJY15 (Fig. 1A). To localize the mutated genetic locus, YJY15 was transformed with a Ycp50-based yeast genomic library. ts⁺ transformants were selected on YPD plate at 37 °C. One clone, which complemented the ts⁻ phenotype, was recovered and named pYJ117 (Fig. 1B). Results from restriction mapping and sequencing to identify the yeast genomic DNA carried by the plasmid indicated that pYJ117 contained a 15-kilobase genomic DNA fragment harboring several genes and open reading frames such as KEM1, NUP49, ROK1, SUA5, PMR1, CUP2, YGL170w, and YGL168w in chromosome 7. The genomic DNA in the pYJ117 mutant was subcloned to identify the specific gene responsible for the phenotype, and it finally was concluded that the wild-type gene for the YJY15 mutation is PMR1, which encodes a Ca²⁺/Mn²⁺-ATPase in the Golgi apparatus.
grow in medium containing even 0.2 mM MnCl₂, which is the typical phenotype of the pmr1 mutant (Fig. 2A). Also, introduction of the wild-type allele PMR1 into the YJY15 cells reverses the Mn²⁺-sensitive phenotype of the pmr1 mutant cells. In addition, the salt-tolerant growth of YJY15 in the presence of 0.8 M NaCl is reduced to wild-type levels by introduction of the wild-type allele of PMR1 (Fig. 2B). This result indicates that the pmr1 mutation indeed is responsible for the salt-tolerant phenotype of YJY15.

Elevated Level of Cytosolic Ca²⁺ under Salt Stress Is Maintained in pmr1 Mutant—Regarding the role of Pmr1p as Ca²⁺-ATPase, the regulation of cytosolic Ca²⁺ homeostasis might be disturbed in the pmr1 mutant. To examine whether the cytosolic Ca²⁺ level in the pmr1 mutant is deregulated, the cytosolic Ca²⁺ level in the pmr1 mutant was measured. For measurements of the cytosolic Ca²⁺ level with Fluo-3/AM, that is Ca²⁺ indicator excited visible light (488 nm), an experimental set-up consisting of a perfusion chamber connected to a laser scanning confocal microscope was used. In both wild type and the pmr1 mutant, Ca²⁺ was elevated immediately after injecting YPD medium containing 0.8 M NaCl (Fig. 3). Although the elevated Ca²⁺ in the cytosol of wild type was gradually reduced to basal level in the period of 1000 s, the Ca²⁺ level in the pmr1 mutant was slowly decreased but did not drop to the basal level like wild type for the same period of time. When the Ca²⁺ level in cytosol was measured after 2000 s, the elevated level in the pmr1 mutant was still maintained (data not shown). This result suggests that the Ca²⁺ level in cytosol is elevated and maintained under high salt stress in the pmr1 mutant.

Salt-Tolerant Growth of the pmr1 Mutant Is Abolished by FK506, a Specific Inhibitor of Calcineurin—As mentioned in the introduction, yeasts are subjected to both osmotic stress and salt toxicity stress under high salt stress. We therefore tested the expression of GDP1, which is required to protect osmotic stress through the high osmolarity glycerol response pathway, by Northern blot analysis. There was no difference in GDP1 expression between wild type and the pmr1 mutant (data not shown). Another harmful effect of salt stress is salt toxicity. In S. cerevisiae, to exclude elevated Na⁺ in cytosol, the expression and activity of Pmr2p is induced by calcineurin pathway (2, 3). To examine whether salt-tolerant growth of the pmr1 mutant depends on the calcineurin-dependent pathway, both wild-type and pmr1 mutant cells were treated with the immunosuppressant FK506, which is a calcineurin-specific inhibitor. Growth of wild type and the pmr1 mutant in liquid medium containing 0.8 M NaCl and 1 μg/ml of FK506 was monitored. When cells were grown in a medium containing 0.8 M NaCl and 1 μg/ml FK506, a concentration in which the effect was known to be the same as the calcineurin-null mutation (9), neither wild-type nor pmr1 mutant cells could grow (Fig. 4). The salt tolerance of the pmr1 mutant is decreased gradually as the amount of FK506 in the medium increases (data not shown). This result indicates that the calcineurin-dependent salt-extrusion pathway plays a crucial role in salt-tolerant growth of the pmr1 mutant.

The pmr2::lacZ Expression Is Enhanced under High Salt Stress in pmr1 Mutant—At the final point of the calcineurin-dependent salt adaptation pathway under high salt stress, Pmr2p was known to extrude excess Na⁺ in cytosol. If the calcineurin-dependent pathway really conferred salt tolerance on the pmr1 mutant, it could be predicted that the PMR2 expression in the pmr1 mutant under high salt conditions would increase. To investigate whether the salt-tolerant growth phenotype of the pmr1 mutant resulted from the overexpression of PMR2 under high salt stress, a β-galactosidase assay was used. In pmr1 mutant cells, the pmr2::lacZ expression was enormously enhanced under high salt stress (0.8 M NaCl); however, a slight increase in the expression was observed in the wild-type cells (Fig. 5). This result indicates that the salt-tolerant growth of the pmr1 mutant is caused by the overexpression of PMR2 via the calcineurin-dependent pathway.

**DISCUSSION**

In this study, we studied the salt-adaptation mechanism using the pmr1 mutant. The pmr1 mutant is one of the mutants generated by EMS random mutagenesis. Pmr1p is a Ca²⁺-ATPase localized in the Golgi apparatus (17) and plays an essential role in the secretory pathway as a Ca²⁺- and Mn²⁺-transporter, which supplies both ions to the Golgi (22–24). It was reported previously that pmr1 mutants displayed hypersensitivity to the growth toxicity of millimolar concentrations of extracellular Mn²⁺ (21). In the present study, the hypersen-
Positive phenotype of the pmr1 mutant to 0.2 mM MnCl$_2$ was observed (Fig. 2A). Elevated cytosolic Mn$^{2+}$ ions are not pumped into the Golgi and are toxic to growth of the pmr1 mutant. It is indicated that delivery into the secretory pathway by Pmr1p and subsequent exocytosis must be a major route for the cellular detoxification of Mn$^{2+}$.

The pmr1 mutant was more tolerant to high salt stress than wild type, and the introduction of extragenic PMR1 into the mutant reduced the salt tolerant growth phenotype (Fig. 2B). Because Pmr1p acts as a Ca$^{2+}$-ATPase, it was predicted that the cytosolic Ca$^{2+}$ level in the pmr1 mutant would be higher than wild type under high salt stress conditions. When the cytosolic Ca$^{2+}$ level was measured, it was elevated and maintained under high salt stress in the pmr1 mutant (Fig. 3). In agreement with our observation, additional Ca$^{2+}$ conferred salt tolerance in S. cerevisiae during high salt stress (14). From these observations it is suggested that the cytosolic Ca$^{2+}$ level is elevated under high salt stress, and the increased Ca$^{2+}$ ions participate in the salt-tolerant growth phenotype of the pmr1 mutant.

However, the elevated Ca$^{2+}$ under high salt stress does not affect the expression of GPD1 required for glycerol production, which means that the antiosmotic defense mechanism is driven normally in the pmr1 mutant. Another defense mechanism against salt stress is the calcineurin-dependent sodium extrusion pathway (10). Calcineurin, the Ser/Thr protein phosphatase protein phosphatase 2B, is required for PMR2 expression. It is also required for T cell activation and proliferation in human and is the target of the T cell-specific immunosuppressants cyclosporin A and FK506 complexed with the intracellular-binding protein cyclophilin A and FKBP12, respectively (25, 26). In yeast, calcineurin plays a central role in adaptive responses to cation stress. Calcineurin is required for yeast cells to survive exposure to high levels of Na$^+$ or Li$^+$ ions. Mutants lacking calcineurin have a decreased ability to export Na$^+$ and Li$^+$ ions, suggesting a defect in the Pmr2p (8, 9). On the other hand, constitutive activation of calcineurin confers increased resistance to Na$^+$ and Li$^+$ ions (10). Calcineurin is activated by a Ca$^{2+}$/calmodulin complex (6, 27). An elevated Ca$^{2+}$ ion level in the pmr1 mutant may induce constitutive activation of calcineurin under high salt stress. Therefore, to determine whether the calcineurin pathway is involved in the salt-tolerant phenotype of the pmr1 mutant, the pmr1 mutant was treated with FK506, a calcineurin-specific inhibitor, and salt-tolerant growth was tested. The growth of FK506-treated cells was inhibited under high salt stress (Fig. 4). Especially both wild-type and pmr1 mutant cells failed to grow when the cells were treated with 1 µg/ml FK506.
Because increased several-fold compared with the wild type (Fig. 5). The growth of wild type (WT) and the salt-tolerant mutant (pmr1) were grown at 30 °C for various times as indicated with YPD or YPD containing 0.8 M NaCl. The results represent the averages from four independent experimental trials with error bars indicating the range of values obtained.

An alternative way for S. cerevisiae to adapt to salt stress involves mechanisms that restrict the influx of sodium into the cell. The K⁺ transport system encoded by the TRK1 and TRK2 genes (28, 29) also admits Na⁺ but increases its preference for K⁺ over Na⁺ at elevated concentrations of NaCl (8, 30). If this pathway is responsible for the salt-tolerant growth of the pmr1 mutant, it could be predicted that FK506 treatment may not affect the salt tolerance of the pmr1 mutant. Because the salt tolerance of the pmr1 mutant completely disappeared with the treatment of FK506 (Fig. 4), this pathway did not play a crucial role in the salt-tolerant phenotype of the pmr1 mutant. Therefore, the calcineurin-dependent pathway presumably acts as a major high salt adaptation mechanism in the pmr1 mutant.

If the calcineurin-dependent pathway is activated in the pmr1 mutant, the expression of PMR2 would be induced. Under salt stress, the expression of PMR2 in the pmr1 mutant was increased several-fold compared with the wild type (Fig. 5). Because pmr1 mutation highly induced the expression of PMR2 by constitutive activation of calcineurin, the pmr1 mutant could obtain the salt-tolerant phenotype. This is evidence that the expression of PMR2 is regulated by the activity of Pmr1p.

It is important to maintain Ca²⁺ homeostasis in normal or stressed conditions. Under high salt stress, increased cytosolic Ca²⁺ is helpful for salt tolerance. If, however, the increased cytosolic Ca²⁺ ion level does not drop to a normal level, Ca²⁺ homeostasis may be disturbed, which may have a harmful effect on the cell viability. In yeast, the Ca²⁺ homeostasis is regulated by three different Ca²⁺ transports, Pmc1p, Vcx1p, and Pmr1p. Pmc1p is a P-type Ca²⁺-ATPase located in the vacuole, and is ~40% identical to plasma membrane Ca²⁺-AT-Pases, and is much less similar to other P-type ion pumps (27, 31). The pmc1 null mutants display a severe sensitivity to Ca²⁺ supplements in the growth medium (27). Vcx1p is a H⁺/Ca²⁺ antiporter and functions completely dependent on the transmembrane pH gradient, which is normally produced by the Pma1p, V-type H⁺-ATPase on the vacuolar membrane (32). Another Ca²⁺ transporter is Pmr1p, which is predominantly localized in the Golgi complex or related secretory compartments (5, 17). Pmr1p is ~30% identical to the members of the SERCA subfamily, which are Ca²⁺-ATPases found in the sarcoplasmic/endoplasmic reticulum of animal cells (22). Pmr1p is also located in the endoplasmic reticulum and functions in Ca²⁺ uptake into the endoplasmic reticulum (24). It has been demonstrated recently that Pmr1p acts as a major Ca²⁺-ATPase under normal growth condition (24, 33). The expression of PMC1, a second Ca²⁺ pump in the vacuole, and the activity of one or more H⁺/Ca²⁺ exchangers are induced in the mutants lacking Pmr1p under normal growth condition (33). Under high salt stress, however, activated calcineurin inhibits the expression of PMC1 (15, 16) and reduces the activity of Vcx1p (13). The cytosolic Ca²⁺ ion level was highly maintained in the pmr1 mutant (Fig. 3). Taken together, these data indicate that Pmr1p might be a major component as a Ca²⁺-ATPase regulating Ca²⁺ homeostasis under high salt stress (Fig. 6).

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