THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 276, No. 37, Issue of September 14, pp. 34441–34444, 2001
Printed in U.S.A.
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The GATA Transcription Factors GLN3 and GAT1 Link TOR to Salt Stress in *Saccharomyces cerevisiae**

Received for publication, April 23, 2001, and in revised form, July 6, 2001
Published, JBC Papers in Press, July 16, 2001, DOI 10.1074/jbc.M103601200

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One of the most recent functions assigned to the TOR signaling pathway in yeast is the coordination of the transcription of genes involved in nutrient utilization. Here we show that transcription of *ENA1*, a gene encoding a lithium and sodium ion transporter essential for salt tolerance in yeast, is controlled by the TOR signaling pathway. First, *ENA1* expression is strongly induced under TOR-inactivating conditions. Second, the absence of the TOR-controlled GATA transcription factors GLN3 and GAT1 results in reduced basal and salt-induced expression of *ENA1*. Third, a *gln3 gat1* mutant displays a pronounced sensitivity to high concentrations of lithium and sodium. Fourth, TOR1, similar to ENA1, is required for growth under saline stress conditions. In summary, our results suggest that TOR plays a role in the general response to saline stress by regulating the transcription of *ENA1* via GLN3 and GAT1.

Yeasts have developed refined mechanisms to adjust their metabolism and growth to alterations in the quality of available nutrients, temperature, acidity, and osmolarity of their environment. The recent application of gene chip technology has revealed that yeast cells respond to environmental changes by altering the expression of a large number of genes (1). Among the different environmental stresses, nitrogen deprivation or exposure to high concentrations of salt causes dramatic effects on the genomic expression program (1–5).

The *ENA1* gene is the first of a tandem array of five homologous open reading frames encoding P-type ATPases involved in the extrusion of Li^+ and Na^+ ions from the cytoplasm (6, 7). Mutants lacking *ENA1* show increased sensitivity to high concentrations of Li^+ and Na^+ (6). The *ENA1* gene is highly regulated at the transcriptional level; its expression is increased in response to salt stress (8) or glucose starvation (9, 10). The salt-mediated induction of *ENA1* is controlled through two different signaling pathways: the high osmolarity glycerol mitogen-activated protein kinase pathway and the calcineurin pathway (11). High osmolarity glycerol-dependent transcription is mediated through the bZIP transcriptional inhibitor SKO1 that binds a cyclic AMP response element-like sequence in the *ENA1* promoter (12). Calcineurin, a Ca^{2+}/calmodulin-dependent phosphatase, controls *ENA1* transcription via the Zn^{2+} finger transcriptional activator CRZ1/TCN1/HAL8 (13–15). The *ENA1* gene is subjected to glucose repression through the general repressor complex MIG1-SSN6-TUP1 (9, 12).

An essential signaling pathway used by all eukaryotic cells is the target of rapamycin (TOR) pathway (reviewed in Ref. 16). The budding yeast *Saccharomyces cerevisiae* contains two TOR genes, *TOR1* and *TOR2*, and their products, the TOR1 and TOR2 kinases, are both inhibited by the FK506-binding protein-rapamycin complex (17–20). The response of cells to TOR depletion or rapamycin treatment mimics a nutrient stress response, including down-regulation of translation initiation, inhibition of ribosomal biogenesis, arrest in the G_1 phase of the cell cycle, glycogen accumulation, and autophagy (17, 18, 21–23). In addition, rapamycin treatment reduces transcription of ribosomal RNA and ribosomal protein genes (24, 25). Thus, TOR is a central controller of cell growth in response to nutrients (16, 21).

Recent studies have revealed that the TOR cascade plays a particularly prominent role in regulating nutrient-responsive transcription (2, 4, 26, 27). The expression of a large number of genes is affected when TOR function is inhibited by rapamycin. Many of these genes are involved in the glycolytic pathway and the tricarboxylic acid cycle, but the most striking set of genes affected by rapamycin treatment is composed of genes involved in the assimilation of different nitrogen sources (2, 4, 27). The molecular mechanism by which TOR controls the expression of nitrogen-regulated genes involves inhibition of the GATA-binding Zn^{2+} finger transcription factor GLN3 (26). In the presence of a good nitrogen source, GLN3 is sequestered in the cytoplasm by the URE2 protein. Rapamycin treatment or nitrogen starvation induces dephosphorylation of GLN3 and consequently induces its dissociation from URE2, allowing GLN3 to move into the nucleus, where it activates its target genes (26). In addition to GLN3, TOR also inhibits the activity of the nutrient-regulated transcription factors GAT1/NIL1, MSN2, MSN4, RTG1, and RTG3 (3, 26). Thus, one important role of TOR appears to be the coordination of the transcription of genes involved in several distinct nutrient-responsive cellular pathways.

Here we demonstrate that TOR regulates expression of *ENA1* via the transcriptional factors GLN3 and GAT1. Our findings indicate that the TOR signaling pathway may play an important role in the control of the cellular response to saline stress.

EXPERIMENTAL PROCEDURES

Strains and Media—S. cerevisiae strains used in this work are listed in Table I. All strains were isogenic JK9-3d**a** or TB50**a** derivatives. The composition of rich medium (YPD) and synthetic minimal medium (SD) supplemented with the appropriate nutrients was as described previously (28). All cultures were incubated at 30 °C. Yeast transformation was performed by the lithium acetate procedure (29). Rapamycin (provided by Sandoz Pharma, Basel, Switzerland) was used at a final concentration of 200 ng/ml. A 1 mg/ml stock solution of rapamycin was

* This work was supported by grants from the Canton of Basel and the Swiss National Science Foundation (to M. N. H.). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

§ Recipient of a Federation of European Biochemical Societies Long-term Fellowship.

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TABLE I
Strains used in this study

Strain	Genotype
JK9–3da	*MAT***a** *leu2–3,112 ura3–52 trp1 his4 rme1 HML***a**
TB50a	*MAT***a** *leu2–3,112 ura3–52 trp1 his3 rme1 HML***a**
AS51–1a	JK9–3da *ure2*::*URA3*
AL11–2c	TB50**a** *gln3*::*kanMX gat1*::*HIS3MX ure2*::*URA3*
AL12–4d	TB50**a** *gat1*::*HIS3MX ure2*::*URA3*
AL13–23b	TB50**a** *gln3*::*kanMX ure2*::*URA3*
TB102–1a	JK9–3d**a** *gat1*::*kanMX*
TB103–1d	TB50**a** *gln3*::*HIS3MX*
TB105–3b	TB50**a** *gln3*::*kanMX gat1*::*HIS3MX*
MH349–3d	JK9–3d**a** *tor1*::*LEU2–4*
JC15–1b	TB50**a** *ena1*::*HIS3MX*
TS64-1a	JK9-3da *sit4*::*KanMX*

prepared in the drug vehicle (90% ethanol and 10% Tween).

Salt Tolerance Assay—The growth of yeast strains under different salt stress conditions was assayed by spotting 2 μl of 5-fold dilutions of overnight saturated cultures onto YPD plates containing the indicated concentration of salts. Wild-type cells transformed with a 2μ plasmid expressing protein kinase HAL4, whose overexpression has been shown to increase tolerance to Li^+ and Na^+ (30), were used as a positive control for growth in salt tolerance assays.

β-Galactosidase Assay—ENA1 expression was followed by assaying β-galactosidase activity in cells containing pFR70i, an integrative plasmid carrying an *ENA1*-lacZ promoter-reporter fusion obtained by cloning a *Sal*I-*Eco*RI fragment from *ENA1* (−1384 to +40) into YIp356R (31). pFR70i was cleaved at the unique *Nco*I site within the *URA3* gene and targeted to the *URA3* locus. Yeast cells were grown in YPD to an early logarithmic phase and then treated with 0.4 M NaCl for 30 min. β-Galactosidase activity was measured as described by Ausubel *et al.* (32). Results presented are the mean values obtained from at least three independent experiments measured in triplicate.

RNA Isolation and Northern Blot Analysis—Yeast cells were collected by centrifugation and washed with distilled water. Cells were broken with glass beads in extraction buffer (0.5 M NaCl, 0.2 M Tris-HCl (pH 7.5), 10 mM EDTA, and 1% SDS) and an equal volume of phenol/chloroform. After centrifugation, RNA contained in the upper phase was re-extracted with phenol/chloroform. Total RNA was precipitated with ethanol and resuspended in diethylpyrocarbonate-treated distilled water. RNA was subjected to electrophoresis on 1.2% agarose gels with subsequent Northern blotting as described by Ausubel *et al.* (32). A fragment of the *lacZ* gene was cut out from plasmid pSEY101 (33) with *Bgl*I, and a fragment of the *ACT1* gene was excised from plasmid pYA301 (34) with *Cla*I. These fragments were labeled with [α-^{32}P]dCTP using the BcaBEST labeling kit (Takara, Kyoto, Japan) and used as probes. The hybridization was performed according to the method of Ausubel *et al.* (32).

RESULTS

TOR Participates in the Regulation of ENA1 Expression—Hardwick *et al.* (2) have shown, by using DNA microarrays, that inhibition of TOR by rapamycin induces genes involved in the response to salt stress. We wanted to investigate how the TOR signaling pathway is implicated in the regulation of the saline stress response. In particular, we wanted to understand the mechanism by which TOR controls the salt-responsive gene *ENA1*.

We found six GATAA motifs in the *ENA1* promoter region (Fig. 1). The presence of multiple GATAA motifs is a good indicator for GLN3-dependent transcription (reviewed in Ref. 35). This observation, together with the fact that GLN3 is controlled by the TOR signaling pathway (26), prompted us to investigate whether the amount of *ENA1* mRNA changes in response to rapamycin. Because yeast cells have closely related *ENA1* homologues, we created a strain carrying genomically integrated *ENA1-lacZ* (see "Experimental Procedures"), enabling us to measure expression of *ENA1* using a *lacZ* probe and thus to avoid cross-reactivity with *ENA1* homologues. As shown in the Northern analysis in Fig. 2, we observed a strong accumulation of *ENA1* mRNA after 20 min of rapamycin treatment. However, disruption of *GLN3* resulted in only a partial decrease in rapamycin-induced *ENA1* transcript levels (Fig. 2), suggesting that there are other transcription factor(s) involved in the rapamycin-mediated induction of *ENA1*. Like GLN3, GAT1 is a GATA-binding transcriptional activator controlled by TOR (26). Furthermore, it has been shown that both GLN3 and GAT1 use the same GATAAG sites to activate expression of some nitrogen-regulated genes (36). Two of the six GATAA motifs in the *ENA1* promoter are followed by a G, *i.e.* GATAAG. We therefore examined whether GAT1 is implicated in the regulation of *ENA1* transcription. As shown in Fig. 2, no *ENA1* transcript was detected in *gln3 gat1* mutant cells upon treatment with rapamycin. Taken together, these results suggest that the TOR signaling pathway is implicated in the regulation of *ENA1* expression via the transcription factors GLN3 and GAT1.

GLN3 and GAT1 Are Required under Salt Stress Conditions—Withee *et al.* (37) have reported that deletion of *URE2* suppresses the sensitivity of calcineurin mutants to Li^+, Na^+, and Mn^{2+}. Because GLN3 (26) and possibly GAT1 (38) are regulated by the cytoplasmic protein URE2, we tested the sensitivity of a *ure2* mutant strain to Li^+ and Na^+ by spotting cells onto medium containing different concentrations of salt. We found that *ure2* mutant cells display a pronounced growth defect on YPD plates and a significant resistance to high concentrations of Li^+ and Na^+ (Fig. 3*A*). Furthermore, cells lacking *URE2* divided significantly faster than wild-type cells under salt stress conditions (Table II). Interestingly, *ure2 gln3* or *ure2 gat1* mutants still showed high tolerance to Li^+ and Na^+, and only the loss of both *GLN3* and *GAT1* completely suppressed the salt resistance of a *ure2* mutant (Fig. 3*A*). From these results, we conclude that the high resistance to toxic concentrations of Li^+ and Na^+ observed for cells lacking URE2 is due to the loss of regulation of GLN3 and GAT1. To further examine whether these two transcription factors play a role in the transcriptional response to saline stress, we investigated whether deletion of *GLN3* and/or *GAT1* affects cell growth on salt-containing medium. Indeed, as depicted in Fig. 3*A*, *gln3 gat1* double mutant cells showed a pronounced sensitivity to both Li^+ and Na^+ as compared with wild-type cells, whereas single deletion of *GLN3* or *GAT1* had no significant effect. In agreement with this observation, we also found that the doubling time of *gln3 gat1* mutant cells in lithium-containing medium was significantly higher (Table II). Thus, GLN3 and GAT1 are regulators of genes whose expression is required under salt stress conditions.

Because we found that TOR controls transcription of *ENA1* via GLN3 and GAT1 and that deletion of both transcription factors confers hypersensitivity to Li^+ and Na^+, we next examined whether *gln3* and *gat1* mutations affect expression of *ENA1* in response to salt stress. For this purpose, we investigated the expression of an integrated *ENA1-lac*Z hybrid gene in wild-type and *gln3 gat1* mutant cells treated with 0.4 M NaCl for 30 min. A 4-fold reduction in basal *ENA1* expression (YPD without salt) was observed in *gln3 gat1* mutant cells (Fig. 3*B*). Upon salt addition, *ENA1* was induced 4–5 times in wild-type and *gln3 gat1* cells, but the overall level of *ENA1* expression was still much lower in *gln3 gat1* mutants (Fig. 3*B*). Activation of GLN3 and GAT1 is a TOR-regulated process mediated by the protein phosphatase SIT4 (26). Therefore, we examined *ENA1* expression in cells lacking *SIT4*. Similar to that seen in *gln3 gat1* cells, *ENA1* expression was reduced under normal and salt stress conditions in *sit4* mutant cells (Fig. 3*B*). From these results, we conclude that GLN3 and GAT1 are required to regulate *ENA1* expression not only under normal growth conditions (YPD without salt) but also under salt stress.

TOR1 Is Required for Growth under Saline Stress Condi-

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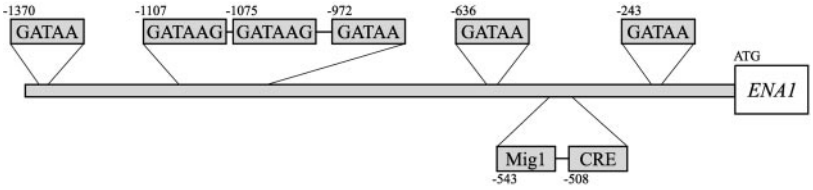

FIG. 1. **Schematic representation of the *ENA1* promoter.** The six GATA motifs (GATAA and GATAAG) found in the *ENA1* promoter are marked by *shaded boxes*. The MIG1- and SKO1-binding sites are also indicated. The *numbers* in each box correspond to the first nucleotide of the motif, considering the ATG start codon of *ENA1* as the first three nucleotides.

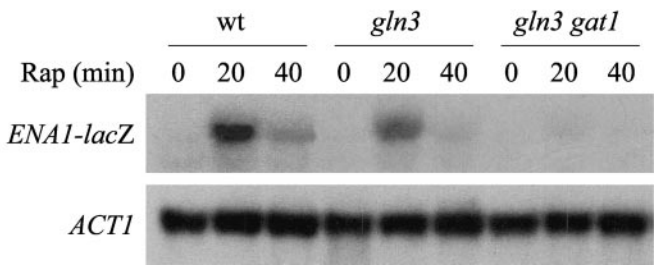

FIG. 2. **TOR controls the expression of *ENA1* via GLN3 and GAT1.** Wild-type (JK9-3d**a**), *gln3* (TB103-1d), and *gln3 gat1* (TB105-3b) cells were grown in YPD medium to an optical density at 600 nm of 0.5 (early log phase). Cells were treated with rapamycin for the indicated times and processed for Northern analysis. *ENA1-lacZ* was detected by using an internal *lacZ* probe (see "Experimental Procedures"). *ACT1* was used as a loading control.

tions—It has been reported previously that *ena1* mutant cells are sensitive to lithium or sodium, but not to potassium or calcium (6, 7, 30). Furthermore, it has been demonstrated that fission yeast TOR1 is required for growth under different stress conditions, including osmotic stress and oxidative stress (39). Given the link between TOR signaling and *ENA1* expression (see above), we investigated whether cells lacking *TOR1* behave similarly to *ena1* mutant cells; cells lacking *TOR2* were not examined because deletion of *TOR2* is lethal. Wild-type cells and cells lacking *TOR1* or *ENA1* were spotted onto YPD plates containing lithium, sodium, potassium, or calcium and incubated at 30 °C. As shown in Fig. 4, *tor1* mutant cells exhibited pronounced sensitivity to lithium and mild sensitivity to sodium. However, cells lacking *TOR1* were not sensitive to potassium or calcium. Although the effects of the cations are weaker in the *tor1* mutant when compared with the *ena1* mutant, the overall phenotype of both strains is remarkably similar (Fig. 4). This result further strengthens the link between TOR and ENA1 and demonstrates that TOR1 is required for the proper cellular response to saline stress.

DISCUSSION

The TOR signaling pathway controls cell growth in response to nutrient availability (reviewed in Ref. 16; see Ref. 21). Recent studies have assigned TOR a crucial role in coordinating the transcription of a large number of nutrient-regulated genes (2–4, 26, 27). Our results extend TOR function to salt stress signaling. We found that transcription of *ENA1,* a gene essential for survival under saline stress conditions, is up-regulated in cells treated with rapamycin (Fig. 2). Proft and Serrano (12) have reported the presence of DNA-binding motifs for the transcriptional repressors MIG1, MIG2, and SKO1 in the promoter region of *ENA1*. In this study, we have reported the presence of six GATA motifs in the promoter region of *ENA1,* two of which consist of the GATAAG sequence that is recognized by both GLN3 and GAT1 (36). We also found that GLN3 and GAT1 do indeed regulate expression of *ENA1*. First, rapamycin-mediated induction of *ENA1* is completely abolished in *gln3 gat1* cells (Fig. 2). Second, *gln3 gat1* mutant cells display a significant hypersensitivity to Li^+ and Na^+ (Fig. 3*A*). Third, *ENA1* expression is decreased in *gln3 gat1* mutant cells under normal growth and saline stress conditions (Fig. 3*B*).

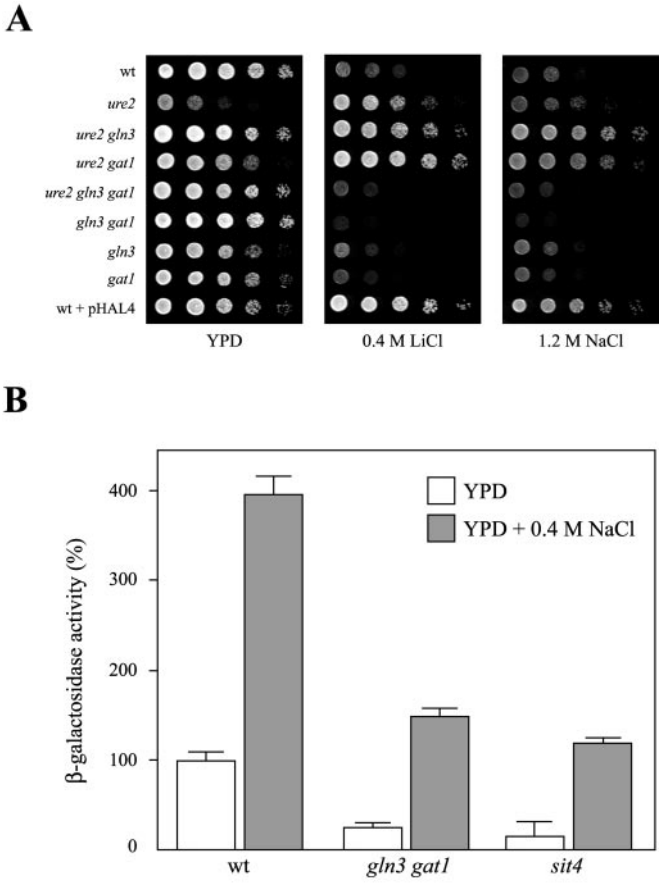

FIG. 3. **Mutations in *GLN3* and *GAT1* confer sensitivity to Li^+ and Na^+.** *A,* growth of wild-type (JK9-3d**a**), *ure2* (AS51-1a), *ure2 gln3* (AL13-23b), *ure2 gat1* (AL12-4d), *ure2 gln3 gat1* (AL11-2c), *gln3 gat1* (TB105-3b), *gln3* (TB103-1d), and *gat1* (TB102-1a) strains in the presence of Li^+ and Na^+. Saturated overnight cultures were subjected to 5-fold serial dilutions and spotted onto YPD plates without salt or onto YPD plates containing 0.4 M LiCl or 1.2 M NaCl. Plates were incubated at 30 °C for 2 (YPD) or 3 days (YPD + salt). Wild-type cells transformed with a 2μ plasmid expressing HAL4 (30) served as a positive control. *B, ENA1* expression is decreased in a *gln3 gat1* mutant. Wild-type (JK9-3d**a**), *gln3 gat1* (TB105-3b), and *sit4* (TS64-1a) strains were grown in YPD to early log phase and incubated with 0.4 M NaCl for 30 min. Samples were processed for β-galactosidase activity measurement as described in "Experimental Procedures." Results are the mean values of three independent experiments measured in duplicate.

TABLE II
Doubling times (min) of wild-type (JK9–3d), ure2 (AS51–1a), gln3 gat1 (TB105–3b), and wild-type cells transformed with 2μ HAL4

Strain	YPD	YPD + 0.3 M LiCl
wt[a]	100 ± 3	281 ± 15
ure2	163 ± 11	193 ± 7
gln3 gat1	113 ± 3	508 ± 40
wt + pHAL4	102 ± 5	164 ± 4

[a] wt, wild-type cells.

GLN3 and GAT1 are activated upon nitrogen deprivation to induce the expression of a large number of genes required under this condition (reviewed in Ref. 35). Our findings that GLN3 and GAT1 control expression of *ENA1* suggest an addi-

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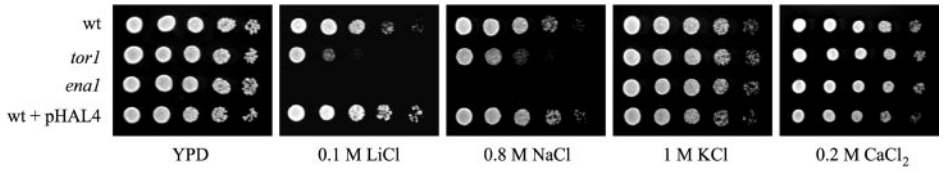

FIG. 4. **TOR1 is required for growth under saline stress.** Growth of wild-type (JK9-3da), *tor1* (MH349-3d), and *ena1* (JC15-1b) cells in the presence of 0.1 M LiCl, 0.8 M NaCl, 1 M KCl, or 0.2 M $CaCl_2$. Salt stress assays were performed as described in the Fig. 3 legend. Wild-type cells transformed with a 2μ plasmid expressing HAL4 (30) served as a positive control.

tional role for these GATA factors in the response to salt stress. Is ENA1 required under conditions of nitrogen limitation in addition to salt stress? *ena1* mutant cells grown in the presence of a poor nitrogen source (such as proline) displayed no growth defect as compared with wild-type cells (data not shown), indicating that ENA1 has no essential role in nitrogen-limited cells. Therefore, the GLN3- and GAT1-dependent activation of *ENA1* expression appears to be related mainly to the saline stress response. Cox *et al.* (40) have proposed a GLN3-dependent regulation of *PMA1* that, like *ENA1*, encodes a plasma membrane P-type ATPase. PMA1 is an essential H^+-transporting ATPase required to maintain the electrochemical potential at the plasma membrane (41). Because amino acid uptake is mediated by proton symport, a reasonable explanation for the GLN3-dependent regulation of *PMA1* is that increased H^+ transport may be required for efficient uptake of amino acids that could then be used as a nitrogen source. Thus, the TOR signaling pathway may play a broad role in the regulation of ion homeostasis.

Loss of *URE2* confers high resistance to Li^+ and Na^+ (Fig. 3*A* and Ref. 37). Mutation of *GLN3* and *GAT1* completely suppressed the salt tolerance of *ure2* mutant cells (Fig. 3*A*), indicating that GLN3 and GAT1 are the proteins responsible for the salt resistance of *ure2* mutant cells. Activation of the TOR-controlled protein phosphatase SIT4 upon rapamycin treatment or nitrogen starvation leads to dephosphorylation of GLN3 and subsequently leads to the dissociation of the GLN3-URE2 complex and the translocation of GLN3 into the nucleus (26). Recently, overexpression of *SIT4* has been shown to confer lithium tolerance in *S. cerevisiae* (42). Our data are consistent with this observation because overexpression of *SIT4* may induce nuclear localization of GLN3 as a result of the enhanced dephosphorylation of GLN3 and dissociation of the transcription factor from URE2. Once GLN3 is in the nucleus, it may activate the transcription of several genes that contribute to lithium resistance, such as *ENA1*. Accordingly, we found that *ENA1* expression is similarly reduced in *sit4* and *gln3 gat1* mutant cells.

The fission yeast TOR homologue *tor1* is required for response to different stresses, such as nitrogen, oxidative, and osmotic stress (39). Furthermore, expression of TOR1 in budding yeast is enhanced in response to heat shock and dithiothreitol treatment (1). Our results suggest that the budding yeast TOR1 is necessary for the proper cellular response to saline stress (Fig. 4). Thus, several lines of evidence point to TOR as a signaling pathway that responds to different types of environmental stress, including nutrient and saline stress. TOR, a central controller of cell growth, may respond to several different types of environmental stress to ensure that growth occurs only when overall conditions are favorable. The finding that *tor1* mutant cells are hypersensitive to salt may reflect an inability of these cells to sense and therefore respond properly to salt stress.

Acknowledgments—We thank Drs. J. M. Pardo and I. Marcos for the generous gift of plasmid pFR70i. We also thank Tobias Schmelzle for helpful discussions and critical review of the manuscript.

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J. Biol. Chem. 2001, 276:34441-34444.
doi: 10.1074/jbc.M103601200 originally published online July 16, 2001

Access the most updated version of this article at doi: 10.1074/jbc.M103601200

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