

## Glucose Regulation of *Saccharomyces cerevisiae* Cell Cycle Genes

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**Nutrient-limited *Saccharomyces cerevisiae* cells rapidly resume proliferative growth when transferred into glucose medium. This is preceded by a rapid increase in *CLN3*, *BCK2*, and *CDC28* mRNAs encoding cell cycle regulatory proteins that promote progress through Start. We have tested the ability of mutations in known glucose signaling pathways to block glucose induction of *CLN3*, *BCK2*, and *CDC28*. We find that loss of the *Snf3* and *Rgt2* glucose sensors does not block glucose induction, nor does deletion of *HXX2*, encoding the hexokinase isoenzyme involved in glucose repression signaling. Rapamycin blockade of the Tor nutrient sensing pathway does not block the glucose response. Addition of 2-deoxy glucose to the medium will not substitute for glucose. These results indicate that glucose metabolism generates the signal required for induction of *CLN3*, *BCK2*, and *CDC28*. In support of this conclusion, we find that addition of iodoacetate, an inhibitor of the glyceraldehyde-3-phosphate dehydrogenase step in yeast glycolysis, strongly downregulates the levels *CLN3*, *BCK2*, and *CDC28* mRNAs. Furthermore, mutations in *PFK1* and *PFK2*, which encode phosphofructokinase isoforms, inhibit glucose induction of *CLN3*, *BCK2*, and *CDC28*. These results indicate a link between the rate of glycolysis and the expression of genes that are critical for passage through G<sub>1</sub>.**

Yeast in common laboratory cultures undergo repeated growth cycles in which cells are inoculated into growth medium, begin to proliferate, deplete the medium, and cease or dramatically slow proliferation. This cycle has been repeated for countless generations in the laboratory and in domestic culture. In many media, a critical element is glucose. In rich medium containing glucose, proliferation is very rapid during log-phase fermentative growth, but it slows dramatically when glucose is exhausted. Cells then enter a plateau phase in which G<sub>1</sub> is prolonged and proliferation ceases, followed by a slow post-log phase of oxidative growth (48, 51, 52). Rapid log-phase proliferation can be restored by the addition of glucose to a post-log culture.

Glucose is known to affect a variety of processes in *Saccharomyces cerevisiae*. These include glucose repression of genes used in growth on alternative carbon sources and the induction of genes needed for glucose transport and protein synthesis (6, 17, 26, 49). Indeed, glucose has a profound effect on the transcription of yeast genes. In pioneering work with cDNA microarrays, Derisi et al. demonstrated that ca. 2,000 genes are regulated by the change from fermentative growth on glucose to oxidative growth at the diauxic shift (9). Many of the expected changes in gene expression were observed in these experiments: genes encoding glycolytic enzymes were downregulated as glucose was exhausted, whereas the expression of genes involved in oxidative metabolism increased. Although the regulation of some of these genes by glucose has been well studied, the mechanism by which glucose regulates many genes remains unknown.

Although the precise mechanisms by which yeast cells sense the presence of glucose are still unclear, several signaling pathways for glucose sensing have been identified in yeast. The *RGT2* and *SNF3* genes encode proteins that resemble hexose transporters in structure. These proteins also have long cytoplasmic tails that are required for signal generation. *Rgt2* and *Snf3* do not transport glucose but instead initiate signals in response to glucose that in turn activate a pathway that allows the *Rgt1* transcription factor to upregulate glucose transporter expression (34, 35). It is presumed that binding of glucose to these cell surface proteins produce signals that allow the cell to synthesize the transport proteins needed for glucose uptake.

An additional pathway directing transcriptional changes in response to glucose involves stimulation of adenylyl cyclase and an increase in intracellular cyclic AMP (cAMP). The Ras-cAMP pathway includes the GTP-binding Ras proteins, encoded by *RAS1* and *RAS2*, the guanine nucleotide exchange factor *Cdc25*, and the Ras GTPase-activating proteins, *Ira1* and *Ira2*, and adenylyl cyclase, encoded by *CYR1*. This pathway plays a key role in activating adenylyl cyclase, since both Ras and *Cdc25* proteins are essential for basal adenylyl cyclase activity and cell viability (24). It has been argued that the Ras pathway is not directly involved in glucose signaling to adenylyl cyclase (7, 46). Instead, a G-protein-coupled receptor is proposed to initiate the glucose signal that increases cAMP (29). *GPR1*, encoding the receptor, was cloned as a prey in two-hybrid studies by using *Gpa2* as bait (29, 56, 57). Strains expressing constitutively active *Gpa1* bypass the requirement for *Gpr1* in cAMP stimulation (41). The G protein, *Gpa2*, was cloned based on homology with mammalian heterotrimeric G<sub>α</sub> proteins and is necessary for the glucose-specific increase in cAMP (7).

Ultimately, glucose activation of adenylyl cyclase leads to activation of the cAMP-dependent protein kinase A (PKA) encoded by the genes *TPK1*, *TPK2*, and *TPK3*. The activity of

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TABLE 1. *S. cerevisiae* strains

Strain	Genotype	Source or reference
DS10	<i>MATa his3-11,15 leu2-3,112 lys1 lys2 ura3-52 trp1Δ</i>	4
DM15	<i>cln3Δ</i> in DS10	21
TL1	<i>bck2Δ::KanMX</i> in DS10	This study
BY4741	<i>MATa his3Δ1, leu2Δ0 met15Δ0 ura3Δ0</i>	Research Genetics
MC996A	<i>MATa his 3-11,15 leu 2-3,112 ura3-52</i>	38
KY73	<i>MATa his 3-11,15 leu 2-3,112 ura3-52 hxt1Δ::HIS3::hxt4Δ hxt5Δ::LEU2 hxt2Δ::HIS3 hxt3Δ::LEU2::hxt6Δ hxt7Δ::HIS3 gal2Δ</i>	31
DTY123	<i>MATa his 4-539 ura 3-52 lys2-801 suc2</i>	D. Thiele
DTY124	<i>MATa his 4-539 ura 3-52 lys2-801 suc2 hsk2Δ::URA3</i>	D. Thiele
FM392	<i>MATα his3Δ1 leu2Δ0 ura3Δ0 lys2Δ0</i>	M. Johnston
YM6370	<i>MATα his3Δ1 leu2Δ0 ura3Δ0 lys2Δ0 snf3Δ::hisG-URA3-hisG rgt2Δ::KanMX</i>	M. Johnston
ENYWA	<i>MATα ura3-52 leu2-3,112 trp1-289 his3-delta1 MAL2-8c MAL3 SUC3</i>	3
EBY.81	<i>MATα ura3-52 leu2-3,112 trp1-289 his3-delta1 MAL2-8c MAL3 SUC3 pfk1Δ::URA3</i>	3
EBY.82	<i>MATα ura3-52 leu2-3,112 trp1-289 his3-delta1 MAL2-8c MAL3 SUC3 pfk2Δ::URA3</i>	3

Rap1, a transcriptional activator of genes encoding ribosomal proteins and proteins required for glycolysis, increases upon activation of PKA by cAMP (28). In addition, PKA targets other transcription factors such as Msn2 and Msn4, to down-regulate expression of stress response element (STRE)-controlled genes in the absence of glucose (43). Upon addition of glucose the increase in PKA activity inactivates these transcription factors, leading to a decrease in expression of STRE-controlled genes (18).

Once inside the cell, glucose activates another pathway involved in repression of genes not needed during growth on glucose. In this pathway, the product of the *HXK2* gene, encoding a hexokinase involved in the initial stage of glucose metabolism, produces a signal that regulates Snf1, a member of the AMP-activated protein kinase family. Snf1 in turn regulates the Mig1 repressor protein (25, 27). In this pathway, the presence of glucose is thought to be sensed by hexokinase II (23, 30).

Nutrient signals are also carried by the Tor phosphatidylinositol 3-kinases encoded by *TOR1* and *TOR2*. This pathway is the target for the drug rapamycin and is involved in signaling glucose and nitrogen limitation. The TOR pathway regulates a diverse set of processes, including ribosome biogenesis, transport of nitrogen sources, and nitrogen-regulated gene expression (45).

In order for nutrient signals to regulate cellular proliferation, these signals must be in some way connected to the cell cycle machinery. Nutrient availability affects the passage from G<sub>1</sub> into S phase: G<sub>1</sub> becomes prolonged at the diauxic shift, and cells cease progress through G<sub>1</sub> altogether as nutrients are depleted. Movement from G<sub>1</sub> into S phase at Start is mediated by a peak in expression of two G<sub>1</sub> cyclins encoded by *CLN1* and *CLN2* (20, 39, 54). The timing of this event is in turn regulated by an additional G<sub>1</sub> cyclin *CLN3* (12, 44, 47), and an unrelated protein encoded by *BCK2* (10, 15, 32). The effects of Cln3 are dependent on the cyclin-dependent protein kinase Cdc28, whereas the effects of Bck2 are largely Cdc28 independent (53). Changes in the expression level of *CLN3* and *BCK2* affect the length of G<sub>1</sub>: overexpression of either *CLN3* or *BCK2* shortens G<sub>1</sub>, the deletion of either lengthens G<sub>1</sub>, and the deletion of both genes leaves the cell barely able to proceed through G<sub>1</sub> at all.

The connections between nutrient-sensing pathways such

as those described above and cell cycle regulatory components have not been completely defined. Connections that have been established include effects of the Tor and cAMP pathways on the translation of the Cln3 G<sub>1</sub> cyclin (1, 21, 37). Grr1, a ubiquitin-protein ligase plays a role in both glucose signaling and G<sub>1</sub> cyclin stability (2). In addition nitrogen starvation affects *CLN3* transcription (19, 36) and Cln3 translation (16). Glucose also increases the transcription of *CLN3* in a process that requires a set of repeated elements upstream of the *CLN3* open reading frame that are binding sites for the Azf1 protein (33). Little is known about nutrient regulation of *BCK2* and *CDC28*; however, we have shown that these transcripts are upregulated when glucose is added to post-log-phase cells (55). In this report we characterize the glucose induction of *CLN3*, *BCK2*, and *CDC28* mRNA. Induction of these genes requires the transport and metabolism of glucose but does not require the cAMP-, Tor-, *RGT2/SNF3*-, or *HXK2*-mediated nutrient signaling pathways. Our results suggest that a pathway that monitors glucose metabolism regulates transcription of cell cycle regulatory genes.

#### MATERIALS AND METHODS

**Yeast strains and growth conditions.** The media used were YEP (1% yeast extract, 2% peptone) and S (0.67% yeast nitrogen base) with the indicated carbon source at 2% (42). The term "post-log" refers to cultures grown for 2 to 3 days in yeast extract-peptone-dextrose (YEPD) to an optical density at 660 nm (OD<sub>660</sub>) of ca. 5 to 7. Rapamycin treatment was as described in (8). Budding indexes are the average of triplicate determinations of 100 cells each. Strains are listed in Table 1.

**RNA preparation and Northern blotting.** Total yeast RNA was isolated as described previously (13) from cells growing in the indicated medium at an OD<sub>660</sub> of ~1. The RNA samples were separated by formaldehyde gel electrophoresis and transferred to a Gene Screen Plus membrane (New England Nuclear). To ensure uniform loading and transfer of RNA, ethidium bromide was added to the samples, and the ethidium-stained rRNA was visualized on the blots under UV illumination. Blots were also probed with a radiolabeled 0.6-kb *SacI* fragment from *U2* to confirm uniform loading. Northern blots were probed with a 3-kb *HinDIII* fragment of *BCK2*, a 1-kb *BamHI/HinDIII* fragment of *CDC28*, or a 1.8-kb *BamHI* fragment from *CLN3*. All probes were radiolabeled to a specific activity of 10<sup>9</sup> cpm/μg by using [α-<sup>32</sup>P]dCTP (3,000 μCi/nmol) and random priming. Blots were analyzed by using a Molecular Dynamics Phosphorimager SI and Molecular Dynamics ImageQuant V1.2 software.

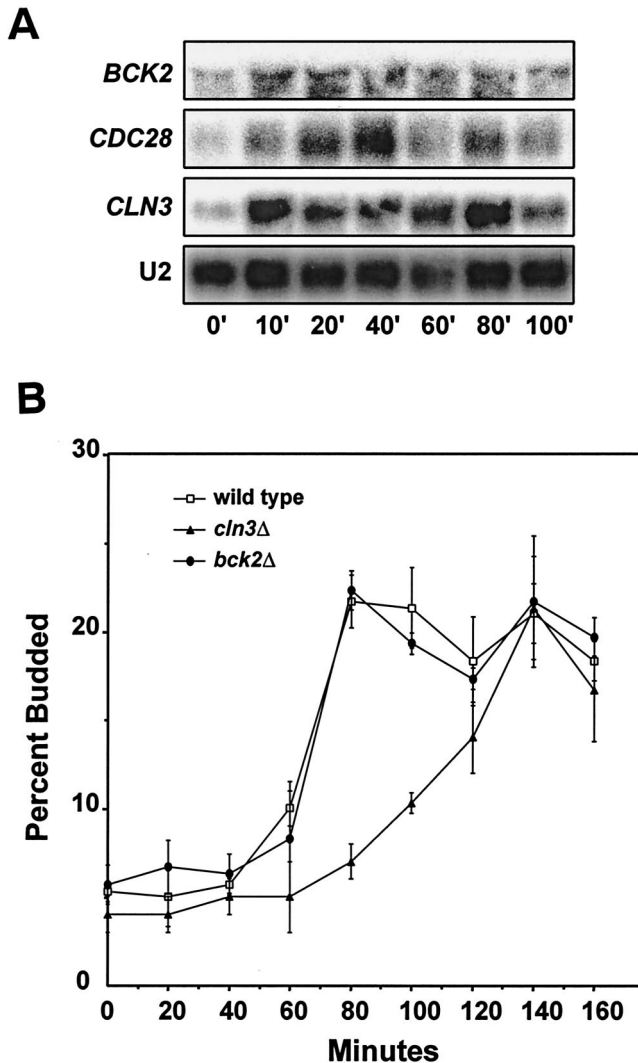


FIG. 1. Glucose induction of *CLN3*, *BCK2*, and *CDC28* mRNAs and return to proliferative growth. (A) Wild-type (DS10) cells were grown overnight to post-log phase in YEPD medium and then transferred to fresh YEPD at an  $OD_{660}$  of 0.8. Samples were collected at the indicated time points for RNA preparation and Northern blotting. U2 RNA was used as a loading and transfer control. (B) Cells were treated as described above, and bud counts on triplicate samples were performed at the indicated times after transfer. At least 300 cells were counted per time point for each strain.

## RESULTS

**Glucose induction of cell cycle mRNAs.** When post-log-phase cells are reinoculated into fresh glucose medium, the mRNAs encoding *CLN3*, *BCK2*, and *CDC28* are induced (Fig. 1A). After the initial induction, we often observe unexplained periodic fluctuations in the levels of these messages: the mRNA is first induced, levels then transiently decrease before increasing again. This is especially true of *CLN3* mRNA but was also observed in several experiments with *CDC28* and *BCK2* mRNA.

The induction of these messages in response to fresh glucose medium precedes a return to proliferative growth. We have previously shown that deletion of *CLN3* delays the initial bud

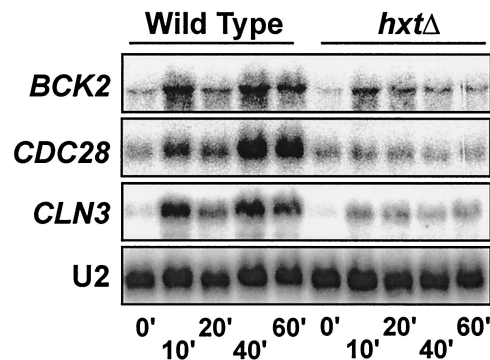


FIG. 2. Glucose transport is required for induction of cell cycle messages. Wild-type (MC996A) and isogenic *hxt1-7Δ gal2Δ* (KY73) cells were grown in YEP-2% glycerol-ethanol and transferred to fresh YEPD at an  $OD_{660}$  of 1.0. Samples were collected at the indicated time points for RNA preparation and Northern blotting.

emergence as cells resume growth (55). To determine whether *BCK2* plays a similar role, we tested the effect of *BCK2* deletion on the time course of bud emergence after the addition of fresh glucose medium (Fig. 1B). As previously observed, deletion of *CLN3* produced a delay in bud emergence in response to fresh glucose medium of about an hour. In contrast, *BCK2* deletion had no effect on the time course of this process. We conclude that, although *CLN3* plays a role in the rapid return to mitotic growth in response to fresh medium, *BCK2* does not play a role that cannot be completely served by the presence of a normal copy of *CLN3*. Deletion of *CDC28* was not tested in this experiment because *CDC28* is an essential gene.

**Glucose signaling.** We found that induction of *CLN3*, *BCK2*, and *CDC28* required the transport of glucose across the cell membrane and was not observed in a strain that lacks functional hexose transporters (Fig. 2). In this experiment, a strain in which the *HXT1-7* and *GAL2* genes encoding hexose transport proteins have been deleted (31), was grown in YEP-2% glycerol-ethanol and transferred to fresh glucose medium. In wild-type cells, glucose produced a substantial increase in the *CLN3*, *BCK2*, and *CDC28* mRNAs. This was markedly decreased in the mutant strain. These results indicate that glucose transport into the cell is required for the observed message induction. In contrast to wild-type cells, glucose addition did not produce an increase in the number of budded cells in the mutant strain (not shown).

*RGT2* and *SNF3* encode cell surface glucose sensors (34, 35). To determine whether Rgt2 or Snf3 carry glucose signals that induce *CLN3*, *BCK2*, and *CDC28*, we compared the response to glucose between a wild-type and an *rgt2Δ snf3Δ* strain. The levels of cell cycle mRNAs in the mutant strain were identical to those observed in the wild-type control strain, indicating that the glucose signals generated by these proteins are not necessary for the response (Fig. 3).

Inhibition of the Tor pathway with rapamycin did not affect the induction of *CLN3*, *BCK2*, and *CDC28* (Fig. 4), in agreement with previous results showing that the Tor pathway is involved in regulating Cln3 translation but not mRNA levels (1, 5).

**Carbon source metabolism and gene induction.** Responses to glucose are also mediated by the hexokinase encoded by



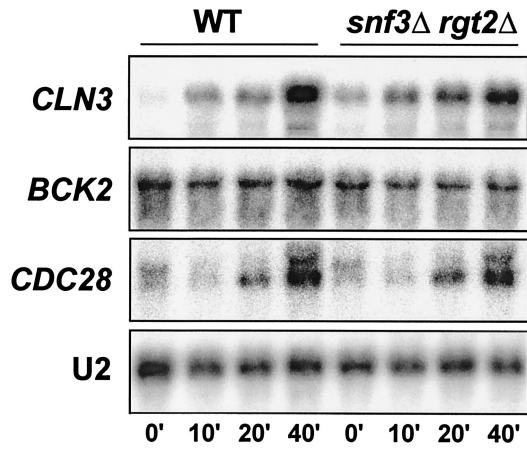


FIG. 3. The Snf3 and Rgt2 glucose sensors are not required for glucose induction. Wild-type (WT; FM392) and *snf3Δ rgt2Δ* (YM6370) cells were grown in YEP-2% ethanol to post-log phase. Cells were transferred to fresh YEPD media at an OD<sub>660</sub> of 0.8. Samples were collected at the indicated time points for RNA preparation and Northern blotting.

*HXK2*. We tested an *hxx2Δ* strain to determine whether the loss of Hxx2 function prevents the induction of the *CLN3*, *BCK2*, and *CDC28* messages by glucose medium (Fig. 5A). We found that the loss of *HXK2* decreases the transcriptional response to a degree but does not block the response.

One possible explanation for this is that Hxx2 activity is necessary for some portion of glucose induction of *CLN3*, *BCK2*, and *CDC28*. To examine this further, we tested the ability of 2-deoxy glucose, an analog of glucose that can be transported into the cell and phosphorylated in the initial step of glycolysis but cannot be further metabolized. Addition of 2-deoxy glucose failed to induce *CLN3*, *BCK2*, and *CDC28* (Fig. 5B). Whereas 2-deoxy glucose is a substrate for Hxx2 and allows the generation of Hxx2-mediated glucose signals (14), it fails to support glycolysis. It is known that loss of *HXK2* pro-

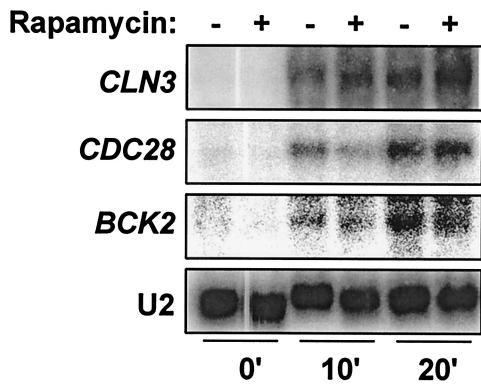


FIG. 4. Rapamycin blockade of the Tor pathway does not prevent induction of cell cycle genes by glucose. Wild-type (DS10) cells were grown overnight in YEPD to post-log phase and rapamycin (200 ng/ml, final concentration) or vehicle (ethanol) alone was added. The samples were incubated for 20 min and then transferred to fresh YEPD at an OD<sub>660</sub> of 0.8, maintaining the previous rapamycin concentration. Samples were collected at the indicated time after transfer to fresh medium for RNA preparation and Northern blotting.

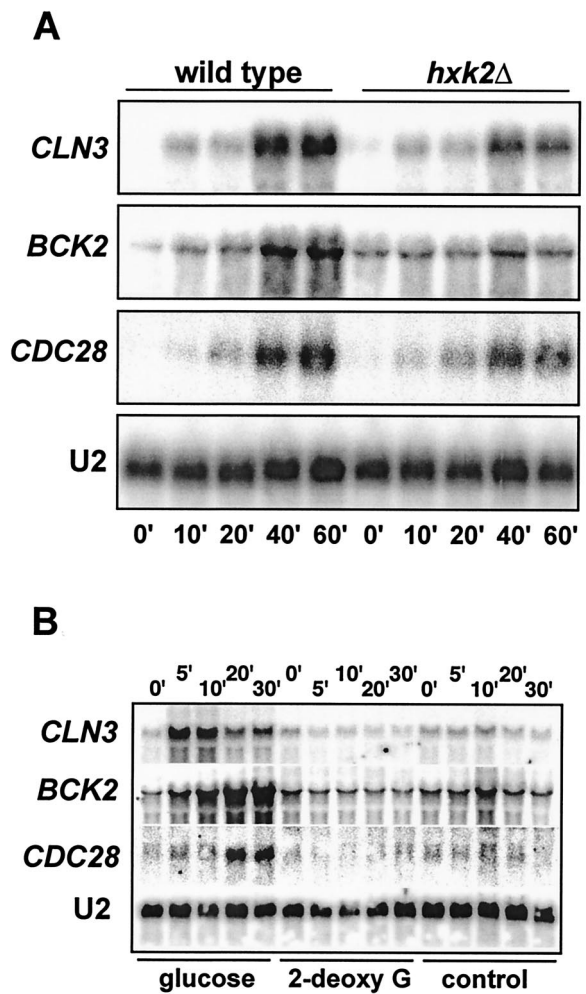


FIG. 5. Hxx2 signaling and glucose induction of *CLN3*, *BCK2*, or *CDC28*. (A) Cells from a wild-type (DTY123) and an isogenic *hxx2Δ* strain (DTY124) were grown overnight in YEPD to post-log phase. Cells were transferred to fresh YEPD medium at an OD<sub>660</sub> of 0.8. Samples were collected at the indicated time after transfer to fresh medium for RNA preparation and Northern blotting. (B) Wild-type cells were grown in YEPD until they had exhausted glucose from the medium (36 h after inoculation, at an OD<sub>660</sub> of 6), and then either D-glucose or 2-deoxy glucose was added to produce a final concentration of 2%. Control cells received an equivalent volume of water. Cells were incubated for the indicated time and then were collected for RNA blotting as described in Materials and Methods.

duces cells with impaired fermentation rates (11). Since 2-deoxy glucose does not support glycolysis, and *HXK2* deletion reduces glycolysis, a possible model is that the transcription of *CLN3*, *BCK2*, and *CDC28* are linked to the rate of glycolysis. To test this, we used iodoacetate, an inhibitor of the glyceraldehyde-3-phosphate dehydrogenase step in glycolysis (50). Addition of iodoacetate reversed the glucose induction of *CLN3*, *BCK2*, and *CDC28* (Fig. 6). These results suggest that glucose produces its effects by stimulating glycolysis.

Because iodoacetate has effects on multiple enzyme systems, the effects of iodoacetate on cell cycle transcript levels might not be specific to inhibition of glycolysis. To produce a more specific effect, we tested the effect of deletions in *PFK1* and

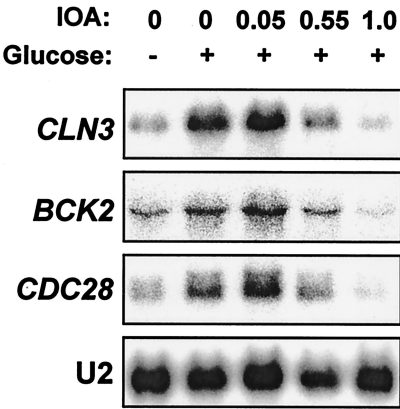


FIG. 6. Inhibition of glycolysis by iodoacetate downregulates *CLN3*, *BCK2*, or *CDC28* mRNAs. Wild-type (DS10) cells were grown overnight in YEPD to post-log phase. A sample was collected, and the remaining cells were inoculated in fresh YEPD at 0.8 OD<sub>660</sub> with iodoacetate at the indicated concentration (mM) and incubated for 1 h at 30°. Samples were then collected for RNA preparation and Northern blotting.

*PFK2*, encoding isoforms of phosphofructokinase, catalyzing an early step in glycolysis. Deletion of either *PFK1* or *PFK2* markedly decreased induction of *CLN3*, *BCK2*, and *CDC28* by glucose (Fig. 7). These results indicate that it is the metabolism of glucose that generates the signal that activates these genes.

We have previously demonstrated that the levels of Cln3 protein and Cln3/Cdc28 kinase activity are higher in cells growing in fermentable carbon sources than in cells grown in non-fermentable carbon sources (21, 36). However, *CLN3* expression appeared to be affected by the lag phase between inoculation of cells into the nonfermentable medium and the beginning of active growth. To examine this in more detail, we measured the levels of *CLN3*, *BCK2*, and *CDC28* mRNAs in wild-type cells during growth after inoculation into fresh medium containing either glucose or ethanol as the carbon source (Fig. 8). As expected, glucose produced higher levels of all

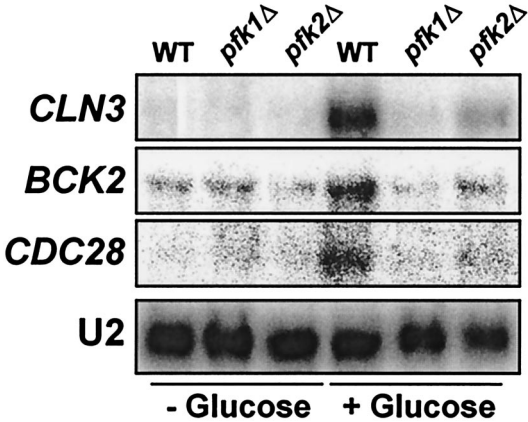


FIG. 7. Deletion of *PFK1* or *PFK2* blocks glucose induction of cell cycle genes. Wild-type (ENYWA-1A), *pfk1Δ* (EBY.81), and *pfk2Δ* (EBY.82) were grown overnight in YEPD. The cells were inoculated in fresh YEPD at an OD<sub>660</sub> of 0.8, and samples were collected at the indicated time for RNA preparation and Northern blotting.

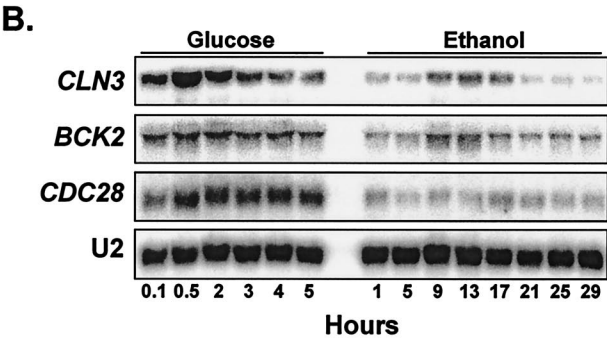
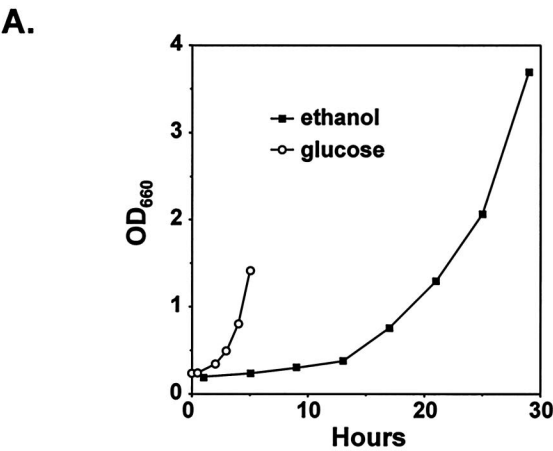


FIG. 8. Growth in different carbon sources. Wild-type (BY4741) cells were grown overnight to post-log phase in YEPD. Cells were transferred to fresh YEPD or YEP-2% ethanol media at an OD<sub>660</sub> of 0.2. Samples were taken for culture density measurement (A) and RNA preparation (B) at the times indicated.

three messages than ethanol medium. However, for both carbon sources, the mRNA levels changed over time. This was especially apparent for *CLN3* mRNA, which peaked shortly before the period of rapid growth.

DISCUSSION

*S. cerevisiae* strains have descended through innumerable cycles of nutrient excess and restriction. This demands that yeast cells regulate the cell cycle so that proliferation is rapid in the presence of rich nutrients and yet ceases during periods of nutrient limitation. Nutrients such as glucose must therefore generate signals that are in some way connected to the gene products that regulate cell cycle progression. We find that *CLN3*, *BCK2*, and *CDC28* mRNAs are all increased when post-log-phase cells are transferred to fresh glucose medium. Our results indicate that some process in glycolysis regulates genes that regulate cell cycle progression.

**Coregulation of *CLN3*, *CDC28*, and *BCK2*.** Although glucose upregulates *CLN3*, *BCK2*, and *CDC28*, we noticed differences in the expression patterns of the three genes. Glucose addition consistently had the greatest effects on *CLN3* mRNA, whereas the effects on *BCK2* were generally the least pronounced of the three messages examined. In addition, al-

though *CLN3* and *BCK2* message levels increased as growth on ethanol got under way, *CDC28* message levels did not. These differences indicate that, although all three messages appear to be affected by a process in glycolysis, they may not be regulated by the same mechanism.

**Glucose signals.** Several distinct pathways are involved in normal yeast responses to glucose. Some of these probably involve the interaction of glucose with cell surface receptors, whereas others require the import of glucose into the cell. These include the Gpr1/Gpa2/cAMP pathway, the Tor pathway, the Snf3 and Rgt2 homologs of hexose transporters, and the Hxk2 hexokinase. None of these signal transduction pathways appear to play an important role in glucose induction of *CLN3*, *BCK2*, or *CDC28* mRNAs, since the message levels are unaffected by the loss of any of these pathways. This was shown by our experiments with *HXK2*, *SNF3*, and *RGT3* deletion mutants, and rapamycin blockade of the Tor pathway, along with previously published work involving the Tor pathway (22), and the cAMP pathway (36, 40).

On the other hand, glucose import and metabolism are clearly required for the induction of *CLN3*, *BCK2*, and *CDC28* mRNAs. The process is blocked in a strain lacking glucose transport genes, and decreased in an *hxk2Δ* strain in which fermentation is slowed (11). Furthermore, 2-deoxy glucose, which cannot enter glycolysis, does not substitute for glucose. *CLN3* is induced by a variety of fermentable carbon sources, suggesting that fermentation produces the signal that regulates *CLN3* transcription (36). Addition of iodoacetate, an inhibitor of glyceraldehyde-3-phosphate dehydrogenase produced an almost complete reversal of the glucose induction of the genes examined. Finally, deletion of the genes encoding phosphofructokinase blocked glucose induction of *CLN3*, *BCK2*, and *CDC28*.

Together, our results indicate that these transcripts are linked to carbon source metabolism. It is intriguing that non-fermentable carbon sources such as ethanol can stimulate an increase in *CLN3* mRNA. Although this effect is considerably smaller than the effect of glucose, it may indicate that the signal is generated at a point in common between fermentable and nonfermentable carbon source metabolism.

Much of the study of glucose effects on *S. cerevisiae* has focused on the repression of genes involved in alternate carbon source metabolism and the induction of genes encoding glucose transport and ribosomal proteins. The landmark microarray experiments by DeRisi et al. examining changes in transcript abundance as yeast cells exhaust the glucose in the medium at the diauxic shift demonstrated the profound effects that glucose has on gene expression in yeast (9). It is not yet clear whether the known glucose-sensing pathways can account for this large-scale regulation. Our results point to an uncharacterized pathway by which glycolysis generates a signal that regulates the mRNA levels for a set of cell cycle genes. Whether this process is restricted to the control of the cell cycle or is also involved in other glucose responses remains to be determined.

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