Glucose is the primary fuel for most cells. Because the amount of available glucose can fluctuate wildly, organisms must sense the amount available to them and respond appropriately. Altering gene expression is one of the major effects glucose has on cells. Two different glucose sensing and signal transduction pathways in the yeast *S. cerevisiae* – one for repression, and one for induction of gene expression – have recently come into focus. What we have learned about these glucose sensing and signaling mechanisms might shed light on how other cells sense and respond to glucose.

Glucose repression mechanism

The central components of a major (though apparently not exclusive) pathway for glucose repression of gene expression are: (1) Mig1, a transcriptional repressor; (2) Snf1, a protein kinase, and its associated regulators (Snf4 and the three members of the Sip family of proteins); and (3) glc7, which encodes protein phosphatase 1 (PP1), and its regulatory subunit (Reg1). The zinc-finger-containing Mig1 repressor (along with its relative Mig2, in some cases), binds to the promoters of many glucose-repressed genes and represses their transcription, probably by recruiting the general repressors Ssn6 and Tup1 (Ref. 14). Mig1 seems to be responsible for most of the repression of glucose-repressed genes; Mig2 collaborates with Mig1 in repressing some genes (Ref. 15). The nuclear localization of Mig1 is regulated by glucose: it moves rapidly into the nucleus when glucose is added to cells, and quickly moves back into the cytoplasm when glucose is removed (Ref. 16). This regulated movement of Mig1 is primarily mediated by Snf1 and its associated regulators, which are activated in response to glucose deprivation. Glucose repression is therefore a Snf1-regulated response to glucose deprivation, and it appears that glucose is sensed by Snf1 through its interaction with Mig1.

Fasting, feasting and fermenting

Glucose sensing in yeast and other cells

Glucose sensing
FIGURE 1. Glucose repression and induction

Mechanisms of glucose repression and induction (see text for details): glucose repression (red) and glucose induction (green) of gene expression; arrows signify activation of function; lines ending in a bar signify inhibition of function. Glucose repression: high levels of glucose are bound to the low-affinity glucose receptor (Snf3), and high levels of glucose bind to the high-affinity glucose receptor (Snt3), causing it to leave the nucleus, thereby derepressing gene expression. Glucose induction: low levels of glucose lead to high AMP levels, which might activate Snf1, which phosphorylates Mig1, because AMP:ATP ratio, which rapidly increases when glucose levels fall, Snf1–Snf4. Because AMP levels are low, Snf1 is inactive, and therefore does not inhibit Mig1, causing it to remain in the nucleus, thereby derepressing gene expression. Glycolytic enzymes that must be phosphorylated for Snf1 be active. The protein phosphatase that acts on Mig1 has not been identified. Reg1–Glc7 (see below) is an attractive candidate to remove phosphate(s) from Snf1 (Ref. 20), which prevents Snf1 from sequestering the regulatory domain, thereby switching Snf1 to its inactive (high glucose) state. The inability of Snf4 to bind to the regulatory domain of Snf1 when glucose levels is high may be due to removal of phosphate from T210, a residue conserved in many protein kinases that is primarily responsible for catalyzing the first step of glycolysis when glucose is abundant, plays a major role in glucose repression.

What is the glucose signal that affects Snf1 function?

An attractive candidate is AMP (or, more likely, the AMP:ATP or ADP:ATP ratio), which is depleted in glucose grown cells due to generation of ATP in glycolysis (Fig. 1). This insight came from the realization that the three components of the Snf1 kinase (Snf1, Snf4, and the Sp proteins) are similar to the subunits of the AMP-activated protein kinase (AMPK) of mammals. Unlike AMPK, Snf1 is not directly activated by AMP (Ref. 14, 26), but its activity correlates remarkably well with the AMP:ATP (and ADP:ATP) ratio, which rapidly increases more than 200-fold upon glucose removal. These observations suggest the satisfying view that in cells growing with abundant glucose, generation of ATP by glycolysis depletes AMP:ATP ratio, leading to inactive Snf1; cells starved for glucose are replete in AMP (high AMP:ATP ratio), which would result in activation of Snf1. Thus, the signal for glucose repression may be generated during metabolism of glucose. This idea is consistent with the observation that hexokinase 2 (Hxk2), the enzyme that is primarily responsible for catalyzing the first step of glycolysis when glucose is abundant, plays a major role in glucose repression.

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Glucose induction mechanism

The second pathway for glucose regulation of gene expression has recently come into view. Among the 20 known or apparent hexose transporters in yeast (reviewed in Ref. 31), only 3 are known for their specificity for glucose, the zinc-finger-containing Rgt1 repressor binds to the HXT promoters when glucose is present (Fig. 3). This is due to relief of Rgt1-mediated repression, which occurs at both low and high concentrations of glucose, and to another pathway (whose components have not yet been identified), that responds only to high glucose concentrations. In addition, Rgt1 becomes a transcriptional activator when glucose levels are high, and this may contribute to high glucose-induced HXTI expression. Because of these overlapping regulatory mechanisms, the cell expresses the glucose transporters appropriate for the amount of glucose available.

Inhibition of Rgt1 repressor function appears to involve ubiquitination (reviewed in Ref. 47). The central component of these SCF complexes is the ubiquitin-conjugating enzyme Cdc4 (also known as Ubc3). The SCF complexes that have been identified contain, in addition to Cdc4, two other proteins (Cdc53 and Skp1) that seem to provide a scaffold for the protein-protein interactions. These complexes differ in the F-box-containing component that interacts with Skp1, which is thought to recruit substrates to the complex. The SCF* complex, for example, contains Cdc4 instead of Grr1. Cdc4 is responsible for recruiting to the complex certain substrates (e.g. the cyclin-dependent

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It is not clear how glucose stimulates the SCF Grr1 complex, the nature of the modification it catalyzes, and the consequence of the modification for Rgt1 function are key questions that remain to be answered.

Grr1 is known to interact with Rgt1 (or its regulator) with ubiquitin availability to gene expression and cell-cycle progression.

It is possible that Rgt1 (or its regulator) is modified instead by one of the ubiquitin-related proteins (Smt3, whose attachment to proteins is catalyzed by Ubc9 (Ref. 50), or Rub1 (Ref. 51)). Determining the target of the SCF\(^{Grr1}\) complex, the nature of the modification it catalyzes, and the consequence of the modification for Rgt1 function are key questions that remain to be answered.

Grr1 is also required for the Cdc34-dependent ubiquitination of Rgt1 function\(^{36,37}\), which leads to the suggestion that Grr1 interacts with Rgt1 (or its regulator) in protein interaction domain, thereby causing them to be ubiquitinated and thus marked for degradation\(^46\). By analogy, it seems reasonable to speculate that Grr1 recruits the Rgt1 repressor (or possibly an unidentified protein that regulates Rgt1) to the SCF\(^{Grr1}\) complex through its protein interaction domain (leucine-rich repeats). In this view, the ensuing modification of Rgt1 (or its regulator) with ubiquitin would inhibit its ability to repress transcription, and stimulate its function as a transcriptional activator.

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However, it is not known if Rgt1 becomes modified with ubiquitin. It is possible that Rgt1 (or its regulator) is modified instead by one of the ubiquitin-related proteins (Smt3, whose attachment to proteins is catalyzed by Ubc9 (Ref. 50), or Rub1 (Ref. 51)). Determining the target of the SCF\(^{Grr1}\) complex, the nature of the modification it catalyzes, and the consequence of the modification for Rgt1 function are key questions that remain to be answered.

Grr1 is also required for the Cdc34-dependent ubiquitination of Rgt1. Perhaps it activates the SCF\(^{Grr1}\) complex. This complex is, in fact, about 10-fold more abundant in cells growing on high levels of glucose than in cells growing without glucose, probably due to more efficient interaction of Grr1 with the components of the complex (rather than to increased levels of Grr1)\(^{54}\). However, it is possible that SCF\(^{Grr1}\) function is unregulated, and that the glucose signal acts elsewhere to stimulate inactivation of the repressor function of Rgt1.

Glucose induction signal

The glucose signal is generated by Snf3 and Rgt2, two glucose sensors that reside in the cell membrane.

Because glucose is a key nutrient whose availability has a major influence on the cell cycle, Grr1 is situated to play a central role in coupling nutrient availability to gene expression and cell-cycle progression.

How is the glucose signal generated by these receptors, and what is its nature? It seems likely that glucose binds to the receptors outside the cell and induces a conformational change in them that affects events inside the cell. In this regard, the nutrient glucose is acting like some hormones, which signal similarly through a receptor-mediated process. Key elements in this process are the unusually long C-terminal tails of the glucose receptors, which are predicted to reside in the cytoplasm\(^{53}\). These unusually long C-terminal tails of the glucose receptors, which are predicted to reside in the cytoplasm, are required for full induction of high glucose induced genes, and what is its nature? It seems likely that glucose binds to the receptors outside the cell and induces a conformational change in them that affects events inside the cell.

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...tissue) that is mediated by the hormone insulin. The insulin-producing beta cells of the pancreas are the primary fuel-sensing cells of mammals, and no indication that they employ a receptor-mediated mechanism for sensing glucose like that in yeast. A wealth of evidence has led to the view that glucose sensing by beta cells also requires glucose metabolism, as it seems to be the case for glucose receptors similar to Snf3 and Rgt2 in yeast (reviewed in Refs 57, 58). It seems worthwhile to keep an eye out for glucose receptors similar to Snf3 and Rgt2 in other cells that must recognize the presence of glucose. Such a receptor has been identified in Neospora caninum, where it seems to play a role in sensing glucose and regulating glucose transporter gene expression (59).

What is particularly exciting about the glucose sensing mechanism for induction of gene expression in yeast is that it may be novel: the likely signaling regions of the glucose receptors (the 23 amino acid repeats) contain sequence motifs that appear in other receptors, and the next component of the signal transduction pathway (an FMN complex involved in protein modification) has only recently been identified in signaling pathways (proteins similar to Gfr1 have recently turned up in signaling pathways in plants (60)). Gfr1 homologs also exist in Caenorhabditis elegans, and in humans (F. Li, unpublished). It seems likely that what we learn about how yeast cells sense and respond to glucose will be relevant to the glucose sensing mechanisms in cells of many different organisms know when they are fasting or feeding.

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References