Feasting, fasting and fermenting

glucose sensing in yeast and other cells

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.

All of us must eat to live; some of us, it seems, live to eat. But whether our fare is dull or delicious makes little difference to our cells: they, for the most part, feast only on the glucose that is the ultimate end product of our meals. Whether it be during the brief periods when we are eating, during the long periods when we sleep, or while we are exercising, most people are able to maintain remarkably constant levels of glucose in their blood. It is fortunate we have this ability, because even small changes in blood glucose levels have the dire consequences to our health known as diabetes.

Glucose, the most abundant monosaccharide in nature, is also the primary fuel for microorganisms. While most microorganisms can utilize a variety of carbon sources, many go to great lengths to ensure that they use up the available glucose before turning to alternative fuels. Myriad mechanisms have evolved to achieve this, including those that act at the levels of gene transcription [called glucose (also 'catabolite') repression][1,2], mRNA stability[3], mRNA translation[4] and protein stability[5].

Like mammals, bakers' (or brewers') yeast (*Saccharomyces cerevisiae*) prefers to eat glucose, and has evolved sophisticated regulatory mechanisms to cope with the wildly fluctuating levels of glucose available to it. These regulatory mechanisms are particularly important to yeast, because they contribute to its fermentative lifestyle by helping to ensure that most of the available glucose is fermented (by inhibiting respiration)[6]. The consequent production of relatively large amounts of ethanol and carbon dioxide have made yeast of great utility to human civilization for thousands of years[7]. A major route by which glucose encourages its own use and stimulates fermentation is by regulating gene expression. Some of the mechanisms by which glucose affects gene expression in bakers' yeast have recently come into focus, and the paradigms that are emerging may inform how cells of other organisms respond to glucose.

Glucose has two major effects on gene expression in *S. cerevisiae*: it represses expression of many genes, including those encoding proteins in the respiratory pathway (e.g. cytochromes) and enzymes for utilization of alternative carbon sources (e.g. galactose, sucrose and maltose); it also induces expression of genes required for glucose utilization, including genes encoding glycolytic enzymes and glucose transporters. We now have the outlines of two signal transduction pathways in yeast responsible for these effects of glucose. First, I describe one responsible for glucose repression (shown in red in Fig. 1), which employs the Mig1 transcriptional repressor, whose function is inhibited by the Snf1 protein kinase. Then I describe a signaling pathway responsible for glucose induction of glucose transporter gene expression (shown in green in Fig. 1), which centers around the Rgt1 transcriptional repressor, whose function is inhibited by the SCF^{Grr1} protein complex.

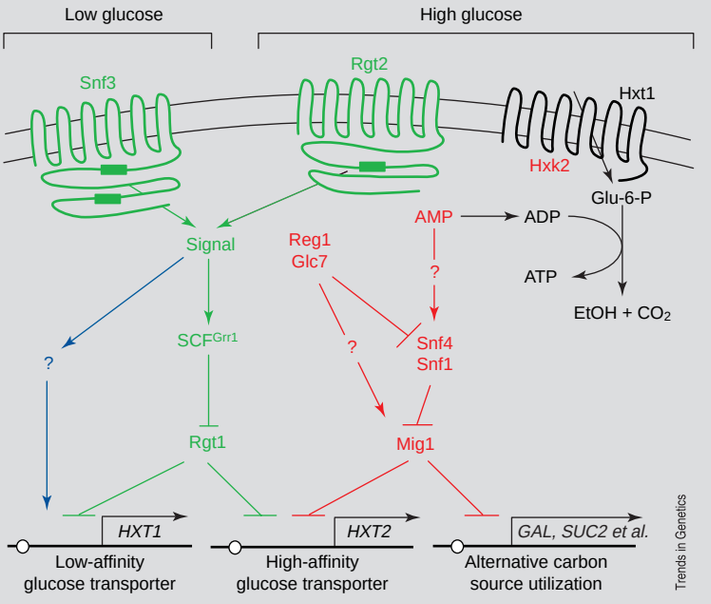
Glucose repression mechanism

The central components of a major (though apparently not exclusive[8]) pathway for glucose repression of gene expression are: (1) Mig1, a transcriptional repressor[9]; (2) Snf1, a protein kinase[10], and its associated regulators (Snf4 and the three members of the Sip family of proteins)[11]; and (3) *glc7*, which encodes protein phosphatase 1 (PP1), and its regulatory subunit (Reg1)[12]. The zinc-finger-containing Mig1 repressor[9] (along with its relative Mig2, in some cases[13]), 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[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[16]. This regulated

Mark Johnston
mj@genetics.wustl.edu

Department of Genetics, Box 8262, Washington University Medical School, 4566 Scott Avenue, St Louis, MO 63110, USA.

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 probably transported into the cell mainly by the low-affinity glucose transporter Hxt1. Intracellular glucose is converted to glucose-6-phosphate primarily by Hxk2, then fermented to ethanol and CO_2. The consequent production of ATP depletes AMP, which might be the signal that activates Snf1–Snf4. Because AMP levels are low, Snf1 is inactive, and therefore does not inhibit Mig1, which enters the nucleus and represses expression of many genes. The Glc7–Reg1 protein phosphatase is also involved in regulating Snf1 function; it could also dephosphorylate Mig1. Low levels of glucose lead to high AMP levels, which might activate Snf1, which phosphorylates Mig1, causing it to leave the nucleus, thereby derepressing gene expression. Glucose induction: low levels of glucose bind to the high-affinity glucose receptor (Snf3), and high levels of glucose bind to the low-affinity glucose receptor (Rgt2) and generate an unidentified intracellular signal that activates the SCF^{Grr1} complex, causing it to inhibit the function of the Rgt1 repressor, thereby derepressing expression of the *HXT* genes. Not shown in the figure is the fact that high glucose levels also activate the transcriptional activator function of Rgt1, a process that also requires Grr1. In addition, high glucose also activates another mechanism (shown in blue), whose components have not been identified, that further stimulates the high glucose-induced *HXT1* gene.

movement of Mig1 appears to be due to phosphorylation, probably catalyzed by the Snf1 protein kinase. Glucose inhibits the activity of the Snf1 kinase[17,18], which leads to underphosphorylation of Mig1 (Refs 14, 16), thereby causing Mig1 to move into the nucleus where it represses gene expression[16]. Removal of glucose activates the Snf1 kinase, which causes Mig1 to become phosphorylated and leave the nucleus, resulting in derepression of glucose-repressed genes. While it has not been rigorously shown that Snf1 directly phosphorylates Mig1, this seems likely, because Mig1 contains four consensus sequences for Snf1 phosphorylation, and changing all four of the residues thought to be phosphorylated reduces the level of phosphorylation of Mig1 (Ref. 19) and causes it always to be in the nucleus, repressing transcription (M. DeVit, unpublished). In addition, Snf1 interacts with Mig1, and phosphorylates the Mig1 that co-immune precipitates with it[19]. The protein phosphatase that acts on Mig1 has not been identified. Reg1–Glc7 (see below) is an attractive candidate, because *reg1* and *glc7* mutations cause Mig1 to be hyperphosphorylated[19] and always in the cytoplasm (M. DeVit, unpublished). A different glucose signal transduction pathway must affect Mig2, because it is regulated differently than Mig1: it is neither affected by Snf1, nor is its nuclear localization regulated by glucose[15]. This is surprising, because these two proteins bind to the same DNA sequences and carry out the same function in response to glucose.

How does glucose regulate the Snf1 protein kinase? The view that emerges from a large body of evidence is that it is due to the interaction of a regulatory domain of Snf1 with either the Snf1 catalytic domain, or with Snf4, a subunit of the Snf1 kinase that enhances its function (Fig. 2)[20,21]. The regulatory domain of Snf1 is thought to mask the catalytic domain when cells are growing on high levels of glucose. When glucose levels fall, Snf4 binds to the regulatory domain of Snf1, thereby activating the enzyme. It may do this actively, by releasing the catalytic domain from its grasp, or passively, by stabilizing the active form of the enzyme. Snf4 is assisted in this process by one of the members of the Sip family of proteins (Sip1, Sip2, Gal83)[11], which seem to serve as scaffolds for the protein complex, and could be responsible for recruiting substrates[22]. An additional contributor to the process is the Glc7 protein phosphatase[23], which is probably targeted to Snf1 through its regulatory subunit, Reg1 (Ref. 12). The evidence suggests that Reg1 binds to the catalytic domain of active (low glucose) Snf1, presumably directing Glc7 to remove phosphate(s) from Snf1 (Ref. 20), which prevents Snf4 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 are high may be due to removal of phosphate from T210, a residue conserved in many protein kinases that must be phosphorylated for Snf1 be active[24]. Thus, two proteins (Snf4 and Reg1) determine whether the regulatory domain inhibits the catalytic domain of Snf1. In addition, Snf1 function appears to be regulated by another, unidentified mechanism, because its activity is regulated by glucose even in the absence of its regulatory domain and Reg1 (Ref. 20).

Glucose repression signal

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 Sip proteins) are similar to the subunits of the AMP-activated protein kinase (AMPK) of mammals[25,26]. Unlike AMPK, Snf1 is not directly activated by AMP (Refs 18, 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[18]. These observations suggest the satisfying view that in cells growing with abundant glucose, generation of ATP by glycolysis depletes AMP (low 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[27]. While this provides a satisfying view, it remains possible that glucose itself, or an early metabolite of glucose is the signal for glucose repression[28–30].

If the AMP:ATP ratio regulates Snf1 activity, it probably does this indirectly, because Snf1 does not appear to be activated by AMP (Refs 18, 26). AMP may activate Snf1 by activating a Snf1 kinase kinase, which appears to exist[18], but has not yet been identified. Again, this is by analogy to AMPK, whose activity, in addition to being directly activated by AMP, is regulated by another protein kinase (AMPK kinase) that is also regulated by AMP (reviewed in Ref. 31).

The Snf1 homolog in mammalian cells – AMPK – is involved in the cellular stress response (reviewed in Ref. 31). Because of its sensitivity to reduction in ATP levels, AMPK has been called the 'fuel gauge' of the mammalian cell[31]. Its activity is increased by a variety of stresses (e.g. heat shock, hypoxia), all of which increase the AMP:ATP ratio and cause AMPK to phosphorylate and inactivate a number of biosynthetic enzymes, probably for the purpose of conserving ATP (Refs 18, 31). Its yeast cousin also plays this role, because starvation for glucose is one of yeast's major stresses (at least during the time it takes cells to mobilize the machinery necessary to use alternative carbon sources), and the result of activation of Snf1 is to increase ATP production (by enabling use of alternative carbon sources). Conversely, AMPK plays a role in regulating gene expression in mammalian cells[33,34], as does Snf1 in yeast. Plants also appear to possess a similar stress-response system, because they possess Snf1 homologs that may also be responsible for repression of gene expression by sucrose[32]. Clearly, this is a mechanism for dealing with stress and starvation that arose early in evolution and has continued to serve cells well.

Glucose induction mechanism

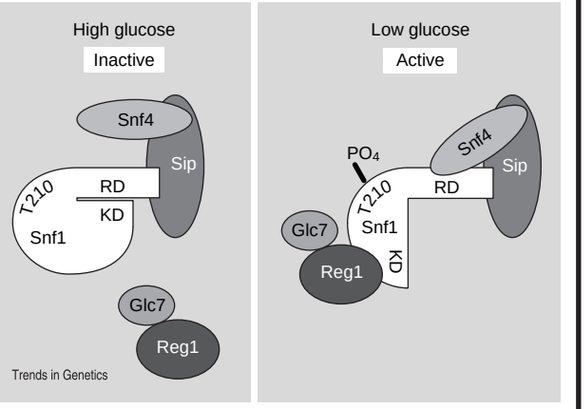
The second pathway for glucose regulation of gene expression helps ensure that yeasts can live well on glucose. Because yeast cells growing on high levels of glucose obtain most of their energy from fermentation[6], which generates only a few ATP molecules per glucose molecule burned, they must pump large amounts of glucose through glycolysis to generate enough energy to live comfortably. To achieve greater glycolytic capacity, expression of most genes encoding enzymes of glycolysis[35], as well as of several of the *HXT* genes encoding glucose transporters[36] is induced by glucose. Separate signal transduction pathways seem to be responsible for induction of expression of these two classes of genes by glucose; the one effecting glucose-induction of the *HXT* genes has recently come into view.

The central players in this pathway are: (1) a transcriptional repressor (Rgt1)[37]; (2) a multiprotein complex (SCF^{Grr1}) that inhibits repressor function[38,39]; and (3) glucose sensors in the membrane that generate an intracellular glucose signal (Snf3 and Rgt2)[42]. In the absence of glucose, the zinc-finger-containing Rgt1 repressor binds to the *HXT* promoters and represses their transcription, probably by recruiting the general repressors Ssn6 and Tup1 (Ref. 37). When glucose is added to cells, it binds to the glucose sensors outside the cell and generates a signal inside the cell that causes the SCF^{Grr1} complex to inactivate the Rgt1 repressor, thereby derepressing *HXT* gene expression and enabling glucose transport.

Yeast cells are able not only to detect glucose in their surroundings, but to determine how much is available and respond by expressing the appropriate transporter. Among the 20 known or apparent hexose transporters in yeast[40,41] are several (Hxt2, -4, -6, -7) with high affinity (Km ~ 1–10 mM) for glucose, and two (Hxt1 and Hxt3) with low affinity (Km ~ 50–100 mM)[43]. The high-affinity (low capacity) transporters are most useful when glucose is scarce, so it is fitting that *HXT2 et al.* are only expressed when glucose levels are low. This is because the promoters of these genes contain Mig1 binding sites, which causes them to be repressed by high levels of glucose[44]. In the absence of glucose, Rgt1 prevents expression of *HXT2 et al.*; Mig1 maintains their repression in cells growing on high glucose. It is only at low glucose levels that repression by Rgt1 is prevented, but Mig1 is not activated, that *HXT2* is expressed. The low-affinity (high capacity) glucose transporters are of greatest use to the cell when glucose is abundant, and, appropriately, the *HXT1* gene is expressed only under those conditions[36]. 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[36]. In addition, Rgt1 becomes a transcriptional activator when glucose levels are high[37], and this may contribute to high glucose-induced *HXT1* 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 ubiquitin, or a ubiquitin-related protein. The key clue that led to this insight came from the discovery that Grr1 is part of an SCF complex (Fig. 3)[38,46]. (SCF complexes are named for their constituent proteins: Skp1, Cdc53 and Cdc34, and an F-box-containing protein[38,46].) Other SCF complexes are known to direct protein ubiquitination[45,46] (reviewed in Ref. 47). The central component of these SCF complexes is the ubiquitin conjugating enzyme Cdc34 (also known as Ubc3). The SCF complexes that have been identified contain, in addition to Cdc34, 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^{Cdc4} complex, for example, contains Cdc4 instead of Grr1. Cdc4 is responsible for recruiting to the complex certain substrates (e.g. the cyclin-dependent

FIGURE 2. Regulation of Snf1



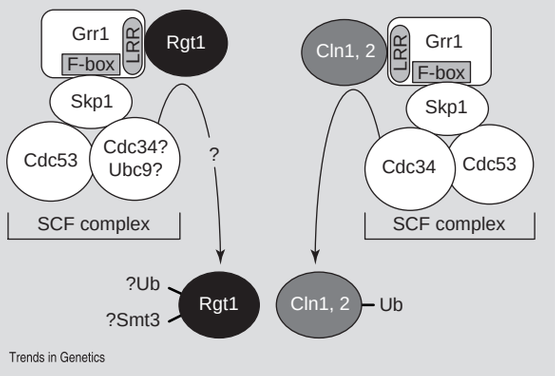
Proposed mechanism of regulation of Snf1 kinase function (after Fig. 1 of Ref. 20; see text for details). Abbreviations: KD, Snf1 kinase domain, responsible for catalytic function of the enzyme; RD, Snf1 regulatory domain that interacts with the kinase domain, and with Snf4; T210, threonine residue conserved in many kinases that must be phosphorylated for the Snf1 kinase to be active.

protein kinase inhibitor Sic1) using its WD40 repeat 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. 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 and subsequent degradation of the G1 cyclins Cln1 and Cln2 (Refs 46, 48), whose function is required for cells to start the cell cycle, and of Gic1 and Gic2, which regulate actin polarization and bud emergence[49]. Grr1 interacts with Cln1 and Cln2, and is thus probably responsible for recruiting these proteins to the SCF^{Grr1} complex (though their SCF^{Grr1}-directed ubiquitination has not yet been demonstrated *in vitro*)[46]. 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.

It is not clear how glucose stimulates the SCF^{Grr1}-mediated modification 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)[38]. 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.

FIGURE 3. Regulation by SCF^{Grr1} complexes



Grr1 is known to interact with Skp1 through its F-box sequence motif, and with Cdc53 (Refs 38, 46). The ubiquitin-conjugating enzyme Cdc34 is likely also part of this complex, because (a) it is part of other SCF complexes[47], (b) Grr1 is known to be required for the Cdc34-dependent ubiquitination of Cln1 and Cln2 (Ref. 48), and (c) Grr1 is known to interact with Cln1 (Ref. 46). Grr1 is also required for modification of Rgt1 function[36,37], which leads to the suggestion that Grr1 interacts with Rgt1. Rgt1 (or its regulator) is probably modified, but this could be with ubiquitin or one of the ubiquitin-like proteins like Smt3. (See text for details.)

Glucose induction signal

The glucose signal is generated by Snf3 and Rgt2, two glucose sensors that reside in the cell membrane. While these two proteins are very similar to glucose transporters, with 12 predicted membrane-spanning domains[42,53], they appear to be unable to transport glucose[54]. Instead, they seem to serve as glucose receptors that generate an intracellular glucose signal upon binding extracellular glucose. Two key observations led to this view. First, Snf3 and Rgt2 are required for induction of *HXT* expression by glucose[36,42,52]. Because Snf3 is required for induction of gene expression by low levels of glucose, it is thought to be a high affinity glucose receptor. Rgt2, which is required for full induction of high glucose induced genes, is probably a low affinity glucose receptor. Second, a mutation that alters a single amino acid of these proteins (an arginine, conserved in all glucose transporters, located in the cytoplasmic loop just before the fifth transmembrane domain) causes them always to generate a glucose signal that induces *HXT* expression, even in the absence of glucose, presumably by converting them into their glucose-bound form[42]. This result demonstrates that metabolism of glucose is not required for the glucose induction signal.

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 long (more than 200 amino acid) cytoplasmic tails, which distinguish Snf3 and Rgt2 from all known glucose transporters (which have cytoplasmic tails of around 50 amino acids or less), are required for glucose signal generation[52–56]. In fact, the Snf3 tail is sufficient for glucose signaling, because its attachment to the C-termini of the known glucose transporters Hxt1 and Hxt2 converts them into glucose sensors that are able to generate a glucose signal[54]. The region of the Snf3 and Rgt2 tails most critical for glucose signaling is the only region they have in common: a 26 amino acid sequence that is nearly identical between the two proteins. Snf3 possesses two of these sequences, Rgt2 has only one. It is tempting to speculate that this 26 amino acid sequence interacts with the next component of the signal transduction pathway, and that the signal generation event is the alteration of the interaction that results when the conformation of the sensors changes upon glucose binding. Whatever the nature of the glucose signal generated by the glucose receptors, it is clear that it is not generated by glucose metabolism[42], unlike the situation for glucose repression[18].

Glucose sensing and signaling in other cells

A major effect of glucose on both mammalian and yeast cells is to increase the number of glucose transporters in the cell membrane. As we have seen, glucose directly increases glucose transporter gene expression in yeast cells. Mammals, being multicellular, have evolved an indirect mechanism for stimulation of glucose transport in the cells primarily responsible for glucose disposal (fat and

muscle cells) that is mediated by the hormone insulin. The insulin-producing beta cells of the pancreas are the primary fuel-sensing cells of mammals, and there is no indication yet 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 requires glucose metabolism, as seems to be the case for glucose repression in yeast, with glucokinase serving as the glucose sensor by determining how much glucose enters glycolysis (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 protein (Rco-3) has been identified in *Neurospora crassa*, 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 no sequence motifs that appear in other receptors, and the next component of the signal transduction pathway (an SCF complex involved in protein modification) has only recently been identified in signaling pathways (proteins similar to Grr1 have recently turned up in signaling pathways in plants[60,61]). Grr1 homologs also exist in *Caenorhabditis elegans*, and in humans[62] (F. Li, unpublished). It seems likely that what we learn about how yeast cells sense and respond to glucose will help us learn how cells of many different organisms know when they are feasting or fasting.

Acknowledgement

I thank Stan Fields for hospitality, and for suggestions for improving the presentation of this story.

References

1 Magasanik, B. (1961) Catabolite repression. *Cold Spring Harbor Symp. Quant. Biol.* 26, 249–256
2 Ullmann, A. (1996) Catabolite repression: a story without end. *Res. Microbiol.* 147, 455–458
3 Cereghino, G.P. and Scheffler, I.E. (1996) Genetic analysis of glucose regulation in *Saccharomyces cerevisiae*: control of transcription versus mRNA turnover. *EMBO J.* 15, 363–374
4 Vallari, R.C. *et al.* (1992) Glucose repression of the yeast ADH2 gene occurs through multiple mechanisms, including control of the protein synthesis of its transcriptional activator, ADR1. *Mol. Cell. Biol.* 12, 1663–1673
5 Jiang, H. *et al.* (1997) Two glucose sensing/signaling pathways stimulate glucose-induced inactivation of maltose permease in *Saccharomyces. Mol. Biol. Cell.* 8, 1293–1304
6 Lagunas, R. (1979) Energetic irrelevance of aerobiosis for *S. cerevisiae* growing on sugars. *Mol. Cell. Biochem.* 27, 139–146
7 Samuel, D. (1996) Investigation of ancient egyptian baking and brewing methods by correlative microscopy. *Science* 273, 488–490
8 Yin, Z. *et al.* (1996) Multiple signalling pathways trigger the exquisite sensitivity of yeast gluconeogenic mRNAs to glucose. *Mol. Micro.* 20, 751–764
9 Ostling, J. *et al.* (1996) Functional domains in the Mig1 repressor *Mol. Cell. Biol.* 16, 753–761
10 Hardie, D.G. *et al.* (1998) The AMP-activated/Snf1 protein kinase subfamily – metaboloid sensors of the eukaryotic cell. *Annu. Rev. Biochem.* 67, 821–855
11 Yang, X. *et al.* (1994) A family of proteins containing a conserved domain that mediates interaction with the yeast SNF1 protein kinase complex. *EMBO J.* 13, 5878–5886.
12 Tu, J. and Carlson, M. (1995) REG1 binds to protein phosphatase type 1 and regulates glucose repression in *Saccharomyces cerevisiae. EMBO J.* 14, 5939–5946
13 Lutfiyya, L.L. and Johnston, M. (1996) Two zinc-finger-containing repressors are responsible for glucose repression of SUC2 Expression. *Mol. Cell. Biol.* 16, 4790–4797
14 Treitel, M.A. and Carlson, M. (1995) Repression by SSN6–TUP1 is directed by MIG1, a repressor/activator protein. *Proc. Natl. Acad. Sci. U. S. A.* 92, 3132–3136
15 Lutfiyya, L.L. and Johnston, M. Characterization of the three related glucose repressors and genes they regulate in *Saccahromyces cerevisiae. Genetics* (in press)
16 Devit, M. *et al.* (1997) Regulated nuclear translocation of the Mig1 glucose repressor. *Mol. Biol. Cell.* 8, 1603–1618
17 Woods, A. *et al.* (1994) Yeast SNF1 is functionally related to mammalian AMP-activated protein kinase and regulates Acetyl-CoA Carboxylase *in vivo. J. Biol. Chem.* 269, 19509–19515
18 Wilson, W.A. *et al.* (1996) Glucose repression/derepression in budding yeast: SNF1 kprotein kinase is activated by phosphorylation under derepressing conditions, and this correlates with a high AMP:ATP ratio. *Curr. Biol.* 6, 1426–1434
19 Treitel, M.A. *et al.* (1998) Snf1 protein kinase regulates phosphorylation of the Mig1 repressor in *Saccharomyces cerevisiae. Mol. Cell. Biol.* 18, 6273–6280
20 Ludin, K. *et al.* (1998) Glucose-regulated interaction of a regulatory subunit of protein phosphatase 1 with the Snf1 protein kinase in *Saccharomyces cerevisiae. Proc. Natl. Acad. Sci. U. S. A.* 95, 6245–6250
21 Jiang, R. and Carlson, M. (1996) Glucose regulates protein interactions within the yeast SNF1 protein kinase complex. *Genes Dev.* 10, 3105–311
22 Jiang, R. and Carlson, M. (1997) The Snf1 protein kinase and its activating subunit, Snf4, interact with distinct domains of the Sip1/Sip2/Gal83 component in the kinase complex. *Mol. Cell. Biol.* 17, 2099–2106
23 Tu, J. and Carlson, M. (1994) The GLC7 type 1 protein phosphatase is required for glucose repression in *Saccharomyces cerevisiae. Mol. Cell. Biol.* 14, 6789–6796
24 Estruch, F. *et al.* (1992) N-terminal mutations modulate yeast SNF1 protein kinase function. *Genetics* 132, 639–650
25 Woods, A. *et al.* (1994) Yeast SNF1 is functionally related to mammalian AMP-activated protein kinase and regulates acetyl-CoA carboxylase *in vivo. J. Biol. Chem.* 269, 19509–19515
26 Stapleton, D. *et al.* (1994) Mammalian 5'-AMP-activated protein kinase non-catalytic subunits are homologs of proteins that interact with yeast Snf1 protein kinase. *J. Biol. Chem.* 269, 29343–29346
27 De Winde, J.H. *et al.* (1996) Differential requirement of the yeast sugar kinases for sugar sensing in establishing the catabolite-repressed state. *Eur. J. Biochem.* 241, 633–643
28 Gancedo, C. and Gancedo, M. (1985) Phosphorylation of 3-O-methyl-D-glucose and catabolite repression in yeast. *Eur. J. Biochem.* 148, 593–597
29 Gancedo, J.M. (1992) Carbon catabolite repression in yeast. *Eur. J. Biochem.* 206, 297–313
30 Meijer, M.M.C. *et al.* (1998) Glucose repression in *Saccharomcyes cerevisiae* is related to the glucose concentration rather than the glucose flux. *J. Biol. Chem.* 273, 24102–24107
31 Hardie, D.G. and Carling, D. (1997) The AMP-activated protein kinase. Fuel guage of the mammalian cell? *Eur. J. Biochem.* 246, 259–273
32 Halford, N.G. *et al.* (1994) Investigating the role of plant SNF1-related protein kinases. *Biochem. Soc. Trans.* 22, 953–957
33 Foretz, M. *et al.* (1998) AMP-activated protein kinase inhibits the glucose-activated expression of fatty acid synthase gene in rat hepatocytes. *J. Biol. Chem.* 273, 14767–14771
34 Leclerc, I. *et al.* (1998) The 5'-AMP-activated protein kinase inhibits the transcriptional stimulation by glucose in liver cells, acting through the glucose response complex. *FEBS Lett.* 431, 180–184
35 Muller, S. *et al.* (1995) Different internal metabolites trigger the induction of glycolytic gene expression in *Saccharomyces cerevisiae. J. Bacteriol.* 177, 4517–4519
36 Özcan, S. and Johnston, M. (1995) Three different regulatory mechanisms enable yeast hexose transporter (HXT) genes to be induced by different levels of glucose. *Mol. Cell. Biol.* 15, 1564–1572
37 Özcan S. *et al.* (1996) Rgt1p of S. *cerevisiae*, a key regulator of glucose-induced genes, is both an activator and repressor of transcription. *Mol. Cell. Biol.* 16, 6419–6426
38 Li, F. and Johnston, M. (1997) Grr1 of *Saccharomyces cerevisiae* is connected to the ubiquitin proteolysis machinery through Skp1: coupling glucose sensing to gene expression and the cell cycle. *EMBO J.* 16, 101–110
39 Kishi, T. *et al.* (1998) Grr1 functions in the ubiquitin pathway in *Saccharomyces cerevisiae* through association with Skp1. *Mol. Gen. Genet.* 257, 143–148
40 Kruckeberg, A.L. (1996) The hexose transporter family of *Saccharomyces cerevisiae. Arch. Microbiol.* 166, 283–292
41 Boles, E. and Hollenberg, C.P. (1997) The molecular genetics of hexose transport in yeasts. *FEMS Micro. Rev.* 21, 85–111
42 Özcan, S. *et al.* (1996) Two glucose transporters in *Saccharomyces cerevisiae* are glucose sensors that generate a signal for induction of gene expression. *Proc. Natl. Acad. Sci. U. S. A.* 93, 12428–12432
43 Reifenberger, E. *et al.* (1997) Kinetic characterization of individual hexose transporters of *Saccharomyces cerevisiae* and their relation to the triggering mechanisms of glucose repression. *Eur. J. Biochem.* 245, 324–333
44 Özcan, S. and Johnston, M. (1996) Two different repressors collaborate to restrict expression of yeast glucose transporter genes HXT2 and HXT4 to low levels of glucose. *Mol. Cell. Biol.* 1996; 16, 5536–5545
45 Bai, C. *et al.* (1996) SKP1 connects cell cycle regulators to the ubiquitin proteolysis machinery through a novel motif, the F-box. *Cell* 86, 263–274
46 Skowyra, D. *et al.* (1997) F-box proteins are receptors that recruit phosphorylated substrates to the SCF ubiquitin-ligase complex. *Cell* 91, 209–219
47 Patton, E.E. *et al.* (1998) Combinatorial control in ubiquitin-dependent proteolysis: don't Skp the F-box hypothesis. *Trends Genet.* 14, 236–243
48 Barral, Y. *et al.* (1995) G1 cyclin turnover and nutrient uptake are controlled by a common pathway in yeast. *Genes Dev.* 9, 399–409
49 Jaquenoud, M. *et al.* (1998) The Cdc42p effector Gic2p is targeted for ubiquitin-dependent degradation by the SCF^{Grr1} complex. *EMBO J.* 18, 5360–5373
50 Johnson, E.S. and Blobel, G. (1997) Ubc9 is the conjugating enzyme for the ubiquitin-like protein Smt3p. *J. Biol. Chem.* 272, 26799–26802
51 Lammer D. *et al.* (1998) Modification of yeast Cdc53p by the ubiquitin-related protein Rub1p affects function of the SCF^{Cdc4} complex. *Genes Dev.* 12, 914–926
52 Wendell, D.L. and Bisson, L.F. (1994) Expression of high-affinity glucose transport protein Hxt2p of *Saccharomyces cerevisiae* is both repressed and induced by glucose and appears to be regulated posttranslationally. *J. Bacteriol.* 176, 3730–3737
53 Marshall-Carlson, L. *et al.* (1990) Mutational analysis of the SNF3 glucose transporter of *Saccharomyces cerevisiae. Mol. Cell. Biol.* 10, 1105–1115
54 Özcan, S. *et al.* (1998) Glucose sensing and signaling by two glucose receptors in the yeast *Saccharomyces cerevisiae. EMBO J.* 17, 2566–2573
55 Coons, D.M. *et al.* (1997) The C-terminal domain of Snf3p is sufficient to complement the growth defect of snf3 null mutations in *Saccharomyces cerevisiae*: SNF3 functions in glucose recognition. *Yeast* 13, 9–20
56 Vagnoli, P. *et al.* (1998) The C-terminal domain of Snf3p mediates glucose-responsive signal transduction in *Saccharomyces cerevisiae. FEMS Micro. Lett.* 160, 31–36
57 Efrat, S. *et al.* (1994) The pancreatic beta-cell glucose sensor. *Trends Biochem. Sci.* 19, 535–538
58 Newgard, C.B. and McGarry, J.D. (1995) Metabolic coupling factors in pancreatic beta-cell signal transduction. *Ann. Rev. Biochem.* 64, 689–719
59 Madi, L. *et al.* (1997) *rco-3*, a gene involved in glucose transport and conidiation in *Neurospora crassa. Genetics* 146, 499–508
60 Ruegger, M. *et al.* (1998) The TIR1 protein of *Arabidopsis* functions in auxin response and is related to human SKP2 and yeast Grr1p. *Genes Dev.* 12, 198–207
61 Xie, D-X. *et al.* (1998) *COI1*: An *Arabidopsis* gene required for jasmonate-regulated defense and fertility. *Science* 280, 1091–1094
62 Zhang, H. *et al.* (1995) p19Skp1 and p45Skp2 are essential elements of the cyclin A–CDK2 S phase kinase. *Cell* 82, 915–925