11-1-2013

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Published in final edited form as:
Biochim Biophys Acta. 2013 November ; 1830(11): 5204–5210. doi:10.1016/j.bbagen.2013.07.025.

The glucose signaling network in yeast

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Abstract

Background—Most cells possess a sophisticated mechanism for sensing glucose and responsing to it appropriately. Glucose sensing and signaling in the budding yeast *Saccharomyces cerevisiae* represents an important paradigm for understanding how extracellular signals lead to changes in the gene expression program in eukaryotes.

Scope of review—This review focuses on the yeast glucose sensing and signaling pathways that operate in a highly regulated and cooperative manner to bring about glucose-induction of *HXT* gene expression.

Major conclusions—The yeast cells possess a family of glucose transporters (*HXT*s), with different kinetic properties. They employ three major glucose signaling pathways— Rgt2/Snf3, AMPK, and cAMP-PKA—to express only those transporters best suited for the amounts of glucose available. We discuss the current understanding of how these pathways are integrated into a regulatory network to ensure efficient uptake and utilization of glucose.

General significance—Elucidating the role of multiple glucose signals and pathways involved in glucose uptake and metabolism in yeast may reveal the molecular basis of glucose homeostasis in humans, especially under pathological conditions, such as hyperglycemia in diabetics and the elevated rate of glycolysis observed in many solid tumors.

Keywords

Glucose uptake and metabolism; glucose transporters; glucose signaling pathways; yeast; cancer

1. Introduction

Glucose serves as a metabolic substrate as well as a signaling molecule that regulates physiological and pathological processes [1-5]. Mammals maintain a constant level of

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glucose in the bloodstream despite intermittent supplies from the gut, and impaired regulation of blood glucose levels causes severe disorders such as diabetes [5,6]. Metastasized tumor cells metabolize large amounts of glucose through glycolysis and produce copious amounts of lactic acid even in the presence of oxygen [7,8], called the Warburg effect, a hallmark of cancer [9]. The well-established elevated glucose consumption of malignant tissue forms the basis of the clinical imaging of cancer, PET (positron emission tomography) [10]. Therefore, normal cells sense glucose levels in their environment and adapt central metabolic pathways to glucose availability [5]. Dysregulation of these pathways likely induces the glycolytic phenotype—increased glycolysis—in cancer cells [7,8].

Glucose is by far the preferred energy source of the budding yeast *S. cerevisiae*, because glucose regulation dictates the organism's distinctive fermentative lifestyle—aerobic ethanol fermentation (the Crabtree effect) [11,12]. This is mediated, in part, by the crosstalk between the two glucose signaling pathways: 1) the Rgt2/Snf3 glucose induction pathway responsible for glucose uptake [1,13,14]; 2) the Snf1/Mig1 glucose repression pathway that negatively regulates the genes involved in the glucose oxidation and the use of alternative sugars [15-17]. Because the generation of the glucose repression signal that inhibits the activity of the Snf1 kinase (the yeast homolog of AMPK) requires glucose uptake and metabolism [18], yeast cells likely lock the signaling pathways in a cross talking network to determine its sensitivity to environmental changes in glucose availability [3,19,20]. The mechanistic basis of the Warburg effect in tumor cells, though not well understood, shows some remarkable similarities to the mechanism responsible for this phenomenon in yeast [14,21].

Since energy generation by fermentation is inefficient, yeast cells pump a large amount of glucose through glycolysis by enhancing the first, rate-limiting step of glucose metabolism —its uptake [1,22]. They do so by increasing expression of glucose transporter (*HXT*) genes. *S. cerevisiae* possesses at least six members of glucose transporter family (Hxt1, 2, 3, 4, 6, and 7), each with different affinities for glucose in order to cope with environmental changes in glucose availability [22,23]. The yeast cells have evolved mechanisms for sensing glucose over a broad concentration range and respond to it promptly and appropriately [3,19,20,24]. They express only those glucose transporters best suited for the amount of glucose available in the environment: the low affinity glucose transporter Hxt1 is only expressed when glucose levels are high (> ~1%); in contrast, the high-affinity glucose transporters Hxt2 and Hxt4 are expressed when glucose levels are low (~0.2%); the intermediate-affinity glucose transporter Hxt3 is expressed in both low and high glucose concentrations [1,25]. Expression of the high affinity glucose transporters Hxt6 and Hxt7 is highly induced under low glucose conditions or in the presence of non-fermentable carbon sources such as glycerol or ethanol, but is strongly repressed by high concentrations of glucose [26-28]. In addition, Hxt6 and Hxt7 are subject to glucose-induced degradation in the vacuole [29]. In this review, we focus on the crosstalk between the glucose signaling pathways that leads to induction of *HXT* gene expression in yeast, as a model to study how cells sense glucose and adapt their gene expression program to glucose availability.

2. Key components of the *HXT* gene repressor complex

Rgt1 binds to the upstream regulatory region of the *HXT* genes in the absence of glucose and brings about repression by recruiting the general repressor complex Ssn6-Tup1. Rgt1 does so in conjunction with the glucose responsive transcription factors Mth1 and Std1. These components form a repressor complex that inhibits transcription of *HXT* genes in the absence of glucose. A unique feature of Rgt1-mediated repression is that, unlike other repressors, Rgt1 cannot recruit Ssn6-Tup1 directly; the interaction between Rgt1 and Ssn6-Tup1 requires Mth1 (Fig. 1). The respective roles of the three components—Rgt1, Mth1/

Std1, and Ssn6-Tup1—in the formation of this complex are discussed in the context of a current model of Rgt1-mediated repression. Rgt1 recognizes a consensus sequence of 5'-CGGANNA-3' (N is any nucleotide) and binds to multiple copies of the DNA sequence in a nonadditive, synergistic manner [30,31]. Functional studies of synthetic, multimerized Rgt1-binding sites without intervening sequences show that reporter genes containing 2 or 3 Rgt1-binding sites provide 2- to 3-fold repression and that those containing 4 and 6 such sites bring about 30- and 90-fold repression, respectively [30-32].

2.1, The Rgt1 repressor

Rgt1 is a member of the Gal4 family of transcription factors that contains the zinc binuclear cluster (Cys_6Zn_2) DNA-binding domain [33]. Most members of the family bind as dimers to two 'CGG' triplets, whereas Rgt1 lacks the coiled-coil dimerization domain and thus binds DNA as a monomer [30]. This synergistic repression is probably due to efficient recruitment of Rgt1 to multiple binding sites [32]. Thus, Rgt1, as a monomer, functions more efficiently through its multiple sites. This is reminiscent of the *Aspergillus nidulans* transcriptional activator AlcR, which binds DNA as a monomer but functions synergistically through multiple sites [34]. Rgt1 is dissociated from the *HXT* promoters within 10 min after addition of glucose to glucose-depleted cultures. Rgt1 is phosphorylated at a basal level in the absence of glucose and hyperphosphorylated by PKA in high levels of glucose. Hyperphosphorylated Rgt1 does not bind DNA, whereas dephosphorylation of Rgt1 *in vitro* restores its DNA-binding ability [30,35,36]. Accordingly, the inhibition of Rgt1 phosphorylation is critical for the formation of the repressor complex (Fig. 1A).

2.2, The glucose responsive transcription factors Mth1 and Std1

Mth1 and Std1 are paralogous proteins that play a key role in regulation of Rgt1 function [37,38]. The main lines of supporting evidence are: 1) *HXT* gene expression is constitutive in the absence of Mth1 and Std1 [37-40] ; 2) Rgt1 does not bind to *HXT* promoters in yeast cells lacking both *MTH1* and *STD1* genes [35,36] ; 3) Mth1 and Std1 directly interact with Rgt1 [40-42]. Since Rgt1 is hyperphosphorylated in the *mth1std1* mutant, Mth1 and Std1 are thought to serve as Rgt1 regulators that modulate the phosphorylation state of Rgt1 [36]. Mth1 and Std1 are downregulated by glucose; they are ubiquitinated by the SCF^{Grr1} ubiquitin ligase complex and degraded via the 26S proteasome in response to glucose [35,43-45] (Fig. 1B). There are also dominant mutations in the *MTH1* gene (*HTR1*-23, *DGT1* or *BCP1*[46,47]) that render Mth1 resistant to glucose-induced degradation [48]. Accumulating evidence shows that Mth1 and Std1 may be not functionally redundant. Deletion of the *STD1* gene alone has little effect on the phosphorylation [42] and DNA-binding of the Rgt1 repressor [35] and the expression of *HXT* genes [48]. Furthermore, transcriptome analysis shows that expression of major *HXT* genes is profoundly upregulated in an *mth1* mutant but is not significantly changed in a *std1* mutant [49]. Therefore, Mth1 but not Std1 seems to be the major regulator of Rgt1, and the role of Mth1 in Rgt1-mediated repression is to block PKA-dependent Rgt1 phosphorylation in the absence of glucose.

2.3, The general corepressor complex Ssn6-Tup1

The Ssn6-Tup1 complex is a general transcriptional corepressor complex, composed of one molecule of Ssn6 and four molecules of Tup1 [50]. The complex contains the tetratrico peptide repeat (TPR) and WD domains, respectively, which serve as protein-protein interaction motifs [51-55]. Ssn6-Tup1 is recruited to its target promoters by sequence-specific DNA-binding repressors [56,57] and mediates transcriptional repression by recruiting global corepressors such as chromatin and nucleosome remodelers [58,59] and/or by interacting with the RNA transcription machinery [56,57]. Ssn6-Tup1 also appears to be involved in the induction of gene expression [60-62] and recruited to its target promoters in a manner independent of sequence-specific DNA-binding proteins [62-65]. In addition,

Ssn6-Tup1 is shown to exert its function by masking the activation domain of a DNA-binding repressor and thereby preventing recruitment of the coactivators necessary for transcriptional activation [66].

Rgt1-mediated repression requires the Ssn6-Tup1 complex [33]. Rgt1 interacts with Ssn6 via the N-terminal domain (aa 210-250), located close to the Zn cluster DNA-binding motif [42]. However, recent studies show that Ssn6-Tup1 negatively regulates the DNA-binding ability of Rgt1. It does so in two ways: (1) by directly interfering with Rgt1 DNA-binding [67]; (2) by repressing expression of the *MTH1* gene via the Snf1-Mig1 pathway [13]. The inhibitory function of Ssn6-Tup1 on Rgt1 is antagonized by Mth1 but becomes effective when Mth1 is degraded in high glucose conditions. The interaction of Rgt1 with Ssn6-Tup1 is unstable and readily dissociated in the absence of Mth1, establishing the role of Mth1 in Rgt1-Ssn6-Tup1 interaction [67] (Fig. 1A).

2.4, Ssn6-Tup1 regulates glucose induction and repression of gene expression

The finding that Ssn6-Tup1, although required for Rgt1-mediated repression, acts to inhibit Rgt1 function provides a new concept of how Ssn6-Tup1 can be appropriately targeted by distinct DNA-binding repressors [67]. Although the biological significance of this phenomenon is not fully understood, it can be related to the differential regulation of Ssn6-Tup1 target genes in response to glucose (Fig. 2). In high glucose conditions, the glucose repressor Mig1 recruits Ssn6-Tup1 to bring about repression of its target genes [68,69]; in contrast, Rgt1 is dissociated from Ssn6-Tup1, leading to derepression of Rgt1-repressed genes. Ssn6-Tup1 is actively involved in preventing the interaction with Rgt1 not only by repressing expression of the *MTH1* gene but also by interfering with the DNA-binding ability of Rgt1 (Fig. 2A and see below). As a result, Ssn6-Tup1 does not interact with Rgt1 while in association with Mig1 in high glucose conditions, leading to highly regulated control of the glucose induction and repression of glucose-regulated genes. Thus, the two glucose responsive repressors Rgt1 and Mig1 are regulated in a similar manner [17,70]. Ssn6-Tup1 is recruited to unphosphorylated Mig1, but not to phosphorylated Mig1 (Fig. 2B). Similarly, the Rgt1-Ssn6-Tup1 interaction is disrupted when Rgt1 is hyperphosphorylated. Therefore, Mig1 and Rgt1 employ phosphorylation as a mechanism to regulate their interaction with Ssn6-Tup1.

3. Mechanism of glucose-induction of *HXT* gene expression

Glucose induces expression of the *HXT* genes by inhibiting the function of Mth1 and Rgt1. Mth1 mRNA and protein levels are down-regulated by glucose via the aforementioned glucose signaling pathways. Rgt1 is phosphorylated by the third glucose signaling pathway, the cAMP-activated kinase (PKA) pathway, which occurs when Mth1 is removed. Thus, three glucose signaling pathways converge at multiple points to induce expression of the *HXT* genes (Fig. 3).

3.1, Proteasomal degradation of Mth1 via the Rgt2/Snf3 pathway

The glucose signal that leads to the proteasomal degradation of Mth1 and Std1 is generated by the two glucose transporter-like proteins Rgt2 and Snf3. These plasma membrane proteins are evolutionarily derived from glucose transporters, with 12 predicted transmembrane spanning domains, but appear to have lost the ability to transport glucose into the cell [71]. The supporting evidence is that growth defect of the *hxt*-null mutant deleted for the seven *HXT* genes (*HXT1-7*[23,26,72]) on glucose is suppressed by expression of any one of the seven *HXT* genes, but not of the *RGT2* or *SNF3* gene [73]. Furthermore, there are constitutive mutations in the glucose sensor genes (*SNF3-1* and *RGT2-1*) that are thought to convert the proteins into the glucose-bound forms and cause

glucose-independent expression of the *HXT* genes [73]. Thus, the prevailing view is that Rgt2 and Snf3 act as cell surface glucose receptors that initiate signal transduction in response to glucose [1,14].

Rgt2 and Snf3 are activated by different levels of glucose, presumably due to their different affinities for glucose. Rgt2 is activated by high levels of glucose and generates a signal that stimulates expression of low affinity glucose transporters such as Hxt1 and Hxt3. Snf3 generates a glucose signal in response to low levels of glucose, which stimulates expression of high affinity glucose transporters such as Hxt2 and Hxt4 [38]. A central player in the transduction of the signal generated by Rgt2 and Snf3 may be the yeast casein kinase I (Yck1 and Yck2), tethered to the plasma membrane through palmitoylation of the C-terminal Cys-Cys sequence by the palmitoyl transferase Akr1 [74-76]. A current view is that glucose-binding to the glucose sensors induces a change in their conformation that activates Yck1/2 [43], which in turn catalyzes phosphorylation of Mth1 and Std1 [43,45]. This phosphorylation marks Mth1 and Std1 for ubiquitination by the SCF^{Grr1} ubiquitin protein ligase and subsequent degradation by the proteasome [35,44,48]. This scenario is supported by the observation that glucose sensors interact with Mth1 and Std1 through their C-terminal, cytoplasmic tails [38,39]. However, a recent study demonstrated that Mth1 degradation occurs without a direct coupling between the glucose sensors and Yck1/2 [45]. Accordingly, there may be an unidentified mechanism for transduction of the glucose signal to Mth1 and Std1.

3.2, Repression of *MTH1* gene expression by the Snf1-Mig1 pathway

Expression of the *MTH1* gene is repressed by glucose via the Snf1-Mig1 pathway. The Snf1 kinase, the yeast homolog of mammalian AMP-activated protein kinase (AMPK), is a heterotrimer composed of the Snf1 catalytic subunit (α), the Snf4 regulatory subunit (γ), and one of the three β–subunits (Sip1, Sip2 or Gal83) that seem to serve as a scaffold in the Snf1 complex. Snf1 activation requires phosphorylation at Thr210 by its upstream kinases (Sak1, Tos3 and Elm1) when glucose is limited [77,78]. Glucose appears to stimulate dephosphorylation of Snf1 by the Reg1-Glc7 PP1 phosphatase at the same Thr^{210}, leading to the conversion of Snf1 from an active to an inactive conformation [79,80]. Snf1 phosphorylates and negatively regulates the Mig1 repressor in glucose-limited conditions; glucose-induced inactivation of Snf1 leads to dephosphorylation and activation of Mig1. Activated Mig1 represses expression of many glucose-repressed genes, such as *SUC2*, *GAL1* and *GAL4*[68,69]. Expression of the *MTH1* gene is repressed by Mig1 and Mig2 in high glucose conditions [13]. Therefore, the extent and rate of Mth1 degradation is substantially reduced in cells missing Mig1 and Mig2 or lacking their binding site in the *MTH1* promoter [48]. The purpose of this regulation is to ensure rapid removal of Mth1 from cells when glucose becomes available so as to enable prompt induction of *HXT* gene expression.

3.3, PKA-mediated Rgt1 phosphorylation disrupts its interaction with Ssn6-Tup1

The third pathway known to affect expression of *HXT* genes is the one that activates the cAMP-dependent protein kinase A (PKA) [81,82]. PKA is involved in many different cellular processes including cell growth, stress resistance, and metabolism [83-86]. PKA is inactive during non-fermentative growth, existing as a tetrameric holoenzyme composed of two catalytic subunits encoded by one of three redundant *TPK* genes (*TPK1*, *TPK2* and *TPK3*) and two regulatory subunits encoded by *BCY1*[87,88]. Addition of glucose to yeast cells grown on a non-fermentable carbon source induces a rapid elevation of cAMP levels due to glucose activation of adenylate cyclase (Cyr1) via the Gpr1/Gpa2 and the Ras1/Ras2 pathways [89-92]. Binding of cAMP to the Bcy1 inhibitory subunit of PKA liberates the catalytic subunits, leading to their activation [93]. A role of PKA in regulation of Rgt1 is

implicated from the observation that glucose-induction of *HXT1* gene expression is abolished in cells with attenuated PKA activity [81,82]. PKA phosphorylates Rgt1 at four serine residues in the amino-terminal region of Rgt1 and modulates its function [81,94], resulting in dissociation of Rgt1 from Ssn6-Tup1 and eventually from the *HXT* promoters [67]. The observation that Rgt1 phosphorylation by PKA does not occur until the Rgt1-Mth1/Std1-Ssn6-Tup1 repressor complex is disrupted suggests that the PKA sites in Rgt1 are available for phosphorylation upon glucose-induced degradation of Mth1.

4. Crosstalk between glucose signaling pathways ensure stringent regulation of glucose utilization

The three glucose signaling pathways play distinctive but interacting roles for glucose induction of *HXT* gene expression (Fig. 3). Glucose induced inactivation of Mth1 is a crucial event for modulating Rgt1 function. Indeed, Mth1 levels are tightly controlled in a feed-forward manner by coordination of the glucose induction and repression pathways. In addition, the glucose repression signal that inactivates Snf1 kinase is generated through glucose metabolism [18].

4.1, Integration of glucose induction and glucose repression pathways in a regulatory network

A gene expression profiling study indicated that the Rgt2/Snf3 glucose induction and the Snf1-Mig1 glucose repression pathways are intertwined in a regulatory network [13]. Glucose stimulates the proteasome-mediated degradation of Mth1 via the Rgt2/Snf3 pathway while also reducing *MTH1* expression via the Snf1-Mig1 pathway [35,43,48], reinforcing the inhibitory effect of glucose on Mth1 function and ensuring maximal glucose induction of Rgt1-repressed genes. Glucose inhibits Std1 function by stimulating its degradation; it also induces *STD1* gene expression through the Rgt2/Snf3 pathway [13]. Therefore, the feedback control of *STD1* gene expression acts to counteract the glucose-induced degradation of Std1 and thus provides for a rapid reestablishment of repression when glucose is depleted. This may contribute to the regulation of glucose repression, because Snf1 activity is enhanced by Std1 [95]. Mig2 is a glucose repressor and collaborates with Mig1 in repression of most glucose-repressed genes. Mig1 and Mig2 bind to the identical DNA sequences but are differently regulated [96,97]. Mig2, unlike Mig1, is not regulated by Snf1, but its expression is induced by glucose via the Rgt2/Snf3 pathway [13]. Therefore, glucose repression is a result of outputs from two glucose signal transduction pathways: the Mig1 component regulated by the Snf1 kinase and the Mig2 component regulated at the level of their transcription by the Snf3/Rgt2 signaling pathway. Expression of the *SNF3* gene is repressed by the Snf1-Mig1 pathway in high levels of glucose, enabling Snf3 to function only in low glucose conditions [13]. Hxk2 is the most active hexokinase isoenzyme during growth on glucose in the cytoplasm, while it interacts with components repressing expression of several glucose-repressed genes in the nucleus [4]. Glucose induces expression of the *HXK2* gene via the Rgt2/Snf3 pathway, providing another functional link between glucose induction and repression pathways [82].

4.2, The glucose repression signal is generated through glucose metabolism

Although the glucose-induced inactivation of Snf1 appears to be critical for establishing glucose repression, the nature of the glucose repression signal that inhibits Snf1 activity is not clearly defined. The AMP-activated protein kinase (AMPK) is known to be activated by an elevated AMP:ATP ratio upon glucose depletion [98]. The AMP:ATP ratio increases more than 200-fold upon glucose removal and decreases when glucose is added. However, Snf1 activity is not directly regulated by the AMP:ATP ratio [99]. Instead, it has been speculated that glucose-6-phosphate (G-6-P) might serve as a glucose repression signal

based on the observations that: (1) Snf1 is constitutively active in a *hxk1hxk2glk1* deletion mutant; (2) addition of the glucose analog 2-deoxyglucose, which can be phosphorylated but not further metabolized, to glycerol-grown cells results in the decreased activity of Snf1; (3) Snf1 activity is not affected by 6-deoxyglucose, which cannot be phosphorylated [100,101]. However, the observations that glucose repression may be related to the glucose concentration rather than glucose flux suggest that the glucose repression signal appears to be upstream of G-6-P [102,103]. In this regard, Ozcan has demonstrated that glucose repression of the Mig1 target genes is abolished in a mutant lacking all 17 hexose transporters or the Rgt2 and Snf3 glucose sensors [18]. Hence, regulation of glucose-induction of *HXT* gene expression plays an important role in the generation of the glucose repression signal, highlighting how glucose induction and glucose repression of gene expression is coordinated to ensure tight control of glucose uptake and metabolism.

5. Conclusions

Glycolysis is facilitated by increased glucose uptake. Glucose uptake in *S. cerevisiae* is a complex process, most notably due to proliferation of glucose transporters and multiple, parallel pathways for signaling glucose availability. In terms of displaying glycolytic phenotype, *S. cerevisiae* and tumor cells share several features. Expression of human glucose transporters (GLUTs) is upregulated by Hif-1α in tumor cells [104]. Hif1, like Rgt1, is regulated by ubiquitin-mediated degradation [105,106]. Snf1/AMPK is a low energy checkpoint, acting as the prime energy sensor in response to energy depletion, and its activation mechanism is conserved in eukaryotes. Several current diabetes therapeutics, such as metformin and thiazolidinediones (TZDs), are thought to lower blood glucose and increase insulin sensitivity by activating AMPK in peripheral tissues [107]. The upstream activating kinase of AMPK is LKB1, which is associated with Peutz-Jeghers cancer-susceptibility syndrome (PJS) [108]. More importantly, AMPK phosphorylates and activates the tumor suppressor TSC2, a critical negative regulator of mTOR (mammalian target of rapamycin) [109]. In addition, the finding that mTOR is a central activation point for expression of Hif-1α independent of oxygen levels implicates the role of AMPK in regulation of glucose transporters [110]. Thus, AMPK, like Snf1, is actively involved in glucose uptake and metabolism. These similarities indicate that further understanding of glucose sensing and signaling mechanisms in yeast may reveal the molecular basis of the enhanced glucose uptake in cancer cells and provide clues for developing therapeutic strategies.

Acknowledgments

This work was supported by NIH Grant GM087470 from the National Institute of General Medical Sciences.

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Highlights

1. The budding yeast *S. cerevisiae*, like tumor cells, exhibits aerobic glycolysis.
2. The yeast possesses a family of glucose transporters (*HXT*s) with different kinetic properties.
3. Expression of HXT genes regulated by the crosstalk between glucose signaling pathways

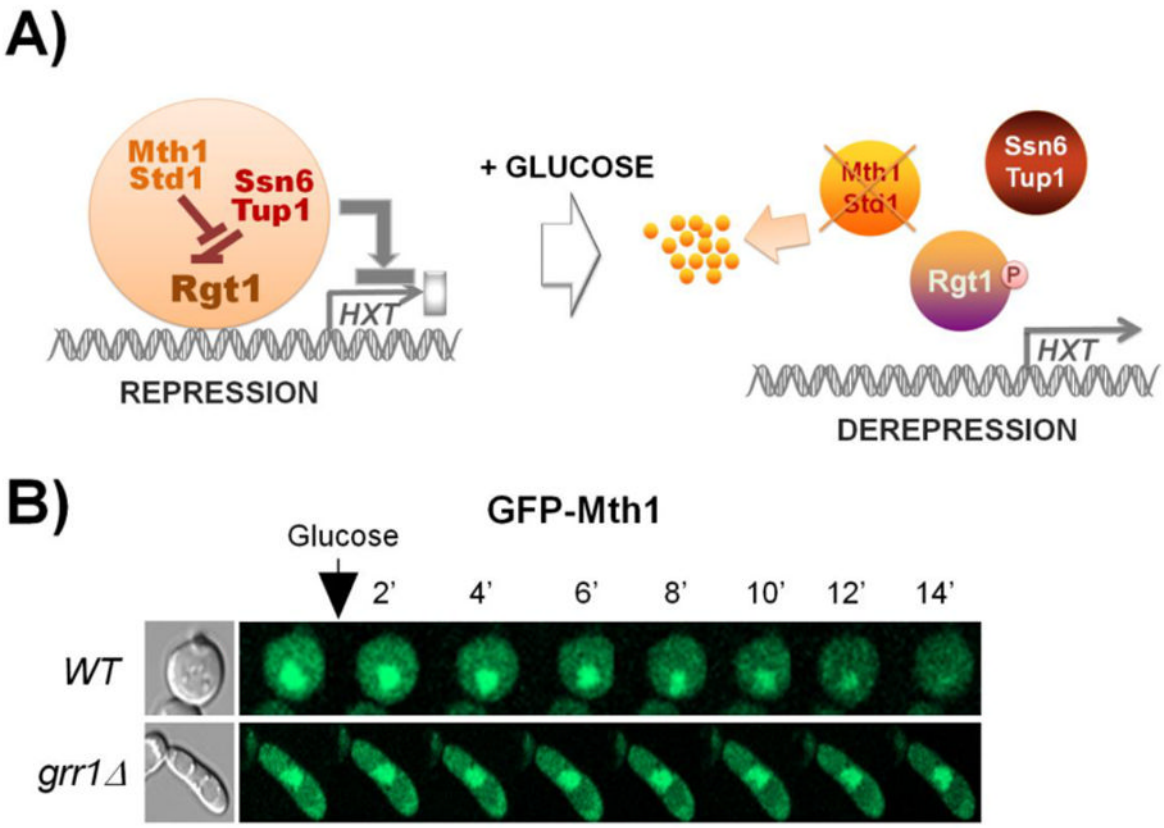

Fig. 1.

Mth1 is required for the interaction of Rgt1 with Ssn6-Tup1 that leads to repression of *HXT* gene expression; indeed, its inactivation is critical for glucose uptake and metabolism. A) Rgt1 recruits Ssn6-Tup1 in an Mth1-dependent manner and brings about repression of its target genes, such as *HXT* and *HXK2* genes. Std1 is a paralog of Mth1 but has little effect on regulating Rgt1 function. Glucose-induction of *HXT* gene expression is achieved by a two-step process: (1) Mth1 and Std1 are degraded by the ubiquitin-proteasome pathway, rendering the PKA phosphorylation sites in Rgt1 available for phosphorylation; (2) Rgt1 phosphorylation by PKA induces its dissociation from Ssn6-Tup1 and consequently from *HXT* promoters. B) Time-lapse observation of Mth1 degradation in high-glucose medium (4%). Mth1 and Std1 are ubiquitinated by the SCF^{Grr1} ubiquitin-ligase, and the ensuing ubiquitination of Mth1 and Std1 targets them to the proteasome for degradation. The figure was adapted from [45].

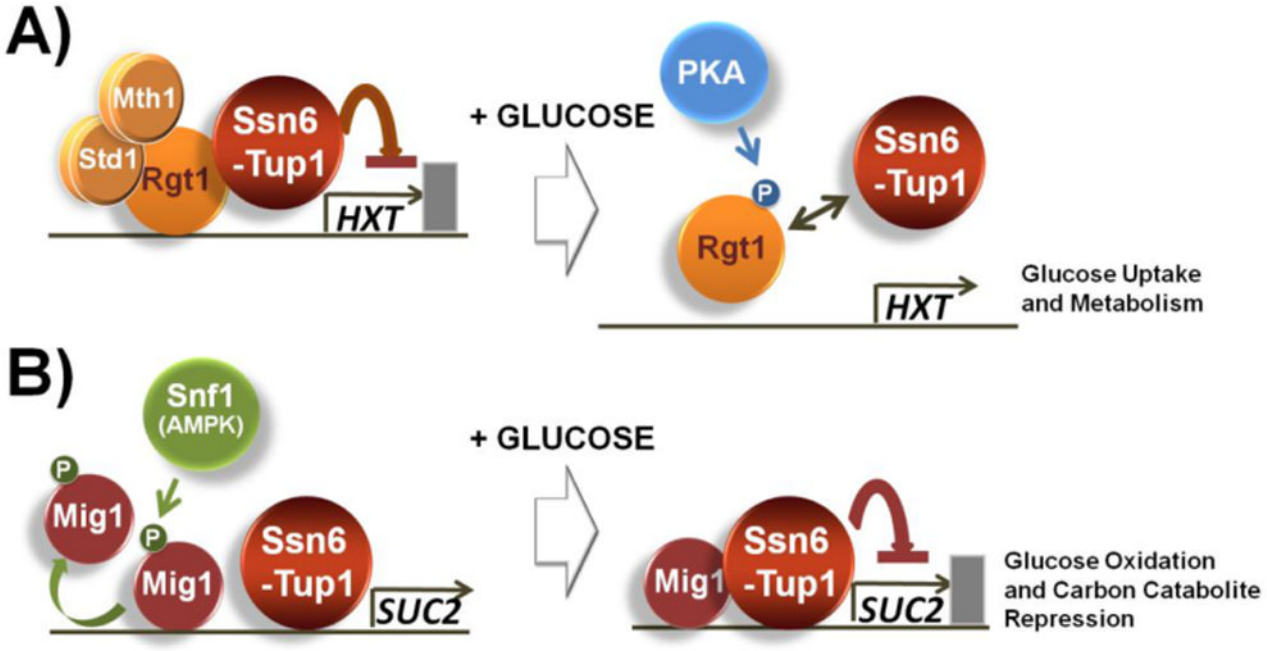

Fig. 2.

The two glucose responsive repressors Rgt1 and Mig1 are regulated in a similar manner. A) Rgt1 recruits Ssn6-Tup1 in the absence of glucose; however, it is hyperphosphorylated by PKA in the presence of high levels of glucose and dissociated from Ssn6-Tup1, resulting in the induction of expression of genes involved in glucose uptake and metabolism. B) Ssn6-Tup1 interacts with only unphosphorylated Mig1 in high levels of glucose and mediates the repression of genes involved in glucose oxidation and carbon catabolite repression. Snf1-dependent phosphorylation of Mig1 in glucose-limited conditions abolishes interaction with Ssn6-Tup1 [62].

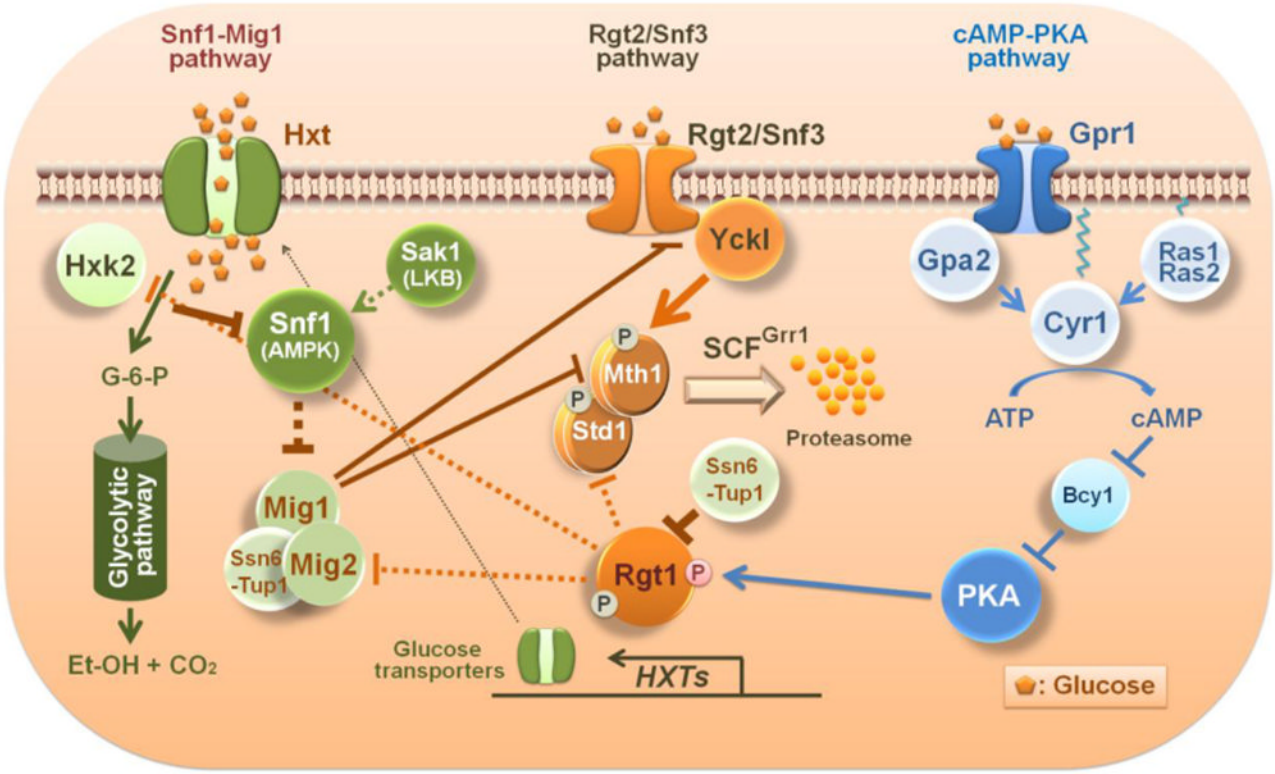

Fig. 3.

Schematic diagram of the crosstalk between glucose signaling pathways in yeast. Yck I (Yck1 and Yck2) phosphorylates Mth1 and Std1 upon activation by glucose-bound Rgt2 and Snf3 glucose sensors. Phosphorylated Mth1 and Std1 are ubiquitinated by the SCF^{Grr1} complex and degraded by the proteasome. The PKA phosphorylation sites in the amino terminal region of Rgt1 are exposed and available for phosphorylation when Mth1 is degraded. Phosphorylated Rgt1 is dissociated form Ssn6-Tup1 and subsequently from DNA, leading to derepression of Rgt1 target genes, such as the *HXT* and *HXK2* genes. The Rgt2/Snf3 pathway regulates itself through glucose-induction of *STD1* gene expression. Consequently, the *STD1* gene is expressed at the same time that the Std1 protein is degraded in response to glucose [13]. By contrast, glucose stimulates Mth1 degradation but also represses Mth1 expression via Mig1 and Mig2. Glucose uptake is required for the generation of the glucose repression signal that leads to inactivation of the Snf1 kinase [18]. Expression of the *MIG2* gene is induced by glucose via the Rgt2/Snf3 pathway. Glucose-repression of *SNF3* gene expression by Mig1 reflects the probable function of Snf3 as a high affinity glucose sensor, representing another important feature of the interaction between the glucose induction and repression pathways.