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Dynamic and diverse sugar signaling

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Sugars fuel life and exert numerous regulatory actions that are fundamental to all life forms. There are two principal mechanisms underlie sugar 'perception and signal transduction' in biological systems. Direct sensing and signaling is triggered via sugar-binding sensors with a broad range of affinity and specificity, whereas sugar-derived bioenergetic molecules and metabolites modulate signaling proteins and indirectly relay sugar signals. This review discusses the emerging sugar signals and potential sugar sensors discovered in plant systems. The findings leading to informative understanding of physiological regulation by sugars are considered and assessed. Comparative transcriptome analyses highlight the primary and dynamic sugar responses and reveal the convergent and specific regulators of key biological processes in the sugar-signaling network.

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Introduction

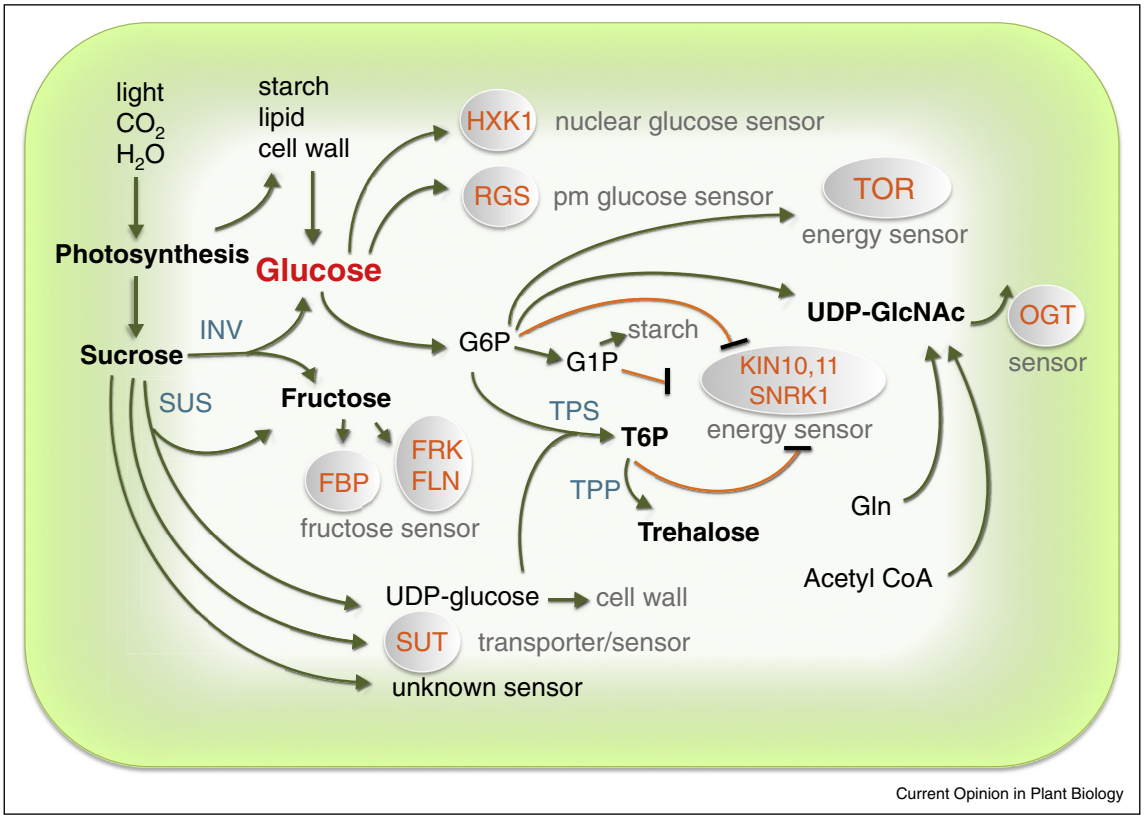
Sugars produced from plant photosynthesis play a central role to support and integrate the functions and actions of internal and external regulatory signals in driving diverse biological processes from embryogenesis to senescence. Although the knowledge on how plants produce, transport, metabolize, store and sense diverse sugar signals has been significantly advanced [1,2,3,4,5,6,7,8,9], the spectrum of sugar signals, sensors and molecular mechanisms mediating primary signaling remained to be fully explored. Many informative review articles presented recent progress on broad aspects of sugar-related research in plant biology, encompassing source-sink communication [9,10], sugar-hormone interactions [11], new sugar transporters and their functions [8], sugar regulation of plant development [9,12,13,14,15], chloroplast-nuclear signaling [16], sucrose, starch and trehalose metabolism and signaling [2,3,5,6,7,10,13,15,17], clock-sugar connections [18], as well as sugar and stress [19]. New discoveries on key regulators of sugar and energy signaling have also been thoroughly reviewed [4,5,20,21,22,23,24,25,26,27]. Extensive efforts of past research on sugar regulation have mainly focused on long-term phenotypic characterization in mutants and transgenic plants. The accumulated knowledge will provide an excellent and comprehensive platform for future research, especially on elucidating the molecular, cellular and biochemical basis of sugar sensing and signaling underlying the plasticity and potential in plant growth and development. Emphasis in this review is placed on the emerging understanding of the dynamic, primary and integrated sugar signaling mechanisms and transcriptional networks triggered by direct and indirect sugar signals via sugar, energy and metabolite sensors.

Sugar signals and intracellular sensors

The complex and intertwined plant metabolic and regulatory pathways provide plastic capacity to generate and regulate a wide range of sugar signals originated from different sources, including active photosynthetic cells, dynamic storage reservoir, and organs for nutrient remobilization (Figure 1) [2,4,6,7,9,19,28,29,30,31•,32•]. Understanding the physiological status and cellular/subcellular actions of each sugar signal relies on the recognition that sugar providing and perceiving cells, as well as sugar metabolic pathways and transport systems in different organs, tissues and cells, are subject to diverse modulations by other nutrient supplies, developmental stages, environmental cues, hormonal regulation, and interactions with microbes and animals [2,7,8,9,19,23,33,34•]. For instance, high sugar signals can either promote leaf development and photosynthesis with abundant nitrogen supplies or lead to photosynthesis gene repression and developmental arrest at low nitrate levels [35,36,37]. Plant sugar responses are also significantly influenced by phosphate levels [33]. Although sucrose is the main sugar for systemic transport from source to sink in plants [38], many of the sugar responses observed in plants are channeled through invertases or sucrose synthases [7,39] to generate glucose and other signaling sugars to trigger signal transduction via direct perception by diverse sensors or indirect signaling by energy and metabolite sensors. However, compelling evidence also supports multiple sucrose signaling pathways (Figure 1) [3,5].

Hexokinases (HXKs) are the first demonstrated intracellular glucose sensors in plants [4,23,36,37,40,41,42,43,44,45]. Plant genomes encode multiple hexokinases (HXKs) and HXK-like (HKL) proteins that appear to serve overlapping

Figure 1



Sugar signals and sensors. Distinct sugar signals are generated locally or systemically via diverse sources. FBP, fructose-1,6-bisphosphtase; FLN, fructokinase-like protein; FRK, fructokinase; G6P, glucose 6-phosphate; G1P, glucose 1-phosphate; Gln, glutamine; HXK1, hexokinase1; INV, invertase; KIN10,11, Arabidopsis protein kinase 10,11; OGT, O-linked N-acetylglucosamine (O-GlcNAc) transferase; pm, plasma membrane; RGS, regulator of G-protein signaling; SnRK1, sucrose-non-fermentation-related protein kinase1; SUS, sucrose synthase; SUT, sucrose transporter; T6P, trehalose 6-phosphate; TOR, target of rapamycin; TPS, T6P synthase.

and distinct functions in signaling and metabolism [4,36,37,40,41,42,43,44,45,46]. In *Arabidopsis*, HXK1 plays dual roles in signaling and metabolism, which can be uncoupled by the S177A mutation that abolishes the glucose phosphorylation activity but possesses full glucose sensor function based on diverse sugar responses [4,23,36,40,41]. The various functions of the *Arabidopsis* HXK1 glucose sensor are likely evolutionarily conserved and shared by specific HXKs in moss, maize, rice, tomato, poplar, *Selaginella moellendorffi* and tobacco [36,37,41,42,43,44,45]. A recent structural study showed that both HXK1 and HXK1(S177A) formed co-crystals with glucose in the single glucose binding pocket and induced similar conformational changes. The findings support the full sensor function of HXK1(S177A) without glucose phosphorylation [36,47]. However, the relatively low *Kd* in the range of 15–89 μM glucose was measured by the isothermal titration calorimetry (ITC) assay based on transient glucose binding in vitro. It seems inconsistent with the physiological requirement of glucose concentrations for biological responses in cells and plants, which would need further investigation [31•,36,40,48,49]. The determination of the physiological *Kd* of HXK1 as a glucose sensor by *in vitro* and *in vivo* analyses will facilitate the molecular dissection of the direct and indirect glucose signaling responses and regulatory networks.

Interestingly, recent research has uncovered new physiological functions of sugar phosphorylation and metabolism mediated by HXK1. For instance, a rare sugar D-allose requires HXK1-mediated sugar phosphorylation but not the sensor function to trigger a long-term activation of abscisic acid biosynthesis and signaling in *Arabidopsis* and rice leading to growth inhibition [50]. Another critical role of HXK1-based metabolic activity was revealed in the *imps1* mutant, which is deficient for the enzyme, myo-inositol 1-phosphate synthase (MIPS) catalyzing the limiting step of myo-inositol synthesis, and exhibits light-dependent formation of lesions on leaves due to salicylic acid-dependent programmed cell death (PCD) [51]. The *somi1* (*suppressor of mips1*) mutant suppressed cell death and defense responses of *mips1* and was

mapped to the T231I mutation critical for glucose phosphorylation. Consistently, *mips1* did not affect the HXK1 glucose sensor function. HXK1 (S177A) with reduced glucose metabolism alleviates PCD in *mips1* [51]. The new findings suggest that HXK1 appears to gate multiple glucose metabolic pathways in plant cells. The channeling and regulation of glucose to myo-inositol metabolism represents an emerging regulatory network, which may explain previously unknown connections between sugar, stress and immune responses in plants [19].

In addition to glucose, ample evidence has indicated that sucrose is perceived as a distinct sugar signal, which cannot be substituted by glucose or fructose, in controlling flowering, seed and storage organ development, branching, and pigmentation [3,5,6,7]. Compelling examples are the sucrose-specific repression of the beet leaf *BvSUT1* gene encoding the sugar proto-sucrose sympoter [52] and the bZIP11 protein translation via the 5′UTR upstream open reading frame (uORF) [53]. Sucrose also specifically stabilizes DELLA proteins to activate *MYB75* expression and anthocyanin biosynthesis, but inhibits cell expansion [54•], whereas both sucrose and glucose activate auxin biosynthesis and cell expansion involving HXK1 and complex actions of PIF transcription factors [11,55]. In contrast to the long-standing theory that auxin controls apical dominance, artificially increasing sucrose levels repress the expression of *BRANCHED1* transcription factor and promote axillary bud outgrowth [34•]. It is interesting to note that sucrose activates calcium signaling and calcium-dependent protein kinases [3] and plants possess a large number of proteins and enzymes with conserved sugar binding domains that play critical roles in sucrose transport and metabolism [7,8]. Future investigation may explore the roles of SUT proton-symporters, voltage-activated calcium channels, and membrane-associated sucrose synthases (SUS) as potential sucrose sensors and signaling effectors distinct from glucose sensors and signaling mechanisms (Figure 1) [56,57,58].

Recent research has implicated a tight link between endogenous sucrose and trehalose 6-phosphate (T6P) levels, and it was proposed that T6P is a signal of sucrose availability and influences the relative amounts of sucrose and starch [6,59]. Extensive genetic and transgenic manipulations of trehalose metabolic enzymes have provided fascinating findings that many metabolic and developmental phenotypes are associated with altered levels of T6P, trehalose synthase (TPS) or T6P phosphatase (TPP) (Figure 1), including gene expression, metabolism, seed development, shoot expansion and flowering in *Arabidopsis*, tobacco and maize plants [5,6,10,12,13,15,59,60,61,62,63•,64,65]. New development based on genetic, biochemical and genomic studies has led to important findings that T6P inhibits the activity of the evolutionarily conserved energy sensor complex SNRK1 (Sucrose NonFermenting1-Related Kinase1) via unknown protein regulators [21,62,66•,67]. It remains a possibility that the surprisingly large plant gene family encoding TPS and TPP proteins lacking prominent enzymatic activities may act as T6P regulators or sensors and modulate SNRK1 activity (Figure 1) [67,68,69].

Novel sugar sensors

Besides glucose, sucrose and T6P, other sugar signals and putative sensors implicated in regulating plant gene expression, metabolism and development are also emerging [32•,70,71,72,73•]. An important example is the discovery of new transcription factors containing β-amylase (BAM)-like domain characteristic of starch degradation enzymes in higher plants but no in algae and mosses. The BAM domain of BAM8 appears to mediate DNA-binding and transcriptional activation based on a synthetic reporter driven by BZR1-BAM responsive cis-elements in plant cells and transgenic plants, whereas BAM7 interacts with BAM8 but may act as a transcription repressor [73•]. Future studies could lead to new advances in supporting their potential role as sensors of starch metabolism.

Intrigued by the observation that *gin2* is insensitive to glucose but still sensitive to fructose, an integrated study using cell-based functional screen and genetic mutations has identified the nuclear localized fructose1-6-bisphosphatase (FBP/FIS1, FRUCTOSE-INSENSITIVE1) as a putative fructose sensor uncoupled from its catalytic activity [71]. It will be interesting to determine whether FBP is connected to the fructose-specific signaling suppressor, the *Arabidopsis* NAC89 transcription factor, in the nucleus sharing downstream interactions with abscisic acid and ethylene signaling pathways [74]. Currently, there is no evidence for the involvement of fructokinases (FRKs), catalyzing irreversible fructose phosphorylation and playing a key role in vascular development, in sugar sensing [4]. However, proteomic and genetic studies have identified FRK-like proteins (FLN1 and FLN2) in the plastid-encoded RNA polymerase complexes and regulate plastic gene transcription and chloroplast development [75].

Sensors of extracellular sugars

Besides intracellular sugar sensing, regulator of G-protein signaling (RGS1) as a seven-transmembrane domain protein on the plasma membrane, has been proposed to play a critical role as external glucose sensor in plants. An important advance is the recent determination of RGS1 phosphorylation by WNK8 (WITH NO LYSINE8), which leads to RGS1 endocytosis and G-protein-mediated sugar signaling and cell proliferation [76]. By combining thorough dose-duration experiments with mathematical modeling, it has been shown that 6% glucose stimulates rapid RGS1 endocytosis through WNK8 and WNK10, whereas 2% glucose slowly activates the pathway through WNK1, allowing the cells to respond similarly to transient, high-intensity signals and sustained, low-intensity signals

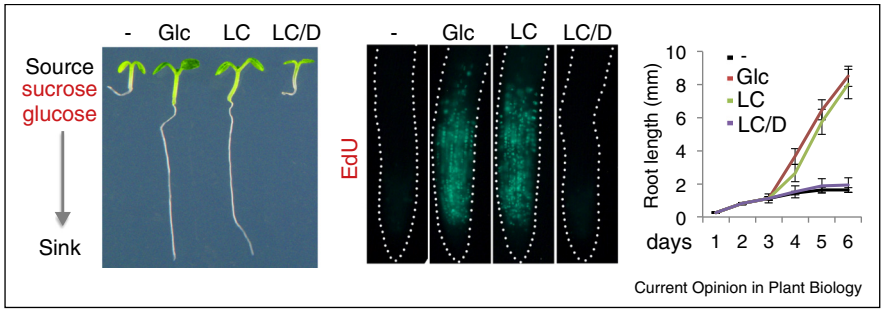
[77•]. The RGS1 signaling pathway appears to be unique in the requirement of extremely high glucose and the *rgs1* mutant diminishes the regulation of a few glucose responsive genes in genome-wide analyses. As the RGS1 specific marker gene *At4g01080* is strongly activated by 100–300 mM D-glucose, D-fructose and sucrose, RGS1 may be a plasma membrane sensor or partner responding to changes of multiple extracellular sugars [78]. It will be a promising investigation to determine whether cell-wall invertases or sucrose transporters are required to generate high local sugar signals to stimulate RGS1 signaling [7]. A significant recent study has implicated a role of RGS1 in soybean nodulation [79•]. Distinct from RGS1 phosphorylation by WNKs to trigger endocytosis in *Arabidopsis* sugar signaling [77•], Nod factor receptor1 (NFR1) phosphorylates RGS1 to accelerate GTPase activity and maintains Gα proteins in inactive trimeric conformation. It will be interesting to determine whether RGS1 also functions as a sensor of extracellular sugars in the soybean nodulation process and how RGS1 senses and transduces sugar signals.

Indirect sugar sensing via energy sensors

Manipulations of key enzymes involved in sugar and starch metabolism have started to provide new insights into how the physiological sugar levels modulated by light, CO_2 and photoperiod alter gene expression and plant developmental processes [7,9,36,38,45,60,61,63•,80,81,82,83,84,85]. Many key questions remain to be answered regarding the signaling actions of physiological levels of sugar signals in extracellular spaces and in different subcellular compartments [7,38]. Besides direct sensing by sugar sensors such as HXK1, intracellular sugar levels can be perceived as metabolic input by energy sensing regulators to coordinate energy status and plant metabolism and growth. Recent research on the evolutionarily conserved energy sensor TOR (target of rapamycin) protein kinase is especially informative in uncovering new aspects of glucose signaling in plants [20,22,23,25,26,27,31•]. Analyses with chemical inhibitors demonstrate that glucose metabolism through glycolysis and the electron transport chain in the mitochondria is required to activate TOR signaling and control global gene transcription. The use of a thymidine analog, 5-ethynyl-2′-deoxyuridine (EdU) also enables *in situ* visualization of photosynthesis- or glucose-stimulated cell-cycle S-phase entry in the primary root meristem from quiescence after the depletion of maternal sugar supplies (Figure 2) [31•]. Glucose-TOR signaling is activated below 1 mM glucose via metabolic and energy signaling relay, which is coordinated by shoot-root sugar communication [31•]. Future investigation will expand our understanding on the connections between physiological sugar levels and putative sugar regulators or particular energy sensors and specific signaling pathways in different biological contexts and processes.

Under sugar deprivation conditions, the evolutionarily conserved energy sensor complex SNRK1 plays central regulatory functions in metabolism, stress signaling and plant development [9,10,15,21,23,24]. In *Arabidopsis*, KIN10/11 protein kinases provide catalytic activities in the SNRK1 complex and orchestrate global gene expression changes to activate catabolism but repress anabolism [21,23,24,70]. Recent exciting progresses have identified new transcription factors as *Arabidopsis* KIN10 phosphorylation targets, including bZIP63, MYC2, NAC2/ATAF1, FUS3 and IDD transcription factors involved in low energy responses in darkness, submergence, starvation, and flowering [15,84,86,87•,88•,89]. Direct phosphorylation by KIN10 protein kinase promotes bZIP63-bZIPS dimerization and the transcriptional activation of bZIPs, NAC2 and FUS3 [84,87•,88•]. Phosphorylation by KIN10 reduces MYC2 protein stability and transcriptional activity of IDD8 [86]. Surprisingly, only KIN10 but not KIN11 directly phosphorylates bZIP63 and IDD, even though the single *kin10* or *kin11* mutants do not show overt phenotypes [70,87•,89]. How KIN10 phosphorylation contributes to the opposite leaf senescence phenotypes of *bzip63* and *bZIP63* overexpression requires further molecular, biochemical and physiological insights

Figure 2



Post-germination seedling development relies on photoautotrophic transition and photosynthesis. After seed sugar depletion at 3 DAG, exogenously supplied Glc (1–15 mM glucose) promotes similar growth based on endogenous sugars derived from photosynthesis in *Arabidopsis* seedlings. C, CO_2; DAG, days after germination; D, DCMU, a photosynthesis inhibitor; EdU, 5-ethynyl-2′-deoxyuridine; L, light.

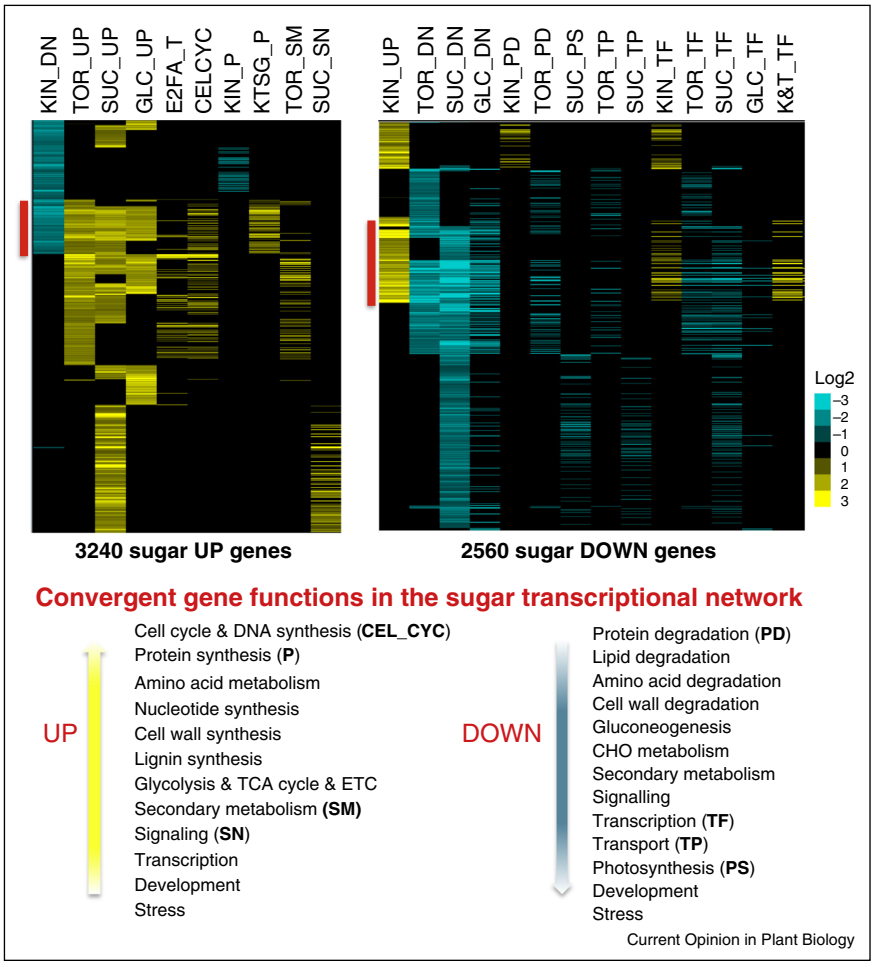
[70,87•]. Besides transcriptional controls, new mechanisms of regulation by mRNA stability and miRNAs provide additional layers of molecular controls in dynamic sugar responses [9,80,81,90,91,92•].

Another novel finding in the indirect sugar signaling mechanism came from the functional characterization of *Arabidopsis SEC* (*SECRET AGENT*) encoding a specific *O*-linked N-acetylgluocosamine (*O*-GlcNAc) transferase (OGT). SEC promotes gibberellin signaling by O-GlcNAcylating DELLA transcription repressors and prevents the interaction and suppression of multiple transcription factors, BZR1, PIF4, PIF5 and JAZ1, involved in brassinosteroid, light and jasmonate signaling, respectively [32•]. Further research advances will resolve the remaining puzzles regarding the physiological and biochemical functions of another *Arabidopsis* OGT paralog SPY, carrying out an opposite repressor role in gibberellin signaling but related functions with SEC in embryogenesis. As *O*-GlcNAc is synthesized from glucose, lipid and glutamine (Figure 1), and DELLAs are the convergent regulators in hormonal, sugar and stress signaling crosstalk [11,93,94], OGT likely act as a pivotal sensor in modulating and integrating nutrient, hormonal and stress signaling pathways central to plant growth and development.

Primary and dynamic sugar signaling network

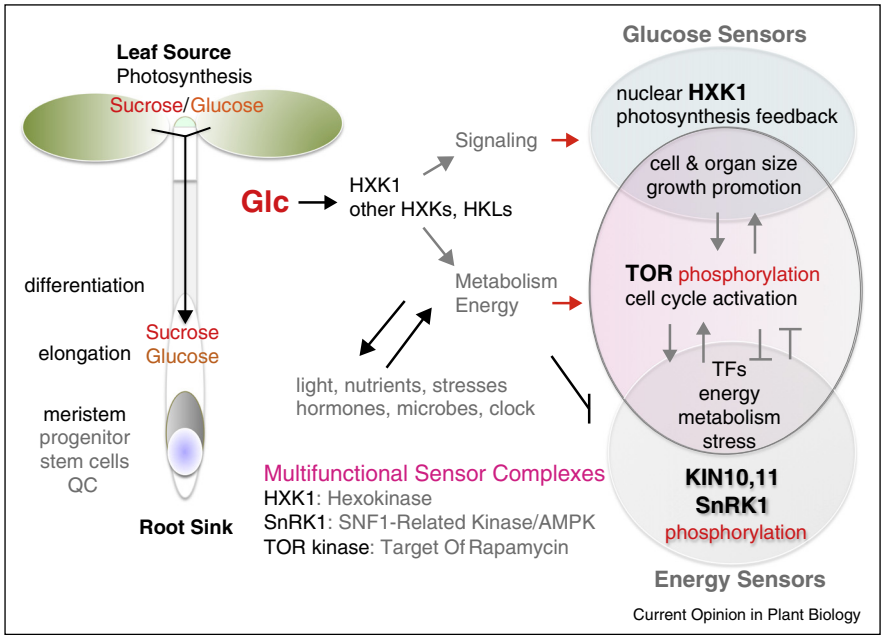
Comprehensive transcriptome analyses provide a powerful approach to explore dynamic and primary sugar responses and to discover new regulators in sugar-mediated processes. Over the past decade, many microarray studies have been performed under different conditions. *Arabidopsis* seedlings and adult leaves were analyzed with different concentrations of exogenous sugars, as well as cell-based

Figure 3



Dynamic Transcriptional control by sugars. *Arabidopsis* ATH1 transcriptome data are clustered based on key functional gene sets regulated by glucose, sucrose, TOR and KIN10 in *Arabidopsis thaliana*. Genes representing KIN10 targets [70], TOR targets [31•], E2Fa targets [31•], sucrose [49] and glucose (4 h data)[96] regulation, cell cycle, protein synthesis, primary metabolism and secondary metabolism are included using hierarchical analyses. Gene lists are chosen from supplemental data from representative studies (Log2 ≥ 1 or ≤ -1; q-value ≤ 0.05). Totally 3240 up regulated genes and 2560 down regulated genes are shown in the heatmap, with 428 convergent up-regulated genes and 863 convergent down-regulated genes as indicated by red lines.

Figure 4



Convergent regulation in the sugar signaling network. The trifurcated model focuses on integrating glucose signaling mediated by glucose and energy sensors. Glucose is produced by photosynthesis or from storage source and transported as sucrose or glucose to the sink tissues and other organs to promote growth and to maintain energy and metabolic homeostasis. The regulatory mechanisms and functions of three master regulators, HXK1, KIN10/11 and TOR, modulated by glucose signals are shown. The glucose signaling networks are tightly intertwined with environmental light, nutrients, stresses and microbes, as well as internal hormones, peptides and clock.
Glc, glucose; HXK, hexokinase; HKLs, hexokinaselike; KIN, Arabidopsis protein kinase; QC, quiescent center; TOR, target of rapamycin.

transient expression systems by manipulating sensors and signaling components [31•,49,70,90,95,96,97,98]. An integrated analysis of four representative genome-wide expression profiling data reveals a convergent energy-signaling network modulating nearly 1,300 genes in rapid sugar responses (2–4 h) (Figure 3). Importantly, TOR and KIN10 protein kinases are central regulators in sugar-mediated energy signaling, but act antagonistically in the regulation of convergent primary sugar responsive genes [31•,49,70,90,91,97,98]. Among the key functional classes regulated by the KIN10-TOR and sucrose/glucose (KTSG) convergent network, genes involved in protein synthesis, cell cycle, signaling, transcription, glycolysis, TCA cycle, mitochondria electron transport chain, as well as secondary carbon metabolism are activated by both glucose and sucrose. On the other hand, genes participating in transcription, diverse transporter functions, as well as the degradation of protein, amino acid, lipid and cell wall are repressed by sugars (Figure 3).

Besides the convergent sugar signaling program, it is important to note that the differences in gene expression profiles may reflect the existence of truly distinct regulatory programs controlled by either sucrose or glucose, or may represent specific features of each experimental system and approach for data generation. For instance, some genes activated by glucose-TOR signaling are missing from seedlings stimulated by both sucrose and glucose. It is likely that the primary root meristem cells expressing cell cycle genes and the TOR targeted transcription factor E2FA target genes are more significantly represented in 3-day seedlings [31•] vs. 8-9 day seedlings [49,96]. In future research, it will be crucial to uncover new biological regulation of specific TOR and KIN10 target genes in not only seedlings but also adult plants, apical meristems and diverse cell types that may act in multiple metabolic, stress and developmental pathways [5,12,15,60,61,63•,70,99]. Notably, sucrose treated seedlings appear to modulate many more uniquely regulated genes that may provide important information for future dissection of the sucrose-specific pathways [3,5,6,7].

Despite the overt convergence between the TOR and KIN10 target genes in rapid sugar responses, how *Arabidopsis* TOR and KIN10 protein kinases regulate the vast primary transcriptional programs of diverse genes in an opposite manner represents a major challenge. In mesophyll protoplasts, KIN10 overexpression inhibits TOR-mediated phosphorylation of S6K1 (Xiong and Sheen, unpublished) [70,100]. However, it remains unclear whether KIN10 directly phosphorylates and inactivates TOR kinase through the phosphorylation of RAPTOR as a regulatory subunit in the TOR sensor complex [26,101]. Although prior studies have emphasized TOR functions

in ribosome biogenesis, protein stability and translational control [22,25,26,27,102,103,104], the identification of E2FA as a direct TOR kinase substrate [31•] opens up new mechanisms of direct and rapid phosphorylation of transcription factors by sugars in central metabolic and growth pathways. Importantly, this type of regulation is independently controlled or co-regulated by the SNRK1 energy sensor and the HXK1 glucose sensor (Figure 4). It is most likely that the modulation of related transcription factors on distinct phosphorylation sites by TOR and SNRK1 to mediate contrast regulation in response to sugar availability and energy status. Sensitive and quantitative phosphoproteomics will further facilitate the integration of SNRK1-TOR signaling networks [105].

Future challenges

The biological functions of plant sugar signals and sensors in embryogenesis, seedling establishment, growth, metabolism, juvenile-adult transition, flowering and senescence have emerged. The molecular regulatory mechanisms of the plant sugar-signaling network are starting to be elucidated in the meristem, expanding and differentiated cells (Figure 4). The application of versatile and integrated molecular, cellular, genetic, genomic, phospho-proteomic and systems analyses will facilitate the discoveries of new regulators and molecular links in diverse mechanisms mediating sugar signaling. Major puzzles await to be resolved include how the different sugar sensors distinguish regulatory ligands with high specificity in different physiological concentration ranges, where these sensors act at the subcellular, cellular and organismal levels [40,77•,102,106,107,108], what the components are in these sensor complexes [26,40,76,77•,109•,110,111], how they mediate the first steps of signal transduction, what the mechanisms are in the convergent or specific regulations by TOR, SNRK1 and HXK1 (Figure 4), as well as how parallel or integrative signaling by other novel sugar sensors and signaling components modulate a large array of downstream effectors and responses (Figure 1). Finally, development of sensitive and quantitative technologies for single-cell based genetic and chemical perturbations and for transcriptome, epigenome and metabolite profiling, as well as application of genetic encoded biosensors for dynamic imaging of sugar, energy or metabolite signaling will likely lead to new discoveries. Much information will be gained in understanding the plant energy-stress signaling network by elucidating the antagonistic functions of TOR and KIN10 as key energy sensors and central regulators of transcriptional, translational and metabolic programs in response to other nutrients, hormones, clock, microbes and diverse environmental cues (Figure 4).

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- • of special interest
- •• of outstanding interest

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