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Dynamic Nutrient Signaling Networks in Plants

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Abstract

Nutrients are vital to life through intertwined sensing, signaling, and metabolic processes. Emerging research focuses on how distinct nutrient signaling networks integrate and coordinate gene expression, metabolism, growth, and survival. We review the multifaceted roles of sugars, nitrate, and phosphate as essential plant nutrients in controlling complex molecular and cellular mechanisms of dynamic signaling networks. Key advances in central sugar and energy signaling mechanisms mediated by the evolutionarily conserved master regulators HEXOKINASE1 (HXK1), TARGET OF RAPAMYCIN (TOR), and SNF1-RELATED PROTEIN KINASE1 (SNRK1) are discussed. Significant progress in primary nitrate sensing, calcium signaling, transcriptome analysis, and root–shoot communication to shape plant biomass and architecture are elaborated. Discoveries on intracellular and extracellular phosphate signaling and the intimate connections with nitrate and sugar signaling are examined. This review highlights the dynamic nutrient, energy, growth, and stress signaling networks that orchestrate systemwide transcriptional, translational, and metabolic reprogramming, modulate growth and developmental programs, and respond to environmental cues.

Contents

INTRODUCTION

Nutrient signaling is emerging as the most ancient and fundamental mechanism to modulate cellular activities and organismal development through integration with other intrinsic regulators and environmental inputs in multicellular plants and animals. In contrast to the previously prevailing notion that nutrients automatically feed into cellular metabolism and growth, nutrient signaling mechanisms are complex due to being part of the tailored regulatory networks in diverse cells, tissues, and organs with specialized physiology, metabolism, and functions. There is increasing recognition of the essential roles of nutrient signaling networks in plant development and agriculture as well as in human health, disease, and aging.

Free from the organic nutrient constraint in animals, plants play a central role in bridging the conversion of inorganic element resources on Earth to the production of organic molecules and nutrients. For example, carbon (C) in the atmosphere as CO_2 is fixed through photosynthesis to generate sugars in the shoot. Inorganic nitrogen (N) in nitrate (NO_3^-) and phosphorus (P) in phosphate [PO_4^{3-}(P_i)] are acquired and assimilated from the soil by roots to synthesize nucleic acids, amino acids, lipids, vitamins, and adenosine triphosphate (ATP). Photosynthetic plants possess remarkable versatility in acquiring and synthesizing nutrients by sensing and responding to wide-ranging inorganic nutrients in soil or inside cells and ultimately fuel, build, and sustain all lives (**Figure 1**). In this review, we examine key molecular and cellular mechanisms intimately linked to sensing of and dynamic primary responses to sugars (Baena-González & Lunn 2020, Broeckx et al. 2016, Dobrenel et al. 2016, Li & Sheen 2016, Ryabova et al. 2019, Sheen 2014, Shi et al. 2018, Wu et al. 2019), nitrate (Liu et al. 2020, Vidal et al. 2020), and phosphate (Chien et al. 2018, Ham et al. 2018, Puga et al. 2017) as major nutrient signals. We highlight and discuss

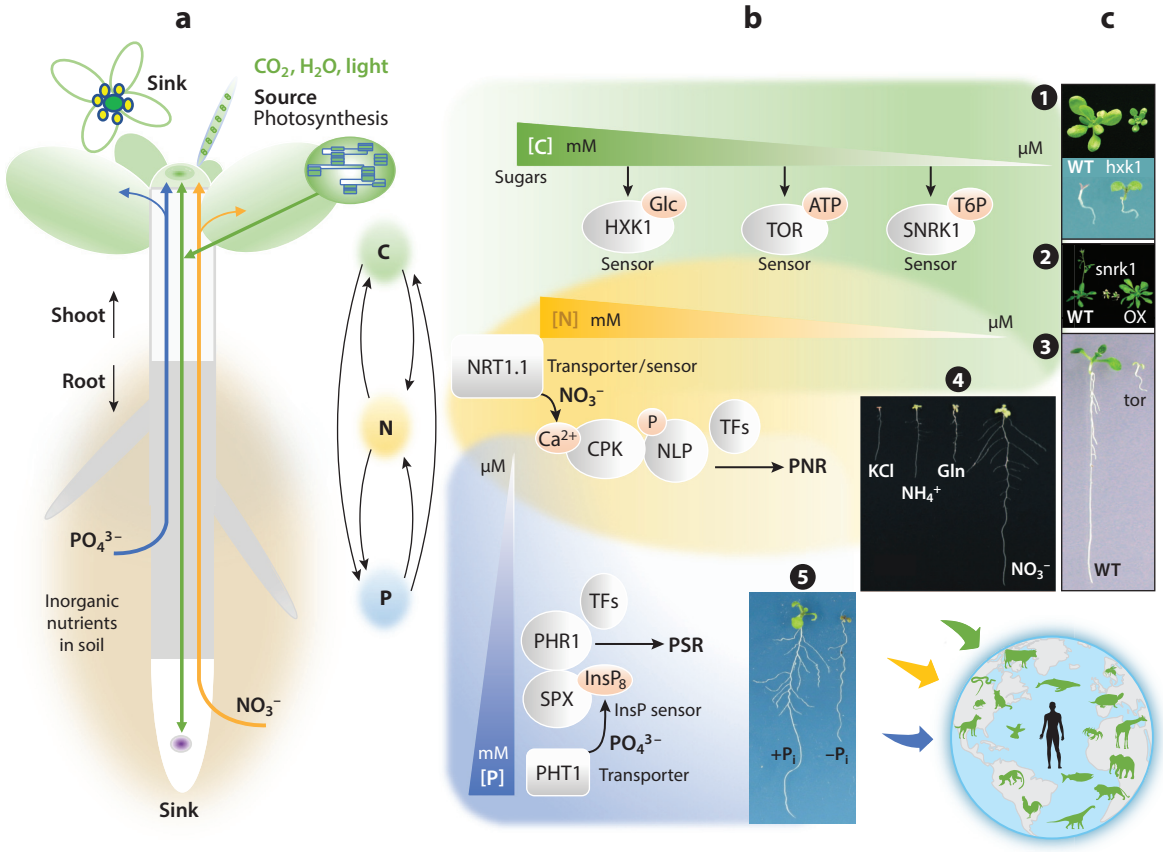

Figure 1

Carbon, nitrogen, and phosphorus are essential nutrients that control integrated signaling networks in plants. (*a*) Sugars are generated by photosynthesis from source leaves and translocated to sink organs. Nitrate (NO_3^-) and phosphate (PO_4^{3-}) are acquired by roots from the soil and transported to shoots. (*b*) Glc-sensor HXK1 and energy sensors TOR and SNRK1 respond to different concentrations of sugars. NRT1.1 is a nitrate transceptor and mediates nitrate-activated CPK-NLP signaling to induced PNRs. Phosphate is taken up by PHT1 and converted to $InsP_8$, which is sensed by SPX to repress PHR1 in PSRs. Other TFs also regulate the PNR and the PSR. (*c*) ❶ (*Top*) HXK1-mediated growth promotion in adult *Arabidopsis* plants and (*bottom*) growth arrest in seedlings on high glucose in WT and *hxk1* plants. ❷ WT, *snrk1*, and *SNRK1-OX* plants. ❸ WT and conditional *tor* seedlings. ❹ Seedlings supplied with KCl (control) and different nitrogen sources, NH_4^+, Gln, and NO_3^-. ❺ Seedlings grown in the medium with (+) or without (−) P_i. Abbreviations: CPK, CALCIUM DEPENDENT PROTEIN KINASE; Glc, glucose; Gln, glutamine; HXK1, HEXOKINASE1; $InsP_8$, inositol pyrophosphate 8; NLP, NIN-LIKE PROTEIN; OX, overexpression; P, phosphorylation; PHR1, PHOSPHATE STARVATION RESPONSE1; PHT1, PHOSPHATE TRANSPORTER1; P_i, inorganic phosphate; PNR, primary nitrate response; PSR, phosphate-starvation response; SNRK1, SNF1-RELATED PROTEIN KINASE1; SPX, SYG1/Pho81/XPR1; T6P, trehalose 6-phosphate; TF, transcription factor; TOR, TARGET OF RAPAMYCIN; WT, wild-type.

emerging new knowledge and universal concepts generated from the rapidly growing repertoire of interdisciplinary experimental approaches and tools largely in *Arabidopsis thaliana* that uncover expanded complexity in plant nutrient sensing and signaling.

SUGAR SENSING AND SIGNALING

In photosynthetic plants, glucose and sucrose show hormonelike activities and modulate many essential processes, including embryogenesis, germination, seedling development, vegetative

growth, reproduction, and senescence. How glucose or other sugars and carbon metabolites function as direct and essential signaling molecules remains an exciting research challenge, as key mutants or severe nutrient deficiency are often lethal or deleterious with pleiotropic phenotypes. There are two leading mechanisms to perceive and transduce sugar signals. Direct sensing is triggered by sugar-binding sensors with diverse affinity and specificity, such as glucose-binding sensor HEXOKINASE1 (HXK1), as well as other potential sugar sensors, including REGULATOR OF G-PROTEIN SIGNALING1 (RGS1) and TREHALOSE 6-PHOSPHATE (T6P) SYNTHASE1 (TPS1). Sugar-derived bioenergetic molecules and metabolites modulate signaling proteins, including glucose-activated TARGET OF RAPAMYCIN (TOR) and sugar-repressed SNF1-RELATED PROTEIN KINASE1 (SNRK1), which relay sugar signals indirectly (**Figure 1**). In this review, we discuss the sugar signals, the potential sugar sensors, and the sugar signaling networks discovered in the plant system (**Figure 2**).

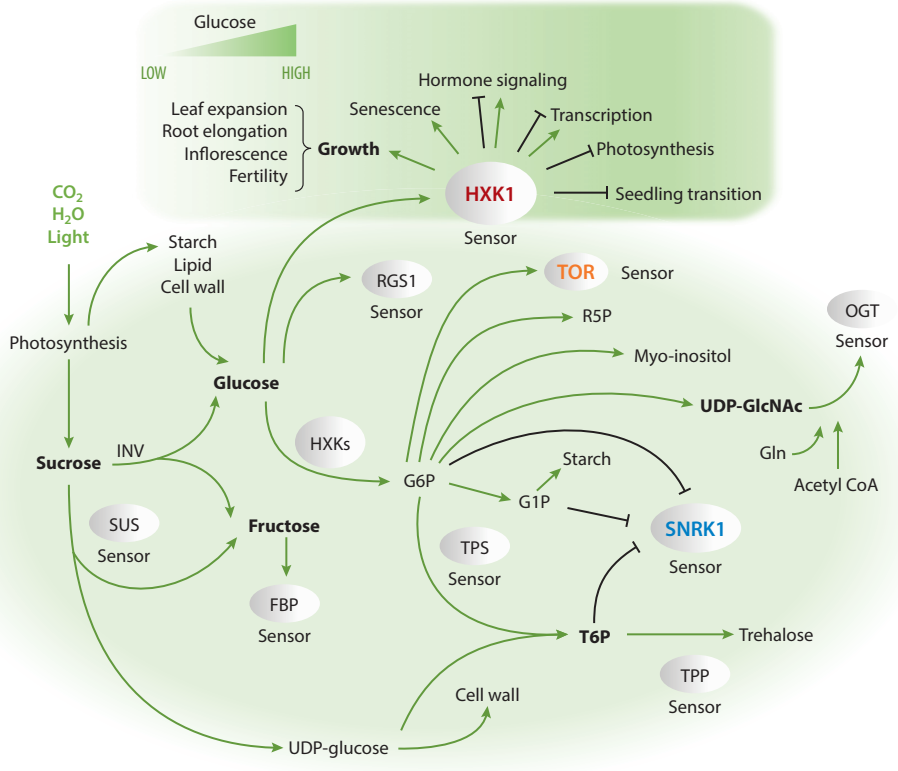

Figure 2

Sugar sensing and signaling in plants. Glucose sensor HXK1 controls multiple biological processes at different glucose concentrations uncoupled from metabolism. Sucrose and glucose metabolism generate diverse sugars and metabolites that could potentially be perceived by distinct sensors. Abbreviations: Acetyl CoA, acetyl coenzyme A; FBP, fructose-1,6-bisphosphatase; G1P, glucose 1-phosphate; G6P, glucose 6-phosphate; Gln, glutamine; GlcNAc, N-acetylglucosamine; HXK, HEXOKINASE; INV, invertase; OGT, *O*-LINKED N-ACETYLGLUCOSAMINE (*O*-GLcNAc) TRANSFERASE; R5P, ribose 5-phosphate; RGS1, REGULATOR OF G-PROTEIN SIGNALING1; SNRK1, SNF-RELATED PROTEIN KINASE1; SUS, SUCROSE SYNTHASE; T6P, trehalose 6-phosphate; TOR, TARGET OF RAPAMYCIN; TPP, T6P PHOSPHATASE; TPS, T6P SYNTHASE; UDP, uridine diphosphate.

Glucose Sensors and Signaling

Using *A. thaliana* as a reference plant, genetic screens have identified *glucose-insensitive* (*gin*) and *glucose-oversensitive* mutants based on the developmental arrest phenotype mediated by high glucose during seedling germination. Extensive characterization of sugar mutants revealed unexpected positive or negative interactions between glucose and plant hormones, including positive abscisic acid (ABA) and auxin relays and antagonistic cytokinin and ethylene signaling (Moore et al. 2003, Rolland et al. 2006, Sheen 2014). Importantly, *gin2* mutants define HXK1 as a prominent glucose sensor (Jang et al. 1997, Moore et al. 2003) despite the presence of five other *HXK* and *HXK-LIKE* (*HKL*) genes that may provide overlapping or distinct functions in sugar sensing and metabolism (Karve et al. 2008). HXK1 mutants lacking catalytic activity but retaining strong glucose binding still support various signaling functions in transcription, cell proliferation, root and inflorescence growth, leaf expansion, fertility, and senescence (**Figure 2**), thus demonstrating the uncoupling of glucose signaling from glucose metabolism (Feng et al. 2015, Jang et al. 1997, Moore et al. 2003). The catalytic activity of HXK1—but not the glucose-sensor function—is required for lesion formation and cell death in myo-inositol-1-phosphate synthase mutants, illustrating the distinct roles of HXK1 in glucose signaling and metabolic pathways (**Figure 2**) (Bruggeman et al. 2015).

Although the majority of HXK1 protein is located at the outer membrane of mitochondria (Karve et al. 2008), HXK1 is detected in the nucleus and is associated with target genes based on proteomic and chromatin immunoprecipitation (ChIP) analyses (Cho et al. 2006). The potential actions of the plant HXK glucose sensor in the nucleus are supported by the loss of the glucose-dependent degradation of the nuclear transcription factor (TF) ETHYLENE INSENSITIVE3 (EIN3) through proteasome and reporter gene expression in *gin2*, as well as the nuclear localization of OsHXK5/6 in rice and specific HXKs from other plant species (Aguilera-Alvarado & Sánchez-Nieto 2017, Cho et al. 2009, Yanagisawa et al. 2003). Apple MdHXK1 appears to phosphorylate and stabilize TF MdbHLH3 in the nucleus to promote anthocyanin synthesis (Hu et al. 2016). To precisely and fully dissect the direct and indirect glucose signaling networks, it will be informative to develop more specific and quantitative glucose-induced phenotypes and molecular readouts in different cell types, organs, and developmental stages (**Figure 1**) (Baena-González et al. 2007, Kelly et al. 2012, Li & Sheen 2016, Moore et al. 2003, Xiong et al. 2013). Systematic and comparative studies of the large numbers of HXKs and HKLs with different subcellular localization in diverse plant species from unicellular green algae to flowering plants may lead to fresh findings in sugar signaling (Aguilera-Alvarado & Sánchez-Nieto 2017, Cho et al. 2009, Karve et al. 2008, Roth et al. 2019, Ulfstedt et al. 2018).

Besides intracellular and nuclear glucose sensing, the seven–transmembrane domain protein RGS1 has been proposed to play a critical role as a glucose sensor on the plasma membrane in plants. High levels of glucose stimulate RGS1 phosphorylation by the protein kinase (PK) WNK8-Gβγ complex, which leads to RGS1 endocytosis and G-protein signaling, cell division, and marker gene activation (Urano et al. 2012). A deep screen for *Arabidopsis* G-protein-interacting proteins has identified that RGS1-HXK1-INTERACTING PROTEIN1 (RHIP1) serves as the physical scaffold for these two sensors. The three mutants *hxk1*, *rgs1*, and *rhip1* exhibit complex relationships in different sugar assays (Huang et al. 2015). It will be crucial to determine whether and how glucose binds directly to RGS1 as a potential sensor and how RHIP1 mediates the distinct regulation of marker genes in different glucose signaling pathways.

Novel Sugar Signaling

Sucrose is transported from photosynthetic leaf sources to support the growth and development of sink organs, including the root apical meristem (RAM) and shoot apical meristem (SAM), where

new cells are supplied from the stem cell niche, growing primary and lateral roots as well as leaf primordia, young leaves, flowers, fruit, and seeds (**Figure 1**). There are several sucrose-specific responses unique to plants. The best studied example is the sucrose-induced repression of translation (Li & Sheen 2016, Rahmani et al. 2009). The 5′ leader of the transcript encoding *Arabidopsis* TF BASIC LEUCINE ZIPPER (bZIP)11 harbors several upstream open reading frames (uORFs). The second uORF encoding a 28-residue peptide can act as an attenuator peptide by stalling ribosomes on the mRNA in the presence of high levels of sucrose but not glucose (Rahmani et al. 2009). For specific sucrose sensing, various sucrose transporters and synthases with different subcellular localizations and potential regulatory functions are candidates to be sucrose sensors (Chen et al. 2015, Stein & Granot 2019).

Intensive research on plant trehalose biosynthesis by T6P SYNTHASES (TPSs) and T6P PHOSPHATASES (TPPs) has suggested unique sugar sensing and signaling mechanisms because of the intriguing regulatory effects of T6P on plant growth, development, and stress resistance (**Figure 2**) (Broeckx et al. 2016, Figueroa & Lunn 2016). The essential role of T6P in plant development was first shown by the recessive embryo lethality of *tps1* mutants (Eastmond et al. 2002). T6P levels were modulated by expressing *Escherichia coli* genes encoding TPS to increase T6P or TPP to lower T6P in transgenic *Arabidopsis* plants or to complement *tps1*. These experiments demonstrated that T6P performs critical roles in regulating carbohydrate use for growth and in modulating shoot growth, branching, and flowering (Schluepmann et al. 2003). By controlling TPS1 expression in both leaves and the SAM, T6P was shown to activate key flowering regulators (Wahl et al. 2013). Direct T6P manipulation using sunlight-triggered release and plant-permeable analogs of T6P during the grain-filling period increases wheat yield. T6P spraying also leads to drought tolerance in wheat plants (Griffiths et al. 2016). However, the molecular basis of T6P sensing and signaling awaits further elucidation. Research findings postulate that T6P may exert its functions by direct or indirect binding to SNRK1, thereby reducing SNRK1's activity (Baena-González & Lunn 2020, Figueroa & Lunn 2016, Zhai et al. 2018, Zhang et al. 2009). Significantly, the characterization of various forms of TPS1 revealed its nuclear localization and the regulatory functions of its noncatalytic domains in the N- and C-termini, suggesting potential mechanisms of regulation by sucrose and T6P (Fichtner et al. 2020). In maize, meristem fate is regulated by TPPs, but the inflorescence branching regulated by TPPs (RAMOSA3 and TPP4) is uncoupled from enzymatic activity, implicating another possible sugar-sensor function (Claeys et al. 2019).

Besides glucose, sucrose, and T6P, other sugar signals and sensors have also been implicated in regulating plant transcription, metabolism, and development (**Figure 2**) (Li & Sheen 2016). An integrated study using a cell-based functional screen and genetic mutations has identified the nuclear-localized FRUCTOSE1–6-BIPHOSPHATASE (FBP) as a putative fructose sensor uncoupled from its catalytic activity (Cho & Yoo 2011). It will be interesting to determine how FBP may be connected to the fructose-specific signaling suppressor TF ANAC089 in the nucleus that shares downstream interactions with ABA and ethylene signaling pathways (Li et al. 2011). Another novel finding in plant sugar signaling is the recent demonstration that *Arabidopsis SEC* encodes a specific *O*-LINKED N-ACETYLGLUCOSAMINE (*O*-GlcNAc) TRANSFERASE (OGT). *O*-GlcNAcylation suppresses DELLA, which is a repressor of multiple TFs, for example BRASSINAZOLE RESISTANT1 (BZR1), PHYTOCHROME INTERACTING FACTOR4 (PIF4) and PIF5, and JASMONATE-ZIM-DOMAIN PROTEIN1 (JAZ1), which are involved in brassinosteroid, light, and jasmonate signaling, respectively (Zentella et al. 2016). Unexpectedly, DELLA is also mono-*O*-fucosylated by the *O*-fucosyltransferase encoded by *SPY* to activate DELLA repression (Zentella et al. 2017). Large-scale proteomic analyses by mass spectrometry

have identified many regulatory proteins with either *O*-GlcNAcylation or phosphorylation, opening the way for future exploration of OGT functions in nutrient signaling (Xu et al. 2017).

TOR IN NUTRIENT AND ENERGY SIGNALING

TOR is an atypical but evolutionarily conserved Ser/Thr PK acting as a master signaling integrator to dynamically orchestrate cell metabolism, biogenesis, organ growth, and developmental transitions in response to nutrient, energy, hormone, and environmental cues (**Figure 3**) (Dobrenel et al. 2016, Ryabova et al. 2019, Shi et al. 2018, Wu et al. 2019). The plant TOR COMPLEX1 (TORC1) has two conserved regulatory subunits, LETHAL-WITH-SEC13-PROTEIN8 (LST8) and REGULATORY-ASSOCIATED-PROTEIN-OF-MTOR (RAPTOR). The generation of conditional *tor* mutants, plants with hyper- or hypoactive TOR expression, regulatory subunit mutants, and specific TOR chemical inhibitors has enabled significant progress in dissecting the plant TOR signaling network by circumventing the embryonic lethality of the null *tor* mutants (Caldana et al. 2013, Deprost et al. 2007, Dobrenel et al. 2016, Menand et al. 2002, Moreau et al. 2012, Ren et al. 2011, Ren et al. 2012, Ryabova et al. 2019, Shi et al. 2018, Xiong & Sheen 2012, Xiong et al. 2013). The conservation of the TOR-S6K (RPS6 KINASE)-RPS6 (RIBOSOMAL PROTEIN S6) phosphorylation cascade provides quantitative assays to monitor in vivo TOR activity based on phosphor-motif-specific antibodies (Dobrenel et al. 2016, Enganti et al. 2018, Schepetilnikov et al. 2013, Xiong & Sheen 2012).

Upstream Regulators of TOR Activity

At the critical checkpoint of photoautotrophic transition from seed to self-sufficient seedling in *Arabidopsis*, photosynthesis-derived glucose drives TOR signaling relays through glycolysis and mitochondrial bioenergetics to control root meristem and leaf primordia activation (Li et al. 2017, Xiong et al. 2013). Sugar and energy supplies from the mitochondria and chloroplasts are critical for the active TORC1 as a dimer promoted by the ATPase cochaperone complex TTT (TEL2-TTI1-TTI2)-WAC-RUVBL (RUVB-LIKE AAA ATPASE1) (Brunkard et al. 2020, Shi et al. 2018, Wu et al. 2019, Van Leene et al. 2019). Plant glucose-TOR signaling cannot be replaced by hormones and dictates very rapid (2-h) global transcriptional reprogramming of remarkable gene sets involved in central and secondary metabolism, the cell cycle, transcription, translation, signaling, transport, protein folding, and nutrient assimilation as well as the biosynthesis of nucleotides, lipids, amino acids, cell walls, lignins, and glucosinolates (Scarpin et al. 2020, Wu et al. 2019, Xiong et al. 2013).

Extensive studies in *Arabidopsis* plants have revealed that glucose metabolism and energy status play pivotal roles in activating TOR by interacting with light, hormone, clock, and other nutrient signals (**Figure 3**) (Mohammed et al. 2018, Wu et al. 2019). Although glucose alone is sufficient to activate root meristem proliferation via TOR signaling, glucose and light are synergistically required to activate cell proliferation by TOR signaling based on the expression of *pCYCB1;1::GUS* as a mitotic marker in leaf primordia (Li et al. 2017, Xiong et al. 2013). Light-enhanced translation is stimulated by white, far-red, and blue light perception via the phyA and CRY1/2 photoreceptors through the convergent CONSTITUTIVELY PHOTOMORPHOGENIC1 (COP1)-auxin-TOR-RPS6 signaling relay (Chen et al. 2018). The requirement for auxin signaling in TOR activation is mediated through Rho-like small GTPase RHO-OF-PLANTS2 (ROP2). Plants expressing constitutively active ROP2 contain high levels of active TOR. ROP2 physically interacts with and, when GTP bound, activates TOR in vitro. TOR activation in response to auxin is abolished in ROP-deficient *rop2,4,6* plants, and green fluorescent protein (GFP)-tagged TOR can associate with endosome-like structures

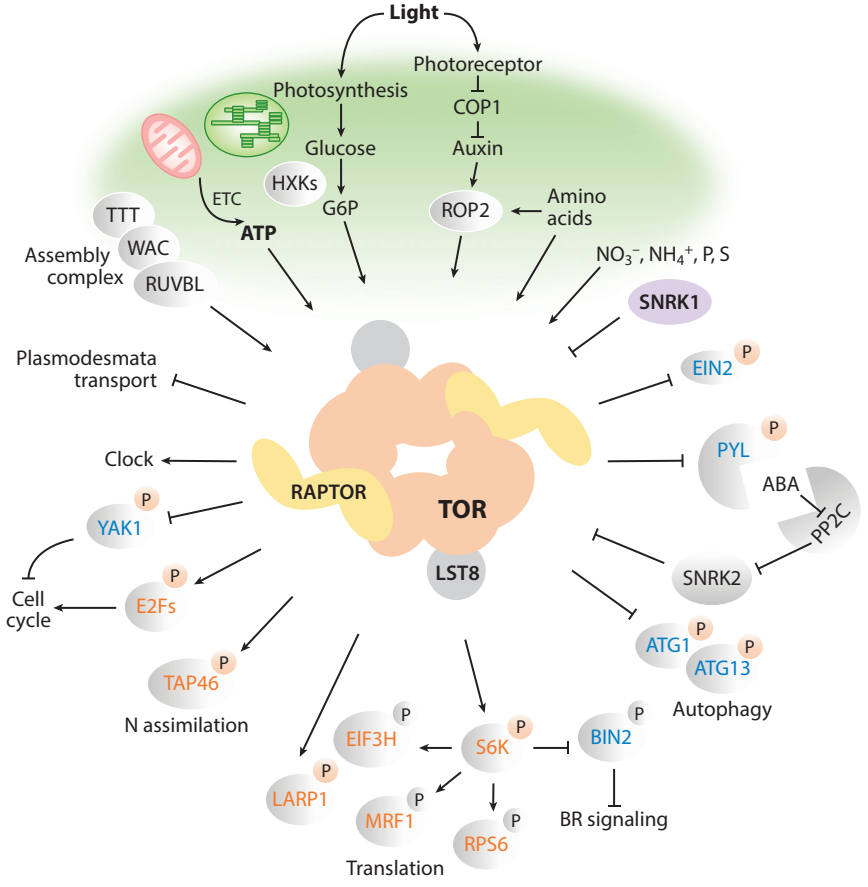

Figure 3

TOR acts as a central hub to integrate nutrient, energy, and environmental cues to orchestrate growth and development. The TOR complex is composed of TOR, RAPTOR, and LST8 and is promoted by the ATPase cochaperone complex TTT-WAC-RUVBL for dimerization and activation. ATP generated from the mitochondrial ETC, glucose, light, nutrients (N, P, or S), and amino acids promotes TOR activation. TOR phosphorylation of substrates (*orange circled Ps*) activates (*orange text*) or represses (*blue text*) their functions in various biological processes. RPS6 KINASE (S6K) can also phosphorylate targets (*gray circled Ps*). TOR is inhibited by SNRK1 and ABA. TOR phosphorylates and inhibits the ABA receptor PYL. Reciprocally, the ABA-PYL-SNRK2 cascade inhibits TOR activity through RAPTOR phosphorylation. Abbreviations: ABA, abscisic acid; ATG, AUTOPHAGY-RELATED; BIN2, BRASSINOSTEROID INSENSITIVE2; BR, brassinosteroid; COP1, CONSTITUTIVELY PHOTOMORPHOGENIC1; E2F, E2 TRANSCRIPTION FACTOR; EIF3H, EUKARYOTIC INITIATION FACTOR 3h; ETC, electron transport chain; G6P, glucose 6-phosphate; HXK, HEXOKINASE; LARP1, LA-RELATED PROTEIN1; LST8, LETHAL-WITH-SEC13-PROTEIN8; MRF1, MA3-DOMAIN-CONTAINING-TRANSLATION-REGULATORY-FACTOR1; P, phosphorylation; PP2C, PROTEIN PHOSPHATASE 2C; PYL, PYRABACTIN RESISTANCE-LIKE; RAPTOR, REGULATORY-ASSOCIATED-PROTEIN-OF-MTOR; ROP2, RHO-OF-PLANTS2; RPS6, RIBOSOMAL PROTEIN S6; RUVBL, RUVB-LIKE AAA ATPASE1; S6K, RPS6 KINASE; SNRK, SNF1-RELATED PROTEIN KINASE; TAP46, 2A PHOSPHATASE ASSOCIATED PROTEIN OF 46 KD; TOR, TARGET OF RAPAMYCIN; TTT, TEL2-TTI1-TTI2; WAC, WW-DOMAIN CONTAINING ADAPTOR WITH COILED-COIL; YAK1, YET ANOTHER KINASE1.

in ROP2-overexpressing plants (Li et al. 2017, Schepetilnikov et al. 2017). Sugar-promoted hypocotyl elongation requires both TOR and brassinosteroid signaling mediated by the TF BZR1, which is degraded via autophagy suppressed by TOR (Zhang et al. 2016b).

In the SAM, sucrose and photoreceptors additively promote the expression of *WUSCHEL* (*WUS*) encoding a homeodomain master TF by suppressing COP1 for stem cell regulation in the organizing center, which is partially prevented by the specific TOR inhibitor AZD8055 (Pfeiffer et al. 2016). However, the expression of *WOX5* related to *WUS* in the root quiescent center is not diminished in the *tor-es* mutant (Xiong et al. 2013). TOR activation stimulated by sugar, energy, and light signaling may exert differential regulations and functions in the RAM and SAM. It will be interesting to identify the molecular regulators mediating the TOR activation of *WUS* in the SAM. TOR is also an essential energy sensor to coordinate the circadian clock and plant growth. Nicotinamide treatment modulates the cytosolic ATP concentration monitored by an ATP biosensor and alters glucose-TOR signaling on period length, meristem activation, and root growth (N. Zhang et al. 2019).

Despite the lack of gene homologs encoding established sensors and transducers mediating TOR activation by amino acids in animals, sulfur (S), P, and N nutrients all influence plant TOR signaling (**Figure 3**) (Wu et al. 2019). For instance, TOR activity has been linked to Leu, Ile, and Val from the characterization of an *Arabidopsis* mutant that overaccumulated branched-chain amino acids with a reorganized actin cytoskeleton and endomembranes (Cao et al. 2019) or to Asp, Ile, and Met that inhibit the Pro- and Ala-stimulated nighttime oxygen consumption rate in *Arabidopsis* leaves (O'Leary et al. 2020). Importantly, a systematic study showed that TOR can be activated by diverse nitrogen signals, including nitrate, ammonium, and 15 amino acids, via convergent ROP2 signaling to promote cell proliferation in the leaf primordium (Liu et al. 2021).

S limitation is transduced to shoot TOR signaling and downregulation of glucose metabolism causing decreased rates of translation, lowered meristematic activity, and elevated rates of autophagy (Y. Dong et al. 2017). In *Chlamydomonas*, phosphate starvation sharply decreases LST8 abundance in TORC1, which is mediated by the TF PSR1 controlling phosphate-starvation responses (PSRs) (Couso et al. 2020). These new findings represent a fertile ground to investigate the diverse nutrient connections and downstream response mechanisms in TOR signaling unique to plants.

Downstream Effectors of the TOR Signaling Network

Direct and indirect TOR effectors have been identified in mediating the downstream TOR signaling network in plants. Systems, cellular, biochemical, and genetic analyses continue to uncover TOR phosphorylation of the TFs E2FA and E2FB, which are critical to S-phase gene activation. The finding reveals a previously unrecognized checkpoint in controlling cell cycle entry based on nutrient-energy status in meristems and primordia. The successful identification of low-abundance TFs offers an innovative approach for discovering novel TOR substrates with complex and combinatorial phosphorylation sites (Li et al. 2017, Xiong et al. 2013). Remarkably, plant TOR promotes protein translation by multiple mechanisms. Over 100 *Arabidopsis* genes encoding ribosomal proteins and protein synthesis machineries are activated by glucose-TOR signaling (Scarpin et al. 2020, Xiong et al. 2013). ChIP studies have revealed that nuclear TOR regulates rRNA synthesis by directly binding to the 45S *rRNA* promoter and the 5′ transcribed spacer DNA motifs (Ren et al. 2011). TOR directly phosphorylates TAP46 to inhibit PROTEIN PHOSPHATASE 2A (PP2A) and promote translation and N assimilation (Ahn et al. 2011). Moreover, S6K activated by TOR phosphorylates RPS6 and MA3-DOMAIN-CONTAINING-TRANSLATION-REGULATORY-FACTOR1 (MRF1) to enhance translation (Chen et al. 2018,

Dobrenel et al. 2016, Enganti et al. 2018, Lee et al. 2017, Ren et al. 2012). Comprehensive phenotypic analyses of *rps6a* and *rps6b* mutants and genetic complementation support downstream roles for RPS6 in light- and nutrient-dependent TOR functions in root, leaf, and flowering regulation (Ren et al. 2012). S6K phosphorylation of MRF1 promotes its association with EUKARYOTIC INITIATION FACTOR4A-1 (EIF4A-1) and light polysomal fractions, which may reboot translation during the dark-to-light transition (Lee et al. 2017). Unexpectedly, TOR-S6K signaling promotes translation reinitiation of uORF-containing mRNAs via phosphorylation of EUKARYOTIC INITIATION FACTOR 3h (EIF3h) (Ryabova et al. 2019, Schepetilnikov et al. 2013, Schepetilnikov et al. 2017). Phosphorylation of plant LA-RELATED-PROTEIN1 (LARP1) is inhibited by Torin2. Rigorous bioinformatics analyses suggest that LARP1 controls translation of conserved and plant-specific mRNAs with 5′-TERMINAL OLIGOPYRIMIDINE (Scarpin et al. 2020, Van Leene et al. 2019).

Recent discoveries have revealed that TOR or S6K phosphorylation can mediate the repression of substrates in surprisingly diverse biological processes in plants (**Figure 3**). The S6K-BIN2 (BRASSINOSTEROID INSENSITIVE2) relay promotes brassinosteroid signaling (Xiong et al. 2017). Direct TOR phosphorylation blocks the PK YAK1 as a negative regulator in cell cycle and flowering (Barrada et al. 2019, Forzani et al. 2019), prevents ATG1 or ATG13 activation in autophagy (Soto-Burgos et al. 2018, Van Leene et al. 2019), and inhibits the ABA receptor PYLs involved in stress responses (P. Wang et al. 2018). ABA-activated SNRK2 phosphorylates RAPTOR to inactivate TORC1, indicating reciprocal negative regulatory loops to balance TOR-growth and ABA-stress signaling (P. Wang et al. 2018). Interestingly, ETHYLENE-INSENSITIVE PROTEIN2 (EIN2), a previously defined key regulator in ethylene signaling, is phosphorylated by TOR to prevent its nuclear translocation and repressor function in glucose-TOR signaling, which is uncoupled from the ethylene responses mediated by the CONSTITUTIVE-TRIPLE-RESPONSE1-EIN2 link through specific phosphorylation sites (Fu et al. 2021). These findings suggest that central signaling hubs can be shared but differentially modulated by diverse hormone and nutrient signaling pathways using distinct phosphorylation codes that can be specified by upstream PKs. Unexpectedly, TOR dynamically represses cell–cell transport and sugar allocation via plasmodesmata during the sink-to-source leaf transition (Brunkard et al. 2020).

Important advances in our understanding of the glucose-TOR signaling network have been greatly facilitated by comprehensive and comparative RNA sequencing (RNA-seq), ribosome sequencing (Ribo-seq), and phosphoproteomics and interactomics analyses using *Arabidopsis* seedlings or cultured cells. These large-scale studies provide rich data resources for future exploration of both upstream and downstream network components and TOR substrate candidates controlling conserved or unique plant processes (Scarpin et al. 2020, Van Leene et al. 2019, Xiong et al. 2013).

SNRK1 IN STRESS AND ENERGY SIGNALING

To adapt to the daily light–dark cycle or unpredictable environmental stresses that compromise photosynthesis and respiration, plants need to control energy homeostasis for sustained growth and survival during sugar and energy deprivation. Studies on the regulation of universal *DARK-INDUCIBLE* (*DIN*) genes have provided crucial evidence to molecularly connect the glucose-repressible *DIN* transcription to the *Arabidopsis* energy sensor PKs KIN10 and KIN11 under diverse stress conditions (Baena-González et al. 2007, Sheen 2014). The *Arabidopsis* SNRK1 heterotrimeric complexes, consisting of the catalytic α subunit (KIN10/11) and the regulatory subunits (KINβ1/2/3 and the plant-specific KINβγ), share evolutionarily conserved structure in yeast SUCROSE-NONFERMENTING1 (SNF1) and human AMP-ACTIVATED PROTEIN KINASE (AMPK) (**Figure 4**). The *Arabidopsis kin10,11* and *kinβγ* mutants are embryonic

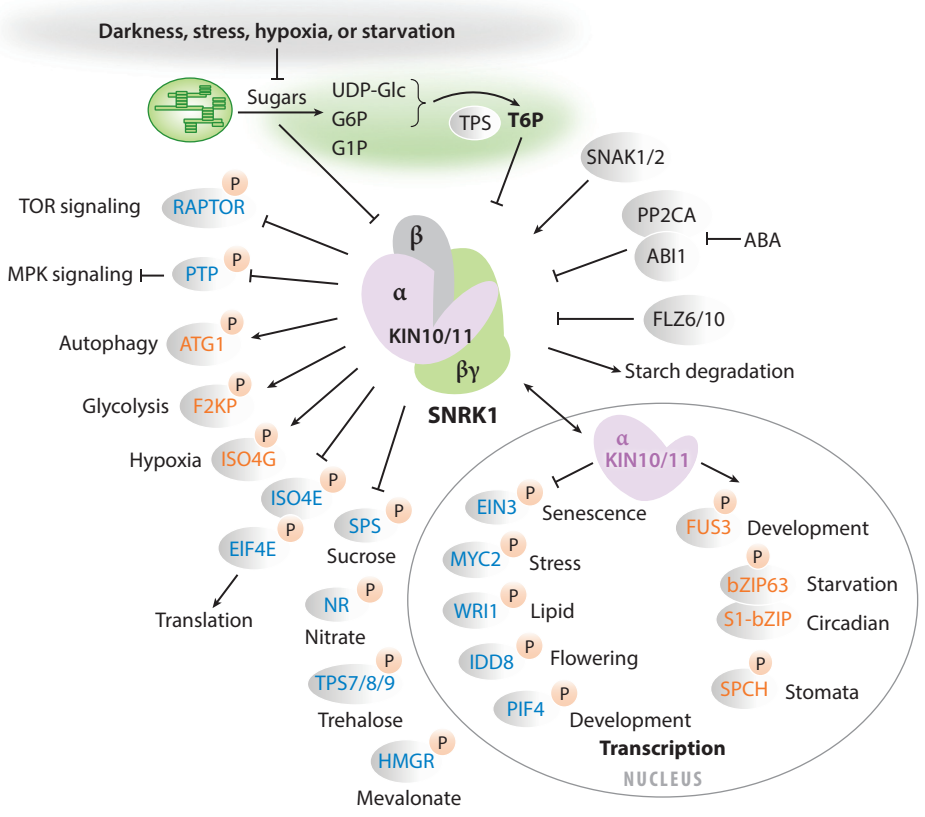

Figure 4

SNRK1 plays a central role in sensing nutrient deprivation and stress to promote catabolism but inhibit anabolism and growth. The SNRK1 complex is composed of catalytic α (KIN10/11) and regulatory β and βγ subunits. SNRK1 is activated by darkness, stress, starvation, hypoxia, and SNAKs but inhibited by sugars, metabolites, and FLZ repressors. SNRK1 phosphorylation positively (*orange text*) or negatively (*blue text*) regulates targets in broad biological processes. The catalytic α subunits (KIN10/11) can translocate to the nucleus to phosphorylate various TFs. KIN10/11 represses EIN3, MYC2, WRI1, IDD8, and PIF4 but activates FUS3, bZIP63, and SPCH. SNRK1 also phosphorylates and inhibits cytosolic enzymes, including SPS, NR, TPS7/8/9, and HMGR; translation regulators ISO4E, ISO4G, and ELF4E; and other signaling proteins in various biological responses. SNRK1 antagonizes TOR complex signaling by phosphorylating RAPTOR. Abbreviations: ABA, abscisic acid; ABI1, ABA INSENSITIVE1; ATG1, AUTOPHAGY RELATED1; bZIP, BASIC LEUCINE ZIPPER; EIF4E, EUKARYOTIC TRANSLATION INITIATION FACTOR 4E; EIN3, ETHYLENE INSENSITIVE3; F2KP, fructose-2,6-bisphosphatase; FLZ, FCS-LIKE ZINC FINGER; FUS3, FUSCA3; G1P, glucose 1-phosphate; G6P, glucose 6-phosphate; HMGR, 3-HYDROXY-3-METHYLGLUTARYL–COA REDUCTASE; IDD8, INDETERMINATE DOMAIN8; KIN10/11, KINASE10/11; MPK, MITOGEN-ACTIVATED PROTEIN KINASE; NR, NITRATE REDUCTASE; P, phosphorylation; PIF4, PHYTOCHROME INTERACTING FACTOR4; PP2CA, PROTEIN PHOSPHATASE 2CA; PTP, PROTEIN TYROSINE PHOSPHATASE; RAPTOR, REGULATORY-ASSOCIATED-PROTEIN-OF-MTOR; SNAK, SNRK1-ACTIVATING KINASE; SNRK1, SNF1-RELATED KINASE1; SPCH, SPEECHLESS; SPS, SUCROSE PHOSPHATE SYNTHASE; T6P, trehalose 6-phosphate; TF, transcription factor; TOR, TARGET OF RAPAMYCIN; TPS, T6P SYNTHASE; UDP, uridine diphosphate; WRI1, WRINKLED1.

lethal, hindering research progress in the past (Baena-González et al. 2007; Broeckx et al. 2016; Emanuelle et al. 2015; Ramon et al. 2013, 2019).

The SNRK1 Transcription Network

Remarkably, the transient expression of KIN10 alone controls the activation and repression of thousands of genes involved in transcription, signaling, catabolism, and anabolism in a cell-based assay. These KIN10 target genes are either positively correlated with stress and starvation genes or negatively correlated with the genes activated by glucose, sucrose, and elevated CO_2 levels identified in cultured cells, seedlings, and adult leaves from genome-wide analyses. The high correlation between KIN10 target genes and the transcriptome reprogramming in multiple physiological responses provides compelling evidence to support a critical and convergent role of KIN10 in mediating sugar- or energy-deprivation responses triggered by darkness, starvation, or diverse stress conditions. Transgenic KIN10 overexpression confers enhanced starvation tolerance and life span extension and alters plant architecture and developmental transitions. Conditional *kin10,11* deficiency abrogates the transcriptional switch in darkness or stress signaling and impairs starch mobilization at night but also arrests growth by unclear mechanisms (Baena-González et al. 2007, Broeckx et al. 2016, Pedrotti et al. 2018, Sheen 2014).

Significant research advances have revealed how direct phosphorylation by KIN10/11 promotes or represses specific TFs involved in various biological functions, primarily plant-specific and not previously recognized (**Figure 4**). The best studied example demonstrated that KIN10 phosphorylates bZIP63 to enhance heterodimerization with TF bZIP-S and activate target genes in alternative mitochondrial metabolic pathways to ensure plant survival in extended darkness (Mair et al. 2015, Pedrotti et al. 2018). The TPS1-T6P-KIN10-bZIP63-PRR7 (PSEUDO-RESPONSE REGULATOR7) signaling cascade regulates the sucrose-dependent circadian phase (Frank et al. 2018). Interestingly, FUSCA3 (FUS3), a key regulator in embryogenesis, is phosphorylated by KIN10 to modulate KIN10-dependent postembryonic development and flowering (Tsai & Gazzarrini 2012). Phosphorylation of SPCHLESS by KIN10 promotes sucrose-dependent stabilization and stomata development (Han et al. 2020). Many studies have shown that KIN10 can also directly phosphorylate and repress TFs controlling diverse biological processes, including MYC2 in the salt-stress response (Im et al. 2014), INDETERMINATE DOMAIN8 (IDD8) in flowering (Jeong et al. 2015), EIN3 in senescence (Kim et al. 2017), WRINKLED1 (WRI1) in lipid biosynthesis (Zhai et al. 2017), and PHYTOCHROME INTERACTING FACTOR4 (PIF4) in thermoresponsive hypocotyl elongation requiring TPS1-T6P signaling (Hwang et al. 2019). KIN10 phosphorylation mediates diverse regulatory mechanisms, reducing MYC2 and EIN3 protein stability or IDD8 transcriptional activity.

The SNRK1 Signaling Network

Besides plant-specific transcriptional controls, similar to human AMPK, KIN10 phosphorylates ATG1 to activate autophagy (Chen et al. 2017) and RAPTOR to repress TOR signaling (Nukarinen et al. 2016). Quantitative phosphoproteomics, proteomics, and metabolomics analyses have been conducted with *Arabidopsis* plants in extended darkness using a conditional *kin10,11* mutant (Nukarinen et al. 2016, Pedrotti et al. 2018) or submergence stress (hypoxia) based on dominant-negative KIN10 plants (Cho et al. 2016). These complementary approaches confirmed the SNRK1-dependent phosphorylation of multiple metabolic enzymes in the cytosol in vivo, supporting an SNRK1-mediated redirection of carbon flux toward glycolysis and mitochondrial respiration. Novel PROTEIN TYROSINE PHOSPHATASE (PTP)-MITOGEN-ACTIVATED PROTEIN KINASE (MPK) signaling (Cho et al. 2016)

and phosphorylation of photosynthesis-related proteins in the chloroplast were also detected (Nukarinen et al. 2016). It remains to be determined whether SNRK1 enters the chloroplast and phosphorylates organelle-specific targets (Ruiz-Gayosso et al. 2018). Surprisingly, KIN10 phosphorylation represses general translation via EIF4E and EIFISO4E inhibition (Bruns et al. 2019) but targets plant-specific EIFISO4G1 to enhance the translation of mRNAs for submergence tolerance (Cho et al. 2016, Cho et al. 2019) (**Figure 4**).

Novel SNRK1 Regulation

Despite structural conservation, the regulation of SNRK1 exhibits many features not found in human AMPK. SNRK1 is insensitive to AMP/ADP activation and resistant to T-loop dephosphorylation by protein phosphatases (PPs). KIN10 is constitutively active by T-loop autophosphorylation. Nuclear KIN10 activates a *DIN6-LUC* reporter but is repressed by myristoylated KINβ1/2 in cell-based assays. Importantly, transgenic plants with altered KIN10 localization modify metabolic stress responses and display novel phenotypes in shoots and roots (Broeckx et al. 2016, Ramon et al. 2019). Significantly, T6P appears to inhibit KIN10 by direct binding, which decreases its interaction with and phosphorylation/activation by upstream SNRK1-ACTIVATING KINASE (SNAK)1/2 in vitro (Shen et al. 2009, Zhai et al. 2018). However, the binding site remains unknown and the K_d is higher than the endogenous T6P level estimated at low micromolar concentrations as a signaling molecule in plants (Baena-González & Lunn 2020, Figueroa & Lunn 2016). Other sugar metabolites can also repress SNRK1 by unknown mechanisms (Nunes et al. 2013, Zhang et al. 2009). KINβ3 and KINβγ are detected in the chloroplast and SNRK1 activity is modulated by maltose (Ruiz-Gayosso et al. 2018). KIN10 activation and ABA signaling share overlapping target genes, and specific PP2Cs appear to serve as the converged hub for the coordinated activation of ABA and energy/stress signaling pathways (Jossier et al. 2009, Rodrigues et al. 2013). FSC-LIKE ZINC FINGER (FLZ)6/10 interacting with SNRK1 in the cytosol represents plant-specific repressors (Jamsheer et al. 2018) (**Figure 4**). Future research may uncover new mechanisms of SNRK1 regulation to clarify additional layers of molecular controls in the dynamic sugar/energy/stress signaling networks.

NITRATE SENSING AND SIGNALING

Plants have evolved sophisticated sensing and signaling networks to respond and adapt to fluctuating nitrate availability from starvation to broad concentrations in the soil (**Figure 5**). Using nitrate reductase–deficient plants, nitrate was demonstrated to act as a signaling molecule uncoupled from its metabolism, and nitrate-induced TF ANR1 regulates root architecture (Scheible et al. 1997, Wang et al. 2004, Zhang & Forde 1998). Extensive transcriptome analyses and network modeling have identified thousands of nitrate-responsive genes and key TFs for the dynamic and spatiotemporal control of nitrogen uptake and assimilation, carbon metabolism, sulfate assimilation, transcription regulation, and hormone metabolism (Canales et al. 2014, Scheible et al. 2004, Vidal et al. 2013, Vidal et al. 2020, Walker et al. 2017, Wang et al. 2004, Y.-Y. Wang et al. 2018). Primary nitrate responses (PNRs) occur in minutes and activate the synthesis and signaling of the plant hormones cytokinin and auxin but degrade ABA. Nitrate-induced cytokinin promotes root meristem proliferation and acts as a systemic signal to promote shoot growth (Liu et al. 2017, Naulin et al. 2020, Sakakibara 2020, Vidal et al. 2013, Yan et al. 2016) (**Figure 5**).

The Nitrate Transcription Network

The characterization of *nin-like-protein*7 (*nlp*7) or dominant-negative *nlp6* mutants and NIN-LIKE PROTEIN (NLP)6/7 binding to nitrate-responsive elements has defined master TFs in

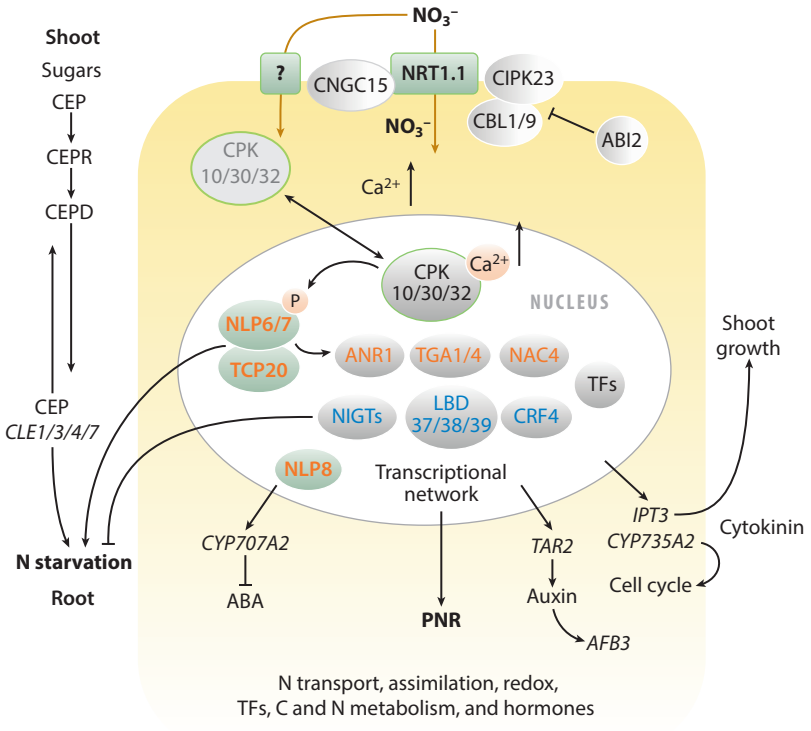

Figure 5

The nitrate sensing and signaling network. Nitrate triggers the nuclear Ca^{2+}-CPK-NLP6/7 cascade and induces genes encoding activators (*orange text*) and repressors (*blue text*) of the PNRs. Nitrate-activated genes encoding TFs, including NIGT1s and LBD37/38/39, repress N-starvation genes. Nitrate activates the synthesis and signaling of the plant hormones cytokinin and auxin but degrades ABA. The activity of the nitrate transceptor NRT1.1 is regulated by CBL1/9-CIPK23, which is inhibited by ABI2/PP2C. Nitrogen starvation activates the CLE1/3/4/7 peptides to repress lateral root development and triggers CEPs to move to the shoot to activate CEPRs. Activated CEPD1/2 proteins in the shoot then translocate to the root to enhance nitrate uptake. Abbreviations: ABA, abscisic acid; ABI2, ABA INSENSITIVE2; AFB, AUXIN-SIGNALING F-BOX; ANR, ARABIDOPSIS NITRATE REGULATED1; CBL, CALCINEURIN B-LIKE; CEP, C-TERMINALLY ENCODED PEPTIDE; CEPD, CEP DOWNSTREAM; CEPR; CEP RECEPTOR; CIPK, CBL-INTERACTING PROTEIN KINASE; CLE, CLAVATA3/EMBRYO SURROUNDING REGION-RELATED; CPK, CALCIUM DEPENDENT PROTEIN KINASE; CRF, CYTOKININ-RESPONSE FACTOR; CYP, cytochrome P450; IPT3, ISOPENTENYLTRANSFERASE3; LBD, LATERAL ORGAN BOUNDARIES DOMAIN; NAC, NAM, ATAF, CUC; NIGT, NITRATE-INDUCIBLE GARP-TYPE TRANSCRIPTIONAL REPRESSOR; NLP, NIN-LIKE PROTEIN; NRT1.1, NITRATE TRANSPORTER 1.1; P, phosphorylation; PNR, primary nitrate response; PP2C, PROTEIN PHOSPHATASE2C; TAR, TRYPTOPHAN AMINOTRANSFERASE RELATED; TCP, TEOSINTE BRANCHED 1/CINCINNATA/PROLIFERATING CELL FACTOR; TF, transcription factor; TGA, TGACG SEQUENCE-SPECIFIC BINDING PROTEIN1.

PNRs (Castaings et al. 2009, Konishi & Yanagisawa 2013, Marchive et al. 2013). Time series ChIP-sequence (ChIP-seq) and DNA-adenine-methyltransferase-identification experiments efficiently captured genomewide transient and stable NLP7 target genes (Alvarez et al. 2020). NLP8 plays a unique role in nitrate-stimulated seed germination by activating *CYP707A2* for ABA degradation (Yan et al. 2016). Nitrate-induced TF genes encoding activators (ANR1, TGA1/4,

and NAC4) and repressors [LATERAL ORGAN BOUNDARIES DOMAIN (LBD)37/38/39, NITRATE-INDUCIBLE GARP-TYPE TRANSCRIPTIONAL REPRESSOR (NIGT)1/2, and CYTOKININ-RESPONSE FACTOR (CRF)4] of nitrate responses have been extensively characterized for unique or overlapping functions in nitrate signaling and root development (Canales et al. 2014, Vidal et al. 2013, Vidal et al. 2020, Y.-Y. Wang et al. 2018). LBD37/38/39 and NIGT1/2 dynamically fine-tune nitrate-regulated transcription (Kiba et al. 2018, Maeda et al. 2018, Medici et al. 2015). The rapid, dynamic, dose-responsive, and hierarchical features of the nitrate regulatory network are demonstrated by the integration of TF-target gene data sets from time series genomewide RNA-seq, ChIP-seq, and DNase-seq experiments with computational and network analyses. TGA1 and CRF4 are proposed TF hubs, and TGA1 overexpression strongly promotes the root system (Alvarez et al. 2019, Brooks et al. 2019, Swift et al. 2020, Varala et al. 2018). Mutant analyses based on nitrogen utilization efficiency in rice have identified key TFs, including GROWTH-REGULATING FACTOR4 promoting N uptake and N/C metabolism (Li et al. 2018) and NITROGEN-MEDIATED TILLER GROWTH RESPONSE5 promoting tilling and/or branching (Wu et al. 2020). Large-scale yeast one-hybrid (Y1H) screens between TFs and promoters in N metabolism have proposed a comprehensive N-related transcriptional regulatory network, providing valuable resources for future research (Gaudinier et al. 2018). Research advances are crucial to connecting the expansive transcription network to upstream nitrate sensing and signaling mechanisms (**Figure 5**).

Nitrate Sensing and Signaling

NRT1.1/CHL1/NITRATE TRANSPORTER1/PEPTIDE TRANSPORTER (NPF)6.3 was the first identified dual-affinity nitrate transporter and transceptor, as the P492L mutant shows compromised nitrate transport but retains nitrate signaling (Ho et al. 2009). T101 in NRT1.1 is phosphorylated by calcium-regulated CALCINEURIN B-LIKE (CBL)1/9-CBL-INTERACTING PROTEIN KINASE (CIPK)23 and modulates nitrate transport, sensing, and signaling (**Figure 5**) (Bouguyon et al. 2015, Ho et al. 2009, Y-Y. Wang et al. 2018, X. Zhang et al. 2019). CBL1/9-CIPK23 is inactivated by a specific ABA INSENSITIVE (ABI)2/PP2C, which integrates nitrate and ABA-stress signaling (Léran et al. 2015). In rice, nitrate promotes OsNRT1.1B-mediated activation of the E3 ubiquitin ligase OsNBIP1 to degrade a repressor OsSPX4 and activate OsNLP3 (Hu et al. 2019). New insights are necessary to distinguish molecular mechanisms for different NRT1.1 states and subcellular localizations in extracellular or intracellular nitrate sensing and signaling. Recent studies (Chen et al. 2021) also suggest that NRT1.13 may be a potential nitrate transceptor in regulating flowering and branching.

Calcium signaling in PNR was first indicated by applying inhibitors of calcium channels and effectors to diminish nitrate-induced transcription (Liu et al. 2017, Liu et al. 2020, Riveras et al. 2015, Sakakibara et al. 1997). The use of an ultrasensitive calcium biosensor was critical to demonstrating that nitrate triggers calcium signaling in the cytosol and nucleus. A targeted functional screen of CALCIUM-DEPENDENT PKs (CPKs) identified group III CPK10/30/32 as redundant key regulators in PNR, which are impaired in a conditional *icpk* triple mutant. S205 phosphorylation by CPK10/30/32 is essential for nuclear NLP7 retention to activate the nitrate-responsive transcriptome and optimal root–shoot development (**Figure 5**). Intriguingly, the calcium channel CYCLIC NUCLEOTIDE-GATED ION CHANNEL15 (CNGC15) has been reported to interact with NRT1.1 and facilitate nitrate-induced calcium influx from the plasma membrane at the root tip (Wang et al. 2021). Future exploration of dynamic protein phosphorylation events and nitrate-regulated genes encoding PKs and PPs may reveal novel mechanisms in PNR (Liu et al. 2017, 2020).

Nitrogen-Starvation Responses

Nitrogen deficiency in plants triggers changes in root foraging, transcriptome, metabolism, and nitrogen uptake (Krapp et al. 2011). Nuclear TEOSINTE BRANCHED1/CINCINNATA/PROLIFERATING CELL FACTOR (TCP)20 and NLP6/7 form heterodimers and regulate nitrate-assimilation genes and primary root meristems under N starvation (Guan et al. 2017). Genomewide Y1H screens identified four related NIGT1s as TF repressors of a N-starvation-responsive promoter. NLP7 activates *NIGT1* transcription, but NIGT1s suppress NLP7 and the N-starvation-responsive transcriptome to optimize dynamic N acquisition, remobilization, and signaling (Kiba et al. 2018, Maeda et al. 2018). Nitrogen starvation also triggers peptide genes for local and systemic N-demand signaling. CLE1/3/4/7 peptides are induced in the root vasculature and repress lateral root development (Araya et al. 2014). Split-root and grafting assays indicate that secreted C-TERMINALLY ENCODED PEPTIDES (CEPs) are induced and move from the N-starved roots through the xylem stream to shoots where the CEPs are perceived by receptor kinases (Tabata et al. 2014). Phloem-specific C-TERMINALLY ENCODED DOWNSTREAM PEPTIDE (CEPD)1/2 proteins are then induced in shoots and translocated to roots through phloem to enhance *NRT2.1* for high-affinity nitrate uptake (**Figure 5**) (Ohkubo et al. 2017). Understanding the sensing mechanisms in N-deficiency responses and their integration with the complex nitrate signaling network represents future research challenges.

PHOSPHATE SENSING AND SIGNALING

The acquisition and assimilation of inorganic phosphate is essential to support plant growth. As phosphate availability is often limited in the soil, plants have evolved PSRs mediated by complex sensing and signaling networks. Universal and organ-specific PSRs occur in shoots and roots as well as through root-to-shoot or shoot-to-root systemic communication and regulation. In shoots, PSRs reduce photosynthesis and leaf expansion but promote anthocyanin, sugar, and starch accumulation and early flowering. In roots, PSRs lead to primary root arrest and meristem exhaustion but promote extensive root exudates (organic acids and phosphatases) to solubilize phosphate as well as lateral root and root-hair development to increase the surface area for phosphate forage. Universal PSRs stimulate uptake, translocation, recycling, and remobilization of phosphate and membrane phospholipid remodeling (**Figure 6*a***) (Chien et al. 2018, Ham et al. 2018, Puga et al. 2017, Raghothama 2000).

Internal Phosphate Sensing and Signaling

Comprehensive characterization of the *ARABIDOPSIS PHOSPHATE-STARVATION-RESPONSE1 (phr1)* and *PHR-LIKE (phl)* mutants has established that PHOSPHATE STARVATION RESPONSE (PHR)1 and related PHLs are central TFs controlling transcriptome reprogramming and a broad range of PSRs in shoots and roots (Bustos et al. 2010, Rubio et al. 2001, Sun et al. 2016, Thibaud et al. 2010). In *Arabidopsis* and rice, the evolutionarily conserved SPX-domain repressors interact with and inhibit PHR1 in a phosphate-dependent manner. Consistently, *spx1,2* mutants enhance PSRs, whereas SPX1-overexpression plants reduce PSRs (Puga et al. 2014, Wang et al. 2014). Comprehensive structural, biochemical, genetic, and phenotypic analyses provide compelling evidence that SPXs are sensors that bind to $InsP_8$ as a metabolite signal indicator of intracellular phosphate levels. Inositol pyrophosphate kinases such as VIP-HOMOLOG1/2 (VIH1/2) play a key role in the phosphate-to-$InsP_8$ signal relay as *vih1,2* plants exhibit constitutive PSR despite abundant phosphate (Dong et al. 2019, Wild et al. 2016, Zhu et al. 2019) (**Figure 6*a***).

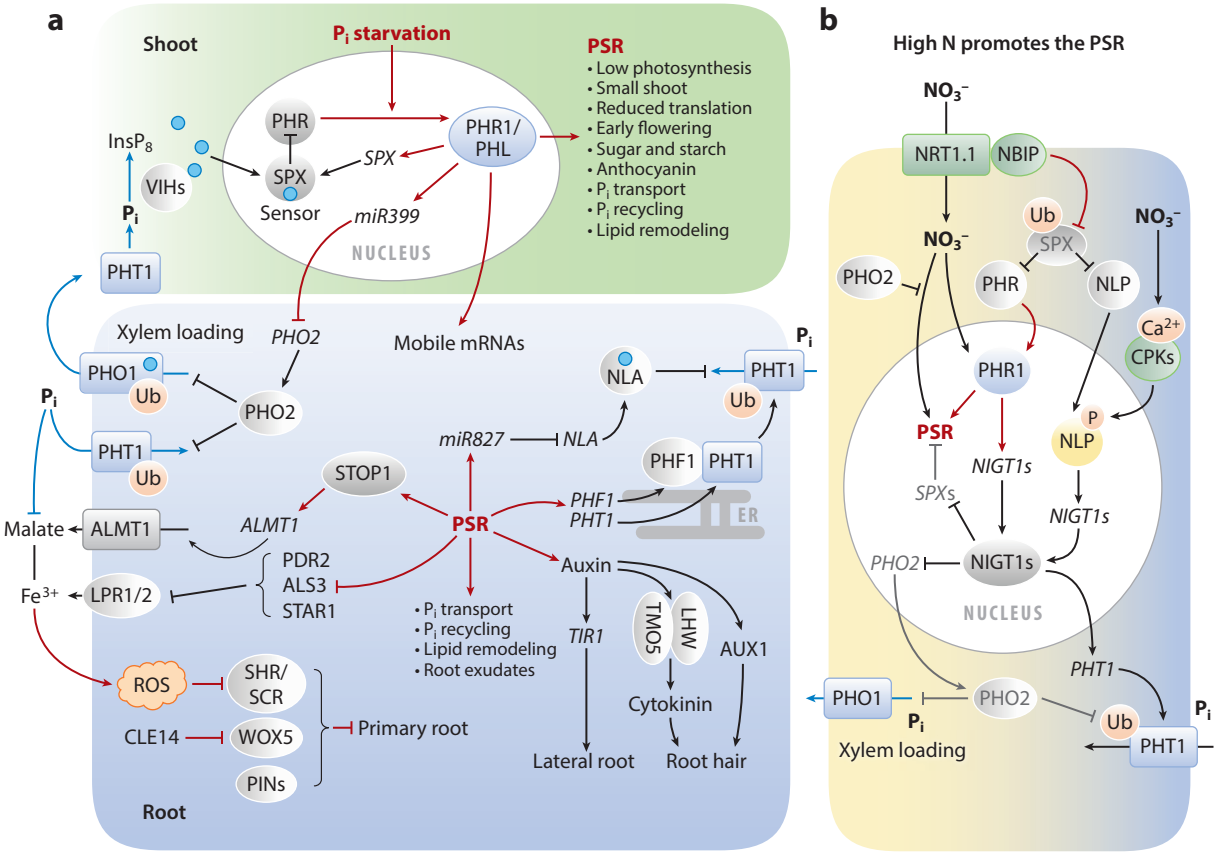

Figure 6

(*a*) PSRs in shoots and roots. P_i is taken up by PHT1 transporters and converted to the signaling molecule $InsP_8$, which is perceived by the SPX sensor to inhibit PHR1. Under P_i starvation, the key TFs PHR1/PHL induce transcriptome reprogramming to promote PSRs in both shoots and roots as well as shoot-to-root mobile mRNAs and miRNAs. Shoot *miR399* inhibits root *PHO2*, encoding a ubiquitin E2 conjugase for the degradation of the PHT1 and PHO1 transporters. In roots, low external P_i induces iron-dependent ROS by derepressing ferroxidase LPR1/2 and promoting nuclear TF STOP1 to enhance malate transporter ALMT1. Activated CLE14 peptide inhibits the key TFs SHR/SCR and WOX5 as well as auxin transporter PINs and arrests the primary root meristem. Root PSRs also induce the hormones auxin and cytokinin to promote lateral root and root hair growth. (*b*) High N levels promote PSRs by multiple mechanisms. Nitrate enhances TF PHR1 by stabilizing the protein and degrading the SPX repressor. The nitrate-NRT1.1-CPK-NLP cascade or the nitrate-NRT1.1-NBIP-SPX-NLP relay activates NIGT1s to repress *SPX*s and *PHO2* encoding repressors of the PSR but activates *PHT1*s to enhance P_i uptake. Nitrate also enhances the PSR by a PHO2-dependent mechanism independent of PHR1. Abbreviations: ALMT1, ALUMINUM-ACTIVATED MALATE TRANSPORTER1; ALS3, ALUMINUM SENSITIVE3; AUX1, AUXIN TRANSPORTER PROTEIN1; CLE14, CLAVATA3/ESR-RELATED14; CPK, CALCIUM-DEPENDENT PROTEIN KINASE; ER, endoplasmic reticulum; $InsP_8$, inositol pyrophosphate8; LHW, LONESOME HIGHWAY; LPR, LOW PHOSPHATE ROOT; miRNA, microRNA; mRNA, messenger RNA; NBIP, NRT1.1B INTERACTING PROTEIN; NIGT1, NITRATE-INDUCIBLE GARP-TYPE TRANSCRIPTIONAL REPRESSOR1; NLA, NITROGEN LIMITATION ADAPTATION; NLP, NIN-LIKE PROTEIN; NRT1.1, NITRATE TRANSPORTER 1.1; P, phosphorylation; PDR2, PHOSPHATE DEFICIENCY RESPONSE2; PHF1, PHOSPHATE TRANSPORTER TRAFFIC FACILITATOR1; PHL, PHR1-LIKE; PHO, PHOSPHATE; PHR, PHOSPHATE STARVATION RESPONSE; PHT1, PHOSPHATE TRANSPORTER1; P_i, inorganic phosphate; PIN, PIN-FORMED; PSR, phosphate-starvation response; ROS, reactive oxygen species; SCR, SCARECROW; SHR, SHORT-ROOT; SPX, SYG1/Pho81/XPR1; STAR1, SENSITIVE TO ALUMINUM RHIZOTOXICITY1; STOP1, SENSITIVE TO PROTON TOXICITY1; TF, transcription factor; TIR1, TRANSPORT INHIBITOR RESPONSE1; TMO5, TARGET OF MONOPTEROS5; Ub, ubiquitination; VIH, VIP-HOMOLOG; WOX5, WUSCHEL RELATED HOMEOBOX5.

The PSR involves extensive systemic signaling between shoots and roots. Older source leaves appear to be the first to suffer phosphate deprivation, and PSRs are subsequently initiated in both shoots and roots. Protein-encoding mRNAs and microRNAs (miRNAs) can play regulatory roles through long-distance communications (**Figure 6*a***). PSR-induced *miRNA399* expression occurs earlier in shoots during the PSR and moves through phloem to roots to suppress mRNAs encoding PHO2, a ubiquitin E2 conjugase, which targets the PHO1 exporter and PHT1 transporters for ubiquitination and degradation (Bari et al. 2006, Chiou et al. 2006, Huang et al. 2013, Lin et al. 2008, Liu et al. 2012). The mRNA encoding an E3 ligase NITROGEN LIMITATION ADAPTATION (NLA) targeting plasma membrane PHT1s is suppressed by *miR827* to elevate cytosolic phosphate levels during PSR (Kant et al. 2011, Lin et al. 2013). Unexpectedly, the EXS domain of PHO1 is sufficient to provide an enigmatic root-to-shoot signal to attenuate phosphate signaling despite low internal phosphate levels in shoots (Wege et al. 2016). Phloem fluid transcriptome analyses discovered abundant mobile mRNAs in *Arabidopsis* and cucumber, which require thorough investigation of their functions in the PSR (Thieme et al. 2015, Zhang et al. 2016a).

External Phosphate Signaling

Transcriptome analyses from split-root experiments support root-specific responses to extracellular phosphate status independent of intracellular phosphate concentrations, which are modulated systemically (Bustos et al. 2010, Thibaud et al. 2010). Primary root arrest is the consequence of iron-dependent reactive oxygen species (ROS) signaling triggered by low external phosphate levels (**Figure 6*a***). Genetic analyses identified *LOW-PHOSPHATE-ROOT1/2* (*LPR1/2*) encoding cell-wall targeted ferroxidases in promoting ROS. LPR1/2 are modulated by three upstream negative regulators, P5-type ATPase PHOSPHATE DEFICIENCY RESPONSE (PDR)2 and ABC transporter complex ALS3/STAR1. Upon P_i limitation, apoplastic iron at low pH stimulates the rapid nuclear accumulation of the TF STOP1 and activates a malate transporter gene *ALMT1* to promote local malate-Fe^{3+} and ROS signaling (Balzergue et al. 2017, Godon et al. 2019, Mora-Macías et al. 2017). Derepressed LPR1/2 levels trigger cell-specific Fe^{3+}, ROS, and callose accumulation, which impairs TF SHR movement and primary root growth in the meristem and elongation zones (Balzergue et al. 2017, J. Dong et al. 2017, Mora-Macías et al. 2017, Müller et al. 2015). Finally, activated CLE14 peptide signaling switches cell differentiation in the stem cell niche via CLAVATA2 (CLV2)/PERCEPTION OF ARABIDOPSIS DANGER SIGNAL2 (PEPR2) receptors, which eventually exhausts the primary root meristem and diminishes the key TFs WOX5, SCARECROW (SCR), and SHORT ROOT (SHR) as well as PIN1 auxin transporters (Gutiérrez-Alanís et al. 2017).

Integrative Phosphate Signaling

PSRs are intimately integrated with plant hormones and other nutrients (**Figure 6*a***) (Chien et al. 2018, Ham et al. 2018, Puga et al. 2017). To forage phosphate resources in the topsoil, the PSR promotes auxin synthesis, transport, and signaling to enhance lateral root initiation and elongation by activating an auxin receptor gene *TIR1* in root pericycle cells (Pérez-Torres et al. 2008). PSR-stimulated root-hair elongation requires auxin from the root tip and is significantly reduced in the *phr1/phl* (Bustos et al. 2010), auxin synthesis *taa1*, and auxin transport *aux1* mutants (Bhosale et al. 2018, Bustos et al. 2010). Moreover, the enhanced root-hair density requires the auxin-activated TFs TARGET OF MONOPTEROS 5 (TMO5)/LONESOME HIGHWAY (LHW) and cytokinin synthesis in the xylem but signaling in the epidermis (Wendrich et al. 2020).

Exciting findings have uncovered the critical role of nitrate signaling in the PSR by multiple mechanisms (**Figure 6*b***). Nitrate controls PHR1 accumulation and is indispensable in

transcriptome reprogramming during PSR. The nitrate-NRT1.1-CPK-NLP7-NIGT1 cascade suppresses *PHO2* expression, but the nitrate requirement can be bypassed in *pho2* independent of PHR1 and NRT1.1 (Medici et al. 2019). Nitrate- and PHR1-activated NIGT1s also suppress *SPX*s encoding a pivotal repressor but activate *PHT1*s in the PSR (Kiba et al. 2018, Maeda et al. 2018, Medici et al. 2015, Medici et al. 2019, Ueda et al. 2020). In rice, nitrate stimulates OsNRT1.1B-OsNBIP1 interaction and OsSPX4 degradation, which leads to nuclear translocation and the activation of OsPHR2 and OsNLP3, a pathway that is likely conserved in other plants (Hu et al. 2019). As phosphate uptake requires high energy, sugars are essential to promote PSR-mediated transcriptome changes by unknown signaling mechanisms. These findings reveal the priority for nutrient acquisition, as PSRs are not activated until both sugars and nitrate are available (Lei et al. 2011, Medici et al. 2019, Müller et al. 2007).

CHALLENGES AND OUTLOOK

Plant nutrient signaling networks form the foundation of the global food chain and support interconnected ecosystems. The fixation of CO_2 and the release of O_2 through photosynthesis have shaped the evolution of all lives in the history of Earth. Advances in our knowledge of the global cycles of C, N, and P and their intertwined nutrient regulatory networks in plants may offer solutions for agricultural innovations as well as mitigating climate changes and balancing ecosystems.

Despite significant research progress and discoveries, many questions remain regarding how the key nutrient, energy, and metabolite sensors and signaling regulators function and integrate into the interdependent nutrient signaling networks as well as interconnected sensor coordination. Diverse sensors perceiving physiological nutrient and metabolite signals with distinct specificity and affinity at broad concentration ranges are only beginning to emerge. The main challenges are to uncouple precise sensing and signaling functions from nutrient transport and metabolic processes, which are tightly intertwined. Specific chemical inhibitors or activators as well as live-imaging and time series analyses of sensitive and specific reporters and biosensors may circumvent mutant limitations due to lethality, redundancy, and long-term pleiotropic effects. Thoughtfully designed global profiling experiments and genome-wide high-throughput screens should enable the discovery of more nutrient sensors, direct downstream targets, subcellular actions, and novel molecular wiring and mechanisms.

Investigation of the complex nutrient, hormone, peptide, and metabolite interactions in organ-, tissue-, and cell-specific responses mediated by local or systemic signaling will lead to new surprises. Both nitrate and phosphate signaling rely on sugars by largely unknown molecular mechanisms. Future discoveries should encompass universal sensors, signaling components, and regulatory mechanisms in multicellular organisms from plants to humans. Unique and specialized regulators in diverse plant species will also be discovered. Understanding and exploration of the emerging relationships of C, N, and P and their integration with intrinsic regulators and diverse environmental cues may inspire new and tailored designs for beneficial or enhanced traits in nutrient uptake, assimilation, mobilization, and utilization and storage while uncoupling stress responses compromising growth and reproduction. Sophisticated plans and practices in agricultural applications for more efficient fertilizer acquisition and usage may help realize the ultimate goals of sustainable agriculture and ecosystems.

DISCLOSURE STATEMENT

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