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Sucrose metabolism: Controls the sugar sensing and generation of signalling molecules in plants

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Abstract
The daily life of photosynthetic plants revolves around sugar manufacturing, transport, storage and utilization, and the complex sucrose (Suc) metabolic and signaling networks integrate internal regulators and environmental cues to govern and sustain plant growth and survival. Suc metabolism plays crucial roles in plant development mainly by generating a range of sugar signaling molecules such as Suc itself, glucose (Glc) and trehalose- 6-phosphate (T6P). Sugars not only fuel cellular carbon and energy metabolism but also play pivotal roles as signaling molecules. Sugars have a central regulatory function in steering plant growth. This review having information presented in the past years on key players in sugar-mediated plant growth regulation, with emphasis on hexokinase, Snf1-related kinase 1, and target of rapamycin kinase regulatory systems, trehalose 6-phosphate.

Keywords: HXK, SnRK1, TOR kinase, bZIP, Sucrose, Trehalose 6-phosphate

1. Introduction
In plants, growth usually is a Complex molecular networks & irreversible change in size involving cell division and cell elongation. These networks must continuously adapt to an ever-changing environment (Gonzalez *et al*., 2012; Powell and Lenhard, 2012) [28, 78]. Plants have played a crucial role in the evolution of life on earth through the making of energy-rich sugar molecules and oxygen by photosynthetic carbon fixation. Sugars are the most important carbon and energy source to cells, and also have important regulatory functions in controlling metabolism, growth and development of plants (Ramon *et al*., 2008) [80]. Sugars operate both as immediate substrates for intermediary metabolism and as effective signaling molecules (Meyer *et al*., 2007; Rolland *et al*., 2006) [67, 86]. Sugars as signaling compounds have intense effects in all stages of the plant's life cycle from germination and vegetative growth to reproductive development and seed formation (Smeekens, 2000) [97]. Plant sugar regulation is mediated by sugar signals, which are generated at different locations depending on environmental conditions and developmental stage. Sucrose (Suc) transport and hydrolysis play key regulatory roles in sugar signal generation (Ruan, 2014) [88]. In plants, sensing and signaling pathways have been described for different sugars (Hanson & Smeekens, 2009; Rolland *et al*., 2006) [37, 86] but only for glucose detailed information on sensing and signaling mechanisms is available (Rolland *et al*., 2006; Ramon *et al*., 2008; Grigston *et al*., 2008) [86, 80, 31]. Over the past decade, integrated cellular, chemical, genetic, proteomic and genomic approaches in the reference plant *Arabidopsis thaliana* have begun to unravel the surprisingly broad range of functions and actions of three glucose-modulated master regulators, HXK1, KIN10/11 and TOR and it controls the expression of thousands of plant genes involved in a wide spectrum of cellular functions (Baena-González and Sheen 2008; Dobrenel *et al*., 2013; Halford *et al*., 2003; Polge and Thomas, 2007; Ramon *et al*., 2008; Robaglia *et al*., 2012; Rolland *et al*., 2002; Rolland *et al*., 2006; Sheen, 2010; Smeekens *et al*., 2010; Xiong and Sheen, 2014) [4, 22, 36, 77, 80, 83, 87, 86,, 92, 96, 113]. In recent years important progress has also been made in identifying the dominant plant growth controlling regulatory systems that receive input from sugars and sugar derived metabolic signals. These systems are either growth promoting or growth inhibiting. Systems that have promoting role on growth are the hexokinase (HXK) glucose (Glc) sensor, the trehalose 6-phosphate (T6P) signal, and the Target of Rapamycin (TOR) kinase system in response to high sugar levels (Deprost *et al*., 2007) [20]. Growth and floral transition halted in the absence of either T6P or TOR kinase (Deprost *et al*., 2007) [20]. Systems that have inhibitory effect on growth are the plant SNF1-related Protein Kinase1 (SnRK1), homologue of the animal AMP-activated protein kinase (AMPK) and yeast sucrose non-fermenting 1 (SNF1) kinase, and C/S1 bZIP transcription factor network in response to low sugar level.

Stimulation of either system results in growth arrest (Smeekens *et al*., 2010; Robaglia *et al*., 2012) [96, 83]. These systems are active throughout the life cycle and are essential for plant survival under stress conditions (Baena-González, 2010) [6]. Activity of TOR and SnRK1 are modulated by the plant's status of sugar, which is sensed by sugar signalling processes and molecules. In this review, recent advances on these regulatory systems are discussed. Probably, they function in a cell autonomous way and new findings provide evidence for their crosstalk.

2. Sucrose metabolism: the birth and death of a sucrose molecule

The different parts of plants have diverse tasks and biochemical requirements. One of the crucial functions of source leaves is the synthesis of energy-rich molecules, while heterotrophic sink organs, such as developing fruits, seeds, roots and tubers are dependent on the import and utilization of these compounds. In most plant species, assimilated carbon is transported as Suc, a disaccharide in which Glc and fructose (Fru) are linked via an *O*-glycosidic bond (Sturm and Tang, 1999) [99, 100]. Two enzymes are involved in synthesis of Suc in cytosol: Suc-phosphate synthase (SPS) and Suc-phosphate phosphatase (SPP). Suc-6-phosphate synthesized by using UDP-Glc and Fru-6-phosphate in the presence of SPS, whereas SPP releases orthophosphate (Pi) from Suc- 6-phosphate, yielding Suc (Leloir and Cardini. 1955) [60]. SPS is a key regulator of Suc synthesis. It can be both activated and deactivated by protein phosphorylation under osmotic stress and light, respectively, probably at different serine residues (Huber and Huber, 1996) [44]. Activity of SPS is stimulated by Glc-6-phosphate and inhibited by Pi (Huber and Huber, 1996) [44]. In *Arabidopsis* leaves, AtSWEET11 and -12, a class of plasma membrane uniporters that export Suc from mesophyll cells to the apoplasm of the phloem parenchyma for loading into the sieve element/companion cell complex is coexpressed with SPS (Chen *et al*., 2012) [14], demonstrating that coupling between Suc biosynthesis and transport. Although Suc is produced primarily in mature leaves, it can be resynthesized in sink tissues. This may particularly be the case in sinks where phloem unloading occurs apoplasmically, which is followed by Suc breakdown into Glc and Fru in the extracellular space. In this situation, resynthesis of Suc is necessary for its storage or further intercellular transport. Suc may also serve as an osmotic protectant and cryoprotectant to enhance tolerance to abiotic stress, as indicated by increased Suc levels in developing leaves in response to cold (Nagele *et al*., 2012) [72]. Suc synthesis in source leaves is obviously critical for plant biomass production. Early studies indicate that overexpression of maize SPS in tomato green tissues increased leaf photosynthesis and Suc synthesis under high CO_2 but had no effect on fruit yield (Micallef *et al*., 1995) [68]. Interestingly, these transgenic plants flowered earlier and produced more flowers. It's unknown whether this phenotype relates to the native increase of Suc that stimulates flowering through newly identified signaling pathways, as recently reported in *Arabidopsis* (Wahl *et al*., 2013; Yu *et al*., 2013Yang *et al*., 2013) [104, 117, 118] Breakdown of Suc initiates its utilization and in plants this reaction is catalyzed by two enzymes with entirely different properties: invertase (INV) and sucrose synthase (Copeland, 1990) [17]. INV is a hydrolase, and cleaves Suc into the two monosaccharides whereas sucrose synthase is a glycosyl transferase which, converts Suc into UDP-Glc and Fru in the presence of UDP. INVs are classified as apoplasmic (cell wall), vacuolar, or cytoplasmic isoforms according to their pH and subcellular localization (Sturm, 1999) [99, 100]. CWINV are involved in Suc unloading from the sieve elements, whereas vacuolar (VINV) and cytosolic/plastidic/mitochondrial INVs (CINV) are associated with Suc metabolism into Glc and Fru (Roitsch and Gonzalez, 2004) [85]. These processes are tightly regulated. Changes in the rates of these processes affect Suc levels and cellular metabolism both locally and systemically, and thereby influence plant growth and development. Suc transport and hydrolysis play key regulatory roles in sugar signal generation.

3. Sugar signals in plants

Sugar regulation is far more complex in plants. First, multicellular organisms need both long-distance and tissue- or even cell-type-specific signaling mechanisms and coordination with both development and physiological and environmental changes. As autotrophic, photosynthetic organisms, plants are made up of sugar exporting (source) and sugar importing (sink) tissues and organs, and sugar signals are generated from different sources at different locations. Sugar metabolism is a very active process, and metabolic fluxes and sugar concentrations alter dramatically both during development and in response to environmental signals such as diurnal changes and biotic and abiotic stress (Blasing *et al*., 2005; Borisjuk *et al*., 2003; Roitsch, 1999; Smith, 2005; Weber *et al*., 2005) [9, 10, 84, 98, 105]. Integration of environmental signals with metabolism is particularly important for sessile organisms. Not surprisingly, intricate regulatory interactions with plant hormones are an essential part of the sugar sensing and signaling network. Finally, photosynthesis and carbon metabolism and allocation are themselves subject to rigorous feedback regulation and a prime target of sugar signaling. In general, source activities like photosynthesis, nutrient mobilization, and export are upregulated under low sugar conditions, whereas sink activities like growth and storage are upregulated when carbon sources are abundantly available. Photosynthesis and sink demand need to be rigorously coordinated, and this synchronization involves both metabolic (substrate and allosteric) regulation and specific sugar-signaling mechanisms. While Suc is the major photosynthetic product and transportable sugar in plants, suc signaling effects on growth and metabolism can be attributed to the action of its hydrolytic hexose products, Glc and Fru, (Rolland *et al*., 2006) [86] and T6P is also a potent sugar signal that putatively coordinates metabolism with development in response to carbon availability and stress (Paul *et al*., 2008) [76].

4. Master regulators in plant sugar signaling networks

HXK1, KIN10/11 and TOR are three sugar modulated master regulators (Fig.1). These regulators control the expression of thousands of plant genes involved in a wide spectrum of cellular functions from signaling, transcription, transport, anabolism, catabolism, development and stress adaptation in response to altered glucose signals (Polge and Thomas, 2007; Baena-González and Sheen 2008; Sheen, 2010; Smeekens *et al*., 2010; Dobrenel *et al*., 2013; Robaglia *et al*., 2012; Xiong and Sheen, 2014) [77, 4, 92, 96, 22, 83, 113]. *Arabidopsis* HXK1 acts as the direct sugar sensor mediating multiple functions in the sugar repression and glucose promotion of transcription and growth (Xiao *et al*., 2000; Moore *et al*., 2003; Cho *et al*., 2006; Cho *et al*., 2009; Yanagisawa *et al*., 2003) [111, 70, 16, 15, 115]. KIN10/11 and TOR sense opposite energy levels The protein kinase activity of KIN10/11 is repressed by sugar (Baena-González *et al*., 2007) [5], whereas TOR kinase is

activated by sugar (Xiong and Sheen, 2012, Xiong *et al*., 2013) [112, 114].

4.1 Direct glucose sensing and signaling via HXK1

The first plant sugar sensor identified was the HEXOKINASE1 (HXK1) protein that senses sugar (Rolland *et al*., 2006) [86]. HXK1 is a multifunctional protein being both an enzyme catalyzing the first step of glycolysis and a glucose sensor. As observed that the majority of HXK1 and closely related HXK proteins are attached to the outer membrane of mitochondria serving the conventional function during glycolysis in *Arabidopsis,* maize, tomato, tobacco and moss, (Kandel-Kfir *et al*., 2006; Kim *et al*., 2006; Granot, 2007; Karve *et al*., 2008; Cho *et al*., 2009; Nilsson *et al*., 2011; Balasubramanian *et al*., 2007; Kim *et al*., 2013) [50, 54, 30, 53, 15, 73, 7, 55]. Virus-induced gene-silencing studies in *Nicotiana benthamiana* suggest a role of tobacco HXKs in the control of programmed cell death (Kim *et al*., 2006) [54], which is reminiscent of the glucokinase function in mice (Danial *et al*., 2003) [19]. However, a number of studies have identified *Arabidopsis* and rice HXK glucose sensor proteins in the nucleus, particularly when the N-terminal region responsible for the association with the mitochondria outer membrane was deleted (Cho *et al*., 2006; Cho *et al*., 2009; Yanagisawa *et al*., 2003) [16, 15, 115]. Complementation studies analyses in *gin2* (Glc Insensitive) indicate that the association of HXK1 with mitochondria is dispensable for the nuclear glucose sensor functions in transgenic plants. Furthermore, extensive efforts have led to the biochemical isolation of the nuclear HXK1 protein complexes in *Arabidopsis* leaves and the identification of multiple HXK1 interacting protein partners. In the nucleus HXK1 interacts with the vacuolar H^+ATPase B1 (VHA-B1) and the 19S regulatory particle of proteasome subunit (RPT5B) in a sugar-dependent manner in a complex that directly binds to promoters of sugar regulated genes (Cho *et al*., 2006) [16]. A regulatory role for HXK in plant hexose sensing was suggested by testing the effects of a variety of sugars, sugar analogs, and metabolic intermediates on photosynthesis and glyoxylate cycle gene repression in cell cultures of *Chenopodium* (Krapp *et al*., 1993) [57] and cucumber (Graham *et al*., 1994) [29], and in a maize protoplast transient expression system (Jang and Sheen, 1994) [48]. Sugars that are substrates of HXK, including mannose and 2-deoxyglucose, which are phosphorylated but inhibit Glc-6-phosphate and ATP production (Klein and Stitt, 1998) [56], cause repression of photosynthetic gene expression at low physiological levels. The repression is blocked by the HXK-specific competitive inhibitor mannoheptulose (Jang and Sheen, 1994) [48]. L-Glc (not transported), 6-deoxyglucose and 3-*O*-methylglucose (transported but not phosphorylated), and sugar phosphates (delivered into the protoplasts by electroporation) do not trigger the same repression. Arabidopsis hxk1 (gin2, glucose insensitive2) mutants show reduced shoot and root growth, late flowering and changed sensitivities to the growth hormones auxin and cytokinin (Ramon *et al.,* 2008) [80]

4.2 Protein kinase (SNRK1 & KIN10/11) are master regulators of the convergent stress

Different types of stress result in both specific and convergent responses that modulate plant growth and development. The evolutionarily preserved genes encoding the catalytic subunit of energy sensor kinases in eukaryotes have been identified for more than two decades, including yeast SNF1 (Sucrose-Non fermentation1), mammalian AMPK and plant SNRK1 (Celenza and Carlson, 1986; Bhalerao *et al*., 1999; Halford *et al*., 2003; Halford and Hardie, 1998; Hardie *et al*., 2012) [13, 8 36, 34, 39]. These conserved heterotrimeric kinases are crucially important regulators of metabolism and energy homeostasis (Hardie, 2007; Hedbacker and Carlson, 2008; Bright *et al*., 2009) [40, 41, 11] (Fig 2). They safeguard cellular energy levels by regulating ATP production and consumption, and thereby growth. Stressful conditions such as starvation or hypoxia result in low energy status and activate the protein kinases leading to adaptation of anabolic and catabolic processes in the cell. As for the TOR kinase, the importance of this protein kinase family in the control of metabolism can hardly be overstated. In animals, severe pathological conditions are associated with dysfunctional TOR or AMPK systems. The existing studies of SNRK1 have been focused on the regulation of cytoplasmic enzymes, for example nitrate reductase (NR) and SPS, involved in nitrogen and sugar metabolism respectively (Halford and Hardie, 1998; Sugden *et al*., 1999; Halford *et al*., 2003) [34, 101, 36]. Biosynthetic processes and plant growth is repressed by SnRK1 under low energy conditions (Baena-González *et al*., 2007; Halford and Hey, 2009; Baena-González, 2010; Polge and Thomas, 2007; Ghillebert *et al*., 2011) [5, 35, 6, 77, 26] (Fig 2). Knowledge of the regulation of SnRK1 and its target processes has increased substantially in recent years. Yeast, mammalian, and plant SNF1, AMPK, and SnRK1, respectively, are heterotrimeric complexes with a α catalytic, and β- and γ regulatory - subunits. Mammalian AMPK, is allosterically regulated by the AMP/ATP ratio but the plant SnRK1 is instead regulated by sugar phosphates (Ghillebert *et al*., 2011) [26]. Glucose-6-phosphate (G6P) and glucose-1-phosphate (G1P) inhibits the activity of SnRK1 and T6P also inhibits SnRK1 at physiological concentrations (O'Hara *et al*., 2012; Nunes *et al*., 2013*a;* Zhang *et al*., 2009) [75, 74, 119]. Suc promotes the accumulation of T6P, thereby inhibiting SnRK1 activity. Generally, when sufficient sugar is available SnRK1 activity (Fig 2) is repressed but, depending on the tissue or developmental phase studied, sucrose might have an SnRK1-stimulating role as well (Baena-González, 2010) [6]. In the regulation of SnRK1 target genes, miRNAs were implicated. An *Arabidopsis* mutant (*dcl1-9*) compromised in miRNA synthesis is unable to induce a transcriptional response to dark-induced stress conditions. Growth-promoting TOR signaling pathway is repressed by mammalian AMPK (Wullschleger *et al*., 2006) [110] and which has a role in cell cycle regulation by phosphorylation of the CDK/ cyclin inhibitor p27KIP1, resulting in inhibition of cellular proliferation. p27KIP1 stabilized by phosphorylation, resulting in cell cycle arrest, apoptosis, and autophagy (Liang *et al*., 2007; Short *et al*., 2010) [61, 95]. Similarly, plant KRP6 and KRP7 proteins that are homologues of the mammalian p27KIP1 CDK/cyclin inhibitor are phosphorylated by AtSnRK1. In the nucleus, SnRK1 interacts with and phosphorylates KRP6, but, extremely, it appears that KRP6 phosphorylation prevents binding to CDK/cyclin and as a result allows cell cycle progression. SnRK1 act as an inhibitor of growth under stress conditions which is contradictory to the role of SnRK1 in cell cycle progression (Guérinier *et al*., 2013) [32]. The connection to plant SnRK1 and TOR signalling and the role of SnRK1 in controlling plant growth and development needs further clarification. In *Arabidopsis*, SnRK1 affects phase transitions as well. By establishing a combination of cellular, biochemical, genomic and genetic tools in *Arabidopsis thaliana*, ample proof now supports novel functions of the redundant *Arabidopsis* KIN10

(SNRK1.1) and KIN11 (SNRK1.2) as central integrators of transcriptional networks in stress and energy signaling (Baena-González *et al*., 2007; Smeekens *et al*., 2010, Baena-González and Sheen, 2008) [5, 4, 96]. The Glc-repressed SNRK1 is likely conserved in all plants and the orthologous genes encoding the catalytic subunit complement the yeast *snf1* mutant, supporting the preserved roles in Glc signaling (Bhalerao *et al*., 1999; Lova *et al*., 2003; Polge and Thomas, 2007; Halford *et al*., 2003; Baena-González and Sheen, 2008; Ramon *et al*., 2008) [8, 63, 77, 36, 4, 80]. Overexpression of the SnRK1 catalytic subunit KIN10 in plants results in late flowering and defects in the formation of siliques and cotyledons. By introduction of the *fus3* mutation which rescued the KIN10 overexpression phenotype. KIN10 and FUS3 proteins interact *in vivo* and KIN10 stabilized FUS3 by phosphorylation (Tsai and Gazzarrini, 2012) [112]. FUS3 protein also stabilized by abscisic acid (ABA), which was shown to be involved in phase change control (Gazzarrini *et al*., 2004) [24]. Role of KIN10/11 in plant growth and development, transgenic and mutant plants have been characterized. Overexpression of KIN10 in plants display delayed senescence and flowering and an altered flower architecture under long-day conditions (Baena-González *et al*., 2007) [5]. Dramatic growth defects was obsereved by silencing of both KIN11 and KIN10 genes (Baena-González *et al*., 2007) [5]. KIN10/11 also have role in antiviral defense along with plant growth and development (Shen and Hanley-Bowdoin, 2006) [93]

4.3 Sugar activation of TOR kinase

TOR is an unusually large protein kinase (2481 aa) with multiple repeats and regulatory domains in the N-terminus and an evolutionarily conserved Ser/Thr protein kinase domain at the C-terminus. In yeast and mammals, TOR have at least two structurally and functionally distinct complexes, TORC1 (TOR complex1) and TORC2. Both complex contains shared and distinct TOR interacting partners, and differentially regulates diverse TOR kinase substrates to control a variety of genetic processes (Wullschleger *et al*., 2006; Robaglia *et al*., 2012; Cornu *et al*., 2013; Kang *et al*., 2013; Yuan *et al*., 2013; Laplante and Sabatini, 2012; Xiong and Sheen, 2014) [110, 83, 18, 51, 118, 59, 113]. Some of the mTORC1 elements and downstream effectors have been recognized in photosynthetic eukaryotes by sequence similarity search, including *Arabidopsis* LST8-1/2 (Lethal With SEC-13 Protein8), Raptor1/2 (Regulatory Associate Protein Of TOR), RPS6a/b (Ribosome Protein Small Subunit6), S6K1/2 (Ribosomal Protein S6 Kinase) and TAP46 (Type 2A-Phosphatase-Associate Protein 46 KD) (Anderson *et al*., 2005; Mahfouz *et al*., 2006; Ahn *et al*., 2011; Ren *et al*., 2012; Moreau *et al*., 2012; Xiong and Sheen, 2014) [3, 65, 1, 82, 71, 113]. The function of TOR in coupling nutrient and energy availability with other environmental signals to synchronize growth, development and survival is likely conserved in yeasts, plants, animals and humans (Fig. 2). Activity of AtTOR is important throughout the complete life cycle of plant and generally expressed in rapidly proliferating tissues like endosperm and meristematic regions (Menand *et al*., 2002) [66]. Simultaneously, AtTOR act as a repressor of autophagy (Liu and Bassham, 2010). Outcome knockdown of TOR is reduction in growth of *Arabidopsis*, accompanied by changes in carbohydrate and amino acid metabolism (Caldana *et al*., 2013) [12]. TOR kinase activity generally promotes by sugars like Glc activates TOR and it further promotes *Arabidopsis* root meristem activity (Robaglia *et al*., 2012; Dobrenel *et al*., 2013; Ren *et al*., 2012; Xiong *et al*., 2013) [83, 22, 82, 114]. The use of specific TOR inhibitors reduced root growth (Montané and Menand, 2013) [69]. Genes regulated by E2F transcription factors overlap with genes regulated by glucose-stimulated TOR signalling, which promote cell cycle progression. Interestingly, E2F directly phosphorylated and activated by TOR, apparently bypassing the CDK/cyclin–Retinoblastoma Related Protein (RBR) cell cycle control system (Xiong *et al*., 2013) [114]. *Arabidopsis* S6 kinase 1 (S6K1) activity regulated by interaction of AtTOR with Regulatory-Associated Protein Of TOR (RAPTOR) (Mahfouz *et al*., 2006) [65]. Mammalian S6K is a target of mTOR and it phosphorylates the 40S ribosomal protein RPS6 to promote mRNA translation and cell growth (Laplante and Sabatini, 2012; Shin *et al*., 2012; Henriques *et al*., 2010) [59, 94, 42]. Fascinatingly, RBR was proposed to control the positive heterotrophy to autotrophy transition in germinating seeds positively and to antagonize the positive effect of sucrose on the cell cycle (Gutzat *et al*., 2011) [33]. Viral transactivator-viroplasmin (TAV) promotes translation reinitiation by interacting with TOR, thereby stimulating S6K1 phosphorylation following termination of translation of long open reading frames (ORFs) on multicistronic mRNAs. TOR knockdown plants fail to reinitiate on polycistronic mRNAs (Schepetilnikov *et al*., 2011) [89].

5. The bZIP growth regulatory system

The Arabidopsis bZIP growth regulatory system encompasses various bZIP transcription factors of the Arabidopsis S1 (bZIP1, 2, 11, 44, 53) and C (bZIP9, 10, 25, 63) class bZIP families. Heterodimers of these S1 and C class bZIPs are effective in planta transcriptional activators and provides extensive regulatory potential to plants (Weltmeier *et al*., 2006; Ehlert *et al*., 2006; Alonso *et al*., 2009) [106, 23, 2] AtbZIP11 overexpression considerably induces reprogramming of metabolism as revealed by metabolomics and transcriptomics experiments (Hanson *et al*., 2008) [38]. Such bZIP11 induction dominantly halts growth, independent of nutrient availability. Extremely, S1 class bZIP activity is repressed by Suc in a concentration-dependent way by arresting translation of S1 bZIP mRNAs via a ribosome stalling mechanism (Hummel *et al*., 2009; Wiese *et al*., 2004; Rahmani *et al*., 2009) [45, 108, 89]. Thus, bZIP mediated reprogramming of metabolism and growth depends on the cellular Suc level. Translation of all five members of the S1 bZIP class mRNA gradually shut down by increasing level of Suc. (Rahmani *et al*., 2009; Weltmeier *et al.,* 2009) [89, 107]. Heterodimerization of S1-group with C-group bZIPs regulates downstream genes (Ehlert *et al*., 2006; Weltmeier *et al*., 2009) [23, 107], including genes involved in metabolism of amino acid. Transcriptional activity of S1-group bZIPs is enhanced to a great extent by KIN10/11 co-expression (Baena-González *et al*., 2007) [5]. S1-group bZIP1, bZIP11, and bZIP53 proteins are involved in metabolic reprogramming in response to low energy signals (Dietrich *et al*., 2011; Ma *et al*., 2011) [21, 64]. growth of the transgenic lines rigorously reduced as a results of overexpression of S1-bZIPs in *Arabidopsis* (*bZIP53 and bZIP11*) or tobacco (*TBZ17*) (Hanson *et al*., 2008; Dietrich *et al*., 2011; Thalor *et al*., 2012) [38, 21, 102], probably due to incapability to metabolize sugars as recommended by the accumulation of Suc and hexose phosphates in these lines and the observation that growth phenotype do not rescue by added sugars (Ma *et al*., 2011; Thalor *et al*., 2012) [64, 102]. Plants overexpressing *bZIP11* have reduced levels of the growth regulator T6P and

increased expression of *TPP5*, *TPP6*, and *TREHALASE1*. Constitutive expression of *bZIP11* in seedlings enables root growth on otherwise inhibitory trehalose levels in the growth medium (Ma *et al*., 2011) [64]. C/S1-bZIPs are vital for seed development where they are involved in regulation of expression of seed maturation genes (Alonso *et al*., 2009) [2]. S1-group *Atbzip44* mutant seed show slower germination, maybe due to the decreased expression of the mannanase-encoding *AtMAN7* gene in this mutant (Fernández *et al*., 2013) [47]. *AtbZIP1* is a sugar-responsive genes regulator and is repressed by Glc through the HXK1 signalling pathway (Kang *et al*., 2010) [52] (Fig 3).

6. Three sugar signal transduction pathways in plants

Although sugar-regulated gene expression has been studied for years, it is not clear what the direct sugar signal is, whether sugar metabolism is important, whether HXK is involved in the sensing process, or whether the signalling and/or catalytic activities of HXK are required. Outcomes of the present study suggest that in plants at least three distinct Glc signal transduction pathways exist. The first is an *At*HXK1- dependent pathway, in which gene expression is mediated through the signaling function of *At*HXK1. Apparently, Glc-phosphorylating activity *per se* is not crucial for this pathway since over-expression of a heterologous *YHXK2* caused dominant negative or little effect on the expression patterns of *CAB1* (Chlorophyll a/b binding protein*)*, *PC* (Plastocyanin), *PLD* (Phospholipsae D), and *rbcS* (Ribulose1, 5-bisphosphate carboxylase small subunit) despite a several fold increase in HXK catalytic activity (Xiao *et al*., 2000) [111]. The simplest interpretation is that YHXK2 can effectively phosphorylate Glc in the cells but fails to provide the signaling function due to other reasons. For example, the conformational change of HXK upon the binding of Glc needs to be specific in order to interact with a second protein that is involved in signal transduction but not metabolism. It is noteworthy that *At*HXK1 and *At*HXK2 are likely to be membrane, whereas YHXK2 is a soluble protein present in both the cytoplasm and the nucleus. Distinct cellular localization has provided a possible rationale for the inability of YHXK2 to replace the signaling function of *At*HXK1 in the regulation of *ERA1* expression. Alternatively, probably that downstream metabolism of hexose phosphorylation has also been changed in *YHXK2* plants and the change could, indirectly but finally, affect the expression of photosynthetic genes. The second pathway is dependent on the catalytic activity of HXK. The Glc-activated expression of *PR1* (Pathogen related gene1) and *PR5* was similar in *35S-AtHXK1* and *35SYHXK2* plants. Thus, the expression of *PR* genes may depend on the levels of an unknown metabolite downstream of HXK in the glycolytic pathway. This glycolysis-dependent pathway may be similar to the pathway for Glc-induced insulin responses in mammals. It is well established that insulin synthesis and secretion requires glycolysis, and the intermediates of anaerobic glycolysis between Fru-1, 6-diphosphate and phosphoenolpyruvate are essential for cell Glc sensing in the pancreatic islets (German, 1993) [25]. It remains unclear what direct metabolic signals and sensors are for the regulation of *PR* genes. Although the *PR* gene expression may belinked to salicylate induction (Herbers *et al*., 1996a) [43], analysis of the regulation of *PAL1* (Phenylalanine ammonia lyase) gene, important for salicylate biosynthesis, suggests that *PAL1* is regulated by a third distinct glucose signaling pathway that is independent of *At*HXK1 (Xiao *et al*., 2000) [111]. The expression of *AGPase* (ADP Glc phosporylase), *AS1* (Asparagine synthetase), *CHS* (Chalcone synthase*)*, and *PAL1* is mediated by an *At*HXK1-independent pathway (Xiao *et al*., 2000) [111]. Nevertheless, the existence of two Glc transporter-like proteins, Rgt2 and Snf3, as sugar sensors in yeast has prompted some speculations that similar mechanisms may exist in plants (LaLonde *et al*., 1999; Roitsch, 1999; Sheen *et al*., 1999) [58, 84, 91]. It is intriguing that neither Rgt2 nor Snf3 appears to be able to transport Glc. Rather, they behave like typical cell surface receptors that can transducer the Glc signal to a HXK-independent signaling pathway, leading to a transcriptional repression of authentic sugar transporters (Johnston, 1999) [49]. Twenty six homologous sequences of monosaccharide transporters have been identified in *Arabidopsis*, (Lalonde *et al*., 1999) [58]. It is possible that sugar transporter-like proteins and other extracellular sugar-binding proteins serve as sugar sensors to perceive and transmit the Glc signal in *At*HXK1-independent pathway(s) (Fig. 3).

7. The essential but enigmatic T6P signaling molecule

Trehalose-6-phosphate synthase1 (TPS1) synthesize a growth signalling molecule T6P from G6P and UDP-glucose (UDPG). Trehalose-6-phosphate phosphatase (TPP) metabolises the T6P, yields trehalose, which is hydrolysed to Glc by Trehalase1. The TPS1 enzyme and its product are essential for growth. T6P is essential for vegetative and reproductive growth, (Gómez *et al*., 2006) [27]. SnRK1 activity inhibited by T6P under low sugar, thereby allowing growth and development (Zhang *et al*., 2009; Schluepmann *et al*., 2012; O'Hara *et al*., 2012) [119, 90, 75]. The strong relationship between Suc and T6P content in stressed plants suggests that T6P/SnRK1 signalling, in response to Suc accretion, primes plants for this growth recovery response (Nunes *et al*., 2013*b*) [74] (Fig 2). Accumulation of T6P in leaves is coupled with the onset of senescence, whereas senescence is deferred in KIN10-overexpressing plants and in plants with reduced T6P levels (Wingler *et al*., 2012) [109]. In shoot apical meristems, *SPL* promotes floral transition but it's expression is inhibited by miRNA156, which reduces *SPL* mRNA expression. miRNA156 expression inhibited by T6P, allowing SPL to accumulate and promote floral transition (Wahl *et al*., 2013) [104]. Glc, T6P also promotes a crucial phase change that is from juvenile to adult phase in *Arabidopsis* through the inhibition of miRNA156 (Yang *et al*., 2013) [116].

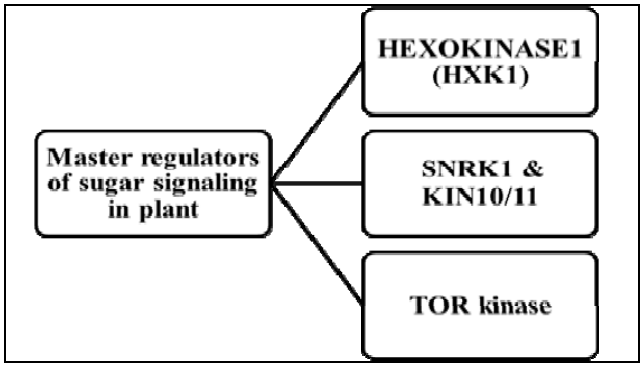

Fig 1: Three Master Regulators in Plants Sugar Signaling

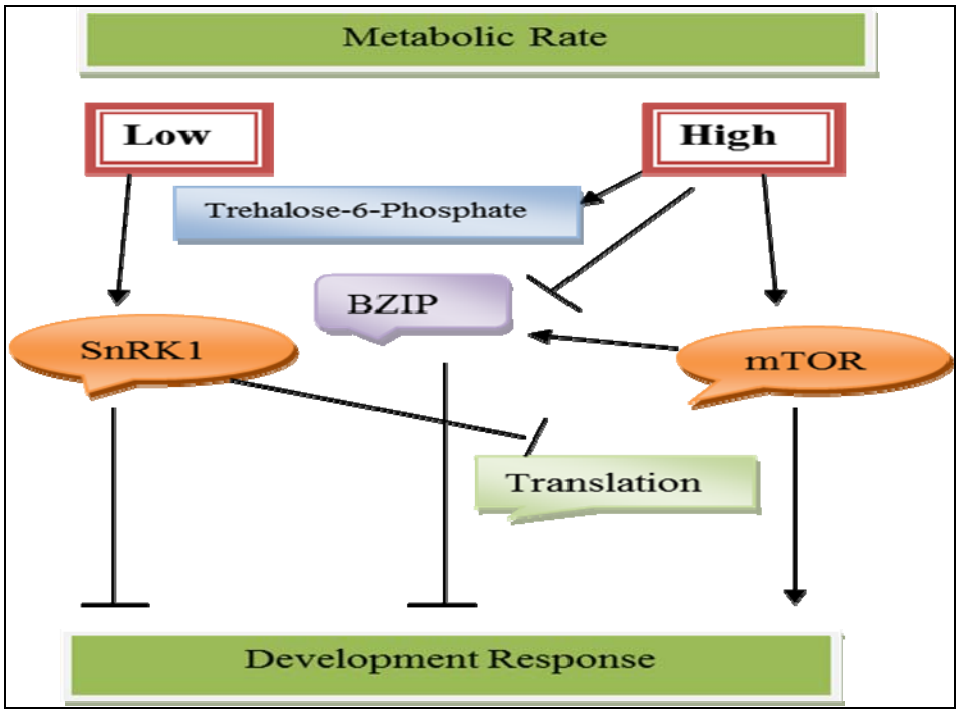

Fig 2: Sugar signalling pathways interconnect and control plant growth. The cellular metabolic status is an important factor in regulating vegetative growth. Nutrient stress activates SnRK1, resulting in an inhibition of growth. The C/S1-bZIP transcription factor network is implicated in the regulation of SnRK1 target genes. A high metabolic status is reflected by sucrose availability, which is correlated with plant T6P levels. Under these conditions, T6P inhibits SnRK1, and the active TOR kinase stimulates translation and growth. Suc inhibits the translation of S1-group *bZIP* mRNAs.

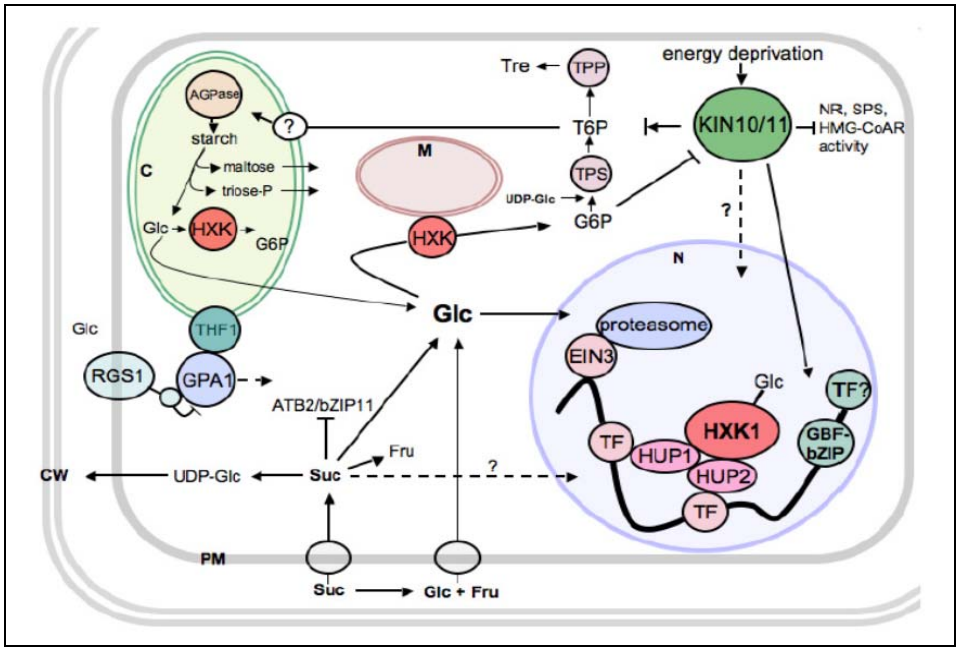

Fig 3: Summary of sugar and energy sensing and signaling models in Arabidopsis. Glc and Fru can be transported into the cell by hexose transporters or mobilized from starch and cytosolic and vacuolar Suc. Glc then enters metabolism after phosphorylation by HXK. HXK1 is mainly associated with mitochondria and a specific isoform is also found in plastids. In addition, HXK1 is present in high-molecular-weight complexes with HXK unconventional partners (HUPs) and transcription factors (TFs) in the nucleus where it controls transcription and modulates proteasome-mediated degradation of the EIN3 TF. KIN10/11 play a key role in plant energy signaling, mediating massive reprogramming of transcription (in part through bZIP TFs) and controlling enzymes post-translationally. Sugar phosphates (especially G6P) inhibit KIN10/11 activity. An important regulatory role is emerging for trehalose (Tre) metabolism, mediated by Tre-6-P (T6P) synthase (TPS) and T6P phosphatase (TPP) enzymes. T6P has been proposed to be a regulatory signaling molecule. KIN10/11 control the expression and phosphorylation status of several of the class II TPS proteins with unknown activity and function. G-protein coupled receptor signaling by RGS1 and GPA1 has been implicated in sensing extracellular glucose and signaling through THF1, located in the plastids. Sucrose, the main transported sugar in Arabidopsis, is found to have specific effects, not triggered by its hydrolysis products Glc and Fru. The ATB2/bZIP11 TF is subject to sucrose-induced repression of translation. C: chloroplast; CW: cell wall; M: mitochondrion; N: nucleus; PM: plasma membrane; NR, nitrate reductase; SPS, sucrose phosphate synthase; HMG-CoAR, 3-hydroxy-3-methylglutarylcoenzyme A reductase (Adopted from Ramon *et al*., 2008) [80].

8. Conclusion

Sugar sensing and communication is mediate by a complex network comprising a multitude of interactions with metabolic and secretion signals. many key players concerned in these processes. In plants, sugars control metabolism, growth, stress responses, and development from embryogenesis to senescence. Plant sugar regulation is mediate by various sugar signals,that are generated at different locations depending on environmental conditions and developmental stage. Suc transport and hydrolysis play key regulatory roles in sugar signal generation. HXKs are evolutionarily preserved eukaryotic Glc sensors. Plants may additionally use membrane receptors for extracellular sugar sensing (Rolland *et al*., 2006) [86]. Cellular activity from transcription and translation to protein stability and activity regulated by sugars. The TOR and SnRK1 kinases are crucial in controlling plant growth in response to carbon convenience. Future studies can clarify the distinctive regulation of SnRK1s by Suc and their vital role in cellular stress signaling, still as novel functions within the regulation of the daily cycle of carbon metabolism in plants. Trehalose metabolism is rising as a completely unique, necessary regulator of plant growth, metabolism, and stress resistance. Elements of sugar signaling networks have various functions throughout the vegetation cycle, and their interactions with alternative signalling pathways presents a difficult challenge.

9. References

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