ENERGY SIGNALING IN THE REGULATION OF GENE EXPRESSION DURING STRESS

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ABSTRACT

Maintenance of homeostasis is pivotal to all forms of life. In the case of plants, homeostasis is constantly threatened by the inability to escape environmental fluctuations, and therefore sensitive mechanisms must have evolved to allow rapid perception of environmental cues and concomitant modification of growth and developmental patterns for adaptation and survival. Re-establishment of homeostasis in response to environmental perturbations requires reprogramming of metabolism and gene expression to shunt energy sources from growth-related biosynthetic processes to defence, acclimation and ultimately adaptation. Failure to mount an initial "emergency" response may result in nutrient deprivation and irreversible senescence and cell death. Early signaling events largely determine the capacity of plants to orchestrate a successful adaptive response. Early events, on the other hand, are likely to be shared by different conditions through the generation of similar signals and before more specific responses are elaborated. Recent studies lend credence to this hypothesis, underpinning the importance of a shared energy signal in the transcriptional response to various types of stress. Energy deficiency is associated with most environmental perturbations due to their direct or indirect deleterious impact on photosynthesis and/or respiration. Several systems are known to have evolved for monitoring the available resources and triggering metabolic, growth and developmental decisions accordingly. In doing so, energy-sensing systems regulate gene expression at multiple levels to allow flexibility in the diversity and the kinetics of the stress response.

STRESS AND ENERGY

As sessile organisms plants are constantly challenged by a wide range of environmental changes. Growth constraints and stress result in significant crop losses and therefore the mechanisms underlying endurance and adaptation to these changes have long been the focus of intense research (Bray, 2000). The response to a particular type of stress is usually composed of both stress-specific adaptive responses as well as general responses that confer basic protection (Kultz, 2005). Specific responses are induced by factors unique to a certain condition, such as the lowered oxygen tension characteristic of hypoxic stress in flooded roots (Magneschi and Perata, 2009). General responses, on the other hand, are probably triggered by signals and signaling components that are shared by multiple pathways, perhaps explaining why adaptation to a particular stress condition often provides tolerance to other types of stress (Bowler and Fluhr, 2000; Kultz, 2005).

In order to achieve acclimation, an initial immediate response is required to re-establish homeostasis, repair damaged cellular components and reprogram metabolism (Wang et al., 2003). Management of energy resources occurs not only at the cellular level, *e.g.* through the arrest of biosynthetic processes, but also at the whole plant level. For example grain filling and fruit development require nutrient remobilization from leaves (Masclaux-Daubresse et al., 2008). However, under conditions of stress, resources are shunted from reproductive activities into metabolic reactions that increase stress tolerance, ultimately resulting in seed abortion and/or accelerated senescence of the reproductive organs (Baldet, 2002; Smith and Stitt, 2007). The ability to direct nutrients to the appropriate processes and to induce the right metabolic adjustments during stress is critical also for survival, as is the case for rice seedlings during flooding. In addition to switching from mitochondrial respiration to anaerobic metabolism, seedling establishment may be influenced by the capacity to shift from energy-costly cell division to less energy-requiring cell expansion for growth into contact with the atmosphere (Magneschi and Perata, 2009).

Early signaling events are probably triggered by small perturbations in the environment to adopt measures that prevent a more severe and perhaps irreversible damage and are more likely to engage shared signals and signaling components than subsequent more specialised events (Smith and Stitt, 2007; Baena-Gonzalez and Sheen, 2008; Usadel et al., 2008). This early response seems to largely determine whether plants can cope with stress. It was shown that the largest transcriptional differences triggered by salt stress in a tolerant versus a sensitive rice variety occurred within the first hour of exposure. Failure to regulate the appropriate genes and at the appropriate time ultimately resulted in cell death in the salt-sensitive variety (Kawasaki et al., 2001).

Various signals are likely to be involved in the stress cross-talk, including calcium fluxes, reactive oxygen species, and energy deprivation (Bowler and Fluhr, 2000; Pastori and Foyer, 2002; Baena-Gonzalez, Rolland, et al., 2007; Baena-Gonzalez and Sheen, 2008). Most environmental perturbations have an impact either on light absorption, carbon fixation, or oxygen availability, diminishing the efficiency of photosynthesis and/or respiration, and in consequence the overall energy status of the cell. Two hours of hypoxic stress, for example, are enough to cause a nearly 50% decrease in the levels of cellular ATP (Branco-Price et al., 2008).

The aim of this review is to provide an overview of the various mechanisms that become engaged upon exposure of plants to stress to modulate gene expression in response to energy signals. For the sake of clarity a distinction has been made between transcriptional and post-transcriptional regulatory mechanisms. However, one has to bear in mind that transcriptional regulation is often attributed to changes in steady-state transcript levels, which are the outcome not only of transcriptional activity, but also of *e.g.* mRNA stability and degradation, in part determined by differential translation.

TRANSCRIPTIONAL REGULATION LINKED TO ENERGY SIGNALS

Large-scale comparisons of expression profiles from a wide range of stress conditions have been conducted to distinguish between ubiquitous and specific stress responses, revealing the existence of a set of genes that are similarly induced or repressed by multiple adverse conditions (Swindell, 2006; Kilian et al., 2007; Ma and Bohnert, 2007). Several *cis*-motifs have been shown to be enriched in the promoters of genes similarly affected by numerous environmental perturbations (Geisler et al., 2006; Ma and Bohnert, 2007; Walley et al., 2007). However, the transcription factors (TFs) that recognise these elements and in particular their upstream regulators are still largely unknown. Furthermore, in most cases, the underlying common signal responsible for the convergent regulation of these genes has not been investigated.

Sucrose-Non-Fermenting Related Kinases 1 (SnRK1s)

Recent work has identified two *Arabidopsis* protein kinases (PKs), KIN10 and KIN11, as central regulators of the transcriptome in response to multiple types of stress (Baena-Gonzalez, Rolland, et al., 2007; Baena-Gonzalez and Sheen, 2008) (Fig. 1). *Arabidopsis* KIN10/11, collectively designated as SnRK1s, are the orthologs of the yeast SNF1 (Sucrose non-fermenting 1) and mammalian AMPK (AMP-activated PK), all members of a highly conserved PK family (Hardie, 2007; Polge and Thomas, 2007; Halford and Hey, 2009). Sensing and signaling stress-associated energy deprivation, KIN10/11 trigger changes in the expression of over a thousand genes that allow the re-establishment of homeostasis by repressing energy consuming processes and promoting catabolism. Besides the obvious impact on metabolism-associated components, KIN10/11 target a wealth of signaling and regulatory factors. This, together with the wide range of developmental aberrations associated with altered SnRK1 signaling (Zhang et al., 2001; Lovas et al., 2003; Thelander et al., 2004; Baena-Gonzalez, Rolland, et al., 2007; Lu et al., 2007) suggests that SnRK1 function extends beyond mere metabolic adjustment to integrate multiple signals that finely modulate growth and development.

In agreement with a role during the stress response, *Arabidopsis* plants overexpressing KIN10 are more tolerant to nutrient-deprivation and silencing of KIN10/11 precludes target gene induction upon stress (Baena-Gonzalez, Rolland, et al., 2007). An impact on stress-related gene expression was also reported in pea embryos with conditional SnRK1 antisense expression (Radchuk et al., 2006). In addition, antisense lines of StubGAL83 (a regulatory ß-subunit of SnRK1) in potato are hypersensitive to salt (Lovas et al., 2003), and, similarly to animals, *Arabidopsis* SnRK1 (AtSnRK1) was shown to phosphorylate a small heat shock protein (Slocombe et al., 2004). SnRK1 activity seems also to be determinant for the tolerance of young rice seedlings to flooding (Lee et al., 2009). On the other hand, a number of studies implicate SnRK1 in the response to biotic stress. Tobacco plants overexpressing SnRK1 are more resistant to geminivirus infection (Hao et al., 2003) and the plant-specific ßγ -fusion SnRK1 subunit interacts in *Arabidopsis* with proteins involved in resistance to nematodes (Gissot et al., 2006). Furthermore, herbivory-triggered resource allocation to roots seems to be mediated by the GAL83 ß-subunit, assigning it an either direct or indirect role in this defence response (Schwachtje et al., 2006).

In budding yeast, activation of SNF1 by glucose starvation has long been known to release the repression of genes required for catabolism of alternative carbon sources, although the exact nature of this metabolic signal is not known (Hedbacker and Carlson, 2008). Mammalian AMPK, on the other hand, is activated by the increase in the ratio of AMP to ATP. AMPK binds directly AMP, which activates the enzyme allosterically but also inhibits its dephosphorylation (Hardie, 2007; Scott et al., 2009). Upon exercise or stresses like heat shock and hypoxia AMPK switches off ATP-consuming processes while activating ATP-generating catabolic pathways through direct enzyme regulation and transcriptional regulation (Hardie, 2007). Increasing lines of evidence implicate AMPK in the regulation of genes involved in energy metabolism, cell signaling, cell growth and proliferation, immunity, transcription and apoptosis (Hardie, 2007; McGee and Hargreaves, 2008). As in yeast, multiple mechanisms account for this regulation, including inhibition of transcriptional repressors, stimulation of activators, mRNA stability and direct activation of the transcriptional machinery (McGee and Hargreaves, 2008).

In contrast to the situation in yeast and mammals, only a few components have thus far been linked to the SnRK1 signaling cascade. These include the *Arabidopsis* S-group of bZIP TFs, bZIP1, bZIP2/GBF5, bZIP11, bZIP44, and bZIP53, all positive downstream effectors that control a subset of KIN10 target genes (Baena-Gonzalez, Rolland, et al., 2007; Hanson et al., 2008) (Fig. 1). Regulation through the bZIP network is rather complex, since the S-group bZIPs appear to function as heterodimers with members of the C-group (Ehlert et al., 2006; Weltmeier et al., 2006). Moreover, members of the two groups are differentially expressed in response to several stimuli, resulting in a large array of possible dimer combinations (Weltmeier et al., 2009). Noticeably, the S-group bZIP TFs are translationally repressed by sucrose (Wiese et al., 2005; Rahmani et al., 2009) (see next section on translational control), providing the framework for antagonistic regulation of the system by energy deficiency and energy abundance.

In addition to the bZIP TFs, yeast-two-hybrid screens have uncovered other transcriptional regulators that interact with SnRK1s and that could thereby play a role in the SnRK1 signaling cascade. This is the case of the recently identified *Arabidopsis* ATAF1, a member of the NAC family of plant specific TFs. Silencing of this family via *ATAF1*-overexpression-induced cosuppression resulted in severe developmental defects (Kleinow, 2009). Iinterestingly, another study shows that *ATAF1* is induced by a wide variety of stresses and that plants overexpressing this TF are more tolerant to drought (Wu et al., 2009). Studies on rice embryos, on the other hand, indicate that SnRK1 acts upstream of the MYBS1 TF to induce the *α*-amylase gene *αAmy3* during the early stages of germination to nourish the embryo through degradation of the starchy endosperm (Lu et al., 2007). This process is of particular importance under conditions of extreme sugar starvation like hypoxia and partly accounts for the ability of certain rice varieties to tolerate flooding during early development (Lu et al., 2007; Lee et al., 2009) .

Other *Arabidopsis* TFs were also identified as multicopy suppressors of the yeast *snf4*Δ2 mutation (Kleinow et al., 2000), suggesting they could be part of the SnRK1 signaling cascade. However, although some of them, like AZF2 and ZAT10, are well known to be involved in stress responses (Sakamoto et al., 2004; Mittler et al., 2006), a direct connection to SnRK1 has not been further explored.

Several upstream kinases have been shown to regulate SNF1/AMPK/SnRK1 through phosphorylation of a conserved threonine residue in the T-loop (Hardie, 2007; Hedbacker and Carlson, 2008; Shen et al., 2009). As for other organisms, the AtSnRK1 kinases do not seem to respond to energy signals (Shen et al., 2009), supporting earlier observations in spinach that the metabolic effect is exerted on the regulatory phosphatase (Sugden et al., 1999). In this context, trehalose-6-phosphate (T6P) was recently shown to potently inhibit AtSnRK1 activity through the action of an unidentified intermediary factor (Zhang et al., 2009) (Fig. 1; see below). The fact that the upstream kinases identified so far as well as the T6P-mediated regulation operate only in young seedlings suggests that SnRK1 regulation depends on the developmental stage and/or type of tissue. Such differential regulation may partly account for the controversial results obtained with regard to the sugar activation or inactivation of the SnRK1 system as well as the reported sucrose-specific effects (Baena-Gonzalez and Sheen, 2008; Halford and Hey, 2009; Jossier et al., 2009). SnRK1 regulation may indeed differ between autotrophic and heterotrophic tissues, in an analogous way as mammalian AMPK responds to leptin in an opposite manner in the liver and the brain (Hardie, 2007). Other important factors to consider when evaluating the effects of sugar on SnRK1 are the sugar concentrations used, which could, beyond physiological levels, trigger stress and defence responses (Wingler and Roitsch, 2008), as well as the physiological status of the cell, since sugar supplied in combination with stress may not be metabolized and/or trigger the same signals than the same amount of sugar supplied under optimal conditions.

In contrast to mammals (Hardie, 2007), AtSnRK1 activity upon exposure to stress does not seem to correlate with its T-loop phosphorylation *in vivo* (Baena-Gonzalez, Rolland, et al., 2007), indicating that, even though this modification is essential, it requires additional mechanisms for triggering downstream gene expression changes. Interestingly, inactive kinase KIN10^{K48M} and T-loop phosphorylation KIN10^{T175A} mutant proteins accumulate to much higher levels than the wild type (WT) KIN10 protein (Baena-Gonzalez, Rolland, et al., 2007), suggesting a connection between protein activity and stability, further supported by recent reports linking SnRK1 half-life to nutrient conditions and proteasomal degradation (Ananieva et al., 2008; Lee et al., 2008). Intriguingly, AtSnRK1 was found to interact with the αPAD subunit of the 26S proteasome in association with an SCF (Skp1-Cullin-F-box) complex (Farras et al., 2001). However, this interaction may underlie a yet unknown regulatory function rather than AtSnRK1 degradation, since no alteration that could be ascribed to ubiquitylation was reported in the molecular weight of AtSnRK1.

Hexokinase 1 (HXK1)

In addition to sensing nutrient deprivation, plants are also able to sense the presence of sugars through various pathways that directly or indirectly recognize trehalose, fructose, glucose or sucrose (Rolland et al., 2006). In most cases the underlying molecular mechanisms are unknown, but work in recent years has led to the identification of *Arabidopsis* HXK1(AtHXK1) as a core component in plant sugar sensing and signaling with distinct metabolic and signaling functions (Moore et al., 2003; Cho et al., 2006) (Fig. 1). In the presence of glucose, AtHXK1 mediates sugar repression *e.g.* of the photosynthetic *CAB* genes through binding to target gene promoters in cooperation with other proteins within a nuclear AtHXK1 complex (Cho et al., 2006). Two AtHXK1 unconventional partners (HUPs) were identified in this complex, the vacuolar H+-ATPase B1 (VHA-B1/HUP1) and a subunit of the 19S regulatory particle of the proteasome (RPT5B/HUP2) (Cho et al., 2006), which in turn were reported to bind several putative TFs. Interestingly, glucose antagonises ethylene signaling by promoting the proteasome-mediated degradation of the central regulator EIN3, and this effect of glucose is absent in the AtHXK1 null mutant *gin2* (*glucose insensitive 2*) (Moore et al., 2003; Yanagisawa et al., 2003). Metabolism of glucose through HXK1 independently of its signaling function induces on the other hand the defence- and pathogenesis-related PR genes (Xiao et al., 2000). A connection between glucose metabolism and defence (Wingler and Roitsch, 2008) may explain why tobacco plants overexpressing HXK1 and HXK2 are more resistant to H_2O_2-induced programmed cell death (Kim et al., 2006).

The product of glucose phosphorylation by HXK, glucose-6-phosphate (G6P), represses SnRK1 activity in spinach leaf extracts (Toroser et al., 2000) (Fig. 1). Nevertheless, the fact that AtSnRK1 marker genes are normally regulated in the *gin2* mutant suggests that this effect is purely metabolic and that, in the absence of AtHXK1, the action of other hexokinases is sufficient to inhibit AtSnRK1 (Baena-Gonzalez, Rolland, et al., 2007). On the other hand, no cross-talk between HXK1 and SnRK1 was reported with regard to the regulation of starch synthesis in potato tubers (Tiessen et al., 2003), further suggesting that these two pathways operate separately.

Regulator of G-protein signaling 1 (RGS1)

Extracellular glucose signals have been proposed to be transduced through heterotrimeric guanine nucleotide binding proteins (G-proteins) (Chen and Jones, 2004) (Fig. 1). In the canonical G-protein signaling scheme, specific signals are relayed to G-proteins through their associated G-protein coupled receptors (GPCRs). RGS proteins accelerate termination of the signal thereby resetting the system. However, in *Arabidopsis*, glucose is proposed to be sensed by a structurally hybrid protein containing both GPCR and RGS features, AtRGS1 (Temple and Jones, 2007). In support of this view, mutants of the G-protein subunits are oversensitive to glucose-induced developmental arrest, whereas *rgs1* mutants are glucose insensitive (Perfus-Barbeoch et al., 2004; Trusov et al., 2007). Interestingly, *Arabidopsis* plants overexpressing AtRGS1 were reported to be more tolerant to drought (Chen et al., 2006) and mutants in the G-protein subunits also exhibit altered responses to a wide variety of stresses (Perfus-Barbeoch et al., 2004; Chen, 2008). However, how this relates to the sugar sensing property of the complex is not clear. Recently, the transcriptional response to starvation and to sugar was compared between WT and *Atrgs1* plants (Grigston et al., 2008), uncovering a small set of sugar-regulated genes in this signaling network. The nearly negligible overlap of these genes with the reported SnRK1 target genes ((Baena-Gonzalez, Rolland, et al., 2007), unpublished observations) may suggest that these two pathways operate independently, although further experiments are required to address this.

Trehalose signaling

The disaccharide trehalose is commonly found in bacteria, fungi, and invertebrates, where it serves as a storage carbohydrate and stress protectant. It is synthesized in two steps, in the first one trehalose-6-phosphate synthase (TPS) synthesizes T6P from UDP-glucose and G6P and in the second one T6P is converted to trehalose by trehalose-6-phosphate phosphatase (TPP) (Fig. 1). In most plants, trehalose accumulates to trace amounts, and recent evidence implicates it in development, the stress response, and metabolism (reviewed in (Ramon and Rolland, 2007; Paul et al., 2008). *Arabidopsis* plants overexpressing AtTPS1 are more resistant to drought and T6P levels are correlated with increased expression of many stress genes as well as those encoding KIN11 and the S6 ribosomal kinase AtS6K2 (Avonce et al., 2004; Schluepmann et al., 2004).

T6P has also been implicated in the regulation of sugar metabolism controlling the rate of starch synthesis through redox modification of ADP-glucose pyrophosphorylase (AGPase) (Kolbe et al., 2005; Lunn et al., 2006). Accordingly, when the T6P pool is depleted upon overexpression of TPP, sugar-phosphates accumulate (Schluepmann et al., 2003). An interplay with SnRK1 in this regulation is suggested by the observation that the activation state of AGPase in potato tubers is dependent on SnRK1 (Tiessen et al., 2003). Furthermore, AtTPS5 was shown to be phosphorylated both by crude AtSnRK1 extracts and mammalian AMPK, and this phosphorylation was essential for its interaction with 14-3-3s (Harthill et al., 2006).

More recently, it was shown that T6P could inhibit AtSnRK1 activity at much lower concentrations (in the µM range) than those reported for G6P (in the mM range) (Toroser et al., 2000; Zhang et al., 2009). This inhibition, nevertheless, was not direct and required the presence of an unidentified intermediary factor that was present in young seedlings and leaves but not in mature leaves (Fig. 1).

POST-TRANSCRIPTIONAL REGULATION LINKED TO ENERGY SIGNALS

Global transcriptome and proteomic analyses have shown that there is often a discrepancy between mRNA and protein abundance (Hegde et al., 2003). Following transcription, gene expression is regulated at multiple steps that altogether determine the final levels of the protein. Stress can induce alternative splicing of pre-mRNAs, generating not only further protein diversity, but also affecting mRNA stability and turnover (Ali and Reddy, 2008). Stress conditions can also block the nuclear export of most mRNAs, allowing only the export of essential transcripts through specific pathways (Chinnusamy et al., 2008). Once in the cytoplasm, the mRNA could be either selectively translated (see below) or compartmentalized *e.g.* into stress granules or processing bodies (P-bodies), determining its fate for sequestration and protection or for degradation through various pathways, respectively (Bailey-Serres et al., 2009; Balagopal and Parker, 2009). Finally, protein levels can be regulated through degradation and an increasingly important role is being attributed to the proteasome during the stress response (Kurepa et al., 2009).

Translation is one of the most energy-costly processes of the cell and therefore, under situations of stress it is one of the first targets of regulation. Within hours, hypoxic stress causes a 50% reduction in the cellular ATP levels, and this is accompanied by a similar reduction in overall translation rates, as estimated by comparing mRNA levels in the non-polysomal (non-translated mRNA) *versus* polysomal (actively translated mRNA) fractions (Branco-Price et al., 2008). Using a similar approach a global decrease in translation has been measured also following mild drought and sugar starvation conditions (Kawaguchi et al., 2004; Nicolai et al., 2006).

Differential translation is achieved through changes *e.g.* in the phosphorylation levels of eIFs (eukaryotic initiation factors) and other translation factors and specific RNA-binding proteins that in turn determine the activity or association of components of the translational machinery. This provides a way to rapidly respond to stress, to fine-tune the strength of the response as well as to integrate multiple input signals.

Targets of regulation

Translation is traditionally divided into three main steps: initiation, elongation and termination. Translation initiation requires the coordinated assembly of multiple factors and is thus considered the rate-limiting step and the major site of control (Van Der Kelen et al., 2009) (Fig. 2). During translation initiation the 43S preinitiation complex (PIC, eIF2-GTP-Met-tRNA-40S ribosomal subunit) is recruited to the 5′ end of mRNA through its 5′end cap structure. The cap structure is recognized by the eIF4E subunit of the eIF4F complex that together with eIF4G serves as a bridge between the PIC (via eIF3) and the mRNA. eIF4B stimulates the ATP-dependent helicase activity of eIF4A and interacts also with eIF3. eIF4G interacts in addition with the poly(A)-binding protein (PABP) at the 3´end, leading to circularization of the mRNA and to the enhancement of translation. Subsequent hydrolysis of eIF2-associated GTP displaces the initiation factors and allows binding of the large 60S ribosomal subunit.

Key regulatory components at this stage are: *i)* the eIF4F complex (eIF4A, eIF4E, and eIF4G) and PABPs, as key factors for the interaction of the mRNA with the translational machinery, *ii)* the 40S ribosome subunit and the eIF3 complex, as determinants of the PIC and its stabilization, and *iii)* the eIF2 complex, as a regulator of the final step of ribosome assembly.

eIFs

In plants, multiple isoforms of the initiation factors and their phosphorylated isoforms have been identified, depending on developmental cues or external signals (reviewed in (Bailey-Serres, 1999; Kawaguchi and Bailey-Serres, 2002). In maize root tissue, oxygen deprivation stimulates eIF4E and eIF4A phosphorylation (Webster et al., 1991; Manjunath et al., 1999). In wheat seedlings, on the other hand, downregulation of translation upon heat shock is correlated with reduced eIF4B phosphorylation (Gallie et al., 1997) and with the induction of the eIF4G, eIFiso4G (an eIF4G isoform), eIF3, and PABP subunits (Gallie, 1998). The absence or presence of eIF4B and its interaction with different eIF4F isoforms confers differential translational efficiency on specific mRNAs, and hence it has been proposed to be a key regulator of translation under varying cellular conditions (Mayberry et al., 2009).

Recent work in *Arabidopsis* suggests that eIF3e is a negative regulator of translation and that its levels are modulated through interactions with the COP9 signalosome and the 26S proteasome (Paz-Aviram et al., 2008; Yahalom et al., 2008). Translation initiation is also regulated by eIF3h, which maintains efficient translation of mRNAs that harbour multiple upstream open reading frames (uORF, see below). As a result, polysome loading and translational rates of uORF-regulated mRNAs such as that of bZIP11 are strongly reduced in *Arabidopsis eif3h* mutants (Kim et al., 2004; Kim et al., 2007) .

Binding of mRNA and the 60S ribosomal subunit to the viable PIC requires GTP hydrolysis, yielding a viable initiation complex and releasing inactive eIF2α-GDP. Phosphorylation of serine 51 of eIF2α prevents the reactivation of eIF2 through eIF2B-mediated GDP exchange with GTP, resulting in the formation of an inactive eIF2–eIF2B complex and inhibition of translation (Van Der Kelen et al., 2009). Wheat eIF2α is also phosphorylated at Ser51 and this correlates with decreased translational rates *in vitro* (Langland et al., 1996; Chang et al., 1999). Although no changes in the level of eIF2α were observed following heat shock (Gallie et al., 1997), wheat eIF2α was phosphorylated and could functionally complement the corresponding yeast mutant under amino acid starvation conditions, suggesting a conserved role for plant eIF2 in translational regulation (Chang et al., 2000). However, whether the possible involvement of eIF2α phosphorylation in translational control is mediated through differential interaction with eIF2B or through some other mechanism remains to be determined.

PABPs

In addition to heterogeneity in the initiation factors, substantial heterogeneity exists also at the level of PABPs and proteins associated to them, suggesting they could contribute to the regulation of mRNA biogenesis, export and translation (Belostotsky, 2003). Through their N-terminal RRM (RNA Recognition Motif) domain, PABPs are able to interact with eIF4B, eIF4(iso)G, and eIF4G (Cheng and Gallie, 2007). Other proteins can interact through their PAM2 (PABP-interacting Motif 2) with the C-terminal PABC domain of PABPs (Wang and Grumet, 2004; Bravo et al., 2005), thereby stimulating or repressing translation. For example, the cucumber PAM2 protein ERD15 (EARLY RESPONSIVE TO DEHYDRATION 15) is induced by stress and, at least *in vitro*, is able to inhibit translation of poly(A)-tailed mRNAs (Wang and Grumet, 2004).

Ribosomal proteins

Another layer of complexity lies on ribosomal proteins, which are encoded by small gene families whose translation is strongly repressed *e.g.* by mild dehydration stress (Kawaguchi et al., 2004). Furthermore, certain ribosomal proteins are also modified *e.g.* through phosphorylation (Chang et al., 2005; Carroll et al., 2008), altogether supporting the idea of a "ribosome code" that could selectively translate specific mRNAs under specific conditions (Komili et al., 2007).

To date, the best characterised ribosomal protein is S6, a component of the 40S subunit. As in other systems (Van Der Kelen et al., 2009), phosphorylation of S6 in maize and *Arabidopsis* is inhibited by stress conditions, including oxygen deprivation and heat shock (reviewed in (Bailey-Serres, 1999)) (Williams et al., 2003).

Translational regulators

TOR (TARGET OF RAPAMYCIN)

TOR is an evolutionarily conserved PI3K-related PK that tightly controls eukaryotic protein synthesis, cell growth and proliferation in response to nutrients, growth factors, ATP, oxygen levels, and stress (Wullschleger et al., 2006) (Fig. 1). Mammalian TOR (mTOR) exists in two complexes with different interacting partners and functions. TORC1 (sensitive to the drug rapamycin) exerts temporal control of cell growth by promoting biosynthetic processes and nutrient uptake while repressing catabolic processes such as autophagy and ubiquitin-dependent protein degradation. TORC2 (rapamycin-insensitive) mediates the spatial control of cell growth through regulation of the actin cytoskeleton.

Work in recent years suggests that the TOR pathway plays an important role in the adaptation to stress. The TOR cascades respond to a wide range of stimuli, including amino acids, ATP, mitogens, low oxygen, and phosphatidic acid, and decreased TOR activity has been associated with increased resistance to several types of stress (Reiling and Sabatini, 2006).

Energy sensing has been proposed to be intrinsic to the TOR complex, which can sense ATP at very high concentrations (Km=1 mM) and thus signal when energy levels are high (Dennis et al., 2001). On the other hand, fine oscillations in energy levels are sensed through AMPK that downregulates TOR activity through the TSC1/2-Rheb axis (Wullschleger et al., 2006). The antagonistic relationship between the mTOR and AMPK pathways is further emphasized by the fact that increased AMPK activity triggers gene expression changes which are similar to those associated with decreased mTOR signaling caused by the lack of one of its main substrates, S6K1 (Selman et al., 2009) (see below).

Regulation of protein synthesis by mTOR is mainly exerted through two main targets: eIF4E-binding proteins (4E-BPs) and 40S ribosomal protein S6 kinases (S6Ks). 4E-BPs prevent translation through the sequestration of eIF4E. mTOR activation results in their phosphorylation and deactivation, triggering the release of eIF4E and allowing translation initiation. S6Ks, on the other hand, are activated by phosphorylation. They phosphorylate in turn the S6 ribosomal protein and eIF4B, stimulating translation by recruitment of eIF4B into complexes with eIF3 (Van Der Kelen et al., 2009) .

Arabidopsis TOR (AtTOR) is a highly conserved protein, with all the key domains found in other organisms and encoded by a single gene. In agreement with its effect in other organisms, AtTOR is also essential for embryogenesis and endosperm development and knocking out TOR leads to developmental arrest at the globular stage (Menand et al., 2004). Nevertheless, plants with varying degrees of AtTOR overexpression or silencing demonstrate that AtTOR is essential also for postembryonic growth (Deprost et al., 2007), affecting root and shoot growth, cell size and seed yield. Induction of total AtTOR silencing, on the other hand, results in growth arrest and premature senescence, and this is accompanied by a reduction in mRNA translation.

Arabidopsis RAPTOR (AtRAPTOR, REGULATORY ASSOCIATED PROTEIN OF TOR) interacts with AtTOR and AtS6K1, resulting in AtS6K1 activation and phosphorylation of the S6 substrate (Mahfouz et al., 2006). Plants overexpressing AtS6K1 are hypersensitive to osmotic stress and the interaction with AtRAPTOR and AtTOR is essential for the sensitivity of AtS6K1 to osmotic stress (Mahfouz et al., 2006). In plants a direct connection between TOR and autophagy has not yet been established (Bassham, 2009). However, in the green alga *Chlamydomonas reinhardtii*, which contrary to plants is rapamycin sensitive, treatment of the cells with this drug induces cell structures reminiscent of autophagosomes (Crespo et al., 2005).

No 4E-BP1 homologues have been described in plants, which seem to have developed alternative mechanisms and/or proteins to regulate translation initiation (Menand et al., 2004). *Arabidopsis* lipoxygenase 2 (AtLOX2), a protein involved in jasmonate synthesis and located both in chloroplasts and the cytoplasm, was identified as an eIF4E interacting protein (Freire et al., 2000). In another study it was shown that *Arabidopsis* chloroplasts import eIF4E mRNA despite not being translated within the organelle (Nicolai et al., 2007). Altogether, these results raise the intriguing possibility that, in response to physiological and nutritional cues, plastids could modulate cytoplasmic translation either directly or through selective sequestration of eIF transcripts.

VPS34 (VACUOLAR PROTEIN SORTING 34)

In addition to the TSC1/2-Rheb axis, a nutrient signal seems to be independently conveyed to mTOR through a class III PI3K, hVPS34 (Wullschleger et al., 2006) (Fig. 1). VPS34 is involved in vesicle trafficking and autophagy, a process triggered by starvation and by which cells degrade cytosolic content in order to recycle nutrients.

Arabidopsis VPS34 (AtVPS34) shares a 40% identity with yeast VPS34, and, when fused to the yeast regulatory domain, its C-terminal catalytic domain is able to complement a yeast Δ*vps34* mutant (Welters et al., 1994). Transgenic plants with reduced AtVPS34 levels are severely impaired in growth and development (Welters et al., 1994) and when exposed to salt stress they are unable to trigger normal endocytosis and ROS production resulting in a salt oversensitive phenotype (Leshem et al., 2007). Moreover, VPS34 and other components of the autophagy machinery play an essential role in plant defence and are required for tolerance to drought and salt stress (Liu et al., 2005; Bassham, 2009). The finding in carrot cell cultures that VPS34 is associated with active nuclear and nucleolar transcription sites raises the possibility that it could exert part of its functions through transcriptional regulation (Bunney et al., 2000) (Fig. 1).

The *Arabidopsis* genome does not encode obvious orthologs of TSC1/2 and its small GTPase superfamily lacks any Ras-type family members like Rheb. However, a new positive regulator of Rheb, TCTP (TRANSLATIONALLY CONTROLLED TUMOR PROTEIN), was recently identified in *Drosophila* that despite its absence in mammals has a homologue in plants (Hsu et al., 2007; Berkowitz et al., 2008). Suppression of TCTP function in *Arabidopsis* leads to growth phenotypes similar to loss of AtTOR, suggesting that TCTP may be involved in TOR signaling also in plants.

GCN2 (GENERAL CONTROL NON-REPRESSED 2)

Another alternative pathway for amino acid and energy sensing is that mediated by the GCN2 kinase, which in yeast is well known to couple amino acid sensing to regulation of translation initiation (Van Der Kelen et al., 2009) (Fig. 1). GCN2 is activated by direct binding of uncharged tRNAs that accumulate during nutrient scarcity and various other stresses. Upon activation, GCN2 phosphorylates eIF2α inhibiting translation in a global manner but activating the translation of a small subset of genes required for the starvation response (*e.g. GCN4*).

Arabidopsis GCN2 (AtGCN2) is able to complement its corresponding yeast mutant under amino acid starvation conditions (Zhang et al., 2003), and conversely, yeast GCN2 phosphorylates wheat eIF2α (Chang et al., 1999; Chang et al., 2000). Furthermore, eIF2α is phosphorylated in response to several stresses and this activation is absent in *Arabidopsis gcn2* mutants (Lageix et al., 2008; Zhang et al., 2008). AtGCN2 is essential for plant growth under nutritional stress and its lack results in a global reduction in protein synthesis. In contrast to the results in yeast, where TOR was shown to negatively regulate GCN2 (Cherkasova and Hinnebusch, 2003), no connection was observed between the TOR and GCN2 pathways (Lageix et al., 2008; Zhang et al., 2008). Interestingly, AMPK downregulates translation by activating the eIF2 kinase (EF2K) (Hardie, 2007). Since AtGCN2 seems to be the only eIF2K in *Arabidopsis* (Lageix et al., 2008), it is possible that it is phosphorylated by AtSnRK1.

Regulation through small RNAs (sRNAs)

Recent years have witnessed profound changes in our view of gene expression, and sRNAs are now well-established key regulatory components in all the eukaryote kingdoms. Endogenous sRNAs in plants can be divided into two broad classes, microRNAs (miRNAs) and small interfering RNAs (siRNAs), based mainly on their biogenesis (Vaucheret, 2006). miRNAs are single-stranded non-coding RNAs of 20-24 nt length that, similarly to TFs act in *trans* on non-self RNAs, negatively regulating their expression post-transcriptionally. In *Arabidopsis*, they are processed from primary miRNA transcripts by a nuclear-localized complex containing DICER-LIKE1 (DCL1), exported to the cytoplasm and incorporated into an RNA-induced silencing complex (RISC) for recognition of targets with a complementary sequence (Vaucheret, 2006). Work in Arabidopsis has recently demonstrated that miRNAs act as regulators of gene expression not only through cleavage of highly complementary target mRNAs, but also through translational regulation (Brodersen et al., 2008; Lanet et al., 2009) (Fig. 1). The underlying molecular mechanism may involve the recruitment of eIF-inhibitory factors upon binding of the mRISC (miRNA-induced silencing complex) to the 3´UTR (Carthew and Sontheimer, 2009). In addition, miRNA regulation could be exerted via sequestration of the target mRNA *e.g.* in P-bodies (Filipowicz et al., 2008), although several alternative models have been proposed (Carthew and Sontheimer, 2009).

Plant sRNAs are emerging as novel important players in adaptive processes, mediating the response to various nutrients and abiotic stresses (Sunkar and Zhu, 2004; Sunkar et al., 2007;

Shukla et al., 2008). A link between miRNA and stress was first established based on the stress-related nature of miRNA predicted targets (Jones-Rhoades and Bartel, 2004; Sunkar and Zhu, 2004). Later on, either the repression or the induction of numerous miRNAs by stress and/or nutrients has been well documented and their impact on stress tolerance has in some cases also been demonstrated (Chiou, 2007; Sunkar et al., 2007; Pant et al., 2009). One such example is miR398, whose expression is downregulated by several stresses and reduced miR398 levels in transgenic lines result in enhanced tolerance to oxidative stress conditions (Sunkar et al., 2006; Jagadeeswaran et al., 2009). Intriguingly, sucrose has an opposite effect on miR398, upregulating its expression (Dugas and Bartel, 2008) and thereby establishing a possible new molecular link between the cellular energy status and the response and tolerance to stress. Such link is further supported by a recent study where the sRNA population associated with hypoxic stress was characterized in *Arabidopsis*: for a set of tested miRNAs similar changes could be triggered through inhibition of mitochondrial respiration, emphasizing the energetic component of the response (Moldovan et al., 2009) (Fig. 1). Noteworthily, a connection between miRNAs and energy signals seems to exist also in animal systems, where miRNAs have been shown to play a role in insulin signaling and glucose homeostasis (Poy et al., 2007).

In addition to oxidative stress, many miRNAs were described to respond to cold, osmotic stress, or salinity (Sunkar and Zhu, 2004). Most interestingly, some of these miRNAs are responsive to multiple stress conditions (Sunkar and Zhu, 2004), in agreement with the findings that mutants with disturbances in the small RNA pathways exhibit altered responses to multiple types of stress (Zhang et al., 2008).

An additional class of endogenous siRNAs that has been linked to stress are natural *cis*-acting siRNAs (nat-siRNAs), which originate from overlapping sense and antisense transcripts

(Borsani et al., 2005; Vaucheret, 2006). The overlap is triggered by the specific induction of one of the transcripts under stress conditions, thereby resulting in the downregulation of the complementary transcript through its nat-siRNA-mediated cleavage. More than two thousand pairs of natural antisense transcripts have been predicted, suggesting that this combination of transcriptional and post-transcriptional regulation could be commonly used in plants under stress (Jin et al., 2008).

Alternative initiation mechanisms

Stress can have an impact on the site of translation initiation promoting the use of alternative initiation sites that result in the synthesis of alternative protein forms (Murray-Zmijewski et al., 2006). In *Arabidopsis* the use of different initiation sites in an organellar DNA polymerase transcript was shown to result in proteins targeted either to the plastid alone or also to the mitochondria (Christensen et al., 2005), but whether stress conditions favoured the use of one site over the other was not investigated.

Another means of controlling translation through alternative initiation is through the use of upstream open reading frames (uORFs) in the 5´UTR of the transcript (Van Der Kelen et al., 2009). Noticeably, the *Arabidopsis* S-group bZIP TFs are translationally repressed through uORFs by sucrose (Wiese et al., 2005; Rahmani et al., 2009) (Fig. 1). The 5´ UTR of their mRNAs harbours an uORF that encodes a sucrose control peptide (SCP). In the presence of sucrose the presence of the SCP causes ribosomes to stall, thereby preventing translation of the main downstream ORF encoding the bZIP TF (Wiese et al., 2005; Rahmani et al., 2009).

Despite the overall suppressing effect of stress on translation, many genes are able to escape the translational arrest and are selectively translated during stress. In addition to the mechanisms already described that may modulate the translational machinery for this purpose, transcripts may also contain internal ribosome entry sites (IRES) in their 5´UTRs that allow their recruitment to the translational machinery independently of the conventional cap-recognition mechanism. Numerous examples of genes containing IRES have been reported in non-plant organisms and their importance for the stress response is widely accepted (Spriggs et al., 2008). Strikingly, it has been estimated that alternative initiation mechanisms could exist for up to 10-15% of genes (Spriggs et al., 2008). In plants, only a few IRES-containing cellular mRNAs have been described, and they contribute to the maintenance of translation *e.g.* of the maize heat shock protein Hsp101 during heat stress (Dinkova et al., 2005). The maize alcohol dehydrogenase-1 gene *ADH1* also contains an IRES element that supports translation under oxygen deprivation, although this element alone cannot account for the observed translation rates of the messenger under hypoxia (Mardanova et al., 2008).

CONCLUSIONS AND OUTLOOK

Fluctuations in environmental conditions pose a great challenge to plants, which, as sessile organisms, depend on their ability to finely sense and adapt to these changes for growth and survival. In addition to stress-specific factors, cells presumably monitor certain parameters with disregard to the condition that generates them. Many stress conditions have an impact on cellular ATP levels and the ensuing energy deficiency signal triggers downstream transcriptional responses that are shared by different types of stress. Such convergent response allows the maintenance of homeostasis and the subsequent implementation of longer-term adaptive measures. Gene expression is also regulated post-transcriptionally, providing further flexibility for the adjustment of the strength and timing of the response. Several components have recently emerged in plants as sensors, mediators and effectors of the energy signals associated with stress, but most of the aspects concerning their regulation and the composition of their respective signaling pathways are still unknown. Future studies will need to address this as well as the connections between these pathways through putative common nodes. Despite the universality of energy signaling and the high evolutionary conservation of its associated signaling components, an increasing body of evidence suggests plant-specific features, as well as the differential regulation and operation of these systems depending on the tissue and developmental stage. A major goal will be to understand how these energy-sensing systems have been modified in plants to interact with systemic and other signals, driving growth and development in an ever-changing environment.

FIGURES

Figure 1. Overview of energy and nutrient sensing systems involved in the regulation of gene expression in response to stress. The blue components are hypothesized to constitute a network that upon sensing nutrient and/or energy deficiency downregulates growth-related energy-consuming processes and promotes nutrient remobilization and tolerance to stress. The network formed by the orange components is proposed to operate in an antagonistic manner to couple nutrient/energy availability with growth. Components displaying both colours may function in both networks. Energy deficiency caused by stress activates SnRK1, which triggers an energy-saving program at several levels, including vast transcriptional reprogramming partly via the S-bZIP TFs. Conversely, sugars, in the form of trehalose-6-phosphate (T6P), glucose-6-phosphate (G6P) or others, have a repressive effect, albeit the specific effect of sugars on the SnRK1 system may differ between tissues and developmental stages. Sucrose has a specific effect on the SnRK1 signaling cascade by repressing translation of the S-group bZIP TFs. Energy availability, on the other hand, is sensed by HXK1 which, in the presence of sugar represses, amongst others, the photosynthesis-related *CAB* genes. Extracellular glucose signals seem to be transduced through the G-protein coupled receptor system involving RGS1 and G-protein (G-P) subunits. In nutrient-rich conditions plant TOR undergoes activation, stimulating translation at multiple levels to promote growth. In situations of amino acid scarcity the GCN2 PK seems to antagonize this response. How nutrient and energy signals are conveyed to plant TOR is not known, but the VPS34 PI3K kinase and the negative regulation by SnRK1 may be involved. VPS34 is found also in the nucleus, where it may perform additional regulatory functions. Changes in nutrient and energy availability associated with stress or optimal growth conditions trigger the differential

accumulation of specific microRNAs (miRNAs) and other small RNAs, which in turn regulate gene expression through translational control or through cleavage of the target transcript. Solid lines designate proven connections, whereas dotted lines represent hypothetical ones. HXK1C, Hexokinase 1 nuclear complex; Glc, glucose; Tre; trehalose; Suc, sucrose; TPS, T6P synthase; TPP, T6P phosphatise; mRISC, miRNA induced silencing complex.

Figure 2. Schematic representation of the circularized translation initiation complex during cap-dependent translation (see text for details). Shaded components represent major targets of regulation and dashed lines indicate differential accumulation or induction of specific isoforms by energy and nutrient signals. Components that are phosphorylated or dephosphorylated in response to energy deficiency are labelled with P or an empty white square, respectively. 1, eIF1; 2, eIF2; 3, eIF3; 4, eIF4; 5, eIF5; S6, S6 protein of the 40S ribosomal subunit; PABP, Poly(A)-binding protein. eIF4F is composed of the eIF4A, eIF4E, and eIF4G subunits.

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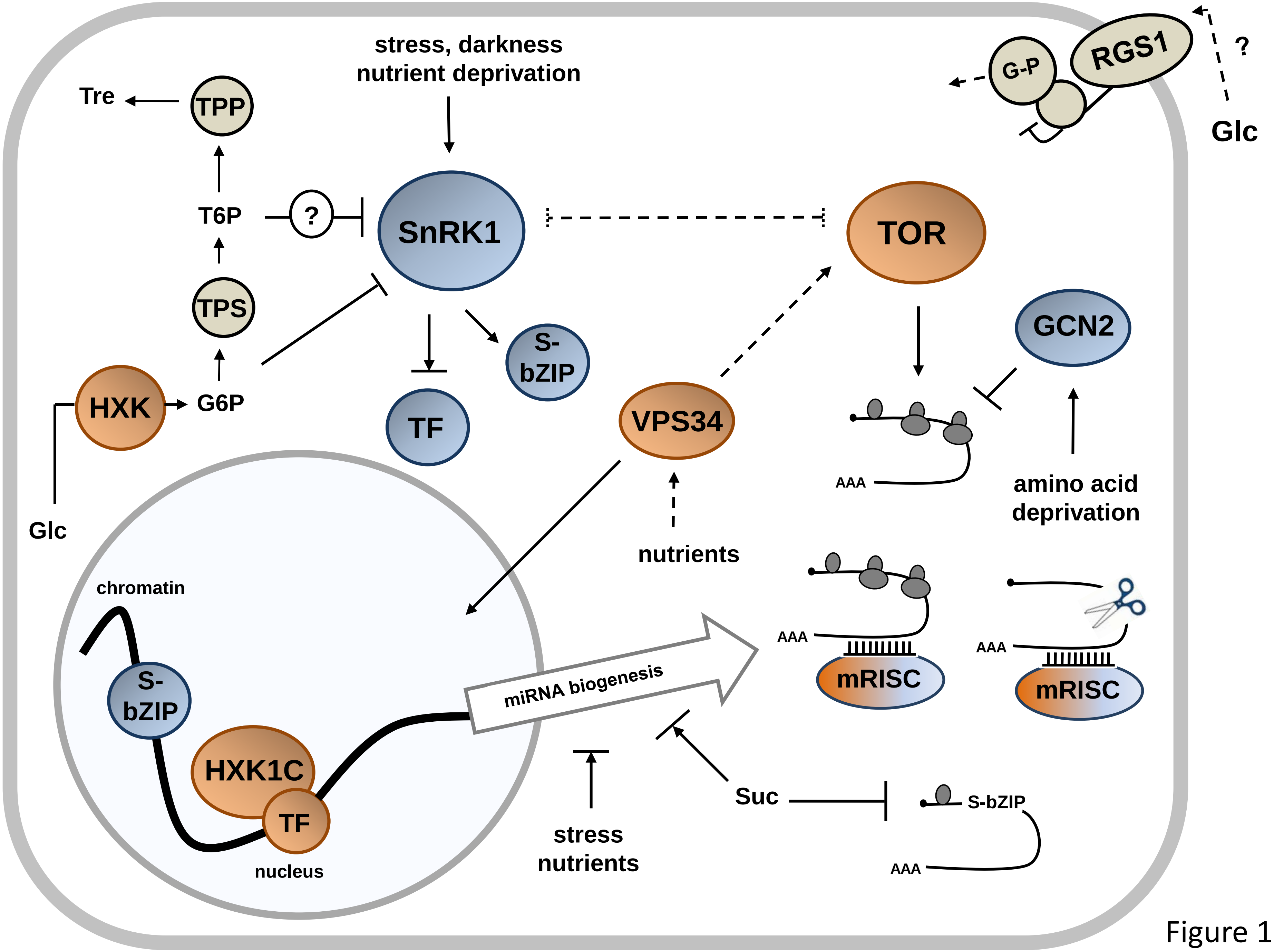
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Figure 1

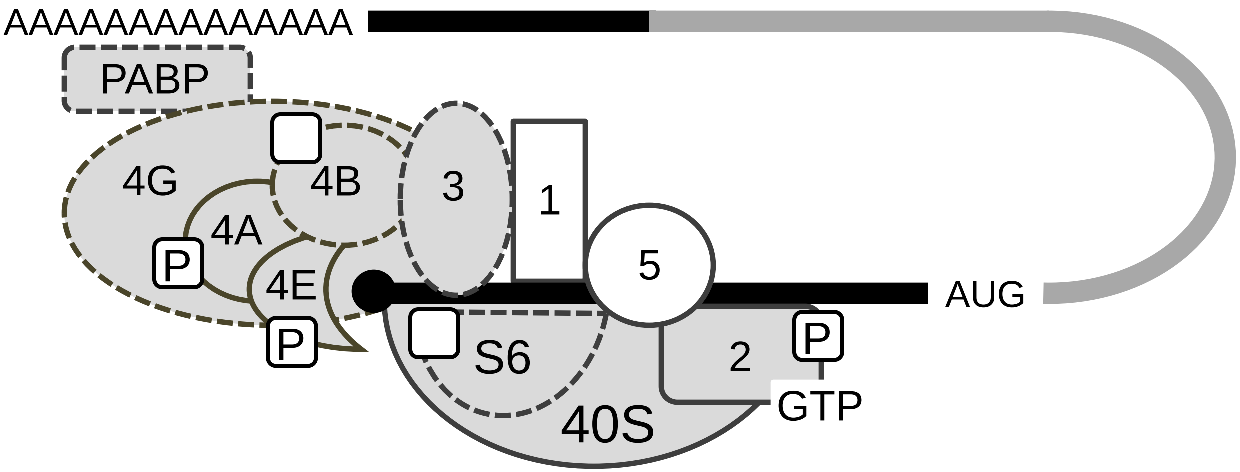

Figure 2