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Translational Regulation of Cytoplasmic mRNAs

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Translation of the coding potential of a messenger RNA into a protein molecule is a fundamental process in all living cells and consumes a large fraction of metabolites and energy resources in growing cells. Moreover, translation has emerged as an important control point in the regulation of gene expression. At the level of gene regulation, translational control is utilized to support the specific life histories of plants, in particular their responses to the abiotic environment and to metabolites. This review summarizes the diversity of translational control mechanisms in the plant cytoplasm, focusing on specific cases where mechanisms of translational control have evolved to complement or eclipse other levels of gene regulation. We begin by introducing essential features of the translation apparatus. We summarize early evidence for translational control from the pre-Arabidopsis era. Next, we review evidence for translation control in response to stress, to metabolites, and in development. The following section emphasizes RNA sequence elements and biochemical processes that regulate translation. We close with a chapter on the role of signaling pathways that impinge on translation.

1. SCOPE

In recent years, proteomics projects have made great strides in detecting and quantifying the levels of individual proteins in Arabidopsis. However, these and other experiments have also revealed that the correlation between mRNA transcript levels and protein levels across the proteome is modest. More surprisingly, even a *change* in mRNA level for a single gene does not necessarily result in the expected change in the corresponding protein level (Bärenfaller et al., 2008; Piques et al., 2009; Bärenfaller et al., 2012). The incomplete coupling between mRNA and protein levels must be attributed primarily to variable translation and variable protein turnover. This article synthesizes the evidence for translational control, and explains the potential mechanisms of translational regulation in plants.

We begin by briefly reviewing the molecular biochemistry of translation, including the roles of the ribosome and the translation factors, and touch on a few plant-specific concepts, but only to the degree needed to understand the following section. An insightful and balanced summary of the plant translation apparatus was presented recently (Muench et al., 2012). The main section on translational control will begin with historical findings from the pre-Arabidopsis era before delving into more recent progress, primarily from Arabidopsis. Aspects of translational control that have been covered well in recent reviews are not described in full detail here, for example on control of translation by sucrose (Hummel et al., 2009), on ribonucleoprotein complexes (Bailey-Serres et al., 2009), the TOR kinase pathway (Dobrenel et al., 2011), eukaryotic initiation factor eIF2α phosphorylation (Hey et al., 2010; Immanuel et al., 2012), ribosomal effects on development (Horiguchi et al., 2012), and on comparing plant with non-plant processes (Munoz and Castellano, 2012). In keeping with an article on Arabidopsis, we do not consider translational control of plant viruses and virus resistance (Dreher and Miller, 2006; Robaglia and Caranta, 2006; Nicholson and White, 2011; Echevarria-Zomeno et al., 2013). Articles linking translation factors with higher-level processes, such as growth and development, are generally omitted unless there is specific evidence for regulation at the mRNA level. Also excluded is the entire body of work on translational control in the chloroplast and mitochondria.

2. BIOCHEMICAL CONTEXT FOR TRANSLATIONAL CONTROL IN THE CELL

The decoding of the mRNA by the ribosome is a complex process that requires a plethora of initiation, elongation, and termination factors (Hinnebusch and Lorsch, 2012), some of which serve as endpoints for translational regulation. The structure of an mRNA is defined by the sites of transcription initiation and termination on the chromosome, the splicing pattern, and by 3' end processing and polyadenylation. The expression level of the mRNA is set by the rates of transcription and degradation (Figure 1). After export

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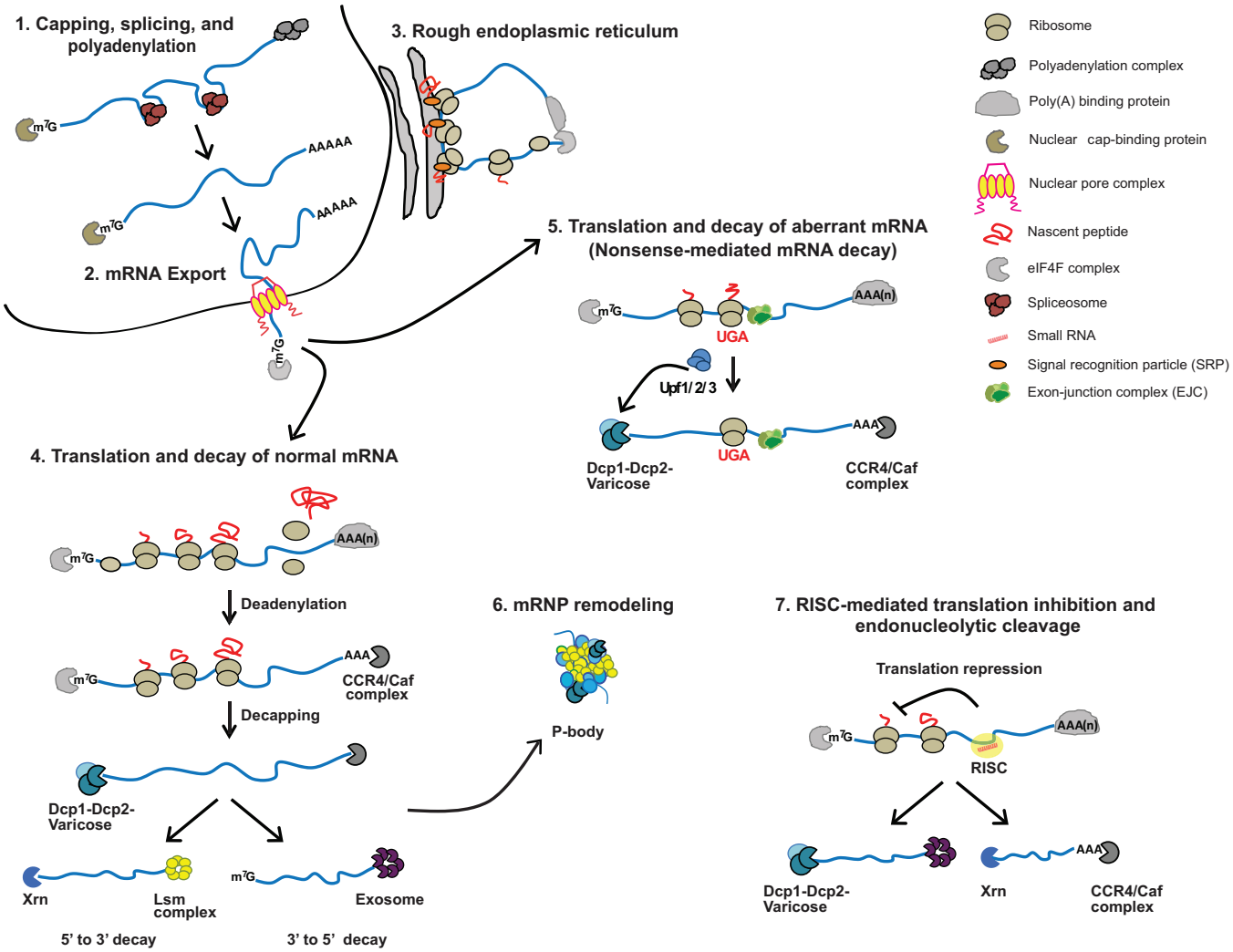

Figure 1. Concept map of the cell biology of RNA.

After processing of the primary transcript by splicing, capping, and polyadenylation has been completed in the nucleus (1), the mature mRNA is exported into the cytoplasm through the nuclear pore complex (2). In the process, the nuclear cap binding protein is replaced with the eIF4F complex. mRNA is translated on ribosomes associated with the endoplasmic reticulum (3) or on free cytosolic ribosomes (4, 5, 7). RISC complexes with small RNAs as sequence-specific guide RNAs have endonuclease activity or may inhibit translation directly (7). XRN exonucleases degrade uncapped mRNA from the 5' end, while the CCR4/Caf complex degrades poly(A) tails. The exosome exonuclease degrades non-polyadenylated mRNA from the 3' end. DCP1/DCP2/Varicose have decapping activity. Nonsense-mediated decay is a quality control process that identifies aberrant mRNAs, often based on a premature termination codon (5). mRNAs may be remodeled by the Lsm ring complex and may be sequestered into a variety of cellular mRNP particles (6). Processing (P-) bodies contain decapping enzymes. Stress granules (not shown) form transiently after heat stress and other stresses.

of the mRNA from the nucleus (Xu and Meier, 2008; Meier and Brkljacic, 2009) it is generally ready to be translated. However, on occasion, mRNAs are first transported to specific subcellular sites (Banerjee et al., 2009). Subcellular targeting of secretory mRNAs to the ER is well appreciated, but other examples are sparse, with the exception of storage protein mRNAs that have been studied extensively (Okita and Choi, 2002; Washida et al., 2009).

mRNAs that are bound by ribosomes are termed polysomes (see glossary for definitions). The translation state of the mRNA is a composite of ribosome occupancy and ribosome density, which can both be measured by polysome fractionation (see Box). Occupancy refers to the fraction of the mRNA found in polysomes, while density refers to the average number of ribosomes per length of mRNA. It should be appreciated that ribosome density does not necessarily predict the protein production rate. After all, a high ribosome density may be the result of effective translation initiation, but may also be due to slow elongation. However, ribosome density is considered to be a good proxy for protein production because, as far as we know, translation regulation at the initiation stage is more common than at the elongation stage.

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TOOLS AND TECHNIQUES FOR INVESTIGATING TRANSLATIONAL CONTROL

The rate of protein synthesis per unit time can be measured by pulse labeling. Plant material is incubated with radioisotopically labeled amino acids, usually S^{35}-methionine/cysteine, over a series of timepoints. Next, the amount of label that has been incorporated into the protein of interest is determined by isolating the protein with an affinity reagent such as a specific antibody followed by scintillation counting or gel electrophoresis and densitometry.

Circumstantial evidence for translational control can come from comparing the level of mRNA with the rate of protein accumulation, keeping in mind that the ratio between the two also depends on protein turnover.

Translational efficiency typically scales with ribosome loading. Polysomes are fractionated by sucrose gradient centrifugation and the ribosome loading of specific mRNAs is determined from the distribution of the mRNA across the gradient. mRNAs may be detected by northern hybridization, quantitative reverse transcription polymerase chain reaction (RT-PCR), microarray, or RNA sequencing. Polysomal mRNAs may also be isolated by co-immunoprecipitation of mRNAs with tagged ribosomal proteins.

Reporter gene expression assays reveal the effect of specific RNA sequence elements on translation. The dual luciferase assay is popular, because the gene of interest and its reference gene can be tested in the same protein extract. Careful monitoring of the cellular mRNA level is advisable when transforming with DNA plasmids. Transformation with in vitro transcribed, capped mRNA is possible in protoplasts.

Translational regulation may occasionally be recapitulated in an in vitro translation system. The wheat germ extract has been the only commercially available plant based system. An Arabidopsis in vitro translation system was recently derived from callus culture (Murota et al., 2011).

Translation inhibitors: Cycloheximide inhibits eukaryotic translation elongation by arresting ribosomes on the mRNA; as a result, nonsense-mediated decay is inhibited and the mRNAs are stabilized. Anisomycin inhibits translation elongation. Puromycin prematurely terminates translation, by releasing the incomplete polypeptide from the ribosome. Chloramphenicol inhibits elongation by plastid ribosomes.

mRNAs may be sequestered into several types of non-translated particles, including transport granules (Hamada et al., 2003a), stress granules, and processing (P-) bodies. Stress granules form transiently during abiotic stress such as heat shock (Nover et al., 1989). P-bodies contain decapping enzymes, and although recruitment into P-bodies may be reversible, the inherent decapping activity would slate the mRNA for inactivation and degradation (Goeres et al., 2007). Seed storage proteins are clients for P-body mediated repression (Xu and Chua, 2009). Decapping and translation can be considered competing pathways. The cytoplasmic mRNA decapping machinery in *Arabidopsis* consists of the catalytic subunit DCP2, its coactivators DCP1 and DCP5, a cofactor, VARICOSE (Xu et al., 2006; Xu and Chua, 2009, 2011), and a highly conserved Lsm ring complex (Perea-Resa et al., 2012).

2.1. Plants Observe the Scanning Model of Translation

The plant cytosolic translation apparatus consists of ribosomes, associated translation factors, and tRNAs. Most of the plant translation machinery resembles that of other higher eukaryotes such as human and yeast. Translation follows Kozak's scanning model (Figure 2) (Kozak, 1992; Hinnebusch and Lorsch, 2012). For the remainder of this section, recent references are cited simply to serve as a primer into the plant literature, since the factual statements qualify as pan-eukaryotic textbook knowledge. The 5' cap of the mRNA is recognized by the eIF4F complex, which consists of the cap binding protein, eIF4E, and a large scaffold protein, eIF4G (Patrick and Browning, 2012). In preparation for initiation, the small (40S) subunit of the ribosome is loaded with a charged methionyl-tRNA, which is delivered by the trimeric GTP-binding protein, eIF2. Several additional initiation factors, eIF1 and eIF1A, eIF3, and presumably eIF5 are also preloaded onto the 40S in the form of a multifactor complex (Dennis et al., 2009). The 40S subunit of the ribosome is brought to the cap by the largest initiation factor, the 13-subunit eIF3 complex (Burks et al., 2001). Next, the 40S ribosome scans down the mRNA in a 5' to 3' direction, a process that is facilitated by the ATP-dependent helicase eIF4A and its cofactor, eIF4B (Bush et al., 2009; Khan et al., 2009; Mayberry et al., 2009; Vain et al., 2011). The ribosome scans until its initiator tRNA basepairs with an AUG start codon in a favorable context (Kozak, 1984, 1989; Sugio et al., 2010), a process controlled by the initiation factors eIF1 and eIF1A. Upon start codon recognition, the eIF5 protein stimulates GTP hydrolysis by eIF2. Most, if not all, eIFs now dissociate from the mRNA. Next, the large 60S ribosomal subunit can join. Subunit joining is catalyzed by another GTPase, eIF5B, thus completing translation initiation. At this stage, the methionyl tRNA resides in the P(eptidyl)-site of the assembled 80S ribosome. The A(minoacyl)-site of the ribosome is free to bind the second charged tRNA.

During the subsequent elongation phase, the enzymatic peptidyltransferase activity of the ribosome catalyzes peptide bond formation between the two amino acids. The ribosome translocates by one codon, thereby shifting the spent initiator tRNA into its E(xit)-site, and opening up a new, empty, A-site. The elongation factors eEF1 and eEF2 mediate tRNA delivery and ribosome translocation, respectively. The elongation cycle repeats until the ribosome reaches a stop codon.

At termination, peptide release requires ribosome release factors. Translation ends with the separation of the two subunits and their dissociation from the mRNA, a process known as recycling. The poly(A)binding protein (PABP) forms a bridge with the initiation factor eIF4G, thus bending the mRNA into a closed loop, which is thought to stimulate the recycling of the post-termination ribosomal subunits to the 5' end of the mRNA for the next round of translation (Cheng and Gallie, 2007, 2010). Very recently, a potential translation termination and ribosome recycling factor homologous to metazoan ABCE1 was cloned as *SIMPLE LEAF3/RLI2*, because

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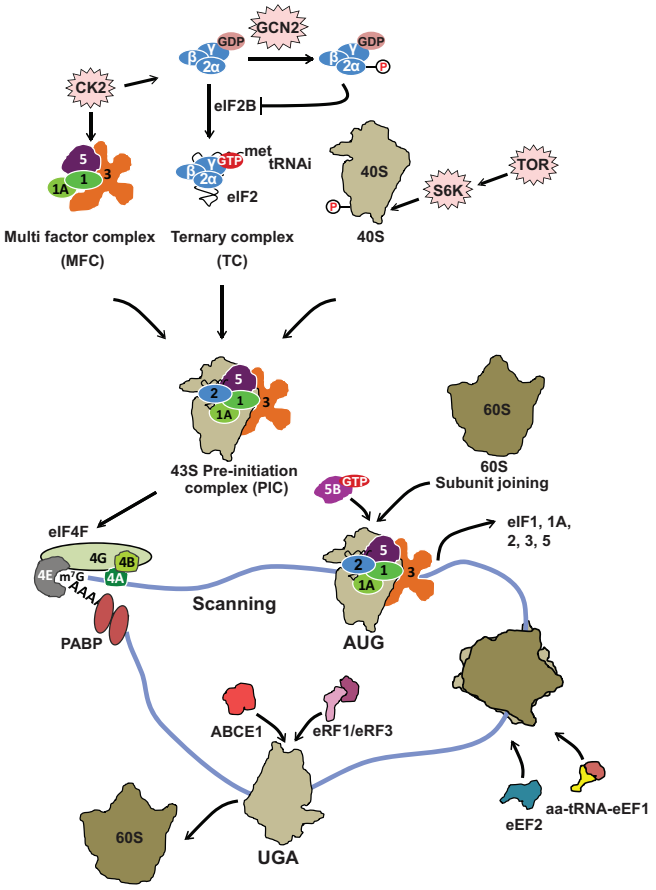

Figure 2. The translation machinery and selected kinase pathways.

The small subunit of the ribosome (40S) is charged with a methionyl-tRNAMet with the help of eIF2 (ternary complex) and loaded with additional initiation factors in the form of a multifactor complex (MFC) to form the 43S preinitiation complex (PIC). The PIC is recruited to the 5' end of the mRNA by the cap-binding complex (eIF4F), which consists of a member of the eIF4E and eIF4G protein families. eIF4A is a loosely associated helicase and eIF4B an accessory protein. The 43S complex scans the mRNA in search of an AUG start codon. Upon start codon recognition, which is thought to be facilitated by eIF1, eIF5 stimulates GTP hydrolysis by eIF2. eIF2 and the other initiation factors dissociate from the 40S. Joining of the 60S large ribosomal subunit is mediated by the GTPase eIF5B. Translation elongation involves cycles of tRNA delivery (by eEF1), peptide bond formation, and ribosome translocation by one codon (triggered by eEF2). Translation termination requires release factors and leads to ribosome subunit dissociation from the mRNA. Kinases known to phosphorylate components of the machinery include casein kinase 2 (CK2), GCN2, and S6 kinase. Phosphorylation of eIF2 by GCN2 inhibits the activity of eIF2's guanine nucleotide exchange factor, eIF2B.

its mutation interferes with leaf lobing in the Arabidopsis relative, *Cardamine hirsuta* (Kougioumoutzi et al., 2013). Under exceptional circumstances the ribosome is able to resume scanning after termination and reinitiate translation farther downstream on the same mRNA, a process with regulatory significance (Wang and Wessler, 1998; Ryabova and Hohn, 2000; Roy et al., 2010; Schepetilnikov et al., 2011). The molecular events during reinitiation and recycling are just coming into focus in other organisms.

2.2. Aspects of Translation Unique to Plants

The basic events of translation are conserved between fungi, metazoans, and plants, with a few well-documented plant-specific modifications. Most importantly, plants possess two quite distinct protein complexes for 5' cap recognition, a classical eIF4F, and a smaller yet more abundant eIFiso4F. Depletion of both eIF4E and eIFiso4E in tobacco with RNA interference results in semi-dwarf phenotypes and reduces polyribosome loading overall (Combe et al., 2005). The reduction in plant growth and development may be attributable to an overall reduction in protein synthesis. Likewise, mutation of Arabidopsis eIFiso4G reduces the protein synthesis rate and causes slower growth and dwarfism (Mayberry et al., 2009; Lellis et al., 2010). It is noteworthy that the developmental phenotypes of a mutation in a core initiation factor, eIFiso4G, do not look identical to those of typical ribosomal protein mutations (Horiguchi et al., 2012). Ribosomal mutations typically cause pointed leaves and a variety of developmental phenotypes that are not apparent in the *eifiso4g* mutant. In other words, defects in translation initiation can be genetically uncoupled from more global defects in ribosome biogenesis.

The plant eIF4E and eIFiso4E proteins each harbor a pair of cysteines, which, when oxidized, form a disulfide bond that may impede guanine nucleotide cap binding, suggesting that plant eIF4E may function as a redox sensor of translation initiation (Monzingo et al., 2007).

The eIF4F and eIFiso4F complexes differ quantitatively in their activities across a panel of client mRNAs, which can be attributed largely to the respective eIF4G isoform (Mayberry et al., 2009; Martinez-Silva et al., 2012). Different client specificities are also apparent for isoforms of eIF4B (Park et al., 2004; Mayberry et al., 2009). Therefore any changes in the relative cellular abundance of these eIF isoforms may alter the translation states of different mRNAs in the cell.

The eIF4F complex in particular is targeted by viruses, which rely on the translation apparatus of their host. In several virus-host pairs, the virus preferentially relies on a particular isoform of eIF4E for optimal virulence; vice versa, a mutation of the preferred eIF4E isoform confers resistance to the virus. This well-documented phenomenon is not covered comprehensively here because it has been reviewed periodically elsewhere (Robaglia and Caranta, 2006; Wang and Krishnaswamy, 2012). When the plant offers two distinct eIF4F isoforms, the virus, being under tremendous selection pressure, may evolve quickly to prefer one isoform to the other. In this situation, the isoform that is not coopted by the virus would remain available for translation of host proteins, including those needed to mount an antiviral defense.

2.3. The Ribosome

The Arabidopsis ribosome possesses a typical complement of four ribosomal RNAs and 80 ribosomal proteins, which mostly decorate the surface of the ribosomal RNAs. The proteins of the Arabidopsis small (RPS) and large (RPL) subunits are encoded by between two and seven paralogous genes each. While nearly all rRNAs and proteins are highly conserved with other eukaryotes, there is one plant-specific protein, P3, in the large subunit

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(Bailey-Serres et al., 1997). Naming of proteins is not entirely uniform in the literature, but a consensus was emerging (Barakat et al., 2001; Carroll et al., 2008; Klinge et al., 2012). The recent X-ray crystal and cryo-electron microscopy structures of eukaryotic ribosomes, including that of wheat (Armache et al., 2010a, b) have transformed our understanding of ribosome structure and will continue to shape future research on this most fundamental cellular machine (Klinge et al., 2012; Wilson and Doudna Cate, 2012). As a result, the locations of 74 ribosomal proteins are now known with precision. Proteomic and transcriptomic studies have yielded evidence that the isoform profile of ribosomal proteins can be modified by cell type, cellular localization, and environmental conditions such as pathogens, nitrogen, UV-B light, and sucrose (Szick-Miranda and Bailey-Serres, 2001; Whittle and Krochko, 2009; Falcone Ferreyra et al., 2010; Sormani et al., 2011a; Hummel et al., 2012). In a number of case studies, scientists have had reason to conclude that two different protein isoforms confer different functions to the ribosome; however, it is not easy to distinguish between the effect of different RNA expression characteristics and the slight differences in amino acid sequences (Barakat et al., 2001; Degenhardt and Bonham-Smith, 2008; Falcone Ferreyra et al., 2010; Horiguchi et al., 2012). Regulation of ribosome functions may also occur through posttranslational modifications. While several proteins are phosphorylated, differential phosphorylation is well established only for a small subset, primarily RPS6 (Bailey-Serres and Dawe, 1996; Williams et al., 2003; Turkina et al., 2011), and the biochemical consequence of such modifications on translation remains unknown.

3. DIVERSITY OF TRANSLATIONAL CONTROL MECHANISMS

3.1. Early Evidence for Translational Control in Plants

At a time when Arabidopsis was still in its infancy as a plant model organism, evidence for translational regulation of gene expression surfaced in a variety of other plant species. These early observations established a conceptual framework for translational regulation that would later be explored using the tools of Arabidopsis, as explained in a subsequent section. Regulation of translation by light was being studied in plants and algae (reviewed in (Wobbe et al., 2008)) and was first discovered for Rubisco small subunit genes (Berry et al., 1986; Elliott et al., 1989; Berry et al., 1990). Of note, the Rubisco model system also proved that translational control may be cell-type specific, given that translational control contributes to the preferential expression of Rubisco in bundle sheath versus mesophyll cells in the C4 plant, amaranth (Patel et al., 2006). The light harvesting chlorophyll binding proteins of photosystems I and II, as well as ferredoxin, are regulated translationally. When plants are shifted from light to darkness, these and other mRNAs are released from polysomes, some within less than 30 minutes (Petracek et al., 1997; Hansen et al., 2001). Upon reillumination, their reassembly into actively translating polysomes requires photosynthetic electron transport (Petracek et al., 1997; Petracek et al., 1998). RNA sequence elements that control posttranscriptional regulation of these mRNAs include a light regulatory element that mediates reversible translation repression and a CATT repeat in the 5' untranslated region (UTR) of pea ferredoxin, which affects mRNA stability (Hansen et al., 2001; Bhat et al., 2004). A heat shock protein may stimulate the translation of the ferredoxin mRNA under light (Ling et al., 2000).

Besides light and abiotic stresses to be covered below, several other environmental conditions were known to regulate translation, i.e. hypoxia, reactive oxygen, and heat. For example, under hypoxia, maize polysome loading in general is inhibited yet the alcohol dehydrogenase mRNA specifically is induced (Bailey-Serres and Dawe, 1996). In response to reactive oxygen, catalase mRNA is regulated by an unusual mechanism, methylation of the 5' cap (Schmidt et al., 2006). Heat shock triggers a rapid and broad inhibition of translation. The heat shock response has an interesting cell biological correlate. Upon heat shock, many mRNAs are sequestered transiently into stress granules. These are ribonucleoprotein complexes that contain heat shock proteins in which translation is stalled and mRNA is stabilized (Nover et al., 1989; Gallie et al., 1995; Gallie and Pitto, 1996; Stuger et al., 1999). The translational block upon heat stress is not universal. In heat-shocked barley aleurone cells, for example, mRNAs for secreted proteins appear to be affected preferentially. Translation of these mRNAs stalls after synthesis of the signal peptide and targeting to the ER membrane (Chu et al., 1997). In species where the translational block by heat shock is more global, it is the heat shock protein mRNAs that remain polysomal, due to sequence elements that may reside in the 5' UTR (Dinkova et al., 2005).

In the early years, only a small number of RNA sequence elements could be defined in detail, and it was not always obvious whether the elements affected only translation, or also RNA stability, or other events (Kawaguchi and Bailey-Serres, 2005). One class of such elements that undoubtedly affect translation are upstream open reading frames (uORFs), e.g. in maize R/Lc (Wang and Wessler, 1998, 2001). uORFs are most common in mRNAs for transcription factors and other regulatory genes and typically inhibit translation. Several early case studies demonstrated that uORFs can render translation sensitive to small molecules such as sucrose or polyamines (Rook et al., 1998b; Hanfrey et al., 2005) (discussed in more detail below).

When it comes to identifying sequence elements for translational control, viruses are a rich source. Because comprehensive coverage of viral translation mechanisms such as cap-independent translational enhancement, alternative initiation, shunting, ribosomal frameshifting, and stop codon readthrough would go well beyond the scope of this chapter, the reader is referred to earlier reviews (e.g. (Dreher and Miller, 2006; Ryabova et al., 2006; Nicholson and White, 2011; Simon and Miller, 2013). Only a few concepts from Arabidopsis as a host species will be mentioned. Viruses vary in their use of a 5' cap and a poly(A) tail, utilizing, for example, a genome linked Vpg protein or a tRNA shaped structure instead. Viruses have also evolved unconventional mechanisms to stimulate translation in the absence of a 5' cap structure. Many utilize cap-independent translational enhancer elements in the 3' UTR or in the 5' UTR. While cellular mRNAs are thought to form a closed loop via the PABP-eIF4G bridge, turnip crinkle virus attracts the 60S ribosomal subunit via a tRNA like structure in the 3' UTR, which then basepairs with a translational enhancer in the 5' UTR to stimulate translation (Stupina et al., 2008; Zuo et al., 2010; Stupina et al., 2011). It will be interesting to discover whether similar

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mechanisms are utilized by plant encoded mRNAs. Two separate, and fairly unconventional, translational control systems were discovered early on in cauliflower mosaic virus, (CaMV, early work reviewed in (Hohn and Futterer, 1992)). The CaMV 5' leader contains several short upstream open reading frames (uORFs). These do not simply disrupt scanning by 40S ribosomes. Instead, the uORFs set the stage for the 40S ribosome to bypass, i.e. 'shunt' past, a large section of the 5' UTR. The bypassed section of the mRNA forms an elaborate stem-loop structure, and the post-termination ribosome appears prone to scan past it without unfolding it (Fütterer et al., 1993; Dominguez et al., 1998; Pooggin et al., 2000; Ryabova and Hohn, 2000).

CaMV's second translational anomaly is translation reinitiation (Dixon and Hohn, 1984). The CaMV genome gives rise to a single long mRNA with multiple protein coding ORFs, an exceptional case for any eukaryote. CaMV accomplishes this by stimulating the ribosome to reinitiate after translation termination. A viral gene product, named transactivator (TAV), which is expressed from a monocistronic (single-ORF) mRNA, is required (Bonneville et al., 1989). TAV binds to polysomes in virus infected cells and directly interacts with the g subunit of eIF3 and with the RPL24 protein in a manner that is sensitive to eIF4B (Park et al., 2001; Park et al., 2004). Remarkably, TAV can stimulate the association of the eIF3 complex with the 80S ribosome, an event predicted by many models of translation reinitiation (Park et al., 2001; Park et al., 2004; Ryabova et al., 2006). TAV does not act alone to stimulate translation reinitiation, but in association with a host factor, re-initiation supporting protein (RISP), whose biochemical interactions suggest that it can bridge between RPL24 on the 60S large subunit and eIF3, which is typically bound to the 40S small subunit (Thiebeauld et al., 2009).

These early case studies established that translational control is accentuated in specific biochemical domains of cellular metabolism; that translation is regulated by external conditions, especially abiotic stresses; that gene-specific mRNA sequence elements must exist; that viruses are particularly poised to utilize translational control mechanisms; and finally, that translational control might be harnessed in a cell-specific context to regulate development.

3.2. Translational Control in Response to Abiotic Stress

Translation is arguably the most energy-intensive biochemical process supporting cell growth. It requires a large fraction of the energy budget as well as a reliable supply of all twenty amino acids. Moreover, the nascent proteins must be folded, assembled, covalently modified, and sorted to the correct cellular compartment. In many eukaryotic organisms, bulk translation is impeded when an unfavorable physical environment compromises translation or processing. Likewise, in plants, many abiotic stresses, such as osmotic stress (Kawaguchi et al., 2003; Matsuura et al., 2010b), cause a dramatic change in polysome loading that affects the bulk of cellular mRNAs. The effects on translation of several environmental conditions have been examined at the global level in Arabidopsis; heat and salt (Matsuura et al., 2010a), drought (Kawaguchi et al., 2004), cadmium heavy metal (Sormani et al., 2011b), hypoxia (Branco-Price et al., 2005; Branco-Price et al., 2008; Mustroph et al., 2009), light and darkness (Juntawong and Bailey-Serres, 2012; Liu et al., 2012), as well as sucrose deprivation (Nicolai et al., 2006). In general, the translational response is often widespread, yet not universal. In every case, a certain fraction of mRNAs appears to escape from the translational block under the stress. To give one example, upon heat stress, heat shock protein mRNAs continue to be actively translated, whereas other mRNAs are sequestered into stress granules and translationally suppressed (Nover et al., 1989; Matsuura et al., 2010a; Sormani et al., 2011a). Some sequence elements responsible for continued translation under heat shock reside in the 5' UTR (Matsuura et al., 2013). For example, in Arabidopsis HSP81-3, a 47 nucleotide (nt) pyrimidine rich element stimulates cap-independent translation after heat shock (Matsuura et al., 2008). There is evidence that the translation initiation machinery is remodeled during heat shock with the help of brassinosteroids (Dhaubhadel et al., 2002).

In response to the stress, certain functional classes of mRNAs change their translation state in a coordinated fashion. For example, mRNAs for ribosomal proteins are inhibited in response to drought and hypoxia (Kawaguchi et al., 2004; Branco-Price et al., 2008). Ribosomal protein mRNAs have also shown coordinated behavior after mutation of a translation factor, albeit in the opposite direction (Kim et al., 2007). Therefore, the ribosomal protein mRNAs are strong candidates for a translational "regulon", defined as a cohort of mRNAs that are regulated translationally in a coordinated fashion.

Another possible translational regulon comprises mRNAs for photosynthetic proteins destined for the chloroplast. A sudden shift of plants from light to darkness in the middle of the day shifts many of these mRNAs into the untranslated mRNA pool. First detected in tobacco and pea, the *ferredoxin-1* (*Fed-1*) mRNA dissociates from the polysomal ribosome fraction within 20 min of shifting plants from light to darkness, followed by mRNA destabilization (Petracek et al., 1997; Dickey et al., 1998; Petracek et al., 1998; Petracek et al., 2000; Hansen et al., 2001; Bhat et al., 2004). Transcriptome-wide analysis in Arabidopsis showed that the response reaches far beyond just photosynthetic proteins (Juntawong and Bailey-Serres, 2012; Liu et al., 2012).

We can now begin to ask whether the response profiles to the different stresses are essentially the same or different. Such analyses are not trivial, in part due to the inherent noise and uncontrolled variables in translational array data from different laboratories. However, the response of Arabidopsis to darkness overlaps substantially with the response to hypoxia (Juntawong and Bailey-Serres, 2012), when GC-rich 5' UTRs were specifically affected. Such a result might indicate shared signaling mechanisms, yet this remains a target for future studies.

Somewhat less dramatic shifts in translation state have been detected in response to virus infection (Moeller et al., 2012) and also under normal growth conditions, for example over the course of the diurnal cycle (Piques et al., 2009). The hallmarks of sugar deprivation are a general decrease in sugar metabolism, nitrogen assimilation, protein synthesis, and cell division (Yu, 1999). Accordingly, sugar deprivation was shown to cause translational repression, primarily affecting genes involved in cell proliferation (Nicolai et al., 2006).

Taken together, environmental conditions as well as nutrient status cause extensive differential translation of specific mRNAs. As such, translation in plants is sensitive to some of the same

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stresses as in metazoans and fungi. Strikingly, however, certain translational responses that are well established in other eukaryotes seem to be absent in plants. Following is one example. Under stress conditions that cause misfolding of proteins in the endoplasmic reticulum (ER), yeast and mammals phosphorylate eIF2α, using a dedicated kinase (PERK), in order to globally reduce translation as part of the unfolded protein response. In contrast, the Arabidopsis unfolded protein response is not accompanied by eIF2α phosphorylation (Kamauchi et al., 2005). In fact, no translational block has been detected. Moreover, the Arabidopsis genome lacks a recognizable PERK homolog, and the only known eIF2α kinase in Arabidopsis, GCN2 (general control non-derepressible 2), does not seem to become activated (Urade, 2007).

What remains to be elucidated are the mechanisms that lead to the selective translation of mRNAs in plant cells. For the response to darkness, photosynthetic electron transport is involved (Petracek et al., 1997). In yeast and metazoans, a major classical signaling pathway for stress responsive translational repression operates via the conserved protein kinase GCN2. Upon phosphorylation, the GCN2 target protein, eIF2α is inhibited because it remains bound to its guanine nucleotide exchange factor, eIF2B. Because eIF2α is the essential cofactor for loading a tRNA onto the 40S ribosome, translation initiation is broadly inhibited. There is evidence for this pathway in plants. First, upon amino acid starvation, which occurs when the synthesis of branched chain or other amino acids in the plastid is disrupted with a herbicide, the Arabidopsis GCN2 kinase is activated and phosphorylates eIF2α (Zhang et al., 2003; Lageix et al., 2008; Zhang et al., 2008; Li et al., 2013a). This is accompanied by a widespread drop in polysome loading of mRNAs. eIF2α phosphorylation and translational regulation also occurs in response to challenge with a bacterial pathogen (Pajerowska-Mukhtar et al., 2012). In summary, it appears possible that GCN2 plays a broader role in Arabidopsis than in metazoans in response to stresses apart from amino acid starvation, although the mechanism for how these stresses activate GCN2 remains unclear. Quite possibly, different stresses and different protein kinases communicate information from the environment onto the translation machinery through a network of interactions rather than separate pathways (Hey et al., 2010).

3.3. Translational Control in Development

Compared to animals, where translational control is known to operate in various cases of development and cell differentiation, for example, egg cells, embryos, and neurons, translational control of plant development is largely unexplored territory. During pollen development, for example, mRNAs that were synthesized prior to the dormancy of the pollen grain may be stored in an inactive, untranslated, form, only to be activated in response to pollen germination (Hulzink et al., 2002; Honys et al., 2009; Wang and Okamoto, 2009). Moreover, several translation factors and ribosomal proteins have pollen-specific isoforms, which may potentially contribute to translational regulation in the pollen. Likewise, in the male gametophyte of the water fern, *Marsilea*, mRNAs are translationally repressed due to intron retention. mRNAs become translationally activated as introns are removed, a process that also requires exon junction complex components (Hart and Wolniak, 1999; van der Weele et al., 2007; Boothby et al., 2013).

Transcriptome-wide datasets that contain evidence for cell-type specific translation of mRNAs have been collected by ribosome immunoprecipitation. In detail, translational inhibition in response to hypoxia is cell type specific for certain clusters of transcripts (Mustroph et al., 2009). Many additional cases of developmental control of translation may remain hidden in the form of differences in mRNA abundance between cell specific transcriptome and cell specific translatome data (Birnbaum et al., 2003; Mustroph et al., 2009; Jiao and Meyerowitz, 2010).

Are there any specific developmental mechanisms dedicated to the translational regulation of mRNAs? If so, classical forward genetic analysis has not revealed them. Instead, complex information on this topic has surfaced from mutants in the basal translation apparatus, i.e. the ribosome and certain initiation factors. Many but not all mutations in ribosomal proteins tend to cause a defect in expansion growth of the leaf lamina leading to characteristic pointed cotyledons and first leaves (Horiguchi et al., 2012). This defect can probably be attributed to a reduction in bulk translation efficiency and should not be considered evidence for translational regulation of development because it is also observed in mutants of nucleolar ribosome biogenesis proteins (Kojima et al., 2007). On the other hand, some ribosomal protein mutations more specifically affect leaf polarity (Byrne, 2009; Horiguchi et al., 2012) judged by their enhancing the rather mild leaf polarity defects of mutations in the transcription factors AS1 or AS2 (Pinon et al., 2008; Yao et al., 2008), for example mutations in ribosomal proteins RPL10a, RPL5, RPL28, and RPL9 (Pinon et al., 2008; Yao et al., 2008). A related situation has been observed for RPS6A and B, where double heterozygotes show leaf polarity defects (Creff et al., 2010). It should be noted that not all *rpl* and *rps* mutations have these same effects. For example, mutations in RPS10B and RPL27aC appear to be more directed at meristem defects although leaf polarity defects are also evident (Szakonyi and Byrne, 2011; Stirnberg et al., 2012).

Horiguchi and coworkers recently proposed an insightful and detailed framework to interpret the growth and developmental phenotypes of ribosomal protein mutations, outlining three molecular models. Such mutations may reveal the effect of ribosome insufficiency (ribosome function is generally too low), ribosome heterogeneity (an isoform of the ribosome that carries out a specialized function is compromised), or ribosome aberrancy (the mutant ribosome is defective in a specific way (Horiguchi et al., 2012)). Ribosome insufficiency is most likely the reason for the embryo lethality and the pointed leaf phenotypes that are characteristic of severe ribosomal protein mutations. Ribosome heterogeneity at the structural level is a fact of life in the plant cell, given that all ribosomal proteins exist in multiple paralogous isoforms. However, whether the two paralogs confer different functions on the ribosome is generally unclear (Horiguchi et al., 2012). When mutations of two different paralogs display different phenotypes, this could easily be due to different expression characteristics of the two isoforms, rather than different biochemical functions of the isoforms as postulated by the ribosome heterogeneity concept. Ribosome aberrancy can be viewed as a more nuanced form of ribosome insufficiency. Consider that, during translation, the ribosome performs a plethora of individual steps on thou-

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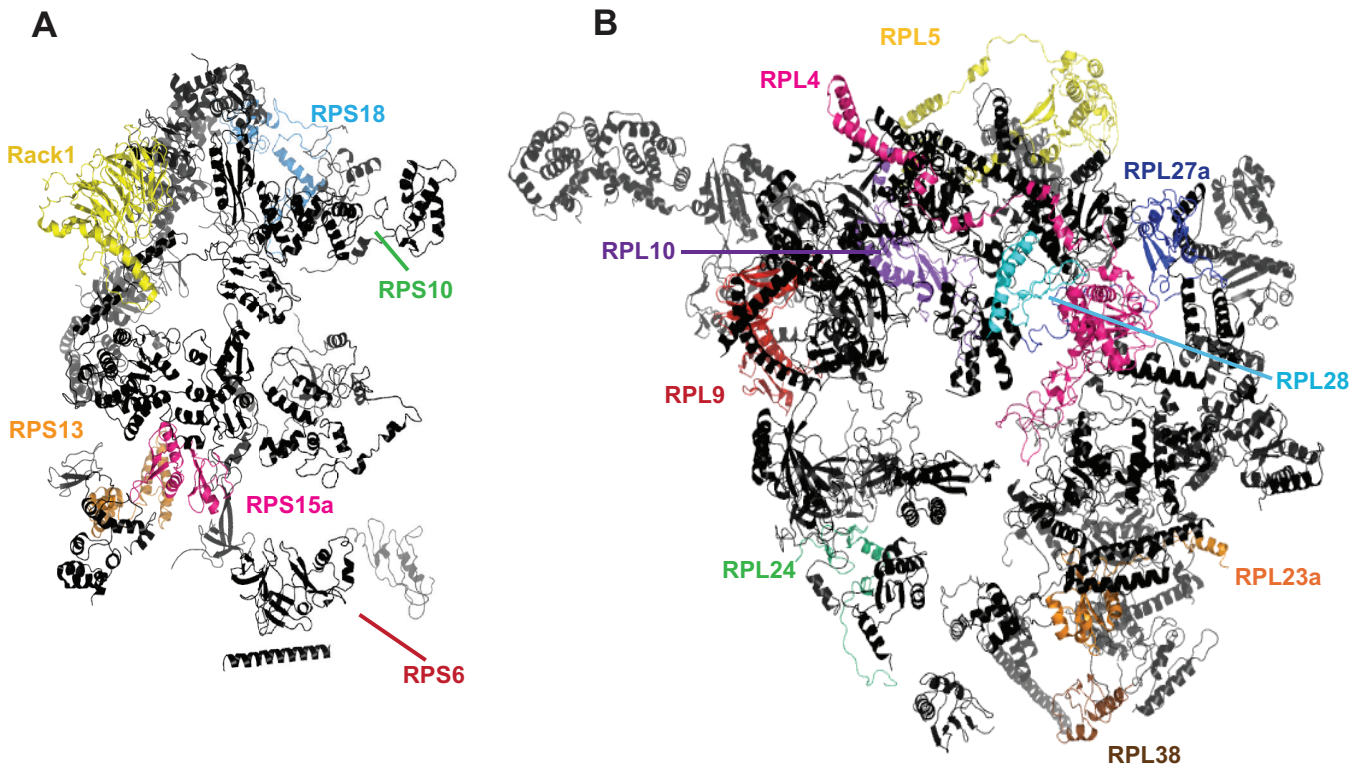

Figure 3. Localization of ribosomal proteins on the solvent side of the wheat 40S (A) and 60S (B) ribosomal subunits.

The images showing ribosomal proteins were created using PyMol (www.pymol.org), and are based on Protein Data Bank codes 31Z6 and 31ZR (Armache et al., 2010a and b). Putative positions of RPS10 and RPS6 have been highlighted based on available yeast and mammalian ribosome structures (Klinge et al., 2012).

sands of mRNAs in order to optimally support cell function. It is self-evident that two given ribosomal mutations will often cause two different biochemical problems, for example a problem during initiation versus elongation. One can postulate that the translation of mRNAs that differ in their nucleotide sequence will be compromised in different ways by the two mutations. Furthermore, given that transcriptomes are cell type specific, the translation defects of the two aberrant mutants may also be cell type specific, and therefore developmentally distinct, as well.

In light of the detailed crystal structures of the ribosome, it is reasonable to ask whether the developmentally relevant ribosomal proteins (Horiguchi et al., 2012) colocalize in the ribosome, possibly near the mRNA channel in the top half of the ribosome. However, this is not the case (Klinge et al., 2012). The relevant proteins are distributed over much of the ribosome surface, including the front edge, as defined by the direction of movement along the mRNA (from top to bottom, RPS18, RPS10, RPL9, RPL24, RPS6) and the rear edge (RPL27a, RPL23a, RPS13, RPL38), without any clear pattern (Figure 3). A few mutated proteins reside away from the subunit interfaces on the solvent side (RPL5, RACK1, RPL4, RPL28, RPS15a). Only one mutated protein is clearly located on the subunit interface, RPL10 (Klinge et al., 2012). In summary, the reason why certain ribosomal mutations cause seemingly specific developmental defects remains to be resolved.

3.4. Translational Control by Metabolites

Translational control of gene expression occurs primarily at the level of initiation, but can also take place later, during elongation or termination. An elegant gene-specific case of exceptional elongation control has been worked out through a combination of in vivo and in vitro analyses for the cystathione gamma synthetase mRNA (CGS1), the first committed step in methionine biosynthesis. In the case of CGS1, a 14 amino acid region in the center of the polypeptide renders translation elongation sensitive to the end product of the pathway, S-adenosyl methionine (SAM). An exciting conclusion that emerged from these data is that SAM itself appears to interact with the nascent CGS1 polypeptide in the ribosome exit tunnel. Autoregulated arrest of translation elongation then leads to mRNA degradation at sites defined by stacking of stalled ribosomes (Murota et al., 2011; Onoue et al., 2011).

The remainder of this section focuses on metabolic control of translation initiation. All of the five examples involve uORFs, which often overlap with each other. As we will see, such patterns of overlapping uORFs are emerging as a paradigm for regulatory logic gates that can make gene expression sensitive to small molecules. As the first example, translation efficiency of the phosphatidyl-choline biosynthetic enzyme, phosphoethanolamine N-methyltransferase is dramatically reduced by phosphocholine via a conserved-pep-

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tide uORF (CP-uORF) in its 5' UTR (Tabuchi et al., 2006; Alatorre-Cobos et al., 2012). A second case exemplifies how uORF-mediated regulation can be linked to nonsense-mediated decay. The Arabidopsis AtMHX1 gene encodes a vacuolar magnesium/zinc - proton antiporter. Translation of its uORF triggers mRNA turnover via nonsense-mediated decay (David-Assael et al., 2005; Nyiko et al., 2009; Saul et al., 2009). Third, many of the mRNAs that are responsible for polyamine synthesis or function are subject to translational regulation by uORFs. Polyamines are small organic polycations that bind RNA, affect start codon recognition, and serve as substrate for certain post-translational modifications in the cell (Ivanov et al., 2010). S-adenosylmethionine decarboxylase (AdoMetDC) catalyzes a commitment step in the pathway leading to the end product, polyamine. Importantly, polyamines cause end product repression of AdoMetDC at the translation level (Hanfrey et al., 2002; Hanfrey et al., 2003; Hanfrey et al., 2005), arguably the best understood model system for metabolic control of translation. The AdoMetDC mRNA harbors two conserved overlapping uORFs in its 5' leader, a highly conserved 'short' uORF of 48–55 codons and a tiny uORF of 2 to 3 codons that overlaps the AUG of the short uORF. This pair of uORFs forms the basis of a negative feedback model for AdoMetDC translation. Under conditions of low polyamine concentration, the scanning ribosome recognizes the AUG of the tiny uORF, translates past the AUG of the short uORF, and, after translation termination, reinitiates efficiently at the downstream AdoMetDC ORF, thereby increasing AdoMetDC activity and raising the polyamine level in the cell. When polyamine levels are sufficiently high, the scanning ribosome ignores the AUG of the tiny uORF, which is in a weak context, and therefore recognizes the stronger AUG of the short uORF. Because the short uORF does not allow reinitiation, the downstream AdoMetDC ORF is not translated (Hanfrey et al., 2005).

Another case study of uORF-mediated regulation, likewise related to polyamine regulation, was discovered around a conserved-peptide CP-uORF in the bHLH transcription factor SAC51, which supports stem elongation in Arabidopsis. In this case, polyamine is needed to suppress the uORF and allow SAC51 translation. Under a physiological polyamine level, this uORF is suppressed, allowing expression of SAC51. This case was dissected by classical forward genetic analysis. For example, a premature stop codon in the SAC51 uORF was discovered as a suppressor mutation of the *acaulis5* polyamine biosynthesis mutant (Imai et al., 2006). The shortening of the uORF is expected to make it less inhibitory for SAC51 expression. The second suppressor of acaulis5 is a mutation in ribosomal protein RPL10A; the mechanism of its action is less clear (Imai et al., 2008).

Finally, uORF-mediated sucrose sensing has come forth as another translational regulatory mechanism for metabolite signaling (Hanson et al., 2008; Hummel et al., 2009; Thalor et al., 2012). The *Arabidopsis* AtbZip11 mRNA harbors four uORFs in its 5' leader (Rook et al., 1998b; Rook et al., 1998a; Wiese et al., 2004). The translation of AtbZip11 is repressed in response to sucrose by virtue of the peptide encoded by uORF2 (Wiese et al., 2004; Rahmani et al., 2009). AtbZip11 regulates amino acid and sugar metabolism, indicating that translational control by the transport form of sugar, sucrose, remodels carbon and nitrogen pathways (Hanson et al., 2008).

Taken together, a variety of small molecule metabolites can regulate the translation of specific mRNAs, and in most cases a uORF or uORF cluster is required. With the exception of *CGS1*, the biochemical mechanism of metabolite recognition, which may be indirect or direct, remains to be elucidated.

3.5. Sequence Elements that Drive Translational Control

The mRNA sequence elements that govern translational regulation of plant mRNAs are generally not well defined. Why is this so? On those occasions when sequence elements are known to function at the post-transcriptional level, it is often not clear whether the element affects translation, RNA stability, or RNA localization. Elements known to drive RNA localization (zipcodes) affect translation indirectly. Many translational control elements have been inferred on theoretical grounds, because they contain non-canonical start codons (Kobayashi et al., 2001; Wamboldt et al., 2009), a short coding region (uORF), or because they are conserved (Hayden and Jorgensen, 2007; Tran et al., 2008; Jorgensen and Dorantes-Acosta, 2012; Vaughn et al., 2012). In contrast, rather few plant translational control elements have been identified de novo by experimental structure-function analysis. RNA structures that regulate translation are very well appreciated in viruses (Zuo et al., 2010; Nicholson and White, 2011; Stupina et al., 2011), but barely characterized for plant mRNAs (Niepel et al., 1999; Wang and Wessler, 2001; Hulzink et al., 2002; Li et al., 2012).

In the following, we summarize pertinent concepts of translational control by uORFs, alternative initiation codons, motifs for cap-independent initiation, and miRNAs, emphasizing recent findings (Kawaguchi and Bailey-Serres, 2005) (Figure 4).

3.5.1 uORFs

uORFs are prevalent in 5' UTRs of mRNAs for transcription factors and kinases, among others, suggesting they play an important role in regulating gene expression, growth and development. For example, several auxin response transcription factors (ARFs) harbor uORFs in their 5' UTR, which render the translation dependent on the translation reinitiation machinery (Nishimura et al., 2005; Zhou et al., 2010; Schepetilnikov et al., 2013). uORFs fall into three classes; (i) the uORF encoded peptide may act *in trans*; (ii) it may have a conserved peptide and act in *cis*; (iii) the uORF may have a non-conserved, presumably inert, coding region that simply acts as a translational barrier before the main ORF.

(i) Trans-acting uORF peptides are those that can affect expression of an RNA molecule different from the one that gave rise to it. They are rare. The best example comes from the *Medicago truncatula* MtHAP2 mRNA, which encodes a transcription factor of the CCAAT enhancer binding protein class. A uORF peptide encoded by the MtHAP2 mRNA binds to the 5' leader, which causes the subsequent degradation of its transcript in the meristematic zone of the *Medicago* nodule (Combier et al., 2006; Combier et al., 2008). It is debatable whether this case should even be regarded as an example for a trans-acting uORF peptide, since the peptide regulates its own mRNA.

(ii) Cis-acting conserved peptide uORFs (CP-uORFs) are uncommon. The uORFs in this class, some of which were discussed in detail in the section on metabolic regulation, are typically conserved at the peptide level across the dicot and monocot plant lin-

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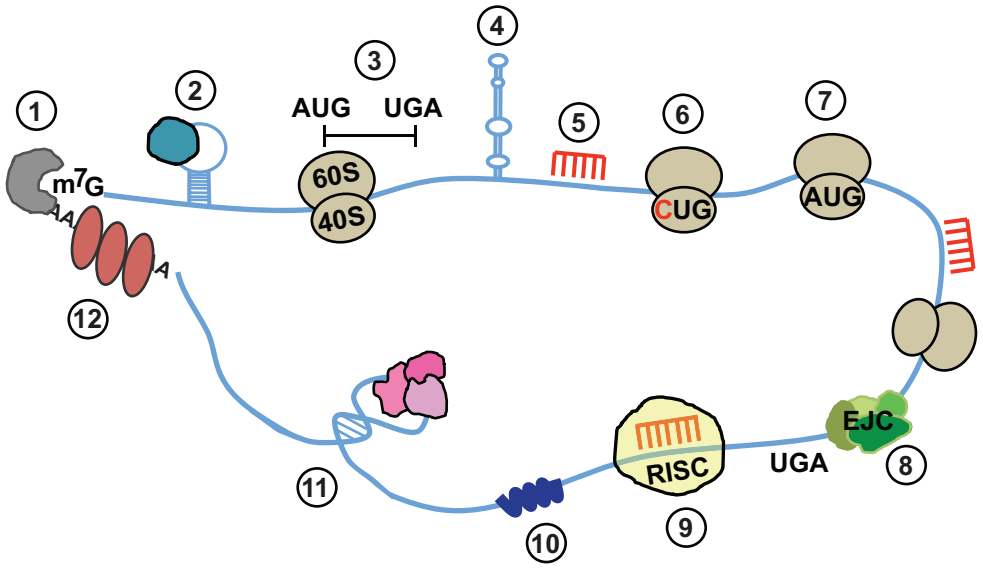

Figure 4. Schematic of post-transcriptionally active sequence elements in a generic mRNA.

Not all elements will be present in every mRNA. (1) The 5' end of the mRNA consists of the 7-methyl-guanosine cap bound by the eIF4 complex. (2-5) The 5' leader may possess an RNA stem loop and stem loop binding protein (2), an upstream open reading frame (uORF) (3), or a translation enhancer motif (4), or a miRNA binding site (5). (6-8) The main open reading frame may commence with a noncanonical start codon (6) or a canonical AUG start codon (7) and may bear an exon junction complex (8). The open reading frame depicted here terminates with UGA as a stop codon. (9-12) The 3' untranslated region (3'UTR) may harbor a miRNA target site (9), a zipcode element (10) for mRNA localization, or a structural element bound by RNA binding protein (11). The poly(A) tail is bound with poly(A) binding protein (12). Ribosomal subunits are indicated by tan ovals.

eages (Hayden and Jorgensen, 2007; Tran et al., 2008; Jorgensen and Dorantes-Acosta, 2012; Vaughn et al., 2012). Most conserved peptides that have been examined strongly inhibit translation. By inference from prior studies on CP-uORF peptides in animals and fungi, these peptides are hypothesized to stall the ribosome, thus blocking the progression of upstream ribosomes or suppressing reinitiation. The number of CP-uORFs is estimated at only a few dozen per genome.

(iii) uORFs with non-conserved peptides represent the vast majority of uORFs. About 35% of Arabidopsis genes give rise to a uORF-containing mRNA, and about half of these have multiple uORFs (Kim et al., 2007). This fraction is similar in all other plant genomes examined (Vaughn, Jia, and von Arnim, unpublished). Thus, the Arabidopsis genome encodes an estimated 23,463 uORFs, a number in the same league as the number of main ORFs. It is difficult to assess whether the position or sequence of these uORFs is actively conserved. Over long evolutionary timescales, the peptides appear unconstrained by selection as judged by synonymous to non-synonymous codon bias, but short timescales have yet to be examined. However, the presence of non-CP-uORFs is often conserved (Vaughn et al., 2012).

Upstream ORFs must be translated regularly, since AUG triplets in any context can be recognized by the scanning ribosome most of the time (Lukaszewicz et al., 1998; Sugio et al., 2010), and recent ribosome footprinting studies in yeast and metazoan mRNAs have proven that existing uORFs regularly engage ribosomes, sometimes even initiating on non-AUG triplets (Ingolia et al., 2009; Ingolia et al., 2011). Non-AUG initiation is probably fairly common in plants as well (Gordon et al., 1992; Kobayashi et al., 2002). Where examined, uORFs suppress translation in a length dependent manner (Wiese et al., 2004; Nyiko et al., 2009; Roy et al., 2010). In detail, uORFs of more than 25 codons strongly inhibit translation while uORFs shorter than 5 often cause no or barely noticeable inhibition.

Generally speaking, it is rare for mutations in uORFs to emerge from genetic screens (Imai et al., 2006). This is most likely because the uORF presents a small target, and premature stop codons are usually needed for a dramatic effect, and the resulting gain-of function phenotypes may be mild. Vice versa, mutations that generate uORFs must create an AUG in the 5' UTR, a rare event. Most such cases will generate uORFs that are fairly short and therefore not highly inhibitory.

3.5.2 Alternative translation initiation sites

Some mRNAs possess more than one translation initiation site for the main ORF, leading to multiple protein isoforms that differ in their amino-terminal amino acid sequence. The two isoforms often differ in their subcellular targeting. The shorter isoform may be targeted to mitochondria, while the longer isoform tends to be targeted to the plastid. The alternative upstream initiation site can even take the form of a non-AUG start codon, or it may be an AUG in a weak context (Kobayashi et al., 2001; Kobayashi et al., 2002; Chabregas et al., 2003; Silva-Filho, 2003; Christensen et al., 2005; Wamboldt et al., 2009). Two related cases deserve special attention. In the regulator of flowering, FCA, the 5' UTR sequence directs all productive ribosomes to initiate at an upstream non-AUG start codon (Simpson et al., 2010). Second, holocar-

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boxylase synthetase is required for post-translational modification with biotin, and the enzyme is found in plastids, mitochondria and cytosol. In this interesting case, the typical unspliced form of the mRNA harbors a uORF, which suppresses initiation at the first AUG of the main ORF, possibly because the first AUG is located too close to the uORF stop codon for efficient reinitiation. Meanwhile, a rare spliced form of the mRNA lacks the uORF, allowing initiation at the first AUG of the main ORF and leading to organellar targeting - an elegant system that combines alternative splicing, uORF-mediated regulation and alternative translation initiation (Puyaubert et al., 2008).

3.5.3 Cap-independent translation initiation

Metazoans have a rich literature on internal ribosome entry sites (IRESs), which are RNA sequence elements downstream from the 5' cap with high affinity for the ribosome. A canonical IRES attracts the 40S by placing a specific codon into the ribosomal P-site, obviating the requirements for both eIF4E and for scanning (Jackson et al., 2010). In plants, cap-independent elements are common in viruses, which often lack a 5' cap (Miller et al., 2007), but where tested they still require eIF4E or eIF4G. In nuclear-encoded plant mRNAs, the experimental evidence for classical IRESs is poor. To date, such elements qualify as cap-independent, i.e., they may still involve eIF4E and scanning (Vanderhaeghen et al., 2006; Mardanova et al., 2008). For example, the preferential translation of a heat shock protein mRNA at high temperature is mediated by a feature of its 5' UTR that renders its translation cap-independent (Stuger et al., 1999; Dinkova et al., 2005; Matsuura et al., 2008; Matsuura et al., 2013).

3.5.4 miRNAs

In contrast to the situation in animals, where miRNAs generally regulate translation rather than mRNA turnover, most plant miRNAs trigger at least some mRNA cleavage via the AGO/slicer degradation pathway. Translational regulation by miRNAs does occur, however, and may even be widespread, in addition to or in lieu of mRNA cleavage (Brodersen et al., 2008; Beauclair et al., 2010). As is the case in animals, incomplete sequence complementarity between the miRNA and the target mRNA is sufficient for translational repression. This finding suggests that 'orphan' miRNAs, those for which no target sequences have been identified, may function as translational regulators. However, translational repression is not confined to just those miRNAs with incomplete basepairing to their target (Brodersen et al., 2008). Even siRNAs may function as translational inhibitors. The first report of translational repression by a plant miRNA concerned miR172 and its target APETALA2, a homeotic gene specifying identities of the sepals and petals during flower development (Aukerman and Sakai, 2003; Chen, 2004). Unlike most other floral homeotic genes, AP2 mRNA is detected in all four floral whorls. Therefore, translational repression of AP2 by a cognate miRNA would be a logical step to confine expression of the AP2 protein to the correct region. In keeping with this, AP2, other targets of miRNA172, and targets of miRNAs in general tend to be poorly translated in flowers (Jiao and Meyerowitz, 2010). Likewise, in the case of the Arabidopsis SBP-box transcription factor, SPL3, translational regulation mediated by its miR156/157 might serve to restrict its expression during the vegetative to floral transition where ectopic SPL3 overexpression causes morphological abnormalities (Gandikota et al., 2007).

Additional evidence for translational effects of miRNAs has come from genetic analysis. Mutations that uncouple the miRNA-mediated mRNA cleavage from translational regulation have unveiled a role for the P-body associated GW protein, SUO (Yang et al., 2012), the decapping factor VARICOSE (VCS)/Ge-1, the microtubule associated protein, katanin, and the ARGONAUTE proteins AGO1 and AGO10 (Brodersen et al., 2008). Very recently, two proteins named AMP1 and LAMP1, which are located in the ER membrane, were shown to be critical for miRNA- and AGO1-mediated translational repression (Li et al., 2013b). Surprisingly, the clients of AMP1 and LAMP1 were not just secretory mRNAs but even free mRNAs, which were however, physically localized to membrane vesicles in these experiments. Together, these findings suggest that yet again, translational control is integrated with other RNA events, in this case decapping and sequestration of mRNAs into translationally inert P-bodies and/or endomembrane vesicle surfaces.

The translational repression by plant miRNA was first detected based on discrepancies between mRNA and protein levels (Aukerman and Sakai, 2003). More direct biochemical evidence for translational repression came from the observation that some, though not all, miRNAs are associated with polysomes, and so is the AGO1 protein, a component of the silencing effector complex. Inhibiting the slicing function of AGO1 yields an increase in mRNA level, but no increase in protein, suggesting that the miRNA continues to repress translation (Lanet et al., 2009).

In summary, it is becoming increasingly evident that miRNAs can inhibit translation. However, as in animals, the mechanism remains unclear (Gu and Kay, 2010; Stadler et al., 2012). Surprisingly, miRNAs can inhibit translation regardless of whether they target the 5'UTR, the coding sequence, or the 3'UTR. In fact, the great majority of plant miRNAs bind to protein coding sequences, rather than 3' or 5' UTRs. A mechanism to explain translational repression by these miRNAs will have to account for the high processivity and helicase activity of the elongating ribosome.

3.6. Translational Control by RNA Binding Proteins, RNA Localization, and via Nonsense-Mediated Decay

3.6.1 RNA binding proteins

Plant genomes code for hundreds of RNA binding proteins, which function in diverse processes from rRNA processing, mRNA transport and localization, to mRNA processing such as alternative splicing, or polyadenylation. In the plastid, proteins with pentatricopeptide repeat (PPR) domains and other RNA binding proteins regulate functions such as mRNA editing, translation, and turnover (Jacobs and Kuck, 2011). In contrast, for cytosolic mRNAs, we know little about how RNA binding proteins might affect translation. One rather exceptional case is the recent discovery of an RNA binding protein named PNT1 (PENTA1) that mediates the translational repression of protochlorophyllide reductase (PORA) mRNA by phytochrome in response to light (Paik et al., 2012). Here we will inspect the roles

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of three types of protein with evidence for a translational role in the cytoplasm: PUF proteins, poly(A) binding proteins, and RNA localization factors.

The PUF domain is a well defined RNA binding domain pioneered by Drosophila *pumilio* (Francischini and Quaggio, 2009; Tam et al., 2010). Arabidopsis possesses 29 PUF protein genes, but few potential target mRNAs are known (Francischini and Quaggio, 2009; Muench et al., 2012). The canonical PUF target motif contains a UGUA core, a motif that also functions in human nuclear polyadenylation (Yang et al., 2010). Interestingly, UGUA motifs are among the most highly conserved 3' UTR sequence motifs in dicots (Vaughn et al., 2012). PUF proteins are deeply involved in translational control in metazoans. However, in plants, the only PUF protein with an experimentally defined cell biological function helps with ribosomal RNA expression in the nucleolus (Abbasi et al., 2010). Thus, the contribution of plant PUF proteins to mRNA translation awaits experimental support.

Poly(A) binding protein (PABP) stimulates translation of mRNAs bearing a 3' poly(A) tail, by recruiting and raising the concentration of eIF initiation factors (Cheng and Gallie, 2007, 2010). PABP stimulates cap-binding by the eIFs (Wei et al., 1998; Luo and Goss, 2001) and RNA helicase activity of eIF4A (Bi and Goss, 2000). Arabidopsis has eight PABP genes, subsets of which are expressed in reproductive and vegetative tissues. PABP may autoregulate its own translation by negative feedback, given that several PAB 5' UTRs have stretches of adenines long enough to recruit PABP (Belostotsky, 2003). PABP is differentially phosphorylated, which affects its interactions with eIF4F and eIF4B (Le et al., 2000). PABP also interacts with other potential translational regulatory proteins, such as PCI6 (PABP-C-terminus interacting6) and ERD15 (EARLY RESPONSE TO DEHYDRATION15) (Wang and Grumet, 2004; Bravo et al., 2005). In summary, PABP bound to the poly(A) tail stimulates translation initiation, and most likely ribosome recycling rather than the primary initiation event. By way of its copy number on the mRNA and its size, it greatly increases the surface area of the 3' mRNP complex beyond that of a single-stranded poly(A) strand. It is conceivable that its multiple interaction partners could serve to integrate diverse cellular signals to regulate translation.

3.6.2 Restricted translation due to mRNA localization

mRNA translation must occasionally be coordinated with mRNA localization. The targeting of secretory mRNAs to the rough ER, with the signal recognition particle functioning as the signal-peptide receptor, constitutes the textbook example. A few other specialized cases are known in plants, and these add several new facets. Generally, one expects that a localized mRNA harbor a sequence element akin to a zipcode that governs the asymmetric distribution of the mRNA. Where characterized, zipcode elements are single stranded motifs or double stranded stem loop structures that are typically located in the untranslated regions of the transcript (Kislauskis and Singer, 1992; Hamada et al., 2003b).

In plants, the targeting of two types of storage protein mRNA has been studied extensively in rice (Crofts et al., 2005; Washida et al., 2012). Prolamine mRNAs are targeted to a special subdomain of the ER, where prolamine protein bodies form. Targeting of prolamine mRNA requires active translation and a zipcode sequence located in the 3'UTR (Choi et al., 2000). Among the many RNA binding proteins associated with these mRNAs, a Tudor-SN protein is involved in mRNA localization to protein bodies (Wang et al., 2008). For comparison, glutelin mRNA is targeted to the regular cortical cisternal ER, and glutelin protein enters the secretory pathway toward protein storage vacuole. Glutelin mRNAs have their own zipcode elements (Hamada et al., 2003b; Washida et al., 2009). Both types of mRNA form cytoskeleton associated granules that move along cytoskeletal elements (Muench et al., 1998; Muench et al., 2000; Okita and Choi, 2002; Wang et al., 2008; Washida et al., 2009).

Polarized tip growth in plants also utilizes localized translation, analogous to neurons. Expansin mRNAs localize to the growing edges of developing xylem cells, which may be important for the asymmetric growth of the xylem cell walls (Im et al., 2000). Expansin mRNA and profilin (actin-binding protein) mRNA also accumulate at the growing tip of root epidermal cells destined to become root hairs (Baluska et al., 2000). Given that mRNA localization is rarely examined, there may be many additional cases.

3.6.3 Translation and nonsense-mediated decay

Plant mRNAs with a premature termination codon (PTCs) can become targets of nonsense-mediated decay (NMD), a pan-eukaryotic mRNA surveillance process. Such mRNAs are devoid of ribosomes for much of their length, which leads to their degradation (Petracek et al., 2000; Isshiki et al., 2001; Yoine et al., 2006). Alternatively, blocking ribosome progression with cycloheximide also triggers NMD, e.g. (Song et al., 2009). Either an exceptionally long 3' UTR or an intron-splice site, which is presumably marked by an exon junction complex, are sufficient to trigger NMD of an mRNA with a PTC (Kerenyi et al., 2008). Biochemical components of the plant NMD machinery include UPF1, UPF2, and UPF3, SMG7, as well as the exon-junction complex subunits, Y14, PYM, eIF4A-III, and Mago (Merai et al., 2012). Recently it was described that NMD is guided by polypyrimidine tagging of the mRNA at the 3' end, which stimulates ribosome release from such mRNAs (Morozov et al., 2012). The cellular location of the NMD machinery is not entirely clear. However, SMG7 can be detected in P-bodies, which are sites of mRNA decapping and a waystation for mRNA degradation.

Typical NMD targets include mis-spliced mRNAs, as well as the alternatively spliced versions of mRNAs for SR proteins and GRP7 splicing factors, which often possess PTCs (Schoning et al., 2007; Palusa and Reddy, 2010). However, not all intron-retention mRNAs trigger NMD (Kalyna et al., 2012). In addition, many noncoding RNAs are subject to NMD (Kurihara et al., 2009). Perhaps surprisingly, uORFs are not always potent triggers of NMD, even though the uORF stop codon masquerades as a PTC. In fact, only unusually long uORFs (50 codons, (Nyiko et al., 2009)), uORFs that overlap the main ORF (Kalyna et al., 2012), and certain conserved uORFs (Saul et al., 2009; Rayson et al., 2012) trigger efficient NMD, while shorter non-overlap uORFs (15 or 30aa) did not (Nyiko et al., 2009), especially in intron-less mRNAs. This is consistent with the hypothesis that long uORFs and overlapping uORFs severely suppress translation reinitiation, thereby leaving the main ORF untranslated and

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prone to trigger NMD. Meanwhile, short uORFs allow reinitiation, thus the main ORF will be translated albeit at a reduced level, which suppresses NMD.

3.7. Signaling Pathways Implicated in Translational Control–TOR, S6K, GCN2, RACK1

In light of our sparse mechanistic knowledge about translational control in plants it is appropriate to take a leaf from other eukaryotes and assess whether the hypotheses founded on metazoan and yeast research are valid in plants. One major pathway that controls the translation machinery in metazoans is stimulated by extracellular signals such as insulin, and proceeds via a kinase cascade, including PI-3-Kinase, Akt kinase, TOR kinase, and S6 kinase (S6K), eventually phosphorylating a variety of components of the translation initiation machinery (Laplante and Sabatini, 2012). Key elements of this pathway, namely TOR and S6K, exist in Arabidopsis, and the pathway must play a critical role in the regulation of plant growth and development. As seen below, however, the upstream signals that stimulate this pathway in plants and the precise downstream targets at the translation level are only beginning to come into focus.

While several components of the translation machinery are phosphorylated, among others, poly(A) binding protein and eIF4E (Le et al., 2000; Pierrat et al., 2007), the responsible kinases are known in only a few cases. Casein kinase 2 (CK2) is one such exception. In contrast to other pathways in this section, phosphorylation by CK2, specifically of eIF5, has the potential to regulate translation directly, namely by regulating interaction between components of the multifactor complex (Dennis and Browning, 2009). This final section of the review will elaborate on TOR/S6K, briefly revisit GCN2 kinase, and conclude with a summary of another emerging translational regulator, the RACK1 protein.

3.7.1 TOR kinase

The TOR – S6 kinase signaling pathway has been studied extensively in animals and yeast where it governs the phosphorylation of a number of components of the translation apparatus. Hormones, growth factors, amino acids and the energy status of the cell, all impinge on this pathway (Laplante and Sabatini, 2012). In animals, TOR stimulates translation in part by phosphorylating the inhibitory eIF4E binding proteins (Thoreen et al., 2012) but no equivalent proteins have been detected in plants. Several components of the TOR pathway have, however, been identified in *Arabidopsis*. This topic has been reviewed regularly (Menand et al., 2004; Dobrenel et al., 2011; Robaglia et al., 2012) and is therefore summarized only in broad strokes here. Besides TOR kinase itself, Arabidopsis encodes two other components of the TORC1 complex, the substrate adapter protein, RAPTOR, the LST8 protein, and an FK506 binding protein FKP12 (Anderson et al., 2005; Moreau et al., 2012; Xiong and Sheen, 2012). Arabidopsis also encodes a major client of TOR in yeast and animals, the ribosomal protein S6 kinase (Mahfouz et al., 2006) and a downstream phosphatase component, Tap46, known from yeast (Ahn et al., 2011). Loss of function of *Arabidopsis* TOR (AtTOR) or RAPTOR both result in embryo lethality (Deprost et al., 2005; Deprost et al., 2007). Moreover, silencing of AtTOR, or inhibition of its activity with rapamycin or torin, causes leaf senescence, arrests organ growth, and reduces ribosomal RNA synthesis and translation. In contrast, overexpression of TOR enhances growth of the root and shoot and increases seed production (Deprost et al., 2007; Ren et al., 2011; Ren et al., 2012; Xiong and Sheen, 2012; Xiong et al., 2013) consistent with a role for AtTOR in growth control.

The input signals for the TOR pathway include energy balance and glucose status (Robaglia et al., 2012; Xiong and Sheen, 2012; Xiong et al., 2013) osmotic stress, and auxin. In response to auxin, TOR kinase activity leads to phosphorylation of S6K, a canonical target of TOR in other organisms, and of eIF3h, a putative reinitiation factor (Schepetilnikov et al., 2013). TOR is also implicated in translation reinitiation on the polycistronic mRNA of cauliflower mosaic virus, given that the RISP reinitiation factor can be a substrate for TOR kinase (Schepetilnikov et al., 2011). In contrast, in response to osmotic stress, S6K phosphorylation is inhibited (Mahfouz et al., 2006). These data indicate that a central kernel of the TOR pathway, i.e. coordinated activation of TOR and S6K, is conserved in plants.

AtTOR, in contrast to its mammalian counterpart, was thought to be insensitive to the drug rapamycin, attributed to a mutation in the rapamycin-binding, TOR partner protein, FKBP12 (Mahfouz et al., 2006). However, the FKBP12 gene does render TOR sensitive to rapamycin, as long as FKBP12 is expressed at a sufficient level (Xiong and Sheen, 2012). Cereals are also sensitive to the drug (Agredano-Moreno et al., 2007; Schepetilnikov et al., 2011), and Arabidopsis TOR becomes more sensitive to rapamycin when a human or yeast FK506 binding protein is expressed in Arabidopsis (Mahfouz et al., 2006; Sormani et al., 2007; Ren et al., 2012). Arabidopsis TOR is also sensitive to the novel mammalian TOR inhibitor, Torin1 (Schepetilnikov et al., 2013).

3.7.2 S6 kinase

S6 kinase is named after a prominent substrate protein, the ribosomal protein RPS6. The phosphorylation status of RPS6 is higher during the day than at night (Turkina et al., 2011), and is also elevated by cold (Williams et al., 2003), UV-B exposure (Casati and Walbot, 2004) and auxin (Beltran-Pena et al., 2002; Turck et al., 2004). In contrast, it is reduced by conditions that suppress translation such as heat (Scharf and Nover, 1982), hypoxia (Williams et al., 2003), and reactive oxygen (Khandal et al., 2009; Reinbothe et al., 2010). Recent crystal structures revealed the surprising result that RPS6 resides on the right (front) foot of the 40S subunit on the interface side (Klinge et al., 2012). However, its carboxyl terminus bends around to the solvent side of the 40S. This alpha-helical tail, whose basic character is conserved between humans and plants, is phosphorylated on multiple serines (Turkina et al., 2011). Thus, RPS6 is located far away from the mRNA channel of the ribosome. In light of the pan-eukaryotic nature of this phosphorylation event, it is surprising that the immediate cell biological consequences for translation remain largely mysterious (Ruvinsky et al., 2009). The existing evidence is largely correlative, tenuous, and often points away from translation (Beltran-Pena et al., 2002; Turck et al., 2004; Tzeng et al., 2009; Henriques et al., 2010; Shin et al., 2012).

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A little bit more is known about the roles of S6 kinase, keeping in mind that this kinase may have multiple targets. In Arabidopsis, S6K is encoded by two tandemly repeated genes. S6K is a direct target of TOR and is activated by it (Menand et al., 2002; Xiong and Sheen, 2012; Xiong et al., 2013). In addition, a PI3-kinase-like protein (PDK1) can phosphorylate and regulate S6K (Mahfouz et al., 2006; Otterhag et al., 2006). Before genetic tools were available, an attempt was made to manipulate the S6K pathway using pharmacology. Wortmannin and LY294002, which target PI3-kinases, can suppress S6K kinase activity. These data are in keeping with the mammalian paradigm that a PI3-kinase and TOR kinase function upstream of S6K. In addition, Arabidopsis S6 kinase activity is also sensitive to auxin and cytokinin (Turck et al., 2004), in keeping with a role for S6K in growth control and auxin stimulation of S6 phosphorylation. Is there evidence that S6K regulates translation? When S6K activity was suppressed by upstream kinase inhibitors, such as wortmannin, the recruitment of mRNAs for RPS6 and RPS18A into the polysome pool after refeeding of tissue culture cells was specifically inhibited (Turck et al., 2004). However, other evidence points to S6K affecting nuclear events. For example, S6K hypomorphic mutants have shown increases in ploidy (Henriques et al., 2010). In contrast, overexpression of S6K may shift the balance between cell enlargement and cell division towards enlargement (Shin et al., 2012), which in turn affects development (Tzeng et al., 2009). These results suggest that S6K plays a key role in translating growth promoting signals to activate protein synthesis and increase cell size, while suppressing the cell cycle.

3.7.3 GCN2

The role of GCN2 has been discussed earlier in the context of the stress response. Here we will revisit GCN2 and focus on the biochemical mechanisms. Phosphorylation of eIF2α is a key switch in metazoans and yeast that down-regulates protein synthesis in response to nutrient starvation or stresses (Wek et al., 2006). One plant kinase targeting eIF2α is GCN2 (Zhang et al., 2003; Immanuel et al., 2012). In response to herbicide (Zhang et al., 2008), amino acid or purine starvation (Lageix et al., 2008), or cadmium stress (Sormani et al., 2011b) the *Arabidopsis* GCN2 kinase (AtGCN2) is activated and phosphorylates eIF2α followed by a reduction in global protein synthesis (Lageix et al., 2008; Zhang et al., 2008). Vice versa, overexpression of GCN2 in wheat causes numerous changes in gene expression and metabolism, most notably a reduction in free asparagine, a vehicle for nitrogen transport in plants (Byrne et al., 2012). AtGCN2 has a domain similar to histidyl tRNA synthetase (Zhang et al., 2003); accordingly, AtGCN2 is activated directly by uncharged tRNA, as is the case in yeast (Li et al., 2013a). Hence, a general amino acid control response is conserved between yeast and plants. However, AtGCN2 is also activated in response to UV, cold shock, and wounding, conditions that at first glance should not cause amino acid starvation. Furthermore, AtGCN2 is essential for optimal plant growth in stress situations (Lageix et al., 2008). Therefore, the plant eIF2α kinase most likely evolved to fulfill a more general function as an upstream sensor and regulator of diverse stress-response pathways.

3.7.4 RACK1

RACK1 is most definitively a ribosome-associated protein that binds to the back (solvent side) of the small subunit near the head (Chang et al., 2005; Giavalisco et al., 2005). This pan-eukaryotic WD40 protein was first crystallized using the Arabidopsis isoform (Ullah et al., 2008). Outside of plants, RACK1 is now known to function in translation and mRNA quality control (Coyle et al., 2009; Kuroha et al., 2010). In Arabidopsis, the functional link of RACK1 to translation is still tenuous, although *rack1* mutants are hypersensitive to the translation inhibitor, anisomycin, and are compromised in ribosome assembly (Guo et al., 2011). Arabidopsis RACK1 is expressed from three differentially expressed, yet functionally equivalent, paralogs (Guo and Chen, 2008; Guo et al., 2011; Hummel et al., 2009). Most of what we know comes from physiological analysis of *rack1* mutants. *Rack1* loss of function mutants display various developmental defects, specifically slow growth, dwarfism, and seedling-lethality in *rack1a rack1b rack1c* triple mutants (Chen et al., 2006; Guo and Chen, 2008; Guo et al., 2009). The *rack1* mutants are less sensitive to gibberellic acid and hypersensitive to abscisic acid and show an mRNA expression profile reminiscent of ABA application (Guo et al., 2011). *Rack1* mutants also have defects in sugar responses (Fennell et al., 2012). Given that the *rack1* mutants do not display the hallmarks of typical ribosomal mutants, RACK1 is likely a regulatory component of the ribosome. As is true for all other regulators of translation discussed in this section, the most exciting discoveries on RACK1 are yet to be made.

4. CONCLUDING REMARKS AND CHALLENGES FOR FUTURE WORK

The control and regulation of translation are tightly interwoven with the basic translation machinery, the ribosome, the initiation, elongation, and termination factors. Prime targets for translational control in plants are the subunits of eIF4F, eIFiso4F, and eIF2, as well as ribosome associated proteins.

Translational control plays a major role in adjusting gene expression to environmental conditions including many types of abiotic stress. Fortunately, most of the plant translation machinery and at least some of the peripheral regulatory apparatus is conserved with fungi and metazoans. This situation is facilitating the process of deciphering how the translation machinery supports plant growth and development, as well as responses to the environment. All said, we are still quite far from understanding these processes in detail. One day, the first entire pathway, from signal to translational response, will be mapped out in its entirety at the biochemical level. This work is still in progress.

Many of the biochemical entities and concepts familiar from the metazoan literature have yet to found in Arabidopsis and may be rare or uncommon: Internal ribosome entry sites, inhibitory eIF4E-Binding Proteins, polypyrimidine tract binding proteins, mRNA-specific translational inhibition via a 3'-5' loop that is closed by 3'UTR RNA binding protein, and eIF2-mediated translational inhibition after ER-stress, are some of the concepts for which evidence in Arabidopsis is sparse or lacking.

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Many additional challenges remain for future work: As in other areas of systems biology, public, well-curated, access to large datasets and the integration of data from disparate sources are bottlenecks for fully interpreting prior studies. Experimentally, it remains difficult to distinguish the relative contribution of translational and other (post-)transcriptional mechanisms; a simple and inexpensive technique to quantify translational efficiency on a genome-wide scale is still lacking. At the sequence level, better tools are needed to mine genome sequences for zipcodes and other RNA-control elements. Finally, plant genomes encode hundreds of yet uncharacterized proteins with RNA binding domains. We have only scratched the surface of understanding this complexity. Their presence in plant genomes is a harbinger of future discoveries in the posttranscriptional control of gene expression.

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GLOSSARY

MRNA STRUCTURE

mRNA cap: 7-methyl guanosine group at the 5' end of eukaryotic mRNAs.

5' leader: The region upstream of the *main ORF* of the mRNA, also commonly called 5' untranslated region (UTR). 5' and 3' UTR are exonic sequences.

Open reading frame (ORF): Nucleotide sequence delineated by in-frame start and stop codon.

Main open reading frame: An ORF that encodes the functional polypeptide of an mRNA.

Upstream open reading frame (uORF): Short ORF present upstream of the main ORF in the 5' leader.

Polypyrimidine tract: Sequence rich in pyrimidine (C/U) nucleotides in the mRNA.

mRNA tail or poly(A) tail: Stretch of adenosine residues at the 3' end of an mRNA.

Polyadenylation: Addition of multiple tandem adenosine monophosphate residues to the cleaved 3' end of the precursor mRNA.

TRANSLATION FUNCTIONS

Ribosome scanning: An ATP-dependent translocation process describing the movement of the 43S pre-initiation ribosomal complex on the 5'UTR of an mRNA.

Leaky scanning: A mode of ribosome scanning that can bypass proximal AUG start codons, usually in an unfavorable context, to initiate at a downstream AUG.

Cap-independent translation enhancer: RNA secondary structural element capable of recruiting initiation complexes to an mRNA.

Ribosome shunting: A discontinuous ribosome scanning mechanism whereby small ribosomal subunits traversing the 5'UTR circumvent downstream RNA structures/sequences to reach the initiation codon.

Initiation codon context: The nucleotide sequence surrounding the start codon determining the favorability of translation initiation from that start codon.

Cis-acting peptide: Nascent peptide, usually encoded by a uORF, that acts to regulate ribosome activity.

Trans-acting peptide: Peptide that regulates the expression of an mRNA after its release from the ribosome.

Ribosomal frameshifting: Switching of the reading frame by a single nucleotide during 80S ribosome translocation.

Polysomes: mRNA molecules with multiple ribosomes engaged in translation.

Translational efficiency: Measure of the ability of an mRNA to be translated.

Transcriptome: All mRNAs of an organism, or a cell, including their abundance.

Translatome: All mRNAs found in ribosome complexes and their abundance.

Ribosome (polysome) loading: The coverage of an mRNA with ribosomes. Ribosome density and ribosome occupancy are both examples for measures of ribosome or polysome loading.

Ribosome density: Average number of ribosomes per length of mRNA.

Ribosome occupancy: Fraction of the mRNA found in polysomes.

Stop codon readthrough: Incorporation of a near-cognate aminoacyl tRNA and insertion of an amino acid at a stop codon, leading to polypeptide chain elongation.

Reinitiation: Scanning and translation initiation *in cis* by an undissociated post-termination 40S ribosomal complex on the same mRNA.

Ribosome recycling: Dissociation of the post-termination ribosome into ribosomal subunits, deacylated tRNA and mRNA, and the use of the released subunits for additional rounds of translation.

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