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Opinion

Redox Regulation of Cytosolic Translation in Plants

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Control of protein homeostasis is crucial for environmental acclimation of plants. In this context, translational control is receiving increasing attention, particularly since post-translational modifications of the translational apparatus allow very fast and highly effective control of protein synthesis. Reduction and oxidation (redox) reactions decisively control translation by modifying initiation, elongation, and termination of translation. This opinion article compiles information on the redox sensitivity of cytosolic translation factors and the significance of redox regulation as a key modulator of translation for efficient acclimation to changing environmental conditions.

Trends

Adjustment of protein biosynthesis is crucial for plants to acclimate to changing environmental conditions and realize their development.

With novel and cost-efficient technologies like polysome fractioning and ribosomal footprints, stress-dependent translational control is a broadly emerging field of research.

Redox regulation of translational elements is evident for almost every step of protein synthesis like initiation, elongation, and termination and is currently researched as an important post-translational modification of the translational machinery.

Redox Reactions and Redox Signaling

Cell metabolism employs redox reactions in multiple processes. Redox reactions fuel cell energetics and often determine thermodynamics and thus flow through metabolic pathways. Proper redox homeostasis depends on tight regulation of important metabolic reactions like photosynthesis [1,2]. Deregulation of redox metabolism (e.g., under abiotic or biotic stress) fosters accumulation of reactive oxygen species (ROS) or reactive nitrogen species (RNS). Thus it is highly purposeful to exploit redox information as feedback input into regulatory networks to accomplish homeostasis. In this context thiol modifications of proteins represent an important mechanism of redox regulation. It includes thiol-/disulphide transitions [3], *S*-nitrosylation (*S*-NO) [4–6], *S*-glutathionylation (*S*-S-G), sulfenylation [7], sulfinylation, and sulfonylation of cysteine thiols [8]. Thiol-/disulphide transition, the best studied mechanism, is achieved by thiol oxidation by ROS, thiol oxidases, or disulphide isomerases and reduction by thioredoxins (Trxs). *S*-S-G and deglutathionylation depend on glutathione-*S*-transferases (GSTs) and glutaredoxins (Grxs). *S*-nitrosylation is achieved by transfer of NO from donors such as nitrosoglutathione, direct reaction with NO, and denitrosylation by *S*-nitrosoglutathione reductase [9]. Grx, GST, and Trx constitute large protein families in higher plants. These form networks with regulatory targets, redox input elements (NADPH, GSH), redox transmitters (Trx, Grx), redox sensors such as peroxiredoxins, and final electron acceptors such as ROS and RNS [10] and are at present being intensely explored. Redox regulation has been recognized as a general and fundamental mechanism involved in switching, tuning, or modulating virtually all metabolic processes, including diverse metabolic pathways, epigenetic processes, transcription, and cell signaling.

Conditional adjustment of protein biosynthesis and turnover is at the core of developmental programs and environmental acclimation [11]. Many studies exclusively consider transcriptional regulation as a measure of gene expression. It is time to bring post-translational and translational regulation back into the focus of research, which is now possible by employing novel technologies such as translatome profiling and ribosome footprinting [12]. Knowledge is needed on regulatory elements and their specific significance especially under stress conditions. Redox regulation is evident in some steps of protein synthesis but awaits detailed investigation. In this opinion article we propose that redox regulation plays a decisive regulatory role in tuning translation in plants. Cell redox state affects translation at the level of mRNA amount and

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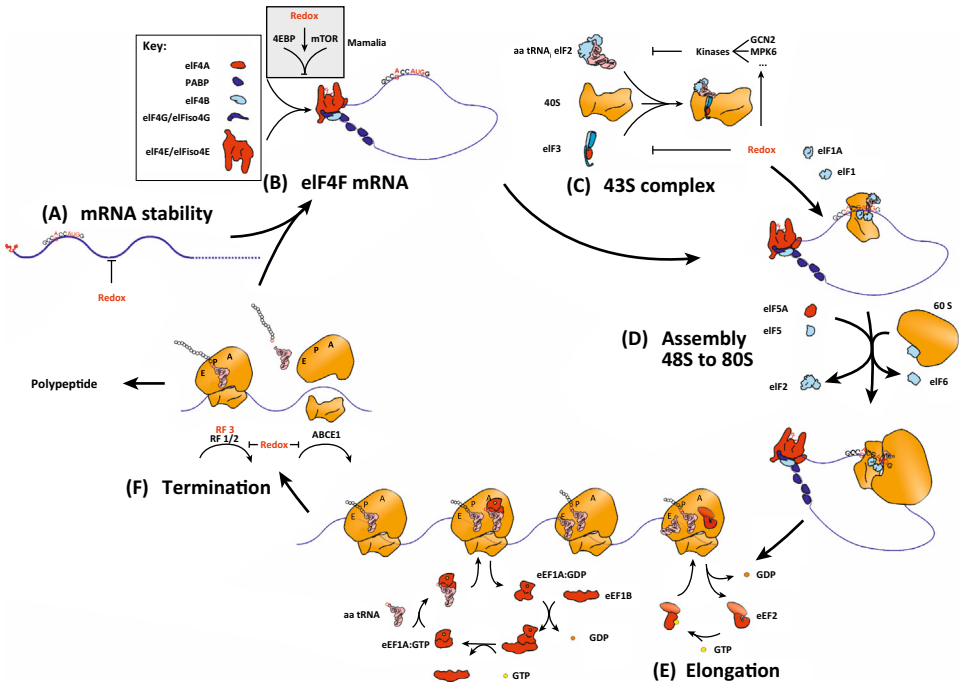
stability, amino acid availability, and activation and each of the three steps of the translation cycle: namely, initiation, elongation, and termination. If not indicated otherwise, the subsequently described regulatory mechanisms are related to the model organism *Arabidopsis thaliana*.

Redox Control of mRNA Accumulation

The availability of translation components, first of all the amount of specific mRNA, is strongly affected by redox conditions (Figure 1A). Abiotic and biotic stresses and the subsequent redox imbalances have been reported to trigger redox-dependent transcription of specific genes, which is needed for subsequent accumulation of preferentially translated transcripts in *Arabidopsis*, barley (*Hordeum vulgare*), and tobacco (*Nicotiana tabacum*) [13–18]. Many translation factors, like initiation factor (eIF) 3f, are among the stress-responsive transcripts [13,19]. The cellular redox state also regulates mRNA stability and thus half-life via direct oxidation of mRNA, particularly at guanines, participates in the development of human neurodegenerative diseases



Trends in Plant Science

Figure 1. Schematics of the Cytosolic Translation Cycle, its Machinery, and Redox Regulation. Reactive oxygen species (ROS)/redox state controls mRNA expression, stability, and degradation before translation initiation (A). Translation is divided into three principal phases: initiation (B–D), elongation (E), and termination (F). Initiation involves the assembly of the 43S complex comprising the small ribosomal subunit, the aminoacyl (aa)-tRNA$_i^{Met}$ initiation factor (eIF) 2, and the eIF3 complex (C), which then binds to the mRNA in a cap-dependent manner via the eIF4F complex (B). The eIF4F complex comprises the eIF4A, eIF4B, eIF4G, eIF4E, and polyA-binding protein (PABP) translation factors. Plant specific are eIFiso4E and eIFiso4G, which are regulated independent of their respective isoforms. The mRNA-associated 43S complex then starts screening for the first ATG, where the aa-tRNA$_i^{Met}$ binds to the P site and the eIF5- and eIF6-dependent assembly of the 80S ribosomal complex occurs (D). During elongation, elongation factor (eEF) 1A binds to free aa-tRNA and guides the appropriate aa-tRNA to the respective codon of the mRNA at the A site of the ribosome. (E) The subsequent peptidyl transfer between the Met$_i$ at the P site and the next aa-tRNA at the A site results in deacylation of the tRNA at the P site. The following translocation of the deacylated tRNA from the P to the E site and the peptidyl-tRNA from the A to the P site is mediated by eEF2. Thereby, the A site is emptied. A new aa-tRNA can bind and initiate the next round of elongation. Termination is triggered when a termination codon enters the A site (F). The eRF1-bound eRF3 can associate with the stop codon and triggers polypeptide release. Subsequently the ribosome is either recycled influenced by ATP-binding cassette E1 (ABCE1) or reassembled on the same mRNA via the eIF3 complex. Protein shapes are adopted from crystallographic structures available at the RCSB Protein Database (http://www.rcsb.org/pdb/home/home.do). Translation factors that have been reported to be subject to redox regulation or identified in redox proteomics screenings are marked in red.

Glossary

4E-binding proteins (E4BPs): proteins that interact with eIF4E and limit eIF4F formation.
A site: site in the ribosome accessed by a new aa-tRNA coupled to eEF1A:GTP.
ATP-binding cassette E1 (ABCE1): participates in ribosome recycling.
Elongation factor 1A (eEF1A): binds aa-tRNAs in GTP-bound state.
Elongation factor 1B (eEF1B): recycles eEF1A:GDP to eEF1A:GTP.
Elongation factor 2 (eEF2): promotes translocation during elongation.
E site: site in the ribosome where deacetylated tRNA can exit.
General control non-derepressible-2 kinase (GCN2): phosphorylates eIF2α limiting its availability for PIC formation.
General control non-derepressible-4 kinase (GCN4): regulates tRNA synthesis under starvation conditions.
Glycyl-tRNA synthase: a stress-sensitive tRNA synthase.
Heme-regulated inhibitor (HRI): a 4EBP that inhibits cap binding of eIF4E in mammals.
High chlorophyll fluorescence (HCF) 147: a mRNA-binding protein associated with *PsbA* mRNA.
High chlorophyll fluorescence (HCF) 244: a mRNA-binding protein associated with *PsbA* mRNA.
Independent ribosomal entry sites (IRESs): secondary RNA structures that allow cap-independent translation initiation.
Initiation factor 1 (eIF1): participates in PIC formation and scanning for start site.
Initiation factor 1 alpha (eIF1A): participates in PIC formation and scanning for start site.
Initiation factor 2 (eIF2): forms complex with GTP and Met-tRNAi^{Met} and binds 40S.
Initiation factor 2 alpha (eIF2α): the target of GCN2.
Initiation factor 3 (eIF3): participates in formation of PIC by binding mRNA to PIC.
Initiation factor 3 subunit g (eIF3g): required for reinitiation of ORF of mRNA after termination.
Initiation factor 3 subunit i (eIF3i): required for reinitiation of ORF of mRNA after termination.
Initiation factor 4A (eIF4A): unwinds mRNA in an ATP-dependent manner.