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Review

Take the (RN)A-train: Localization of mRNA to the endoplasmic reticulum☆

Orit Hermesh, Ralf-Peter Jansen *

Interfaculty Institute for Biochemistry, Eberhard-Karls-Universität Tübingen, Hoppe-Seyler-Strasse 4, 72076 Tübingen, Germany

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ABSTRACT

Protein translocation into the endoplasmic reticulum (ER) generally requires targeting of mRNAs encoding secreted or membrane proteins to the ER membrane. The prevalent view is that these mRNAs are delivered co-translationally, using the signal recognition particle (SRP) pathway. Here, SRP delivers signal sequence-containing proteins together with associated ribosomes and mRNA to the SRP receptor present on the ER surface. Recent studies demonstrate the presence of alternative pathways to recruit mRNAs to ER or to specific subdomains of the ER independent of SRP or translation. Such targeting of specific mRNAs to the ER subdomains allows the cell to sort proteins before translocation or to ensure co-localization of ER and mRNAs at specific locations. Translation-independent association of mRNAs involves ER-linked RNA-binding proteins and represents an alternative pathway of mRNA delivery to the ER. This article is part of a Special Issue entitled: Functional and structural diversity of endoplasmic reticulum.

1. Introduction

The endoplasmic reticulum (ER) presents the major biosynthesis site of membrane proteins as well as secreted proteins or those destined to organelles like the Golgi apparatus or lysosomes. The general view of how proteins are targeted to the ER is based on the signal sequence hypothesis originally proposed by Gunther Blobel [1], which predicts specific amino acid sequences to function as sorting signals of proteins destined to specific target organelles including the ER. In case of ER targeting, we can generally distinguish two protein-targeting mechanisms, a co-translational targeting and a more recently established post-translational targeting pathway. The prevalent mechanism of ER targeting works co-translationally and requires the recognition of an aminoterminal signal sequence emerging from the ribosome during synthesis of a protein. The signal sequence is recognized by the signal recognition particle (SRP) complex. Upon binding to the ribosome–mRNA–nascent peptide chain complex, the SRP pauses further translation elongation by blocking access to the ribosome's A site [2]. It subsequently targets the mRNA–ribosome–nascent chain complex to the cytoplasmic surface of the ER via an interaction with the SRP receptor in the ER membrane [3]. After release of the SRP, translation by the ribosome continues and the peptide chain will be synthesized and translocated into the ER lumen or the ER membrane via the Sec61 translocon. Post-translational targeting to the ER can occur via two different pathways. In the specific case of tail-anchored proteins, a transmembrane domain at the carboxyterminus of the protein is recognized by specific cytosolic chaperones (Get3p/TRC40) and the protein is subsequently targeted to Get1/Get2p receptor complex in the ER membrane. Upon ATP hydrolysis of Get3p/TRC40, the protein is then released and inserted into the membrane bilayer [4]. A second but less well understood pathway has been described in yeast. Reconstitution experiments using partially purified ER protein complexes and liposomes indicated that translocation of fully synthesized proteins requires besides the Sec61p-containing translocon complex additional membrane proteins like Sec62p and Sec63p [5].

The traditional view of mRNA trafficking to the ER is based on the co-trafficking of mRNAs together with the ribosome–nascent chain complex, which is targeted to the ER by the SRP–SRP receptor interaction (Fig. 1A). In addition, this targeting is generally thought to function only for mRNAs that encode a signal peptide containing protein. However, recent studies suggest additional targeting modes for mRNAs to the ER, which are SRP and translation independent. In this review, we would like to recapitulate experimental evidence for SRP- and translation-independent mRNA targeting to the ER surface based upon research in different model systems. We will also speculate on the role of translation-independent ER targeting for mRNA localization and translation.

2. Association of mRNA with ER

Although the primary role of the co-translational, SRP-mediated targeting of mRNAs to the ER is well established, several studies have indicated additional pathways that result in an association of transcripts with the ER.

One line of argument speaking for alternative pathways stems from early observations in yeast that SRP components are not essential [6,7].

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* Corresponding author at: Interfaculty Institute for Biochemistry, Hoppe-Seyler-Strasse 4, 72076 Tübingen, Germany. Tel.: +49 7071 2972453.
E-mail address: ralf.jansen@uni-tuebingen.de (R.-P. Jansen).

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Studies on siRNA-mediated knockdown of SRP components in mammalian cells showed that knockdown of SRP54 [8,9] or SRP72 [9] resulted in only modest effects on membrane protein synthesis or global mRNA partitioning between cytosol and ER [8,9]. ER localization of specific mRNAs like GRP94, which encodes an ER luminal protein occurred even if they lacked a start codon or upon deletion of the encoded signal sequence. It therefore appears that additional, SRP-independent pathways can replace signal peptide-mediated targeting by ER localization of mRNAs or ribosome–mRNA complexes due to cis-signals within these mRNAs.

Genome-wide analyses of mRNAs partitioning to the cytosol and ER compartments further corroborated this conclusion. In these studies, various cell fractionation assays were used to separate cytosolic polysomes from membrane bound ones and to characterize the mRNA fractions bound by these two polysome groups [8,10–12]. As expected, mRNAs with an encoded signal sequence showed a very high correlation with ER co-fractionation [8,10–12]. However, all experiments additionally identified in the ER-bound fraction cohorts of mRNAs encoding cytosolic or nuclear proteins that were previously assumed to be exclusively translated by free ribosomes (i.e. non-membrane bound). Different hypotheses have been suggested to explain this phenomenon. Potter and Nicchitta [12] showed that ER-bound ribosomes that were engaged in the synthesis of cytosolic proteins (i.e. proteins lacking a signal sequence) detach from ER to complete translation in the cytoplasm whereas ribosomes translating a protein with a signal sequence were kept at the ER membrane. This suggests that translation at the cytoplasmic surface of the ER represents a default pathway followed by sorting of transcripts for further translation at the ER or in the cytosol. Targeting to the ER might also be facilitated by the fact that the ER, together with the outer nuclear membrane represents the largest membrane surface of the cell. A recent study that investigated the ribosome loading of ER-associated mRNAs on a global scale suggests an even further reaching model. In this work, Reid and Nicchitta found that the ribosome density (hence, translational efficiency) of ER-associated mRNAs encoding cytosolic or ER proteins is similar, suggesting that both groups are equally well translated at the ER [12]. Furthermore, the overall ribosome loading on ER-associated transcripts was higher than that of transcripts not associated with the ER, implying a more pronounced role of the ER for efficient protein synthesis. Taken together, the above-mentioned results suggest that the ER is a major site for translation initiation of different mRNA groups, including those coding for ER or cytosolic proteins [12].

Partitioning mRNAs to the ER might also play an important role during stress situations or viral infection since directing to the ER keeps these mRNAs in a translation-competent state. Coxsackie B virus infection leads to inhibition of cap-dependent translation initiation by virus-induced cleavage of eukaryotic translation initiation factor 4 G (eIF4G) and poly(A)-binding protein [13,14]. Whereas cytosolic translation is effectively inhibited after infection with Coxsackie B virus, translation at the ER is ongoing, although at reduced rate [15]. Therefore, partitioning of mRNAs to the ER could allow a virus-infected cell to continue with translation of endogenous mRNAs. Similar to viral infection,

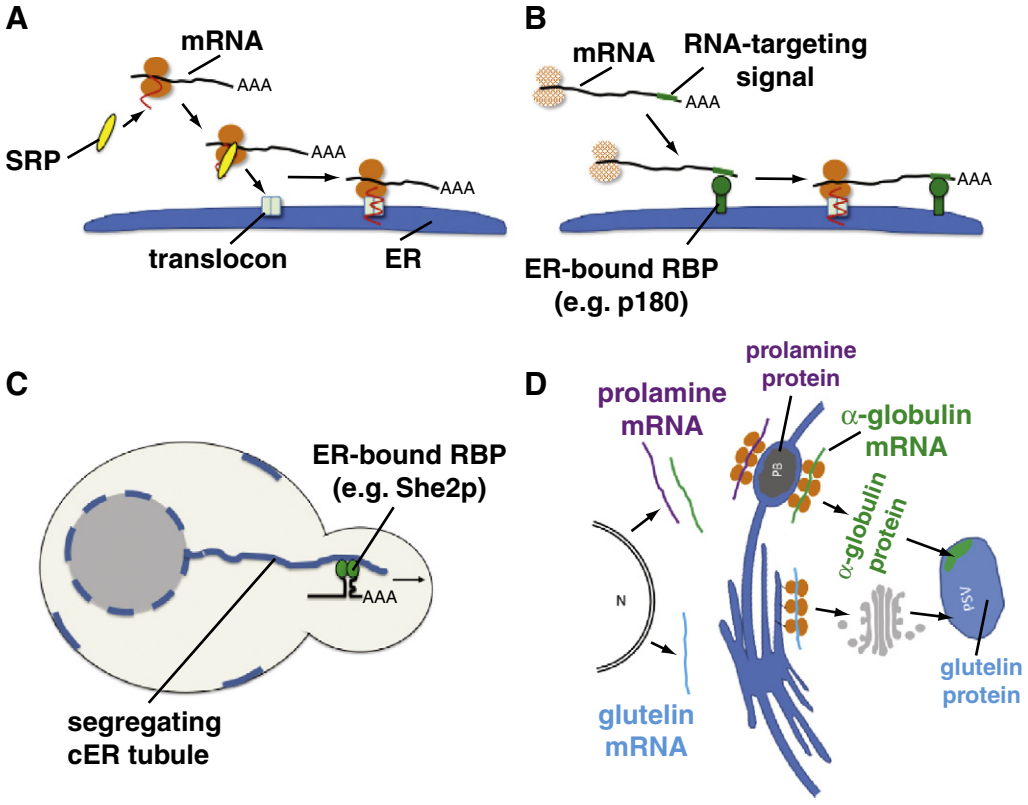

Fig. 1. (A) SRP-mediated mRNA targeting to ER. Ribosomes translating membrane protein-encoding mRNAs are recognized by the signal recognition particle (SRP) due to a signal sequence in the nascent peptide chain. SRP then targets the mRNA containing complex to the ER surface where translation continues and the protein is translocated into the ER via the translocon. (B) SRP-independent targeting of mRNAs to the ER. ER resident RNA-binding proteins (RBPs) like p180 direct mRNAs to ER via cis-signals in the mRNA or by electrostatic interaction with the negatively charged RNA backbone. Ribosomes might associate with these mRNAs before (shaded ribosomes) or after ER targeting. (C) Co-transport of localized mRNAs and cortical ER in yeast. ER tubules giving rise to cortical ER in the yeast bud move from the mother cell into the bud. Some localized mRNAs targeted to the bud tip are co-transported with the tubule. Association of mRNAs and ER appears to be mediated by the RBP She2p. (D) Schematic model for mRNA targeting to ER subdomains and the subsequent protein localization in the rice seed. mRNAs from the Globulin family (blue) like rice glutelin and maize leugemin are localized to the cisternal ER(C-ER). Local translation of the encoded protein is followed by transport via the golgi complex to the protein storage vacuole (PSV). mRNA of the Prolamine superfamily like rice prolamine (purple) and α-globulin (green) are targeted to the protein body ER (PB-ER). Translation of these mRNAs results in protein translocated into the PB-ER except for α-globulin, which is transported to the PSV. N = nucleus.

cytotoxic stress triggers translational inhibition and appearance of RNA-containing particles called stress granules [16]. While cytosolic mRNAs accumulate in these granules, ER-bound transcripts like the P-glycoprotein encoding *MDR1* mRNA escape this sequestration [17]. Furthermore, upon stress, ER-associated ribosomes are not released from their bound mRNAs therefore allowing these mRNAs to recover translation much faster than their cytosolic counterparts. These findings suggest that the ER represents a special environment for translation that is less sensitive to stress situations, allowing the cell to translate a specific set of mRNAs under these conditions.

Despite the evidence for the SRP-independent RNA partitioning to the ER, a molecular mechanism that explains how the RNA binds the ER in this case, is still missing. Although recent reports indicate that RNA targeting to membranes in prokaryotes can occur translation-independent and might not implicate RNA-binding proteins [18], the most likely mechanism in eukaryotes involves RNA-binding proteins at the ER membrane. A comprehensive analysis of mRNAs associated with a representative sample of yeast RNA-binding proteins (RBPs) revealed that mRNAs encoding proteins of the yeast cell wall, plasma membrane, or ER bind to specific RBPs. These RBPs include Bfr1p, Whi3p, the pumilio-like proteins Puf1p and Puf2p, or the hnRNP K homology (KH) domain containing proteins Scp160p and Khd1p [19–21]. However, it remains unclear if any of these proteins is required for RNA targeting to the ER. Of the above-mentioned RBPs, only Whi3p, Scp160, and Bfr1p have been found to co-localize with the ER [19,22–24]. Localization of Scp160 is disrupted by EDTA treatment, indicating a requirement for intact ribosomes [22]. It therefore seems likely that at least some of these proteins are indirectly targeted to the ER via their mRNA targets that are translated by membrane-associated ribosomes.

More recently, a biochemical approach has identified the abundant mammalian ER membrane protein p180 as a candidate for mRNA targeting to the ER [25]. p180 was identified by mass spectrometry analysis of proteins associated with ER-bound polysomes. Originally described as a mammalian ribosome receptor of the ER [26], it has later been shown that this function is primarily fulfilled by the Sec61 translocon complex [27]. p180 contains a single transmembrane domain and a large carboxyterminal lysine-rich domain. This domain directly binds RNA and is required for the maintenance of mRNAs at the cytoplasmic face of the ER membrane [25]. Furthermore, overexpression of p180 promotes increased ER association of bulk mRNA including *t-ftz* RNA. Importantly, depletion of p180 decreases translation-dependent as well as -independent ER association of two potential target mRNAs encoding calreticulin and alkaline phosphatase [25]. p180 is only found in metazoans, but its overexpression in yeast leads to an enhancement of the ER–mRNA association [28], indicating that it can mediate RNA binding to ER in the absence of additional cell-specific factors (Fig. 1B).

3. Co-trafficking of localized mRNAs and ER

3.1. Sea squirts (Ascidians)

Ascidians represent a class of marine invertebrate filter feeders. In ascidians, the formation of at least three kinds of tissue (tail muscle, endoderm and mesoderm) is controlled by the correct localization of maternal mRNAs. These are divided into postplasmic type I and II mRNAs according to their pattern of localization. Type I postplasmic mRNAs, including *HrPEM* (homologue of posterior end mark) and *macho1* are already localized in a vegetal to animal gradient before fertilization. After fertilization they become concentrated at the vegetal pole and relocalize to the posterior cortex before cleavage. At the 8 cells stage these mRNAs concentrate in a macroscopic cortical structure called the centrosome-attracting body (CAB) (reviewed in [29]). Similar to the localization of these mRNAs, the cER network in ascidian eggs also undergoes reorganization and polarization, which is required for axis formation and development. The cER is a highly polarized ER network lining the plasma membrane. In the unfertilized egg the cER is distributed over the vegetal-to-animal gradient. Upon fertilization, the cER is further concentrated to the vegetal pole by cortical contraction via actin filaments. Subsequently, the concentrated cER is moved to the posterior pole using the microtubule cytoskeleton. At the 8-call stage cER is tightly condensed in the CAB [30,31]. In a study by Sardet and co-workers [32] it was demonstrated that both *macho1* and *HrPEM* mRNAs co-localize with the cER at the different stages of redistribution from egg to zygote [32]. The association of ER and localized mRNAs suggested by this tight co-localization was further corroborated by their similar dependency on common cytoskeleton components in three species of ascidians. The translocation of cER and type I postplasmic mRNAs to the vegetal pole was found to be actin dependent while their movement to the posterior pole was microtubule dependent [33,34]. Interestingly, a different pattern characterized the localization of the type II mRNAs which exhibit delayed localization to the posterior vegetal cytoplasm after fertilization. Type II mRNA localization only depends on actin filaments, suggesting the existence of two distinct localization pathways, one of them in conjunction with ER trafficking [34]. Despite the reported connection of cER and type I mRNA localization, direct evidence for an association of localized transcripts and cER including the identification of factors involved is still missing.

3.2. Clawfrog (Xenopus laevis)

In *Xenopus laevis* oocytes, the localized *Vg1* mRNA encodes a transforming growth factor (TGF) ß-like molecule involved in mesoderm induction [35]. In the early oocyte (stage I), *Vg1* mRNA is uniformly distributed in the cytoplasm. During the end of stage II and in the early part of stage III, *Vg1* mRNA and ER become enriched in a wedge shaped region between the nucleus and the vegetal cortex. In late stage III, *Vg1* mRNA and ER are transported to the vegetal cortex in a microtubule dependent manner [36]. Co-localization studies showed that *Vg1* mRNA shows a high degree of overlap with ER markers in a globular substructure within the wedge of stages II and III [37,38]. UV crosslinking studies with the *Vg1* RNA sequence responsible for *Vg1* localization (the *Vg1* localization elements; VgLE) identified the Vera protein (VgLE binding and ER association). Vera, also called Vg1RBP (*Vg1* RNA binding protein) is essential for *Vg1* localization and co-fractionates with an ER enriched fraction [37]. Double labeling studies demonstrated that Vera co-localizes with ER in the vegetal subcortical region of the oocyte [39]. Upon meiotic maturation and ER reorganization Vera is released from its vegetal docking and does not co-localize with ER anymore but is redistributed in the cytoplasm [40]. Later studies showed that Vera co-localization with the ER depends on the phosphorylation state of Vera since inhibition of phosphorylation prevents release of Vera from the vegetal cortex upon meiotic maturation and sustains Vera-cER co-localization. This phosphorylation appears to be mediated by Erk2 MAP kinase [40]. In contrast to its effect on co-localization or co-fractionation with ER, phosphorylation does not affect RNA binding of Vera or its dimerization [40]. However, direct evidence that Vera functions by tethering *Vg1* mRNA to the ER is still lacking.

3.3. Baker's yeast (Saccharomyces cerevisiae)

Several examples for mRNA and ER co-trafficking have been found in budding yeast. In *Saccharomyces cerevisiae* more than 30 mRNAs are transported to the bud tip using the She1p–She3p protein machinery [41–43]. This transport complex, also defined as the locasome, includes the RNA binding protein She2p [44–46] that binds localized mRNAs already in the nucleus [47] and escorts them to the cytoplasm [47,48]. After nuclear export, the primary mRNP complex binds to She3p, which is associated with the myosin V motor protein Myo4p

(She1p) [44,49]. Myo4 is required for the active transport of the mRNP to the bud tip [44,49–51]. Besides mRNA transport, Myo4p and She3p are required for the proper segregation of a subclass of the ER, the cortical ER (cER) to the future daughter cell [52]. Recently it was found that Myo4p is also required for the cER delivery to the yeast mating projection tip (shmoo) [52,53]. Cortical ER is one of the two classes of ER that can be found in yeast. In contrast to the perinuclear ER, which consists of membrane sheets surrounding the nucleus and is continuous with the nuclear envelope, cER (also called peripheral ER) forms a highly dynamic network of interconnected tubules positioned right underneath the cortex [54,55]. This network needs to be inherited to the yeast bud upon cell division. Segregation of cER begins with ER tubules emanating from the mother cell ER and moving into the bud where they either attach to the bud tip before spreading along the cell cortex [56,57] or, alternatively spread from the bud center to the cortex to form the bud's cER [58].

Several studies indicate that mRNA localization to the new bud is coordinated with cER segregation. Live imaging showed that bud localized *ASH1* mRNP, a cell fate determinant expressed normally during late mitosis, and tubular ER can move in a coordinated way to the bud and that the mRNP is often seen at the tip of an ER tubule [59]. Deletion of the motor protein Myo4p resulted in mRNPs left in the mother cell. However, they were still associated with ER tubules, suggesting that their co-localization with the ER tubules is Myo4p independent [59]. Subcellular fractionation revealed that yeast localized mRNAs are enriched in the ER fraction and this enrichment is dependent on She2p [41]. Flotation and sucrose gradient centrifugation assays further demonstrated that a significant fraction of the RNA-binding protein She2p also co-fractionates with ER membranes independent of Myo4p, She3p and ER-attached ribosomes [59]. Taken together these results imply that She2p might tether mRNPs containing localized mRNAs to the ER (Fig. 1C).

Genetic studies also suggest a tight connection between segregation of ER and mRNA localization since mutations in several genes affect both processes. Bud localization of mRNAs encoding polarity and secretion factors (POLs) like *CDC42*, *SEC4* and *SRO7* [41] is disturbed in mutants lacking Sec3p, a non-essential component of the exocyst complex [60] and Srp101p, encoding a component of the SRP receptor [61]. A more recent study suggests that bud localization of only a subset of localized mRNAs requires proper cER inheritance [62]. Like the POL mRNAs, these mRNAs encode membrane or ER associated proteins. Localization of at least one of the mRNAs, which codes for Wsc2p, a stress sensor protein for the maintenance of cell wall integrity, occurs independent of translation, ruling out co-translational targeting of the mRNA due to the association of its nascent chain with the translocation apparatus in the ER. The investigated mRNAs are localized during the early cell cycle (S phase) and their expression pattern overlaps with the time when cER segregation occurs. Localization of this subset of mRNAs was specifically affected by mutants blocking or slowing early steps of ER inheritance (e.g. *aux1*) or cER docking at the bud tip (*sec3*). Aux1p is the yeast auxilin homologue involved in clathrin uncoating [63] and has a so far unknown role in ER segregation [64]. Fundakowski and co-workers [62] also demonstrated that mRNA localization requires correct formation of tubular ER since loss of the reticulon Rtn1p [65] in conjunction with loss of Yop1 [66] not only disrupts tubular ER formation but also blocks mRNA localization. This dependence of cytoplasmic RNA transport on proper ER segregation does not hold true for all localized mRNAs. mRNAs like *ASH1* that are expressed late in the cell cycle (e.g. during mitosis) are localized independently of functional ER segregation [62]. It therefore seems that, in yeast, two alternative pathways of RNA localization exist, of which the one active at earlier stages in the cell cycle requires in addition to the well-characterized She2p/She3p/Myo4p complex, components of the cER segregation machinery. Since the RNA-binding protein She2p appears to play a key role in attaching localized mRNA to cER but is also the key factor for ER-independent mRNA localization, it will be interesting to see how this protein differentially mediates RNA localization at different stages of the cell cycle.

Localization of mRNA and ER transport in yeast is not only coordinated in dividing cells but also in cells undergoing a highly polarized growth program called shmooing [53]. Haploid yeast cells treated with a mating factor form polarized membrane extension called the shmoo, which are more elongated projection than buds. POL mRNAs are localized in a Myo4p- and Sec3p-dependent manner to the shmoo, suggesting that their localization might also depend on proper ER delivery to the shmoo. Surprisingly, their localization is independent of the RNA-binding proteins She2p and She3p but requires the KH domain protein Scp160, a RNA-binding G protein effector protein of the mating response pathway [67,68]. Scp160 was shown to localize to the ER [24] and to the shmoo tip and, similar to She2p to co-immunoprecipitate with Myo4p [53]. These results suggest that yeast cells use an mRNA-cER co-transport not only in dividing cells but also during the mating program.

4. Localization of mRNAs to specific ER subdomains

4.1. Rice seed storage protein mRNAs

Developing rice endosperm displays two distinct types of rough ER, cisternal ER (to distinguish it from the cER in yeast, cisternal ER will be referred here as C-ER) and protein body ER (PB-ER). Protein bodies contain aggregates of storage proteins and are delimited from the rough ER membranes, which are interconnected to the cisternal ER network (Fig. 1D). The seeds of most plants contain one of the two kinds of storage proteins: globulin or prolamine. Rice seeds are unique in that they accumulate both type of storage protein, glutelin (a globulin like protein) and prolamine. During rice development these storage proteins are translated at the ER, translocated into the ER lumen and then transported to different compartments. Prolamines are retained in the ER lumen as PB whereas glutelins are transported to protein storage vacuole (PSV) via the Golgi complex [69,70]. Sorting of prolamine and glutelin depends on the localization of their mRNAs to distinct ER domains, namely the PB-ER and C-ER [71]. Deletion analysis of the *prolamine* mRNA revealed that its localization is independent of the region coding for the signal peptide sequence but required the presence of an initiation codon and hence translation [72]. RNA localization is mediated by two partially redundant localization elements (LEs) in the coding sequence and the 3′ UTR. A transcript that lacked both LEs exclusively went to the C-ER, implying a default mRNA localization pathway to the C-ER that has to be overcome by specific LEs. Interestingly, fusion of the *prolamine* transcript to the 3′UTR of *glutelin* resulted in complete C-ER localization, implying dominance of the *glutelin* C-ER LE over the PB-ER LE [73]. This localization pattern seen in rice is also conserved in maize. Similar to rice, maize accumulate zeins mRNAs, which are homologue to prolamines in PB-ER [74]. The maize *δ-zein* sequence contains four partially redundant LEs in the coding sequence and the 3′ UTR. Proper localization of *δ-zein* mRNA was found to be crucial for the correct protein localization as relocalizing *δ-zein* mRNA to C-ER resulted in the mislocalization of *δ-zein* protein from PB-ER to the PSV [75].

Interestingly, α-globulin, another storage protein in rice, shows a different RNA-protein localization relationship. Like glutelin, α-globulin protein is localized to the PSV, specifically to the periphery of PSV. In contrast to *glutelin*, though, *α-globulin* mRNA localize to the PB-ER, where it is translated and subsequently transported to the PSV. Mislocalization of *α-globulin* mRNA to the C-ER upon fusion with the 3′ UTR of *glutelin* alters the spatial distribution of α-globulin protein in the PSV and the morphology of the PSV. α-globulin is not localized to the peripheral PSV anymore but spread all over the PSV. In addition, α-globulin particles were detected in the cytoplasm [75]. These results indicate that the localization of *α-globulin* mRNA and its translation on

the PB-ER is essential for the efficient transport of α-globulin protein to the PSV as well for its specific localization to subregions within the PSV.

What might be the reason for restricting mRNA localization to specific ER subdomains? One possibility is to prevent deleterious protein interactions. As mentioned before, *prolamine* mRNA is translated at PB-ER and *glutelin* at C-ER. Protein Disulfide Isomerase 1-1 (PDI1-1) is an ER luminal chaperone that is asymmetrically distributed in the ER and found mainly in C-ER [76]. Upon PDI1-1 deletion the glutelin precursor proglutelin and prolamines interact via intermolecular disulfide bonds and form intracisternal aggregates within the ER lumen. In these mutants PB-ER is not formed but a new type of protein body containing both proglutelin and prolamine [77]. These results exemplify the destructive effect that might also be caused by localization of mRNAs and their respective encoded proteins to the same ER subdomain. Only little is known about the mechanistic details of this subcompartment-specific mRNA localization. Biochemical and immunofluorescence studies imply an involvement of the actin cytoskeleton in the transport of prolamine mRNA [73]. In addition, two RBPs were found to specifically bind *prolamine* and *glutelin* mRNA. OsTudor-SN binds both *prolamine* and *glutelin* mRNAs in vivo as shown by immunoisolation of OSTudor-SN-containing ribonucleoprotein complexes and reverse transcription-PCR (RT-PCR). This RBP is found not only at the PB-ER and C-ER but also in cytoplasmic particles [78] and might therefore not mediate the specific localization of its bound RNA. The second protein associating with *prolamine* and *glutelin* mRNAs is RBP-A. However, since it can be found in several different compartments in the cell like the nucleus, at microtubules and at C-ER [74], it is still unclear if it has any specific role in mRNA targeting to PB-ER or C-ER.

4.2. Drosophila gurken and wingless mRNAs

Other examples underscoring the importance of mRNA localization to specific ER subdomain have been reported from *Drosophila* oocytes and embryos. Localization of *gurken* (*grk*) mRNA to the dorsal anterior (D/A) corner of the *Drosophila* oocyte in stages 9–10 of its development specifies the anteroposterior and dorsoventral axes of the future embryo. *grk* encodes a transforming growth factor alpha like protein that is secreted to the extracellular space between the oocyte and the overlying follicle cells, where it induces a signaling cascade leading the follicle cells to adopt a dorsal fate [79]. Newly synthesized gurken protein leaves the ER at specialized ER exit sites called transitional ER [80,81]. Although stage 9 oocytes contain about 1000 transitional ER (tER) sites that are distributed evenly throughout the ooplasm, the majority of gurken protein can be found at tER sites and tER-Golgi units located at the D/A corner and in the intercellular place between the oocyte and the follicle cells. In *merlin* mutants, where *grk* mRNA is localized to the posterior pole, only tER-Golgi units located at the posterior pole are positive for gurken protein [82]. A similar observation can be made in *K10* and *squid* mutants where *grk* mRNA is mislocalized to the oocyte's anterior but more ventral cortex. In these mutants *grk* is located close to tER-Golgi sites along the anterior side and the anterior ventral cortex even though it can also be found in the D/A corner [82]. These results indicate that localization of *grk* mRNA to a specific fraction of ER determines the future exocytic sites for the encoded protein.

Another secreted protein in *Drosophila* is wingless (Wg), a major signaling molecule controlling cell-fate choices during embryonic development [83]. In the ectoderm of stage 8 *Drosophila* embryos, *wg* mRNA is found to be confined to a small area just below the apical cell membrane. This localization is controlled by a localization element in its 3′-UTR. Disruption of this LE in the 3′-UTR leads to a uniform distribution of *wg* mRNA and Wg protein [84]. Although there is no evidence so far for a co-localization of *wg* with ER at the apical site, as Wg is a secreted protein, it is tempting to speculate that the function of *wg* mRNA localization is similar to *gurken* localization, namely, marking future exocytosis sites for Wg protein at the apical site.

4.3. Yeast HAC1 mRNA

The unfolded protein response (UPR) is an ER stress response triggered when proper folding of proteins in the ER is disrupted. The main sensor of ER stress is Ire1p, a transmembrane kinase/endoribonuclease [85,86]. In yeast, Ire1p removes an intron from *HAC1* mRNA in an unconventional splicing event, which also requires the tRNA ligase Rlg1. Only the spliced form of *HAC1* can be translated into a protein that is subsequently translocated to the nucleus, where it acts as a transcription factor for genes required for the stress response [87,88]. Recruitment and splicing occurs at specific foci at the ER membrane [89]. These foci are generated by stress-induced oligomerization of Ire1p. The recruitment of *HAC1* depends on a targeting element found in its 3′-UTR. In order to function as targeting sequence, translation has to be repressed. Disruption of either Ire1p foci formation or *HAC1* recruitment impairs functional UPR in yeast [89]. This study exemplifies how mRNA localization to specific ER sites marked by Ire1 can serve to ensure an efficient ER signaling. However, this specific targeting mechanism is not conserved. Similar to yeast, mammalian UPR depends on cytoplasmic splicing of an mRNA encoding a response factor, *XBP1*. In contrast to *HAC1* mRNA, unspliced *XBP1* mRNA (named *XBP1u*) is delivered to the ER independently of IRE1a, as *XBP1u* is present in the membrane fraction in IRE1a knock-out mouse fibroblasts [90].

4.4. Plant RNA virus ribonucleoproteins

The analysis of plant virus spreading has also revealed a so far unknown targeting of RNAs to subregions of the ER. Plant RNA viruses spread via plasmodesmata, a communication channel between adjacent plant cells. Plasmodesmata contain the plasma membrane extension, a cytoplasmic sleeve and a desmotubule that is continues with the cortical ER network [91]. Potexovirus, a major RNA virus in plants contains a genome with 5 ORFs that encode the replicase, the three TGB (Triple Gene Block) movement proteins and capsid protein (CP). TGB1 and CP are both RNA binding proteins [92] while TGB2 and TGB3 are small integral ER membrane proteins [93]. TGB2 was shown to interact in vivo with both TGB1 and CP and to be targeted by TGB3 to peripheral puncta next to the plasmodesmata that co-localize with ER tubules. TGB2 targeting by TGB3 is mediated by a sorting signal sequence in the carboxy-terminal domain of TGB3 [94]. Using sorting defective mutants in plants it could be demonstrated that the sorting signal is crucial for viral spread. These results suggest that TGB3 target a RNP complex comprising of TGB1, CP, TGB2 and the viral RNA to cER in the proximity of the plasmodesmata and functions in virus spreading.

5. Conclusion

Evidence is accumulating that besides the well-understood localization of mRNA to the ER in the context of SRP-mediated ribosome-nascent chain targeting, additional pathways exist. Transcriptome and translatome studies support the idea that even mRNAs coding for cytosolic proteins initiate their translation at the ER before leaving the ER to continue translation in the cytosol, which suggests that targeting to the ER might be a default pathway for all cellular mRNAs. For a subset of mRNAs targeting does not require translation of the corresponding mRNA but its binding to membrane-associated proteins like mammalian p180 or yeast She2p. Since translation-dependent and -independent pathways are not mutually exclusive, it is conceivable that they act together in order to increase the efficiency of translation at the ER. Targeting of mRNAs to specific regions of the ER as demonstrated for plant seeds might be required if the translocated protein needs a 'tailored environment' in the ER. Co-segregation of cortical ER and mRNAs associated with it might facilitate the local translation of these mRNAs. However, many questions are still open. Is there a default pathway of targeting all kinds of mRNAs to ER? What RNA binding proteins mediate the observed interaction and how do they recognize mRNA in

general or specific targets? What specific RNA-binding proteins are involved in targeting mRNAs to definite ER subregions? How are these hypothetic proteins themselves targeted to these subregions? Many of these questions will need to be answered to fully understand and accept the existence of RNA-mediated pathways that target membrane or secreted proteins to the ER.

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