Message on the web: mRNA and ER co-trafficking

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In eukaryotes, mRNAs encoding secreted and integral membrane proteins are targeted to the endoplasmic reticulum (ER) to facilitate translation and protein translocation into the ER lumen. However, mRNAs encoding cytosolic proteins also associate with ER membranes in yeast, plants and animal cells. mRNAs encoding both cytosolic and secreted proteins have been observed in association with the cortical ER (cER) network, which consists of interconnected tubular and sheet-like structures that extend to the plasma membrane and to sites of polarized growth. This physical association enables cytoskeleton-mediated co-trafficking and anchoring of cER-mRNA, which might regulate protein synthesis in areas of new growth (i.e. during cell division in yeast), or enable confined spatial responses to environmental stimuli (i.e. during synaptic remodeling or in cases of neuronal injury).

mRNA targeting to the ER – in the beginning

If proteins can undergo translation on ribosomes in the cytosol, why do mRNAs target to the endoplasmic reticulum (ER)? Studies performed nearly half a century ago revealed that mRNAs encoding secreted and integral membrane proteins target to the ER to expedite nascent polypeptide synthesis and entry into the secretory pathway. A central conserved mechanism (Figure 1a) that enables the co-translational translocation of newly synthesized polypeptides into the ER is the signal recognition particle (SRP) pathway, which targets ribosome–mRNA–nascent chain complexes formed in the cytosol to the ER membrane [1–4]. Delivery to the ER is mediated by an SRP receptor composed of a GTPase heterodimer that enables subsequent attachment of the ribosome–mRNA–nascent chain complex to the Sec61 translocon complex, which functions as a translocation channel for newly synthesized polypeptides to enter the ER lumen from the ribosome. The existence of SRP-dependent recruitment of ribosome–mRNA complexes to the ER suggests that mRNAs encoding secreted or integral membrane proteins generally exist either in a free unbound state or as ER-bound polysomes, but not as free polypeptides in the cytoplasm. After the termination of polypeptide synthesis mRNA and ribosomal subunits can theoretically recycle to a cytosolic pool for further rounds of protein synthesis (via the SRP pathway) or for degradation [1–3]. However, translation re-initiation of ER-bound mRNAs after chain termination has usually been observed, even in the context of mRNAs encoding cytosolic proteins [4,5]. Thus, there is some propensity for mRNAs to be maintained in an ER-bound polysomal pool in contrast to the potential termination-coupled release of both ribosome and mRNA to the cytosol.

Although SRP-mediated trafficking of ribosome–mRNA–nascent chain complexes is generally recognized as the major determinant for the association of translating mRNAs with ER membranes, later work demonstrated that elements of the SRP can be removed, by either RNA knockdown or gene deletion, and in many cases this results only in cell-growth defects, but not lethality [4,6–8]. This suggests that the SRP pathway is not requisite for mRNA delivery to the ER for protein synthesis, but that it might provide an efficient means of ribosome-mRNA delivery to the translocon. Landmark studies using yeast showed that inactivation of the SRP led to an unfolded protein response that could be compensated for by both transcriptional control and expansion of the ER surface [6], which might increase the likelihood of ribosome–mRNA complexes reaching translocons. In any event, bypass of the SRP pathway implies that there are other means for delivery and anchoring of mRNAs to the ER. Different avenues of investigation have led to the discovery of these additional ER–mRNA connections. This review aims to consolidate the indirect and direct evidence obtained from mRNA localization, localized protein synthesis and endomembrane trafficking studies to create a more coherent and unambiguous understanding of the connection between these cellular processes. Evidence for the existence of ER–mRNA co-trafficking and conservation in eukaryotic cells will be discussed, along with its proposed role in facilitating the localized translation of proteins that control cell fate, polarization and body plan development in a wide range of organisms. A schematic exemplifying the co-trafficking of mRNA and cortical ER (cER) in several different organisms is shown in Figure 2.

ER–mRNA interactions: a web of information that controls cell development

Three principal avenues of investigation have contributed to the idea of ER–mRNA co-trafficking – the study of localized protein translation in the extrasomatic regions of neurons, cell fractionation, and the detection of RNA in the resulting fractions and direct observation by microscopy. In the following sections we summarize these different lines of evidence.

Protein synthesis and secretory pathway components in neurons: functional evidence for ER–mRNA interactions

Because the distance between neuronal processes (e.g. axons, dendrites) and the cell soma can be large, a
mechanism involving mRNA transport and localization [9–11] could enable localized protein synthesis to control distal cellular responses. Work dating back to the early 1960s described the presence of RNA and ribosomes in axonal preparations from snails, squid, fish and mammals [12,13]. Moreover, de novo protein synthesis of cytosolic and secreted proteins in extra-somatic regions of neuronal cells was demonstrated [12,13] and, thus, would also necessitate the existence of a localized secretory apparatus (e.g. ER and Golgi).

More recently, studies have shown that mRNAs encoding specific cytosolic, secreted and membrane proteins undergo localized translation in axons and dendrites. For example, the mRNAs encoding sensorin, a secreted neurotransmitter, and syntaxin, a Qa/t-SNARE involved in synaptic vesicle exocytosis localize to the processes of Aplysia sensory neurites [14,15], in which clustered ER and Golgi membranes have also been identified [16]. In higher organisms, localized mRNA translation along the length of axons is a major determinant of growth responses to environmental stimuli distal to the cell soma [12,13,17–19]. For example, neurotrophin treatment regulates growth cone motility and axon guidance in Xenopus and mammalian neurons via localized β-actin translation [19–22]. Similarly, the localized translation of importin-β and vimentin mRNAs upon nerve injury leads to retrograde signaling to the nucleus via the delivery of activated Erk kinases [23,24]. In contrast to neurotrophins, axonal guidance mediated by semaphorin3A signaling directs localized RhoA (a lipid-anchored small GTPase) translation in the growth cone and leads to its collapse [25]. In fact, transcriptional and translational profiling of cultured dorsal root ganglia neurons has revealed that >200 proteins, including secreted and membrane proteins, are upregulated via local synthesis upon nerve insult and after treatment with neurotrophic factors [26,27]. These results also...
suggest that different extracellular signals can bi-directionally regulate mRNA levels to yield alternative growth-promoting or growth-inhibitory responses. Thus, peripheral stimulation by divergent signaling pathways can lead to changes in mRNA delivery and control local protein levels in axons. This might necessitate the retrograde transport of instructive signals back to the nucleus, as in the case of localized importin-β and vimentin mRNA translation to transduce a post-injury transcriptional response [23].

In dendrites, mRNAs encoding proteins involved in synaptic remodeling, such as neurotransmitter receptors (e.g. N-methyl-D-aspartate, metabotropic glutamine, AMPA, and BDNF receptors), signaling molecules (i.e. αCaMKII), and structural proteins (e.g. Arc), as well as secreted proteins (i.e. tissue plasminogen activator, matrix metalloprotease 9) undergo activity-dependent local translation back to the nucleus, as in the case in localized importin-β and vimentin mRNA translation to transduce a post-injury transcriptional response [23].

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Because axonal responses to neurotrophic factors are faster than can be accounted for by axonal transport [12,31] and because many axon-localized mRNAs encode secreted and membrane proteins, a mechanism for protein translation and secretion distal to the cell body would necessitate ER and a means to deliver proteins to the cell surface. Although conclusive evidence for the presence of ER and Golgi along the length of axons is lacking, ultrastructural and immunocytochemical studies have demonstrated the presence of ribosomes and smooth ER in axonal processes [12,31–33], with tRNA and protein enriched in domains called periaxoplasmatic ribosomal plaques [33]. Notably, a recent study [26] showed that ER proteins, such as calreticulin, BiP and ERp29 undergo direct translation in axons, implying the existence of ER in injury-conditioned neurons. Stronger evidence exists for the presence of cER and Golgi in dendritic processes. Several studies demonstrated the presence of ‘satellite’ ER and Golgi in dendrites and dendritic spines from Drosophila and mammalian neurons [32,34–37]. A recent study [37] even identified...
mutations that greatly inhibit dendrite formation and outgrowth in neurons isolated from Drosophila embryos. Several of the mutations were in genes encoding proteins of the early secretory pathway involved in COPII vesicle formation (e.g. SARI, SEC23), which mediates ER–Golgi transport. These mutations affected both dendrite length and the degree of arborization, but did not affect axonal growth (although the contribution of maternal components in axon formation was not excluded). Golgi structures were also identified in the dendrites of wild-type neurons, using a medial Golgi marker (e.g. GFP-labeled mannosidase II), and their distribution to the distal ends of dendrites was blocked in a sar1 mutant [37].

RBPs involved in mRNA localization (e.g. Staufen, FMRP) were found to co-precipitate with Pura-containing ER-bound polysomes from neuronal tissue, and to detach from the ER on treatment with EDTA [30], which dissociates membrane-bound ribosomes. Correspondingly, mRNAs encoding a variety of ER, Golgi and synapic vesicle proteins were found in RNP granules that contain IMP1 (human zipcode-binding protein 1, ZBP1) in transfected HEK293 cells [38]. Because IMP1/ZBP1 is involved in mRNA localization and transport in both motile cells and neurons [20–22,38], the mRNAs present in IMP1-containing RNP granules in HEK293 cells are probably transported along with β-actin mRNA in polarized cell types. Together, a plethora of circumstantial evidence implies the presence of mRNA and the necessary translational machinery (i.e. ribosomes, ER) distal to the cell body in neurons.

**mRNA partitioning to sub-cellular membrane fractions: evidence from biochemical studies**

Although functional evidence for co-trafficking comes from observations in neurons, biochemical evidence for ER–mRNA partitioning comes from cell fractionation studies using yeast, Drosophila and mammalian cells and employing reverse-transcription PCR (RT-PCR) and/or in situ cDNA hybridization-microarray analyses [39–44]. Groups investigating the association of mRNAs with either free or ER-bound ribosomal fractions have determined that mRNAs encoding cytosolic proteins are significantly enriched in ER-containing fractions, along with the mRNAs encoding secreted and membrane proteins. Thus, in contrast to the model of SRP-dependent recruitment of mRNAs (encoding secreted proteins) to the ER, mRNAs encoding cytosolic proteins also partition with ER membranes. This was first noted in studies using cDNA hybridization techniques [39,40] and microarray-based screens later identified mRNAs encoding cytosolic and nuclear proteins with ER-bound polysomes in Drosophila embryos [41], and in yeast and human Jurkat cells [42]. Because of concerns for cross-contamination during mechanical cell fractionation less destructive techniques, including digito- nin-based permeabilization and fractionation of Jurkat and J558 cells (to separate free and ER-bound polysomes) and in situ hybridization of NIH3T3 cells, were used to show that a large subset of mRNAs encoding cytosolic proteins are either enriched on membrane-bound polysomes (i.e. Hsp90) or are distributed to both free and bound polysomes (i.e. β-catenin, protein kinase C β) [43].

Moreover, >80% of the arbitrary mRNAs detected by array hybridization (~400 mRNAs) were at least twofold more enriched in the ER-bound polysome fraction. Thus, mRNAs encoding cytosolic proteins are more likely to be associated with ER-bound than with free polysomes. Recent work in yeast using RT-PCR, in combination with fluorescence microscopy studies (discussed in following section), showed that daughter cell-localized mRNAs encoding cytosolic factors, such as Ash1 (a cell-fate determinant) and Srp7 (a SNARE regulator and polarity factor), are highly enriched in ER-containing fractions [44]. This ER–mRNA association was dependent on Sec3, a component of a multi-subunit complex (termed exocyst) involved in secretion, as well as both mRNA and ER trafficking in yeast daughter cells [44,45]. Thus, the results of fractionation-based studies indicate that most mRNAs are ER membrane-associated to some degree, but whether this physical association is absolutely necessary for the intracellular localization of mRNAs encoding cytosolic proteins, their subsequent translation, or both, are open questions. According to an elongation-coupled ribosome release model [4], illustrated in part in Figure 1b, mRNAs encoding cytosolic proteins (i.e. lacking a signal peptide) would dissociate bound ribosomes from ER membranes to allow for subsequent translation in the cytosol. Such a mechanism could enable translation-coupled release of mRNA–ribosome–nascent chain complexes from the ER, perhaps as a result of ER–mRNA delivery and anchoring to distal sites where localized signals (i.e. ligand-mediated extracellular signals) could effect translation initiation.

**Mechanisms of ER–mRNA interactions**

Direct observation by microscopy has also provided evidence for ER–mRNA interactions and has revealed several insights into the mechanisms by which these associations occur.

**Motif-based mRNA targeting to the ER** In plants, mRNAs encoding Oryza seed storage proteins – prolamines and glutelins – target and anchor to separate and distinct ER sub-domains via separate RNA-based mechanisms involving sequences in their coding regions and 3’UTRs [46,47]. Prolamine mRNAs localize to ER-derived prolamine-enriched bodies known as type-I protein bodies, whereas glutelin mRNAs are targeted to the cisternal (or cortical) ER. The separation of storage proteins is important because their physical properties affect aggregation and storage body formation, and distinct RNA trafficking pathways to the cER sub-domains are needed to prevent non-productive interactions from occurring between the newly synthesized proteins. Both glutelin and prolamine mRNAs have cis motifs (zipcodes) that determine mRNA localization and the site of storage protein synthesis. These pathways are both hierarchical and independent of the constitutive targeting of mRNAs (encoding other secretory proteins) to the ER. For example, substitution of the prolamine 3’UTR with that of glutelin is sufficient to redirect targeting and protein synthesis to the cER [48]. Similar mechanisms operate with other plant storage proteins, such as maize zeins, which associate with type-I bodies,
whereas maize legumin mRNAs associate with cER [49].
Thus, RNA targeting to the ER is readily used in plants to
differentiate storage body formation from the cER.

In Ascidians, numerous maternal mRNAs, such as
macha and posterior end mark (PEM) 1–9 mRNAs, associ-
ate directly with cER in ascidian (i.e. Ciona sp., Halocynthia sp.)
zygotes during formation of the posterior pole, and co-partition with cER during mitosis to the
vegetal blastomeres [50,51]. How these mRNAs associate
with the cER and become polarized is not entirely under-
stood, but also seems to involve zipcode sequences present
in their 3′UTRs. For example, injection of the 3′UTR
of macha linked to a reporter molecule is sufficient for
localization to the vegetal pole in Xenopus [52]. Thus,
and ER-retained proteins (i.e. Eph2A, Integrin-
a3, grp78/
BiP) in axons and dendrites [26,27,53–55], as well as the
presence of rRNA and protein, and ER therein [12,13,32–
37], as discussed previously. Moreover, the data suggest
that motifs that facilitate the localization of these mRNAs
to ER membranes will probably be found. Notably, a recent
study demonstrated that a subunit of the COPI coat com-
plex, which mediates several intracellular transport steps,
aids in the localization and transport of k opioid receptor
mRNA in the axons of dorsal root ganglia (DRG) neurons
[56]. This result implies a potential role for membrane
transport in mRNA delivery in mammalian cells and also
that motifs might target mRNAs to sites of COPI vesicle
formation.

Membrane trafficking and mRNA co-transport
Definitive examples of ER–mRNA co-trafficking come from studies
using the budding yeast, Saccharomyces cerevisiae. ASH1
mRNA, which encodes a transcriptional repressor involved
in cell-fate determination, is polarized to newly forming
daughter cells to enable local translation of Ash1 protein
and the suppression of mating-type switching [9,57].
Earlier work demonstrated a connection between defects
in intracellular protein transport and the subsequent
mislocalization of ASH1 mRNA [58,59], and recent
studies reveal that ASH1 mRNA associates tightly with
cER, based on fluorescence microscopy and cell
fractionation studies [44,60]. Other polarized mRNAs,
such as those encoding polarity and secretion factors (i.e.
SRO7, SEC4, CDC42), were also found associated with
cER structures [44] (Figure 3). This ER–mRNA association
is dependent on She2, an RBP involved in polarized mRNA
transport [9,57], Myo4/She1, a type V myosin involved in
mRNA transport and the delivery of cER to the growing
bud [57,61,62] and Sec3, an exocyst component involved in
cER anchoring to the bud [45,62,63]. The deletion of SHE2
led to the dissociation of ASH1 mRNA from the cER, but
not nuclear ER [44,60], whereas the deletion of SEC3
resulted in a complete loss of binding to ER membranes
[44]. Notably, a loss of She2, Myo4/She1, or Sec3 function
mislocalized all bud-targeted mRNAs to the mother cells
and caused their dissociation from cER membranes [44].
Although She2 and Sec3 both have a role in polarized
mRNA delivery and anchoring to the cER, only Sec3 has
been shown to affect cER entry into the daughter cell and
the fusion of secretory vesicles at the site of exocytosis.
Thus, Sec3 is involved in multiple cellular functions
leading to cER–mRNA trafficking and exocytosis. Some
functions could relate to specific Sec3 interactions with Rho
family GTPases involved in actin regulation (i.e. Cdc42,
Rho3) or as an exocyst component involved in the docking
of secretory vesicles at the cell surface [63]. Alternatively,
the cER–mRNA trafficking functions of Sec3 could be
independent of previously described interactions.
Because SHE2 overexpression compensates for the loss
of all Sec3 functions (R. Gelin-Licht and J.E.G.,
unpublished), it would appear that She2 also confers
multiple functions in cER–mRNA transport in yeast.

Figure 3. cER–mRNA co-localization in yeast. SRO7 mRNA (green label) in yeast
cells can be visualized using fluorescence microscopy by using a bacteriophage
RNA-binding protein (MS2-CP) fused to GFP (e.g. MS2-CP–GFP). On induced
expression in yeast, MS2-CP–GFP binds directly to SRO7 mRNA that has been
modified with MS2-CP binding sites inserted between the coding region of
SRO7 and its 3′UTR. MS2-CP–GFP-labeled SRO7 mRNA is seen as a granule that localizes
at the tips of newly forming daughter cells. The co-localization of SRO7 mRNA and
cER membranes can be observed using Sec63-RFP (red fluorescent protein) as an
ER marker protein (red label). Note that the GFP signal overlaps with cER present in
the small buds and not with the perinuclear ER visible in some of the mother cells.
The white tracings indicate the outlines of cell shape (i.e. position of the cell wall).
kinesin, respectively) and RBPs (i.e. Staufen) [9,11,64]. Interestingly, other polarized mRNAs, such as grk (grk), encode secreted proteins that form morphogen gradients and facilitate embryonic patterning [64]. Thus, one might predict that translational control of localized messages encoding either secreted or membrane proteins, such as grk or bitesize [65], would necessitate elements that mediate ER–mRNA associations. Indeed, grk mRNA localizes to ER exit sites (known as transitional ER, tER) that are associated with Golgi to form specific tER–Golgi units located at the dorso-anterior corner of stage 9–10 oocytes [66]. The sorting and secretion of Grk, a transforming growth factor-α (TGFα)-like molecule, is also blocked by mutations in cornichon, an ER protein necessary for export. Thus, grk mRNA localization dynamics and ER sorting affect dorso-ventral patterning. More recently, a screen for mutants in embryonic axis formation identified trailer hitch (tral) as another gene responsible Grk protein trafficking and subsequent dorso-ventral patterning [67]. Although microtubule (MT) polarity is unaffected and grk mRNA neither mislocalized nor translationally repressed in tral mutants, Grk-containing puncta were not localized to ER exit sites. Tral mutants showed additional defects in ER exit-site formation, as revealed by Sar1 (an initiator of COPII vesicle formation) mislocalization, as well as defects in the trafficking of another secreted protein, the YI vitellogenin receptor [67]. Notably, Tral protein localizes to the ER in oocytes and concentrates at the ends of tubules that are reminiscent of cER. Moreover, protein-interaction experiments [67] revealed that Tral binds to a complex involved in mRNA metabolism, including an eIF4E-binding protein (Cup), a poly(A) binding protein (PABP), an RBP (Yps), and an RNA helicase (Me31B). This Tral-containing complex also binds to mRNAs encoding proteins involved in tER formation, namely sar1 and sec13, although grk mRNA itself was not bound. Thus, changes in the regulation of mRNA metabolism and translation in the dorso-anterior corner of oocytes could lead to local changes in COPII vesicle and tER formation and affect patterning. Together, these results demonstrate direct connections between mRNA localization, a cytoplasmic mRNA processing complex and ER exit-site formation. Another recent study demonstrated that the long isoform of Oskar (whose cellular localization at the posterior pole is mRNA-dependent) targets to endocytic membranes and facilitates asymmetric actin filament formation and clathrin-mediated endocytosis [68]. In addition, other works have shown that Rab proteins (small GTPases involved in endomembrane transport) are necessary for oocyte polarization by affecting oskar mRNA localization [69–71]. These diverse studies strongly reinforce the idea that targeted mRNA localization and translation necessitates co-trafficking of the translational machinery (i.e. ER) and a functional secretory pathway.

In amphibians, vegetal cortex-localized mRNAs associate with ER membranes and aid in both axis and germline formation. For example, *Xenopus* Vg1 mRNA, which encodes a TGFβ-like molecule similar to *Drosophila* Grk, tethers to ER present in a wedge-like structure rich in both mitochondria and RNA at the vegetal cortex of stage II–III oocytes [72,73]. Vg1 mRNA co-localizes with ER markers (i.e. TRAPs and GRP78/eI3P) and associates with Vera/Vg1 RNA-binding protein (Vg1RBP), the *Xenopus* ortholog of ZBP1 that is present in ER-enriched fractions and necessary for mRNA localization [74,75]. In addition, cER sub-domains trap germ plasm mRNAs (i.e. Xcat2, Xdazl) to the mitochondrial cloud region of stage-1 oocytes, before delivery to the vegetal cortex [73,76,77]. Thus, cortex-localized mRNAs might follow distinct localization pathways, although ultimately both Vg1 and germ plasm mRNAs co-distribute with Vera/Vg1RBP and ER membranes at the vegetal pole.

Given the wealth of evidence obtained from a wide variety of different organisms it seems likely that ER–mRNA associations involved in localized mRNA translation are evolutionarily conserved and have a role in spatial responses to cellular signals both internal (i.e. yeast cell division) and external (i.e. neuronal stimulation by neurotrophic factors).

**Delivering ER (and the message!)**

The movement of mRNA and formation of cER both involve dynamic regulation of the cytoskeleton. Thus, it is not surprising that actin- and microtubule (MT)-based transport systems are both implicated. The ER can form flattened sheets, interconnected cisternae and tubules that emanate from the nuclear periphery to form the polygonal network of smooth ER that constitutes the cER [62,78,79]. ER tubules themselves undergo active morphogenesis, extending into areas of polarized growth, such as yeast daughter cells, nerve growth cones and the leading edges of motile cells. This process is multi-stage, requiring the linear extension of tubules, anchorage at the sites of polarized growth and formation of a uniform reticulated network. Thus, it is of great importance to understand the mechanisms that underlie mRNA and ER co-transport.

In animal cells, smooth ER tubules extend to the cell periphery along MT-based transport networks *in vivo* and can reconstitute a meshed tubular network *in vitro* [62,78,79]. Likewise, cER networks can collapse into cell interior on MT disruption using either de-polymerizing agents or antibodies. MT-dependent ER movement to the cell exterior and interior is dependent on plus- and minus-end directed motor proteins, that is kinesin and dynein, respectively. Thus, the association of motor proteins with the ER probably constitutes the driving force behind directional ER motility and tubule formation. In addition to molecular motors, several proteins have been shown to mediate MT–ER interactions, ER tubule extension and the formation of curved cER structures (e.g. CLIMP-63, huntingtin, p22, VAPs, reticulons and DIP/Yop1). ER-associated proteins involved in MT attachment include: CLIMP-63, which binds MTs and anchors them to tubular ER membranes in a cell-cycle-dependent fashion, Huntington’s disease protein (huntingtin), a palmitoylated MT- and dynactin-interacting protein that associates with ER membranes and p22, a myristoylated Ca2+- and MT-interacting protein that regulates MT bundling [79–81]. Notably, either the knockdown of, or interference with, any of these proteins results in strong defects in ER organization and reticulation. ER proteins conserved from simple eukaryotes, such as yeast, also have a role in network
organization. They include the ER-localized VAP proteins, which interact with phosphatidylinositol transfer proteins of the Nir family [79,82], and proteins belonging to the reticulon/Nogo and DP1/Yop1 families [78,83,84]. The latter are notable in that they bear two transmembrane domains flanking a hydrophilic hairpin loop that might impart positive curvature to the outer-leaflet of cER membranes and, thus, yield its tubular appearance [78,83,84]. Interestingly, aberrant localization of reticulon/Nogo family members to the cell surface inhibits axonal growth in mammals and might have a significant role in neurodegeneration [85].

In yeast and plants, ER tubules in the cytoplasm also extend into areas of new growth, however, in contrast to animal cells they use actin- and myosin-based membrane transport to create the cER network [62,84]. The movement of smooth ER in insect and animal cells also necessitates the actin cytoskeleton. For example, dilute-lethal mice lack a functional myosin Va necessary for ER (and mRNA) movement into dendritic spines in neurons [62,86,87]. In yeast, the inheritance of cER into the bud is mediated by several factors, including the reticulons (Rtn1–4) and Yop1, which function together to maintain cER organization [84]. Interestingly, Rtn1 associates with Yip3, which interacts with Rab GTPases [88] and suggests that ER membrane curvature might be connected to Rab function and vice versa. Rtn1 also interacts with Sec6 [89], another exocyst component shown to have a prominent role in cER inheritance [45,90]. Other proteins involved in cER inheritance include Ptc1, a phosphatase that regulates a MAP kinase cascade involved in cell wall remodeling [91], and Ice2, a membrane protein whose deletion results in defects in cER inheritance [92]. Given the recent demonstration of Sec3 involvement in mRNA localization [44], it seems likely that all mutations affecting cER inheritance should affect polarized mRNA placement. Some of these components might have a direct role in RNP anchoring to the ER and, perhaps, in connecting RNP-binding to cER tubule formation.

Although few studies have examined both mRNA localization and disposition of the ER under conditions of disturbance of ER organization, numerous reviews have documented the role that MTs and kinesin/dynein motors have in mRNA transport in neuronal processes and in both Drosophila and Xenopus oocytes, as well as the role actin and type V myosins have in mRNA transport in axons and dendritic spines, the leading edge of fibroblasts and yeast [9,10,18,22,33,64,72,87]. Thus, defects in shared components involved in mRNA–ER trafficking are expected to lead to mRNA mislocalization and disorganization of the cER network. Indeed, mutations in a type V myosin greatly affect both cER inheritance and polarized mRNA transport in yeast [44,61,62], and smooth ER delivery and mRNA transport into dendritic spines [62,86]. Similar effects are also observed in cells treated with drugs that interfere with actin assembly. Thus, mRNA and ER transport from yeast to mammals seems to employ a shared common mechanism.

Concluding remarks – Lex parsimonioae

Although it remains possible that ER and mRNA trafficking are, in principle, separate events that use the same intracellular transport machinery, it seems far more likely that they are interconnected processes (Figure 1c), based on the multiple lines of evidence presented in this review and the application of Occam’s razor. Use of Occam’s razor would suggest that targeted ER–mRNA trafficking is the most efficient means of regulating intracellular protein concentration in a spatial and temporal manner, in response to either internal or external stimuli. Studies using fluorescent markers to simultaneously monitor ER dynamics, mRNA trafficking and nascent chain labeling in vivo should help demonstrate the veracity of this hypothesis. Similarly, the identification of ER proteins that act as anchors for mRNA-containing RNP’s should help unravel the mechanism of ER–mRNA co-transport.

Acknowledgements
The author would like to thank Rita Gelin-Licht and Eitan Bibi for fruitful discussions and critical reading of the manuscript, as well as the editor, Katherine Giles, and specialist reviewers for their helpful suggestions. This work was supported by a grant from the Kahn Center for Systems Biology, Weizmann Institute of Science, Israel. J.E.G. holds the Henry Kaplan Chair in Cancer Research.

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