



Endoplasmic reticulum – condensate interactions in protein synthesis and secretion

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Abstract

In the past decade, a growing amount of evidence has demonstrated that organelles do not act autonomously and independently but rather communicate with each other to coordinate different processes for proper cellular function. With a highly extended network throughout the cell, the endoplasmic reticulum (ER) plays a central role in interorganelle communication through membrane contact sites. Here, we highlight recent evidence indicating that the ER also forms contacts with membrane-less organelles. These interactions contribute to the dynamic assembly and disassembly of condensates and controlled protein secretion. Additionally, emerging evidence suggests their involvement in mRNA localization and localized translation. We further explore exciting future directions of this emerging theme in the organelle contact site field.

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Introduction

Compartmentalization is a distinguishing feature of eukaryotic cells, in which various highly regulated biochemical processes are spatiotemporally executed within a crowded environment. This organization is achieved by partitioning the intracellular space into distinct compartments consisting of membrane-bound

organelles and less well-characterized non-membrane-bound compartments. The correct spatiotemporal organization of cellular processes is essential for cellular function. In highly polarized cells, such as neurons, maintaining this compartmentalization is likely more challenging and must require tight regulation to ensure domain-specific tasks.

The endoplasmic reticulum (ER) plays a particularly central role in cellular compartmentalization. It is the largest dynamic membrane compartment that consists of interconnected structural subdomains, including reticulated tubules and flat cisternal sheets [1]. Constant remodeling and structural reorganization of the ER facilitates multiple biological processes, including protein and lipid synthesis, and calcium homeostasis [1]. Contacts between the ER and other membranous compartments at membrane contact sites unveil additional roles of the ER in the regulation of organelle dynamics and functions. These membranous organelles, in turn, can independently or coordinately regulate the distribution, morphology, and dynamics of the ER. These complex and essential interactions between the ER and other membrane-bound organelles have been recently reviewed [2–4].

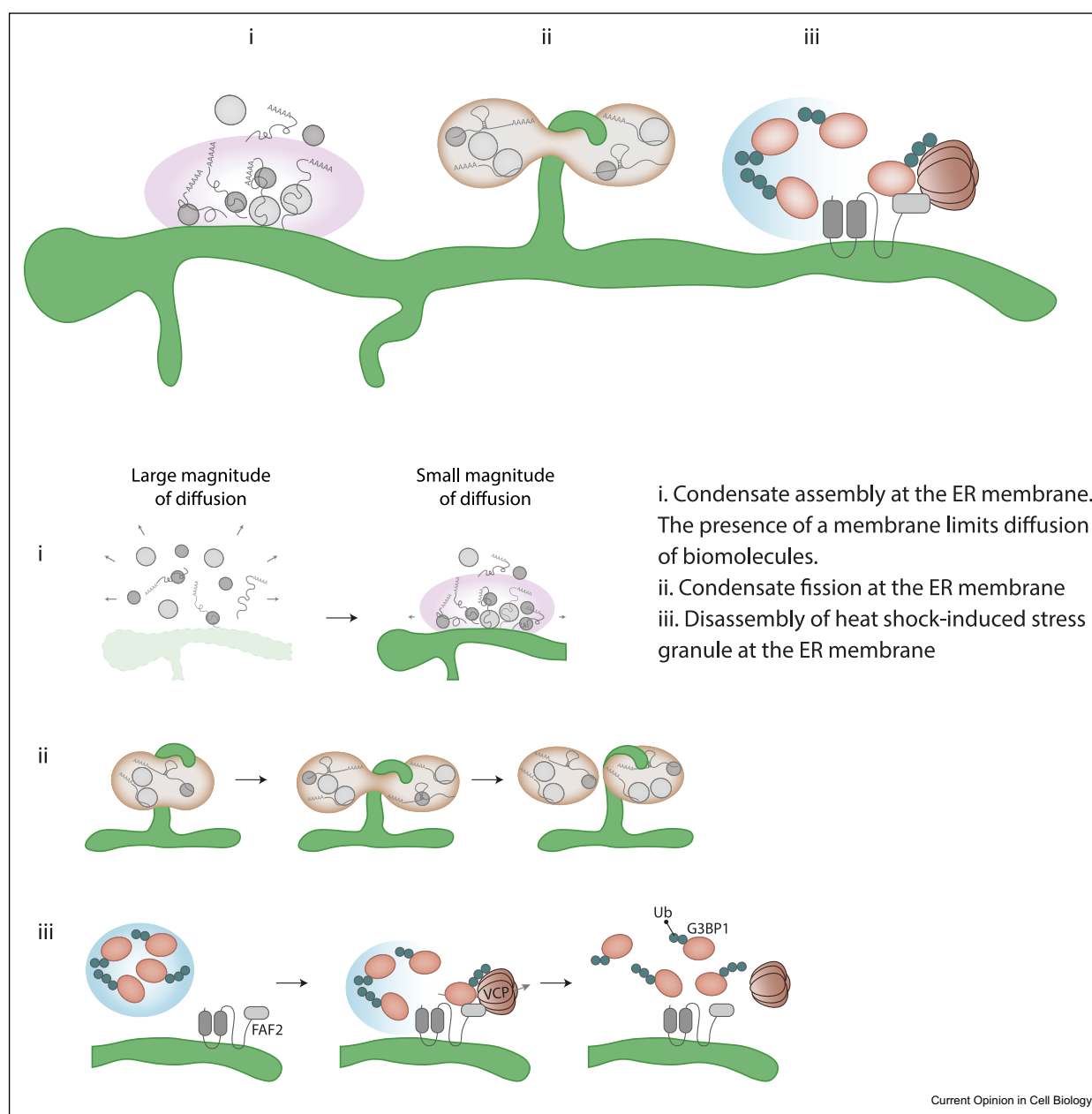
Intriguingly, the ER also interacts with organelles lacking a limiting membrane. These membrane-less organelles or condensates exist as confined compartments for spatiotemporally tuned reactions and biochemical activities, which contribute to cellular fitness [5]. A rapidly increasing amount of evidence indicates that dysregulation of membrane-less organelle dynamics is involved in disease development [6,7]. Unlike membrane-bound organelles, little is known about the interactions between membrane-less compartments and the master communication hub of the cell, the ER. Emerging evidence indicates that the ER is a platform for condensate formation, dynamics, and disassembly. At the same time, the recruitment of condensates to the ER membrane can regulate ER functions such as mRNA localization, localized translation, and secretion. These recent advances, highlighted here, have thus far been mainly addressed in unpolarized cells and for just a few membrane-less organelles and open new questions and venues to understand the role of these interactions in health and disease.

The ER regulates the biogenesis, size, and disassembly of membrane-less organelles

Membrane-less organelles form by liquid-liquid phase separation, a process in which biomolecules, including proteins and nucleic acids, undergo dynamic self-assembly into condensates within cytoplasmic or

nucleoplasmic environments [5]. The liquid nature and the absence of a limiting membrane allow these condensates to quickly exchange molecules with the surrounding environment and enable greatly dynamic features that allow them to assemble, fuse, undergo fission, and disassemble in response to various signals

Figure 1



Interactions between the ER and membrane-less organelles and their role in condensate dynamics. (i) The ER membrane facilitates and regulates condensate formation by locally concentrating proteins and reducing their diffusion. Size and the number of gray arrows indicate magnitude of diffusion. (ii) Stress granules (SGs) and P-bodies can undergo fission at the ER to regulate their size. (iii) Ubiquitin-dependent disassembly of heat-shock-induced SGs at the ER membrane. ER-resident protein FAF2 recruits ubiquitinated SG-localized G3BP1 and the ATPase VCP to the ER surface and facilitates their interaction. This allows VCP to extract ubiquitinated G3BP1 from SGs, leading to SG dissolution. Abbreviations: SG = stress granule.

[8]. In recent years, membrane surfaces have started to arise as an important regulatory platform for the formation of condensates, raising the possibility that the ER—the largest cellular membrane—can control the assembly, dynamics and dissolution of membrane-less organelles.

Studies in yeast and fungi have shown that different biomolecular condensates localize in the vicinity of the ER and are tightly associated with the ER membrane [9,10]. A recent study by Snead *et al.* proposed that the ER membrane provides a means to reduce protein diffusion and concentrate proteins, which facilitates and controls condensate formation (Figure 1) [10]. In mammalian U-2 OS cells, cytoplasmic RNA condensates were also found to frequently contact the ER membrane. Around 60% of all P-bodies (PBs) interact with the ER, from which ~40% and ~20% are stably or dynamically associated to the ER, respectively [11]. It remains elusive whether PBs that do not contact the ER represent another subpopulation harboring different properties, or whether PB size can instruct its recruitment to the ER membrane. Interestingly, PBs were found to undergo fission in contact with the ER to regulate PB size (Figure 1) [11]. The association and possible biogenesis of stress granules (SGs) at the ER membrane have also been reported [11,12], and SG fission at the ER was observed upon relief after sodium arsenite stress [11]. This suggests a role for the ER in SG disassembly by facilitating SG size reduction. A different mechanism by which the ER controls SG disassembly was recently shown. This involved the ER-resident protein FAF2/UBXD8 that recruits both ubiquitinated G3BP1, a core SG component, and the ATPase VCP to the ER surface. This allows the ubiquitin-dependent extraction of G3BP1 from heat-shock-induced SGs by VCP to promote SG disassembly (Figure 1) [13].

Regulating SG size and disassembly could be critical for translational regulation [14,15], and ER–SG interactions could thus play an essential role in maintaining a healthy SG life cycle. Moreover, disturbed disassembly and alterations in physical properties and content of SGs have been heavily implicated in disease pathology [6,7]. Future studies are required to fully elucidate the functional consequences of disturbed ER–SG or ER–PB interactions in cells, which may provide new insights into the enigmatic physiological functions of these condensates.

Although tethering proteins involved in membrane-bound organelle–organelle interactions are well known [2,4], the molecular players that mediate and regulate the contacts between the ER and membrane-less organelles such as SGs or PBs remain completely unknown. A recent study found that VAPB, a key tethering protein involved in membrane-bound contact sites is

also involved in the recruitment of another condensate, the IRS-1 signalosome, to the ER [16]. Identifying key regulators of these ER–condensate interactions will help to understand the functions of these contacts.

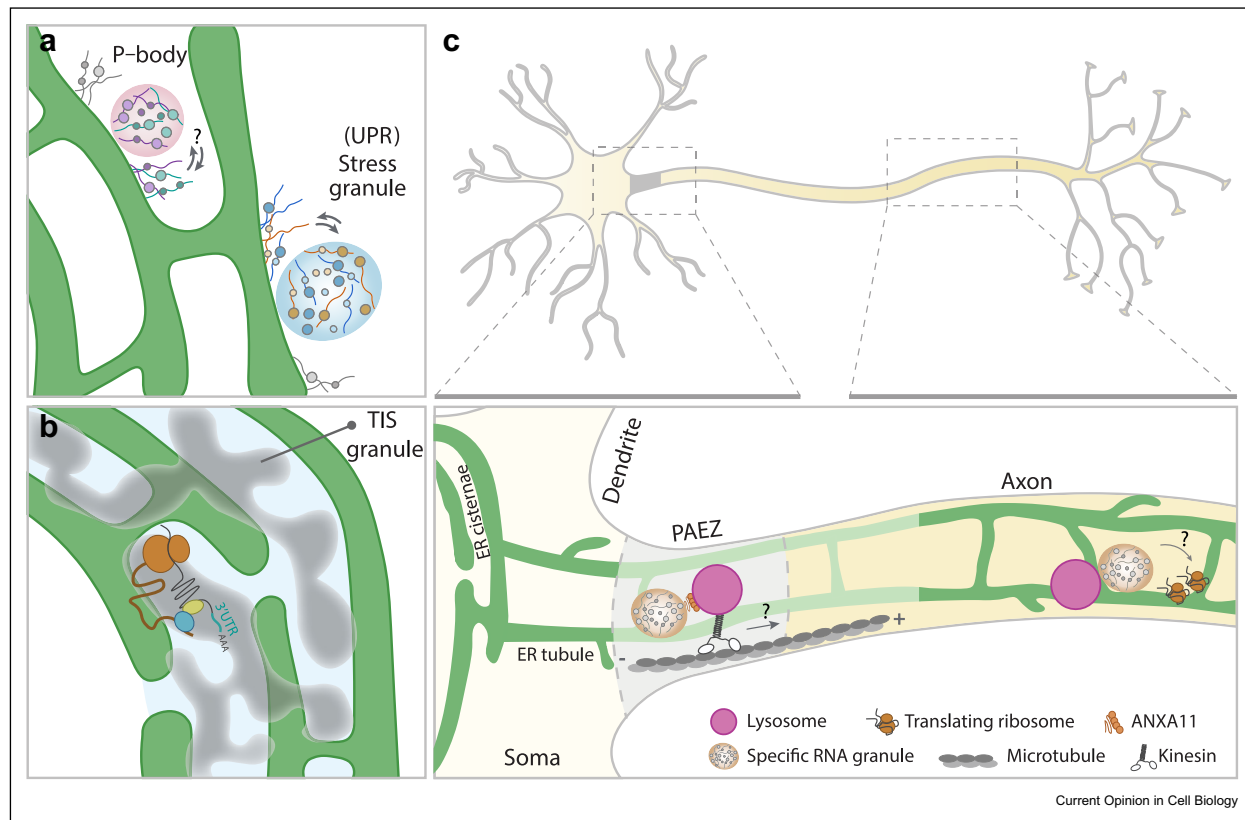
Together, these studies reveal a potentially essential role of the ER membrane in the life cycle of biomolecular condensates by controlling their biogenesis, size, and disassembly. Considering that different condensates differ in their composition, functions, physical properties, and dimensions [17], it remains to be explored if distinct sets of proteins and/or RNAs control their biogenesis, dynamics, and dissolution, in association with the ER. It will also be intriguing to understand if various stimuli and stress factors regulate these contacts differently. These recent advances come from evidence in unpolarized cells, and it remains largely unknown if highly polarized cells such as neurons possess similar or different mechanisms to regulate ER-dependent condensate assembly, size, and disassembly. SG composition is known to differ between cell types and can have subcellular variation in neurons [18]. Moreover, it is possible that the unique subcellular organization of the ER in neurons [19] locally affects condensates dynamics.

ER and condensate contacts in mRNA localization and localized translation

Cytoplasmic biomolecular condensates such as SGs, PBs, and neuronal RNA transport granules are functionally linked to mRNA localization and (localized) translation. The studies discussed earlier therefore render it highly likely that ER–condensate contacts play an important role in mRNA localization and local translation.

PBs have been suggested to be sites for mRNA storage and decay [20,21]. PB number and their contact with the ER is altered by changes in ER shape [11]. PBs were found to interact with ER tubules, which are presumed to possess a lower translational capacity than ER sheets. This suggests a relationship between translation capacity and ER–PB interactions. In accordance with this observation, translation inhibition remarkably promoted PB biogenesis and their association to the ER [11]. It remains unknown how ER-tubule-mediated PB contact and fission is mechanistically and functionally linked to translation capacity and what the consequence is on PB function. An intriguing possibility is that the ER regulates PB content and properties by allowing exchange of proteins and/or mRNAs at contact sites (Figure 2a). This may contribute to which mRNAs are translated, stored, or destined for mRNA decay. Two recent studies raise the possibility that mRNA exchange also occurs between the ER and SGs (Figure 2a). First, relocalization of a subset of membrane mRNAs to granules was observed upon unfolded protein response (UPR) activation, whereas other membrane mRNAs remained ER

Figure 2



Regulation of mRNA localization and localized translation through ER-membrane-less organelle contacts. (a) Exchange of mRNAs between the ER and stress granules (SGs) and P-bodies (PBs) at ER-condensate contact sites. Only specific subsets of mRNAs (colored mRNAs) might be selectively exchanged, whereas others (gray mRNAs) are retained at the ER. **(b)** The formation of ER-associated TIS granules allows an enrichment and translation of membrane-protein encoding mRNAs. This mRNA subset contains multiple AU-rich elements in their 3'UTR, which facilitates specific 3'UTR-mediated protein-protein interactions and confers such encoded membrane proteins diverse functions. **(c)** The ER may regulate mRNA trafficking into neuronal axons by controlling lysosome-mediated RNA transport granule hitchhiking. In the axon, contacts between RNA-transport granules and the ER may control localized disassembly and translation. Abbreviation: PAEZ = pre-axonal exclusion zone.

membrane-associated [22]. Analysis of mRNA characteristics revealed that transcript length, 3'UTR length and AU content are positive predictors of mRNA recruitment to SGs [22]. Second, selective recruitment of specific ER-targeted and cytosolic mRNAs into ER-associated SGs was observed upon stress-induced UPR activation [12]. Interestingly, localization of mRNAs to the ER itself or specific ER subdomains can also be regulated by the 3'UTR of mRNAs [23–25]. Whether the recruitment of these ER-localized mRNAs to SGs is for storage or to regulate the translation of essential stress-responsive genes remains to be studied. In addition, it remains unclear whether two functionally and compositionally distinct SG populations (cytosolic and ER-associated) coexist.

The recent discovery of the TIS granules represents another intimate link between the ER and biomolecular condensates [26]. TIS granules, marked by the RBP

TIS11B, form a gel-like condensate meshwork around the rough ER and provide a specialized environment that enables the translation of specific mRNAs (Figure 2b) [26]. A wide range of mRNAs, including cytosolic mRNAs, are present and can be translated at the rough ER and in TIS granules [27]. Whether mRNA exchange between the ER and TIS granules occurs or how mRNA content and translation in these compartments is affected by physiological conditions and stimuli remains unknown.

Regulation of mRNA localization and local translation is essential for proper cellular function and is arguably more crucial in polarized cells. Increasing evidence from polarized cells suggests that, besides the rough ER, mRNA localization and local translation also occurs at ER tubules. In the mouse preimplantation embryo, RNA foci were observed to be closely associated with ER tubules along with translation initiation factors in apical

regions, which show a higher translational activity [28]. In neurons, ER tubules, which extend into the long axon, were frequently found to associate with ribosomes and regulate local axonal translation [29]. While there is thus far only limited evidence of an association between mRNA and the axonal ER [30], the presence of ribosomes and occurrence of translation on axonal ER tubules means that mRNA is present and suggests that RNA granule binding at ER tubules in polarized cells can also occur (Figure 2c).

It is well known that mRNA localization into axons and dendrites is mediated by membrane-less RNA transport granules [31]. The possible interaction between the neuronal ER and RNA transport granules suggests that this may regulate mRNA localization. Based on several recent studies, a picture may emerge, in which a complex interplay between these RNA transport granules, the ER, and lysosomes could play a pivotal role in mRNA localization. At least, a portion of neuronal RNA transport granules are trafficked into the axon via endolysosome- or mitochondria-mediated hitchhiking [30,32,33]. In neuronal cell bodies, ER tubules regulate the entry of lysosomes into the axon [34]. Together, this suggests that the ER could play a similar role for RNA transport granules, either directly or via regulation of organelle hitchhiking (Figure 2c). Interestingly, a recent elegant study in U-2 OS cells showed the presence of lysosomes at three-way junctions of ER tubules to support the local synthesis of transmembrane and secretory proteins by supplying amino acids [35]. It is tempting to speculate that lysosomes also deliver mRNAs to these ER sites via RNA granule hitchhiking. In neurons, this leads to the possibility that in the axon, a complex interaction between the ER, lysosomes, and RNA granules is involved in regulating localized translation (Figure 2c).

Deciphering the molecular workings of this intricate interplay between the ER, RNA condensates, and other organelles and investigating how this is affected by external stimuli may provide crucial insights into the precise regulation of the subcellular localization and translation of mRNAs.

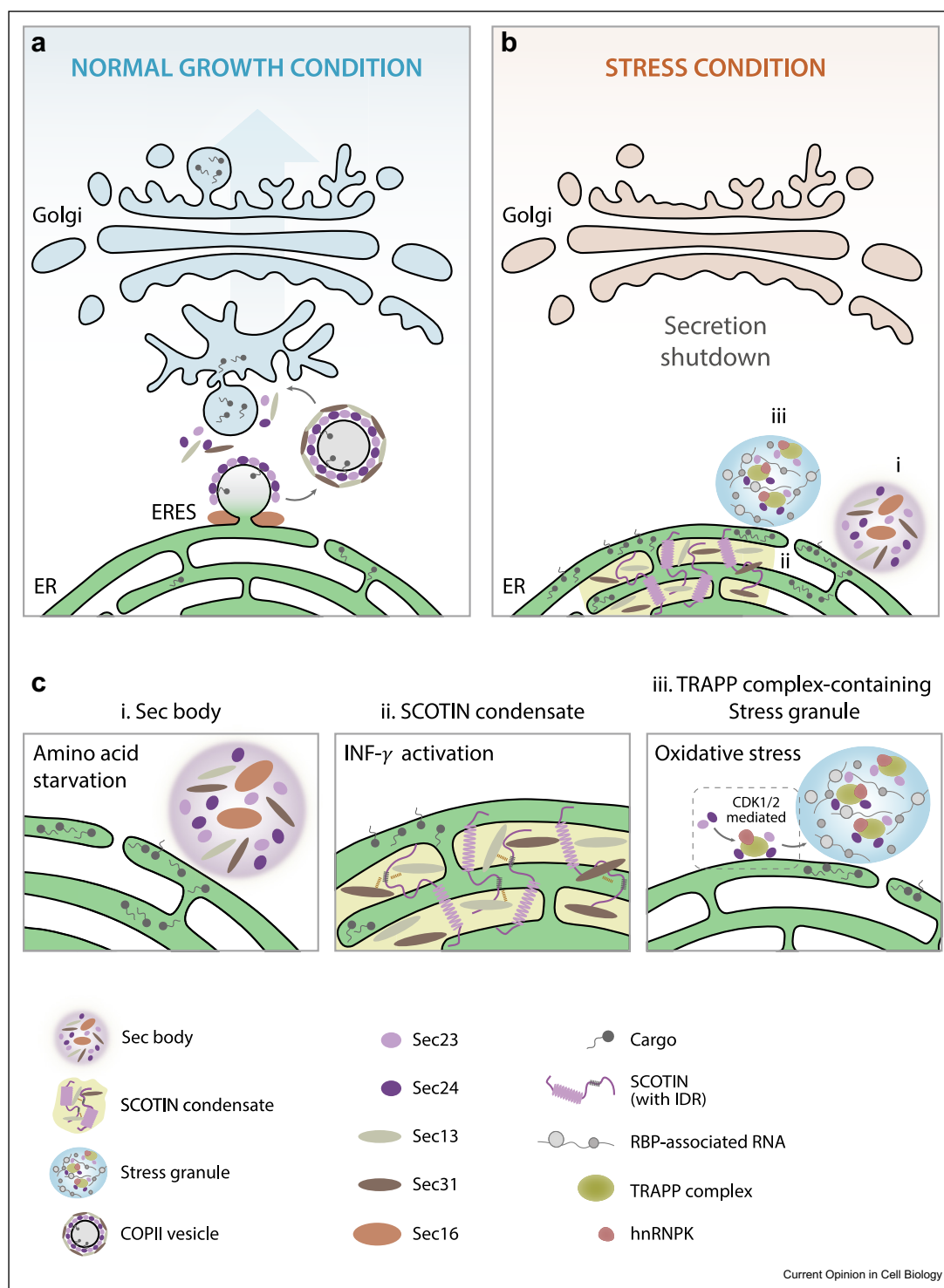
ER-associated condensates in neosynthesized protein secretion

ER-exit-sites (ERESs), subdomains of the ER membrane, involved in the secretion of transmembrane and secretory proteins, have also been recently linked to condensates. Initial studies in *Drosophila* S2 cells reported the inclusion of several ERES proteins into membrane-less organelles called Sec bodies, upon amino acid starvation [36]. A recent study found that these Sec bodies also form in mammalian secretory cells such as insulin secretory cells and developing neurons [37]. These membrane-less organelles form by fusion of ERESs and were in close proximity to the ER membrane [37]. The ERES protein Sec16A, containing an

intrinsically disordered region, is responsible for the formation of these large condensates [36,37]. Most ERES components are contained in these Sec bodies (Sec16A/B, Sec23, Sec24, Sec13 and Sec31, but not Sar1). Intriguingly, the formation of these large structures is restricted to a few cell types, which are highly secretory in nature. Sec bodies may form to protect ERES components from degradation upon stress, but the formation of these assemblies could also mediate secretion inhibition. The fusion between ERESs to assemble Sec bodies has been shown to precede secretion inhibition and appears to deplete the number of functional ERESs (Figure 3) [37]. Mysteriously, the formation of these large Sec bodies is stress-specific, suggesting that specific and undefined signaling pathways are involved. It remains unknown whether smaller Sec bodies could play any role in regulating protein secretion. Another recent study in HeLa cells found that SCOTIN, an interferon-inducible transmembrane protein of the ER forms condensates sequestering ERES components such as Sec31 and Sec13 but not Sec16 or Sec24 into SCOTIN condensates. The recruitment of these ERES components into these condensates impairs protein secretion (Figure 3) [38]. An earlier study also found that sodium arsenite-induced stress in HeLa cells leads to the recruitment of the TRAPP complex and the ERES components Sec23 and Sec24 into SGs. The TRAPP protein TRAPPC2 was required for this recruitment. The relocation of these two ERES components was mainly observed in highly proliferating cells and was dependent on cyclin kinases CDK1/2 (Figure 3) [39]. Intriguingly, mutations in the TRAPP complex cause different neurodevelopmental disorders, affecting nondividing neurons [40]. It is puzzling why in different cell types and upon different stressors, different ERES components are sequestered into distinct condensates. It appears that no matter what the cell status or external stimuli is, the ERESs are highly regulated by phase separation in order to control protein secretion at the ER. Interestingly, the ERESs themselves have been found to phase separate in normal conditions, and this liquid-like state is essential for their function in protein secretion [41]. How their condensate formation and composition is regulated in basal conditions and reorganized upon stress conditions remains an open question. Recent studies have revealed that a dynamic equilibrium between the kinase DYRK3 and serine/threonine phosphatases is required for Sec16 phase separation and manganese-tuning controls Sec23/24 condensation [41,42].

A more complex interplay between protein secretion and RNA granule assembly could be also speculated. Previous evidence has shown that mutants of the secretory pathway components induce PB assembly [9]. The exact link between RNA granule assembly and ER-associated protein secretion machinery remains unclear. The close proximity of membrane-less organelles such as Sec bodies, SGs, PBs, and other condensates to the ER

Figure 3



Roles of ER-associated condensates in secretion of neosynthesized proteins. (a) Trafficking of newly synthesized transmembrane and secretory proteins (cargoes) from the ER to intermediate compartments and the Golgi apparatus in normal growth condition. Protein cargoes are packaged into COPII vesicles at ER-exit sites (ERESs). (b) Under certain stress conditions, shutdown of protein secretion occurs due to sequestration of ERES components into different membrane-less organelles, including (i) Sec bodies, (ii) SCOTIN condensates, and (iii) TRAPP-complex-containing stress granule. (c) Enlarged view of each condensate structure in contact with the ER membrane. Abbreviations: IDR = intrinsically disordered region.

would allow a fast adaptation to control and coordinate protein synthesis and secretion at the ER in basal conditions, upon stimuli or stress and stress-relief.

Future perspectives

Here we have highlighted recent studies revealing interactions between the ER and membrane-less organelles. This is an emerging theme in the contact site field as the focus has been on the contacts between two opposed membranes, with the ER playing a central role in interorganelle communication. In the past few years, we have acquired increased knowledge on the mechanisms governing membrane contact sites, as well as on their many roles in different cellular processes [2–4]. One of the most exciting developments regarding the interaction between the ER membrane and membrane-less organelles is the proof that this is not limited to one type of membrane-less organelle but seems to expand to many distinct condensates that form at or form contacts with the ER membrane. We are only starting to comprehend the significance of these interactions, with just a few known examples. Many questions emerge from these studies. For instance, what is the exact composition of the diverse membrane-less condensates in contact with the ER membrane? Is the composition of condensates associated to the ER different from the cytosolic ones? Which molecular players mediate these contact sites? What is the functional relevance of these interactions and how are they regulated by cellular state or external stimuli?

Novel proximity-labeling techniques such as split APEX, split-TurboID, and the recently developed TransitID could reveal the dynamic proteome associated to ER–condensate interactions [43–46]. Thus far, most evidence comes from overexpressed proteins, which can alter the assembly of condensates, and/or promote/inhibit contact formation. CRISPR technologies could help in the visualization of endogenous proteins, although it is not always feasible due to low protein expression levels and microscope detection limitations. The use of bimolecular fluorescence complementation approaches to study contact sites has allowed us to visualize dynamic interactions below 20-nm distance, but not all of them are reversible [11,47,48]. These new technological advances may reveal key players involved in the establishment and maintenance of these stable/dynamic interactions. In addition, they may elucidate the behavior of these contacts in basal conditions and in response to different external and internal cues or stress signals and clarify any cell-type specific or cellular domain-specific differences.

It is intriguing that in neurological disorders such as amyotrophic lateral sclerosis and hereditary spastic paraplegia, the organization and/or function of the ER and condensates are both dysregulated [31,49]. Increasing our knowledge on the functions and molecular players of

ER–condensate interactions could therefore help understand the etiology of these and possibly that of other human disorders.

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Declaration of competing interest

Nothing declared.

Data availability

No data was used for the research described in the article.

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