The Endoplasmic Reticulum-the caring mother of the cell

Anne Spang
Biozentrum, University of Basel, Klingelbergstrasse 70, CH-4056 Basel, Switzerland

Abstract

In eukaryotic cells, various cellular functions are compartmentalized and performed by sophisticated and specialized organelles. However, the membrane bounded organelles need to communicate with each other, the cytoplasm and sense the outside through the plasma membrane to coordinate various functions and to maintain cellular homeostasis. In order to maintain homeostasis, the information on the cellular state must be collected and appropriated responses must be initiated. The endoplasmic reticulum fulfills these functions. In this review, I will discuss various aspects on how the ER senses and relays information and acts to protect the cell, in what sometimes could be interpreted as an altruistic behavior.

Introduction - The endoplasmic reticulum as potential sensor and signaling platform

The well-being, in terms of fitness, of the cell needs to be assessed and closely monitored at all times. In addition, all the information gathered on the metabolic status, growth, etc. needs to be integrated at one point to be able to mount appropriate responses. But how does a cell sense that something goes wrong in one of its membrane constituents or sample what is happening on the outside of the cell? Of course, many signals are generated at the plasma membrane and intracellular organelles and are transmitted through the cytoplasm using different signaling cascades such as MAP kinases or TOR signaling [1,2]. Yet, in spite of being very important, they are not sufficiently well-equipped and connected to survey all organelles and the extracellular environment. In addition, the way signaling pathways are depicted in textbooks is to some extent misleading. Usually there is a signal, which results in the activation of a kinase (mostly depicted as a round sphere in the cytoplasm) followed by an arrow which points to the downstream target (a differently colored sphere in the cytoplasm) and so on, ending generally with a transcription factor in the nucleus (Figure 1). However, if the activated kinase has first to explore the entire cytoplasm to find its

substrate, the signal transmission would not be very efficient and not very fast. Locating the kinase and the substrate on the same membrane of an organelle would reduce the complexity of the time and space needed for signal relay. Nevertheless, this organelle must be able to stretch from the cell center up to the plasma membrane. The endoplasmic reticulum (ER) fulfils this function. The ER contacts every other organelle in the cell and the plasma membrane [3,4] (Figure 1). With its network-like –reticulate– appearance and its dynamic nature, the ER reaches every corner of the cell. Moreover, it has also outstanding access to the state of the nucleus through because of the continuity of the ER and the nuclear envelope and the ER lumen being just separated from the nucleus through the nuclear membrane. Finally, the ER is embedded in the cytoplasm and communicate with it as well.

The sensor system at the ER

Then the next questions are, if the ER acts as the senor of cellular well-being, how does it perform the sensing and how does it relay signals to react to changes in the environment, stress, loss of functionality and protein aggregation? The ER maintains a large array of contact sites with other organelles [4]. What are the minimal requirements for such ER-organellar contacts? First one would need something that enables and stabilizes the contacts, a tether. Second, the ER has to sense what is going on in the other organelles, so at least one type of sensor is required. This sensor could either sense something on the membrane of the contacted organelle, such as lipids, or the inside of the organelle through ions and the redox state. Third, the contacts should be able to mount a response in case something is wrong, thus some signal relay system is needed to recruit appropriate factors to contact sites, in the worst case the autophagic machinery to remove a damaged organelle or piece thereof.

The tether can be one protein or a protein complex, which are often anchored by a transmembrane domain to the ER and then reach out to the contacting organelle. It turns out that most tethers have built-in sensors. For example, in ER-plasma membrane (PM) contacts, ER-anchored extended synaptotagmins (E-Syts, TCBs in *S. cerevisiae*) stretch to the PM, where they bind to PI4,5P_2 to provide connections and concomitantly sense PI4,5P2 levels [5-8]. Thus, this interaction with the target organelle could either sense the lipid composition or spacing and hence the permeability of the bilayer. In response to

changes/insults, ER-localized lipid transfer proteins, such as oxysterol binding proteins and their relatives, which are recruited by VAP/Scs2/22, could counteract these changes [9]. For example, ORP5/8 can be recruited to contact sites and regulate the level of both PI4P and $PI4,5P_2$ at the plasma membrane [10]. Since the ER is also the major site of lipid synthesis, lipid production can be streamlined. In addition, E-Syts contain Ca^{2+}-binding domains and thus sense at the same time Ca^{2+} concentration, which induce a conformational change, and under high Ca^{2+}, reduces the distance between ER and PM by 50 % [11-13]. In yeast, it has been reported that lipid asymmetry is sensed by the Rim 101 signaling pathway, and that this pathway was constitutively activated when ER-PM contact sites were disrupted, which might provide either an alternative or backup pathway of sensing changes [14].
Another common component of contact sites appears to be ion channels on both sites of the contact. They function to allow the ER to potentially probe Ca^{2+} levels and balance them, if needed. In the case of the ER-mitochondria contacts, the ER-localized IP3R and SERCA would cooperate with mitochondrial VDAC, while at ER-endosomes IP3R and SERCA would liaise with TRP channels[15]. The corresponding pair at ER-PM contacts would be Orai1 in the plasma membrane and STIM in the ER [16,17]. These mechanisms provide the ER with a mean to sense the contacting organelle; in a rather similar way than it monitors the cytoplasm.

Moreover, the ER may use the contact sites to sense the redox state of the organelle in question. The best studied system here are the ER-mitochondrial contacts. The ER contains oxo-reductases such as ERp44 and ERO1α, which initially were thought to regulate disulfide bond formation in the ER [18,19]. However, more recent evidence suggests their presence in ER-mitochondrial contacts, suggesting that they may also sense the redox state of mitochondria [20]. In addition to sensing the redox state and to serve as a buffer- for both redox equivalents and Ca^{2+}-, the ER might also communicate with other organelles to elicit a response. For example, it has been proposed that at ER-endosome contacts, peroxiredoxin (ER) inhibits G-CSF signaling on early endosomes [21].

The various sensor systems for a particular organelle could be located in either the same sub-compartment or in different ones in the ER membrane. Given that in the yeast *S. cerevisiae* all ER-PM tethers -lipid sensors/exchangers and ion channels alike- must be

deleted to eliminate membrane contacts, may suggest that the sensors at contact sites can act independently and must not reside in the same sub-compartment. Moreover, knockout of all three E-Syts in mouse did not affect viability nor ER function [22]. Dependent on the state of the cell, different contacts may be spread to increase the sensing ability, but then may congregate upon insults to generate a stronger and faster response to the stress or imbalance. To achieve these dynamics, the cell requires modulators of contact sites, which would potentially control the size and the numbers of contacts. This process could be in analogy to processing bodies and stress granules, that form and change composition depending on the stressor the cell gets hit by [23,24]. The yeast StARkin family member Lam6 is present at multiple membrane contact sites and was proposed to regulate the extent of contacts [25]. StARkin proteins are evolutionary conserved lipid transfer proteins, indicating that local lipid composition changes might at least in part influence the size and number of contacts. In addition, such processes might be regulated by GTP-binding proteins. Small GTPases of the Arf/Sar and Rab families have been reported to impact contact sites [26-30]. Likewise, ER-mitochondrial contact sites appear to rely on the mitochondrial fission and fusion machineries, most notably the dynamin-like protein Drp1/Dnm1 and mitofusins. Their precise effect is still a matter of debate as for example mitofusin 2 has been proposed to either positively or negatively regulate ER-mitochondrial contacts [31,32]. Finally, organellar movement on the cytoskeleton influence contact site dynamics [26,33]. We are seeing just the tip of the iceberg and are still far away from understanding the complexity, number and dynamics of membrane contact sites. For an overview of membrane contact site components, I suggest as further readings [3,34].

The clearance system of the ER

Besides sensing the state of the cellular environment, the ER of course provides the environment to fold proteins and assemble protein complexes that resides either in membrane bounded organelles along the secretory and endocytic pathways or the plasma membrane. In this capacity, the ER acts also as a safeguard in that proteins that cannot be folded properly will be translocated into the cytoplasm for degradation in a process termed ER-associated degradation (ERAD)[35]. Depended on whether the misfolding happened on the cytoplasmic face of the ER, in trans-membrane domains, or in the luminal parts of client proteins, the regulation of the ERAD pathways seem to differ. Yet at the end, the misfolded

protein will be extracted from the ER through the help of an AAA ATPase, Cdc48/VCP, ubiquitinated and then brought to the proteasome for degradation. While a certain level of misfolding and hence ERAD takes place all the time, this response can be easily modulated and upregulated by the unfolded protein response pathway (UPR)[36]. There are at least three independent signaling pathways requiring the action of either PERK, AFT6 or IRE1 that can cause the upregulation of proteins such as chaperones to overcome the burden of unfolded proteins. Most intriguingly perhaps is the IRE1 signaling in that upon accumulation of unfolded proteins in the ER, IRE1 dimerizes and acts as endoribonuclease and promotes the unconventional splicing of HAC1/XBP1 mRNA, whose protein product is a transcriptional activator of UPR genes [36]. Of note at least in yeast, Ire1 does not only sense unfolded proteins but also lipid bilayer stress, which can be caused by impairments in lipid metabolism [37].

The ER is involved in ensuring the well-being of future generations

Yet, in spite of the well-characterized UPR, the ER nevertheless can accumulate protein aggregates in particular under stress conditions. Those aggregates could be detrimental for the cell and might be involved in neurodegeneration and dementia. From the yeast *S. cerevisiae*, we learnt that the ER actually keeps protein aggregates in the mother cell and allow the daughter cell to flourish, using the ER stress surveillance (ERSU) pathway [38]. This is even more remarkable as the ER cannot be *de novo* synthesized but must be inherited. However, aggregates will only be retained in the mother cell, if the UPR pathway has been turned on; aggregates that are not sensed by the ER, will be inherited into the daughter cell [38,39]. But not only protein aggregates in the ER are retained in the mother; such a retention also applies to at least a subset of cytoplasmic aggregates as well. For example, Q-bodies, which are aggregates form by polyQ stretch containing proteins such as huntingtin associate with ER and are retained in the mother [40]. Likewise, P-bodies, which are the sites of mRNA storage and decay, are associated with the ER [23,41]. Thus, the ER might control protein aggregate distribution in the cell. In this scenario, the action of the ER is aided by septins, which are GTP binding proteins, that can form filaments and which can restrict diffusion of proteins at the plasma membrane and the ER [42,43]. Intriguingly, the association of the ER with septins is mediated by Scs2, which is part of the ER-PM tethers [44]. The retention of protein aggregates is dependent on the diffusion barrier at the bud

neck in yeast, and presumably also in neurons. However, the ER is not only responsible for retention of bad things in the mother, but also for providing good things -such as fate determinants- to the daughter in yeast. The best studied example is the inheritance of ASH1 mRNA, encoding a transcriptional repressor of HO endonuclease, a key player in mating type switch. ASH1 mRNA is transported via the SHE machinery to the bud and is anchored there at the cortical ER [45-47]. After cytokinesis ASH1 is expressed only in the daughter, preventing mating type switch, while the mother can switch the mating type. As a result, the mother and daughter can mate and form a diploid cell, which has a better survival chance than the haploid cells. While ASH1 mRNA localization to the bud is independent of cortical ER, a number of other mRNAs use the cortical ER inheritance system to for their enrichment in the daughter cell [48,49].

Even though the inheritance of good aspects -such as mRNAs that provide a growth or developmental advantage- and the retention of garbage -such as protein aggregates- in yeast sounds rather specific, it is probably conserved. At least in *C. elegans* zygotes, the ER is present on the spindle and at the spindle poles/centrosomes during mitosis, and after cell division, the anterior AB cell, the stem cell giving raise to most somatic cells, will acquire a higher concentration of ER than the posterior P1 cell, the precursor of the future germline [50]. Moreover, there is essentially no absolutely symmetric cell division in eukaryotes. Even during a cell division in a tissue culture dish, which would be at first site symmetric, one of the cells will retain for example the 'old' centrosome, while one of the cells will obtain the 'new' centrosome, which was assembled during in prophase. The centrosome could be the organelle that specifies the 'young' versus the 'old' cell, which retains potentially damaging parts. Finally, the ER is involved in the regulation of organellar dynamics, in that it can induce fission of mitochondria and endosomes[51,52]. Again, the regulation of this activity might act to separate damaged parts from organelles and then promote their degradation through autophagy or as in the case of mitochondria help the mDNA distribution[53].

Conclusion and outlook

The ER fulfills a sensor function in the cell, integrate signaling and induce appropriate responses under various condition during growth and cell division. Like a caring mother, it ensures the functionality and well-being of cellular constituents. Even though, we are able

to describe this function, a lot more research is needed to understand how the ER achieves and coordinate all the different tasks.

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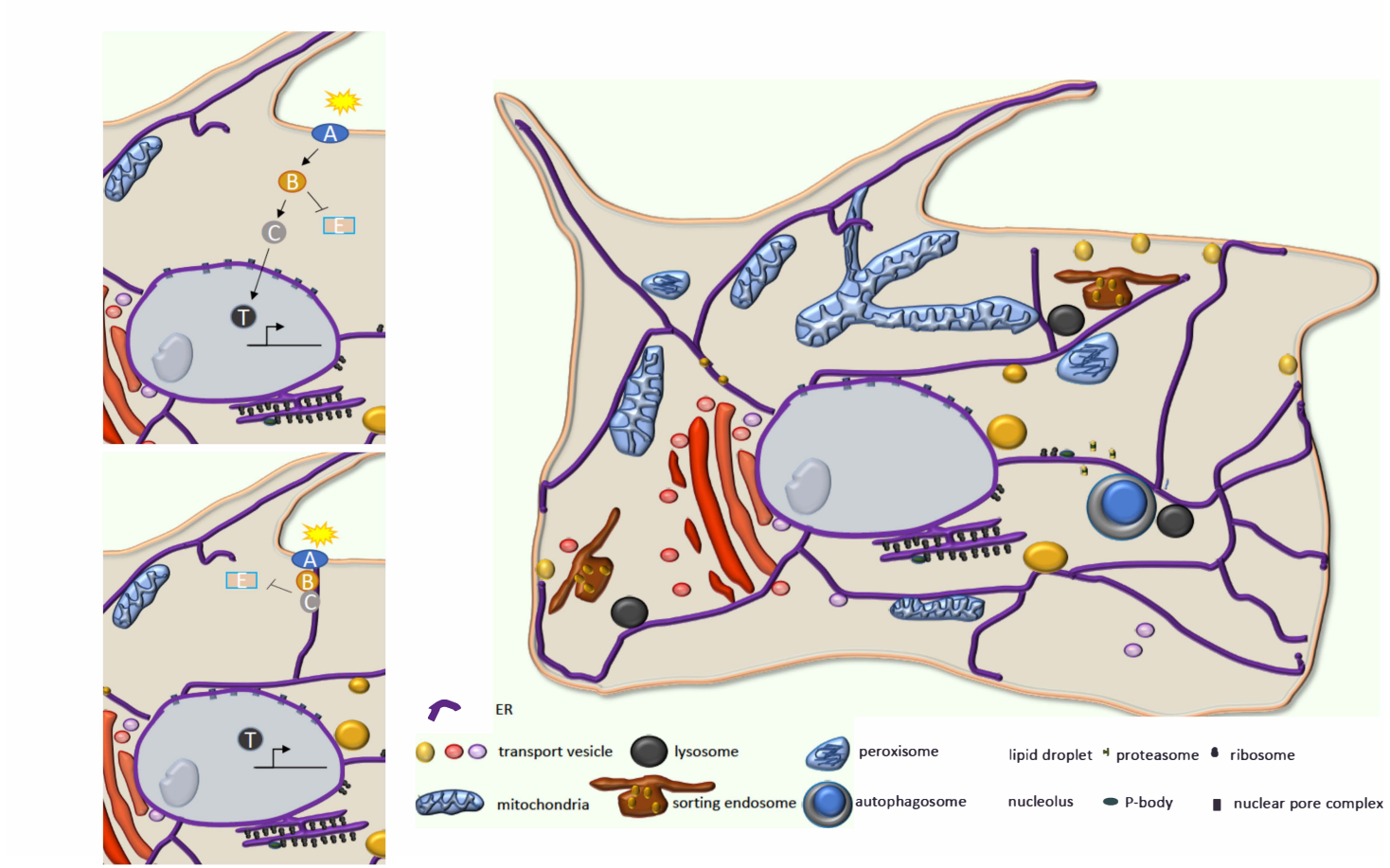

Figure 1: Schematic depiction of a cell with special emphasis on ER contacting various cellular organelles. **Left upper corner**. Typically drawn signal transduction cascade not involving any membrane compartment. **Left lower corner**. Possible signal transduction cascade involving membrane, in this case the ER, but also other membranes can certainly contribute to such a communication.