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The endoplasmic reticulum-the caring mother of the cell

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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 and with the cytoplasm, and sense the outside through the plasma membrane to coordinate various functions and to maintain cellular homeostasis. To maintain homeostasis, the information on the cellular state must be collected and appropriate responses initiated. The endoplasmic reticulum fulfils these functions. In this review, I will discuss various aspects of how the ER senses and relays information and acts to protect the cell, in what sometimes could be interpreted as an altruistic behavior.

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Introduction — the endoplasmic reticulum as potential sensor and signaling platform

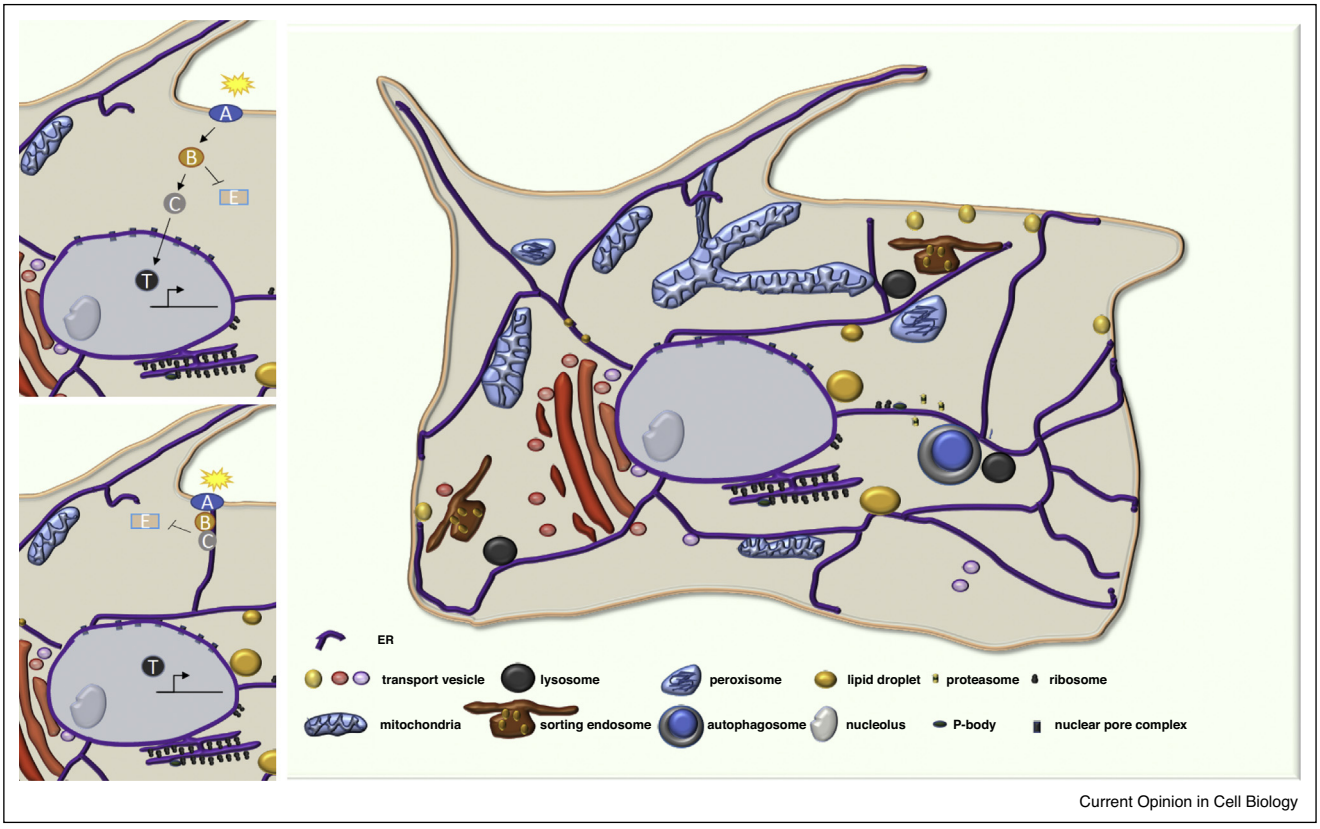
The well-being, in terms of fitness, of the cell needs to be assessed and closely monitored at all times. In addition, all the information gathered on the metabolic status, growth, etc. needs to be integrated at one point to be able to mount appropriate responses. But how does a cell sense that something goes wrong in one of its membrane constituents, or sample what is happening on the outside of the cell? Clearly, 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 that 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 also has outstanding access to the state of the nucleus because of the continuity of the ER and the nuclear envelope and the ER lumen being separated from the nucleus just through the inner nuclear membrane. Finally, the ER is embedded in the cytoplasm and communicate with it as well.

The sensor system at the ER

If the ER acts as the sensor of cellular well-being, this raises the following questions. How does the ER 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 or 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 will be recruited to remove a damaged organelle or a piece thereof.

The tether can be one protein or a protein complex, which is often anchored by a transmembrane domain to the ER and then reaches 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 $PI4,5P_2$ levels [5,6•,7,8]. Thus, this interaction with the target organelle could either sense the lipid composition or

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 membranes. In this case the ER, but also other organelles, can certainly contribute to such a communication.

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 induces a conformational change, and under high Ca^{2+}, reduces the distance between ER and PM by 50% [11,12•,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 means to sense the contacting organelle; in a rather similar way that 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 for this are the ER-mitochondrial contacts. The ER contains oxidoreductases such as ERp44 and ERO1α, which initially were thought to regulate disulfide bond formation in the ER [18,19]. However, more recent evidence supports 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 serving as both a Ca^{2+} buffer and a redox buffer, 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].