True Cell Simulations Inc.
cell blog
Sep/3/2025, Kazuhisa Ichikawa

16. Real intracellular structure 3

— Structure and function of endoplasmic reticulum —

Endoplasmic Reticulum (ER) is not easy to express in short, because its shape is amorphous with multiple functions, preventing us from reaching a holistic view of ER. This situation is different from mitochondria. ER, however, covers 35% of the cytoplasmic volume (Perkins, H.T., et al., Cells, 2021), extending every region in the cytoplasm, including the outer surface of the nuclear envelope*1. This strongly suggests that ER obeys universal and important roles for a cell. Here, we focus on the shape, structure, and function of the ER.

*1 ER is a single organelle composed of a single continuous surface of the lipid bilayer. Recent textbooks draw this continuity. But its extension in the whole cytoplasmic space is not well drawn, because it is almost impossible to draw a complete structure in a paper book. If we employ a computer screen, the ER 3D structure is displayed on it, and the structure of ER is easily understood through the operation of enlargement/shrinkage, rotation, slicing, and navigation by users. Instead, we recognize the real structure of the ER by watching a flip book on a screen. If interested, contact us via the contact form on our website.

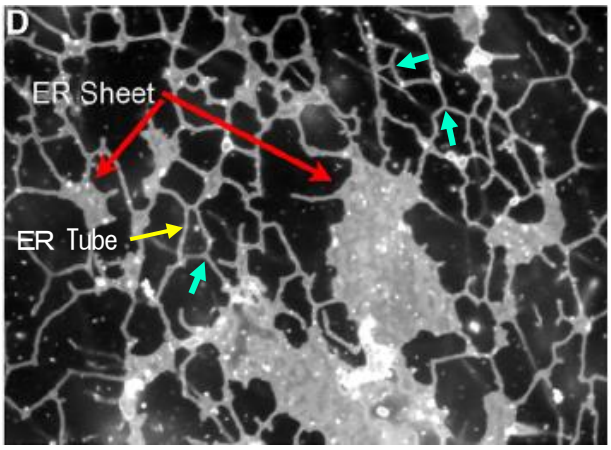

Fig.1 ER sheets and tubes (Xenopus egg extracts、Schwarz, D.S., et al, Cell.Mol.Life Sci, 79, 2016). Green arrows indicate three-way junctions of ER tubes, and yellow arrow shows ER tube (added by the blog author).

Structure of ER: ER is shown in gray in Fig.1. If we look at its cross-section, we only see a homogeneous lumen flanked by lipid bilayers in a low-resolution EM image. But we can find two different morphologies of tubular (yellow arrow) and sheet-like ER (red arrows), connecting to each other*2. ER tubules form three-way junctions (green arrows), by which ER networks are formed. The diameter of the ER tube and the thickness of the ER sheet are both 80-100 nm. The length of the ER tube is 1 μm on average (Perkins, H.T., et al., Cells, 2011). A membrane protein may act as a spacer for two opposing membranes (Shibata, Y., et al., Cell, 2006; Perkins, H.T., et al., Cells, 2021). Fenestrated ER sheets exist, which are speculated to be related to the creation of ER tubes (West, M., et al., JCB, 2011; Schroeder, L.K., et al., JCB, 2019). Although the fenestrated ER was reported to be due to the limited resolution of microscopy viewing dense regions by ER tubes (Nixon-Abell, J., et al., Science, 2016), its existence was confirmed later (Schroeder, L.K., et al., JCB, 2019). The ratio between ER tubes and sheets is different by cell types (Schwarz, D.S., et al., Cell.Molec.Life Sci., 2016), and altered by external stimuli (Pendin, D., et al., Curr.Opin.Cell Biol., 2011).

*2 These two different appearances of the ER may be a cause of the ambiguity in understanding the ER.

ER is also categorized into rough ER, to which ribosomes are embedded, and smooth ER, to which ribosome is not embedded. Although rough ER and smooth ER are said to coincide with ER sheets and ER tubes, respectively, it should be noted that ribosomes exist on ER tubes too (Schwarz, D.S., et al., Cell.Molec.Life Sci., 2016). It is also thought that ER sheets reside mainly around the nucleus, and ER

tubes in the peripheral region of the cytoplasm. However, ER sheets at the peripheral region are found (Perkins, H.T., et al., Cells, 2011).

A recent report has shown that the morphology at the connecting region between continuous perinuclear ER and outer membrane of the nuclear envelope in high resolution (Bragulat-Teixidor, H., et al., EMBO Rep., 2024). They reported an hourglass shape at the connecting region with a width of 7-20 nm. This strongly suggests that the lumen of the ER and that of the outer nuclear membrane will be isolated, because the thickness of the lipid bilayer is 5-10 nm. Membrane contact sites, such as the ER and mitochondria, will be discussed in a future blog.

Functions of ER: ER is a place of protein translation, where one-third of cell proteins are synthesized (Almanza, A., et al., FEBS J., 2019). By the dissociation of mRNA:ribosome complexes from the surface of ER sheet, the proportion of ER-sheets to ER-tubes decreases. Thus, mRNA:ribosome complex is postulated to stabilize the shape of the ER sheet (Schwarz, D.S., et al., Cell.Molec.Life Sci., 2016). ER is also a place of protein quality control. Accumulation of misfolded proteins on the ER evokes unfolded protein response (UPR), leading to the ER degradation (ER-phagy) (Almanza, A., et al., FEBS J., 2019). Low glucose condition also triggers ER stress. ER-phagy keeps the ER shape and its abundance.

ER also regulates the intracellular calcium ion (Ca^{2+}) concentration. Extracellular, intracellular, and intra-ER Ca^{2+} concentrations are 2 mM, 100 nM, and 100-800 nM, respectively. Ca^{2+} releasing channels and Ca^{2+} pumps in the ER membrane regulate the intracellular Ca^{2+} concentration. Ca^{2+} induces apoptosis, but at the same time, it activates a kinase that regulates the ER stress. ER is also important for lipid synthesis, which may regulate plasma and organellar membranes. This role is reported to be activated at the membrane contact sites. In addition, ER contributes to the synthesis of lipid droplets, energy storage, and glucose metabolism.

ER-related diseases: Impaired ER function is the cause of metabolic and neurological diseases such as diabetes, pulmonary hypertension, cardiac pathologies, Parkinson's disease, ALS, and Alzheimer's disease (Yamanaka, T., et al., Front.Neurosci., 2018; Gubas, A., et al., Molec.Cell, 2022). Impaired ER function also leads to disease development and treatment resistance (Almanza, A., et al., FEBS J., 2019).

The ER obeys many functions. Among them, lipid biogenesis is important for the preservation of the membrane system, cell shape, and organellar homeostasis. The ER is distributed throughout the cytoplasmic space. If ER exerts common functions locally everywhere in the cytoplasm, a wide distribution of ER in the cytoplasm is convincing. The local activation of Ca^{2+}-dependent proteins by locally released Ca^{2+} from the ER is a candidate for supporting this view. This mechanism can activate a protein by Ca^{2+}, avoiding the risk of apoptosis. The depleted Ca^{2+} in the ER can be replenished via its lumen. This may be a reason for the structural continuity of ER. In addition, if protein synthesis proceeds by ribosomes on ER-tubules, proteins can be synthesized locally, which is advantageous, especially in neurons[3]. But a mechanism carrying mRNA to distant sites without degradation will be required. This local protein synthesis will also be involved in the cellular response to RNA virus infection. Establishing these will lead to a birds-eye view of the ER structure and function.

3) The local protein synthesis is known in neurons.