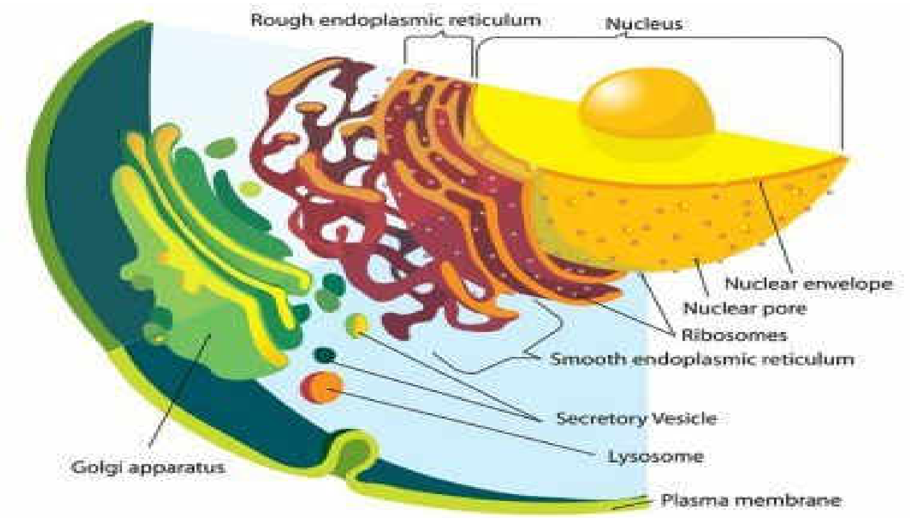
Endoplasmic Reticulum

The ER is the largest organelle in the cell and is a major site of protein synthesis and transport, protein folding, lipid and steroid synthesis, carbohydrate metabolism and calcium storage. The multi-functional nature of this organelle requires a myriad of proteins, unique physical structures and coordination with and response to changes in the intracellular environment. Work from a variety of systems has revealed that the ER is composed of multiple different structural domains, each of which is associated with a specific function or functions.

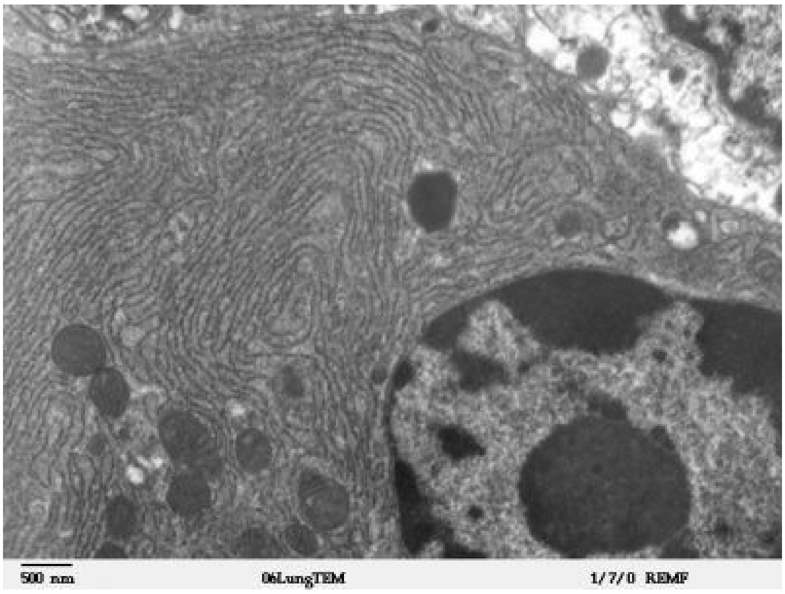
Endoplasmic Reticulum Overview

The entire structure can account for a large proportion of the endomembrane system of the cell. For instance, in cells such as liver hepatocytes that are specialized for protein secretion and detoxification, the ER can account for more than 50% of the total lipid bilayer of the cell. Similarly, the ER membrane system is particularly prominent in pancreatic beta cells that secrete insulin, or within activated B-lymphocytes that produce antibodies.



Endomembrane system diagram

As seen in the image, the membranes of the endoplasmic reticulum are contiguous with the outer nuclear membrane, even though their compositions can be different. The ER contains special membrane-embedded proteins that stabilize its structure and curvature. This organelle acts as an important regulator of cell function because it interacts closely with a number of other organelles. Products of the endoplasmic reticulum often travel to the Golgi body for packaging and additional processing before being secreted.



Mammalian lung tissue
This is a microscopic image of a section from mammalian lung tissue. The bottom right corner of the image shows the nucleus and the rest of the picture illustrates the extensive nature of the ER. Small dark circles are mitochondria that exist in physical proximity with the membranes of the ER.

Structure of the Endoplasmic Reticulum

The endoplasmic reticulum membrane system can be morphologically divided into two structures–cisternae and sheets. Cisternae are tubular in structure and form a three-dimensional polygonal network. They are about 50 nm in diameter in mammals and 30 nm in diameter in yeast. ER sheets, on the other hand, are membrane-enclosed, two-dimensional flattened sacs that extend across the cytoplasm. They are frequently associated with ribosomes and special proteins called translocons that are necessary for protein translation within the RER.

Both reticulons and DP1/Yop1 proteins form oligomers and interact with the cytoskeleton. Oligomerization seems to be one of the mechanisms used by these proteins to shape the lipid bilayer into a tubule. Additionally, they also appear to use a wedge-like structural motif that causes the membrane to curve. These two classes of proteins are redundant, since the over expression of one protein can compensate for the lack of the other protein.

The construction of the ER is intimately involved with the presence of cytoskeletal elements, especially microtubules. ER membranes, especially cisternae, move and branch along microtubules. When microtubule structure is temporarily disrupted, the ER network collapses and reforms only after the microtubule cytoskeleton are reestablished. In addition, changes to the pattern of microtubule polymerization are reflected in changes to ER morphology.

Endoplasmic Reticulum Location

The endoplasmic reticulum processes most of the instructions from the nucleus. As such, the endoplasmic reticulum surrounds the nucleus and radiates outward. In cells that secrete many products for the rest of the body, the endoplasmic reticulum can account for more than 50% of the cell.

In general, the nucleus expresses mRNA (messenger RNA), which tells the cell how to build proteins. The rough endoplasmic reticulum has many ribosomes, which are the primary location of protein production. This portion of the organelle creates proteins and begins to fold them into the proper formation. The smooth endoplasmic reticulum is the primary location for lipid synthesis. As such, it does not contain any ribosomes. Rather, it conducts a series of reactions which create the phospholipid molecules necessary to create various membranes and organelles.

The rough version of the endoplasmic reticulum is often closer to the nucleus, whereas the smooth endoplasmic reticulum is further from the nucleus. However, both versions are connected to each other and the nucleus through a series of small tubules.

Types of Endoplasmic Reticulum

There are two major types of ER within each cell – 1) smooth endoplasmic reticulum (SER) and 2) rough endoplasmic reticulum (RER). Each has distinct functions, and often, differing morphology.

The SER is involved in lipid metabolism and acts as the calcium store for the cell. This is particularly important in muscle cells that need Ca^{2+} ions for contraction. The SER is also involved in the synthesis of phospholipids and cholesterol. It is often located near the periphery of the cell.

On the other hand, **the RER** is commonly seen close to the nucleus. It contains membrane-bound ribosomes that give it the characteristic ‘rough’ appearance. These ribosomes are creating proteins that are destined for the lumen of the ER and are moved into the organelle as they are being translated. These proteins contain a short signal created by a few amino acids in their N-terminus and are initially translated in the cytoplasm.

However, as soon as the signal is translated, special proteins bind to the growing polypeptide chain and move the entire ribosome and associated translation machinery to the ER. These polypeptides could be resident proteins of the RER, or be moved towards the Golgi network to be sorted and secreted.

Endoplasmic Reticulum Function

The ER plays a number of roles within the cell, from protein synthesis and lipid metabolism to detoxification of the cell. Cisternae, each of the small folds of the endoplasmic reticulum, are commonly associated with lipid metabolism. This creates the plasma membrane of the cell, as well as additional endoplasmic reticulum and organelles. They also appear to be important in maintaining the Ca^{2+} balance within the cell and in the interaction of the ER with mitochondria. This interaction also influences the aerobic status of the cell.

ER sheets appear to be crucial in the response of the organelle to stress, especially since cells alter their tubules-to-sheets ratio when the number of unfolded proteins increases. Occasionally, apoptosis is induced by the ER in response to an excess of unfolded protein within the cell. When ribosomes detach from ER sheets, these structures can disperse and form tubular cisternae.

Although ER sheets and tubules appear to have distinct functions, there isn't a perfect delineation of roles. For instance, in mammals tubules and sheets can interconvert, making the cells adaptable to various conditions. The relationship between structure and function in the ER has not been completely elucidated.

1. ***Protein Synthesis and Folding***

Protein synthesis occurs in the rough endoplasmic reticulum. Although translation for all proteins begins in the cytoplasm, some are moved into the ER in order to be folded and sorted for different destinations. Proteins that are translocated into the ER during translation are often destined for secretion. Initially, these proteins are folded within the ER. For this folding major chaperon of the ER lumen, BiP (Binding Protein)is mainly responsible. and then moved into the Golgi apparatus where they can be dispatched towards other organelles. In this way rough ER participates in the activity of GERL system.

For instance, the hydrolytic enzymes in the lysosome are generated in this manner. Alternately, these proteins could be secreted from the cell. This is the origin of the enzymes of the digestive tract. The third potential role for proteins translated in the ER is to remain within the endomembrane system itself. This is particularly true for chaperone proteins that assist in the folding of other proteins. The genes encoding these proteins are upregulated when the cell is under stress from unfolded proteins.

2. ***Phospholipid Synthesis:***

Fatty acids used in the production of phosphoacyl glycerols are produced in the cytosol and being insoluble, are transferred to SER membrane by fatty acid binding proteins for incorporation into the cytosolic leaflet of membrane. The enzymes that form phospholipids are all found in the cytosolic face of the SER membrane. Their active sites face the cytosol, where their substances are found. Cytoplasmic lipid transfer proteins (LTPs) bind membrane lipids and transfer them to the membranes of other organelles.

3. ***Steroid biosynthesis:***

   Large amount of SER membrane is also found in the cells of Adrenal that synthesize the steroid, cortisol and in the cells of gonads that produce sex hormones. SER is also associated with plastids in the plant cells and is possibly involved in the production of plant hormones.

4. ***Calcium Store***

The SER is an important site for the storage and release of calcium in the cell. A modified form of the SER called sarcoplasmic reticulum forms an extensive network in contractile cells such as muscle fibers. Calcium ions are also involved in the regulation of metabolism in the cell and can change cytoskeletal dynamics.

The extensive nature of the ER network allows it to interact with the plasma membrane and use Ca^{2+} for signal transduction and modulation of nuclear activity. In association with mitochondria, the ER can also use its calcium stores to induce apoptosis in response to stress.

5. ***Detoxification:***

   Many toxins are relatively hydrophobic and so cannot easily be excreted by the kidneys. Detoxification by the SER, particularly in hepatocytes, converts them to compounds that are more water soluble and therefore more easily removed by the kidneys. This detoxification occurs in following way-

   i) Phase I: In this phase the drug is typically oxidized and / or hydroxilated by a number of cytochrome P-450 monooxygenase family. Then epoxides are produced which are the substrates for Epoxide hydroxilase that catalyses their conversion to a glycol. The hydroxyl groups on products of these reactions make them more water soluble compared to the original drug or other toxic element.

   ii) Phase II: This phase links polar compounds, such as a glucuronate or sulphate groups, to the oxidized product to form compounds that are even more water soluble. Enzymes that catalyze these addition reactions include glucuronosyl transferases of the SER membrane and sulphotransferase in the cytosol.

Key Takeaways

- A cell's endoplasmic reticulum (ER) contains a network of tubules and flattened sacs. The ER performs multiple functions in both plant and animal cells.
- Endoplasmic reticulum has two major regions: smooth endoplasmic reticulum and rough endoplasmic reticulum. Rough ER contains attached ribosomes while smooth ER does not.
- Via the attached ribosomes, rough endoplasmic reticulum synthesizes proteins via the translation process. Rough ER also manufactures membranes.
- Smooth endoplasmic reticulum serves as a transitional area for transport vesicles. It also functions in carbohydrate and lipid synthesis. Cholesterol and phospholipids are examples.
- Rough and smooth ERs are typically connected to one another so that the proteins and membranes made by the rough ER can freely move into the smooth ER for transport to other parts of the cell.

References:

1. Regina Bailey, 2019
2. Dianne S. Schwarz, 2016
3. Wang et al, 2013
4. Pollard et al.,2017