Endoplasmic Reticulum

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Endoplasmic Reticulum

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ENDOPLASMIC RETICULUM

The endoplasmic reticulum is the largest single membrane bound intracellular compartment. It is found almost in all plants and animal cells. The only exceptions are mature erythrocytes and prokaryotes. With the aid of Light microscope technique, the structure of endoplasmic reticulum is described as filamentous which was basophilic in staining property. This basophilic material was termed as "**ergastoplasm**". Study through electron microscope by porter, Claude and Fullan revealed it as a network of delicate strands and vesicles. Later, Porter and kallman in 1952 termed it as "endoplasmic reticulum". Thus the structure of endoplasmic reticulum is an extensive network of membrane enclosed channels present throughout the cell. The enclosed compartment is called the lumen. The membrane of the endoplasmic reticulum is physiologically active and is continuous with the outer nuclear membrane, which was demonstrated by Watson. The space of the endoplasmic reticulum opens into perinuclear space between the two nuclear membranes. Porter and Machado considered endoplasmic reticulum as the extension of the nuclear membrane.

Endoplasmic reticulum membrane may assume the form of cisternae, tubules or vesicles. The **cisternae** are broad, flat; membrane bound spaces arranged parallel to each other. The **tubules** appear in circles in the endoplasmic reticulum sections. The **vesicles** or sac appear as membrane-bound, isolated globose cavities. Endoplasmic reticulum can be recognized in most cells on the basis of ribosome association. Accordingly, known as smooth endoplasmic reticulum and rough endoplasmic reticulum, depending on whether ribosomes are associated with their cytoplasmic surfaces.

The main function of ER is lipid and protein biosynthesis and modification. Its membrane is the site of production of all the transmembrane proteins

and lipids for most of the cell's organelles (the Golgi apparatus, lysosomes, endosomes, secretory vesicles, and the plasma membrane). The ER membrane also contributes to mitochondrial and peroxisomal membranes by producing most of their lipids.

Origin of Endoplasmic reticulum

The origin of endoplasmic reticulum is not definitely known. According to Dallmer (1966), endoplasmic reticulum originated from the plasma membrane by the process of invagination. According to De Robertis 1970, endoplasmic reticulum originates from the evagination of nuclear envelope (Figure 1). At telophase, the nuclear envelope is reformed with the help of vesicles of endoplasmic reticulum.

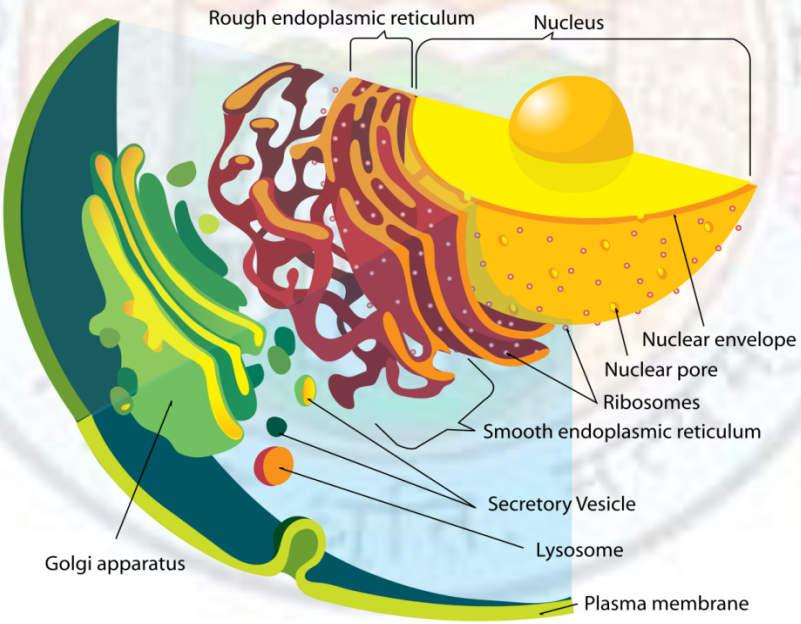
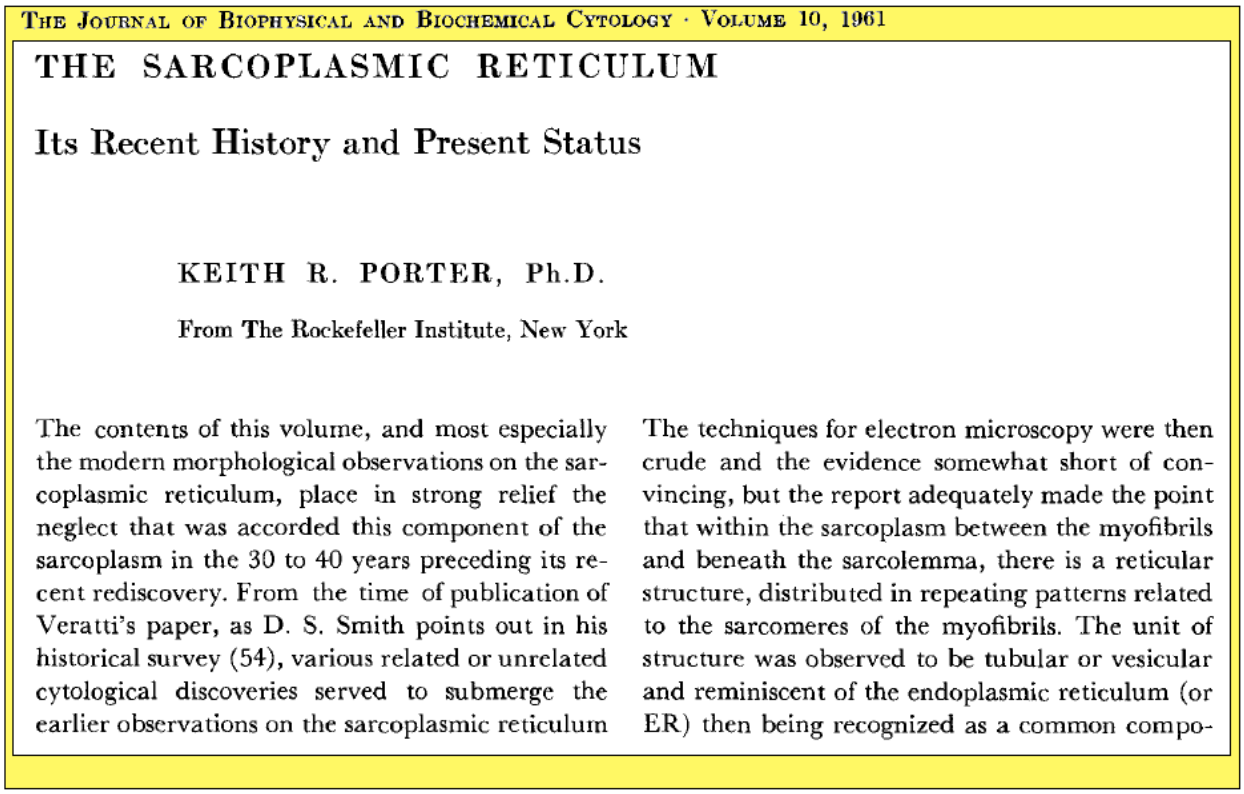


Figure 1: Origin of Endoplasmic Reticulum

Source: https://commons.wikimedia.org

Endoplasmic Reticulum



THE JOURNAL OF BIOPHYSICAL AND BIOCHEMICAL CYTOLOGY · VOLUME 10, 1961

THE SARCOPLASMIC RETICULUM

Its Recent History and Present Status

KEITH R. PORTER, Ph.D.

From The Rockefeller Institute, New York

The contents of this volume, and most especially the modern morphological observations on the sarcoplasmic reticulum, place in strong relief the neglect that was accorded this component of the sarcoplasm in the 30 to 40 years preceding its recent rediscovery. From the time of publication of Veratti's paper, as D. S. Smith points out in his historical survey (54), various related or unrelated cytological discoveries served to submerge the earlier observations on the sarcoplasmic reticulum

The techniques for electron microscopy were then crude and the evidence somewhat short of convincing, but the report adequately made the point that within the sarcoplasm between the myofibrils and beneath the sarcolemma, there is a reticular structure, distributed in repeating patterns related to the sarcomeres of the myofibrils. The unit of structure was observed to be tubular or vesicular and reminiscent of the endoplasmic reticulum (or ER) then being recognized as a common compo-

Value Addition: Screenshot of historical research article by K.R. Poter on sarcoplasmic reticulum.

Structure and Composition of Endoplasmic Reticulum

The endoplasmic reticulum, enclosed by a continuous membrane, is the largest organelle of most eukaryotic cells. Its membrane account for approximately 50% of all cell membranes and the space enclosed by the ER represents about 10% of the total cell volume. The Endoplasmic reticulum membrane is like a unit membrane (typical of three-layered) in some regions while at other regions it may show a micellar (globular) structure. Hence shows a combination of both structures. The endoplasmic reticulum membrane is thinner than the plasma membrane which measures about 50 A.

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Microsomes are mostly the fragments of endoplasmic reticulum, when the cells are homogenized and the cell membrane breaks up into fragments. The lipid content of microsomes is approximately 30-50% of which about 70% is phospholipid. Roughly 50-90% of the phospholipid content is in the form of **lecithin** and **cephalin**.

The lipids present in the microsomal fraction are mostly phospholipids that consist of phosphatidylcholine, phosphatidylthanolamine,phosphatidylinositol and phosphatidyglycerol. **Ribophorins** or ribosome receptor proteins are the membrane proteins of RER which aid in binding of ribosomes to the microsomal membrane. Many other permanent proteins are found in the cisternae which are known as **reticuloplasmins**. These include several enzymes that modify proteins after they are made. Rough microsomes are denser than the smooth ones, enabling the separation between the two.

Weiss (1953) referred the cisternal elements as ergastoplasmic sacs. In nerve cells, such areas are called as Nissle bodies

Endoplasmic Reticulum

Electron micrograph of endoplasmic reticulum
Source: thinglink.com

Value Addition

Types of Endoplasmic Reticulum

Endoplasmic reticulum (ER) is of two types–**Smooth endoplasmic reticulum** (SER) and **Rough endoplasmic reticulum** (RER) (Figure 3). RER arises from nuclear membrane. RER consists of tubules studded with ribosomes and is associated with protein modification and trafficking. SER is primarily associated with synthesis of lipids and helps in detoxification. The two contiguous membrane domains-RER and transitional ER function in protein processing. The transitional ER is the site where vesicles exit to the Golgi apparatus. The smooth ER is involved in lipid, rather than protein, metabolism.

ER encompasses a membrane system that enfolds a lumen, estranged from the surrounding cytosol. The symphony of the luminal space is different from that of the adjacent cytosolic space. RER and SER share many proteins

and activities like synthesis of lipid and cholesterol. Fluorescent microscopy using labeled proteins and lipids indicates that their membranes are incessant as these could diffuse from one side of lumen to another side. Besides, RER and SER have various different protein components which mark their structural and functional differences.

So, there are basically two morphological types of endoplasmic reticulum: the Rough endoplasmic reticulum (RER) or the granular form (ergastoplasm) and Smooth endoplasmic reticulum (SER) or agranular form (Figure 2 & Table 1). The RER is composed of flattened sacs-cisternae. Outer membrane of the nuclear envelope continues to form RER which bears ribosomes on its cytosolic façade. The difference is that the rough endoplasmic reticulum is covered in ribosomes, giving it a rough appearance in the electron microscope. The main function of RER is protein synthesis; integral membrane proteins in the plasma membrane, and proteins that the cell will export to the extracellular medium (such as the proteins of the extracellular matrix). Hence presence of RER is predominantely in cells which are actively synthesizing proteins, e.g. enzyme secreting cells. Whereas Smooth endoplasmic reticulum is one lacking ribosomes.

SER forms highly curved, tubular and interconnecting system. The membranous elements of the SER are highly curved and tubular, forming an interconnecting pipelines system. Smooth endoplasmic reticulum is one lacking ribosomes. The function of the smooth endoplasmic reticulum varies from tissue to tissue. It is characteristic of cells in which synthesis of non-protein substance like phospholipids, glycolipids and steroids takes plce, e.g. adipose tissues cells, adrenocorticals etc. In the ovaries, testes, and the adrenal gland synthesis of steroid hormones takes place; in the liver it is the site of detoxication. RER transfers the synthesized product, protein, to the Golgi bodies and also helps in store of minerals such as calcium. Inversely the function of the smooth endoplasmic reticulum is the storage and sudden

release of calcium ions during the contraction of muscles. The ratio of RER and SER in a cell depends on the cell type and its function. For example the cells of pancreas or salivary glands have more RER as these structures are related to synthesis of protein in large amount which is the function of RER.

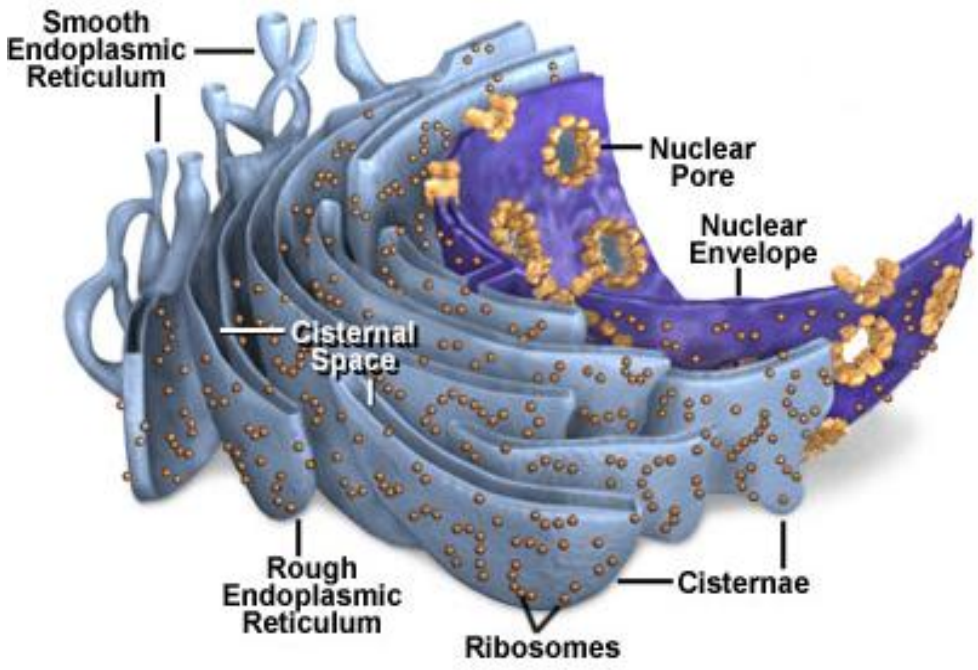

Figure 2: Structure and association of endoplasmic reticulum with nuclear membrane

Source: http://eobiology.wikispaces.com

Pancreatic exocrine cells possess only granular or Rough endoplasmic reticulum.

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A modified form of smooth endoplasmic reticulum is found which is referred as "**Sarcoplasmic reticulum**", in the striated muscles. It is a plexus surrounding the myofibrils. The **myeloid body**, which is present in the pigment cells of the retina of the frog, is probably modified smooth endoplasmic reticulum.

In epithelial cells of the frog retina and interstitial cells of the testis the endoplasmic reticulum is completely Smooth (SER).

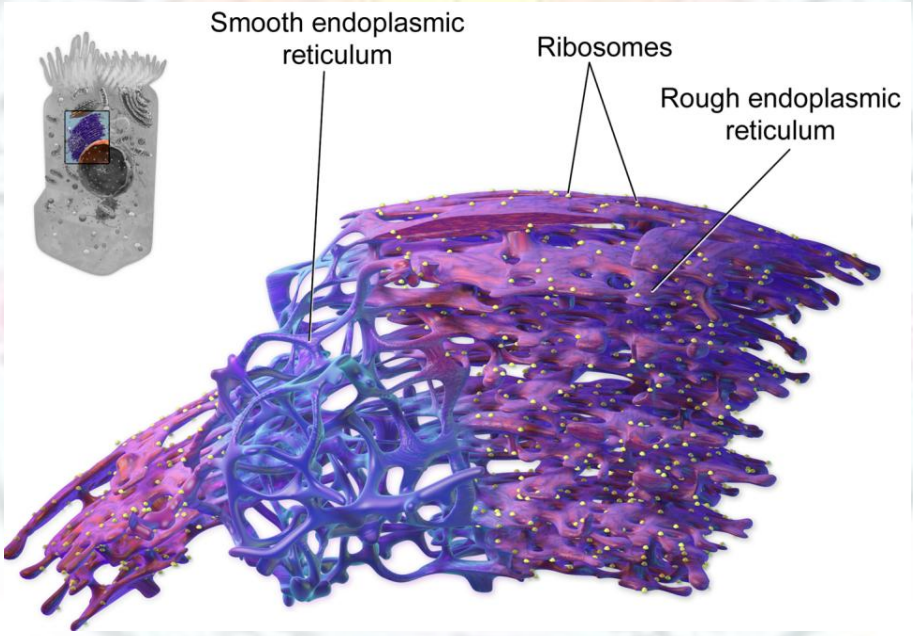


Figure 3: Rough and Smooth Endoplasmic Reticulum

Source: https://en.wikipedia.org

Table 1: Difference between Smooth Endoplasmic Reticulum and Rough Endoplasmic Reticulum

Endoplasmic Reticulum

Smooth Endoplasmic Reticulum	Rough Endoplasmic Reticulum
Not associated with ribosomes.	Studded with ribosomes.
Mainly composed of tubules.	Mainly composed of cisternae.
Generally associated with plasma membrane.	Generally associated with nuclear membrane.
Less stable	More stable
Found in Epithelial cells, Intestinal cells, Sarcoplasmic Reticulum	Found in Pancreatic Exocrine cells
Main function is lipid synthesis and hence mostly seen in cells associated with synthesis of steroid hormones.	Main function is protein synthesis and hence mostly seen in cells associated with secretion of proteins.

FUNCTIONS OF ENDOPLASMIC RETICULUM

1. Mechanical Support: The endoplasmic reticulum gives additional mechanical support to the cytoplasm as it divides the fluid content of the cell into compartments.

2. Synthesis of secretory proteins:

The proteins are synthesized on RER with a hydrophobic signal by which they can be embedded in the lipid bilayer. Ribosomes present on these ER are the actual site of protein synthesis. In addition ER is also the site of synthesis of a group of proteins which are for storage or for export outside of the cell.

3. Glycosylation of proteins:

Nearly all the proteins produced on the ribosomes attached to the ER membrane, whether integral components of a membrane, lysosomal enzyme, or parts of extra cellular matrix, become glycoproteins as a result of glycosylation in the presence of enzyme **glycosylatransferases**.

4. ER and carbohydrate metabolism:

Cell wall polysaccharide synthesis of plant occurs by SER, while in mammalian liver cells, glycogen is deposited on the surface of the SER. Conversion of stored glycogen to glucose in starved animal is stimulated by hormone glucagon. Enzyme **glucose 6-phosphate** has been reported in the ER. It is responsible for breakdown of glycogen (**glycogenolysis**). It is suggested that SER membranes play an important role in glycogenesis.

5. Lipid synthesis and storage:

Stein and Stein suggested that the ER was the site of triglyceride formation. ER plays an indispensable role in lipid anabolism as it possesses a number of enzymes that are involved in the process.

Specialized lipids like terpene oils and sticky fluid on the stigma of flowers are synthesized by SER of plant tissues. Whereas the animal organs like testis, ovary, adrenal gland etc have large amount of SER for synthesizing steroid hormones.

6. Electron Transport and Detoxification:

Cytochrome P450 is the electron acceptor between NADPH and O_2, which is located on the outer surface of SER. Various forms of P450 are responsible for carrying out diverse function including electron transport. Cytochrome P450 family is an important example of detoxification enzymes, which render

the drugs water soluble, enabling it to leave the cell and are excreted in the urine. SER membranes contain this enzyme system with detoxification properties. Phenobarbital injections produce increased synthesis of detoxification enzymes in the endoplasmic reticulum. Abundant SER with **P450** carry out biotransformation of xenobiotics which enter the body through the digestive system, which are inactivated by P450 oxidation.

7. Circulation and exchange:

Endoplasmic reticulum acts as an intracellular transport system for various substances. The exchange between the nucleus and the cytoplasm occurs through nuclear openings which communicate with the Endoplasmic reticulum. This was suggested by Watson. It also provides an extensive internal surface for exchange of material between the maxtrix of cytoplasm and the lumen of the cisternae. It was postulated that presence of permeases and carriers present on ER membrane facilitates the active transportation.

8. Synthesis of cholesterol and steroid hormones:

Cholesterol is an important precursor of steroid hormones. Endoplasmic reticulum is the major site of cholesterol synthesis. The SER of liver cells is concerned with both the synthesis and storage of cholesterol. Other sites of synthesis of steroid hormones are the SER of Testis, ovary and the adrenal. the capacity to synthesize steroid hormones is directly realted to the amount of SER present in cells.

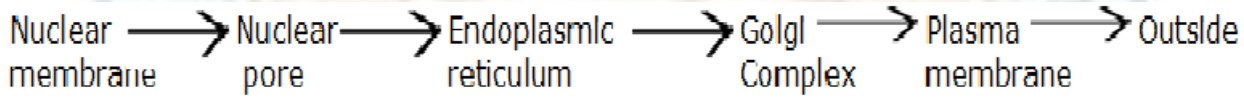
9. Other functions:

Sarcoplasmic reticulum, which is SER of muscles is involved the the concentration of Ca^{2+} ions utilizing ATP. Calcium ions which are stored in the sarcoplasmic reticulum are released when the muscles are stimulated by

impulse or hormones resulting in contraction of muscles. Oxyntic cells present in stomach ER are implicated in chloride ion secretion.

Endoplasmic reticulum is connected with the formation of nuclear envelope. Both are connected to each another with the endoplasmic reticulum space opens into the perinuclear space between the two membranes. Both endoplasmic reticulum and nuclear envelope resembles physically and chemically to some extent. Hence it is supposed to that endoplasmic reticulum is involved in nuclear membrane formation.

Transport of ions, molecules and particles into and out of the cells may also take place through membrane flow (Figure 4). Thus substances like RNA and nuclear proteins may pass out from the nucleus outside the cell by the following route:



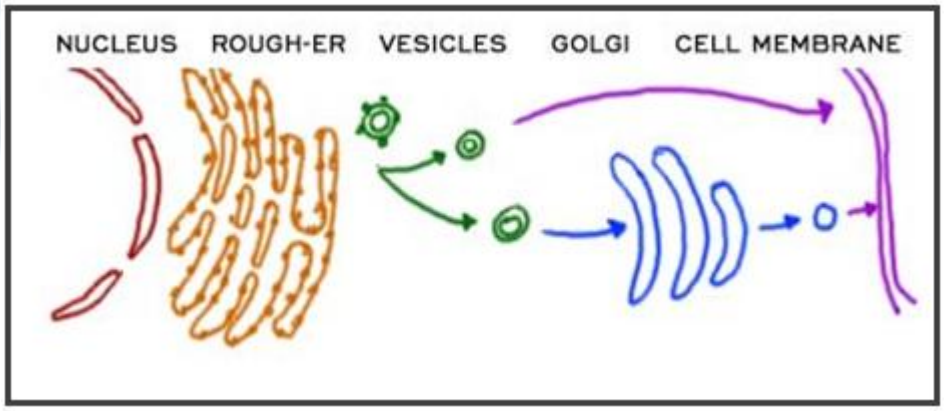


Figure 4: Rough Endoplasmic Reticulum at work

Source: http://welkescience.wikispaces.com

Electron microscopic studies advocate that the endoplasmic reticulum in plants also acts in the formation of the interconnection of cells called plasmodesmata, through the cytoplasmic strands.

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Import of proteins into Endoplasmic reticulum:

The endoplasmic reticulum network serves as a unit for the production of lipids for the cell. Cytosolic surface is used for synthesis of majority of proteins. All proteins synthesized in the cytosol are intended either for secretion or meant for insertion to different cell organelles (ER, Golgi apparatus, lysosomes, endosomes etc.) and the plasma membrane. These proteins are first imported into the ER lumen from the cytosol where they fold and oligomerize. In this process the **disulphide bonds** are formed and **N-linked oligosaccharides** are added to form glycoproteins.

The proteins which are imported into the ER lumen always carry a special hydrophobic signal peptide which facilitates their transport. This signal peptide is recognized by a **signal recognition particle (SRP)** which binds to the growing polypeptide chain and also to the ribosomes taking part in the synthesis. SRP, after binding, directs the ribosomes along with the growing polypeptide chain to a SRP receptor located on the cytosolic surface of the RER membrane. Thus, the process of translocation is initiated. In course of time a loop of growing polypeptide chain traverses the ER membrane through a hydrophilic pore in a protein translocator. SRP is an elongated complex, made up of six protein subunits and one RNA molecule, known as **SRP-RNA** (Figure 5). One end of SRP binds to the ER signal peptide (present in growing polypeptide chain) and to the ribosome, which will temporarily stop the translocation.

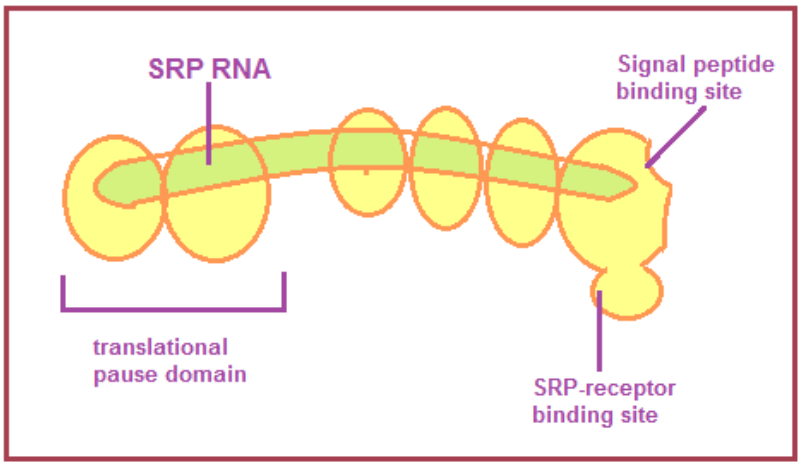

Figure 5: Structure of Signal Recognition Particle (SRP) with six protein subunits and one molecule of SRP-RNA
Source: Author

Thus the import of proteins into endoplasmic reticulum is co-translational as compared to other organelles viz. Mitochondria, chloroplast, peroxisomes etc. where it is post-translational. The proteins are never released in to the cytosol, which were destined for endoplasmic reticulum, and there is no requirement of any chaperones to keep these proteins unfolded. These proteins which are destined to endoplasmic reticulum can be of two types:

i. Soluble proteins: can pass across the endoplasmic reticulum and get to its lumen.
ii. Transmembrane proteins: intended for the endoplasmic reticulum membrane or other cell membrane. These proteins are not released in the lumen and stay anchored in the lipid bilayer. This anchoring is facilitated by one or more **hydrophobic α-helical regions**, which functions as start-transfer or stop-transfer signals during translocation.

The ribosome binding to protein translocation complex in ER membrane is followed by insertion of signal sequence into the membrane channel or translocon. GTP binds to SRP and SRP receptor during the process.

Hydrolysis of GTP to GDP leads to dissociation of SRP from both the receptor and ribosome-mRNA complex.

Proteins from yeast and few proteins from mammals are known to get targeted to ER after complete translation rather than co-translationally. Such protein does not require SRP for the transfer to the lemen of ER. In this case, signal sequences are recognized by separate receptor proteins, known as **Sec62/63 complex,** associated with translocon. Also, cytosolic chaperons (HSP70) are required to maintain the unfolded conformation of polypeptide in cytosol. For entering in the lumen, there is a separate chaperon (HSP70), called as **BiP,** is required to pull the polypeptide inside.

Protein Folding and Processing

The ER is site for the protein folding and modification where assembly of different subunits of a protein, formation of disulfide bond, glycosylation at initial stages and addition of glycoprotein anchor take place. Lumen proteins help in folding of translocated proteins (Figure 6). Protein translocation through the membrane takes place cotranslationally in an unfolded state. Three dimensional folding of proteins takes place in the lumen of ER. This folding is assisted by molecular chaperons. As the unfolded polypeptide crosses the membrane, a **HSP70 chaperon, BiP,** binds to it to assist the protein folding and assembly of multi subunits of the protein (Figure 6). After correct folding, the protein, released from the BiP, is ready to be transported to the golgibody. In case of any misfolding, the protein gets degraded. During the process of folding, the disulfide bond is formed by the enzyme **disulfide isomerase** present in the lumen.

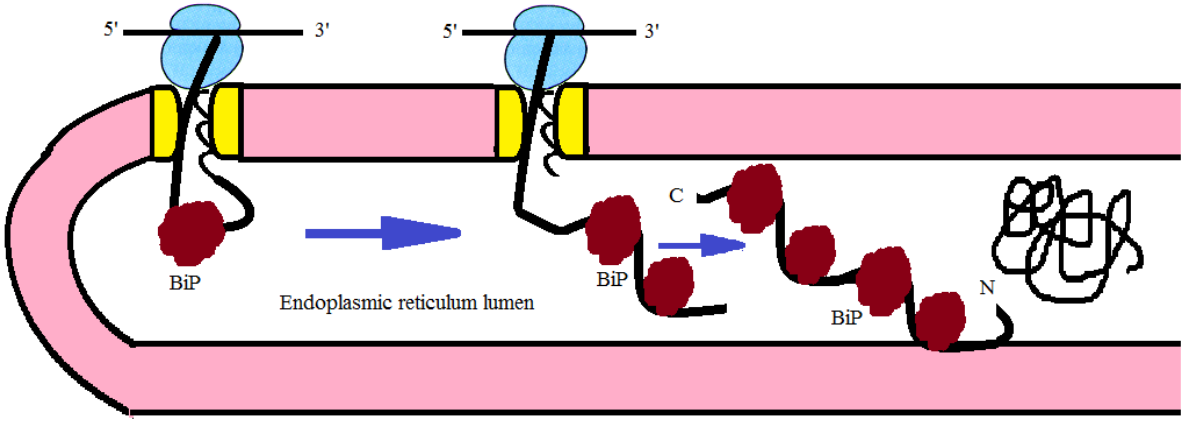

Figure 6: Protein folding in ER

Source: Author

Protein and Lipid Export from ER

Both protein and lipid molecules are exported from the ER in vesicles as result of budding from the transitional ER and the cargo is carried to Golgi apparatus through ER-Golgi intermediate and finally through Golgi and lysosomes to the exterior. The topographic orientation is very important during the transport. The current understanding suggests that there should be some default pathway where all the unmarked proteins in ER lumen transported to Golgi apparatus and beyond. The proteins or enzymes naturally residing in the lumen, which help in modification and transportation of other proteins, have a sequence Lys-Asp-Glu-Leu (KDEL) at their carboxy terminus which directs their retrieval to ER otherwise those protein would be lost to cytoplasm. Similarly, some transmembrane proteins have short C-terminus sequence which has two lysine residues (KKXX). Both these sequences help ER native Proteins in their retrieval and interestingly do not prevent their packaging.

Endoplasmic Reticulum

Summary

- Endoplasmic reticulum was reported by Porter, Claude and Fullman (1945).
- Morphologically Endoplasmic reticulum consists of three types: cisternae, vesicles, and tubules.
- ER is of two types –Smooth endoplasmic reticulum (SER) and Rough endoplasmic reticulum (RER).
- RER is one which possesses ribosomes, made up of cisternae. These arise from nuclear membrane. RER primarily functions in protein synthesis.
- SER lack ribosomes, consisting of tubules mainly. SER helps to synthesize lipids and helps in detoxification.
- In muscles, endoplasmic reticulum is called sarcoplasmic reticulum, in eyes called as myeloid bodies and in nerves as Nissle granules.

Endoplasmic Reticulum

- Microsomal membrane is lipoprotein. Lipids are mostly phospholipids and ribophorins are the membrane proteins of RER.
- ER forms intracellular transport system and provides mechanical support to cytoplasm.
- ER helps in synthesis of secretory proteins.
- ER also helps in protein glycosylation and carbohydrate metabolism.
- Detoxification and electron transport with the help of cytochrome P450 is also one of the important function of ER.
- The proteins which are imported into the ER lumen always carry a special hydrophobic signal peptide which is recognized by a signal recognition particle (SRP) that binds to the growing polypeptide chain and also to the ribosomes taking part in the synthesis.
- Protein folding is assisted by molecular chaperons. A HSP70 chaperon, BiP, binds to it to assist the protein folding and assembly of multi subunits of the protein inside the lumen of ER.
- A sequence Lys-Asp-Glu-Leu (KDEL) at carboxy terminus of native proteins of ER directs their retrieval to ER otherwise those proteins would be lost to cytoplasm.

Exercise/ Practice

1. Describe the structure of Smooth Endoplasmic Reticulum and Rough Endoplasmic Reticulum.
2. Define the role of SRP.
3. What are Microsomes?
4. Describe the various functional aspects of Endoplasmic Reticulum.
5. Write short note on:
    a. Ribophorin

b. P450
c. Sarcoplasmic reticulum
d. BiP
e. Sec62/63

Fill in the blanks:

1. Endoplasmic reticulum was previously known as .....
2. Rough Endoplasmic reticulum is the site for synthesis of .....
3. SRP stands for .....
4. **.....** are the membrane proteins of RER.
5. Fragments of endoplasmic reticulum are known as .....
6. .....is responsible for detoxification.
7. .....stores calcium ions.
8. Rough endoplasmic reticulum is .....stable.
9. Myeloid bodies are .....endoplasmic reticulum.
10. .....is a precursor of steroid hormone.

Glossary

Cytochrome P450: is Electron acceptor, possessing detoxificating enzymes.

Microsomes: are the fragments of endoplasmic reticulum.

Myeloid body: present in the pigment cells of the retina of the frog, is a modified smooth endoplasmic reticulum.

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Reticuloplasmins: permanent proteins are found in the cisternae, possess enzymes that modify proteins after they are made.

Ribosome: RNA and protein complex required for protein synthesis.

Ribophorins or ribosome receptor proteins are the membrane proteins of rough endoplasmic reticulum.

Rough endoplasmic reticulum (RER): is a series of connected flattened sacs that have many ribosomes on their outer surface.

Sarcoplasmic reticulum (SR): It is a specialised form of endoplasmic reticulum and is a Ca storage organelle within muscles

Signal recognition particle (SRP) special hydrophobic signal peptide which facilitates transport of proteins which are imported into the ER lumen.

Smooth endoplasmic reticulum (SER): is tubular in form and devoid of ribosomes.

References/ Bibliography/ Further Reading

Lodish, Harvey; et al. (2003). Molecular Cell Biology (5th ed.). W. H. Freeman. pp. 659–666.

Alberts B, Johnson A, Lewis J, et al. Molecular Biology of the Cell. 4th edition.New York: Garland Science; 2002.

Haguenau, F. (1958). The ergastoplasm: its history, ultrastructure and biochemistry. Intern. Rev. cytol. 7, 425.

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Levine T (September 2004). "Short-range intracellular trafficking of small molecules across endoplasmic reticulum junctions". Trends Cell Biol. **14** (9): 483–90.

Palade, G.E., and Porter, K.R. (1954). Studies om Endoplsmic reticulum. I. Its identification in cells. Ital. J. Exper. Med. 100: 641-656.

Weblinks

http://www.encyclopedia.com/topic/Endoplasmic_Reticulum.aspx

http://en.wikipedia.org/wiki/Endoplasmic_reticulum

http://www.britannica.com/EBchecked/topic/187020/endoplasmic-reticulum-ER/

http://study.com/academy/lesson/rough-endoplasmic-reticulum-definition-structure-functions.html

http://www.ncbi.nlm.nih.gov/books/NBK26841/