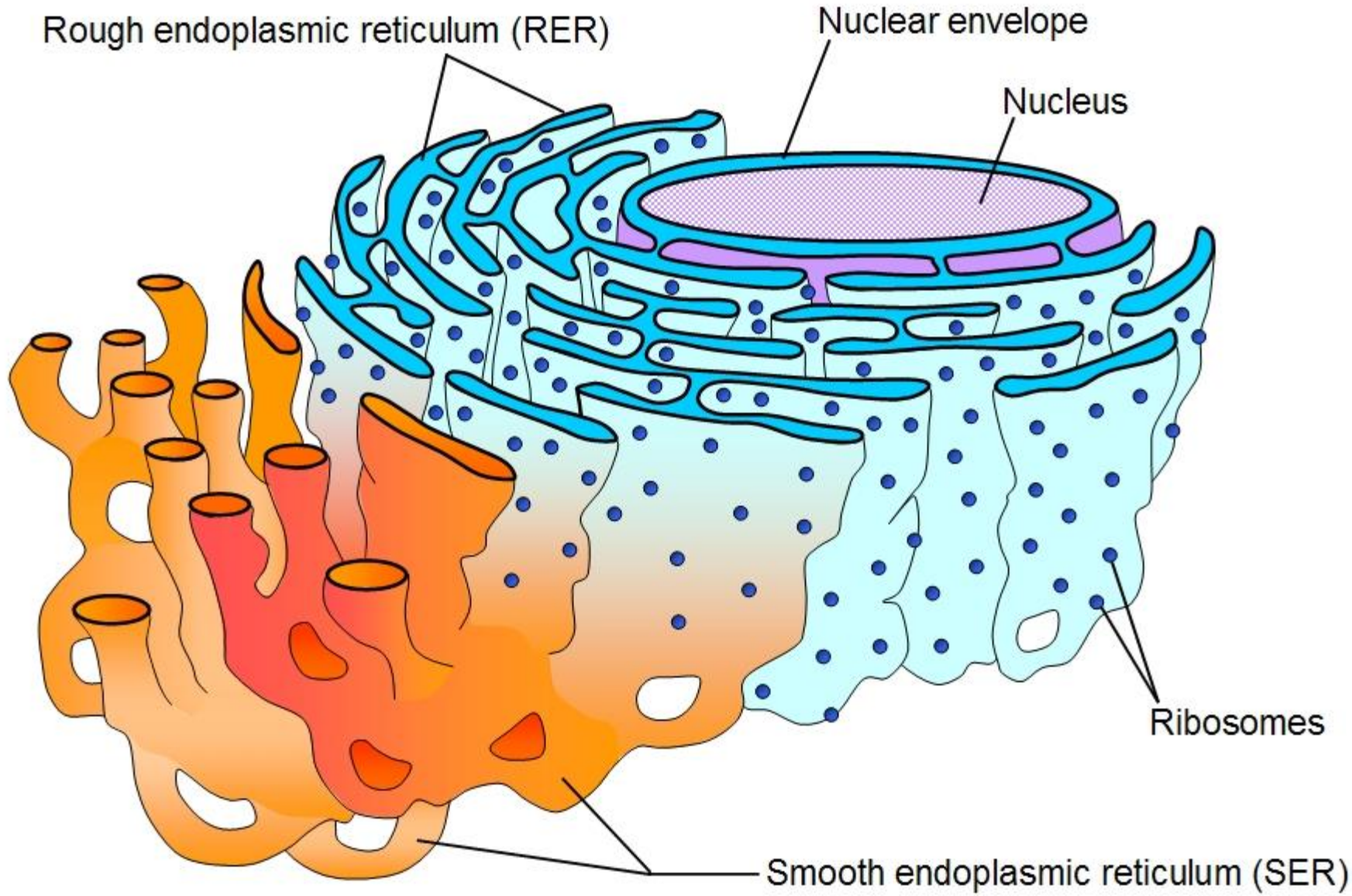
Endoplasmic reticulum

- **Endoplasmic reticulum (ER)**, in biology, a continuous membrane system that forms a series of flattened sacs within the cytoplasm of eukaryotic cells and serves multiple functions, being important particularly in the synthesis, folding, modification, and transport of proteins .
- All eukaryotic cells contain an endoplasmic reticulum (ER).
- In animal cells, the ER usually constitutes more than half of the membranous content of the cell.
- Differences in certain physical and functional characteristics distinguish the two types of ER, known as rough ER and smooth ER.


Rough endoplasmic reticulum (RER)
Nuclear envelope
Nucleus
Ribosomes
Smooth endoplasmic reticulum (SER)

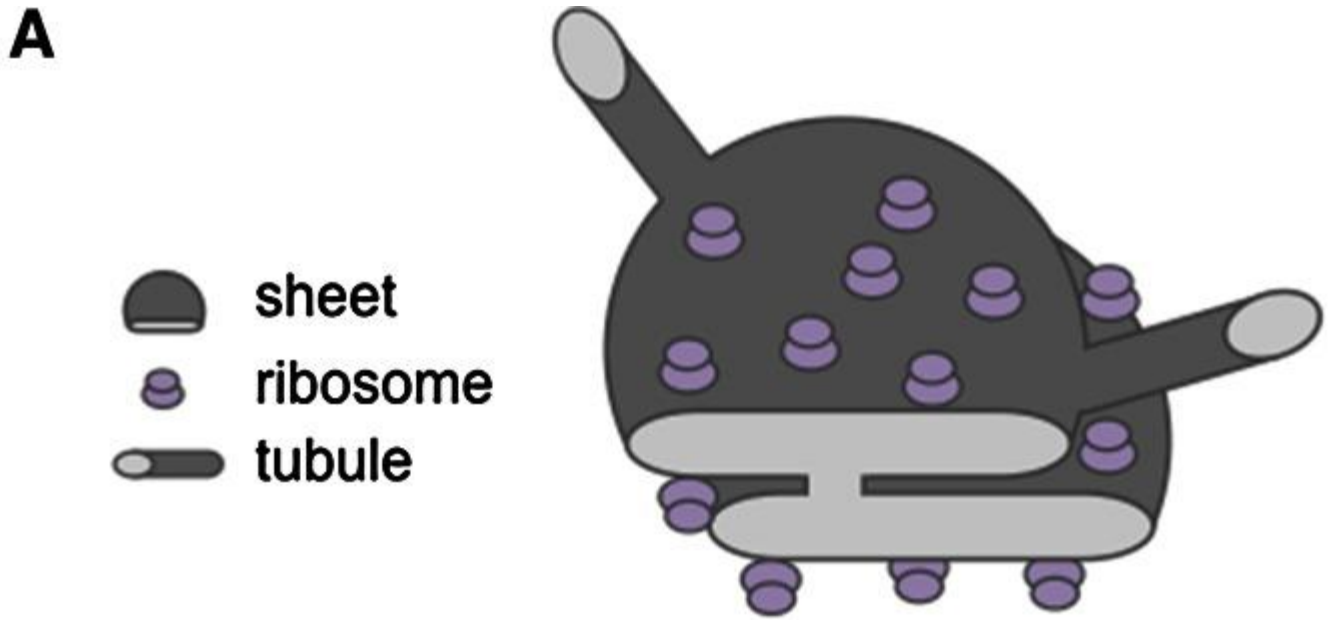
- The ER is the largest organelle in the cell.
- ER is a major site of protein synthesis and transport, protein folding, lipid and steroid synthesis, carbohydrate metabolism and calcium storage.
- The multi-functional nature of this organelle requires a myriad of proteins, unique physical structures and coordination with and response to changes in the intracellular environment.
- ER is composed of multiple different structural domains, each of which is associated with a specific function or functions.
- However, it is not yet clear how these functional subdomains are organized and how different functional domains translate into different structures.

ER structure

- The ER consists of the nuclear envelope and the peripheral ER, which includes smooth tubules and rough sheets. While the ER is defined as an interconnected network with a continuous membrane, the different structures that make up the ER perform very diverse and specialized functions within the cell.
- The nuclear envelope is made up of two lipid bilayers, the inner nuclear membrane (INM) and outer nuclear membrane (ONM), and shares a common lumen with the peripheral ER. Hundreds of nuclear pores spanning the ONM and INM of the nuclear envelope allow transport of molecules, including RNAs and proteins, at various rates of diffusion or regulated transport depending on the size of the molecule.
- The nuclear envelope is connected to sheets, or cisternae, that make up part of the peripheral ER. Sheets are flat in nature consisting of two lipid bilayers with an intervening lumen, with curved regions located only at the membrane edges. Peripheral ER Sheets may vary in size, but the luminal spacing is very consistent, usually about 50 nm in mammals and 30 nm in yeast
- Sheets are usually observed in a stacked conformation and are connected via regions of twisted membranes with helical edges

ER structure

- These rough sheets, as defined by the high density of ribosomes on the cytosolic surface are the main site of synthesis, folding and post-translational modifications for secreted or membrane-bound proteins.
- In turn, far fewer ribosomes are present on the membrane surface of ER tubules , which is highly curved and smooth and may not accommodate the binding of large polysomes



Structure of ER sheets and tubules. **a** ER sheets and tubules have a diameter of 30–50 nm in eukaryotes. Eukaryotic ribosomes are 25–30 nm and localize to the flat regions of ER sheets, giving the sheets a rough appearance (rough ER). Ribosomes are present in much lower numbers on tubules, giving the tubules a more smooth appearance (smooth ER).

Protein synthesis and folding

- Rough ER is named because of its rough surface due to presence of ribosomes.
- Rough ER is in continuation with the outer nuclear membrane. Lies adjacent to the nucleus.
- The ribosomes on rough ER specialize in the synthesis of secreted and integral membrane proteins and also subpopulation of cytosolic proteins.
- Translation of secretory or integral membrane proteins initiates in the cytosol, then ribosomes containing these mRNAs are recruited to the ER membrane via a signal sequence within the amino terminus of the nascent polypeptide that is recognized and bound by the signal recognition particle (SRP)
- The complex of mRNA:ribosome:nascent polypeptide:SRP is targeted to the ER where it docks on the SRP receptor .
- Translation continues on the ER and the emerging polypeptide can co-translationally enter the ER through the translocon, which is a channel that contains several Sec proteins and spans the lipid bilayer.

Protein synthesis and folding

- At this point the protein will be shifted laterally and become anchored within the phospholipid bilayer where it remains
- If the protein is not destined to be integrated into the membrane, but instead enter the secretory pathway or the lumen of membrane-bound organelles, the protein begins the process of transport.
- Once translation is complete and the signal peptide has been cleaved the ribosomes are released back into the cytosol
- For mRNAs translated by stably-bound ER ribosomes, mRNAs are released and ribosomes may remain bound to the ER and participate in multiple rounds of translation

Protein synthesis and folding

- Following protein synthesis and translocation into the ER lumen, a protein destined for secretion must undergo proper folding and modifications, with the aid of chaperones and folding enzymes.
- These modifications include N-linked glycosylation, disulfide bond formation and oligomerization
- At this point the fate of the secretory proteins is determined. If the protein functions in the ER, for example as a chaperone, then proper folding will commence.
- If the protein is destined for secretion, it will be released by the chaperones and packaged for travel through the Golgi on to a final destination (such as the plasma membrane or secreted) or move into peroxisomes.
- On the other hand, even with several proteins and complexes dedicated to folding proteins properly, a fraction of proteins do not achieve native and functional form and are either misfolded or aggregated. These proteins can either remain in the ER or enter the ER-associated degradation (ERAD) pathway mediated by the proteasome, assuring that aberrant polypeptides do not inadvertently enter the secretory pathway.

Lipid biogenesis, Calcium (Ca^{2+}) metabolism

- While the ER is a major site of protein synthesis, it is also a site of bulk membrane lipid biogenesis , which occurs in the endomembrane compartment that includes the ER and Golgi apparatus.
- ER is also a major store of intracellular Ca^{2+}