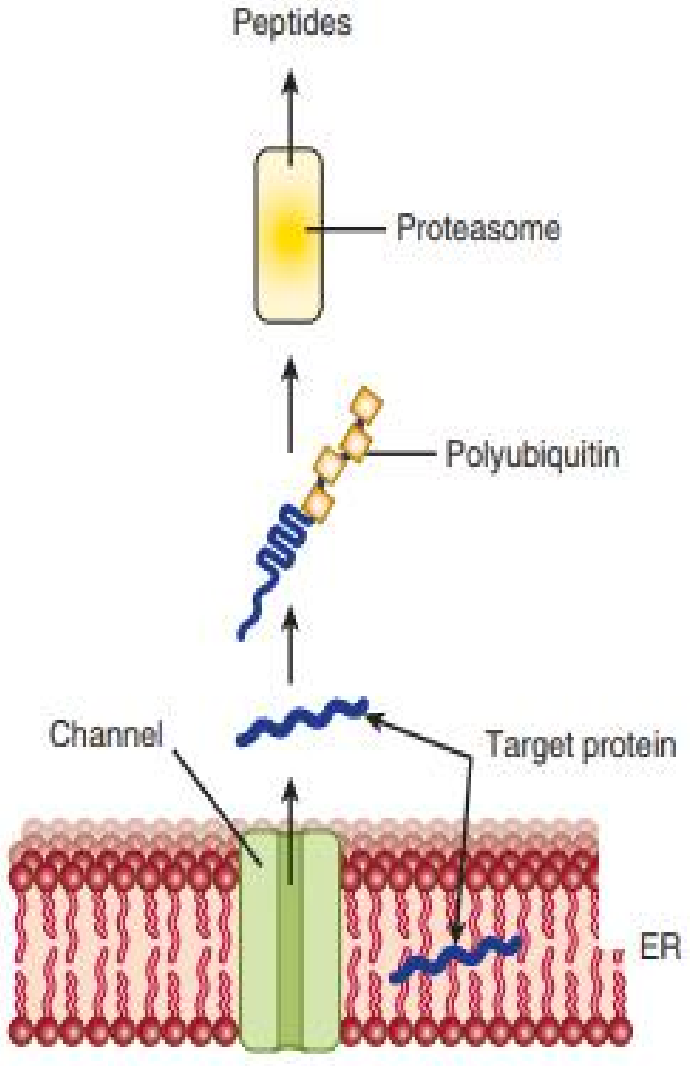
Scheme of the events in ERAD

- A target protein which is misfolded undergoes retrograde transport through the ER membrane into the cytosol, where it is subjected to polyubiquitination.
- Following polyubiquitination, it enters a proteasome, inside which it is degraded to small peptides that exit.
- Several proteins, including Sec61, Derlin 1 and the ERAD E3 ligases, Hrd1 and Doa10, are potential ERAD channel candidates.



THE NOBEL PRIZE IN CHEMISTRY 2004

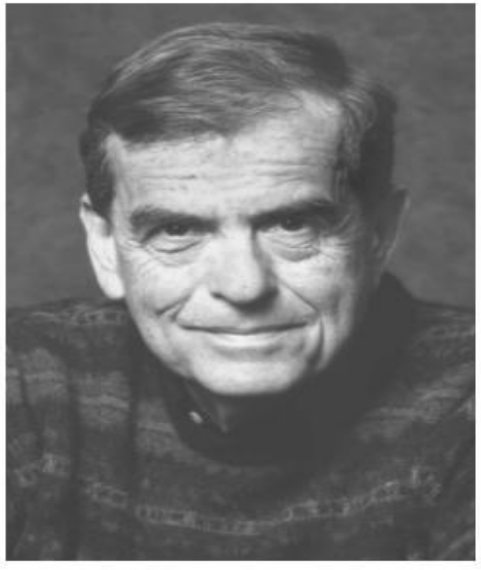


Photo: D. Porges

Aaron Ciechanover

Prize share: 1/3

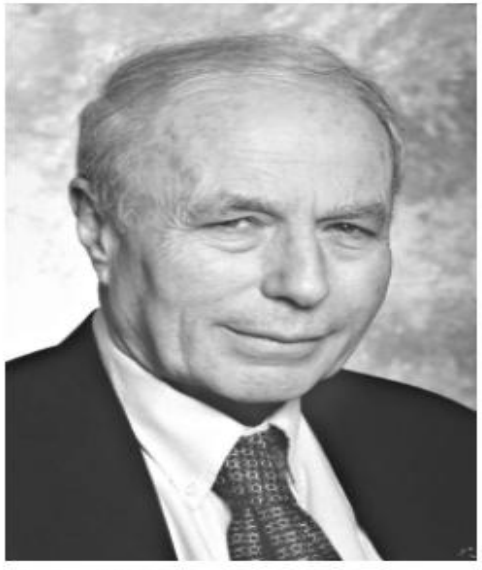


Photo: D. Porges

Avram Hershko

Prize share: 1/3

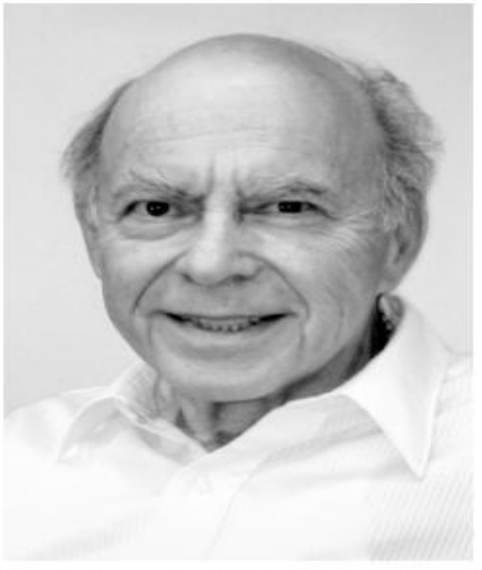


Photo from the Nobel Foundation archive.

Irwin Rose

Prize share: 1/3

The Nobel Prize in Chemistry 2004 was awarded jointly to Aaron Ciechanover, Avram Hershko and Irwin Rose "for the discovery of ubiquitin-mediated protein degradation."

Ubiquitin-Dependent Degradation

- Ubiquitin is a small (8.5 kDa, 76 residue) polypeptide that targets many intracellular proteins for degradation.
- Ubiquitin molecules are attached by non-α-peptide bonds formed between the carboxyl terminal of ubiquitin and the ε-amino groups of lysyl residues in the target protein.
- The residue present at its amino terminus affects whether a protein is ubiquitinated.
- Amino terminal Met or Ser residues retard, whereas Asp or Arg accelerate ubiquitination
- Attachment of a single ubiquitin molecule to transmembrane proteins alters their subcellular localization and targets them for degradation.
- Subsequent degradation of ubiquitin-tagged proteins takes place in the proteasome, a macromolecule that also is ubiquitous in eukaryotic cells.

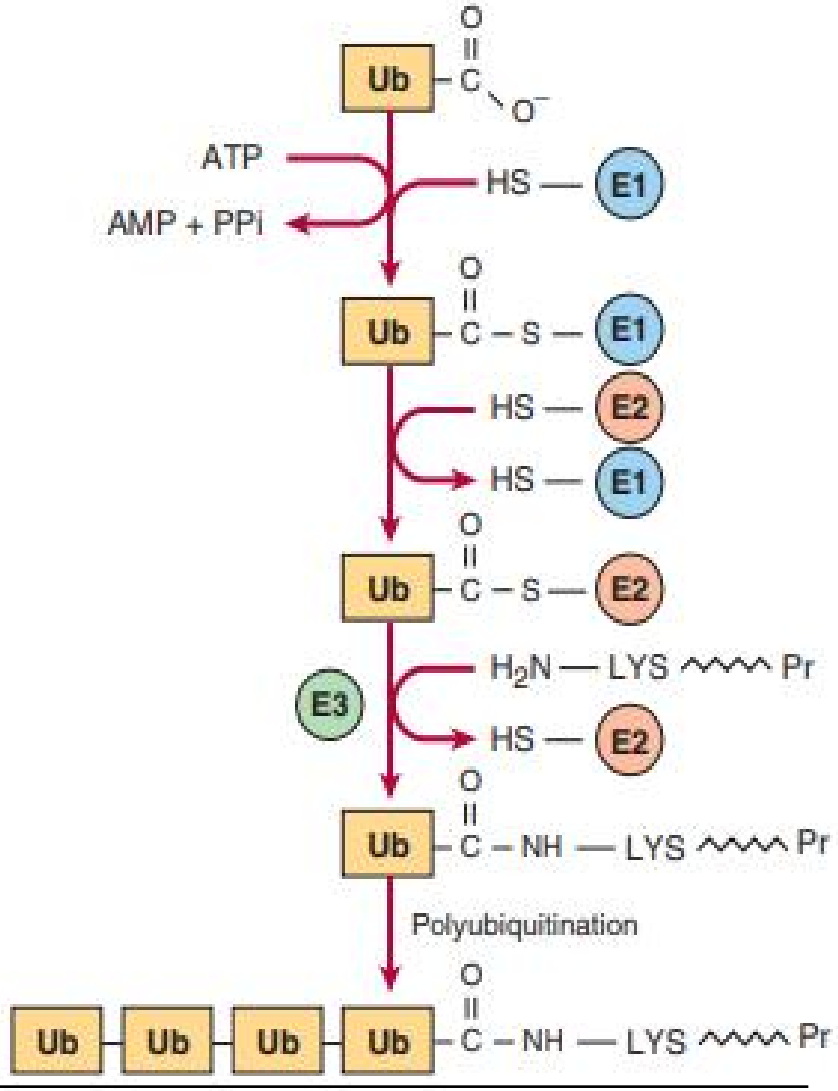
Reactions in attachment of ubiquitin to proteins.

E1 - activating enzyme,

E2 - ligase, and

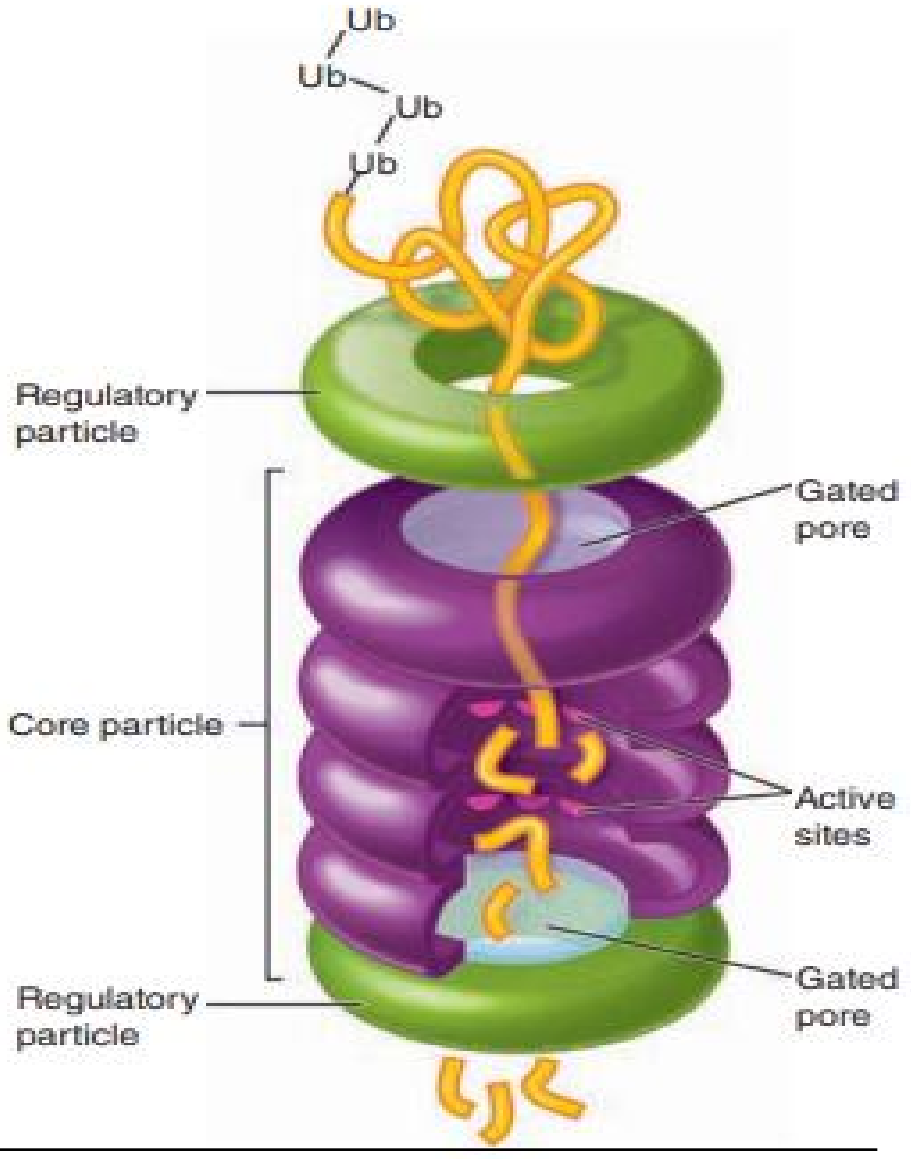
E3 - transferase

- The terminal COOH of ubiquitin first forms a thioester.
- The coupled hydrolysis of PPi by pyrophosphatase ensures that the reaction will proceed readily.
- A thioester exchange reaction now transfers activated ubiquitin to E2.
- E3 then catalyzes the transfer of ubiquitin to the ε-amino group of a lysyl residue of the target protein.
- Additional rounds of ubiquitination result in subsequent polyubiquitination



Proteasome

- The proteasome consists of a macromolecular, cylindrical complex of proteins, whose stacked rings form a central pore that harbors the active sites of proteolytic enzymes
- For degradation, a protein thus must first enter the central pore.



- Entry into the core is regulated by the two outer rings that recognize polyubiquitinated proteins .
- The regulatory particle recognizes the ubiquitinated protein which are unfolded by ATPases present in the regulatory particles or caps.
- Protease active sites in the core of the proteosome attack peptide bonds and degrade the protein.
- Peptides are released into the cytosol for further degradation by cytosolic peptidases.
- Both normally and abnormally folded proteins are substrates for the proteasome.
- Liberated ubiquitin molecules are recycled.

- The proteasome plays an important role in presenting small peptides produced by degradation of various viruses and other molecules to MHC class I molecules, a key step in antigen presentation to T lymphocytes

- Genetic disorders that result from defects in the genes that encode ubiquitin, ubiquitin ligases, or deubiquitinating enzymes include

  Angelman syndrome

  Autosomal recessive juvenile Parkinson's disease

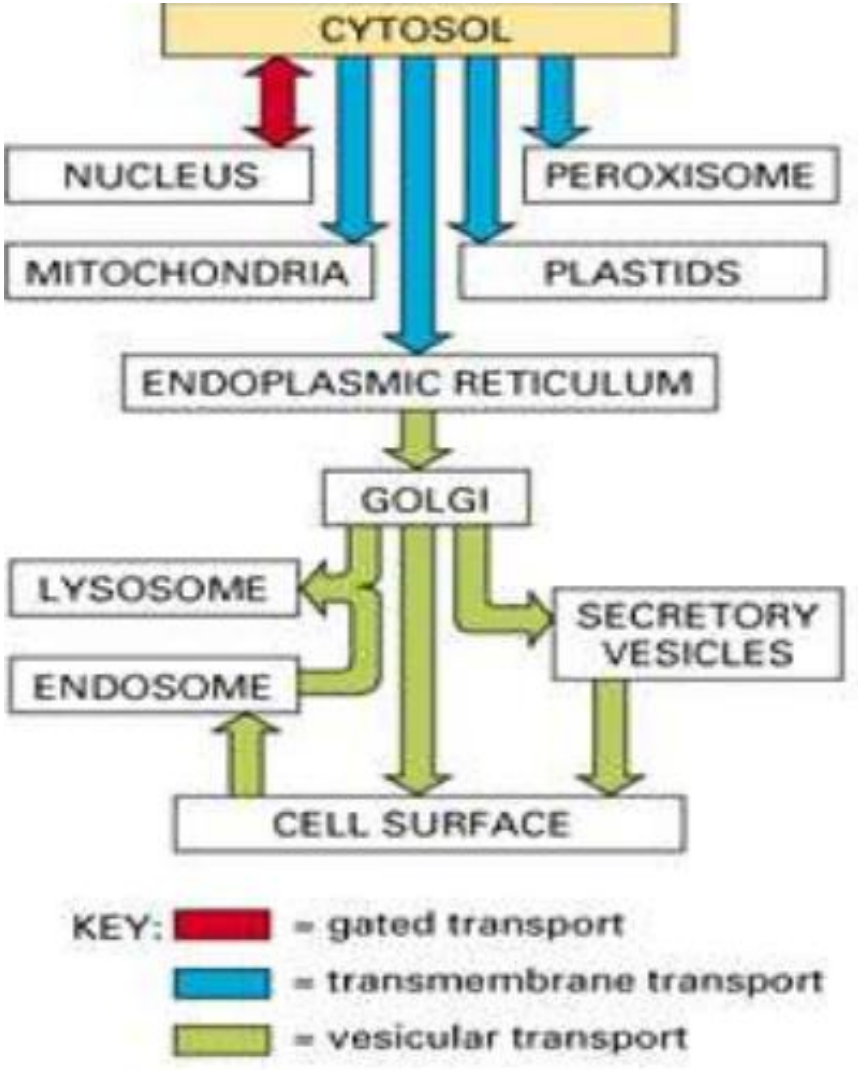
  Von Hippel-Lindau syndrome, and

  Congenital polycythemia

TRANSPORT VESICLES

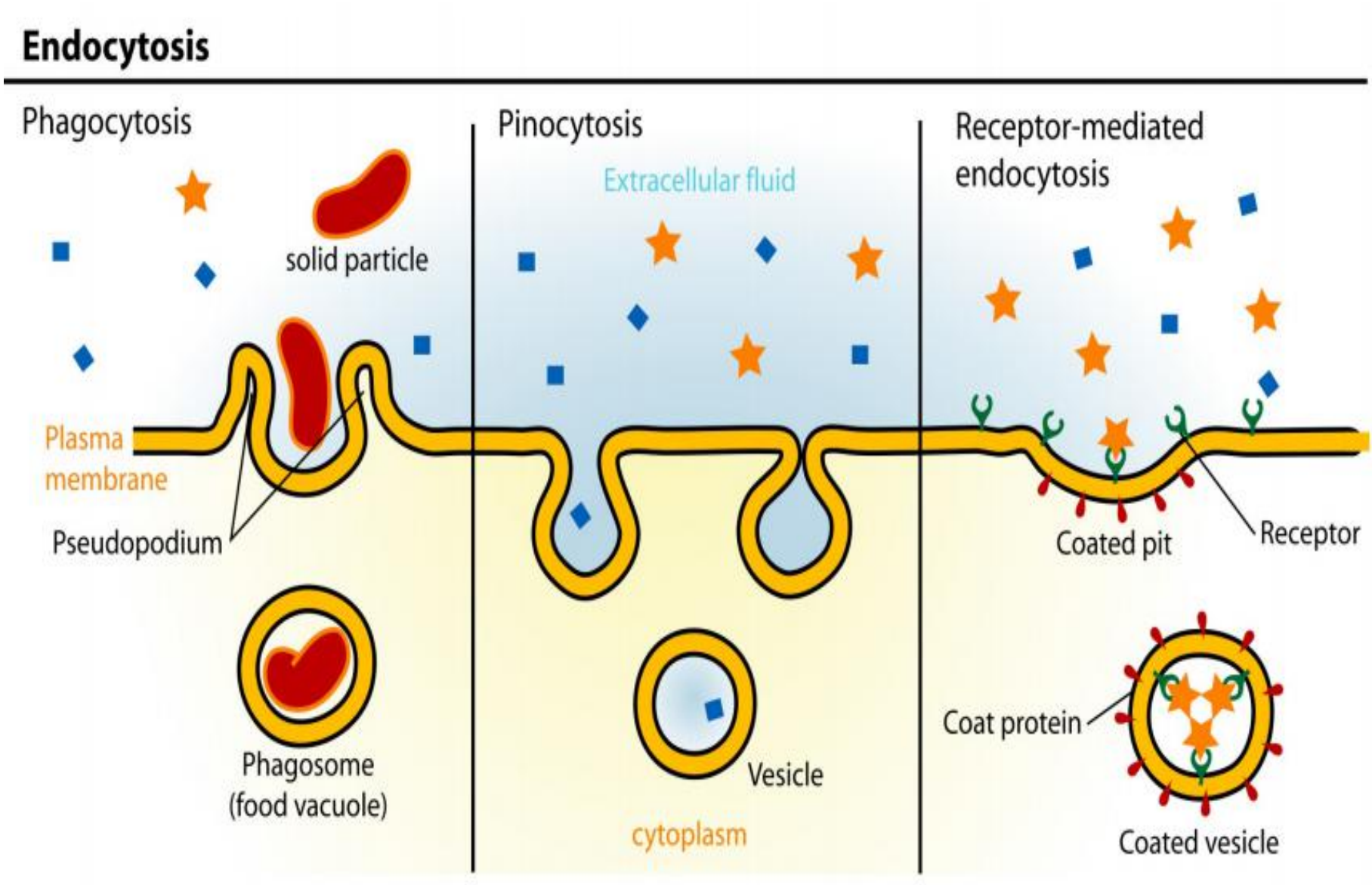
- Proteins that are synthesized on membrane-bound polyribosomes and are destined for the GA or PM reach these sites inside transport vesicles

- Each vesicle has its own set of coat proteins.



Vesicular Transport

- Vesicular transport is the predominant mechanism for exchange of proteins and lipids between membrane-bound organelles in eukaryotic cells
- This form of transport involves the movement of various elements with the aid of the bubble like vesicles created from the cell membrane
- It is fundamentally divided into endocytosis and exocytosis
- Endocytosis is divided into 3 distinct mechanisms
  Phagocytosis
  Pinocytosis and
  Receptor mediated endocytosis



Receptor Mediated Endocytosis

- The major mechanism of vesicular transport between ER and Golgi.
- Takes place in the regions of the membranes known as coated pits
- The coated pits has high concentration of protein clarthrin and this mechanism of receptor mediated endocytosis is the clarthin coated vesicle method
- However there is another method in which the receptor mediated endocytosis takes place without the clarthin coated vesicles
- The SNARE proteins helps in the later type of the receptor

Some Types of Vesicles and Their Functions

Vesicle	Function
COPI	Involved in intra-GA transport and retrograde transport from the GA to the ER
COPII	Involved in export from the ER to either ERGIC or the GA
Clathrin	Involved in transport in post-GA locations including the PM, TGN and endosomes
Secretory vesicles	Involved in regulated secretion from organs such as the pancreas (eg, secretion of insulin)
Vesicles from the TGN to the PM	They carry proteins to the PM and are also involved in constitutive secretion