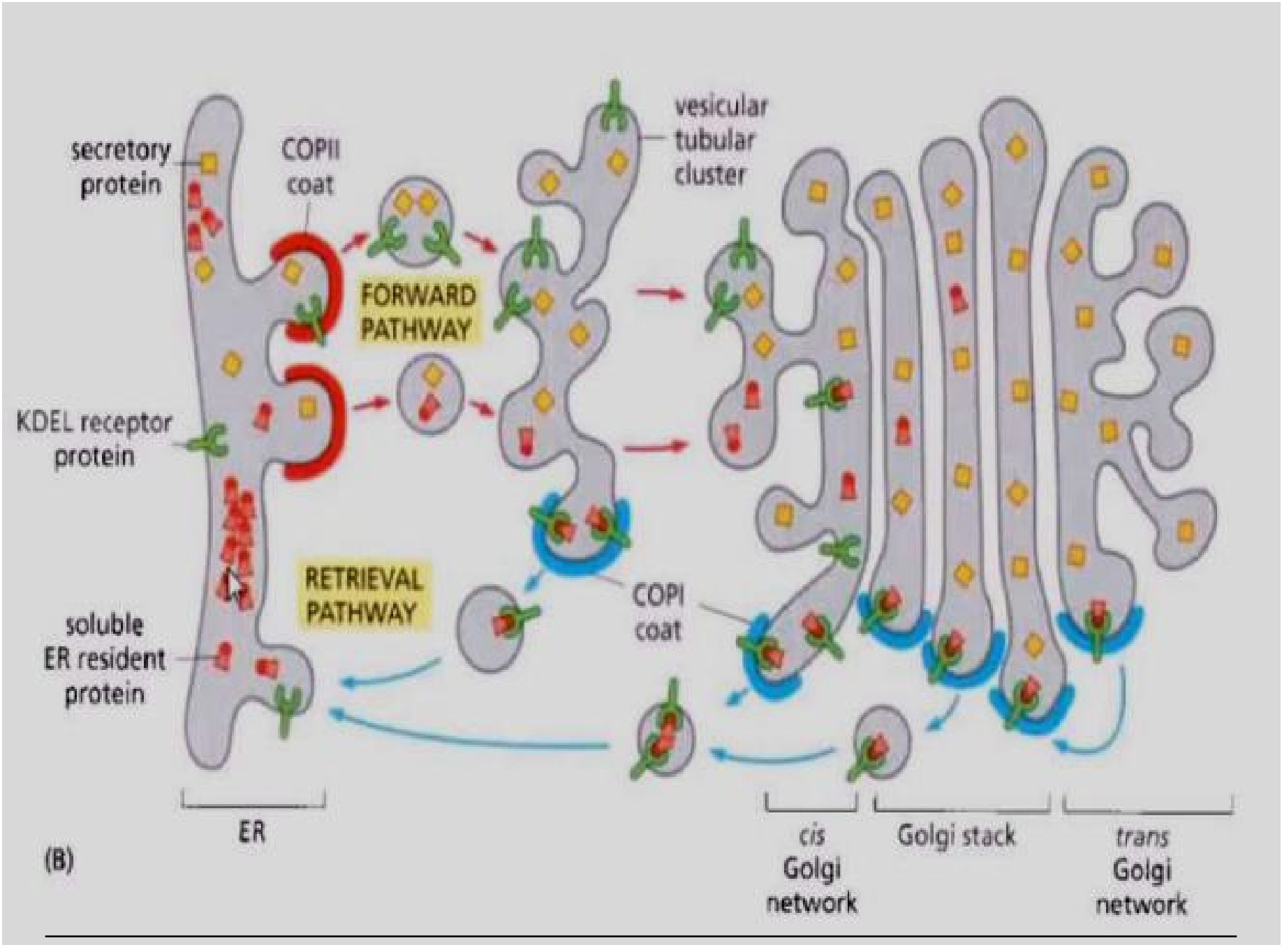

- A number of proteins possess the amino acid sequence KDEL (Lys-Asp-Glu-Leu) at their carboxyl terminal
- KDEL-containing proteins first travel to the GA in vesicles coated with coat protein II (COPII)
- This process is known as anterograde vesicular transport.
- In the GA they interact with a specific KDEL receptor protein, which retains them transiently.
- They then return to the ER in vesicles coated with COPI (retrograde vesicular transport), where they dissociate from the receptor, and are thus retrieved
- Certain other non-KDEL-containing proteins also pass to the Golgi and then return, by retrograde vesicular transport, to the ER to be inserted therein.

THE ER FUNCTIONS AS THE QUALITY CONTROL COMPARTMENT OF THE CELL

- After entering the ER, newly synthesized proteins attempt to fold with the assistance of chaperones and folding enzymes.
- Some Chaperones and Enzymes Involved in Folding That Are Located in the Rough Endoplasmic Reticulum:

1. BiP (immunoglobulin heavy chain binding protein)
2. GRP94 (glucose-regulated protein)
3. Calnexin
4. Calreticulin
5. PDI (protein disulfide isomerase)
6. PPI (peptidyl prolyl cis-trans isomerase)

1. Calnexin

- The chaperone calnexin is a calcium-binding protein
- located in the ER membrane.
- This protein binds a wide variety of proteins, including major histocompatibility complex (MHC) antigens and a variety of plasma proteins.
- Calnexin binds the monoglucosylated species of glycoproteins that occur during processing of glycoproteins, retaining them in the ER until the glycoprotein has folded properly

2. GRP94 (glucose-regulated protein)

- It is the most abundant protein in the ER lumen, and is ubiquitously present in nucleated cells.
- GRP94 function as molecular chaperones and can bind to malfolded proteins and unassembled complexes.
- They are induced in response to stress, but once the stress is removed the GRPs are posttranscriptionally modified into biologically inactive forms.

3. Calreticulin:

- Calreticulin, which is also a calcium binding protein, has properties similar to those of calnexin
- But it is not membrane-bound.

4. Protein disulfide isomerase (PDI):

- Protein disulfide isomerase (PDI) promotes rapid formation and reshuffling of disulfide bonds until the correct set is achieved

5. Peptidyl prolyl isomerase (PPI):

- It accelerates folding of proline-containing proteins by catalyzing the cis–trans isomerization of X-Pro bonds, where X is any amino acid residue.

- Misfolded or incompletely folded proteins interact with chaperones, which retain them in the ER and prevent them from being exported to their final destinations.
- If such interactions continue for a prolonged period of time, the misfolded proteins are usually disposed of by endoplasmic reticulum associated degradation (ERAD).
- This avoids a harmful build-up of misfolded proteins.
- In a number of genetic diseases, such as cystic fibrosis, retention of misfolded proteins occurs in the ER, and in some cases, the retained proteins still exhibit some functional activity

Conformational Diseases That Are Caused by Abnormalities in Intracellular Transport of Proteins and Enzymes due to Mutations

Disease	Affected Protein
α_1-Antitrypsin deficiency with liver disease	α_1-Antitrypsin
Chediak-Higashi syndrome	Lysosomal trafficking regulator
Combined deficiency of factors V and VIII	ERGIC53, a mannose-binding lectin
Cystic fibrosis	CFTR
Diabetes mellitus [some cases]	Insulin receptor (α-subunit)
Familial hypercholesterolemia, autosomal dominant	LDL receptor
Gaucher disease	β-Glucosidase
Hemophilia A and B	Factors VIII and IX
Hereditary hemochromatosis	HFE
Hermansky-Pudlak syndrome	AP-3 adaptor complex β3A subunit
I-cell disease	*N*-acetylglucosamine 1-phosphotransferase
Lowe oculocerebrorenal syndrome	PIP_2 5-phosphatase
Tay-Sachs disease	β-Hexosaminidase
von Willebrand disease	von Willebrand factor

Endoplasmic Reticulum Stress

- Maintenance of homeostasis in the ER is important for normal cell function.
- The unique environment within the lumen of the ER is disturbed
    - changes in ER Ca2+,
    - alterations of redox status,
    - exposure to various toxins or
    - some viruses

  can lead to reduced protein folding capacity and the accumulation of misfolded proteins
- The accumulation of misfolded proteins in the ER is referred to as ER stress.

- The cell responds to ES by unfolded protein response to restore the ER homeostasis.
- The unfolded protein response is initiated by ER stress sensors responds in many ways:

1. Transient inhibition of translation to decrease the protein load entering the ER.
2. Increased expression of chaperons to enhance protein folding.
3. Increased synthesis of protein required for degradation of protein.

- If the ES persists, cell undergoes apoptosis.

- Degradation of misfolded proteins occur after these proteins are transported back across the ER into cytosol. (retrotranslocation or dislocation)
- Proteins are degraded in two ways -

A. By lysosomal proteases – which do not require ATP

B. By Proteasome – the proteasomal degradation requires ubiquitin and ATP.

The protein to be degraded are marked by attachment of ubiquitin .

It is major pathway of protein degradation.