Day 11 (Cell Biology)

Only properly folded proteins can leave ER.

- to exit from ER, proteins must be properly folded and assembled
- misfolded or incomplete → transiently bound to chaperones → escorted to cytosol → degraded in proteosomes
- failures surprisingly common → most of the newly synthesised subunits of T cell receptor and acetylcholine receptor are normally degraded.
- drawbacks of stringent control — mutated, but potentially active Cl^- transporter destroyed in cystic fibrosis

Vesicular tubular clusters mediate transport from ER to Golgi Apparatus.

- after shedding coat, membranes fuse with one another, — homotypic and heterotypic.

Homotypic fusion - fusion of membranes from same compartment
↳ set of matching SNAREs reqd.

e.g.,
Vesicular tubular clusters - formed when ER-derived vesicles fuse with one another
↳ function as transport containers that bring material from ER to Golgi

- As soon as they form, clusters bud off transport vesicles
- COPI coated;
  formed of coatomers — composed of components that make up inner and outer layers as preassembled units
- function as retrieval pathway carrying back escaped ER resident proteins, cargo receptors and SNAREs.
- COPI assembly starts only few seconds after COPII is shed — mechanism unknown

Retrieval Pathway

- retrieval pathway to ER uses sorting signals (ER retrieval signals)
- Resident ER memb proteins have retrieval sequences like KKXX at their extreme C-Terminal
- Lumen proteins have KDEL motif, to return to ER. To leave ER, retrieval sequence must be cleaved off.
  ↳ If the KDEL sequence is removed from a protein, it is slowly secreted from the cell.
- affinity of the KDEL receptor increases in Golgi due to pH sensitive interactions.

The Golgi Apparatus

- collection of flattened, membrane enclosed compartments called cisternae (often connected by tubular connections)
- localised near nucleus and centrosome, connected by microtubules

- generates the heterogenous oligosaccharide str. seen in mature proteins

⇓

proteins in cis Golgi network (CGN) — multistage processing unit

↓

medial cisterna

↓

trans cisterna (glycosylation is completed)

- resident proteins are all memb-bound
- 2 broad classes of N-linked oligosaccharides

complex (formed when original N-linked sugar is trimmed & new sugars are added)

high-mannose (trimmed but no new sugars are added)

Whether a given oligosaccharide remains high mannose depends on its position in the protein

↓

if it is inaccessible to processing enzymes because sugars are tightly linked to surface → likely to remain in high-mannose form.

Proteoglycans are assembled in Golgi

- often sugar is added to hydroxyl group of serine and threonine (O-linked glycosylation)
  - ↳ use sugar nucleotides in lumen of Golgi to add sugars

to protein one at a time.

- heaviest O-linked glycosylation conferred on mucins & on proteoglycan core proteins to form proteoglycans.
  1. polymerization of one or more glycosaminoglycan chains onto serines of a core protein.

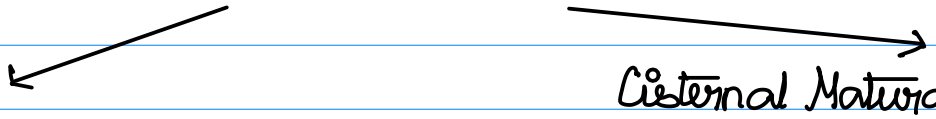
Many proteoglycans are secreted and become components of ECM, while others remain anchored to extracellular surface of memb., and others are secreted as mucus

- sugars incorporated into glycosaminoglycans are heavily sulfated in the Golgi apparatus immediately after these polymers are made (adding negative charge)

↓

sulfation depends on sulfate donor 3'-phosphoadenosine-5'-phosphosulfate (PAPS) which is transported from cytosol into lumen of Trans-Golgi network

Transport Through the Golgi Apparatus Occurs by Multiple Mechanisms



Vesicle Transport Mechanism

Cisternal Maturation Mechanism

Cisternal Maturation Mechanism

- new cis cisternae continually form as vesicular tubular clusters arrive from the ER & fuse with Golgi transport vesicles

In this way, a cisterna full of cargo moves through the Golgi stack while different subsets of Golgi resident proteins transit backwards in COPI-coated vesicles from later to earlier cisternae.

- Golgi matrix proteins (golgins) help org. stack.