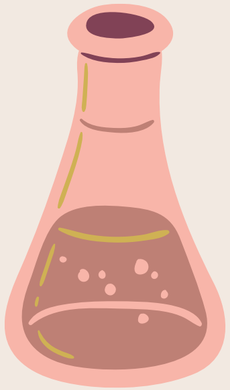
Impuls Medical Institute

CELL BIOLOGY

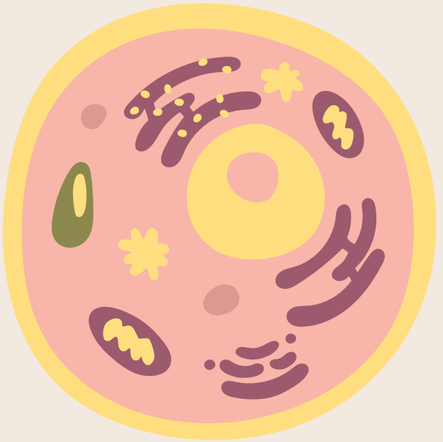
Presented by:
Doctor Cardion

TOPIC OUTLINE:



cell cycle

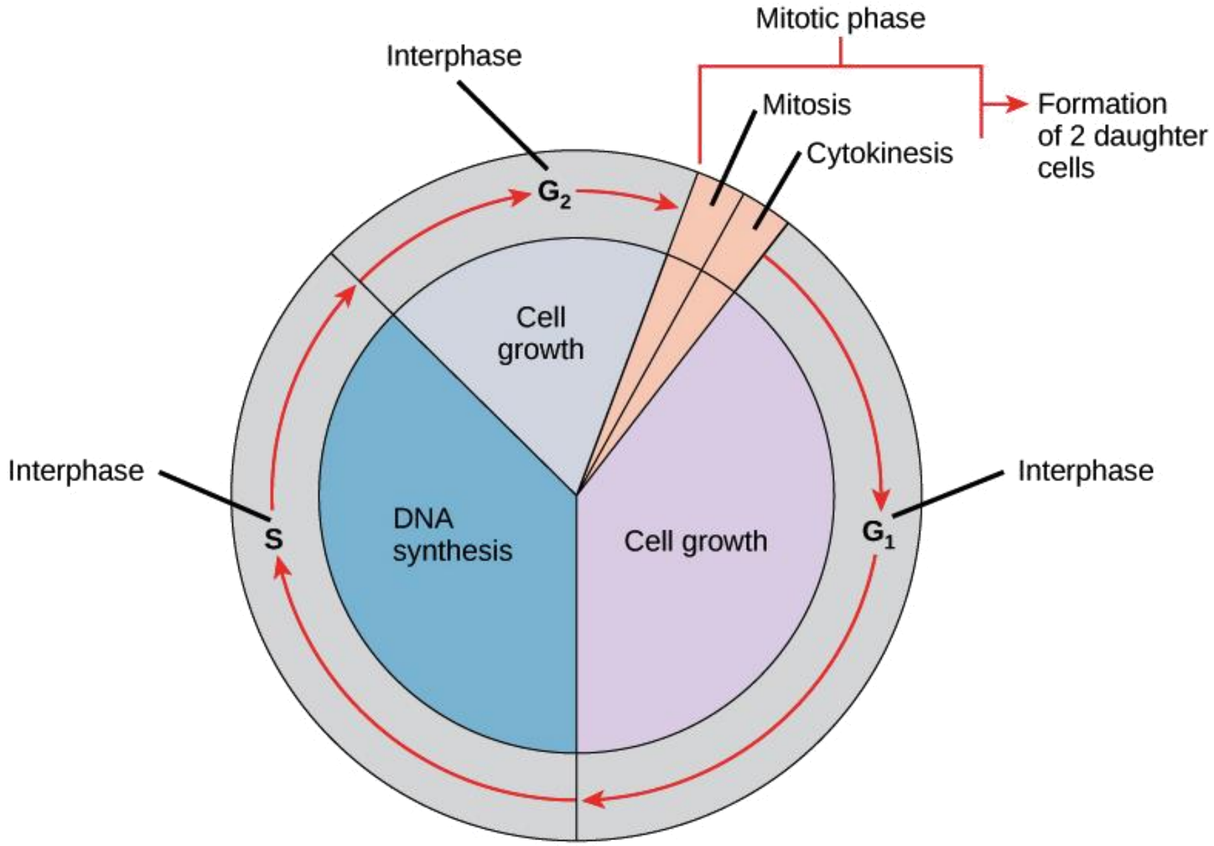
organoids



cell

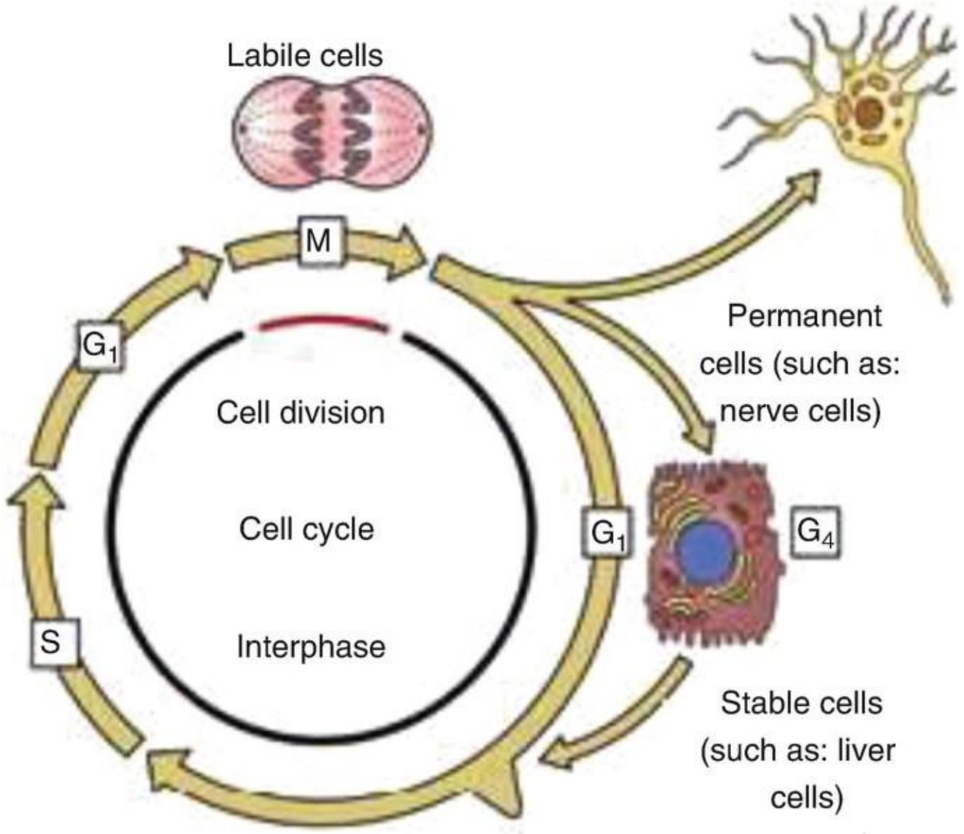
CELL CYCLE PHASES

Checkpoints control transitions between phases of cell cycle. This process is regulated by cyclins, cyclin-dependent kinases (CDKs), and tumor suppressors. M phase (shortest phase of cell cycle) includes mitosis (prophase, prometaphase, metaphase, anaphase, telophase) and cytokinesis (cytoplasm splits in two). G_1 is of variable duration.

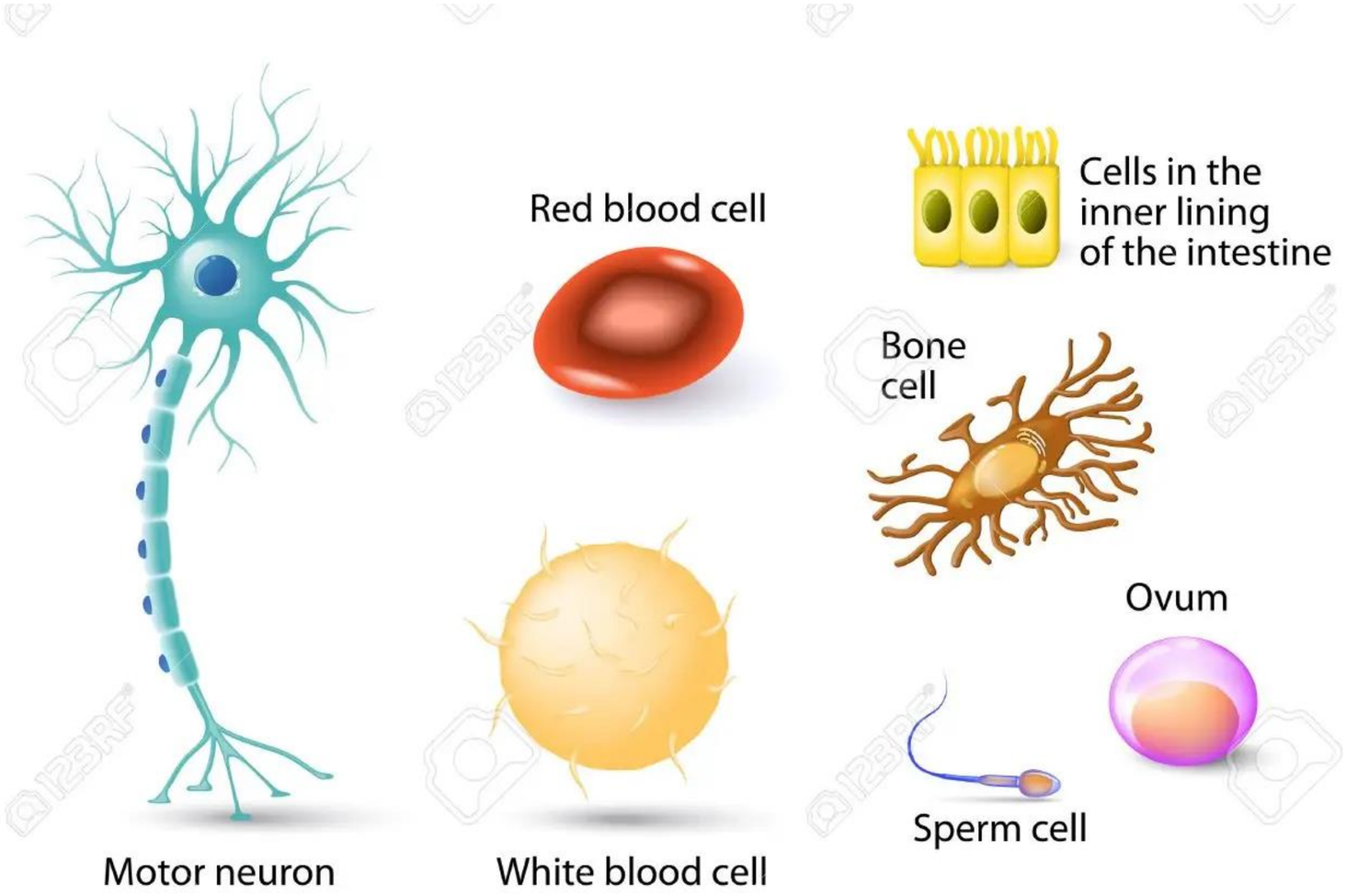


CELL TYPES

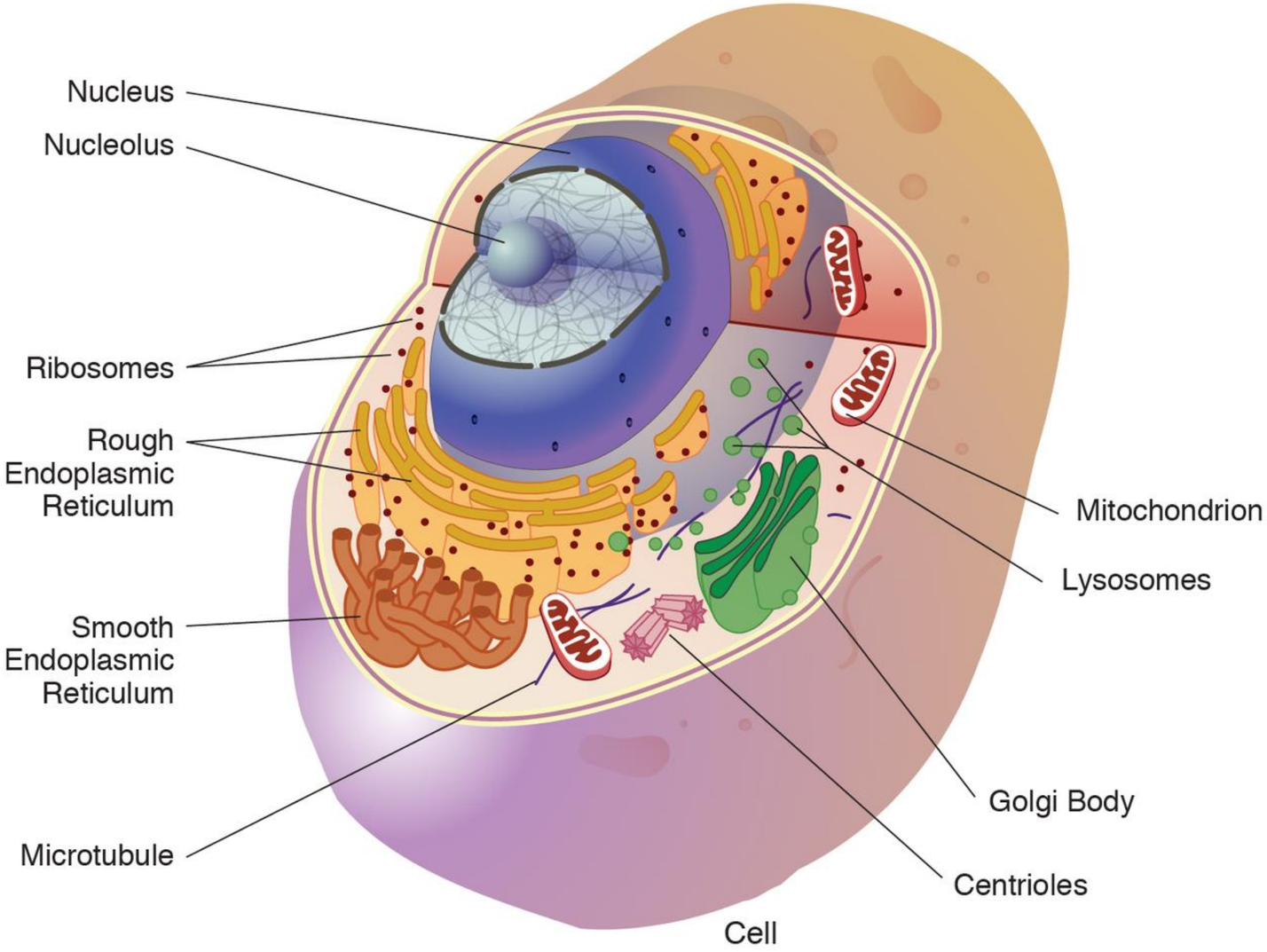
Permanent	Remain in G_0, regenerate from stem cells.	Neurons, skeletal and cardiac muscle, RBCs.
Stable (quiescent)	Enter G_1 from G_0 when stimulated.	Hepatocytes, lymphocytes, PCT, periosteal cells.
Labile	Never go to G_0, divide rapidly with a short G_1. Most affected by chemotherapy.	Bone marrow, gut epithelium, skin, hair follicles, germ cells.



CELL TYPES

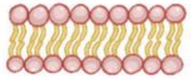


CELL STRUCTURE



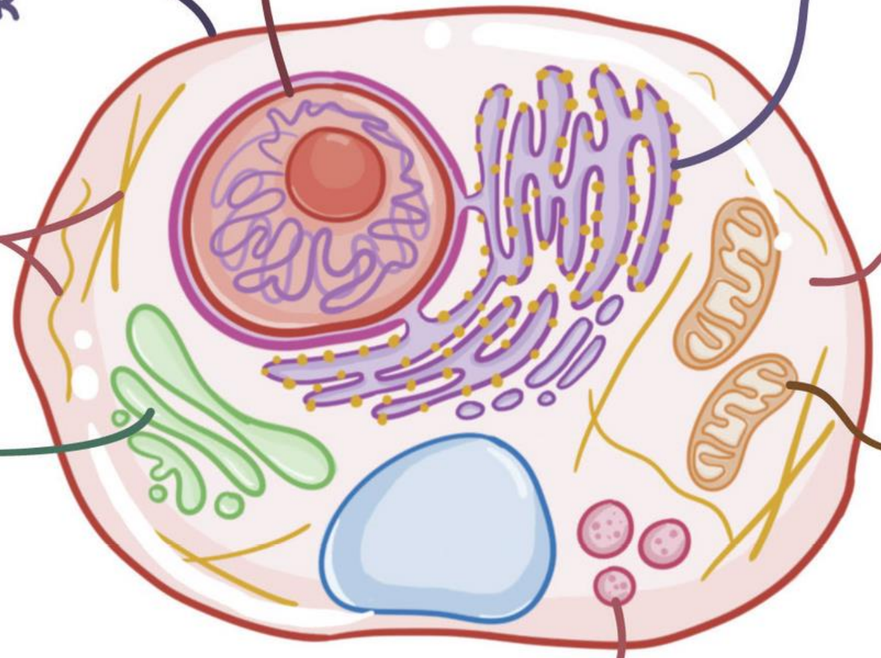
CELL

CELL MEMBRANE
- PHOSPHOLIPID BILAYER



NUCLEUS
- GENETIC MATERIAL

ENDOPLASMIC RETICULUM
- GENERATES
  - ~ PROTEINS, LIPIDS, STEROIDS



CYTOSKELETON
- STRUCTURAL STABILITY

CYTOSOL
- INTRACELLULAR FLUID

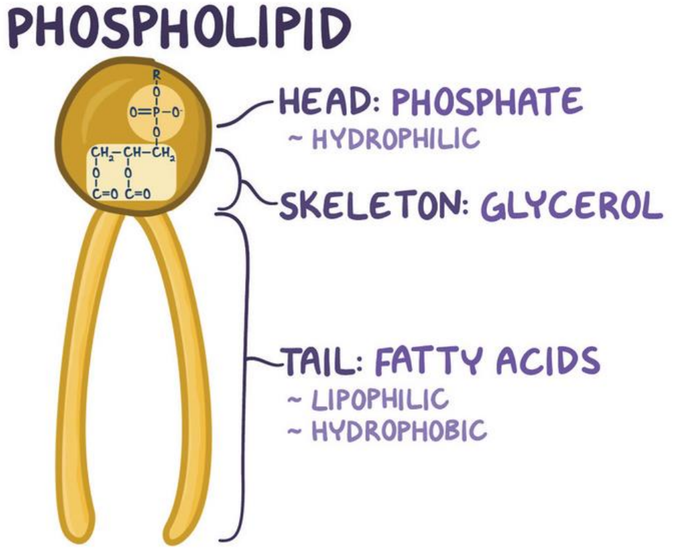
GOLGI APPARATUS
- PACKAGES PROTEINS, LIPIDS, & HORMONES INTO VESICLES

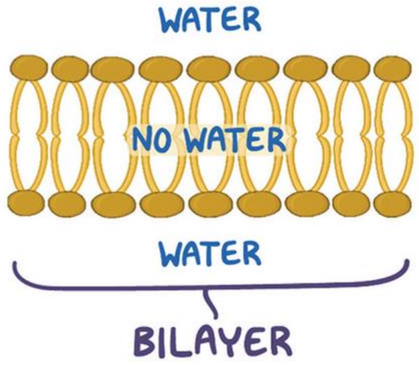
MITOCHONDRIA
- ENERGY
  - ~ AEROBIC, BETA RESPIRATION
    - ↓
    - burns glucose, fatty acids

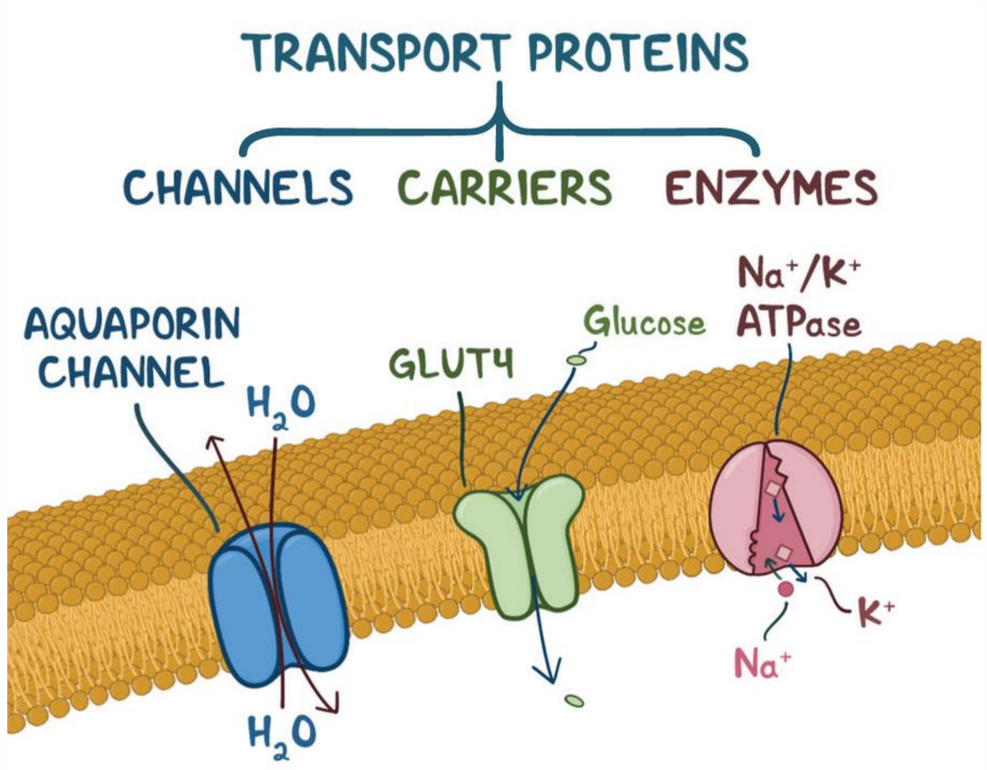
PEROXISOME
- CHOPS LONG FATTY ACIDS
  - ↓
  - MEDIUM FATTY ACIDS

CELL STRUCTURE BASICS

. Basic structural, biological, functional unit
that comprise organism
. Smallest self-replicating life-form
. Over 200 types in human body
. Cells = tissue = organ = organ systems = organism







- Plasma membrane
- Cytoplasm
  - Fluid suspension
  - Composition: cytosol, organelles

NUCLEUS

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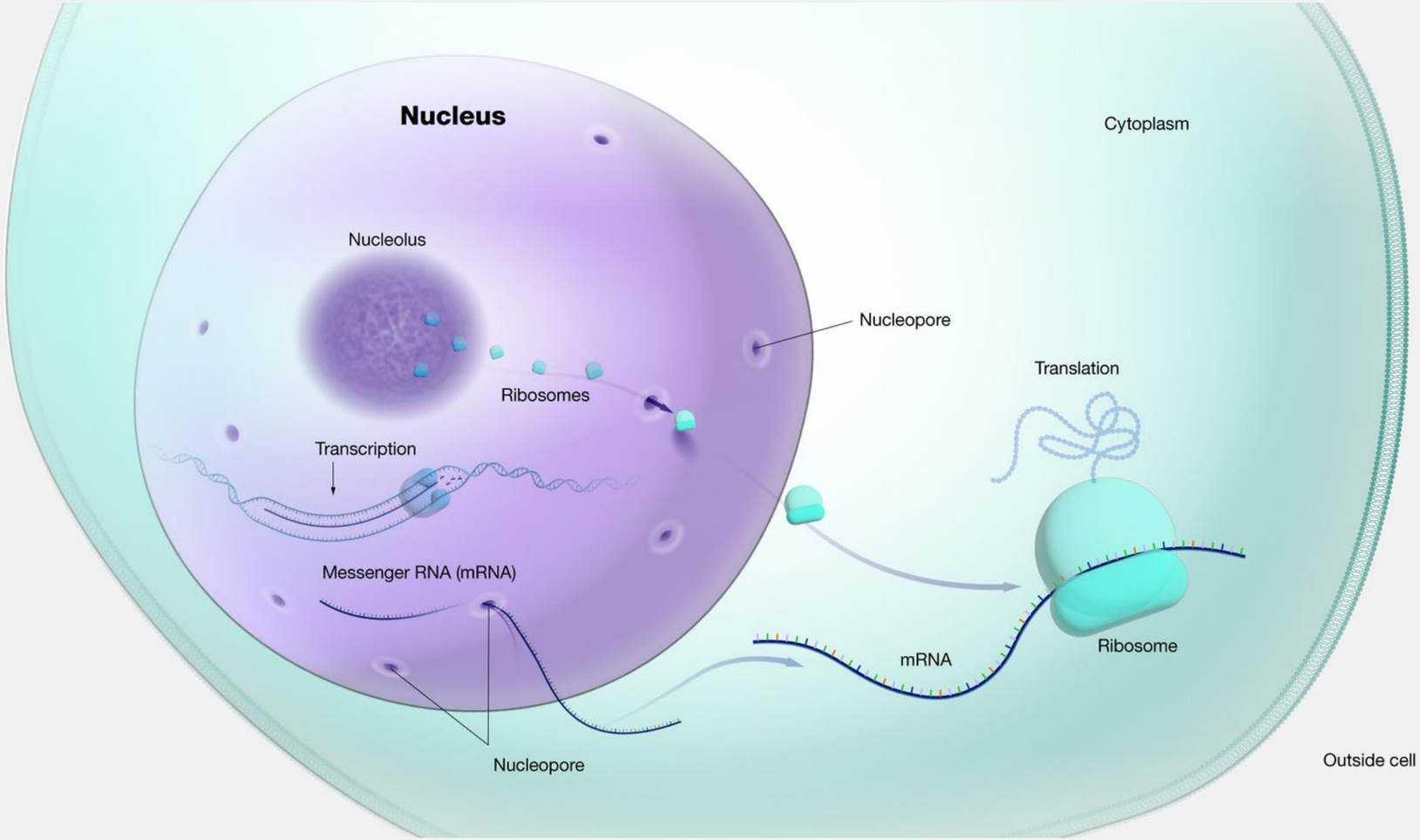
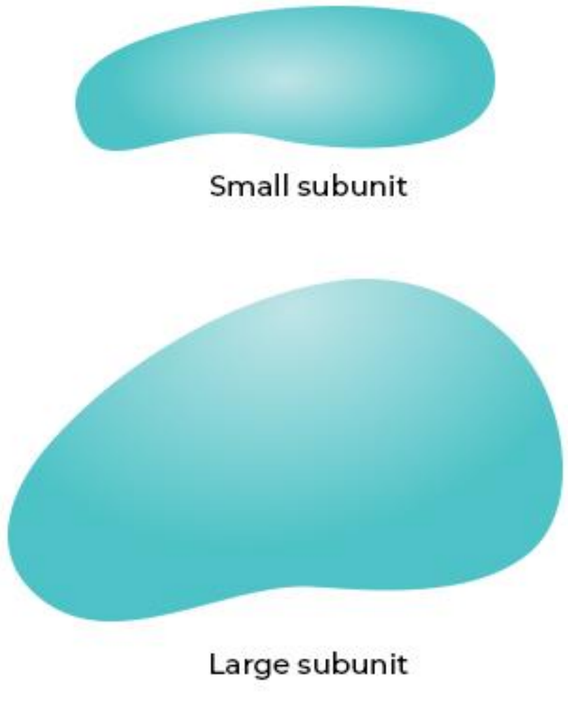
. Large, membrane-enclosed organelle present in all cells except mature erythrocytes
. Contains genetic material (DNA, tightly packed into chromatin); coordinates cellular activities
. Most cells contain one nucleus; some cells have more (e.g. skeletal muscle cells, osteoclasts, hepatocytes)

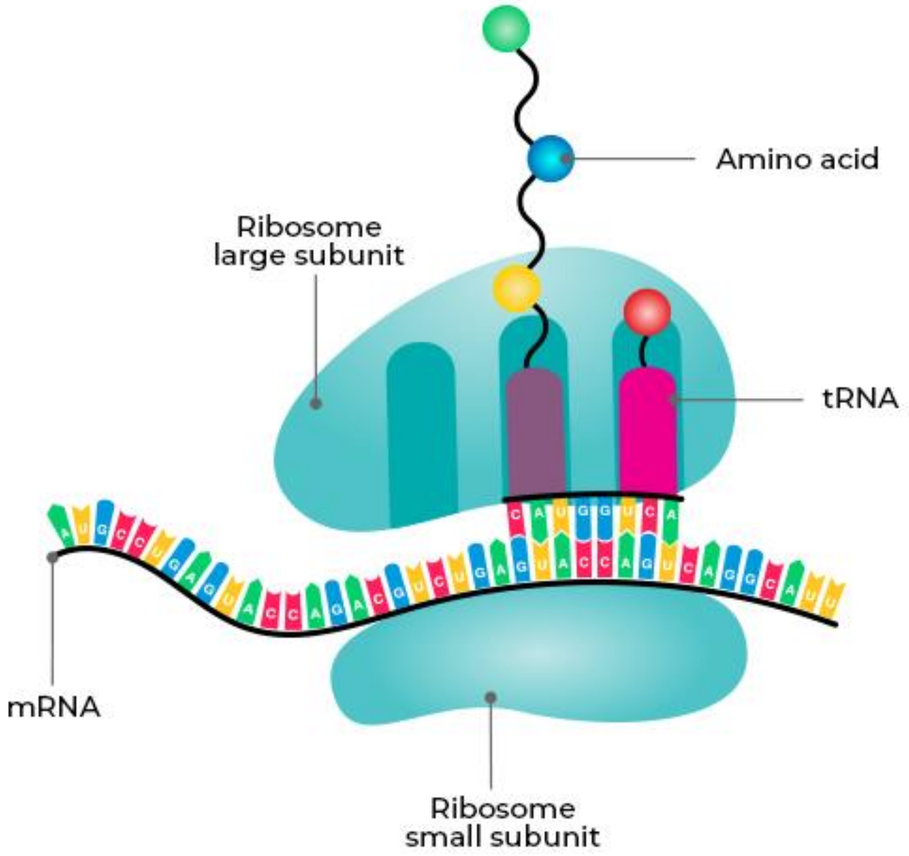


. Usually spherical, may take on other shapes
. Lobulated (e.g. polymorphonuclear leukocytes)
. Elongated (e.g. columnar epithelium)

RIBOSOMES

. Composition: rRNA, ribosomal proteins
. Can exist freely in cytoplasm/bound to endoplasmic reticulum (forms rough endoplasmic reticulum)
. Turns mRNA into protein via translation
. Organized into two subunits (40s, 60s)





. Small subunit: binding sites for mRNA, tRNA

. Larger subunit: has ribozyme to catalyze peptide bond formation (for bonds between amino acids)

ROUGH ENDOPLASMIC RETICULUM

Site of synthesis of secretory (exported) proteins and of N-linked oligosaccharide addition to lysosomal and other proteins.

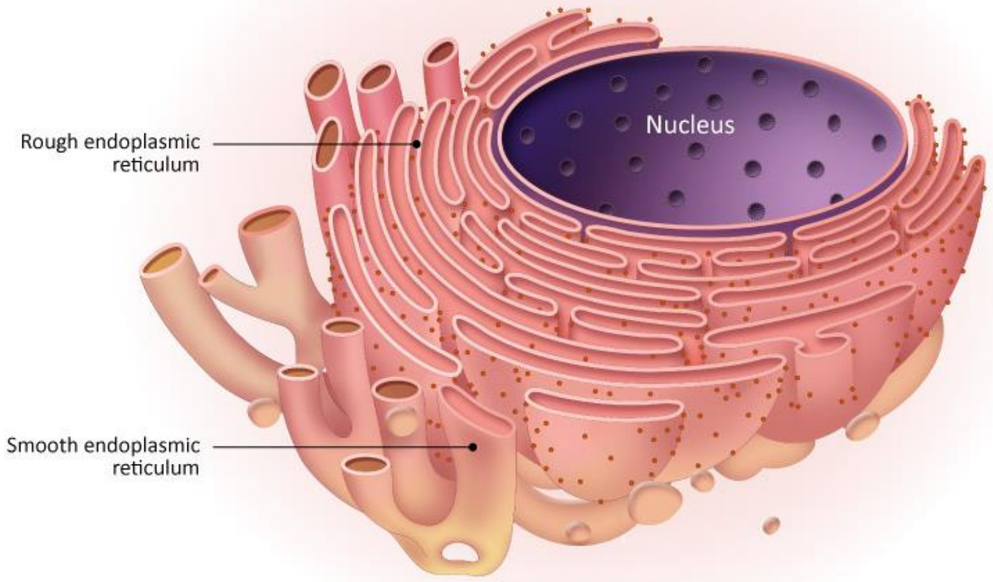
Nissl bodies (RER in neurons)—synthesize peptide neurotransmitters for secretion.

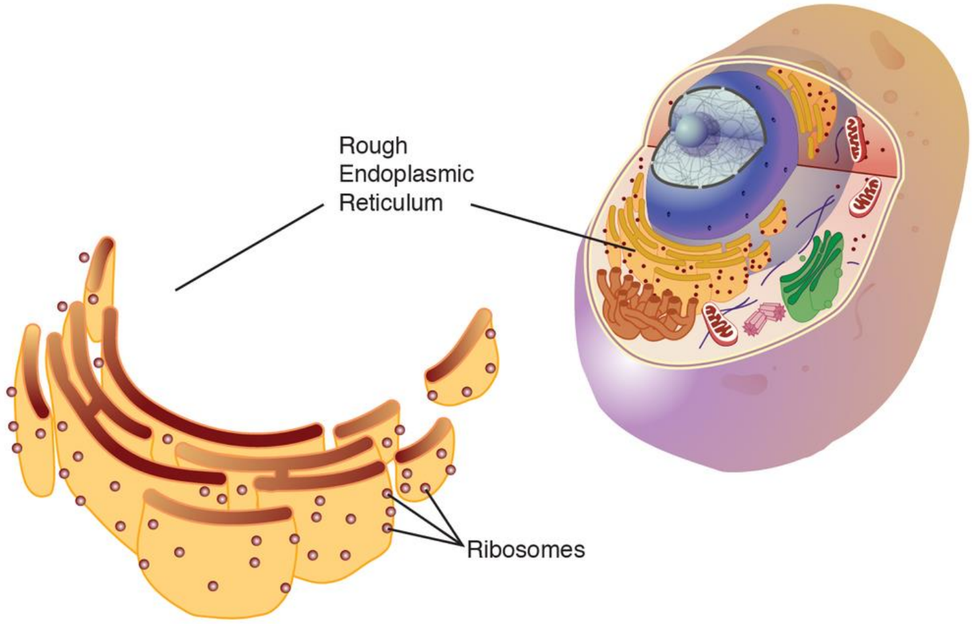
Free ribosomes—unattached to any membrane; site of synthesis of cytosolic, peroxisomal, and mitochondrial proteins.

N-linked glycosylation occurs in the e**N**doplasmic reticulum.

Mucus-secreting goblet cells of small intestine and antibody-secreting plasma cells are rich in RER.

Proteins within organelles (eg, ER, Golgi bodies, lysosomes) are formed in RER.





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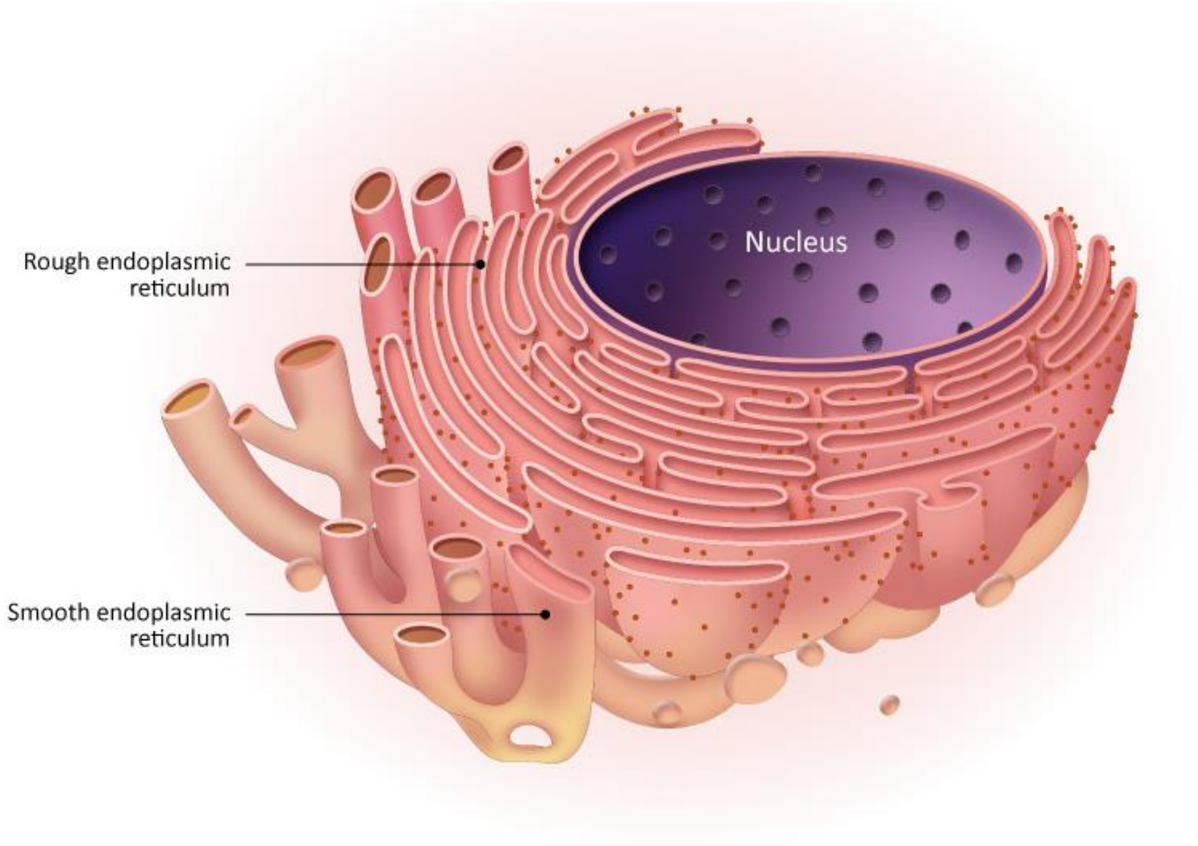
SMOOTH ENDOPLASMIC RETICULUM

Site of steroid synthesis and detoxification of drugs and poisons. Lacks surface ribosomes. Location of glucose-6-phosphatase (last step in both glycogenolysis and gluconeogenesis).

Hepatocytes and steroid hormone–producing cells of the adrenal cortex and gonads are rich in SER.



GOLGI APPARATUS (COMPLEX)

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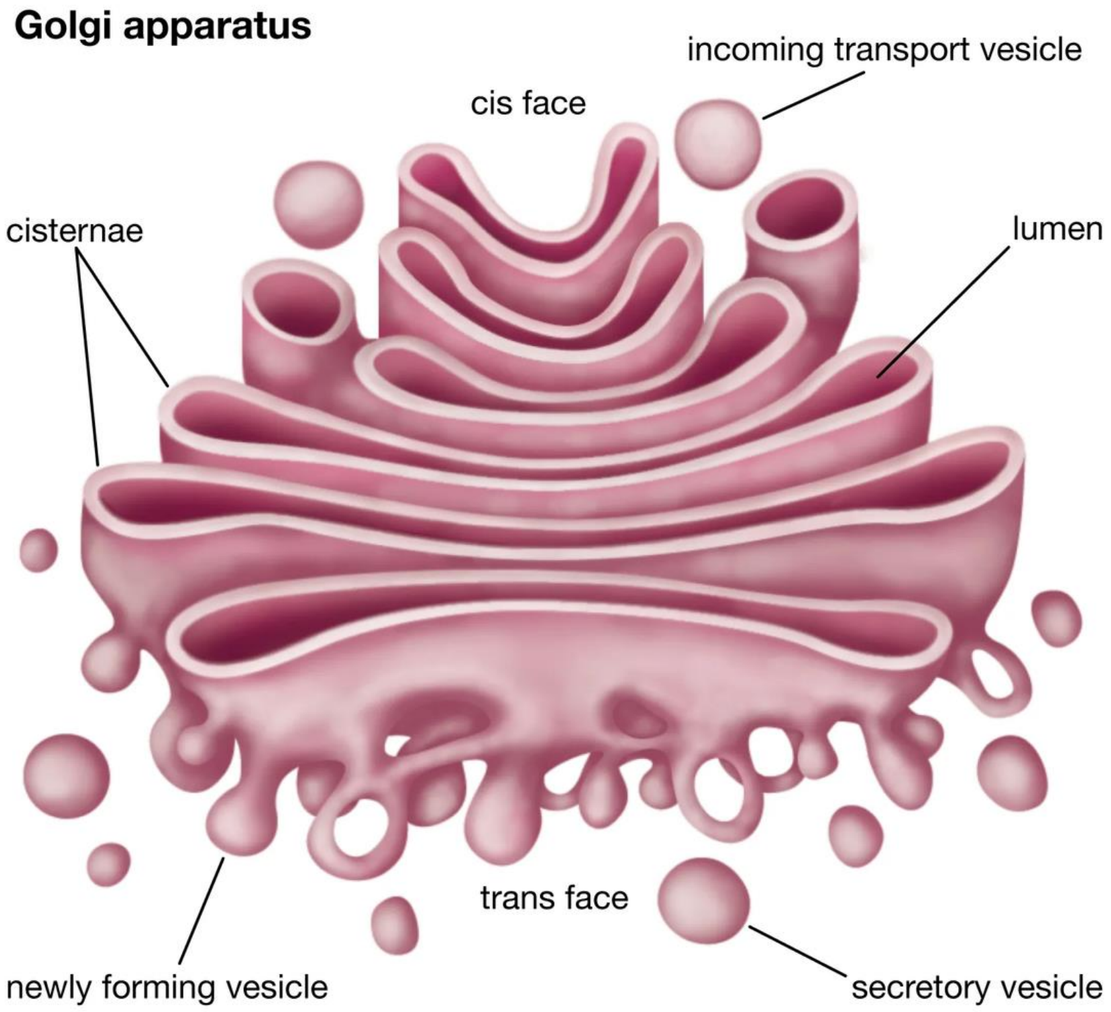
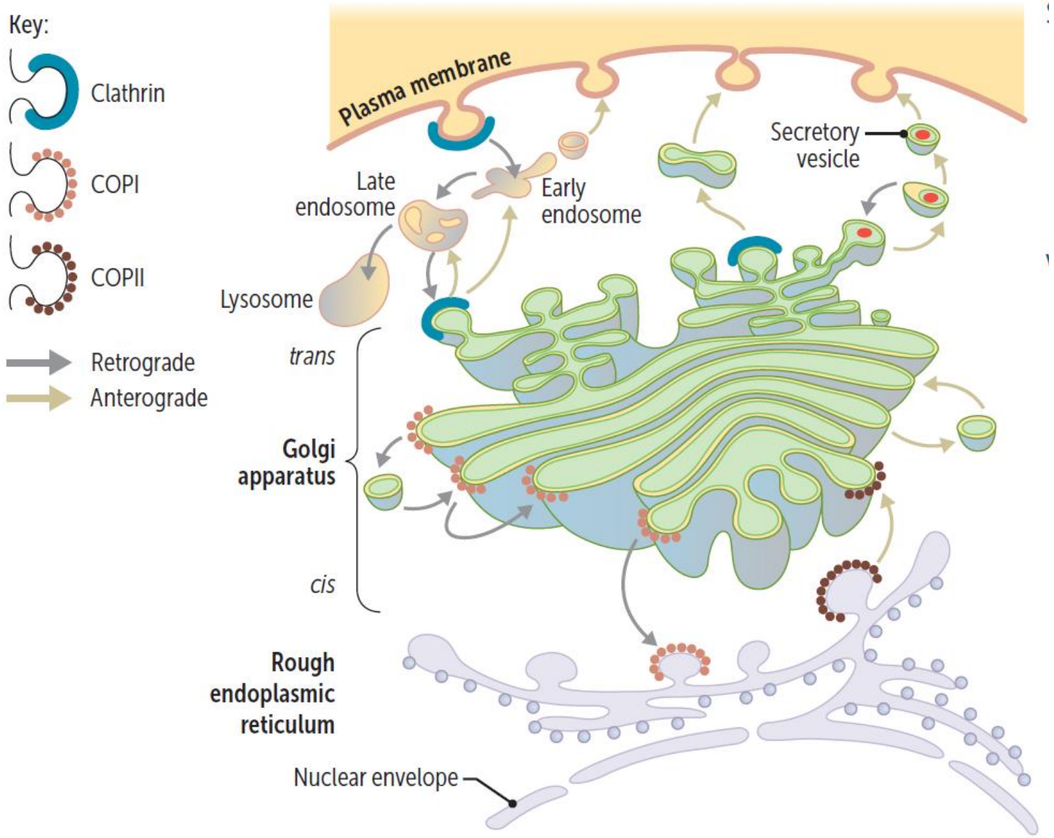


. Membrane-enclosed organelle
. Appearance: collection of fused, fl attened sacs (cisterns) with associated vesicles, vacuoles
. Two sides
. Cis side: receives proteins from RER (entry)
. Trans side: opposite side, releases vesicles towards plasma membrane (exit)
. Post-translational modifi cation site (e.g. phosphorylation, glycosylation, sulfonation) of proteins, lipids, hormones ŕË sorted, packaged into secretory vesicles ŕË secreted out of cell/lysosomal fusion/plasma membrane insertion

CELL TRAFFICKING

Golgi is distribution center for proteins and lipids from ER to vesicles and plasma membrane.
Posttranslational events in GOlgi include modifying N-oligosaccharides on asparagine, adding O-oligosaccharides on serine and threonine, and adding mannose-6-phosphate to proteins for lysosomal and other proteins.

Endosomes are sorting centers for material from outside the cell or from the Golgi, sending it to lysosomes for destruction or back to the membrane/Golgi for further use.



Signal recognition particle (SRP)—abundant, cytosolic ribonucleoprotein that traffics polypeptide-ribosome complex from the cytosol to the RER. Absent or dysfunctional SRP → accumulation of protein in cytosol.

Vesicular trafficking proteins

- COPI: Golgi → Golgi (retrograde); *cis*-Golgi → ER.
- COPII: ER → *cis*-Golgi (anterograde). "Two (COPII) steps forward (anterograde); one (COPI) step back (retrograde)."
- Clathrin: *trans*-Golgi → lysosomes; plasma membrane → endosomes (receptor-mediated endocytosis [eg, LDL receptor activity]).

CELL TRAFFICKING

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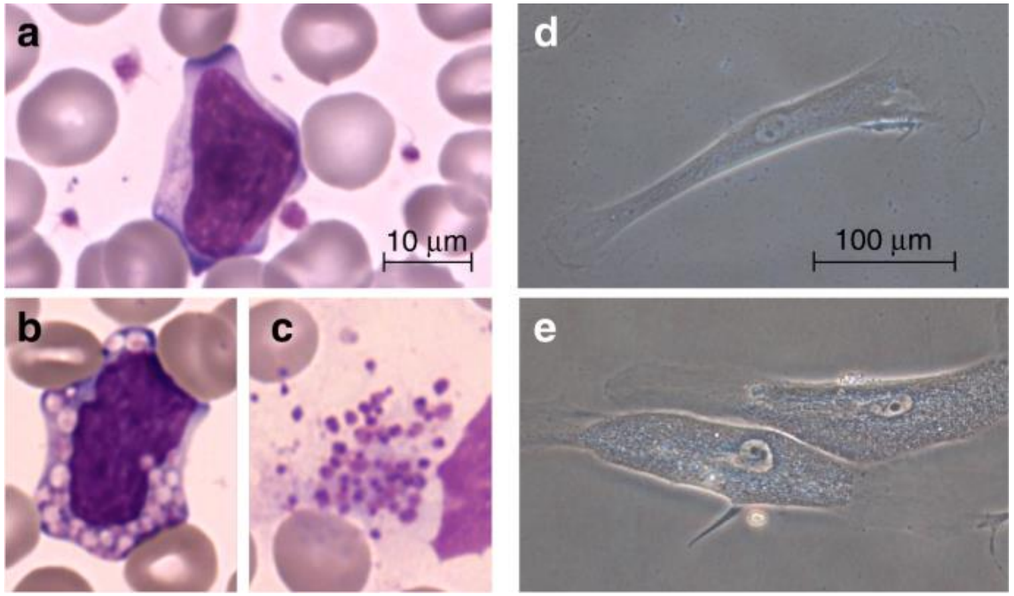
I-cell disease (inclusion cell disease/mucolipidosis type II)—inherited lysosomal storage disorder (autosomal recessive); defect in N-acetylglucosaminyl-1-phosphotransferase → failure of the Golgi to phosphorylate mannose residues (↓ mannose-6-phosphate) on glycoproteins → enzymes secreted extracellularly rather than delivered to lysosomes → lysosomes deficient in digestive enzymes → buildup of cellular debris in lysosomes (inclusion bodies). Results in coarse facial features, gingival hyperplasia, corneal clouding, restricted joint movements, claw hand deformities, kyphoscoliosis, and ↑ plasma levels of lysosomal enzymes. Symptoms similar to but more severe than Hurler syndrome. Often fatal in childhood.



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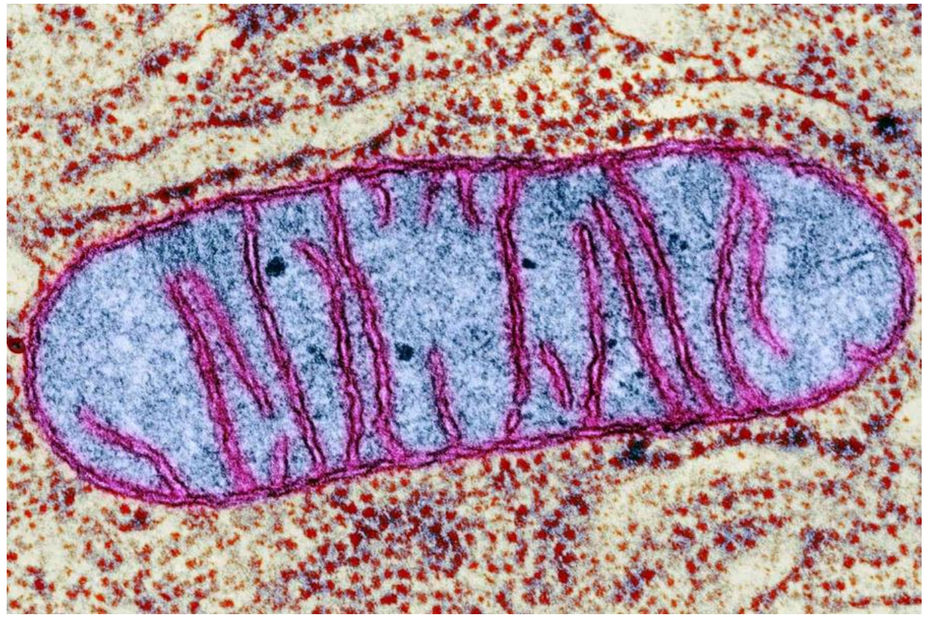
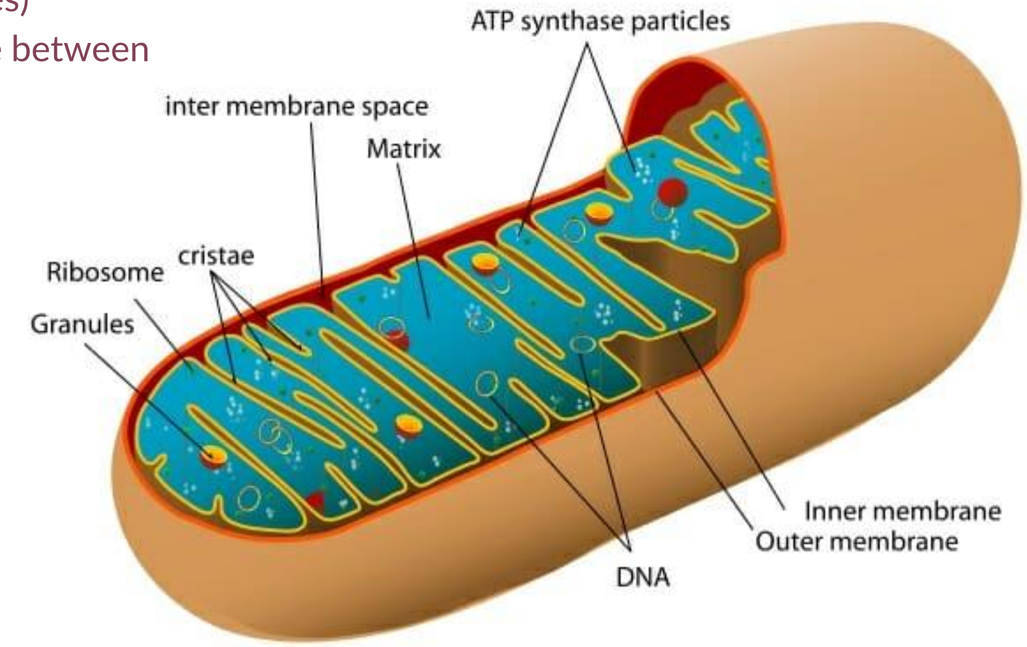
MITOCHONDRIA



. Double membrane-enclosed organelle; synthesizes ATP for cell via aerobic respiration
. Outer smooth membrane: encloses whole organelle
. Inner membrane: forms folds, caverns called cristae (contain proteins needed for aerobic respiration); encloses mitochondrial matrix (contains mitochondrial DNA, ribosomes)
. Intermembrane space: space between inner, outer membrane

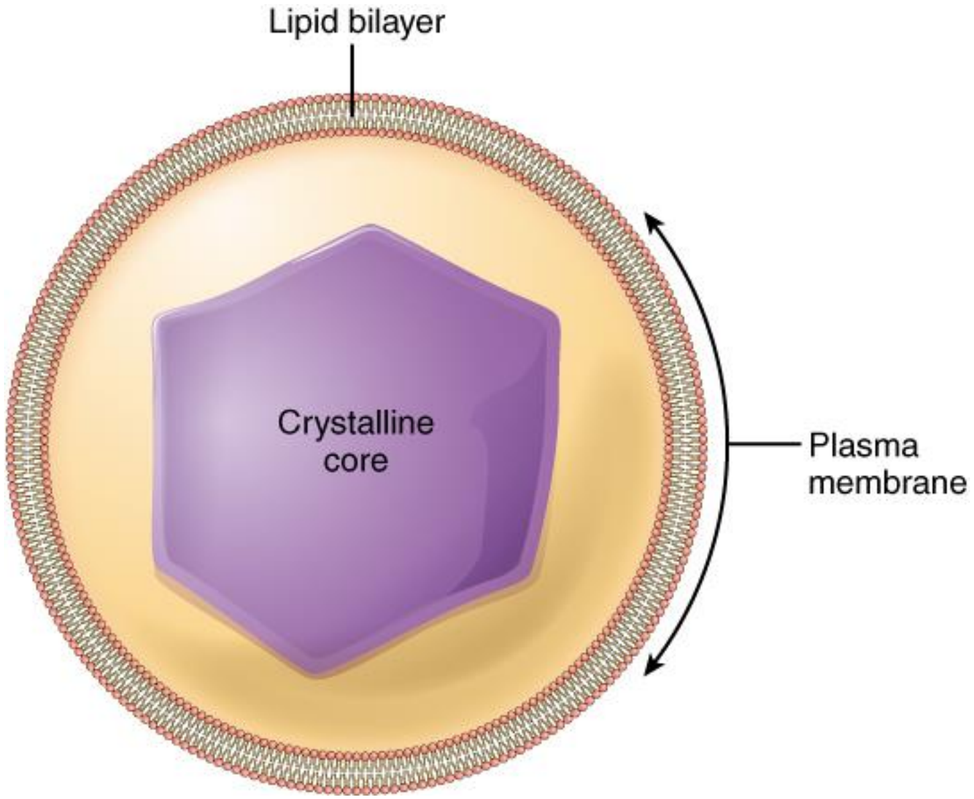


In cytoplasm glucose undergoes glycolysis, glucose cleaved into pyruvate
. Pyruvate enters mitochondria = citric acid cycle (Krebs cycle), electron transport chain (require oxygen)
. In glucose absence, mitochondria can use fatty acids as fuel via beta oxidation (only medium sized fatty acids used; longer ones chopped by peroxisome)
. Mitochondria number: correlates with cell activity/energy requirements

PEROXISOME

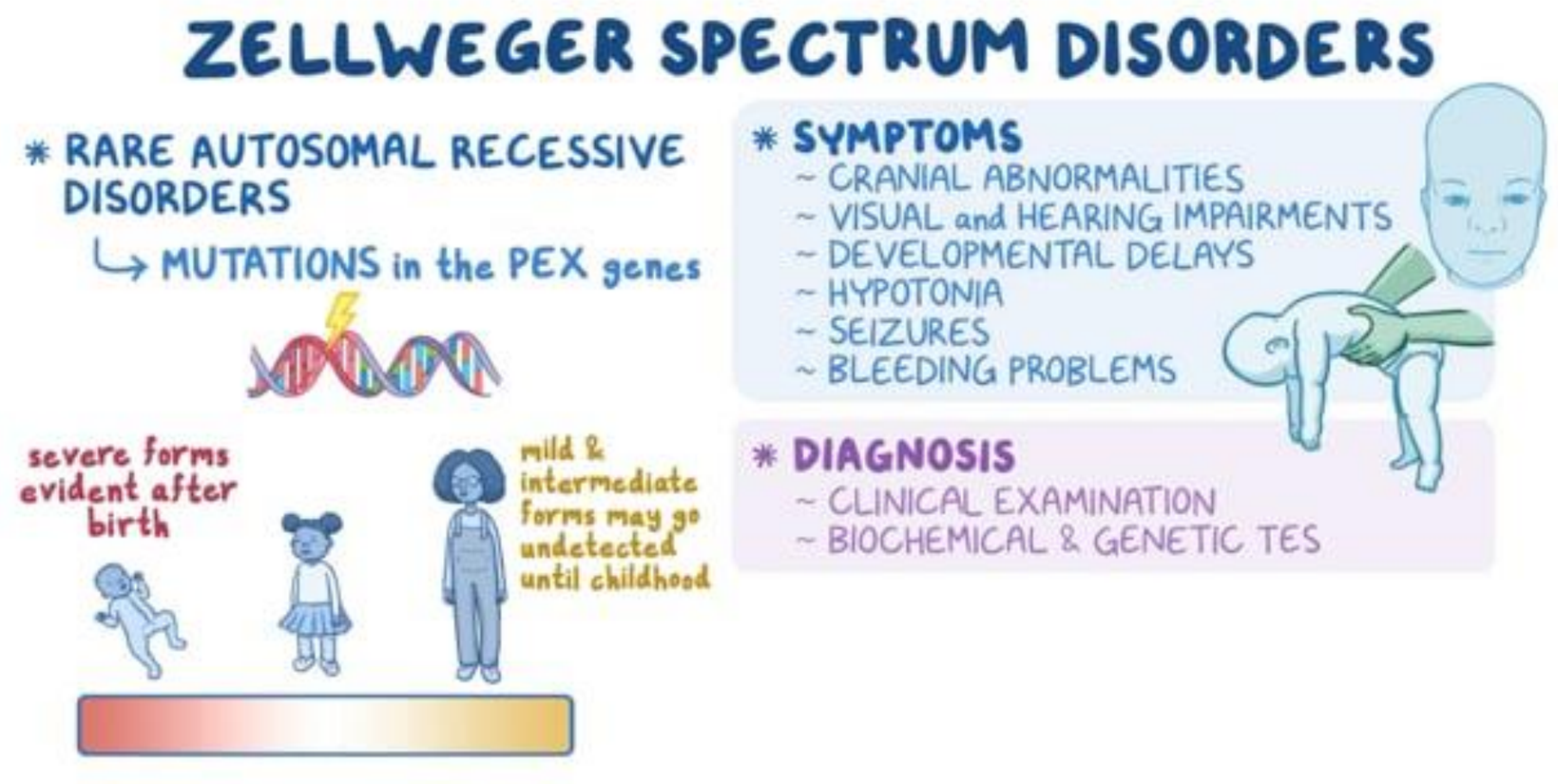
Membrane-enclosed organelle involved in:

- β-oxidation of very-long-chain fatty acids (VLCFA) (strictly peroxisomal process)
- α-oxidation of branched-chain fatty acids (strictly peroxisomal process)
- Catabolism of amino acids and ethanol
- Synthesis of bile acids and plasmalogens (important membrane phospholipid, especially in white matter of brain)



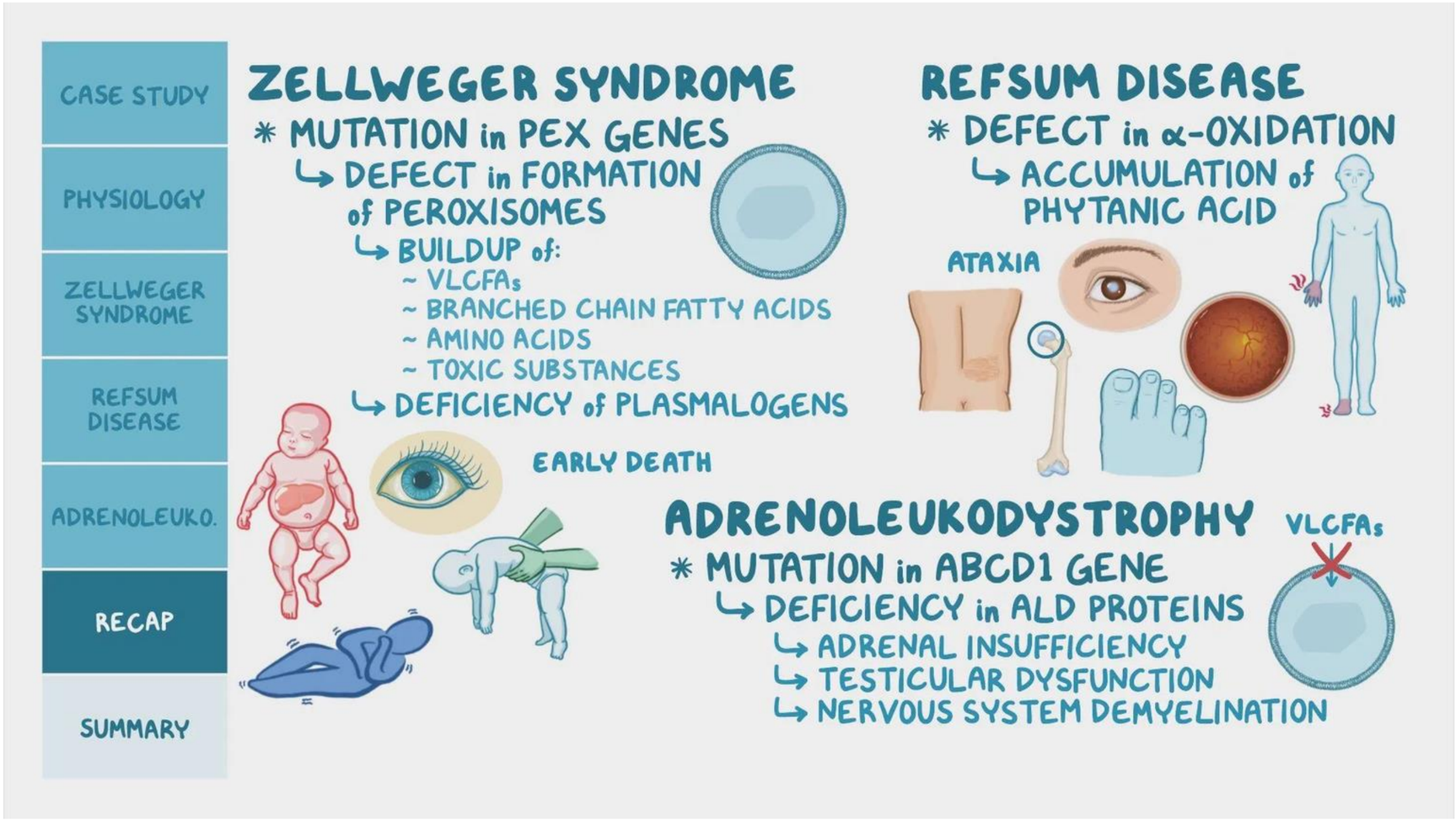
ZELLWEGER SYNDROME

Zellweger syndrome—autosomal recessive disorder of peroxisome biogenesis due to mutated *PEX* genes. Hypotonia, seizures, jaundice, craniofacial dysmorphia, hepatomegaly, early death.



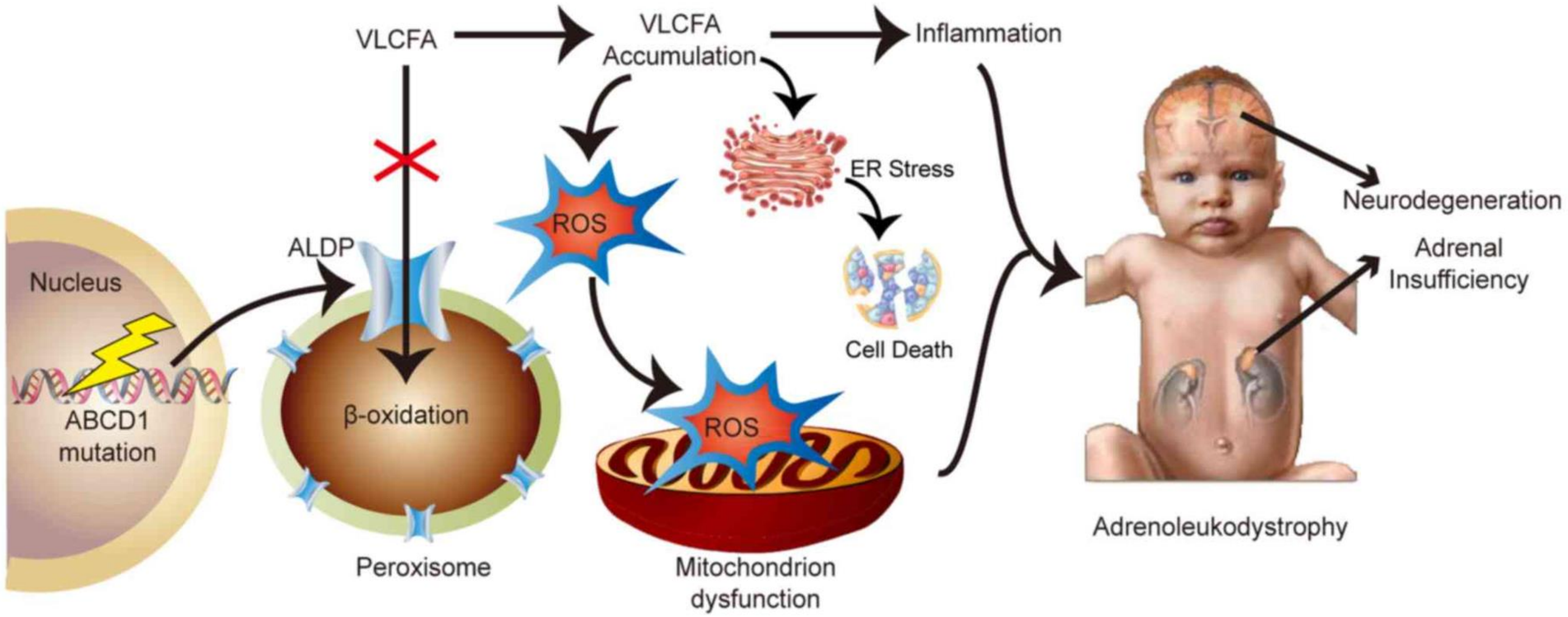
REFSUM DISEASE

Refsum disease—autosomal recessive disorder of α-oxidation → buildup of phytanic acid due to inability to degrade it. Scaly skin, ataxia, cataracts/night blindness, shortening of 4th toe,



ADRENOLEUKODYSTROPHY

Adrenoleukodystrophy—X-linked recessive disorder of β-oxidation due to mutation in *ABCD1* gene → VLCFA buildup in **adrenal** glands, white (**leuko**) matter of brain, testes. Progressive disease that can lead to adrenal gland crisis, progressive loss of neurologic function, death.



PROTEASOME

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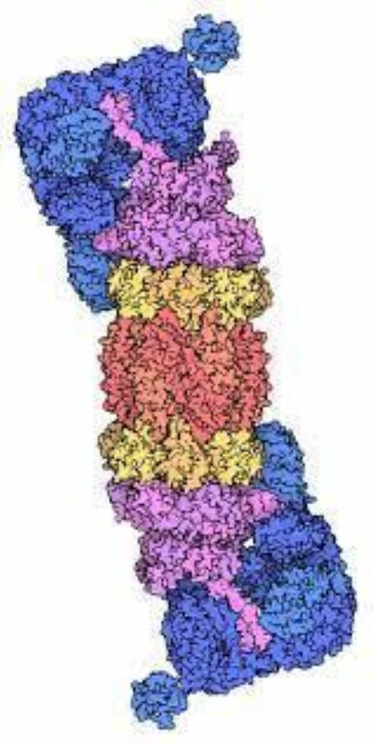
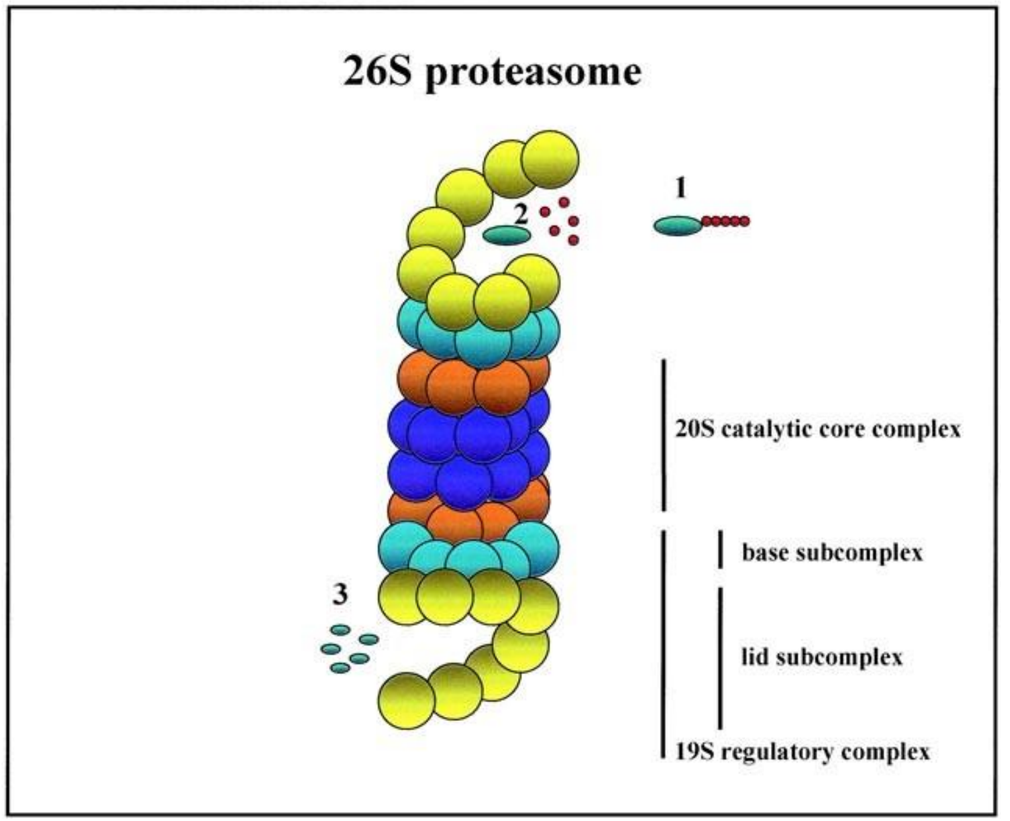
Barrel-shaped protein complex that degrades ubiquitin-tagged proteins. Defects in the ubiquitin-proteasome system have been implicated in some cases of Parkinson disease.

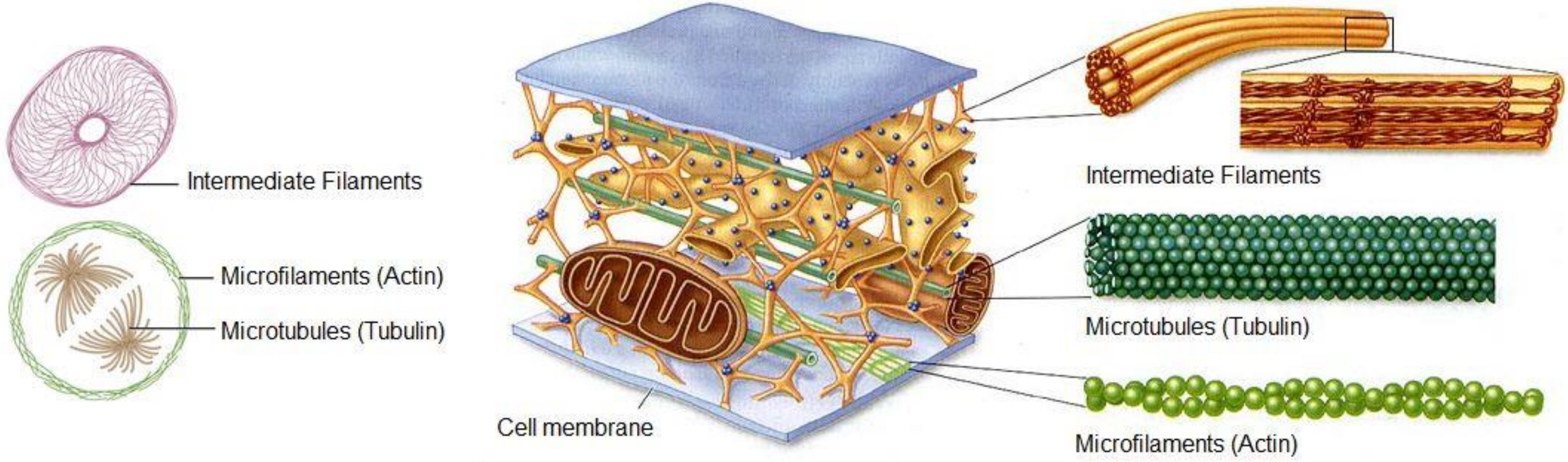




CYTOSKELETAL ELEMENTS

Cytoskeletal elements A network of protein fibers within the cytoplasm that supports cell structure, cell and organelle movement, and cell division.

TYPE OF FILAMENT	PREDOMINANT FUNCTION	EXAMPLES
Microfilaments	Muscle contraction, cytokinesis	Actin, microvilli.
Intermediate filaments	Maintain cell structure	Vimentin, desmin, cytokeratin, lamins, glial fibrillary acidic protein (GFAP), neurofilaments.
Microtubules	Movement, cell division	Cilia, flagella, mitotic spindle, axonal trafficking, centrioles.



CYTOSKELETAL ELEMENTS

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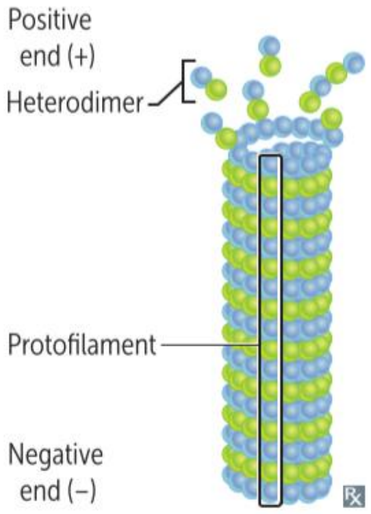
Microtubule



Cylindrical outer structure composed of a helical array of polymerized heterodimers of α- and β-tubulin. Each dimer has 2 GTP bound. Incorporated into flagella, cilia, mitotic spindles. Also involved in slow axoplasmic transport in neurons.

Molecular motor proteins—transport cellular cargo toward opposite ends of microtubule.

- **Re**trograde to microtubule (+ → –)—**dy**nein.
- **A**nterograde to microtubule (– → +)—**k**inesin.

Clostridium tetani toxin, herpes simplex virus, poliovirus, and rabies virus use dynein for retrograde transport to the neuronal cell body.

Drugs that act on microtubules (**m**icrotubules **g**et **c**onstructed **v**ery **t**erribly):

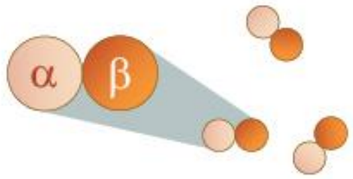
- **M**ebendazole (antihelminthic)
- **G**riseofulvin (antifungal)
- **C**olchicine (antigout)
- **V**inca alkaloids (anticancer)
- **T**axanes (anticancer)

Negative end **n**ear **n**ucleus.
Positive end **p**oints to **p**eriphery.

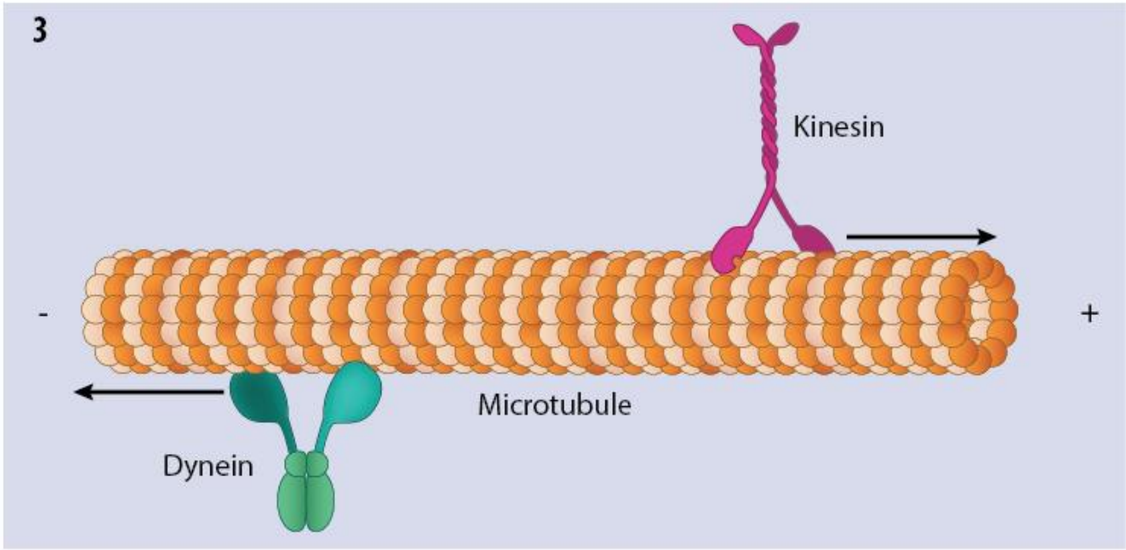
Ready? **A**ttack!

Microtubule assembly

1 Tubulin heterodimers



2 Protofilament



CILIA STRUCTURE

Motile cilia consist of 9 doublet + 2 singlet arrangement of microtubules (axoneme) A.
Basal body (base of cilium below cell membrane) consists of 9 microtubule triplets B with no central microtubules.
Nonmotile (primary) cilia work as chemical signal sensors and have a role in signal transduction and cell growth control. Dysgenesis may lead to polycystic kidney disease, mitral valve prolapse, or retinal degeneration.
Axonemal dynein—ATPase that links peripheral 9 doublets and causes bending of cilium by differential sliding of doublets.
Gap junctions enable coordinated ciliary movement.

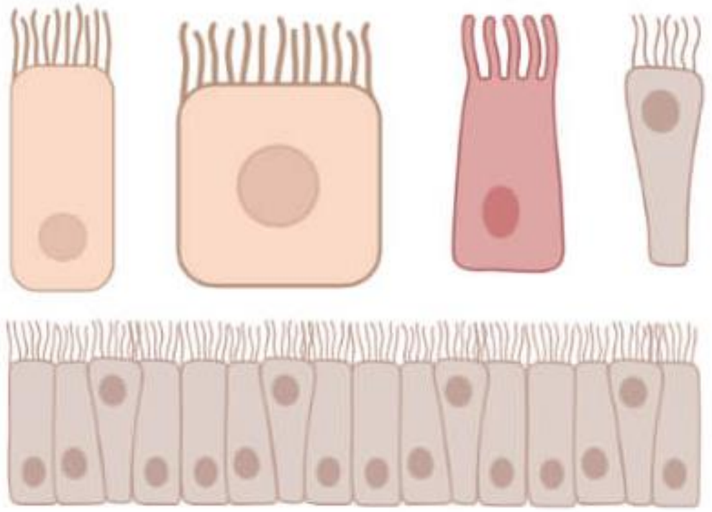
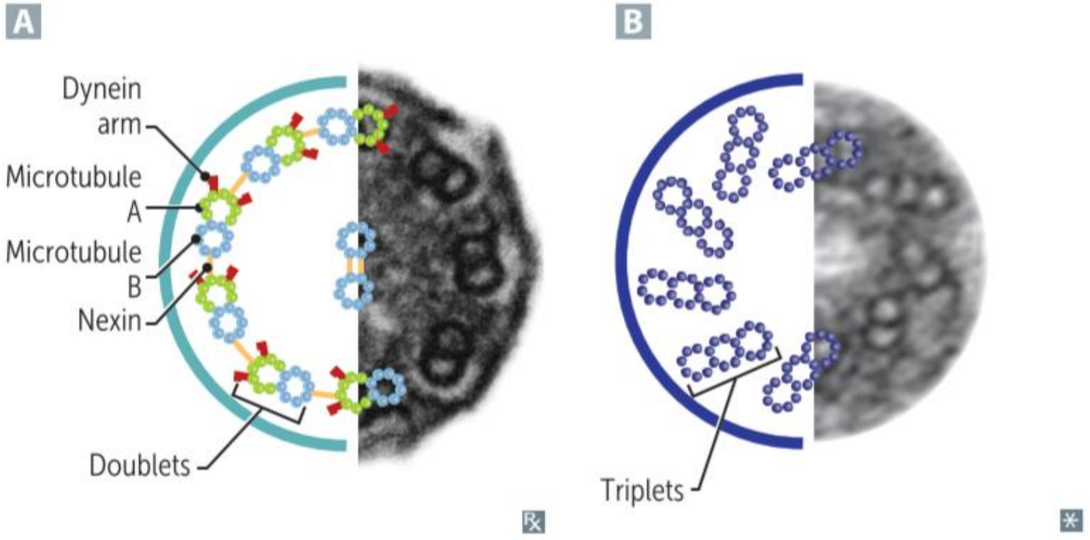
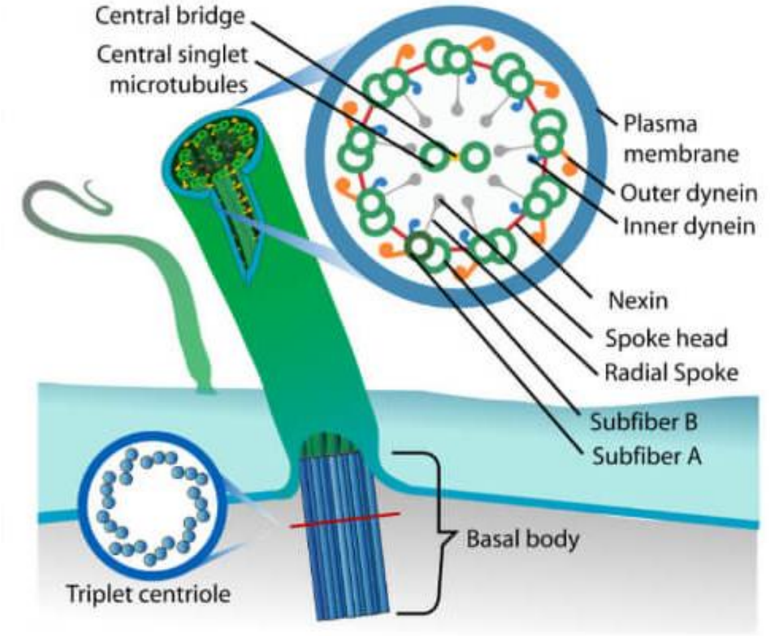


Figure: Cilia in ciliated epithelium



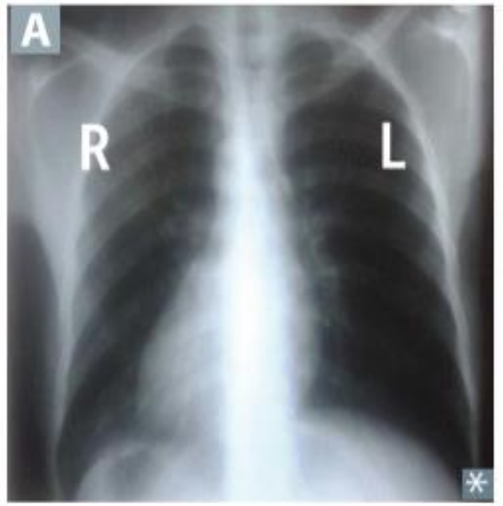


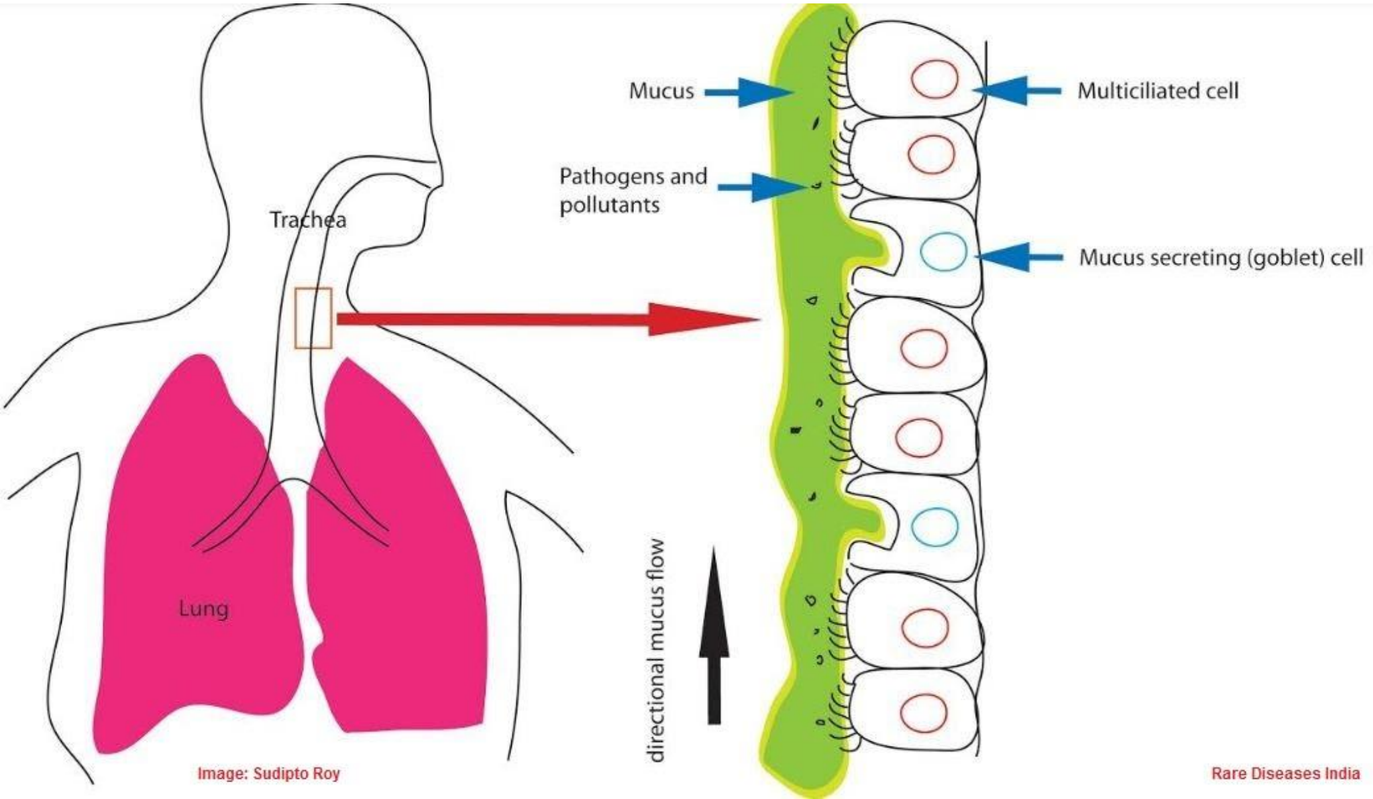
PRIMARY CILIARY DYSKINESIA

Also called Kartagener syndrome. Autosomal recessive. Dynein arm defect → immotile cilia → dysfunctional ciliated epithelia.

Developmental abnormalities due to impaired migration and orientation (eg, situs inversus **A**, hearing loss due to dysfunctional eustachian tube cilia); recurrent infections (eg, sinusitis, ear infections, bronchiectasis due to impaired ciliary clearance of debris/pathogens); infertility (↑ risk of ectopic pregnancy due to dysfunctional fallopian tube cilia, immotile spermatozoa).

Lab findings: ↓ nasal nitric oxide (used as screening test).





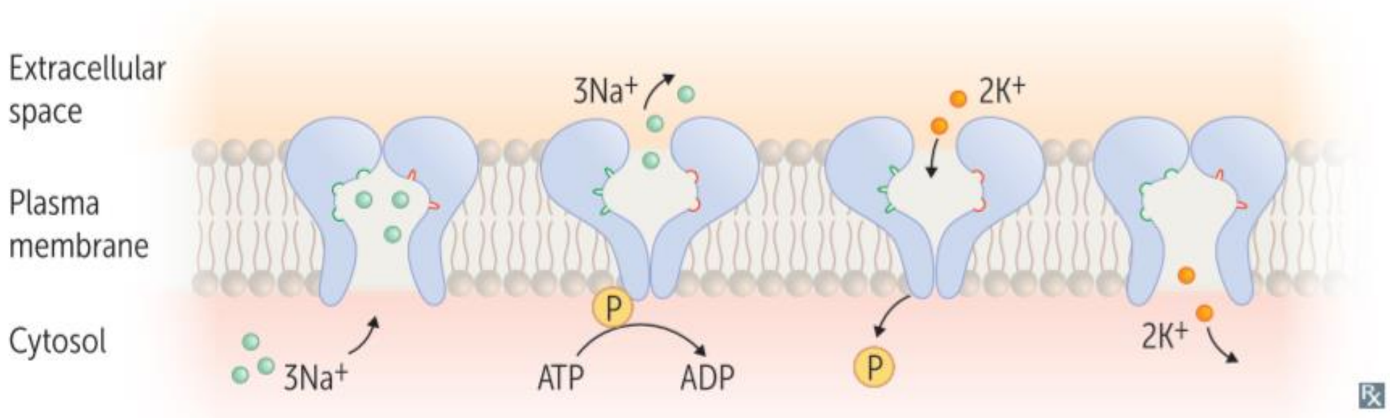
PRIMARY CILIARY DYSKINESIA

Sodium-potassium pump

Na^+/K^+-ATPase is located in the plasma membrane with ATP site on cytosolic side. For each ATP consumed, 2 K^+ go **in** to the cell (pump dephosphorylated) and 3 Na^+ go **out** of the cell (pump phosphorylated).

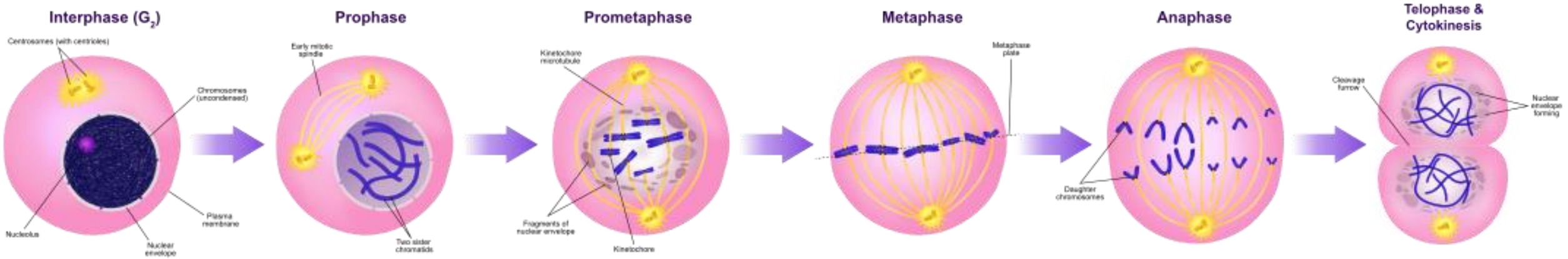
2 strikes? **K**, you're still **in**. **3** strikes? **Nah**, you're **out**!

Cardiac glycosides (digoxin and digitoxin) directly inhibit Na^+/K^+-ATPase → indirect inhibition of Na^+/Ca^{2+} exchange → ↑ $[Ca^{2+}]_i$ → ↑ cardiac contractility.



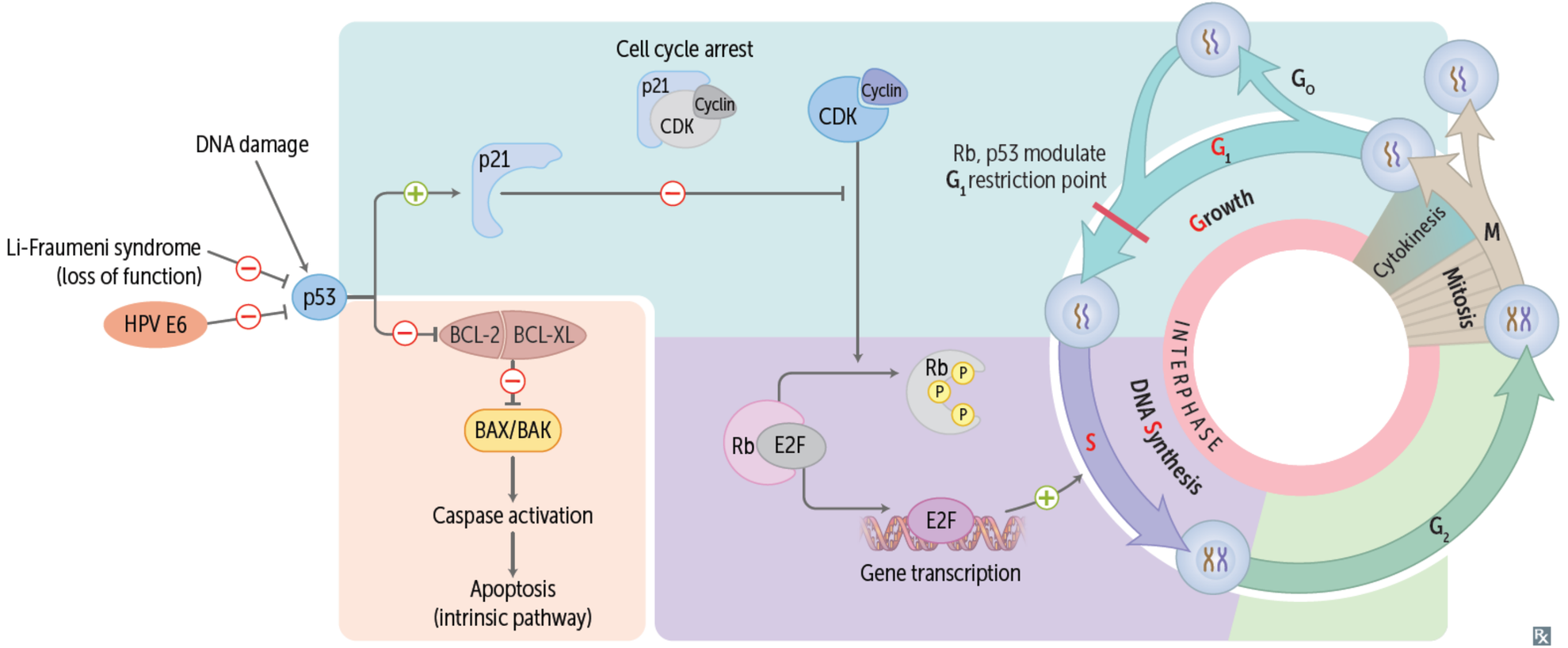
CELL CYCLE PHASES

Checkpoints control transitions between phases of cell cycle. This process is regulated by cyclins, cyclin-dependent kinases (CDKs), and tumor suppressors. M phase (shortest phase of cell cycle) includes mitosis (prophase, prometaphase, metaphase, anaphase, telophase) and cytokinesis (cytoplasm splits in two). G_1 is of variable duration.

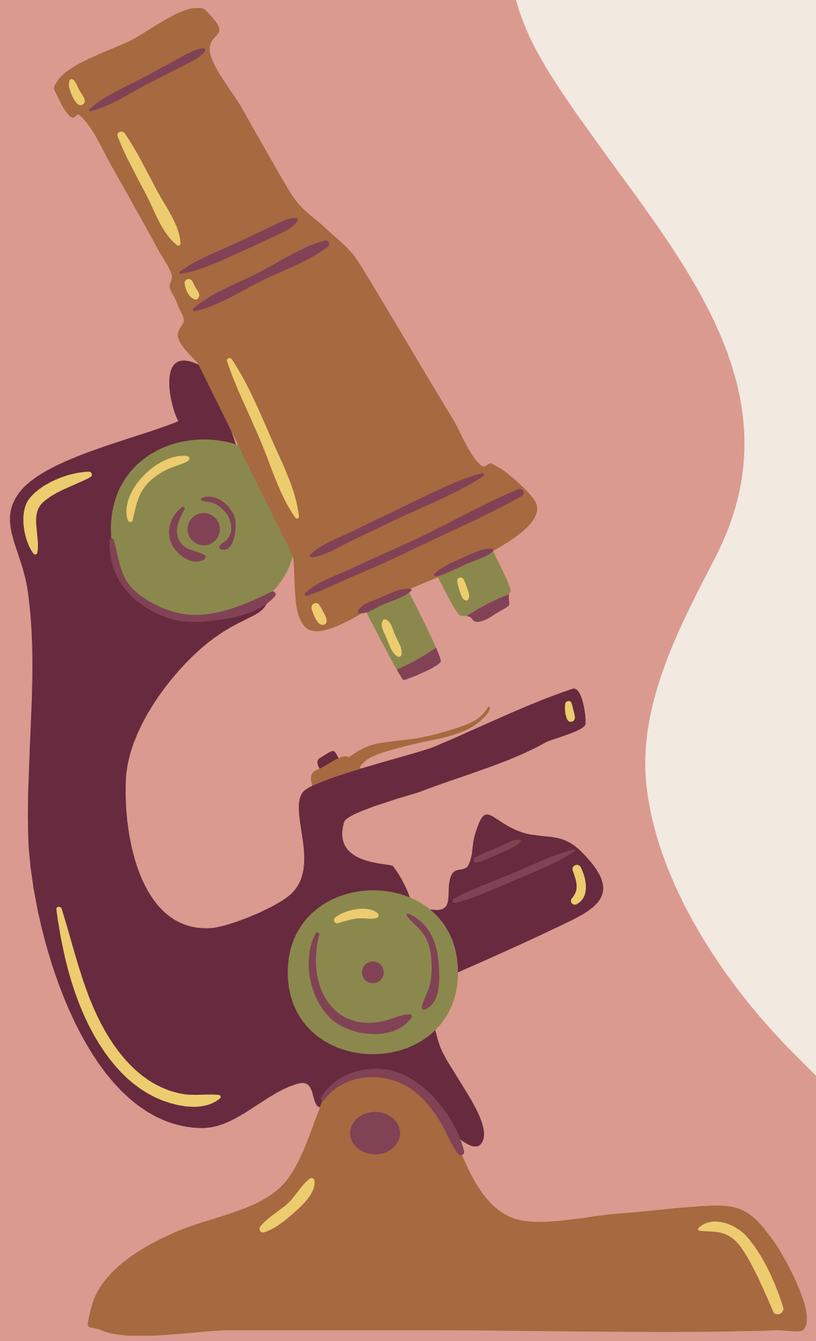


Cyclin-dependent kinases	Constitutively expressed but inactive when not bound to cyclin.
Cyclin-CDK complexes	Cyclins are phase-specific regulatory proteins that activate CDKs when stimulated by growth factors. The cyclin-CDK complex can then phosphorylate other proteins (eg, Rb) to coordinate cell cycle progression. This complex must be activated/inactivated at appropriate times for cell cycle to progress.
Tumor suppressors	p53 → p21 induction → CDK inhibition → Rb hypophosphorylation (activation) → G_1-S progression inhibition. Mutations in tumor suppressor genes can result in unrestrained cell division (eg, Li-Fraumeni syndrome).

Growth factors (eg, insulin, PDGF, EPO, EGF) bind tyrosine kinase receptors to transition the cell from G_1 to S phase.



Dr.Cardion



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