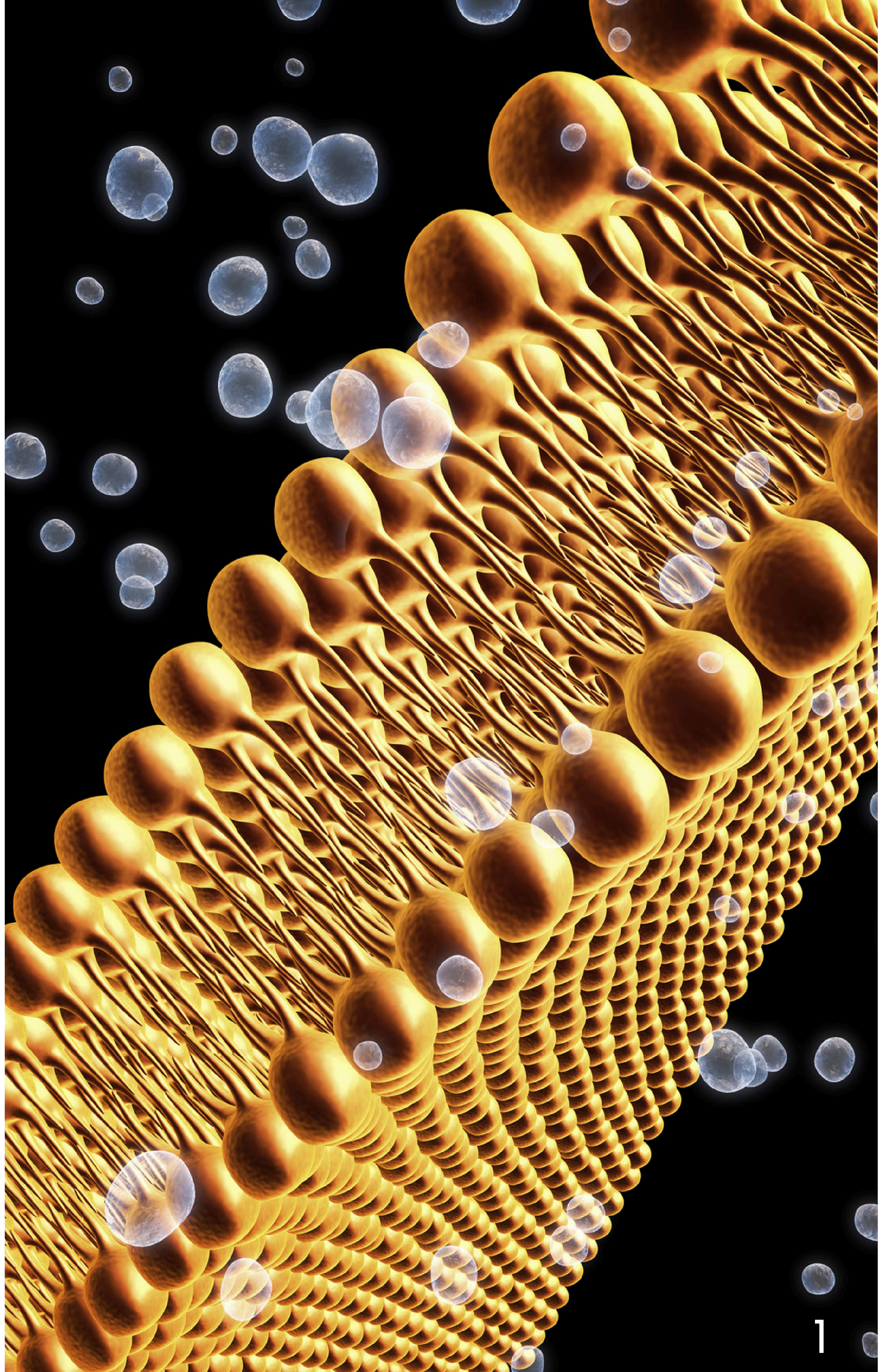
CELL ORGANIZATION AND MOVEMENT

(cell membrane, cytoskeleton, cell adhesion, and cell junction)

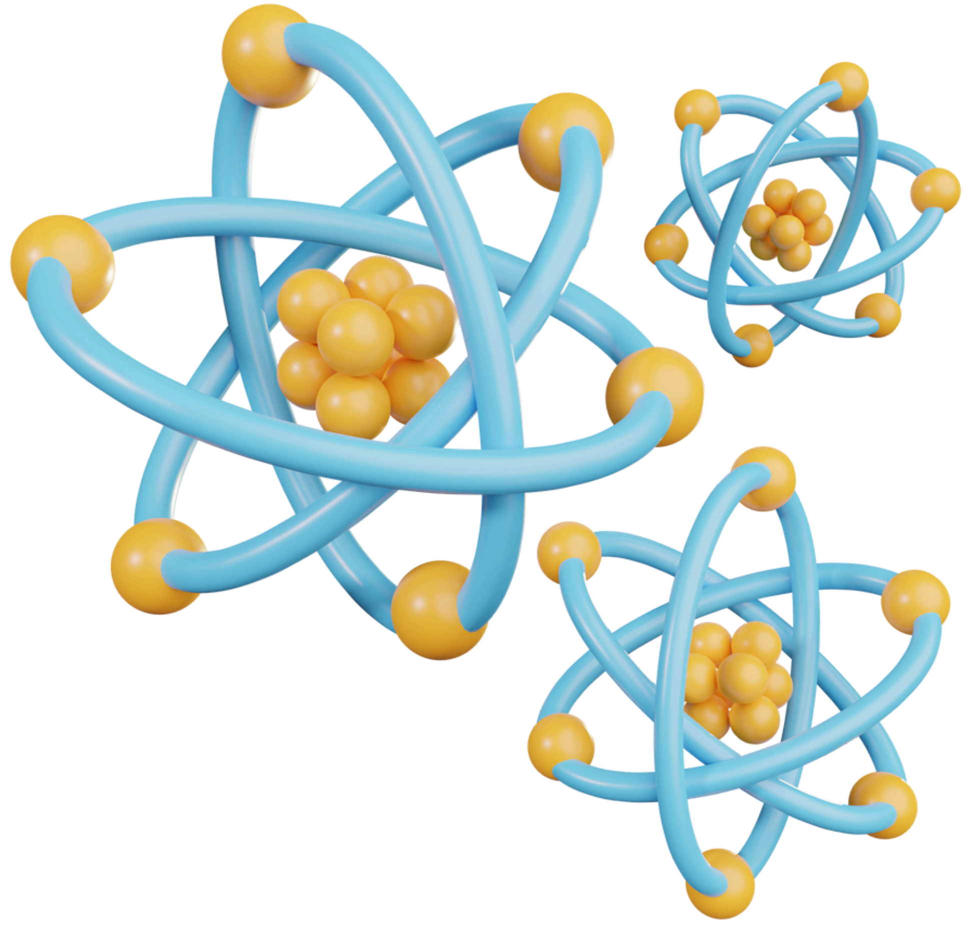
Lectured by:
Wanchana PHROMKRASAE, PhD
Department of Anatomy
Faculty of Medicine, Khon Kaen University
Email: wanphrom@kku.ac.th



OBJECTIVES

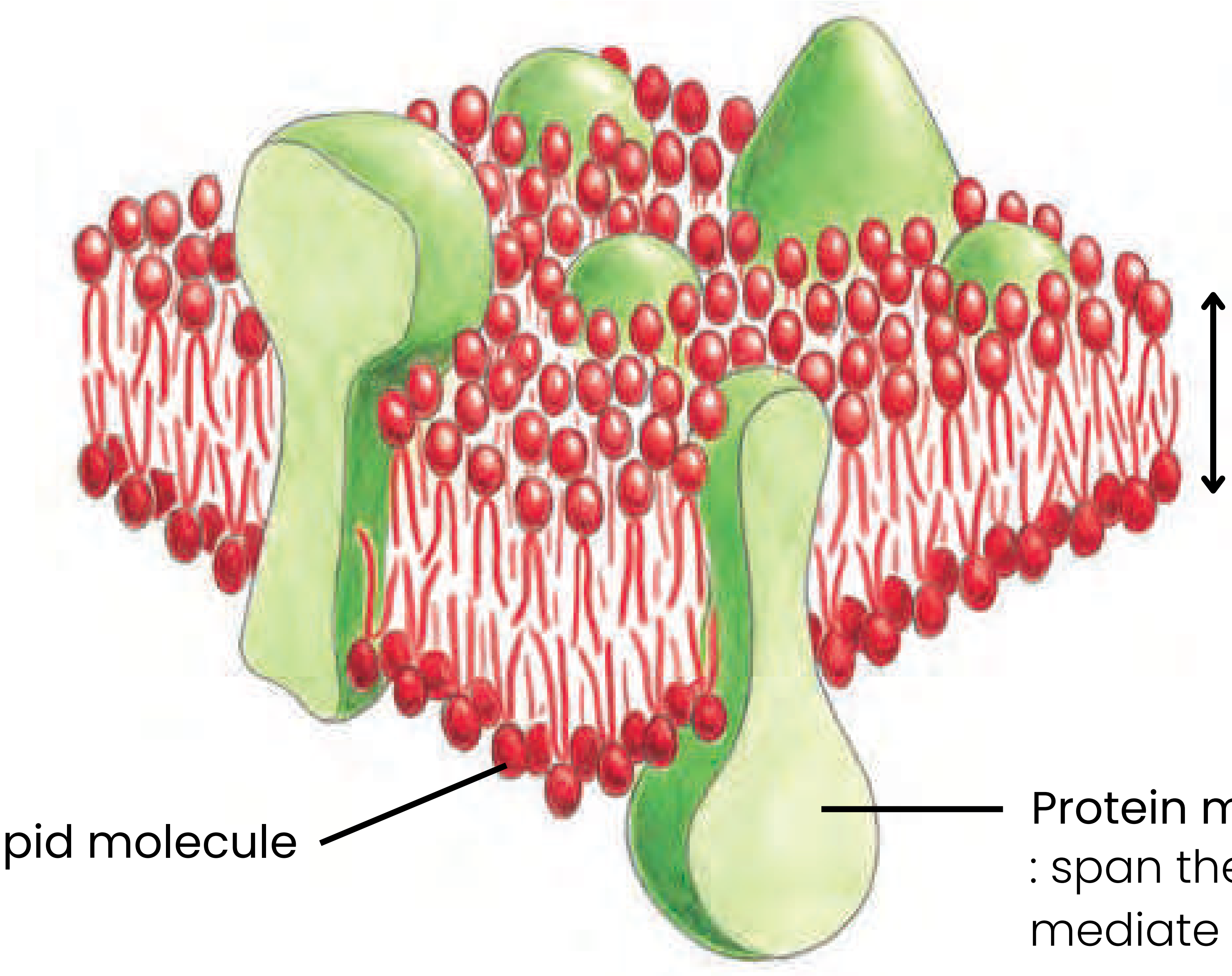
Students should be able to describe the following items in detail:

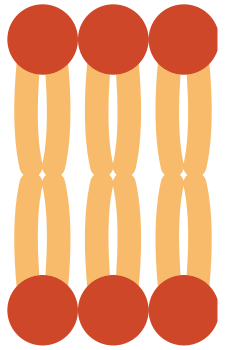
- Cell membrane
- Cytoskeleton
- Cell Adhesion
- Cell Junction



INTRODUCTION OF CELL MEMBRANE

All cells are surrounded by a **cell membrane**, which defines the boundary of the cell and separates its internal contents from the environment





Lipid bilayer (5 nm)
: impermeable barrier to the passage of most water-soluble molecules

Lipid molecule

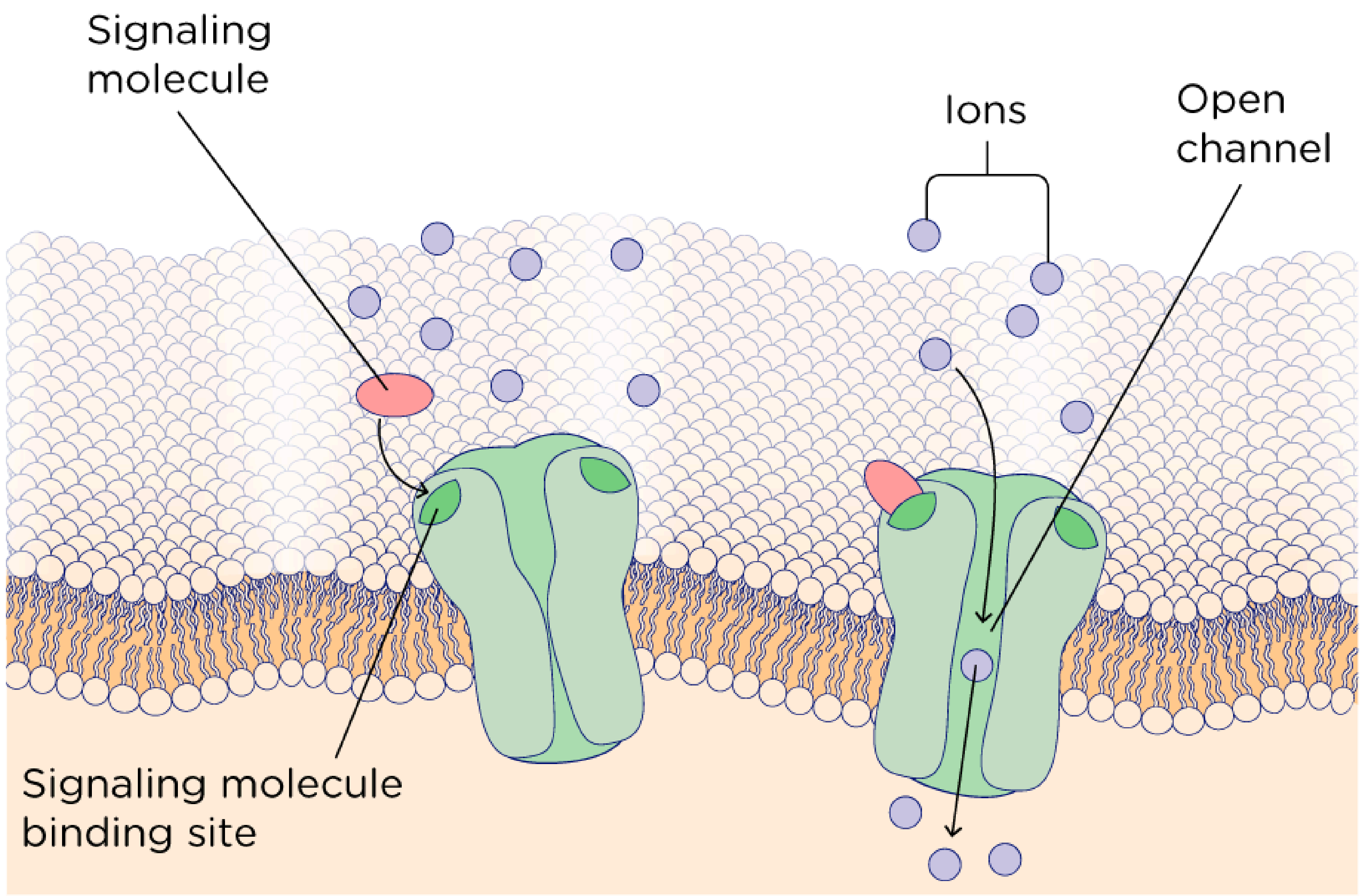
Protein molecule
: span the lipid bilayer and mediate nearly all of the other functions of the membrane

The **trilaminar appearance** of membranes
(a layer of hydrophobic tails of phospholipids sandwiched between two layers of hydrophillic heads)

FUNCTIONS OF CELL MEMBRANE

Responding to external signals

The plasma membrane plays a critical role in the response of a cell to external stimuli, a process known as signal transduction.

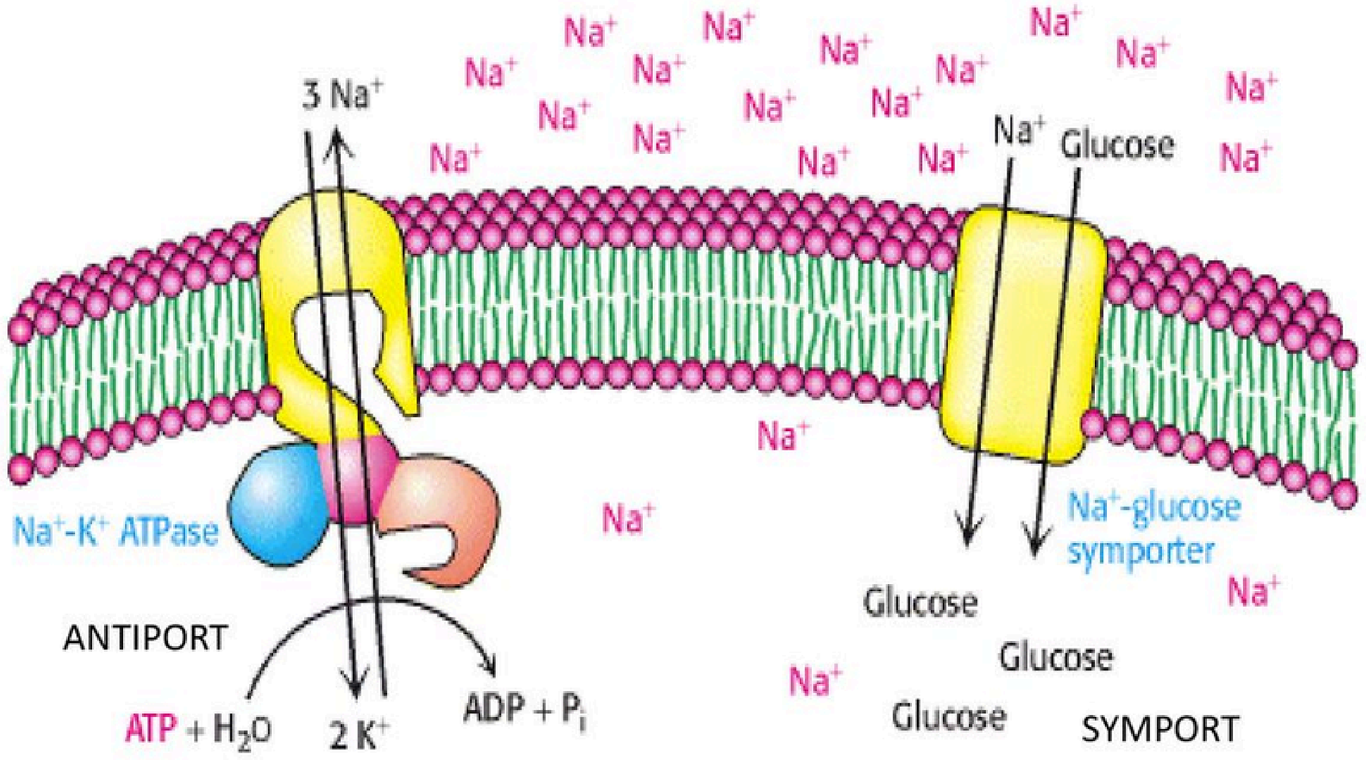


Intercellular interaction

The plasma membrane of multicellular organisms mediates the interactions between a cell and its neighbors.

Energy transduction

Membranes are intimately involved in the processes by which one type of energy is converted to another type (energy transduction).

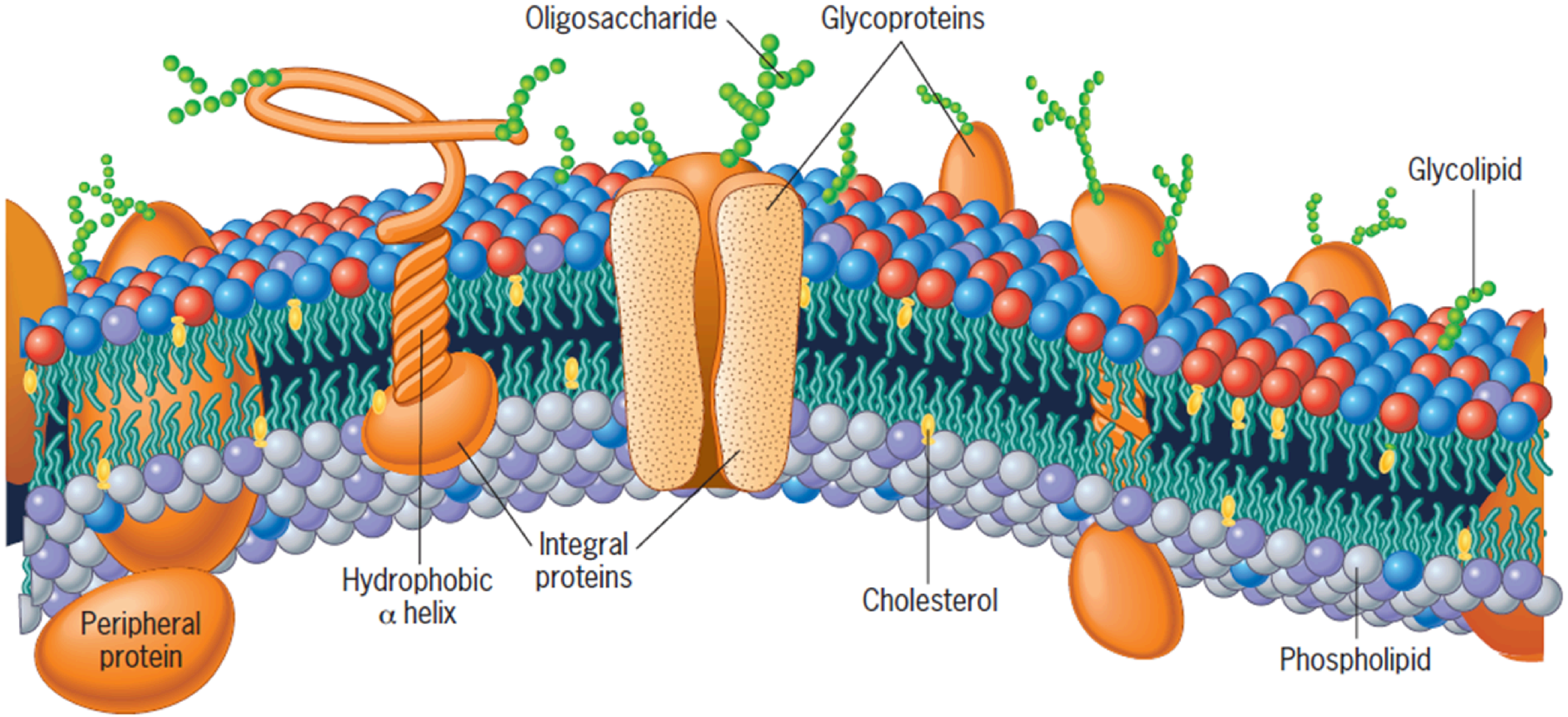


BRIEF HISTORY OF CELL MEMBRANE

The fluid-mosaic model of membrane structure as initially proposed by Singer and Nicolson in 1972.

Meaning

- "Fluid": Components can move freely within the layer.
- "Mosaic": The membrane is made up of various components—lipids, proteins, carbohydrates—that create a patchwork appearance.

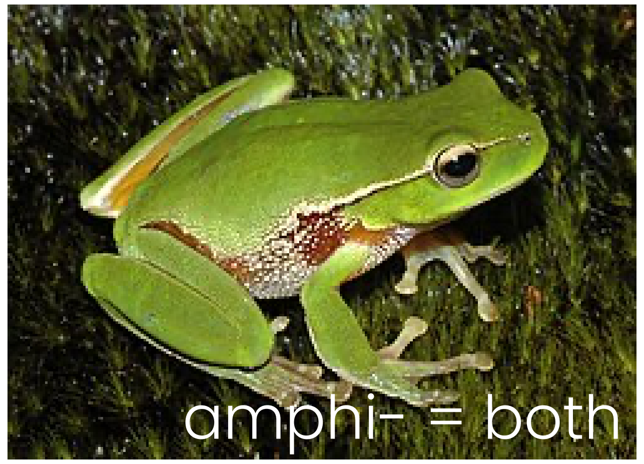


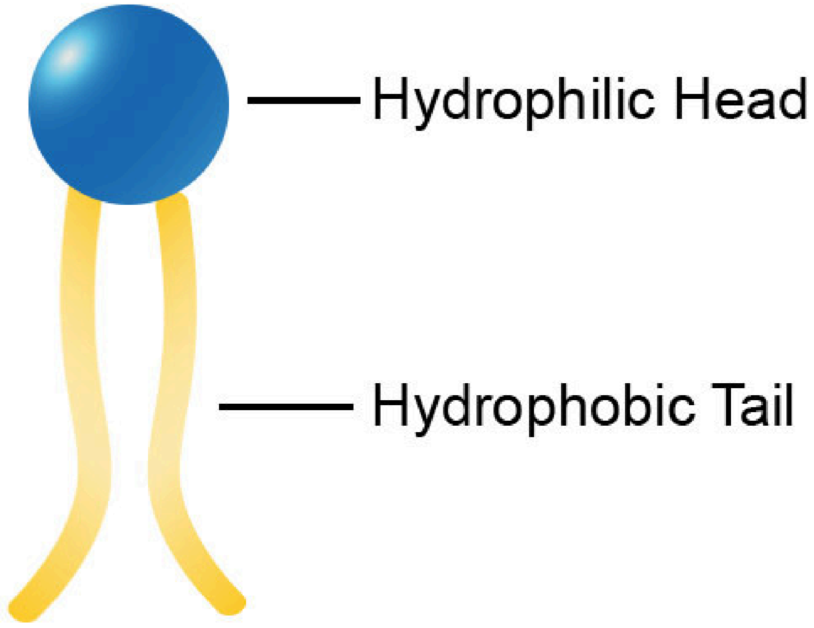
Chemical components of the membrane

- Lipid
- Carbohydrate
- Protein

The lipid bilayer provides the basic structure for all cell membranes

- constitute about 50% of the mass of most animal cell membranes
- All of the lipid molecules in cell membranes are **amphiphilic** (amphiphatic)

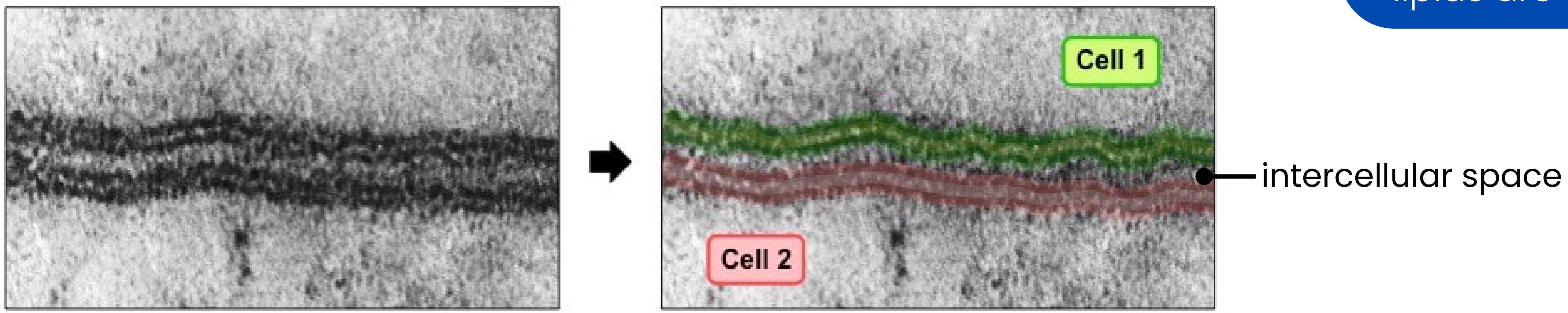




Amphiphilic molecule

- Hydrophilic (polar) end = water-loving
- Hydrophobic (non polar) end = water-fearing

The most abundant membrane lipids are the **phospholipids**



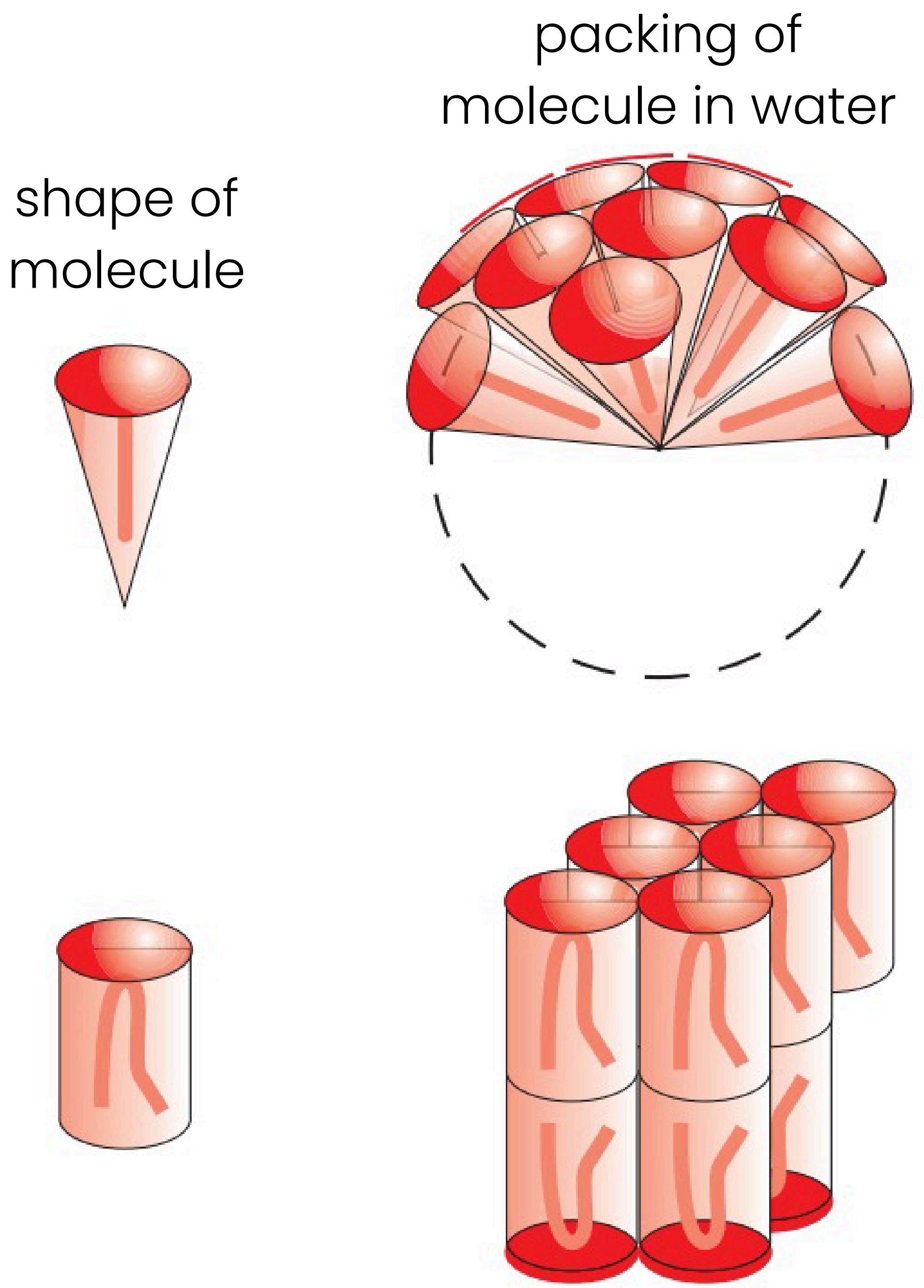
Membrane of two adjoining cells

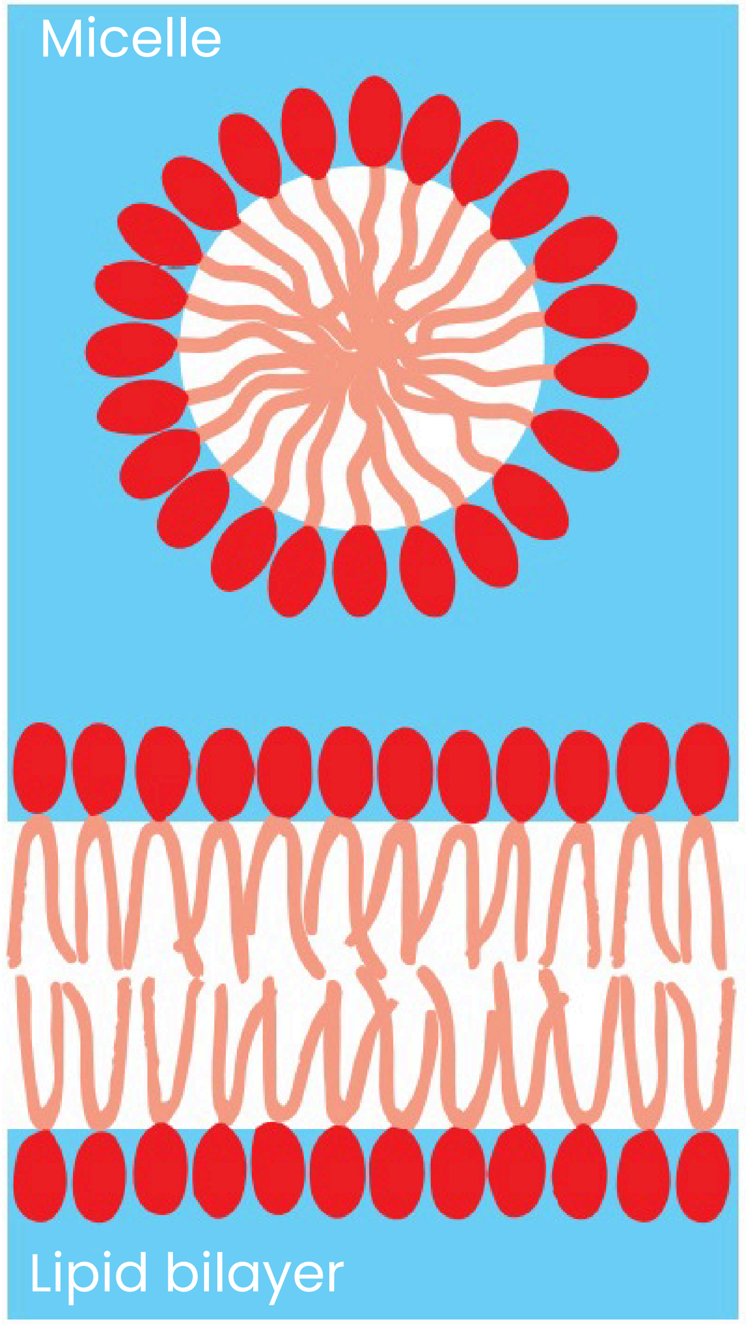
'Trilaminar' appearance highlighted

It is easily seen by electron microscopy

Phospholipids spontaneously form bilayers in aqueous environments

When amphiphilic molecules are in water, they naturally aggregate so that their water-hating (hydrophobic) tails are hidden inside, and their water-loving (hydrophilic) heads face the water.



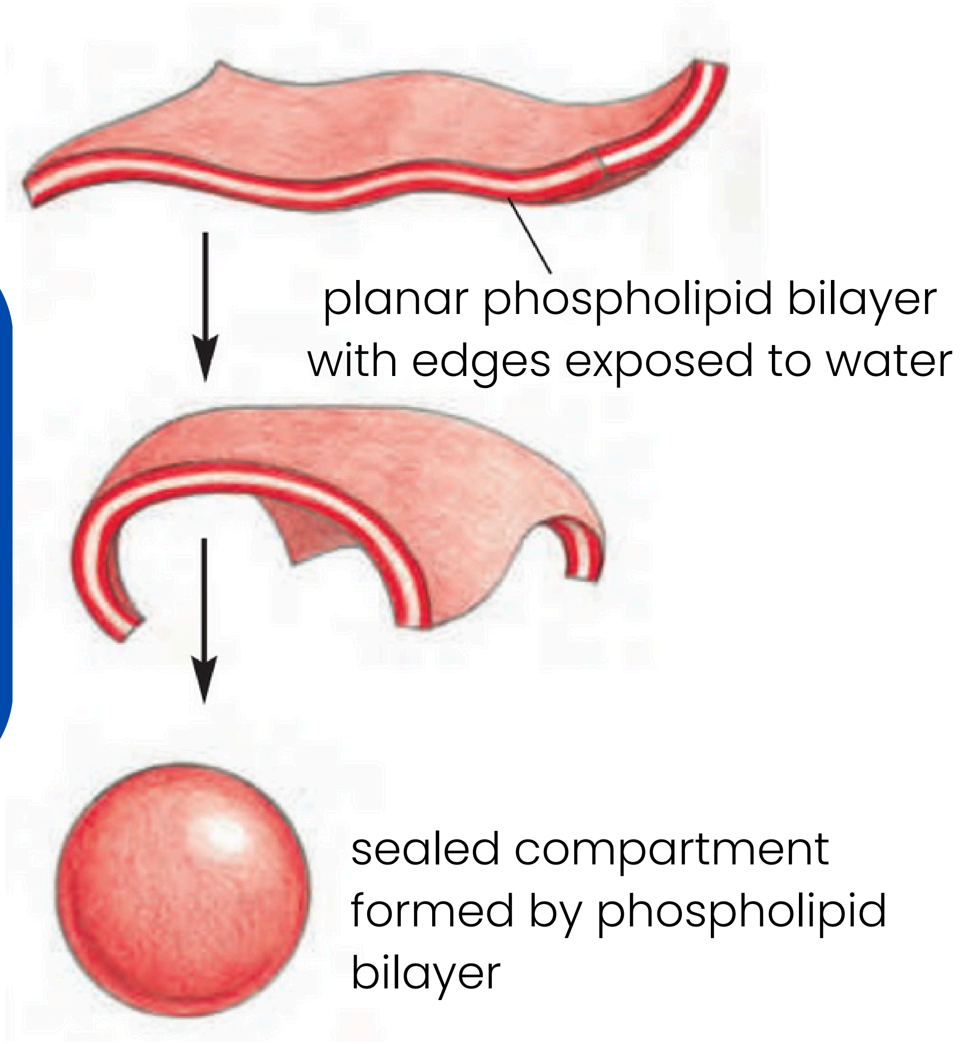


Two possible aggregate forms:
- Spherical micelles
- Lipid bilayer

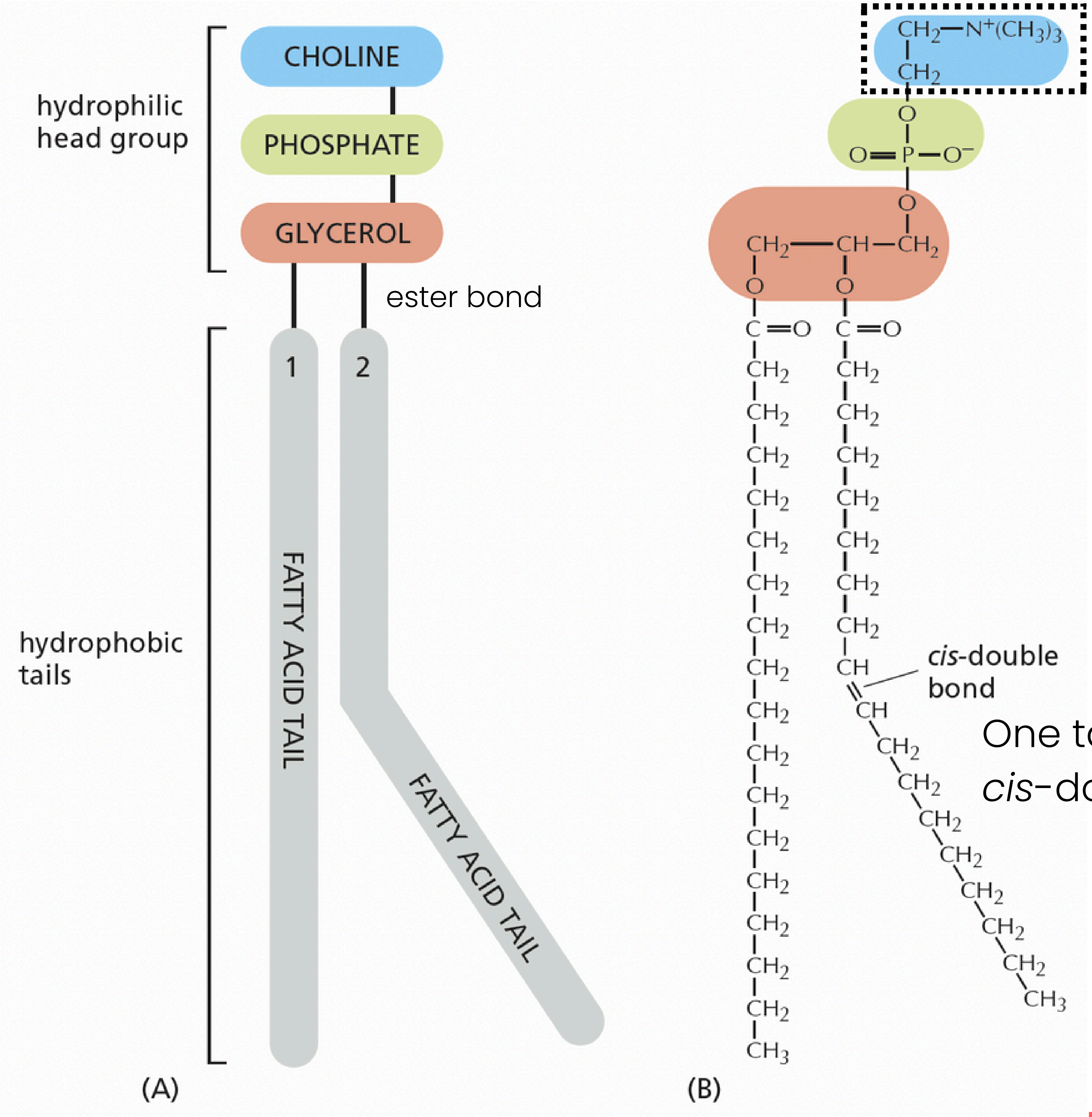
(Depending on their shape)

- Cone-shaped molecules ⟶ Micelle
- Cylinder-shaped molecules ⟶ Lipid bilayer

the only way for a bilayer to avoid having edges is by closing in on itself and forming a sealed compartment



Phospholipids have a polar head group containing a phosphate group and two hydrophobic hydrocarbon tails



head group

One tail typically has one or more *cis*-double bonds (unsaturated)

Differences in the length and saturation of the fatty acid tails

↓ affect

Molecules pack against one another

↓ affect

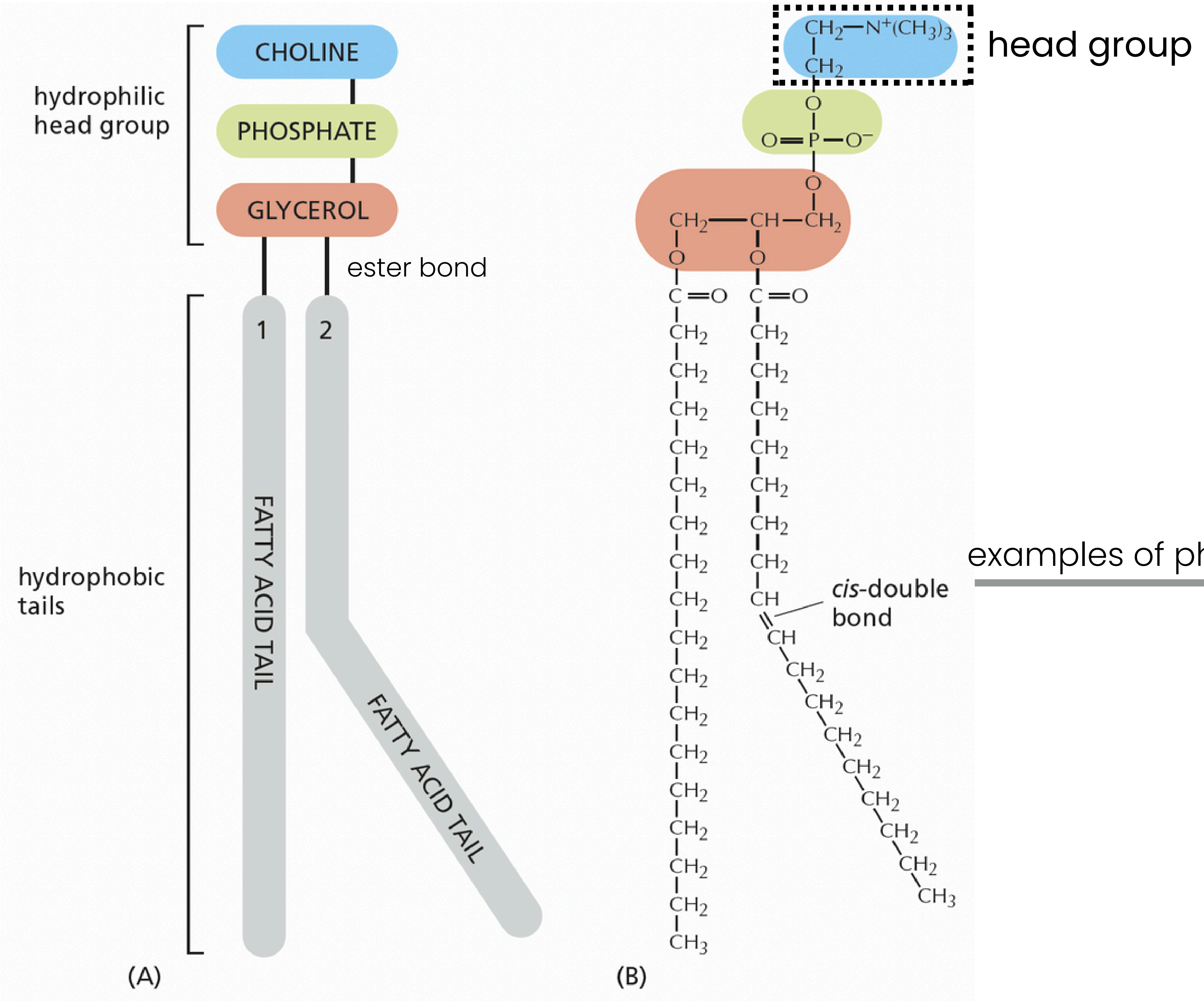
Fluidity of membrane

(We will talk about this soon)

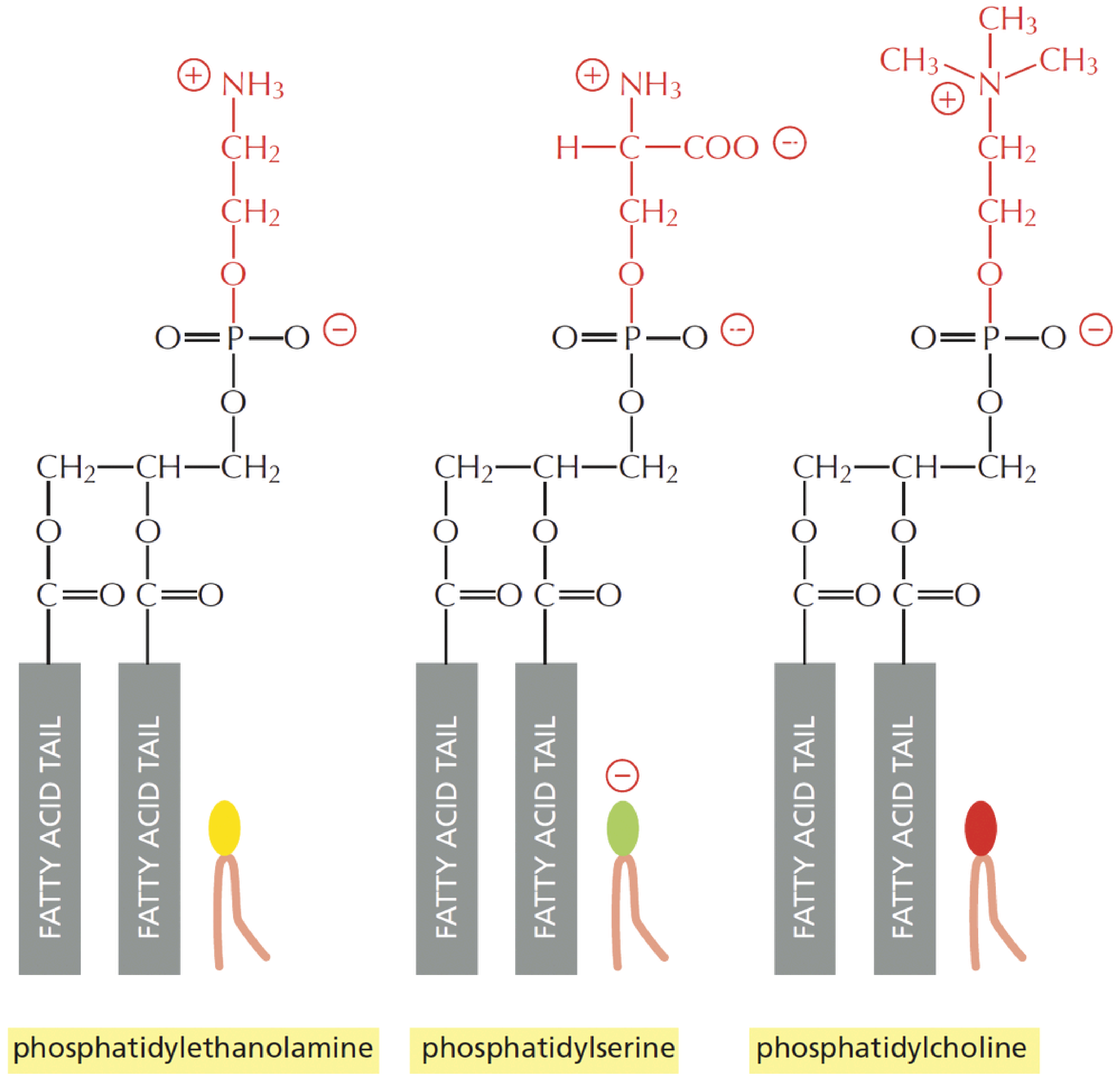
The main phospholipids in most animal cell membranes are the **phosphoglycerides**, which have a three-carbon glycerol backbone

LIPID BILAYER

Cells create many kinds of phosphoglycerides by mixing different fatty acids and head groups

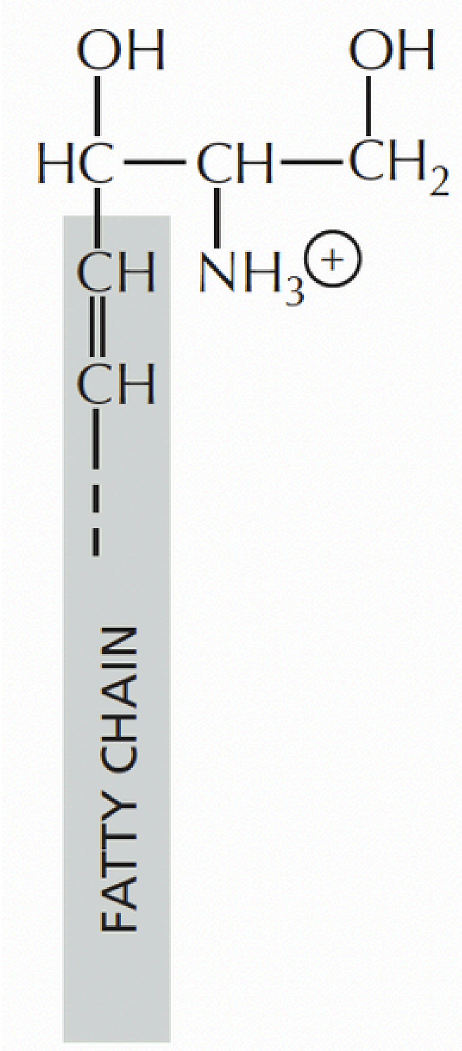


examples of phosphoglycerides



These are the most abundant ones in mammalian cell membranes

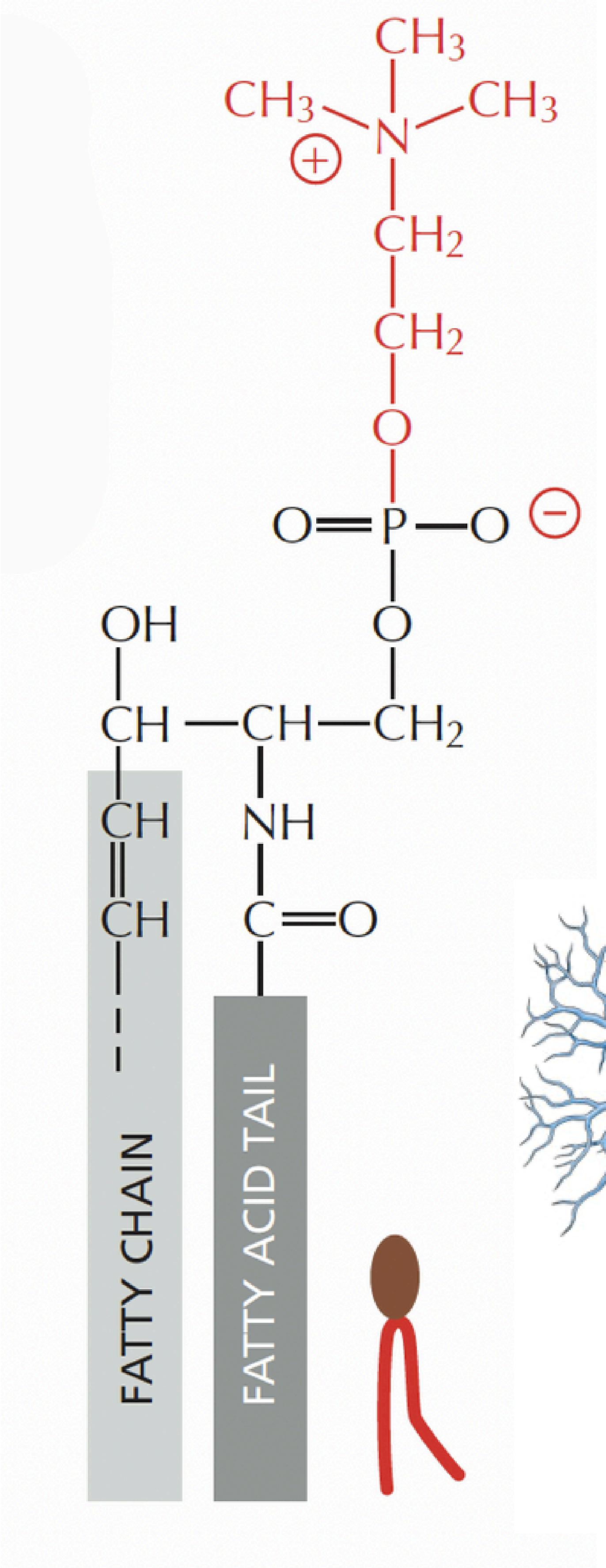
Another important class of phospholipids are the **sphingolipids** (Made from **sphingosine** instead of glycerol)



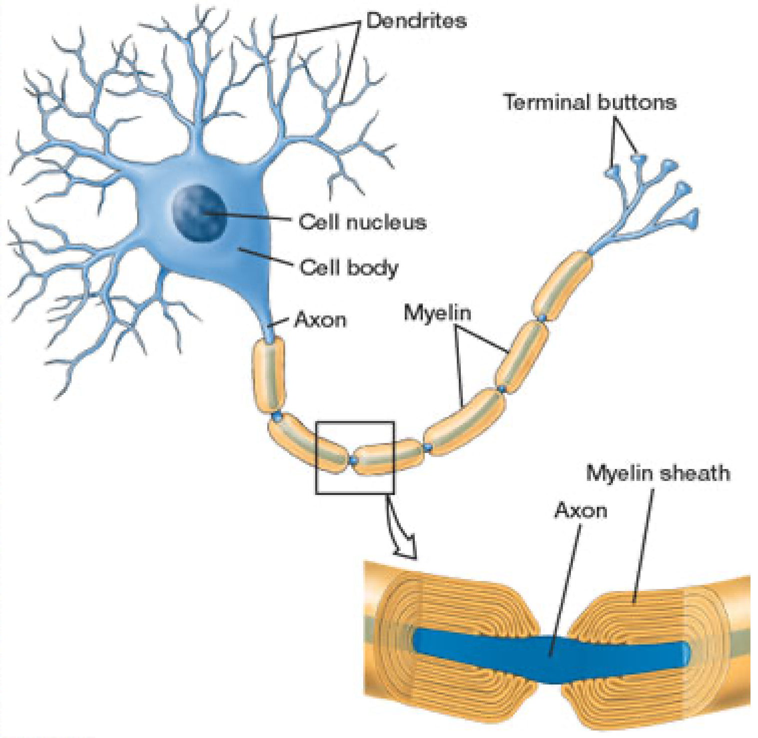
sphingosine

- **Sphingosine** = a long acyl chain with an amino group (NH2) and two hydroxyl groups (OH) at one end
- The most common sphingolipid = **sphingomyelin**
- **Sphingomyelin** =
  - fatty acid tail is attached to the amino group
  - phosphocholine group is attached to the terminal hydroxyl group

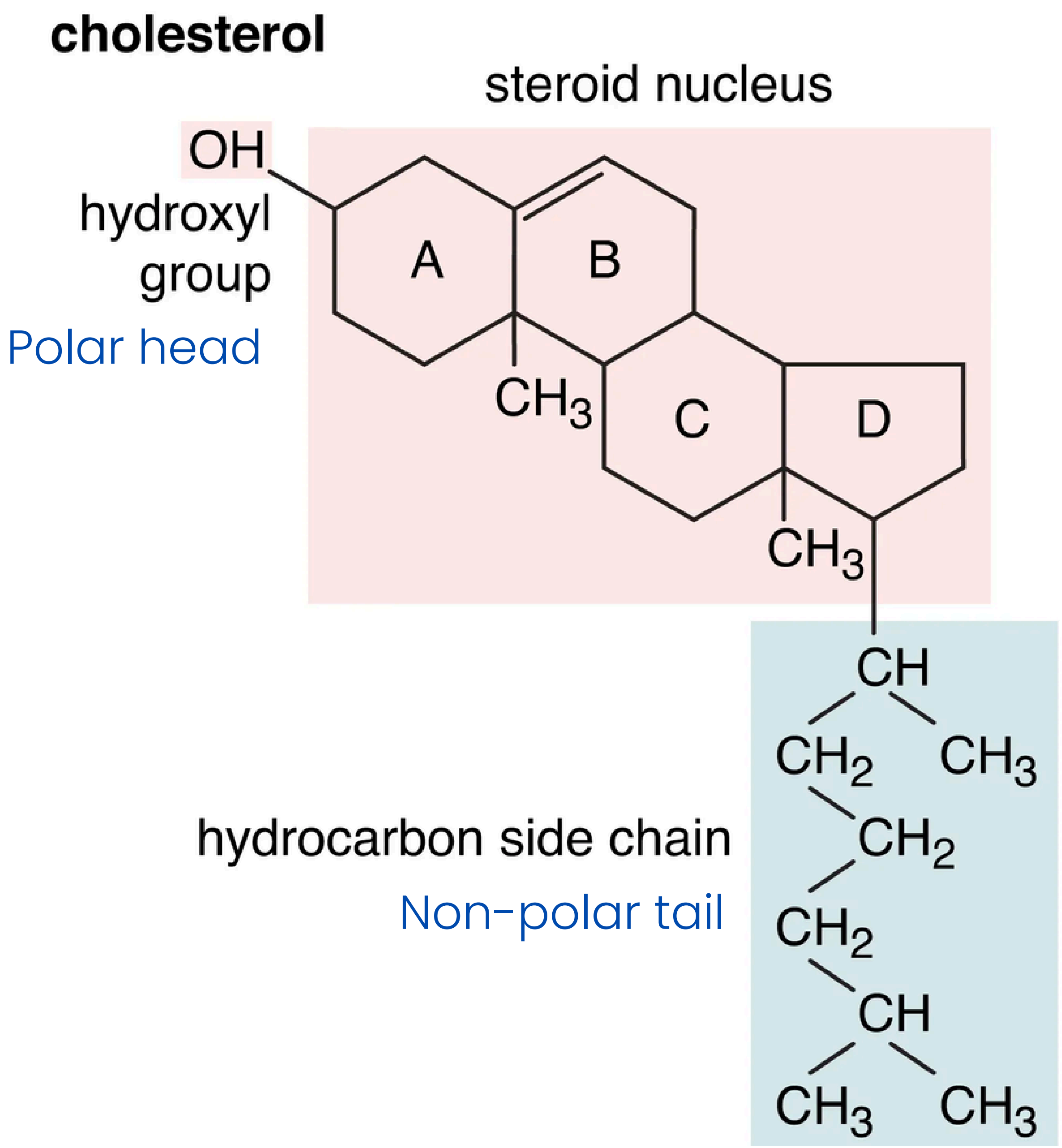
Sphingomyelin is found in animal cell membranes, especially in the myelin sheath that wraps around nerve cell axon

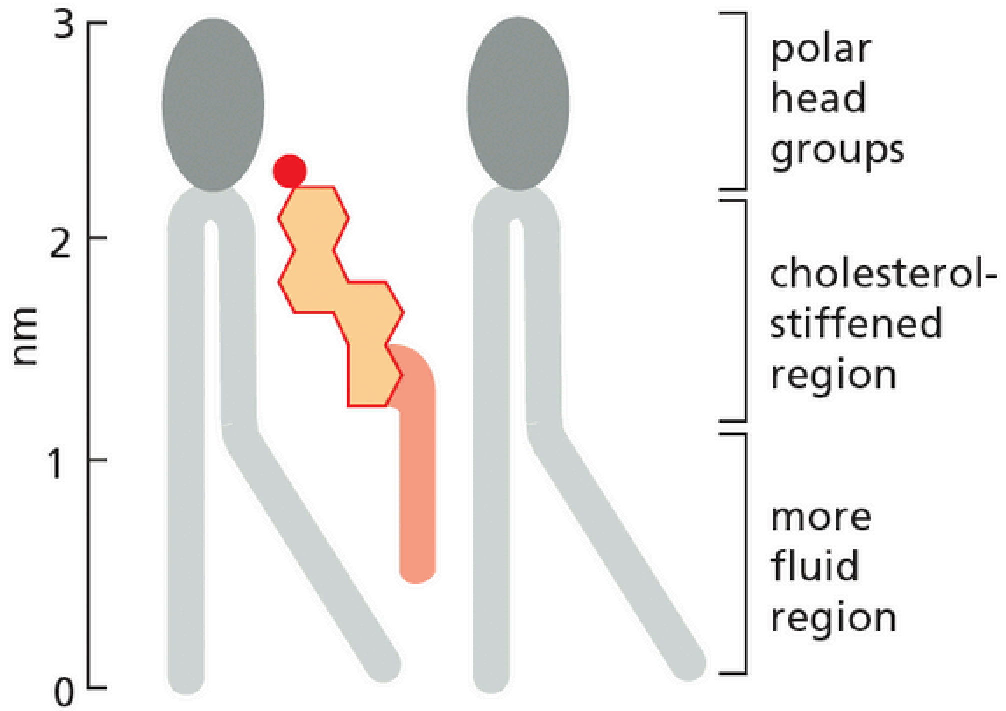


sphingomyelin



Besides phospholipids, many cell membrane lipid bilayers also have **glycolipids** and **cholesterol**



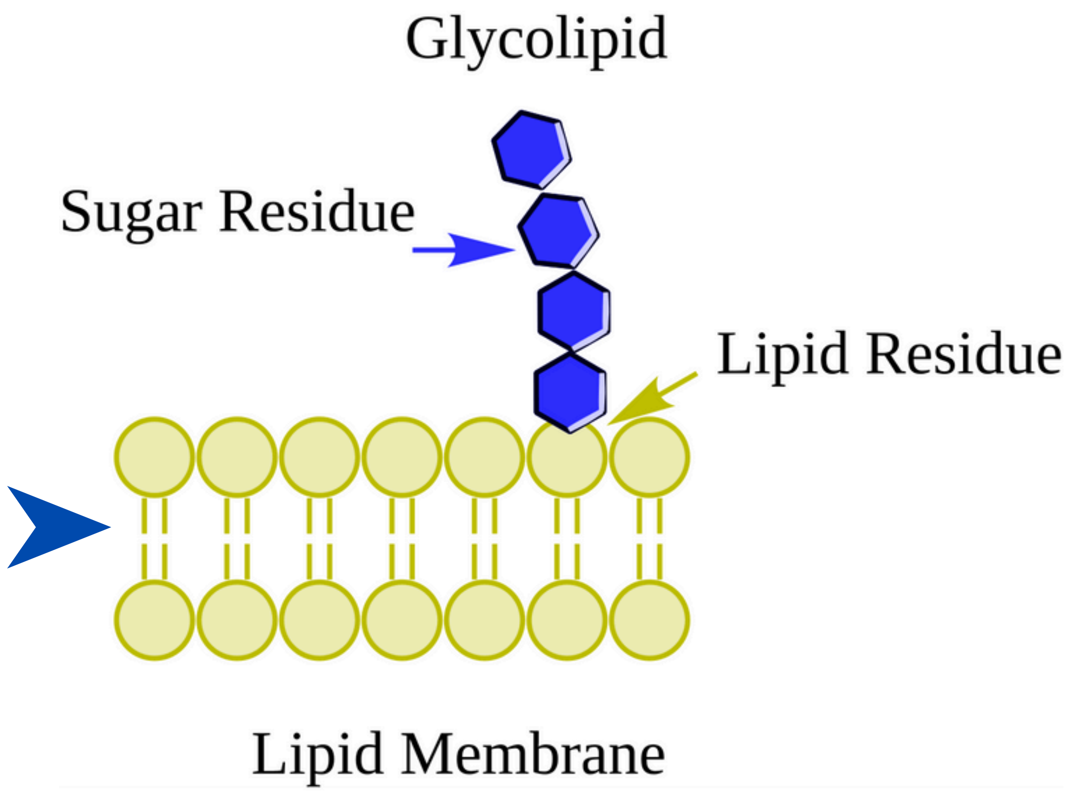


Cholesterol in the bilayer orients with its polar head group facing the aqueous environment and its non-polar region facing the membrane interior

Cholesterol contains a rigid steroid ring structure

- attached a single polar hydroxyl group
- short nonpolar hydrocarbon chain

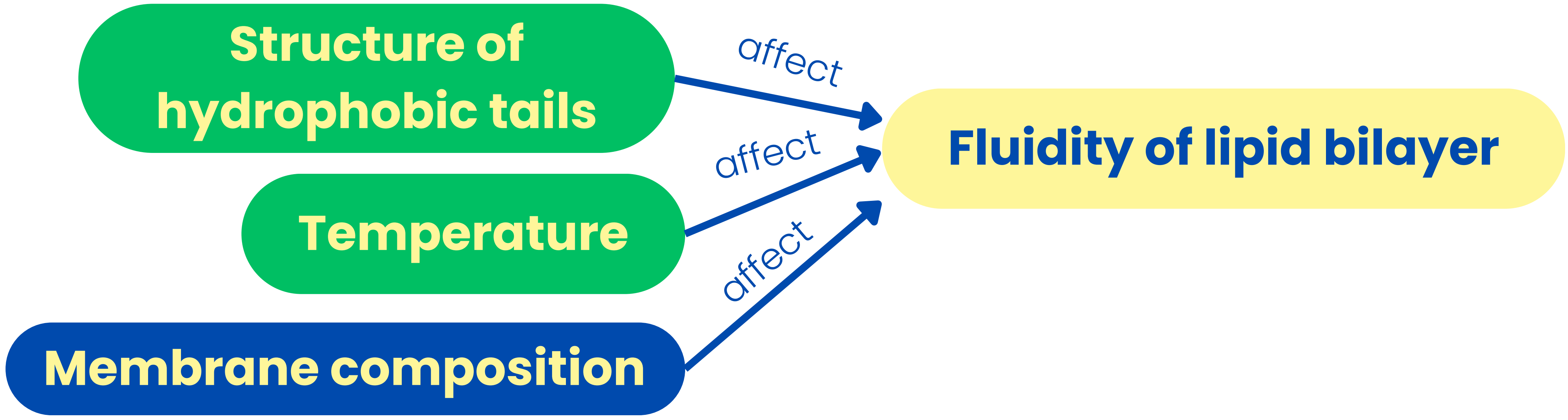
Glycolipids are like sphingolipids, but instead of having a phosphate group, they have sugars attached



FLUIDITY OF A LIPID BILAYER

Some membrane transport processes and enzyme activities stop working when the membrane becomes too viscous

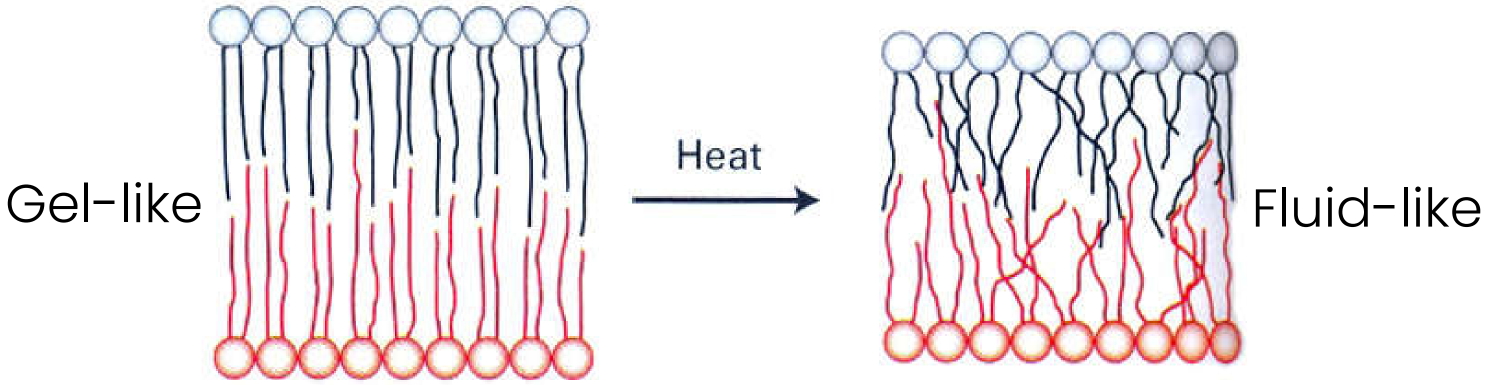
Factors that affect the fluidity



Temperature

Higher temperature → Fluid-like

Lower temperature → Gel-like

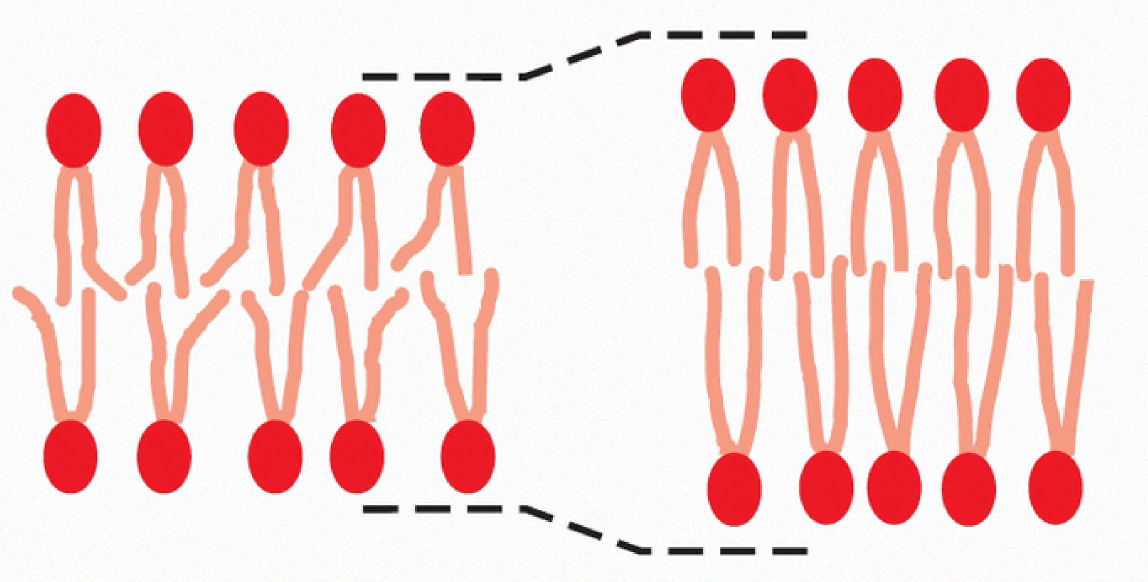


Structure of hydrophobic tails

- Saturated hydrocarbon chains → Pack tightly
- Unsaturated hydrocarbon chains → Pack loosely (remains fluid at the low temperature)
- Shorter hydrocarbon chains → Reduce tendency to interact with one another

↕ Increase fluidity

membranes with unsaturated chain are thinner than those made only of saturated lipids

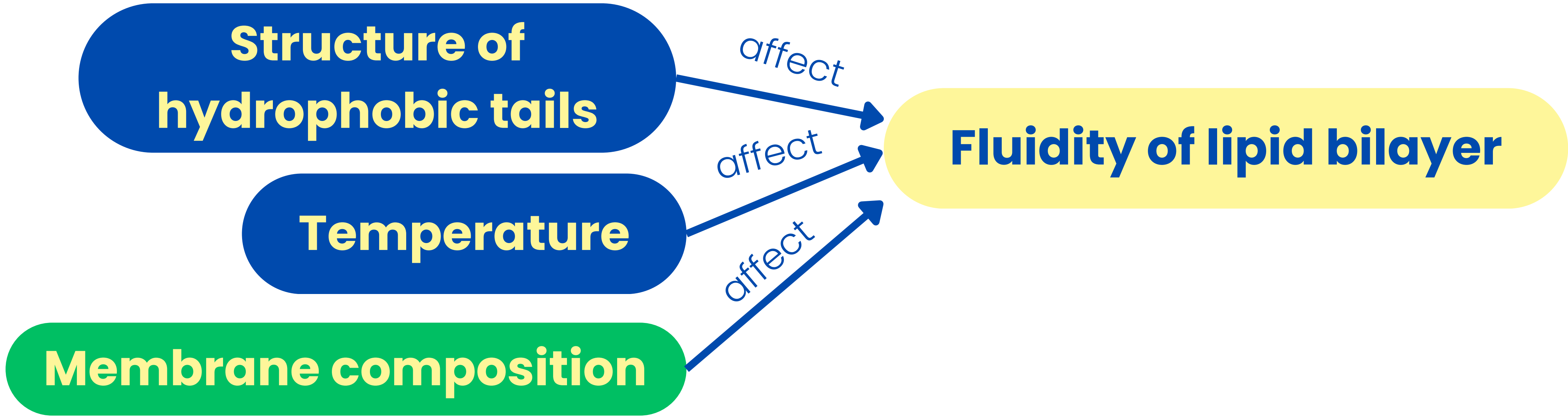


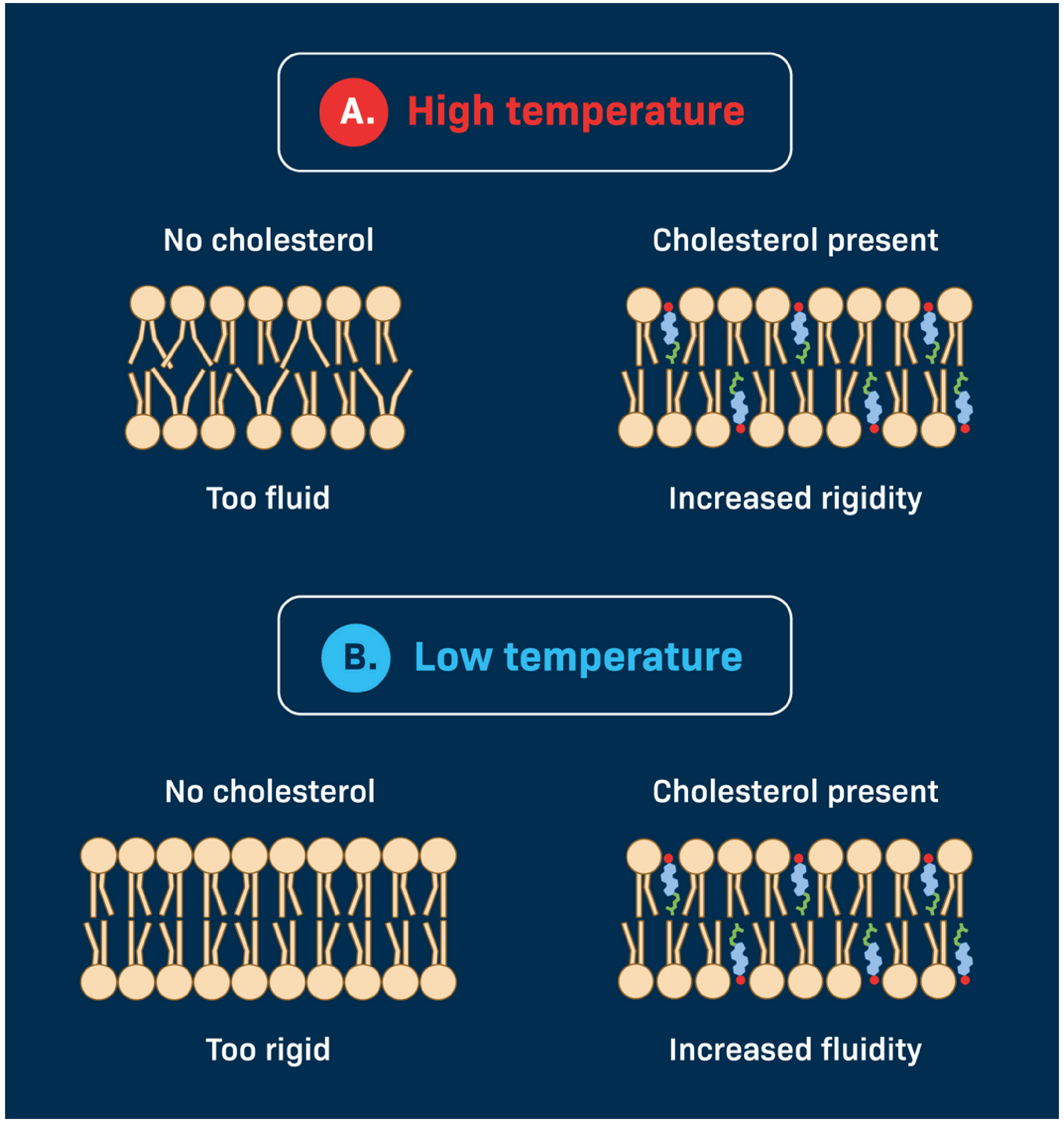
unsaturated hydrocarbon chains with *cis*-double bonds

saturated hydrocarbon chains

FLUIDITY OF A LIPID BILAYER

Factors that affect the fluidity



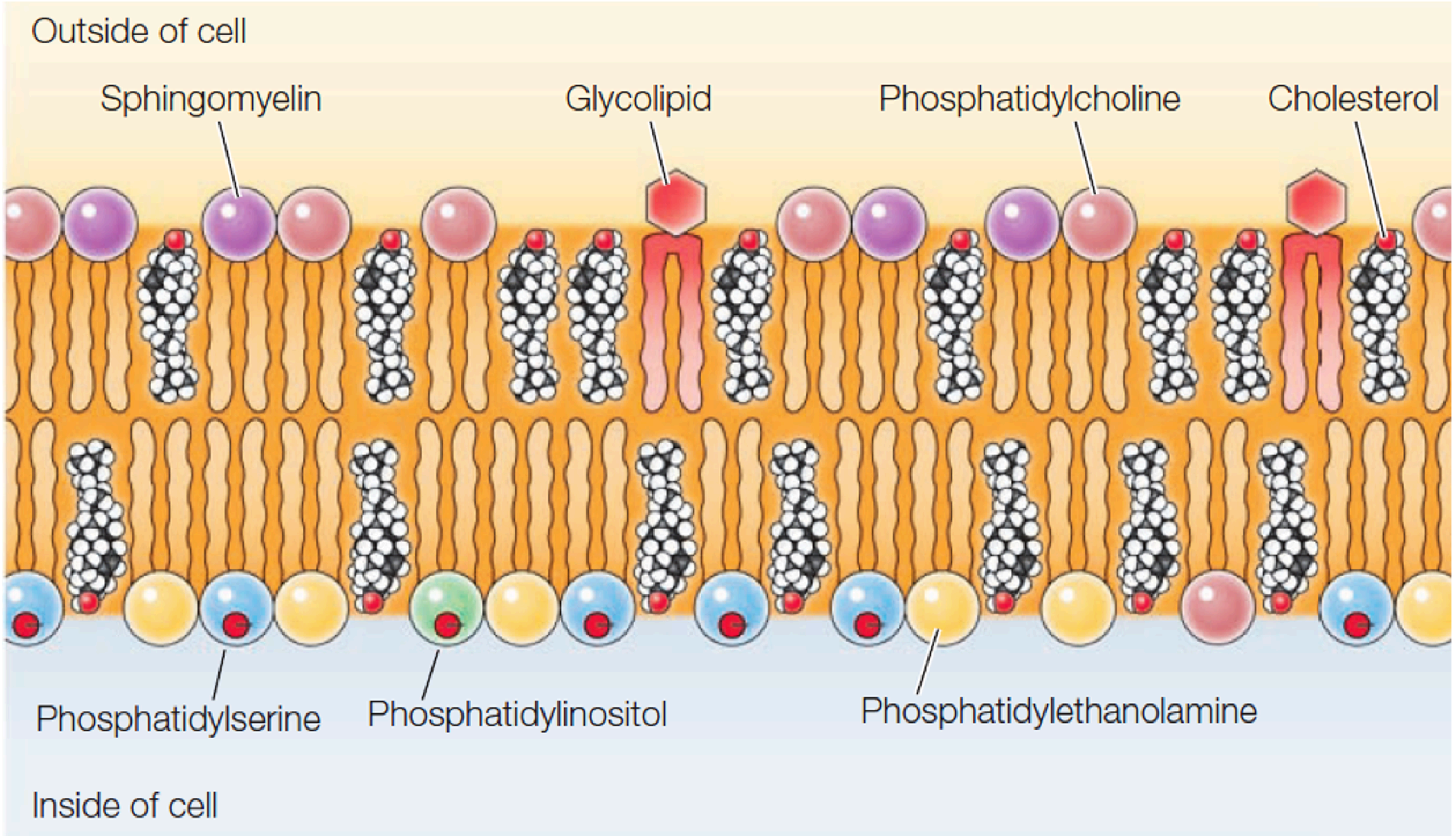


Cholesterol

- Temperature buffer
- At higher temperatures:
  - Cholesterol constrains motion of hydrocarbon chain → decrease fluidity
- At Lower temperatures:
  - Cholesterol disrupts close packing of hydrocarbon chain → increase fluidity

ORGANIZATION OF PLASMA MEMBRANE LIPIDS

the outer and inner leaflets of the cell membrane (also called the plasma membrane) are structurally and functionally **different**



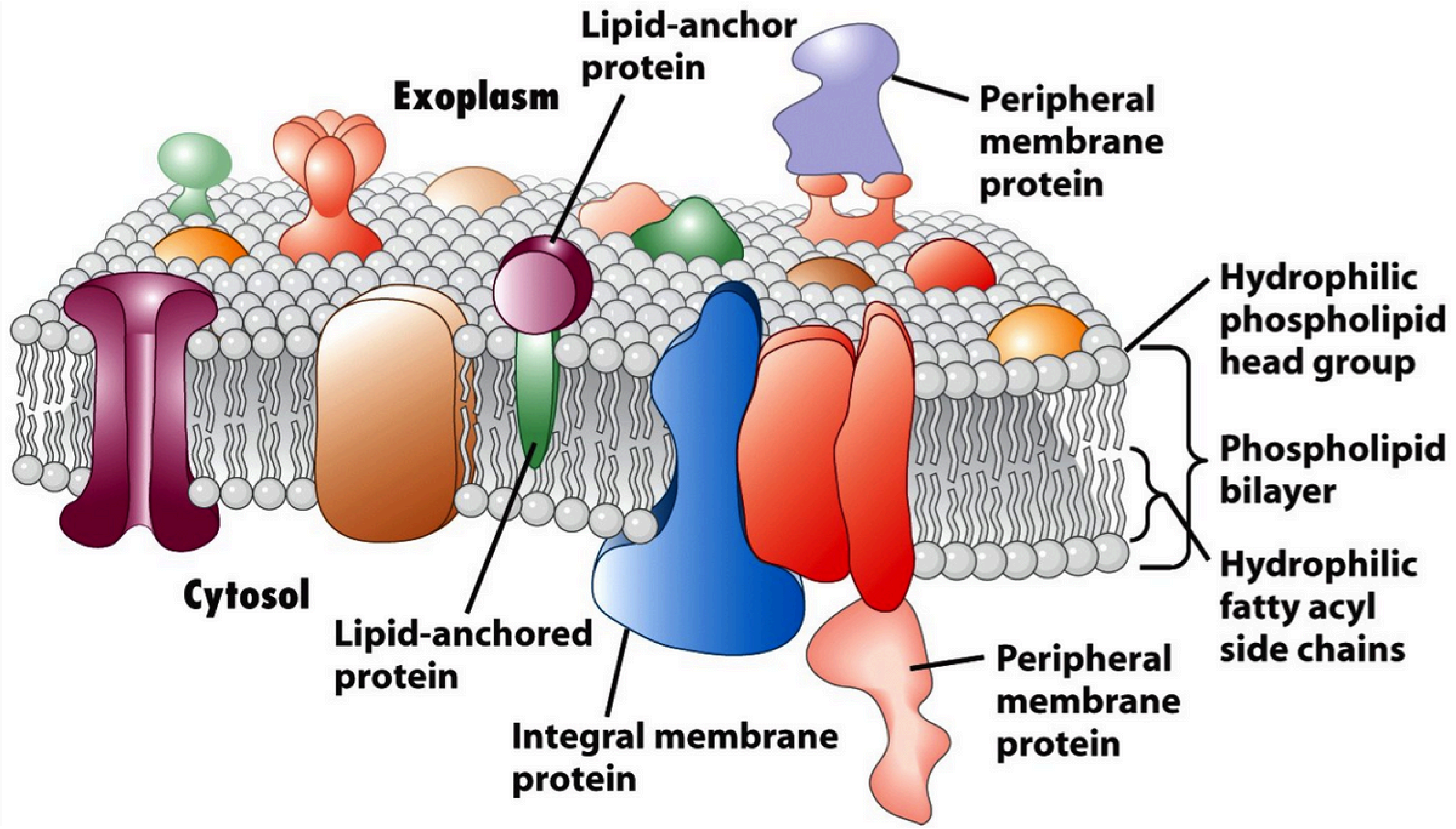
Outer leaflet consists predominantly
- phosphatidylcholine
- sphingomyelin
- glycolipids

Inner leaflet contains predominantly
- phosphatidylethanolamine
- phosphatidylserine
- phosphatidylinositol

MEMBRANE PROTEIN

Although the lipid bilayer provides the basic structure of biological membranes, the membrane proteins perform most of the membrane's specific tasks

Membrane proteins are amphiphilic
(having hydrophobic and hydrophilic regions)

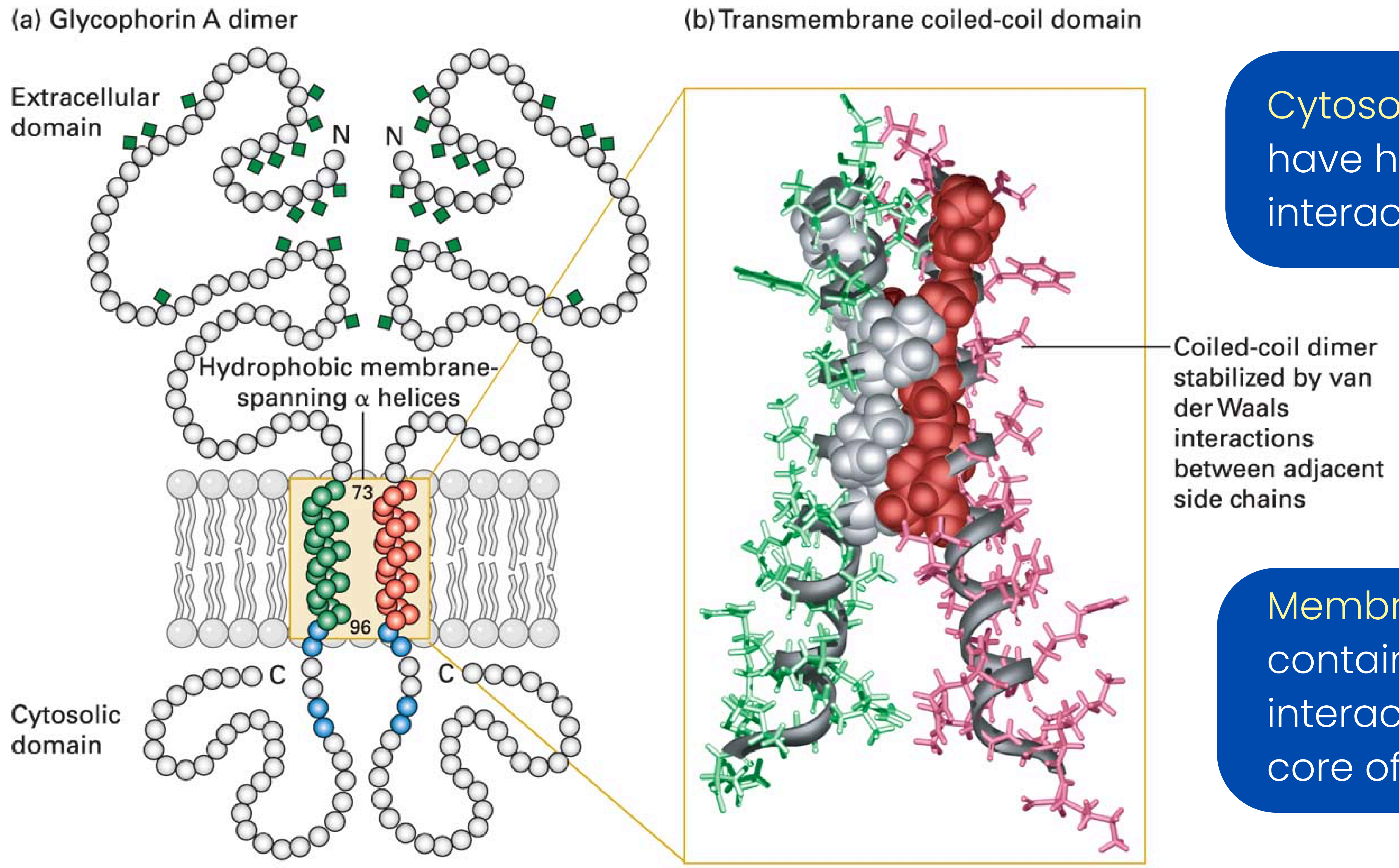


Structural Classification

1. Integral (transmembrane) protein: spans the entire lipid bilayer of a cell membrane
2. Peripheral membrane protein: only temporarily attached to the lipid bilayer or to other integral proteins (attached via non-covalent bonds)
3. Lipid-anchored protein: covalently attached to lipid molecules

INTEGRAL MEMBRANE PROTEIN

Integral membrane proteins are structurally divided into three parts: extracellular domain, membrane-spaning segment, and cytoplasmic domain



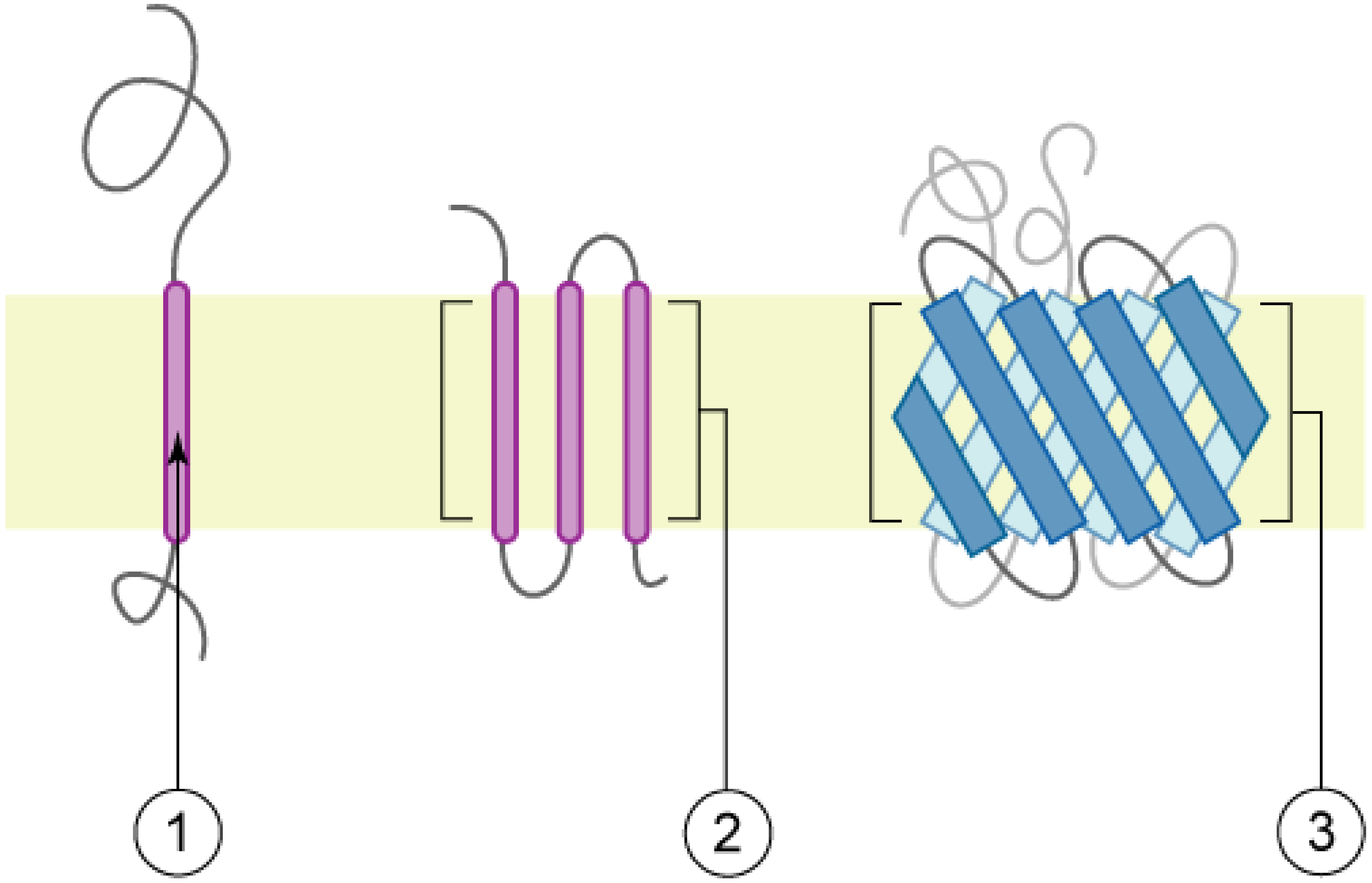
Cytosolic & exoplasmic domains have hydrophilic exterior surfaces that interact with aqueous solutions

Membrane-spanning segments contain hydrophobic amino acids that interact with hydrophobic hydrocarbon core of phospholipid bilayer

Structure of glycophorin A (an example of integral membrane protein)

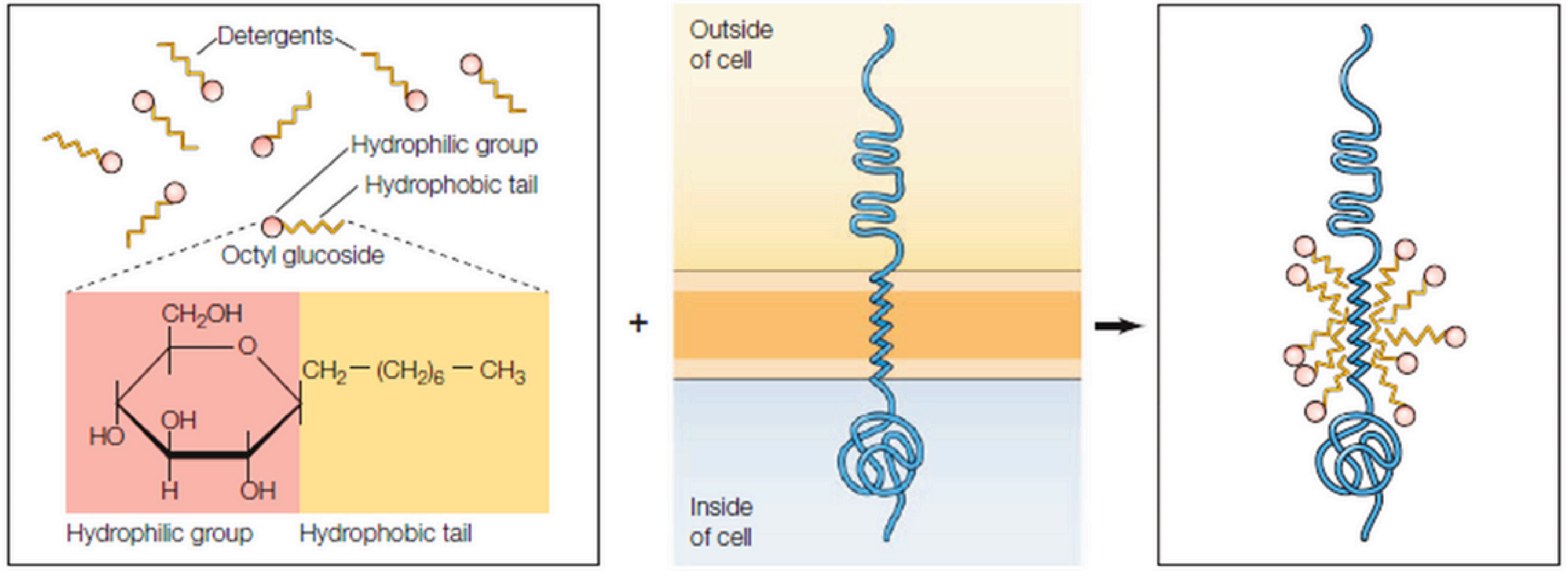
INTEGRAL MEMBRANE PROTEIN

Membrane-Spanning Segment
(Transmembrane Domain) may consist of
- one or several alpha-helices
- transmembrane beta barrel



? Can an integral membrane protein be soluble?

No, under normal biological conditions (hydrophobic parts make them insoluble in aqueous environments)
They need detergents (e.g. SDS, Triton X-100) to be soluble in water

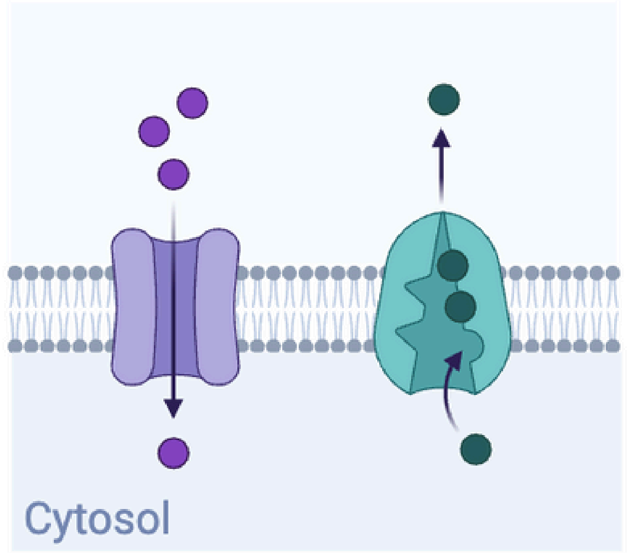


Solubilization of integral membrane proteins by detergents
Detergents (e.g., octyl glucoside) are amphipathic molecules containing hydrophilic head groups and hydrophobic tails. The hydrophobic tails bind to the hydrophobic regions of integral membrane proteins, forming detergent–protein complexes that are soluble in aqueous solution.

MEMBRANE PROTEIN FUNCTIONS

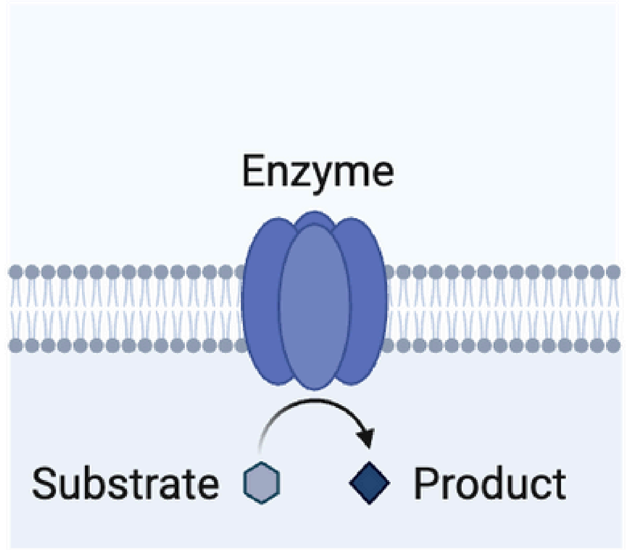
Depending on their type and position in the membrane, they serve a wide range of purposes

Ⓐ **Transport** of molecules throughout the membrane



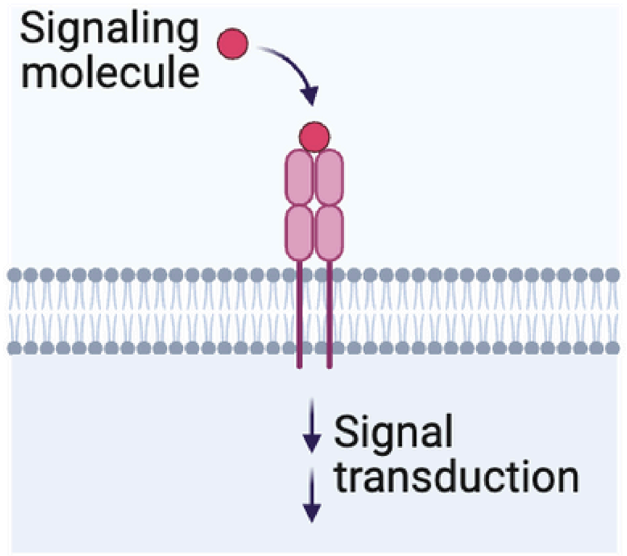
e.g. Channel proteins, carrier proteins

Ⓑ **Enzymatic activity** transforming substrates into products



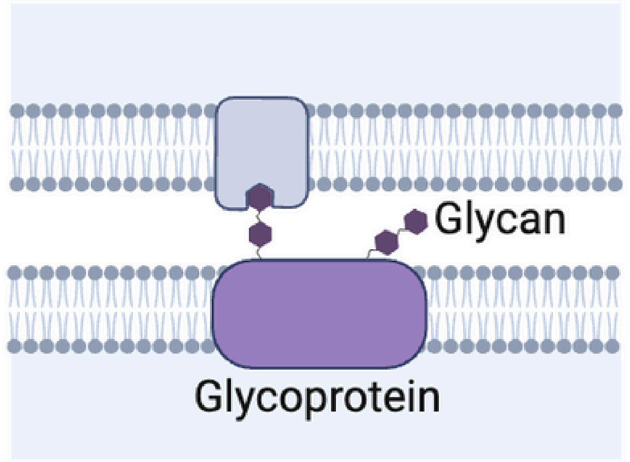
e.g. ATP synthase

Ⓒ Molecule recognition and **signal transduction**



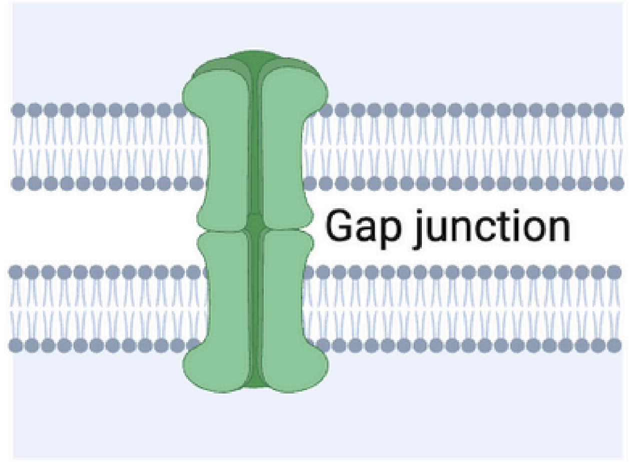
e.g. Hormone receptors

Ⓓ **Cell-cell recognition** based on glycan recognition.



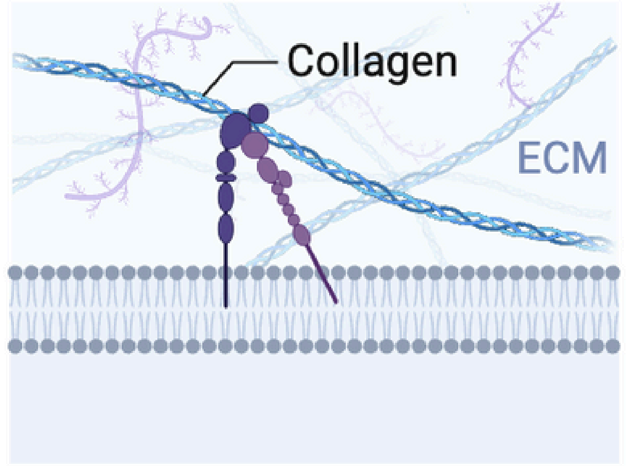
e.g. MHC proteins (for infected cells)

Ⓔ **Intercellular joining** of two adjacent cells



e.g. Tight junction, desmosome

Ⓕ **Attachment** to the cytoskeleton and ECM



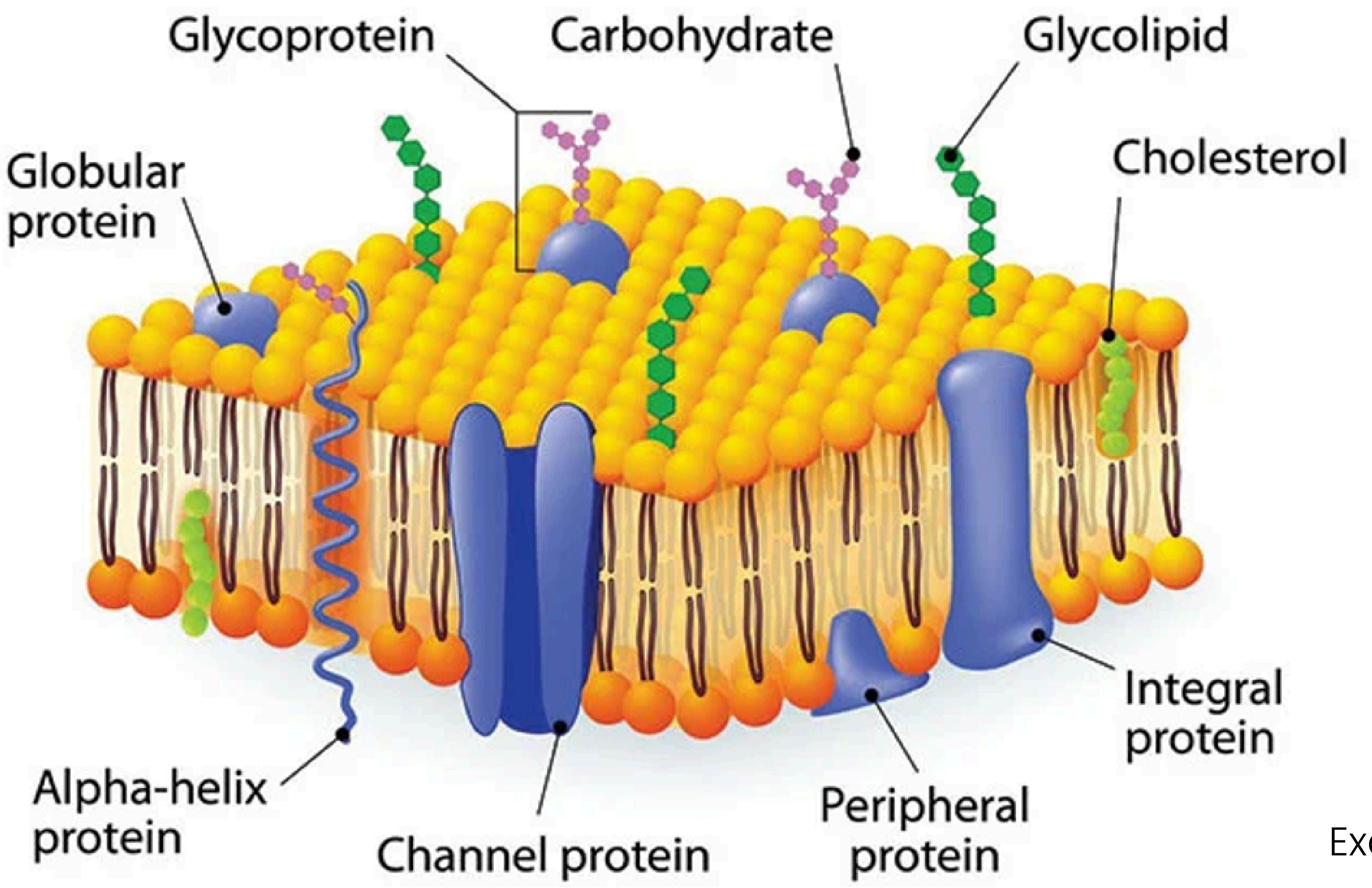
e.g. Integrins, anchoring proteins

MEMBRANE CARBOHYDRATES

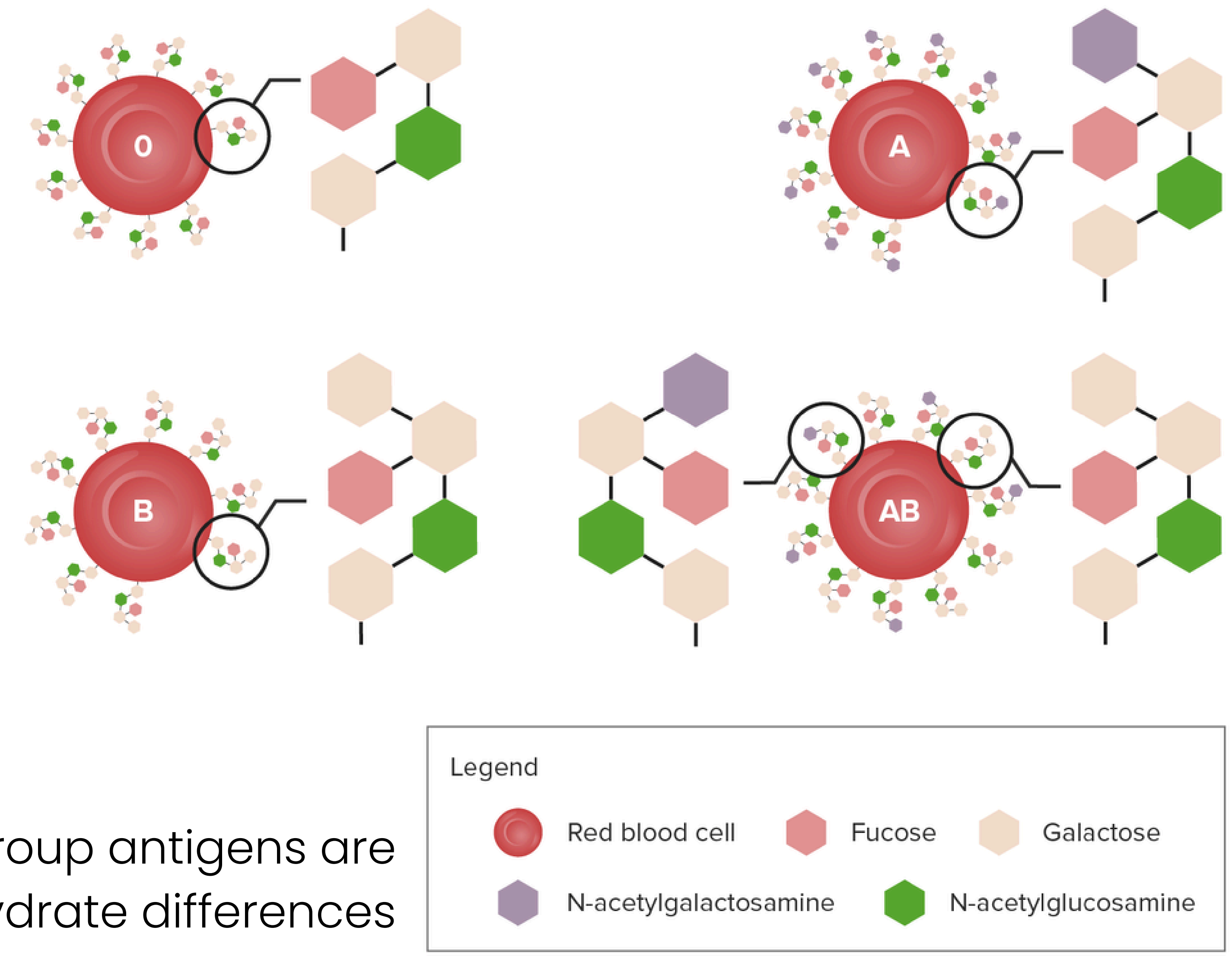
Membrane carbohydrates (oligosaccharides) that are attached to proteins or lipids on the outer surface of the cell membrane

- Protein + carbohydrate = glycoprotein
- Lipid + carbohydrate = glycolipid

- Play a key role in cell-cell recognition
- In cell-cell recognition, both carbohydrates and proteins are important
- carbohydrates on proteins and lipids (glycoprotein and glycolipid) are often most critical for specificity



Always on the extracellular side

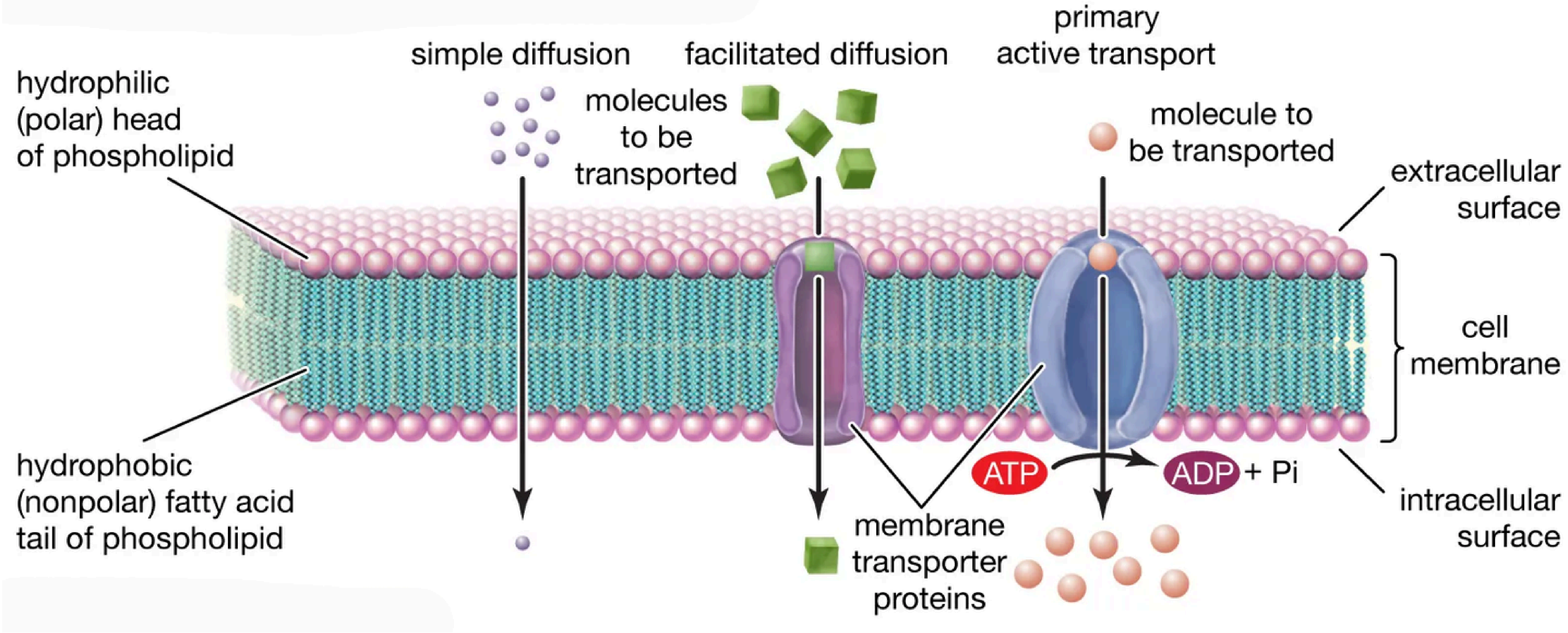


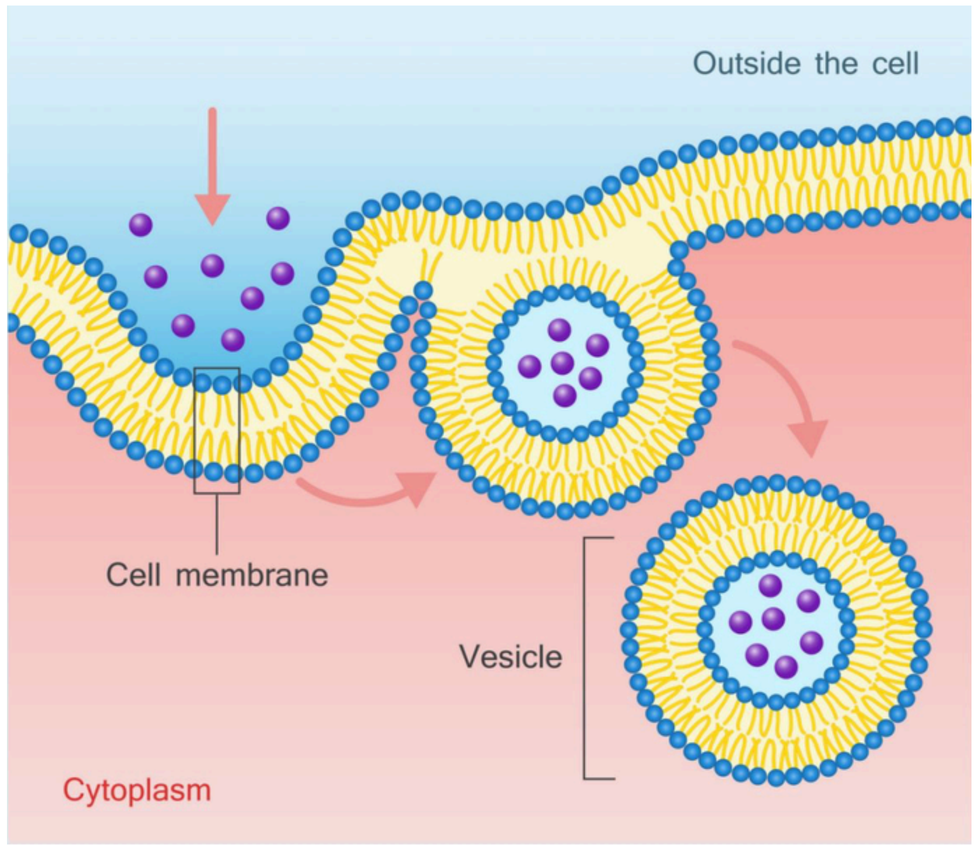
Example: blood group antigens are carbohydrate differences

Membrane transport refers to the movement of substances across a cell membrane

Types of membrane transport

- Passive transport: moves substances from high to low concentration (e.g. simple diffusion, facilitated diffusion)
- Active transport: moves substances against their concentration gradient (energy required)
- Bulk transport: for the large molecules or a lot of materials (e.g. endocytosis, exocytosis)

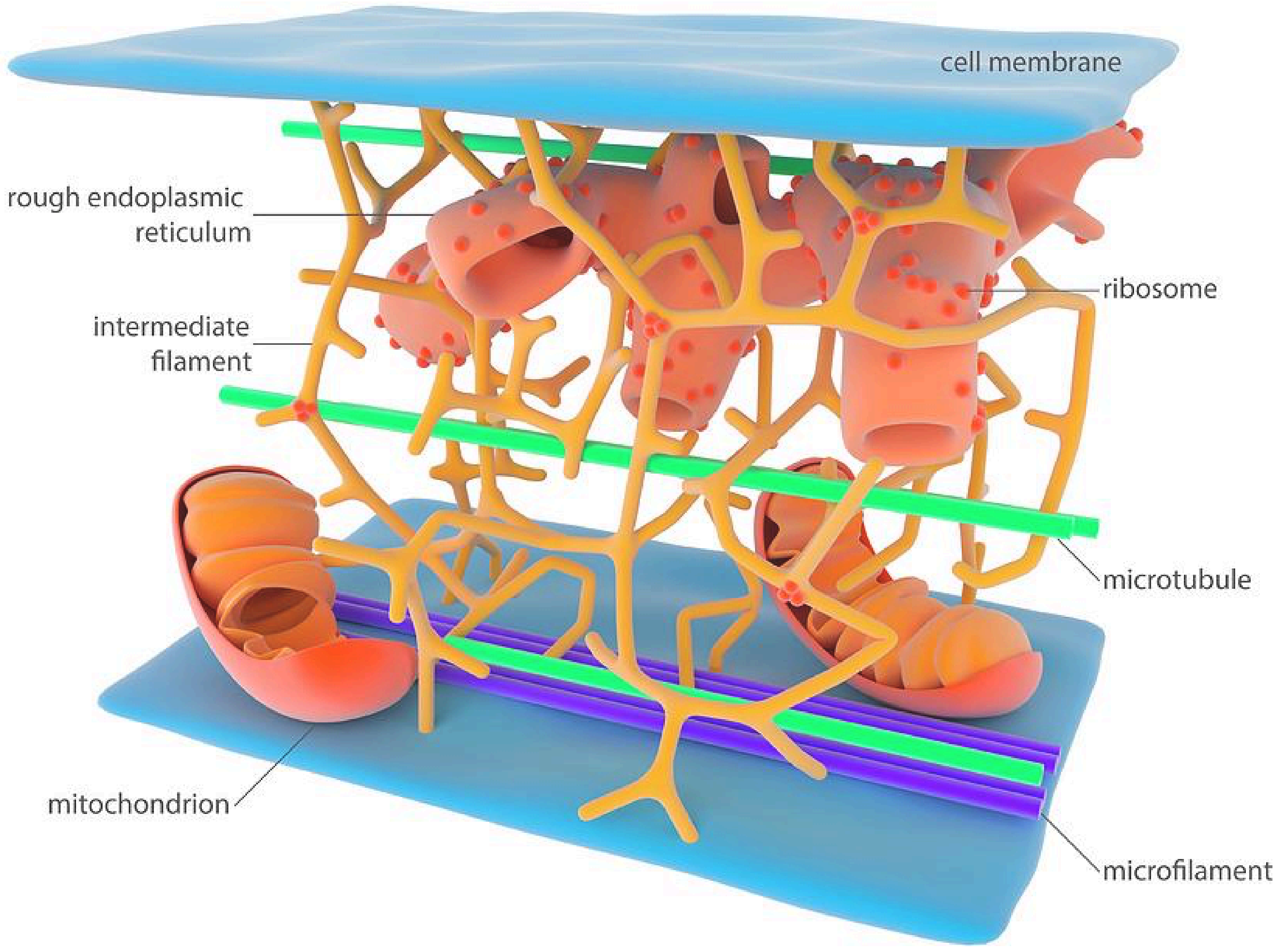




endocytosis

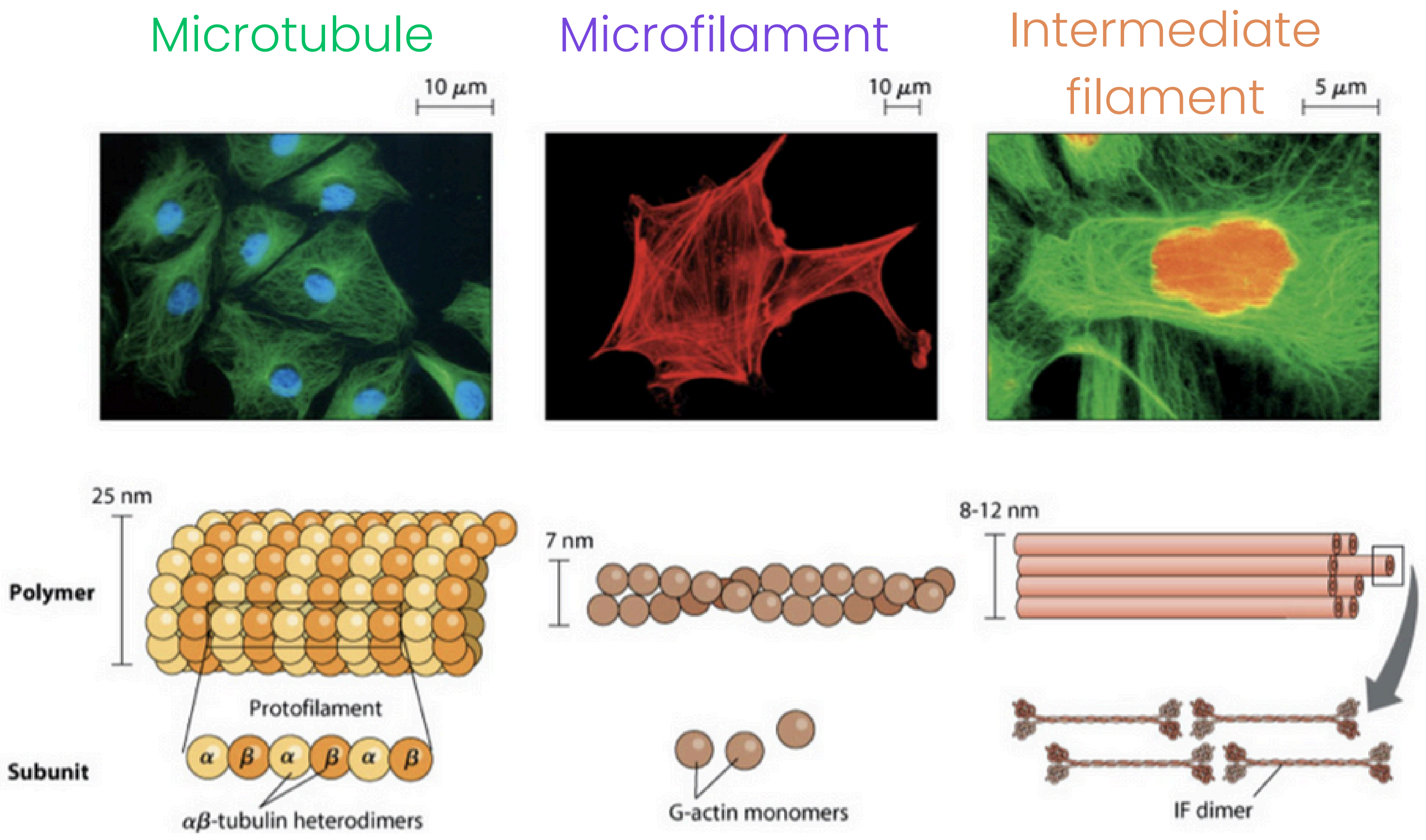
INTRODUCTION OF CYTOSKELETON

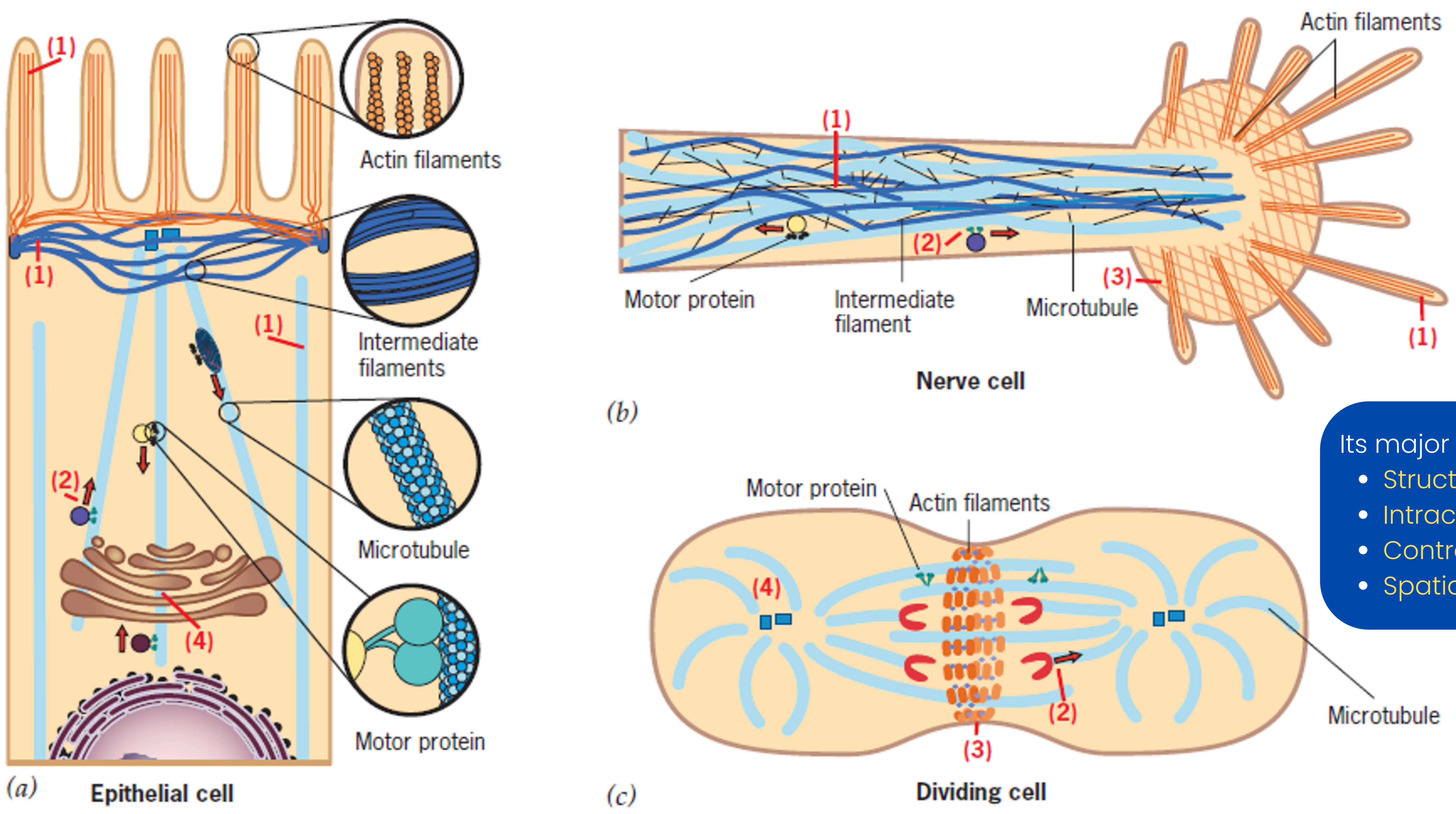
The cytoskeleton is a three-dimensional network of protein filaments found throughout the cytoplasm. It provides a structural framework that supports cell shape, organization, and internal transport.



<u>Three major cytoskeletal filaments</u>

- **Microtubule**: involves the positions of membrane-enclosed organelles, direct intracellular transport, and form the mitotic spindle
- **Microfilament** (actin filament): involves the shape of the cell's surface and are necessary for whole-cell locomotion
- **Intermediate filament**: provides mechanical strength



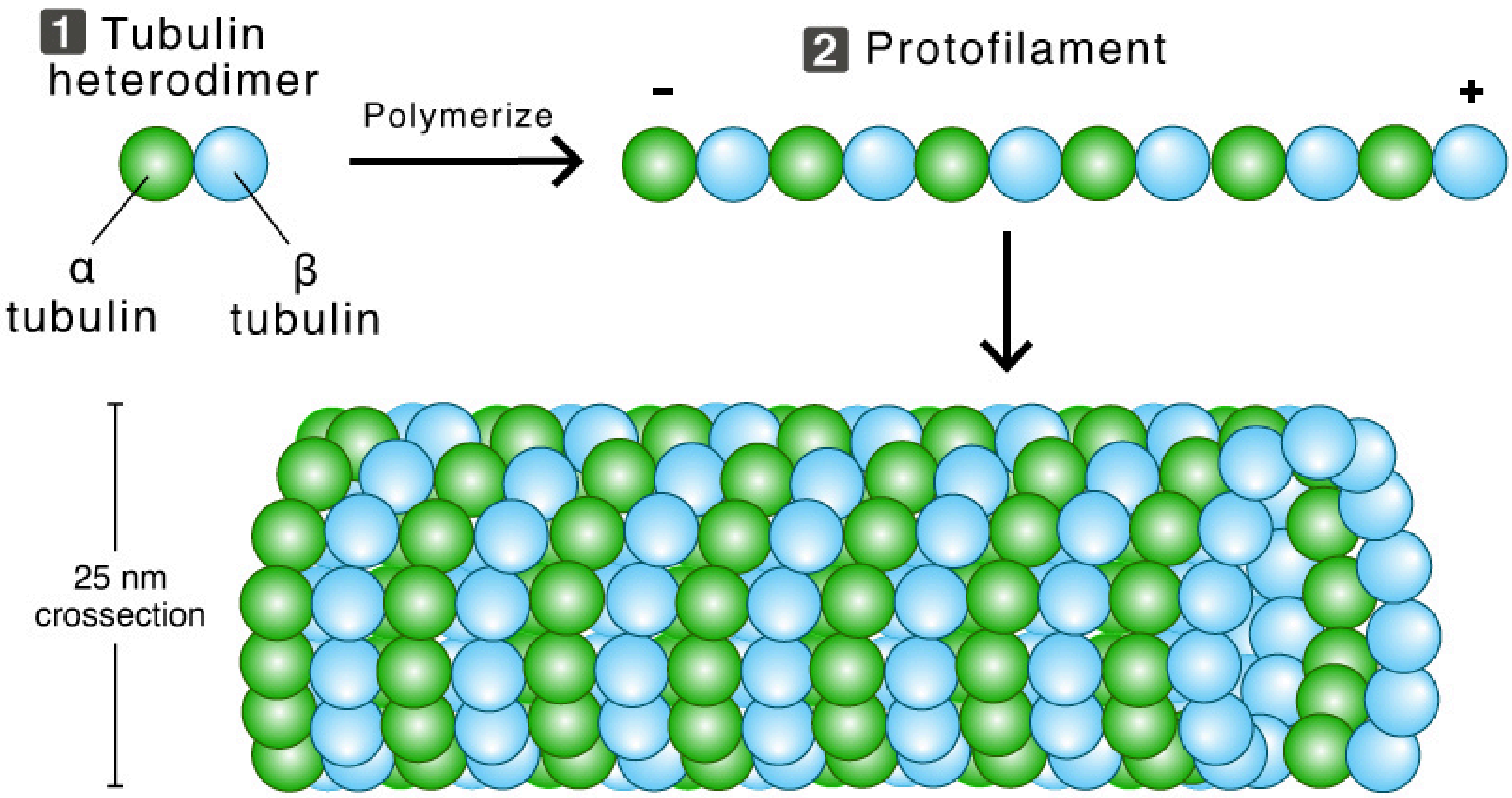


Its major roles include:

- Structure and Support (1)
- Intracellular transport (2)
- Contractility and motility (3)
- Spatial organization (4)

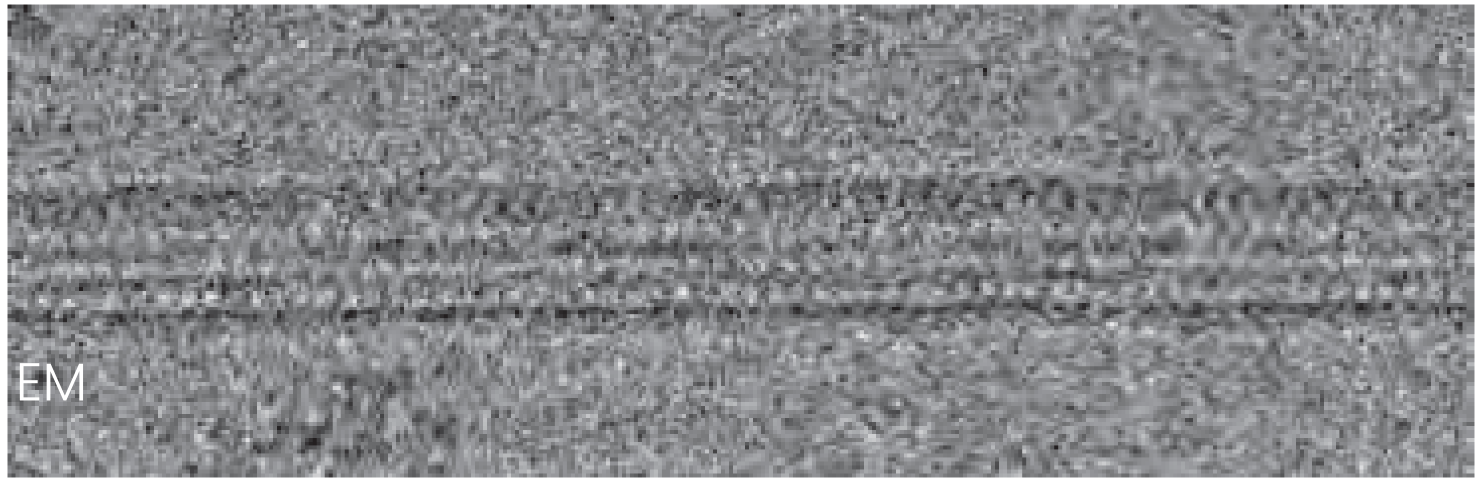
Microtubules are long, hollow cylinders made of the tubulin dimers (α and β tubules)

- Tubulin dimers polymerize to form linear chain (protofilament)
- Each protofilament contains β-tubulin end (+ end) and α-tubulin end (- end)
- Outer diameter = 25 nm



3 13 Protofilaments make up the microtubule

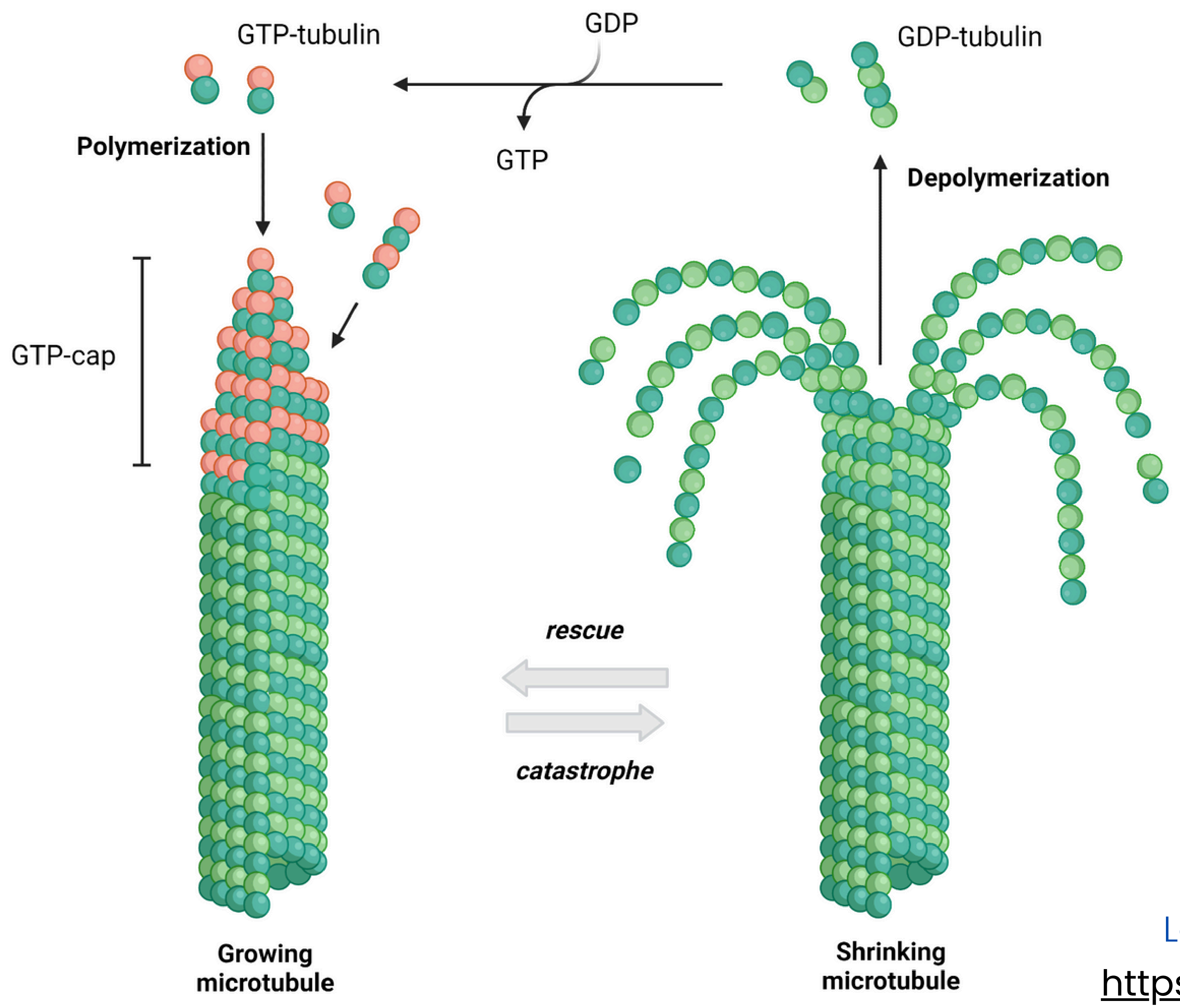
- each α or β monomer has a binding site for one molecule of GTP
- neighboring protofilaments form lateral contacts
- multiple contacts among subunits make microtubules stiff and difficult to bend (stiffest and straightest structure found in cells)



single microtubule

MICROTUBULE INSTABILITY

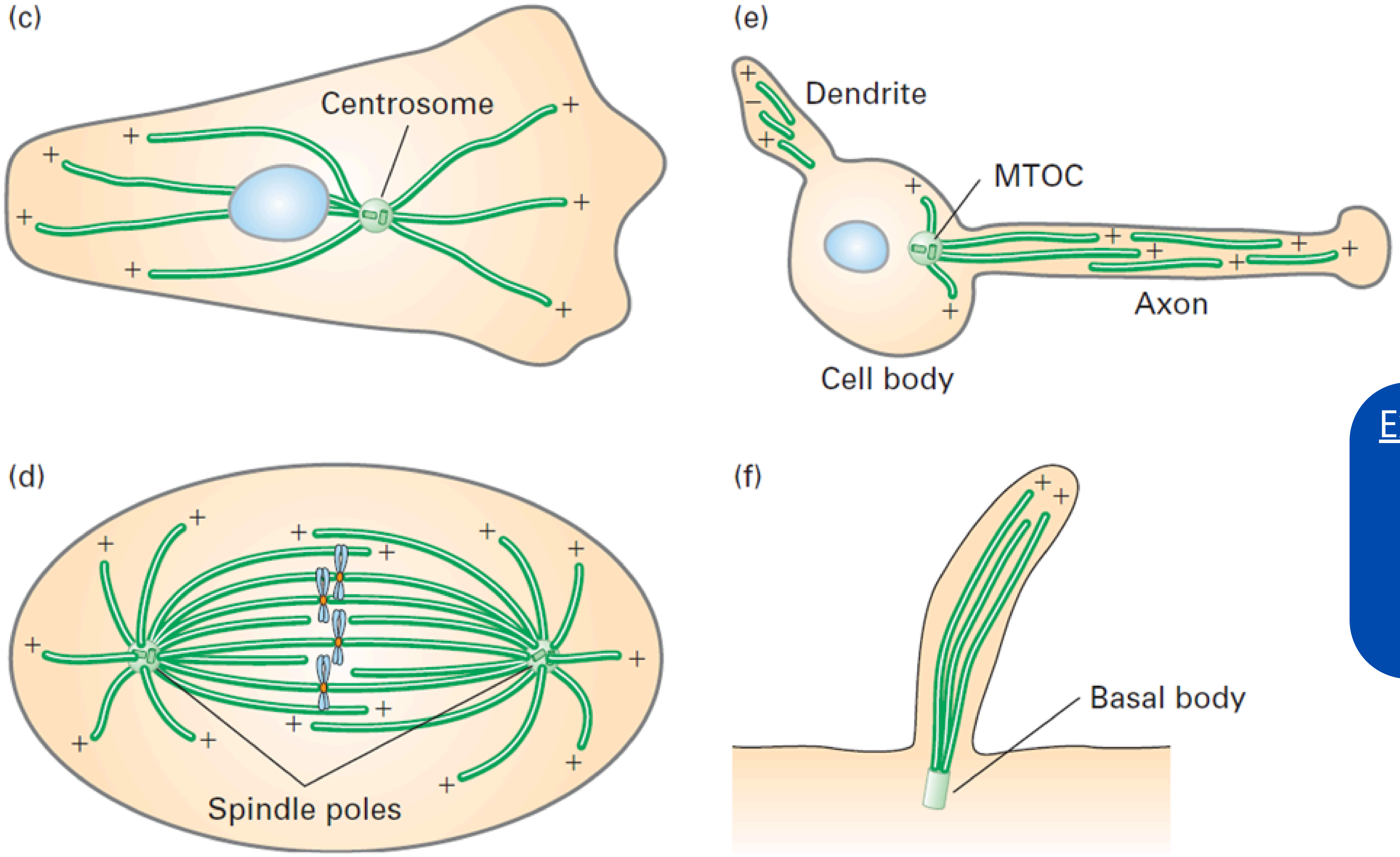
Microtubule instability is a core property of microtubules that describes their inherent ability to rapidly switch between polymerization (growth) and depolymerization (shrinkage) - allows them to reorganize quickly in response to cellular needs)



- Polymerization
  - Tubulin dimers with GTP bind to the growing plus end of a microtubule
- Catastrophe
  - If the GTP cap is lost (due to GTP hydrolysis to GDP) → the microtubule becomes unstable → rapid depolymerization
- Depolymerization
  - Tubulin subunits fall off rapidly from the plus end
- Rescue
  - a shrinking microtubule can start growing again if it regains a GTP cap

Let's see how it looks like in live cell! Click the link
https://www.youtube.com/watch?v=ZL3_BwrB6AM

Microtubules are generally nucleated from a specific intracellular location known as a microtubule-organizing center (MTOC) = structure inside the cell that starts and organizes the growth of microtubules



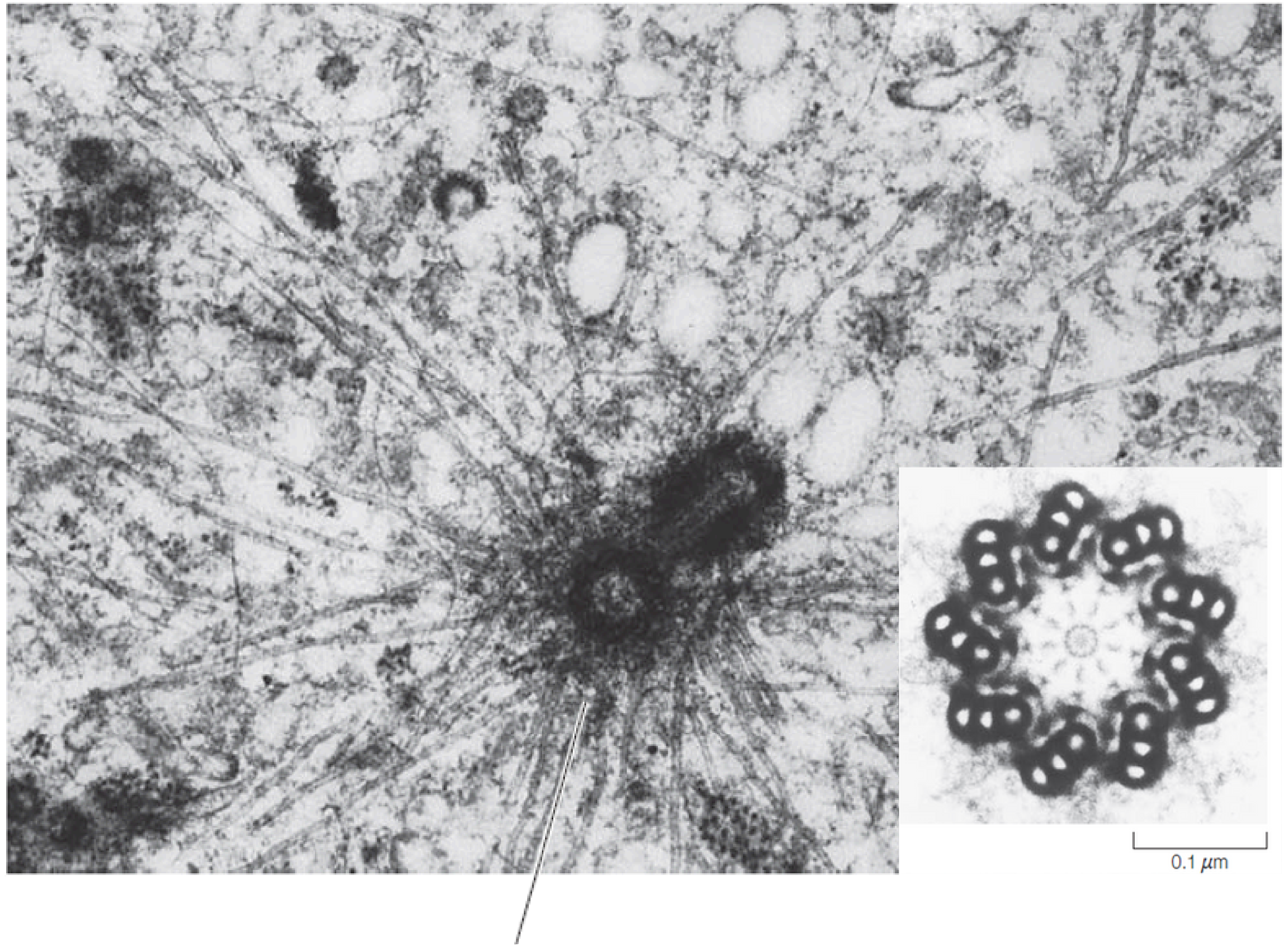
Example of MTOC

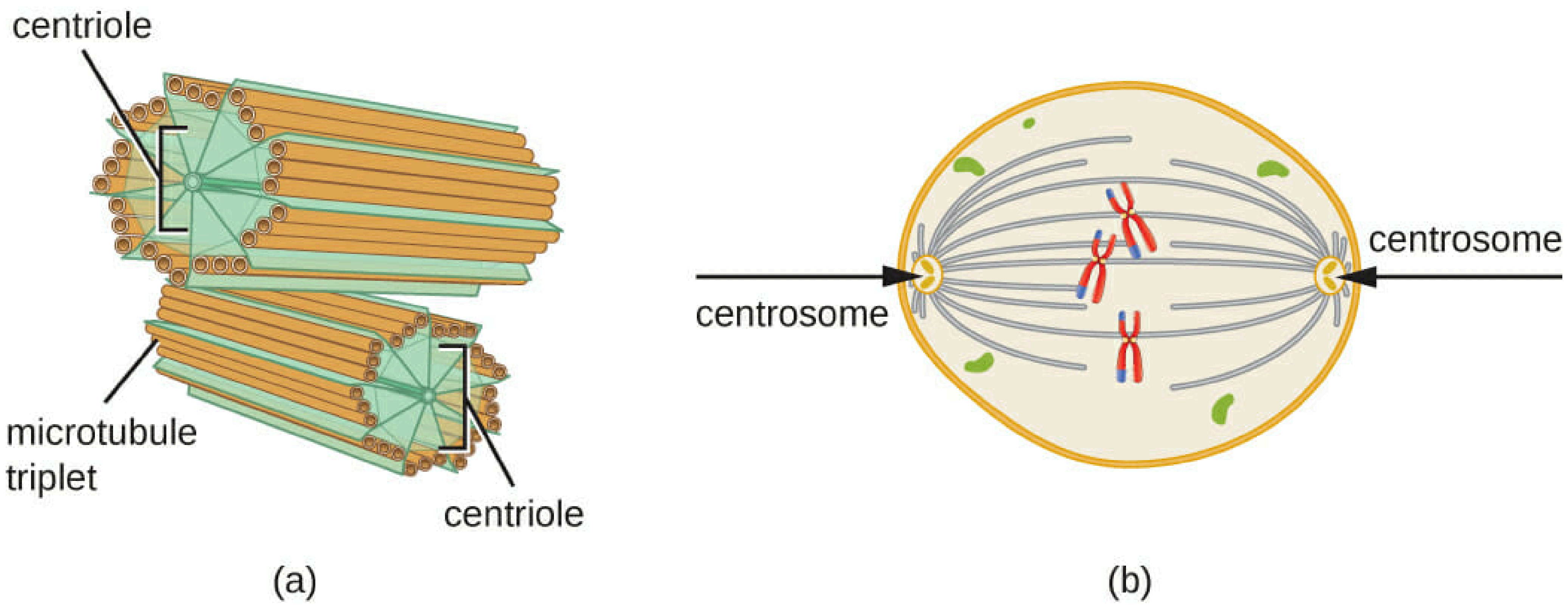
- Centrosome = the major MTOC in animal cells
- Basal body = act as MTOCs in cilia and flagella formation

CENTROSOME

Centrosome is located near the nucleus (animal cells have a single centrosome)

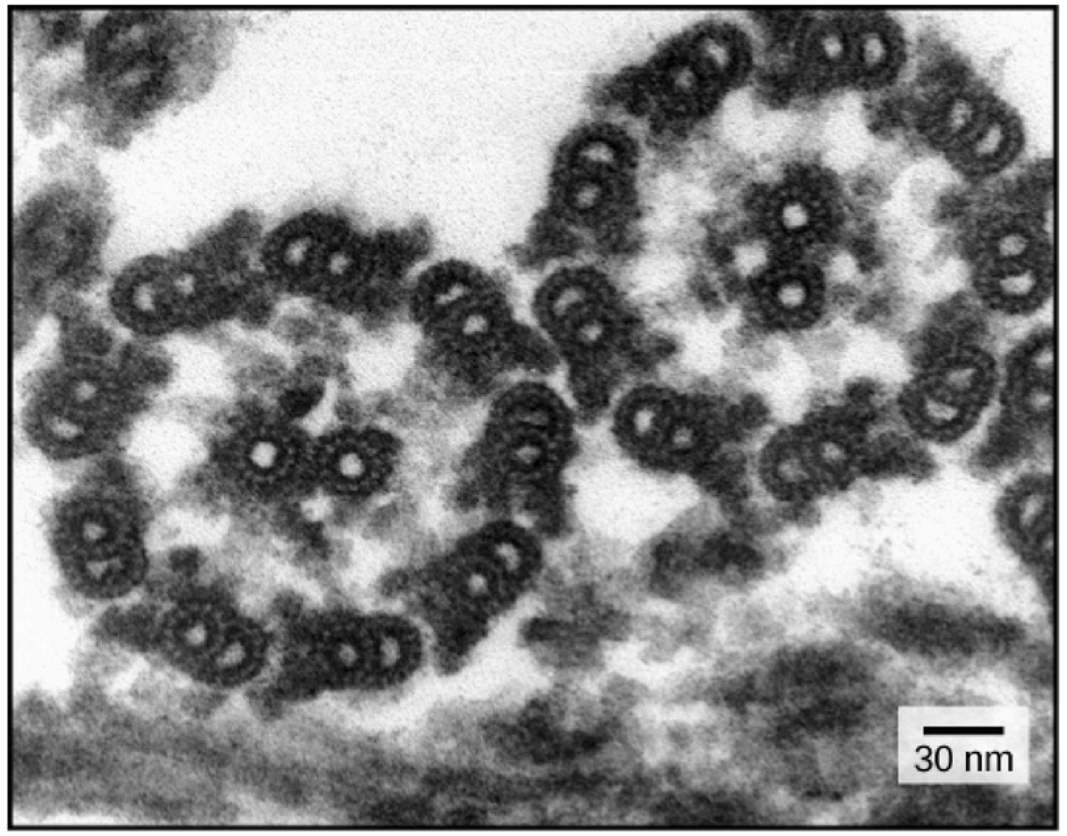
- It consists of two centrioles — oriented at right angles to each other
- pericentriolar material is the gel-like area that surrounds the centrioles in the centrosome



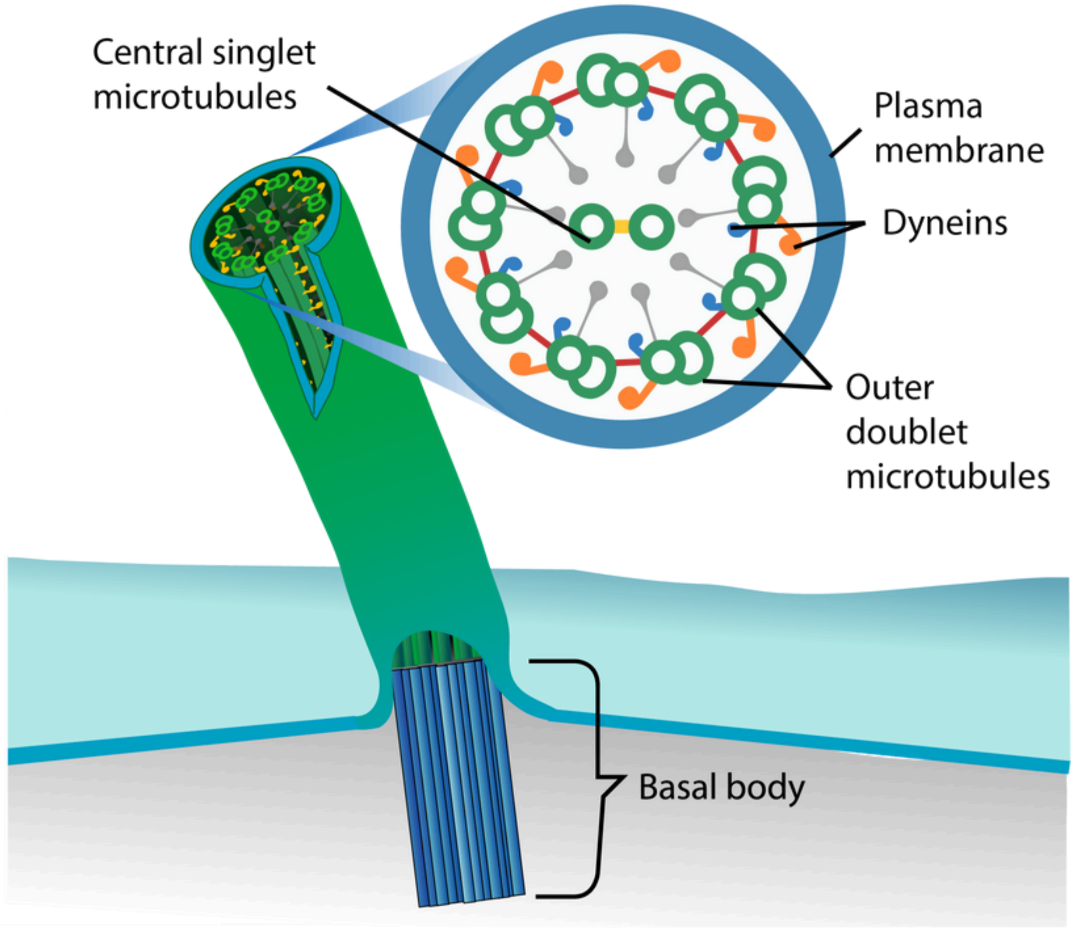


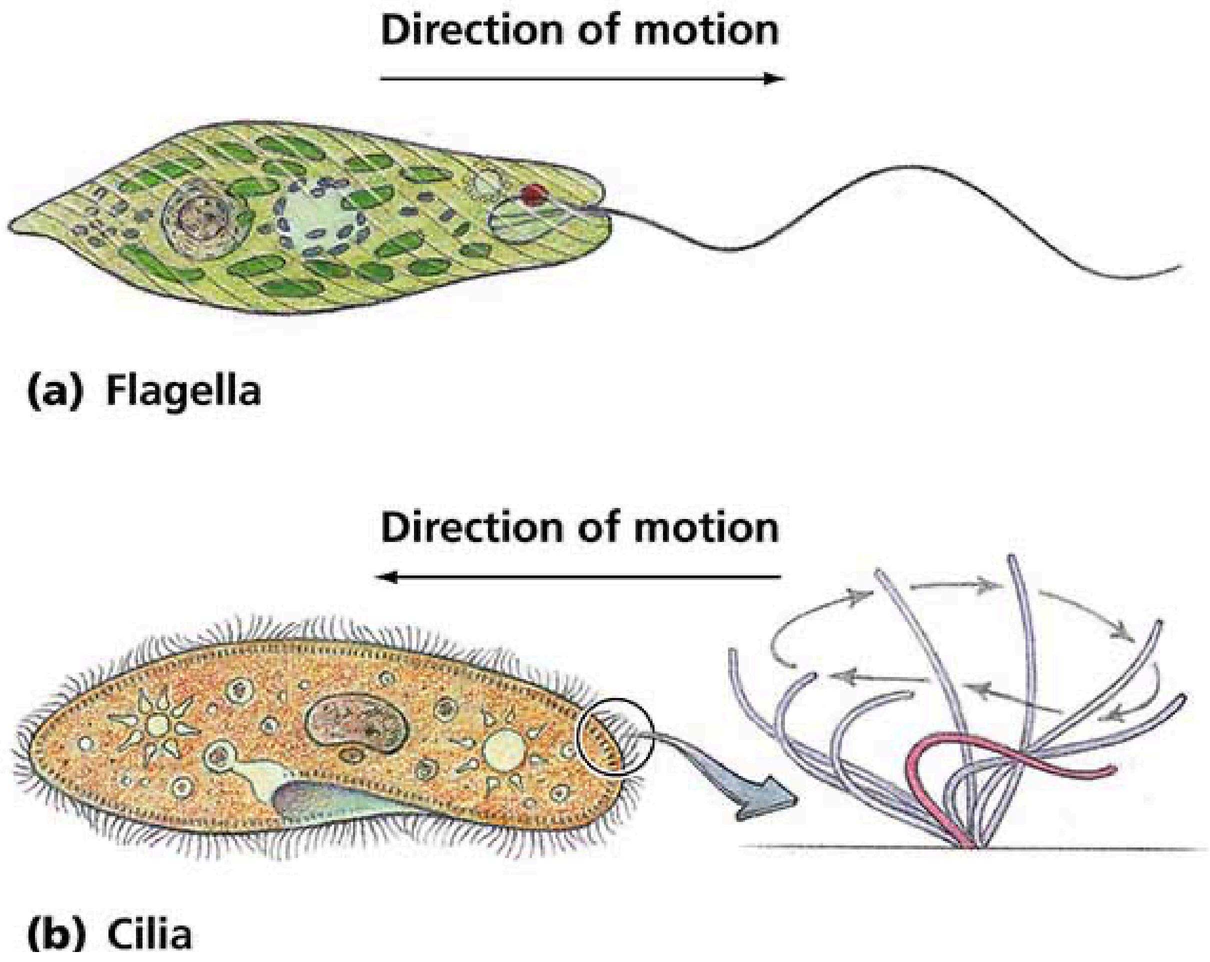
- pericentriolar material is rich in proteins that are essential for microtubule nucleation
- The centrosome nucleates and anchors microtubules
- During cell division, the centrosomes duplicate and move to opposite sides of the cell
- Centrioles align mitotic spindle during cell division

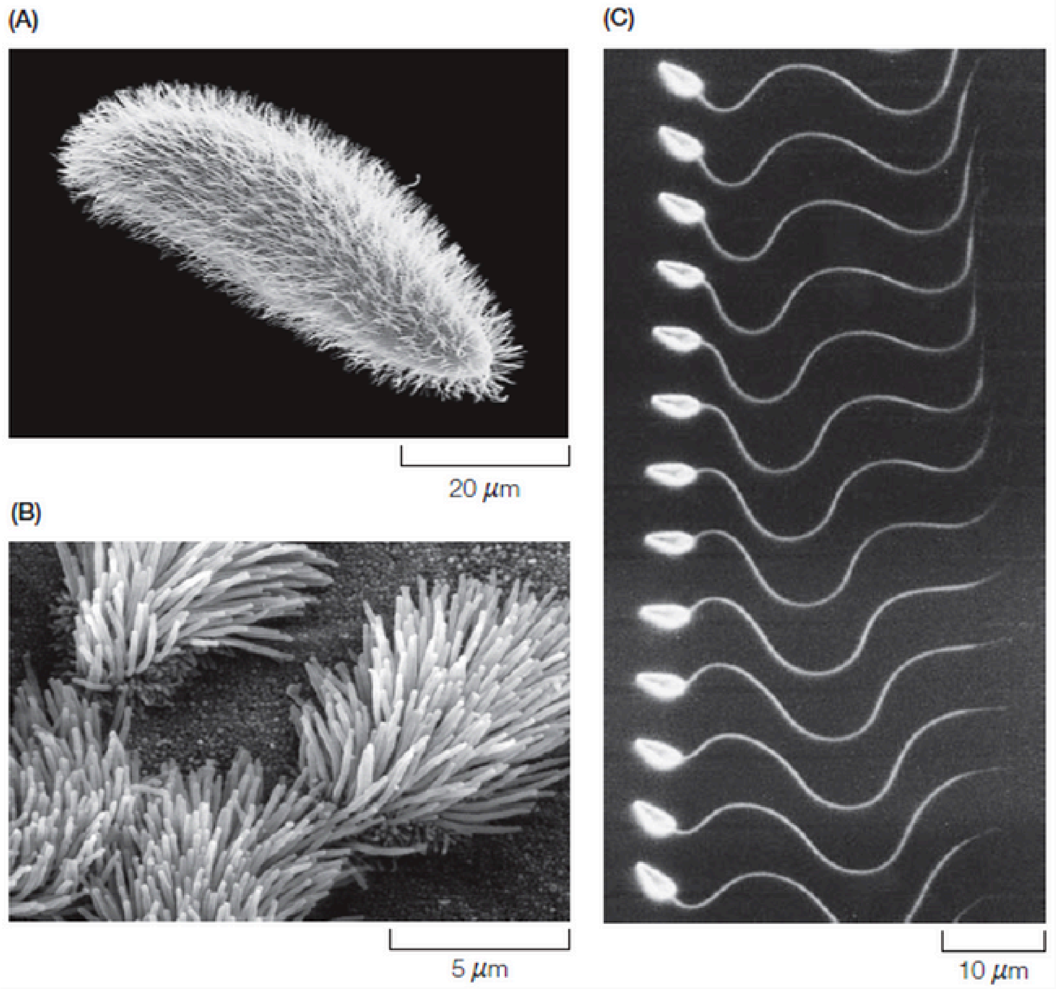
CILIA AND FLAGELLA



- Motile cilia & flagella are microtubule-based structures with a central pair of singlet microtubules and 9 sets of outer doublet microtubules
- All cilia & flagella grow from basal bodies, structures with 9 sets of outer triplet microtubules







Examples: (A) paramecium, (B) ciliated epithelial cells lining the surface of a trachea, (C) sea urchin sperm

- Cilia are short
- Flagella are long

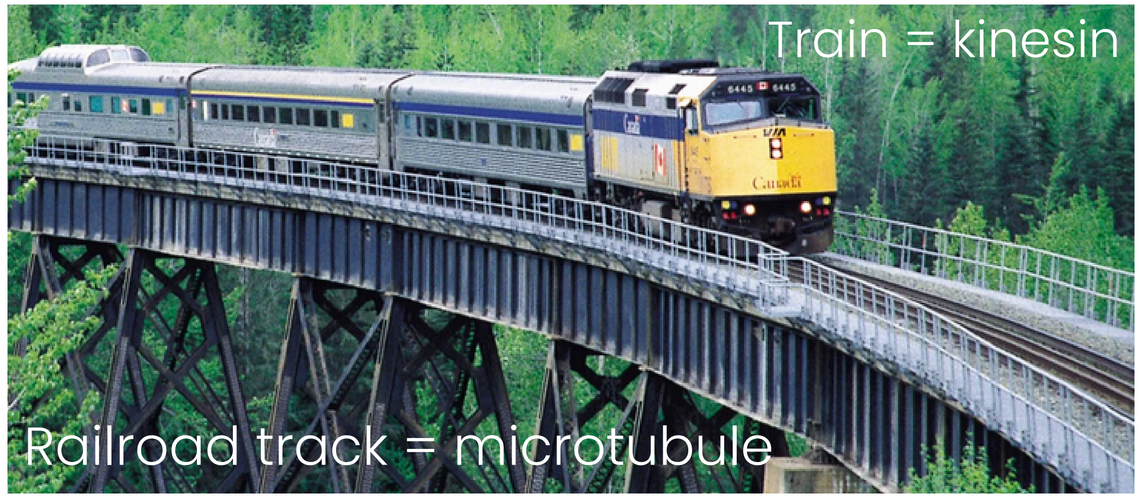
MOTOR PROTEINS

Microtubules also use motor proteins to transport cargo

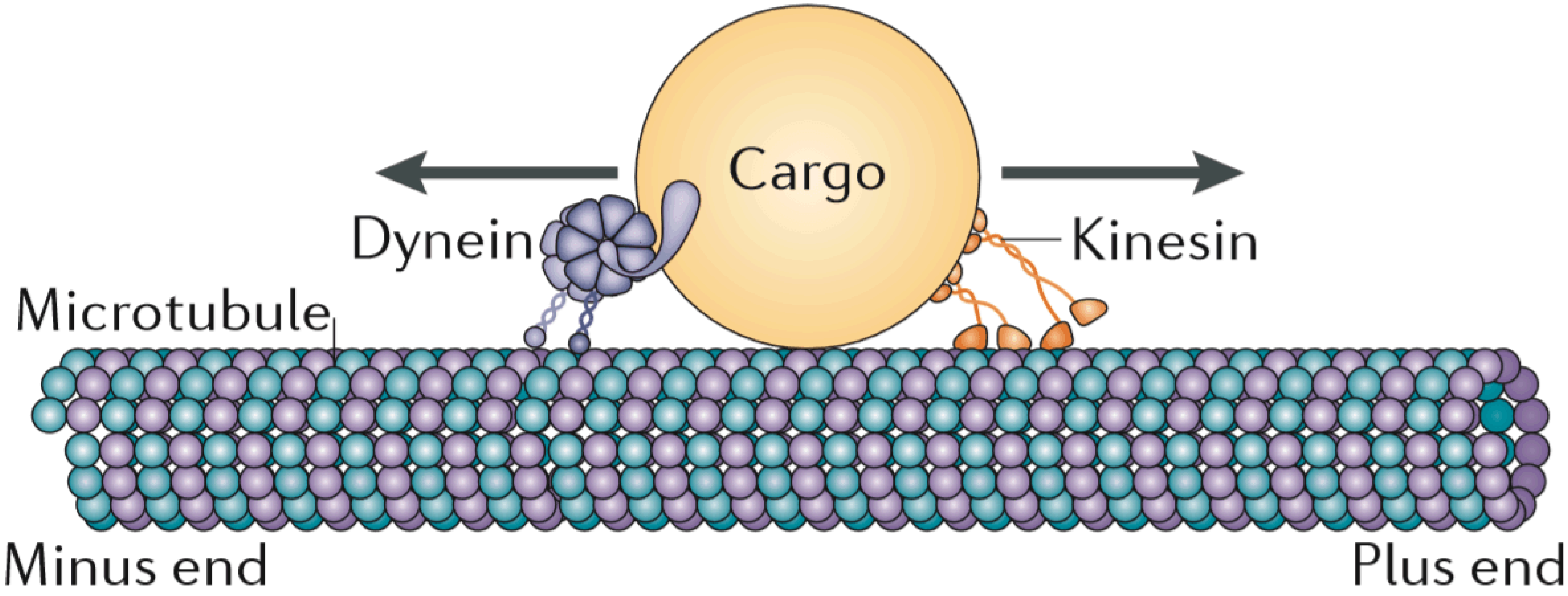
Two types of motor proteins are responsible for movement along microtubules

- **Kinesin**: move toward the plus (+) ends of microtubule
- **Dynein**: move toward the minus (-) end of microtubules

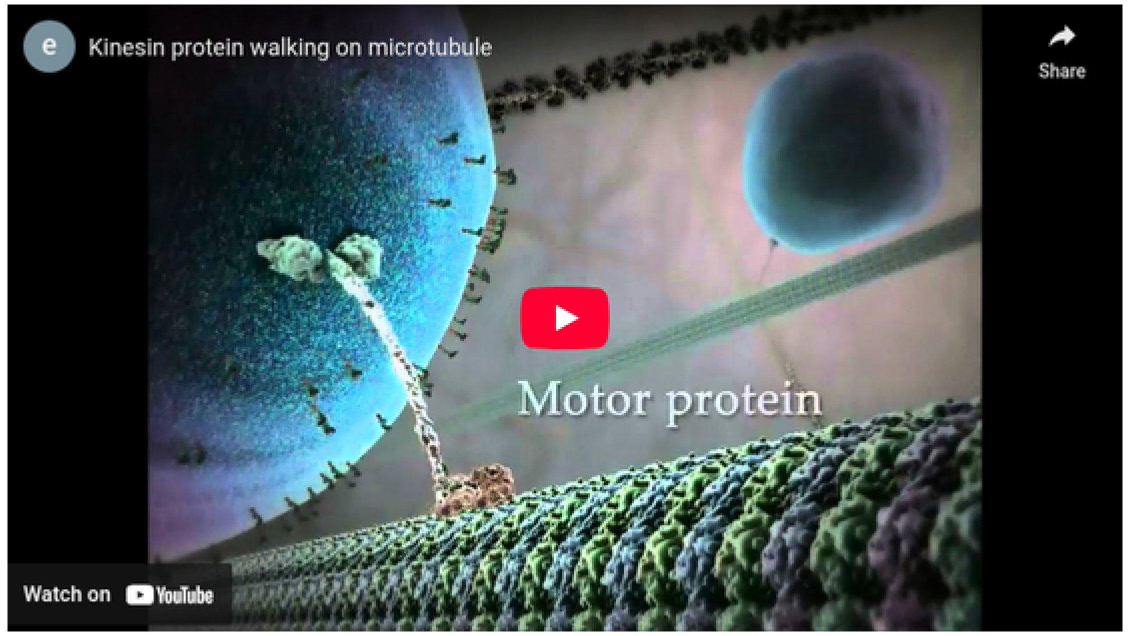
Kinesin and dynein use microtubules as tracks for the transport of vesicle and nonvesicle cargos to their destinations



Simple concept



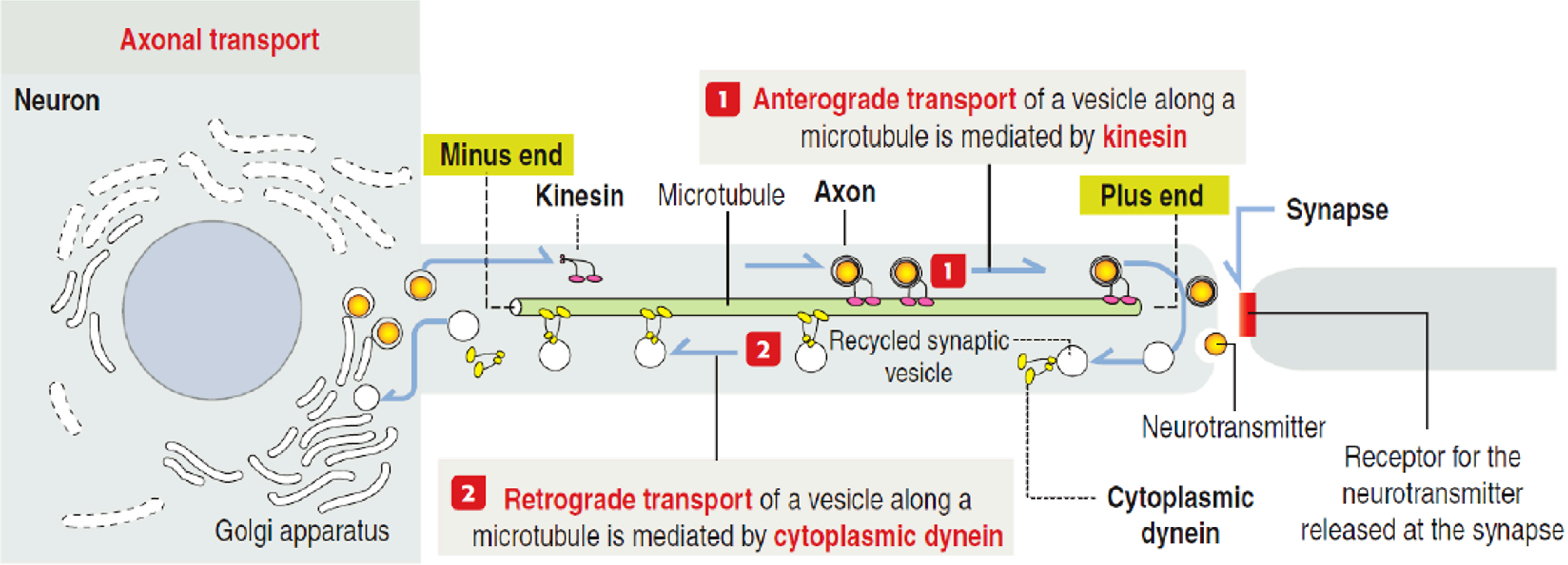
Let's see how it works! Click the link
https://www.youtube.com/watch?v=y-uuk4Pr2i8

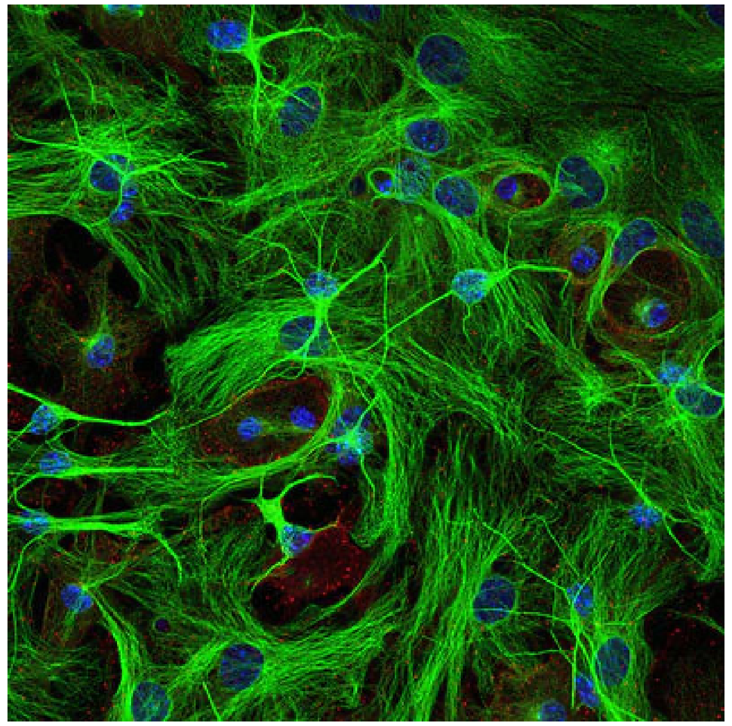


Axonal transport

Neurons also contain complex cytoskeletal structures

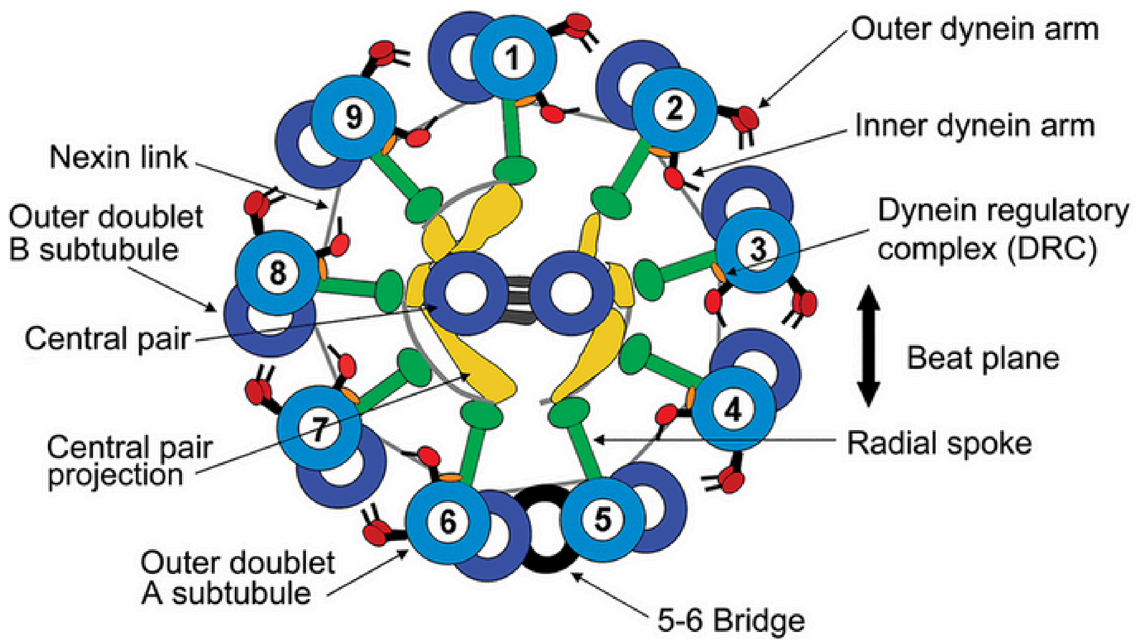
- Both axons and dendrites are filled with bundles of microtubules
- In axons, all the microtubules are oriented in the same direction
  - toward cell body = minus end, toward axon terminal = plus end
- crucial for the traffic of neurotransmitter-containing vesicles to neuronal synapses



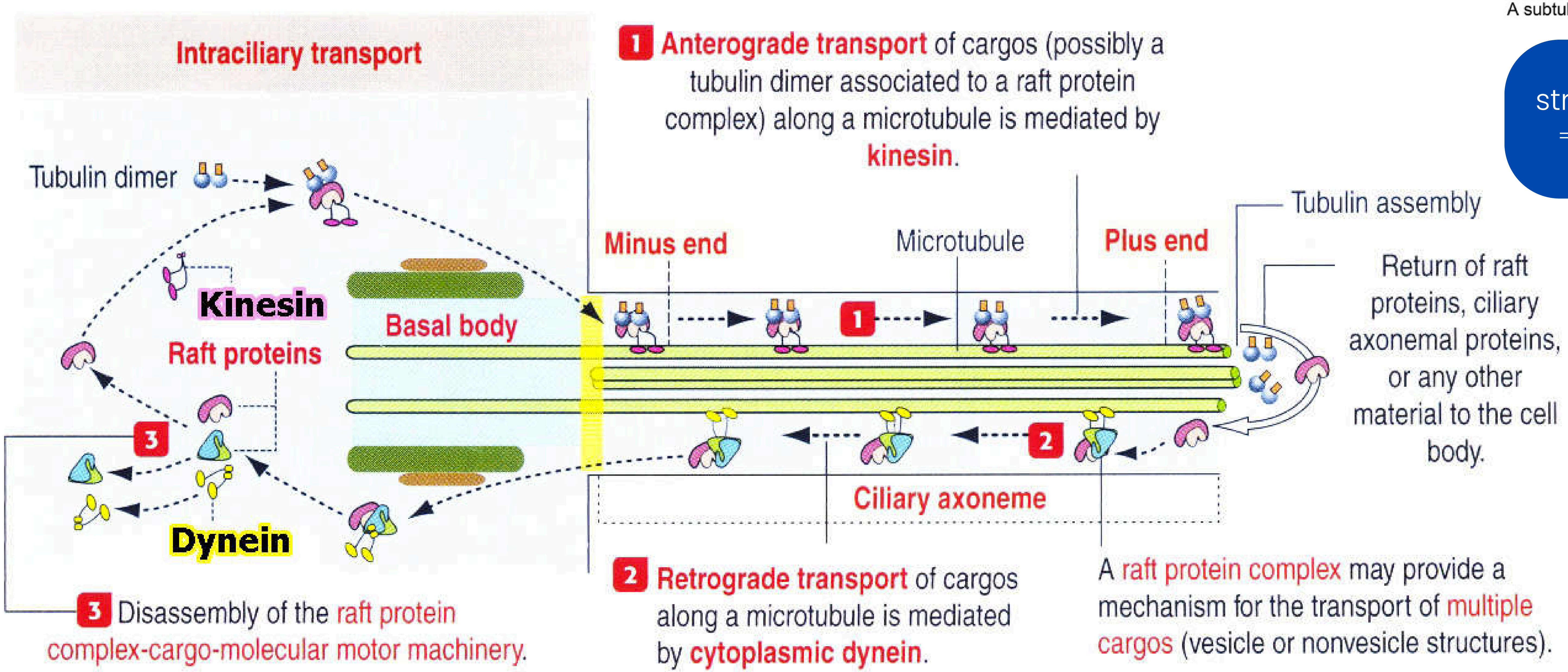


Axonemal transport (intracillary and intraflagellar transport)

- Essential for delivery of tubulin dimers to the distal end of microtubules of cilia & flagella
- Axonemes originate from basal bodies, centriole-derived, microtubule containing structures

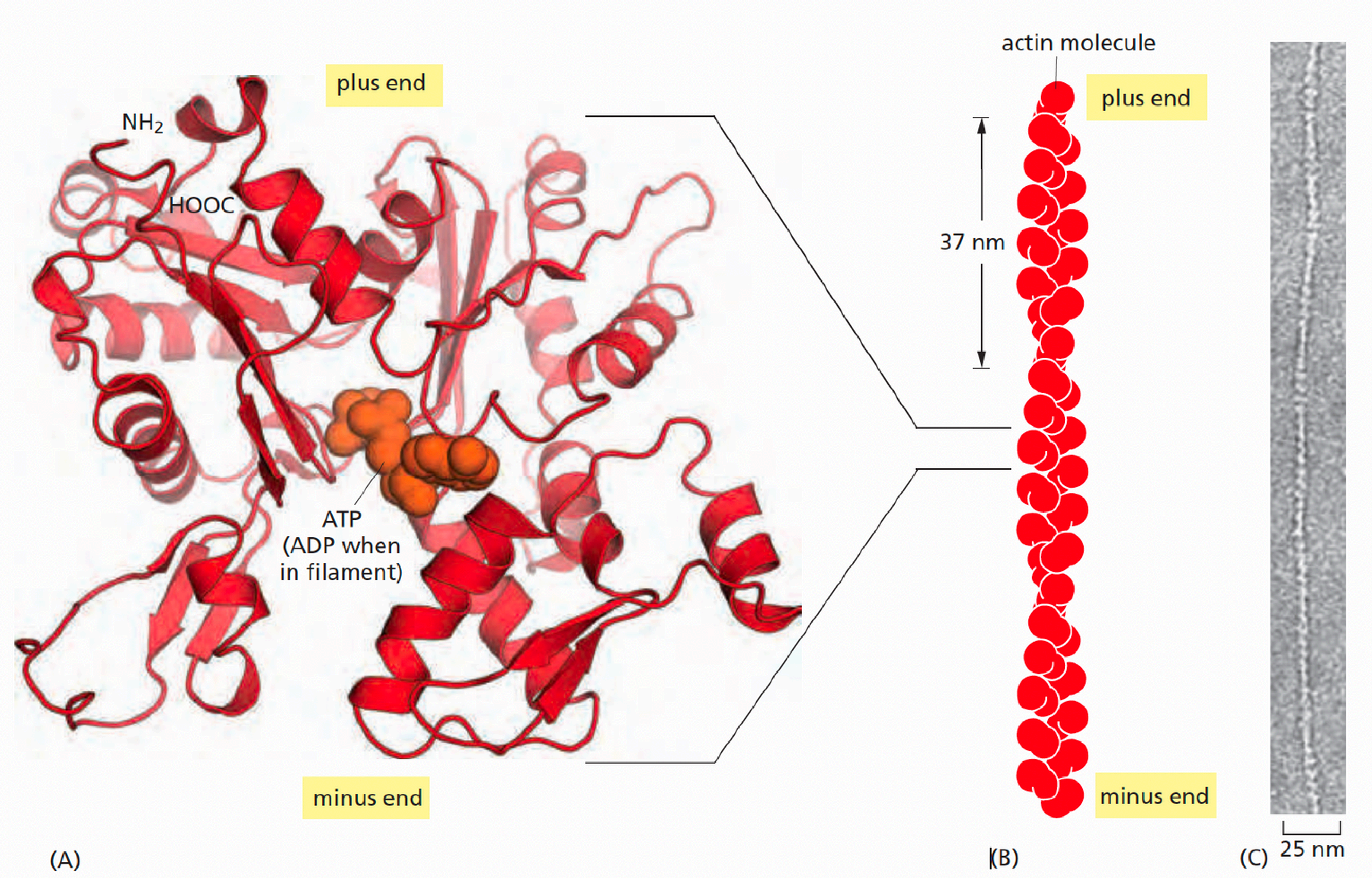


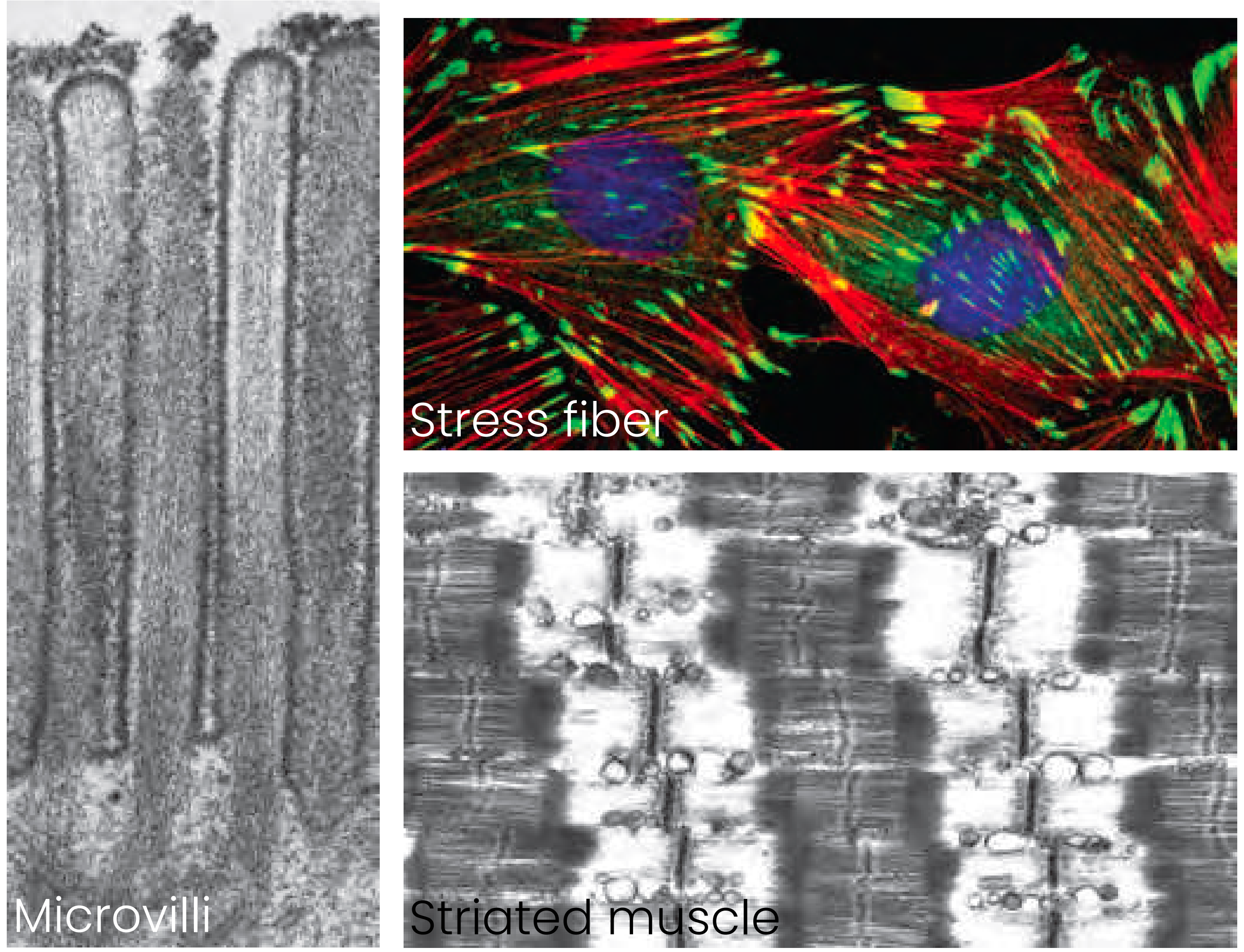
The axoneme, the core structure of cilia and flagella
= microtubules + dynein motors + regulatory complexes



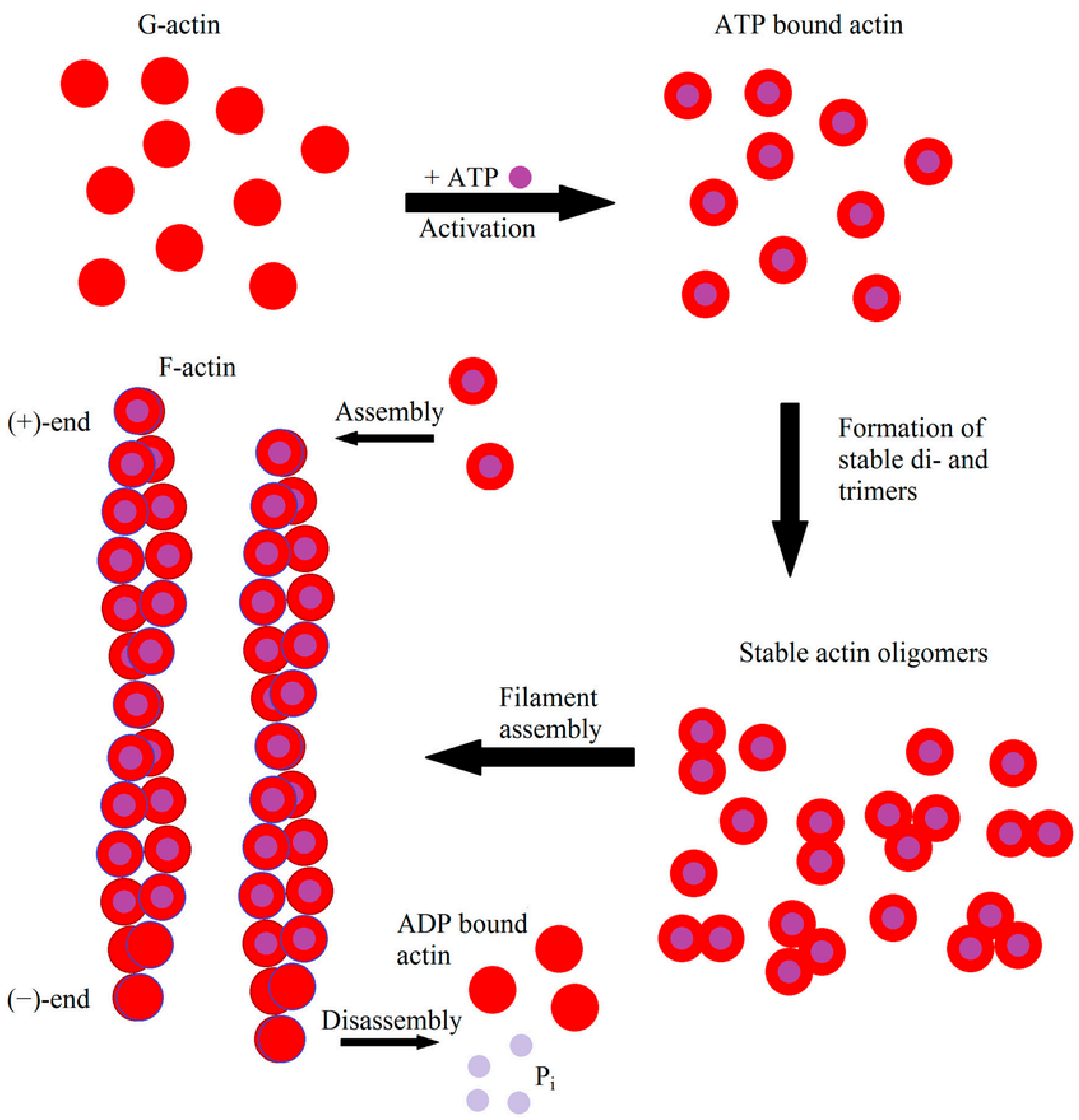
Actin filaments are polar structures composed of globular molecules of actin arranged as a helix

- composed of globular monomers (G-actin), which polymerize to form helical and asymmetrical filaments (F-actin)





ACTIN POLYMERIZATION



Steps of actin polymerization

G-actin + ATP
↓
Actin oligomers (di- and trimers)
↓ Filament assembly
F-actin
↓ Filament disassembly
ADP bound actin

- Plus end → add new monomers
- Minus end → loss monomers

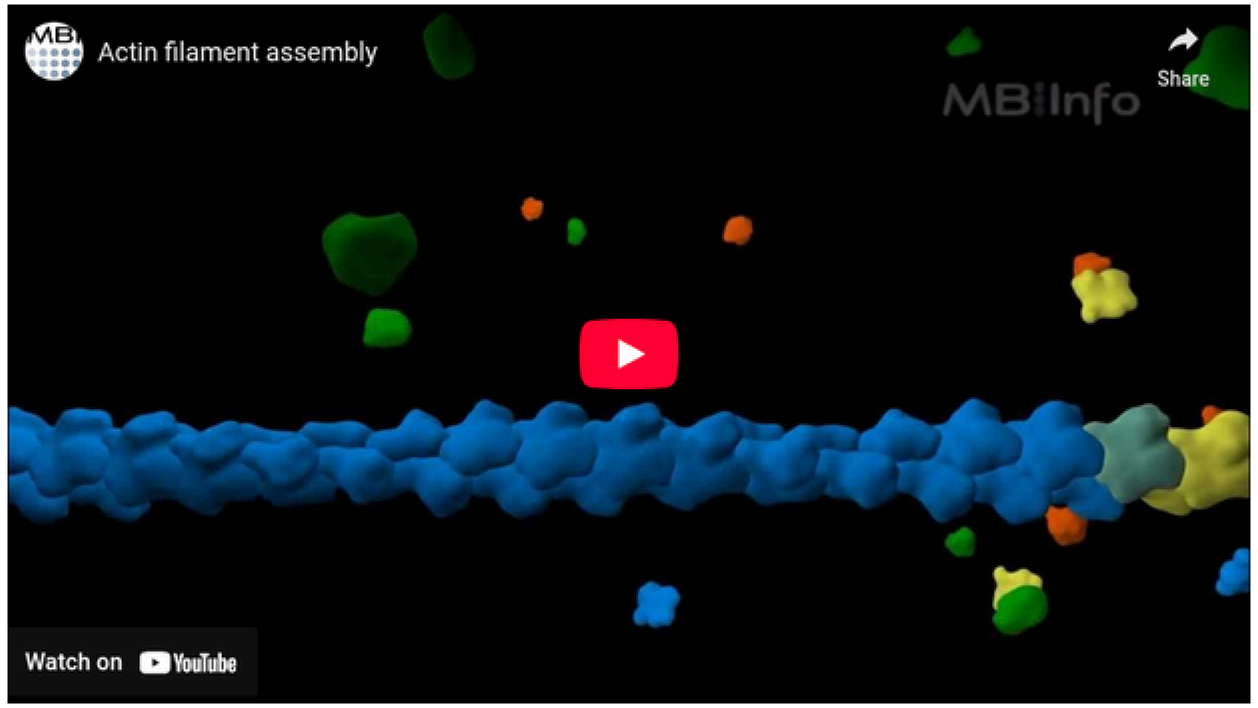
Actin polymerization requires ATP, which is hydrolyzed to ADP after each G-actin molecule is incorporated into the filament

THREADMILLING PHENOMENON

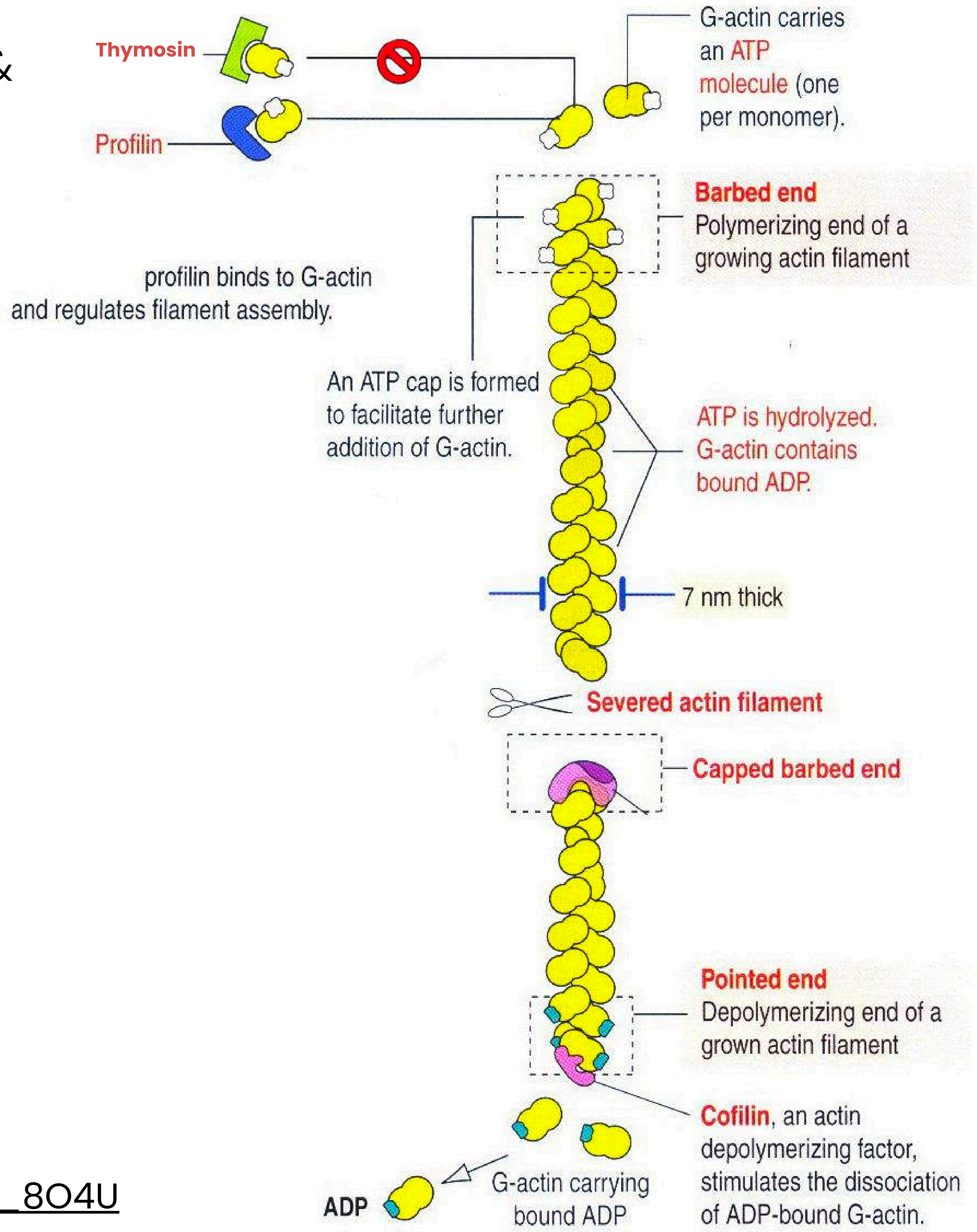
Treadmilling is the dynamic balance between the polymerizing & depolymerizing ends to maintain the length of actin filament

Proteins control thread milling:

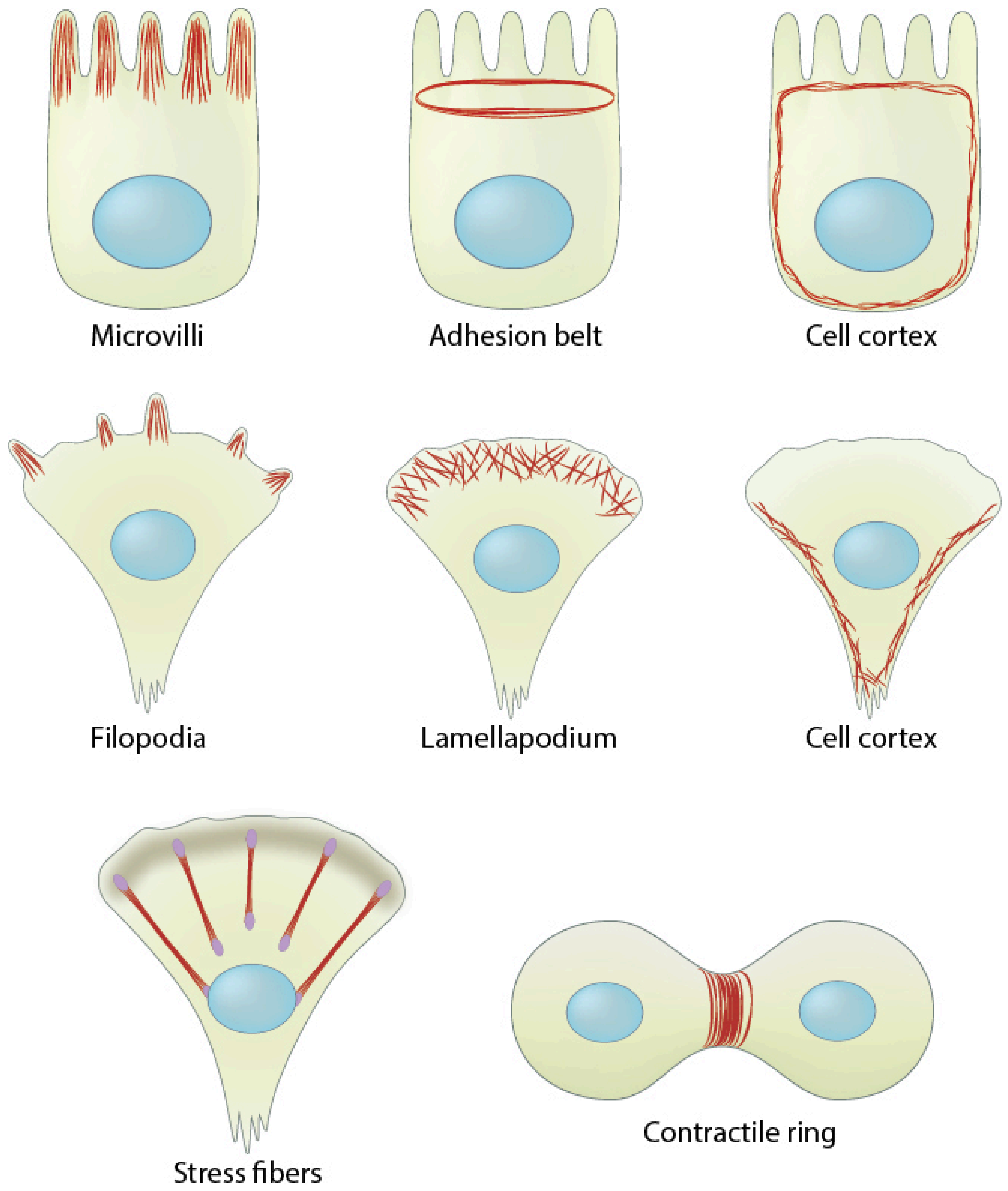
- Thymosin: sequesters G-actin from polymerization
- Profilin: enhances polymerization of ATP-bound actin to (+) end
- Cofilin: removes ADP-bound actins from minus end
- Gelsolin: has a dual role: a severing and capping protein



Let's see how it works! Click the link https://www.youtube.com/watch?v=VVgXDW_8O4U

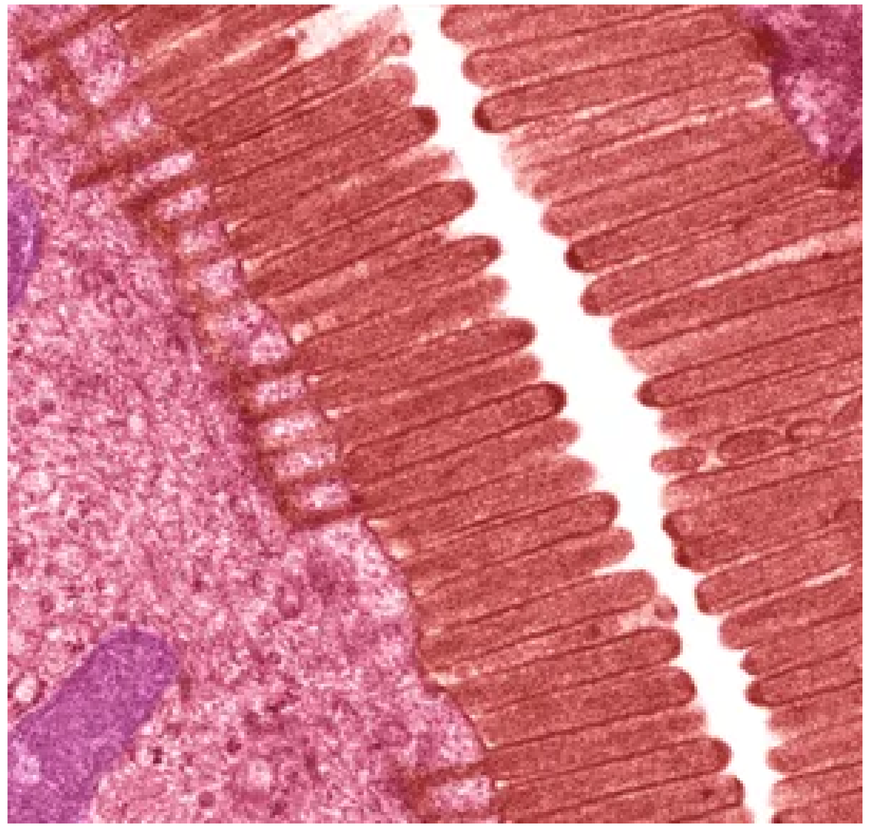


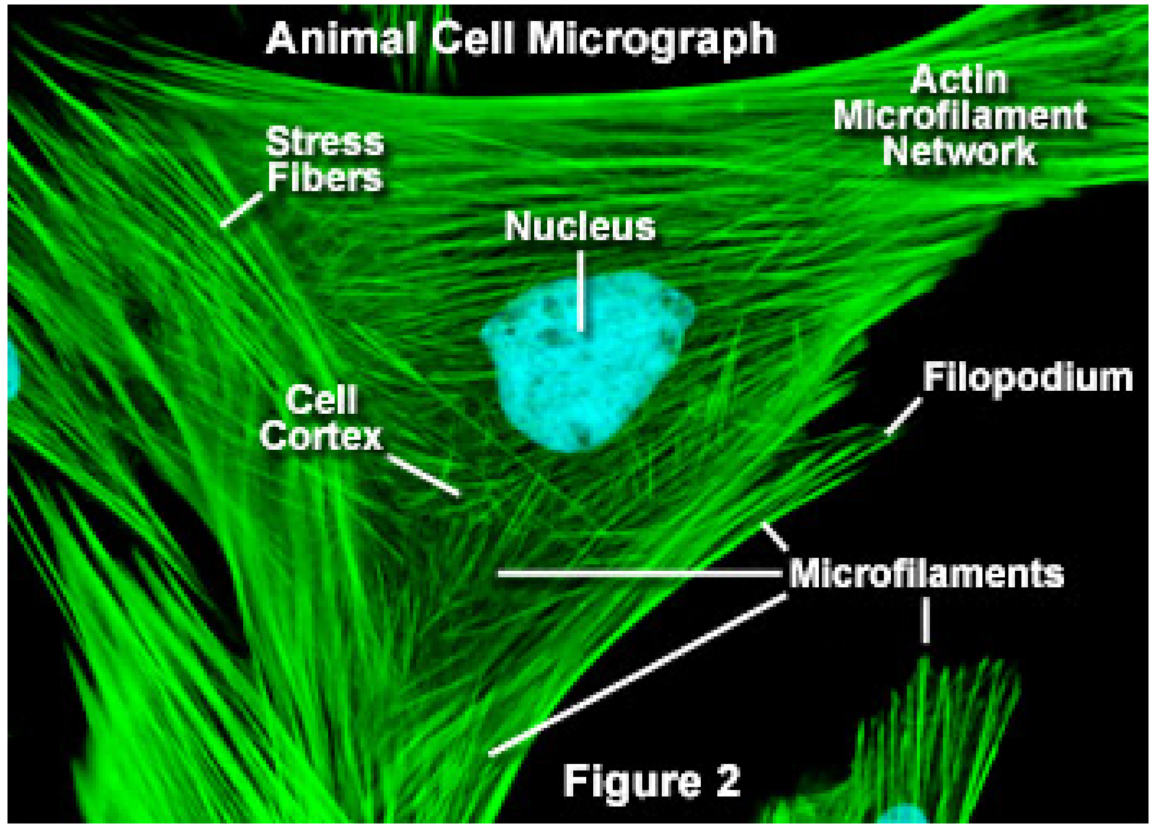
ACTIN FILAMENT DISTRIBUTION



Example of microfilament-based structures

- Actin bundle in microvilli of the intestinal epithelium
- Filopodia (pointed protrusions),
- lamellipodia (flatted protrusions),
- ameboid movement
- Actin stress fibers
- Actin contractile ring in cytokinesis of animal and fungal cells

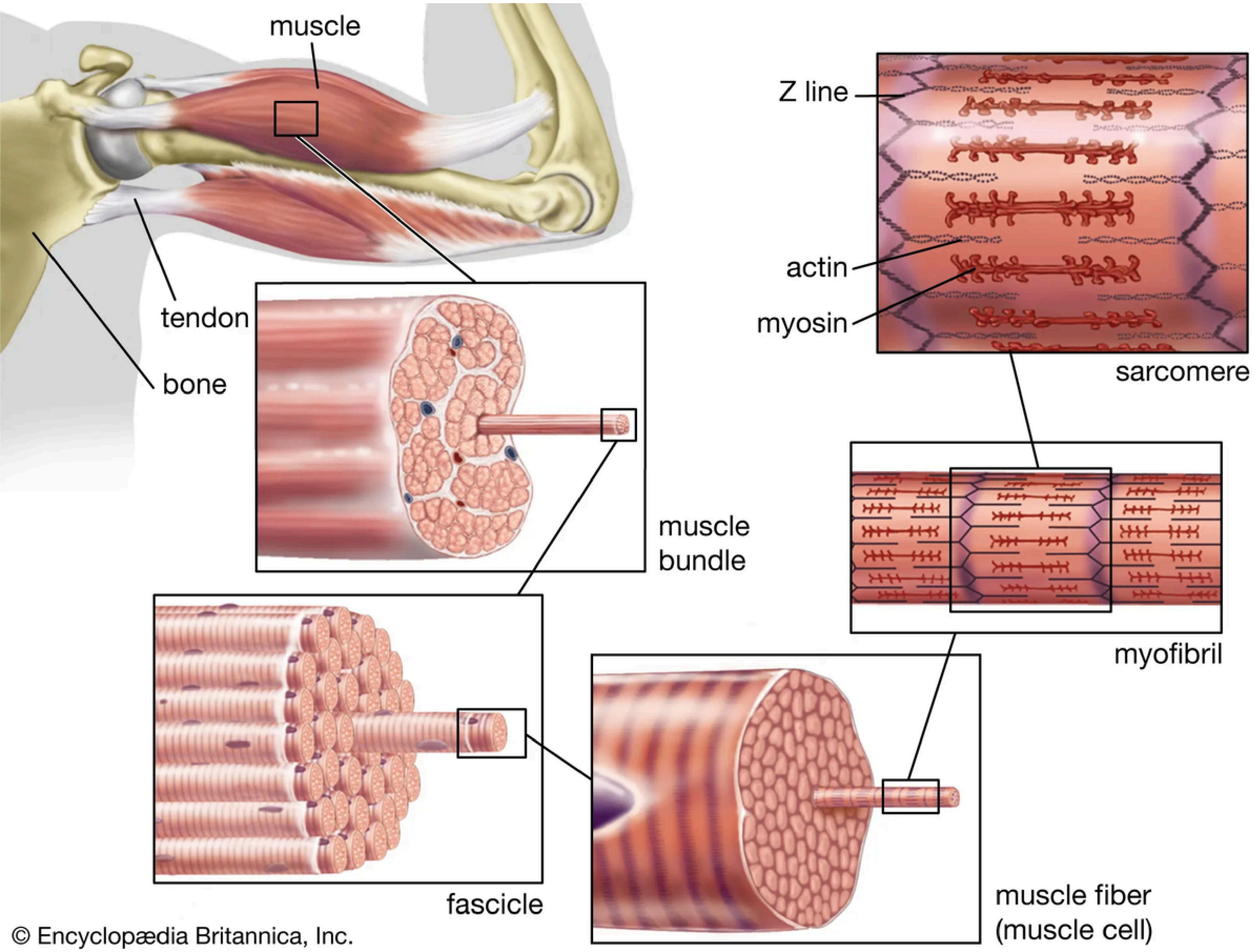


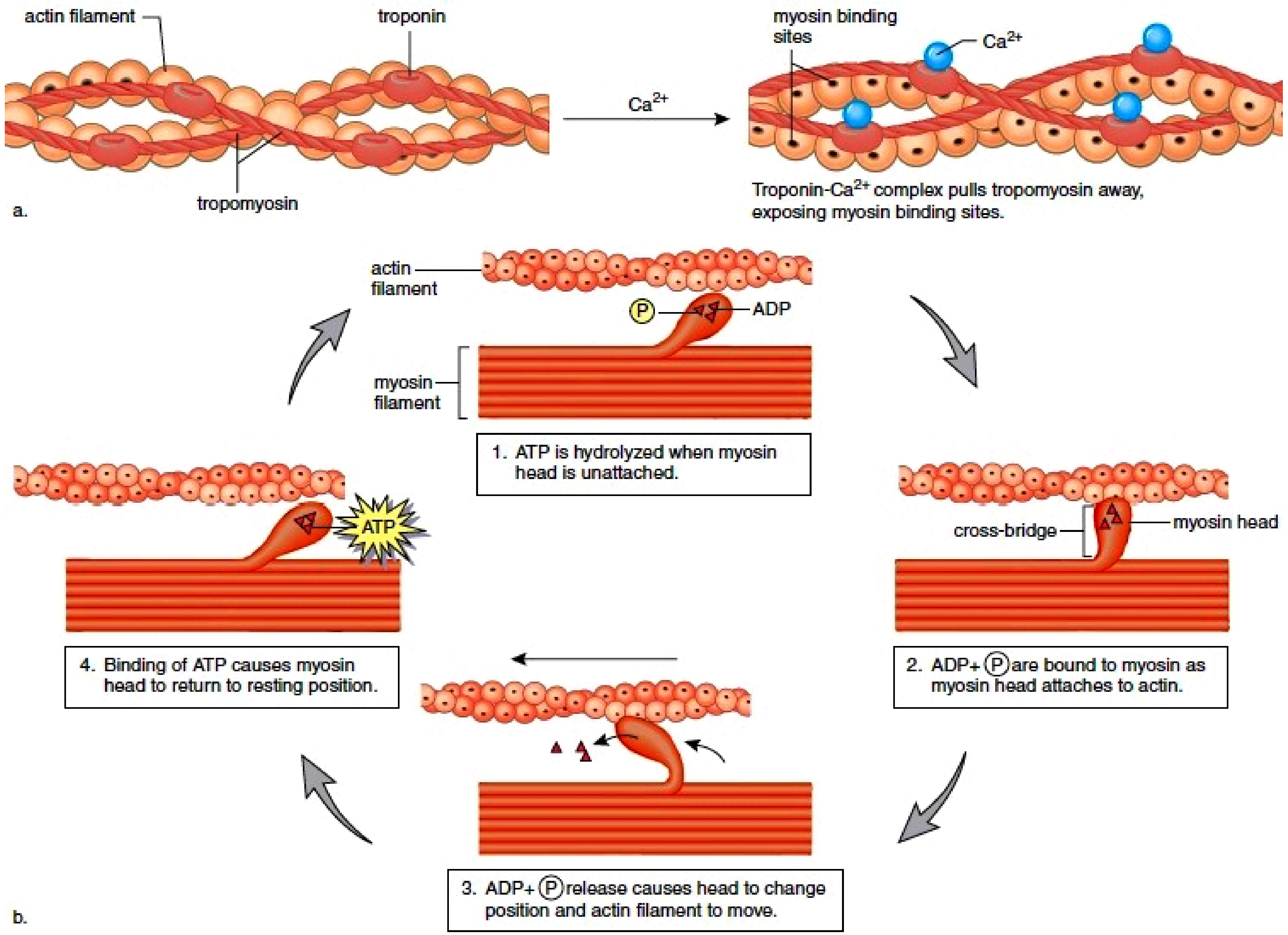


ACTIN-ASSOCIATED MOTOR SYSTEM

Actin filaments, often in association with myosin, are responsible for many types of cell movements.

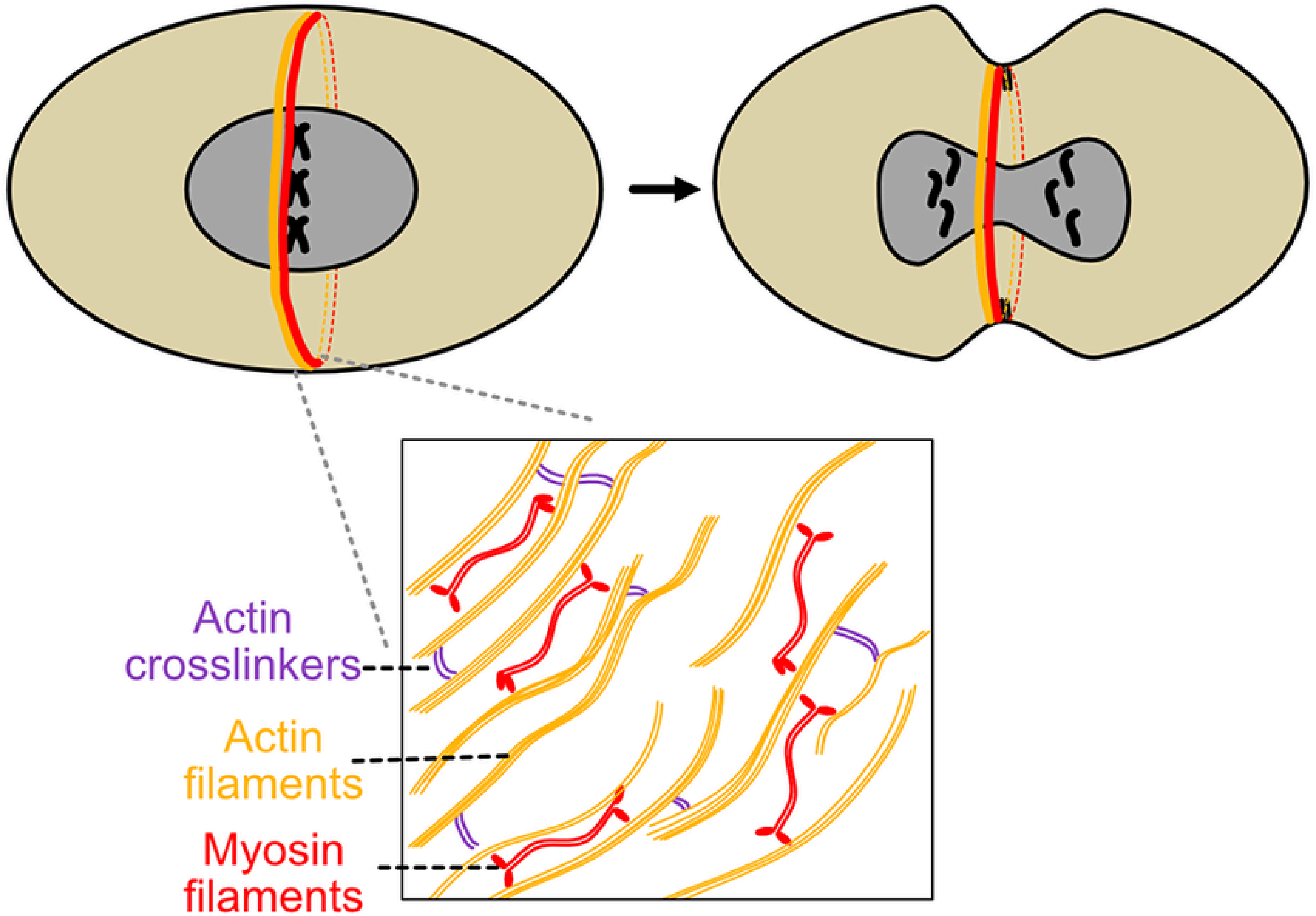
Muscle contraction involves the relative movements of actin-myosin, which bring the Z lines closer together

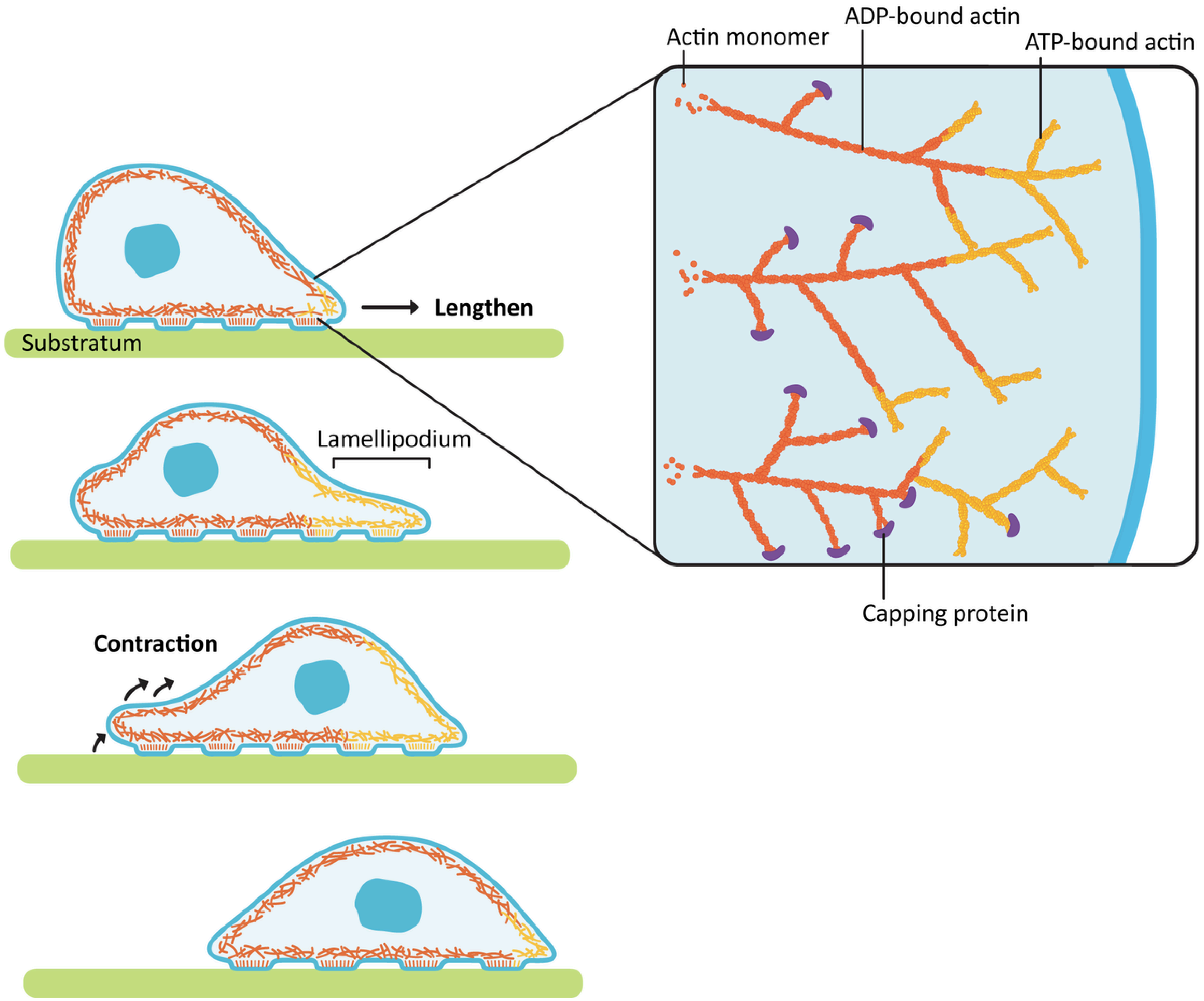




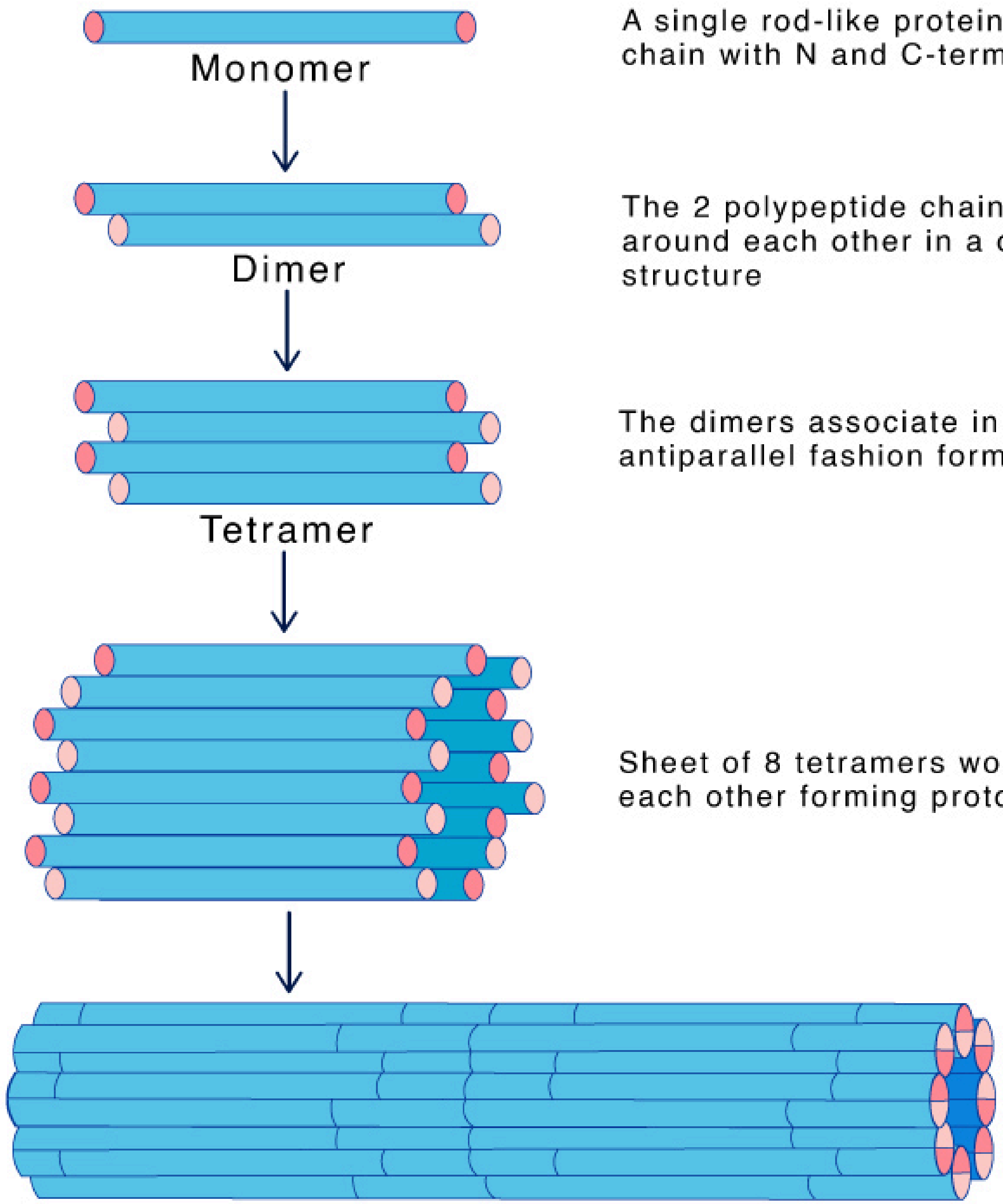
ACTIN-ASSOCIATED MOTOR SYSTEM

- Cytokinesis is the contraction of a ring of actin/myosin resulting in formation of two daughter cells
- Locomotion (cell migration) is achieved by the force exerted by actin filaments by polymerization at their growing ends





INTERMEDIATE FILAMENT



A single rod-like protein polypeptide chain with N and C-terminal domains

The 2 polypeptide chains wound around each other in a coiled-coil structure

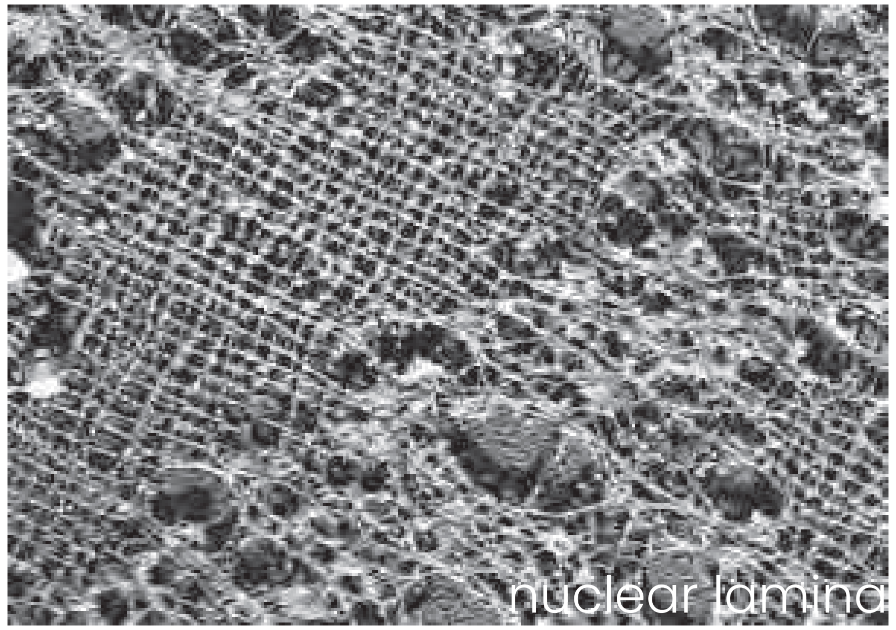
The dimers associate in a staggered antiparallel fashion forming tetramers

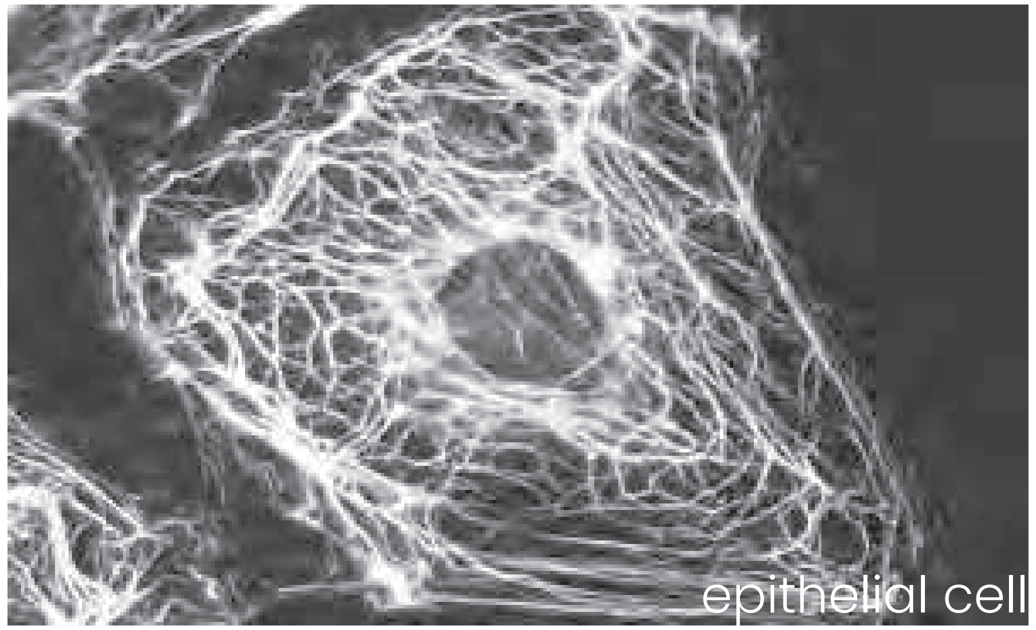
Sheet of 8 tetramers would around each other forming protofilaments

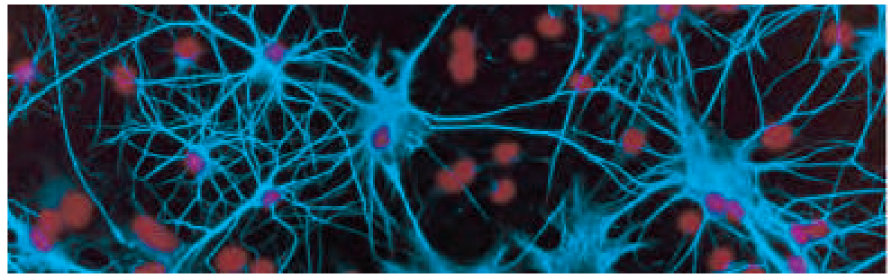
A rope-like **intermediate filament** bundle (~10 nm)

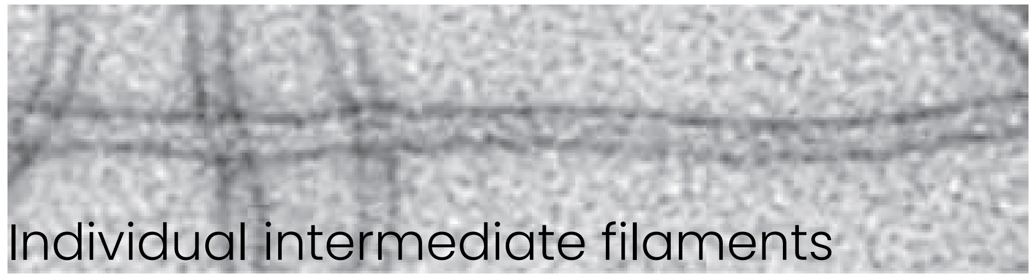
Intermediate filaments provide mechanical support to cells and help maintain their shape and structural integrity

- specialized for bearing tension
- a rope-like structure
- stable structures in the cell and provides mechanical strength to animal cells
- reinforce cell shape and fix organelle location
- typically 10 nm in diameter

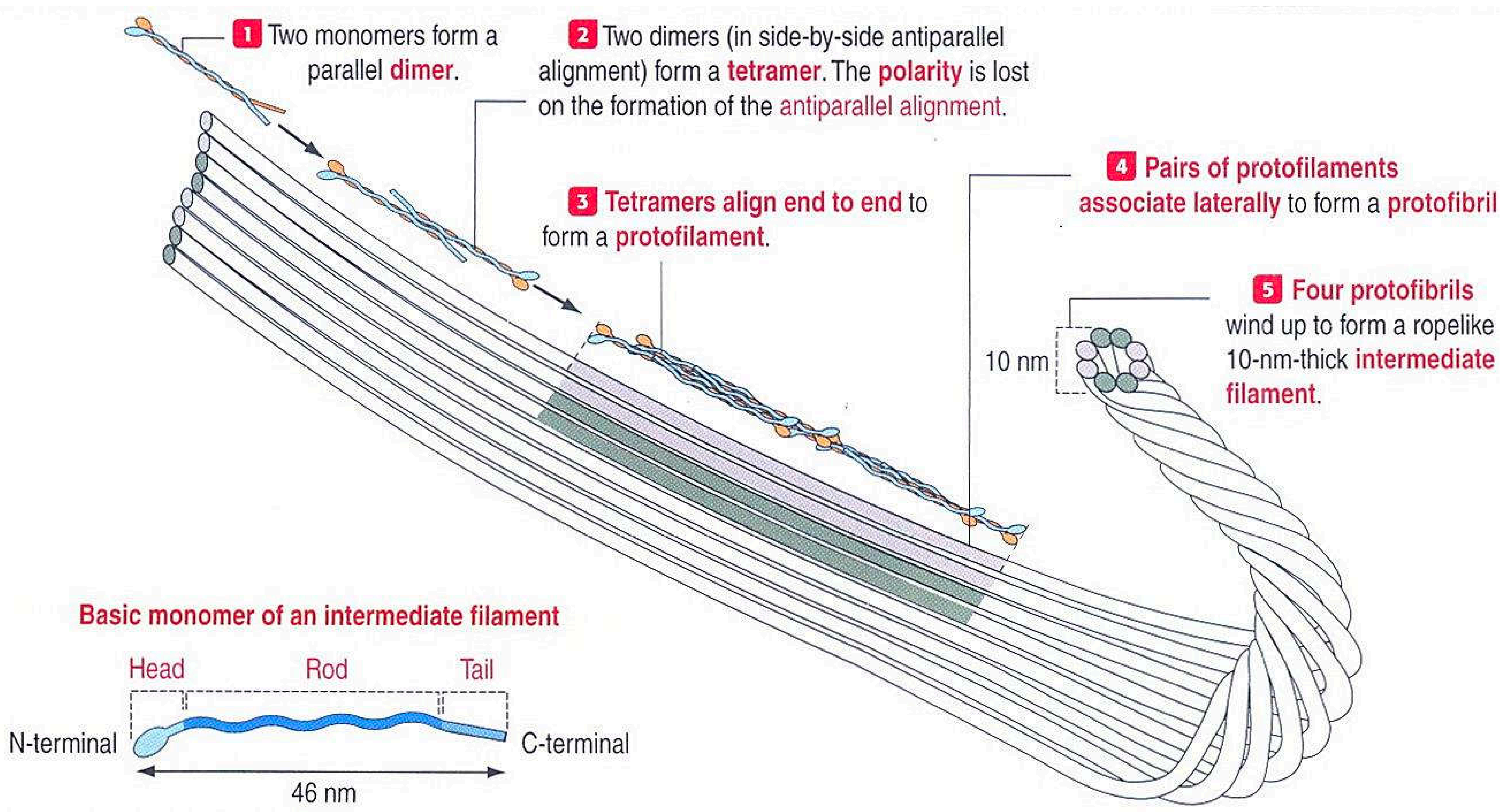




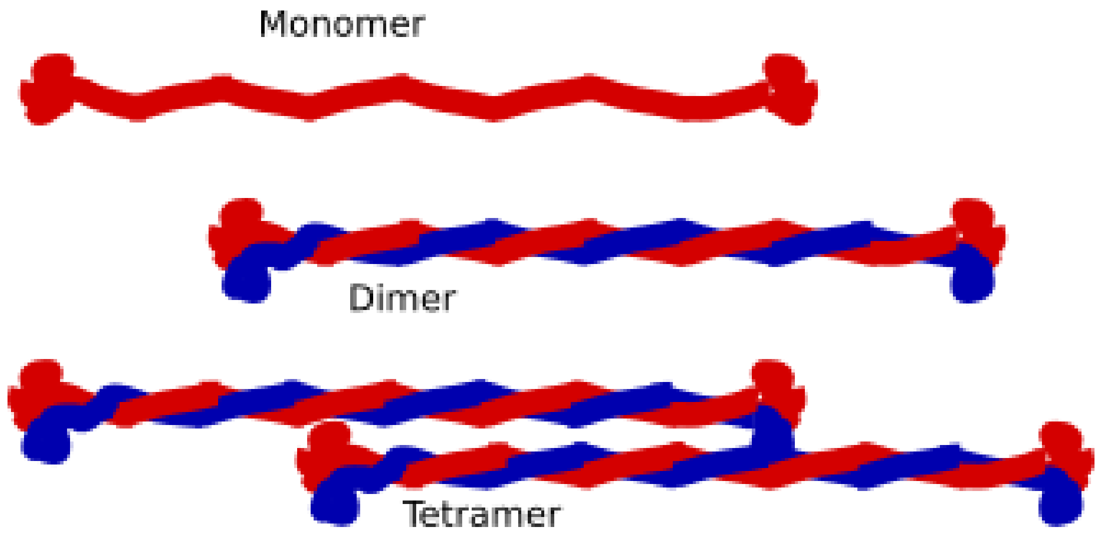




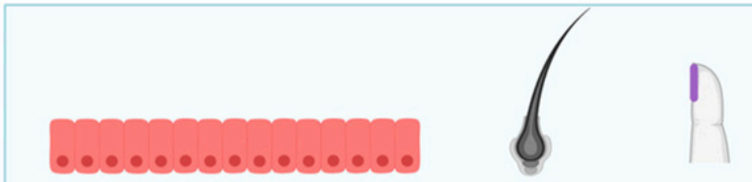
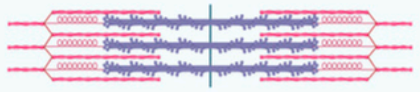
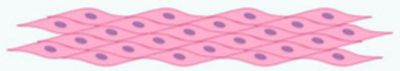
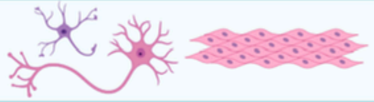
Steps of intermediate filament polymerization



Monomer
↓
Dimer
↓
Tetramer
↓
Protofilament
↓
Protofibril
↓
Rope-like intermediate filament



TYPES OF INTERMEDIATE FILAMENT

IF CLASS	IF TYPE	IF CATEGORY	IF PROTEINS	IF DISTRIBUTION
CYTOSOLIC	TYPE I	IF heterodimers	Acidic keratins	 Epithelium, Hair, Nail
	TYPE II		Basic keratins	
	TYPE III	IF homo- and heteropolymers	Vimentin	 Sarcomere
			Desmin	
			Glial fibrillary acidic protein	 Glial cells
			Peripherin	 Neurons of the peripheral nervous system
			Syncoilin	 Muscle cells
	TYPE IV	IF heteropolymers	Neurofilaments (NF-H, NF-M, NF-L)	 Neuronal cells
			α-internexin	
			Synemin-α and synemin-β	 Astrocytes, neurons, and muscle cells
			Nestin	 Stem cells and endothelial cells
NUCLEAR	TYPE V	Lamin-forming IF	Lamin A, lamins B, and lamins C	 Nuclear lamina
LENS	TYPE VI	Lens-specific IF	Phakinin and filensin	 Eye lens

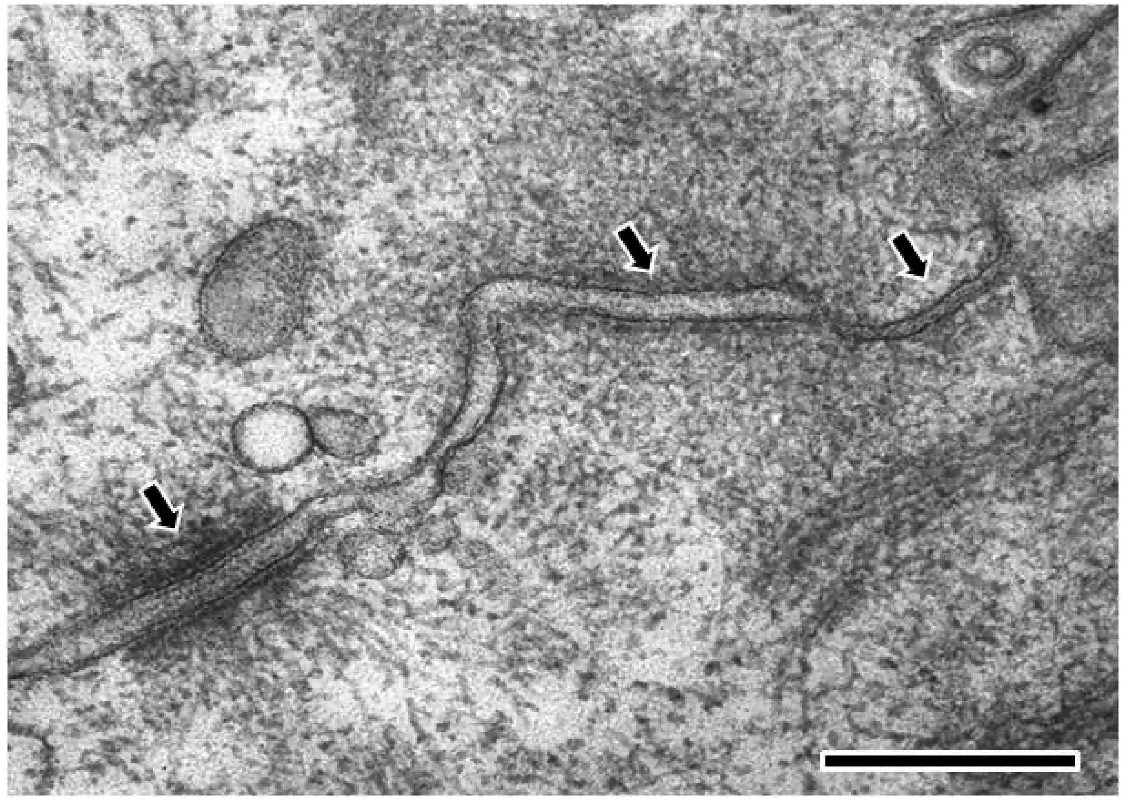
There are six types of intermediate filaments, classified based on their protein composition and tissue distribution

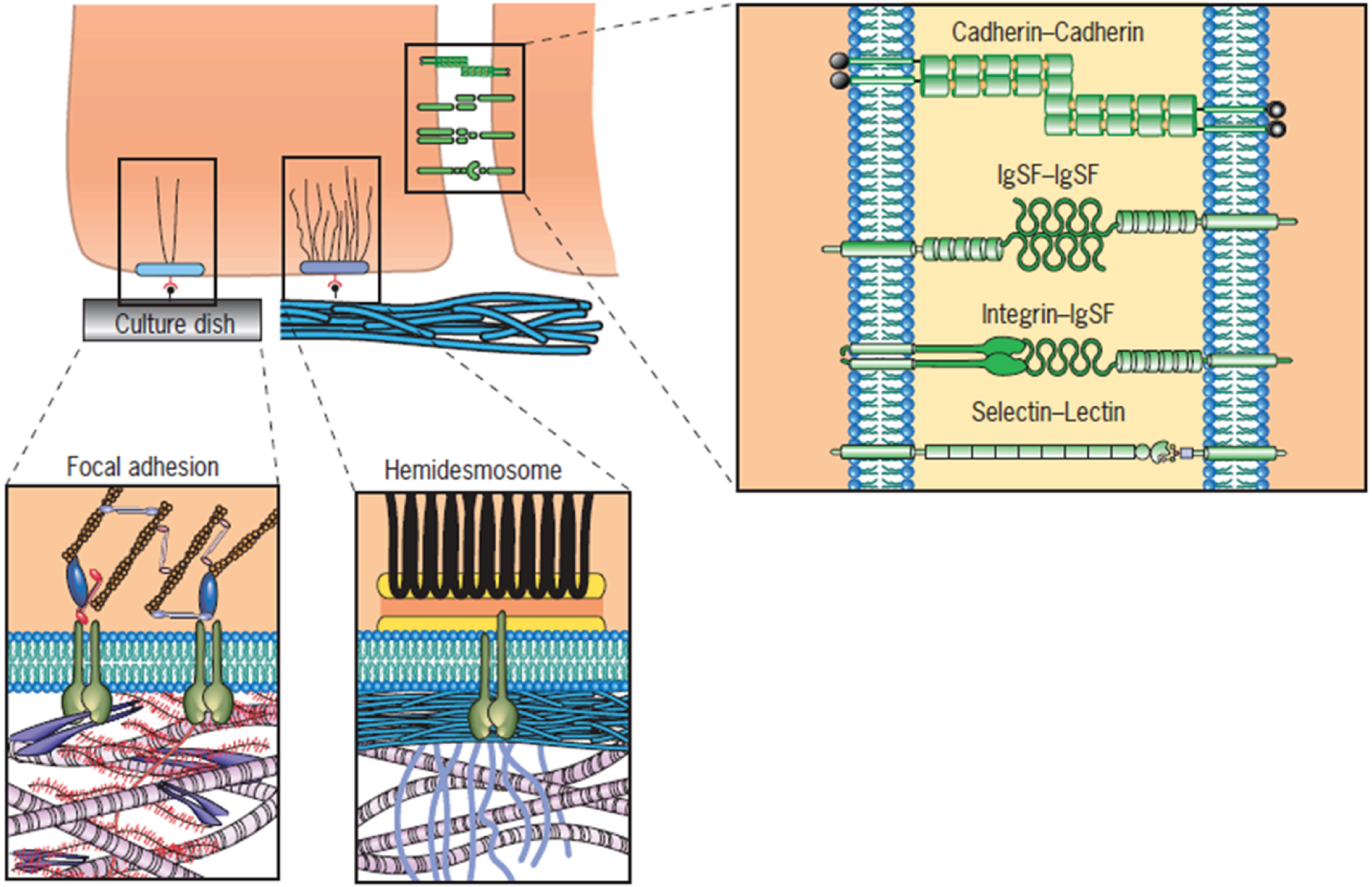
CELL ADHESION

Cell adhesion is the process by which cells interact with and attach to neighboring cells or to the extracellular matrix (ECM) using specialized proteins on their surface

Cell adhesion is mediated by cell adhesion molecules (CAMs)

- proteins located on the cell surface
- involved in binding with other cells or with the extracellular matrix (ECM)





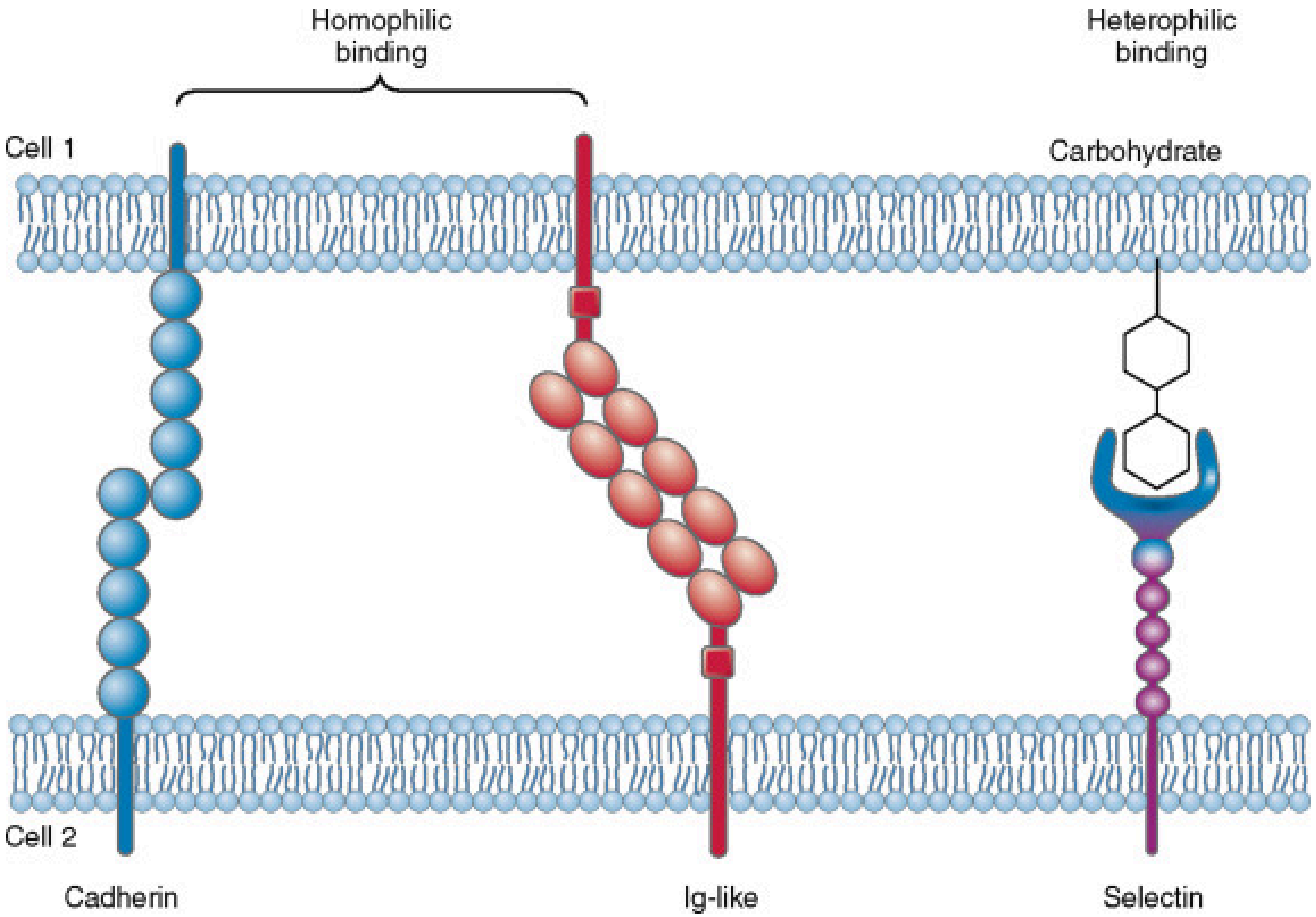
CELL ADHESION MOLECULES (CAMS)

Mechanisms by which CAMs mediate cell-cell adhesion

- **Homophilic binding**: CAMs on one cell bind to identical CAMs on another cell
  - Strong, stable
  - Example = Cadherins, Ig superfamily
- **Heterophilic binding**: CAMs on one cell bind to a different type of CAM or ligand on another cell
  - Dynamic, specific
  - Example = Selectins, Integrins

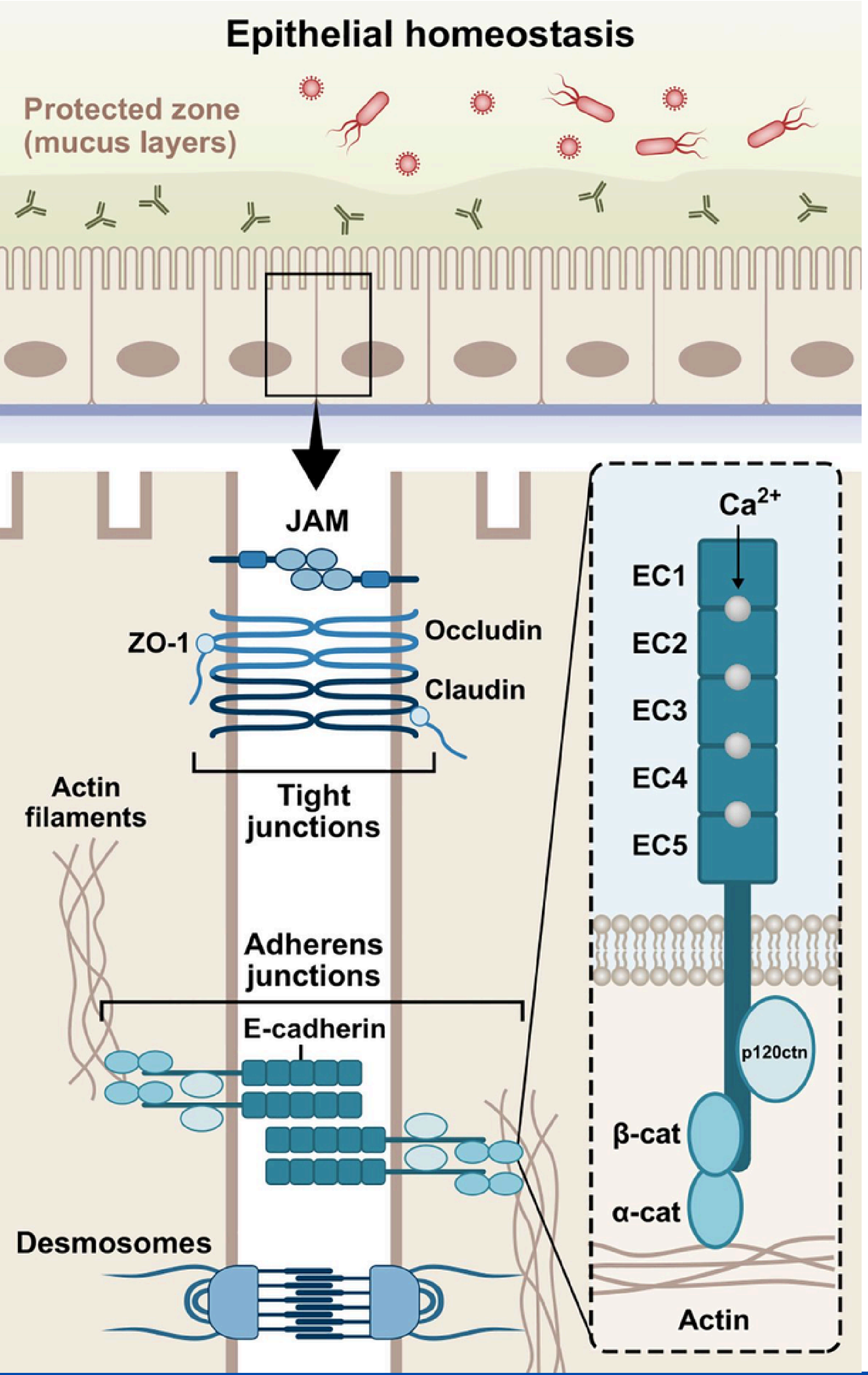
Major families of cell adhesion molecules

1. Ca2+ dependent molecules
   a. Cadherin
   b. Selectin
2. Ca2+ independent molecules
   a. Integrin
   b. Ig superfamily



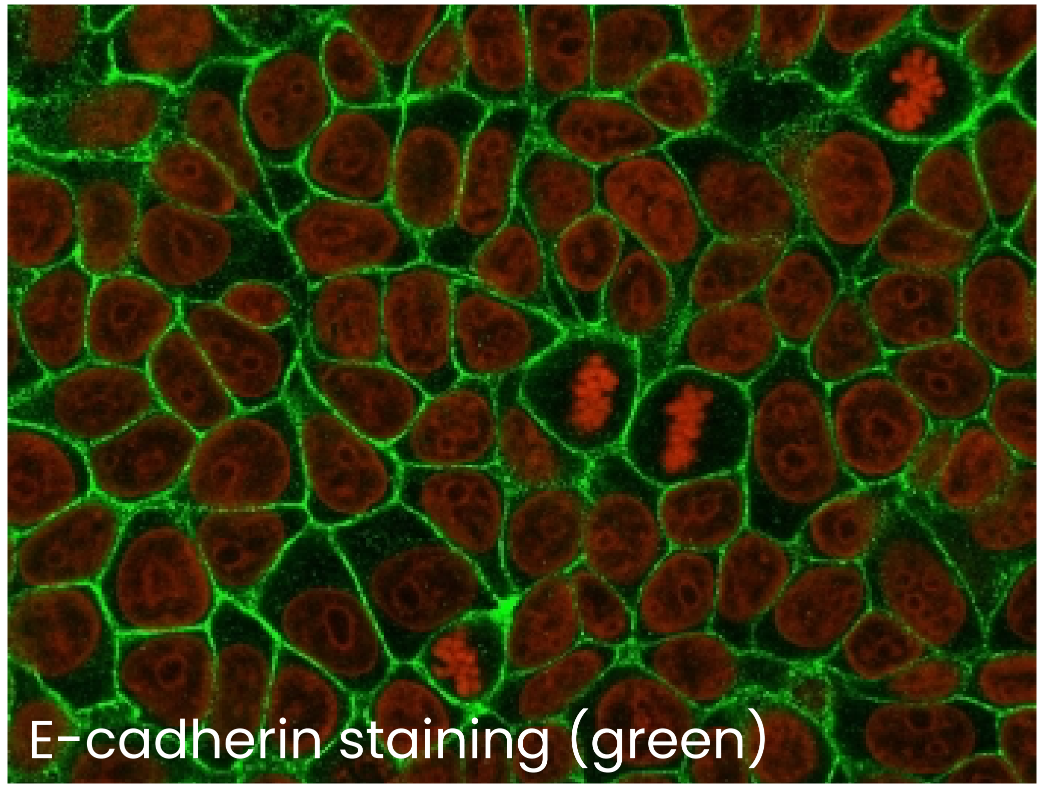
Cadherins are critical for maintaining the structure and organization of tissues

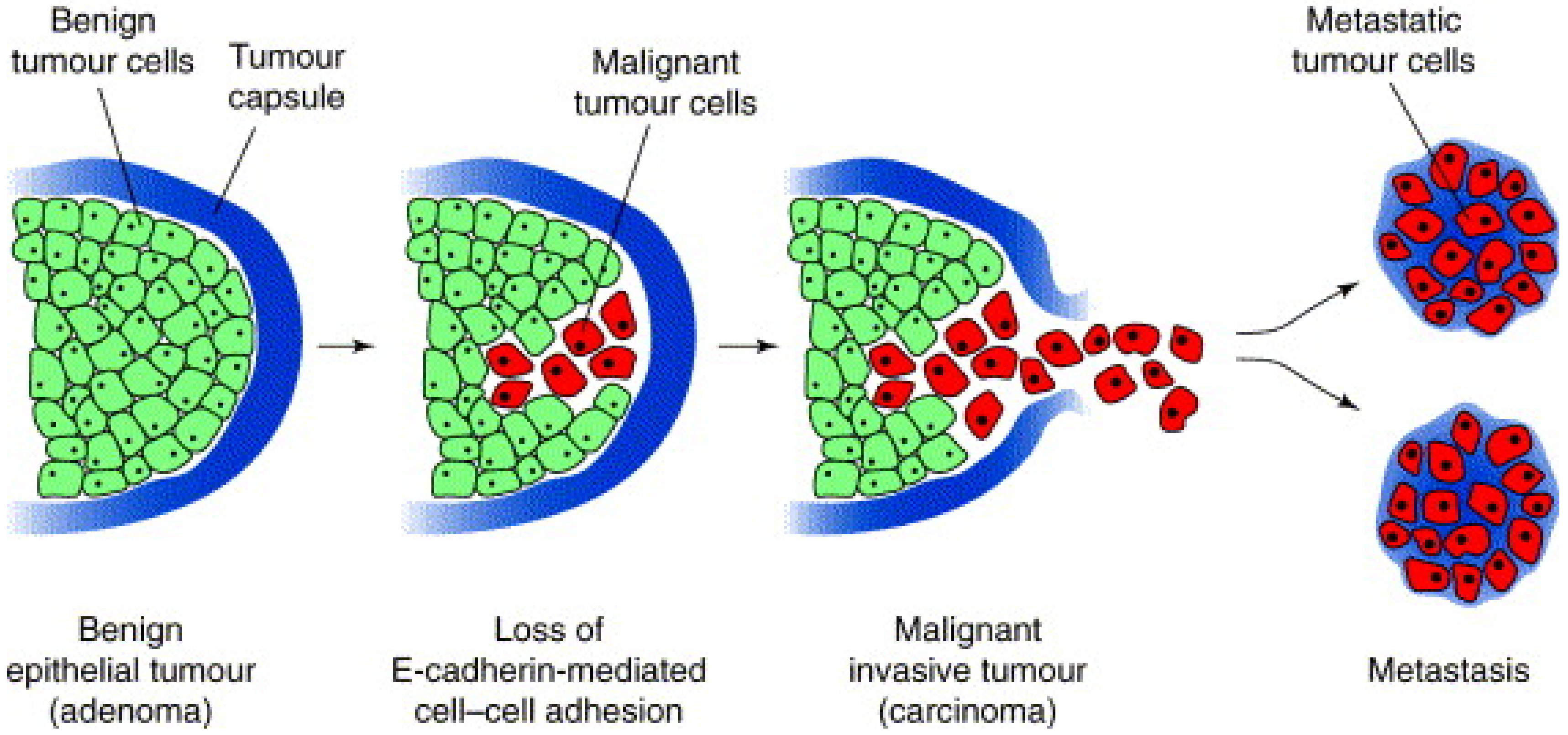
- Main adhesion protein holding epithelial cells together



Cadherin family members

- E-cadherin: found in epithelial sheets
- N-cadherin: found in the CNS, lens, skeletal and cardiac muscles
- P-cadherin: found in placenta


E-cadherin staining (green)

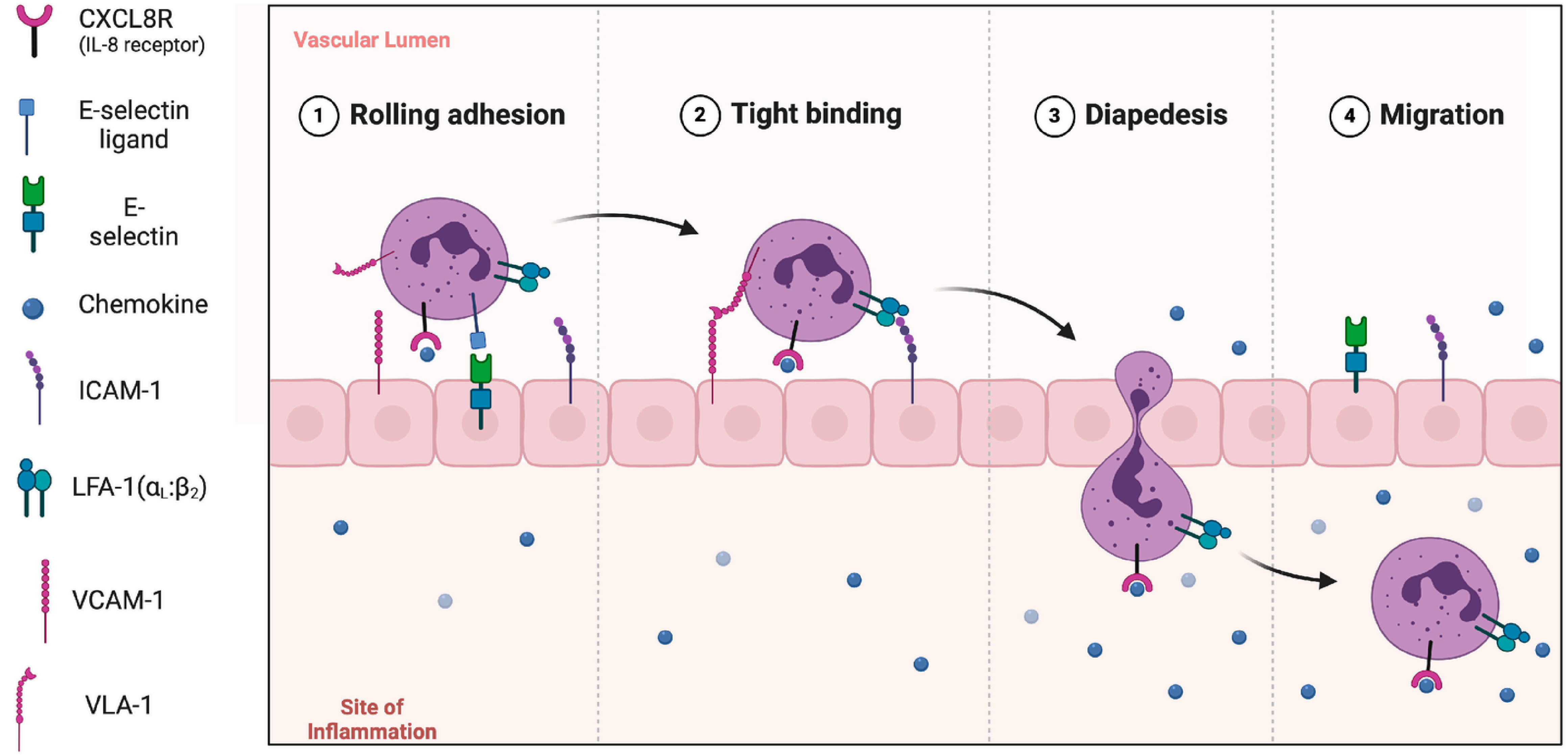


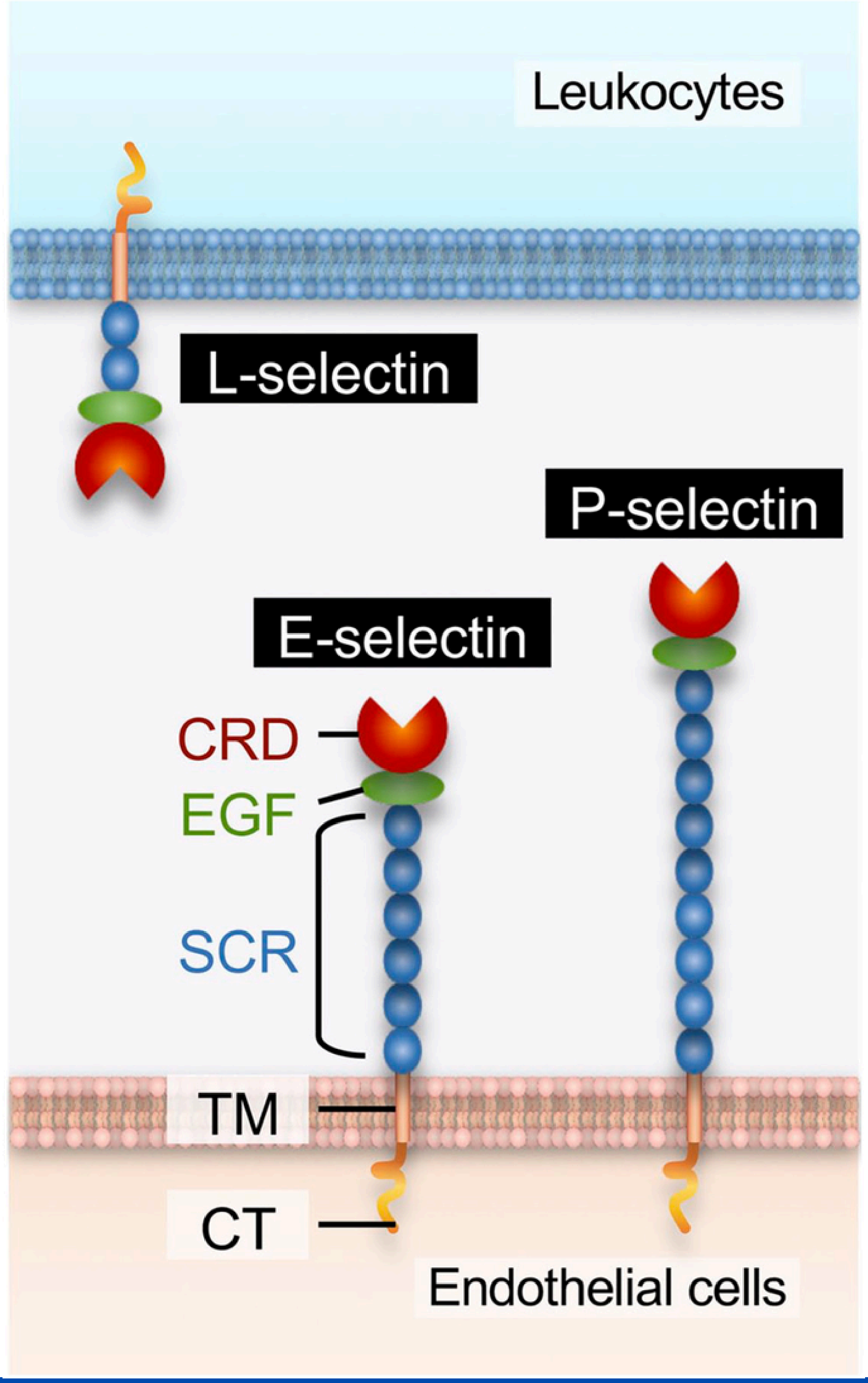
A loss of cadherins is associated with cancer metastasis

SELECTIN

Selectin plays a crucial role in the immune system, particularly in mediating the interaction between white blood cells and endothelial cells lining blood vessels during inflammation

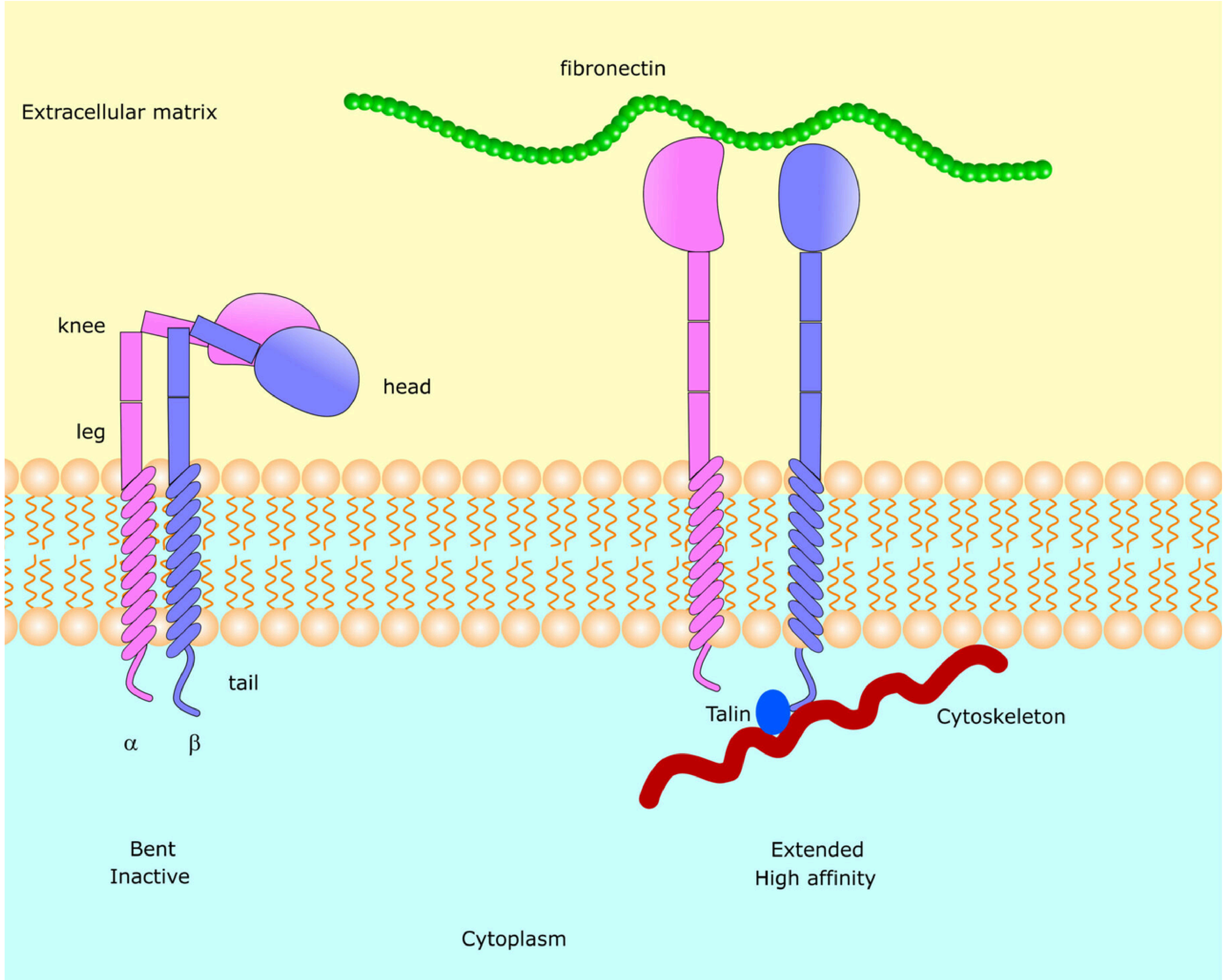
Major types of selectins
- E-selectin, present on endothelial cells
- P-selectin, present on platelets and endothelial cells
- L-selectin, present on leukocytes (white blood cells)



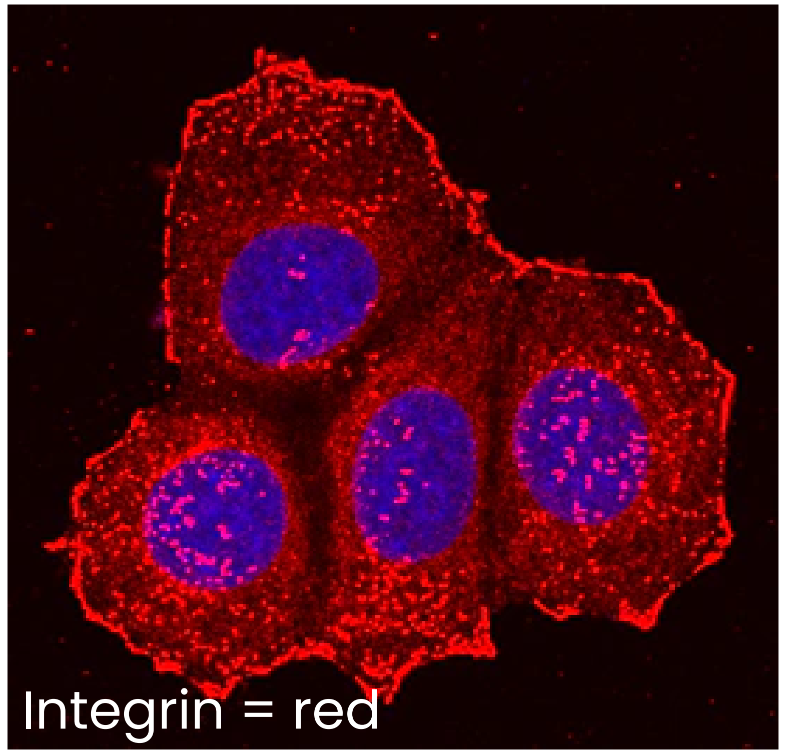


INTEGRIN

Integrin is essential for communication between the inside of a cell and its external environment, allowing cells to respond to mechanical and chemical signals

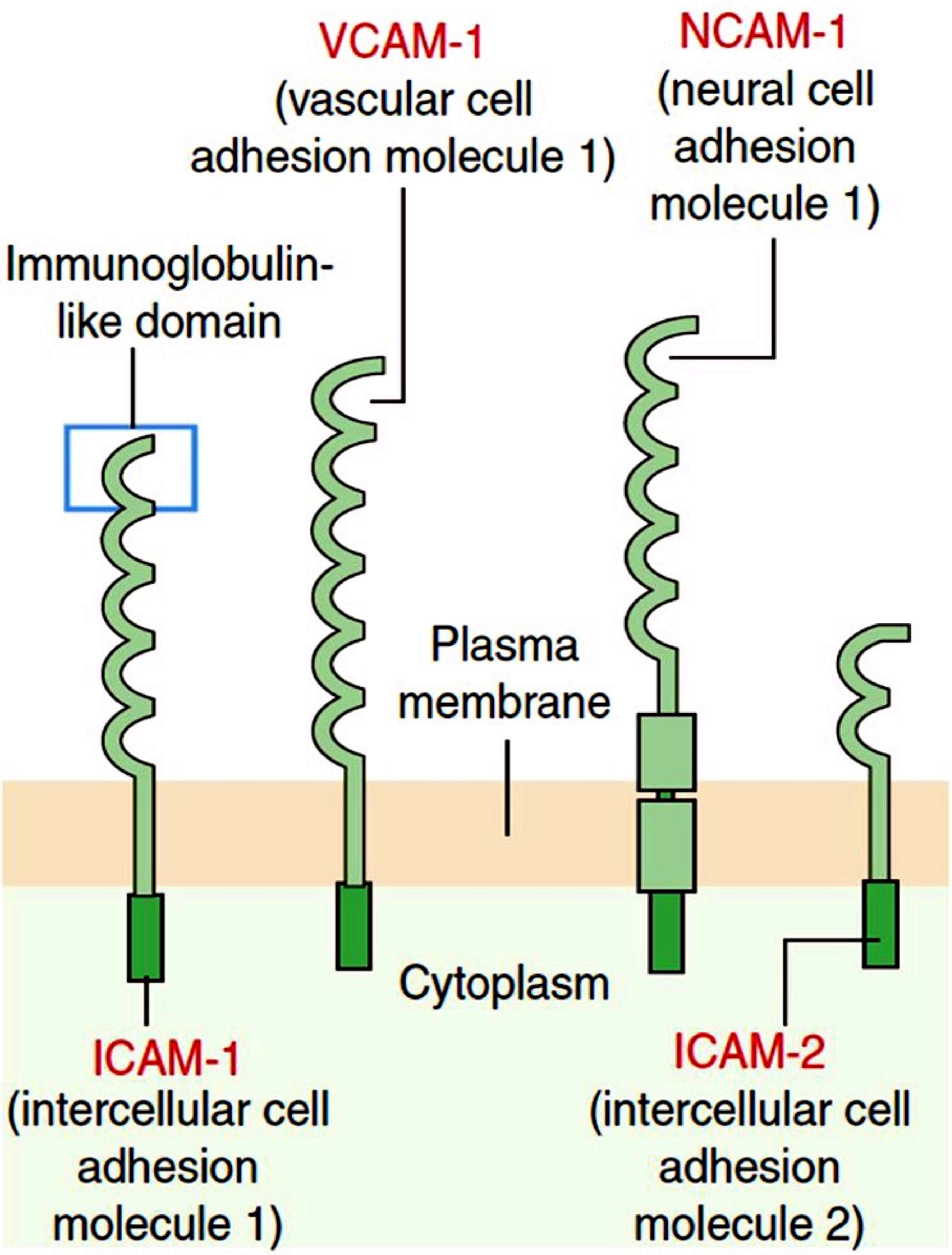


- Integrin consists of 2 subunits (β & α subunits)
- It binds to the extracellular matrix (ECM) and the internal cytoskeleton
  - The cytoplasmic domain (β subunit) interacts with actin filaments
  - The extracellular domain (α subunit) binds to ECM (fibronectin & laminin)

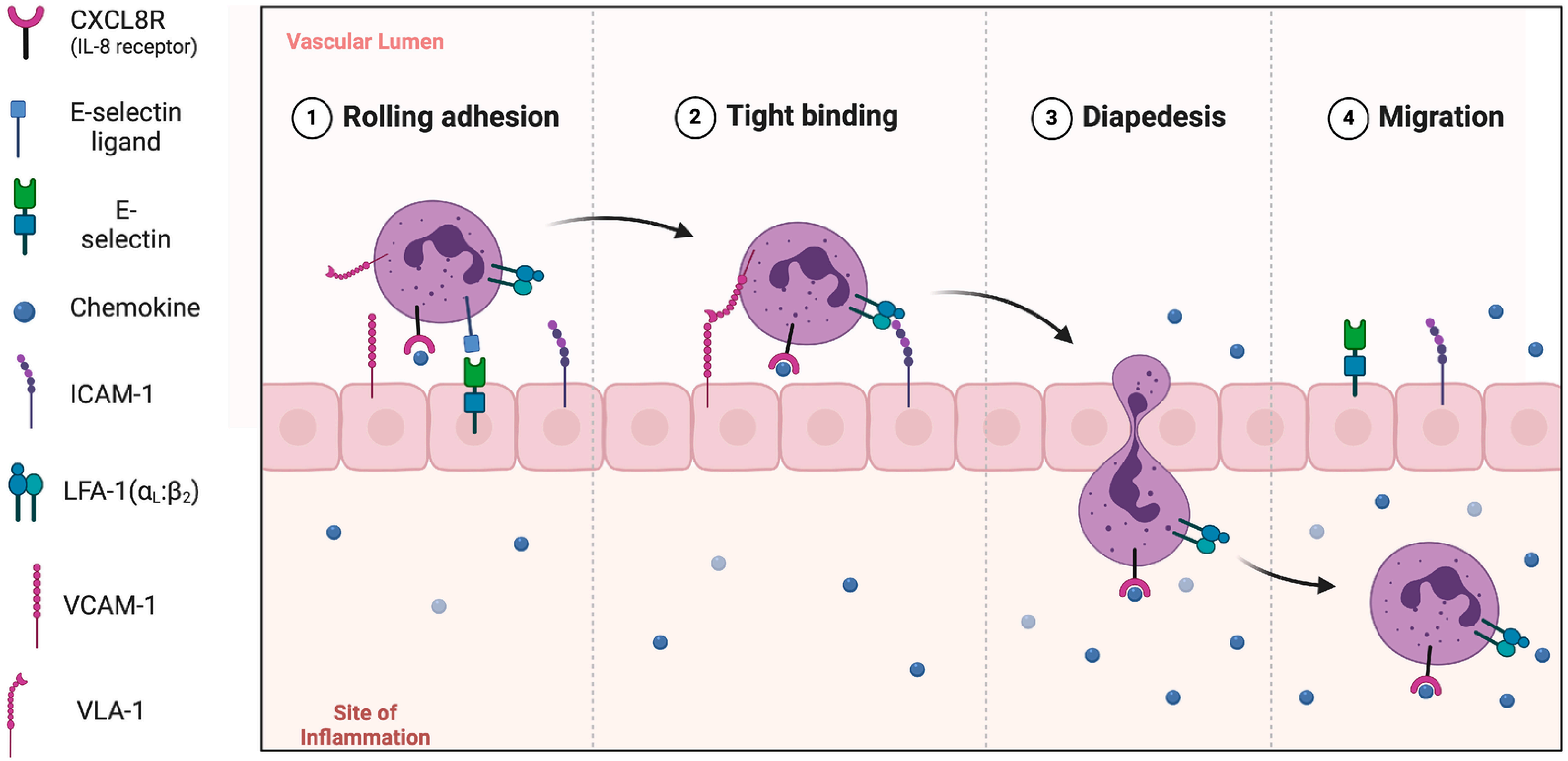


IMMUNOGLOBULIN SUPERFAMILY

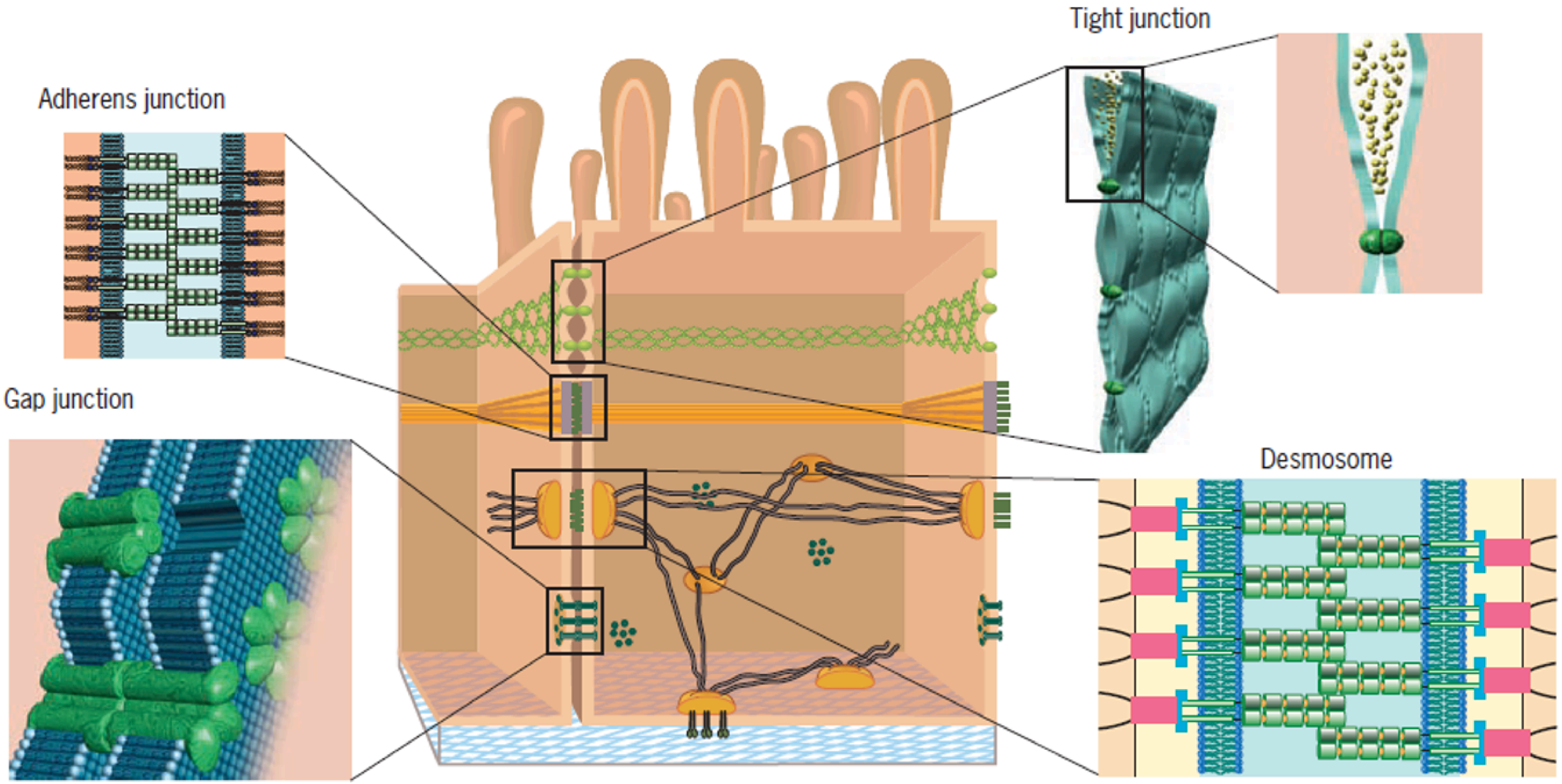
Ig superfamily consists of cell surface proteins that are primarily involved in cell–cell adhesion, especially in the immune systems



ICAM and VCAM molecules play an important role in T cell interactions and binding of leukocytes to activated or resting endothelial cells in the inflammatory areas



The adhesion molecules, along with other associated proteins and cytoskeleton elements, cluster on the plasma membrane to form identifiable cell junctions

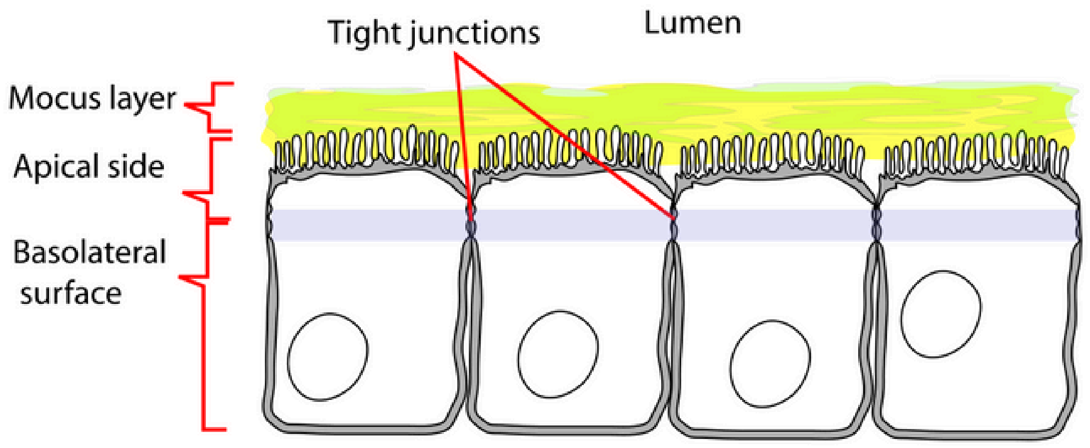


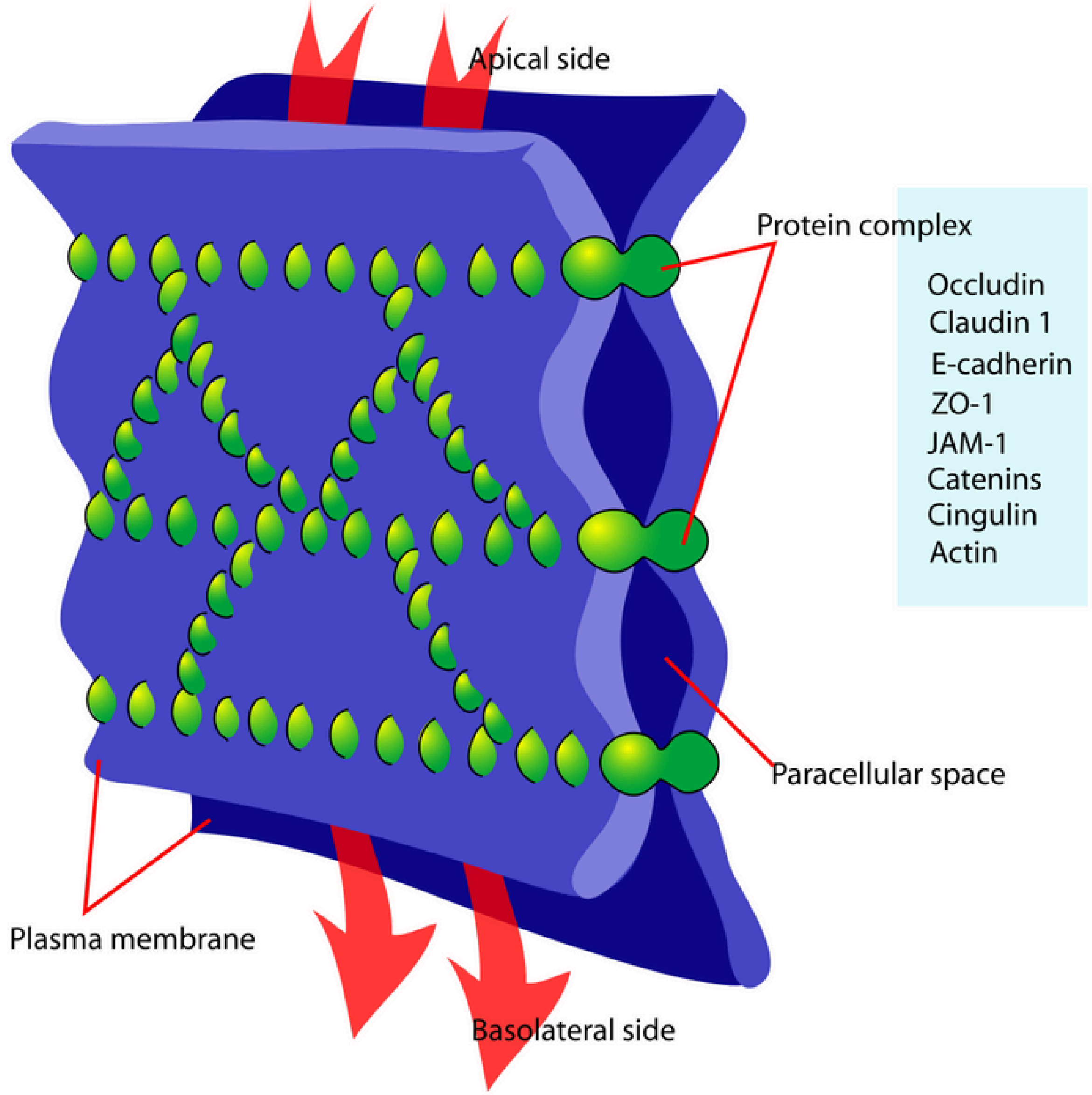
Occluding junctions
- Tight junctions

Anchoring junctions
- Adherens junctions
- Desmosomes

Communicating junctions
- Gap junctions

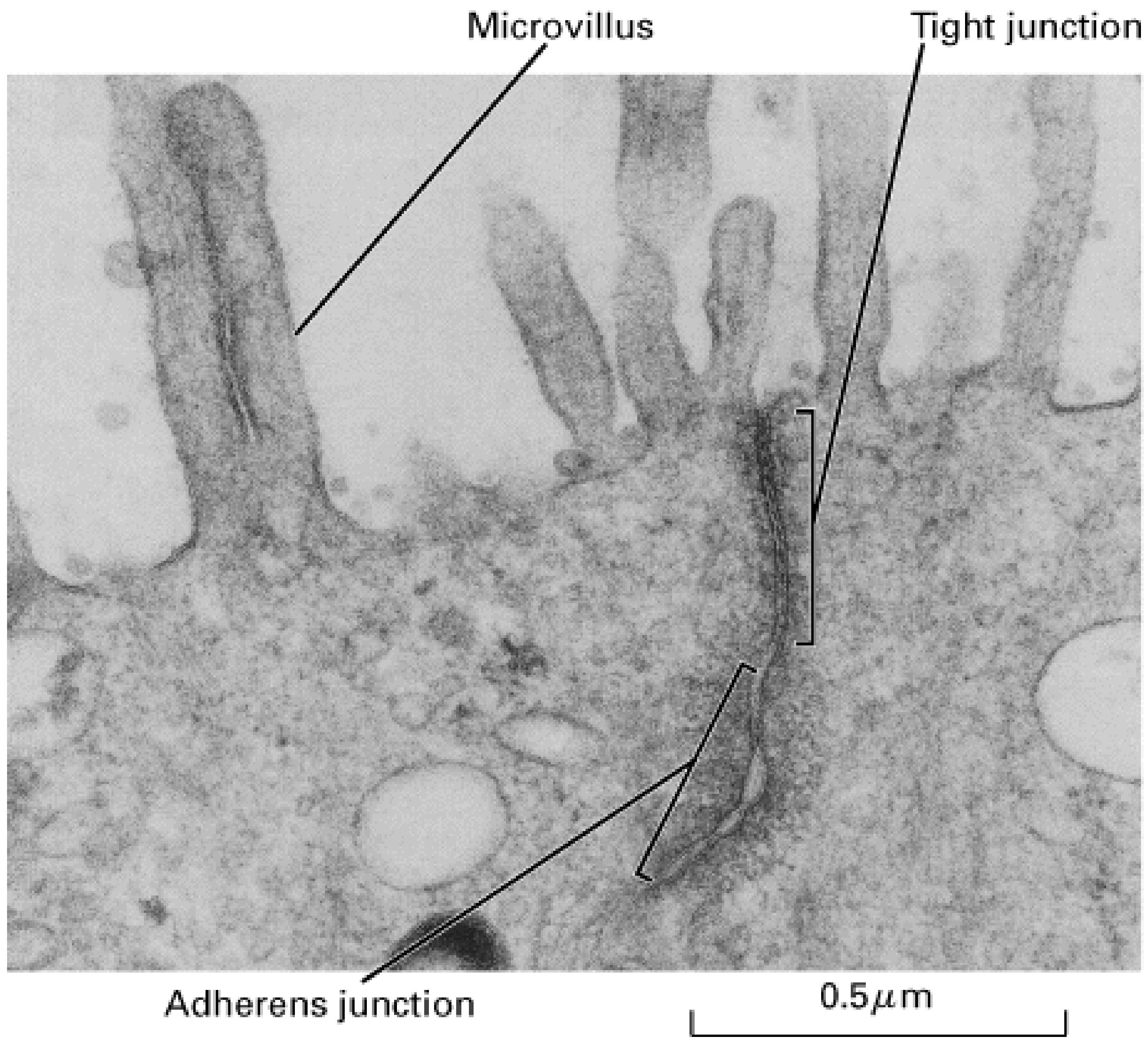
TIGHT JUNCTION





Tight junctions are circumferential belts at the apical domain of epithelial cells and linking adjacent cells

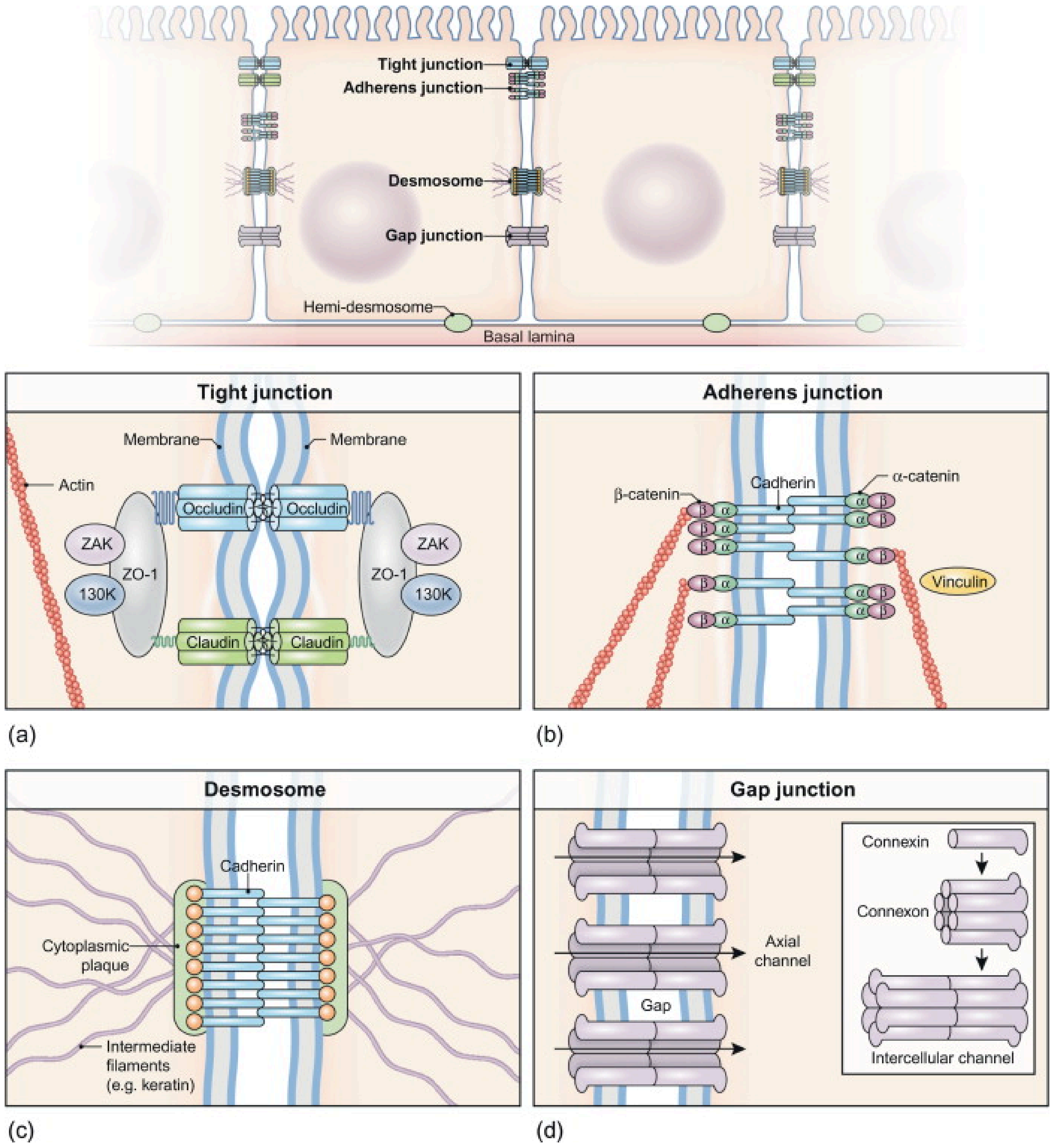
They seal the space between epithelial cells and regulate the passage of water and flux of ions between adjacent epithelial cells (paracellular pathway)



Major components:

- Transmembrane Proteins: Claudin, occluding, Junctional Adhesion Molecules (JAM), cadherin
- Scaffold/Adaptor Proteins
- Cytoskeletal Components: actin filament

OTHER JUNCTIONS



(a) (b) (c) (d)

Adherens junctions are anchor-like protein complexes similar to desmosomes, but they are linked to the actin cytoskeleton.

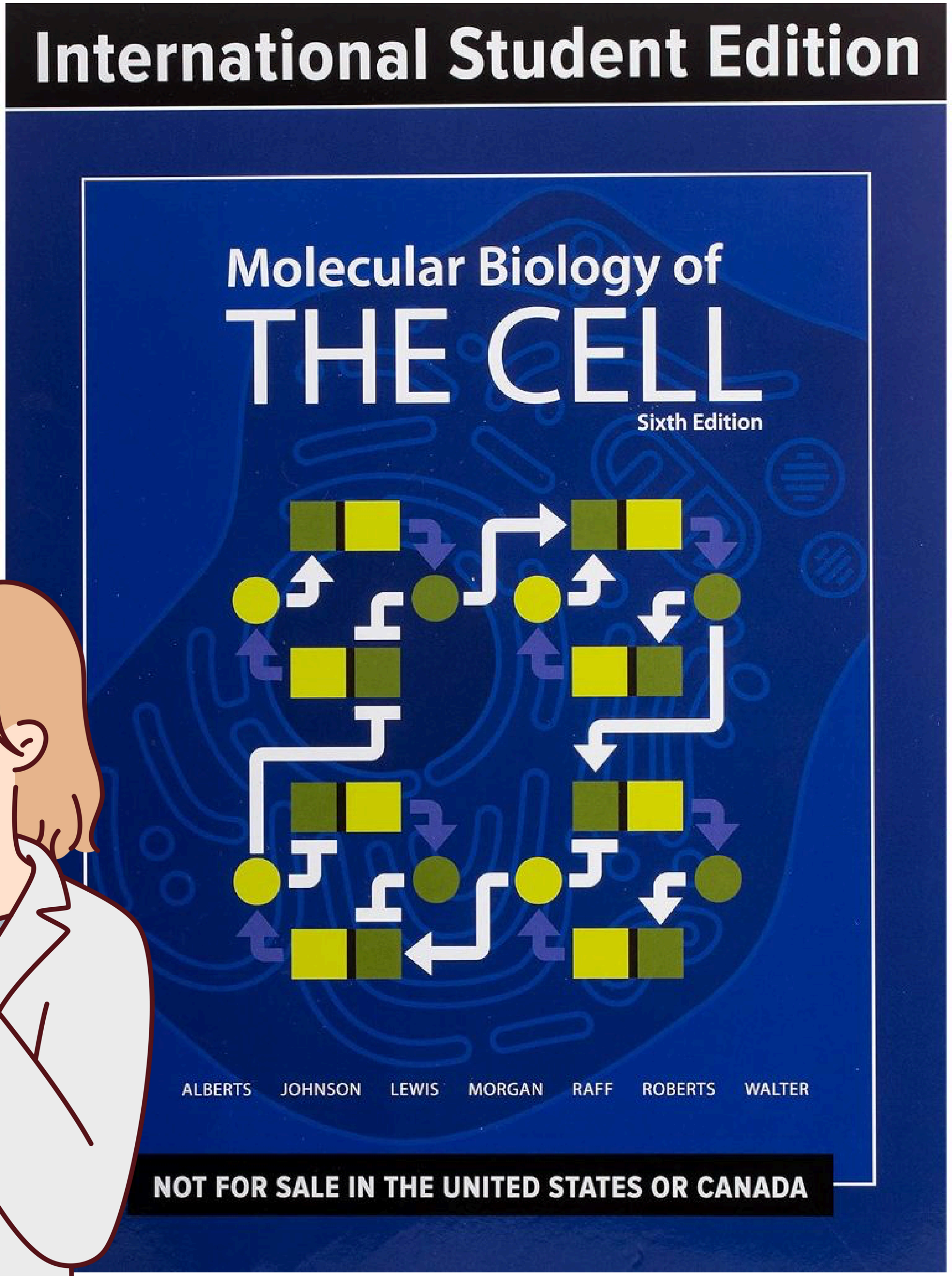
- To support the tight junctions

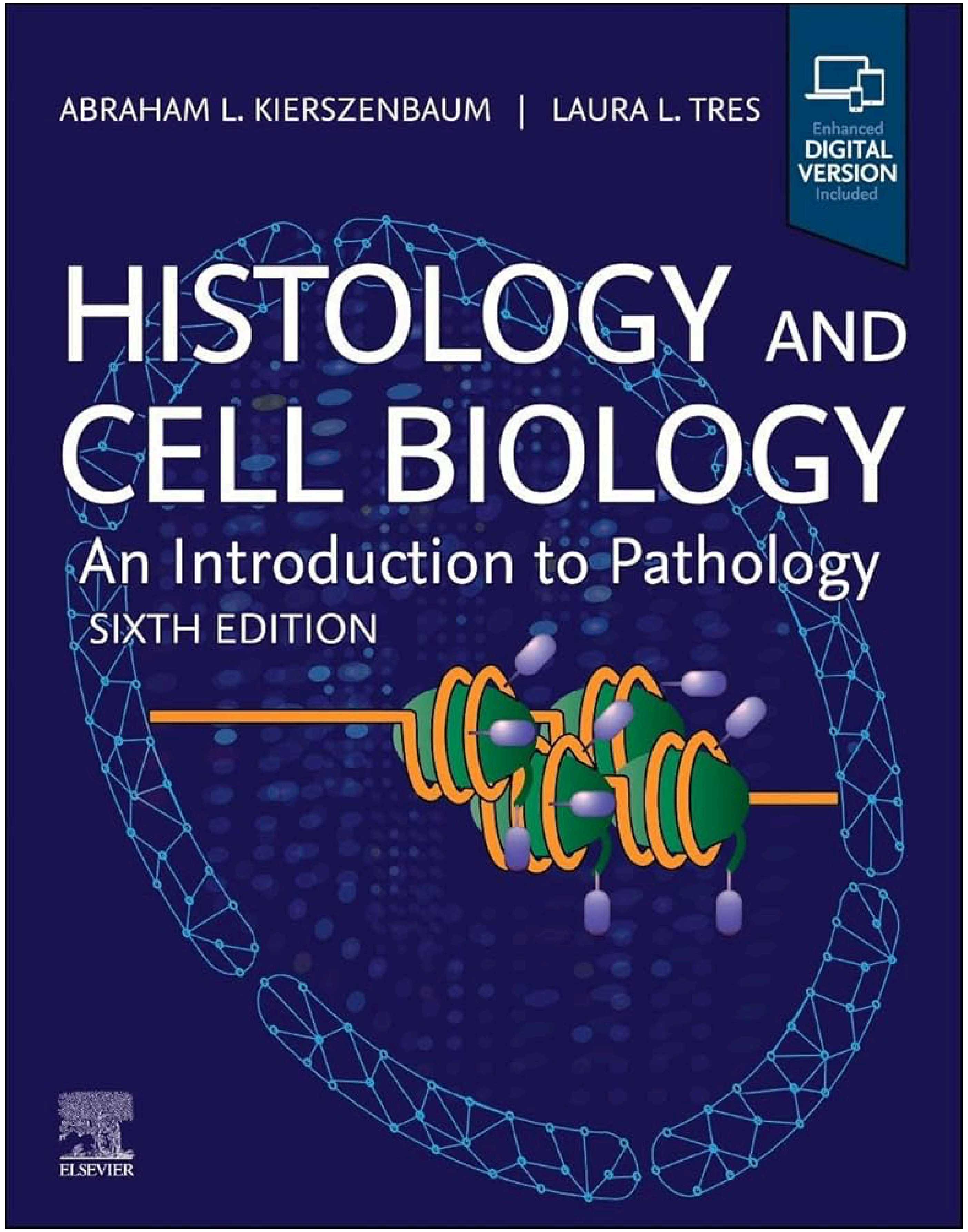
Desmosome

- The largest cell junctions
- disk-shaped adhesive junctions approximately 1 μm in diameter that are found in a variety of tissues.
- protein complexes: connect the keratin fibers of two cells like a hook-and-loop fastener
- help the tissue to resist shearing forces.

Gap junction

- Intercellular channels
- direct communication among cells
- small molecules, ions and electrical impulses move between cells through gap junctions





Any questions? send the e-mail: wanphrom@kku.ac.th