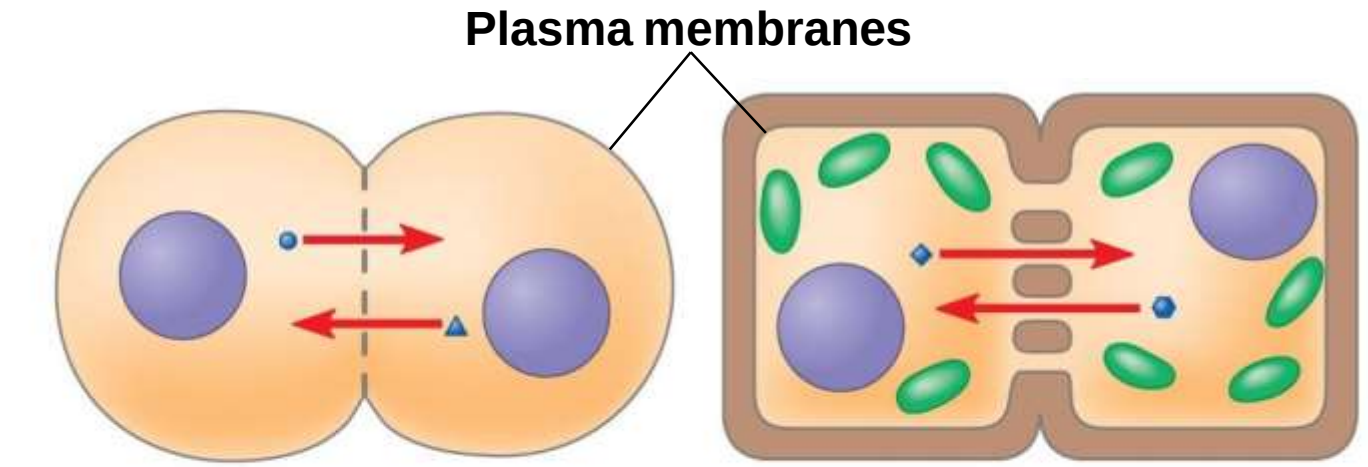
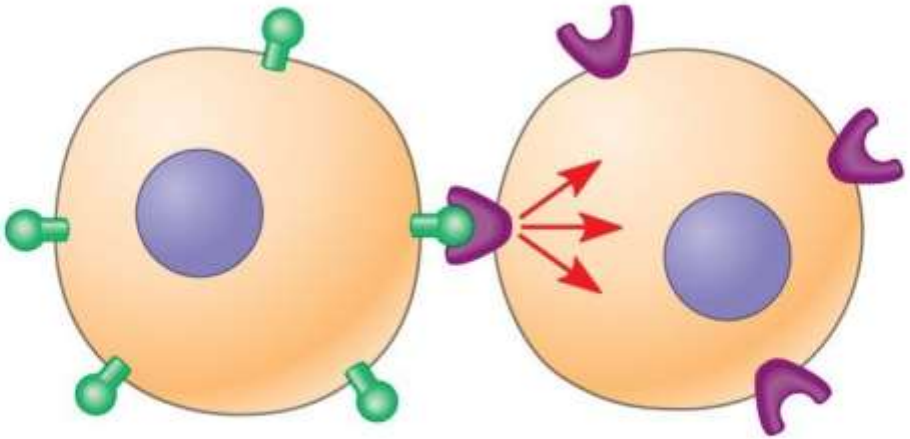
Cell to Cell Communication



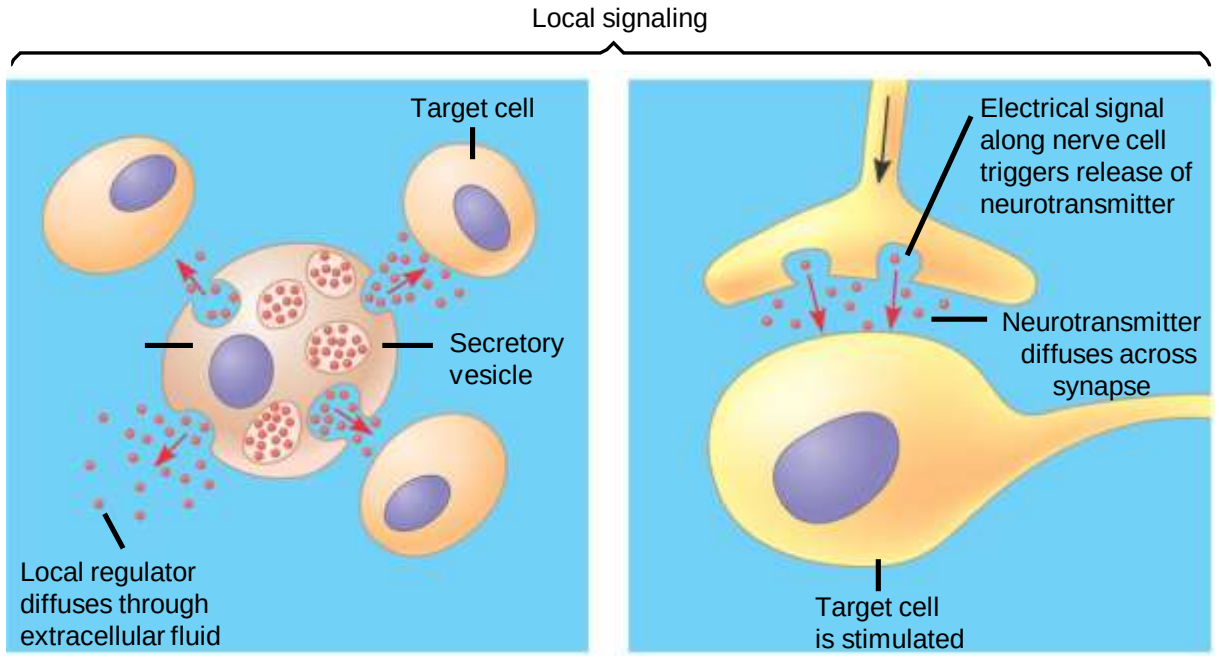
(a) Cell junctions



(b) Cell-cell recognition

- In local signaling, animal cells
  - May communicate via direct contact

- In other cases, animal cells
  - Communicate using local regulators



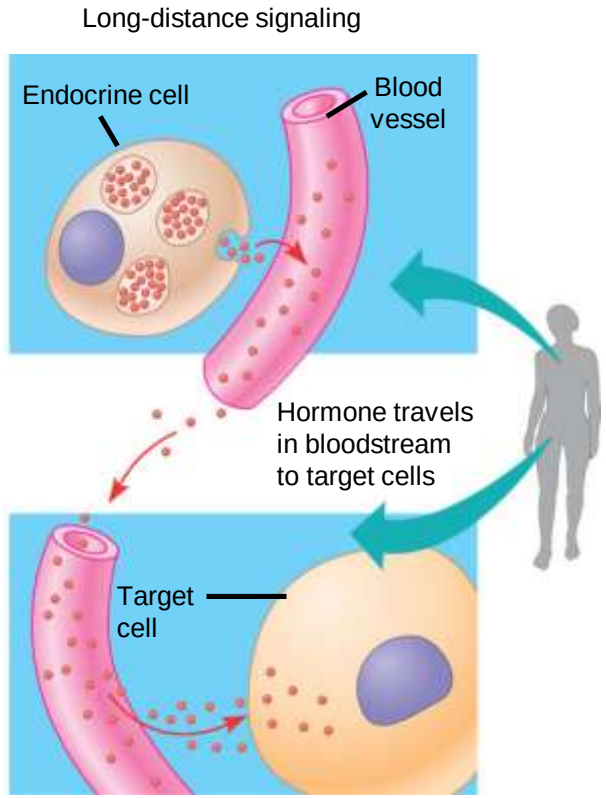
(a) Paracrine signaling. A secreting cell acts on nearby target cells by discharging molecules of a local regulator (a growth factor, for example) into the extracellular fluid.

(b) Synaptic signaling. A nerve cell releases neurotransmitter molecules into a synapse, stimulating the target cell.

Local and Long-Distance Signaling

- Cells in a multicellular organism communicate by chemical messengers
- Animal and plant cells have cell junctions that directly connect the cytoplasm of adjacent cells
- In local signaling, animal cells may communicate by direct contact, or cell-cell recognition

- In long-distance signaling
  - Both plants and animals use hormones



(c) Hormonal signaling. Specialized endocrine cells secrete hormones into body fluids, often the blood. Hormones may reach virtually all body cells.

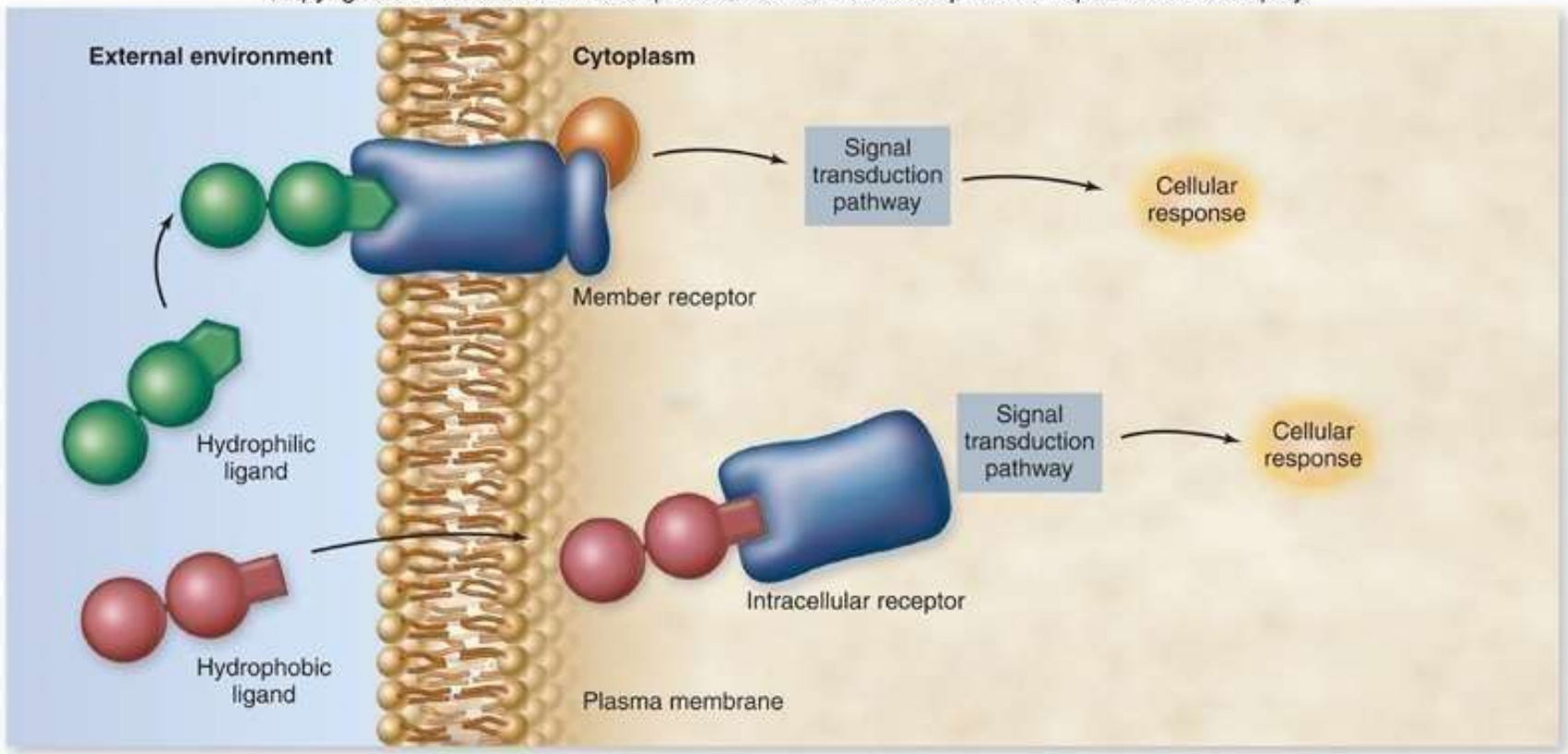
Cell to Cell Communication

Communication between cells requires:

ligand: the signaling molecule

receptor protein: the molecule to which the receptor binds

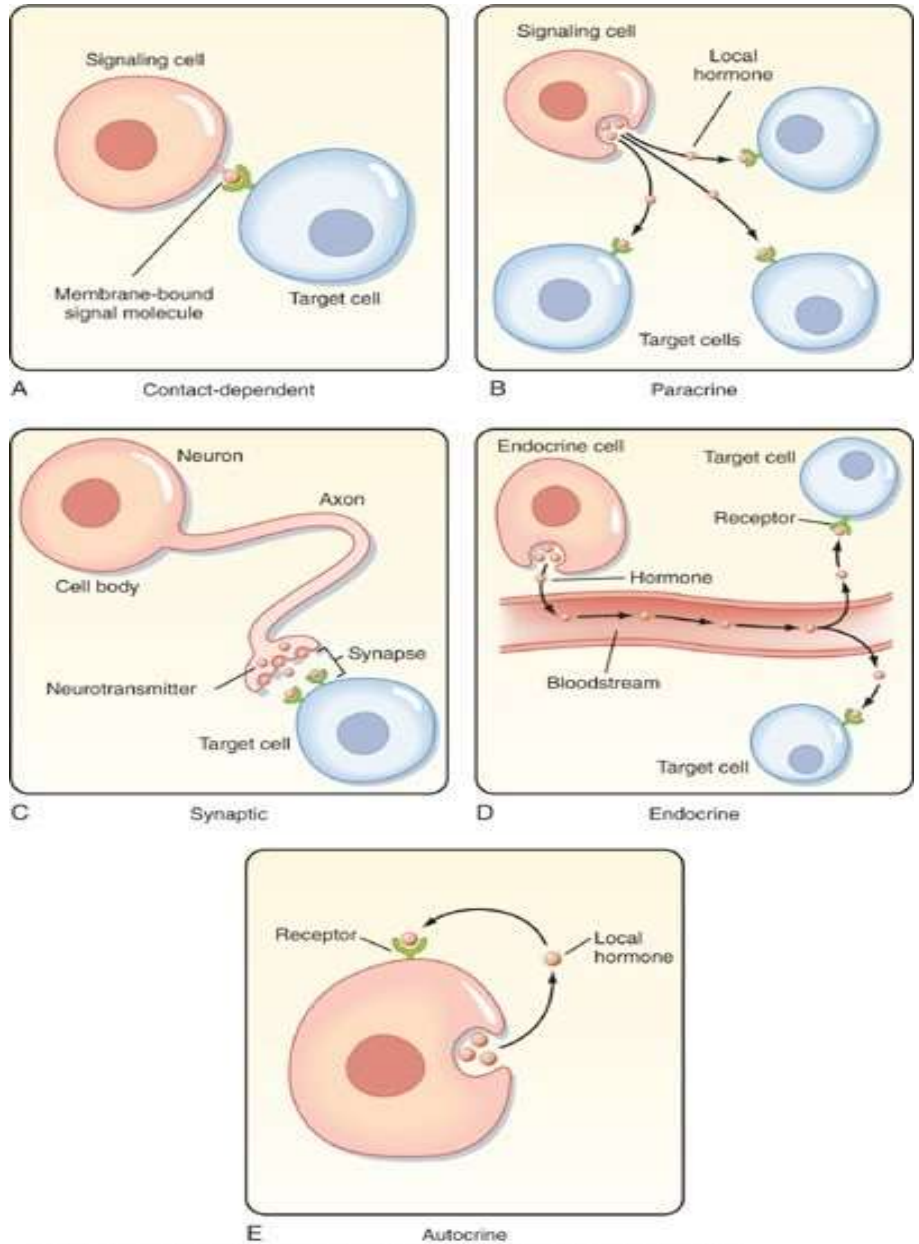
-may be on the plasma membrane or within the cell



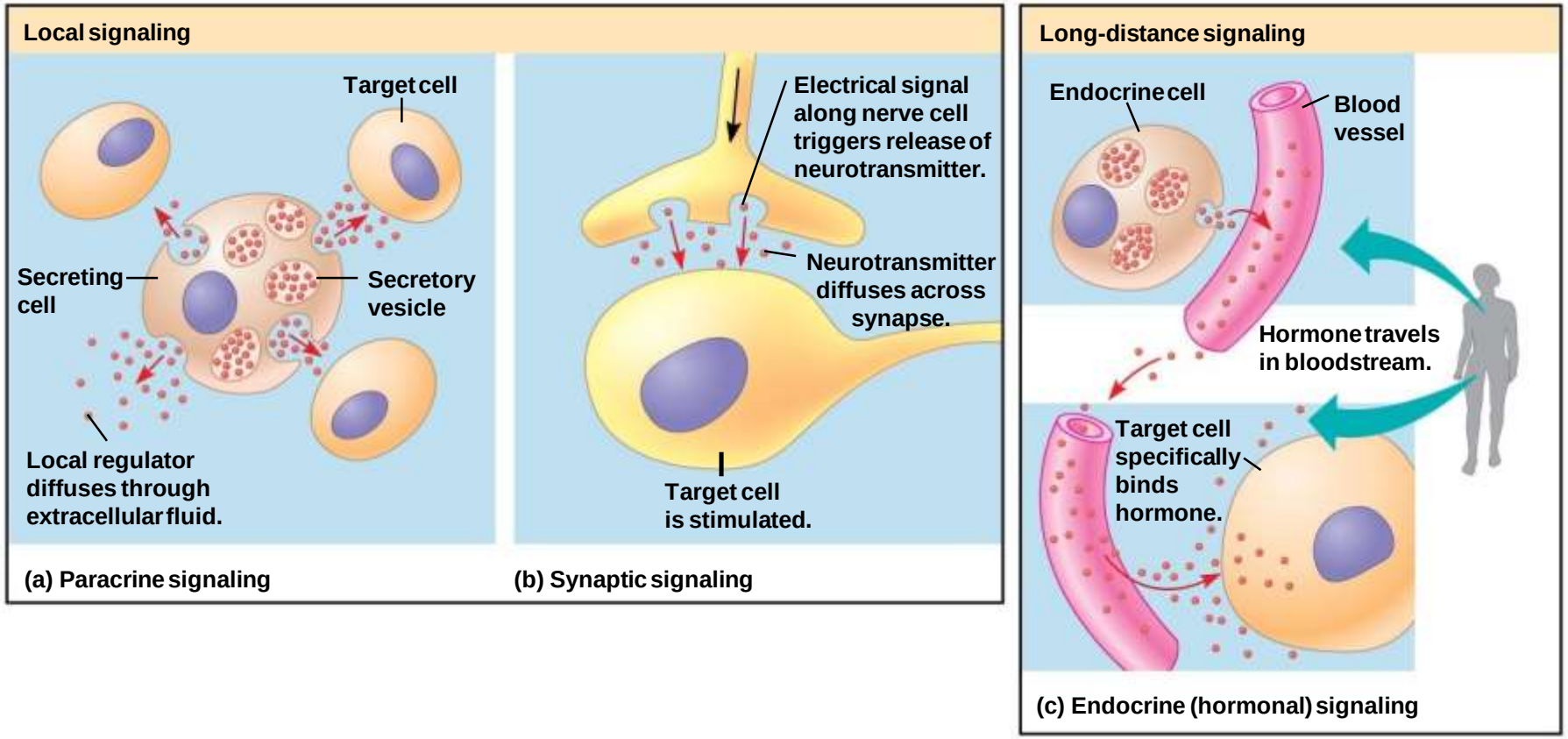
Cell Communication

There are five basic mechanisms for cellular communication:

1. Direct contact
2. Paracrine and Autocrine signaling
3. Synaptic signaling
4. Endocrine signaling

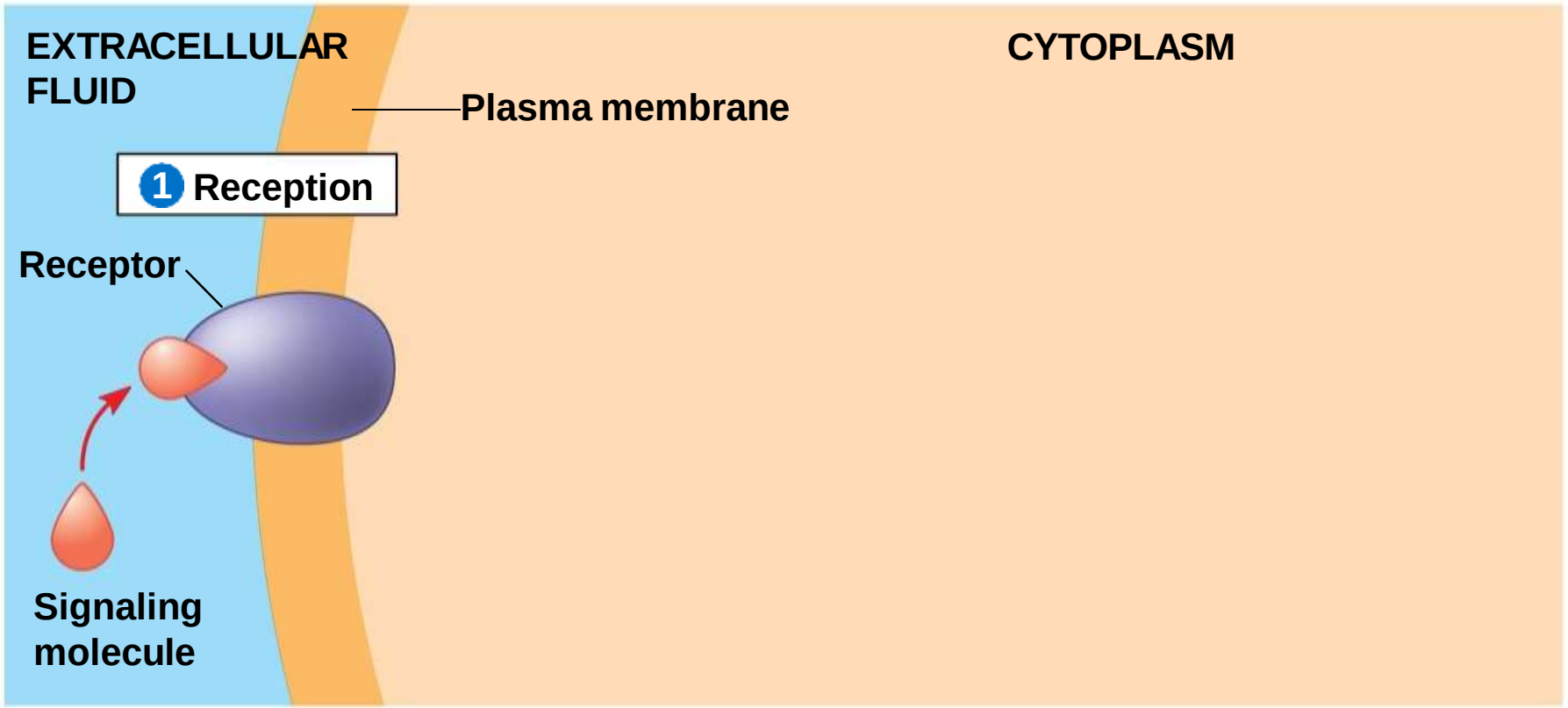


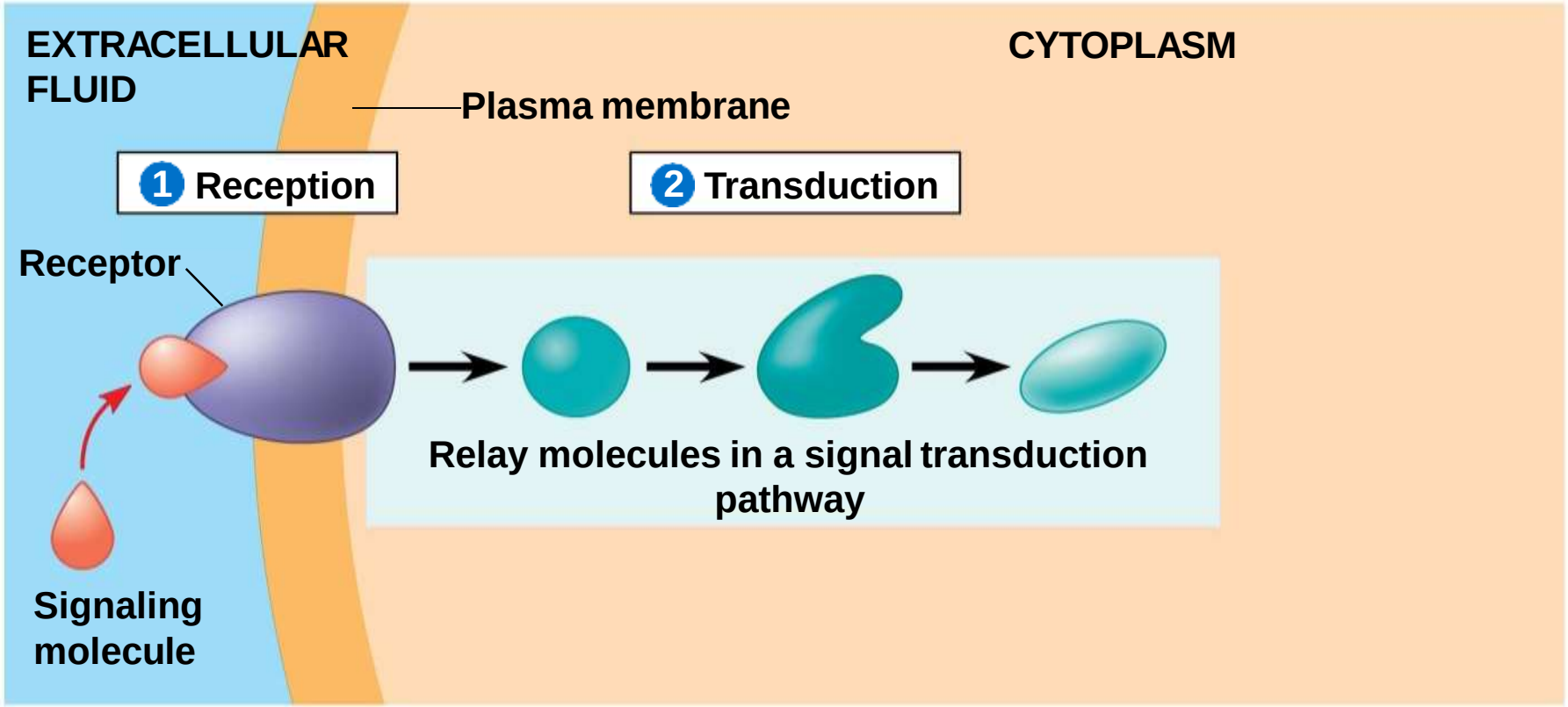
- In many cases, animal cells communicate using **local regulators**, messenger molecules that travel only short distances
- In long-distance signaling, plants and animals use chemicals called **hormones**
- The ability of a cell to respond to a signal depends on whether or not it has a receptor specific to that signal

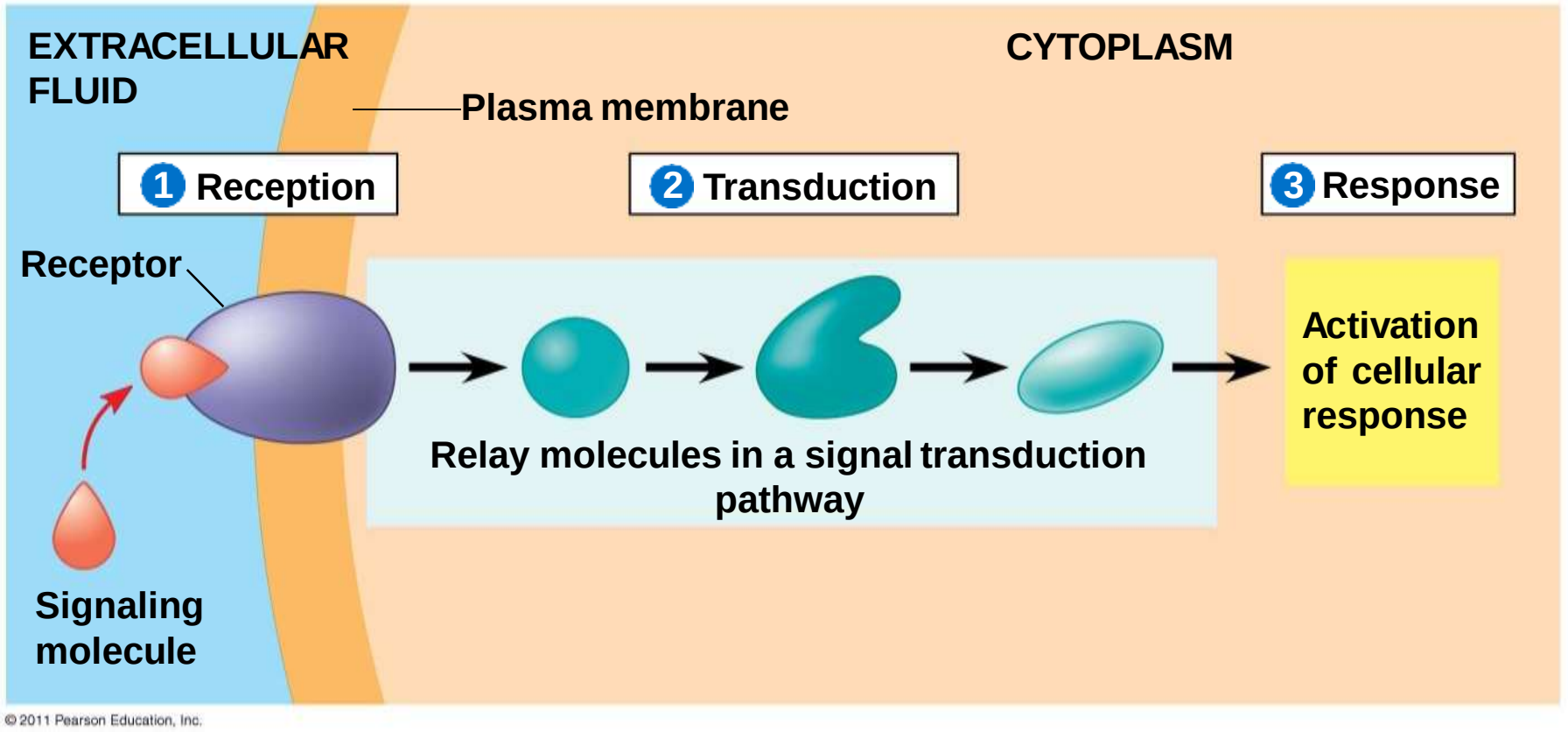


The Three Stages of Cell Signaling:

- Earl W. Sutherland discovered how the hormone epinephrine acts on cells
- Sutherland suggested that cells receiving signals went through three processes
  - **Reception**
  - **Transduction**
  - **Response**







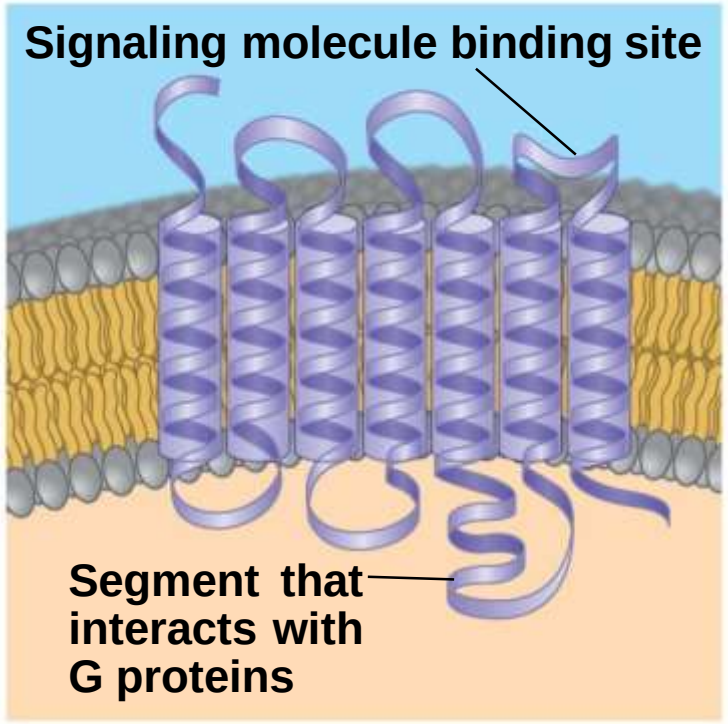
Reception: A signaling molecule binds to a receptor protein, causing it to change shape

- The binding between a signal molecule (**ligand**) and receptor is highly specific
- A shape change in a receptor is often the initial transduction of the signal
- Most signal receptors are plasma membrane proteins

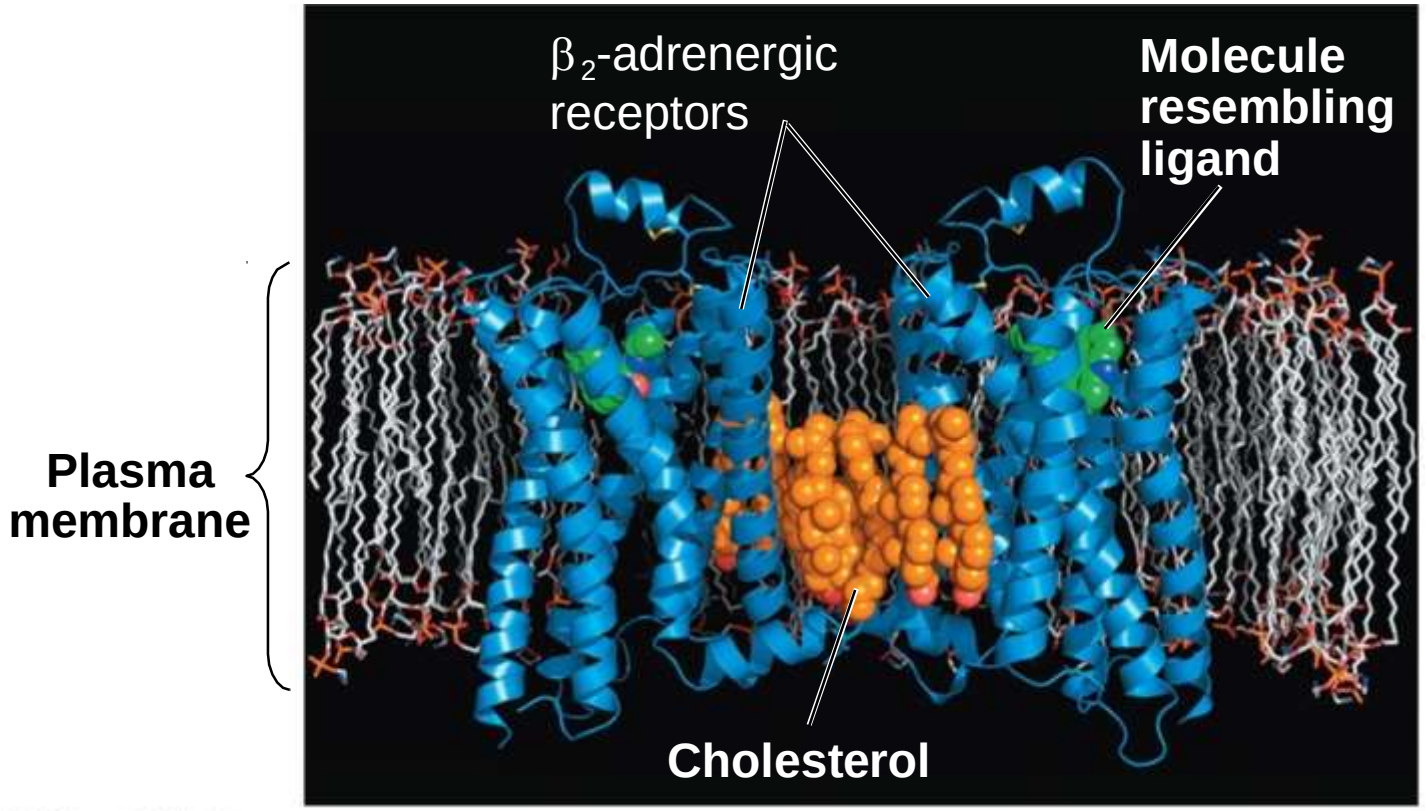
Receptors in the Plasma Membrane

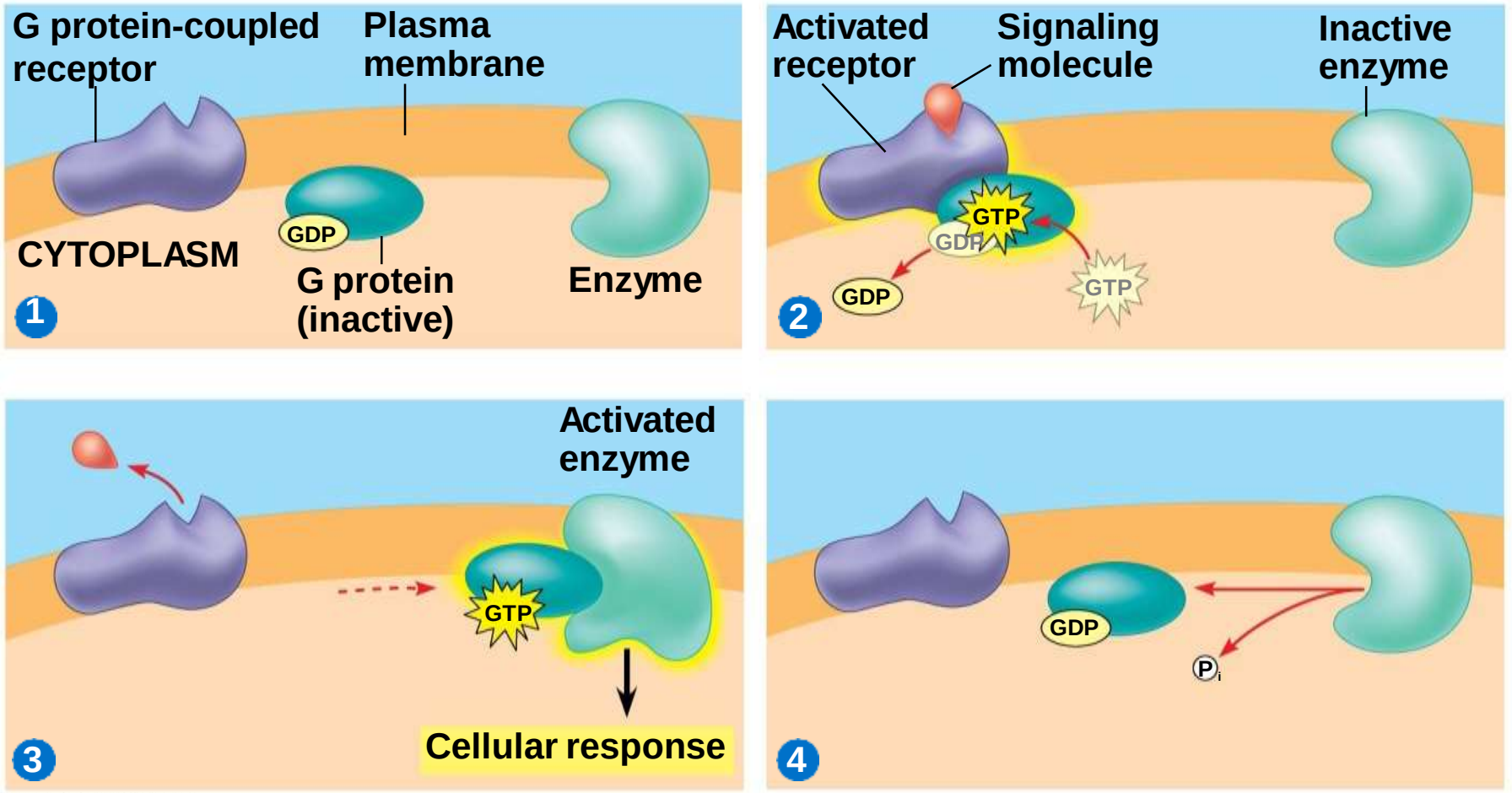
- Most water-soluble signal molecules bind to specific sites on receptor proteins that span the plasma membrane
- There are three main types of membrane receptors
  - G protein-coupled receptors
  - Receptor tyrosine kinases
  - Ion channel receptors

- **G protein-coupled receptors (GPCRs)** are the largest family of cell-surface receptors
- A GPCR is a plasma membrane receptor that works with the help of a **G protein**
- The G protein acts as an on/off switch: If GDP is bound to the G protein, the G protein is inactive

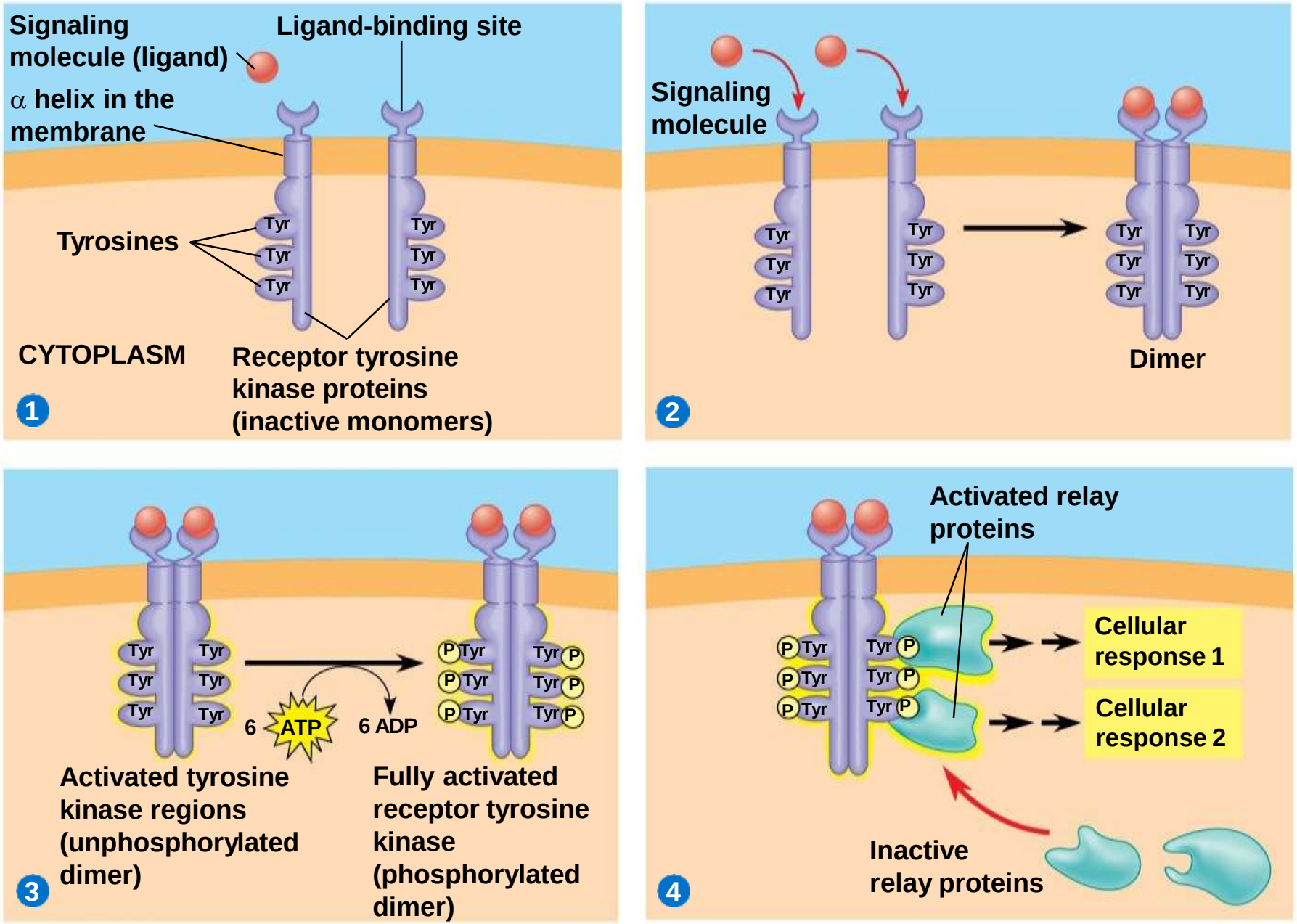


G protein-coupled receptor

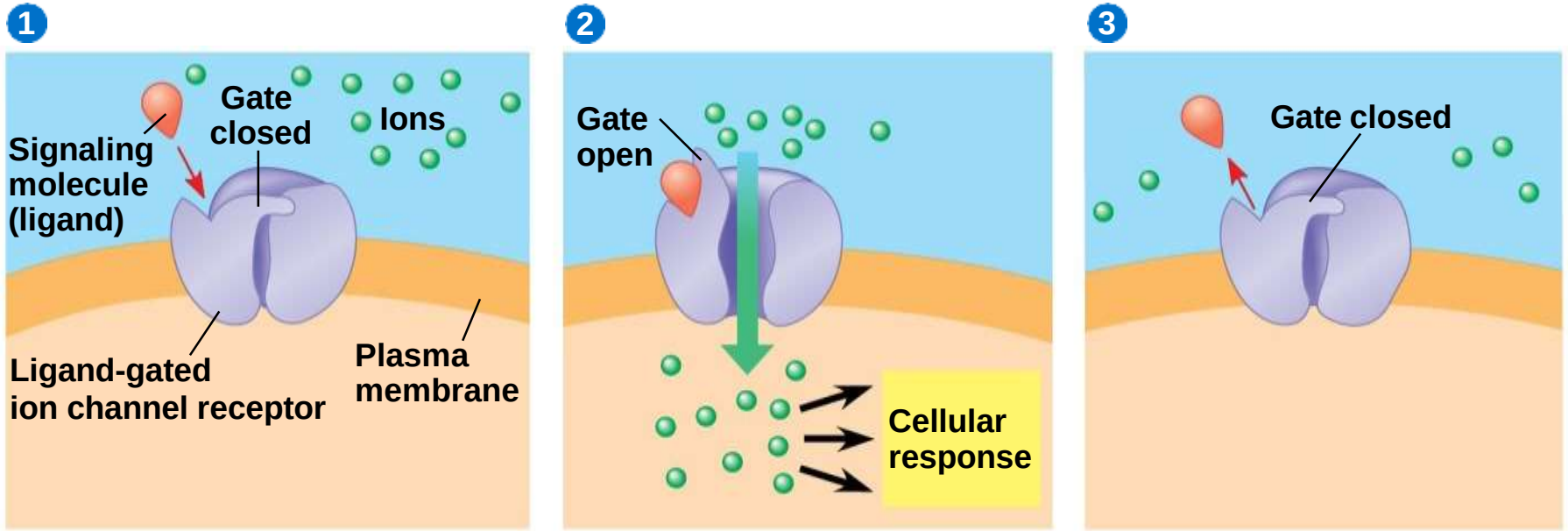




- **Receptor tyrosine kinases (RTKs)** are membrane receptors that attach phosphates to tyrosines
- A receptor tyrosine kinase can trigger multiple signal transduction pathways at once
- Abnormal functioning of RTKs is associated with many types of cancers

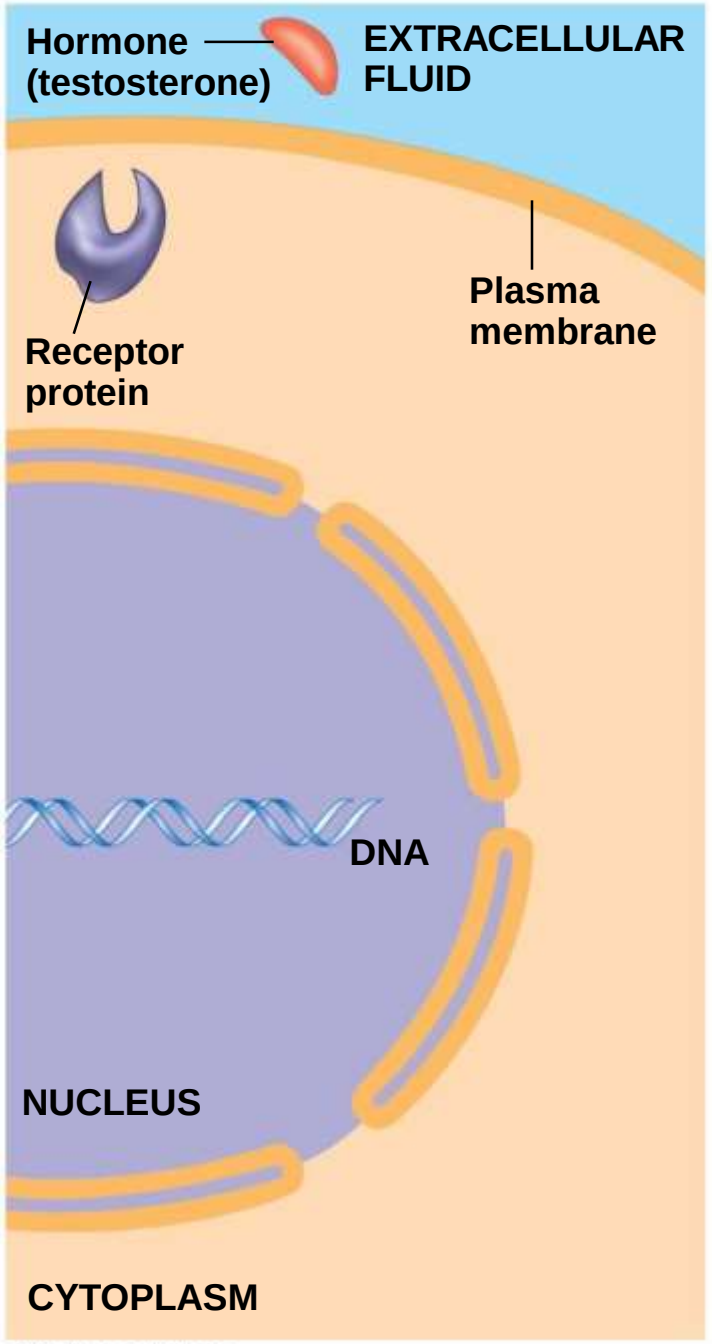


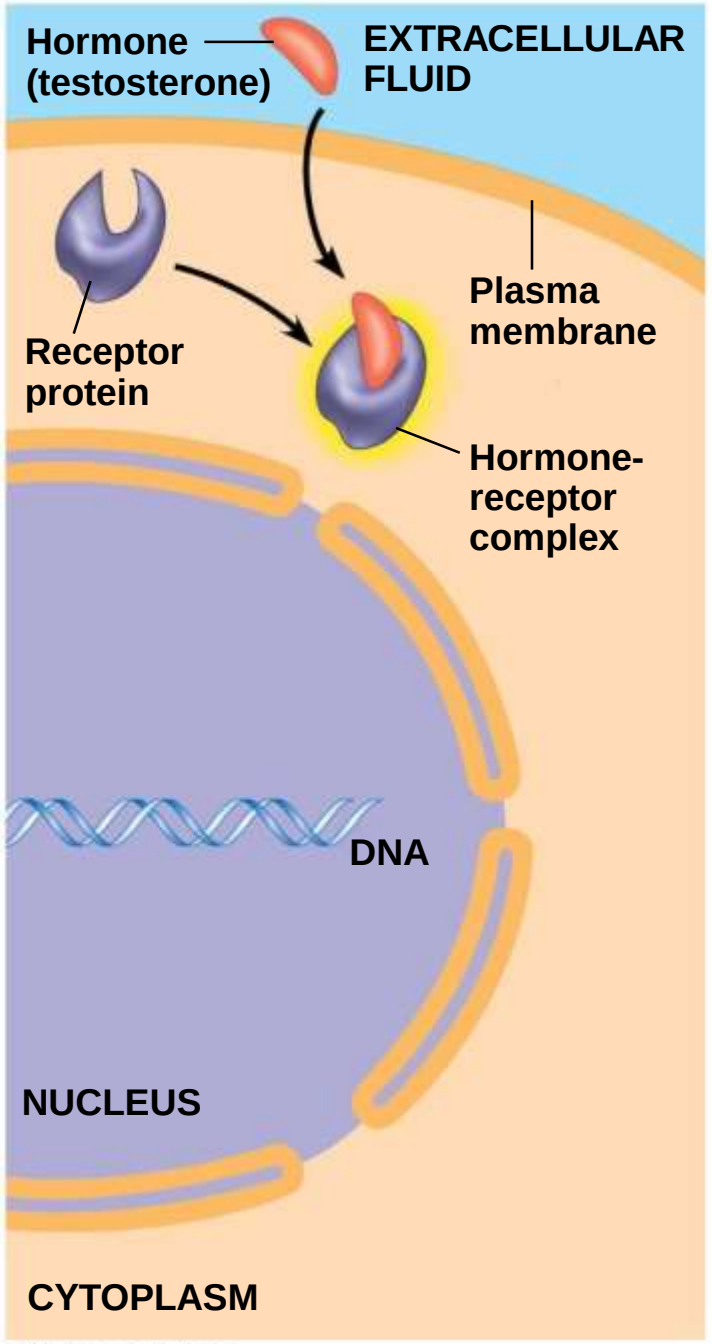
- A **ligand-gated ion channel** receptor acts as a gate when the receptor changes shape
- When a signal molecule binds as a ligand to the receptor, the gate allows specific ions, such as Na^{+} or Ca^{2+}, through a channel in the receptor

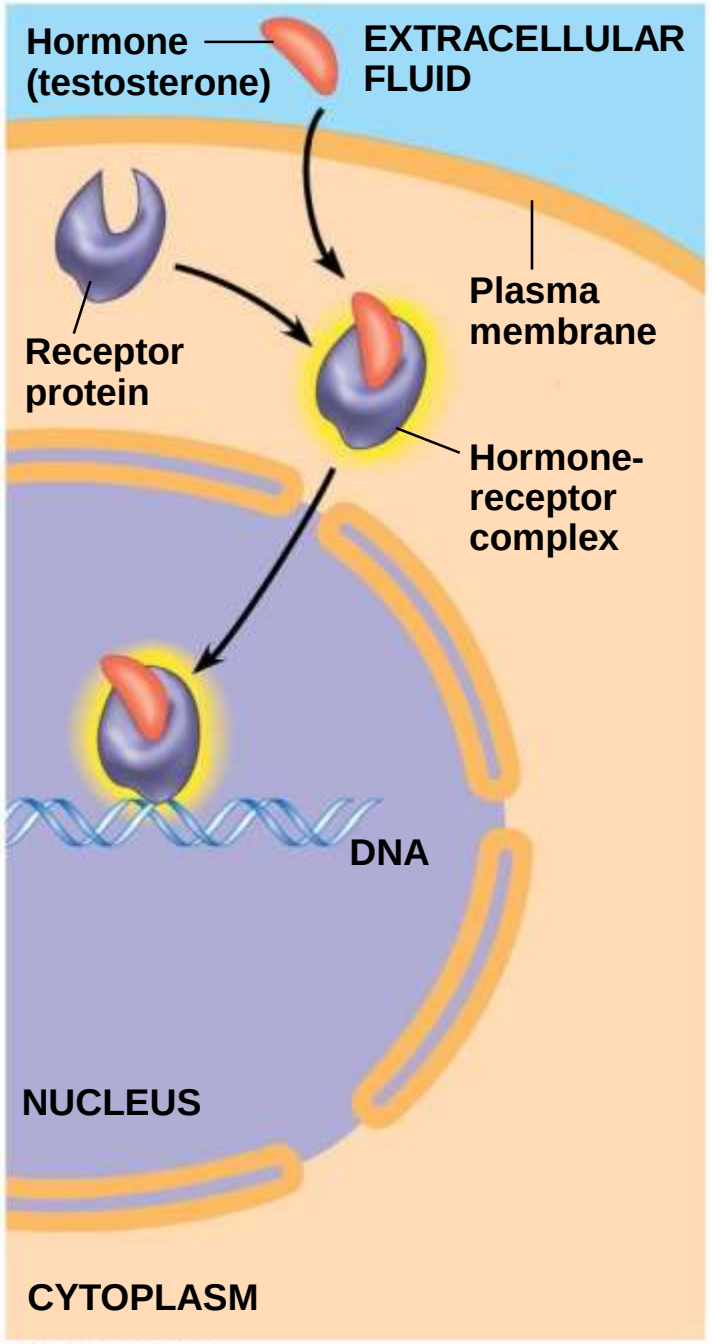


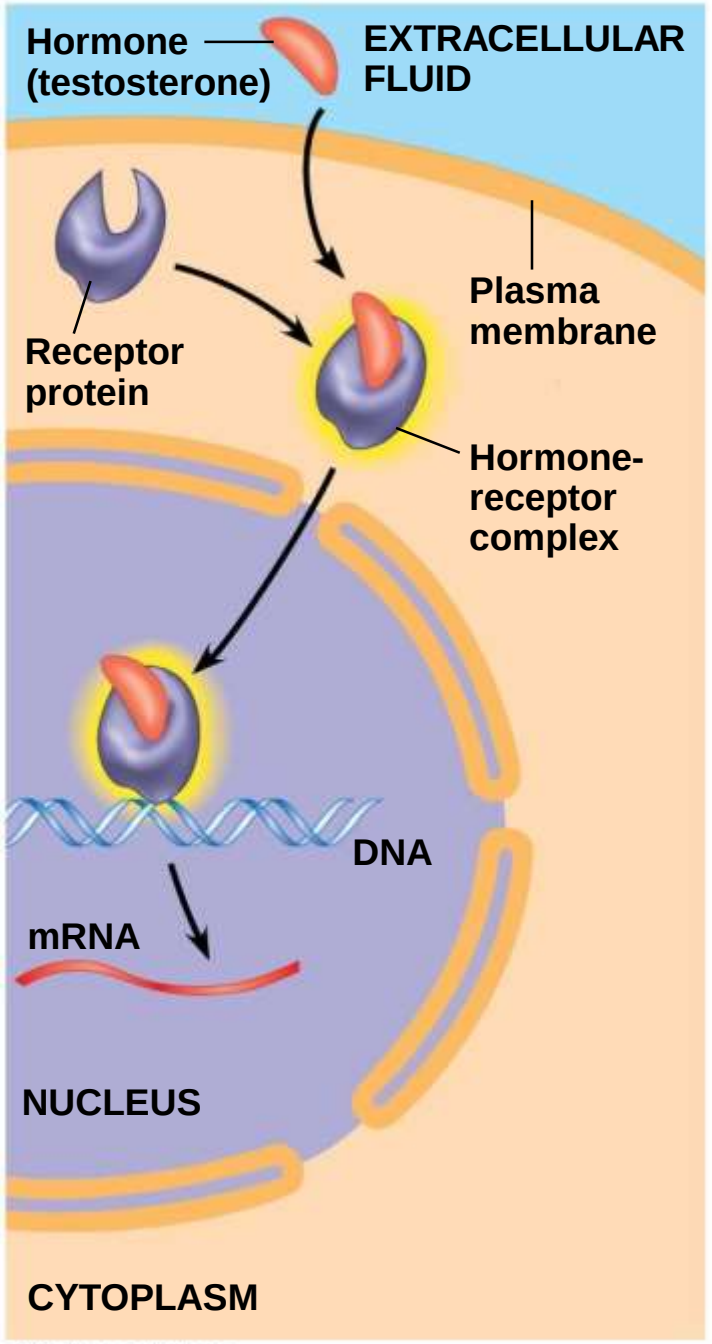
Intracellular Receptors

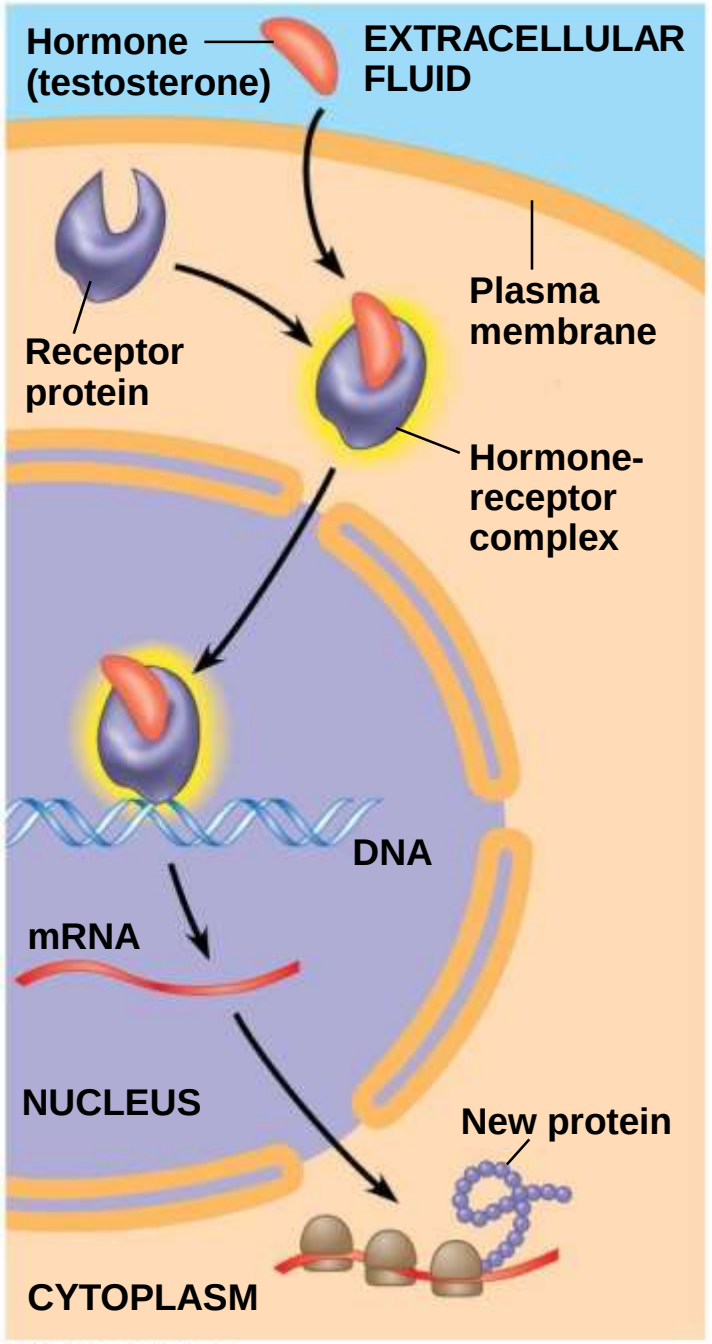
- Intracellular receptor proteins are found in the cytosol or nucleus of target cells
- Small or hydrophobic chemical messengers can readily cross the membrane and activate receptors
- Examples of hydrophobic messengers are the steroid and thyroid hormones of animals
- An activated hormone-receptor complex can act as a transcription factor, turning on specific genes











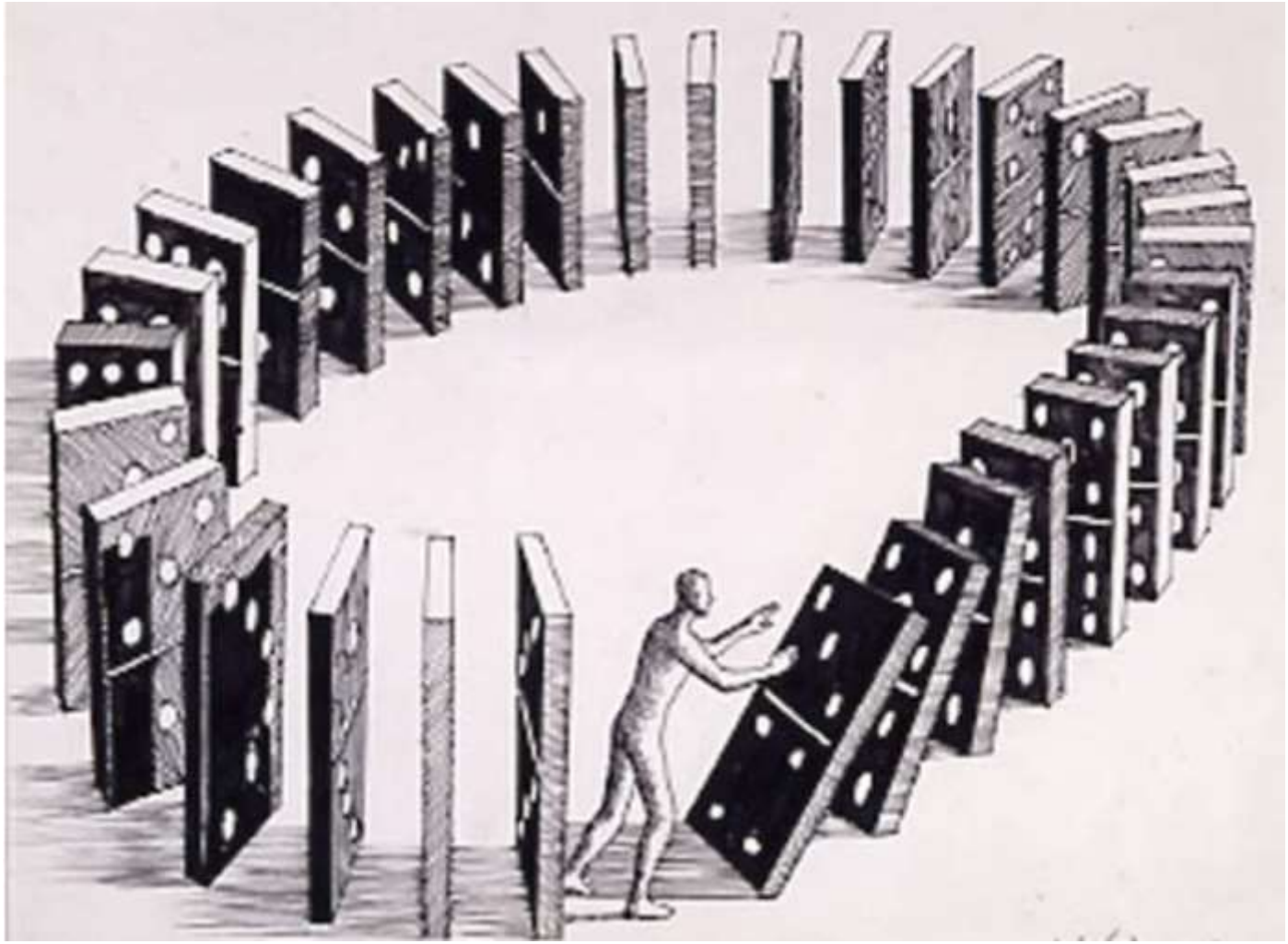
Transduction: Cascades of molecular interactions relay signals from receptors to target molecules in the cell

- Signal transduction usually involves multiple steps
- Multistep pathways can amplify a signal: A few molecules can produce a large cellular response
- Multistep pathways provide more opportunities for coordination and regulation of the cellular response

Signal Transduction Pathways

- The molecules that relay a signal from receptor to response are mostly proteins
- Like falling sequential dominoes, the receptor activates another protein, which activates another, and so on, until the protein producing the response is activated
- At each step, the signal is transduced into a different form, usually a shape change in a protein

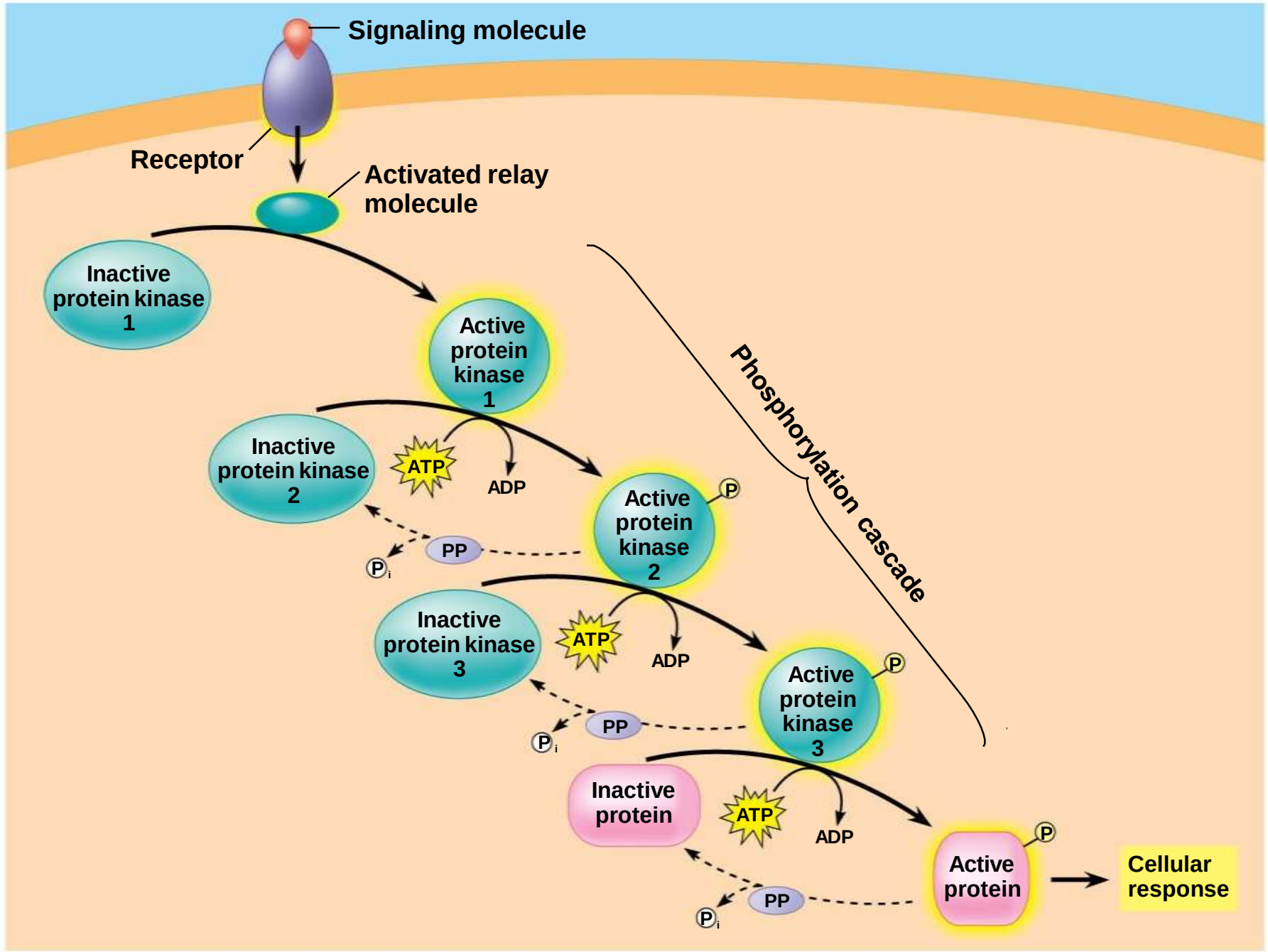
Falling Dominoes

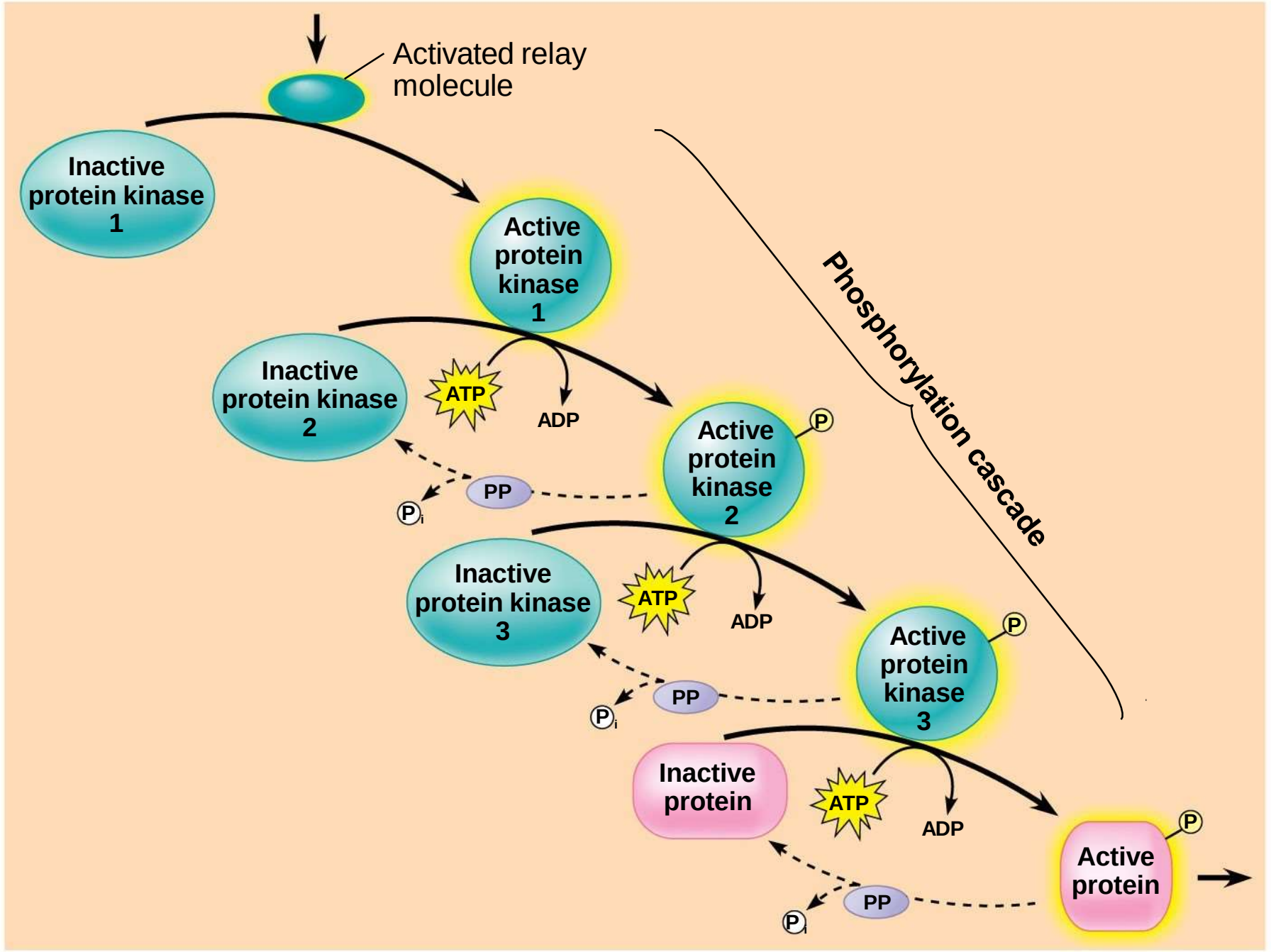


Protein Phosphorylation and Dephosphorylation

- In many pathways, the signal is transmitted by a cascade of protein phosphorylations
- **Protein kinases** transfer phosphates from ATP to protein, a process called phosphorylation

- **Protein phosphatases** remove the phosphates from proteins, a process called dephosphorylation
- This phosphorylation and dephosphorylation system acts as a molecular switch, turning activities on and off or up or down, as required



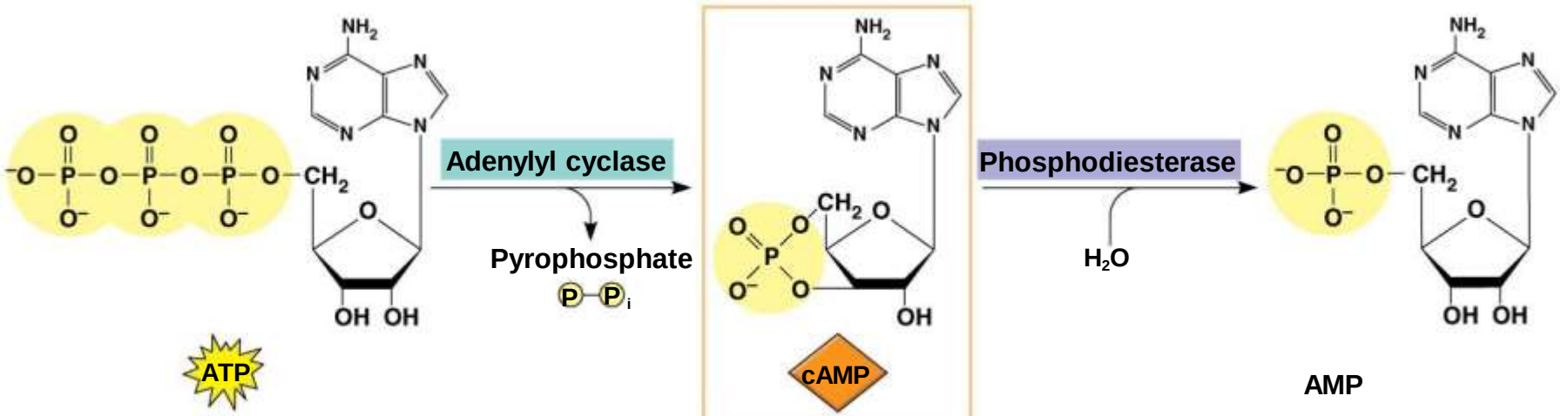


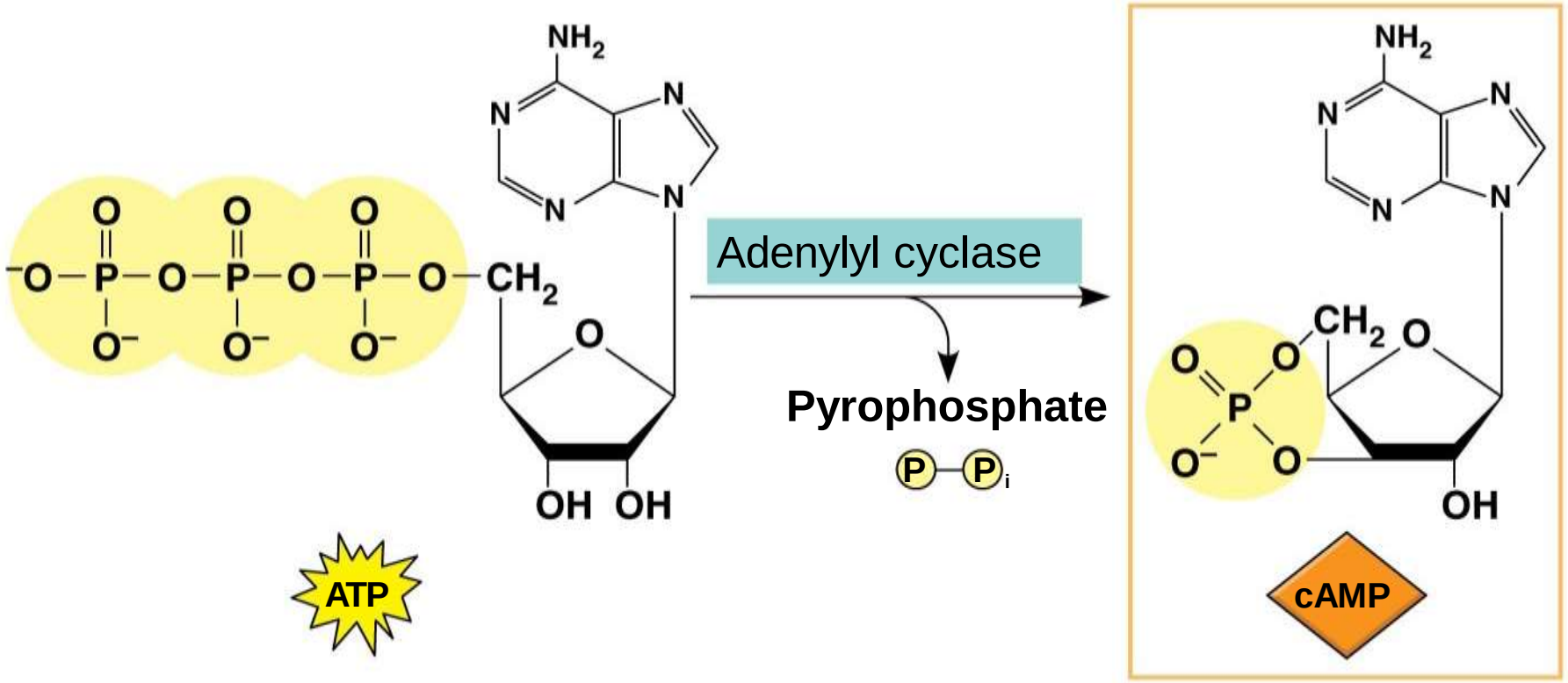
Small Molecules and Ions as Second Messengers

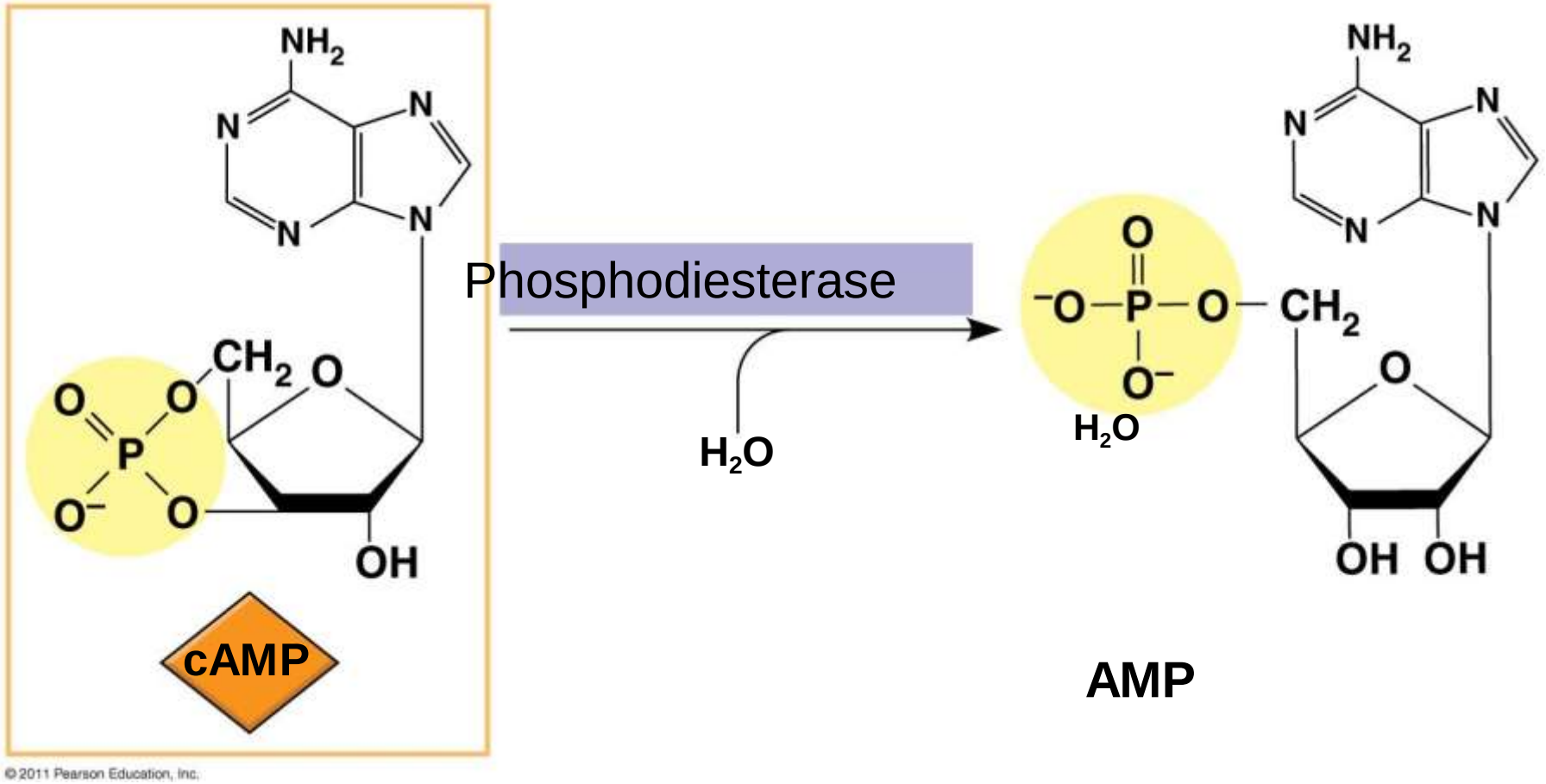
- The extracellular signal molecule (ligand) that binds to the receptor is a pathway's "first messenger"
- **Second messengers** are small, nonprotein, water-soluble molecules or ions that spread throughout a cell by diffusion
- Second messengers participate in pathways initiated by GPCRs and RTKs
- Cyclic AMP and calcium ions are common second messengers

Cyclic-AMP

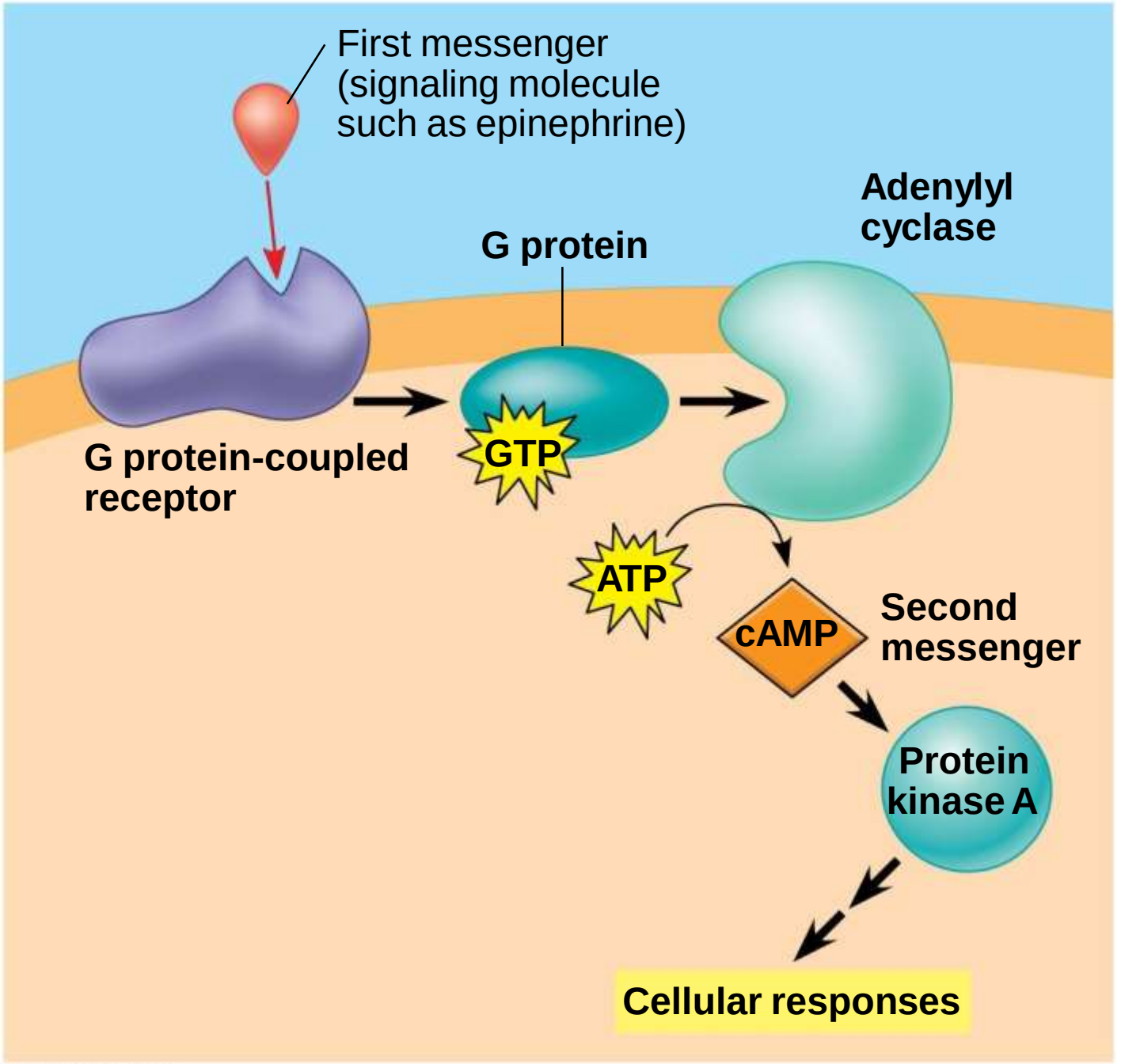
- **Cyclic AMP (cAMP)** is one of the most widely used second messengers
- **Adenylyl cyclase**, an enzyme in the plasma membrane, converts ATP to cAMP in response to an extracellular signal





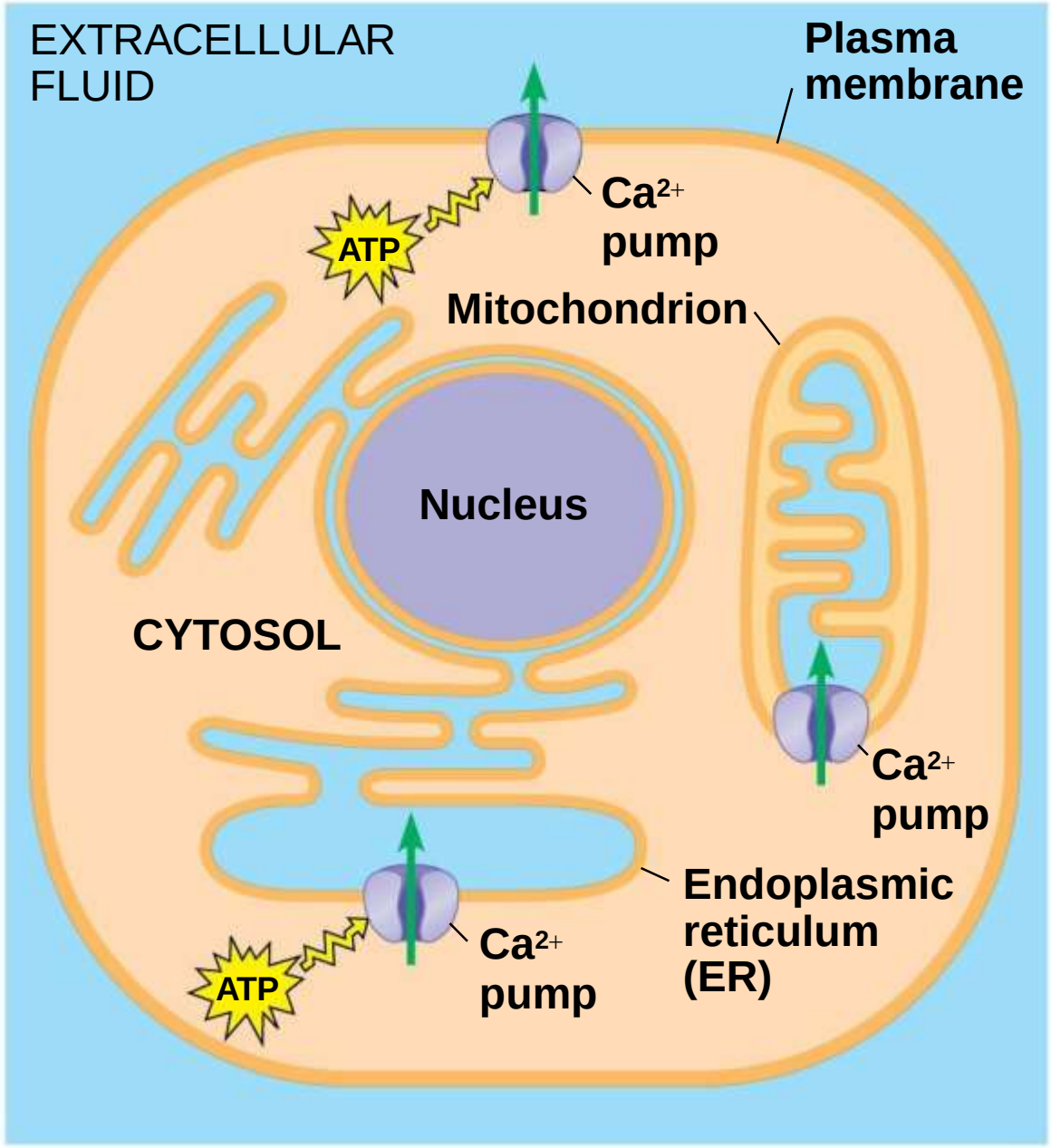


- Many signal molecules trigger formation of cAMP
- Other components of cAMP pathways are G proteins, G protein-coupled receptors, and protein kinases
- cAMP usually activates protein kinase A, which phosphorylates various other proteins
- Other type of regulation of cell metabolism is provided by G-protein systems that inhibit adenylyl cyclase

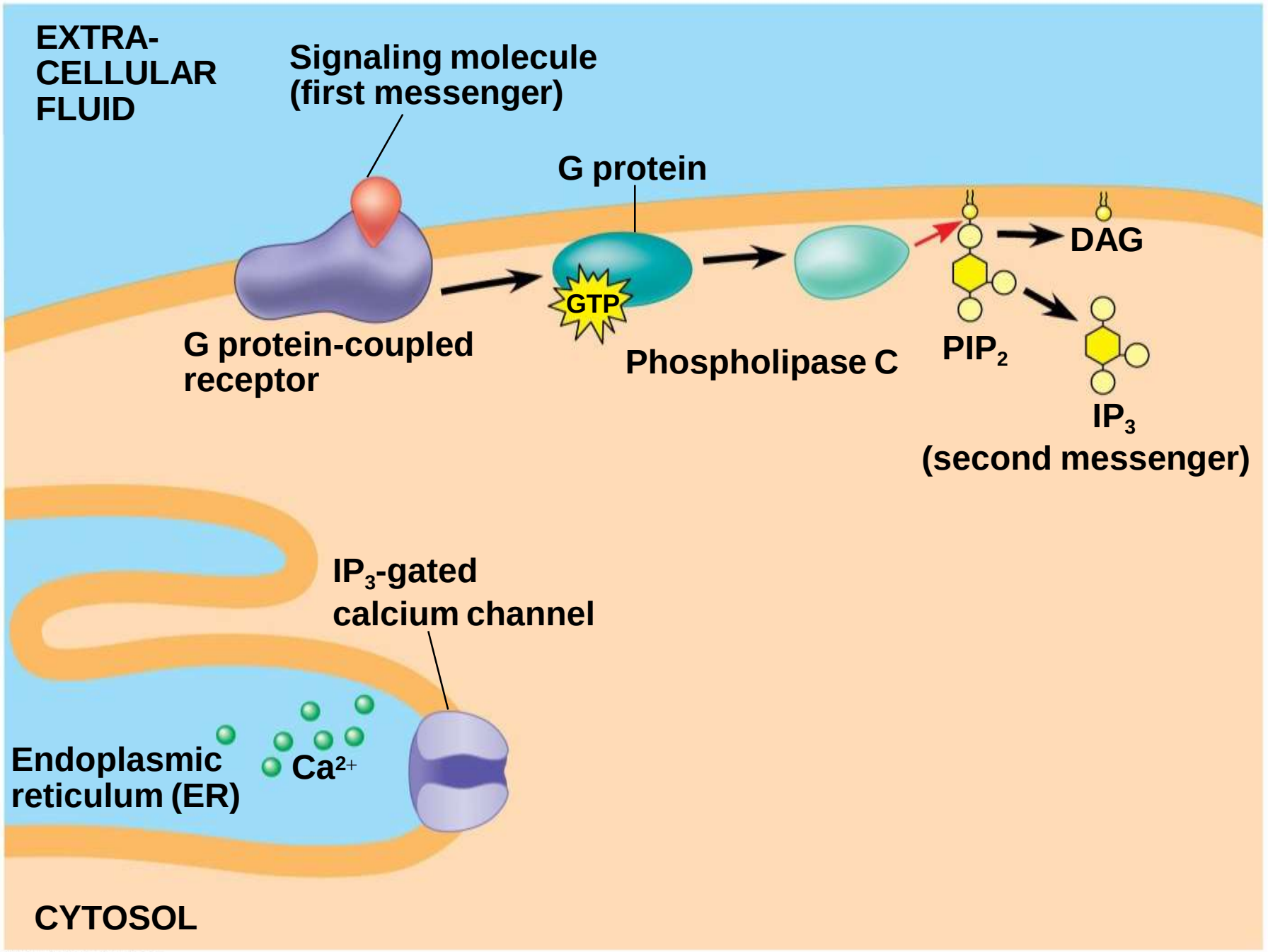


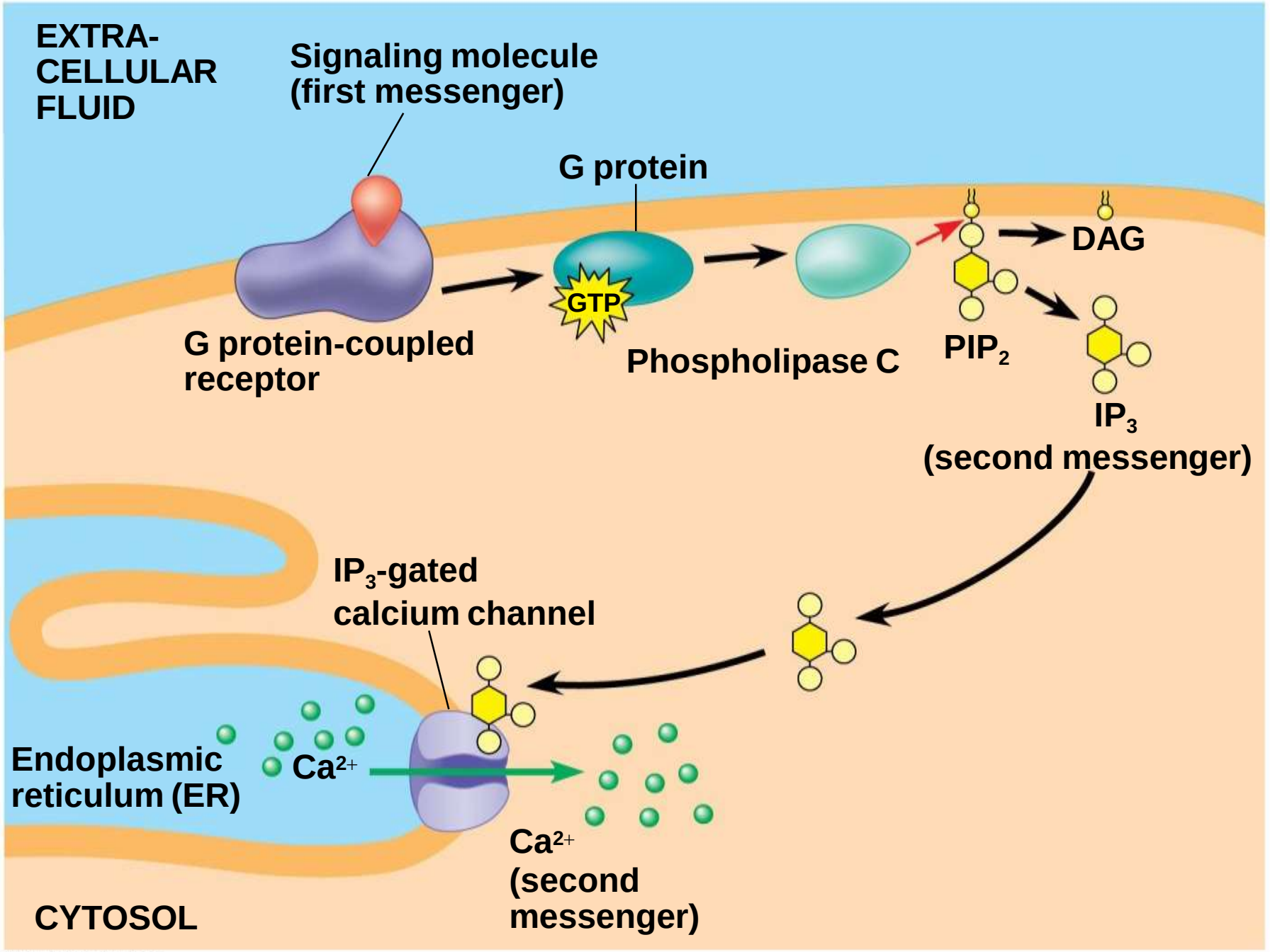
Calcium Ions and Inositol Triphosphate (IP_3)

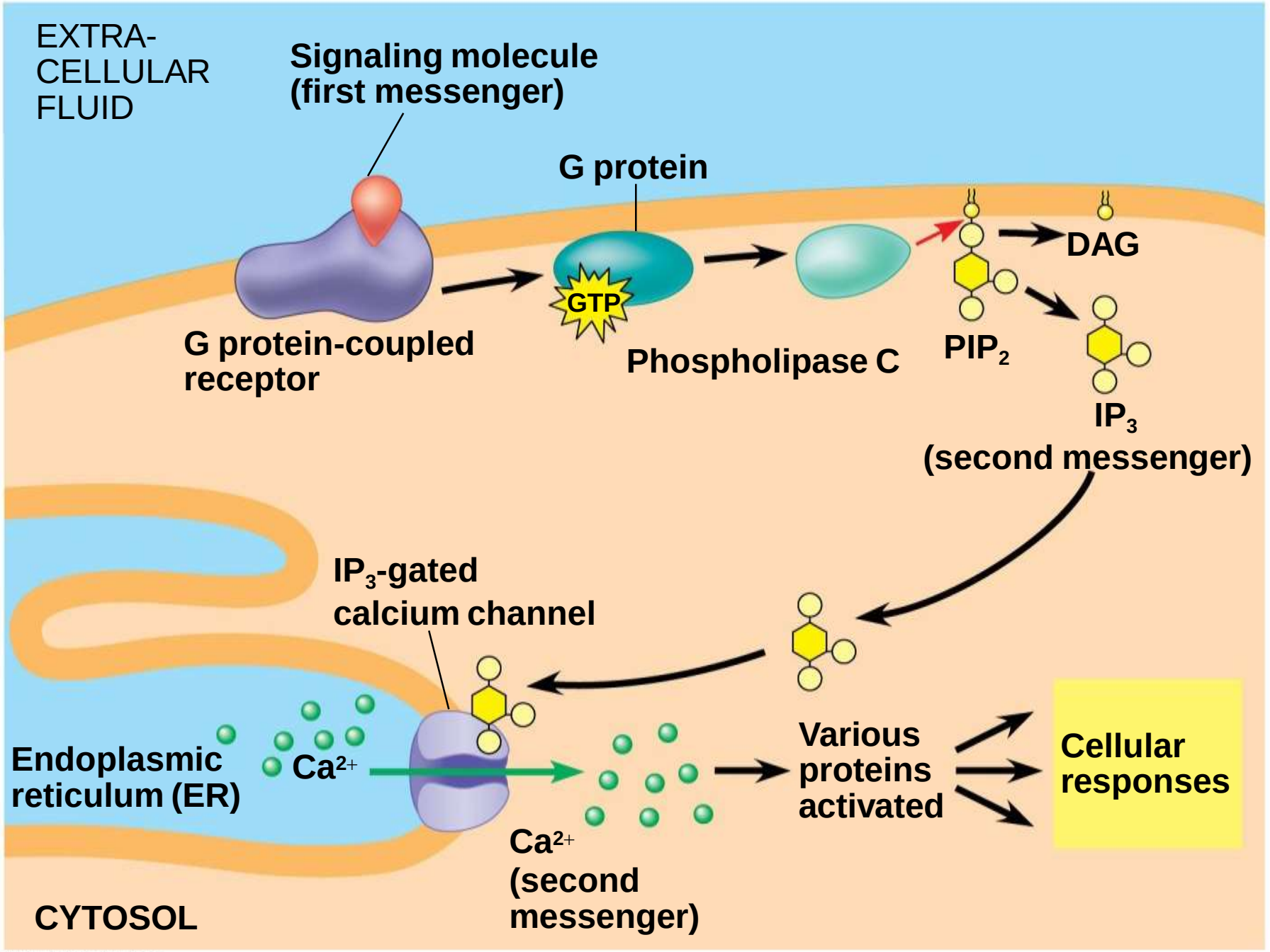
- Calcium ions (Ca^{2+}) act as a second messenger in many pathways
- Calcium is an important second messenger because cells can regulate its concentration



- A signal relayed by a signal transduction pathway may trigger an increase in calcium in the cytosol
- Pathways leading to the release of calcium involve **inositol triphosphate (IP_3)** and **diacylglycerol (DAG)** as additional second messengers





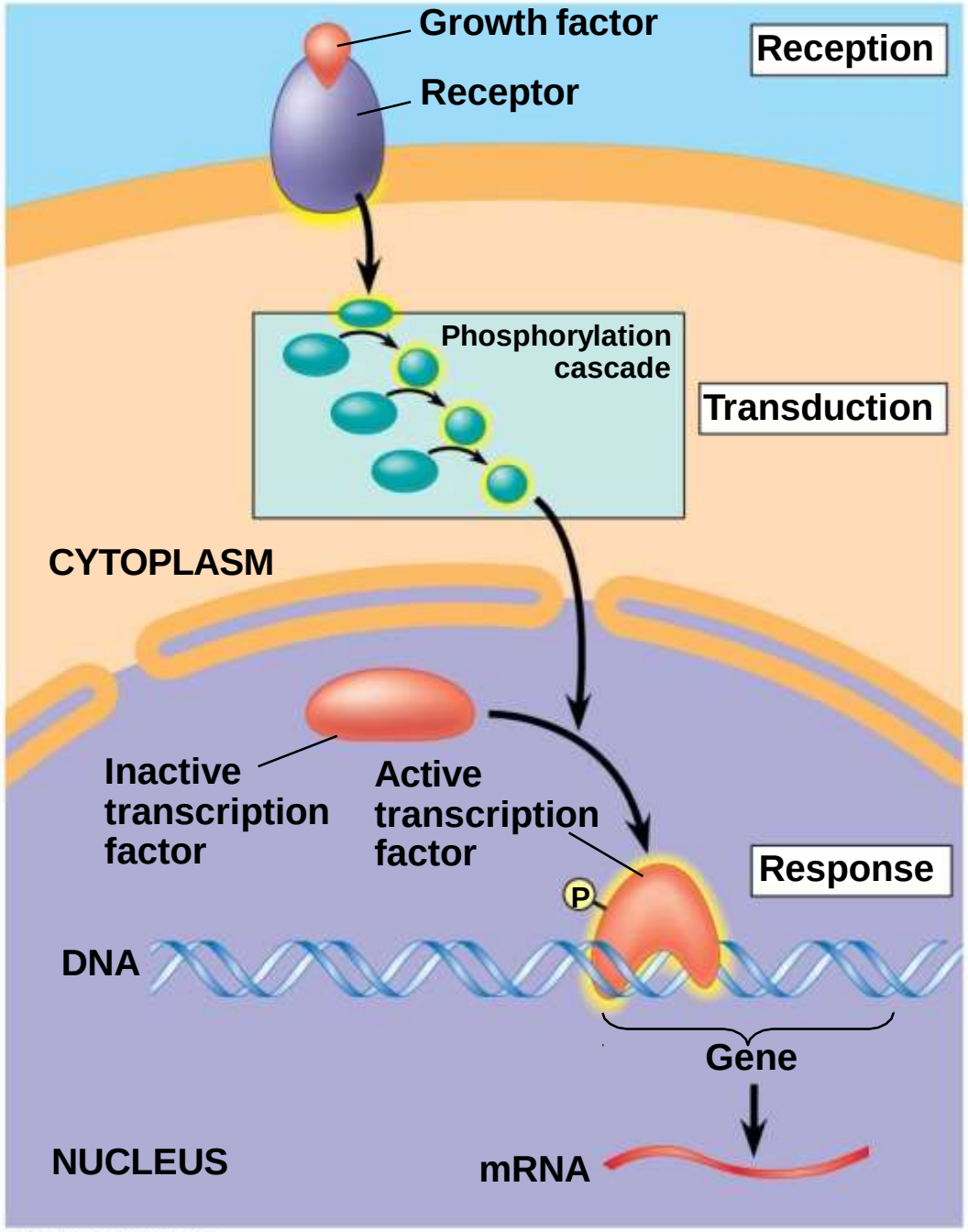


Response: Cell signaling leads to regulation of transcription or cytoplasmic activities

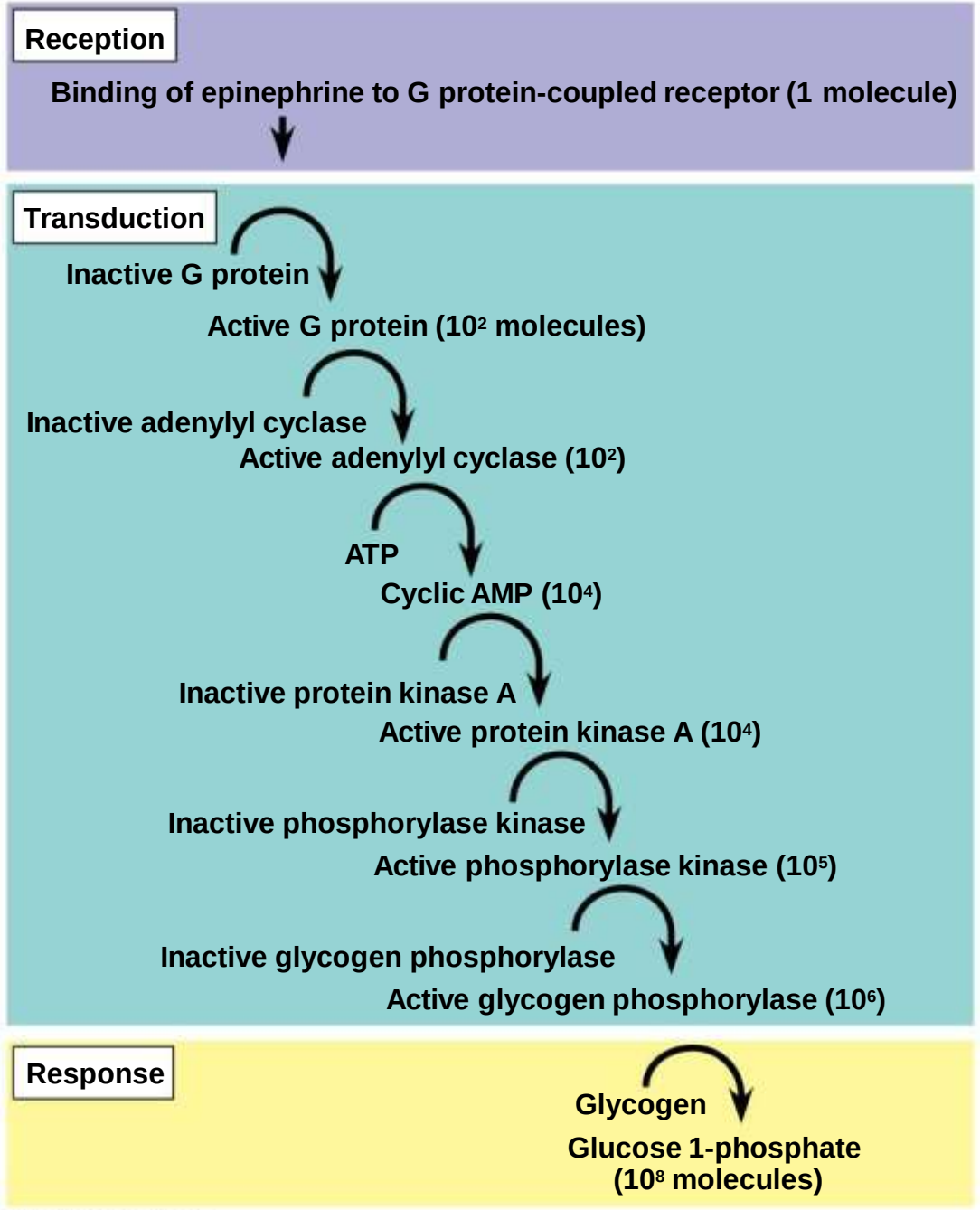
- The cell's response to an extracellular signal is sometimes called the "output response"

Nuclear and Cytoplasmic Responses

- Ultimately, a signal transduction pathway leads to regulation of one or more cellular activities
- The response may occur in the cytoplasm or in the nucleus
- Many signaling pathways regulate the synthesis of enzymes or other proteins, usually by turning genes on or off in the nucleus
- The final activated molecule in the signaling pathway may function as a transcription factor



- Other pathways regulate the activity of enzymes rather than their synthesis



Cell Communication

- A cell's response to a signal often involves activating or inactivating proteins.
- Phosphorylation is a common way to change the activity of a protein.
- **protein kinase** – an enzyme that adds a phosphate to a protein
- **phosphatase** – an enzyme that removes a phosphate from a protein

- Signaling pathways can also affect the overall behavior of a cell, for example, changes in cell shape

Cell-to-Cell Interactions

- Cells can identify each other by cell surface markers.
- -glycolipids are commonly used as tissue- specific markers
- -major histocompatibility complex (MHC) proteins are used by cells to distinguish “self” from “non-self”

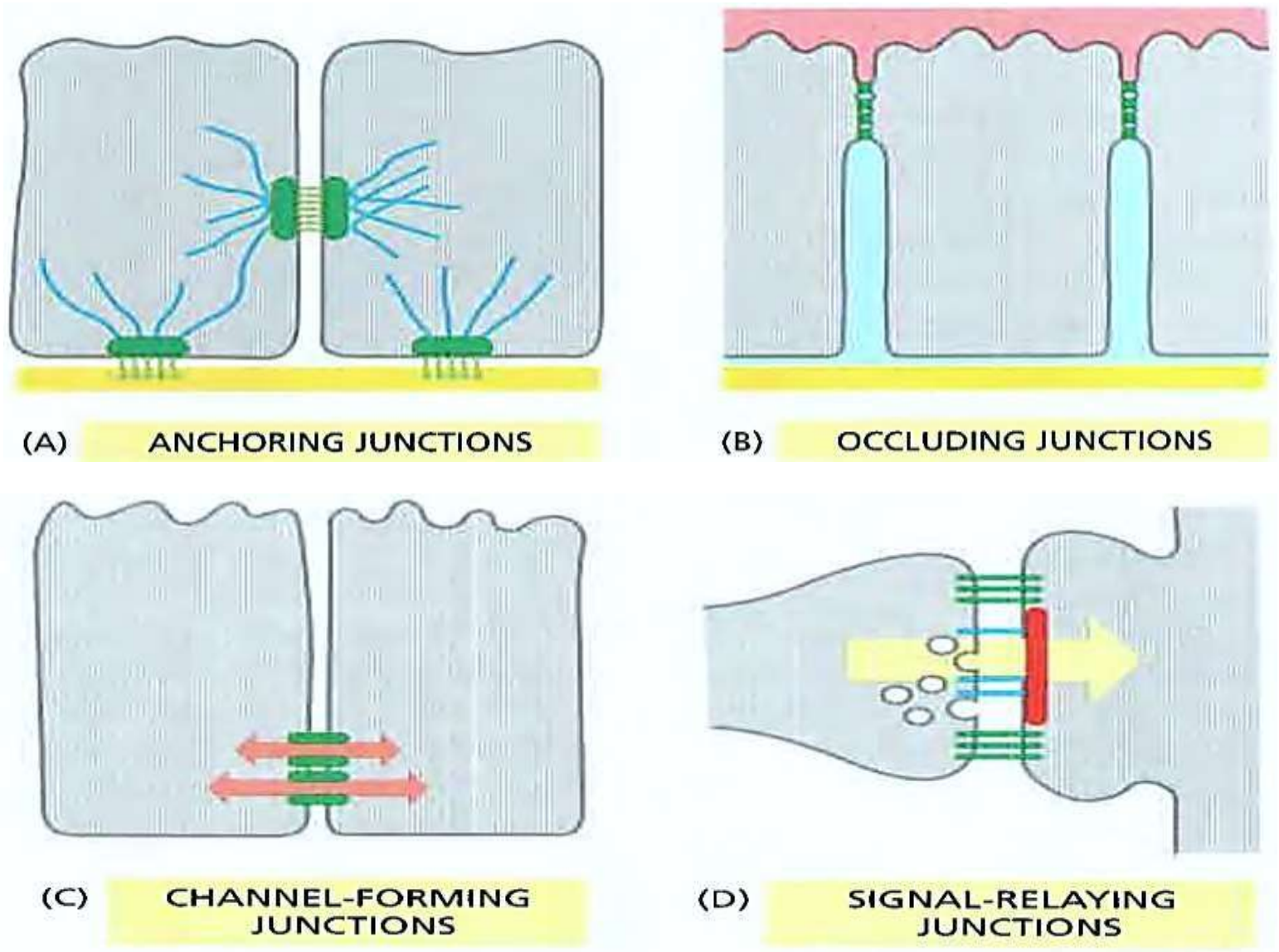
Cell-to-Cell Interactions

Cells within a tissue are connected to each other by **cell junctions**

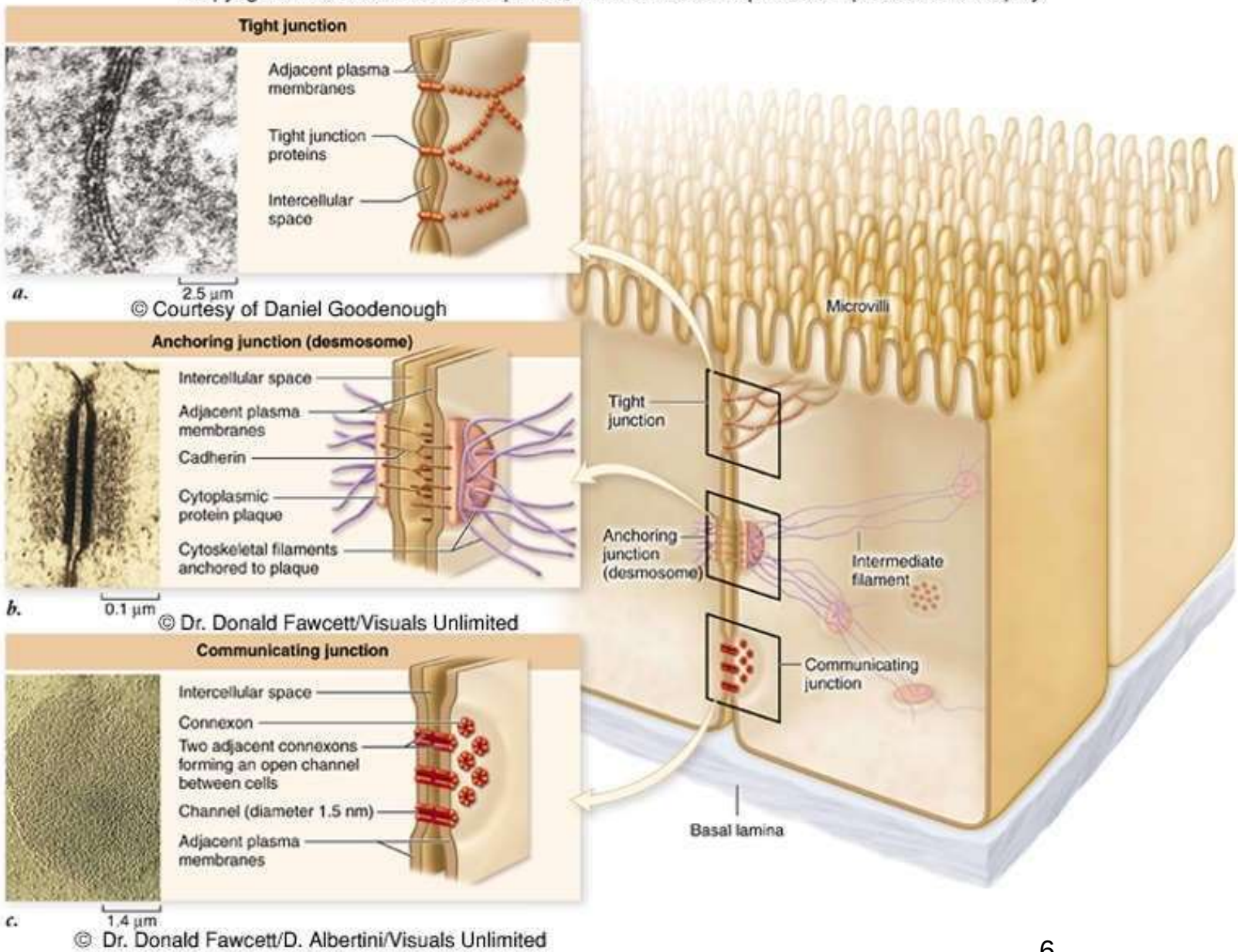
1. **Anchoring junctions** – connect the cytoskeletons of adjacent cells
2. **Tight junctions (occluding junctions)** – create sheets of cells
3. **Signal-relaying junctions**
4. **Communicating (channel forming) junctions** – permit small molecules to pass between cells

   - **gap junctions**

Major Adhesive Interactions



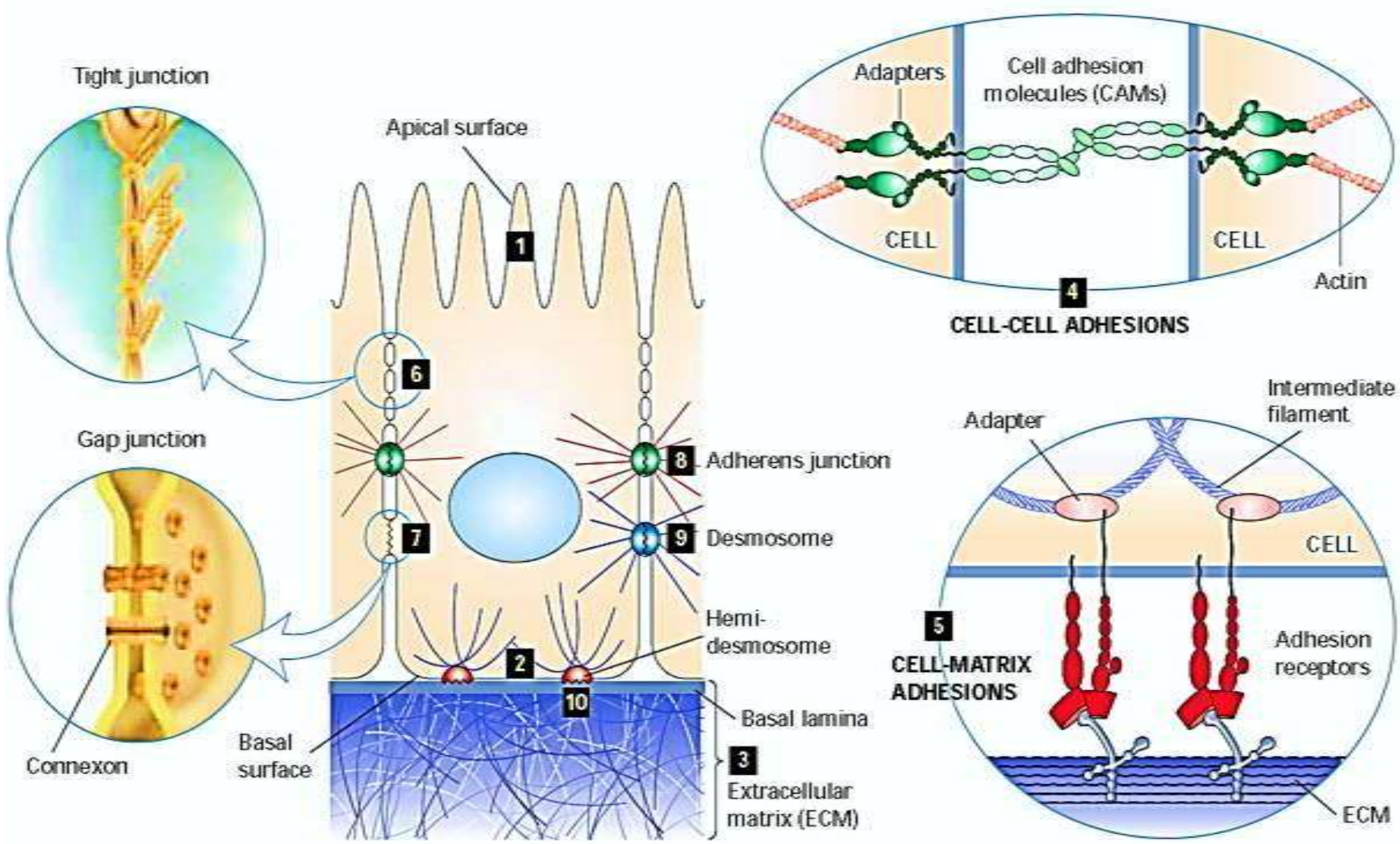
Molecular Biology of the Cell (2008, Garland Publishing)



Cell-Cell Interactions

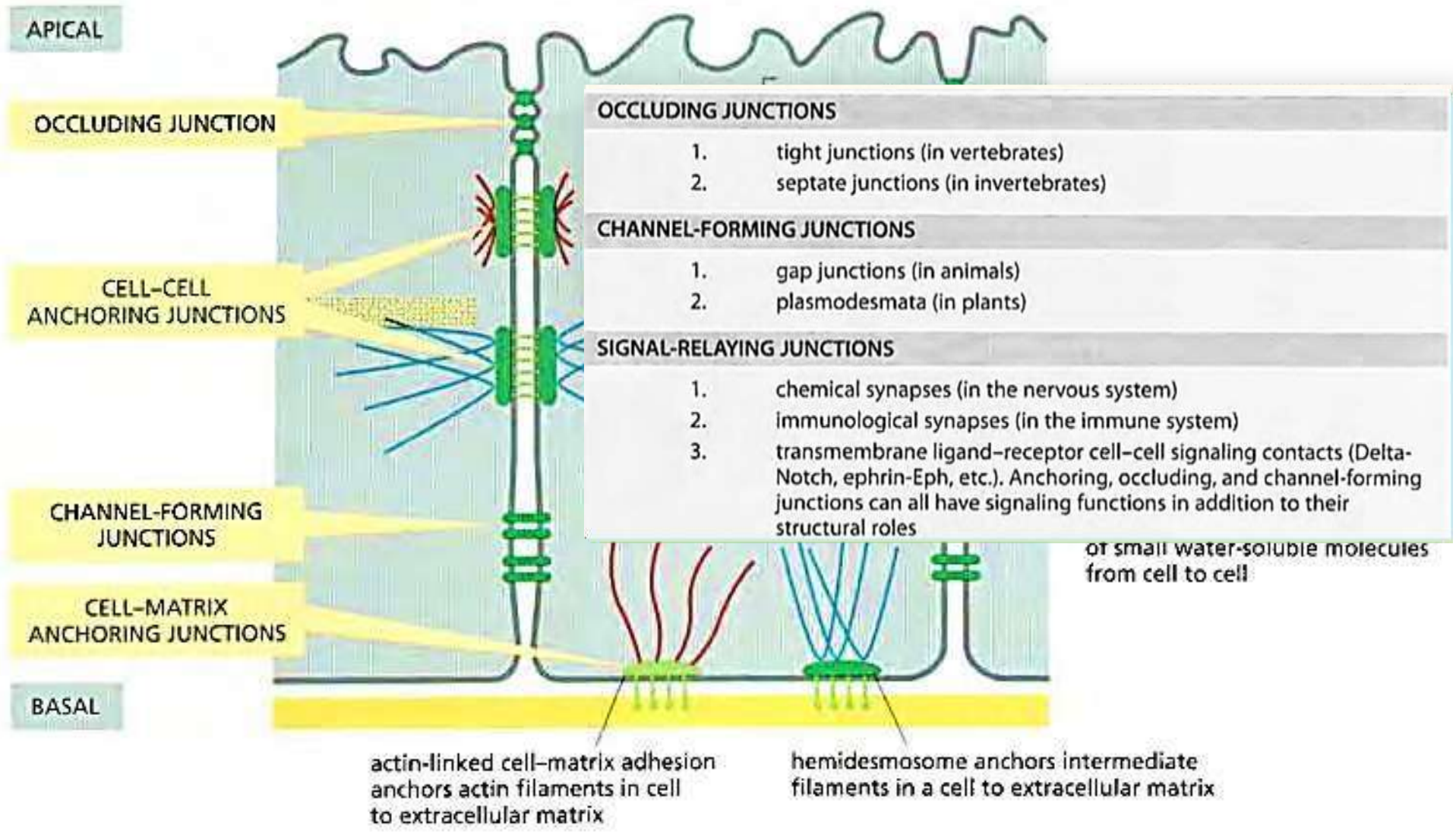
- Cell Signals one another with chemicals (Cell Signalling)
- Integration of cells into tissues : Cell surface Proteins Mediates Cell-Cell Interactions
  - Expression of cell identity
  - Cell-Cell adhesion-(via cell adhesion molecules or CAMs)
  - Cell matrix adhesion
- CAMs and ECM can bind cell together, and transfer of information between the exterior and interior cells.

Major Adhesive Interactions



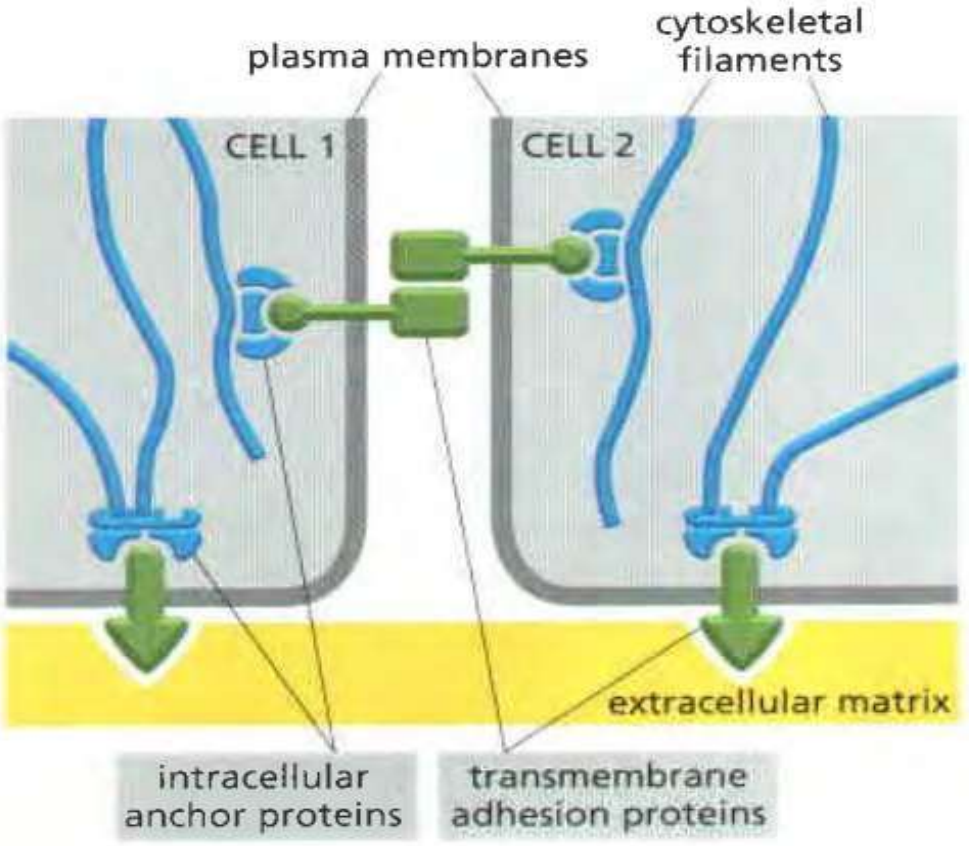
Molecular Cell Biology (2004, W H Freeman)

Major Adhesive Interactions



Molecular Biology of the Cell (2008, Garland Publishing)

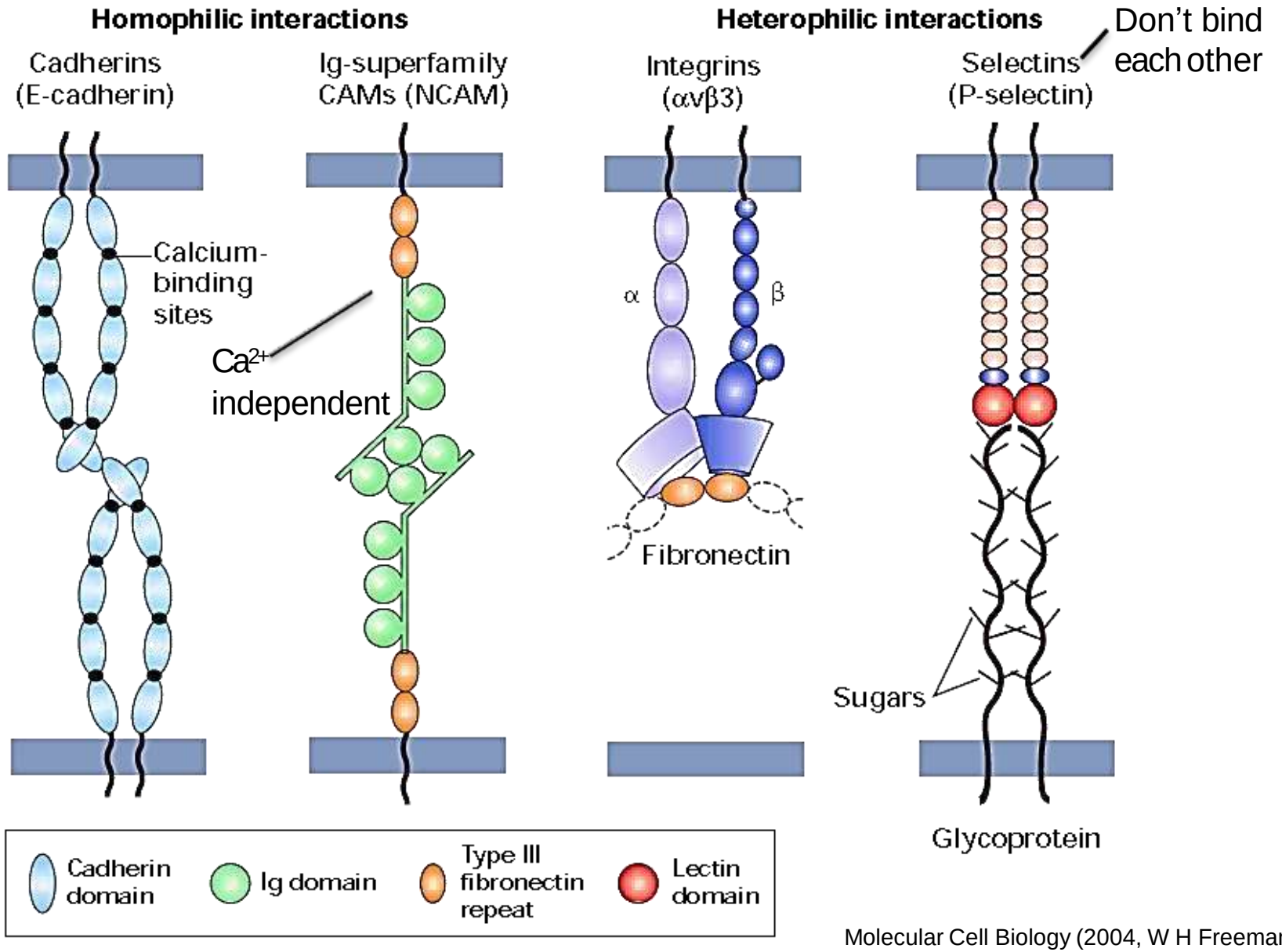
Transmembrane Adhesion Proteins



Molecular Biology of the Cell (2008, Garland Publishing)

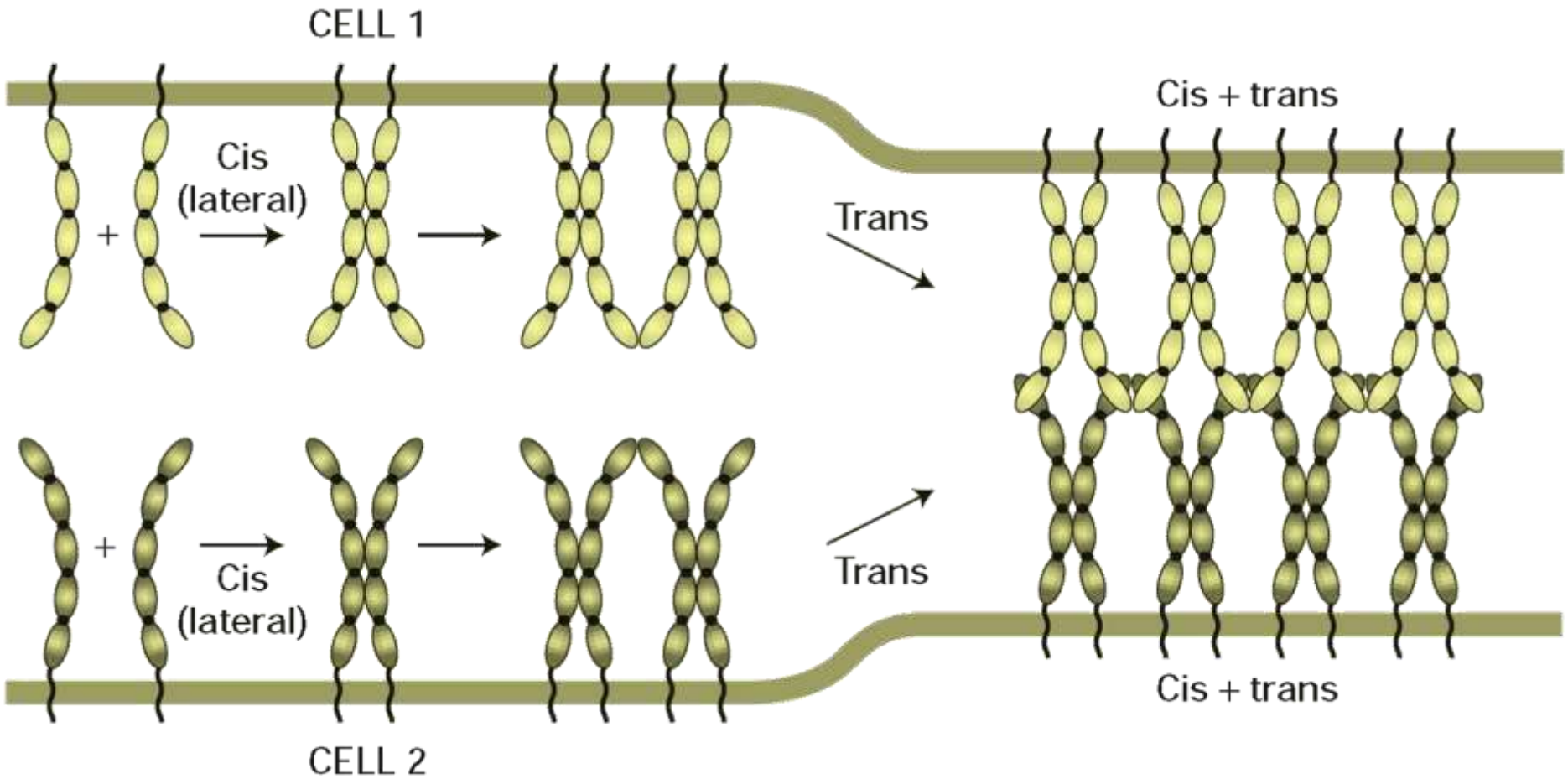
JUNCTION	TRANSMEMBRANE ADHESION PROTEIN	EXTRACELLULAR LIGAND	INTRACELLULAR CYTOSKELETAL ATTACHMENT	INTRACELLULAR ANCHOR PROTEIN
Cell-cell				
Adherens Junction	Cadherin (classical cadherin)	Cadherin in other cell	Actin filaments	α- catenin, β-catenin, plakoglobin (γ-catenin)
Desmosome	Cadherin (desmoglein, desmocollin)	desmoglein, desmocollin in other cell	Intermediate filaments	plakoglobin (γ-catenin), plakophilin, desmoplakin
Cell-Matrix				
Actin-linked cell-matrix adhesion	integrin	ECM proteins	Actin filaments	Talin, viculin etc.
Hemidesmosome	Integrin α6β4, type XVII collagen	ECM proteins	Intermediate filaments	Plectin, dystonin

Cell Adhesion Molecules (CAMs)



Molecular Cell Biology (2004, W H Freeman)

Cell Adhesion Molecules (CAMs)



Cadherins- Classical Vs Non-Classical

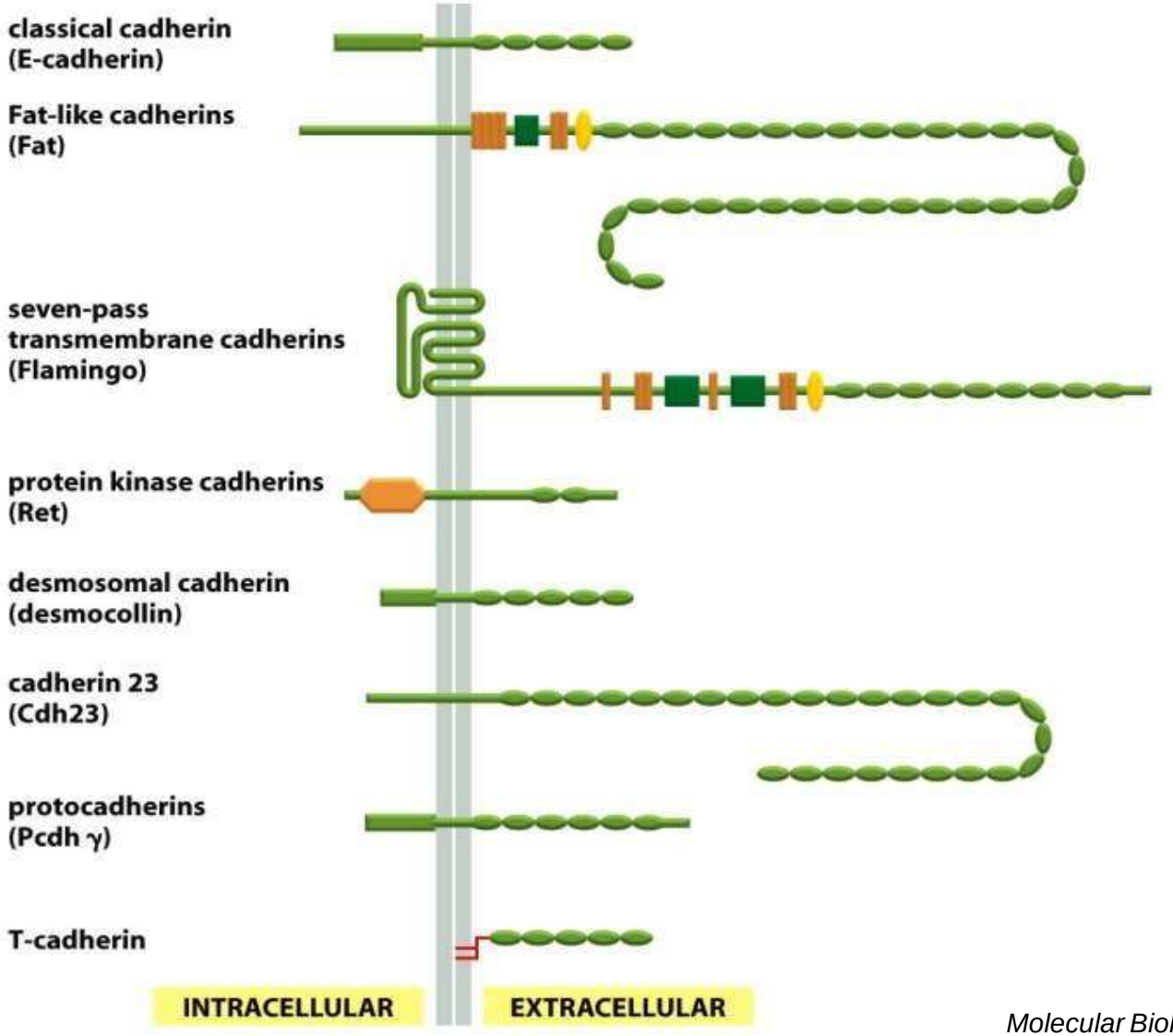
Name	Main Location
Classical (are major components of cell-cell adhesion)	
E- Cadherin	Expressed on early embryonic cells in mammals. Later becomes restricted to embryonic and adult epithelial tissue
N- Cadherin	First mesodermal, later CNS (Neurons, heart, skeletal m., kens and fibroblast)
P- Cadherin	Trophoblast cells (Placenta), epidermis, breast epithelium
VE- Cadherin	Endothelial cells

Non-Classical Cadherins

Desmosomal	**Desmocollin**	Skin
	Desmoglein	Skin
Lacks a transmembrane domain	**T-Cadherin**	Neurons, muscle and Heart
	Cadherin-23	Inner year, other epithelia
	Fat (*Drosophila*)	Epithelia and CNS
	Fat-1 (*Mammals*)	Epithelia and CNS
	α, β and γ-Protocadherins	Neurons
a Seven-Pass Transmembrane Cadherin	**Flamingo**	Sensory & some other epithelia

Cadherins and Cell-Cell Adhesion

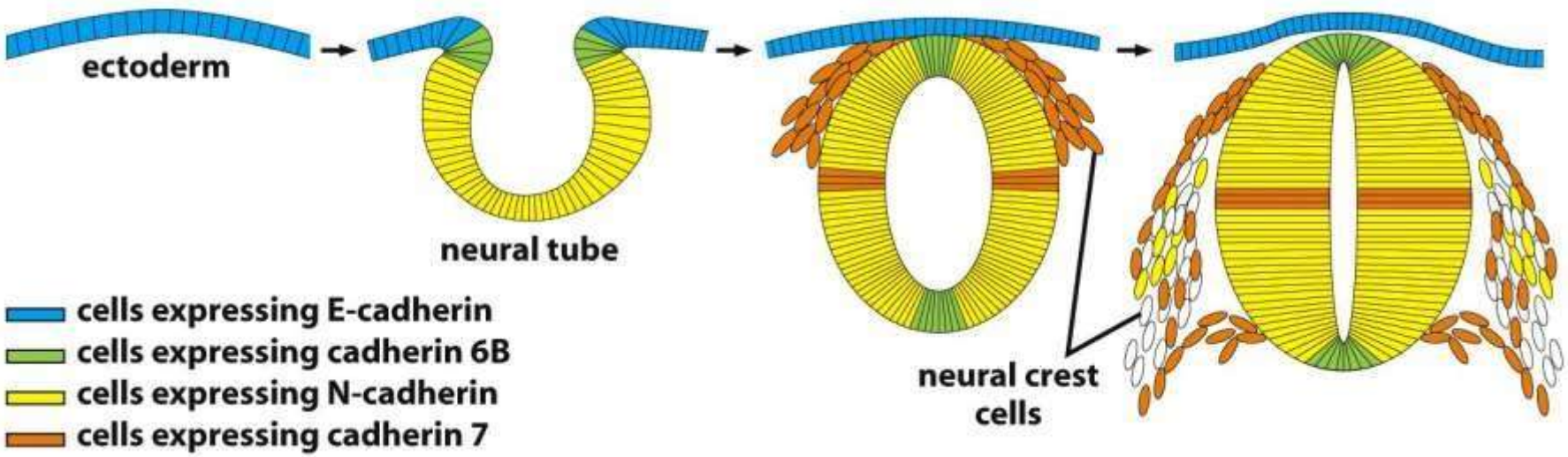
The C-terminal cytoplasmic domain associates with cytoskeleton



The N-terminal extracellular domains form dimer and through homoplilic interactions, form tetramers

Molecular Biology of the Cell (2008, Garland Publishing)

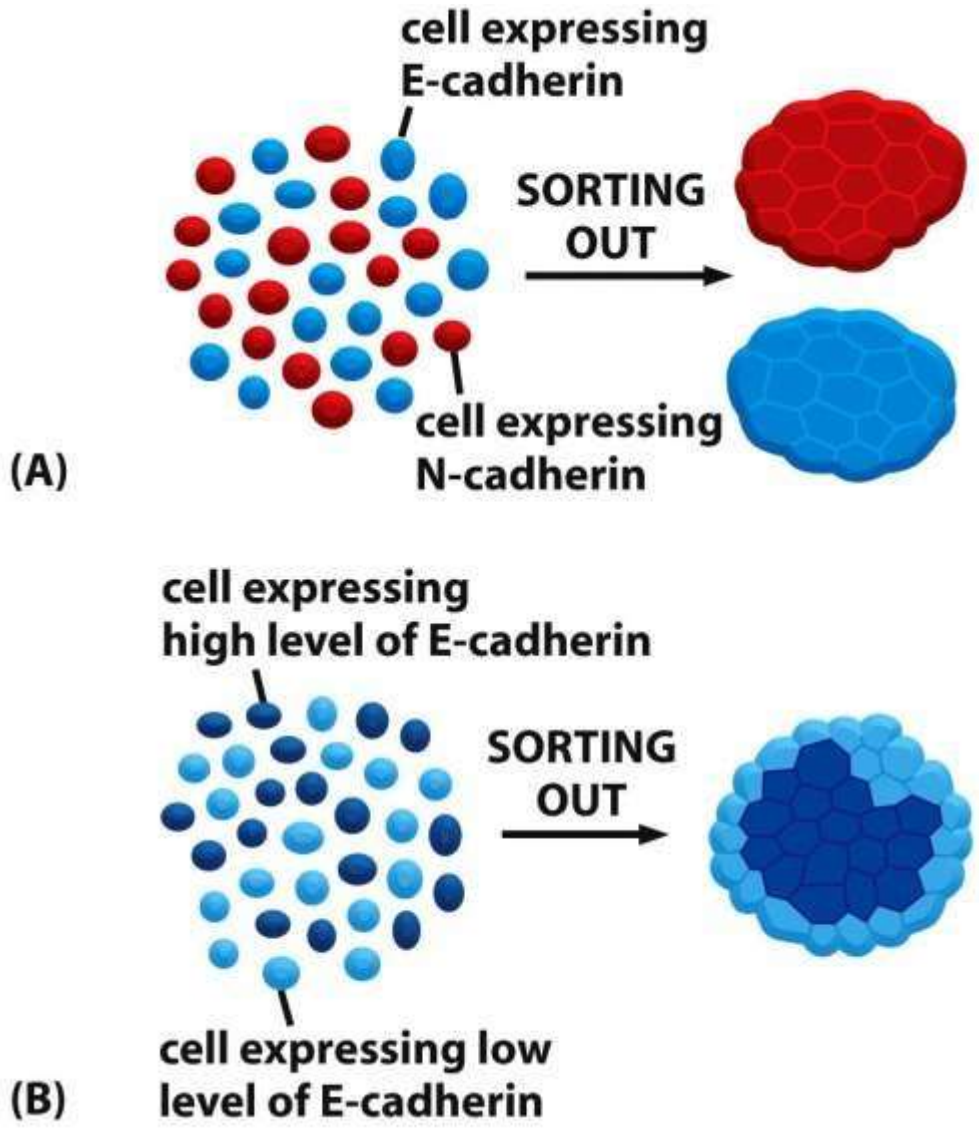
Cadherins and Cell-Cell Adhesion



The cells segregate according to the cadherins they express

Molecular Biology of the Cell (2008, Garland Publishing)

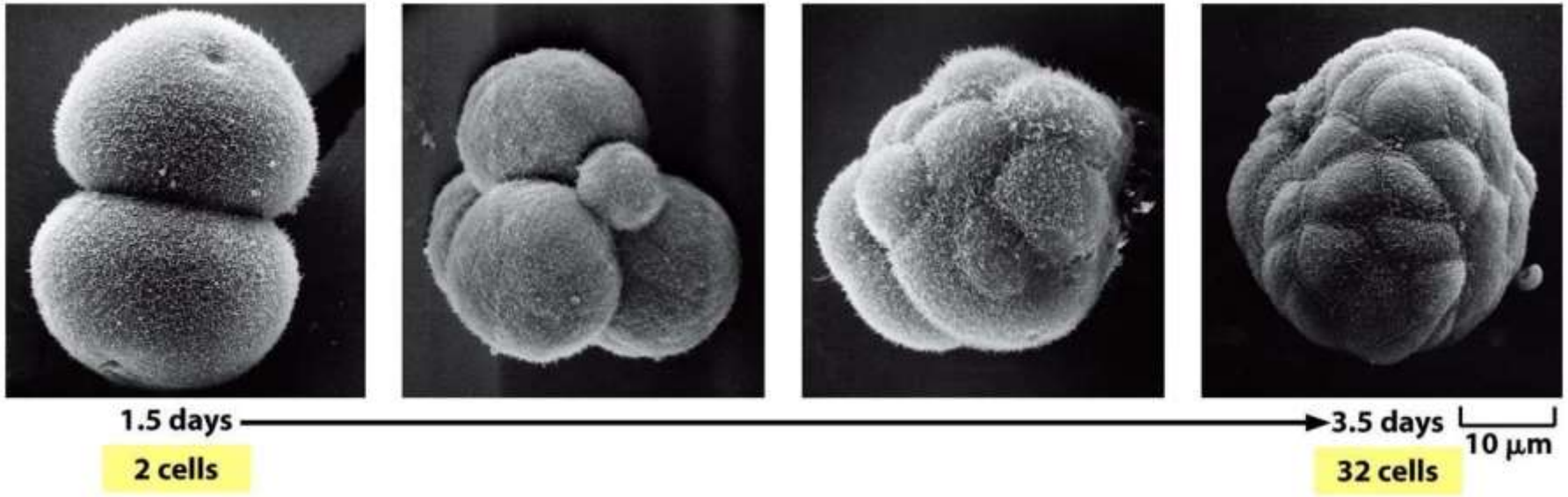
Cadherins and Cell-Cell Adhesion



Cadherin-dependent cell sorting

Molecular Biology of the Cell (2008, Garland Publishing)

Compaction of an Early Mouse Embryo



At eight-cell stage, begin to express E-cadherin

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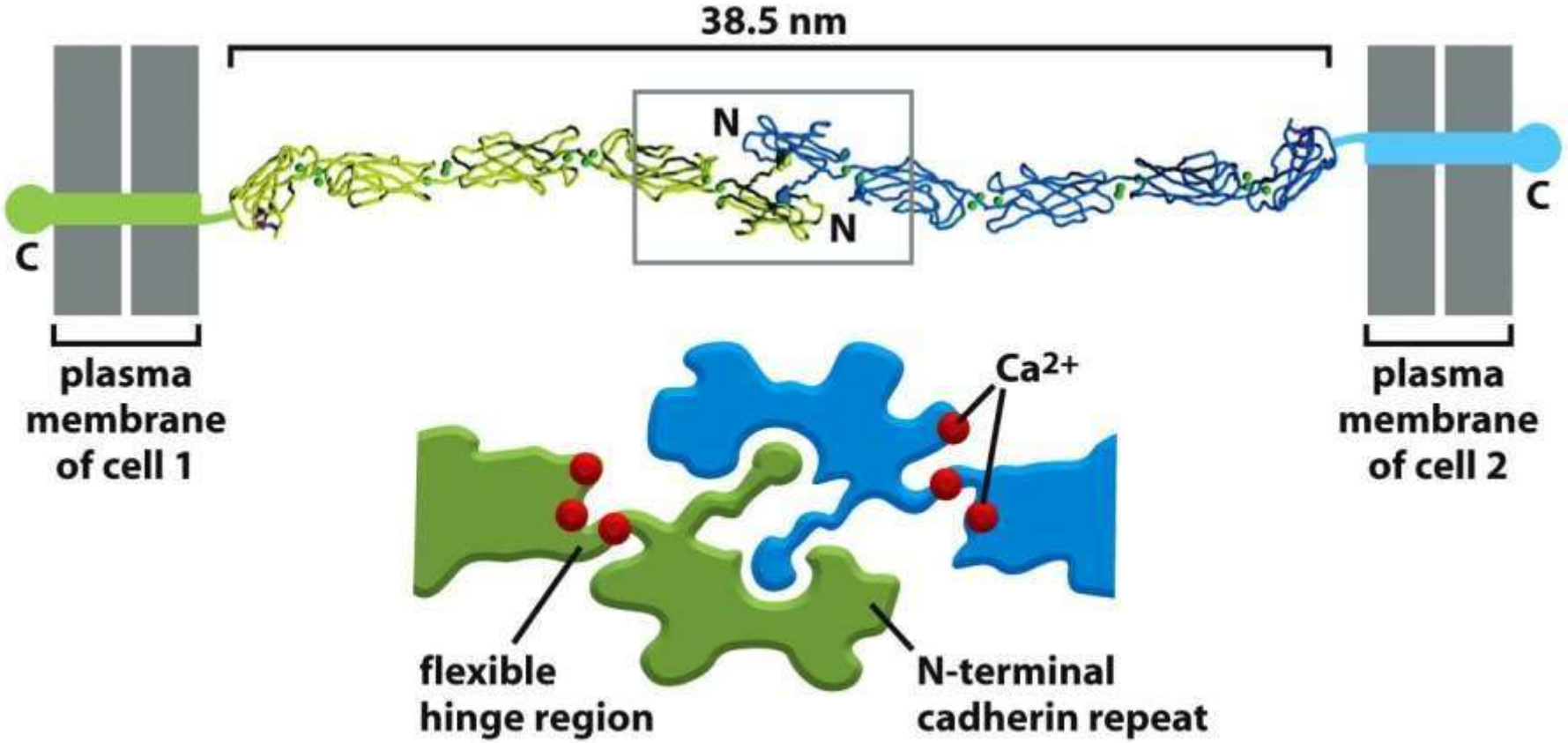
Cadherins mediate Ca^{2+}-dependent homophilic cell-cell adhesion



Extracellular domains of a classical cadherin (C-cadherin)

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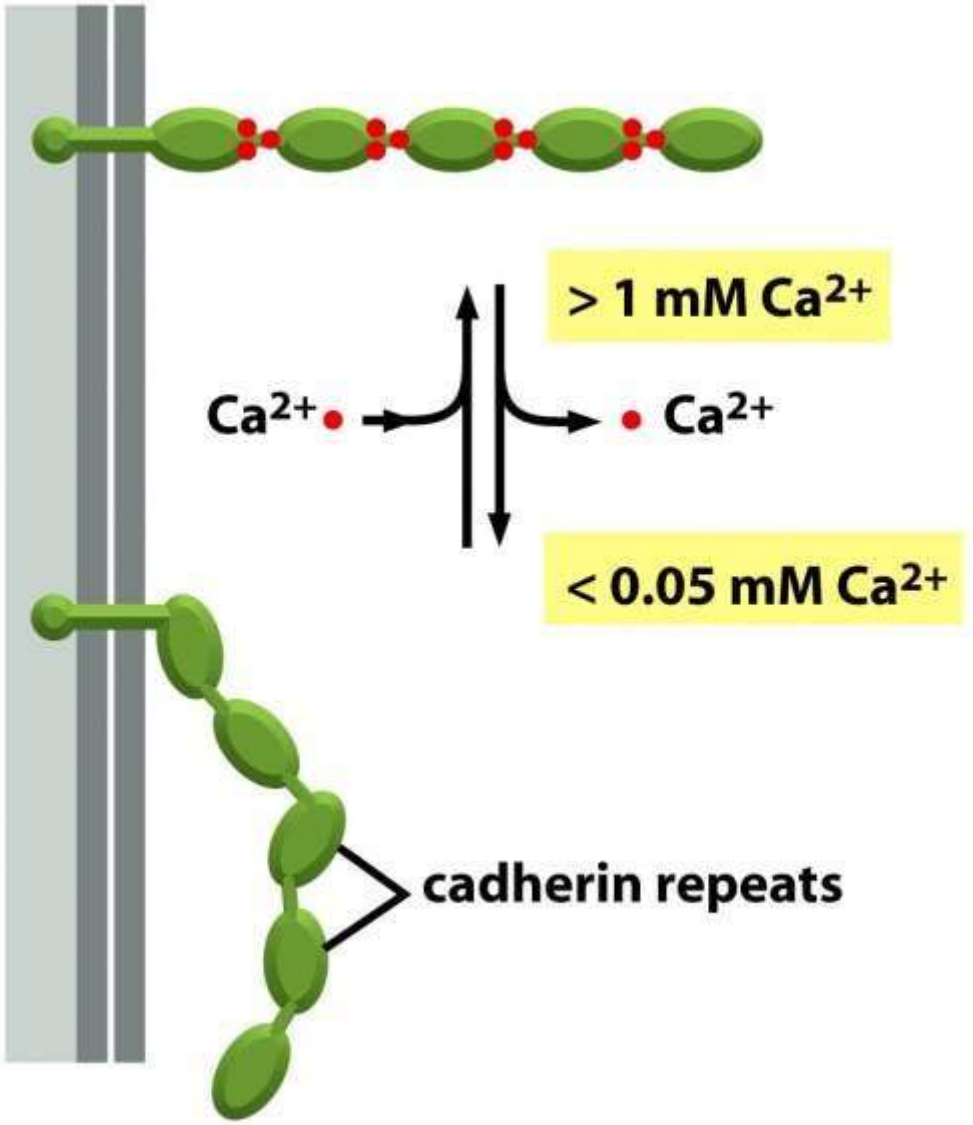
Cadherins mediate Ca^{2+}-dependent homophilic cell-cell adhesion



- **Ca binds in the hinge regions between cadherin domains, and prevent the flexing.**
- **Without Ca the molecule is floppy and adhesion fails**

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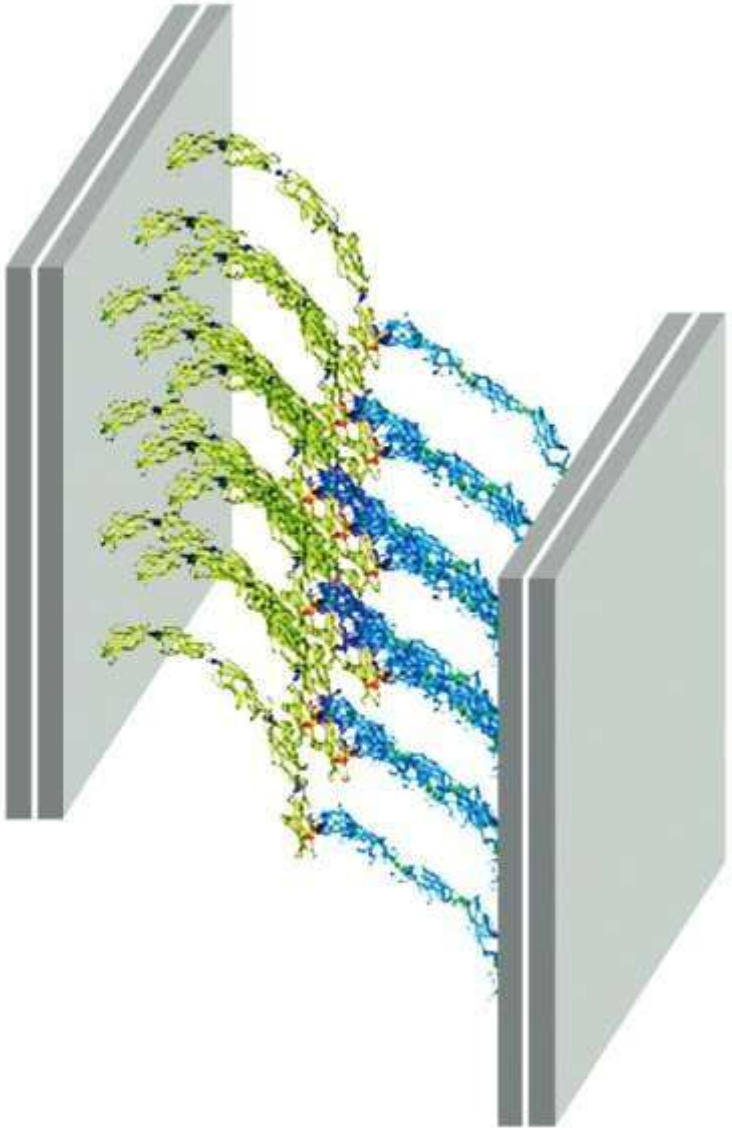
Hook and Loop Fasteners

Velcro !!!



Many cadherin molecules are in a junction, functioning like a Velcro.

Molecular Biology of the Cell (2008, Garland Publishing)