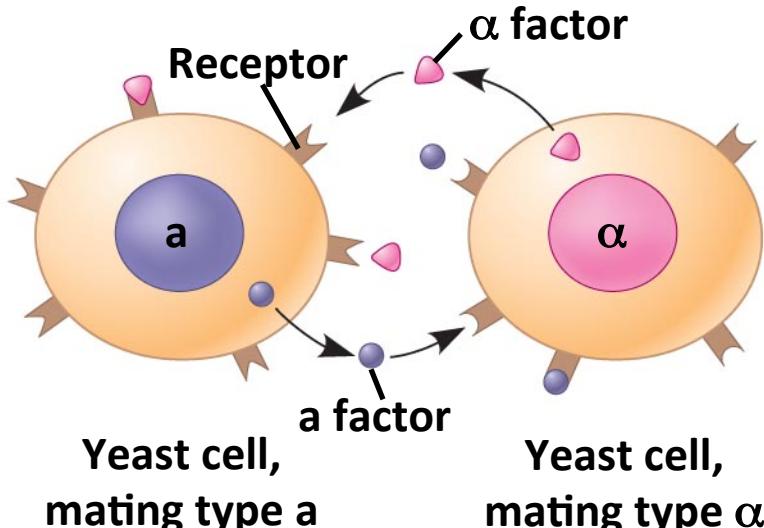


How cells communicate with each other or cell signaling

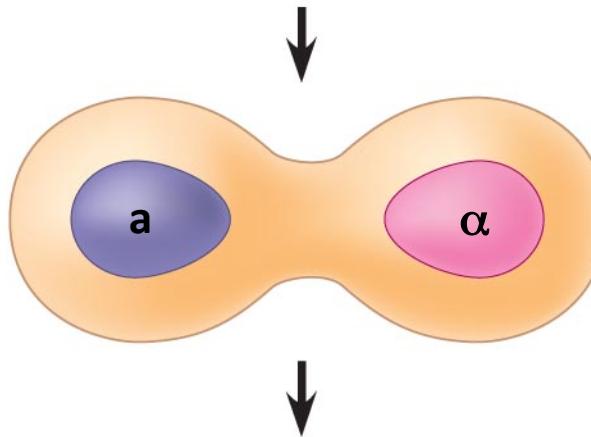
The Cellular Internet: Cell Signaling

- Cell-to-cell communication is **essential for multicellular organisms**
- Biologists have discovered **some universal mechanisms of cellular regulation**
- The **combined effects** of multiple signals determine **cell response**
- For example, the dilation of blood vessels is controlled by multiple molecules
- A **signal transduction pathway** is a **series of steps** by which a signal on a cell's surface is converted into a specific **cellular response**

**1 Exchange
of mating
factors**



2 Mating



3 New a/α cell

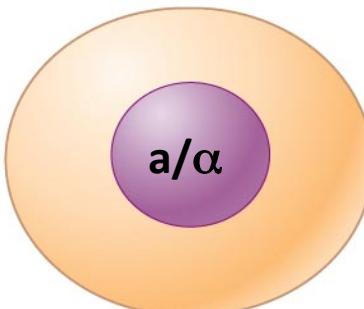
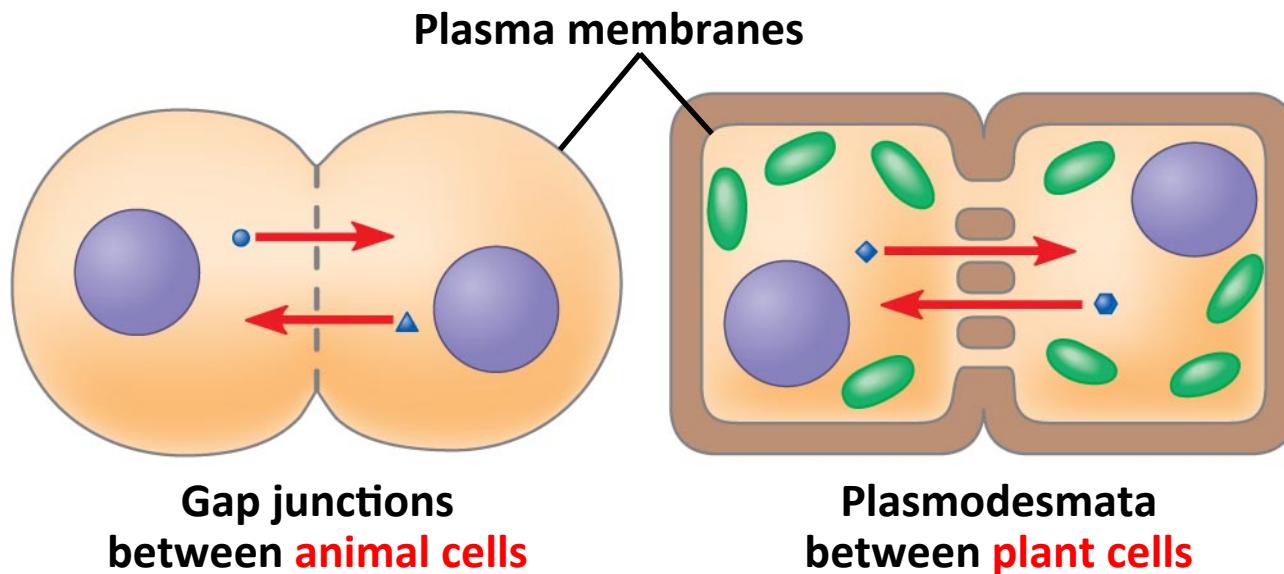


Fig. 11-2

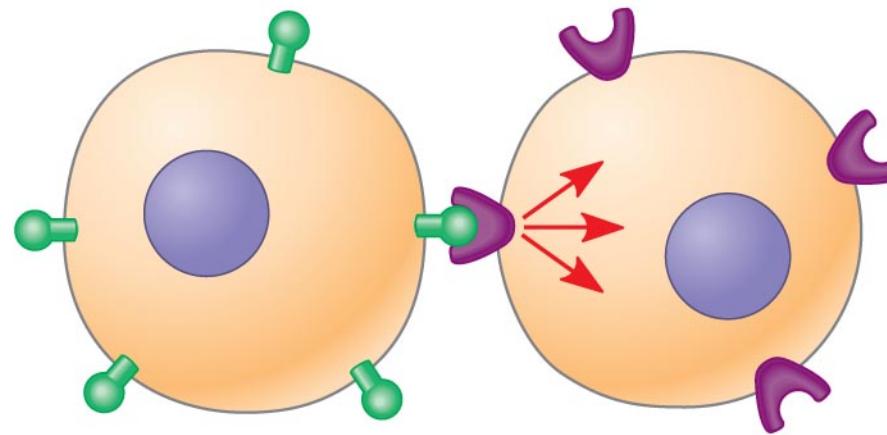
Local and Long-Distance Signaling

- 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**

Fig. 11-4



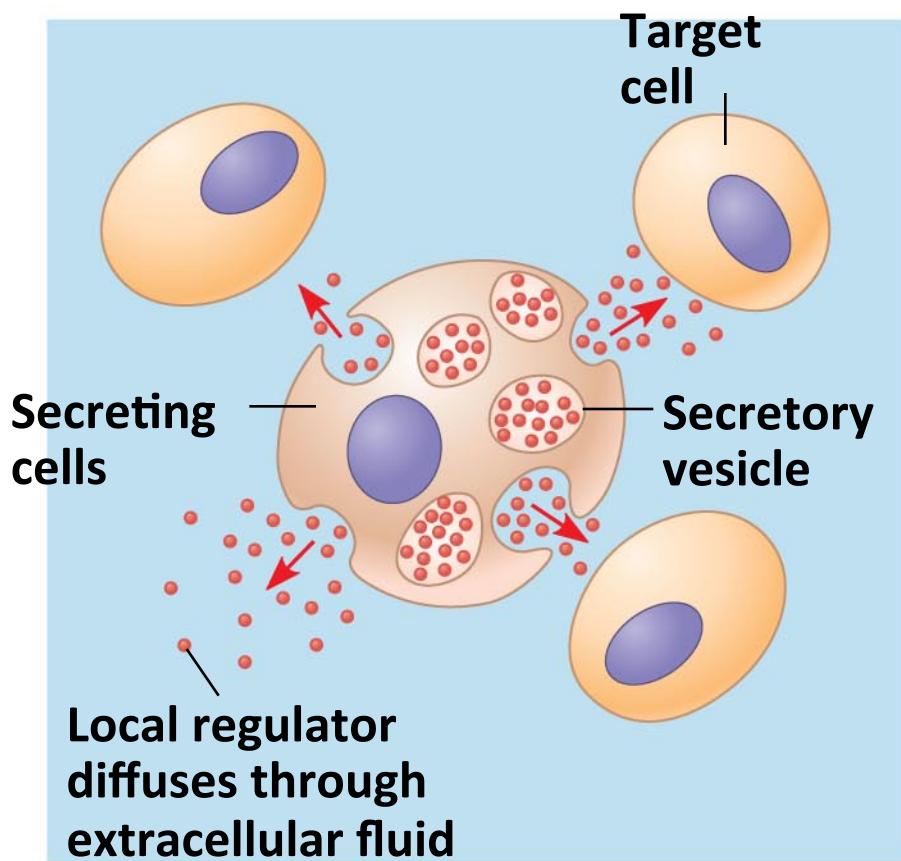
(a) Cell junctions



(b) Cell-cell recognition

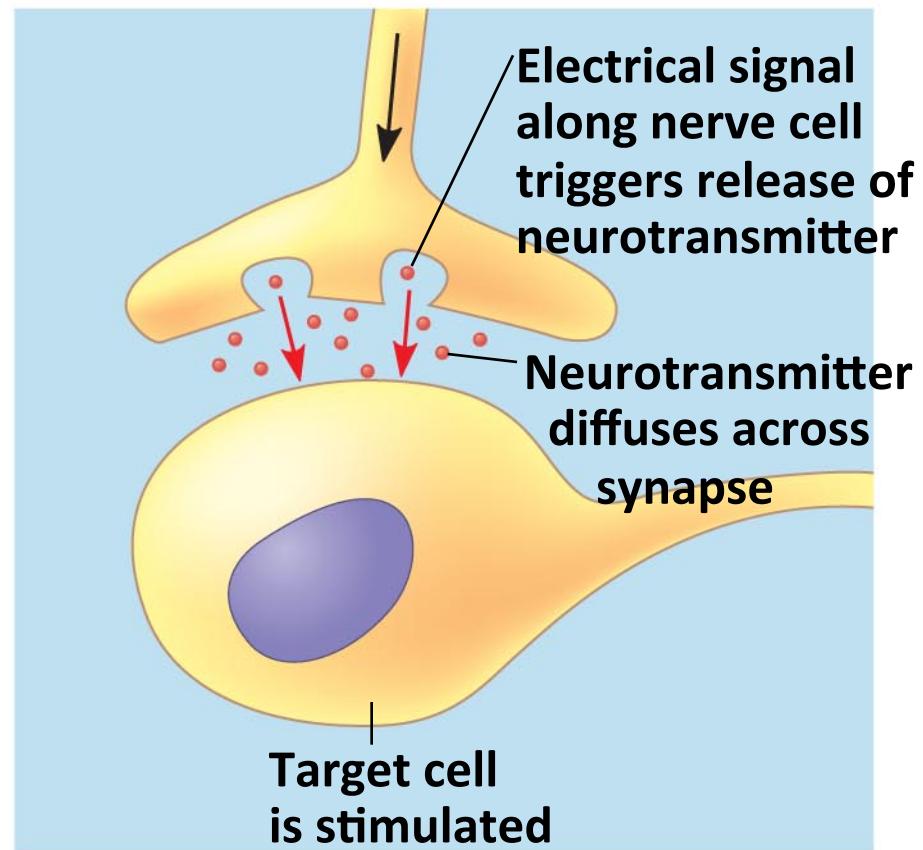
-
- In many other cases, animal cells communicate using **local regulators**, messenger molecules that travel only short distances
 - In **long-distance signaling**, plants and animals use chemicals called **hormones**

Local signaling



(a) Paracrine signaling

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(b) Synaptic signaling

Long-distance signaling

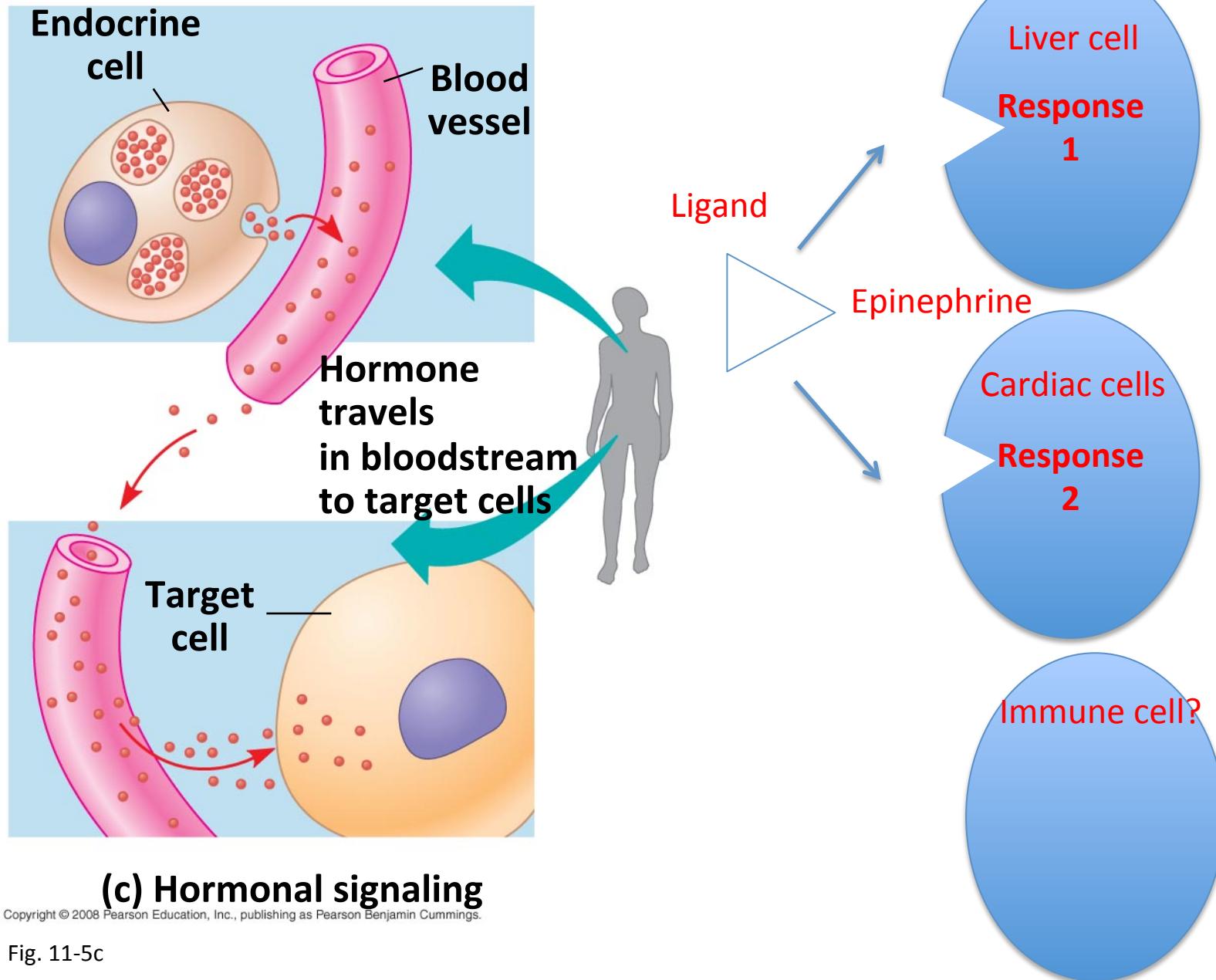
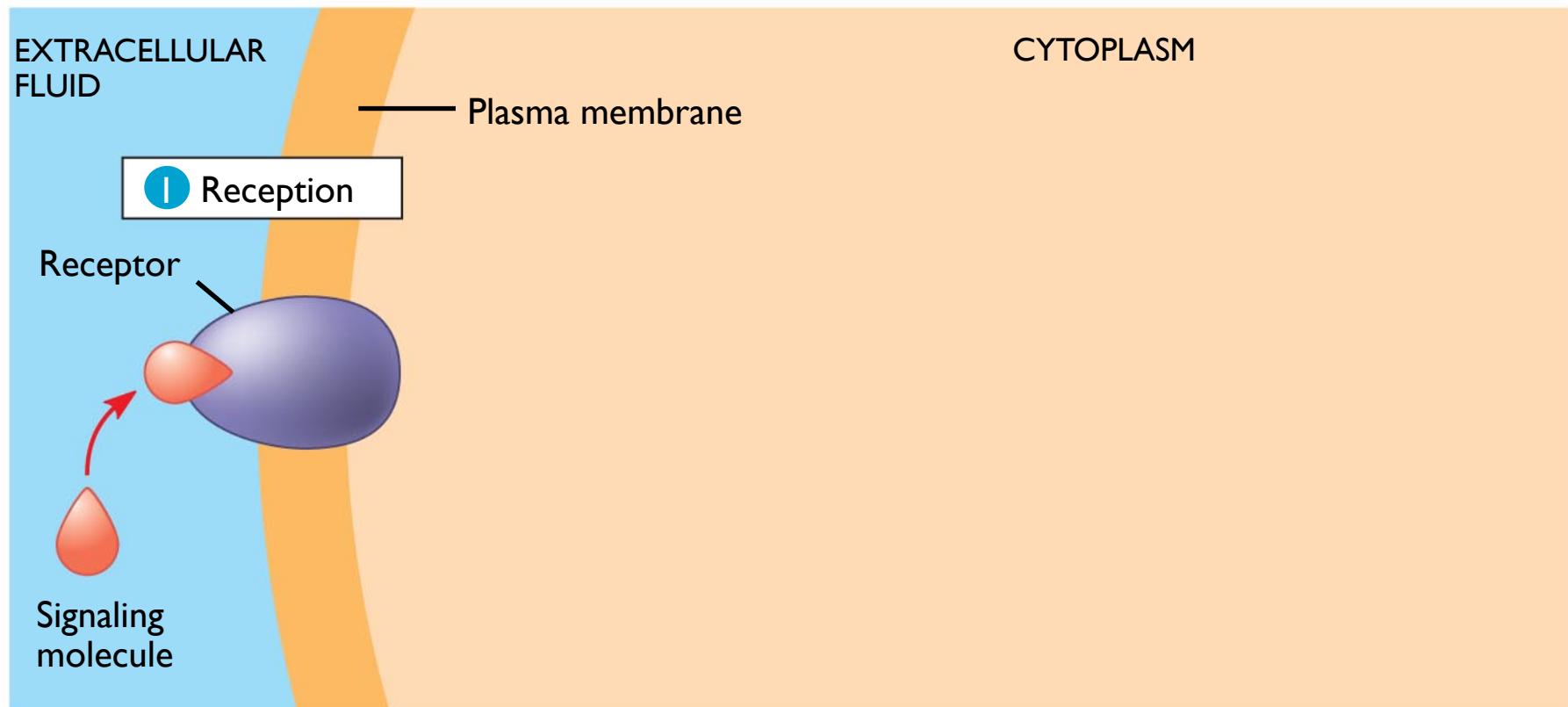


Fig. 11-5c

The Three Stages of Cell Signaling

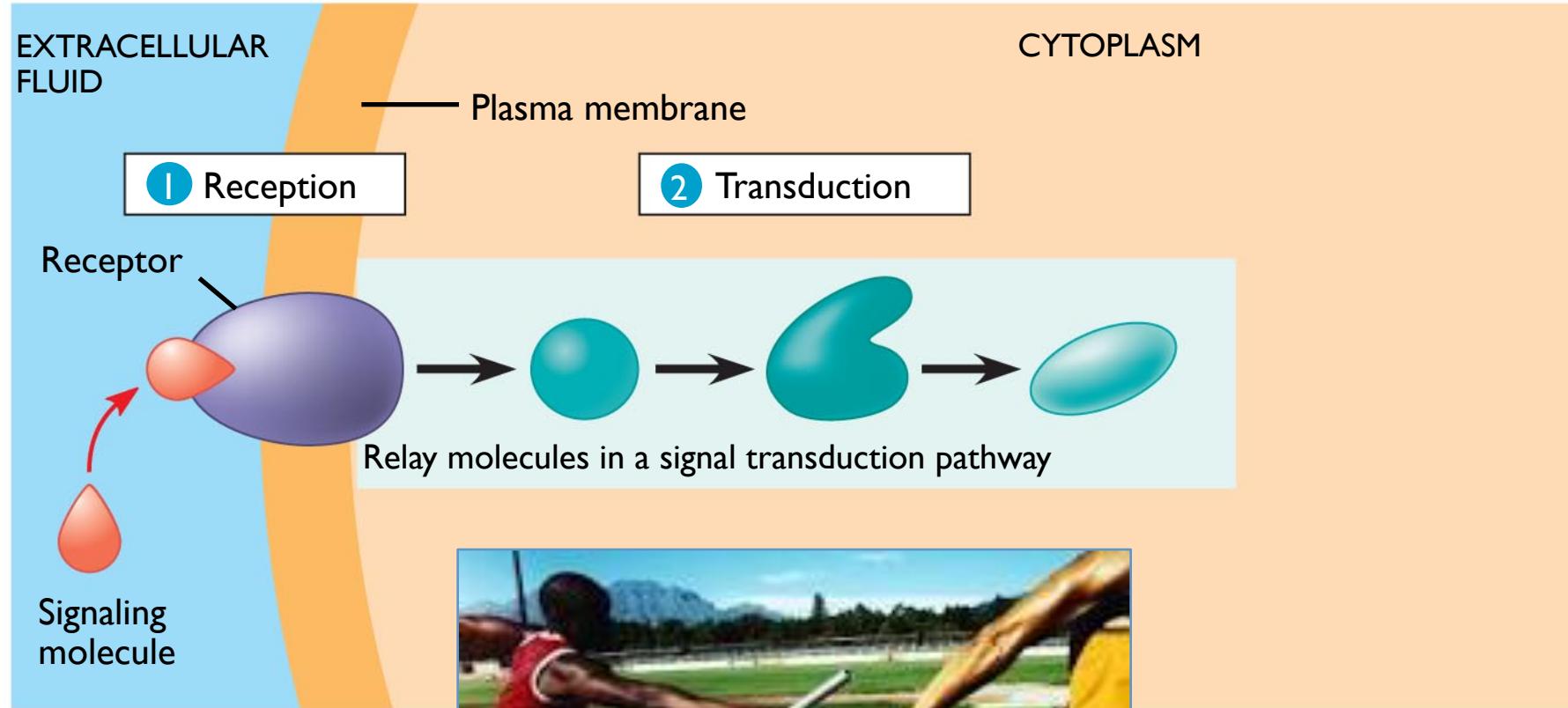
- Earl W. Sutherland discovered how the hormone epinephrine acts on cells
- Sutherland suggested that cells receiving signals went through three processes:
 - **Reception**
 - **Transduction**
 - **Response**
- He showed how signals from one cell to another are conveyed by a messenger- the hormone.
- He showed that cAMP serves as the second messenger

Fig. 11-6-1



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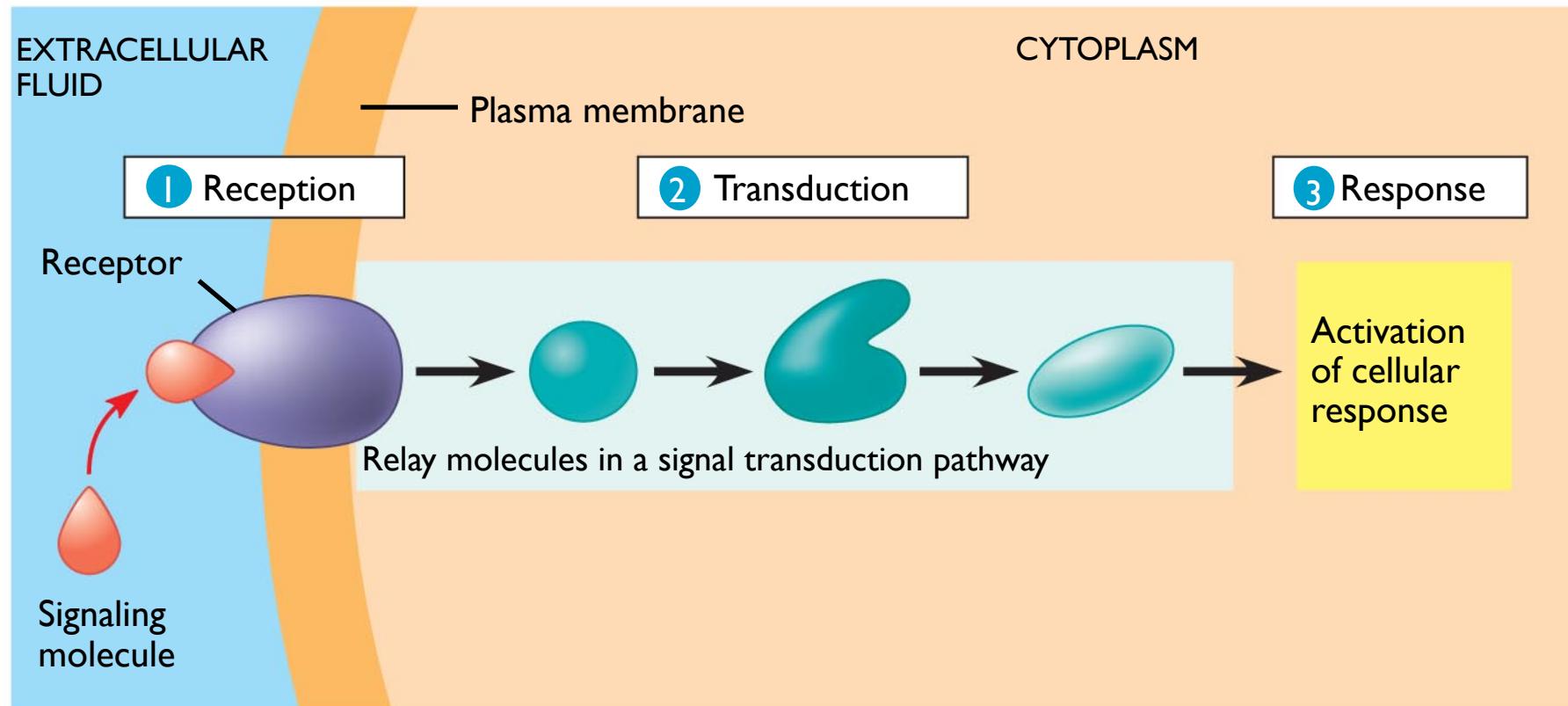
Fig. 11-6-2



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Fig. 11-6-3



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Reception : A signal 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 in the plasma membrane
- There are three main types of membrane receptors:
 - G protein-coupled receptors
 - Receptor tyrosine kinases
 - Ion channel receptors

A G protein-coupled receptor 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

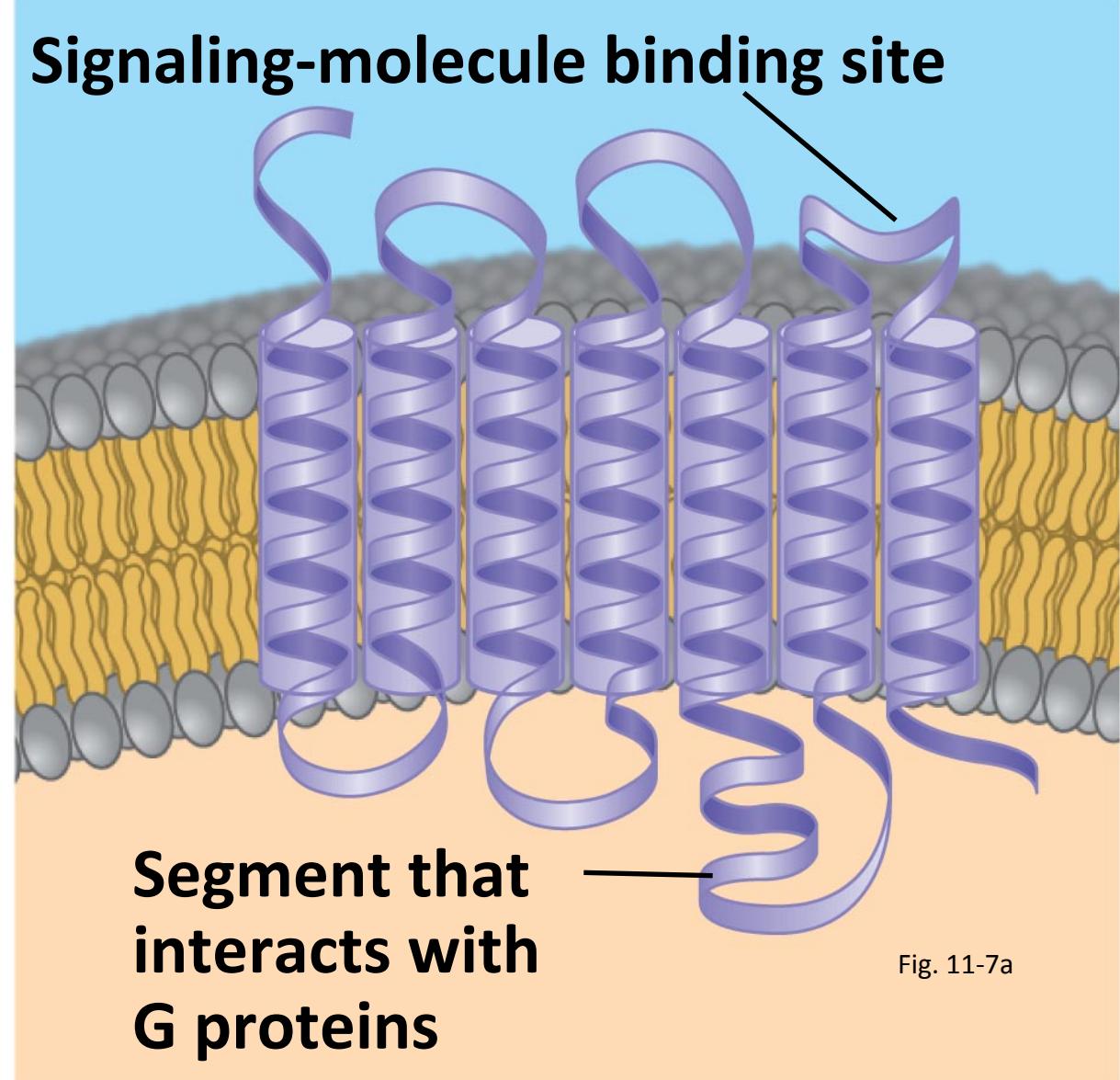
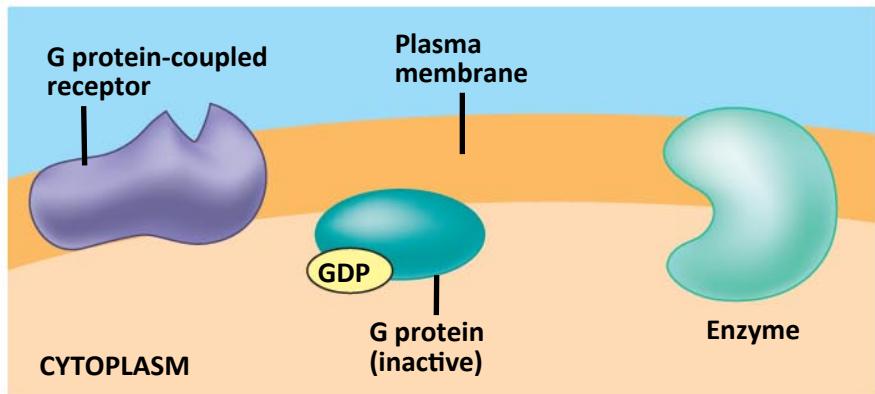
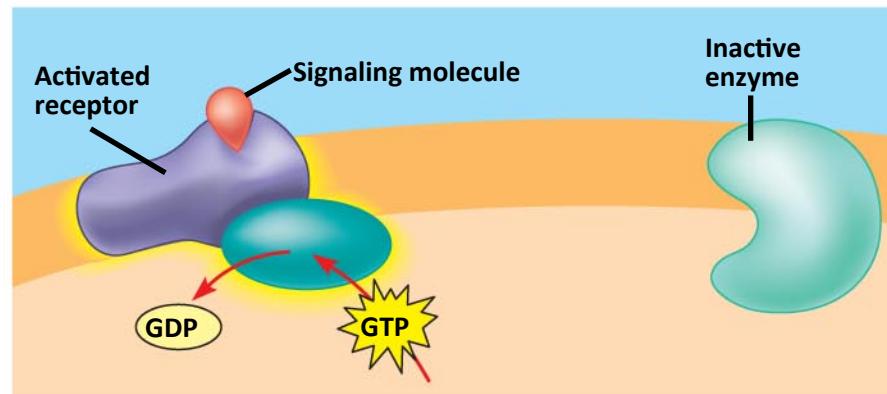


Fig. 11-7a

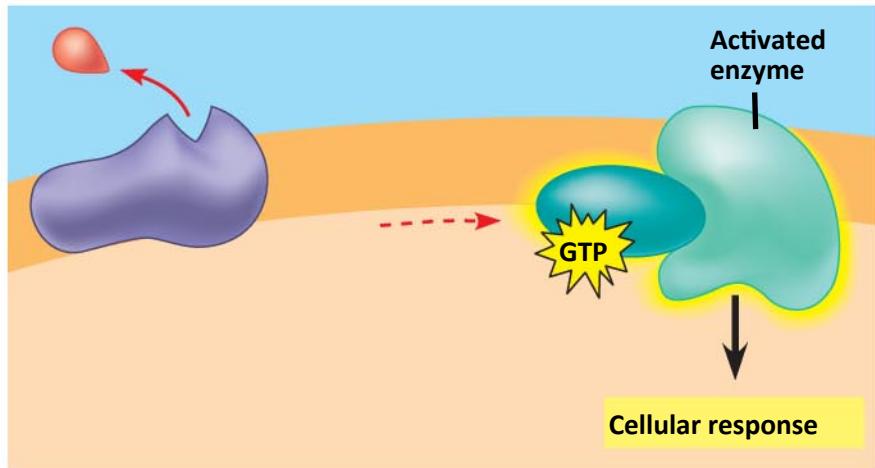
G protein-coupled receptor



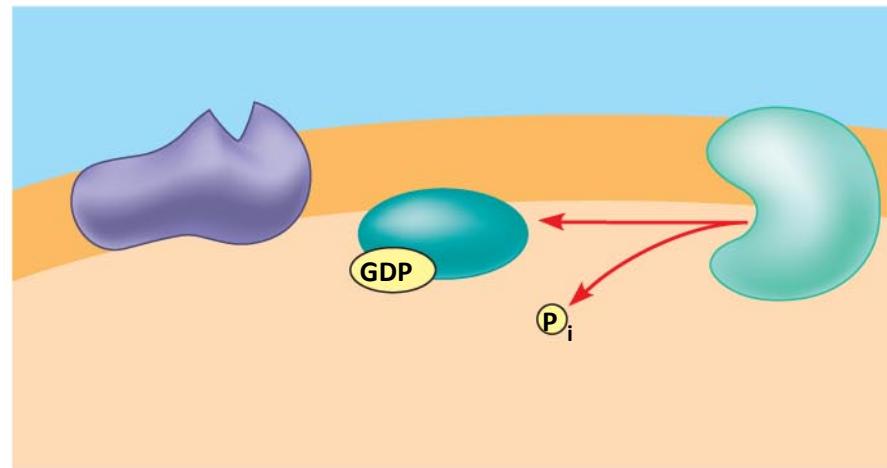
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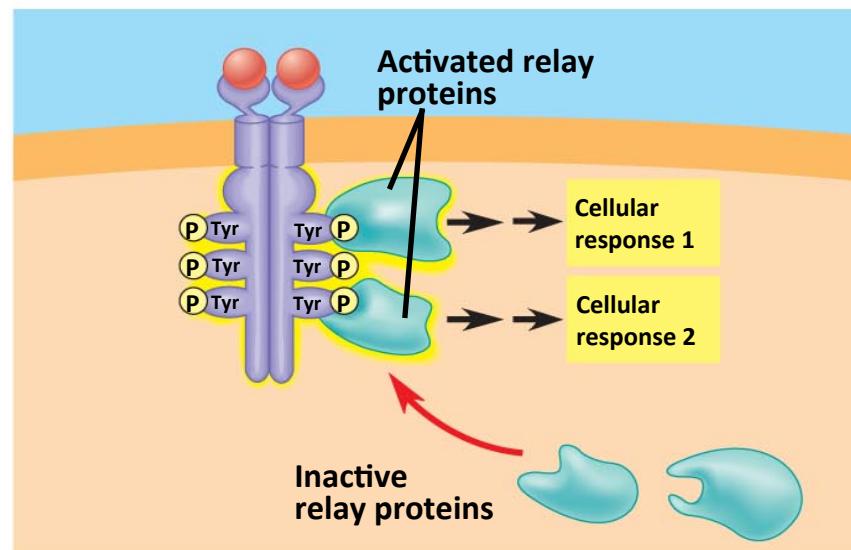
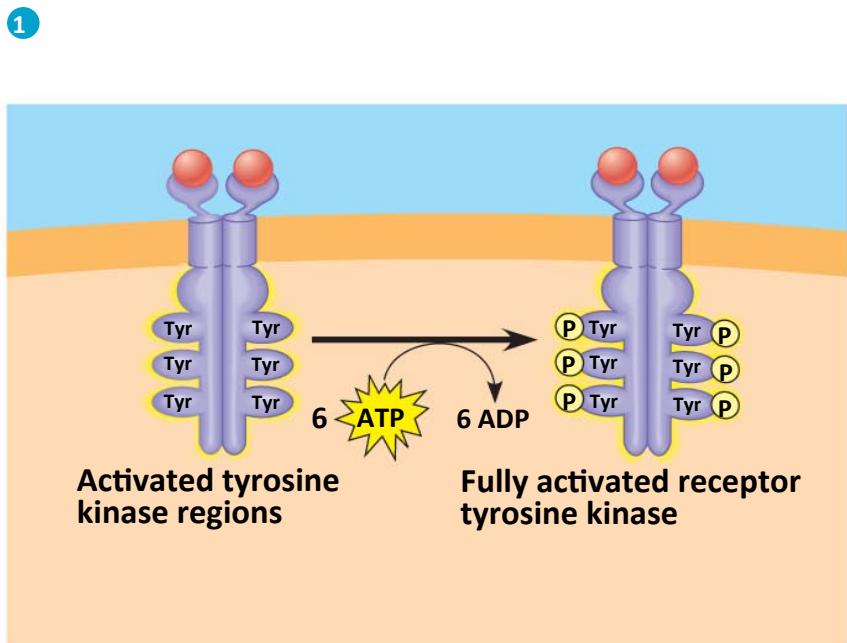
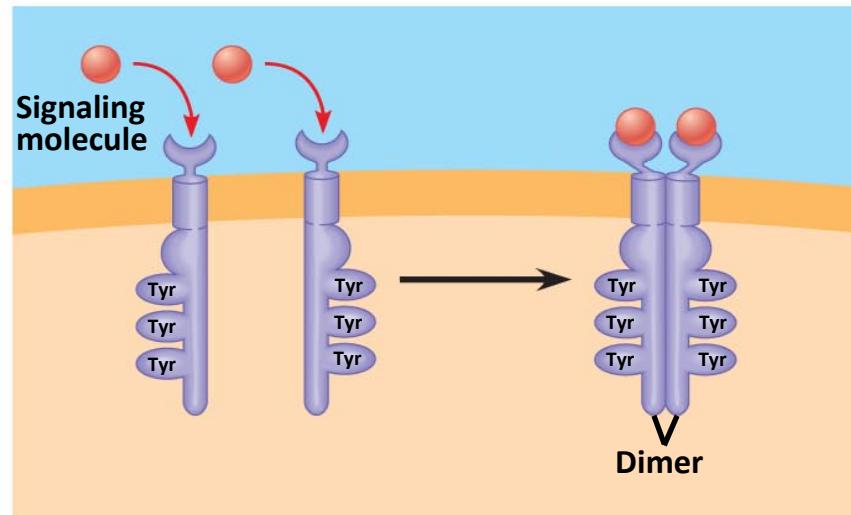
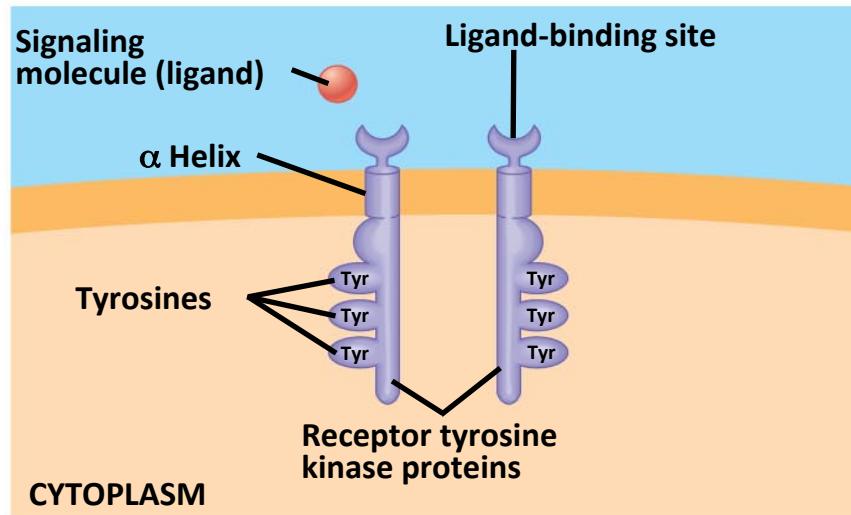


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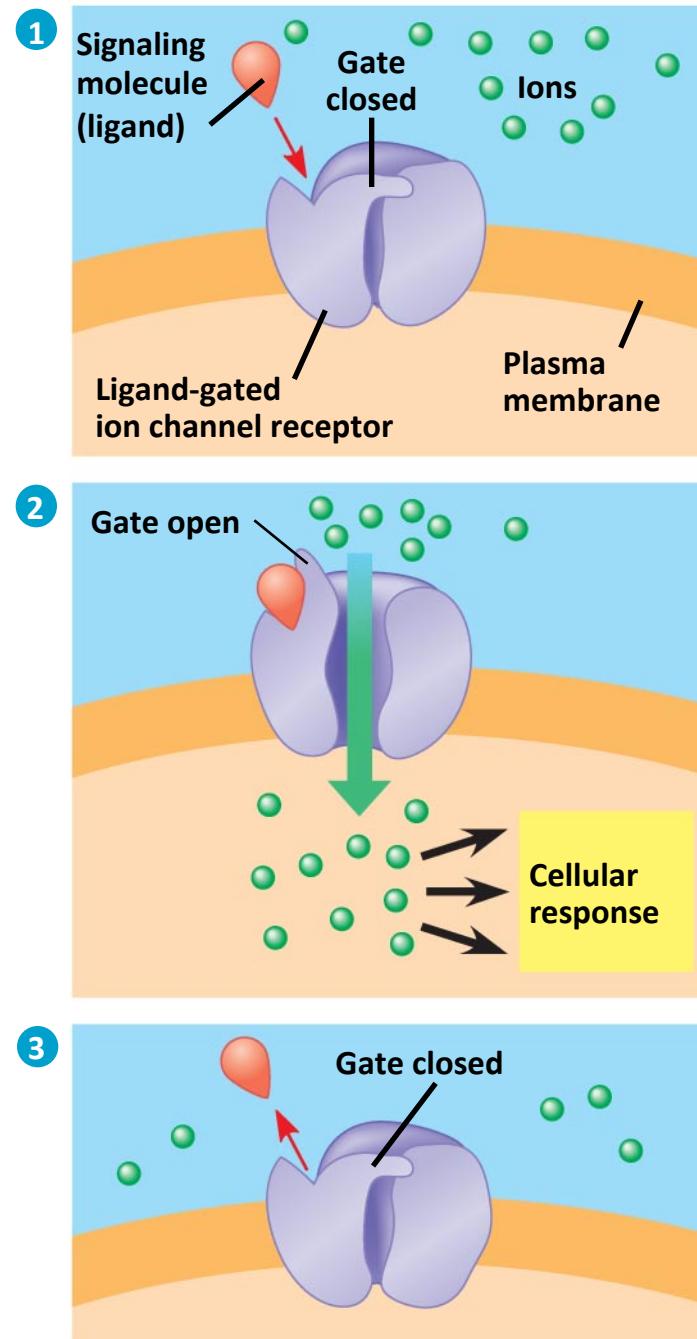
Receptor tyrosine kinases are membrane receptors that attach phosphates to tyrosines

A receptor tyrosine kinase can trigger multiple signal transduction pathways at once



-
- 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

Fig. 11-7d



Intracellular Receptors

- Some receptor proteins are intracellular, 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

Fig. 11-8-1

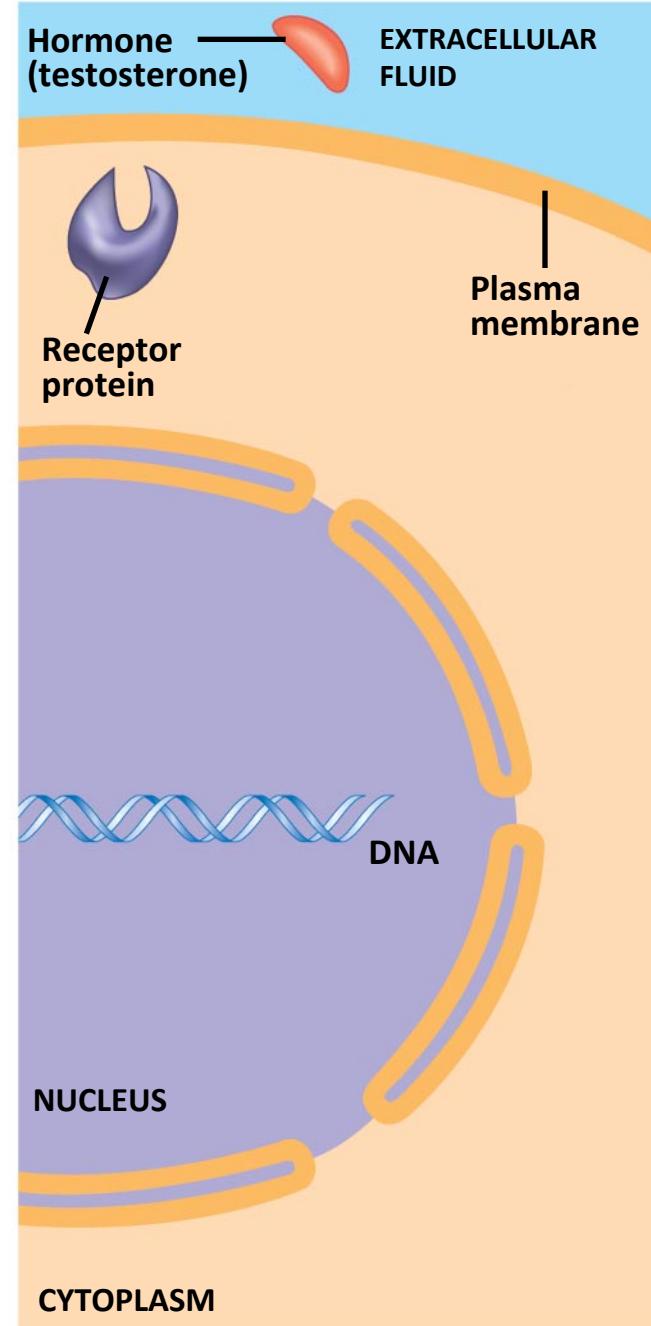


Fig. 11-8-2

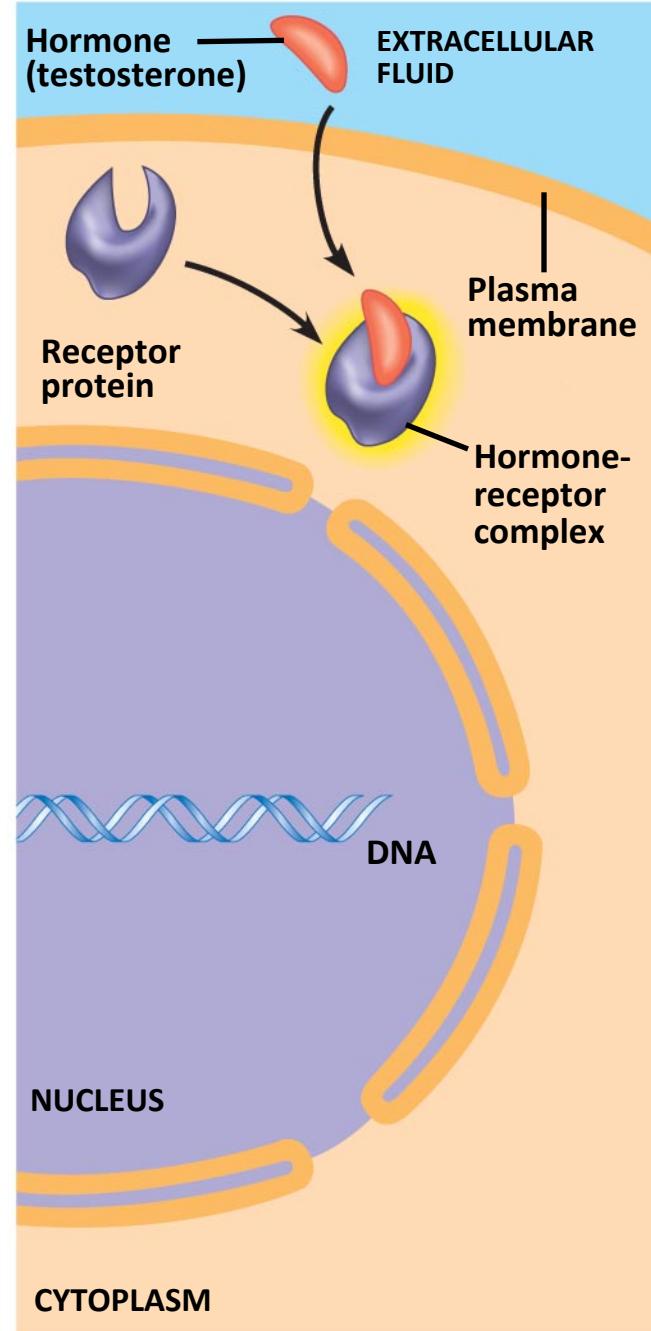


Fig. 11-8-3

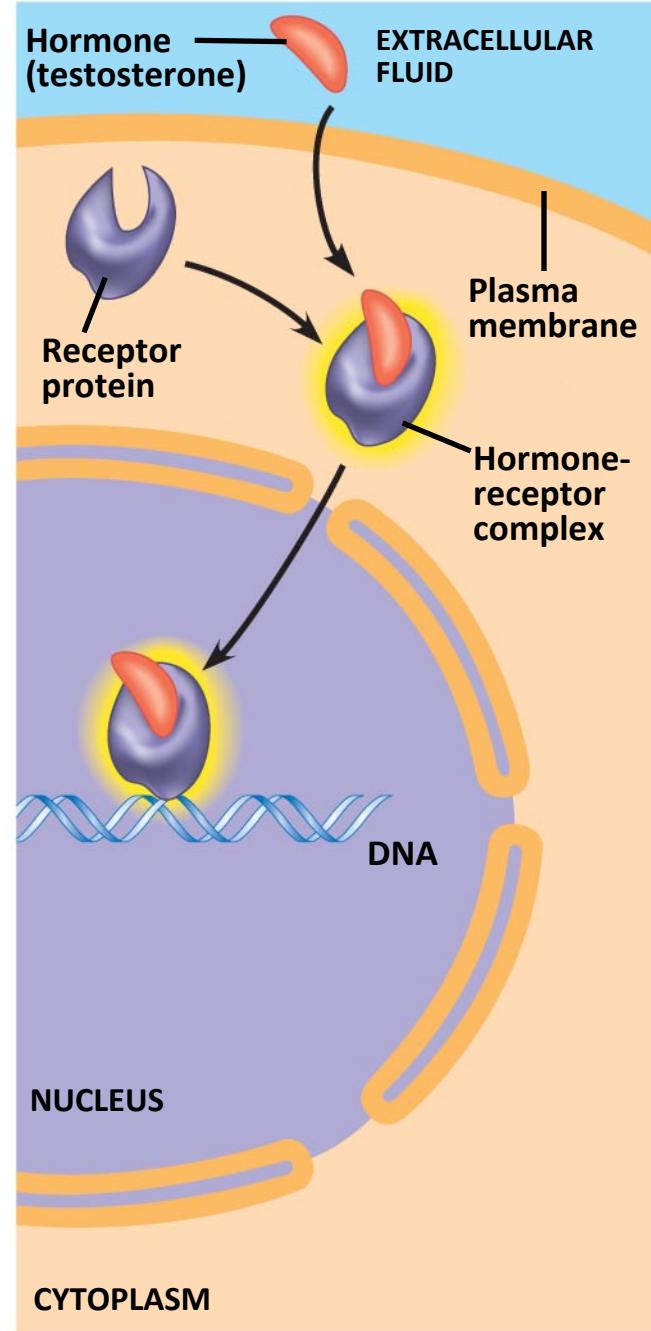


Fig. 11-8-4

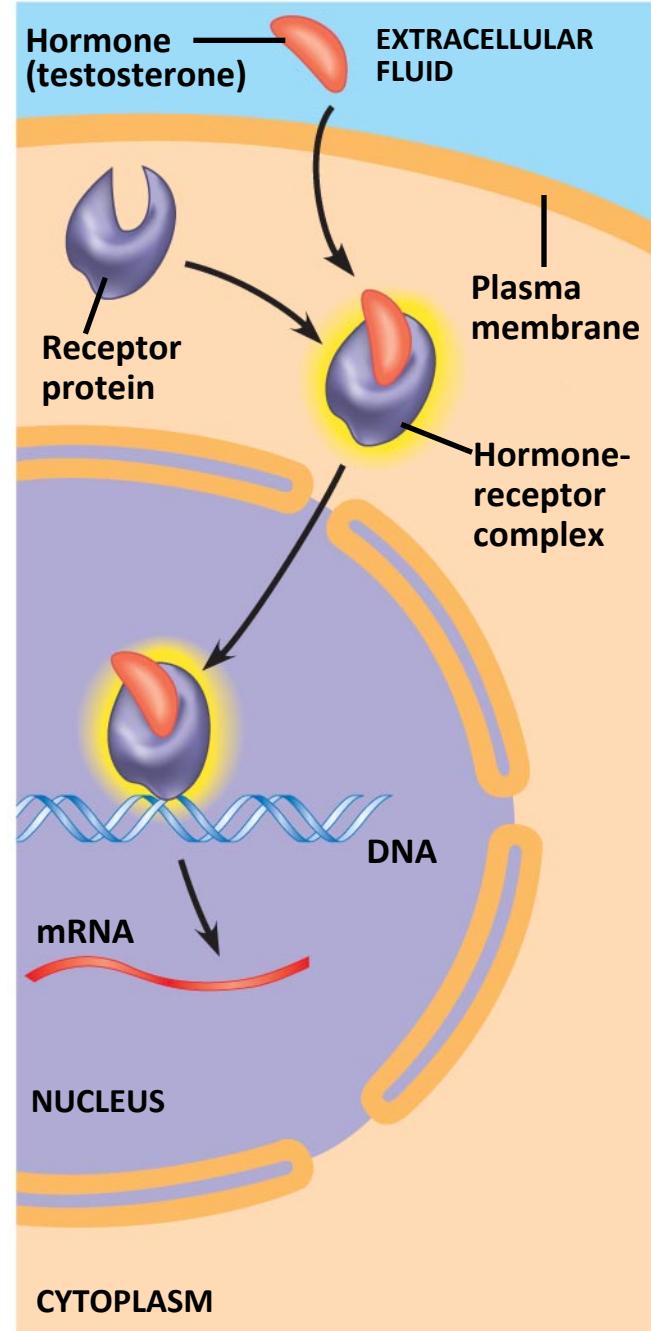
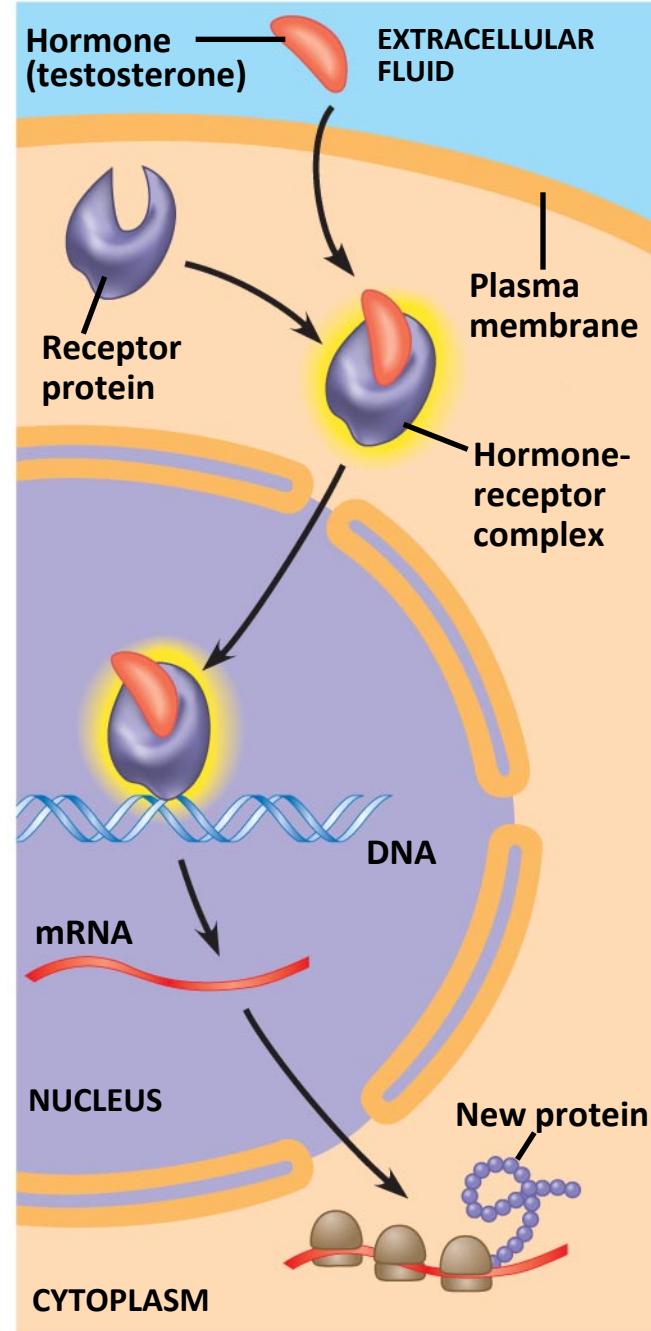


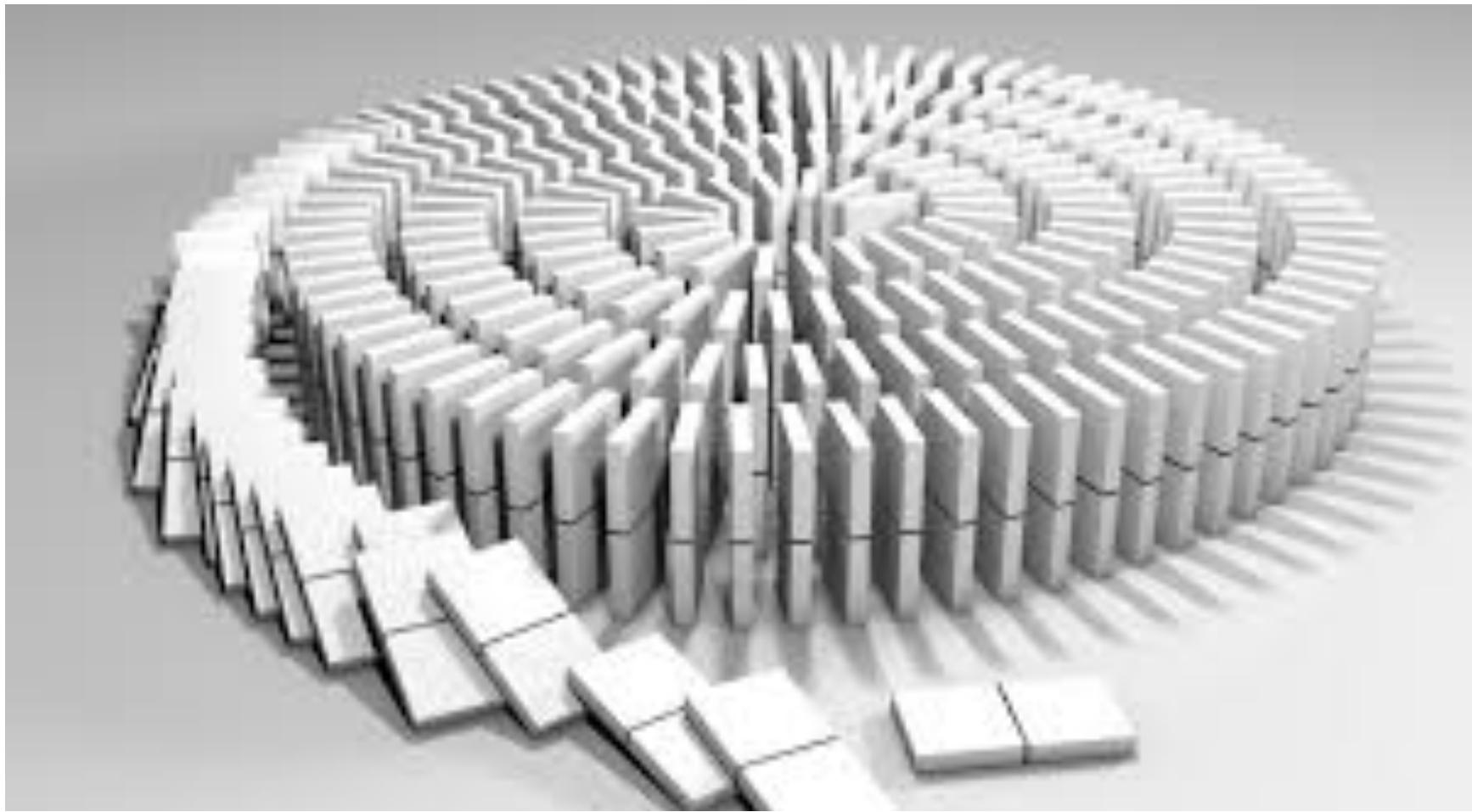
Fig. 11-8-5



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
- The molecules that relay a signal from receptor to response are mostly proteins
- Like falling 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

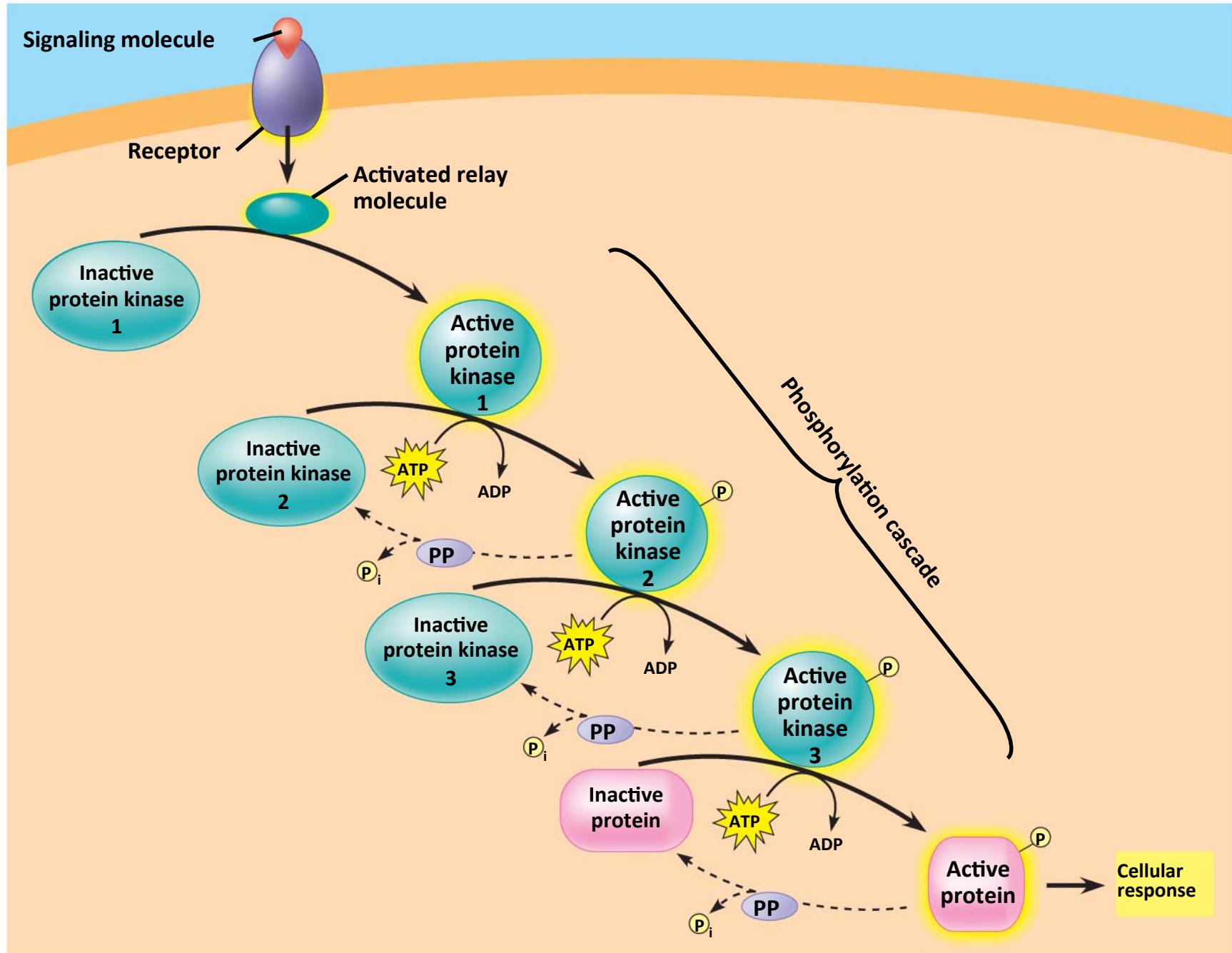
Domino effect



Protein Phosphorylation and Dephosphorylation

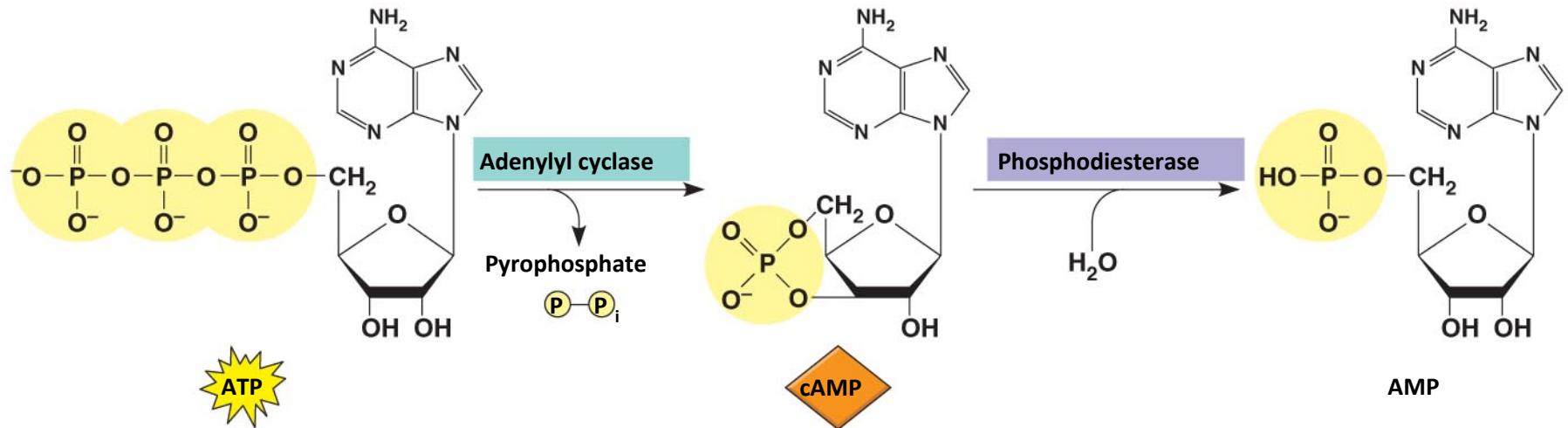
- In many pathways, the signal is transmitted by a cascade of protein phosphorylations
- **Protein kinases** transfer phosphates from ATP to protein, a process called phosphorylation
- **Protein phosphatases** remove the phosphates from proteins, a process called dephosphorylation
- This phosphorylation and dephosphorylation system acts as a molecular switch, turning activities on and off

Fig. 11-9



Small Molecules and Ions as Second Messengers

- The extracellular signal molecule 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 G protein-coupled receptors and receptor tyrosine kinases
- **Cyclic AMP and calcium ions are common second messengers**
- **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



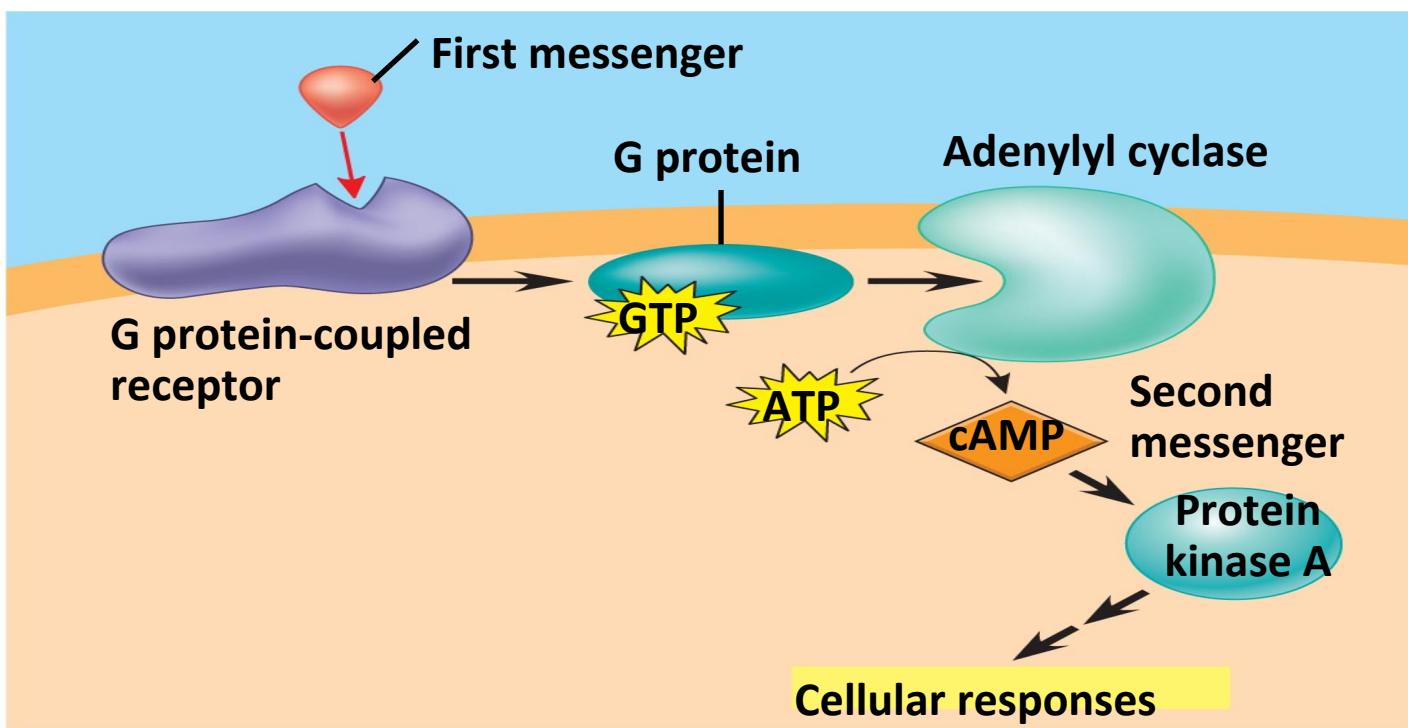
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Second messengers

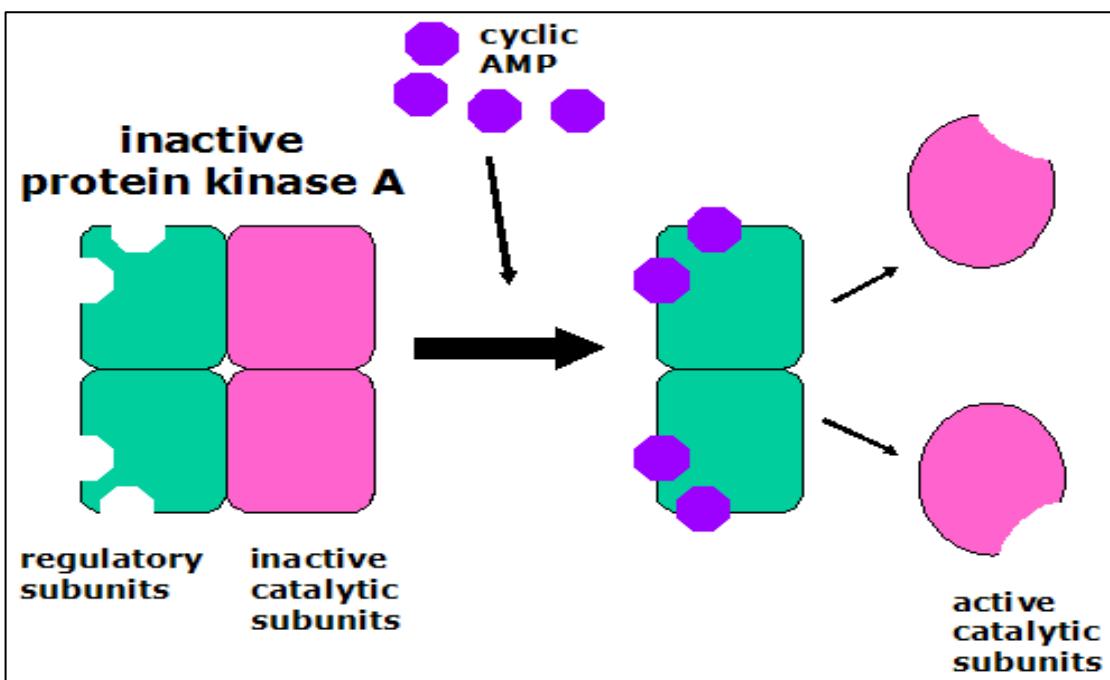
Hydrophobic molecules: Phosphatidyl inositol, Diacyl glycerol (DAG)

Hydrophilic molecules: cAMP, cGMP, Inositol triphosphate (IP₃), Ca⁺⁺

Gases: NO, CO, H₂S

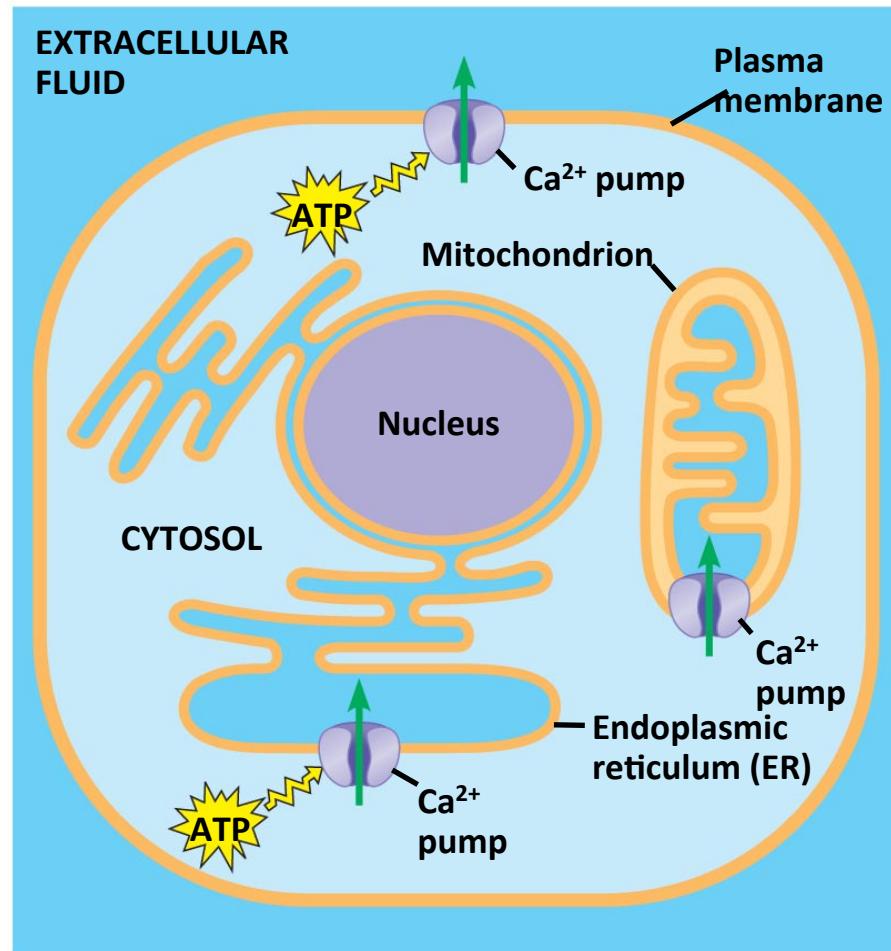


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Calcium ions as second messenger

- 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 (IP₃)** and **diacylglycerol (DAG)** as additional second messengers

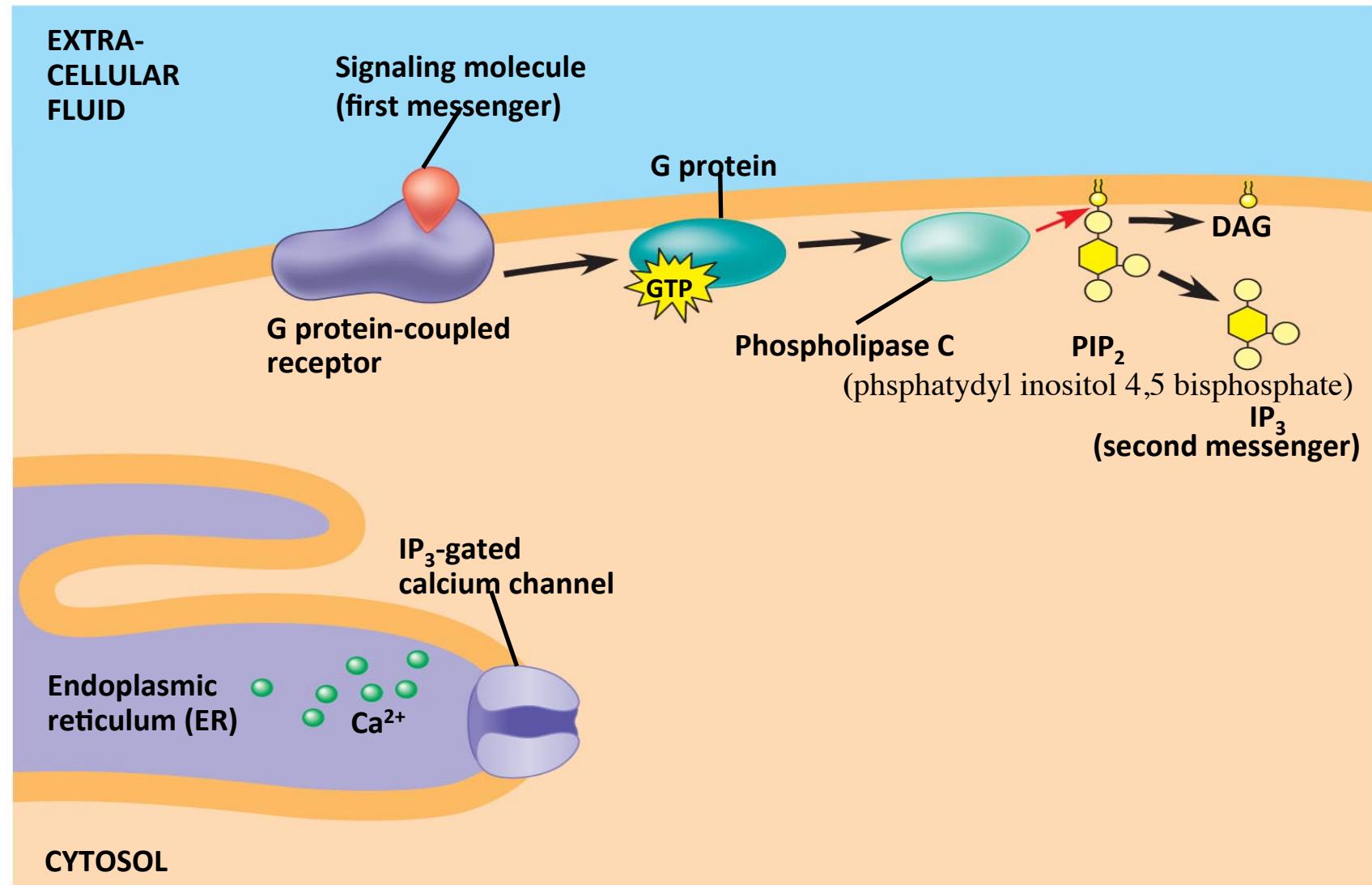


Fig. 11-13-2

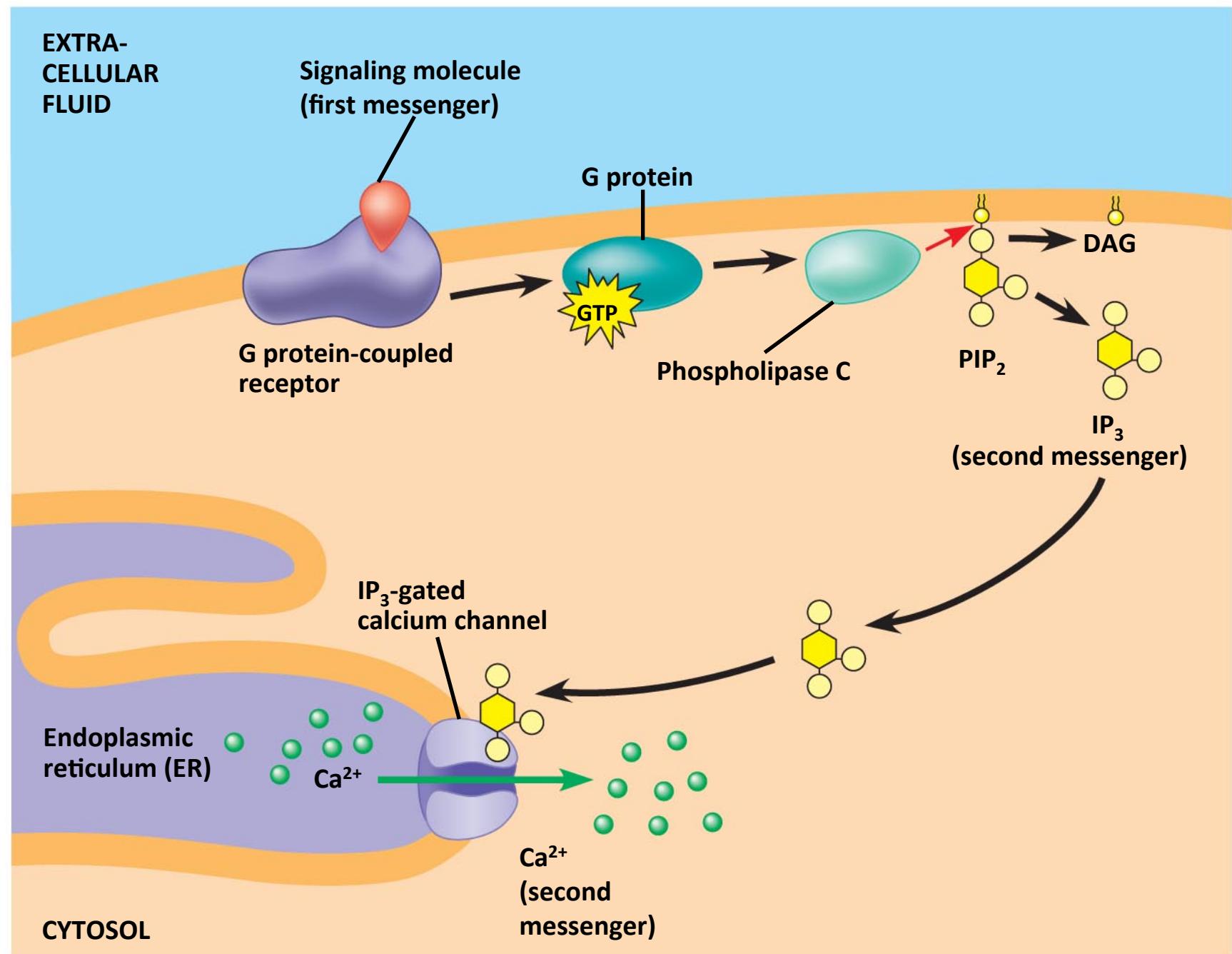
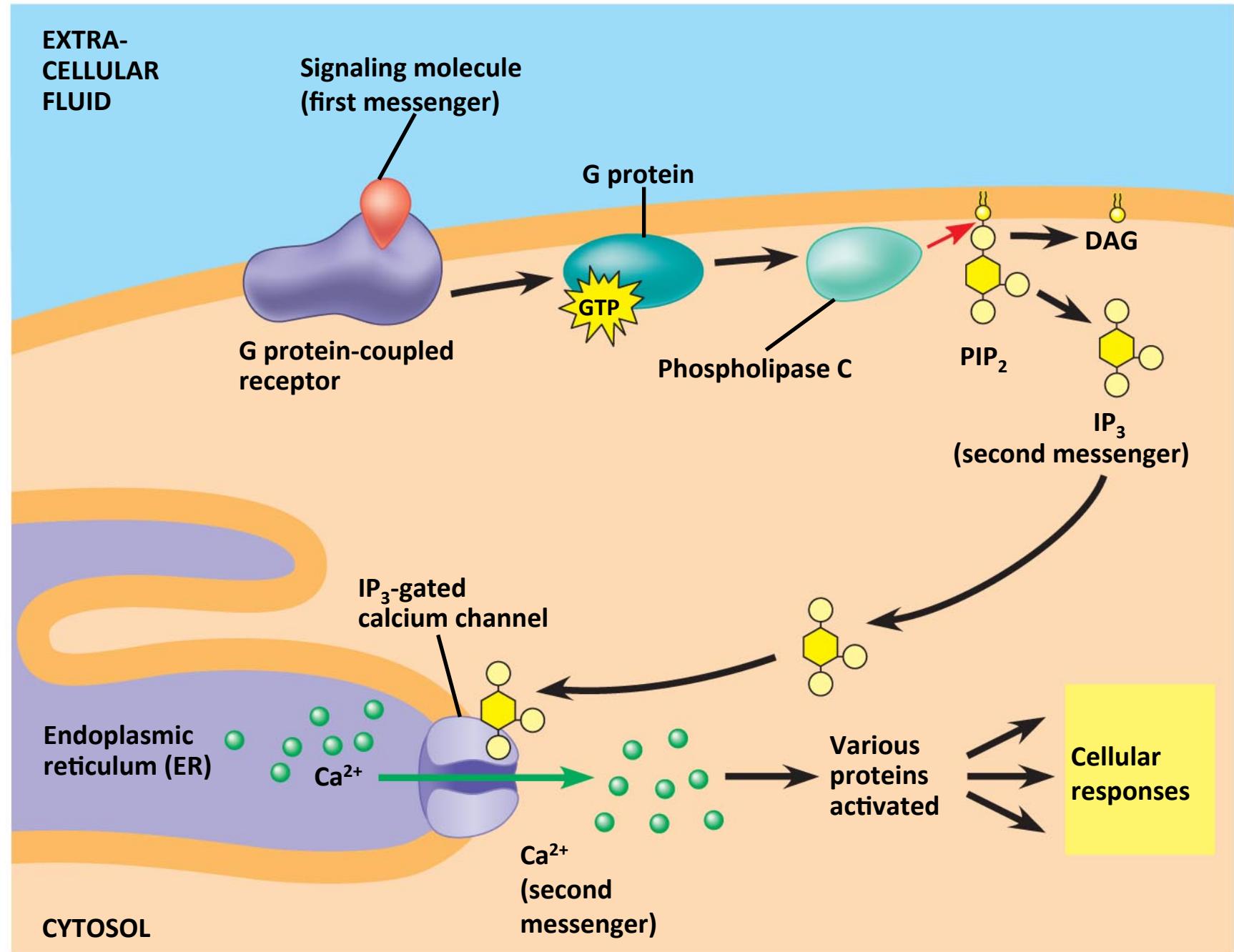


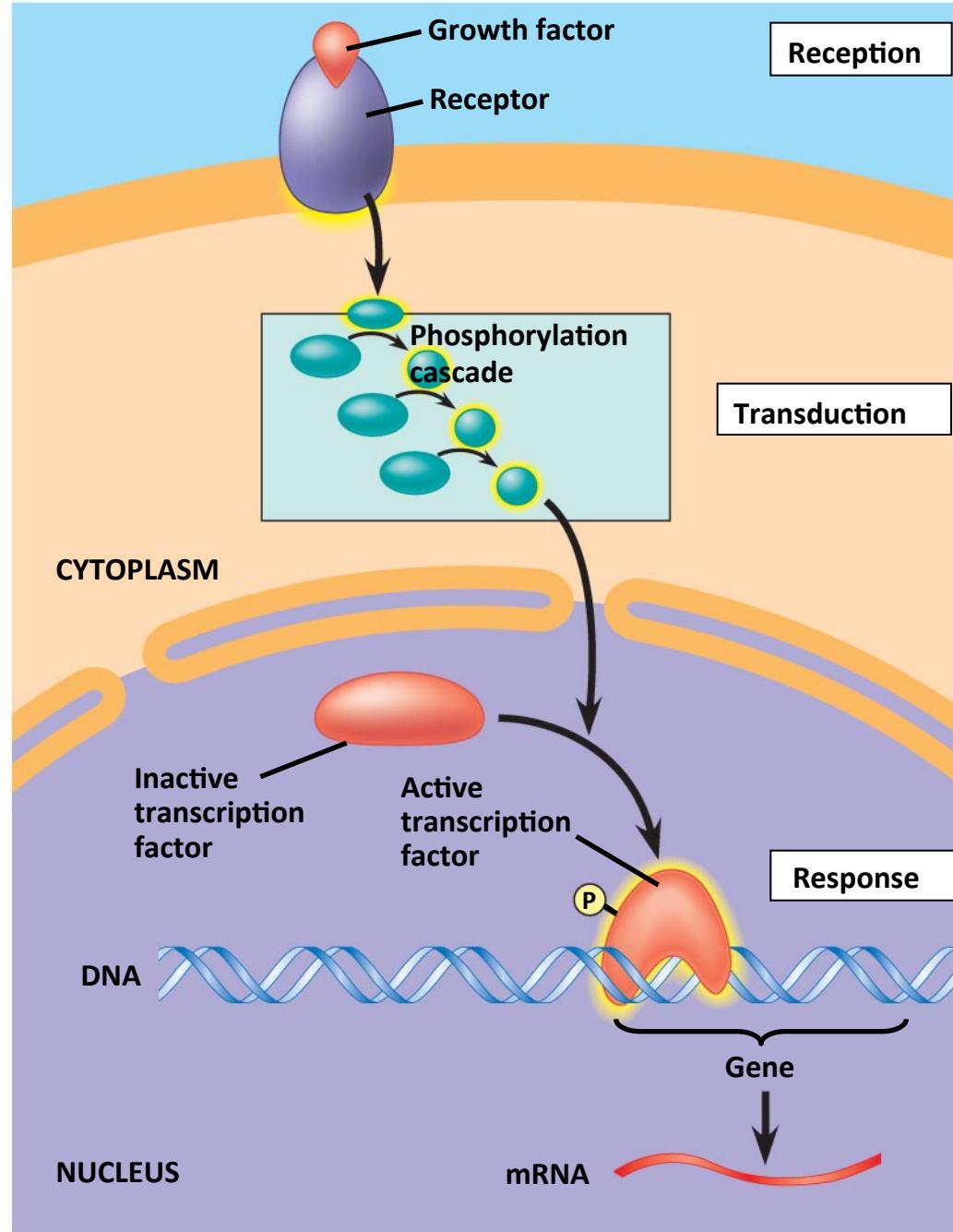
Fig. 11-13-3



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 may involve action 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 may function as a transcription factor

Fig. 11-14



Reception

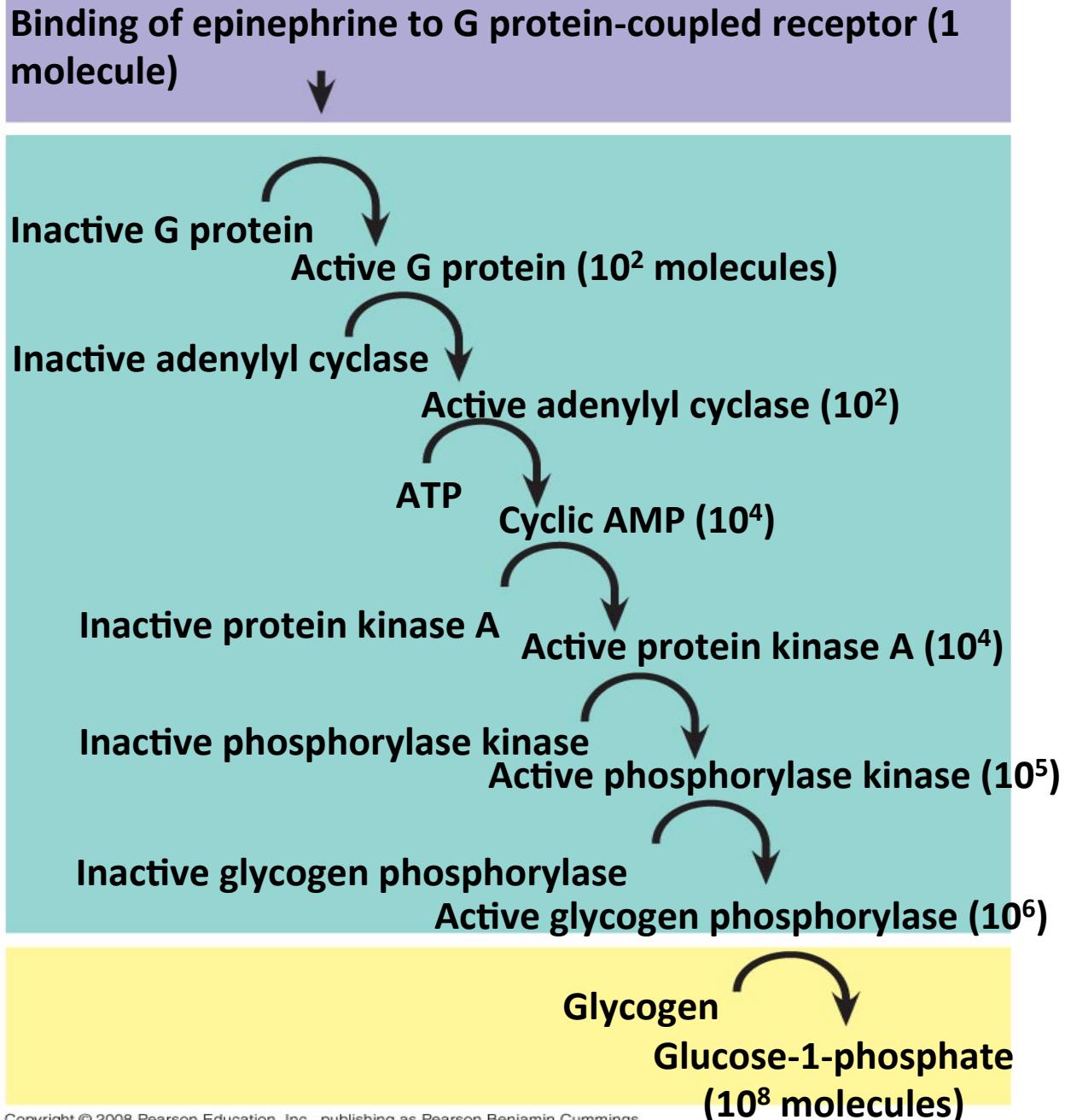
Transduction

Signal Amplification

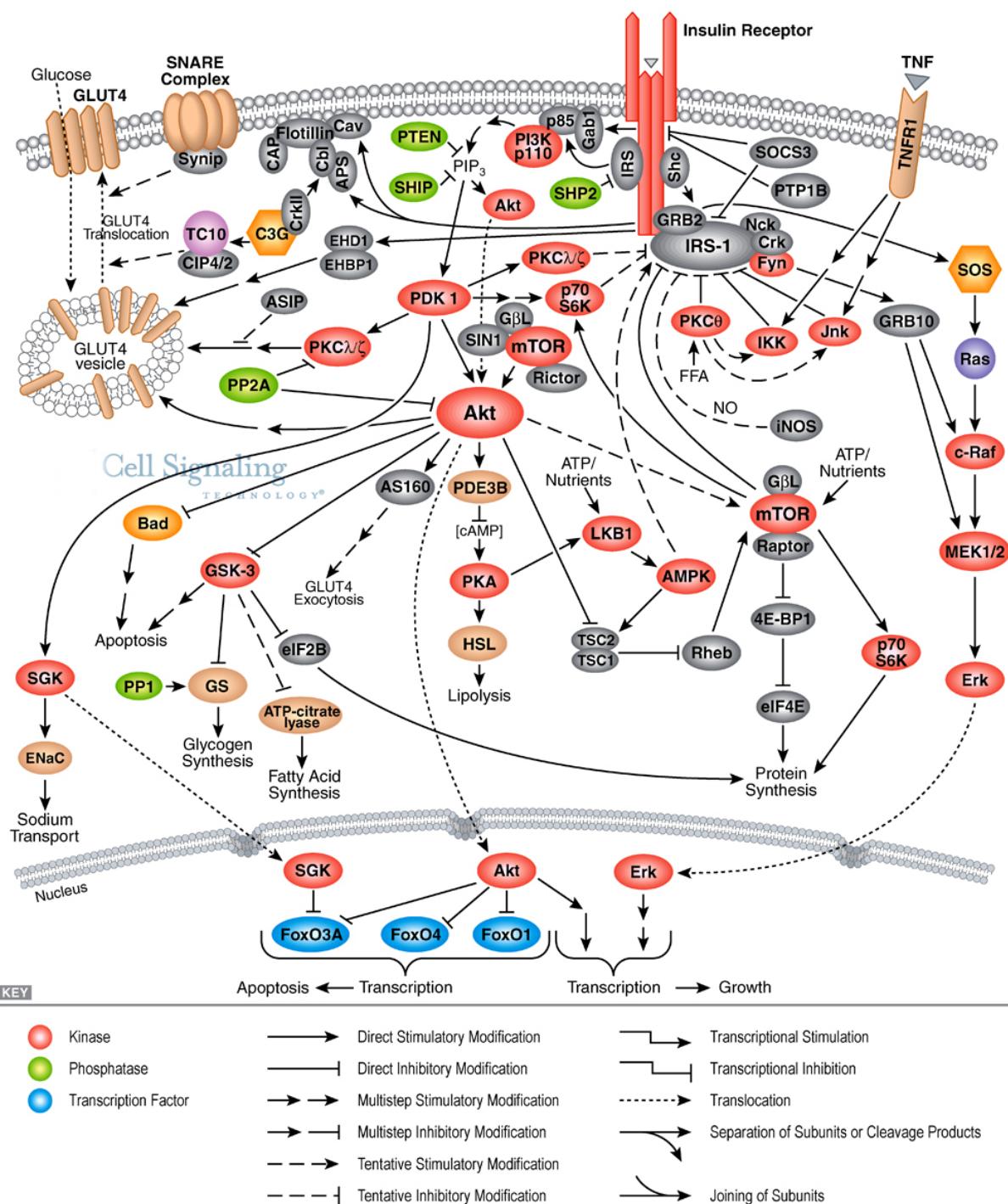
Enzyme cascades amplify the cell's response

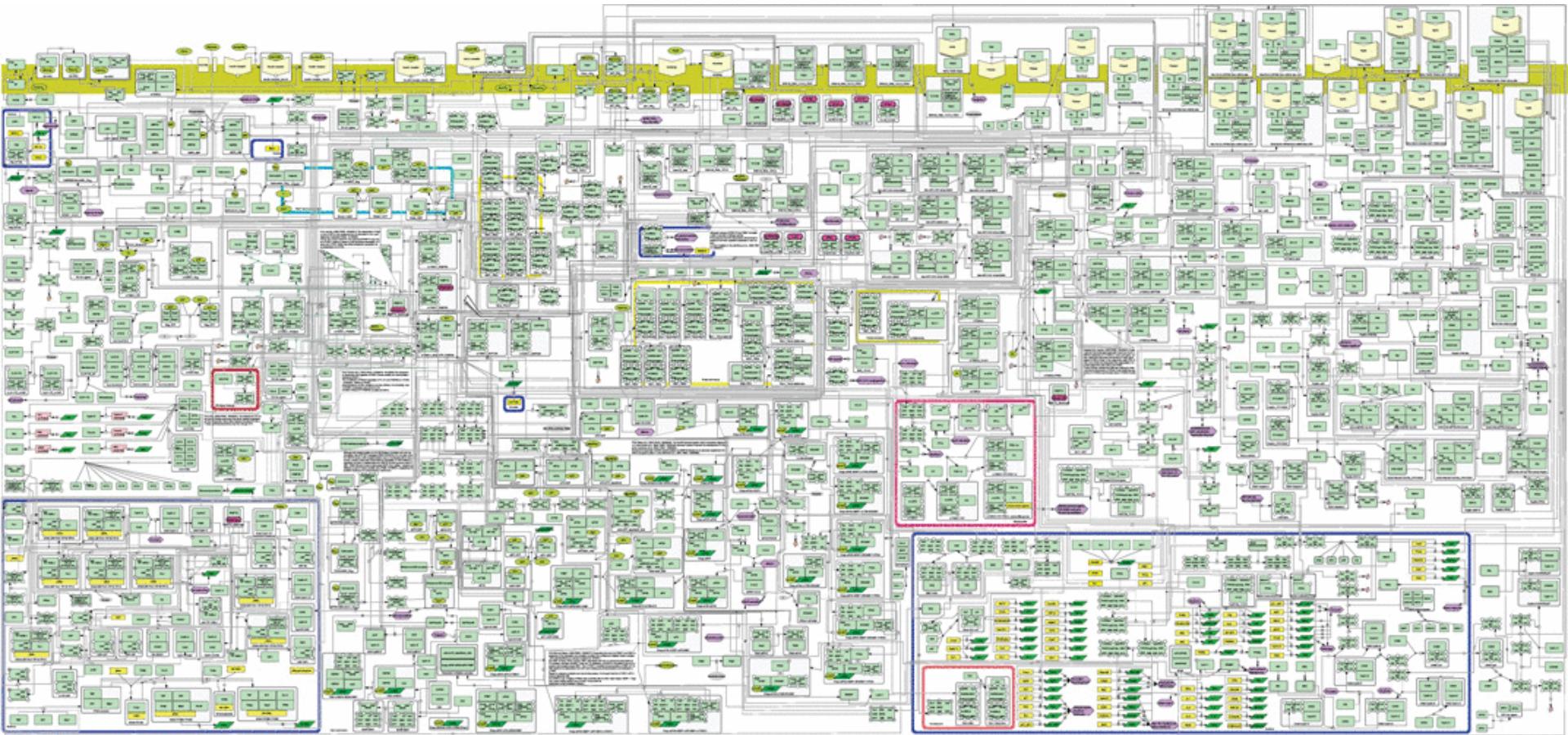
At each step, the number of activated products is much greater than in the preceding step

Response

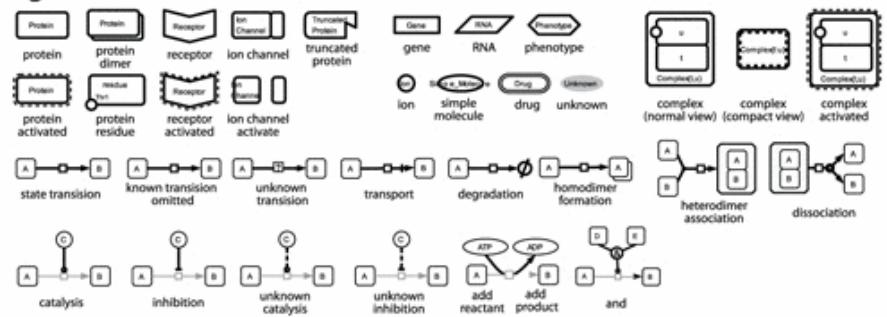


An example of signaling network



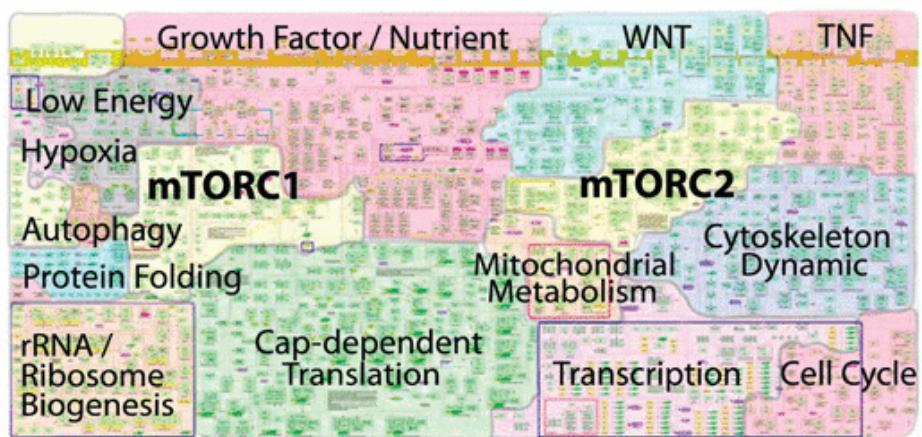


Legend



produced by

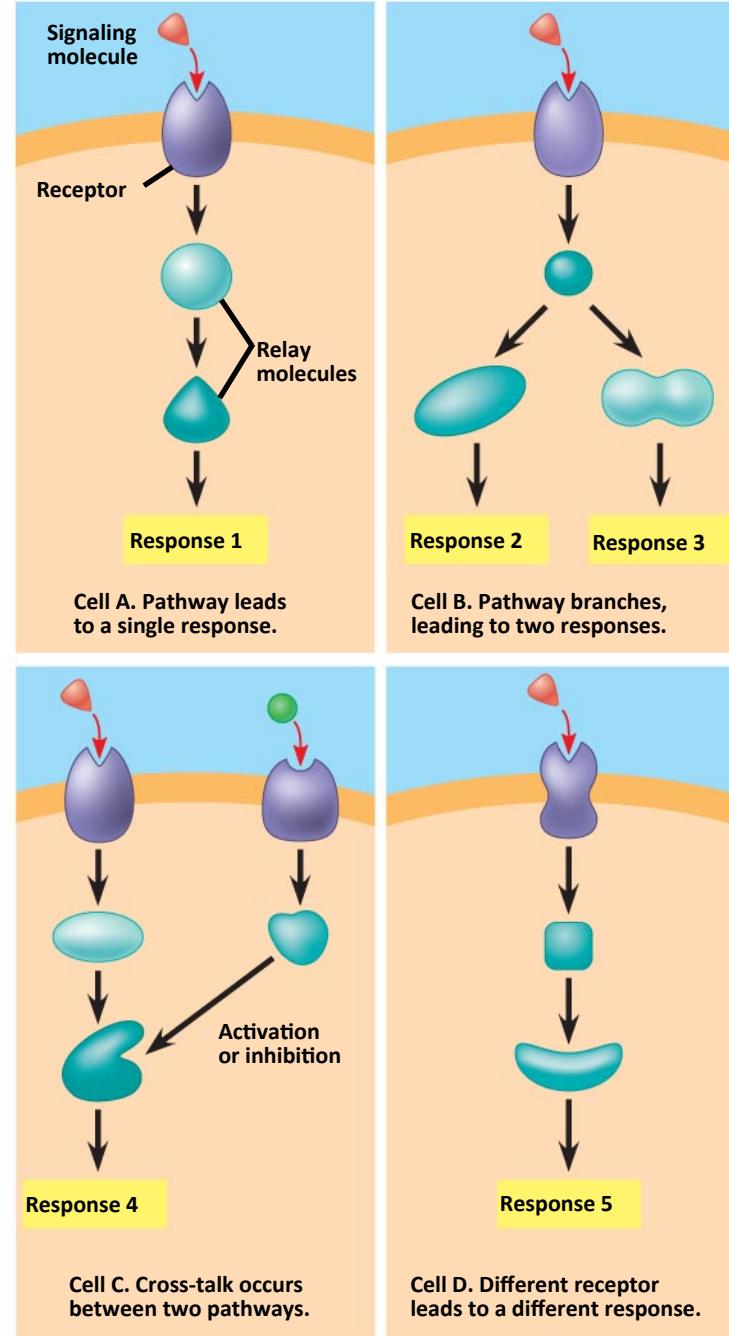
CellDesigner™ ver4.0.1



The Specificity of Cell Signaling and Coordination of the Response

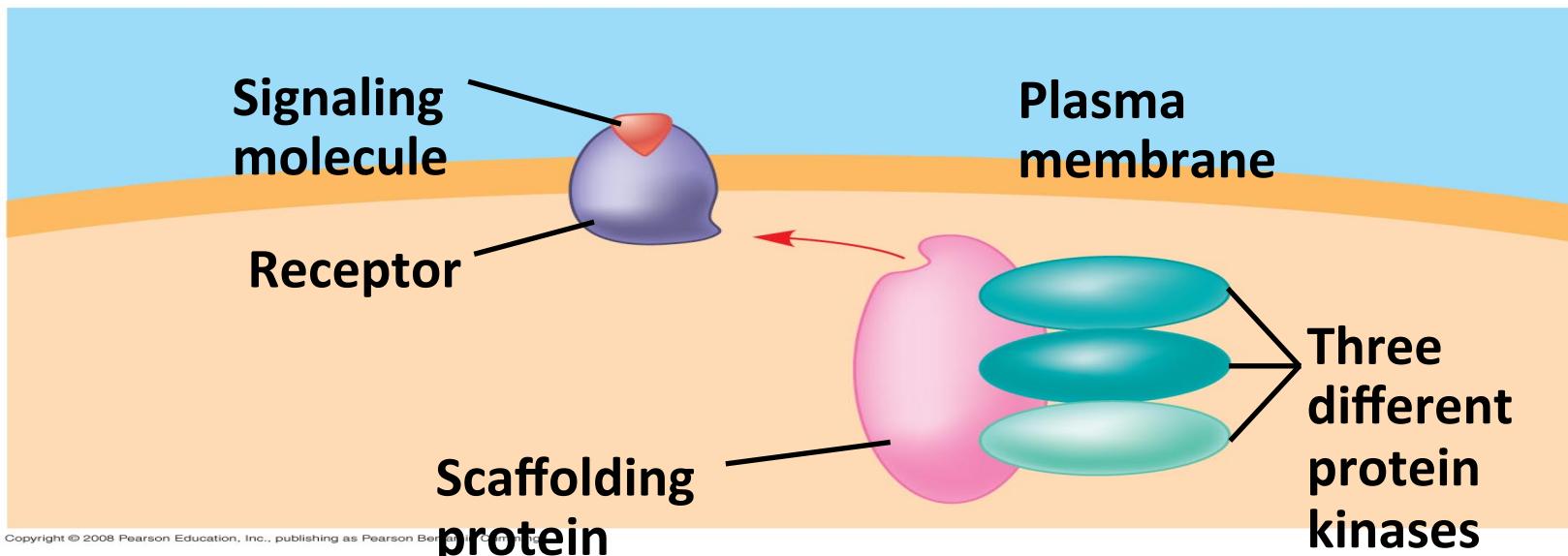
- Different kinds of cells have different collections of proteins
- These different proteins allow cells to detect and respond to different signals
- Even the same signal can have different effects in cells with different proteins and pathways
- Pathway branching and “cross-talk” further help the cell coordinate incoming signals

Fig. 11-17



Signaling Efficiency: Scaffolding Proteins and Signaling Complexes

- **Scaffolding proteins** are large relay proteins to which other relay proteins are attached
- Scaffolding proteins can increase the signal transduction efficiency by grouping together different proteins involved in the same pathway



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Termination of the Signal

- Inactivation mechanisms are an essential aspect of cell signaling
 - When signal molecules leave the receptor, the receptor reverts to its inactive state
 - Enhanced activities of dephosphorylase
 - Regulatory pathways initiated

Summary

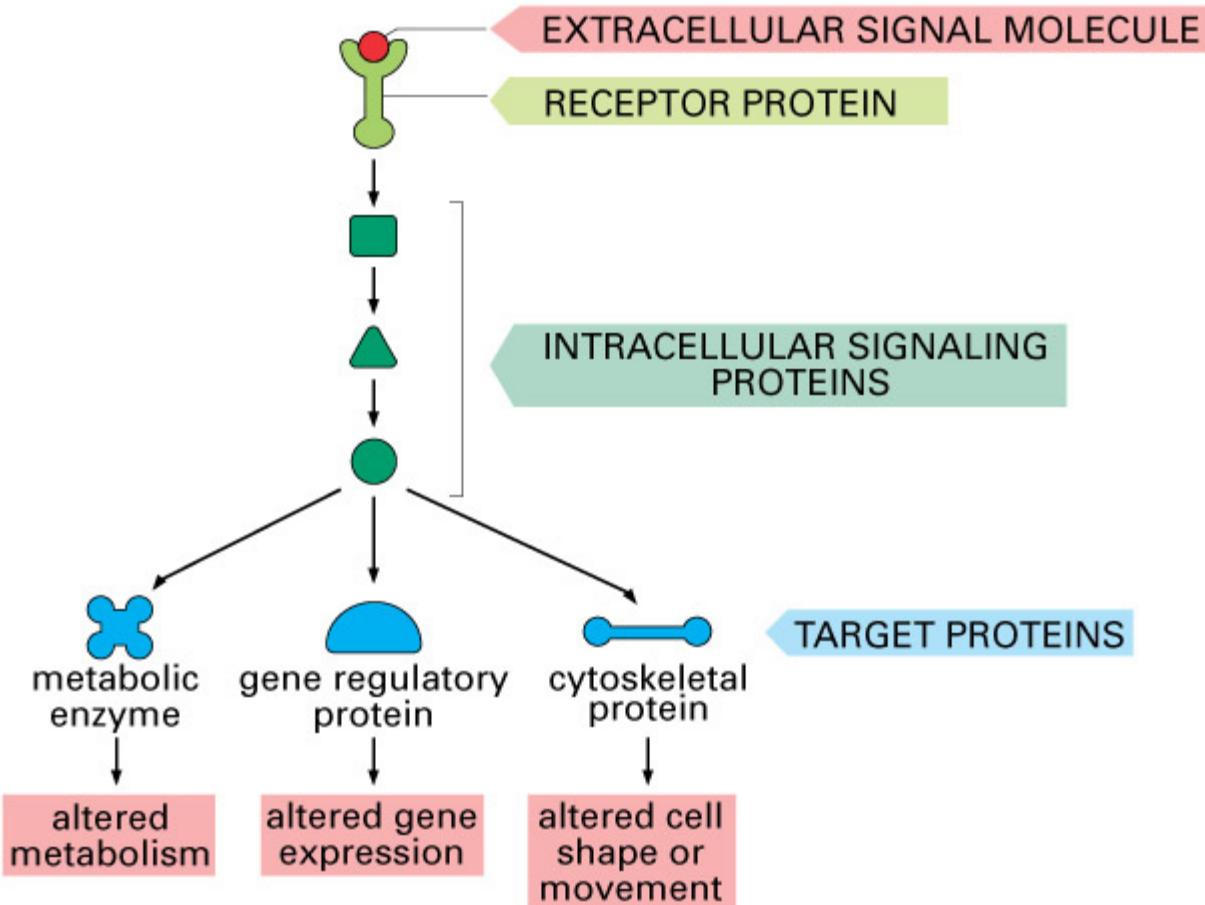


Figure 16-7 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Target Cell Action:

Depends upon ----

Signals That are Present

Receptors That Target Cell Synthesizes

Intracellular Relay Systems = Signaling Cascades That
Target Cell Synthesizes

Intracellular Targets That Target Cell Synthesizes

Any target cell type at any one time has only a subset
of all possible

Receptors,

Intracellular Relay Systems,

Intracellular Targets

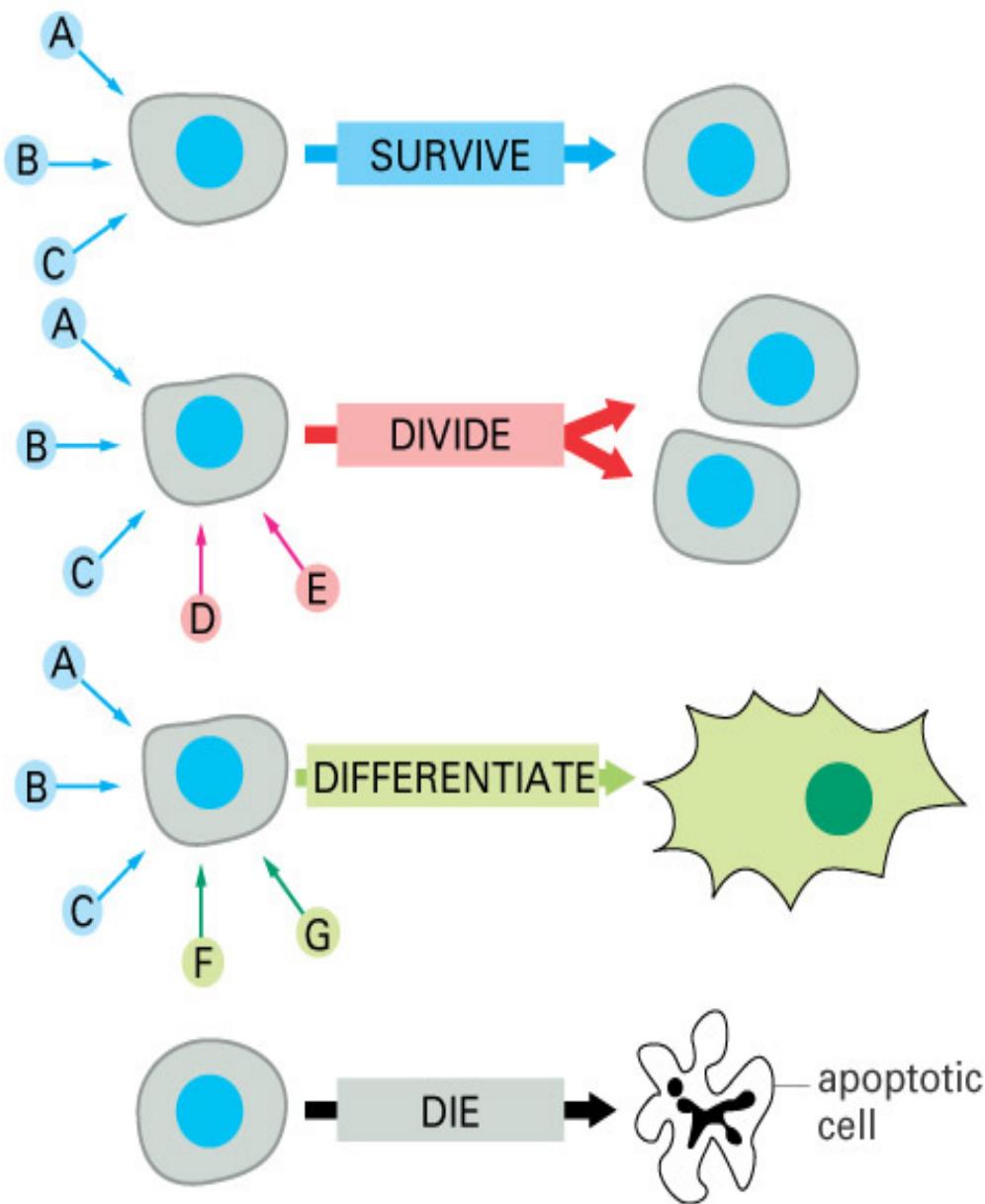
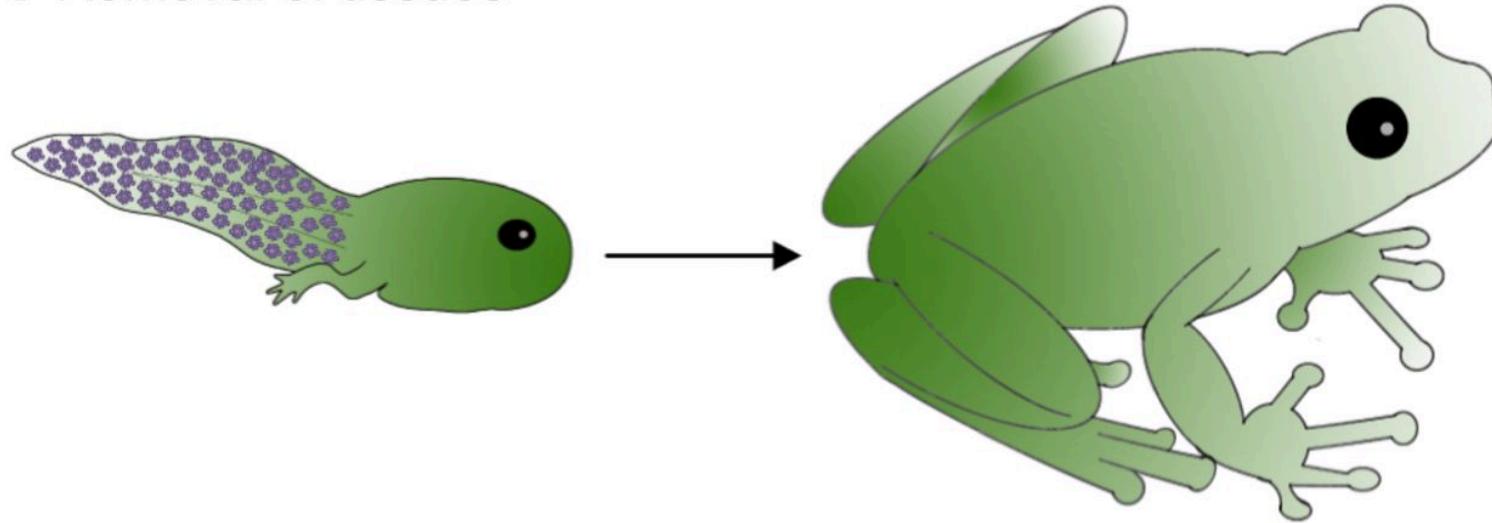


Figure 16-6 Essential Cell Biology, 2/e. (© 2004 Garland Science)

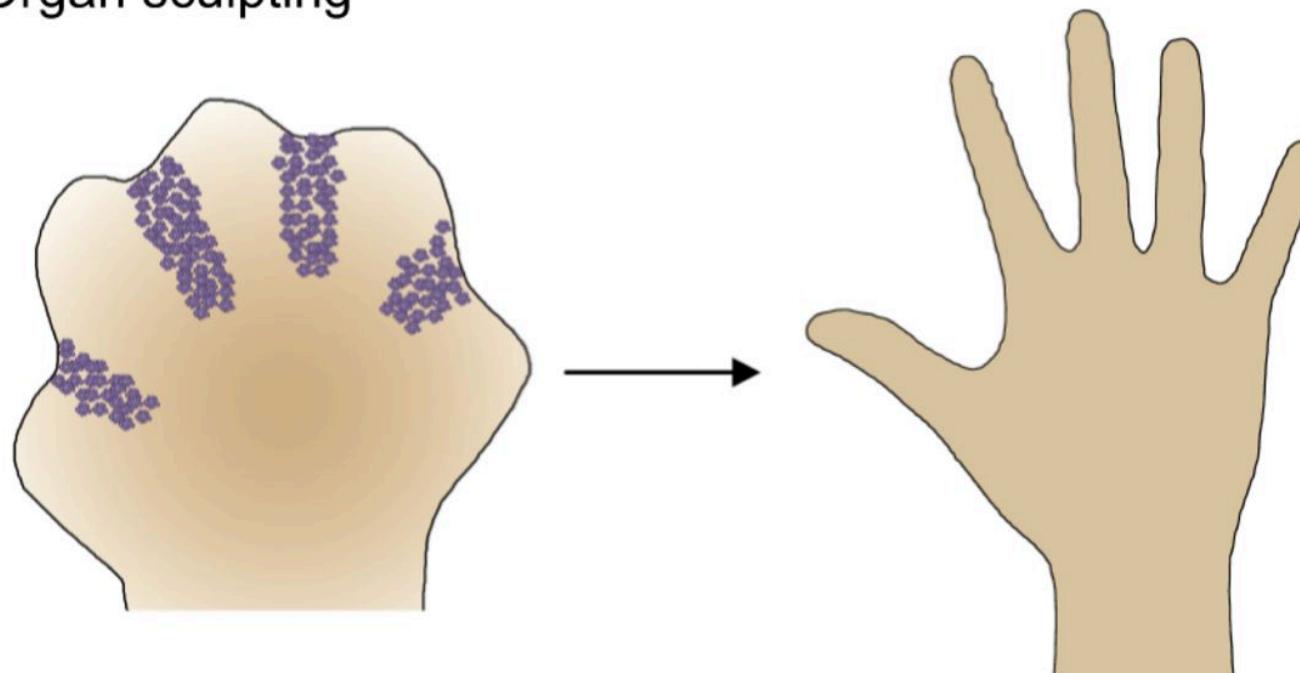
Apoptosis (programmed cell death) integrates multiple cell-signaling pathways

- **Apoptosis** is programmed or controlled cell suicide
- A cell is chopped and packaged into vesicles that are digested by scavenger cells
- Apoptosis prevents enzymes from leaking out of a dying cell and damaging neighboring cells

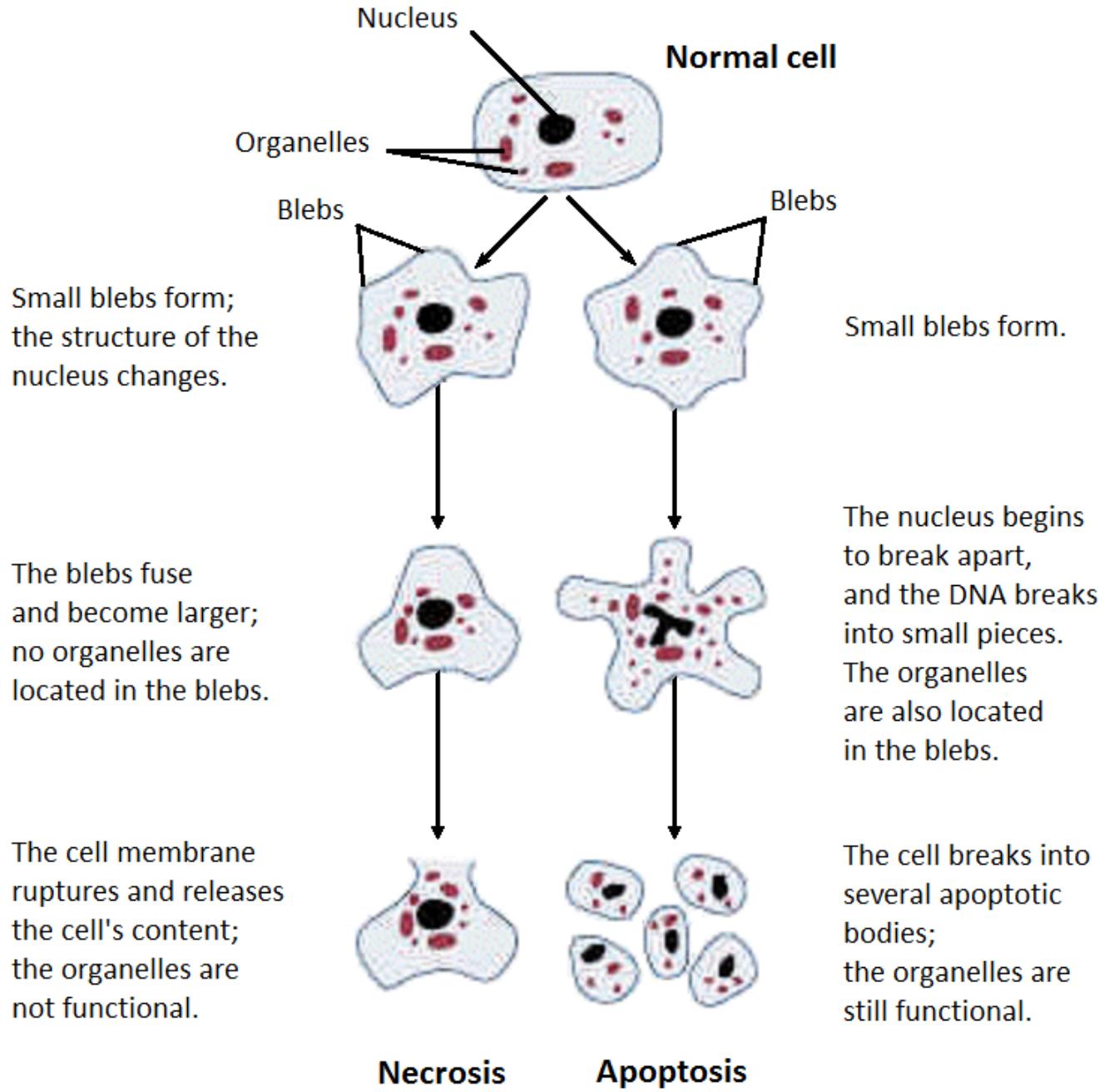
A Removal of tissues



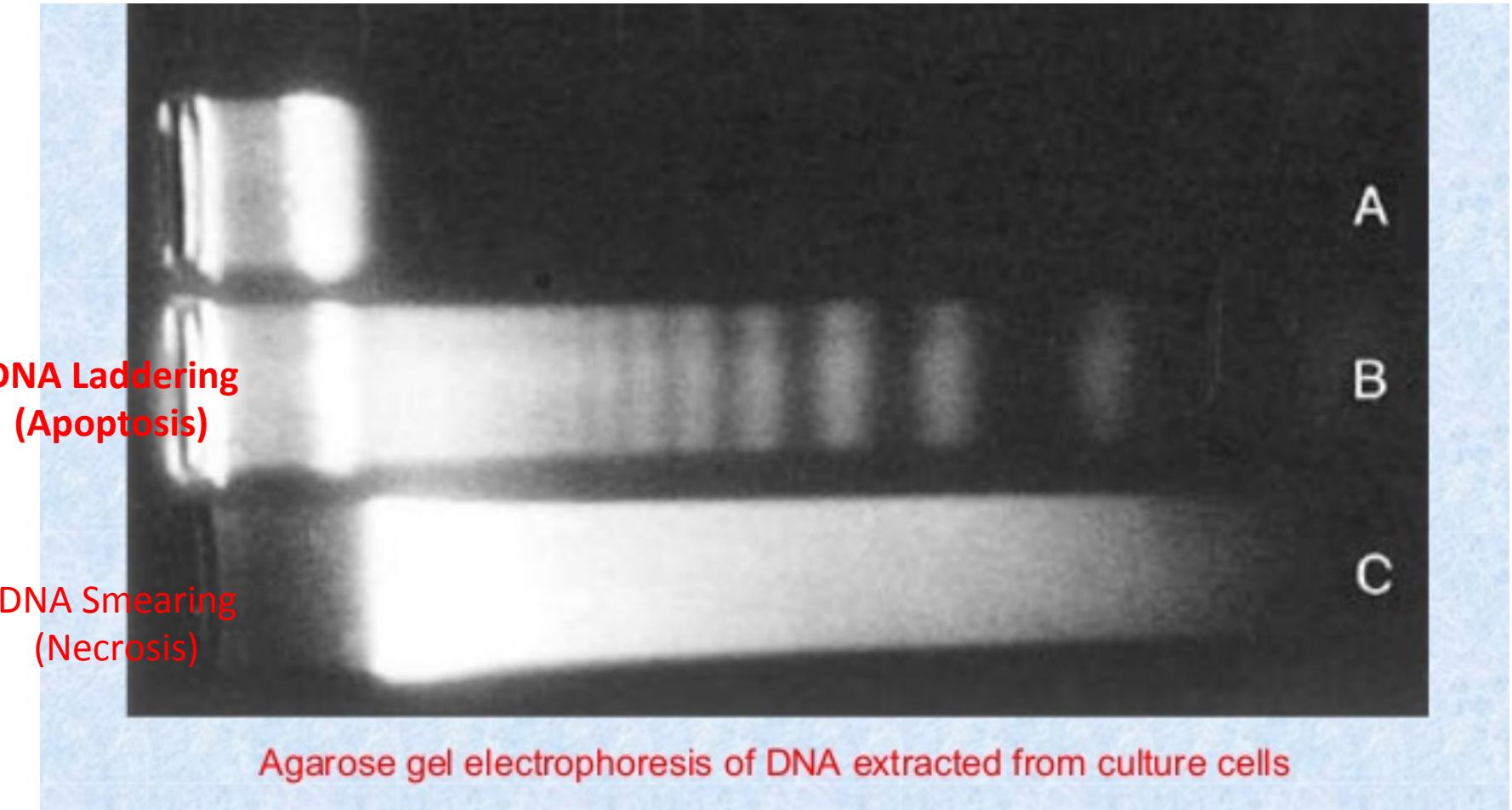
B Organ sculpting



Key Apoptotic cell



Knowing whether death is by apoptosis or necrosis



Cytotoxicity detected by flow cytometry

Annexin/PI Staining

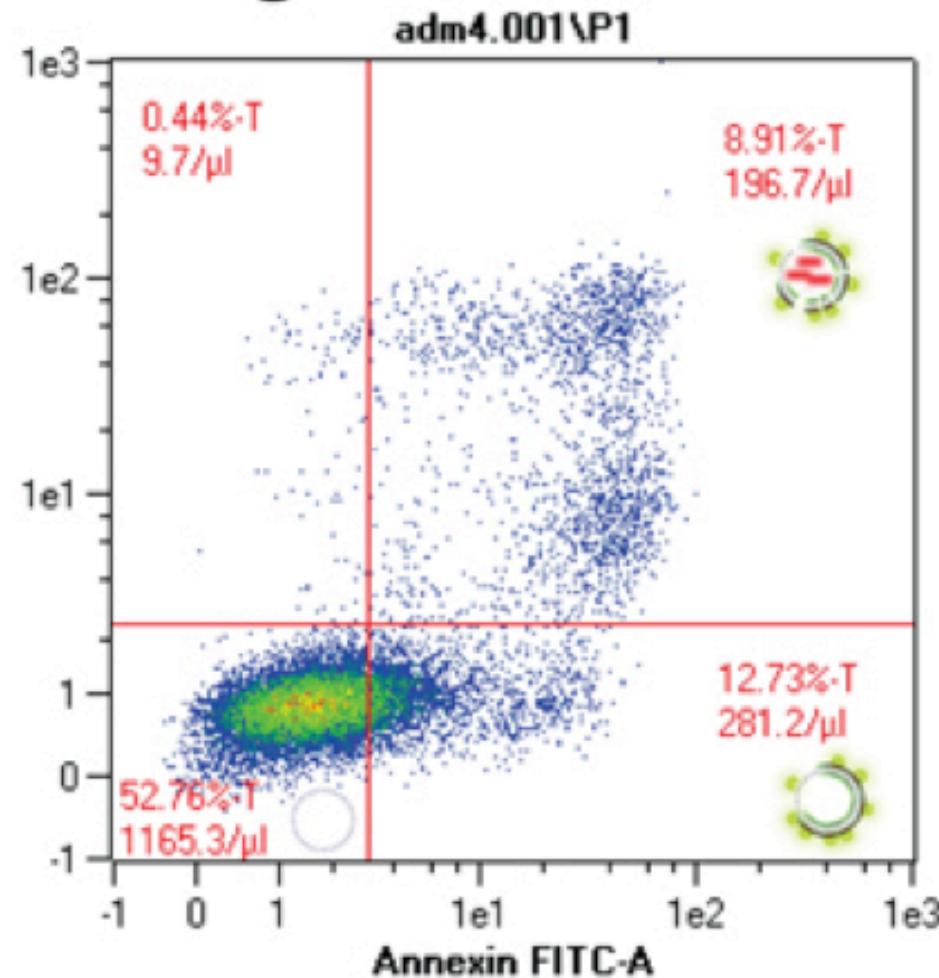
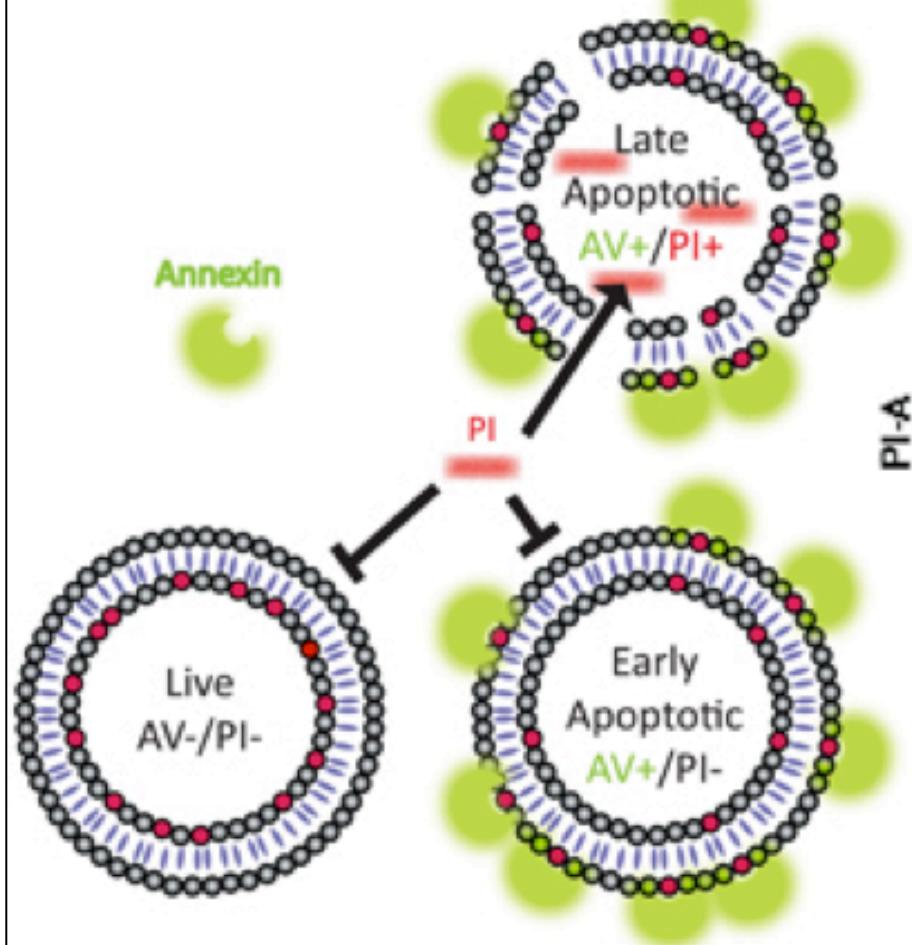
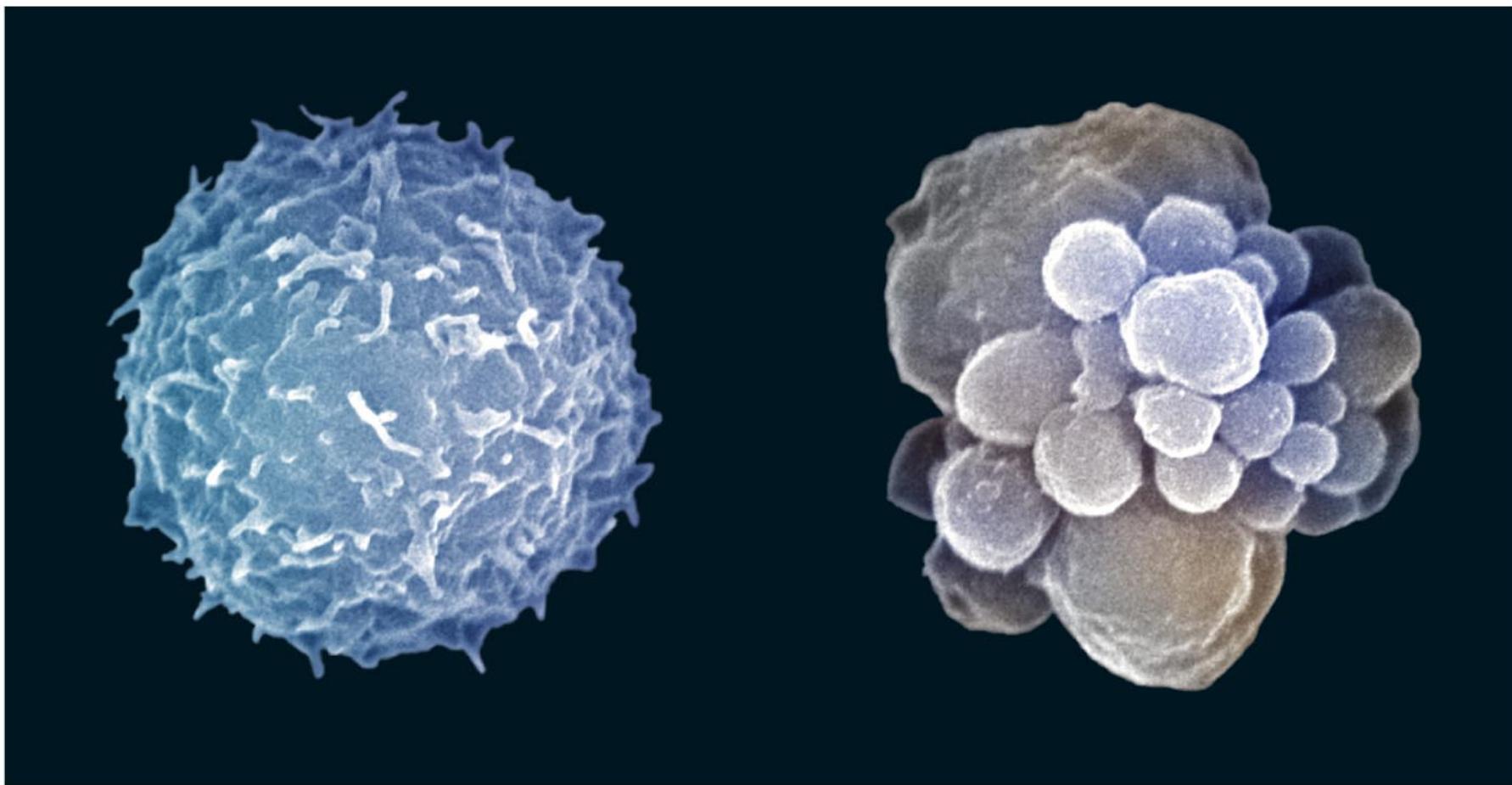


Fig. 11-19

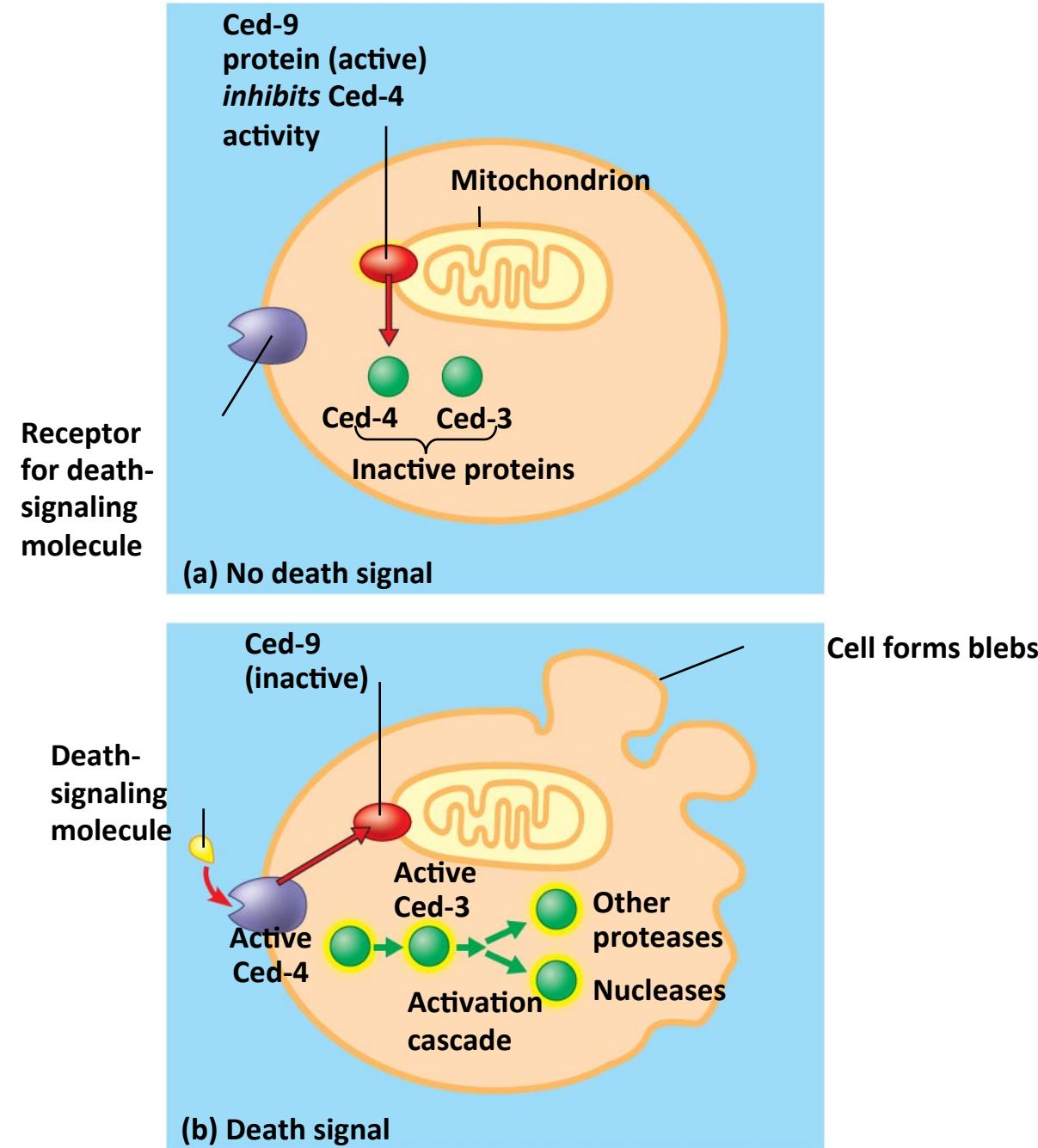


2 μm

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Feature	Apoptosis	Necrosis
Cell membrane	Intact	Leaky
Inflammation	Absent	Present
Cytosolic proteins	Normal	Altered
Cell death	Programmed	Unregulated
Leakage of contents	No leakage	Leakage occurs
Setting	Occurs normally also	Always pathological
Mechanisms	Similarities exist	Similarities exist
Number of cells involved	Single cell or a few cells	Numerous cells
Cell death	Final event	Initial event

Fig. 11-20



Apoptotic Pathways and the Signals That Trigger Them

- **Caspases** are the main proteases (enzymes that cut up proteins) that carry out apoptosis
- Apoptosis can be triggered by:
 - An extracellular death-signaling ligand
 - DNA damage in the nucleus
 - Protein misfolding in the endoplasmic reticulum
- Apoptosis evolved early **in animal evolution** and is essential for the development and maintenance of all animals
- Apoptosis may be involved in some diseases (for example, Parkinson's and Alzheimer's); interference with apoptosis may contribute to some cancers

Fig. 11-UN2

