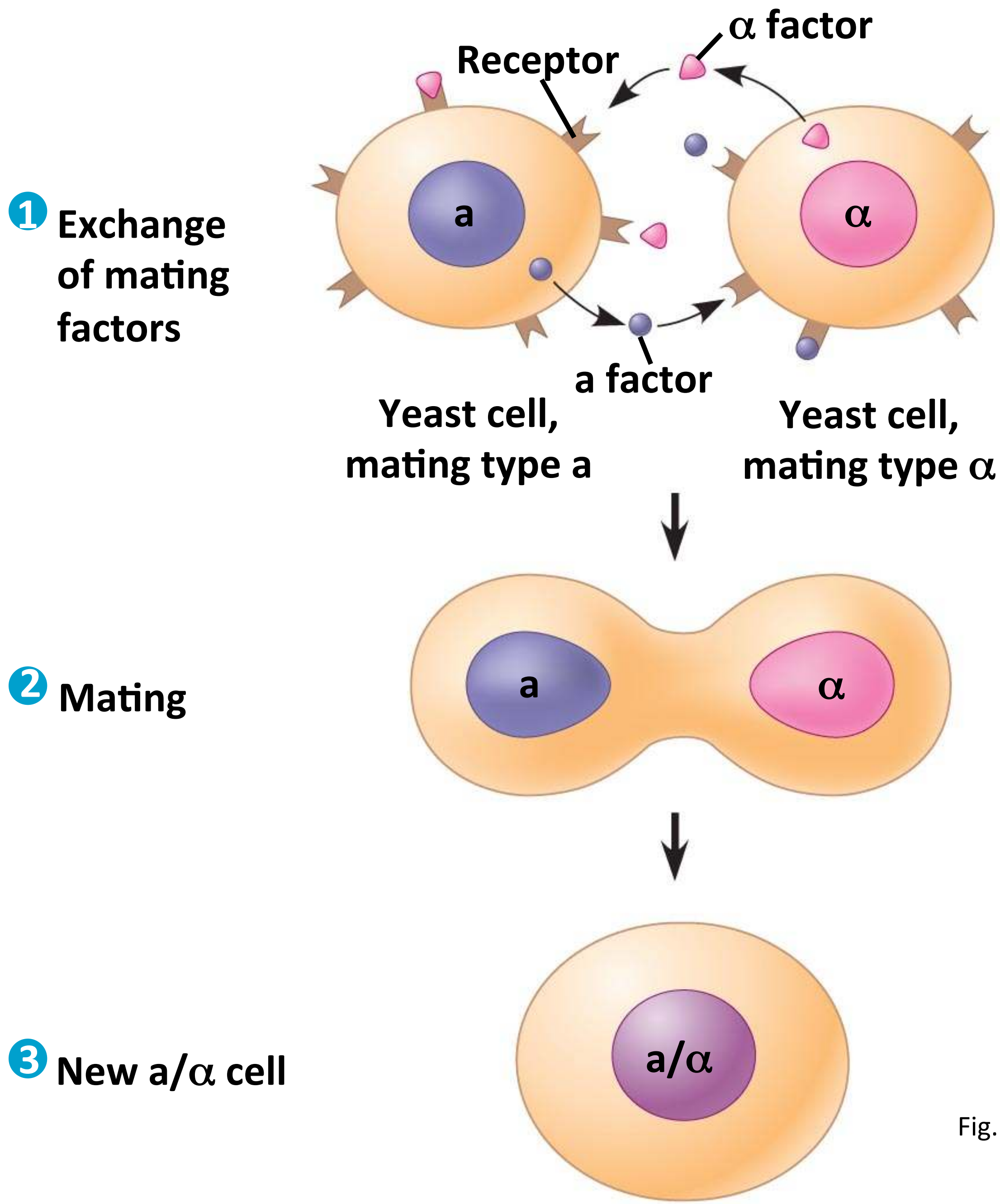
How cells communicate with each other or cell signaling

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



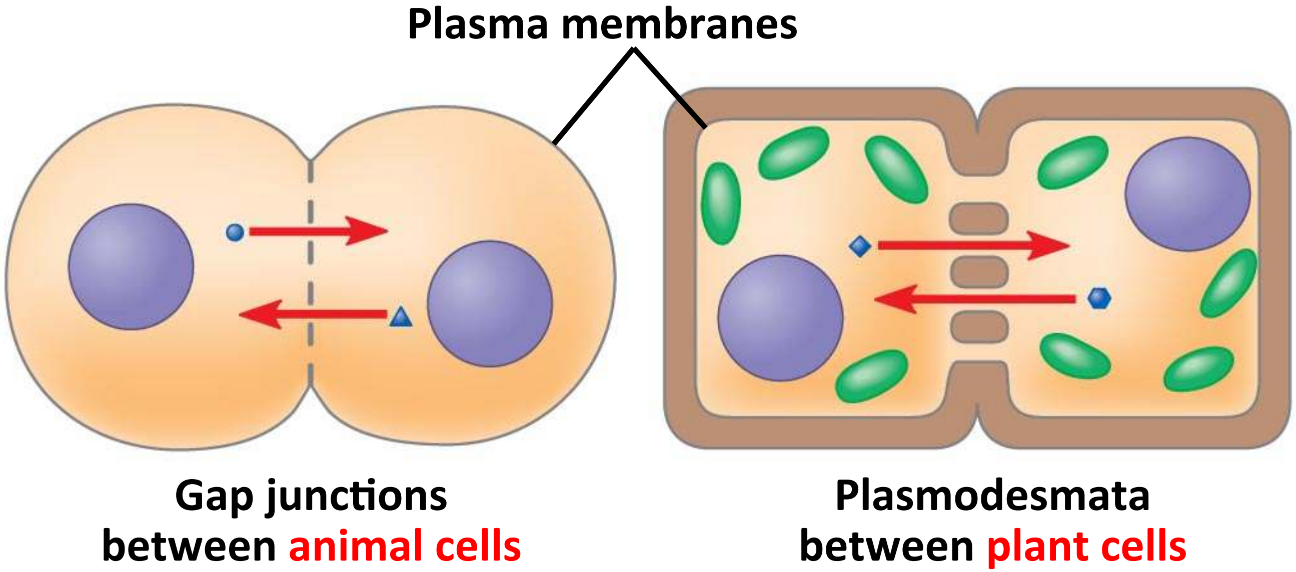
α factor
Receptor
a
α
1 Exchange of mating factors
a factor
Yeast cell, mating type a
Yeast cell, mating type α
2 Mating
a
α
3 New a/α cell
a/α

Fig. 11-2

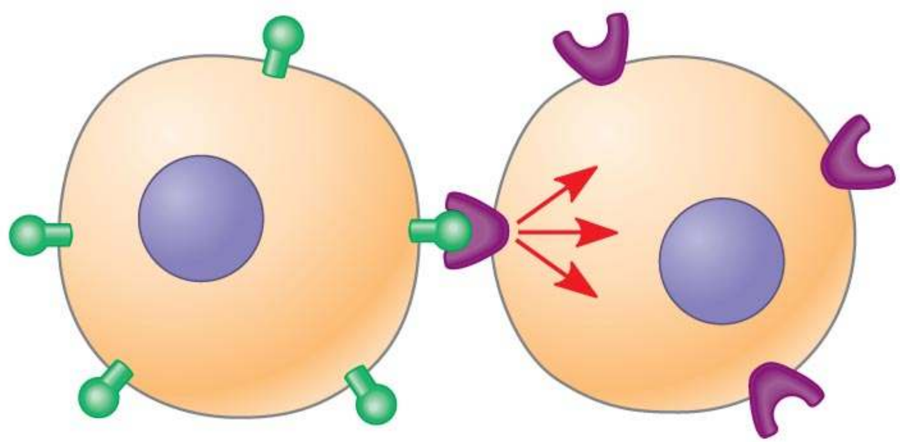
Local and Long-Distance Signaling

- 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



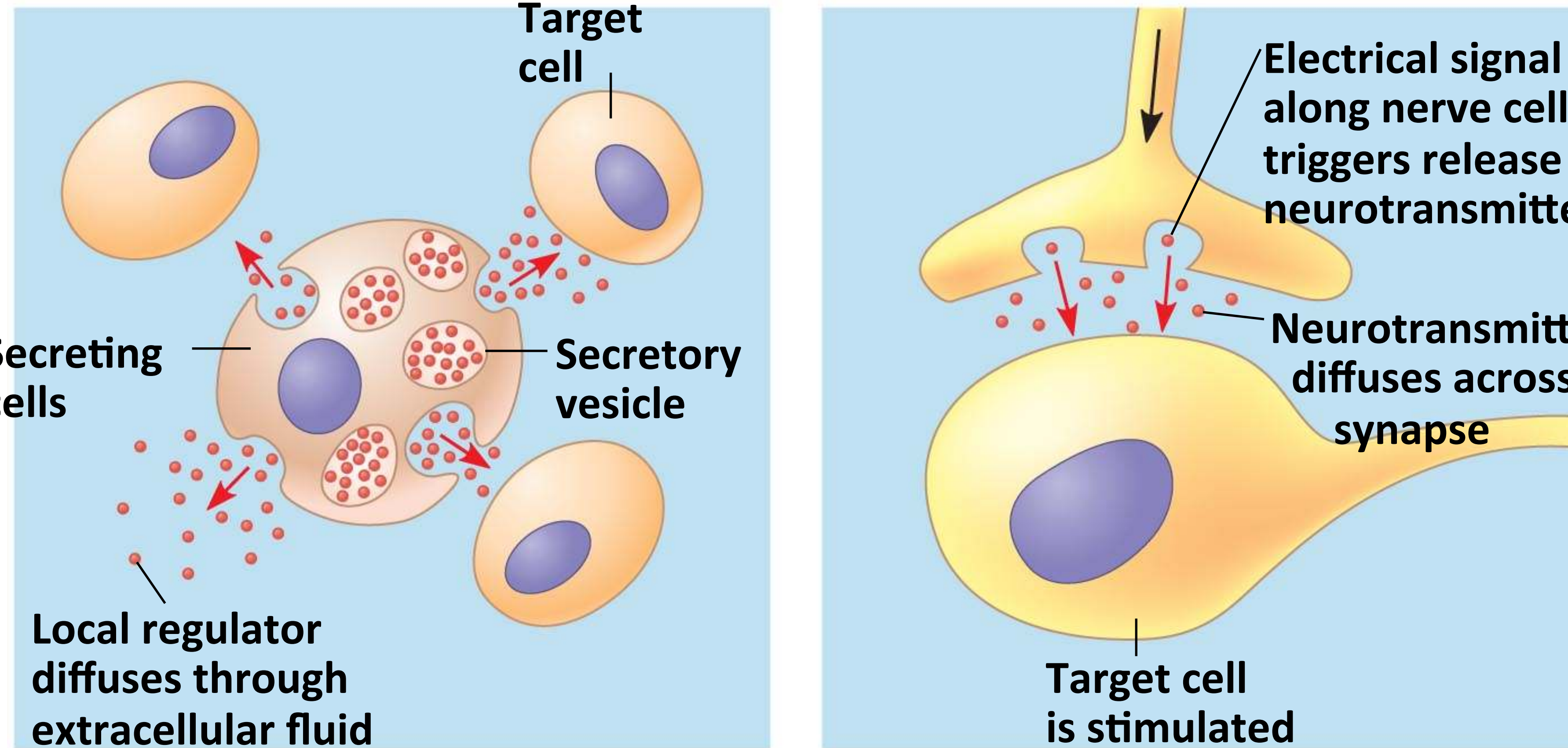
(a) Cell junctions



(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

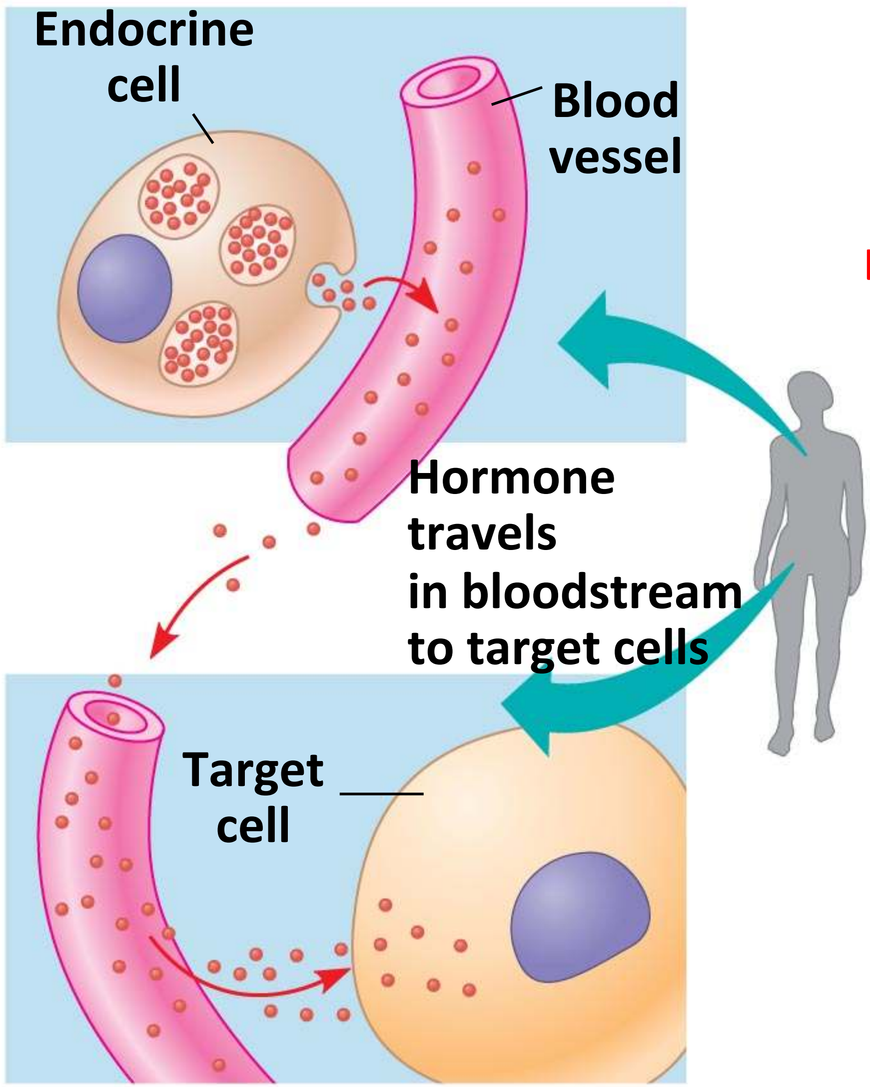


(a) Paracrine signaling

(b) Synaptic signaling

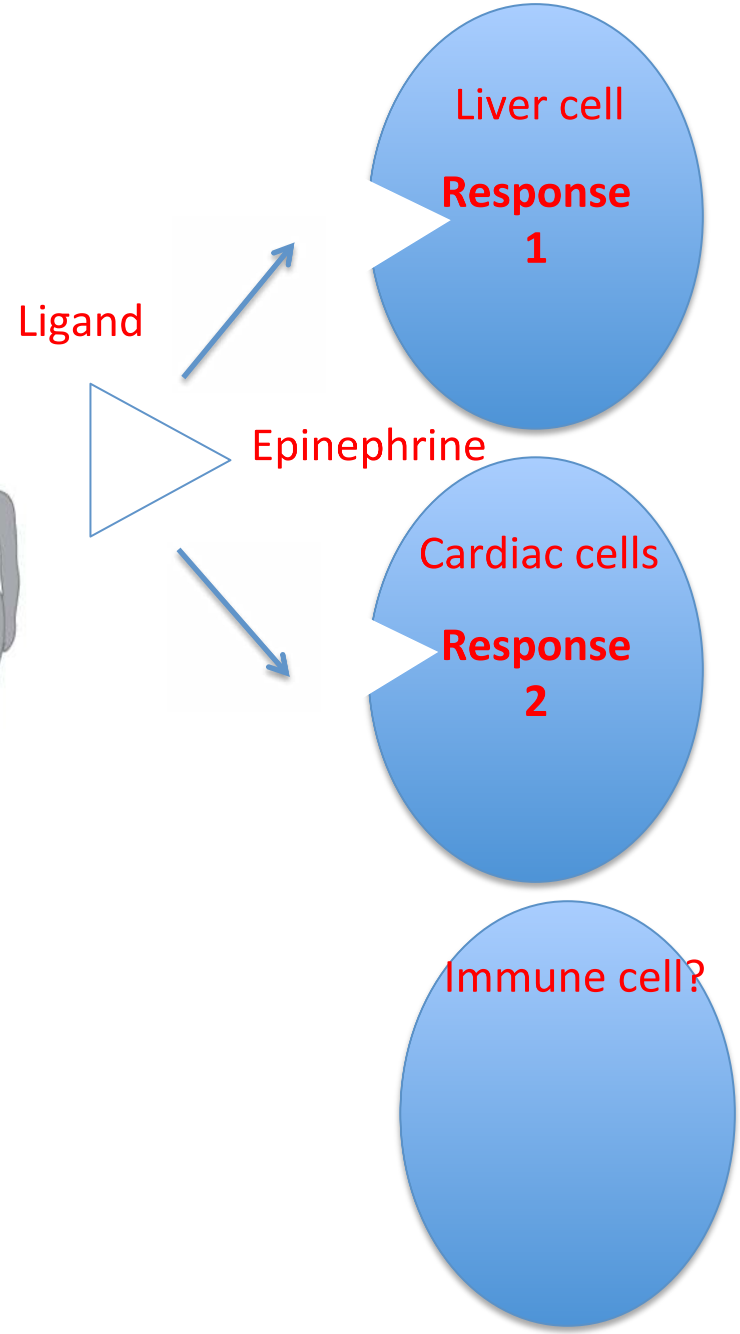
Fig. 11-5ab

Long-distance signaling



(c) Hormonal 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

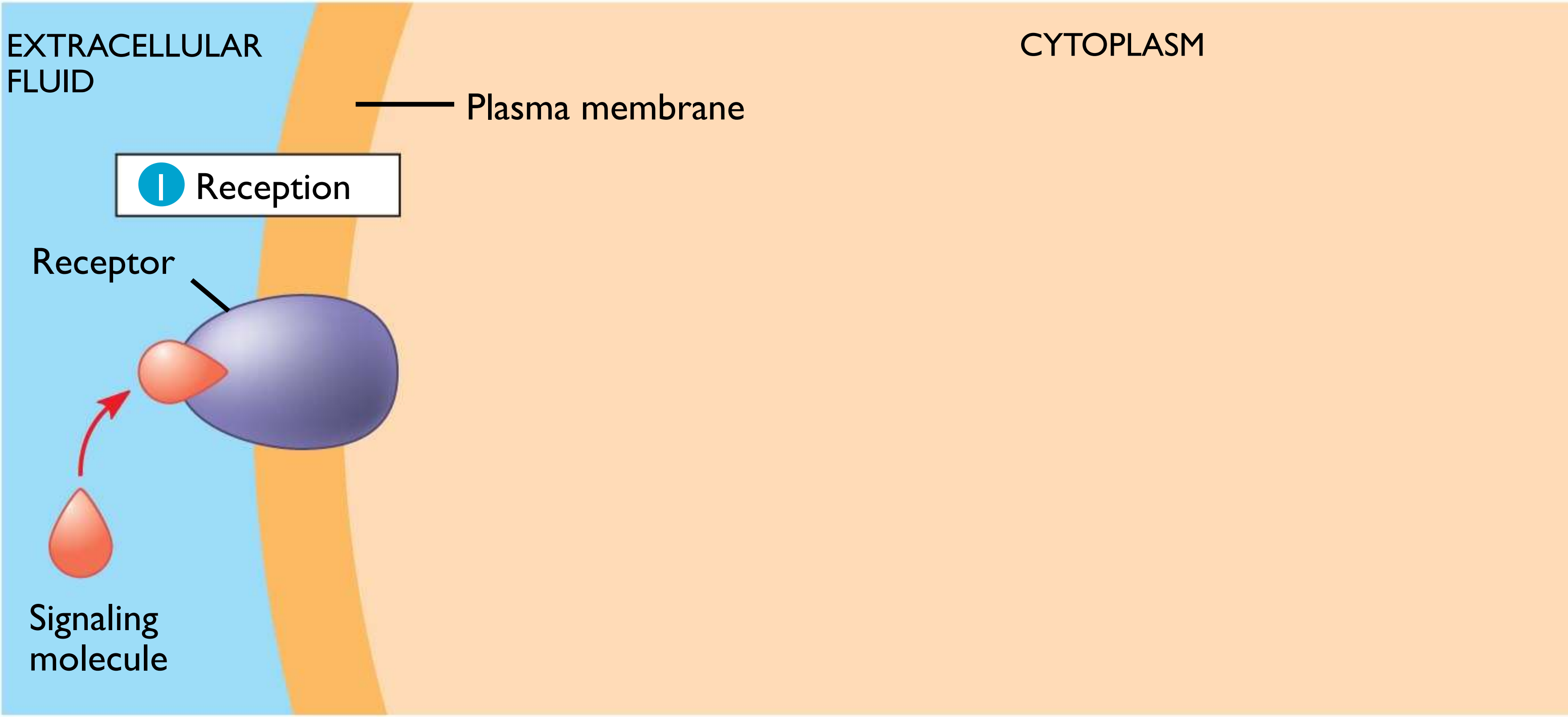

EXTRACELLULAR FLUID
CYTOPLASM
Plasma membrane
1 Reception
Receptor
Signaling molecule

Fig. 11-6-2

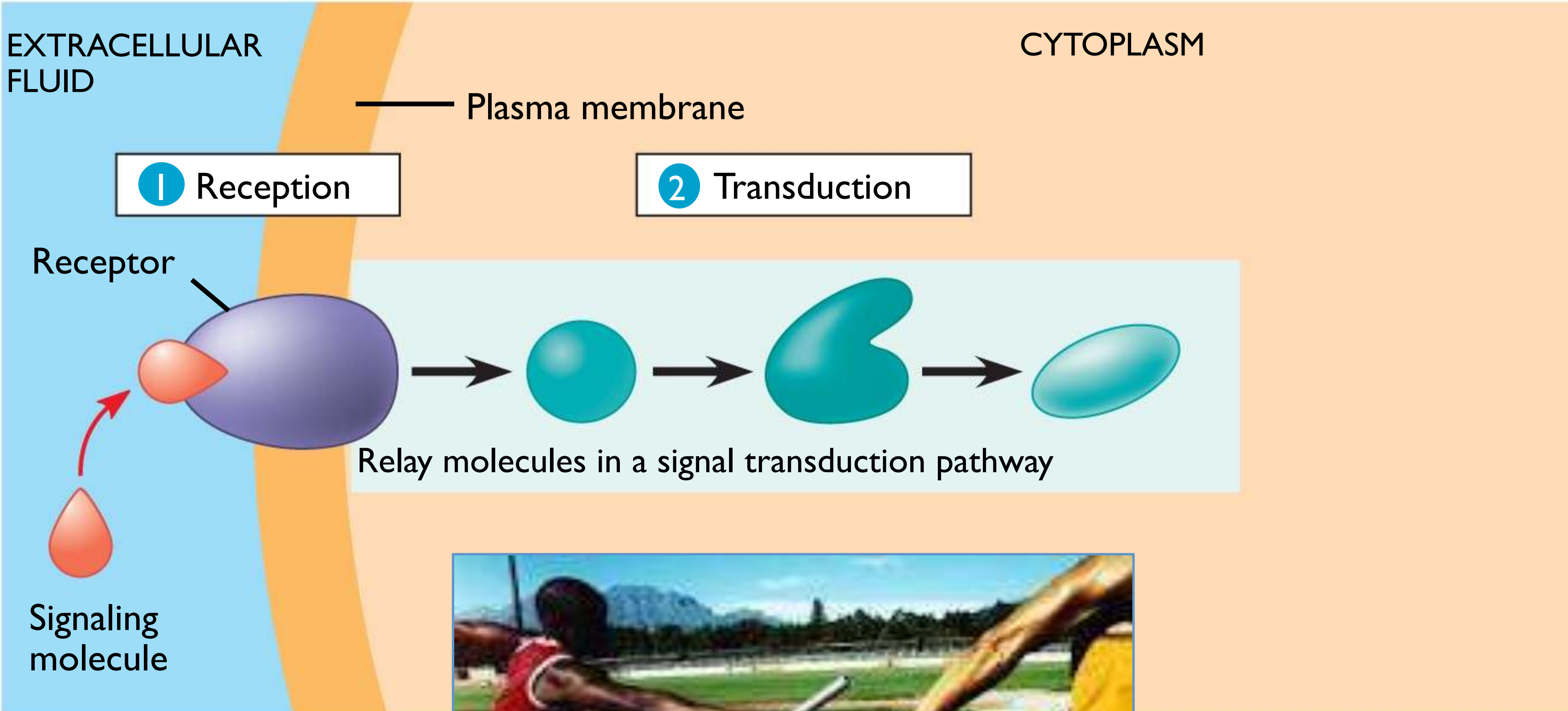
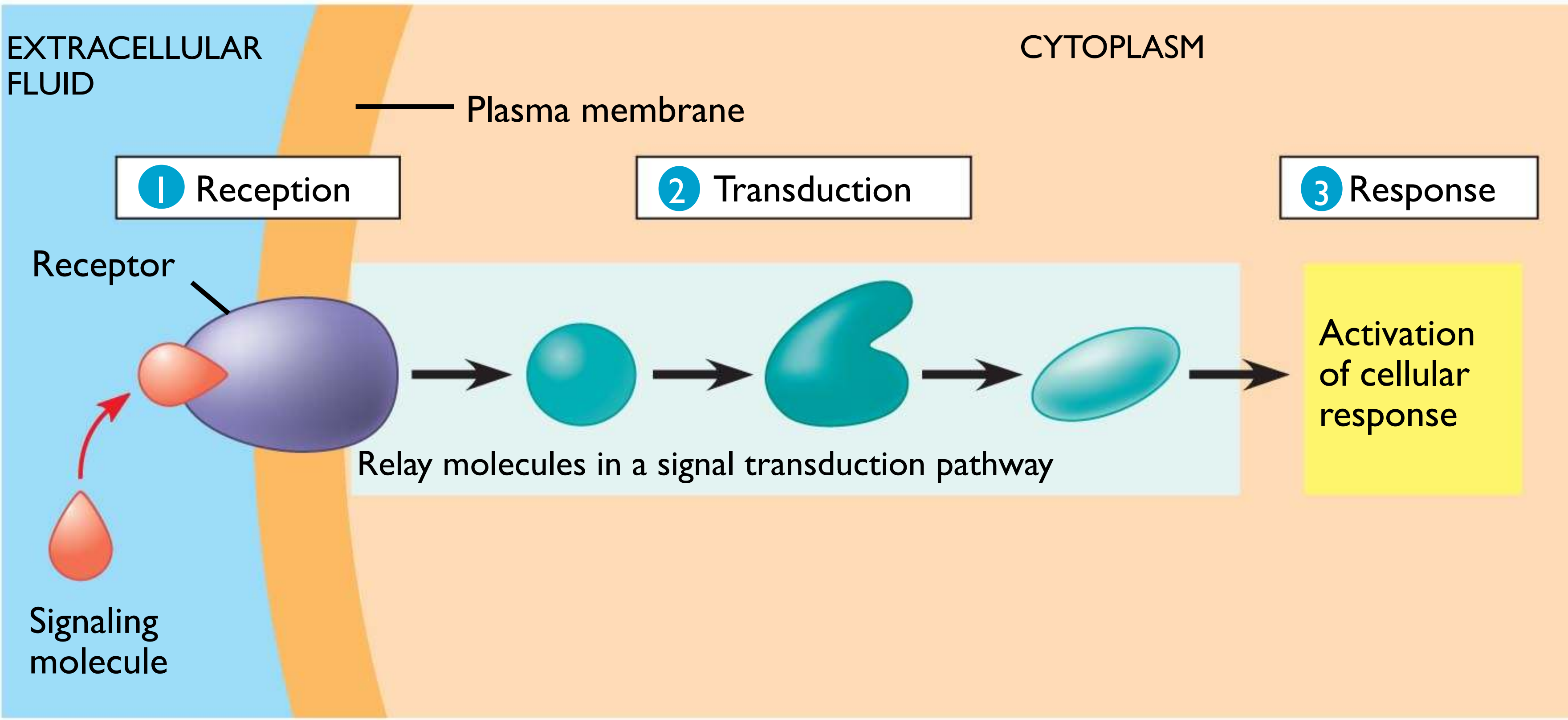

EXTRACELLULAR FLUID
CYTOPLASM
Plasma membrane
1 Reception
2 Transduction
Receptor
Relay molecules in a signal transduction pathway
Signaling molecule

Fig. 11-6-3



EXTRACELLULAR FLUID
CYTOPLASM
Plasma membrane
1 Reception
2 Transduction
3 Response
Receptor
Activation of cellular response
Relay molecules in a signal transduction pathway
Signaling molecule

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

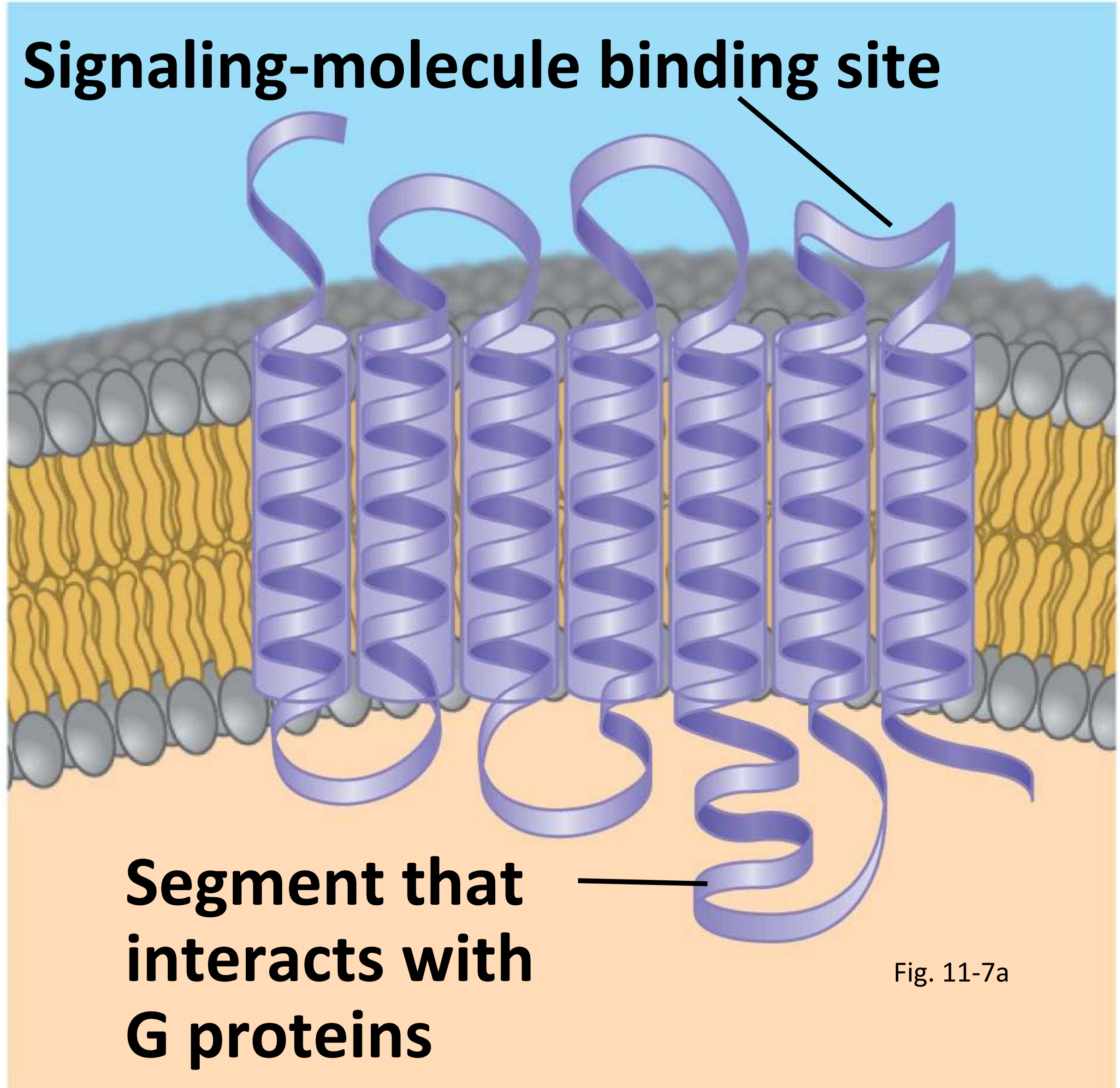
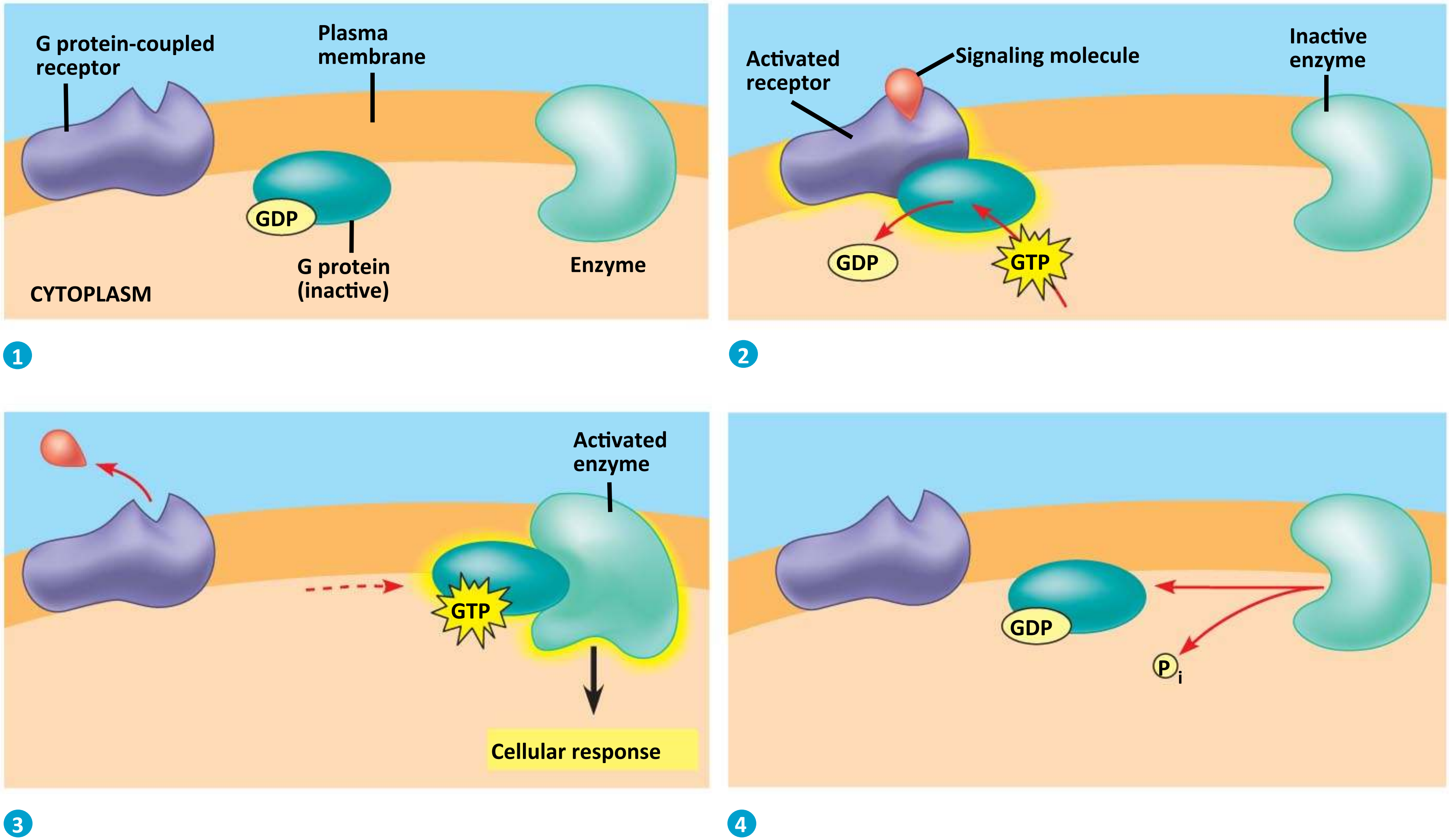


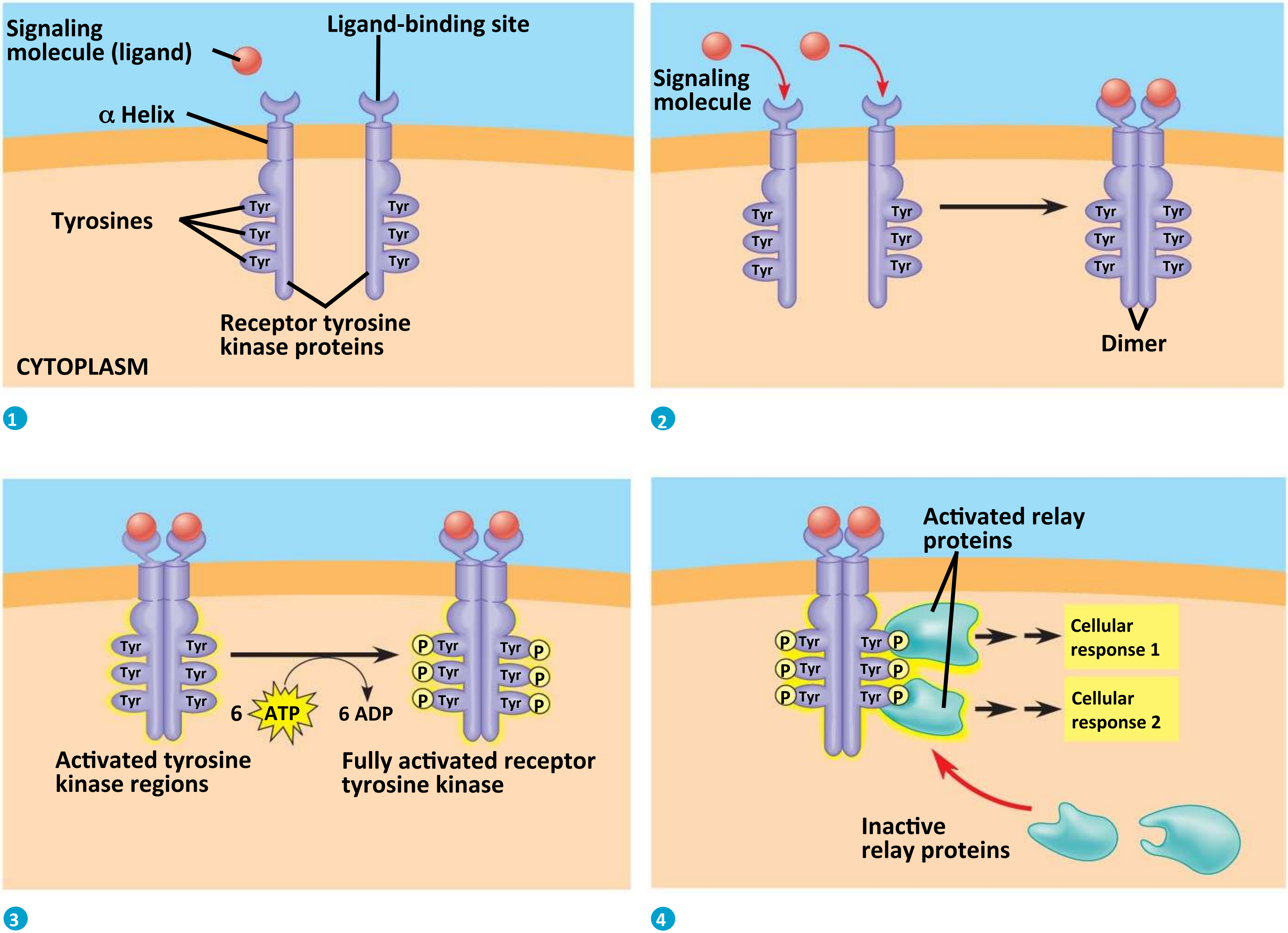
Fig. 11-7a

G protein-coupled receptor


G protein-coupled receptor
Plasma membrane
GDP
G protein (inactive)
Enzyme
CYTOPLASM
1
Activated receptor
Signaling molecule
Inactive enzyme
GDP
GTP
2
Activated enzyme
GTP
Cellular response
3
GDP
P i
4

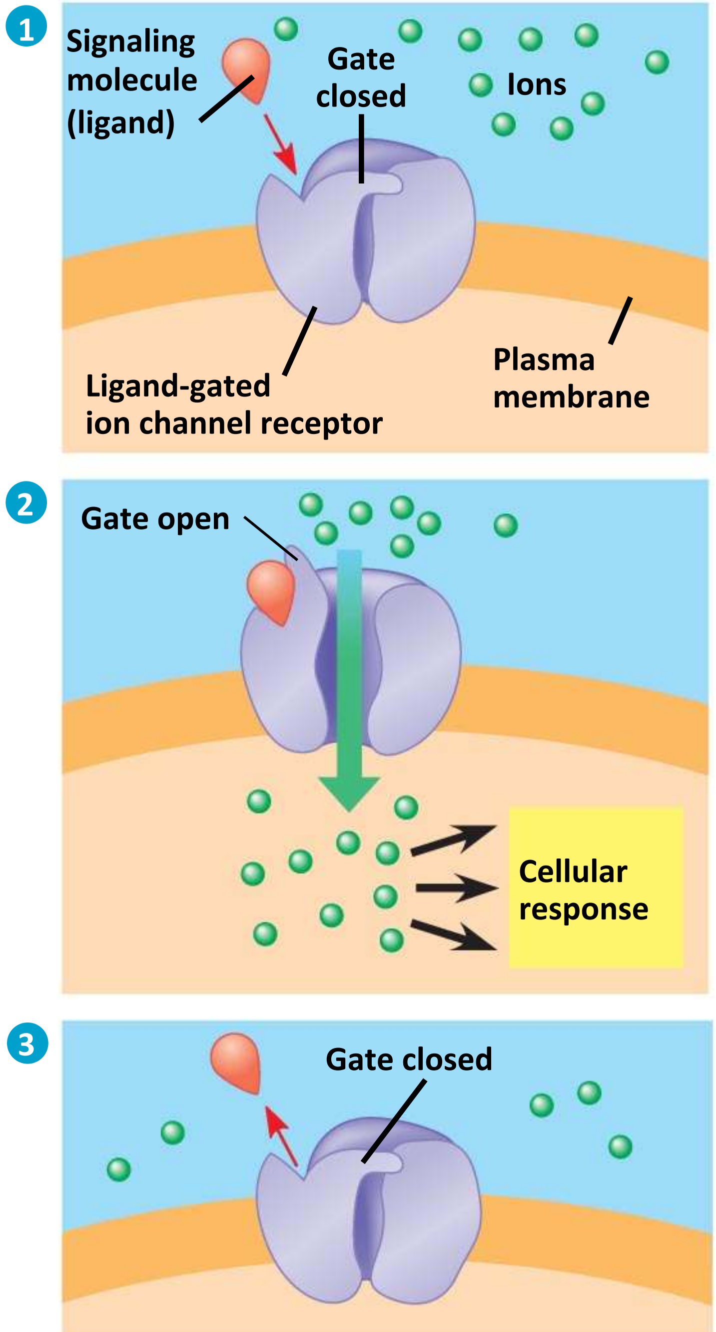
Receptor tyrosine kinases are membrane receptors that attach phosphates to tyrosines

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

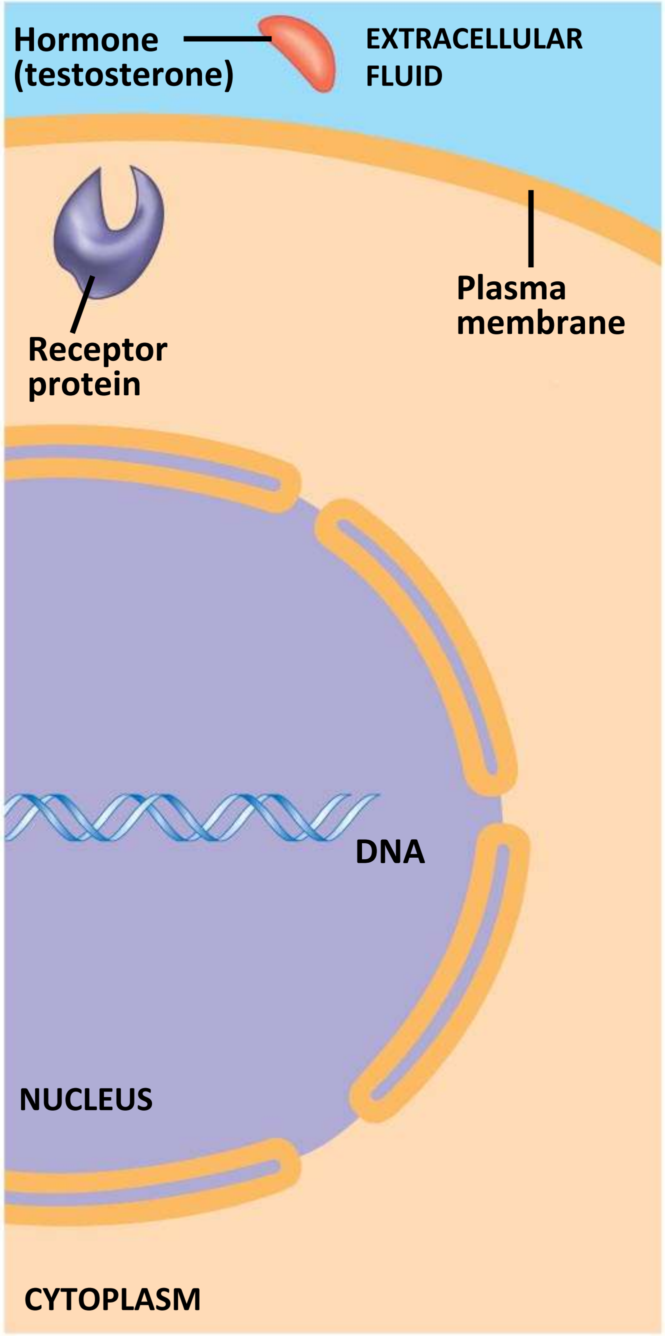
Fig. 11-7d


1
Signaling molecule (ligand)
Gate closed
Ions
Ligand-gated ion channel receptor
Plasma membrane
2
Gate open
Cellular response
3
Gate closed

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



Hormone
(testosterone)
EXTRACELLULAR
FLUID
Receptor
protein
Plasma
membrane
DNA
NUCLEUS
CYTOPLASM

Fig. 11-8-2

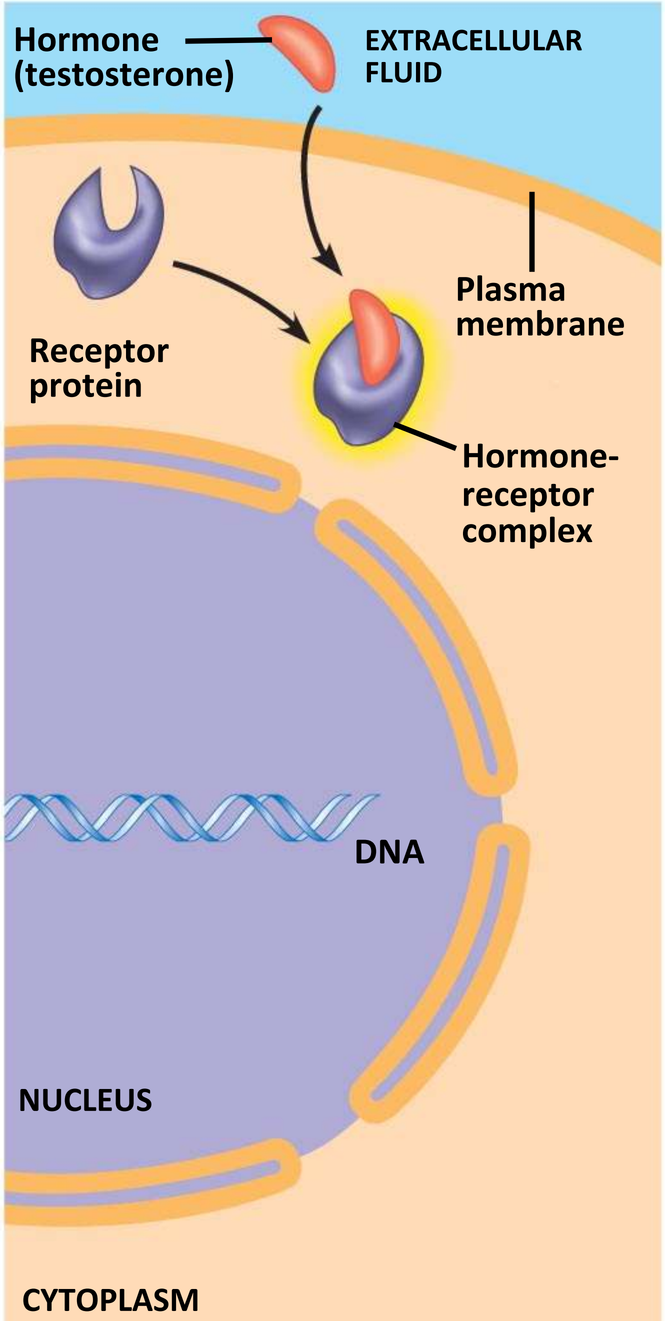
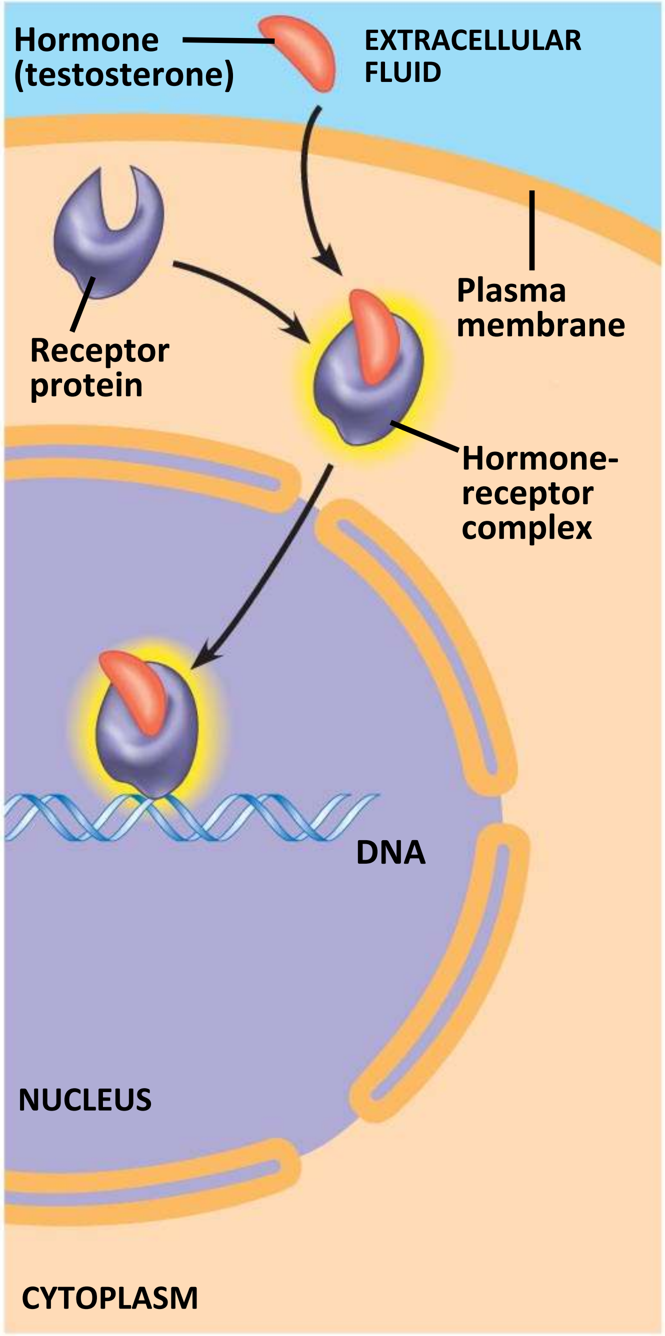
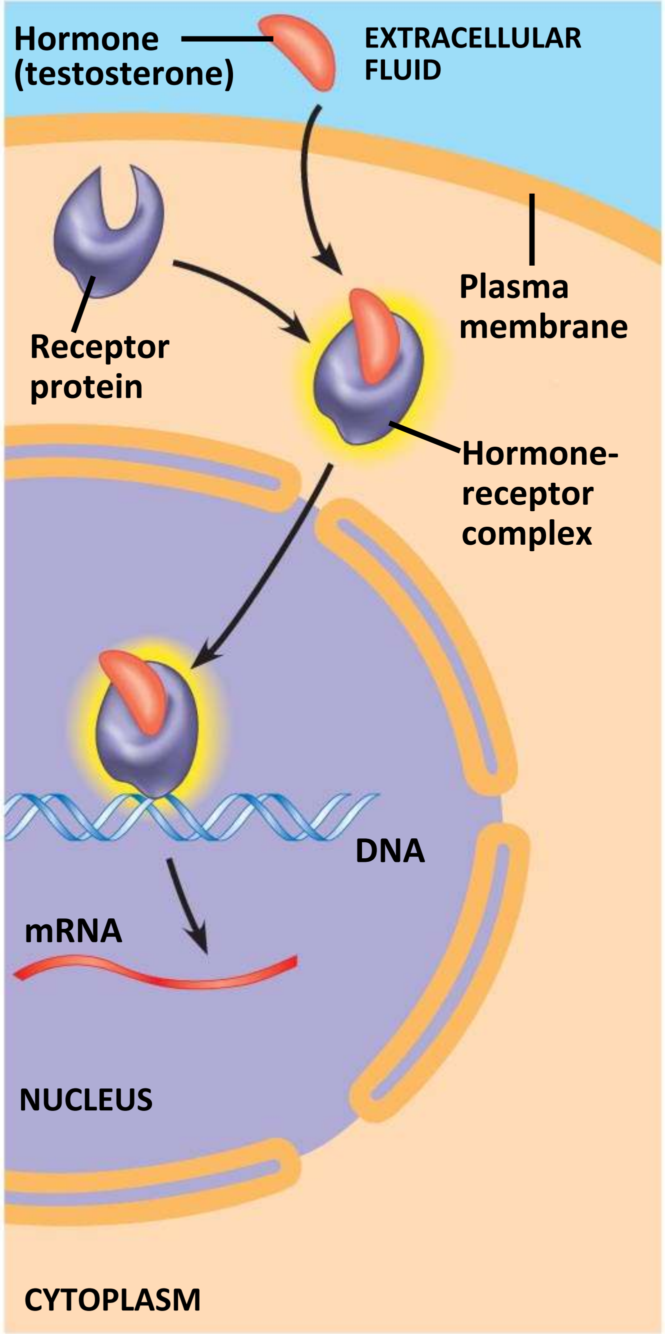

Hormone
(testosterone)
EXTRACELLULAR
FLUID
Plasma
membrane
Receptor
protein
Hormone-
receptor
complex
DNA
NUCLEUS
CYTOPLASM

Fig. 11-8-3



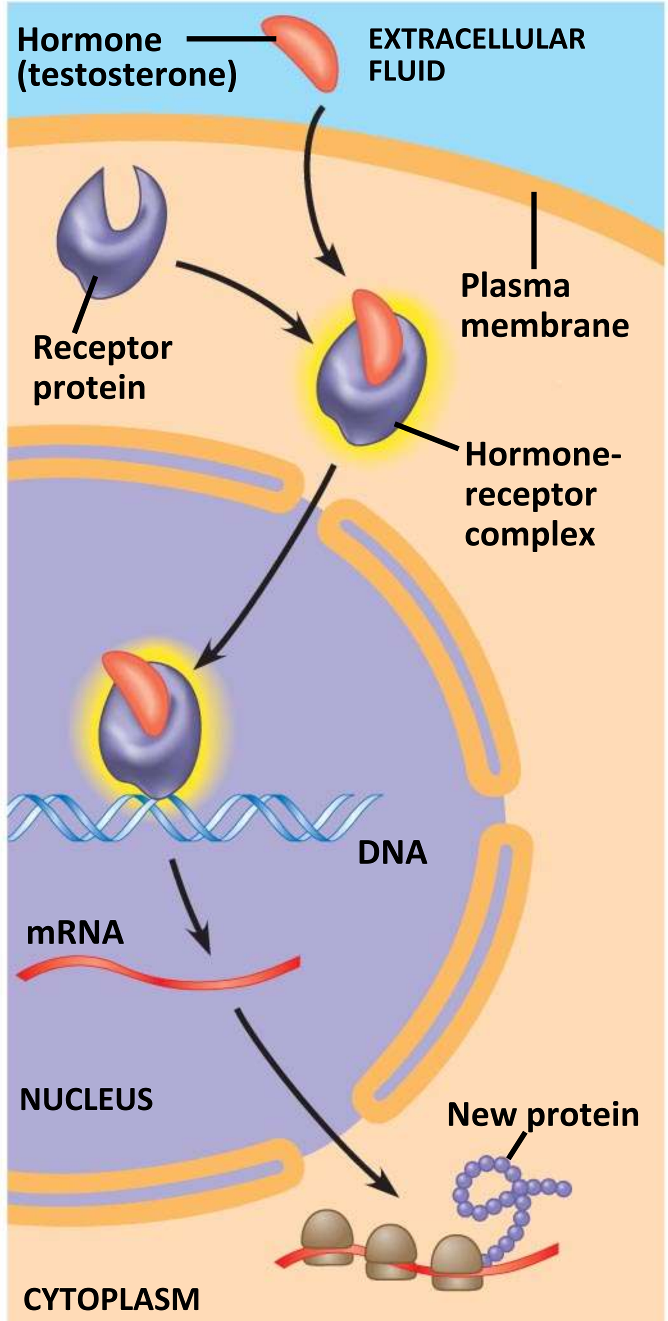
Hormone
(testosterone)
EXTRACELLULAR
FLUID
Plasma
membrane
Receptor
protein
Hormone-
receptor
complex
DNA
NUCLEUS
CYTOPLASM

Fig. 11-8-4



Hormone
(testosterone)
EXTRACELLULAR
FLUID
Plasma
membrane
Receptor
protein
Hormone-
receptor
complex
DNA
mRNA
NUCLEUS
CYTOPLASM

Fig. 11-8-5



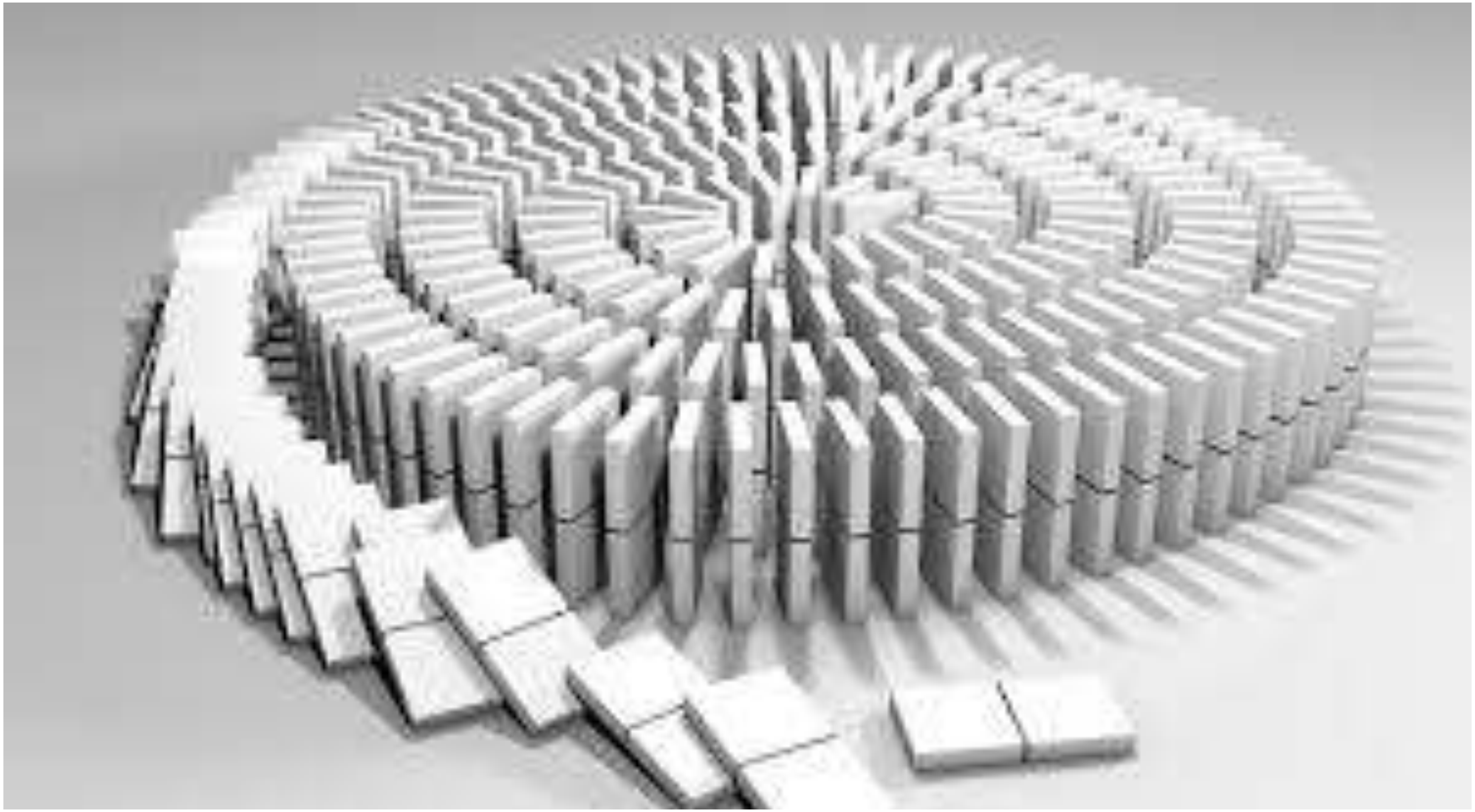
Hormone
(testosterone)
EXTRACELLULAR
FLUID
Receptor
protein
Plasma
membrane
Hormone-
receptor
complex
DNA
mRNA
NUCLEUS
New protein
CYTOPLASM

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

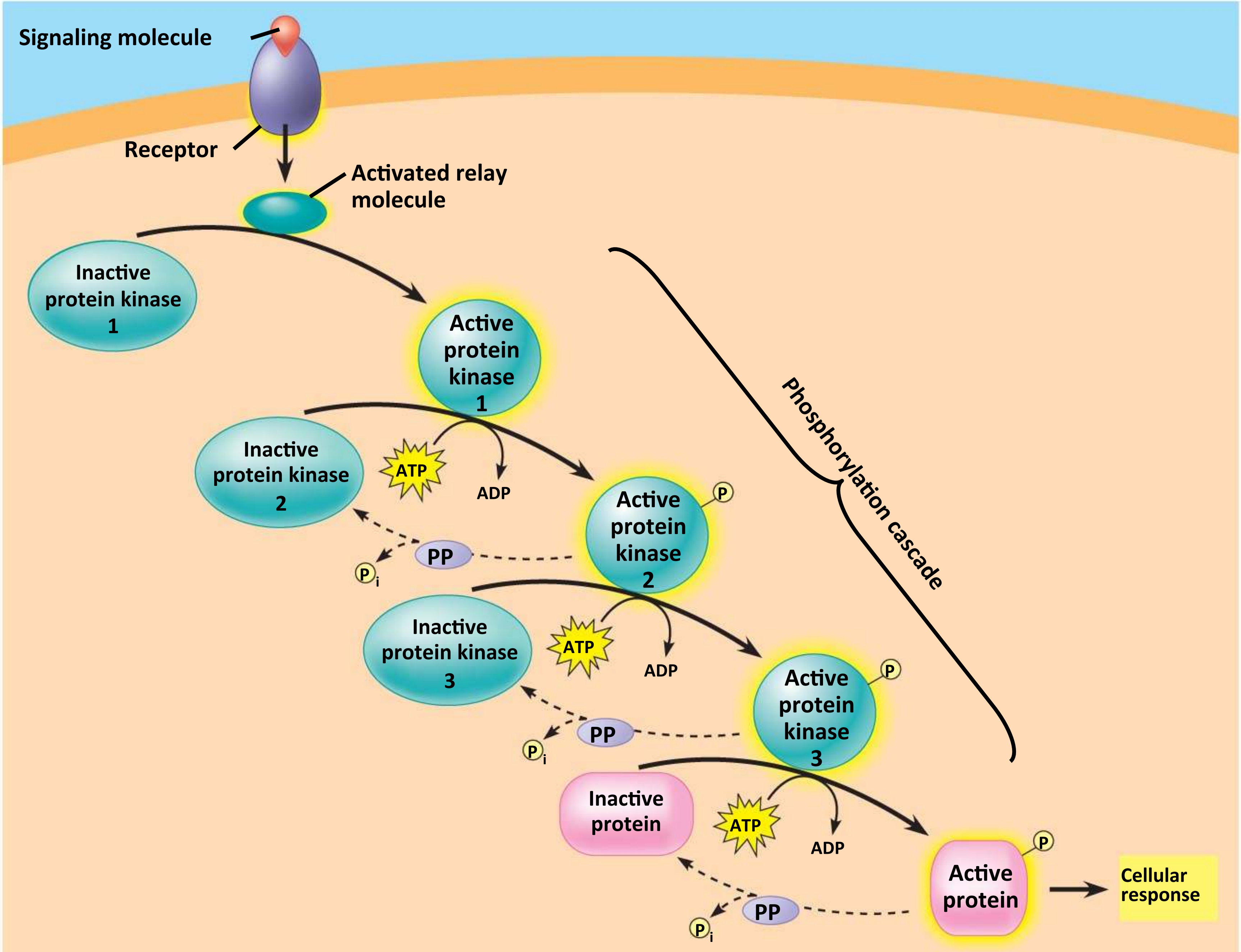


Protein Phosphorylation and Dephosphorylation

- 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

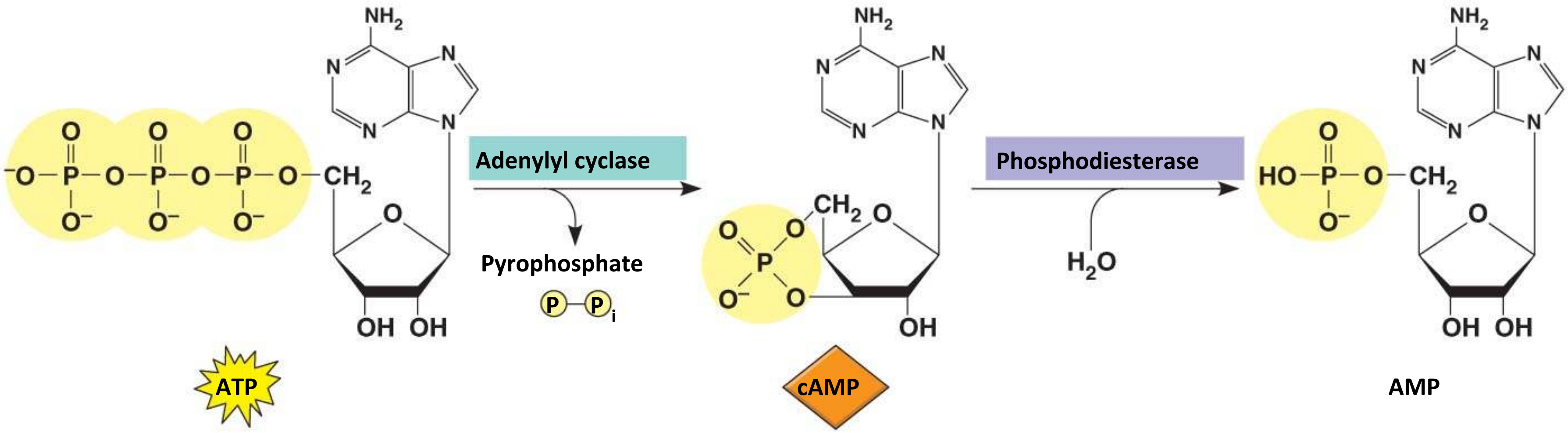
Fig. 11-9



Signaling molecule
Receptor
Activated relay molecule
Inactive protein kinase 1
Active protein kinase 1
Inactive protein kinase 2
ATP
ADP
Active protein kinase 2
P
PP
Pi
Inactive protein kinase 3
ATP
ADP
Active protein kinase 3
P
PP
Pi
Inactive protein
ATP
ADP
Active protein
P
PP
Pi
Cellular response
Phosphorylation cascade

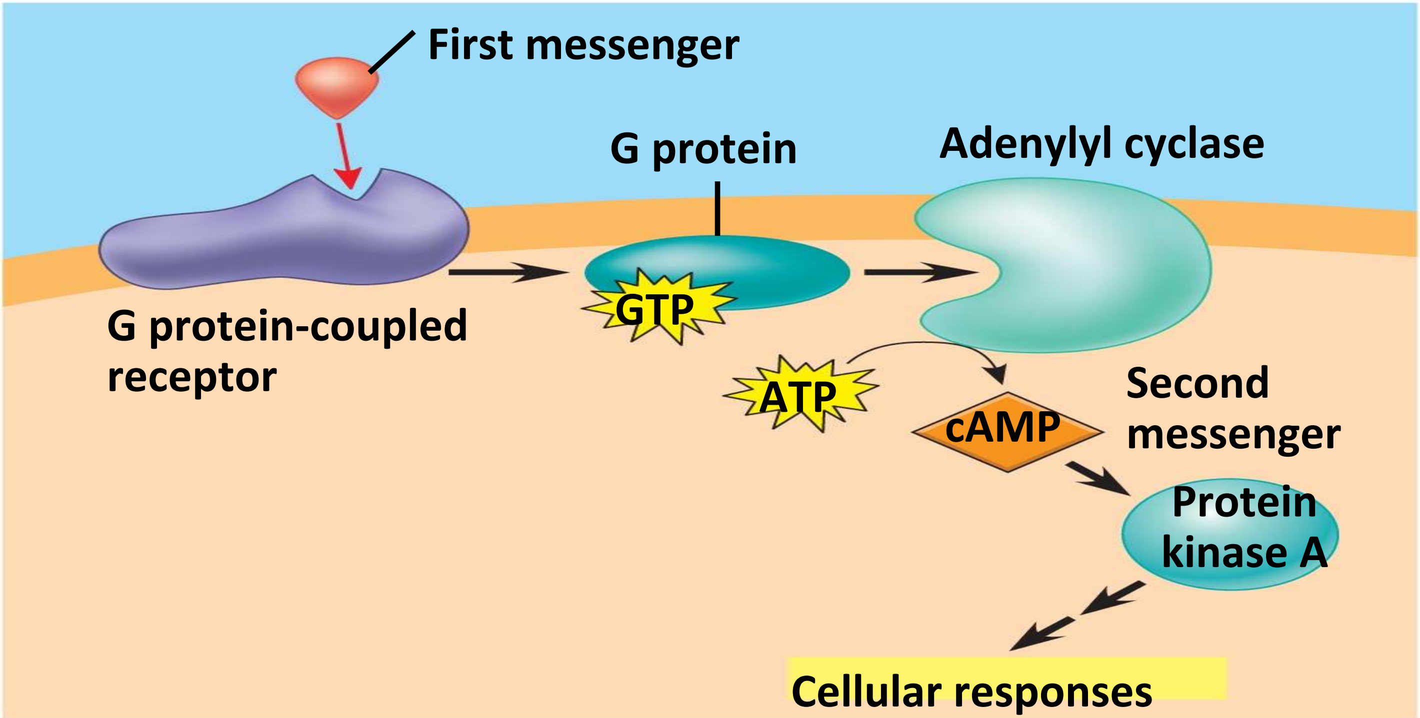
Small Molecules and Ions as Second Messengers

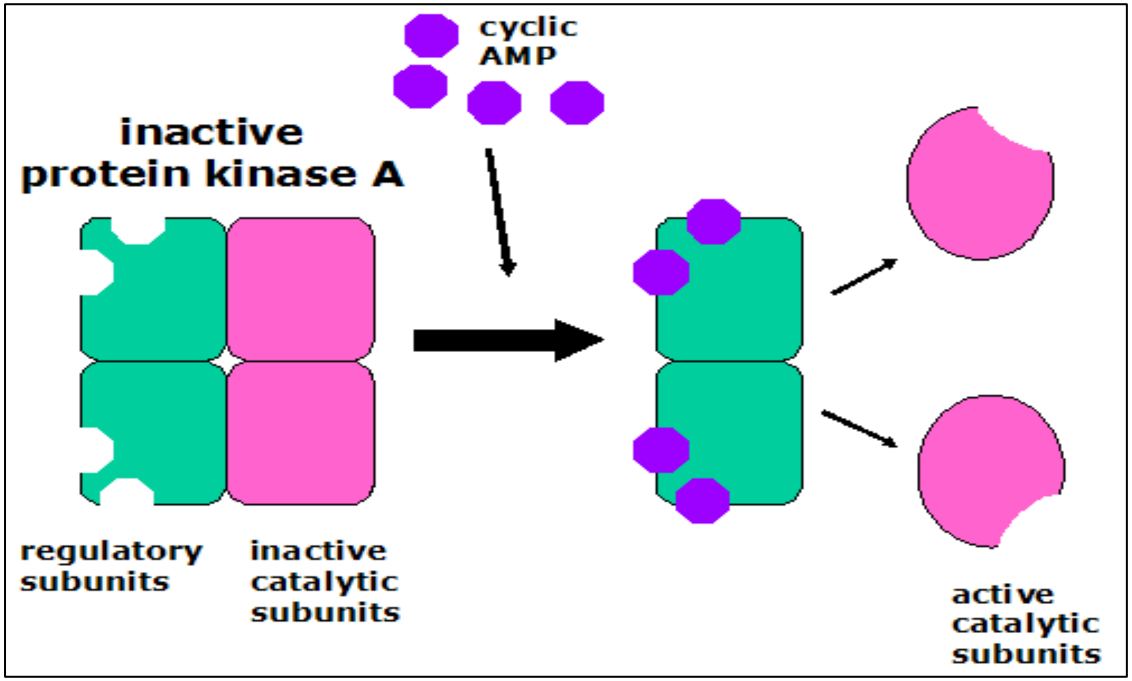
- The extracellular signal molecule that binds to the receptor is a pathway's "first messenger"
- **Second messengers** are small, nonprotein, water-soluble molecules or ions that spread throughout a cell by diffusion
- Second messengers participate in pathways initiated by G protein-coupled receptors 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



Second messengers

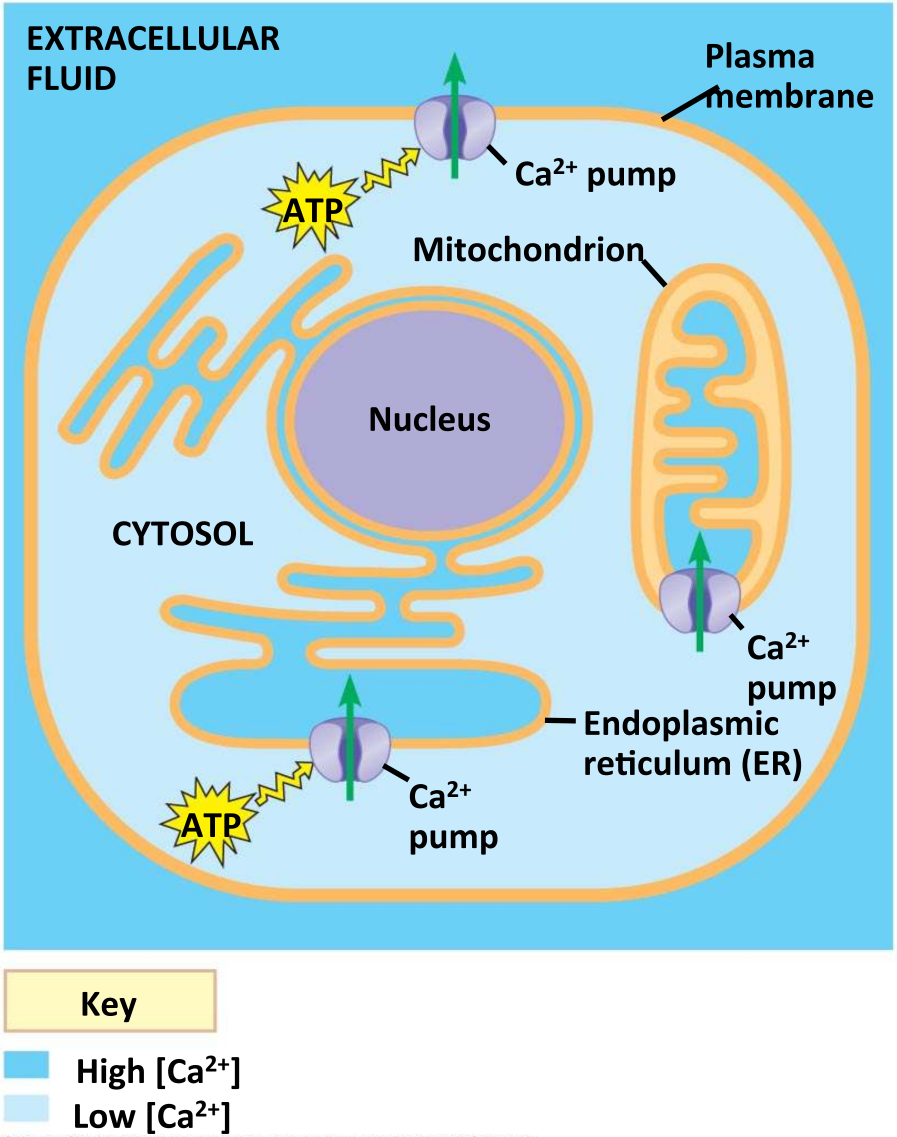
Hydrophobic molecules:, Phospatidyl inositol, Diacyl glycerol (DAG)
Hydrophilic molecules: cAMP, cGMP, Inositol triphosphate (IP3), Ca++
Gases: NO, CO, H_2S


First messenger
G protein
Adenylyl cyclase
G protein-coupled receptor
GTP
ATP
cAMP
Second messenger
Protein kinase A
Cellular responses


cyclic AMP
inactive protein kinase A
regulatory subunits
inactive catalytic subunits
active catalytic subunits

Calcium Ions as second mesenger

- 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

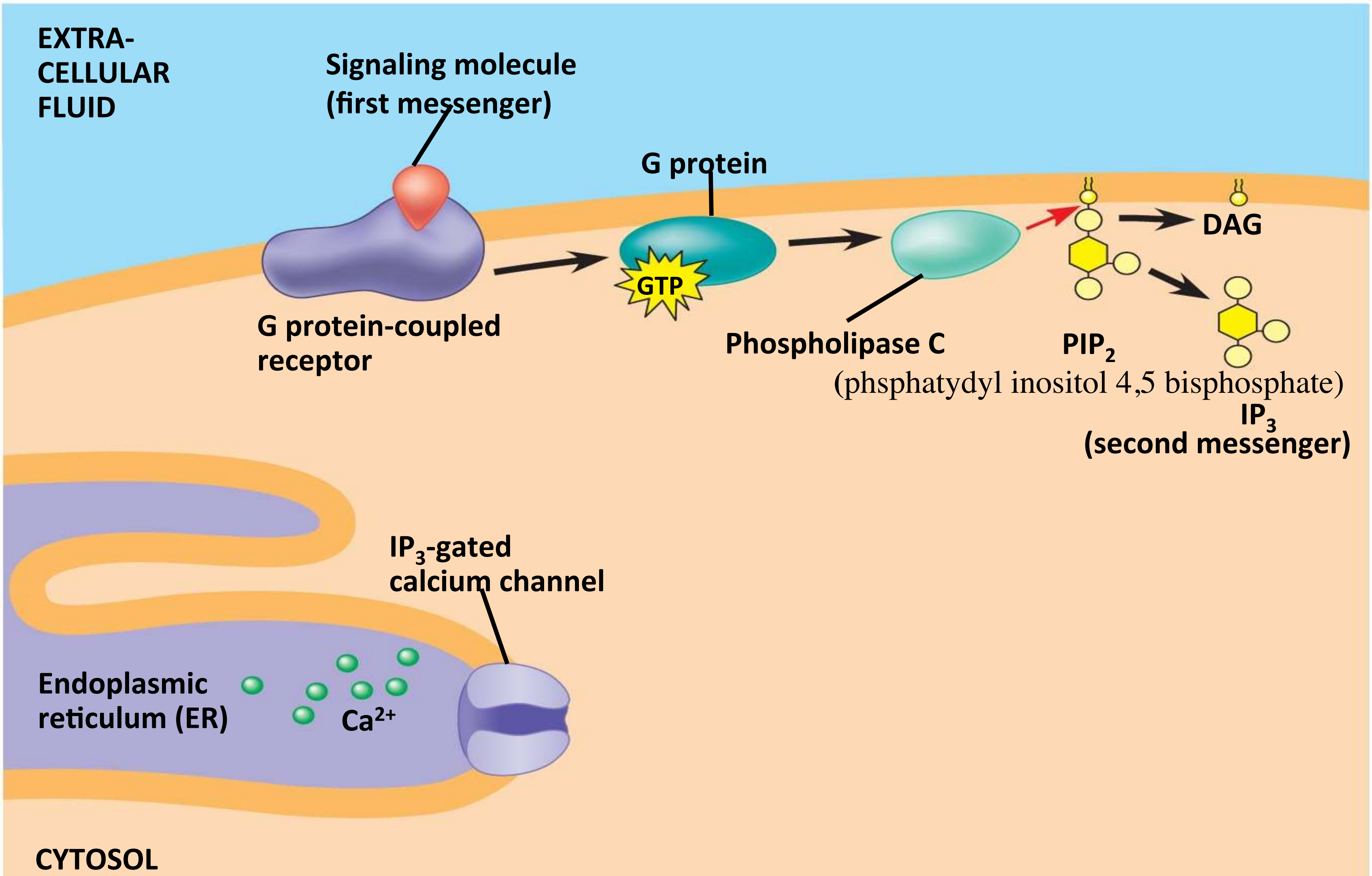
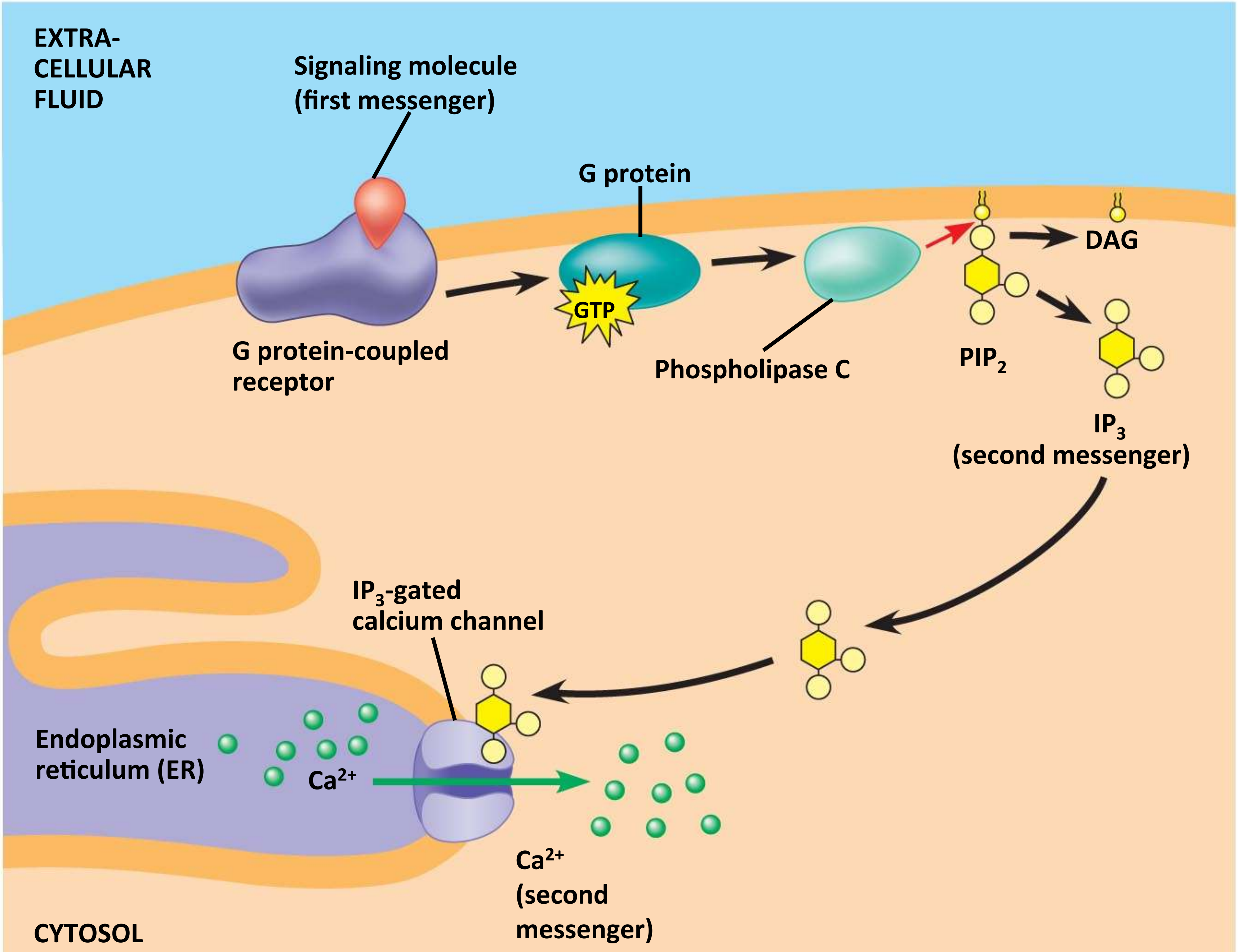
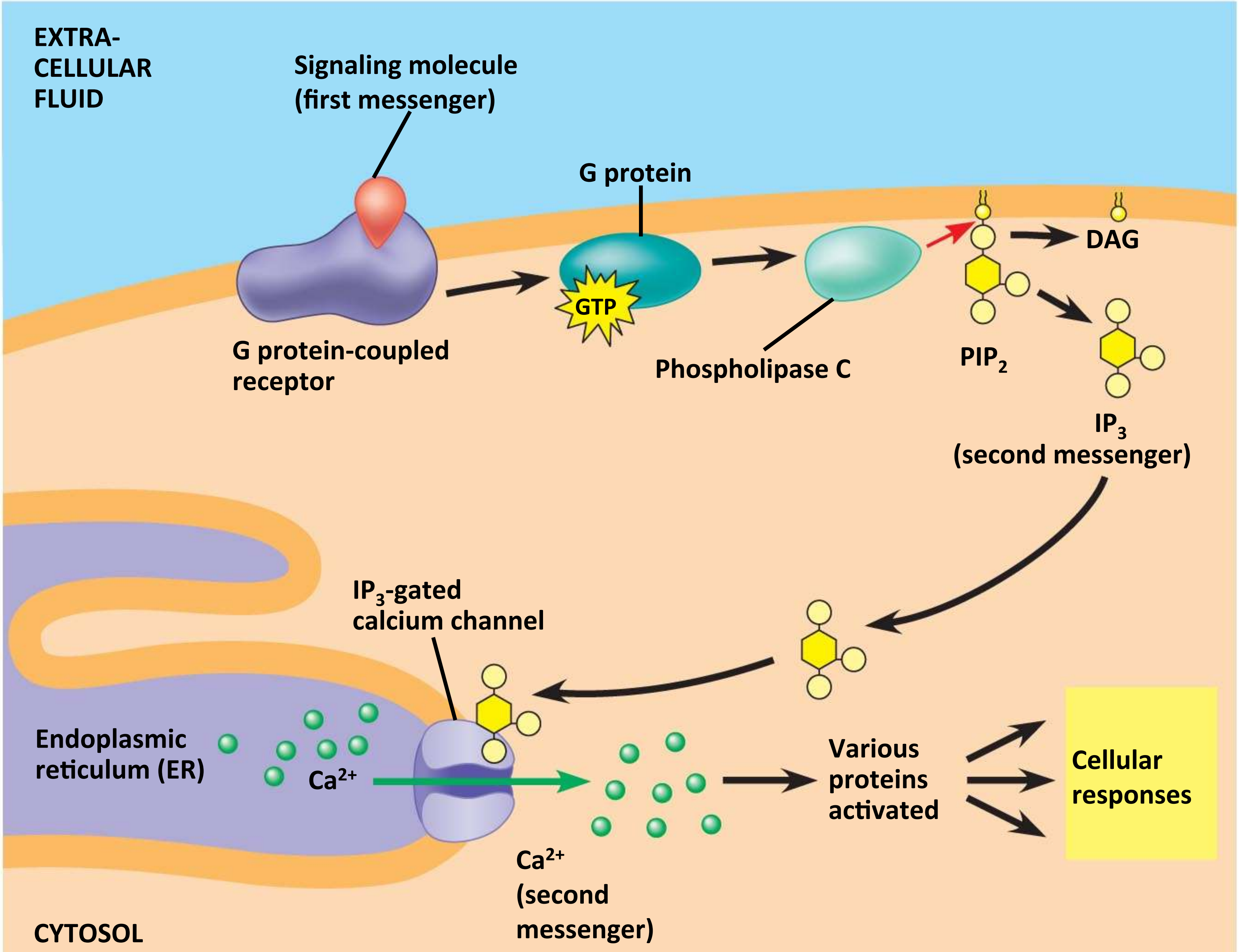


Fig. 11-13-2



EXTRA-
CELLULAR
FLUID
Signaling molecule
(first messenger)
G protein
GTP
DAG
G protein-coupled
receptor
Phospholipase C
PIP$_2$
IP$_3$
(second messenger)
IP$_3$-gated
calcium channel
Endoplasmic
reticulum (ER)
Ca^{2+}
Ca^{2+}
(second
messenger)
CYTOSOL

Fig. 11-13-3



EXTRA-
CELLULAR
FLUID
Signaling molecule
(first messenger)
G protein
DAG
GTP
G protein-coupled
receptor
Phospholipase C
PIP_2
IP_3
(second messenger)
IP_3-gated
calcium channel
Endoplasmic
reticulum (ER)
Ca^{2+}
Various
proteins
activated
Cellular
responses
Ca^{2+}
(second
messenger)
CYTOSOL

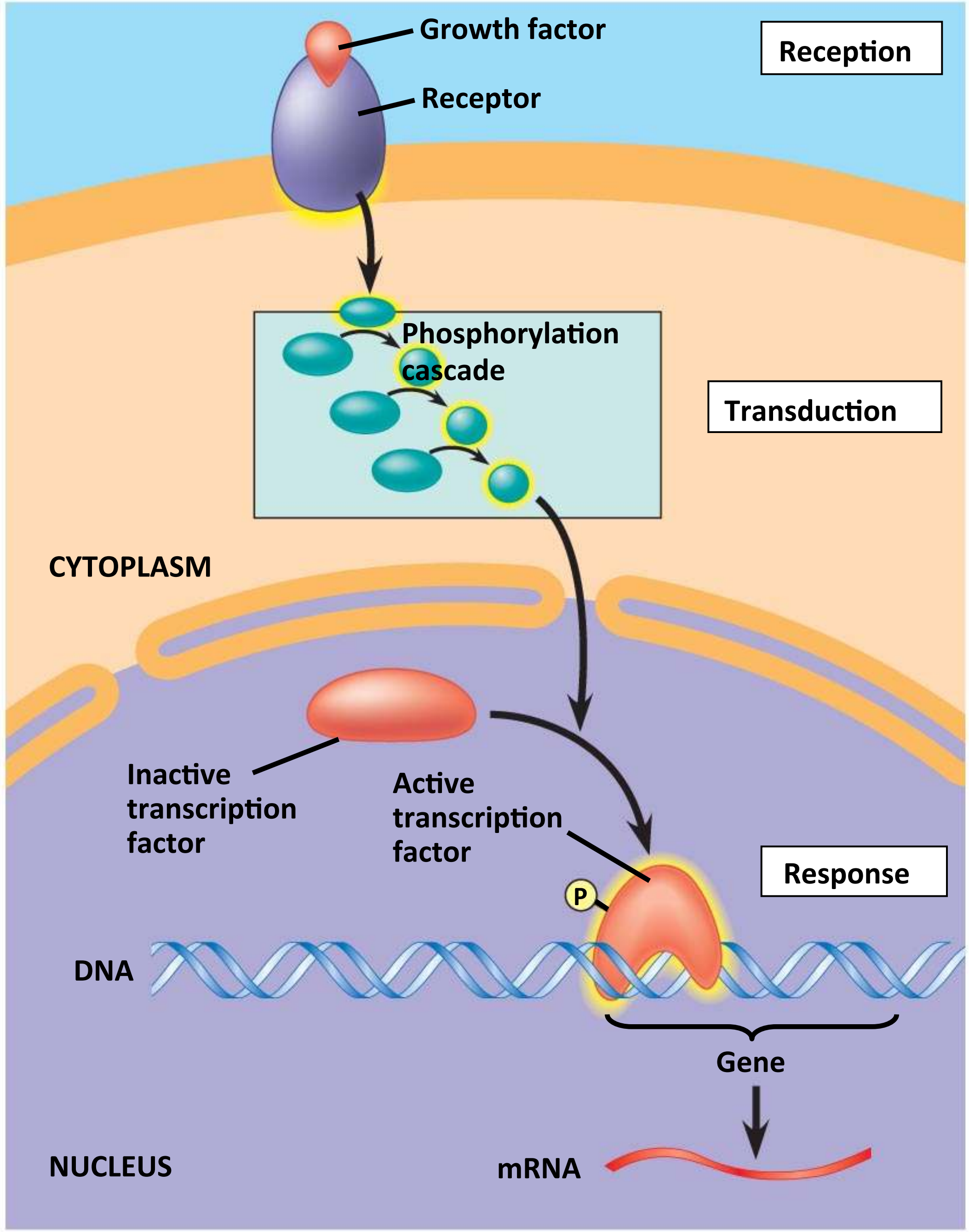
Response: Cell signaling leads to regulation of transcription or cytoplasmic activities

- 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


Growth factor
Receptor
Reception
Phosphorylation cascade
Transduction
CYTOPLASM
Inactive transcription factor
Active transcription factor
Response
P
DNA
Gene
NUCLEUS
mRNA

Reception

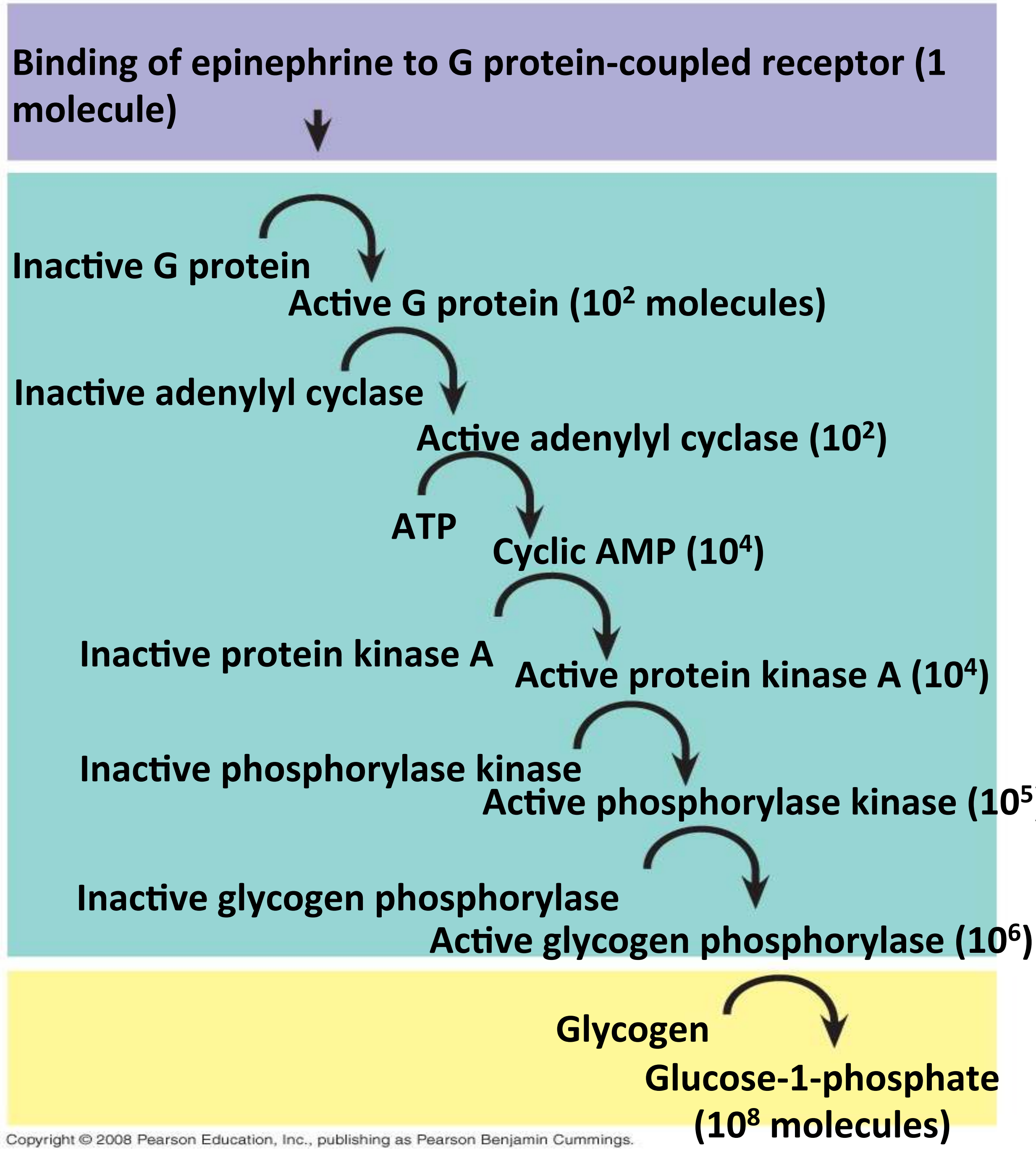
Transduction

Signal Amplification

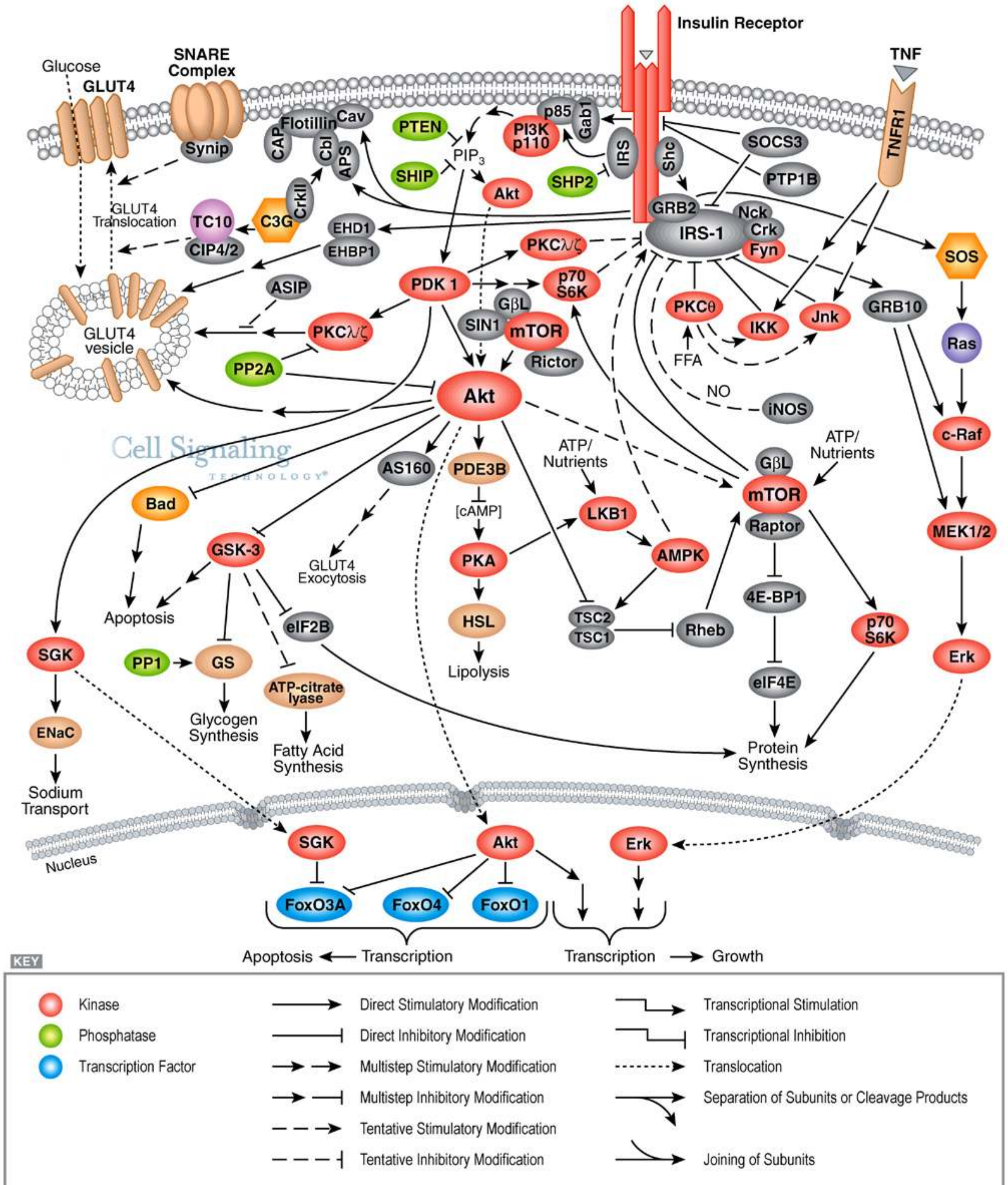
Enzyme cascades amplify the cell's response

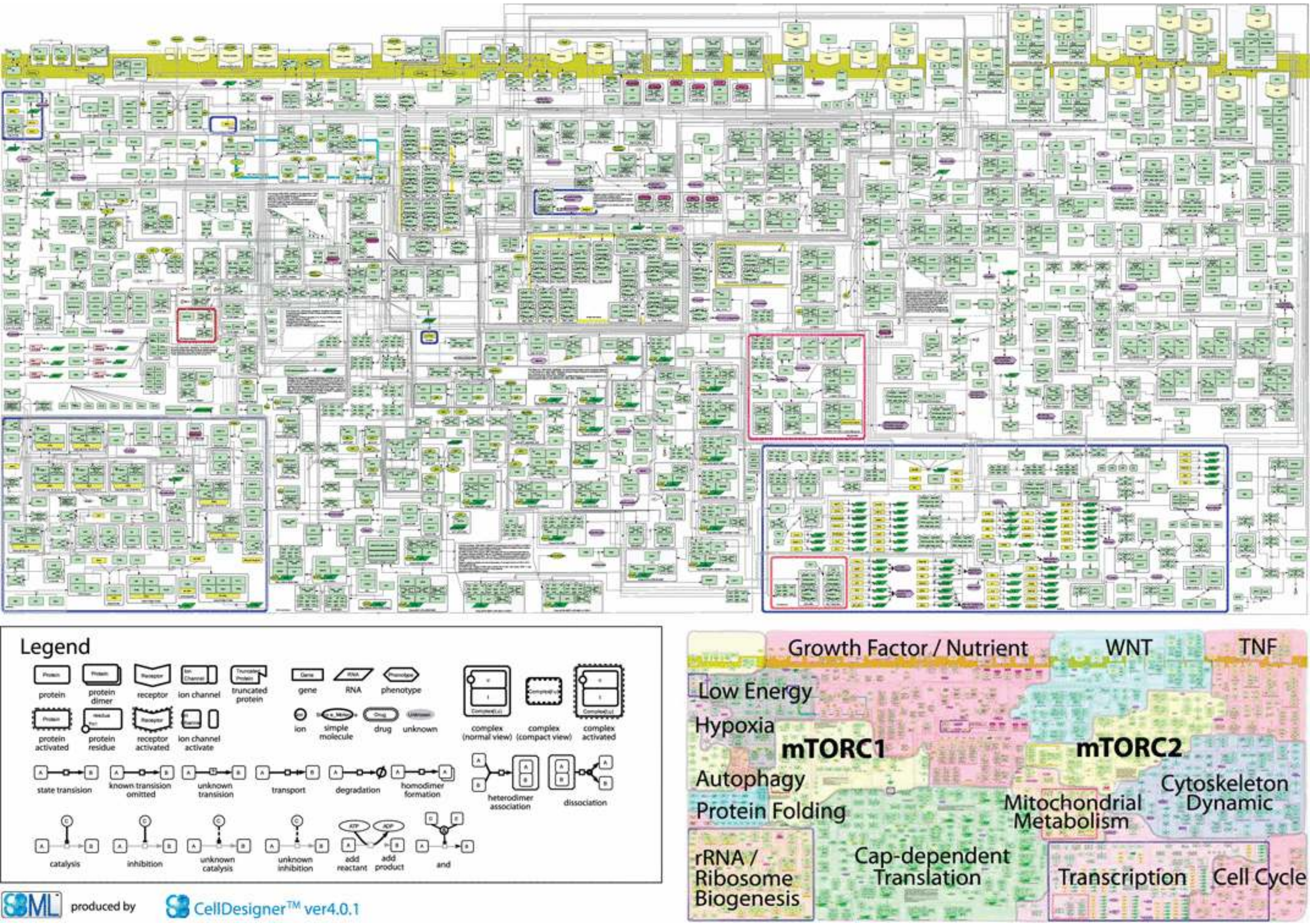
At each step, the number of activated products is much greater than in the preceding step

Response



An example of signaling network



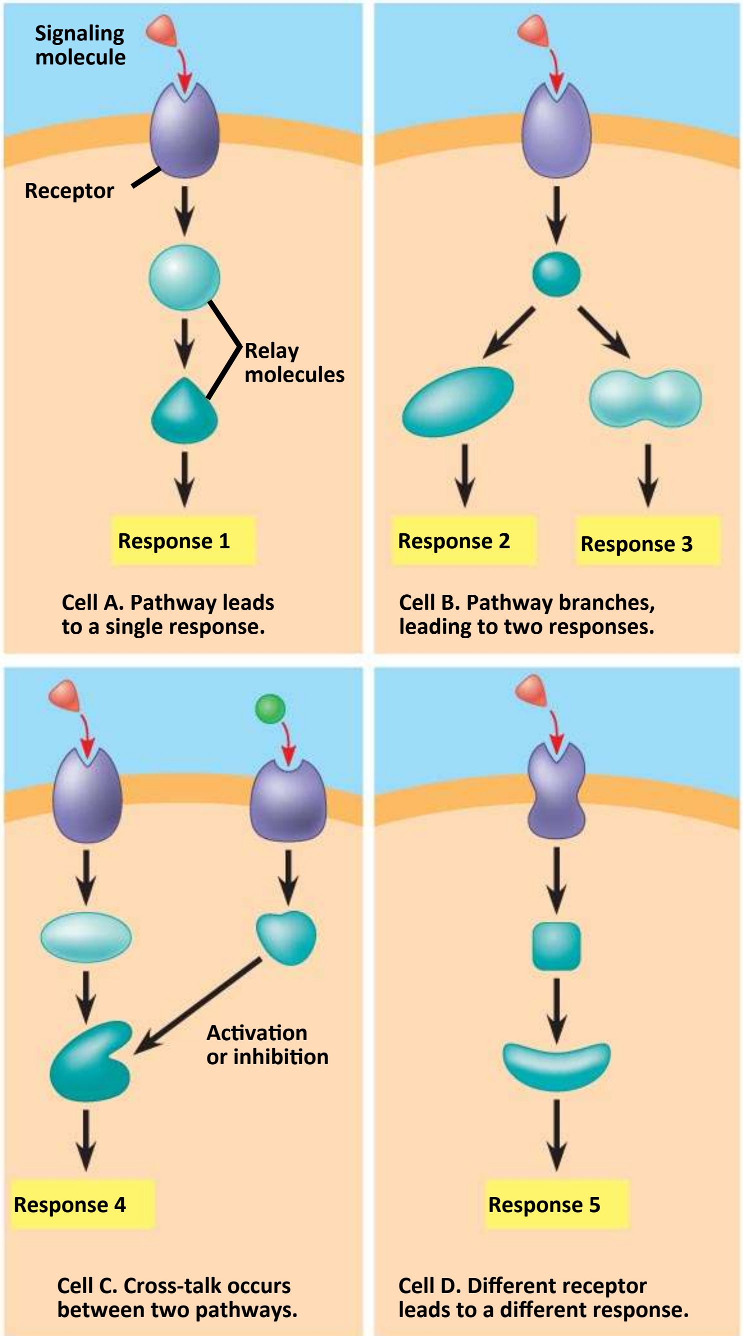


Legend
protein
protein dimer
receptor
ion channel
truncated protein
gene
RNA
phenotype
protein activated
protein residue
receptor activated
ion channel activate
ion
simple molecule
drug
unknown
complex (normal view)
complex (compact view)
complex activated
state transition
known transition omitted
unknown transition
transport
degradation
homodimer formation
heterodimer association
dissociation
catalysis
inhibition
unknown catalysis
unknown inhibition
add reactant
add product
and
SBML produced by CellDesigner™ ver4.0.1
Growth Factor / Nutrient
WNT
TNF
Low Energy
Hypoxia
mTORC1
mTORC2
Autophagy
Protein Folding
Cytoskeleton Dynamic
Mitochondrial Metabolism
rRNA / Ribosome Biogenesis
Cap-dependent Translation
Transcription
Cell Cycle

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

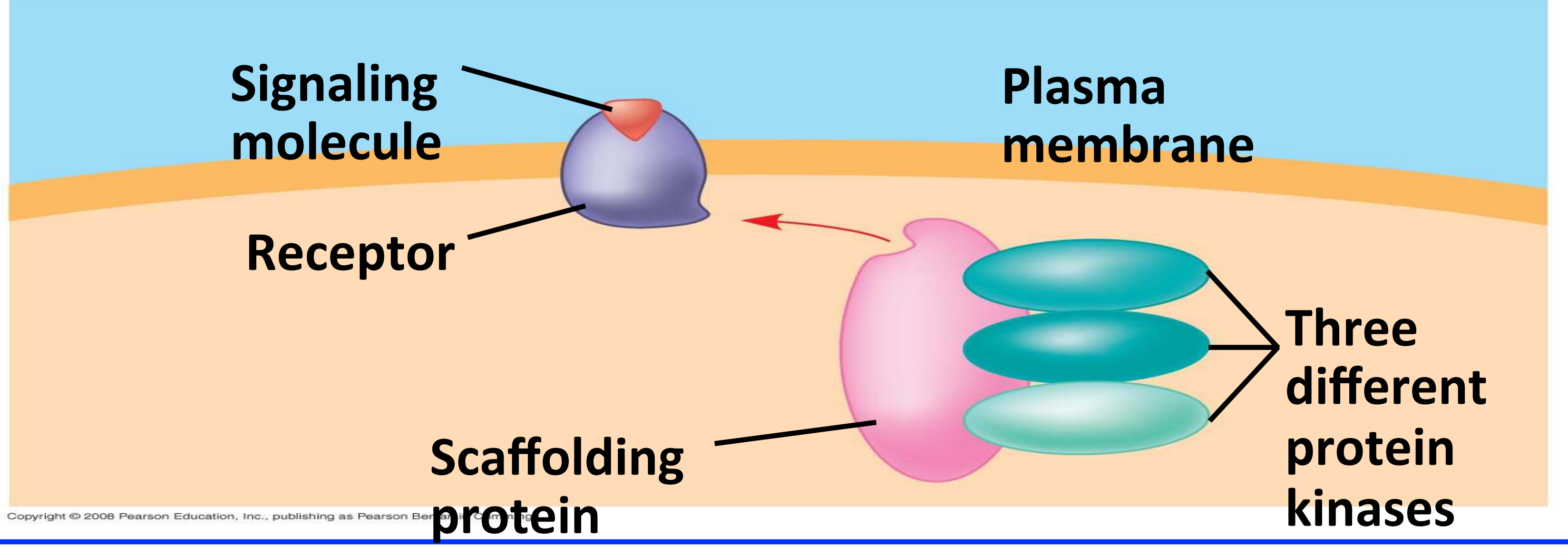
Fig. 11-17



Signaling molecule
Receptor
Relay molecules
Response 1
Cell A. Pathway leads to a single response.
Response 2
Response 3
Cell B. Pathway branches, leading to two responses.
Activation or inhibition
Response 4
Cell C. Cross-talk occurs between two pathways.
Response 5
Cell D. Different receptor leads to a different response.

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



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 dephosporylase
  - Regulatory pathways initiated

Summary

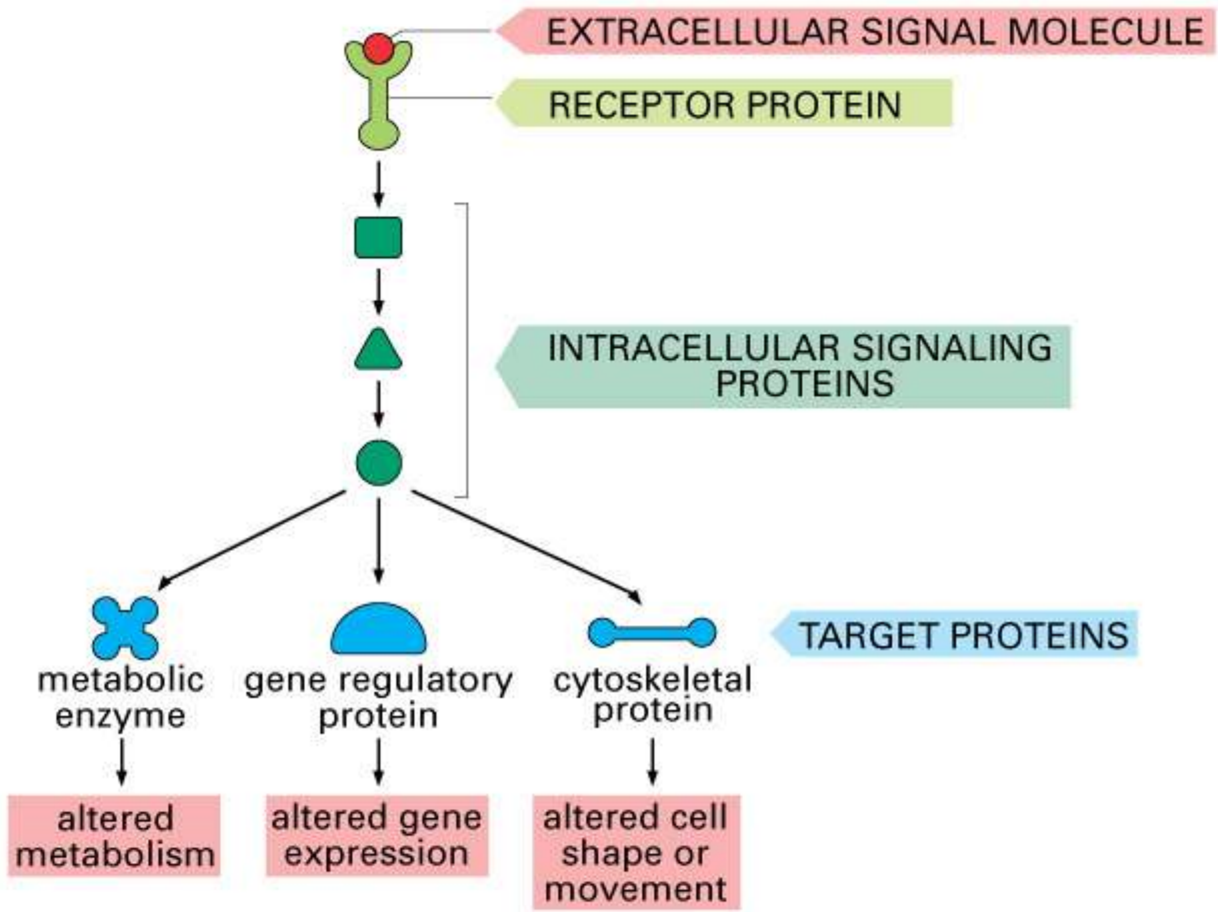


Figure 16-7 Essential Cell Biology, 2/e. (© 2004 Garland Science)

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

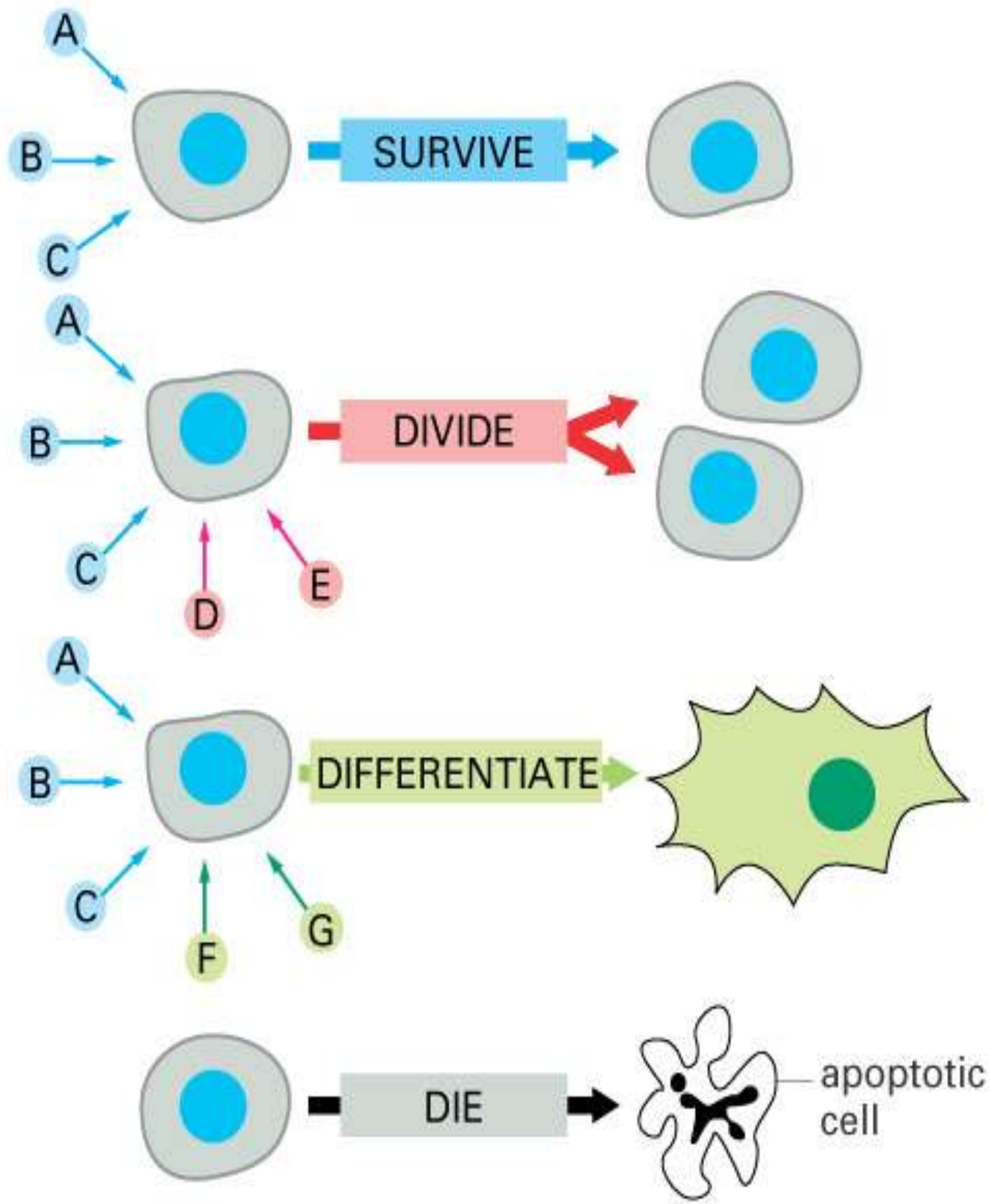
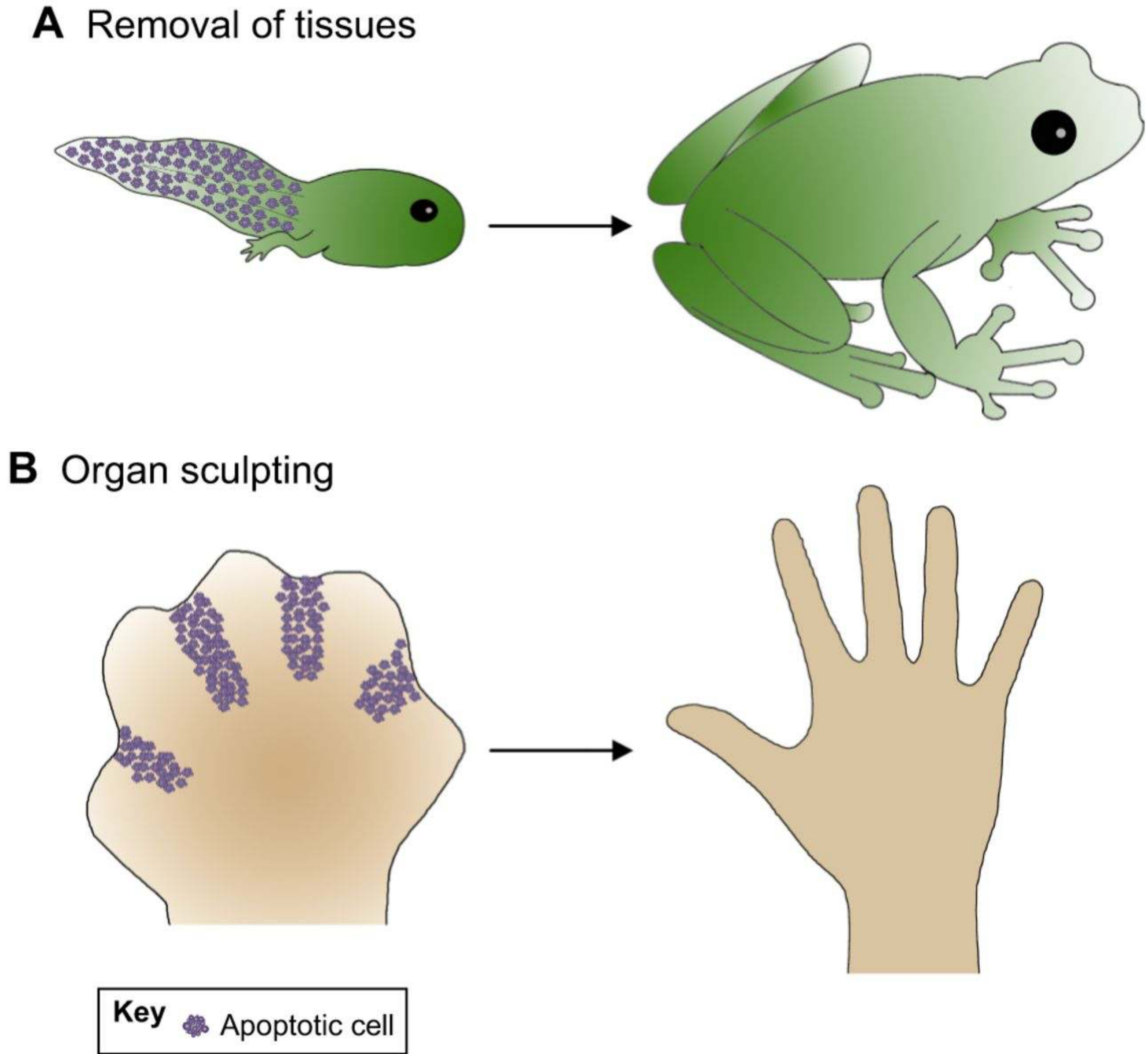
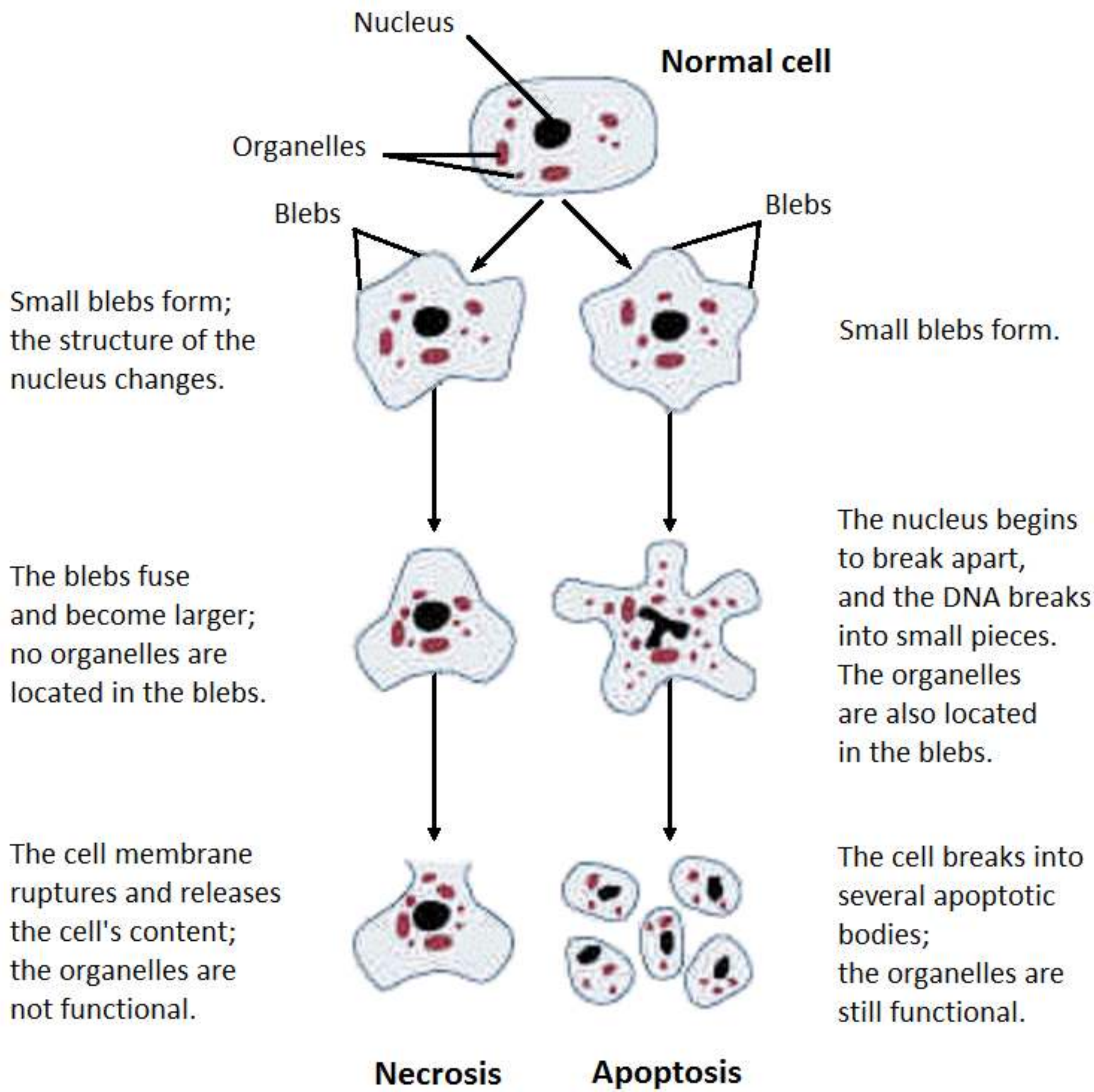


Figure 16-6 Essential Cell Biology, 2/e. (© 2004 Garland Science)

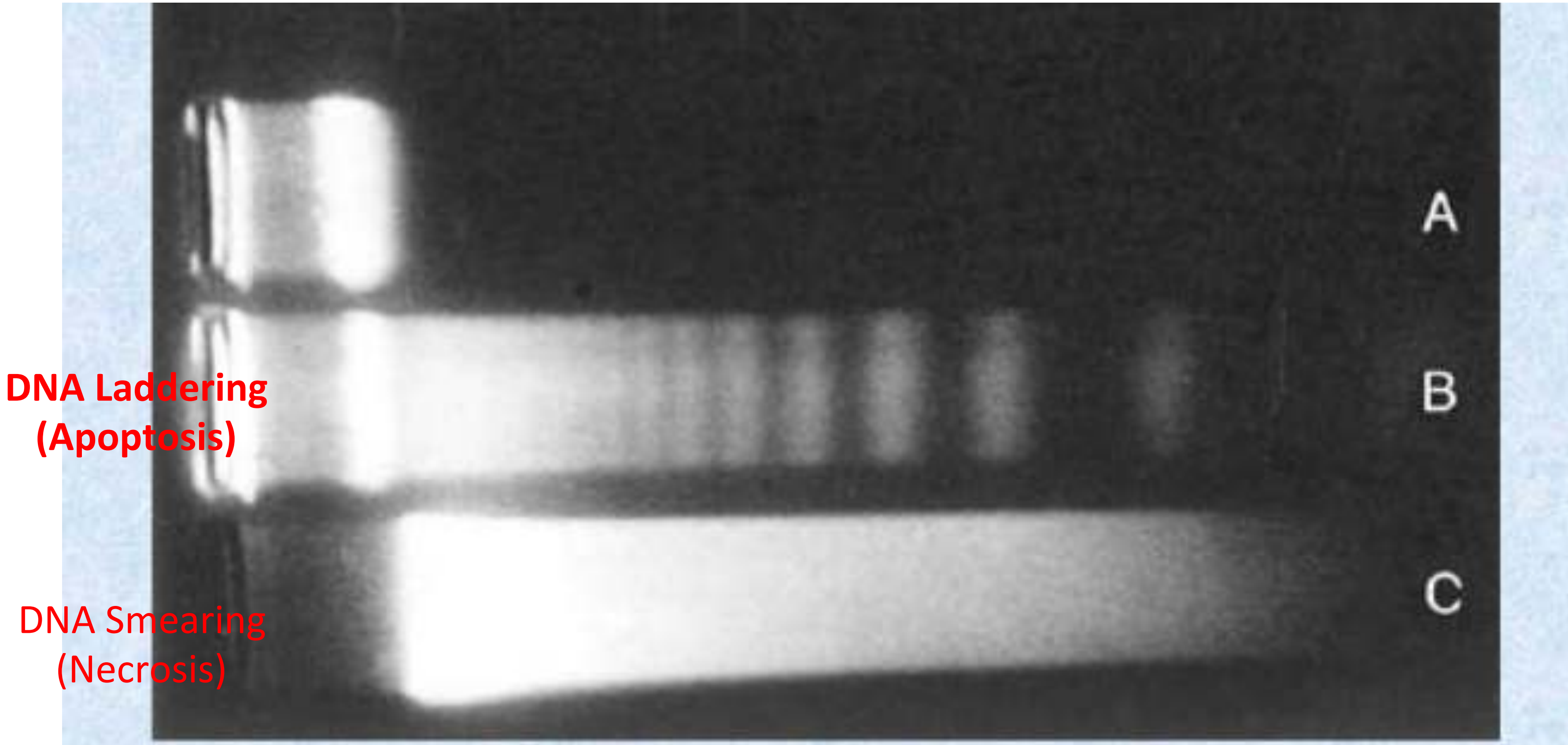
Apoptosis (programmed cell death) integrates multiple cell-signaling pathways

- **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


Nucleus
Normal cell
Organelles
Blebs
Blebs
Small blebs form; the structure of the nucleus changes.
Small blebs form.
The blebs fuse and become larger; no organelles are located in the blebs.
The nucleus begins to break apart, and the DNA breaks into small pieces. The organelles are also located in the blebs.
The cell membrane ruptures and releases the cell's content; the organelles are not functional.
The cell breaks into several apoptotic bodies; the organelles are still functional.
Necrosis
Apoptosis

Knowing whether death is by apoptosis or necrosis



Agarose gel electrophoresis of DNA extracted from culture cells

Cytotoxicity detected by flow cytometry

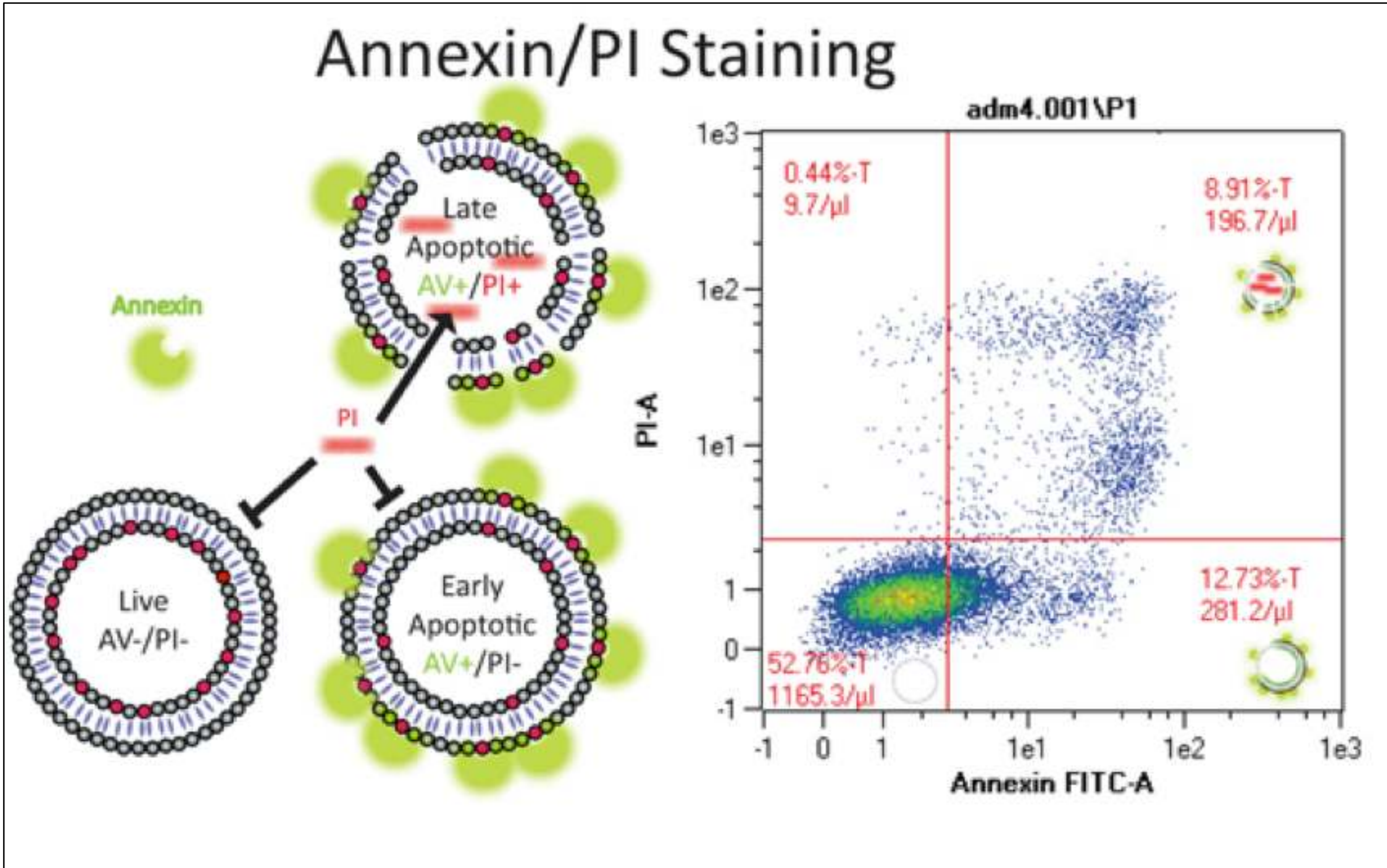
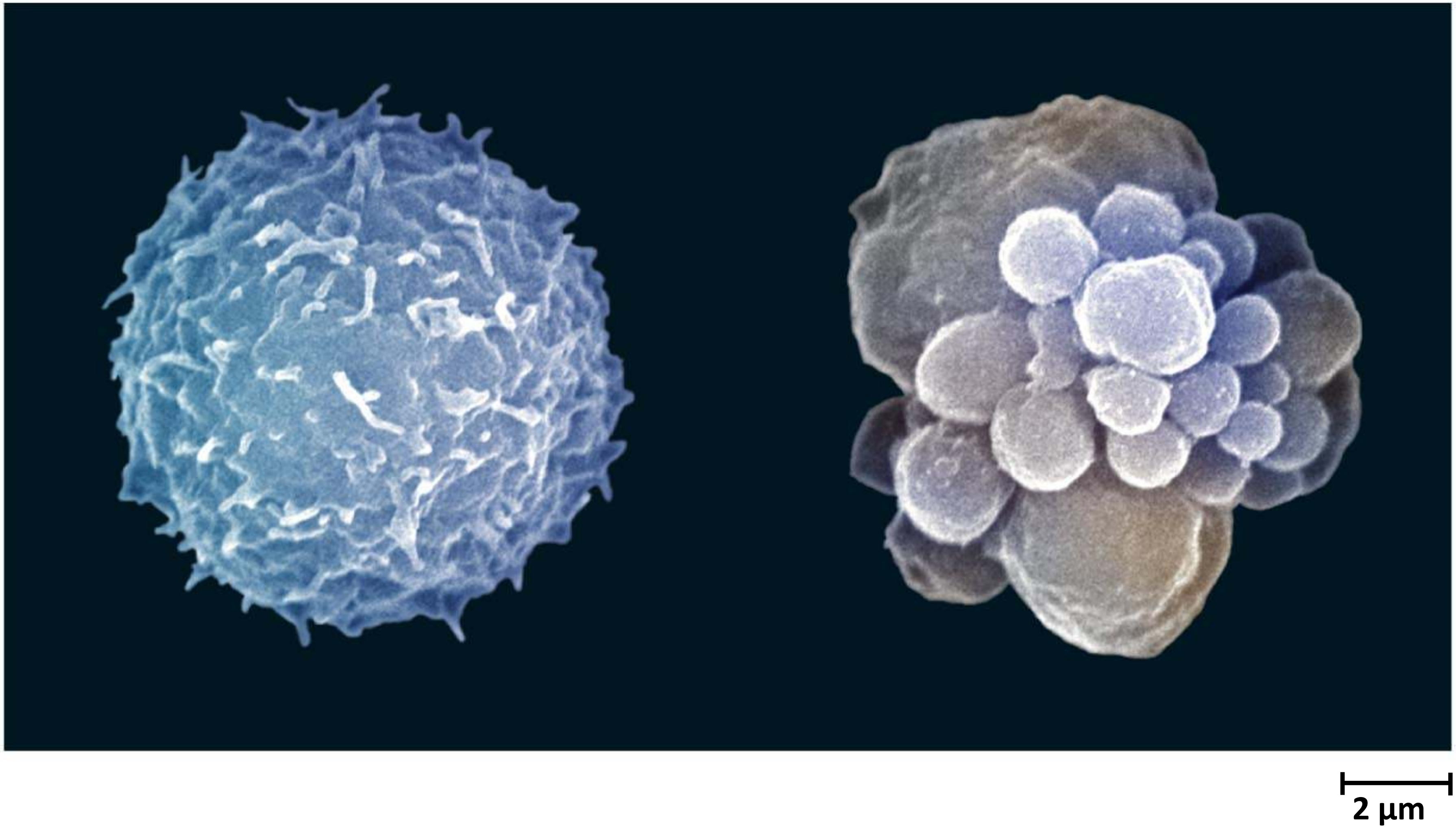
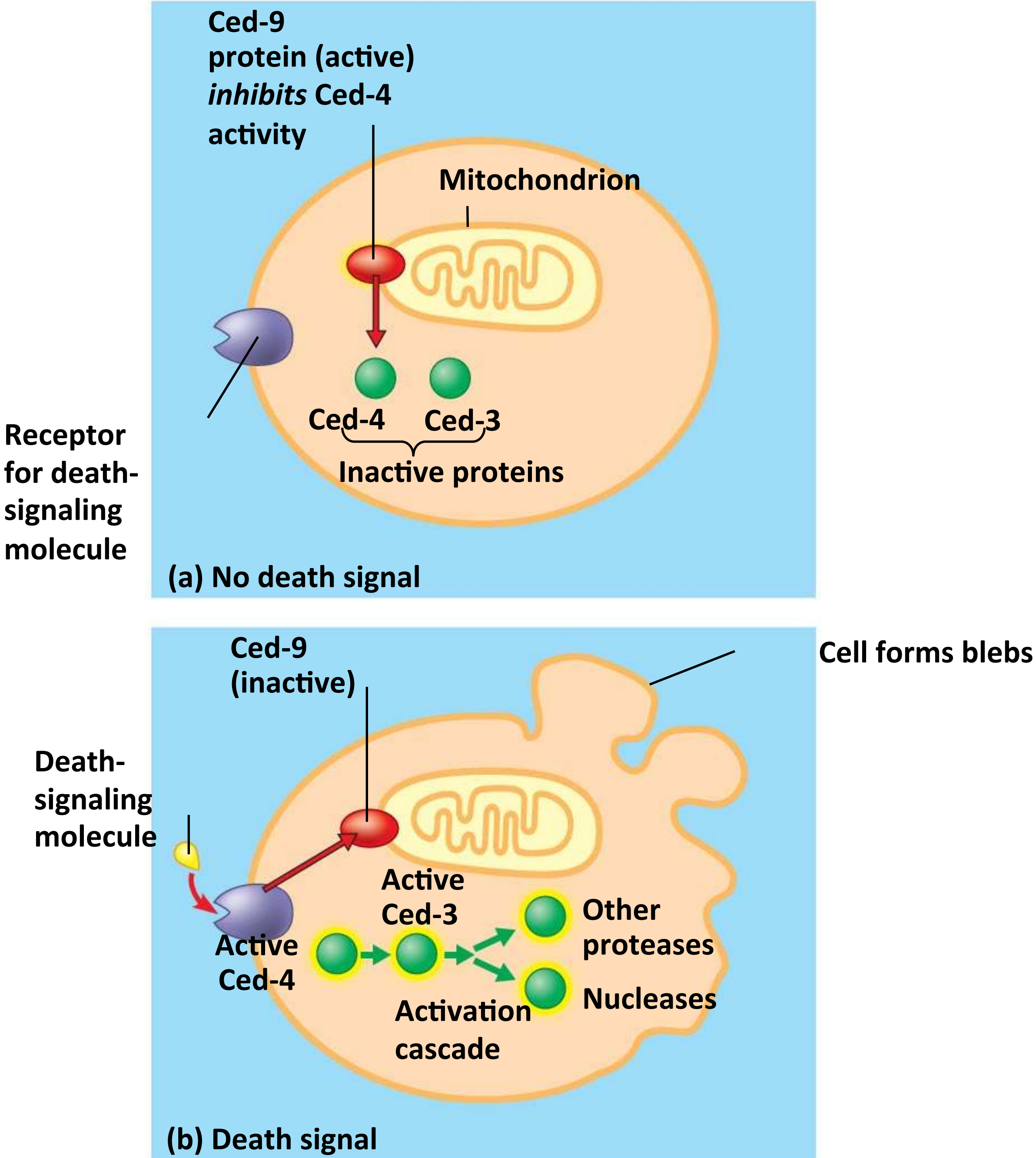


Fig. 11-19



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

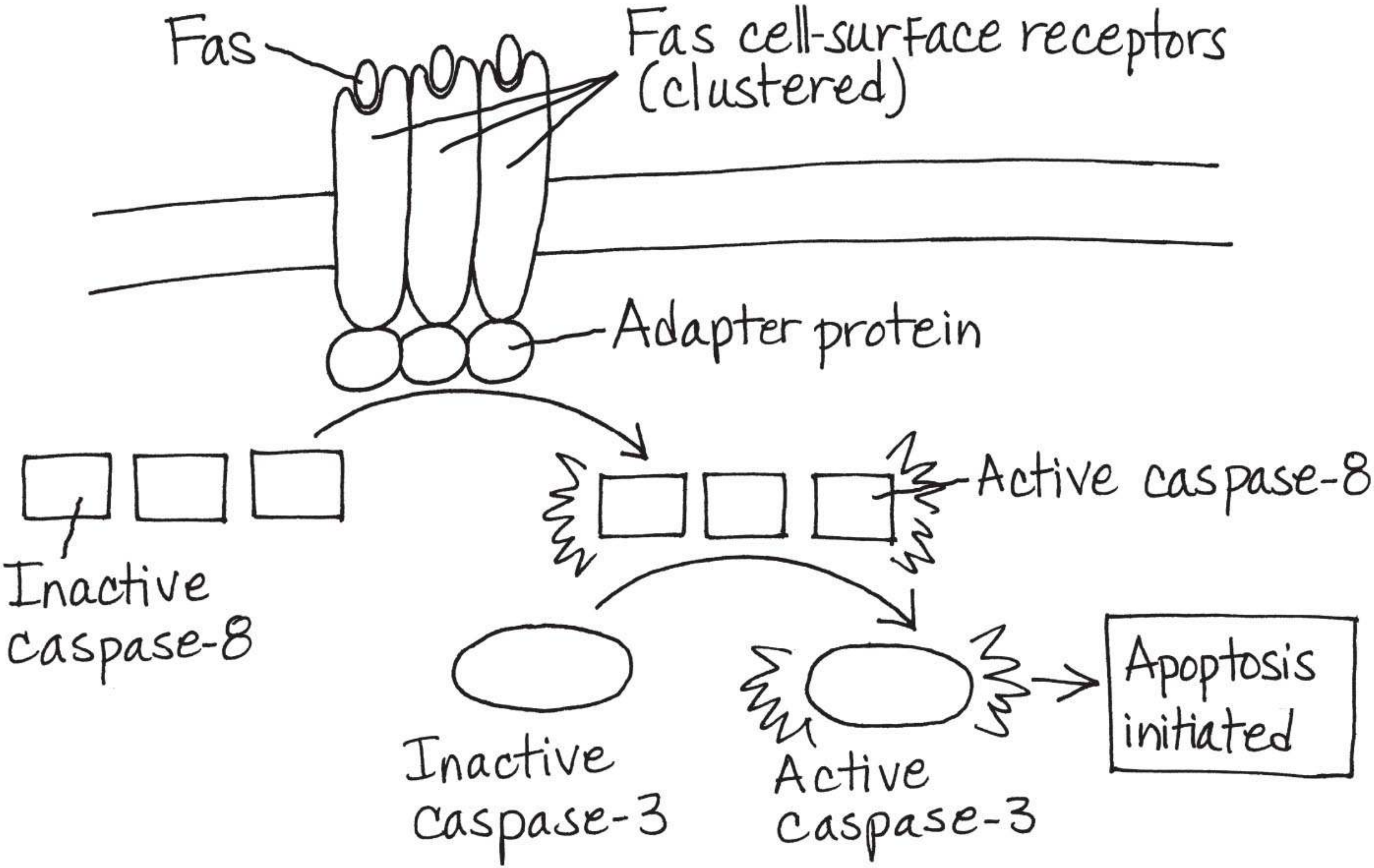
Fig. 11-20


Ced-9
protein (active)
inhibits Ced-4
activity
Mitochondrion
Receptor
for death-
signaling
molecule
Ced-4
Ced-3
Inactive proteins
(a) No death signal
Ced-9
(inactive)
Cell forms blebs
Death-
signaling
molecule
Active
Ced-4
Active
Ced-3
Other
proteases
Nucleases
Activation
cascade
(b) Death signal

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


Fas
Fas cell-surface receptors (clustered)
Adapter protein
Active caspase-8
Inactive caspase-8
Inactive caspase-3
Active caspase-3
Apoptosis initiated