

Chapter 11

Cell Communication



AP Biology

Overview: The Cellular Internet

- Cell-to-cell communication is important for multicellular organisms
 - The trillions of cells that make up these organisms have to be able to communicate with each other so they can coordinate their activities
 - This communication enables organisms to not only develop from a fertilized egg, but also to survive and reproduce
 - Biologists have recently discovered some universal mechanisms for cell recognition, which provides additional evidence for the evolutionary relatedness of all life
 - The same small set of cell-signaling mechanisms shows up time and again in many lines of biological research, including:
 - Embryonic development
 - Hormone action
 - Cancer
 - Cells most often communicate with each other by chemical signals
 - In this chapter, we focus on the main mechanisms by which cells receive, process, and respond to chemical signals sent from other cells

**Concept 11.1:
External Signals Are Converted to
Responses Within the Cell**

Cell Signaling in Microorganisms

- Communication among microorganisms is a window into the role of cell signaling in the evolution of life on Earth
 - Researchers have learned much about cell signaling by studying mating in yeast cells
 - They have discovered that cells of a yeast known as *Saccharomyces cerevisiae* identify their mates by chemical signaling

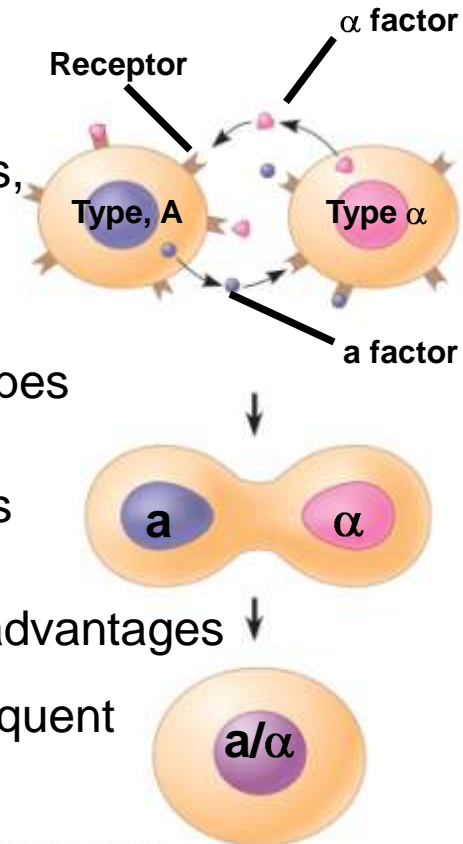
Communication Between Mating Yeast Cells

- There are 2 sexes (mating types) in this species of yeast:
 - **Type a**: secrete a signaling molecule called “a” factor that binds to receptor proteins on nearby α cells
 - **Type α** : secrete a signaling factor called α factor that binds receptors on nearby “a” cells

– Though these mating factors do not actually enter the cells, they cause the 2 types of cells to grow toward each other

- This results in fusion (mating) of 2 cells of opposite types
- The new a/ α cell contains all genes both original cells

– This combination of genetic resources provides advantages to descendants of these cells that arise by subsequent cellular division



Evolution of Cell Signaling

- Thus, mating in yeast involves a change (*transduction*) in the signaling molecule into some form that brings about the cellular response of mating
 - 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
- Many signal transduction pathways have been extensively studied in both yeast and animal cells
 - The molecular details of signal transduction are similar, even though these 2 groups of organisms diverged over a billion years ago
 - This suggests that early versions of cell signaling evolved before the first multicellular organisms

Cell Signaling in Prokaryotes: Quorum Sensing

- Scientists believe that signaling mechanisms first evolved in ancient prokaryotes and single-celled eukaryotes
 - Even today, cell signaling has remained important in the microbial world
 - Cells of many bacterial species secrete small molecules that can be detected by other bacterial cells
 - The concentration of these signaling molecules allows bacteria to sense the local density of bacterial cells
 - This phenomenon is called *quorum sensing*

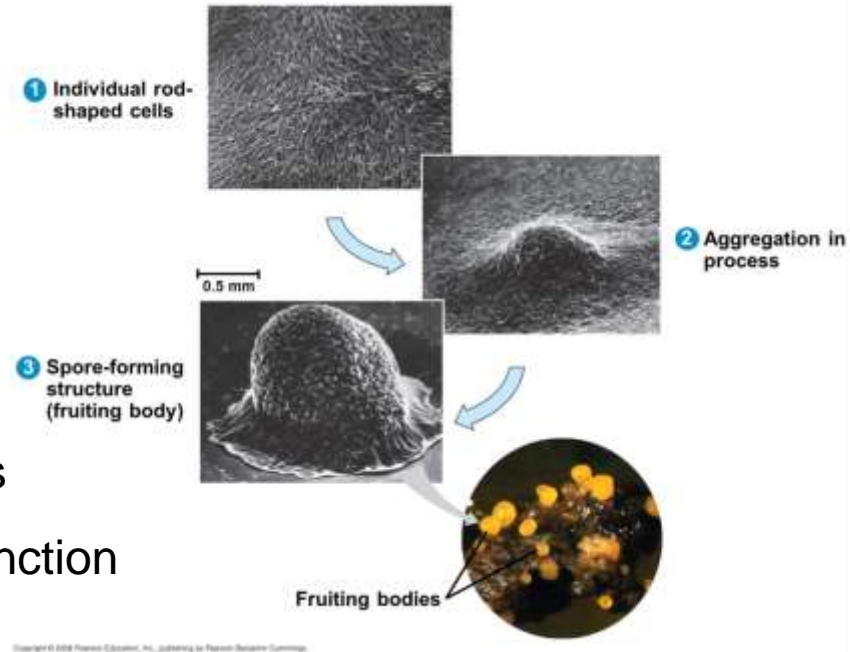
Cell Signaling in Prokaryotes: Biofilms

- Signaling among members of a bacterial population can also lead to coordination of their activities

- In response to the signal, bacterial cells are able to come together to form aggregations called *biofilms*

- These biofilms often form structures containing regions of specialized function

- Ex) When food is scarce, aggregations of a soil-dwelling bacterium called myxobacteria form a structure called a fruiting body that produces thick-walled spores capable of surviving until the environment improves



Communication by Direct Contact

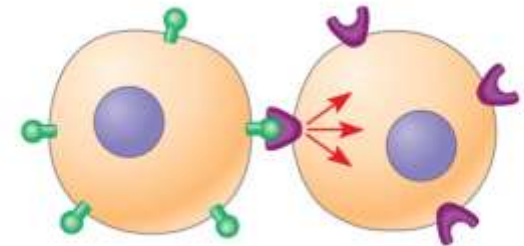
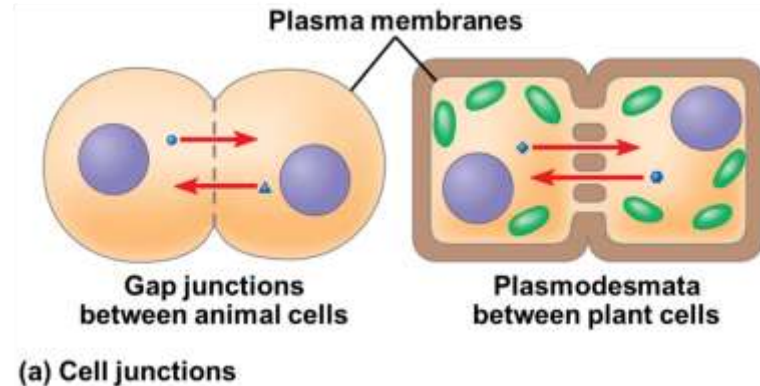
Cells in a multicellular organism also usually communicate by chemical messengers

– They may communicate by direct contact, either:

- 1) Through cell junctions that connect cytoplasm of adjacent cells
 - Gap junctions in animal cells; plasmodesmata in plant cells
 - In these cases, signaling substances dissolved in cytosol can pass freely between adjacent cells

- 2) Between cell-surface molecules bound to their plasma membranes
 - This type of communication occurs in animal cells and is called *cell-cell recognition*

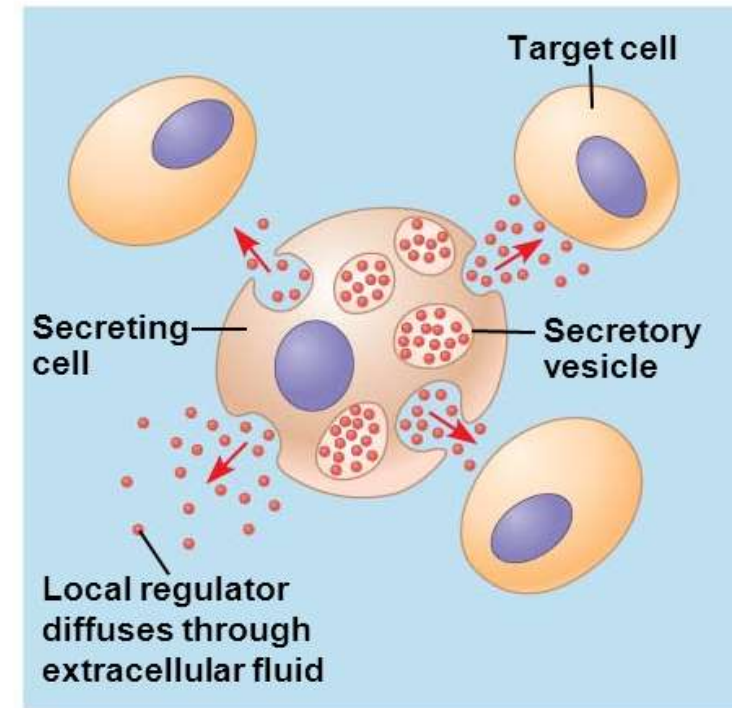
- This method of signaling is important in many processes, including embryonic development and the immune response



(b) Cell-cell recognition

Local Signaling: Paracrine Signaling

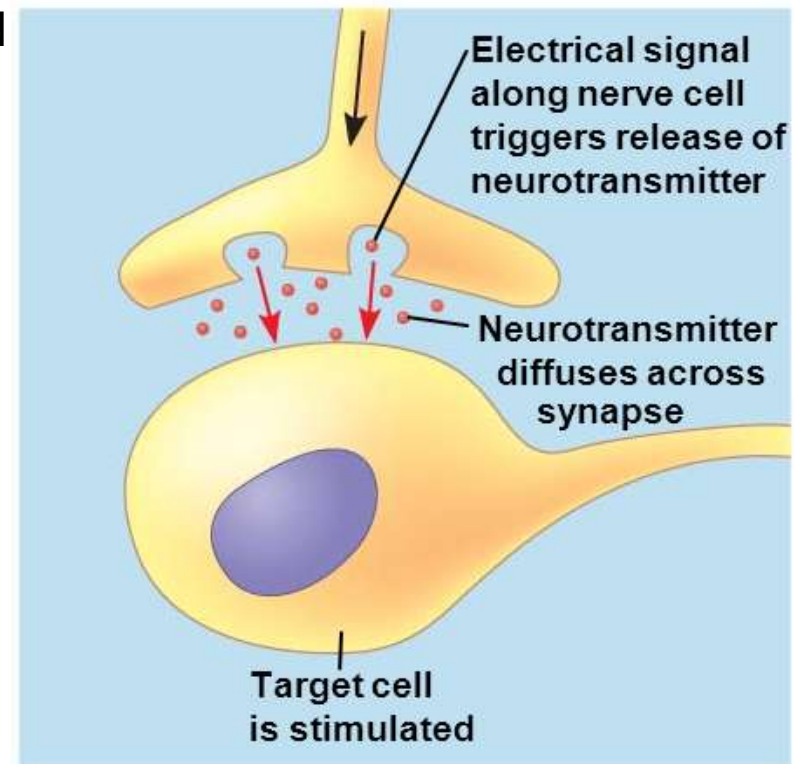
- Messenger molecules can also be secreted by cells, allowing communication between cells that are close to one another but not necessarily adjacent to one another
 - Some of these messenger molecules travel only short distances to influence cells in the vicinity
 - These types of chemical messengers are called **local regulators**
 - *Growth factors* are one class of local regulators in animals that consist of compounds that stimulate nearby target cells to grow and divide
 - Molecules of growth factor produced by a single cell can thus be simultaneously received to responded to by numerous cells in the vicinity
 - This type of local signaling is called *paracrine signaling*



(a) Paracrine signaling

Local Signaling: Synaptic Signaling

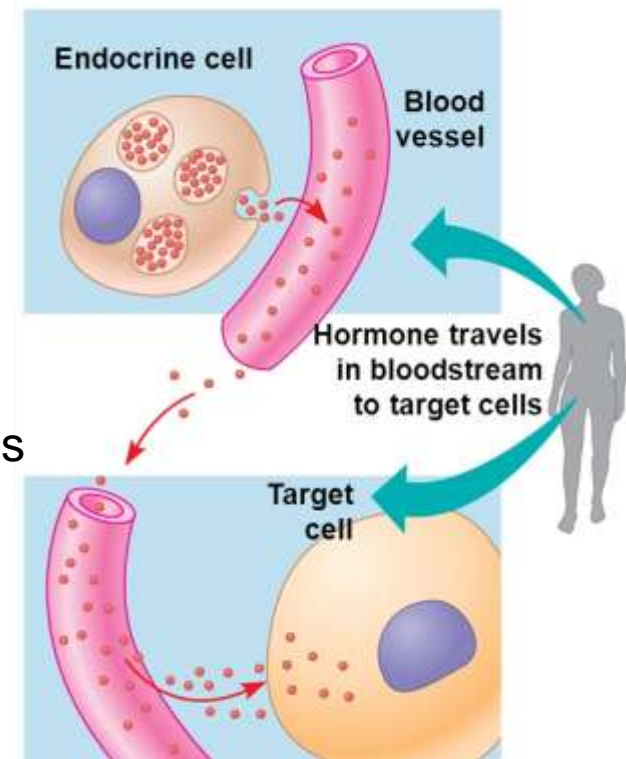
- Another, more specialized type of local signaling occurs in the animal nervous system and is called *synaptic signaling*
 - In this form of signaling, an electrical signal along a nerve cell triggers secretion of a chemical signal carried by neurotransmitter molecules
 - These neurotransmitters carrying the chemical signal diffuse across a narrow space between the nerve and target cell (often another nerve cell) called the synapse
 - The release of the neurotransmitter molecules into the synapse then stimulates the target cell
- Local signaling in plants is not well understood
 - Because of their cell walls, plants must use mechanisms somewhat different from those operating locally in animals



(b) Synaptic signaling

Long-Distance Signaling

- Both animal and plant cells use chemicals called **hormones** for long-distance signaling
 - In animals, these hormones travel through the circulatory system to target cells in other parts of the body
 - The process of hormonal signaling in animals is also called *endocrine signaling*
 - In plant cells, hormones called *plant growth regulators* most often reach target cells by moving through cells or by diffusing through the air as a gas
 - Sometimes, however, these plant hormones do travel in vessels within the plant



Long Distance Signaling: Nerve Impulses

- The transmission of a signal through the nervous system can also be considered an example of long-distance signaling
 - An electrical signal travels the length of a nerve cell
 - This electrical signal is then converted back to a chemical signal when a signaling molecule is released and crosses the synapse to another nerve cell
 - Here, it is converted back to an electrical signal
 - In this way, a nerve signal can quickly travel great distances, from one region of the body to another

Epinephrine and the Understanding of Signal Transduction Pathways

- Our current understanding of how chemical messengers act via signal transduction pathways has its origins in the work of Earl W. Sutherland
 - Sutherland and his colleagues investigated how the animal hormone epinephrine stimulates the breakdown of the storage polysaccharide glycogen in liver and skeletal muscle cells
 - Glycogen breakdown releases the sugar glucose-1-phosphate, which the cell then converts to glucose-6-phosphate
 - The cell can then use this compound (an early intermediate in glycolysis) for energy production
 - Alternatively, the compound can instead be stripped of phosphate and released from the cell and into the blood as glucose,
 - This glucose can then be absorbed and used as fuel by other cells throughout the body
 - Thus, one effect of epinephrine is the mobilization of fuel reserves during times of physical or mental stress

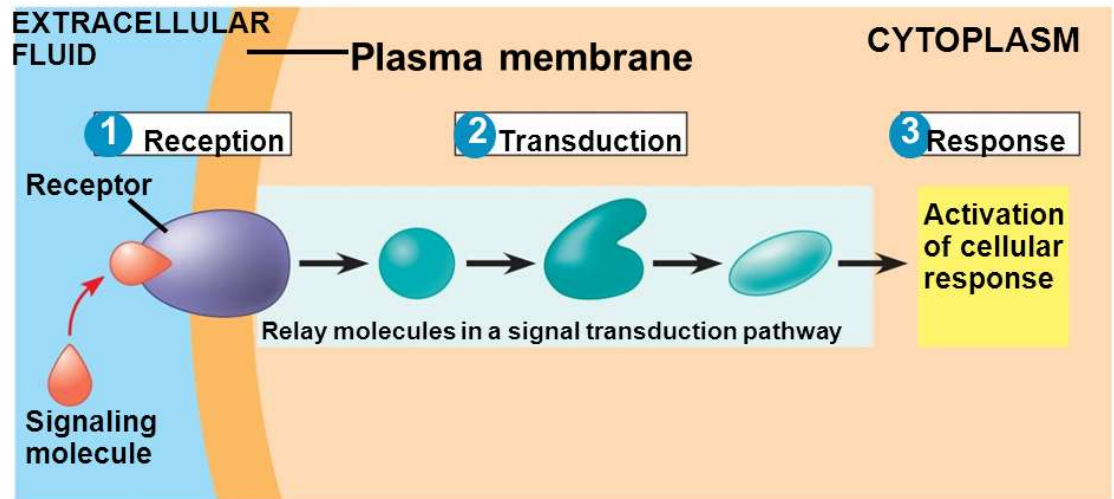
Epinephrine and the Understanding of Signal Transduction Pathways

- Sutherland's research team discovered that epinephrine stimulates glycogen breakdown by somehow activating a cytosolic enzyme called glycogen phosphorylase
 - Glycogen breakdown, however, only occurred in intact cells
 - When epinephrine was added to a test-tube mixture containing the enzyme and its substrate, glycogen, no breakdown occurred
 - This result showed that:
 - 1) Epinephrine does not interact directly with glycogen phosphorylase
 - Instead, an intermediate step or series of steps must be occurring inside the cell
 - 2) The plasma membrane is somehow involved in transmitting the epinephrine signal

Stages of Cell Signaling: Reception

- Sutherland's early work thus suggested that the process going on at the receiving end of a cellular conversation can be dissected into 3 stages:

- Reception
- Transduction
- Response



1) Reception: the target cell detects a signaling molecule coming from outside cell

- A chemical signal is “detected” when the signaling molecule binds to receptor protein located either at the cell surface or inside the cell
 - Ex) Epinephrine binds to receptor proteins on/in liver and skeletal muscle cells

Stages of Cell Signaling: Transduction

- **2) Transduction:** binding of the signaling molecule changes the receptor protein in some way that initiates the process of transduction

- The signal is then converted to a form that can bring about a specific cellular response

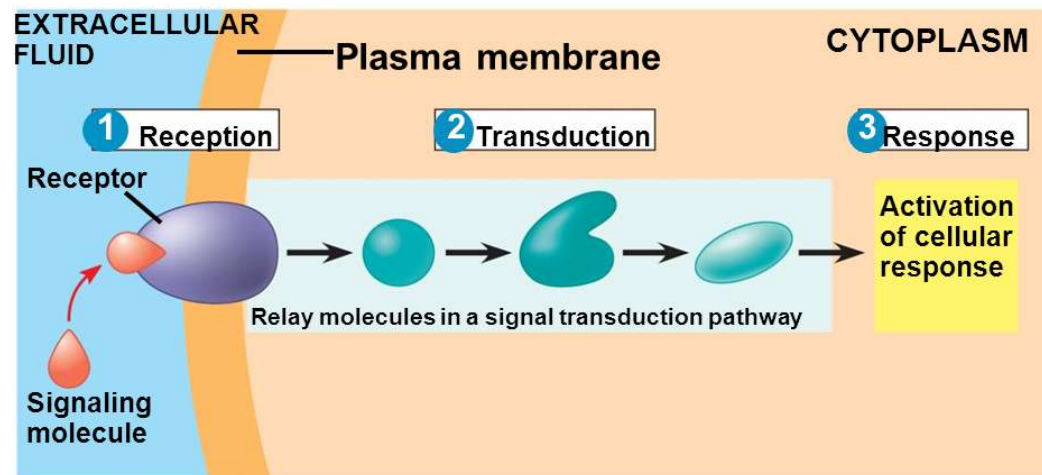
- Ex) In Sutherland's system, binding of epinephrine to a receptor protein in a liver or skeletal muscle cell's plasma membrane leads to activation of glycogen phosphorylase

- This sometimes occurs in a single step

- More often, however, it requires a sequence of changes in a series of different molecules

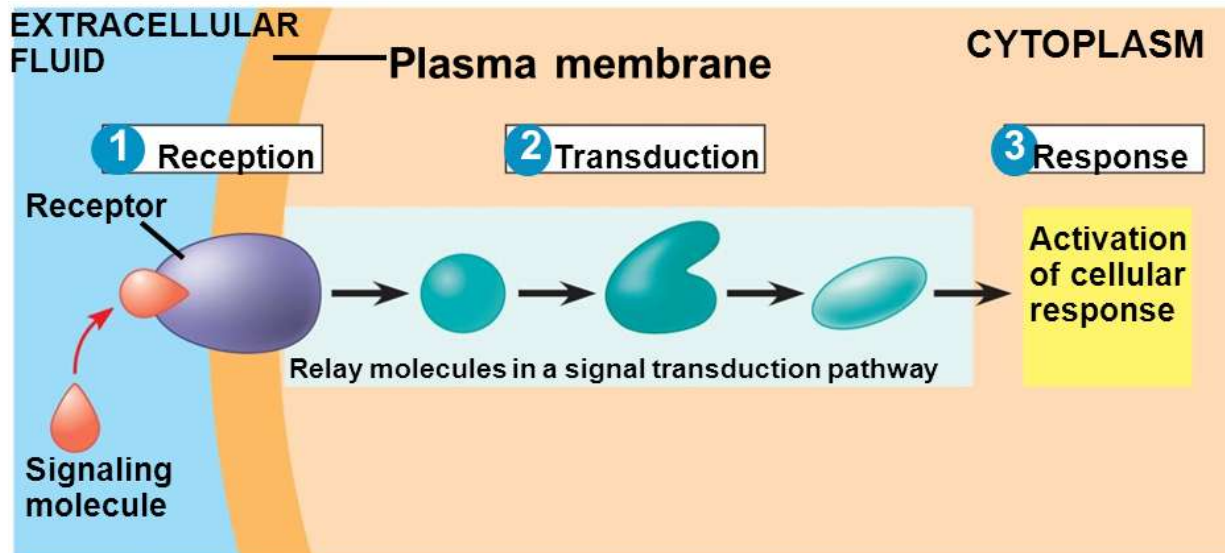
- This type of transduction is referred to as a *signal transduction pathway*

- The molecules in this type of pathway are often called relay molecules



Stages of Cell Signaling: Response

- **3) Response:** the transduced signal triggers a specific cellular response
 - Ex) The breakdown of glycogen by the activated glycogen phosphorylase
- The cell-signaling process helps ensure that crucial activities occur in the right cells at the right times and in proper coordination with other cells of the organism



Concept Check 11.1

- 1) Explain how signaling is involved in ensuring that yeast cells only fuse with cells of the opposite mating type.
- 2) Explain how nerve cells provide examples of both local and long-distance signaling.
- 3) When epinephrine is mixed with glycogen phosphorylase and glycogen in a test tube, is glucose-1-phosphate generated? Why or why not?
- 4) In liver cells, glycogen phosphorylase acts in which of the 3 stages of the signaling pathway associated with an epinephrine-initiated signal?

Concept 11.2:

Reception:

A signal molecule binds to a receptor protein, causing it to change shape

Specificity of Signaling Molecules

- Receptor proteins on or in target cell allow only these cells to “hear” signals and respond to them
 - This is because the signaling molecule is complementary in shape to a specific site on the receptor, allowing it to attach there with a lock/key fit
 - The signaling molecule is called a **ligand**
 - Binding of a ligand generally causes the receptor protein to change shape
 - This shape change may directly activate the receptor, allowing it to interact with other cellular molecules
 - Alternatively, the shape change may cause aggregation of 2 or more receptor molecules, leading to further molecular events inside the cell

Ligand Binding and Signal Receptors

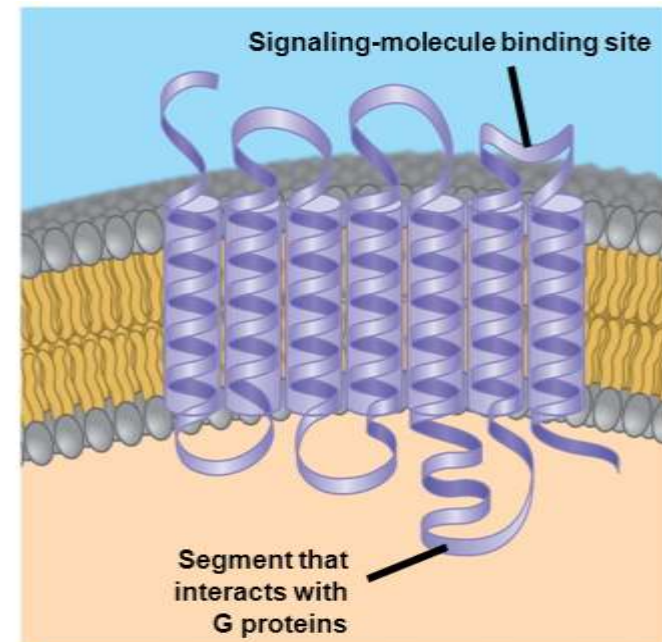
- In a general way, ligand binding is similar to the binding of an allosteric regulator to an enzyme
 - Recall: binding of an allosteric regulator causes a shape change that either promotes or inhibits enzyme activity
 - In the case of signal transduction, ligand binding alters the ability of the receptor to transmit the signal
- Most signal receptors are plasma membrane proteins, though some are located inside the cell
 - Their ligands are water-soluble and often too large to pass freely through plasma membrane

Receptors in the Plasma Membrane

- Most water-soluble ligands bind to specific sites on receptor proteins embedded in the plasma membrane
 - These receptors then transmit information from the extracellular environment to the inside of the cell
- There are three main types of membrane receptors:
 - G protein-coupled receptors
 - Receptor tyrosine kinases
 - Ion channel receptors

G Protein-Coupled Receptors

- A **G protein-coupled receptor** is a plasma membrane receptor that works with the help of a **G protein**
 - G proteins are special proteins that bind the energy-rich molecule GTP
 - The G protein acts as an on/off switch:
 - If GDP is bound to the G protein, the G protein is inactive
 - If GTP is bound to the G protein, the G protein is active
- G protein-coupled receptor proteins are similar in structure
 - Each have 7 alpha helices spanning their plasma membranes
 - Specific loops between helices form binding sites for signaling molecules and G protein molecules

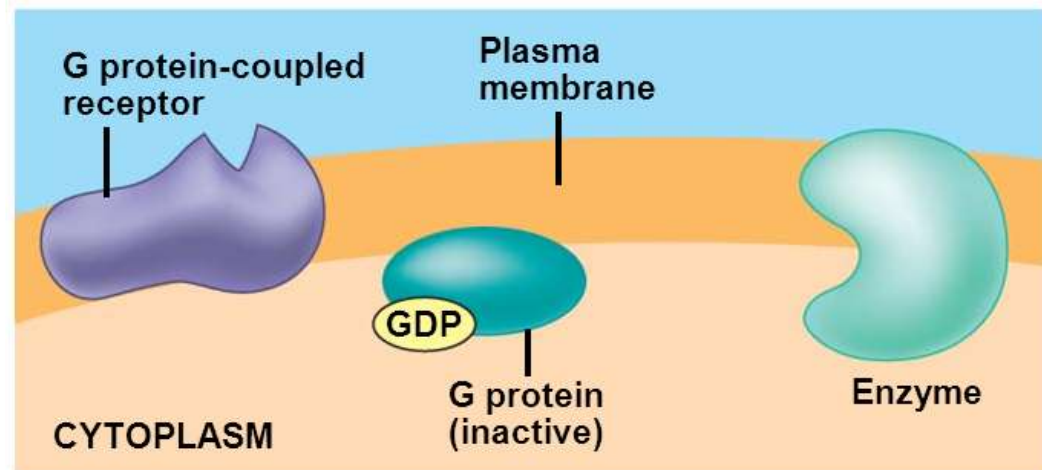


G Protein-Coupled Receptor Function

- G protein-coupled receptor systems are widespread and diverse in function
 - They are involved in embryonic development, as well as sensory reception (vision and smell in humans)
 - They are also involved in many human diseases:
 - Bacterial infections that cause cholera, pertussis (whooping cough), and botulism all cause illness by producing toxins that interfere with G-protein function
 - Pharmacologists estimate that up to 60% of all medicines used today exert their effects by influencing G-protein pathways

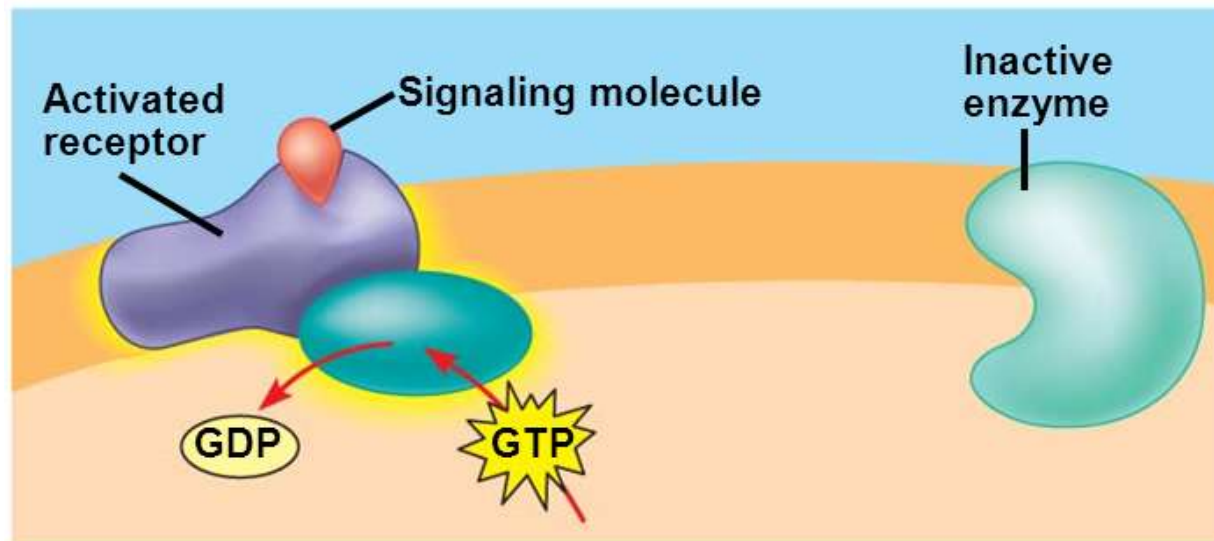
G Protein-Coupled Receptors: Step 1

- The G protein is loosely attached to cytoplasmic side of membrane
 - It functions as a molecular switch that is either “on” or “off”
 - Inactive form: GDP (guanosine diphosphate) is bound to G protein
 - Active form: GTP (guanosine triphosphate) is bound to G protein
 - The receptor and G protein work together with another protein
 - This other protein is usually an enzyme



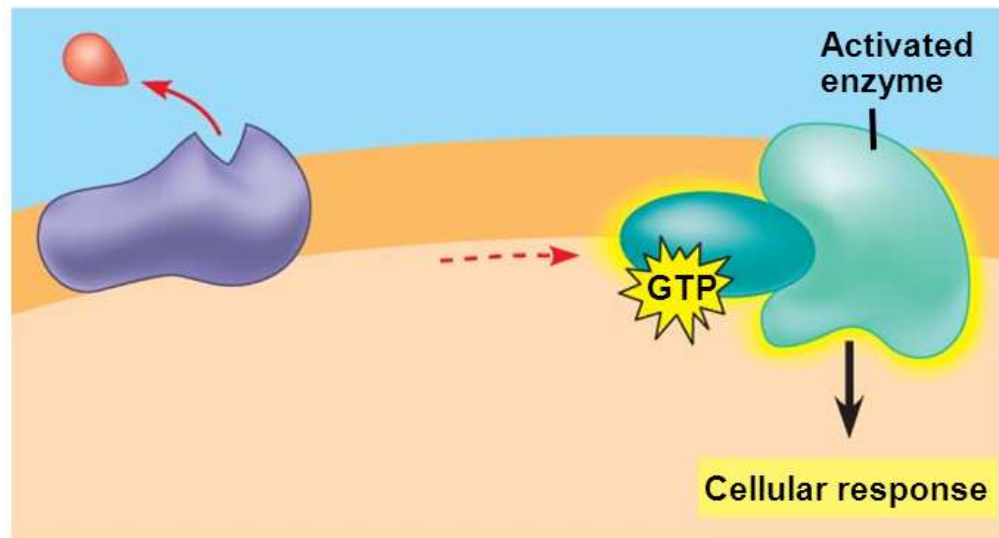
G Protein-Coupled Receptors: Step 2

- When the appropriate signaling molecule binds to extracellular side of receptor:
 - The receptor changes shape
 - The receptor is now activated
 - The cytoplasmic side of the receptor can then bind an inactive G protein
 - This causes GTP to displace GDP
 - This, in turn, activates the G protein



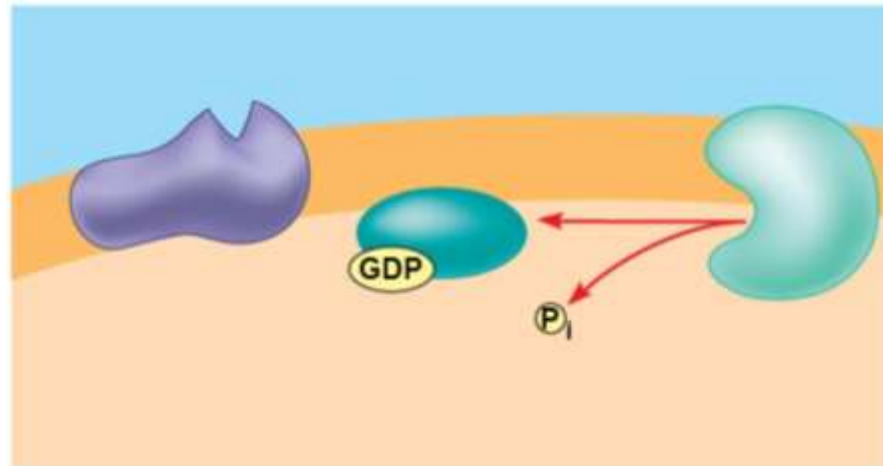
G Protein-Coupled Receptors: Step 3

- The activated G protein dissociates from receptor and diffuses along membrane
 - The G protein then binds to an enzyme
 - This enzyme, in turn, changes shape and becomes activated
 - The activated enzyme can then trigger the next step in a pathway leading to a cellular response



G Protein-Coupled Receptors: Step 4

- The changes in the enzyme and G protein are only temporary
 - The G protein also functions as a GTPase enzyme and hydrolyzes its bound GTP to GDP
 - This causes the G protein to become inactivated and leave the enzyme
 - The enzyme can then return to its original state
 - Thus, both the G protein and the enzyme are now available for reuse
 - The GTPase function of the G protein allows the pathway to shut down rapidly when its signaling molecule is no longer present

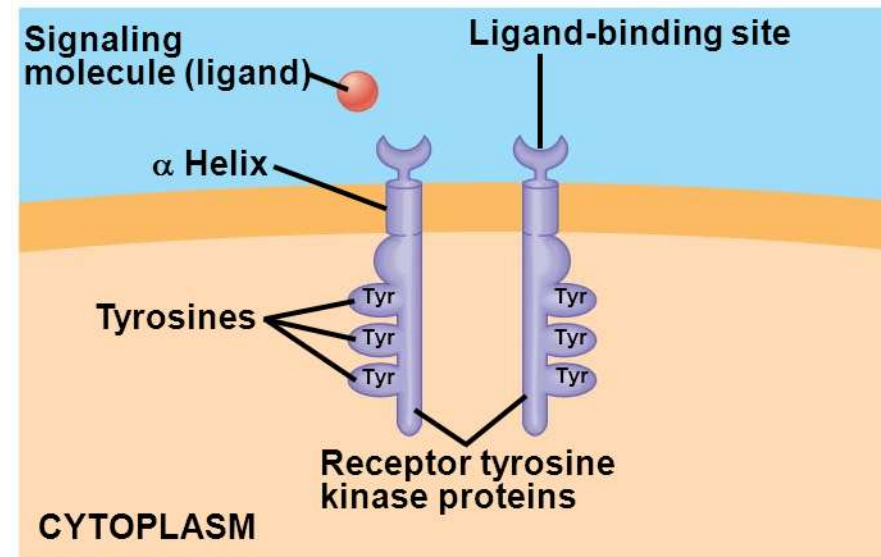


Receptor Tyrosine Kinases

- **Receptor tyrosine kinases** belong to a major class of plasma membrane receptors that are characterized by having enzymatic activity
 - A *kinase* is an enzyme that catalyzes the transfer of phosphate groups
- The part of the receptor protein extending into the cytoplasm functions as a tyrosine kinase
 - It catalyzes the transfer of a phosphate group from ATP to the amino acid tyrosine on a substrate protein
- A receptor tyrosine kinase complex can trigger multiple signal transduction pathways at once
 - This helps the cell regulate and coordinate many aspects of cell growth and reproduction
 - This ability of a single ligand-binding event to trigger so many pathways is also a key difference between receptor tyrosine kinases and G protein-coupled receptors
- Abnormal receptor tyrosine kinases that function even in the absence of signaling molecules may contribute to some kinds of cancer

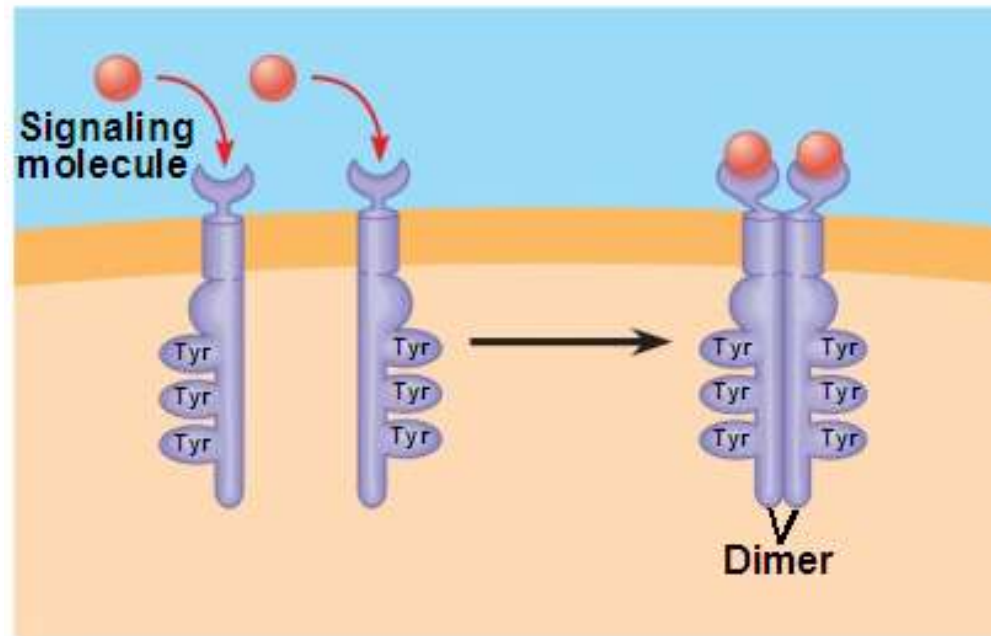
Receptor Tyrosine Kinases: Step 1

- Before the signaling molecule binds, the receptors exist as individual polypeptides
 - The structure of each polypeptide includes:
 - An extracellular ligand-binding site
 - An alpha helix spanning the membrane
 - An intracellular tail containing multiple tyrosines



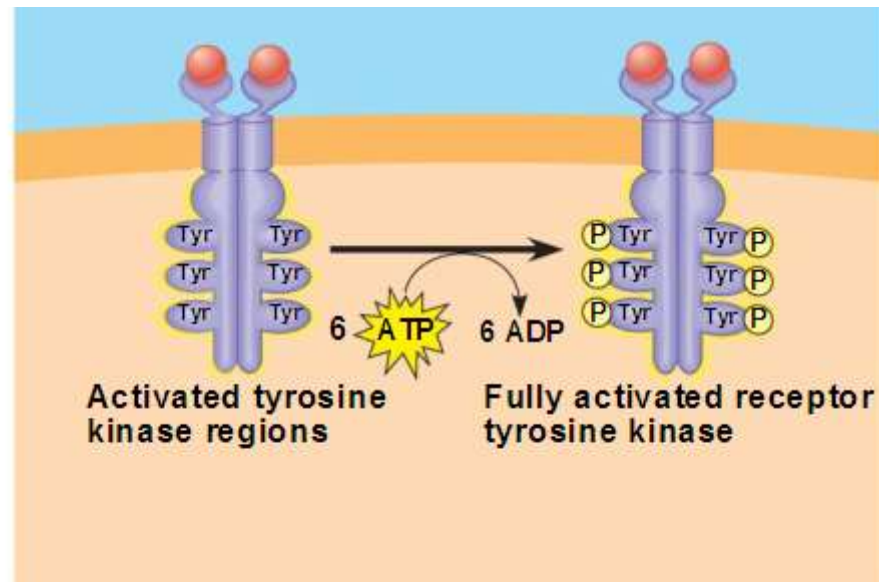
Receptor Tyrosine Kinases: Step 2

- Binding of a signal molecule (often a growth factor) causes 2 receptor polypeptides to associate closely with each other
 - This forms a structure called a *dimer*
 - This process is called dimerization



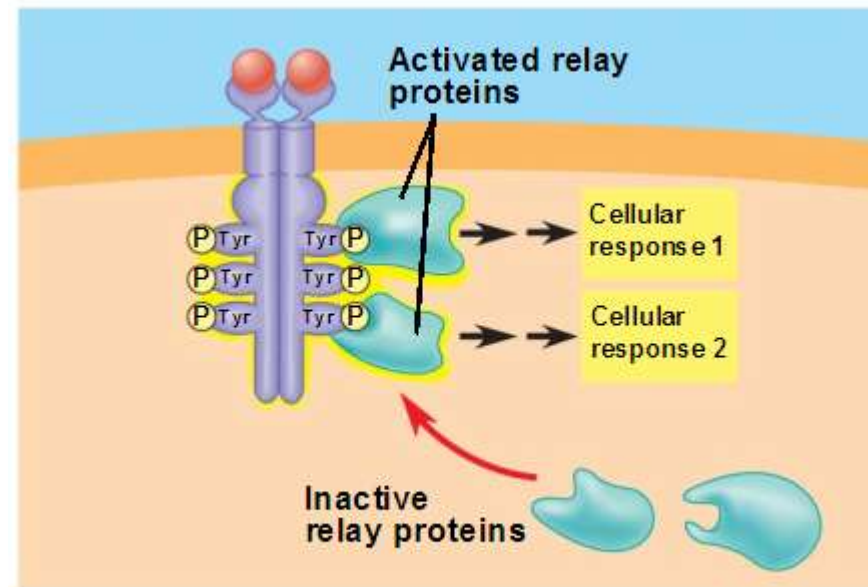
Receptor Tyrosine Kinases: Step 3

- Dimerization activates the tyrosine kinase region of each polypeptide
 - Each tyrosine adds a phosphate from ATP to a tyrosine on the tail of the other polypeptide



Receptor Tyrosine Kinases: Step 4

- The now fully activated receptor protein is recognized by specific relay proteins inside the cell
 - These relay proteins each bind to a specific phosphorylated tyrosine
 - Binding results in a structural change that activates the bound relay protein
 - Each of these activated relay proteins can then trigger a transduction pathway that leads to a specific cellular response

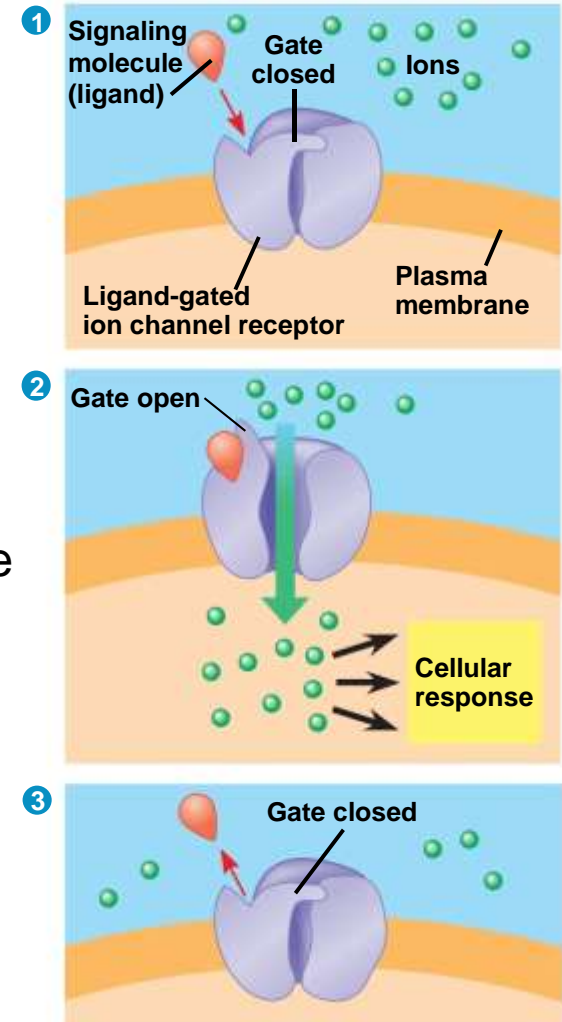


Ligand-Gated Ion Channels

- A **ligand-gated ion channel** is a type of membrane receptor containing a region that can act as a “gate” when the receptor changes shape
 - When a signaling molecule binds as a ligand to the receptor, the gate open or closes, allowing or blocking the flow of specific ions (ex: Na⁺ or Ca²⁺) through a channel in the receptor
 - Like other membrane receptors, ligand-gated ion channels bind their ligands at a specific site on their extracellular sides
 - Ligand-gated ion channels are particularly important in the nervous system
 - Neurotransmitter molecules released at a synapse between 2 nerve cells bind as ligands to ion channels on the receiving cell, causing the channels to open
 - Ions can thus flow in (or out), which then triggers an electrical signal that propagates down the length of the receiving cell
 - Some gated ion channels are controlled by electrical signals rather than ligands
 - These are known as voltage-gated ion channels and are also crucial to the functioning of the nervous system

Ligand-Gated Ion Channels

- 1) The gate of a ligand-gated ion channel receptor remains closed until a ligand binds to the receptor
- 2) The ligand binds to the receptor, causing its gate to open
 - Specific ions can then flow through the channel
 - This can cause a rapid change in the concentrations of these ions inside the cell
 - This change may directly affect the activity of the cell in some way
- 3) When the ligand dissociates from its receptor, the gate closes and ions can no longer enter/leave the cell



Intracellular Receptors

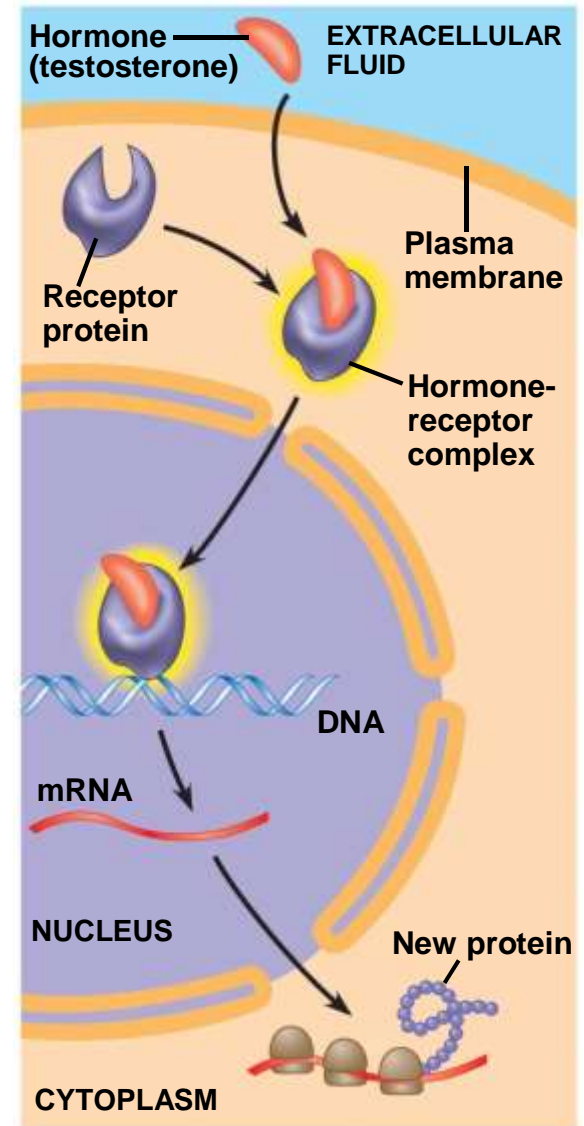
- Some receptor proteins are intracellular, found either in the cytosol or the nucleus of target cells
 - To reach these receptors, chemical messengers must pass through the target cell's plasma membrane
 - Small or hydrophobic chemical messengers can readily cross the phospholipid interior of the membrane and activate receptors
 - Ex) Steroid and thyroid hormones of animals, gases like NO (nitric oxide)

Intracellular Receptors: Testosterone

- The behavior of testosterone is representative of steroid hormones
 - Testosterone is secreted by cells of the testis and travels through the blood to enter cells all over the body
 - In the cytoplasm of target cells, testosterone binds to the receptor protein and activates it
 - With the testosterone attached, the active form of the receptor protein then enters the nucleus
 - Here, the activated hormone-receptor complex acts as a transcription factor, turning on specific genes that control male sex characteristics
 - *Transcription factors* are special proteins that control which genes are transcribed into mRNA (and thus which genes are turned “on”) in a particular cell at a particular time

Intracellular Receptors: Testosterone As An Example

- 1) The steroid hormone testosterone passes through the plasma membrane
- 2) Testosterone binds to a receptor protein in the cytoplasm, activating it
- 3) The hormone-receptor complex enters the nucleus and binds to and turns on specific genes that control male sex characteristics
- 4) The bound receptor protein acts as a transcription factor, stimulating the transcription of the gene into mRNA
- 5) The mRNA is translated into a specific protein



Concept Check 11.2

- 1) Nerve growth factor (NGF) is a water-soluble signaling molecule. Would you expect the receptor for NGF to be intracellular or in the plasma membrane? Why?
- 2) What would the effect be if a cell made defective receptor tyrosine kinase proteins that were unable to dimerize?

Concept 11.3:

Transduction:

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

Transduction: Multi-Step Pathways

- The transduction stage of cell signaling is usually a multistep pathway
 - Steps often include:
 - Activation of proteins by addition or removal of phosphate groups
 - Release of other small molecules or ions that act as messengers
 - One benefit of multiple steps is that it can amplify a signal
 - This means that only a few molecules can produce a large cellular response
 - Multistep pathways also provide more opportunities for coordination and regulation of the cellular response
 - This allows fine-tuning of the cellular response

Signal Transduction Pathways

- In multistep pathways, the binding of a specific signaling molecule to a plasma membrane receptor triggers the 1st step in a chain of molecular interactions
 - This chain of events is known as a signal transduction pathway
- Similar to falling dominoes, the signal-activated receptor activates another molecule, and so on, until the protein that produces the final cellular response is activated
 - The molecules that relay a signal from receptor to response, also known as relay molecules, are mostly proteins
- It is important to remember that the original signaling molecule is not physically passed along the signal transduction pathway
 - In most cases, this signaling molecule never even enters the cell
 - Rather, the signal is relayed along the pathway as certain information is passed on
 - At each step, the signal is transduced into a different form, usually a shape change in a protein
 - This shape change is often brought about by phosphorylation

Protein Phosphorylation

- Recall: the general name for an enzyme that transfers phosphate groups from ATP to a protein is a **protein kinase**
 - Most cytoplasmic protein kinases act on proteins different from themselves (unlike receptor tyrosine kinases)
 - Another distinction is that most cytoplasmic protein kinases phosphorylate either the amino acid serine or threonine (rather than tyrosine)
 - Many of the relay molecules in signal transduction pathways are protein kinases
 - In turn, these protein kinase relay molecules often act on other protein kinases in the pathway
 - Phosphorylation of the proteins along a signal transduction pathway causes these molecules to change shape
 - Each shape change results from the interaction of newly added phosphate groups with charged and polar amino acids
 - The addition of a phosphate group also usually changes the protein from an inactive to an active form

Importance of Protein Kinases

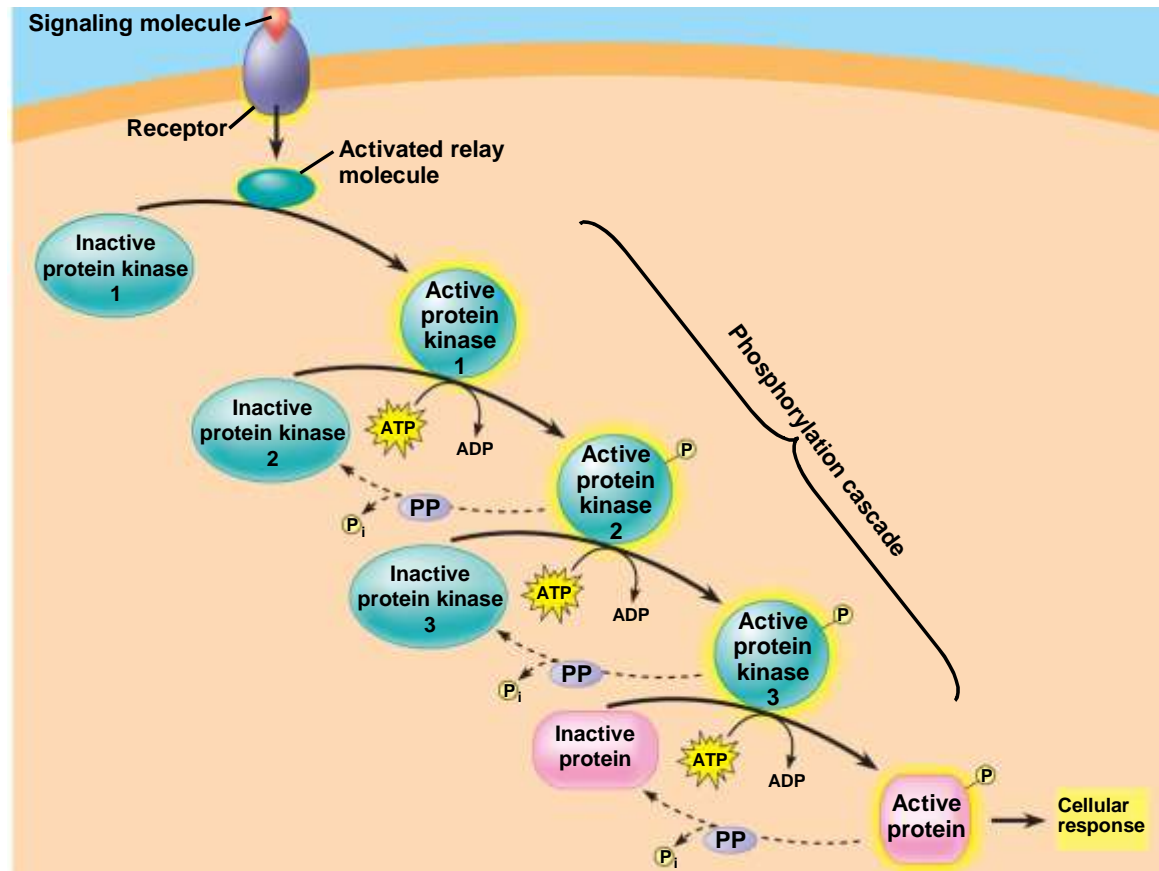
- Protein kinases are very important in maintaining normal body function
 - About 2% of human genes are thought to code for various protein kinases
 - A single cell, in fact, may have 100s of different kinds of protein kinases, each specific for a different substrate protein
 - Together, these protein kinases likely regulate most of the 1000s of proteins in a cell
 - These proteins, in turn, regulate functions such as cell reproduction
 - Thus, abnormal activity of such kinases can cause abnormal cell growth and contribute to the development of cancer

Protein Dephosphorylation

- Dephosphorylation is equally important in the phosphorylation cascade of a signal transduction pathway
 - **Protein phosphatases** are enzymes that can rapidly remove phosphate groups from proteins
 - Dephosphorylation inactivates protein kinases
 - Thus, if the initial signal is no longer present, protein phosphatases provide a way to turn off signal transduction pathways
 - Protein phosphatases also recycle protein kinases that have been phosphorylated
 - This allows the cell to continually respond to new extracellular signals
- The activity of a protein regulated by phosphorylation thus depends on a balance between active kinase molecules and active phosphatase molecules
 - The system of phosphorylation and dephosphorylation acts a molecular switch in the cell, turning activities on or off as required

A Phosphorylation Cascade

- 1) A relay molecule activates protein kinase 1
- 2) The active protein kinase 1 transfers a phosphate group from ATP to an inactive protein kinase 2, thus activating this 2nd kinase
- 3) The now-active protein kinase 2 catalyzes the phosphorylation and activation of protein kinase 3
- 4) Active protein kinase 3 phosphorylates a protein (pink) that elicits a cellular response
- 5) Enzymes called protein phosphatases (PP) catalyze removal of phosphate groups, making them inactive and available for reuse



Small Molecules and Ions as Second Messengers

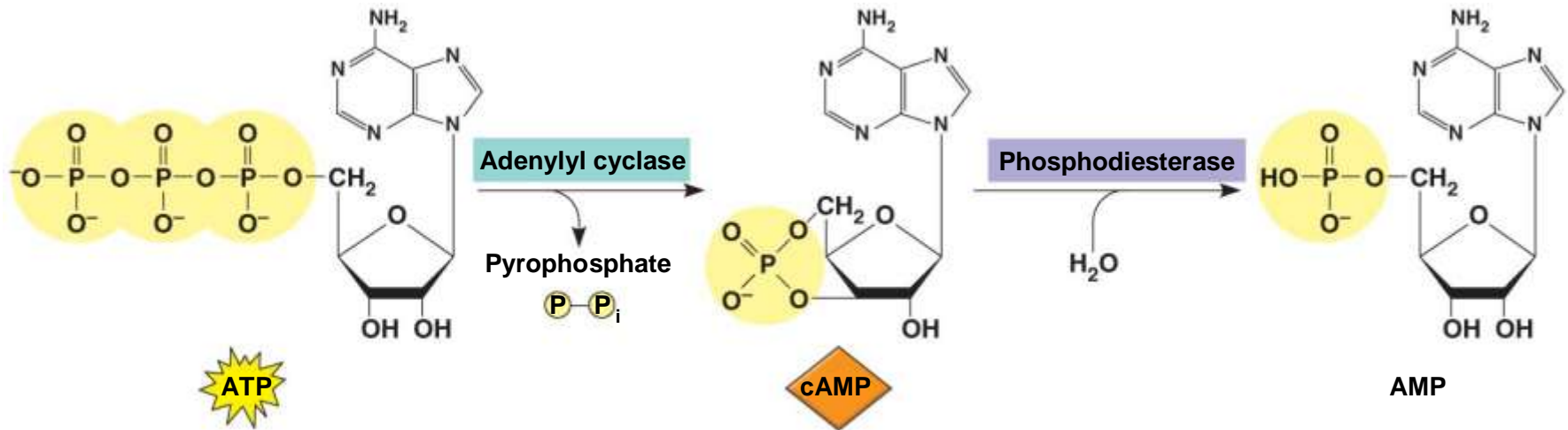
- Not all components of signal transduction pathways are proteins
 - Many signaling pathways also involve small nonprotein, water-soluble molecules or ions called second messengers
 - The extracellular signaling molecule that binds to the membrane receptor is a pathway's “first messenger”
 - Second messengers can spread through the cell by simple diffusion because of their chemical nature
 - Second messengers participate in pathways initiated by both G protein-coupled receptors and receptor tyrosine kinases
 - Cyclic AMP and calcium ions are two commonly used second messengers
 - A large variety of relay proteins are sensitive to the cytosolic concentration of one or the other of these second messengers

Cyclic AMP

- **Cyclic adenosine monophosphate (cyclic AMP or cAMP)** is one of the most widely used second messengers in signal transduction pathways

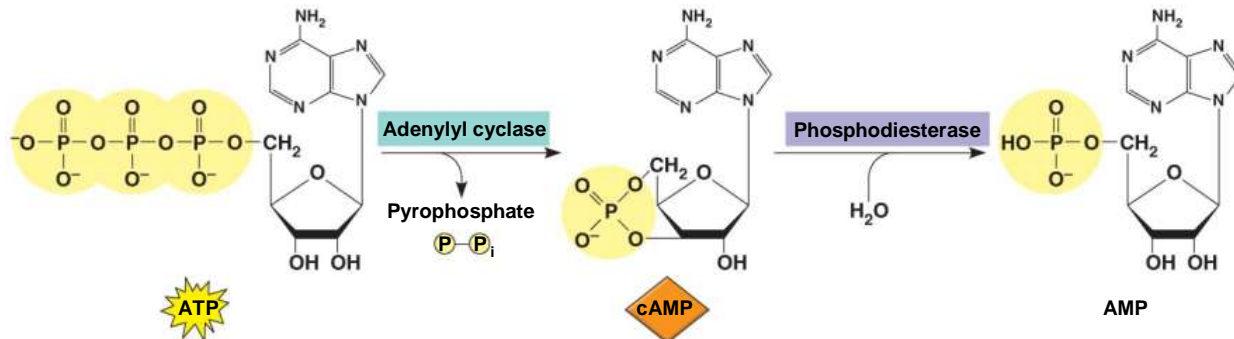
- An enzyme embedded in the plasma membrane called **adenylyl cyclase** converts ATP to cAMP in response to an extracellular signal

- Ex) Epinephrine is just one of many hormones and other signaling molecules that trigger formation of cAMP



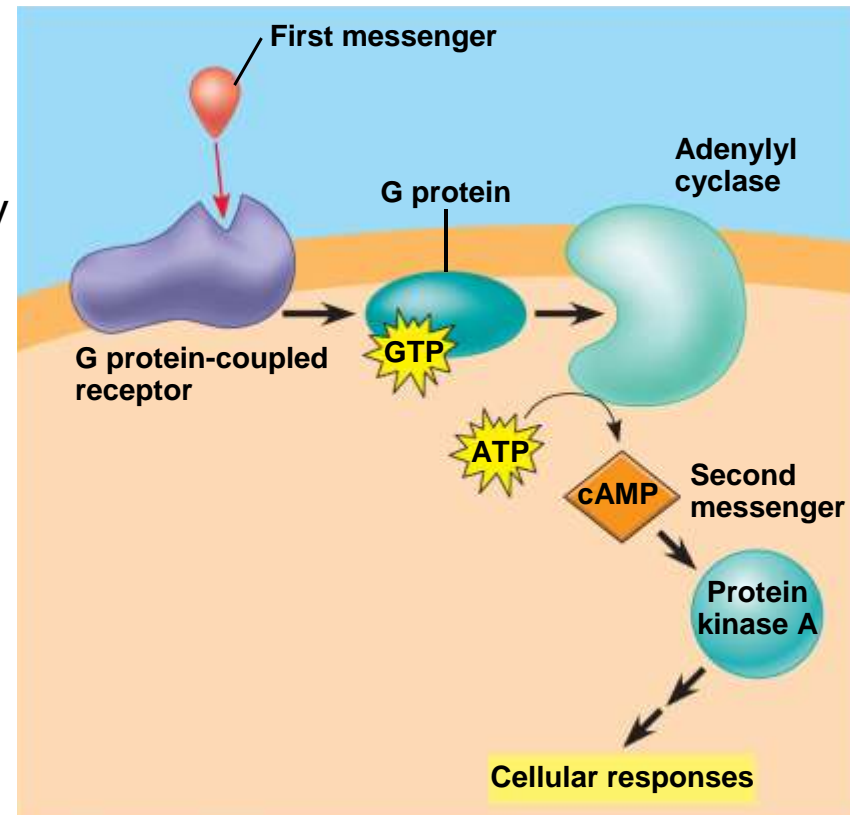
Cyclic AMP and Epinephrine

- In the case of epinephrine, adenylyl cyclase is not stimulated by epinephrine directly
 - Instead, epinephrine outside the cell binds to a specific receptor protein which, in turn, activates adenylyl cyclase, thus catalyzing the synthesis of many cAMP molecules
 - In this way, the normal cellular concentration of cAMP can be boosted 20-fold in just a matter of seconds
- cAMP does not persist for long in the absence of an extracellular signal, however
 - Another enzyme called *phosphodiesterase* converts cAMP to AMP
 - Another surge of epinephrine would be necessary to boost cytosolic concentrations of cAMP again



Receptors Involved in the Regulation of cAMP

- Research has brought to light other components of cAMP pathways
 - These include G proteins, G protein-coupled receptors, and protein kinases
- The immediate effect of cAMP is usually the activation of a serine/threonine kinase called *protein kinase A*
 - This activated kinase then phosphorylates various other proteins
- Cell metabolism is also regulated by other G-protein systems that inhibit adenylyl cyclase
 - In this case, a different molecule activates a different receptor, activating an inhibitory G protein



cAMP and Cholera

- Cholera is a disease that is frequently epidemic in places where the water supply is contaminated with human feces
 - People acquire the cholera bacterium (*Vibrio cholerae*) by drinking this contaminated water
 - These bacteria then colonize the lining of the small intestine and produce a toxin
 - The cholera toxin is an enzyme that chemically modifies a G protein involved in regulating salt and water secretion
 - This modified G protein is unable to hydrolyze GTP to GDP, leaving the protein “stuck” in its active form
 - This means that adenylyl cyclase is continuously stimulated to make cAMP
 - The resulting high concentration of cAMP causes intestinal cells to secrete large amounts of salts, also causing water to quickly follow by osmosis
 - Thus, an infected person quickly develops profuse diarrhea, and if left untreated, can soon die from the loss of water and salts

Useful Application of cAMP

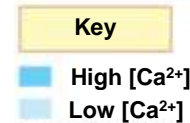
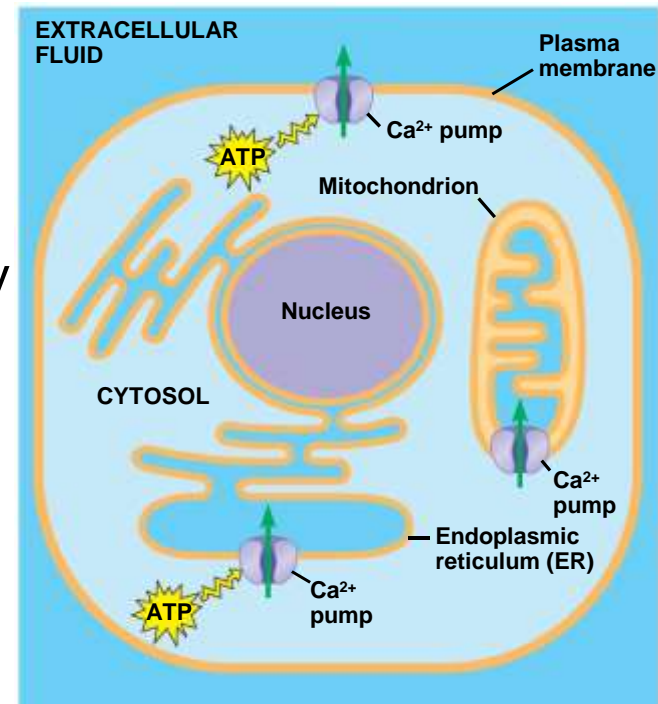
- Our understanding of signaling pathways involving cAMP and related messengers has also allowed us to develop treatments for certain human conditions
 - Cyclic GMP (cGMP) is a related signaling molecule whose effects include relaxation of smooth muscle cells in artery walls
 - A compound that inhibits hydrolysis of cGMP to GMP thus prolongs the signal
 - This compound was originally prescribed for chest pains because it increased blood flow to the heart
 - Under the trade name Viagra, however, this compound is now widely used as a treatment for erectile dysfunction
 - It allows increased blood flow to the penis, which optimizes physiological conditions for penile erections

Calcium Ions as Second Messengers

- Calcium ions (Ca^{2+}) are even more widely used than cAMP as second messengers in signal transduction pathways
 - Increasing the cytosolic calcium concentration causes many responses in animal cells, including:
 - Muscle cell contraction
 - Secretion of certain substances
 - Cell division
 - Increases in cytosolic calcium concentrations can also trigger various signaling pathways in plants, including the pathway for greening in response to light
- Cells use calcium ions as a second messenger in both G-protein and receptor tyrosine kinase pathways

Calcium Ions Regulation

- The cytosolic Ca^{2+} concentration is normally much lower than concentrations in the extracellular environment and in the ER
 - The level of calcium in the blood and extracellular fluid of an animal often exceeds that in the cytosol by more than 10,000X
- Cells maintain this concentration gradient by actively transporting Ca^{2+} ions out of the cell by protein pumps
- At the same time, they are also actively imported out of the cell and into the ER

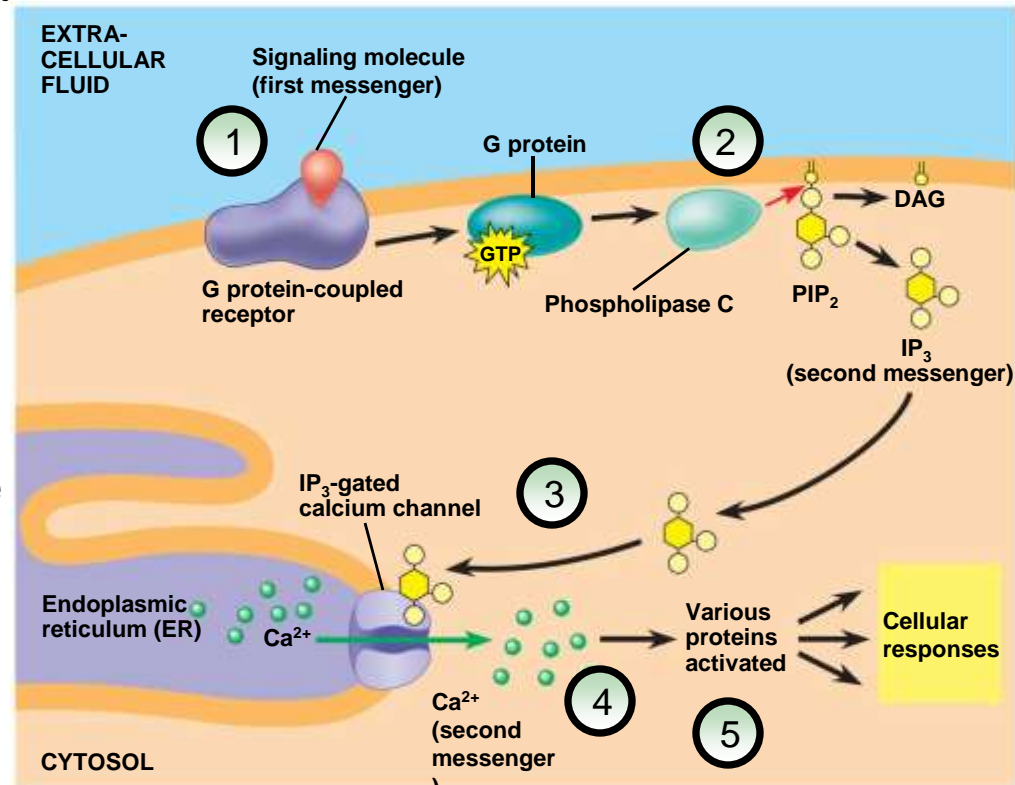


Calcium Ions and Inositol Triphosphate (IP₃)

- Certain signals relayed by a signal transduction pathway may trigger an increase in cytosolic calcium levels
 - Rises in cytosolic calcium concentrations usually occur by mechanisms that release calcium ions from the ER
 - Pathways leading to calcium release involve still other second messengers, including:
 - **Inositol triphosphate (IP₃)**
 - **Diacylglycerol (DAG)**
 - These 2 messengers are produced by cleavage of a certain type of phospholipid in the plasma membrane called PIP₂

Calcium Ions and IP_3 in Signaling Pathways

- 1) A signaling molecule binds to a receptor, leading to activation of phospholipase C
- 2) Phospholipase C cleaves a plasma membrane phospholipid (PIP_2) into DAG and IP_3
 - DAG also functions as a 2nd messenger in other pathways
- 3) IP_3 diffuses through the cytosol and binds to IP_3 -gated calcium channels in the ER, causing them to open
- 4) Ca^{2+} ions flow out of the ER (down their concentration gradients), raising cytosolic Ca^{2+} concentration
- 5) The released Ca^{2+} ions activate the next protein in one or more signaling pathways



Concept Check 11.3

- 1) What is a protein kinase, and what is its role in signal transduction pathways?
- 2) When a signal transduction pathway involves a phosphorylation cascade, how does the cell's response get turned off?
- 3) What is the actual “signal” that is being transduced in any signal transduction pathway. In other words, in what way is information passed from the exterior to the interior of the cell?
- 4) Upon activation of phospholipase C by ligand binding to a receptor, what effect does the IP_3 -gated calcium channel have on calcium ion concentration in the cytosol?

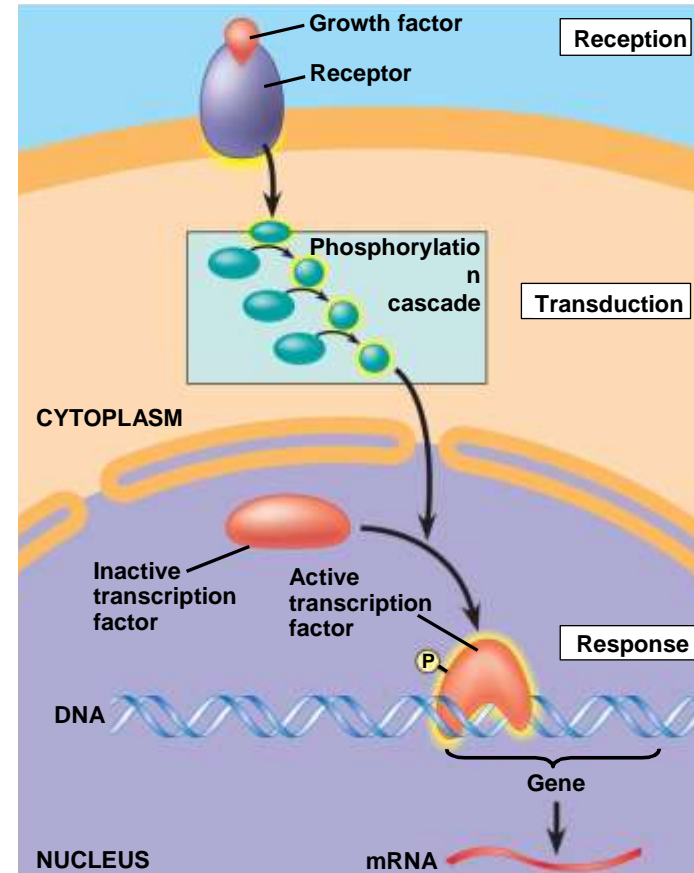
Concept 11.4:

Response:

**Cell Signaling Leads to Regulation of
Transcription or Cytoplasmic
Activities**

Nuclear Responses

- Signal transduction pathways ultimately lead to regulation of one or more cellular activities
 - This response may occur in nucleus or cytoplasm
 - Many pathways regulate protein synthesis by turning genes “on” or “off” in the nucleus
 - The final activated molecule may function as a transcription factor
 - This activated transcription factor may turn a gene “on” so it can be transcribed and translated into a specific protein
 - In other cases, a transcription factor may turn a gene “off,” so that a protein stops being manufactured



Cytoplasmic Responses

- Other pathways regulate the *activity* of proteins rather than their synthesis

- Ex) A signal may cause a change in cell metabolism

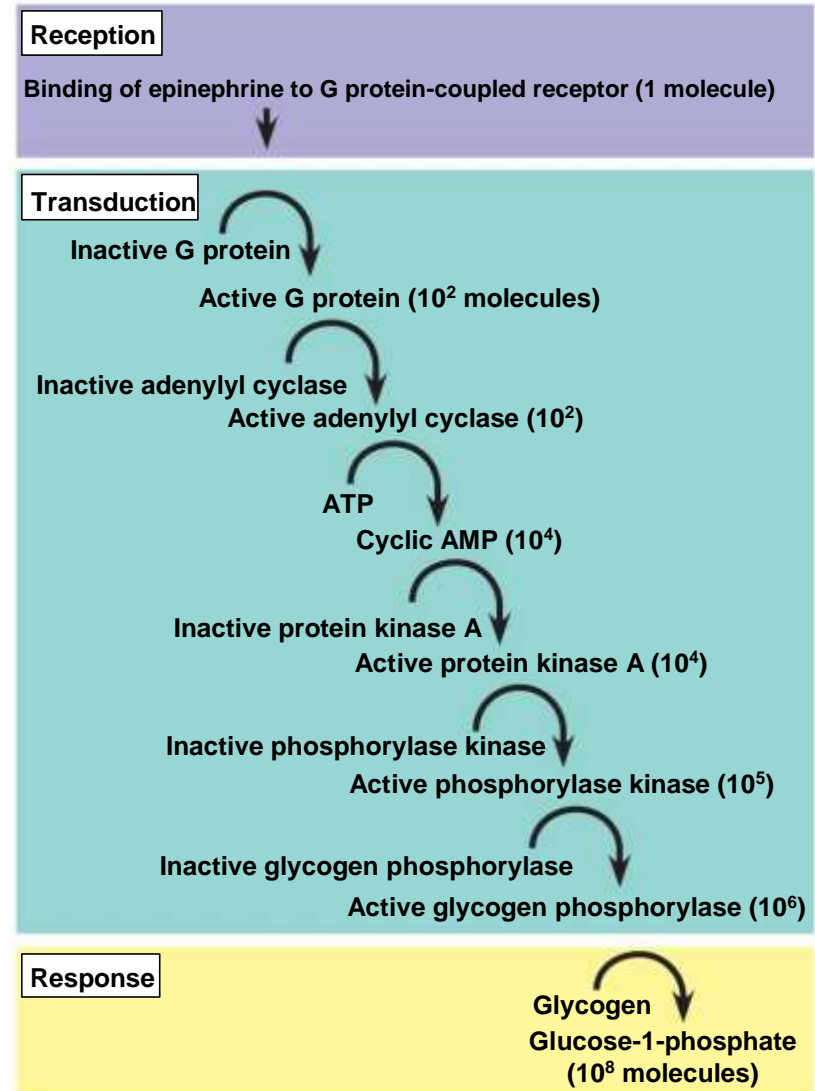
- The response of liver cells to signaling by the hormone epinephrine helps regulate cell energy metabolism by affecting enzyme activity

- As each molecule is activated, the response is amplified

- 1 receptor protein can activate ~100 G proteins

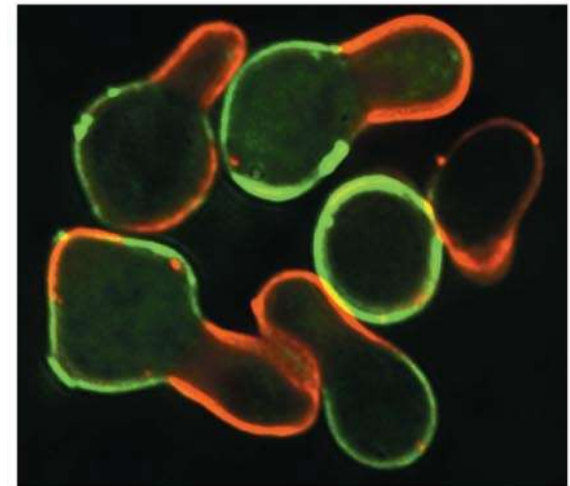
- Each activated enzyme can then act on many of its substrates during the next reaction in the cascade

- Binding of epinephrine eventually activates an enzyme that catalyzes breakdown of glycogen into glucose-1-phosphate molecules



Directional Growth in Yeast

- Signaling pathways can also lead to responses that affect the physical characteristics of a cell, such as cell shape
 - Ex) The mating of yeast depends on the growth of projections in one cell toward another cell of opposite mating type
 - Binding of the mating factor causes this directional growth
 - When the mating factor binds, it activates signaling-pathway kinases that affect the orientation and growth of cytoskeletal filaments
 - The cell projections emerge from regions of the plasma membrane exposed to the highest concentration of the mating factor
 - As a result, projections are oriented toward cell of opposite mating type (the source of the signaling molecule)



Fine-Tuning of the Response

- Regardless of whether the response occurs in the nucleus or cytoplasm, multistep pathways allow fine-tuning of responses at multiple points
 - These multistep pathways provide 2 important benefits:
 - The signals can be amplified, thus amplifying the response
 - They provide different points at which the cell's response can be regulated
 - This allows coordination of different signaling pathways
 - It also contributes to the specificity of the response
- The overall efficiency of the response is also enhanced by scaffolding proteins
- Termination of the signal is also a crucial point in fine-tuning a response

Signal Amplification

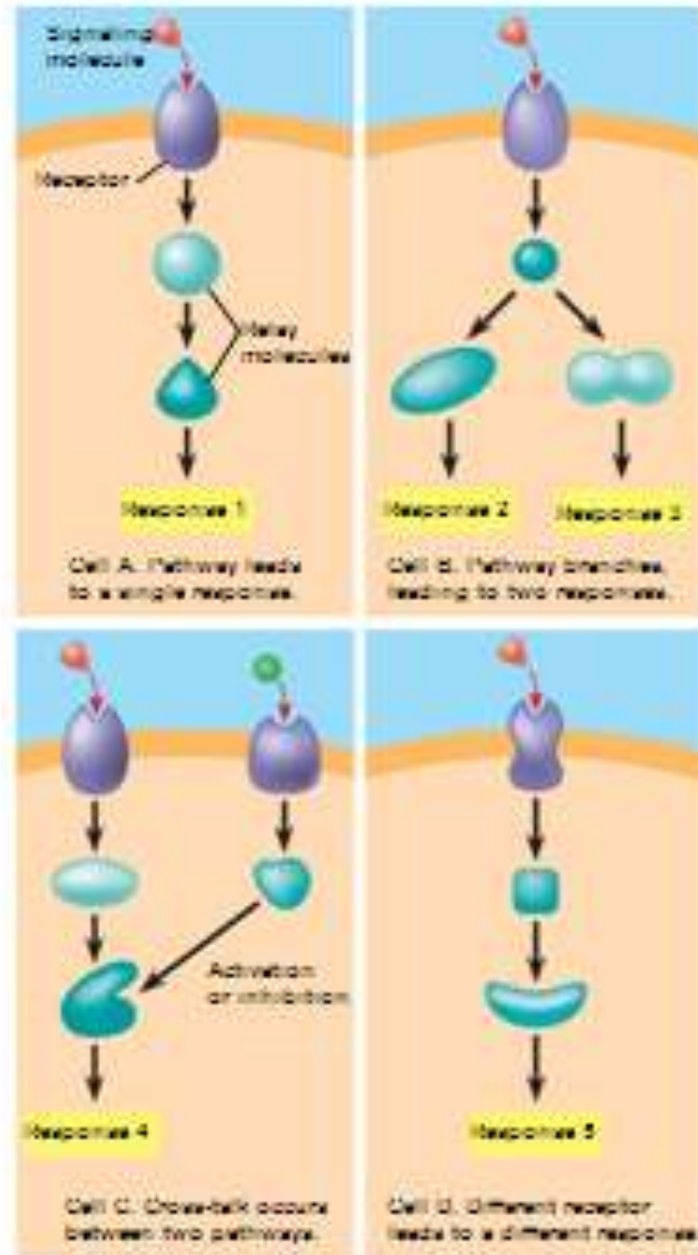
- Enzyme cascades amplify the cell's response to a signal
 - At each step in the cascade, the number of activated products is much greater than in preceding step
 - This amplification effect occurs because activated proteins persist long enough to process many substrate molecules before becoming inactive
 - Ex) Only a small number of epinephrine molecules binding to receptors on the surfaces of liver and muscle cells can lead to the release of millions of glucose molecules from glycogen

The Specificity of Cell Signaling and Coordination of the Response

- Different cells respond only to specific signals, even though they are constantly exposed to many different signaling molecules
 - In addition, even though some signals trigger responses in more than one type of cell, these responses can be different
 - Ex) Epinephrine stimulates liver cells to break down glycogen; in heart cells, this hormone causes contraction, leading to a more rapid heartbeat

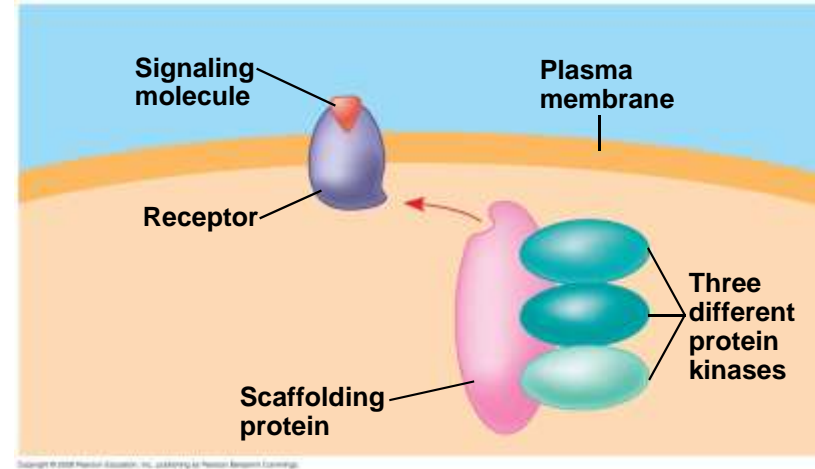
The Specificity of Cell Signaling

- The explanation for this specificity is that different kinds of cells have different collections of proteins
 - This is due to the fact that different cells turn on different sets of genes
- The response of a particular cell to a signal depends on its collection of signal receptor proteins, relay proteins, and proteins necessary to carry out the response
 - Two different cells thus respond differently to the same signal because they differ in the proteins that handle and respond to the signal
 - Ex) A liver cell responds appropriately to epinephrine by having the necessary proteins that are part of the signal transduction pathway leading to glycogen breakdown



Signaling Efficiency: Scaffolding Proteins

- The efficiency of signal transduction may be increased by the presence of **scaffolding proteins**
 - These are large relay proteins to which other relay proteins are simultaneously attached
 - Scaffolding proteins can increase the signal transduction efficiency by grouping together different proteins involved in the same pathway
 - In this way, proteins are not slowed by diffusion through the viscous cytosol
 - Ex) One scaffolding protein isolated from mouse brain cells holds 3 protein kinases and carries these kinases with it when it binds to an appropriately activated membrane receptor



Termination of the Signal

- Inactivation mechanisms are also an essential aspect of cell signaling
 - For cells to remain alert and capable of responding to incoming signals, each molecular change in their signaling pathways must last only a short time
 - Thus, these changes that the binding of signaling molecules to their receptors produce must be reversible
 - When signal molecules leave the receptor, the receptor reverts to its inactive state
 - Then, by a variety of means, the relay molecules in that pathway also return to their inactive forms
 - GTPase activity hydrolyzes bound GTP
 - The enzyme phosphodiesterase converts cAMP to AMP
 - Protein phosphatases inactivate phosphorylated kinases and other proteins
 - Eventually, the signal transduction pathway is terminated once the cellular response is complete

Concept Check 11.4

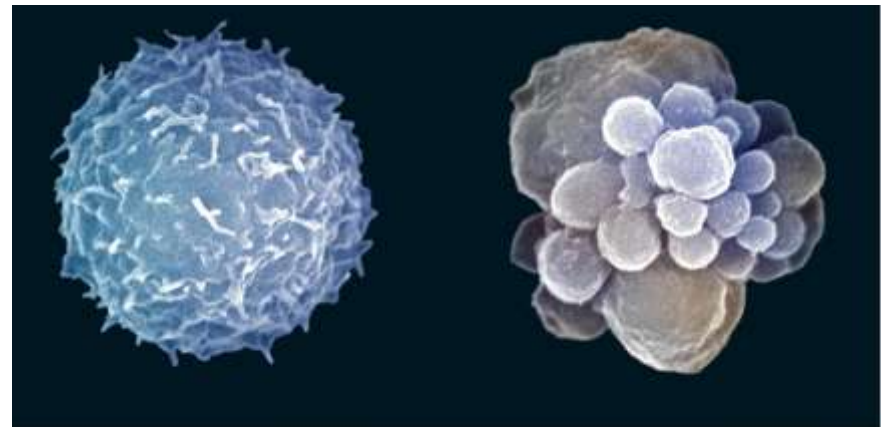
- 1) How can a target cell's response to a hormone be amplified more than a million-fold?
- 2) If 2 cells have different scaffolding proteins, explain how they could behave differently in response to the same signaling molecule.

Concept 11.5:

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

Apoptosis

- One of the most elaborate networks of signaling pathways in the cell is apoptosis
 - **Apoptosis** is programmed or controlled cell suicide
 - It occurs in damaged or infected cells or when cells have reached the end of their functional life span
 - During this process, cellular agents chop up DNA and fragment the organelles and other cytoplasmic components
 - The cell also shrinks and cell parts are packaged into vesicles that are engulfed and digested by scavenger cells
 - Apoptosis protects neighboring cells from damage
 - It prevents potentially destructive enzymes from leaking out of a dying cell



Apoptosis in the Soil Worm *Caenorhabditis elegans*

- Apoptosis is important in shaping an organism during embryonic development
 - The role of apoptosis in embryonic development was first studied in the nematode *Caenorhabditis elegans*
 - In these soil worms, as well as in other species, apoptosis is triggered by signals that activate a cascade of “suicide” proteins in cells that are destined to die
 - There are 2 key apoptosis genes in *C. elegans*: *ced-3* and *ced-4* (“ced” stands for “cell death”)
 - Proteins coded for by these genes (Ced-3 and Ced-4, respectively) are always present, but in their inactive forms
 - Regulation therefore occurs by way of regulating protein activity rather than protein synthesis

Apoptosis in *C. Elegans*

- In *C. elegans*, a protein in the outer mitochondrial membrane called Ced-9 serves as the master regulator of apoptosis

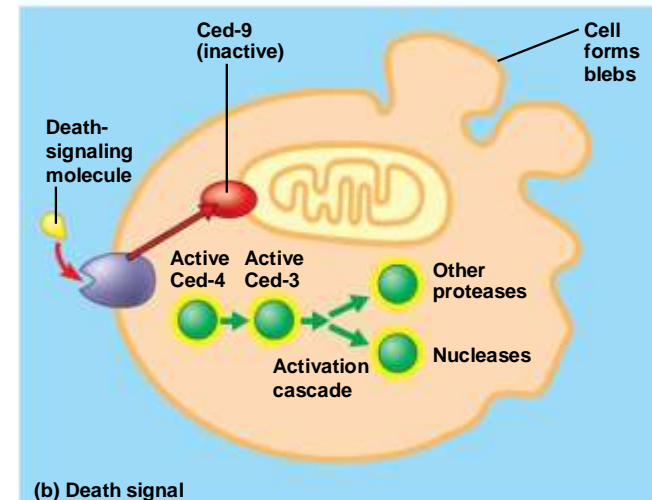
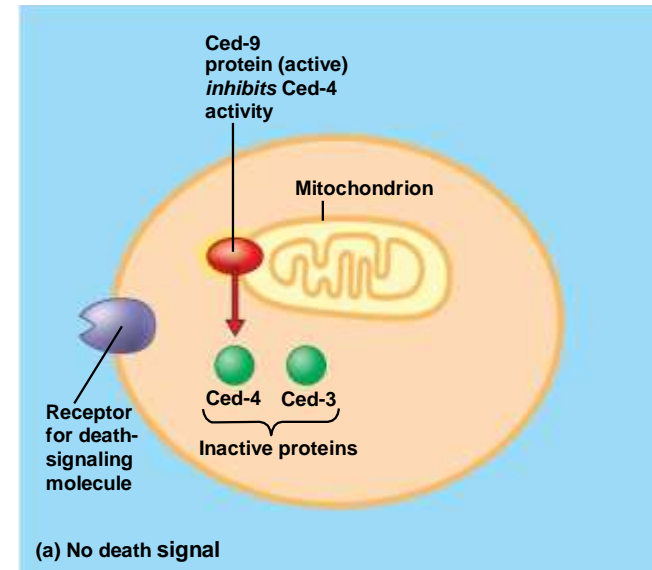
- This protein acts as a “brake” in the absence of a signal promoting apoptosis

- Ced-9 stops apoptosis by inhibiting Ced-4 activity
- When a death signal is received by the cell, it overrides these brakes

- Ced-9 is then inactivated, preventing its inhibition of Ced-3 & Ced-4

- Active Ced-3 then triggers a cascade of reactions leading to activation of proteases and nucleases that cut up proteins and DNA in the cell

- The main proteases of apoptosis are called *caspases*



Apoptotic Pathways in Mammals

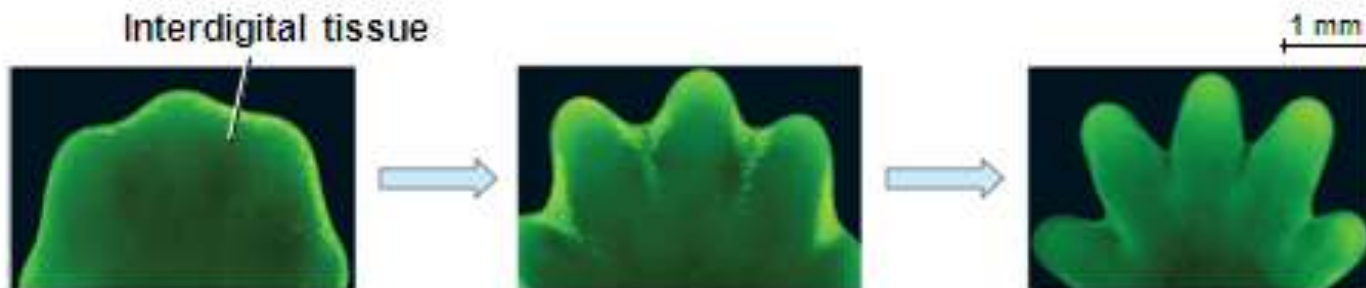
- In humans and other mammals, several different pathways that involve ~15 different caspases can carry out apoptosis
 - The pathway that is used depends on the type of cell and on the particular signal that triggers apoptosis
- One major pathway involves mitochondrial proteins
 - Apoptotic proteins can form molecular pores in the outer mitochondrial membrane
 - This causes the membrane to leak and release proteins that promote apoptosis
 - The process of mitochondrial apoptosis in mammals uses proteins similar to the nematode proteins Ced-3, Ced-4, and Ced-9

Apoptotic Pathways and the Signals That Trigger Them

- Apoptosis can be triggered in by a variety of mechanisms, including:
 - An extracellular death-signaling ligand released by a neighboring cell
 - When a death-signaling ligand occupies a cell-surface receptor, this binding leads to activation of caspases and other enzymes that carry out apoptosis
 - Alarm signals can also originate inside the cell under certain circumstances:
 - One of these alarm signals comes from the nucleus when its DNA has suffered irreparable damage
 - A second alarm signal comes from the ER when excessive protein misfolding occurs

Role of Apoptosis in Animal Function & Development

- A built-in suicide mechanism is essential to development and maintenance in all animals
 - Similarities in apoptosis genes and mechanisms among different organisms indicates that apoptosis evolved early in animal evolution
 - Apoptosis is essential for the normal development of vertebrate nervous and immune systems, as well as morphogenesis of human hands and feet (paws in other mammals)
 - Apoptosis eliminates the cells in the interdigital regions, thus forming the digits
 - A lower level of apoptosis in developing limbs accounts for webbed feet in water birds
 - In the case of humans, failure of appropriate apoptosis can result in webbed fingers and toes
 - Apoptosis may be involved in certain degenerative diseases of the nervous system (Parkinson's and Alzheimer's)
 - Interference with apoptosis may contribute to some cancers



Concept Check 11.5

- 1) Give an example of apoptosis during embryonic development, and explain its function in the developing embryo.
- 2) What type of protein defects could result in apoptosis occurring when it should not? What type could result in apoptosis not occurring when it should?

You should now be able to:

1. Describe the nature of a ligand-receptor interaction and state how such interactions initiate a signal-transduction system
2. Compare and contrast G protein-coupled receptors, tyrosine kinase receptors, and ligand-gated ion channels
3. List two advantages of a multistep pathway in the transduction stage of cell signaling
4. Explain how an original signal molecule can produce a cellular response when it may not even enter the target cell
5. Define the term *second messenger*; briefly describe the role of these molecules in signaling pathways
6. Explain why different types of cells may respond differently to the same signal molecule
7. Describe the role of apoptosis in normal development and degenerative disease in vertebrates