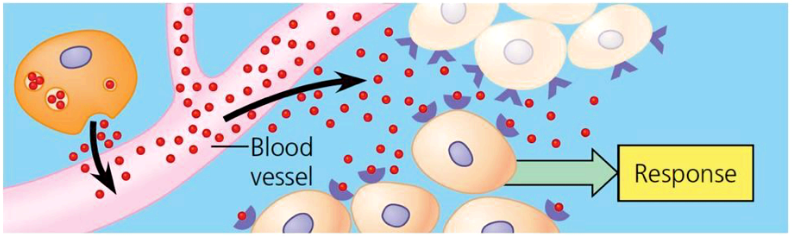
Ch. 11:

Cell Communication

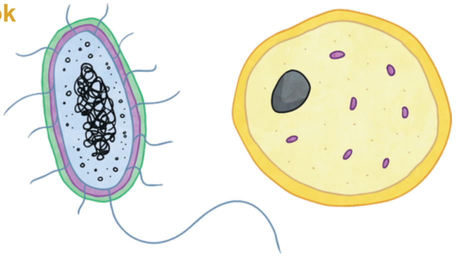


Life is made up of cells

- Cells can interpret signals received from other cells and the external environment.
  - Environmental signals can include light, touch, and most often other chemicals.
- Cells can also communicate with each other.
  - Cells receive, process, and respond to chemical signals sent from other cells

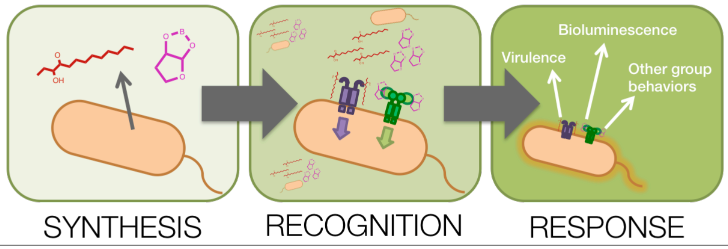
External Signals are Converted to Responses Within the Cell

- The early versions of cell signaling mechanisms evolved hundreds of millions of years before the first multicellular creatures appeared on Earth
  - Cell signaling mechanisms first evolved in ancient prokaryotes and single-celled eukaryotes like yeasts
- Unicellular organisms communicate about matters of interpersonal or community importance.
  - Let's take a closer look at communication in prokaryotes like bacteria and and single-celled eukaryotes like yeast cells.



Quorum Sensing in Bacteria

- It was initially believed that bacteria made behavioral decisions at the individual rather than the community level.
  - Today, it is known that many species of bacteria engage in a mode of cell-cell signaling called quorum sensing:
    - Bacteria use chemical signals to detect population density *(how many other bacteria are in the area).*
    - When the concentration of chemical signals reaches a certain threshold level, all bacteria in the population change their behavior or gene expression in unison.



Mechanism of Bacterial Quorum Sensing

- Bacteria continually produce, secrete, and detect autoinducers
  - Autoinducers are signaling molecules secreted by bacteria to announce their presence to their neighbors
    - Each species of bacteria has its own autoinducer, with a matching receptor that's highly specific (won't be activated by the autoinducer of a different bacterium). This allows for bacteria to communicate with its own kind.
    - Some types of autoinducers can be produced and detected by multiple species of bacteria. Scientists are investigating how these molecules may allow for between-species communication.
      - In some types of bacteria, the secreted autoinducers are small, hydrophobic molecules such as acyl-homoserine lactone (AHL).
      - In other types of bacteria, the autoinducers may instead be hydrophilic peptides (short proteins) or other types of small molecules

Mechanism of Bacterial Quorum Sensing

- Quorum sensing was first discovered in *A. fischeri*, a bacterium that has a symbiotic (mutually beneficial) relationship with the Hawaiian bobtail squid
  - *A. fischeri* form colonies inside the squid's "light organ."
  - The squid gives the bacteria food, and in return, the bacteria bioluminesce (emit light).
    - When *A. fischeri* bacteria are inside of a squid's light organ, they glow, but when they're free-living in the ocean, they don't.
  - The glow of the bacteria prevents the squid from casting a shadow, hiding it from predators swimming beneath.

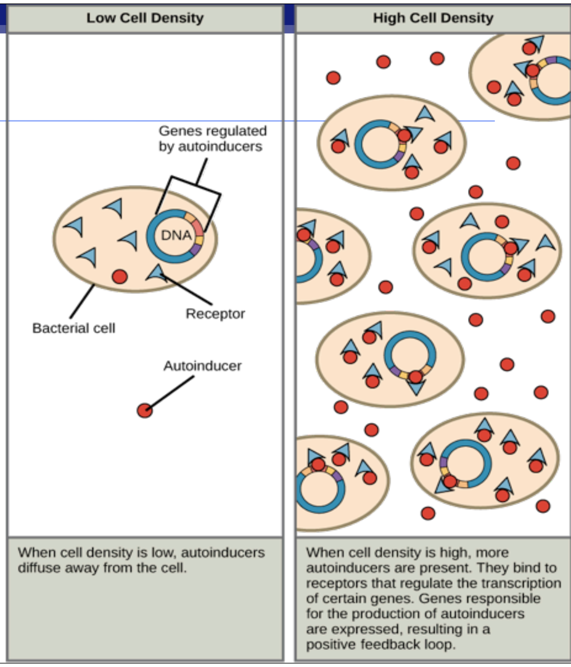
Bacteria in the light organ, in the center of the mantle cavity of the squid, emit bioluminescent light downward so that at night, the squid blends in with moon- or starlight when viewed from below.

Mechanism of Bacterial Quorum Sensing

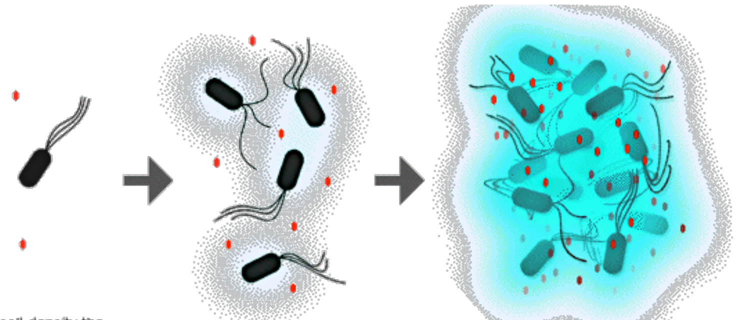
- It would be a metabolic waste for a lone bacterium in the open ocean to carry out chemical reactions that emit light.
  - When many bacteria are concentrated in a light organ, however, glowing in unison provides an advantage:
    - It allows the bacteria to keep their squid host (their food source) alive, preventing it from being eaten by predators.
- AHL is the autoinducer made by *A. fischeri*
  - Because AHL is small and hydrophobic, it can diffuse freely across the membranes of the bacterial cells.
    - When there are few cells in the area, the little AHL that's made will diffuse into the environment, and the AHL concentration inside bacterial cells remains low.
    - When more bacteria are present, the AHL concentration inside bacterial cells becomes high *(since there are now more and more bacteria secreting AHL)*

Mechanism of Bacterial Quorum Sensing

- High concentration of AHL indicate a critical density of bacteria.
  - AHL will bind to and activate a receptor protein inside cells.
    - The active receptor acts as a transcription factor, proteins that activate target genes in the bacteria's DNA.
      - In *A. fischeri,* the transcription factor turns on genes that encode enzymes and substrates required for bioluminescence, as well as the gene for the enzyme that makes AHL itself *(amplifying the response in a positive feedback loop)*



Mechanism of Bacterial Quorum Sensing



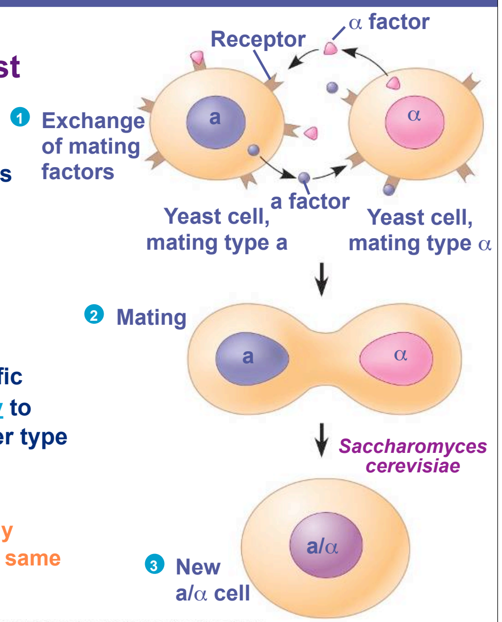
At low cell density the autoinducers (red dots) that are produced diffuse through the cell membrane into the growth media.

As the cell growth continues, the level of autoinducers in the media will start to accumulate in a confined environment. A very low intensity of light emission can be detected.

High levels of autoinducers activate the luminescent systems of the luminous bacteria in the media. The regulatory response to the autoinducer leading to induction of expression of the *lux*CDABE genes is termed "QUORUM SENSING."

Cell Communication in Single-Celled Yeast

- Yeast *(S. cerevisiae)* produce chemical signals that allow them to find mates & reproduce
- There are two sexes or "mating types:" a and α
  - Each secrete a specific factor that binds only to receptors on the other type of cell
    - This unique match ensures mating ony among cells of hte same species of year

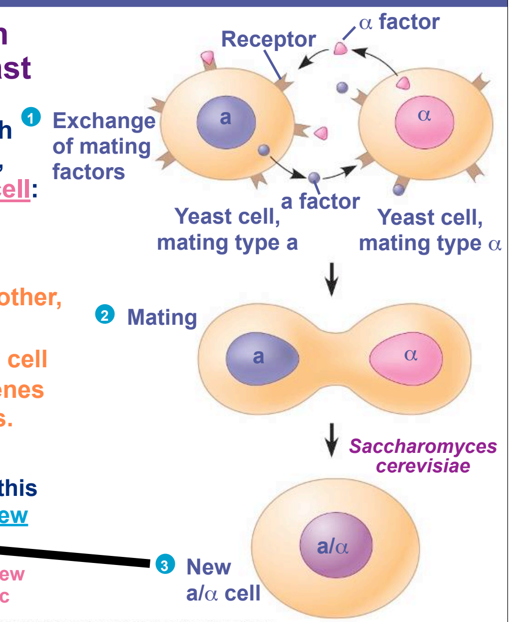


Cell Communication in Single-Celled Yeast

- When exposed to each others mating factors, one a cell and one α cell:
  1. change shape
  2. grow towards each other, and
  3. fuse, forming an a/α cell with contains the genes of both original cells.

★ Subsequent division of this new a/α cell produces new cells (offspring).

➡ These offspring have new combinations of genetic material.



Cell Communication is ESSENTIAL

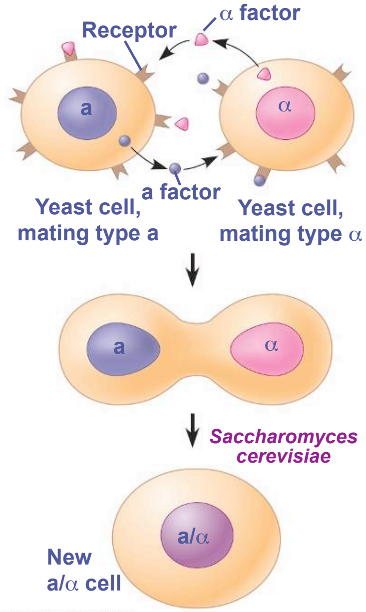
- The combined effects of multiple signals often determine cell response
- External signals are converted to responses within the cell

Why communicate?

To coordinate the processes of life.

Multicellular organisms:
Must communicate to develop and survive.

Unicellular organisms:
Must communicate to locate nutrients or even identify mating partners.



Communication between cells in Multicellular Organisms

- Cells in multicellular organisms also usually communicate via signaling molecules targeting cells that may or may not be immediately adjacent to the cell originating the signal
  - Cells in a multicellular organism communicate by chemical messengers too

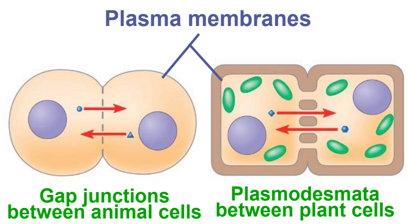
TWO TYPES OF SIGNALING EXIST:

1. Local Signaling

2. Long-Distance Signaling

How do cells communicate in multicellular organisms?

- **Local Signaling:**
  - 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 between proteins in each cells' plasma membrane

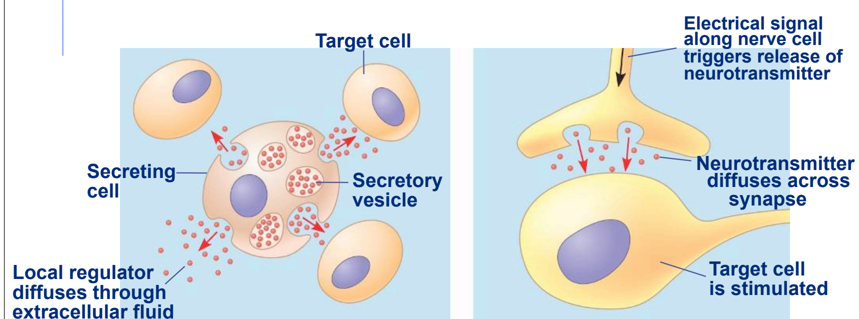


(a) Cell junctions

(b) Cell-cell recognition

How do cells communicate in multicellular organisms?

- **Local:**
  - In many other cases, animal cells communicate using local regulators, messenger molecules that travel only short distances



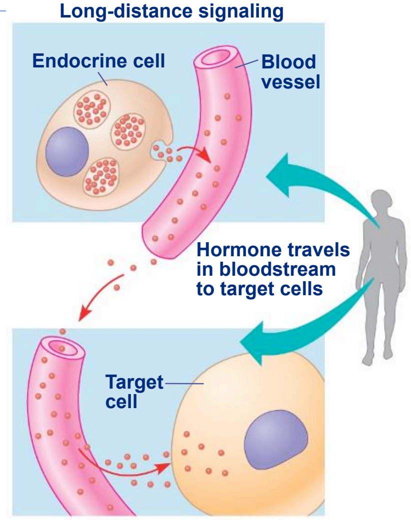
(a) Paracrine signaling

(b) Synaptic signaling

How do cells communicate in multicellular organisms?

- **Long Distance:**
  - In long-distance signaling, plants and animals use chemicals called hormones
    - In animals, hormones are signaling molecules carried in the blood from endocrine cells that secrete them to target cells that respond to them.
    - In plants, hormones may travel through the xylem or the phloem (vascular tissue of the plant cell) to target cells distant from the secreting cell.

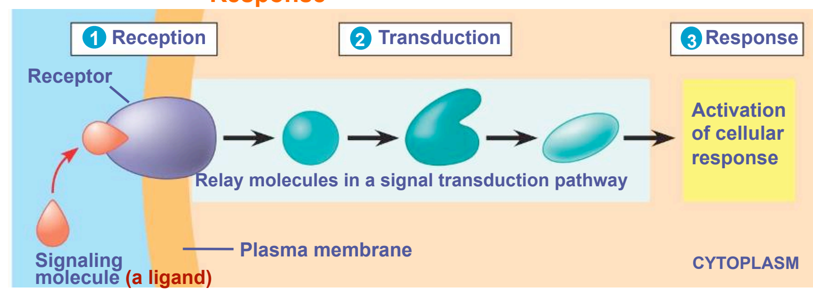
Long-distance signaling



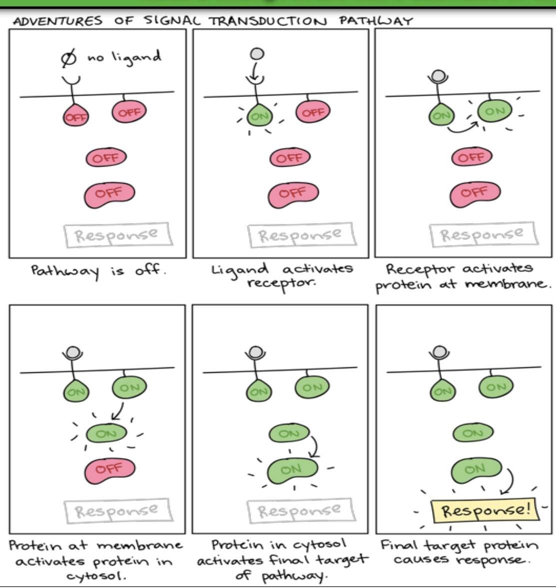
(c) Hormonal signaling

How do cells translate information from the exterior to the interior?

- Through SIGNAL TRANSDUCTION PATHWAYS.
  - A series of steps by which a signal on a cell's surface is converted into a specific cellular response
  - Convert signals on a cell's surface into cellular responses
    - Three processes:
      - Reception
      - Transduction
      - Response



A change in the receptor after ligand binding, activates signaling molecules inside of the cell, which in turn activate still other molecules in a chain reaction that eventually leads a change in the cell's activities or characteristics.



The molecules that relay a signal are often (but not always) proteins.

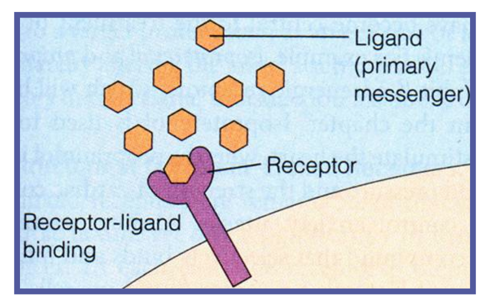
The term upstream is used to describe molecules and events that come earlier in a signal transduction pathway compared to other molecules or events in that pathway.

The term downstream is used to describe molecules and events that come later in a signal transduction pathway compared to other molecules or events in that pathway.

➡ For instance, in the diagram, the receptor is downstream of the ligand but upstream of the proteins in the cytosol.

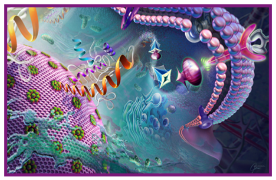
Reception: A signal molecule binds to a receptor protein, causing it to change shape

- The binding between a signal molecule, a 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

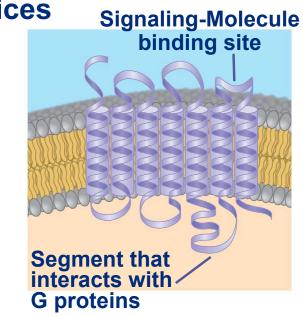
- Most water-soluble signal molecules bind to specific sites on receptor proteins in the plasma membrane
- There are three main types of membrane receptors:

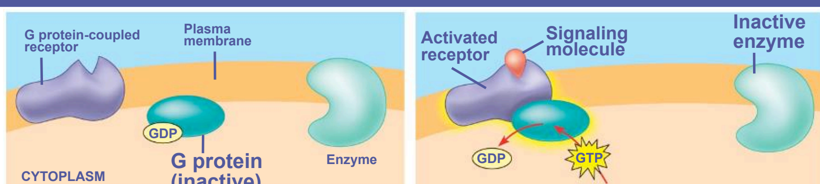


1. G protein-coupled receptors
2. Receptor tyrosine kinases
3. Ion channel receptors

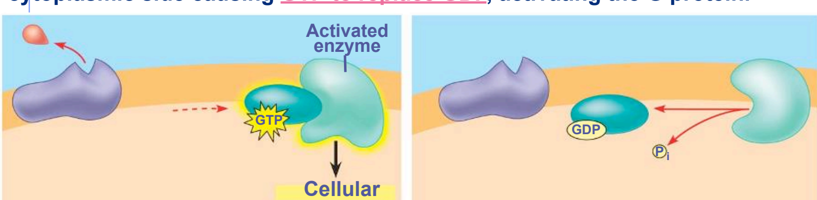
G protein-coupled receptor

- A G protein-coupled receptor is a plasma membrane receptor that works with the help of a G protein, a protein that can bind to an energy-rich molecule, GTP.
- A G protein-coupled receptor:
  - Made of 7 transmembrane α helices
- The G protein acts as an on/off switch for relaying an external message into the cell
  - 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





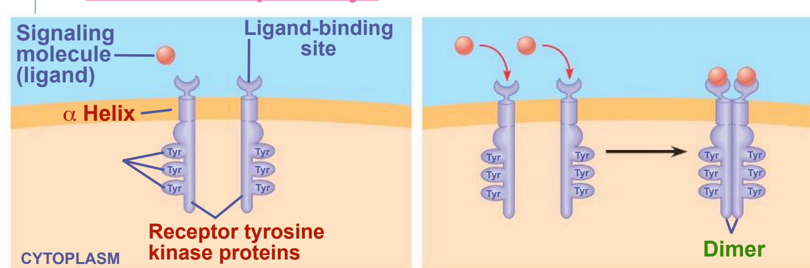
Signaling molecules bind to extracellular side of the receptor, the receptor is activated and changes shape. Inactive G protein binds the receptors cytoplasmic side causing GTP to replace GDP, activating the G protein.



Activated G protein separates from the receptor, diffuses along the membrane and binds an enzyme which changes shape and activity. Activated enzymes trigger other steps of the pathway leading to a cellular response. Changes are temporary since G protein is also a GTPase enzyme, hydrolyzing its own bound GTP to GDP, inactivating itself. *This allows the pathway to shut down rapidly when signal molecule no longer present.*

Receptors Tyrosine Kinases -
receptors with enzymatic activity

- Receptor tyrosine kinases are membrane receptors that attach phosphates from ATP to neighboring tyrosine kinase's tyrosines
- A receptor tyrosine kinase can trigger multiple signal transduction pathways at once.

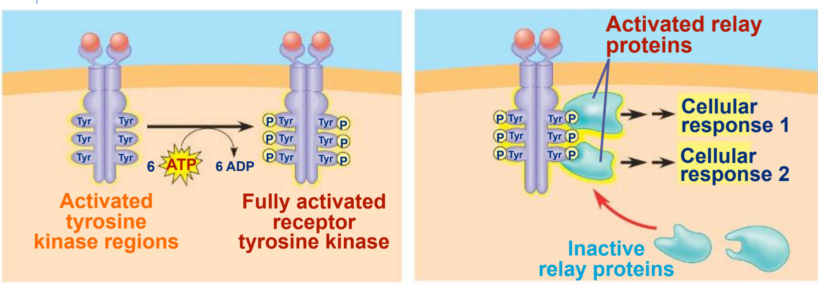


Before ligand binding, receptors exist as single polypeptides.
After binding, pairs of polypeptides dimerize.

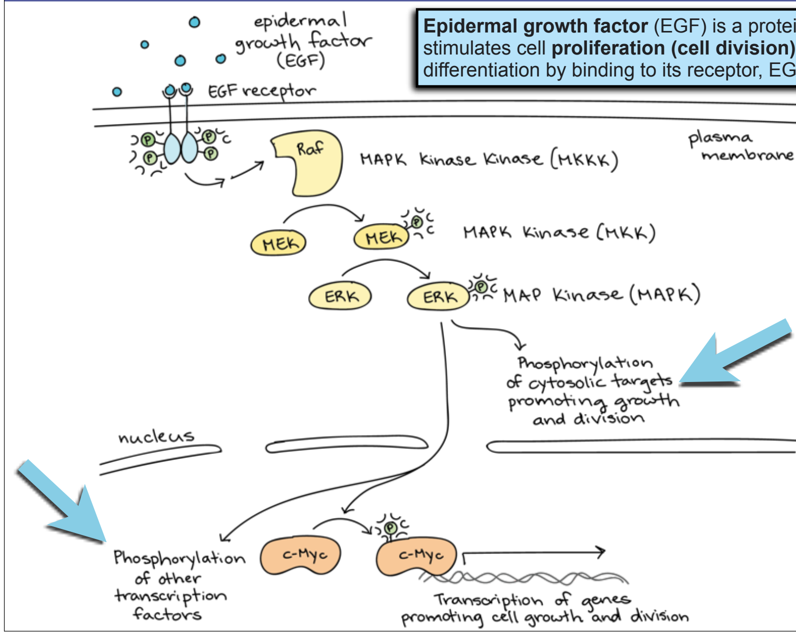
Receptors Tyrosine Kinases -
receptors with enzymatic activity

Pairing activates the cytoplasmic tyrosine kinase of each polypeptide causing them to add phosphate groups from ATP to tyrosines on the other polypeptide. This fully activates the receptor.

Relay proteins that bind the phosphorylated tyrosines, undergo conformational changes that activate the now temporarily bound proteins which in turn activate more proteins in the cell resulting in cellular response.

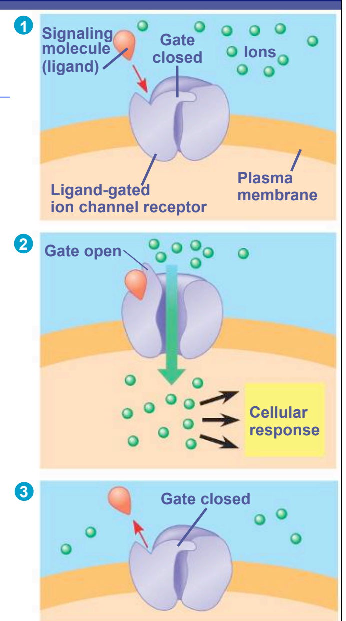


Epidermal growth factor (EGF) is a protein that stimulates cell **proliferation (cell division)** and differentiation by binding to its receptor, EGFR.



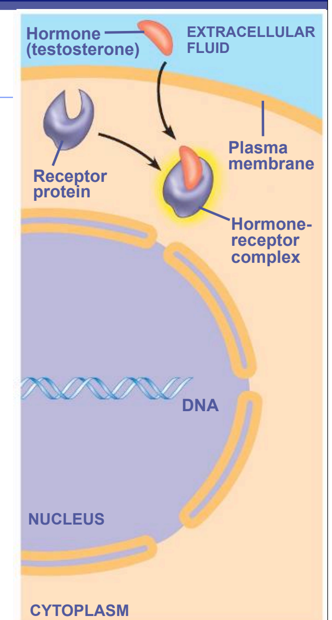
Ligand-gated ion channels

- A ligand-gated ion channel receptor is a type of membrane channel receptor that has a region that can act as a "gate," opening or closing the channel when the receptor changes shape.
- When a signal molecule binds as a ligand to the receptor, the gate allows specific ions, such as Na^+ or Ca^{2+}, through a channel in the receptor



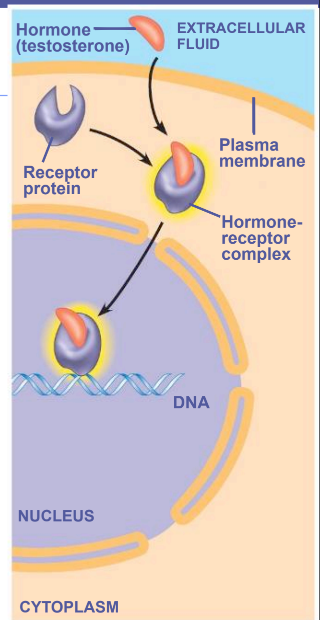
Intracellular Receptors

- Some receptor proteins are intracellular, found in the cytosol or nucleus of target cells
- Small hydrophobic chemical messengers can readily diffuse across cell membranes and activate receptors
  - Examples of hydrophobic messengers are the steroid and thyroid hormones of animals



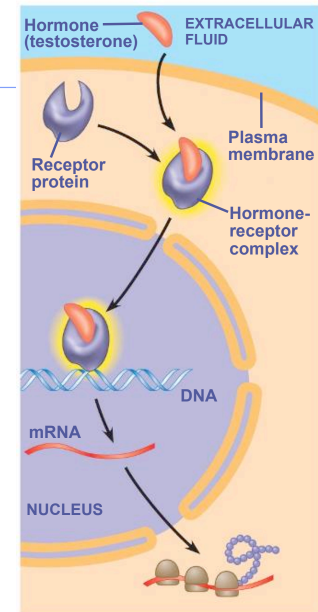
Intracellular Receptors

- An activated hormone-receptor complex can act as a <u>transcription factor</u>, *turning on specific genes*



Intracellular Receptors

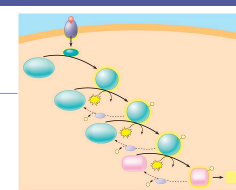
- Once a gene is activated, <u>mRNA</u> (or other RNA) can be produced.
  - The mRNA will eventually be translated by ribosomes in the cytoplasm into the primary structure of a protein: <u>the polypeptide</u>



<u>Transduction</u> involves cascades of molecular interactions that relay signals from the original receptors to target molecules inside the cell

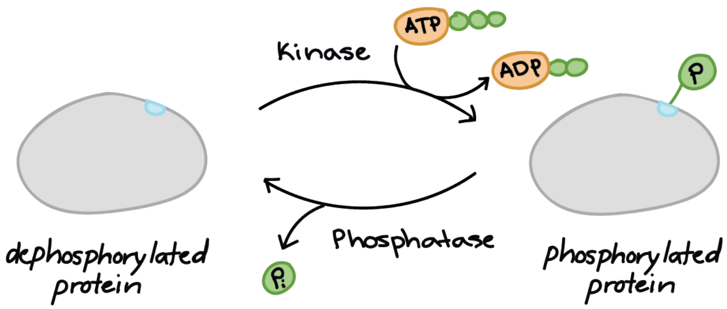
- <u>Signal transduction</u> usually involves multiple steps
- <u>Signal Transduction Pathways</u>
  - The molecules that relay a signal from receptor to response are mostly <u>proteins</u>
  - Like falling dominoes, the receptor activates another protein, which activates another, and so on, until the protein producing the response is activated
    - At each step, the signal is transduced into a different form, usually a <u>shape change in a protein</u>

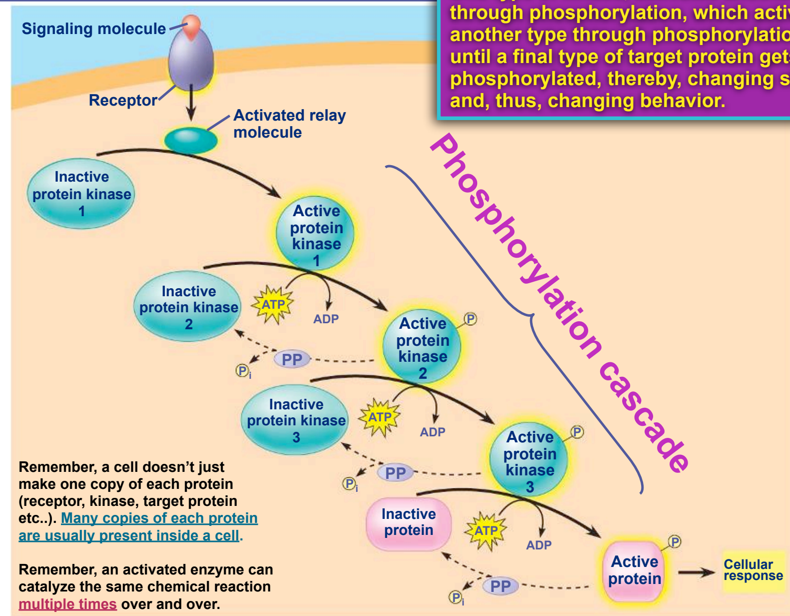
Protein Phosphorylation and De-phosphorylation



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

Phosphorylation isn't permanent, but it does temporarily change the proteins shape and thus function





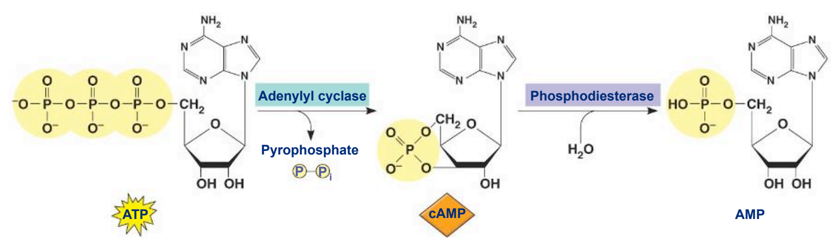
One type of kinase, activates another type through phosphorylation, which activates another type through phosphorylation, until a final type of target protein gets phosphorylated, thereby, changing shape and, thus, changing behavior.

Small Molecules and Ions May be Used as Second Messengers

- The extracellular signal molecule that binds to the receptor is a pathway's "first messenger"
- Second messengers are small, non-protein, water-soluble molecules or ions on the inside of the cell that spread throughout a cell by diffusion
  - Cyclic AMP and Ca^{2+} are common second messengers
    - Second messengers participate in pathways initiated by G protein-coupled receptors and receptor tyrosine kinases

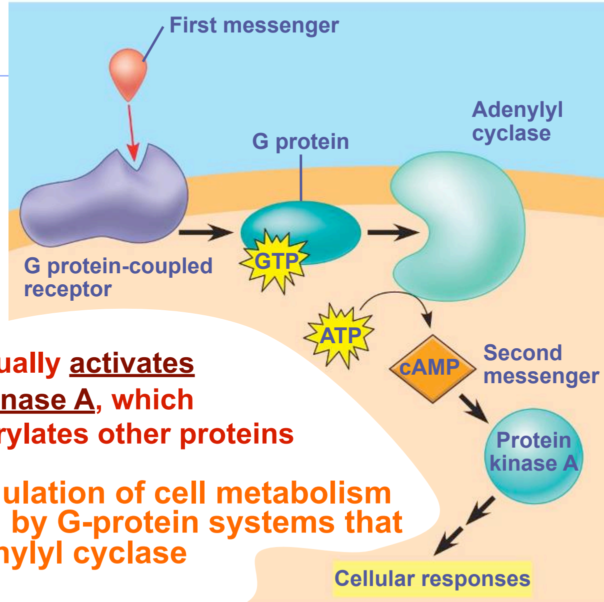
Cyclic AMP

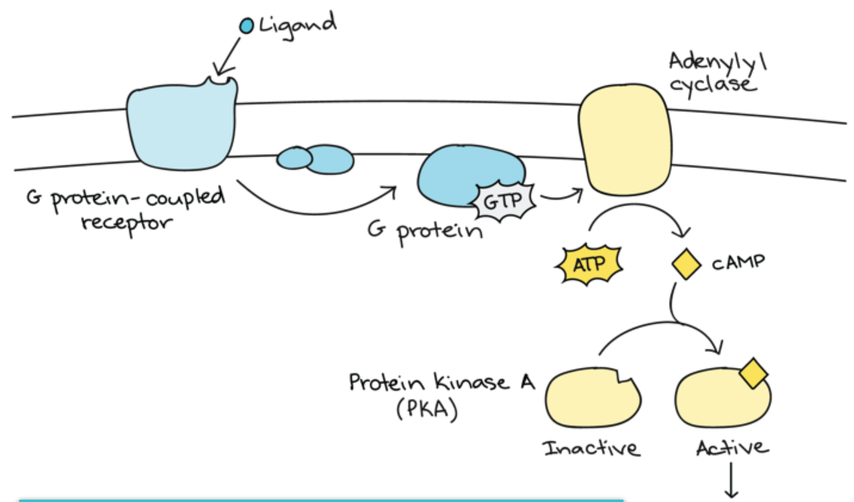
- Cyclic AMP (cAMP) is one of the most widely used second messengers
  - Adenylyl cyclase, an enzyme in the plasma membrane, converts ATP to cAMP in response to an extracellular signal



Cyclic AMP

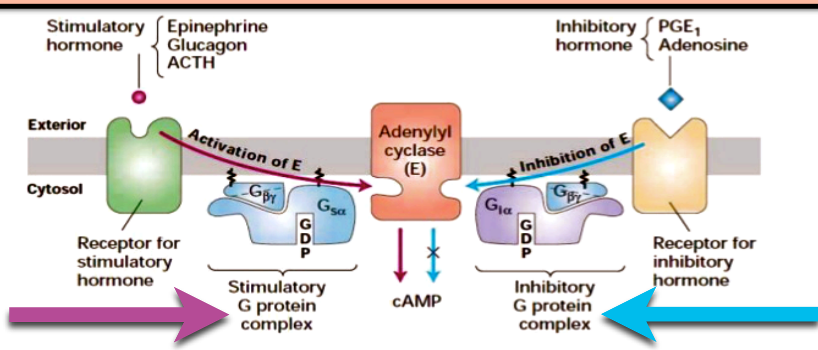
- Many signal molecules trigger formation of cAMP
  - cAMP usually activates protein kinase A, which phosphorylates other proteins
- Further regulation of cell metabolism is provided by G-protein systems that inhibit adenylyl cyclase





Since second messengers like cAMP can be produced rapidly and are small, they can quickly diffuse from the area they are made throughout the cell's cytoplasm in order to quickly activate their target proteins, located in the cell's interior.

Adenylyl Cyclase can be activated or inhibited depending on which receptor gets activated and thus which type of G protein gets activated, which depends on the type of hormone that arrives at the surface of the cell

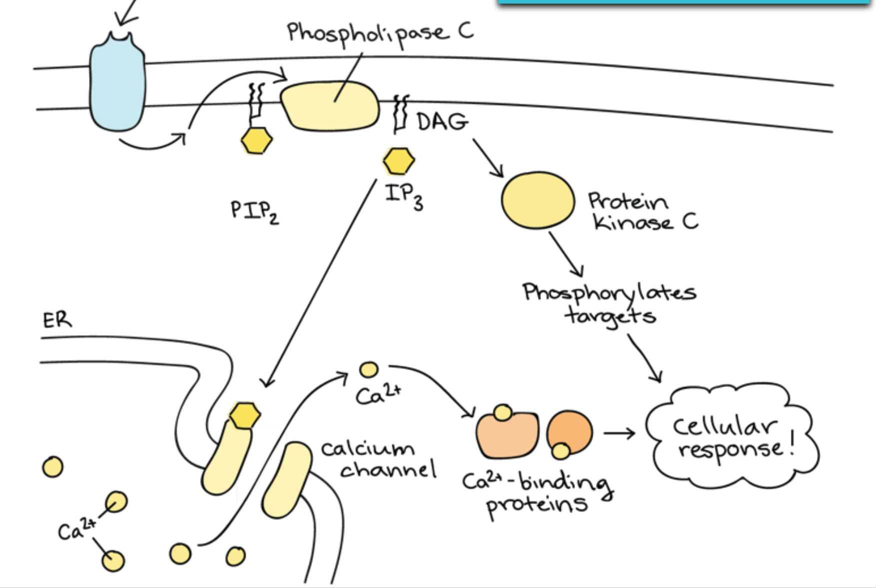


Hormone-induced activation and inhibition of adenylyl cyclase in adipose cells. Ligand binding to G_s-coupled receptors causes activation of adenylyl cyclase, whereas ligand binding to G_i-coupled receptors causes inhibition of the enzyme. The $G_{\beta\gamma}$ subunit in both stimulatory and inhibitory G proteins is identical; the G_α subunits and their corresponding receptors differ. Ligand-stimulated formation of active G_α·GTP complexes occurs by the same mechanism in both G_s and G_i proteins. However, $G_{s\alpha}$·GTP and $G_{i\alpha}$·GTP interact differently with adenylyl cyclase, so that one stimulates and the other inhibits its catalytic activity.

In addition to cAMP, DAG, IP_3, and Ca^{2+} are Also Second Messengers Used in Signaling Pathways

- Some G-protein-coupled or tyrosine kinase receptors help activate the intracellular enzyme, phospholipase C.
  - Phospholipase C hydrolyzes a certain phospholipid (PIP2), found in the inner layer of the plasma membrane.
  - Hydrolysis of PIP2 produces two products:
    1. DAG
       - DAG remains in the inner layer of the plasma membrane, where it attracts Protein Kinase C (PKC), activating it (some forms of PKC may also need calcium ions to bind to fully activate it)
         - Activated Kinase C phosphorylates target proteins, changing cell behavior.
    2. IP_3
       - IP_3 diffuses through the cytosol and binds to gated ion-channel receptors in the membrane of the smooth endoplasmic reticulum (an organelle that in certain cells stores calcium ions).
         - IP_3 binding to the channel proteins, causes them to open, releasing of calcium ions (Ca^{2+}) into the cytosol.
         - The rise in intracellular calcium, changes the shape and thus activity of proteins like Protein Kinase C or other internal proteins.

Another example of Secondary Messenger Use: DAG & IP_3 Signaling



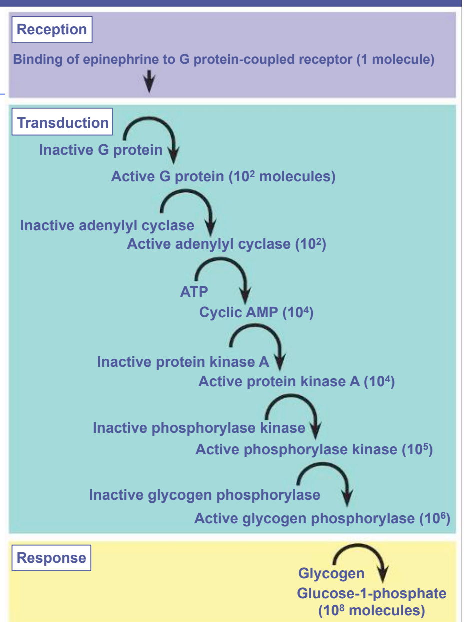
Nuclear and Cytoplasmic Responses

- Ultimately, a signal transduction pathway leads to regulation of one or more cellular activities.

- The response may occur in:
  1. the cytoplasm or may involve
  2. action in the nucleus

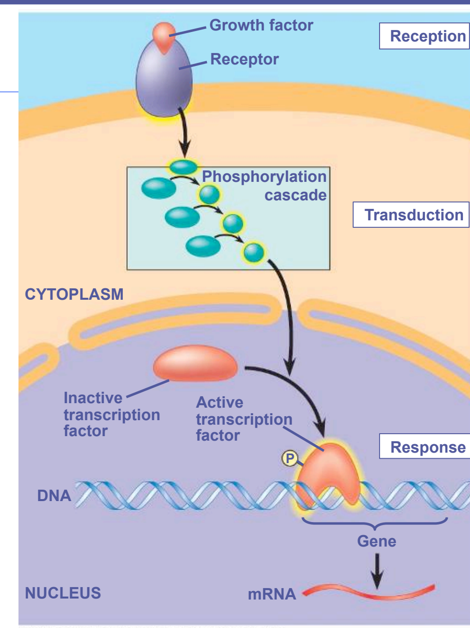
REGULATING ACTIVITY

- Pathways may regulate the activity of existing enzymes and proteins or…
  - Ex: Hormone epinephrine (adrenaline) makes cells breakdown glycogen to release the glucose stored herein when the cell needs energy



REGULATING SYNTHESIS

- 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 (protein that turns on or off gene expression)
  - Ex: Growth Factors signal cells to divide by turning on or off key genes involved in the cell cycle leading up to mitosis

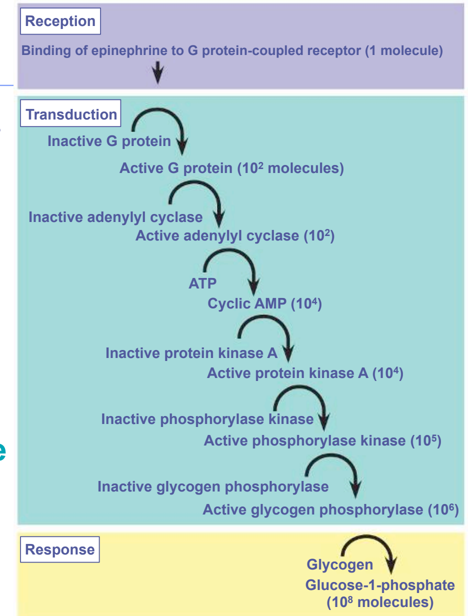


Benefits of Signal Transduction Pathways

- **Multistep pathways have important benefits:**
  1. Multistep pathways can **amplify a signal**: A few molecules can produce a large cellular response
  2. Multistep pathways provide **more opportunities for coordination and regulation of the cellular response**
  3. Multistep pathways **to the specificity of the response**

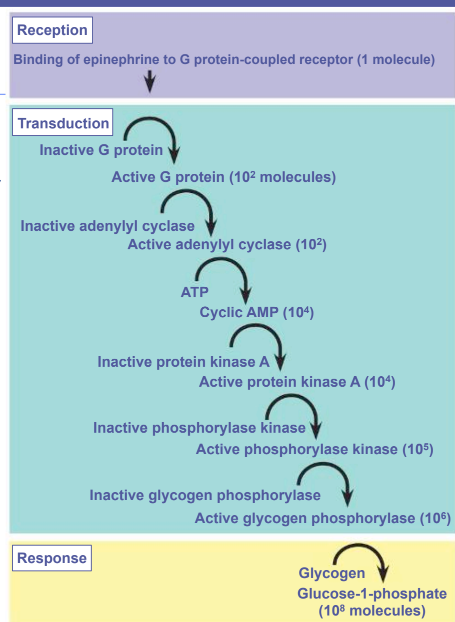
Signal Amplification

- Enzyme cascades **amplify** the cell's response
- At each step, the number of activated products is much greater than in the preceding step
  - What is the benefit?



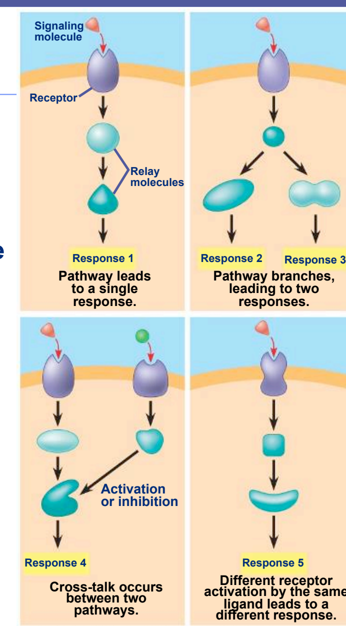
Signal Amplification

- The amplification effect stems from the fact that enzymes persist in their active form long enough to process multiple molecules of substrate before they become inactive again
  - As a result, a **small** number of ligand molecules binding to receptors on the surface of a cell can have a **large effect** on cell activity or cell activity consequence

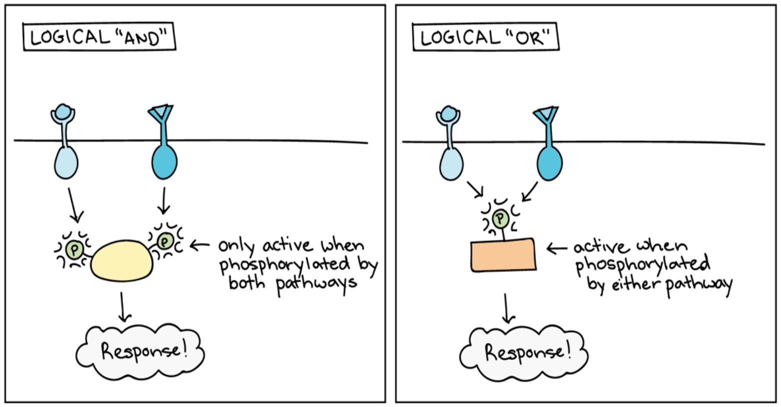


Fine-Tuning of the Response

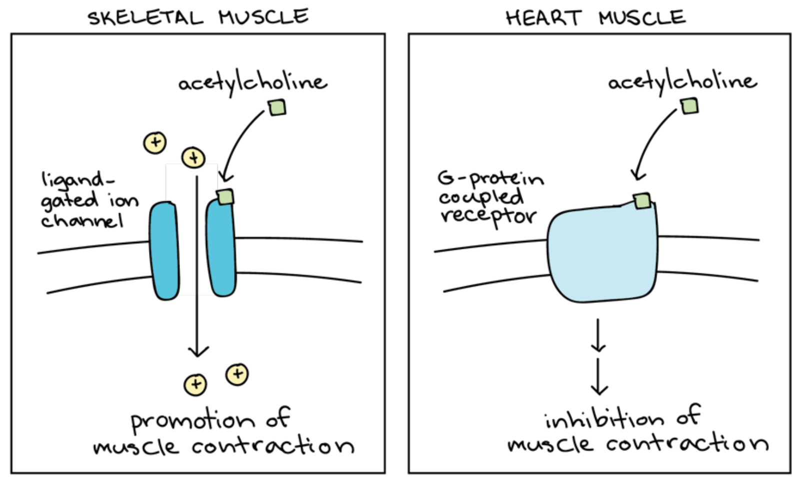
- **Cell Signaling is Specific & Responses are Coordinated inside Cells:**
  - Different kinds of cells contain different collections of membrane and cytoplasmic proteins, **depending on which genes they activate**
    - These different proteins allow cells to detect and **respond to different signals**
    - Even the **same** signal can have **different** effects in cells with different relay and target proteins.
  - Pathway branching and "cross-talk" further help the cell coordinate incoming signals



When pathways interact, a cell could change its behavior only when it gets multiple messages to do so or when it gets at least one message to do so.



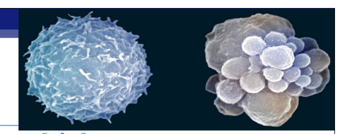
The same signaling molecule may produce different results depending on what molecules are already present in the cell



Signaling pathways last only a short time: they turn back "OFF"

- The ability of a cell to receive new signals depends on reversibility of the changes produced by prior signals.
  - Binding of signaling molecules to receptors is reversible
    - When receptors return to their inactive form, relay molecules inside the cell return to their inactive forms
  - GTPAse activity intrinsic to G proteins hydrolyzes its bound GTP, deactivating the G protein
  - Phosphodiesterase converts cAMP to AMP
  - Protein phosphatases inactive phosphorylated kinases and other proteins
  - External concentration of signaling molecules falls, unbound receptors reverting to their inactive forms
    - Cellular response occurs only when the concentration of receptors with bound signaling molecules is above a certain threshold

Apoptosis



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

- A cell's contents are hydrolyzed and packaged into vesicles (blebbing) that are digested by scavenger cells
  - Apoptosis prevents enzymes from leaking out of a dying cell and damaging neighboring cells
- Apoptosis can be triggered by:
  - External signals:
    - An extracellular death-signaling ligand can activate a signal transduction pathway that ends up activating transcription factors and thus genes for making the caspase proteins that cause apoptosis.
  - Internal Signals:
    - DNA damage in the nucleus
    - Protein miss-folding in the endoplasmic reticulum

Any questions?