The cell biology(part 4)

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Cell signaling

Overview of cell signaling

Forms of signaling

- Paracrine signaling
- Synaptic signaling
- Autocrine signaling
- Endocrine signaling

Signaling through cell-cell contact

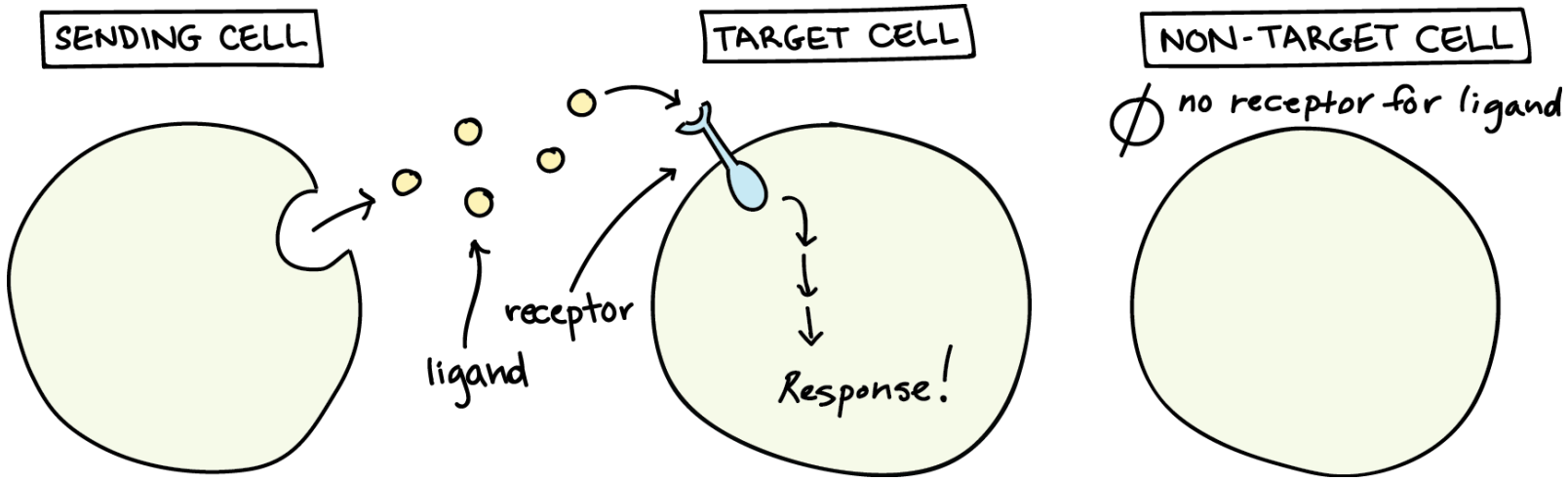
Introduction

Think your cells are just simple building blocks, unconscious and static as bricks in a wall? If so, think again! Cells can detect what's going on around them, and they can respond in realtime to cues from their neighbors and environment. At this very moment, your cells are sending and receiving millions of messages in the form of chemical signaling molecules!

In the following slides, we'll examine the basic principles of how cells communicate with one another. We'll first look at how cell-cell signaling works, then consider different kinds of short- and long-range signaling that happen in our bodies

Overview of cell signaling

Cells typically communicate using chemical signals. These chemical signals, which are proteins or other molecules produced by a **sending cell**, are often secreted from the cell and released into the extracellular space. There, they can float – like messages in a bottle – over to neighboring cells.



Overview of cell signaling

Not all cells can “hear” a particular chemical message. In order to detect a signal (that is, to be a **target cell**), a neighbor cell must have the right **receptor** for that signal. When a signaling molecule binds to its receptor, it alters the shape or activity of the receptor, triggering a change inside of the cell. Signaling molecules are often called **ligands**, a general term for molecules that bind specifically to other molecules (such as receptors).

The message carried by a ligand is often relayed through a chain of chemical messengers inside the cell. Ultimately, it leads to a change in the cell, such as alteration in the activity of a gene or even the induction of a whole process, such as cell division. Thus, the original **intercellular** (between-cells) signal is converted into an **intracellular** (within-cell) signal that triggers a response.

Forms of signaling

Cell-cell signaling involves the transmission of a signal from a sending cell to a receiving cell. However, not all sending and receiving cells are next-door neighbors, nor do all cell pairs exchange signals in the same way.

There are four basic categories of chemical signaling found in multicellular organisms: **paracrine** signaling, **autocrine** signaling, **endocrine** signaling, and signaling by **direct contact.** The main difference between the different categories of signaling is the **distance** that the signal travels through the organism to reach the target cell

Paracrine signaling

Often, cells that are **near** one another communicate through the release of chemical messengers (ligands that can diffuse through the space between the cells). This type of signaling, in which cells communicate over relatively short distances, is known as **paracrine signaling**.

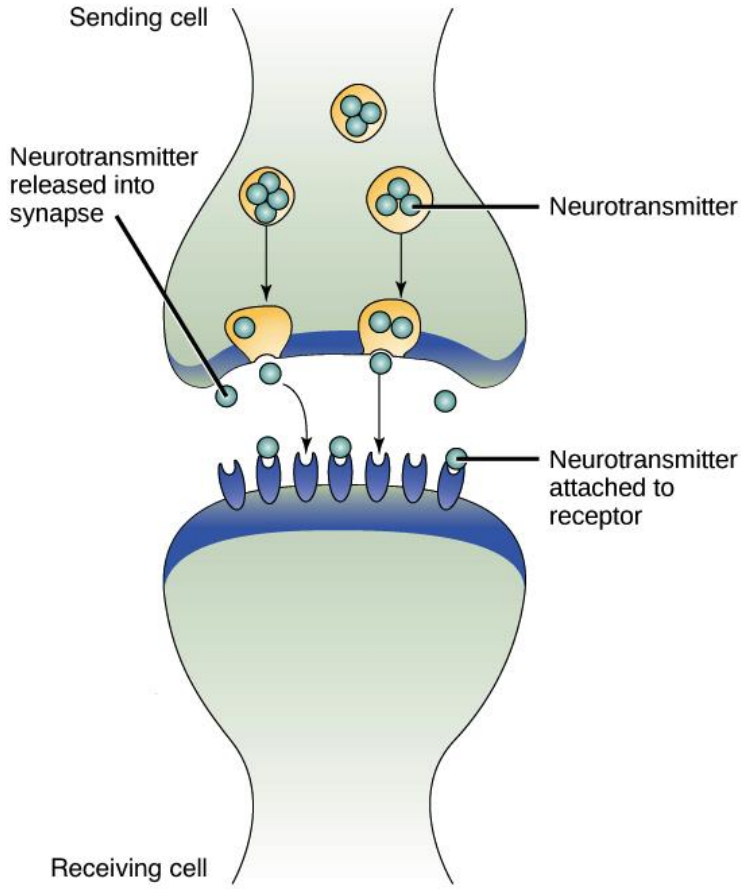
Paracrine signaling allows cells to **locally** coordinate activities with their neighbors. Although they're used in many different tissues and contexts, paracrine signals are especially important during **development**, when they allow one group of cells to tell a neighboring group of cells what cellular identity to take on

Synaptic signaling

One unique example of paracrine signaling is **synaptic signaling**, in which nerve cells transmit signals. This process is named for the **synapse**, the junction between two nerve cells where signal transmission occurs.

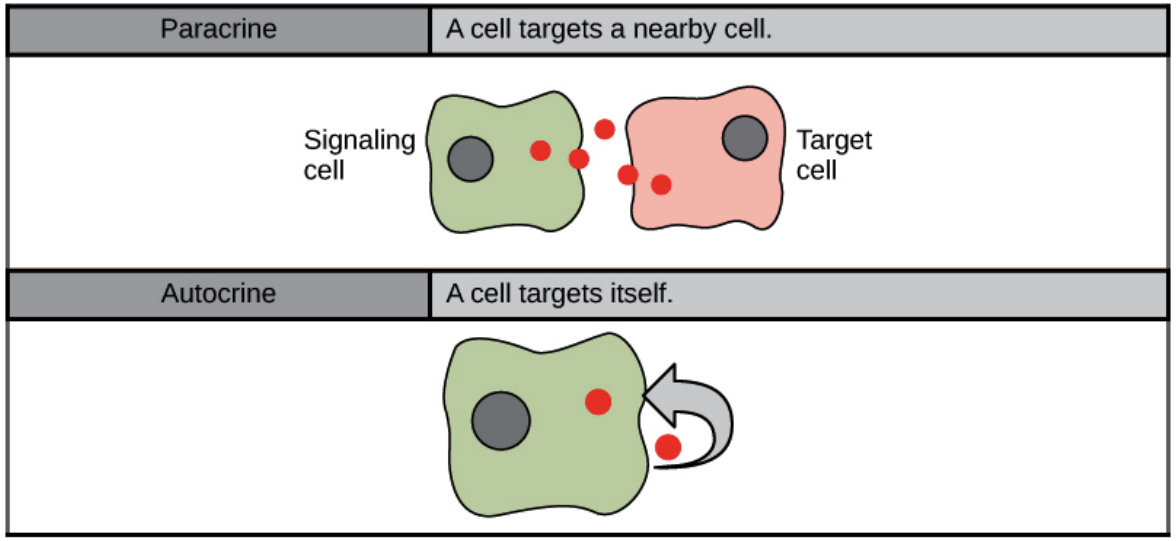
When the sending neuron fires, an electrical impulse moves rapidly through the cell, traveling down a long, fiber-like extension called an axon. When the impulse reaches the synapse, it triggers the release of ligands called **neurotransmitters**, which quickly cross the small gap between the nerve cells. When the neurotransmitters arrive at the receiving cell, they bind to receptors and cause a chemical change inside of the cell (often, opening ion channels and changing the electrical potential across the membrane)

Synaptic signaling



Autocrine signaling

In **autocrine signaling**, a cell signals to itself, releasing a ligand that binds to receptors on its **own surface** (or, depending on the type of signal, to receptors inside of the cell). This may seem like an odd thing for a cell to do, but autocrine signaling plays an important role in many processes



Autocrine signaling

For instance, autocrine signaling is important during **development**, helping cells take on and reinforce their correct identities. From a medical standpoint, autocrine signaling is important in **cancer** and is thought to play a key role in **metastasis** (the spread of cancer from its original site to other parts of the body).

In many cases, a signal may have both autocrine and paracrine effects, binding to the sending cell as well as other similar cells in the area

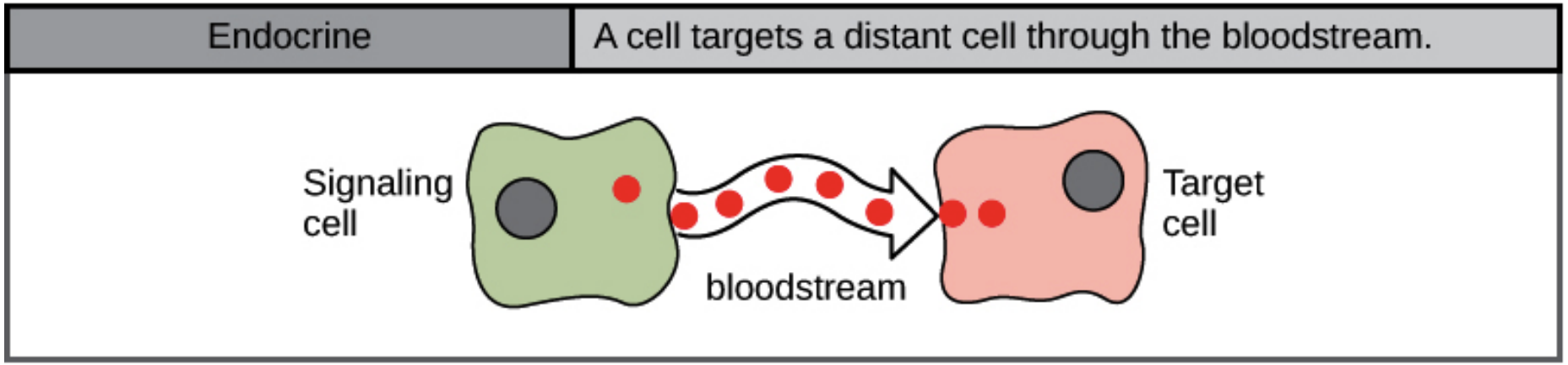
Endocrine signaling

When cells need to transmit signals over long distances, they often use the **circulatory system** as a distribution network for the messages they send. In long-distance **endocrine signaling**, signals are produced by specialized cells and released into the bloodstream, which carries them to target cells in distant parts of the body. Signals that are produced in one part of the body and travel through the circulation to reach far-away targets are known as **hormones**.

In humans, endocrine glands that release hormones include the **thyroid**, the **hypothalamus**, and the **pituitary**, as well as the **gonads** (testes and ovaries) and the **pancreas**. Each endocrine gland releases one or more types of hormones, many of which are master regulators of development and physiology

Endocrine signaling

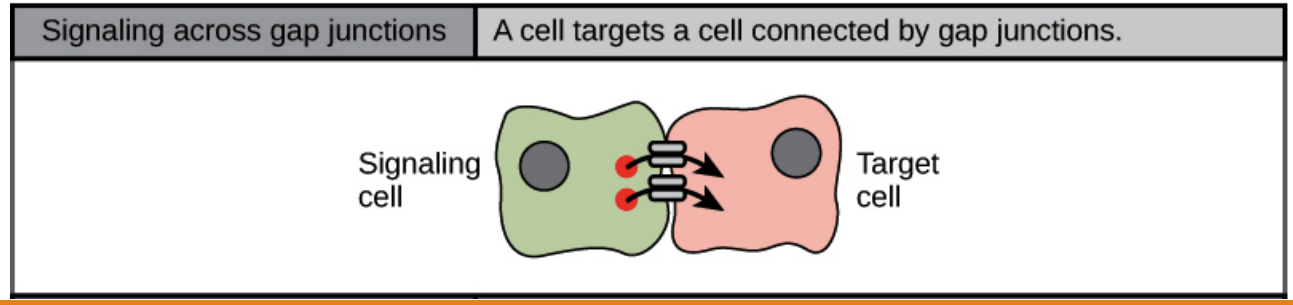
For example, the pituitary releases **growth hormone** (**GH**), which promotes growth, particularly of the skeleton and cartilage. Like most hormones, GH affects many different types of cells throughout the body. However, cartilage cells provide one example of how GH functions: it binds to receptors on the surface of these cells and encourages them to divide



Signaling through cell-cell contact

Gap junctions in animals and **plasmodesmata** in plants are tiny channels that directly connect neighboring cells. These water-filled channels allow small signaling molecules, called **intracellular mediators**, to diffuse between the two cells. Small molecules, such as calcium ions (Ca2+), are able to move between cells, but large molecules like proteins and DNA cannot fit through the channels without special assistance.

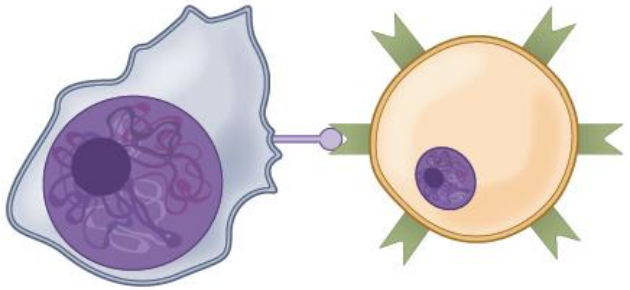
The transfer of signaling molecules transmits the current state of one cell to its neighbor. This allows a group of cells to coordinate their response to a signal that only one of them may have received. In plants, there are plasmodesmata between almost all cells, making the entire plant into one giant network



Signaling through cell-cell contact

In another form of direct signaling, two cells may bind to one another because they carry complementary **proteins** on their **surfaces**. When the proteins bind to one another, this interaction changes the shape of one or both proteins, transmitting a signal. This kind of signaling is especially important in the **immune system**, where immune cells use cell-surface markers to recognize “self” cells (the body's own cells) and cells infected by pathogens.

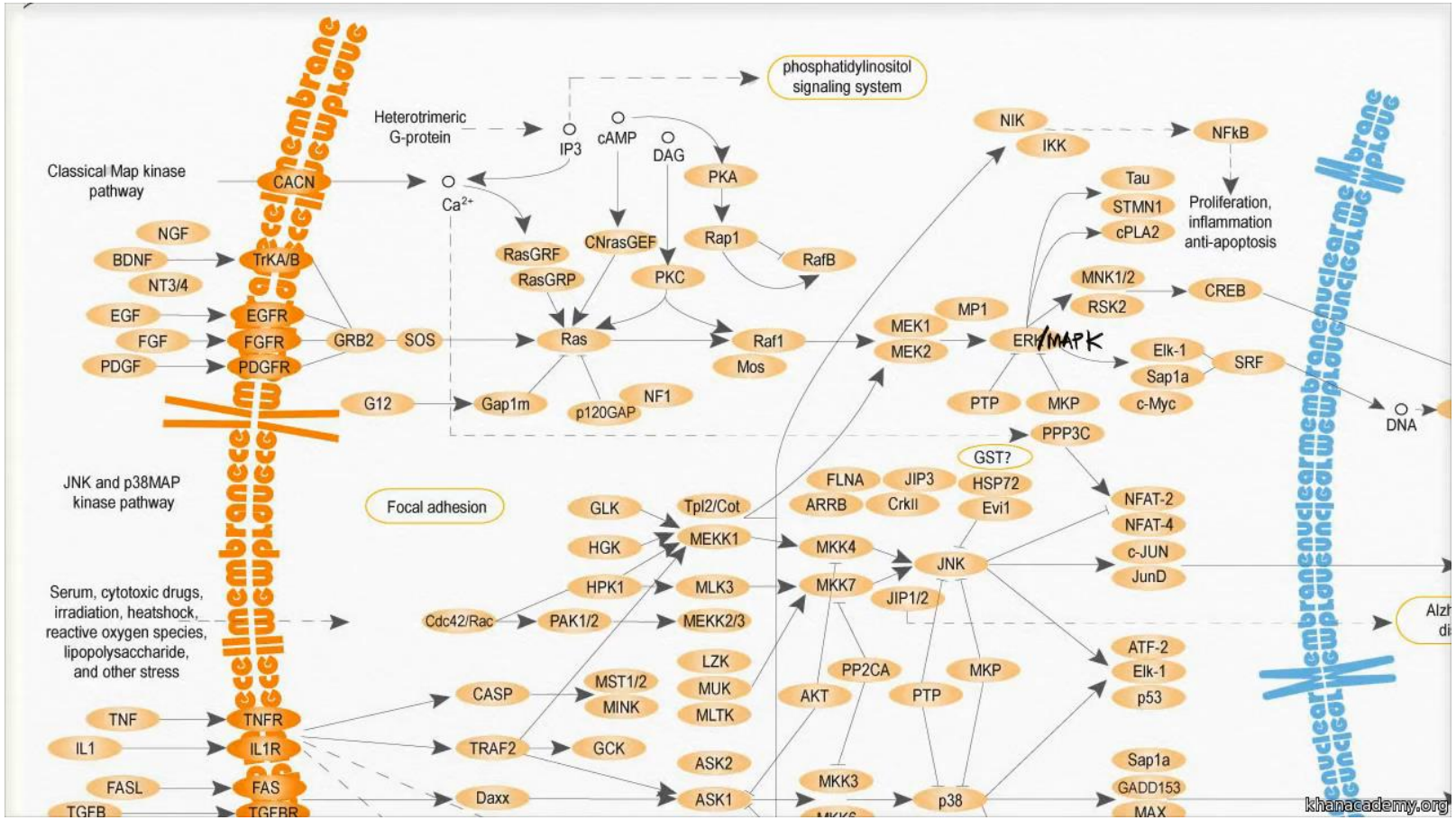
A natural killer (NK) immune cell recognizes a healthy cell of the body by binding to a "self" marker on the cell's surface.



NK cell Healthy cell

Overview of cell signaling

example of signal transduction pathway



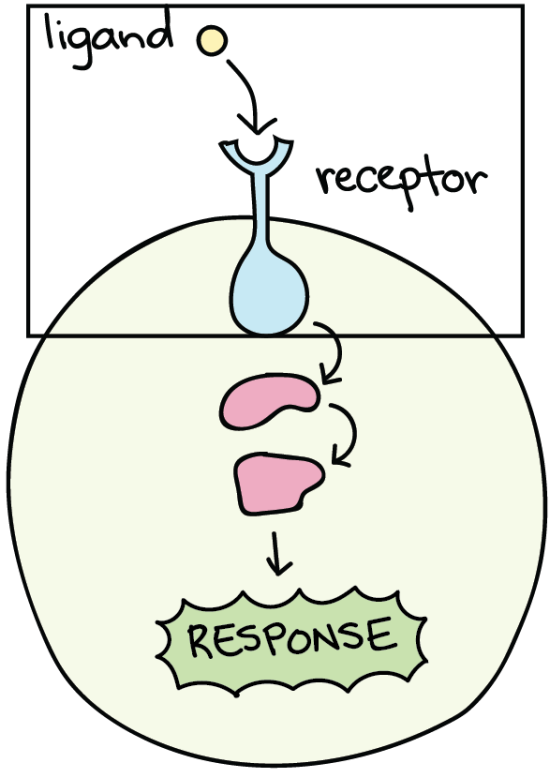
Ligands and receptors

- Types of receptors
  - Intracellular receptors
  - Cell-surface receptors
    - Ligand-gated ion channels
    - G protein-coupled receptors
    - Receptor tyrosine kinases
- Types of ligands
  - Ligands that can enter the cell
  - Ligands that bind on the outside of the cell

Ligands and receptors

Just as a journey of a thousand miles begins with a single step, so a complex signaling pathway inside of a cell begins with a single key event – the binding of a signaling molecule, or **ligand**, to its receiving molecule, or **receptor**.

Receptors and ligands come in many forms, but they all have one thing in common: they come in closely matched pairs, with a receptor recognizing just one (or a few) specific ligands, and a ligand binding to just one (or a few) target receptors. Binding of a ligand to a receptor changes its shape or activity, allowing it to transmit a signal or directly produce a change inside of the cell



Intracellular receptors

Intracellular receptors are receptor proteins found on the inside of the cell, typically in the cytoplasm or nucleus.

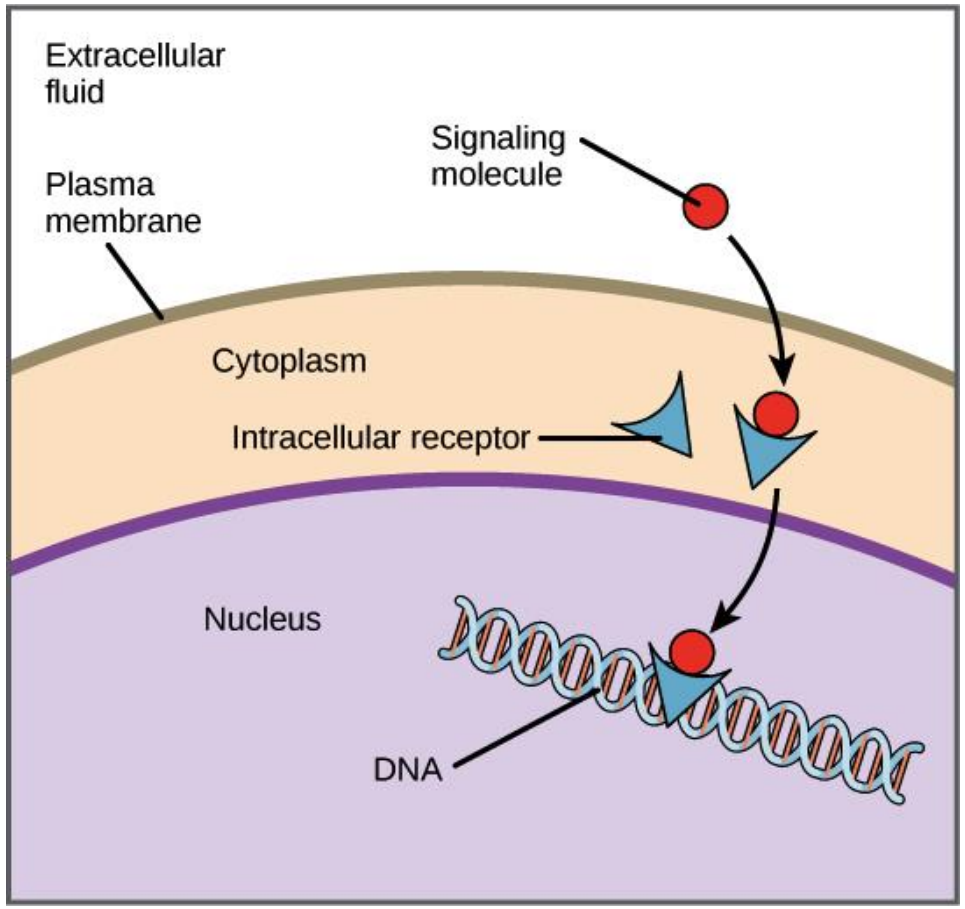
In most cases, the ligands of intracellular receptors are small, hydrophobic (water-hating) molecules, since they must be able to cross the plasma membrane in order to reach their receptors. For example, the primary receptors for hydrophobic steroid hormones, such as the sex hormones estradiol (an estrogen) and testosterone, are intracellular.

Many signaling pathways, involving both intracellular and cell surface receptors, cause changes in the **transcription** of genes. However, intracellular receptors are unique because they cause these changes very directly, binding to the DNA and altering transcription themselves.

Intracellular receptors

When a hormone enters a cell and binds to its receptor, it causes the receptor to change **shape**, allowing the receptor-hormone complex to enter the nucleus (if it wasn't there already) and **regulate gene activity**. Hormone binding exposes regions of the receptor that have DNA-binding activity, meaning they can attach to specific sequences of DNA.

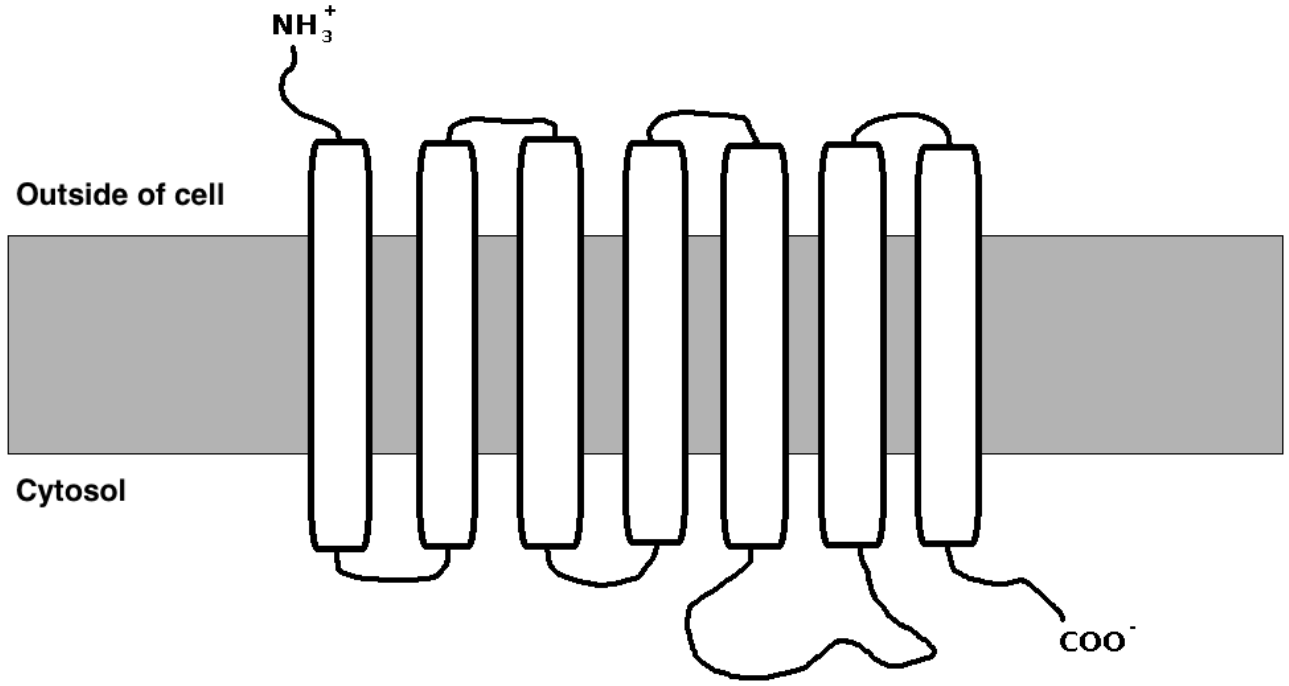
These sequences are found next to certain genes in the DNA of the cell, and when the receptor binds next to these genes, it alters their level of **transcription**



Cell-surface receptors

Cell-surface receptors are membrane-anchored proteins that bind to ligands on the outside surface of the cell. In this type of signaling, the ligand does not need to cross the plasma membrane. So, many different kinds of molecules (including large, hydrophilic or "water-loving" ones) may act as ligands.

A typical cell-surface receptor has three different **domains**, or protein regions: a extracellular ("outside of cell") ligand-binding domain, a hydrophobic domain extending through the membrane, and an intracellular ("inside of cell") domain, which often transmits a signal. The size and structure of these regions can vary a lot depending on the type of receptor, and the hydrophobic region may consist of multiple stretches of amino acids that criss-cross the membrane



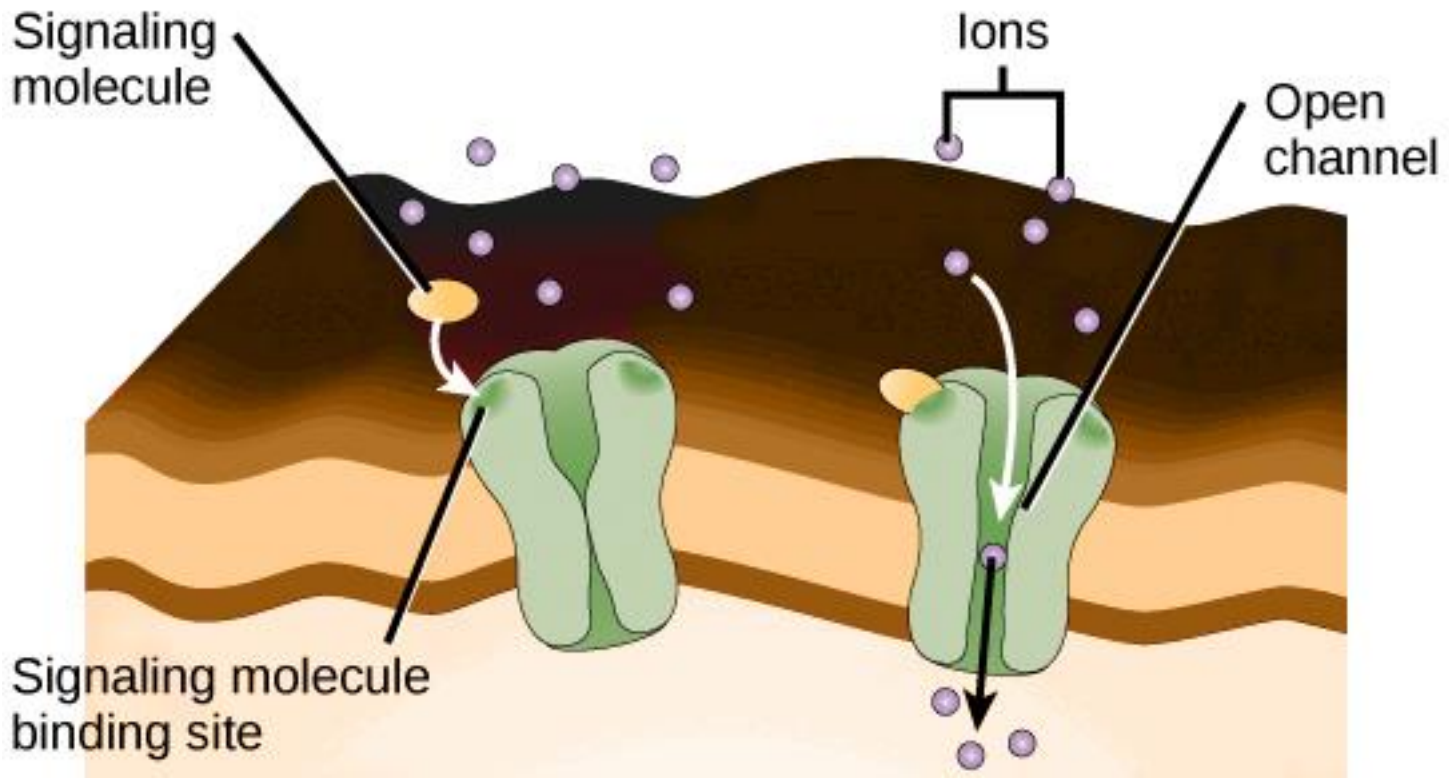
This diagram shows a G protein-coupled receptor (GPCR), a type of receptor we'll examine in more detail later in the article. GPCRs have seven membrane-spanning domains, as shown by the seven segments crossing the gray region that represents the plasma membrane.

Ligand-gated ion channels

Ligand-gated ion channels are ion channels that can open in response to the binding of a ligand. To form a channel, this type of cell-surface receptor has a membrane-spanning region with a hydrophilic (water-loving) channel through the middle of it. The channel lets ions to cross the membrane without having to touch the hydrophobic core of the phospholipid bilayer.

When a ligand binds to the extracellular region of the channel, the protein's structure changes in such a way that ions of a particular type, such as Ca^{2+} or Cl^{-}, can pass through. In some cases, the reverse is actually true: the channel is usually open, and ligand binding causes it to close. Changes in ion levels inside the cell can change the activity of other molecules, such as ion-binding enzymes and voltage-sensitive channels, to produce a response. Neurons, or nerve cells, have ligand-gated channels that are bound by neurotransmitters

Ligand-gated ion channels



G protein-coupled receptors

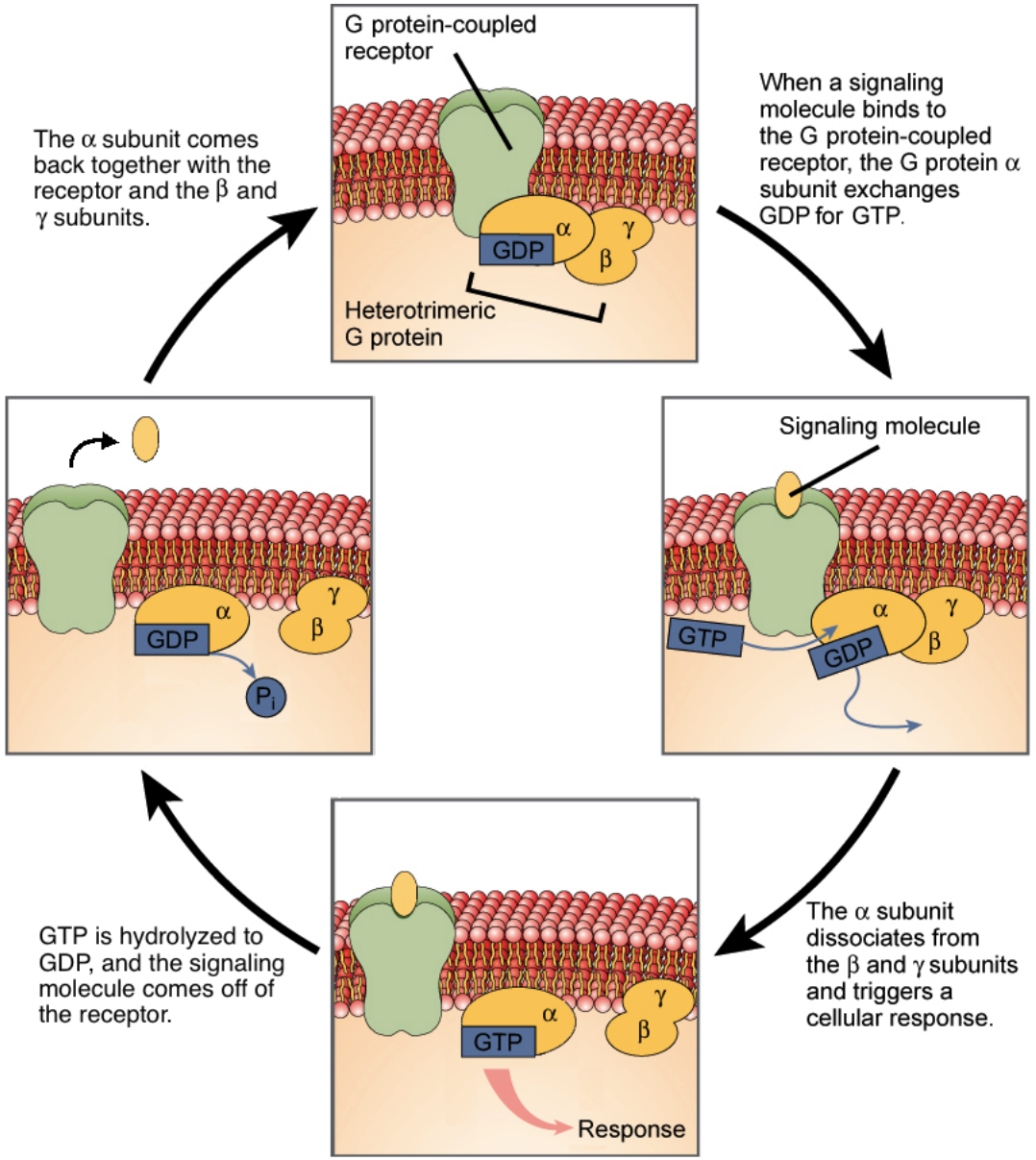
G protein-coupled receptors (**GPCRs**) are a large family of cell surface receptors that share a common structure and method of signaling. The members of the GPCR family all have seven different protein segments that cross the membrane, and they transmit signals inside the cell through a type of protein called a G protein.

GPCRs are diverse and bind many different types of ligands. One particularly interesting class of GPCRs is the odorant (scent) receptors. There are about 800800 of them in humans, and each binds its own “scent molecule” – such as a particular chemical in perfume, or a certain compound released by rotting fish – and causes a signal to be sent to the brain, making us smell a smell.

G protein-coupled receptors

When its ligand is not present, a G protein-coupled receptor waits at the plasma membrane in an inactive state. For at least some types of GPCRs, the inactive receptor is already docked to its signaling target, a **G protein**.

G proteins come in different types, but they all bind the nucleotide guanosine triphosphate (GTP), which they can break down (hydrolyze) to form GDP. A G protein attached to GTP is active, or "on," while a G protein that's bound to GDP is inactive, or "off." The G proteins that associate with GPCRs are a type made up of three subunits, known as **heterotrimeric G proteins**. When they're attached to an inactive receptor, they're in the "off" form (bound to GDP).


G protein-coupled receptor
When a signaling molecule binds to the G protein-coupled receptor, the G protein α subunit exchanges GDP for GTP.
Heterotrimeric G protein
GDP
α
β
γ
Signaling molecule
GTP
The α subunit dissociates from the β and γ subunits and triggers a cellular response.
Response
GTP is hydrolyzed to GDP, and the signaling molecule comes off of the receptor.
P_i
The α subunit comes back together with the receptor and the β and γ subunits.

G protein-coupled receptors

Ligand binding, however, changes the picture: the GPCR is activated and causes the G protein to exchange GDP for GTP. The now-active G protein separates into two pieces (one called the α subunit, the other consisting of the β and γ subunits), which are freed from the GPCR. The subunits can interact with other proteins, triggering a signaling pathway that leads to a response.

Eventually, the α subunit will hydrolyze GTP back to GDP, at which point the G protein becomes inactive. The inactive G protein reassembles as a three-piece unit associated with a GPCR. Cell signaling using G protein-coupled receptors is a cycle, one that can repeat over and over in response to ligand binding.

G protein-coupled receptors play many different roles in the human body, and disruption of GPCR signaling can cause disease

Receptor tyrosine kinases

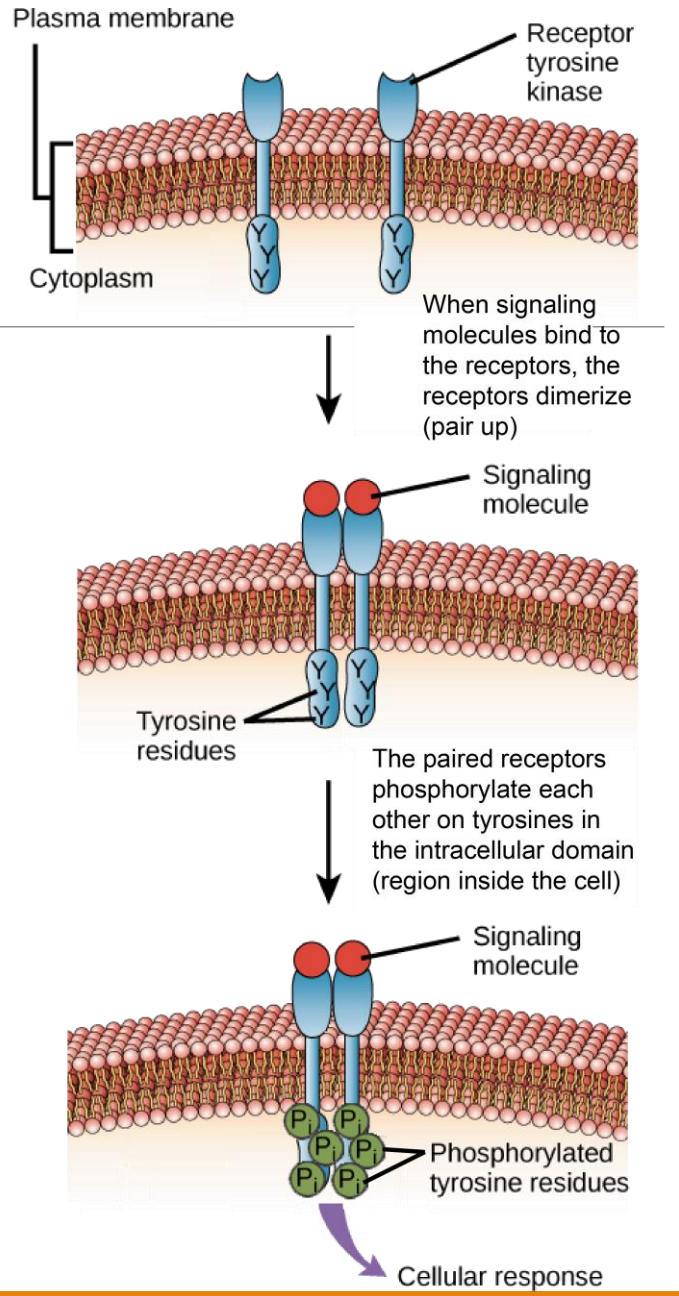
Enzyme-linked receptors are cell-surface receptors with intracellular domains that are associated with an enzyme. In some cases, the intracellular domain of the receptor actually *is* an enzyme that can catalyze a reaction. Other enzyme-linked receptors have an intracellular domain that interacts with an enzyme.

Receptor tyrosine kinases (**RTKs**) are a class of enzyme-linked receptors found in humans and many other species. A **kinase** is just a name for an enzyme that transfers phosphate groups to a protein or other target, and a receptor tyrosine kinase transfers phosphate groups specifically to the amino acid tyrosine.

Receptor tyrosine kinases

How does RTK signaling work? In a typical example, signaling molecules first bind to the extracellular domains of two nearby receptor tyrosine kinases.

The two neighboring receptors then come together, or dimerize. The receptors then attach phosphates to tyrosines in each others' intracellular domains. The phosphorylated tyrosine can transmit the signal to other molecules in the cell.



Receptor tyrosine kinases

In many cases, the phosphorylated receptors serve as a docking platform for other proteins that contain special types of binding domains. A variety of proteins contain these domains, and when one of these proteins binds, it can initiate a downstream signaling cascade that leads to a cellular response.

Receptor tyrosine kinases are crucial to many signaling processes in humans. For instance, they bind to **growth factors**, signaling molecules that promote cell division and survival. Growth factors include platelet-derived growth factor (PDGF), which participates in wound healing, and nerve growth factor (NGF), which must be continually supplied to certain types of neurons to keep them alive. Because of their role in growth factor signaling, receptor tyrosine kinases are essential in the body, but their activity must be kept in balance: overactive growth factor receptors are associated with some types of cancers

Types of ligands

Ligands, which are produced by signaling cells and interact with receptors in or on target cells, come in many different varieties. Some are proteins, others are hydrophobic molecules like steroids, and others yet are gases like nitric oxide.

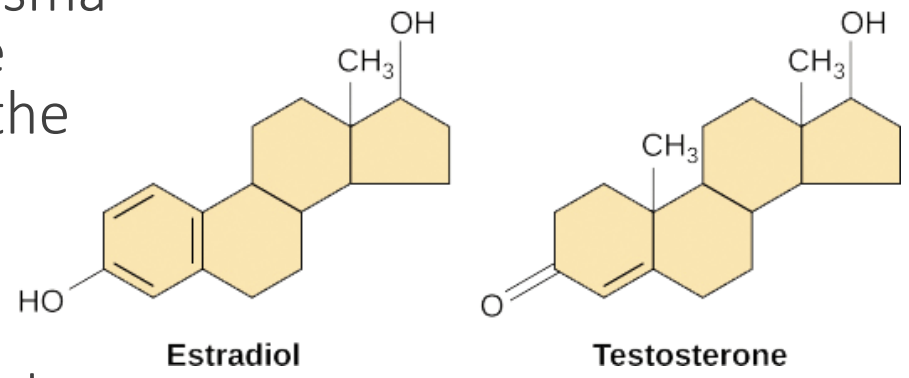
We can divide them in two categories:

- Ligands that can enter the cell
- Ligands that bind on the outside of the cell

Ligands that can enter the cell

Small, hydrophobic ligands can pass through the plasma membrane and bind to intracellular receptors in the nucleus or cytoplasm. In the human body, some of the most important ligands of this type are the **steroid hormones**.

Familiar steroid hormones include the female sex hormone **estradiol**, which is a type of estrogen, and the male sex hormone **testosterone**. **Vitamin D**, a molecule synthesized in the skin using energy from light, is another example of a steroid hormone. Because they are hydrophobic, these hormones don't have trouble crossing the plasma membrane, but they must bind to carrier proteins in order to travel through the (watery) bloodstream.



Estradiol **Testosterone**

Ligands that can enter the cell

Nitric oxide (NO) is a gas that acts as a ligand. Like steroid hormones, it can diffuse directly across the plasma membrane thanks to its small size. One of its key roles is to activate a signaling pathway in the smooth muscle surrounding blood vessels, one that makes the **muscle relax** and allows the blood vessels to expand (dilate).

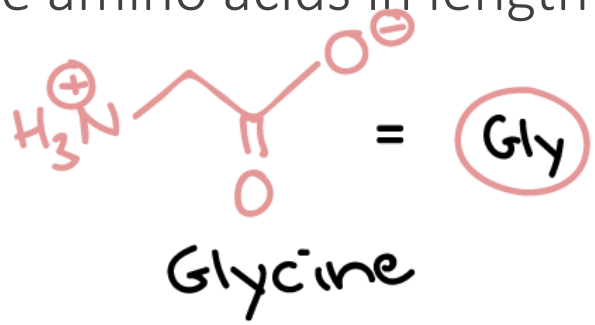
In fact, the drug **nitroglycerin** treats heart disease by triggering the release of NO, dilating vessels to restore blood flow to the heart.

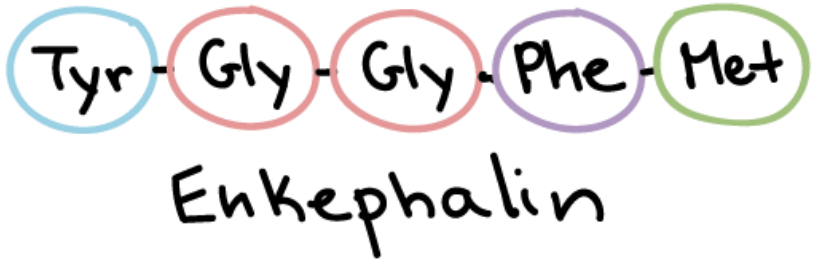
NO has become better-known recently because the pathway that it affects is targeted by prescription medications for erectile dysfunction, such as **Viagra**

Ligands that bind on the outside of the cell

Water-soluble ligands are polar or charged and cannot readily cross the plasma membrane. So, most water-soluble ligands bind to the extracellular domains of cell-surface receptors, staying on the outer surface of the cell.

Peptide (protein) ligands make up the largest and most diverse class of water-soluble ligands. For instance, **growth factors**, **hormones** such as insulin, and certain **neurotransmitters** fall into this category. Peptide ligands can range from just a few amino acids long, as in the pain-suppressing enkephalins, to a hundred or more amino acids in length

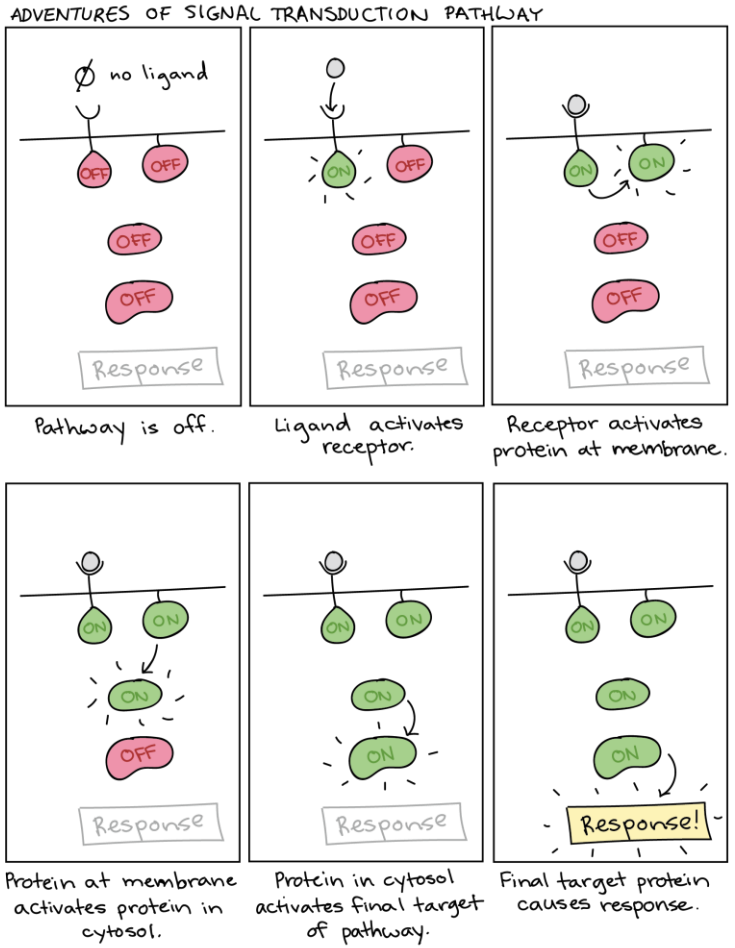




Signal relay pathways

- Binding initiates a signaling pathway
- Phosphorylation
- Second messengers
  - Calcium ions
  - Cyclic AMP (cAMP)
  - Inositol phosphates
- Other signaling pathways

Binding initiates a signaling pathway

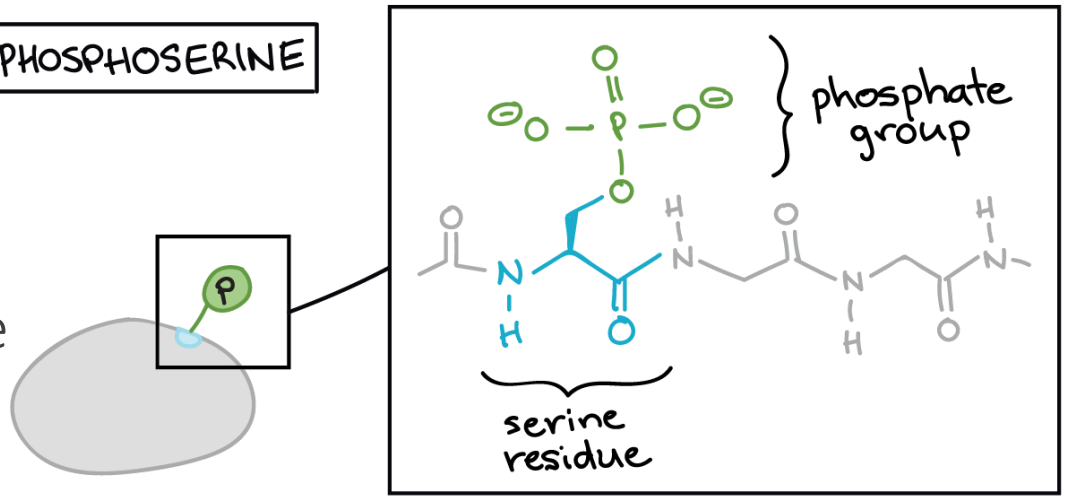


Because of the directional flow of information, the term **upstream** is often used to describe molecules and events that come earlier in the relay chain, while **downstream** may be used to describe those that come later (relative to a particular molecule of interest). For instance, in the diagram, the receptor is downstream of the ligand but upstream of the the proteins in the cytosol. Many signal transduction pathways amplify the initial signal, so that one molecule of ligand can lead to the activation of many molecules of a downstream target. The molecules that relay a signal are often proteins. However, non-protein molecules like ions and phospholipids can also play important roles.

Phosphorylation

The previous diagram features a bunch of blobs (signaling molecules) labeled as "**on**" or "**off**." What does it actually mean for a blob to be on or off?

Proteins can be activated or inactivated in a variety of ways. However, one of the most common tricks for altering protein activity is the addition of a phosphate group to one or more sites on the protein, a process called **phosphorylation**.



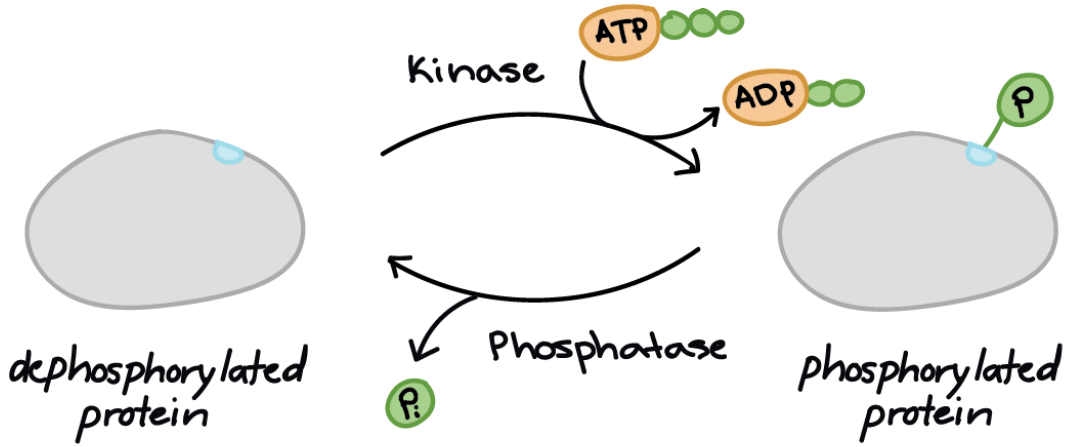
Phosphorylation

Phosphate groups can't be attached to just any part of a protein. Instead, they are typically linked to one of the three amino acids that have **hydroxyl (-OH)** groups in their side chains: **tyrosine**, **threonine**, and **serine**. The transfer of the phosphate group is catalyzed by an enzyme called a **kinase**, and cells contain many different kinases that phosphorylate different targets.

Phosphorylation often acts as a switch, but its effects vary among proteins. Sometimes, phosphorylation will make a protein more active (for instance, increasing catalysis or letting it bind to a partner). In other cases, phosphorylation may inactivate the protein or cause it to be broken down.

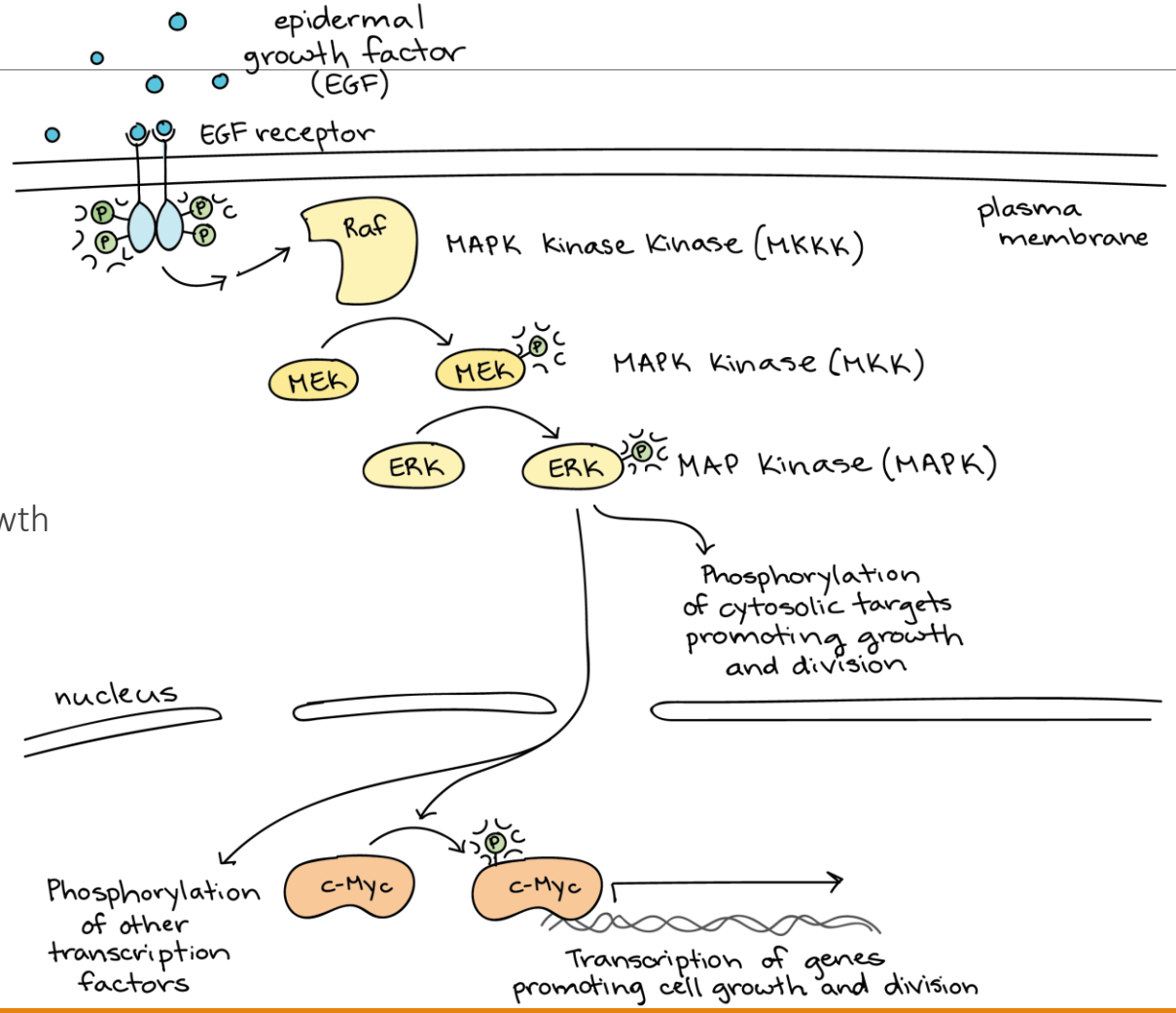
Phosphorylation

In general, phosphorylation isn't permanent. To flip proteins back into their non-phosphorylated state, cells have enzymes called **phosphatases**, which remove a phosphate group from their targets



Phosphorylation example: MAPK signaling cascade

This diagram shows part of the epidermal growth factor signaling pathway:



Phosphorylation example: MAPK signaling cascade

Phosphorylation (marked as a P) is important at many stages of this pathway.

When growth factor ligands bind to their receptors, the receptors pair up and act as kinases, attaching phosphate groups to one another’s intracellular tails.

The activated receptors trigger a series of events (skipped here because they don't involve phosphorylation). These events activate the kinase Raf.

Active Raf phosphorylates and activates MEK, which phosphorylates and activates the ERKs.

The ERKs phosphorylate and activate a variety of target molecules. These include transcription factors, like c-Myc, as well as cytoplasmic targets. The activated targets promote cell growth and division

Phosphorylation example: MAPK signaling cascade

Together, Raf, MEK, and the ERKs make up a three-tiered kinase signaling pathway called a **mitogen-activated protein kinase** (**MAPK**) cascade. (A *mitogen* is a signal that causes cells to undergo *mitosis*, or divide.) Because they play a central role in promoting cell division, the genes encoding the growth factor receptor, Raf, and c-Myc are all proto-oncogenes, meaning that overactive forms of these proteins are associated with cancer.

MAP kinase signaling pathways are widespread in biology: they are found in a wide range of organisms, from humans to yeast to plants. The similarity of MAPK cascades in diverse organisms suggests that this pathway emerged early in the evolutionary history of life and was already present in a common ancestor of modern-day animals, plants, and fung

Second messengers

Although proteins are important in signal transduction pathways, other types of molecules can participate as well. Many pathways involve **second messengers**, small, non-protein molecules that pass along a signal initiated by the binding of a ligand (the “first messenger”) to its receptor.

Second messengers include Ca2+ ions; cyclic AMP (cAMP), a derivative of ATP; and inositol phosphates, which are made from phospholipid.

Calcium ions

Calcium ions are a widely used type of second messenger. In most cells, the **concentration** of calcium ions (Ca^{2+}) in the cytosol is **very low**, as ion pumps in the plasma membrane continually work to remove it. For signaling purposes, Ca^{2+} may be stored in compartments such as the endoplasmic reticulum.

In pathways that use calcium ions as a second messenger, **upstream signaling events** release a ligand that binds to and **opens ligand-gated calcium ion channels**. These channels open and allow the higher levels of Ca^{2+} that are present outside the cell (or in intracellular storage compartments) to flow into the cytoplasm, raising the concentration of cytoplasmic Ca^{2+}.

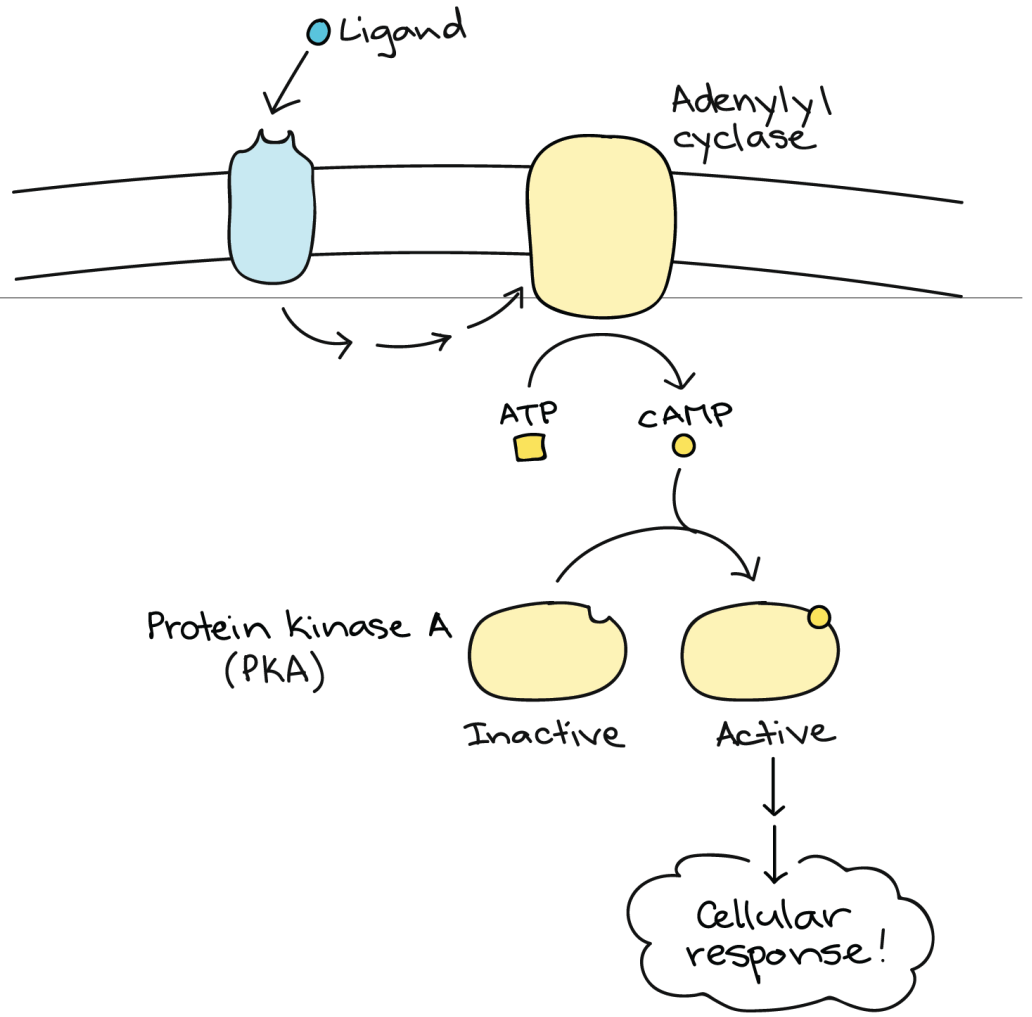
How does the released Ca^{2+} help pass along the signal? **Some proteins** in the cell have **binding sites for Ca^{2+}** ions, and the released ions attach to these proteins and **change** their **shape** (and thus, their **activity**). The proteins present and the response produced are different in different types of cells. For instance, Ca^{2+} signaling in the β-cells of the pancreas leads to the release of insulin, while Ca^{2+} signaling in muscle cells leads to muscle contraction.

Cyclic AMP (cAMP)

Another second messenger used in many different cell types is **cyclic adenosine monophosphate** (**cyclic AMP** or **cAMP**), a small molecule made from ATP. In response to signals, an enzyme called **adenylyl cyclase** converts ATP into cAMP, removing two phosphates and linking the remaining phosphate to the sugar in a ring shape.

Once generated, cAMP can activate an enzyme called **protein kinase A** (**PKA**), enabling it to phosphorylate its targets and pass along the signal. Protein kinase A is found in a variety of types of cells, and it has different target proteins in each. This allows the same cAMP second messenger to produce different responses in different contexts

Cyclic AMP (cAMP)



cAMP signaling is turned off by enzymes called **phosphodiesterases**, which break the ring of cAMP and turn it into adenosine monophosphate (AMP)

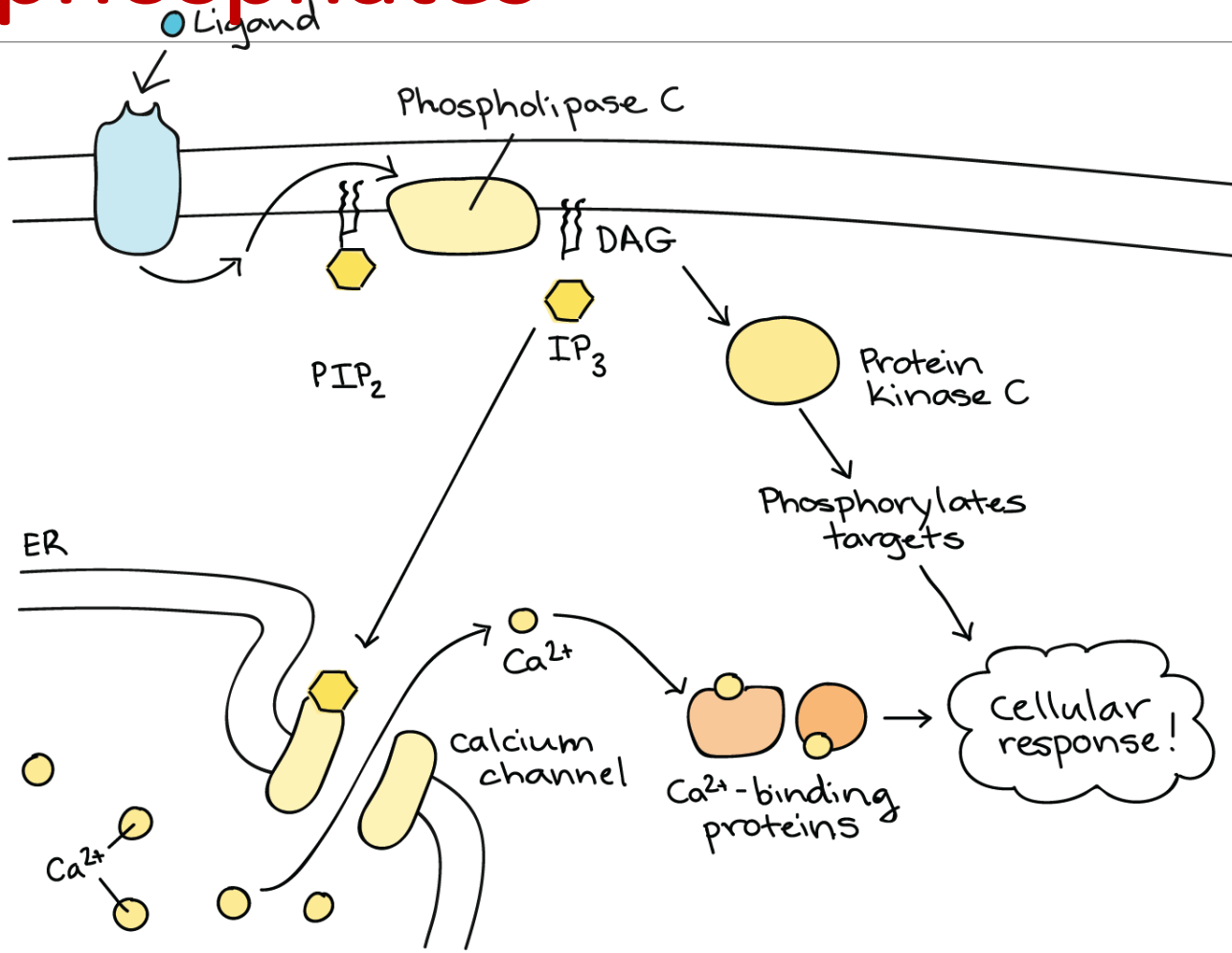
Inositol phosphates

Although we usually think of plasma membrane phospholipids as structural components of the cell, they can also be important participants in signaling. Phospholipids called **phosphatidylinositols** can be phosphorylated and snipped in half, releasing two fragments that both act as second messengers.

One lipid in this group that's particularly important in signaling is called **PIP2**. In response to a signal, an enzyme called **phospholipase C** cleaves (chops) PIP2 into two fragments, **DAG** and **IP3**. These fragments made can both act as second messengers.

DAG stays in the plasma membrane and can activate a target called **protein kinase C (PKC),** allowing it to phosphorylate its own targets. IP3 diffuses into the cytoplasm and can bind to ligand-gated calcium channels in the endoplasmic reticulum, releasing **Ca2+** that continues the signal cascade

Inositol phosphates

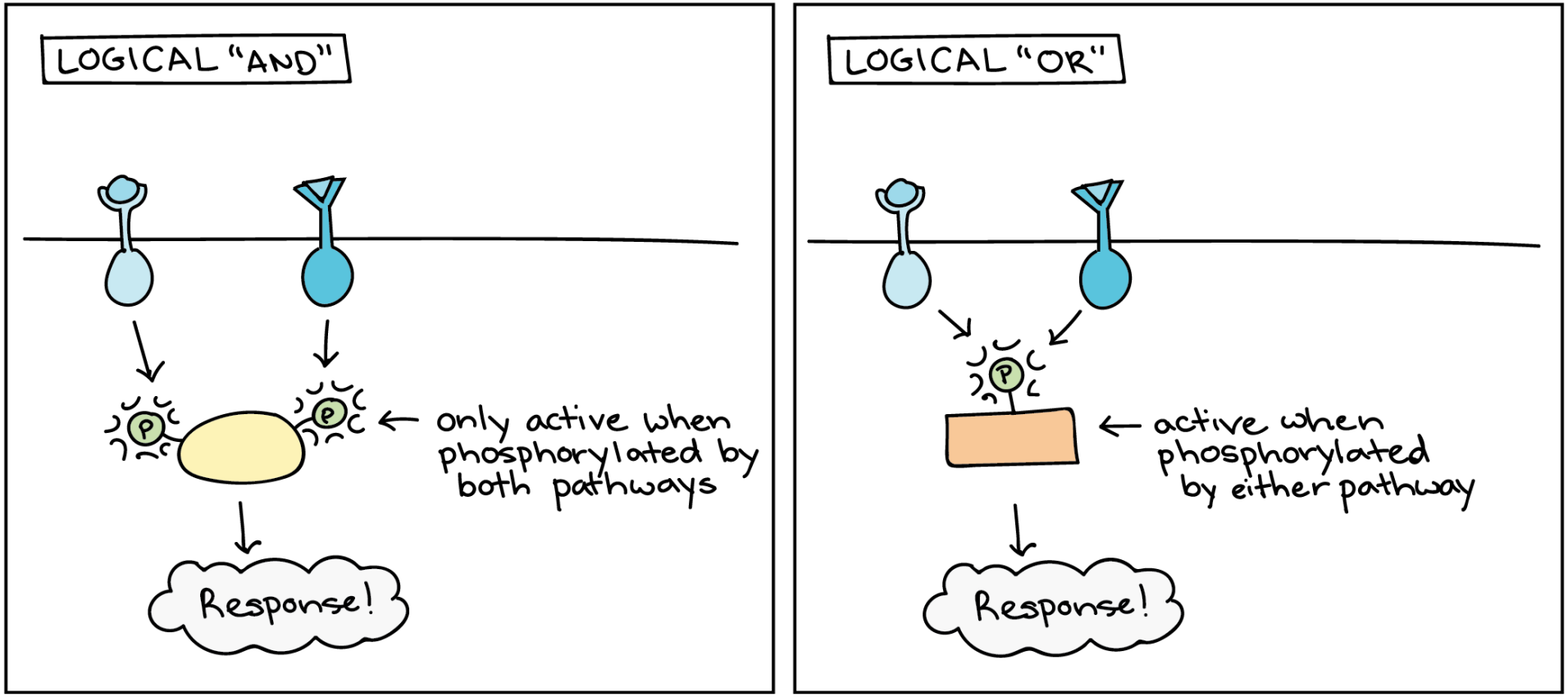


And…it's even more complicated than that!

Signaling pathways can get very complicated very quickly. For instance, the full version of the epidermal growth factor signaling pathway we saw earlier looks like a huge hairball and takes up an entire poster if you try to draw it out!

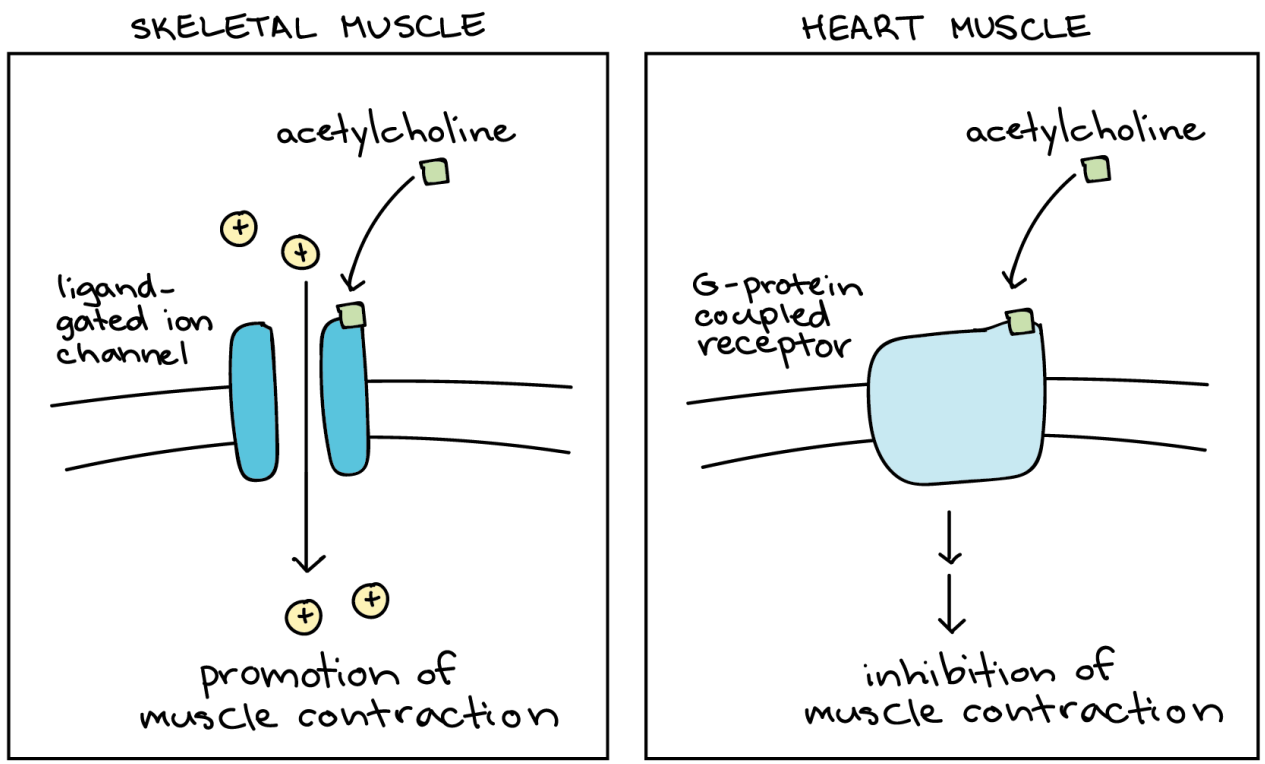
This complexity arises because pathways can, and often do, interact with other pathways. When pathways interact, they basically allow the cell to perform logic operations and "**calculate**" the best response to multiple sources of information. For instance, signals from two different pathways may be needed to activate a response, which is like a logical "**AND**." Alternatively, *either* of two pathways may trigger the same response, which is like a logical "**OR**."

Other ways of signaling



Other ways of signaling

Another source of complexity in signaling is that the same signaling molecule may produce different results depending on what molecules are already present in the cell. For example, the ligand **acetylcholine** causes opposite effects in skeletal and heart muscle because these cell types produce different kinds of acetylcholine receptors that trigger different pathways



Response to a signal

At the molecular level

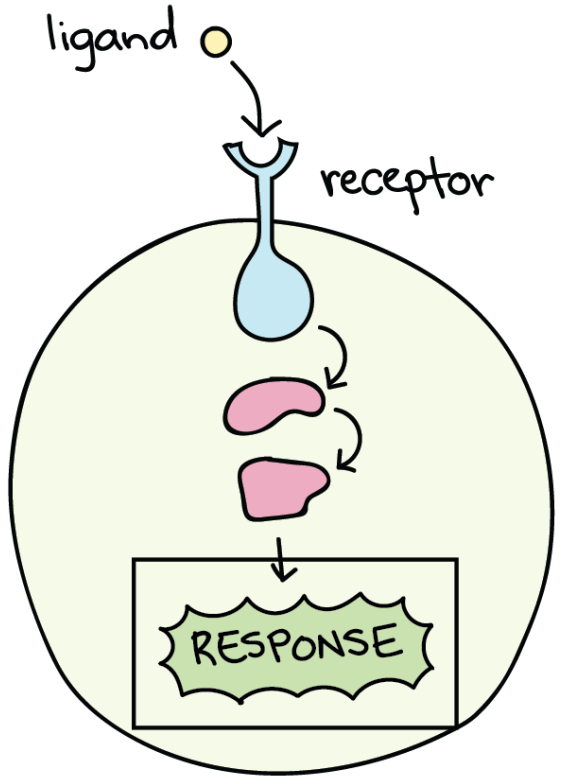
- Gene expression
- Cellular metabolism

At the macroscopic level

Response to a signal

Cell signaling pathways vary a lot. Signals (a.k.a. ligands) and receptors come in many varieties, and binding can trigger a wide range of signal relay cascades inside the cell, from short and simple to long and complex.

Despite these differences, signaling pathways share a common goal: to produce some kind of cellular response. That is, a signal is released by the sending cell in order to make the receiving cell change in a particular way.



Gene expression

Many signaling pathways cause a cellular response that involves a change in gene expression. **Gene expression** is the process in which information from a gene is used by the cell to produce a functional product, typically a protein. It involves two major steps, **transcription** and **translation**.

Transcription makes an RNA transcript (copy) of a gene's DNA sequence.

Translation reads information from the RNA and uses it to make a protein.

Signaling pathways can target either or both steps to alter the amount of a particular protein produced in a cell.

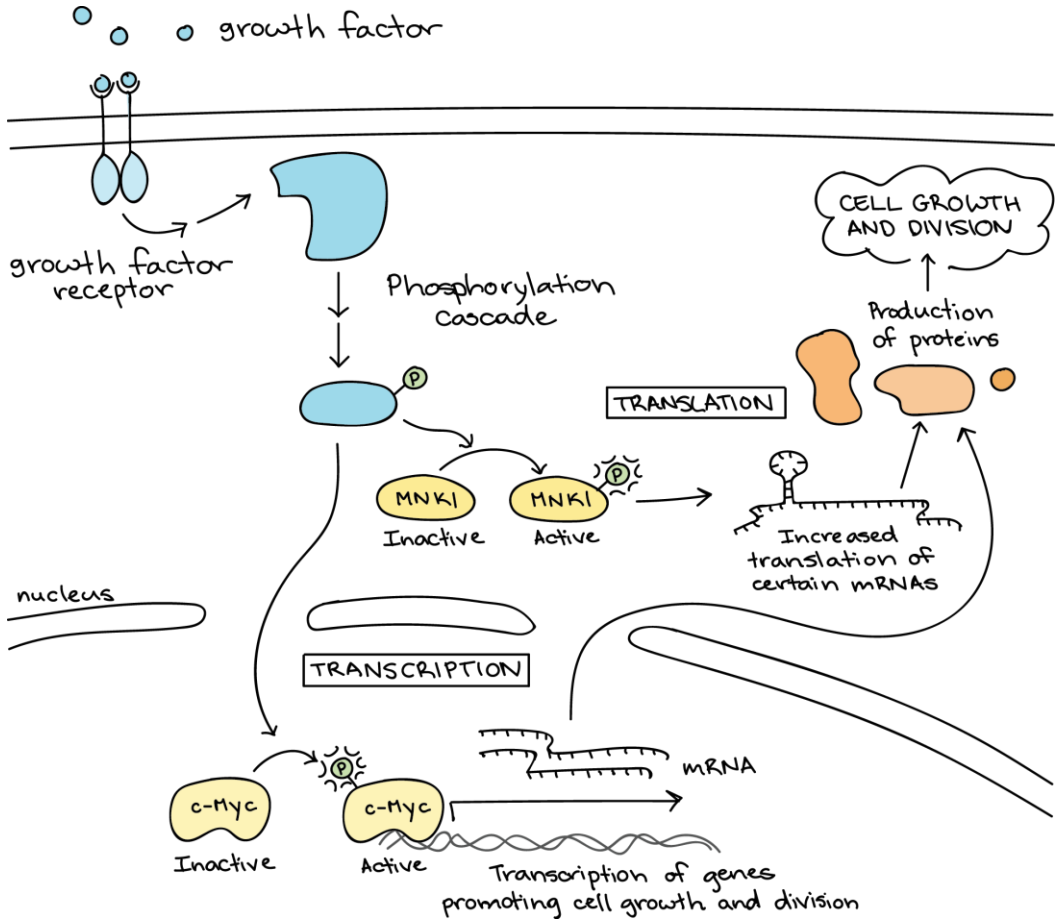
Example: Growth factor signaling

We can use the growth factor signaling pathway from the signal relay article as an example to see how signaling pathways alter transcription and translation.

This growth factor pathway has many targets, which it activates through a signaling cascade that involves phosphorylation (addition of phosphate groups to molecules). Some of the pathway's targets are transcription factors, proteins that increase or decrease transcription of certain genes.

In the case of growth factor signaling, the genes have effects that lead to cell growth and division. One transcription factor targeted by the pathway is c-Myc, a protein that can lead to cancer when it is too active ("too good" at promoting cell division)

Example: Growth factor signaling



Example: Growth factor signaling

The growth factor pathway also affects gene expression at the level of **translation**. For instance, one of its targets is a translational regulator called MNK1. Active MNK1 increases the rate of mRNA translation, especially for certain mRNAs that fold back on themselves to make hairpin structures (which would normally block translation). Many key genes regulating cell division and survival have mRNAs that form hairpin structures, and MNK1 allows these genes to be expressed at high levels, driving growth and division.

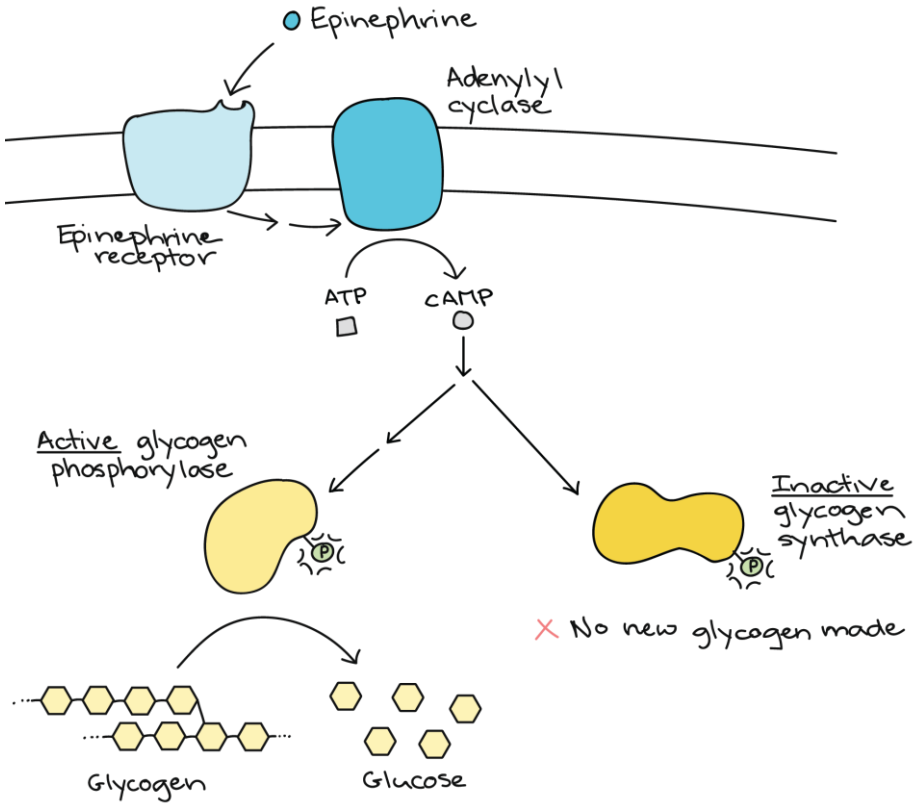
Notably, neither c-Myc nor MNK1 is a "final responder" in the growth factor pathway. Instead, these regulatory factors, and others like them, promote or repress the production of other proteins (the orange blobs in the illustration above) that are more directly involved in carrying **out cell growth and division**.

Cellular metabolism

Some signaling pathways produce a **metabolic response**, in which metabolic enzymes in the cell become more or less active. We can see how this works by considering adrenaline signaling in muscle cells. Adrenaline, also known as epinephrine, is a hormone (produced by the adrenal gland) that readies the body for short-term emergencies. If you're nervous before a test or competition, your adrenal gland is likely to be pumping out epinephrine.

When epinephrine binds to its receptor on a muscle cell (a type of G protein-coupled receptor), it triggers a signal transduction cascade involving production of the second messenger molecule cyclic AMP (cAMP). This cascade leads to phosphorylation of two metabolic enzymes— that is, addition of a phosphate group, causing a change in the enzymes' behavior

Cellular metabolism



Cellular metabolism

The first enzyme is glycogen phosphorylase (GP). The job of this enzyme is to break down glycogen into glucose. Glycogen is a storage form of glucose, and when energy is needed, glycogen must be broken down. Phosphorylation activates glycogen phosphorylase, causing lots of glucose to be released.

The second enzyme that gets phosphorylated is glycogen synthase (GS). This enzyme is involving in building up glycogen, and phosphorylation inhibits its activity. This ensures that no new glycogen molecules are built when the current need is for glycogen to be broken down.

Through regulation of these enzymes, a muscle cell rapidly gets a large, ready pool of glucose molecules. The glucose is available for use by the muscle cell in response to a sudden surge of adrenaline—the “fight or flight” response.

At the macroscopic level

The types of responses we've discussed above are events at the molecular level. However, a signaling pathway typically triggers a molecular event (or a whole array of molecular events) to in order to produce some larger outcome.

For instance, growth factor signaling causes a variety of molecular changes, including activation of the c-Myc transcription factor and MNK1 translational regulator, to promote the larger response of cell proliferation (growth and division). Similarly, epinephrine triggers the activation of glycogen phosphorylase and the breakdown of glycogen in order to provide a muscle cell with fuel for a rapid response.

Other important large-scale outcomes of cell signaling include cell migration, changes in cell identity, and induction of apoptosis (programmed cell death)

Example: Apoptosis

When a cell is damaged, unneeded, or potentially dangerous to an organism, it may undergo programmed cell death, or **apoptosis**. Apoptosis allows a cell to die in a controlled manner that prevents the release of potentially damaging molecules from inside the cell.

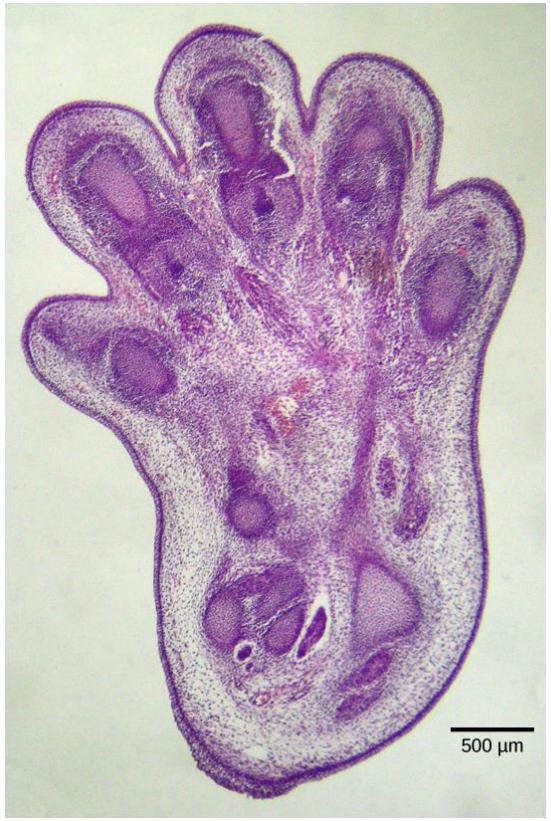
Internal signals (such as those triggered by damaged DNA) can lead to apoptosis, but so can signals from outside the cell. For example, most animal cells have receptors that interact with the extracellular matrix, a supportive network of proteins and carbohydrates. If the cell moves away from the extracellular matrix, signaling through these receptors stops, and the cell undergoes apoptosis. This system keeps cells from traveling through the body and proliferating out of control (and is "broken" in cancer cells that metastasize, or spread to new sites)

Example: Apoptosis

Apoptosis is also essential for normal embryological development.

In vertebrates, for example, early stages of development include the formation of tissue between what will become individual fingers and toes.

During the course of normal development, these unneeded cells must be eliminated, enabling fully separated fingers and toes to form. A cell signaling mechanism triggers apoptosis, which destroys the cells between the developing digits



Good Luck