Cell Communication

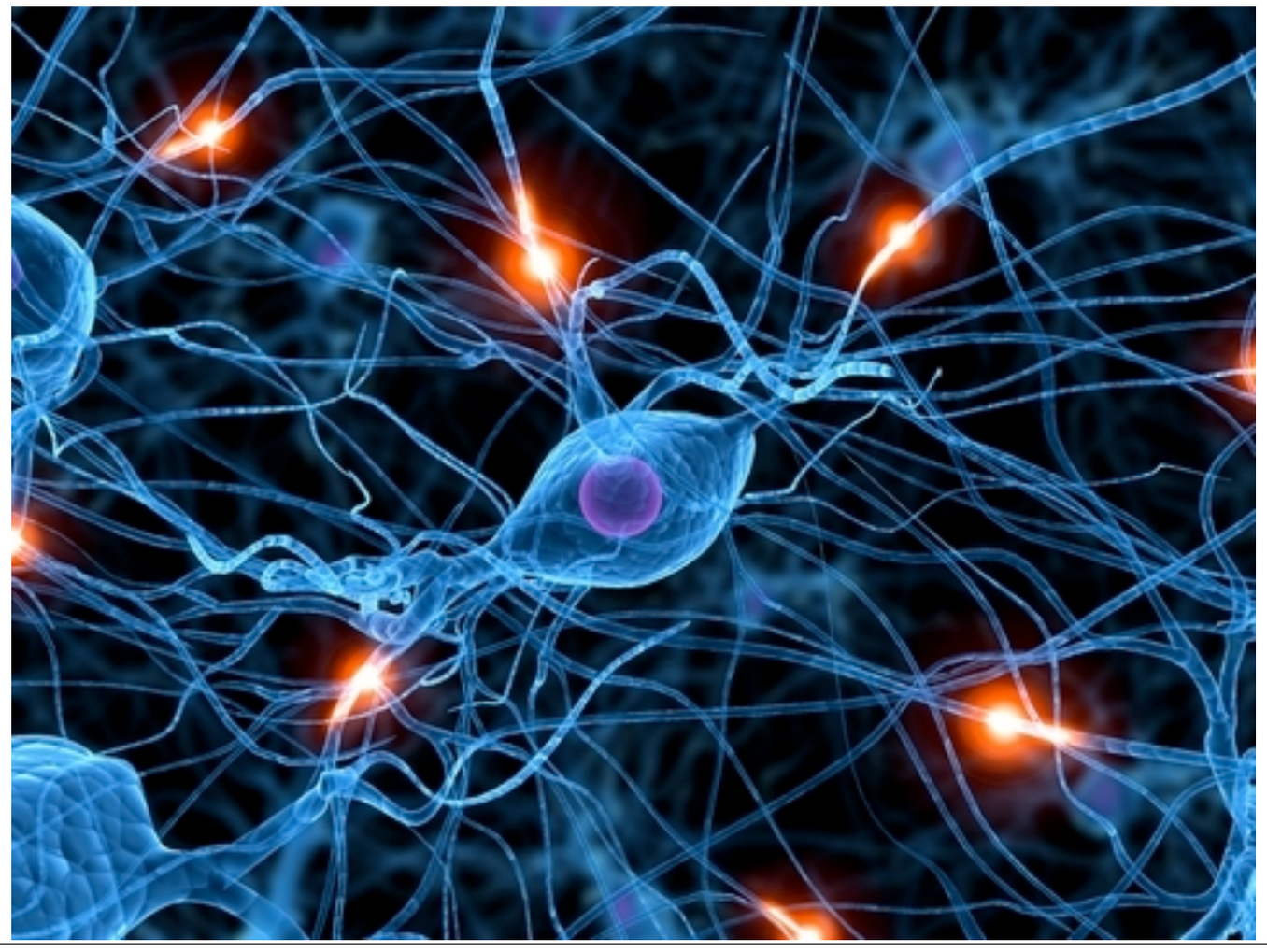
PREFACE

- You will recall that *Sensing* and consequently *Responding* to the environment is an essential function of living organisms...**Cell to Cell Communication** underlies this essential function!
- We will focus on those *universal* mechanisms of **Cellular Communication**.
- Evidence suggests that **Cell Communication** *evolved in early* in earth's history because so many diverse organisms share universal mechanisms and signaling molecules.
- Although cells can sense and respond to variety of stimuli, we will focus on **Cellular Communication** that involves *chemical messaging* between cells.

Cell Communication

I.

Main Idea: External signals, many times chemical, are converted to cellular responses.



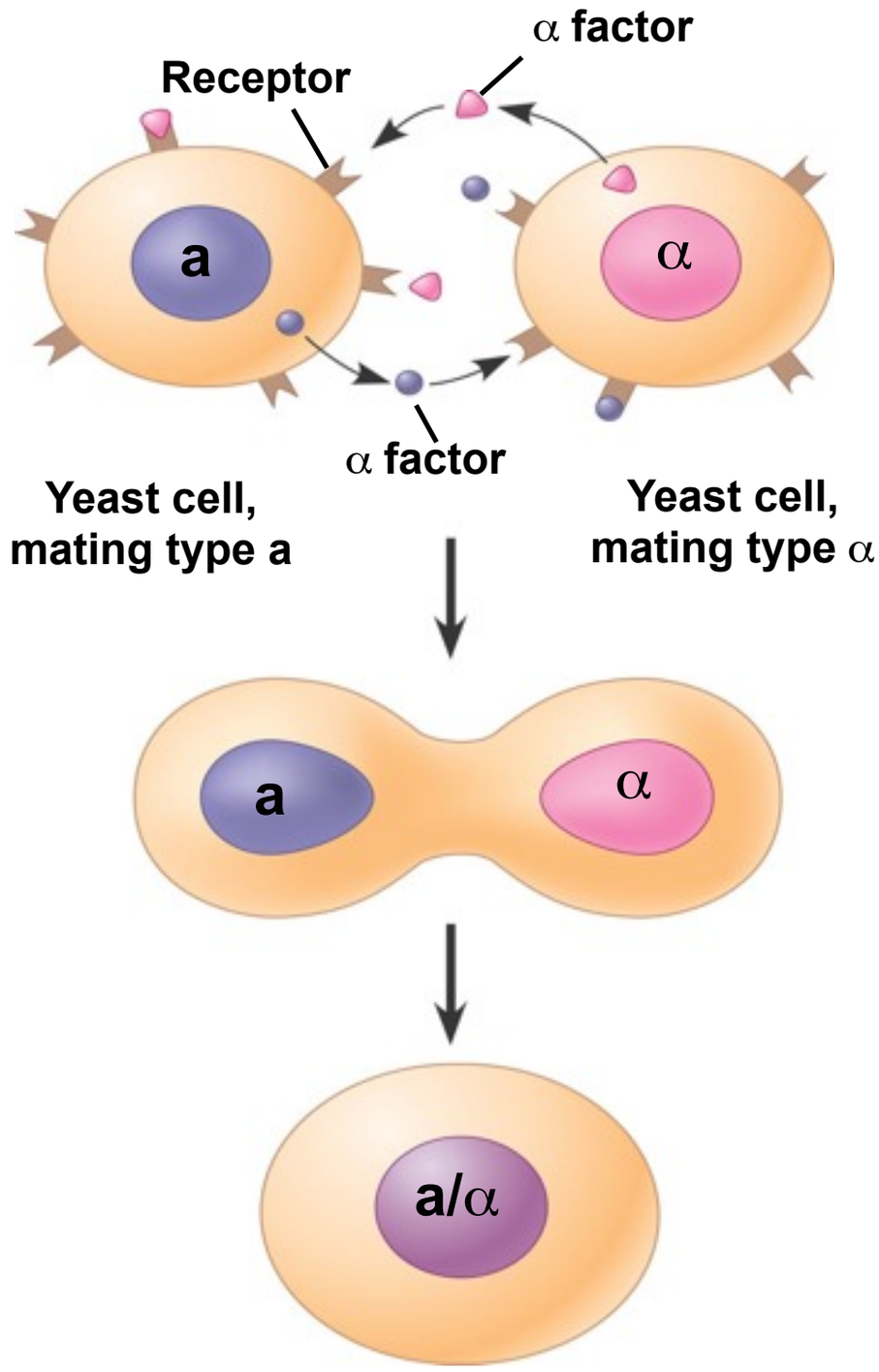
- Yeasts identify their mates through cell signaling
  - Turns out this mechanism is very similar to mechanisms in eukaryotic animal cells

The similarities in the signal transduction pathway can be explained through common ancestry, but the common ancestor of yeast and animals dates back to over a billion years ago.

1. **Exchange of mating factors.** Each cell type secretes a mating factor that binds to receptors on the other cell type.

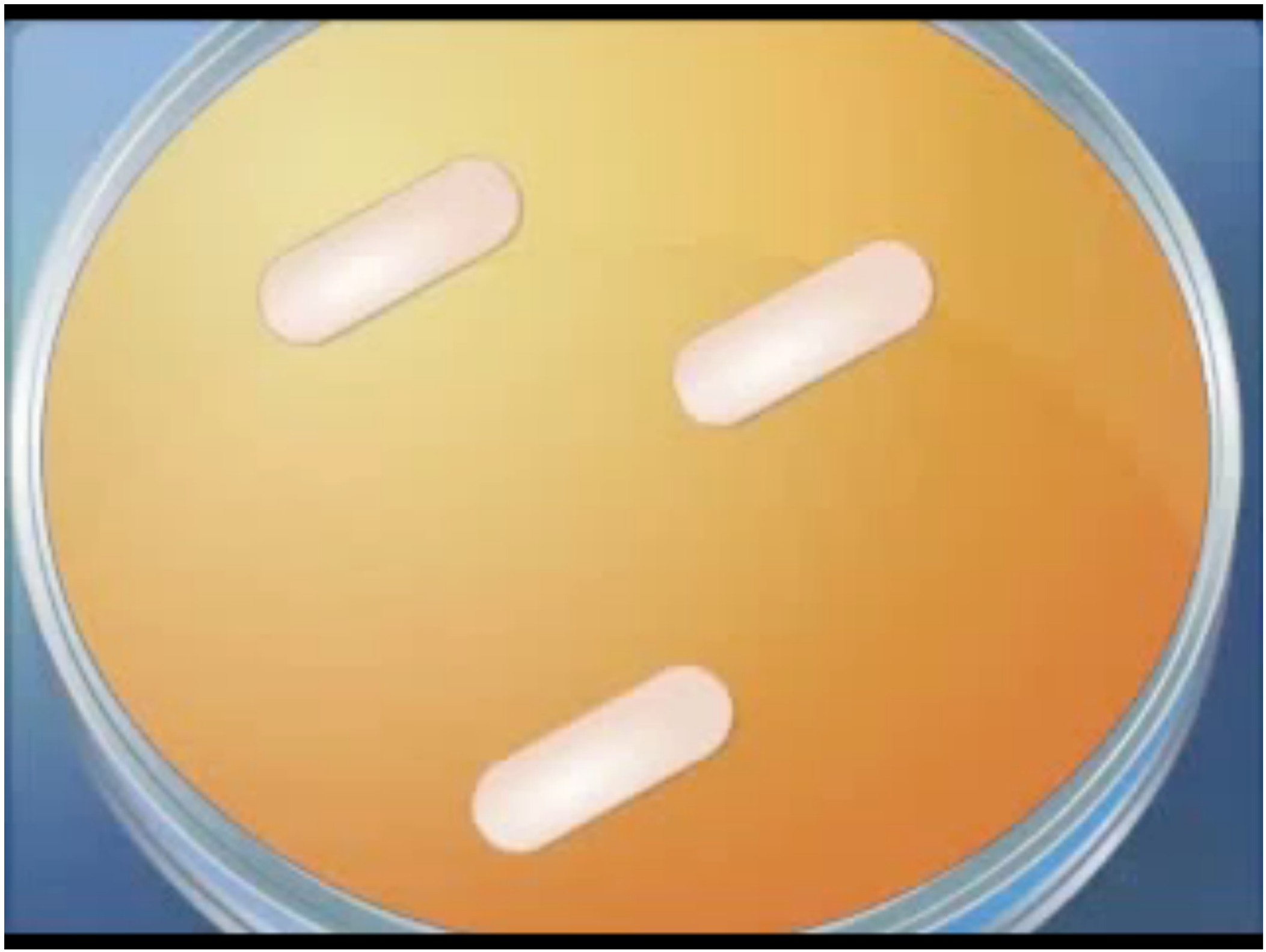
2. **Mating.** Binding of the factors to receptors induces changes in the cells that lead to their fusion.

3. **New a/α cell.** The nucleus of the fused cell includes all the genes from the a and a cells.



- Recently biologists have uncovered very similar to mechanisms between bacteria and plant cells.
  - Some evidence suggests that cell communication first evolved in ancient bacteria and then later organisms adopted these mechanisms for multicellular benefits.
  - In fact cell signaling remains important to bacteria even today.
    - *Quorum sensing*, bacteria sense chemicals signals, bacteria in turn can monitor their density, this allows bacteria to alter behavior and synchronize their actions.
      - *Biofilms*, is such an aggregation of cells where they stick to a surface and derive nutrition from it.

Quorum Sensing



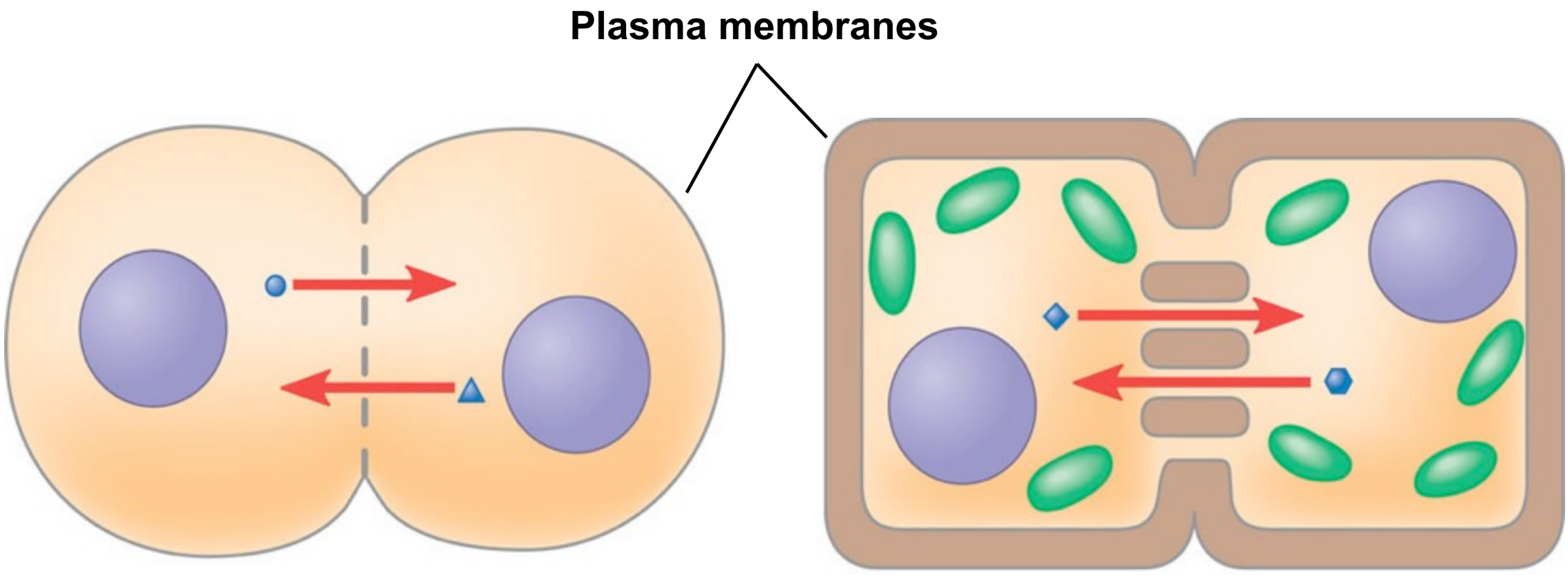
Local Signaling

- A multicellular organism is a society of specialized cells, each performing a task that is essential in maintaining homeostasis and thus keeping the organism as a whole alive.
- Like human society, communication is an inherent requirement for any society to function properly.
- Cell communication that takes place between cells that are in close physical proximity is called **local signaling.**
- ***Local Signaling can take place in one of three ways:***
  - ***1. Between Cell Junctions of two fused cells***
  - ***2. The direct contact between two cell surfaces***
  - ***3. Using chemical messages to signal many cells in a generalized area***

Local Signaling (I)

Cell junctions

Both animals and plants have cell junctions that allow molecules



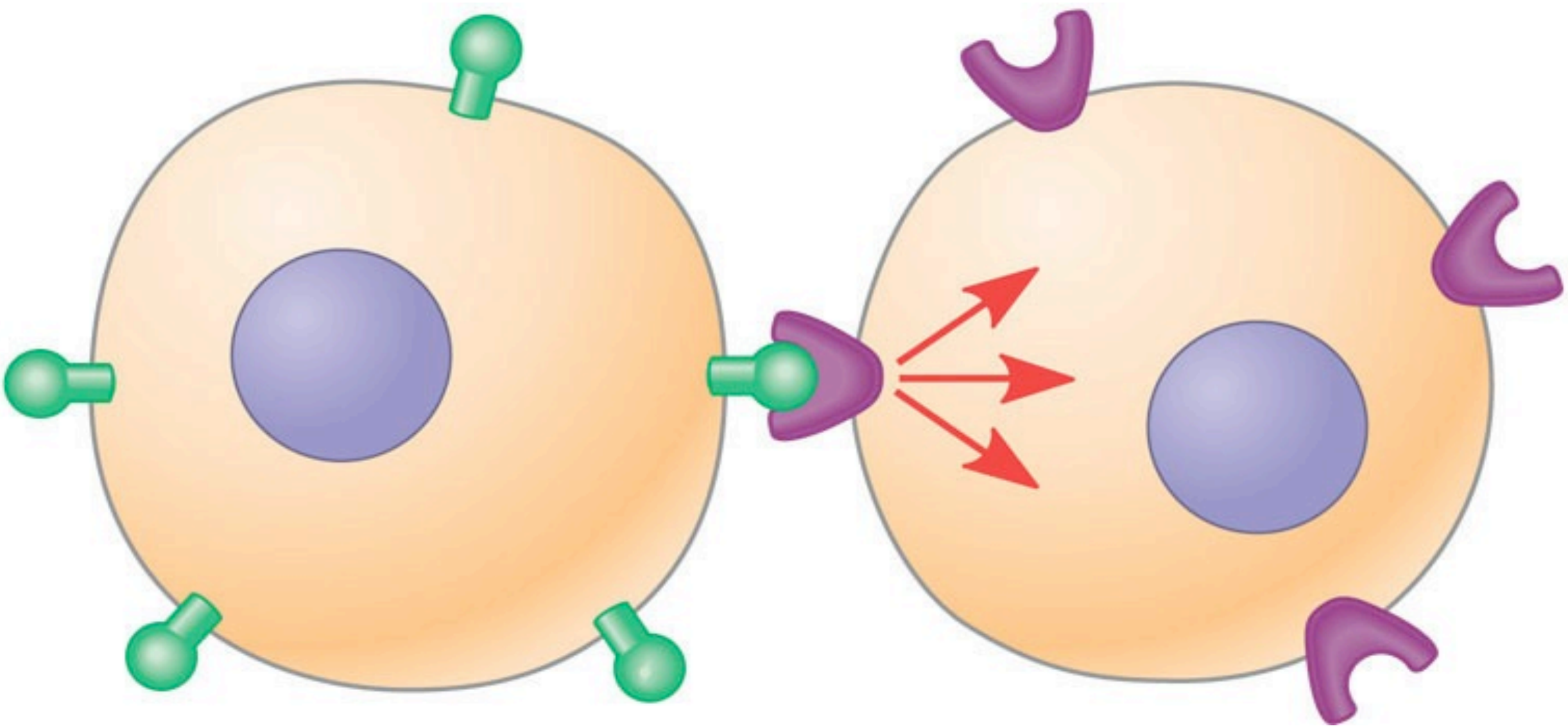
Gap junctions between animal cells

Plasmodesmata between plant cells

Local Signaling (2)

Cell-Cell recognition

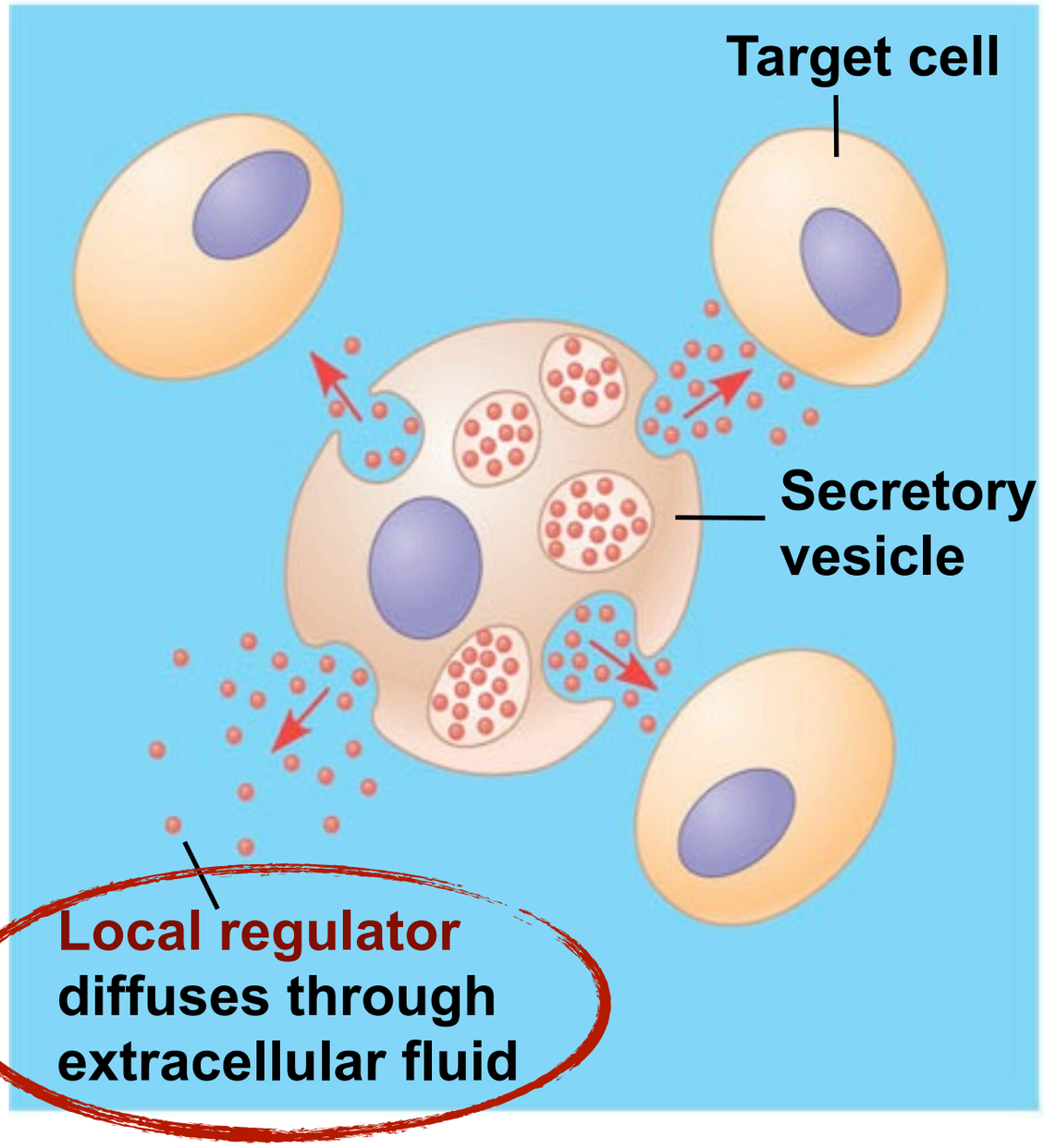
Two cells in an animal may communicate by interaction between molecules protruding from



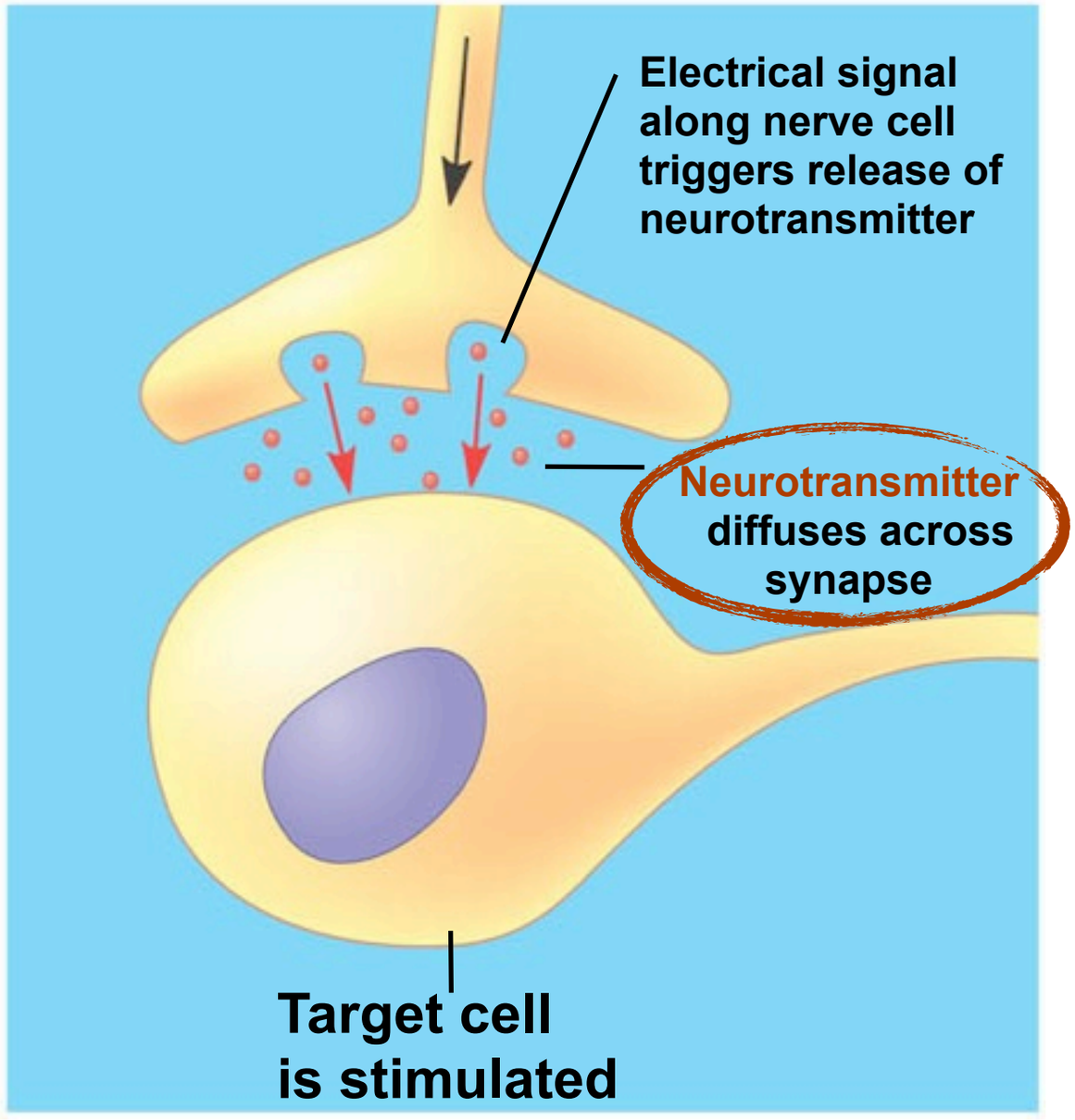
Where have we seen this before?

Answer: Cell Recognition in immune system

Local Signaling (3)



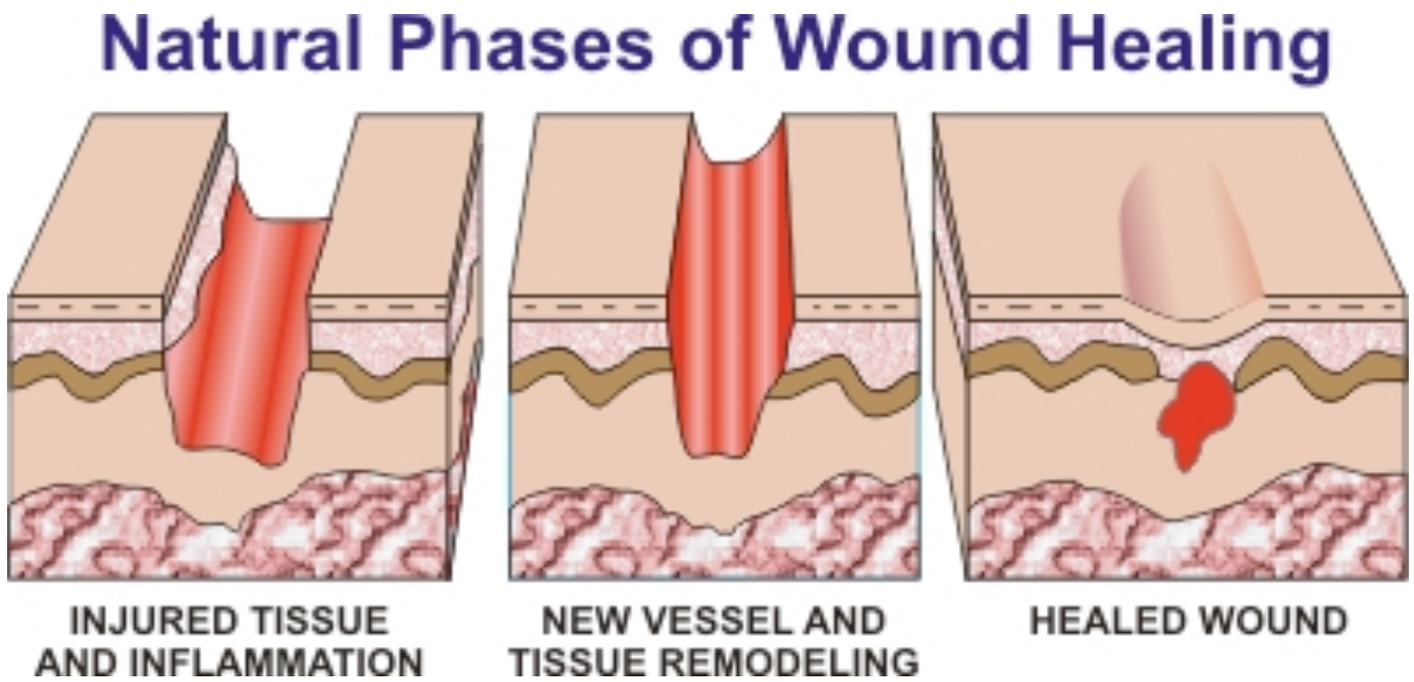
(a) Paracrine signaling. A secreting cell acts on nearby target cells by discharging molecules of a local regulator (a growth factor, for example) into the extracellular fluid.



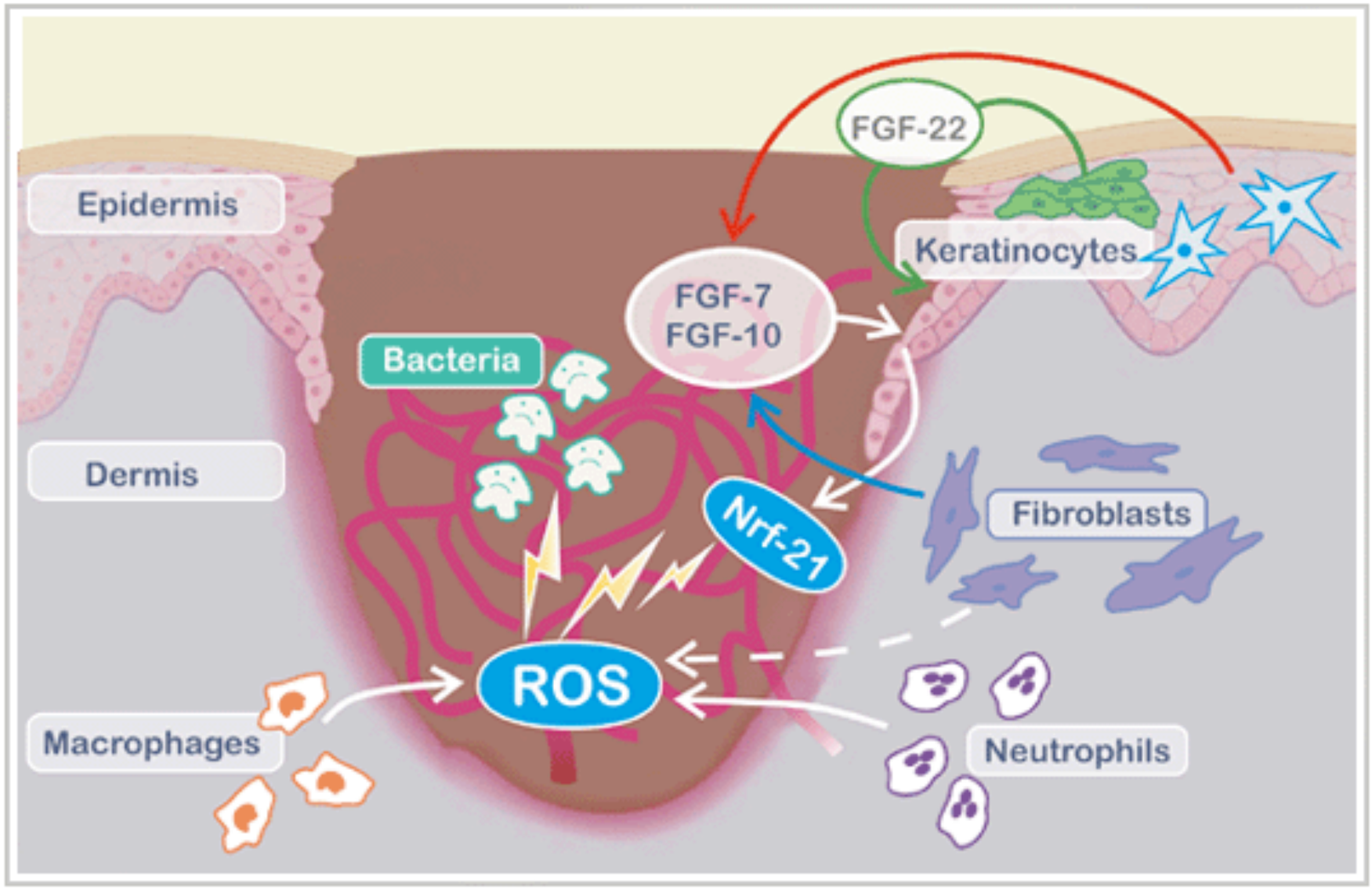
(b) Synaptic signaling. A nerve cell releases neurotransmitter molecules into a synapse, stimulating the target cell.

Local Regulators

- An example of a local regulator includes- ***growth factors***.
- Imagine a cut or a wound, after the bleeding stops the body slowly begins to repair the area and after some time the wound heals and perhaps leaves a scar as a reminder .
- The damaged cells release **growth factors** to the undamaged cells in the vicinity, communicating the need the divide and thus repair the wound.



Local Regulators



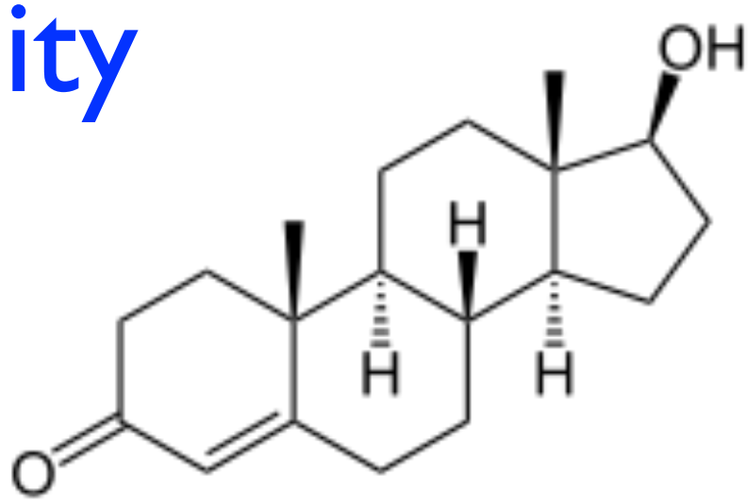
Cartoon to illustrate the functions of FGFs in a healing skin wound. Upon lesions, dermal fibroblasts (violet) and __ T cells (red) secrete FGF-7 and FGF-10; suprabasal keratinocytes (green) express FGF-22. In a paracrine (blue and red arrows) or autocrine manner (green arrow), respectively, they activate keratinocytes at the wound edge and stimulate reepithelialization. In addition, they induce the expression of cytoprotective genes in keratinocytes, including the gene that encodes the Nrf2 transcription factor. Nrf2 then regulates the expression of proteins involved in the detoxification of ROS (Reactive Oxygen Species). The latter are produced in large amounts by neutrophils and macrophages as a defense against invading bacteria.

Long Distance Signaling

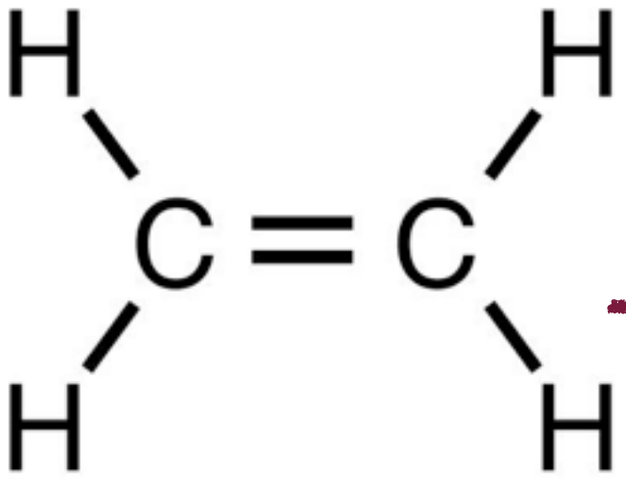
- Chemical signals that travel longer distances are known as **hormones** or **plant growth regulators**
  - Hormones are found in both animals and plants respectively
  - They travel in vessels or in some cases through the air
  - They can be water soluble or fat soluble
  - They vary greatly in size

Hormone Diversity

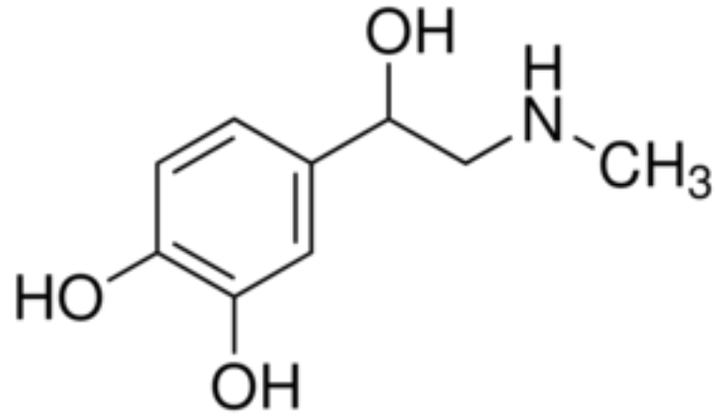
Insulin
-very large



Testosterone
-lipid soluble



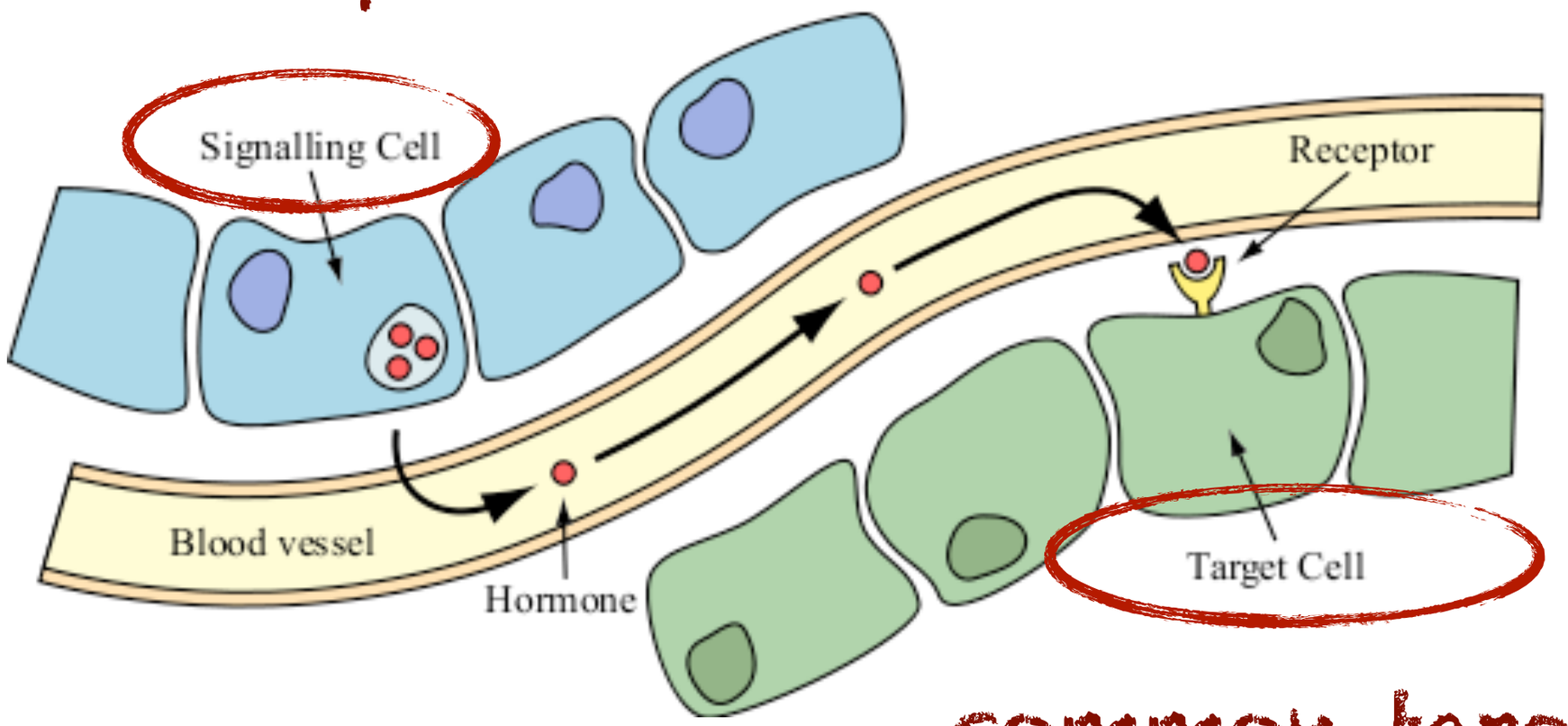
Ethylene
-very small



Epinephrine
-water soluble

Long Distance Signaling

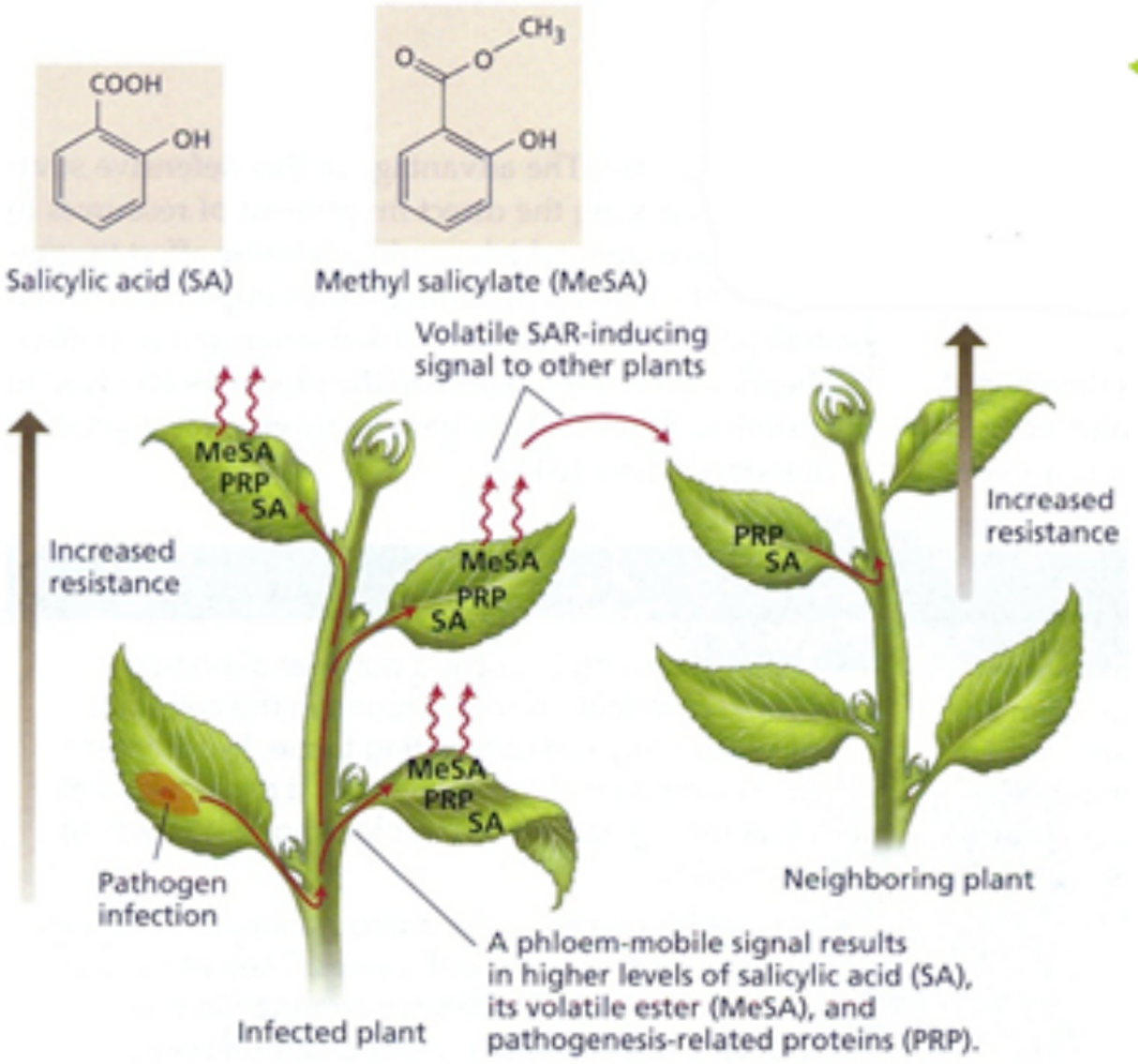
common signaling cells
make up glands

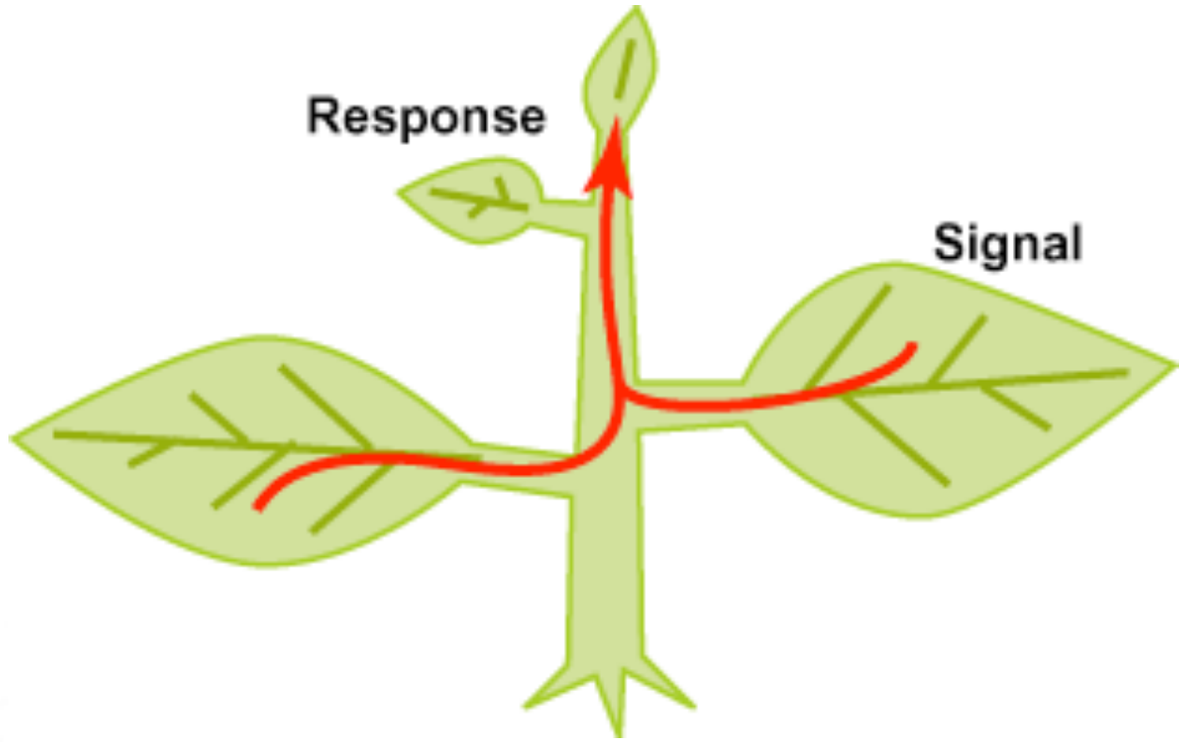


common target cells
include glands,
muscles and
neurons

Long Distance Signaling

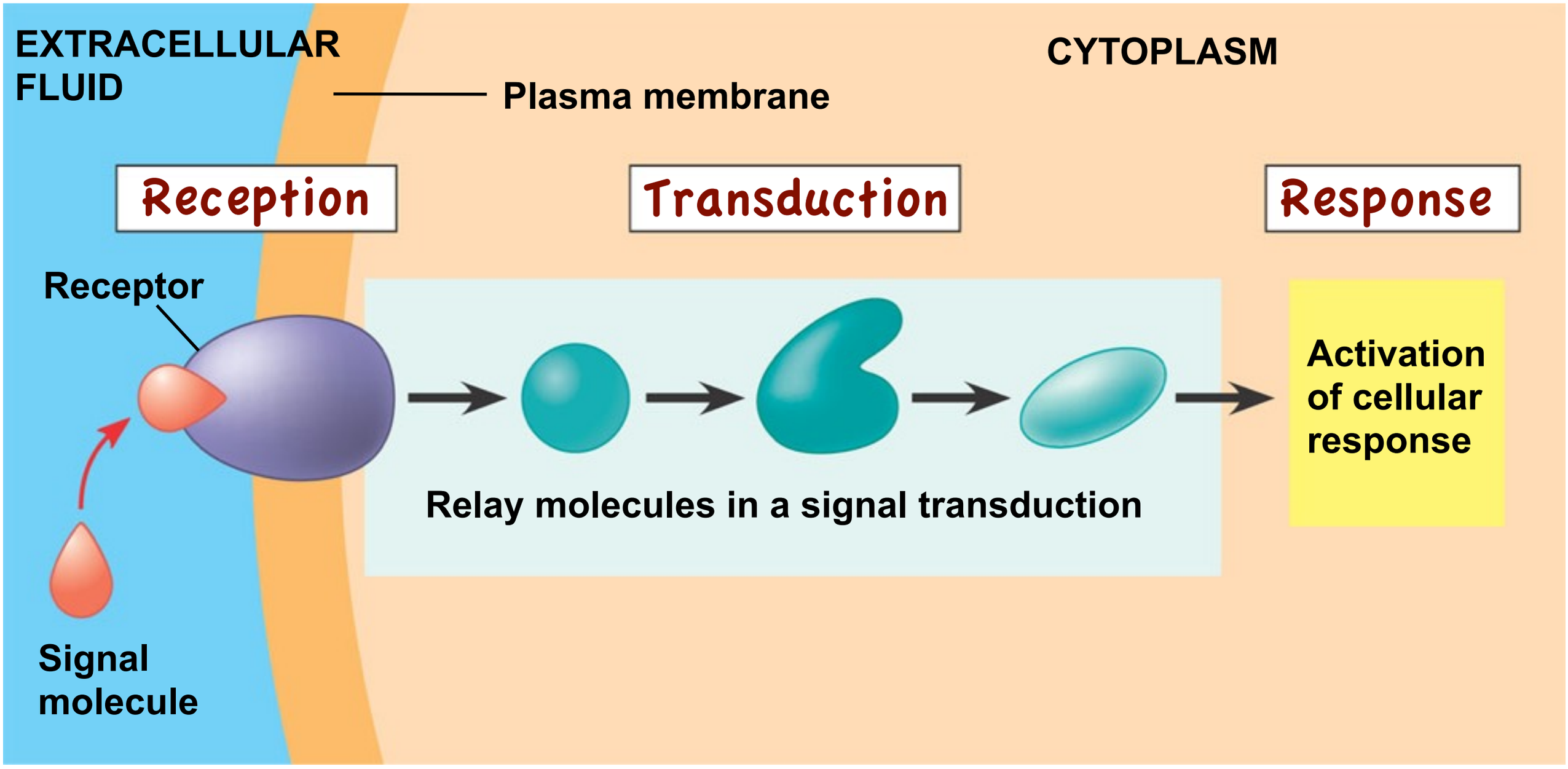
between plants





within a plant itself

Overview of Cell Signaling

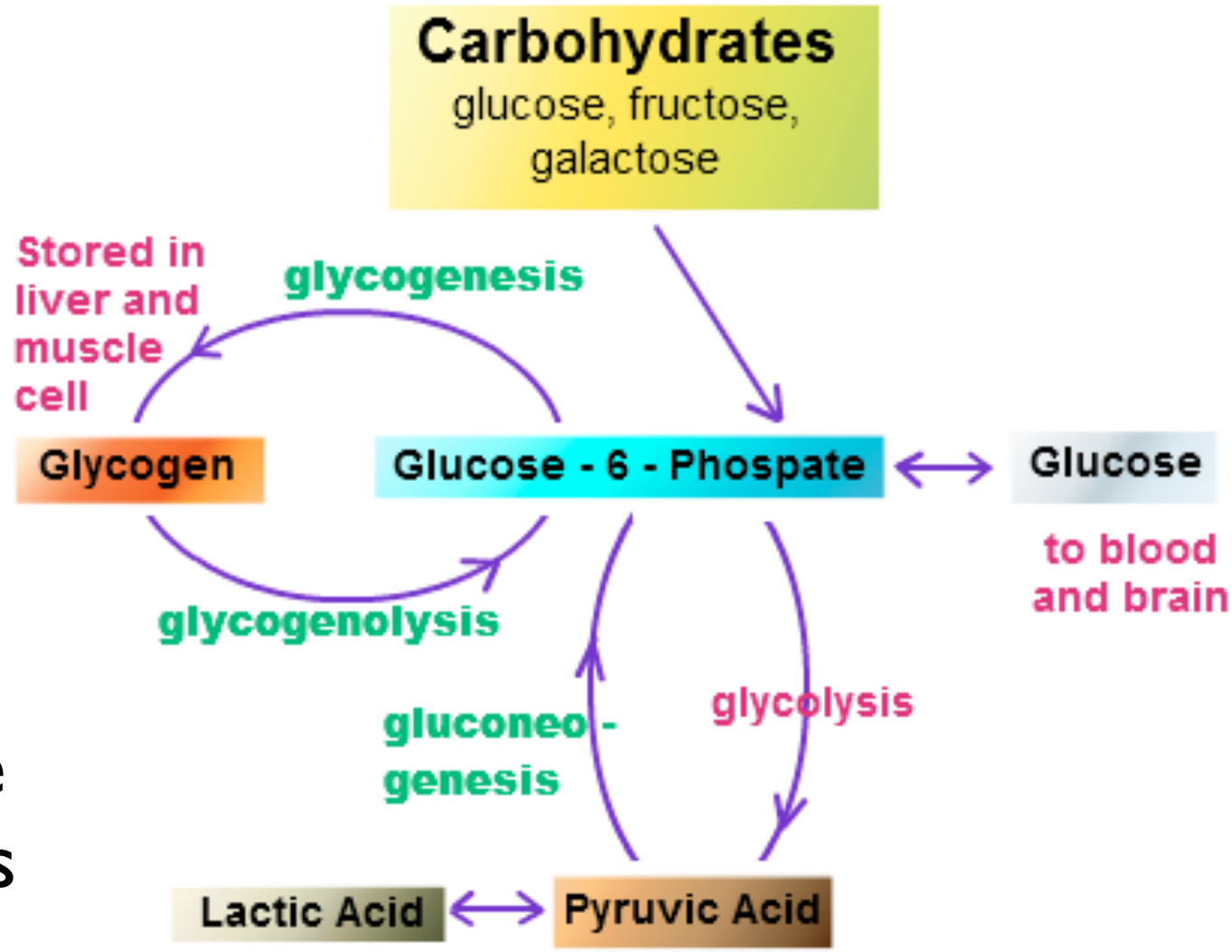


Earl W. Sutherland- Nobel Prize 1971

- Was a major contributor in our understanding of cell communication.

- Investigated how epinephrine stimulates liver and muscle cells to breakdown glycogen

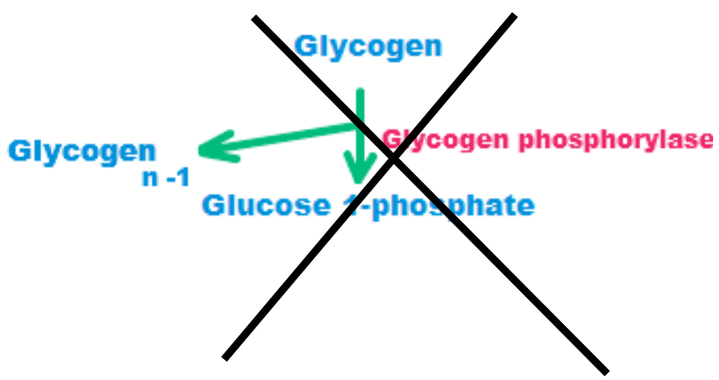
- The breakdown of glycogen releases simple sugars which the cells themselves use to produce ATP or these simple sugars may be released into the blood stream to feed other cells

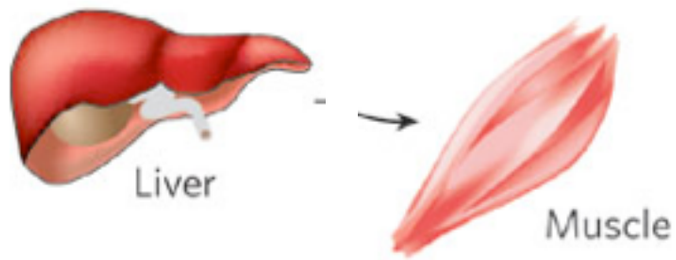


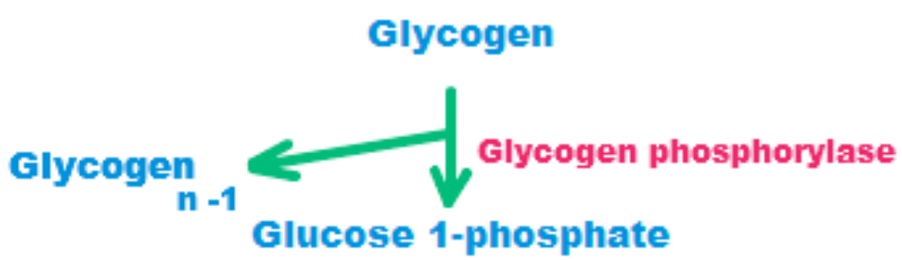
Earl W. Sutherland- Experiment

- Sutherland discovered that epinephrine stimulates glycogen breakdown by somehow activating glycogen-phosphorylase.

Epinephrine + Glycogen + Glycogen-phosphorylase







Conclusions

1. epinephrine does not interact directly with the catabolic enzyme, must be intermediates

2. the plasma membrane is somehow involved in transmitting the signal

Overview of Cell Signaling

Reception

- The target cell's detection of the signal *(ligand- chemical messenger)*
- The signal is detected by receptors, each specific to the signal
- The receptors are either located on the cell's surface or inside the cell.

Overview of Cell Signaling

Transduction

- Molecular conversions that lead to a cellular response
  - The binding of signal molecules to receptors changes the shape of the receptor and starts the transduction pathway
  - Transduction continues with series of molecular interactions where each interacting molecule is either activated or deactivated by another
  - The last molecule in the pathway leads to a cellular response.

Overview of Cell Signaling

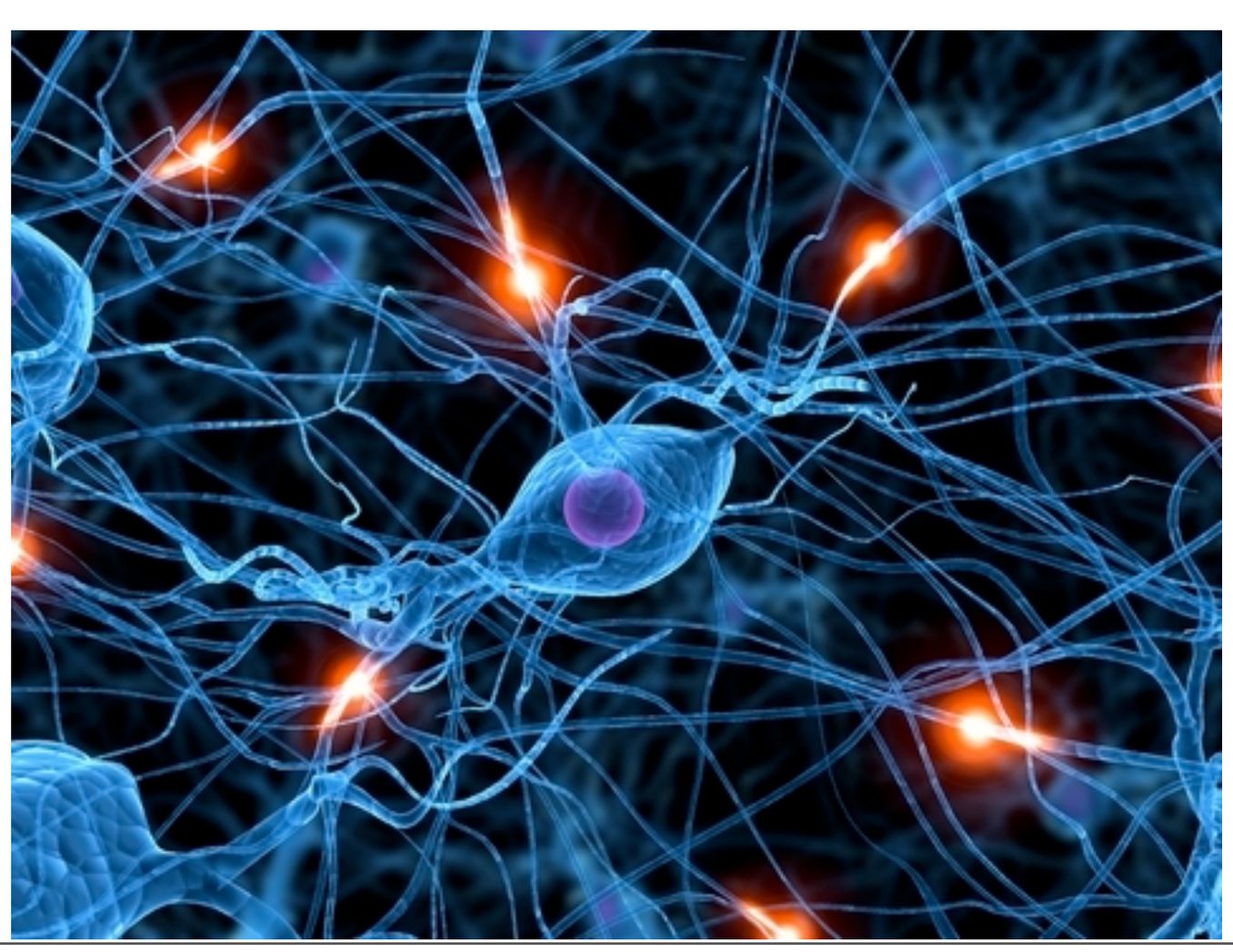
Response

- Cellular responses can include any cellular activity
  - activating/deactivating genes, activating/deactivating enzymes, rearranging the cytoskeleton, exportation of molecules, etc
  - **Cell Communication ensures that crucial activities in cells occur at the right time, the right place and in proper coordination with the activities of other cells in the organism.**

Cell Communication

II.

Main Idea: All cell communication requires a signal and something that can receive or detect the signal .



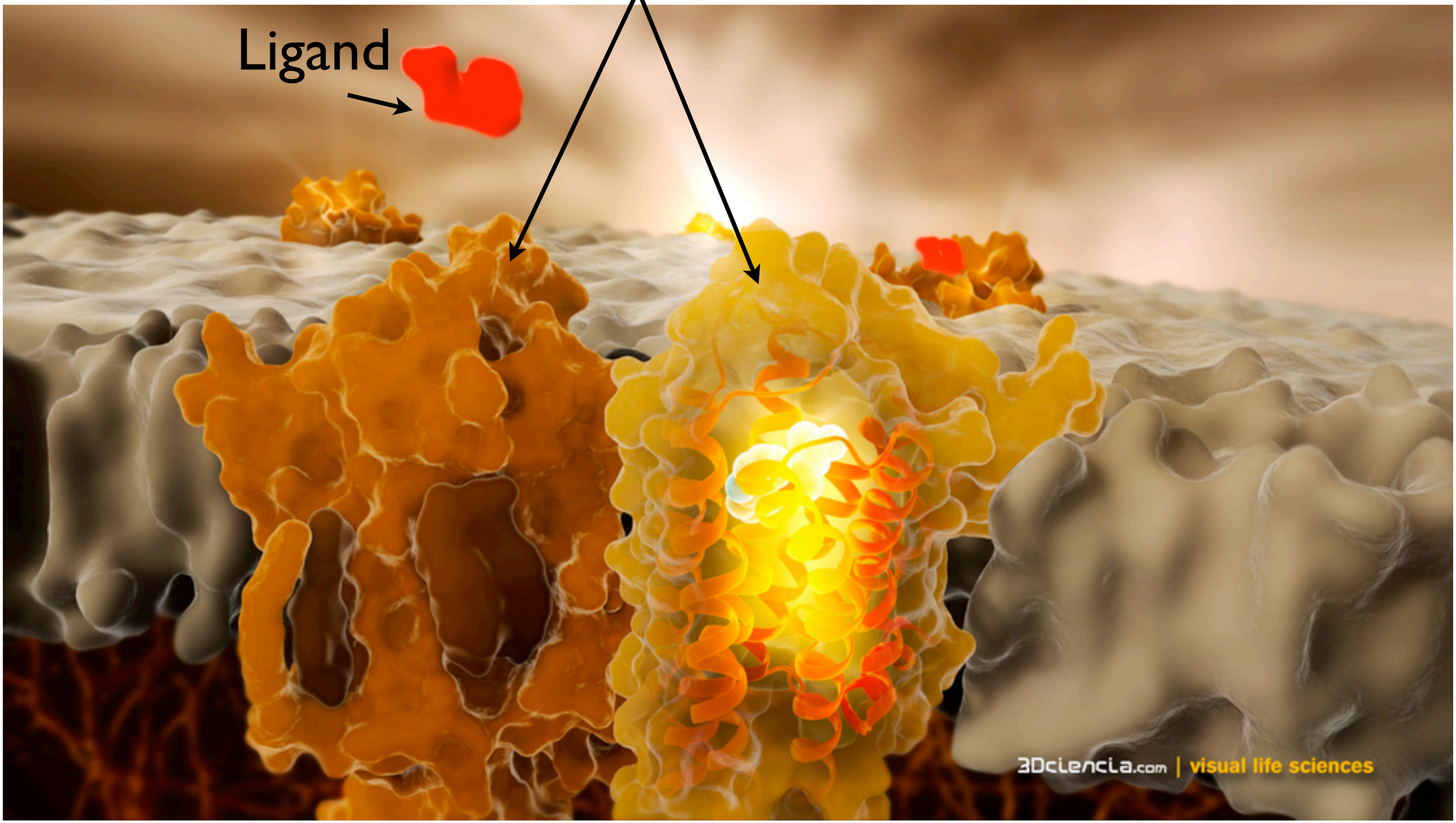
Step 1: Reception

- Ligands (signal molecules) move randomly throughout the body
- Ligands will therefore contact many cells
- However, only some cells detect this signal and consequently respond
    - Every ligand has a complimentary receptor, usually a protein whose shape allows it to bind with the ligand like a puzzle piece
- The binding of ligand-to-receptor is the beginning of the cell communication mechanism
    - The receptors are generally found in one of two places
        - the plasma membrane or un the cytosol

Receptors in the Plasma Membrane

- Plasma membrane receptors bind water soluble ligands.
- Water soluble signals can not pass freely through the plasma membrane
    - recall the characteristics of molecules that pass freely through membranes
- The receptors that bind water soluble signals are transmembrane receptors (they span the entire membrane from inside to outside)
- The ligand binds to the exposed outside portion of the membrane, the binding changes the shape of the internal portion of the membrane, which in turn leads to the next step in cell communication...transduction

Transmembrane Proteins (receptors)



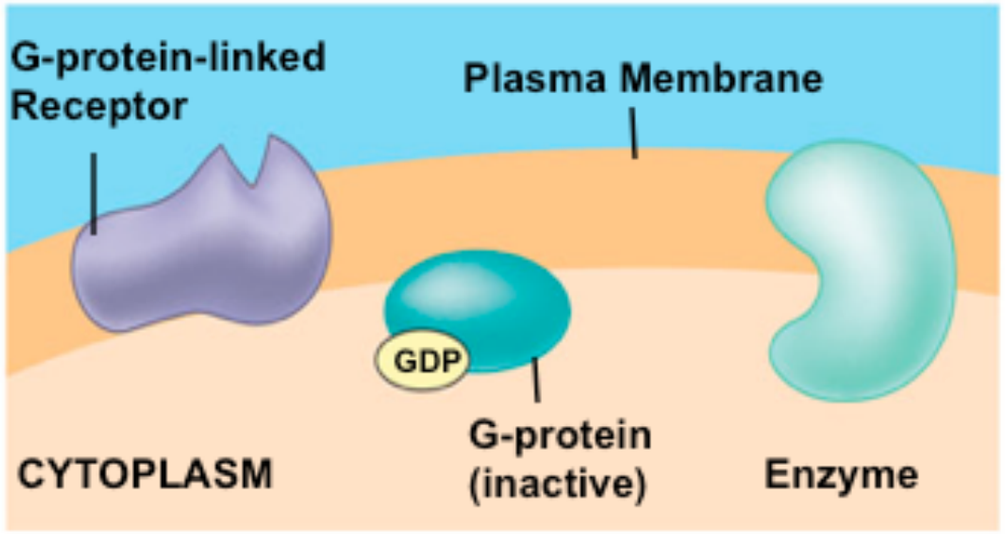
Hydrophobic amino acids make up the core of the polypeptide

Hydrophilic amino acids make up the internal and external portions of the polypeptide

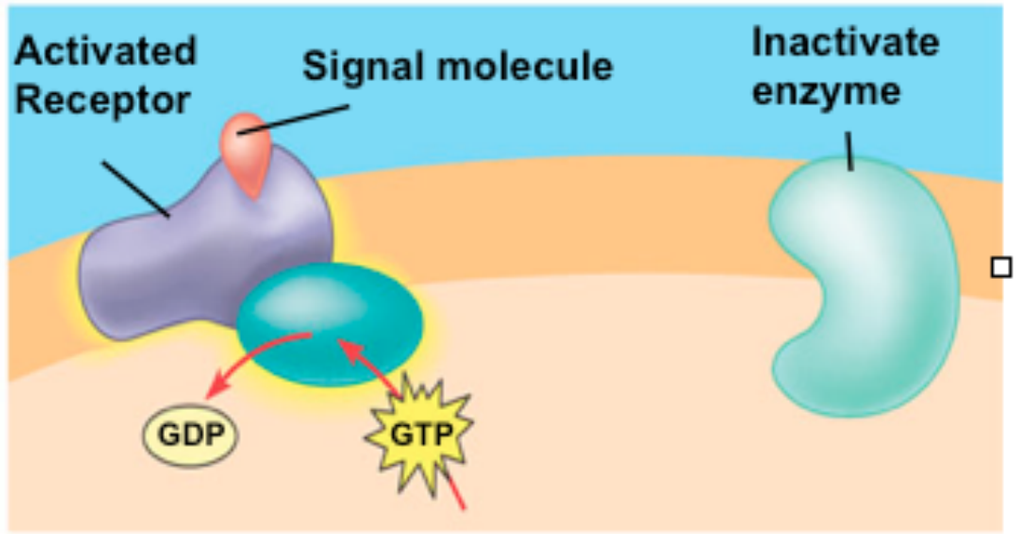
Receptors in the Plasma Membrane

- Plasma membrane receptors play crucial roles in biological systems.
- It should come as no surprise to find out that many diseases are associated with malfunctions of these receptors.
- It should also come as no surprise to find out that many drugs (up to 60%) developed by pharmaceutical companies target these same receptors.
- To better understand the role(s) of membrane receptors we will look at three different classes of membrane receptors
  - **G-Protein Coupled Receptors (GPCR)**
  - **Receptor Tyrosine-Kinase (RTKs)**
  - **Ion Channel Receptors**

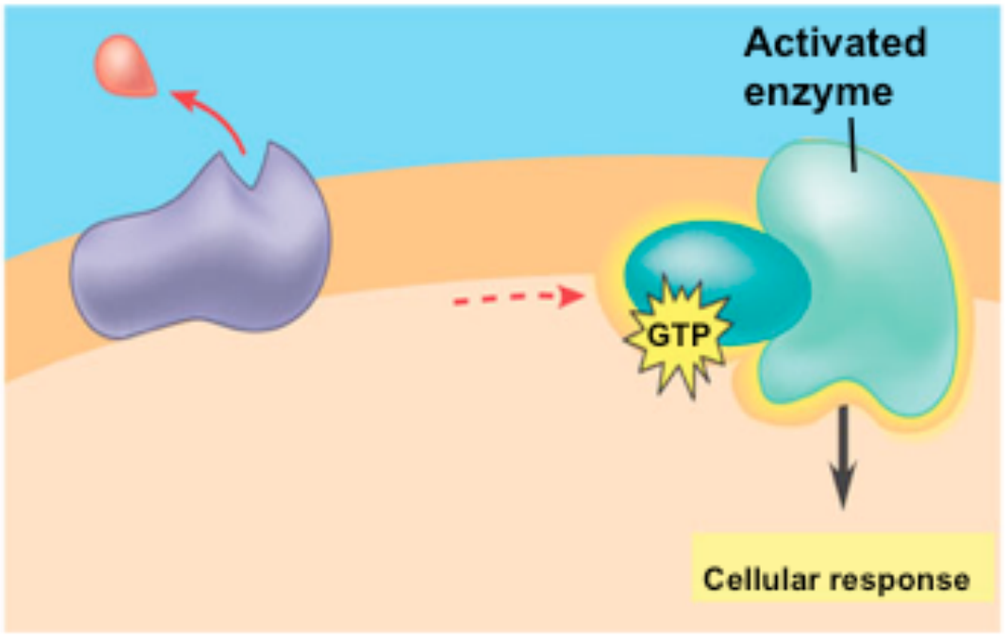
G Protein-Coupled Receptors



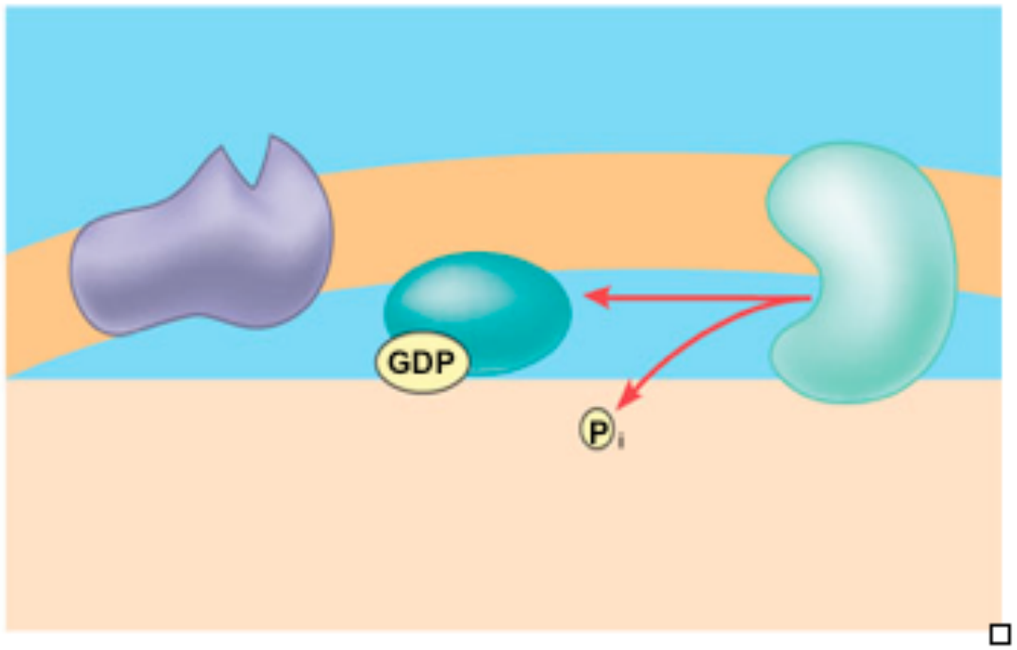
1. Attached to cytoplasmic side, the G protein acts as an on/off switch
2. if GDP is bound = G protein is off
3. if GTP is bound = G protein is on



1. Ligand binds receptor,
2. receptor changes shape,
3. altered shape in turns replaces GDP with GTP,
4. activates G protein



1. Activated G protein releases from receptor,
2. moves along membrane
3. binds to another molecule (ie enzyme),
4. the binding in turn activates the enzyme

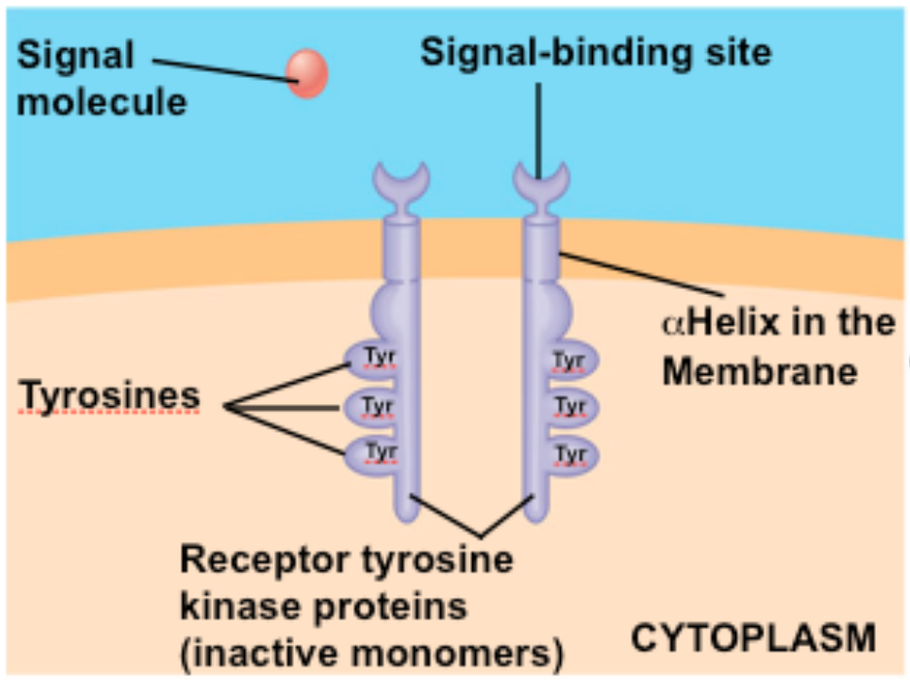


1. All activated forms are temporary,
2. they fall back to the inactive state, wait to be activated again,
3. a higher concentration of ligand results in more activations and thus a larger response

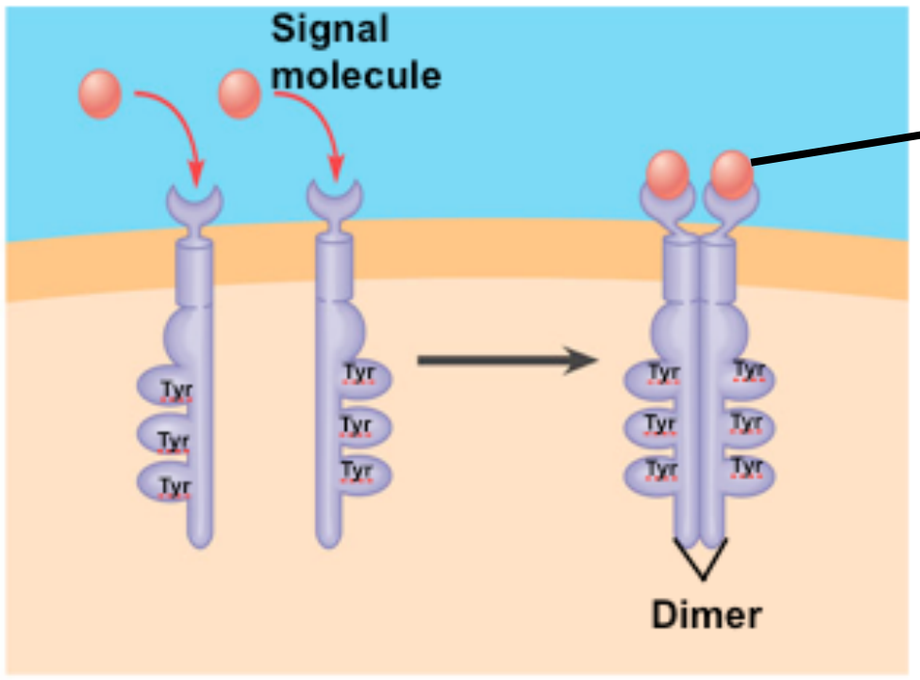
G Protein-Coupled Receptors

G Protein-Cholera Toxin Mode of Action

Receptor Tyrosine Kinases

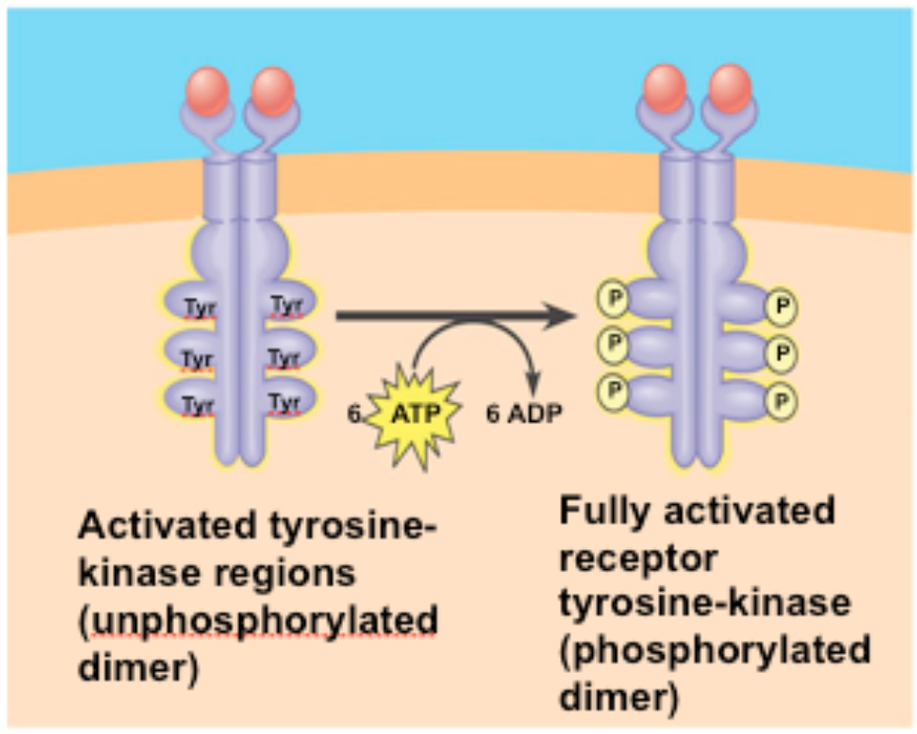


1. Receptors are separate in the inactive state

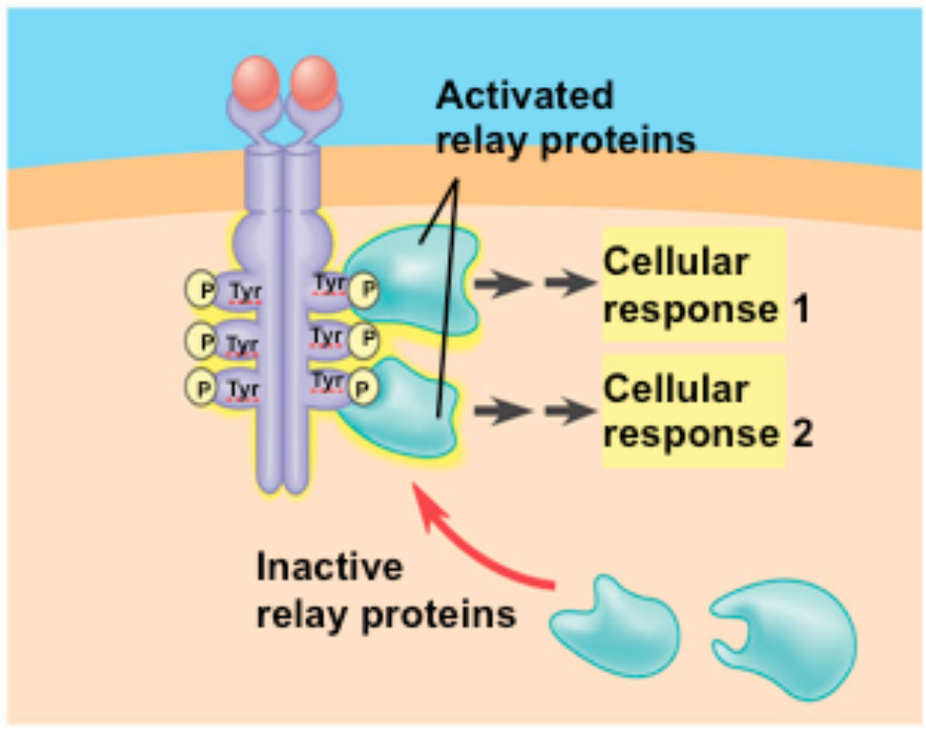


often growth factors

1. Binding of signal cause the formation of a dimer, the active form

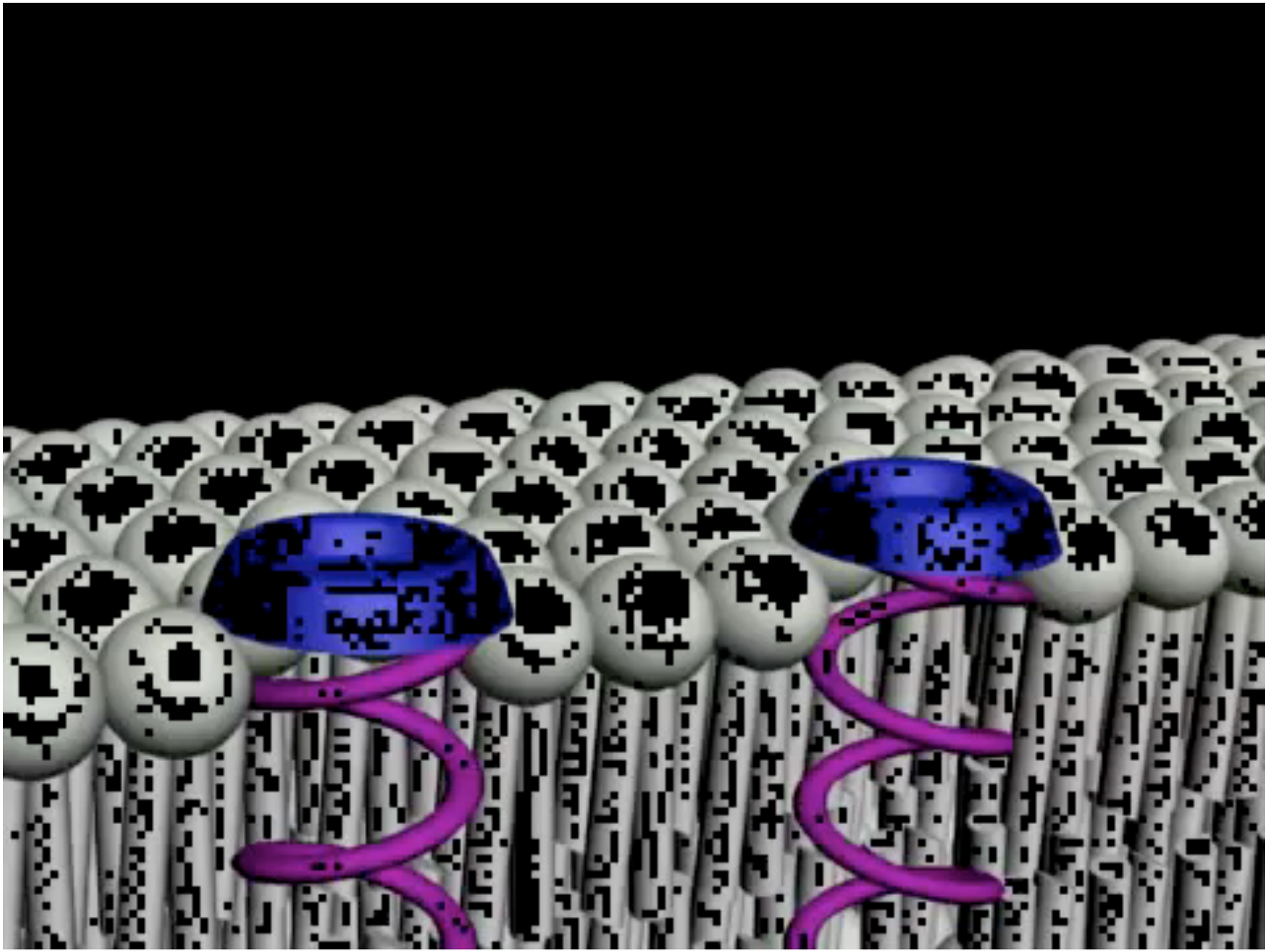


1. Each Tyrosine Kinase adds a phosphate to a tyrosine



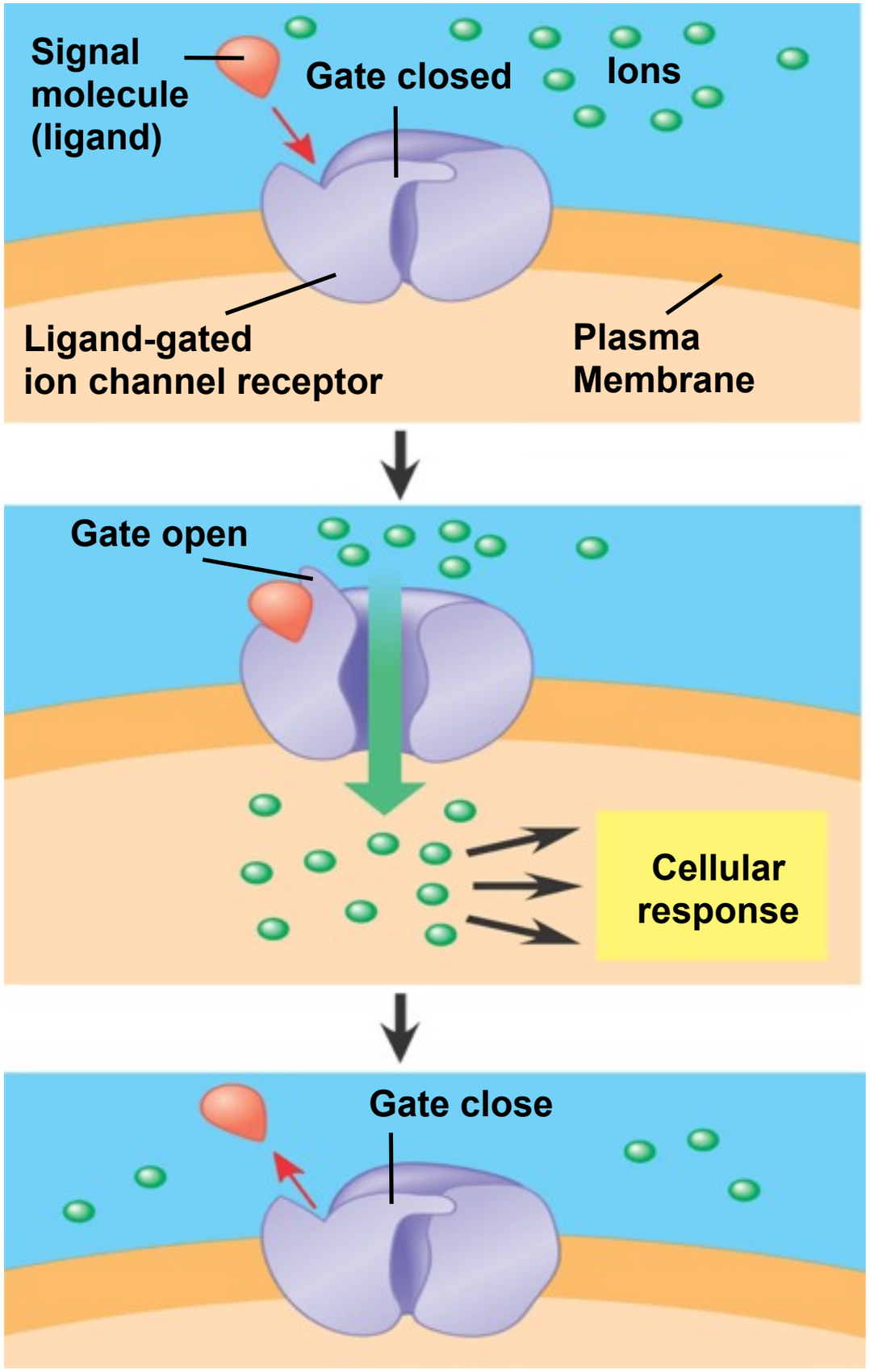
1. Each activated Tyrosine Kinase can activate a different relay protein

Receptor Tyrosine Kinases



Ion Channel Receptors

1. **Ligand gated ion channels are closed until a ligand binds**
2. **Ligand gated ion channels are specific to certain ions**

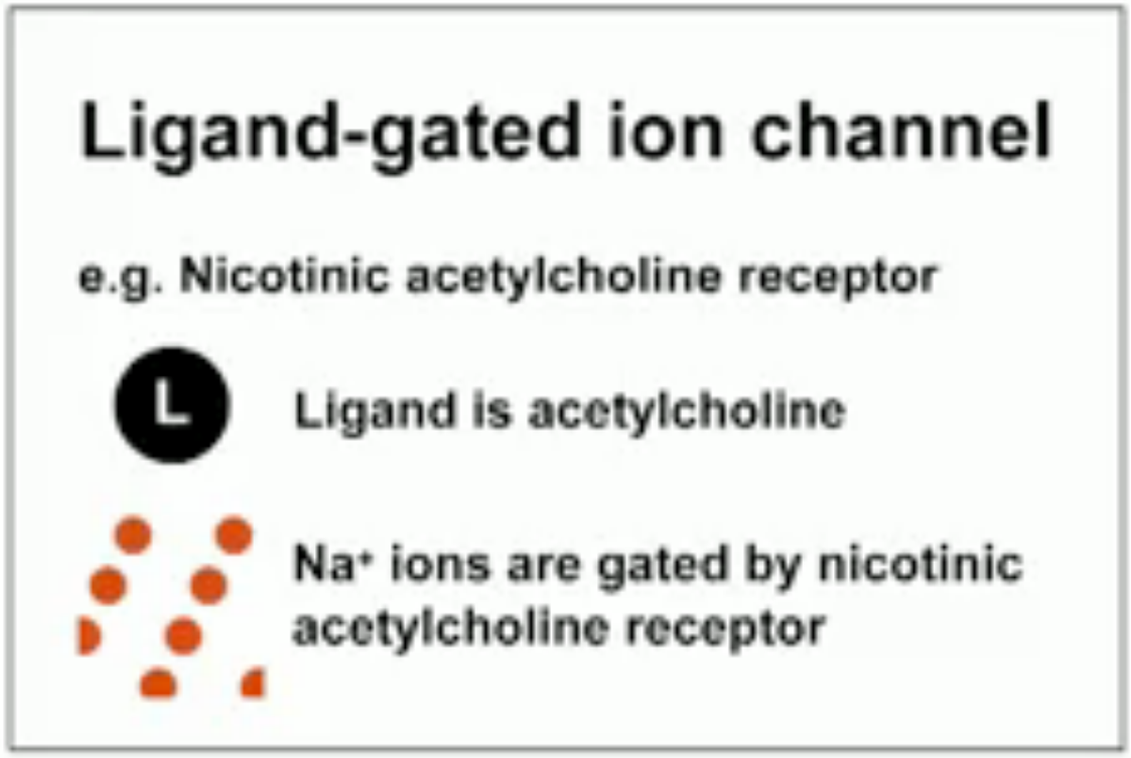


1. **Ligand gated ion channels open when a ligand binds**
2. **Ions move passively down their electrochemical gradients**

1. **Ligands bind temporarily, when they fall off the ion channel closes**

Ion Channel Receptors

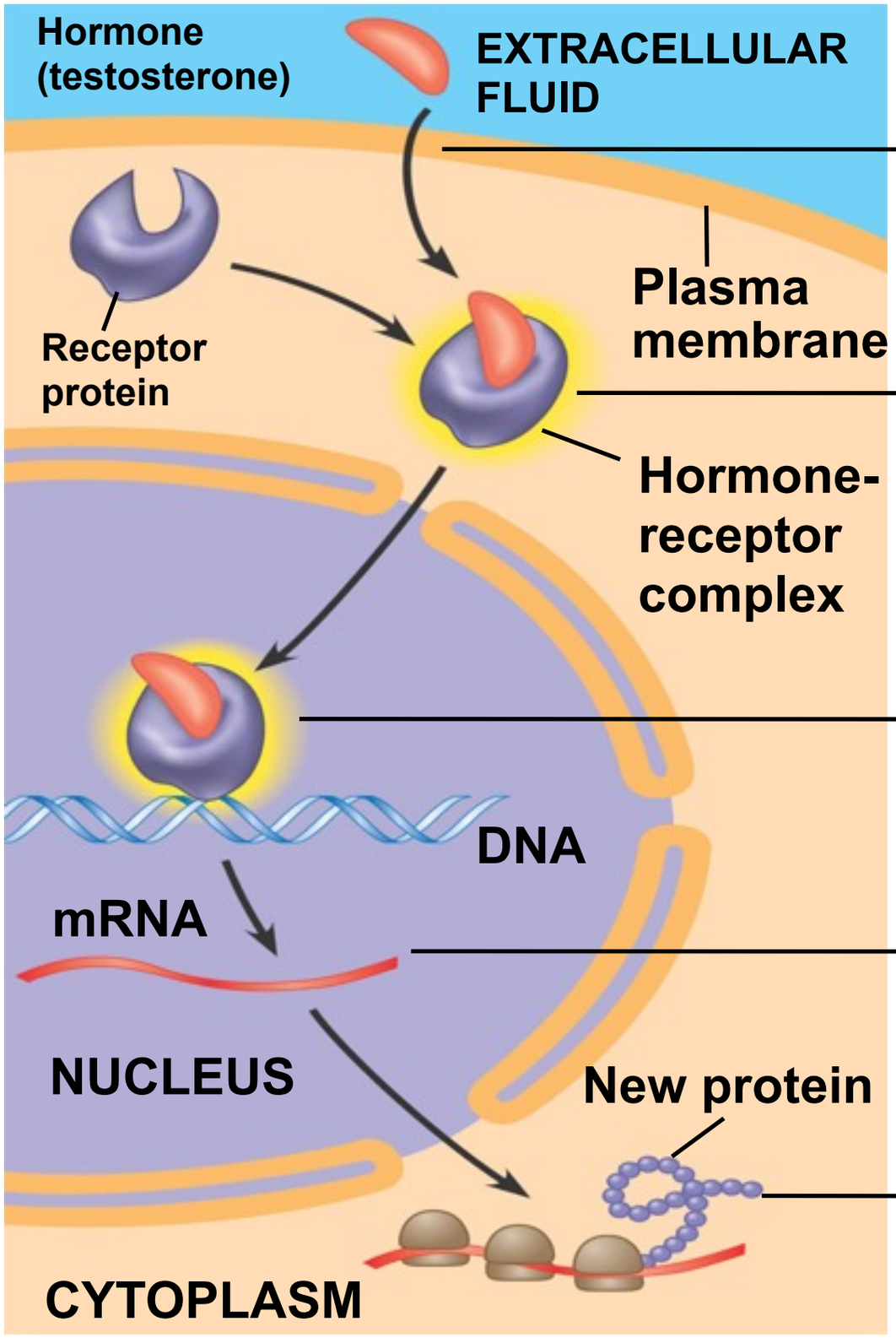
Ligand gated ion channel - structure and function



Intracellular Receptors

- Located in cytosol or nucleus
- Ligand must be able to pass through membrane
  - small (nitric oxide gas) and/or hydrophobic (steroids)
- The cell must have the receptor for the ligand or can not respond to the signal
- These lipid soluble signals often work by turning genes on/off
  - their receptors are often *transcription factors*, special proteins that control gene expression
  - many of these intracellular receptors / transcription factors are very similar in structure which suggests evolutionary kinship

Intracellular Receptors



The steroid hormone testosterone passes through the plasma membrane.

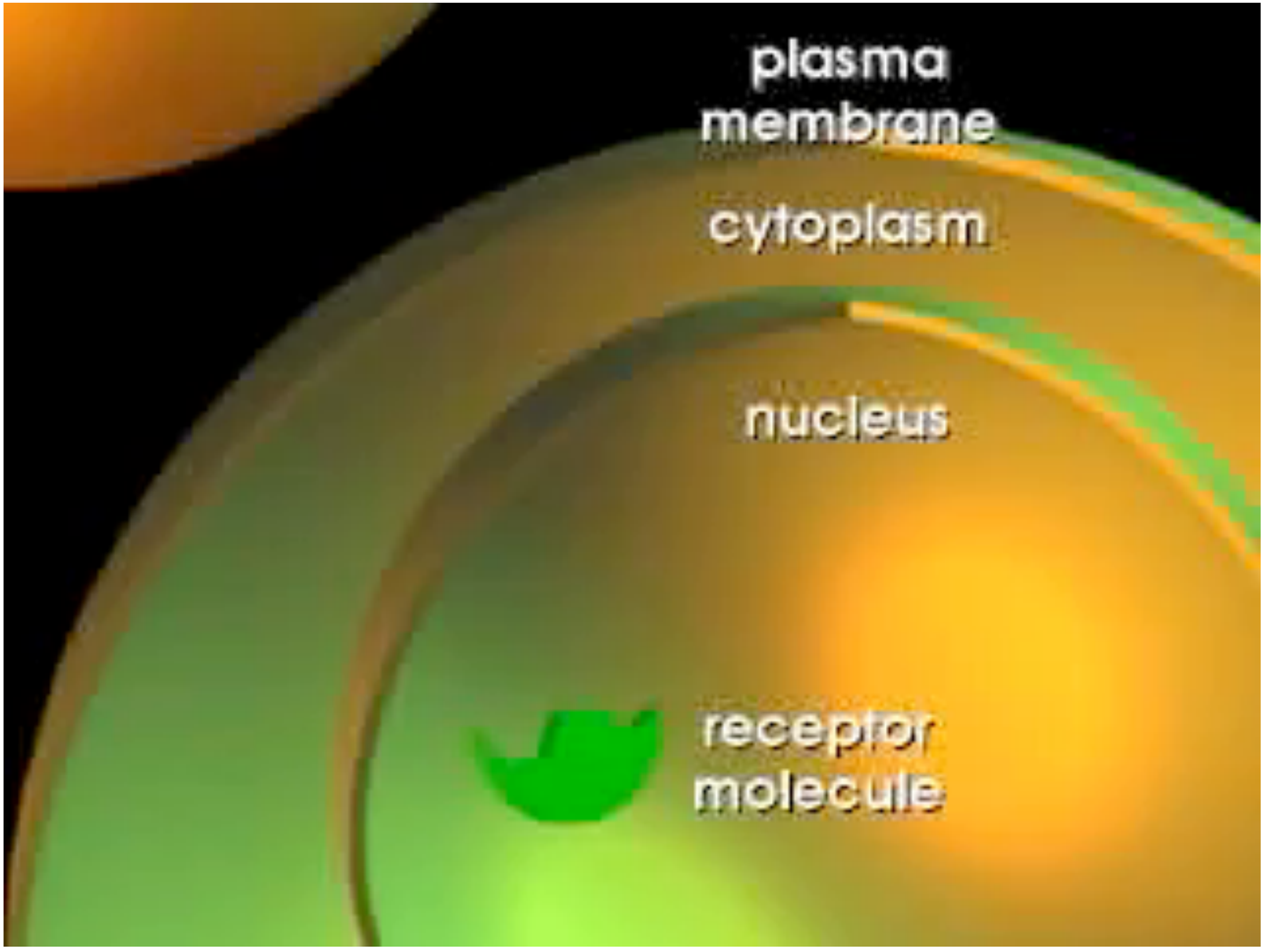
Testosterone binds to a receptor protein in the cytoplasm, activating it.

The hormone-receptor complex enters the nucleus and binds to specific genes.

The bound protein stimulates the transcription of the gene into mRNA.

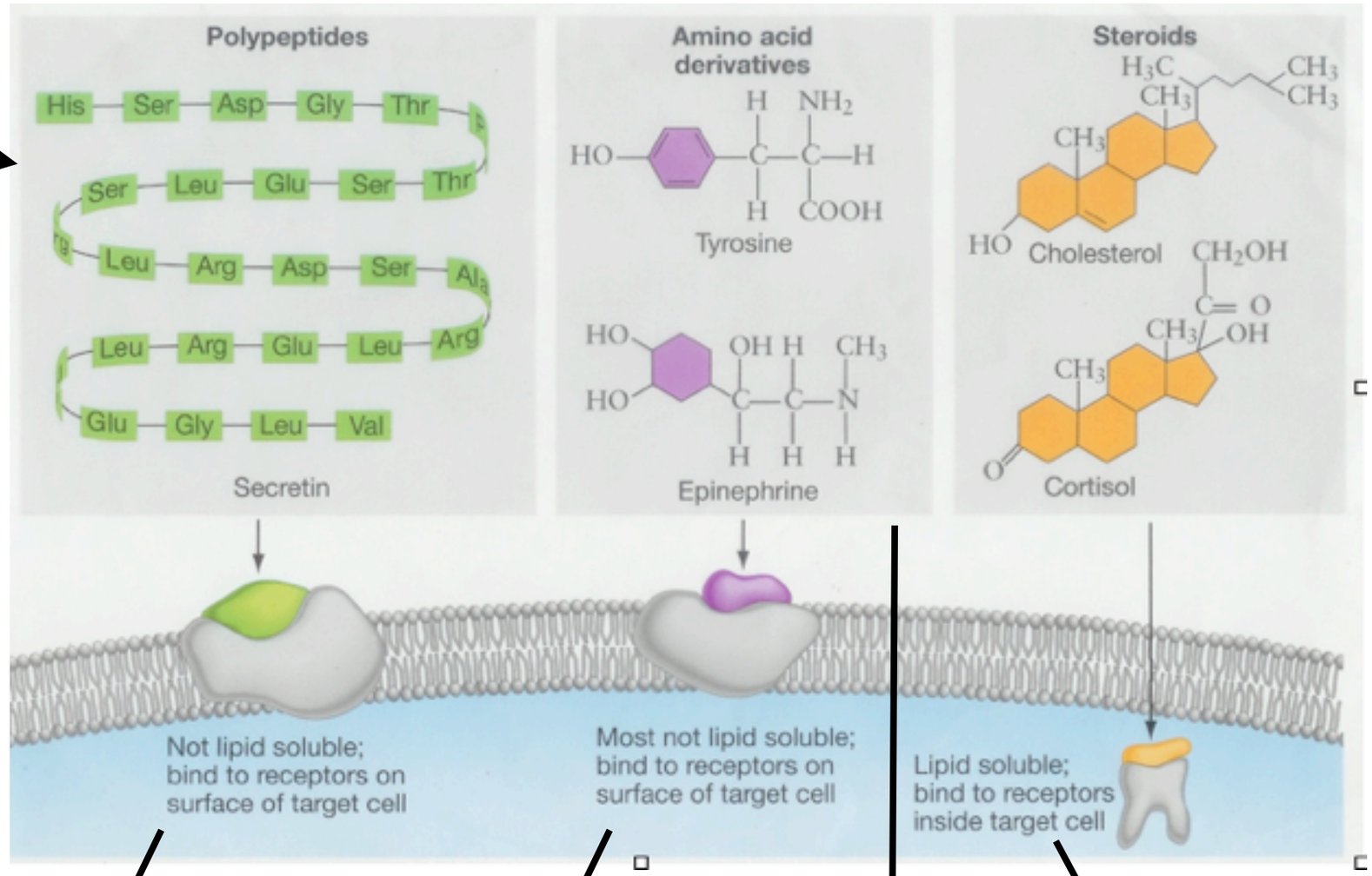
The mRNA is translated into a specific protein.

Intracellular Receptors



The Bakery Analogy

The Customer →



The Bakery →

Usually turns proteins already present in the cell on or off

"Selecting bakery items already made from the display case"

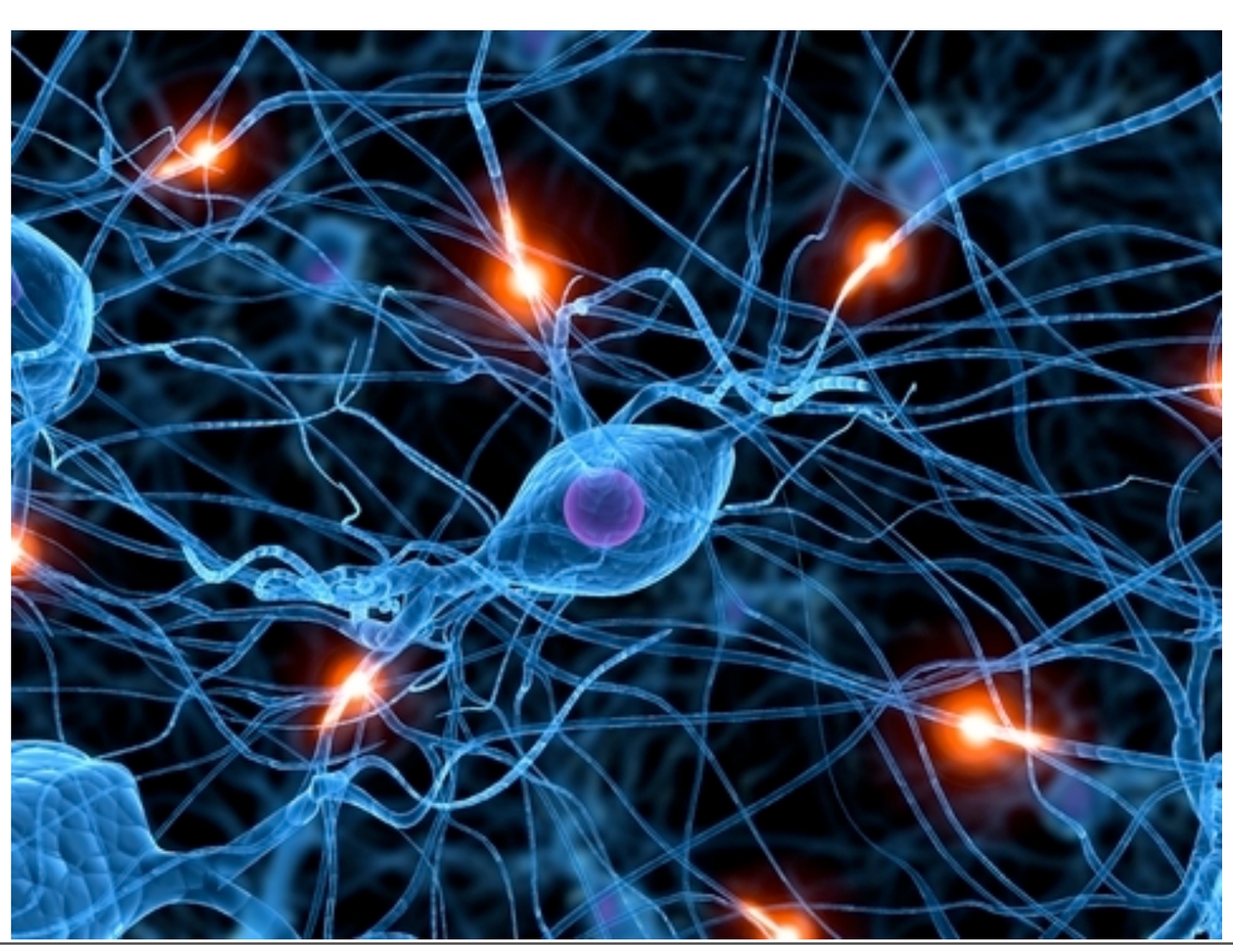
Usually turns genes on or off to effect the production of proteins

"Ordering special bakery that need to be made"

Cell Communication

III.

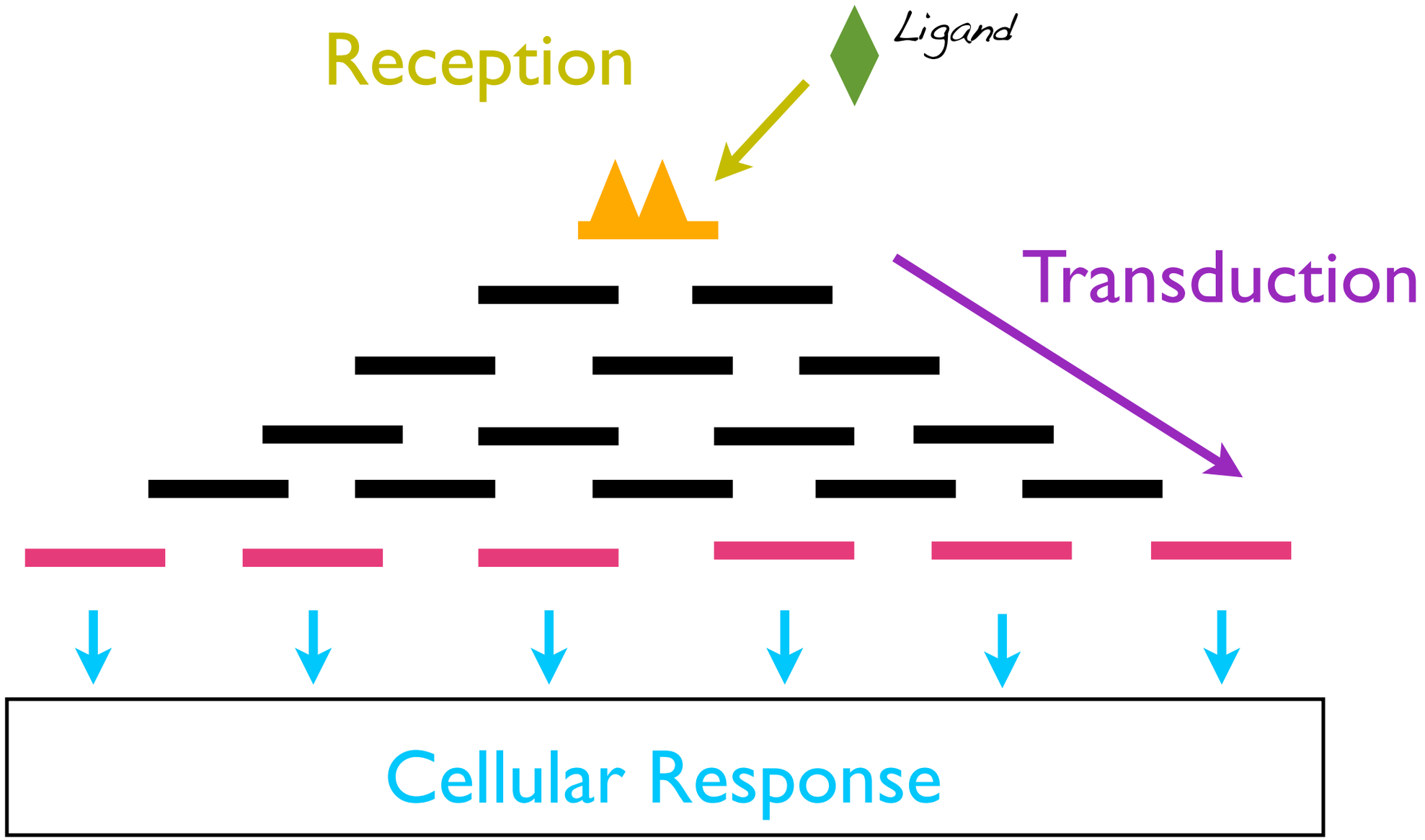
Main Idea: The chemical signal binds receptors, but receptors can not cause the cellular response, moving the information from the receptor to the molecule responsible for the cellular response is called transduction.



Signal Transduction: Relaying information from receptors to target molecules.

- Transduction usually involves multiple steps
- Molecules are activated / deactivated along the way
- Activation / Deactivation involves adding and removing phosphate groups respectively
- Multi-step pathways can greatly amplify chemical signals
- Multi-step pathways can provide greater opportunities for regulation and coordination

Signal Transduction Pathways



Are a lot like dominoes, where the first domino is the **receptor**, its activation in turn activates other **relay molecules** until finally the **target molecules** are themselves activated.

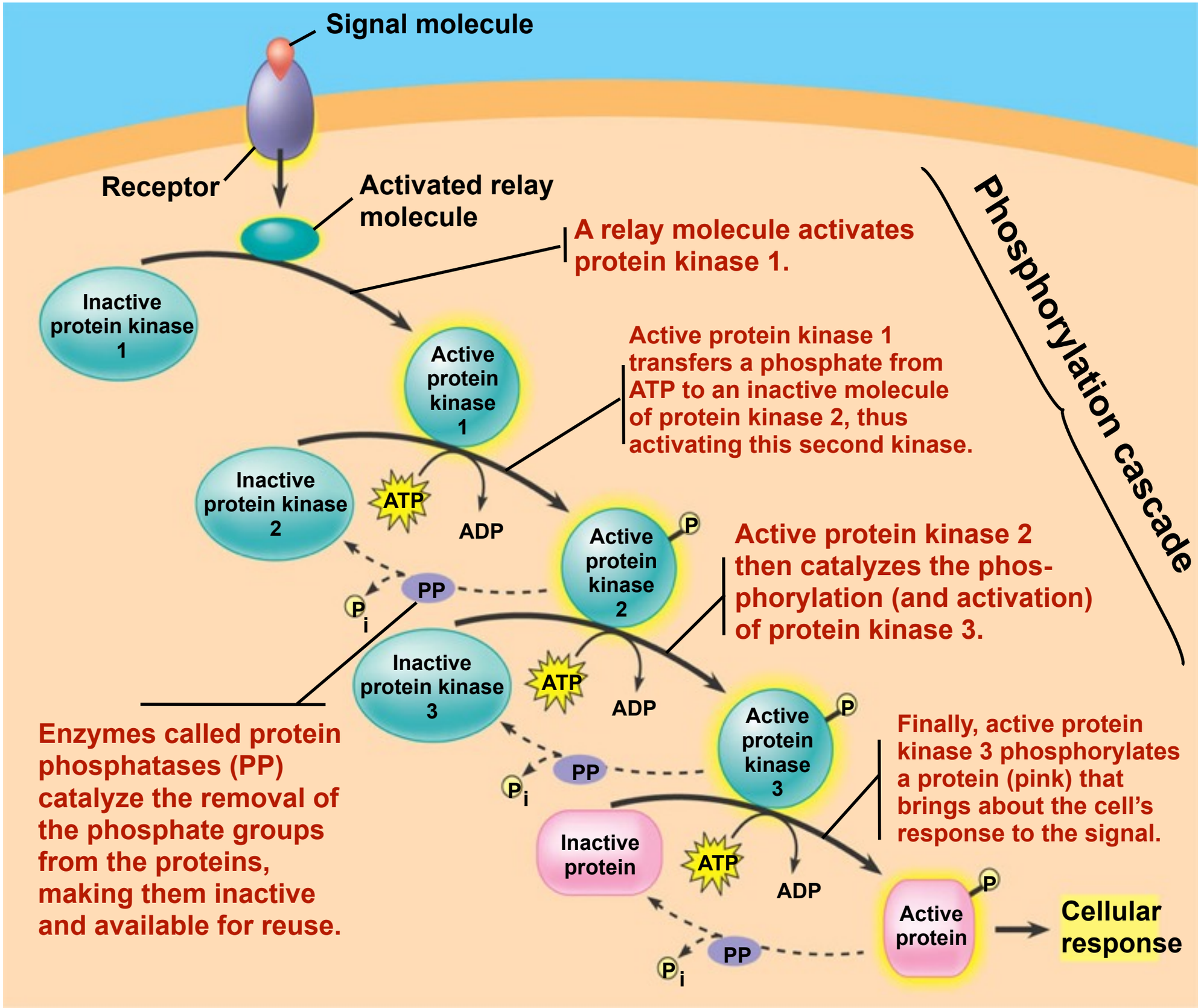
Phosphorylation & Dephosphorylation

- Adding & Removing phosphate groups is a widespread cellular mechanism for regulating protein activity
  - adding phosphates changes the shape of the protein
- Adding "P" (usually) activates or turns on
  - ***Protein Kinases***- transfer phosphates from ATP to the protein (usually amino acid serine or threonine)

Phosphorylation & Dephosphorylation

- Adding & Removing phosphate groups is a widespread cellular mechanism for regulating protein activity
  - removing phosphates changes the shape of the protein
- Removing "P" deactivates or turns off
  - also resets the kinases (pathway) for future use
  - ***Phosphatases***- removes phosphates from proteins
- The ratio of kinases:phosphatases determines in the cellular pathway is on or off!

Signal Transduction Pathways



Second Messengers: Molecules & Ions

- Not all components of signal transduction pathways are proteins
- ***Second Messengers-*** small water soluble molecules or ions
- They spread rapidly throughout the cell by diffusion
- They are used in both G-protein and tyrosine kinase pathways
    - The most common second messengers include:
        - cyclic AMP (cAMP) or calcium ions

Recall Sutherland- Experiment

Conclusions

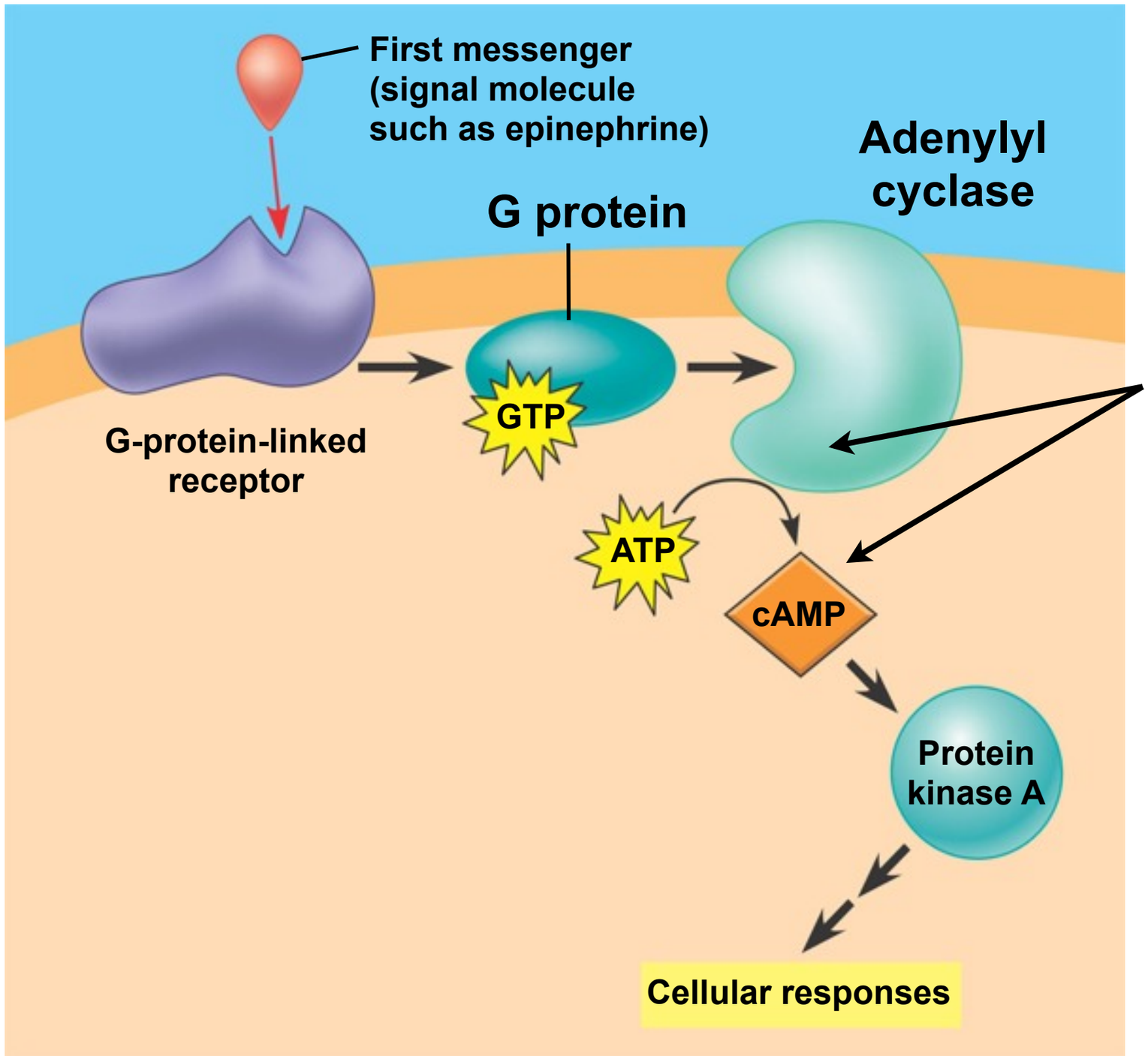
1. epinephrine does not interact directly with the catabolic enzyme, must be intermediates

2. the plasma membrane is somehow involved in transmitting the signal

- Sutherland discovered that epinephrine stimulates glycogen breakdown without passing through membrane.
- Sutherland discovered that epinephrine binds to the membrane and cyclic AMP elevates in cytosol.
- It was known that adenylyl cyclase converts ATP to cAMP, in response to epinephrine, but epinephrine does not stimulate adenylyl cyclase directly

The hunt was on to discover the second messengers involved and uncover the mechanism as a whole, here is what we know today...

Cyclic AMP (cAMP)

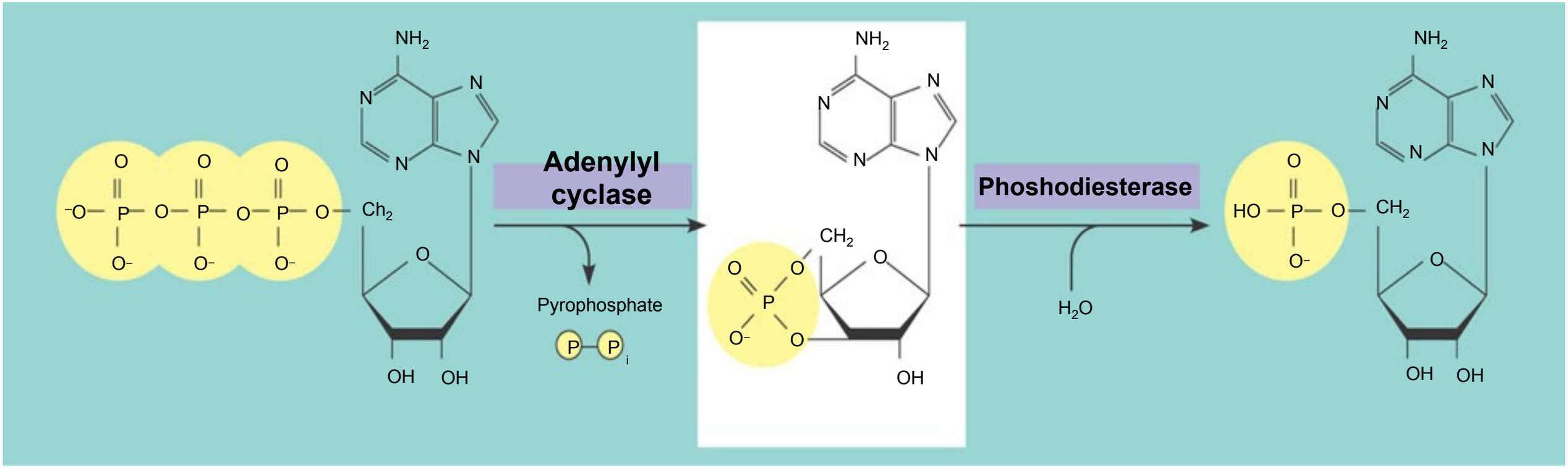


Although the this enzyme stays activate for a limited time, during that time it can cause a 20X increase in the concentration of cAMP

Epinephrine is <u>not</u> the only ligand that increases the concentration of cAMP

Keep mind that other pathways exist to inhibit adenylyl cyclase

Cyclic AMP (cAMP)



ATP

Cyclic AMP

AMP

(second messenger)

What would happen if a molecule that inactivated phospodiesterase were introduced into the cell?

In general the cellular response would continue, but specifically it would depend on the transduction pathway and the cell...checkout the next two slides

Understanding Pathways Leads to Applications

- Consider a similar pathway that uses cGMP
  - this particular cGMP pathway results in the relaxation of smooth muscle cells in the walls of arteries
  - a drug was developed to inhibit the hydrolysis of cGMP to GMP, thus prolonging the relaxation of smooth muscle
  - it was prescribed to lessen chest pains by increasing blood flow to the heart
- Turns out a that the drug had an interesting side effect, the arteries of the chest weren't the only arteries dilating

Viagra

- Works by inhibiting phosphodiesterase 5 which then prevents the degradation cGMP
  - Originally developed as heart medication, it soon became the number drug used to treat erectile disfunction in males
  - In its first year (1998) sales exceeded 1billion dollars, since then it remains one of the most sold drugs worldwide
- Today viagra is mainly sold for erectile disfunction, but it continues to be used for pulmonary hypertension (high blood pressure) and recently prescribed for altitude sickness
- Non-medical uses have seen viagra used to increase libido, athletes using to increase performance, treat jet lag and florists have found a small amount increases the shelf life of flowers

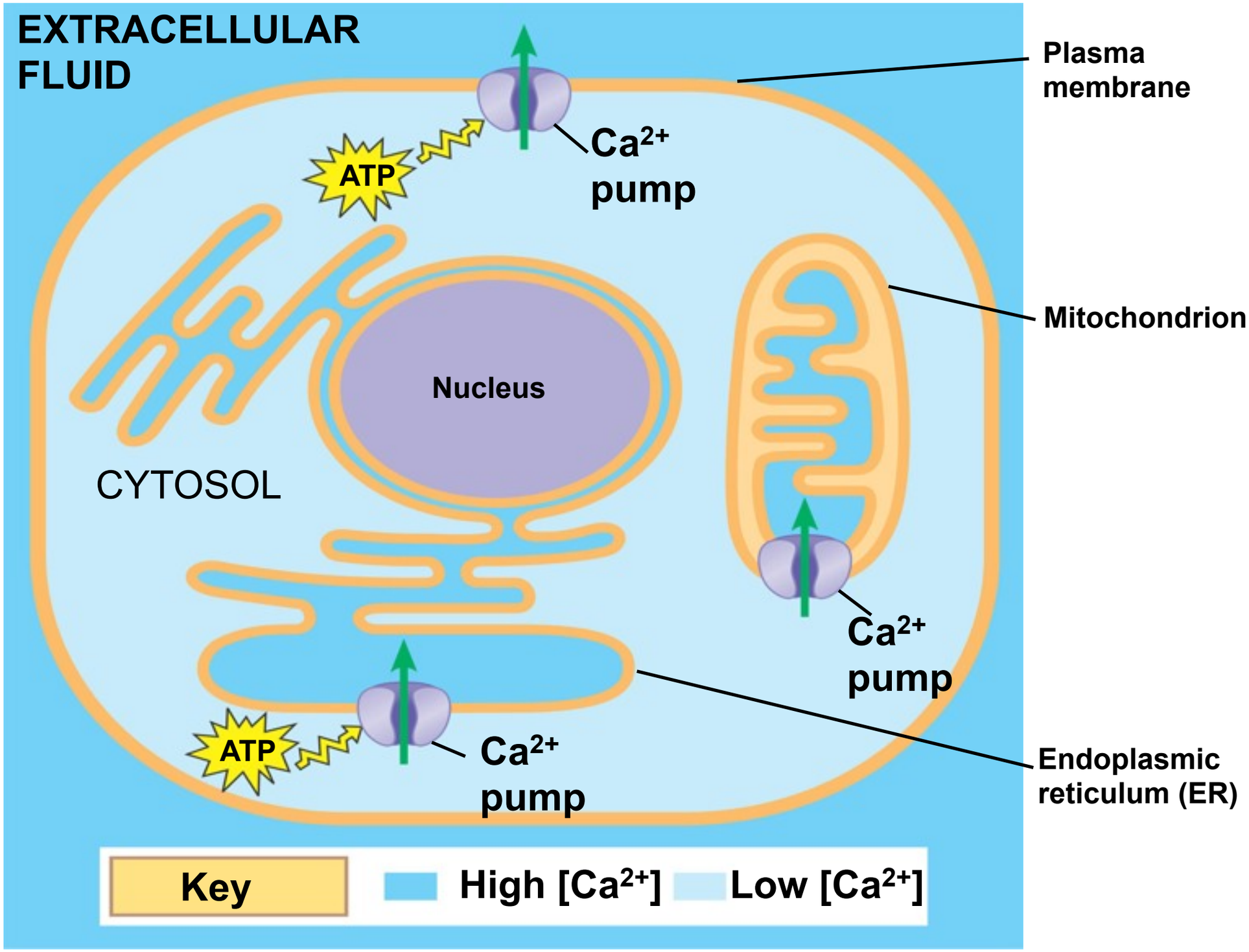
Calcium Ions & Inositol Triphosphate (IP_3)

- Many cell communication pathways use calcium as second messenger
  - (calcium is more common, than cAMP)
- Increasing cytosolic calcium concentration can lead to *muscle contraction, **secretion of substances and cell division.
- Plants even use calcium as part of the "greening" process

*remember sliding filament theory

**remember synaptic transmission in nerve transmission

Calcium Ions



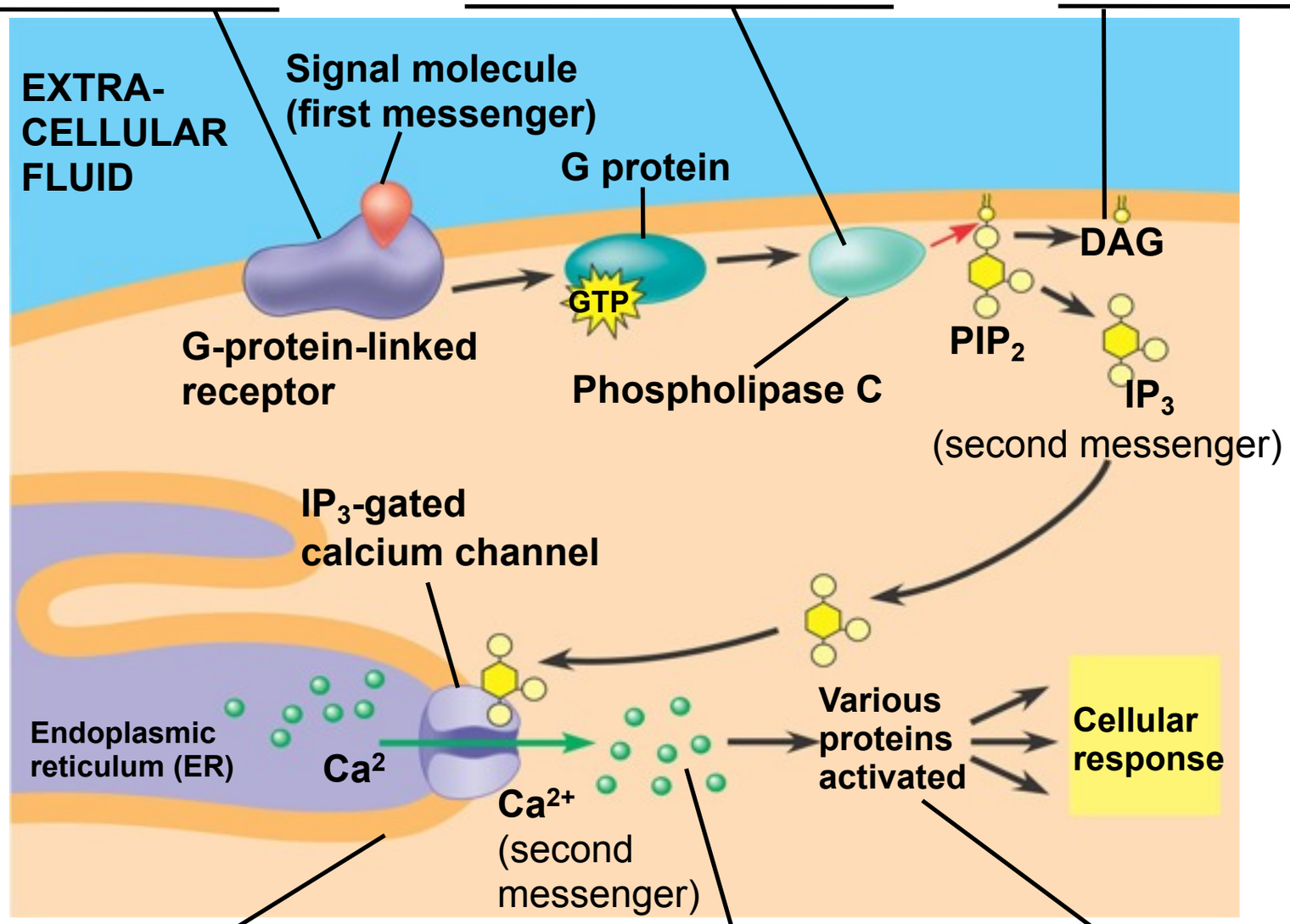
Calcium Ions & Inositol Triphosphate (IP_3)

- The release of calcium involves yet more second messengers

1. A signal molecule binds to a receptor, leading to activation of phospholipase C.

2. Phospholipase C cleaves a plasma membrane phospholipid called PIP_2 into DAG and IP_3.

3. DAG functions as a second messenger in other pathways.



4. IP_3 quickly diffuses through the cytosol and binds to an IP_3–gated calcium channel in the ER membrane, causing it to open.

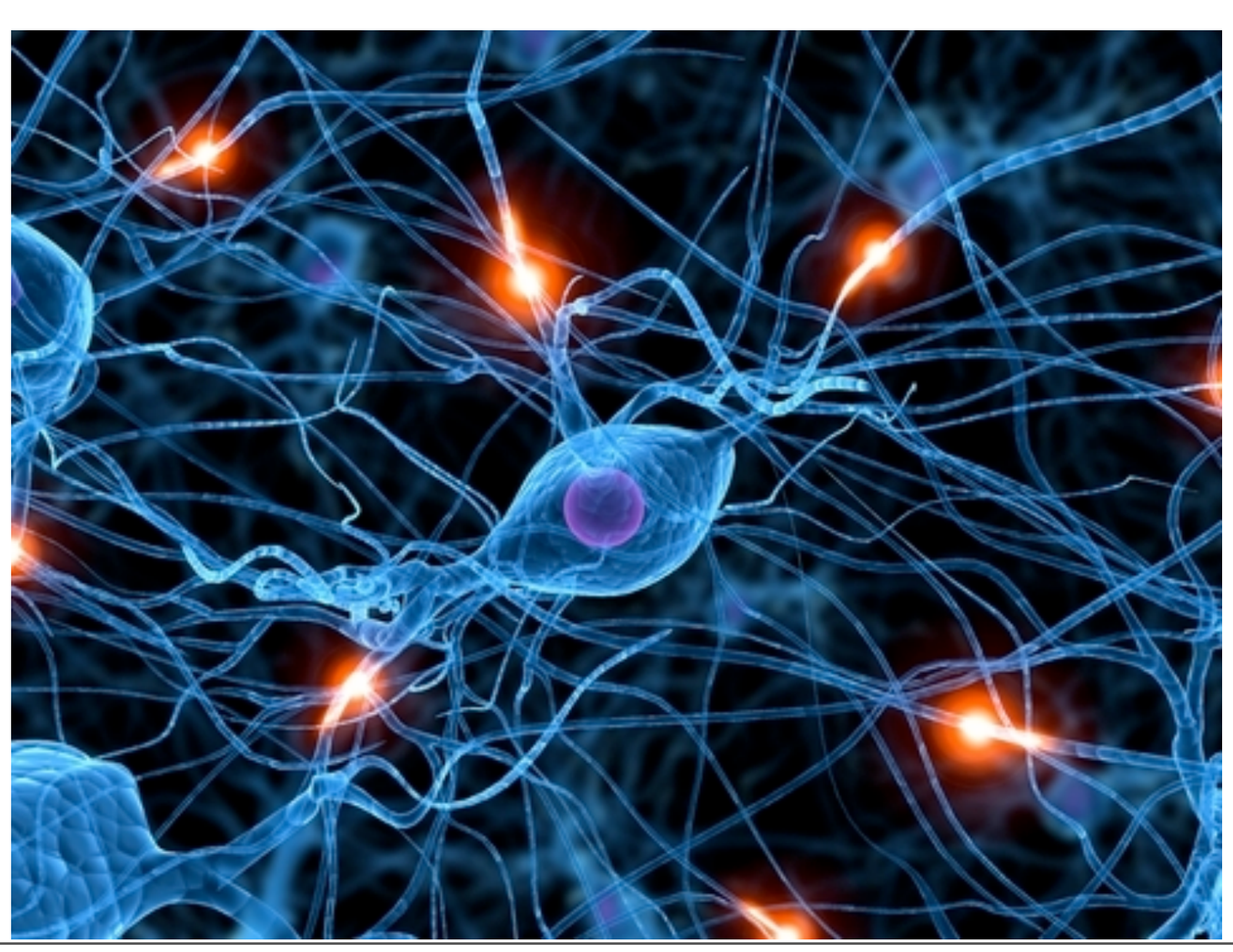
5. Calcium ions flow out ofthe ER (down their concentration gradient), raising the Ca^{2+} level in the cytosol.

6. The calcium ions activate the next protein in one or more signaling pathways.

Cell Communication

IV.

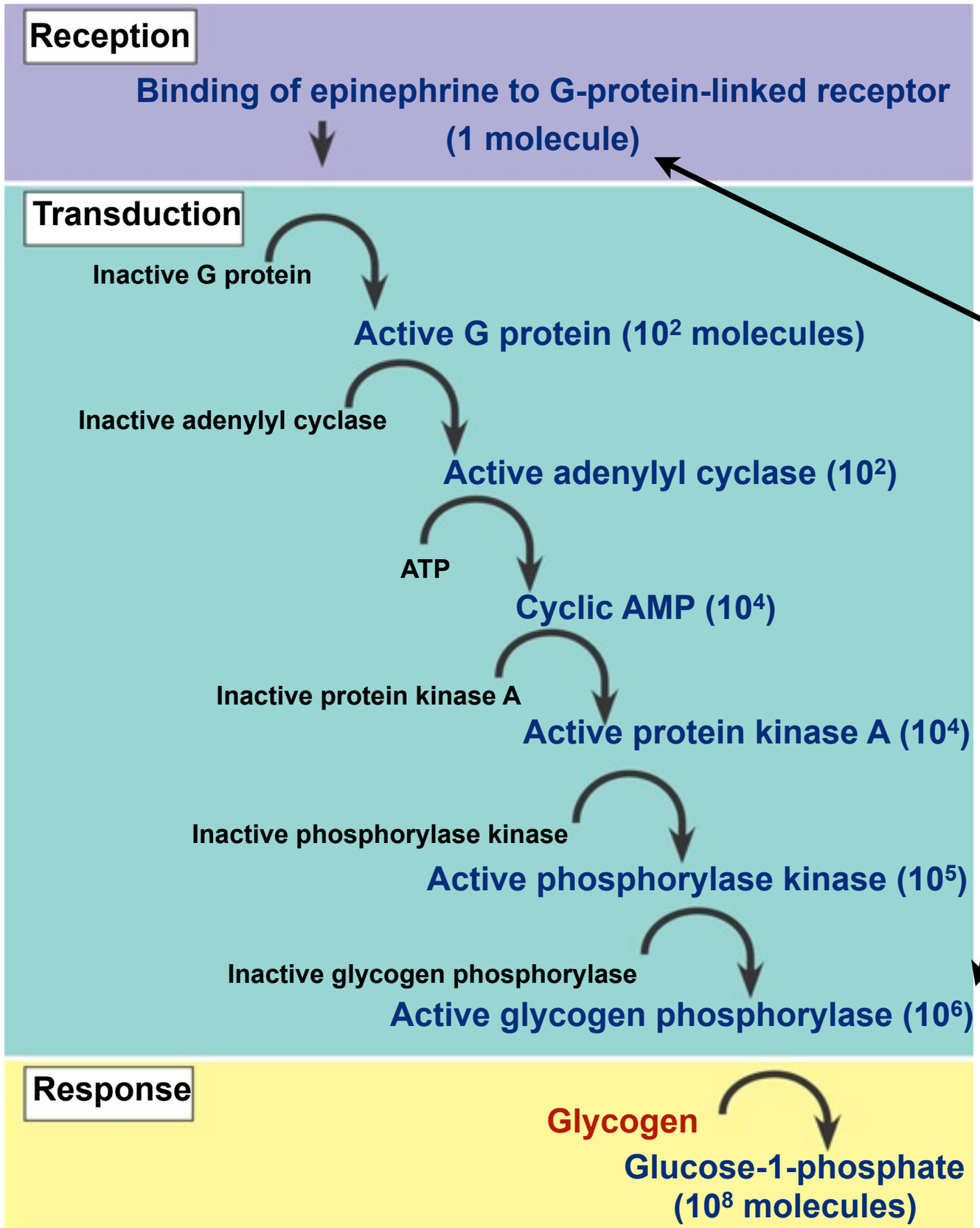
Main Idea: Cellular responses lead to of two outcomes: 1) it turns proteins in the cytosol on/off OR 2) it turns certain genes on/off.



Output Responses: Cytosolic & Nuclear

- Signaling pathways often regulate the activity of proteins already present in the cell.
    - The regulated proteins might be *enzymes*, *ion channels* or even the *cytoskeleton* itself.
- Signaling pathways can also regulate the activity of genes.
    - In these cases the final protein in the transduction pathway is often a *transcription factor*, a protein that controls genes.

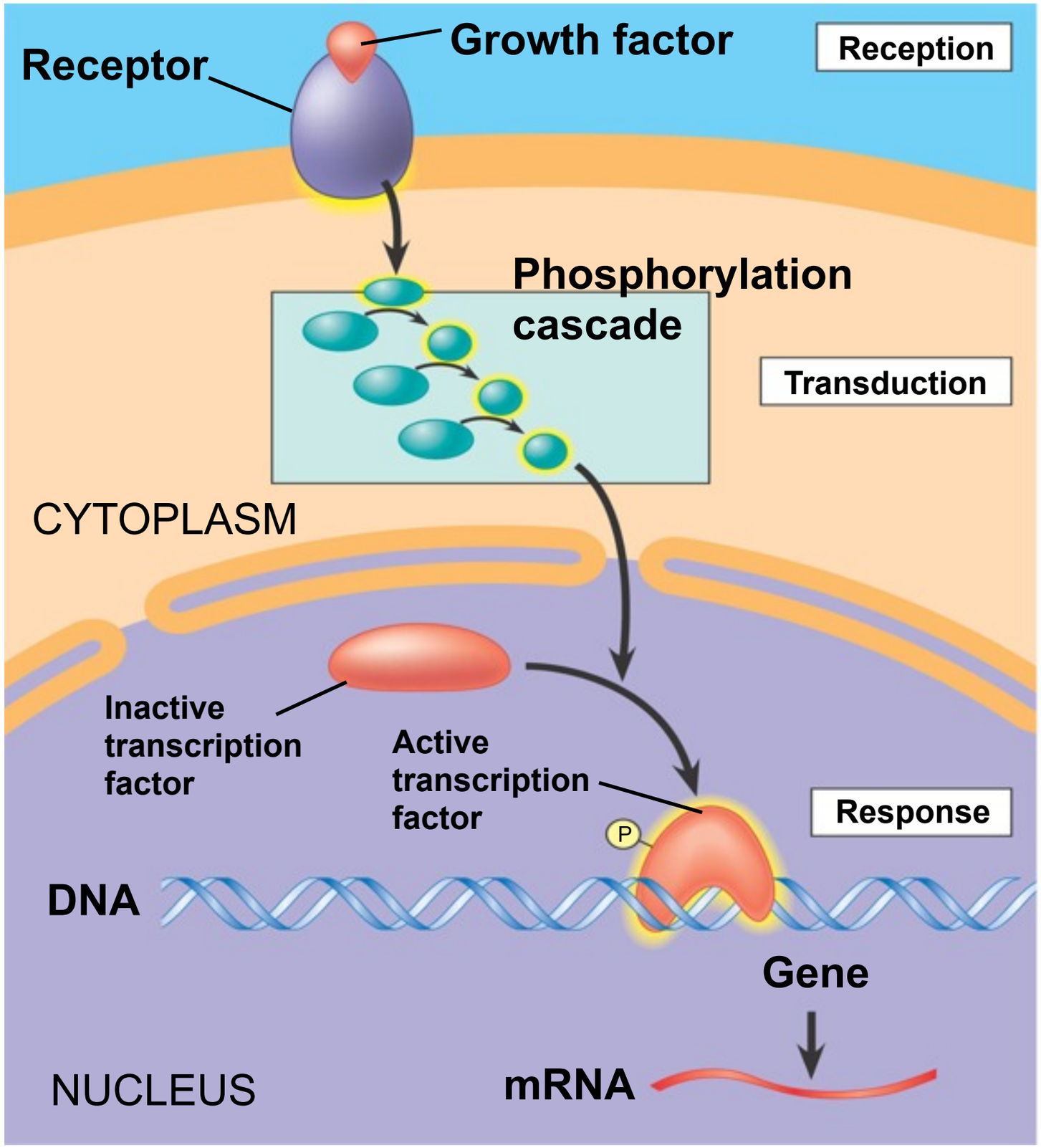
Output Responses: Cytosolic



Notice the amplification that occurs in this pathway

Here is the pathway for glycogen breakdown that Sutherland helped work out

Output Responses: Nuclear



This example shows a water soluble growth factor but most of time water soluble ligands will activate and deactivate proteins already present, lipid soluble ligands more commonly work at the gene level

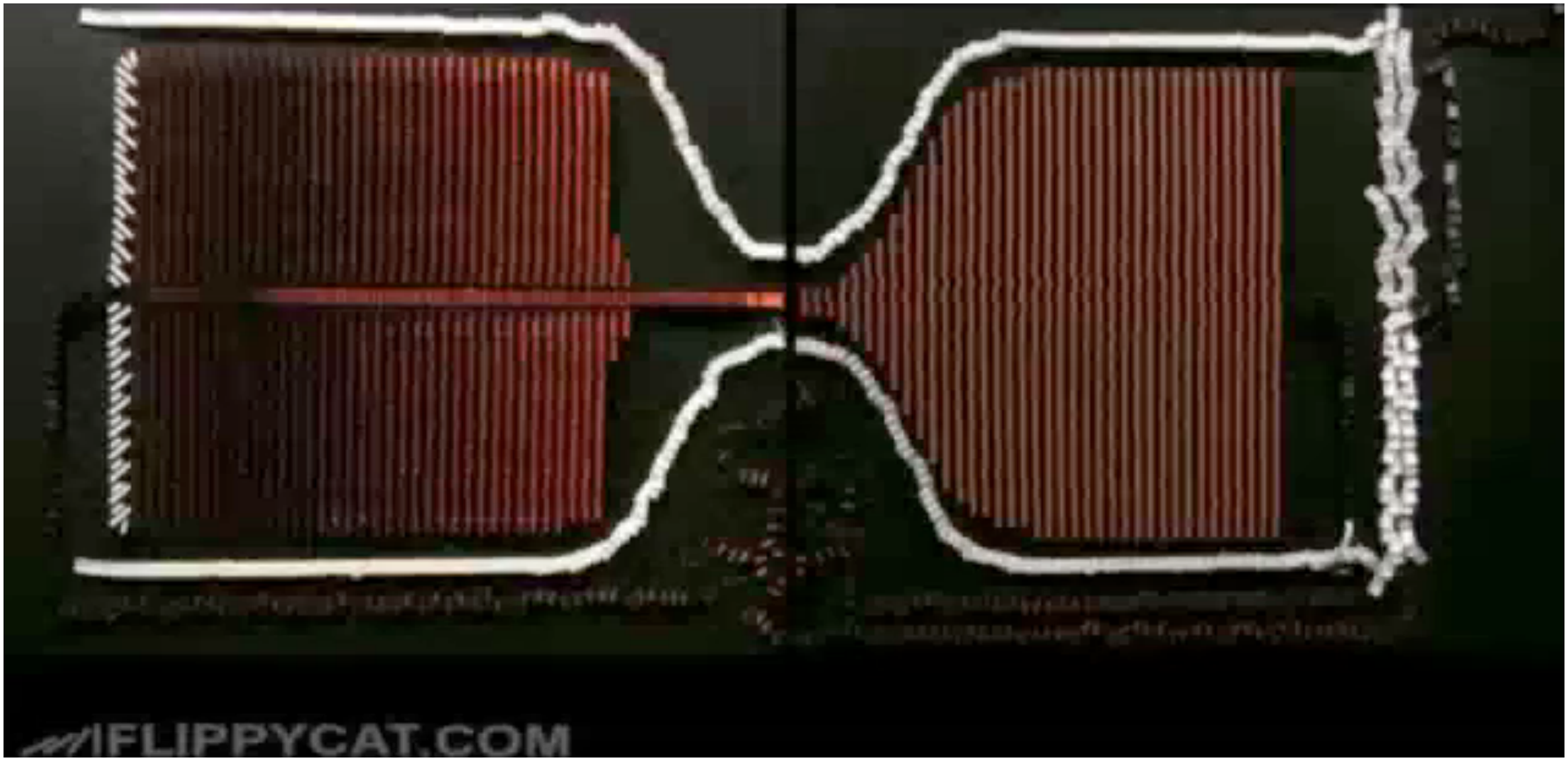
Fine Tuning the Response

- Regardless of the response, the cell has the ability to finely regulate the response rather than simply operating from a on/off position.
    - Here is analogy- cell responses are not like "standard light switches" but rather "dimmer switches". A dimmer switch can turn lights on/off but also control the brightness as well.
- There are four ways in which a cell can finely tune its response.
    - 1. signal amplification
    - 2. signal specificity & coordination
    - 3. signal efficiency
    - 4. signal termination

Signal Amplification

- Proteins persist in the active form long enough to activate numerous molecules of the next substrate in the pathway before they become inactive.

- This results in one molecule, the ligand activating millions of target molecules like glycogen phosphorylase.



Signal Specificity & Coordination

- Consider the following:
  - 2 Different Cells- both in contact with blood, exposed to lots of different ligands yet cell #1 detects/responds to certain ligands and ignores others and cell #2 does the same
  - 2 Different Cells- cell #1 detects a certain ligand responds in one way meanwhile cell #2 does detects the same ligand but responds in completely different manner

<u>The explanation is the same in all cases</u>

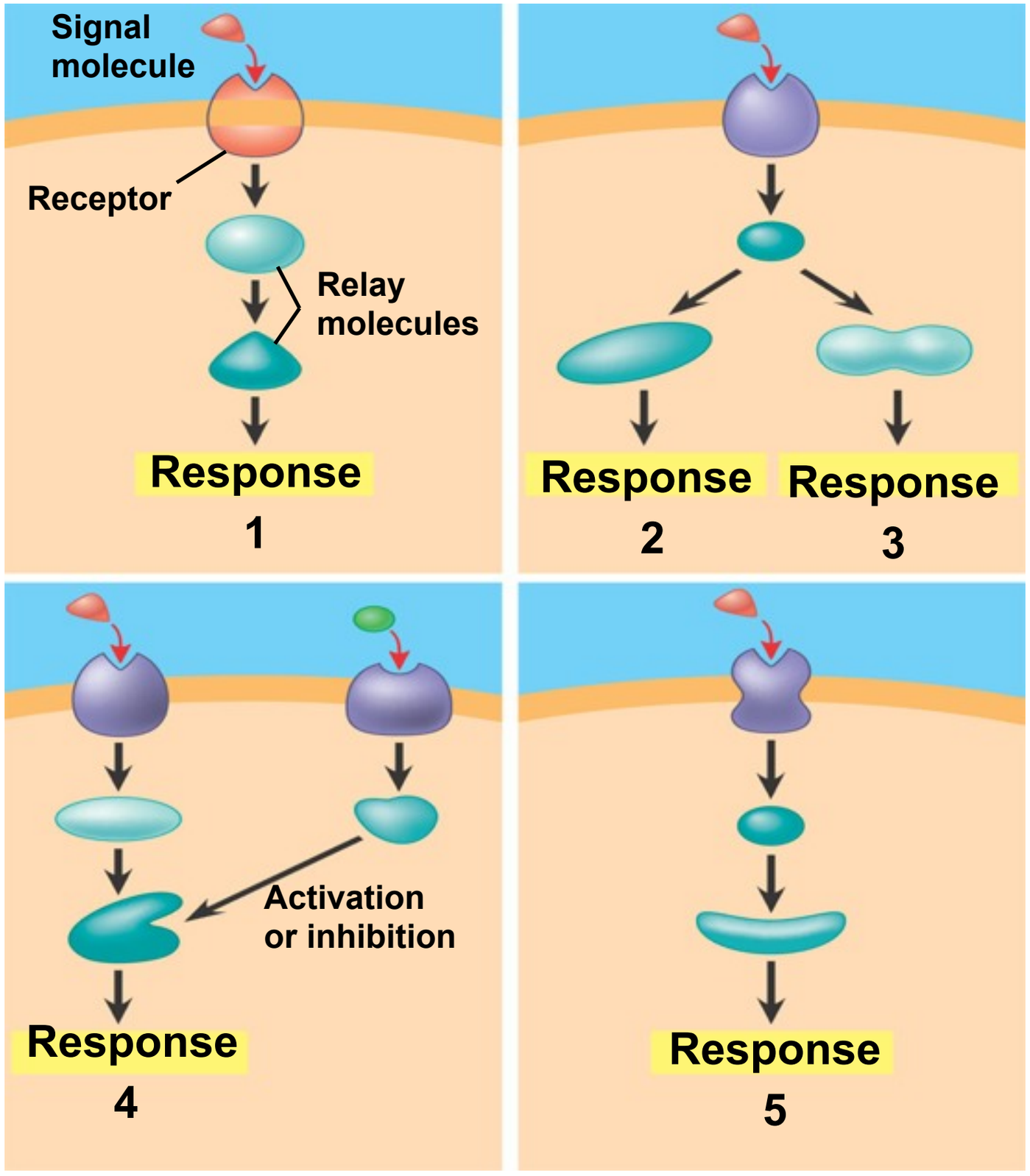
-different cells use different genes,

-different genes produce different collection of proteins (receptors, enzymes, relay proteins, structural proteins)

-cell response depends on the collection of proteins

Look for the similarities and more importantly the differences that account for the different responses

Cell A. Pathway leads to a single response



Cell B. Pathway branches, leading to two responses

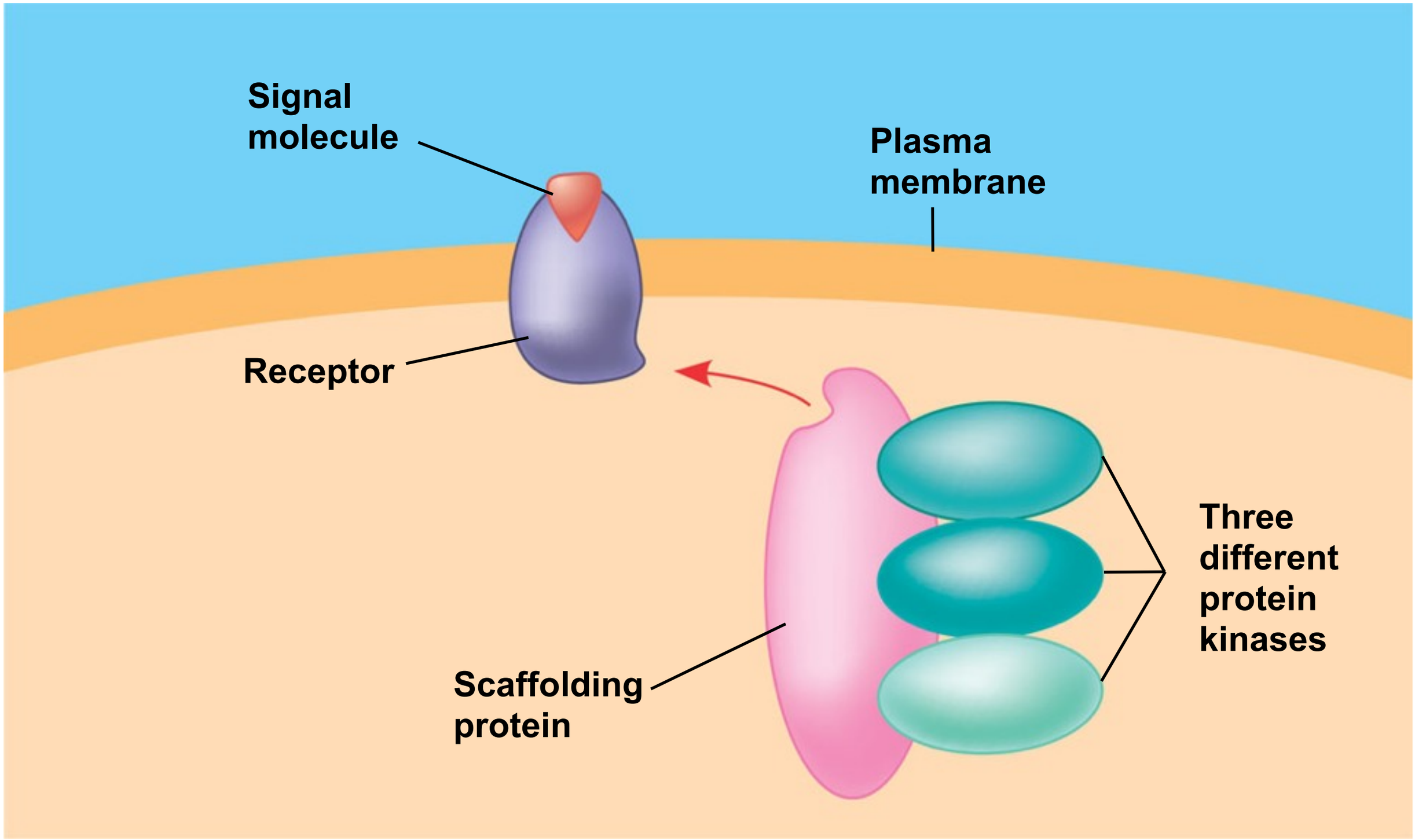
Cell C. Cross-talk occurs between two pathways

Cell D. Different receptor leads to a different response

Signal Efficiency

- The signal pathways depicted thus far in the presentation have all been ver simplified in this regard...the relay proteins are not generally floating in the cytosol.
    - Proteins are large, there diffusion slow.
- These signaling pathways would be very inefficient if all the proteins involved in a pathway had to randomly find one another.
- Instead the efficiency is increased through **scaffolding proteins**.
- ***Scaffolding proteins-*** are large relay proteins to which several other relay proteins are attached.
    - This holds all or many of the proteins involved in a pathway together close to one another

Signal Efficiency



This "hardwiring" enhances the speed and accuracy of signal transfer

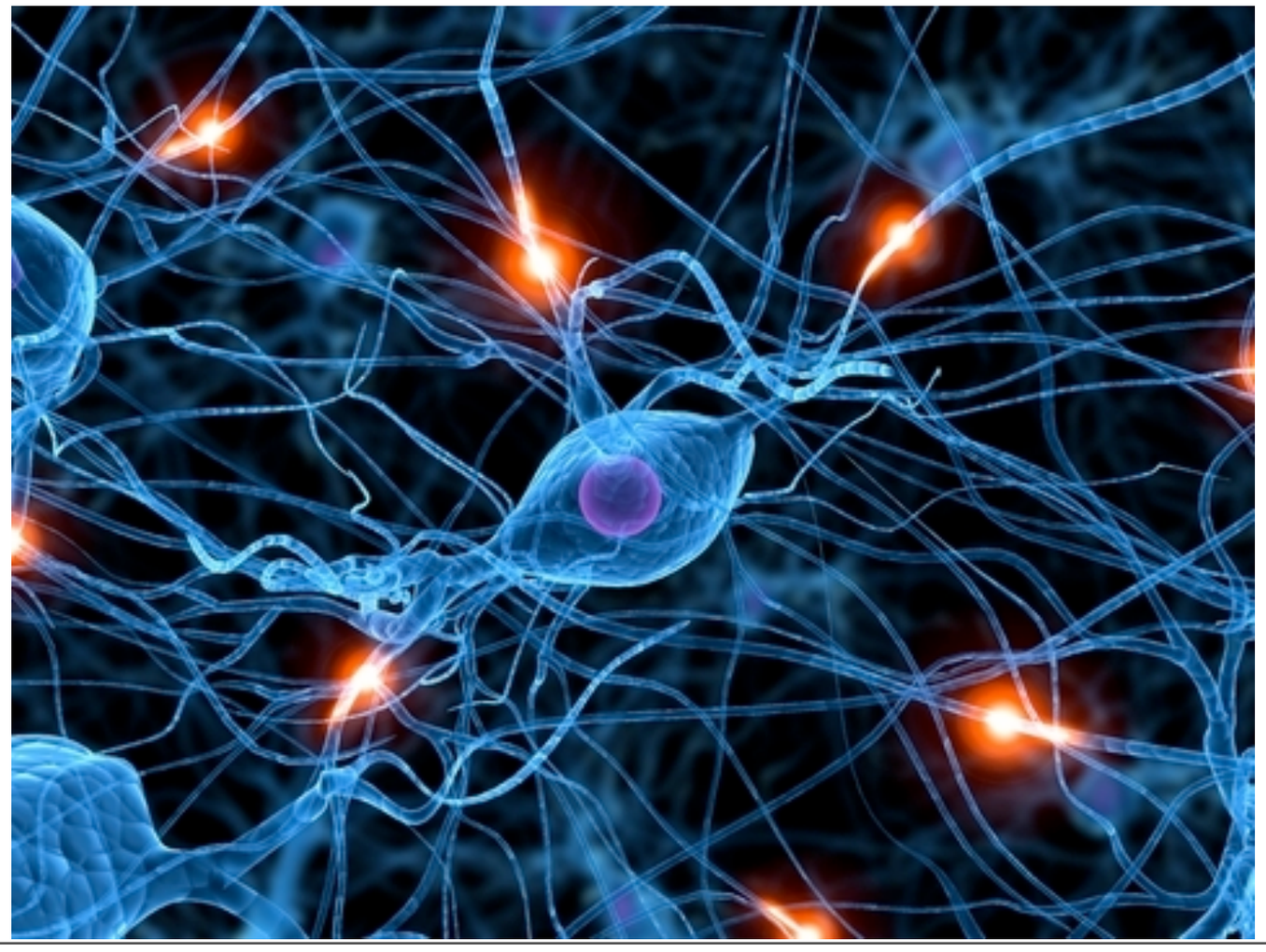
Signal Termination

- The signal pathways depicted thus far in the presentation have all been ver simplified in this regard...few details regarding the *inactivation* of pathways have been depicted.
- If cells are to respond to another signal then they must "reset" or inactivate the pathways after they illicit a response.
    - we saw in the cholera example what can happen when the signal pathway remains active
- The binding of ligands to receptors is reversible.
    - concentration of ligands relates to the number of bound ligands, the ratio of bound:unbound ligands determines whether a cell responds to the signal or not
- The relay molecules are made inactive in variety of ways:
    - ie. phosphatases remove phosphates, thereby inactivating relay molecules

Cell Communication

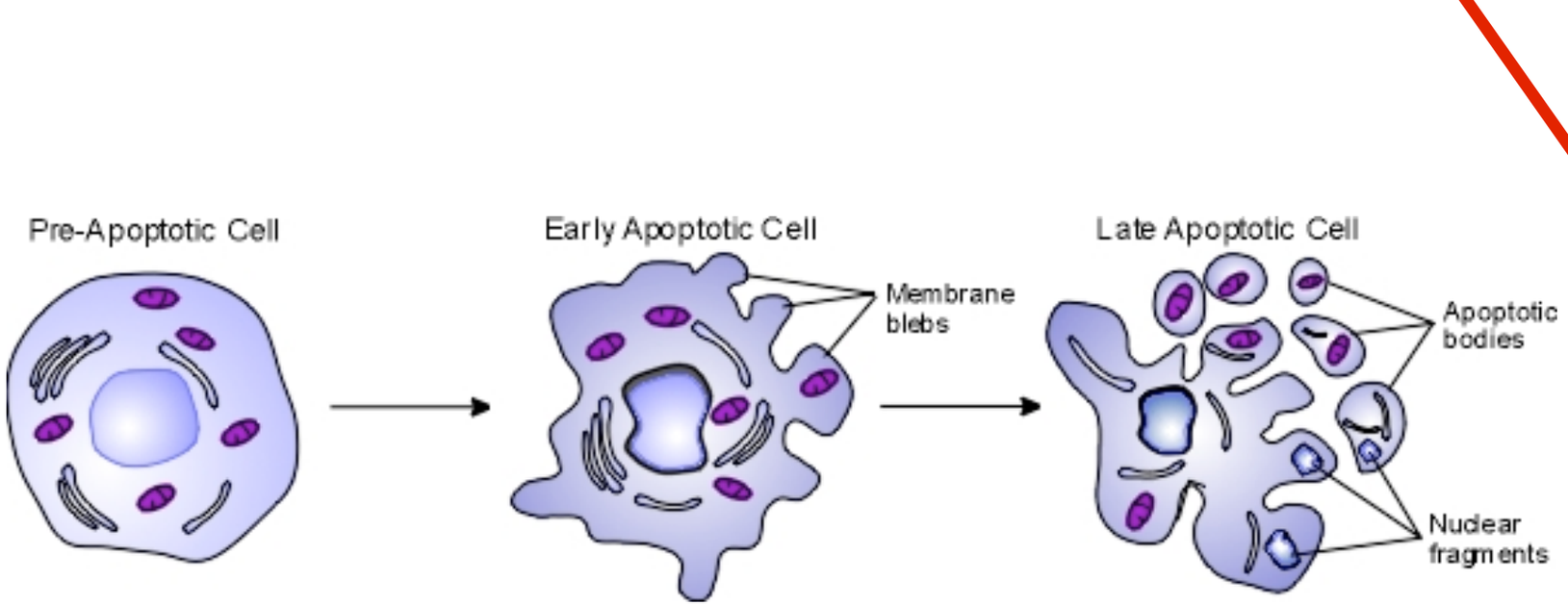
V.

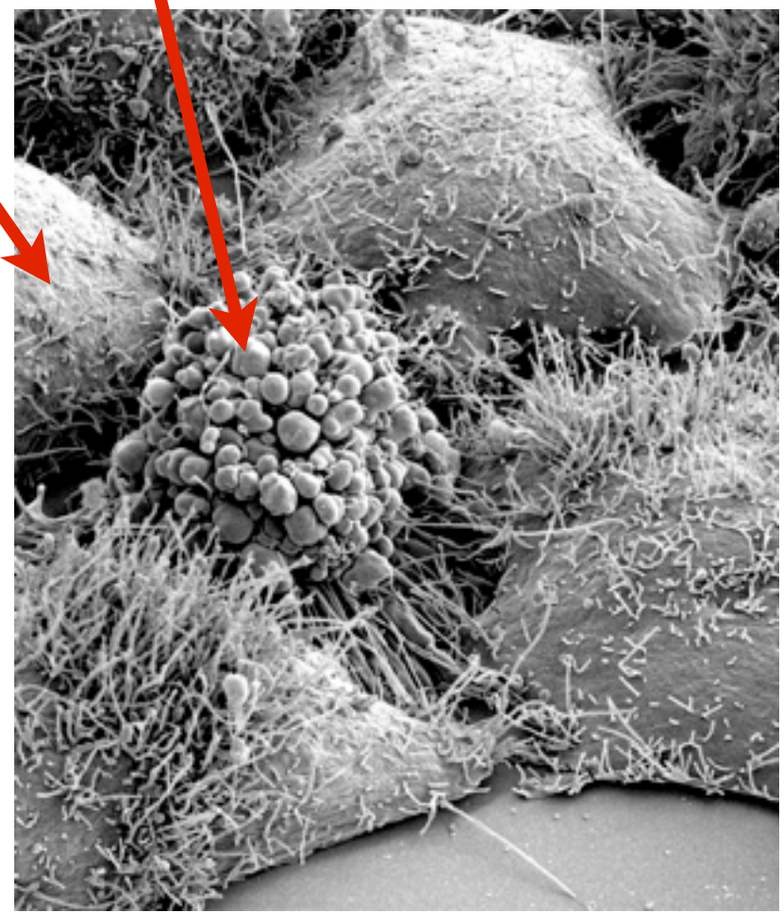
Main Idea: One of the most important and elaborate signal pathways involves "programmed cell death".



Programmed Cell Death: Apoptosis

- Cells that are infected, damaged or have reached the end of their functional life span often undergo ***apoptosis*** (programmed cell death)
  - Cellular DNA and organelles are cut into pieces, the pieces are packaged into vesicles, cell becomes lobed and the lobes are engulfed and eaten by scavenger cells

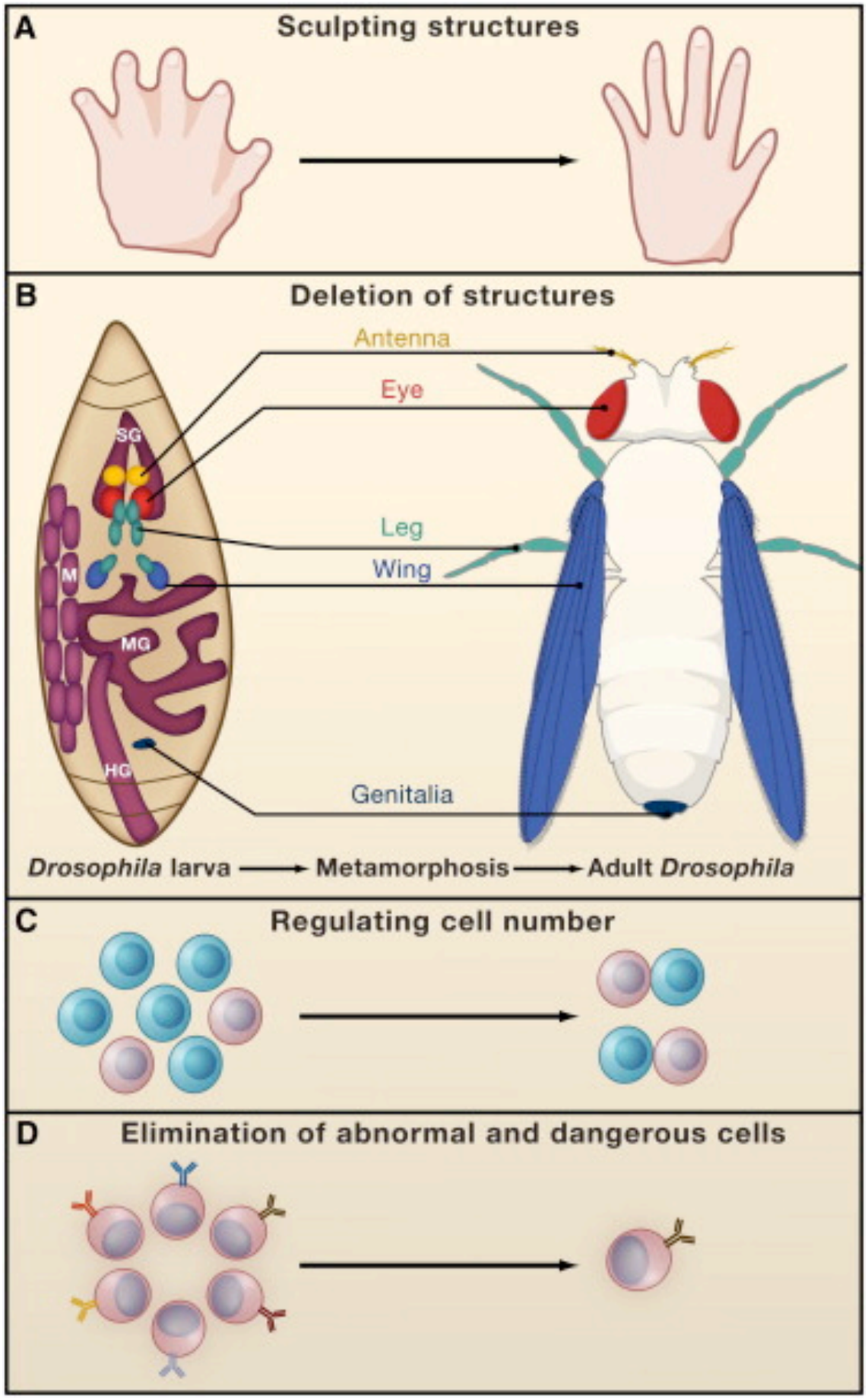




Apoptosis- Roles in Organisms

- *Apoptosis* (programmed cell death) is important mechanism for ***organisms***:
  - stops cancer cells from spreading
  - stops/slows viral spreading
  - protects neighboring cells from damage that they would incur when dead cells leak their digestive enzymes.
  - important for embryological development of hands & feet
  - important for embryological development of the nervous system
  - vital for normal immune system operation

Apoptosis-
Roles in Organisms



Apoptosis- Roles in Populations

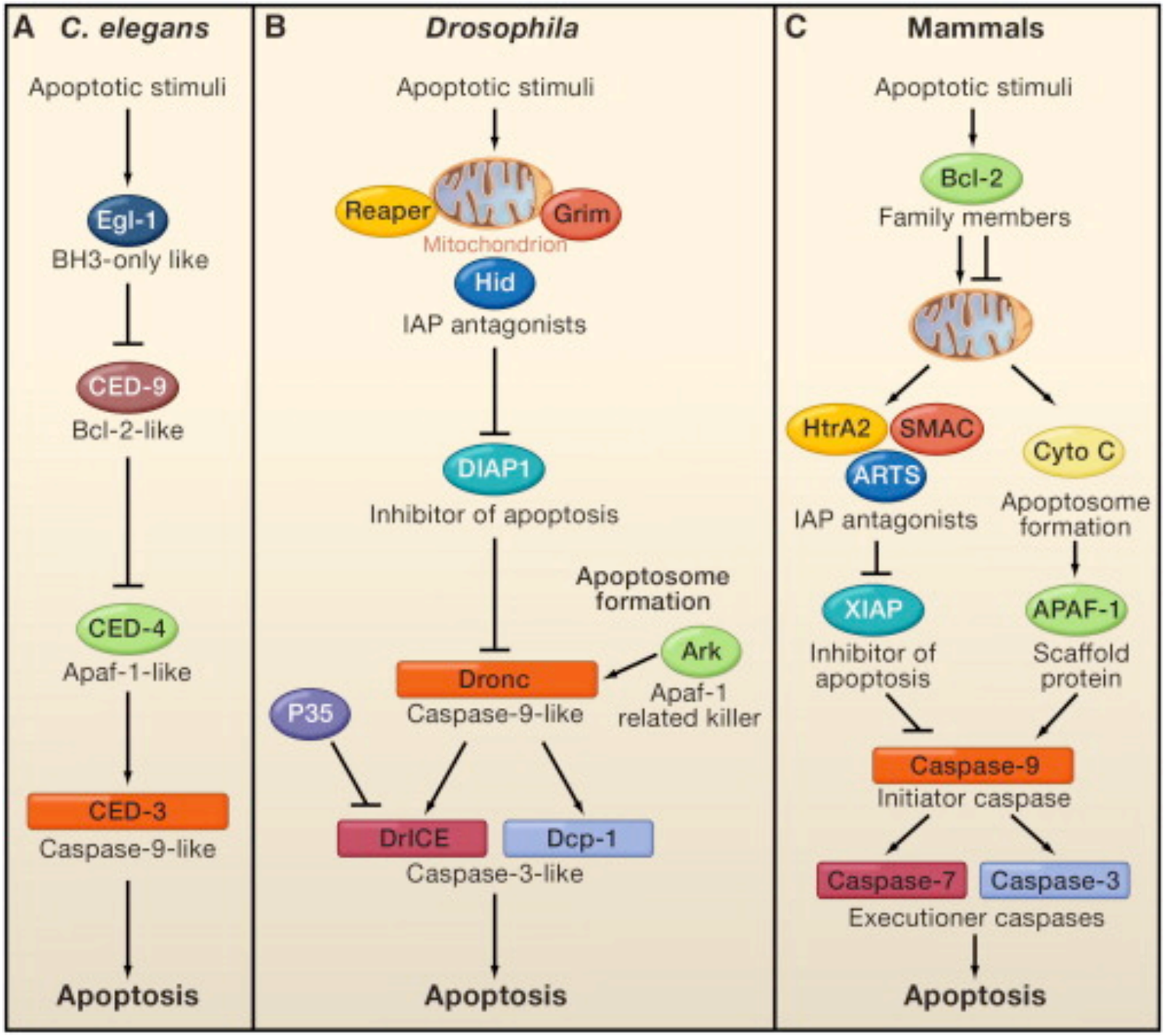
- *Apoptosis* (programmed cell death) is indirectly important for ***populations***:
  - cell death underlies the death of individuals
    - death is necessary to change allele frequencies
    - death eliminates less fit individuals
    - death results in better adapted populations
    - death removes species (extinction) and without death no new species could emerge
    - death effects competition, resources
    - death is necessary for genetic drift

Apoptosis- Ancient & Beneficial

- *Apoptosis* (programmed cell death) appears to have a played a vital role to both populations and organisms themselves for a long time.
    - apoptosis is found in most living organisms from single celled yeast to multicellular animals
    - in addition the enzymes, the pathways and mechanisms of apoptosis are very similar in these organisms
        - both of these observations support the idea that apoptosis evolved early and was beneficial over time

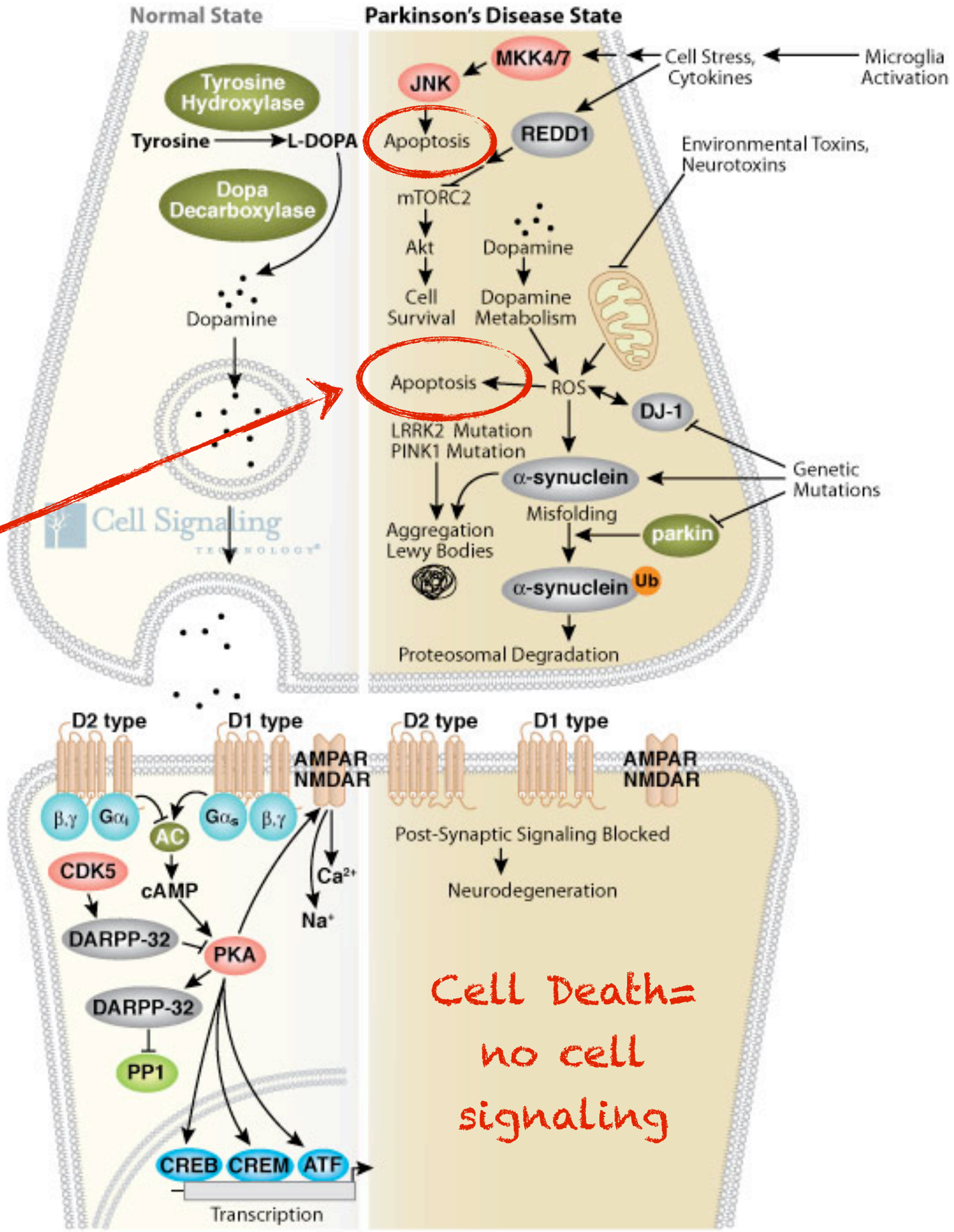
Apoptosis- Ancient & Beneficial

Here we see the evolutionary "conservation" and "expansion" of the core apoptotic machinery



Apoptosis-Disease

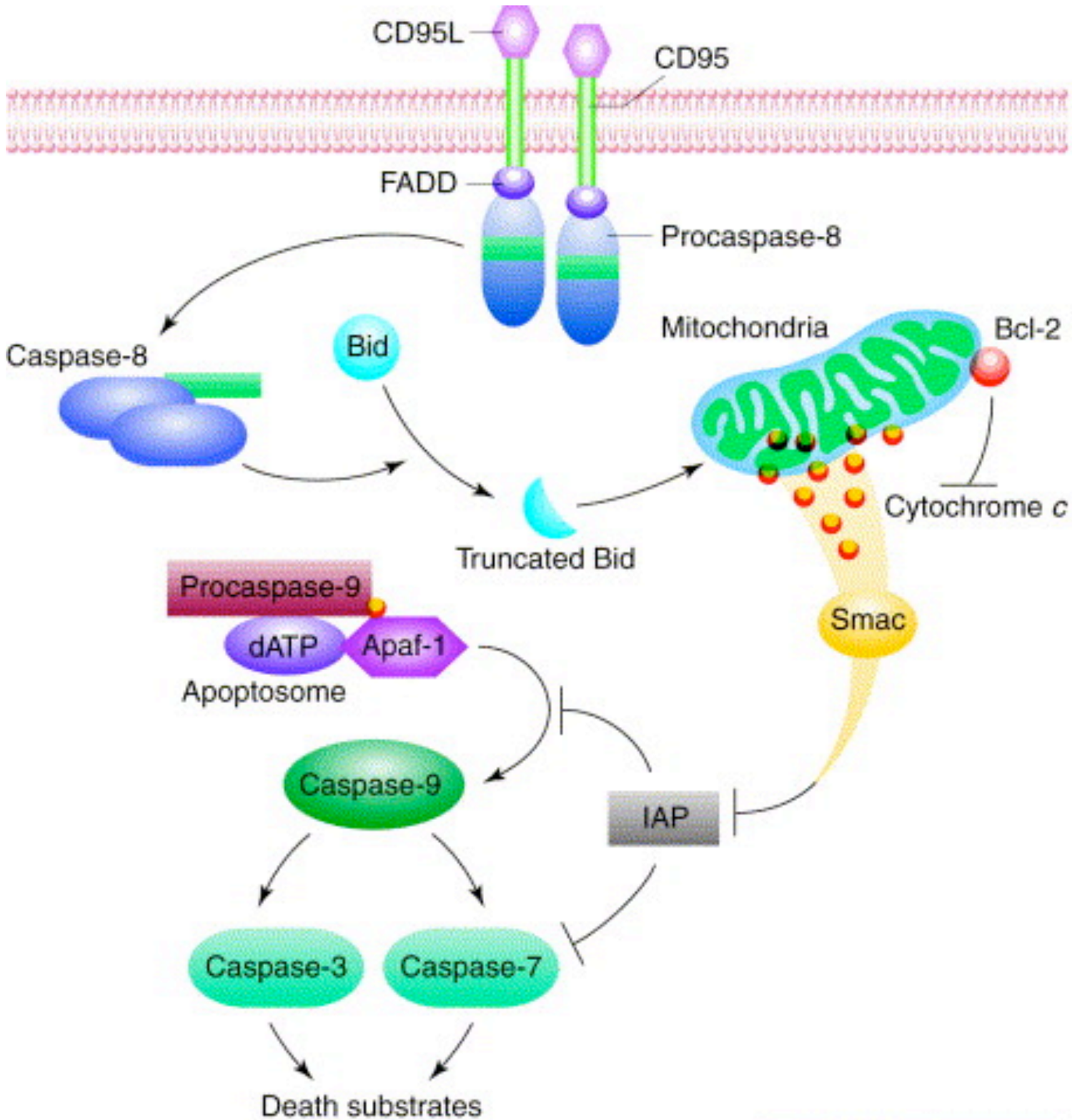
- *Apoptosis* (programmed cell death) appears to play a role in certain degenerative diseases.
- Such as Parkinson's & Alzheimer's
- Certain cancers are linked to malfunctions in apoptotic pathways



Apoptosis- Mode of Action

- *Apoptosis* (programmed cell death) appears to have a several different pathways depending on cell type and the type of signal.
- We can start with some general traits of apoptosis:
  - it involves enzymes called *caspases*
  - the mitochondria almost always plays a part in the pathway
  - the endoplasmic reticulum sometimes plays a role
  - the death signal can originate inside the cell itself or come from the outside of the cell

Apoptosis- General Mode of Action



Apoptosis- Not so General Mode of Action