Big Idea 3: Living systems store, retrieve, transmit and respond to information essential to life processes.

Enduring understanding 3.D: Cells communicate by generating, transmitting and receiving chemical signals.

Essential knowledge 3.D.3: Signal transduction pathways link signal reception with cellular response.

a. Signaling begins with the recognition of a chemical messenger, a ligand, by a receptor protein.

Evidence of student learning is a demonstrated understanding of each of the following:

1. Different receptors recognize different chemical messengers, which can be peptides, small chemicals or proteins, in a specific one-to-one relationship.

2. A receptor protein recognizes signal molecules, causing the receptor protein's shape to change, which initiates transduction of the signal.

Essential knowledge 3.D.3: Signal transduction pathways link signal reception with cellular response.

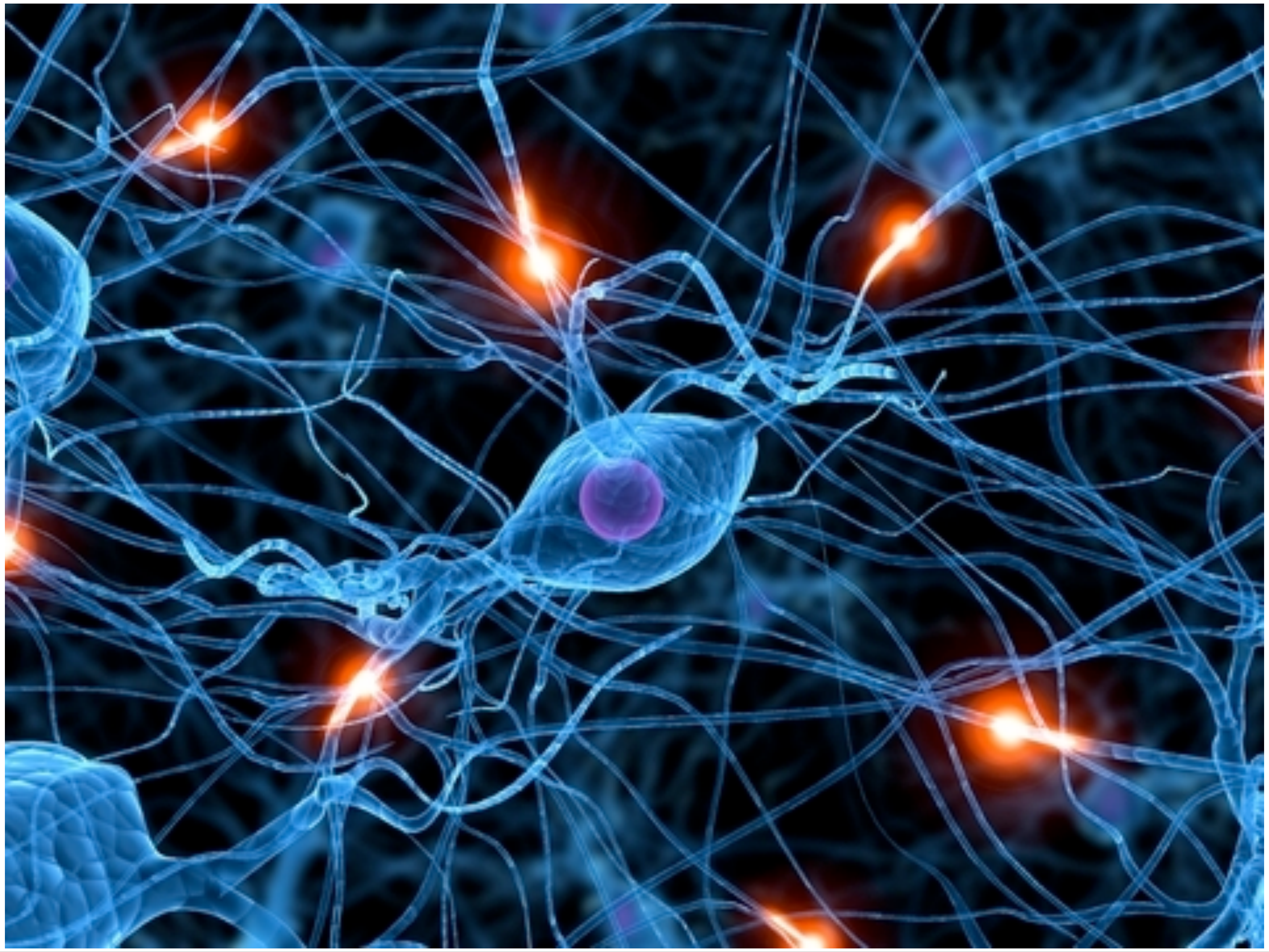
To foster student understanding of this concept, instructors can choose an illustrative example such as:

- G-protein linked receptors
- Ligand-gated ion channels
- Receptor tyrosine kinases

✘✘ No particular system is required for teaching the concepts above. Teachers are free to choose a system that best fosters student understanding.

Cell Communication

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



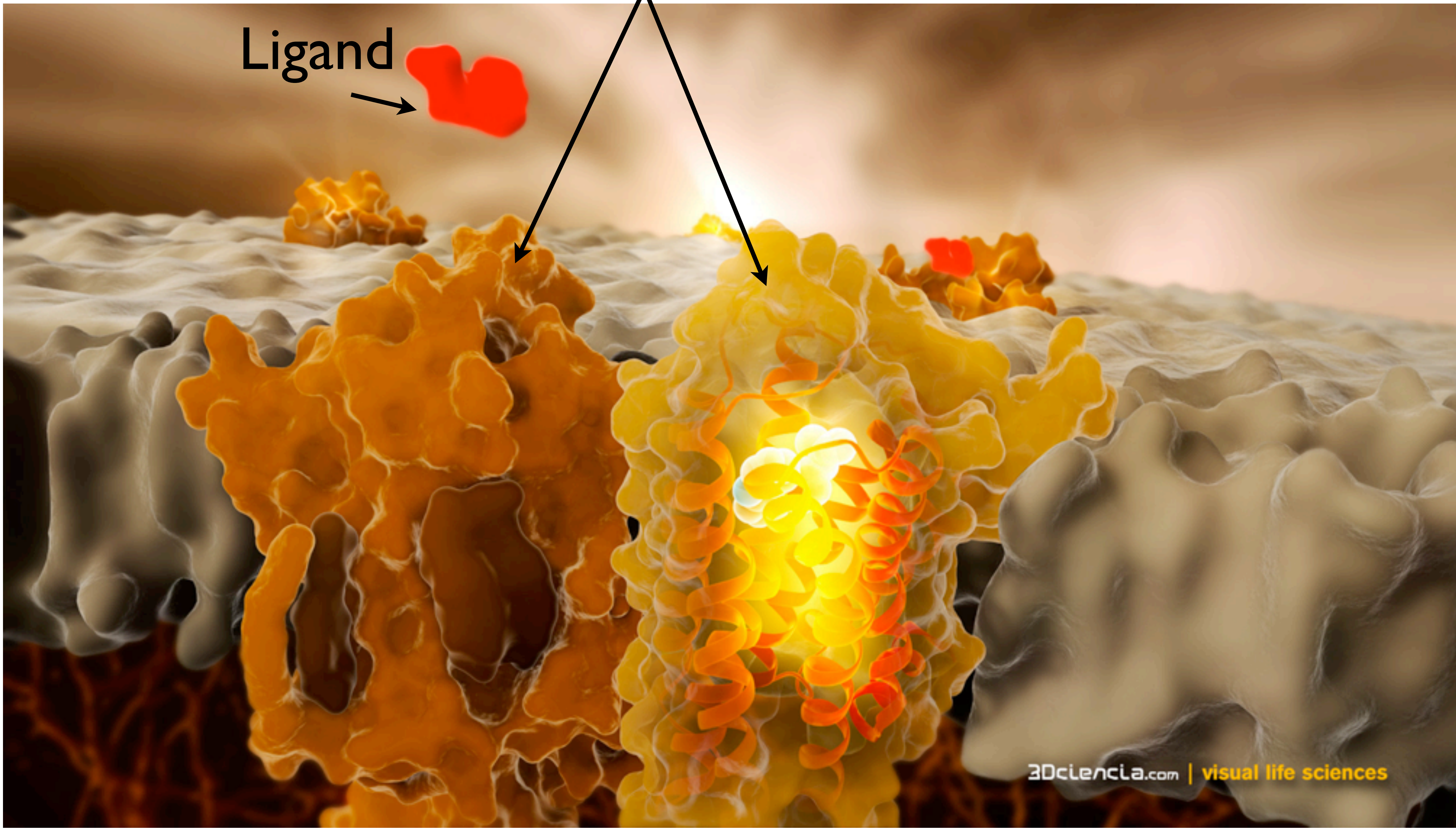
Step 1: Reception

- 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)



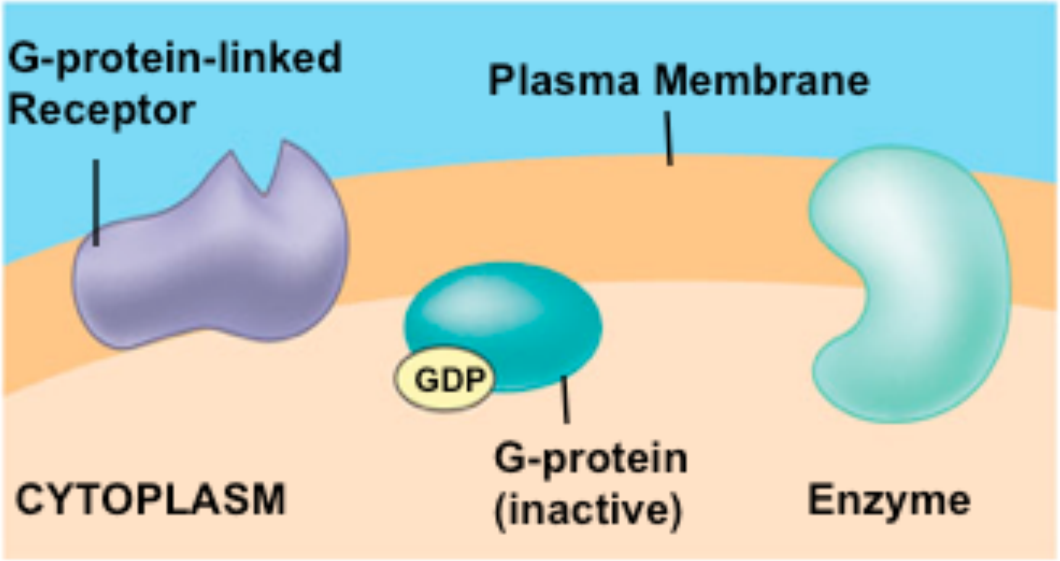
Hydrophobic amino acids make up the core of the polypeptide

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

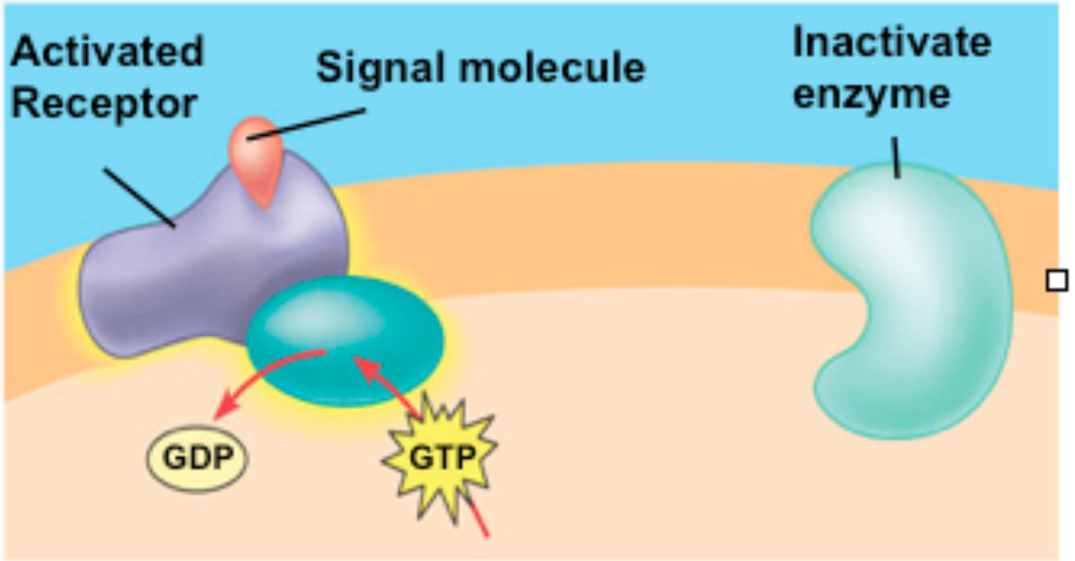
Receptors in the Plasma Membrane

- 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**

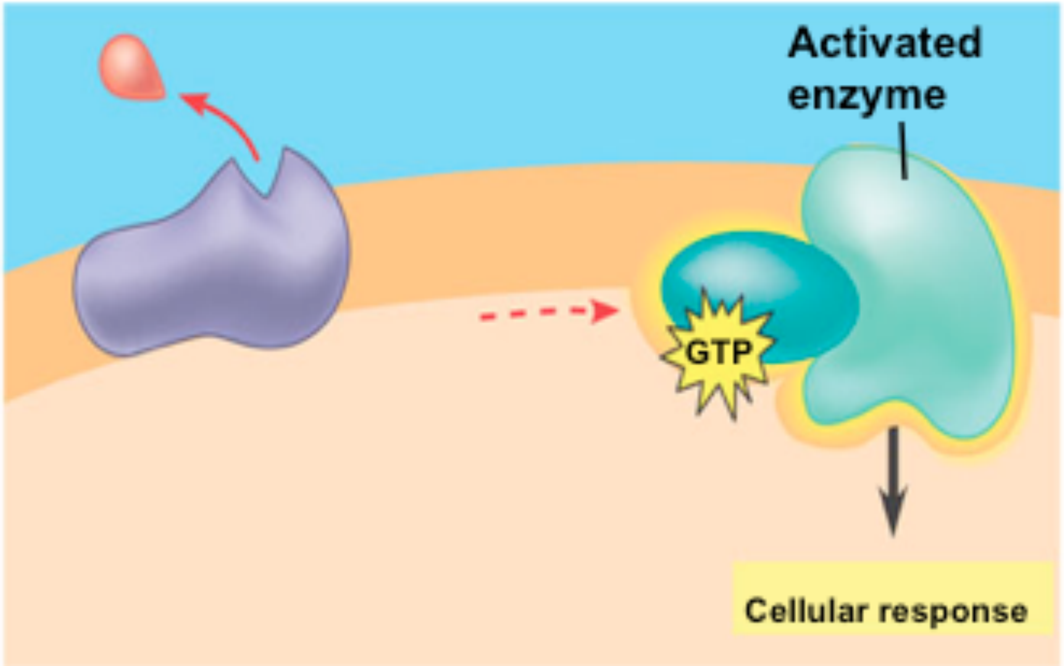
G Protein-Coupled Receptors



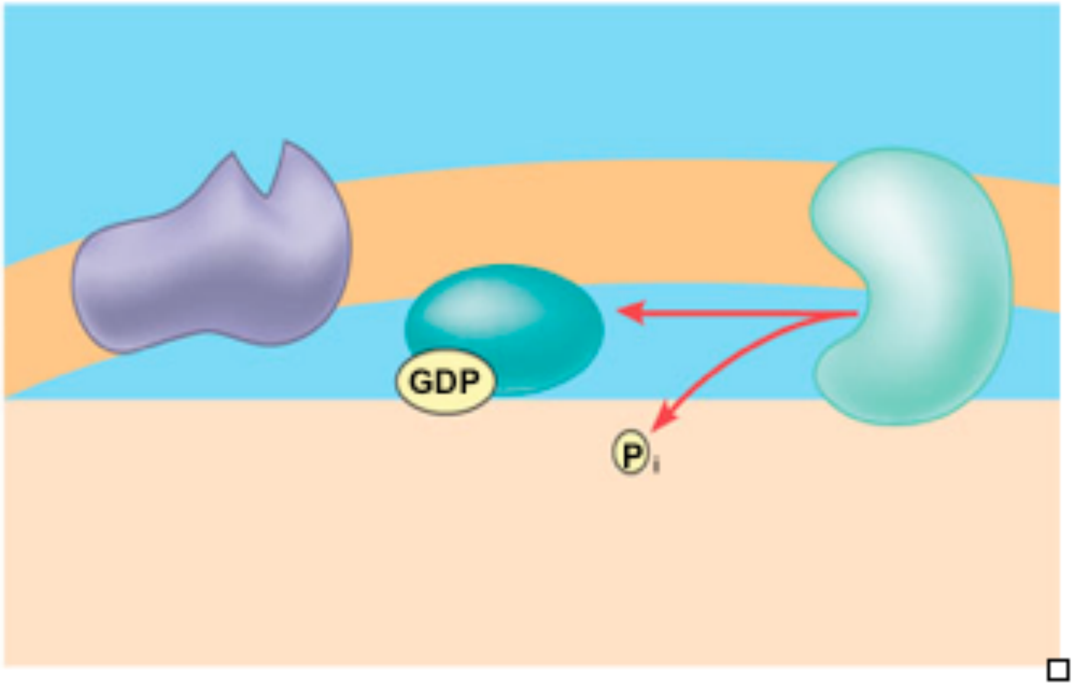
1. **Attached to cytoplasmic side, the G protein acts as an on/off switch**
2. **if GDP is bound = G protein is off**
3. **if GTP is bound = G protein is on**



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

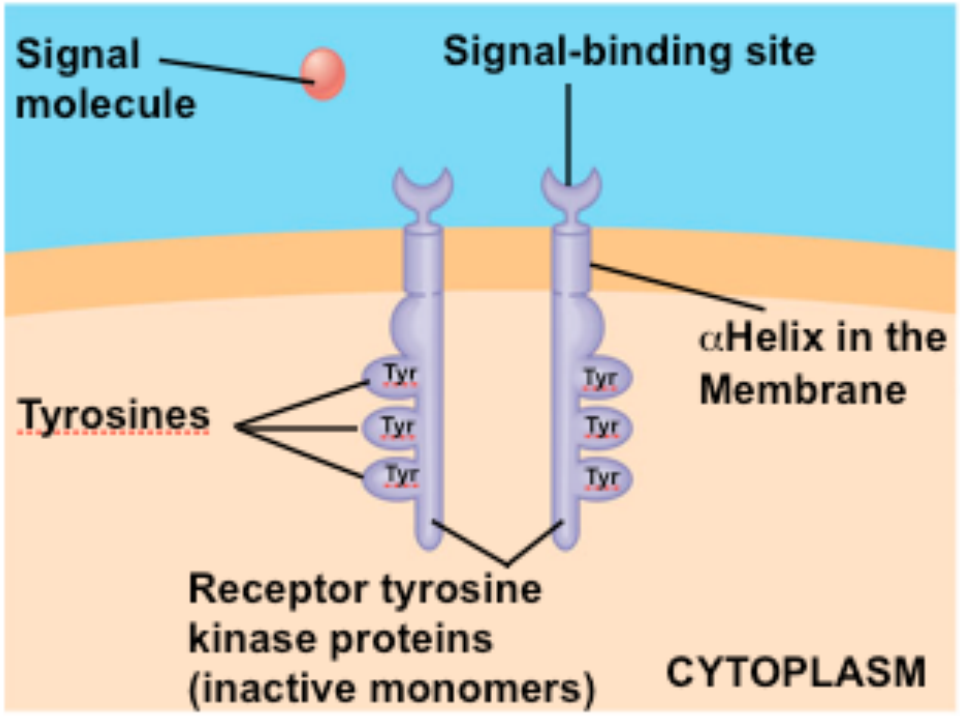


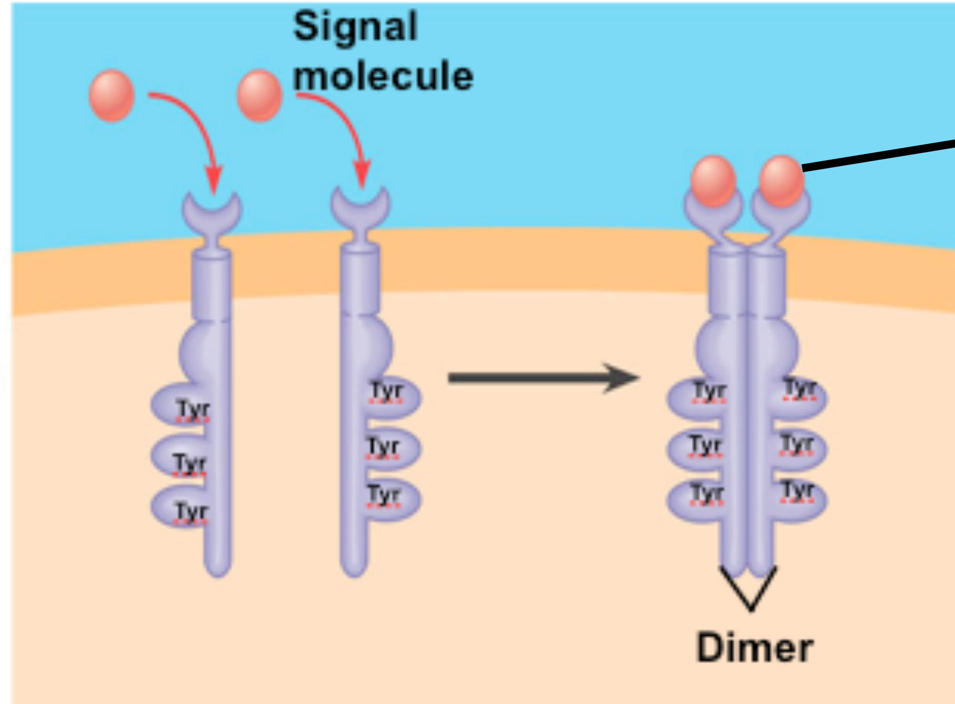
1. **Activated G protein releases from receptor,**
2. **moves along membrane**
3. **binds to another molecule (ie enzyme),**
4. **the binding in turn activates the enzyme**



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**

Receptor Tyrosine Kinases

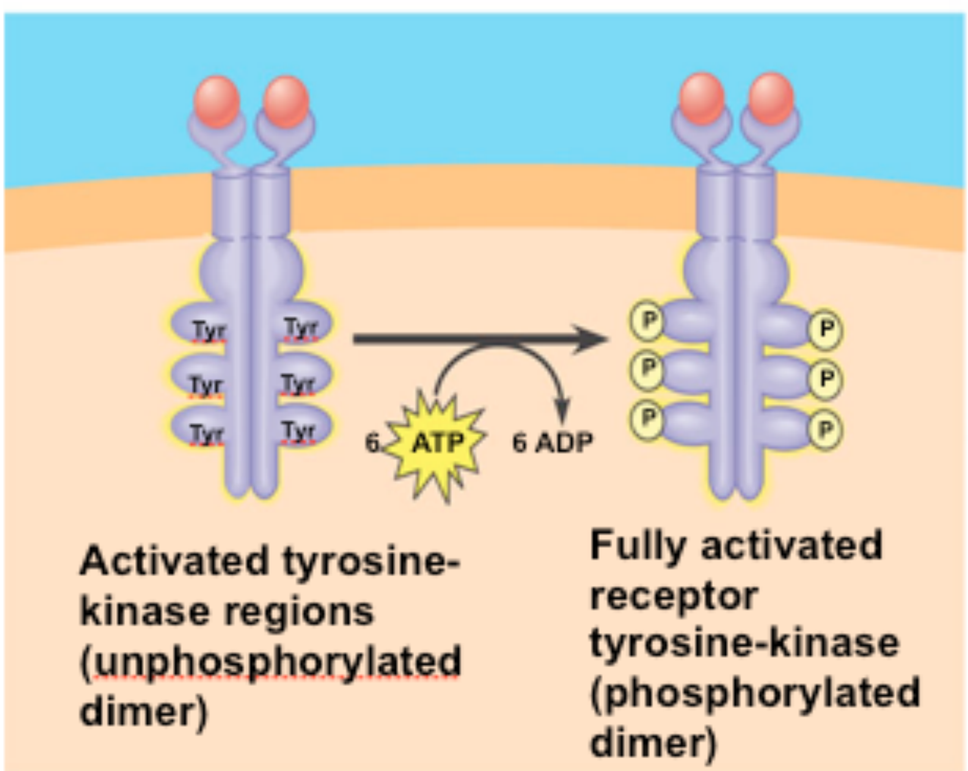


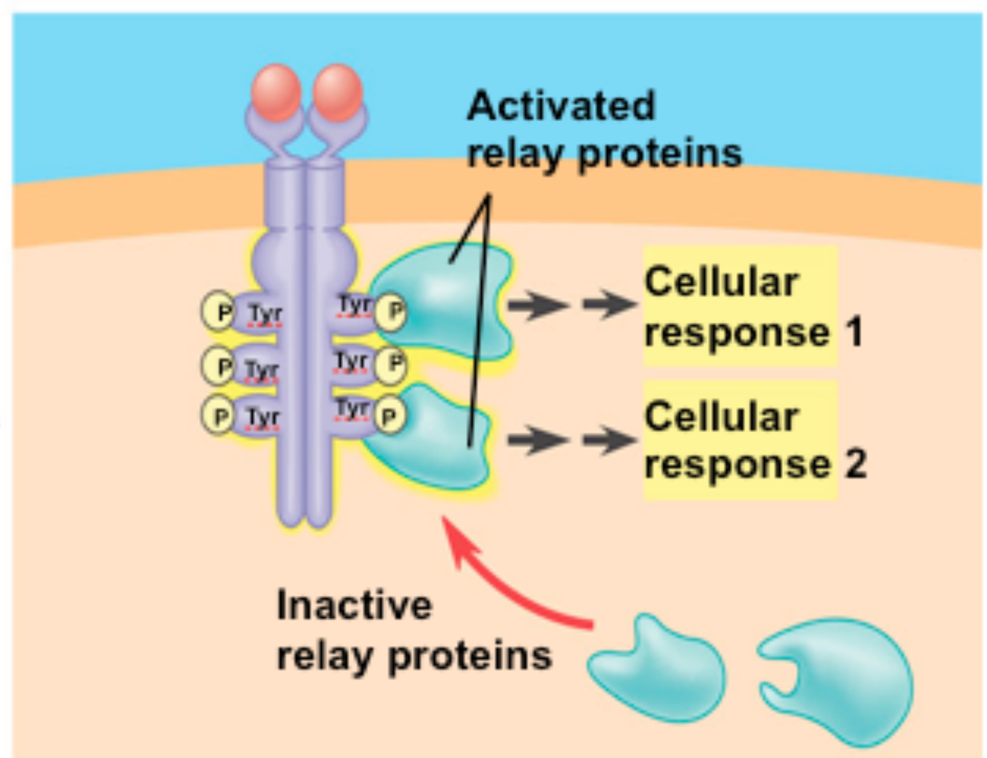


often
growth factors

1. Receptors are separate in the inactive state

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



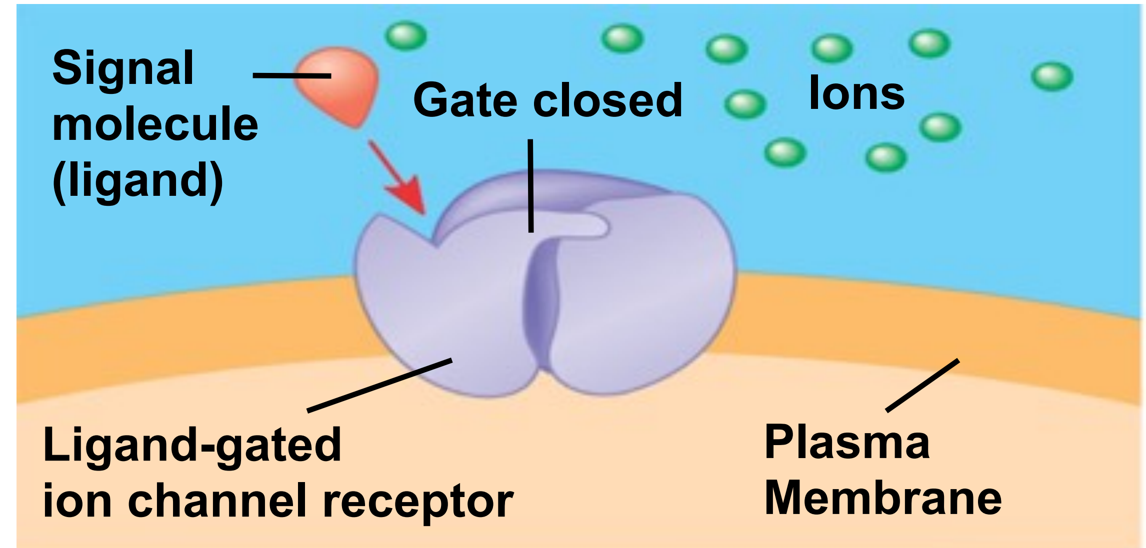


1. Each Tyrosine Kinase adds a phosphate to a tyrosine

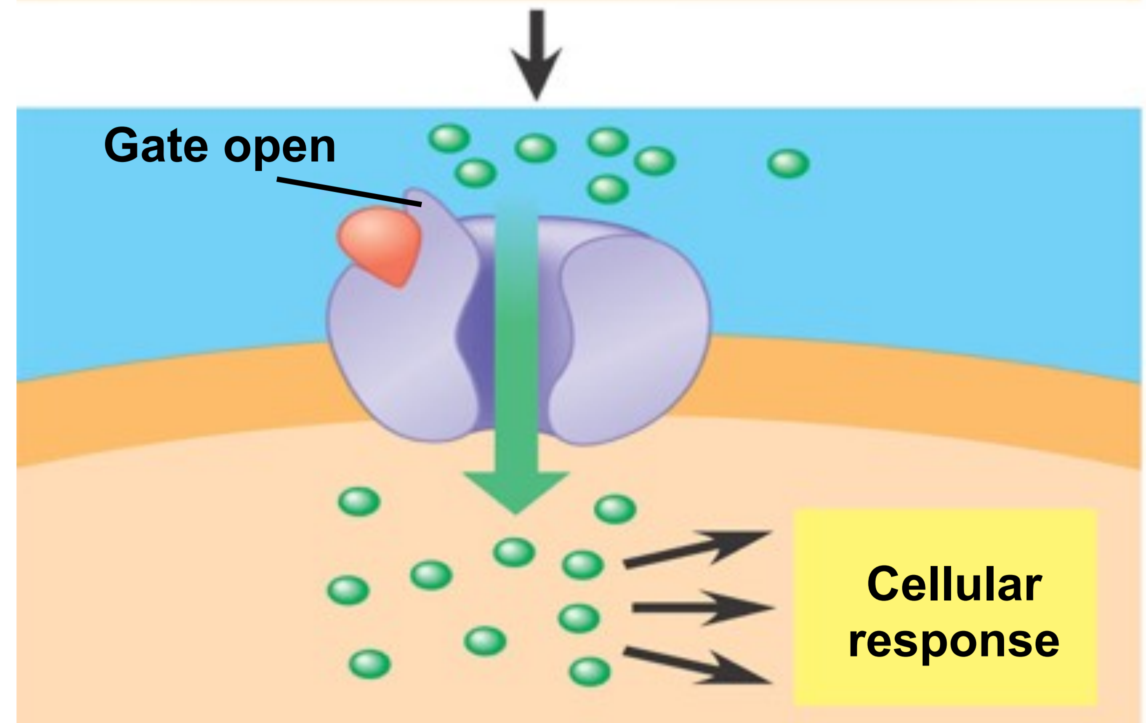
1. Each activated Tyrosine Kinase can activate a different relay protein

Ion Channel Receptors

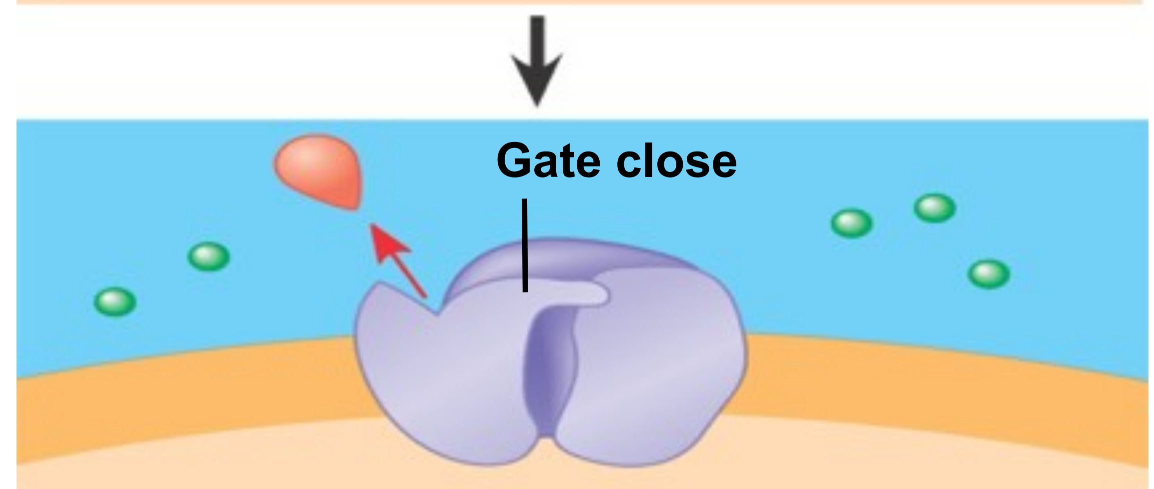
1. Ligand gated ion channels are closed until a ligand binds
2. Ligand gated ion channels are specific to certain ions



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



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

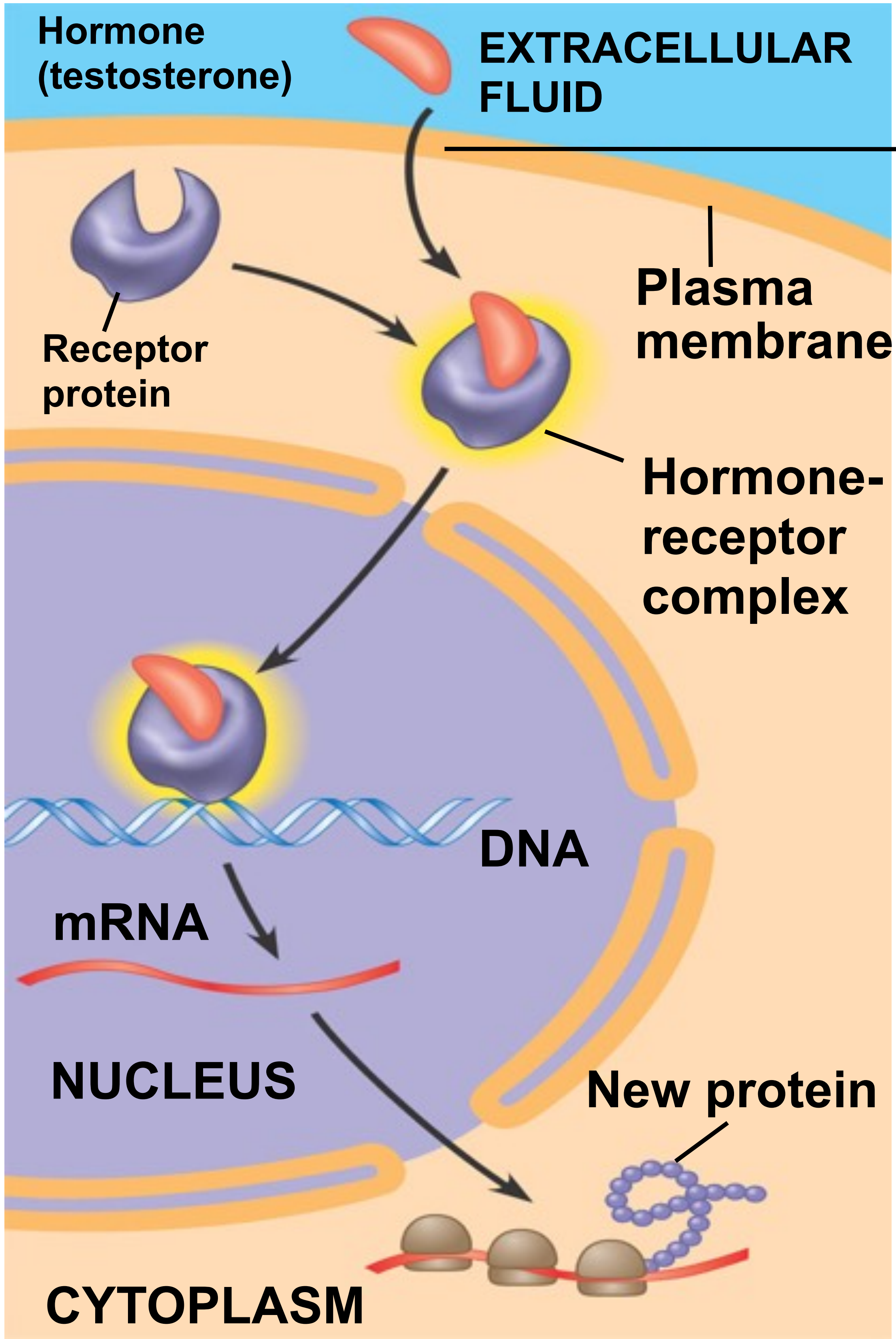
The steroid hormone testosterone passes through the plasma membrane.

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.

Intracellular Receptors



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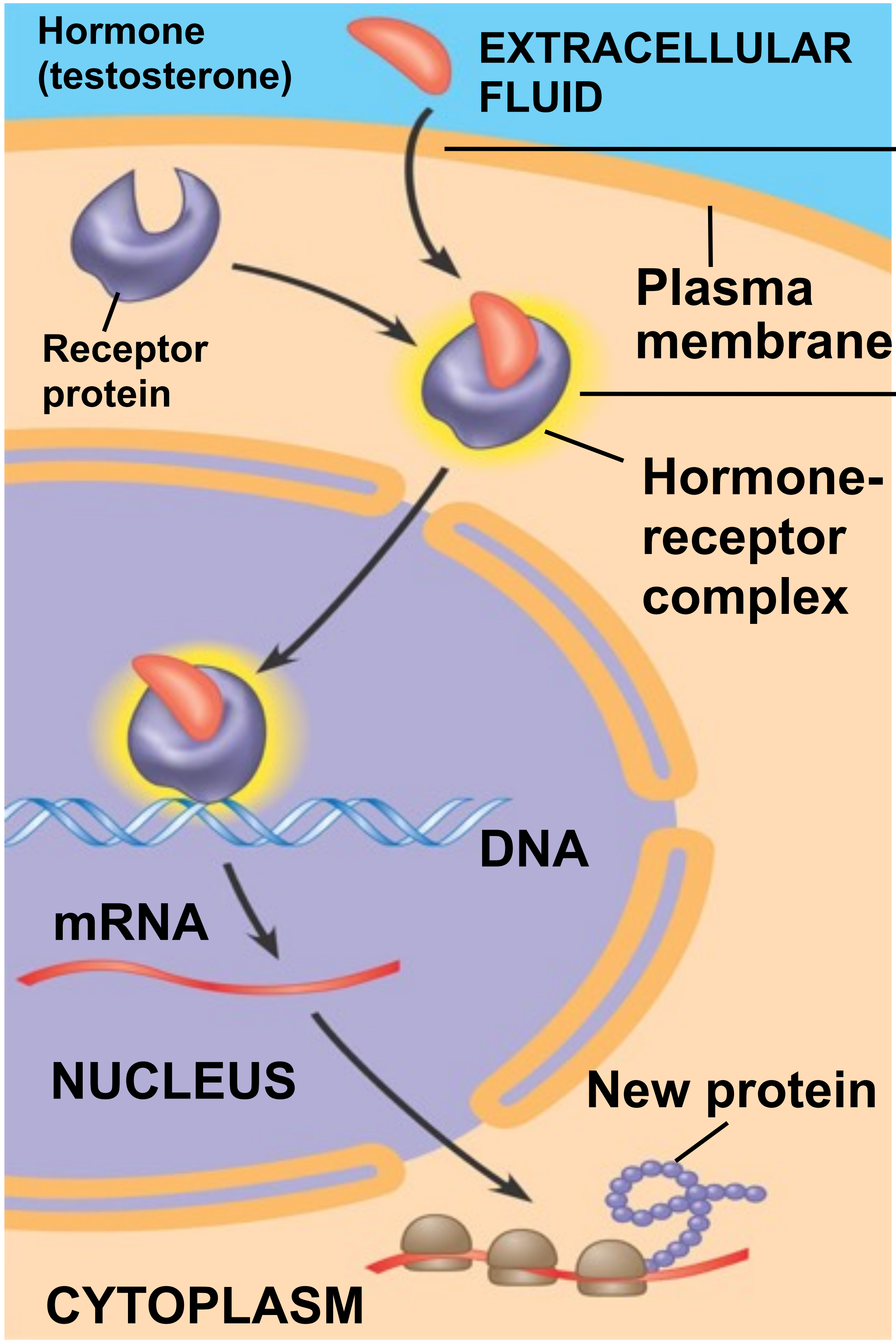

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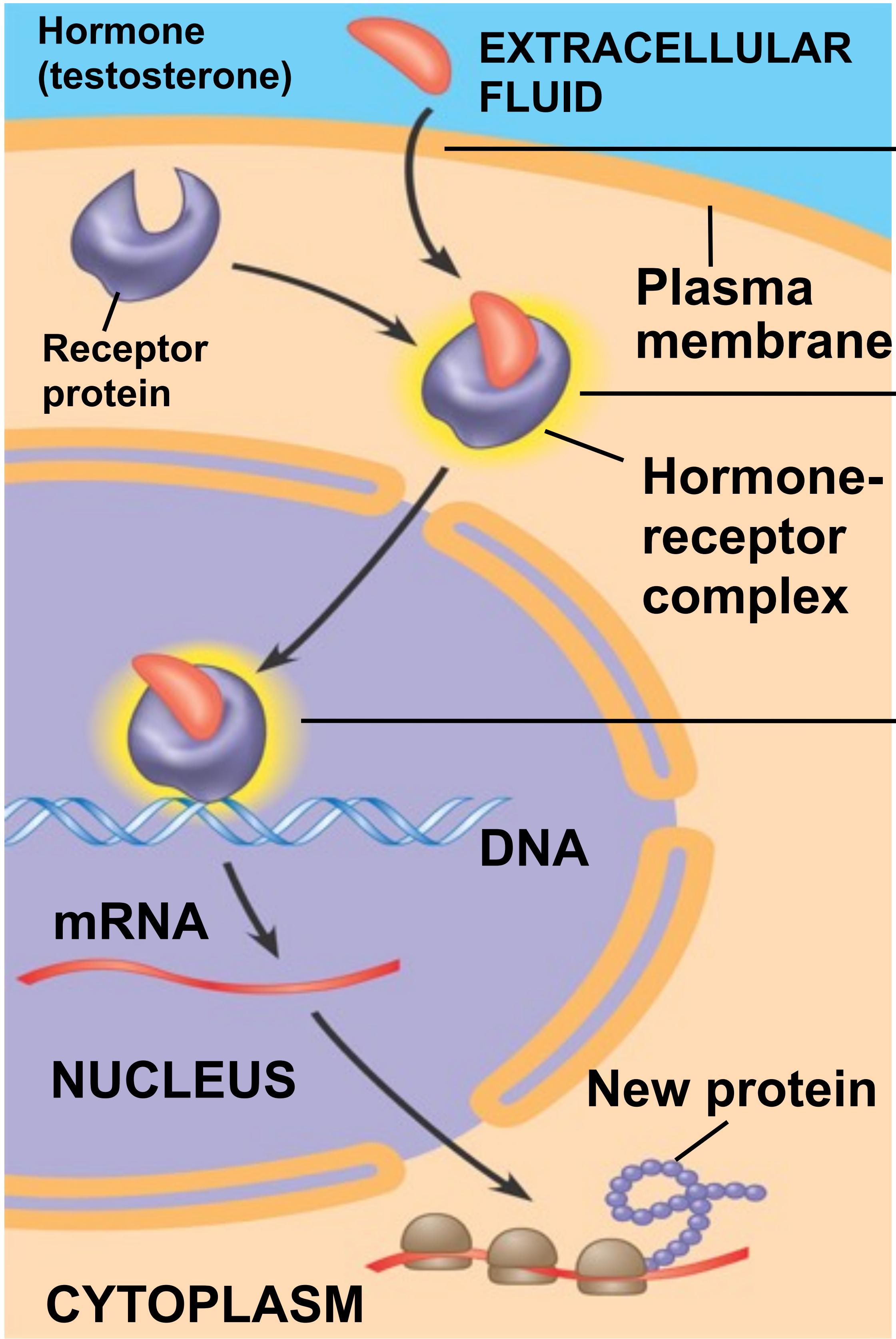

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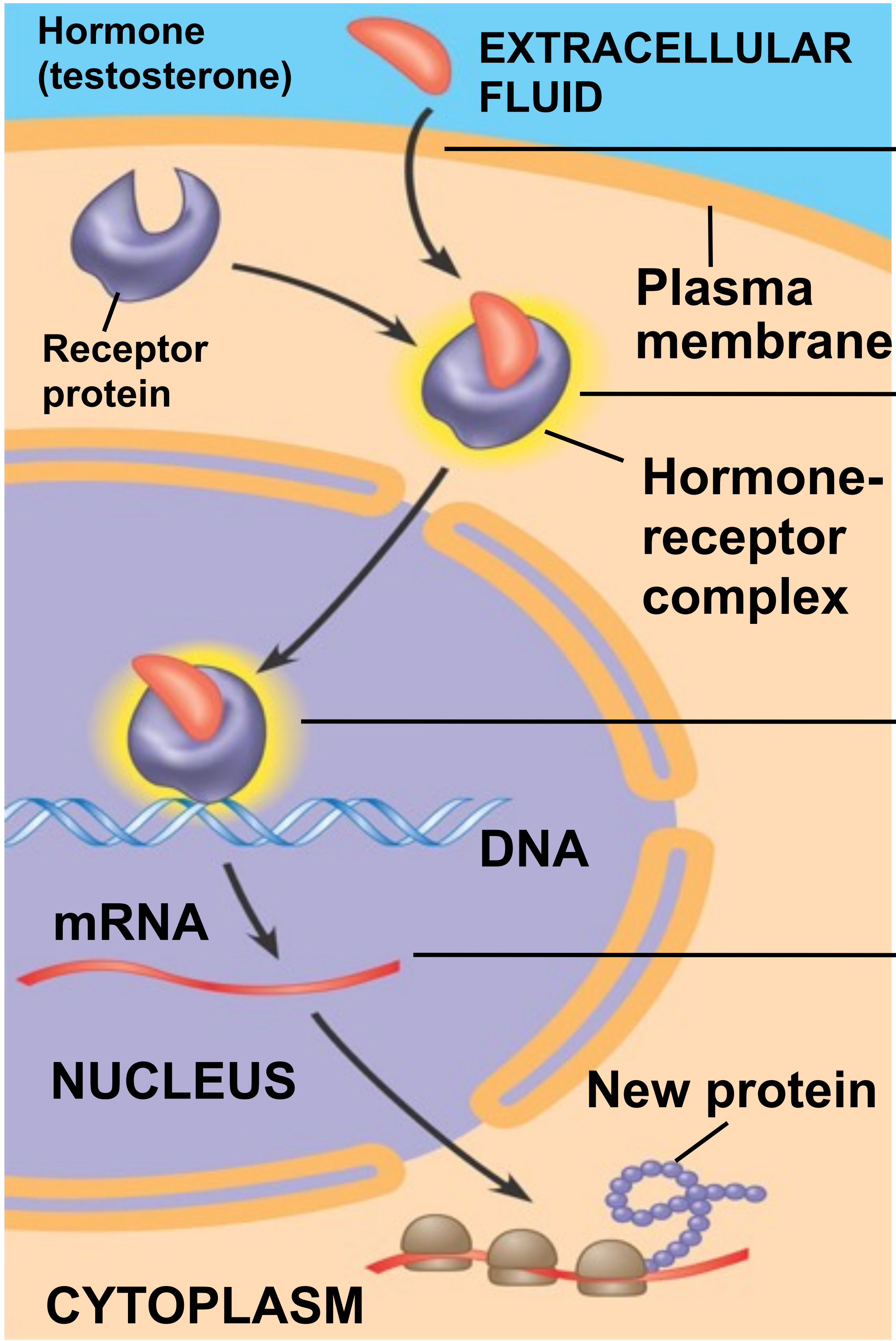

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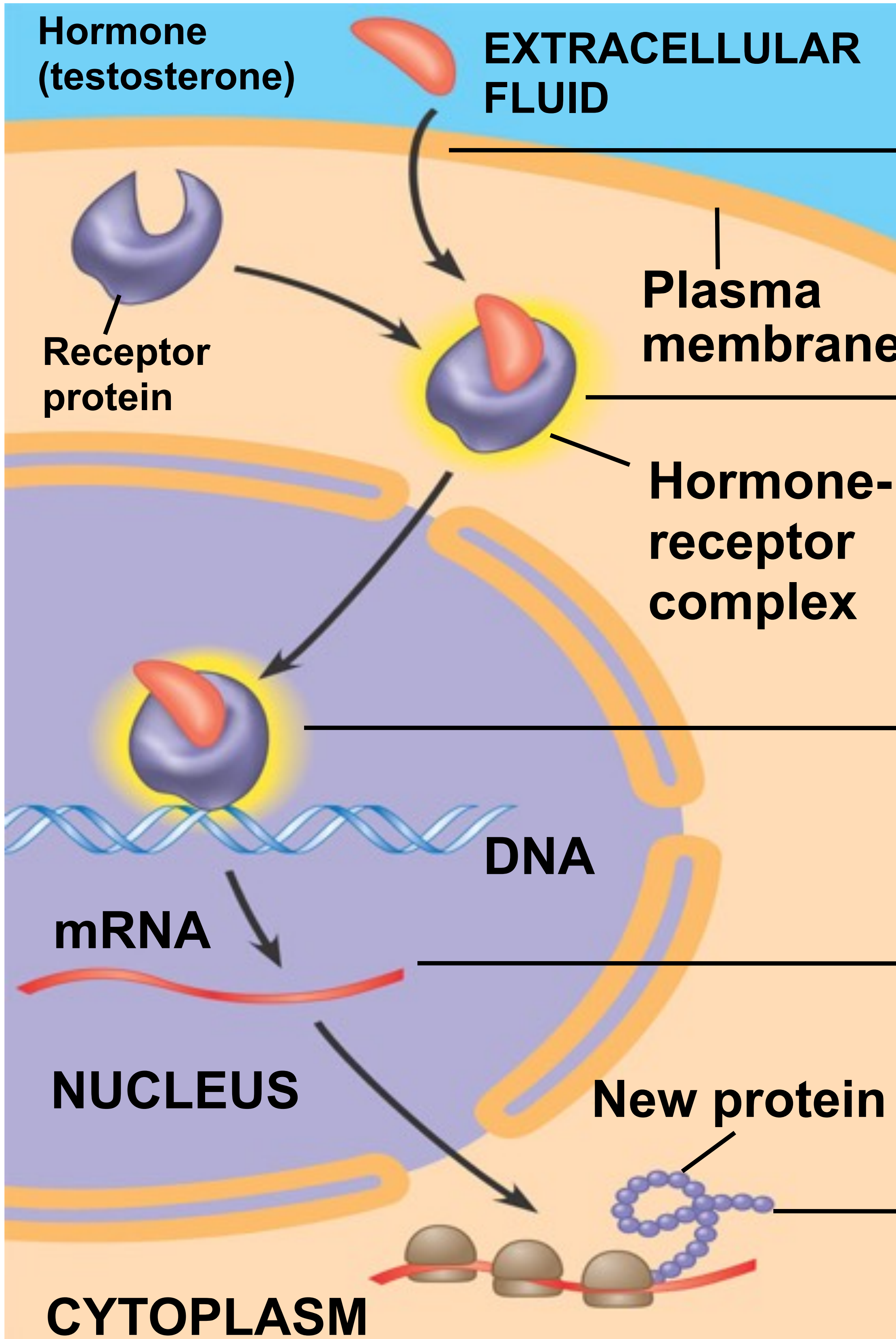


The steroid hormone testosterone passes through the plasma membrane.

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

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

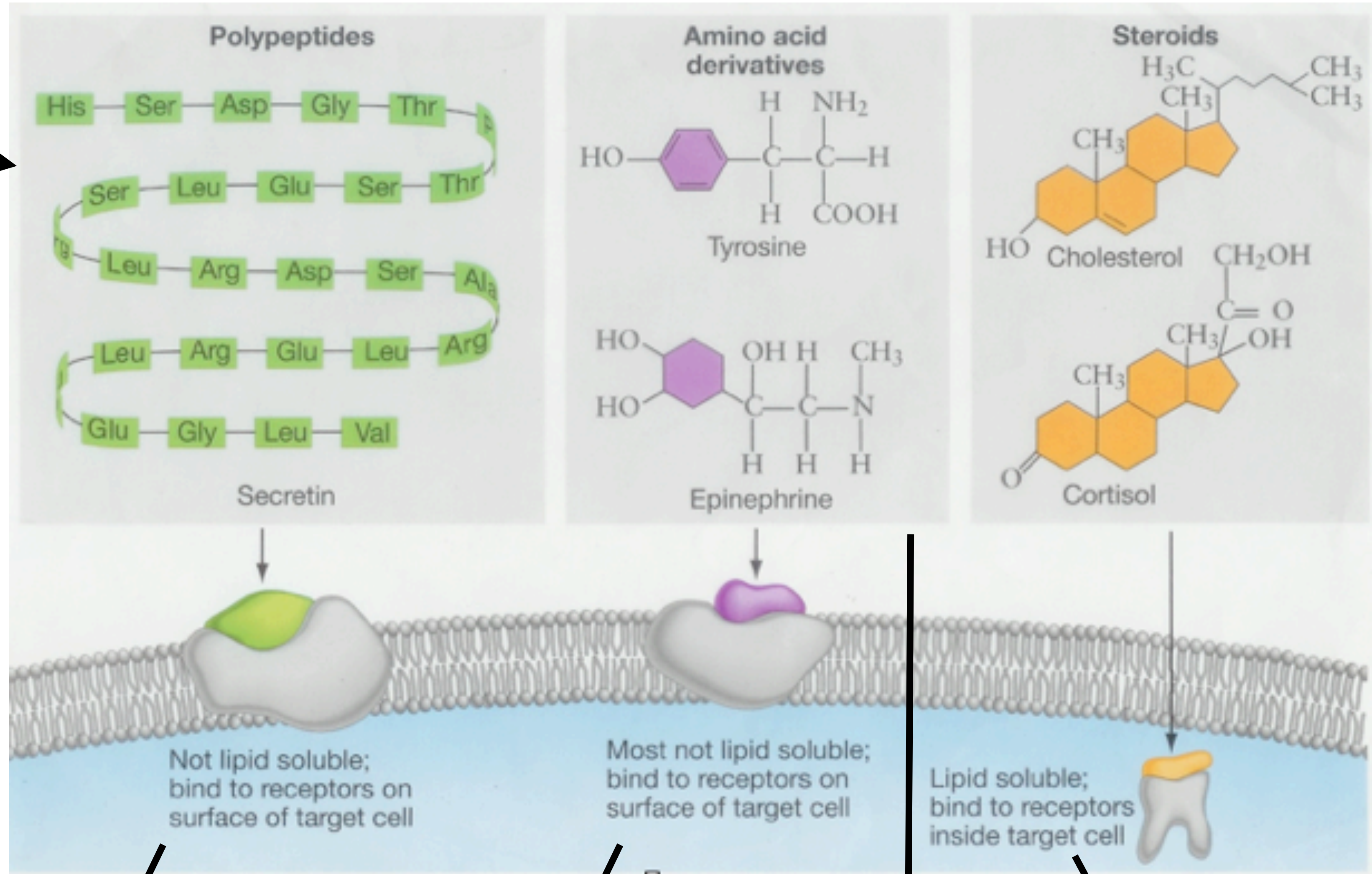
The bound protein stimulates the transcription of the gene into mRNA.

The mRNA is translated into a specific protein.

The Bakery Analogy

The Customer

The Bakery



Usually turns proteins already present in the cell on or off

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

"Selecting bakery items already made from the display case"

"Ordering special bakery that need to be made"

Essential knowledge 3.D.3: Signal transduction pathways link signal reception with cellular response.

b. Signal transduction is the process by which a signal is converted to a cellular response.

Evidence of student learning is a demonstrated understanding of each of the following:

1. Signaling cascades relay signals from receptors to cell targets, often amplifying the incoming signals, with the result of appropriate responses by the cell.

Essential knowledge 3.D.3: Signal transduction pathways link signal reception with cellular response.

2. Second messengers are often essential to the function of the cascade.

To foster student understanding of this concept, instructors can choose an illustrative example such as:

- Ligand-gated ion channels
- Second messengers, such as cyclic GMP, cyclic AMP calcium ions, and inositol triphosphate

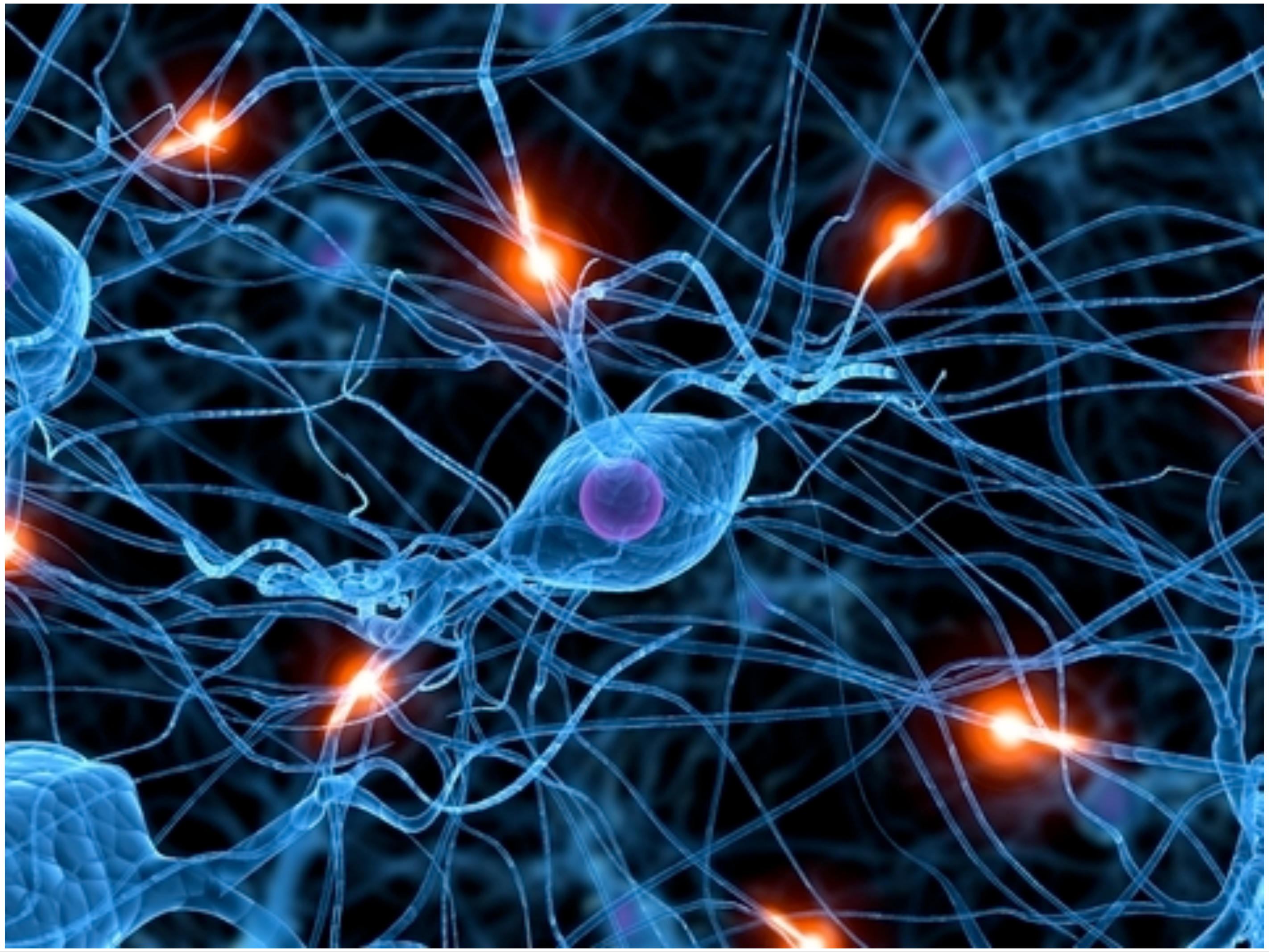
3. Many signal transduction pathways include:

i. Protein modifications (an illustrative example could be how methylation changes the signaling process)

ii. Phosphorylation cascades in which a series of protein kinases add a phosphate group to the next protein in the cascade sequence

Cell Communication

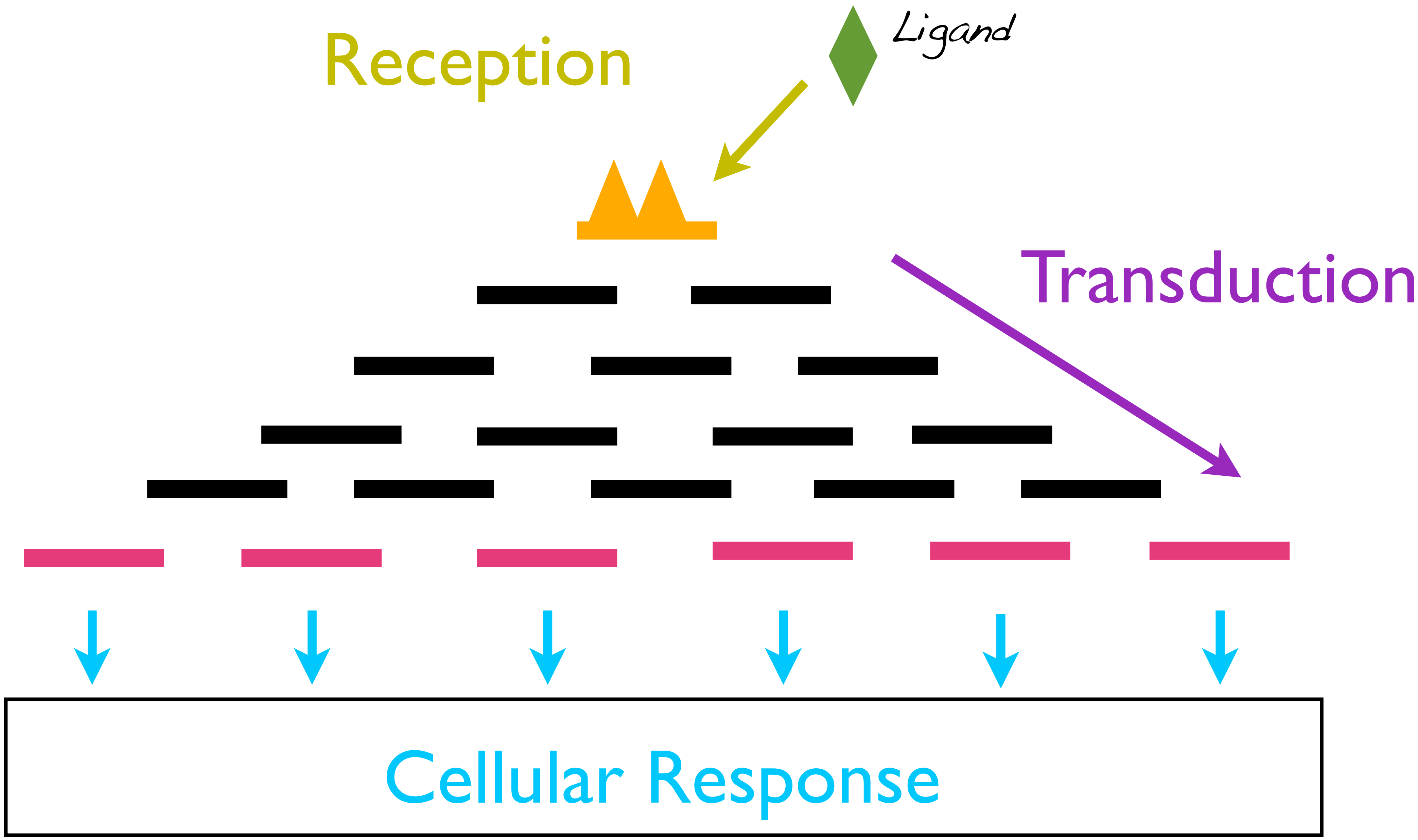
Main Idea: The chemical signal binds receptors, but receptors can not cause the cellular response, moving the information from the receptor to the molecule responsible for the cellular response is called transduction.



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)

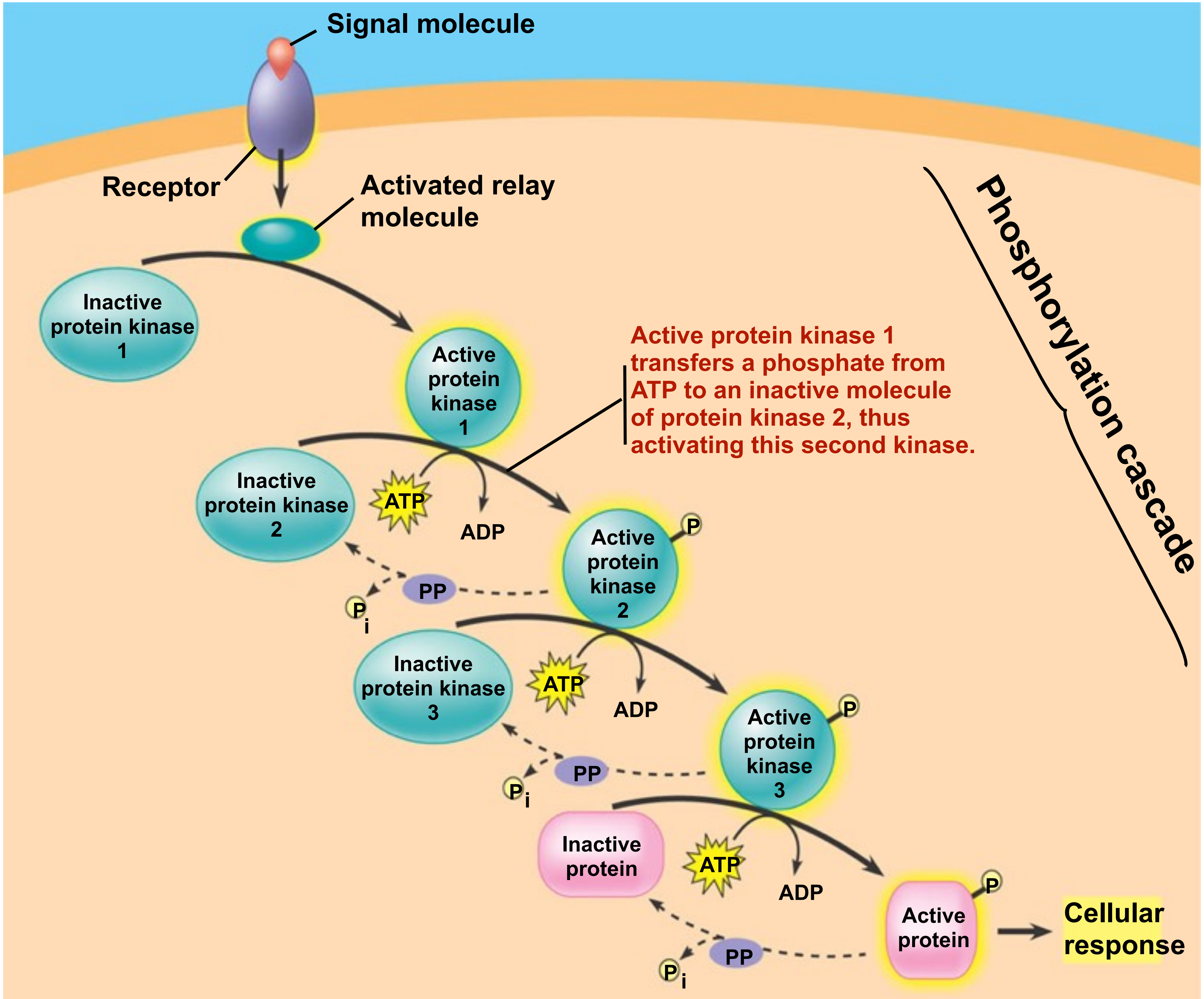
Phosphorylation & Dephosphorylation

- 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!

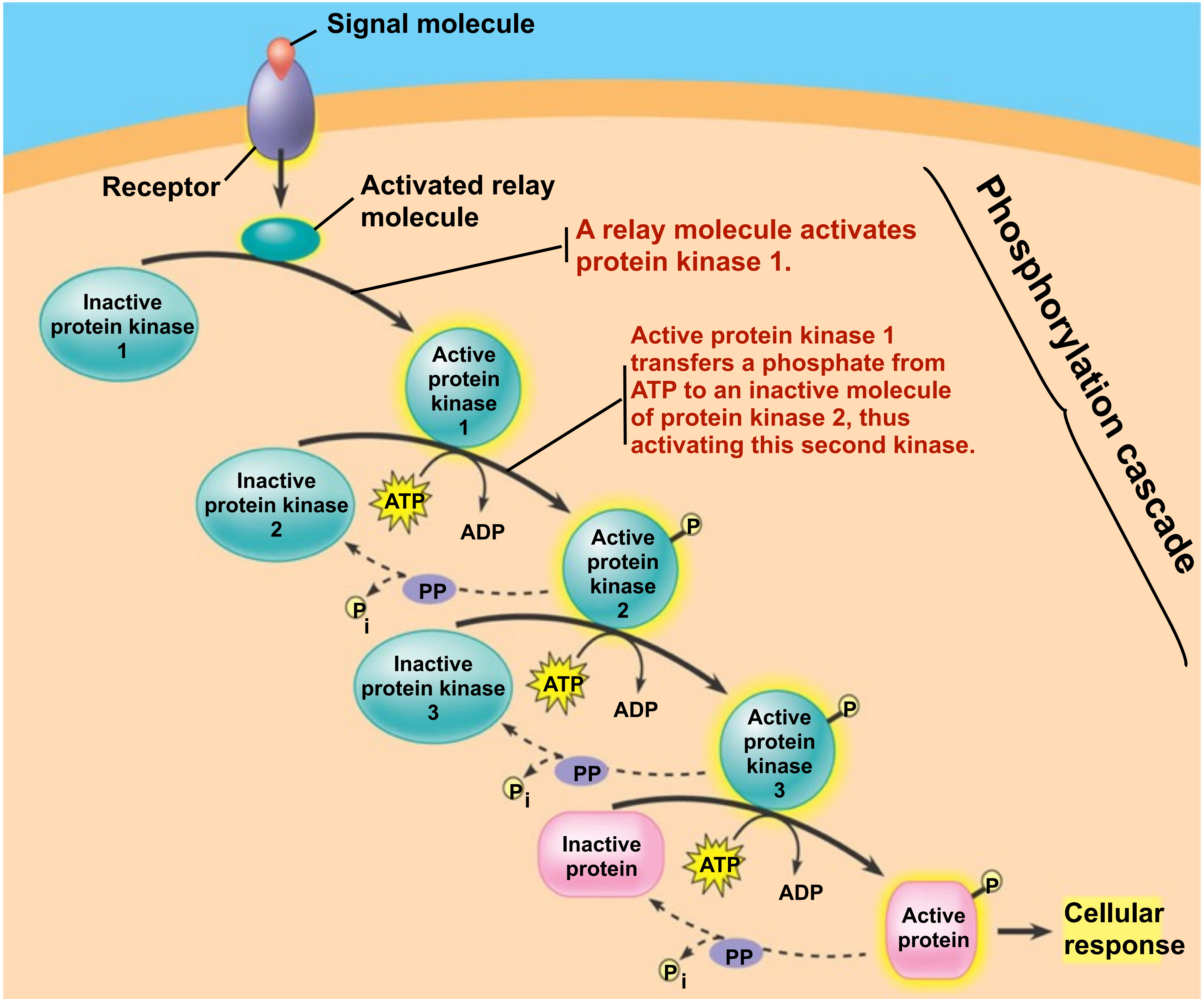
Signal Transduction Pathways

Active protein kinase 1 transfers a phosphate from ATP to an inactive molecule of protein kinase 2, thus activating this second kinase.

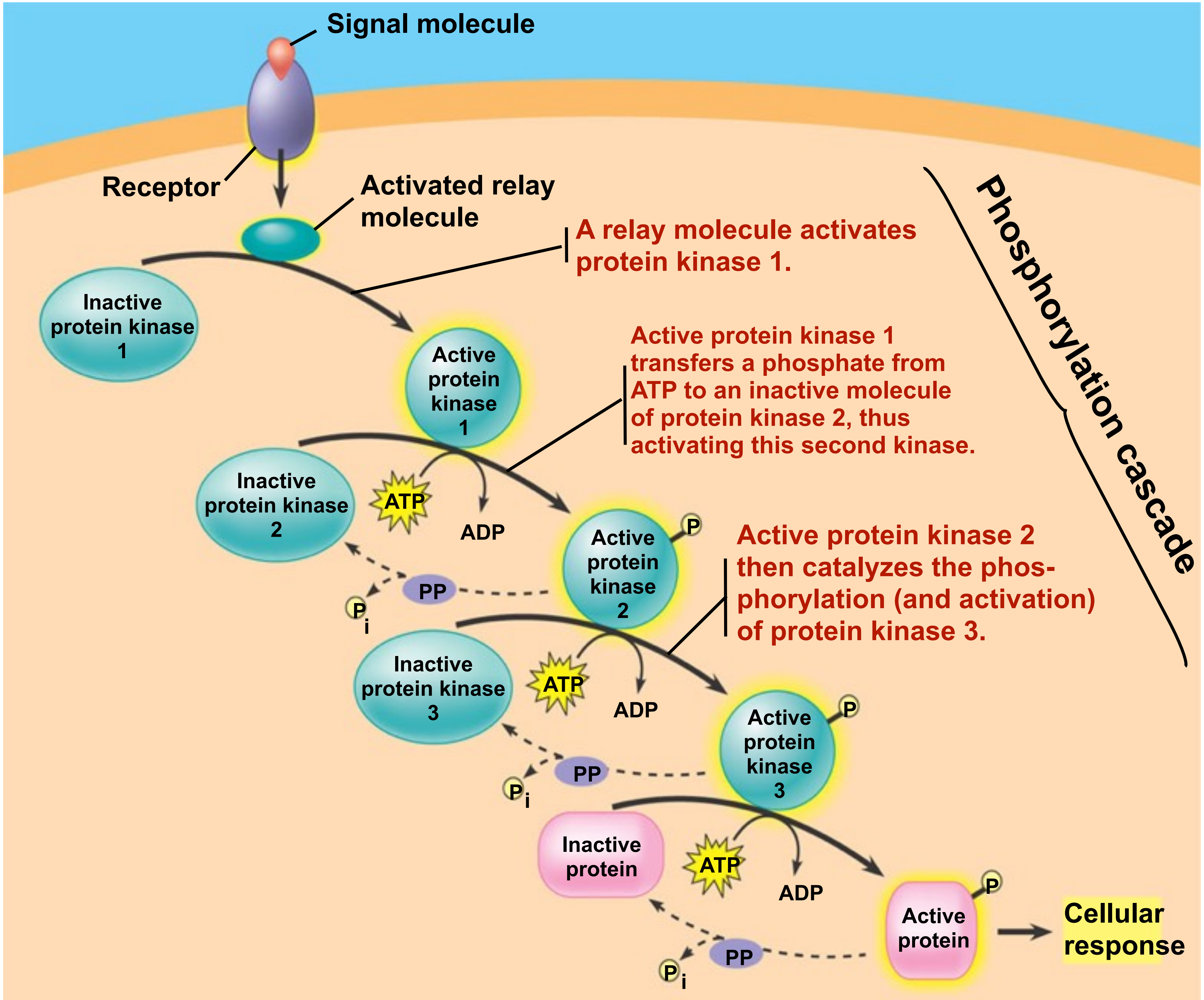
Signal Transduction Pathways



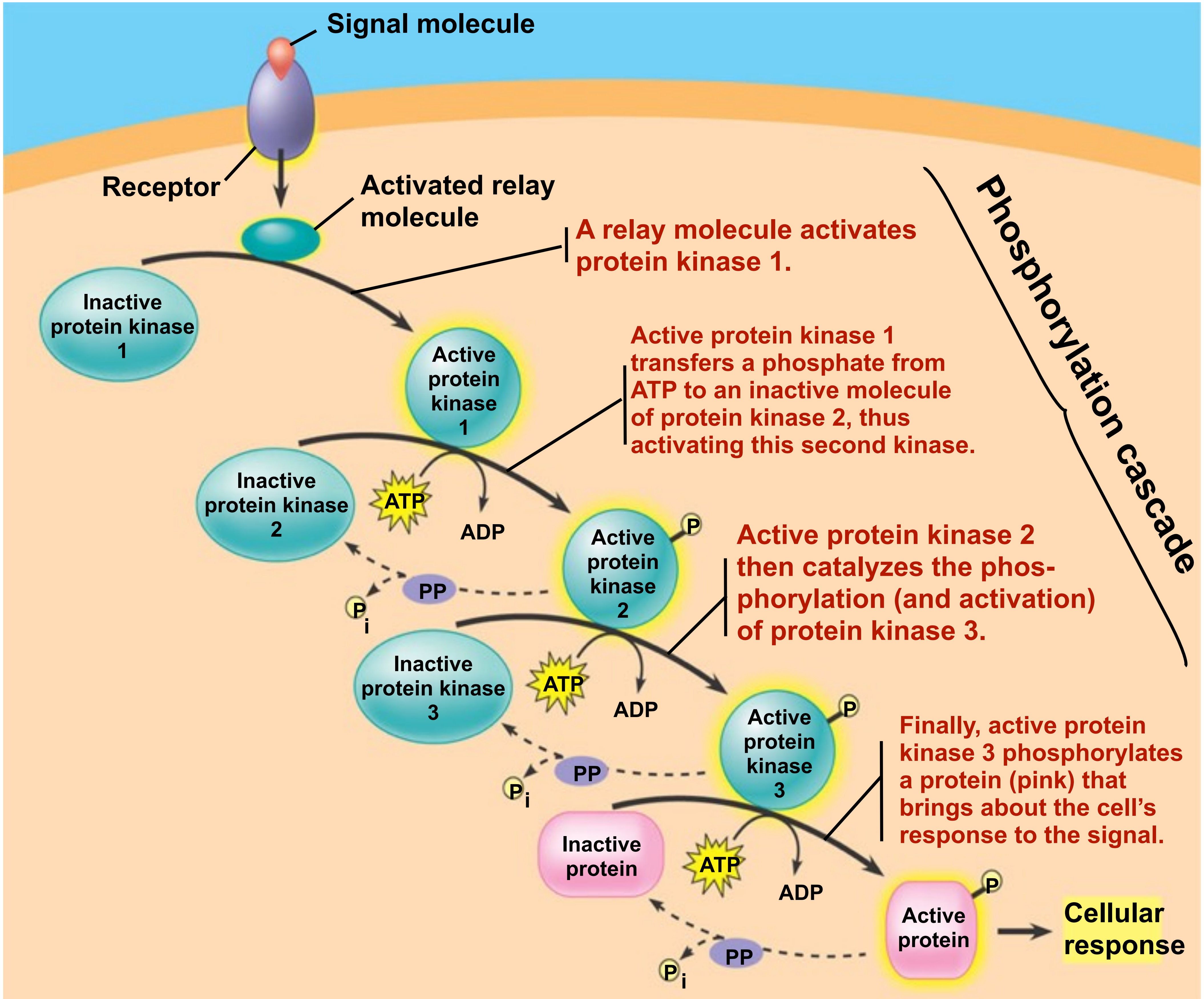
Signal Transduction Pathways



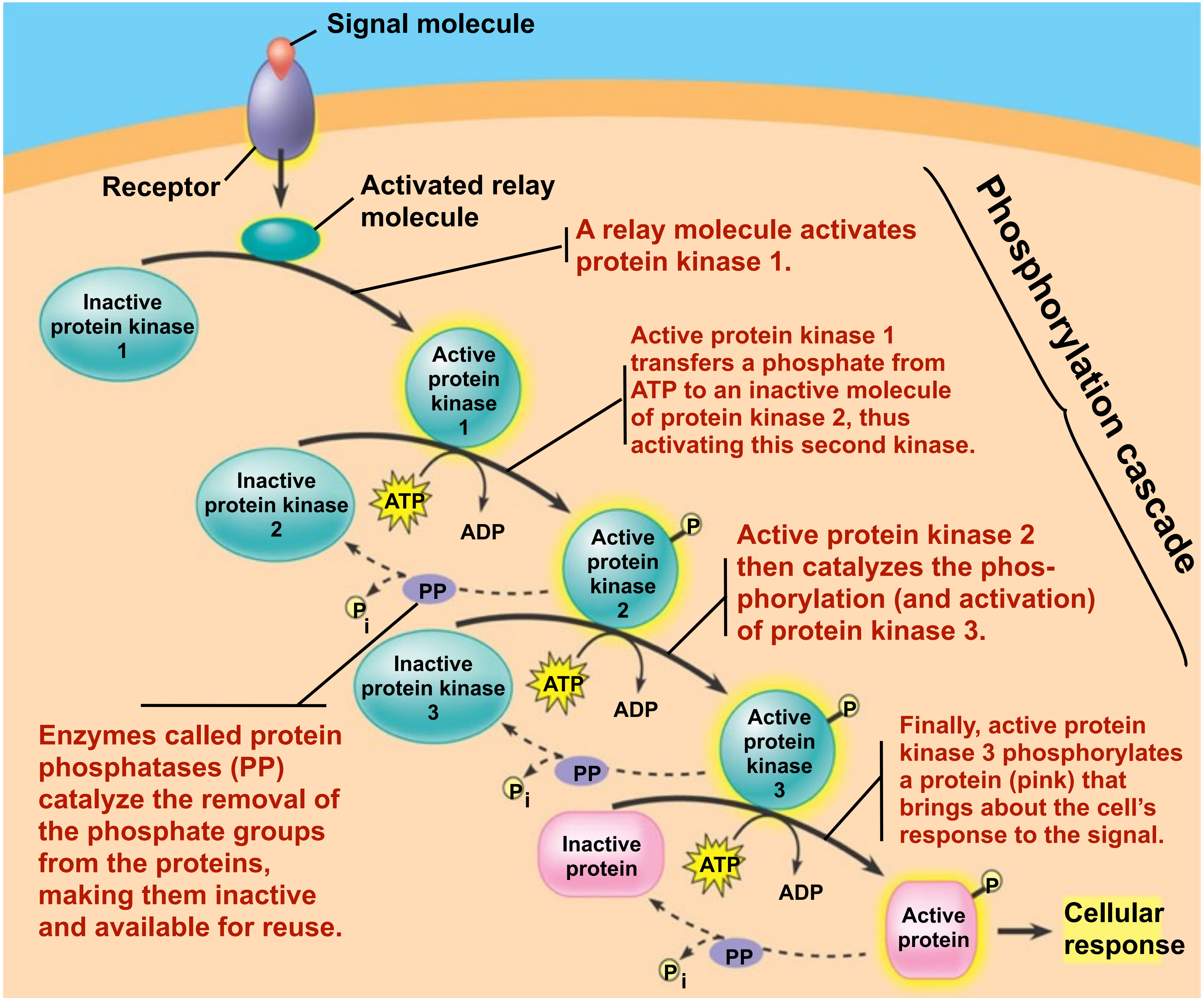
Signal Transduction Pathways



Signal Transduction Pathways



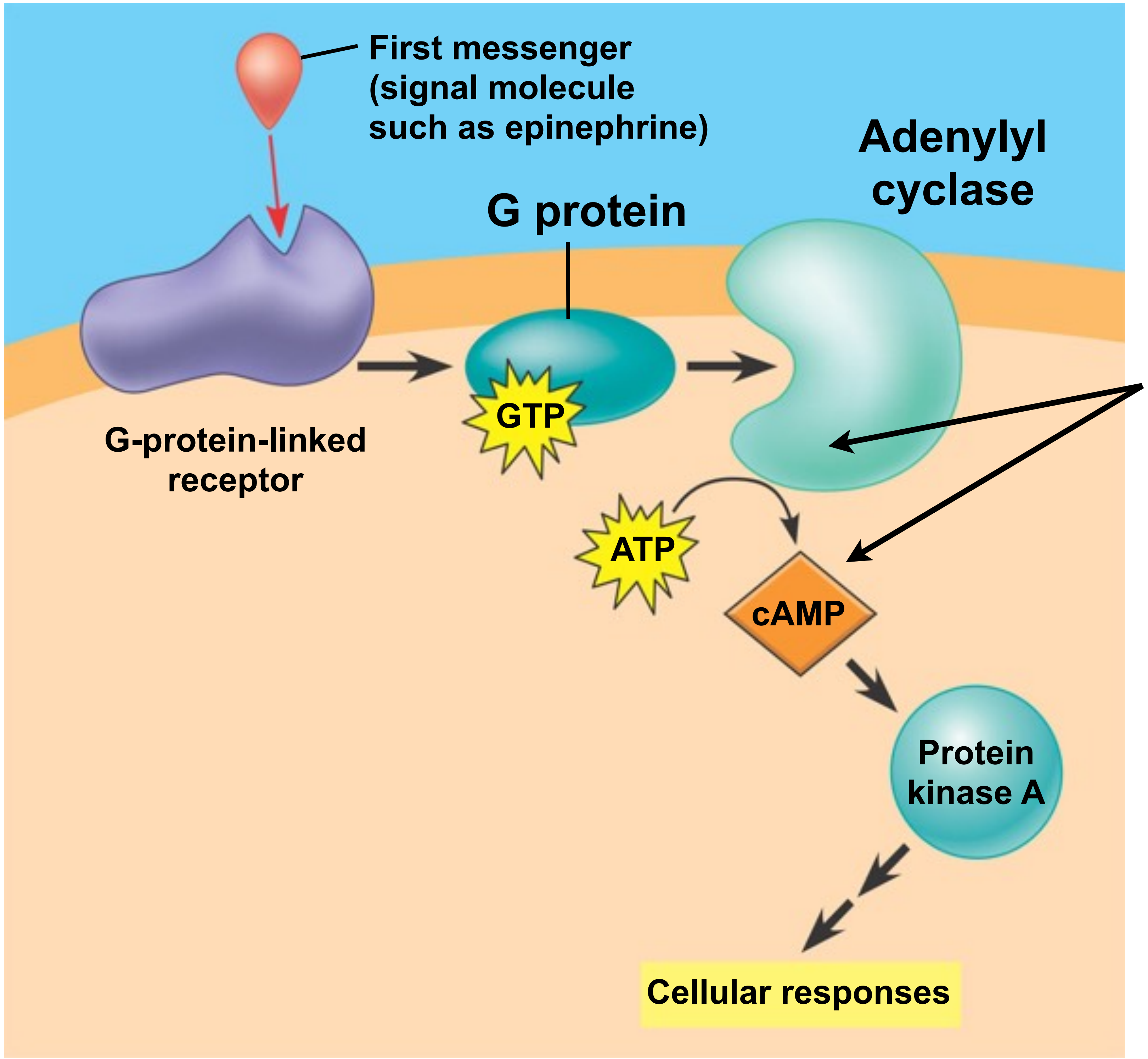
Signal Transduction Pathways



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

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

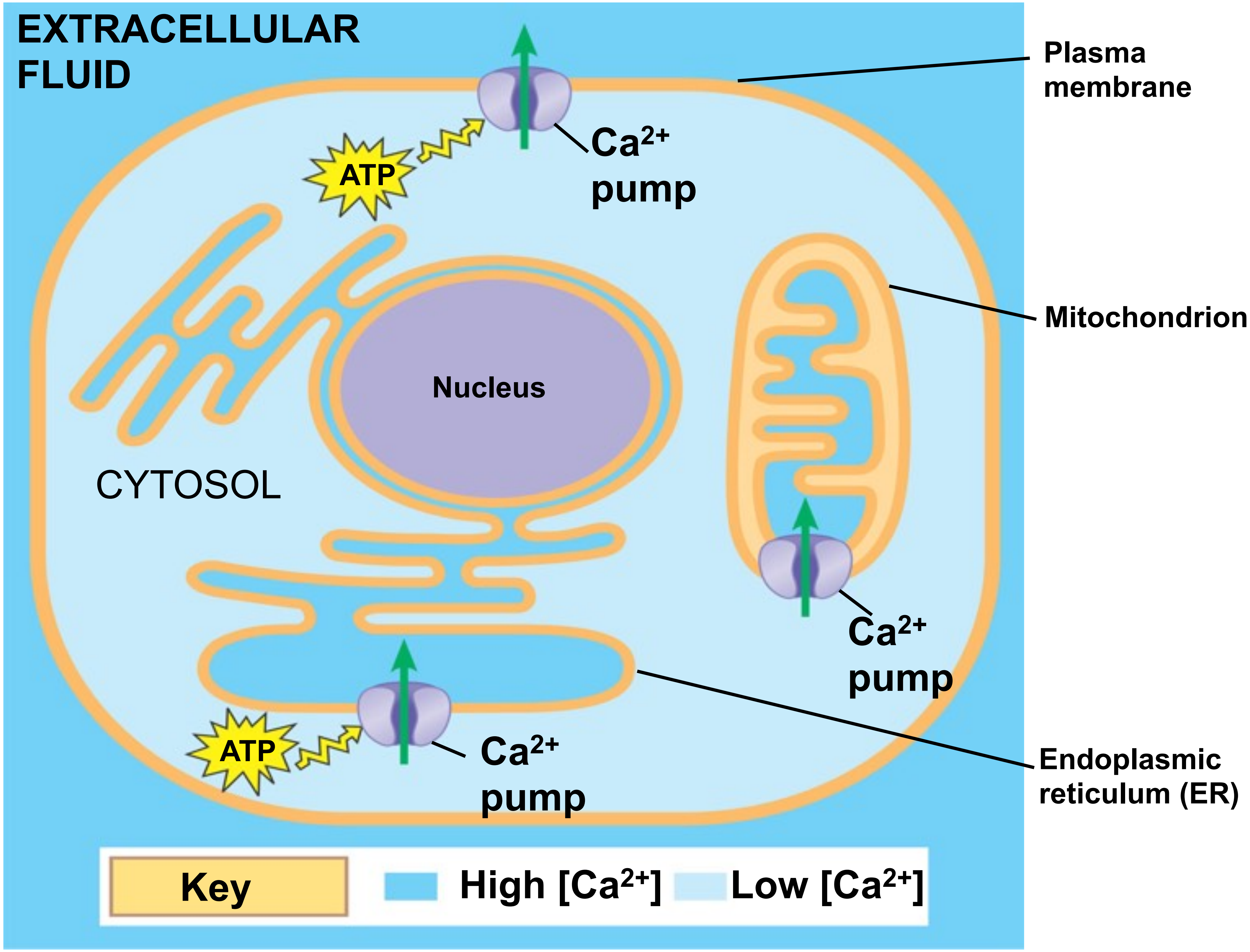
Calcium Ions & Inositol Triphosphate (IP_3)

- 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

* sliding filament theory

** synaptic transmission in nerve transmission

Calcium Ions



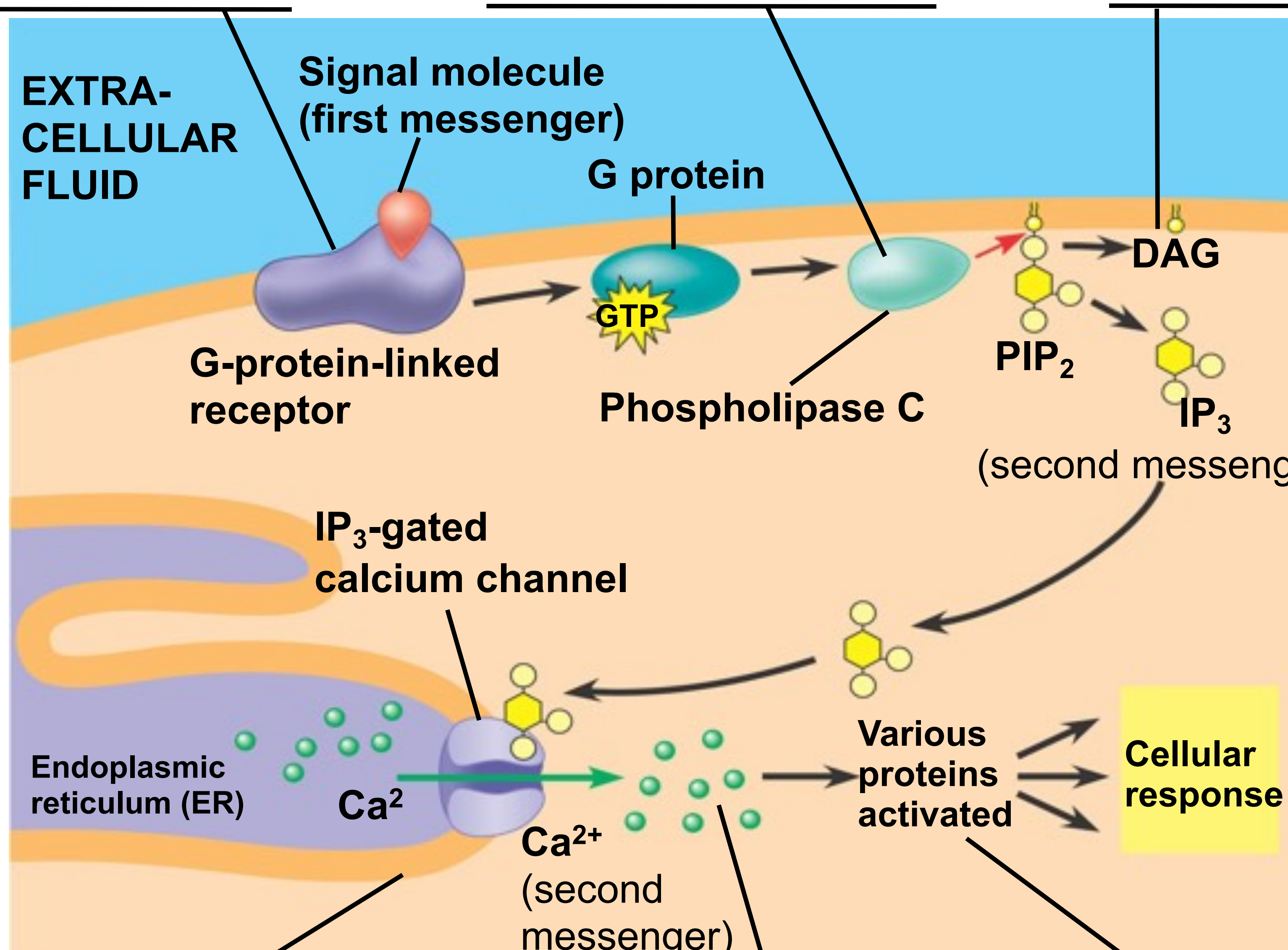
Calcium Ions & Inositol Triphosphate (IP_3)

- 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.

Learning Objectives:

LO 3.36 The student is able to describe a model that expresses the key elements of signal transduction pathways by which a signal is converted to a cellular response. [See SP 1.5]