

Cell Signaling (Part II)

BIOL366

4.10.25

Matthew Ellis, PhD

Learning Objectives for Today's Lecture:

Upon completing this module, **you should be able to:**

- Describe how **ion channels** can be used to propagate cellular signals by leveraging electrochemical gradients
- Understand the four main methods of **intercellular signaling** (e.g., endocrine, paracrine, juxtacrine, autocrine)
- Appreciate the complexity of cellular signaling, and devise ways to dissect signaling pathways
- Review main concepts from Ch 11-16 (Part I) prior to the exam Tuesday

Key Terms

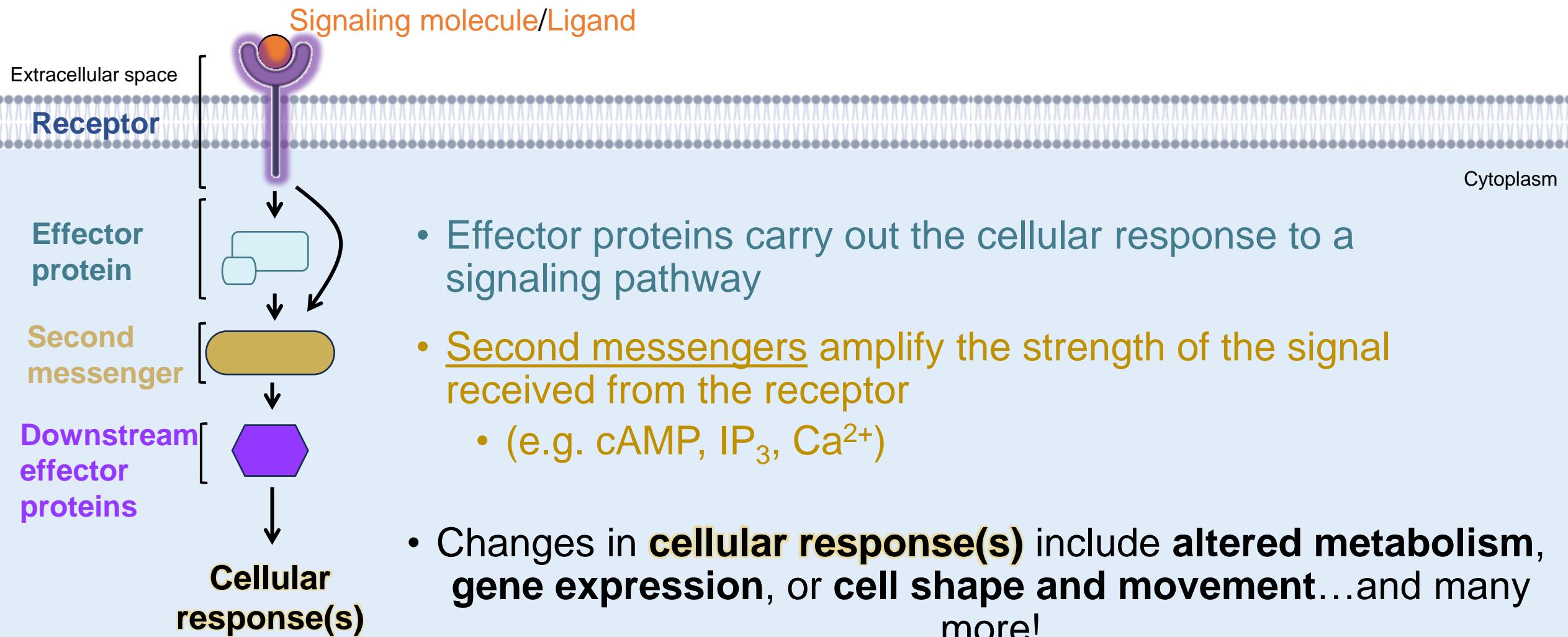
- **Ion channels:** Highly selective, narrow pores allowing passage of one type of charged ion through the membrane while excluding others
- **Endocrine Signaling:** Long distance intercellular communication where hormones are released into the blood stream to reach distant target cells
- **Paracrine Signaling:** Short distance intercellular communication where signaling molecules diffuse over short distances to reach target cells
- **Contact Dependent (Juxtacrine) Signaling:** A form of intercellular communication where a membrane-bound protein on one cell directly interacts with a receptor on an adjacent cell
- **Autocrine Signaling:** A “self-signaling” type of cell signaling where a cell releases a signaling molecule that binds to receptors on the same cell

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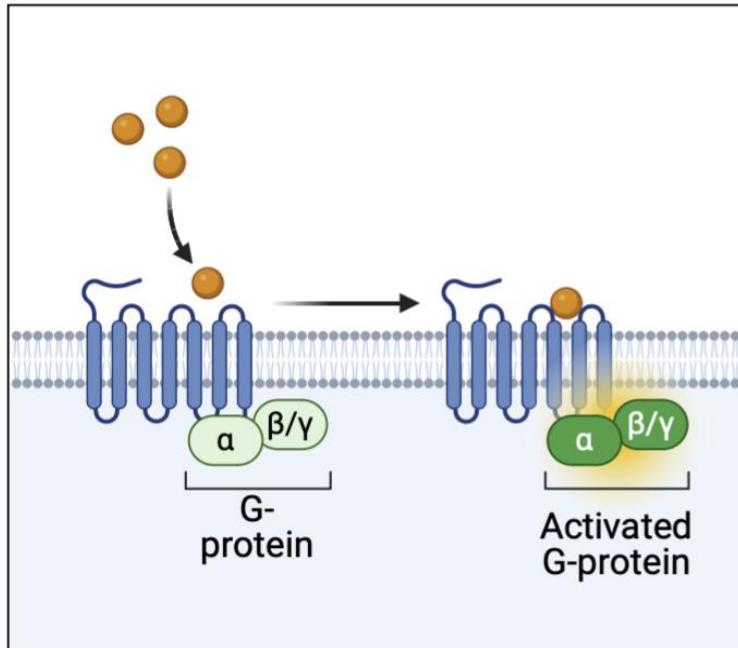
Recall: Signal transduction: the process of converting external signals into intracellular responses



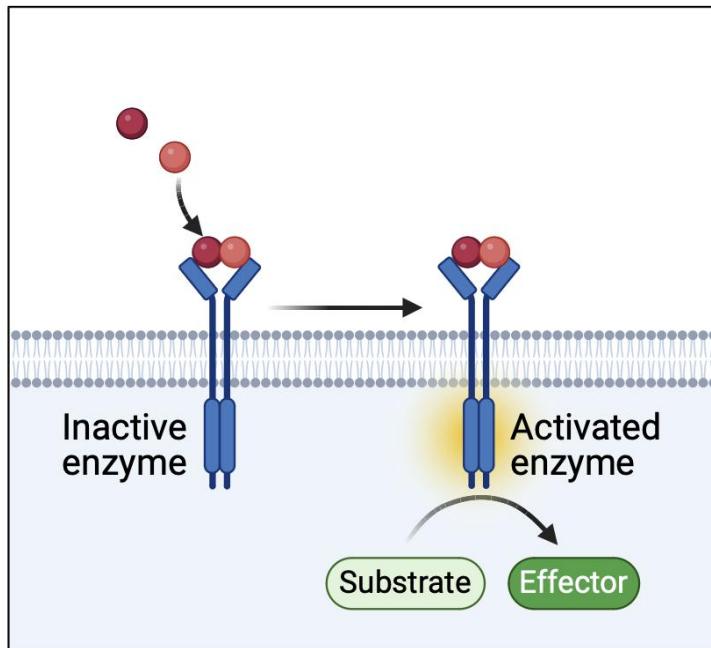
- Effector proteins carry out the cellular response to a signaling pathway
- Second messengers amplify the strength of the signal received from the receptor
 - (e.g. cAMP, IP₃, Ca²⁺)
- Changes in **cellular response(s)** include **altered metabolism**, **gene expression**, or **cell shape and movement**...and many more!

There are 3 main types of Cell Surface Receptors

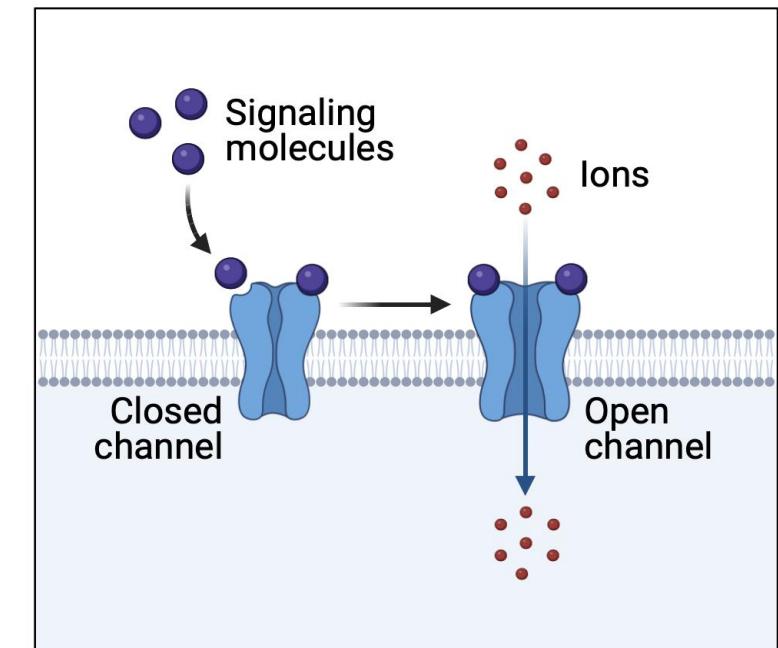
G-protein-coupled receptors



Enzyme-linked receptors

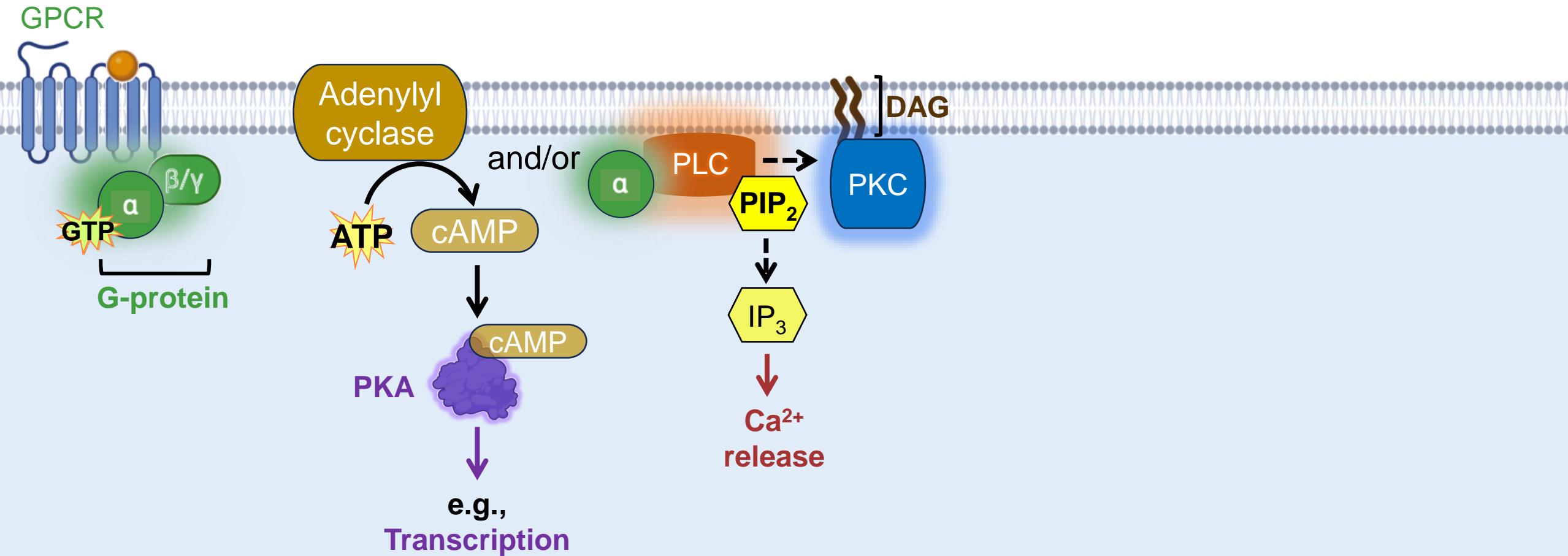


Ion channel-linked receptors

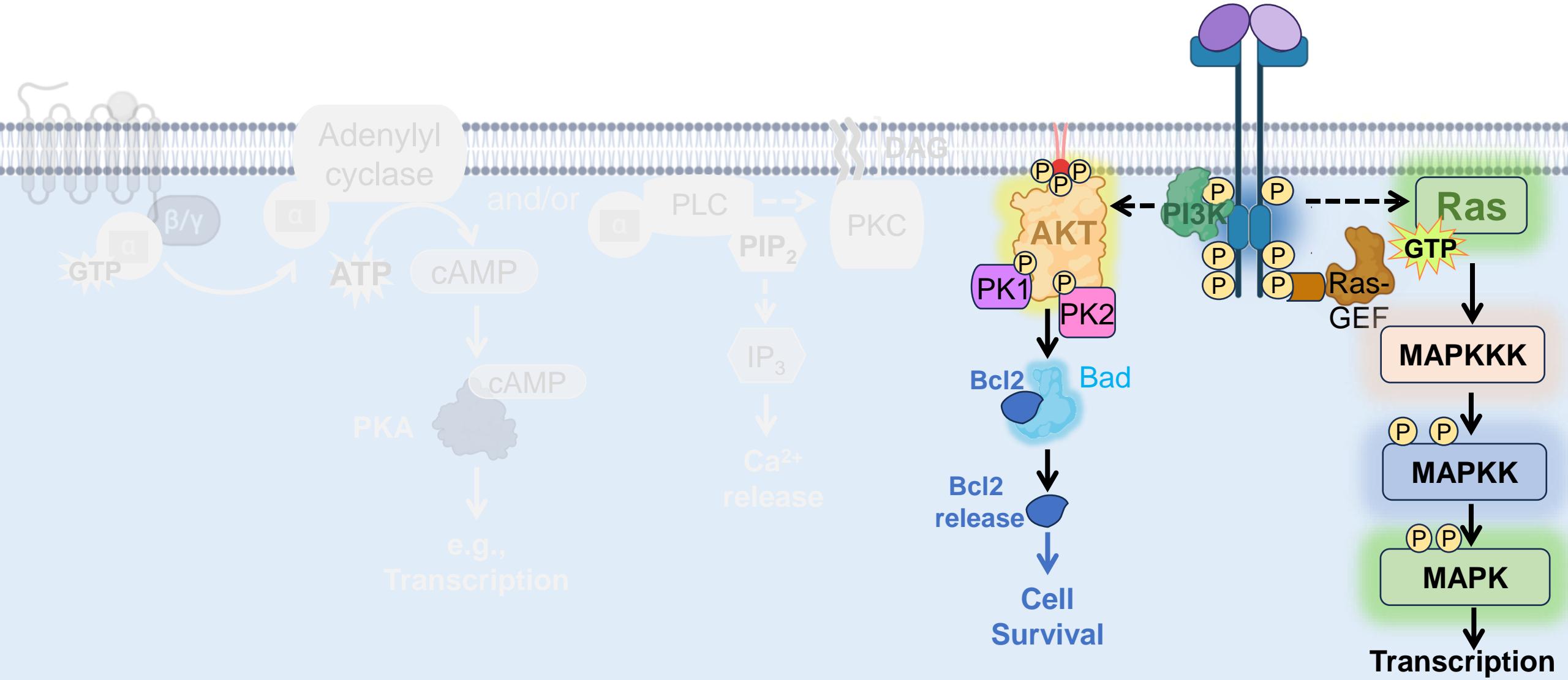


All are activated by signaling molecules (ligands) that trigger intracellular signaling pathways

Recall: GPCRs elicit intracellular responses

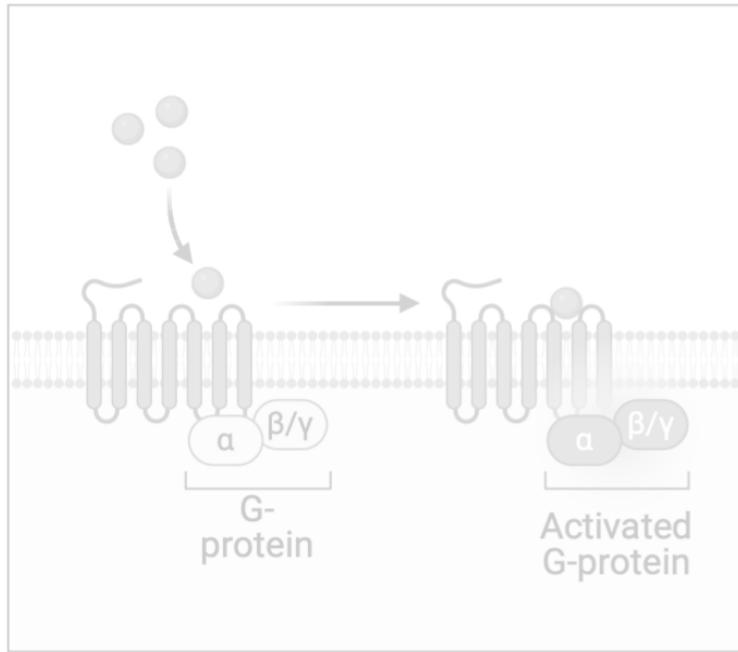


Recall: RTKs elicit intracellular responses

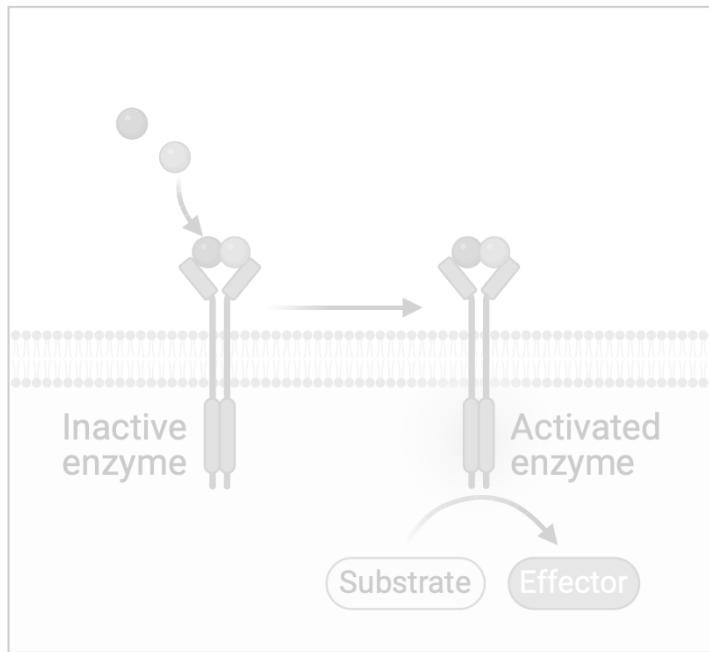


There are 3 main types of Cell Surface Receptors

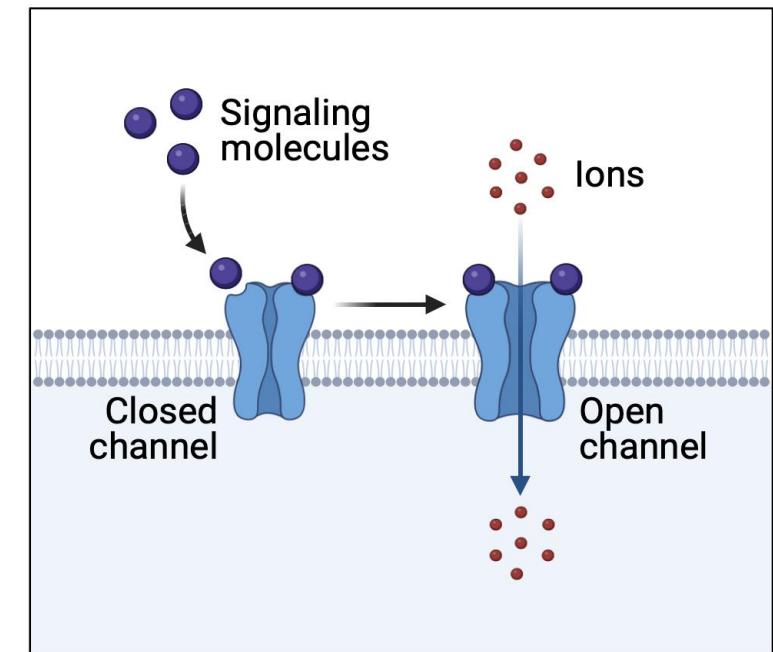
G-protein-coupled receptors



Enzyme-linked receptors

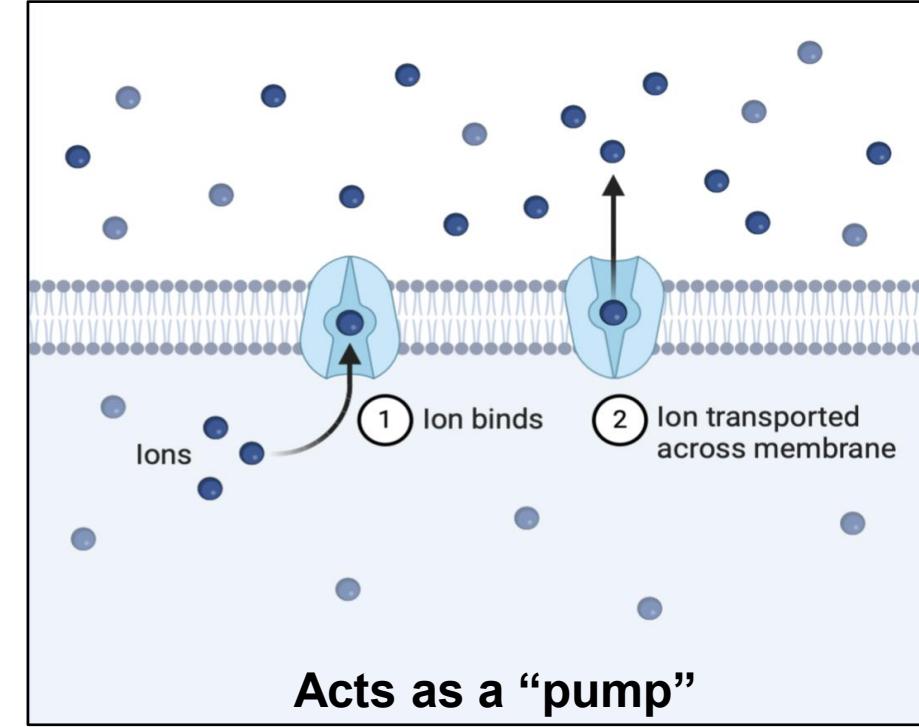
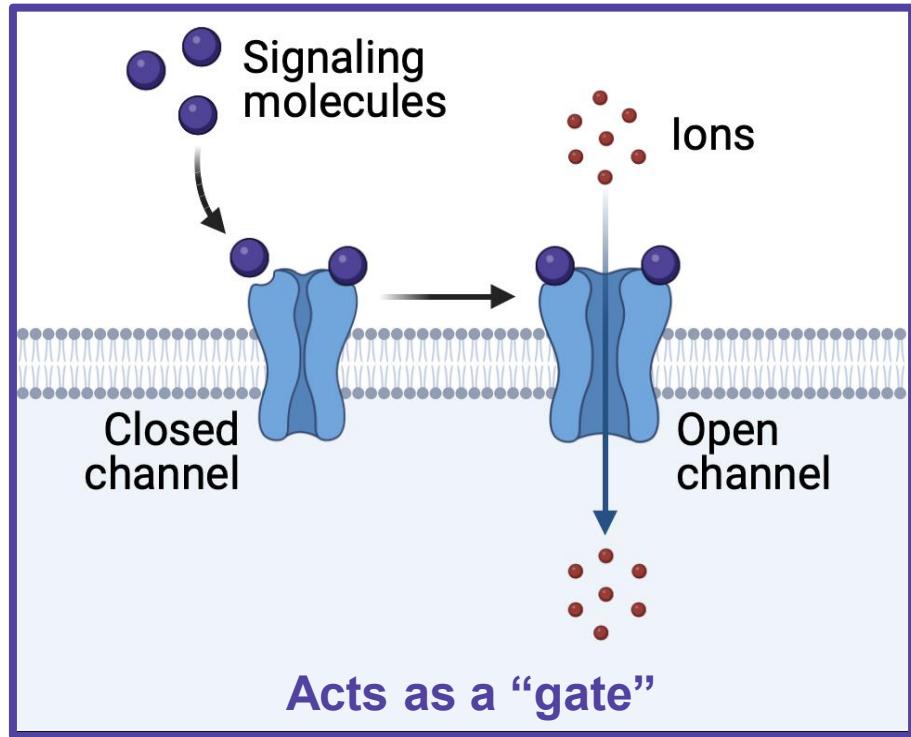


Ion channel-linked receptors



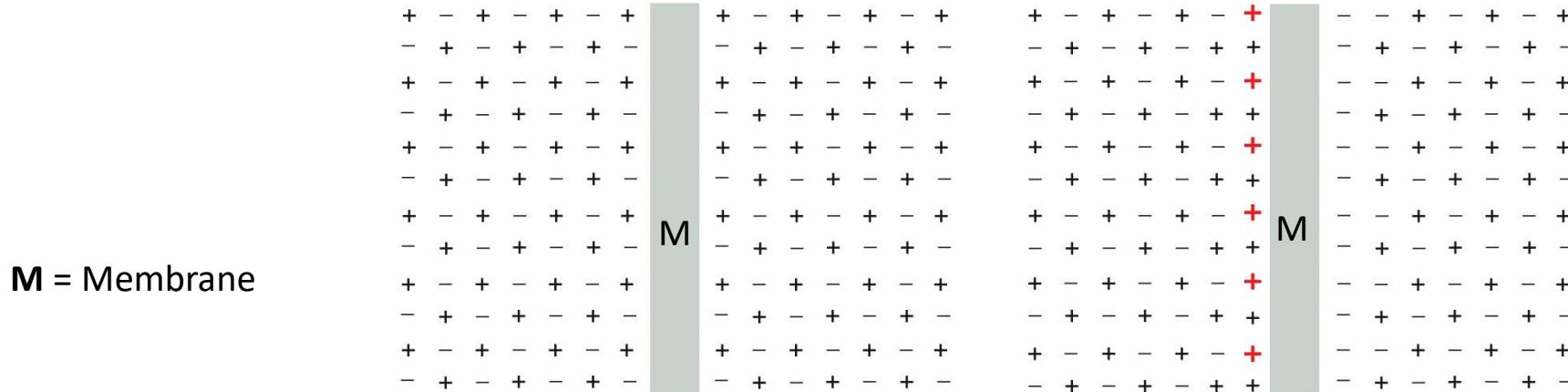
All are activated by signaling molecules (ligands) that trigger intracellular signaling pathways

Ion channel-linked receptors vs. Ion transporter



- Signaling molecules bind to ion channels, causing the channel to open and ions to move
- Ions move down their electrochemical gradient
- Ions bind to ion channel, causing channel to open and ions to move
- Ions move against their electrochemical gradient

The membrane potential influences passive transport of charged solutes



(A) exact balance of charges on each side
of the membrane: membrane potential = 0

charge balanced =
no membrane potential

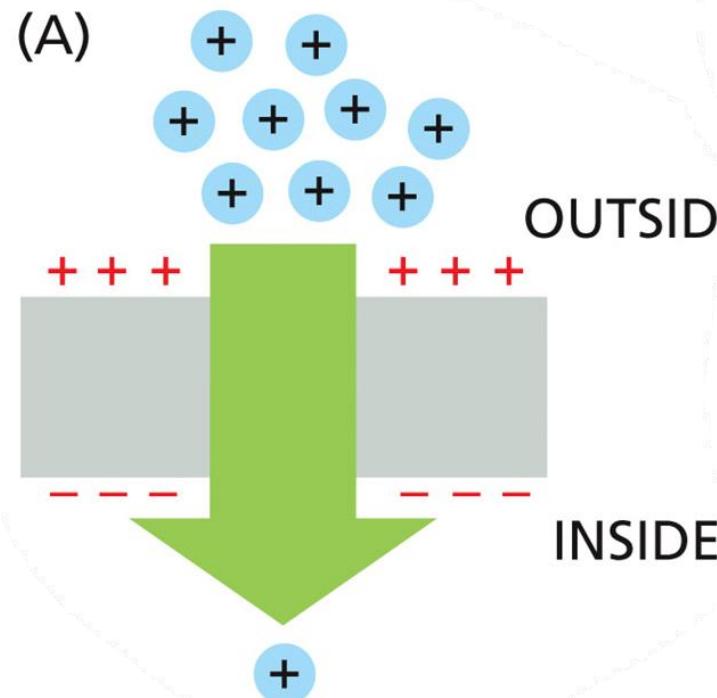
(B) a few positive ions (red) cross the
membrane from right to left, setting up
a nonzero membrane potential

charge not balanced =
membrane potential

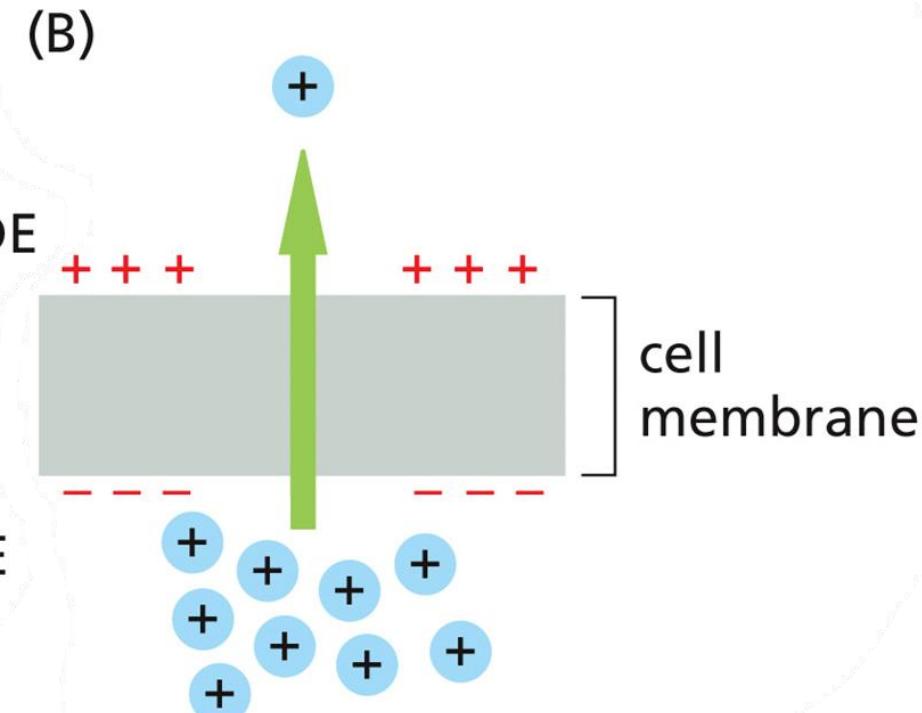
- Unequal distribution of charged ions on either side of a cell membrane gives rise to the "membrane potential," or the difference in voltage on one side of the membrane versus the other
- In general, the outside of the cell is positive (high Na^+) and the inside of the cell is negative (high Cl^-) so cells tend to draw in positively charged and expel negatively charged molecules
 - The overall membrane potential of a cell at rest is negative

The electrochemical gradient for a solute is the net sum of the **concentration gradient** and the **membrane potential**

The concentration gradient
& the membrane potential
can work in the **SAME** direction



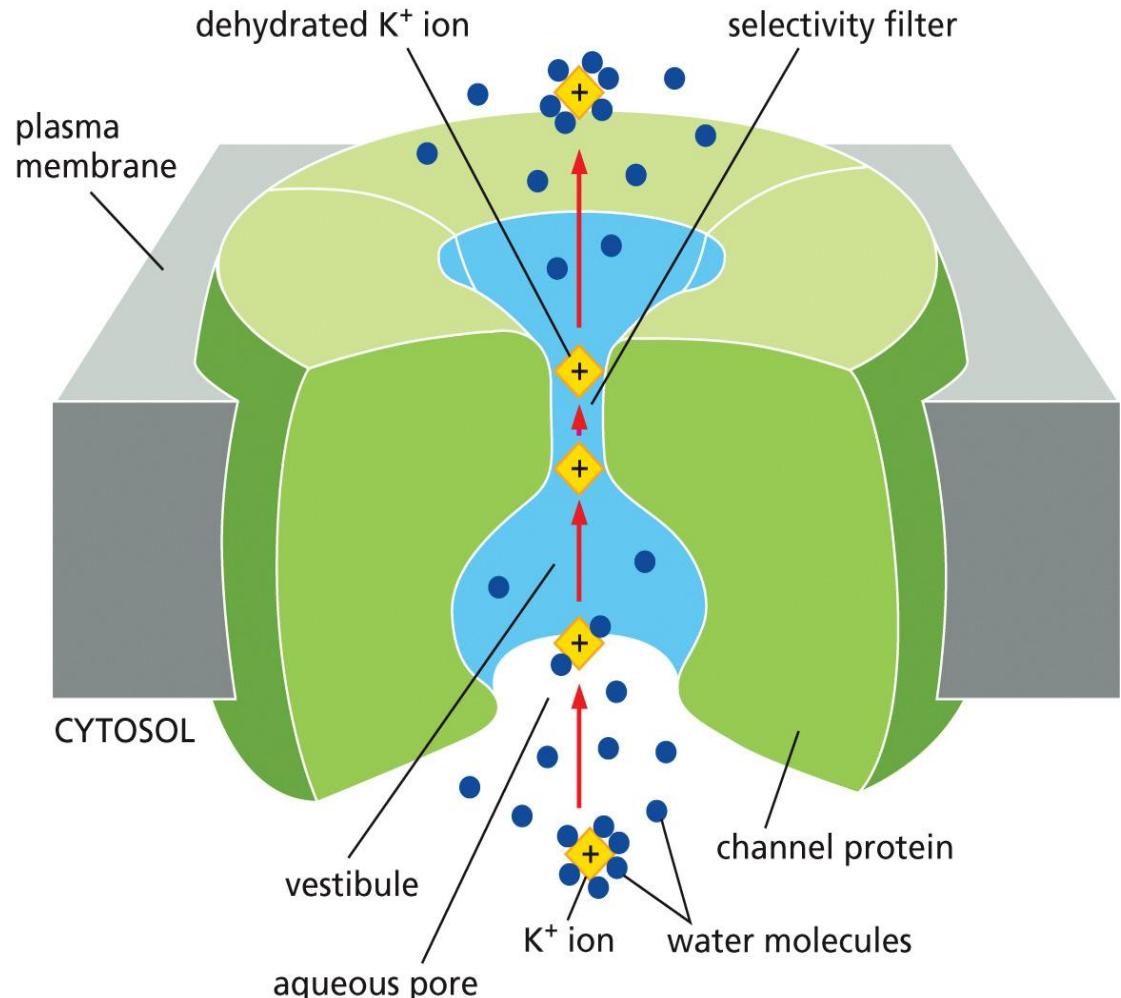
The concentration gradient
& the membrane potential
can also work in the **OPPOSITE**



→ = direction and magnitude
(width of arrow) of the
electrochemical gradient

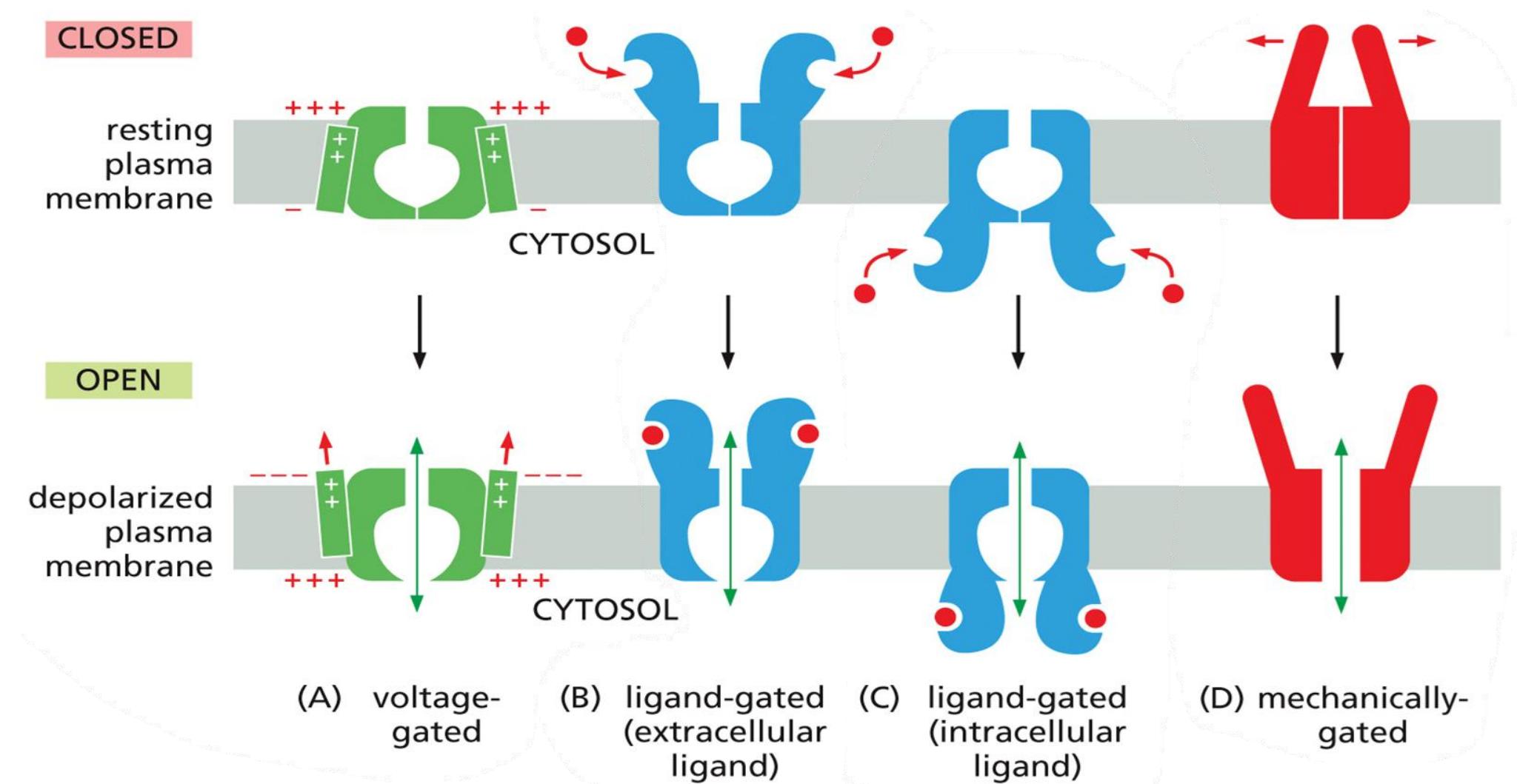
Ion channels are highly selective, narrow pores for allowing passage of one type of charged ion through the membrane while excluding others

- Example: K⁺ channels have polar amino acid side-chains that create a selectivity filter for dehydrated K⁺ ions based on size and charge
- When channels are open, ions flow rapidly through, down their electrochemical gradients

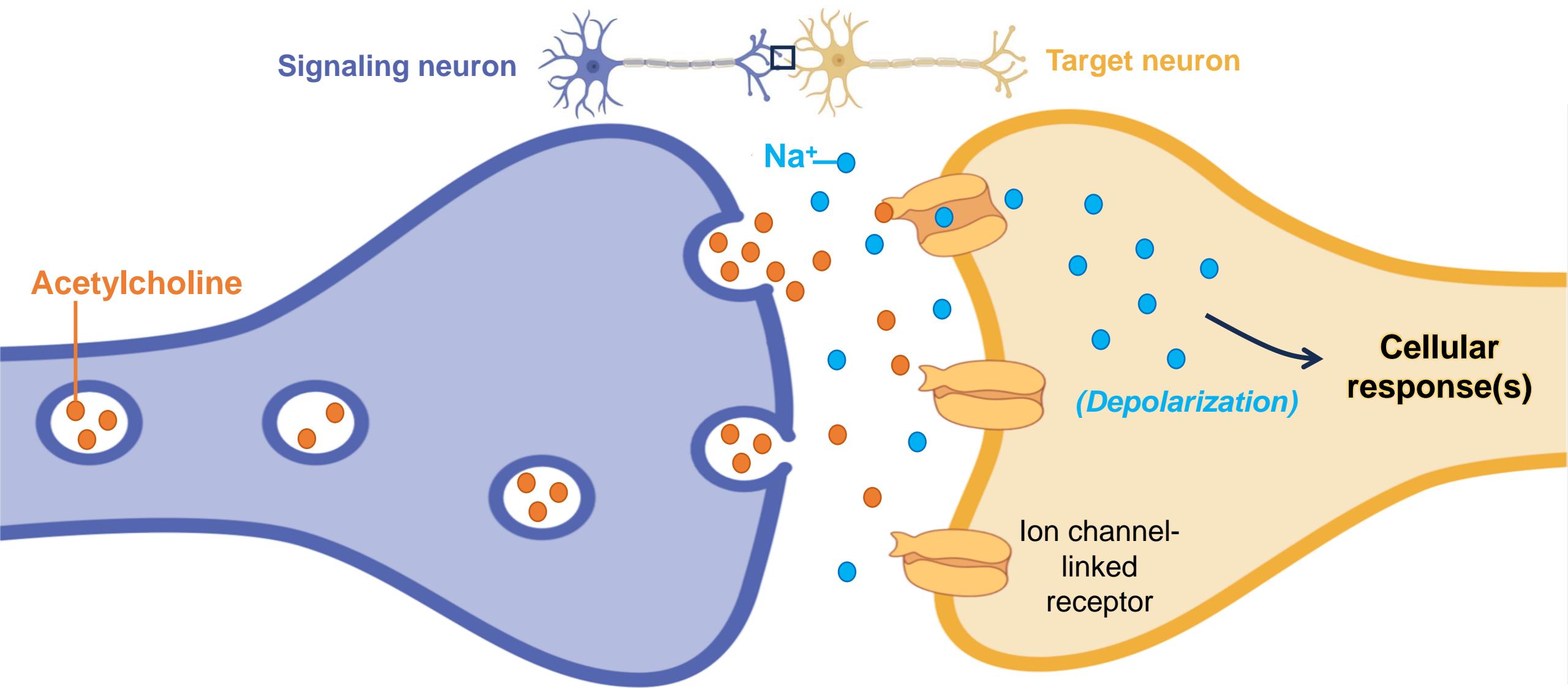


Adapted from D.A. Doyle et al., *Science* 280:69–77, 1998.

Most ion channels are gated so that different stimuli regulate their opening



Post-synaptic neurons rely on ligand (neurotransmitter) binding for rapid signal transmission between neurons

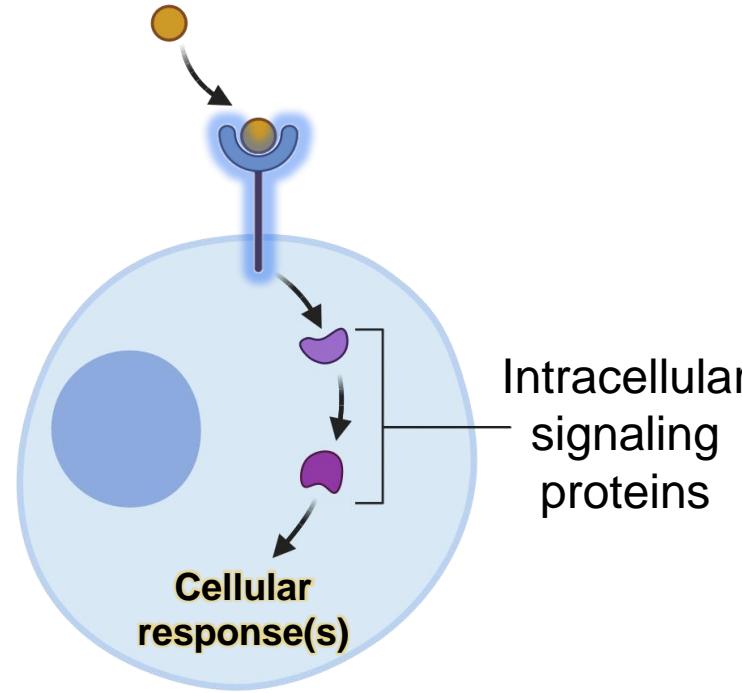


Learning Objectives for Today's Lecture:

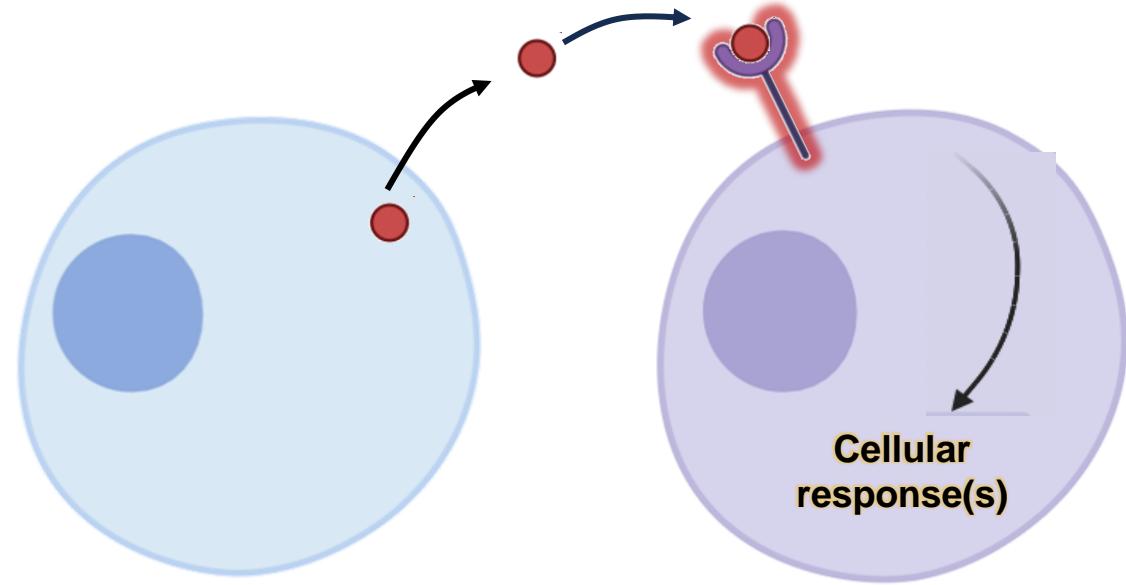
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Cells can communicate to themselves via signaling molecules or to one another



Intracellular Signaling



Source Cell

Target Cell

Intercellular Signaling

Cells communicate through various styles of signaling

Endocrine
signaling

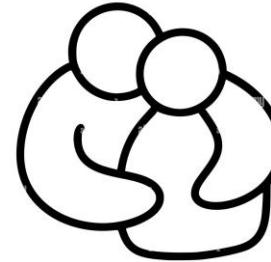


Paracrine
signaling

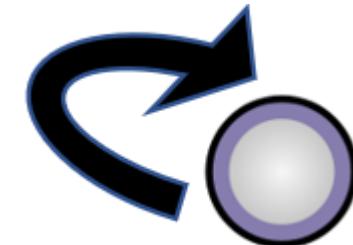


Synaptic
signaling

Contact-dependent
signaling

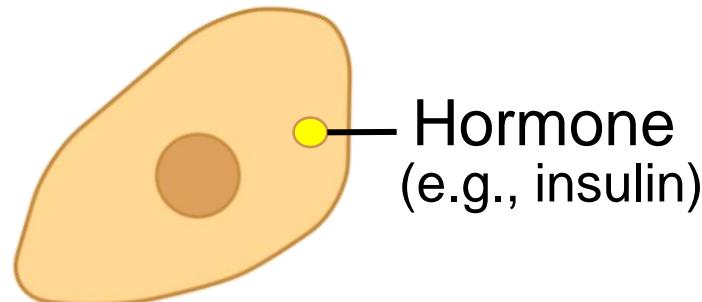


Autocrine
signaling



Intercellular signaling: Endocrine

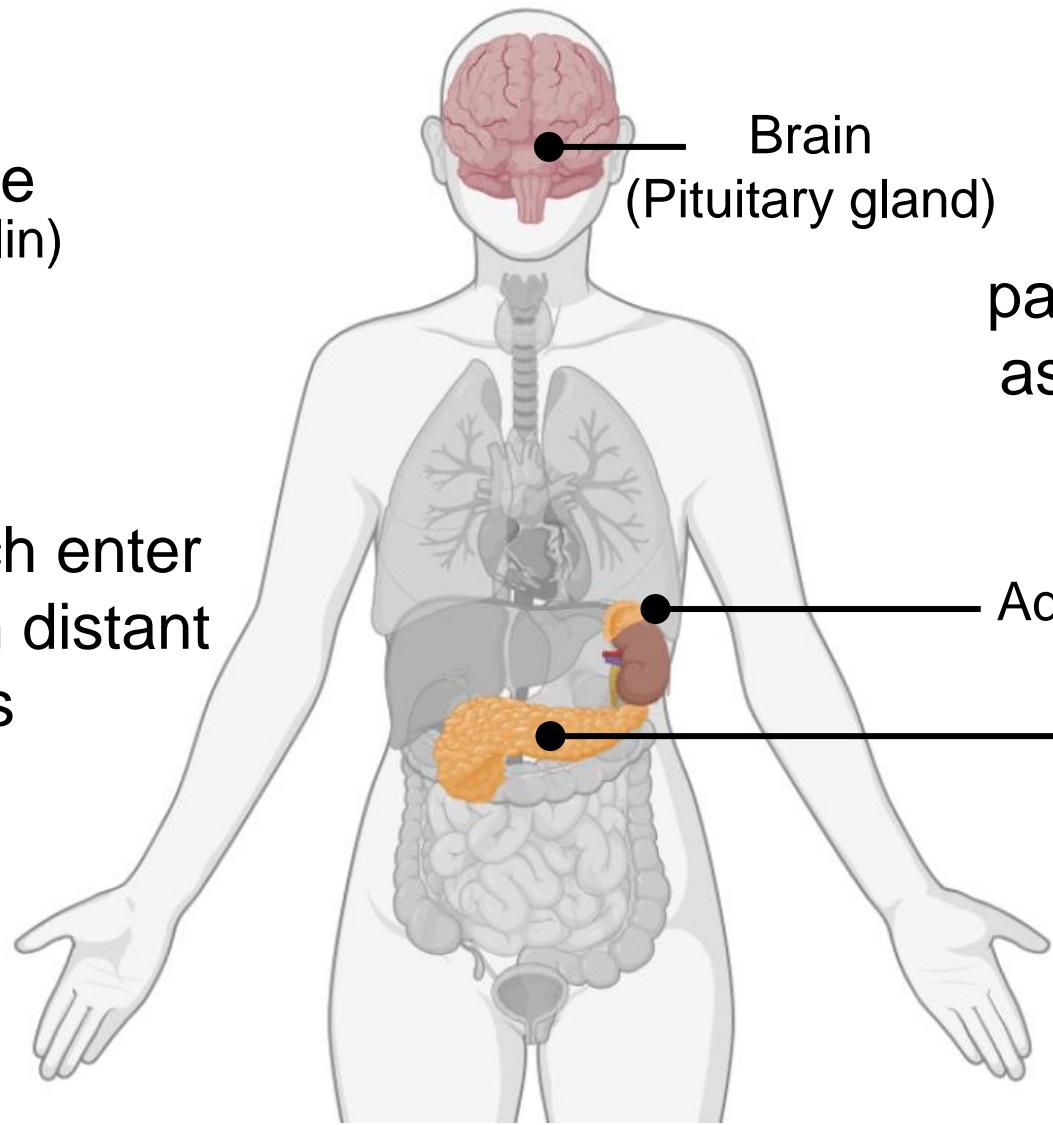
Endocrine cell



Hormone
(e.g., insulin)

Endocrine cells

produce hormones, which enter the bloodstream to reach distant target destinations



Endocrine cells

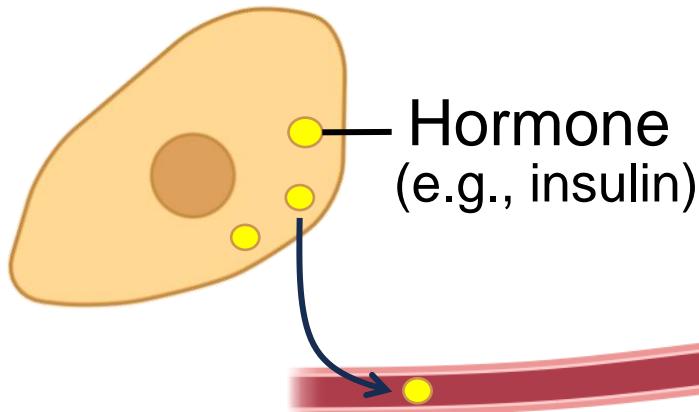
are found in the brain, pancreas, and adrenal gland, as well as in the ovaries and gastrointestinal and respiratory tracts

Adrenal gland

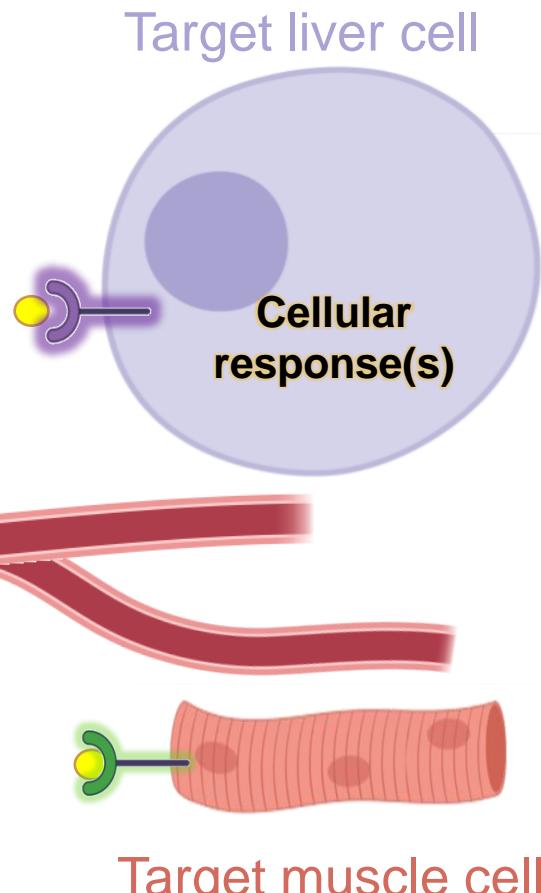
Pancreas

Intercellular signaling: Endocrine

Endocrine cell



Hormone
(e.g., insulin)



Target liver cell

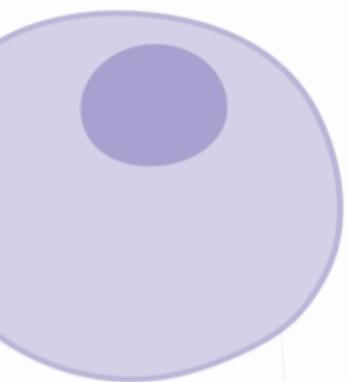
Cellular
response(s)



Target muscle cell

- Hormones bind to target cell(s) in other organs
- Endocrine signaling happens over long distances

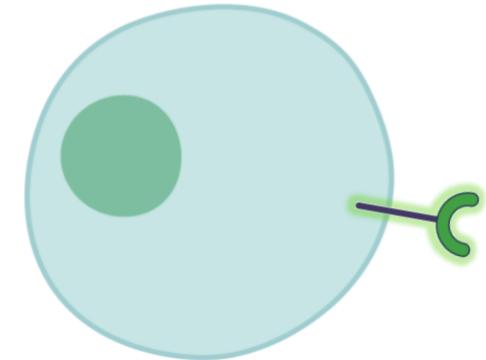
Intercellular signaling: Paracrine



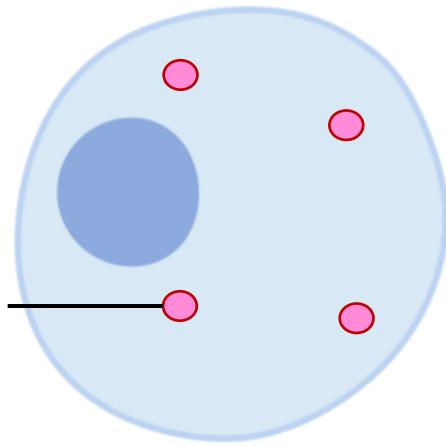
Non-targeted cell

This cell would NOT receive the signal due to distance

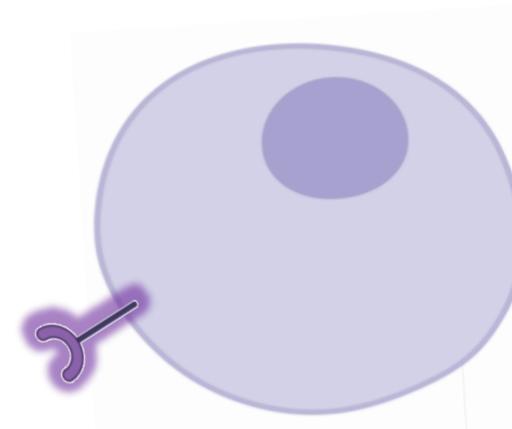
- Signaling occurs over a short distance
- Uses diffusion to send signaling molecules to nearby target cells
- Example: Cells near a wound release growth factors to repair damage



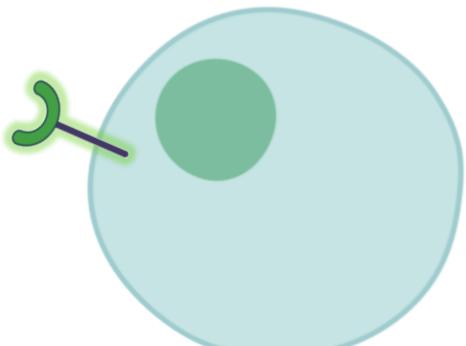
Target cell



Signaling cell

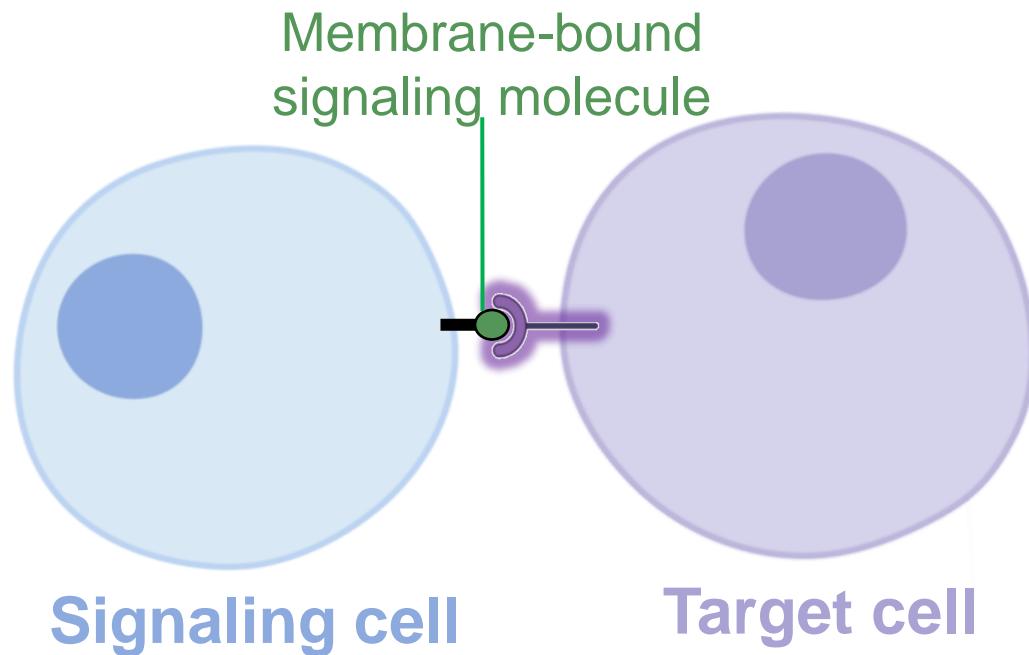


Target cell

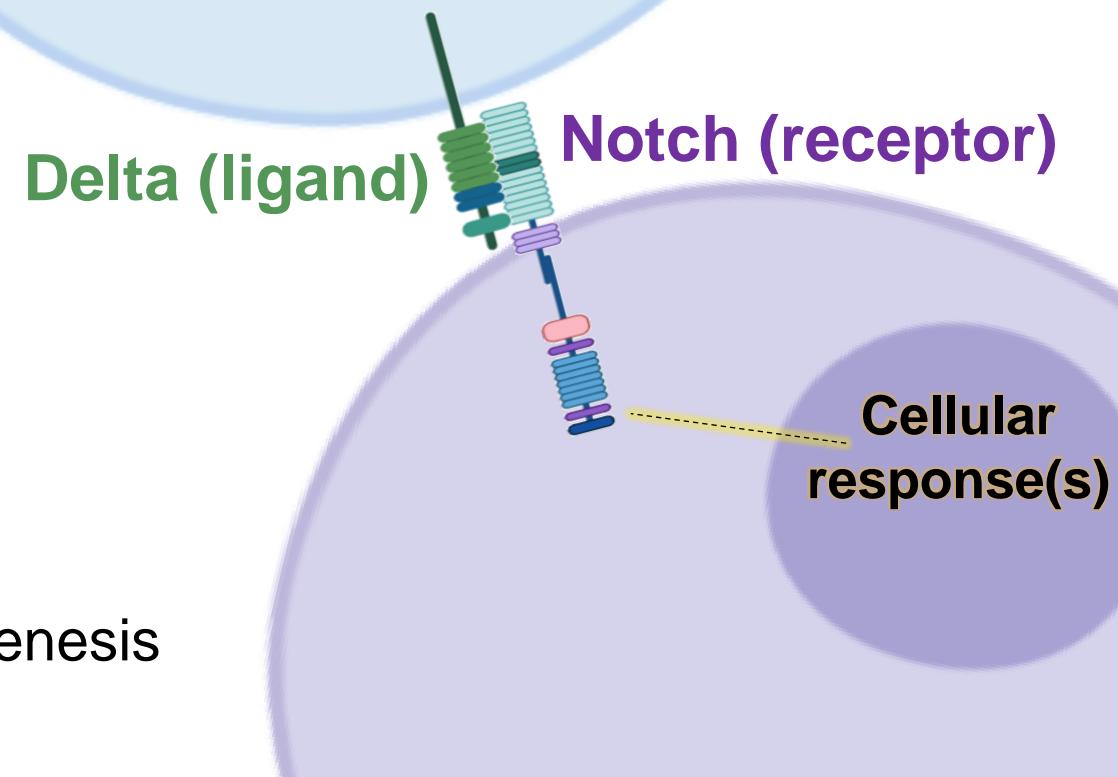


Target cell

Intercellular signaling: Contact-dependent (Juxtacrine)

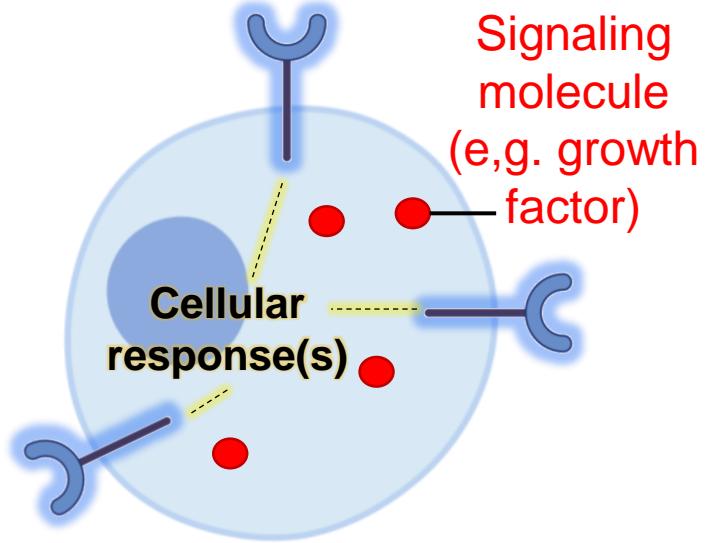


- Cells physically interact to send signals
- Signaling molecule is bound to the plasma membrane of the signaling cell
- Example: **Delta-Notch** signaling during embryogenesis



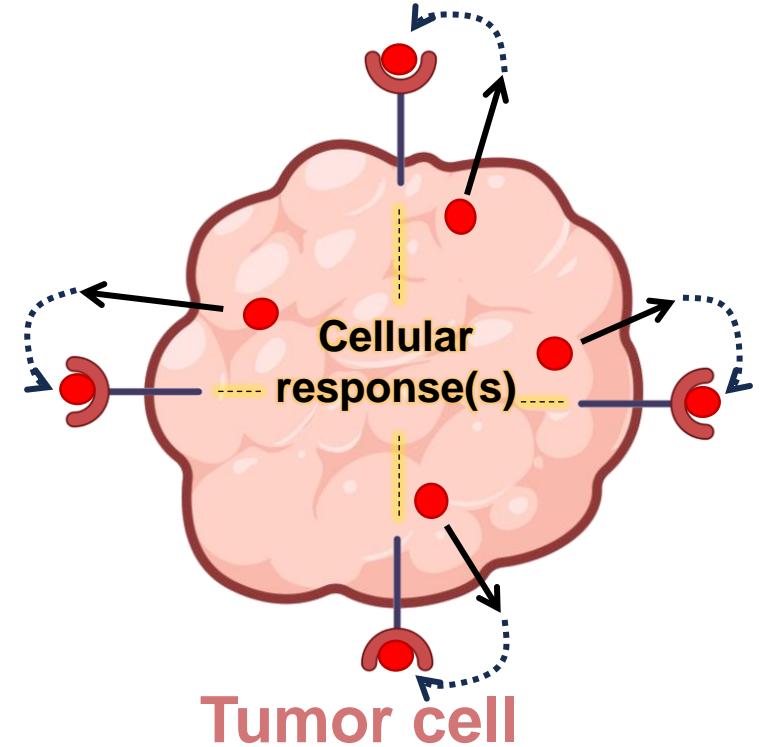
Intercellular signaling: Autocrine

- Signaling molecule released by cell acts only on the signaling cell itself



Signaling cell

“Self-targeting”



Tumor cell

- **Autocrine signaling** is used to promote growth and survival of tumors

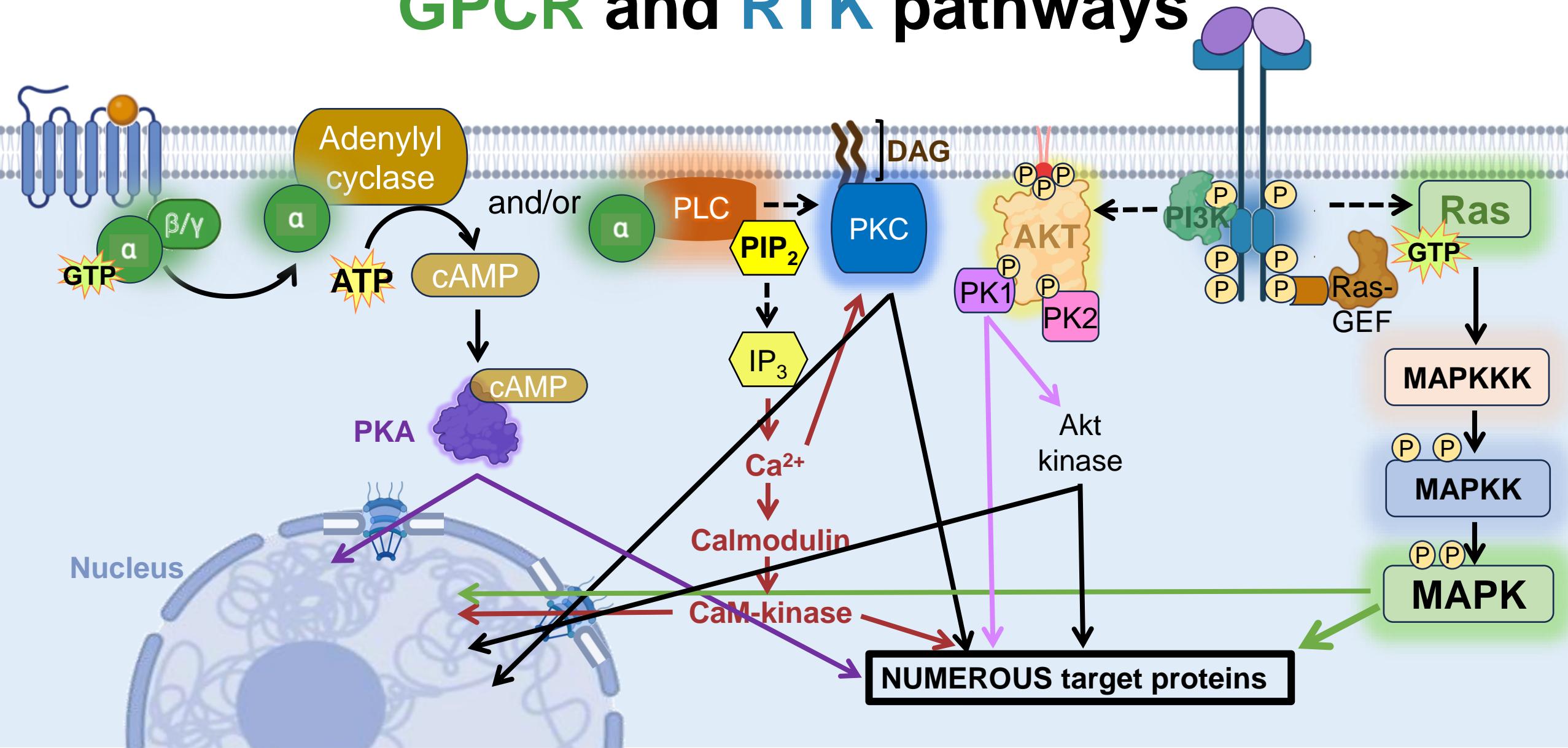
Squarecap #1-2

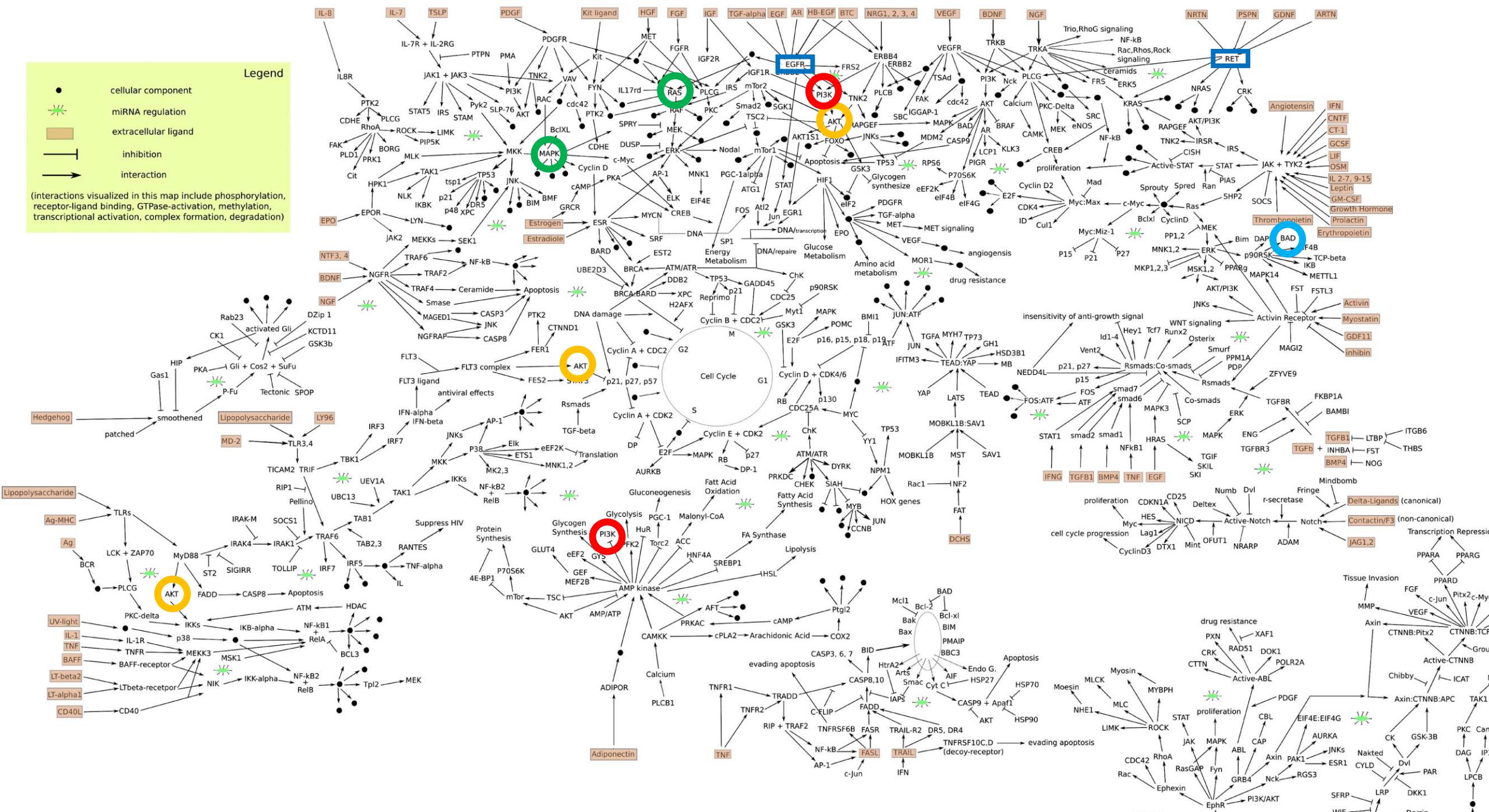
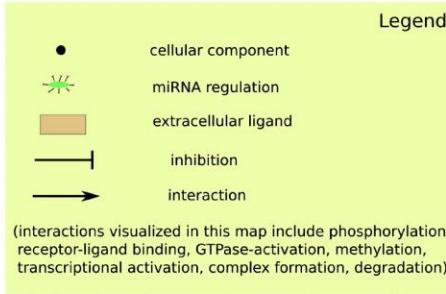
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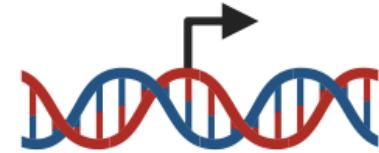
Molecular crosstalk occurs downstream of GPCR and RTK pathways



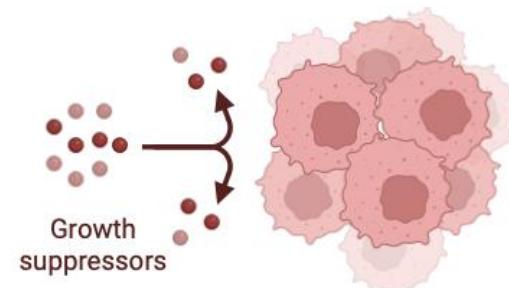


Uncontrolled Cell Signaling can lead to Cancer

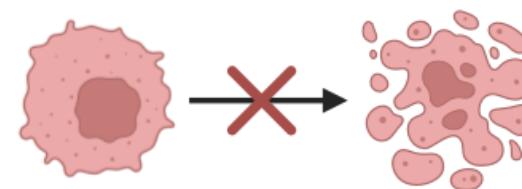
Sustained cell proliferation



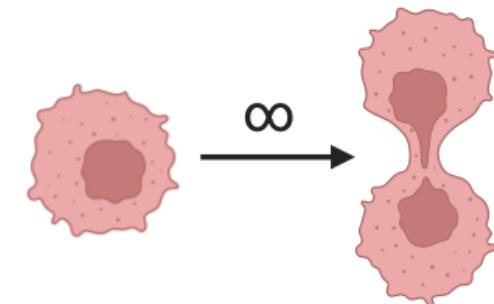
Evading growth suppressors



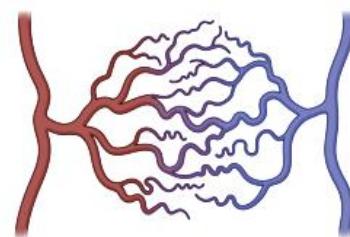
Resisting cell death



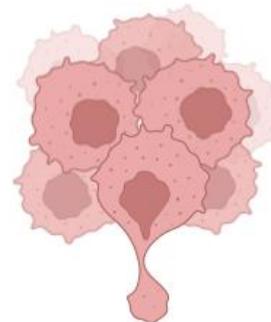
Enabling replicative immortality



Inducing Angiogenesis



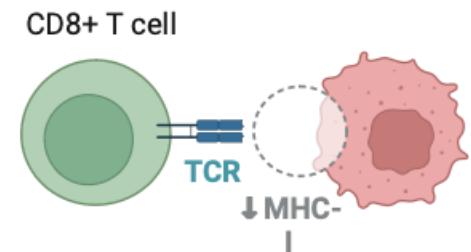
Activating invasion and metastasis



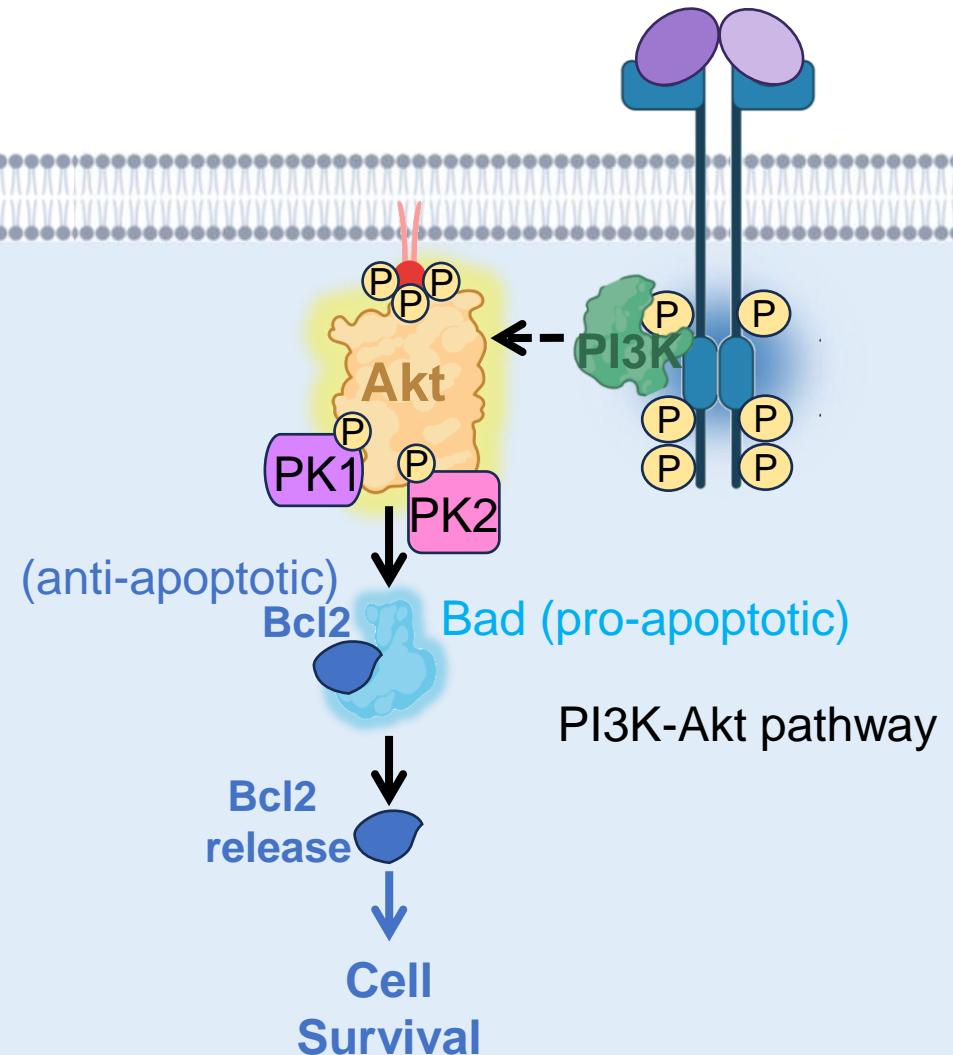
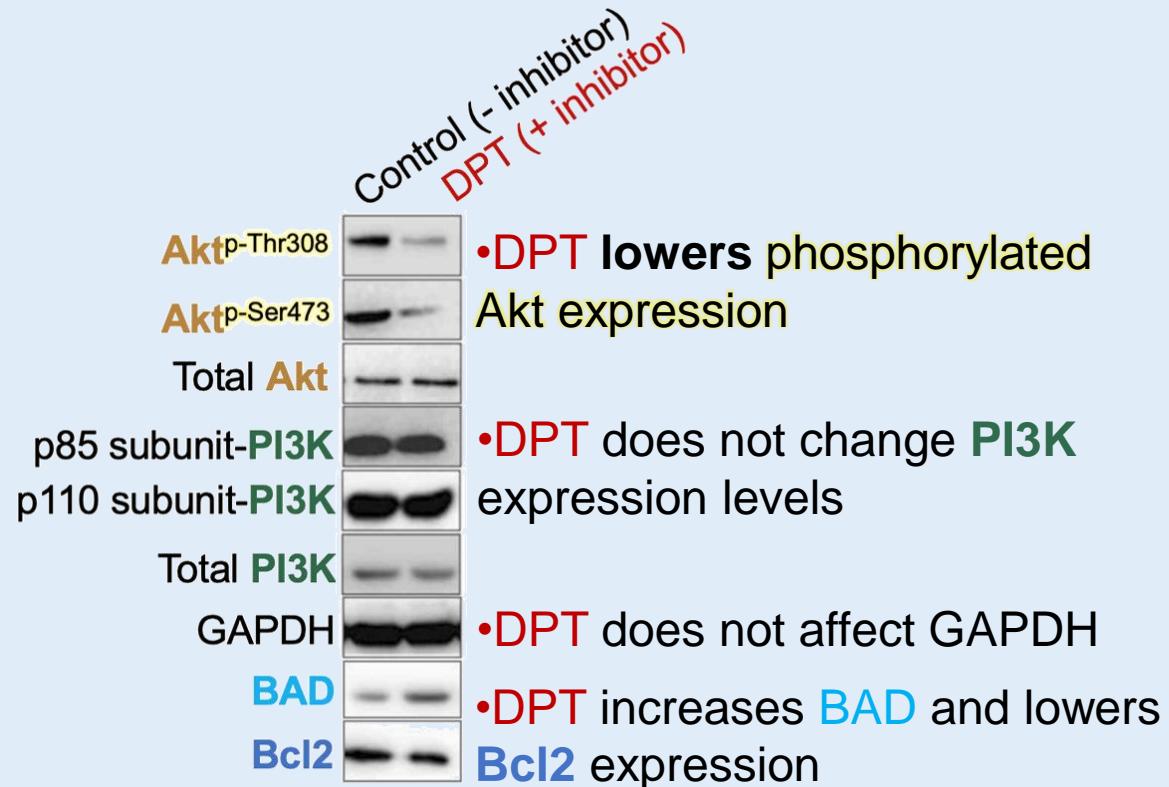
Reprogramming cellular metabolism



Avoiding immune destruction

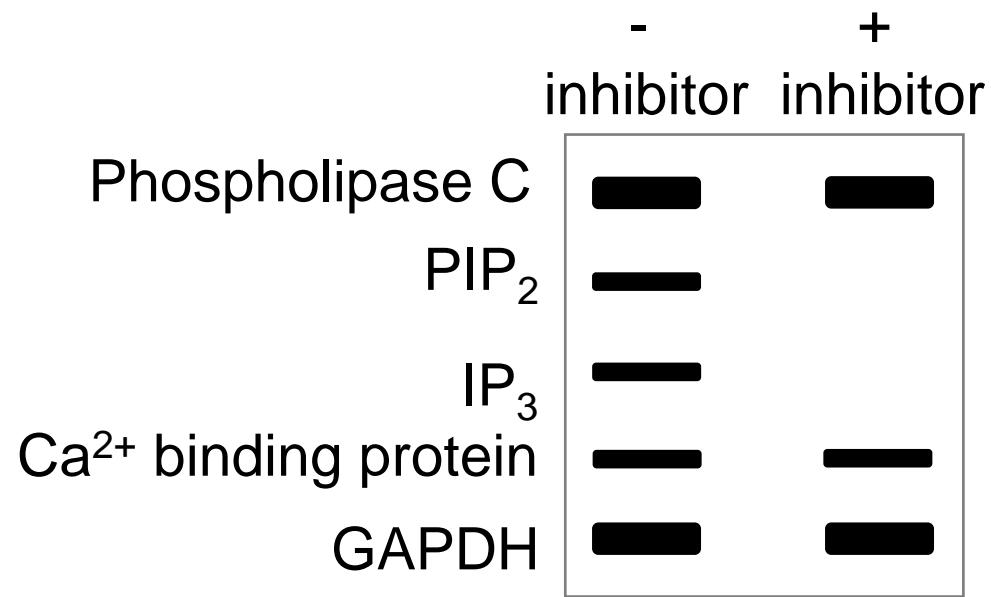


Untangling and targeting Cell Signaling pathways in Research



Case Study

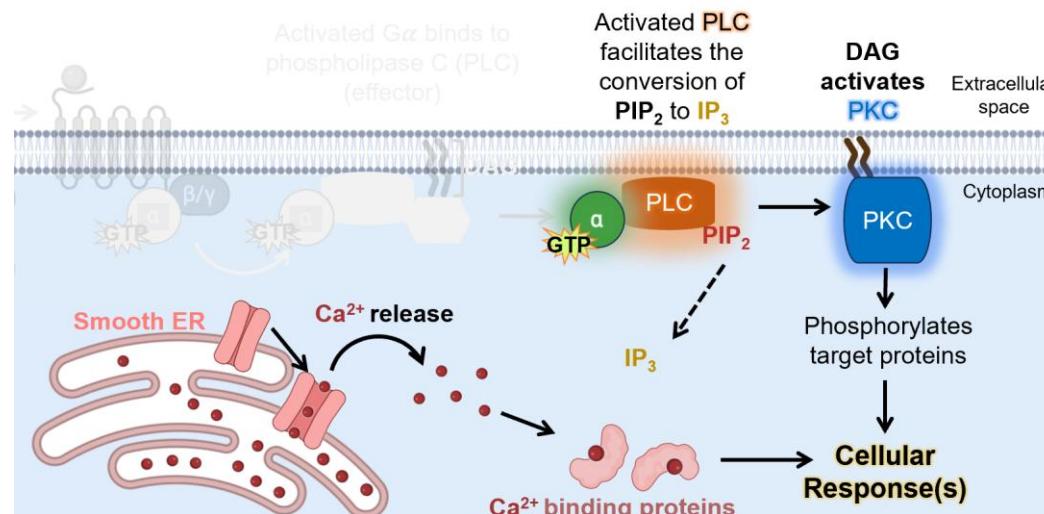
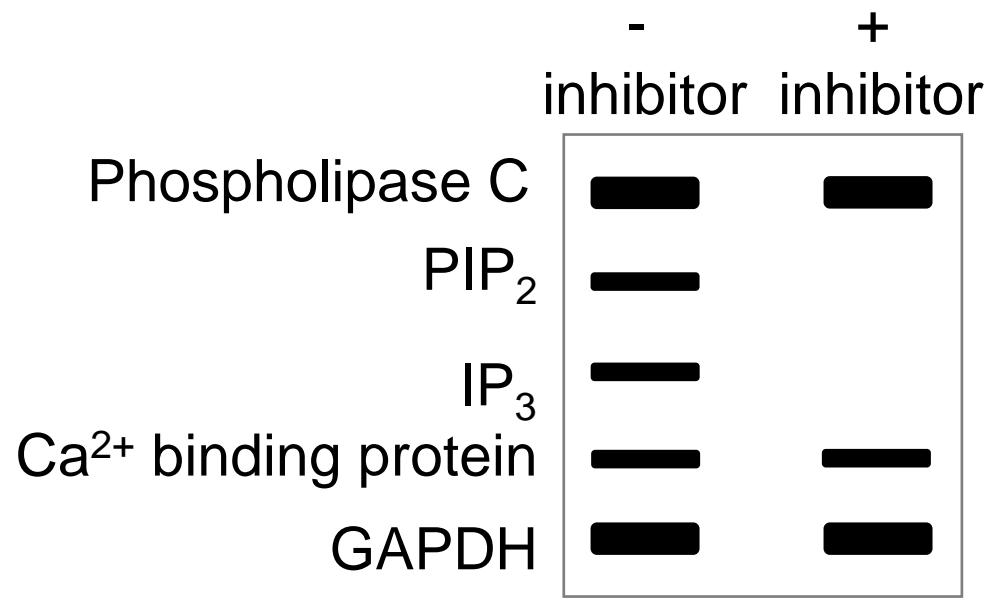
You are a researcher who is interested in studying how GPCRs trigger Ca^{2+} release in a mammalian cell line. To start your project, you first treat the cells with an inhibitor that primarily blocks PIP_2 expression. You then collect the treated cells, as well as cells that were not treated, and perform a western blot. Here are your results:



Please answer the following questions and **explain your answer**.

1. Why is IP_3 expression affected in cells treated with the inhibitor?
2. Would Ca^{2+} be released? Why or why not?
3. Why do you think that the Ca^{2+} binding protein expression did not change?

Case Study



1. Why is IP₃ expression affected in cells treated with the inhibitor?
 - IP₃ cannot be expressed since it follows PIP₂ in the signaling cascade
2. Would Ca²⁺ be released? Why or why not?
 - Ca²⁺ would not be released because there would be no IP₃ to bind to the smooth ER to trigger Ca²⁺ release
3. Why do you think that the Ca²⁺ binding protein expression did not change?
 - Ca²⁺ binding protein is not affected by PIP₂ inhibitor and is not reliant on expression of PIP₂ so its expression does not change

Case Study

There has been a curious case of amnesia going around the scientific community, and everyone seems to have forgotten the order of the signaling cascade leading to protein kinase A (PKA) nuclear translocation. You have been tasked with re-discovering this order.

You know that cAMP, a GPCR, adenylyl cyclase, and a G-protein are involved, and you have the following inhibitors at your disposal:

Inhibitor X binds to the active site of adenylyl cyclase, preventing its catalytic activity

Inhibitor Y prevents GTP binding to the G-protein

Inhibitor Z blocks nuclear import of PKA

You are able to measure the concentration of cAMP, the nuclear localization of PKA, and whether the G-protein and adenylyl cyclase are bound together or exist separately.

Which of these inhibitors would provide useful information toward dissecting this signaling cascade? Describe what would happen to your readouts compared to the absence of inhibitor condition.

Case Study

Inhibitor X binds to the active site of adenylyl cyclase, preventing its catalytic activity

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Inhibitor Z blocks nuclear import of PKA

You are able to measure the concentration of cAMP, the nuclear localization of PKA, and whether the G-protein and adenylyl cyclase are bound together or exist separately.

Which of these inhibitors would provide the most useful information toward dissecting this signaling cascade? Describe what would happen to your readouts compared to the absence of inhibitor condition.

Inhibitor X and **Inhibitor Y** would provide useful information, as Inhibitor Z would prevent the final translocation of PKA but provide no information on how we got there.

By contrast, Inhibitor Y would prevent the cascade from beginning at all while, indicating that GTP-binding to the G-protein is an upstream event.

Inhibitor X would differentiate from the control condition by having low cAMP, have no nuclear localization of PKA, while showing G-protein and adenylyl cyclase association. This would provide insight that adenylyl cyclase is downstream of G-protein activation but upstream of PKA nuclear translocation, likely driven by cAMP.

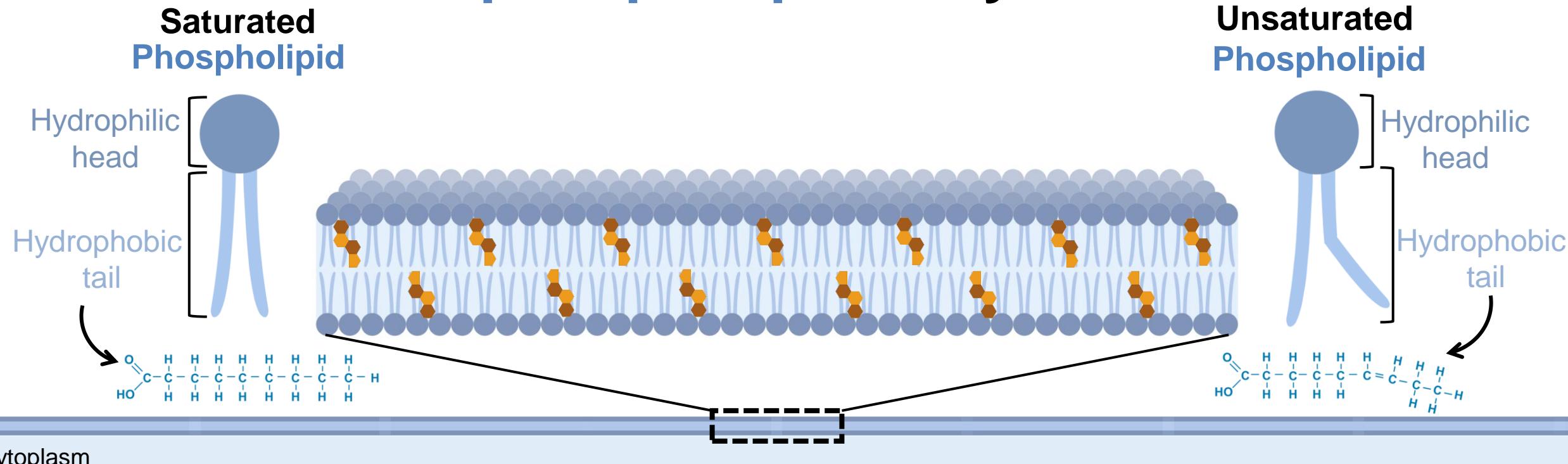
Mini-Review for Exam #3

**Tuesday, April 15
Ch. 11-16 (Part I)**

Ch. 11 & 12

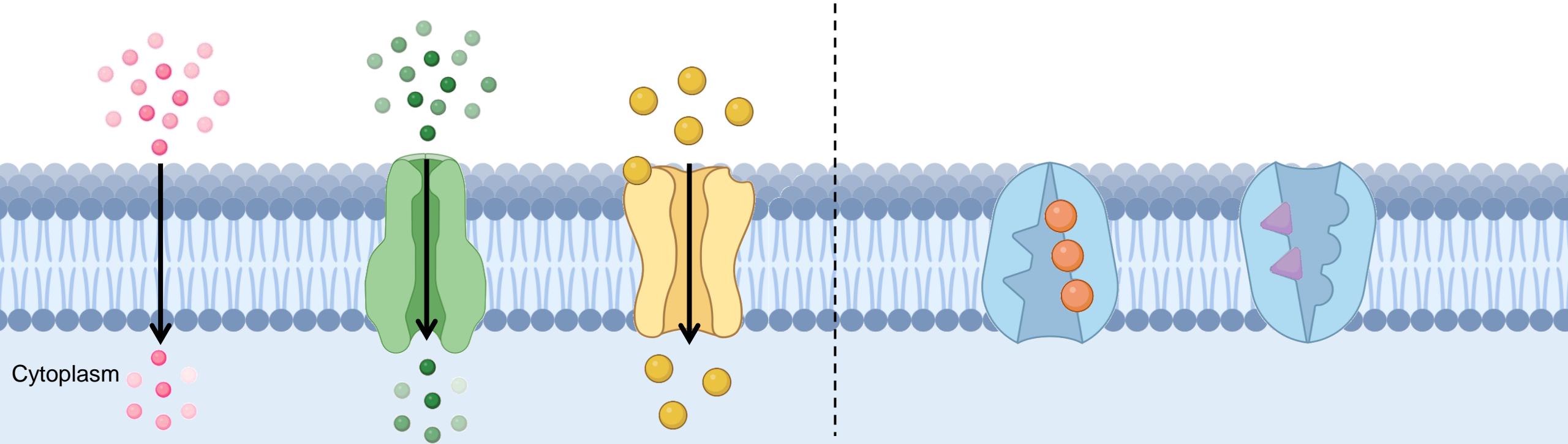
Cell Membrane Structure and Transport

The cell membrane is comprised of a phospholipid bilayer



- Saturated phospholipids have tightly packed hydrophobic tails, which increase cell membrane rigidity
- Unsaturated phospholipids have a bend (“kink”) in the hydrophobic tails, which increase cell membrane fluidity
 - Cholesterol is a type of lipid in the phospholipid bilayer and helps maintain optimal cell membrane fluidity
 - At high temperatures, cholesterol reduces fluidity by interacting with phospholipids, reducing their movement.
At low temperatures, cholesterol prevents phospholipids from packing tightly.

Molecules move across the cell membrane by passive transport or active transport

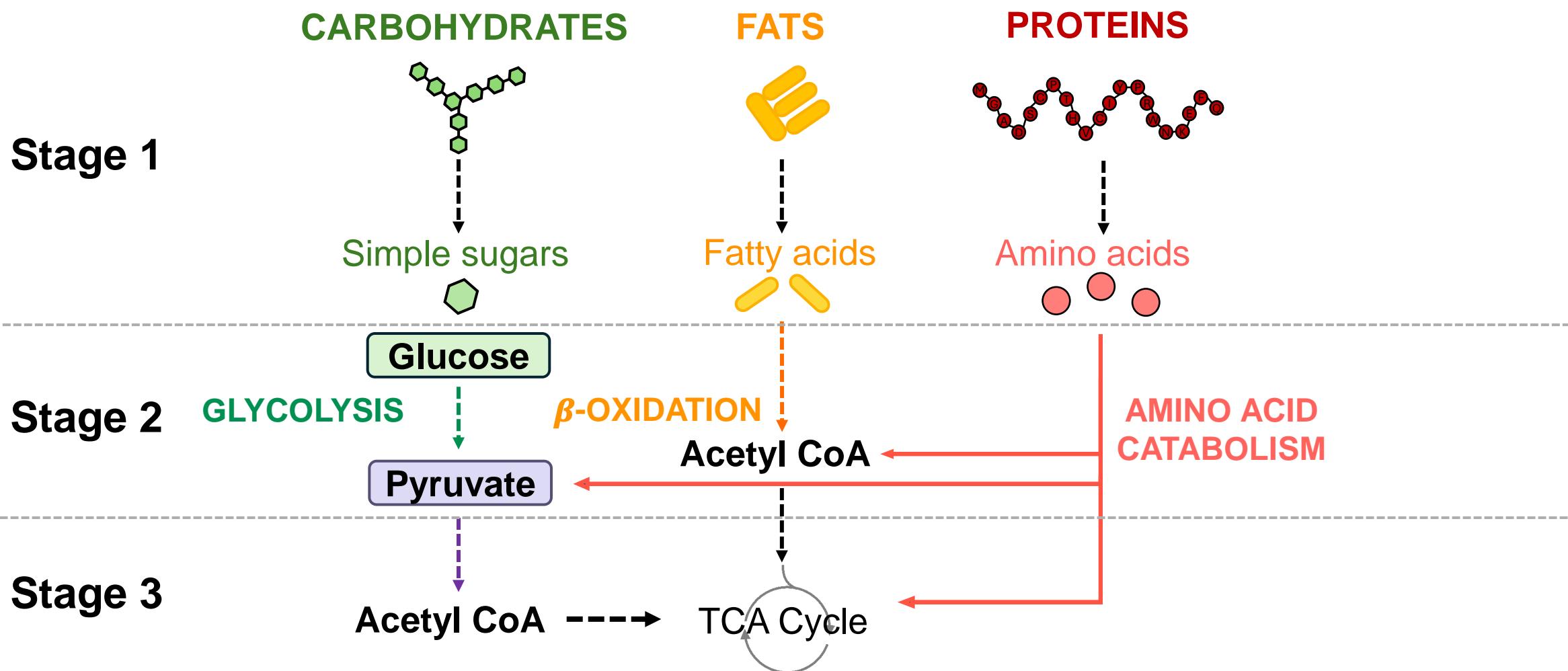


- Passive and active transport involve the movement of molecules either in or out of the cell
- Passive and active transport utilize specific membrane proteins to facilitate the movement of molecules
- Passive and active transport require a concentration gradient in order for molecules to be transported

Ch. 13

How Cells Obtain Energy from Food

The breakdown of FOOD occurs in 3 stages



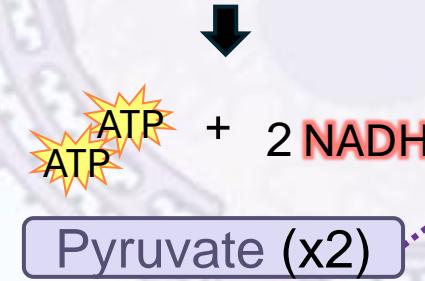
Cellular Respiration

The degradation of biomolecules to generate energy that cells can utilize

a.k.a

Aerobic Respiration

GLYCOLYSIS



TCA CYCLE



OXIDATIVE PHOSPHORYLATION

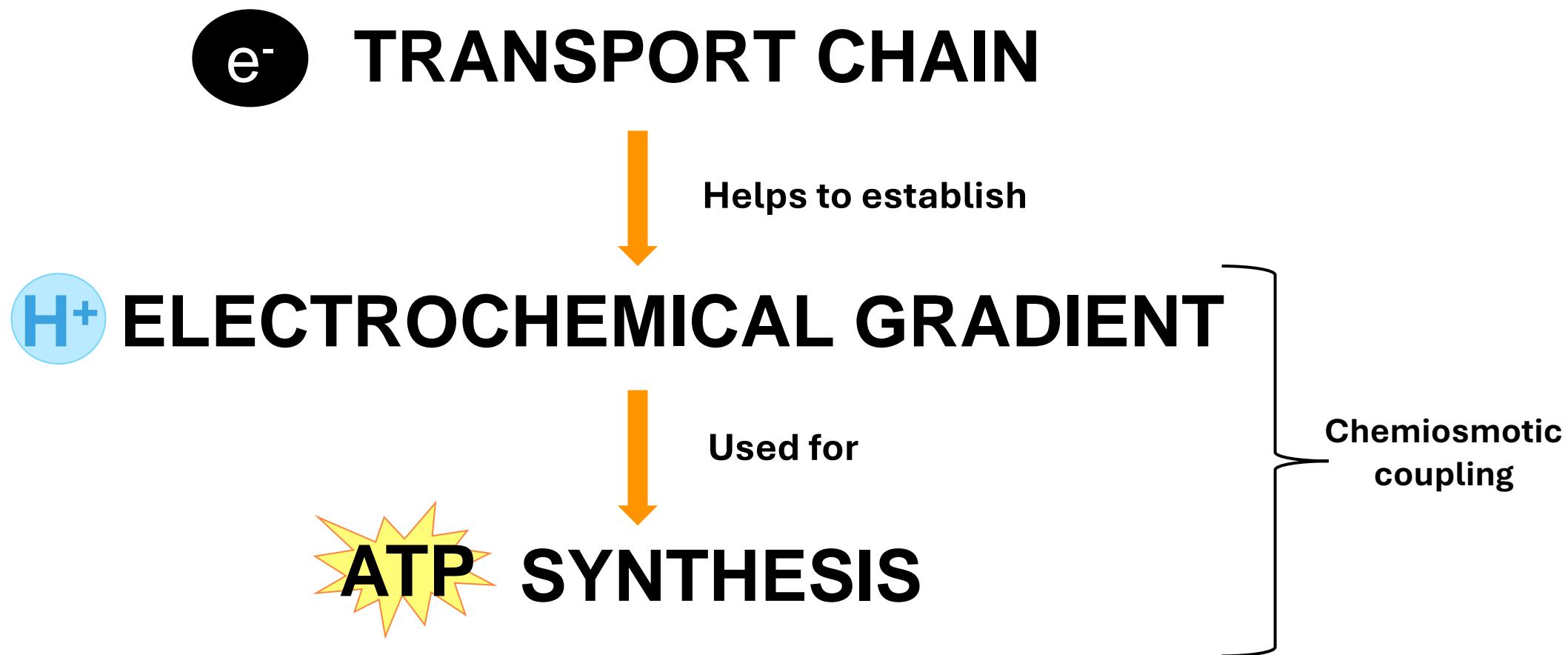
Converting our high energy electrons into ATP



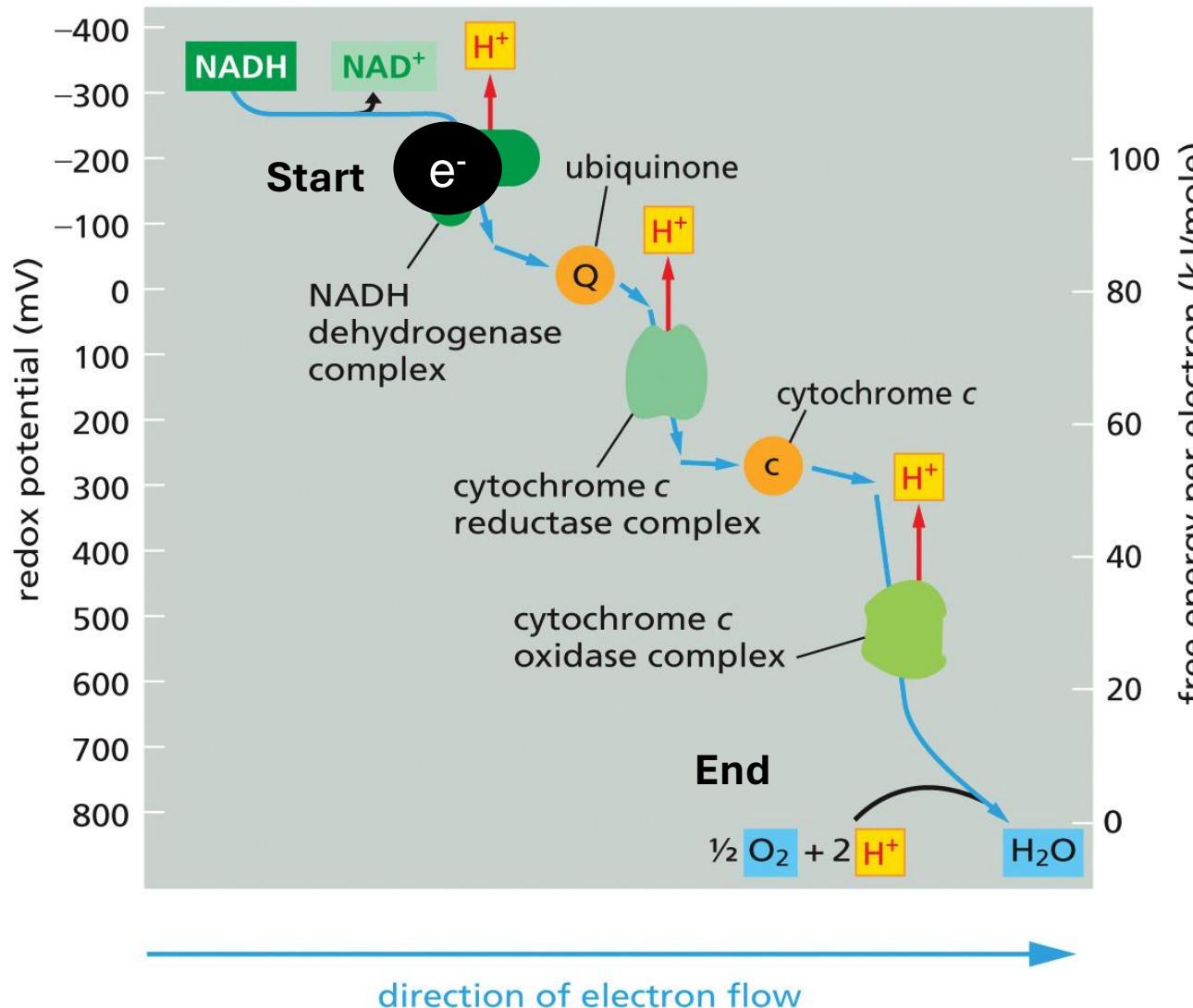
Ch. 14

Energy Generation in Mitochondria and Chloroplasts

Key Steps in Oxidative Phosphorylation

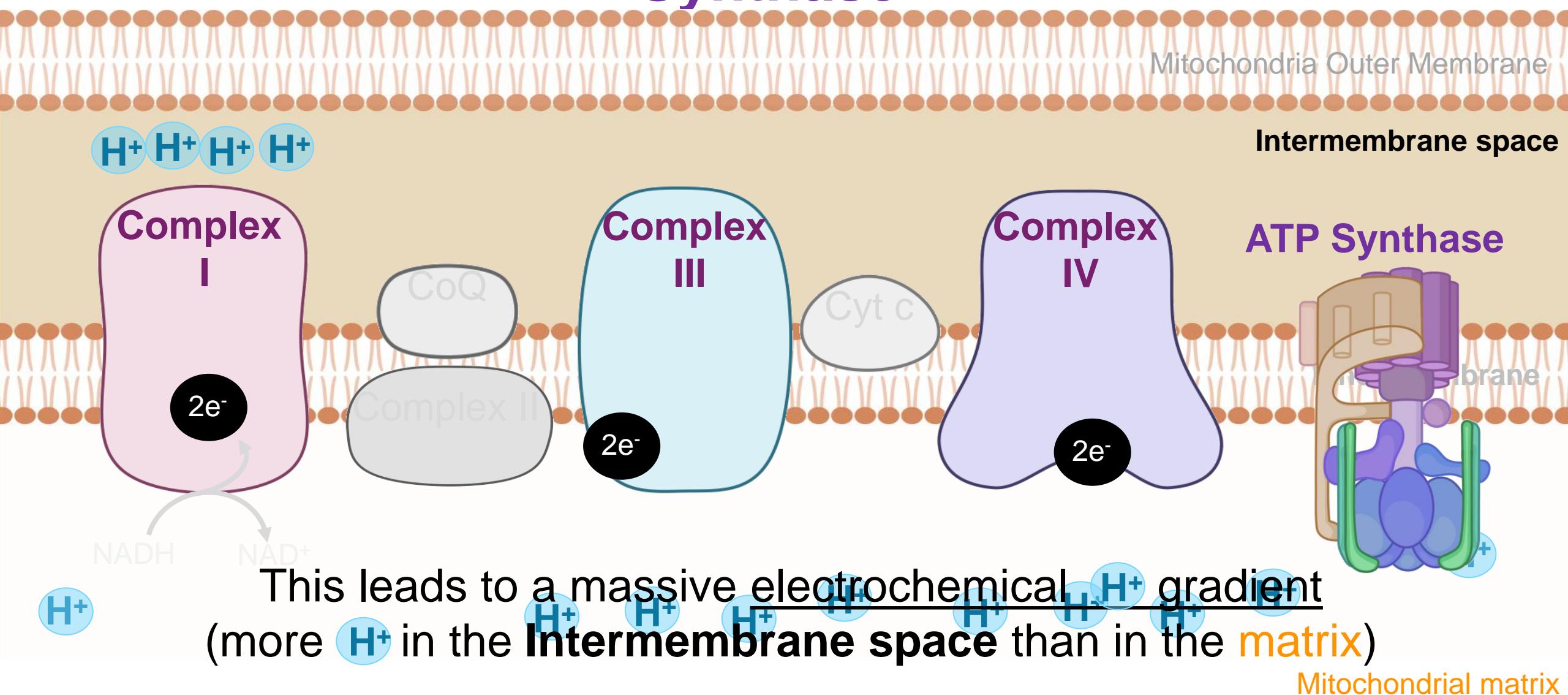


Redox potential **increases** along the mitochondrial electron-transport chain

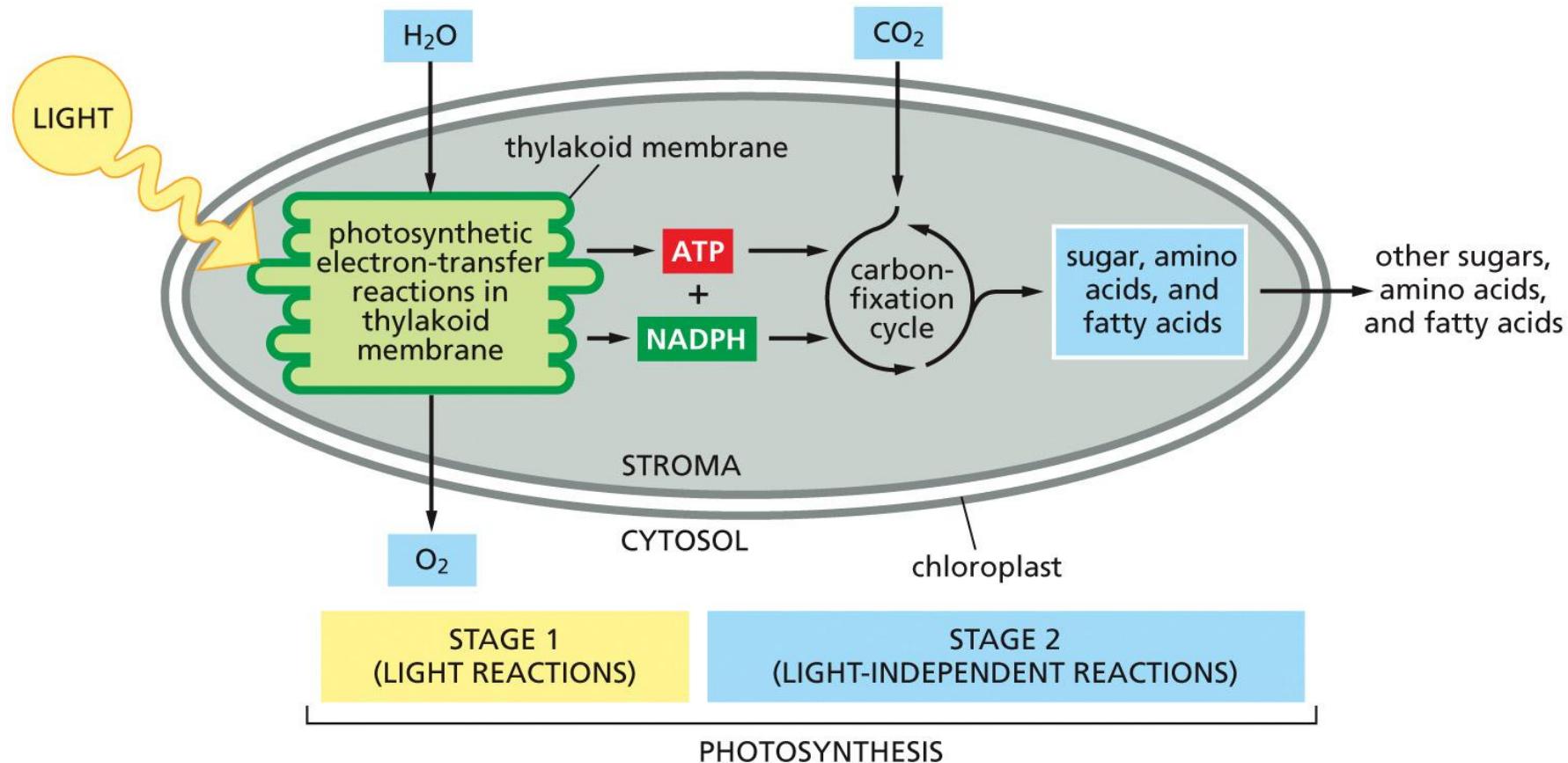


This means electrons spontaneously move through the chain from NADH all the way to oxygen (O₂)

H⁺ from the **mitochondrial matrix** are pumped into the **Intermembrane space** and used to power **ATP Synthase**



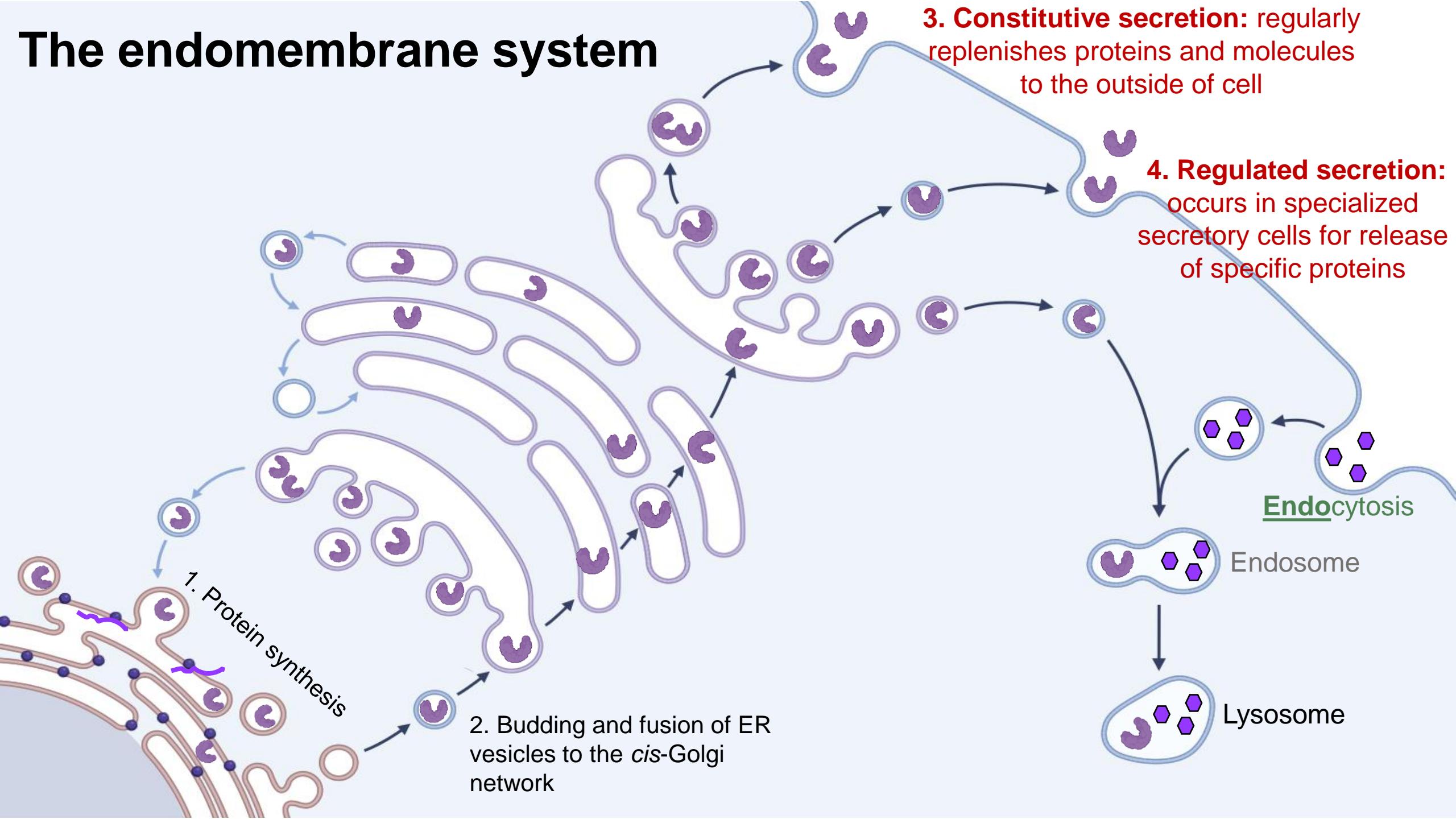
Photosynthesis is essentially the opposite of cellular respiration, leveraging the energy of light to produce sugars and oxygen from carbon dioxide and water



Ch. 15

Protein Localization and Transport

The endomembrane system



Signal sequences direct proteins to the correct cellular compartment

A signal sequence is comprised of a specific sequence of amino acids

Examples of signal sequences

-P-P-K-K-K-R-K-V-

M-E-E-L-S-Q-A-L-A-S-S-F-

H₃N-M-M-S-F-V-S-L-L-L-V-G-I-L-F-
A-T-E-A-E-Q-L-T-K-C-E-V-F-Q-

-K-D-E-L-COO-

Function of the signal sequence

Import into the Nucleus

Export from the Nucleus

Import into the ER

Retention in the ER

H₃N = N-terminus of protein

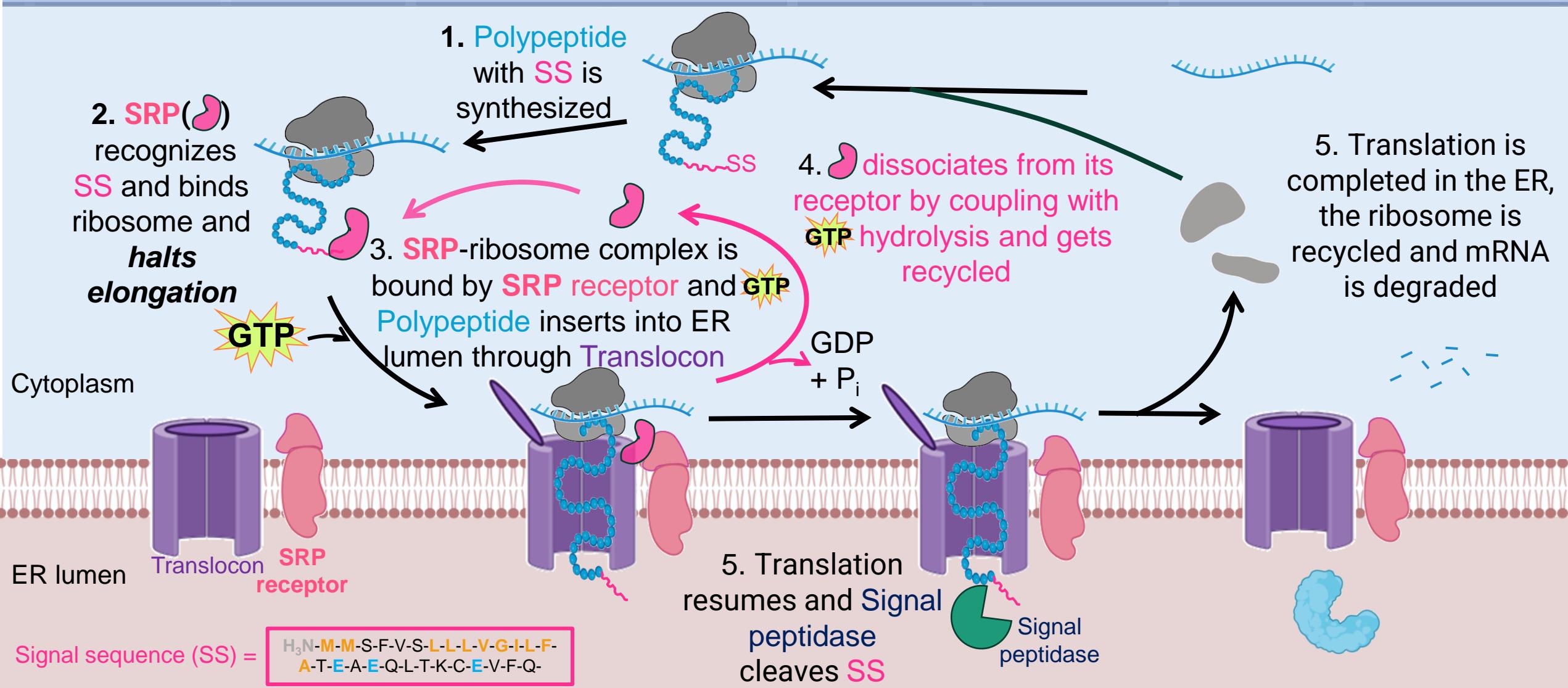
Hydrophobic amino acids

(-) charged amino acids

(+) charged amino acids

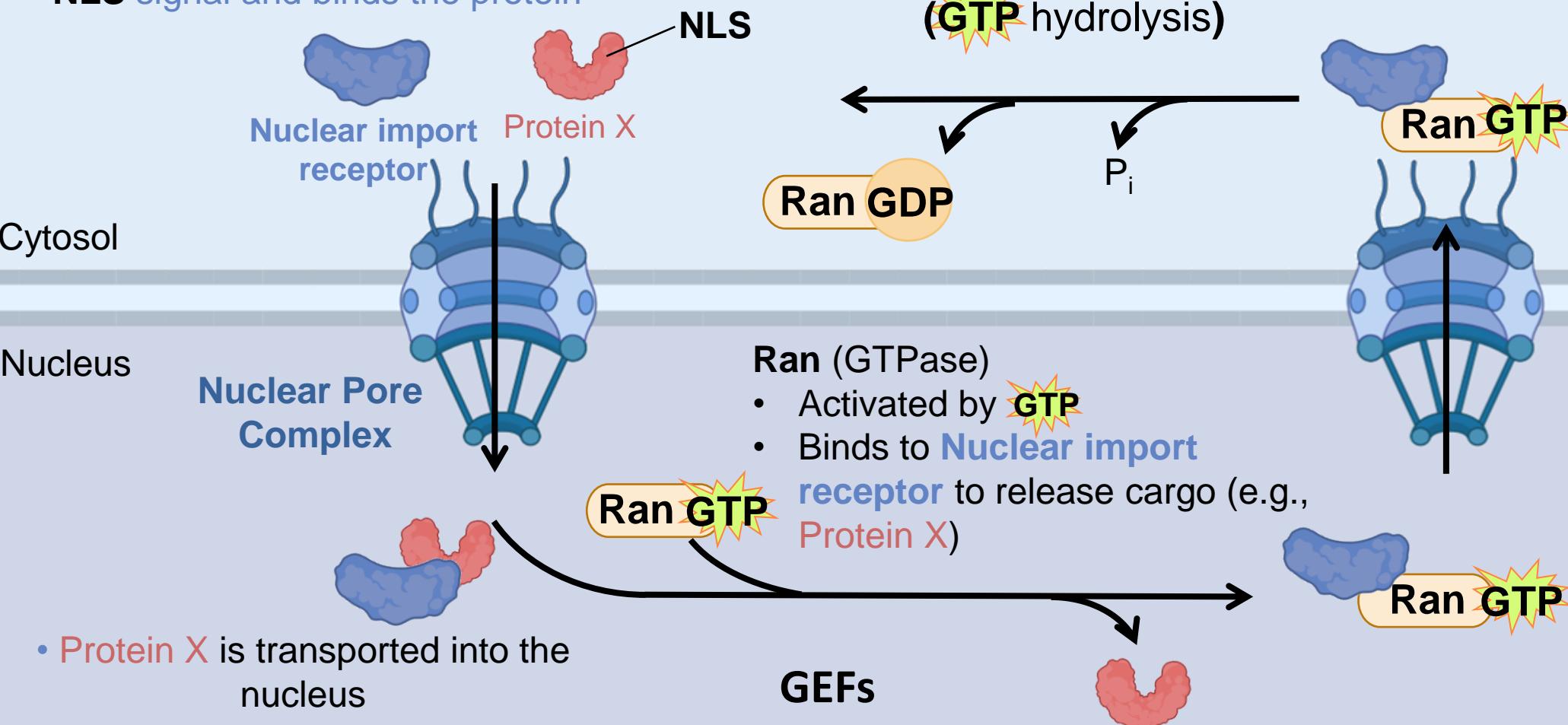
COO⁻ = C-terminus of protein

Targeting Proteins to the ER with Signal Recognition Particle (SRP)



GTP hydrolysis drives the transport of proteins from cytosol → nucleus

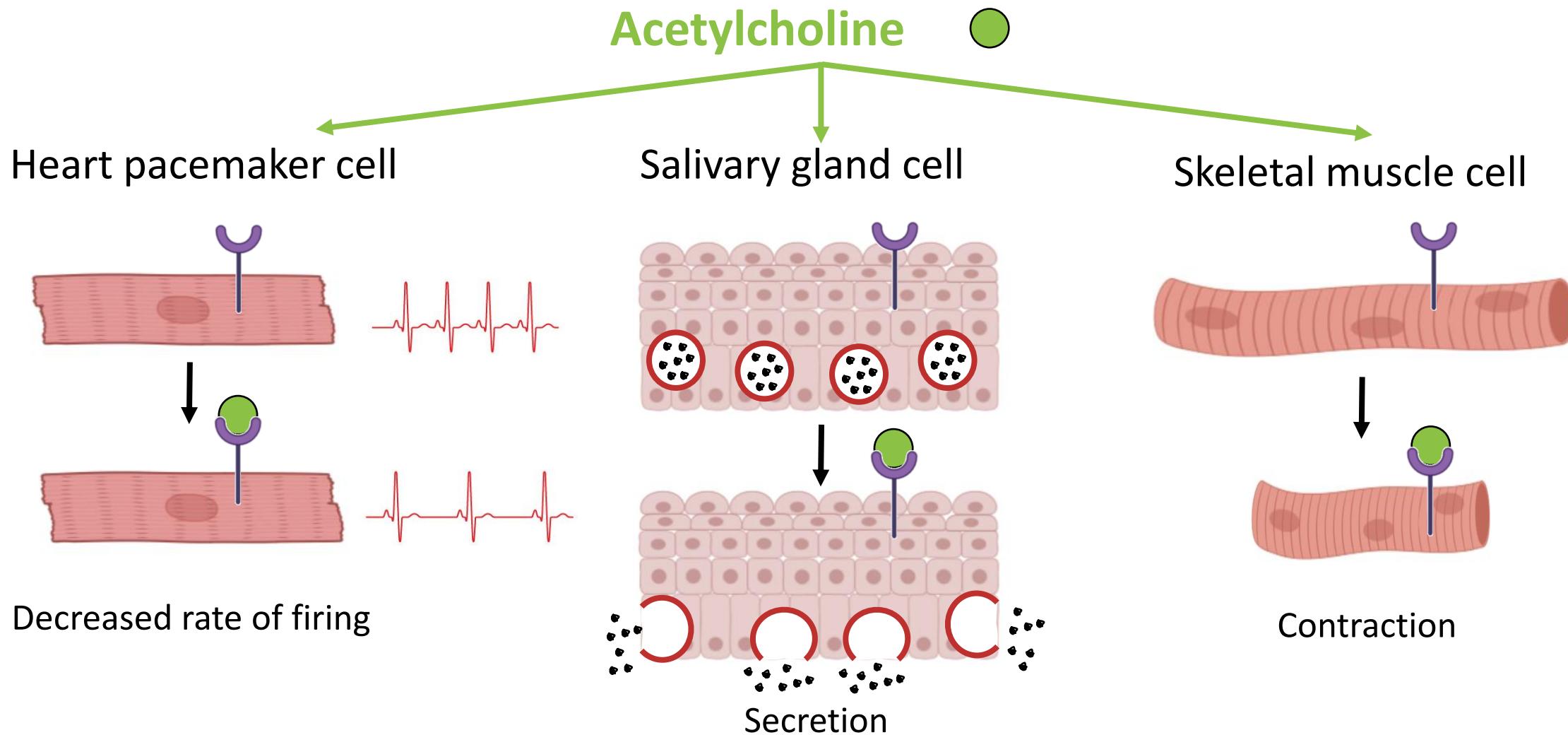
- Nuclear import receptor recognizes NLS signal and binds the protein



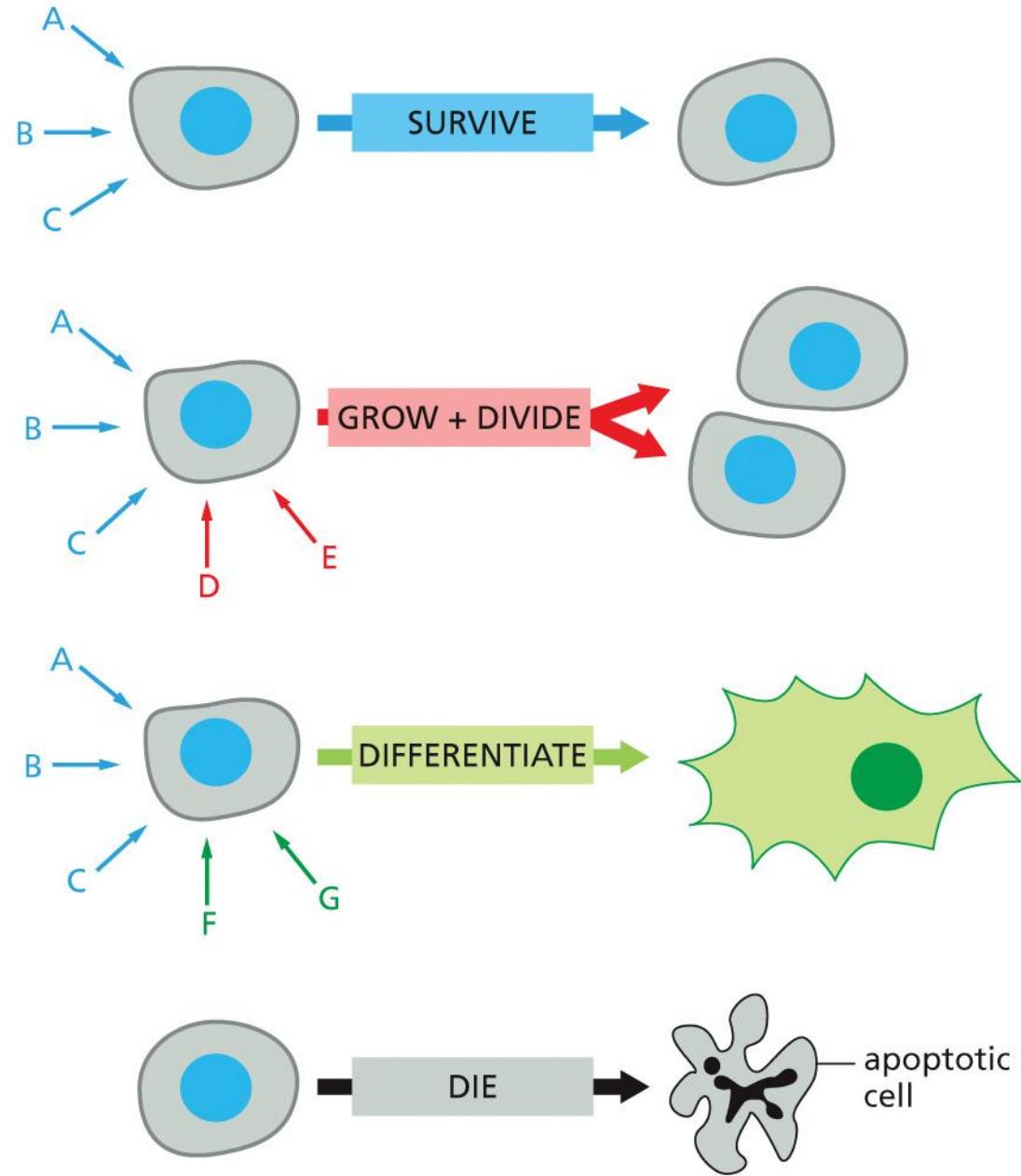
Ch. 16

Cell Signaling

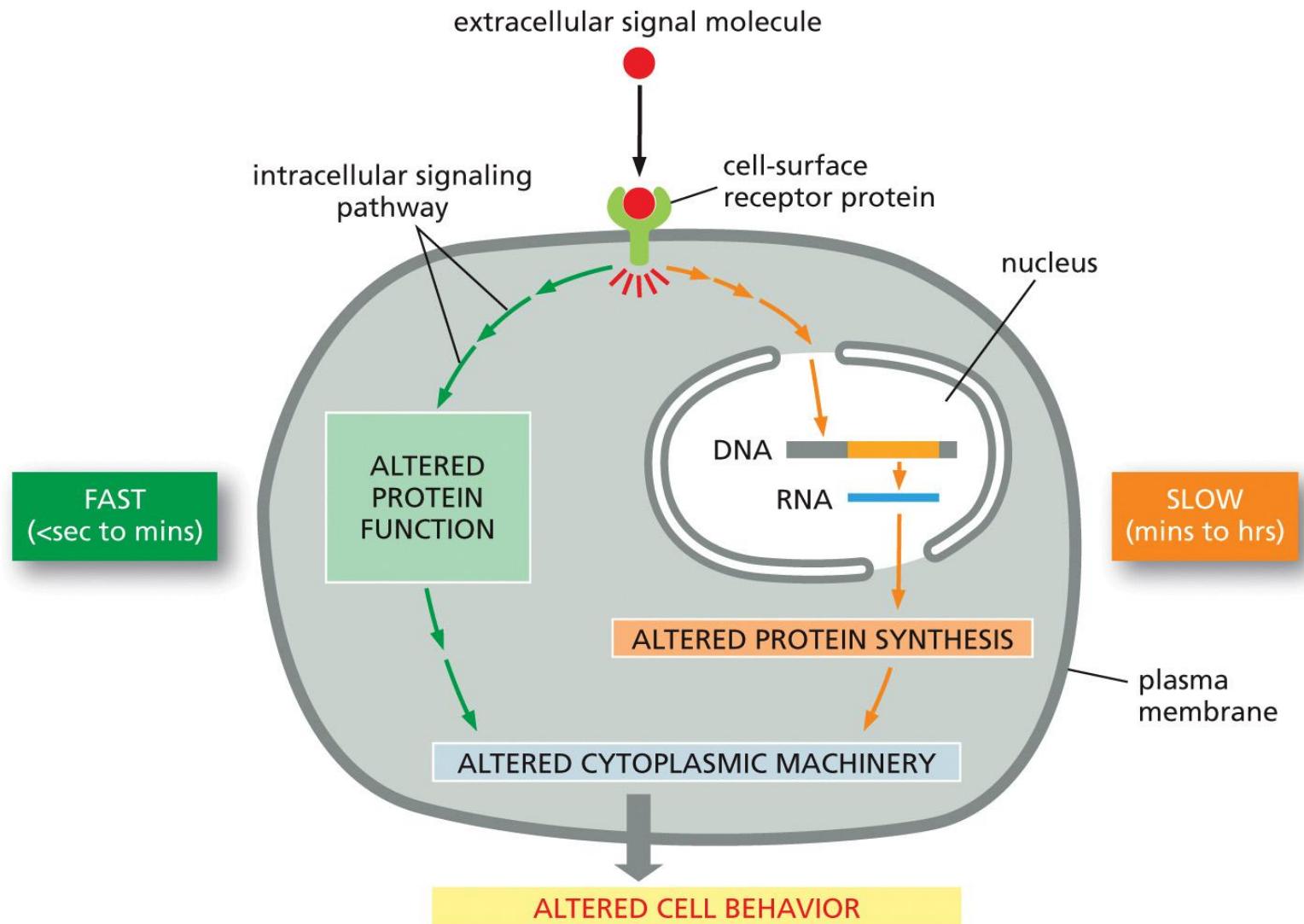
A single signaling molecule can induce different responses in different target cells



Cellular response depends on multiple extracellular signals



Cell signals can act slowly or rapidly



Learning Objectives for Today's Lecture:

Upon completing this module, **you should be able to:**

- Describe how **ion channels** can be used to propagate cellular signals by leveraging electrochemical gradients
- Understand the four main methods of **intercellular signaling** (e.g., endocrine, paracrine, juxtacrine, autocrine)
- Appreciate the complexity of cellular signaling, and devise ways to dissect signaling pathways
- Review main concepts from Ch 11-16 (Part I) prior to the exam Tuesday

Metacognitive Reflection Form

