

Cell Biology Part 1

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Table of Contents

1	Introduction	3
2	Major Components of The Cell	4
3	Major Eukaryote Organelles	6
3.1	The Nucleus	6
3.2	The Endomembrane System	7
3.3	Vacuoles	8
3.4	Vesicle Fusion	9
3.5	Energy Providing Organelles	9
4	Cellular Transport	10
4.1	Simple Diffusion	10
4.1.1	Osmosis	11
4.1.2	Effects of Osmolarity on Cells	12
4.2	Types of Transport	12
4.3	Cellular Ingestion	14
5	The Cytoskeleton	15
5.1	Cytoskeleton Filaments	15
5.2	Cell-Cell Junctions	18
5.3	Extracellular Matrix (ECM)	19
6	The Cell Membrane	19
6.1	Phospholipids	19
6.2	Cholesterol	20
6.3	Lipid Rafts	20
6.4	Transmembrane Proteins	20
7	Cell Communication	22
7.1	G-Protein Coupled Receptors	22
7.2	Receptor Tyrosine Kinases	23
7.3	Gated Ion Channels	24
7.4	Signal Transduction	25

7.5 Intracellular Receptors	27
8 Closing Statement	28

1 Introduction

The cell is the basic unit of structure and function for life. Whether you are human with trillions of cells or an *Euglena* with only one, every single organism consists of cells. This handout will dive deeper into the inner workings of how the complex cell operates. After all, have you ever wondered how can trillions of cells automatically operate to keep you alive?

For this lesson, the following diagrams may be useful for reference:

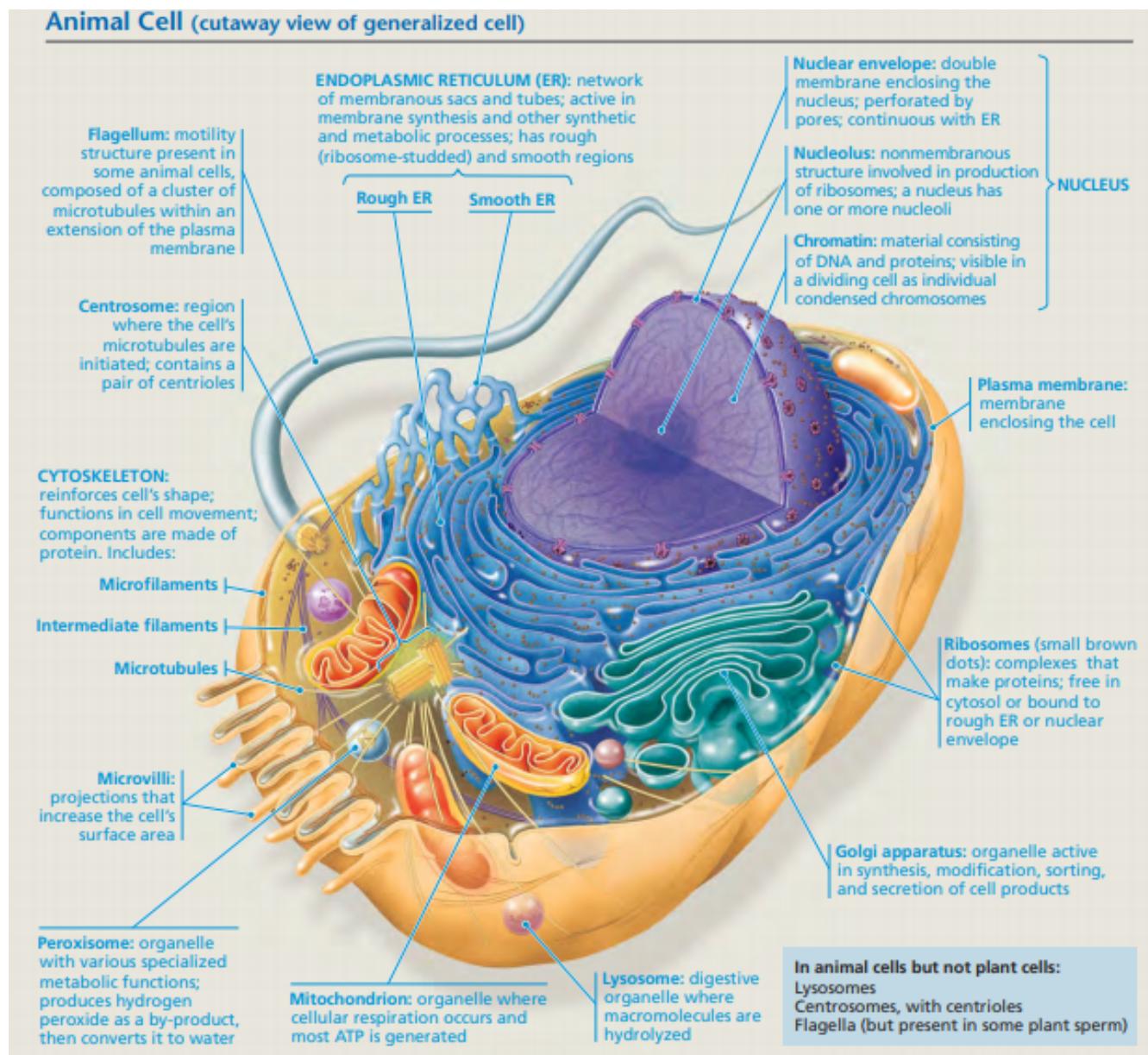


Figure 1: Diagram of a typical animal cell. (Source: Capmbell's 12th Edition)

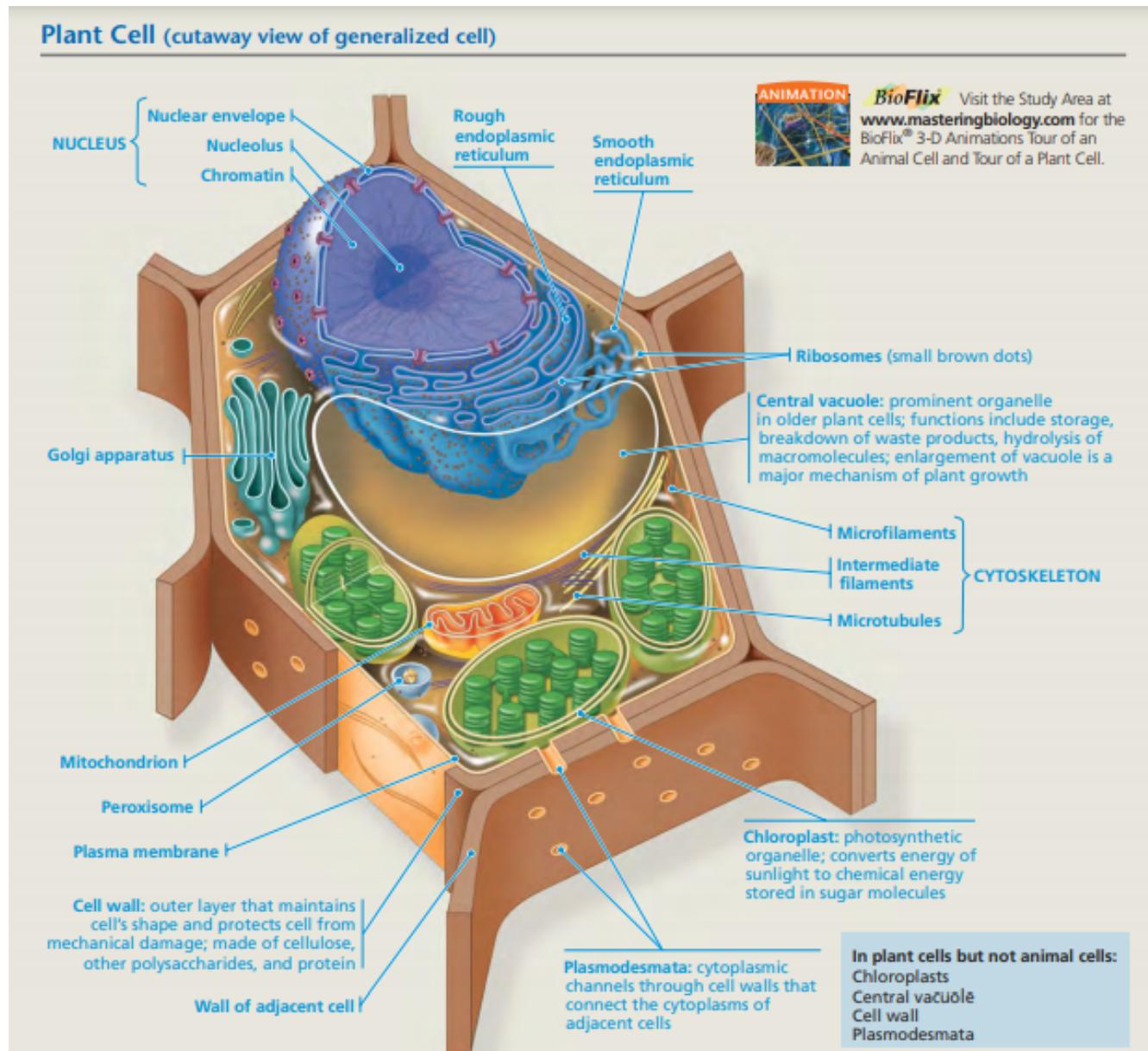


Figure 2: Diagram of a typical plant cell. (Source: Capmbell's 12th Edition)

2 Major Components of The Cell

Despite the fact that we look very different to bacteria, our cells have striking similarities. All organisms can be classified into 3 main domains: **Bacteria**, **Archaea**, and **Eukarya**. Each of these domains consist of distinct cells, yet they all still show many similarities. The *plasma membrane*, *cytosol*, and *ribosomes* are common to all cells.

- The **plasma membrane** is a double membrane that acts as selective barrier, separating the inside of the cell from the rest of the environment. The plasma membrane is rich in lipids and proteins.

- Some organisms also have a **cell wall**. Similar to the plasma membrane, the cell wall acts as a barrier to protect the plant cell. However, it is more rigid, providing structure and strength.

In fungi, the cell wall is made of **chitin**, while in plant cells the cell wall consists of mostly **cellulose**, along with **lignin** for structure. All plant cells have a **primary cell wall**, which is rigid but still allows for growth, repair, and metabolic processes.

The gooey space connecting the primary walls of adjacent plant cells is called the **middle lamella**. **Pectin** is the main substance that gives the middle lamella its plasticity, however Ca^{2+} and **hemicellulose** can make the middle lamella more rigid.

Some specialized plant cells can also grow a **secondary cell wall** interior to the primary wall, adding more layers for more strength. These cells are often dead at maturity.

- The **cytosol** is a gel-like substance inside the cell that everything else is suspended in, which allows molecules to travel across the cell. The cytosol is a reducing environment, which makes it rare for disulfide bridges or oligosaccharides to be present.
 - The **cystoplasm** is a term that consists of the cytosol and all of the cell's organelles.
- The **ribosomes** are tiny complexes scattered throughout the cell responsible for creating proteins from the genetic information of DNA. Ribosomes are categorized depending on their **sedimentation coefficient (S)**, which is determined by how fast they move during a sedimentation assay. A prokaryotic bacteria will have 70S ribosomes, while eukaryotes will have 80S ribosomes.
 - Ribosomes are complexes consisting of two different subunits. One subunit is small, while the other is large. Eukaryotes have 40S and 60S subunits, while prokaryotes have the 30S and 50S subunits. These subunits associate with each other when translation is initiated.

Example 2.1 (USABO Semifinals 2018)

2. **What is the sedimentation value for one eukaryotic ribosome?**

- A. 40S
- B. 50S
- C. 60S
- D. 70S
- E. 80S

Solution: As mentioned before, eukaryotic ribosomes have a sedimentation coefficient of 80S. Therefore, the **answer is E**. The 80S ribosome consists of two subunits, a 40S and a 60S subunit. It should be noted that subunit sedimentation coefficients do not add up. A way to remember that eukaryotes have the 80S ribosome is that they have even sedimentation coefficient numbers (40S, 60S, 80S) while prokaryotes have odd sedimentation coefficient numbers (30S, 50S, and 70S).

3 Major Eukaryote Organelles

3.1 The Nucleus

Cells are either called **prokaryotes** or **eukaryotes**, depending on whether or not they contain an organelle called the **nucleus**. Prokaryotes *lack* a nucleus, instead containing a region called the **nucleoid** that contains concentrated DNA. Additionally, prokaryotes lack any membrane-bound organelle, which explains why many non-complex cells are prokaryotes.

- The **nucleus** is the cell's information center and contains DNA. It has a double membrane with **nuclear pores** lining the surface, allowing molecules to pass in and out. Directly interior to this membrane lies the **nuclear lamina**, which is a net of intermediate filaments (more on them later) that maintains the shape of the nucleus.

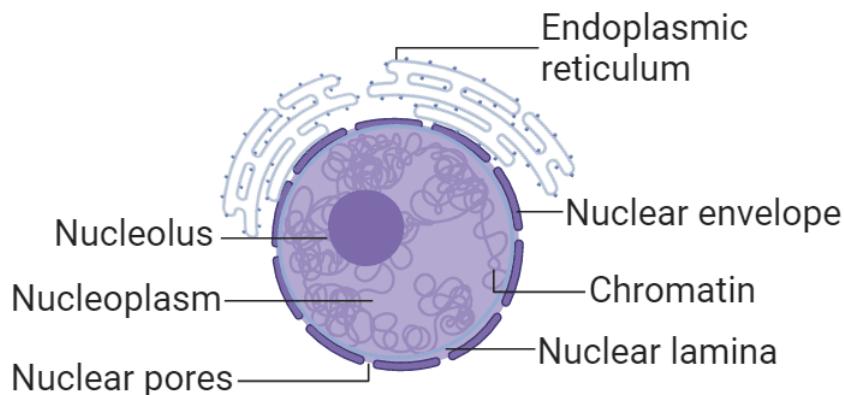


Figure 3: A diagram of the nucleus. The endoplasmic reticulum is continuous with the nuclear membrane, which will be explained later in Section 3.2. (Source: Ahmad)

- Inside the nucleus is the **nucleolus**, which is a region that contains special DNA coding for *ribosomal RNA* (rRNA). rRNA plays an important role in ribosomes.

3.2 The Endomembrane System

The **endomembrane system** regulates protein transport and performs metabolic functions within the cell. It consists of multiple membrane-bound organelles, including the nuclear envelope, the *endoplasmic reticulum*, *golgi apparatus*, *lysosomes*, *vesicles*, and the plasma membrane. This system oversees the process of secreting proteins, metabolism and movement of lipids, and detoxification.

The **endoplasmic reticulum (ER)** is an organelle containing an extensive amount of membranes. The ER contains numerous tubules and *cisternae* sacs which store proteins and lipids for transport. The inside of the ER is separated from the rest of the cytosol by the ER membrane, with the inside of the ER being called the *lumen*. The ER is continuous and attached to the nuclear envelope to allow RNA and other molecules to pass freely through the nuclear pores. There are two distinct, connected regions of the ER. Once molecules are synthesized or transported through the ER, they then leave through **transport vesicles** which are responsible for safely moving around material.

- The **Smooth ER** is a region of the ER that is responsible for synthesizing lipids (including those needed for the plasma membrane), detoxification of poisons, and storage of calcium ions (e.g. the *sarcoplasmic reticulum*).
- The **Rough ER** is a region of the ER that is studded with ribosomes on the outside, hence why it is called “rough”. The proteins synthesized by ribosomes attached to the rough ER are mostly signaled to be secreted outside the cell. The rough ER also synthesizes membrane phospholipids.
- Once proteins/molecules leave the ER, they travel through transport vesicles to the **Golgi Apparatus**. The Golgi is the shipping center of the cell, responsible for directing vesicles to the correct location. The Golgi is assymetrical on two ends, with vesicles from the ER entering through the **cis face**. Vesicles then mature through numerous sacs and cisternae until they reach the **trans face** of the Golgi.

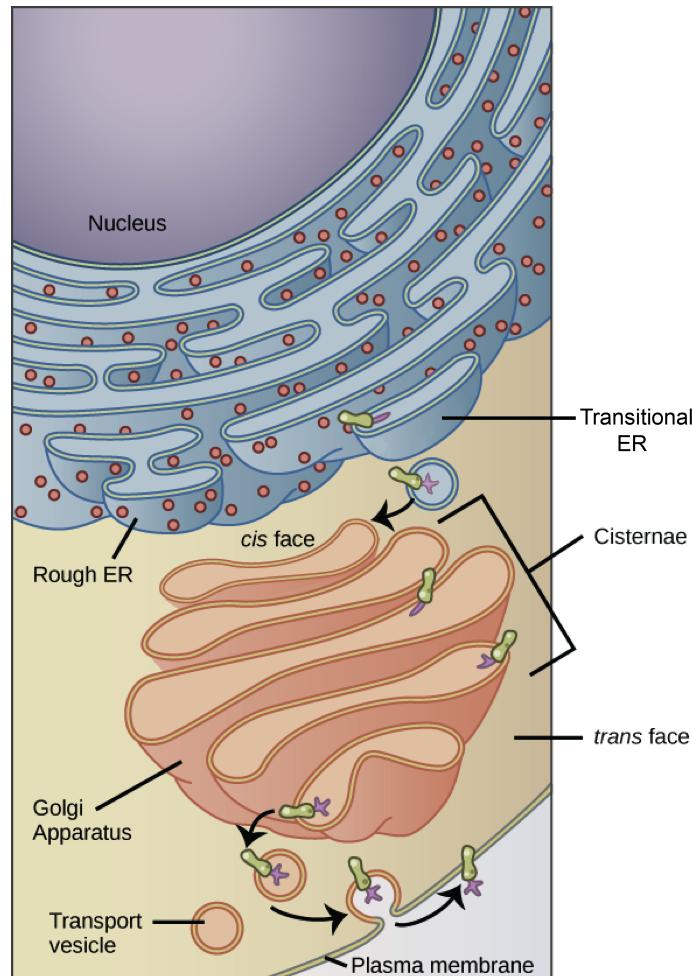


Figure 4: The endomembrane system. The system is responsible for modifying, packaging, and tagging proteins to be transported around the cell.
(Source: Khan Academy)

Currently, scientists are debating on two different models to explain how vesicle transport works in the Golgi. One model is called the **Cisternal Maturation Model**, where the cisternae are dynamic structures that move along with incoming vesicles. Vesicles are thought to fuse with newly produced *cis* cisternae and mature, which signals the vesicles to bud off and move to the next cisternae.

On the other hand, the **vesicular transport model** believes that cisternae are more stable, not newly made as often, and stay in place. Each cisternae is distinct from one another and they rarely fuse their contents with each other. Nevertheless, when vesicles finally reach the trans end of the Golgi, they can travel to the plasma membrane to be secreted, to a lysosome, or directed to a vacuole.

- The cell contains three main transport vesicles, each with their own specific function. **COPI** transport vesicles are responsible for moving molecules *retrograde* (backwards) from the Golgi Apparatus back to the ER. **COPII** vesicles do the opposite, moving molecules from the ER to the Golgi. **Clathrin** vesicles move molecules from the Golgi to the Plasma Membrane. These clathrin-coated vesicles are surrounded by a protein shell that is called a *triskelion skeleton*.
- Vesicles can then merge to **lysosomes** to be digested. Lysosomes are found *only* in animal cells, contain an acidic pH of around 4.5, and contain enzymes for degrading molecules. The lysosome's ability to break down structures allows it to be the “recycling center” of the cell, breaking down old organelles for their parts.
- Additionally, vesicles can also fuse with **peroxisomes**, which are similar to lysosomes except that they contain the enzyme **catalase** to break down *hydrogen peroxide* (hence, the name peroxisome) into hydrogen and oxygen. Plant seeds contain a special type of peroxisome called *glyoxysomes*, which converts lipids to starch during germination.

3.3 Vacuoles

Vacuoles are large vesicles that have many important functions.

- **Food Vacuoles** are responsible for storing food. Food vacuoles mostly merge with lysosomes (becoming a *phagolysosome*) to digest the food inside the compartment.
- **Contractile Vacuoles** are found in many unicellular protists living in freshwater environments. These vacuoles are responsible for expelling excess water out of the cell to prevent freshwater protists from bursting.
- **Central Vacuoles** are found in plant cells. They are much larger than other vacuoles and are the main storage center for inorganic ions and water. Plant cells contain only one central vacuole which is important in maintaining turgor pressure (explained in cell transport).

3.4 Vesicle Fusion

When membranes fuse together, they utilize **SNARE proteins** to make the process easier.

- The vesicle contains **V-SNARE** proteins (“V” stands for vesicle). Now, they are called R-SNARE due to the presence of arginine.
- The plasma membrane contains **T-SNARE** proteins (“T” stands for target, which is typically the plasma membrane). Now, they are called Q-SNARE due to the presence of glutamine.
- When the membranes fuse together, V and T SNARE proteins combine to make **Cis-SNARE**.

3.5 Energy Providing Organelles

Organisms need to efficiently gain energy from their surroundings in order to survive. Both *mitochondria* and *chloroplasts* play an important role in harvesting and using energy in the cell. These cells are thought to have been their own organism in the past because of their high complexity compared to other organelles. Both chloroplasts and mitochondria contain their own DNA, ribosomes, double membrane, and replicate on their own. These complex traits gave scientists the reason to believe that the mitochondria and chloroplast were once organisms that were actually ingested by another organism and then kept alive because of their ability to generate ATP and food. This symbiotic relationship theory is called the **Endosymbiosis Theory** (explained in biosystematics handout).

- The **Mitochondria** is the powerhouse of the cell. They are the location of cellular respiration and are responsible for breaking down large molecules that store energy into usable energy. The space between the two membranes of the mitochondria is called the **intermembrane space**. This space is important for generating ATP, which we will discuss in Part 2. The inner membrane consists of numerous tiny folds called **cristae**, which greatly increases the inner membrane’s surface area. This is also important for generating ATP. The space inside the inner membrane is called the **matrix**.
- **Chloroplasts** are found in plants and some protists, but not animal cells. These organelles are the site of photosynthesis and are responsible for converting solar energy to chemical energy for the cell to use later. Inside of the chloroplast are numerous tiny disc-like stacks called **thylakoid stacks**. These are important for photosynthesis. The fluid that surrounds the thylakoids is called the **stroma**.

Other types of plastids also exist:

- During senescence in plants, the chloroplast is deconstructed, forming a **gerontoplast**.
- **Chromoplastids**, which only contain carotenoids (red/orange/yellow pigments), may be formed when a chloroplast loses its chlorophyll. The function of chromoplastids is unknown, but they may help with ripening fruit.
- **Leucoplastids** lack pigments entirely and are plastids that store food. It is an **amyloplast** if it stores starch and an **elaioplast** if it stores lipids.

- Proplastids are the small colorless precursors to plastids. One example is etioplasts, which turn into chlorophyll when exposed to light.

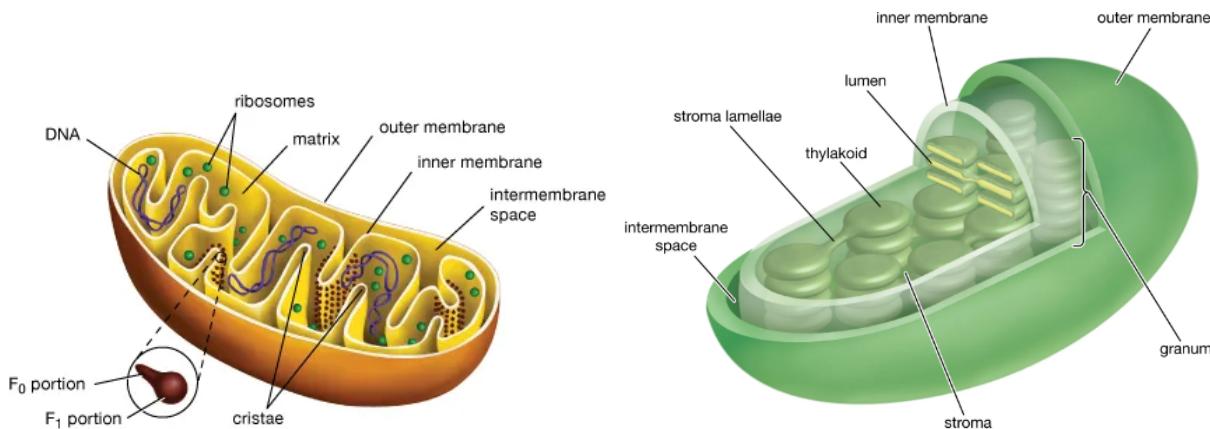


Figure 5: (left) Diagram of a mitochondrion, showing ATP synthase embedded in the inner membrane, which allows the mitochondrion to generate ATP.
 (right) Diagram of a chloroplast. (Source: Britannica)

4 Cellular Transport

The cell membrane protects the cell, keeping the harmful substances of the environment outside and the nutrients used by organelles within. However, this also presents an issue: how will the cell transport nutrients in and wastes out?

4.1 Simple Diffusion

When you add a drop of food coloring to water, something interesting happens. The food coloring, which began concentrated as a single drop, disperses until it is everywhere and all parts of the water have the same **concentration**. This process is known as **diffusion** and it follows a simple rule: **Molecules will diffuse from high concentration to low concentration**.

To understand why substances move down their **concentration gradient** from high to low, we can go back to our food coloring. Every molecule moves randomly. Therefore, by chance, some molecules from the more concentrated side will move to the less concentrated side and some molecules from the less concentrated will move to the more concentrated side. However, since the more concentrated side has more molecules, that means there will be a *net* movement from the more concentrated side to the less concentrated side.

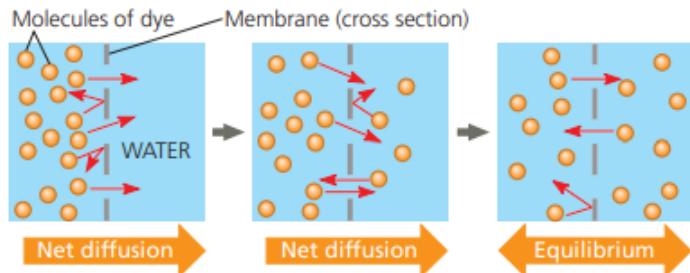


Figure 6: A substance will diffuse from high to low due to the random motion of its particles.
 (Source: Campbell's 12th Edition)

As a result, any molecule that can freely pass through the cell membrane will move into/out of the cell via **simple diffusion**, going from high to low. As will be discussed later, the phospholipid bilayer that makes up the cell membrane has a *hydrophobic* interior. As a result, only *nonpolar* and *small* molecules (e.g. CO_2 , O_2) use simple diffusion.

4.1.1 Osmosis

Sometimes, instead of solutes diffusing, it is water that moves across the membrane. This diffusion of water is known as **osmosis**. As with any other substance, water will move from a high concentration of *water* (and therefore low concentration of solute), to a low concentration of *water* (and therefore high concentration of solute). This is why some sources will say that water moves from low to high.

We can demonstrate the effects of osmosis by using a *U-tube* with the two halves separated by a **semi-permeable membrane**. Like the cell membrane, this membrane is specially built so it only lets some substances through, but not others. In this case, our membrane can let water through, but not glucose (the solute).

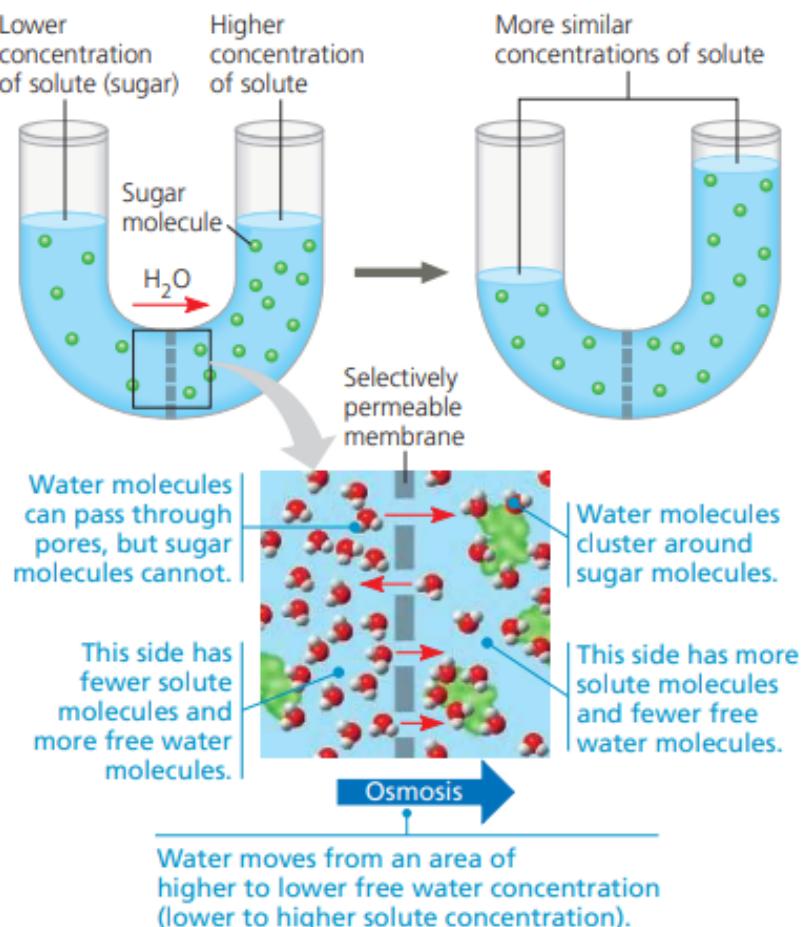


Figure 7: A U-Tube demonstrating the effects of osmosis. Note that in the end, the side that started off with a higher concentration of solute will now have more water. As a result, the concentration on both sides are equal in the end. (Source: Campbell's 12th Edition)

4.1.2 Effects of Osmolarity on Cells

Since water is the main component of the cytosol, a cell's size is largely determined by how much water it has. As a result, the **osmolarity** (the relative concentration of solutes) of the environment can change how much water is inside a cell through osmosis.

If the environment is *more* concentrated than the interior of the cell, then it is **hypertonic** and water will flow *out* of the cell. If the environment is *less* concentrated than the interior of the cell, then it is **hypotonic** and water will flow *into* the cell. If the environment has the *same* concentration of solutes as the interior of the cell, then it is **isotonic** and there will be *no movement* of water.

Animal cells perform best in an isotonic environment. Plant cells, on the other hand, have a cell wall that exerts **turgor pressure** on the cell. Since the cell wall tries to squeeze water out of the cell, plant cells actually do best in a hypotonic environment. In an isotonic environment, there is not enough pressure on the cell wall and the cell becomes **flaccid**, or limp. If placed in a hypertonic environment, water will move out of the plant cell, causing the cell membrane to shrink. However, since the cell wall is rigid, it will not shrink. Therefore, the cell membrane peels away from the cell wall, which is known as **plasmolysis**.

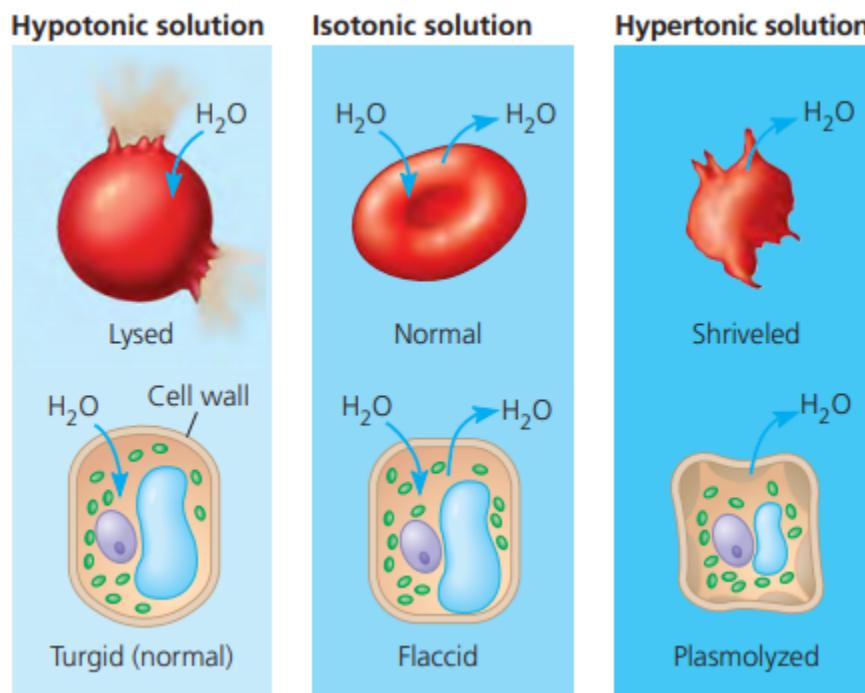


Figure 8: The effects of different environments on plant and animal cells.
(Campbell's 9th Edition)

4.2 Types of Transport

For most substances, simple diffusion is not an option. Thus, the cell must resort to other means. For each type of transport, I've included examples from the human body. The types of transport are important to know but the specific examples are not.

- **Facilitated diffusion:** Like simple diffusion, here molecules move from high to low. However, if they are *polar* or *charged ions*, they can not cross the hydrophobic interior of the cell membrane on their own. This is where **transport proteins** come in, providing a hydrophilic path for these molecules to enter the cell! They come in two types:

- **Channel proteins** form a tunnel for the molecule to pass through. **Aquaporins** are channel proteins (made of 4 identical subunits) that are used to transport water.
- **Carrier proteins** have binding sites for the molecule. Carrier proteins are exposed to only one side of the cell at a time, but the binding of the molecule changes which side the protein faces. **GLUT transporters** are used to bring glucose into the cell.

However, sometimes the cell wants to transport a molecule *against* its concentration gradient. In these cases, the energy to move the molecules must come from a different source: **ATP**. Since the cell uses ATP, these types of transport are known as **active transport**.

- **Primary active transport** directly uses ATP to move a molecule against its concentration gradient.

- The most famous example is the **Na⁺-K⁺ pump**, which transports 3 Na⁺ out of the cell for every 2K⁺ it brings into the cell. This pump maintains the low intracellular concentration of Na⁺ and the high intracellular concentration of K⁺, which is important for many cellular functions.

The pump has a **transport cycle** with two states. The **E1** state faces the inside of the cell and has a high affinity for Na⁺ (releasing K⁺) while the **E2** state faces the outside of the cell and has a high affinity for K⁺ (releasing Na⁺). *Cardiac glycosides* inhibit the Na⁺-K⁺ pump by binding to the E2 state.

- The **Ca²⁺ pump** is used to maintain low intracellular Ca²⁺ concentrations, which is important for cell signaling.
- The **H⁺-K⁺ pump** is found in the parietal cells of the stomach and the α -intercalated cells of the collecting ducts. It is inhibited by *Omeprazole*.

- **Secondary active transport** uses the concentration gradient generated by primary active transport. The energy from one molecule (*typically* Na⁺) moving down its concentration gradient is used to move another molecule against its concentration gradient.

- **Cotransport/symport** is when the two molecules move in the same direction.
 - * **Na⁺-glucose cotransport (SGLT)** and Na⁺-amino acid cotransports found in the small intestines and proximal tubules are important for the body to absorb nutrients.
 - * **Na⁺-K⁺-2Cl⁻ cotransport** is used to establish the Na⁺ gradient in the thick ascending limbs.

- **Countertransport/antiport/exchange** is when the two molecules move in opposite directions.
 - * **Ca²⁺-Na⁺ exchange** keeps the intracellular Ca²⁺ concentration low.
 - * **Na⁺-H⁺ exchange**

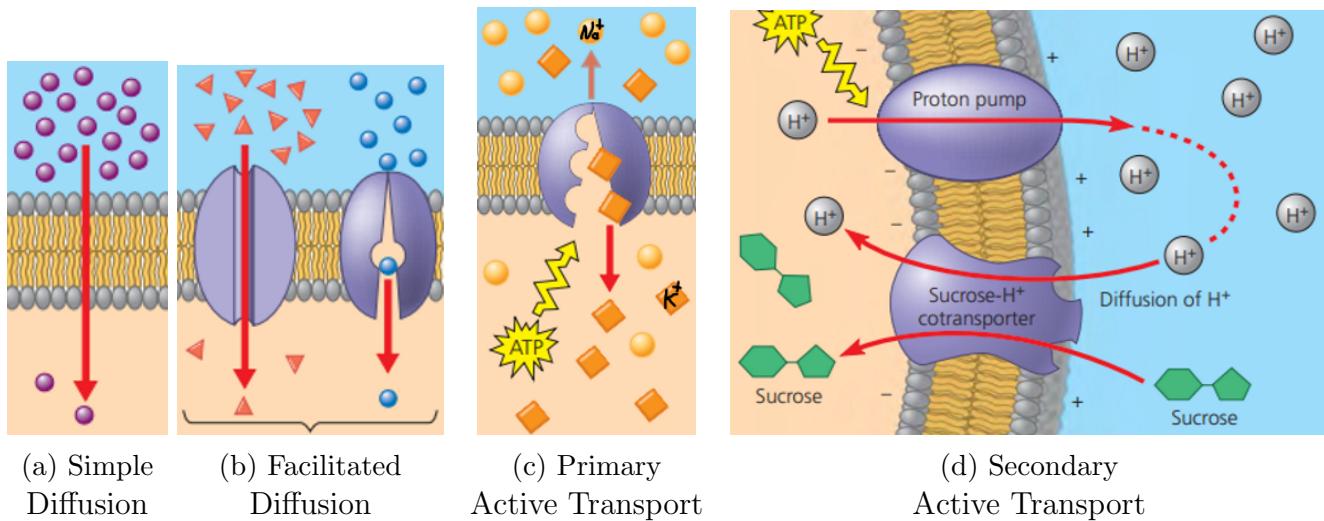


Figure 9: Types of transport. **(b)** shows a channel (left) and carrier (right) protein, **(c)** is the classic Na^+-K^+ pump, **(d)** is a cotransporter found in plants to transport sucrose.
(Source: Campbell's 9th Edition)

4.3 Cellular Ingestion

For especially big molecules, or liquids, even the previous forms of transportation do not work. In these cases, **Endocytosis** is used instead. In endocytosis, a part of the membrane invaginates, creating a pocket for the molecules to enter before that pocket closes off and forms a vacuole. Endocytosis comes in 3 main types:

- In **Receptor-mediated endocytosis**, molecules must attach to a specific receptor to start the vesicle invagination process. Compared to regular endocytosis, this process is much more specific and only starts once the receptor is activated.
- **Pinocytosis** is similar to endocytosis in that it creates invaginations, except that it is responsible for much smaller molecules such as water. Pinocytosis involves mostly the ingestion of fluids rather than big molecules.
- **Phagocytosis** involves the ingestion of very large molecules. Found commonly in white blood cells, they ingest bacteria via phagocytosis to kill them.

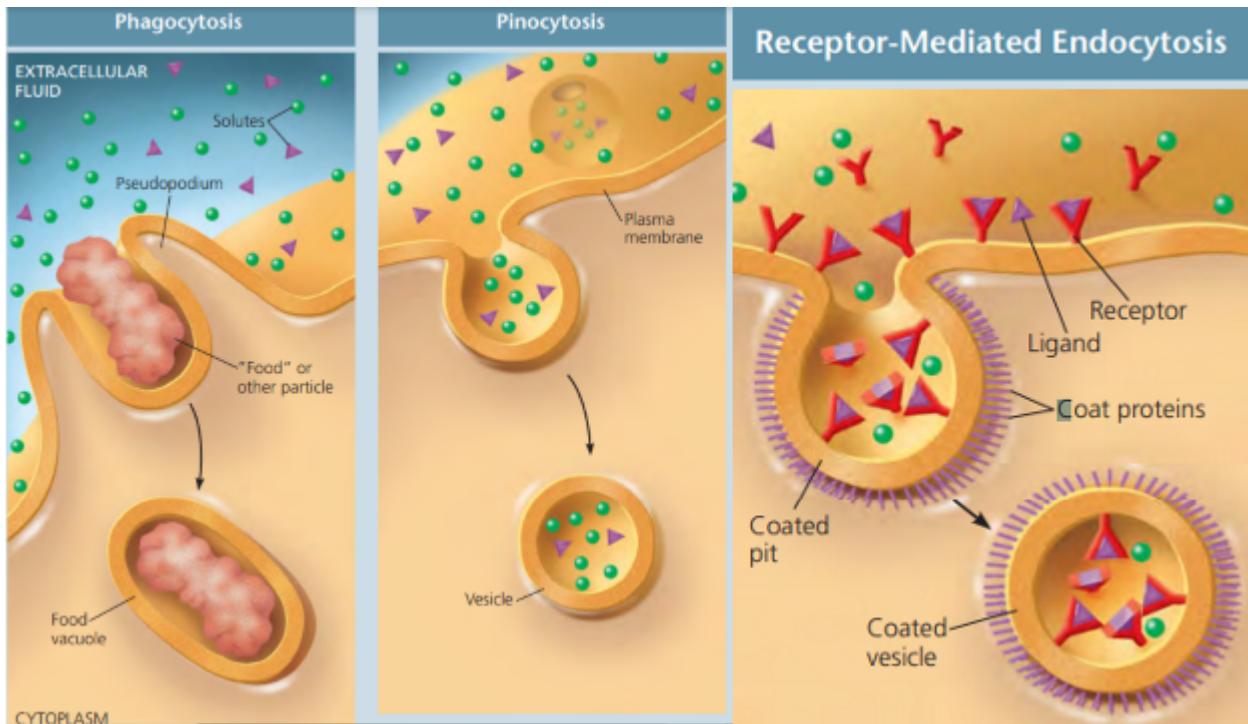


Figure 10: the three types of endocytosis. (Source: Campbell's 9th Edition)

5 The Cytoskeleton

The **cytoskeleton** is a network of fibers strung throughout the cell, which plays a major role in structural integrity and organization. It is found predominantly in eukaryotes, but rudimentary forms of the cytoskeleton are found in prokaryotes. The cytoskeleton contains numerous filaments, each responsible for different functions in the cell. There are 3 types of filaments: *microtubules*, *microfilaments*, and *intermediate filaments*. Filaments typically have a + and - end. On *both* of these ends, the filaments change their length rapidly by adding *and* removing subunits, a process known as **dynamic instability**. However, this process is quicker on the + end.

5.1 Cytoskeleton Filaments

Microtubules are hollow rods created from two types of globular protein subunits: alpha-tubulin and beta-tubulin. They act as support and serve as tracks that vesicles attach to. They are found in centrosomes, cilia, and flagella.

- Certain organelles have special arrangements of microtubules. Cilia and flagella contain a **9+2** arrangement, which means that they contain a ring of 9 microtubule doublets, with a pair of microtubules in the center. At the base of a cilia and flagella where it connects to the cell membrane, the microtubules make a **9+0 doublet** microtubule arrangement. This part of the cilia or flagella is non-motile and is called a **basal body**. Centrioles contain a **9+0 triplet** arrangement. Centrioles are responsible for cell division, which will be explained in the genetics handout.

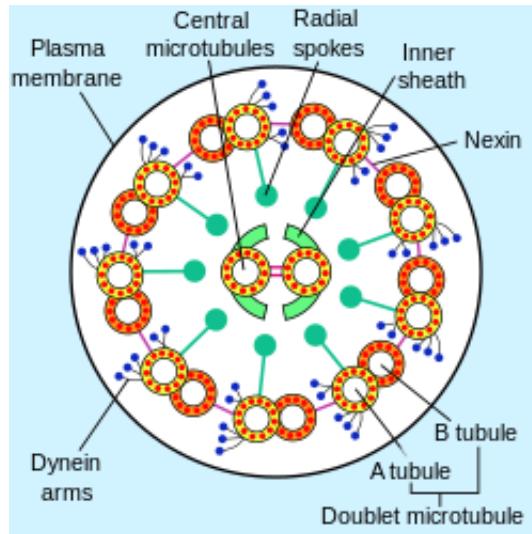


Figure 11: Structure of microtubule arrangement in flagella and cilia. They contain a 9+2 doublet arrangement. (Source: Wikipedia)

- Vesicles attach and move along microtubules using *motor proteins*. **Kinesin** and **dynein** are two important motor proteins which attach the vesicle to the microtubule. Kinesin is responsible for moving cells to the plus end (towards plasma membrane) of the microtubule, while dynein is responsible for retrograde transport to the minus end (towards nucleus).

Microfilaments are thin solid rods also known as *actin filaments*. They are made of globular **actin** proteins, and resemble a twisted double chain. The role of actin is to bear tension against forces. Microfilaments are present in the cell cortical and are responsible for forming the shape of a cell. They also function in **pseudopodia** for movement, work together with **myosin** in muscle, bind to integrin proteins, and are responsible for cytoplasmic streaming of molecules in plant cells.

- **Myosin** is a (anterograde) motor protein responsible for moving muscles, closing the contractile ring in cytokinesis, and transporting cargo.

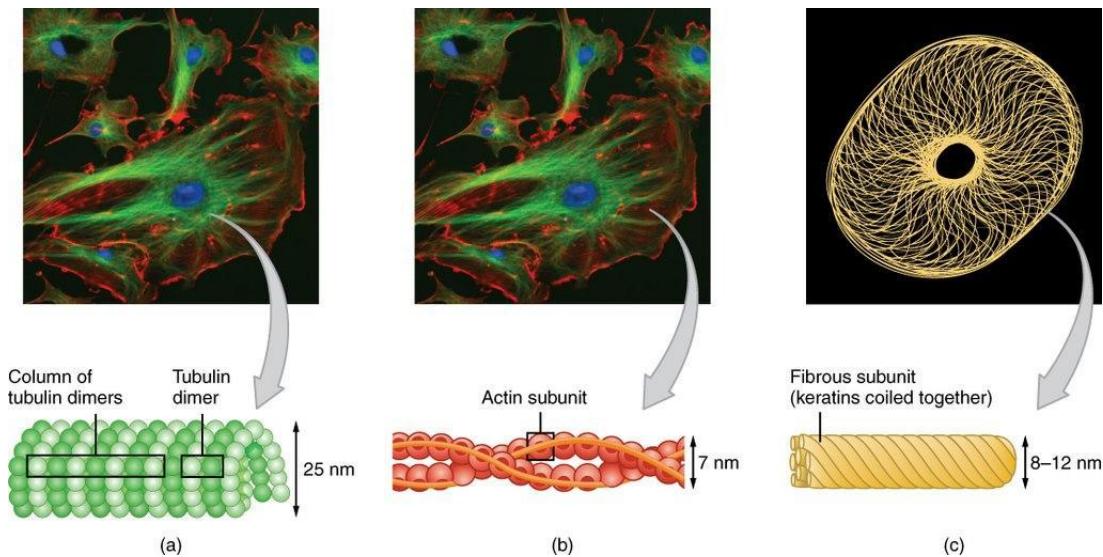


Figure 12: The three types of filaments in the cell cytoskeleton. (a) represents microtubules, (b) represents microfilaments, (c) represents intermediate filaments. (Source: OpenALG)

Intermediate Filaments are more permanent structures than microfilaments and microtubules and are less dynamically unstable. They are used for structural support and strength in keratin and keeping organelles fixated in place.

Example 5.1 (USABO Opens 2018)

Questions 1 and 2. Please use the following options to answer the following three questions. Each choice may be used once, more than once, or not at all.

- A. Actin.
- B. Myosin.
- C. Dynein.
- D. Kinesin.
- E. Cyclin.

1. In the extracellular matrix of an animal cell, you would like to test the binding partner of integrins *in vitro*. Integrins would most likely require firm attachment to which of the above option?
2. You are working with Dr. Lee at University of Wisconsin-Madison to investigate cytokinesis in a newly discovered marine worm. You generated antibodies to conserved proteins involved in cell division in other organism to look for proteins that localize to important structures during cell division. What molecular motor protein should you look for in the contractile ring?

Solution: The answer for **1 is A**. As explained earlier, one of actin's roles is to bind to integrin transmembrane proteins. Integrin is responsible for connecting the extracellular matrix to the actin cytoskeleton.

The answer for **2 is B**. Myosin plays an important role in forming the contractile ring during cytokinesis. Although actin also composes the contractile ring, the question asks for a *motor protein*, which would leave B as the correct choice.

5.2 Cell-Cell Junctions

Cells connect with each other using junctions, which provide numerous uses:

- **Plasmodesmata** are junctions found only in plant cells. Since plant cells have cell walls, they can not connect to each other by plasma membranes. Instead, plasmodesmata are small holes in cell walls that allow direct cytoplasmic exchange between plant cells. The remaining cell junctions are found in animal cells.
- **Gap Junctions** are like the plasmodesmata of animal cells. They function as holes directly connecting the cytoplasm of two animal cells. *Connexins* are the main protein that make up gap junctions.
- **Tight Junctions** are named so because they create a watertight seal between two cells, preventing liquids from passing in between the gaps of two cells. These junctions are especially important for epithelial cells in the bladder to prevent leakage of urine.
- **Desmosomes** connect two cells together using **intermediate filaments**. They function to create structure between cells to prevent them from separating from each other.
- **Adherens Junctions** connect two cells together using **actin microfilaments**. *Cadherins* are the main protein that make up adherens junctions.

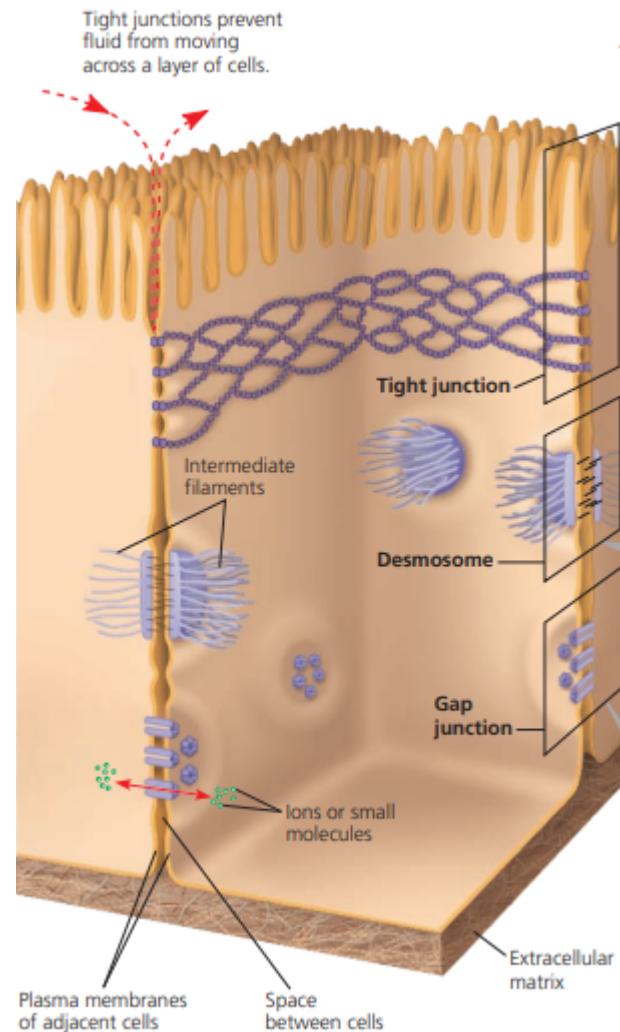


Figure 13: The types of junctions found in animal cells (Source: Campbell's 12th Edition)

5.3 Extracellular Matrix (ECM)

Animal cells also contain a system of proteins *outside* of the cell membrane that helps provide structure and is useful in cell communication. This system is known as the **Extra-cellular Matrix**, and the diagram below highlights its most important components:

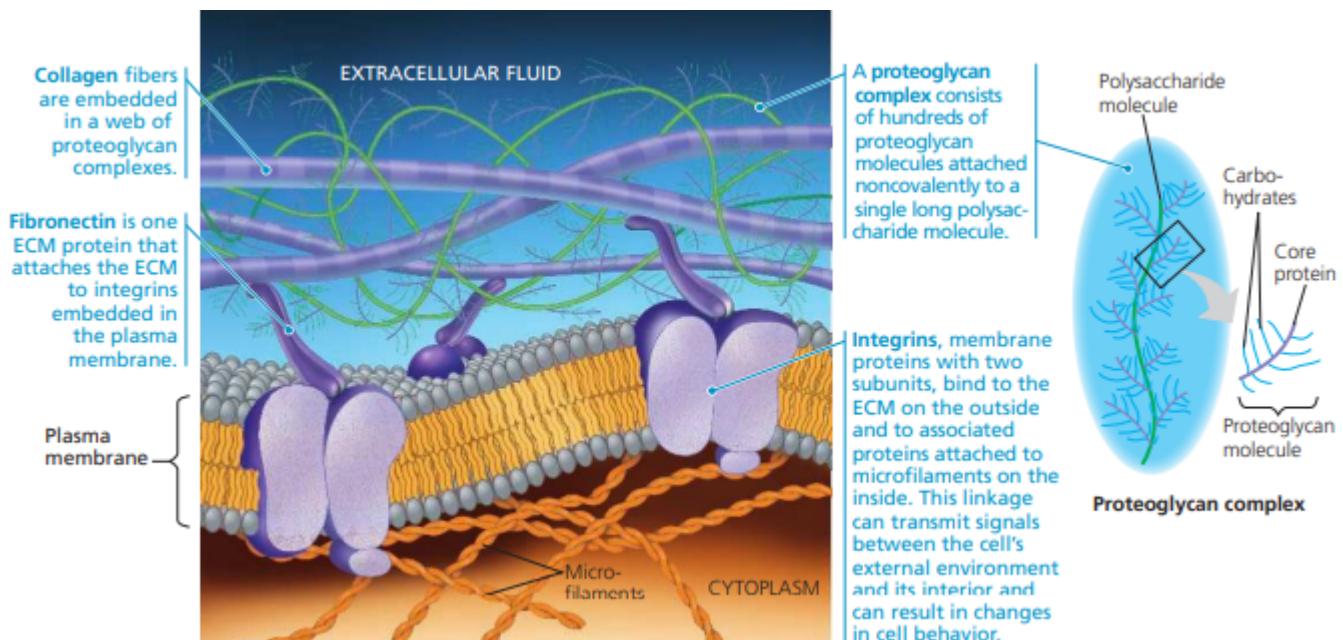


Figure 14: The ECM of an animal cell, highlighting the collagen, fibronectin, and proteoglycan molecules that make it up. (Source: Campbell's 12th Edition)

6 The Cell Membrane

The cell membrane is crucial to a cell's life. It separates the cell from the harsh surrounding environment with a selectively permeable barrier. The cell membrane is composed of a *lipid bilayer*.

6.1 Phospholipids

Lipid molecules in the cell membrane are **amphiphilic** (amphipathic), meaning they have both a **hydrophilic** head and a **hydrophobic** tail. As a result, lipids must form a bilayer with hydrophilic heads facing outwards (exposed to water) and hydrophobic tails facing inward.

The most abundant lipids in the cell membrane are **phospholipids**, which are lipids containing two hydrocarbon tails and a hydrophilic head containing phosphate. Two common types of phospholipids are *phosphoglycerides* and *sphingolipids*.

- **Phosphoglycerides** are the main type of phospholipids in animal cell membranes and consist of a 3-carbon glycerol molecule with two fatty acid tails and a head.
- **Sphingolipids** are similar to phosphoglycerides, except that they contain a *sphingosine* molecule instead of a glycerol. These lipids are primarily found in nervous tissue.

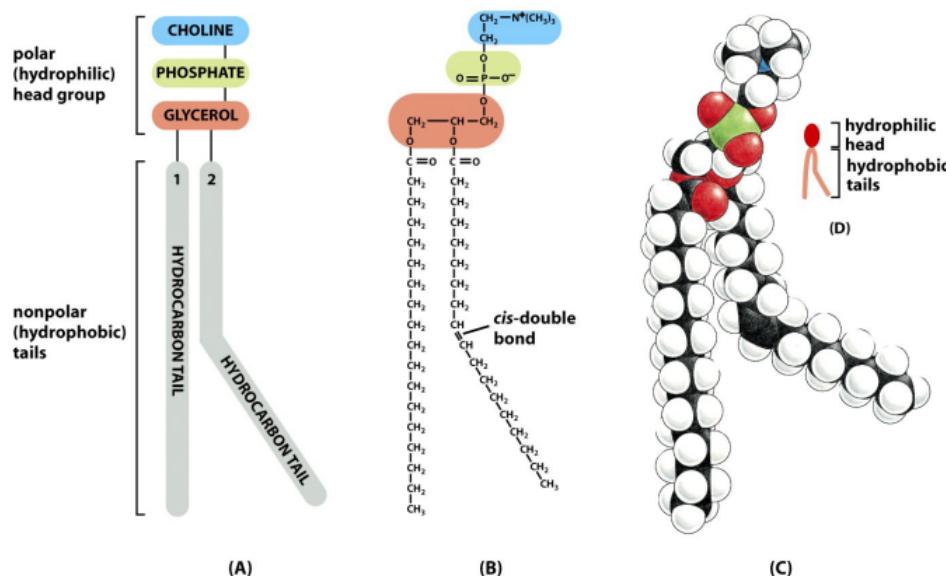


Figure 15: Structure of phospholipids represented (A) schematically, (B) by a formula, (C) as a space-filling model, and (D) as a symbol. (Source: Alberts)

6.2 Cholesterol

Scattered throughout the cell membrane, **cholesterol** is responsible for maintaining cell fluidity. Cholesterol is a *sterol* and is therefore made of 4 carbon rings. Interestingly, cholesterol is found in every cell except bacteria. Bacteria maintain cell fluidity by instead altering their lipid fatty acid composition.

6.3 Lipid Rafts

Although the cell membrane may seem very disorganized and dynamic, there are regions of the membrane that are highly organized. One such region is a **lipid raft**. Lipid rafts are microdomain regions consisting of sphingolipids, cholesterol, and protein receptors that are closely concentrated to each other. The discovery of lipid rafts is somewhat recent, therefore the actual function of them remains controversial.

6.4 Transmembrane Proteins

Transmembrane proteins are proteins that are embedded into the plasma membrane and span its entirety. Some functions of transmembrane proteins include signaling, transport, and protein trafficking. To stabilize inside the membrane, transmembrane proteins require hydrogen bonding created from peptide bonds in the nonpolar region of the membrane. Since alpha helices maximize the amount of hydrogen bonding, they are commonly seen in the transmembrane region of these proteins. This subsection will give two common transmembrane proteins.

- **Porin channels** are transmembrane proteins which create water-filled channels to allow small hydrophilic molecules to cross the membrane. They consist of polar amino acids in the interior facing the water filled hole and hydrophobic amino acids that touch the lipid bilayer. Inside the pore, some polypeptide chains protrude out to block some molecules while being highly specific to others. They are responsible for passive diffusion.

- Porin channels are made of **beta-barrels**, which are proteins made of mostly beta-sheets that roll up into cylinders. In general, beta-barrels are found commonly in bacterial, mitochondrial, and chloroplast membranes. In addition to acting as porins, they can also function as receptors.

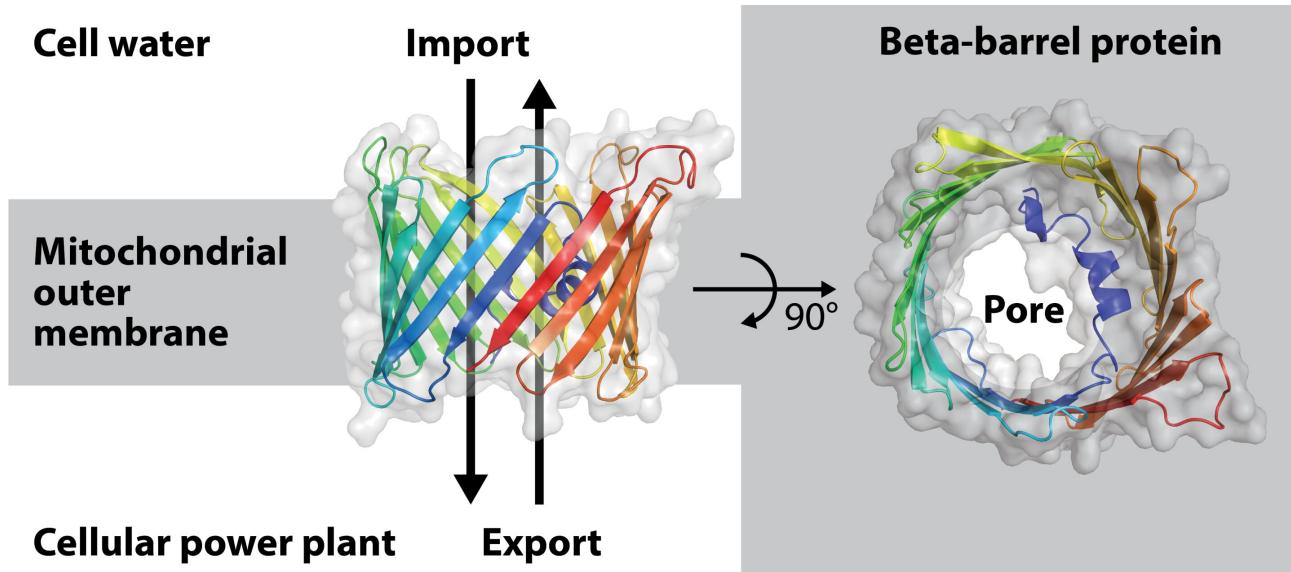


Figure 16: Example of a beta-barrel found in the mitochondrial outer membrane. They consists of mostly beta-pleated sheets which hydrogen bond to each other to form a hollow cylinder to allow exchange of molecules between the cytosol and mitochondria (Source: Christophe Wirth)

- **Aquaporins** are transmembrane proteins made of 6 alpha helices responsible for efficiently diffusing water. They allow for one water molecule to enter the protein at a time, while preventing ions from entering.

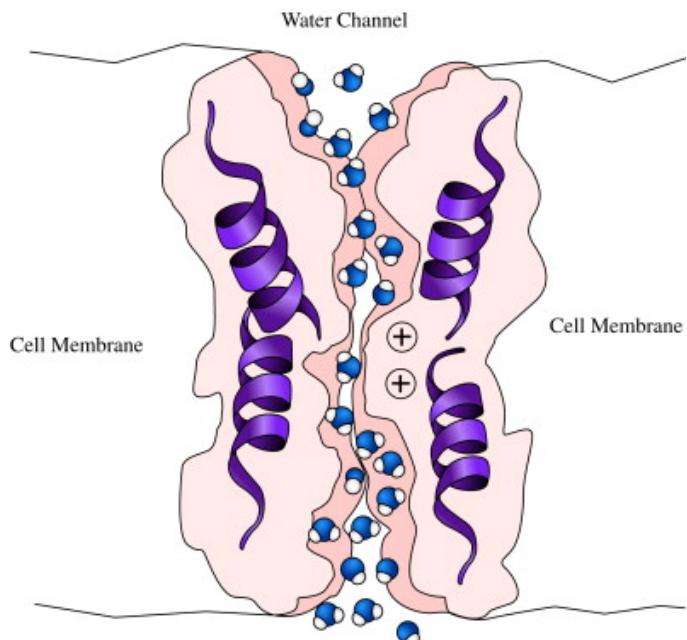


Figure 17: Diagram of an aquaporin. They contain two asparagine-proline-alanine (NPA) motifs, which are responsible for creating a positive charge to prevent ions from entering the aquaporin. (Source: William Stillwell)

- *Flippases*, *floppases*, and *scramblases* are transmembrane proteins responsible for moving around phospholipids to maintain *membrane asymmetry*. The inner and outer lipids of the bilayer are different in composition to preserve several key functions in a cell, such as preventing apoptosis.
 - **Flippases** use ATP to translocate amino phospholipids to the cytosolic side to prevent signals of apoptosis. One key amino phospholipid for apoptosis is *phosphatidylserine*, and when a cell is detected with too much of this on the outer plasma membrane, they are signaled for phagocytosis and apoptosis.
 - **Floppases** move cytosolic phospholipids to extracellular side and use ATP.
 - **Scramblases** move phospholipids down their concentration gradient, which does not use ATP. Their activity increases with an increase of cytosolic Ca^{2+} .

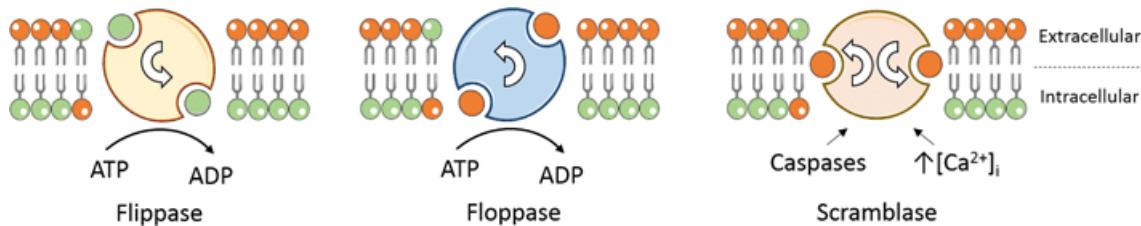


Figure 18: Diagram of flippase, floppase, and scramblase. (Source: Elvas et al. 2017)

7 Cell Communication

A cell needs to be able to interact with other cells and respond to changes in its environment. **Cell communication** is the process by which a cell detects and acts in response to these signals. Cell communication can be split into 3 steps:

1. **Signal Reception:** A molecule from outside the cell is detected when it attaches to a receptor of the cell. This molecule that binds to the receptor is called a **ligand**. The three main types of receptors that you will encounter are: *GPCRs*, *RTKs*, and *gated ion channels*.
2. **Signal Transduction:** The binding of the ligand changes the shape of the receptor protein, activating enzymes that bring the signal *into* the cell. It is important that signal transduction has a way to *amplify* the signal, so that the binding of a single ligand can produce a large effect in the cell. There are 2 main ways through which signal transduction occurs: *Phosphorylation cascades* and *Second messengers*.
3. **Cellular Response:** This is the activity that cell performs to respond to the signal.

7.1 G-Protein Coupled Receptors

The **G-Protein Coupled Receptor (GPCR)** is a transmembrane protein created by *7 alpha helices*. It works in conjunction with the **G protein**, which is a nearby protein that binds to GDP, which is very similar ADP except it uses guanine instead of adenine. When bound to GDP, the G protein is inactive. When bound to GTP, the G protein is active.

1. A ligand binds to the GPCR, changing its shape. This allows it to bind to a nearby inactive G protein and replace its GDP with a GTP, activating the G-protein.

The GPCR is an example of a **GEF (guanine exchange factor)** because it exchanges the GDP on the G protein for a GTP. GEF's turn on downstream signalling.

2. The now active G protein dissociates from the GPCR and can diffuse along the membrane to activate other nearby proteins (usually enzymes that initiate transduction).

The enzyme that the G protein acts on is an example of a **GAP (GTPase activating protein)**, because when the G protein binds to the enzyme, the enzyme also activates the GTPase on the G protein, which causes the next step.

3. The GTPase hydrolyzes the GTP on the G protein, turning it into a GDP and deactivating the G protein. The G protein then dissociates from the protein it was activating and the cycle can repeat.

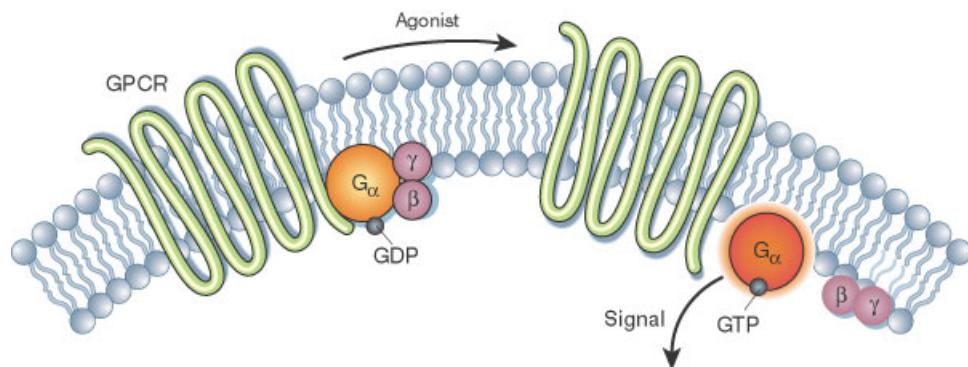


Figure 19: A diagram of the G-protein coupled receptor. Here you can see the 7 transmembrane domains of the GPCR. When an agonist binds to the GPCR, it activates the coupled G protein, leading to signal transduction. You can also see the three subunits of the G protein (α , β , γ) in this diagram. (Source: Nature Education)

GPCR is used for a wide range of pathways, including embryonic development, sensory reception, and for senses.

7.2 Receptor Tyrosine Kinases

Like GPCRs, **Receptor Tyrosine Kinases (RTKs)** are receptors embedded into the plasma membrane. RTK is a *protein kinase*, an enzyme responsible for transferring phosphate from ATP to activate another protein. The part of the RTK that sticks outside the membrane is the receptor, and the tail section that extrudes into the cytoplasm acts as the kinase. The tail is made up of numerous tyrosine amino acids.

1. While inactive, RTKs are seen as monomers. Once a ligand binds, two RTK monomers associate with each other to create a dimer. This process is called **dimerization**.
2. The active RTK dimer now adds a phosphate from ATP to each its tyrosine amino acids on its tail (3 on each monomer means $3 \times 2 = 6$ total). The RTK is now fully active.

3. Once active, proteins specific to the RTK recognize the activated RTK and bind to the phosphorylated tyrosine, which activates the protein. These activated proteins can then start a cellular response. Since an RTK has multiple tyrosines, they can activate multiple proteins at the same time!

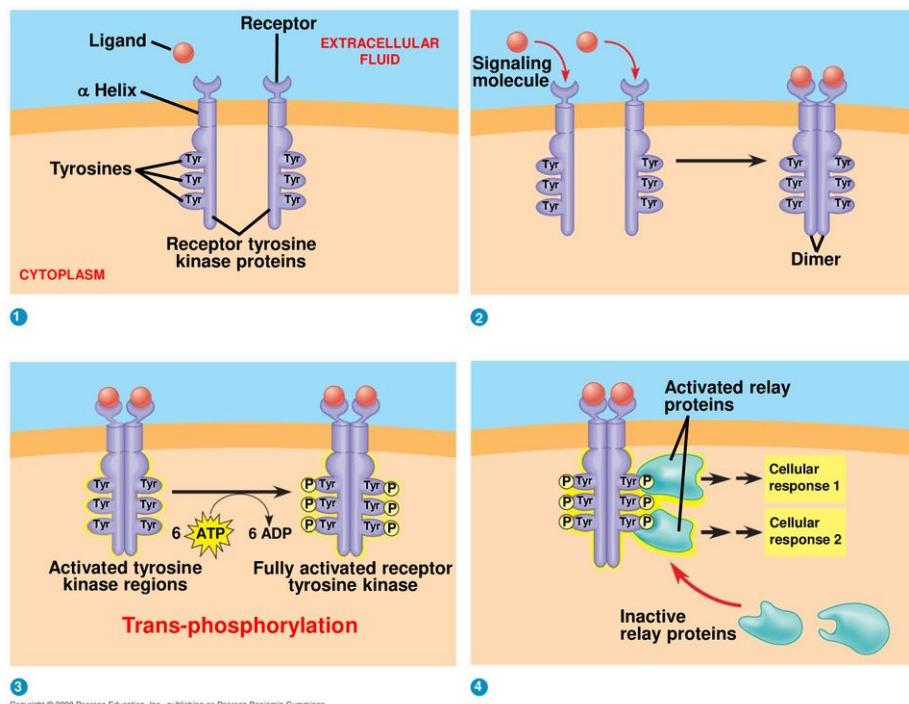


Figure 20: A diagram of the Receptor Tyrosine Kinases. (Source: Campbell)

RTKs are commonly used for cell growth and reproduction. When RTKs malfunction, they can cause cancer due to their important function in normal cell homeostasis.

7.3 Gated Ion Channels

A **Gated Ion Channel** is a receptor embedded into the membrane which acts as a valve, allowing certain ions to enter when open. When the channel opens, the sudden rush of ions can act as a *second messenger* and cause a cellular response.

1. At first, the gated ion channel is closed. There are numerous types of gated ion channels, each having their own way of opening up. The most common types of gated ion channels are *voltage gated* and *ligand gated*. Either a certain voltage, caused by a movement of ions across the membrane, or a ligand binding to the ion channel causes it to open.
2. Now open, specific ions can flow through the channel, which causes a sudden influx of ions to the inside region. This sudden change in concentration creates a signal.
3. The ligand that attached to the gated ion channel then dissociates or the voltage of the cell returns to its normal value, causing the channel to close again.

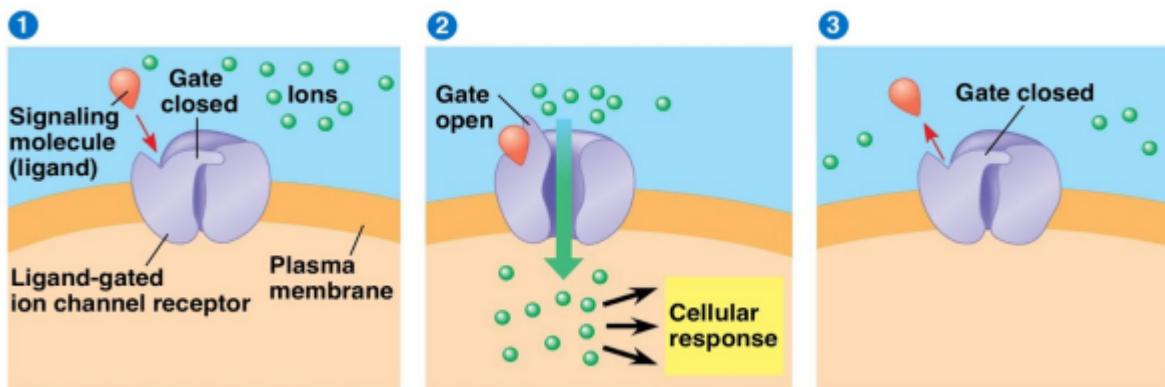


Figure 21: A diagram of the gated ion channel. This example depicts an ion channel controlled by a ligand, rather than voltage. (Source: Campbell)

Gated ion channels are commonly seen as voltage gated channels in neurons, allowing for the transfer of neurotransmitters and allowing for nerves to communicate.

7.4 Signal Transduction

Now that we have seen the different ways a signal can be received, how is that signal then transmitted into the cell? One method of action is a **phosphorylation cascade**, which is a chain of enzymes where each enzyme activates the next:

- **Protein kinases** add a phosphate to proteins, *activating* them.
- **Protein phosphatases** remove a phosphate from proteins, *de-activating* them.

Keep in mind that this is a general trend that is not always true, as phosphorylating certain proteins can actually de-activate them.

- **Scaffolding proteins** act as a scaffold, holding together multiple kinases. Since the kinases no longer have to float around the cytoplasm to find the next enzyme in the cascade, this greatly improves the efficiency of the signal transduction.

By having multiple steps in the cascade, the signal can quickly be amplified. For example, if each kinase can phosphorylate 10 enzymes, then after 6 steps in the cascade, a single ligand binding to a receptor can result in $10^3 = 1,000,000$ proteins being activated! In addition, multiple steps allows for multiple opportunities for *regulation*. This becomes extremely important as it allows cells to fine-tune their responses to certain signals.

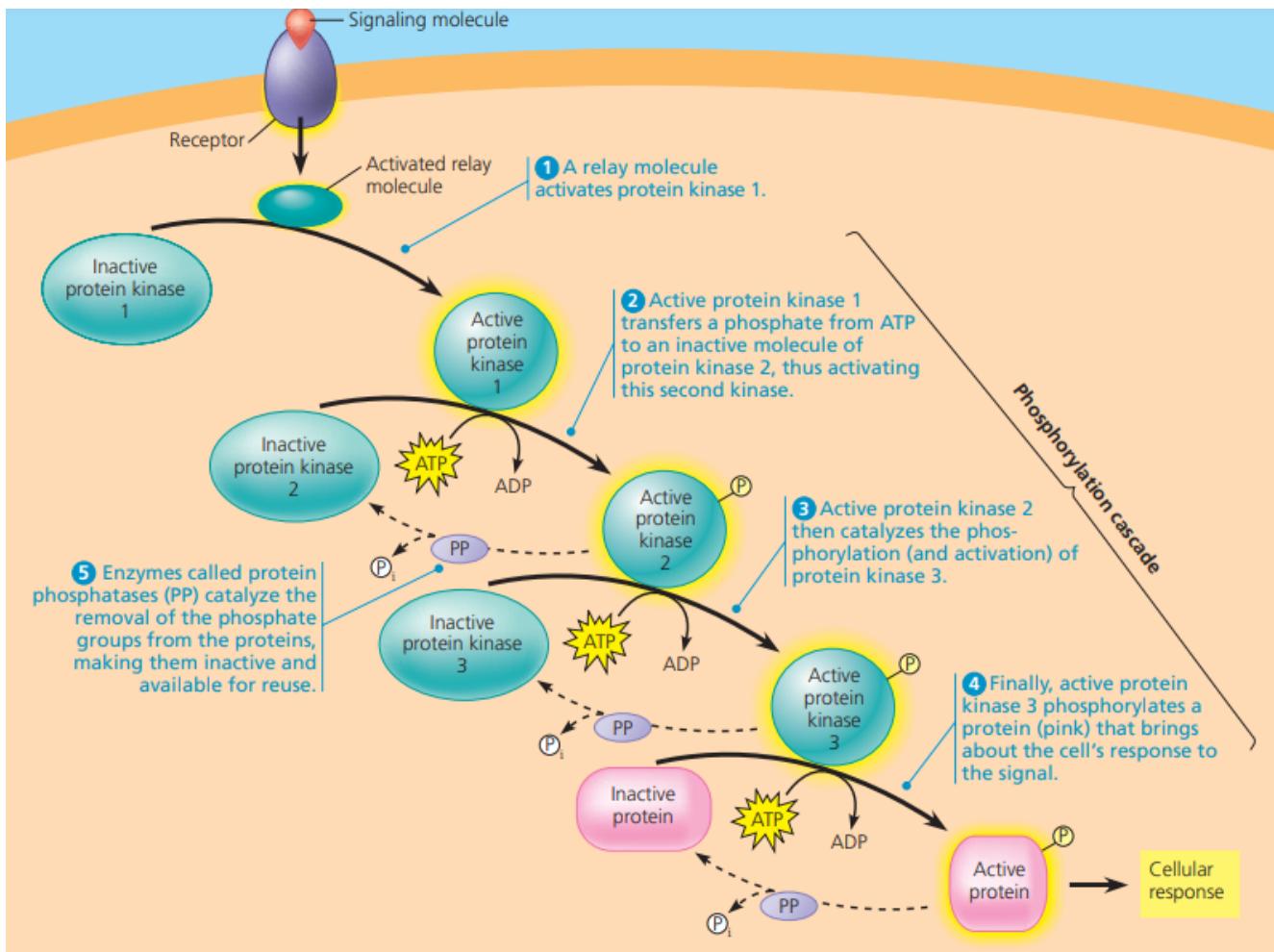


Figure 22: Diagram of a phosphorylation cascade. (Campbell's 9th Edition)

The other major form of signal transduction is through **second messengers**, which are molecules that typically have a low intracellular concentration. As a result, they can amplify a signal by diffusing throughout the cell. There are 3 pathways commonly observed:

- **cAMP:** Some GPCRs activate the enzyme **adenylyl cyclase**, which converts ATP to **cAMP (cyclic AMP)**, which acts as a second messenger. The most common example of this pathway is **epinephrine** binds to the GPCR → adenylyl cyclase is activated → cAMP is produced → **protein kinase a** is activated, which can lead to a phosphorylation cascade that eventually causes the cellular response.
- **Ca²⁺:** This pathway is more complicated. A GPCR activates the enzyme **phospholipase C**, which cleaves a membrane phospholipid called **PIP₂ (Phosphatidylinositol 4,5-bisphosphate)** into two molecules:
 - **DAG (diacylglycerol)**, which remains in the membrane, can act as a second messenger, activating the enzyme **protein kinase C**.
 - **IP₃ (Inositol 1,4,5-triphosphate)**, which acts as a second messenger. It diffuses across the cell, binding to a IP₃-gated calcium channel. This causes the channel to open, letting **Ca²⁺** into the cell, which diffuses everywhere and acts as a second messenger for various processes.

- In any gated ion channel, the ion being let in acts as a second messenger.

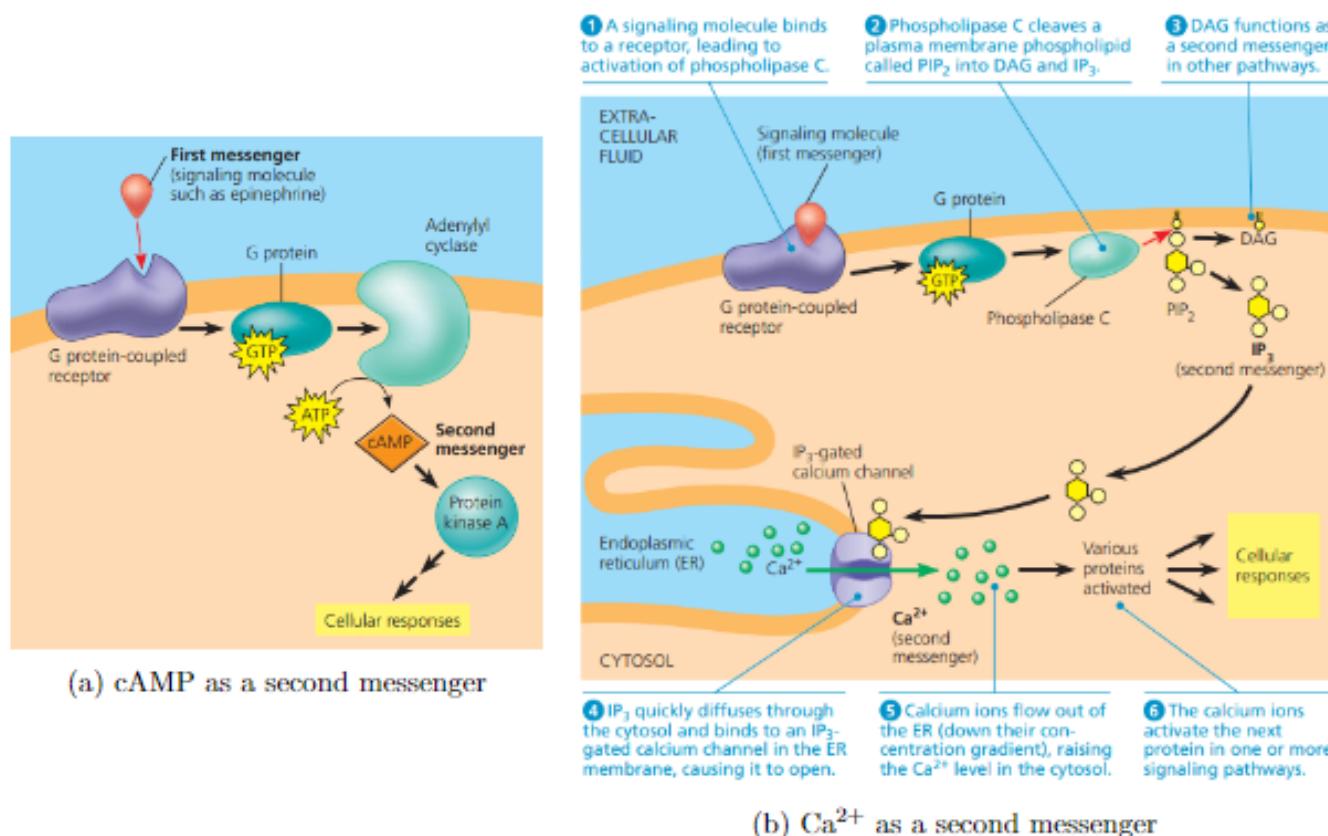


Figure 23: Diagrams of common second messenger pathways. (Source: Campbell's 9th Edition)

7.5 Intracellular Receptors

Some ligands bypass signal reception and transduction by diffusing across the cell membrane, directly initiating a cellular response themselves. Since they must be able to diffuse across the membrane, it is only seen in nonpolar molecules such as **Steroids**, **Thyroid hormones**, and **NO (nitric oxide)**

Example 7.1: (USABO Opens 2017)

20. One of your colleagues is attempting to isolate the receptor for testosterone. He decides to copy your protocol for isolating the receptor for epinephrine by radiolabeling the hormone, isolating the membrane fraction, and purifying radioactive protein complexes. Realizing that your colleague has probably not slept in days, you review the experimental procedure to ensure that it actually works. Which one of the following is a reason why your colleague's experiment would not work?
- Radiolabels on testosterone do not last very long.
 - Testosterone is a steroid hormone and diffuses across the cell membrane.
 - Testosterone binds only briefly to its receptor and then rapidly dissociates.
 - Radiolabeling the hormone would result in cell death.
 - None of the above.

Solution: Testosterone is a steroid hormone, which have intracellular receptors. Therefore, a method designed to detect a receptor on the cell membrane will not work as testosterone diffuses across the cell membrane. The **answer is B.**

8 Closing Statement

Although the topic of cell biology is so vast, this handout aims to cover the basic of cellular organelles. By the end of this handout, you should have learned that the cell is a complex unit that consists of numerous organelles that work with each other to perform many different functions.