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## Essentials of Cell Biology

What do an amoeba and an elephant have in common? If liver cells have the same DNA as brain cells, why are they different? What goes wrong during cancer? The answers to these questions depend on the properties of cells, the fundamental units of life. *Essentials of Cell Biology* introduces readers to the core concepts of cell biology. This course can provide an introduction to cell biology for beginning students of all ages or be a springboard to more specialized topics for advanced students. The course begins with a discussion of the fundamental properties of cells: the origin of the cell, how cells are organized, how they reproduce, and how they use energy. Other units in the course expand these topics and provide insight into the processes that regulate cell function and generate the amazing variety of cell types seen in living organisms. Topics include the decoding process that produces distinct sets of proteins in different cell types, the cellular structures responsible for cell function, the signals that cells use to communicate with one another, and the intricate controls on cell division. At the end of each unit in this eBook there is the option to test your knowledge with twenty multiple-choice questions.

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## Unit 1: What Is a Cell? What Are the Essential Characteristics of Cells?

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What are these living units called cells? Much like mini-fiefdoms, cells have all the equipment and expertise necessary to carry out the functions of life. A cell can eat, grow, and move. It can perform necessary maintenance, recycle parts, and dispose of wastes. It can adapt to changes in its environment; and it can even replicate itself.

Despite these similarities, all cells are not equal. Some are truly self-sustaining, as with single-celled bacteria or yeast, whereas others live communally, sometimes as part of complex multicellular organisms. Cells also differ in size. Although cells can be quite large — consider a frog's egg, for example — most are too small to see with the naked eye. Indeed, the development of light microscopy was essential to man's discovery of cells.

Don't be lulled by familiar schematic drawings of oval-shaped cells, either. Real cells are three-dimensional, of course, and they exist in a variety of intricate and remarkable shapes. For instance, a single human nerve cell can be over one meter long, extending from your backbone to your big toe. Compare that with the cells that line your small intestine, which have dozens of tiny, fingerlike projections to maximize the surface area across which nutrients can pass.

But how, exactly, do cells accomplish the complex tasks of life? What tools and materials do they need? And what are the key characteristics that define a cell? This unit answers these questions and provides a basic overview of the inner workings of the cell.

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## Unit 1: What Is a Cell? What Are the Essential Characteristics of Cells?

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## 1.1 Cells Are the Basic Units of Living Organisms

Trees in a forest, fish in a river, horseflies on a farm, lemurs in the jungle, reeds in a pond, worms in the soil — all these plants and animals are made of the building blocks we call **cells**. Like these examples, many living things consist of vast numbers of cells working in concert with one another. Other forms of life, however, are made of only a single cell, such as the many species of **bacteria** and **protozoa**. Cells, whether living on their own or as part of a multicellular organism, are usually too small to be seen without a light microscope.

Cells share many common features, yet they can look wildly different. In fact, cells have adapted over billions of years to a wide array of environments and functional roles. Nerve cells, for example, have long, thin extensions that can reach for meters and serve to transmit signals rapidly. Closely fitting, brick-shaped plant cells have a rigid outer layer that helps provide the structural support that trees and other plants require. Long, tapered muscle cells have an intrinsic stretchiness that allows them to change length within contracting and relaxing biceps.

Still, as different as these cells are, they all rely on the same basic strategies to keep the outside out, allow necessary substances in and permit others to leave, maintain their health, and replicate themselves. In fact, these traits are precisely what make a cell a cell.

### What Defines a Cell?

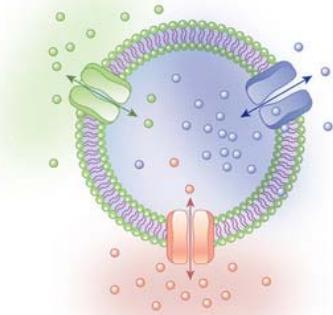
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Figure 1: Transport proteins in the cell membrane

A plasma membrane is permeable to specific molecules that a cell needs.

Transport proteins in the cell membrane allow for selective passage of specific molecules from the external environment. Each transport protein is specific to a certain molecule (indicated by matching colors).

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Cells are considered the basic units of life in part because they come in discrete and easily recognizable packages. That's because all cells are surrounded by a structure called the **cell membrane** — which, much like the walls of a house, serves as a clear boundary between the cell's internal and external environments. The cell membrane is sometimes also referred to as the **plasma membrane**.

Cell membranes are based on a framework of fat-based molecules called **phospholipids**, which physically prevent water-loving, or hydrophilic, substances from entering or escaping the cell. These membranes are also studded with proteins that serve various functions. Some of these proteins act as gatekeepers, determining what substances can and cannot cross the membrane. Others function as markers, identifying the cell as part of the same organism or as foreign. Still others work like fasteners, binding cells together so they can function as a unit. Yet other membrane proteins serve as communicators, sending and receiving signals from neighboring cells and the environment — whether friendly or alarming (Figure 1).

Within this membrane, a cell's interior environment is water based. Called **cytoplasm**, this liquid environment is packed full of cellular machinery and structural elements. In fact, the concentrations of proteins inside a cell far outnumber those on the outside — whether the outside is ocean water (as in the case of a single-celled alga) or blood serum (as in the case of a red blood cell). Although cell membranes form natural barriers in watery environments, a cell must nonetheless expend quite a

bit of energy to maintain the high concentrations of intracellular constituents necessary for its survival. Indeed, cells may use as much as 30 percent of their energy just to maintain the composition of their cytoplasm.

### What Other Components Do Cells Have?

As previously mentioned, a cell's cytoplasm is home to numerous functional and structural elements. These elements exist in the form of molecules and organelles — picture them as the tools, appliances, and inner rooms of the cell. Major classes of intracellular organic molecules include nucleic acids, proteins, carbohydrates, and lipids, all of which are essential to the cell's functions.

**Nucleic acids** are the molecules that contain and help express a cell's genetic code. There are two major classes of nucleic acids: **deoxyribonucleic acid (DNA)** and **ribonucleic acid (RNA)**. DNA is the molecule that contains all of the information required to build and maintain the cell; RNA has several roles associated with expression of the information stored in DNA. Of course, nucleic acids alone aren't responsible for the preservation and expression of genetic material: Cells also use proteins to help replicate the genome and accomplish the profound structural changes that underlie **cell division**.

**Proteins** are a second type of intracellular organic molecule. These substances are made from chains of smaller molecules called **amino acids**, and they serve a variety of functions in the cell, both **catalytic** and structural. For example, proteins called **enzymes** convert cellular molecules (whether proteins, carbohydrates, lipids, or nucleic acids) into other forms that might help a cell meet its energy needs, build support structures, or pump out wastes.

**Carbohydrates**, the starches and sugars in cells, are another important type of organic molecule. **Simple carbohydrates** are used for the cell's immediate energy demands, whereas **complex carbohydrates** serve as intracellular energy stores.

Complex carbohydrates are also found on a cell's surface, where they play a crucial role in cell recognition.

Finally, **lipids** or fat molecules are components of cell membranes — both the plasma membrane and various intracellular membranes. They are also involved in energy storage, as well as relaying signals within cells and from the bloodstream to a cell's interior (Figure 2).

Some cells also feature orderly arrangements of molecules called **organelles**. Similar to the rooms in a house, these structures are partitioned off from the rest of a cell's interior by their own intracellular membrane. Organelles contain highly technical equipment required for specific jobs within the cell. One example is the **mitochondrion** — commonly known as the cell's "power plant" — which is the organelle that holds and maintains the machinery involved in energy-producing chemical reactions (Figure 3).

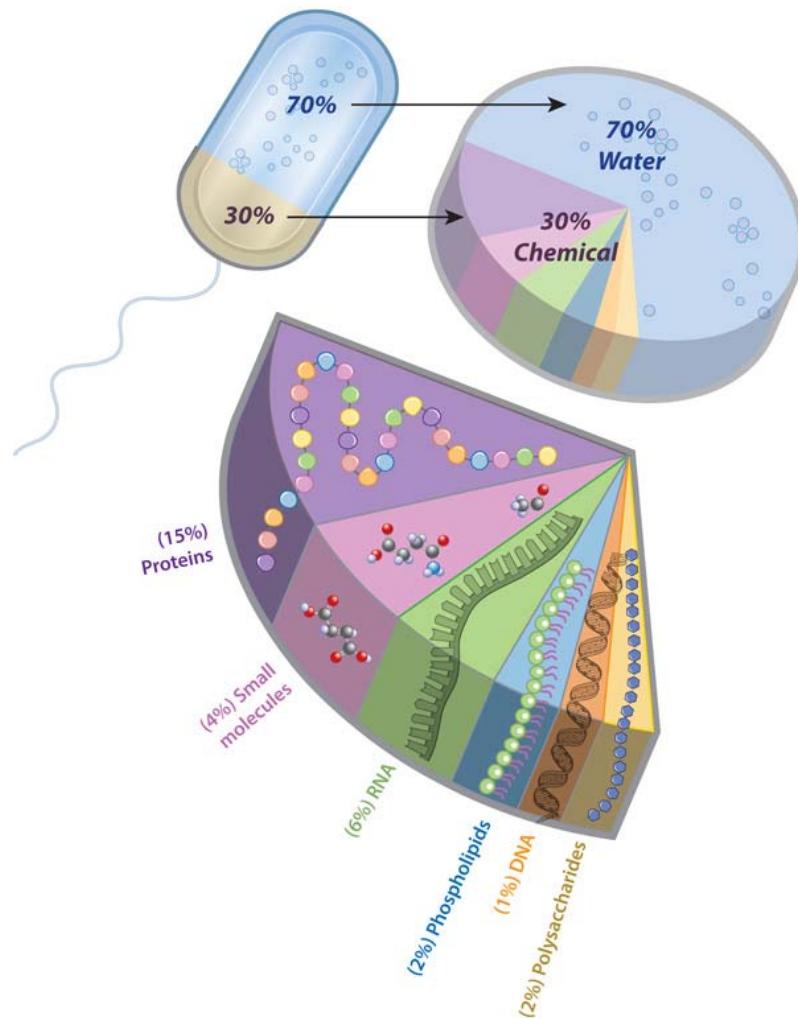


Figure 2: The composition of a bacterial cell

Most of a cell is water (70%). The remaining 30% contains varying proportions of structural and functional molecules.

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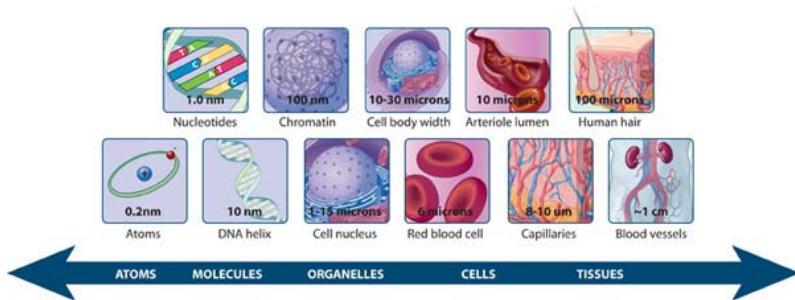


Figure 3: The relative scale of biological molecules and structures

Cells can vary between 1 micrometer ( $\mu\text{m}$ ) and hundreds of micrometers in diameter. Within a cell, a DNA double helix is approximately 10 nanometers (nm) wide, whereas the cellular organelle called a nucleus that encloses this DNA can be approximately 1000 times bigger (about 10  $\mu\text{m}$ ). See how cells compare along a relative scale axis with other molecules, tissues, and biological structures (blue arrow at bottom). Note that a micrometer ( $\mu\text{m}$ ) is also known as a micron.

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## What Are the Different Categories of Cells?

Rather than grouping cells by their size or shape, scientists typically categorize them by how their genetic material is packaged. If the DNA within a cell is not separated from the cytoplasm, then that cell is a **prokaryote**. All known prokaryotes, such as bacteria and **archaea**, are single cells. In contrast, if the DNA is partitioned off in its own membrane-bound room called the **nucleus**, then that cell is a **eukaryote**. Some eukaryotes, like amoebae, are free-living, single-celled entities. Other eukaryotic cells are part of multicellular organisms. For instance, all plants and animals are made of eukaryotic cells — sometimes even trillions of them (Figure 4).

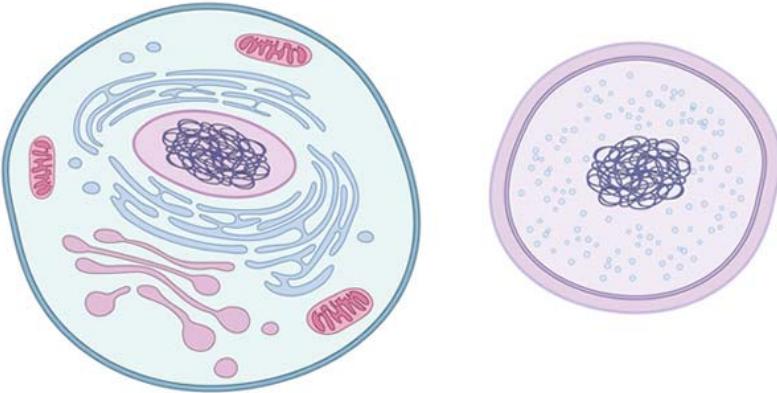


Figure 4: Comparing basic eukaryotic and prokaryotic differences

A eukaryotic cell (left) has membrane-enclosed DNA, which forms a structure called the nucleus (located at center of the eukaryotic cell; note the purple DNA enclosed in the pink nucleus). A typical eukaryotic cell also has additional membrane-bound organelles of varying shapes and sizes. In contrast, a prokaryotic cell (right) does not have membrane-bound DNA and also lacks other membrane-bound organelles as well.

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## How Did Cells Originate?

Researchers hypothesize that all organisms on Earth today originated from a single cell that existed some 3.5 to 3.8 billion years ago. This original cell was likely little more than a sac of small organic molecules and RNA-like material that had both informational and catalytic functions. Over time, the more stable DNA molecule **evolved** to take over the information storage function, whereas **proteins**, with a greater variety of structures than nucleic acids, took over the catalytic functions.

As described in the previous section, the absence or presence of a nucleus — and indeed, of all membrane-bound organelles — is important enough to be a defining feature by which cells are categorized as either prokaryotes or eukaryotes. Scientists believe that the appearance of self-contained nuclei and other organelles represents a major advance in the evolution of cells. But where did these structures come from? More than one billion years ago, some cells "ate" by engulfing objects that floated in the liquid environment in which they existed. Then, according to some theories of cellular **evolution**, one of the early eukaryotic cells engulfed a prokaryote, and together the two cells formed a **symbiotic** relationship. In particular, the engulfed cell began to function as an organelle within the larger eukaryotic cell that consumed it. Both chloroplasts and mitochondria, which exist in modern eukaryotic cells and still retain their own genomes, are thought to have arisen in this manner (Figure 5).

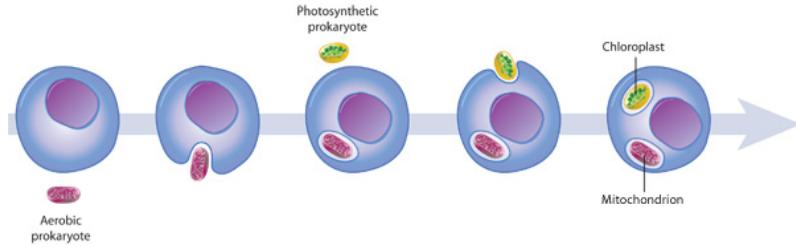


Figure 5: The origin of mitochondria and chloroplasts

Mitochondria and chloroplasts likely evolved from engulfed prokaryotes that once lived as independent organisms. At some point, a eukaryotic cell engulfed an aerobic prokaryote, which then formed an endosymbiotic relationship with the host eukaryote, gradually developing into a mitochondrion. Eukaryotic cells containing mitochondria then engulfed photosynthetic prokaryotes, which evolved to become specialized chloroplast organelles.

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Of course, prokaryotic cells have continued to evolve as well. Different species of bacteria and archaea have adapted to specific environments, and these prokaryotes not only survive but thrive without having their genetic material in its own compartment. For example, certain bacterial species that live in thermal vents along the ocean floor can withstand higher temperatures than any other organisms on Earth.

## Conclusion

Cells are the smallest common denominator of life. Some cells are organisms unto themselves; others are part of multicellular organisms. All cells are made from the same major classes of organic molecules: nucleic acids, proteins, carbohydrates, and lipids. In addition, cells can be placed in two major categories as a result of ancient evolutionary events: prokaryotes, with their cytoplasmic genomes, and eukaryotes, with their nuclear-encased genomes and other membrane-bound organelles.

Though they are small, cells have evolved into a vast variety of shapes and sizes. Together they form tissues that themselves form organs, and eventually entire organisms.

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## 1.2 Eukaryotic Cells Possess a Nucleus and Membrane-Bound Organelles

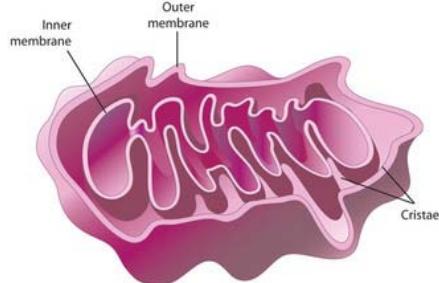
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Figure 1: A mitochondrion

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How do cells accomplish all their functions in such a tiny, crowded package? Eukaryotic cells — those that make up cattails and apple trees, mushrooms and dust mites, halibut and readers of Scitable — have evolved ways to partition off different functions to various locations in the cell. In fact, specialized compartments called organelles exist within eukaryotic cells for this purpose. Different organelles play different roles in the cell — for instance, mitochondria generate energy from food molecules; lysosomes break down and recycle organelles and **macromolecules**; and the endoplasmic reticulum helps build membranes and transport proteins throughout the cell. But what characteristics do all organelles have in common? And why was the development of three particular organelles — the nucleus, the **mitochondrion**, and the **chloroplast** — so essential to the evolution of present-day eukaryotes (Figure 1, Figure 2)?

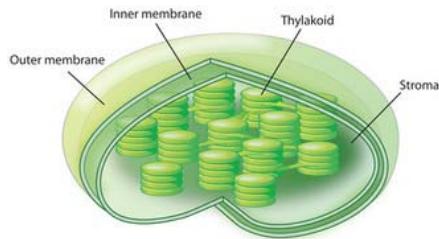


Figure 2: A chloroplast

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**What Defines an Organelle?**

In addition to the nucleus, eukaryotic cells may contain several other types of organelles, which may include mitochondria, chloroplasts, the endoplasmic reticulum, the Golgi apparatus, and lysosomes. Each of these organelles performs a specific function critical to the cell's survival. Moreover, nearly all eukaryotic organelles are separated from the rest of the cellular space by a membrane, in much the same way that interior walls separate the rooms in a house. The membranes that surround eukaryotic organelles are based on lipid bilayers that are similar (but not identical) to the cell's outer membrane. Together, the total area of a cell's internal membranes far exceeds that of its plasma membrane.

Like the plasma membrane, organelle membranes function to keep the inside "in" and the outside "out." This partitioning permits different kinds of biochemical reactions to take place in different organelles. Although each organelle performs a specific function in the cell, all of the cell's organelles work together in an integrated fashion to meet the overall needs of the cell. For example, biochemical reactions in a cell's mitochondria transfer energy from fatty acids and pyruvate molecules into an energy-rich molecule called **adenosine triphosphate** (ATP). Subsequently, the rest of the cell's organelles use this ATP as the source of the energy they need to operate.

Because most organelles are surrounded by membranes, they are easy to visualize — with magnification. For instance, researchers can use high resolution **electron microscopy** to take a snapshot through a thin cross-section or slice of a cell. In this way, they can see the structural detail and key characteristics of different organelles — such as the long, thin

compartments of the endoplasmic reticulum or the compacted chromatin within the nucleus. An electron micrograph therefore provides an excellent blueprint of a cell's inner structures. Other less powerful microscopy techniques coupled with organelle-specific stains have helped researchers see organelle structure more clearly, as well as the distribution of various organelles within cells. However, unlike the rooms in a house, a cell's organelles are not static. Rather, these structures are in constant motion, sometimes moving to a particular place within the cell, sometimes merging with other organelles, and sometimes growing larger or smaller. These dynamic changes in cellular structures can be observed with video microscopic techniques, which provide lower-resolution movies of whole organelles as these structures move within cells.

### Why Is the Nucleus So Important?

Of all eukaryotic organelles, the nucleus is perhaps the most critical. In fact, the mere presence of a nucleus is considered one of the defining features of a eukaryotic cell. This structure is so important because it is the site at which the cell's DNA is housed and the process of interpreting it begins.

Recall that DNA contains the information required to build cellular proteins. In eukaryotic cells, the membrane that surrounds the nucleus — commonly called the **nuclear envelope** — partitions this DNA from the cell's protein synthesis machinery, which is located in the cytoplasm. Tiny pores in the nuclear envelope, called **nuclear pores**, then selectively permit certain macromolecules to enter and leave the nucleus — including the RNA molecules that carry information from a cellular DNA to protein manufacturing centers in the cytoplasm. This separation of the DNA from the protein synthesis machinery provides eukaryotic cells with more intricate regulatory control over the production of proteins and their RNA intermediates.

In contrast, the DNA of prokaryotic cells is distributed loosely around the cytoplasm, along with the protein synthesis machinery. This closeness allows prokaryotic cells to rapidly respond to environmental change by quickly altering the types and amount of proteins they manufacture. Note that eukaryotic cells likely evolved from a symbiotic relationship between two prokaryotic cells, whereby one set of prokaryotic DNA eventually became separated by a nuclear envelope and formed a nucleus. Over time, portions of the DNA from the other prokaryote remaining in the cytoplasmic part of the cell may or may not have been incorporated into the new eukaryotic nucleus (Figure 3).



Figure 3: Origin of a eukaryotic cell

A prokaryotic host cell incorporates another prokaryotic cell. Each prokaryote has its own set of DNA molecules (a genome). The genome of the incorporated cell remains separate (curved blue line) from the host cell genome (curved purple line). The incorporated cell may continue to replicate as it exists within the host cell. Over time, during errors of replication or perhaps when the incorporated cell lyses and loses its membrane separation from the host, genetic material becomes separated from the incorporated cell and merges with the host cell genome. Eventually, the host genome becomes a mixture of both genomes, and it ultimately becomes enclosed in an endomembrane, a membrane within the cell that creates a separate compartment. This compartment eventually evolves into a nucleus.

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### Why Are Mitochondria and Chloroplasts Special?

Besides the nucleus, two other organelles — the mitochondrion and the chloroplast — play an especially important role in eukaryotic cells. These specialized structures are enclosed by double membranes, and they are believed to have originated back when all living things on Earth were single-celled organisms. At that time, some larger eukaryotic cells with flexible membranes "ate" by engulfing molecules and smaller cells — and scientists believe that mitochondria and chloroplasts arose as a result of this process. In particular, researchers think that some of these "eater" eukaryotes engulfed smaller prokaryotes, and a symbiotic relationship subsequently developed. Once kidnapped, the "eaten" prokaryotes continued to generate energy and carry out other necessary cellular functions, and the host eukaryotes came to rely on the contribution of the "eaten" cells. Over many generations, the descendants of the eukaryotes developed mechanisms to further support this system, and concurrently, the descendants of the engulfed prokaryotes lost the ability to survive on their own, evolving into present-day mitochondria and chloroplasts. This proposed origin of mitochondria and chloroplasts is known as the **endosymbiotic hypothesis**.

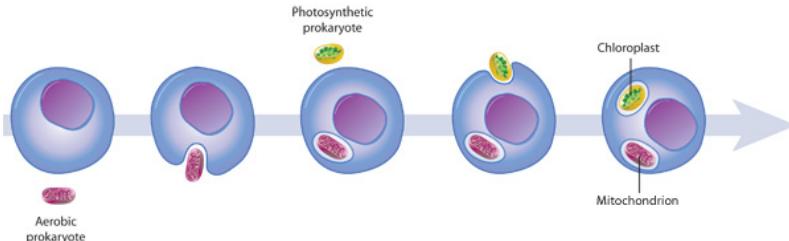


Figure 4: The origin of mitochondria and chloroplasts

Mitochondria and chloroplasts likely evolved from engulfed bacteria that once lived as independent organisms. At some point, a eukaryotic cell engulfed an aerobic bacterium, which then formed an endosymbiotic relationship with the host eukaryote, gradually developing into a mitochondrion. Eukaryotic cells containing mitochondria then engulfed photosynthetic bacteria, which evolved to become specialized chloroplast organelles.

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In addition to double membranes, mitochondria and chloroplasts also retain small genomes with some resemblance to those found in modern prokaryotes. This finding provides yet additional evidence that these organelles probably originated as self-sufficient single-celled organisms.

Today, mitochondria are found in fungi, plants, and animals, and they use oxygen to produce energy in the form of ATP molecules, which cells then employ to drive many processes. Scientists believe that mitochondria evolved from **aerobic**, or

oxygen-consuming, prokaryotes. In comparison, chloroplasts are found in plant cells and some algae, and they convert solar energy into energy-storing sugars such as glucose. Chloroplasts also produce oxygen, which makes them necessary for all life as we know it. Scientists think chloroplasts evolved from **photosynthetic** prokaryotes similar to modern-day **cyanobacteria** (Figure 4). Today, we classify prokaryotes and eukaryotes based on differences in their cellular contents (Figure 5).

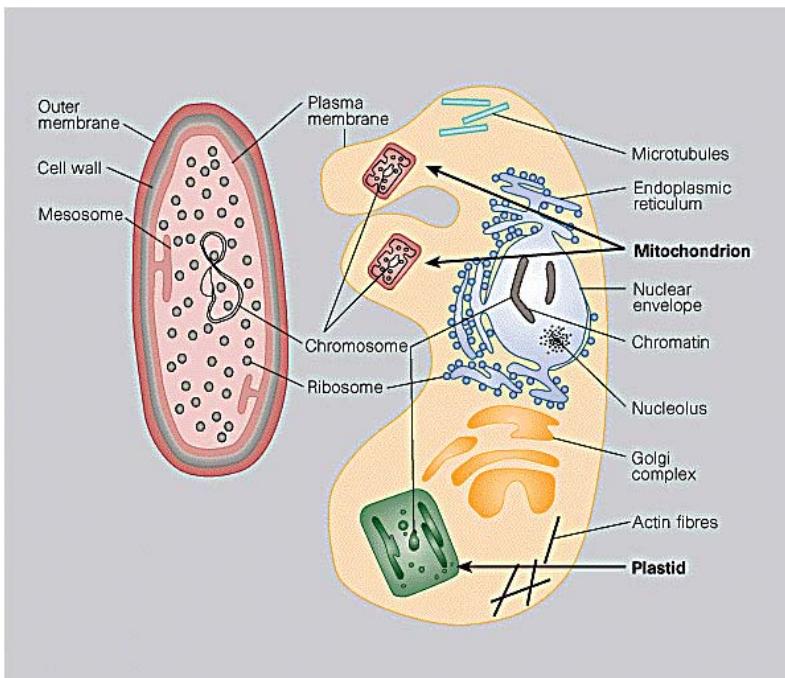


Figure 5: Typical prokaryotic (left) and eukaryotic (right) cells

In prokaryotes, the DNA (chromosome) is in contact with the cellular cytoplasm and is not in a housed membrane-bound nucleus. In eukaryotes, however, the DNA takes the form of compact chromosomes separated from the rest of the cell by a nuclear membrane (also called a nuclear envelope). Eukaryotic cells also contain a variety of structures and organelles not present in prokaryotic cells.

Throughout the course of evolution, organelles such as mitochondria and chloroplasts (a form of plastid) may have arisen from engulfed prokaryotes.

© 1998 Nature Publishing Group Doolittle, W. F. A paradigm gets shifty. *Nature* 392, 15-16 (1998) doi:10.1038/32033. All rights reserved.

## How Do Eukaryotic Cells Handle Energy?

Mitochondria — often called the powerhouses of the cell — enable eukaryotes to make more efficient use of food sources than their prokaryotic counterparts. That's because these organelles greatly expand the amount of membrane used for energy-generating electron transport chains. In addition, mitochondria use a process called **oxidative metabolism** to convert food into energy, and oxidative metabolism yields more energy per food molecule than non-oxygen-using, or **anaerobic**, methods. Energywise, cells with mitochondria can therefore afford to be bigger than cells without mitochondria.

Within eukaryotic cells, mitochondria function somewhat like batteries, because they convert energy from one form to another: food nutrients to ATP. Accordingly, cells with high metabolic needs can meet their higher energy demands by increasing the number of mitochondria they contain. For example, muscle cells in people who exercise regularly possess more mitochondria than muscle cells in sedentary people.

Prokaryotes, on the other hand, don't have mitochondria for energy production, so they must rely on their immediate environment to obtain usable energy. Prokaryotes generally use electron transport chains in their plasma membranes to provide much of their energy. The actual energy donors and acceptors for these electron transport chains are quite variable, reflecting the diverse range of habitats where prokaryotes live. (In aerobic prokaryotes, electrons are transferred to oxygen, much as in the mitochondria.) The challenges associated with energy generation limit the size of prokaryotes. As these cells grow larger in volume, their energy needs increase proportionally. However, as they increase in size, their surface area — and thus their ability to both take in nutrients and transport electrons — does not increase to the same degree as their volume. As a result, prokaryotic cells tend to be small so that they can effectively manage the balancing act between energy supply and demand (Figure 6).

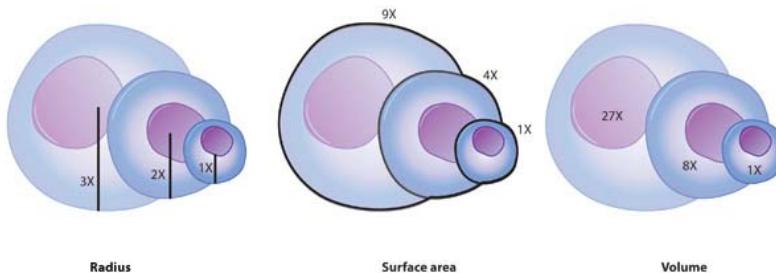


Figure 6: The relationship between the radius, surface area, and volume of a cell

Note that as the radius of a cell increases from 1x to 3x (left), the surface area increases from 1x to 9x, and the volume increases from 1x to 27x.

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## Conclusion

Organelles serve specific functions within eukaryotes, such as energy production, photosynthesis, and membrane construction. Most are membrane-bound structures that are the sites of specific types of biochemical reactions. The nucleus is particularly important among eukaryotic organelles because it is the location of a cell's DNA. Two other critical organelles are mitochondria and chloroplasts, which play important roles in energy conversion and are thought to have their evolutionary origins as simple single-celled organisms.

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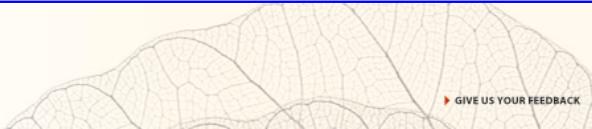
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### 1.3 Cell Function Depends on the Continual Uptake and Conversion of Energy

Cells manage a wide range of functions in their tiny package — growing, moving, housekeeping, and so on — and most of those functions require energy. But how do cells get this energy in the first place? And how do they use it in the most efficient manner possible?

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#### Where Do Cells Obtain Their Energy?

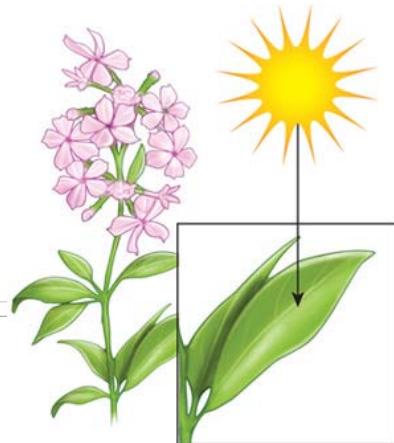


Figure 1: For photosynthetic cells, the main energy source is the Sun.

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Cells, like humans, cannot generate energy without locating a source in their environment. However, whereas humans search for substances like fossil fuels to power their homes and businesses, cells seek their energy in the form of food molecules or sunlight. In fact, the Sun is the ultimate source of energy for almost all cells, because photosynthetic prokaryotes, algae, and plant cells harness solar energy and use it to make the complex organic food molecules that other cells rely on for the energy required to sustain growth, metabolism, and reproduction (Figure 1).

Cellular nutrients come in many forms, including sugars and fats. In order to provide a cell with energy, these molecules have to pass across the cell membrane, which functions as a barrier — but not an impassable one. Like the exterior walls of a house, the plasma membrane is semi-permeable. In much the same way that doors and windows allow necessities to enter the house, various proteins that span the cell membrane permit specific molecules into the cell, although they may require some energy input to accomplish this task (Figure 2).

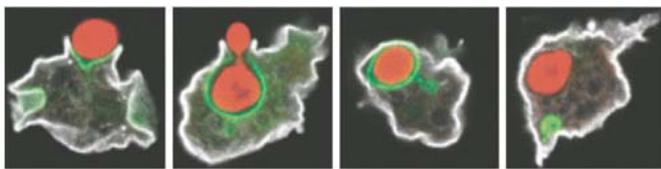


Figure 2: Cells can incorporate nutrients by phagocytosis.

This amoeba, a single-celled organism, acquires energy by engulfing nutrients in the form of a yeast cell (red). Through a process called phagocytosis, the amoeba encloses the yeast cell with its membrane and draws it inside. Specialized plasma membrane proteins in the amoeba (in green) are involved in this act of phagocytosis, and they are later recycled back into the amoeba after the nutrients are engulfed.

© 2008 Nature Publishing Group Swanson, J. A. Shaping cups into phagosomes and macropinosomes.

*Nature Reviews Molecular Cell Biology* 9, 639-649 (2008) doi:10.1038/nrm2447. All rights reserved.

#### How Do Cells Turn Nutrients into Usable Energy?

Complex organic food molecules such as sugars, fats, and proteins are rich sources of energy for cells because much of the energy used to form these molecules is literally stored within the chemical bonds that hold them together. Scientists can measure the amount of energy stored in foods using a device called a **bomb calorimeter**. With this technique, food is placed inside the calorimeter and heated until it burns. The excess heat released by the reaction is directly proportional to the amount of energy contained in the food.

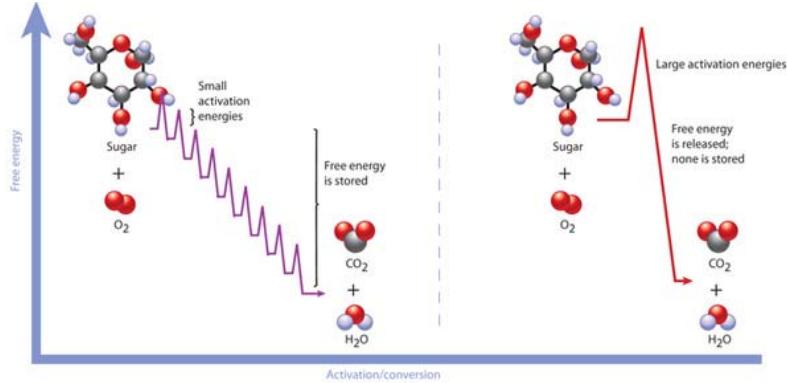


Figure 3: The release of energy from sugar  
Compare the stepwise oxidation (left) with the direct burning (right) of sugar. On the left, through a series of small steps, free energy is released from the sugar and stored in carrier molecules in the cell (ATP and NADH, not shown). On the right, the direct burning of sugar requires a larger activation energy. In this reaction, the same total free energy is released as in stepwise oxidation, but none is stored in carrier molecules, so most of it will be lost as heat (free energy). This direct burning is therefore very inefficient, because it does not harness energy for later use.

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In reality, of course, cells don't work quite like calorimeters. Rather than burning all their energy in one large reaction, cells release the energy stored in their food molecules through a series of oxidation reactions. **Oxidation** describes a type of chemical reaction in which electrons are transferred from one molecule to another, changing the composition and energy content of both the donor and acceptor molecules. Food molecules act as electron donors. During each oxidation reaction involved in food breakdown, the product of the reaction has a lower energy content than the donor molecule that preceded it in the pathway. At the same time, electron acceptor molecules capture some of the energy lost from the food molecule during each oxidation reaction and store it for later use. Eventually, when the carbon atoms from a complex organic food molecule are fully oxidized at the end of the reaction chain, they are released as waste in the form of carbon dioxide (Figure 3). Cells do not use the energy from oxidation reactions as soon as it is released. Instead, they convert it into small, energy-rich molecules such as ATP and **nicotinamide adenine dinucleotide (NADH)**, which can be used throughout the cell to power metabolism and construct new cellular components. In addition, workhorse proteins called enzymes use this chemical energy to catalyze, or accelerate, chemical reactions within the cell that would otherwise proceed very slowly. Enzymes do not force a reaction to proceed if it wouldn't do so without the catalyst; rather, they simply lower the energy barrier required for the reaction to begin (Figure 4).

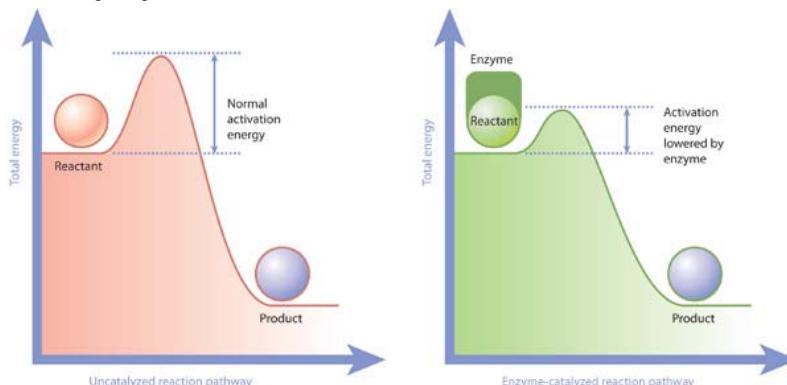


Figure 4: Enzymes allow activation energies to be lowered.  
Enzymes lower the activation energy necessary to transform a reactant into a product. On the left is a reaction that is not catalyzed by an enzyme (red), and on the right is one that is (green). In the enzyme-catalyzed reaction, an enzyme will bind to a reactant and facilitate its transformation into a product. Consequently, an enzyme-catalyzed reaction pathway has a smaller energy barrier (activation energy) to overcome before the reaction can proceed.

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## What Specific Pathways Do Cells Use?

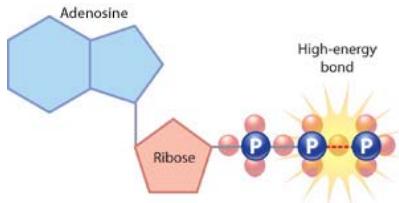


Figure 5: An ATP molecule

ATP consists of an adenosine base (blue), a ribose sugar (pink) and a phosphate chain. The high-energy phosphate bond in this phosphate chain is the key to ATP's energy storage potential.

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The particular energy pathway that a cell employs depends in large part on whether that cell is a eukaryote or a prokaryote. Eukaryotic cells use three major processes to transform the energy held in the chemical bonds of food molecules into more readily usable forms — often energy-rich carrier molecules. Adenosine 5'-triphosphate, or ATP, is the most abundant energy carrier molecule in cells. This molecule is made of a nitrogen base (adenine), a ribose sugar, and three phosphate groups. The word adenosine refers to the adenine plus the ribose sugar. The bond between the second and third phosphates is a high-energy bond (Figure 5).

The first process in the eukaryotic energy pathway is **glycolysis**, which literally means "sugar splitting." During glycolysis, single molecules of **glucose** are split and ultimately converted into two molecules of a substance called **pyruvate**; because each glucose contains six carbon atoms, each resulting pyruvate contains just three carbons. Glycolysis is actually a series of ten chemical reactions that requires the input of two ATP molecules. This input is used to generate four new ATP molecules, which means that glycolysis results in a net gain of two ATPs. Two NADH molecules are also produced; these molecules serve as electron carriers for other biochemical reactions in the cell.

Glycolysis is an ancient, major ATP-producing pathway that occurs in almost all cells, eukaryotes and prokaryotes alike. This process, which is also known as **fermentation**, takes place in the cytoplasm and does not require oxygen. However, the fate of the pyruvate produced during glycolysis depends upon whether oxygen is present. In the absence of oxygen, the pyruvate cannot be completely oxidized to carbon dioxide, so various intermediate products result. For example, when oxygen levels are low, skeletal muscle cells rely on glycolysis to meet their intense energy requirements. This reliance on glycolysis results in the buildup of an intermediate known as lactic acid, which can cause a person's muscles to feel as if they are "on fire." Similarly, yeast, which is a single-celled eukaryote, produces alcohol (instead of carbon dioxide) in oxygen-deficient settings. In contrast, when oxygen is available, the pyruvates produced by glycolysis become the input for the next portion of the eukaryotic energy pathway. During this stage, each pyruvate molecule in the cytoplasm enters the mitochondrion, where it is converted into **acetyl CoA**, a two-carbon energy carrier, and its third carbon combines with oxygen and is released as carbon dioxide. At the same time, an NADH carrier is also generated. Acetyl CoA then enters a pathway called the **citric acid cycle**, which is the second major energy process used by cells. The eight-step citric acid cycle generates three more NADH molecules and two other carrier molecules: FADH<sub>2</sub> and GTP (Figure 6, middle).

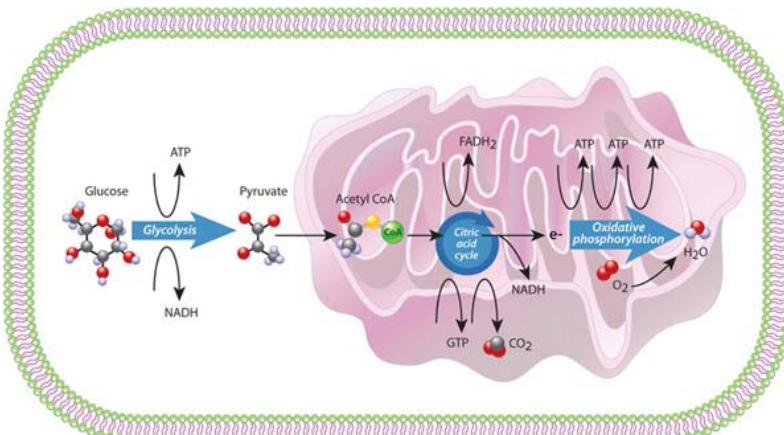


Figure 6: Metabolism in a eukaryotic cell: Glycolysis, the citric acid cycle, and oxidative phosphorylation  
Glycolysis takes place in the cytoplasm. Within the mitochondrion, the citric acid cycle occurs in the mitochondrial matrix, and oxidative metabolism occurs at the internal folded mitochondrial membranes (cristae).

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The third major process in the eukaryotic energy pathway involves an **electron transport chain**, catalyzed by several protein complexes located in the mitochondrial inner membrane. This process, called **oxidative phosphorylation**, transfers electrons from NADH and FADH<sub>2</sub> through the membrane protein complexes, and ultimately to oxygen, where they combine to form water. As electrons travel through the protein complexes in the chain, a gradient of hydrogen ions, or protons, forms across the mitochondrial membrane. Cells harness the energy of this proton gradient to create three additional ATP molecules for every electron that travels along the chain. Overall, the combination of the citric acid cycle and oxidative phosphorylation yields much more energy than fermentation - 15 times as much energy per glucose molecule! Together, these processes that occur inside the mitochondrion, the citric acid cycle and oxidative phosphorylation, are referred to as **respiration**, a term used for processes that couple the uptake of oxygen and the production of carbon dioxide (Figure 6).

The electron transport chain in the mitochondrial membrane is not the only one that generates energy in living cells. In plant and other photosynthetic cells, chloroplasts also have an electron transport chain that harvests solar energy. Even though they

do not contain mitochondria or chloroplasts, prokaryotes have other kinds of energy-yielding electron transport chains within their plasma membranes that also generate energy.

### How Do Cells Keep Energy in Reserve?

When energy is abundant, eukaryotic cells make larger, energy-rich molecules to store their excess energy. The resulting sugars and fats — in other words, polysaccharides and lipids — are then held in reservoirs within the cells, some of which are large enough to be visible in electron micrographs.

Animal cells can also synthesize branched polymers of glucose known as **glycogen**, which in turn aggregate into particles that are observable via electron microscopy. A cell can rapidly mobilize these particles whenever it needs quick energy.

Athletes who "carbo-load" by eating pasta the night before a competition are trying to increase their glycogen reserves. Under normal circumstances, though, humans store just enough glycogen to provide a day's worth of energy. Plant cells don't produce glycogen but instead make different glucose polymers known as **starches**, which they store in granules.

In addition, both plant and animal cells store energy by shunting glucose into fat synthesis pathways. One gram of fat contains nearly six times the energy of the same amount of glycogen, but the energy from fat is less readily available than that from glycogen. Still, each storage mechanism is important because cells need both quick and long-term energy depots. Fats are stored in droplets in the cytoplasm; adipose cells are specialized for this type of storage because they contain unusually large fat droplets. Humans generally store enough fat to supply their cells with several weeks' worth of energy (Figure 7).

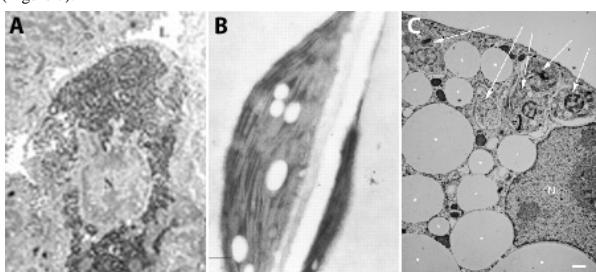


Figure 7: Examples of energy storage within cells  
(A) In this cross section of a rat kidney cell, the cytoplasm is filled with glycogen granules (black dots) surrounding the nucleus, N. (B) In this cross section of a plant cell, starch granules are present near the thylakoid membranes (striped pattern). (C) In this paramecium, asterisks indicate lipid (fat) droplets in the cell, near the nucleus (N).

© 2010 Nature Publishing Group (A) Bendayan 2003 (doi: 10.1097/01.LAB.0000078687.21634.69); (B) Park *et al.* 1998 (doi: 10.1093/emboj/17.4.859); (C) Nagajyothi *et al.* 2008 (doi: 10.1038/oby.2008.331) All rights reserved.

### Conclusion

Cells need energy to accomplish the tasks of life. Beginning with energy sources obtained from their environment in the form of sunlight and organic food molecules, eukaryotic cells make energy-rich molecules like ATP and NADH via energy pathways including photosynthesis, glycolysis, the citric acid cycle, and oxidative phosphorylation. Any excess energy is then stored in larger, energy-rich molecules such as polysaccharides (starch and glycogen) and lipids.

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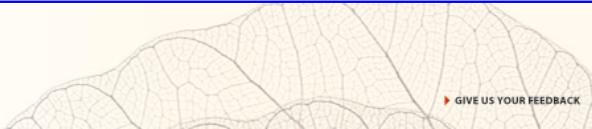
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## Unit 1: What Is a Cell? What Are the Essential Characteristics of Cells?

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## 1.4 Photosynthetic Cells Capture Light Energy and Convert It to Chemical Energy

[Figure 1](#)

Cells get nutrients from their environment, but where do those nutrients come from? Virtually all organic material on Earth has been produced by cells that convert energy from the Sun into energy-containing macromolecules. This process, called photosynthesis, is essential to the global carbon cycle and organisms that conduct photosynthesis represent the lowest level in most food chains (Figure 1).

[◀◀ Prev Page](#)[Next Page ▶▶](#)[Prev Page](#)[Next Page ▶▶](#)**What Is Photosynthesis? Why Is it Important?**

Most living things depend on photosynthetic cells to manufacture the complex organic molecules they require as a source of energy. Photosynthetic cells are quite diverse and include cells found in green plants, phytoplankton, and cyanobacteria. During the process of photosynthesis, cells use carbon dioxide and energy from the Sun to make sugar molecules and oxygen. These sugar molecules are the basis for more complex molecules made by the photosynthetic cell, such as glucose. Then, via respiration processes, cells use oxygen and glucose to synthesize energy-rich carrier molecules, such as ATP, and carbon dioxide is produced as a waste product. Therefore, the synthesis of glucose and its breakdown by cells are opposing processes.

[Figure 2](#)

The building and breaking of carbon-based material — from carbon dioxide to complex organic molecules (photosynthesis) then back to carbon dioxide (respiration) — is part of what is commonly called the **global carbon cycle**. Indeed, the fossil fuels we use to power our world today are the ancient remains of once-living organisms, and they provide a dramatic example of this cycle at work. The carbon cycle would not be possible without photosynthesis, because this process accounts for the "building" portion of the cycle (Figure 2).

However, photosynthesis doesn't just drive the carbon cycle — it also creates the oxygen necessary for respiring organisms. Interestingly, although green plants contribute much of the oxygen in the air we breathe, phytoplankton and cyanobacteria in the world's oceans are thought to produce between one-third and one-half of atmospheric oxygen on Earth.

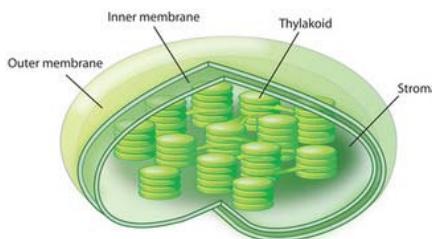
**What Cells and Organelles Are Involved in Photosynthesis?**

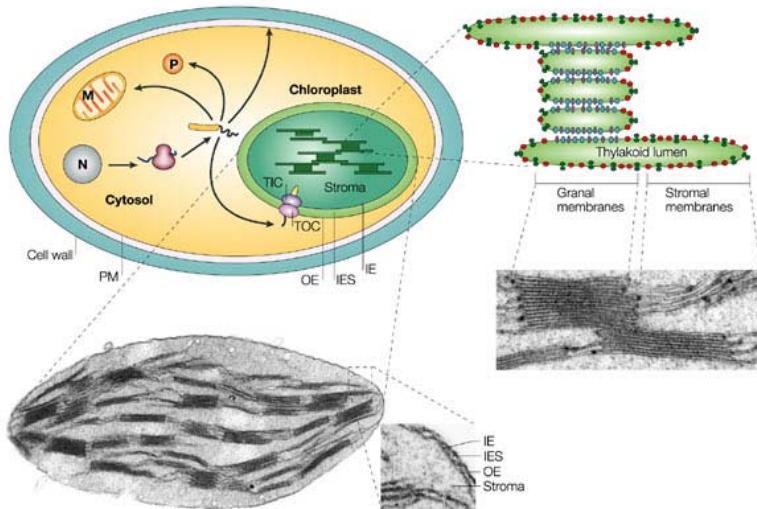
Figure 3: Structure of a chloroplast

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Photosynthetic cells contain special pigments that absorb light energy. Different pigments respond to different wavelengths of visible light. **Chlorophyll**, the primary pigment used in photosynthesis, reflects green light and absorbs red and blue light

most strongly. In plants, photosynthesis takes place in chloroplasts, which contain the chlorophyll. Chloroplasts are surrounded by a double membrane and contain a third inner membrane, called the **thylakoid membrane**, that forms long folds within the organelle. In electron micrographs, thylakoid membranes look like stacks of coins, although the compartments they form are connected like a maze of chambers. The green pigment chlorophyll is located within the thylakoid membrane, and the space between the thylakoid and the chloroplast membranes is called the **stroma** (Figure 3, Figure 4).

Chlorophyll A is the major pigment used in photosynthesis, but there are several types of chlorophyll and numerous other pigments that respond to light, including red, brown, and blue pigments. These other pigments may help channel light energy to chlorophyll A or protect the cell from photo-damage. For example, the photosynthetic protists called dinoflagellates, which are responsible for the "red tides" that often prompt warnings against eating shellfish, contain a variety of light-sensitive pigments, including both chlorophyll and the red pigments responsible for their dramatic coloration.



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Figure 4: Diagram of a chloroplast inside a cell, showing thylakoid stacks

Shown here is a chloroplast inside a cell, with the outer membrane (OE) and inner membrane (IE) labeled. Other features of the cell include the nucleus (N), mitochondrion (M), and plasma membrane (PM). At right and below are microscopic images of thylakoid stacks called grana. Note the relationship between the granal and stromal membranes.

© 2004 Nature Publishing Group Soll, J. & Schleiff, E. Protein import into chloroplasts. *Nature Reviews Molecular Cell Biology* 5, 198-208 (2004) doi:10.1038/nrm1333. All rights reserved.

### What Are the Steps of Photosynthesis?

Photosynthesis consists of both **light-dependent reactions** and **light-independent reactions**. In plants, the so-called "light" reactions occur within the chloroplast thylakoids, where the aforementioned chlorophyll pigments reside. When light energy reaches the pigment molecules, it energizes the electrons within them, and these electrons are shunted to an electron transport chain in the thylakoid membrane. Every step in the electron transport chain then brings each electron to a lower energy state and harnesses its energy by producing ATP and NADPH. Meanwhile, each chlorophyll molecule replaces its lost electron with an electron from water; this process essentially splits water molecules to produce oxygen (Figure 5).

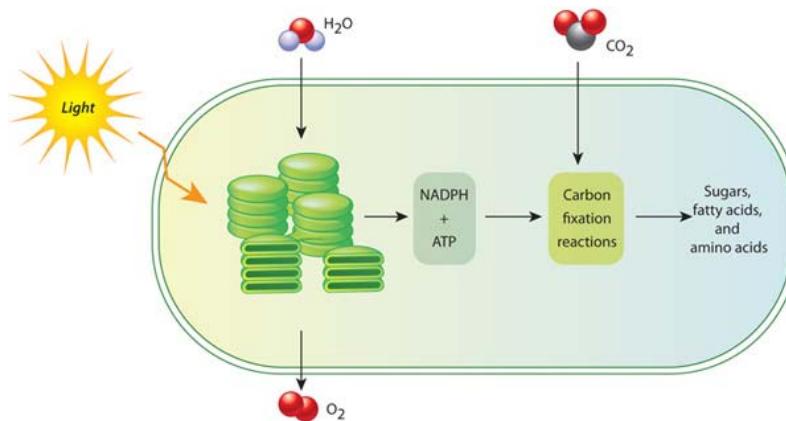


Figure 5: The light and dark reactions in the chloroplast  
The chloroplast is involved in both stages of photosynthesis. The light reactions take place in the thylakoid. There, water ( $H_2O$ ) is oxidized, and oxygen ( $O_2$ ) is released. The electrons that freed from the water are transferred to ATP and NADPH. The dark reactions then occur outside the thylakoid. In these reactions, the energy from ATP and NADPH is used to fix carbon dioxide ( $CO_2$ ). The products of this reaction are sugar molecules and various other organic molecules necessary for cell function and metabolism. Note that the dark reaction takes place in the stroma (the aqueous fluid surrounding the stacks of thylakoids) and in the cytoplasm.

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Once the light reactions have occurred, the light-independent or "dark" reactions take place in the chloroplast stroma. During this process, also known as carbon fixation, energy from the ATP and NADPH molecules generated by the light reactions drives a chemical pathway that uses the carbon in carbon dioxide (from the atmosphere) to build a three-carbon sugar called glyceraldehyde-3-phosphate (G3P). Cells then use G3P to build a wide variety of other sugars (such as glucose) and organic molecules. Many of these interconversions occur outside the chloroplast, following the transport of G3P from the stroma. The products of these reactions are then transported to other parts of the cell, including the mitochondria, where they are broken down to make more energy carrier molecules to satisfy the metabolic demands of the cell. In plants, some sugar molecules are stored as sucrose or starch.

## Conclusion

Photosynthetic cells contain chlorophyll and other light-sensitive pigments that capture solar energy. In the presence of carbon dioxide, such cells are able to convert this solar energy into energy-rich organic molecules, such as glucose. These cells not only drive the global carbon cycle, but they also produce much of the oxygen present in atmosphere of the Earth. Essentially, nonphotosynthetic cells use the products of photosynthesis to do the *opposite* of photosynthesis: break down glucose and release carbon dioxide.

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#### 1.5 Metabolism is the Complete Set of Biochemical Reactions within a Cell

A cell's daily operations are accomplished through the biochemical reactions that take place within the cell. Reactions are turned on and off or sped up and slowed down according to the cell's immediate needs and overall functions. At any given time, the numerous pathways involved in building up and breaking down cellular components must be monitored and balanced in a coordinated fashion. To achieve this goal, cells organize reactions into various enzyme-powered pathways.

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##### What Do Enzymes Do?

Enzymes are protein catalysts that speed biochemical reactions by facilitating the molecular rearrangements that support cell function. Recall that **chemical reactions** convert **substrates** into **products**, often by attaching chemical groups to or breaking off chemical groups from the substrates. For example, in the final step of **glycolysis**, an enzyme called pyruvate kinase transfers a phosphate group from one substrate (phosphoenolpyruvate) to another substrate (ADP), thereby generating pyruvate and ATP as products (Figure 1).

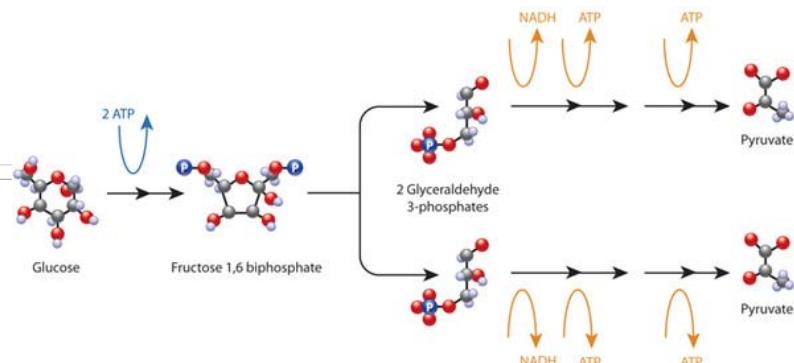


Figure 1: Glycolysis

Energy is used to convert glucose to a six-carbon form. Thereafter, energy is generated to create two molecules of pyruvate.

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Enzymes are flexible proteins that change shape when they bind with substrate molecules. In fact, this binding and shape changing ability is how enzymes manage to increase reaction rates. In many cases, enzymes function by bringing two substrates into close proximity and orienting them for easier electron transfer. Shape or conformational changes can also act as an on/off switch. For example, when **inhibitor molecules** bind to a site on an enzyme distinct from the substrate site, they can make the enzyme assume an inactive conformation, thereby preventing it from catalyzing a reaction. Conversely, the binding of **activator molecules** can make an enzyme assume an active conformation, essentially turning it on (Figure 2).

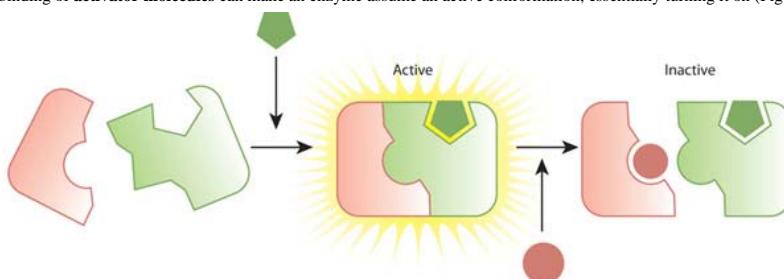


Figure 2: Activation and inactivation of enzyme reactions

Enzymes are proteins that can change shape and therefore become active or inactive. An activator molecule (green pentagon) can bind to an enzyme (light green puzzle shape) and change its overall shape. Note the transformation of the triangular point on the green enzyme into a rounded shape. This transformation enables the enzyme to better bind with its substrate (light pink puzzle piece). In contrast, an inhibitor molecule (pink circle) can prevent the interaction of an enzyme with its substrate and render it inactive.

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#### What Are Metabolic Pathways?

Many of the molecular transformations that occur within cells require multiple steps to accomplish. Recall, for instance, that cells split one glucose molecule into two pyruvate molecules by way of a ten-step process called glycolysis. This coordinated series of chemical reactions is an example of a [metabolic pathway](#) in which the product of one reaction becomes the substrate for the next reaction. Consequently, the intermediate products of a metabolic pathway may be short-lived (Figure 3).

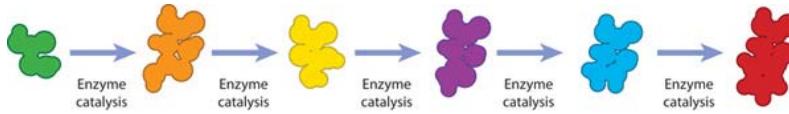


Figure 3: Reaction pathway

Enzymes can catalyze every step in a reaction pathway. At each step, the molecule is transformed to another form due to the presence of a specific enzyme. Such a reaction pathway can create a new molecule (biosynthesis), or it can break down an existing molecule (degradation).

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Sometimes, the enzymes involved in a particular metabolic pathway are physically connected, allowing the products of one reaction to be efficiently channeled to the next enzyme in the pathway. For example, pyruvate dehydrogenase is a complex of three different enzymes that catalyze the path from pyruvate (the end product of glycolysis) to acetyl CoA (the first substrate in the citric acid cycle). Within this complex, intermediate products are passed directly from one enzyme to the next.

### How Do Cells Keep Chemical Reactions in Balance?

Cells are expert recyclers. They disassemble large molecules into simpler building blocks and then use those building blocks to create the new components they require. The breaking down of complex organic molecules occurs via **catabolic pathways** and usually involves the release of energy. Through catabolic pathways, **polymers** such as proteins, nucleic acids, and polysaccharides are reduced to their constituent parts: amino acids, nucleotides, and sugars, respectively. In contrast, the synthesis of new macromolecules occurs via **anabolic pathways** that require energy input (Figure 4).

Cells must balance their catabolic and anabolic pathways in order to control their levels of critical **metabolites** — those molecules created by enzymatic activity — and ensure that sufficient energy is available. For example, if supplies of glucose start to wane, as might happen in the case of starvation, cells will synthesize glucose from other materials or start sending fatty acids into the citric acid cycle to generate ATP. Conversely, in times of plenty, excess glucose is converted into storage forms, such as glycogen, starches, and fats.

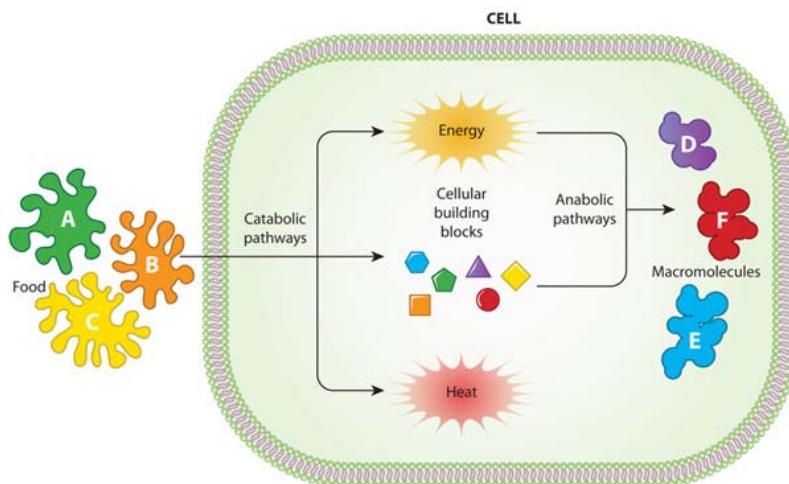


Figure 4: Catabolic and anabolic pathways in cell metabolism

Catabolic pathways involve the breakdown of nutrient molecules (Food: A, B, C) into usable forms (building blocks). In this process, energy is either stored in energy molecules for later use, or released as heat. Anabolic pathways then build new molecules out of the products of catabolism, and these pathways typically use energy. The new molecules built via anabolic pathways (macromolecules) are useful for building cell structures and maintaining the cell.

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### How Do Cells Manage All Their Chemical Reactions?

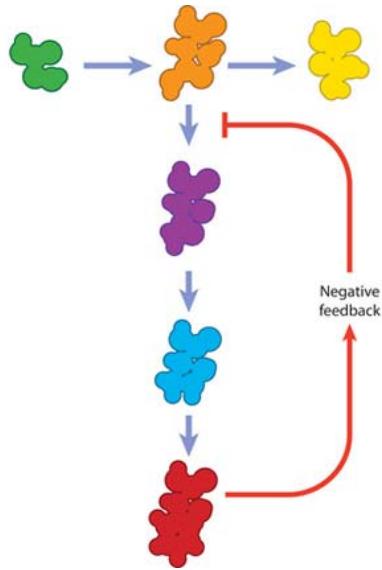


Figure 5: Feedback inhibition

When there is enough product at the end of a reaction pathway (red macromolecule), it can inhibit its own synthesis by interacting with enzymes in the synthesis pathway (red arrow).

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Not only do cells need to balance catabolic and anabolic pathways, but they must also monitor the needs and surpluses of all their different metabolic pathways. In order to bolster a particular pathway, cells can increase the amount of a necessary (rate-limiting) enzyme or use activators to convert that enzyme into an active conformation. Conversely, to slow down or halt a pathway, cells can decrease the amount of an enzyme or use inhibitors to make the enzyme inactive.

Such up- and down-regulation of metabolic pathways is often a response to changes in concentrations of key metabolites in the cell. For example, a cell may take stock of its levels of intermediate metabolites and tune the glycolytic pathway and the synthesis of glucose accordingly. In some instances, the products of a metabolic pathway actually serve as inhibitors of their own synthesis, in a process known as **feedback inhibition** (Figure 5). For example, the first intermediate in glycolysis, glucose-6-phosphate, inhibits every enzyme that produces it, hexokinase.

## Conclusion

The management of biochemical reactions with enzymes is an important part of cellular maintenance. Enzymatic activity allows a cell to respond to changing environmental demands and regulate its metabolic pathways, both of which are essential to cell survival.

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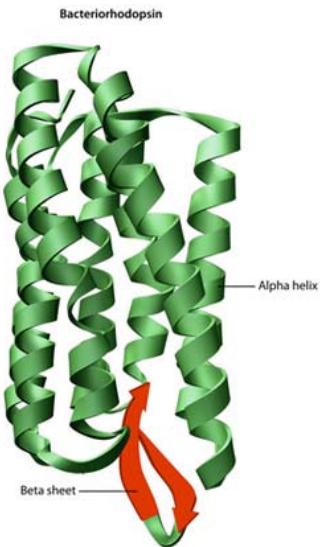
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How is a cell's genetic information used? Cells archive this information in DNA, which serves as a master set of instructions for building proteins. It is a beautiful system made complex by many levels of control, on-off switches, feedback, and fine-tuning. Segments of DNA are transcribed into RNA, and this RNA is then translated into proteins. The resulting proteins then fold into their three-dimensional configurations and combine with other proteins, or are decorated with sugars or fats to create finely-crafted tools for carrying out specific cellular functions. Protein functions range from structural supports and motors to catalysts of biochemical reactions and monitors of the cell's internal and external environments.

Every step in the protein production pathway can be adjusted up or down as the cell's needs dictate. The ability to carefully regulate transcription, translation, protein folding and modification, and protein function is a feature that makes cells such resilient and versatile life-forms.

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## Unit 2: How Do Cells Decode Genetic Information into Functional Proteins?

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**2.1 Information Transfer in Cells Requires Many Proteins and Nucleic Acids**

The genetic information stored in DNA is a living archive of instructions that cells use to accomplish the functions of life. Inside each cell, catalysts seek out the appropriate information from this archive and use it to build new proteins — proteins that make up the structures of the cell, run the biochemical reactions in the cell, and are sometimes manufactured for export. Although all of the cells that make up a multicellular organism contain identical genetic information, functionally different cells within the organism use different sets of catalysts to express only specific portions of these instructions to accomplish the functions of life.

**How Is Genetic Information Passed on in Dividing Cells?**

When a cell divides, it creates one copy of its genetic information — in the form of DNA molecules — for each of the two resulting daughter cells. The accuracy of these copies determines the health and inherited features of the nascent cells, so it is essential that the process of DNA replication be as accurate as possible (Figure 1).

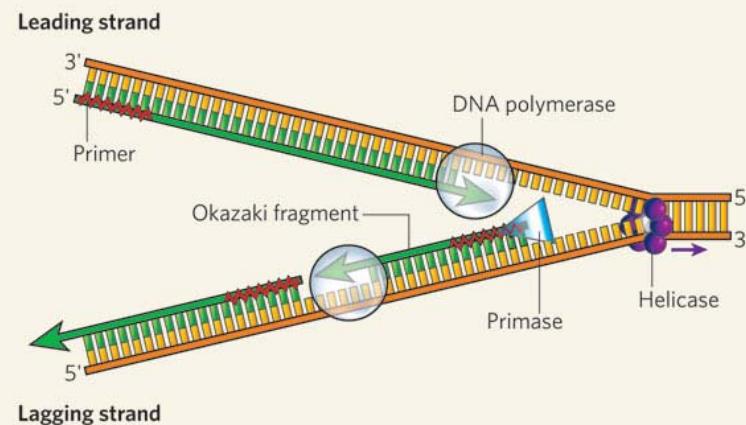
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Figure 1: DNA replication of the leading and lagging strand

The helicase unzips the double-stranded DNA for replication, making a forked structure. The primase generates short strands of RNA that bind to the single-stranded DNA to initiate DNA synthesis by the DNA polymerase. This enzyme can work only in the 5' to 3' direction, so it replicates the leading strand continuously. Lagging-strand replication is discontinuous, with short Okazaki fragments being formed and later linked together.

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One factor that helps ensure precise replication is the double-helical structure of DNA itself. In particular, the two strands of the DNA double helix are made up of combinations of molecules called nucleotides. DNA is constructed from just four different nucleotides — **adenine** (A), **thymine** (T), **cytosine** (C), and **guanine** (G) — each of which is named for the nitrogenous base it contains. Moreover, the nucleotides that form one strand of the DNA double helix always bond with the nucleotides in the other strand according to a pattern known as **complementary base-pairing** — specifically, A always pairs with T, and C always pairs with G (Figure 2). Thus, during cell division, the paired strands unravel and each strand serves as the template for synthesis of a new complementary strand.



Figure 2: Each nucleotide has an affinity for its partner: A pairs with T, and C pairs with G

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In most multicellular organisms, every cell carries the same DNA, but this genetic information is used in varying ways by different types of cells. In other words, what a cell "does" within an organism dictates which of its genes are expressed. Nerve cells, for example, synthesize an abundance of chemicals called neurotransmitters, which they use to send messages to other cells, whereas muscle cells load themselves with the protein-based filaments necessary for muscle contractions.

### What Are the Initial Steps in Accessing Genetic Information?

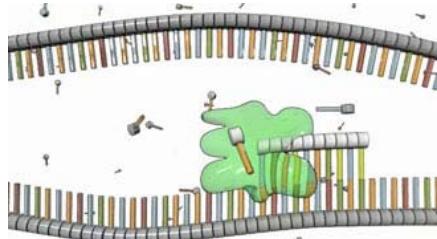


Figure 3: RNA polymerase at work  
RNA polymerase (green) synthesizes a strand of RNA that is complementary to the DNA template strand below it.

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**Transcription** is the first step in decoding a cell's genetic information. During transcription, enzymes called **RNA polymerases** build RNA molecules that are complementary to a portion of one strand of the DNA double helix (Figure 3). RNA molecules differ from DNA molecules in several important ways: They are single stranded rather than double stranded; their sugar component is a ribose rather than a deoxyribose; and they include **uracil (U)** nucleotides rather than thymine (T) nucleotides (Figure 4). Also, because they are single strands, RNA molecules don't form helices; rather, they fold into complex structures that are stabilized by internal complementary base-pairing.

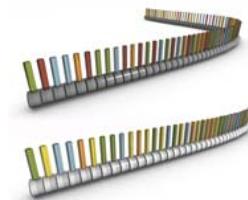


Figure 4: DNA (top) includes thymine (red); in RNA (bottom), thymine is replaced by uracil (yellow)

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Three general classes of RNA molecules are involved in expressing the genes encoded within a cell's DNA. **Messenger RNA** (mRNA) molecules carry the coding sequences for protein synthesis and are called transcripts; **ribosomal RNA** (rRNA) molecules form the core of a cell's ribosomes (the structures in which protein synthesis takes place); and **transfer RNA** (tRNA) molecules carry amino acids to the ribosomes during protein synthesis. In eukaryotic cells, each class of RNA has its own polymerase, whereas in prokaryotic cells, a single RNA polymerase synthesizes the different class of RNA. Other types of RNA also exist but are not as well understood, although they appear to play regulatory roles in gene expression and also be involved in protection against invading viruses.

mRNA is the most variable class of RNA, and there are literally thousands of different mRNA molecules present in a cell at any given time. Some mRNA molecules are abundant, numbering in the hundreds or thousands, as is often true of transcripts encoding structural proteins. Other mRNAs are quite rare, with perhaps only a single copy present, as is sometimes the case for transcripts that encode signaling proteins. mRNAs also vary in how long-lived they are. In eukaryotes, transcripts for structural proteins may remain intact for over ten hours, whereas transcripts for signaling proteins may be degraded in less than ten minutes.

Cells can be characterized by the spectrum of mRNA molecules present within them; this spectrum is called the **transcriptome**. Whereas each cell in a multicellular organism carries the same DNA or genome, its transcriptome varies widely according to cell type and function. For instance, the insulin-producing cells of the pancreas contain transcripts for

insulin, but bone cells do not. Even though bone cells carry the gene for insulin, this gene is not transcribed. Therefore, the transcriptome functions as a kind of catalog of all of the genes that are being expressed in a cell at a particular point in time.

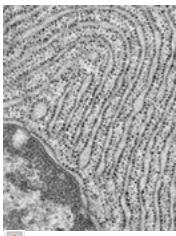
### What Is the Function of Ribosomes?



**Figure 5**

**Ribosomes** are the sites in a cell in which protein synthesis takes place. Cells have many ribosomes, and the exact number depends on how active a particular cell is in synthesizing proteins. For example, rapidly growing cells usually have a large number of ribosomes (Figure 5).

Ribosomes are complexes of rRNA molecules and proteins, and they can be observed in electron micrographs of cells. Sometimes, ribosomes are visible as clusters, called polyribosomes. In eukaryotes (but not in prokaryotes), some of the ribosomes are attached to internal membranes, where they synthesize the proteins that will later reside in those membranes, or are destined for secretion (Figure 6). Although only a few rRNA molecules are present in each ribosome, these molecules make up about half of the ribosomal mass. The remaining mass consists of a number of proteins — nearly 60 in prokaryotic cells and over 80 in eukaryotic cells.



**Figure 6**

Within the ribosome, the rRNA molecules direct the catalytic steps of protein synthesis — the stitching together of amino acids to make a protein molecule. In fact, rRNA is sometimes called a ribozyme or catalytic RNA to reflect this function. Eukaryotic and prokaryotic ribosomes are different from each other as a result of divergent evolution. These differences are exploited by antibiotics, which are designed to inhibit the prokaryotic ribosomes of infectious bacteria without affecting eukaryotic ribosomes, thereby not interfering with the cells of the sick host.

### How Does the Whole Process Result in New Proteins?

After the transcription of DNA to mRNA is complete, **translation** — or the reading of these mRNAs to make proteins — begins. Recall that mRNA molecules are single stranded, and the order of their bases — A, U, C, and G — is complementary to that in specific portions of the cell's DNA. Each mRNA dictates the order in which amino acids should be added to a growing protein as it is synthesized. In fact, every amino acid is represented by a three-nucleotide sequence or **codon** along the mRNA molecule. For example, AGC is the mRNA codon for the amino acid serine, and UAA is a signal to stop translating a protein — also called the **stop codon** (Figure 7).

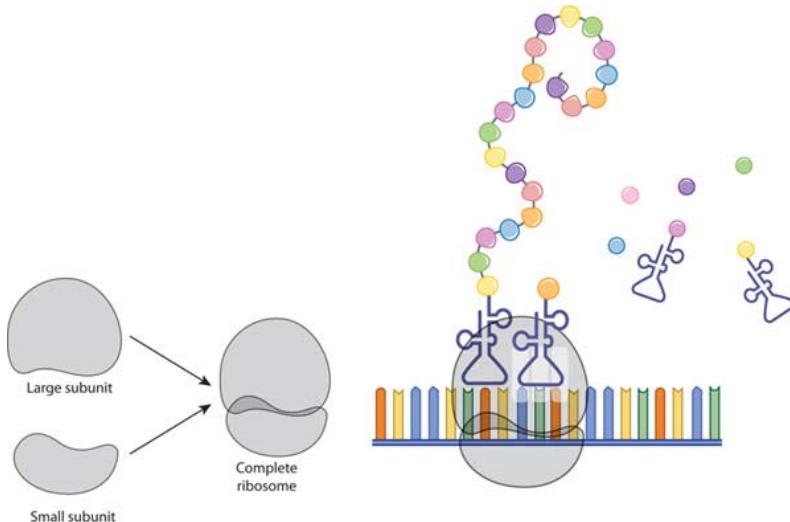


Figure 7: The ribosome and translation

A ribosome is composed of two subunits: large and small. During translation, ribosomal subunits assemble together like a sandwich on the strand of mRNA, where they proceed to attract tRNA molecules tethered to amino acids (circles). A long chain of amino acids emerges as the ribosome decodes the mRNA sequence into a polypeptide, or a new protein.

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Molecules of tRNA are responsible for matching amino acids with the appropriate codons in mRNA. Each tRNA molecule has two distinct ends, one of which binds to a specific amino acid, and the other which binds to the corresponding mRNA codon. During translation, these tRNAs carry amino acids to the ribosome and join with their complementary codons. Then, the assembled amino acids are joined together as the ribosome, with its resident rRNAs, moves along the mRNA molecule in a ratchet-like motion. The resulting protein chains can be hundreds of amino acids in length, and synthesizing these molecules requires a huge amount of chemical energy (Figure 8).

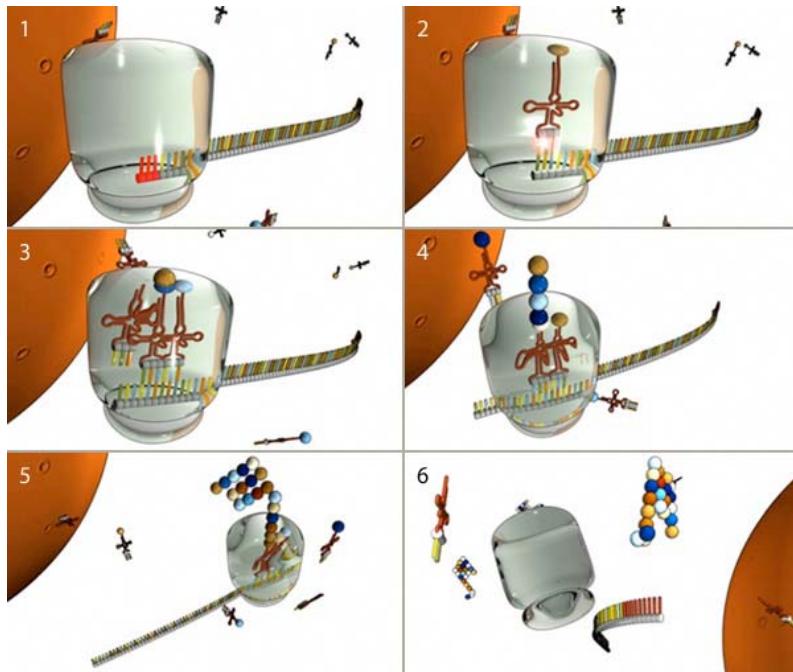


Figure 8: The major steps of translation

(1) Translation begins when a ribosome (gray) docks on a start codon (red) of an mRNA molecule in the cytoplasm. (2) Next, tRNA molecules attached to amino acids (spheres) dock at the corresponding triplet codon sequence on the mRNA molecule. (3, 4, and 5) This process repeats over and over, with multiple tRNAs docking and connecting successive amino acids into a growing chain that elongates out of the top of the ribosome. (6) When the ribosome encounters a stop codon, it falls off the mRNA molecule and releases the protein for use in the cell.

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In prokaryotic cells, transcription (DNA to mRNA) and translation (mRNA to protein) are so closely linked that translation usually begins before transcription is complete. In eukaryotic cells, however, the two processes are separated in both space and time: mRNAs are synthesized in the nucleus, and proteins are later made in the cytoplasm.

## Conclusion

Cellular DNA contains instructions for building the various proteins the cell needs to survive. In order for a cell to manufacture these proteins, specific genes within its DNA must first be transcribed into molecules of mRNA; then, these transcripts must be translated into chains of amino acids, which later fold into fully functional proteins. Although all of the cells in a multicellular organism contain the same set of genetic information, the transcriptomes of different cells vary depending on the cells' structure and function in the organism.

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### Unit 2: How Do Cells Decode Genetic Information into Functional Proteins?

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## 2.2 DNA Is Extensively Compacted with Proteins Chromosomes

Cells package their DNA not only to protect it, but also to regulate which genes are accessed and when. Cellular genes are therefore similar to valuable files stored in a file cabinet — but in this case, the cabinet's drawers are constantly opening and closing; various files are continually being located, pulled, and copied; and the original files are always returned to the correct location.

Of course, just as file drawers help conserve space in an office, [DNA packaging](#) helps conserve space in cells. Packaging is the reason why the approximately two meters of human DNA can fit into a cell that is only a few micrometers wide. But how, exactly, is DNA compacted to fit within eukaryotic and prokaryotic cells? And what mechanisms do cells use to access this highly compacted genetic material?

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### What Are Chromosomes?

Cellular DNA is never bare and unaccompanied by other proteins. Rather, it always forms a complex with various protein partners that help package it into such a tiny space. This DNA-protein complex is called **chromatin**, wherein the mass of protein and nucleic acid is nearly equal. Within cells, chromatin usually folds into characteristic formations called **chromosomes**. Each chromosome contains a single double-stranded piece of DNA along with the aforementioned packaging proteins.

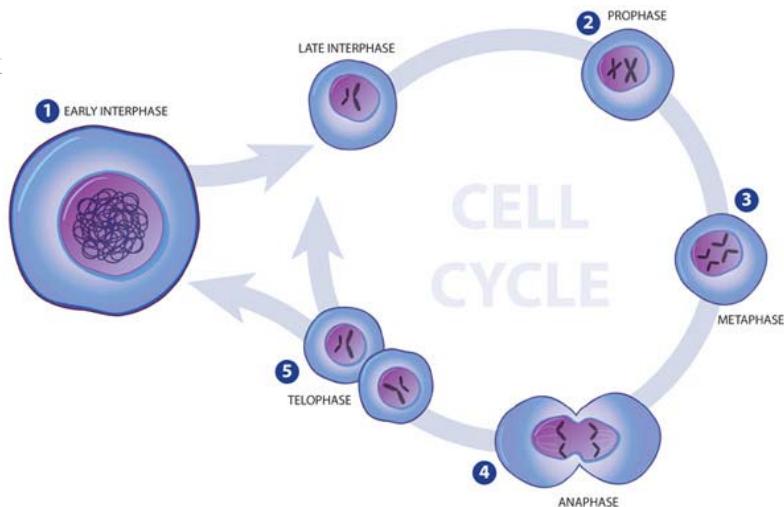


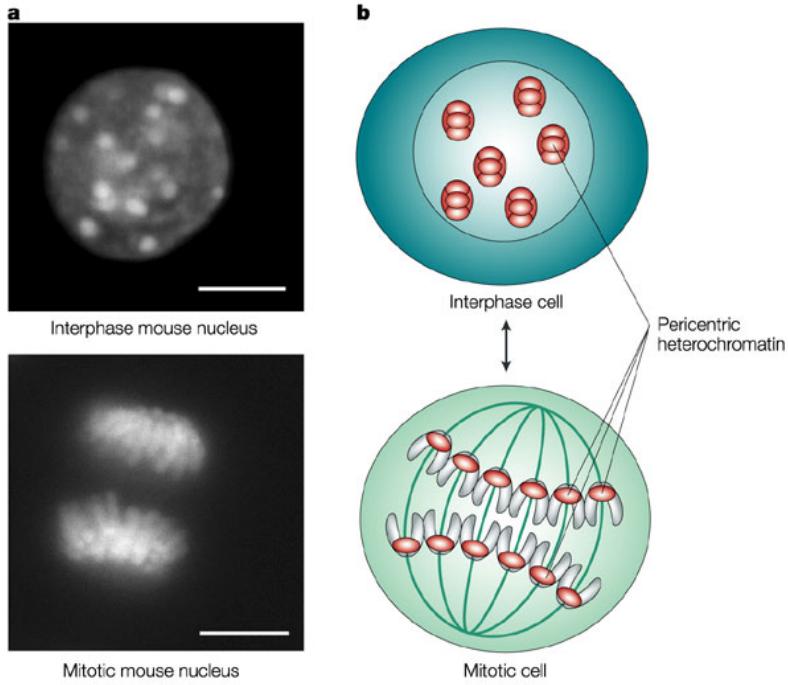
Figure 1: Chromatin condensation changes during the cell cycle

During interphase (1), chromatin is in its least condensed state and appears diffused distributed throughout the nucleus. Chromatin condensation begins during prophase (2) and chromosomes become visible. Chromosomes remain condensed throughout the various stages of mitosis (2-5).

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Eukaryotes typically possess multiple pairs of linear chromosomes, all of which are contained in the cellular nucleus, and these chromosomes have characteristic and changeable forms. During cell division, for example, they become more tightly packed, and their condensed form can be visualized with a light microscope. This condensed form is approximately 10,000 times shorter than the linear DNA strand would be if it was devoid of proteins and pulled taut. However, when eukaryotic cells are not dividing — a stage called **interphase** — the chromatin within their chromosomes is less tightly packed. This looser configuration is important because it permits transcription to take place (Figure 1, Figure 2).

In contrast to eukaryotes, the DNA in prokaryotic cells is generally present in a single circular chromosome that is located in the cytoplasm. (Recall that prokaryotic cells do not possess a nucleus.) Prokaryotic chromosomes are less condensed than their eukaryotic counterparts and don't have easily identified features when viewed under a light microscope.



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Figure 2: A the appearance of DNA during interphase versus mitosis

During interphase, the cell's DNA is not condensed and is loosely distributed. A stain for heterochromatin (which indicates the position of chromosomes) shows this broad distribution of chromatin in a mouse cell (upper left). The same stain also shows the organized, aligned structure of the chromosomes during mitosis. Scale bars = 10 microns.

© 2004 Nature Publishing Group Maisan, C. & Almouzni, G. HP1 and the dynamics of heterochromatin maintenance.

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### How Are Eukaryotic Chromosomes Structured?

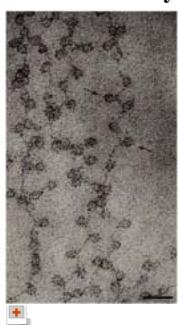


Figure 3

Eukaryotic chromosomes consist of repeated units of chromatin called **nucleosomes**, which were discovered by chemically digesting cellular nuclei and stripping away as much of the outer protein packaging from the DNA as possible. The chromatin that resisted digestion had the appearance of "beads on a string" in electron micrographs — with the "beads" being nucleosomes positioned at intervals along the length of the DNA molecule (Figure 3).

Nucleosomes are made up of double-stranded DNA that has complexed with small proteins called **histones**. The core particle of each nucleosome consists of eight histone molecules, two each of four different histone types: H2A, H2B, H3, and H4. The structure of histones has been strongly conserved across evolution, suggesting that their DNA packaging function is crucially important to all eukaryotic cells (Figure 4).

Histones carry positive charges and bind negatively charged DNA in a specific conformation. In particular, a segment of the DNA double helix wraps around each histone core particle a little less than twice. The exact length of the DNA segment associated with each histone core varies from species to species, but most such segments are approximately 150 base pairs in length. Furthermore, each histone molecule within the core particle has one end that sticks out from the particle. These ends are called **N-terminal tails**, and they play an important role in higher-order chromatin structure and gene expression.

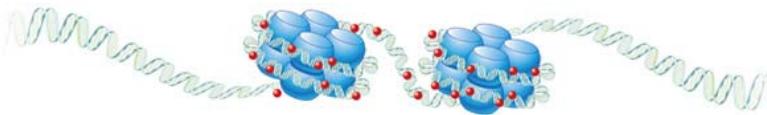


Figure 4: The nucleosome structure within chromatin. Each nucleosome contains eight histone proteins (blue), and DNA wraps around these histone structures to achieve a more condensed coiled form.

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### Why Is Complex Packing Critical for Eukaryotic Chromosomes?

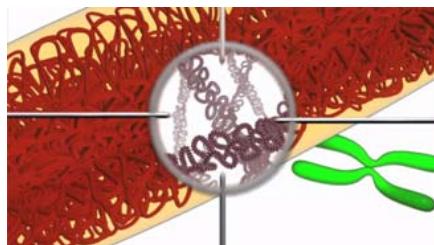


Figure 5: To better fit within the cell, long pieces of double-stranded DNA are tightly packed into structures called chromosomes.

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Although nucleosomes may look like extended "beads on a string" under an electron microscope, they appear differently in living cells. In such cells, nucleosomes stack up against one another in organized arrays with multiple levels of packing. The first level of packing is thought to produce a fiber about 30 nanometers (nm) wide. These 30 nm fibers then form a series of loops, which fold back on themselves for additional compacting (Figure 5).

The multiple levels of packing that exist within eukaryotic chromosomes not only permit a large amount of DNA to occupy a very small space, but they also serve several functional roles. For example, the looping of nucleosome-containing fibers brings specific regions of chromatin together, thereby influencing gene expression. In fact, the organized packing of DNA is malleable and appears to be highly regulated in cells.

Chromatin packing also offers an additional mechanism for controlling gene expression. Specifically, cells can control access to their DNA by modifying the structure of their chromatin. Highly compacted chromatin simply isn't accessible to the enzymes involved in DNA transcription, replication, or repair. Thus, regions of chromatin where active transcription is taking place (called **euchromatin**) are less condensed than **regions where transcription is inactive or is being actively inhibited or repressed** (called **heterochromatin**) (Figure 6).



Figure 6: The structure of chromatin in interphase.

Heterochromatin is more condensed than euchromatin. Typically, the more condensed chromatin is, the less accessible it is by transcription factors and polymerases.

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The dynamic nature of chromatin is regulated by enzymes. For example, chromatin can be loosened by changing the position of the DNA strands within a nucleosome. This loosening occurs because of chromatin remodeling enzymes, which function to slide nucleosomes along the DNA strand so that other enzymes can access the strand. This process is closely regulated and allows specific genes to be accessed in response to metabolic signals within the cell. Another way cells control gene expression is by modifying their histones with small chemical groups, such as methyl and acetyl groups in the N-terminal tails that extend from the core particle. Different enzymes catalyze each kind of N-terminal modification. Scientists occasionally refer to the complex pattern of histone modification in cells as a "histone code." Some of these modifications increase gene expression, whereas others decrease it.

### How Are Chromosomes Organized in the Nucleus?

In electron micrographs, eukaryotic interphase chromatin appears much like a plate of spaghetti — in other words, there is no obvious pattern of organization. In recent years, however, investigators have begun using fluorescent probes for each of the different interphase chromosomes. In doing so, they have discovered that these chromosomes have functional and decidedly nonrandom arrangements.

One of the first things these scientists noted was that uncondensed chromosomes occupy characteristic regions of the nucleus, which they termed **chromosome territories**. The spatial localization of these **territories** is thought to be important for gene expression. In fact, with the advent of gene-specific probes, researchers are beginning to understand how the arrangement of chromosome territories can bring particular genes closer together. A second major observation related to chromosome territories is that the position of chromosomes relative to one another differs from cell to cell. Such differences reflect variation in gene expression patterns.

### Conclusion

The prokaryotic genome typically exists in the form of a circular chromosome located in the cytoplasm. In eukaryotes, however, genetic material is housed in the nucleus and tightly packaged into linear chromosomes. Chromosomes are made up of a DNA-protein complex called chromatin that is organized into subunits called nucleosomes. The way in which eukaryotes compact and arrange their chromatin not only allows a large amount of DNA to fit in a small space, but it also helps regulate gene expression.

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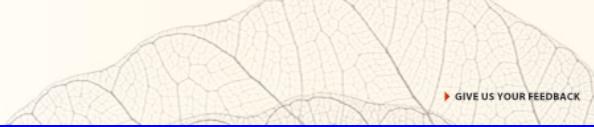
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## Unit 2: How Do Cells Decode Genetic Information into Functional Proteins?

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### 2.3 Differential Control of Transcription and Translation Underlies Changes in Cell Function

Genes encode proteins and proteins dictate cell function. Therefore, the thousands of genes expressed in a particular cell determine what that cell can do. Moreover, each step in the flow of information from DNA to RNA to protein provides the cell with a potential control point for self-regulating its functions by adjusting the amount and type of proteins it manufactures.

At any given time, the amount of a particular protein in a cell reflects the balance between that protein's synthetic and degradative biochemical pathways. On the synthetic side of this balance, recall that protein production starts at transcription (DNA to RNA) and continues with translation (RNA to protein). Thus, control of these processes plays a critical role in determining what proteins are present in a cell and in what amounts. In addition, the way in which a cell processes its RNA transcripts and newly made proteins also greatly influences protein levels.

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#### How Is Gene Expression Regulated?

The amounts and types of mRNA molecules in a cell reflect the function of that cell. In fact, thousands of transcripts are produced every second in every cell. Given this statistic, it is not surprising that the primary control point for gene expression is usually at the very beginning of the protein production process — the initiation of transcription. RNA transcription makes an efficient control point because many proteins can be made from a single mRNA molecule.

Transcript processing provides an additional level of regulation for eukaryotes, and the presence of a nucleus makes this possible. In prokaryotes, translation of a transcript begins before the transcript is complete, due to the proximity of ribosomes to the new mRNA molecules. In eukaryotes, however, transcripts are modified in the nucleus before they are exported to the cytoplasm for translation.

Eukaryotic transcripts are also more complex than prokaryotic transcripts. For instance, the primary transcripts synthesized by RNA polymerase contain sequences that will not be part of the mature RNA. These intervening sequences are called **introns**, and they are removed before the mature mRNA leaves the nucleus. The remaining regions of the transcript, which include the protein-coding regions, are called **exons**, and they are spliced together to produce the mature mRNA. Eukaryotic transcripts are also modified at their ends, which affects their stability and translation.

Of course, there are many cases in which cells must respond quickly to changing environmental conditions. In these situations, the regulatory control point may come well after transcription. For example, early development in most animals relies on translational control because very little transcription occurs during the first few cell divisions after fertilization. Eggs therefore contain many maternally originated mRNA transcripts as a ready reserve for translation after fertilization (Figure 1).

On the degradative side of the balance, cells can rapidly adjust their protein levels through the enzymatic breakdown of RNA transcripts and existing protein molecules. Both of these actions result in decreased amounts of certain proteins. Often, this breakdown is linked to specific events in the cell. The eukaryotic cell cycle provides a good example of how protein breakdown is linked to cellular events. This cycle is divided into several phases, each of which is characterized by distinct **cyclin** proteins that act as key regulators for that phase. Before a cell can progress from one phase of the cell cycle to the next, it must degrade the cyclin that characterizes that particular phase of the cycle. Failure to degrade a cyclin stops the cycle from continuing.

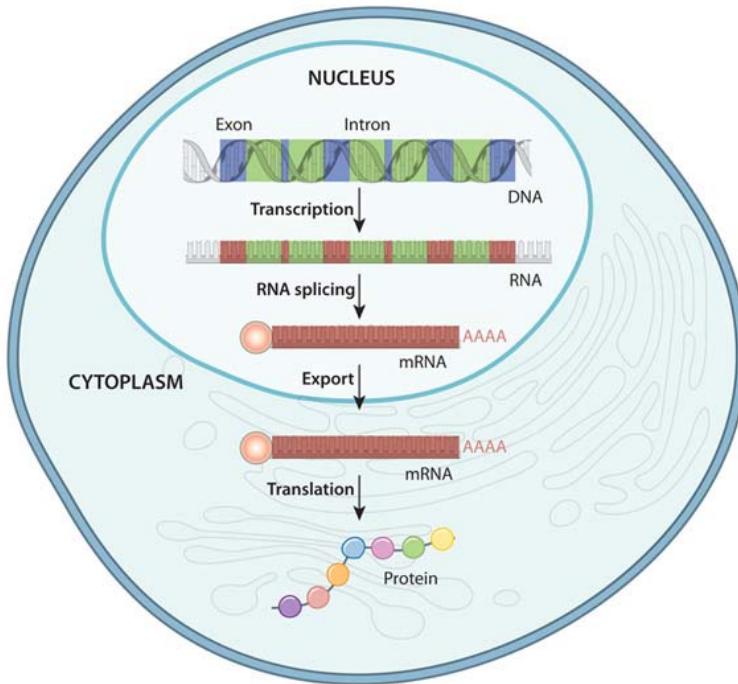


Figure 1: An overview of the flow of information from DNA to protein in a eukaryote

First, both coding and noncoding regions of DNA are transcribed into mRNA. Some regions are removed (introns) during initial mRNA processing. The remaining exons are then spliced together, and the spliced mRNA molecule (red) is prepared for export out of the nucleus through addition of an endcap (sphere) and a polyA tail. Once in the cytoplasm, the mRNA can be used to construct a protein.

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### How Do Different Cells Express the Genes They Need?

Only a fraction of the genes in a cell are expressed at any one time. The variety of gene expression profiles characteristic of different cell types arise because these cells have distinct sets of transcription regulators. Some of these regulators work to increase transcription, whereas others prevent or suppress it.

Normally, transcription begins when an RNA polymerase binds to a so-called **promoter sequence** on the DNA molecule. This sequence is almost always located just upstream from the starting point for transcription (the 5' end of the DNA), though it can be located downstream of the mRNA (3' end). In recent years, researchers have discovered that other DNA sequences, known as **enhancer sequences**, also play an important part in transcription by providing binding sites for regulatory proteins that affect RNA polymerase activity. Binding of regulatory proteins to an enhancer sequence causes a shift in chromatin structure that either promotes or inhibits RNA polymerase and transcription factor binding. A more open chromatin structure is associated with active gene transcription. In contrast, a more compact chromatin structure is associated with transcriptional inactivity (Figure 2).

Some regulatory proteins affect the transcription of multiple genes. This occurs because multiple copies of the regulatory protein binding sites exist within the genome of a cell. Consequently, regulatory proteins can have different roles for different genes, and this is one mechanism by which cells can coordinate the regulation of many genes at once.

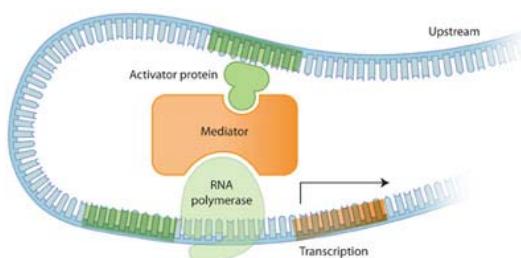


Figure 2: Modulation of transcription

An activator protein bound to DNA at an upstream enhancer sequence can attract proteins to the promoter region that activate RNA polymerase (green) and thus transcription. The DNA can loop around on itself to cause this interaction between an activator protein and other proteins that mediate the activity of RNA polymerase.

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### How Is Gene Expression Increased or Decreased in Response to Environmental Change?

In prokaryotes, regulatory proteins are often controlled by nutrient availability. This allows organisms such as bacteria to rapidly adjust their transcription patterns in response to environmental conditions. In addition, regulatory sites on prokaryotic DNA are typically located close to transcription promoter sites — and this plays an important part in gene expression.

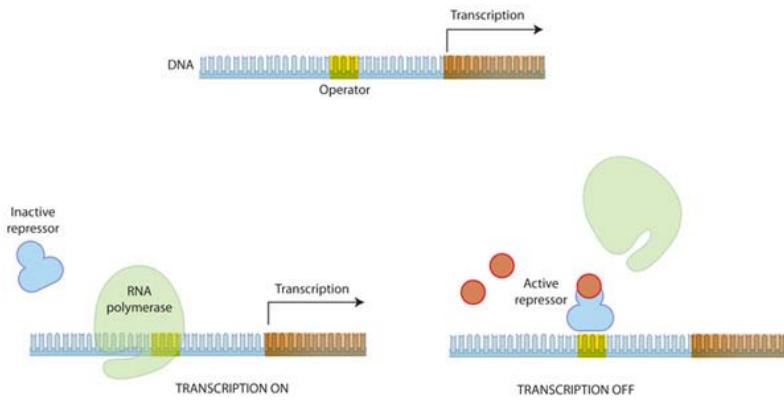


Figure 3: Transcription repression near the promoter region

Molecules can interfere with RNA polymerase binding. An inactive repressor protein (blue) can become activated by another molecule (red circle). This active repressor can bind to a region near the promoter called an operator (yellow) and thus interfere with RNA polymerase binding to the promoter, effectively preventing transcription.

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For an example of how this works, imagine a bacterium with a surplus of amino acids that signal the turning "on" of some genes and the turning "off" of others. In this particular example, cells might want to turn "on" genes for proteins that metabolize amino acids and turn "off" genes for proteins that synthesize amino acids. Some of these amino acids would bind to positive regulatory proteins called **activators**. Activator proteins bind to regulatory sites on DNA nearby to promoter regions that act as on/off switches. This binding facilitates RNA polymerase activity and transcription of nearby genes. At the same time, however, other amino acids would bind to negative regulatory proteins called **repressors**, which in turn bind to regulatory sites in the DNA that effectively block RNA polymerase binding (Figure 3).

The control of gene expression in eukaryotes is more complex than that in prokaryotes. In general, a greater number of regulatory proteins are involved, and regulatory binding sites may be located quite far from transcription promoter sites. Also, eukaryotic gene expression is usually regulated by a combination of several regulatory proteins acting together, which allows for greater flexibility in the control of gene expression.

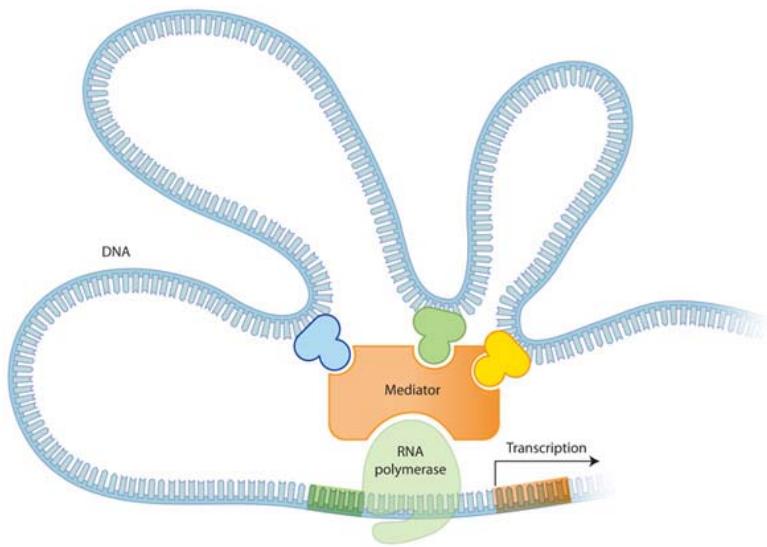


Figure 4: The complexity of multiple regulators

Transcriptional regulators can each have a different role. Combinations of one, two, or three regulators (blue, green, and yellow shapes) can affect transcription in different ways by differentially affecting a mediator complex (orange), which is also composed of proteins. The effect is that the same gene can be transcribed in multiple ways, depending on the combination, presence, or absence of various transcriptional regulator proteins.

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As previously mentioned, enhancer sequences are DNA sequences that are bound by an activator protein, and they can be located thousands of base pairs away from a promoter, either upstream or downstream from a gene. Activator protein binding is thought to cause DNA to loop out, bringing the activator protein into physical proximity with RNA polymerase and the other proteins in the complex that promote the initiation of transcription (Figure 4).

Different cell types express characteristic sets of transcriptional regulators. In fact, as multicellular organisms develop, different sets of cells within these organisms turn specific combinations of regulators on and off. Such developmental patterns are responsible for the variety of cell types present in the mature organism (Figure 5).

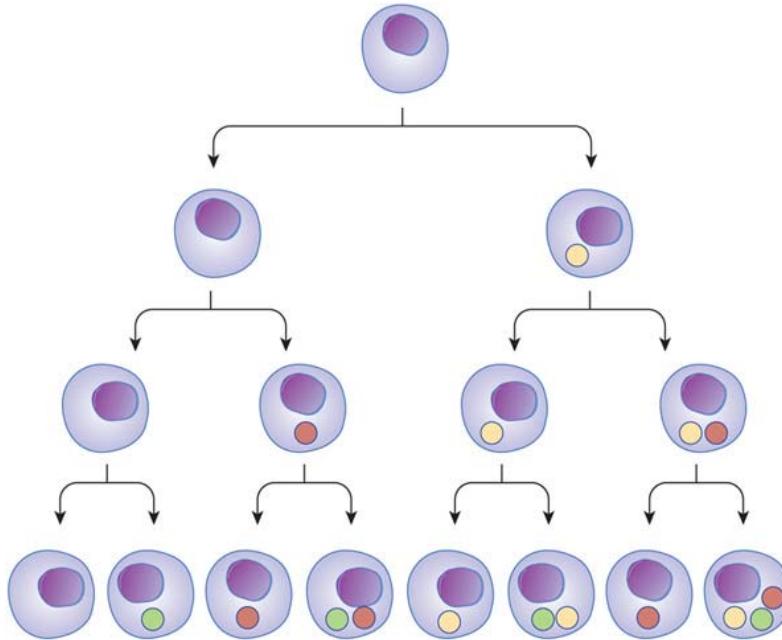


Figure 5: Transcriptional regulators can determine cell types

The wide variety of cell types in a single organism can depend on different transcription factor activity in each cell type. Different transcription factors can turn on at different times during successive generations of cells. As cells mature and go through different stages (arrows), transcription factors (colored balls) can act on gene expression and change the cell in different ways. This change affects the next generation of cells derived from that cell. In subsequent generations, it is the combination of different transcription factors that can ultimately determine cell type.

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## Conclusion

To live, cells must be able to respond to changes in their environment. Regulation of the two main steps of protein production — transcription and translation — is critical to this adaptability. Cells can control which genes get transcribed and which transcripts get translated; further, they can biochemically process transcripts and proteins in order to affect their activity. Regulation of transcription and translation occurs in both prokaryotes and eukaryotes, but it is far more complex in eukaryotes.

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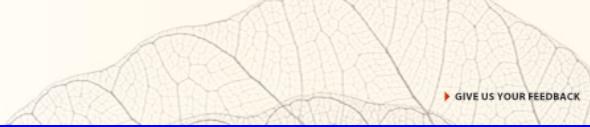
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#### 2.4 The Functions of Proteins Are Determined by Their Three-Dimensional Structures

Proteins are the end products of the decoding process that starts with the information in cellular DNA. As workhorses of the cell, proteins compose structural and motor elements in the cell, and they serve as the catalysts for virtually every biochemical reaction that occurs in living things. This incredible array of functions derives from a startlingly simple code that specifies a hugely diverse set of structures.

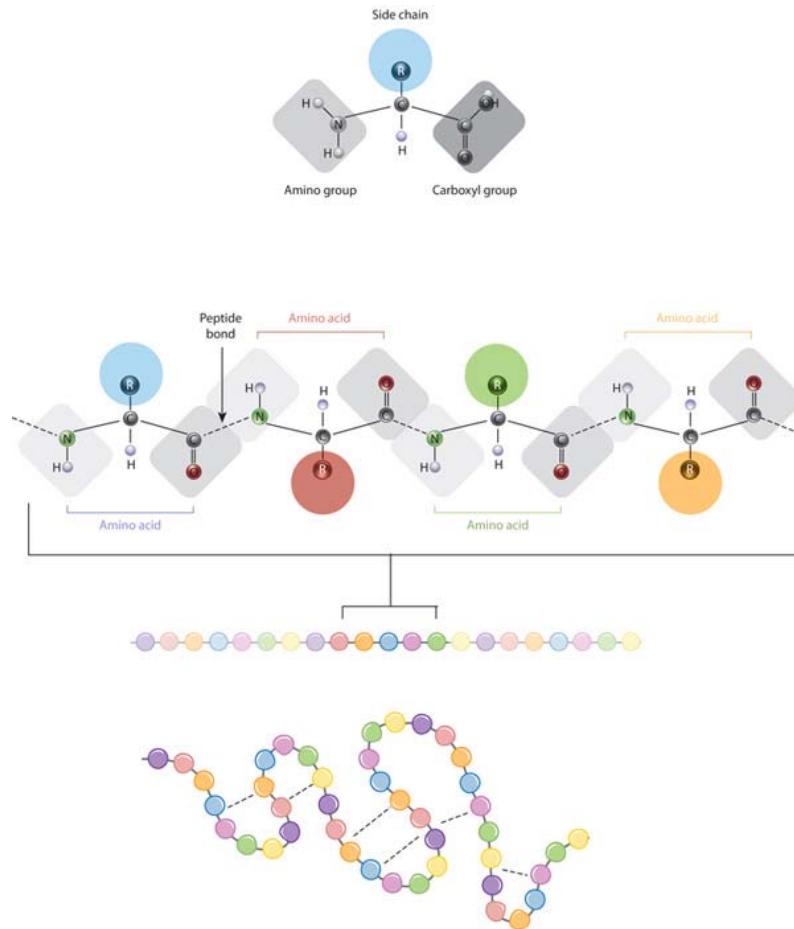
In fact, each gene in cellular DNA contains the code for a unique protein structure. Not only are these proteins assembled with different amino acid sequences, but they also are held together by different bonds and folded into a variety of three-dimensional structures. The folded shape, or conformation, depends directly on the linear amino acid sequence of the protein.

#### What Are Proteins Made Of?

The building blocks of proteins are amino acids, which are small organic molecules that consist of an alpha (central) carbon atom linked to an amino group, a carboxyl group, a hydrogen atom, and a variable component called a side chain (see below). Within a protein, multiple amino acids are linked together by **peptide bonds**, thereby forming a long chain. Peptide bonds are formed by a biochemical reaction that extracts a water molecule as it joins the amino group of one amino acid to the carboxyl group of a neighboring amino acid. The linear sequence of amino acids within a protein is considered the **primary structure** of the protein.

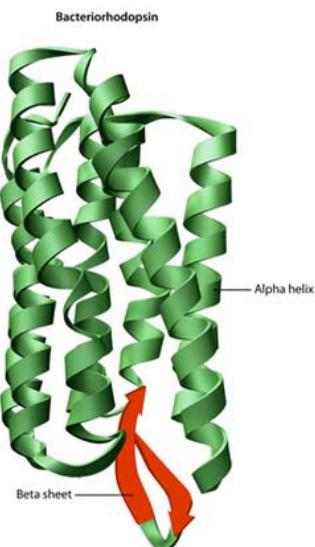
Proteins are built from a set of only twenty amino acids, each of which has a unique side chain. The side chains of amino acids have different chemistries. The largest group of amino acids have nonpolar side chains. Several other amino acids have side chains with positive or negative charges, while others have polar but uncharged side chains. The chemistry of amino acid side chains is critical to protein structure because these side chains can bond with one another to hold a length of protein in a certain shape or conformation. Charged amino acid side chains can form ionic bonds, and polar amino acids are capable of forming hydrogen bonds. Hydrophobic side chains interact with each other via weak van der Waals interactions. The vast majority of bonds formed by these side chains are noncovalent. In fact, cysteines are the only amino acids capable of forming covalent bonds, which they do with their particular side chains. Because of side chain interactions, the sequence and location of amino acids in a particular protein guides where the bends and folds occur in that protein (Figure 1).

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**Figure 1:** The relationship between amino acid side chains and protein conformation  
The defining feature of an amino acid is its side chain (at top, blue circle; below, all colored circles). When connected together by a series of peptide bonds, amino acids form a polypeptide, another word for protein. The polypeptide will then fold into a specific conformation depending on the interactions (dashed lines) between its amino acid side chains.

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**Figure 2:** The structure of the protein bacteriorhodopsin  
Bacteriorhodopsin is a membrane protein in bacteria that acts as a proton pump. Its conformation is essential to its function. The overall structure of the protein includes both alpha helices (green) and beta sheets (red).

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The primary structure of a protein — its amino acid sequence — drives the folding and intramolecular bonding of the linear amino acid chain, which ultimately determines the protein's unique three-dimensional shape. Hydrogen bonding between

amino groups and carboxyl groups in neighboring regions of the protein chain sometimes causes certain patterns of folding to occur. Known as **alpha helices** and **beta sheets**, these stable folding patterns make up the **secondary structure** of a protein. Most proteins contain multiple helices and sheets, in addition to other less common patterns (Figure 2). The ensemble of formations and folds in a single linear chain of amino acids — sometimes called a **polypeptide** — constitutes the **tertiary structure** of a protein. Finally, the **quaternary structure** of a protein refers to those macromolecules with multiple polypeptide chains or subunits.

The final shape adopted by a newly synthesized protein is typically the most energetically favorable one. As proteins fold, they test a variety of conformations before reaching their final form, which is unique and compact. Folded proteins are stabilized by thousands of noncovalent bonds between amino acids. In addition, chemical forces between a protein and its immediate environment contribute to protein shape and stability. For example, the proteins that are dissolved in the cell cytoplasm have hydrophilic (water-loving) chemical groups on their surfaces, whereas their hydrophobic (water-averse) elements tend to be tucked inside. In contrast, the proteins that are inserted into the cell membranes display some hydrophobic chemical groups on their surface, specifically in those regions where the protein surface is exposed to membrane lipids. It is important to note, however, that fully folded proteins are not frozen into shape. Rather, the atoms within these proteins remain capable of making small movements.

Even though proteins are considered macromolecules, they are too small to visualize, even with a microscope. So, scientists must use indirect methods to figure out what they look like and how they are folded. The most common method used to study protein structures is **X-ray crystallography**. With this method, solid crystals of purified protein are placed in an X-ray beam, and the pattern of deflected X rays is used to predict the positions of the thousands of atoms within the protein crystal.

### How Do Proteins Arrive at Their Final Shapes?

In theory, once their constituent amino acids are strung together, proteins attain their final shapes without any energy input. In reality, however, the cytoplasm is a crowded place, filled with many other macromolecules capable of interacting with a partially folded protein. Inappropriate associations with nearby proteins can interfere with proper folding and cause large aggregates of proteins to form in cells. Cells therefore rely on so-called **chaperone proteins** to prevent these inappropriate associations with unintended folding partners.

Chaperone proteins surround a protein during the folding process, sequestering the protein until folding is complete. For example, in bacteria, multiple molecules of the chaperone GroEL form a hollow chamber around proteins that are in the process of folding. Molecules of a second chaperone, GroES, then form a lid over the chamber. Eukaryotes use different families of chaperone proteins, although they function in similar ways.

Chaperone proteins are abundant in cells. These chaperones use energy from ATP to bind and release polypeptides as they go through the folding process. Chaperones also assist in the refolding of proteins in cells. Folded proteins are actually fragile structures, which can easily denature, or unfold. Although many thousands of bonds hold proteins together, most of the bonds are noncovalent and fairly weak. Even under normal circumstances, a portion of all cellular proteins are unfolded. Increasing body temperature by only a few degrees can significantly increase the rate of unfolding. When this happens, repairing existing proteins using chaperones is much more efficient than synthesizing new ones. Interestingly, cells synthesize additional chaperone proteins in response to "heat shock."

### What Are Protein Families?

All proteins bind to other molecules in order to complete their tasks, and the precise function of a protein depends on the way its exposed surfaces interact with those molecules. Proteins with related shapes tend to interact with certain molecules in similar ways, and these proteins are therefore considered a **protein family**. The proteins within a particular family tend to perform similar functions within the cell.

Proteins from the same family also often have long stretches of similar amino acid sequences within their primary structure. These stretches have been conserved through evolution and are vital to the catalytic function of the protein. For example, cell receptor proteins contain different amino acid sequences at their binding sites, which receive chemical signals from outside the cell, but they are more similar in amino acid sequences that interact with common intracellular signaling proteins. Protein families may have many members, and they likely evolved from ancient gene duplications. These duplications led to modifications of protein functions and expanded the functional repertoire of organisms over time.

### Conclusion

Proteins are built as chains of amino acids, which then fold into unique three-dimensional shapes. Bonding within protein molecules helps stabilize their structure, and the final folded forms of proteins are well-adapted for their functions.

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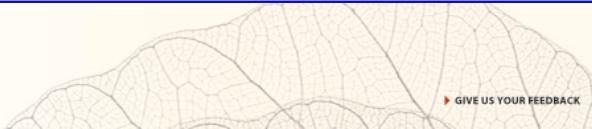
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## Unit 2: How Do Cells Decode Genetic Information into Functional Proteins?

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## 2.5 Proteins Are Responsible for a Diverse Range of Structural and Catalytic Functions in Cells

The collection of proteins within a cell determines its health and function. Proteins are responsible for nearly every task of cellular life, including cell shape and inner organization, product manufacture and waste cleanup, and routine maintenance. Proteins also receive signals from outside the cell and mobilize intracellular response. They are the workhorse macromolecules of the cell and are as diverse as the functions they serve.

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## How Diverse Are Proteins?

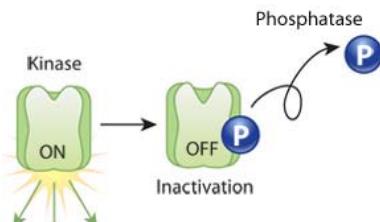
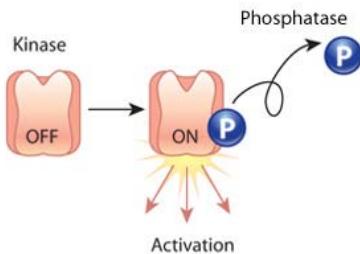


Figure 1: The phosphorylation of a protein can make it active or inactive.

Phosphorylation can either activate a protein (orange) or inactivate it (green). Kinase is an enzyme that phosphorylates proteins. Phosphatase is an enzyme that dephosphorylates proteins, effectively undoing the action of kinase.

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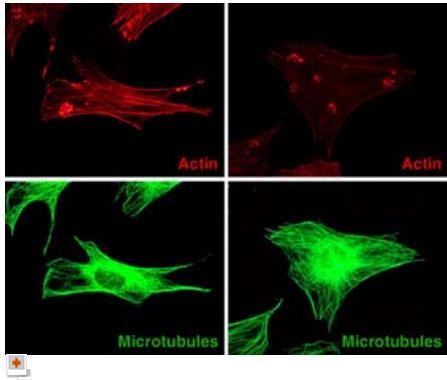
Proteins can be big or small, mostly hydrophilic or mostly hydrophobic, exist alone or as part of a multi-unit structure, and change shape frequently or remain virtually immobile. All of these differences arise from the unique amino acid sequences that make up proteins. Fully folded proteins also have distinct surface characteristics that determine which other molecules they interact with. When proteins bind with other molecules, their conformation can change in subtle or dramatic ways.

Not surprisingly, protein functions are as diverse as protein structures. For example, structural proteins maintain cell shape, akin to a skeleton, and they compose structural elements in connective tissues like cartilage and bone in vertebrates.

Enzymes are another type of protein, and these molecules catalyze the biochemical reactions that occur in cells. Yet other proteins work as monitors, changing their shape and activity in response to metabolic signals or messages from outside the cell. Cells also secrete various proteins that become part of the extracellular matrix or are involved in intercellular communication.

Proteins are sometimes altered after translation and folding are complete. In such cases, so-called **transferase enzymes** add small modifier groups, such as phosphates or carboxyl groups, to the protein. These modifications often shift protein conformation and act as molecular switches that turn the activity of a protein on or off. Many post-translational modifications are reversible, although different enzymes catalyze the reverse reactions. For example, enzymes called **kinases** add phosphate groups to proteins, but enzymes called **phosphatases** are required to remove these phosphate groups (Figure 1).

## How Do Proteins Provide Structural Support for Cells?



**Figure 2:** Proteins can have a structural role in a cell.

Actin filaments (red) and microtubules (green) are two different kinds of proteins that provide structure to cells.

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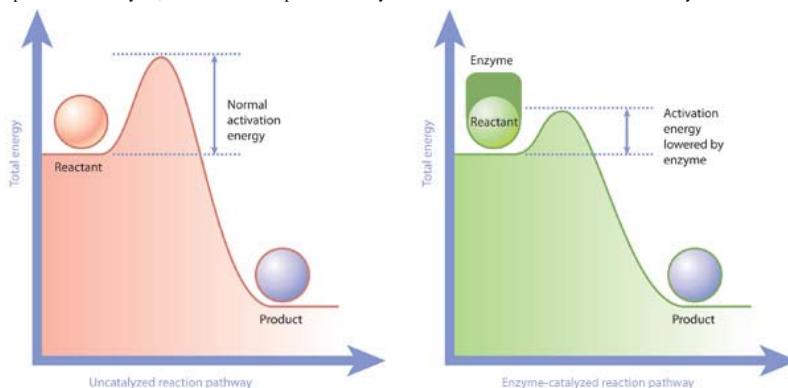
Enteropathogenic Escherichia coli activates the RhoA signaling pathway via the stimulation of GEF-H1. *The EMBO Journal* 23, 3570-3582 (2004) doi:10.1038/sj.emboj.7600359. All rights reserved.

The cytoplasm is highly structured, thanks to proteins. Particularly in eukaryotic cells, which tend to be bigger and need more mechanical support than prokaryotic cells, an extensive network of filaments — microtubules, actin filaments, and intermediate filaments — can be detected with a variety of microscopic methods. **Microtubules** play a major role in organizing the cytoplasm and in the distribution of organelles. They also form the mitotic spindle during cell division. **Actin filaments** are involved in various forms of cell movement, including cell locomotion, contraction of muscle cells, and cell division (Figure 2). **Intermediate filaments** are strong fibers that serve as architectural supports inside cells.

### How Do Proteins Aid the Biochemical Reactions of a Cell?

Cells rely on thousands of different enzymes to catalyze metabolic reactions. Enzymes are proteins, and they make a biochemical reaction more likely to proceed by lowering the activation energy of the reaction, thereby making these reactions proceed thousands or even millions of times faster than they would without a catalyst. Enzymes are highly specific to their substrates. They bind these substrates at complementary areas on their surfaces, providing a snug fit that many scientists compare to a lock and key. Enzymes work by binding one or more substrates, bringing them together so that a reaction can take place, and releasing them once the reaction is complete. In particular, when substrate binding occurs, enzymes undergo a conformational shift that orients or strains the substrates so that they are more reactive (Figure 3).

The name of an enzyme usually refers to the type of biochemical reaction it catalyzes. For example, proteases break down proteins, and dehydrogenases oxidize a substrate by removing hydrogen atoms. As a general rule, the "-ase" suffix identifies a protein as an enzyme, whereas the first part of an enzyme's name refers to the reaction that it catalyzes.



**Figure 3:** Enzymes and activation energy

Enzymes lower the activation energy necessary to transform a reactant into a product. On the left is a reaction that is not catalyzed by an enzyme (red), and on the right is one that is (green). In the enzyme-catalyzed reaction, the enzyme binds to the reactant and facilitates its transformation into a product. Consequently, the enzyme-catalyzed reaction pathway has a smaller energy barrier (activation energy) to overcome before the reaction can proceed.

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### What Do Proteins Do in the Plasma Membrane?

The proteins in the plasma membrane typically help the cell interact with its environment. For example, plasma membrane proteins carry out functions as diverse as ferrying nutrients across the plasma membrane, receiving chemical signals from outside the cell, translating chemical signals into intracellular action, and sometimes anchoring the cell in a particular location (Figure 4).

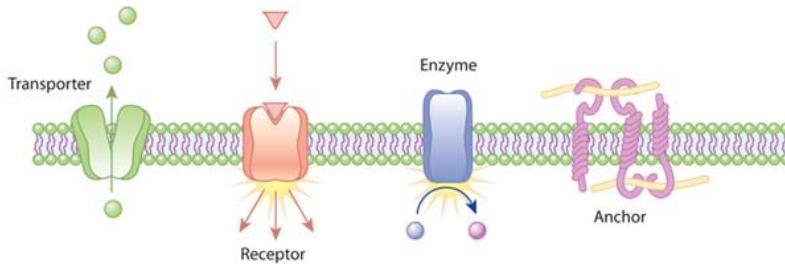


Figure 4: The diverse functions of proteins in the plasma membrane

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The overall surfaces of membrane proteins are mosaics, with patches of hydrophobic amino acids where the proteins contact lipids in the membrane bilayer and patches of hydrophilic amino acids on the surfaces that extend into the water-based cytoplasm. Many proteins can move within the plasma membrane through a process called **membrane diffusion**. This concept of membrane-bound proteins that can travel within the membrane is called the **fluid-mosaic model** of the cell membrane. The portions of membrane proteins that extend beyond the lipid bilayer into the extracellular environment are also hydrophilic and are frequently modified by the addition of sugar molecules. Other proteins are associated with the membrane but not inserted into it. They are sometimes anchored to lipids in the membrane or bound to other membrane proteins (Figure 5).

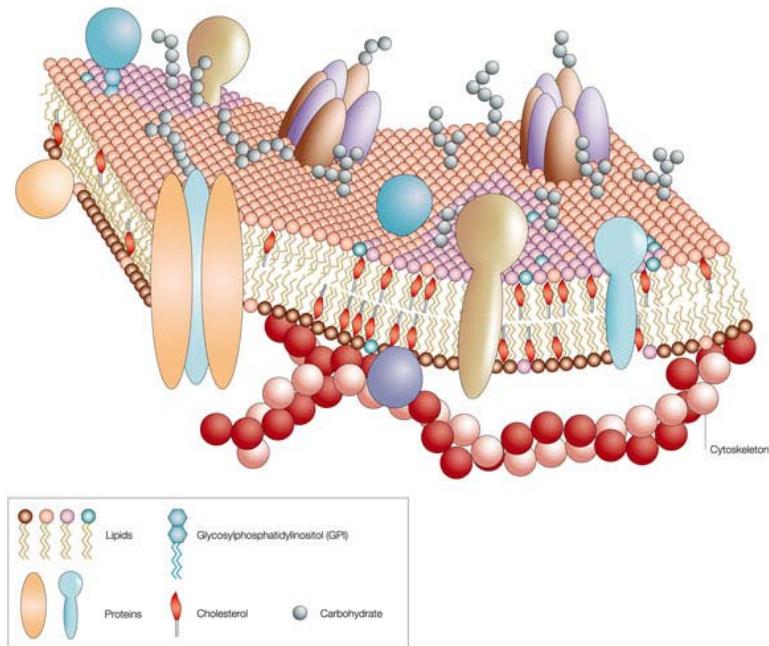


Figure 5: The fluid-mosaic model of the cell membrane

Like a mosaic, the cell membrane is a complex structure made up of many different parts, such as proteins, phospholipids, and cholesterol. The relative amounts of these components vary from membrane to membrane, and the types of lipids in membranes can also vary.

© 2004 Nature Publishing Group Pietzsch, J. Mind the membrane. *Horizon Symposia: Living Frontier*, 1-4 (2004).

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## Conclusion

Proteins serve a variety of functions within cells. Some are involved in structural support and movement, others in enzymatic activity, and still others in interaction with the outside world. Indeed, the functions of individual proteins are as varied as their unique amino acid sequences and complex three-dimensional physical structures.

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## Unit 2: How Do Cells Decode Genetic Information into Functional Proteins?

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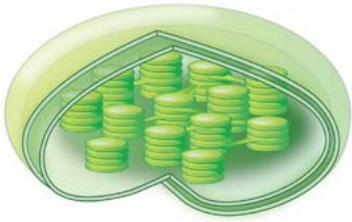
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## Unit 3: How Are Eukaryotic Cells Organized into Smaller Parts?

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Scientists aren't just interested in the individual molecules found in cells or in cells' metabolic functions and pathways; they also seek to learn more about the ways in which larger groupings of molecules serve cells. These groupings take on many forms and are responsible for a wide variety of functions. For instance, a cell's membranes make up its outer boundary and partition off its organelles, and its cytoskeleton provides three-dimensional support and the means for movement. Other specialized structures, such as mitochondria, chloroplasts, and cell walls, have evolved to carry out vital functions, but they are found only in specific categories of cells. Therefore, understanding these structures not only provides insight into cellular function, but it also helps elucidate the differences between various types of organisms.

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[Specialized Membranes Organize the Eukaryotic Cell](#)  
[Cytoplasm into Compartments](#)

[Cytoskeletal Networks Provide Spatial Organization and Mechanical Support to Eukaryotic Cells](#)

[The Endoplasmic Reticulum, Golgi Apparatus, and Lysosomes Are Part of an Extensive Endomembrane System in Eukaryotic Cells](#)

[Mitochondria Are Independently Replicating Organelles That Supply Much of the Energy of the Cell](#)

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### Unit 3: How Are Eukaryotic Cells Organized into Smaller Parts?

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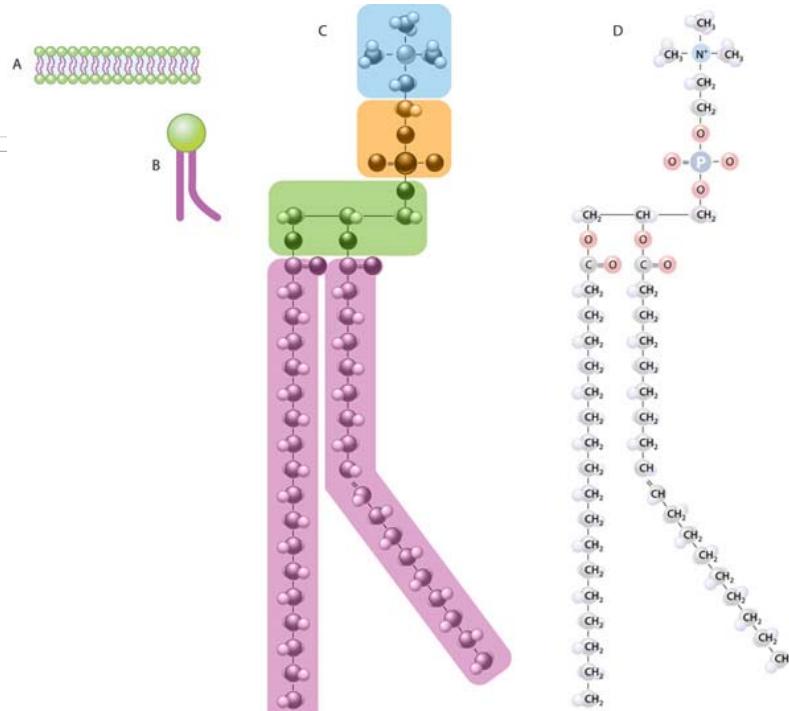
### 3.1 Specialized Membranes Organize the Eukaryotic Cell Cytoplasm into Compartments

Cell membranes protect and organize cells. All cells have an outer plasma membrane that regulates not only what enters the cell, but also how much of any given substance comes in. Unlike prokaryotes, eukaryotic cells also possess internal membranes that encase their organelles and control the exchange of essential cell components. Both types of membranes have a specialized structure that facilitates their gatekeeping function.

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#### What Are Cellular Membranes Made Of?

With few exceptions, cellular membranes — including plasma membranes and internal membranes — are made of **glycerophospholipids**, molecules composed of glycerol, a phosphate group, and two fatty acid chains. **Glycerol** is a three-carbon molecule that functions as the backbone of these membrane lipids. Within an individual glycerophospholipid, fatty acids are attached to the first and second carbons, and the phosphate group is attached to the third carbon of the glycerol backbone. Variable head groups are attached to the phosphate. Space-filling models of these molecules reveal their cylindrical shape, a geometry that allows glycerophospholipids to align side-by-side to form broad sheets (Figure 1).



**Figure 1:** The lipid bilayer and the structure and composition of a glycerophospholipid molecule  
 (A) The plasma membrane of a cell is a bilayer of glycerophospholipid molecules. (B) A single glycerophospholipid molecule is composed of two major regions: a hydrophilic head (green) and hydrophobic tails (purple). (C) The subregions of a glycerophospholipid molecule; phosphatidylcholine is shown as an example. The hydrophilic head is composed of a choline structure (blue) and a phosphate (orange). This head is connected to a glycerol (green) with two hydrophobic tails (purple) called fatty acids. (D) This view shows the specific atoms within the various subregions of the phosphatidylcholine molecule. Note that a double bond between two of the carbon atoms in one of the hydrocarbon (fatty acid) tails causes a slight kink on this molecule, so it appears bent.

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Glycerophospholipids are by far the most abundant lipids in cell membranes. Like all lipids, they are insoluble in water, but their unique geometry causes them to aggregate into bilayers without any energy input. This is because they are two-faced molecules, with hydrophilic (water-loving) phosphate heads and hydrophobic (water-fearing) hydrocarbon tails of fatty acids. In water, these molecules spontaneously align — with their heads facing outward and their tails lining up in the bilayer's

interior. Thus, the hydrophilic heads of the glycerophospholipids in a cell's plasma membrane face both the water-based cytoplasm and the exterior of the cell.

Altogether, lipids account for about half the mass of cell membranes. Cholesterol molecules, although less abundant than glycerophospholipids, account for about 20 percent of the lipids in animal cell plasma membranes. However, cholesterol is not present in bacterial membranes or mitochondrial membranes. Also, cholesterol helps regulate the stiffness of membranes, while other less prominent lipids play roles in cell signaling and cell recognition.

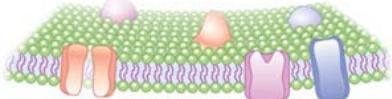


Figure 2: The glycerophospholipid bilayer with embedded transmembrane proteins

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In addition to lipids, membranes are loaded with proteins. In fact, proteins account for roughly half the mass of most cellular membranes. Many of these proteins are embedded into the membrane and stick out on both sides; these are called

**transmembrane proteins**. The portions of these proteins that are nested amid the hydrocarbon tails have hydrophobic surface characteristics, and the parts that stick out are hydrophilic (Figure 2).

At physiological temperatures, cell membranes are fluid; at cooler temperatures, they become gel-like. Scientists who model membrane structure and dynamics describe the membrane as a fluid mosaic in which transmembrane proteins can move laterally in the lipid bilayer. Therefore, the collection of lipids and proteins that make up a cellular membrane relies on natural biophysical properties to form and function. In living cells, however, many proteins are not free to move. They are often anchored in place within the membrane by tethers to proteins outside the cell, cytoskeletal elements inside the cell, or both.

### What Do Membranes Do?

Cell membranes serve as barriers and gatekeepers. They are semi-permeable, which means that some molecules can diffuse across the lipid bilayer but others cannot. Small hydrophobic molecules and gases like oxygen and carbon dioxide cross membranes rapidly. Small polar molecules, such as water and ethanol, can also pass through membranes, but they do so more slowly. On the other hand, cell membranes restrict diffusion of highly charged molecules, such as ions, and large molecules, such as sugars and amino acids. The passage of these molecules relies on specific transport proteins embedded in the membrane.

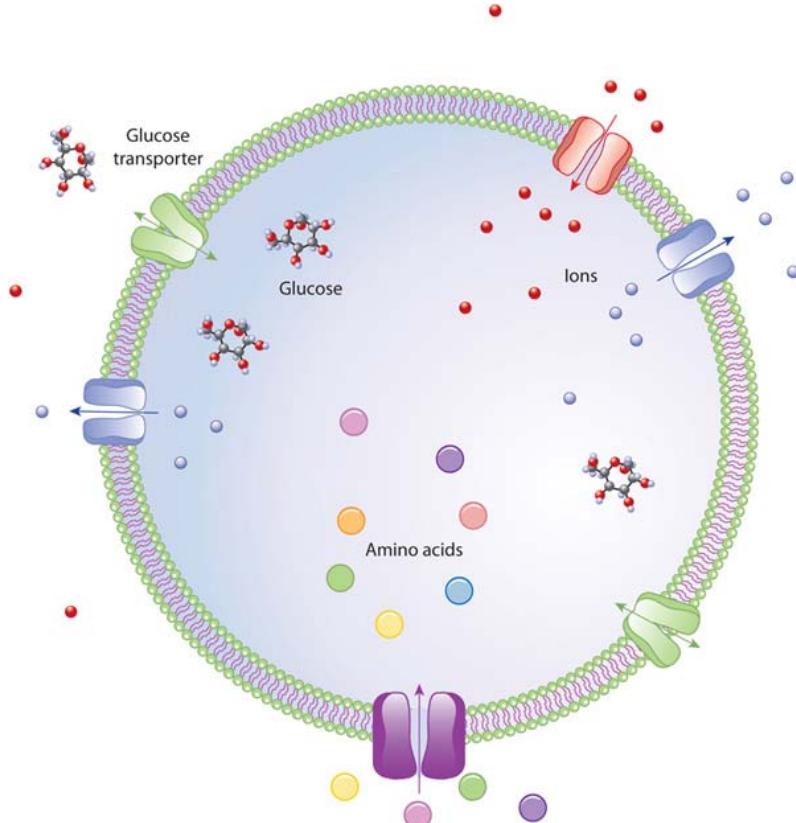


Figure 3: Selective transport  
Specialized proteins in the cell membrane regulate the concentration of specific molecules inside the cell.

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Membrane transport proteins are specific and selective for the molecules they move, and they often use energy to catalyze passage. Also, these proteins transport some nutrients against the concentration gradient, which requires additional energy. The ability to maintain concentration gradients and sometimes move materials against them is vital to cell health and

maintenance. Thanks to membrane barriers and transport proteins, the cell can accumulate nutrients in higher concentrations than exist in the environment and, conversely, dispose of waste products (Figure 3).

Other transmembrane proteins have communication-related jobs. These proteins bind signals, such as hormones or immune mediators, to their extracellular portions. Binding causes a conformational change in the protein that transmits a signal to intracellular messenger molecules. Like transport proteins, receptor proteins are specific and selective for the molecules they bind (Figure 4).

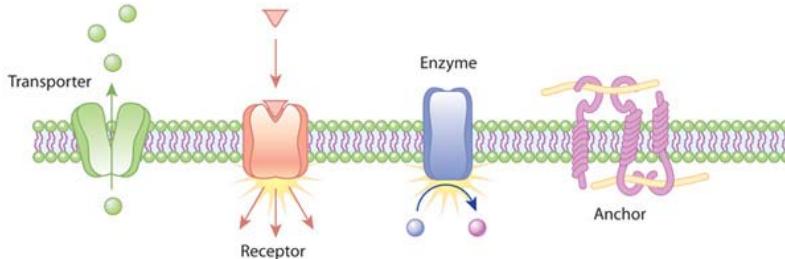


Figure 4: Examples of the action of transmembrane proteins

Transporters carry a molecule (such as glucose) from one side of the plasma membrane to the other. Receptors can bind an extracellular molecule (triangle), and this activates an intracellular process. Enzymes in the membrane can do the same thing they do in the cytoplasm of a cell: transform a molecule into another form. Anchor proteins can physically link intracellular structures with extracellular structures.

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**Peripheral membrane proteins** are associated with the membrane but are not inserted into the bilayer. Rather, they are usually bound to other proteins in the membrane. Some peripheral proteins form a filamentous network just under the membrane that provides attachment sites for transmembrane proteins. Other peripheral proteins are secreted by the cell and form an extracellular matrix that functions in cell recognition.

### How Diverse Are Cell Membranes?

In contrast to prokaryotes, eukaryotic cells have not only a plasma membrane that encases the entire cell, but also intracellular membranes that surround various organelles. In such cells, the plasma membrane is part of an extensive **endomembrane system** that includes the endoplasmic reticulum (ER), the nuclear membrane, the Golgi apparatus, and lysosomes. Membrane components are exchanged throughout the endomembrane system in an organized fashion. For instance, the membranes of the ER and the Golgi apparatus have different compositions, and the proteins that are found in these membranes contain sorting signals, which are like molecular zip codes that specify their final destination.

Mitochondria and chloroplasts are also surrounded by membranes, but they have unusual membrane structures — specifically, each of these organelles has two surrounding membranes instead of just one. The outer membrane of mitochondria and chloroplasts has pores that allow small molecules to pass easily. The inner membrane is loaded with the proteins that make up the electron transport chain and help generate energy for the cell. The double membrane enclosures of mitochondria and chloroplasts are similar to certain modern-day prokaryotes and are thought to reflect these organelles' evolutionary origins.

### Conclusion

Membranes are made of lipids and proteins, and they serve a variety of barrier functions for cells and intracellular organelles. Membranes keep the outside "out" and the inside "in," allowing only certain molecules to cross and relaying messages via a chain of molecular events

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## 3.2 Cytoskeletal Networks Provide Spatial Organization and Mechanical Support to Eukaryotic Cells

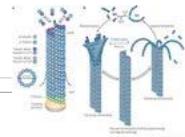
The **cytoskeleton** is a structure that helps cells maintain their shape and internal organization, and it also provides mechanical support that enables cells to carry out essential functions like division and movement. There is no single cytoskeletal component. Rather, several different components work together to form the cytoskeleton.

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### What Is the Cytoskeleton Made Of?

The cytoskeleton of eukaryotic cells is made of filamentous proteins, and it provides mechanical support to the cell and its cytoplasmic constituents. All cytoskeletons consist of three major classes of elements that differ in size and in protein composition. Microtubules are the largest type of filament, with a diameter of about 25 nanometers (nm), and they are composed of a protein called **tubulin**. Actin filaments are the smallest type, with a diameter of only about 6 nm, and they are made of a protein called **actin**. Intermediate filaments, as their name suggests, are mid-sized, with a diameter of about 10 nm. Unlike actin filaments and microtubules, intermediate filaments are constructed from a number of different subunit proteins.

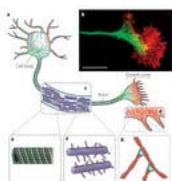
### What Do Microtubules Do?



[Figure 1](#)

Tubulin contains two polypeptide subunits, and dimers of these subunits string together to make long strands called **protofilaments**. Thirteen protofilaments then come together to form the hollow, straw-shaped filaments of microtubules. Microtubules are ever-changing, with reactions constantly adding and subtracting tubulin dimers at both ends of the filament (Figure 1). The rates of change at either end are not balanced — one end grows more rapidly and is called the **plus end**, whereas the other end is known as the **minus end**. In cells, the minus ends of microtubules are anchored in structures called **microtubule organizing centers** (MTOCs). The primary MTOC in a cell is called the **centrosome**, and it is usually located adjacent to the nucleus. Microtubules tend to grow out from the centrosome to the plasma membrane. In nondividing cells, microtubule networks radiate out from the centrosome to provide the basic organization of the cytoplasm, including the positioning of organelles.

### What Do Actin Filaments Do?



[Figure 2](#)

The protein actin is abundant in all eukaryotic cells. It was first discovered in skeletal muscle, where actin filaments slide along filaments of another protein called **myosin** to make the cells contract. (In nonmuscle cells, actin filaments are less organized and myosin is much less prominent.) Actin filaments are made up of identical actin proteins arranged in a long spiral chain. Like microtubules, actin filaments have plus and minus ends, with more ATP-powered growth occurring at a filament's plus end (Figure 2).

In many types of cells, networks of actin filaments are found beneath the **cell cortex**, which is the meshwork of membrane-associated proteins that supports and strengthens the plasma membrane. Such networks allow cells to hold — and move — specialized shapes, such as the brush border of microvilli. Actin filaments are also involved in cytokinesis and cell movement (Figure 3).

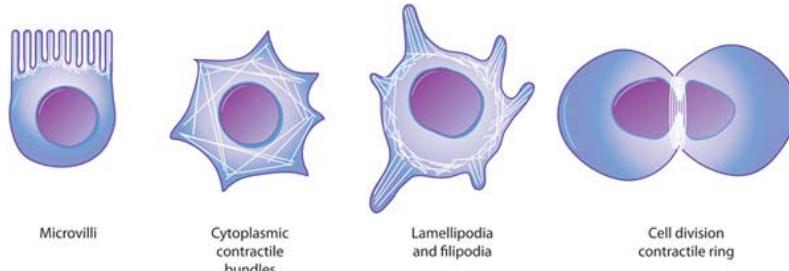


Figure 3: Actin filaments support a variety of structures in a cell.

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### What Do Intermediate Filaments Do?

Intermediate filaments come in several types, but they are generally strong and ropelike. Their functions are primarily mechanical and, as a class, intermediate filaments are less dynamic than actin filaments or microtubules. Intermediate filaments commonly work in tandem with microtubules, providing strength and support for the fragile tubulin structures. All cells have intermediate filaments, but the protein subunits of these structures vary. Some cells have multiple types of intermediate filaments, and some intermediate filaments are associated with specific cell types. For example, neurofilaments are found specifically in neurons (most prominently in the long axons of these cells), desmin filaments are found specifically in muscle cells, and keratins are found specifically in epithelial cells. Other intermediate filaments are distributed more widely. For example, vimentin filaments are found in a broad range of cell types and frequently colocalize with microtubules. Similarly, lamins are found in all cell types, where they form a meshwork that reinforces the inside of the nuclear membrane. Note that intermediate filaments are not polar in the way that actin or tubulin are (Figure 4).

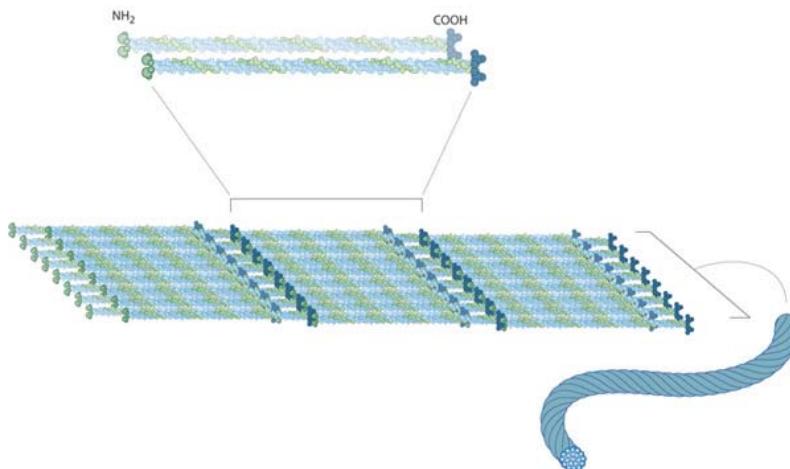


Figure 4: The structure of intermediate filaments

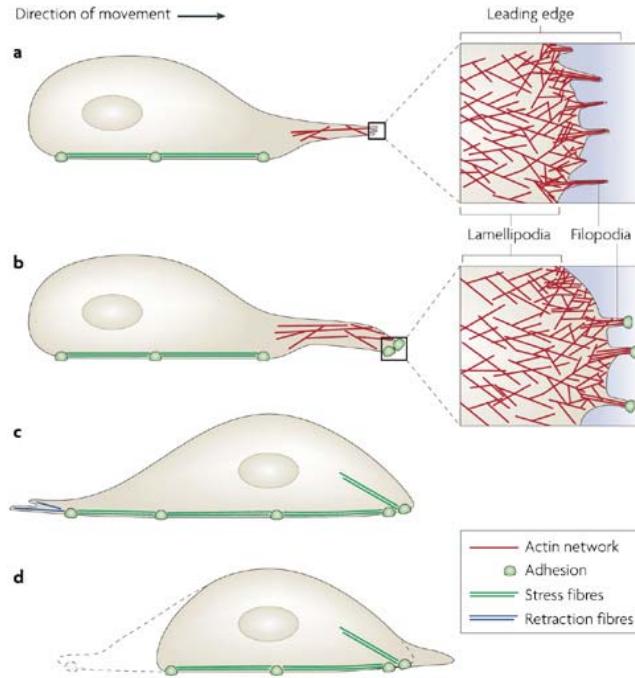
Intermediate filaments are composed of smaller strands in the shape of rods. Eight rods are aligned in a staggered array with another eight rods, and these components all twist together to form the rope-like conformation of an intermediate filament.

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### How Do Cells Move?

Cytoskeletal filaments provide the basis for cell movement. For instance, **cilia** and (eukaryotic) **flagella** move as a result of microtubules sliding along each other. In fact, cross sections of these tail-like cellular extensions show organized arrays of microtubules.

Other cell movements, such as the pinching off of the cell membrane in the final step of cell division (also known as cytokinesis) are produced by the contractile capacity of actin filament networks. Actin filaments are extremely dynamic and can rapidly form and disassemble. In fact, this dynamic action underlies the crawling behavior of cells such as amoebae. At the leading edge of a moving cell, actin filaments are rapidly polymerizing; at its rear edge, they are quickly depolymerizing (Figure 5). A large number of other proteins participate in actin assembly and disassembly as well.



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Figure 5: Cell migration is dependent on different actin filament structures.

(A) In a cell, motility is initiated by an actin-dependent protrusion of the cell's leading edge, which is composed of armlike structures called lamellipodia and filopodia. These protrusive structures contain actin filaments, with elongating barbed ends orientated toward the plasma membrane. (B) During cellular arm extension, the plasma membrane sticks to the surface at the leading edge. (C) Next, the nucleus and the cell body are pushed forward through intracellular contraction forces mediated by stress fibers. (D) Then, retraction fibers pull the rear of the cell forward.

© 2008 Nature Publishing Group Mattila, P.K. & Lappalainen, P. Filopodia: molecular architecture and cellular functions. *Nature Reviews Molecular Cell Biology* 9, 446-454 (2008)  
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## Conclusion

The cytoskeleton of a cell is made up of microtubules, actin filaments, and intermediate filaments. These structures give the cell its shape and help organize the cell's parts. In addition, they provide a basis for movement and cell division.

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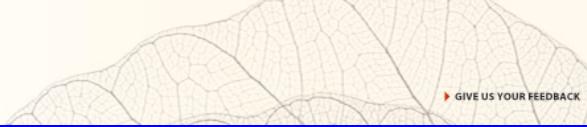
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## Unit 3: How Are Eukaryotic Cells Organized into Smaller Parts?

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### 3.3 The Endoplasmic Reticulum, Golgi Apparatus, and Lysosomes Are Part of an Extensive Endomembrane System in Eukaryotic Cells

Cells have extensive sets of intracellular membranes, which together compose the **endomembrane system**. The endomembrane system was first discovered in the late 1800s when scientist Camillo Golgi noticed that a certain stain selectively marked only some internal cellular membranes. Golgi thought that these intracellular membranes were interconnected, but advances in microscopy and biochemical studies of the various membrane-enclosed organelles later made it clear the organelles in the endomembrane system are separate compartments with specific functions. These structures do exchange membrane material, however, via a special type of transport.

Today, scientists know that the endomembrane system includes the **endoplasmic reticulum (ER)**, **Golgi apparatus**, and **lysosomes**. **Vesicles** also allow the exchange of membrane components with a cell's plasma membrane.

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#### How Are Cell Membranes Synthesized?

Membranes and their constituent proteins are assembled in the ER. This organelle contains the enzymes involved in lipid synthesis, and as lipids are manufactured in the ER, they are inserted into the organelle's own membranes. This happens in part because the lipids are too hydrophobic to dissolve into the cytoplasm.

Similarly, transmembrane proteins have enough hydrophobic surfaces that they are also inserted into the ER membrane while they are still being synthesized. Here, future membrane proteins make their way to the ER membrane with the help of a signal sequence in the newly translated protein. The signal sequence stops translation and directs the ribosomes — which are carrying the unfinished proteins — to dock with ER proteins before finishing their work. Translation then recommences after the signal sequence docks with the ER, and it takes place within the ER membrane. Thus, by the time the protein achieves its final form, it is already inserted into a membrane (Figure 1).

The proteins that will be secreted by a cell are also directed to the ER during translation, where they end up in the **lumen**, the internal cavity, where they are then packaged for vesicular release from the cell. The hormones insulin and erythropoietin (EPO) are both examples of vesicular proteins.

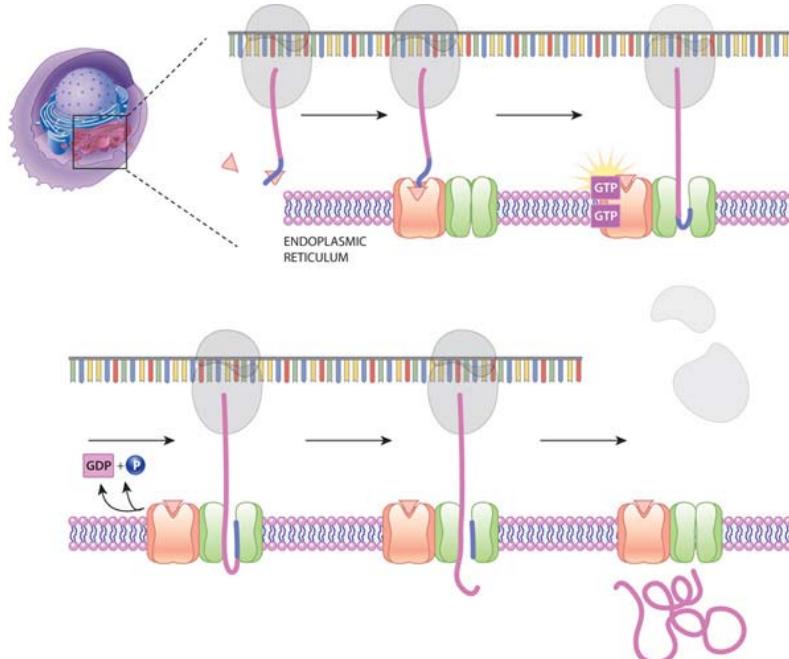


Figure 1: Co-translational synthesis

A signal sequence on a growing protein will bind with a signal recognition particle (SRP). This slows protein synthesis. The SRP then binds to a location on the surface of the nearby ER. Then, the SRP is released, and the protein-ribosome complex is at the correct location for movement of the protein through a translocation channel.

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## How Are Organelle Membranes Maintained?

The ER, [Golgi apparatus](#), and lysosomes are all members of a network of membranes, but they are not continuous with one another. Therefore, the membrane lipids and proteins that are synthesized in the ER must be transported through the network to their final destination in membrane-bound [vesicles](#). Cargo-bearing vesicles pinch off of one set of membranes and travel along microtubule tracks to the next set of membranes, where they fuse with these structures. Trafficking occurs in both directions; the forward direction takes vesicles from the site of synthesis to the Golgi apparatus and next to a cell's lysosomes or plasma membrane. Vesicles that have released their cargo return via the reverse direction. The proteins that are synthesized in the ER have, as part of their amino acid sequence, a signal that directs them where to go, much like an address directs a letter to its destination.

Soluble proteins are carried in the lumens of vesicles. Any proteins that are destined for a lysosome are delivered to the lysosome interior when the vesicle that carries them fuses with the lysosomal membrane and joins its contents. In contrast, the proteins that will be secreted by a cell, such as insulin and EPO, are held in storage vesicles. When signaled by the cell, these vesicles fuse with the plasma membrane and release their contents into the extracellular space.

## What Does the Golgi Apparatus Do?

The Golgi apparatus functions as a molecular assembly line in which membrane proteins undergo extensive post-translational modification. Many Golgi reactions involve the addition of sugar residues to membrane proteins and secreted proteins. The carbohydrates that the Golgi attaches to membrane proteins are often quite complex, and their synthesis requires multiple steps.

In electron micrographs, the Golgi apparatus looks like a set of flattened sacs. Vesicles that bud off from the ER fuse with the closest Golgi membranes, called the **cis-Golgi**. Molecules then travel through the Golgi apparatus via vesicle transport until they reach the end of the assembly line at the farthest sacs from the ER — called the **trans-Golgi**. At each workstation along the assembly line, Golgi enzymes catalyze distinct reactions. Later, as vesicles of membrane lipids and proteins bud off from the trans-Golgi, they are directed to their appropriate destinations — either lysosomes, storage vesicles, or the plasma membrane (Figure 2).

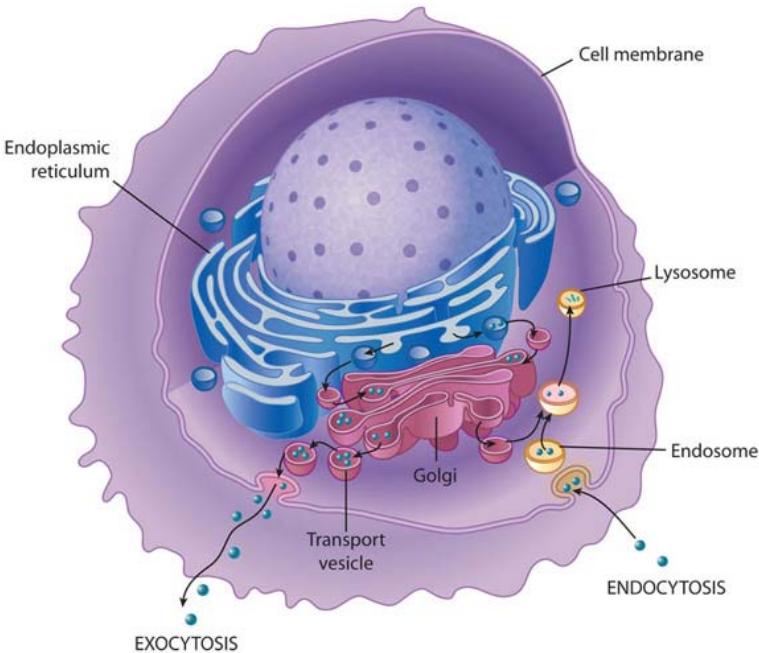
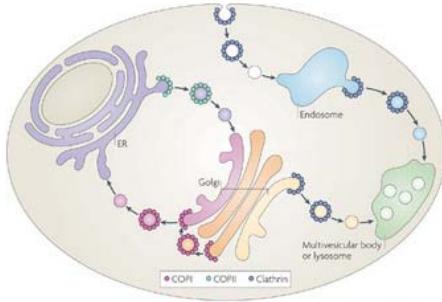


Figure 2: Membrane transport into and out of the cell

Transport of molecules within a cell and out of the cell requires a complex endomembrane system. Endocytosis occurs when the cell membrane engulfs particles (dark blue) outside the cell, draws the contents in, and forms an intracellular vesicle called an endosome. This vesicle travels through the cell, and its contents are digested as it merges with vesicles containing enzymes from the Golgi. The vesicle is then known as a lysosome when its contents have been digested by the cell. Exocytosis is the process of membrane transport that releases cellular contents outside of the cell. Here, a transport vesicle from the Golgi or elsewhere in the cell merges its membrane with the plasma membrane and releases its contents. In this way, membranes are continually recycled and reused for different purposes throughout the cell. Membrane transport also occurs between the endoplasmic reticulum and the Golgi.

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## What Do Lysosomes Do?



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Figure 3: Pathways of vesicular transport by the specific vesicle-coating proteins

A protein called coat protein II (COPII; green) forms vesicles that transport from the endoplasmic reticulum (ER) to the Golgi. A different protein called coat protein I (COPI; red) forms vesicles for transport in the other direction, from the Golgi to the ER. COPI also forms vesicles for intra-Golgi transport. Clathrin (blue) forms multiple complexes based on its association with different adaptor proteins (APs). Clathrin that is associated with AP1 and AP3 forms vesicles for transport from the trans-Golgi network to the later endosomal compartments, and also for transport that emanates from the early endosomal compartments. Clathrin that is associated with AP2 forms vesicles from the plasma membrane that transport to the early endosomes.

© 2009 Nature Publishing Group Hsu, V. W., Lee, S. Y., & Yang,

J. S. The evolving understanding of COPI vesicle formation. *Nature*

*Reviews Molecular Cell Biology* 10, 360-364 (2009)

doi:10.1038/nrm2663. All rights reserved.

Lysosomes break down macromolecules into their constituent parts, which are then recycled. These membrane-bound organelles contain a variety of enzymes called **hydrolases** that can digest proteins, nucleic acids, lipids, and complex sugars. The lumen of a lysosome is more acidic than the cytoplasm. This environment activates the hydrolases and confines their destructive work to the lysosome. In plants and fungi, lysosomes are called acidic [vacuoles](#).

Lysosomes are formed by the fusion of vesicles that have budded off from the trans-Golgi. The sorting system recognizes address sequences in the hydrolytic enzymes and directs them to growing lysosomes. In addition, vesicles that bud off from the plasma membrane via **endocytosis** are also sent to lysosomes, where their contents — fluid and molecules from the extracellular environment — are processed. The process of endocytosis is an example of reverse vesicle trafficking, and it plays an important role in nutrition and immunity as well as membrane recycling. Lysosomes break down and thus disarm many kinds of foreign and potentially pathogenic materials that get into the cell through such extracellular sampling (Figure 3).

## Conclusion

The endomembrane system of eukaryotic cells consists of the ER, the Golgi apparatus, and lysosomes. Membrane components, including proteins and lipids, are exchanged among these organelles and the plasma membrane via vesicular transport with the help of molecular tags that direct specific components to their proper destinations.

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### 3.4 Mitochondria Are Independently Replicating Organelles That Supply Much of the Energy of the Cell

Mitochondria are unusual organelles. They act as the power plants of the cell, are surrounded by two membranes, and have their own genome. They also divide independently of the cell in which they reside, meaning mitochondrial replication is not coupled to cell division. Some of these features are holdovers from the ancient ancestors of mitochondria, which were likely free-living prokaryotes.

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#### What Is the Origin of Mitochondria?

Mitochondria are thought to have originated from an ancient symbiosis that resulted when a nucleated cell engulfed an aerobic prokaryote. The engulfed cell came to rely on the protective environment of the host cell, and, conversely, the host cell came to rely on the engulfed prokaryote for energy production. Over time, the descendants of the engulfed prokaryote developed into mitochondria, and the work of these organelles — using oxygen to create energy — became critical to eukaryotic evolution (Figure 1).

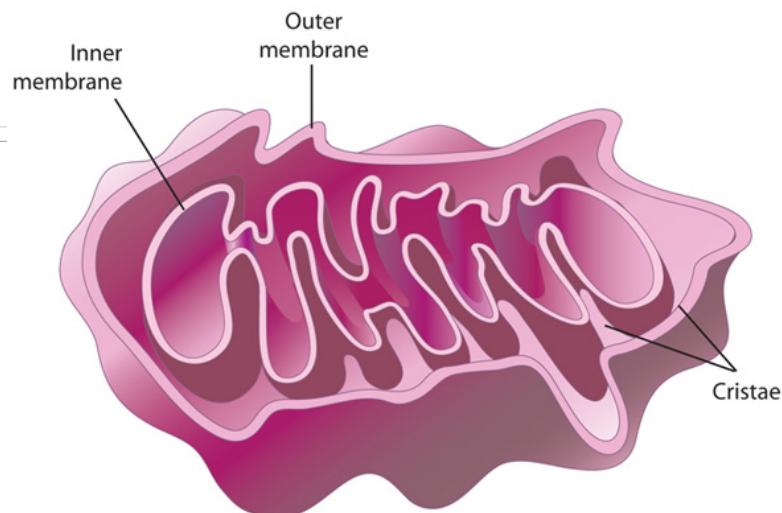


Figure 1: A mitochondrion

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Modern mitochondria have striking similarities to some modern prokaryotes, even though they have diverged significantly since the ancient symbiotic event. For example, the inner mitochondrial membrane contains electron transport proteins like the plasma membrane of prokaryotes, and mitochondria also have their own prokaryote-like circular genome. One difference is that these organelles are thought to have lost most of the genes once carried by their prokaryotic ancestor. Although present-day mitochondria do synthesize a few of their own proteins, the vast majority of the proteins they require are now encoded in the nuclear genome.

#### What Is the Purpose of a Mitochondrial Membranes?

As previously mentioned, mitochondria contain two major membranes. The outer mitochondrial membrane fully surrounds the inner membrane, with a small **intermembrane space** in between. The outer membrane has many protein-based pores that are big enough to allow the passage of ions and molecules as large as a small protein. In contrast, the inner membrane has much more restricted permeability, much like the plasma membrane of a cell. The inner membrane is also loaded with proteins involved in electron transport and ATP synthesis. This membrane surrounds the **mitochondrial matrix**, where the citric acid cycle produces the electrons that travel from one protein complex to the next in the inner membrane. At the end of this electron transport chain, the final electron acceptor is oxygen, and this ultimately forms water ( $H_2O$ ). At the same time, the electron transport chain produces ATP. (This is why the process is called oxidative phosphorylation.)

During electron transport, the participating protein complexes push protons from the matrix out to the intermembrane space. This creates a concentration gradient of protons that another protein complex, called **ATP synthase**, uses to power synthesis of the energy carrier molecule ATP (Figure 2).

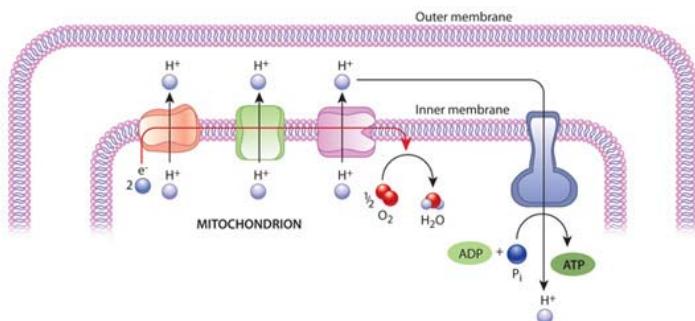


Figure 2: The electrochemical proton gradient and ATP synthase

At the inner mitochondrial membrane, a high energy electron is passed along an electron transport chain. The energy released pumps hydrogen out to the matrix space between the mitochondrial membranes. The gradient created by this high concentration of hydrogen outside of the inner membrane drives hydrogen back through the inner membrane, through ATP synthase. As this happens, the enzymatic activity of ATP synthase synthesizes ATP from ADP.

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### Is the Mitochondrial Genome Still Functional?

**Mitochondrial genomes** are very small and show a great deal of variation as a result of divergent evolution. Mitochondrial genes that have been conserved across evolution include rRNA genes, tRNA genes, and a small number of genes that encode proteins involved in electron transport and ATP synthesis. The mitochondrial genome retains similarity to its prokaryotic ancestor, as does some of the machinery mitochondria use to synthesize proteins. In fact, mitochondrial rRNAs more closely resemble bacterial rRNAs than the eukaryotic rRNAs found in cell cytoplasm. In addition, some of the codons that mitochondria use to specify amino acids differ from the standard eukaryotic codons.

Still, the vast majority of mitochondrial proteins are synthesized from nuclear genes and transported into the mitochondria. These include the enzymes required for the citric acid cycle, the proteins involved in DNA replication and transcription, and ribosomal proteins. The protein complexes of the respiratory chain are a mixture of proteins encoded by mitochondrial genes and proteins encoded by nuclear genes. Proteins in both the outer and inner mitochondrial membranes help transport newly synthesized, unfolded proteins from the cytoplasm into the matrix, where folding ensues (Figure 3).

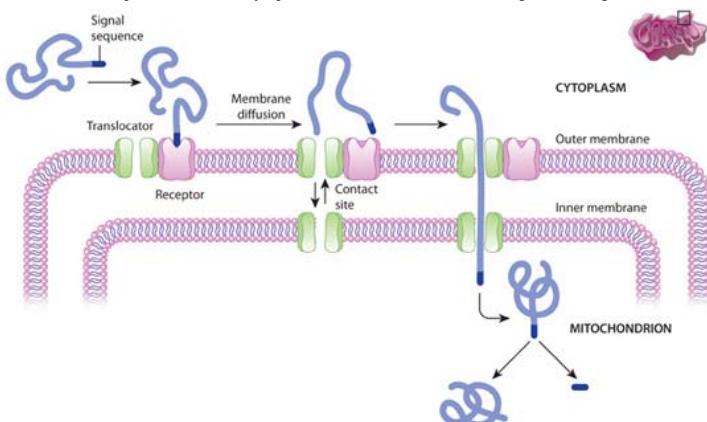


Figure 3: Protein import into a mitochondrion

A signal sequence at the tip of a protein (blue) recognizes a receptor protein (pink) on the outer mitochondrial membrane and sticks to it. This causes diffusion of the tethered protein and its receptor through the membrane to a contact site, where translocator proteins line up (green). When at this contact site, the receptor protein hands off the tethered protein to the translocator protein, which then channels the unfolded protein past both the inner and outer mitochondrial membranes.

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### How Many Mitochondria Do Cells Have?

Mitochondria cannot be made "from scratch" because they need both mitochondrial and nuclear gene products. These organelles replicate by dividing in two, using a process similar to the simple, asexual form of cell division employed by bacteria. Video microscopy shows that mitochondria are incredibly dynamic. They are constantly dividing, fusing, and changing shape. Indeed, a single mitochondrion may contain multiple copies of its genome at any given time. Logically, mitochondria multiply when the energy needs of a cell increase. Therefore, power-hungry cells have more mitochondria than cells with lower energy needs. For example, repeatedly stimulating a muscle cell will spur the production of more mitochondria in that cell, to keep up with energy demand.

### Conclusion

Mitochondria, the so-called "powerhouses" of cells, are unusual organelles in that they are surrounded by a double membrane and retain their own small genome. They also divide independently of the cell cycle by simple fission. Mitochondrial division

is stimulated by energy demand, so cells with an increased need for energy contain greater numbers of these organelles than cells with lower energy needs.

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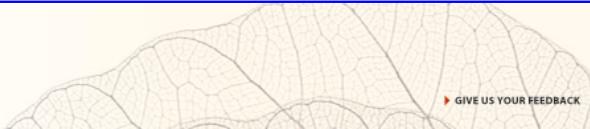
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80%

100%

### 3.5 Plant Cells Have Chloroplasts and Other Structures Not Present in Animal Cells

Plant cells have several structures not found in other eukaryotes. In particular, organelles called [chloroplasts](#) allow plants to capture the energy of the Sun in energy-rich molecules; cell walls allow plants to have rigid structures as varied as wood trunks and supple leaves; and vacuoles allow plant cells to change size.

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#### What Is the Origin of Chloroplasts?

Like mitochondria, chloroplasts likely originated from an ancient symbiosis, in this case when a nucleated cell engulfed a photosynthetic prokaryote. Indeed, chloroplasts resemble modern cyanobacteria, which remain similar to the cyanobacteria of 3 million years ago. However, the evolution of photosynthesis goes back even further, to the earliest cells that evolved the ability to capture light energy and use it to produce energy-rich molecules. When these organisms developed the ability to split water molecules and use the electrons from these molecules, photosynthetic cells started generating oxygen — an event that had dramatic consequences for the evolution of all living things on Earth (Figure 1).

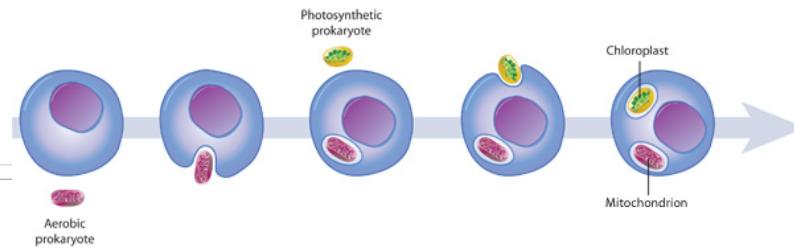


Figure 1: The origin of mitochondria and chloroplasts

Mitochondria and chloroplasts likely evolved from engulfed prokaryotes that once lived as independent organisms. At some point, a eukaryotic cell engulfed an aerobic prokaryote, which then formed an endosymbiotic relationship with the host eukaryote, gradually developing into a mitochondrion. Eukaryotic cells containing mitochondria then engulfed photosynthetic prokaryotes, which evolved to become specialized chloroplast organelles.

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Today, chloroplasts retain small, circular genomes that resemble those of cyanobacteria, although they are much smaller. (Mitochondrial genomes are even smaller than the genomes of chloroplasts.) Coding sequences for the majority of chloroplast proteins have been lost, so these proteins are now encoded by the nuclear genome, synthesized in the cytoplasm, and transported from the cytoplasm into the chloroplast.

#### What Is the Function of Chloroplast Membranes?

Like mitochondria, chloroplasts are surrounded by two membranes. The outer membrane is permeable to small organic molecules, whereas the inner membrane is less permeable and studded with transport proteins. The innermost matrix of chloroplasts, called the stroma, contains metabolic enzymes and multiple copies of the chloroplast genome.

Chloroplasts also have a third internal membrane called the thylakoid membrane, which is extensively folded and appears as stacks of flattened disks in electron micrographs. The thylakoids contain the **light-harvesting complex**, including pigments such as chlorophyll, as well as the electron transport chains used in photosynthesis (Figure 2).

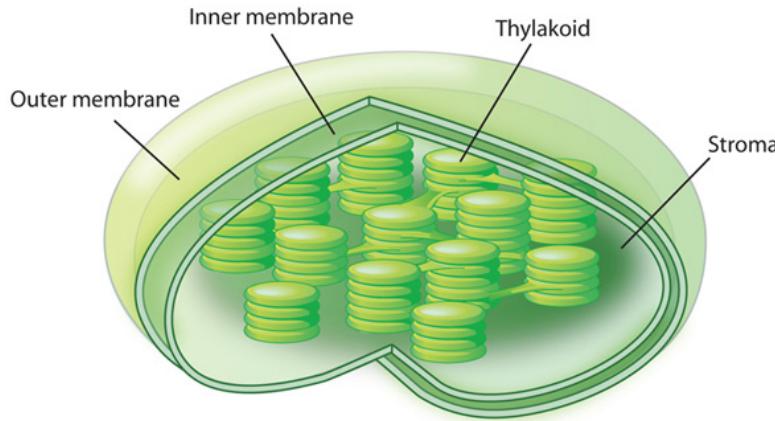


Figure 2: Structure of a chloroplast  
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### What Is the Cell Wall?

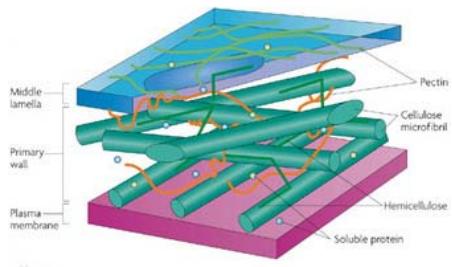


Figure 3: Plant plasma membrane and cell-wall structure  
A plant cell wall contains a variety of components.  
There are three major layers: a plasma membrane, a primary cell wall, and a middle lamella. These layers contain cellulose microfibrils, hemicellulose, pectin, lignin, and soluble proteins.

© 2008 Nature Publishing Group Sticklen, M. B. Plant genetic engineering for biofuel production: towards affordable cellulosic ethanol. *Nature Reviews Genetics* 9, 433-443 (2008) doi:10.1038/nrg2336.  
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Besides the presence of chloroplasts, another major difference between plant and animal cells is the presence of a **cell wall**. The cell wall surrounds the plasma membrane of plant cells and provides tensile strength and protection against mechanical and osmotic stress. It also allows cells to develop **turgor pressure**, which is the pressure of the cell contents against the cell wall. Plant cells have high concentrations of molecules dissolved in their cytoplasm, which causes water to come into the cell under normal conditions and makes the cell's central **vacuole** swell and press against the cell wall. With a healthy supply of water, turgor pressure keeps a plant from wilting. In drought, a plant may wilt, but its cell walls help maintain the structural integrity of its stems, leaves, and other structures, despite a shrinking, less turgid vacuole.

Plant cell walls are primarily made of **cellulose**, which is the most abundant macromolecule on Earth. Cellulose fibers are long, linear polymers of hundreds of glucose molecules. These fibers aggregate into bundles of about 40, which are called **microfibrils**. Microfibrils are embedded in a hydrated network of other polysaccharides. The cell wall is assembled in place. Precursor components are synthesized inside the cell and then assembled by enzymes associated with the cell membrane (Figure 3).

### What Are Vacuoles?

Plant cells additionally possess large, fluid-filled vesicles called **vacuoles** within their cytoplasm. Vacuoles typically compose about 30 percent of a cell's volume, but they can fill as much as 90 percent of the intracellular space. Plant cells use vacuoles to adjust their size and turgor pressure. Vacuoles usually account for changes in cell size when the cytoplasmic volume stays constant.

Some vacuoles have specialized functions, and plant cells can have more than one type of vacuole. Vacuoles are related to lysosomes and share some functions with these structures; for instance, both contain degradative enzymes for breaking down macromolecules. Vacuoles can also serve as storage compartments for nutrients and metabolites. For instance, proteins are stored in the vacuoles of seeds, and rubber and opium are metabolites that are stored in plant vacuoles.

### Conclusion

Plant cells have certain distinguishing features, including chloroplasts, cell walls, and intracellular vacuoles. Photosynthesis takes place in chloroplasts; cell walls allow plants to have strong, upright structures; and vacuoles help regulate how cells handle water and storage of other molecules.

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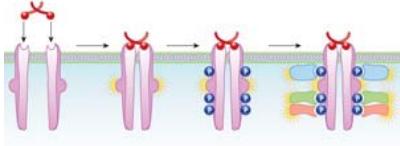
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## Unit 4: How Do Cells Sense Their Environment?

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Cells may be self-sustaining units of life, but they don't live in isolation. Their survival depends on receiving and processing information from the outside environment, whether that information pertains to the availability of nutrients, changes in temperature, or variations in light levels.

Cells also can communicate with one another — and change their own internal workings in response — by way of a variety of chemical and mechanical signals. In multicellular organisms, cell signaling allows for specialization of groups of cells. Multiple cell types can then join together to form tissues, such as muscle, blood, and brain tissue. In single-celled organisms, signaling allows populations of cells to coordinate with one another and work as a team to accomplish tasks no single cell could carry out on its own.

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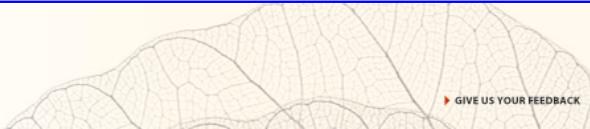
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## Unit 4: How Do Cells Sense Their Environment?

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## 4.1 Cells Receive and Process a Diverse Set of Chemical Signals and Sensory Stimuli

In order to respond to changes in their immediate environment, cells must be able to receive and process signals that originate outside their borders. Individual cells often receive many signals simultaneously, and they then integrate the information they receive into a unified action plan. But cells aren't just targets. They also send out messages to other cells both near and far.

### What Kind of Signals Do Cells Receive?

Most cell signals are chemical in nature. For example, prokaryotic organisms have sensors that detect nutrients and help them navigate toward food sources. In multicellular organisms, growth factors, hormones, neurotransmitters, and extracellular matrix components are some of the many types of chemical signals cells use. These substances can exert their effects locally, or they might travel over long distances. For instance, **neurotransmitters** are a class of short-range signaling molecules that travel across the tiny spaces between adjacent neurons or between neurons and muscle cells. Other signaling molecules must move much farther to reach their targets. One example is follicle-stimulating hormone, which travels from the mammalian brain to the ovary, where it triggers egg release.

Some cells also respond to mechanical stimuli. For example, sensory cells in the skin respond to the pressure of touch, whereas similar cells in the ear react to the movement of sound waves. In addition, specialized cells in the human vascular system detect changes in blood pressure — information that the body uses to maintain a consistent cardiac load.

### How Do Cells Recognize Signals?

Cells have proteins called **receptors** that bind to signaling molecules and initiate a physiological response. Different receptors are specific for different molecules. Dopamine receptors bind dopamine, insulin receptors bind insulin, nerve growth factor receptors bind nerve growth factor, and so on. In fact, there are hundreds of receptor types found in cells, and varying cell types have different populations of receptors. Receptors can also respond directly to light or pressure, which makes cells sensitive to events in the atmosphere.

Receptors are generally transmembrane proteins, which bind to signaling molecules outside the cell and subsequently transmit the signal through a sequence of molecular switches to internal signaling pathways. Membrane receptors fall into three major classes: G-protein-coupled receptors, ion channel receptors, and enzyme-linked receptors. The names of these receptor classes refer to the mechanism by which the receptors transform external signals into internal ones — via protein action, ion channel opening, or enzyme activation, respectively. Because membrane receptors interact with both extracellular signals and molecules within the cell, they permit signaling molecules to affect cell function without actually entering the cell. This is important because most signaling molecules are either too big or too charged to cross a cell's plasma membrane (Figure 1).

Not all receptors exist on the exterior of the cell. Some exist deep inside the cell, or even in the nucleus. These receptors typically bind to molecules that can pass through the plasma membrane, such as gases like nitrous oxide and steroid hormones like estrogen.

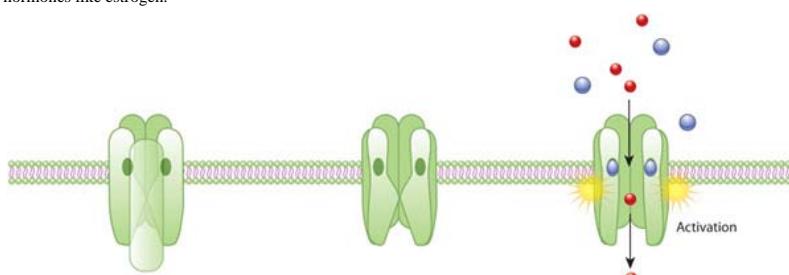


Figure 1: An example of ion channel activation

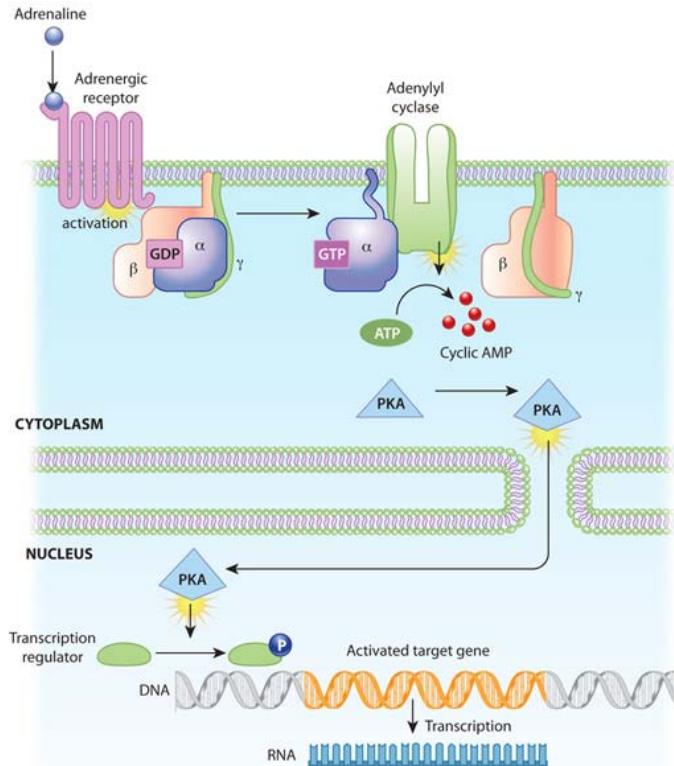
An acetylcholine receptor (green) forms a gated ion channel in the plasma membrane. This receptor is a membrane protein with an aqueous pore, meaning it allows soluble materials to travel across the plasma membrane when open. When no external signal is present, the pore is closed (center). When acetylcholine molecules (blue) bind to the receptor, this triggers a conformational change that opens the aqueous pore and allows ions (red) to flow into the cell.

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### How Do Cells Respond to Signals?

Once a receptor protein receives a signal, it undergoes a conformational change, which in turn launches a series of biochemical reactions within the cell. These intracellular signaling pathways, also called **signal transduction cascades**, typically amplify the message, producing multiple intracellular signals for every one receptor that is bound. Activation of receptors can trigger the synthesis of small molecules called **second messengers**, which initiate and coordinate intracellular signaling pathways. For example, **cyclic AMP** (cAMP) is a common second messenger involved in signal transduction cascades. (In fact, it was the first second messenger ever discovered.) cAMP is synthesized from ATP by the enzyme **adenylyl cyclase**, which resides in the cell membrane. The activation of adenylyl cyclase can result in the manufacture of hundreds or even thousands of cAMP molecules. These cAMP molecules activate the enzyme **protein kinase A** (PKA), which then **phosphorylates** multiple protein substrates by attaching phosphate groups to them. Each step in the cascade further amplifies the initial signal, and the phosphorylation reactions mediate both short- and long-term responses in the cell (Figure 2). How does cAMP stop signaling? It is degraded by the enzyme phosphodiesterase.

Other examples of second messengers include **diacylglycerol** (DAG) and **inositol 1,4,5-triphosphate** (IP<sub>3</sub>), which are both produced by the enzyme **phospholipase**, also a membrane protein. IP<sub>3</sub> causes the release of Ca<sup>2+</sup> — yet another second messenger — from intracellular stores. Together, DAG and Ca<sup>2+</sup> activate another enzyme called **protein kinase C** (PKC).



**Figure 2:** An example of a signal transduction cascade involving cyclic AMP  
The binding of adrenaline to an adrenergic receptor initiates a cascade of reactions inside the cell. The signal transduction cascade begins when adenylyl cyclase, a membrane-bound enzyme, is activated by G-protein molecules associated with the adrenergic receptor. Adenylyl cyclase creates multiple cyclic AMP molecules, which fan out and activate protein kinases (PKA, in this example). Protein kinases can enter the nucleus and affect transcription.

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## How Do Signals Affect Cell Function?

Protein kinases such as PKA and PKC catalyze the transfer of phosphate groups from ATP molecules to protein molecules. Within proteins, the amino acids serine, threonine, and tyrosine are especially common sites for phosphorylation. These phosphorylation reactions control the activity of many enzymes involved in intracellular signaling pathways. Specifically, the addition of phosphate groups causes a conformational change in the enzymes, which can either activate or inhibit the enzyme activity. Then, when appropriate, protein phosphatases remove the phosphate groups from the enzymes, thereby reversing the effect on enzymatic activity.

Phosphorylation allows for intricate control of protein function. Phosphate groups can be added to multiple sites in a single protein, and a single protein may in turn be the substrate for multiple kinases and phosphatases.

At any one time, a cell is receiving and responding to numerous signals, and multiple signal transduction pathways are operating in its cytoplasm. Many points of intersection exist among these pathways. For instance, a single second messenger

or protein kinase might play a role in more than one pathway. Through this network of signaling pathways, the cell is constantly integrating all the information it receives from its external environment.

## Conclusion

Cells typically receive signals in chemical form via various signaling molecules. When a signaling molecule joins with an appropriate receptor on a cell surface, this binding triggers a chain of events that not only carries the signal to the cell interior, but amplifies it as well. Cells can also send signaling molecules to other cells. Some of these chemical signals — including neurotransmitters — travel only a short distance, but others must go much farther to reach their targets.

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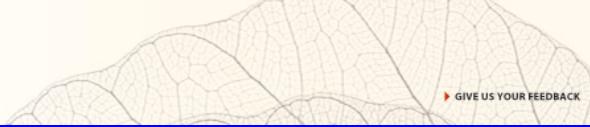
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## 4.2 G-Protein-Coupled Receptors Play Many Different Roles in Eukaryotic Cell Signaling

**G-protein-coupled receptors** (GPCRs) are the largest and most diverse group of membrane receptors in eukaryotes. These cell surface receptors act like an inbox for messages in the form of light energy, peptides, lipids, sugars, and proteins. Such messages inform cells about the presence or absence of life-sustaining light or nutrients in their environment, or they convey information sent by other cells.

GPCRs play a role in an incredible array of functions in the human body, and increased understanding of these receptors has greatly affected modern medicine. In fact, researchers estimate that between one-third and one-half of all marketed drugs act by binding to GPCRs.

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### What Do GPCRs Look Like?

GPCRs bind a tremendous variety of signaling molecules, yet they share a common architecture that has been conserved over the course of evolution. Many present-day eukaryotes — including animals, plants, fungi, and protozoa — rely on these receptors to receive information from their environment. For example, simple eukaryotes such as yeast have GPCRs that sense glucose and mating factors. Not surprisingly, GPCRs are involved in considerably more functions in multicellular organisms. Humans alone have nearly 1,000 different GPCRs, and each one is highly specific to a particular signal.

GPCRs consist of a single polypeptide that is folded into a globular shape and embedded in a cell's plasma membrane. Seven segments of this molecule span the entire width of the membrane — explaining why GPCRs are sometimes called **seven-transmembrane receptors** — and the intervening portions loop both inside and outside the cell. The extracellular loops form part of the pockets at which signaling molecules bind to the GPCR.

### What Do GPCRs Do?

As their name implies, GPCRs interact with G proteins in the plasma membrane. When an external signaling molecule binds to a GPCR, it causes a conformational change in the GPCR. This change then triggers the interaction between the GPCR and a nearby G protein.

**G proteins** are specialized proteins with the ability to bind the nucleotides guanosine triphosphate (GTP) and guanosine diphosphate (GDP). Some G proteins, such as the signaling protein Ras, are small proteins with a single subunit. However, the G proteins that associate with GPCRs are **heterotrimeric**, meaning they have three different subunits: an alpha subunit, a beta subunit, and a gamma subunit. Two of these subunits — alpha and gamma — are attached to the plasma membrane by lipid anchors (Figure 1).

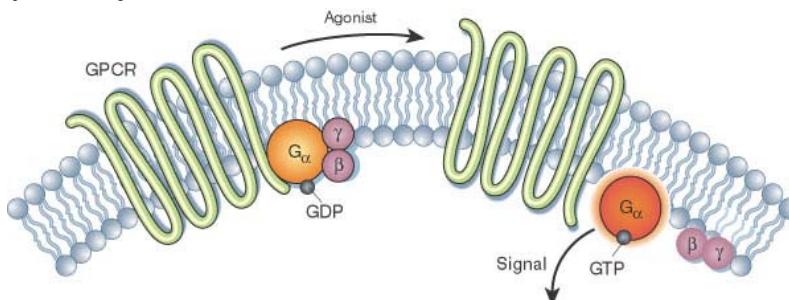


Figure 1: Activation of the G alpha subunit of a G-protein-coupled receptor

In unstimulated cells, the state of G alpha (orange circles) is defined by its interaction with GDP, G beta-gamma (purple circles), and a G-protein-coupled receptor (GPCR; light green loops). Upon receptor stimulation by a ligand called an agonist, the state of the receptor changes. G alpha dissociates from the receptor and G beta-gamma, and GTP is exchanged for the bound GDP, which leads to G alpha activation. G alpha then goes on to activate other molecules in the cell.

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A G protein alpha subunit binds either GTP or GDP depending on whether the protein is active (GTP) or inactive (GDP). In the absence of a signal, GDP attaches to the alpha subunit, and the entire G protein-GDP complex binds to a nearby GPCR. This arrangement persists until a signaling molecule joins with the GPCR. At this point, a change in the conformation of the GPCR activates the G protein, and GTP physically replaces the GDP bound to the alpha subunit. As a result, the G protein subunits dissociate into two parts: the GTP-bound alpha subunit and a beta-gamma dimer. Both parts remain anchored to the plasma membrane, but they are no longer bound to the GPCR, so they can now diffuse laterally to interact with other

membrane proteins. G proteins remain active as long as their alpha subunits are joined with GTP. However, when this GTP is hydrolyzed back to GDP, the subunits once again assume the form of an inactive heterotrimer, and the entire G protein reassociates with the now-inactive GPCR. In this way, G proteins work like a switch — turned on or off by signal-receptor interactions on the cell's surface.

Whenever a G protein is active, both its GTP-bound alpha subunit and its beta-gamma dimer can relay messages in the cell by interacting with other membrane proteins involved in signal transduction. Specific targets for activated G proteins include various enzymes that produce second messengers, as well as certain ion channels that allow ions to act as second messengers. Some G proteins stimulate the activity of these targets, whereas others are inhibitory. Vertebrate genomes contain multiple genes that encode the alpha, beta, and gamma subunits of G proteins. The many different subunits encoded by these genes combine in multiple ways to produce a diverse family of G proteins (Figure 2).

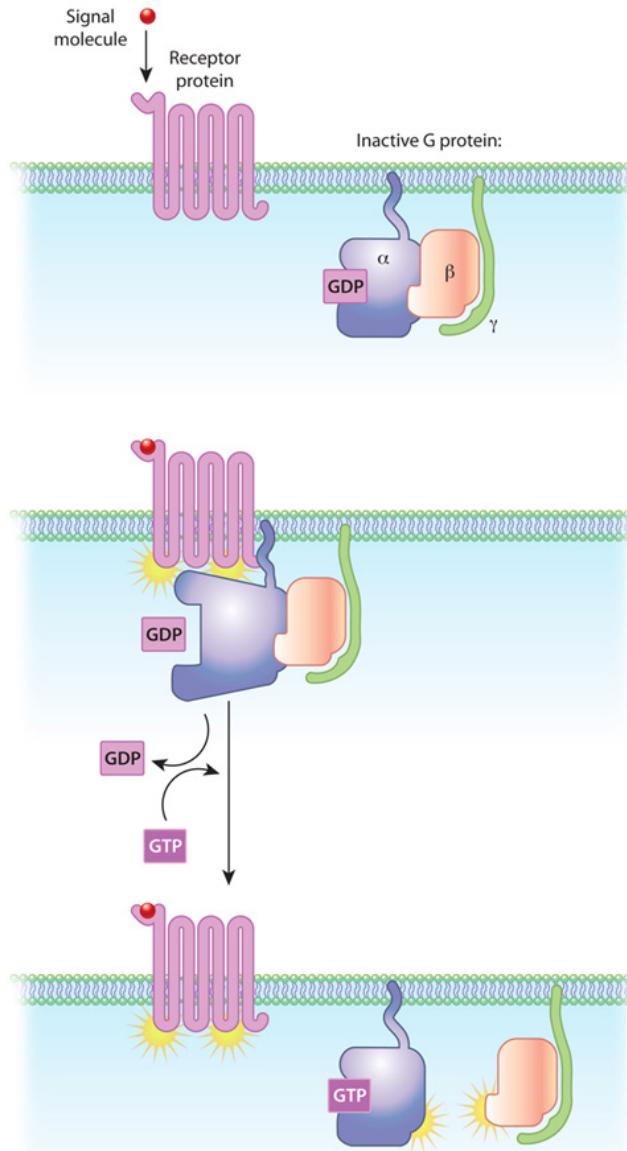


Figure 2: The relationships of G proteins to the plasma membrane

In this diagram of G-protein-coupled receptor activation, the alpha, beta, and gamma subunits are shown with distinct relationships to the plasma membrane. After exchange of GDP with GTP on the alpha subunit, both the alpha subunit and the beta-gamma complex may interact with other molecules to promote signaling cascades. Note that both the alpha subunit and the beta-gamma complex remain tethered to the plasma membrane while they are activated. These activated subunits can act on ion channels in the cell membrane, as well as cellular enzymes and second messenger molecules that travel around the cell.

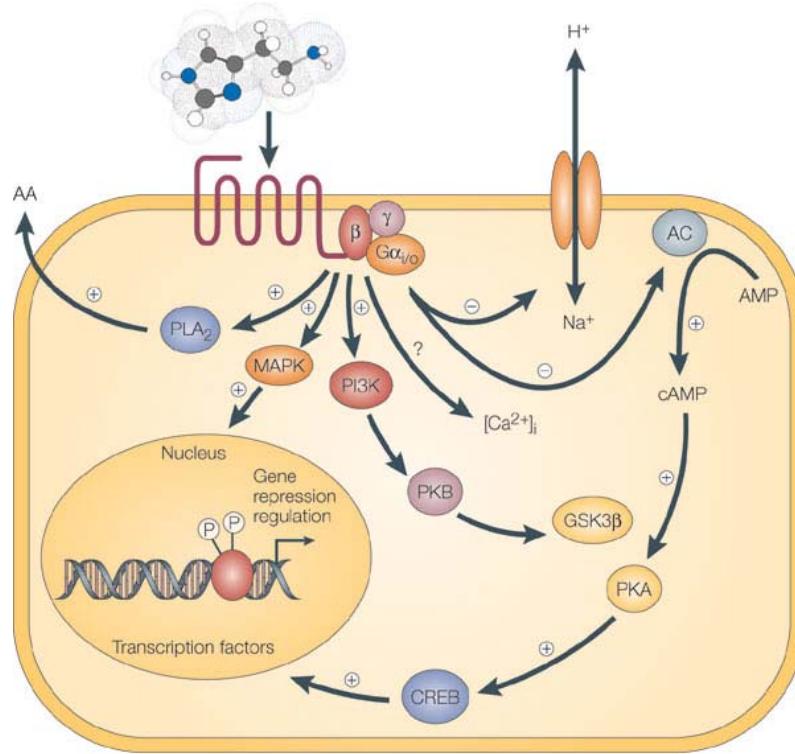
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### What Second Messengers Do GPCR Signals Trigger in Cells?

Activation of a single G protein can affect the production of hundreds or even thousands of second messenger molecules. (Recall that second messengers — such as cyclic AMP [cAMP], diacylglycerol [DAG], and inositol 1, 4, 5-triphosphate [IP3] — are small molecules that initiate and coordinate intracellular signaling pathways.) One especially common target of activated G proteins is adenylyl cyclase, a membrane-associated enzyme that, when activated by the GTP-bound alpha

subunit, catalyzes synthesis of the second messenger cAMP from molecules of ATP. In humans, cAMP is involved in responses to sensory input, hormones, and nerve transmission, among others.

Phospholipase C is another common target of activated G proteins. This membrane-associated enzyme catalyzes the synthesis of not one, but two second messengers — DAG and IP<sub>3</sub> — from the membrane lipid phosphatidyl inositol. This particular pathway is critical to a wide variety of human bodily processes. For instance, thrombin receptors in platelets use this pathway to promote blood clotting (Figure 3).



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Figure 3: Signaling cascades within a cell can interact to affect multiple molecules in the cell, leading to secretion of substances from the cell, ion channel opening, and transcription.

The seven-transmembrane protein receptor in the plasma membrane activates a pathway that involves G proteins as well as cAMP-related pathways that modulate cellular signaling. Activated G alpha proteins inhibit (-) adenylyl cyclase (AC, on the right), the enzyme that induces formation of cAMP, which in turn results in the activation of protein kinase A (PKA). This in turn activates a molecule called cAMP-responsive element-binding protein (CREB), which modulates gene transcription. Gα proteins can also have a variety of other effects, shown at the left. These include mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways. Activation of the enzyme phospholipase A2 (PLA<sub>2</sub>) may also occur, which induces the release of arachidonic acid (AA), as well as inhibition of the Na<sup>+</sup>/H<sup>+</sup> exchanger in the plasma membrane, and the lowering of intracellular Ca<sup>2+</sup> levels (exact mechanism unknown, ?). Subsequent activation of the MAPK and PI3K pathways results in the phosphorylation of extracellular signal-regulated kinases (ERKs) and protein kinase B (PKB), respectively. Activated PKB will subsequently phosphorylate and thereby inhibit the action of glycogen synthase kinase 3beta (GSK3 $\beta$ ), a major kinase in the brain.

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*Nature Reviews Drug Discovery* 4, 107-120 (2005) doi:10.1038/nrd1631. All rights reserved.

## Conclusion

GPCRs are a large family of cell surface receptors that respond to a variety of external signals. Binding of a signaling molecule to a GPCR results in G protein activation, which in turn triggers the production of any number of second messengers. Through this sequence of events, GPCRs help regulate an incredible range of bodily functions, from sensation to growth to hormone responses.

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### 4.3 Ion Channel Receptors Generate Electrical Signals in Response to Chemical Signals

Certain cells, commonly called **excitable cells**, are unique because of their ability to generate electrical signals. Although several types of excitable cells exist — including neurons, muscle cells, and touch receptor cells — all of them use ion channel receptors to convert chemical or mechanical messages into electrical signals.

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Like all cells, an excitable cell maintains a different concentration of ions in its cytoplasm than exists in its extracellular environment. Together, these concentration differences create a small electrical potential across the plasma membrane. Then, when conditions are right, specialized channels in the plasma membrane open and allow rapid ion movement into or out of the cell, and this movement creates an electrical signal. But what do these channels look like, and how do they function? Also, how do the electrical signals generated by excitable cells differ from the other types of signals involved in cellular communication?

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#### What Are Ion Channel Receptors?

**Ion channel receptors** are usually multimeric proteins located in the plasma membrane. Each of these proteins arranges itself so that it forms a passageway or pore extending from one side of the membrane to the other. These passageways, or **ion channels**, have the ability to open and close in response to chemical or mechanical signals. When an ion channel is open, ions move into or out of the cell in single-file fashion. Individual ion channels are specific to particular ions, meaning that they usually allow only a single type of ion to pass through them. Both the amino acids that line a channel and the physical width of the channel determine which ions are able to wiggle through from the cell exterior to its interior, and vice versa. The opening of an ion channel is a fleeting event. Within a few milliseconds of opening, most ion channels close and enter a resting state, where they are unresponsive to signals for a short period of time (Figure 1).

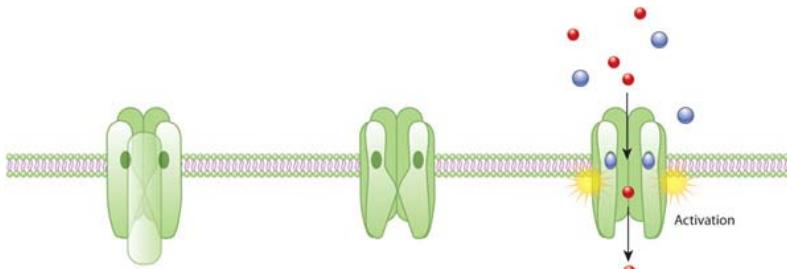


Figure 1: An example of ion channel receptor activation

An acetylcholine receptor (green) forms a gated ion channel in the plasma membrane. This receptor is a membrane protein with an aqueous pore, meaning it allows soluble materials to travel across the plasma membrane when open. When no external signal is present, the pore is closed (center). When acetylcholine molecules (blue) bind to the receptor, this triggers a conformational change that opens the aqueous pore and allows ions (red) to flow into the cell.

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#### How Are Electrical Signals Propagated?

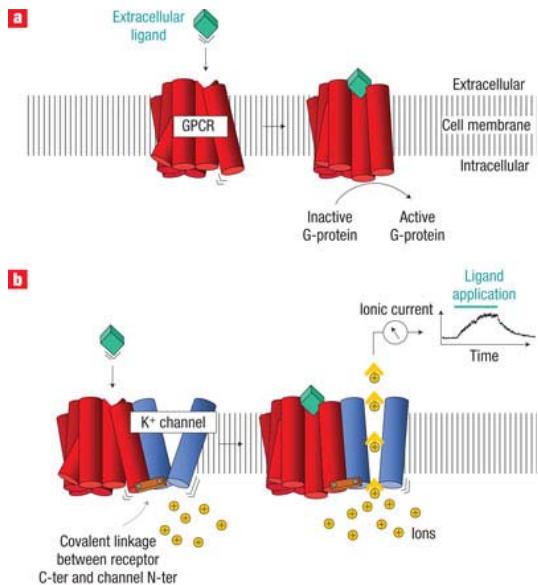


Figure 2: Comparing the activation of an ion channel receptor with that of a G-protein-coupled receptor

Activation of both a G-protein-coupled receptor (a) and an ion channel receptor (b) cause a conformational change in the receptor protein. G protein activation can lead to multiple intracellular events through a variety of intracellular proteins, and this signaling can take seconds to minutes. When a G protein activates transcription, this can take up to 20 minutes. In contrast, ion channel receptors open pores in the cell membrane, causing the formation of electrical current. This receptor activation therefore causes a much faster response within the cell, on the order of milliseconds.

© 2008 Nature Publishing Group Moreau, C. J. *et al.* Coupling ion channels to receptors for biomolecule sensing. *Nature Nanotechnology* 3, 620-625 (2008)  
doi:10.1038/nnano.2008.242. All rights reserved.

The opening of ion channels alters the charge distribution across the plasma membrane. Recall that the ionic composition of the cytoplasm is quite different from that of the extracellular environment. For instance, the concentration of sodium ions in the cytoplasm is far lower than that in the cell's exterior environment. Conversely, potassium ions exist at higher concentrations within a cell than outside it. Such differences create a so-called **electrochemical gradient**, which is a combination of a **chemical gradient** and a **charge gradient**. The opening of ion channels permits the ions on either side of the plasma membrane to flow down this dual gradient. The exact direction of flow varies by ion type, and it depends on both the concentration difference and the voltage difference for each variety of ion. This ion flow results in the production of an electrical signal. The actual number of ions required to change the voltage across the membrane is quite small. During the short times that an ion channel is open, the concentration of a particular ion in the cytoplasm as a whole does not change significantly, only the concentration in the immediate vicinity of the channel. In excitable cells, the electrical signal initiated by ion channel receptor activity travels rapidly over the surface of the cell due to the opening of other ion channels that are sensitive to the voltage change caused by the initial channel opening.

Electrical signals travel much more rapidly than chemical signals, which depend on the process of molecular diffusion. As a consequence, excitable cells respond to signals much more rapidly than cells that rely solely on chemical signals (Figure 2). In fact, an electrical signal can traverse the entire length of a human nerve cell — a distance of as much as one meter — within only milliseconds.

### How Do Different Types of Excitable Cells Work?

Neurons, muscle cells, and touch receptor cells are all excitable cells — which means they all have the capacity to transmit electrical signals. Each of these cells also has ion channel receptors clustered on a particular part of its surface. For example, the receptors that respond to chemical signals are generally located at **synapses** — or points of near contact between adjacent cells.

Of the various types of excitable cells that respond to chemical signals, neurons are perhaps the most familiar. When electrical signals reach the end of neurons, they trigger the release of chemical messengers called neurotransmitters. Each neurotransmitter then diffuses from its point of release on one side of the synapse to the cell on the other side of the synapse. If the neurotransmitter binds to an ion channel receptor on the target cell, the related ion channel opens, and an electrical signal propagates itself along the length of the target cell.

Neurons have ion channel receptors specific to many kinds of neurotransmitters. Some of these neurotransmitters act in an excitatory capacity, bringing their target cells ever closer to signal propagation. Other neurotransmitters exert an inhibitory effect, counteracting any excitatory input and lessening the chance that the target cell will fire.

Skeletal muscle cells also rely on chemical signals in order to generate electrical signals. These cells have synapses that are packed with receptors for **acetylcholine**, which is the primary neurotransmitter released by motor neurons. When acetylcholine binds to the receptors on a skeletal muscle cell, ion channels in that cell open, and this launches a sequence of events that results in contraction of the cell.

In contrast to neurons and skeletal muscle cells, some excitable cells have ion channels that open in response to mechanical stimuli rather than chemical signals. These include the hair cells of the mammalian inner ear and the touch receptor cells of

both human finger pads and Venus fly traps. Cells that respond to touch have their ion channel receptors clustered at the position where contact usually occurs.

## Conclusion

Excitable cells, such as fast-acting neurons and muscle cells, have specialized channels that open in response to a signal and permit rapid ion movement across the cell membrane. The opening of just a single ion channel alters the electrical charge on both sides of the membrane. The resulting charge differential then causes adjacent voltage-sensitive channels to open in chain-reaction fashion, creating a self-propagating electrical signal that travels down the entire length of the cell. Sometimes, this sequence of events is triggered when a chemical signal — such as a neurotransmitter — binds to an ion channel receptor on cell's surface. Other times, a cell's ion channels open in response to mechanical (rather than chemical) stimuli.

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## 4.4 Receptor Tyrosine Kinases Regulate Cell Growth, Differentiation, and Survival

Although all cell membrane receptors receive and transmit signals from the environment, some of these receptors also double as enzymes. In such cases, the binding of a signaling molecule to the membrane receptor activates the receptor's inherent enzymatic activity. Of the various receptors that exhibit this capability, **receptor tyrosine kinases** (RTKs) make up the largest class. These cell surface receptors bind and respond to growth factors and other locally released proteins that are present at low concentrations. RTKs play important roles in the regulation of cell growth, differentiation, and survival. When signaling molecules bind to RTKs, they cause neighboring RTKs to associate with each other, forming cross-linked dimers. Cross-linking activates the tyrosine kinase activity in these RTKs through phosphorylation — specifically, each RTK in the dimer phosphorylates multiple tyrosines on the other RTK. This process is called **cross-phosphorylation**.

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### What Do RTKs Look Like?

Once cross-phosphorylated, the cytoplasmic tails of RTKs serve as docking platforms for various intracellular proteins involved in signal transduction. These proteins have a particular domain — called SH2 — that binds to phosphorylated tyrosines in the cytoplasmic RTK receptor tails. More than one SH2-containing protein can bind at the same time to an activated RTK, allowing simultaneous activation of multiple intracellular signaling pathways. Ultimately, RTK activation brings about changes in gene transcription. Signaling becomes complex as signals travel from the membrane to the nucleus, due to crosstalk between intermediates in various signaling pathways in the cell (Figure 1).

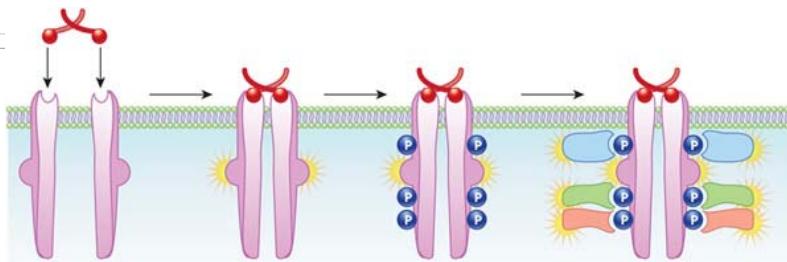


Figure 1: RTK activation involves the joining together and phosphorylation of proteins. On the left, an unactivated RTK receptor (pink) encounters a ligand (red). Upon binding, the receptor forms a complex of proteins that phosphorylate each other. In turn, this phosphorylation affects other proteins in the cell that change gene transcription (not shown).

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One of the most common intracellular signaling pathways triggered by RTKs is known as the **mitogen-activated protein (MAP) kinase cascade**, because it involves three **serine-threonine kinases**. The pathway starts with the activation of **Ras**, a small G protein anchored to the plasma membrane. In its inactive state, Ras is bound to GDP. However, when SH2-containing proteins join with activated RTKs, they cause Ras to bind GTP in place of GDP and become active. Next, the GTP-bound Ras (which is not itself a kinase) activates the first serine-threonine kinase in the MAP kinase cascade. Each of the three kinases in this cascade then activates the next by phosphorylating it. Because all three kinases in this pathway phosphorylate multiple substrates, the initial signal is amplified at each step. Then, the final enzyme in the pathway phosphorylates transcription regulators, leading to a change in gene transcription (Figure 2). Many growth factors, including nerve growth factor and platelet-derived growth factor, use this pathway.

Not all RTKs use the MAP kinase cascade to send information to the nucleus. For example, insulin-like growth factor receptors activate the enzyme phosphoinositide 3-kinase, which phosphorylates inositol phospholipids in the cell membrane, leading in turn to a protein kinase cascade (distinct from the MAP kinase cascade) that relays the signal to the nucleus. Other RTKs use a more direct route to the nucleus. Transcriptional regulators known as **STAT** proteins, an acronym for signal transducers and activators of transcription, bind to the phosphorylated tyrosines in the receptors for cytokines and some hormones. Once activated, STAT proteins move directly into the nucleus, causing changes in transcription.

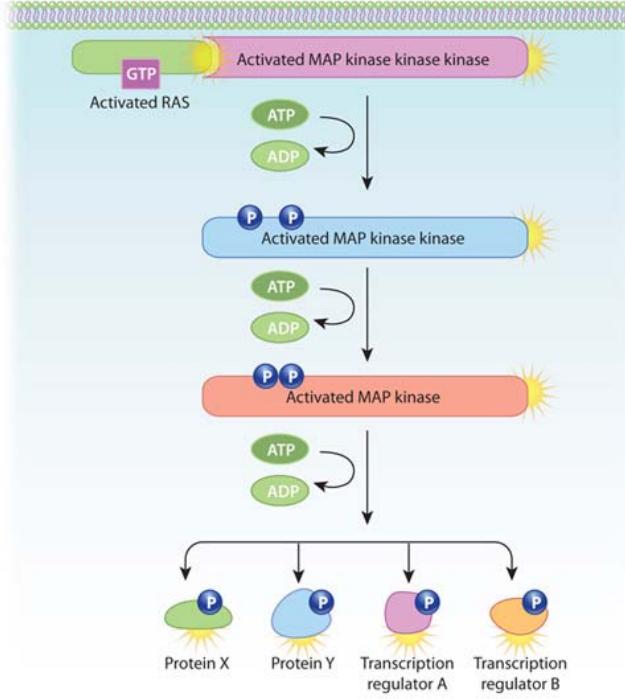


Figure 2: Ras MAP kinase activation: A common pathway activated by growth factors  
RTKs can activate Ras, a protein that is tethered to the plasma membrane, by causing it to bind GTP. Once activated, Ras can do a variety of things. In this example, it activates an enzymatic cascade of MAP kinases. This results in potent changes in the cell, such as the alteration of key proteins and changes in gene transcription.

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### How Do RTK Signals Regulate Cells?

Cells possess many different RTKs that bind to a diverse set of extracellular signaling molecules, many of which are locally produced and present in low concentrations. These local cell-to-cell interactions are important for developing and maintaining the spatial orientation of tissues, which is crucial for higher-level functioning.

Growth factors and hormones are two especially important categories of signaling molecules that bind to RTKs. These molecules direct cell differentiation by determining patterns of gene transcription. Extracellular matrix proteins and certain surface proteins on neighboring cells can also bind to and activate RTKs. For example, upon binding to RTKs, surface proteins called **ephrins** help guide developmental processes involved in tissue architecture, final placement of nerve endings, and blood vessel maturation.

When RTKs don't function properly, cell growth and differentiation go awry. For instance, many cancers appear to involve mutations in RTKs. For this reason, RTKs are the targets of various drugs used in cancer chemotherapy. For example, the breast cancer drug Herceptin is an antibody that binds to and inhibits ErbB-2 — an RTK that is overexpressed in many metastatic breast cancers.

### Conclusion

RTKs are transmembrane protein receptors that help cells interact with their neighbors in a tissue. RTKs differ from other cell surface receptors in that they contain intrinsic enzyme activity. In particular, the binding of a signaling molecule with an RTK activates tyrosine kinase in the cytoplasmic tail of the receptor. This activity then launches a series of enzymatic reactions that carry the signal to the nucleus, where it alters patterns of protein transcription.

### Unit 4

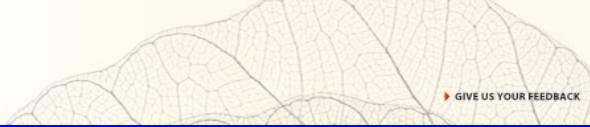
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## Unit 4: How Do Cells Sense Their Environment?

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### 4.5 Cells Sense the Presence of Other Cells and Their Environment

All cells rely on [cell signaling](#) to detect and respond to cues in their environment. This process not only promotes the proper functioning of individual cells, but it also allows communication and coordination among groups of cells — including the cells that make up organized communities called **tissues**. Because of cell signaling, tissues have the ability to carry out tasks no single cell could accomplish on its own.

Different types of tissues, such as bone, brain, and the lining of the gut, have characteristic features related to the number and types of cells they contain. Cell spacing is also critical to tissue function, so this geometry is precisely regulated. To preserve proper tissue architecture, adhesive molecules help maintain contact between nearby cells and structures, and tiny tunnel-like junctions allow the passage of ions and small molecules between adjacent cells. Meanwhile, signaling molecules relay positional information among the cells in a tissue, as well as between these cells and the extracellular matrix. These signaling pathways are critical to maintaining the state of equilibrium known as **homeostasis** within a tissue. For example, the processes involved in wound healing depend on positional information in order for normal tissue architecture to be restored. Such positional signals are also crucial for the development of adult structures in multicellular organisms. As tissues develop, clumps of unorganized cells grow and sort themselves according to signals they send and receive.

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#### How Do Integrins Promote Tissue Structure and Function?

Within tissues, adhesive molecules allow cells to maintain contact with one another and with structures in the extracellular matrix. One especially important class of adhesive molecules is the **integrins**. Integrins are more than just mechanical links, however: They also relay signals both to and from cells. In this way, integrins play an important role in sensing the environment and controlling cell shape and motility.

Integrins are a diverse family of transmembrane proteins found in all animal cells. Even simple animals like sponges have these proteins. Each individual integrin consists of two main parts: an alpha subunit and a beta subunit. Variation in the alpha and beta subunits accounts for the wide variety of integrins observed throughout the animal kingdom. For example, humans alone have over 20 different kinds of integrins.

Integrins link the actin cytoskeleton of a cell to various external structures. The cytoplasmic portion of each integrin molecule binds to adaptor proteins that connect to the actin filaments inside the cell. The extracellular portion of the integrin then binds to molecules in the extracellular matrix or on the surface of other cells. Integrin attachments to neighboring cells can break and reform as a cell moves (Figure 1).

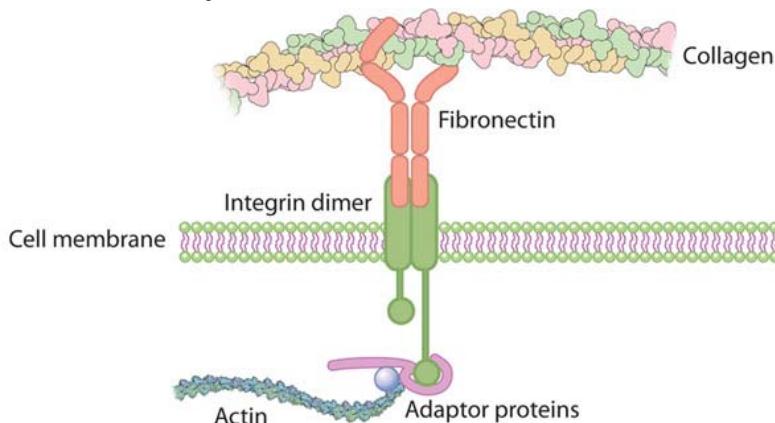


Figure 1: Integrin connects the extracellular matrix with the actin cytoskeleton inside the cell.

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#### How Else Do the Cells within a Tissue Stay in Contact?

Beyond integrins, cells rely on several other adhesive proteins to maintain physical contact. As an example, consider the epithelial cells that line the inner and outer surfaces of the human body — including the skin, intestines, airway, and reproductive tract. These cells provide a dramatic example of the different kinds of cell-to-cell junctions, but the same junctions also exist in a wide range of other tissues.

The side surfaces of epithelial cells are tightly linked to those of neighboring cells, forming a sheet that acts as a barrier. Within this sheet, each individual cell has a set orientation. Through integrins, the basal end of each cell connects to a specialized layer of extracellular matrix called the **basal lamina**. In contrast, the apical end of each cell faces out into the environment — such as the inner cavity or **lumen** of the gut.

The side-to-side junctions that link epithelial cells are diverse in their protein makeup and function. The adhesive transmembrane proteins anchoring these junctions have extracellular portions that interact with similar proteins on adjacent cells. Protein complexes within each cell further connect the transmembrane adhesive proteins to the cytoskeleton. In particular, adaptor complexes bind **adherens junctions** to cytoskeletal actin, and other adaptor complexes bind **desmosomes** to intermediate filaments. Both of these types of junctional complexes provide cells and tissues with mechanical support, and they additionally recruit intracellular signaling molecules to relay positional information to the nucleus.

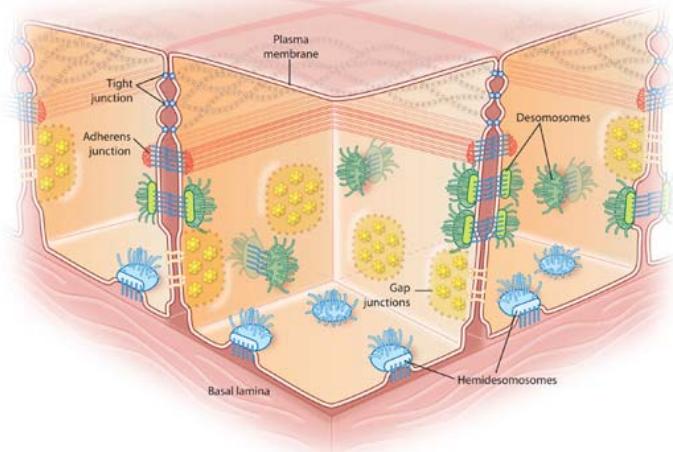


Figure 2: The different types of cell junctions

Tight junctions (blue dots) between cells are connected areas of the plasma membrane that stitch cells together. Adherens junctions (red dots) join the actin filaments of neighboring cells together. Desmosomes are even stronger connections that join the intermediate filaments of neighboring cells. Hemidesmosomes (light blue) connect intermediate filaments of a cell to the basal lamina, a combination of extracellular molecules on other cell surfaces. Gap junctions (yellow) are clusters of channels that form tunnels of aqueous connectivity between cells.

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The lateral surfaces of epithelial cells also contain several other types of specialized junctions. **Tight junctions** form a seal between cells that is so strong that not even ions can pass across it. **Gap junctions** are involved in cellular communication — not just in epithelial tissue, but in other tissue types as well. Gap junctions are specialized connections that form a narrow pore between adjacent cells. These pores permit small molecules and ions to move from one cell to another. In this way, gap junctions provide metabolic and electrical coupling between cells. For example, cardiac tissue has extensive gap junctions, and the rapid movement of ions through these junctions helps the tissue beat in rhythm. Gap junctions may also open and close in response to metabolic signals (Figure 2, Figure 3).

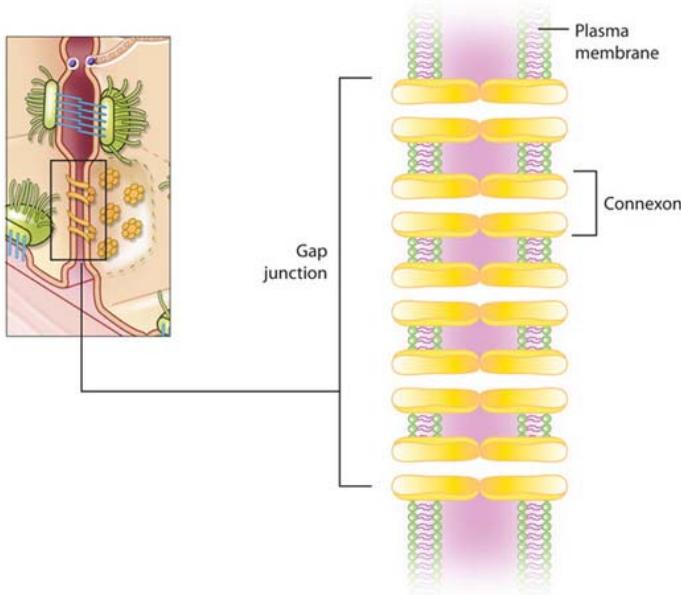


Figure 3: A gap junction

In a gap junction, the lipid bilayer of adjacent cells is pierced through by proteins called connexons. These proteins group together and effectively form a group of communication tunnels between adjacent cells.

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### Cell Death Can Be Prompted by a Signal

Cell signaling isn't just central to tissue architecture and function: It also plays an important role in the balance between cell growth and death. Although it sounds like a bad thing, **apoptosis** — or the process of programmed cell death — is an essential aspect of development. Without it, repair and replenishment processes would overrun tissues with new cells. The orderly demise of a certain proportion of cells is therefore necessary for normal tissue turnover and maintenance of homeostasis. Apoptosis is distinct from **necrosis**, a messier form of cell death that causes cells to literally swell and burst. Necrotic cell death is not programmed; rather, it occurs in response to trauma or injury.

A range of extracellular and intracellular signals can trigger either cell growth or apoptosis. When cells receive these signals from their neighbors or from other aspects of the external environment, they carefully weigh them against each other before choosing a course of action. For instance, signals that indicate a lack of nutrients or the presence of toxins would likely stall cell growth and promote apoptosis. Within the cell, damage to the DNA or loss of mitochondrial integrity might also result in programmed cell death.

Cells self-destruct cleanly and quickly during apoptosis, thanks to the activation of a variety of enzymes — proteases and nucleases — that break down proteins and nucleic acids, respectively. In fact, scientists look for a characteristic pattern of fragmentation and nuclear condensation within tissues as evidence that apoptosis has occurred.

### Conclusion

Some cell signaling occurs on a local level, such as when cells interact with the surrounding extracellular matrix or with their immediate neighbors. This type of signaling is especially important to the structure and function of tissues. Various signaling molecules allow the cells within a tissue to share information about internal and external conditions. This information helps the cells arrange themselves, coordinate their functions, and even know when to grow and when to die. Some of these signaling molecules also function in an adhesive capacity — not just relaying messages between the cells in a tissue, but physically joining these cells to one another.

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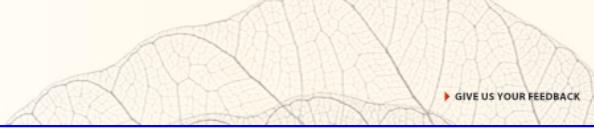
4.6 Test Your Knowledge [NEXT ►](#)

You are about to take a twenty-question test. Each question is multiple-choice. After choosing one answer, select "NEXT" and you will proceed to the next question in the test. At the end of the test, you will be given your score. You will have the option to "VIEW RESULTS," which will give you explanations of each of your correct and incorrect answers. You will also have the option to take another version of this unit test. If you would like to skip this test and proceed directly to the next unit, please select "NEXT PAGE" at the upper right.

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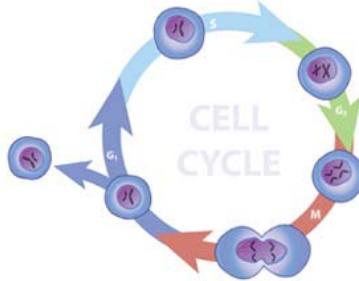
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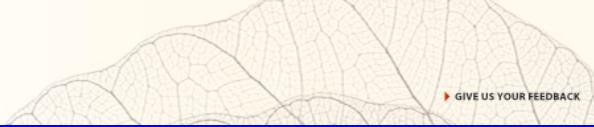
Cells can replicate themselves. The ability to reproduce is part of what defines cells as living things. This single characteristic also helps explain many other phenomena of life as we know it, including the emergence of multicellular organisms, the wide variety of tissues observed in living things, and even the scourge of cancer.

The process by which a single cell divides into two daughter cells is called mitosis. Mitosis is an important part of a cell's life cycle — but the rest of this cycle, collectively known as interphase, is hardly static. During interphase, the cell carries out the everyday biochemical reactions associated with metabolism, and it also engages in several processes that will guide it through the next round of division. In addition, throughout the cell cycle there are multiple monitoring systems and checkpoints that help the cell determine if and when it should divide, whether it's time to advance to the next phase, or whether it's time to die and make room for a younger, healthier cell.

The various checks on cell growth that occur during interphase allow tissues to revitalize themselves without increasing in size. When these restraints fail, the results — including the growth and spread of cancer — can be devastating.

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## Unit 5: How Do Cells Know When to Divide?

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### 5.1 The Eukaryotic Cell Cycle Consists of Discrete Phases

The cellular life cycle, also called the **cell cycle**, includes many processes necessary for successful self-replication. Beyond carrying out the tasks of routine metabolism, the cell must duplicate its components — most importantly, its genome — so that it can physically split into two complete daughter cells. The cell must also pass through a series of **checkpoints** that ensure conditions are favorable for division.

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#### What Phases Make Up the Eukaryotic Cell Cycle?

In eukaryotes, the cell cycle consists of four discrete phases: G<sub>1</sub>, S, G<sub>2</sub>, and M. The S or **synthesis phase** is when DNA replication occurs, and the M or **mitosis phase** is when the cell actually divides. The other two phases — G<sub>1</sub> and G<sub>2</sub>, the so-called **gap phases** — are less dramatic but equally important. During G<sub>1</sub>, the cell conducts a series of checks before entering the S phase. Later, during G<sub>2</sub>, the cell similarly checks its readiness to proceed to mitosis. Together, the G<sub>1</sub>, S, and G<sub>2</sub> phases make up the period known as **interphase**. Cells typically spend far more time in interphase than they do in **mitosis**. Of the four phases, G<sub>1</sub> is most variable in terms of duration, although it is often the longest portion of the cell cycle (Figure 1).

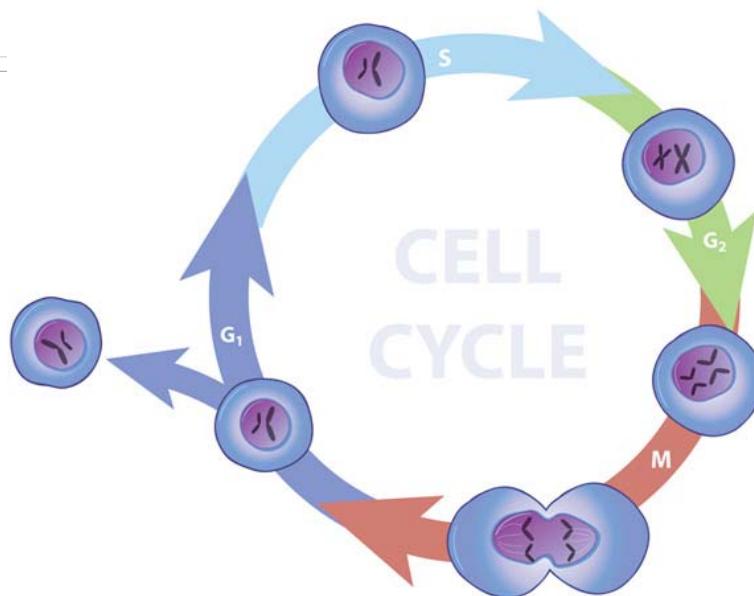


Figure 1: The eukaryotic cell cycle

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#### How Do Cells Monitor Their Progress through the Cell Cycle?

In order to move from one phase of its life cycle to the next, a cell must pass through numerous **checkpoints**. At each checkpoint, specialized proteins determine whether the necessary conditions exist. If so, the cell is free to enter the next phase. If not, progression through the cell cycle is halted. Errors in these checkpoints can have catastrophic consequences, including cell death or the unrestrained growth that is cancer.

Each part of the cell cycle features its own unique checkpoints. For example, during G<sub>1</sub>, the cell passes through a critical checkpoint that ensures environmental conditions (including signals from other cells) are favorable for replication. If conditions are not favorable, the cell may enter a resting state known as G<sub>0</sub>. Some cells remain in G<sub>0</sub> for the entire lifetime of the organism in which they reside. For instance, the neurons and skeletal muscle cells of mammals are typically in G<sub>0</sub>.

Another important checkpoint takes place later in the cell cycle, just before a cell moves from G<sub>2</sub> to mitosis. Here, a number of proteins scrutinize the cell's DNA, making sure it is structurally intact and properly replicated. The cell may pause at this point to allow time for DNA repair, if necessary.

Yet another critical cell cycle checkpoint takes place mid-mitosis. This check determines whether the chromosomes in the cell have properly attached to the **spindle**, or the network of microtubules that will separate them during cell division. This step decreases the possibility that the resulting daughter cells will have unbalanced numbers of chromosomes — a condition called **aneuploidy**.

### How Do Scientists Study the Cell Cycle?

The cell cycle and its system of checkpoint controls show strong evolutionary conservation. As a result, all eukaryotes — from single-celled yeast to complex multicellular vertebrates — pass through the same four phases and same key checkpoints. This universality of the cell cycle and its checkpoint controls allows scientists to use relatively simple model organisms to learn more about cell division in eukaryotes of all types — including humans. In fact, two of the three scientists who received Nobel Prizes for cell cycle research used yeast as the subject of their investigations.

### Conclusion

The eukaryotic cell cycle includes four phases necessary for proper growth and division. As a cell moves through each phase, it also passes through several checkpoints. These checkpoints ensure that mitosis occurs only when environmental conditions are favorable and the cellular genome has been precisely replicated. Collectively, this set of checks on division helps prevent chromosomal imbalance in newly produced daughter cells.

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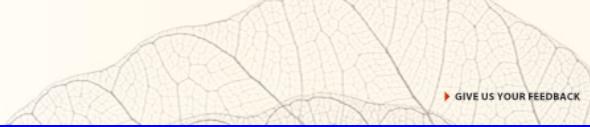
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## 5.2 Cyclin-Dependent Kinases Regulate Progression through the Cell Cycle

Multiple checkpoints in the eukaryotic cell cycle ensure that division occurs only after sufficient growth and faithful DNA replication, and only when favorable conditions exist. At each checkpoint, numerous proteins engage in a series of carefully coordinated biochemical reactions. This complexity allows for precise regulation of all steps in the cell cycle — and it is essential to preventing the devastating consequences of cell division gone awry (Figure 1).

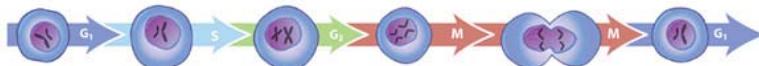


Figure 1: The sequence of eukaryotic cell cycle phases

Between each arrow, the cell passes through a particular cell cycle checkpoint.

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### What Are Cyclin-Dependent Kinases?

Of the many proteins involved in cell cycle control, **cyclin-dependent kinases** (CDKs) are among the most important. CDKs are a family of multifunctional enzymes that can modify various protein substrates involved in cell cycle progression.

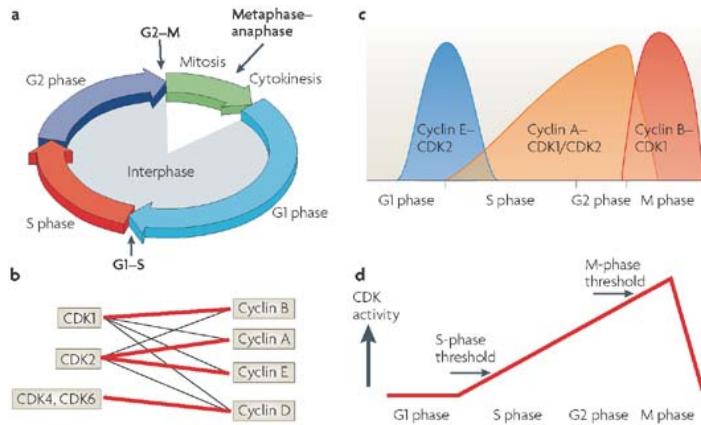
Specifically, **CDKs phosphorylate** their substrates by transferring phosphate groups from ATP to specific stretches of amino acids in the substrates. Different types of eukaryotic cells contain different types and numbers of CDKs. For example, yeast have only a single CDK, whereas vertebrates have four different ones.

As their name suggests, CDKs require the presence of **cyclins** to become active. Cyclins are a family of proteins that have no enzymatic activity of their own but activate CDKs by binding to them. CDKs must also be in a particular phosphorylation state — with some sites phosphorylated and others dephosphorylated — in order for activation to occur. Correct phosphorylation depends on the action of other kinases and a second class of enzymes called phosphatases that are responsible for removing phosphate groups from proteins.

### How Do CDKs Control the Cell Cycle?

All eukaryotes have multiple cyclins, each of which acts during a specific stage of the cell cycle. (In organisms with multiple CDKs, each CDK is paired with a specific cyclin.) All cyclins are named according to the stage at which they assemble with CDKs. Common classes of cyclins include G<sub>1</sub>-phase cyclins, G<sub>1</sub>/S-phase cyclins, S-phase cyclins, and M-phase cyclins. M-phase cyclins form M-CDK complexes and drive the cell's entry into mitosis; G<sub>1</sub> cyclins form G<sub>1</sub>-CDK complexes and guide the cell's progress through the G<sub>1</sub> phase; and so on.

All CDKs exist in similar amounts throughout the entire cell cycle. In contrast, cyclin manufacture and breakdown varies by stage — with cell cycle progression dependent on the synthesis of new cyclin molecules. Accordingly, cells synthesize G<sub>1</sub>- and G<sub>1</sub>/S-cyclins at different times during the G<sub>1</sub> phase, and they produce M-cyclin molecules during the G<sub>2</sub> phase (Figure 2). Cyclin degradation is equally important for progression through the cell cycle. Specific enzymes break down cyclins at defined times in the cell cycle. When cyclin levels decrease, the corresponding CDKs become inactive. Cell cycle arrest can occur if cyclins fail to degrade.



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Figure 2: The classical and minimal models of cell cycle control

Where and when do cyclins act on the cell cycle? (A) Cyclin cells undergo three major transitions during their cell cycle. The beginning of S phase is marked by the onset of DNA replication, the start of mitosis (M) is accompanied by breakdown of the nuclear envelope and chromosome condensation, whereas segregation of the sister chromatids marks the metaphase-to-anaphase transition. Cyclin-dependent kinases (CDKs) trigger the transition from G1 to S phase and from G2 to M phase by phosphorylating distinct sets of substrates. (B) CDK1 and CDK2 bind to multiple cyclins (cyclin types A, B, D and E), whereas CDK4 and CDK6 only partner D-type cyclins. Thick lines represent the preferred pairing for each kinase. (C) According to the classical model of cell cycle control, D-type cyclins and CDK4 or CDK6 regulate events in early G1 phase (not shown), cyclin E-CDK2 triggers S phase, cyclin A-CDK2 and cyclin A-CDK1 regulate the completion of S phase, and CDK1-cyclin B is responsible for mitosis. (D) Based on the results of cyclin and CDK-knockout studies, scientists have constructed a new threshold model of cell cycle control. Accordingly, either CDK1 or CDK2 bound to cyclin A is sufficient to control interphase, whereas cyclin B-CDK1 is essential to take cells into mitosis. The differences between interphase and mitotic CDKs are not necessarily due to substrate specificity, but are more likely a result of different localization and a higher activity threshold for mitosis than interphase.

© 2008 Nature Publishing Group Hochegger, H., Takeda, S., & Hunt, T. Cyclin-dependent kinases and cell-cycle transitions: does one fit all? *Nature Reviews Molecular Cell Biology* 9, 910-916 (2008)  
doi:10.1038/nrm2510. All rights reserved.

## Which Proteins Do CDKs Modify?

Each of the cyclin-CDK complexes in a cell modifies a specific group of protein substrates. Proper phosphorylation of these substrates must occur at particular times in order for the cell cycle to continue. Because cyclin-CDK complexes recognize multiple substrates, they are able to coordinate the multiple events that occur during each phase of the cell cycle. For example, at the beginning of S phase, S-CDK catalyzes phosphorylation of the proteins that initiate DNA replication by allowing DNA replication complexes to form. Later, during mitosis, M-CDKs phosphorylate a wide range of proteins. These include condensin proteins, which are essential for the extensive condensation of mitotic chromosomes, and lamin proteins, which form a stabilizing network under the nuclear membrane that disassembles during mitosis. M-CDKs also influence the assembly of the mitotic spindle by phosphorylating proteins that regulate microtubule behavior. The net effect of these coordinated phosphorylation reactions is the accurate separation of chromosomes during mitosis.

## Conclusion

The life cycle of a cell is a carefully regulated series of events orchestrated by a suite of enzymes and other proteins. The main regulatory components of cell cycle control are cyclins and CDKs. Depending on the presence and action of these proteins, the cell cycle can be speedy or slow, and it may even halt altogether.

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#### 5.3 Mitosis Produces Two Daughter Cells with the Same Genetic Makeup

Mitosis is the process in which a eukaryotic cell nucleus splits in two, followed by division of the parent cell into two daughter cells. The word "mitosis" means "threads," and it refers to the threadlike appearance of chromosomes as the cell prepares to divide. Early microscopists were the first to observe these structures, and they also noted the appearance of a specialized network of microtubules during mitosis. These tubules, collectively known as the spindle, extend from structures called **centrosomes** — with one centrosome located at each of the opposite ends, or poles, of a cell. As mitosis progresses, the microtubules attach to the chromosomes, which have already duplicated their DNA and aligned across the center of the cell. The spindle tubules then shorten and move toward the poles of the cell. As they move, they pull the one copy of each chromosome with them to opposite poles of the cell. This process ensures that each daughter cell will contain one exact copy of the parent cell DNA.

#### What Are the Phases of Mitosis?

Mitosis consists of five morphologically distinct phases: prophase, prometaphase, metaphase, anaphase, and telophase. Each phase involves characteristic steps in the process of chromosome alignment and separation. Once mitosis is complete, the entire cell divides in two by way of the process called cytokinesis (Figure 1).

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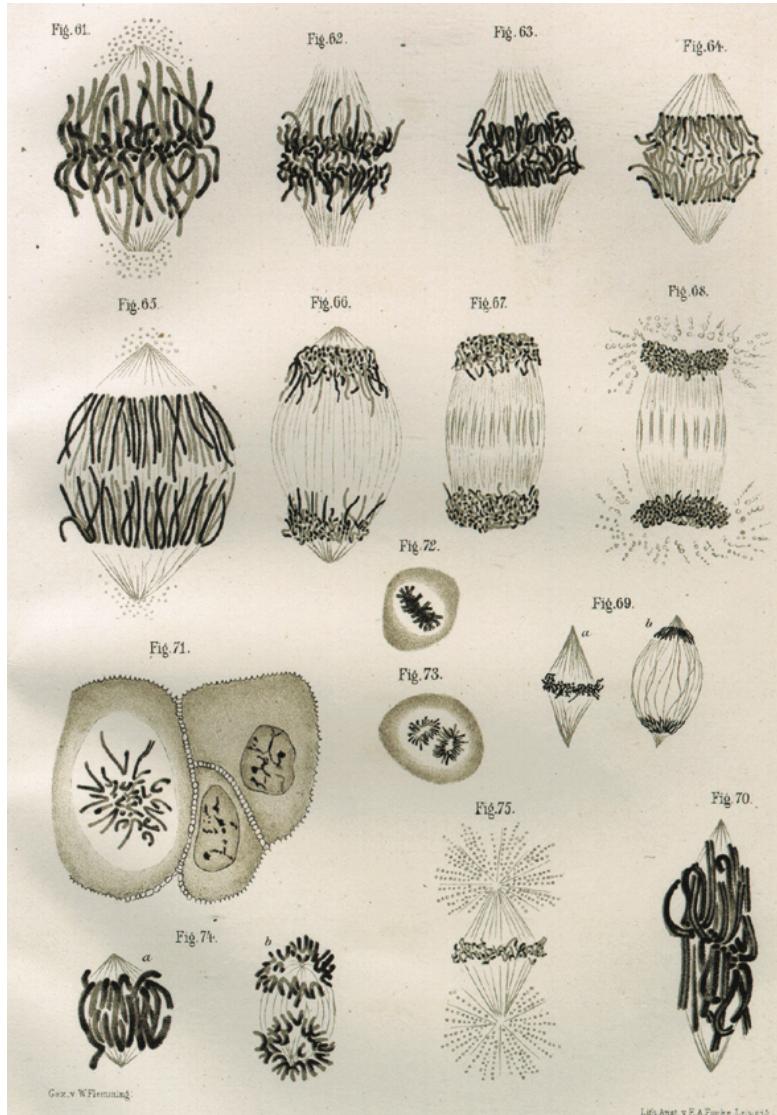


Figure 1: Drawing of chromosomes during mitosis by Walther Flemming, circa 1880

This illustration is one of more than one hundred drawings from Flemming's "Cell Substance, Nucleus, and Cell Division." Flemming repeatedly observed the different forms of chromosomes leading up to and during cytokinesis, the ultimate division of one cell into two during the last stage of mitosis.

© 2001 Nature Publishing Group Paweletz, N. Walther Flemming: pioneer of mitosis research. *Nature Reviews Molecular Cell Biology* 2, 72. Used with permission. All rights reserved.

## What Happens during Prophase?

**Prophase** is the first stage in mitosis, occurring after the conclusion of the G<sub>2</sub> portion of interphase. During prophase, the parent cell chromosomes — which were duplicated during S phase — condense and become thousands of times more compact than they were during interphase. Because each duplicated chromosome consists of two identical **sister chromatids** joined at a point called the **centromere**, these structures now appear as X-shaped bodies when viewed under a microscope. Several DNA binding proteins catalyze the condensation process, including **cohesin** and **condensin**. Cohesin forms rings that hold the sister chromatids together, whereas condensin forms rings that coil the chromosomes into highly compact forms. The mitotic spindle also begins to develop during prophase. As the cell's two centrosomes move toward opposite poles, microtubules gradually assemble between them, forming the network that will later pull the duplicated chromosomes apart.

## What Happens during Prometaphase?

When prophase is complete, the cell enters **prometaphase** — the second stage of mitosis. During prometaphase, phosphorylation of nuclear lamins by M-CDK causes the nuclear membrane to break down into numerous small vesicles. As a result, the spindle microtubules now have direct access to the genetic material of the cell. Each microtubule is highly dynamic, growing outward from the centrosome and collapsing backward as it tries to locate a chromosome. Eventually, the microtubules find their targets and connect to each chromosome at its **kinetochore**, a complex of proteins positioned at the centromere. The actual number of microtubules that attach to a kinetochore varies between species, but at least one microtubule from each pole attaches to the kinetochore of each chromosome. A tug-of-war then ensues as the chromosomes move back and forth toward the two poles.

### What Happens during Metaphase and Anaphase?

As prometaphase ends and **metaphase** begins, the chromosomes align along the cell equator. Every chromosome has at least two microtubules extending from its kinetochore — with at least one microtubule connected to each pole. At this point, the tension within the cell becomes balanced, and the chromosomes no longer move back and forth. In addition, the spindle is now complete, and three groups of spindle microtubules are apparent. **Kinetochore microtubules** attach the chromosomes to the spindle pole; **interpolar microtubules** extend from the spindle pole across the equator, almost to the opposite spindle pole; and **astral microtubules** extend from the spindle pole to the cell membrane.

Metaphase leads to **anaphase**, during which each chromosome's sister chromatids separate and move to opposite poles of the cell. Enzymatic breakdown of cohesin — which linked the sister chromatids together during prophase — causes this separation to occur. Upon separation, every chromatid becomes an independent chromosome. Meanwhile, changes in microtubule length provide the mechanism for chromosome movement. More specifically, in the first part of anaphase — sometimes called **anaphase A** — the kinetochore microtubules shorten and draw the chromosomes toward the spindle poles. Then, in the second part of anaphase — sometimes called **anaphase B** — the astral microtubules that are anchored to the cell membrane pull the poles further apart and the interpolar microtubules slide past each other, exerting additional pull on the chromosomes (Figure 2).

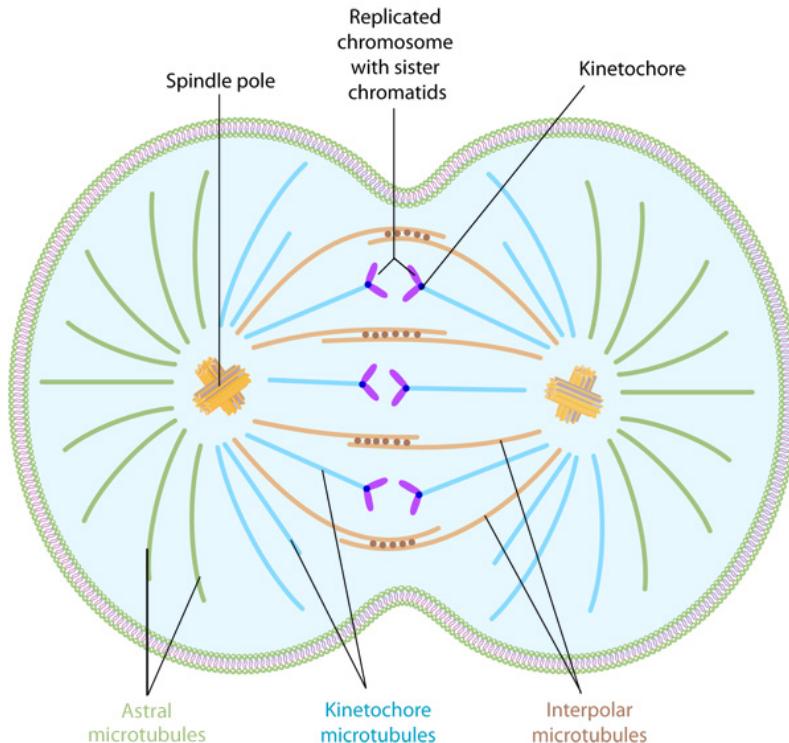


Figure 2: Types of microtubules involved in mitosis

During mitosis, several types of microtubules are active. The motor proteins associated with the interpolar microtubules drive the assembly of the spindle. Note the other types of microtubules involved in anchoring the spindle pole and pulling apart the sister chromatids.

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### What Happens during Telophase?

During **telophase**, the chromosomes arrive at the cell poles, the mitotic spindle disassembles, and the vesicles that contain fragments of the original nuclear membrane assemble around the two sets of chromosomes. Phosphatases then dephosphorylate the lamins at each end of the cell. This dephosphorylation results in the formation of a new nuclear membrane around each group of chromosomes.

### When Do Cells Actually Divide?

**Cytokinesis** is the physical process that finally splits the parent cell into two identical daughter cells. During cytokinesis, the cell membrane pinches in at the cell equator, forming a cleft called the **cleavage furrow**. The position of the furrow depends on the position of the astral and interpolar microtubules during anaphase.

The cleavage furrow forms because of the action of a contractile ring of overlapping actin and myosin filaments. As the actin and myosin filaments move past each other, the contractile ring becomes smaller, akin to pulling a drawstring at the top of a purse. When the ring reaches its smallest point, the cleavage furrow completely bisects the cell at its center, resulting in two separate daughter cells of equal size (Figure 3).

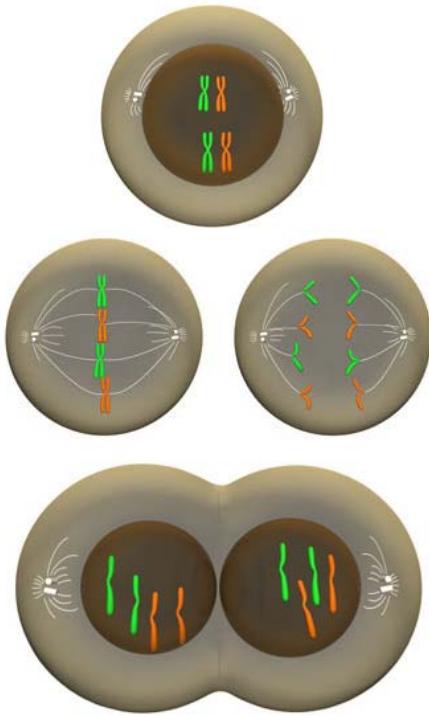


Figure 3: Mitosis: Overview of major phases

The major stages of mitosis are prophase (top row), metaphase and anaphase (middle row), and telophase (bottom row).

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## Conclusion

Mitosis is the process of nuclear division, which occurs just prior to [cell division](#), or cytokinesis. During this multistep process, cell chromosomes condense and the spindle assembles. The duplicated chromosomes then attach to the spindle, align at the cell equator, and move apart as the spindle microtubules retreat toward opposite poles of the cell. Each set of chromosomes is then surrounded by a nuclear membrane, and the parent cell splits into two complete daughter cells.

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## Unit 5: How Do Cells Know When to Divide?

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## 5.4 Tissues Are Organized Communities of Different Cell Types

Within multicellular organisms, tissues are organized communities of cells that work together to carry out a specific function. The exact role of a tissue in an organism depends on what types of cells it contains. For example, the endothelial tissue that lines the human gastrointestinal tract consists of several cell types. Some of these cells absorb nutrients from the digestive contents, whereas others (called goblet cells) secrete a lubricating mucus that helps the contents travel smoothly. However, the multiple cell types within a tissue don't just have different functions. They also have different transcriptional programs and may well divide at different rates. Proper regulation of these rates is essential to tissue maintenance and repair. The spatial organization of the cells that form a tissue is also central to the tissue's function and survival. This organization depends in part on **polarity**, or the orientation of particular cells in their place. Of course, external signals from neighboring cells or from the extracellular matrix are also important influences on the arrangement of cells in a tissue.

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### What Is the Source of New Cells for Tissues?

Without cell division, long-term tissue survival would be impossible. Inside every tissue, cells are constantly replenishing themselves through the process of division, although the rate of turnover may vary widely between different cell types in the same tissue. For example, in adult mammal brains, neurons rarely divide. However, glial cells in the brain continue to divide throughout a mammal's adult life. Mammalian epithelial cells also turn over regularly, typically every few days. Neurons are not the only cells that lose their ability to divide as they mature. In fact, many differentiated cells lose this ability. To help counteract this loss, tissues maintain **stem cells** to serve as a reservoir of undifferentiated cells. [Stem cells](#) typically have the capacity to mature into many different cell types. **Transcription factors** — proteins that regulate which genes are transcribed in a cell — appear to be essential to determining the pathway particular stem cells take as they differentiate. For example, both intestinal absorptive cells and goblet cells arise from the same stem cell population, but divergent transcriptional programs cause them to mature into dramatically different cells (Figure 1).

Whenever stem cells are called upon to generate a particular type of cell, they undergo an **asymmetric cell division**. With asymmetric division, each of the two resulting daughter cells has its own unique life course. In this case, one of the daughter cells has a finite capacity for cell division and begins to differentiate, whereas the other daughter cell remains a stem cell with unlimited proliferative ability.

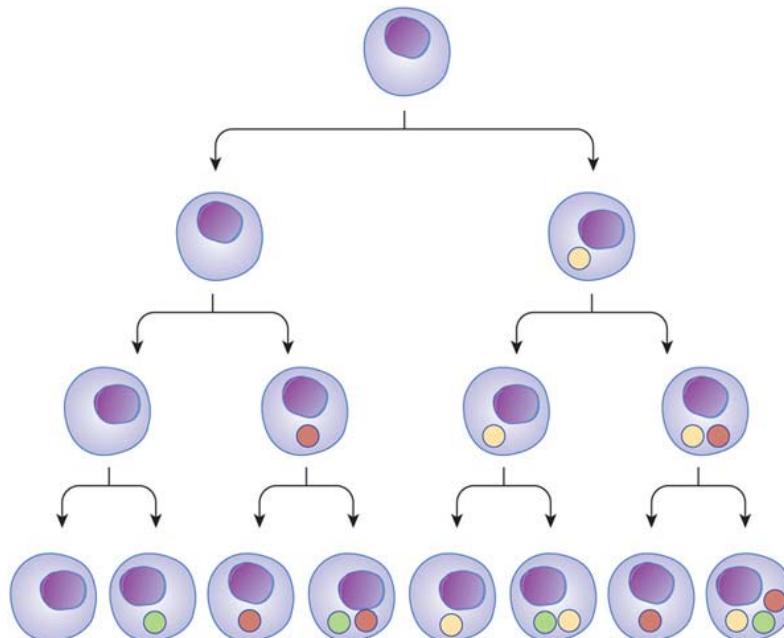


Figure 1: Transcriptional regulators can act at different stages, and in different combinations, through the path of cell development and differentiation.

Transcription factors can turn on at different times during cell differentiation. As cells mature and go through different stages (arrows), transcription factors (colored balls) can act on gene expression and change the cell in different ways. This change affects the next generation of cells derived from that cell. In subsequent generations, it is the combination of different transcription factors that can ultimately determine cell type.

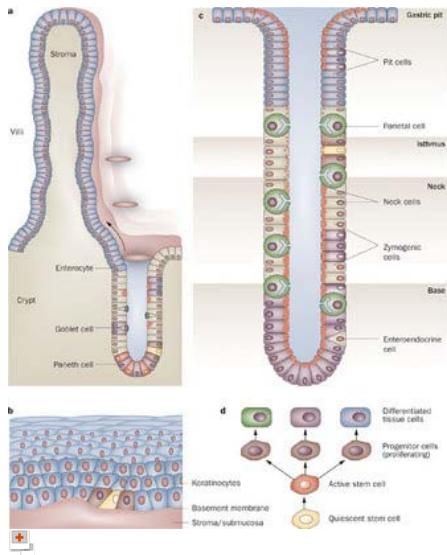
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## How Do Non-Growing Tissues Maintain Themselves?

Although most of the tissues in adult organisms maintain a constant size, the cells that make up these tissues are constantly turning over. Therefore, in order for a particular tissue to stay the same size, its rates of cell death and cell division must remain in balance.

A variety of factors can trigger cell death in a tissue. For example, the process of apoptosis, or programmed cell death, selectively removes damaged cells — including those with DNA damage or defective mitochondria. During apoptosis, cellular proteases and nucleases are activated, and cells self-destruct. Cells also monitor the survival factors and negative signals they receive from other cells before initiating programmed cell death. Once apoptosis begins, it proceeds quickly, leaving behind small fragments with recognizable bits of the nuclear material. Specialized cells then rapidly ingest and degrade these fragments, making evidence of apoptosis difficult to detect.

## What Cellular Components Support Tissue Structure?



**Figure 2: Different cell types in the mammalian gut**

The gut contains a mixture of differentiated cells and stem cells. The (a) intestine, (b) esophagus, and (c) stomach are shown. Through asymmetric division, quiescent stem cells (d) probably give rise to more rapidly dividing active stem cells, which then produce progenitor cells while losing their multipotency and ability to proliferate. All these progeny cells have defined positions in the different organs. To maintain its function and continue to produce new stem cells, a stem cell can also divide into and produce more stem cells at the same position (symmetric division).

© 2009 Nature Publishing Group Quante, M. & Wang, T. C. Stem cells in gastroenterology and hepatology. *Nature Reviews Gastroenterology & Hepatology* 6, 724-737 (2009)  
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Tissue function depends on more than cell type and proper rates of death and division: It is also a function of cellular arrangement. Both cell junctions and cytoskeletal networks help stabilize tissue architecture. For instance, the cells that make up human epithelial tissue attach to one another through several types of adhesive junctions. Characteristic transmembrane proteins provide the basis for each of the different types of junctions. At these junctions, transmembrane proteins on one cell interact with similar transmembrane proteins on adjacent cells. Special adaptor proteins then connect the resulting assembly to the cytoskeleton of each cell. The many connections formed between junctions and cytoskeletal proteins effectively produces a network that extends over many cells, providing mechanical strength to the epithelium.

The gut endothelium — actually an epithelium that lines the inner surface of the digestive tract — is an excellent example of these structures at work. Here, tight junctions between cells form a seal that prevents even small molecules and ions from moving across the endothelium. As a result, the endothelial cells themselves are responsible for determining which molecules pass from the gut lumen into the surrounding tissues. Meanwhile, adherens junctions based on transmembrane cadherin proteins provide mechanical support to the endothelium. These junctions are reinforced by attachment to an extensive array of actin filaments that underlie the apical — or lumen-facing — membrane. These organized collections of actin filaments also extend into the **microvilli**, which are the tiny fingerlike projections that protrude from the apical membrane into the gut

lumen and increase the surface area available for nutrient absorption. Additional mechanical support comes from **desmosomes**, which appear as plaque-like structures under the cell membrane, attached to intermediate filaments. In fact, desmosome-intermediate filament networks extend across multiple cells, giving the endothelium sheetlike properties. In addition, within the gut there are stem cells that guarantee a steady supply of new cells that contribute to the multiple cell types necessary for this complex structure to function properly (Figure 2).

### How Does the Extracellular Matrix Support Tissue Structure?

The extracellular matrix (ECM) is also critical to tissue structure, because it provides attachment sites for cells and relays information about the spatial position of a cell. The ECM consists of a mixture of proteins and polysaccharides produced by the endoplasmic reticula and Golgi apparatuses of nearby cells. Once synthesized, these molecules move to the appropriate side of the cell — such as the basal or apical face — where they are secreted. Final organization of the ECM then takes place outside the cell.

To understand how the ECM works, consider the two very different sides of the gut endothelium. One side of this tissue faces the lumen, where it comes in contact with digested food. The other side attaches to a specialized ECM support structure called the basal lamina. The basal lamina is composed of collagen and laminin proteins, as well as various other macromolecules. On this side of the endothelium, adhesive junctions attach cells to the ECM. Transmembrane integrin proteins in the junctions bind components of the ECM and recruit signaling proteins to their cytoplasmic sides. From there, the signals travel to the nucleus of each cell.

### Conclusion

Tissues are communities of cells that have functions beyond what any single cell type could accomplish. Healthy tissues require the proper mix of cells, and the cells within them must be oriented correctly and dividing at an appropriate rate. In order to coordinate their function, organization, and rates of death and division, the cells in a tissue are constantly processing and responding to signals from one another and from the ECM around them.

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### 5.5 Normal Controls on Cell Division Are Lost during Cancer

**Cancer cells** are cells gone wrong — in other words, they no longer respond to many of the signals that control cellular growth and death. Cancer cells originate within tissues and, as they grow and divide, they diverge ever further from normalcy. Over time, these cells become increasingly resistant to the controls that maintain normal tissue — and as a result, they divide more rapidly than their progenitors and become less dependent on signals from other cells. Cancer cells even evade programmed cell death, despite the fact that their multiple abnormalities would normally make them prime targets for apoptosis. In the late stages of cancer, cells break through normal tissue boundaries and metastasize (spread) to new sites in the body.

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#### How Do Cancer Cells Differ from Normal Cells?

In normal cells, hundreds of genes intricately control the process of cell division. Normal growth requires a balance between the activity of those genes that promote cell proliferation and those that suppress it. It also relies on the activities of genes that signal when damaged cells should undergo apoptosis.

Cells become cancerous after **mutations** accumulate in the various genes that control cell proliferation. According to research findings from the Cancer Genome Project, most cancer cells possess 60 or more mutations. The challenge for medical researchers is to identify which of these mutations are responsible for particular kinds of cancer. This process is akin to searching for the proverbial needle in a haystack, because many of the mutations present in these cells have little to nothing to do with cancer growth.

Different kinds of cancers have different mutational signatures. However, scientific comparison of multiple tumor types has revealed that certain genes are mutated in cancer cells more often than others. For instance, growth-promoting genes, such as the gene for the signaling protein Ras, are among those most commonly mutated in cancer cells, becoming super-active and producing cells that are too strongly stimulated by growth receptors. Some chemotherapy drugs work to counteract these mutations by blocking the action of growth-signaling proteins. The breast cancer drug Herceptin, for example, blocks overactive receptor tyrosine kinases (RTKs), and the drug Gleevec blocks a mutant signaling kinase associated with chronic myelogenous leukemia.

Other cancer-related mutations deactivate the genes that suppress cell proliferation or those that signal the need for apoptosis. These genes, known as tumor suppressor genes, normally function like brakes on proliferation, and both copies within a cell must be mutated in order for uncontrolled division to occur. For example, many cancer cells carry two mutant copies of the gene that codes for p53, a multifunctional protein that normally senses DNA damage and acts as a transcription factor for checkpoint control genes.

#### How Do Cancerous Changes Arise?

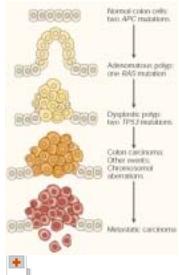
Gene mutations accumulate over time as a result of independent events. Consequently, the path to cancer involves multiple steps. In fact, many scientists view the progression of cancer as a microevolutionary process.



Figure 1: Microevolution of a cancer cell

A series of mutations in a cell causes it to proliferate more than its immediate neighbors. As the cluster of dividing cells grows over time, further mutations turn atypical hyperplasia into a cancer (carcinoma). The spreading of cancer cells to other tissues and organs (metastasis) occurs when the adhesion of these cancerous cells breaks down, and they are able to travel easily to new locations.

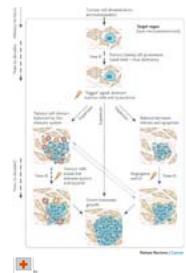
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**Figure 2**

To understand what this means, consider the following: When a mutation gives a cancer cell a growth advantage, it can make more copies of itself than a normal cell can — and its offspring can outperform their noncancerous counterparts in the competition for resources. Later, a second mutation might provide the cancer cell with yet another reproductive advantage, which in turn intensifies its competitive advantage even more. And, if key checkpoints are missed or repair genes are damaged, then the rate of damage accumulation increases still further. This process continues with every new mutation that offers such benefits, and it is a driving force in the evolution of living things — not just cancer cells (Figure 1, Figure 2).

### How Do Cancer Cells Spread to Other Tissues?

During the early stages of cancer, tumors are typically **benign** and remain confined within the normal boundaries of a tissue. As tumors grow and become **malignant**, however, they gain the ability to break through these boundaries and invade adjoining tissues.

**Figure 3**

Invasive cancer cells often secrete proteases that enable them to degrade the extracellular matrix at a tissue's boundary. Proteases also give cancer cells the ability to create new passageways in tissues. For example, they can break down the junctions that join cells together, thereby gaining access to new territories.

**Metastasis** — literally meaning "new place" — is one of the terminal stages of cancer. In this stage, cancerous cells enter the bloodstream or the lymphatic system and travel to a new location in the body, where they begin to divide and lay the foundation for secondary tumors. Not all cancer cells can metastasize. In order to spread in this way, the cells must have the ability to penetrate the normal barriers of the body so that they can both enter and exit the blood or lymph vessels. Even traveling metastatic cancer cells face challenges when trying to grow in new areas (Figure 3).

### Conclusion

Cancer is unchecked cell growth. Mutations in genes can cause cancer by accelerating cell division rates or inhibiting normal controls on the system, such as cell cycle arrest or programmed cell death. As a mass of cancerous cells grows, it can develop into a tumor. Cancer cells can also invade neighboring tissues and sometimes even break off and travel to other parts of the body, leading to the formation of new tumors at those sites.

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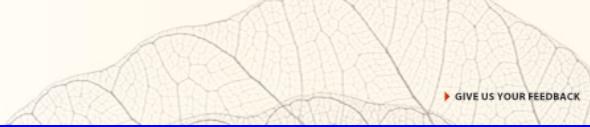
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