11 How Genes Are Controlled

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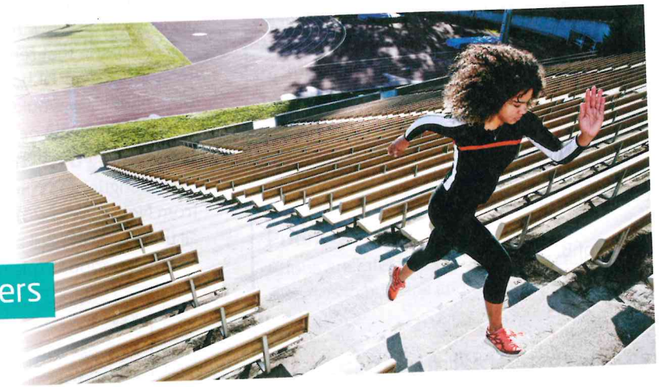
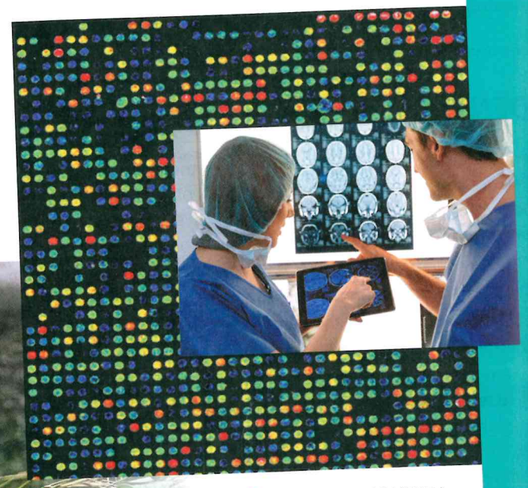
Why Gene Regulation Matters

No organism uses all its genes all the time. Instead, cells turn genes on and off depending on the situation. The ability to regulate genes therefore underlies all of life's processes, such as growth, metabolism, and the ability to adapt to a changing environment.



SIMPLE CHANGES IN LIFESTYLE CAN DRAMATICALLY REDUCE YOUR RISK OF CANCER.



A DNA CHIP MAY SOON BECOME A DIAGNOSTIC TOOL AS COMMON AS X-RAYS.

CLONING MAY HELP SAVE THE GIANT PANDA FROM EXTINCTION.

CHAPTER THREAD

Cancer

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BIOLOGY AND SOCIETY Canc

Breast Cancer and Chemo

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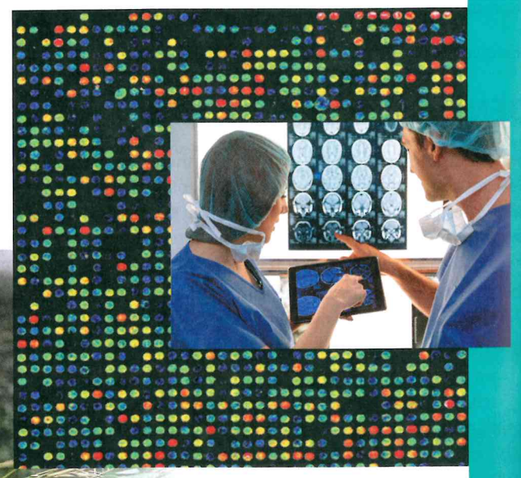

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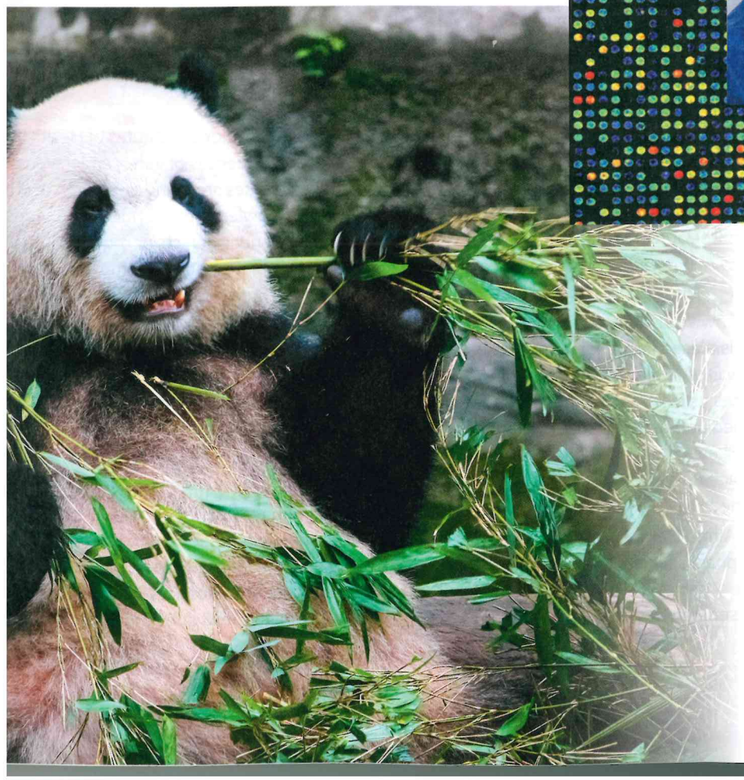

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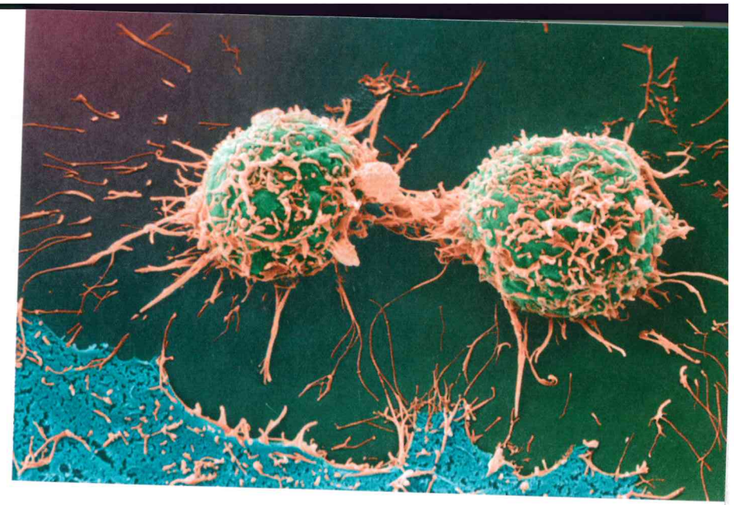


Human cancer cells. These cells from a cancerous cervical tumor have lost the ability to control their growth.

BIOLOGY AND SOCIETY Cancer

Breast Cancer and Chemotherapy

First, some bad news: About one out of every eight women will develop breast cancer. But there is also some good news: If a woman's breast cancer is treated in its earliest stages, her chance of surviving five years or more is nearly 100%. On the other hand, if her breast cancer is not treated until it has spread throughout her body, the five-year survival rate is less than 25%. Treatment typically involves surgery, followed by hormone therapy and radiation to kill cancer cells. Chemotherapy may serve as a final step. Unfortunately, chemotherapy has many negative side effects, such as nausea and hair loss, and in a small percentage of women, long-term nerve, blood, or heart disorders.

Cancer specialists traditionally determine whether a woman should have chemotherapy by using clinical factors, such as the size of her tumor and how many lymph nodes had cancer cells in them. As an analogy, suppose that you knew a car with no brakes was headed toward a cliff. Should you shoot out the tires? Is the intervention worth the risk? The clinical factors are like looking at how far the car is from the edge of the cliff. The closer to the edge, the more it makes sense to use an extreme intervention. However, a woman may have a large tumor and several affected lymph nodes because she has had a slow-growing cancer for a long time. Her risk may actually be low. Giving her chemotherapy might be an unnecessary intervention, like shooting out the tires on a car that is never going to reach the cliff.

How can doctors tell which cases are risky enough to warrant chemotherapy? What determines how fast cancer cells spread and therefore the risk posed by a particular tumor? First, it's helpful to know how mutations lead to cancer. Many cancer-associated genes encode proteins that turn other genes on or off. When these genes are mutated, the proteins malfunction and the cell may become cancerous. Scientists can now tell which genes are mutated in a given tumor. This information is like knowing the size of the engine of the car headed for the cliff. It allows medical professionals to predict the potential growth rate of the cancer. Soon, the genes of all cancer patients may be evaluated in this way, allowing therapy to be optimized for each patient. Such research may someday provide a strong barrier between cars and the edge of the cliff.

The ability to properly control which genes are active at any given time is crucial to normal cell function. How genes are controlled and how the regulation of genes affects cells and organisms—including ways that gene regulation affects your own life—are the subjects of this chapter.

11
HOW GENES ARE CONTROLLED

How and Why Genes Are Regulated

Every cell in your body—and, indeed, all the cells in the body of every sexually reproducing organism—was produced through successive rounds of mitosis starting from the zygote, the original cell that formed after fusion of sperm and egg. Mitosis exactly duplicates the chromosomes. Therefore, every cell in your body has the same DNA as the zygote. To put it another way: Every somatic (body) cell contains every gene. However, the cells in your body are specialized in structure and function; a neuron, for example, looks and acts nothing like a red blood cell. But if every cell contains identical genetic instructions, how do cells develop differently from one another? To help you understand this idea, imagine that every restaurant in your hometown uses the same cookbook. If that were the case, how could each restaurant develop a unique menu? The answer is obvious: Even though each restaurant has the same cookbook, different restaurants pick and choose different recipes from this book to prepare. Similarly, cells with the same genetic information can develop into different types of cells through **gene regulation**, mechanisms that turn on certain genes while other genes remain turned off. Regulating gene activity allows for specialization of cells within the body, just as regulating which recipes are used allows for varying menus in multiple restaurants.

As an example of gene regulation, consider the development of a single-celled zygote into a multicellular organism. During embryonic growth, groups of cells follow different paths, and each group becomes a particular kind of tissue. In the mature organism, each cell type—neuron or red blood cell, for instance—has a different pattern of turned-on genes.

What does it mean to say that genes are turned on or off? Genes determine the nucleotide sequence of specific mRNA molecules, and mRNA in turn determines the sequence of amino acids in proteins (in summary: DNA → RNA → protein; see Chapter 10). A gene that is turned on is being transcribed into mRNA, and that message is being translated into specific proteins. The overall process by which genetic information flows from genes to proteins is called **gene expression**. The control of gene expression makes it possible for cells to produce specific kinds of proteins when and where they are needed, allowing cells to respond quickly and efficiently to information from the environment.

As an illustration of this principle, Figure 11.1 shows the patterns of gene expression for four genes in three different specialized cells of an adult human. Note that the genes for "housekeeping" enzymes, such as those that provide energy through glycolysis, are "on" in all the cells. In contrast, the genes for some proteins, such as insulin and hemoglobin, are expressed only by particular kinds of cells. One protein, hemoglobin, is not expressed in any of the cell types shown in the figure. ✓

✓ CHECKPOINT

If your blood cells and skin cells have the same genes, how can they be so different?

■ Answer: Each cell type expresses different genes than the other cell type.

Gene Regulation in Bacteria

To understand how a cell can regulate gene expression, consider the relatively simple case of bacteria. In the course of their lives, bacteria must regulate their genes in response to environmental changes. For example, when a nutrient is plentiful, bacteria do not squander valuable resources to make the nutrient from scratch. Bacterial cells that can conserve resources and energy have a survival advantage over cells that are unable to do so. Thus, natural selection has favored bacteria that express only the genes whose products are needed by the cell.

Imagine an *Escherichia coli* bacterium living in your intestines. It will be bathed in various nutrients, depending on what you eat. If you drink a milk shake, for example, there will be a sudden rush of the sugar lactose. In response, *E. coli* will express three genes for enzymes that enable the bacterium to absorb and digest this sugar. After the lactose is gone, these genes are turned off; the bacterium does not waste its energy continuing to produce these enzymes when they are not needed. Thus, a bacterium can adjust its gene expression to changes in the environment. Such regulation is at the heart of metabolism, the chemical reactions that transform energy and matter within all cells.

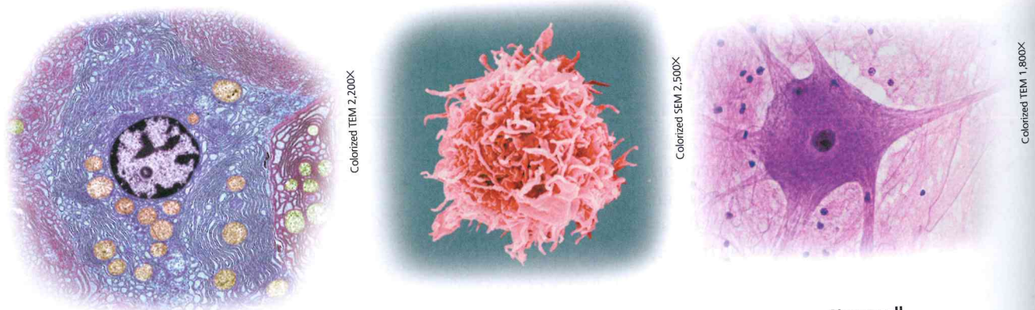
How does a bacterium "know" if lactose is present or not? In other words, how does the presence or absence of lactose influence the activity of the genes that code for the lactose enzymes? The key is the way the three lactose-digesting genes are organized: They are adjacent in the DNA and turned on and off as a single unit. This regulation is achieved through short stretches of DNA that help turn all three genes on and off at once, coordinating their expression. Such a cluster of related genes and sequences that control them is called an **operon** (Figure 11.2). The operon considered here, the *lac* (short for lactose) operon, illustrates principles of gene regulation that apply to a wide variety of prokaryotic genes.

How do DNA control sequences turn genes on or off? One control sequence, called a **promoter** (green in the figure), is the site where the enzyme RNA polymerase attaches and initiates transcription—in our example, transcription of the genes for lactose-digesting enzymes. Between the promoter and the enzyme genes, a DNA segment called an **operator** (yellow) acts as a switch that is turned on or off, depending on whether a specific protein is bound there. The operator and protein together determine whether RNA polymerase can attach to the promoter and start transcribing the genes (light blue). In the *lac* operon, when the operator switch is turned on, all the enzymes needed to metabolize lactose are made at once.

The top half of Figure 11.2 shows the *lac* operon in "off" mode, its status when there is no lactose available. Transcription is turned off because 1 a protein called a **repressor** ( ) binds to the operator ( ) and 2 physically blocks the attachment of RNA polymerase ( ) to the promoter ( ).

The bottom half of Figure 11.2 shows the operon in "on" mode, when lactose is present. The lactose ( )

▶ **Figure 11.1 Patterns of gene expression in three types of human cells.** Different types of cells express different combinations of genes. The specialized proteins whose genes are represented here are an enzyme involved in glucose digestion; an antibody, which aids in fighting infection; insulin, a hormone made in the pancreas; and the oxygen transport protein hemoglobin, which is expressed only in red blood cells.



	Pancreas cell	White blood cell	Nerve cell
Gene for a glycolysis enzyme	✓	✓	✓
Antibody gene	X	✓	X
Insulin gene	✓	X	X
Hemoglobin gene	X	X	X

Key
✓ = Active gene
X = Inactive gene

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▼ **Figure 11.2 The *lac***

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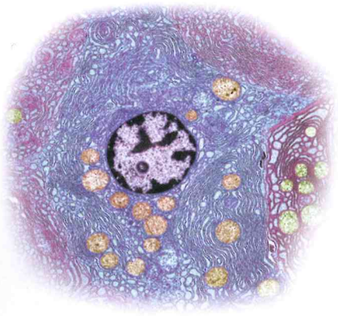

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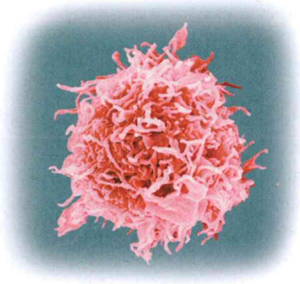

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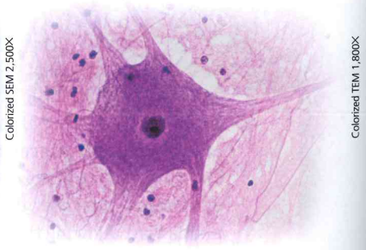

Colorized TEM 1,800×

	Pancreas cell	White blood cell	Nerve cell
Gene for a glycolysis enzyme	✓	✓	✓
Antibody gene	X	✓	X
Insulin gene	✓	X	X
Hemoglobin gene	X	X	X

Gene Regulation in Bacteria

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The bottom half of Figure 11.2 shows the operon in "on" mode, when lactose is present. The lactose ( ) interferes with attachment of the *lac* repressor to the operator by 1 binding to the repressor and 2 changing the repressor's shape. As we so often see in biological systems, structure and function are related. In this case, altering the repressor's shape changes how it acts. In its new shape ( ), the repressor cannot bind to the operator, and the operator switch remains on. 3 RNA polymerase is no longer blocked, so it can now bind to the promoter and from there 4 transcribe the genes for the lactose enzymes into mRNA. 5 Translation produces all three lactose enzymes (purple).

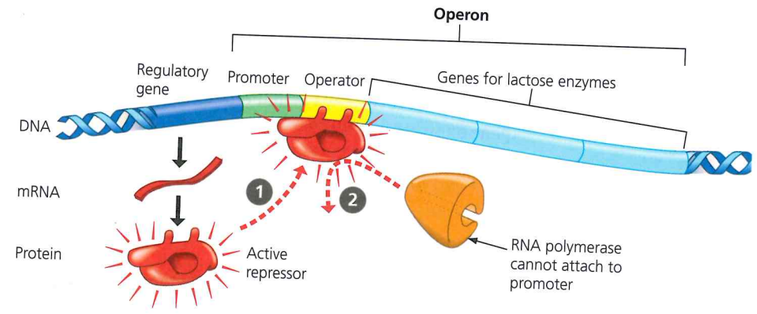
Many operons have been identified in bacteria. Some are quite similar to the *lac* operon, whereas others have somewhat different mechanisms of control. For example, operons that control amino acid synthesis cause bacteria to stop making these molecules when they are already present in the environment, saving materials and energy for the cells. In these cases, the amino acid *activates* the repressor. Armed with a variety of operons, *E. coli* and other prokaryotes can thrive in frequently changing environments. ✓

✓ CHECKPOINT

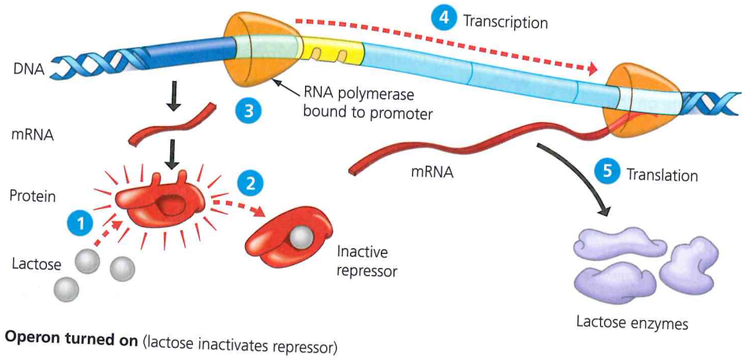
A mutation in *E. coli* makes the *lac* operator unable to bind the active repressor. How would this mutation affect the cell? Why would this effect be a disadvantage?

■ *Answer: The cell would wastefully produce the enzymes for lactose metabolism continuously, even in the absence of lactose.*

▼ **Figure 11.2** The *lac* operon of *E. coli*.



Operon turned off (lactose absent)



Operon turned on (lactose inactivates repressor)

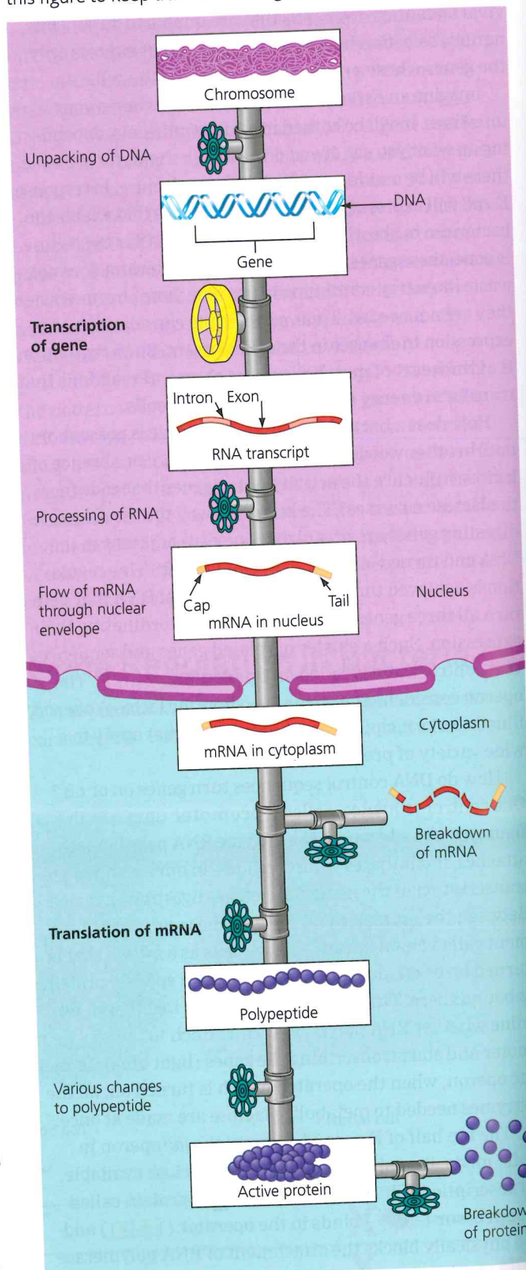
Gene Regulation in Eukaryotic Cells

Eukaryotes, especially multicellular ones, have more sophisticated mechanisms than bacteria for regulating the expression of their genes. This is not surprising because a prokaryote, being a single cell, does not have different types of specialized cells, such as neurons and red blood cells. Therefore, it does not require the elaborate regulation of gene expression that leads to cell specialization in multicellular eukaryotic organisms.

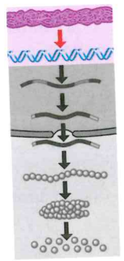
The pathway from gene to protein in eukaryotic cells is a long one, providing a number of points where the process can be turned on or off, speeded up or slowed down. Picture the series of pipes that carry water from your local reservoir to a faucet in your home. At various points, valves control the flow of water. We use this analogy in **Figure 11.3** to illustrate the flow of genetic information from a eukaryotic chromosome—a reservoir of genetic information—to an active protein that has been made in the cell's cytoplasm. The multiple mechanisms that control gene expression are analogous to the control valves in your water pipes. In the figure, each control knob indicates a gene expression "valve." All these knobs represent possible control points, although only one or a few control points are likely to be important for a typical protein.

Using a reduced version of Figure 11.3 as a guide, we will explore several ways that eukaryotes can control gene expression, starting within the nucleus.

▼ **Figure 11.3 The gene expression "pipeline" in a eukaryotic cell.** Each valve in the pipeline represents a stage at which the pathway from gene to functioning protein can be regulated, turned on or off, or speeded up or slowed down. Throughout this discussion we will use a miniature version of this figure to keep track of the stages as they are discussed.



The Regulation of DNA Packing



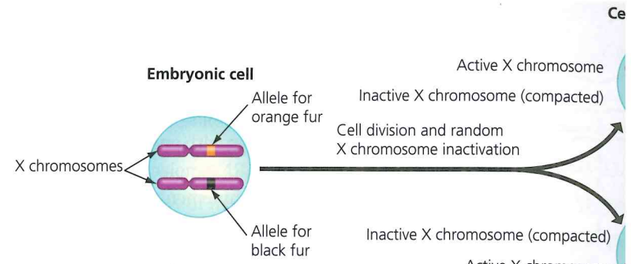
Eukaryotic chromosomes may be in a more or less condensed state, with the DNA and accompanying proteins more or less tightly wrapped together (see Figure 8.4). DNA packing tends to prevent gene expression by preventing RNA polymerase and other transcription proteins from binding to the DNA.

Cells may use DNA packing for the long-term inactivation of genes. One intriguing case is seen in female mammals, where one X chromosome in each somatic cell is highly compacted and almost entirely inactive. This X chromosome inactivation first takes place early in embryonic development, when one of the two X chromosomes in each cell is inactivated at random. After one X chromosome is inactivated in each embryonic cell, all of that cell's descendants will have the same X chromosome turned off. Consequently, if one X chromosome in the embryonic cell has one allele and the other has a different allele, about half of the cell's descendants will express one allele, while the other half will express the other allele **(Figure 11.4)**. ✅

✅ CHECKPOINT

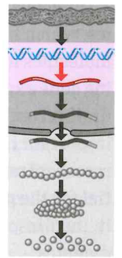
Would a gene on the X chromosome be expressed more in human females (who have two copies of the X chromosome) than in human males (who have one copy)?

■ *Answer: No, because in females one of the X chromosomes in each cell is inactivated.*



▲ **Figure 11.4 X chromosome inactivation: the tortoiseshell pattern on a female cat.** The tortoiseshell phenotype requires two different alleles: an allele for orange fur on one X chromosome and an allele for black fur on the other X chromosome. Orange patches are formed by populations of cells in which the X chromosome with the allele for orange fur is active; black patches have cells in which the X chromosome with the allele for black fur is active.

The Initiation of Transcription



The most important stage for regulating gene expression is the determination of whether transcription is initiated or not. That is why this control point is emphasized with the large yellow valve in Figure 11.3. In both prokaryotes and eukaryotes, regulatory proteins bind to DNA and turn the transcription of genes on and off. Unlike prokaryotic genes, however, most eukaryotic genes are not grouped into operons. Instead, each eukaryotic gene usually has its own promoter and other control sequences.

Transcriptional regulation in eukaryotes is complex, typically involving many proteins **(Figure 11.5)**. To do its job, RNA polymerase requires the assistance of proteins called **transcription factors**. Some are essential for transcribing all genes, and others are specific to a few or just one gene. Transcription factors (purple in the figure) bind to noncoding DNA sequences called **enhancers** (yellow) and help RNA polymerase (orange) bind to the promoter (green). Genes coding for related enzymes, such as those in a metabolic pathway, may share a specific kind of enhancer (or collection of enhancers), allowing these genes to be activated at the same time. (Not shown in the figure are repressor proteins, which may bind to DNA sequences called **silencers**, inhibiting the start of transcription.)

In fact, repressor proteins that turn genes off are less common in eukaryotes than **activators**, proteins that

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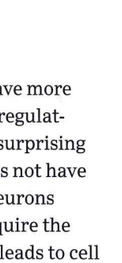
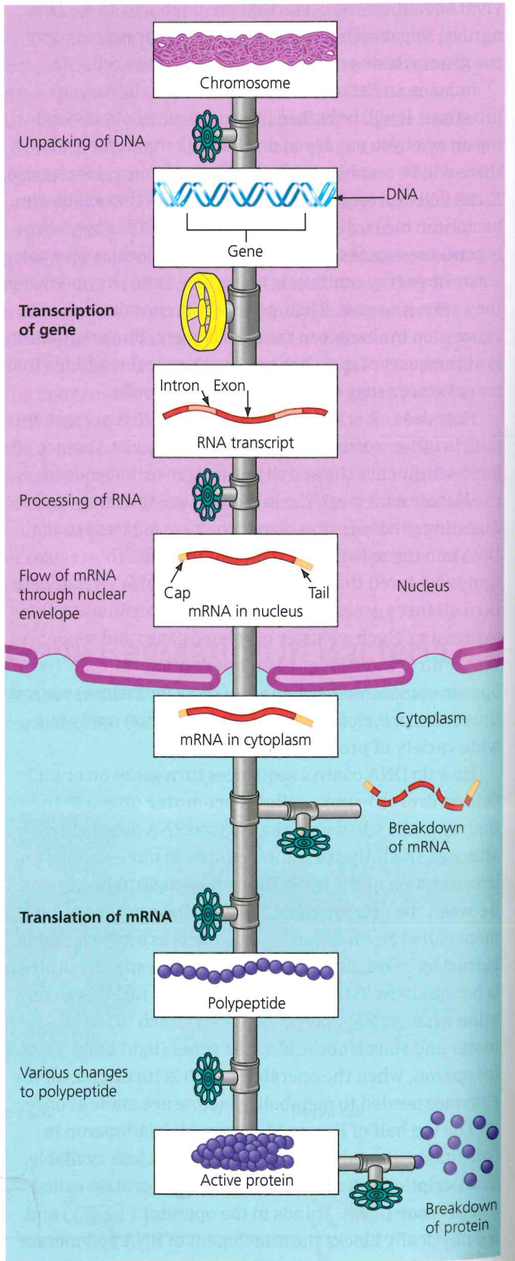


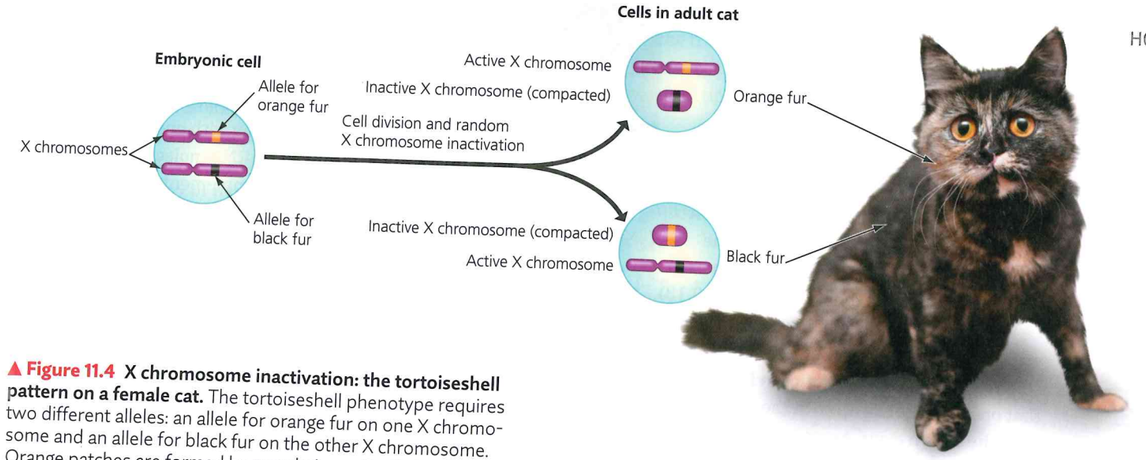
The Regulation of DNA Packing

Eukaryotic chromosomes may be in a more or less condensed state, with the DNA and accompanying proteins more or less tightly wrapped together (see Figure 8.4). DNA packing tends to prevent gene expression by preventing RNA polymerase and other transcription proteins from binding to the DNA.

Cells may use DNA packing for the long-term inactivation of genes. One intriguing case is seen in female mammals, where one X chromosome in each somatic cell is highly compacted and almost entirely inactive. This X chromosome inactivation first takes place early in embryonic development, when one of the two X chromosomes in each cell is inactivated at random. After one X chromosome is inactivated in each embryonic cell, all of that cell's descendants will have the same X chromosome turned off. Consequently, if one X chromosome in the embryonic cell has one allele and the other has a different allele, about half of the cell's descendants will express one allele, while the other half will express the other allele **(Figure 11.4)**. ✅

▼ Figure 11.3 The gene expression "pipeline" in a eukaryotic cell. Each valve in the pipeline represents a stage at which the pathway from gene to functioning protein can be regulated, turned on or off, or speeded up or slowed down. Throughout this discussion we will use a miniature version of this figure to keep track of the stages as they are discussed.

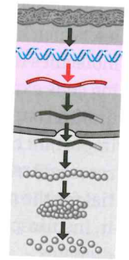




▲ Figure 11.4 X chromosome inactivation: the tortoiseshell pattern on a female cat. The tortoiseshell phenotype requires two different alleles: an allele for orange fur on one X chromosome and an allele for black fur on the other X chromosome. Orange patches are formed by populations of cells in which the X chromosome with the allele for orange fur is active; black patches have cells in which the X chromosome with the allele for black fur is active.

The Initiation of Transcription

The most important stage for regulating gene expression is the determination of whether transcription is initiated or not. That is why this control point is emphasized with the large yellow valve in Figure 11.3. In both prokaryotes and eukaryotes, regulatory proteins bind to DNA and turn the transcription of genes on and off. Unlike prokaryotic genes, however, most eukaryotic genes are not grouped into operons. Instead, each eukaryotic gene usually has its own promoter and other control sequences.



Transcriptional regulation in eukaryotes is complex, typically involving many proteins **(Figure 11.5)**. To do its job, RNA polymerase requires the assistance of proteins called **transcription factors**. Some are essential for transcribing all genes, and others are specific to a few or just one gene. Transcription factors (purple in the figure) bind to noncoding DNA sequences called **enhancers** (yellow) and help RNA polymerase (orange) bind to the promoter (green). Genes coding for related enzymes, such as those in a metabolic pathway, may share a specific kind of enhancer (or collection of enhancers), allowing these genes to be activated at the same time. (Not shown in the figure are repressor proteins, which may bind to DNA sequences called **silencers**, inhibiting the start of transcription.)

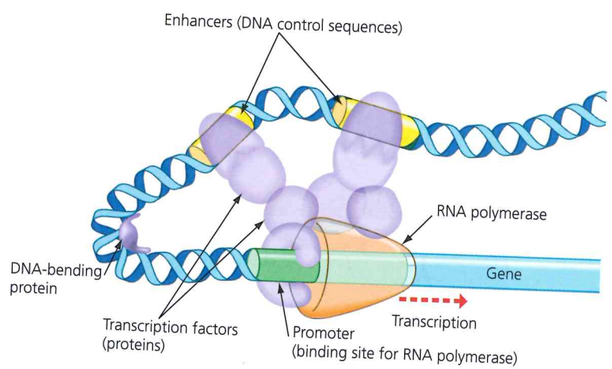
In fact, repressor proteins that turn genes off are less common in eukaryotes than **activators**, proteins that turn genes on by binding to DNA. Activators act by making it easier for RNA polymerase to bind to the promoter. The use of activators is efficient because a typical animal or plant cell needs to turn on (transcribe) only a small percentage of its genes, those required for the cell's specialized structure and function. The default state for most genes in multicellular eukaryotes seems to be off; research indicates that a typical human cell expresses only about 20% of its protein-coding genes at any given time. ✅

✅ CHECKPOINT

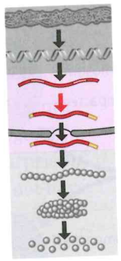
Of all the control points of DNA expression shown in Figure 11.3, which is under the tightest regulation?

■ Answer: the initiation of transcription

▼ Figure 11.5 A model for turning on a eukaryotic gene. Transcription is regulated by noncoding DNA sequences called enhancers. DNA-bending proteins help bring the enhancers close to the transcription site. Once this is done, transcription factors help RNA polymerase bind to the promoter, where it begins transcription of the gene.



RNA Processing and Breakdown



Within a eukaryotic cell, transcription occurs in the nucleus, where RNA transcripts are processed into mRNA before moving to the cytoplasm for translation by the ribosomes (see Figure 10.19). RNA processing includes the addition of a cap and a tail, the removal of introns (the noncoding DNA segments that interrupt the genetic message), and RNA splicing (the splicing together of exons) (see Figure 10.13).

Within a cell, exon splicing can occur in more than one way, generating different mRNA molecules from the same starting RNA molecule. Notice in **Figure 11.6**, for example, that one mRNA ends up with the green exon and the other with the brown exon. As a result of this process, called **alternative RNA splicing**, an organism can produce more than one type of polypeptide from a single gene. A typical human gene contains about ten exons; nearly all genes are spliced in at least two different ways, and some are spliced hundreds of different ways.

After an mRNA is produced in its final form, its "lifetime" can be highly variable, from hours to weeks to months. Controlling the timing of mRNA breakdown provides another opportunity for regulation. But all mRNAs are eventually broken down and their parts recycled. ✅

✅ CHECKPOINT

After a gene is transcribed in the nucleus, name three ways that the RNA may be processed.

■ *Answer: by the addition of cap and tail, the removal of introns, and the splicing of exons*

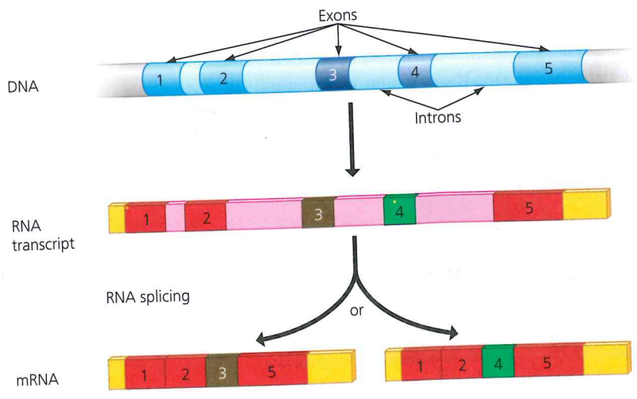
microRNAs

The vast majority of human DNA does not code for proteins. This DNA has long been thought to be lacking any genetic information. In fact, many biologists used to refer to these regions as "junk DNA" because they performed no discernible function. However, a significant amount of the genome is transcribed into functioning but non–protein-coding RNAs. For example, small, single-stranded RNA molecules, called **microRNAs (miRNAs)**, can bind to complementary sequences on mRNA molecules **(Figure 11.7)**. Each miRNA ❶ forms a complex with one or more proteins that can ❷ bind to any mRNA molecule with at least seven or eight nucleotides of complementary sequence. If the mRNA molecule contains a sequence complementary to the full length of the miRNA, the complex ❸ degrades the target mRNA. If the mRNA molecule matches the sequence along just part of the miRNA, the complex ❹ blocks its translation.

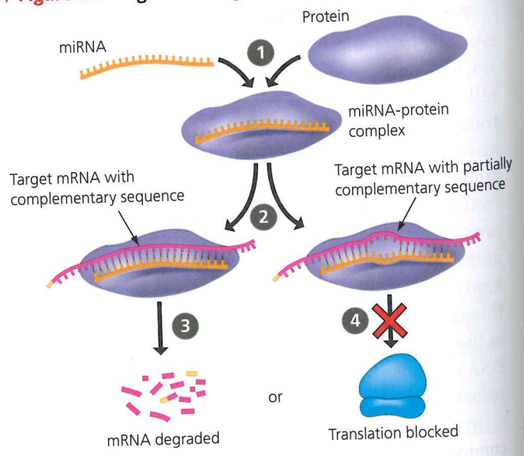
In addition to microRNAs, there is another class of small RNA molecules called small interfering RNAs (siRNAs). The blocking of gene expression by siRNAs is called **RNA interference (RNAi)**. Researchers can take advantage of siRNAs to artificially control gene expression. For example, injecting siRNA into a cell can turn off expression of a gene with a sequence that matches the siRNA. RNAi, therefore, allows researchers to disable specific genes in order to investigate their functions.

Biologists are excited about these recent discoveries, which hint at a large, diverse population of RNA molecules in the cell that play crucial roles in regulating gene expression but have gone largely unnoticed until recently. Our improved understanding may lead to important clinical applications. For example, in 2009, researchers discovered a particular miRNA that is essential for the proper functioning of the pancreas. Without it, insulin-producing beta cells die, which can lead to diabetes.

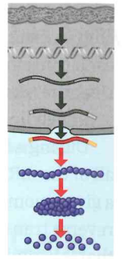
▼ Figure 11.6 Alternative RNA splicing: producing multiple mRNAs from the same gene. Two different cells can use the same DNA gene to synthesize different mRNAs and proteins. In this example, one mRNA has ended up with exon 3 (brown) and the other with exon 4 (green). These mRNAs, which are just two of many possible outcomes, can then be translated into different proteins.



▼ Figure 11.7 Regulation of gene expression by an miRNA.



The Initiation of Translation



The process of translation—in which an mRNA is used to make a protein—offers additional opportunities for control by regulatory molecules. Red blood cells, for instance, have a protein that prevents the translation of hemoglobin mRNA unless the cell has a supply of heme, an iron-containing chemical group essential for hemoglobin function.

Protein Activation and Breakdown

The final opportunities for regulating gene expression occur after translation. For example, the hormone insulin is synthesized as one long, inactive polypeptide that must be chopped into pieces before it comes active. Other proteins require chemical modification before they become active.

Another control mechanism operating after translation is the selective breakdown of proteins. Some proteins that trigger metabolic changes in cells are broken down within a few minutes or hours. This regulation allows a cell to adjust the kinds and amounts of its proteins in response to changes in its environment.

Cell Signaling

So far, we have considered gene regulation only within a single cell. **Within a multicellular organism, information must be communicated between cells.** For example, a cell can produce and secrete chemicals, such as hormones, that affect gene regulation in another cell. This allows the organism as a whole to alter its activities in response to signals from the environment. Consider an analogy from your own experience: In grade school, did you ever station a classmate near the door to signal the teacher's return? Information from outside the room (the teacher's approach) was used to alter behavior within the classroom ("Stop messing around!"). In a similar way, cells use protein "lookouts" to convey information into the cell, resulting in changes to cellular functions.

A signal molecule can act by binding to a receptor protein and initiating a **signal transduction pathway**, a series of molecular changes that converts a signal received outside a cell to a specific response inside the target cell. **Figure 11.8** shows an example of cell-to-cell signaling in which the target cell's response is the transcription (turning on) of a gene. ❶ First, the signaling cell secretes the signal molecule ( ). ❷ This molecule binds to a specific receptor protein ( ) embedded in the target cell's plasma membrane. ❸ The binding activates a signal transduction pathway consisting of a series of relay proteins (green) within the target cell. Each relay molecule activates the next. ❹ The last relay molecule

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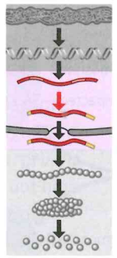

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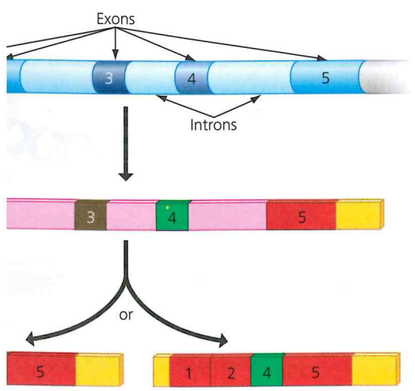

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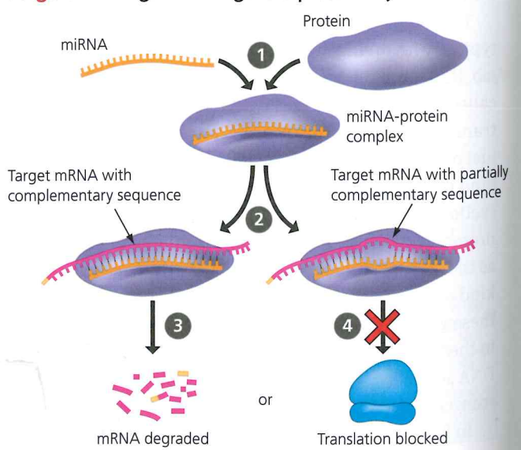
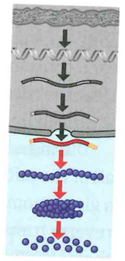


The Initiation of Translation



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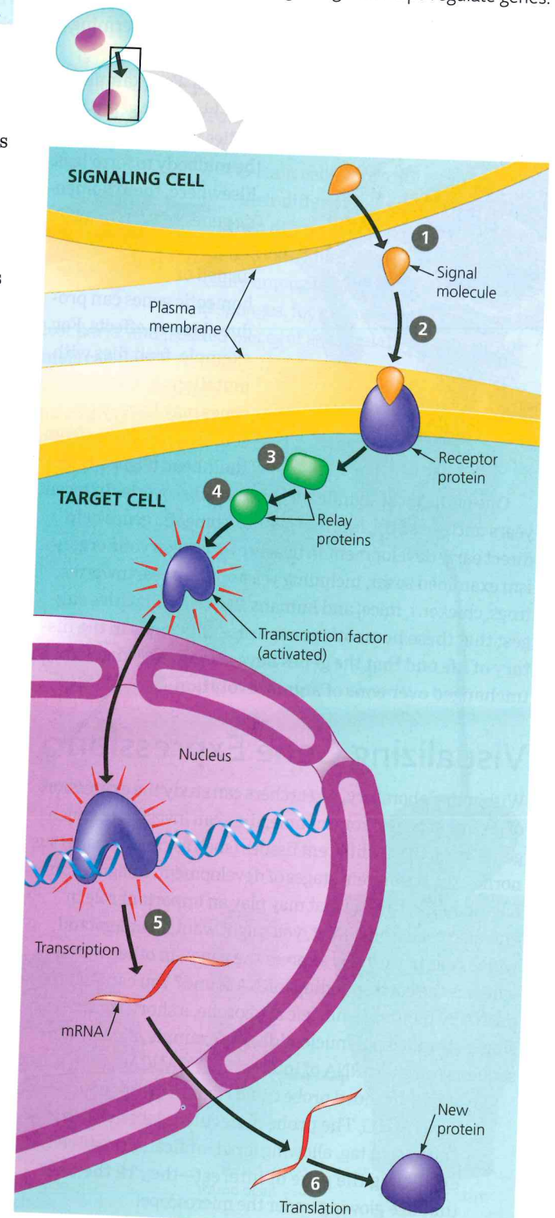
▼ Figure 11.8 A cell-signaling pathway that turns on a gene. The coordination of cellular activities in a multicellular organism depends on cell-to-cell signaling that helps regulate genes.



✅ CHECKPOINT

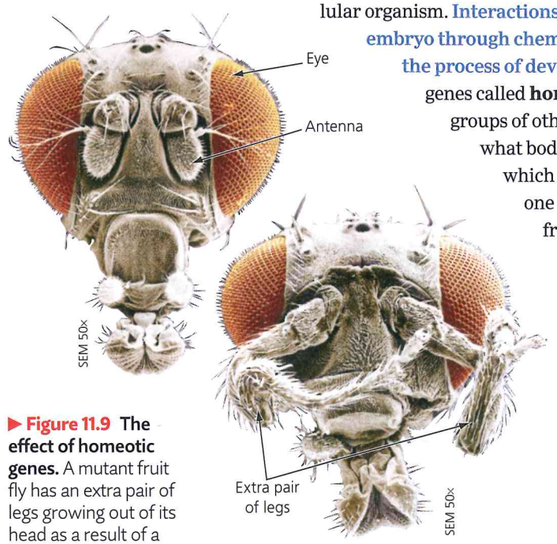
How can a signal molecule from one cell alter gene expression in a target cell without entering the target cell?

■ Answer: by binding to a receptor protein in the membrane of the target cell and triggering a signal transduction pathway that activates transcription factors

Figure Walkthrough
Mastering Biology
goo.gl/tztnY6

Homeotic Genes

Cell-to-cell signaling and the control of gene expression are particularly important during early embryonic development, when a single-celled zygote develops into a multicellular organism. Interactions between the cells of an embryo through chemical signals coordinate the process of development. Master control genes called **homeotic genes** regulate groups of other genes that determine what body parts will develop in which locations. For example, one set of homeotic genes in fruit flies instructs cells in the midbody to form legs. Elsewhere, these homeotic genes remain turned off, while others are turned on. Mutations in homeotic genes can produce bizarre effects. For example, fruit flies with mutations in homeotic genes may have extra sets of legs growing from their head (Figure 11.9).



▶ **Figure 11.9 The effect of homeotic genes.** A mutant fruit fly has an extra pair of legs growing out of its head as a result of a mutation in a homeotic (master control) gene.

One of the most significant biological discoveries in recent years uncovered the fact that similar homeotic genes help direct early development in nearly every eukaryotic organism examined so far, including yeasts, plants, earthworms, frogs, chickens, mice, and humans. These similarities suggest that these homeotic genes arose very early in the history of life and that the genes have remained remarkably unchanged over eons of animal evolution. ✅

✅ CHECKPOINT

How can a mutation in just one homeotic gene drastically affect an organism's physical appearance?

■ *Answer: Because homeotic genes control many other genes, a single change can affect the expression of many of the proteins that control appearance.*

Visualizing Gene Expression

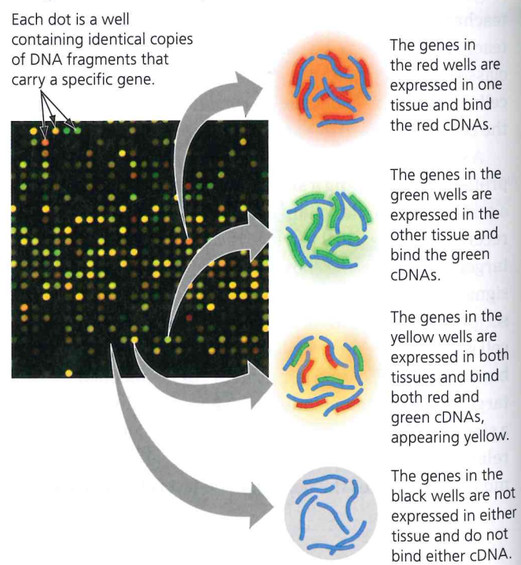
Within the laboratory, researchers can study the expression of groups of genes. For example, they can investigate which genes are active in different tissues (such as cancerous versus normal) or at different stages of development. Imagine you have identified a gene that may play an important role in an inherited disease. First, you might want to understand which cells in the body express the gene—in other words, where is the corresponding mRNA found? You can find the mRNA by building a nucleic acid probe, a short, synthetic, single-stranded polynucleotide. For example, if part of the sequence on the mRNA of interest is CUCAUCAC, then a single-stranded probe could contain the sequence GAGTAGTG. The probe molecule is labeled with a fluorescent tag, allowing for identification of all cells expressing the gene of interest—they're the ones that are glowing under the microscope!

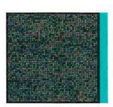
Rather than studying just one gene, researchers can study many or even all genes at once using DNA microarrays. A **DNA microarray** (also called a DNA chip or gene chip) is a glass slide with many tiny wells, each containing a different fragment of single-stranded DNA that derives from a particular gene. The wells are arranged in a tightly spaced array, or grid.

During a DNA microarray study, a researcher collects all of the mRNA transcribed in a particular type of cell at a given moment. This collection of mRNA is mixed with reverse transcriptase, a viral enzyme that produces DNA that is complementary to each mRNA sequence. These fragments are called **complementary DNAs (cDNAs)** because each one is complementary to one of the mRNAs. The cDNAs are synthesized using nucleotides that have been modified to fluoresce (glow). The fluorescent cDNA collection represents all of the genes being actively transcribed in that particular cell at that particular time. The fluorescently labeled cDNA mixture is added to the DNA fragments of the microarray. If a molecule in the cDNA mixture is complementary to a DNA fragment at a particular location on the grid, the cDNA molecule binds to it, producing a detectable glow in the microarray. Often, the cDNAs from two samples (for example, two tissues) are labeled with molecules that emit different colors and tested on the same microarray (Figure 11.10). The pattern of glowing spots enables the researcher to determine which genes are being transcribed in one tissue compared with another.

DNA microarrays hold great promise in medical research. One study showed that DNA microarray data can classify different types of leukemia into specific subtypes based on the activity of 17 genes. It may become standard practice for every cancer patient to have DNA microarray analysis to discover the specific mutations involved in their cancer.

▼ **Figure 11.10 Visualizing gene expression using a DNA microarray.**





A DNA CHIP MAY BECOME A TOOL AS COMMON AS X-RAYS.

Cloning Plants and

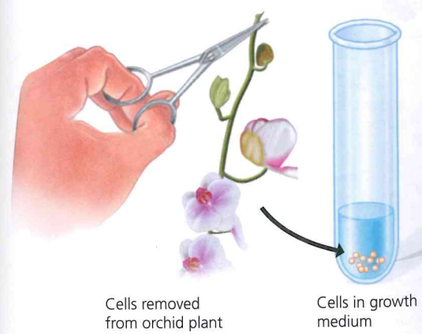
Now that we have examined how gene expression is regulated, we will devote the rest of this chapter to discuss how gene regulation affects two important processes: cloning and cancer.

The Genetic Potential of Ce

One of the most important take-home lessons from this chapter is that all body cells contain a complete set of genes, even if they are not expressing all of them. If you've ever grown a plant from a small cutting, you've seen evidence of this yourself: A single differentiated plant cell can undergo cell division and give rise to a complete adult plant, a task that requires a complete set of genes. On a larger scale, the technique described in Figure 11.11 can be used to produce hundreds or thousands of genetically identical organisms—clones—from the cells of a single plant.

Plant cloning is now used extensively in agricul For some plants, such as orchids, cloning is the onl mercially practical means of reproducing plants. I cases, cloning has been used to reproduce a plant v

▼ **Figure 11.11 Test-tube cloning of an orchid.** Tissue removed from the stem of an orchid plant and placed growth medium may begin dividing and eventually grc into an adult plant. The new plant is a genetic duplicate the parent plant. This process proves that mature plan cells can reverse their differentiation and develop into specialized cells of an adult plant.



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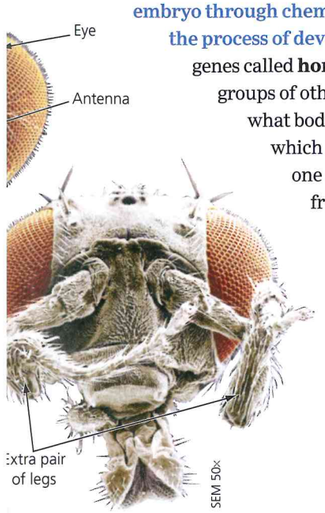

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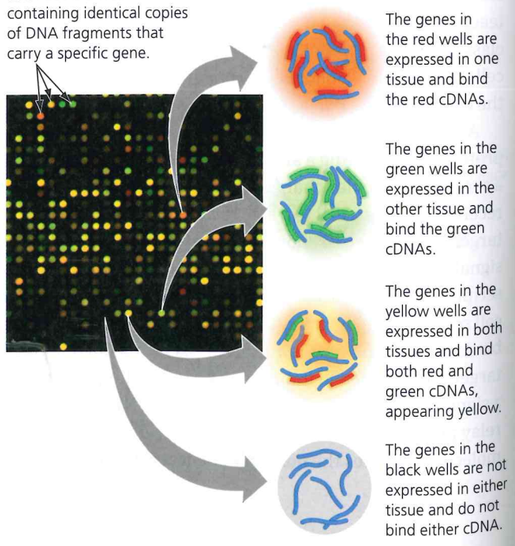
▼ **Figure 11.10 Visualizing gene expression using a DNA microarray.**



Cloning Plants and Animals

Now that we have examined how gene expression is regulated, we will devote the rest of this chapter to discussing how gene regulation affects two important processes: cloning and cancer.

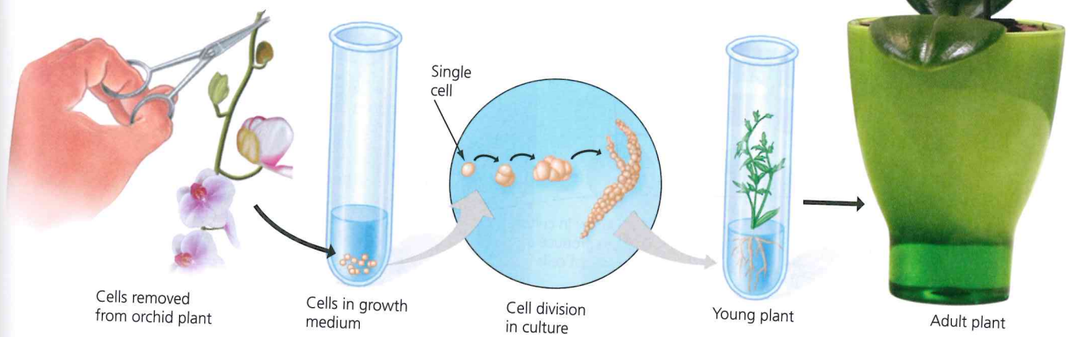
The Genetic Potential of Cells

One of the most important take-home lessons from this chapter is that all body cells contain a complete set of genes, even if they are not expressing all of them. If you've ever grown a plant from a small cutting, you've seen evidence of this yourself: A single differentiated plant cell can undergo cell division and give rise to a complete adult plant, a task that requires a complete set of genes. On a larger scale, the technique described in Figure 11.11 can be used to produce hundreds or thousands of genetically identical organisms—clones—from the cells of a single plant.

Plant cloning is now used extensively in agriculture. For some plants, such as orchids, cloning is the only commercially practical means of reproducing plants. In other cases, cloning has been used to reproduce a plant with specific desirable traits, such as high fruit yield or resistance to disease. Seedless plants (such as seedless grapes, watermelons, and oranges) cannot reproduce sexually, leaving cloning as the sole means of mass-producing these common foods. In fact, every navel orange in supermarkets today is a clone of a single tree that grew on the grounds of a Brazilian monastery in the early 1800s.

Is this sort of cloning possible in animals? A good indication that some animal cells can also tap into their full genetic potential is **regeneration**, the regrowth of lost body parts. When a salamander loses a tail, for example, certain cells in the tail stump reverse their differentiated state, divide, and then differentiate again to give rise to a new tail. Many other animals, especially among the invertebrates (sea stars and sponges, for example), can regenerate lost parts, and isolated pieces of a few relatively simple animals can dedifferentiate and then develop into an entirely new organism (see Figure 8.1).

▼ **Figure 11.11 Test-tube cloning of an orchid.** Tissue removed from the stem of an orchid plant and placed in growth medium may begin dividing and eventually grow into an adult plant. The new plant is a genetic duplicate of the parent plant. This process proves that mature plant cells can reverse their differentiation and develop into all the specialized cells of an adult plant.



Reproductive Cloning of Animals

Animal cloning is achieved through a procedure called **nuclear transplantation** (Figure 11.12). First performed in the 1950s on frog embryos and in the 1990s on adult mammals, nuclear transplantation involves replacing the nucleus of an egg cell or a zygote with a nucleus from an adult body cell. If properly stimulated, the recipient cell may then begin to divide. Repeated cell divisions form a hollow ball of about 100 cells. At this point, the cells may be used for different purposes, as indicated by the two branches in Figure 11.12.

If the animal to be cloned is a mammal, further development requires implanting the early embryo into the uterus of a surrogate mother (Figure 11.12, upper branch). The resulting animal will be a clone (genetic copy) of the donor. This type of cloning is called **reproductive cloning** because it results in the birth of a new animal.

In 1996, researchers used reproductive cloning to produce the first mammal cloned from an adult cell, a sheep named Dolly. The researchers fused specially treated sheep cells with eggs from which they had removed the nuclei. After several days of growth, the resulting embryos were implanted in the uteruses of surrogate mothers. One of the embryos developed into Dolly—and, as expected, Dolly resembled the nucleus donor, not the egg donor or the surrogate mother.

CLONING MAY HELP SAVE THE GIANT PANDA FROM EXTINCTION.

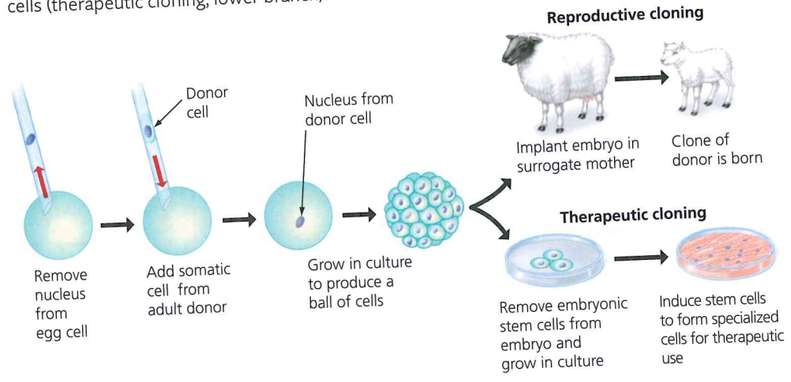
Practical Applications of Reproductive Cloning

Since the first success in 1996, researchers have cloned many species of mammals, including mice, horses, dogs, mules, cows, pigs, rabbits, ferrets, camels, goats, and cats (Figure 11.13a). Why would anyone want to do this? In agriculture, farm animals with specific sets of desirable traits might be cloned to produce identical herds. In research, genetically identical animals can provide perfect "control animals" for experiments. The pharmaceutical industry is experimenting with cloning animals for potential medical use (Figure 11.13b). For example, researchers have produced pig clones that lack a gene for a protein that can cause immune system rejection in humans. Organs from such pigs may one day be used in human patients who require life-saving transplants. Other animals (such as dogs and cats) are cloned to serve as pets.

Perhaps the most intriguing practical application of the technique of reproductive cloning is to restock populations of endangered animals. Some of the rare animals that have been cloned are a banteng (an Asian cow) and a gaur (an Asian ox) (Figure 11.13c). Meanwhile, the scientists who cloned Dolly are now trying to clone a giant panda in an effort to help maintain this unique species.

In 2003, a banteng was cloned using frozen cells from a zoo-raised banteng that had died 23 years prior. Scientists obtained banteng skin tissue from "The Frozen Zoo," a facility in San Diego, California, where samples from rare or endangered animals are stored for

▼ **Figure 11.12 Cloning by nuclear transplantation.** In nuclear transplantation, a nucleus from an adult body cell is injected into a nucleus-free egg cell. The resulting embryo may then be used to produce a new organism (reproductive cloning, shown in the upper branch) or to provide stem cells (therapeutic cloning, lower branch).



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The use of cloning to repopulate endangered speci holds tremendous promise. However, cloning may al create new problems. Conservationists argue that clo ing may detract from efforts to preserve natural habi They correctly point out that cloning does not increa genetic diversity and is therefore not as beneficial to endangered species as natural reproduction. In addi- tion, an increasing body of evidence suggests that clo animals are less healthy than animals produced by fe tilization: Many cloned animals exhibit defects such susceptibility to obesity, pneumonia, liver failure, ar

▼ **Figure 11.13 Reproductive cloning of mammals.**

(c) Clones of endangered animals

Banteng

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The use of cloning to repopulate endangered species holds tremendous promise. However, cloning may also create new problems. Conservationists argue that cloning may detract from efforts to preserve natural habitats. They correctly point out that cloning does not increase genetic diversity and is therefore not as beneficial to endangered species as natural reproduction. In addition, an increasing body of evidence suggests that cloned animals are less healthy than animals produced by fertilization: Many cloned animals exhibit defects such as susceptibility to obesity, pneumonia, liver failure, and premature death. Dolly, the cloned sheep, for example, was euthanized in 2003 after suffering complications from a lung disease usually seen only in much older sheep. She was 6 years old, while her breed has a life expectancy of 12 years. Some evidence suggests that chromosomal changes in the cloned animals are the cause, but the effects of cloning on animal health are still being investigated.

Human Cloning

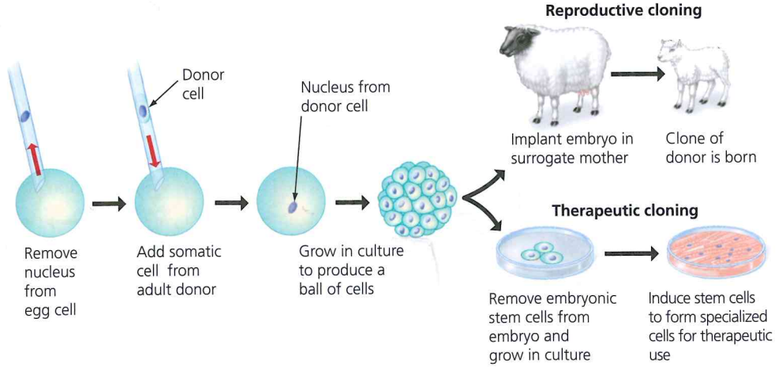
The cloning of various mammals has heightened speculation that humans could be cloned. Critics point out the many practical and ethical objections to human cloning. Practically, cloning of mammals is extremely difficult and inefficient. Only a small percentage of cloned embryos (usually less than 10%) develop normally, and they appear less healthy than naturally born kin. Ethically, the discussion about whether or not people should be cloned—and if so, under what circumstances—is far from settled. Meanwhile, the research and the debate continue. ✅

✅ CHECKPOINT

Imagine that mouse coat color is always passed down from parent to offspring. Suppose a nucleus from an adult body cell of a black mouse is injected into an egg removed from a white mouse, and then the embryo is implanted into a brown mouse. What would be the color of the resulting cloned mice?

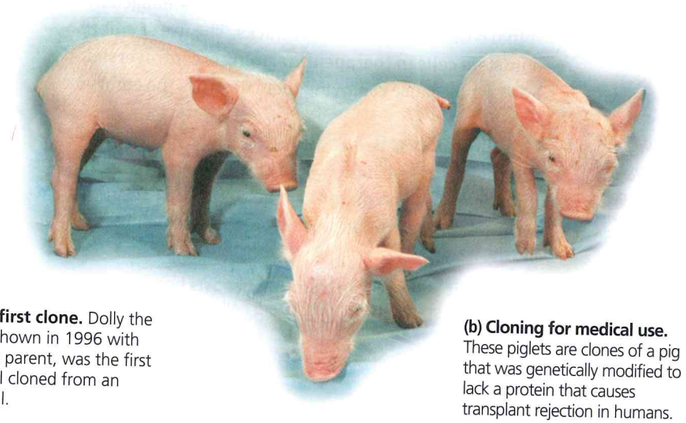
■ *Answer: black, the color of the nucleus donor*

▼ **Figure 11.12 Cloning by nuclear transplantation.** In nuclear transplantation, a nucleus from an adult body cell is injected into a nucleus-free egg cell. The resulting embryo may then be used to produce a new organism (reproductive cloning, shown in the upper branch) or to provide stem cells (therapeutic cloning, lower branch).



▼ **Figure 11.13 Reproductive cloning of mammals.**

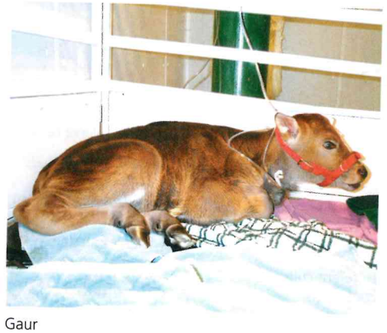
(a) The first clone. Dolly the sheep, shown in 1996 with her lone parent, was the first mammal cloned from an adult cell.



(b) Cloning for medical use. These piglets are clones of a pig that was genetically modified to lack a protein that causes transplant rejection in humans.

(c) Clones of endangered animals

Banteng



Gaur

Therapeutic Cloning and Stem Cells

The lower branch of Figure 11.12 shows the process of **therapeutic cloning**. The purpose of this procedure is not to create a living organism but rather to produce embryonic stem cells.

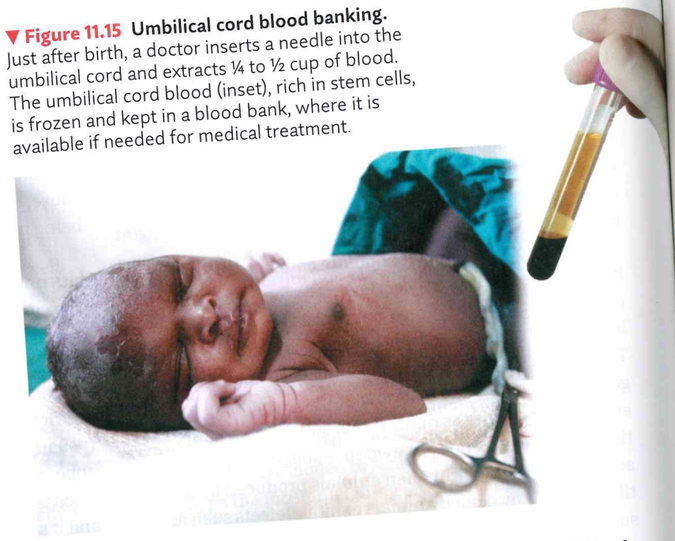
Embryonic Stem Cells

In mammals, **embryonic stem cells (ES cells)** are obtained by removing cells from a several-day-old embryo (which, at this stage, is a ball of cells). The removed cells are then grown in laboratory culture. Embryonic stem cells can divide indefinitely, and under the right conditions—such as the presence of certain growth-stimulating proteins—can (hypothetically) develop into a wide variety of different specialized cells (Figure 11.14). If scientists can discover the right conditions, they may be able to grow cells for the repair of injured or diseased organs. Some people speculate, for example, that embryonic stem cells may one day be used to replace cells damaged by spinal cord injuries or heart attacks. The use of embryonic stem cells in therapeutic cloning is controversial, however, because removing them destroys the embryo.

Umbilical Cord Blood Banking

Another source of stem cells is blood collected from the umbilical cord and placenta at birth (Figure 11.15). Such stem cells appear to be partially differentiated. In 2005, doctors reported that an infusion of umbilical cord blood stem cells appeared to cure some babies of Krabbe disease, a fatal inherited disorder of the nervous system. Other people have received cord blood as a treatment for leukemia. To date, however, most attempts at umbilical cord blood therapy have not been successful. At present, the American Academy of Pediatrics recommends cord blood banking only for babies born into families with a known genetic risk.

▼ Figure 11.15 Umbilical cord blood banking. Just after birth, a doctor inserts a needle into the umbilical cord and extracts ¼ to ½ cup of blood. The umbilical cord blood (inset), rich in stem cells, is frozen and kept in a blood bank, where it is available if needed for medical treatment.



Adult Stem Cells

Adult stem cells can also generate replacements for some of the body's cells. Adult stem cells are further along the road to differentiation than embryonic stem cells and can therefore give rise to only a few related types of specialized cells. For example, stem cells in bone marrow generate different kinds of blood cells. Adult stem cells from donor bone marrow have long been used as a source of immune system cells in patients whose own immune systems have been destroyed by disease or cancer treatments. Adult animals have only tiny numbers of stem cells, but scientists are learning to identify and isolate these cells from various tissues and, in some cases, to grow them in culture.

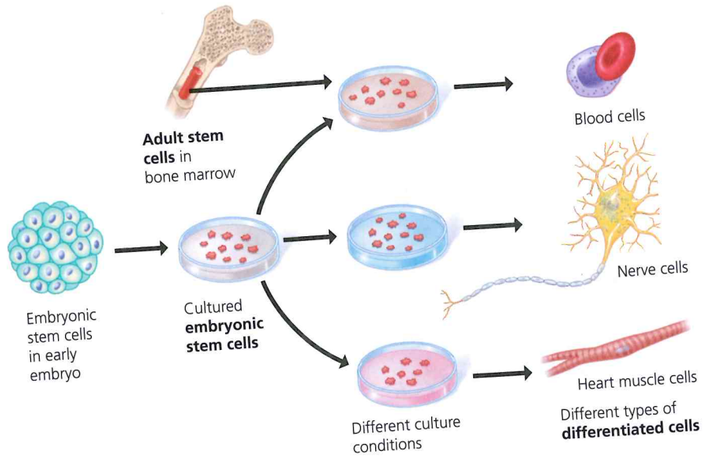
Because no embryonic tissue is involved in their harvest, adult stem cells are less ethically problematic than embryonic stem cells. However, many researchers hypothesize that only embryonic stem cells are likely to lead to groundbreaking advances in human health because they are more versatile. Recent research has shown that some adult cells, such as human skin cells, may be reprogrammed to act like embryonic stem cells. In the near future, such cells may prove to be both therapeutically useful and ethically clear. ✅

✅ **CHECKPOINT**

How do the results of reproductive cloning and therapeutic cloning differ?

■ Answer: Reproductive cloning results in the production of a live individual; therapeutic cloning produces stem cells.

▼ Figure 11.14 Differentiation of embryonic stem cells in culture. Scientists hope to someday discover growth conditions that will stimulate cultured stem cells to differentiate into specialized cells.



The Genetic Basis of C

Cancer occurs when cells escape from the control mechanisms that normally limit their growth and division (as introduced in Chapter 8). This escape involves changes in gene expression.

Genes That Cause Cancer

One of the earliest clues to the role of genes in cancer was the discovery in 1911 of a virus that causes cancer in chickens. Viruses that cause cancer can become permanent residents in host cells by inserting their nucleic acid into the DNA of host chromosomes. Over the last century, researchers have identified a number of viruses that harbor cancer-causing genes. One example is the human papillomavirus (HPV), which can be transmitted through sexual contact and is associated with several types of cancer, including cervical cancer.

Oncogenes and Tumor-Suppressor Genes

In 1976, American molecular biologists J. Michael Bishop, Harold Varmus, and their colleagues made a startling discovery. They found that a cancer-causing chicken virus contains a cancer-causing gene that is an altered version of a normal chicken gene. A gene that causes cancer is called an **oncogene** ("tumor gene"). Subsequent research has shown that the chromosomes of many animals, including humans, contain genes that can be converted to oncogenes. A normal gene with the potential to become an oncogene is called a **proto-oncogene**. (These terms can be confusing, so let's repeat them: A *proto-oncogene* is a normal, healthy gene that, if changed, can become a cancer-causing *oncogene*.) A cell can acquire an oncogene from a virus or from the mutation of one of its own proto-oncogenes.

How can a change in a gene cause cancer? Searching for the normal roles of proto-oncogenes in the cell, researchers found that many of these genes code for **growth factors**—proteins that stimulate cell division—or for other proteins that affect the cell cycle. When all these proteins are functioning normally, in the right amounts at the right times, they help keep the rate of cell division at an appropriate level. When they malfunction—if a growth factor becomes hyperactive, for example—cancer (uncontrolled cell growth) may result.

For a proto-oncogene to become an oncogene, a mutation must occur in the cell's DNA. Figure 11.16 illustrates three kinds of changes in DNA that can produce active oncogenes. In all three cases, abnormal gene expression stimulates the cell to divide excessively.

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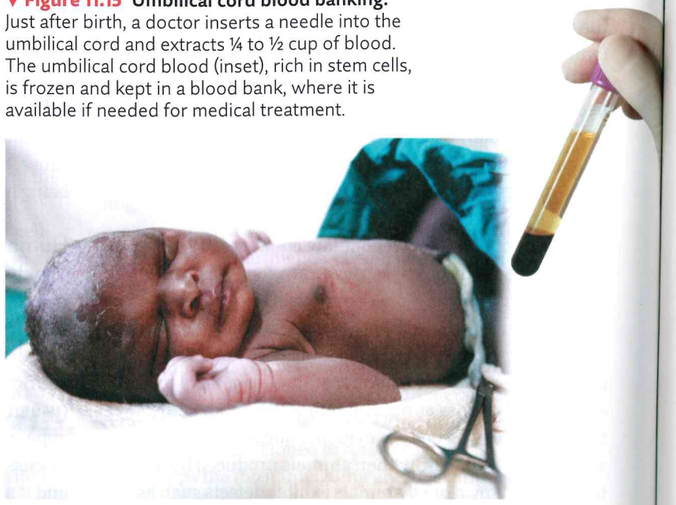

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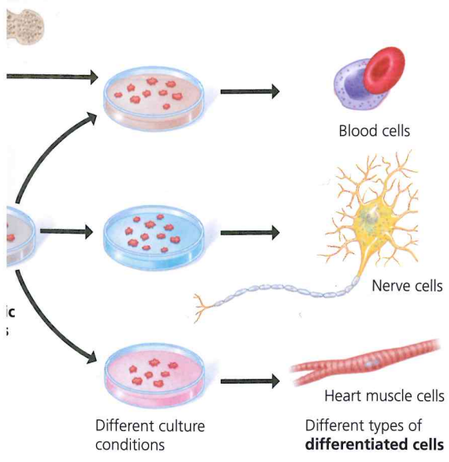

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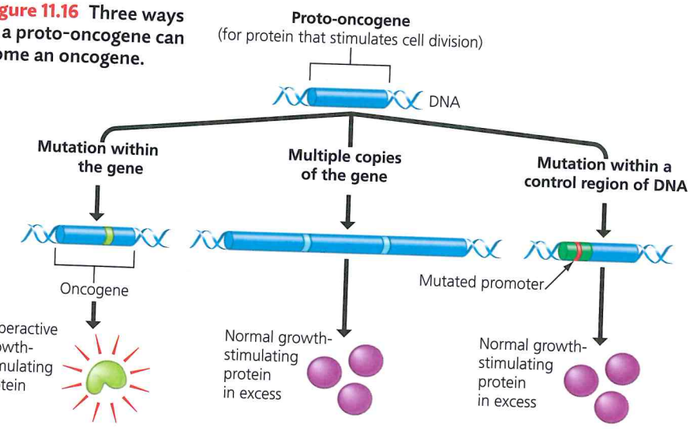
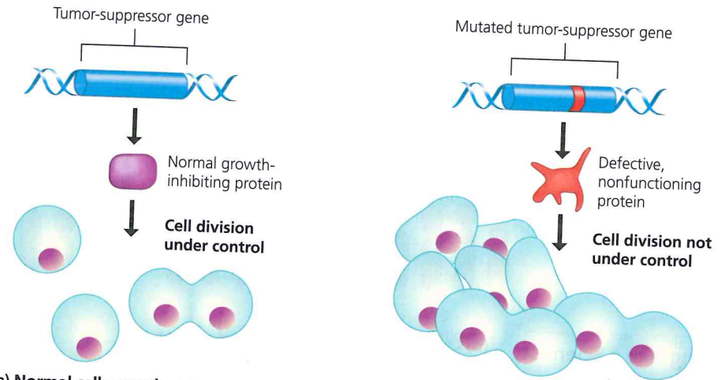
Changes in genes whose products inhibit cell division are also involved in cancer. These genes are called **tumor-suppressor genes** because the proteins they encode normally help prevent uncontrolled cell growth (Figure 11.17). Any mutation that keeps a growth-inhibiting protein from being made or from functioning may contribute to the development of cancer. Researchers have identified many mutations in both tumor-suppressor and growth factor genes that are associated with cancer, as we'll discuss next.

▼ Figure 11.16 Three ways that a proto-oncogene can become an oncogene.



▼ Figure 11.17 Tumor-suppressor genes.



(a) Normal cell growth. A tumor-suppressor gene normally codes for a protein that inhibits cell growth and division. Such genes help prevent cancerous tumors from arising or spreading.

(b) Uncontrolled cell growth (cancer). When a mutation in a tumor-suppressor gene makes its protein defective, cells that are usually under the control of the normal protein may divide excessively, forming a tumor.

THE PROCESS OF SCIENCE | Cancer

Can Avatars Improve Cancer Treatment?

BACKGROUND

Imagine visiting your doctor because you have generalized stomach pain. You'd be quite surprised if your doctor suggested a treatment without first making a definitive diagnosis. And yet, cancer treatment usually proceeds in such a manner. Typically, a doctor knows the general type of cell involved in a tumor and will try treatments that work on that broad category of cancer. But taking an antacid won't cure appendicitis. Similarly, treatment that helps one type of cancer may not help patients with cancer arising from another mutation. Misdirected treatments waste valuable time and can cause complications. To avoid such pitfalls, a group of cancer researchers from Johns Hopkins University conducted a study that used mouse avatars to test potential treatments. As in computer gaming, an avatar is a stand-in for the real participant. In this case, live mice were standing in for the cancer patients.

METHOD

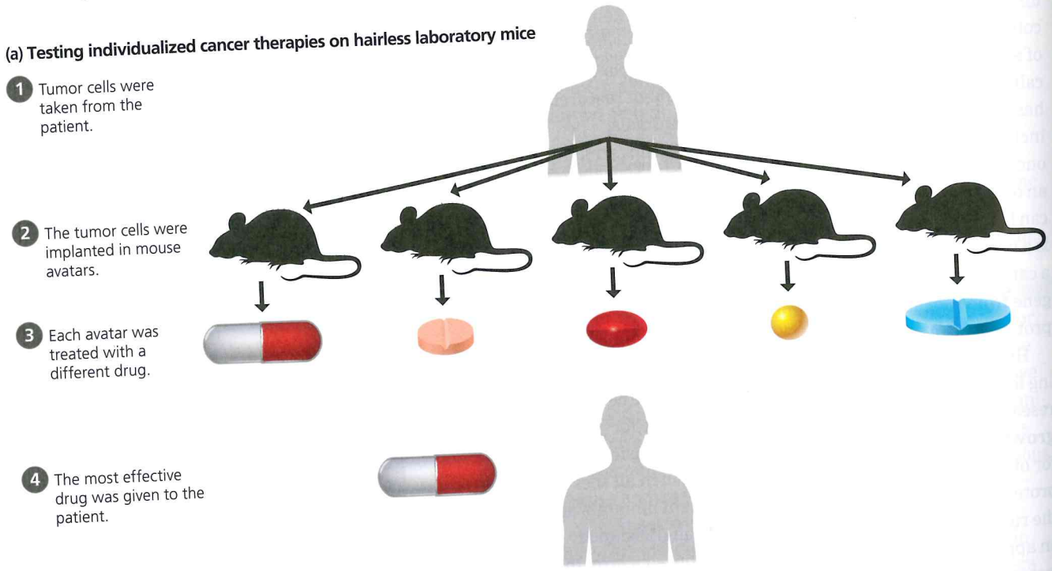
Researchers implanted cells from the tumors of 14 patients with high-risk cancers into mouse avatars **(Figure 11.18a)**. After treating each mouse with a different drug, they determined which treatments were effective at fighting the tumors. The therapies that showed the most promise were then given to the human patients.

RESULTS

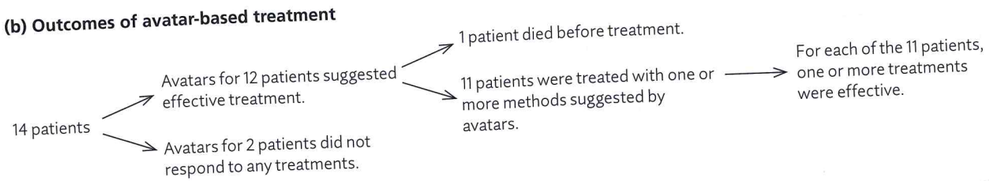
In every case, treating a patient with a drug that was first shown to be effective in the avatar provided benefit to the human **(Figure 11.18b)**. Often, the treatment that was most effective would not have been identified without the use of avatars. In the future, such personalized therapies using an avatar may become standard treatment for otherwise deadly cancers.

▶ Figure 11.18 Using mouse avatars to test cancer therapies.

(a) Testing individualized cancer therapies on hairless laboratory mice



(b) Outcomes of avatar-based treatment

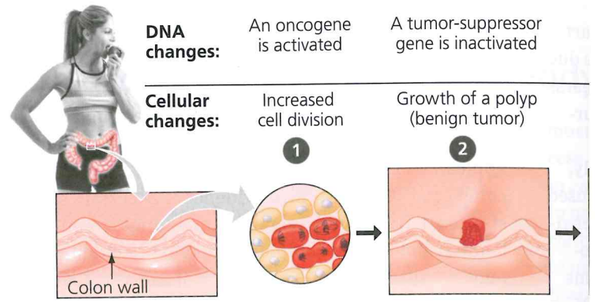


Thinking Like a Scientist

Why do you think the researchers didn't just induce cancers in the mice and then test the drugs?

For the answer, see Appendix D.

▼ Figure 11.19 Stepwise development of colon cancer.



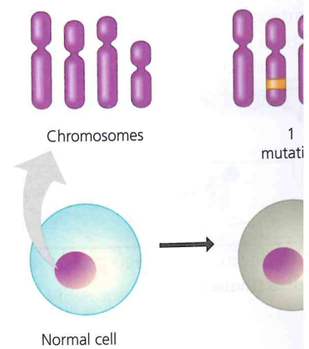
The Progression of a Cancer

Nearly 150,000 Americans will be stricken by cancer of the colon this year. One of the best-understood types, it illustrates a principle about how cancer develops: More than one mutation is needed to produce a cancer cell. As in many cancers, development of colon cancer is gradual.

As shown in **Figure 11.19**, 1 colon cancer begins when an oncogene arises through mutation, causing unusually frequent division of normal-looking cells in the colon lining. 2 Later, additional DNA mutations (such as the inactivation of a tumor-suppressor gene) cause the growth of a small benign tumor (called a polyp) in the colon wall. The cells of the polyp look normal, although they divide unusually frequently. If detected during a colonoscopy, suspicious polyps can usually be removed before they become a serious risk. 3 Further mutations lead to formation of a malignant tumor—one that can metastasize (spread). It typically takes at least six mutations (usually creating at least one active oncogene and disabling at least one tumor-suppressor gene) before a cell becomes cancerous.

The development of a malignant tumor is accompanied by a gradual accumulation of mutations that convert proto-oncogenes to oncogenes and knock out tumor-suppressor genes **(Figure 11.20)**. The requirement for several DNA mutations explains why cancers can take a long time to develop. It may also help explain why the longer we live, the more likely we are to accumulate mutations.

▶ Figure 11.20 Accumulation of mutations in the development of a cancer cell. Mutations leading to cancer accumulate in a lineage of cells. In this figure, colors distinguish the normal cells from cells with one or more mutations, leading to increased cell division and cancer. Once a cancer-promoting mutation occurs (orange band on chromosome), it is passed to all the descendants of the cell carrying it.



THE PROCESS OF SCIENCE | Cancer

Can Avatars Improve Cancer Treatment?

BACKGROUND

Imagine visiting your doctor because you have generalized stomach pain. You'd be quite surprised if your doctor suggested a treatment without first making a definitive diagnosis. And yet, cancer treatment usually proceeds in such a manner. Typically, a doctor knows the general type of cell involved in a tumor and will try treatments that work on that broad category of cancer. But taking an antacid won't cure appendicitis. Similarly, treatment that helps one type of cancer may not help patients with cancer arising from another mutation. Misdirected treatments waste valuable time and can cause complications. To avoid such pitfalls, a group of cancer researchers from Johns Hopkins University conducted a study that used mouse avatars to test potential treatments. As in computer gaming, an avatar is a stand-in for the real participant. In this case, live mice were standing in for the cancer patients.

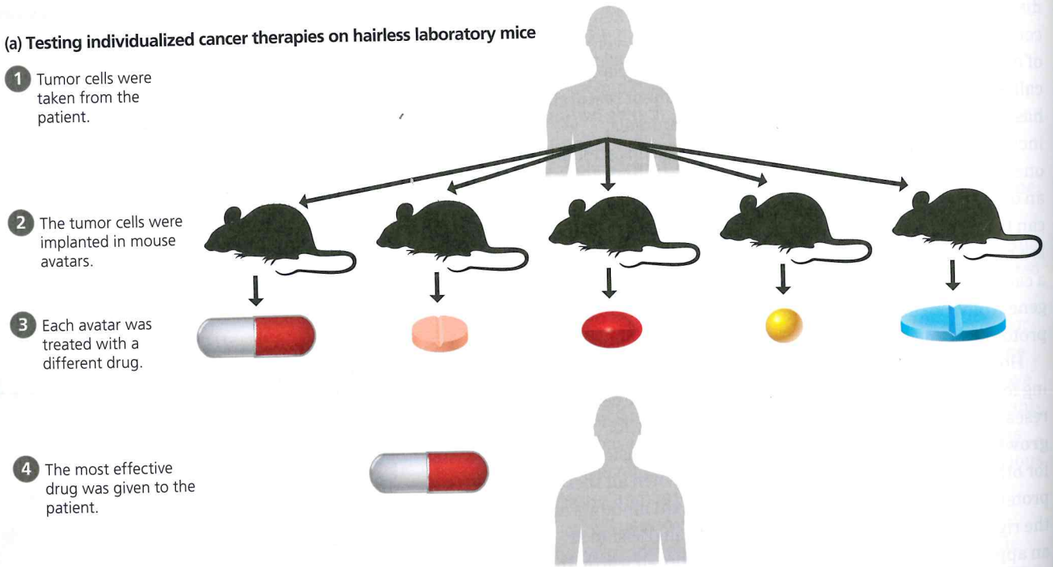
METHOD

Researchers implanted cells from the tumors of 14 patients with high-risk cancers into mouse avatars **(Figure 11.18a)**. After treating each mouse with a different drug, they determined which treatments were effective at fighting the tumors. The therapies that showed the most promise were then given to the human patients.

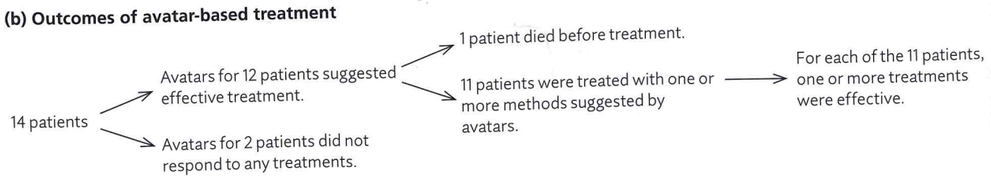
RESULTS

In every case, treating a patient with a drug that was first shown to be effective in the avatar provided benefit to the human **(Figure 11.18b)**. Often, the treatment that was most effective would not have been identified without the use of avatars. In the future, such personalized therapies using an avatar may become standard treatment for otherwise deadly cancers.

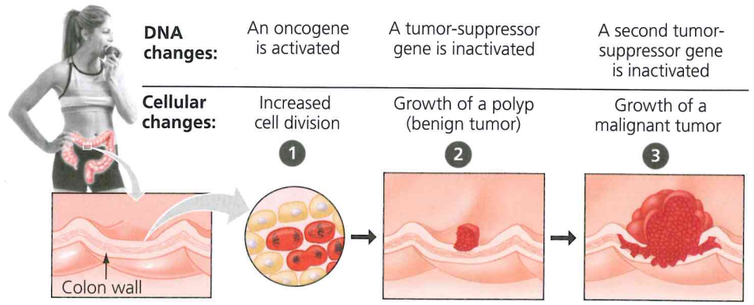
(a) Testing individualized cancer therapies on hairless laboratory mice



(b) Outcomes of avatar-based treatment



▼ **Figure 11.19** **Stepwise development of colon cancer.**



The Progression of a Cancer

Nearly 150,000 Americans will be stricken by cancer of the colon this year. One of the best-understood types, it illustrates a principle about how cancer develops: More than one mutation is needed to produce a cancer cell. As in many cancers, development of colon cancer is gradual.

As shown in **Figure 11.19**, (1) colon cancer begins when an oncogene arises through mutation, causing unusually frequent division of normal-looking cells in the colon lining. (2) Later, additional DNA mutations (such as the inactivation of a tumor-suppressor gene) cause the growth of a small benign tumor (called a polyp) in the colon wall. The cells of the polyp look normal, although they divide unusually frequently. If detected during a colonoscopy, suspicious polyps can usually be removed before they become a serious risk. (3) Further mutations lead to formation of a malignant tumor—one that can metastasize (spread). It typically takes at least six mutations (usually creating at least one active oncogene and disabling at least one tumor-suppressor gene) before a cell becomes cancerous.

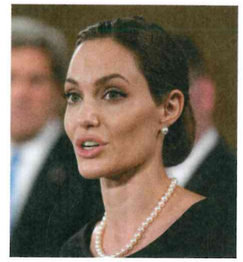
The development of a malignant tumor is accompanied by a gradual accumulation of mutations that convert proto-oncogenes to oncogenes and knock out tumor-suppressor genes **(Figure 11.20)**. The requirement for several DNA mutations explains why cancers can take a long time to develop. It may also help explain why the longer we live, the more likely we are to accumulate mutations.

Inherited Cancer

The fact that multiple genetic changes are required to produce a full-fledged cancer cell helps explain the observation that cancers can run in families. An individual inheriting an oncogene or a mutant version of a tumor-suppressor gene is one step closer to accumulating the necessary mutations for cancer to develop than is an individual without any such mutations. Geneticists are therefore devoting much effort to identifying inherited cancer mutations so that predisposition to certain cancers can be detected early in life.

About 15% of colorectal cancers, for example, involve inherited mutations. There is also evidence that inheritance plays a role in 5–10% of patients with breast cancer, a disease that strikes one out of every ten American women **(Figure 11.21)**. Mutations in either or both of two genes—called *BRCA1* (pronounced "braca-1") and *BRCA2*—are found in at least half of inherited breast cancers. Both *BRCA1* and *BRCA2* are considered tumor-suppressor genes because the normal versions protect against breast cancer. A woman who inherits one mutant *BRCA1* allele has a 60% probability of developing breast cancer before the age of 50, compared with only a 2% probability for an individual lacking the mutations. Tests using DNA sequencing can now detect these mutations. Surgical removal of the breasts and/or ovaries is the only preventive option currently available to women who carry the mutant genes. ☑

▼ **Figure 11.21**
Breast cancer. In 2013, at age 37, the actress Angelina Jolie underwent a preventive double mastectomy after learning she had a mutant *BRCA1* gene. Jolie's mother, grandmother, and aunt all died young from breast or ovarian cancer.

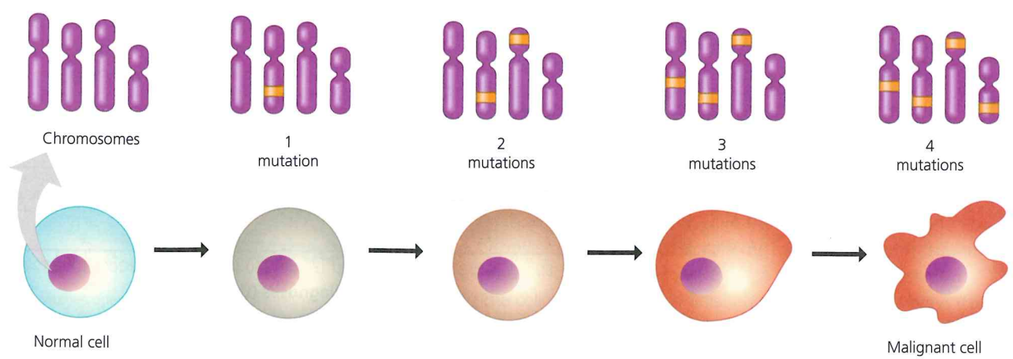


☑ CHECKPOINT

How can a mutation in a tumor-suppressor gene contribute to the development of cancer?

■ Answer: A mutated tumor-suppressor gene may produce a defective protein unable to function in a pathway that normally inhibits cell division and therefore normally suppresses tumors.

▶ **Figure 11.20** **Accumulation of mutations in the development of a cancer cell.** Mutations leading to cancer accumulate in a lineage of cells. In this figure, colors distinguish the normal cells from cells with one or more mutations, leading to increased cell division and cancer. Once a cancer-promoting mutation occurs (orange band on chromosome), it is passed to all the descendants of the cell carrying it.



Cancer Risk and Prevention

Cancer is the second-leading cause of death (after heart disease) in most industrialized countries. Death rates due to certain forms of cancer have decreased in recent years, but the overall cancer death rate is still on the rise, currently increasing at about 1% per decade.

Although some cases of cancer occur spontaneously, most often a cancer arises from mutations that are caused by **carcinogens**, cancer-causing agents found in the environment. Mutations often result from decades of exposure to carcinogens. One of the most potent carcinogens is ultraviolet (UV) radiation. Excessive exposure to UV radiation from the sun can cause skin cancer, including a deadly type called melanoma. You can decrease your risk by using sun protection (clothing, lotion, hats, etc.).

The one substance known to cause more cases and types of cancer than any other is tobacco. By a wide margin, more people die from lung cancer (nearly 156,000 Americans in 2017) than from any other form of cancer. Most tobacco-related cancers are due to smoking cigarettes, but smoking cigars, inhaling secondhand smoke, and smokeless tobacco also pose risks. As Figure 11.22 indicates, tobacco use, sometimes in combination with alcohol consumption, causes several types of cancer. Exposure to some of the most lethal carcinogens is often a matter of choice: Tobacco use, the consumption of alcohol, and excessive time spent in the sun are all avoidable behaviors that affect cancer risk.

Some food choices significantly reduce a person's odds of developing cancer. For instance, eating 20–30 g of plant fiber daily (about the amount found in seven apples), while eating less animal fat, may help prevent colon cancer. There is also evidence that certain substances in fruits and vegetables, including vitamins C and E and certain compounds related to vitamin A, may help protect against a variety of cancers. Cabbage and its relatives, such as broccoli and cauliflower, are thought to be especially rich in substances that help prevent cancer, although some of the specific substances have not yet been identified. Determining how diet influences cancer has become an important focus of nutrition research. It is encouraging that we can help reduce our risk of acquiring some of the most common forms of cancer by the choices we make in our daily lives. The battle against cancer is being waged on many fronts, and there is reason for optimism in the progress being made. Next, in the Evolution Connection section, you'll see how knowledge of evolutionary processes may be applied to cancer treatment. ✓

SIMPLE CHANGES IN LIFESTYLE CAN DRAMATICALLY REDUCE YOUR RISK OF CANCER.

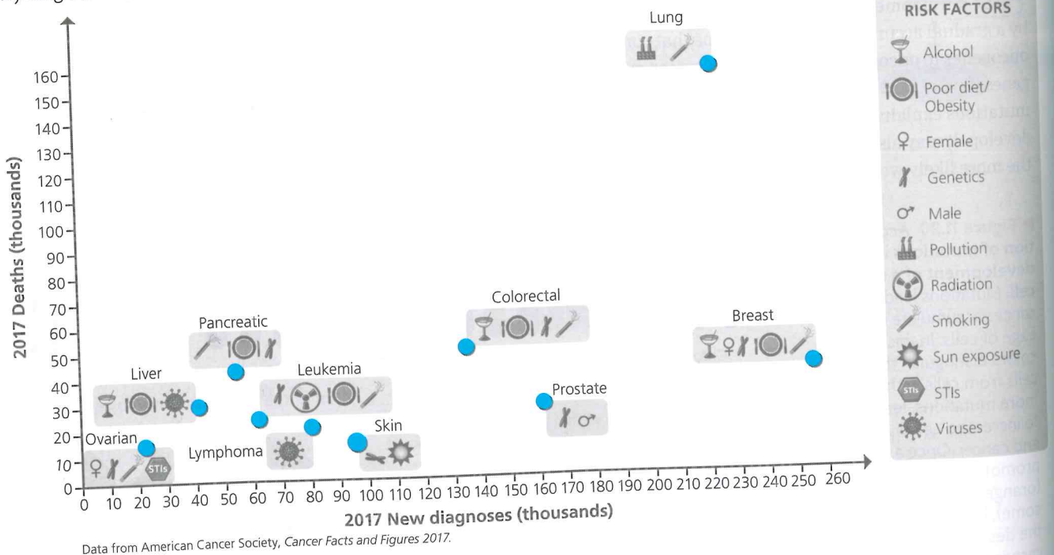
✓ CHECKPOINT

Of all known behavioral factors, which one causes the most cancer cases and deaths?

■ Answer: tobacco use

VISUALIZING THE DATA

▼ Figure 11.22 Cancer in the United States in 2017. Each data point (blue dot) corresponds to the number of deaths and number of new diagnoses for a particular type of cancer. Risk factors are anything that increases the likelihood of developing that cancer.



Data from American Cancer Society, *Cancer Facts and Figures 2017.*

EVOLUTION CONNECTION Cancer

The Evolution of Cancer in the Body

The theory of evolution describes natural selection acting on populations. Recently, medical researchers have been using an evolutionary perspective to gain insight into the development of tumors, such as the bone tumor shown in Figure 11.23. A tumor can be thought of as a population of cancer cells. Just as a population of organisms is driven to evolve by natural selection, a population of cancer cells may evolve in response to cancer treatments.

Recall that there are several assumptions behind Darwin's theory of natural selection (see Chapter 1). Let's consider how each one can be applied to cancer. First, all evolving populations have the potential to produce more offspring than can be supported by the environment. Cancer cells, with their uncontrolled growth, clearly demonstrate overproduction. Second, there must be variation among individuals of the population. Studies of tumor cell DNA show genetic variability within tumors. Third, variations in the population must
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Chapter Review

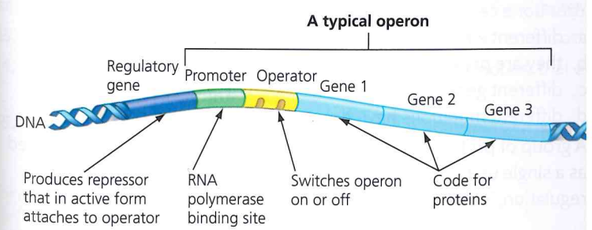
SUMMARY OF KEY CONCEPTS

How and Why Genes Are Regulated

The various types of cells in a multicellular organism owe their distinctiv
ness to different combinations of genes being turned on and off by gen
regulation in each cell type.

Gene Regulation in Bacteria

An operon is a cluster of genes with related functions together with a promoter and other non–protein-coding DNA sequences that control their transcription. For example, the *lac* operon allows *E. coli* to produce enzymes for lactose use only when the sugar is present.



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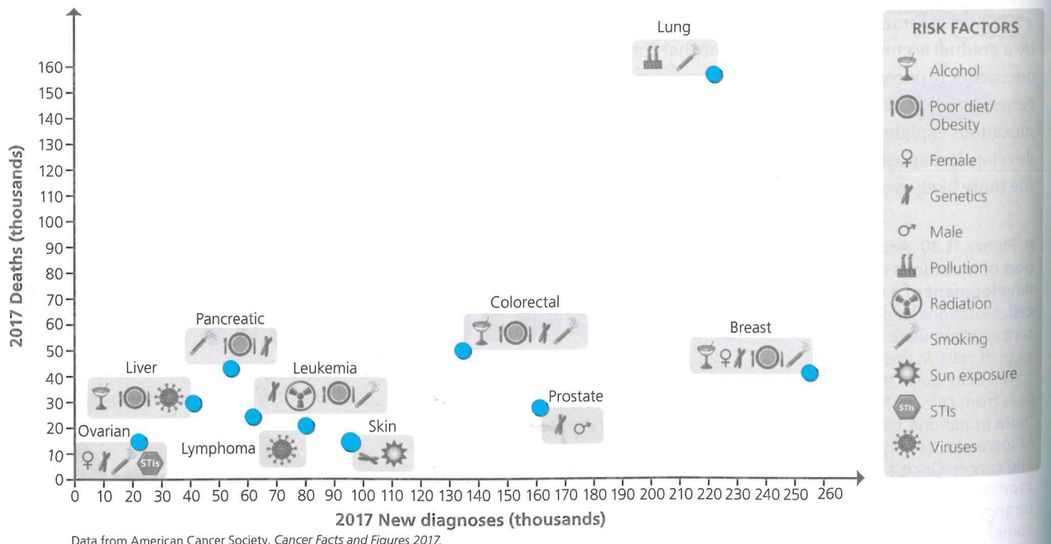

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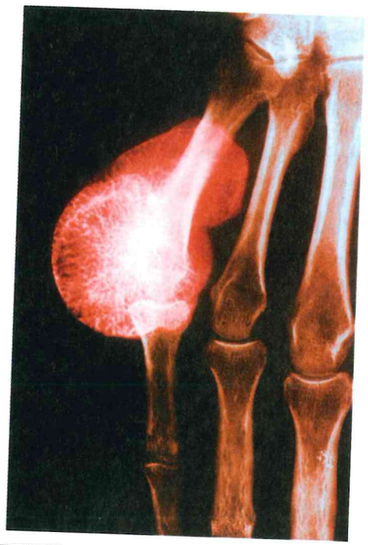
Viewing the progression of cancer through the lens of evolution helps explain why there is no easy "cure" for cancer but may also pave the way for novel therapies. For example, some researchers are attempting to "prime" tumors for treatment by increasing the reproductive success of only those cells that will be susceptible to a chemotherapy drug. Our understanding of cancer, like all other aspects of biology, benefits from an evolutionary perspective.

▼ Figure 11.23 X-ray of a hand, revealing a large bone tumor.



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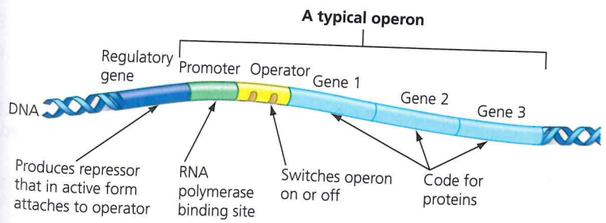
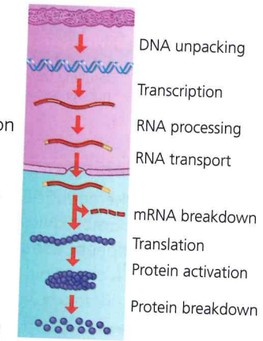


Gene Regulation in Eukaryotic Cells

In the nucleus of eukaryotic cells, there are several possible control points in the pathway of gene expression.

- DNA packing tends to block gene expression by preventing access of transcription proteins to the DNA. An extreme example is X chromosome inactivation in the cells of female mammals.
- The most important control point in both eukaryotes and prokaryotes occurs at the start of gene transcription. Various regulatory proteins interact with DNA and with each other to turn the transcription of eukaryotic genes on or off.
- There are also opportunities for the control of eukaryotic gene expression after transcription, when introns are cut out of the RNA and a cap and tail are added to process RNA transcripts into mRNA.
- In the cytoplasm, presence of microRNAs may block the translation of an mRNA, and various proteins may regulate the start of translation.
- Finally, the cell may activate the finished protein in various ways (for instance, by cutting out portions or chemical modification). Eventually, the protein may be selectively broken down.



Cell Signaling

Cell-to-cell signaling is key to the development and functioning of multicellular organisms. Signal transduction pathways convert molecular messages to cell responses, such as the transcription of particular genes.

Homeotic Genes

Evidence for the evolutionary importance of gene regulation is apparent in homeotic genes, master genes that regulate other genes that in turn control embryonic development.

Visualizing Gene Expression

Researchers can visualize which genes are active in which tissues using a variety of techniques, including the use of probes and DNA microarrays.

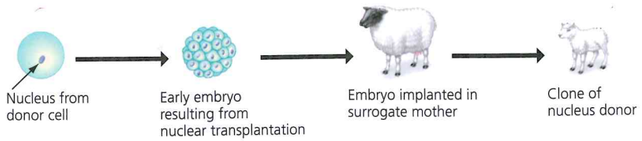
Cloning Plants and Animals

The Genetic Potential of Cells

Most differentiated cells retain a complete set of genes, so an orchid plant, for example, can be made to grow from a single orchid cell. Under controlled conditions, animals can also be cloned.

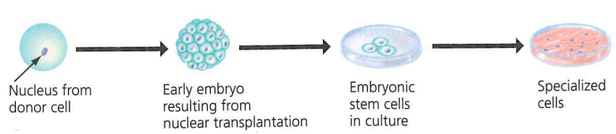
Reproductive Cloning of Animals

Nuclear transplantation is a procedure whereby a donor cell nucleus is inserted into an egg from which the nucleus has been removed. First demonstrated in frogs in the 1950s, reproductive cloning was used in 1996 to clone a sheep from an adult cell and has since been used to create many other cloned animals.



Therapeutic Cloning and Stem Cells

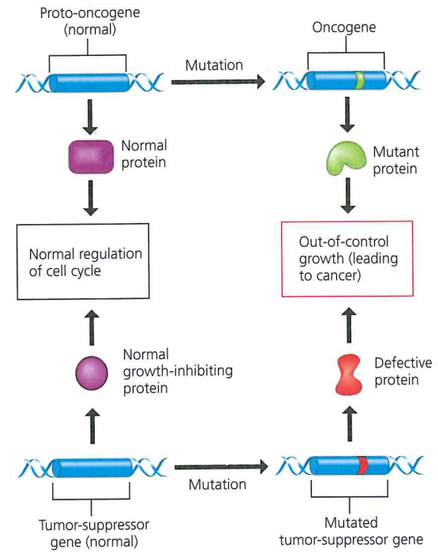
The purpose of therapeutic cloning is to produce embryonic stem cells for medical uses. Embryonic, umbilical cord, and adult stem cells all show promise for therapeutic uses.



The Genetic Basis of Cancer

Genes That Cause Cancer

Cancer cells, which divide uncontrollably, can result from mutations in genes whose protein products regulate the cell cycle.



Many proto-oncogenes and tumor-suppressor genes code for proteins active in signal transduction pathways regulating cell division. Mutations of these genes cause malfunction of the pathways. Cancer results from a series of genetic changes in a cell lineage. Researchers have identified many genes that, when mutated, promote the development of cancer.

Cancer Risk and Prevention

Reducing exposure to carcinogens (which induce cancer-causing mutations) and making other healthful lifestyle choices can help reduce cancer risk.

Mastering Biology

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SELF-QUIZ

1. Your bone cells, muscle cells, and skin cells look different because
   a. different kinds of genes are present in each kind of cell.
   b. they are present in different organs.
   c. different genes are active in each kind of cell.
   d. different mutations have occurred in each kind of cell.
2. A group of prokaryotic genes with related functions that are regulated as a single unit, along with the control sequences that perform this regulation, is called a(n) _____.
3. The regulation of gene expression must be more com
   multicellular eukaryotes than in prokaryotes because
   a. eukaryotic cells are much larger.
   b. in a multicellular eukaryote, different cells are spec
   c. prokaryotes are restricted to stable environments.
   d. eukaryotes have fewer genes, so each gene must c
4. A eukaryotic gene was inserted into the DNA of a bacte
   bacterium then transcribed this gene into mRNA and tra
   into protein. The protein produced was useless and con
   amino acids than the protein made by the eukaryotic cel
   a. The mRNA was not spliced as it is in eukaryotes.
   b. Eukaryotes and prokaryotes use different genetic c
   c. Repressor proteins interfered with transcription an
   d. Ribosomes were not able to bind to tRNA.
5. How does DNA packing in chromosomes prevent gene
6. What evidence demonstrates that differentiated cells i
   animal retain their full genetic potential?
7. The most common procedure for cloning an animal is _
8. What is learned from a DNA microarray?
9. Which of the following is a substantial difference betwe
   stem cells and the stem cells found in adult tissues?
   a. In laboratory culture, only adult stem cells are immo
   b. In nature, only embryonic stem cells give rise to all th
      of cells in the organism.
   c. Only adult stem cells can be made to differentiate in
   d. Only embryonic stem cells are in every tissue of the
10. Name three potential sources of stem cells.
11. What is the difference between oncogenes and proto-o
    can one turn into the other? What function do proto-on
12. A mutation in one gene may cause a major change in the
    fly. Yet it takes many genes to produce a wing or leg. Ho
    in one gene cause a big change? What are such genes ca

For answers to the Self Quiz, see Appendix D.

IDENTIFYING MAJOR THEMES

For each statement, identify which major theme is evident (the
structure to function, information flow, pathways that transform
matter, interactions within biological systems, or evolution) and
the statement relates to the theme. If necessary, review the ther
(see Chapter 1) and review the examples highlighted in blue in th

13. Changing the shape of the *lac* repressor affects how the
14. A cell can produce and secrete chemicals, such as hormo
    gene regulation in another cell.
15. Master control genes regulate other genes that determine
    parts will develop in which locations.

For answers to Identifying Major Themes, see Appendix D.

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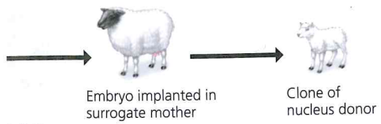

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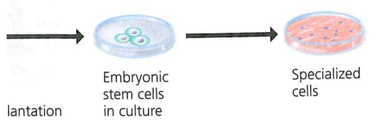

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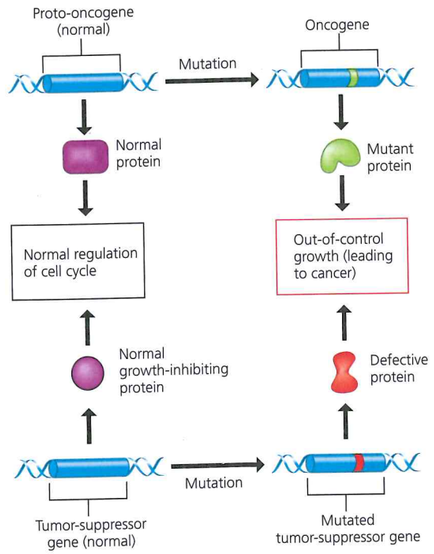

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   c. prokaryotes are restricted to stable environments.
   d. eukaryotes have fewer genes, so each gene must do several jobs.
4. A eukaryotic gene was inserted into the DNA of a bacterium. The bacterium then transcribed this gene into mRNA and translated the mRNA into protein. The protein produced was useless and contained many more amino acids than the protein made by the eukaryotic cell. Why?
   a. The mRNA was not spliced as it is in eukaryotes.
   b. Eukaryotes and prokaryotes use different genetic codes.
   c. Repressor proteins interfered with transcription and translation.
   d. Ribosomes were not able to bind to tRNA.
5. How does DNA packing in chromosomes prevent gene expression?
6. What evidence demonstrates that differentiated cells in a plant or animal retain their full genetic potential?
7. The most common procedure for cloning an animal is _____.
8. What is learned from a DNA microarray?
9. Which of the following is a substantial difference between embryonic stem cells and the stem cells found in adult tissues?
   a. In laboratory culture, only adult stem cells are immortal.
   b. In nature, only embryonic stem cells give rise to all the different types of cells in the organism.
   c. Only adult stem cells can be made to differentiate in the laboratory.
   d. Only embryonic stem cells are in every tissue of the adult body.
10. Name three potential sources of stem cells.
11. What is the difference between oncogenes and proto-oncogenes? How can one turn into the other? What function do proto-oncogenes serve?
12. A mutation in one gene may cause a major change in the body of a fruit fly. Yet it takes many genes to produce a wing or leg. How can a change in one gene cause a big change? What are such genes called?

For answers to the Self Quiz, see Appendix D.

IDENTIFYING MAJOR THEMES

For each statement, identify which major theme is evident (the relationship of structure to function, information flow, pathways that transform energy and matter, interactions within biological systems, or evolution) and explain how the statement relates to the theme. If necessary, review the theme descriptions (see Chapter 1) and review the examples highlighted in blue in this chapter.

13. Changing the shape of the *lac* repressor affects how the repressor acts.
14. A cell can produce and secrete chemicals, such as hormones, that affect gene regulation in another cell.
15. Master control genes regulate other genes that determine what body parts will develop in which locations.

For answers to Identifying Major Themes, see Appendix D.

THE PROCESS OF SCIENCE

16. Study the depiction of the *lac* operon in Figure 11.2. Normally, the genes are turned off when lactose is not present. Lactose activates the genes, which code for enzymes that enable the cell to use lactose. Predict how the following mutations would affect the function of the operon in the presence and absence of lactose:
    a. mutation of regulatory gene; repressor will not bind to lactose
    b. mutation of operator; repressor will not bind to operator
    c. mutation of regulatory gene; repressor will not bind to operator
17. The human body has a far greater variety of proteins than genes, highlighting the importance of alternative RNA splicing. Suppose you have samples of two types of adult cells from one person. Design an experiment using microarrays to determine whether different gene expression is due to alternative RNA splicing.
18. Because a cat must have both orange and non-orange alleles to be tortoiseshell (see Figure 11.4), we would expect only female cats, which have two X chromosomes, to be tortoiseshell. Normal male cats (XY) can carry only one of the two alleles. Male tortoiseshell cats are rare and usually sterile. What might be their genotype?
19. Design a DNA microarray experiment that measures the difference in gene expression between normal colon cells and cells from a colon tumor.
20. **Interpreting Data** Review Figure 11.22. We can estimate the deadliness of each type of cancer by dividing the number of deaths by number of cases. (Although someone diagnosed may not die the same year, it's a useful approximation.) If nearly everyone diagnosed with a certain cancer dies, that ratio will be near 1 (100% deadly). If many more people receive diagnoses than die, the ratio will be near 0 (near 0% deadly). Which region of the graph represents the more deadly cancers? The least deadly? Calculate the diagnosis/death rate for different cancers.

BIOLOGY AND SOCIETY

21. A chemical called dioxin is present in Agent Orange, a defoliant used during the Vietnam War. There has been controversy over its effects on soldiers exposed to Agent Orange. Animal tests have suggested that dioxin can cause multiple health problems and at high dosage can be lethal. Researchers have discovered that dioxin enters a cell and binds to a protein that attaches to the cell's DNA. How might this mechanism help explain the variety of effects on different body systems and different animals? How might you determine whether a person became ill as a result of dioxin?
22. There are genetic tests for several types of "inherited cancer." The results cannot usually predict that someone will get cancer. Rather, they indicate only an increased risk of developing cancer. For many cancers, lifestyle changes cannot decrease risk. Therefore, some people consider the tests useless. If your close family had a history of cancer and a test were available, would you get screened? What would you do with this information?