

The beautifully colored spheres you see above are dividing plant cells. If you look carefully, you can identify among them cells in each of the several stages of the cell division process, the subject of this chapter. The squiggly lines within individual cells are chromosomes, each tagged with a fluorescent chemical that makes it glow. Within each dividing cell, you can see that half of the chromosomes are being drawn to one of the two opposite ends of the cell, pulled by microtubules too tiny to be visible to our eyes. Some human cells divide frequently, particularly those subjected to a lot of wear and tear. The epithelial cells of your skin divide so often that your skin replaces itself every two weeks. The lining of your stomach is replaced every few days! Nerve cells, on the other hand, can live for 100 years without dividing. Cells use a battery of genes to regulate when and how frequently they divide. If some of these genes become disabled, a cell may begin to divide ceaselessly, a condition we call cancer. Exposure to DNA-damaging chemicals such as those in cigarette smoke greatly increases the chance of this sort of event occurring in the tissues exposed to the smoke, which is why smokers will more likely get lung cancer than colon cancer.

9 Mitosis

Chapter-at-a-Glance

Cell Division

- 9.1 Prokaryotes Have a Simple Cell Cycle**
Prokaryotes divide by splitting in two, after duplicating their DNA. The process is called binary fission.
- 9.2 Eukaryotes Have a Complex Cell Cycle**
The eukaryotic cell cycle consists of a growth stage called interphase, a stage of nuclear division called mitosis, and a stage of cytoplasmic division called cytokinesis.
- 9.3 Chromosomes**
Chromosomes consist of DNA efficiently packaged with proteins. The packaging of DNA into chromosomes allows a great deal of DNA to be easily managed during cell division.
- 9.4 Cell Division**
Mitosis is the key phase of eukaryotic cell division. During mitosis, the replicated DNA is distributed to daughter cells.
- 9.5 Controlling the Cell Cycle**
The cell cycle is regulated at three checkpoints. Cell division does not proceed if a problem is encountered at any of these checkpoints.

Cancer and the Cell Cycle

- 9.6 What Is Cancer?**
Cancer is the unrestrained growth of cells caused by genetic mutations.
- 9.7 Cancer and Control of the Cell Cycle**
Cancer results from damage to the mechanisms that control cell division, and certain key genes are often involved.

Cell Division



(a)

9.1 Prokaryotes Have a Simple Cell Cycle

All species reproduce, passing their hereditary information on to their offspring. In this chapter, we begin our consideration of heredity with a look at how cells reproduce. Cell division in prokaryotes takes place in two stages, which together make up a **simple cell cycle**. First the DNA is copied, and then the cell splits by a process called **binary fission**. The cell in figure 9.1a is undergoing binary fission.

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In prokaryotes, the hereditary information—that is, the genes that specify the prokaryote—is encoded in a single circle of DNA, called a prokaryotic chromosome. Before the cell itself divides, the DNA circle makes a copy of itself, a process called *replication*. Starting at one point, the origin of replication (the point where the two strands of DNA are connected at the top of figure 9.1b), the double helix of DNA begins to unzip, exposing the two strands. The enlargement on the right of figure 9.1b shows how the DNA replicates. The purple strand is from the original DNA and the red strand is the newly formed DNA. The new double helix is formed from each naked strand by placing on each exposed nucleotide its complementary nucleotide (that is, A with T, G with C, as discussed in chapter 4). DNA replication is discussed in more detail in chapter 12. When the unzipping has gone all the way around the circle, the cell possesses two copies of its hereditary information.

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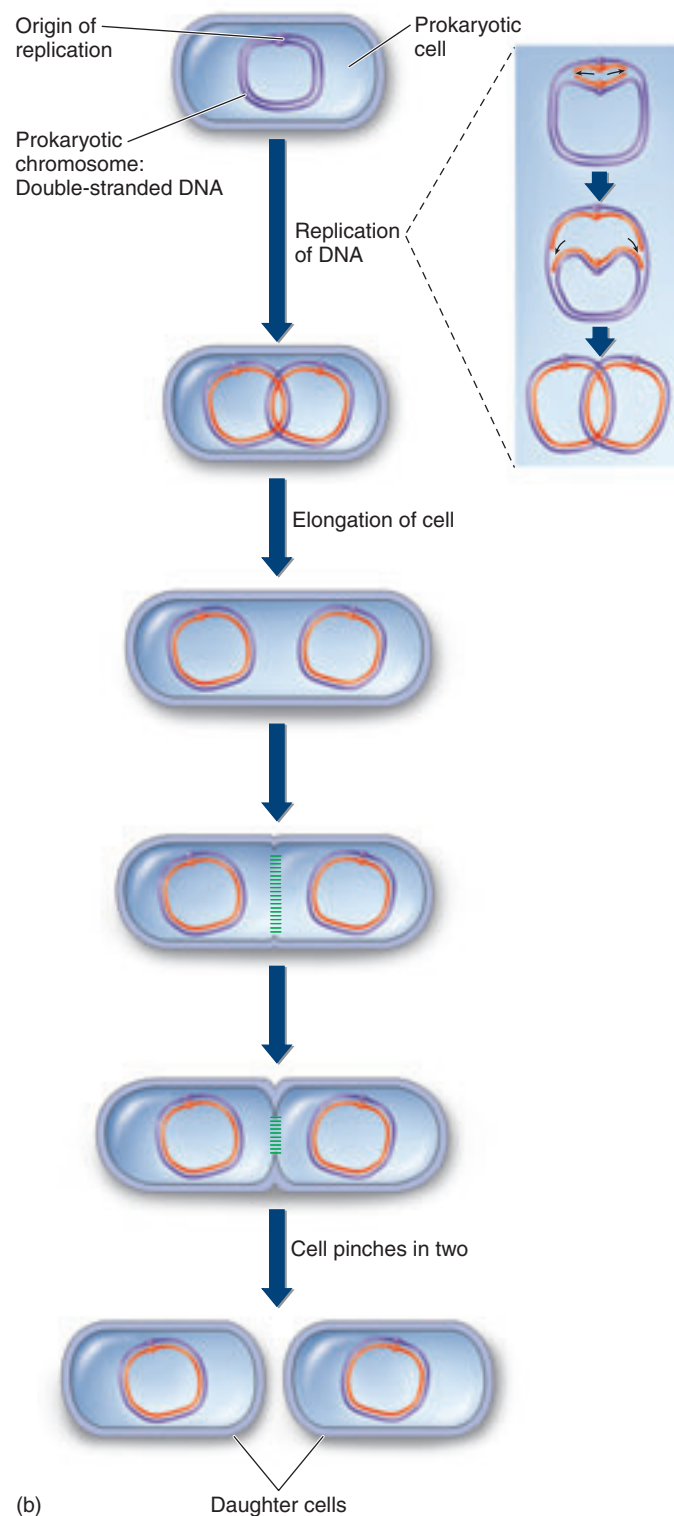
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When the DNA has been copied, the cell grows, resulting in elongation. The newly replicated DNA molecules are partitioned toward each end of the cell. This partitioning process involves DNA sequences near the origin of replication, and results in these sequences being attached to the membrane. When the cell reaches an appropriate size, the prokaryotic cell begins to split into two equal halves. New plasma membrane and cell wall are added at a point between where the two DNA copies are partitioned, indicated by the green divider in figure 9.1b. As the growing plasma membrane pushes inward, the cell is constricted in two, eventually forming two **daughter cells**. Each contains one prokaryotic chromosome and is a complete living cell in its own right.

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9.1 Prokaryotes divide by binary fission after the DNA has replicated.



(b)

Daughter cells

Figure 9.1 Cell division in prokaryotes.

(a) Prokaryotes divide by a process of binary fission. Here, a cell has divided in two and is about to be pinched apart by the growing plasma membrane. (b) Before the cell splits, the circular DNA molecule of a prokaryote initiates replication at a single site, called the origin of replication, moving out in both directions. When the two moving replication points meet on the far side of the molecule, its replication is complete. The cell then undergoes binary fission, where the cell divides into two daughter cells.

9.2 Eukaryotes Have a Complex Cell Cycle

The evolution of the eukaryotes introduced several additional factors into the process of cell division. Eukaryotic cells are much larger than prokaryotic cells, and they contain much more DNA. Eukaryotic DNA is contained in a number of linear chromosomes, whose organization is much more complex than that of the single, circular DNA molecules in prokaryotes. A eukaryotic **chromosome** is a single, long DNA molecule wound tightly around proteins, called histones, into a compact shape.

Cell division in eukaryotes is more complex than in prokaryotes, both because eukaryotes contain far more DNA and because it is packaged differently. The cells of eukaryotic organisms either undergo mitosis or meiosis to divide up the DNA. **Mitosis** is the mechanism of cell division that occurs in an organism's nonreproductive cells, or **somatic cells**. A second process, called **meiosis**, divides the DNA in cells that participate in sexual reproduction, or **germ cells**. Meiosis results in the production of gametes, such as sperm and eggs, and is discussed in chapter 10.

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The events that prepare the eukaryotic cell for division and the division process itself constitute a **complex**

cell cycle. Figure 9.2 walks you through the phases of the cell cycle:

Interphase. This is the first phase of the cell cycle, step 1 in figure 9.2, and is usually considered a resting phase, but the cell is far from resting. Interphase is itself made up of three phases:

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G₁ phase. This “first gap” phase is the cell’s primary growth phase. For most organisms, this phase occupies the major portion of the cell’s life span.

S phase. In this “synthesis” phase, the DNA replicates, producing two copies of each chromosome.

G₂ phase. Cell division preparation continues in the “second gap” phase with the replication of mitochondria, chromosome condensation, and the synthesis of microtubules.

M phase. In mitosis, a microtubular apparatus binds to the chromosomes and moves them apart, shown in steps 2 through 5.

C phase. In cytokinesis, the cytoplasm divides, creating two daughter cells, shown in step 6.

9.2 Eukaryotic cells divide by separating duplicate copies of their chromosomes into daughter cells.

The Cell Cycle

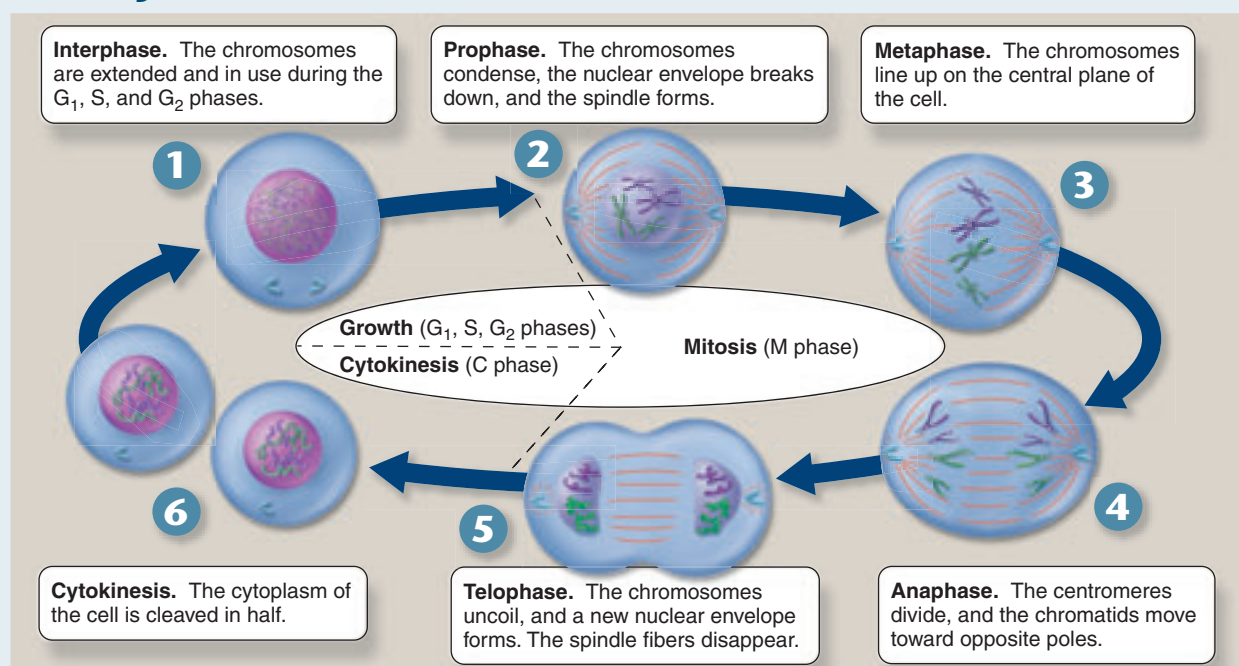


Figure 9.2 How the cell cycle works.

Human cells growing in culture typically have a 22-hour cell cycle. Most cell types take about 80 minutes in this 22 hours to complete cell division: prophase—23 minutes, metaphase—29 minutes, anaphase—10 minutes, telophase—14 minutes, and cytokinesis—4 minutes. The proportion of the cell cycle spent in any one phase of mitosis varies considerably in different tissues.

9.3 Chromosomes

Chromosomes were first observed by the German embryologist Walther Fleming in 1882, while he was examining the rapidly dividing cells of salamander larvae. When Fleming looked at the cells through what would now be a rather primitive light microscope, he saw minute threads within their nuclei that appeared to be dividing lengthwise. Fleming called their division *mitosis*, based on the Greek word *mitos*, meaning “thread.”

Chromosome Number

Since their initial discovery, chromosomes have been found in the cells of all eukaryotes examined. Their number may vary enormously from one species to another. A few kinds of organisms—such as the Australian ant *Myrmecia* spp.; the plant *Haplopappus gracilis*, a relative of the sunflower that grows in North American deserts; and the fungus *Penicillium*—have only 1 pair of chromosomes, while some ferns have more than 500 pairs. Most eukaryotes have between 10 and 50 chromosomes in their body cells.

Homologous Chromosomes

Chromosomes exist in somatic cells as pairs, called **homologous chromosomes**, or **homologues**. Homologues carry information about the same traits at the same locations on each chromosome but the information can vary between homologues, which will be discussed in chapter 11. Cells that have two of each type of chromosome are called **diploid cells**. One chromosome of each pair is inherited from the mother (colored green in figure 9.3) and the other from the father (colored purple). Before cell division, each homologous chromosome replicates, resulting in two identical copies, called **sister chromatids**. You’ll see in figure 9.3 that the sister chromatids remain joined together after replication at a special linkage site called the **centromere**, the knoblike structure in the middle of each chromosome. Human body cells have a total of 46 chromosomes, which are actually 23 pairs of homologous chromosomes. In their duplicated state, before mitosis, there are still only 23 pairs of chromosomes, but each chromosome has duplicated and consists of two sister chromatids, for a total of 92 chromatids. The duplicated sister chromatids can make it confusing to count the number of chromosomes in an organism, but keep in mind that the number of centromeres doesn’t increase with replication, and so you can always determine the number of chromosomes simply by counting the centromeres.

The Human Karyotype

The 46 human chromosomes can be paired as homologues by comparing size, shape, location of centromeres, and so on. This arrangement of chromosomes is called a *karyotype*. An example of a human karyotype is shown in figure 9.4. You can see how the different sizes and shapes of chromosomes allow scientists to pair together the ones that are homologous. For example, chromosome 1 is much larger than chromosome

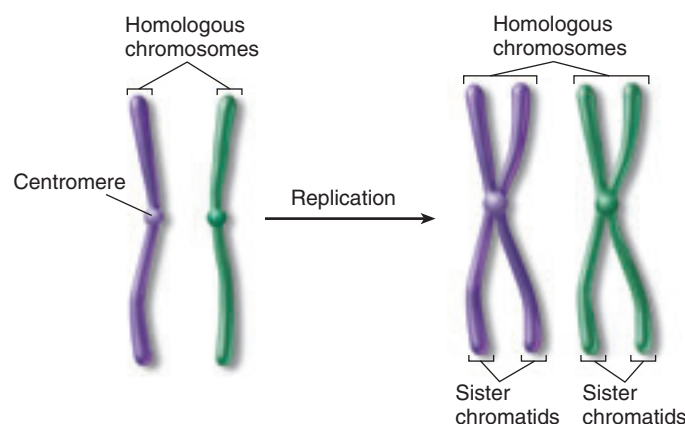


Figure 9.3 The difference between homologous chromosomes and sister chromatids.

Homologous chromosomes are a pair of the same chromosome—say, chromosome number 16. Sister chromatids are the two replicas of a single chromosome held together by the centromere after DNA replication. A duplicated chromosome looks somewhat like an X.

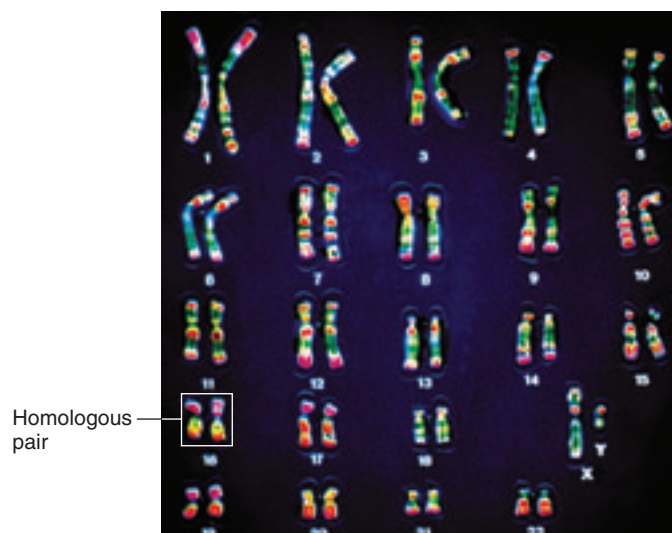


Figure 9.4 The 46 chromosomes of a human.

In this presentation, photographs of the individual chromosomes of a human male have been cut out and paired with their homologues, creating an organized display called a *karyotype*. The chromosomes are in a duplicated state, and the sister chromatids can actually be seen in many of the homologous pairs.

14, and its centromere is more centrally located on the chromosome. Each chromosome contains thousands of genes that play important roles in determining how a person’s body develops and functions. For this reason, possession of all the chromosomes is essential to survival. Humans missing even one chromosome, a condition called monosomy, do not usually survive embryonic development. Nor does the human embryo develop properly with an extra copy of any one chromosome, a condition called trisomy. For all but a few of the smallest chromosomes, trisomy is fatal; even in those cases, serious problems result. We will revisit this issue of differences in chromosome number in chapter 11.

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Figure 9.5 Human chromosomes.

The photograph (950 \times) shows human chromosomes as they appear immediately before nuclear division. Each DNA strand has already replicated, forming identical copies held together by the centromere.

Chromosome Structure

Chromosomes are composed of **chromatin**, a complex of DNA and protein; most are about 40% DNA and 60% protein. A significant amount of RNA is also associated with chromosomes because chromosomes are the sites of RNA synthesis. The DNA of a chromosome is one very long, double-stranded fiber that extends unbroken through the entire length of the chromosome. A typical human chromosome contains about 140 million (1.4×10^8) nucleotides in its DNA. Furthermore, if the strand of DNA from a single chromosome were laid out in a straight line, it would be about 5 centimeters (2 inches) long. The amount of information in one human chromosome would fill about 2,000 printed books of 1,000 pages each! Fitting such a strand into a nucleus is like cramming a string the length of a football field into a baseball—and that's only 1

of 46 chromosomes! In the cell, however, the DNA is coiled, allowing it to fit into a much smaller space than would otherwise be possible.

Chromosome Coiling

The DNA of eukaryotes is divided into several chromosomes, although the chromosomes you see in figure 9.5 hardly look like long double-stranded molecules of DNA. These chromosomes, duplicated as sister chromatids, are formed into the shape we see here by winding and twisting the long DNA strands into a much more compact form. Winding up DNA presents an interesting challenge. Because the phosphate groups of DNA molecules have negative charges, it is impossible to just tightly wind up DNA because all the negative charges would simply repel one another. In figure 9.6 you can see how the cell solves this problem. The DNA doesn't wind around itself. Instead, as you can see on the right, the DNA helix wraps around proteins with positive charges called **histones** (the pink balls). The positive charges of the histones counteract the negative charges of the DNA, so that the complex has no net charge. Every 200 nucleotides, the DNA duplex is coiled around a core of eight histone proteins, forming a complex known as a **nucleosome**. The nucleosomes, which resemble beads on a string in figure 9.6, are further coiled into a solenoid. This solenoid is then organized into looped domains. The final organization of the chromosome is not known, but it appears to involve further radial looping into rosettes around a preexisting scaffolding of protein. These are the flower-shaped structures in the figure. This complex of DNA and histone proteins, coiled tightly, forms a compact chromosome.

9.3 All eukaryotic cells store their hereditary information in chromosomes, but different kinds of organisms use very different numbers of chromosomes to store this information. Coiling of the DNA into chromosomes allows it to fit in the nucleus.

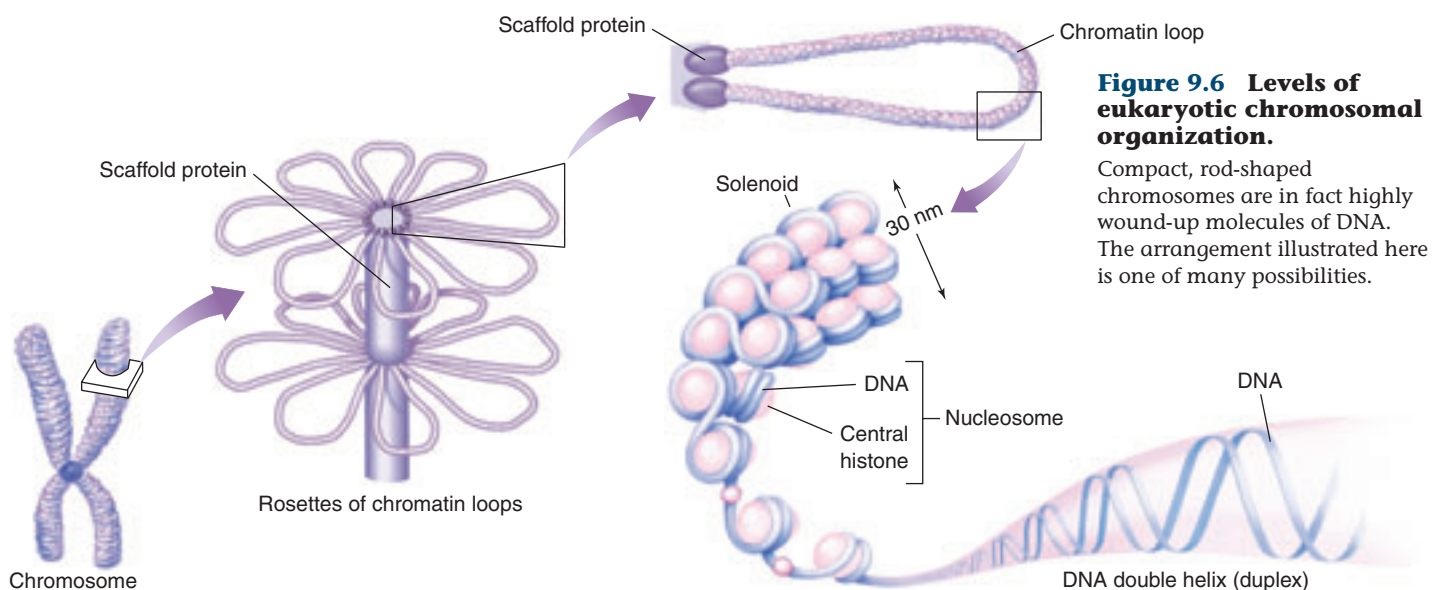
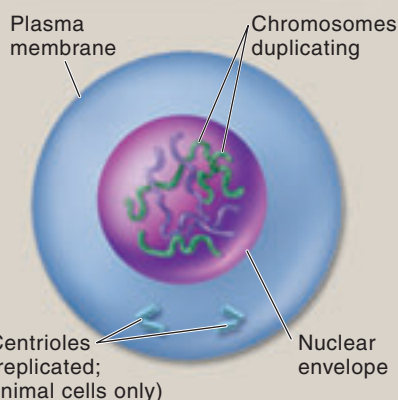


Figure 9.6 Levels of eukaryotic chromosomal organization.

Compact, rod-shaped chromosomes are in fact highly wound-up molecules of DNA. The arrangement illustrated here is one of many possibilities.

Interphase

1

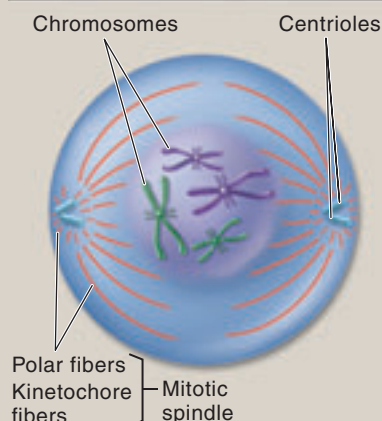


DNA replicates and begins to condense. Centrioles, if present, also replicate, and the cell prepares for division.

Mitosis

2

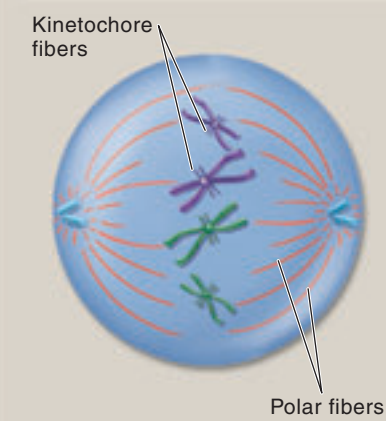
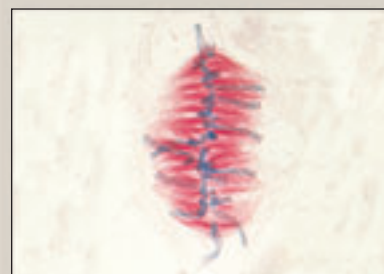
Prophase



The nuclear envelope begins to break down. DNA further condenses into chromosomes. The mitotic spindle begins to form; it is complete at the end of prophase.

3

Metaphase



The chromosomes align on a plane in the center of the cell. The kinetochore fibers attach to the kinetochores on opposite sides of the centromeres.

Figure 9.7 How cell division works.

Cell division in eukaryotes begins in interphase, carries through the four stages of mitosis, and ends with cytokinesis. Several features of the spindle illustrated in the drawings above appear in dividing animal cells but not in plant cells, and cannot be seen in the photographs, which are of the African blood lily *Haemanthus katherinae*. (In these exceptional photographs, the chromosomes are stained blue and microtubules stained red.)

9.4 Cell Division

Interphase

When cell division begins in interphase, chromosomes first replicate, and then begin to wind up tightly, a process called **condensation**. Sister chromatids are held together by a complex of proteins called *cohesin*. Chromosomes are not usually visible during interphase, but to clarify what is happening, they are shown in panel 1 of figure 9.7 as if they were.

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Mitosis

Interphase is not a phase of mitosis, but it sets the stage for cell division. It is followed by nuclear division, called *mitosis*. Although the process of mitosis is continuous, with the stages flowing smoothly one into another, for ease of study, mitosis is traditionally subdivided into four stages: prophase, meta-

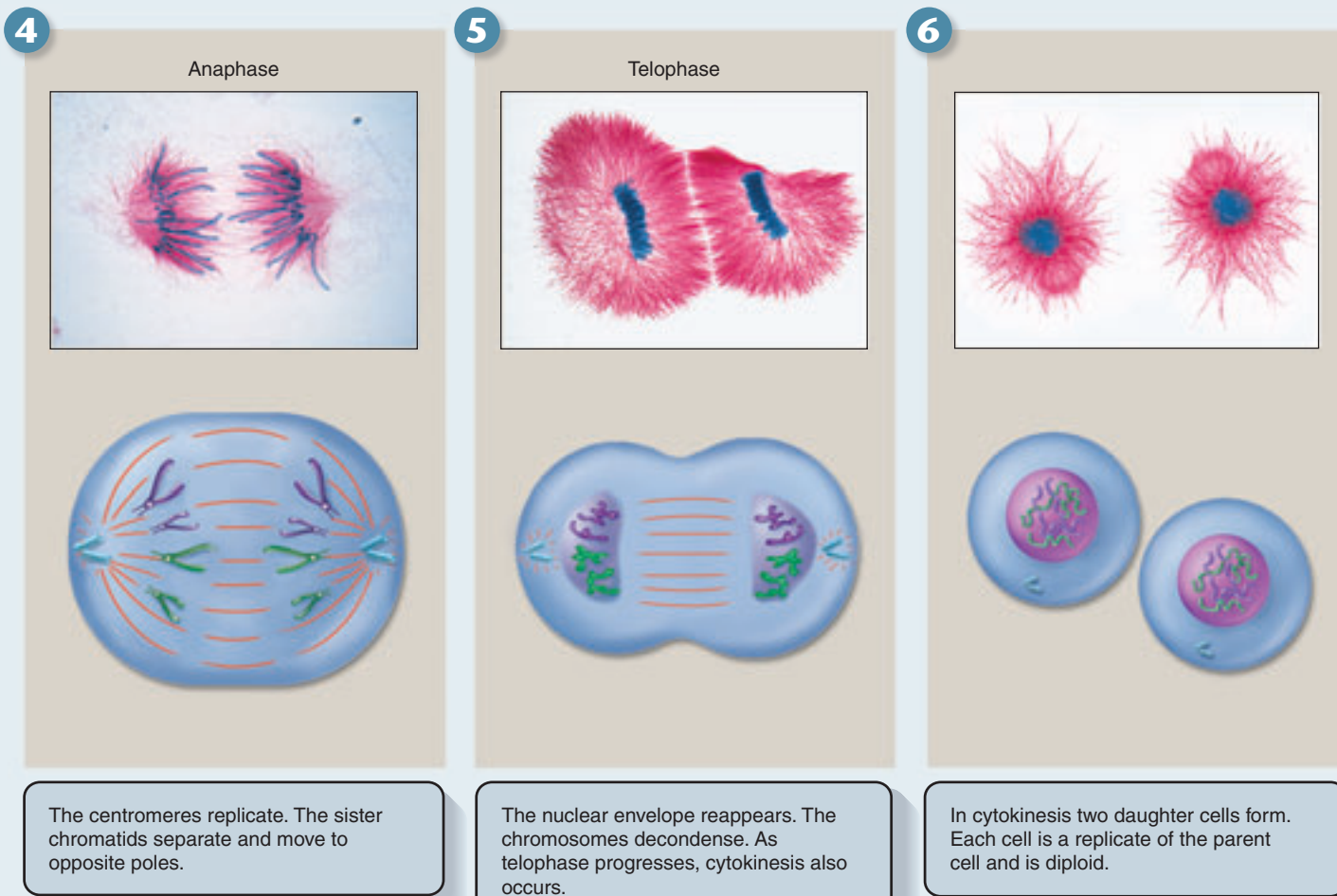
phase, anaphase, and telophase. We will be referring to the panels in figure 9.7 in the following descriptions.

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Prophase: Mitosis Begins. In **prophase**, the individual condensed chromosomes, the blue structures in the photo of panel 2, first become visible with a light microscope. As the replicated chromosomes condense, the nucleolus disappears and the cell dismantles the nuclear envelope and begins to assemble the apparatus it will use to pull the replicated sister chromatids to opposite ends (“poles”) of the cell. In the center of an animal cell, the pairs of centrioles separate; the two pairs of centrioles move apart toward opposite poles of the cell, forming between them as they move apart a network of protein cables called the **spindle**. In panel 2, the centrioles are positioned at the poles; the red structures in the drawing and photo are the protein cables that make up the spindle. Each cable is called a *spindle fiber* and is made of microtubules, which are long, hollow tubes of protein. Plant cells lack centrioles and instead brace the ends of the spindle toward the poles.

SECOND PASS

Cytokinesis



As condensation of the chromosomes continues, a second group of microtubules extends out from the poles toward the centromeres of each chromosome. Each set of microtubules continues to grow longer until it makes contact with a disk of protein, called a *kinetochore*, associated with each side of the centromere. When the process is complete, one sister chromatid of each pair is attached by microtubules to one pole and the other sister chromatid to the other pole.

Metaphase: Alignment of the Chromosomes. The second phase of mitosis, **metaphase**, begins when the chromosomes, each consisting of a pair of sister chromatids, align in the center of the cell along an imaginary plane that divides the cell in half, referred to as the equatorial plane. Panel 3 shows the chromosomes beginning to align along the equatorial plane. Microtubules attached to the kinetochores of the centromeres are fully extended back toward the opposite poles of the cell.

Anaphase: Separation of the Chromatids. In **anaphase**, enzymes cleave the cohesin link holding sister chromatids together, the kinetochores split, and the sister chromatids are freed from each other. Cell division is now simply a matter of reeling in the microtubules, dragging to the poles the sister chromatids, now referred to as daughter chromosomes. In panel 4 you see the daughter chromosomes being pulled by their centromeres, the arms of the chromosomes dangling behind. The ends of the microtubules are dismantled, one bit after another, making the tubes shorter and shorter and so drawing the chromosome attached to the far end closer and closer to the opposite poles of the cell. When they finally arrive, each pole has one complete set of chromosomes.

Telophase: Re-formation of the Nuclei. The only tasks that remain in **telophase** are the dismantling of the stage and the removal of the props. The mitotic spindle is disassembled, and a nuclear envelope forms around each set of chromosomes while they begin to uncoil, as shown in panel 5, and the nucleolus reappears.

Cytokinesis

At the end of telophase, mitosis is complete. The cell has divided its replicated chromosomes into two nuclei, which are positioned at opposite ends of the cell. Mitosis is also referred to as **karyokinesis**. You may recall from chapter 5 that the nucleus is also referred to as *karyon* (Latin for “kernel”); therefore, karyokinesis is the division of the nucleus. Toward the end of mitosis, **cytokinesis**, the division of the cytoplasm, occurs, and the cell is cleaved into roughly equal halves. Cytoplasmic organelles have already been replicated and resorted to the areas that will separate and become the daughter cells. Cytokinesis, the formation of daughter cells shown in the last panel in figure 9.7, signals the end of cell division.

In animal cells, which lack cell walls, cytokinesis is achieved by pinching the cell in two with a contracting belt of actin filaments. As contraction proceeds, a **cleavage furrow** becomes evident around the cell’s circumference, where the cytoplasm is being progressively pinched inward by the decreasing diameter of the actin belt. In figure 9.8a you see an animal cell pinching in half during cytokinesis. Imagine the cleavage furrow deepening further, until the cell is literally pinched in two.

Plant cells have rigid walls that are far too strong to be deformed by actin filament contraction. A different approach to cytokinesis has therefore evolved in plants. Plant cells assemble membrane components in their interior, at right angles to the mitotic spindle. In figure 9.8b, you can see how membrane is deposited between the daughter cells by vesicles that fuse together. This expanding partition, called a **cell plate**, grows outward until it reaches the interior surface of the plasma membrane and fuses with it, at which point it has effectively divided the cell in two. Cellulose is then laid down over the new membranes, forming the cell walls of the two new cells.

Cell Death

Despite the ability to divide, no cell lives forever. The ravages of living slowly tear away at a cell’s machinery. To some degree damaged parts can be replaced, but no replacement process is perfect. And sometimes the environment intervenes. If food supplies are cut off, for example, animal cells cannot obtain the energy necessary to maintain their lysosome membranes. The cells die, digested from within by their own enzymes.

During fetal development, many cells are programmed to die. In human embryos, hands and feet appear first as “paddles,” but the skin cells between bones die on schedule to form the separated toes and fingers. Figure 9.9 shows a developing human hand looking like a paddle. The cells in the tissue between the bones will later die, leaving behind a set of fingers. In ducks, this cell death is not part of the developmental program, which is why ducks have webbed feet and you don’t.

Human cells appear to be programmed to undergo only so many cell divisions and then die, following a plan written into the genes. In tissue culture, cell lines divide about 50 times, and then the entire population of cells dies off. Even if some of the cells are frozen for years, when they are thawed

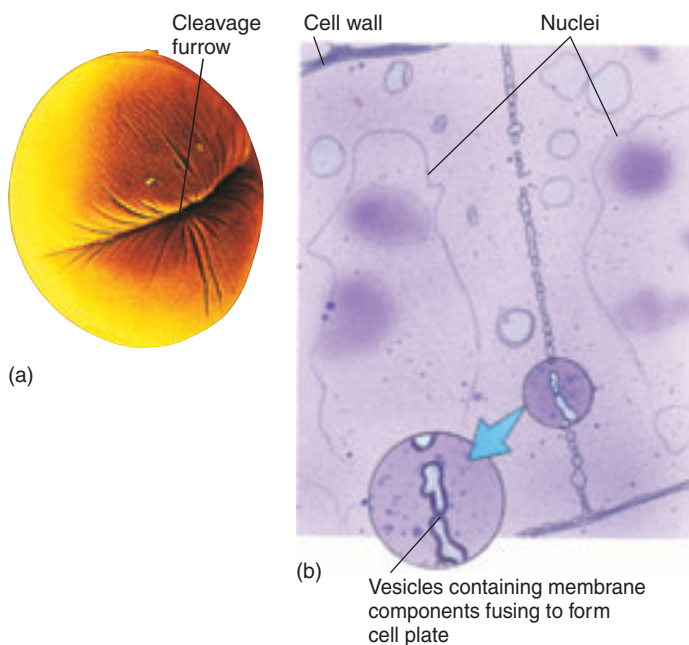


Figure 9.8 Cytokinesis.

The division of cytoplasm that occurs after mitosis is called cytokinesis and cleaves the cell into roughly equal halves. (a) In an animal cell, such as this sea urchin egg, a cleavage furrow forms around the dividing cell. (b) In this dividing plant cell, a cell plate is forming between the two newly forming daughter cells.



Figure 9.9 Programmed cell death.

In the human embryo, programmed cell death results in the formation of fingers and toes from paddlelike hands and feet.

they simply resume where they left off and die on schedule. Only cancer cells appear to thwart these instructions, dividing endlessly. All other cells in your body contain a hidden clock that keeps time by counting cell divisions, and when the alarm goes off the cells die.

9.4 The eukaryotic cell cycle starts in interphase with the condensation of replicated chromosomes; in mitosis, these chromosomes are drawn by microtubules to opposite ends of the cell; in cytokinesis, the cell is split into two daughter cells.

9.5 Controlling the Cell Cycle

The events of the cell cycle are coordinated in much the same way in all eukaryotes. The control system human cells use first evolved among the protists over a billion years ago; today, it operates in essentially the same way in fungi as it does in humans.

The goal of controlling any cyclic process is to adjust the duration of the cycle to allow sufficient time for all events to occur. In principle, a variety of methods can achieve this goal. For example, an internal clock can be employed to allow adequate time for each phase of the cycle to be completed. This is how many organisms control their daily activity cycles. The disadvantage of using such a clock to control the cell cycle is that it is not very flexible. One way to achieve a more flexible and sensitive regulation of a cycle is simply to let the completion of each phase of the cycle trigger the beginning of the next phase, as a runner passing a baton starts the next leg in a relay race. Until recently, biologists thought this type of mechanism controlled the cell division cycle. However, we now know that eukaryotic cells employ a separate, centralized controller to regulate the process: at critical points in the cell cycle, further progress depends upon a central set of “go/no-go” switches that are regulated by feedback from the cell.

This mechanism is the same one engineers use to control many processes. For example, the furnace that heats a home in the winter typically goes through a daily heating cycle. When the daily cycle reaches the morning “turn on” checkpoint, sensors report whether the house temperature is below the set point (for example, 70°F). If it is, the thermostat triggers the furnace, which warms the house. If the house is already at least that warm, the thermostat does not start the furnace. Similarly, the cell cycle has key checkpoints where feedback signals from the cell about its size and the condition of its chromosomes can either trigger subsequent phases of the cycle or delay them to allow more time for the current phase to be completed.

Three principal checkpoints control the cell cycle in eukaryotes:

- 1. Cell growth is assessed at the G_1 checkpoint.**

Located near the end of G_1 and just before entry into S phase, the G_1 checkpoint (indicated by the lower red star in figure 9.10) makes the key decision of whether the cell should divide, delay division, or enter a resting stage. In yeasts, where researchers first studied this checkpoint, it is called START. If conditions are favorable for division, the cell begins to copy its DNA, initiating S phase. The G_1 checkpoint is where the more complex eukaryotes typically arrest the cell cycle if environmental conditions make cell division impossible or if the cell passes into an extended resting period called G_0 (figure 9.11).

- 2. DNA replication is assessed at the G_2 checkpoint.**

The second checkpoint, indicated by the red star at the

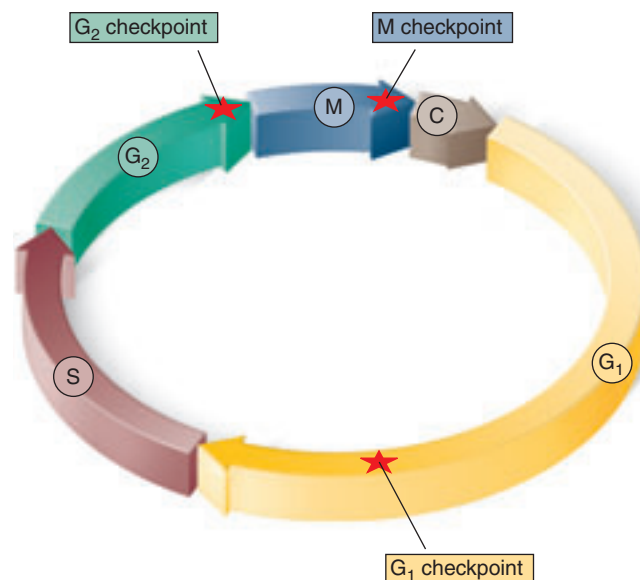


Figure 9.10 Control of the cell cycle.

Cells use a centralized control system to check whether proper conditions have been achieved before passing three key checkpoints in the cell cycle.



Figure 9.11 The G_1 checkpoint.

Feedback from the cell determines whether the cell cycle will proceed to the S phase, pause, or withdraw into G_0 for an extended rest period.

end of G_2 in figure 9.10, triggers the start of M phase. If this checkpoint is passed, the cell initiates the many molecular processes that signal the beginning of mitosis.

- 3. Mitosis is assessed at the M checkpoint.** The third checkpoint, indicated by the red star on the arrowhead of the M phase in figure 9.10, occurs at metaphase and triggers the exit from mitosis and cytokinesis and the beginning of G_1 .

9.5 The complex cell cycle of eukaryotes is controlled by feedback at three checkpoints.

9.6 What Is Cancer?

Cancer is a growth disorder of cells. It starts when an apparently normal cell begins to grow in an uncontrolled way, spreading out to other parts of the body. The result is a cluster of cells, called a **tumor**, that constantly expands in size. The cluster of pink lung cells in the photo in figure 9.12 have begun to form a tumor. Benign tumors are completely enclosed by normal tissue and are said to be encapsulated. These tumors do not spread to other parts of the body and are therefore noninvasive. Malignant tumors are invasive and not encapsulated. Because they are not enclosed by normal tissue, cells are able to break away from the tumor and spread to other areas of the body. The tumor you see in figure 9.13, called a *carcinoma*, grows larger and eventually begins to shed cells that enter the bloodstream. Cells that leave a tumor and spread throughout the body, forming new tumors at distant sites, are called **metastases**.

Cancer is perhaps the most devastating and deadly disease. Of the children born in 1985, one-third will contract cancer at some time during their lives; one-fourth of the male children and one-third of the female children will someday die of cancer. Most of us have had family or friends affected by the disease. In 2005, 570,280 Americans died of cancer.

Not surprisingly, researchers are expending a great deal of effort to learn the cause of this disease. Scientists have made considerable progress in the last 30 years using molecular biological techniques, and the rough outlines of understanding are now emerging. We now know that cancer is a gene disorder of somatic tissue, in which damaged genes fail to properly

control cell growth and division. The cell division cycle is regulated by a sophisticated group of proteins.

Cancer results from the damage of these genes encoding these proteins. Damage to DNA, such as damage to these genes, is called **mutation**.

Most cancers are the direct result of mutations in growth-regulating genes. There are two general classes of genes that are usually involved in cancer: proto-oncogenes and tumor-suppressor genes. Genes known as **proto-oncogenes** encode proteins that stimulate cell division. Mutations to these genes can cause cells to divide excessively. Mutated proto-oncogenes become cancer-causing genes called **oncogenes**.

The second class of cancer-causing genes are called **tumor-suppressor genes**. Cell division is normally turned off in healthy cells by proteins encoded by tumor-suppressor genes. Mutations to these genes essentially “release the brakes,” allowing the cell containing the mutated gene to divide uncontrolled.

Cancer can be caused by chemicals or environmental factors such as UV rays that damage DNA, or in some instances by viruses that circumvent the cell’s normal growth and division controls. Whatever the immediate cause, however, all cancers are characterized by unrestrained cell growth and division. The cell cycle never stops in a cancerous line of cells. Cancer cells are virtually immortal—until the body in which they reside dies.

9.6 Cancer is unrestrained cell growth and division caused by damage to genes regulating the cell division cycle.

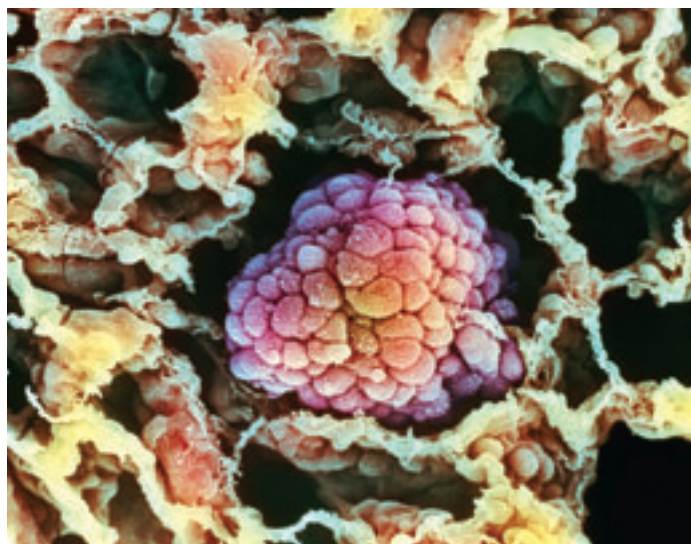


Figure 9.12 Lung cancer cells (300×).

These cells are from a tumor located in the alveolus (air sac) of a human lung.

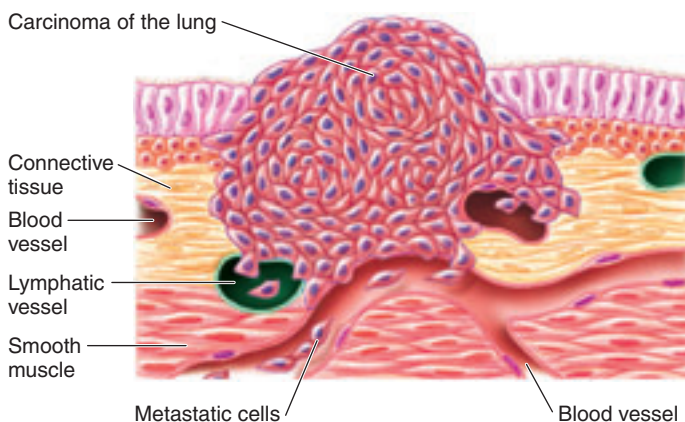


Figure 9.13 Portrait of a cancer.

This ball of cells is a carcinoma (cancer tumor) developing from epithelial cells that line the interior surface of a human lung. As the mass of cells grows, it invades surrounding tissues, eventually penetrating lymphatic and blood vessels, both of which are plentiful within the lung. These vessels carry metastatic cancer cells throughout the body, where they lodge and grow, forming new masses of cancerous tissue.

9.7 Cancer and Control of the Cell Cycle

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Cancer results from damaged genes failing to control cell division. Researchers have identified several of these genes. One particular gene seems to be a key regulator of the cell cycle. Officially dubbed *p53* (researchers italicize the gene symbol to differentiate it from the protein), this gene plays a key role in the G₁ checkpoint of cell division. Figure 9.14 illustrates how the product of this gene, the p53 protein, monitors the integrity of DNA, checking that it is undamaged. If the p53 protein detects damaged DNA, as it does in the upper panel of this figure, it halts cell division and stimulates the activity of special enzymes to repair the damage. Once the DNA has been repaired, p53 allows cell division to continue, indicated by the upper set of arrows. In cases where the DNA cannot be repaired, p53 then directs the cell to kill itself, activating an apoptosis (cell suicide) program, indicated by the lower set of arrows.

By halting division in damaged cells, *p53* prevents the formation of tumors (even though its activities are not limited to cancer prevention). Scientists have found that *p53* is itself damaged beyond use in the majority of cancerous cells they have examined. It is precisely because *p53* is nonfunctional that these cancer cells are able to repeatedly undergo cell division without being halted at the G₁ checkpoint. The lower panel of figure 9.14 shows what happens when p53 doesn't function properly. The damaged strand is not repaired by the abnormal p53 and upon replication, leads to damaged cells. As more and more damage occurs to these cells, they become cancerous. To test this, scientists administered healthy p53 protein to rapidly dividing cancer cells in a petri dish: the cells soon ceased dividing and died. Scientists have further reported that cigarette smoke causes mutations in the *p53* gene, reinforcing the strong link between smoking and cancer described in chapter 26.

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9.7 Mutations disabling key elements of the G₁ checkpoint are associated with many cancers.

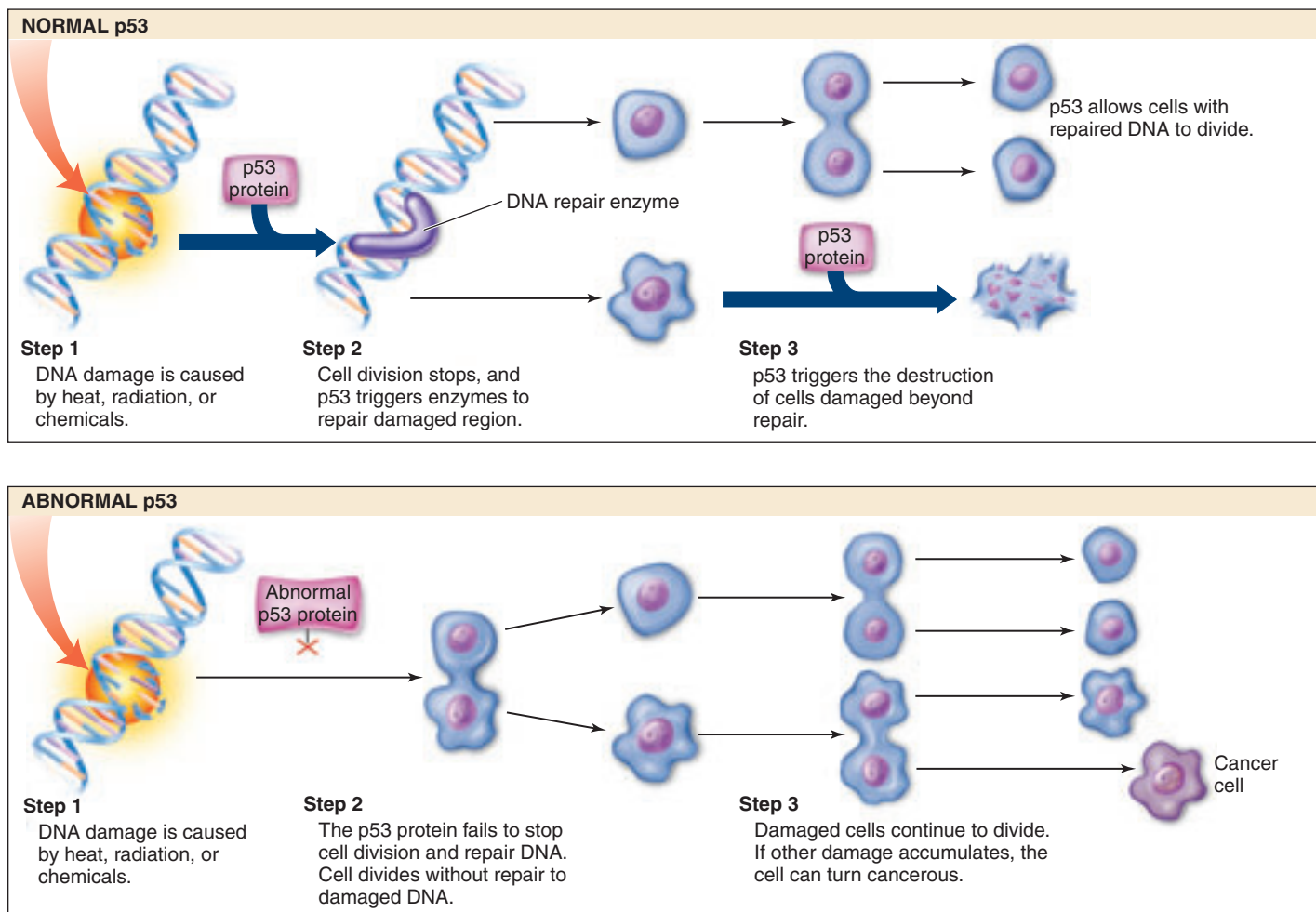


Figure 9.14 Cell division and p53 protein.

Normal p53 protein monitors DNA, destroying cells with irreparable damage to their DNA. Abnormal p53 protein fails to stop cell division and repair DNA. As damaged cells proliferate, cancer develops.

A Closer Look

Curing Cancer

Potential cancer therapies are being developed on many fronts. Some act to prevent the start of cancer within cells. Others act outside cancer cells, preventing tumors from growing and spreading. The figure on the right indicates targeted areas for the development of cancer treatments. The following discussion will examine each of these areas.

Preventing the Start of Cancer

Many promising cancer therapies act within potential cancer cells, focusing on different stages of the cell's "Shall I divide?" decision-making process.

1. Receiving the Signal to Divide.

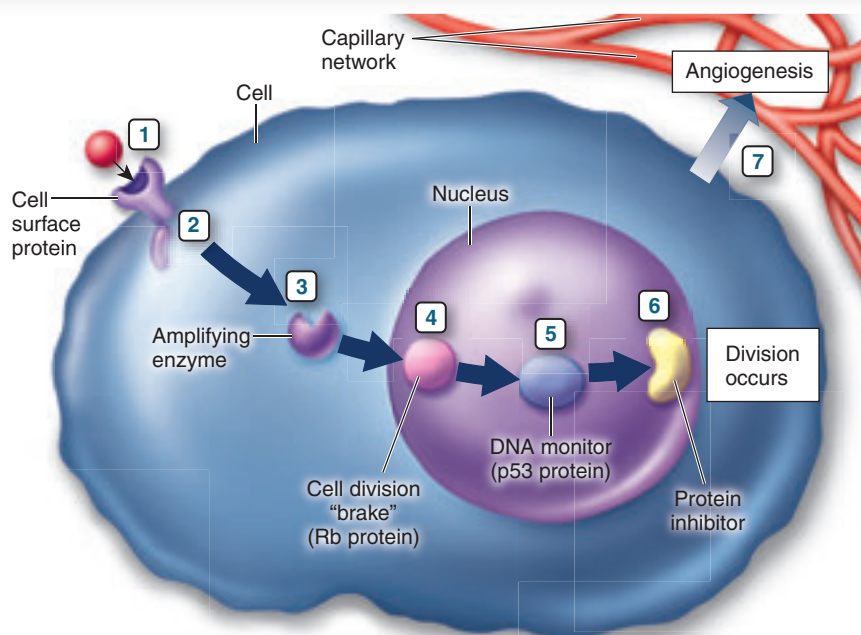
The first step in the decision process is receiving a "divide" signal, usually a small protein called a growth factor released from a neighboring cell. The growth factor, the red ball at #1 in the figure, is received by a protein receptor on the cell surface. Like banging on a door, its arrival signals that it's time to divide. Mutations that increase the number of receptors on the cell surface amplify the division signal and so lead to cancer. Over 20% of breast cancer tumors prove to overproduce a protein called HER2 associated with the receptor for epidermal growth factor (EGF).

Therapies directed at this stage of the decision process utilize the human immune system to attack cancer cells. Special protein molecules called *monoclonal antibodies*, created by genetic engineering, are the therapeutic agents. These monoclonal antibodies are designed to seek out and stick to HER2. Like waving a red flag, the presence of the monoclonal antibody calls down attack by the immune system on the HER2 cell. Because breast cancer cells overproduce HER2, they are killed preferentially. The biotechnology research company Genentech's recently approved monoclonal antibody, called herceptin, has given promising results in clinical tests.

Up to 70% of colon, prostate, lung, and head/neck cancers have excess copies of a related receptor, epidermal growth factor 1 (HER1). The monoclonal antibody C225, directed against HER1, has succeeded in shrinking 22% of advanced, previously incurable colon cancers in early clinical trials. Apparently blocking HER1 interferes with the ability of tumor cells to recover from chemotherapy or radiation.

Seven different stages in the cancer process.

(1) On the cell surface, a growth factor's signal to divide is increased. (2) Just inside the cell, a protein relay switch that passes on the divide signal gets stuck in the "ON" position. (3) In the cytoplasm, enzymes that amplify the signal are amplified even more. In the nucleus, (4) a "brake" preventing DNA replication is inoperable, (5) proteins that check for damage in the DNA are inactivated, and (6) other proteins that inhibit the elongation of chromosome tips are destroyed. (7) The new tumor promotes angiogenesis, the formation of new blood vessels that promote growth.



2. Passing the Signal via a Relay Switch. The second step in the decision process is the passage of the signal into the cell's interior, the cytoplasm. This is carried out in normal cells by a protein called Ras that acts as a relay switch, #2 in the figure. When growth factor binds to a receptor like EGF, the adjacent Ras protein acts like it has been "goosed," contorting into a new shape. This new shape is chemically active, and initiates a chain of reactions that passes the "divide" signal inward toward the nucleus. Mutated forms of the Ras protein behave like a relay switch stuck in the "ON" position, continually instructing the cell to divide when it should not. Thirty percent of all cancers have a mutant form of Ras. So far, no effective therapies have been developed targeting this step.

3. Amplifying the Signal. The third step in the decision process is the amplification of the signal within the cytoplasm. Just as a TV signal needs to be amplified in order to be received at a distance, so a "divide" signal must be amplified if it is to reach the nucleus at the interior of the cell, a very long journey at a molecular scale. To get a signal all the way into the nucleus, the cell employs a sort of pony express. The "ponies" in this case are enzymes called *tyrosine kinases*, #3 in the figure. These enzymes add phosphate groups to proteins, but only at a particular amino acid, tyrosine. No other enzymes in the cell do this, so the tyrosine kinases form an elite core



of signal carriers not confused by the myriad of other molecular activities going on around them.

Cells use an ingenious trick to amplify the signal as it moves toward the nucleus. Ras, when “ON,” activates the initial protein kinase. This protein kinase activates other protein kinases that in their turn activate still others. The trick is that once a protein kinase enzyme is activated, it goes to work like a demon, activating hoards of others every second! And each and every one it activates behaves the same way too, activating still more, in a cascade of ever-widening effect. At each stage of the relay, the signal is amplified a thousandfold.

Mutations stimulating any of the protein kinases can dangerously increase the already amplified signal and lead to cancer. Some 15 of the cell’s 32 internal tyrosine kinases have been implicated in cancer. Five percent of all cancers, for example, have a mutant hyperactive form of the protein kinase Src. The trouble begins when a mutation causes one of the tyrosine kinases to become locked into the “ON” position, sort of like a stuck doorbell that keeps ringing and ringing.

To cure the cancer, you have to find a way to shut the bell off. Each of the signal carriers presents a different problem, as you must quiet it without knocking out all the other signal pathways the cell needs. The cancer therapy drug Gleevec, a monoclonal antibody, has just the right shape to fit into a groove on the surface of the tyrosine kinase called “abl.” Mutations locking abl “ON” are responsible for chronic myelogenous leukemia, a lethal form of white blood cell cancer. Gleevec totally disables abl. In clinical trials, blood counts revert to normal in more than 90% of cases.

4. Releasing the Brake. The fourth step in the decision process is the removal of the “brake” the cell uses to restrain cell division. In healthy cells this brake, a tumor-suppressor protein called Rb, blocks the activity of a protein called E2F, #4 in the figure. When free, E2F enables the cell to copy its DNA. Normal cell division is triggered to begin when Rb is inhibited, unleashing E2F. Mutations that destroy Rb release E2F from its control completely, leading to ceaseless cell division. Forty percent of all cancers have a defective form of Rb.

Therapies directed at this stage of the decision process are only now being attempted. They focus on drugs able to inhibit E2F, which should halt the growth of tumors arising from inactive Rb. Experiments in mice in which the E2F genes have been destroyed provide a model system to study such drugs, which are being actively investigated.

5. Checking That Everything Is Ready. The fifth step in the decision process is the mechanism used by the cell to ensure that its DNA is undamaged and ready to divide. This job is carried out in healthy cells by the tumor-suppressor protein p53, which inspects the integrity

of the DNA, #5 in the figure. When it detects damaged or foreign DNA, p53 stops cell division and activates the cell’s DNA repair systems. If the damage doesn’t get repaired in a reasonable time, p53 pulls the plug, triggering events that kill the cell. In this way, mutations such as those that cause cancer are either repaired or the cells containing them eliminated. If p53 is itself destroyed by mutation, future damage accumulates unrepaired. Among this damage are mutations that lead to cancer. Fifty percent of all cancers have a disabled p53. Fully 70% to 80% of lung cancers have a mutant inactive p53—the chemical benzo[a]pyrene in cigarette smoke is a potent mutagen of p53.

6. Stepping on the Gas. Cell division starts with replication of the DNA. In healthy cells, another tumor suppressor “keeps the gas tank nearly empty” for the DNA replication process by inhibiting production of an enzyme called *telomerase*. Without this enzyme, a cell’s chromosomes lose material from their tips, called *telomeres*. Every time a chromosome is copied, more tip material is lost. After some 30 divisions, so much is lost that copying is no longer possible. Cells in the tissues of an adult human have typically undergone 25 or more divisions. Cancer can’t get very far with only the five remaining cell divisions, so inhibiting telomerase is a very effective natural brake on the cancer process, #6 in the figure. It is thought that almost all cancers involve a mutation that destroys the telomerase inhibitor, releasing this brake and making cancer possible. It should be possible to block cancer by reapplying this inhibition. Cancer therapies that inhibit telomerase are just beginning clinical trials.

Preventing the Spread of Cancer

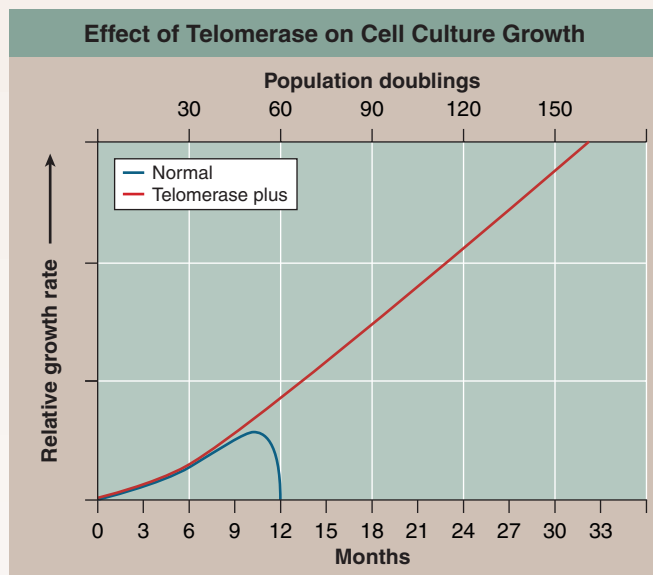
7. Stopping Tumor Growth. Once a cell begins cancerous growth, it forms an expanding tumor. As the tumor grows ever-larger, it requires an increasing supply of food and nutrients, obtained from the body’s blood supply. To facilitate this necessary grocery shopping, tumors leak out substances into the surrounding tissues that encourage the formation of small blood vessels, a process called *angiogenesis*, #7 in the figure. Chemicals that inhibit this process are called *angiogenesis inhibitors*. Two such natural angiogenesis inhibitors, angiostatin and endostatin, caused tumors to regress to microscopic size in mice, but initial human trials were disappointing.

Laboratory drugs are more promising. A monoclonal antibody drug called Avastin, targeted against a blood vessel growth promoting substance called vascular endothelial growth factor (VEGF), destroys the ability of VEGF to carry out its blood-vessel-forming job. Given to hundreds of advanced colon cancer patients in 2003 as part of a large clinical trial, Avastin improved colon cancer patients’ chance of survival by 50% over chemotherapy.

INQUIRY & ANALYSIS

Why Do Human Cells Age?

Human cells appear to have built-in life spans. In 1961 cell biologist Leonard Hayflick reported the startling result that skin cells growing in tissue culture, such as those growing in culture flasks in the photo below, will divide only a certain number of times. After about 50 population doublings cell division stops (a **doubling** is a round of cell division producing two daughter cells for each dividing cell, for example going from a population of 30 cells to 60 cells). If a cell sample is taken after 20 doublings and frozen, when thawed it resumes growth for 30 more doublings, and then stops. An explanation of the “Hayflick limit” was suggested in 1986 when researchers first glimpsed an extra length of DNA at the end of chromosomes. Dubbed telomeres, they proved to be composed of the simple DNA sequence TTAGGG, repeated nearly a thousand times. Importantly, telomeres were found to be substantially shorter in the cells of older body tissues.



TTAGGG TTAGGG TTAGGG TTAGGG TTAGGG-----

This led to the hypothesis that a run of some 16 TTAGGGs was where the DNA replicating enzyme, called polymerase, first sat down on the DNA (16 TTAGGGs being the size of the enzyme’s “footprint”), and because of being its docking spot, the polymerase was unable to copy that bit. Thus a 100-base portion of the telomere was lost by a chromosome during each doubling as DNA replicated. Eventually, after some 50 doubling cycles, each with a round of DNA replication, the telomere would be used up and there would be no place for the DNA replication enzyme to sit. The cell line would then enter senescence, no longer able to proliferate.

This hypothesis was tested in 1998. Using genetic engineering, researchers transferred into newly established human cell cultures a gene that leads to expression of an enzyme called *telomerase* that all cells possess but no body cell uses. This enzyme adds TTAGGG sequences back to the end of telomeres, in effect rebuilding the lost portions of the telomere. Laboratory cultures of cell lines with (telomerase plus) and without (normal) this gene were then monitored for many generations. The graph above displays the results.

1. Applying Concepts

a. Variable. In the graph, what is the dependent variable?

b. Comparing Continuous Processes. How do normal skin cells (blue line) differ in their growth history from telomerase plus cells with the telomerase gene (red line)?

2. Interpreting Data

a. After how many doublings do the normal cells cease to divide? Is this consistent with the telomerase hypothesis?



b. After how many doublings do the telomerase plus cells cease to divide in this experiment?

3. Making Inferences After 9 population doublings, would the rate of cell division be different between the two cultures? after 15? Why?

4. Drawing Conclusions How does the addition of the telomerase gene affect the senescence of skin cells growing in culture? Does this result confirm the telomerase hypothesis this experiment had set out to test?

5. Further Analysis

a. Cancer cells are thought to possess mutations disabling the cell’s ability to keep the telomerase gene shut off. How would you test this hypothesis?

b. Sperm-producing cells continue to divide throughout a male’s adult life. How might this be possible? How would you test this idea?

Summary

Cell Division

9.1 Prokaryotes Have a Simple Cell Cycle

- Prokaryotic cells divide in a two-step process: DNA replication and binary fission. The DNA is a single loop of DNA called a chromosome. The DNA begins replication at a site called the origin of replication. The DNA double strand unzips and new strands form along the original strands, producing two circular chromosomes that separate to the ends of the cell. New plasma membrane and cell wall is added down the middle of the cell, splitting the cell in two, producing two daughter cells that are genetically identical to the parent cell (figure 9.1).



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9.2 Eukaryotes Have a Complex Cell Cycle

- Eukaryotes have a more complex cell cycle. The replicated DNA is packaged into chromosomes that are distributed into daughter cells through the processes of mitosis and cytokinesis (figure 9.2).

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9.3 Chromosomes

- Eukaryotic DNA is organized into chromosomes, and two chromosomes that carry copies of the same genes are called homologous chromosomes. Before cells divide, the DNA replicates forming two identical copies of each chromosome, called sister chromatids (figures 9.3 and 9.4).
- DNA in the nucleus of eukaryotic cells is packaged into compact structures called chromosomes. The DNA wraps around histone proteins, and the DNA-histone complex is tightly coiled, forming a compact chromosome (figures 9.5 and 9.6).

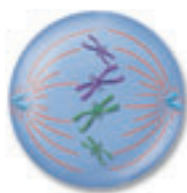


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9.4 Cell Division

- When a eukaryotic cell begins to divide, it enters a stage in the cell cycle called interphase. During interphase, the DNA replicates and toward the end, the DNA begins to condense into chromosomes.
- Interphase is followed by mitosis, which consists of four phases: prophase, metaphase, anaphase, and telophase (figure 9.7).
- Prophase signals the beginning of mitosis. The DNA condenses into chromosomes that stay attached to their replicated partners (sister chromatids) at sites called centromeres. The nucleolus and nuclear envelope disappear, and centrioles when present begin forming the spindle. Microtubules also form from the poles and extend to the kinetochores, which are proteins located at the centromere areas of the chromosomes.
- Metaphase involves the alignment of sister chromatids along the equatorial plane. Microtubules connect the kinetochores of sister chromatids to each of the poles.
- During anaphase, the microtubules shorten, pulling the sister chromatids



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apart and toward opposite poles, such that each pole receives one copy of each chromosome.

- Telophase signals the completion of nuclear division. The microtubule spindle is dismantled, the nuclear envelope and nucleolus re-form.
- Following mitosis, the cell separates into two daughter cells in a process called cytokinesis (figure 9.8). Cytokinesis in animal cells involves a pinching in of the cell around its equatorial plane, until the cell eventually splits into two cells. Cytokinesis in plant cells involved the formation of cell membrane and cell wall between the two poles, eventually forming two separate cells.

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9.5 Controlling the Cell Cycle

- The cell cycle is controlled at three checkpoints (figure 9.10). At the G₁ checkpoint, before entering the S phase, the cell either initiates division or enters a period of rest called G₀ (figure 9.11).
- If cell division is initiated at the G₁ checkpoint, DNA replication begins and is checked at the G₂ checkpoint. Mitosis is either initiated or delayed, depending on the successful replication of DNA. The third checkpoint is toward the end of mitosis, before cytokinesis (figure 9.10).

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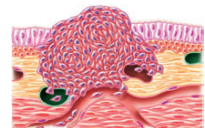
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Cancer and the Cell Cycle

9.6 What Is Cancer?

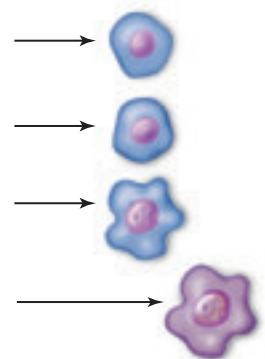
- Cancer is a growth disorder of cells, where there is a loss of control over cell division. Cells begin to divide in an uncontrolled way, forming a mass of cells called a tumor. A tumor that is encapsulated by normal tissue is called benign, but a situation in which cells can break away from the mass and spread to other tissues is called metastases. Mutations in proto-oncogenes and tumor-suppressor genes lead to uncontrolled growth—cancer (figure 9.13).



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9.7 Cancer and Control of the Cell Cycle

- Mutations of the p53 gene are found in many types of cancer cells. This gene plays a key role in the G₁ checkpoint, checking the condition of the DNA. If the DNA is damaged, the p53 protein will stop cell division and give the cell the opportunity to correct the damaged DNA. If the DNA cannot be repaired, the p53 protein will trigger the destruction of the cell (figure 9.14). When the p53 gene is damaged by mutations, the DNA is not checked, and cells with damaged DNA can divide. Further mutations to the DNA can accumulate in the cells and result in cells that become cancerous.



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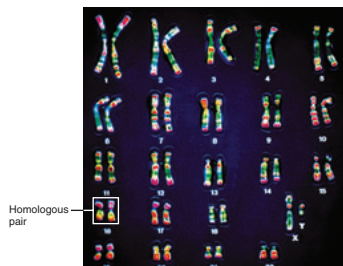
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Self-Test

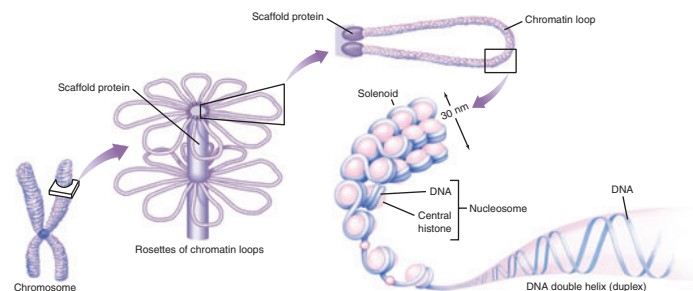
- Prokaryotes reproduce new cells by
 - copying DNA then undergoing binary fission.
 - splitting in half.
 - undergoing mitosis.
 - copying DNA then undergoing the M phase.
- The eukaryotic cell cycle is different from prokaryotic cell division in all the following ways except
 - the amount of DNA present in the cells.
 - how the DNA is packaged.
 - in the production of daughter cells.
 - the involvement of microtubules.
- In eukaryotes, the genetic material is found in chromosomes
 - and the more complex the organism, the more pairs of chromosomes it has.
 - and many organisms have only one chromosome.
 - and most eukaryotes have between 10 and 50 pairs of chromosomes.
 - and most eukaryotes have between 2 and 10 pairs of chromosomes.
- Homologous chromosomes
 - are also referred to as sister chromatids.
 - are genetic identical.
 - carry information about the same traits located in the same places on the chromosomes.
 - are connected to each other at their centromeres.
- In mitosis, when the duplicated chromosomes line up in the center of the cell, that stage is called
 - prophase.
 - metaphase.
 - anaphase.
 - telophase.
- The division of the cytoplasm in the eukaryotic cell cycle is called
 - interphase.
 - karyokinesis.
 - cytokinesis.
 - binary fission.
- The cell cycle is controlled by
 - a series of checkpoints.
 - an internal clock.
 - the completion of one phase triggering the next phase.
 - cell size—when it grows large enough the cell cycle is triggered.
- When cell division becomes unregulated, and a cluster of cells begins to grow without regard for the normal controls, that is called
 - a mutation.
 - cancer.
 - metastases.
 - oncogenes.
- Which of the following is a cancer-causing gene?
 - a proto-oncogene
 - a tumor-suppressor gene
 - an oncogene
 - the *p53* gene
- The normal function of the *p53* gene in the cell is
 - as a tumor-suppressor gene.
 - to monitor the DNA for damage.
 - to trigger the destruction of cells not capable of DNA repair.
 - All of the above.

Visual Understanding

- Figure 9.4** This shows a set of human chromosomes. At what stage of the cell cycle are such photos taken, and why?



- Figure 9.6** During interphase the DNA is not visible through a microscope. Why isn't the DNA visible during interphase and why would this be the case?



Challenge Questions

- Why does the DNA need to change periodically from a long, double-helix chromatin molecule into a tightly wound-up chromosome? What does it do at each stage that it cannot do at the other?
- Despite all we know about cancer today, some types of cancers are still increasing in frequency. Lung cancer in women is one of those. What reason(s) might there be for this increasing problem?