cases is the loss of control over the cell cycle. Research has identified numerous so-called **oncogenes,** genes that can, when introduced into a cell, cause it to become a cancer cell. This identification then led to the discovery of **proto-oncogenes,** which are normal cellular genes that become oncogenes when mutated.

The action of proto-oncogenes is often related to signaling by growth factors, and their mutation can lead to loss of growth control in multiple ways. Some proto-oncogenes encode receptors for growth factors, and others encode proteins involved in signal transduction that act after growth factor receptors. If a receptor for a growth factor becomes mutated such that it is permanently "on," the cell is no longer dependent on the presence of the growth factor for cell division. This is analogous to a light switch that is stuck on: The light will always be on. PDGF and EGF receptors both fall into the category of proto-oncogenes. Only one copy of a proto-oncogene needs to undergo this mutation for uncontrolled division to take place; thus, this change acts like a dominant mutation.

The number of proto-oncogenes identified has grown to more than 50 over the years. This line of research connects our understanding of cancer with our understanding of the molecular mechanisms governing cell-cycle control.

Tumor-suppressor genes

After the discovery of proto-oncogenes, a second category of genes related to cancer was identified: the tumor-suppressor genes. We mentioned earlier in this section that the *p53* gene acts as a tumor-suppressor gene, and a number of other such genes exist.

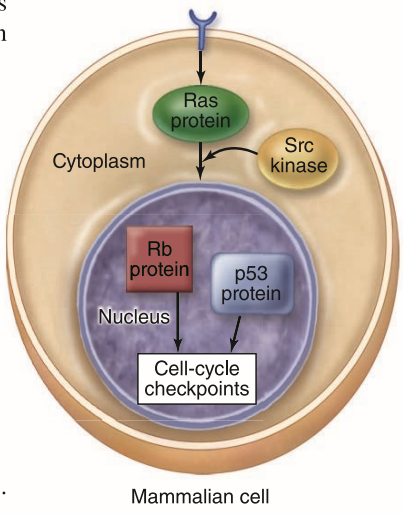
Both copies of a tumor-suppressor gene must lose function for the cancerous phenotype to develop, in contrast to the mutations in proto-oncogenes. Put another way, the proto-oncogenes act in a dominant fashion, and tumor suppressors act in a recessive fashion.

The first tumor suppressor identified was the **retinoblastoma susceptibility gene *(Rb),*** which predisposes individuals for a rare form of cancer that affects the retina of the eye. Despite the fact that a cell heterozygous for a mutant *Rb* allele is normal, it is inherited as a dominant in families. The reason is that inheriting a single mutant copy of *Rb* means the individual has only one "good" copy left, and during the hundreds of thousands of divisions that occur to produce the retina, any error that damages the remaining good copy leads to a cancerous cell. A single cancerous cell in the retina then leads to the formation of a retinoblastoma tumor.

The role of the Rb protein in the cell cycle is to integrate signals from growth factors. The Rb protein is called a "pocket protein" because it has binding pockets for other proteins. Its role is therefore to bind important regulatory proteins and prevent them from stimulating the production of the necessary cell-cycle proteins, such as cyclins or Cdks (see figure 10.21) discussed earlier in this section.

The binding of Rb to other proteins is controlled by phosphorylation: When it is dephosphorylated, it can bind a variety of regulatory proteins, but loses this capacity when phosphorylated. The action of growth factors results in the phosphorylation of Rb protein by a Cdk. This then brings us full circle, because the phosphorylation of Rb releases previously bound regulatory proteins, resulting in the production of S phase cyclins that are necessary for the cell to pass the G_1/S boundary and begin chromosome replication.

Figure 10.24 summarizes the types of genes that can cause cancer when mutated.



Proto-oncogenes

Growth factor receptor: more per cell in many breast cancers.

Ras protein: activated by mutations in 20–30% of all cancers.

Src kinase: activated by mutations in 2–5% of all cancers.

Tumor-suppressor Genes

Rb protein: mutated in 40% of all cancers.

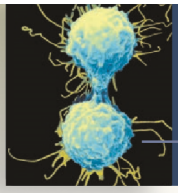
p53 protein: mutated in 50% of all cancers.

Figure 10.24 Key proteins associated with human cancers. Mutations in genes encoding key components of the cell division–signaling pathway are responsible for many cancers. Among them are proto-oncogenes encoding growth factor receptors, protein relay switches such as Ras protein, and kinase enzymes such as Src, which act after Ras and growth factor receptors. Mutations that disrupt tumor-suppressor proteins, such as Rb and p53, also foster cancer development.

Learning Outcomes Review 10.6

Cyclin proteins are produced in synchrony with the cell cycle. These proteins complex with cyclin-dependent kinases to drive the cell cycle. Three checkpoints exist in the cell cycle: the G_1/S checkpoint, the G_2/M checkpoint, and the spindle checkpoint. The cell cycle can be halted at these checkpoints if the process is not accurate. The anaphase-promoting complex/cyclosome (APC/C) triggers anaphase by lifting inhibition on a protease that removes cohesin holding chromatids together. The loss of cell cycle control leads to cancer, which can occur by a combination of two basic mechanisms: proto-oncogenes that gain function to become oncogenes, and tumor-suppressor genes that lose function and allow cell proliferation.

- *How can you distinguish between a tumor-suppressor gene and a proto-oncogene?*



Chapter Review

10.1 Bacterial Cell Division

Binary fission is a simple form of cell division.

Prokaryotic cell division is clonal, resulting in two identical cells. Bacterial DNA replication and partitioning of the chromosome are concerted processes.

Bacterial cells control chromosome separation and septum formation.

DNA replication begins at a specific point, the origin, and proceeds bidirectionally to a specific termination site. Newly replicated chromosomes are segregated to opposite poles at the same time as they are replicated. New cells are separated by septation, which involves insertion of new cell membrane and other cellular materials at the midpoint of the cell. A ring of FtsZ and proteins embedded in the cell membrane expands radially inward, pinching the cell into two new cells.

10.2 Eukaryotic Chromosomes

Chromosome number varies among species.

The gain or loss of chromosomes is usually lethal.

Eukaryotic chromosomes exhibit complex structure.

Chromosomes are composed of chromatin, a complex of DNA, and protein. Heterochromatin is not expressed and euchromatin is expressed. The DNA of a single chromosome is a very long, double-stranded fiber. The DNA is wrapped around a core of eight histones to form a nucleosome, which can be further coiled into a 30-nm fiber in interphase cells. During mitosis, chromosomes are further condensed by arranging coiled 30-nm fibers radially around a protein scaffold.

Newly replicated chromosomes remain attached at a constricted area called a centromere, consisting of repeated DNA sequences. After replication, a chromosome consists of two sister chromatids held together at the centromere by a complex of proteins called cohesins (figure 10.7).

10.3 Overview of the Eukaryotic Cell Cycle (figure 10.8)

The cell cycle is divided into five phases.

The phases of the cell cycle are gap 1 (G_1), synthesis (S), gap 2 (G_2), mitosis, and cytokinesis (C). G_1, S, and G_2 are collectively called interphase, and mitosis and cytokinesis together are called M phase.

The duration of the cell cycle varies depending on cell type.

The length of a cell cycle varies with age, cell type, and species. Cells can exit G_1 and enter a nondividing phase called G_0; the G_0 phase can be temporary or permanent.

10.4 Interphase: Preparation for Mitosis

G_1, S, and G_2 are the three subphases of interphase. G_1 is the primary growth phase; during S phase, DNA synthesis occurs. G_2 phase occurs after S phase and before mitosis.

The centromere binds proteins assembled into a disklike structure called a kinetochore where microtubules attach during mitosis. The centromeric DNA is replicated, but the two DNA strands are held together by cohesin proteins.

10.5 M Phase: Chromosome Segregation and the Division of Cytoplasmic Contents (figure 10.11)

During prophase, the mitotic apparatus forms.

In prophase, chromosomes condense, the spindle is formed, and the nuclear envelope disintegrates. In animals cells, centriole pairs separate and migrate to opposite ends of the cell, establishing the axis of nuclear division.

During prometaphase, chromosomes attach to the spindle.

In metaphase, chromosomes align at the equator.

Chromatids of each chromosome are connected to opposite poles by kinetochore microtubules. They are held at the equator of the cell by the tension of being pulled toward opposite poles.

At anaphase, the chromatids separate.

At this point, cohesin proteins holding sister chromatids together at the centromeres are destroyed, and the chromatids are pulled to opposite poles. This movement is called anaphase A, and the movement of poles farther apart is called anaphase B.

During telophase, the nucleus re-forms.

Telophase reverses the events of prophase and prepares the cell for cytokinesis.

In animal cells, a belt of actin pinches off the daughter cells.

A contractile ring of actin under the membrane contracts during cytokinesis.

In plant cells, a cell plate divides the daughter cells.

Fusion of vesicles produces a new membrane in the middle of the cell to produce the cell plate.

In fungi and some protists, daughter nuclei are separated during cytokinesis.

10.6 Control of the Cell Cycle (figure 10.18)

Research uncovered cell-cycle control factors.

Experiments showed that there are positive regulators of mitosis, and that there are proteins produced in synchrony with the cell cycle (cyclins). The positive regulators are cyclin-dependent kinases (Cdks). Cdks are complexes of a kinase and a regulatory molecule called cyclin. They phosphorylate proteins to drive the cell cycle.

The cell cycle is controlled at three checkpoints.

Checkpoints are points at which the cell can assess the accuracy of the process and stop if needed. The G_1/S checkpoint is a commitment to divide; the G_2/M checkpoint ensures DNA integrity; and the spindle checkpoint ensures that all chromosomes are attached to spindle fibers, with bipolar orientation.

Cyclin-dependent kinases drive the cell cycle.

The cycle progresses by the action of Cdks. Yeast have only one CDK enzyme; vertebrates have more than four enzymes. During the G_1 phase, G_1 cyclin combines with Cdc2 kinase to form the Cdk that triggers entry into S phase.

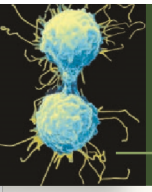
The anaphase-promoting complex/cyclosome (APC/C) activates a protease that removes cohesins holding the centromeres of sister chromatids together; the result is to trigger anaphase, separating the chromatids and drawing them to opposite poles. The APC/C also triggers destruction of mitotic cyclins to exit mitosis.

In multicellular eukaryotes, many Cdks and external signals act on the cell cycle.

Growth factors, like platelet-derived growth factor (PDGF), stimulate cell division. This acts through a MAP kinase cascade that results in the production of cyclins and activation of Cdks to stimulate cell division in fibroblasts after tissue injury.

Cancer is a failure of cell-cycle control.

Mutations in proto-oncogenes have dominant, gain-of-function effects leading to cancer. Mutations in tumor-suppressor genes are recessive; loss of function of both copies leads to cancer.



Review Questions

UNDERSTAND

1. Binary fission in prokaryotes does not require the
   a. replication of DNA.
   b. elongation of the cell.
   c. separation of daughter cells by septum formation.
   d. assembly of the nuclear envelope.
2. Chromatin is composed of
   a. RNA and protein.
   b. DNA and protein.
   c. sister chromatids.
   d. chromosomes.
3. What is a nucleosome?
   a. A region in the cell's nucleus that contains euchromatin
   b. A region of DNA wound around histone proteins
   c. A region of a chromosome made up of multiple loops of chromatin
   d. A 30-nm fiber found in chromatin
4. What is the role of cohesin proteins in cell division?
   a. They organize the DNA of the chromosomes into highly condensed structures.
   b. They hold the DNA of the sister chromatids together.
   c. They help the cell divide into two daughter cells.
   d. They connect microtubules and chromosomes.
5. The kinetochore is a structure that functions to
   a. connect the centromere to microtubules.
   b. connect centrioles to microtubules.
   c. aid in chromosome condensation.
   d. aid in chromosomes cohesion.
6. Separation of the sister chromatids occurs during
   a. prophase.
   b. prometaphase.
   c. anaphase.
   d. telophase.
7. Why is cytokinesis an important part of cell division?
   a. It is responsible for the proper separation of genetic information.
   b. It is responsible for the proper separation of the cytoplasmic contents.
   c. It triggers the movement of a cell through the cell cycle.
   d. It allows cells to halt at checkpoints.
8. What steps in the cell cycle represent irreversible commitments?
   a. The S/G_2 checkpoint
   b. The G_1/S checkpoint
   c. Anaphase
   d. Both b and c are correct.

APPLY

1. Cyclin-dependent kinases (Cdks) are regulated by
   a. the periodic destruction of cyclins.
   b. bipolar attachment of chromosomes to the spindle.
   c. DNA synthesis.
   d. Both a and b are correct.
2. The bacterial SMC proteins, eukaryotic cohesin proteins, and condensin proteins share a similar structure. Functionally they all
   a. interact with microtubules.
   b. can act as kinase enzymes.
   c. interact with DNA to compact or hold strands together.
   d. connect chromosomes to cytoskeletal elements.
3. Genetically, proto-oncogenes act in a dominant fashion. This is because
   a. there is only one copy of each proto-oncogene in the genome.
   b. they act in a gain-of-function fashion to turn on the cell cycle.
   c. they act in a loss-of-function fashion to turn off the cell cycle.
   d. they require that both genomic copies are altered to affect function.
4. The metaphase to anaphase transition involves
   a. new force being generated to pull the chromatids apart.
   b. an increase in force on sister chromatids to pull them apart.
   c. completing DNA replication of centromeres allowing chromosomes to be pulled apart.
   d. loss of cohesion between sister chromatids.
5. The main difference between bacterial cell division and eukaryotic cell division is that
   a. because bacteria only have one chromosome, they can count the number of copies in the cell.
   b. eukaryotes mark their chromosomes to identify them and bacteria do not.
   c. bacterial DNA replication and chromosome segregation are concerted processes but in eukaryotes they are separated in time.
   d. None of the above is correct.
6. In animal cells, cytokinesis is accomplished by a contractile ring containing actin. The related process in bacteria is
   a. chromosome segregation, which also appears to use an actinlike protein.
   b. septation via a ring of FtsZ protein, which is an actinlike protein.
   c. cytokinesis, which requires formation of a cell plate via vesicular fusion.
   d. septation via a ring of FtsZ protein, which is a tubulin-like protein.

SYNTHESIZE

1. Regulation of the cell cycle is very complex and involves multiple proteins. In yeast, a complex of cdc2 and a mitotic cyclin is responsible for moving the cell past the G_2/M checkpoint. The activity of the cyclin-dependent kinase cdc2 is inhibited when it is phosphorylated by the kinase, Wee-1. What would you predict would be the phenotype of a Wee-1 mutant yeast? What other genes could be altered in a Wee-1 deficient mutant strain that would make the cells act normally?
2. Review your knowledge of signaling pathways (chapter 9). Create an outline illustrating how a growth factor (ligand) can lead to the production of a cyclin protein that would trigger S phase.
3. Compare and contrast how mutations in cellular proto-oncogenes and in tumor-suppressor genes can lead to cancer cells.