

CHAPTER 9 THE CELL CYCLE AND CELLULAR REPRODUCTION

Chapter Outline

.1 The Cell Cycle

1. The cell cycle is an orderly set of stages from the first division to the time the *daughter cells* divide.
2. When a cell is preparing for division, it grows larger, the number of organelles doubles, and the DNA replicates.

A. Interphase

1. Most of a cell's life is spent in **interphase**, in which the cell performs its usual functions.
2. Time spent in interphase varies by cell type: nerve and muscle cells do not complete the cell cycle and remain in the **G₀** stage while embryonic cells complete the cycle every few hours.
3. The **G₁** stage is just prior to DNA replication; a cell grows in size, organelles increase in number, and material accumulates for DNA synthesis.
4. The **S** stage is the DNA synthesis (replication) period; proteins associated with DNA are also synthesized; at the end of the S stage, each chromosome has two identical DNA double helix molecules, called *sister chromatids*.
5. The **G₂** stage occurs just prior to cell division; the cell synthesizes proteins needed for cell division, such as proteins in microtubules.
6. Interphase therefore consists of G₁, S, and G₂.

B. M (Mitotic) Stage

1. **M stage (M = mitosis)** is the entire cell division stage, including both mitosis and cytokinesis.
2. **Mitosis** (also known as **karyokinesis**) is nuclear division, **cytokinesis** is division of the cytoplasm.
3. When division of the cytoplasm is complete, two *daughter cells* are produced.

C. Control of the Cell Cycle

1. A **signal** is an agent that influences the activities of a cell.
2. **Growth factors** are external signals received at the plasma membrane.
3. Cell Cycle Checkpoints
 - a. There appear to be three checkpoints where the cell cycle either stops or continues onward, depending on the internal signals it receives.
 - b. Researchers have identified a family of proteins called *cyclins*, internal signals that increase or decrease during the cell cycle.
 - c. Cyclin must be present for the cell to move from the G₁ stage to the S stage, and from the G₂ stage to the M stage.
 - d. The primary checkpoint of the cell cycle is the G₁ checkpoint.
 - e. DNA damage stops the cycle at the G₁ checkpoint by the protein **p53**; if the DNA is not repaired, p53 triggers **apoptosis**.
 - f. Another protein, **RB** (*retinoblastoma*), is responsible for interpreting growth and nutrient availability signals.
 - g. The cell cycle stops at the G₂ stage if DNA has not finished replicating; stopping the cell cycle at this stage allows time for repair of possible damaged DNA.
 - h. Also, the cycle stops if chromosomes are not properly attached to the **mitotic spindle**.

D. Apoptosis

1. Apoptosis is programmed cell death and involves a sequence of cellular events involving:
 - a. fragmenting of the nucleus,
 - b. blistering of the plasma membrane, and
 - c. engulfing of cell fragments by macrophages and/or neighboring cells.
2. Apoptosis is caused by enzymes called **caspases**.
3. Cells normally hold caspases in check with inhibitors.
4. Caspases are released by internal or external signals.
5. Apoptosis and cell division are balancing processes that maintain the normal level of **somatic** (body) **cells**.

6. Cell death is a normal and necessary part of development: frogs, for example, must destroy tail tissue they used as tadpoles, and the human embryo must eliminate webbing found between fingers and toes.
 7. Death by apoptosis prevents a tumor from developing.
- E. The G₁ Checkpoint (*Science Focus* box)
1. During cell division, only certain cells in an adult body are actively dividing.
 2. Once cell division occurs, cells enter G₁ stage.
 3. Following the G₁ stage, cells enter the G₁ checkpoint to make sure that the correct conditions occur to continue cell division.
 4. Evaluating Growth Signals
 - a. Signal molecules are sent to encourage or discourage cells from entering the cell cycle. Cells may enter a G₀ stage, complete G₁ and enter S stage.
 - b. Cell division promoting signals can cause a cyclin-dependent-kinase (CDK) to add a phosphate group to RB, which is a regulator of the G₁ checkpoint.
 - c. When RB is phosphorylated, the shape of RB changes and it releases the protein E2F, rather than binding to E2F.
 - d. E2F then binds to DNA and activates genes to complete the cell cycle.
 - e. If growth signals are sufficient, a cell will pass through the G₁ checkpoint and cell division will occur.
 5. Determining Nutrient Availability
 - a. Cells require adequate nutrient levels prior to cell division.
 - b. When nutrients are available, CDKs bring about phosphorylation of RB, which releases E2F. E2F binds to DNA to produce proteins.
 - c. When nutrients are not available, the cell enters the G₀ stage and does not progress to the G₁ stage.
 6. Assessing DNA Integrity
 - a. DNA must be free of errors and damage in order for cell division to occur.
 - b. If DNA damage is detected, CDK phosphorylates p53. Rather than being broken down, p53 levels in the nucleus rise.
 - c. The phosphorylated p53 binds to DNA to produce DNA repair proteins.
 - d. If DNA damage cannot be repaired, p53 levels continue to rise to trigger apoptosis. However, if DNA damage is repaired, p53 levels fall, and cell completes G₁ stage as long as other requirements are met.

9.2 Mitosis and Cytokinesis

- A. Eukaryotic Chromosomes
1. DNA in chromosomes of eukaryotic cells is associated with proteins; **histones** organize chromosomes.
 2. When a cell is not undergoing division, DNA in the nucleus is a tangled mass of threads called **chromatin**.
 3. At cell division, chromatin becomes highly coiled and condensed and is now visible as individual chromosomes.
 4. Each species has a characteristic number of chromosomes.
 - a. The **diploid (2n) number** includes two sets of chromosomes of each type.
 - 1) The diploid number is found in all the non-sex cells of an organism's body (with a few exceptions).
 - b. The **haploid (n) number** contains one of each kind of chromosome.
 - 1) In the life cycle of many animals, only sperm and egg cells have the haploid number.
- B. Preparations for Mitosis
1. Cell division in eukaryotes involves nuclear division and cytokinesis.
 - a. Somatic cells undergo mitosis for development, growth, and repair.
 - 1) This nuclear division leaves the chromosome number constant.
 - 2) A 2n nucleus replicates and divides to provide daughter nuclei that are also 2n.
 - b. A chromosome begins cell division with two **sister chromatids**.
 - 1) **Sister chromatids** are two strands of genetically identical chromosomes.
 - 2) At the beginning of cell division, they are attached at a **centromere**, a region of constriction on a chromosome.
 2. The **centrosome**, the main microtubule organizing center of the cell, divides before mitosis begins.
 3. Each centrosome contains a pair of barrel-shaped organelles called **centrioles**.
 4. The mitotic spindle contains many fibers, each composed of a bundle of microtubules.
 5. Microtubules are made of the protein **tubulin**.

- a. Microtubules assemble when tubulin subunits join, disassemble when tubulin subunits become free, and form interconnected filaments of cytoskeleton.
- b. Microtubules disassemble as spindle fibers form.

C. Phases of Mitosis

- 1. Mitosis is divided into five phases: prophase, prometaphase, metaphase, anaphase, and telophase.
- 2. Prophase
 - a. Nuclear division is about to occur: chromatin condenses and chromosomes become visible.
 - b. The nucleolus disappears and the nuclear envelope fragments.
 - c. Duplicated chromosomes are composed of two sister chromatids held together by a centromere; chromosomes have no particular orientation in the cell at this time.
 - d. The spindle begins to assemble as pairs of centrosomes migrate away from each other.
 - e. An array of microtubules called **asters** radiates toward the plasma membrane from the centrosomes.
- 3. Prometaphase (Late Prophase)
 - a. Specialized protein complexes (**kinetochores**) develop on each side of the centromere for future chromosome orientation.
 - b. An important event during prometaphase is attachment of the chromosomes to the spindle and their movement as they align at the metaphase plate (equator) of the spindle.
 - c. The kinetochores of sister chromatids capture *kinetochore spindle fibers*.
 - d. Chromosomes move back and forth toward alignment at the metaphase plate.
- 4. Metaphase
 - a. Chromosomes, attached to kinetochore fibers, are now aligned at the **metaphase plate**.
 - b. Non-attached spindle fibers, called *polar spindle fibers*, can reach beyond the metaphase plate and overlap.
 - c. A cell checkpoint called the *M checkpoint* delays the start of anaphase until kinetochores are properly attached to the spindle fibers, and chromosomes are properly aligned along metaphase plate.
- 5. Anaphase
 - a. The two sister chromatids of each duplicated chromosome separate at the centromere.
 - b. Daughter chromosomes, each with a centromere and single chromatid, move to opposite poles.
 - 1) Polar spindle fibers lengthen as they slide past each other.
 - 2) Kinetochore spindle fibers disassemble at the kinetochores; this pulls daughter chromosomes to poles.
 - 3) The motor molecules *kinesin* and *dynein* are involved in this sliding process.
 - 4) Anaphase is the shortest stage of mitosis.
- 6. Telophase
 - a. Spindle disappears in this stage.
 - b. The nuclear envelope reforms around the daughter chromosomes.
 - c. The daughter chromosomes diffuse, again forming chromatin.
 - d. The nucleolus reappears in each daughter nucleus.

D. Cytokinesis in Animal and Plant Cells

- 1. Cytokinesis in Animal Cells
 - a. A *cleavage furrow* indents the plasma membrane between the two daughter nuclei at a midpoint; this deepens to divide the cytoplasm during cell division.
 - b. Cytoplasmic cleavage begins as anaphase draws to a close and organelles are distributed.
 - c. The cleavage furrow deepens as a band of actin filaments, called the *contractile ring*, constricts between the two daughter cells.
 - d. A narrow bridge exists between daughter cells during telophase until constriction completely separates the cytoplasm.
- 2. Cytokinesis in Plant Cells
 - a. The rigid cell wall that surrounds plant cells does not permit cytokinesis by furrowing.
 - b. The Golgi apparatus produces vesicles, which move along the microtubules to a small flattened disc that has formed.
 - c. Vesicles fuse forming a **cell plate**; their membranes complete the plasma membranes of the daughter cells.
 - d. The new membrane also releases molecules from the new plant cell walls; the cell walls are strengthened by the addition of cellulose fibrils.

E. The Functions of Mitosis

1. Mitosis permits growth and repair.
2. In flowering plants, the *meristematic tissue* retains the ability to divide throughout the life of the plant; this accounts for the continued growth, both in height and laterally, of a plant.
3. In mammals, mitosis is necessary as a fertilized egg becomes an embryo and as the embryo becomes a fetus; throughout life, mitosis allows a cut to heal or a broken bone to mend.

F. Stem Cells

1. Many mammalian organs contain *stem cells* (or *adult stem cells*), which retain the ability to divide.
2. Red bone marrow stem cells repeatedly divide to produce the various types of blood cells.
3. **Therapeutic cloning** to produce human tissues can begin with either adult stem cells or embryonic stem cells.
4. Embryonic stem cells can be used for **reproductive cloning**, the production of a new individual.

G. Reproductive and Therapeutic Cloning (*Science Focus* box)

1. There are two types of cloning: reproductive cloning and therapeutic cloning.
2. Reproductive (somatic cell) cloning
 - a. In reproductive cloning, the donor cells are first starved, then the nucleus is taken out of cell and transplanted into enucleated egg.
 - b. The donor cell stops dividing and goes into G₀ stage.
 - c. Embryonic stem cells are formed and implanted into the embryo of a surrogate mother.
 - d. When embryo is fully developed, a clone is born.
3. Therapeutic cloning
 - a. One way to conduct therapeutic cloning is by the same procedure as reproductive cloning, *embryonic stem cells* are separated and subjected to treatment that causes it to develop into different types of cells: red blood cells, muscle cells, nerve cells.
 - b. The other way to conduct therapeutic cloning is to use *adult stem cells*.
 - c. One drawback to using adult stem cells is they are limited in the number of cell types they may become. However, researchers are trying to overcome this obstacle.

9.3 The Cell Cycle and Cancer

1. **Cancer** is a cellular growth disorder that occurs when cells divide uncontrollably; i.e., cancer results from the loss of control and a disruption of the cell cycle.
2. Most cancers begin as abnormal cell growth that is **benign**, or not cancerous
3. When additional mutations occur, the growth becomes **malignant**, or cancerous, and possesses the ability to spread.

A. Characteristics of Cancer Cells

1. Cancer cells lack differentiation.
 - a. Unlike normal cells that differentiate into muscle or nerves cells, cancer cells have an abnormal form and are nonspecialized.
 - b. Normal cells enter the cell cycle only about 50 times; cancer cells are immortal in that they can enter the cell cycle repeatedly.
2. Cancer cells have abnormal nuclei.
 - a. The nuclei may be enlarged and may have an abnormal number of chromosomes.
 - b. The chromosomes have mutated; some chromosomes may be duplicated or deleted.
3. Cancer cells do not undergo apoptosis
 - a. Whereas ordinary cells with DNA damage undergo apoptosis, cancer cells do not.
4. Cancer cells form tumors.
 - a. Normal cells are anchored and stop dividing when in contact with other cells; i.e., they exhibit *contact inhibition*.
 - b. Cancer cells invade and destroy normal tissue and their growth is not inhibited.
 - c. Cancer cells pile on top of each other to form a **tumor**.
5. Cancer cells undergo metastasis and angiogenesis.
 - a. A *benign tumor* is encapsulated and does not invade adjacent tissue.
 - b. Many types of cancer can undergo **metastasis**, in which new tumors form which are distant from the primary tumor.
 - c. **Angiogenesis**, the formation of new blood vessels, is required to bring nutrients and oxygen to the tumor.

B. Origin of Cancer

1. **Proto-oncogenes** code for proteins that stimulate the cell cycle and prevent apoptosis.
2. **Tumor-suppressor genes** code for proteins that inhibit the cell cycle and promote apoptosis.
3. Mutations of either of these genes can cause cancer.

4. Proto-oncogenes are at the end of a *stimulatory pathway* from the plasma membrane to the nucleus; a growth factor binding at the plasma membrane can result in turning on an oncogene.
5. Proto-oncogenes can undergo mutation to become **oncogenes** (cancer-causing genes).
6. An oncogene may code for a faulty receptor in the stimulatory pathway.
7. Or an oncogene can specify an abnormal protein product or abnormally high levels of a normal product that stimulates the cell cycle.
8. Tumor-suppressor genes are at the end of an *inhibitory pathway*; a growth-inhibitory factor can result in turning on a tumor suppressor gene that inhibits the cell cycle.
9. The balance between stimulatory and inhibitory signals determines whether proto-oncogenes or tumor-suppressor genes are active, and therefore whether or not cell division occurs.
10. Researchers have identified about a half dozen tumor-suppressor genes.
11. The *RB* tumor-suppressor gene prevents retinoblastoma, a cancer of the retina, and has been found to malfunction in cancers of the breast, prostate, bladder, and small-cell lung carcinoma.
12. The *p53* tumor-suppressor gene is more frequently mutated in human cancers than any other known gene; it normally functions to trigger cell cycle inhibitors and stimulate apoptosis.
13. In some cancer cells, mutation of an enzyme that regulates the length of **telomeres** causes the telomeres to remain at a constant length, which allows the cancer cells to continue dividing.

9.4 Prokaryotic Cell Division

1. Unicellular organisms reproduce via **asexual reproduction**, in which the offspring are genetically identical to the parent.
- A. The Prokaryotic Chromosome
1. Prokaryotic cells (bacteria and archaea) lack a nucleus and other membranous organelles.
 2. The prokaryotic chromosome is composed of DNA and associated proteins, but much less protein than eukaryotic chromosomes.
 3. The chromosome appears as a **nucleoid**, an irregular-shaped region that is not enclosed by a membrane.
 4. The chromosome is a circular loop attached to the inside of the plasma membrane; it is about 1,000 times the length of the cell.
- B. Binary Fission
1. **Binary fission** of prokaryotic cells produces two genetically identical daughter cells.
 2. Before cell division, DNA is replicated—both chromosomes are attached to a special site inside the plasma membrane.
 3. The two chromosomes separate as a cell lengthens and pulls them apart.
 4. When the cell is approximately twice its original length, the plasma membrane grows inward, a *septum* (consisting of new cell wall and plasma membrane) forms, dividing the cell into two daughter cells.
 5. The generation time of bacteria depends on the species and environmental conditions; *Escherichia coli*'s generation time is about 20 minutes.
- C. Comparing Prokaryotes and Eukaryotes
1. Both binary fission and mitosis ensure that each daughter cell is genetically identical to the parent.
 2. Bacteria and protists use asexual reproduction to produce identical offspring.
 3. In multicellular fungi, plants, and animals, cell division is part of the growth process that produces and repairs the organism.
 4. Prokaryotes have a single chromosome with mostly DNA and some associated protein; there is no spindle apparatus.
 5. Eukaryotic cells have chromosomes with DNA and many associated proteins; *histone* proteins organize the chromosome.
 6. The spindle is involved in distributing the daughter chromosomes to the daughter nuclei.