Chapter 12

The Cell Cycle

Lecture Outline

Overview: The Key Roles of Cell Division

- The ability of organisms to produce more of their own kind is the one characteristic that best distinguishes living things from nonliving matter.

- The continuity of life is based on the reproduction of cells, or cell division.
  - Cell division functions in reproduction, growth, and repair.
  - The division of a prokaryotic cell or unicellular eukaryote reproduces an entire organism, thereby increasing the population. Cell division enables a multicellular organism to develop from a single cell such as a fertilized egg.
  - In a multicellular organism, cell division functions to repair and renew cells that die from normal wear and tear or accidents.

- Cell division is an integral part of the **cell cycle**, the life of a cell from its origin in the division of a parent cell until its own division into two daughter cells.

Concept 12.1 Most cell division results in genetically identical daughter cells.

- In both prokaryotes and eukaryotes, most cell division involves the distribution of identical genetic material—DNA—to two daughter cells.
  - The exception is meiosis, the special type of eukaryotic cell division that can produce sperm and eggs.

- What is remarkable is the fidelity with which DNA is passed along, without dilution, from one generation to the next.

- A dividing cell duplicates its DNA, allocates the two copies to opposite ends of the cell, and only then splits into daughter cells.

- A cell's genetic information, packaged as DNA, is called its **genome**.
  - In prokaryotes, the genome is often a single long DNA molecule.
  - In eukaryotes, the genome consists of a number of DNA molecules.

- A human cell must copy or replicate about 2 m of DNA and separate the two copies so that each daughter cell ends up with a complete genome.

- DNA molecules are packaged into **chromosomes**.

- Every eukaryotic chromosome consists of one long, linear DNA molecule associated with many proteins. Together, the complex is referred to as **chromatin**.
  - The DNA molecule carries several hundred to a few thousand genes.
  - The proteins maintain the structure of the chromosome and help control the activity of the genes.

- Each eukaryotic species has a characteristic number of chromosomes in each cell nucleus.
  - Human **somatic cells** (all body cells except sperm and egg) have 46 chromosomes, made up of two sets of 23 (one from each parent).
  - Human reproductive cells or **gametes** (sperm or eggs) have one set of 23 chromosomes, half the number in a somatic cell.
  - The number of chromosomes in somatic cells varies widely among species.

Chromosomes are distributed during eukaryotic cell division.

- When a cell is not dividing, each chromosome is in the form of a long, thin chromatin fiber.
- Before cell division but after DNA relication, the chromatin condenses, coiling and folding to make a smaller package.
- Each duplicated chromosome consists of two **sister chromatids**, joined together, which contain identical copies of the chromosome's DNA.
  - The chromatids are initially attached along their lengths by protein complexes called *cohesins*. This attachment is known as *sister chromatid cohesion*.
- As the chromosomes condense, the region where the chromatids connect shrinks to a narrow area, made up of two **centromeres**.
  - Each centromere is a specialized region of one chromatid with specific DNA sequences.
  - Associated proteins bound to these centromeric DNA sequences attach the two chromatids of a duplicated chromosome to each other most closely at this region.
- The part of a chromatid on either side of the centromere is called an *arm* of the chromatid.
- Later in cell division, the sister chromatids separate and move into two new nuclei at opposite ends of the parent cell.
  - After the sister chromatids separate, they are considered individual chromosomes.
- Each new nucleus receives a group of chromosomes identical to the original group in the parent cell.
- **Mitosis**, the division of the nucleus, is usually followed by the division of the cytoplasm, **cytokinesis**.
- These processes start with one cell and produce two cells that are genetically identical to the original parent cell.
  - Each of us inherited 23 chromosomes from each parent: one set in an egg and one set in sperm, for a total of 46.
  - The chromosomes were combined in the nucleus of a single cell when a sperm from your father united with an egg from your mother to form a fertilized egg, or zygote.
- The zygote underwent cycles of mitosis and cytokinesis to produce a fully developed multicellular human made up of 200 trillion somatic cells.
  - These processes continue every day to replace dead and damaged cells.
  - Essentially, these processes produce clones—cells with identical genetic information.
- In contrast, gametes (eggs or sperm) are produced only in gonads (ovaries or testes) by a variation of cell division called **meiosis**.
- *Meiosis* yields four nonidentical daughter cells, each with half the chromosomes of the parent.
  - In humans, meiosis occurs only in the gonads (ovaries or testes) and reduces the number of chromosomes from 46 (two sets) to 23 (one set).
  - Fertilization fuses two gametes together and returns the number of chromosomes to 46 again.

Concept 12.2 The mitotic phase alternates with interphase in the cell cycle.

- The **mitotic (M) phase** of the cell cycle, which includes mitosis and cytokinesis, alternates with the much longer **interphase**.
  - Interphase accounts for about 90% of the cell cycle.
- Interphase has three subphases: the **G₁ phase** ("first gap"), the **S phase** ("synthesis"), and the **G₂ phase** ("second gap"). The daughter cells may then repeat the cycle.
  - During all three subphases, a cell that will eventually divide grows by producing proteins and cytoplasmic organelles such as mitochondria and endoplasmic reticulum.
  - Chromosomes are duplicated only during the S phase.
- A typical human cell might divide once every 24 hours.
  - Of this time, the M phase would last less than an hour and the S phase might take 10–12 hours, or half the cycle.
  - The rest of the time would be divided between the G_1 and G_2 phases.
  - The G_1 phase varies most in length from cell to cell.
- Some cells in a multicellular organism divide very infrequently or not at all.
  - These cells spend their time in G_1 phase.
- For convenience, mitosis is usually divided into five subphases: **prophase**, **prometaphase**, **metaphase**, **anaphase**, and **telophase**.
- Cytokinesis, overlapping with the latter stages, completes the mitotic phase.
- In late interphase, the chromosomes have been duplicated but are not condensed.
  - A nuclear membrane bounds the nucleus, which contains one or more nucleoli.
  - The centrosome has replicated to form two centrosomes.
  - In animal cells, each centrosome features two centrioles.
- In prophase, the chromosomes are tightly coiled, with sister chromatids joined together.
  - The nucleoli disappear.
  - The mitotic spindle begins to form. It is composed of centrosomes and the microtubules that extend from them.
  - The radial arrays of shorter microtubules that extend from the centrosomes are called asters.
  - The centrosomes move away from each other, apparently propelled by lengthening microtubules.
- During prometaphase, the nuclear envelope fragments, and microtubules from the spindle interact with the condensed chromosomes.
  - Each of the two chromatids of a chromosome has a **kinetochore**, a specialized protein structure located at the centromere.
  - Kinetochore microtubules from each pole attach to one of two kinetochores.
  - Nonkinetochore microtubules interact with those from opposite ends of the spindle.
- The spindle fibers push the sister chromatids until they are all arranged at the **metaphase plate**, an imaginary plane equidistant from the poles, defining metaphase.
- At anaphase, the centromeres divide, separating the sister chromatids.
  - Each chromatid is pulled toward the pole to which it is attached by spindle fibers.
  - By the end, the two poles have equivalent collections of chromosomes.
- At telophase, daughter nuclei begin to form at the two poles.
  - Nuclear envelopes arise from the fragments of the parent cell's nuclear envelope and other portions of the endomembrane system.
  - The chromosomes become less tightly coiled.

- Cytokinesis, division of the cytoplasm, is usually well under way by late telophase.
  - In animal cells, cytokinesis involves the formation of a cleavage furrow, which pinches the cell in two.
  - In plant cells, vesicles derived from the Golgi apparatus produce a cell plate at the middle of the cell.

The mitotic spindle distributes chromosomes to daughter cells: a closer look.

- The **mitotic spindle**, fibers composed of microtubules and associated proteins, is a major driving force in mitosis.

- As the spindle assembles during prophase, the elements come from partial disassembly of the other microtubules of the cytoskeleton.

- The spindle fibers elongate (polymerize) by incorporating more subunits of the protein tubulin and shorten (depolymerize) by losing subunits.

- Assembly of the spindle microtubules starts in the **centrosome**, or *microtubule-organizing center*, a subcellular region that organizes the cell's microtubules.

  - In animal cells, the centrosome has a pair of centrioles at the center, but the centrioles are not essential for cell division. If the centrosomes of an animal cell are destroyed by laser, a spindle still forms during mitosis.
  - The centrosomes of most plants lack centrioles, but still form mitotic spindles.

- During interphase, the single centrosome replicates to form two centrosomes.

- As mitosis starts, the two centrosomes are located near the nucleus.
  - As the spindle microtubules grow from them, the centrioles are pushed apart.
  - By the end of prometaphase, they are at opposite ends of the cell.

- An **aster**, a radial array of short microtubules, extends from each centrosome.

- The spindle includes the centrosomes, the spindle microtubules, and the asters.

- Each sister chromatid of a duplicated chromosome has a **kinetochore** of proteins and chromosomal DNA.
  - The kinetochores of the joined sister chromatids face in opposite directions.

- During prometaphase, some spindle microtubules (called kinetochore microtubules) attach to the kinetochores.

- When a chromosome's kinetochore is "captured" by microtubules, the chromosome moves toward the pole from which those microtubules come.
  - When microtubules attach to the other pole, this movement stops and a tug-of-war ensues.
  - Eventually, the chromosome settles midway between the two poles of the cell, on the **metaphase plate.**

- Nonkinetochore "polar" microtubules from opposite poles overlap and interact with each other.

- By metaphase, the microtubules of the asters have grown and are in contact with the plasma membrane.

- The spindle is now complete.

- Anaphase commences suddenly when the cohesins holding the sister chromatids together are cleaved by an enzyme called *separase*.

- Once the chromosomes are separate, full-fledged chromosomes, they move toward opposite poles of the cell.

- How do the kinetochore microtubules function in the poleward movement of chromosomes?
  - Two mechanisms are in play, both involving motor proteins.
  - Gary Borisy, of the University of Wisconsin, suggests that motor proteins on the kinetochores "walk" the chromosomes along the microtubules, which depolymerize at their kinetochore ends after the motor proteins have passed.
  - Other researchers have shown that chromosomes are "reeled in" by motor proteins at the spindle poles and that the microtubules depolymerize after they pass by the motor proteins.
  - The relative contributions of these two mechanisms vary among cell types.

- What is the function of the *non*kinetochore microtubules?
  - Nonkinetochore microtubules are responsible for lengthening the cell along the axis defined by the poles.
  - In a dividing animal cell, these microtubules elongate the cell during anaphase.
  - Nonkinetochore microtubules interdigitate and overlap across the metaphase plate.
  - During anaphase, the area of overlap is reduced as motor proteins attached to the microtubules walk them away from one another, using energy from ATP.
  - As the microtubules push apart, they lengthen by the addition of new tubulin monomers to their overlapping ends, allowing continued overlap.

- At the end of anaphase, duplicated chromosomes have arrived at opposite ends of the elongated parent cell.

- Nuclei re-form during telophase.

- Cytokinesis usually starts during the later stages of mitosis, and the spindle eventually disassembles by depolymerization of microtubules.

Cytokinesis divides the cytoplasm: a closer look.

- Cytokinesis, division of the cytoplasm, typically follows mitosis.

- In animal cells, cytokinesis occurs by a process called **cleavage**.
  - The first sign of cleavage is the appearance of a **cleavage furrow** in the cell surface near the old metaphase plate.
  - On the cytoplasmic side of the cleavage furrow is a contractile ring of actin microfilaments associated with molecules of the motor protein myosin.
  - Contraction of the ring pinches the cell in two.

- Cytokinesis in plants, which have cell walls, involves a completely different mechanism.
  - During telophase, vesicles from the Golgi apparatus move along microtubules to the middle of the cell, where they coalesce to form a **cell plate**.
  - Cell wall materials carried in the vesicles collect in the cell plate as it grows.
  - The plate enlarges until its membranes fuse with the plasma membrane at the perimeter.
  - The contents of the vesicles form new cell wall material between the daughter cells.

Mitosis in eukaryotes may have evolved from binary fission in bacteria.

- Asexual reproduction of single-celled eukaryotes, such as an amoeba, includes mitosis and occurs by a type of cell division called **binary fission**, or "division in half."
  ○ Prokaryotes also reproduce by binary fission, but the process does not involve mitosis.

- Most bacterial genes are located on a single *bacterial chromosome* that consists of a circular DNA molecule and associated proteins.

- Although bacteria are smaller and simpler than eukaryotic cells, they still have large amounts of DNA that must be copied and distributed equally to two daughter cells.
  ○ The circular bacterial chromosome, although 500 times as long as the cell when fully stretched out, is highly folded and coiled.

- In the bacterium *Escherichia coli*, the process of cell division begins when the DNA of the bacterial chromosome starts to replicate at a specific place on the circular chromosome, the **origin of replication**, producing two origins.
  ○ As the chromosome continues to replicate, one origin moves toward each end of the cell.

- While the chromosome is replicating, the cell elongates.

- When replication is complete, the plasma membrane pinches inward to divide the parent *E. coli* cell into two daughter cells, each with a complete genome.

- Researchers use fluorescence microscopy to observe the movement of bacterial chromosomes**.**
  ○ The movement is similar to the poleward movements of the centromere regions of eukaryotic chromosomes.
  ○ However, bacterial chromosomes lack visible mitotic spindles or even microtubules.

- In most bacterial species studied, the two origins of replication end up at opposite ends of the cell or in some other very specific location, possibly anchored there by one or more proteins.

- The mechanism behind the movement of the bacterial chromosome is still not fully understood**.**
  ○ Several proteins have been identified and play important roles.
  ○ One protein resembling eukaryotic actin apparently functions in bacterial chromosome movement during cell division, and another related to tubulin seems to help pinch the plasma membrane inward to separate the two daughter cells.

- How did mitosis evolve?

- There is evidence that mitosis had its origins in bacterial binary fission.
  ○ The fact that some of the proteins involved in bacterial binary fission are related to eukaryotic proteins that function in mitosis supports this hypothesis.

- As eukaryotes evolved, the ancestral process of binary fission gave rise to mitosis.

- Variations in cell division in different groups of organisms may be similar to mechanisms used by ancestral species and thus may resemble steps in the evolution of mitosis from binary fission.
  ○ Two unusual types of nuclear division are found in certain unicellular eukaryotes: dinoflagellates, diatoms, and some yeast cells.
  ○ These two examples are thought to be cases where ancestral mechanisms have remained relatively unchanged over evolutionary time.
  ○ In both types, the nuclear envelope remains intact throughout nuclear division.

Concept 12.3 The eukaryotic cell cycle is regulated by a molecular control system.

- The timing and rate of cell division in different parts of an animal or plant are crucial for normal growth, development, and maintenance.

- The frequency of cell division varies with cell type.
  - Some human cells divide frequently throughout life (skin cells).
  - Others human cells have the ability to divide but keep it in reserve (liver cells).
  - Mature nerve and muscle cells do not appear to divide at all after maturity.

- Investigation of the molecular mechanisms regulating these differences provides important insights into the operation of normal cells and may also explain how cancer cells escape controls.

Cytoplasmic signals drive the cell cycle.

- The cell cycle appears to be driven by specific chemical signals present in the cytoplasm.

- Some of the initial evidence for this hypothesis came from experiments in which cultured mammalian cells at different phases of the cell cycle were fused to form a single cell with two nuclei.
  - Fusion of an S phase cell and a G_1 phase cell induces the G_1 nucleus to start S phase.
  - This process suggests that signaling molecules present in the S phase nucleus stimulated the fused cell.
  - Fusion of a cell in mitosis (M phase) with one in interphase (even G_1 phase) induces the second cell to enter mitosis.

- The sequential events of the cell cycle are directed by a distinct **cell cycle control system**.

- Cyclically operating molecules trigger and coordinate key events in the cell cycle.
  - The control cycle has a built-in clock, but it is also regulated by external adjustments and internal controls.

- A **checkpoint** in the cell cycle is a control point where stop and go-ahead signals regulate the cycle.
  - The signals are transmitted within the cell by signal transduction pathways.

- Animal cells generally have built-in stop signals that halt the cell cycle at checkpoints until they are overridden by go-ahead signals.

- Many signals registered at checkpoints come from cellular surveillance mechanisms.
  - These mechanisms indicate whether key cellular processes have been completed correctly.
  - Checkpoints also register signals from outside the cell.

- Three major checkpoints are found in the G_1, G_2, and M phases.

- For many cells, the G_1 checkpoint, the "restriction point" in mammalian cells, is the most important.

- If the cell receives a go-ahead signal at the G_1 checkpoint, it usually completes the cell cycle and divides.

- If the cell does not receive a go-ahead signal, the cell exits the cycle and switches to a nondividing state, the G_0 phase.

- Most cells in the human body are in the G_0 phase.
  - Liver cells can be "called back" to the cell cycle by external cues, such as growth factors released during injury.

- Highly specialized nerve and muscle cells never divide.

The cell cycle clock is regulated by cyclins and cyclin-dependent kinases.

- Rhythmic fluctuations in the abundance and activity of cell cycle control molecules pace the events of the cell cycle.

- These regulatory molecules are mainly proteins of two types: protein kinases and cyclins.

- Protein kinases are enzymes that activate or inactivate other proteins by phosphorylating them.
  - Particular protein kinases give the go-ahead signals at the G_1 and G_2 checkpoints.

- The kinases that drive the cell cycle are present at constant concentrations but require the attachment of a second protein, a **cyclin**, to become activated.
  - Levels of cyclin proteins fluctuate cyclically.
  - Because of the requirement for binding of a cyclin, the kinases are called **cyclin-dependent kinases**, or **Cdks**.

- Peaks in the activity of one cyclin-Cdk complex, **MPF**, correspond to peaks in cyclin concentration.
  - Cyclin level rises sharply during the S and G_2 phases and then falls abruptly during mitosis**.**

- MPF ("maturation-promoting factor" or "M-phase-promoting factor") triggers the cell's passage past the G_2 checkpoint to the M phase.
  - MPF promotes mitosis by phosphorylating a variety of proteins.
  - MPF acts both directly as a kinase and indirectly by activating other kinases.
  - MPF stimulates fragmentation of the nuclear envelope by phosphorylation of various proteins of the nuclear lamina during prometaphase of mitosis.
  - MPF also contributes to the molecular events required for chromosome condensation and spindle formation during prophase.

- MPF triggers the breakdown of cyclin, reducing cyclin and MPF levels during mitosis and inactivating MPF.
  - The noncyclin part of MPF, the Cdk, persists in the cell in inactive form until it associates with new cyclin molecules synthesized during the S and G_2 phases of the next round of the cycle.

- At least three Cdk proteins and several cyclins regulate the key G_1 checkpoint.

- Fluctuating activities of different cyclin-Cdk complexes are of major importance in controlling all the stages of the cell cycle.

Internal and external cues help regulate the cell cycle.

- Research scientists are currently working out the pathways that link signals originating inside or outside the cell with responses by cyclin-dependent kinases and other proteins.

- The M phase checkpoint ensures that the kinetochores of all the chromosomes are properly attached to the spindle at the metaphase plate before anaphase.

- In this case, the regulatory molecule is not a cyclin-Cdk complex but a complex made up of several proteins.
  - Once activated, the complex sets off a chain of molecular events that activates the separase enzyme, which cleaves the cohesins and allows the sister chromatids to separate.
  - This ensures that daughter cells do not end up with missing or extra chromosomes.

- A variety of external chemical and physical factors can influence cell division.
  - For example, cells fail to divide if an essential nutrient is left out of the culture medium.

- Particularly important for mammalian cells are **growth factors**, proteins released by certain cells that stimulate other cells to divide.
  - Researchers have discovered at least 50 different growth factors.
  - Different cell types respond specifically to a certain growth factor or combination.

- *Platelet-derived growth factors (PDGFs),* produced by blood platelets, are required for the division of fibroblasts in culture.
  - Fibroblasts, a type of connective tissue cell, have PDGF receptors on their plasma membranes.
  - PDGF molecules bind to these receptor tyrosine kinases, triggering a signal transduction pathway that allows cells to pass the G_1 checkpoint and divide.

- In a living organism, platelets release PDGF in the vicinity of an injury. The resulting proliferation of fibroblasts helps heal the wound.

- The effect of an external physical factor on cell division can be seen in **density-dependent inhibition** of cell division.
  - Cultured cells normally divide until they form a single layer on the inner surface of the culture container. If a gap is created, the cells will grow to fill the gap.
  - The binding of a cell-surface protein to its counterpart on an adjoining cell sends a growth-inhibiting signal to both cells, preventing them from moving forward in the cell cycle, even in the presence of growth factors.

- Most animal cells also exhibit **anchorage dependence** for cell division.
  - To divide, the cells must be anchored to a substratum, typically the extracellular matrix of a tissue.
  - Experiments suggest that, like cell density, anchorage is signaled to the cell cycle control system via pathways involving plasma membrane proteins and elements of the cytoskeleton linked to them.

- Cancer cells exhibit neither density-dependent inhibition nor anchorage dependence.

Cancer cells have escaped from cell cycle controls.

- Cancer cells divide excessively and invade other tissues because they are free of the body's control mechanisms.
  - Cancer cells do not stop dividing when growth factors are depleted.
  - This is because a cancer cell manufactures its own growth factors, has an abnormality in the signaling pathway, or has an abnormal cell cycle control system.
  - The underlying basis of these abormalities is one or more genetic changes that alter the function of the cancer cell's protein products, resulting in faulty cell cycle control.

- If and when cancer cells stop dividing, they do so at random points, not at the normal checkpoints in the cell cycle.

- Cancer cells may divide indefinitely if they have a continuous supply of nutrients.
  - In contrast, nearly all mammalian cells divide 20–50 times under culture conditions before they stop, age, and die. Cancer cells may be "immortal."
  - HeLa cells from a tumor removed from a woman (Henrietta Lacks) in 1951 are still reproducing in culture.

- The abnormal behavior of cancer cells begins when a single cell in a tissue undergoes a **transformation** that converts it from a normal cell to a cancer cell.
  - Normally, the immune system recognizes and destroys transformed cells.

- Cells that evade destruction proliferate to form a tumor, a mass of abnormal cells.

- If the abnormal cells remain at the originating site, the lump is called a **benign tumor**.
  - Most benign tumors do not cause serious problems and can be fully removed by surgery.

- A **malignant tumor** includes cells whose genetic and cellular changes enable them to spread to new tissues and impair the functions of one or more organs.
  - An individual with a malignant tumor is said to have cancer.

- Cancer cells are abnormal in many ways.
  - Cancer cells may have an unusual number of chromosomes, their metabolism may be disabled, and they may cease to function in any constructive way.
  - Cancer cells may secrete signal molecules that cause blood vessels to grow toward the tumor.

- In addition to chromosomal and metabolic abnormalities, cancer cells often lose their attachment to nearby cells, are carried by the blood and lymph system to other tissues, and start more tumors in an event called **metastasis**.

- Treatments for metastasizing cancers include high-energy radiation and chemotherapy with toxic drugs.
  - These treatments target actively dividing cells.
  - Chemotherapeutic drugs interfere with specific steps in the cell cycle.
  - For example, Taxol prevents microtubule depolymerization, preventing cells from proceeding past metaphase.

- The side effects of chemotherapy are due to the drug's effects on normal cells.
  - For example, nausea results from chemotherapy's effects on intestinal cells, hair loss results from its effects on hair follicle cells, and susceptibility to infection results from its effects on immune system cells.

- Researchers now know a great deal about cell signaling pathways and how their malfunction is involved in the development of cancer through effects on the cell cycle.
  - Coupled with new molecular techniques, such as the ability to rapidly sequence the DNA of cells in a particular tumor, medical treatments for cancer are beginning to become more "personalized" to each patient's tumor.

- The development of cancer is a very complex process, with many areas that remain to be explored.
  - Perhaps the reason there are so many unanswered questions about cancer cells is that there is still so much to learn about the functioning of normal cells.