Chapter 12 The Cell Cycle
Lecture Outline

Overview: The Key Roles of Cell Division

- The ability of organisms to reproduce their 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 unicellular organism reproduces an entire organism, increasing the population.
- Cell division on a larger scale can produce progeny for some multicellular organisms.
  - This includes organisms that can grow by cuttings.
- Cell division enables a multicellular organism to develop from a single fertilized egg or zygote.
- In a multicellular organism, cell division functions to repair and renew cells that die from normal wear and tear or accidents.
- Cell division is 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.

Concept 12.1 Cell division results in genetically identical daughter cells

- Cell division requires the distribution of identical genetic material—DNA—to two daughter cells.
- 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 then splits into two 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 several DNA molecules.
- A human cell must duplicate about 2 m of DNA and separate the two copies such that each daughter cell ends up with a complete genome.
- DNA molecules are packaged into **chromosomes.**
  - Every eukaryotic species has a characteristic number of chromosomes in each cell nucleus.
    - Human somatic cells (body cells) have 46 chromosomes, made up of two sets of 23 (one from each parent).

    - Human gametes (sperm or eggs) have one set of 23 chromosomes, half the number in a somatic cell.
- Eukaryotic chromosomes are made of **chromatin,** a complex of DNA and associated protein.
    - Each single chromosome contains one long, linear DNA molecule carrying hundreds or thousands of genes, the units that specify an organism's inherited traits.
- The associated proteins maintain the structure of the chromosome and help control gene activity.
- When a cell is not dividing, each chromosome is in the form of a long, thin chromatin fiber.
- Before cell division, chromatin condenses, coiling and folding to make a smaller package.
- Each duplicated chromosome consists of two **sister chromatids,** which contain identical copies of the chromosome's DNA.
    - The chromatids are initially attached by adhesive proteins along their lengths.
    - As the chromosomes condense, the region where the chromatids connect shrinks to a narrow area, the **centromere.**
- Later in cell division, the sister chromatids are pulled apart and repackaged into two new nuclei at opposite ends of the parent cell.
    - Once the sister chromatids separate, they are considered individual chromosomes.
- **Mitosis,** the formation of the two daughter nuclei, is usually followed by 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.
    - The fertilized egg, or 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 reduces the number of chromosomes from 46 to 23.
    - Fertilization fuses two gametes together and doubles 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 alternates with the much longer **interphase.**
  - The M phase includes mitosis and cytokinesis.
  - Interphase accounts for 90% of the cell cycle.
- During interphase, the cell grows by producing proteins and cytoplasmic organelles, copies its chromosomes, and prepares for cell division.
- Interphase has three subphases: the **G_1 phase** ("first gap"), the **S phase** ("synthesis"), and the **G_2 phase** ("second gap").
  - During all three subphases, the cell grows by producing proteins and cytoplasmic organelles such as mitochondria and endoplasmic reticulum.
  - However, chromosomes are duplicated only during the S phase.
- The daughter cells may then repeat the cycle.
- A typical human cell might divide once every 24 hours.
  - Of this time, the M phase would last less than an hour, while 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.
- Mitosis is a continuum of changes.
- For convenience, mitosis is usually broken into five subphases: **prophase, prometaphase, metaphase, anaphase,** and **telophase.**
- 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 is now 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 underway 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 cytoskeleton.
- The spindle fibers elongate by incorporating more subunits of the protein tubulin.
- Assembly of the spindle microtubules starts in the **centrosome.**
  - The centrosome *(microtubule-organizing center)* is a nonmembranous organelle 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.
- 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 has a **kinetochore** of proteins and chromosomal DNA at the centromere.
  - 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 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 when the proteins holding the sister chromatids together are inactivated.
  - Once the chromosomes are separate, full-fledged chromosomes, they move toward opposite poles of the cell.
- How do the kinetochore microtubules function into the poleward movement of chromosomes?
- One hypothesis is that the chromosomes are "reeled in" by the shortening of microtubules at the spindle poles.
- Experimental evidence supports the hypothesis that motor proteins on the kinetochore "walk" the attached chromosome along the microtubule toward the nearest pole.
  - Meanwhile, the excess microtubule sections depolymerize at their kinetochore ends.
- What is the function of the *non*kinetochore microtubules?
- Nonkinetochore microtubules are responsible for lengthening the cell along the axis defined by the poles.
  - These 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 microtubules push apart, the microtubules lengthen by the addition of new tubulin monomers to their overlapping ends, allowing continued overlap.

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 coalesce at the metaphase plate, forming a **cell plate.**
    - 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.

- Prokaryotes reproduce by **binary fission,** not mitosis.
- Most bacterial genes are located on a single *bacterial chromosome* that consists of a circular DNA molecule and associated proteins.
- While 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 is highly folded and coiled in the cell.
- In binary fission, chromosome replication begins at one point in the circular chromosome, the **origin of replication** site, 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, its plasma membrane grows inward to divide the parent cell into two daughter cells, each with a complete genome.
- Researchers have developed methods to allow them 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.

- The mechanism behind the movement of the bacterial chromosome is becoming clearer but is still not fully understood.
  - Several proteins have been identified and play important roles.
- How did mitosis evolve?
  - There is evidence that mitosis had its origins in bacterial binary fission.
  - Some of the proteins involved in binary fission are related to eukaryotic proteins.
  - Two of these are related to eukaryotic tubulin and actin proteins.
- As eukaryotes evolved, the ancestral process of binary fission gave rise to mitosis.
- Possible intermediate evolutionary steps are seen in the division of two types of unicellular algae.
  - In dinoflagellates, replicated chromosomes are attached to the nuclear envelope.
  - In diatoms, the spindle develops within the nucleus.
- In most eukaryotic cells, the nuclear envelope breaks down and a spindle separates the chromosomes.

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

- The timing and rates 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 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 provide important insights into the operation of normal cells, and may also explain 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 suggests that chemicals 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 critical 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 overridden by go-ahead signals.
  - Many signals registered at checkpoints come from cellular surveillance mechanisms.
  - These 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 it 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 this 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.
- Rhythmic fluctuations in the abundance and activity of cell cycle control molecules pace the events of the cell cycle.
  - These regulatory molecules include protein kinases that activate or deactivate other proteins by phosphorylating them.
- These kinases are present in constant amounts but require 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.**
- Cyclin levels rise sharply throughout interphase, and then fall abruptly during mitosis.

- Peaks in the activity of one cyclin-Cdk complex, **MPF,** correspond to peaks in cyclin concentration.
- 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 other protein kinases.
  - MPF stimulates fragmentation of the nuclear envelope by phosphorylation of various proteins of the nuclear lamina.
  - It also triggers the breakdown of cyclin, dropping 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 G2 phases of the next round of the cycle.
- At least three Cdk proteins and several cyclins regulate the key G_1 checkpoint.
- Similar mechanisms are also involved in driving the cell cycle past the M phase checkpoint.

Internal and external cues help regulate the cell cycle.

- While research scientists know that active Cdks function by phosphorylating proteins, the identity of all these proteins is still under investigation.
- Scientists do not yet know what Cdks actually do in most cases.
- Some steps in the signaling pathways that regulate the cell cycle are clear.
  - Some signals originate inside the cell, others outside.
- The M phase checkpoint ensures that all the chromosomes are properly attached to the spindle at the metaphase plate before anaphase.
  - This ensures that daughter cells do not end up with missing or extra chromosomes.
- A signal to delay anaphase originates at kinetochores that have not yet attached to spindle microtubules.
  - This keeps the anaphase-promoting complex (APC) in an inactive state.
  - When all kinetochores are attached, the APC activates, triggering breakdown of cyclin and inactivation of proteins holding sister chromatids together.
- 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 one group of cells that stimulate other cells to divide.

- For example, *platelet-derived growth factors (PDGF),* produced by platelet blood cells, bind to tyrosine-kinase receptors of fibroblasts, a type of connective tissue cell.
- This triggers a signal-transduction pathway that allows cells to pass the G_1 checkpoint and divide.

- Each cell type probably responds specifically to a certain growth factor or combination of factors.
- The role of PDGF is easily seen in cell culture.
  - Fibroblasts in culture will only divide in the presence of a medium that also contains PDGF.
- In a living organism, platelets release PDGF in the vicinity of an injury.
  - The resulting proliferation of fibroblasts helps heal the wound.
- At least 50 different growth factors can trigger specific cells to divide.
- 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.
  - At high densities, the amount of growth factors and nutrients is insufficient to allow continued cell growth.
- Most animal cells also exhibit **anchorage dependence** for cell division.
  - To divide, they must be anchored to a substratum, typically the extracellular matrix of a tissue.
  - Control appears to be mediated by 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 either because a cancer cell manufactures its own growth factors, has an abnormality in the signaling pathway, or has an abnormal cell cycle control system.
- 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 continual supply of nutrients.
  - In contrast, nearly all mammalian cells divide 20 to 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.
    - However, 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 do not cause serious problems and can be fully removed by surgery.
- In a **malignant tumor,** the cells become invasive enough to impair the functions of one or more organs.
- In addition to chromosomal and metabolic abnormalities, cancer cells often lose attachment to nearby cells, are carried by the blood and lymph system to other tissues, and start more tumors in an event called **metastasis.**
    - Cancer cells are abnormal in many ways.
    - They 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.
- 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 mitotic depolymerization, preventing cells from proceeding past metaphase.
    - The side effects of chemotherapy are due to the drug's effects on normal cells.
- Researchers are beginning to understand how a normal cell is transformed into a cancer cell.
    - The causes are diverse, but cellular transformation always involves the alteration of genes that influence the cell cycle control system.