

9: Chromosomes, the Cell Cycle, and Cell Division

Introduction

- Since all living cells are mortal, cell reproduction or replacement is universal among living organisms.
- Depending on the organism, this may be simple replacement, differentiation, or specialization.

Systems of Cell Reproduction

- Four events occur before and during cell division.
 - A signal to reproduce must be received.
 - Replication of DNA and vital cell components must occur.
 - DNA must distribute to the new cells.
 - The cell membrane (and cell wall in some organisms) must separate the two new cells.

Prokaryotes divide by fission

- Prokaryotic cells grow in size, replicate DNA, and divide into two new cells.
- This process is called *fission*.
- *Escherichia coli* (a bacterium) simply divides as quickly as resources permit. At 37°C, this is about once every 40 minutes.
- When resources are abundant, *E. coli* can divide every 20 minutes.
- Prokaryotes generally have just one circular chromosome.
 - The *E. coli* chromosome is 1.6 mm in diameter, making the unfolded circle 100 times greater than the size of the cell.
 - The molecule is packaged by folding in on itself with the aid of basic proteins that associate with the acidic DNA. (See Figure 9.2.)
 - Circular chromosomes appear to be characteristic of all prokaryotes.
- The prokaryotes have a site called *ori*, where DNA replication begins, and a site *ter*, where it ends.
 - *Ori* is short for origin of replication.
 - *Ter* is short for terminus of replication.
- As DNA replicates, each of the two resulting DNA molecules attaches to the plasma membrane.
- As the bacterium grows, new plasma membrane is added between the attachment points, and the DNA molecules are moved apart. (See Figure 9.3.)
- Cytokinesis, which is cell partitioning, begins around 20 minutes after chromosome duplication is completed.
 - A pinching of the plasma membrane to form a constricting ring separates the one cell into two, each with a complete chromosome.
 - A tubulin-like fiber is involved in the purse-string constriction.

Eukaryotic cells divide by mitosis or meiosis

- All reproduction involves reproduction signals, DNA replication, segregation, and cytokinesis. (See Figure 9.4.)
- Unlike prokaryotes, eukaryotic cells do not constantly divide whenever environmental conditions are adequate, although unicellular eukaryotes do so more often than the cells of multicellular organisms.
 - Some differentiated cells of multicellular organisms rarely or never divide.
 - Signals to divide are related to the needs of the entire organism, not simply the opportunity created by resources.

- Eukaryotes usually have many chromosomes.
- Eukaryotes have a nucleus, which must replicate and, with few exceptions, divide during cell division.
- Mitosis generates two cells with the same genetic information as the original cell.
- Meiosis is a specialized cell division used for sexual reproduction. The genetic information of the chromosomes is shuffled, and the cells, called gametes, typically get one-half of the original DNA complement.

Interphase and the Control of Cell Division

- Interphase is the period between divisions of the cytoplasm.
- A typical eukaryotic cell will spend most of its life in interphase.
- Some cells lose the capacity to divide altogether and stay in interphase indefinitely. Examples of such cells in humans are nerve cells and muscle cells.
- Other cells divide regularly, others occasionally.
- Most cells have two major phases: mitosis and interphase, often referred to as the *cell cycle*.
- For most tissues at any given time, only a few cells are in mitosis, and most are in interphase.
- Interphase consists of three subphases. (See Figure 9.4.)
 - G1 is Gap 1, the period just after mitosis and before the beginning of DNA synthesis.
 - Next is S (synthesis), which is the time when the cell's DNA is replicated.
 - G2 is the time after S and prior to mitosis.
- Mitosis and cytokinesis are referred to as M phase.
- The G1-to-S transition commits the cell to enter another cell cycle.

Cyclins and other proteins signal events in the cell cycle

- Transitions from G1 to S and G2 to M depend on activation of a protein called cyclin-dependent kinase, or Cdk.
 - A kinase is an enzyme that transfers a phosphate from ATP to different protein(s). This is called phosphorylation.
 - Activated Cdk transfers phosphates from ATP to certain amino acids of proteins that then move the cell in the direction of cycling.
- The Cdk effect on the cell cycle is a common mechanism in eukaryotic cells.
 - Studies in sea urchin eggs uncovered a protein called the maturation promoting factor.
 - A mutant yeast that lacked Cdk was found, which stalled at the G1–S boundary.
 - These two proteins, one from sea urchins and the other from yeast, were similar in structure and function. Other Cdks have been found in other organisms, including humans.
- Cyclin is a protein that interacts with Cdk.
- Cyclin binding of Cdk exposes the active site of the kinase.
- The cyclin-Cdk complex acts as a protein kinase that triggers transition from G1 to S. The cyclin then breaks down and the Cdk becomes inactive.
- Several different cyclins exist, which, when bound to Cdk, phosphorylate different target proteins. (See Figure 9.5.)
 - Cyclin D-Cdk4 acts during the middle of G1. This is the restriction point in G1, beyond which the rest of the cell cycle is inevitable.
 - Cyclin E-Cdk2 acts at the boundary of G1 to S to initiate DNA replication.
 - Cyclin A-Cdk2 acts during S and also stimulates DNA replication.
 - Cyclin B-Cdk1 acts at the G2-to-M boundary, initiating mitosis.

- Cyclin-Cdk complexes act as checkpoints. When functioning properly, they allow or prevent the passage to the next cell cycle stage, depending on the extra- and intracellular conditions.
 - An example is the effect of p21 on the G1-to-S phase transition.
 - If DNA is damaged by UV radiation, p21 is synthesized (a protein of 21,000 daltons).
 - It binds to the two different types of G1 Cdk molecules, preventing their activation until damaged DNA is repaired. The p21 is then degraded, allowing the cell cycle to proceed.
- Some targets for cyclin-Cdk complexes include proteins that condense chromosomes and others that cause fragmentation of the nuclear envelope.
- Cyclin-Cdk defects have been found in some cancer cells.
 - A breast cancer with too much cyclin D has been found.
 - The protein p53, which inhibits activation of Cdk, is found defective in half of all human cancers.

Growth factors can stimulate cells to divide

- Cyclin-Cdk complexes provide internal control for cell cycle decisions.
- Cells in multicellular organisms must divide only when appropriate. They must respond to external signals, controls called growth factors.
- Some cells respond to growth factors provided by other cells.
 - Platelets release platelet-derived growth factor, which diffuses to the surface of cells to stimulate wound healing.
 - Interleukins are released from one type of blood cell to stimulate division of another type resulting in body immune system defenses.
 - The cells of the kidney make erythropoietin, which stimulates bone marrow cells to divide and differentiate into red blood cells.
- Cancer cells cycle inappropriately because they either make their own growth factors or no longer require them to start cycling.

Eukaryotic Chromosomes

- Apart from gametes, most human cells contain two full sets of genetic information, one from the mother and the other from the father.
- Eukaryotes have more than one chromosome, and the number varies from organism to organism; for example, humans have 46 and horses have 64. (The Instructor's Resource CD-ROM includes a micrograph of 46 metaphase chromosomes from a normal human cell.)
- Each eukaryotic chromosome consists of a single, double-stranded molecule of DNA; the molecule is extremely long relative to the size of the cell.
- Many proteins associate with the DNA molecule.
- After the DNA of a chromosome replicates during S phase, each chromosome consists of two joined chromatids.
- The two chromatids are joined at a region called the centromere. (See Figure 9.6.)

Chromatin consists of DNA and proteins

- The complex of the DNA and proteins is called chromatin. (The Instructor's Resource CD-ROM includes a TEM showing chromatin in a monkey liver cell.)
- The DNA carries the genetic information.
- The proteins organize the DNA physically and regulate the activities of the DNA.
- By mass, chromatin consists of about equal parts DNA and protein.
- Chromatin condenses, becoming highly coiled and compacted during mitosis or meiosis.

- This makes it possible to get copies of the DNA into separate cells.
- Without condensation of the chromatin, the strands, which are much longer than the cell, would fail to properly partition into the two sister cells. (See Figure 9.7.)

Chromatin proteins organize the DNA in chromosomes

- DNA of a human cell has a total length of 2 meters.
- The nucleus is just 5 μm in diameter.
- During interphase, the DNA is decondensed or “unwound,” although proteins still package it.
- Interphase chromosomes are wrapped around proteins called histones.
- These wraps of DNA and histone proteins are called nucleosomes and resemble beads on a string. (The Instructor’s Resource CD-ROM includes a TEM of nucleosome beads on strings of DNA.)
- There are five classes of histones.
- The core of a nucleosome contains eight histone molecules, two each from four of the histone classes.
- There are 146 base pairs of DNA wrapped around the core, or 1.65 turns of DNA.
- One molecule from the remaining histone class, histone H1, clamps the DNA to the core, and helps form the next level of packaging.
- During mitosis and meiosis, the chromatin becomes even more coiled and condensed.

Mitosis: Distributing Exact Copies of Genetic Information

- A single nucleus gives rise to two genetically identical nuclei, one for each of the two new daughter cells.
- Mitosis is a continuous event, but it is convenient to look at it as a series of steps. (See Figure 9.8. The Instructor’s Resource CD-ROM includes a series of fluorescent micrographs showing mitosis in a newt cell.)
 - When the cell enters S phase and DNA is replicated, the centrosome replicates to form two centrosomes.
 - This event is controlled by cyclin E-Cdk2, whose concentration peaks at the G1-to-S transition.
 - This is the key event initiating the direction of mitosis.
 - During G2-to-M transition, the two centrosomes separate from each other and move to opposite ends of the nuclear envelope. The orientation of the centrosomes determines the cell’s plane of division.
 - In many organisms, each centrosome contains a pair of centrioles that have replicated during interphase.
 - Centrosomes are regions where microtubules form. These microtubules will orchestrate the movement of chromosomes.

The spindle forms during prophase

- In prophase, polar microtubules form between the two centrosomes and make up the developing spindle. (See Figure 9.9. The Instructor’s Resource CD-ROM includes the TEM from Figure 9.9 and a TEM of two centriole pairs before migration.)
- Each polar microtubule runs from one mitotic center to just beyond the middle of the spindle, where it overlaps and interacts with a microtubule from the other side.
- Initially, these microtubules are constantly forming and *depolymerizing* (“falling apart”) during this period. Recall that microtubules grow by addition of tubulin dimers to the + end of the microtubule.
- When microtubules from one centrosome contact microtubules from the other, they become more stable.

- The mitotic spindle serves as a “railroad track” along which chromosomes will move later in mitosis.

A prophase chromosome consists of two chromatids

- During prophase, chromosomes compact and coil, becoming more dense.
- Prophase chromosomes consist of two chromatids, held together over much of their length.
- The region of tight binding between the chromatids, the centromere, is where the microtubules will associate with the chromatids. (See Figure 9.6.)
- Late in prophase, the kinetochores develop. (See Figure 9.9.)
 - The kinetochore is located in the region around the centromere and is the site where microtubules attach to the chromatids.

Chromosome movements are highly organized

- The movement phases of chromosomes are designated prometaphase, metaphase, and anaphase.
- During prometaphase, the nuclear lamina disintegrates and the nuclear envelope breaks into small vesicles permitting the fibers of the spindle to “invade” the nuclear region.
 - The spindle microtubules then associate with kinetochores.
 - These are called kinetochore microtubules.
 - The microtubules from one pole associate with the kinetochore of one of the members of a pair of chromatids. Microtubules from the other pole associate with the kinetochore of the other member.
 - Repulsive forces from the poles push chromosomes toward the center, or equatorial plate, in a rather aimless back and forth motion.
 - The two chromatids are held together, presumably by proteins called cohesins.
- During metaphase, the kinetochores arrive at the equatorial plate.
 - Chromosomes are fully condensed and have distinguishable shapes.
 - Cohesins break down.
 - DNA topoisomerase II unravels the interconnected DNA molecules at the centromere, and all the chromatids separate simultaneously.
- Anaphase begins when the centromeres separate.
 - The process takes 10 to 60 minutes for the chromosomes to move to opposite poles.
 - Molecular motors at the kinetochores move the chromosomes toward the poles, accounting for about 75% of the motion.
 - About 25% of the motion comes from shortening of the microtubules at the poles.
 - Additional distance is gained by the separating of the mitotic centers. This increase in distance between the poles is done by the polar microtubules, which have motor proteins associated in the overlapping regions. By this process the distance between the poles doubles.

Nuclei re-form during telophase

- When chromosomes finish moving, telophase begins.
- Nuclear envelopes and nucleoli coalesce and re-form.

Cytokinesis: The Division of the Cytoplasm

- Animal cells divide by a furrowing (a “pinching in” or constriction) of the plasma membrane.

- Microfilaments of actin and the motor protein filament myosin first form a ring beneath the plasma membrane.
- Actin and myosin contract to produce the constriction. (See Figure 9.10. The Instructor's Resource CD-ROM includes both the sea urchin and plant cell micrographs from Figure 9.10.)
- Plants have cell walls and the cytoplasm divides differently.
 - After the spindle breaks down, vesicles from the Golgi apparatus appear in the equatorial region.
 - The vesicles fuse to form a new plasma membrane, and the contents of the vesicles combine to form the cell plate, which is the beginning of the new cell wall.
- Organelles and other cytoplasmic resources do not need to be distributed equally in daughter cells, as long as some of each are present in both new cells to assure additional generation of organelles as needed.

Reproduction: Sexual and Asexual

- Mitosis by repeated cell cycles can give rise to vast numbers of identical cells.
- Meiosis results in just four progeny, which usually do not further duplicate. The cells can be genetically different.

Reproduction by mitosis results in genetic constancy

- *Asexual reproduction* involves the generation of a new individual that is essentially genetically identical to the parent. It involves a cell or cells that were generated by mitosis. (See Figure 9.11. The Instructor's Resource CD-ROM includes the micrograph of fungal spores from this figure.)
 - Variation of cells is likely due to mutations or environmental effects.
- *Sexual reproduction* involves meiosis.
 - Two parents each contribute one cell that is genetically different from the parents.
 - These cells often combine to create variety among the offspring beyond that attributed to mutations or the environment.

Reproduction by meiosis results in genetic diversity

- Sexual reproduction fosters genetic diversity among progeny.
- Two parents each contribute a set of chromosomes in a sex cell or gamete.
- Gametes fuse to produce a single cell, the zygote, or fertilized egg.
- Fusion of gametes is called fertilization.
- In each recognizable pair of chromosomes, one comes from each of the two parents.
- The members of the pair are called homologous chromosomes and are similar, but not identical, in size and appearance. (An exception for sex chromosomes exists in some species.)
- The homologous chromosomes have corresponding but generally not identical genetic information.
- *Haploid* cells contain just one homolog of each pair. The number of chromosomes in a single set is denoted by n .
- When haploid gametes fuse in fertilization, they create the zygote, which is $2n$, or *diploid*.
- Some organisms have a predominant life cycle in a $1n$ (haploid) state. (See Figure 9.12.)
- Some organisms have both a $1n$ vegetative life stage and a $2n$ vegetative life stage.
- In diplontic organisms, which include animals, the organism is usually diploid. (Some insects are excepted.)

- Homologous chromosomes exchange parts and recombine during meiosis so that the chromosomes passed on to gametes are mixtures of those received from two parents.
- The two chromosomes of a mixed homologous pair then segregate randomly into haploid gametes.
- This shuffling greatly increases the diversity of the population and opportunities for evolution.

The number, shapes, and sizes of the metaphase chromosomes constitute the karyotype

- It is possible to count and characterize individual chromosomes.
- Cells in metaphase can be killed and prepared in a way that spreads the chromosomes around a region on a glass slide.
- A photograph of the slide can be taken, and images of each chromosome can be organized based on size, number and shape. This spread is called a *karyotype*. (See Figure 9.13. The Instructor's Resource CD-ROM includes normal and Down syndrome karyotypes.)
- Table 9.1 provides information on the characteristic number of homologous chromosome pairs found in some plant and animal species. Note that there is no simple relation between the size of an organism and its chromosome number.

Meiosis: A Pair of Nuclear Divisions

- Meiosis consists of two nuclear divisions that reduce the number of chromosomes to the haploid number.
- The nucleus divides twice, but the DNA is replicated only once.
- The functions of meiosis are to reduce the chromosome number from diploid to haploid, to ensure each gamete gets a complete set, and to promote genetic diversity among products.
- Meiosis I is unique for the pairing and synapsis of homologous chromosomes in prophase I of the first nuclear division. After metaphase I, homologous chromosomes separate into different cells.
- Individual chromosomes, each with two chromatids, remain intact until metaphase of meiosis II (second nuclear division) is completed and the chromatids separate to become chromosomes.
- See Figure 9.14 for a complete review of meiosis. The Instructor's Resource CD-ROM includes a complete series of micrographs showing meiosis in a lily.

The first meiotic division reduces the chromosome number

- Like mitosis, meiosis I is preceded by an interphase in which DNA is replicated.
- Meiosis I begins with a long prophase.
- During prophase I, *synapse* occurs: The two homologs are joined together held by a synaptonemal complex of proteins.
- This forms a tetrad, or "bundle of four," which consists of two homologous chromosomes with two sister chromatids.
- At a later point, the chromosomes appear to repel each other except at the centromere and at points of attachments, called *chiasmata*, which appear x-shaped.
- These chiasmata reflect the exchange of genetic material between homologous chromosomes, a phenomenon called *crossing-over*. (See Figure 9.15.)
- This crossing-over increases genetic variation by "mixing and matching" the genes on the homologs.
- In the testis cells of human males, prophase I takes about a week.

- In the egg cells of human females, prophase I begins before birth in some eggs and can continue for 50 years in others depending on their release in the monthly ovarian cycle.
- Following telophase I, in some species, there is a reappearance of nuclear envelopes. If this occurs, it is called interkinesis, a stage similar to mitotic interphase, but there is no replication of genetic material and no crossing-over in subsequent stages.

The second meiotic division separates the chromatids

- Meiosis II is similar to mitosis.
- One difference is that DNA does not replicate before meiosis II.
- The number of chromosomes is therefore half that found in diploid mitotic cells.
- In meiosis II, sister chromatids are not identical and there is no crossing-over.
- See Figure 9.17 for a comparison of mitosis and meiosis.

Meiosis leads to genetic diversity

- The products of meiosis I are genetically diverse.
- Synapsis and crossing over during prophase I mix genetic material of the maternal with that of the paternal homologous chromosomes.
- Which member of a homologous pair segregates or goes to which daughter cell at anaphase I is simply chance.
- Since most species of diploid organisms have more than two pairs of chromosomes, the possibilities for variation in combinations becomes huge.

Meiotic Errors

- Nondisjunction is when homologous chromosomes or sister chromatids fail to separate during anaphase I.
- The result is a condition called aneuploidy. (See Figure 9.18.)

Aneuploidy can give rise to genetic abnormalities

- Failure of chromosome 21 to separate in humans results in trisomy 21—Down syndrome, characterized by impaired intelligence, cardiac abnormalities and disease susceptibility. (The Instructor's Resource CD-ROM includes normal and Down syndrome karyotypes.)
- Translocation, when a part of a chromosome attaches to another, can also cause abnormality.
- Trisomies and monosomies are surprisingly common in human zygotes. Most affected embryos fail to develop.

Polyploids can have difficulty in cell division

- Polyploids have extra whole sets of chromosomes, and this abnormality in itself does not prevent mitosis.
- Triploids are $3n$; tetraploids are $4n$.
- While mitosis usually is unimpaired, meiosis is problematic, especially for odd numbers of sets, as in triploidy.
 - The gamete might get two of certain chromosomes and one of others causing a genetic imbalance. One-third of the chromosomes would lack partners at synapse.
 - Organisms that can tolerate variance in ploidy, such as plants, fish, and amphibians, need to have complete additional sets of chromosomes, not just partial sets.
 - *Seedless varieties of plants, like bananas, grapes, and watermelons, are triploid and may be produced by gene manipulation in plant breeding.*
 - *They grow normally as triploids, but fail to produce viable gametes.*

- Modern bread wheat plants are hexaploids, the result of the accidental crossing of three different grasses, each having its own diploid set of 14 chromosomes.

Cell Death

- Cells die in one of two ways: necrosis and apoptosis. (See Table 9.2.)
 - Necrosis occurs when cells either are damaged by poisons or are starved of essential nutrients. These cells swell and burst. Healing of the tissue may occur as seen in scabs forming around wounded areas.
 - Cell death more typically occurs in a controlled fashion, a process called *apoptosis*.
 - This is genetically programmed cell death.
 - An example of programmed cell death is the elimination of the cells of the weblike tissue between the fingers of a developing human fetus.
 - Another is when the cell is old or damaged and needs to be replaced.
 - There are signals controlling the process of apoptosis, such as the lack of a mitotic signal to divide.
 - The cell is isolated, chops up its own chromatin, and gets ingested by surrounding living cells. (See Figure 9.19.)