Chapter 9: Chromosomes, the Cell Cycle, and Cell Division

I Systems of Cell Reproduction

Four events occur before and during cell division.

1). A signal to divide must be received.
2). Replication of DNA must occur.
3). DNA must distribute to the new cells.
4). Cell membrane must separate into two new cells.

A. Prokaryotes divide by fission

- Prokaryotic cells grow in size, replicate DNA, and divide into two new cells. This is called fission.
- *Escherichia coli* simply divides as quickly as resources permit. At 37^{o}C, this is about once every 40 minutes; when resources are abundant, they 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 100X greater than the size of the cell (1um x 4um).
  - 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 are 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.
- The two molecules are separated as they replicate. Association to different regions of the membrane, which move apart as the cell elongates, assure the equal distribution of the DNA. *(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.
  - A tubulin-like fiber is involved in the purse-string constriction.

B. Eukaryotic cells divide by mitosis or meiosis

- All reproduction involves reproduction signals, DNA replication, segregation, and cytokinesis. *(See Figure 9.4)*
- Not all eukaryotic cells divide whenever environmental conditions are adequate.
  - Unicellular eukaryotes do, more so than the cells of multicellular organisms.
  - Some differentiated cells of multicellular organisms rarely or never divide.

    - Signals to divide integrate the needs of the organism, and not simply the opportunity in terms of resources.
    - Eukaryotes have many chromosomes.
    - Eukaryotes have a nucleus, which must become two during, or just subsequent to division.
    - Mitosis simply 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 just one of two copies of the DNA molecules.

II Interphase and the Control of Cell Division

- Interphase is the period between divisions.
- Some cells lose the capacity to divide altogether and stay in interphase indefinitely. Examples of such cells in humans would be nerve, red blood cells and muscle cells.
- Other cells divide, some regularly, others occasionally.
- Most cells have two major phases: mitosis and interphase.
- For most types of cells, just a few are in mitosis, and most are in interphase.
- Interphase consists of three sub-phases.
    - G1 is Gap1 and is the period just after mitosis and before the beginning of DNA synthesis.
    - Next is S, which is the time when the DNA of the nucleus is replicated.
    - G2 is the time after S and prior to mitosis.
- Mitosis is M phase.
- The G1 to S transition commits the cell to enter another cell cycle.

A. Cyclin 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, which is also called 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 cell cycle is a common mechanism in eukaryotic cells.
    - Studies in sea urchin eggs uncovered a protein called the *Maturation Promoting Factor* (MFP).
    - A mutant yeast that lacked Cdk was found, which stalled at G1 to S boundary.
    - These two proteins, one from sea urchins and the other from yeast, were similar in structure and function.
- Cyclin is another protein, which interacts with Cdk.

- Cyclin binding of Cdk exposes the active site of the kinase.
- Together the Cyclin-Cdk complex acts as a protein kinase that triggers G1 to S phase transition.
- Several different cyclins exist, which when bound to Cdk, phosphorylate different target proteins. *(See Figure 9.5)*
- Cyclin E-Cdk 2 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, appropriately to the extra- and intra-cellular 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.
  - It binds to the two different types of G1 Cdk molecules, preventing their activation until damaged DNA is repaired.
- 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.

B. Growth factors can stimulate cells to divide

- Cyclin-Cdk complexes provide internal control for cell cycle decisions.
- Cells in multi-cellular organisms must divide only when appropriate. They must respond to external signals.
- 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.
  - The cells of the kidney make erythropoietin, which stimulate 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.

III Eukaryotic Chromosomes

- Human cells, other than gametes, contain two full sets of genetic information, one from the mother, and the other from the father.
- Eukaryotes have more than just one chromosome; for example, humans have 46.
- Each eukaryotic chromosome consists of a single, double-stranded molecule of DNA of extreme length, relative to the size of the cell.

- 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.

A. Chromatin consists of DNA and protein.

- The complex of the DNA and protein is called chromatin.
- The proteins organize the DNA, physically, and regulate its use.
- By mass, protein and DNA in chromatin are about equal.
- Chromatin condenses 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)*

B. 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, although proteins still package it.
- Interphase chromosomes are wrapped around histones.
- These wraps of DNA and histone proteins are called nucleosomes, and resemble beads on a string.
- Nucleosomes contain eight histone molecules, two each of H2A H2B, H3 and H4, and form the core particle.
- There are 146 base pairs of DNA wrapped around the core, or 1.65 turns of DNA.
- Histone H1 clamps the DNA to the core, and helps form the next level of packaging, called the solenoid structure.
- During mitosis and meiosis, condensation becomes much greater.

IV Mitosis: Distributing Exact Copies of Genetic Information

- A single nucleus gives rise to two nuclei, one for each of the two new sister cells.
- Mitosis - the M phase - has been subdivided into a series of subphases. (See Figure 9.8)

A. The centrosomes determine the plane of cell division.

- When the cell enters S phase, a *centrosome* replicates to form two.
- This event is controlled by cyclin E-Cdk2, whose concentration peaks at the G1 to S transition.
- During G2 to M transition, the two centrosomes separate from each other and move to opposite ends of the nuclear envelope.
- Often, each centrosome contains a pair of centrioles.

- Centrosomes are regions where microtubules form.

B. The spindle forms during prophase

- Polar microtubules that form between the two centrosomes (mitotic centers) make up the developing spindle.
- 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.
- These microtubules are constantly forming and depolymerizing, during this period. *(See Figure 9.9)*

C. A prophase chromosome consists of two chromatids

- During prophase, chromosomes compact.
- Prophase chromosomes consist of two chromatids, held together over much of their length.
- The region of close association, the centromere, is where the microtubules associate. *(See Figure 9.6)*
- Late in prophase, the kinetochores develop. *(See Figure 9.9)* The kinetochore is located in the region around the centromere.

D. Chromosome movements are highly organized

- During *Prometaphase* the nuclear lamina disintegrates and the nuclear envelope breaks into small vesicles.
  - 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 towards the center or equatorial plate.
  - 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.
- *Anaphase* is 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.

        - About 25% of the motion come from shortening of the microtubules at the poles.
        - Additional distance is gained by the separating of the mitotic centers. This is done by the polar microtubules, which have motor proteins associated in the overlapping regions. The distance doubles.

E. Nuclei re-form during telophase

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

V Cytokinesis: The Division of the Cytoplasm

- Animal cells divide by a furrowing of the plasma membrane.
- Microfilaments of actin and myosin first form a ring beneath the plasma membrane.
- Actin and the motor protein-filament, myosin, contract to produce the constriction. *(See Figure 9.10)*
- Plants have cell walls.
    - After the spindle breaks down, vesicles from the Golgi appear in the equatorial region.
    - The vesicles fuse to form a new plasma membrane, and the contents of the vesicles begin the making of the cell wall in the dividing region.
- Organelles and other cytoplasmic resources usually partition evenly in cytokinesis.

VI Reproduction: Sexual and Asexual

- Mitosis can give rise to vast numbers of identical cells.
- Meiosis results in just four progeny. The cells can be genetically different.

A. Reproduction by mitosis results in genetic constancy

- Asexual reproduction involves the generation of a new individual that is essentially genetically the identical to the parent. It involves a cell or cells that were generated by mitosis.
- If there is any variation among the offspring, it is likely due to mutations or environmental effects.
- Sexual reproduction involves meiosis.
    - Two parents each contribute one cell.
    - Genetically different offspring from the parents are produced.

B. Reproduction by meiosis results in genetic diversity

- Sexual reproductions foster genetic diversity amongst 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 in size and appearance. (An exception for sex chromosomes exists in some species.)
- The homologous chromosomes have corresponding genetic information.
- Haploid cells contain just one homologue of each pair. The number of chromosomes in a single set is denoted by *n*.
- When haploid gametes fuse in fertilization, the zygote is 2N.
- Some organisms have a predominant life cycle in a 1N state. *(See Figure 9.12)*
- Some organisms have a 1N vegetative life stage, and also a 2N vegetative life stage.
- In diplontic organisms, which include animals, the organism is diploid.
- Homologous chromosomes recombine during meiosis in such ways that the chromosomes passed on to gametes are mixtures of those the parent received from its two parents.
- The two chromosomes of a homologous pair segregate randomly into gametes.
- This greatly increases the diversity of the population.

C. The number, shape, and size of the metaphase chromosomes constitute the karyotype.

- 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. *(See Figure 9.13)*
- Table 9.1 provides information on the characteristic number of chromosomes found in some plants and animal species.

VI. Meiosis: A Pair of Nuclear Divisions

- 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. Also, after metephase I, homologous chromosomes separate into different cells.
- Individual chromosomes each with two chromatids remain until metaphase II is completed and the chromatids separate to become chromosomes.
- DNA is replicated in the S phase preceding the beginning of meiosis. *(See Figure 9.14 for a visually complete review of meiosis.)*

A. First meiotic division reduces the chromosome number

- Meiosis I has a long prophase.
- During this prophase, a synaptonemal complex forms that joins the two homologs along their entire length.
- This forms a tetrad, which are two homologous chromosomes times 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.
- These chiasmata reflect the exchange of genetic material between homologous chromosomes. *(See Figure 9.15)*
- In human males, prophase I takes about a week.
- In human females, it begins before birth and can continue for 50 years.
- Following telophase I, in some species there is a reappearance of nuclear envelopes. If this occurs it is called interkinesis.

B. The second meiotic division separates chromatids

- Meiosis II is similar to mitosis.
- Differences are that the DNA does not replicate before Meiosis II.
- The sister chromatids are not identical.
- The number of chromosomes is half what is found in diploid mitotic cells.
- *See Figure 9.17 for a comparison of mitosis and meiosis.*

C. Meiosis leads to genetic diversity

- The products of meiosis I are genetically diverse.
- Synapsis and crossover during prophase I mix the maternal with the paternal homologous chromosomes.
- Which member of a homologous pair goes to which daughter cell at anaphase I is simply chance.

VII Meiotic Errors

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

A. Aneuploidy can give rise to genetic abnormalities

- Failure of chromosome 21 to separate results in trisomy 21 - Down syndrome.
- 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.

B. Polyploids can have difficulty during meiotic cell division

- Polyploids have extra whole sets.

- Triploids are 3N; tetraploids are 4N.
- Mitosis usually is unimpaired. However, meiosis is problematic, especially for odd numbers of sets, like in triploidy.
  - The gamete might get two of certain chromosomes and one of others.
  - This causes a genetic imbalance.
  - Organisms such as plants, fish and amphibians, which can tolerate variance in ploidy, need to have complete additional sets, not just partial sets.
  - Seedless varieties of plants, like bananas, grapes and watermelons are triploid.
  - 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.

VIII Cell Death

- Cells die in one of two ways. *(See Table 9.2)*
  - Necrosis occurs when cells either are damaged by poisons or are starved of essential nutrients. These cells swell and burst.
  - Cell death often occurs in a controlled fashion, a process called apoptosis.
    - This is called genetically programmed cell death.
    - An example of program cell death is the elimination of the cells of the web-like 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.
    - The cell is isolated, chops up its own chromatin and gets ingested by surrounding living cells. *(See Figure 9.19)*