Cell Cycle Notes

1. Importance of Cell Division
   a. For single celled organisms, cell division increases the number of individuals.
   b. In a multicellular organism, cell division functions to repair and renew cells that die from normal wear and tear or accidents.
   c. Cell division enables a multicellular organism to develop from a single fertilized egg or zygote.
      i. Approximately 100 trillion cells in the human body all arose from a single cell by mitosis. *E.g.*, red blood cells are made at the rate of one million per second
   d. 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 daughter cells.
   e. A cell's genetic information, packaged as DNA, is called its genome.
      i. In prokaryotes, the genome is often a single long DNA molecule.
      ii. Eukaryotic chromosomes are made of **chromatin,** a mixture of DNA and protein. Each single chromosome contains one long, linear DNA molecule carrying hundreds or thousands of genes. The associated proteins maintain the structure of the chromosome and help control gene activity.
         (1) Every eukaryotic species has a characteristic number of chromosomes in each cell nucleus.
         (2) 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.
      iii. When a cell is not dividing, each chromosome is in the form of a long, thin chromatin fiber but before cell division, chromatin condenses, coiling and folding to make a smaller package.
   f. The basic steps of cell division are:
      i. Duplicate the DNA and form two identical daughter nuclei (**mitosis**)
         (1) Each duplicated chromosome consists of two **sister chromatids,** which contain identical copies of the chromosome's DNA.
         (2) The chromatids remain attached by proteins at a region called the **centromere**.
         (3) 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 again considered individual chromosomes.
      ii. Divide the chromosomes so that each cell gets a complete set.
      iii. Divide the cell into two daughter cells (**cytokinesis**)
   g. Prokaryotes reproduce by **binary fission,** not mitosis.
      i. Most bacterial genes are located on a single bacterial chromosome that consists of a circular DNA molecule and associated proteins.
      ii. The circular bacterial chromosome is highly folded and coiled in the cell.
      iii. While the chromosome is replicating, the cell elongates.
      iv. When replication is complete, its cell membrane grows inward to divide the parent cell into two daughter cells, each with a complete genome.
      v. The movement of bacterial chromosomes is similar to the movements of the centromere regions of eukaryotic chromosomes. However, bacterial chromosomes lack visible mitotic spindles or even microtubules.

2. The Mitotic Cell Cycle
    a. The **mitotic (M) phase** of the cell cycle alternates with the much longer **interphase** (which accounts for 90% of the cell cycle). It includes mitosis, the formation of the two daughter nuclei and cytokinesis. division of the cytoplasm into two separate cells.
    b. These processes result in two cells that are genetically identical to the original parent cell.
    c. Interphase includes all cell activity between mitotic divisions during which the cell is preparing for division. These activities include growing by producing proteins and cytoplasmic organelles and copying its chromosomes.
        i. Interphase has three subphases: the **G_1 phase** ("first gap"), the **S phase** ("synthesis"), and the **G_2 phase** ("second gap").
            (1) During all three subphases, the cell grows by producing proteins and cytoplasmic organelles such as mitochondria and endoplasmic reticulum.
            (2) However, chromosomes are duplicated only during the S phase.
    d. Mitosis is usually broken into five subphases: **prophase, prometaphase, metaphase, anaphase,** and **telophase.**
        i. Prophase
            (1) The chromosomes (which are now sister chromatids joined together) shorten and thicken.
            (2) The nucleoli disappear.
            (3) The mitotic spindle, protein tubes that will later separate the chromosomes, begins to form.
            (4) Centrioles move to opposite poles of the cell.
            (5) Spindle fibers are constructed to extend from the centrioles toward each chromosome.
        ii. Prometaphase
            (1) The nuclear envelope fragments.
            (2) Spindle fibers connect to the condensed chromosomes at the centromere.
            (3) When a fiber attaches to a chromosome the chromosome moves toward the pole from which that fiber came. When fibers attach from 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**, an imaginary line across the middle of the cell.
        iii. At metaphase the chromatids are aligned at the metaphase plate.
        iv. Anaphase
            (1) The centromeres divide, separating the sister chromatids as they are pulled toward opposite poles by the spindle fibers. Once separated, the chromatids are again called chromosomes. We think tiny motor proteins pull the chromosomes along the fibers as they depolymerize behind the point of attachment.
            (2) By the end of this phase, the two poles have equivalent collections of chromosomes.
        v. Telophase
            (1) Daughter nuclei begin to form at the two poles as new nuclear envelopes form.
            (2) The chromosomes become less tightly coiled.
            (3) Spindle fibers dissolve and the cell elongates.
        vi. Cytokinesis
            (1) The division of the cytoplasm begins near the end of telophase.
            (2) In animal cells the cleavage furrow forms as the cell membrane is pinched inward to divide the cell into two daughter cells.

(3) In plant cells, a new cell wall forms to divide the two daughter cells.

3. Regulation of the Cell Cycle
   a. The timing and rates of cell division in different parts of an animal or plant are crucial for normal growth, development, and maintenance.
   b. The frequency of cell division varies with cell type.
      i. Some human cells divide frequently throughout life (*e.g.*, cells lining the small intestine).
      ii. Others have the ability to divide, but keep it in reserve (*e.g.*, liver cells).
      iii. Mature nerve and muscle cells do not appear to divide at all after maturity.
   c. The cell monitors several signals to determine whether it will divide or not. Some signals originate inside the cell, others outside. 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.
      i. For example, cells fail to divide if an essential nutrient is left out of the culture medium.
      ii. Particularly important for mammalian cells are **growth factors,** proteins released by one group of cells that stimulate other cells to divide. At least 50 different growth factors can trigger specific cells to divide.
      iii. The effect of an external physical factor on cell division can be seen in **density-dependent inhibition** of cell division.
         (1) Cultured cells normally divide until they form a single layer on the inner surface of the culture container.
         (2) If a gap is created, the cells will grow to fill the gap.
         (3) At high densities, the amount of growth factors and nutrients is insufficient to allow continued cell growth.
      iv. Most animal cells also exhibit **anchorage dependence** for cell division. To divide, they must be anchored to a surface, typically the extracellular matrix of neighboring cells.
      v. 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.
   d. For many cells, the G_1 checkpoint, the "restriction point" in mammalian cells, is the most important.
      i. If the cell receives a go-ahead signal at the G_1 checkpoint, it usually completes the cell cycle and divides.
      ii. If it does not receive a go-ahead signal, the cell exits the cycle and switches to a nondividing state, the **G_0 phase.**
   e. The cell has regulatory proteins called kinases that activate or deactivate other proteins by phosphorylating them.
      i. These kinases are present in constant amounts but require attachment of a second protein, a **cyclin,** to become activated.
      ii. The amount of cyclin in the cell changes cyclically. It rises sharply throughout interphase, and then falls abruptly during mitosis.
      iii. Peaks in the activity of one cyclin-Cdk complex, **MPF,** correspond to peaks in cyclin concentration.
      iv. MPF ("maturation-promoting factor" or "M-phase-promoting-factor") is a protein made from cyclin and Cdk binding together. It triggers the cell's passage past the G_2 checkpoint to the M phase.
         (1) MPF promotes mitosis by phosphorylating a variety of other proteins.

(2) It also triggers the breakdown of cyclin, dropping cyclin and MPF levels during mitosis and inactivating MPF.
(3) Cdk remains 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.

4. Cancer cells have escaped from cell cycle controls.
   a. 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.
      i. Normally, the immune system recognizes and destroys transformed cells.
      ii. Cells that evade destruction proliferate to form a **tumor,** a mass of abnormal cells.
         (1) 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.
         (2) In a **malignant tumor,** the cells become invasive enough to impair the functions of one or more organs.
   b. Cancer cells do not exhibit density-dependent inhibition. Cancer cells divide excessively and invade other tissues because they have escaped the body's control mechanisms.
      i. Cancer cells do not stop dividing when growth factors are depleted.
      ii. This is either because a cancer cell manufactures its own growth factors, has an abnormal response to cell signals, or has an abnormal cell cycle control system.
      iii. If and when cancer cells stop dividing, they do so at random points, not at the normal checkpoints in the cell cycle.
      iv. Cancer cells can secrete signal molecules that cause blood vessels to grow toward the tumor.
   c. Cancer cells are able to lengthen their telomeres so they 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."
      i. HeLa cells from a tumor removed from a woman (Henrietta Lacks) in 1951 are still reproducing in cultures all over the world.
   d. Cancer cells do not exhibit anchorage dependence. Normal cells tend to stick to similar cells while cancer cells do not. Cancer cells tend to break away and are carried by the blood and lymph system to other tissues and start more tumors in an event called **metastasis.**
   e. Cancer cells do not maintain their function but behave as unspecialized cells. They consume large amounts of resources to grow and divide but do not contribute to the functioning of the organism.
   f. The disease is believed to arise from changes in genes which normally help to control cell growth and division.
      i. Certain genes regulate cell division and function normally in their normal location. If they get transposed to another location they become over-active and cause cells to continue dividing. This can lead to cancer. These genes are called **oncogenes**.
      ii. Certain genes tend to suppress cell growth. When these **tumor-suppressor genes** become mutated, they no longer suppress cell growth and cancer can result.
   g. Treatments for metastasizing cancers include high-energy radiation and chemotherapy with toxic drugs.
      i. These treatments target actively dividing cells.

ii. Chemotherapeutic drugs interfere with specific steps in the cell cycle. For example, Taxol prevents depolymerization of the mitotic spindle, preventing cells from proceeding past metaphase.
iii. The side effects of chemotherapy are due to the drug's effects on normal cells.

5. Differentiation
   a. For the first several divisions after fertilization, every cell produced is identical.
      i. As the number of cells increases, groups of cells differentiate to form tissues and organs.
      ii. Because each cell has the same DNA, they each have all the instructions to produce a complete organism. These cells are is called **totipotent**.
      iii. As they differentiate, most animal cells lose totipotency while most plant cells do not. At birth, most cells are already differentiated and simply grow and divide to adulthood.
      iv. Stem cells that can differentiate into a few different cell types are called **pluripotent**.
   b. Cell differentiation allows specialization and division of labor. *E.g.*, a skin cell never becomes any other type of cell.
   c. A cell remains a specific type because of the information it receives from nearby cells and/or the external environment. The signals that trigger cell differentiation are not yet well understood.
   d. Differentiated cells perform selected tasks for the organism and ensure that a multicellular organism is as efficient as a unicellular one.

6. Cloning
   a. Production of genetically identical individuals
      i. Fetal cow cells or cells from the ovary are harvested because they are still totipotent.
      ii. An electrical jolt triggers cell division and the growing embryo is then implanted into the uterus of the surrogate mother.
      iii. The offspring is genetically identical to the original donor.
   b. Producing genetically identical organisms which carry a useful gene.
      i. Construct a piece of DNA carrying a gene of interest and a gene for antibiotic resistance. Insert this DNA into fetal cells.
      ii. Grow the cells on a medium containing the antibiotic so that only the cells with the inserted DNA will survive.
      iii. Insert the nuclei from surviving cells into enucleated egg cells.
      iv. Implant the egg cells into the surrogate mother
      v. Clones are born which all carry the useful gene
   c. Applications
      i. Can produce cows which produce a useful protein in their milk
      ii. Produce genetically identical organs for transplantation
      iii. Repopulate endangered species
      iv. Produce human tissue