"…Breaking Up is Hard to Do"
(At Least in Eukaryotes)
Mitosis

Chromosomes

- Chromosomes were first observed by the German embryologist Walther Fleming in 1882.
- Chromosome number varies among organisms
  - most eukaryotes have between 10 and 50 chromosomes in their somatic cells
- Chromosomes are paired in somatic cells
  - these pairs are called **homologous chromosomes**, or **homologues**
  - homologues contain information about the same traits but the information may vary
  - cells that have two of each type of chromosome are called **diploid cells**
    - one chromosome of each pair is inherited from the mother and the other is inherited from the father

- Prior to cell division, each of the homologous chromosomes replicates, forming two identical copies called **sister chromatids**
  - the sister chromatids are joined together by a structure called a **centromere**
  - humans have 23 pairs of homologous chromosomes

    The difference between homologous chromosomes and sister chromatids

- A **karyotype** is an arrangement of chromosomes
- Chromosomes can be compared based on size, shape, and centromere location
- The karyotype at right shows the 23 pairs of human chromosomes
- Chromosomes are comprised of **chromatin**, a complex of DNA (~ 40%) and protein (~ 60%).
- A typical human chromosome contains about 140 million nucleotides in its DNA.
  - This is equivalent to
    - About 5 cm in stretched length
    - 2,000 printed books of 1,000 pages each!
  - there is also some RNA associated with chromosomes
  - the DNA in a chromosome is one very long double-stranded fiber that extends unbroken for the length of the chromosome
  - the DNA is coiled in order to allow it to fit into a small space despite being very long

- DNA is coiled around proteins called **histones**
  - the histones have positive charges to counteract the negative charges associated with the phosphate groups of the DNA

- The DNA coils around a core of eight histone proteins to form a complex called a **nucleosome**
  - the nucleosomes in turn can be coiled together further to form ultimately a compact chromosome

Levels of eukaryotic chromosomal organization

Eukaryotes Have a More Complex Cell Cycle

- Eukaryotic cells contain more DNA than prokaryotic cells and the DNA is also packaged differently
  - cell division in eukaryotic cells is more complex
  - DNA in eukaryotic cells is linear and packaged into a compact chromosome
    - there is more than one chromosome in a eukaryotic cell

- Eukaryotic cells undergo two different mechanisms to divide up the DNA
  - **mitosis** is a cell division mechanism that occurs in non-reproductive cells
    - these cells are called **somatic cells**
  - **meiosis** is a cell division mechanism that occurs in cells that participate in sexual reproduction
    - these cells are called **germ cells**

The Cell Cycle

- The cell cycle is an ordered set of events, culminating in cell growth and division into two daughter cells.
- Non-dividing cells are not considered to be in the cell cycle.
- The phases in the cell cycle are G_1-S-G_2-M.
- G_1-S-G_2 together make up what is known commonly as Interphase.
- These are the traditional subdivisions used, however, sometimes there is a G_0 phase.

The G Phases of the Cell Cycle

- The G_1 phase stands for "GAP 1".
- It is the interval between the completion of mitosis and the beginning of DNA synthesis.
- Most cells spend the majority of their lifespan in this phase
- The G_2 phase stands for "GAP 2".
- It is the interval between the end of DNA synthesis and the beginning of mitosis.
- Further preparation for cell division, including replication of mitochondria and synthesis of microtubules

- During G_1, the cell looks over its environment and its current size.
- If everything looks right, the step is taken to commit the cell to DNA replication and completion of the cell cycle.
- The G_2 phase provides a safety gap for the cell to ensure that DNA replication is complete before the cell is thrown into cell division.
- G_0 is a place where, the cell can rest or pause, if the cell has not committed itself to DNA replication.

The S Phase

- The S phase stands for "Synthesis". This is the stage when DNA replication occurs.
- In this phase, the cell's genome (DNA) is doubled.
- The DNA in this phase is, at this point, prepared to undergo division in the M phase.

- The M phase stands for "mitosis", and is when nuclear (chromosomes separate) and cytoplasmic (cytokinesis) division occur.

Cell Division

- Interphase sets the stage for cell division
  - chromosomes are first duplicated
  - although not visible, chromosomes begin to wind up tightly in a process called **condensation**
  - sister chromatids are held together by a protein complex called **cohesin**

- The cell division that follows interphase is a division of the nuclear contents, known as **mitosis**
  - mitosis is a continuous process but it is divided, for ease of study, into four distinct stages
    1. Prophase
    2. Metaphase
    3. Anaphase
    4. Telophase

Prophase

- The beginning of mitosis and the point where the condensed chromosomes first become visible
- The nuclear envelope begins to disintegrate and the nucleolus disappears
- Centrioles separate in the center of the cell and migrate to opposite ends ("poles") of the cell
    - the centrioles start to form a network of protein cables called the spindle
    - each cable in the spindle is made of microtubules
    - some of the microtubules extend toward the centromere of the chromosomes
      - these microtubules will grow from each pole until attached to a centromere at a disc of protein called a kinetochore

Metaphase

- Spindle fibers align the chromosomes along the middle of the cell nucleus.
- The centromeres are aligned along an imaginary plane that divides the cell in half, known as the **equatorial plane**
- This organization helps to ensure that in the next phase, when the chromosomes are separated (into individual chromatids), each new nucleus will receive one copy of each chromosome.

Anaphase

- The centromeres replicate and the paired chromosomes separate at the kinetochores and move to opposite sides of the cell.
- Enzymes break the cohesin and the kinetochores
- Motion results from a combination of kinetochore movement along the spindle microtubules and through the physical interaction of polar microtubules.
- Simply, the microtubules are reeled in towards the centrioles.
- This gives each pole a set of chromosomes.

Telophase

- Chromosomes arrive at opposite poles of cell, and new membranes form around the daughter nuclei.
- The chromosomes disperse and are no longer visible under the light microscope.
- The spindle fibers disperse, and cytokinesis or the partitioning of the cell may also begin during this stage.

Cytokinesis

- Occurs at the end of mitosis and is a division of the cytoplasm into roughly equal halves
  - in animals, cytokinesis occurs by actin filaments contracting and pinching the cell in two
    - this action is evident as a **cleavage furrow** that appears between the daughter cells (which can be seen at the end of Telophase)
  - in plants, a new cell wall is laid down to divide the two daughter cells
    - the cell wall grows at right angles to the mitotic spindle and is called the **cell plate**

Controlling the Cell Cycle

- The cell cycle is controlled by checkpoints to ensure that a previous phase is fully completed before advancing to the next phase
  - feedback from the cell determines whether the cycle switches to the next stage
  - three principal checkpoints control the cycle in eukaryotes
    - G_1, G_2, and M checkpoints

- G_1 checkpoint
  - this checkpoint makes the decision about whether the cell should divide and enter S
  - some cells never pass this point and are said to be in G_0
- G_2 checkpoint
  - this checkpoint leads to mitosis
- M checkpoint
  - this checkpoint occurs during metaphase and triggers the exit process of the M phase and entry to the G_1 phase

Nothing lasts forever…

- Cells can die by injury due to exposure to toxic chemicals, hard mechanical damage, or programmed cell death.
- Programmed cell death (apoptosis) is a process in which the cell ends its own life.
- Apoptosis results in cell shrinking, the mitochondria releasing toxic substances, the nuclear material degrading, etc.

How does it know?

- Well, signals alert the cell as to when it should die.
- If positive signals are withdrawn (growth factors are gone), then the cell sees no reason to carry on.
- If negative signals are given (toxicity or oxidative damage) then the cell will die to

prevent harm to the organism that it resides in.

- Unprogrammed cell death (necrosis) occurs when the cell dies by the other means mentioned.
- Injury, mechanical stress, and lack of blood flow can all be classified as necrosis.

What Is Cancer?

- **Cancer** is a growth disorder of cells
  - begins when apparently normal cells grow uncontrollably and spread to other parts of the body
  - the result is a growing cluster of cells called a **tumor**
    - benign tumors are surrounded by a healthy layer of cells (also known as encapsulated) and do not spread to other areas
    - malignant tumors are not encapsulated and are invasive
      - cells from malignant tumors leave and spread to different areas of the body to form new tumors
        - » these cells are called **metastases**

- Cancer is caused by a genetic disorder in somatic tissue in which damaged genes fail to properly control the cell cycle
  - **mutations** cause damage to genes
    - may result from chemical or environmental exposure, such as UV rays
  - viral exposure may also alter DNA

- There are two general classes of genes that are usually involved in cancer
  - **proto-oncogenes**
    - these genes encode proteins that stimulate cell division
    - mutations to these genes can cause cell to divide excessively
      - when mutated, these genes become **oncogenes**
  - **tumor-suppressor genes**
    - these genes normally turn off cell division in healthy cells
    - when mutated, these genes allow uncontrolled cell division

Cancer and Control of the Cell Cycle

- Cancer results from damaged genes failing to control cell division
  - one such gene, *p53*, affects the G_1 checkpoint
    - its normal action is to detect abnormal DNA
      - it prevents cell division of a cell with damaged DNA until the DNA is repaired or directs the cell to be destroyed if the damage cannot be fixed
    - if this gene itself becomes damaged, it will allow damaged cells to divide unchecked