The Cell Cycle and Cellular Reproduction

**Chapter 9**: pp. 150 - 168

- **G₀** (growth): If DNA is damaged, apoptosis will occur. Otherwise, the cell is committed to divide when growth signals are present and nutrients are available.

- **G₁** (growth): Cell cycle main checkpoint. If DNA is damaged, apoptosis will occur. Otherwise, the cell is committed to divide when growth signals are present and nutrients are available.

- **S** (growth and DNA replication): Mitosis will occur if DNA has replicated properly. Apoptosis will occur if the DNA is damaged and cannot be repaired.

- **G₂** (growth and final preparations for division): Mitosis checkpoint. Mitosis will occur if DNA has replicated properly. Apoptosis will occur if the DNA is damaged and cannot be repaired.

- **M** checkpoint: Spindle assembly checkpoint. Mitosis will not continue if chromosomes are not properly aligned.

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*Insert figure 9.1 here*
Outline

- The Cell Cycle
  - Interphase
  - Mitotic Stage
  - Cell Cycle Control
  - Apoptosis
- Mitosis & Cytokinesis
- Mitosis in Animal Cells
- The Cell Cycle & Cancer
- Prokaryotic Cell Division
The Cell Cycle

- An orderly set of stages from the first division to the time the daughter cells divide

- Just prior to next division:
  - The cell grows larger
  - The number of organelles doubles
  - The DNA is replicated

- The two major stages of the cell cycle:
  - Interphase
  - Mitosis
The Cell Cycle

G1 checkpoint
Cell cycle main checkpoint. If DNA is damaged, apoptosis will occur. Otherwise, the cell is committed to divide when growth signals are present and nutrients are available.

G2 checkpoint
Mitosis checkpoint. Mitosis will occur if DNA has replicated properly. Apoptosis will occur if the DNA is damaged and cannot be repaired.

M checkpoint
Spindle assembly checkpoint. Mitosis will not continue if chromosomes are not properly aligned.

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Most eukaryotic cells follow a process of growth and division called the cell cycle. These events include a growth stage, mitosis or nuclear division and cytokinesis or division of the cytoplasm.
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The process of cell growth and division in eukaryotes is called the cell cycle. This cycle is divided into phases based on what is happening in the cell at a given time. A cell grows during the G1 phase.
Regulation at the G1 Checkpoint

a. CDK not present → no DNA damage
   RB protein + E2F → E2F not released

b. CDK present → DNA damage
   p53 + P → phosphorylated p53
   p53 binds to DNA.

E2F binds to DNA.
DNA repair proteins → apoptosis

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Interphase

- Most of the cell cycle is spent in interphase
- Cell performs its usual functions
- Time spent in interphase varies by cell type
- Nerve and muscle cells do not complete the cell cycle (remain in the G0 stage)
Interphase

- Interphase consists of: G1, S and G2 phases
  - **G_1** Phase:
    - Recovery from previous division
    - Cell doubles its organelles
    - Cell grows in size
    - Accumulates raw materials for DNA synthesis (DNA replication)
  - **S** Phase:
    - DNA replication
    - Proteins associated with DNA are synthesized
    - Chromosomes enter with 1 chromatid each
    - Chromosomes leave with 2 identical chromatids each
  - **G_2** Phase:
    - Between DNA replication and onset of mitosis
    - Cell synthesizes proteins necessary for division
Mitotic (M) Stage

- **Includes:**
  - Mitosis (karyokinesis)
    - Nuclear division
    - Daughter chromosomes distributed to two daughter nuclei
  - Cytokinesis
    - Cytoplasm division
    - Results in two genetically identical daughter cells
Cell Cycle Control

- Cell cycle controlled by internal and external signals
- A *signal* is a molecule that either stimulates or inhibits a metabolic event.
  - External signals
    - Growth factors
      - Received at the plasma membrane
      - Cause completion of cell cycle
  - Internal signals
    - Family of proteins called cyclins
    - Increase and decrease as cell cycle continues
    - Without them cycle stops at G₁, M or G₂ (checkpoints)
    - Allows time for any damage to be repaired
Apoptosis

- Apoptosis is programmed cell death
- It involves a sequence of cellular events:
  - fragmenting of the nucleus,
  - blistering of the plasma membrane
  - engulfing of cell fragments.
- Apoptosis is caused by enzymes called caspases.
- Mitosis and apoptosis are opposing forces
  - Mitosis increases cell number
  - Apoptosis decreases cell number
Apoptosis

- Cells harbor caspases in check by inhibitors
  - Can be unleashed by internal or external signals

- Signal protein P53
  - Stops cycle at \( G_1 \) when DNA damaged
  - Initiates DNA attempt at repair
    - If successful, cycle continues to mitosis
    - If not, apoptosis is initiated
Cell rounds up, and nucleus collapses.

Chromatin condenses, and nucleus fragments.

Plasma membrane blisters, and blebs form.

Cell fragments contain DNA fragments.

Apoptosis

Courtesy Douglas R. Green/LaJolla Institute for Allergy and Immunology
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Mitosis: Preparation

- DNA is in very long threads
  - Chromosomes
  - Stretched out and intertangled between divisions
  - DNA is associated with histone proteins
  - Collectively called chromatin

- Before mitosis begins:
  - Chromatin condenses (coils) into distinctly visible chromosomes
  - Each species has a characteristic chromosome number
    - Humans 46
    - Corn 20
    - Goldfish 94
During interphase of the cell cycle, the genetic material of the cell is found in the form of chromatin and located within the nucleus of the cell, which is surrounded by the nuclear envelope.
Chromosome Number

- The **diploid (2n) number** includes two sets of chromosomes of each type:
  - Humans have 23 different types of chromosomes:
    - Each type is represented twice in each body cell (Diploid)
    - Only sperm and eggs have one of each type (haploid)
  - The number for humans is = 23:
    - Two representatives of each type
    - Makes a total of 2 = 46 in each nucleus:
      - One set of 23 from individual’s father (paternal)
      - Other set of 23 from individual’s mother (maternal)
### Diploid Chromosome Numbers of Some Eukaryotes

<table>
<thead>
<tr>
<th>Type of Organism</th>
<th>Name of Chromosome</th>
<th>Chromosome Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungi</td>
<td>Saccharomyces cerevisiae (yeast)</td>
<td>32</td>
</tr>
<tr>
<td>Plants</td>
<td>Pisum sativum (garden pea)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Solanum tuberosum (potato)</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Ophioglossum vulgatum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Southern adder’s tongue fern)</td>
<td>1,320</td>
</tr>
<tr>
<td>Animals</td>
<td>Drosophila melanogaster (fruit fly)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Homo sapiens (human)</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Carassius auratus (goldfish)</td>
<td>94</td>
</tr>
</tbody>
</table>
Chromosome Structure

- At end of S phase:
  - Each chromosome internally duplicated
  - Consists of two identical DNA chains
    - Sister chromatids (two strands of genetically identical chromosomes)
    - Attached together at a single point (called centromere)

- During mitosis:
  - Centromeres holding sister chromatids together simultaneously break
  - Sister chromatids separate
  - Each becomes a daughter chromosome
  - Sisters of each type distributed to opposite daughter nuclei
Duplicated Chromosome

a. 9,850×

b. one chromatid

sister chromatids

centromere

kinetochore

© Andrew Syred/Photo Researchers, Inc.
Mitosis in Animal Cells

- Just outside nucleus is the centrosome
  - This is the microtubule organizing center
  - Organizes the mitotic spindle
    - Contains many fibers
    - Each composed of a bundle of microtubules
  - In animals, contains two barrel-shaped centrioles
    - Oriented at right angles to each other within centrosome
    - Each with 9 triplets of microtubules arranged in a cylinder

- Centrosome was also replicated in S-phase, so now two centrosomes
Mitosis in Animal Cells: Prophase

- **Prophase**
  - Chromatin has condensed
    - Chromosomes distinguishable with microscope
    - Visible double (two sister chromatids attached at centromere)
  - Nucleolus disappears
  - Nuclear envelope disintegrates
  - Spindle begins to take shape
  - Two centrosomes move away from each other
  - Form microtubules in star-like arrays – asters
Mitosis in Animals

Animal cell (Early prophase, Prophase, Metaphase, Anaphase, Telophase): © Ed Reschke; Animal cell (Prometaphase): © Michael Abbey/Photo Researchers, Inc.; Plant cell (Early prophase, Prometaphase): © Ed Reschke; Plant cell (Prophase, Metaphase, Anaphase): © R. Calentine/Visuals Unlimited; Plant cell (Telophase): © Jack M. Bostrack/Visuals Unlimited;

Animal Cell at Interphase
- Centrosome
- Nuclear envelope fragments
- Chromatids condense
- Nucleolus disappears

Early Prophase
- Centrosomes have duplicated.
- Chromatids condense into chromosomes, and the nuclear envelope is fragmenting.

Prophase
- Nucleolus has disappeared, and duplicated chromosomes are visible.
- Centrosomes begin moving apart, and spindle is in process of forming.

Prophase
- Nucleolus has disappeared, and duplicated chromosomes are visible.
- Centrosomes begin moving apart, and spindle is in process of forming.

Metaphase
- Centromeres of duplicated chromosomes are aligned at the metaphase plate (center of fully formed spindle).
- Kinetochore spindle fibers attached to sister chromatids come from opposite spindle poles.

Anaphase
- Sister chromatids part and become daughter chromosomes that move toward the spindle poles.
- In this way, each pole receives the same number and kinds of chromosomes as the parent cell.

Telophase
- Daughter cells are forming as nuclear envelopes and nucleoli reappear.
- Chromosomes will become indistinct chromatin.

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Mitosis in Animal Cells: Prometaphase

- Prometaphase
  - Centromere of each chromosome develops two kinetochores
    - Specialized protein complex
  - One over each sister chromatid
    - Physically hook sister chromatids up with specialized microtubules (kinetochore fibers)
    - These connect sisters to opposite poles of mother cell
Mitosis in Animal Cells: Metaphase & Anaphase

- **Metaphase**
  - Chromosomes are pulled around by kinetochore fibers
  - Forced to align across equatorial plane of cell
    - Appear to be spread out on a piece of glass
    - Metaphase plate
    - Represents plane through which mother cell will be divided

- **Anaphase**
  - Centromere dissolves, releasing sister chromatids
  - Sister chromatids separate
    - Now called daughter chromosomes
    - Pulled to opposite poles along kinetochore fibers
Mitosis in Animal Cells: Telophase

- **Telophase**
  - Spindle disappears
  - Now two clusters of daughter chromosomes
    - Still two of each type with all types represented
    - Clusters are incipient daughter nuclei
  - Nuclear envelopes form around the two incipient daughter nuclei
    - Chromosomes uncoil and become diffuse chromatin again
    - Nucleolus reappears in each daughter nucleus
Cytokinesis: Animal Cells

- Division of cytoplasm
- Allocates mother cell’s cytoplasm equally to daughter nucleus
- Encloses each in its own plasma membrane
- Often begins in anaphase

Animal cytokinesis:
- A cleavage furrow appears between daughter nuclei
- Formed by a contractile ring of actin filaments
- Like pulling on a draw string
- Eventually pinches mother cell in two
Cytokinesis: Plant Cells

- Rigid cell walls outside plasma membrane do not permit furrowing
- Begins with formation of a cell plate
  - Many small membrane-bounded vesicles
  - Eventually fuse into one thin vesicle extending across the mother cell
  - The membranes of the cell plate become the plasma membrane between the daughter cells
    - Contents of vesicles become the middle lamella between the two daughter cells
    - Daughter cells later secrete primary cell walls on opposite sides of middle lamella
Cytokinesis in Plant Cells

Vesicles containing cell wall components fusing to form cell plate

Cell plate forming

Microtubules

Cell wall

Nuclei

Cell plate forming

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Function of Mitosis

- Permits growth and repair.
  - In plants it retains the ability to divide throughout the life of the plant
  - In mammals, mitosis is necessary:
    - Fertilized egg becomes an embryo
    - Embryo becomes a fetus
    - Allows a cut to heal or a broken bone to mend
Many mammalian organs contain *stem cells*:
- Retain the ability to divide
- Red bone marrow stem cells divide to produce various types of blood cells

**Therapeutic cloning** to produce human tissues can begin with either adult stem cells or embryonic stem cells.

Embryonic stem cells can be used for **reproductive cloning**, the production of a new individual.
Two Types of Cloning

a. Reproductive cloning

- G0 cells from animal to be cloned
- remove G0 nucleus
- fuse egg with G0 nucleus
- culture
- embryonic stem cells
- implant embryo into surrogate mother
- clone is born

b. Therapeutic cloning

- G0 somatic cells
- remove G0 nucleus
- fuse egg with G0 nucleus
- culture
- embryonic stem cells
- nervous
- blood
- muscle
The Cell Cycle and Cancer

- Abnormal growth of cells is called a neoplasm
  - Benign neoplasms are not cancerous
    - Encapsulated
    - Do not invade neighboring tissue or spread
  - Malignant neoplasms are cancerous
    - Not encapsulated
    - Readily invade neighboring tissues
    - May also detach and lodge in distant places — metastasis
    - Results from mutation of genes regulating the cell cycle

- Carcinogenesis – development of cancer
  - Tends to be gradual
  - May be years before cell is obviously cancerous
Characteristics of Cancer Cells

- Lack differentiation
  - Are nonspecialized
  - Are immortal (can enter cell cycle repeatedly)

- Have abnormal nuclei
  - May be enlarged
  - May have abnormal number of chromosomes
  - Extra copies of genes

- Form tumors
  - Mitosis controlled by contact with neighboring cells – contact inhibition
  - Cancer cells have lost contact inhibition
Characteristics of Cancer Cells

- Undergo metastasis
  - Original tumor easily fragments
  - New tumors appear in other organs
- Undergo angiogenesis
  - Formation of new blood vessels
    - Brings nutrient and oxygen to tumor
Progression of Cancer

New mutations arise, and one cell (brown) has the ability to start a tumor.

Cancer in situ. The tumor is at its place of origin. One cell (purple) mutates further.

Cancer cells now have the ability to invade lymphatic and blood vessels and travel throughout the body.

New metastatic tumors are found some distance from the primary tumor.
### Cancer Cells Versus Normal Cells

<table>
<thead>
<tr>
<th>Cancer Cells</th>
<th>Normal Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondifferentiated cells</td>
<td>Differentiated cells</td>
</tr>
<tr>
<td>Abnormal nuclei</td>
<td>Normal nuclei</td>
</tr>
<tr>
<td>Do not undergo apoptosis</td>
<td>Undergo apoptosis</td>
</tr>
<tr>
<td>No contact inhibition</td>
<td>Contact inhibition</td>
</tr>
<tr>
<td>Disorganized, multilayered</td>
<td>One organized layer</td>
</tr>
<tr>
<td>Undergo metastasis and angiogenesis</td>
<td></td>
</tr>
</tbody>
</table>
Origins of Cancer: Oncogenes

- Mutations in DNA repair mechanisms
- Oncogenes
  - Proto-oncogenes promote the cell cycle in various ways
  - Tumor suppressor genes inhibit the cell cycle in various ways
  - Both normally regulated in coordination with organism’s growth plan
  - If either mutates, may lose control and become oncogene
Origins of Cancer: Telomerase

- Chromosomes normally have special material at each end called telomeres (end parts)
- These get shorter each cell division
- When they get very short
  - The cell will no longer divide
  - Almost like running out of division tickets
- Telomerase is an enzyme that adds telomeres
- Mutations in telomerase gene:
  - Keeps adding new telomeres
  - Allow cancer cells to continually divide
  - Like counterfeit tickets
Causes of Cancer

a. Influences that cause mutated proto-oncogenes (called oncogenes) and mutated tumor suppressor genes

b. Effect of growth factor

c. Stimulatory pathway and inhibitory pathway

d. Cancerous skin cell

e. Activated signaling proteins in a stimulatory pathway that extends to the nucleus.

f. Codes for a growth factor, a receptor protein, or a signaling protein in a stimulatory pathway. If a proto-oncogene becomes an oncogene, the end result can be active cell division.

g. Codes for a signaling protein in an inhibitory pathway. If a tumor suppressor gene mutates, the end result can be active cell division.

h. Gene product promotes cell cycle

i. Gene product inhibits cell cycle

j. Growth factor

k. Receptor protein

l. Signaling protein

m. Phosphate

n. Proto-oncogene

o. Oncogene

p. Tumor suppressor gene

q. Heredity

r. Radiation sources

s. Pesticides and herbicides

1. Viruses

m. C. Stimulatory pathway and inhibitory pathway

n. Gene product promotes cell cycle

o. Gene product inhibits cell cycle

p. Tumor suppressor gene

q. Proto-oncogene

r. Oncogene

s. Tumor suppressor gene
Animation

During the first phase of the cell cycle, G₁, there is a chemical "checkpoint" that a cell must pass to begin the process that leads to cell division.
Prokaryotic Cell Division

- Prokaryotic chromosome a ring of DNA
  - Folded up in an area called the nucleoid
  - 1,000 X length of cell
  - Replicated into two rings prior to division
  - Replicate rings attach to plasma membrane

- Binary fission
  - Splitting in two between the two replicate chromosomes
  - Produces two daughter cells identical to original cell – Asexual Reproduction
Binary Fission of Prokaryotes

1. Attachment of chromosome to a special plasma membrane site indicates that this bacterium is about to divide.

2. The cell is preparing for binary fission by enlarging its cell wall, plasma membrane, and overall volume.

3. DNA replication has produced two identical chromosomes. Cell wall and plasma membrane begin to grow inward.

4. As the cell elongates, the chromosomes are pulled apart. Cytoplasm is being distributed evenly.

5. New cell wall and plasma membrane has divided the daughter cells.

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Functions of Cell Division

<table>
<thead>
<tr>
<th>Type of Organism</th>
<th>Cell Division</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prokaryotes</strong></td>
<td>Binary fission</td>
<td>Asexual reproduction</td>
</tr>
<tr>
<td>Bacteria and archaea</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Eukaryotes</strong></td>
<td>Mitosis and cytokinesis</td>
<td>Asexual reproduction</td>
</tr>
<tr>
<td>Protists, and some fungi (yeast)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other fungi, plants, and animals</td>
<td>Mitosis and cytokinesis</td>
<td>Development, growth, and repair</td>
</tr>
</tbody>
</table>
Review

- The Cell Cycle
  - Interphase
  - Mitotic Stage
  - Cell Cycle Control
  - Apoptosis
- Mitosis & Cytokinesis
- Mitosis in Animal Cells
- The Cell Cycle & Cancer
- Prokaryotic Cell Division
The Cell Cycle and Cellular Reproduction

**Cell Cycle Phases**
- **G₁** checkpoint: Cell cycle main checkpoint. If DNA is damaged, apoptosis will occur. Otherwise, the cell is committed to divide when growth signals are present and nutrients are available.
- **S** (growth and DNA replication): prepares for cell division.
- **G₂** checkpoint: Mitosis checkpoint. Mitosis will occur if DNA has replicated properly. Apoptosis will occur if the DNA is damaged and cannot be repaired.
- **M** checkpoint: Spindle assembly checkpoint. Mitosis will not continue if chromosomes are not properly aligned.

**Apoptosis**
- If DNA is damaged, apoptosis will occur. Otherwise, the cell is committed to divide when growth signals are present and nutrients are available.

**Interphase**
- **G₀** (growth) is a period of cell growth and preparation for cell division.
- **G₁** (growth) prepares the cell for DNA replication.
- **S** (growth and DNA replication) is the period of DNA replication.
- **G₂** (growth and final preparations for division) prepares the cell for cell division.
- **M** (division): Cell division occurs if DNA has replicated properly.

**Mitosis**
- Spindle assembly checkpoint ensures chromosomes are properly aligned before cell division.

**Apoptosis**
- Occurs when DNA is damaged and cannot be repaired.

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