Chapter 12: The Cell Cycle

1. Overview of Cell Division
2. Mitosis & Cytokinesis
3. Cell Cycle Regulation
1. Overview of Cell Division

Chapter Reading – pp. 233-235
Roles of Cell Division

(a) Reproduction

(b) Growth and development

(c) Tissue renewal
Bacterial Cell Division

**Binary Fission**

1. Chromosome replication begins.

2. Replication continues.

3. Replication finishes.

4. Two daughter cells result.
Eukaryotic Cell Division

Meiosis
- occurs in gamete production (sperm & egg)
- \( \frac{1}{2} \) the normal chromosome # (haploid or “1n”)
- generates cells that are genetically unique

Mitosis
- occurs in somatic cells (all cells except gametes)
- generates cells \textit{genetically} identical to original cell
Chromosomes

**CHROMOSOME:** a distinct piece of DNA in a cell

**CHROMATIN:** DNA complexed with histone proteins

Chromatin can be in a condensed or uncondensed state.
Chromosome Content

- somatic cells are diploid (2n)
  - 2 of each chromosome
  - i.e., 1 from each parent

- gametes are haploid (1n)
  - 1 of each chromosome

karyotype of human male
Chromosome Duplication

• before cell division, chromosomes are copied by the process of DNA replication

• the identical copies (sister chromatids) are connected via cohesin proteins at the region of the chromosome called the centromere

Still considered a single chromosome until sister chromatids separate.
The Cell Cycle

- G₁
- S (DNA synthesis)
- G₂

INTERPHASE

MITOTIC (M) PHASE

Cytokinesis

Mitosis
Stages of the Cell Cycle

\( \text{G}_1 \):
- preparation for DNA replication
- non-dividing cells are arrested at this stage of the cell cycle (referred to as \( \text{G}_0 \))

\( \text{S} \) phase:
- replication of genetic material (DNA Synthesis)

\( \text{G}_2 \):
- preparation for cell division

\( \text{M} \) phase:
- cell division (Mitosis or Meiosis)

***\( \text{G}_1 \), S & \( \text{G}_2 \) collectively make up “Interphase”***
2. Mitosis & Cytokinesis

Chapter Reading – pp. 235-241
Stages of Mitosis

Prophase > Prometaphase > Metaphase > Anaphase > Telophase

• results in the division of the cell nucleus
• the cell may or may not undergo cytokinesis
**G₂ of Interphase**

- Centrosomes (with centriole pairs)
- Chromatin (duplicated)
- Nucleolus
- Nuclear envelope
- Plasma membrane

**Prophase**

- Early mitotic spindle
- Centromere
- Chromosome, consisting of two sister chromatids

**Prometaphase**

- Fragments of nuclear envelope
- Nonkinetochore microtubules
- Kinetochore
- Kinetochore microtubule
**Interphase**

- $G_1$, S phase & $G_2$ (all events in preparation for cell division)

**Prophase**

- duplicated chromosomes begin to condense
- mitotic spindle begins to form
- nucleoli disappear
- centrosomes move toward opposite poles

**Prometaphase**

- nuclear envelope breaks down
- microtubules penetrate nuclear region, begin to attach to kinetochores of chromosomes
- other microtubules interact from opposite poles
Metaphase

- Metaphase plate
- Spindle
- Centrosome at one spindle pole
- Daughter chromosomes

Anaphase

- Cleavage furrow
- Nuclear envelope forming
- Nucleolus forming

Telophase and Cytokinesis

- Nucleolus forming
- Cleavage furrow
- Nuclear envelope forming
- Daughter chromosomes
Metaphase

- alignment of duplicated chromosomes along the metaphase plate of the cell
- centrosomes now at opposite poles

Anaphase

- *cohesins* connecting sister chromatids cleaved
- microtubules mediate separation of sister chromatids and elongation of the cell

Telophase

- opposite of prophase
  - chromosomes decondense, nuclear envelope reforms, spindle fibers disassemble, nucleoli reappear
The Mitotic Spindle

Kinetochore microtubules shorten while non-kinetochore microtubules “push” against each other to extend the cell.
Shortening of Microtubules

- Microtubules are labeled with a fluorescent dye.
- "Bleach" region of microtubules (via laser) to mark them.
- Observe shortening of microtubules relative to mark.

Revealed that kinetochore microtubules shorten at the kinetochore end.
Cytokinesis in Animal Cells

- actin microfilaments form a **contractile ring** at the center of the cell inside the plasma membrane
- motor proteins drive the contraction of the ring, forming a **cleavage furrow** which eventually fuses resulting in 2 separate cells!
The stages of mitosis in plants are essentially the same as in animal cells.
Cytokinesis in Plant Cells

- vesicles transport new cell wall material to the middle of cell
- cell plate begins to form, eventually becoming a complete cell wall separating the 2 daughter cells
3. Cell Cycle Regulation

Chapter Reading – pp. 242-248
General Cell Cycle Features

Proceeds in only 1 direction:

\[ G_1 > S > G_2 > M > G_1 > S > G_2 > M > \ldots \]

Controlled (internally) by **Cyclins** & **Cyclin Dependent Kinases (CDK’s)**

- extracellular signals influence cyclin & CDK activity (i.e., cell division)

Each phase of the cell cycle has characteristic “check points”

- ensures cell cycle progression only when appropriate
Checkpoints in the Cell Cycle

- $G_1$ checkpoint
- $G_2$ checkpoint
- M checkpoint
- Control system
The $G_1$ Checkpoint

This is the key checkpoint determining if the cell will remain in $G_0$ or commit to dividing by entering $G_1$.

(a) Cell receives a go-ahead signal.

(b) Cell does not receive a go-ahead signal.
Experiment 1
When a cell in the S phase was fused with a cell in G\(_1\), the G\(_1\) nucleus immediately entered the S phase—DNA was synthesized.

Experiment 2
When a cell in the M phase was fused with a cell in G\(_1\), the G\(_1\) nucleus immediately began mitosis—a spindle formed and chromatin condensed, even though the chromosome had not been duplicated.

These “cytoplasmic factors” move the cell forward, not backward, in the cell cycle.
(a) Fluctuation of MPF activity and cyclin concentration during the cell cycle

(b) Molecular mechanisms that help regulate the cell cycle

Cyclins, CDKs & Cell Cycle Progression

Maturation Promoting Factor (MPF) = complex of cyclin protein & CDK

- this particular cyclin-CDK complex mediates passage from G₂ into M phase
- other cyclin-CDK complexes mediate passage to other stages of the cell cycle

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Cyclins & CDK Activity

Cyclins control CDK activity:

- CDK’s are only active when complexed with a cyclin
  - able to phosphorylate appropriate substrates

- cyclin levels fluctuate in a regular pattern throughout the cell cycle
  - CDK levels are constant

- cyclins also determine CDK substrates
The Amount of Cyclin Oscillates during cell cycle

- add labeled amino acid to synchronous cells
- remove regular samples
- run on a gel
- cyclins seen to oscillate
  - undergo periodic degradation
Growth Factors

Most cells require “growth factors” to re-enter the cell cycle.

1. A sample of human connective tissue is cut up into small pieces.

2. Enzymes digest the extracellular matrix, resulting in a suspension of free fibroblasts.

3. Cells are transferred to culture vessels.

4. PDGF is added to half the vessels.

Growth factors are soluble signaling molecules that result in cells entering G₁.
Contact Inhibition

Anchorage dependence

Density-dependent inhibition

Density-dependent inhibition

Normal cells exit the Cell Cycle when in contact with neighboring cells, cancer cells do not.

(a) Normal mammalian cells

(b) Cancer cells
What is Cancer?

It is a deadly disease due to the loss of cell cycle regulation caused largely by somatic mutations in key genes.

- individuals do not inherit cancer although they may inherit varying degrees of predisposition to cancer
- can be manifested in many different ways
- exhibits varying degrees of virulence depending on factors such as metastasis and vascularization of the cancer tissue
Cancer requires “Multiple Hits”

Prevailing evidence indicates that “one mutant gene does not a cancer make…”

- mutations in multiple genes are typically necessary for a cancer cell to survive and proliferate
- individuals may inherit some of these mutant genes, but more must be “hit” for a cell to become cancerous
- this is an extremely rare event, but all it takes is 1 cell to produce a cancer
The sequential acquisition of these characteristics is typical of many cancers:
Metastasis: spread of cancer cells from the original tumor to other locations in the body.

1. A tumor grows from a single cancer cell.
2. Cancer cells invade neighboring tissue.
3. Cancer cells spread through lymph and blood vessels to other parts of the body.
4. Cancer cells may survive and establish a new tumor in another part of the body.
Cancers Increase Dramatically with Age

consistent with “multi-hit” hypothesis
Key Terms for Chapter 12

• cell cycle, mitosis, meiosis, binary fission
• haploid, diploid, somatic cell, gamete
• interphase, prophase, metaphase, prometaphase, anaphase, telophase, cytokinesis
• centromere, centrosome, kinetochore, cohesin
• chromosome, chromatin, chromatid, sister chromatid
• spindle, aster, cytokinesis
• cleavage furrow, contractile ring, cell plate
• checkpoint, cyclin, CDK, metastasis, angiogenesis
• contact inhibition, growth factor

Relevant Chapter Questions 1-11