

CHAPTER 11: HOW CELLS DIVIDE

CHAPTER SYNOPSIS

Cellular division in bacteria is simple since the genome is one double-stranded circle of DNA attached to the interior of the cell at a single point. Duplication is an enzyme mediated process that begins at that point and continues around the circle resulting in two side-by-side DNA circles. Physical division occurs when the cell attains a certain size. New membrane materials are laid down between the points of attachment of the DNA circles and pinch inward, binary fission.

Eukaryotic cell division is more complicated because the eukaryotic genome is larger and more complex. Eukaryotic chromosomes are linear structures composed of chromatin, mostly DNA and protein with a small amount of RNA. Eukaryotic DNA is a long double-stranded fiber. Every 200 nucleotides it coils around a core of eight histone polypeptides forming a nucleosome. The string of nucleosomes is further wrapped into supercoils. Heterochromatin is highly condensed chromatin while euchromatin is relatively uncondensed. Some portions of the DNA are permanently heterochromatic to prevent DNA expression; the remainder is uncondensed at the proper time to facilitate transcription.

The number of chromosomes in eukaryotic organisms varies widely from species to species. Human cells possess a diploid complement of 23 homologous pairs of chromosomes each with a characteristic appearance. Prior to cell division each homologue replicates producing two identical sister chromatids joined by a common centromere. The process of growth and division in a typical eukaryotic cell is called the cell cycle and is composed of five phases. The G_1 phase is the cell's primary growth phase while the genome is replicated during the S phase. During the G_2 phase, various organelles are replicated, the chromosomes start to condense, and microtubules are synthesized. All of these are preparatory for mitosis or M phase. Actual cell division occurs in the final C phase, cytokinesis.

Mitosis is a continuous process that is divided into four stages for ease of examination: prophase, metaphase, anaphase, and telophase. Much of the preparation for mitosis occurs during

interphase, a collective stage that includes G_1 , S, and G_2 . Preparations include chromosome replication, centriole replication (in animals only), and tubulin synthesis. Chromatin condensation begins near the end of interphase and continues through prophase when individual chromosomes become visible. At the same time, the nuclear envelope breaks down and the centrioles of animal cells move apart. One set of microtubules assembles between the nucleolar organizing regions while another set grows outward from each centromere toward the poles. Metaphase begins when the pairs of sister chromatids align across the center of the cell at the metaphase plate. The end of this phase is signalled by the division of the centromeres. During anaphase, each chromatid moves toward the pole to which it is attached. Separation occurs when the central spindle fibers slide past one another, moving the poles farther apart. The chromatids also move toward the poles as the microtubules to which they are attached shorten. The nucleus begins to reform around the uncoiling chromosomes during telophase. The spindle apparatus breaks down and the nucleolus reappears as rRNA genes are again expressed.

There are significant differences in cytokinesis in animals and plants. Animal cells are pinched in two by a belt of constricting microfilaments at the cleavage furrow. Rigid plant cells are not easily deformed and divide from the inside outward. This expanding partition is called the cell plate. The final addition of cellulose to either side of the membrane results in two separate cells.

Cell cycle control is based on a check-point feedback system. When certain conditions at a checkpoint are met, the cell proceeds to the next stage of activity or division. Cyclin-dependent kinases (Cdk's) and cyclins are intimately associated with these control processes. Unicellular organisms make independent decisions on whether or not to divide. Multicellular organisms must limit independent cell proliferation to maintain the integrity of the whole. Eukaryotes utilize various growth factors to do this. Disruption of these control mechanisms is characteristic of cancer.

CHAPTER OBJECTIVES

- ä Discuss the molecular composition of eukaryotic chromosomes and their association with RNA, histones, and nucleosomes.
- ä Describe the structure of a condensed eukaryotic chromosome and identify the structure that most accurately indicates the number of chromosomes present in a given cell.
- ä Understand the differences between heterochromatin and euchromatin.
- ä Understand the genetic composition of individual eukaryotic chromosomes, chromosome pairs, and sex chromosomes.
- ä Identify the five phases of the cell cycle and describe the events that highlight each stage.
- ä Identify the four stages of mitosis and describe the most characteristic events of each stage.
- ä Understand the composition and function(s) of the spindle apparatus.
- ä Understand the purpose of mitosis in terms of the genetic composition of progeny cells and the survival of a given cell line.
- ä Explain how mitosis differs in plant and animal cells.
- ä Describe the process of cytokinesis in both animals and plants.
- ä Understand how cyclin-dependent kinases and cyclins control the cell cycle normally and in cancer.
- ä Identify several growth factors and describe how they affect cell division.

KEY TERMS

anaphase	diploid (2N)	kinetochore
aster	euchromatin	M phase
binary fission	G ₀ phase	metaphase
C phase	G ₁ phase	metaphase plate
cell cycle	G ₂ phase	microtubule
cell plate	gamete	middle lamella
centriole	genome	mitosis
centromere	growth factor	nucleosome
chromatid	haploid (1N)	prophase
chromatin	heterochromatin	replication origin
chromosome	homologue	S phase
cleavage furrow	homologous chromosome	sister chromatids
condensation	interphase	telophase
cytokinesis	karyotype	

CHAPTER OUTLINE

11.0 Introduction

I. ALL ORGANISMS GROW AND REPRODUCE

A. All Species Pass Their Hereditary Information on to Their Offspring

B. How Do Cells Reproduce?

fig 11.1

11.1 Bacteria divide far more simply than do eukaryotes

I. CELL DIVISION IN PROKARYOTES

A. Binary Fission Is Bacterial Cell Division

1. Cell splits into two equal halves fig 11.2
2. Composition of the bacterial genome
 - a. Exists as one double-stranded circle of DNA
 - b. Attached to replication origin on the interior of the cell membrane
3. Genome replicated early in the life of the cell fig 11.3
 - a. Copying of the DNA circle begins at the replication origin
 - b. Requires a battery of enzymes
 - c. Proceeds around entire DNA circle
 - d. End result: Two side-by-side circles of DNA on membrane

B. Division Initiated when Cell Size Is Doubled

1. Two daughter cells actively partitioned
 - a. New plasma membrane and cell wall materials laid down
 - b. Occurs in zone between attachment sites of daughter genomes
 - c. Plasma membrane grows between genomes
 - d. Eventually divides cell in two
2. Growing membrane divides two genomes
3. Each cell contains a copy of the genome
4. New cell wall forms around membranes

II. CELL DIVISION IN EUKARYOTES

A. Eukaryotic Genome Is Larger than Bacterial Genome

B. Eukaryotic DNA Located within Linear Chromosomes

1. Organization more complex
2. DNA forms a complex with histone proteins and is tightly coiled

11.2 Chromosomes are highly ordered structures

I. DISCOVERY OF CHROMOSOMES

A. Eukaryotic Chromosomes

1. Chromosomes first observed in dividing salamander larvae cells
2. Division of cells called mitosis, derivative of word for thread

B. Chromosome Number

1. The number of chromosomes varies within species tbl 11.1
2. Humans have 46 chromosomes, 23 identical pairs fig 11.4
 - a. All chromosomes are necessary for survival
 - b. In monosomy only one chromosome missing, lack of embryonic development
 - c. With extra chromosome, trisomy, development proceeds improperly
 - 1) Most trisomy's are fatal
 - 2) Down syndrome is trisomy in chromosome 21

II. THE STRUCTURE OF EUKARYOTIC CHROMOSOMES

A. Composition of Chromatin

1. Chromosomes are composed of chromatin
 - a. Complex of 40% DNA and 60% protein
 - b. Contains some RNA since DNA is the site of RNA synthesis
2. DNA exists as a long double-stranded fiber
3. DNA is highly coiled to fit within cell

B. Chromosome Coiling

1. DNA resembles a string of beads fig 11.5
 - a. DNA is coiled around histone polypeptides every 200 nucleotides
 - b. Eight histones form a core called a nucleosome
 - c. Basic, positively charged histones attract negatively charged DNA
 - d. String of nucleosomes further wrapped into supercoils
2. Heterochromatin
 - a. Highly condensed portions of chromatin
 - b. Some portions permanently condensed to prevent DNA expression
3. Euchromatin
 - a. Remainder of chromatin condensed only during cell division
 - b. Movement of chromosomes facilitated by packaging
 - c. DNA is uncondensed to allow for gene expression

C. Chromosome Karyotypes

1. Chromosomes vary widely in appearance
 - a. Size and staining properties
 - b. Location of the centromere
 - c. Relative length of the arms on either side of the centromere
 - d. Position of additional constricted regions along arms
2. Karyotype: Array of an individual's chromosomes fig 11.6
 - a. In humans, blood sample collected, cells induced to divide
 - b. Chemicals stop division at metaphase when chromosomes are most condensed
 - c. Contents spread out, stained, and then photographed
 - d. Chromosomes cut out and arranged in order

D. How Many Chromosomes Are in a Cell?

1. All human body cells are diploid (2n)
 - a. Contain 46 chromosomes composed of 23 pairs
 - b. Pairs are nearly identical
2. Human gametes have haploid (1n) complement with 23 chromosomes
3. Nearly identical pairs are called homologous chromosomes or homologues
4. Before division each of the two homologues replicates
 - a. Produce two identical copies called sister chromatids
 - b. Chromatids remain joined together at the centromere fig 11.7
 - c. Cells have 46 replicated chromosomes, each with two chromatids
 - 1) Possess 46 centromeres, 92 chromatids
 - 2) Number of chromosomes indicated by number of centromeres

11.3 Mitosis is a key phase of the cell cycle

I. PHASES OF THE CELL CYCLE

A. Division Process Diagramed as the Cell Cycle

fig 11.8

B. The Five Phases

1. G₁ phase: Primary growth phase, most of cell's life span
2. S phase: Genome replica synthesized
3. G₂ phase: Preparations made for genomic separation
 - a. Replication of mitochondria and other organelles
 - b. Chromosome condensation
 - c. Restructuring of microtubules and assembly at spindle
4. G₁, S, and G₂ constitute interphase
5. M phase: Mitosis
 - a. Microtubular apparatus assembled, binds to chromosomes
 - b. Sister chromatids moved apart from one another
 - c. Continuous process, traditionally divided into four stages
 - d. Mitosis subdivided into four continuous stages
 - 1) Prophase
 - 2) Metaphase
 - 3) Anaphase
 - 4) Telophase
6. C phase: Cytokinesis
 - a. Physical division of the cell, creates two daughter cells
 - b. Animal spindle helps position contracting cleavage furrow actin ring
 - c. Plants and other cells with cell wall form plate between dividing cells

C. Duration of the Cell Cycle

1. Greatly variable among organisms
2. Embryos exhibit shorter cycles
 - a. Divide as quickly as DNA can be replicated
 - b. Half of cycle is S, half is M, virtually no G₁ or G₂
3. Mature cells have longer cycles
 - a. Mammalian cell cycle averages 24 hours
 - b. Growth occurs during G₁ and G₂
 - 1) G phases may be referred to as gap phases
 - 2) They separate the S phase from the M phase
 - c. M phase takes only small portion of cycle
4. Length of cycle variability is usually in G₁
 - a. Many cells pause in a G₀ resting stage
 - b. May remain there for days to years, some remain permanently
 - c. Most body cells are in G₀ at any one time
 - d. Injury may stimulate some cells to resume G₁ phase

II. INTERPHASE: PREPARING FOR MITOSIS

A. Events of Interphase Necessary for Successful Completion of Mitosis

1. G₁ phase: Cells undergo major portion of growth
2. S phase: Chromosome replicates to produce sister chromatids
 - a. Remain attached at the centromere
 - b. Specific DNA sequence bound to a protein kinetochore
 - c. Location specific to each chromosome

fig 11.9

B. Cell Grows throughout Interphase

1. G₁ and G₂ are periods of active growth, protein synthesis, organelle replication
2. Cell's DNA replicates only during S phase
3. After S replication, chromosomes remain extended and uncoiled

4. G₂ phase: Chromosomes begin process of condensation
 - a. Motor proteins involved in rapid, final condensation
 - b. In G₂, cells assemble machinery used to move chromosomes apart
 - 1) Animals replicate centriole, nuclear microtubule-organizing centers
 - 2) Eukaryotic cells synthesize tubulin, microtubule protein component

III. MITOSIS

A. Prophase: Formation of the Mitotic Apparatus

1. Characteristics that indicate beginning of prophase
 - a. Individual condensed chromosomes become visible
 - b. Condensation continues through prophase
 - c. Ribosomal RNA synthesis ceases
2. Assembling the spindle apparatus
 - a. Microtubule apparatus made of spindle fibers continues to assemble
 - 1) In animal cells the two centrioles move apart
 - 2) Spindle apparatus, a bridge of microtubules, forms between them
 - 3) In plant cells, spindle apparatus forms without visible centrioles
 - 4) Nuclear envelope breaks down, materials absorbed by ER
 - 5) Position of spindle microtubules determines plane of cell division
 - 6) Division occurs at right angles through the spindle
 - b. Animal cells form an arrangement called an aster
 - 1) Centrioles at opposite poles extend radial array of microtubules
 - 2) Function to stiffen point of microtubular attachment
 - 3) Rigid plant cells do not form asters
3. Linking sister chromatids to opposite poles
 - a. Each chromosome possesses two kinetochores fig 11.9
 - b. Second group of microtubules grow out from centromeres to poles
 - 1) Two sets of microtubules extend from each chromosome
 - 2) Kinetochore of each sister chromatid connected to one pole
 - 3) Microtubules grow until they make contact with poles
 - c. Sister chromatids won't separate if both connected to same pole

B. Metaphase: Alignment of the Centromeres

1. Stage where chromosomes align in center of the cell
2. Alignment occurs along the metaphase plate fig 11.10
 - a. Not a physical structure
 - b. Indicates where future axis of cell division occurs
 - c. Centromeres are equidistant from each pole
3. Centromeres divide at the end of metaphase fig 11.11
 - a. Marks end of metaphase stage
 - b. Centromere arrayed in neat circle equidistant from poles of cell
 - c. Microtubules extend back toward opposite poles of cell forming the spindle

C. Anaphase and Telophase: Separation of the Chromatids and Reformation of the Nuclei

1. Anaphase
 - a. Shortest phase, begins when sister centromeres divide
 - 1) Each centromere splits in two
 - 2) Sister chromatids freed from each other
 - b. Chromatid drawn to pole to which its kinetochore is attached
 - c. Separation achieved by two simultaneous microtubular actions
 - d. Poles move apart fig 11.12
 - 1) Microtubular spindle fibers slide past one another
 - 2) Chromosome microtubules are anchored at poles

- 3) Chromatids attached to poles move apart as well
- e. Centromeres move toward poles
 - 1) Shortening process of centromere microtubules is not a contraction
 - 2) Microtubules shorten as tubulin subunits are removed
 - 3) Chromatids are therefore pulled toward poles
- 2. Telophase
 - a. Separation of chromatids completes partitioning of replicated genome
 - b. Spindle apparatus is disassembled
 - c. Tubulin units of microtubules are used to build new cytoskeleton
 - d. Nuclear envelope reforms around each new set of chromosomes
 - e. Chromosomes begin to uncoil to allow gene expression
 - f. rRNA genes begin transcription, nucleolus reappears

IV. CYTOKINESIS

A. Mitosis Complete at End of Telophase

- 1. Replicated genome divided into two new nuclei at opposite ends of cell
- 2. Cytoplasmic organelles assort to regions that will become separated
- 3. Cleavage of the cell into two halves constitutes cytokinesis

B. Cytokinesis in Animal Cells

- 1. Cell is pinched in two by a constricting belt of microfilaments
 - a. Actin filaments slide past one another
 - b. Produces distinct cleavage furrow around circumference of cell
- 2. Furrow deepens until the cell pinched in two

fig 11.13a

fig 11.13b

C. Cytokinesis in Plant Cells

- 1. Rigid cell wall, cannot be deformed by microfilament contraction
- 2. Membrane components assembled in the cell interior
 - a. Occurs at right angles to the spindle apparatus
 - b. Expanding partition called the cell plate
 - c. Grows outward to the interior surface of the cell membrane
 - d. Cellulose then added on the membrane making two new cells
- 3. Middle lamellae: Space between cells impregnated with pectins

fig 11.14

D. Cytokinesis in Fungi and Protists

- 1. In fungi and some protists, mitosis is confined to the nucleus
- 2. After completion of mitosis, nucleus divides into daughter nuclei
- 3. Distribution of other cell organelles
 - a. No discrete process similar to mitosis
 - b. Organelles replicate increasing number of individuals
 - c. Cell division distributes at least one organelle in each cell, can later replicate

11.4 The cell cycle is carefully controlled

I. GENERAL STRATEGY OF CELL CYCLE CONTROL

A. Events of Cell Cycle Coordinated Similarly in All Eukaryotes

B. Goal of Cell Cycle Control Is to Optimize Duration of Cycle

- 1. Internal clock control cannot provide sufficient flexibility
- 2. Eukaryotes use a centralized controller based on cellular feedback
 - a. Analogy: Furnace heating a house
 - b. At points in cycle, feedback determines if cycle continues or is delayed

- C. Architecture of the Control System
 - 1. Three principal check points fig 11.15
 - 2. Cell growth assessed at G_1 check point
 - 3. Determines if cell divides, delays division or enters resting stage fig 11.16
 - a. Check point called START in yeasts
 - b. If conditions favorable, cell starts copying DNA, starting S phase
 - 4. The success of DNA replication is assessed at G_2 check point
 - 5. Mitosis is assessed at M check point

II. MOLECULAR MECHANISMS OF CELL CYCLE CONTROL

- A. Basic Mechanism of Cell Cycle Control Is Simple
 - 1. Associated with interactions of proteins sensitive to cell conditions
 - 2. Two key types of proteins fig 11.17
 - a. Cyclin-dependent protein kinases
 - b. Cyclins

- B. The Cyclin Control System
 - 1. Cyclin-dependent protein kinases (Cdk's)
 - a. These enzymes phosphorylate serine and threonine of certain proteins
 - b. Phosphorylate histones, nuclear membrane filaments, microtubule proteins at G_2
 - c. Phosphorylation initiates activities that carry cycle past checkpoint to mitosis
 - 2. Cyclins
 - a. Bind to Cdk's, enable them to act as enzymes
 - b. Are destroyed and resynthesized at each turn of cell cycle
 - c. Different kinds of cyclins regulate at the two check points fig 11.18
 - 3. The G_2 check point
 - a. Cell accumulates G_2 cyclin (mitotic cyclin) during G_2
 - 1) Binds to Cdk, forming mitosis promoting factor, MPF
 - 2) MPF are phosphorylated and activated by cellular enzymes
 - 3) Positive feedback increases this activity, more MPF activated
 - 4) G_2 ends when sufficient activated MPF
 - b. Duration of M phase determined by MPF activity
 - 1) MPF also activates proteins that destroy cyclin
 - 2) Degradation of G_2 cyclin decreases activity of MPF, ending mitosis
 - 4. The G_1 check point
 - a. Similar to G_2 control
 - b. Main factor triggering DNA replication in yeast is cell size
 - c. Yeasts compare volume of cytoplasm to size of genome
 - d. In growth size increases, amount of DNA constant
 - e. Threshold ration reached promoting cyclin production

- C. Controlling the Cell Cycle in Multicellular Eukaryotes
 - 1. Cells of multicellular organisms can't make individual decisions
 - 2. Organization dependent limiting cell proliferation
 - 3. In cell culture, cells stop dividing when sufficient numbers
 - a. Growing cells take up growth factors like MPF
 - b. Example of positive regulatory signal
 - c. If other cells take up factor, none left to trigger division in any cell

D. Growth Factors and the Cell Cycle

1. Growth factors trigger intracellular signalling systems
2. Example: Fibroblasts
 - a. Possess membrane receptors for platelet-derived growth factor, PDGF
 - b. Binding PDGF and receptor initiates amplifying chain of events
 - c. Tissue injury causes release of PDGF to promote healing
3. Characteristics of growth factors
 - a. Isolation of fifty growth factor proteins tbl 11.2
 - b. Each factor specifically recognized by specific cell surface receptor fig 11.19
 - c. Some affect broad range of cell types, PDGF and E (epidermal) GF
 - d. Some affect only certain cell types, N (nerve) GF, and erythropoietin
4. The G_0 phase
 - a. Cells deprived of growth factors stop at G_1 , stay in G_0
 - b. G_0 is a non-growing state distinctly different from G_1 , S, and G_2
 - c. Accounts for great diversity in length of cell cycle among different organisms
 - 1) Gut lining cells divide twice per day
 - 2) Liver cells divide once per year or two
 - 3) Mature neurons and muscle cells usually stay in G_0

III. CANCER AND THE CONTROL OF CELL PROLIFERATION

A. Cancer Is A Disease of Altered Control of the Cell Cycle

1. Discovery of *p53* gene (gene name italicized, not protein name)
2. Involved in G_1 check point of cell division
 - a. Gene's product is p53 protein, monitors integrity of DNA
 - b. If p53 detects damaged DNA, cell division halted, enzyme repair initiated
 - c. DNA replication continued after DNA is repaired
 - d. If DNA irreparable, *p53* directs cell to kill itself (apoptosis)
3. Halting division prevents development of numerous mutated cells
 - a. *p53* considered a tumor-suppressor gene
 - b. Activities not limited to cancer prevention
4. *p53* absent or grossly damaged in all examined cancerous cells
 - a. Cancer cells undergo repeated division without halt at G_1 check point fig 11.20
 - b. If p53 protein added to dividing cancer cells, their division stops
 - c. Cigarette smoking causes mutations in *p53* gene

B. Growth Factors and Cancer

1. Proto-oncogenes
 - a. Normally stimulate cell division, positive approach
 - b. Trigger passage through G_1 check point
 - 1) Aid formation of cyclins
 - 2) Activate genes that promote cell division
 - c. Mutations causing them to overact change them into oncogenes
 - 1) Mutations are dominant
 - 2) Leads to excessive cell proliferation characteristic of cancer
 - d. 30 different proto-oncogenes exist
 - e. *myc*, *fos*, *jun* cause unrestrained cell growth and division
 - 1) *myc* in normal cell helps to regulate G_1 check point fig 11.21
 - 2) Genes also stimulate delayed response genes that produce cyclins, Cdk
2. Tumor-suppressor genes
 - a. Normally inhibit cell division, negative approach
 - 1) Prevents binding of cyclins to Cdk, block passage through G_1
 - 2) Mutations are recessive, unrestrained division only if both copies mutated

- b. Retinoblastoma (*Rb*) gene is tumor-suppressor gene, causes rare eye cancer
 - 1) Normal gene is a cancer suppressor
 - 2) *Rb* gene encodes protein present in nucleus
 - 3) *Rb* protein is dephosphorylated in G_0 phase fig 11.19
 - 4) Binds regulatory proteins needed for cell proliferation
 - 5) Inhibit cell division
- c. When *Rb* is phosphorylated it releases regulatory proteins
 - 1) Cell division thus promoted
 - 2) Cells produce cyclins and Cdk, pass G_1 check point
3. Summary of genes that cause cancer when mutated fig 11.22

INSTRUCTIONAL STRATEGY

PRESENTATION ASSISTANCE:

It is more efficient to move by packing your belongings in boxes and bags than to move each item individually. Similarly, condensing the chromatin into discrete chromosomes makes it easier to separate them during mitosis.

Remember the order of mitotic stages via PMAT (or IPMAT if interphase is included). Any student named Matthew deserves apologies on this mnemonic!

Stress that the purpose of mitosis is to produce many identical copies of a cell.

Most students merely memorize when the nucleolus disappears and reappears. If they associate its presence with its function synthesizing rRNA, it is obvious when the transient organelle will be present and when it will be absent.

VISUAL RESOURCES:

Bring in a ball of yarn to simulate DNA as chromosomes and some unraveled yarn to represent DNA in chromatin form. Question the likelihood of knitting a scarf with the yarn in a ball. This is like trying to transcribe DNA as chromosomes. Also question the ease of separating two bunches of identically colored yarn when unraveled as compared to the same yarn when rolled into two separate balls.

In a small classroom, use clay or plastic foam and colored straws to represent chromosomes. In a large classroom with an overhead projector, cut rod-shaped chromosomes out of colored acetate. Make a second set to show chromatid replication

during the S phase and hold the two chromatids together with overlapped post-it-note centromere circles. Cut similar-shaped, but different-colored chromosomes to show homologues.

Use colored beads and two sets of spaghetti to simulate chromosomes and spindle microtubules in a cell bounded by yarn. The pieces of spaghetti anchored at the poles push the yarn boundary apart as they slide past one another. Shorten the spaghetti attached to each chromosome to move the chromosomes to the poles. (One might want to use string instead of spaghetti, but the latter is more accurate.)