CHAPTER 12
THE CELL CYCLE

OUTLINE

I. The Key Roles of Cell Division
   A. Cell division functions in reproduction, growth, and repair
   B. Cell division distributes identical sets of chromosomes to daughter cells

II. The Mitotic Cell Cycle
   A. The mitotic phase alternates with interphase in the cell cycle: *an overview*
   B. The mitotic spindle distributes chromosomes to daughter cells: *a closer look*
   C. Cytokinesis divides the cytoplasm: *a closer look*
   D. Mitosis in eukaryotes may have evolved from binary fission in bacteria

III. Regulation of the Cell Cycle
   A. A molecular control system drives the cell cycle
   B. Internal and external cues help regulate the cell cycle
   C. Cancer cells have escaped from cell-cycle controls

OBJECTIVES

After reading this chapter and attending lecture, the student should be able to:

1. Describe the structural organization of the genome.
2. Overview the major events of cell division that enable the genome of one cell to be passed on to two daughter cells.
3. Describe how chromosome number changes throughout the human life cycle.
4. List the phases of the cell cycle and describe the sequence of events that occurs during each phase.
5. List the phases of mitosis and describe the events characteristic of each phase.
6. Recognize the phases of mitosis from diagrams or micrographs.
7. Draw or describe the spindle apparatus including centrosomes, nonkinetochore microtubules, kinetochore microtubules, asters, and centrioles (in animal cells).
8. Describe what characteristic changes occur in the spindle apparatus during each phase of mitosis.
9. Explain the current models for poleward chromosomal movement and elongation of the cell's polar axis.
10. Compare cytokinesis in animals and plants.
11. Describe the process of binary fission in bacteria and how this process may have evolved to mitosis in eukaryotes.
12. Describe the roles of checkpoints, cyclin, Cdk, and MPF, in the cell-cycle control system.

13. Describe the internal and external factors which influence the cell-cycle control system.
14. Explain how abnormal cell division of cancerous cells differs from normal cell division.

KEY TERMS

cell cycle	chromosomes	kinetochore	growth factor
cell division	interphase	metaphase plate	density-dependent inhibition
genome	G_1 phase	cleavage furrow	anchorage dependence
somatic cell	S phase	cell plate	transformation
gametes	G_2 phase	binary fission	tumor
chromatin	prophase	cell-cycle control system	benign tumor
sister chromatids	prometaphase	checkpoint	malignant tumor
centromere	metaphase	G_0 phase	metastasis
mitosis	anaphase	cyclin	
cytokinesis	telophase	cyclin-dependent kinase	
mitotic (M) phase	mitotic spindle	MPF	

LECTURE NOTES

The ability to reproduce distinguishes living organisms from nonliving objects; this ability has a cellular basis.

All cells arise from preexisting cells. This fundamental principle, known as the cell doctrine, was originally postulated by Rudolf Virchow in 1858, and it provides the basis for the continuity of life.

A cell reproduces by undergoing a coordinated sequence of events in which it duplicates its contents and then divides in two. This cycle of duplication and division, known as the *cell cycle*, is the means by which all living things reproduce.

I. The Key Roles of Cell Division

A. Cell division functions in reproduction, growth, and repair

Cells reproduce for many reasons.

- In unicellular organisms, the division of one cell to form two reproduces an entire organism (e.g., bacteria, yeast, *Amoeba*) (see Campbell, Figure 12.1a).
- In multicellular organisms, cell division allows:
  - Growth and development from the fertilized egg (see Campbell, Figure 12.1b)
  - Replacement of damaged or dead cells

Cell division is a finely controlled process that results in the distribution of identical hereditary material—DNA—to two daughter cells. A dividing cell:

- Precisely replicates its DNA
- Allocates the two copies of DNA to opposite ends of the cell
- Separates into two daughter cells containing identical hereditary information

B. Cell division distributes identical sets of chromosomes to daughter cells

The total hereditary endowment of a cell of a particular species is called its genome.

The genomes of some species are quite small (e.g., prokaryotes), while the genomes of other species are quite large (e.g., eukaryotes).

The replication, division, and distribution of the large genomes of eukaryotes is possible because the genomes are organized into multiple functional units called *chromosomes* (see Campbell, Figure 12.2).

Eukaryotic chromosomes have the following characteristics:

- They are supercoils of a DNA-protein complex called *chromatin.* Each chromosome consists of the following:
  - A single, long, double-stranded molecule of DNA, segments of which are called *genes*
  - Various proteins which serve to maintain the structure of the chromosome or are involved with the expression of genes, DNA replication, and DNA repair
- They exist in a characteristic number in different species (e.g., human somatic cells have 46); gamete cells (sperm or ova) possess half the number of chromosomes of somatic cells (e.g., human gametes have 23)
- The exist in different states at different stages of the cell cycle.
  - During interphase, the chromosomes are loosely folded; cannot be seen with a light microscope
  - During the mitotic phase, chromosomes are highly folded and condensed; can be seen with a light microscope

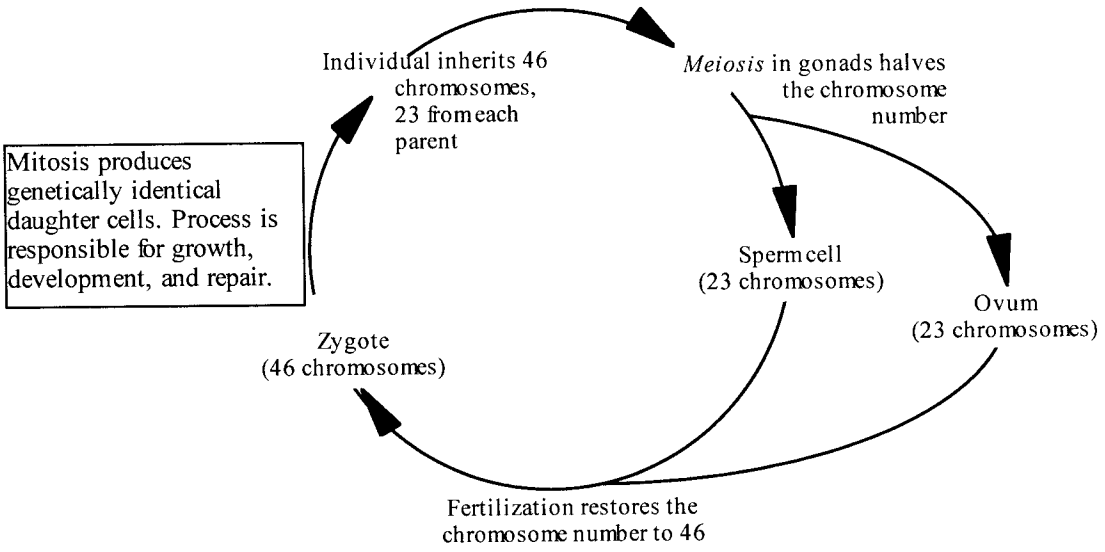
In preparation for eukaryotic cell division, the complete genome is duplicated. As a result of this duplication, each chromosome consists of two *sister chromatids.* The two chromatids possess identical copies of the chromosome's DNA and are initially attached to each other at a specialized region called the *centromere* (see Campbell, Figure 12.3).

Cell division usually proceeds in two sequential steps: nuclear division (*mitosis*) and division of the cytoplasm (*cytokinesis*). Not all cells undergo cytokinesis following mitosis.

In mitosis, the sister chromatids are pulled apart, and this results in the segregation of two sets of chromosomes, one set at each end of the cell.

In cytokinesis, the cytoplasm is divided and two separate daughter cells are formed, each containing a single nucleus with one set of chromosomes.

HUMAN LIFE CYCLE



In plant cells, cytokinesis occurs by *cell plate* formation across the parent cell's midline (old metaphase plate).

- Golgi-derived vesicles move along microtubules to the cell's center, where they fuse into a disc-like cell plate.

- Additional vesicles fuse around the edge of the plate, expanding it laterally until its membranes touch and fuse with the existing parent cell's plasma membrane.
- A new cell wall forms as cellulose is deposited between the two membranes of the cell plate.

II. The Mitotic Cell Cycle

A. The mitotic phase alternates with interphase in the cell cycle: *an overview*

Cell division is just a portion of the life, or *cell cycle,* of a cell (see Campbell, Figure 12.4).

The cell cycle is a well-ordered sequence of events in which a cell duplicates its contents and then divides in two.

- Some cells go through repeated cell cycles.
- Other cells never or rarely divide once they are formed (e.g., vertebrate nerve and muscle cells).

The cell cycle alternates between the *mitotic (M) phase*, or dividing phase, and *interphase*, the nondividing phase:

- M phase, the shortest part of the cell cycle and the phase during which the cell divides, includes:
  1. *Mitosis* - Division of the nucleus
  2. *Cytokinesis* - Division of the cytoplasm
- *Interphase*, the nondividing phase, includes most of a cell's growth and metabolic activities.
  - Is about 90% of the cell cycle
  - Is a period of intense biochemical activity during which the cell grows and copies its chromosomes in preparation for cell division
  - Consists of three periods:
    1. *G_1 phase* - First growth phase (G stands for "gap")
    2. *S phase* - Synthesis phase occurs when DNA is synthesized as chromosomes are duplicated (S stands for "synthesis")
    3. *G_2 phase* - Second growth phase

Mitosis is unique to eukaryotes and may be an evolutionary adaptation for distributing a large amount of genetic material.

- Details may vary, but overall process is similar in most eukaryotes.
- It is a reliable process with only one error per 100,000 cell divisions.

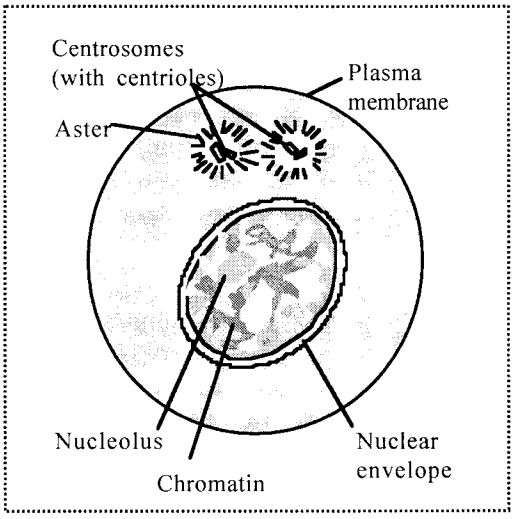
Mitosis is a continuous process, but for ease of description, mitosis is usually divided into five stages: *prophase*, *prometaphase*, *metaphase*, *anaphase,* and *telophase* (see Campbell, Figures 12.5 and 12.9):

When cytokinesis occurs, it usually is concomitant with telophase of mitosis. The details of mitosis and cytokinesis follow (as exemplified by the pattern of cell division displayed by animal cells):

G_2 of interphase

A G_2 cell is characterized by:

- A well-defined nucleus bounded by a nuclear envelope
- One or more nucleoli
- Two centrosomes adjacent to the nucleus (formed earlier by replication of a single centrosome)
- In animals, a pair of centrioles in each centrosome
- In animals, a radial microtubular array (*aster*) around each pair of centrioles
- Duplicated chromosomes that cannot be distinguished individually due to loosely packed chromatin fibers. (Chromosomes were duplicated earlier in S phase.)
- See also Campbell, Figure 12.5



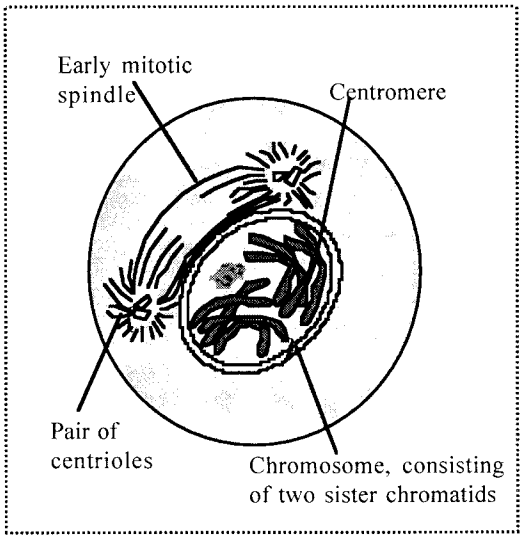
Prophase

In the nucleus:

- Nucleoli disappear
- Chromatin fibers condense into discrete, observable chromosomes, composed of two identical sister chromatids joined at the centromere.

In the cytoplasm:

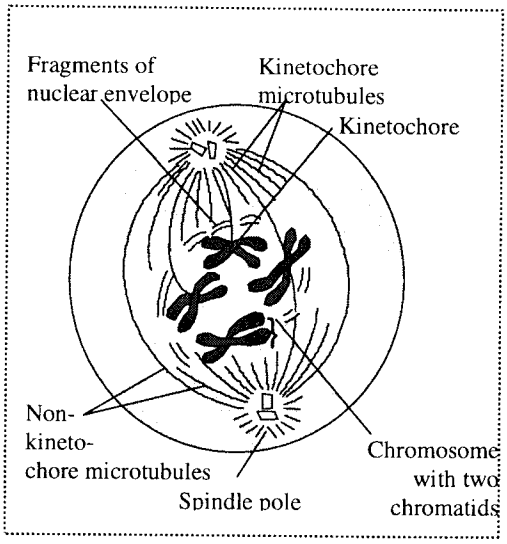
- Mitotic spindle forms. It is composed of microtubules between the two *centrosomes* or microtubule-organizing centers.
- Centrosomes move apart, apparently propelled along the nuclear surface by lengthening of the microtubule bundles between them.
- See also Campbell, Figure 12.5



Prometaphase

During prometaphase:

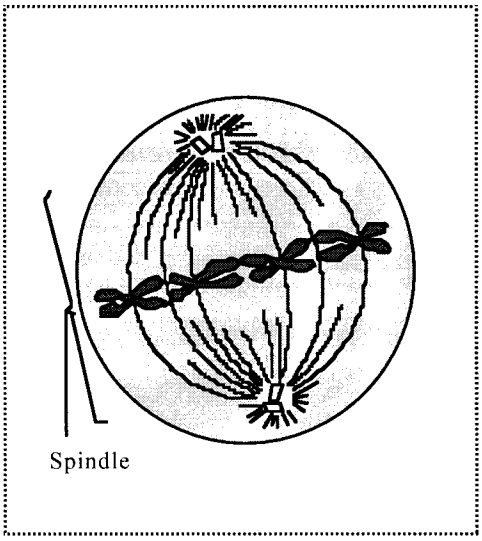
- Nuclear envelope fragments, which allows microtubules to interact with the highly condensed chromosomes.
- *Spindle fibers* (bundles of microtubules) extend from each pole toward the cell's equator.
- Each chromatid now has a specialized structure, the *kinetochore*, located at the centromere region.
- *Kinetochore microtubules* become attached to the kinetochores and put the chromosomes into agitated motion.
- *Nonkinetochore microtubules* radiate from each centrosome toward the metaphase plate without attaching to chromosomes. Nonkinetochore microtubules radiating from one pole overlap with those from the opposite pole.
- See also Campbell, Figure 12.5



Metaphase

During metaphase:

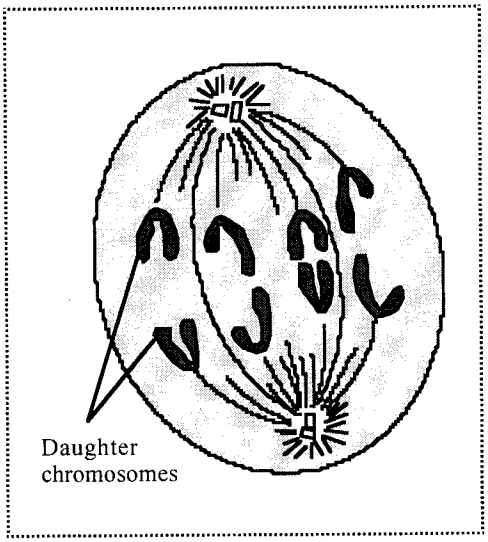
- Centrosomes are positioned at opposite poles of the cell.
- Chromosomes move to the *metaphase plate*, the plane equidistant between the spindle poles.
- Centromeres of all chromosomes are aligned on the metaphase plate.
- The long axis of each chromosome is roughly at a right angle to the spindle axis.
- Kinetochores of sister chromatids face opposite poles, so identical chromatids are attached to kinetochore fibers radiating from opposite ends of the parent cell.
- Entire structure formed by nonkinetochore microtubules plus kinetochore microtubules is called the *spindle*.
- See also Campbell, Figure 12.6



Anaphase

Anaphase is characterized by movement. It begins when paired centromeres of each chromosome move apart.

- Sister chromatids split apart into separate chromosomes and move towards opposite poles of the cell.
- Because kinetochore fibers are attached to the centromeres, the chromosomes move centromere first in a "V" shape.
- Kinetochore microtubules shorten at the kinetochore end as chromosomes approach the poles (see Campbell, Figure 12.7).
- Simultaneously, the poles of the cell move farther apart, elongating the cell.



At the end of anaphase, the two poles have identical collections of chromosomes.

Telophase and Cytokinesis

During telophase:

- Nonkinetochore microtubules further elongate the cell.
- Daughter nuclei begin to form at the two poles.
- Nuclear envelopes form around the chromosomes from fragments of the parent cell's nuclear envelope and portions of the endomembrane system.
- Nucleoli reappear.
- Chromatin fiber of each chromosome uncoils and the chromosomes become less distinct.

By the end of telophase:

- Mitosis, the equal division of one nucleus into two genetically identical nuclei, is complete.
- Cytokinesis has begun and the appearance of two separate daughter cells occurs shortly after mitosis is completed.

A lecture on mitosis may not last the entire period if it is limited to just a description of mitotic stages. Though it may be tempting to continue with meiosis during the same class period, it is not recommended. Students easily confuse the two processes because they are somewhat similar, so it helps to allow some time for students to assimilate the mitosis material, before discussing meiosis. It is effective to summarize with a comparison of the two processes after the topic of meiosis has been discussed.

B. The mitotic spindle distributes chromosomes to daughter cells: *a closer look*

Many of the events of mitosis depend on the formation of a *mitotic spindle.* The mitotic spindle forms in the cytoplasm from *microtubules* and associated proteins.

- Microtubules of the cytoskeleton are partially disassembled during spindle formation.
  - Spindle microtubules are aggregates of two proteins, α- and β-tubulin.
  - Spindle microtubules elongate by the adding tubulin subunits at one end.
- The assembly of spindle microtubules begins in the *centrosome* or microtubule organizing center.

- In animal cells, a pair of centrioles is in the center of the centrosome, but there is evidence that centrioles are not essential for cell division:
  - If the centrioles of animal cells are destroyed with a laser microbeam, spindles still form and function during mitosis.
  - Plant centrosomes generally lack centrioles.

The chronology of mitotic spindle formation is as follows:

Interphase. The centrosome replicates to form two centrosomes located just outside the nucleus.

Prophase. The two centrosomes move farther apart.

- Spindle microtubules radiate from the centrosomes, elongating at the end away from their centrosome.

Prometaphase. By the end of prometaphase, the two centrosomes are at opposite poles and the chromosomes have moved to the cell's midline.

- Each chromatid of a replicated chromosome develops its own *kinetochore*, a structure of proteins and chromosomal DNA on the centromere. The chromosome's two distinct kinetochores face opposite directions.
- Some spindle microtubules attach to the kinetochores and are called kinetochore microtubules.
- Some spindle microtubules extend from the centrosomes and overlap with those radiating from the cell's opposite pole. These are called nonkinetochore microtubules.

Kinetochore microtubules interact to: (1) arrange the chromosomes so kinetochores face the poles and (2) align the chromosomes at the cell's midline.

The most stable arrangement occurs when sister kinetochores are attached by microtubules to opposite spindle poles.

- Initially, kinetochore microtubules from one pole may attach to a kinetochore, moving the chromosome toward that pole. This movement is checked when microtubules from the opposite pole attach to the chromosome's other kinetochore.
- The chromosome oscillates back and forth until it stabilizes and aligns at the cell's midline.
- Microtubules can remain attached to a kinetochore only if there is opposing tension from the other side. It is this opposing tension that stabilizes the microtubule-kinetochore connection and allows the proper alignment and movement of chromosomes at the cell's midline.

Metaphase. All the duplicated chromosomes align on the cell's midline, or *metaphase plate.*

Anaphase. The chromosome's centromeres split and the sister chromatids move as separate chromosomes toward opposite ends of the cell. The kinetochore and nonkinetochore microtubules direct the segregation of the chromosomes (see Campbell, Figure 12.7).

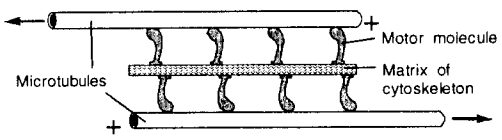
The kinetochore microtubules function in the poleward movement of chromosomes. Based on experimental evidence, the current model is that:

- Kinetochore microtubules shorten during anaphase by depolymerizing at their kinetochore ends; pulling the chromosomes poleward.
- The mechanism of this interaction between kinetochores and microtubules may involve microtubule-walking proteins similar to dynein that "walk" a chromosome along the shortening microtubules.

The function of the nonkinetochore microtubules:

- Nonkinetochore tubules elongate the whole cell along the polar axis during anaphase.

- These tubules overlap at the middle of the cell and slide past each other away from the cell's equator, reducing the degree of overlap.
- It is hypothesized that dynein cross-bridges may form between overlapping tubules to slide them past one another. Alternatively, motor molecules may link the microtubules to other cytoskeletal elements to drive the sliding.



- ATP provides the energy for this endergonic process.

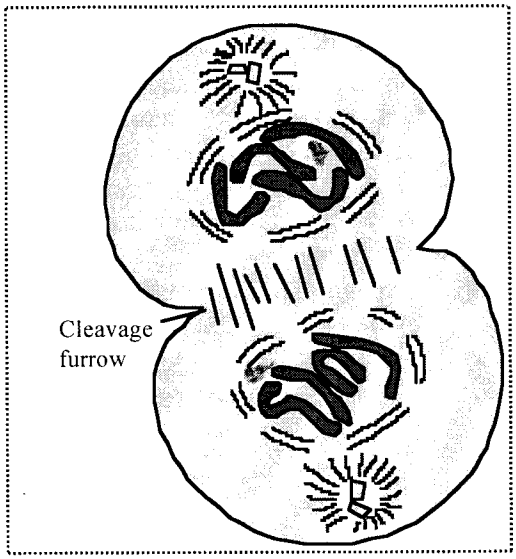
Telophase. At the end of anaphase, the duplicate sets of chromosomes are clustered at opposite ends of the elongated parent cell.

- Nuclei reform during telophase.
- Cytokinesis usually divides the cell's cytoplasm and is coincident with telophase of mitosis. In some exceptional cases, mitosis is not followed by cytokinesis (e.g., certain slime molds form multinucleated masses called *plasmodia*).

C. Cytokinesis divides the cytoplasm: *a closer look*

Cytokinesis, the process of cytoplasmic division, begins during telophase of mitosis. The process by which cytokinesis is accomplished differs in animal and plant cells. In animal cells, cytokinesis occurs by a process called *cleavage*:

- First, a *cleavage furrow* forms as a shallow groove in the cell surface near the old metaphase plate (see Campbell, Figure 12.8).
- A contractile ring of actin microfilaments forms on the cytoplasmic side of the furrow; this ring contracts until it pinches the parent cell in two.
- Finally, the remaining mitotic spindle breaks, and the two cells become completely separate.



Campbell, Figure 12.9 shows mitosis in a plant cell.

D. Mitosis in eukaryotes may have evolved from binary fission in bacteria

Because prokaryotes (bacteria) are smaller and simpler than eukaryotes and because they preceded eukaryotes on Earth by billions of years, it is reasonable to suggest that the carefully orchestrated process of mitosis had its origins in prokaryotes. Prokaryotes contain:

- Most genes in a single circular chromosome composed of a double-stranded DNA molecule and associated proteins.
- Only about 1/1000 the DNA of eukaryotes, but prokaryotic chromosomes still contain a large amount of DNA relative to the small prokaryotic cell. Consequently, bacterial chromosomes are highly folded and packed within the cell.

Prokaryotes reproduce by *binary fission*, a process during which bacteria replicate their chromosomes and equally distribute copies between the two daughter cells (see Campbell, Figure 12.10).

- The chromosome is replicated; each copy remains attached to the plasma membrane at adjacent sites.
- Between the attachment sites the membrane grows and separates the two copies of the chromosome.
- The bacterium grows to about twice its initial size, and the plasma membrane pinches inward.
- A cell wall forms across the bacterium between the two chromosomes, dividing the original cell into two daughter cells.

Certain modern algae display unusual patterns of nuclear division which may represent intermediate stages between bacterial binary fission and eukaryotic mitosis (see Campbell, Figure 12.11).

III. Regulation of the Cell Cycle

A. A molecular control system drives the cell cycle

Normal growth, development and maintenance depend on the timing and rate of mitosis. Various cell types differ in their pattern of cell division; for example:

- Human skin cells divide frequently.
- Liver cells only divide in appropriate situations, such as wound repair.
- Nerve, muscle and other specialized cells do not divide in mature humans.

The cell cycle is coordinated by the *cell-cycle control system,* a molecular signaling system which cyclically switches on the appropriate parts of the cell-cycle machinery and then switches them off (see Campbell, Figure 12.13).

The cell-cycle control system consists of a cell-cycle molecular clock and a set of *checkpoints,* or switches, that ensure that appropriate conditions have been met before the cycle advances. When the control system malfunctions, as will be seen later, cancer may result.

The cell-cycle control system has checkpoints in the G_1, G_2, and M phases of the cell cycle.

- Signals registered at the checkpoints report the status of various cellular conditions (e.g., Is the environment favorable? Is the cell big enough? Are all DNA replicated?
- Checkpoints integrate a variety of internal (intracellular) and external (extracellular) information.
- For many cells, the G_1 checkpoint (known as the "restriction point" in mammalian cells) is the most important.
  - A go-ahead signal usually indicates that the cell will complete the cycle and divide.
  - In the absence of a go-ahead signal, the cell may exit the cell cycle, switching to the nondividing state called *G_0 phase.*
  - Many cells of the human body are in the G_0 phase. Muscle and nerve cells will remain in G_0 until they die. Liver cells may be recruited back to the cell cycle under certain cues, such as growth factors.

The ordered sequence of cell cycle events is synchronized by rhythmic changes in the activity of certain *protein kinases.*

- Protein kinases are enzymes that catalyze the transfer of a phosphate group from ATP to a target protein.

- Phosphorylation, in turn, induces a conformational change that either activates or inactivates a target protein.
- Changes in target proteins affect the progression through the cell cycle.

Cyclical changes in kinase activity are controlled by another class of regulatory proteins called *cyclins*.

- These regulatory proteins are named cyclins, because their concentrations change cyclically during the cell cycle.
- Protein kinases that regulate cell cycles are *cyclin-dependent kinases* (*Cdks*); they are active only when attached to a particular cyclin.
- Even though Cdk concentration stays the same throughout the cell cycle, its activity changes in response to the changes in cyclin concentration (see Campbell, Figure 12.14a).

An example of a cyclin-Cdk complex is *MPF (maturation promoting factor)*, which controls the cell's progress through the G_2 checkpoint to mitosis (see Campbell, Figure 12.14b).

Cyclin's rhythmic changes in concentration regulate MPF activity, and thus acts as a mitotic clock that regulates the sequential changes in a dividing cell.

- Cyclin is produced at a uniform rate throughout the cell cycle, and it accumulates during interphase.
- Cyclin combines with Cdk to form active MPF, so as cyclin concentration rises and falls, the amount of active MPF changes in a similar way.
- MPF phosphorylates proteins that participate in mitosis and initiates the following process:
  - Chromosome condensation during prophase
  - Nuclear envelope dispersion during prometaphase
- In the latter half of mitosis, MPF activates proteolytic enzymes.
  - The proteolytic enzymes destroy cyclin which leads to the reduction of MPF activity (the Cdk portion of MPF is not degraded).
  - The proteolytic enzymes also are involved in driving the cell cycle past the M-phase checkpoint, which controls the onset of anaphase.
- Continuing cyclin synthesis raises the concentration again during interphase. This newly synthesized cyclin binds to Cdk to form MPF, and mitosis begins again.

Rhythmic changes in different cyclin-Cdk complexes regulate other cell cycle stages.

B. Internal and external cues help regulate the cell cycle

The cell-cycle control system integrates a variety of internal (intracellular) and external (extracellular) information. Knowledge of the chemical signaling pathways that transduce this information into modulation of the cell-cycle machinery is just emerging.

The kinetochores provide internal cues that signal the M-phase checkpoint about the status of chromosome-spindle interactions. All chromosomes must be attached to spindle microtubules before the M-phase checkpoint allows the cycles to proceed to anaphase. This ensures that daughter cells do not end up with missing or extra chromosomes.

- Kinetochores not attached to spindles trigger a signaling pathway that keeps the anaphase promoting complex (APC) in an inactive state.
- Once all kinetochores are attached, the wait signal stops, and the APC complex becomes active. The APC complex contains proteolytic enzymes which break down cyclin.

Using tissue culture, researchers have identified several external factors, both chemical and physical, that can influence cell division:

1. Chemical factors

- If essential nutrients are left out of the culture medium, cells will not divide.
- Specific regulatory substances called *growth factors* are necessary for most cultured mammalian cells to divide, even if all other conditions are favorable. For example:
  - Binding of platelet-derived growth factor (PDGF) to cell membrane receptors, stimulates cell division in fibroblasts. This regulation probably occurs not only in cell culture, but in the animal's body as well—a response that helps heal wounds.
  - Other cell types may have membrane receptors for different growth factors or for different combinations of several growth factors.

2. Physical factors

- Crowding inhibits cell division in a phenomenon called *density-dependent inhibition*. Cultured cells stop dividing when they form a single layer on the container's inner surface. If some cells are removed, those bordering the open space divide again until the vacancy is filled (see Campbell, Figure 12.15a).
  - Density-dependent inhibition is apparently a consequence of the fact that quantities of nutrients and growth regulators may be insufficient to support cell division, if cell density is too high.
  - Most animal cells also exhibit anchorage dependence. To divide, normal cells must adhere to a substratum, such as the surface of a culture dish or the extracellular matrix of a tissue. anchorage is signaled to the cell-cycle control system via pathways involving membrane proteins and elements of the cytoskeleton that are linked to them.
- Density-dependent and anchorage-dependent inhibition probably occur in the body's tissues as well as in cell culture. Cancer cells are abnormal and do not exhibit density-dependent or anchorage-dependent inhibition.

C. Cancer cells have escaped from cell-cycle controls

Cancer cells do not respond normally to the body's control mechanisms. They divide excessively, invade other tissues and, if unchecked, can kill the whole organism.

- Cancer cells in culture do not stop growing in response to cell density (density-dependent inhibition); they do not stop dividing when growth factors are depleted (see Campbell, Figure 12.15b).
- Cancer cells may make growth factors themselves.
- Cancer cells may have an abnormal growth factor signaling system.
- Cancer cells in culture are immortal in that they continue to divide indefinitely, as long as nutrients are available. Normal mammalian cells in culture divide only about 20 to 50 times before they stop.
- Cancer cells that stop dividing do so at random points in the cycle instead of at checkpoints.

Abnormal cells which have escaped normal cell-cycle controls are the products of mutate or *transformed* normal cells.

The immune system normally recognizes and destroys transformed cells that have converted from normal to cancer cells.

- If abnormal cells evade destruction, they may proliferate to form a *tumor*, an unregulated growing mass of cells within otherwise normal tissue.

- If the cells remain at this original site, the mass is called a *benign tumor* and can be completely removed by surgery.
- A *malignant tumor* is invasive enough to impair normal function of one or more organs of the body. Only an individual with a malignant tumor is said to have cancer (see Campbell, Figure 12.16).

Properties of malignant (cancerous) tumors include:

- Anomalous cell cycle; excessive proliferation
- May have unusual numbers of chromosomes
- May have aberrant metabolism
- Lost attachments to neighboring cells and extracellular matrix—usually a consequence of abnormal cell surface changes.

Cancer cells also may separate from the original tumor and spread into other tissues, possibly entering the blood and lymph vessels of the circulatory system.

- Migrating cancer cells can invade other parts of the body and proliferate to form more tumors.
- This spread of cancer cells beyond their original sites is called *metastasis*.
- If a tumor metastasizes, it is usually treated with radiation and chemotherapy, which is especially harmful to actively dividing cells.

Researchers are beginning to understand how a normal cell is transformed into a cancerous one. Although the causes of cancer may be diverse, cellular transformation always involves the alteration of genes that somehow influence the cell-cycle control system.

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