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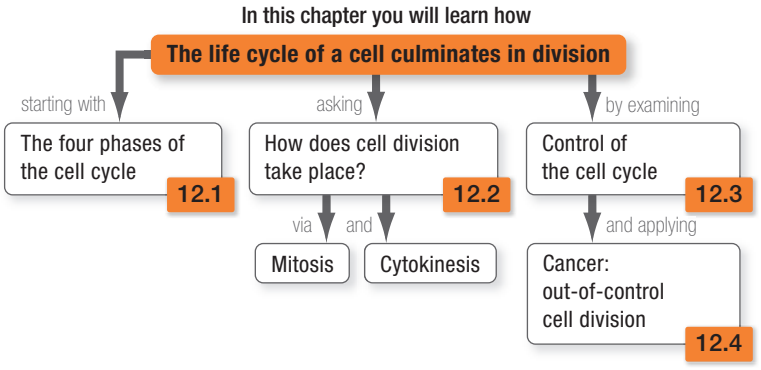
12 The Cell Cycle

This cell, from a hyacinth plant, is undergoing a type of nuclear division called mitosis. Understanding how mitosis occurs is a major focus of this chapter.



The cell theory maintains that all organisms are made of cells and that all cells arise from preexisting cells (Chapter 1). Although the cell theory was widely accepted among biologists by the 1860s, most thought that new cells arose within preexisting cells by a process that resembled the growth of mineral crystals. But Rudolf Virchow proposed that new cells are formed by the splitting of preexisting cells—that is, by **cell division.**

In the late 1800s, microscopic observations of newly developing organisms, or **embryos,** confirmed Virchow's hypothesis. Plants and animals start life as single-celled embryos and grow through a series of cell divisions.

Early studies revealed two fundamentally different ways that nuclei divide before cell division: meiosis and mitosis. In animals, **meiosis** leads to the production of sperm and eggs, which are the male and female reproductive cells termed **gametes.** Meiosis is equally important in other eukaryotes, but the cells produced are not gametes. In plants, for example, the products of meiosis are **spores. Mitosis** leads to the production of the other cell types, referred to as **somatic** (literally, "body-belonging") **cells.** (You can see how meiosis and mitosis are related to each other and to the transmission of genetic information in the Big Picture on pages 408–409.)

BIG PICTURE

This chapter is part of the Big Picture. See how on pages 408–409.

Mitosis and meiosis are usually accompanied by **cytokinesis**—the division of the cytoplasm into two distinct cells. When cytokinesis is complete, a so-called parent cell has given rise to two daughter cells.

Mitotic and meiotic cell divisions are responsible for one of the five fundamental attributes of life: reproduction (see Chapter 1). But even though mitosis and meiosis share many characteristics, they are fundamentally different. During mitotic division, the genetic material is copied and then divided equally between two cells. This is referred to as cellular *replication*, since the daughter cells are genetically identical to the parent cell. In contrast, meiosis results in daughter cells that are genetically different from each other and that have half the amount of hereditary material as the parent cell.

This chapter focuses on mitotic cell division; meiotic cell division is the subject of another chapter (Chapter 13). Let's begin with a look at the key events in a cell's life cycle, continue with an in-depth analysis of mitosis and the regulation of the cell cycle, and end by examining how uncontrolled cell division can lead to cancer.

12.1 How Do Cells Replicate?

For life on Earth to exist, cells must replicate. The basic steps in cellular replication are **(1)** copying the DNA (deoxyribonucleic acid), **(2)** separating the copies, and **(3)** dividing the cytoplasm to create two complete cells. This chapter focuses on a process that has been studied for well over a century: how eukaryotic cells replicate. Like much work in biology, the research on eukaryotic cell replication began with simple observations of the process.

What Is a Chromosome?

As studies of cell division in eukaryotes began, biologists found that certain chemical dyes made thread-like structures visible within nuclei. In 1879, Walther Flemming used a dye made from a coal tar to observe these structures and watch them change in the dividing cells of salamander embryos. The threads first appeared in pairs just before cell division and then split to produce single, unpaired threads in the daughter cells. Flemming introduced the term "mitosis," from the Greek *mitos* ("thread"), to describe this process.

Others studied the roundworm *Ascaris* and noted that the number of threads in a cell was the same before and after mitotic division. All of these cells had the same number of threads.

In 1888, Wilhelm Waldeyer coined the term **chromosome** ("coloured body") to refer to these thread-like structures (visible in the chapter-opening photo). Research carried out since then has shown that a chromosome consists of a single long DNA double helix that is wrapped around proteins, called **histones,** in a highly organized manner (see Chapter 19). DNA encodes the cell's hereditary information, or genetic material. A **gene** is a region of DNA in a chromosome that codes for a particular protein or ribonucleic acid (RNA).

Before mitosis, each chromosome is replicated. As mitosis starts, the chromosomes condense into compact structures that can be moved around the cell efficiently. Then one copy of each chromosome is distributed to each of two daughter cells.

Figure 12.1 illustrates an unreplicated chromosome, the same chromosome after it has been replicated, and the replicated chromosome that has condensed at the start of mitosis. Each of the double-stranded DNA copies in a replicated chromosome is called a **chromatid.** The two chromatids are held together by proteins at a large DNA region called the **centromere** ("centre part"). Centromeres are often, but not always, found in the

Unreplicated chromosome

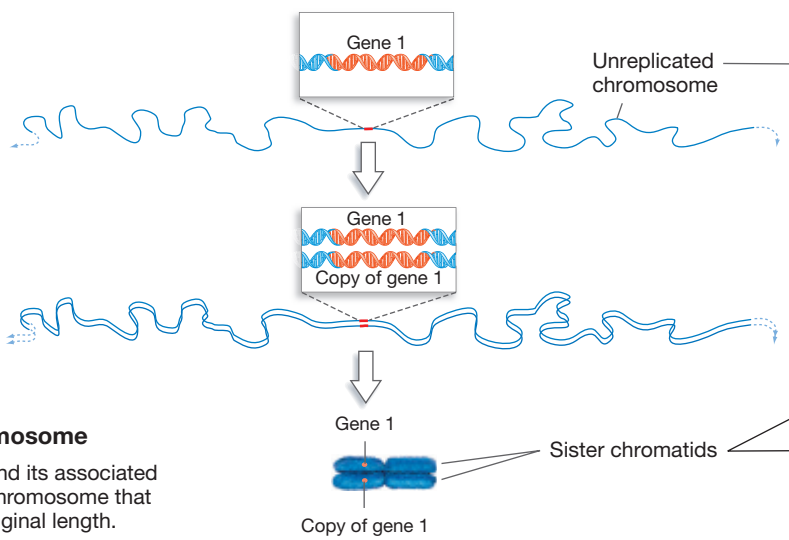
Consists of a single, long DNA double helix wrapped around proteins (which are too small to distinguish at this scale).

Replicated chromosome

Consists of two copies of the same DNA double helix.

Condensed replicated chromosome

Consists of DNA condensed around its associated proteins, resulting in a compact chromosome that is 10 000 times shorter than its original length.



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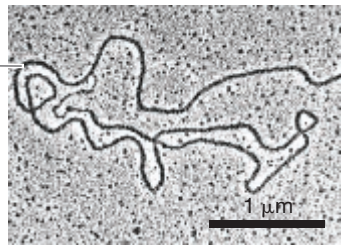

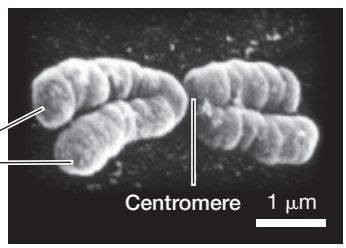

Dr. Gopal Murti/Photo Researchers, Inc./Science Source

Figure 12.1 Changes in Chromosome Morphology. After chromosomes replicate, the two identical copies of the double-stranded DNA are attached to each other along their entire length. Early in mitosis, replicated chromosomes condense and sister chromatids remain attached at a region called the centromere.

middle of chromosomes. Even though a replicated chromosome consists of two chromatids, it is still considered a single chromosome. During mitosis the "sister" chromatids are separated, at which time they become "daughter" chromosomes.

✔ **If you understand how a chromosome can be made of one or two pieces of DNA, you should be able to draw a model to represent a cell with two different chromosomes before and after the chromosomes are replicated. Use a circle to represent the cell and one of the models above to represent the chromosomes. Label the chromatids.**

Cells Alternate between M Phase and Interphase

The division of eukaryotic cells is like a well-choreographed stage performance. The most visually stimulating part of the show occurs when cells are in the process of separating their chromosomes, called **M** (*m*itotic or *m*eiotic) **phase.** Stained chromosomes can be observed with a light microscope when they condense into compact structures during M phase.

The rest of the time, the cell is in **interphase** ("between phase"). No dramatic changes in the nucleus are visible by light microscopy during interphase. The chromosomes uncoil into the extremely long, thin structures shown in Figure 12.1 and no longer appear as individual threads. However, this does not mean that the cell is idle. Interphase is an active time: The cell is either growing and preparing to divide or fulfilling its specialized function in a multicellular individual. Cells actually spend most of their time in interphase.

The Discovery of S Phase

Once M phase and interphase were identified by microscopy, researchers could start assigning roles to these distinct phases. They could see that the separation of chromosomes and cytokinesis take place during M phase, but when are the chromosomes replicated?

To answer this question, researchers needed to distinguish cells that were making copies of their DNA from those that were not. They were able to do this by adding radioactive phosphorus, in the form of phosphates, to cells. Those cells that were synthesizing DNA would incorporate the radioactive isotope into nucleotides. (See Chapter 4 to review where phosphates are in DNA.) There were three steps in this procedure:

1. Label DNA as chromosomes were being replicated.
2. Wash away any radioactive phosphorus that hadn't been incorporated and remove RNA, which would also incorporate phosphorus.
3. Visualize the radioactive, newly synthesized DNA by exposing the treated cells to X-ray film. Emissions from radioactive phosphorus create black dots in the film.

The scientists who found success with this technique were Alma Howard and Stephen Pelc. Howard was born in Montreal and earned her Ph.D. at McGill before moving to England to collaborate with Pelc. In 1951, they performed this procedure and found black dots—indicating active DNA synthesis—in some interphase cells, but not in M-phase cells. This result showed that DNA replication occurs during a period in interphase. Several years later, this result was verified using radioactive thymidine, which is incorporated into DNA but not RNA.

Thus, biologists had identified a new stage in the life of a cell. They called it **S** (or synthesis) **phase.** S phase is part of interphase. The process of copying the genetic material is separated, in time, from the partitioning of replicated chromosomes during M phase.

Howard and Pelc coined the term **cell cycle** to describe the orderly sequence of events that leads a eukaryotic cell through the duplication of its chromosomes to the time it divides.

The Discovery of the Gap Phases

In addition to discovering S phase, Howard and Pelc made another key observation—not all interphase cells were radioactive. This meant that there was at least one "gap" in interphase when DNA was not being replicated.

Howard and Pelc, along with researchers in other labs, followed up on these early results by asking where S phase was positioned in interphase. There were three possible scenarios:

1. The cell cycle has a single gap between the end of M phase and the start of S phase.
2. The cell cycle has a single gap between the end of S phase and the start of M phase.
3. Two gaps exist, one before and one after S phase.

To address which of these scenarios, if any, was correct, many experiments were done on cells in culture. Cultured cells are powerful experimental tools because they can be manipulated much more easily than cells in an intact organism (see **BioSkills 9**). In most of these experiments, researchers used cultures that were *asynchronous*, meaning that the cells were randomly distributed in various stages of the cell cycle.

To understand the value of asynchronous cultures, imagine the cell cycle as a clock. Every complete rotation of the second hand around the clock would represent one cell division, and each tick would represent a different point in the cycle. At any given time, an asynchronous culture would have at least one cell at each of the ticks on the clock. As time passed, these cells would move around this cell-cycle clock at the same rate and in the same direction.

In one experiment, researchers added radioactively labelled thymidine to the cells in a human cell culture. A short time later, they stopped the process by flooding the solution surrounding the cultured cells with nonradioactive thymidine, which washed away any radioactive thymidine that had not already been incorporated into DNA. This pulse—chase approach (introduced in Chapter 7) labelled only those cells that were in S phase during the radioactive pulse. Imagine these radioactive cells moving together through the cell cycle like the second hand moving around a clock.

Once the pulse ended, the researchers took samples of cells from the culture at different times during the chase. In each sample, they recorded how many radioactive cells were undergoing mitosis, meaning how many cells that were in S phase during the pulse had entered M phase. **Figure 12.2** summarizes the results of this experiment.

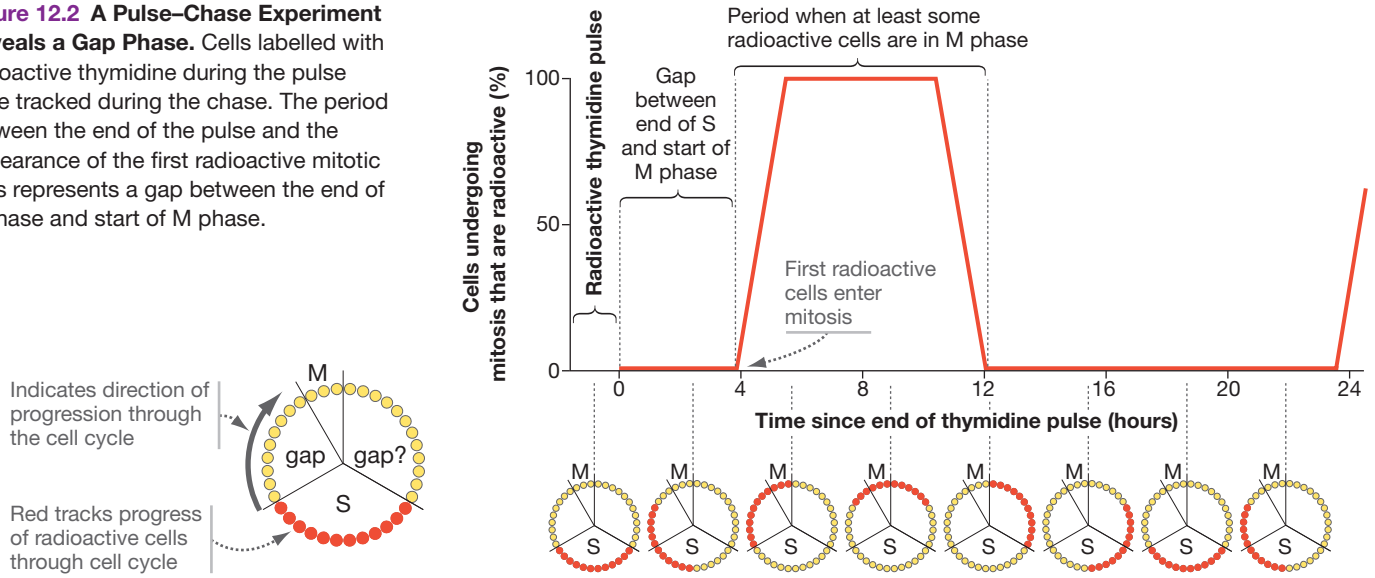

Figure 12.2 A Pulse–Chase Experiment Reveals a Gap Phase. Cells labelled with radioactive thymidine during the pulse were tracked during the chase. The period between the end of the pulse and the appearance of the first radioactive mitotic cells represents a gap between the end of S phase and start of M phase.

One striking result emerged early on: None of the radioactive cells started mitosis immediately. Because the cultures were asynchronous, at least some of the cells must have been at the very end of their S phase when they were exposed to the pulse. If S phase were immediately followed by M phase, then some of these radioactive cells would have entered M phase just as the chase began. Instead, it took several hours before any of the radioactive cells began mitosis.

The time between the end of the pulse and the appearance of the first radioactive mitotic nuclei corresponds to a gap between the end of S phase and the beginning of M phase. This gap is a period when chromosome replication is complete but mitosis has not yet begun. The graph in Figure 12.2 shows how cells labelled with radioactive thymidine can be tracked as they progress through M phase.

✔ **If you understand how the pulse–chase approach was used in Figure 12.2, you should be able to predict how the graph would appear if the *y*-axis represented the percentage of all cells that were radioactive, not just the radioactive cells undergoing mitosis.**

This result narrowed the possible scenarios for the organization of the cell cycle: There could be either one gap between the end of S phase and the start of M phase, or two gaps flanking S phase. Which scenario represents the eukaryotic cell cycle? Once researchers determined the lengths of the S and M phases, they found that the combined time, including the gap between them, was shorter than the length of the cell cycle. This discrepancy indicated that there must be an additional gap between the end of M phase and the start of S phase.

The cell cycle was thus finally mapped out. The gap between the end of M phase and the start of S phase is called **G_1 phase.** The second gap, between the end of S phase and the start of M phase, is called **G_2 phase.**

The Cell Cycle

Figure 12.3 pulls these results together into a comprehensive view of the cell cycle. The cell cycle involves four phases: M phase and an interphase consisting of the G_1, S, and G_2 phases. In the cycle diagrammed here, G_1 phase is about twice as long as G_2 phase, but their actual durations vary depending on the cell type and growth conditions.

Why do the gap phases exist? In multicellular organisms, cells perform their functional roles mostly during G_1 phase. G_1 is also the period when the cell "decides" to begin replication and transitions to S phase (as will be explained in Section 12.3). Before mitosis can take place, a cell uses G_2 phase to prepare for M phase. The time spent in both G_1 and G_2 allows the cell to grow and replicate organelles so it will be able to divide into two cells that can function normally.

Now let's turn to M phase. Once the genetic material has been copied in S phase, how is it divided between daughter cells?

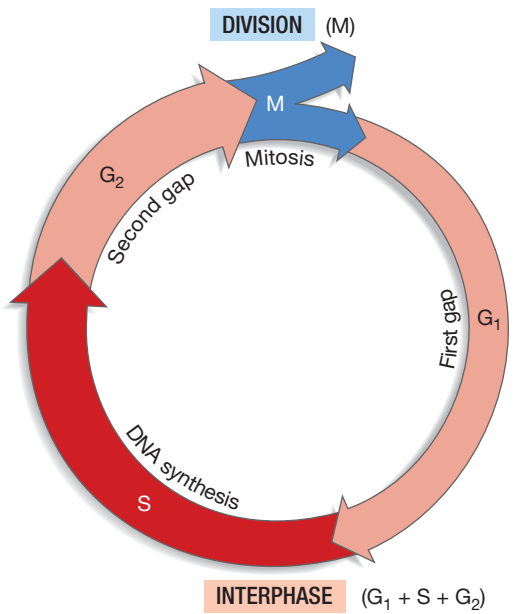

Figure 12.3 The Cell Cycle Has Four Phases. The duration of the G_1 and G_2 phases varies dramatically among cells and organisms.