**Cell Division Is Essential to Life**

Cell division is the only way single-celled organisms can reproduce.Multicellular organisms need cell division to grow and to replace dead or damaged cells.

In humans, many types of cells divide. For example, repeated divisions allow a single fertilized egg cell to develop into an adult with more than 37 trillion cells.

After growth, division remains important in normal cell turnover, such as in our skin and gut, where cells are continuously renewed. Other cells have to divide to heal wounds like skin cuts or broken bones.

Learn more about cell division on the following slides by pressing the arrow at the top right corner. Then close this tab to explore the cell cycle.

**Cells Divide, Differentiate, or Die**

Cells divide in response to specific molecular signals, typically from growth factors. But cells can also receive signals from other molecules that cause cells to differentiate or die.

Cells divide to produce two identical daughter cells. Cells stop dividing to specialize in structure and function, a process called differentiation. Once differentiated, some cells may divide again under certain conditions.

Cells can also undergo programmed cell death, or apoptosis, a process that eliminates unnecessary cells during development and removes unhealthy or damaged cells in the mature organism.

**Cell Division, Differentiation, and Death Are Carefully Balanced Processes**

To remain healthy, it's critical for an organism to maintain the right number of cells. This is achieved primarily by regulating the "cell cycle." Cell cycle regulators are molecular signals that may stimulate or halt cell division, instruct cells to differentiate, or initiate cell death.

**Cell Cycle Regulators Can Send Wrong Signals**

If regulators don’t function properly, an organism may end up with too few or too many cells. This can cause problems of varying severity—from harmless hair loss or the growth of warts to the development of life-threatening tumors.

too few cells-hair loss

too many cells- warts, tumors

The eukaryotic cell cycle is a sequence of events that culminate in cell division.

The cell cycle events are regulated by various checkpoint proteins, which either stimulate or inhibit cell division until conditions are right to proceed to the next phase.

When a cell specializes (or differentiates), it generally stops dividing and "exits" the cell cycle. Once differentiated, some cells can divide again.

Cancer is the uncontrolled division of cells, which results from an improperly regulated cell cycle.

**Cell Cycle Phases**

Each time the cell divides into two, it goes through a sequence of events that may include **growth**, **DNA replication**, **preparation to divide**, and finally **division**. We collectively refer to these events as the "cell cycle," and to the four major events as "phases." The cycle begins right after division and continues until the cell divides into two daughter cells, each with a complete set of chromosomes.

Specialized proteins called "cell cycle regulators" or "checkpoint proteins" regulate the progression from one phase of the cell cycle to the next. The progression through these checkpoints is a strictly regulated process that usually works without errors. When errors do occur, they can have catastrophic consequences, including the development of cancer. Cell division occurs during **Mitosis**

**Interphase**

Together, **G1**, **S**, and **G2** make up interphase: the period during which a cell grows and replicates its DNA. A dividing cell repeatedly cycles through interphase and mitosis; in other words, it goes through cycles of growth and division.

**G1 Phase**

***First Gap Phase:*** The newly divided cell enters this phase right after completing cell division (or mitosis). During G1, the cell increases in size and prepares to replicate its DNA.

**G1-Checkpoint: Rest or Divide?**  
  
Toward the end of G1, the cell has to be sufficiently healthy to replicate its DNA. If the DNA is undamaged and enough resources are available for the cell to keep growing and divide, growth signals will stimulate the cell to proceed to the DNA synthesis, or S, phase. Otherwise, either the cell dies or it enters a resting state, also referred to as G0 phase.  
  
Checklist summary:  
**✓** No DNA damage  
**✓** Sufficient resources

**G0 Phase**

Toward the end of the G1 phase, a cell can "exit" the cell cycle when it receives a signal to differentiate, or when resources are insufficient to grow and divide. Whether or not a cell exits the cell cycle depends on the organism’s stage in development, the type of cell, and the resources available. The cell is then said to be in G0—a resting, or nondividing, stage.

Many nondividing, fully differentiated cells in the body, such as neurons and muscle cells, remain in G0 and never reenter the cycle. But in some tissues, such as the liver, injury can cause cells to leave G0 and progress through the cell cycle to divide.

**S Phase**

***Synthesis Phase***: The cell replicates its DNA. At the end of this phase, the cell has two complete sets of chromosomes.

**S-Checkpoint: DNA OK?**  
  
Throughout the S phase, DNA is continuously monitored for replication errors. If DNA synthesis progresses without errors, growth signals will stimulate the cell to proceed to G2, during which the cell matures.  
  
Checklist summary:

**✓** No errors during DNA replication

**G2 Phase**

***Second Gap Phase***: The cell continues to grow and prepares for division.

**G2-Checkpoint: Fully Equipped?**  
  
To proceed to the next phase, all chromosomes have to be fully replicated and contain no other types of damage. Only then can it enter mitosis, or M phase, and divide.  
  
Checklist summary:  
**✓** DNA without damage  
**✓** Chromosome set complete  
**✓** Enough cell components

**Mitosis**

During mitosis, the DNA that makes up each chromosome becomes tightly packed. Because the DNA was replicated during S phase, each chromosome contains two copies (or chromatids) that are bound together at the centromere. Under a microscope, they can be seen as the familiar four-armed X shapes. The chromosomes line up in the middle of the dividing cell, and each chromosome copy is pulled to opposite ends of the cell. Each half of the cell now has a complete set of chromosomes, and the cell can divide into two daughter cells.

**M Phase**

***Mitosis***: In this last phase of the cell cycle, the cell stops growing and divides into two daughter cells, each with the same number of chromosomes.

**M-Checkpoint:**

**Are Any Sister Chromatids Unattached?**

For mitosis to proceed correctly, the two copies in a duplicated chromosome (each called a sister chromatid) should both be attached to the mitotic spindle. If they are, mitosis continues: The two sister chromatids separate, becoming two chromosomes. The two identical sets of chromosomes move to opposite ends of the dividing cell.  
  
Checklist summary:

**✓** All sister chromatids attached to mitotic spindle

**Cell Cycle Regulators and Cancer**

Cell cycle regulators are proteins that control the progression of a cell through the cell cycle and can either stimulate or inhibit cell cycle progression. Genes that encode these proteins are referred to as **proto-oncogenes** and tumor **suppressor genes**, respectively, and mutations in these genes can lead to cancer (see “Cancer Overview” tab).

**Stimulating** proteins (encoded by proto-oncogenes)

**Inhibitory** proteins (encoded by tumor suppressor genes)

The most important cell cycle regulators are the **cyclin-dependent kinases (CDKs)**. Kinases are enzymes that add a phosphate to other proteins to activate or inhibit their function—a process known as phosphorylation. CDKs are always present in the cell but become active only when they are bound to other proteins called **cyclins**, whose concentration inside the cell cycles up and down, depending on the phase of the cycle. As a result, the concentration of different CDK-cyclin complexes fluctuates, regulating the progression through each phase like clockwork. Some proteins activate CDK-cyclin complexes, **stimulating** the cell cycle. Others inactivate CDK-cyclins or prevent their activation, which **inhibits** cell cycle progression.

**G1 Checkpoint: Stimulating Proteins**

G1-phase CDK-cyclins drive cells through G1 into S phase.  
  
Growth factors—small proteins that circulate in the bloodstream—stimulate signals inside cells that cause G1-phase cyclin concentrations to rise. The cyclins bind to the appropriate CDKs, which then phosphorylate other proteins to drive the cell cycle into S phase.

**G1 Checkpoint: Inhibiting Proteins**

An important protein at the G1 checkpoint is **p53**. If DNA is damaged, p53 stops the progression to S phase by inhibiting the G1 CDK-cyclin complex. Stalling the cell cycle allows for the DNA to be repaired, but if the damage is excessive and can’t be fixed, p53 can initiate cell death, or apoptosis. p53 plays a similar role at the G2 checkpoint.  
  
**Retinoblastoma protein (Rb)** prevents cells from entering S phase in the absence of signals from growth factors. When growth-stimulating signals are present, they activate CDK-cyclins, which phosphorylate Rb and inhibit its function.  
  
The genes that encode p53 and Rb are called **tumor suppressor genes**, because they suppress or prevent the development of tumors by keeping cell division in check. Mutations that inactivate the tumor suppressor function of p53 and Rb may then lead to cancer (or tumor) development. These mutations are recessive and have to occur on both alleles for cell cycle regulation to be affected. Mutated Rb and p53 genes are associated with the development of many cancer types.

**S Checkpoint: Stimulating Proteins**

Once the concentration of S-phase cyclins reaches a threshold in the cell, **CDK-cyclin** complexes signal the cell to duplicate its DNA. Growth factors present at the G1/S transition typically stimulate the rise in S-phase cyclin concentrations.

**S Checkpoint: Inhibiting Proteins**

If DNA damage or errors in DNA replication occur during the replication process, several proteins recognize these errors and trigger signals that stall the cell cycle until the problem is fixed.

For example, breaks in the two DNA strands during replication activate the **ataxia telangiectasia mutated (ATM)** protein, which halts the cell cycle and activates other proteins involved in repairing the break. One of the proteins that can become activated is called **Breast Cancer 1 (BRCA1)**. It interacts with a series of proteins to mediate either DNA repair or, if the damage is too excessive, cell death.

The genes that encode ATM and BRCA1 are tumor suppressor genes. When mutated, both *ATM* and *BRCA1* can contribute to the development of cancer. People who inherit mutations in the *ATM* gene are at high risk of developing cancer, particularly leukemia and lymphomas. Mutations in the *BRCA1* gene are involved in the development of breast and ovarian cancers.

**G2 Checkpoint: Stimulating Proteins**

During G2, the concentration of mitotic (M-phase) cyclins rises, and they bind to the appropriate CDKs. If there is DNA damage or incomplete replication, a number of inhibitory proteins prevent activation of the CDK-cyclin complex. Once the damage is fixed, the CDK-cyclin complex is activated and the cell can progress from G2 to M phase.

**G2 Checkpoint: Inhibiting Proteins**

If DNA is damaged, the **p53** protein will stop cell cycle progression until the damage is repaired. If the damage is excessive and can’t be fixed, p53 can initiate cell death, or apoptosis. p53 also acts as a checkpoint protein at the G1 checkpoint.

**M Checkpoint: Stimulating Proteins**

M-phase cyclins and CDKs activate a protein complex called the **anaphase-promoting complex/cyclosome (APC/C)**. APC/C is activated when all chromosomes are attached to the mitotic spindle during **metaphase**—the stage in mitosis during which chromosomes are tightly packed, or condensed, and aligned at the equator of the cell. The active APC/C stimulates the destruction of proteins that hold the two copies of each chromosome (or chromatids) together at the centromere, allowing the chromatids to separate and move to opposite sides of the cell. The stage of mitosis when this separation occurs is called **anaphase**.

**M Checkpoint: Inhibiting Proteins**

M-checkpoint inhibitory proteins include two **mitotic arrest deficient (MAD)** proteins. When chromosomes are not properly attached to the mitotic spindle, MAD proteins inhibit the **anaphase-promoting complex/cyclosome (APC/C)**, preventing entry into anaphase. This prevents chromatids from being pulled apart into two daughter cells with an unequal number of chromosomes—one with too few and one with too many.

**Cancer and the Cell Cycle**

Cancer results from an improperly regulated cell cycle. As a result, cells replicate indefinitely and form tumors.

Too much cell division

Too little cell death

**Unregulated Cell Division and Cancer Development**

Uncontrolled division of cells is caused by mutations affecting proteins that normally regulate the cell cycle.

Watch what happens if a mutation disrupts the normal life cycle of a cell.

**Mutations in Cell Cycle Regulators Contribute to Cancer**

Proteins that normally *stimulate* the cell cycle are encoded by **proto-oncogenes**. Mutated versions of these genes, called **oncogenes**, are analogous to putting the foot on the accelerator, increasing stimulation. **Tumor suppressor genes** produce proteins that normally *inhibit* the cell cycle. Mutations in these genes can cause a loss of inhibition, which is similar to taking the foot off the brake. Both types of mutations lead to uncontrolled cell division.

**Mutations in Cell Cycle Regulators Contribute to Cancer**

Mutations in proto-oncogenes cause a *gain* of function and are dominant: a mutation in just *one* allele will produce a protein that puts the cell cycle into overdrive. Tumor suppressor gene mutations, which result in a *loss* of function, are recessive: *both* alleles have to be mutated for the cell cycle to be affected.