Cell Cycle Regulation

Student Guide

Supplemental reading for cat# M3023

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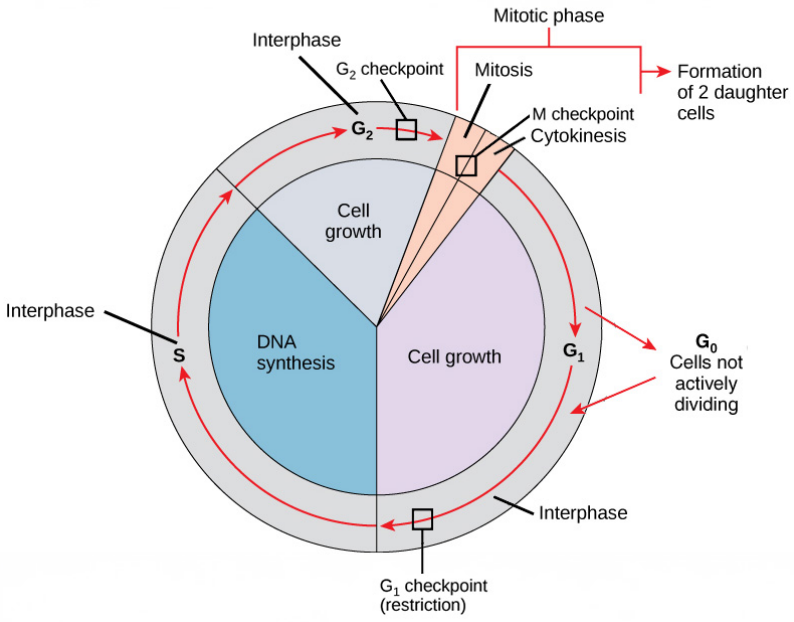


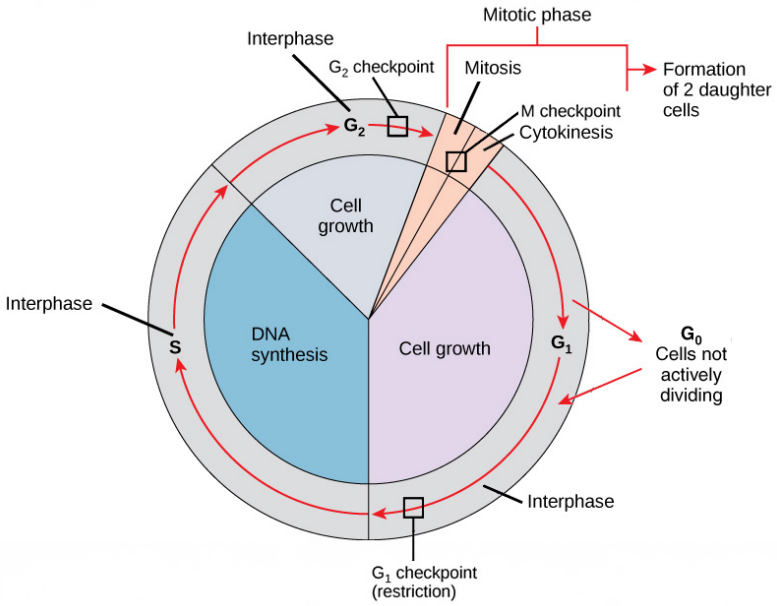
Importance of Cell Cycle Regulation and Consequences of Failure

As we discussed earlier, the cell cycle is a carefully controlled assembly line, where a cell grows, copies its DNA, and divides into two new cells. To make sure everything happens correctly and at the right time, the cell cycle is regulated by special checkpoints and proteins that function at those checkpoints. Regulation means controlling the process to ensure that the cell only moves to the next step when the previous step has been properly completed. Just as you should not start driving if the traffic light is red, a cell should not move to the next stage unless certain conditions are met. Let's look at the importance of cell cycle regulation and the consequences of failure.

There are three main checkpoints that are involved in the regulation of the cell cycle, the G1 checkpoint, G2 checkpoint, and M checkpoint. The G1 checkpoint, also known as the Start Checkpoint, occurs at the end of the G1 phase and acts like a gate that controls whether the cell is ready to start copying its DNA in the S Phase. During this checkpoint, the cell ensures that it has grown enough during G1 phase and has the necessary organelles to divide into two viable daughter cells. If the cell is too small or has not grown enough, it will not proceed past this checkpoint. Additionally, the cell also inspects its DNA for any damage or mutations that may cause problems during DNA replication. If DNA damage is detected, the cell can either pause to repair the damage, or if the damage is too severe, trigger apoptosis (programmed cell death), to prevent the proliferation of damaged cells. Finally, the cell checks to make sure that it has enough energy and nutrients available to support DNA replication and cell division. If everything is good, the cell gets the green light from the G1 checkpoint to move into the S phase, where DNA is copied.

The G2 checkpoint is the final checkpoint in the cell cycle before the cell enters the M phase. The G2 checkpoint is primarily responsible for detecting any DNA damage that might have occurred during replication or earlier in the cell cycle. This damage can include mismatched bases, broken DNA strands, or other errors that arose during the replication process. If DNA damage is detected, the cell activates repair mechanisms to fix these errors. This may involve several repair pathways, such as nucleotide excision repair or homologous recombination. Once again, if the damage is too extensive and cannot be repaired, the cell may initiate apoptosis to prevent the propagation of damaged DNA. Before transitioning into the M phase, the cell verifies that it has grown sufficiently and has enough resources to support cell division. Once these conditions are met, the cell then moves into prophase.

The M checkpoint, also known as the spindle checkpoint, is the final checkpoint in the cell cycle. It occurs during mitosis, specifically at the transition from metaphase to anaphase. Recall that during metaphase, chromosomes line up along the metaphase plate, an imaginary line in the center of the cell. The M checkpoint checks that all chromosomes are properly aligned at the metaphase plate, ensuring that they are ready for separation. The checkpoint also ensures that each chromosome's centromere (the region where sister chromatids are joined) is correctly attached to spindle fibers from opposite poles of the cell. These spindle fibers, made of microtubules, will pull the sister chromatids apart during anaphase. Finally, the checkpoint assesses the tension on each chromosome. Proper tension indicates that the chromosomes are



correctly attached to the spindle fibers and are ready to be pulled apart. If the M checkpoint detects any problems, such as a chromosome not being properly attached to the spindle fibers, not aligned correctly, or the tension is not adequate, the cell will pause in metaphase. The cell will attempt to resolve these issues by adjusting the spindle fibers or re-aligning the chromosomes to ensure everything is correct before proceeding.

These checkpoints, G1, G2, and M, act as quality control stations, where the cell assesses whether it is safe to proceed to the next stage of the cycle. Failure at each cell cycle checkpoint can have significant consequences. Overall, checkpoint failures can cause uncontrolled cell division, DNA damage accumulation, genetic instability, and an increased risk of cancer and other diseases.

Pre-Lab Questions

1. **Summarize** what occurs at each checkpoint and how that helps maintain the integrity of the cell prior to the next stage of the cell cycle.

   G1 Checkpoint -

   G2 Checkpoint -

M Checkpoint -

2. **Explain** the importance of the checkpoints and **discuss** the consequences of failure at these checkpoints.

Role of Cyclins and Cyclin-Dependent Kinases in Cell Cycle Regulation

Proteins called cyclins and cyclin-dependent kinases (CDKs) play crucial roles in controlling progression through the G1, G2, and M checkpoints. Cyclins are proteins that act like "timers" and their levels fluctuate throughout the cell cycle, rising and falling at specific points. The increase and decrease in the levels of cyclins during the cell cycle help determine when it is time for the cell to start the next phase. Meanwhile, CDKs are enzymes that work like "switches". They need to be activated by cyclins. When a cyclin binds to a CDK, it activates the CDK, which then adds a phosphorus group to specific target proteins, in a process known as phosphorylation. This phosphorylation triggers various cellular processes necessary to begin the next phase of the cell cycle.

Cyclins and CDKs work together to ensure that the cell cycle progresses in a controlled and orderly manner, allowing the cell to grow, replicate its DNA, and divide. Each stage of the cell cycle is regulated by specific cyclin-CDK complexes, which act as signals that move the cell from one phase to the next.

Pre-Lab Question

3. **Explain** the role that cyclins and cyclin-dependent kinases play in cell cycle regulation and **summarize** how they work.

Signaling Pathways in Cell Cycle Regulation and the Role of Growth Factor Receptors

Signal transduction is the process by which the signal from the growth factor outside the cell is transmitted inside the cell, resulting in a specific cellular response. During signal transduction, the signal from the growth factor is relayed through the signaling pathway, ultimately leading to the activation of cyclins and cyclin-dependent kinases (CDKs), which are essential for progressing through the cell cycle. There are several signaling pathways activated by growth factor receptors which promote cell division, or cell survival and growth. Once activated, these pathways lead to the expression of genes that push the cell through the cell cycle, leading to cell division.

Growth factor receptors are like "antennae" on the cell's surface that detect and respond to growth factors from the outside environment. These receptors are proteins on the surface of cells that help regulate when and how cells divide. They are responsible for receiving signals from growth factors, which are molecules that stimulate cells to grow, divide, and differentiate. Under normal conditions, they ensure that cells only divide when necessary, such as during growth, tissue repair, or in response to environmental signals. When a growth factor binds to its corresponding receptor on the cell surface, it triggers a series of signals inside the cell, often referred to as a signaling pathway, which communicate the message that the cell should prepare to divide. Signaling pathways transmit the message from the growth factor receptor to the cell's nucleus, where the DNA is housed. The message typically prompts the cell to prepare for division, leading to the activation of specific proteins that drive the cell through the different phases of the cell cycle (G1, S, G2, M).

The interaction between growth factors, receptors, and signaling pathways is critical for proper cell cycle regulation. If this communication is disrupted, such as by a mutation in the receptor or overproduction of a growth factor, the cell may divide uncontrollably, leading to cancer.

Pre-Lab Question

4. **Explain** what growth factor receptors are and what their role is in cell cycle regulation.

Proto-Oncogenes, Oncogenes, and Tumor Suppressor Genes

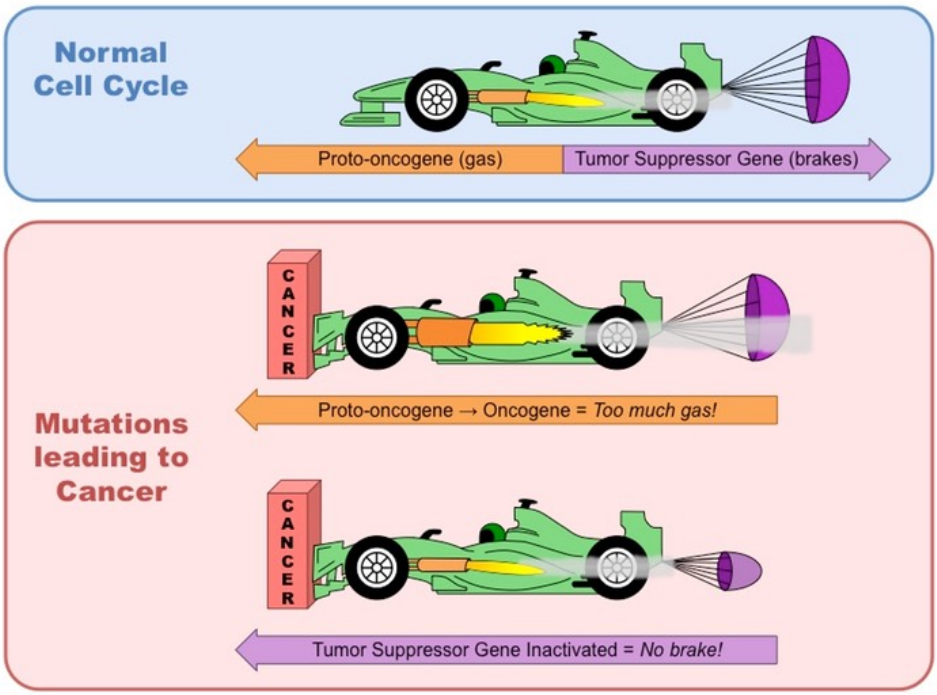
Proto-oncogenes are genes that normally promote healthy cell growth and division. When mutated, they can become overactive, pushing the cell to divide uncontrollably. When proto-oncogenes become mutated or abnormally activated, they are referred to as oncogenes. Oncogenes can lead to cancer by pushing cells to divide excessively. They do this by producing excessive growth signals, causing signaling pathways to be constantly active, or by helping cells inhibit cell death by avoiding apoptosis.

Tumor suppressor genes help maintain cellular integrity by preventing cells from dividing too rapidly or without proper checks. They normally function to slow down cell division, repair DNA errors, and initiate apoptosis if the damage is too severe. When these genes are inactivated by mutations, cells lose the ability to control their growth and repair DNA damage, increasing the risk of cancer. Unlike oncogenes, which typically involve a gain of function mutation, cancer-related mutations in tumor suppressor genes often involve a loss of function, where the protective role of the gene is diminished or lost entirely. Some examples of tumor suppressor genes are BRCA1 and BRCA2, which are genes that are involved in DNA repair and are linked to an increased risk of breast and ovarian cancers when mutated.

In a healthy cell, proto-oncogenes and tumor suppressor genes work together to maintain a balance between cell growth and division. Proto-oncogenes promote division when needed, while tumor suppressor genes ensure that cells only divide under appropriate conditions and that any errors are corrected. The proper functioning of these genes is essential for preventing cancer. Oncogenes must be kept in check by tumor suppressor genes to prevent uncontrolled cell growth. If either proto-oncogenes become overactive or tumor suppressor genes are lost, this balance is disrupted, leading to cancer.

Imagine that your cell is like a car driving on the road, where the journey represents the cell's growth and division. The car has both a gas pedal and brakes, and you control how fast the car goes and when it stops. The gas pedal is pressed gently and at the right times, ensuring the car moves forward only when it's safe and appropriate. If the gas pedal gets jammed or stuck, the car keeps accelerating uncontrollably, even when you don’t want it to. Proto-oncogenes are like the car's gas pedal, controlling safe cell growth and division during growth or tissue repair. When a proto-oncogene mutates into an oncogene, it causes the cell to keep dividing rapidly and uncontrollably, even when it shouldn’t, which can lead to cancer. Oncogenes are like a gas pedal that is stuck or jammed.

Brakes slow down or stop the car when needed. These brakes are crucial for keeping the car under control, especially when the road is rough or when you need to stop. If your brakes are broken, even if you want to slow down or stop the car, you can’t. Tumor suppressor genes are like the car's brakes, and slow down or stop cell division when DNA is damaged in the cell or to prevent damaged cells from dividing. When tumor suppressor genes are mutated or inactivated, it’s like having broken brakes. In cells, this means that even when there’s DNA damage, the cell can’t stop dividing because the tumor suppressor genes are not working. This loss of braking power can contribute to uncontrolled cell growth and cancer.



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Pre-Lab Question

5. **Explain** what proto-oncogenes and oncogenes are, and **describe** the main difference between them.

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