

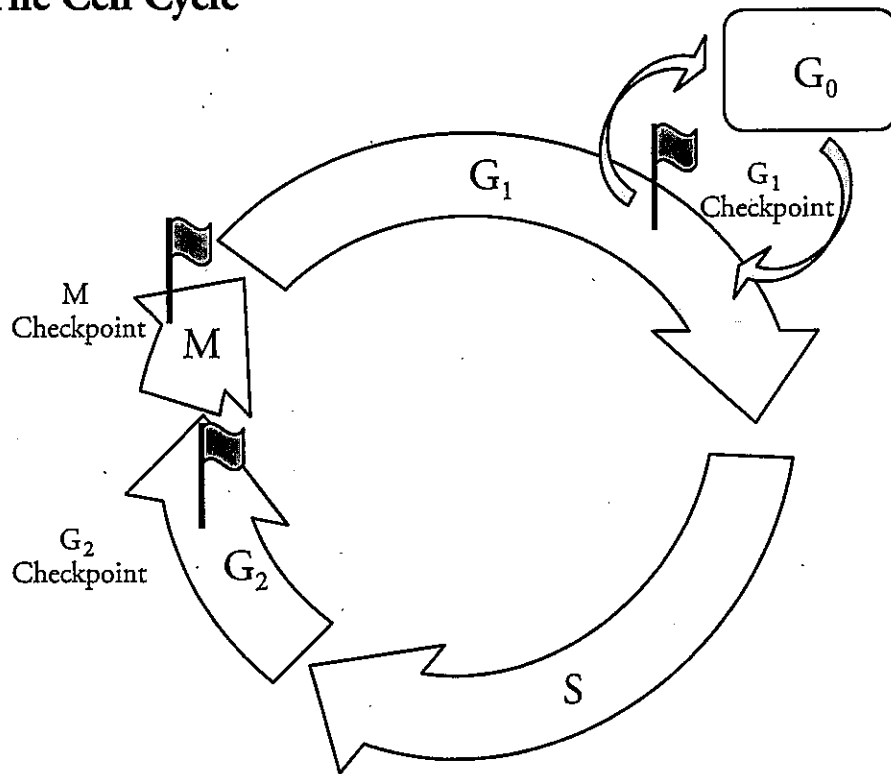
Cell Cycle Regulation

How does a cell know it is time to divide?

Why?

Quality control inspectors typically do not limit their product testing to the final product at the end of the assembly line. They monitor all aspects of production in hopes of preventing larger problems down the line. Likewise, when cells are progressing through the cell cycle there are processes in place that check on the cell's progress. Is everything happening according to plan? Are there sufficient resources to complete the task of cell division? Tightly regulating the cell cycle keeps a multicellular organism healthy by conserving materials. This ensures that new cells receive accurate genetic information, and also prevents uncontrolled growth that may lead to diseases like cancer.

Model 1 – The Cell Cycle



1. Review the phases of the cell cycle in Model 1 by placing the abbreviated phase name (G_1 , S , G_2 or M) next to the proper description.

<u>G_1</u>	The cell grows by producing more proteins and organelles.
<u>S</u>	DNA replication occurs.
<u>G_2</u>	The cell prepares for cell division with the appearance of centrosomes.
<u>M</u>	Mitosis and cytokinesis occurs.

2. Some cells, like mature nerve cells or muscle cells, do not divide. Other cells will divide only when the cellular environment signals that it is necessary. According to Model 1, what "phase" of the cell cycle are these cells said to be in when they are not dividing or planning to divide?

When cells are not dividing or planning to divide, they go into a "phase" called G_0 .

3. There are three regulatory checkpoints built into the cell cycle.

a. Name the three checkpoints as shown on Model 1.

G₁ checkpoint, G₂ checkpoint, and M checkpoint.

b. Indicate the phase of the cell cycle, and what part of the phase (early or later), where each checkpoint occurs.

The G₁ checkpoint occurs in the later part of G₁.

The G₂ checkpoint occurs in the later part of G₂.

The M checkpoint occurs in the later part of Mitosis.



4. Progression through the cell cycle is dependent on both extra- and intracellular conditions. Consider the following conditions. Indicate which checkpoint(s) most likely responds to that condition.

a. The DNA has been completely replicated and checked for errors.

G₂ checkpoint.

b. There is ample supply of energy and raw materials available.

G₁ and G₂ checkpoints.

c. All chromosomes are attached to the spindles.

M checkpoint.

d. There is adequate room in the environment for more cells.

G₁ checkpoint.

5. Which checkpoint appears to regulate whether the cell is in G₀ or not?

The G₁ checkpoint is the point in the cycle where the cell goes into or out of G₀.

6. Predict the result of a mutation that allows a cell to move past checkpoint G₁ even though the cell has not grown sufficiently.

The daughter cells would be small and possibly not able to store enough nutrients within the cell to survive.

7. Predict the result of a mutation that allows a cell to move past checkpoint G₂ even though DNA replication has not been completed.

The DNA in the daughter cells would not be complete and the cells would not survive.

8. Predict the result of a mutation that allows a cell to move past checkpoint M even though the chromosomes were not prepared for division.

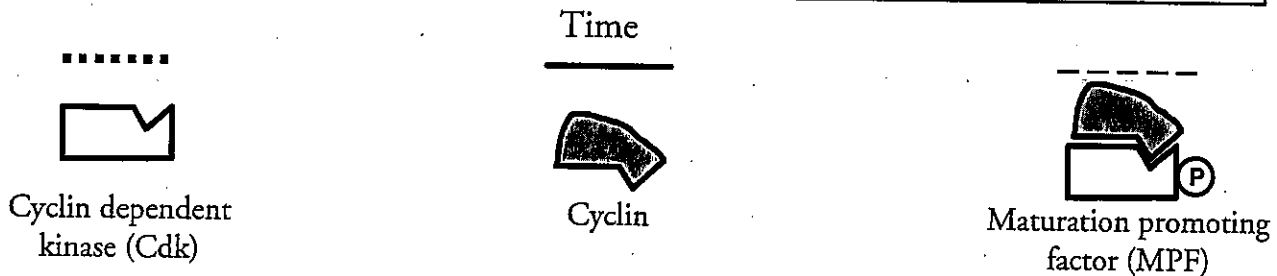
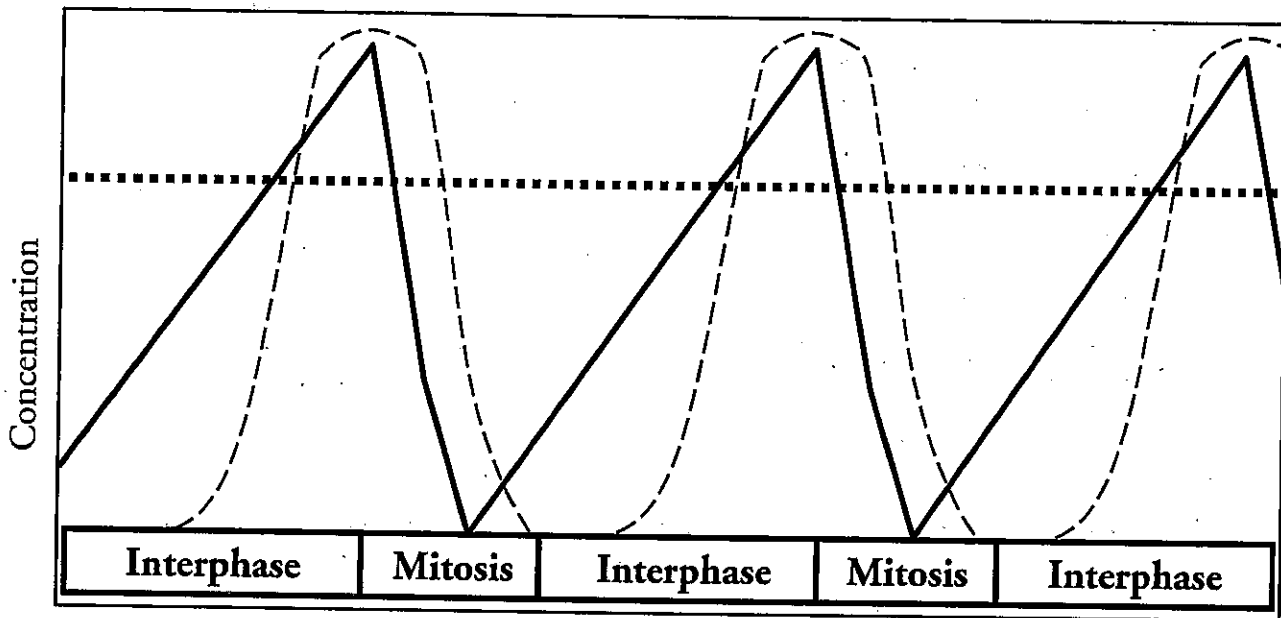
The chromosomes might end up in the wrong daughter cell. For example, one cell might get both copies of a chromosome while the other gets none.



Read This!

What determines if a cell is in G^0 or going through the cell cycle? What determines a "pass" at a checkpoint during the cell cycle? These questions are answered by both intracellular and extracellular chemical signals. **Growth factors** are one type of chemical signal. These proteins are released by specialized cells and trigger cell division. Surface proteins tell cells to stop dividing if the environment gets too crowded and cells are touching with too much pressure. Enzymes called **kinases** provide the energy (through phosphorylation) for many of the processes that must happen for successful mitosis to occur.

Model 2 – Cyclin and Kinase



9. Draw the shape that represents the kinase in Model 2.



10. Draw the shape that represents cyclin in Model 2.



11. Recall that the purpose of the kinases is to phosphorylate other molecules, thus bringing them to a higher energy state. With this in mind, identify the three parts of the maturation promoting factor (MPF) shown in Model 2.

The MPF is made from a kinase (Cdk), a cyclin, and a phosphate group (P).

12. The graph in Model 2 divides the cell cycle into “interphase” and “mitosis.” Which of the phases of the cell cycle in Model 1 fall into the “interphase” time frame?

G_1 , S, and G_2 are part of interphase.

13. Consider the graph in Model 2.

- a. Describe the changes in the concentration of cyclin dependent kinase (Cdk) as the cell moves through different phases of the cell cycle.

The concentration of Cdk does not vary throughout the cell cycle.

- b. Describe the changes in the concentration of cyclin as the cell moves through different phases of the cell cycle.

The concentration of cyclin is minimal at the start of G_1 , but steadily increases until partially through mitosis, and then quickly drops to a minimal level once again.

14. Propose an explanation for the change in the maturation promoting factor (MPF) concentration throughout the cell cycle based on your knowledge of the concentrations of Cdk and cyclin.

As the concentration of cyclin increases, there is more cyclin to bind to the Cdk, so the concentration of MPF increases.

15. Can the change in cyclin concentration during mitosis be explained by the fact that the cell divides in two and thus divides the material in the cell into two smaller volumes? If no, propose an explanation for the change in concentration that is seen.

No. When the cell divides there would be fewer cyclin molecules in each daughter cell than in the parent cell, but the daughter cells have a smaller volume, so the concentration should be the same. The graph indicates that the cyclin concentration approaches zero after mitosis, so the molecule must be used up in a reaction or decomposed after mitosis.

16. Considering both Model 1 and Model 2, which checkpoint in the cell cycle is regulated by the concentration of MPF? Justify your reasoning.

The G_2 checkpoint because the MPF concentration is highest just before the cell goes into M phase.

Read This!

After MPF has done its job of phosphorylation, the cyclin portion of the complex is degraded. This means that the protein is broken up into parts that can be recycled by the cell. The kinase is not degraded, but instead used again as the cell goes through another cycle of division.

17. If cyclin was always available in the cell at high concentrations, what effect would this have on the cell cycle?

Cells would progress through mitosis even if they were not ready.

18. How might a cell be affected by the development of a degradation-resistant cyclin mutant? Explain.

If the cyclin could not be degraded, the MPF would always be active. Therefore, the cell would be continuously pressured to move through the G_2 checkpoint, even if the conditions were not right.

Read This!

Cyclin proteins are encoded by a group of genes called **proto-oncogenes**. Besides cyclins, which function inside the cell, other proteins made by genes from this group are embedded in the cell membrane and receive extracellular signals that help to regulate the cell cycle and slow down the differentiation of new cells. **Tumor suppressor** genes make up another group of genes that regulate cell division. Genes from this group produce proteins that signal cells when they are getting too crowded, proteins whose function is to repair DNA, and still other proteins that regulate apoptosis (pre-programmed cell death). A tumor suppressor gene called p53 causes apoptosis when the cell is worn out or when defects are detected.

19. At which checkpoint in the cell cycle would a tumor suppressor gene

a. repair DNA function?

G_2

b. check for adequate room for more cells?

G_1

20. Create an analogy for the function of proto-oncogenes and tumor suppressor genes by assigning the role of a car's accelerator and brake pedals to each group. Using your previous knowledge, the information given above, and information in Model 2, complete the table below.

Regulatory Genes	Pedal	Justification
Proto-oncogenes	Accelerator (gas)	<i>Cyclin allows cells to pass through G_2 and divide.</i>
Tumor suppressor genes	Brake	<i>Would tend to slow down division when cells are crowded (suppressor means to slow down or stop something from happening).</i>



Extension Questions

21. Cancer, which can be considered as unregulated cell division, often results from mutations in proto-oncogenes and tumor suppressor genes. Usually mutation in more than one gene from each group is involved. Suggest two or more combinations of mutations that would tend to allow the cell cycle to become unregulated.

Answers may vary. A mutation in the gene that degrades cyclin along with a mutation in a tumor suppressor gene that gives information about cell crowding would result in extra cells being made.

A mutation in any proto-oncogene along with a mutation in p53 would allow a defective cell to continue dividing.

A mutation in a gene that repairs DNA would allow additional mutations in either or both groups to go unrepaired and allow the cell cycle to continue.

22. Paclitaxel is a chemotherapy drug used to treat a variety of cancers. Paclitaxel inhibits both assembly and disassembly of microtubules.

- a. Which checkpoint in the cell cycle is affected by Paclitaxel?

Microtubules are responsible for the movement of chromosomes on the spindle. Inhibiting the assembly and disassembly of microtubules would prevent the cell from separating chromosomes during mitosis, effectively stalling the cell in mitosis. The cell would not pass checkpoint M.

- b. How does this drug inhibit the growth of cancer?

The cell will never divide because it never finished mitosis.

- c. Paclitaxel affects not only cancer cells, but normal cells as well. Would the effects of Paclitaxel be seen first in organs that have quickly dividing cells (like the intestine and hair follicles) or in organs that have slow or nondividing cells (like muscles and the nervous system). Justify your reasoning.

Organs with cells that frequently divide will be the most affected. Organs with cells that do not divide, or divide very slowly, are in G_0 for the most part and would not be affected by a drug that targets the M phase of the cycle.