Cell cycle checkpoints

How cells use checkpoints at the end of G1 phase, end of G2 phase, and partway through M phase (the spindle checkpoint) to regulate the cell cycle.

Introduction

As cells move through the cell cycle, do they breeze through from one phase to the next? If they're cancer cells, the answer might be yes. Normal cells, however, move through the cell cycle in a regulated way. They use information about their own internal state and cues from the environment around them to decide whether to proceed with cell division. This regulation makes sure that cells don't divide under unfavourable conditions (for instance, when their DNA is damaged, or when there isn't room for more cells in a tissue or organ).

Cell cycle checkpoints

A **checkpoint** is a stage in the eukaryotic cell cycle at which at which the cell examines internal and external cues and "decides" whether or not to move forward with division.
There are a number of checkpoints, but the three most important ones are:

- The G1 checkpoint, at the G1/S transition.
- The G2 checkpoint, at the G2/M transition.
- The spindle checkpoint, at the transition from metaphase to anaphase.

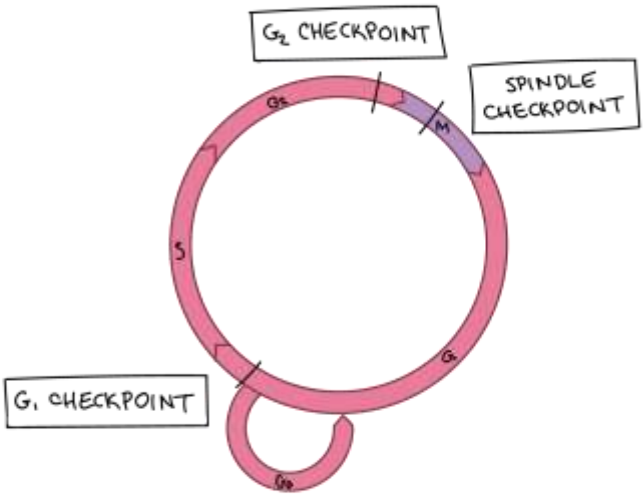
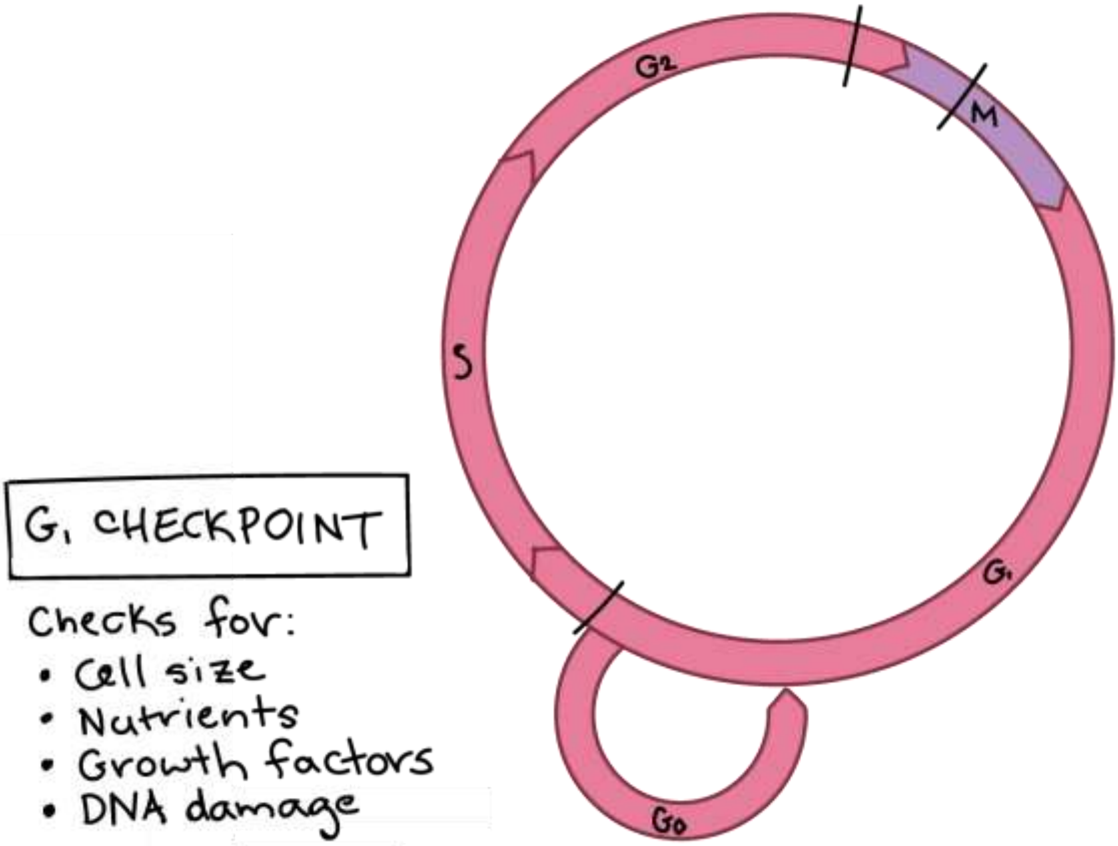


Diagram of cell cycle with checkpoints marked. G1 checkpoint is near the end of G1 (close to the G1/S transition). G2 checkpoint is near the end of G2 (close to the G2/M transition). Spindle checkpoint is partway through M phase, and more specifically, at the metaphase/anaphase transition.

The G_1 checkpoint

The **G1 checkpoint** is the main decision point for a cell – that is, the primary point at which it must choose whether or not to divide. Once the cell passes the G1 checkpoint and enters S phase, it becomes irreversibly committed to division. That is, barring unexpected problems, such as DNA damage or replication errors, a cell that passes the G1 checkpoint will continue the rest of the way through the cell cycle and produce two daughter cells.



The G1 checkpoint. The G1 checkpoint is located at the end of G1 phase, before the transition to S phase. If cells don't pass the G1 checkpoint, they may "loop out" of the cell cycle and into a resting state called G0, from which they may subsequently re-enter G1 under the appropriate conditions.

At the G1 checkpoint, cells decide whether or not to proceed with division based on factors such as:

- Cell size
- Nutrients
- Growth factors
- DNA damage

At the G1 checkpoint, a cell checks whether internal and external conditions are right for division. Here are some of the factors a cell might assess:

- **Size.** Is the cell large enough to divide?
- **Nutrients.** Does the cell have enough energy reserves or available nutrients to divide?
- **Molecular signals.** Is the cell receiving positive cues (such as growth factors) from neighbours?
- **DNA integrity.** Is any of the DNA damaged?

These are not the only factors that can affect progression through the G1 checkpoint, and which factors are most important depend on the type of cell. For instance, some cells also need

mechanical cues (such as being attached to a supportive network called the extracellular matrix) in order to divide
.
If a cell doesn't get the go-ahead cues it needs at the G1 checkpoint, it may leave the cell cycle and enter a resting state called **G0 phase**. Some cells stay permanently in G0, while others resume dividing if conditions improve.

The G2 checkpoint

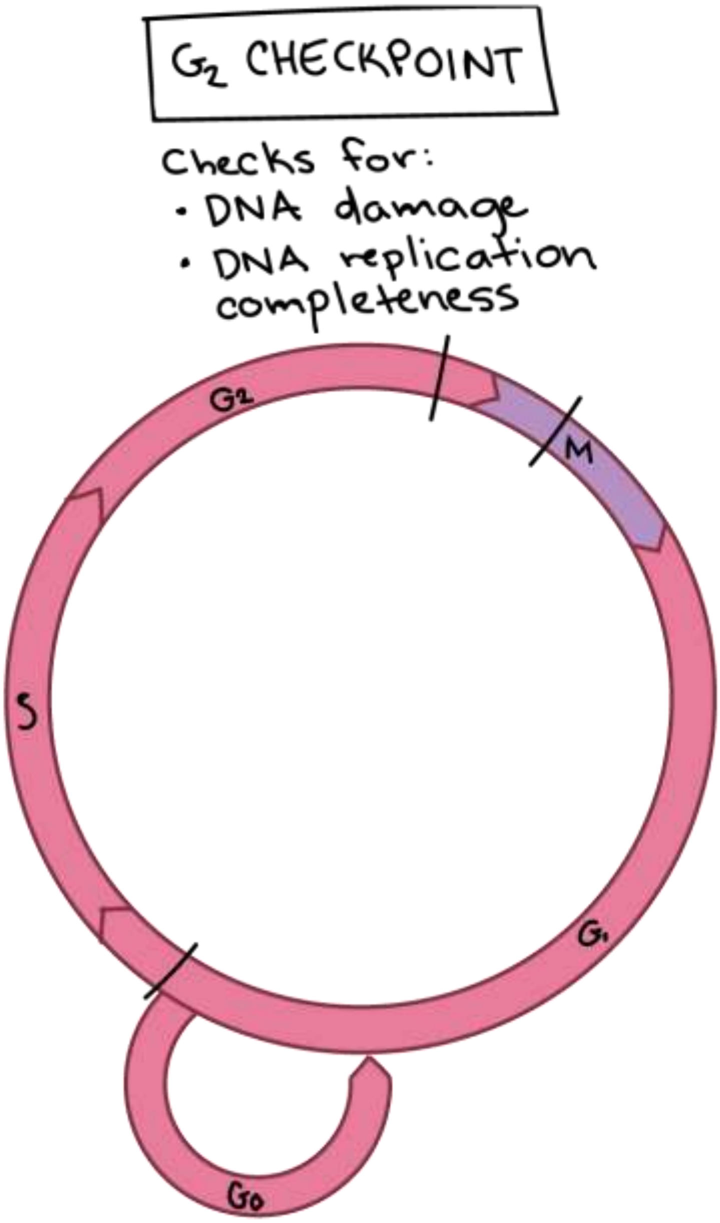


Image of the cell cycle with the G2 checkpoint marked. At the G2 checkpoint, the cell checks for:

- DNA damage
- DNA replication completeness

To make sure that cell division goes smoothly (produces healthy daughter cells with complete, undamaged DNA), the cell has an additional checkpoint before M phase, called the **G2 checkpoint**. At this stage, the cell will check:

- **DNA integrity.** Is any of the DNA damaged?
- **DNA replication.** Was the DNA completely copied during S phase?

If errors or damage are detected, the cell will pause at the G2 checkpoint to allow for repairs. If the checkpoint mechanisms detect problems with the DNA, the cell cycle is halted, and the cell attempts to either complete DNA replication or repair the damaged DNA.

If the damage is irreparable, the cell may undergo apoptosis, or programmed cell death. This self-destruction mechanism ensures that damaged DNA is not passed on to daughter cells and is important in preventing cancer.

The spindle checkpoint

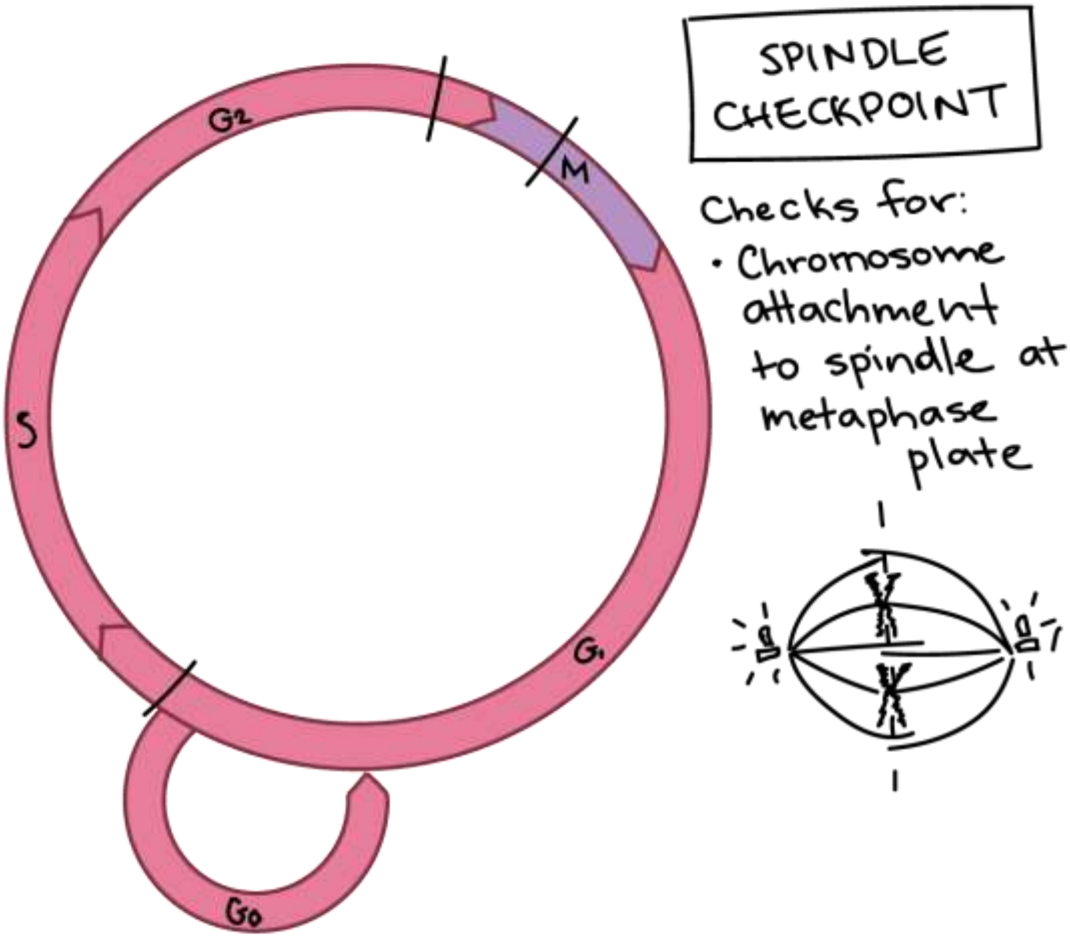


Image of the cell cycle with the spindle checkpoint marked. At the spindle checkpoint, the cell checks for:

- Chromosome attachment to spindle at the metaphase plate

The M checkpoint is also known as the **spindle checkpoint**: here, the cell examines whether all the sister chromatids are correctly attached to the spindle microtubules. Because the separation of the sister chromatids during anaphase is an irreversible step, the cycle will not proceed until all the chromosomes are firmly attached to at least two spindle fibres from opposite poles of the cell. How does this checkpoint work? It seems that cells don't actually scan the metaphase plate to confirm that all of the chromosomes are there. Instead, they look for "straggler" chromosomes that are in the wrong place (e.g., floating around in the cytoplasm). If a chromosome is misplaced, the cell will pause mitosis, allowing time for the spindle to capture the stray chromosome.

How do the checkpoints actually work?

This article gives a high-level overview of cell cycle control, outlining the factors that influence a cell's decision to pause or progress at each checkpoint. However, you may be wondering what these factors actually do to the cell, or change inside of it, to cause (or block) progression from one phase of the cell cycle to the next.

The general answer is that internal and external cues trigger signalling pathways inside the cell that activate, or inactivate, a set of core proteins that move the cell cycle forward. You can learn more about these proteins, and see examples of how they are affected by cues such as DNA damage, in the article on cell cycle regulators.