Cell Cycle

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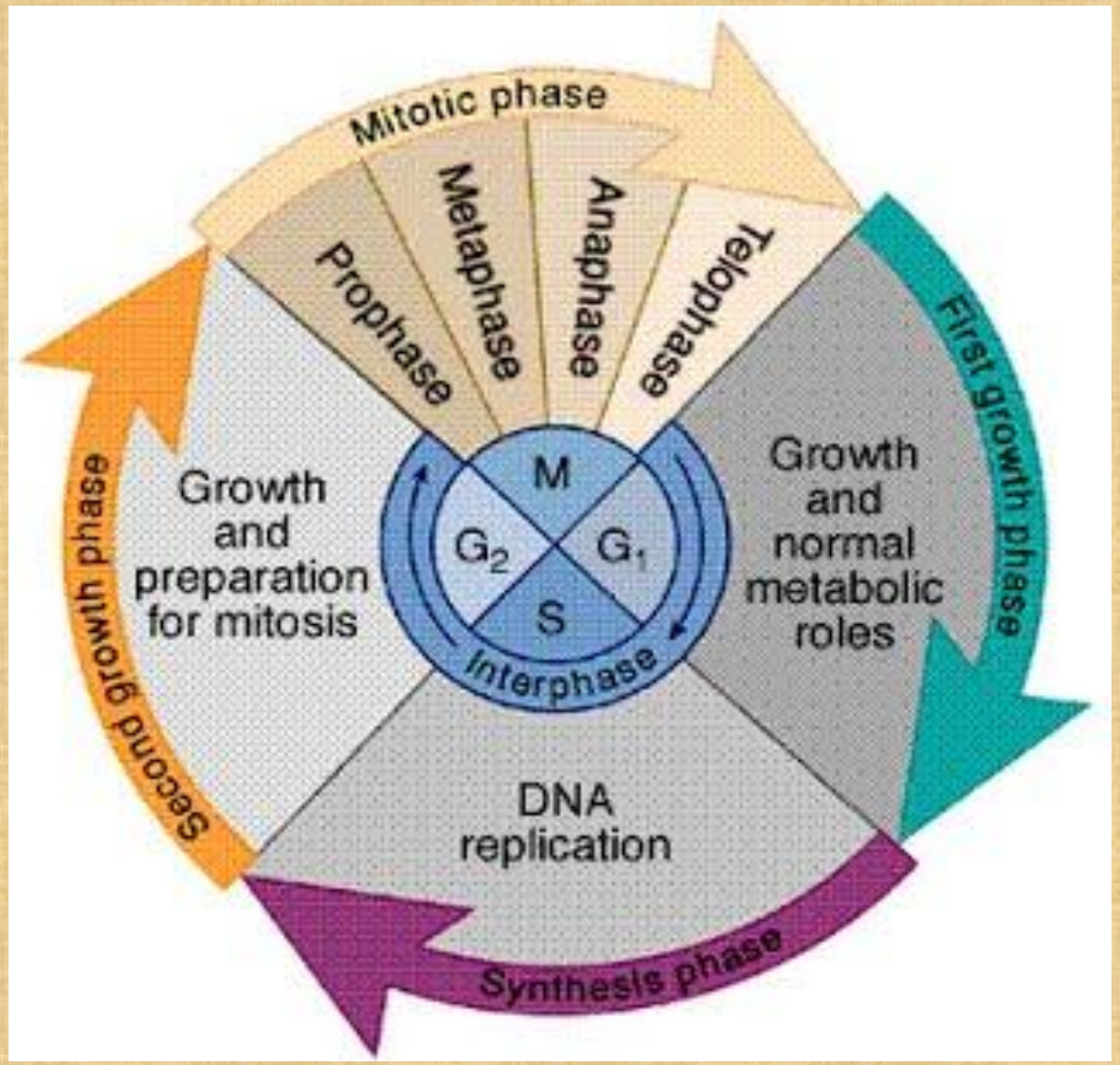

Mitotic phase
Prophase
Metaphase
Anaphase
Telophase
First growth phase
Growth and normal metabolic roles
DNA replication
Synthesis phase
Second growth phase
Growth and preparation for mitosis
M
G2
G1
S
Interphase

Introduction

- The cell cycle is a cycle of stages that cells pass through to allow them to divide and produce new cells. It is sometimes referred to as the “cell division cycle” for that reason.
- New cells are born through the division of their “parent” cell, producing two “daughter” cells from one single “parent” cell.
- Daughter cells start life small, containing only half of the parent cell’s cytoplasm and only one copy of the DNA that is the cell’s “blueprint” or “source code” for survival. In order to divide and produce “daughter cells” of their own, the newborn cells must grow and produce more copies of vital cellular machinery – including their DNA.
- The two main parts of the cell cycle are mitosis and interphase.
- Mitosis is the phase of cell division, during which a “parent cell” divides to create two “daughter cells.”
- The longest part of the cell cycle is called “interphase” – the phase of growth and DNA replication between mitotic cell divisions.

Phases of Cell Cycle

- **G1 Phase**: In G_1 phase, the newly formed daughter cell grows. The "G" is most often said to stand for "gap," since these phases appear to an outside observer with a light microscope to be relatively inactive "gaps" in the cell's activity. In this phase, the cell produces many essential materials such as proteins and ribosomes. The cell's size may increase as it assimilates more material from its environment into its machinery for life.
- **S Phase**: During S phase, the cell replicates its DNA. The "S" stands for "synthesis" – referring to the synthesis of new chromosomes from raw materials. When the S phase is completed, the cell will have two complete sets of its genetic material. This is crucial for cell division, as it ensures that both daughter cells can receive a copy of the "blueprint" they need to survive and reproduce.

Phases of Cell Cycle

- **G 2 Phase**: Just like the first "gap" phase of the cell cycle, the G_2 phase is characterized by lots of protein production.
- During G_2, many cells also check to make sure that both copies of their DNA are correct and intact. If a cell's DNA is found to be damaged, it may fail its "G_2/M checkpoint" – so named because the this "checkpoint" happens at the end of the G_2 phase, right between G_2 and "M phase" or "Mitosis."
- This "G_2/M checkpoint" is a very important safety measure for multicellular organisms like animals. Cancers, which can result in the death of the entire organism, can occur when cells with damaged DNA reproduce. By checking to see if a cells' DNA has been damaged immediately before replication, animals and some other organisms reduce the risk of cancer.
- Interestingly, some organisms can skip G_2 altogether and go straight into mitosis after DNA is synthesized during S phase. Most organisms, however, find it safer to use G_2 and its associated checkpoint!
- If the G_2/M checkpoint is passed, the cell cycle begins again. The cell divides through mitosis, and new daughter cells begin the cycle that will take them through G_1, S, and G_2 phases to produce new daughter cells of their own.

Phases of Cell Cycle

- **Mitosis**: During mitosis, the “parent” cell goes through a complex series of steps to ensure that each “daughter” cell will get the materials it needs to survive, including a copy of each chromosome. Once the materials are properly sorted, the “parent” cell divides down the middle, pinching its membrane in two.
- Each of the new “daughters” are now independently living cells. But they’re small, and have only one copy of their genetic material. This means they can’t divide to produce their own “daughters” right away. First, they must pass through “interphase”

Regulation of cell cycle

- The cell cycle is controlled by regulator molecules that either promote the process or stop it from progressing.

- **1.Positive regulation of cell cycle:**
- Two groups of proteins; **cyclins** and **cyclin-dependent kinases** (Cdks), are responsible for the progress of the cell through the various checkpoints.

Cyclin:

- Cyclins are cell-signaling molecules that regulate the cell cycle
- There are four types of cyclins proteins- A, B, D and E
- The levels of the four cyclin proteins (A,B,D,E) fluctuate throughout the cell cycle in a predictable pattern
- Cyclin B is very important in mitosis.
- After the cell moves to the next stage of the cell cycle, the cyclins that were active in the previous stage are degraded.
- Cyclins regulate the cell cycle only when they are tightly bound to Cdks.
- To be fully active, the Cdk/cyclin complex must also be phosphorylated in specific locations.

- **Cyclin dependent kinases(CDKs):**
- Cdks are kinase enzymes that phosphorylate other proteins or enzymes. Phosphorylation activates the protein by changing its shape.
- The proteins phosphorylated by Cdks are involved in advancing the cell to the next phase.
- The levels of Cdk proteins are relatively stable throughout the cell cycle; however, the concentrations of cyclin fluctuate and determine when Cdk/cyclin complexes form or not.
- The different cyclins and Cdks bind at specific points in the cell cycle and thus regulate different checkpoints.

- **2. Negative regulation of cell cycle:**
- Negative regulators halt the cell cycle.
- Negative regulatory molecules are retinoblastoma protein (Rb), p53, and p21.
- If negative regulator proteins are damaged or become non-functional then it results in uncontrolled cell division leading to tumor or cancer.

- **i. Retinoblastoma proteins:**
- **Rb** are a group of tumor-suppressor proteins common in many cells.

- **ii. P53**
- **P53** is a multi-functional protein. It is activated during G1 phase when there is DNA damage in the cell and cell employed the mechanism to repair the damage.
- When damaged DNA is detected, p53 protein halts the cell cycle and recruits enzymes to repair the DNA. If the DNA cannot be repaired, p53 can trigger apoptosis to prevent the duplication of damaged chromosomes.
- As p53 levels rise, the production of p21 is triggered.

- **iii. p21:**
- p21 enforces the halt in the cell cycle dictated by p53 by binding to and inhibiting the activity of the Cdk/cyclin complexes.
- In case of DNA damage condition or inadequate cell size, more and more p53 and p21 are produced which halt the cell cycle and prevent the cell to enter S phase.
- These negative regulators are known as tumor suppressor protein and gene that codes for such proteins are called tumor suppressor gene.
- Tumor suppressor either halt the cell until repair or leads to apoptosis thus preventing damaged cell from division. If mutation occurs in tumor suppressor gene, then those negative regulator proteins lost the function to halt the cell cycle leading cancerous cell of continuous growth and division.

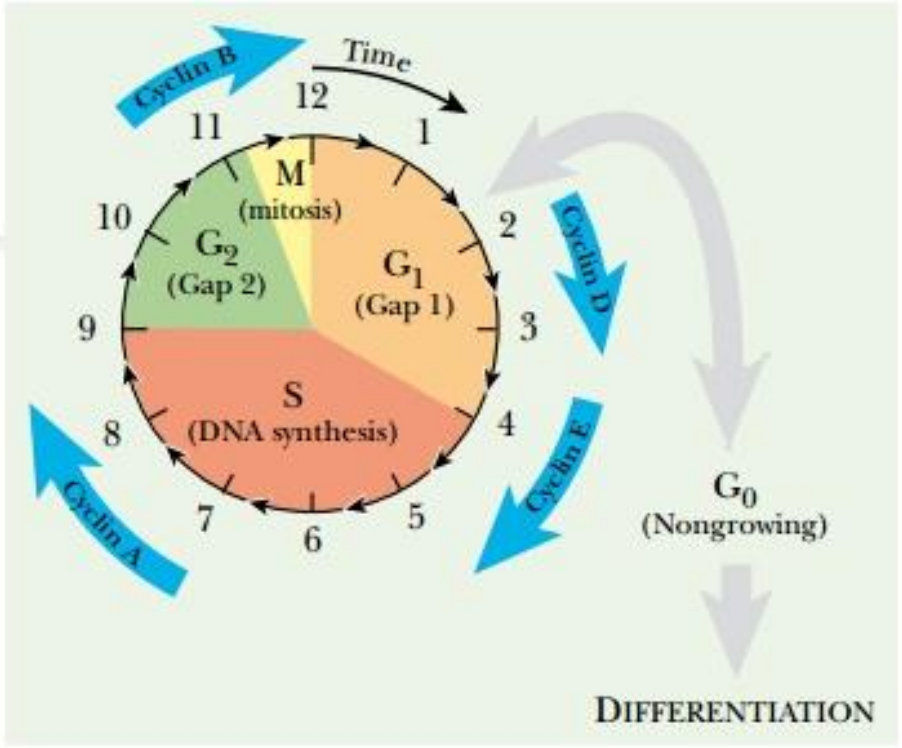


FIGURE 18.2
Eukaryotic Cell Cycle: Division versus Differentiation
The cell cycle normally consists of the four stages G_1, S, G_2, and M. However, if the conditions are right, rather than going from G_1 into the S phase, the cell may differentiate and enter G_0. If the cell does not differentiate, a signal is received from cyclin D and E, and the cell enters S phase and replicates its DNA. After about 5 hours another signal from cyclin A triggers the cell to enter G_2. After cyclin B becomes active, the cell enters mitosis and divides.

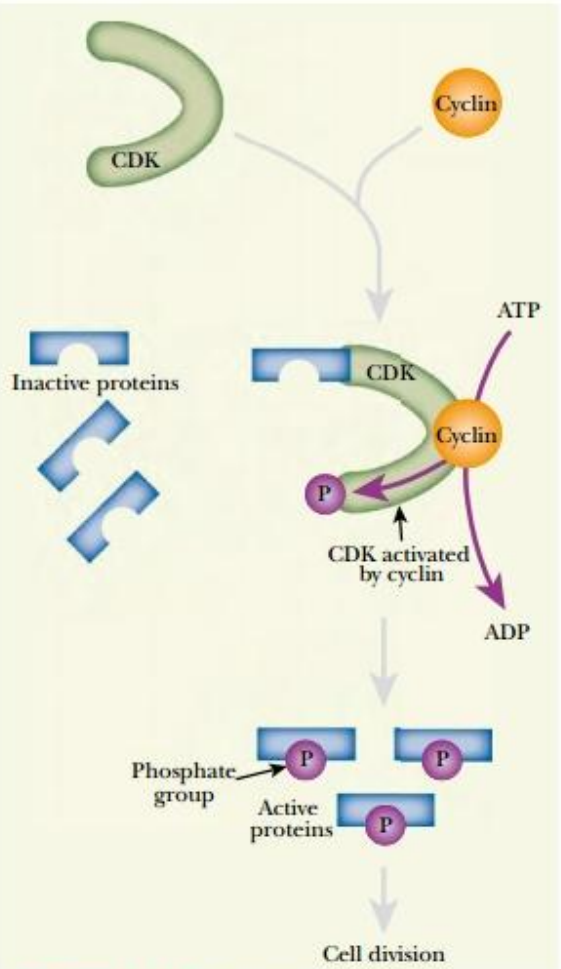


FIGURE 18.3 Cyclins Operate via Cyclin-Dependent Kinases
Before each cell can enter a new phase of the cell cycle, the cyclin must complex with a cyclin-dependent kinase (CDK). Addition of a phosphate from ATP activates the cyclin/CDK complex. The active complex then transfers the phosphate to other proteins that execute cell division.

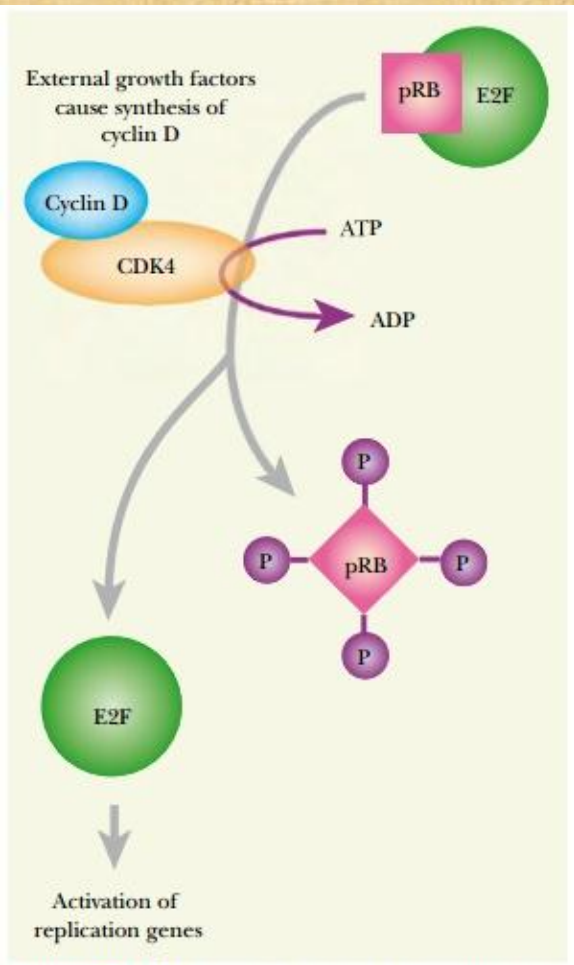


FIGURE 18.4 Control of G_1 to S Transition by pRB and E2F

At the end of G_1, cyclin D must be activated to initiate transition into S phase. This requires binding of cyclin D to its partner, CDK4. Once they are together, ATP is hydrolyzed and a phosphate is transferred to the cyclinD/CDK4 complex. This phosphate is then transferred to pRB, which releases E2F to transcribe genes needed to initiate DNA replication.

Mechanism of action of p53 and p21

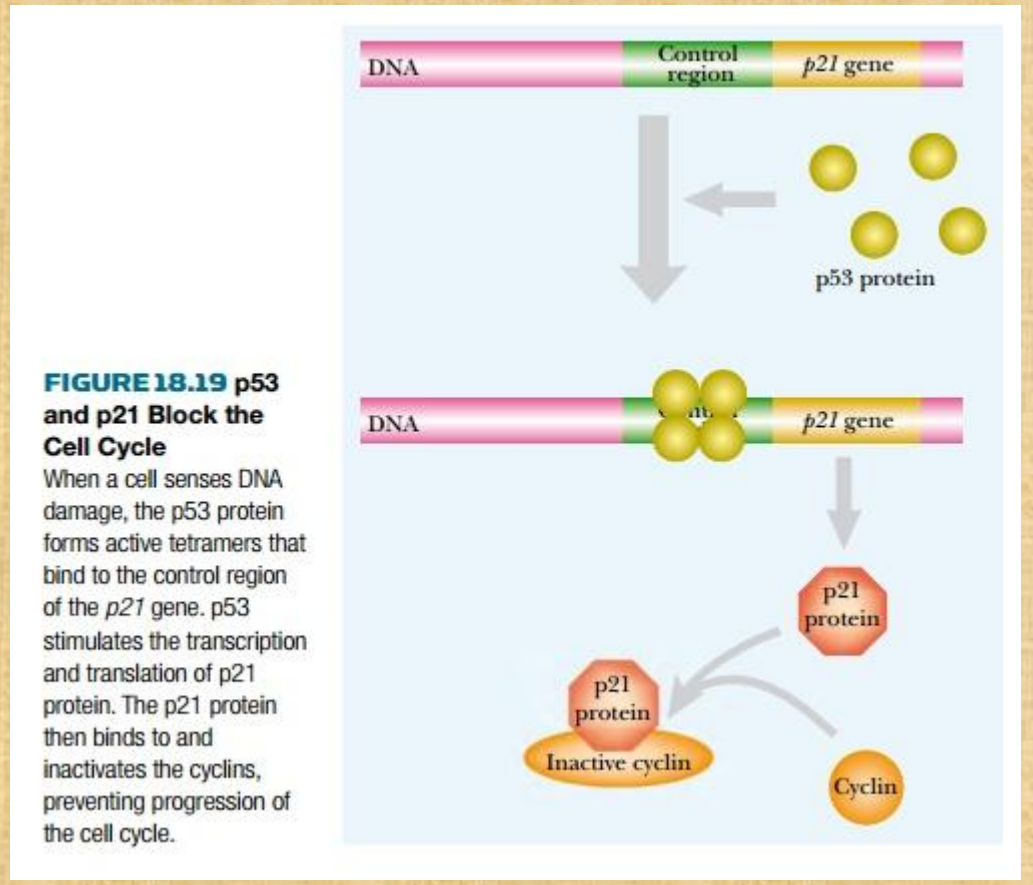
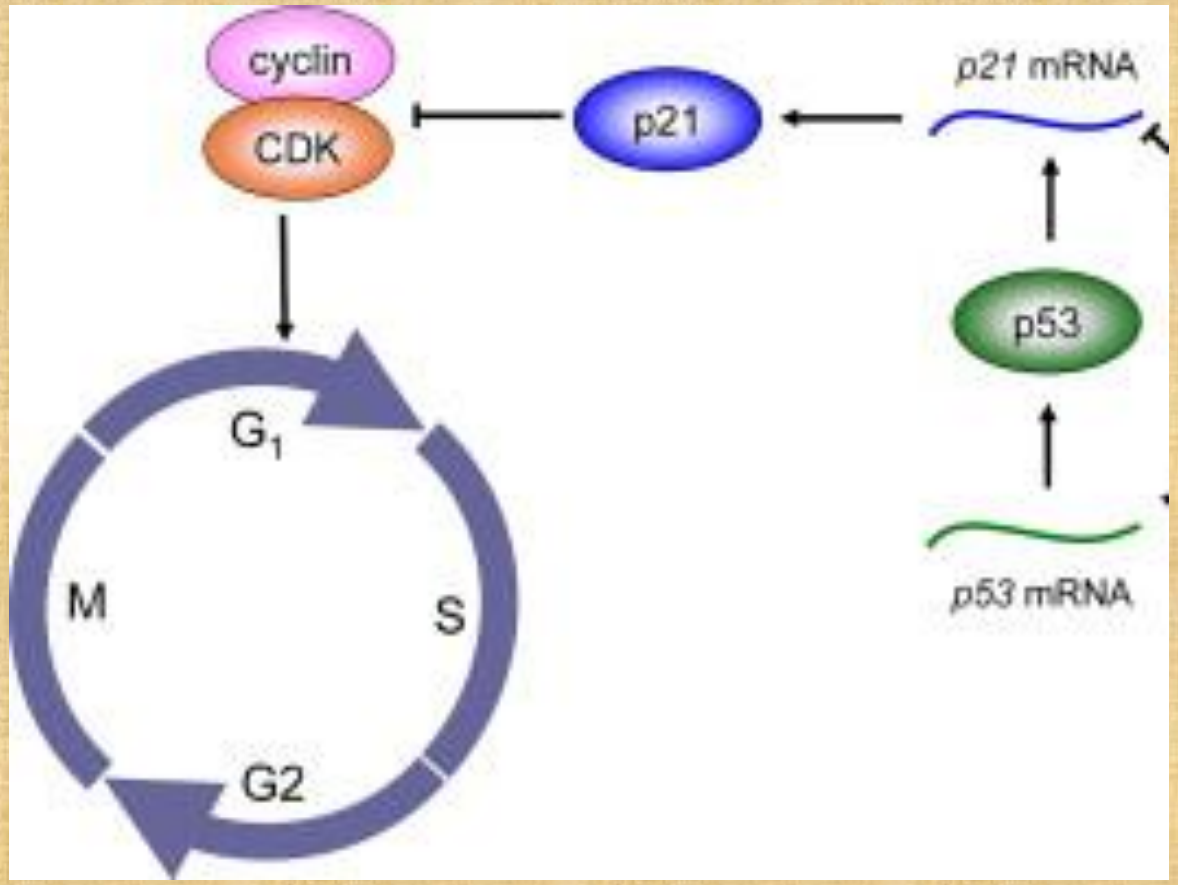
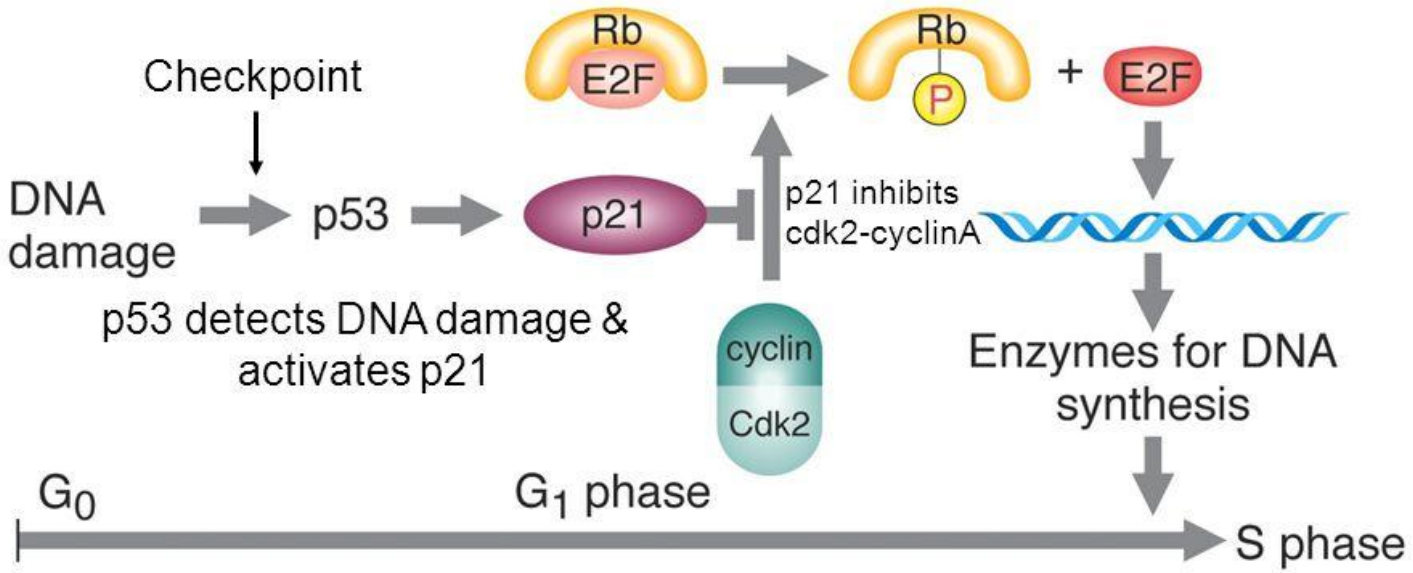


FIGURE 18.19 p53 and p21 Block the Cell Cycle
When a cell senses DNA damage, the p53 protein forms active tetramers that bind to the control region of the *p21* gene. p53 stimulates the transcription and translation of p21 protein. The p21 protein then binds to and inactivates the cyclins, preventing progression of the cell cycle.



Intracellular Regulation of Cell Cycle & Apoptosis

Negative regulation of cell cycle by intracellular signals



Checkpoints: block cell from proceeding through cell cycle if cell is damaged.

Importance of cell cycle checkpoints and regulation

- The cell cycle of each cell must be precisely controlled and timed to faithfully and reproducibly complete the developmental program in every individual. Each type of cell in every tissue must control its replication precisely for normal development of
- complex organs such as the brain or the kidney. In a normal adult, cells divide only when and where they are needed. However, loss of normal controls on cell replication is the fundamental defect in **cancer**.
- Cell cycle occurs with high accuracy and fidelity to assure that each daughter cell inherits the equal number of chromosome as of parent cell.
- Chromosome replication and cell division must occur in the proper order in every cell division. If a cell undergoes the events of mitosis before the replication of all chromosomes has been completed, at least one daughter cell will lose genetic information.
- Similarly, if a second round of replication occurs in one region of a chromosome before cell division occurs, the genes encoded in that region are increased in number out of proportion to other. Therefore, single round of DNA replication occurs in a cell.

Reference: https://biologydictionary.net/cell-cycle

References:

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