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3-Cell cycle checkpoints

- To ensure that each phase of the cell cycle is carried out correctly, essential steps are followed by a checkpoint. It is a control mechanism where certain conditions must be met before the cell can progress to the next step. Checkpoint failure induces cell cycle arrest, preventing the cell from proceeding until it has solved the issues.
- The cell cycle includes several checkpoints, where the major ones are the G_1, G_2 and M checkpoint.
- **G1 Checkpoint:**
- The G1 checkpoint is the first checkpoint in the cell cycle of a mammalian cell and the start point in the yeast cell that determines whether the cell enters the cell cycle or not.
- The checkpoint is present between the G1 phase and S phase and is responsible for the entry of the cell in the division phase.
- Depending on the external and internal factors and stimuli, the decision of whether the cell enters the cell cycle or undergoes the G0 phase is determined.
- The checkpoints are essential in the cell cycle as they limit the chances of genomic instability arising due to DNA damage during the cycle.
- The G1 checkpoint is regulated by p53 which aids in the downregulation of tumors and cell lines.
- In order to cause G1 checkpoint arrest, the p53 regulates the transcription of CDK inhibitor p21.
- The arrest is stimulated by factors like a break in the DNA double-strand, which prevents the proliferation of irreparably damaged cells.

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- The G1 checkpoint arrest is a positive feedback mechanism where the presence of breaks in the DNA strand enhances the expression of the p53 gene.
- Because of the proteins involved in the checkpoint, the G1 checkpoint is an important checkpoint during tumor suppression and prevention of excessive cell proliferation.
- Cells with reparable DNA damage are held at the checkpoint to provide time for repair while others are either signaled for apoptosis or moved to the G0 phase.
- **G2 Checkpoint:**
- The G2 checkpoint is the second checkpoint in the cell cycle where is present at the transition between G2 and S phase.
- The checkpoint prevents the entry of cells into the S phase of the cycle by preventing the activation of regulators like cyclins and CDKs.
- This checkpoint, like the G1 checkpoint, looks for DNA damage and breaks to prevent the proliferation of mutated or damaged cells.
- As the checkpoint helps maintain genomic stability, studies on the checkpoint help to understand the molecular mechanism of cancer.
- The target of the G2 checkpoint arrest is the CDK2 that usually drives the transition from G2 to the S phase.
- In the checkpoint, DNA damage triggers the activation of the ATM pathway, which causes phosphorylation of ATM and inactivation of checkpoint kinases.
- The checkpoint also involves the p53 genes which inactivate enzymes by the expression of p21 proteins.

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- Additional pathways in the G2 checkpoint ensure the stability of the arrest by the expression of proteins like Rb and downregulation of several genes that code for proteins required for the S phase.

- **3. Metaphase Checkpoint (Spindle checkpoint)**

- The metaphase checkpoint or M phase checkpoint or Spindle checkpoint is the checkpoint during mitosis which checks if all the sister chromatids are correctly attached to the spindle fibers.

- The checkpoint ensures that all the chromosomes of cells entering the anaphase are firmly attached to at least two spindle fibers from opposite poles of the cell.

- The separation of chromosomes in anaphase is an irreversible process, which is why this checkpoint is crucial in mitosis.

- The proteins in the checkpoint look for straggler chromosomes that can be detected in the cytoplasm.

- The checkpoint acts by negative regulation of CDC20 which prevents the activation of ubiquitin tag by the anaphase-promoting complex.

- There are different mechanisms to deactivate the checkpoint once all chromosomes are correctly attached.

- One of the important mechanisms is by transporting the motor complex proteins away from the kinetochores. The proteins are then redistributed to the spindle poles.

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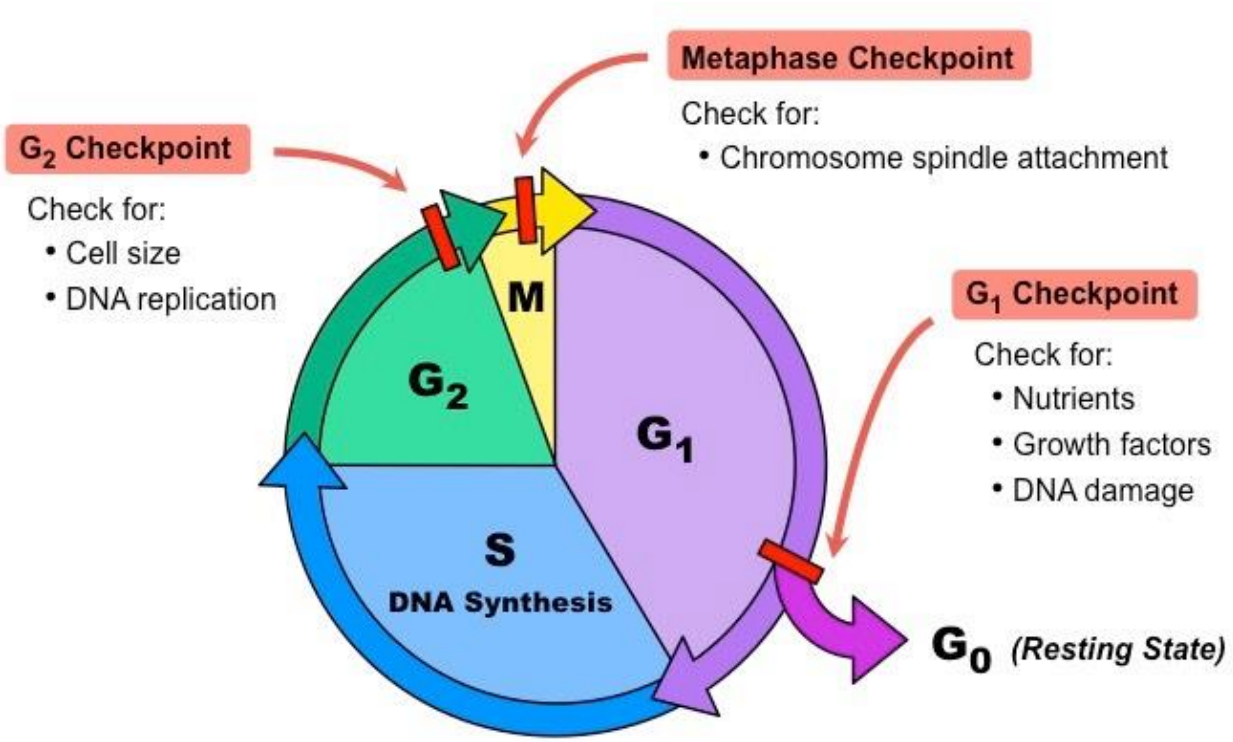

➢ **Cell Cycle Regulation**

Cyclins

- Cyclins are a group of proteins that together work to regulate different phases of the cell cycle as core regulators.
- These proteins regulate the various phases of the cell cycle by either activating the cyclin-dependent kinases or by activating some other enzymes or complexes.
- Cyclins are specific to different phases as work to regulate different phases of the cycle.
- In humans, four different cyclins are known, G1 cyclins, G1/S cyclins, S cyclins, and M cyclins. These cyclins, as the name suggests, regulate different phases.

The term 'cyclin' was given to this class of proteins because of the varying concentration of these proteins in the cell during the cell cycle.

Cyclin-dependent kinases (CDKs)

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- Cyclin-dependent kinases (CDKs) are a group of enzymes that work to regulate different processes in the cell cycle after activation by the binding of a cyclin molecule.

- CDKs are a part of the CMGC group of enzymes consisting of serine or threonine units that are characterized by their dependency on protein subunits.

Maturation-promoting factor (MPF)

- Maturation-promoting factor or M-phase promoting factor (MPF) is a large-sized diffusible protein that regulates the M-phase of a cell cycle.
- The protein consists of two subunits; an inert subunit and a kinase subunit. The kinase subunit is capable of activating the inert subunit as well as other molecules.
- MPF is the regulator of the G2/M transition where it activates activities like nuclear envelope breakdown and chromosome condensation.

p53

- p53, also called TP53 or tumor protein, is a gene that encodes for the protein that regulates cell proliferation and also acts as a tumor suppressor.
- The p53 gene is often termed the 'guardian of the genome' as it helps in conserving stability of the genome by preventing genome mutation.
- In eukaryotic organisms, it is important as it suppresses cancer.
- It also stimulates apoptosis if DNA damage is detected that is irreparable.

Retinoblastoma protein (Rb)

- Retinoblastoma protein is a nuclear phosphoprotein that helps in cell cycle regulation while also acting as a tumor suppression protein.
- The primary function of Rb is to prevent excessive cell growth during the cell cycle progression.
- It acts as a negative regulator of the cell cycle as inhibiting the process.
- The protein is expressed in both cycling and resting cells which functions by inhibiting a variety of nuclear proteins involved in the cell cycle.
- It regulates the transition of a cell from the G1 phase to the S phase by inhibiting DNA replication.

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Apoptosis

What happens if a cell fails a checkpoint? It will be arrested at the checkpoint and the cell will attempt to repair the damage. However, if the damage cannot be repaired, the cell will undergo **apoptosis**. Apoptosis, or programmed cell death, allows a cell to die in a controlled manner that prevents the release of potentially damaging molecules from inside the cell. Apoptosis is highly regulated, and depends on a series of protein-protein interactions.