Cell Cycle Checkpoints

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Cell Cycle Checkpoints

- **Cell cycle checkpoints** are control mechanisms in eukaryotic cells which ensure proper division of the cell.

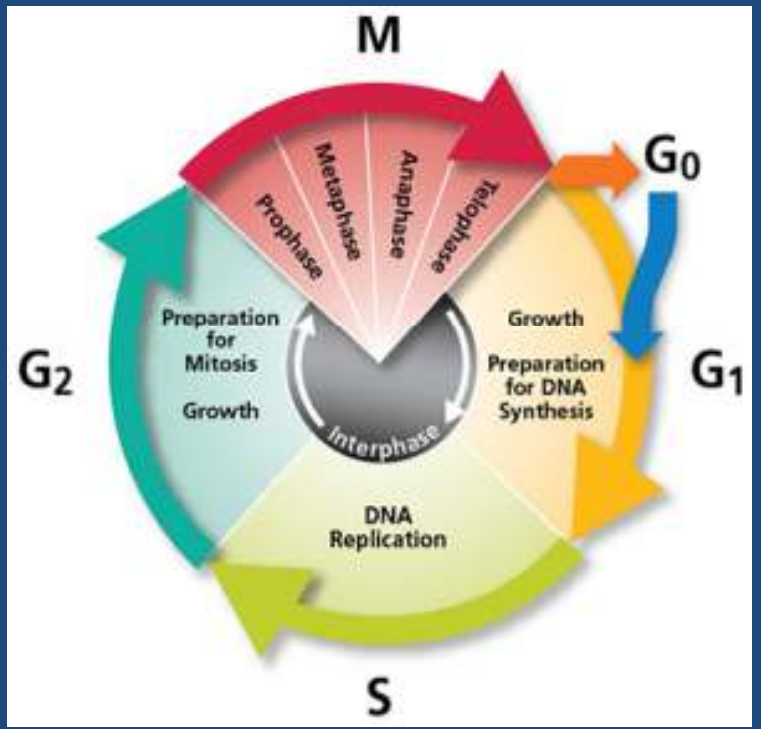
- Each checkpoint serves as a potential halting point along the cell cycle, during which the conditions of the cell are assessed, with progression through the various phases of the cell cycle occurring when favorable conditions are met.

Cell Cycle Checkpoints

- The main mechanism of action of the cell cycle checkpoints is through the regulation of the activities of a family of protein kinases known as the cyclin-dependent kinases (CDKs), which bind to different classes of regulator proteins known as cyclins, with specific cyclin-CDK complexes being formed and activated at different phases of the cell cycle.
- Those complexes, in turn, activate different downstream targets to promote or prevent cell cycle progression.

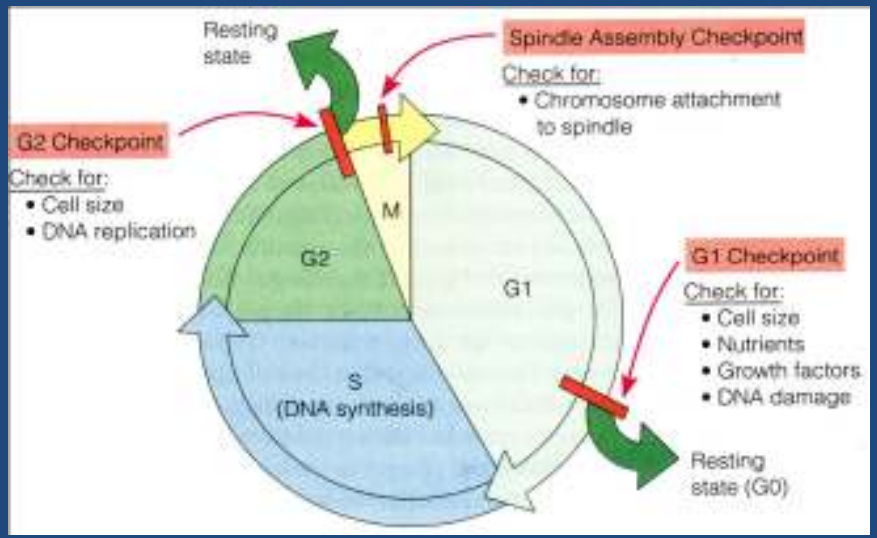
Cell Cycle Checkpoints

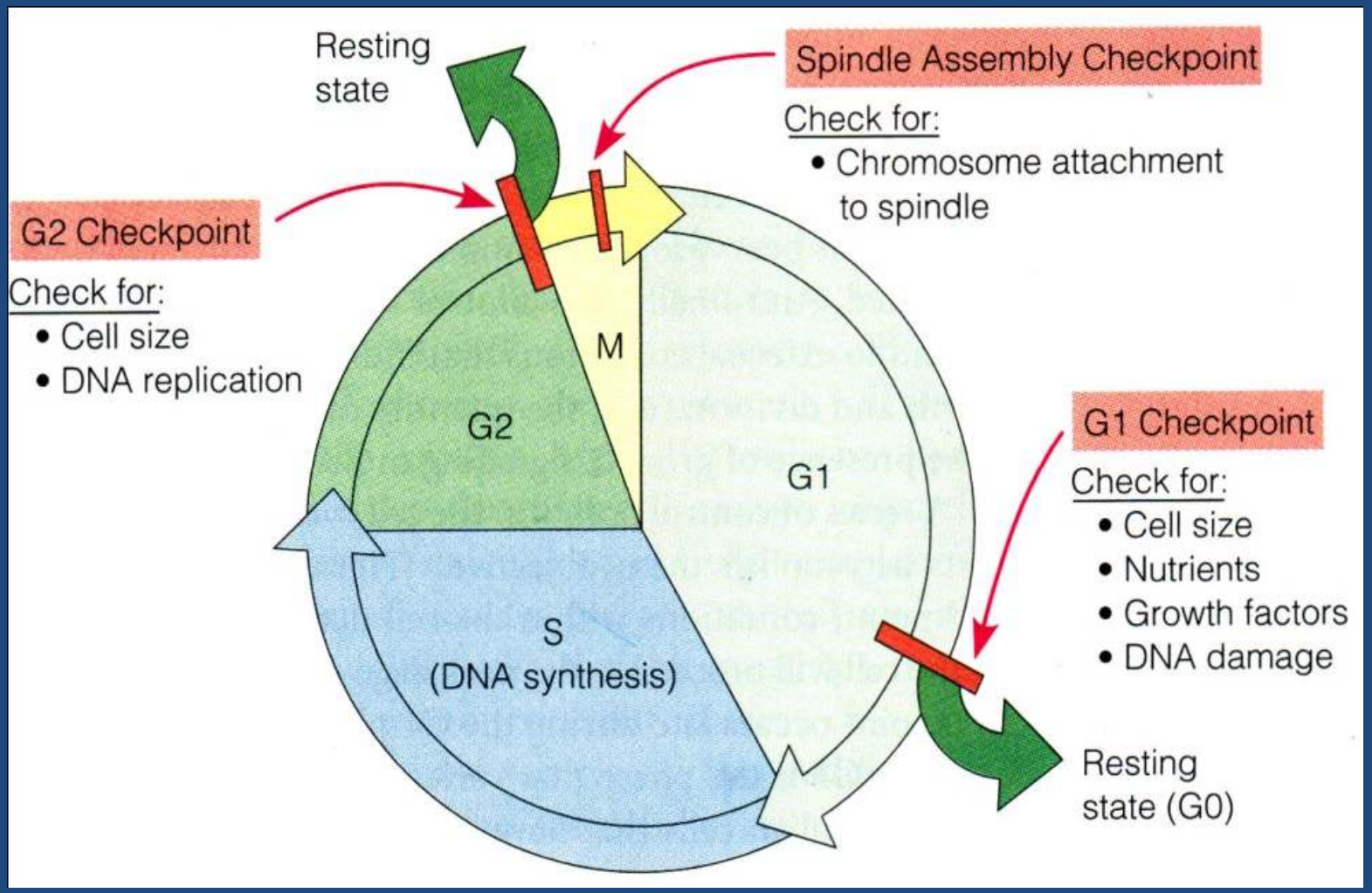
- The cell cycle is an ordered set of events. The G1 phase stands for “GAP-1” and is required for cell growth and preparation of DNA synthesis. The S-phase stands for “Synthesis” and replicates the genome.
- The G2 phase is “GAP-2” and needed for cell growth and preparation for mitosis. The last phase is M and it stands for “Mitosis” in which cells segregate duplicated chromosomes.



Cell Cycle Checkpoints

- Currently, there are three known checkpoints:
1) the G1 checkpoint, also known as the restriction or start checkpoint;
2) the G2/M checkpoint; and
3) the metaphase checkpoint, also known as the spindle checkpoint.




Resting state
Spindle Assembly Checkpoint
Check for:
• Chromosome attachment to spindle
G2 Checkpoint
Check for:
• Cell size
• DNA replication
M
G2
G1
S
(DNA synthesis)
G1 Checkpoint
Check for:
• Cell size
• Nutrients
• Growth factors
• DNA damage
Resting state (G0)

Cell Cycle Checkpoints

- G_1 (Restriction) Checkpoint
- The G1 checkpoint, also known as the **restriction point** in mammalian cells and the **start point** in yeast, is the point at which the cell becomes committed to entering the cell cycle.
- Start is controlled by extracellular signals depending upon availability of nutrient and cell size. For example, if yeast is faced shortage of nutrients, they arrest their cell cycle at start and enter to the restriction stage rather than proceeding to S phase.

Cell Cycle Checkpoints

- The animal cells are similar regulated at G1 phase known as **Restriction point** which is controlled by various growth factors. If growth factors are not available during G1 the cell enter to the resting phase Go.

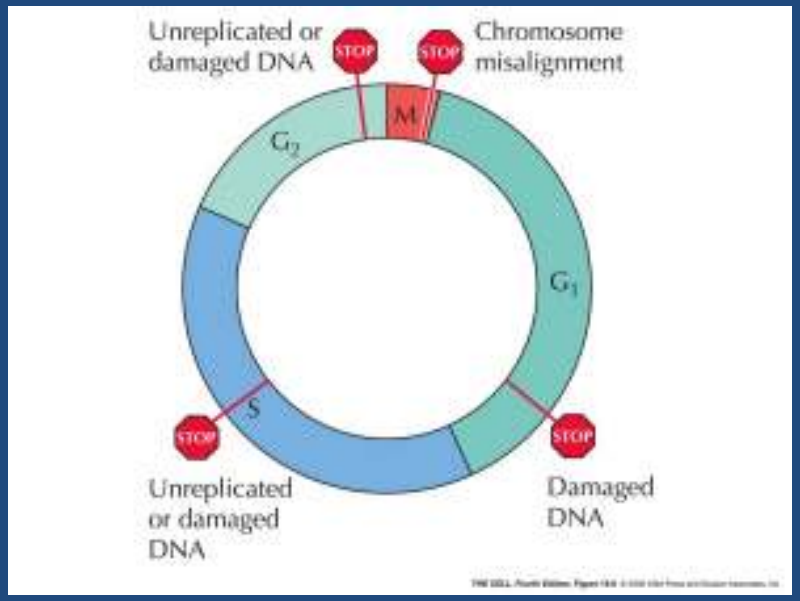
Cell Cycle Checkpoints

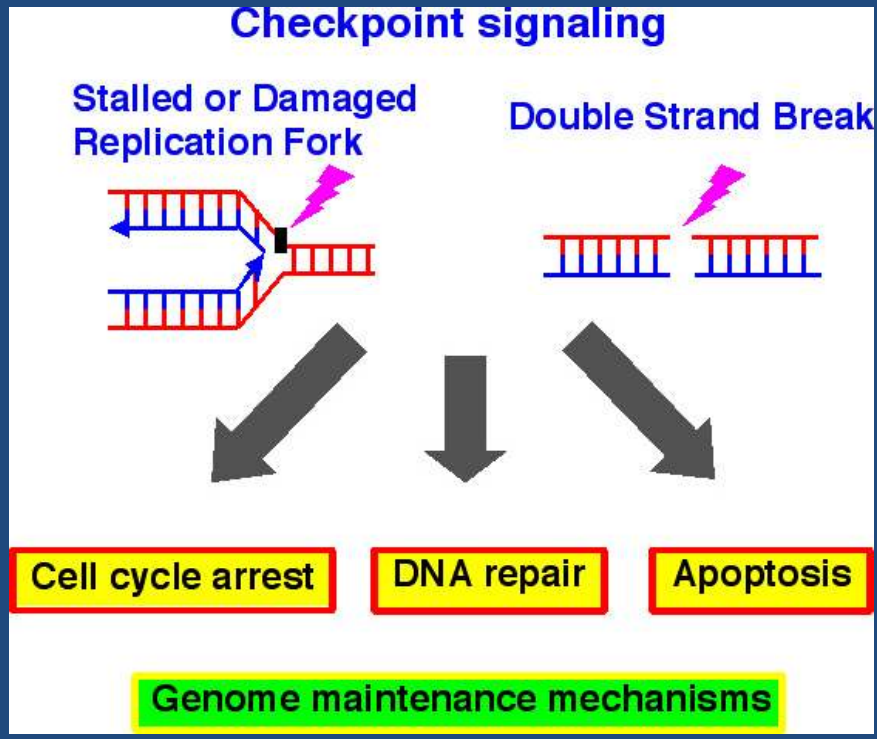
- G2 Checkpoint
- Following the decision to enter the cell cycle and undergo division, the cell goes through S phase, in which it replicates its DNA, rapid growth and protein synthesis in preparation for mitosis.
- The G2/M checkpoint, also known as the DNA damage checkpoint, ensures that the cell underwent all of the necessary changes during the S and G2 phases and is ready to divide.

Cell Cycle Checkpoints

- DNA damage checkpoint
- DNA damage checkpoints ensure the fidelity of genetic information both by arresting cell cycle progression and facilitating DNA repair pathways.
- Studies on many different species have uncovered a network of proteins that form the DNA damage checkpoints. Central to this network are protein kinases of ATM/ATR.
- A complex of sensor protein binds to damaged and un-replicated DNA and activate the ATR and ATM protein.

Cell Cycle Checkpoints





Cell Cycle Checkpoints

- **Metaphase Checkpoint**
- The mitotic spindle checkpoint occurs at the point in metaphase where all the chromosomes should/have aligned at the mitotic plate.
- During the process of cell division, the spindle checkpoint prevents separation of the duplicated chromosomes until each chromosome is properly attached to the spindle apparatus.
- In order to preserve the cell's identity and proper function, it is necessary to maintain the appropriate number of chromosomes after each cell division.

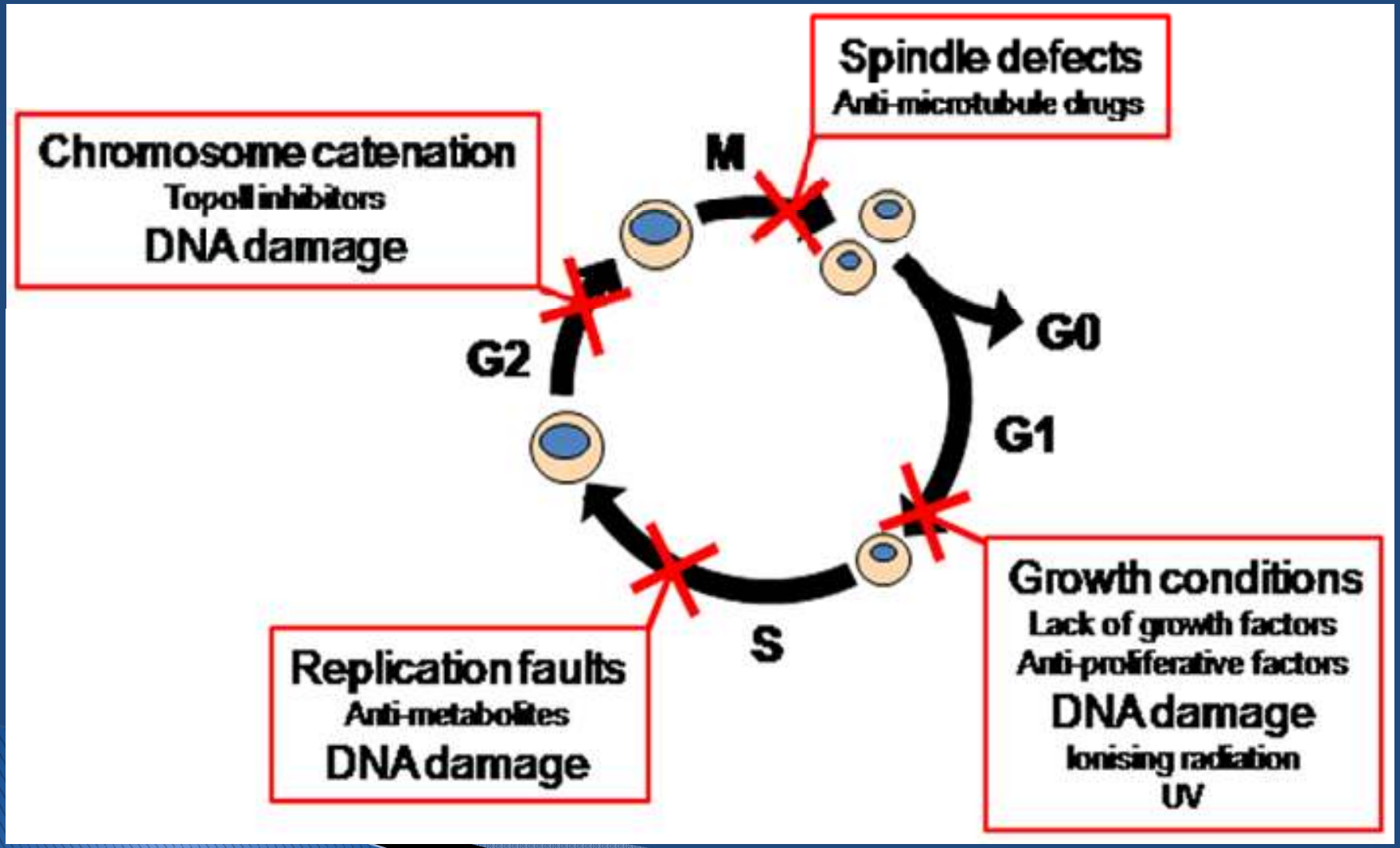
Cell Cycle Checkpoints

- An error in generating daughter cells with fewer or greater number of chromosomes than expected (a situation termed aneuploidy), may lead in best case to cell death, or alternatively it may generate catastrophic phenotypic results.
- The checkpoint ensuring that chromosome segregation is correct is termed spindle assembly checkpoint (SAC), spindle checkpoint or mitotic checkpoint. During mitosis or meiosis, the spindle checkpoint prevents anaphase onset until all chromosomes are properly attached to the spindle.

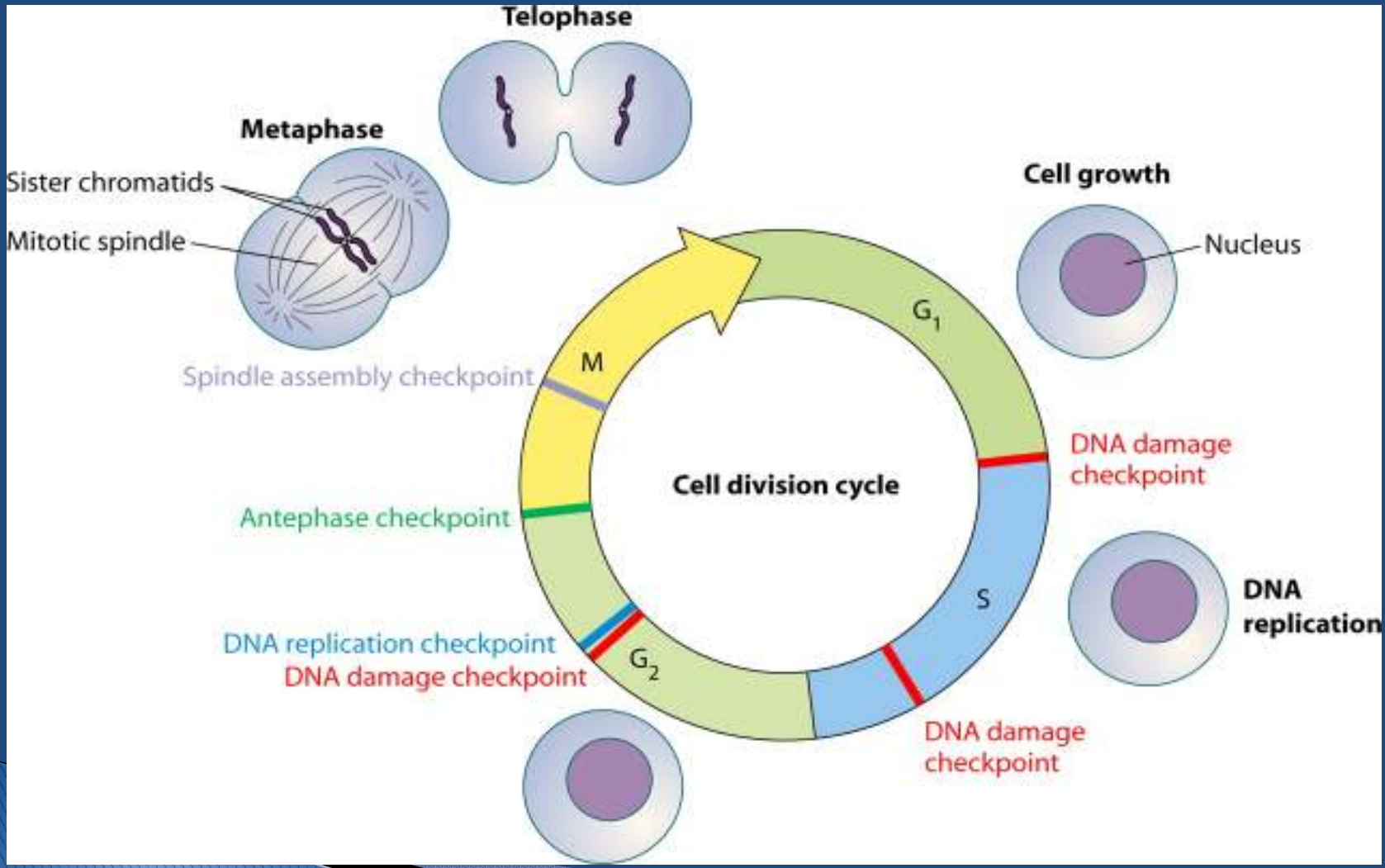
Cell Cycle Checkpoints

- To achieve proper segregation, the two kinetochores on the sister chromatids must be attached to opposite spindle poles (bipolar orientation). Only this pattern of attachment will ensure that each daughter cell receives one copy of the chromosome.

Cell Cycle Checkpoints



Cell Cycle Checkpoints



Cell Cycle Checkpoints

- Cell cycle checkpoints and cancer
- DNA repair processes and cell cycle checkpoints have been intimately linked with cancer due to their functions regulating genome stability and cell progression, respectively.
- The precise molecular mechanisms that connect dysfunctions in these pathways to the onset of particular cancers are not well understood in most cases.

Cell Cycle Checkpoints

- The loss of ATM has been shown to precede lymphoma development presumably due to excessive homologous recombination, leading to high genomic instability.
- Disruption of Chk1 in mice led significant misregulation of cell cycle checkpoints, an acculumation of DNA damage, and an increased incidence of tumorigenesis.

Cell Cycle Checkpoints

- Perhaps most famously, single mutant inheritance of BRCA1 or BRCA2 predisposes women toward breast and ovarian cancers.BRCA1 is known to be required for S and G2/M transitions, and is involved in the cellular response to DNA damage.
- BRCA2 is believed to be involved in homologous recombination and regulating the S-phase checkpoint, and mutations of deficiencies in BRCA2 are strongly linked to tumorigenesis

Thankyou