CELL CYCLE
&
ITS REGULATION

CELL CYCLE

Cell cycle was described by Howard and Pele in 1953.

Cell cycle is defined as the stages through which a cell passes from one cell division to the next. During this phase the cell grows and prepares for the division.

Whole of the cell cycle is alternated with –

- **Doubling of genome (DNA) in synthesis phase (S phase)**
- **Halving of that genome during mitosis (M phase)**

CELL CYCLE

Cell cycle – Completes in 2 phases

(I) Interphase – Preparatory phase, divided into 3 sub phases

- **(i) G1 (GAP 1) phase**
- **(ii) S (Synthesis) phase**
- **(iii) G2 (GAP 2) phase**

Leading to Doubling of genome (DNA)

(II) M phase – Phase of division, divided into 2 sub phases

- **(i) Karyokinesis (Nuclear division) – divided into 4 sub phases**
  - **(a) Prophase**
  - **(b) Metaphase**
  - **(c) Anaphase**
  - **(d) Telophase**
- **(ii) Cytokinesis (Division of cytoplasm)**

Leading to Halving of that genome, passing into daughter cells

CELL CYCLE

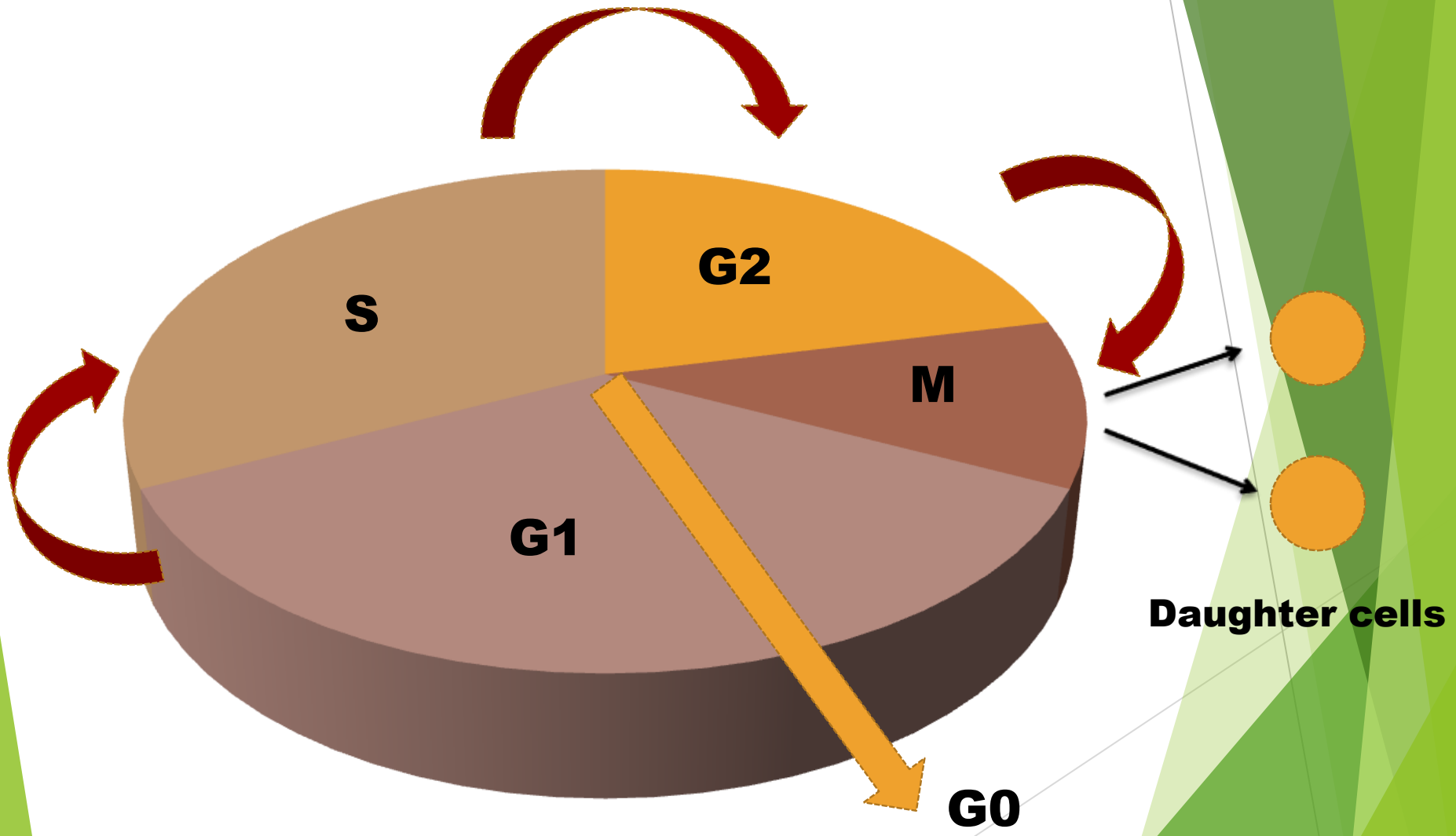


Fig.1: Different phases of cell cycle (cell growth & cell division)

CELL CYCLE

EVENTS OCCURRING IN G1 PHASE:

1. SYNTHESIS OF ENZYMES REQUIRED FOR DNA REPLICATION
2. SYNTHESIS OF RNA NEEDED FOR TRANSCRIPTION AND TRANSLATION
3. SYNTHESIS OF ATP
4. SYNTHESIS OF RAW MATERIALS (PENTOSE SUGAR, PHOSPHORIC ACID AND NITROGENASES) FOR DNA DUPLICATION IN S PHASE
5. SO MANY THINGS ARE SYNTHESIZED IN THIS PHASE, THEREFORE, THE SIZE OF THE CELL INCREASES

NOW THE CELL IS READY TO ENTER THE NEXT S PHASE.

EVENTS OCCURRING IN S PHASE:

1. DNA REPLICATION
2. CENTRIOLE DIVIDES (ONLY IN ANIMALS)
3. SYNTHESIS OF HISTOINE PROTEINS

NOW THE CELL IS READY TO ENTER THE NEXT G2 PHASE.

CELL CYCLE

EVENTS OCCURRING IN G2 PHASE:

1. SYNTHESIS OF TUBULIN PROTEIN REQUIRED FOR SPINDLE FORMATION
2. SYNTHESIS OF PROTEIN REQUIRED FOR PLASME MEMBRANE FORMATION
3. CELL ORGANELLES ARE DOUBLED
4. LOTS OF ATP MOLECULES REQUIRED FOR MOVEMENT OF CHROMOSOMES FROM EQUATOR TO POLE (30 ATP/ CHROMOSOME). SO ATP SYNTHESIS INCREASES.
5. RNA SYNTHESIS TAKES PLACE

NOW THE CELL IS READY TO ENTER THE NEXT M PHASE.

CELL CYCLE

EVENTS OCCURRING IN M PHASE:

KARYOKINESIS INCLUDES

1. **PROPHASE: CHROMATID COILING, DISINTEGRATION OF NUCLEAR MEMBRANE AND NUCLEOLUS, SPINDLE FORMATION**
2. **METAPHASE: CHROMOSOMAL ORIENTATION AT THE EQUATORIAL PLANE**
3. **ANAPHASE: MOVEMENTS OF CHROMATIDS TOWARDS THE OPPOSITE POLES**
4. **TELOPHASE: RECONSTRUCTION OF DAUGHTER NUCLEI**

CYTOKINESIS INCLUDES

FORMATION OF CELL PLATE LEADING TO EQUAL DIVISION OF CYTOPLASM, NUCLEI, CELL ORGANELLES AND CELL MEMBRANE INTO TWO DAUGHTER CELLS

CELL CYCLE

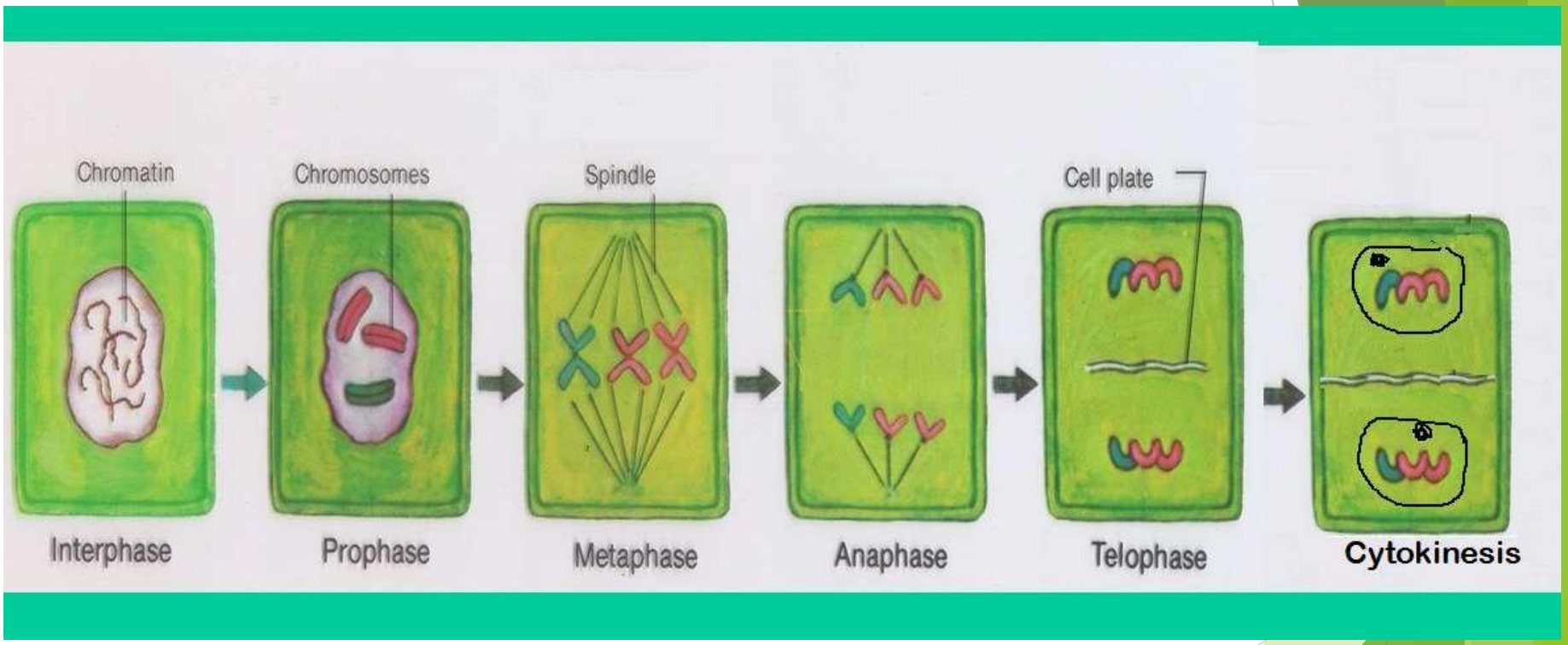


Fig.2: Stages of cell cycle

CELL CYCLE

AFTER CELL DIVISION, EACH OF THE DAUGHTER CELL BEGINS THE INTERPHASE OF A NEW CYCLE.

SOME CELLS (eg. CELLS OF HEART, KIDNEY, LIVER, NEURONS etc.) AFTER REMAINING IN G1 PHASE FOR SOMETIME COME OUT OF THE CELL CYCLE AND ENTER Go PHASE KNOWN AS QUIESCENT PHASE.

IN QUIESCENT PHASE THE CELL DIVISION STOPS BUT OTHER ACTIVITIES OF THE CELL CONTINUE.

SOMETIMES THE CELL REENTERS THE CELL CYCLE FROM QUIESCENT PHASE WHEN REQUIRED.

Eg. DURING FORMATION OF PERIDERM

CELL CYCLE

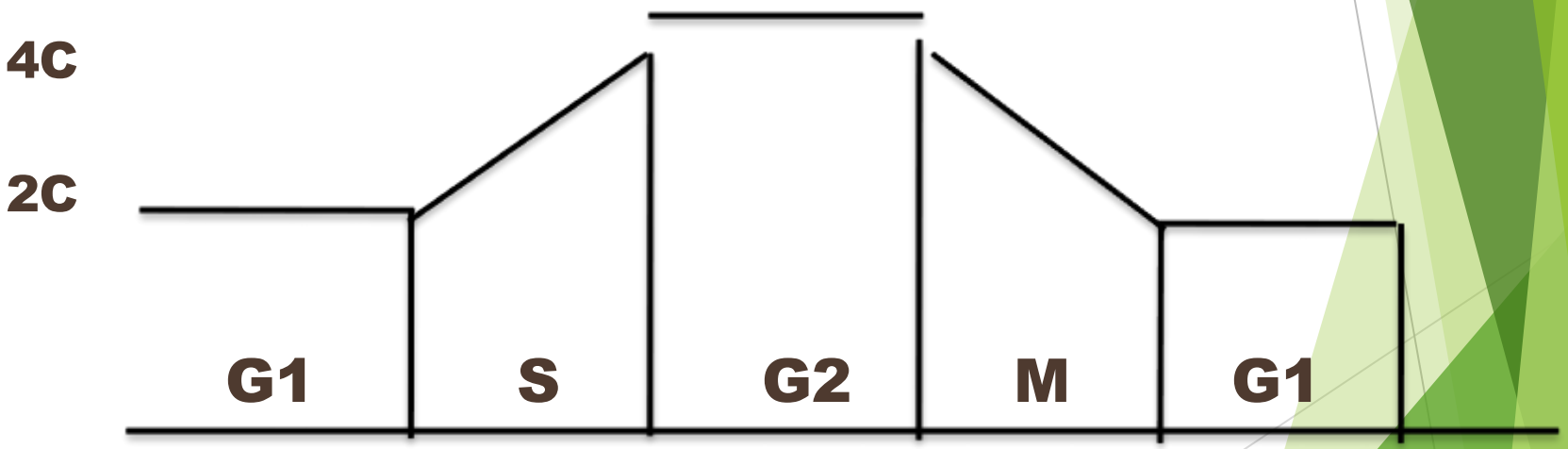


Fig.3: Cell cycle of a cell showing the changes in DNA content during various phases

REGULATION OF CELL CYCLE

Cell cycle does not occur in unchecked manner. The preparations of the cell are checked by regulatory molecules. It includes the detection and repair of genetic damage as well as prevention of uncontrolled cell division.

There are two key classes of regulatory molecules that determine a cell's proper progress through the cell cycle. These are -

- **Cyclins**
- **Cyclin dependent kinases (Cdk)**

The Nobel Prize in Physiology or Medicine 2001 was awarded jointly to Leland H. Hartwell, Tim Hunt and Sir Paul M. Nurse for their discoveries of key regulators of the cell cycle.

REGULATORY MOLECULES

Cyclins-

G1 Cyclins (D cyclins)

S-phase cyclins (cyclins E and A)

M-phase cyclins (B cyclins)

- **Their levels in the cell rise and fall with the stages of the cycle.**

Cyclin dependent kinases

G1 Cdk (Cdk 4)

S-phase Cdk (Cdk 2)

M-phase Cdk (Cdk 1)

- **Their levels in the cell remain stable.**
- **Remain inactive.**
- **Bind to the appropriate cyclin in order to be activated.**
- **Their function is to provide phosphate gr to a no. of proteins that control processes in the cell cycle.**

REGULATORY MOLECULES

Table 1: Cyclin – Cyclin dependent kinases (Cdk) complexes formed during cell cycle reguation and their functions

Phase of cell cycle	Cyclin	Cdk	Cyclin-Cdk complx	Function
G1	Cyclin D	Cdk 4	G1 Cyclin-G1 Cdk	Inhibits Rb protein and signals the cell to prepare the chromosome for replication
S	Cyclin E and Cyclin A	Cdk 2	S phase cyclin – S phase Cdk	Activates DNA replication
G2	Cyclin B	Cdk 1	Mitotic cyclins – M phase Cdk	Activates mitosis

CELL CYCLE CHECKPOINTS

CELL CYCLE CHECKPOINTS ARE USED BY THE CELL TO MONITOR AND REGULATE THE PROGRESS OF THE CELL CYCLE. THE CELL CANNOT PROCEED TO THE NEXT PHASE UNTIL CHECKPOINT REQUIREMENTS HAVE BEEN MET.

THREE MAIN CHECKPOINTS ARE:

(I) G1/S CHECKPOINT (before cell enters S phase)

(II) G2/M CHECKPOINT (after S phase)

(III) APC/C CHECKPOINT (during mitosis)

CELL CYCLE CHECKPOINTS

(I) G1/S CHECKPOINT (before cell enters S phase):

- **Checks for cell size**
- **Checks for nutrients**
- **Checks for DNA damage**
- **Checks for all the preparations (all proteins, ATP etc. requires in S phase)**
- **Checks whether S phase Cyclins and Cdk complex is activated to initiate DNA replication**

Then the cell passes to next S phase.

CELL CYCLE CHECKPOINTS

- (I) G2/M CHECKPOINT (after S phase):
  - Checks for proper DNA replication
  - Checks for all the preparations (all proteins,
  - ATP etc. required in M phase)
  - Checks for Tubulin synthesis
  - Checks whether M phase Cyclins and Cdk
  - complex is activated to initiate mitosis

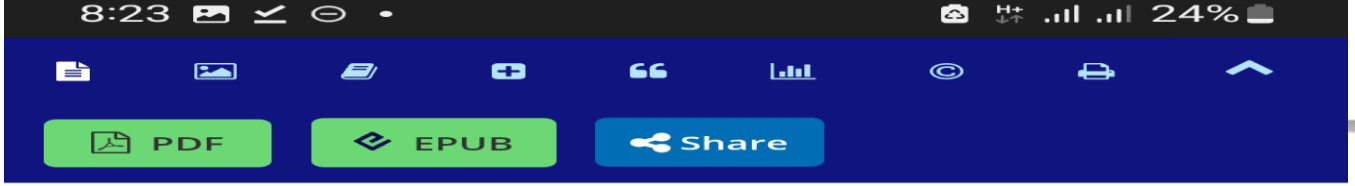
Then the cell passes to next M phase.

CELL CYCLE CHECKPOINTS

ALL THE CHECKPOINTS REQUIRE THE SERVICES OF A COMPLEX OF PROTEINS. THE LEVELS OF THESE PROTEINS ARE INCREASED IN DAMAGED CELLS. THEY ALLOW TIME TO REPAIR DNA BY BLOCKING THE CELL CYCLE.

P53 IS ONE SUCH PROTEIN WHICH SENSES DNA DAMAGE AND CAN HALT PROGRESSION OF THE CELL CYCLE IN G1 PHASE BY BLOCKING THE ACTIVITY OF Cdk 2 UNTIL DAMAGE CAN BE REPAIRED. IF THE DAMAGE IS SO SEVERE THAT IT CAN NOT BE REPAIRED, THEN THE CELL DESTRUCTS ITSELF BY APOPTOSIS.

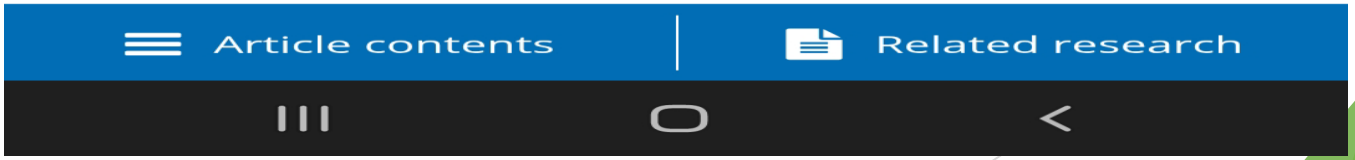
IN CASE OF DAMAGE TO DNA AFTER S PHASE, THE ACTION OF CDK 1 IS INHIBITED, THUS STOPPING PROGRESSION OF THE CELL FROM G2 TO MITOSIS.



Research

ABSTRACT

In chronic liver injury, quiescent hepatic stellate cells (HSCs) transdifferentiate into activated myofibroblast-like cells and produce large amounts of extracellular matrix components, e.g. collagen type 1. Cellular senescence is characterized by irreversible cell-cycle arrest, arrested cell proliferation and the acquisition of the senescence-associated secretory phenotype (SASP) and reversal of HSCs activation. Previous studies reported that H_2S prevents induction of senescence via its antioxidant activity. We hypothesized that inhibition of endogenous H_2S production induces cellular senescence and reduces activation of HSCs. Rat HSCs were isolated and culture-activated for 7 days. After activation, HSCs treated with H_2S slow-releasing donor GYY4137 and/or DL-propargylglycine (DL-PAG), an inhibitor of the H2S-producing enzyme cystathionine γ-lyase (CTH), as well as the PI3K inhibitor LY294002. In our result, CTH expression



Research Paper

Inhibition of endogenous hydrogen sulfide production reduces activation of hepatic stellate cells via the induction of cellular senescence

Turtushikh Damba, Mengfan Zhang, Sandra A. Serna Salas, Zongmei Wu, Harry van Goor, Aaron Fierro Arenas, ...show all

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Study Questions

1. Describe the key events that occur during the G1 phase of the cell cycle and explain their significance for cell growth and preparation for DNA replication.
2. Explain the role of the cyclin-dependent kinases (CDKs) in regulating the progression of the cell cycle. How do cyclins control CDK activity?
3. Discuss the molecular checkpoints in the cell cycle, specifically the G1/S checkpoint, the G2/M checkpoint, and the spindle assembly checkpoint. Why are these checkpoints crucial for maintaining genomic integrity?
4. What is the difference between mitosis and meiosis, and how does the cell cycle prepare the cell for these two processes?

Study Questions

5. Outline the phases of mitosis and describe the key events that occur during each phase (prophase, metaphase, anaphase, telophase). How is chromosomal segregation ensured during mitosis?
6. What is the significance of the S phase in the cell cycle, and what mechanisms ensure the accuracy of DNA replication during this phase?
7. Discuss the role of tumor suppressor genes, such as p53, in regulating the cell cycle and preventing uncontrolled cell division.
8. How do external signals, like growth factors, influence the progression of the cell cycle? Provide examples of how these signals can either promote or inhibit cell division.

THANK YOU