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Topic- Eukaryotic cell cycle and Regulation of cell cycle

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EUKARYOTLC CELL CYCLE AND REGULATION OF CELL CYCLE

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

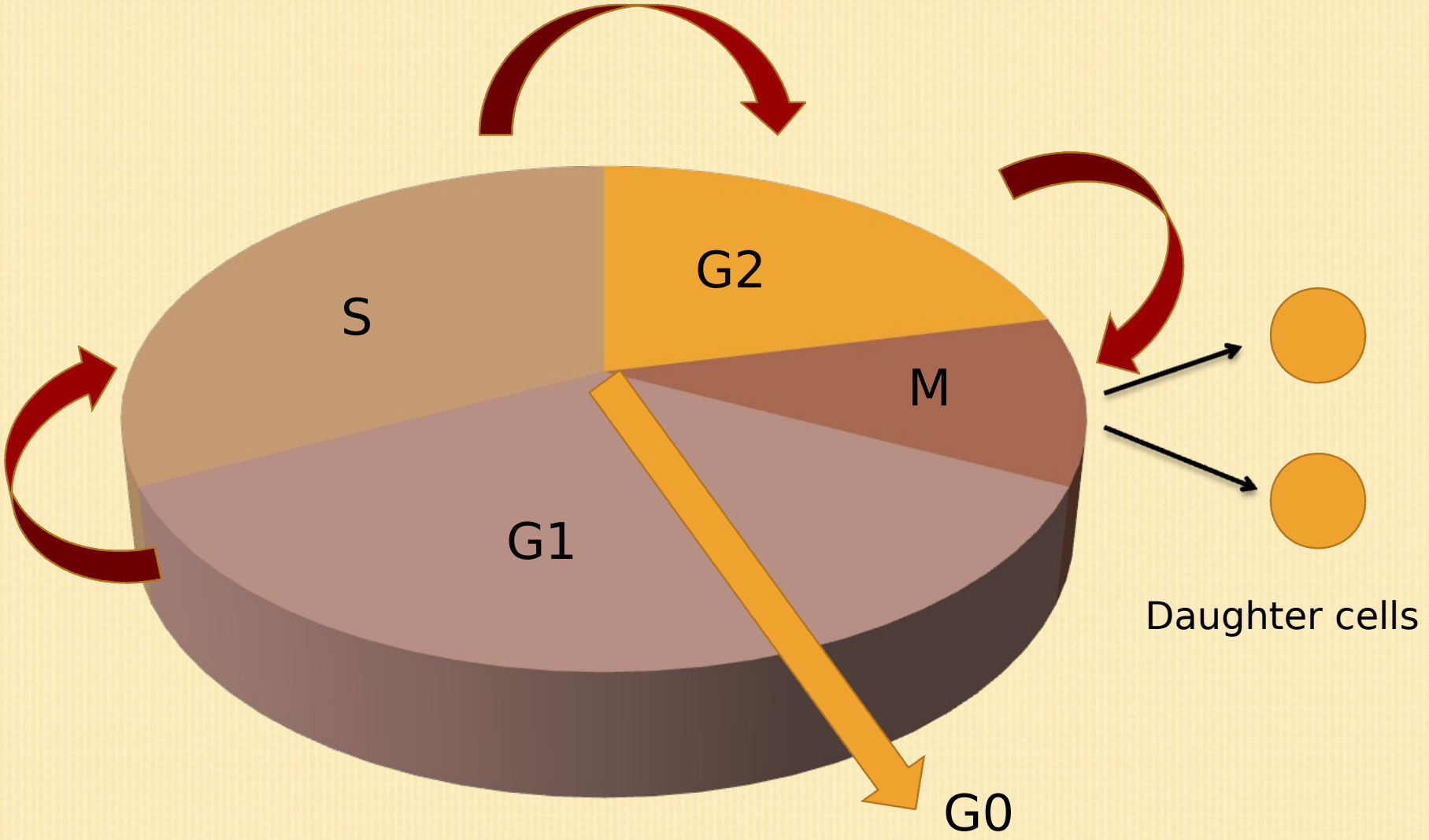

Fig.1: Different phases of cell cycle (cell growth & cell division)

CELL CYCLE

EVENTS OCCURRING IN G1 PHASE:

1. Synthesis of Enzymes required For DNA replication :
   - > DNA Helicase – unwinds DNA double helix
   - > RNA Primase – builds an RNA polymer (primer)
   - > DNA Polymerase – carries daughter nucleotides
   - > DNA ligase – helps to join fragments of DNA

2. Synthesis of RNA needed for Transcription and Translation

3. Synthesis of ATP

CELL CYCLE

EVENTS OCCURRING IN G1 PHASE:

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.

CELL CYCLE

EVENTS OCCURRING IN S PHASE:

1. DNA replication
2. Centriole divides (only in animals)
3. Synthesis of Histone 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 are 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: formation of nuclear membrane and nucleolus and reconstruction of daughter nuclei

CELL CYCLE

EVENTS OCCURRING IN M PHASE:

CYTOKINESIS INCLUDES

Formation of cell plate leading to equal division of cytoplasm, nuclei, cell organelles and cell membrane into two daughter cells, genetically identical to each other and to their parent cell.

CELL CYCLE

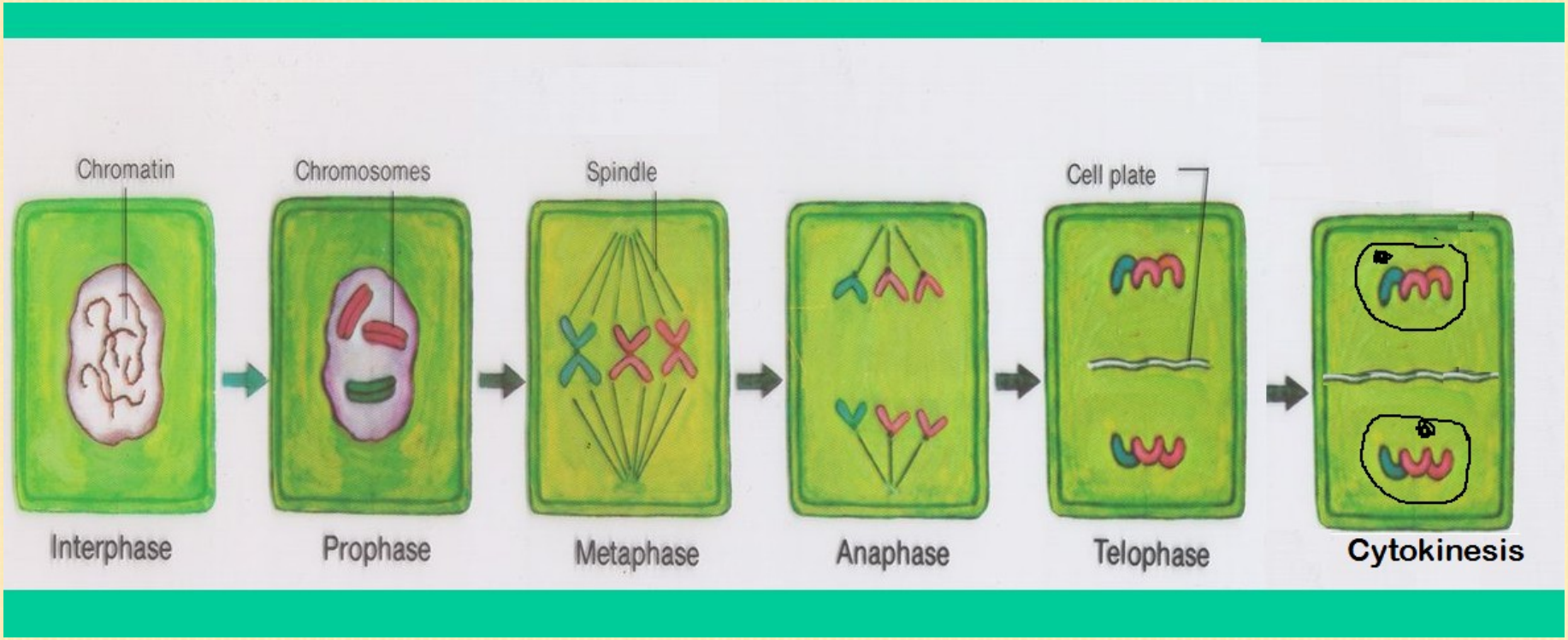

Fig.2: Stages of cell cycle

CELL CYCLE

After cell division, each of the daughter cells 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. Then the cells are said to be differentiated.

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, lymphocytes in human blood

CELL CYCLE

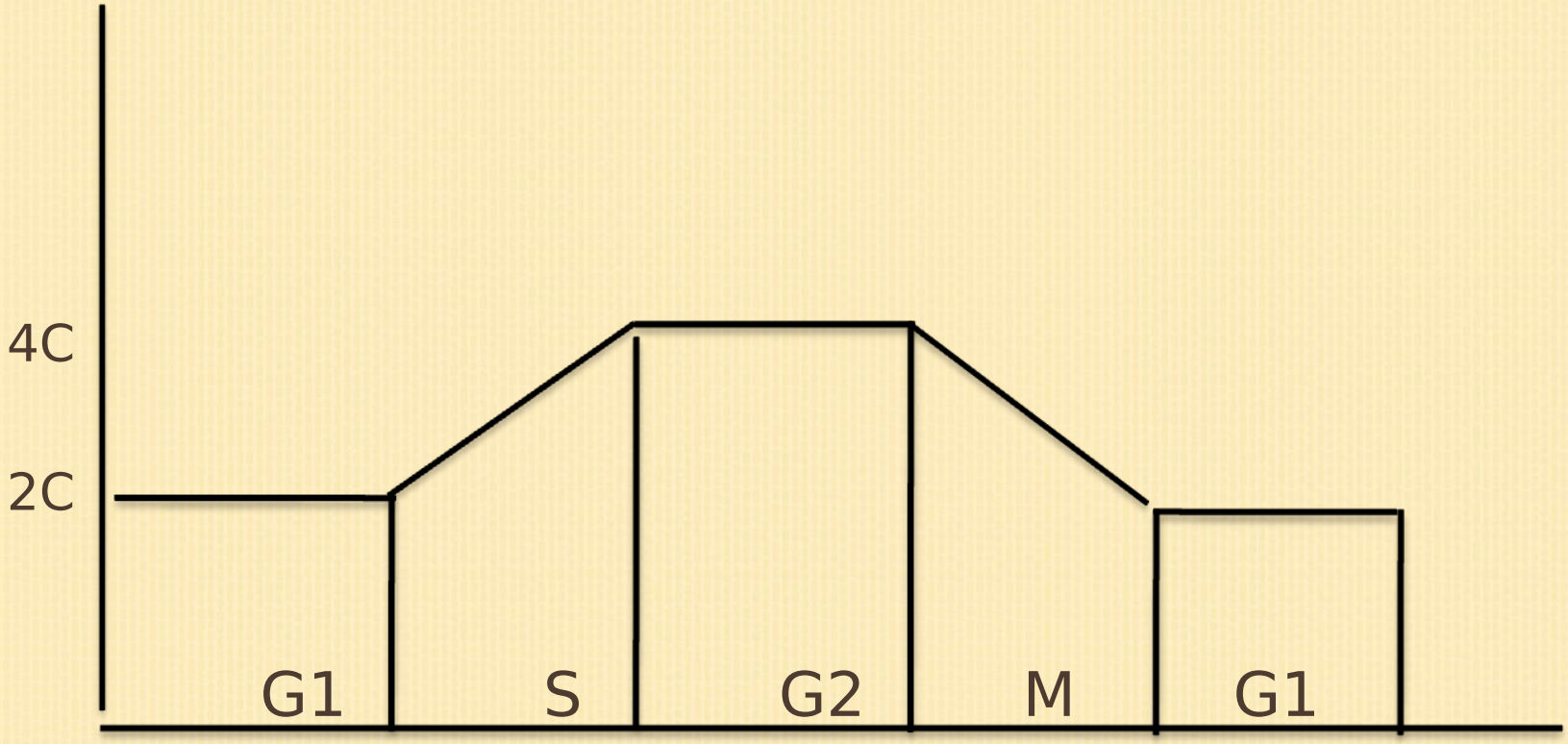

Fig.3: Cell cycle of a cell showing the changes in DNA content during various phases

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.

REGULATORY MOLECULES

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 group to a number of proteins that control processes in the cell cycle.

Eg. Rb protein (Retinoblastoma) when active inhibits mitosis, but when phosphorylated, it becomes inactive and allows cell cycle progression.

Due to its role as mitosis inhibitor, it is identified as tumour suppressor.

REGULATION OF CELL CYCLE WITH THE HELP OF REGULATORY MOLECULE

STEPS IN THE CYCLE

1. A rising level of G1-cyclins (D cyclins) bind to G1 Cdk (Cdk 4) and signal the cell to prepare the chromosomes for replication.

2. A rising level of S phase cyclins - which includes cyclins A and E bound to S phase Cdk (Cdk 2)- enters the nucleus and prepares the cell to duplicate its DNA and its centrosomes.

3. As DNA replication continues, cyclins E is destroyed and the level of mitotic cyclins begins to rise in G2.

REGULATION OF CELL CYCLE WITH THE HELP OF REGULATORY MOLECULE

4. The complex of mitotic cyclins (B cyclins) and M phase Cdk (Cdk 1) in G2 phase initiates the followings-

- Cessation of all gene transcription
- Condensation of chromosomes
- Assembly of the mitotic spindle
- Breakdown of the nuclear envelope
- Invasion of spindle fibre in the central area

REGULATION OF CELL CYCLE WITH THE HELP OF REGULATORY MOLECULE

5. These events take the cell to metaphase of mitosis which leads to orientation of the chromosomes at the equatorial plane.
6. At this point, the M phase promoting factor activates the Anaphase Promoting Complex (APC/C) which performs the following functions –
   - Destroys Securin and allows the sister chromatids to separate and move to opposite poles
   - Destroys B cyclins
   - Turns on synthesis of G1 cyclins for next turn of cycle
   - Degrades Geminin protein

REGULATION OF CELL CYCLE WITH THE HELP OF REGULATORY MOLECULE

Separation of sister chromatids depends on the breakdown of the Cohesin protein that holds them together. Cohesin breakdown is caused by an enzyme Separase. Separase is kept inactive by Securin. The APC/C complex destroys Securin, then the Separase becomes active and destroys Cohesin thus sister chromatids separate.

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 does not progress in unchecked manner. 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. The cell has several systems for interrupting the cell cycle if something goes wrong. For instance, the cell cycle is halted in response yo DNA damage, progress into mitosis is stopped when DNA replication is ongoing and separation of sister chromatids is delayed until all kinetochores are attached to the spindle. In case of any damage, the cell cycle is arrested until the damage is repaired. If the damage is so severe that it cannot be repaired then the cell self- destructs by apoptosis, also known as ‘programmed death’.

CELL CYCLE CHECKPOINTS

Two main checkpoints are:

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

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

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 and undergoes cell division and the daughter cells enter their own new cell cycles.

CELL CYCLE CHECKPOINTS

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

Damage to DNA before cell enters S phase inhibits the action of Cdk 2 thus stopping progression of the cell cycle until the damage can be repaired otherwise cell destructs itself by apoptosis.

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

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.

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. P53 levels are increased in damaged cells. This allows time to repair DNA by blocking the cell cycle. A p53 mutation is the most frequent mutation leading to cancer. More than half of all human cancers harbour p53 mutations and have no functioning p53 protein.

A genetically engineered adenovirus, called ONYX-015, can only replicate in human cells lacking p53. Thus it infects, replicates and ultimately kills many types of cancer *in vitro.*

THANK YOU