Cell cycle

Cell cycle and its regulation :

I. Cell cycle :

- An ordered series of events takes place in a eukaryotic cell leading to the duplication of chromosomes and division of (division phase and interphase) lasts for 20-24 hrs.
- Interphase is the longest phase in cell cycle. Based on synthetic activities it is divided into **G_1, S** and **G_2, phases.**
- Among them G, is an active preparatory phase that begins after mitosis.
- Many cytoplasmic elements like ribosomes, membrane bound organelles, substrates and enzymes necessary for DNA replication are synthesized during this phase.
- In S phase DNA replication occurs. During this phase the total content of DNA doubles up. G_2 phase is the period following s phase and preceeds M phase.
- It is characterised by increased nuclear volume. Proteins required for spindle formation are produced during this phase.
- The division phase in the cell cycle is termed as **M phase**. In this phase the cell completes the mitotic division.
- Cells spend most of the time in interphase especially in G_1 phase. It varies in different cell types. But the time for **S** and **G_2** phases remains constant.
- Some rapidly dividing cells (meristematic cell in plants and dermal cells in the skin of humanbeings) undergo cell cycles continuously.
- But the cells like nerve cells, muscle cells, RBC etc. withdraw from the G_1 phase and permanently enter into a nondividing state called G_0 phase after the G_1 phase.
- Some cells like **lymphocytes reenter the cell cycle from G_0 phase.**

II. Cell cycle regulation :

1. Two proteins namely **Cyclins** and **Kinases** regulate the series of events in cell cycle.
2. **Cyclins :**
   a) These are regulatory subunits.
   b) The levels of cyclins rise and fall with the phases of the cell cycle.
   c) Three different cyclins namely G_1 cyclin (cyclin D), S cyclin (cyclin E and A) and M cyclin (cyclin B) are identified.
3. **Kinases :**
   a) These are **phosphorylating enzymes**.
   b) The levels of kinases remain stable in cell cycle.
   c) They add phosphate group to various proteins that control the process of cell cycle.
   d) They are catalytic and can not act independently until they are associated with cyclins. Hence they are called **Cyclin dependent Kinases** (Cdk).
   e) Specific CdKs associate with the specific cyclins forming Cdk cyclin complexes. They are G–Cdk (Cdk4 or Cdk6), S–Cdk (Cdk2) and M–Cdk (Cdk1) cyclin complexes.

   G_1 – Cdk cyclin complex :
   a) They appear first when cells are stimulated to divide.
   b) This complex prepares the cell for S-phase.
   c) It activates the transcription factors required for DNA replication in S-phase.
   d) They are also required for the expression of S-Cdk complex genes.

   S – Cdk cyclin complex :
   a) These are inhibited by inhibitor and this inhibitor is degraded by G_1 Cdk – cyclin complex.
   b) It phosphorylates the proteins necessary for DNA replication in S-phase.

   M – Cdk cyclin complex :
   a) It is synthesised during **S-phase and G_2 phase**, but its activation is under the check till the end of DNA replication.
   b) The activated M Cdk complex induces **chromosome condensation**, **breakdown of nuclear membrane** and **mitotic spindle formation**.
   c) This complex also activates **Anaphase Promoting Complex** (APC) which promotes the anaphase changes in the cell division.

   APC triggers the destruction of cohesions and allow the sister chromatids to separate.

   APC also stimulates mitotic cyclins by activating a protein called **Ubiquitin**

   d) Decrease in M-Cdk complex helps in the decondensation of chromosomes and reorganization of nuclear membrane thus completing the cell division. The cell now starts new cycle.

Check points :

- The different check points are **G_1 checkpoint, G_2 checkpoint** and **M checkpoint**, or **final checkpoint.**
- The critical point in the cell cycle is **G_1 checkpoint**. It allows the transition of G_1 phase in to S phase. The concentration, and activity of G_1 Cdk-cyclin complex act as G_1 checkpoint.
- Once the transition occurs, the remaining cycle can be completed. A second transition occurs at **G_2 checkpoint**.
- The concentration, and activity of M-Cdk cyclin complex act as G_2 checkpoint. Through G_2 checkpoint, cycle enters division phase. The **final checkpoint** is during division itself.
- This checkpoint regulates formation of spindle fibre and their attachment to the centromere. This checkpoint is not controlled by Cdk complex, but by enzymes.

Genes regulating the cycle :

- cdc 2 gene (cell division cycle), whose product kinase, is associated with the formation of different cyclin complexes. In mammals p^{53} gene is also associated with cell cycle regulation.
- The product of this gene functions as a **transcriptional activator**. It regulates the expression of other genes that control the cycle.
- Some times this P^{53} protein induces the production of cyclin kinase inhibitor (CKI), which inactivates Cdk-cyclin complex. Cell is arrested at G_1 checkpoint.
- Thus allowing the cell to repair the damaged DNA.
- Paul Nurse, Leland Hartwell and Tim Hunt were awarded Noble prize in Medicine for the year 2001 for their discovery of cdc gene mutants and cell cycle regulation events.
- Cell cycle regulation research promises new possibilities for cancer treatment and skin repair without grafting.