MOLECULAR MECHANISM OF REGULATION OF CELL CYCLE

The regulation of the cell cycle is critical for the normal development of the multicellular organism. The length of the cell cycle varies among different cell types, depending on their role in the organism

Study of cytochemical and genetic technique as well as by recombinant DNA technology have revealed that, the cell replication is controlled by two events.

1) Mitosis
2) Nuclear DNA replication

These two events are regulated by some heterodimer protein kinases called cycline

Cycline has two subunits 1) regulatory and 2) catalytic subunit.

The catalytic subunit is called cycline dependent kinase, CdK because they have no kinase activity until unless they are associated with the cycline.

Activities of cell cycle-controlled process

a) Cell cycle-controlled process activates the enzymes necessary for different phases of the cell cycle at appropriate time. At the same time,they inactivate them when they are not required.
b) The cell cycle-controlled process also ensures that each stage of the cycle is completed before entering the next stage
eg before mitosis, the cell must split before entering into DNA replication stage.
c) The cell cycle-controlled system also takes the account of the condition outside the cell eg the conditions which stimulates the cell division where more cells are required. Malfunctioning of the controlled system leads to cancer.
Cell cycle-controlled system thereby regulates the number of cells in the tissue.
d) The events of the cell cycle occur in a sequential manner and the sequence must be preserved even if one stage of the cycle takes longer time as usual. All the nuclear..DNA must be replicated before entering into M phase. If DNA synthesis is slowed down, then other stages like mitosis and cell division must also be delayed.
e) The cell cycle-controlled mechanism also controls the size of cells. The size of cells must be doubled before undergoing division. Otherwise the cells would get smaller with each division.

Cell Cycle Chek points-

The cell cycle controlled system achieve all these by means of molecular breaks which can stop the cell cycle at various Checkpoints. At each checkpoint, conditions within the cell determine whether or not the cell will proceed to the next stage of the cell cycle.

There are two checkpoints – G1 checkpoint and G2 checkpoint.

G1 checkpoint- the findings suggest that passing from G1 into S-phase is a critical control point in the cell cycle. In yeast, this G1 checkpoint is called **Start**. Yeast must have sufficient nutrient and must reach a certain size before they can pass through Start. In animal cells, the G1 v is called the **Restriction point**. The ability to pass through the restriction point is controlled to a large extent by extracellular growth stimulating proteins called **growth factor,** which can stimulate or inhibit cell proliferation in multicellular organism.

G2 check point-

G1 check point allow the system to halt before entering into mitosis. It allows the cell to check the completion of DNA replication before entering into mitosis.

Spindle assembly check point –

It is located at the junction between metaphase and Anasphase. Before cells can pass through this check point, all the chromosome must be properly attached to the spindle, otherwise the cell cycle is temporarily arrested at this point.

Mitosis promoting factor(MPF)-

The proceeding cell fusion experiment suggest that specific molecules present in the cytoplasm are responsible for moving cells through the G1 and G2 check points- that is for triggering the onset of DNA replication (S-Phase) and Mitosis (M-phase)

The cell cycle is controlled by Cyclin dependant kinase (CdK) molecule-

Studies have revealed that control of the eukaryotic cell cycle involve several kinds of CdK molecules and their interactions with multiple form of cyclin, thereby creating a variety of different Cdk – cycline complexes.

There are three types of cycline –CdK complexes-

i) G1 CdK complex

ii) S phase CdK complex

iii) Mitotic CdK complex

i) G_1 CdK complex- The G1 CdK complex prepare the cell for S-phase by activating transcribing factors which are required for the DNA synthesis. It also encodes the S-phase CDK complex.

Extracellular growth factor called Mitogencan regulate the G_1 CdK complex. The point at which G1 is independent of mitogen in carrying out the cell cycle is called restriction point.

The activity of the S-phase initially checked by a specific inhibitor.In late G1 phase, the the G1 CdK complex induce the degradation of S-phase inhibitor and thereby stimulate the S-phase CdK.

ii) S-phase CdK complex- It phosphorylates the regulatory sites in the protein and activates the inhibition of DNA replication and also prevent the reassembly of pre-replication complex. Because of this inhibition chromosome is replicated just once in the cell cycle thereby maintaining the constant chromosome number in the daughter cell.

iii) Mitotic CdK complex- Also called MPF. They are synthesized during S- phase and G2-phase. Mitotic CdK complex induce chromosome condensation, breakdown nuclear envelope, assembly of spindle fibre apparatus, alignment of condensed chromosome at the metaphase.

After the association of condensed chromosome with spindle fibre mitotic CdK complex activates anaphase promoting complex (APC), a large protein complex that controls many events associated with the final phases of mitosis. APC directs the ubiquitin mediated protiolysis of anaphase inhibitor leading to the inactivation of the protein complex that connects the sister chromatids. Because of this the sister chromatids move to the opposite poles.

APC also degrades the mitotic CdK complex which causes the reformation of nuclear envelope around the daughter cell nucleus during telophase and promote cytokinesis. During early G1 of the next cell cycle the pre replication complexes are formed by dephosphorylation which inhibits the APC. It causes the accumulation of the mitotic CdK during S-phase and G2 phase.

All the above three phases are irreversible because this transition is regulated by degradation of protein which is an irreversible process.