**Regulation of cell cycle - checkpoints**

As a cell grows the cell wall and most of the components of cytosol increase in size and quantity. When cell reaches a critical mass, it divides producing two smaller progeny cells. Under appropriate conditions, the progeny cells will in turn grow and divide. As cells proceeds through cell cycle two key process takes place in accurate and coordinated manner 1) The genetic materials are duplicated, 2) two copies of genetic material must be faithfully divided into two progeny cells.

The **cell division cycle (*cdc*)** study shows that there are two points at which a cell makes a commitment to proceed through the ensuing stages of the cell cycle. The **first point**, called ***start***, **occurs near the end of the *G1* phase**. At start cell become committed to the **initiation of DNA synthesis** a short time later at the onset of the *S* phase of the cell cycle. The **second point** is the commitment to proceed through the chromosomal condensation and chromatid separation events of mitosis, this occurs at the very beginning of the M phase of the cell cycle. Recent evidence indicates that certain key regulatory proteins function as signals in both steps.

A ***mitosis promoting factor (MPF)*** of ***M phase*** has been shown to contain two essential components, 1) proteins called **cyclins** that undergoes cycles of synthesis and accumulation during *G1* Phase and *G2* phase and degradation during *M* phase and 2) a start and *M* phase specific protein kinase called *pp34* (pp for phosphoprotein, a protein that may have phosphate groups on side chains of specific amino acids and 34 for 34000 molecular weight), which is the product of *cdc2* gene of *Schizosaccharomyces pombe* and *CDC28 Sccharomyces* *cerevisiae*. *Pp34* involved in both the commitment events: ***start*** and ***onset*** of *M* phase. Moreover results shows phosphorylation and dephosphorylation of a single tyrosine residue, that may directly regulate both initiation of DNA replication and the onset of *M* phase when *pp34* protein kinase interacts two classes of cyclins, one class ***M-cyclins***, involved in *M* phase and second class ***G1-cyclins***, involved in start decision.

Although additional components are also involved in the regulation of cell cycle, the cyclins and *pp34* protein kinase are the key components. One of the important aspects of having one or more of the same molecules involved in both commitment steps is that it provides a **mechanism by which a cell can remember, based on the conformational states of these molecules, where it is in the cell cycle, and thus accurately coordinate start and onset of *M* phase.**

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**Fig: diagram showing regulation of cell cycle**

**Checkpoints**

Cell cycle checkpoints function to ensure that incomplete or damaged chromosomes are not replicated and passed on to daughter cells. In most cells, there are several checkpoints in the cell cycle at which the cycle can be arrested if previous events have not been completed. The cell cycle is a highly regulated and a dependent series of events, mediated by a number of checkpoints. In most cells, there are several checkpoints in the cell cycle which can be classified into: cell cycle checkpoints, DNA damage checkpoint and spindle assembly checkpoints.

* 1. **Cell cycle checkpoints-** It ensures the fidelity of cell division. These checkpoints verify whether the processes at each phase of cell cycle have been accurately completed before progression into the next phase. An important checkpoint in G1 is start or restriction point, at which the cell becomes committed to DNA replication and completes a cell cycle. During the G1 phase the cell integrates mitogenic and growth inhibitory signals, and makes the decision to proceed, pause or exit the cell cycle.
  2. **DNA damage checkpoint or mitotic checkpoint-** It ensures that anaphase onset is initiated only when all chromosomes are properly attached to microtubules and aligned at the metaphase plate. It monitors the correct attachment of chromosomes to the mitotic spindles, It prevents segregation of sister chromatids until they are properly aligned on the metaphase plate. During mitosis, Chromosome segregation is carefully monitored to prevent aneuploidy. When microtubules from two opposite spindle poles attach to the kinetochores of a metaphase chromosome, tension develops across the paired kinetochores owing to the mitotic force that tends to pull the sister chromatids.

Kinetochore eliminates incorrect microtubule attachments by sensing whether or not the centromere is under tension. Thus kinetochores have a crucial role in cell cycle progression. The mechanism that monitors and responds to kinetochore-microtubule attachment is the **spindle assembly checkpoint (SAC**). During metaphase proper metaphase kinetochore–spindle microtuble attachment takes place. Until proper attachments formed SAC inhibits to undergo further steps. When problems are sensed and SAC activated and **mitotic checkpoints complex** formed inhibiting further progress. SAC failure results in **aneupoidy**.

* 1. **Spindle assembly checkpoints-** It involves a signal transduction pathway induced by DNA damage that blocks cell cycle progression until DNA is properly repaired. Its function to ensure that incomplete or damaged chromosome not replicated and passed on to daughter cells. According to the cell cycle stages, DNA damage checkpoints are classified into at least 3 checkpoints: **G1/S checkpoint, intra-S phase checkpoint and G2/M checkpoint**. The G1/S checkpoint inhibits G1/S phase transition in cells that have not yet committed to DNA replication. The intra-S checkpoints prevents initiation of DNA replication origin at origins that have not yet been activated. The G2/M checkpoint inhibits entry into mitosis. The replication checkpoint, a specialized branch of the DNA damage checkpoint, monitors fork problems, and triggers a cellular response aimed at preserving genome integrity.

**Role of protein Kinase**

Mitotic promoting factor of regulation of cell division is a large-sized protein comprising two subunits-an inert subunit and a kinase subunit, which can phosphoregulate (and activate) the inert subunit (called self activation) and other molecules. Thus MPF kinase directly phosphorylates several substances, including histone H1, thereby promoting chromosome condensation and it may be through a cascade of phosphorylation that MPF triggers all the complex events of mitosis such as nuclear envelope breakdown and cytoskeletal change.