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CELL CYCLE

Cell Cycle is an ordered series of events. It is a period from one cell division to the next. The cell cycle has two main phases — (i) Interphase and M-phase. The period of actual division, corresponding to the visible mitosis is called M phase. The interphase is further divided into the — G_1, S and G_2 periods. (G_1, the gap period between the end of mitosis and the start of DNA replication; S, the period during which DNA synthesis occurs; and G_2, the gap period following DNA replication and preceding the initiation of the mitotic prophase) Cells may withdraw from the cycle into G_0 or re-entered from it.

The engines that drive progression from one step of the cell cycle to the next are a series of protein complexes composed of two sub-units; a cyclin and a cyclin dependent protein kinase. (CDK). Cyclin is regulatory component whereas CDK is catalytic and acts as protein kinase. Cyclins are so called because they undergo a cycle of synthesis and degradation in each division cycle of the cell. There are three major classes of cyclins, each defined by the stage of the cell cycle at which they bind CDK's and function: * G_1-cyclins * S-cyclins and * M-cyclins. Cyclins bind to CDK molecules and controlled their ability to phosphorylate appropriate target proteins.

Regulation of Activity of Cyclin-CDK Complexes:

Cyclin undergoes a cycle of synthesis and degradation in each cell cycle. CDK's level by contrast are constant during cell cycle. Cyclical changes in the cyclin levels result in the cyclic assembly and activation of the cyclin-CDK complexes. Cyclin-CDK complexes are inactivated by regulated proteolysis of cyclins at specific cell cycle stages. This cyclin destruction occurs by a ~~Ubi~~ Ubiquitin dependent proteolysis. Cyclin levels in cells are controlled not only by changes in cyclin destruction but also by changes in cyclin synthesis. Ubiquitin mediated proteolysis of cyclin is catalysed by enzyme ubiquitin ligase. * Skp 1 - Cullin - F-Box (SCF), a ubiquitin ligase is responsible for the ubiquitylation and destruction of G_1 and S phase cyclin. Another ubiquitin ligase, anaphase promoting complex (APC) is responsible for the ubiquitylation and

& destruction of M phase-cyclins. The rise and fall of cyclin levels is the primary determinant of CDK activity during the cell cycle. Several additional mechanisms also controls the CDK activities at specific stages in the cell cycle. CDK activity is governed by three mechanisms:

(1) Cyclin synthesis and Degradation.
(2) Phosphorylation / de-phosphorylation reaction.
(3) Binding of CDK inhibitor proteins.

CONTROL OF CELL CYCLE EVENTS

Each of the different cyclin-CDK complexes serves as a molecular switch that triggers a specific cell cycle events. When cells are stimulated to divide, G_1 cyclin-CDK complexes are expressed first. These prepare the cell for the S-phase by inducing enzymes synthesis required for DNA replication and S-phase cyclins and CDK's.

Mitotic CDK complexes or maturation promoting factor (MPF) are synthesised during the S-phase and G_2. Mitotic CDK complexes induced chromosome condensation, breakdown of the nuclear envelope, assembly of the mitotic spindle apparatus, and alignment of condensed chromosomes at the metaphase plate. After the proper association of all chromosomes with spindle microtubules has occurred, the mitotic CDK complexes activate the anaphase promoting complex (APC). This multiprotein complex directs the obiqwitin mediated proteolysis of anaphase inhibitors leading to inactivation of the protein complexes that connect sister chromatids at metaphase. Degradation of these inhibitors thus permits the onset of anaphase. The destruction of cyclin is as important for exit from mitosis as its synthesis is for entry.

The resulting decrease in mitotic CDK activity permits the separated chromosomes to de-condensed, the nuclear envelope to re-form around daughter cells nuclei during telophase, and the cytoplasm to divide at cytokinesis yielding the two daughter cells.

Passage through three critical cell cycle transition s, G_1-S phase, metaphase to anaphase, and anaphase to telophase and cytokinesis, is irreversible because these transitions are triggered by the regulated degradation of p proteins.

As a consequence, cells are forced to traverse the cell cycle in one direction only.

CELL CYCLE CHECK POINTS

The cell cycle is a highly regulated and a dependent series of events, mediated by a number of check points. Cell cycle check points function to ensure that incomplete or damaged chromosomes are not replicated and passed on to daughter cells. In most cells there are several check points in the cell cycle at which the cycle can be arrested if previous events have not been completed. It is during the G_1 phase that the cell integrates mitogenic and ~~both~~ growth inhibitory signals and makes the decision to proceed, pause or exit the cell cycle. An important check point in G_1 has been identified in both yeast and mammalian cells. Referred to as start in yeast and the restriction point in mammalian cells this is the point at which the cell becomes committed to DNA replication and completing a cell cycle.

Two fundamental checkpoints i.e.
*Replication checkpoint and *Spindle checkpoint, operate in every round of cell cycle. The replication checkpoint monitors progress of DNA replication; and arrests cell cycle at G_2/M transition until DNA replication is complete. The Spindle assembly checkpoint monitors attachment of chromosomes to the mitotic spindles; it prevents segregation of sister-chromatids until they are properly aligned on the metaphase plate.

Perturbation in the cellular environment can activate additional checkpoints, leading to an observed inhibition of cell cycle progression. When cells have DNA damages that have to be repaired, cells activate DNA damage checkpoints that arrests cell cycle. According to the cell cycle stages, DNA damage checkpoints are classified into atleast three checkpoints: * G_1/S checkpoint, *Intra S-phase checkpoint and * G_2/M checkpoint.

The G_1/S checkpoint inhibits S-phase entry in G_1 cells that have not yet committed to DNA replication.

The Intra S checkpoint prevents initiation of DNA replication at origins that have not yet been activated.

The G_2/M checkpoint inhibits entry into mitosis.

During mitosis, chromosome segregation is carefully monitored to prevent aneuploidy. The Spindle assembly checkpoint or mitotic checkpoint guarantees that anaphase onset is initiated only when all chromosomes are properly attached to microtubules and aligned at the metaphase plate. The Spindle checkpoint blocks anaphase entry by inhibiting the anaphase chromatin complex. When the kinetochores donot receives spindle fibres from both poles of the cell, protein Mad 2 (Mitotic Arrest Defective Yeast Mutant) binds to Cdc 20 and doesnot allow the APC to bind to the Cdc 20. At the same time that Mad 2 is sequestering Cdc 20, the centromere protein (CENP) – E activates BubR1, which also blocks anaphase. The localization of Mad 2 and BubR1 to the kinetochore may be dependent on the Aurora B-Kinase. Cells lacking Aurora B fail to arrest in metaphase event when chromosomes lack microtubule attachment.