CELL CYCLE AND GENES

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Cell cycle consist of all the events and phases through which a cell passes to divide into two cells.

Two phases of cell cycle:

1. Interphase
2. Mitosis

INTERPHASE

- G-1 Phase – pre-synthetic phase, phase of cell before DNA synthesis
- S-Phase – phase of DNA Synthesis (DNA replication)
- G-2 Phase – cell prepares to divide the nuclear genetic material equally into two daughter cells
    - Post synthetic phase
    - Pre mitotic phase

MITOSIS

Cell divides into two daughter cells.

Mitosis – division of nuclear material

Cytokinesis – division of cytoplasm

G_0 Phase

After mitosis, some cells directly goes to G-1 phase while other cells may go to resting stage called growth phase or G_0 phase.

LABILE CELLS

Cells with no G_0 phase and hence are multiplying all the time e.g skin cells, GIT cells, bone marrow cells

STABLE CELLS

Cell having a G_0 phase are called stable cells. They proliferate upon proper stimulus e.g hepatocytes (liver cells), nephrons, pancreatic cells.

PERMAMENT CELLS

Permanent cells are cells that are incapable of regeneration. These cells are considered to be terminally differentiated and non-proliferative in postnatal life e.g neurons, heart cells, skeletal muscle cells, myocardial cells, RBCs

G-1 PHASE

- Cell grows in preparation for DNA replication
- Certain intracellular components such as centrosomes undergo replication

G-2 PHASE

- Prep the cell for mitosis
- Cell grows and produce any molecules it needs to divide

MITOSIS

PROPHASE

- Chromosomes condense into double-structured chromosomes by histone proteins
- Nuclear membrane dissolves
- Centrioles move to opposite poles
- The nucleus has laminin proteins. Some enzymes phosphorylate these laminin proteins due to which the nuclear membrane starts dissolving.

METAPHASE

- Microtubules extend
- Double-structured chromosomes arranged on equatorial plane
- Microtubules attach to kinetochore

ANAPHASE

- Each chromatid starts moving to opposite pole

TELOPHASE

- Chromatids reach poles
- Nuclear membrane appears
- Chromosomes uncondenses
- Cytokinesis takes place

What regulates cell division?

Cell division is regulated by two check points.

G1 checkpoint is located at the end of G1 phase, before the transition of S phase. At G1 checkpoint cells decide whether or not to proceed with division.

G2 checkpoint regulates cell entry to mitosis and prevents cells from entering mitosis when DNA is damaged, providing an opportunity for repair and stopping the proliferation of damaged cells.

p53 gene in the cell acts as both G1 and G2 checkpoints.

ACTIVATOR GENES

The genes having a positive effect on DNA replication are activator genes. These include:

1. Growth factor (mitogen) releasing gene

2. Growth factor receptor releasing gene
3. Signal transducer releasing gene

DNA REPLICATION ON MOLECULAR LEVEL

The first gene produce growth factors and secrete them out of nucleus.

The second gene then express itself and produce growth factor receptor which gets inserted in the nuclear membrane. The growth factor then acts on this growth factor receptor.

The third gene produce signal transducer protein which interact with growth factor receptor (GFR) and gives signal back to the nucleus towards the responder gene which produce special type of transcription factor. These transcription factors will act on a special kind of genes which will express itself and produce cyclin proteins.

Another gene on DNA which is active all the time produce cyclin-dependant kinases (CDK). In the cell CDK are present all the time but only becomes active when relevant cyclins are produced.

The cyclins and CDK interact with each other and form a complex which become enzymatically active and phosphorylate the RB protein (Retino Blastoma protein). This RB protein release E2F transcriptional factor which further activates genes for DNA replication.

DETAIL

GROWTH FACTORS

The growth factors may be:

1. Platelet derived growth factors
2. Epidermal growth factors
3. Vascular endothelial growth factors
4. Neuronal growth factors

GROWTH FACTOR RECEPTORS

Most of the growth factors can only lead to cell progression if cell is expressing receptor for the growth factor. These receptors should have one extracellular domain which should bind the growth factor and one intracellular domain to activate the signaling protein (signal transducer).

The receptors may be different kinds such as:

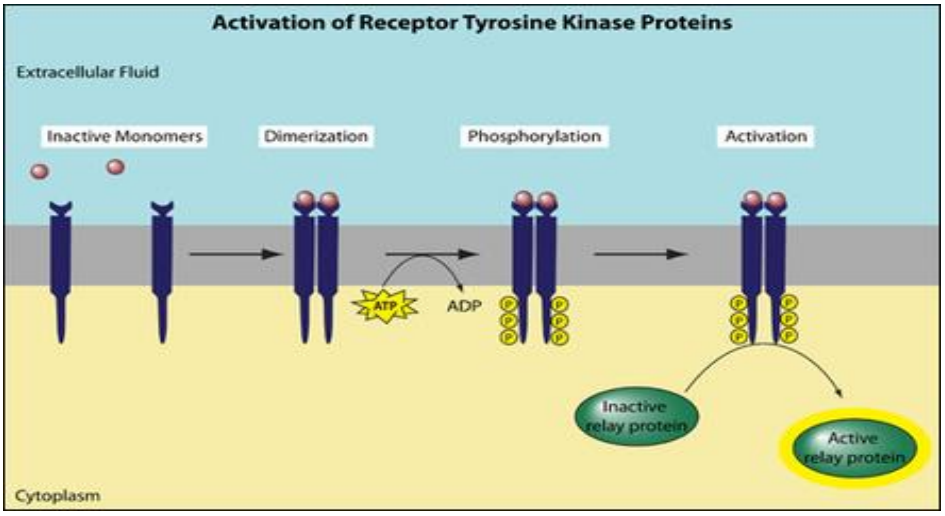
1. Tyrosine Kinase receptors
2. JAK-STAT Pathway
3. Seven path receptors

1. TYROSINE KINASE RECEPTORS (ONE PATH RECEPTORS)

The intracellular domains of these receptors have enzymes called tyrosine kinase. Whenever growth factor bind to these receptors, the tyrosine kinase leads to phosphorylation of its own tyrosine.

When growth factors bind to the receptors, the receptors dimerize (pair up). The paired receptors phosphorylate each other on tyrosines in the intracellular domain.

When receptor tyrosine kinase is activated, it will stimulate another protein call Ras protein (signal transducer). Ras protein activates Raf protein which in turn activate mitogen activating protein (MAP) kinases which eventually gives signal to the nucleus to express the transcription factor.



2. JAK-STAT PATHWAY

Some growth factors such as cytokines and interleukins lead to this pathway. Such growth factors act on different receptors to activate a protein called JaK (Janus Kinase) which will activate another protein called STAT (Signal Transducing and Activator of Transcription) which will in turn activate the transcription factor.

The JaK-STAT pathway is involved in processes such as immunity, cell divisions, cell death and tumor formation.

Whatever may be the pathway for signal transduction, we are concerned with the release of transcription factors so eventually cyclin is released. This cyclin is the main product which promotes DNA replication.

PROTO-ONCOGENES

The growth factor genes, GFR genes, signal transducer genes, responder genes, cyclin genes and CDK genes are together called proto-oncogenes.

When a cell is required to proliferate, all these proto-oncogenes are activated.

If proto-oncogenes become mutant and they are over-expressed, it can contribute to cancer. When proto-oncogenes become defective, they are called oncogenes.

RB PROTEINS

RB proteins are produced by RB genes. As long as both or even a single RB alleles are functioning well, they can control the over proliferation of cell and prevent the formation of tumor. So these genes are also called tumor-suppressor genes.

Every cell has RB proteins which keeps the cell in G1 phase and only under certain circumstances let the cell enter into S-phase

ATM PROTEINS

ATM proteins are produced by ATM genes. ATM proteins assist cell in recognizing damaged or broken DNA strands. ATM proteins activate p53 genes if defective gene is detected.

p53 GENES

p53 genes produce p53 proteins which acts as guardian of cell. When defective gene is detected, p53 genes will be activated producing p53 proteins. These proteins will activate CDK inhibitors i-e p21, p27, p57 genes which will de-activate CDK complex and stop DNA replication.

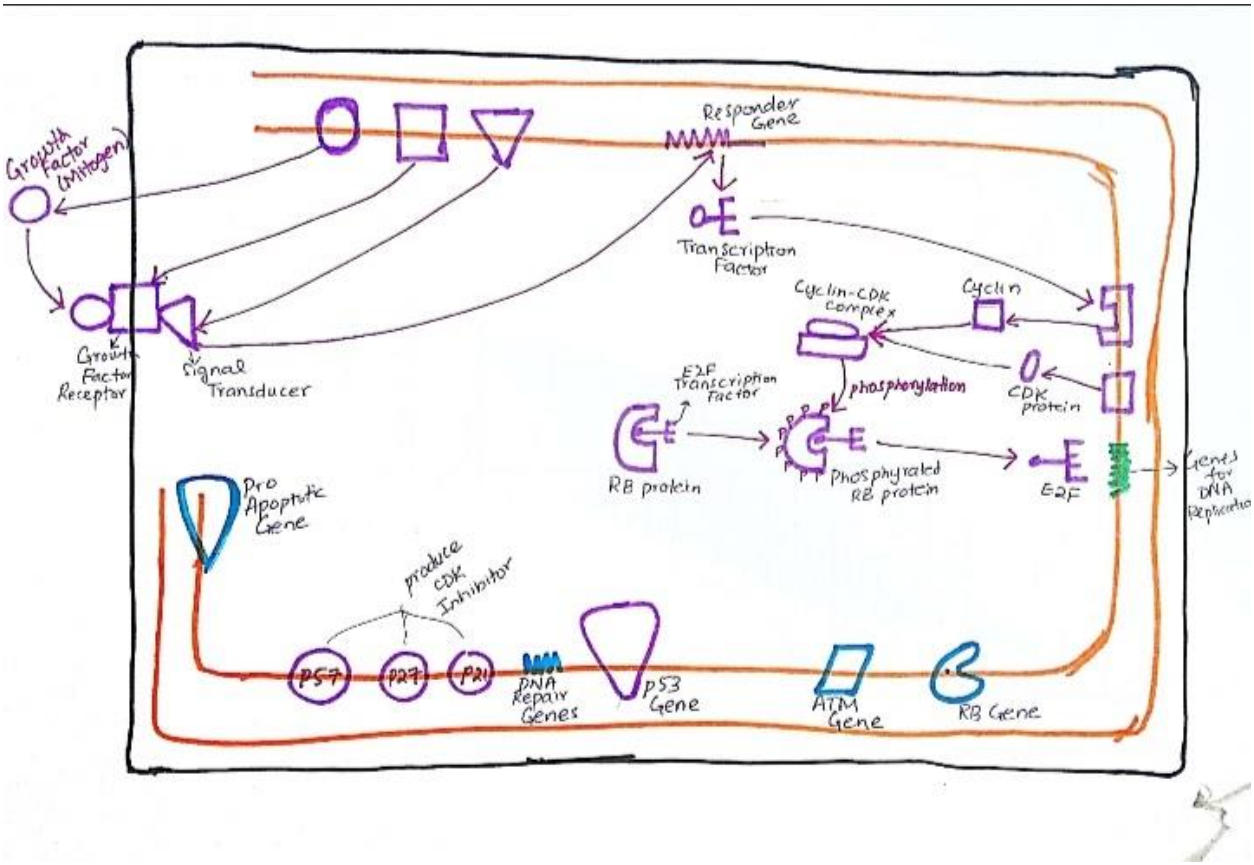
P53 proteins will also activate DNA repair genes and give the cell a chance to repair. If repair is done, cell will continue replication.

If cell can't be repaired, cell will either go to scenescence in which cell remains alive but cannot replicate further. If the DNA is too much damaged, cell will be forced to commit suicide because eventually p53 will activate pro-apoptotic gene.

So p53 is a tumor suppressor gene i-e its activity stops the formation of tumor. It is p53 that act as both G1 and G2 checkpoints.

Almost 70% of cancer have defective p53 gene.

If proto-oncogenes are mutated but p53 gene is working well, then the proto-oncogenes will be forced to repair by p53. But if by radiation or chemical injury the p53 is damaged, cell will lead to cancer.


Growth Factor (Mitogen)
Responder Gene
Transcription Factor
Cyclin-CDK complex
Cyclin
Growth Factor Receptor
Signal Transducer
E2F Transcription Factor
phosphorylation
CDK protein
RB protein
Phosphorylated RB protein
E2F
Genes for DNA Replication
Pro Apoptotic Gene
produce CDK Inhibitor
P57
P27
P21
DNA Repair Genes
P53 Gene
ATM Gene
RB Gene