***Carcinogenesis***

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***Carcinogenesis:*** is a multistep process at both *phenotypic & genetic levels.*

**Phenotypic level** includes:

 *I. Excessive growth.*

 *II. Local invasion.*

 *III. Metastasis.*

 *These three criteria are called collectively* ***Tumor Progression****.*

**Genetic level** includes:

***Six changes in normal cell physiology, that results in cancer formation.***

 These changes are including:-

**1. Autonomous growth:**

This pattern of growth of cancer is under the control of ***oncogenes*** (genes *derived from Proto oncogenes).*

***These oncogenes produced oncoproteins (growth factors), which result in autonomous growth of cancer***.

***Mechanisms of action of oncoproteins:***

By following steps:-

***Step-I.*** The ***binding of growth factor*** (oncoproteins) to ***specific receptors*** on cell membrane.

***Malignant cells acquire autonomous growth by followings:-***

*1. Acquiring the ability to synthesize the same growth factors to which they responsive (gene overexpression).*

*2. Pathological overexpression of normal growth factor receptors, e.g.* ***Her2 receptors*** *are overexpressed in 25- 30% of breast, lung carcinoma.*

***Step- II. Growth factor & receptor complex activate several proteins on inner side of cell membrane*** (transient activation under normal state while persistent activation under neoplastic conditions).

***Step- III.*** *Transmission of signals from these proteins* along inner side of cell membrane along the cytoplasm *to the nucleus via secondary messenger.*

***Step- II & III: this is called (singling pathway)****.*

Two important genes that control this pathway (**Ras**….increase cells proliferation & **ABL…**……inhibit cell proliferation).

Cancer cells acquire autonomous growth is by ***mutation in these genes that control the signaling pathway***(transfer of signal from inner side of cell membrane to nucleus).

*So* ***mutant Ras*** *is the most common oncogene abnormalities in human tumors.*

*Mutant Ras gene are present in 35% of human cancers (carcinoma of colon, carcinoma of pancreas……etc).*

***Step- IV.***  *Activation of transcription inside the nucleus*.

Mutations affect the genes that regulate transcription of DNA may result in autonomous growth of cancers.

e.g. ***Myc gene*** is commonly involved in human tumors like in carcinoma of colon, breast, lung)..

***Step- V*.** *Entry of cell into the cell cycle* & result in cell division.

Normal cell cycle is consists of five phases (G0 ,G1 , S, G2 , M).

All these phases are under control of proteins (Cyclins & Cyclins dependent Kinase).

Cyclin D overexpression is seen in many cancers (breast, esophagus & liver).

***2. Insensitivity to inhibitory signals*** (*disruption of tumor suppressor genes):*-

Disruptions of **tumor suppressor genes** make the *cells resistant to inhibition of growth & increase their proliferation.*

 All tumor suppressor genes are caused inhibition of cell growth by two pathways:-

*I. stimulate antigrowth signal, causing cells to enter G0 phase.*

*II. Prevent the cell to pass from phase G1 to S phase.*

**Examples of Tumor suppressor genes:**

***1. RB gene:***

This is the *first discovered suppressor gene*, *loss of normal RB gene was discovered initially in Retinoblastoma, but recently proved it lost in many tumors (breast cancer, bladder & lung cancer, osteosarcoma).*

 **Both alleles of RB gene most be mutant** in order to regard this gene is mutant.

***2. Adenomatous Polyposis coli (APC) gene:***

*Loss of this gene can be seen in 70- 85% of sporadic carcinoma of colon.*

Individuals born with Loss or mutant of one of alleles of APC gene, they develop hundreds to thousands of adenomatous polyps in the colon which on second decade of life one or more of these polyps will undergo malignant transformation.

***3. TP53:***

It is one of most commonly mutated in human cancers, it exert its ***antiproliferative effects by***:-

*I. Arrest cell cycle at late G1 phase & remain the cells in the G0 phase (cell cycle pause) to allow a time for DNA repair.*

*II. Stimulate apoptosis.*

*III. Helping in repair of DNA.*

More than 70% of malignant human tumor show defect in functions of TP53.

Most of mutations in TP53 are acquired & less commonly they are inherited mutations like ***Li- fraumeni syndrome*** (patient have many cancers like sarcomas, breast cancer, leukemia, brain tumors, adrenal tumors).