1. ***Evasion of apoptosis***

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**Normally,** the mechanism of *apoptosis is mediated by many genes, & achieve by two phases*

1. **Initiation phase**, which is mediated by *TNF- Fas receptor* & inhibited by FLIP protein.

*Or initiation phase (caspases activation) is mediated by* BAX, BAD genes & inhibited by bcl2 gene.

1. **Execution phase,** which is result in cellular degradation by caspases.

***Changes in mechanism of apoptosis in malignant tumors are:***

*1. Decrease level of Fas protein (as in Hepatocellular carcinoma).*

*2. Loss of Tp53 (Tp53 is responsible for action of Fas protein).*

*3. Increase level of FLIP protein which inhibits apoptosis.*

*4. Increase level of Bcl2 gene which inhibits apoptosis (as in 85% of B-cell lymphoma).*

***4. Limitless replicative potential***

Most of normal human cells have capacity of 60 to 70 doublings, after this, the cells lose the capacity to divide (due to loss of Telomerase enzymes which is important in DNA replication).

In malignant tumors, there is increased level of Telomerase.

***5. Developed sustained Angiogenesis:***

***Angiogenesis has dual effects on tumor growth:***

*1. Supplies nutrients & oxygen.*

*2. Newly formed endothelial cells during angiogenesis, will stimulate the growth of adjacent tumor cells by secretion of polypeptides (like platelets growth factor).*

**Angiogenesis is also important for development of metastasis.**

Most of cancers cannot grow more than 1 to 2 mm in diameter or thickness unless they are vascularized, because after this size the tumors fail to enlarge without vascularization (because hypoxia increases apoptosis).

Cells of malignant tumor are the main inducer of angiogenesis by their production of growth factors (**Angiogenetic factors).**

***6. ABILITY TO INVADE & METASTASIZE***

The Metastatic pathway of cancer can be divided into two phases:

***1. Invasion of Extracellular matrix:***

Include the following steps

**I. Detachment of tumor cells from each other (by losing of E- cadherin & B- catenin molecules).**

**II. Attachment of tumor cells to matrix components.**

**III. Degradation of Extracellular Matrix (by Metalloproteinase).**

**IV. Migration of tumor cells to the vessels (mediated by Cytokines).**

***2. Vascular dissemination & Homing of tumor cells:***

* ***In circulation****, Tumor cells are liable to destruct by immunity cells of host*.

**To avoid such destruction, tumor cells are arranged themselves into small emboli (by adhesion to WBCS, PLATELETS).**

* ***Then*** *tumor cells leave circulation by adhesion to the endothelial cells & destruction of basement membrane of vessels, to enter the extracellular matrix of metastatic site.*
* ***Distribution of metastasis*** can be *predicted by the location of primary tumor & its vascular & lymphatic drainage e.g. cancer of breast is expected to involve the lung & bones of thorax.*
* Some cancers have *unexpected metastatic pathway e.g. caner of lung metastasize to the adrenal glands.*

***Karyotype changes of Tumors***

The genetic damage that activate oncogenes & inactivate tumor suppressor genes is either **point mutation** (**not change the karyotype**), or **large mutation (change the karyotype).**

***The common structural abnormalities in the genome of tumor cells are:***

1. *Balanced translocation: (commonest abnormality)*.

More common in hemopoietic tumors e.g. ***chronic myeloid leukemia t(9,22).***

2*. Deletion:*

* More common in non hemopoietic solid tumor e.g. deletion in chromosome ***13 in retinoblastoma***, deletion ***in chromosome 5*** in carcinoma of colon.

3*. Gene amplification:* e.g. ***breast carcinoma associated with amplification of Myc & HER2 genes.***

***Carcinogenesis according to carcinogens:***

Carcinogenesis can be divided **into three steps:-**

***A. initiation step:*** in which there is ***DNA damage*** (*lies at the heart of tumor)*, usually *due to (CHEMICALS, VIRUSES & RADIATION)*, these are called ***initiators.***

 ***B. promotion step:*** ***maintained the damage of DNA*** (*HORMONES, DRUGS, PHENOL)*, these are called ***promoters*** which *augment replication of cells with DNA damage.*

***C. Tumor progression***: *local increase in the size of tumor, local invasion & metastasis.*

***Important notes on these steps of carcinogenesis:***

1. Application of promoters before the initiators will not result in completion of carcinogenesis.

2. Some of carcinogens can act as initiators, promoters, this is called complete carcinogens.

3. Not all carcinogens induced DNA damage & will not necessary result in initiation of cancer.

4. Initiators are mutagenic but are not induce cells proliferation, while promoters are non-mutagenic but can induce cells proliferation.

***Chemical carcinogenesis:***

*General principles of chemical carcinogens;*

**I.** Could be ***natural or synthetic chemical***.

**II.** Chemicals either ***direct acting chemical*** (*active without transformation in the body)*, *or* ***indirect acting chemical*** (*procarcinogens need transformation inside the body by liver enzymes) to become active (ultimate carcinogens).*

**III.** All ***direct chemicals*** are highly ***reactive electrophiles (Free radicals)*** *that react with electron rich atoms in the cells like RNA, DNA.*

**IV.** Several chemicals can ***act in association with other carcinogens like viruses to induce neoplasia***.

***Mechanism of Chemical carcinogenesis****:*

* **Most of chemical carcinogens are *mutagenic (initiators)****.*
* The ***commonest protooncogenes*** that affect by chemical is ***Ras(mutational activation)****,* while the ***commonest Tumor suppressor gene affected by chemicals is TP53 (there is inhibition of TP53).***
* ***Some of chemicals*** ***carcinogenesis*** is ***augmented by promoters*** (*dugs, hormones, phenol)*, nonmutagenic but increase proliferation.
* *Repeated & sustained exposure* to promoters ***must follow the exposure to chemical mutagenic agent or initiator.***

*Chemicals can induce cancer more in patient with hereditary defect like in Xeroderma Pigmentoza (such patient has DNA damage).*

***Radiation Carcinogenesis:***

* Radiation is a well-established carcinogen (*like UV light, nuclear fission, radionuclides).*
* ***Examples*** of cancers induce by radiation are (***skin cancer, leukemia, thyroid cancer, pulmonary caner).***
* Even *therapeutic irradiation* can induce cancer (***irradiation of neck during infancy & childhood induce papillary carcinoma of thyroid).***

***Mechanism of carcinogenesis by radiation:***

* *Radiation is mutagenic carcinogens (initiator); it causes chromosome breakage (commonest), translocation & less commonly point mutation.*
* *There is a long latent period* associated with radiation induced cancer & this cancer occurs in initially damaged cells by other environmental factor.

***Viral & Microbial carcinogenesis:***

Oncogenic viruses are of *two types*

***1. RNA ONCOGENIC VIRUSES (RETROVIRUS):***

These viruses cause cancer in animals & human *by two mechanisms*:-

 I. *acute transformation virus,* contain *Oncogenes* that cause cancer formation.

 II. *Slow transformation virus,* not contain Oncogenes & induce carcinogenesis by *mutation*.

***Example on RNA virus is***

 ***Human T- cell leukemia type- 1 virus*** (HTCL-Type – 1)

* It cause ***T- cell Leukemia / Lymphoma*** (endemic in japan).
* Viruses ***induce proliferation of CD4 T- lymphocytes***.
* ***Human acquired this infection by*** transmission of *infected T- cells by sexual intercourse, blood products, breast feeding.*
* ***Only 1% of infected patient will develop leukemia after long latent period 2-3 years.***
* These *viruses contain area which called* ***PX that is responsible for malignant transformation capacity of viruses,*** which cause ***increase transcription of oncogenes of hosts & inhibit P53.***

***2. DNA oncogenic viruses:***

Include ***4 viruses:***

 *I. Human papilloma virus (HPV).*

 *II. Epstein Barr virus (EBV).*

*III. Hepatitis B virus (HBV).*

*IV. Human Herpes virus – 8 (HHV-8).*

***Human Papilloma virus (HPV)***

 Cause many types of tumors:

*1. Benign squamous papilloma of skin (Wart), (by virus type 1, 2, 4, 7).*

*2. Invasive malignant tumors (carcinoma of cervix, carcinoma of larynx by virus 16, 18, 31).*

*3. Low malignant potential tumors, (by viruses 6, 11).*

***HPV can cause cancer by*** production of viral genes ***E6,E7***, which result in followings:

*1. Stimulate oncogenes & inhibit TP53.*

*2. Inhibit Apoptosis.*

***EBV***

Cause the *following diseases:*

*1. Burkitt lymphoma.*

*2. CNS tumors.*

*3. AIDS related lymphoma.*

*4. Nasopharyngeal carcinoma.*

*5. Hodgkin lymphoma.*

* *EBV mainly infects B lymphocytes; result in proliferation of B lymphocytes.*
* *EBV also inhibits Apoptosis.*

***HBV***

*Strong association with HCC,*

**Can induce cancer by followings:-**

*1. Increase mutation of hepatocytes.*

*2. HBV contains protein, which is called HBX, which disrupt the normal growth of infected liver cell, by increase transcription of DNA & inhibit TP53.*

Note *another virus* that can predispose to *HEPATOCELLULAR CARCINOMA* is ***HCV***.

***Helicobacter pylori:***

Cause the *following diseases:*

*1. Chronic gastritis.*

*2. Gastric ulcer.*

*3. Duodenal ulcer.*

*4. Carcinoma of stomach.*

*5. Lymphoma of stomach.*

***Host defence mechanism against cancer:***

***Immune surveillance:*** refer to recognition & destruction of non-self-tumor cell on their appearance.

***Anti-tumor effector mechanisms***

Both *cellular & humeral immunity* can have antitumor effect.

***Cellular Immunity:*** include

1. *Cytotoxic T lymphocyte (*mainly ***against virus induced neoplasm like Burrkit lympnoma****).*

2. *Natural killer cells* (**first line of defense against tumors**).

3. *Macrophage:*

This cell act *in coordination with lymphocytes, NKC*.

***Mechanism of action of macrophage:***

*1. by production TNF.*

*2. Free radical production.*

***Humeral Immunity:***

*Can act against tumors by* the followings:

1. *Activation of Complement system.*

2. *Increase effectiveness of cellular immunity (killing by NK cell*).