

# BIOCHEMISTRY OF CANCER

# LEARNING OBJECTIVE

- *ETIOLOGY OF CANCER*
- *MOLECULAR BASIS OF CARCINOGENESIS*
- *ONCOGENES*
- *ONCOSUPPRESSOR GENES*
- *CELL CYCLE*
- *APOPTOSIS*
- *TUMOUR MARKERS*
- *BIOCHEMICAL BASIS OF CANCER THERAPY*

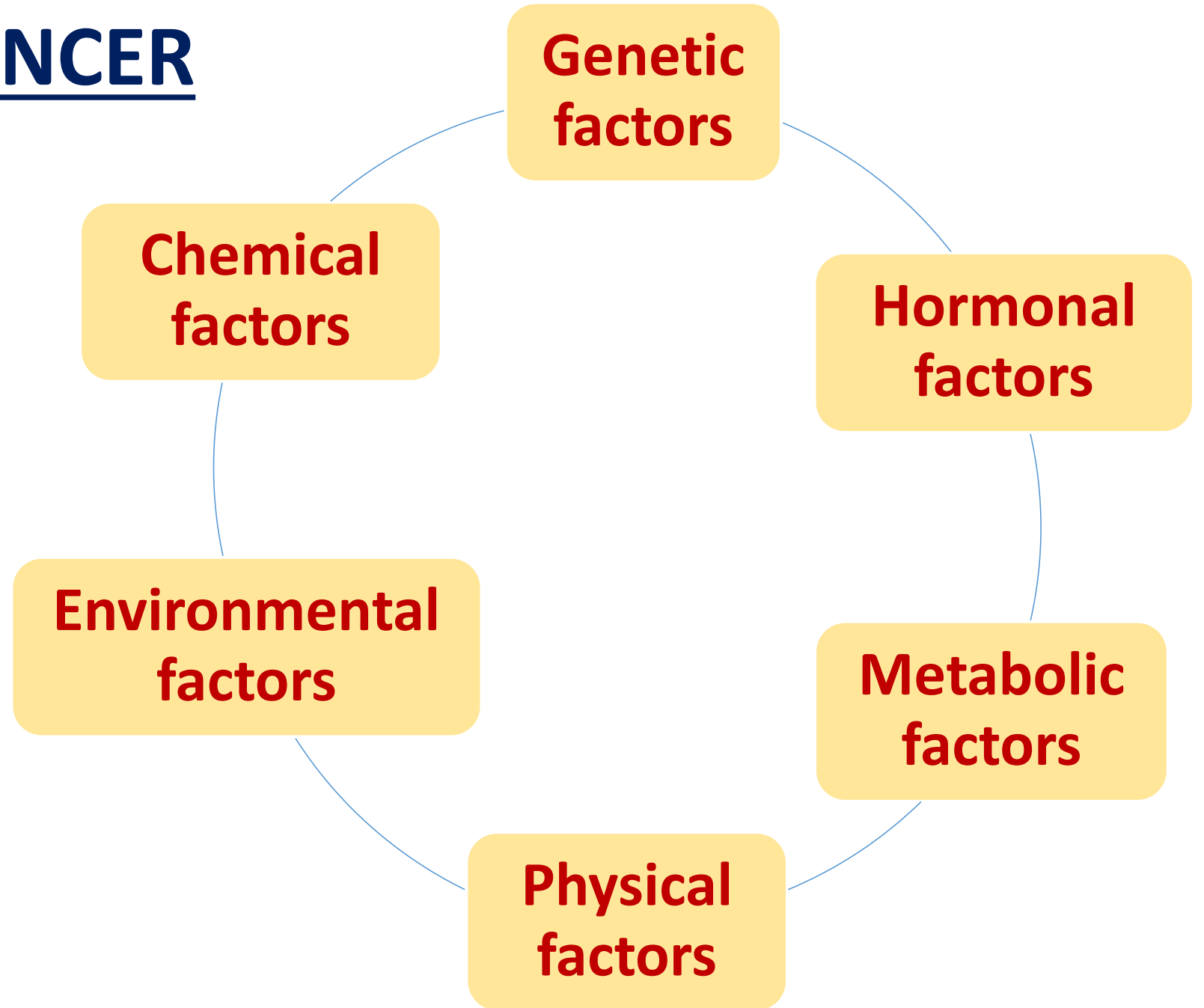
❖ *Cancer is defined as a disturbance of growth, characterized by excessive proliferation of cells without apparent relation to physiological demands of the organ involved.*

❖ Cancer cells are characterized by 3 properties:

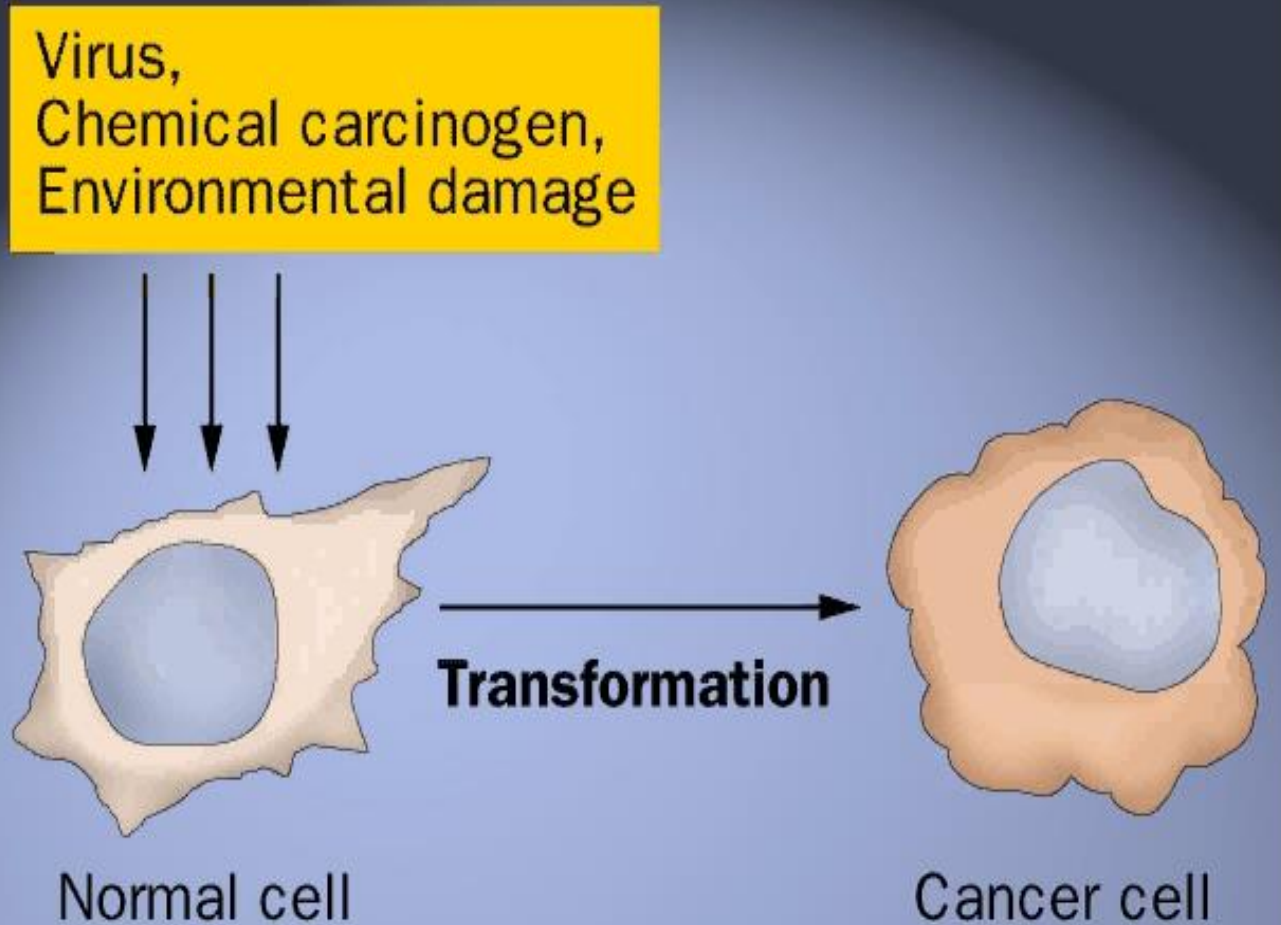
1. Immortalization- Unrestrained control of growth.
2. Invasion of local tissues.
3. Spread or metastasis to other parts of the body.

# ETIOLOGY OF CANCER

❖ **Multifactorial**



# ***MOLECULAR BASIS OF CARCINOGENESIS***



- **Carcinogenesis:**  
*Process by which normal cells are transformed to cancer cells.*
- **Important hallmark:**  
*Uncontrolled Cell Division*

- 3 Stages – Initiation ,Promotion,progression

- Mutagens:

*any substance which increase rate of mutation can also enhance rate of incidence of cancer*

- **Promoters** : carcinogen produces a mutation, but promoter gives drive for unchecked cell division.

# CARCINOGENS

❖ *Physical, chemical or biological agents which can cause cancer are called Carcinogens.*

❖ All the carcinogens are mutagens.

❖ PHYSICAL AGENTS: UV rays, X-rays, gamma rays



Cause damage to DNA;

or

Formation of free radicals in tissues - molecular damage

## • CHEMICALS:

- introduced into the body by means of

- *Occupation – aniline, asbestos*
- *Diet – aflatoxins, food additives, colouring agents*
- *Lifestyle – tobacco smoking ,chewing– benzopyrene*
- *Methyl cholanthrene -powerful*

**TABLE 42.1** Some chemical carcinogens.

|                                  |                                                             |
|----------------------------------|-------------------------------------------------------------|
| Polycyclic aromatic hydrocarbons | Benzopyrenes, Cholanthrenes, Dimethyl-benzanthracene (DMBA) |
| Aromatic amines                  | N-Methyl-4-aminoazobenzene (MAB)                            |
| Nitroso compounds                | Dimethyl nitrosamine                                        |
| Natural compounds                | Aflatoxins                                                  |

# BIOLOGICAL CARCINOGENS/ ONCOGENIC VIRUS

- Some viruses are carcinogenic.
- Oncogenic virus may be a RNA or a DNA virus
- Transformation by oncogenic virus

**TABLE 42.3** Human oncogenic viruses.

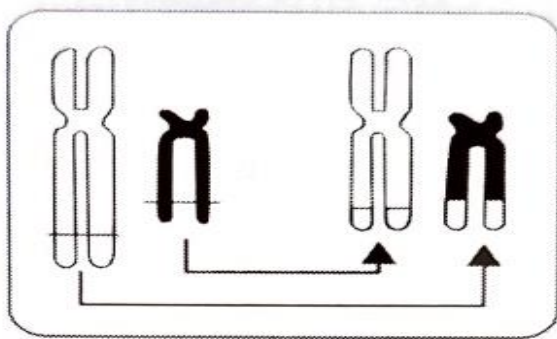
| <i>Virus</i>          | <i>Abbreviation</i> | <i>Associated human disease</i>                            |
|-----------------------|---------------------|------------------------------------------------------------|
| Epstein-Barr virus    | EBV                 | Burkitt's lymphoma (BL);<br>Nasopharyngeal carcinoma (NPC) |
| Human papilloma virus | HPV                 | Uterine cervical carcinoma                                 |
| Hepatitis B virus     | HBV                 | Hepatoma                                                   |

# ANTIMUTAGENS

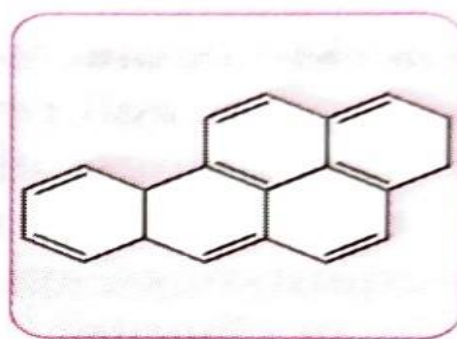
- Any substance that interfere with tumor promotion. Eg :
  - *Vitamin A & Carotenoids, Vitamin E, Vitamin C*
  - *Curcumin , Flavonoids*
  - *Phenolic compounds in fruits [like grapes,strawberries,walnuts]*
  - *Tubers,beans,leafy vegetables*
- Low protein,low fat diet,good fiber content
- Green tea



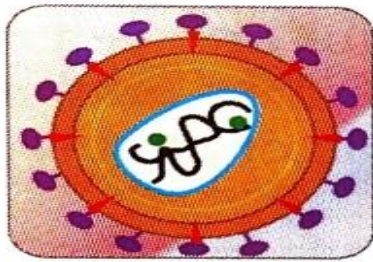
Ionizing radiation



Chromosome translocation



Chemical carcinogens



Oncogenic viruses

Spontaneous mutations

Oncogene activation or deletion of oncosuppressor gene



Malignant transformation

Cancerous transformation - due to changes in function of 2 classes of genes.

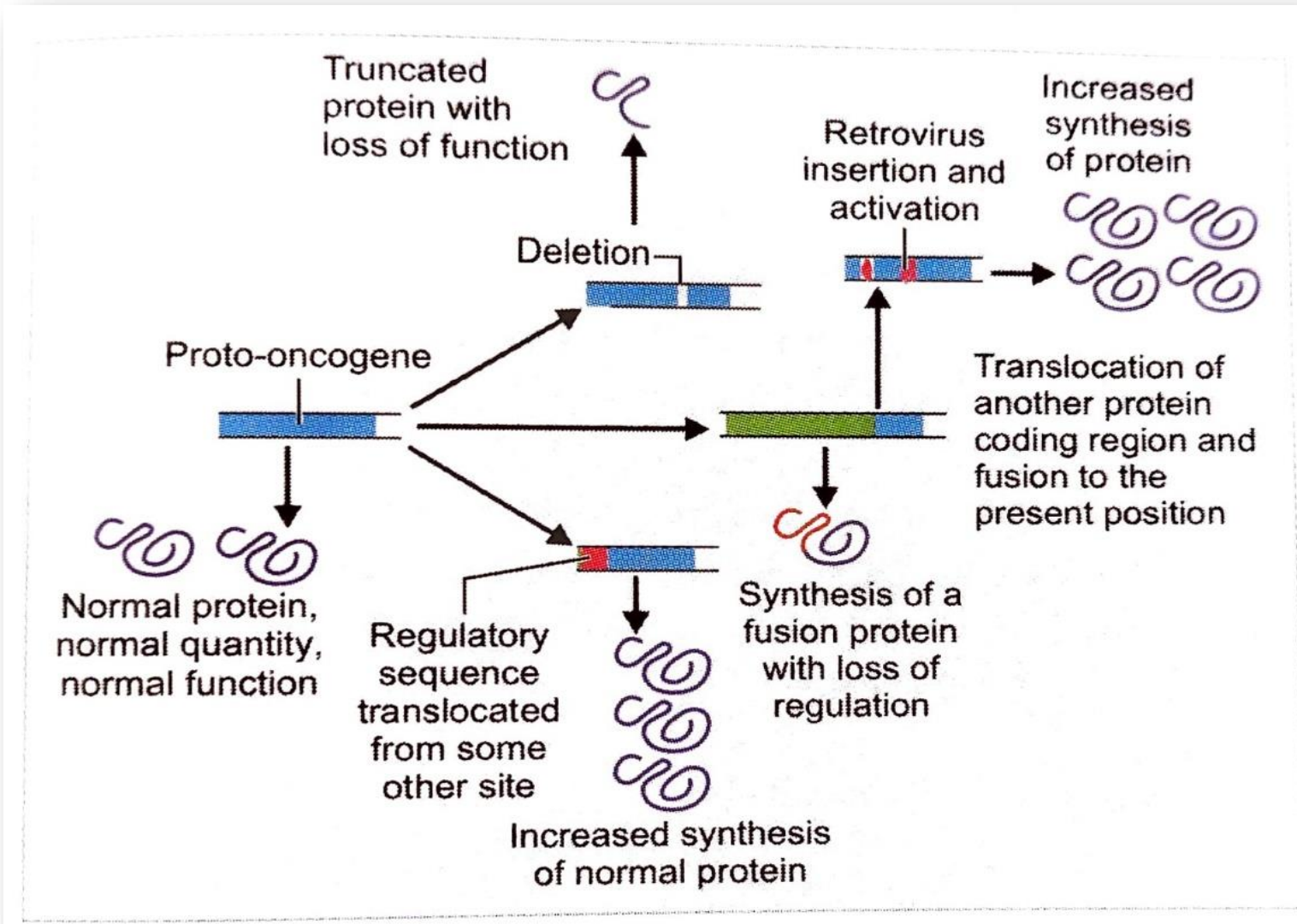
■ **Oncogenes**

■ **Oncosuppressor genes**

# ONCOGENES

- **Oncogenes:** genes capable of producing cancer.
- **Proto-oncogenes:** Oncogenes present in normal cells
  - Important **regulatory genes** of the cell.
  - May be **converted to oncogenes**  
due to: **Environmental factors** [chemicals, radiation ,viruses].  
**Inherited mutations**
- Ex:
  - src** - Rous sarcoma in chicken
  - ras** - rat sarcoma
  - erb-B** - erythroblastosis virus in chicken
  - sis** - simian sarcoma virus in monkey

# PROTO ONCOGENE ACTIVATION BY VARIOUS MEANS



- Point mutation
- Gene amplification
- Gene translocation
- Insertion of a viral promoter/enhancer

**TABLE 42.4** Some cellular oncogenes.

| <b><i>Oncogene</i></b> | <b><i>Virus carrying the gene</i></b> | <b><i>Oncogene product</i></b>              | <b><i>Subcellular localization of the oncogene product</i></b> |
|------------------------|---------------------------------------|---------------------------------------------|----------------------------------------------------------------|
| Abl                    | Abelson leukemia virus in mouse       | Tyrosine kinase                             | Plasma membrane                                                |
| erb-B                  | Erythroblastosis virus in chicken     | Receptor for epidermal growth factor (EGFR) | Membrane                                                       |
| Myc                    | Myelocytoma virus in chicken          | DNA-binding protein                         | Nucleus                                                        |
| sis                    | Simian sarcoma virus in monkey        | Platelet-derived growth factor (PDGF)       | Membrane                                                       |
| Ras                    | Rat sarcoma                           | GTPase                                      | Cytoplasm                                                      |

# ONCOSUPPRESSOR GENES / TUMOR SUPPRESSOR GENES/ANTI-ONCOGENES

- Genes ,which normally protect the individual cell from developing a cancer.
- Mutation / abnormality [deleted]of these genes may result in cancer.
- Examples : *p53*  
Retinoblastoma gene (*RB*)

**TABLE 42.5 Important oncosuppressor genes.**

| <i>Name of the oncosuppressor</i> | <i>Abbreviation</i> |
|-----------------------------------|---------------------|
| Retinoblastoma                    | RB                  |
| Wilms' tumor                      | WT                  |
| Familial adenomatous polyposis    | FAP                 |
| Deleted in colon cancer           | DCC                 |
| Gene for protein-53               | p53                 |
| Familial breast cancer            | BRCA                |

# ONCO SUPPRESSOR GENE- *RB*

- RB-Governor of Proliferation
- *RB* gene expressed to form Rb protein.[p105], (M.wt-105kd)
- Rb protein –suppress cell proliferation
- Mutation -both allele of RB gene deleted - causes  
Retinoblastoma

# ONCO SUPPRESSOR GENE – *P53*

- ‘Guardian genome’ or ‘Molecular policeman’.
- Gene encodes p53, Phosphoprotein [M.wt -53kd]
- It blocks cells with damaged DNA – by triggering blocking of cell division, until damage is repaired.
- If damage is severe, p53 trigger apoptosis of cell.
- p53- Suppress transformation ability of oncogenic virus  
Activate expression of genes that suppress cell proliferation.

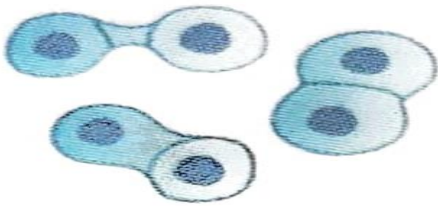
# GROWTH FACTOR

- Stimulate Cell proliferation .
- Overexpression / increased secretion of growth factors, associated with carcinogenesis.
- Eg: - Platelet-derived Growth Factor (PDGF)- Glioblastomas  
Transforming Growth Factor A (TGF-  $\alpha$ ) - Sarcomas

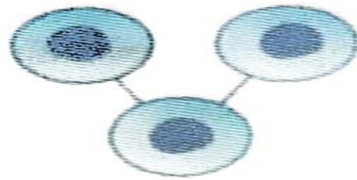
| <b>Growth factor</b>                  | <b>Abbreviation</b> | <b>Produced by</b>                | <b>Function</b>                                      |
|---------------------------------------|---------------------|-----------------------------------|------------------------------------------------------|
| Epidermal growth factor               | EGF                 | Fibroblasts, submaxillary gland   | Stimulates epidermal and epithelial cells            |
| Transforming growth factor-beta       | TGF- $\beta$        | Platelets, placenta               | Inhibition of fibroblasts                            |
| Platelet-derived growth factor        | PDGF                | Platelets                         | Accelerates wound healing                            |
| Nerve growth factor                   | NGF                 | Submaxillary gland                | Growth of sensory neurons                            |
| Erythropoietin                        | EP                  | Kidney                            | Stimulates erythropoiesis                            |
| Granulocyte colony-stimulating factor | GCSF                | Endothelial cells and fibroblasts | Stimulates granulocytes                              |
| Monocyte colony-stimulating factor    | MCSF                | Endothelial cells                 | Stimulates monocytes                                 |
| Tumor necrosis factor alpha           | TNF- $\alpha$       | Monocyte                          | Necrosis of tumor cells, proliferation of leukocytes |

# NORMAL CELL VS CANCER CELL

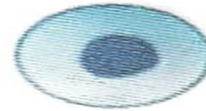
## Normal cells



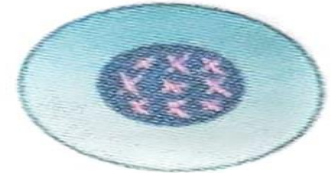
Contact inhibition



Cells are of equal size and shape



Nucleus small

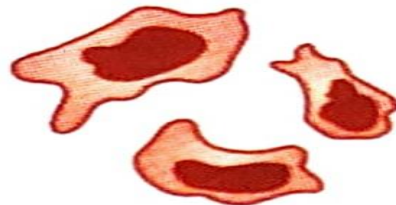


Normal number of chromosomes

## Cancerous cells



Cancer cells continue to grow



Cancer cells are of different sizes and shapes



Nucleus larger and darker



Abnormal number of chromosomes

# **TUMOR IMMUNOLOGY**

# TUMOR ANTIGENS

## Tumor specific antigens [TSA]

- Occur only in tumor cells
- Can be abnormal product of oncovirus/mutated oncogenes.
- Eg: Ras Protein

## Tumor Associated antigens [TSA]

- Occur only in both healthy & tumor cells
- Eg: oncofetal antigens[AFP,CEA ]

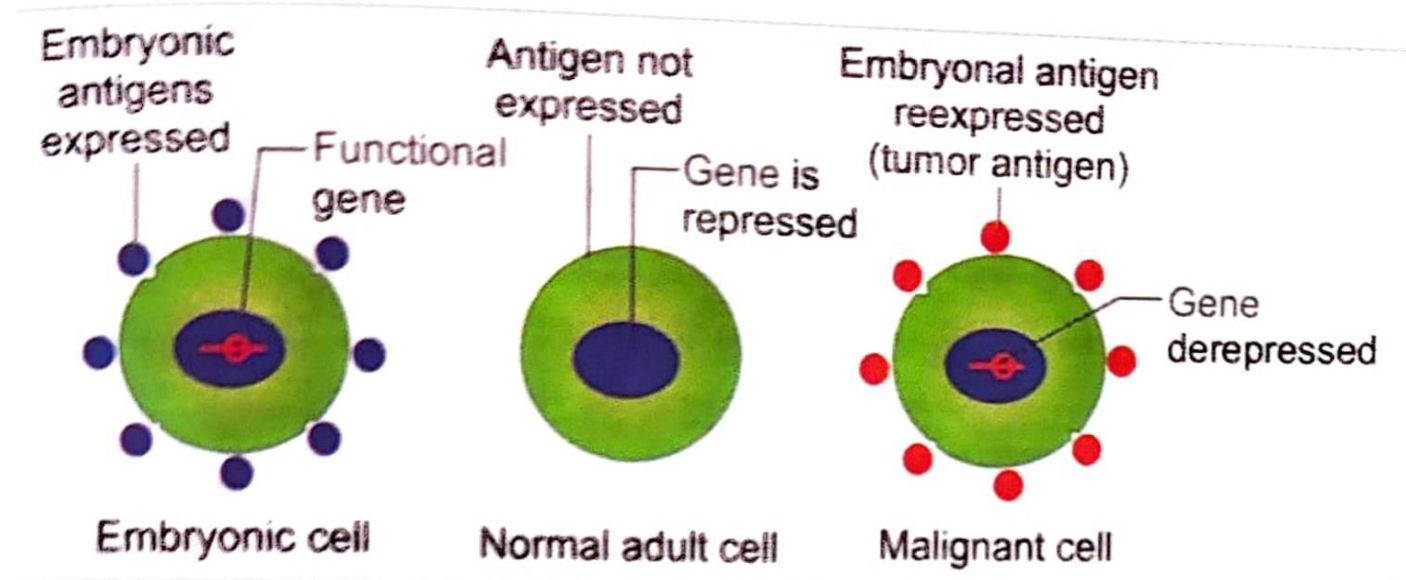


Fig. 42.21: Oncofetal antigen

# TUMOR MARKERS

- Also called **tumor index substances**.
- *Are factors released from the tumor cells, which could be detected in blood & therefore indicate the presence of tumor in the body.*
- Some are specific for one type of cancer , while others are seen in several cancers.

# IDEAL TUMOR MARKER ???

- **Highly specific** : detectable in only one tumor type
- **Highly sensitive** : Non detectable in physiological or benign disease state
- **Long lead time** : Sufficient time for alteration of natural course of disease

# USES OF TUMOR MARKERS

- ❑ For follow-up of cancer & to monitor the effectiveness of therapy & also to detect recurrence of tumor
- ❑ For Screening and Early Detection of Cancer
- ❑ Diagnosing Cancer
- ❑ For assessing the prognosis of cancer

# COMMON TUMOR MARKERS

| Name                                                                                                                                                                   | Serum level increased in                                                                                 |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| <u><b>Oncofetal proteins</b></u><br>Alpha feto protein[ <b>AFP</b> ]<br>Carcino embryonic antigen ( <b>CEA</b> )                                                       | <b>Hepatoma</b> , germ cell cancer<br><b>Colorectal</b> , lung & gastrointestinal cancers                |
| <u><b>Tumor associated antigens</b></u><br><u><b>/Carbohydrate Antigens</b></u> <ul style="list-style-type: none"><li>• <b>CA125</b></li><li>• <b>CA19-9</b></li></ul> | <ul style="list-style-type: none"><li>• Epithelial ovarian cancer</li><li>• Carcinoma pancreas</li></ul> |
| Tissue Antigens <ul style="list-style-type: none"><li>• Tissue polypeptide antigen</li></ul>                                                                           | <ul style="list-style-type: none"><li>• General cancer load</li></ul>                                    |

## Enzymes

- Alkaline phosphatase [**ALP**]
- Placental type ALP
- Prostate specific antigen **PSA**
- PAP
- NSE

- Bone secondaries
- Lung, Seminoma
- Prostate cancer
- Prostate cancer
- Nervous system tumors

## Hormones

- Beta human chorionic gonadotropin [**beta-Hcg**]
- Calcitonin
- ACTH
- VIP
- VMA
- Hydroxyindole acetic acid

- Choriocarcinoma
- Medullary thyroid Ca
- Lung oat cell Ca
- Apudomas
- Pheochromocytoma
- Carcinoid Syndrome

| <b>Tissue catabolic product</b><br>Hydroxy proline                                                                                     | Bone metastasis                                               |
|----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| <b>Serum proteins</b><br><b>Ig</b><br>Bence jones proteins [urine]                                                                     | <b>Multiple myeloma</b>                                       |
| <b>Receptor tumor markers</b><br><b>Estrogen receptor [ER]</b><br><b>Progesterone receptor [PR]</b><br><b>HER2/neu[erbB2 or EGFR2]</b> | <b>Carcinoma breast,uterus</b><br><br><b>Carcinoma breast</b> |

# Breast cancer

- At the time of diagnosis, breast cancer tissue should be tested for : **estrogen & progesterone receptors, HER2 antigen**
  - Response to hormone therapy in early or advanced breast cancer
  - May be used to determine prognosis
- Serum markers such as **CA 15-3 & CA 27.29.**