NEOPLASIA
(Carcinogenesis and cancer diagnosis)

Dr Ahmed Roshdi, *PhD*

Prof of Pathology,

Faculty of Medicine, Sohag University

2024

Outlines

By the end of this lecture; students should learn the following:

- Carcinogenesis (Tumor genetics: proto-oncogenes, cancer suppressor genes, apoptosis regulating genes and DNA repair genes)
- Etiology of cancer (carcinogens, co-carcinogens and precancerous lesions)
- Multistep carcinogenesis
- Clinical aspects of cancer diagnosis and early detection of malignant tumors

CARCINOGENESIS

(The molecular basis of cancer)

Carcinogenesis

Definition: It is the process of cancer initiation and progression

Rules:

- Cancer pathogenesis is **a very complex process**
- Cancer is **genetic** in origin.
- Cancer is **a multistep** process
- Cancer starts from one cells (**transformed cell**) that undergoes unlimited proliferation; The tumor is described as **monoclonal** in origin

Carcinogenesis

Pathogenesis:

- Cancer is **genetic in origin**: means that changes of certain genes leads to cancer initiation
- **How can genetic change happen**?
  - ***Acquired***: Due to exposure to environmental factors (commonest) as chemical, physical, viral or hormonal factors
  - ***Inherited***: Dominant or recessive germ line mutations

- **What are the genes involved in cancer initiation?**

  Four main gene groups are involved in carcinogenesis

  a. **Proto-oncogenes**
  b. **Cancer suppressor genes**
  c. **Apoptosis regulating genes**
  d. **DNA repair genes**

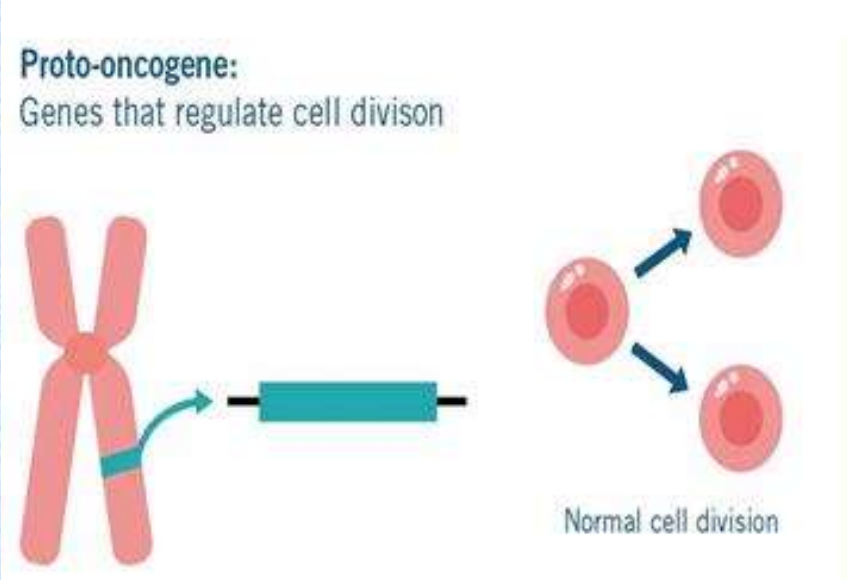
Carcinogenesis

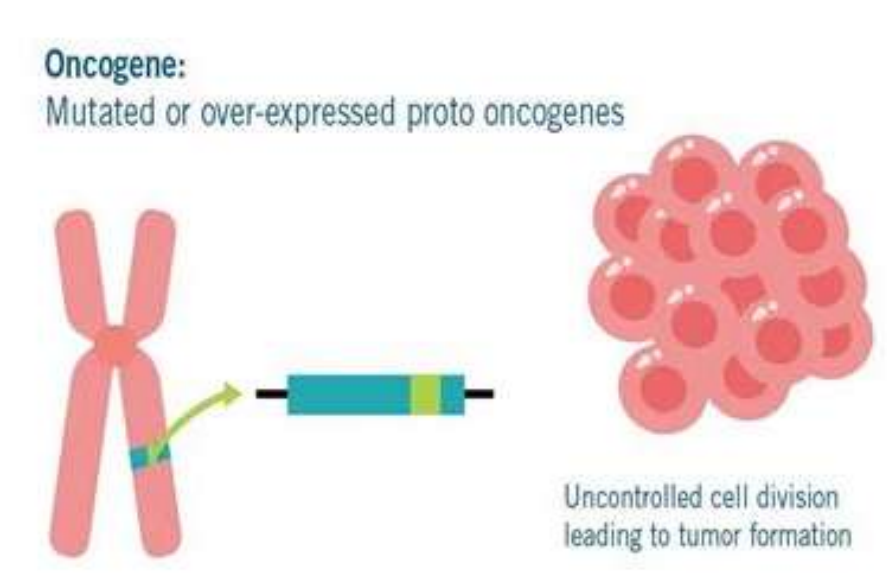
A. Proto-oncogenes or oncogenes

- Proto-oncogenes are genes that stimulate cell proliferation **in normal cells**.
- If over-expressed or over-stimulated ➡ **autonomous growth power** and **initiation of cancer cell (transformed cell)**
- Over-expression of Proto-oncogenes occurs due to:
  - ***Point mutations*** as in *RAS* oncogene in cancer colon
  - ***Chromosome translocations*** as *t-9:22 Philadelphia chromosome* in chronic leukemia
  - ***Amplification*** as *HER2* gene amplification in breast cancer

Carcinogenesis

A. Proto-oncogenes or oncogenes





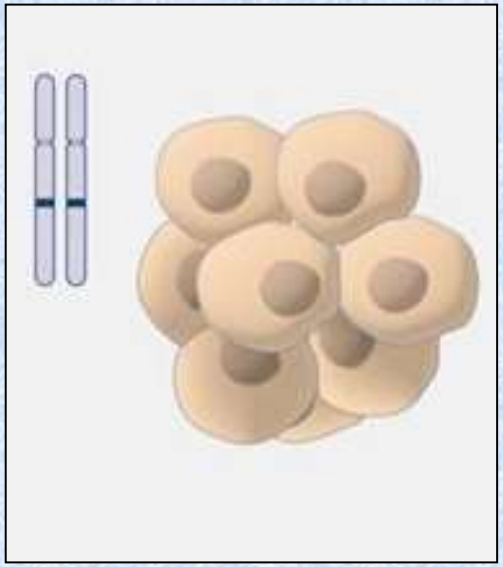
Carcinogenesis

B. Cancer suppressor genes

- Genes that are regulate cell proliferation and control steps of cell cycle **in normal cells**.
- If under-expressed or under-stimulated ➡ **insensitivity to growth inhibitory signals** ➡ **continuous proliferation.**
- Both alleles of the gene must be involved for inactivation of cancer suppressor genes (two hits).
- Examples:
  1. ***P53* gene (Guardian of the genome):** Inactivation of P53 gene (by mutation) occurs in about 50% of human cancers.
  2. ***Adenomatous polyposis coli (APC) gene***: Inactivation of APC gene (by mutation) leads to development of hundreds of colonic adenomas and colon cancer.

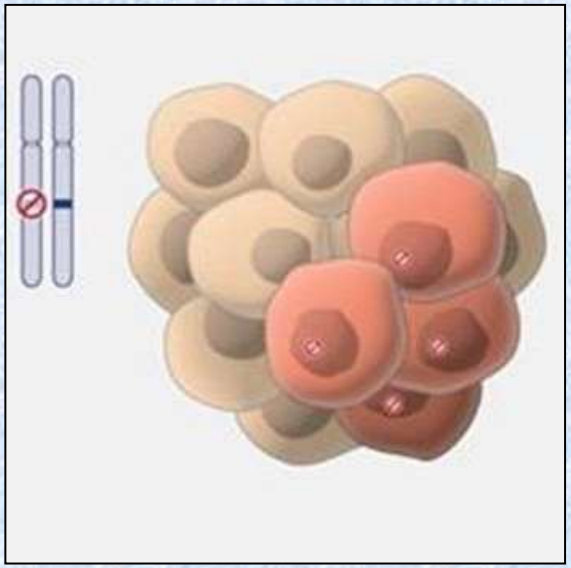
Carcinogenesis

B. Cancer suppressor genes



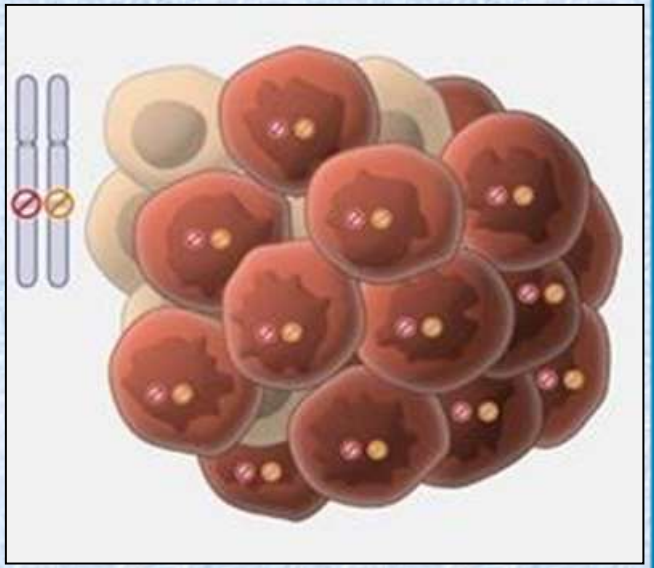
Normal two alleles of cancer suppressor gene

Controlled growth



Mutation of one allele of cancer suppressor gene due to one hit

Controlled cell growth (cells liable for another hit)



Mutation of both alleles of cancer suppressor gene (two hits)

Uncontrolled cell growth (Transformed cells)

Carcinogenesis

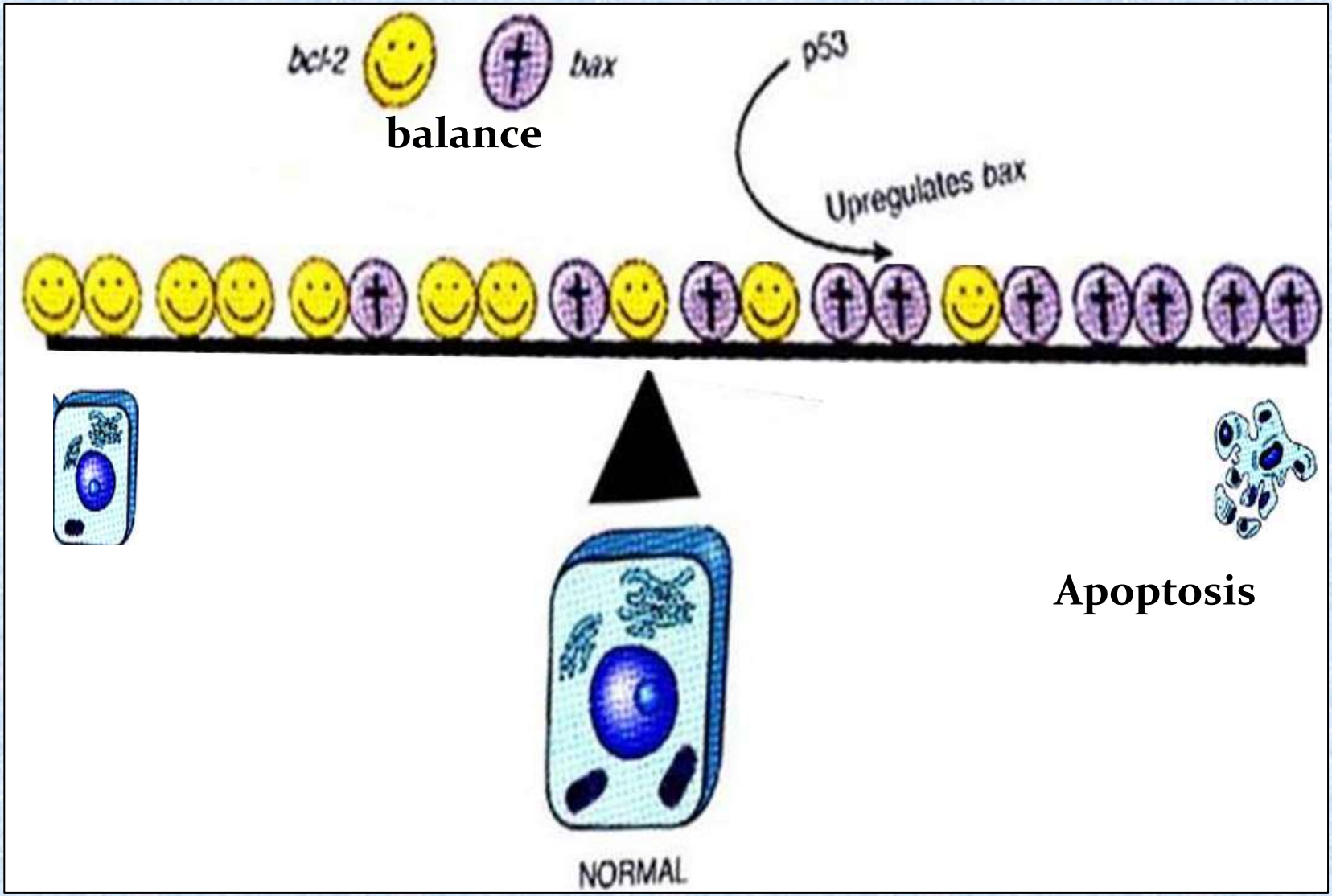
C. Apoptosis regulating genes

- Apoptosis or programmed cell death is controlled by two family of genes:
  - Apoptosis inhibitors (**anti-apoptosis**): as *Bcl-2*
  - Apoptosis promoters (**pro-apoptosis**): as *Bax*

- **Over-expression of anti-apoptotic OR under-expression of pro-apoptotic molecules** → **escaping of cells from apoptosis** and **overcoming of cellular aging** → **cancer progression**

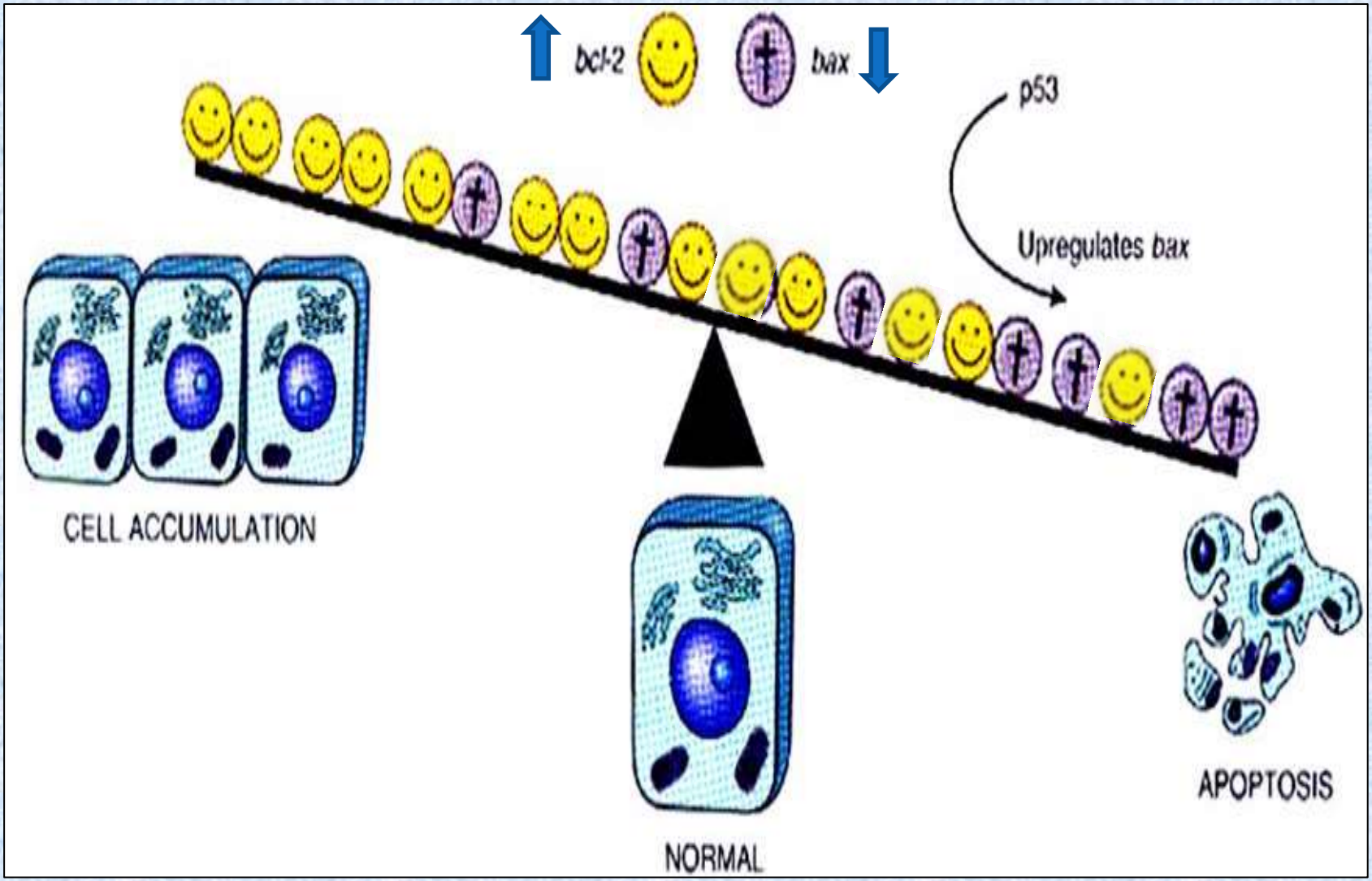
Carcinogenesis

C. Apoptosis regulating genes



Carcinogenesis

C. Apoptosis regulating genes



Carcinogenesis

D. DNA repair genes

- Normally; DNA is exposed every second to damaging factors (such as radiation, sunlight, chemical and dietary carcinogens).
- Normal cells contain a group of genes responsible for repair of damaged DNA during cell division called **DNA repair genes**; and thus prevent mutations to pass to next cellular generations.
- Defects in DNA repair gene leads to genomic instability with permanent mutations in genes regulating cell growth and proliferation ⟹ **cancer progression**.
- Examples:
  - Defects in *BRCA1* and *BRCA2* genes leads to hereditary breast and ovarian cancer
  - Defects in certain DNA repair genes leads to *Xeroderma pigmentosa* with skin cancer (Sq. cell carcinoma, basal cell carcinoma and melonoma)

Carcinogenesis

Multi-step carcinogenesis

- Carcinogenesis is a multistep process at genetic levels.
- Tumors are induced by successive accumulation of multiple genetic damage of proto-oncogenes, cancer suppressor genes…….etc.
- Oncogenic factors either acquired (as chemical, radiation or viruses) or inherited act as initiating or promoting factors
- Tumorigenesis passes through these steps:
  1. Initiation
  2. Promotion
  3. Transformation

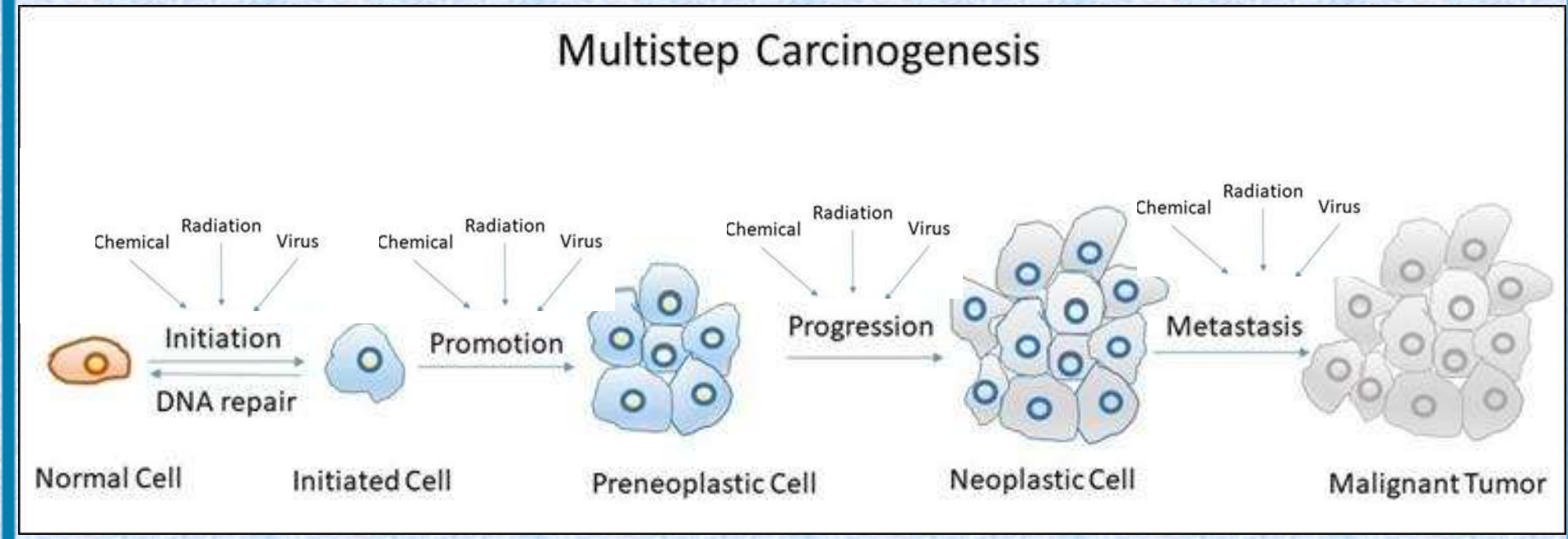
Carcinogenesis

Multi-step carcinogenesis

1. ***Initiation***:
   - The cells are subjected to irreversible genetic damage
   - Although carrying genetic damage, these cells don`t have ability of growth autonomy
   - Such cells may live for a long period (up to 10 years) before being transformed, called latent period
2. ***Promotion***:
   - Latent cells are subjected to further genetic damage, so become able of autonomous growth and proliferation
   - Early stages of promoted cells can be reversible
3. ***Transformation***: further genetic damage allows cell to acquire uncontrolled and unlimited proliferation

Carcinogenesis

Multi-step carcinogenesis



ETIOLOGY OF TUMORS

Etiology of tumors

- **Etiology of cancer is multi-factorial**, multiple causative factors are usually involved.
- A single definitive cause of all forms of tumours has not been yet reported.

Carcinogens: Substances known to cause cancer or produces an increase in incidence of cancer in animals or humans

Carcinogens can be

A. Chemical
B. Radiation
C. Viral
D. Hormonal
E. Nutritional
F. Hereditary factors

Co-carcinogens: factors that, by their own are not considered as causative factors for cancer, but help cancer to occur

Pre-cancerous lesions: lesions that are well known to precede cancer progression

Etiology of tumors

Carcinogens

A. Chemical carcinogens

- ***Mechanism***: direct damage of DNA leading to gene mutation
- ***Examples***:
  1. Polycyclic hydrocarbones (as benzpyrenes present in **Cigarette smoking** is associated with high risk of lung, oropharynx and esophageal and UB cancers.
  2. Asbestos caused lung cancer and mesothelioma
  3. Aromatic amines cause cancer bladder
  4. Anticancer drugs: alkylating agents (as cyclophosphamide) causes leukaemia

Etiology of tumors

Carcinogens

B. Radiation carcinogens

-***Mechanism***: Chromosome breakage, translocation and point mutation

-***Examples***:

1. Prolonged exposure to **ultraviolet rays** of the sun predisposes to skin tumors (squamous cell carcinoma, basal cell carcinoma and malignant melanoma).
2. **Ionizing radiation** (used in industry and in treatment of some tumors) can lead to leukemia, skin, lung and thyroid cancers.
3. **X-ray** is associated with high risk of skin cancer & leukemia

Etiology of tumors

Carcinogens

C. Microbial carcinogens

Viral oncogenes:

1. Epstein Barr virus (EBV): involved in progression of Burkitt`s lymphoma and nasopharyngeal carcinoma
2. Hepatitis B and hepatitis C viruses: inked to hepatocellular carcinoma by chromosomal damage and inactivation of tumor suppressor genes
3. Human herpes virus 8 (HHV8): Kaposi sarcoma
4. Human papilloma virus (HPV): are implicated in progression of squamous papilloma and squamous cell carcinoma of cervix, skin cancer and cancer larynx.

Etiology of tumors

Carcinogens

C. Microbial carcinogens

Bacterial oncogenes:

Helicobacter pylori: gastric carcinoma and gastric lymphoma

Fungal oncogenes:

Fungus aspergillus produces aflatoxins predisposing to hepatocellular carcinoma

Parasitic oncogenes

Chistosma haematobium: can lead to cancer bladder.

Etiology of tumors

Carcinogens:

D. Hormonal carcinogens

1. Excess estrogen ➡ high risk of breast and endometrial cancers.
2. Excess androgen ➡ high risk of prostatic cancer.
3. Contraceptives (in some cases) ➡ hepatocellular adenoma

***Clinical hint*: hormone dependent tumors:**

- Tumors depend on hormone for their growth.
- Examples: some of breast, endometrial, prostatic and thyroid cancers
- Decrease exposure to postulated hormone or use of antagonist of these hormones can be used as a treatment tool, e.g. use of tamoxafen (anti-estrogen) in treatment of breast cancer

Etiology of tumors

Carcinogens:

E. Hereditary factors:

- Only 5-10% of cancers can be inherited.
- Inherited gene mutation predisposes for malignant change
- Main features of hereditary tumors:
  - Malignancy at younger age
  - Tumors multiplicity
  - Tumors involve relative patients
- Common examples:

1. BRCA1 and BRCA2: high risk of breast and ovarian cancers.
2. P53 gene mutation (***Li-Fraumeni syndrome***): high risk of leukaemia, childhood sarcomas, and brain tumours
3. Wilm`s tumor gene mutation leads to Wilm`s tumor of kidney

Etiology of tumors

Co-carcinogens (helping factors)

These are factors that, by their own are not considered as causative factors for cancer, but help cancer to occur; ***examples***:

1. **Age:** older patients are more susceptible to malignant tumors (due to prolonged exposure to carcinogens)
2. **Sex:** In general; males are generally more susceptible to cancers than females. Some tumors as breast and thyroid cancers are more common in females
3. **Diet:** fat-rich diet is related to colorectal cancer while smoked fish is related to gastric cancer
4. **Habits:** smoking is related to several tumors as lung, oropharynx, esophagus and lip cancers.
5. **Occupational:** farmers are more susceptible to skin cancers due to prolonged exposure to sun
6. **Environmental:** air pollution is associated with increased risk of lung cancer

Etiology of tumors

Pre-cancerous lesions

These are lesions that are well known to precede cancer progression; ***examples***:

1. **Inflammatory diseases: as**
   - UB bilharziasis ➡ TCC and Sq CC
   - Ulcerative colitis ➡ colo-rectal carcinoma
   - H pylori gastritis ➡ cancer stomach
   - Lupus vulgaris (TB of skin): ➡ Sq CC of skin
2. **Hyperplastic lesions:**
   - Mammary cystic hyperplasia ➡ breast cancer
   - Endometrial hyperplasia ➡ endometrial carcinoma
   - Hyperplasia of transitional epithelium ➡ Transitional cell carci.
   - Hyperplastic nodule of liver cirrhosis ➡ Hepatocellular carci.

Etiology of tumors

Pre-cancerous lesions

3. **Chronic irritation:**
   - Ur bladder stones, gall bladder stones and chronic smoking ➡ squamous metaplasia ➡ Sq CC
   - Chronic varicose vein, chronic ulcer and scar of old lesion ➡ Sq cell carcinoma (Marjolin ulcer)
   - Sinuses that drain chronic supportive inflammation (as chronic osteomyelitis) ➡ Sq cell carcinoma

4. **Benign tumours:**
   - Villous papilloma of the Ur bladder ➡ TCC
   - Adenomatous polyposis of the colon ➡ colon cancer

Diagnostic tools of TUMORS

Diagnosis of tumors

Early detection:

- Early detection of malignancy is essential for curative treatment of malignancy before metastasis
- Early detection is achieved by ***screening of high risk people*** using simple techniques such as:
  - Clinical examination and self-examination as in case of breast cancer
  - Evaluation of serum tumor markers as serum PSA in cases of cancer prostate
  - Cytology smears as in cases of cancer cervix

Diagnosis of tumors

Accurate diagnosis (pathological)

- Diagnosis of benign and malignant tumor is achieved by ***microscopic evaluation of tumor tissue***

- There are several pathological tools for diagnosis of tumors:

  1. Cytological diagnosis:

  - ***Definition***: Means microscopic evaluation of cells obtained from the tumor.
  - ***Examples***:
    a. Cells obtained from urine in cancer bladder
    b. Cells obtained from ascetic fluid in ovarian cancer
    c. Cells obtained from pleural fluid in cancer lung

Diagnosis of tumors

Accurate diagnosis (pathological)

2. Histological diagnosis (biopsy):

- ***Definition***: obtaining a piece of tumor tissue for histopthological examination.
- ***Clinical importance***: Tissue biopsy is standard for tumor diagnosis. Microscopic examination is essential for definitive tumor diagnosis.
- ***Types of biopsies:***
  1. Tru-cut needle biopsy (TCNB): obtaining core of tissue from the tumor by a wide cored cutting needle
  2. Incesional biopsy: part of the tumor is obtained by an incision
  3. Excision of whole tumor: e.g. excision of breast mass, thyroid nodule, subcutaneous lipoma…….etc.
  4. Radical excision: excision of the whole organ with the tumor and draining LN: e.g. radical mastectomy for cancer breast and radical cystectomy for cancer bladder

Diagnosis of tumors

Other methods

a. *Tumor markers:*

- Tumour cells produce certain antigenic proteins (called tumour associated antigens or tumor markers)
- Tumour markers can be:

a. Serum tumour marker:

- The tumor antigen can be detected in patient`s serum by biochemical tests
- Examples prostatic specific antigen (PSA) is elevated in cancer prostate and alpha-feto protein (AFP) is elevated in hepatocellular carcinoma

a. Tissue tumor marker:

- The tumor antigen is not circulating in the serum and can be detected only in tumor tissue by a technique called **immunohistochemistry (IHC).**
- IHC is essential to detect origin of the tumor in cases of undifferentiated malignant tumor

Good luck

Dr. Ahmed Roshdi