NEOPLASIA

LEC. 5

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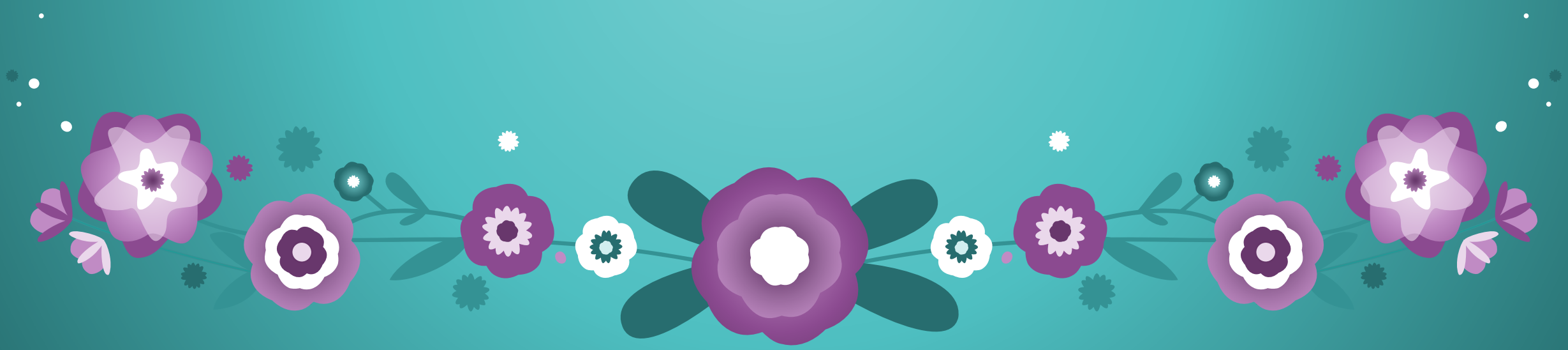
ETIOLOGY OF CANCER: CARCINOGENIC AGENTS



- **Carcinogenic agents** cause genetic damage, which lies at the heart of carcinogenesis.
- **Three classes of carcinogenic agents** have been identified:

(1) Chemicals

(2) Radiant energy

(3) Microbial products.

• The steps of cancer development are:

1- Initiation: result from exposure of the cell to an appropriate dose of carcinogen **(initiator).** Those factors cause permanent DNA damage (mutation), so it is irreversible.

2- Promotion: means induction of tumor in initiated cell but the **promoters** are non-tumorigenic by themselves.

Initiator:

1- It is the **first** step in the development of tumor &it should be followed by a promoter.

- Initiator alone --- no tumor.
- Promoter alone --- no tumor.

2- It is **rapid** (within minutes), that it does not need time to get **permanent irreversible damage** e.g. atomic bomb exposure---the damage will occur immediately &last for 2 ,3 generations.

3- It is **dose independent**: i.e. even small doses may lead to damage e.g. pregnant female is avoided to have an XR although the radiological amount is small.

4- Initiators should be **followed** by promoters.

Promoters:

1- Comes **after** the initiator.

2- It is **dose dependent.** e.g. increase in the amount of estrogen hormone to certain level will produce the changes.

3- It is **reversible.**

4- Induce tumors in initiated cells, but they are non-tumorigenic by themselves.

- **e.g.** on promoters are: (dugs, hormones, phenol).

1- Chemical carcinogens

- Classified into **two categories:**

I. Direct acting agents

- **Require no metabolic conversion to become carcinogenic.** They are typically weak carcinogens but are important because some of them are cancer chemotherapy drugs **(e.g., alkylating agents)** used in regimens that may cure certain types of cancer (e.g., Hodgkin lymphoma), only to evoke a subsequent, second form of cancer, usually leukemia.
- This situation is even more tragic when the initial use of such agents has been for non-neoplastic disorders, such as rheumatoid arthritis or granulomatosis with polyangiitis. The associated risk for induced cancer is low, but its existence dictates cautious use of such agents.

II. Indirect acting agents

- **Need transformation inside the body by liver enzymes to become active (ultimate carcinogens).**
- Examples include:

a. Polycyclic aromatic hydrocarbon.

Benzopyrine in cigarette smoke, smoked meet , the most potent carcinogens.

b. Aromatic amines, amides &azo dyes.

(ß naphthylamine) → Carcinoma of urinary bladder

c- Natural plant and microbial products

* Aflatoxin B1 (substance present in stored grains produced from certain fungus)---hepatocellular carcinoma.

d- Others

*Nitrosamine &amides; in preservatives and can cause gastric carcinoma.

* Asbestos: bronchogenic carcinomas.

* Vinyl chloride---angiosarcoma.

* Chromium---lung carcinoma.

*Nickel---nasopharyngeal carcinoma.

* Cadmium---prostatic carcinoma

Mechanism of Chemical carcinogenesis:

- Most of chemical carcinogens are mutagenic **(initiators)**.
- The commonest **proto-oncogenes** that affect by chemical is **Ras** (mutational activation), while the commonest **Tumor suppressor gene** affected by chemicals is **P53** (there is inhibition of P53).
- Some of chemicals carcinogenesis is **augmented by promoters** (dugs, hormones, phenol) non mutagenic but increase proliferation.
- Repeated & sustained exposure to promoters **must follow the exposure to chemical mutagenic agent or initiator.**

2- Radiation Carcinogenesis:

- Radiation, whatever its source **(UV rays of sunlight, radiographs, nuclear fission, radionuclides)**, is a well-established carcinogen.

A. Ionizing radiation e.g. XR, gamma ray, proton, neutron.

- **Those at risk are:**

1. Radiologists.

2. Unprotected miners of radioactive elements.

3. Survivors of atomic bomb.

4. Therapeutic irradiation. Even therapeutic irradiation can induce cancer e.g.(Therapeutic irradiation of the head and neck can give rise to papillary, thyroid cancers years later).

- **Examples** of cancers induce by ionizing radiation are (**leukemia, Thyroid cancer, pulmonary caner).**

- ## Mechanism:

* The oncogenic properties of ionizing radiation are related to its mutagenic effects **(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.

2. Ultraviolet light in sunlight

- Natural UV radiation derived from the sun can cause skin cancers (melanomas, squamous cell carcinomas, and basal cell carcinomas). At greatest risk are **fair-skinned people** who live in locales such as Australia and New Zealand that receive a great deal of sunlight.

Mechanism:

- Ability to damage DNA by forming pyrimidine dimers. This type of DNA damage is repaired by the nucleotide excision repair pathway.
- With extensive exposure to UV light, the repair systems may be overwhelmed, and skin cancer results.
- As mentioned earlier, patients with the inherited disease *xeroderma pigmentosum* have a defect in the nucleotide excision repair pathway.

3- Viral & Microbial carcinogenesis

- Oncogenic viruses are of ***two types*:**

1. ***RNA oncogenic viruses:***

- Only one human retrovirus, human T-cell leukemia virus type 1 (HTLV-1), is firmly implicated in the pathogenesis of cancer in humans.

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

- It causes **T- cell Leukemia / Lymphoma** (endemic in japan).
- Similar to the human immunodeficiency virus, which causes AIDS, HTLV-1 has **tropism for CD4+ T cells**, and this subset of T cells is the major target for neoplastic transformation.

- Several aspects of HTLV-1's **transforming activity are attributable to Tax, the protein product of the *tax* gene**. Tax is essential for viral replication, also alters the transcription of several host cell genes and contributes to the acquisition of several cancer hallmarks, including the following:

Increased survival and growth of infected cells.

*** *Increased genomic instability;*** by interfering with DNA-repair functions and inhibiting cell cycle checkpoints activated by DNA damage.

- **Human acquired this infection by** transmission of infected T- cells by sexual intercourse, blood products, breast feeding.
- Leukemia develops in **only 3% to 5%** of the infected individuals, typically after a long latent period of 40 to 60 years.

2. DNA oncogenic viruses:

- Include ***4 viruses:***

1. Human Papilloma virus (HPV)

- Cause **many types** of tumors:

1. Benign squamous papilloma of skin (Wart) (by virus type **1, 2, 4, 7).**
2. Genital warts have low malignant potential and are also associated with low-risk HPVs, predominantly **HPV-6 and HPV-11.**
3. Squamous cell carcinoma of the cervix and anogenital region. Caused by high-risk HPVs (e.g., **types 16 and 18)**
4. Oropharyngeal carcinomas: at least 20% of these are associated with HBV.

- ***HPV can cause cancer by*** production of two viral genes **E6 and E7.**
- The **E7** protein binds to the **RB** protein and displaces the E2F transcription factors that are normally sequestered by RB, promoting progression through the cell cycle.
- The **E6** protein binds to and mediates the degradation of **p53 and BAX** (pro-apoptotic member).
- However, infection with HPV itself is not sufficient for carcinogenesis, and full-blown transformation requires the acquisition of mutations in host cancer genes, such as ***RAS.***

*2. EBV (*Epstein-Barr Virus)

- EBV, a member of the herpesvirus family, was the first virus linked to a human tumor, Burkitt lymphoma.
- Cause the *following tumors:*

1. Burkitt lymphoma;
2. B-cell lymphomas in immunosuppressed Individuals;
3. A subset of Hodgkin lymphoma;
4. A subset of nasopharyngeal carcinoma.

- EBV mainly infects B lymphocytes; result in proliferation of

B lymphocytes.

- EBV uses the complement **receptor CD21** to attach to and infect B cells. such infection leads to polyclonal B cell proliferation and generation of immortal B lymphoid cell lines.
- One EBV-encoded gene, *LMP1* (latent membrane protein 1), **acts as an oncogene, promotes B cell proliferation.**
- Another EBV-encoded protein, EBNA2, **trans activates** several host genes, including **cyclin D.**

3. Hepatitis B and Hepatitis C Viruses

- It is estimated that **70% to 85%** of hepatocellular carcinomas worldwide are caused by HBV or HCV.
- However, the mode of action of these viruses in tumorigenesis is not fully explained. Indeed, the oncogenic effects of HBV and HCV are multifactorial, but **the dominant effect seems to be immunologically mediated chronic inflammation with hepatocyte death, leading to regeneration and genomic damage.**

- One key molecular step seems to be activation of the nuclear factor-κB (NF-κB) pathway in hepatocytes caused by mediators derived from the activated immune cells.
- Activation of the NF-κB pathway blocks apoptosis, allowing the dividing hepatocytes to sustain genotoxic stress and to accumulate mutations. Although this seems to be the dominant mechanism in the pathogenesis of virus-induced hepatocellular carcinoma, both HBV and HCV also contain proteins within their genomes that may more directly promote the development of cancer.
- The HBV genome contains a gene known as *HBx, (*directly or indirectly activate a variety of **transcription factors and several signal transduction pathways, and may interfere with p53 function).**

Helicobacter pylori (H. Pylori)

- The first bacterium classified as a carcinogen.
- Implicated in the genesis of both gastric adenocarcinomas and gastric lymphomas.
- It involves increased epithelial cell proliferation on a background of chronic inflammation. As in viral hepatitis, the inflammatory location contains numerous genotoxic agents, such as reactive oxygen species.
- The sequence of histopathologic changes consists of initial development of chronic inflammation/gastritis, followed by gastric atrophy, intestinal metaplasia of the lining cells, dysplasia, and cancer.
- This sequence takes decades to complete and occurs in only 3% of infected patients.

- *H. pylori* genome also contains genes directly implicated in oncogenesis.
- Strains associated with gastric adenocarcinoma have been shown to contains cytotoxin-associated A gene **(*CagA*).**
- Although *H. pylori* is noninvasive, ***CagA* is injected into gastric epithelial cells,** where it has a variety of effects, including the **initiation of a signaling cascade that mimics unregulated growth factor stimulation.**

- *H. pylori* is associated with an increased risk for the development of gastric lymphomas
- Their molecular pathogenesis is incompletely understood but seems to involve **strain-specific *H. pylori* factors, as well as host genetic factors.**
- *H. pylori* infection leads to the activation of *H. pylori*–reactive T cells, which in turn cause polyclonal B cell proliferation. In time, a monoclonal B cell tumor emerges from the proliferating B cells, perhaps as a result of accumulation of mutations in growth regulatory genes.

THANK YOU