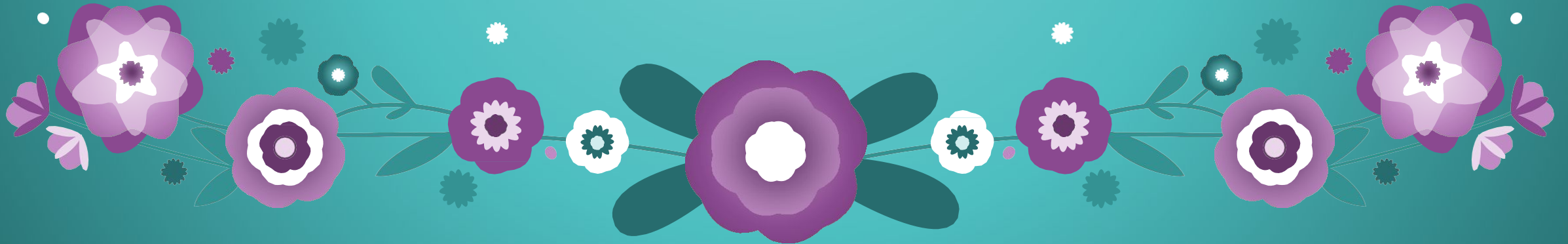


NEOPLASIA

Etiology of cancer

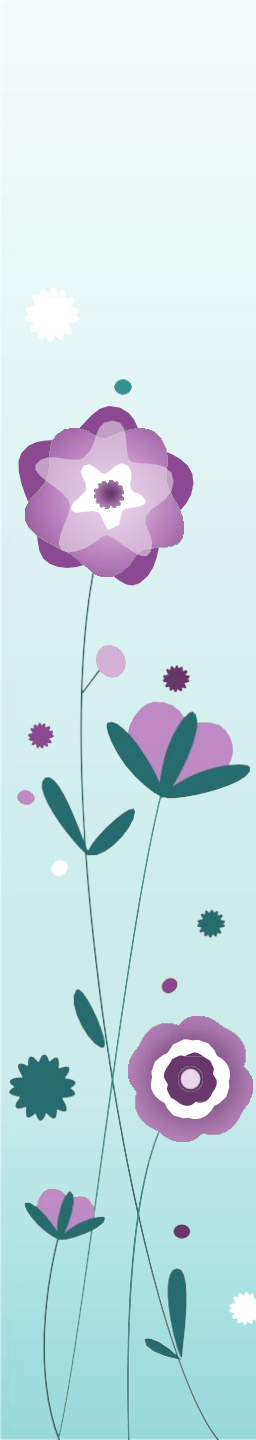
LEC.6

Dr. Raghad Hanoon



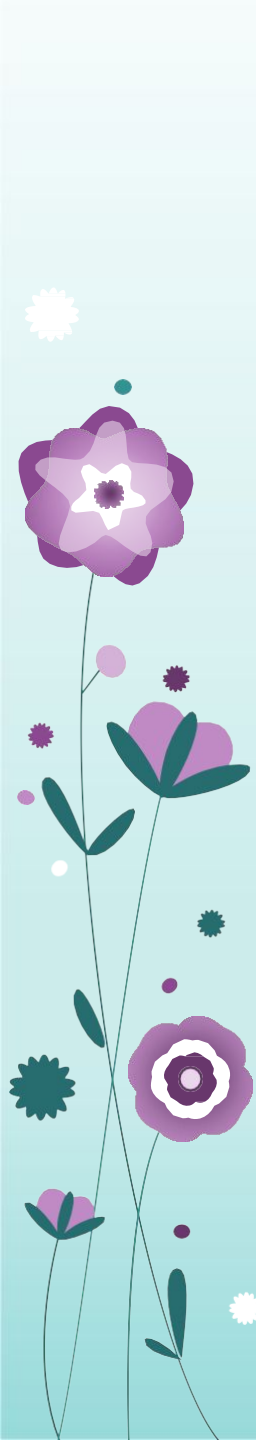
• **The steps of cancer development are:**

- 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.
- 



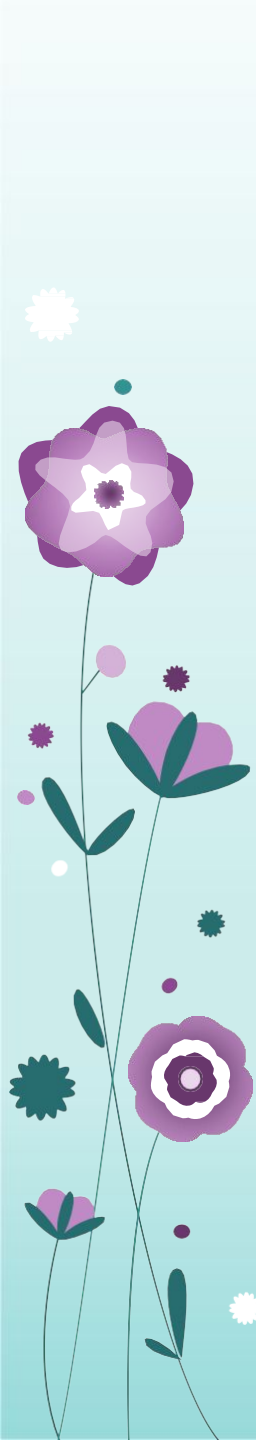
Initiator:

- 1 It is the **first** step in the development of tumor & it should be followed by a promoter.
 - 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).
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- **Carcinogenic agents** cause genetic damage, which lies at the heart of carcinogenesis.

- **Three classes of carcinogenic agents** have been identified:

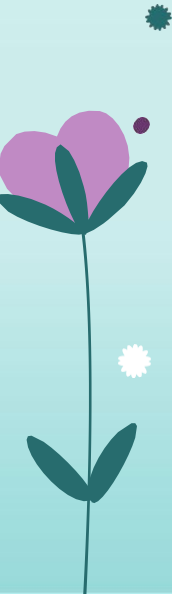
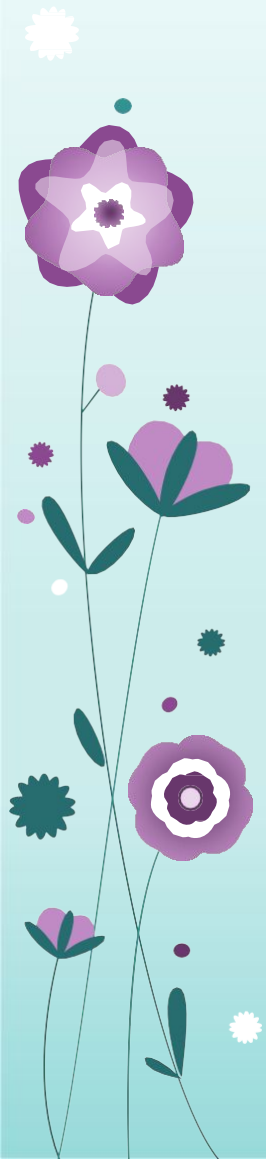
- (1) Chemicals
 - (2) Radiant energy
 - (3) Microbial products.
- 

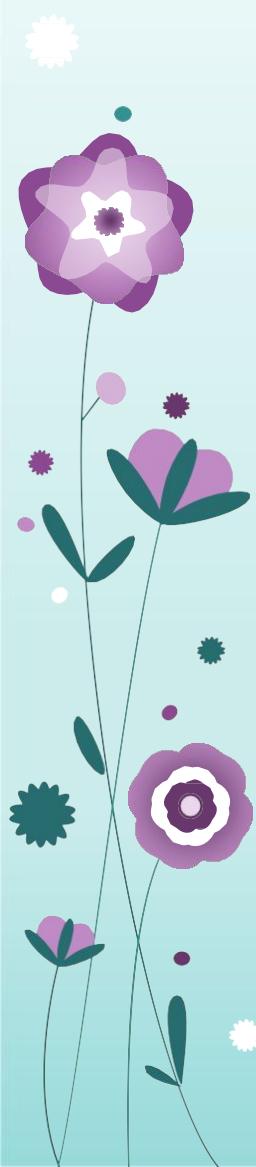
1- Chemical carcinogens

- 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.





II. Indirect acting agents

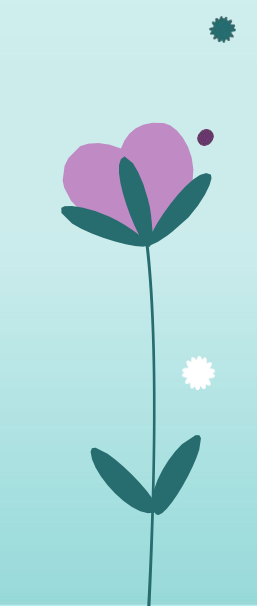
- Need transformation inside the body by liver enzymes to become active (ultimate carcinogens).
- Examples include:

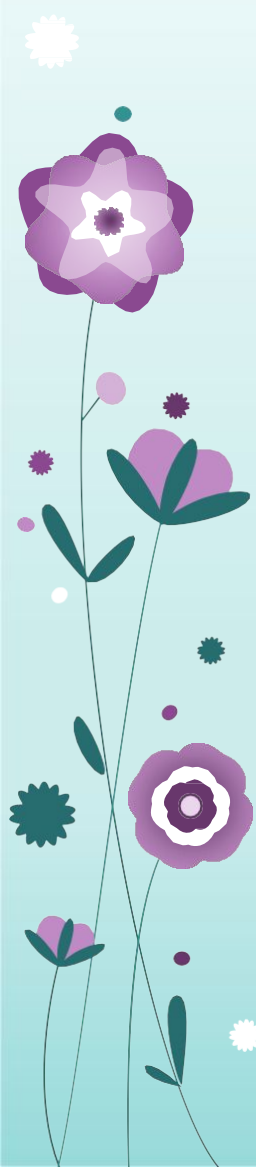
a. Polycyclic aromatic hydrocarbon.

Benzopyrine in cigarette smoke, smoked meat.

b. Aromatic amines, amides & azo dyes.

(β naphthylamine) $\square$ Carcinoma of urinary bladder

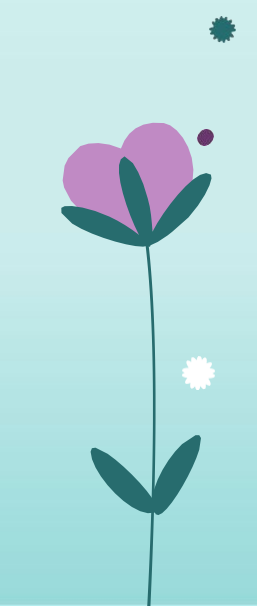


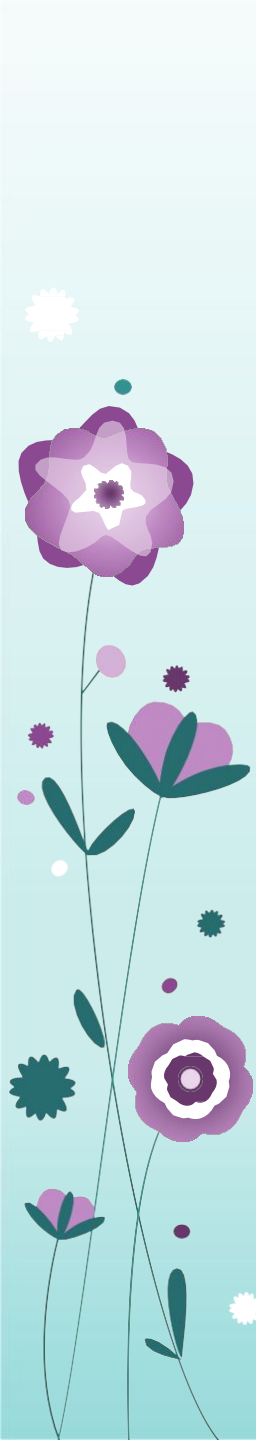
A decorative illustration on the left side of the slide featuring a tall, thin green stem with several stylized flowers. The flowers are in shades of purple and pink, with some having white centers. There are also small white star-like shapes and green leaves scattered along the stem.

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
- 
- A decorative illustration on the right side of the slide featuring a tall, thin green stem with several stylized flowers. The flowers are in shades of purple and pink, with some having white centers. There are also small white star-like shapes and green leaves scattered along the stem.



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) non mutagenic but increase proliferation.
- 

2- Radiation Carcinogenesis

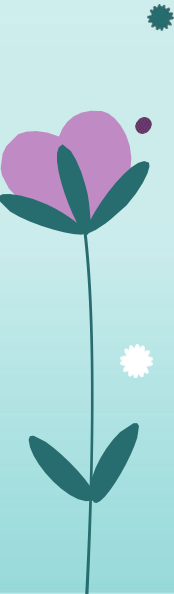
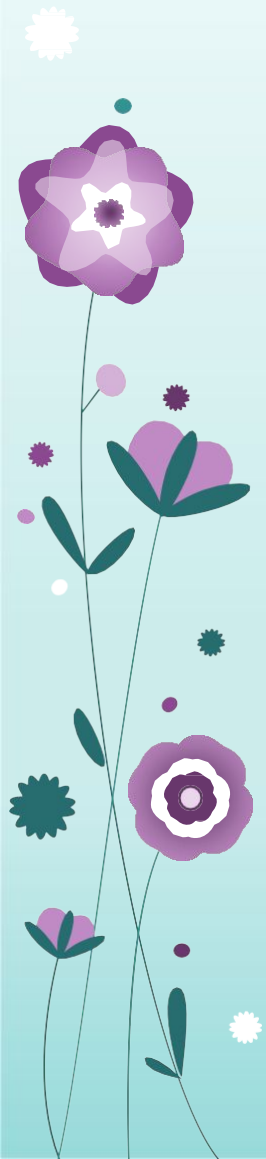
- Radiation, whatever its source (**UV rays of sunlight, radiographs, nuclear fission, radionuclides**), is a well-established carcinogen.

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

- **Those at risk are:** *Radiologists, *Unprotected miners of radioactive elements, *Survivors of atomic bomb and *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 induced by ionizing radiation are (**leukemia, Thyroid cancer, pulmonary cancer**).
- **Mechanism:**
*The oncogenic properties of ionizing radiation are related to its mutagenic effects (**initiator**); it causes **chromosome breakage (commonest)**, translocation, & less commonly point mutation.

B. 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*:

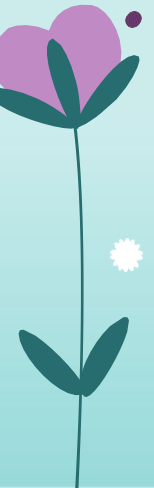
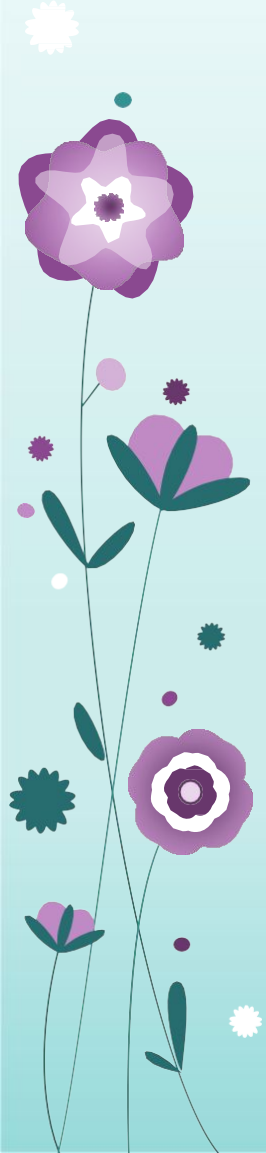
- Only one human retrovirus, human T-cell leukemia virus type 1 (HTLV-1), is firmly implicated in the pathogenesis of cancer in humans.

***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.

• **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.



- **Mechanism:**

- 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.

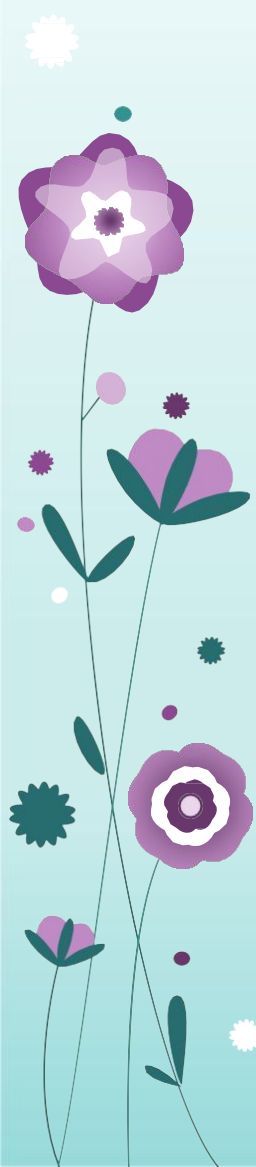


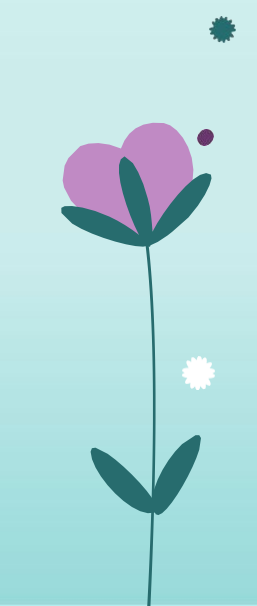
2. DNA oncogenic viruses:

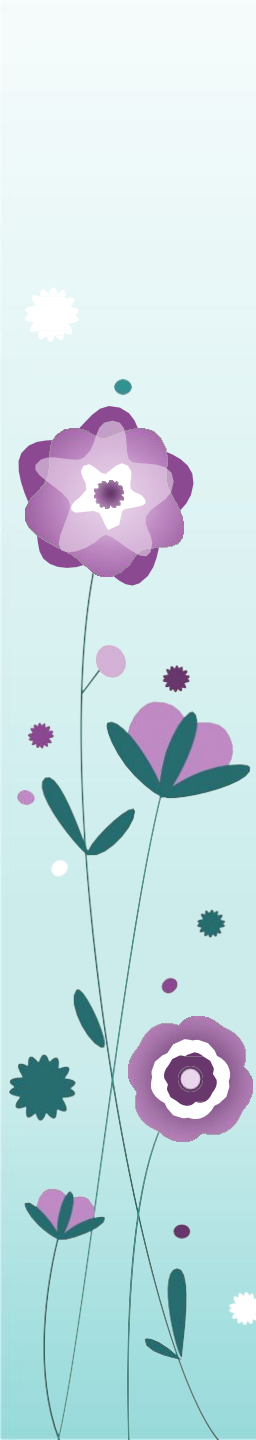
- Include **4 viruses**:

1. Human Papilloma virus (HPV)

- Cause **many types** of tumors:
2. Benign squamous papilloma of skin (Wart) (by virus type **1, 2, 4, 7**).
 3. 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**.
- 

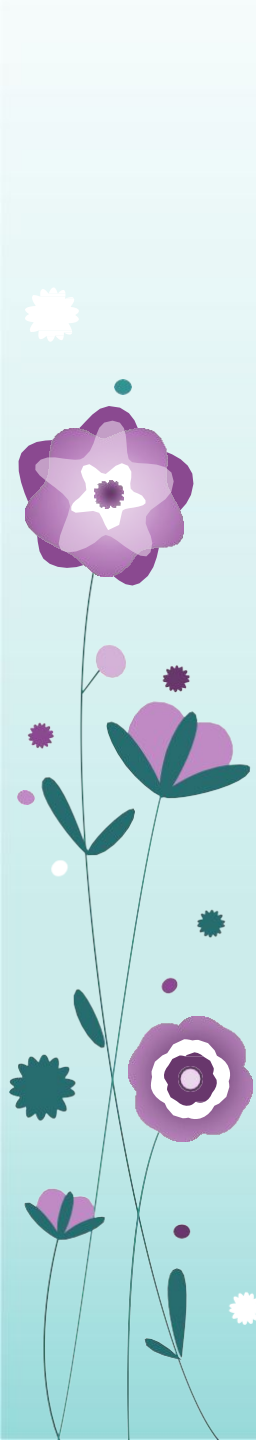


2. *EBV* (Epstein-Barr Virus)

- 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.
- 

- **Mechanism:**

- 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

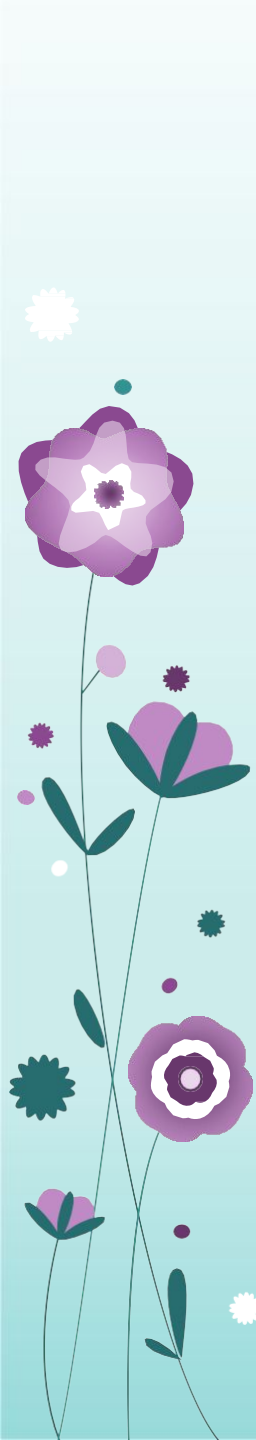
- It is estimated that **70% to 85%** of hepatocellular carcinomas worldwide are caused by HBV or HCV.
 - Indeed, the oncogenic effects of HBV and HCV are multifactorial, but **the dominant effect seems to be immunologically mediated chronic inflammation with hepatocyte death, leading to regeneration and genomic damage.**
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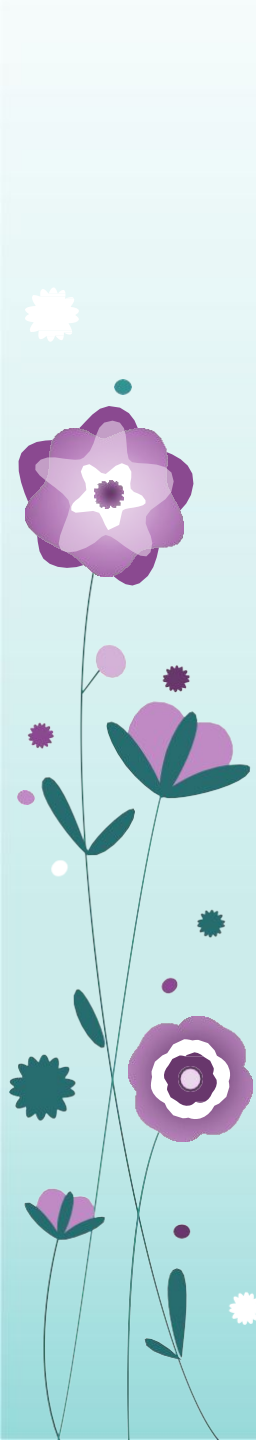
- **Mechanism:**

- One key molecular step seems to be **activation of the nuclear factor- κ B (NF- κ B) pathway** in hepatocytes that **blocks apoptosis**, allowing the **dividing hepatocytes to sustain genotoxic stress and to accumulate mutations**.
 - 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 contain 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.**
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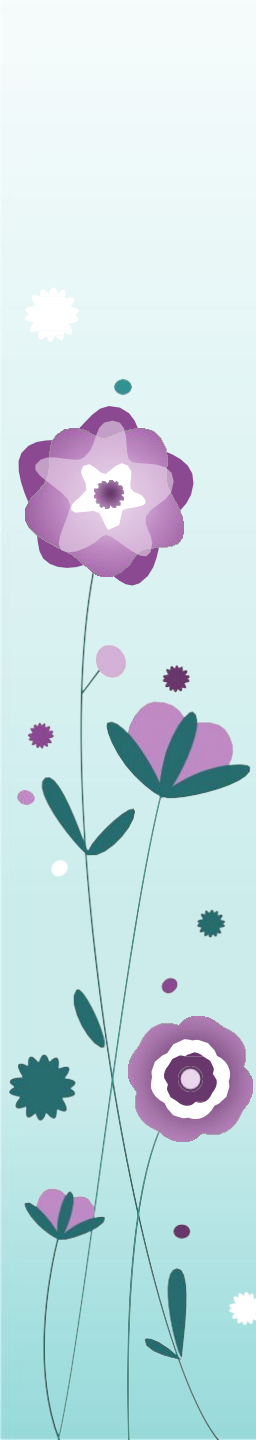
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- *H. pylori* is associated with an increased risk for the development of **gastric lymphomas**
 - Their molecular pathogenesis is incompletely understood but seems to involve **strain-specific *H. pylori* factors, as well as host genetic factors.**
 - *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.**

Tumor Antigens

- Antigens present on tumors that *elicit the immune response*.
- The modern classification of tumor antigens **is based on their molecular structure and source:**

1. Products of mutated genes:

- Neoplastic transformation, as we have discussed, results from genetic alterations in proto-oncogenes and tumor suppressor genes or other mutated genes; these mutated proteins represent tumor antigens.

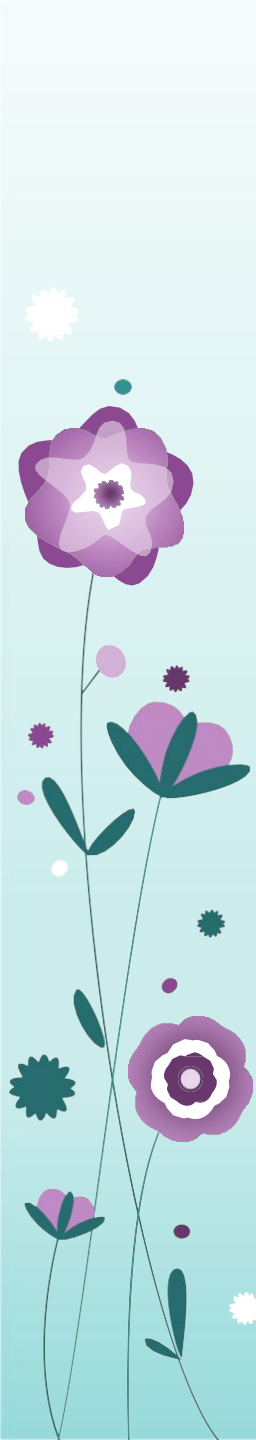


2. Overexpressed or aberrantly expressed cellular proteins:

- Tumor antigens may be normal cellular proteins that are abnormally expressed in tumor cells.
- One such antigen is **tyrosinase**, an enzyme involved in melanin biosynthesis that is expressed only in normal melanocytes and melanomas.

3. Tumor antigens produced by oncogenic viruses:

- Oncogenic viruses (e.g.; HPV, EBV, HBV) produce proteins that are recognized as foreign by the immune system.
- 



4. *Oncofetal antigens:*

- These are proteins that are **expressed at high levels on cancer cells and in normal developing (fetal) but not adult tissues.** The two most characterized oncofetal antigens are;

a. Carcinoembryonic antigen (CEA)

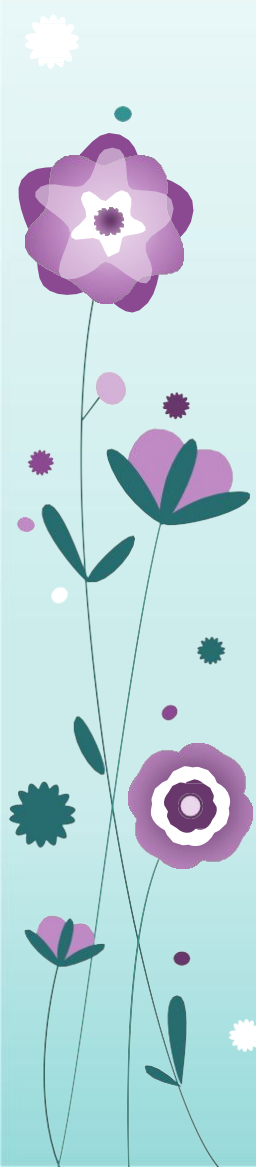
- GIT, pancreas, biliary system and breast cancer.

b. Alpha fetoprotein(AFP):

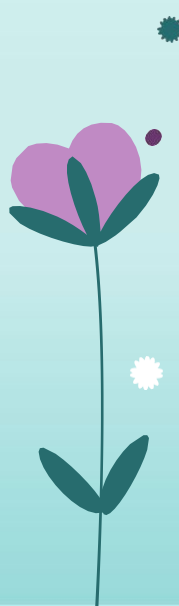
- hepatocellular carcinoma
- 

5. Altered Cell Surface Glycolipids and Glycoproteins:

- Expression of higher than normal levels and abnormal forms of surface glycoproteins and glycolipids. These include;
- **CA-125** - expressed on ovarian carcinomas
- **CA-19-9** - expressed on carcinoma in pancreas & biliary tract
- **MUC-1** - expressed on breast carcinomas

A decorative floral illustration on the left side of the slide, featuring a tall stem with several purple flowers of different sizes and shapes, some with white centers, and small green leaves. The background is a light blue gradient.

6. Cell type-specific differentiation antigens:

- Tumors express molecules that are normally present on the cells of origin, important for identifying the tissue of origin of tumors. These antigens are called **differentiation antigens** because they are specific for particular lineages or differentiation stages of various cell types.
 - Example, ***lymphomas** may be diagnosed as **B-cell-derived tumors** by the detection of surface markers characteristic of this lineage, such as **CD10 and CD20**.*
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THANKYOU

