

Neoplasia 2023/24

lecture 4: Environmental causes of cancer

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ILOS

- 1. list the main environmental causative agents of cancer.
- 2. understand the difference between direct and indirect acting chemical carcinogens.
- 3. understand the pathogenesis of cancer development due to several etiologic agents.

Carcinogenesis.. review

- Carcinogenesis, as we discussed in the previous lectures, results from one single clone that acquires certain mutations which allow this clone to proliferate rapidly.
- As the tumor mass grows, extra mutations occur that add certain phenotypes to this mass (subclones are formed).

- SO: how do these mutations are acquired... what are the etiologic agents that can cause cancer???
- This is the main topic of this lecture.

Etiology of cancer

- Cancer can be caused by inherited or acquired mutations.
- We will discuss some inherited mutations in the coming lectures: like RB, BRACA ...
- Environmental factors that cause mutations are mainly:
 - Chemicals
 - Radiation
 - infections

Chemical carcinogenesis

- One of the first cancers linked to chemical carcinogens is scrotal squamous cell carcinoma
- Sir Percival Pott .. A London surgeon noted that scrotal cancer is common in chimney sweeps and he thought it is related to soot exposure.
- Danish chimney sweeps guild ruled that its members bathe daily
- This reduced scrotal cancer.. It is a very successful story about how to prevent cancer with life style changes (a daily bath in this instance!)

So: chemicals can cause cancer



Chemical carcinogens

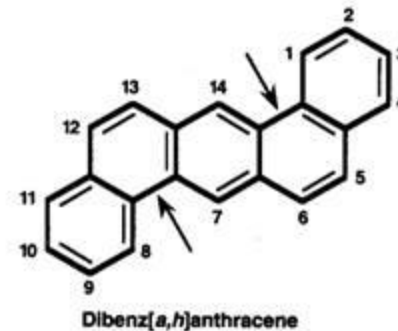
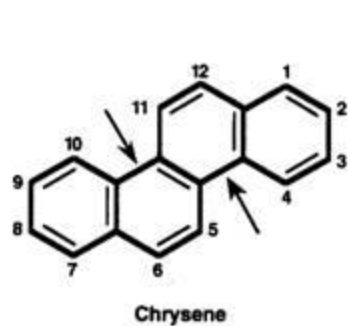
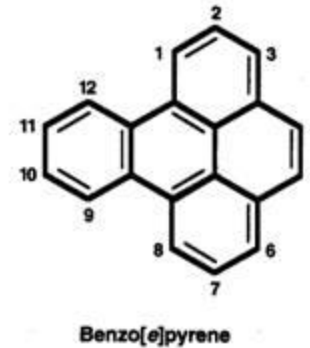
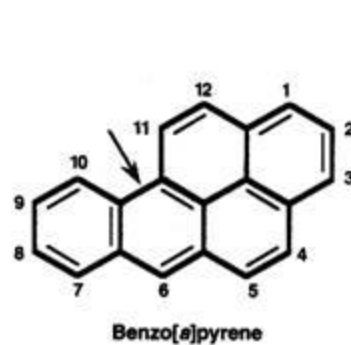
- Chemicals cause cancer directly (**direct** acting agents) or by being converted to a carcinogenic metabolite (**indirect** acting agents)

Direct acting agents

- These are weak carcinogens that don't need metabolic conversion
- Examples: chemotherapy drugs (alkylating agents) can cause cancer, usually leukemia

Indirect acting agents

- These **need metabolic conversion** to become carcinogenic
- Example: polycyclic hydrocarbons which are present in fossil fuel



Indirect acting agents

- Benzo (a) pyrene is a polycyclic hydrocarbon present in cigarette smoke and can cause lung cancer
- polycyclic hydrocarbons are also present in smoked meat .Produced from animal fat during broiling meat.
- The main active product in polycyclic hydrocarbons is epoxides
- Epoxides react with DNA, RNA and cellular proteins

Indirect agents

- **Aromatic amines and azo dyes. Example beta naphthalamine...**
increases bladder cancer in workers in the aniline dye and rubber industries.
- **Aflatoxin B ..** Is a naturally occurring agent produced by aspergillus which is a fungus that grows on improperly stored grains and nuts. It increases incidence of hepatocellular carcinoma
- **Nitrites** used as food preservatives can produce nitrosamines which are probably carcinogenic.. Linked to gastric cancer

Mechanisms of action of chemical agents

- Chemical carcinogens have **reactive electrophile group** that form chemical adducts with DNA, RNA and proteins
- Any gene can be a target for chemicals.. But mostly mutated are RAS and TP53.
- Aflatoxin causes TP53 mutation

- Some chemical carcinogens are augmented by subsequent promoters (hormones, drugs, phenols)
- The promoters are not carcinogenic by themselves .
- Promoter effect has to come after the initiator (tumorigenic substance)
- How do promoters work???? They induce cell proliferation which causes clonal expansion of the mutated cells.. These mutated cells now proliferate and accumulate additional mutations

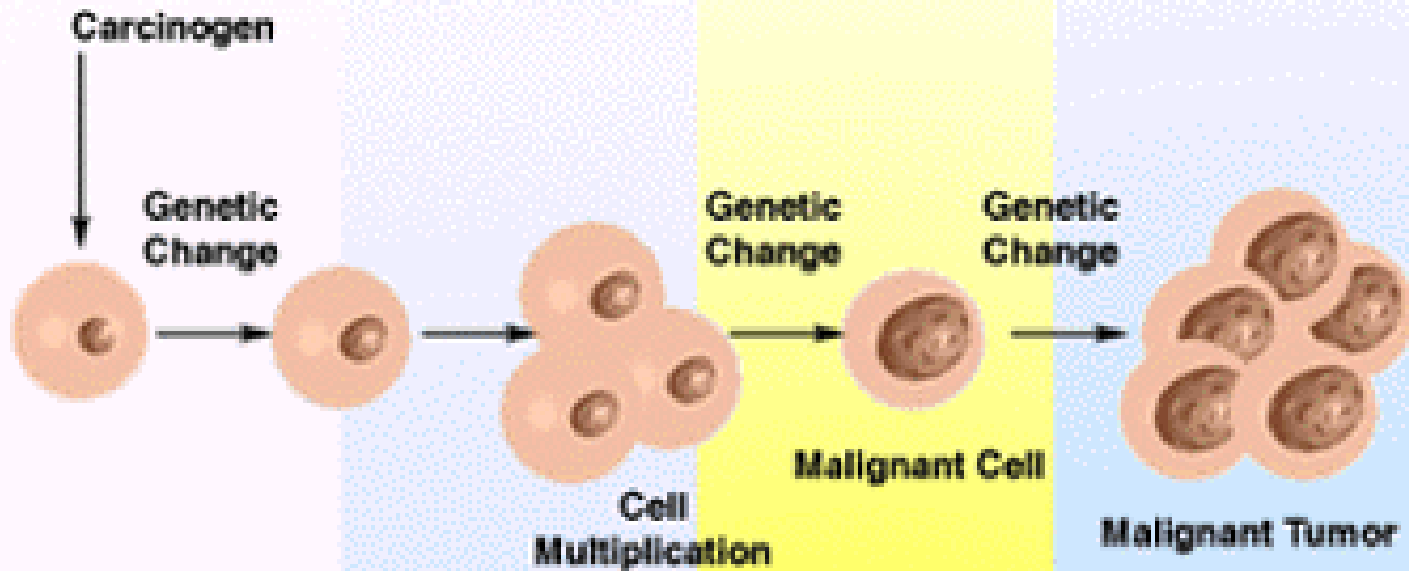
CARCINOGENESIS

INITIATION

PROMOTION

TRANSFORMATION

PROGRESSION



Radiation carcinogenesis

- Miners of radioactive elements have 10 fold increase of lung cancer
- Survivors of atomic bombs in Hiroshima and Nagasaki .. Have increased incidence of leukemia... latent periods of 7 years. They also have increased risk of thyroid, breast ,colon and lung cancer
- Chernobyl nuclear power accident.. Also increased cancer
- Therapeutic radiotherapy of head and neck can cause papillary thyroid cancer years later

- Ionizing radiation causes chromosomal breakage, translocation and less commonly point mutations
- Ultraviolet radiation causes pyrimidine dimers.. Not repaired in xeroderma pigmentosum causing increased risk of skin cancers
- Non-melanoma skin cancers (squamous cell carcinoma and basal cell carcinoma) are associated with total accumulation of UV exposure
- Melanoma associated with intense intermittent exposure.. Like in sunbathing

Viral and microbial carcinogens

- Oncogenic RNA viruses: HTLV 1, hepatitis C
- Oncogenic DNA viruses: human papillomavirus , EBV, hepatitis B
- Bacteria: H pylori

HTLV 1= human T lymphocyte virus 1

- A retrovirus involved in T cell lymphoma/ leukemia
- The virus is endemic in Japan and the Caribbean
- It targets CD 4 T cells
- Transmitted sexually and through blood or breast feeding
- Leukemia develops in 3- 5% of those infected after 20-50 years
- Very latent period.. Suggests multistep process of accumulation of multiple oncogenic mutations

HPV = human papilloma virus

- There are several types of HPV. Some produce benign warts (benign squamous cell papillomas), others cause cancer
- HPV 16 and 18 cause cancer . 16 and 18 are called high risk HPV
- Cancers associated with HPV:
 1. Squamous cell carcinoma of the cervix and anogenital region
 2. Oropharyngeal and nasopharyngeal carcinoma

EBV = Epstein Barr virus

- It Causes:

1. Burkitt lymphoma
2. B cell lymphomas especially in people with low immunity and HIV infection
3. Hodgkin lymphoma
4. Nasopharyngeal carcinoma
5. T cell lymphomas
6. Gastric carcinoma
7. Natural killer lymphoma
8. Sarcomas especially in the immunocompromized

Hepatitis B and C viruses

- 70-85% of hepatocellular carcinomas are associated with B or C

Helicobacter pylori

- Can cause gastric carcinoma and lymphoma (MALTOMA)
- **H pylori cause cancer by inducing chronic inflammation**
- Sequence: inflammation, atrophy, metaplasia, dysplasia, Cancer
- This sequence needs decades to be completed and it occurs only in 3% of people with H pylori infection
- H pylori also have genes that are tumorigenic like cagA= cytotoxic associated A which simulates growth factors