

Neoplasia lec9+10

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).
- 8 phenotypic hallmarks are needed to sustain the tumor mass.
- These hallmarks are acquired via mutations.
- No single mutation is enough for transformation of cells.
- Several mutations are needed to acquire the 8 hallmarks.
- One mutation might result in several hallmarks.
- 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 discussed many of the inherited mutations in the previous 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.
- 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.
- 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.

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.
- Carcinogenic effect of HPV is related to two viral genes E7 and E6
- E7 binds RB protein and releases E2F
- E7 also inactivates CDKIs
- E6 binds to and degrades p53

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
- Hep B and C do not encode an oncogene
- Hep B genome is integrated in hepatocyte genome but with no consistent pattern
- So how they cause cancer. It's thought that the effect is multifactorial and related to immunologically mediated chronic inflammation with regeneration and genomic instability.
- Chronic inflammation and immunologic reaction is associated with increased cytokines, growth factors, angiogenic factors
- Also ROS (reactive oxygen species) produced and can cause DNA damage
- So: this is an example of inflammation as an enabler of malignancy

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.

Clinical aspects of malignancy

Tumor location

- Even small tumors can be dangerous
- CNS tumors can cause increased intracranial pressure

Effects by hormonal secretions

- Pituitary adenoma can secrete ACTH and cause Cushing syndrome.

Cancer cachexia

- = progressive loss of body fat with associated weakness, anorexia and anemia
- Cachexia is not caused by the nutritional demands of the tumor
- There is some correlation between cachexia and the size and extent of spread of the cancer.

Causes of cachexia

- Anorexia plays a role, however chemical factors are the main reason
- Cachectic patients have high metabolic rate and muscle wasting
- TNF produced from macrophages is probably the main factor for these changes
- The only satisfactory treatment of cancer cachexia is removal of the primary tumor.

Para-neoplastic syndromes

- = symptoms that cannot be explained by local or distant metastases or by hormones endogenous to the site of origin.
- These are usually caused by ectopic hormone secretion
- Most common para neoplastic syndromes: hypercalcemia, Cushing syndrome (the hormone that causes it is secreted from somewhere different than the location of cancer), and nonbacterial thrombotic endocarditis
- Most common tumors that are associated with paraneoplastic syndromes: lung, breast and hematologic malignancies.

Hypercalcemia as paraneoplastic

- Caused by
- 1. PTHrP (parathyroid hormone related protein)
- 2. TGF alpha activate osteoclasts and the active form of vit D
- 3. TNF and IL1
- NOTE: Skeletal mets cause hyperkalemia but this is not a paraneoplastic syndrome.
- Clubbing of fingers is paraneoplastic, mainly due to lung cancer, etiology is unknown.

