Neoplasia

ETIOLOGY OF CANCER: CARCINOGENIC AGENTS

- **Carcinogenic agents inflict 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

Chemical Carcinogens

- **1-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)
- Can evoke a subsequent second form of cancer usually leukemia.
- The associated risk for induced cancer is low

- **2. The designation indirect-acting refers to chemicals that require metabolic conversion to an ultimate carcinogen.**
- Some of the most potent indirect chemical carcinogens are polycyclic hydrocarbons that are created with burning of fossil fuels, plant, and animal material.
- For example

-benzo[a]pyrene and other carcinogens formed during the combustion of tobacco are implicated in the causation of lung cancer

-benzo[a]pyrene created during the burning of coal was likely responsible for the high incidence of scrotal cancer in chimney sweeps.

Major Chemical Carcinogens

- **1-Direct-Acting Carcinogens**
- **Alkylating Agents**

  β-Propiolactone

  Dimethyl sulfate

  Diepoxybutane

  Anti-cancer drugs (cyclophosphamide, chlorambucil, nitrosoureas, and others)
- **Acylating Agents**

  1-Acetyl-imidazole

  Dimethylcarbamyl chloride

- **2- Procarcinogens That Require Metabolic Activation**
- **Polycyclic and Heterocyclic Aromatic Hydrocarbons**

  Benz(*a*)anthracene

  Benzo(*a*)pyrene

  Dibenz(*a,h*)anthracene

  3-Methylcholanthrene

  7,12-Dimethylbenz(*a*)anthracene

- **Polycyclic hydrocarbons also may be produced from animal fats during the process of broiling meats and are present in smoked meats and fish.**
- **In the body, benzo[a]pyrene is metabolized to epoxides which form covalent adducts (addition products) with molecules in the cell, principally DNA, but also with RNA and proteins.**

- **The aromatic amines and azo dyes constitute indirect-acting carcinogens.**
- **β-naphthylamine was responsible for a 50-fold increased incidence of bladder cancers in heavily exposed workers in the aniline dye and rubber industries.**

- **Aflatoxin B1 is a naturally occurring agent produced by some strains of *Aspergillus,* a mold that grows on improperly stored grains and nuts.**
- **A strong correlation has been found between the dietary level of this food contaminant and the incidence of hepatocellular carcinoma in some parts of Africa and the Far East.**

- **Vinyl chloride, arsenic, nickel, chromium, insecticides, fungicides, and polychlorinated biphenyls are potential carcinogens in the workplace and about the house.**
- **Nitrites used as food preservatives since they cause nitrosylation of amines contained in food producing nitrosamines that are suspected to be carcinogenic.**

Direct- acting carcinogens	Type of cancer	
Alkylating Agents	leukemia	
β- Propiolactone	lymphoma	
Dimethyl sulfate	Hodgkins lymphoma	
Diepoxybutane		
Anticancer drugs (cyclophosphamide, chlorambucil, nitrosoureas, and others)	Ovarian tumors	
Acylating agents		
1-Acetyl-imidazole		
Dimethylcarbamyl chloride		

Indirectly-acting agents	source	Type & site of cancer
Polycyclic and hetercyclic armotic hydrocarbons	Smoked meats & fish	
Benz(a)anthracene		
Benzo(a)pyrene	Combustion of tobacco	Lung cancer
Dibenzanthracene		
3-Methylcholanthrene		
dimethylbenz(a)anthracene		
Aromatic amines, amides, amides, azo dyes		
2- Napththylamine (β-naphthylamine) Benzidine	Aniline dye Rubber industry	Bladder cancer
2- Acetylaminofluorene		
Dimethylaminoazobenzene (butter yellow)		

	source	Type & site of cancer
Aflatoxin B1	Aspergillus	Hepatocellular carcinoma
Betel nuts	chewing	Oral carcinoma
benzene	Paint,rubber,dry cleaning	Leukemia,lymphoma
Arsenic compounds	Electrical devices,herbicides,fungicides	Lung,skin angiosarcoma
asbestos	Floor tiles,roofing paper,brakes lining	Mesothelioma Lung carcinoma
Cadmium compounds	Batteries,metal coating	Prostate cancer
Nitrosamine and amides	Food preservatives	
Vinyl chloride nickel Chromium compounds	Adhesive for plastics Nickelplating,ceramics, Batteries Paints,preservatives, pigments	Liver angiosarcoma Nose & lung cancer Lung cancer
Insecticides, fungicides		

Mechanisms of Action of Chemical Carcinogens

- **Most chemical carcinogens are mutagenic.**
- **All direct carcinogens contain highly reactive electrophile groups that form chemical adducts with DNA, as well as with proteins and RNA.**
- **Any gene may be the target of chemical carcinogens as *RAS* and *T53***
- **Aflatoxin B1 produce characteristic mutations in *T53***

- **Carcinogenicity of some chemicals is augmented by subsequent administration of *promoters* (e.g., phorbol esters, hormones, phenols, certain drugs**
- **Repeated or sustained exposure to the promoter must follow the application of the mutagenic chemical, or *initiator***

- **The application of an initiator causes the mutational activation of an oncogene such as *RAS***
- **Subsequent application of promoters leads to clonal expansion of initiated (mutated) cells**
- **Induction of proliferation of the initiated clone of cells causes additional mutations developing eventually into a malignant tumor.**

Radiation Carcinogenesis

- **Radiation, whatever its source (UV rays of sunlight, radiographs, nuclear fission, radionuclides) is an established carcinogen.**
- **Unprotected miners of radioactive elements have a 10-fold increased incidence of lung cancers.**
- **A follow-up study of survivors of the atomic bombs dropped on Hiroshima and Nagasaki disclosed a markedly increased incidence of leukemia after an average latent period of about 7 years, as well as increased mortality rates for thyroid, breast, colon, and lung carcinomas.**

- **The nuclear power accident at Chernobyl in the former Soviet Union continues to exact its toll in the form of high cancer incidence in the surrounding areas.**
- **It is feared that radiation release from a nuclear power plant in Japan damaged by a massive earthquake and tsunami will result in significantly increased cancer incidence in the surrounding geographic areas.**

- **Therapeutic irradiation of the head and neck can give rise to papillary thyroid cancers years later.**
- **The oncogenic properties of ionizing radiation are related to its mutagenic effects as chromosome breakage, chromosomal rearrangements such as translocations and inversions, and point mutations.**
- **Biologically, double-stranded DNA breaks seem to be the most important form of DNA damage caused by radiation.**

- **Natural UV radiation derived from the sun can cause skin cancers (melanomas, squamous cell carcinomas, and basal cell carcinomas)**
- **Risk factors are:**

1. Fair-skin

2. Areas as Australia and New Zealand that receive a great deal of sunlight.

- **Nonmelanoma skin cancers are associated with total cumulative exposure to UV radiation**
- **Melanomas are associated with intense intermittent exposure—as occurs with sunbathing.**
- **UV light causes damage of 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.**
- **Patients with the inherited disease *xeroderma pigmentosum* have a defect in the nucleotide excision repair pathway and increased risk of skin cancer**

Viral and Microbial Oncogenesis

Oncogenic RNA Viruses

- Human T-cell leukemia virus type 1 (HTLV-1) is firmly implicated in the pathogenesis of cancer in humans

- **HTLV-1 causes *adult T-cell leukemia/lymphoma* (ATLL), a tumor that is endemic in certain parts of Japan, the Caribbean basin, South America, and Africa, and found sporadically elsewhere, including the United States.**
- **Worldwide, it is estimated that 15 to 20 million people are infected with HTLV-1.**
- **Similar to the human immunodeficiency virus, which causes AIDS, HTLV-1 has**
- **Tropism for CD4+ T cells, and hence this subset of T cells is the major target for neoplastic transformation.**
- **Human infection requires transmission of infected T cells via sexual intercourse, blood products, or breastfeeding.**
- **Leukemia develops in only 3-5% of the infected individuals, typically after a long latent period of 40-60 years.**

- **HTLV-1 does not contain an oncogene and no consistent pattern of proviral integration next to a proto-oncogene has been discovered.**
- **In leukemic cells, however, viral integration shows a clonal pattern.**

- Although the site of viral integration in host chromosomes is random the site of integration is identical within all cells of a given cancer.
- This would not occur if HTLV-1 were merely a passenger that infects cells after transformation
- It means that HTLV-1 must have been present at the moment of transformation placing it at the “scene of the crime.”

- **The HTLV-1 genome contains the *gag, pol, env,* and longterminal-repeat regions typical of all retroviruses**
- **In contrast to other leukemia viruses it also contains another gene referred to as *tax.***

- **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 because it stimulates transcription of viral RNA from the 5' longterminal repeat.**
- **Tax also alters the transcription of several host cell genes and interacts with certain host cell signaling proteins.**

- **Tax contribute to cell transformation through the following:**

1. Increased survival and growth of infected cells.

Tax appears to interact with PI3 kinase and thereby stimulate the downstream signaling cascade romotes both cell survival and metabolic alterations that enhance cell growth.

2. Upregulation of the expression of cyclin D and repression of the expression of multiple CDK inhibitors promoting cycle progression

3. **Tax can activate the transcription factor NF-κB, which promotes the survival of many cell types jincluding lymphocytes.**
4. **Increased genomic instability**.

Tax may also cause genomic instability by interfering with DNA-repair functions and inhibiting cell cycle checkpoints activated by DNA damage..

- **In line with these defects, HTLV-1–associated leukemias tend to be highly aneuploid**

Oncogenic DNA Viruses

- **1. Human papilloma virus (HPV)**
- **2. Epstein-Barr virus (EBV)**
- **3. Kaposi sarcoma herpesvirus (KSHV, also called human herpesvirus-8 [HHV-8])**
- **4. Polyoma virus called Merkel cell virus**
- **5. Hepatitis B virus (HBV)**

1-Human papilloma virus (HPV)

- **HPV has been associated with:**
- 1- Benign squamous papilloma (warts) (HPV 1,2,4,7).
- 2- Genital warts (HPV 6,11).
- 2- Cervical cancer (HPV 16 & 18).
- 3- Oropharyngeal cancer.

- **The oncogenic ability of HPV is related to the expression of two viral oncoproteins, E6 and E7.**
- **1-They bind to RB and p53**
- **2-Inhibit CDKIs p21 &27.**
- **E6 and E7 from high- risk HPV also activate cyclins E & A.**

- **Oncogenic activities of E6.**

1. **The E6 protein binds to and mediates the degradation of p53**
2. **It stimulates the expression of telomerase contributing to the immortalization of cells.**
3. **E6 from high-risk HPV types has a higher affinity for p53 than E6 from low-risk HPV types**

Oncogenic activities of E7

1. It binds to the RB protein and displaces the E2F transcription factors that are normally sequestered by RB, promoting progression through the cell cycle.

2. E7 proteins from high-risk HPV types have a higher affinity for RB than do E7 proteins from low-risk HPV types.

3. E7 also inactivates the CDK inhibitors p21 and p27, and binds and presumably activates cyclins E and A.

- **High-risk HPVs encode oncogenic proteins that inactivate RB and p53, activate cyclin/CDK complexes, and combat cellular senescence.**
- **The primacy of HPV infection in the causation of cervical cancer is confirmed by the effectiveness of HPV vaccines in preventing it.**
- **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*