

## **NEOPLASIA (Lecture 4)**

### **ETIOLOGY OF CANCER: CARCINOGENIC AGENTS**

#### Objective:

List the various causes of neoplasms

#### Carcinogenic Agents:

- *Chemicals*
- *Radiation*
- *Microbial agents*

#### Carcinogenic Agents (Chemical Carcinogens):

- Natural or synthetic
- Direct reacting or indirect (Direct: Once they come to the body they are active to produce a mutation to the genome)
- Indirect → need metabolic conversion to be active and carcinogenic
- Indirect chemicals are called “procarcinogens” (and they are activated in the body by metabolic reactions, oxygenation, conjugation...etc) and their active end products are called “ultimate carcinogens”

Indirect (smoked food and cigarettes) activated by oxygenase enzyme

- All direct reacting and ultimate chemical carcinogens are highly reactive as they have electron-deficient atoms
- They react with the electron rich atoms in RNA, DNA and other cellular proteins

### Examples:

- Alkylating agents (Chemotherapeutic agent that is used to cure cancer, but they can cause delayed cancer – After 10 years -)
- Polycyclic hydrocarbons:
- Cigarette smoking
- Animal fats during broiling meats
- Smoked meats and fish

### Aromatic amines and azo dyes:

- B-naphthylamine cause bladder cancer in rubber industries and aniline dye
- Some azo dyes are used to color food also can cause bladder cancer

Dyes enter the body in an inactive form “Procarcinogen”

First they go to the liver and become slightly active due to hydroxylation, next they go to the blood, next to the kidneys and the second hydroxylation occurs and they become very active, finally they go to the bladder and cause cancer.

If they go directly to the bladder they do not cause cancer because they are inactive.

### Other substances:

- Nitrosamines and nitrosamides are used as preservatives. They cause gastric cancer.
- Aflatoxin B: produced by *Aspergillus* growing on improperly stored grains. It cause hepatocellular carcinoma

### Mechanism of action of chemical carcinogens:

- Most of them are mutagenic. i.e. cause mutations
- RAS and P53 are common targets

### Radiation Carcinogenesis (Direct Carcinogens)

- UV rays of sunlight
- X-rays
- Nuclear radiation
- Therapeutic irradiations

Radiation has mutagenic effects: chromosomes breakage, translocations, and point mutations

Skin cancer is found more in light colored people

### UV rays of sunlight :

- Can cause skin cancers: melanoma, squamous cell carcinoma, and basal cell carcinoma
- It is capable to damage DNA
- With extensive exposure to sunlight, the repair system is overwhelmed → skin cancer
- They cause mutations in P53 gene

### Viral and Microbial oncogenesis

- DNA viruses
- RNA viruses
- other organisms

### Viral Carcinogenesis:

- carry genes that induce cell replication as part of the viral life cycle
- host cell has endogenous genes that maintain the normal cell-cycle
- Viral infection mimics or blocks these normal cellular signals necessary for growth regulation

### **RNA Oncogenic viruses**

#### Human T-Cell Leukemia Virus type 1 (HTLV-1)

- RNA retrovirus targets / transforms T-cells
- causes T-Cell leukemia/Lymphoma
- Endemic in Japan and Caribbean
- Transmitted like HIV but only 1% of infected develop T-Cell leukemia/Lymphoma
- 20-30 year latent period
- No cure or vaccine
- Treatment : chemotherapy with common relapse

### **DNA Oncogenic Viruses**

- virus DNA forms stable association with host's DNA
- transcribed viral DNA transforms host cell

Examples: Human papilloma viruses (HPV)

Epstein-Barr (EBV)

Hepatitis B (HBV)

Kaposi sarcoma herpes virus

## Human Papillomavirus (HPV)

70 types

### HPV causes benign tumors

- Genital warts: **types 6 and 11**

### squamous cell carcinoma of

- cervix
- anogenital region
- mouth
- Larynx
- Cervical cancer : **85% have types 16 and 18**
- sexually transmitted

### HPV causing malignant tumors :

- types 16, 18, 31
- vDNA integrates w/ host

### HPV (types 16 and 18)

- over-expression of Exon 6 and 7
- E6 protein binds to Rb tumor suppressor
- replaces normal transcription factors
- decreases Rb synthesis
- E7 protein binds to P53
- facilitates degradation of P53

(There are more than 70 types of HPV, Type 6 and 11 cause benign tumors – warts- Types 16, 18, 33, 55 cause cancers)

**HPV infection alone is not sufficient -**

- **other risk factors:**
- cigarette smoking
- coexisting infections
- hormonal changes

Epstein-Barr Virus

- common virus worldwide
- Infects B lymphocytes and epithelial cells of oropharynx
- causes infectious mononucleosis
- causes B lymphocyte cell proliferation
- loss of growth regulation
- predisposes to mutation, esp. t(8:14)
- EBV infection may cause malignancy
  - Burkitt's Lymphoma
  - B cell lymphoma in immunosuppressed
  - Nasopharyngeal carcinoma

Nasopharyngeal carcinoma

- Cancer of nasopharyngeal epithelium

- Endemic in South China, parts of Africa
- 100% of tumors contain EBV genome in endemic areas
  
- **Burkitt Lymphoma** (Common in jaw and intestine)
  - highly malignant B cell tumor
  - sporadic rare occurrence worldwide
  - most common childhood tumor in Africa
  - all cases have t(8:14)

### Hepatitis B virus (HBV)

- Strong association with Liver Cancer
- World-wide, but HBV infection is most common in Far East and Africa
- HBV infection incurs up to 200-fold risk to hepatocellular carcinoma

### Helicobacter Pylori

- bacteria infecting stomach
- implicated in:
  - peptic ulcers
  - gastric lymphoma
  - Mucosal Associated Lymphoid Tumor (MALT)
  - gastric carcinoma

Chemical carcinogen	Disease	Other information
<b>B-naphthylamine</b>	<b>Bladder cancer</b>	<b>Use in rubber industries and aniline dyes</b>
<b>Nitrosamides\Nitrosamines</b>	<b>Gastric cancer</b>	<b>Preservatives</b>
<b>Aflatoxins B</b>	<b>hepatocellular carcinoma</b>	<b>produced by aspergillus growing on improperly stored grains</b>
<b>Azo dyes</b>	<b>Bladder cancer</b>	<b>( food colors )</b>
<b>UV rays</b>	<b>Skin cancers: Melanoma , squamous and basal carcinoma</b>	<b>Cause damage in DNA Mutation in P53</b>
<b>HTLV-1 ( RNA)</b>	<b>T cells leukemia\lymphoma</b>	<b>In japan and caribbean</b>
<b>HPV ( DNA)</b>	<b>70 types squamous cell carcinoma of: cervix,anogenitalregion, mouth and larynx</b>	<b>Cervical cancer 16,18 Genital cancer 6,11 Benign 6,11 Malignant 16,18,31 There are more details about 16,18 type in slide</b>
<b>EBV ( DNA)</b>	<b>causes infectious mononucleosis</b>	<b>Has 3 types</b>
<b>1-Nasopharyngeal carcinoma</b>	<b>cancer of nasopharyngeal</b>	<b>South China, parts of Africa</b>
<b>2- Burkitt lymphoma</b>	<b>malignant B cell tumor</b>	<b>Childhood in Africa \ have t(8:14)</b>
<b>3-B cell lymphoma</b>		
<b>HBV ( DNA )</b>	<b>Linked with liver cancer</b>	<b>200 fold risk</b>
<b>Helicobacter Pylori</b>	<b>bacteria infecting stomach</b>	<b>peptic ulcers gastric lymphoma,MALT gastric carcinoma and</b>