Course: Toxicology, Path-438

- Radiation Injury & Carcinogenesis.
- Review of Microbial Carcinogenesis

Learning Objectives:

- List the types of radiation.
- Describe briefly the long-term consequences of total body radiation.
- Explain briefly the mechanism of radiation carcinogenesis.
- Describe the NER pathway.
- Enumerate the biologic agents associated with increased incidence of cancers.
- List oncogenic viruses and name tumors associated with them.
- Explain microbial carcinogenesis using the example of HPV/EBV/ HTLV/ Hepatitis B/H pylori.

Radiation Injury:

- **Radiation is energy distributed across the electromagnetic spectrum as waves *(long wavelengths, low frequency)* or particles *(short wavelengths, high frequency).***

- **Approximately 80% of radiation is derived from natural sources, including *cosmic radiation, UV light, and natural radioactive isotopes especially radon gas*. The remaining 20% is derived from manufactured sources that include e.g. *nuclear power plant.***

- **Types of radiation:**
  - ***Nonionizing radiation* (long wavelength & low frequency): e.g. electric power, radio waves & microwave, infrared, and UV light.**
  - ***Ionizing radiation* (short wave lengths & high frequency): This type can ionize biologic target molecules and eject electrons, e.g X-rays, gamma rays, and cosmic rays.**
  - ***Particulate radiation* which is classified by the type of particles emitted (alpha, beta, electrons, protons, neutrons, …etc).**

Radiation Carcinogenesis:

- **Radiation energy, whether in the form of UV (*of sun light*) or as ionizing electromagnetic and particulate radiation, can transform virtually all cell types in vitro and induce neoplasms in vivo:**

  - **UV light:**
    - **It is known to cause skin cancers.**

  - **Ionizing radiation:**
    - **Electromagnetic (X-rays, γ rays) and particulate (α particles, β particles, protons, neutrons) radiations are all carcinogenic.**
    - **Exposures due to medical therapy or occupational hazards, nuclear plant accidents, and atomic bomb detonations have produced a large variety of malignant neoplasm in humans.**

Ultraviolet Rays:

- **The UV portion of the solar spectrum can be divided into three wavelength ranges:**

  - **UVA (320 to 400 nm).**

  - **UVB (280 to 320 nm):**
    - ✓ ***UVB is believed to be responsible for the induction of cutaneous cancers.***
    - ✓ ***The carcinogenicity of UVB light is attributed to its formation of pyrimidine dimers in DNA, and this type of DNA damage is repaired by the nucleotide excision repair (NER) pathway.***
    - ✓ ***As with other carcinogens, UVB also causes mutations in oncogenes and tumor suppressor genes (as RAS & p53).***

  - **UVC (200 to 280 nm):**
    - ✓ ***UVC, although a potent mutagen, is not considered significant because it is filtered out by the ozone shield around the earth (hence the concern about ozone depletion).***

Ultraviolet Rays:

- **UVB derived skin cancers include *squamous cell carcinoma, basal cell carcinoma, and possibly malignant melanoma.***

- **As mentioned before, the UV induced DNA damage is repaired by *NER* pathway that involves the following steps:**

  - ***Recognition of DNA lesion.***
  - ***Incision of the damaged strand on both sides of the lesion.***
  - ***Removal of the damaged nucleotide.***
  - ***Synthesis of a nucleotide patch.***
  - ***Ligation of the nucleotide patch.***

- **With excessive sun exposure (excessive UV exposure), the capacity of NER is overwhelmed, hence some DNA damage remains unrepaired.This leads to large transcriptional errors and in some instances cancer.**

Ionizing Radiation: *Evidences…….*

- **Many of the pioneers in the development of X-rays developed *skin cancers.***

- **Miners of radioactive elements in central Europe and the Rocky Mountain region of the United States have a ten fold increased incidence of *lung cancers.***

- **In survivors of the atomic bombs dropped on Hiroshima and Nagasaki, initially, there was a marked increase in the incidence of leukemia-principally *acute and chronic myelocytic leukemia*-after an average latent period of about 7 years. Subsequently the incidence of many *solid tumors* with longer latent periods (e.g., *breast, colon, thyroid, and lung*) increased.**

Ionizing Radiation: *Evidences…….*

- **Residents of the Marshall Islands were exposed on one occasion to accidental fallout from a *hydrogen bomb* test that contained thyroid-seeking *radioactive iodines*. As many as 90% of the children under age 10 years on Rongelap Island developed *thyroid nodules* within 15 years, and about 5% of these nodules proved to be *thyroid carcinomas*.**

- **A marked increase in the incidence of *thyroid cancer* has also been noted in areas exposed to the fallout from the *nuclear power plant* accident in Chernobyl in 1986.**

- ***Thyroid cancers* have developed in approximately 9% of those exposed during infancy and childhood to *head and neck radiation*.**

- **The previous practice of treating *ankylosing spondylitis** with *therapeutic irradiation* yielded a *10- to 12-fold* increase in the incidence of *leukemia* years later.**

**A polyarthritis involving the spine, which is characterized by progressive, painful stiffening of the joints and ligaments. It almost exclusively affects young men.*

Radiation Injury – *Ionizing Radiation:*

- **The dose of ionizing radiation is measured in several units; e.g. Roentgen, Rad, Gray, …etc.**
- **In addition to the physical properties of the radioactive material & the dose, the biologic effects of ionizing radiation depend on several factors:**
  - ***Dose rate:* a single dose can cause greater injury than divided dose.**
  - ***Since DNA is the most important subcellular target, rapidly dividing cells (e.g. Hematopoietic cells, germ cells, GIT epithelium , ..etc) are more radiosensitive than quiescent cells.***
  - ***A single dose of external radiation administered to the whole body is more lethal than regional doses with shielding.***
  - ***Cells in G_2 & mitotic phases of the cell cycle are most sensitive.***
  - ***Different cells subtypes differ in the extent of their adaptive and reparative responses.***
  - ***Since ionizing radiation produces oxygen-derived radicals from the radiolytic cleavage of water, cell injury induced by x-rays & gamma rays is enhanced by hyperbaric oxygen.***

Ionizing Radiation – *Acute Injury & Delayed Complications:*

- **The acute effect of ionizing radiation ranges from *overt necrosis at high doses (>10 Gy), killing of proliferating cells at intermediate doses (1-2 Gy), and no histopathologic effect at doses less than 0.5 Gy.***

- **Cells usually shows adaptive & reparative responses to low doses of ionizing radiation while extensive radiation induced DNA damage will lead to apoptosis.**

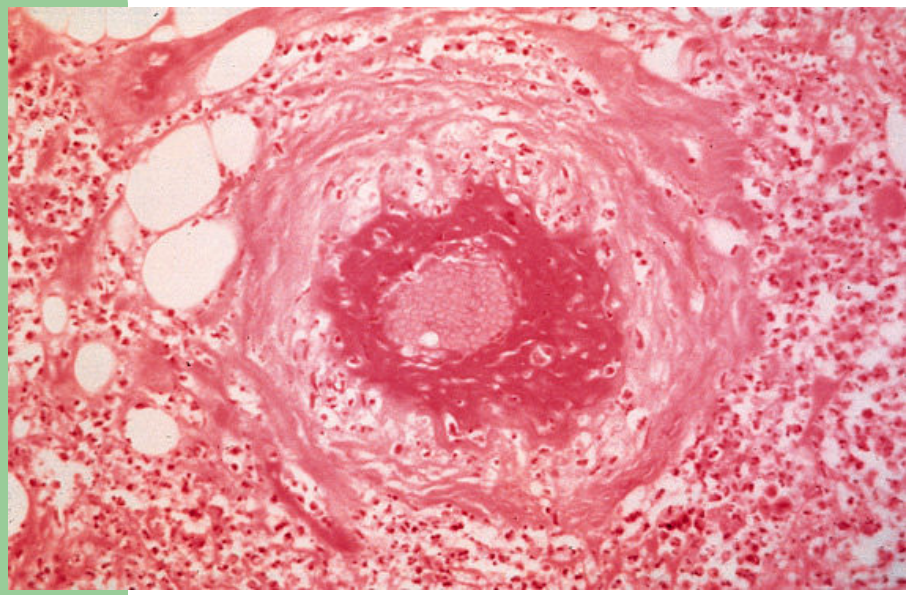
- **Cells which survive DNA damage, may show delayed effects as mutations, chromosomal aberrations, and genetic instability, these cells will become malignant.**

- **Total body irradiation associated with three syndromes:**
  - ***Hematopoietic** (200-500 rad): nausea, vomiting, lymphopnia, thrombocytopnia, neutropnia, and later anemia.*
  - ***GIT** (500-1000 rad): sever GIT symptoms including diarrhea, hemorrhage, emaciation, and at higher doses ; death within days.*
  - ***Cerebral** (>5000 rad): listlessness and drowsiness followed by convulsions, coma, and death within hours.*

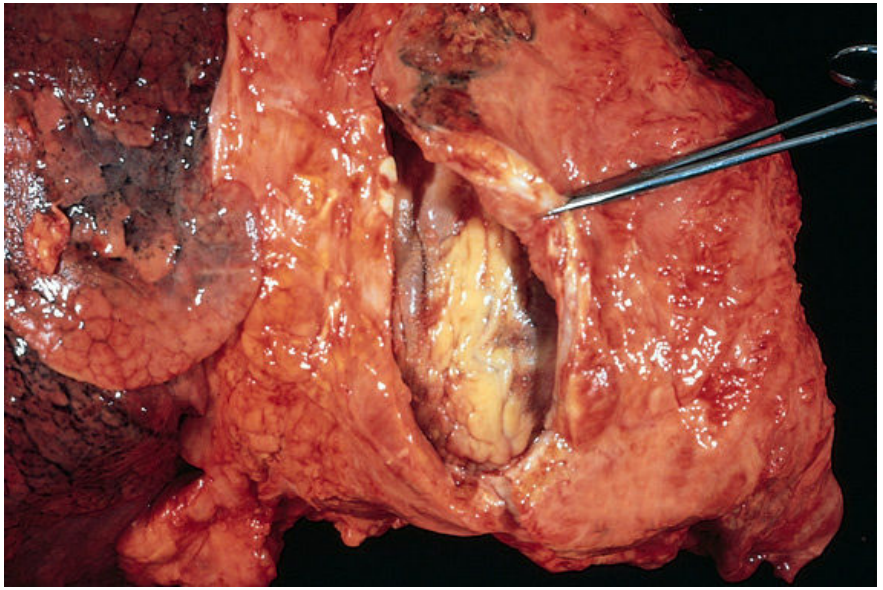
Acute Injury & Delayed Complications Caused by Ionizing Radiation:

Organ	Acute injury	Delayed complications
Bone marrow	Atrophy	Hypoplasia, leukemia
Skin	Erythema	Atrophy of epidermis & fibrosis of dermis; cancer.
Heart	-	Interstitial fibrosis
Lung	Edema, endothelial & epithelial cell death	Interstitial & intra-alveolar fibrosis; cancer
GIT	Edema, mucosal ulcers	Ulcers, fibrosis; strictures, adhesions, cancer
Liver	veno-occlusive disease	Cirrhosis; liver tumor
Kidney	Vasodilation	Cortical atrophy, interstitial fibrosis
Urinary bladder	Mucosal erosions	Submucosal fibrosis; cancer
Brain	Edema, necrosis	Necrosis of white matter, gliosis; brain cancer
Testis	Necrosis	Tubular atrophy
Ovary	Atresia of follicles	Stromal fibrosis
Thyroid	-	Hypothyroidism; cancer
Breast	-	Fibrosis; cancer
Thymus, LNs	Atrophy	Lymphoma

Radiation Injury:



Acute vascular injury with fibrinoid necrosis and edema after exposure to ionizing radiation



Extensive mediastinal fibrosis after radiotherapy for CA lung. Note the markedly thickened pericardium

Microbial Carcinogenesis:

❖ **A large number of DNA & RNA viruses have proved to be oncogenic in many animals, and there is a strong evidence that some human cancers are of viral origin.**

❖ **Oncogenic DNA viruses:**

- ***Papillomaviruses [HPV]:***
  - ✓ ***Squamous Papillomas and carcinoma cervix.***
- ***Epstein-Barr virus [EBV]:***
  - ✓ ***Burkitt lymphoma.***
- ***Hepatitis B virus [HBV] and Hepatitis C virus [HCV]:***
  - ✓ ***Hepatocellular carcinoma.***
- ***Kaposi sarcoma herpesvirus [KSHV]:***
  - ✓ ***Kaposi sarcoma in AIDS patients.***

❖ **Oncogenic RNA viruses:**

- ***Human T-cell leukemia virus [HTLV-1]:***
  - ✓ ***T-cell leukemia/lymphoma that is endemic in certain parts of Japan and the Caribbean basin.***

Viral Carcinogenesis:

- **The *genomes* of *oncogenic DNA viruses* *integrate* into and form stable associations with the *host cell genome*:**

  - ***The virus is unable to complete its replicative cycle because the viral genes essential for completion of replication are interrupted during integration of viral DNA. Thus, the virus can remain in a latent state for years.***

  - ***Those viral genes that are transcribed early in the viral life cycle (early genes) are important for transformation, and are expressed in transformed cells.***

Human Papillomavirus:

- Approx. 70 *genetically distinct types* of HPV have identified; *1,2,4,and 7* causes *benign squamous papilloma (warts)* in human while *16, 18, and less commonly 31, 33, 35, and 51* are associated with *cancer of the cervix, anogenital region and some cases of oral & laryngeal cancers.*

- In *benign warts* and in *preneoplastic lesions*, the *HPV genome* is maintained in an episomal (*nonintegrated*) form, whereas in *cancers*, the viral DNA is usually *integrated into the host cell genome*. *This suggests that integration of viral DNA is important in malignant transformation.*

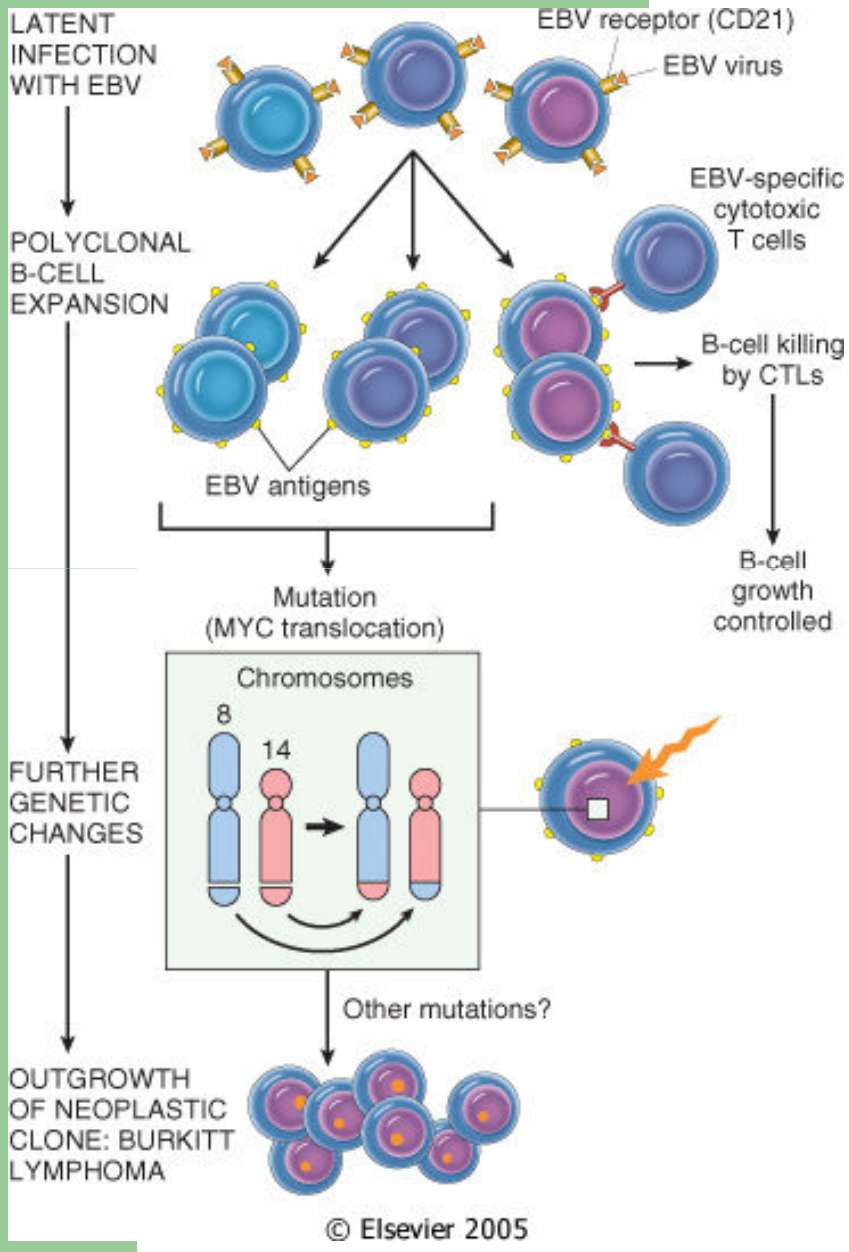
- Furthermore, the viral DNA is interrupted at a fairly constant site in the process of integration: It is almost always within the *E1/E2* open reading frame of the viral genome. Because the *E2* region of the viral DNA normally represses the transcription of the *E6* and *E7* early viral genes, its interruption causes *overexpression* of the *E6* and *E7* proteins of *HPV 16* and *HPV 18*.

- *E6* and *E7* bind & block *p53* & *RB* cell cycle suppression pathways respectively.

Epstein-Barr Virus (EBV):

- **EBV, a member of the herpes family has been implicated in the pathogenesis of 4 types of human tumors:**
  - ***The African form of Burkitt lymphoma.***
  - ***B-cell lymphomas in immunosuppressed individuals (particularly AIDS patients).***
  - ***Some cases of Hodgkin lymphoma.***
  - ***Nasopharyngeal carcinoma.***

Epstein-Barr Virus (EBV):



- ***EBV is not directly oncogenic, but by acting as a polyclonal B-cell mitogen.***

- ***Normally, EBV infection is readily controlled by effective immune response through cytotoxic T-cells, but in regions of Africa where Burkitt lymphoma is endemic, poorly understood cofactors (e.g. chronic malaria) favor sustained proliferation of B-cells immortalized by EBV.***

- ***The cells undergo t(8:14) translocation that juxtapose MYC oncogen with one of the immunoglobulin gene loci. This provides growth advantage to the affected cell owing to activation of MYC oncogen.***

- ***Additional mutations in p53 or other defects affecting the p14ARF /MDM2/ p53 pathway and inactivation of p16INK4a by deletion or hyper methylation ultimately release the cells from normal growth regulation.***

Hepatitis B Virus:

- **Epidemiologic studies strongly suggest a close association between HBV infection & the occurrence of liver cancer (high incidence of hepatocellualr carcinoma in endemic areas for HBV like *far east & Africa*).**

- **The effect of HBV is *indirect* and possibly *multifactorial*:**

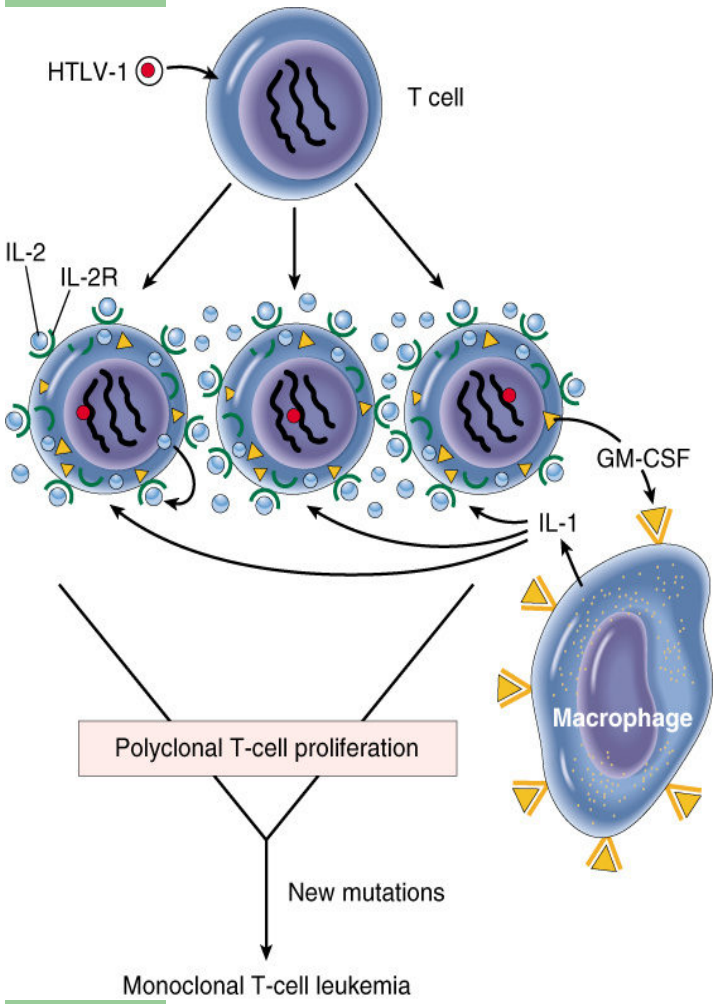
  (1) By causing chronic liver cell injury and accompanying regenerative hyperplasia, HBV expands the pool of cycling cells at risk for subsequent genetic changes.

  (2) HBV encodes a regulatory element called HBx protein, which disrupts normal growth control of infected liver cells by transcriptional activation of several growth-promoting genes, such as insulin-like growth factor II and receptors for insulin-like growth factor I.

  (3) HBx binds to p53 and appears to interfere with its growth-suppressing activities.

- **Although it is not a DNA virus, *hepatitis C* virus is also strongly linked to liver cancer through causing *chronic liver cell injury* & *inflammation.***

Human T-Cell Leukemia Virus Type 1:



- ***HTLV-1*** **causes a form of T-cell lymphoma / leukemia that is endemic in Japan & Caribbean basin.**
- **Infection by *HTLV-1* causes the expansion of a nonmalignant polyclonal cell population through stimulatory effects of a viral protein called TAX on cell proliferation.**
- **Tax protein causes transcriptional activation of several host cell genes including genes encoding the cytokine IL-2 and its receptor (autocrine proliferation) and the gene for GM-CSF acting on nearby macrophages which in turn secret IL-1 (paracrine proliferation).**
- **Tax can also repress the function of several tumor suppressor genes that control the cell cycle like CDKIs, CDKN2A/p16, TP53.**
- **The proliferating T cells are at increased risk of mutations and genomic instability induced by TAX.**
- **Eventually a monoclonal neoplastic T-cell population emerges from clonally expanding nonmalignant cells.**
- **The malignant cells replicate independent of IL-2 and contain molecular and chromosomal abnormalities.**

Helicobacter Pylori:

- **The infection is associated with gastric *adenocarcinomas* of the intestinal type through a sequence that involves *chronic gastritis, multifocal atrophy with lower gastric acid secretion, intestinal metaplasia, dysplasia, and carcinoma.***

- **Gastric lymphomas arise in mucosa-associated lymphoid tissue (MALT); they sometimes are called *MALTomas*.**

- **The B cells that give rise to these tumors normally reside in the marginal zones of lymphoid follicles; hence, the alternative name of *marginal zone lymphoma.***

- **It is thought that chronic infection with *H. pylori* leads to formation of lymphoid infiltrates in which B cells actively proliferate and may acquire genetic abnormalities, such as a *t(11;18)* translocation. *Tumor growth is initially dependent on immune stimulation by H. pylori, but at later stages it no longer requires the presence of the bacterium.***