NEOPLASIA SHEET

Lectures 8&9

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Notes regarding previous lectures:

1. Lecture 5 p.6:

   P53 induces neoplastic transformation by three interlocking mechanisms:

   1) Activation of temporary cell cycle arrest (termed quiescence).
   2) Induction of permanent cell cycle arrest (termed senescence),
   3) Triggering of programmed cell death (termed apoptosis).

   These are the mechanisms by which p53 inhibits and prevents neoplastic transformation.

2. Lecture 5 p.7:

   "Prevents phosphorylation of RB essential for cells to enter S phase, thereby arresting the cell in G1 phase." It was "... to enter G1 phase"
   Resource: Robbins 10th ed. Chapter 6 page 207.

These are for you to understand, as I can't change the doctor's slides whenever I want and however I want, so I kept them as is.

So please accept this idea.

وفي نهاية الفصل الحاليّ:

رح تنقضي هذه الفترة ويأتي اليسر الموعود بعد العسر المعقود (فَإِنَّ مَعَ الْعُسْرِ يُسْرًا).

اجتهد هاي الأيام وصارع راحتك ولَهْوك عشان ما يتخللك الندم آخر يوم وتقول يا ليتني عملت، رح تعدّي رح تعّدي, خليها تعدي وانت فخور من تعبك الي تعبته.

-ع.م (جزاه الله الخير)

NEOPLASIA SHEET

LECTURES 8 AND 9.

❖NEPLASIA 8:

➢ 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.
2. Indirect acting.

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.

✓ Specific examples: (Major chemical carcinogens)

1. Direct-Acting Carcinogens:
   - A. Alkylating Agents
     - i. β-Propiolactone.
     - ii. Dimethyl sulfate.
     - iii. Diepoxybutane.
     - ii. Anti-cancer drugs (cyclophosphamide, chlorambucil, nitrosoureas, and others)
   - B. Acylating Agents
     - i. Acetyl-imidazole

ii. Dimethylcarbamyl chloride

2. Procarcinogens That Require Metabolic Activation:
   - Polycyclic and Heterocyclic Aromatic Hydrocarbons
     i. Benz(*a*)anthracene
     ii. Benzo(*a*)pyrene
     iii. Dibenz(*a*)anthracene
     iv. 3-Methylcholanthrene
     v. 7,12-Dimethylbenz(*a*)anthracene

✓ In the body, benzo[a]pyrene is metabolized to **epoxides (toxic)** 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.

➢ Polycyclic hydrocarbons also may be produced from animal fats during the process of broiling meat and are present in smoked meats and fish.

- **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 can be carcinogenic** since they cause **nitrosylation** of amines contained in food producing nitrosamines that are suspected to be carcinogenic.

1

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		

2

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)		

3

	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 such as *RAS* and *T53*.
- **Aflatoxin B1** produces 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**. (recall carcinogenesis from cytology)

➢ 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** (thymine dimers for example).
- 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. (see mole 19)

➢ Viral and Microbial Oncogenesis:

1. Oncogeneic RNA viruses (HTLV-1).
2. Oncogenic DNA viruses (HBV, HPV, KSHV(HHV-8), EBV and polyoma virus).
3. Helicobacter pylori (next lecture)

A. 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 (HIV), which causes AIDS, HTLV-1 has [(1)]tropism (specific binding) for CD4+ T cells which are the major target for neoplastic transformation. [(2)]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 (with HTLV-1) 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 **aclonal** 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 l**ong terminal-repeat regions** typical of all retroviruses.
- In contrast to other leukemia viruses, it also contains another gene referred to as ***tax*** *gene*.
- 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 contributes 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 that promote 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 including 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.**

2. 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)

✓ ONLY HPV is discussed, others are in the following lecture.

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).
3. Cervical cancer (HPV 16 & 18).
4. Oropharyngeal cancer.

❖ The oncogenic ability of HPV is related to the expression of two viral oncoproteins, E6 and E7: (general activities)

i. They bind to RB and p53
ii. Inhibit CDKIs p21 & 27.
iii. 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*.

Here's a quiz on this lecture.

❖ Neoplasia 9:

➢ Epstein Barr virus (EBV):

- EBV is a member of the **herpesvirus family.**
- It was the **first** virus linked to a human tumor**, Burkitt lymphoma**.
- Burkitt lymphoma is an **aggressive** tumor that is endemic in certain parts of Africa and occurs sporadically elsewhere.
- In endemic areas the tumor cells in virtually all affected patients carry the EBV genome.
- EBV uses the complement receptor **CD21 to attach to and infect B cells.**
- The infection leads to polyclonal B cell proliferation and generation of **immortal** B lymphoblastoid cell lines.
- One EBV-encoded gene**, *LMP1*** (latent membrane protein 1) acts as an **oncogene.**
- EBV gene (LMP-1) products contribute to oncogenesis by stimulating a normal B-cell proliferation pathway.
- **LMP1** stimulates signaling through the **NF-κB** and **JAK/STAT** pathways**,** both of which **promote** B cell **proliferation** and **survival**.
- **LMP-1 prevents apoptosis through BCL-2.**
- EBV gene **EBNA-2** activates **cyclin D**.
- **vIL-10 prevents** macrophages & monocytes from **activating T-cells** & killing the infected cells.
- In regions of the world where Burkitt lymphoma is endemic**,** concomitant infections such as **malaria** impair immune competence allowing **sustained B-cell proliferation.**

- Eventually, **cytotoxic T cells eliminate most of the EBV- infected B cells but a small number survive.**
- Concomitant compromise of immune competence allows sustained B-cell proliferation and eventually development of lymphoma with occurrence of additional mutations such **as t(8,14)** leading to activation of the **MYC** gene.
- In nonendemic areas 80% of these tumors are unrelated to EBV, but virtually all endemic and sporadic tumors possess the t(8;14) translocation or other translocations that dysregulate *MYC*.
- **Sporadic Burkitt** lymphomas are triggered by **mechanisms other than EBV infection** but they appear to **develop through similar oncogenic pathways**.
- ***Nasopharyngeal carcinoma*** also is associated with **EBV infection**.
    - This tumor is endemic in southern China, in some parts of Africa.
- In contrast to Burkitt lymphoma, 100% of nasopharyngeal carcinomas obtained from all parts of the world contain EBV.
- The integration site of the viral genome is identical (clonal) in all of the tumor cells within individual tumors
- Unlike Burkitt lymphoma, L**MP-1** is expressed in **nasopharyngeal carcinoma** cells and in B cells that activates the NF-κB pathway.
- **NF-κB upregulates** the expression of factors such as **VEGF** and matrix **metalloproteases** that may contribute to **oncogenesis**.
- **EBV has been implicated in the pathogenesis of :**
    1. Burkitt lymphomas
    2. Lymphomas in immunosuppressed individuals with HIV infection or organ transplantation.
    3. Some forms of Hodgkin lymphoma.
    4. Nasopharyngeal carcinoma.
    5. T cell lymphomas, NK cell lymphomas.
    6. Gastric carcinomas.
    7. Sarcomas, mainly in the immunosuppressed.

➢ Hepatitis B & Hepatitis C viruses:

- 70%-85% of **hepatocellular** carcinomas worldwide are due to infection with **HBV or HCV**.
- The oncogenic effects of HBV and HCV are multifactorial but the dominant effect seems to be **immunologically mediated chronic inflammation, hepatocellular injury, stimulation** of hepatocyte **proliferation,** and production of **reactive oxygen species** that can **damage DNA**.
- The **HBx** protein of **HBV** and **the HCV core protein** can activate a variety of signal transduction pathways that may also contribute to **carcinogenesis**.

- As with any cause of hepatocellular injury chronic viral infection leads to the compensatory proliferation of hepatocytes.
- This regenerative process is aided and abetted by a plethora of growth factors, cytokines, chemokines, and other bioactive substances produced by activated immune cells that promote cell survival, tissue remodeling, and angiogenesis.
- The activated immune cells also produce other mediators, such as reactive oxygen species, that are **genotoxic** and **mutagenic**.
- A key molecular step seems to be **activation** of the nuclear factor-κB (**NF-κB**) pathway in hepatocytes caused by mediators derived from the activated immune cells.
- Activation of the NF-κB pathway **blocks apoptosis**, allowing the dividing hepatocytes to cause **genotoxic stress and to accumulate mutations**.
- The HBV genome contains a gene known as *HBx, HBx* can **directly** or **indirectly** activate a variety of transcription factors and several signal transduction pathways that **interfere with p53 function**.
- Viral integration can cause **secondary rearrangements** of chromosomes, **including multiple deletions that may harbor unknown tumor suppressor genes.**

➢ Helicobacter Pylori:

- **H. pylori infection has been implicated in both:**

1. Gastric adenocarcinoma

- The mechanism of H. pylori-induced gastric cancers is multifactorial, including Immunologically mediated chronic inflammation, **stimulation** of gastric cell **proliferation**, and production of **reactive oxygen species** that **damage DNA**.
- H.pylori pathogenicity genes, such as **CagA**, may also contribute by **stimulating growth factor pathway**.
- It involves increased epithelial cell proliferation on a background of chronic inflammation.
- The sequence of histopathologic changes consists of initial development of chronic inflammation/gastritis followed by gastric atrophy, intestinal metaplasia of the lining cells, dysplasia, and cancer.
- This sequence takes decades to complete and occurs in only 3% of infected patients.

- Strains associated with gastric adenocarcinoma have been shown to contain a "**pathogenicity island**" that contains cytotoxin-associated A gene (*CagA*).
- *CagA* is injected into gastric epithelial cells leading to initiation of a signaling cascade that mimics unregulated growth factor stimulation.

2. MALT lymphoma.

- *H. pylori* is associated with an increased risk for the development of gastric lymphomas.
- The gastric lymphomas are of B-cell and referred to as *MALT lymphomas.*
- Their molecular pathogenesis is incompletely understood but seems to involve strain-specific.
- *H. pylori* infection leads to the activation of *H. pylori* reactive T cells which in turn cause polyclonal B cell and MALT lymphoma.

➢ Laboratory Diagnosis of Cancer:

1. Morphologic Methods.
2. Immunocytochemistry.
3. Molecular Diagnosis.
4. Flow cytometry
5. Tumor Markers:
   A. PSA.
   B. Carcinoembryonic antigen (CEA).
   C. α-fetoprotein.

✓ Explanations:

1. morphologic methods:

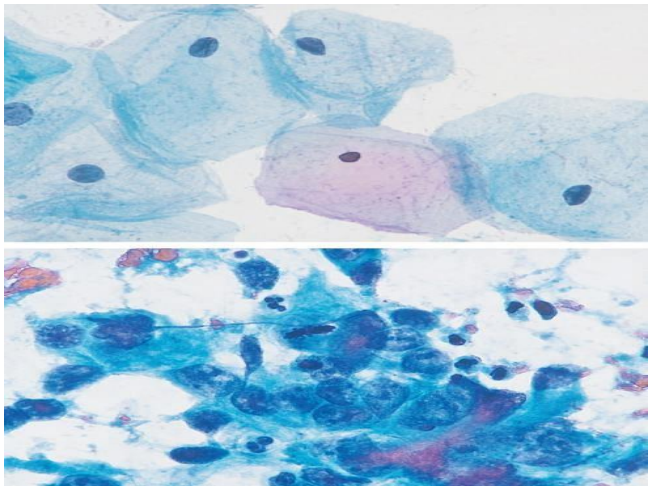
H&E stain

A-Excision or biopsy.

B-Fine-needle aspiration.

C-Cytologic smears (Papanicolaou).

D-Frozen sections.



2. Immunohistochemistry:

- Cytokeratin
- Prostate-specific antigen (PSA) =prostate carcinoma.
- Estrogen receptors =breast cancers.

3. Molecular Diagnosis:

a) Diagnosis of cancer (CML, PCV)
b) Prognosis and behavior (*HER2* and *NMYC).*
c) Detection of minimal residual disease (CML).
d) Diagnosis of hereditary predisposition to cancer (BRCA1 gene).
e) Therapeutic decision-making.

4. **Flow cytometry:**

- It is used routinely in the classification of leukemias and lymphomas.
- Fluorescent antibodies against cell surface molecules and differentiation antigens are used to obtain the phenotype of malignant cells.

5. **Tumor Markers** :

A- PSA

- Prostatic carcinoma can be suspected when elevated levels of PSA are found in the blood.
- Although PSA levels are often elevated in cancer, PSA levels also may be elevated in benign prostatic hyperplasia
- *PSA test suffers from both low sensitivity and low specificity*.

B- Carcinoembryonic antigen (CEA)

- carcinomas of the colon, pancreas, stomach, and breast.

C- α-fetoprotein, produced by:

1- hepatocellular carcinomas.
2- yolk sac remnants in the gonads.
3- Teratocarcinomas.
4- embryonal cell carcinomas.
5- neural tube defect of the fetus.

✓ CEA and α-fetoprotein assays lack both specificity and sensitivity.

➢ [1]Grading and [2]Staging of Cancer:

- Methods to quantify the probable clinical aggressiveness of a given neoplasm and its apparent extent and spread in the individual patient are determinants of prognosis and treatment protocols.

1. Grading:

- Grading of a cancer is based on the degree of differentiation of the tumor cells and in some cancers the number of mitoses and the presence of certain architectural features.
- Grading schemes have evolved for each type of malignancy and generally range from two categories (low grade-high grade) to four categories; I, II, III, IV.
- It is common practice to characterize a particular neoplasm in descriptive terms
- For example
- Well-differentiated, mucin-secreting adenocarcinoma of the stomach Poorly differentiated pancreatic adenocarcinoma.

2. Staging:

- The staging of solid cancers is based on:
    1. The size of the primary lesion
    2. Its extent of spread to regional lymph nodes
    3. The presence or absence of bloodborne metastases.
- The major staging system currently in use is the American Joint Committee on Cancer Staging
- This system uses a classification called the *TNMsystem:*
    - *T* for primary tumor
    - *N* for regional lymph node involvement
    - *M* for metastases.
- TNM staging varies for specific forms of cancerbut there are general principles.
- The primary lesion is characterized as T1 - T4 based on increasing size.
- **To** is used to indicate an **in situ lesion**.
- **No** indicates **no nodal** involvement.
- **N1 - N3** mean involvement of an **increasing number and range of nodes**.
- **Mo** signifies **no distant metastases**
- **M1** or sometimes **M2** reflects the **presence and estimated number of metastases.**

Here's a quiz on this lecture.

feedback

تم بحمد الله, شكرا لثقتكم.