Neoplasia

2-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**

- **<u>EBV has been implicated in the pathogenesis of :</u>**
- **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**

- **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, LMP-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.**

3-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**

4-Helicobacter Pylori

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

  1-Gastric adenocarcinoma

  2-MALT lymphoma.

- **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**.

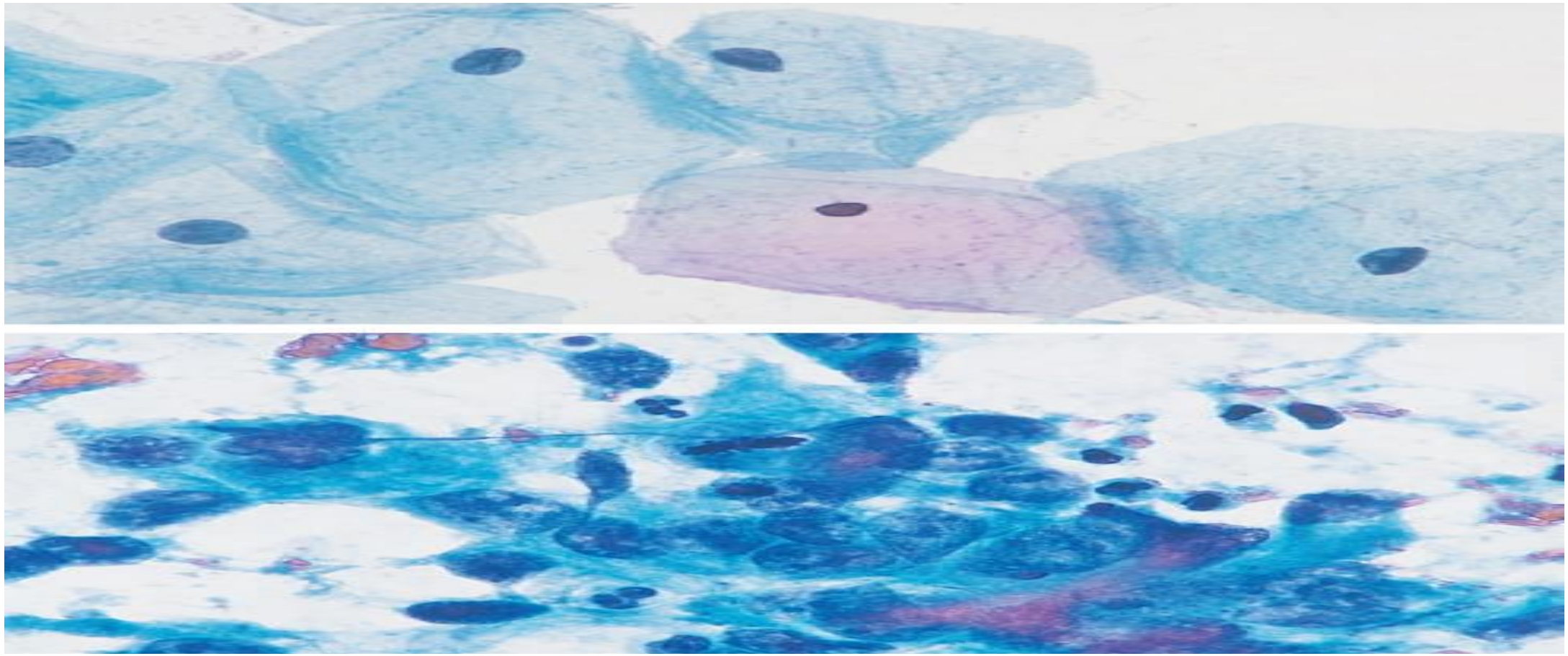
- **This sequence takes decades to complete and occurs in only 3% of infected patients.**
- **Strains associated with gastric adenocarcinoma have been shown to contain a “pathogenicity island” that contains cytotoxin-associated A gene (*CagA*).**
- ***CagA* is injected into gastric epithelial cells leading to initiation of a signaling cascade that mimics unregulated growth factor stimulation**

- ***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 :**
- **H&E stain**
- **A-Excision or biopsy.**
- **B-Fine-needle aspiration.**
- **C-Cytologic smears (Papanicolaou) .**
- **D-Frozen sections.**



- **<u>2- Immunocytochemistry:</u>**
- **Cytokeratin**
- **Prostate-specific antigen (PSA) =prostate carcinoma.**
- **Estrogen receptors =breast cancers.**

- **<u>3- Molecular Diagnosis</u>**
- **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**

- **<u>4- Flow cytometry</u>**
- **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**

Grading and 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 determinents of prognosis and treatment protocols.**

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 adenocarinoma

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 cancer but there are general principles.**
- **The primary lesion is characterized as T1 - T4 based on increasing size.**
- **T0 is used to indicate an in situ lesion.**
- **N0 indicates no nodal involvement**
- **N1 - N3 mean involvement of an increasing number and range of nodes.**

- **M0 signifies no distant metastases**
- **M1 or sometimes M2 reflects the presence and estimated number of metastases.**