Pathology

Subject :

Lec no : lec-24-

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وَقُل رَّبِّ زِدْنِي عِلْمًا

NEOPLASIA

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in this lecture we will talk about the second and the third types of carcinogens

2- Radiation and Physical Carcinogens:

- Sources:

-UV rays of sunlight, X-rays, radioactive isotopes, & nuclear fission (Bomb or reactors).

❑U-V light:

- Effect depends on the intensity of exposure & quantity of melanin.
- At greatest risk are fair-skinned people who live in areas that receive a great deal of sunlight.

حوي البشره العاتحه معرضين اكثر لحدوث سرطانات

Skin Cancers, including:

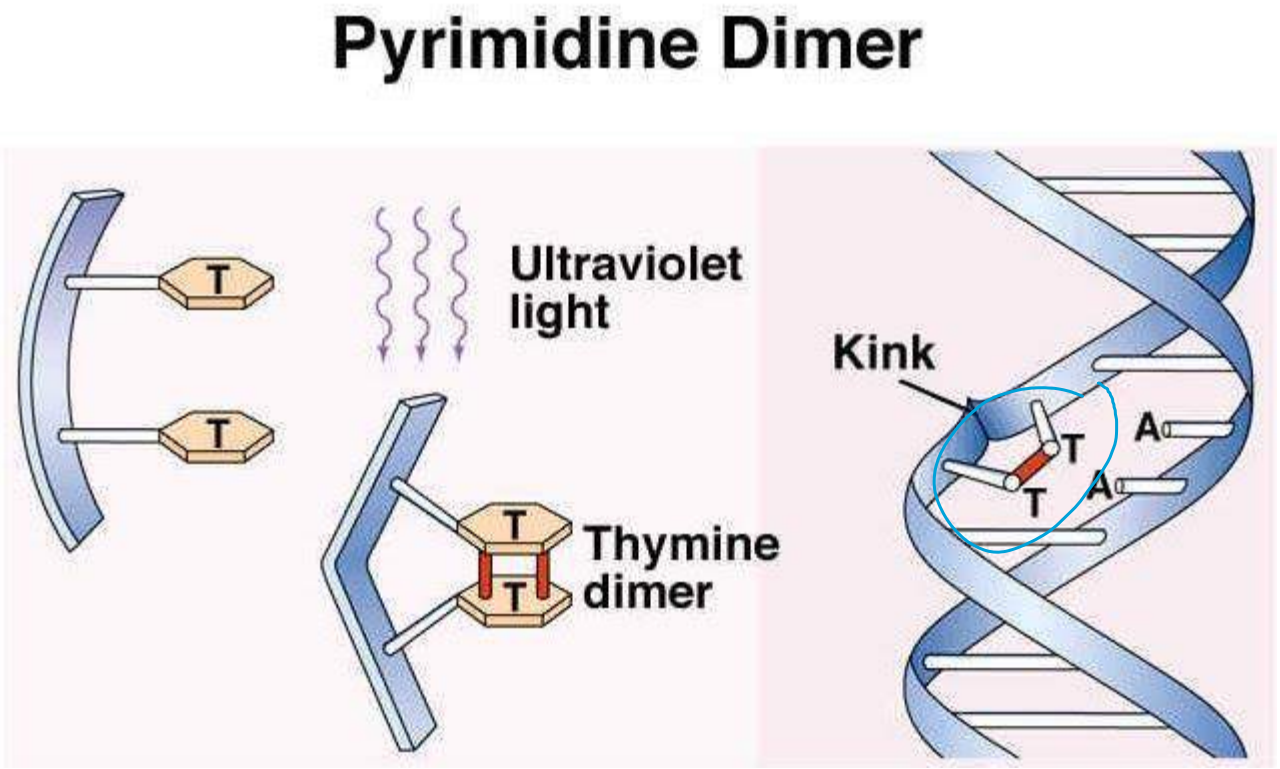
1. *Squamous Cell CA
2. *Basal Cell CA
3. *Melanoma

* يعمل روابط بين البيوكيميائيات المتجاورة في ال strain الواحد

- Damage 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.

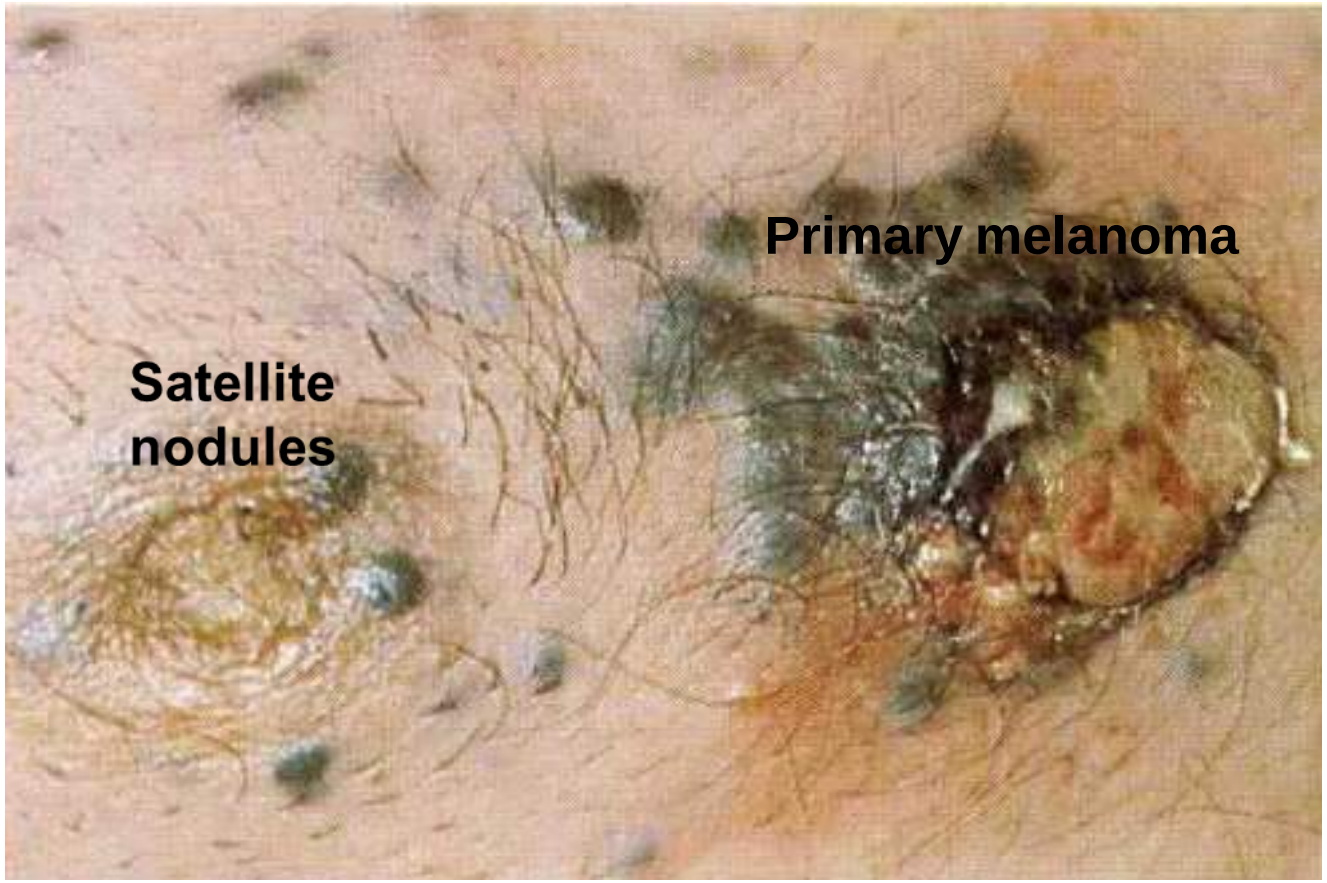
نظام اصلاح ال mutations في الخلايا

نسبة كبيرة ال (mutations) لا يوجد repair system قادر على اصلاح الخلل



black / Brown

Chest wall: Malignant melanoma with local spread: Many small metastatic satellite nodules have formed in the tissue around the pigmented primary melanoma.



❑Ionizing Radiation:

- Explosions: ↑ Leukemia, Breast, colon, thyroid, lung CA.

- Therapeutic radiation exposure of the head and neck → ↑ Thyroid CA, Leukemia.

- Miners of radioactive elements (e. g uranium) have suffered a ten-fold increased incidence of lung cancer.

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

Mechanism: Free radical injury → chromosome breakage, translocations & less frequent point mutations.

❑Asbestos fiber inhalation: Mesothelioma & Lung CA

3- Microbial Carcinogens:

-Oncogenic DNA Viruses.

1. HPV
2. EBV
3. Hepatitis B. virus.
4. HHV-8 (Kaposi sarcoma herpes virus in AIDS)
5. Polyomavirus called Merkel cell virus

-Oncogenic RNA Viruses.

- HTLV-1

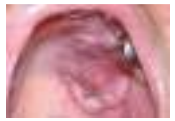
- H. pylori بكتيريا

1- HPV-Human Papilloma Virus:

sexually transmitted

- Several genetically distinct types:
  - **Types 1, 2, 4 & 7** → Benign squamous papilloma (wart) skin

  - **Low-risk types (6, 11)** → Genital Squamous Cell Papilloma (wart)
  - **High-risk types (16, 18)** → - Squamous Cell Carcinoma in cervix, vulva, perianal
    - Cervical severe **dysplasia**, SCCa **in situ**.
    - Oropharyngeal Carcinoma.



Increase proliferation
Inactivation for tumor suppressor (يثبط حياته تنشط الخلايا) genes
pro-oncogenic activity
* كيف يساعد (HPV) في حدوث الـ Cancer عند بعض الأشخاص؟ عن طريق تعبير الـ early genes (HPV) حيث تسمى

Mode of action:

(E6) (E7)

- HPV has transforming early genes **(E6, E7),** each of which has several activities that are pro-oncogenic and inactivate suppressor genes:

(tumor suppressor gene)

E6 protein binds & degrades **p53** → no apoptosis

(retinoblastoma gene) → tumor suppressor gene

E7 protein binds to **Rb** → releasing E2F transcription effect → activates cyclins & inhibit CDKIs--- promoting progression through the cell cycle.

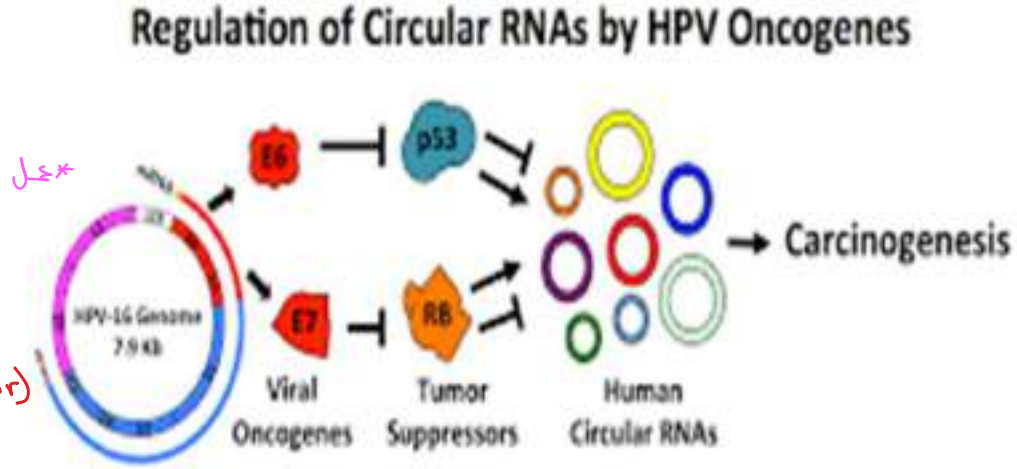
* Rb ← تثبيط عمل ← activation of cyclin ← وبالتالي ← that lead inactivation of
promoting growth ← cell cycle

- E7 and E6 of high-risk types - higher affinity for Rb and P53.

low – lower

- In benign warts, the HPV genome is maintained in a nonintegrated form, while in cancers, the HPV genome is randomly integrated into the host genome. (benign tumor)

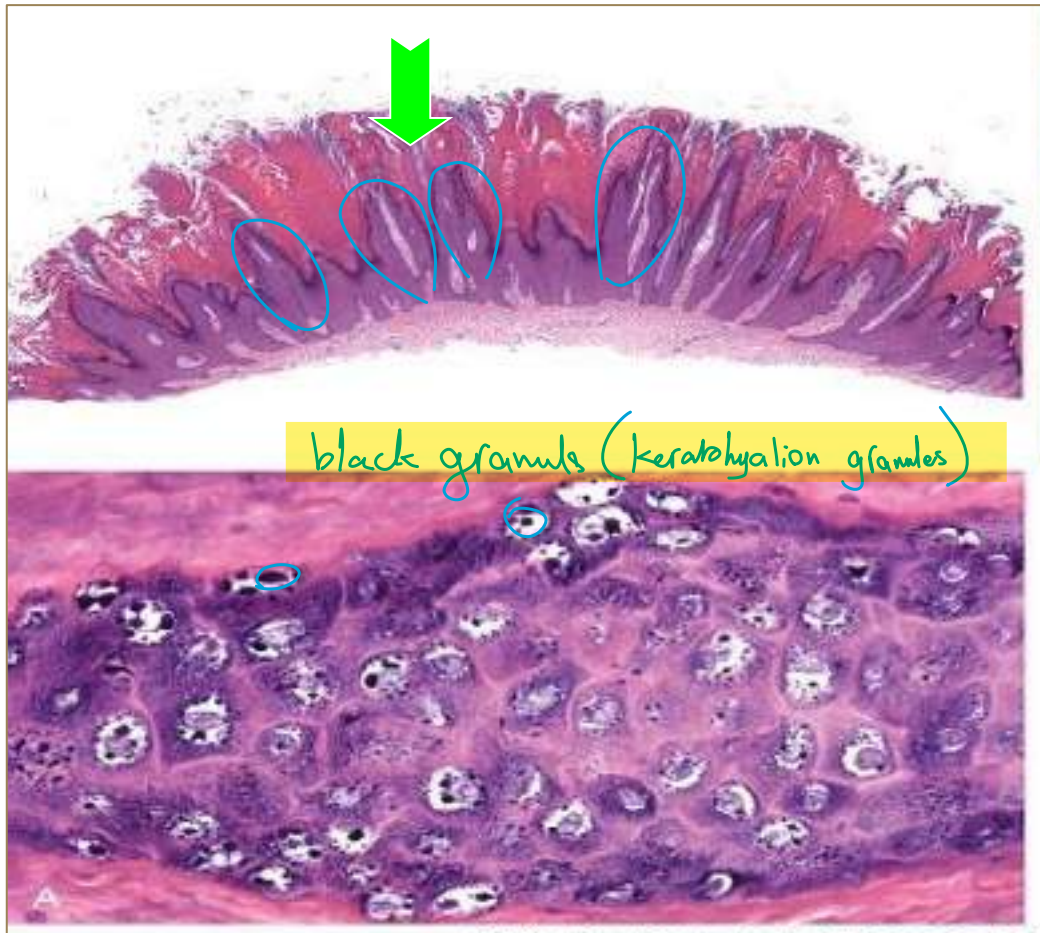
- Integration interrupts a negative regulatory region in the viral DNA, resulting in overexpression of the E6 and E7 oncoproteins → Cell proliferation.



A: Squamous papilloma: benign → finger like projection

Symmetrical papillary epidermal proliferation(top).

Histology shows nuclear pallor, prominent keratohyalin granules



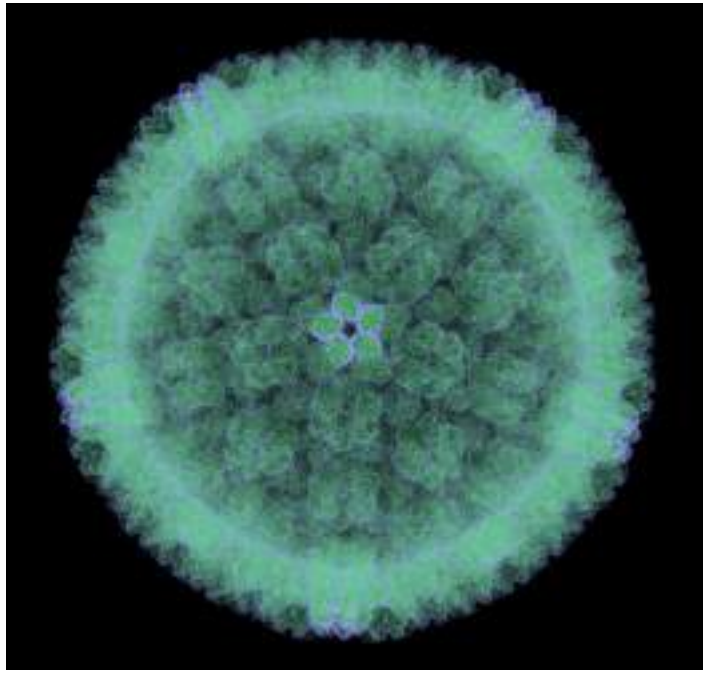
B: Squamous papilloma: Multiple papules with rough, pebble-like surfaces at infection sites

2- EBV - Epstein Barr Virus

- A member of the herpesvirus family.

Associated with:

1- Burkitt Lymphoma malignant tumor of lymphocyte
2- Other B-cell Lymphoma
3- Hodgkin lymphoma (Subset)
4- Nasopharyngeal Carcinoma



malignant

Mode of action in Burkitt lymphoma:

- In endemic cases, EBV is identified in tumor cells.

B-lymphocyte (infection) لـ

- EBV (has **LMP1** oncogene) enters B cells → Induction of proliferation

Induces B cell proliferation

Prevents apoptosis by activating BCL2.

Controlled POLYCLONAL B proliferation which is controlled by cytotoxic T cells →

تفاعل خلايا B

and the affected patient either remains Asymptomatic.

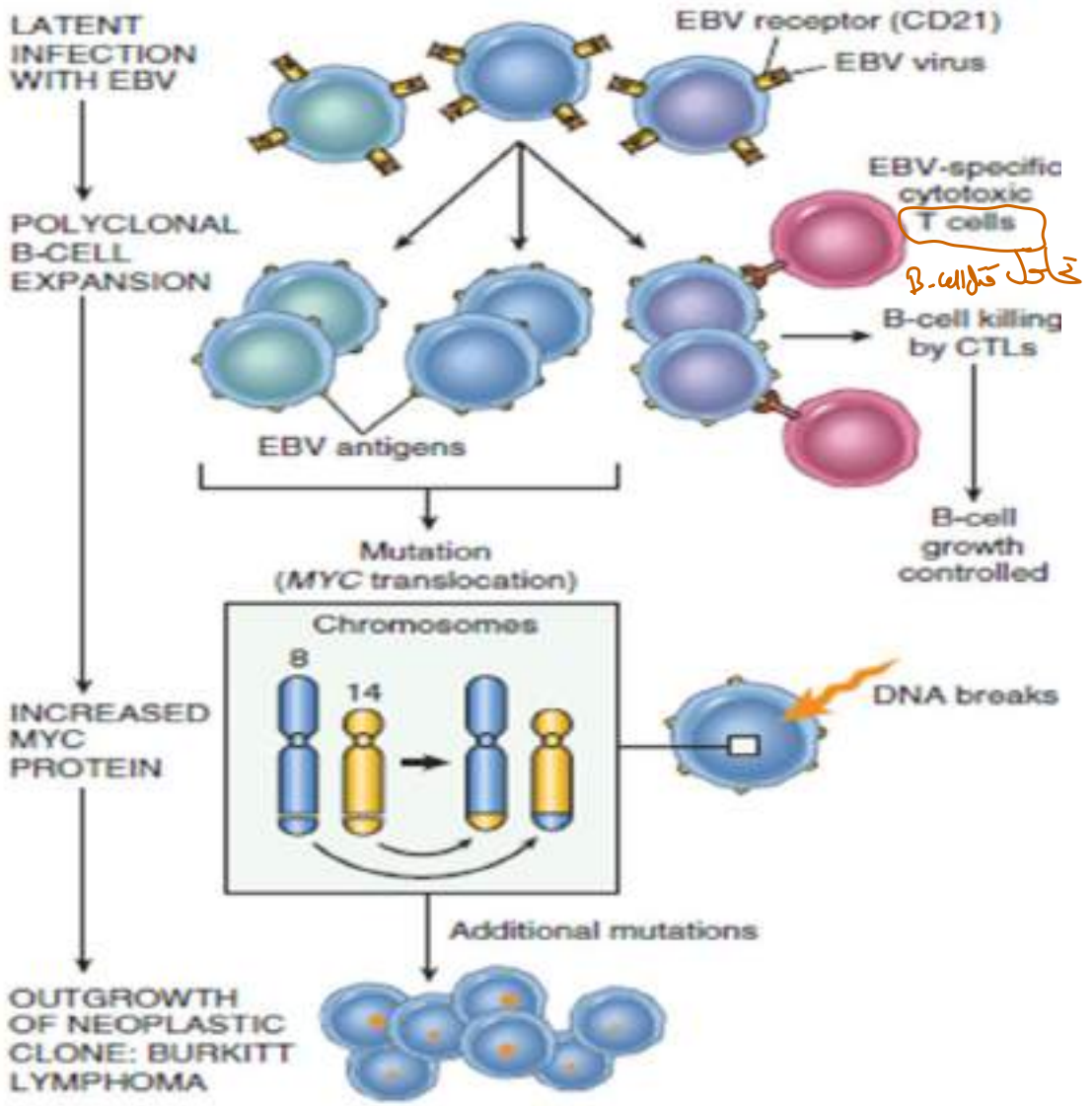


Fig. 6.34 Possible evolution of EBV-induced Burkitt lymphoma.

But...

-Endemic infection & Malnutrition may play a role in ↓ immunity (Lost T cell control)---

So a small number of the EBV-infected B cells survive and with the acquisition of specific mutations, most notably ➡ Dysregulation of c-MYC by translocation t(8;14) ➡ BURKITT Lymphoma

Proliferation تحفيز الخلية

In nasopharyngeal carcinoma:

- In contrast to Burkitt lymphoma, 100% of nasopharyngeal carcinomas obtained from all parts of the world contain EBV.

- The uniform association of EBV with nasopharyngeal carcinoma suggests that EBV has a central role in the genesis of the tumor, but the restricted geographic distribution indicates that genetic or environmental cofactors, or both, also contribute to tumor development.

- LMP1 is expressed on epithelial cells activating cell proliferation

DNA virus RNA virus

3- Hepatitis B & Hepatitis C Viruses

- About 70% to 85% of hepatocellular carcinomas are caused by HBV or HCV.

- The HBV and HCV genomes do not encode any viral oncoproteins

-Multifactorial oncogenic effect but mainly Immunologically mediated chronic inflammation with hepatocyte death, leading to regeneration and genomic damage.

good media for more mutations ← regeneration ← hepatocellular death ← infection in hepatocyte ← hepatitis B/C virus *

<u>The oncogenic effect of HBV seems to be:</u>

(1) First, by causing chronic liver cell injury & accompanying regeneration, HBV predisposes the cells to mutations, caused possibly by environmental agents

(2) virus-induced gene damage in regenerating liver cells may set the stage for multistep carcinogenesis.

In addition:

The HBV (hepatitis B virus) contains HBx gene, may more directly promote the development of cancer:

1. Acts as growth-promoting gene
2. HBx inactivates suppressor functions, such as TP53.

The HCV (RNA virus) has HCV core protein which may induce proliferation

4- Oncogenic RNA Viruses:

HTLV-1 (Human T-Cell Leukemia Virus Type 1):

(T lymphocytes) ل (Infection) لا *

- HTLV-1 has a tropism for **CD4+** T cells, and T cells are the major target for neoplastic transformation.

-Induces adult T-cell leukemia/lymphoma (ATLL)

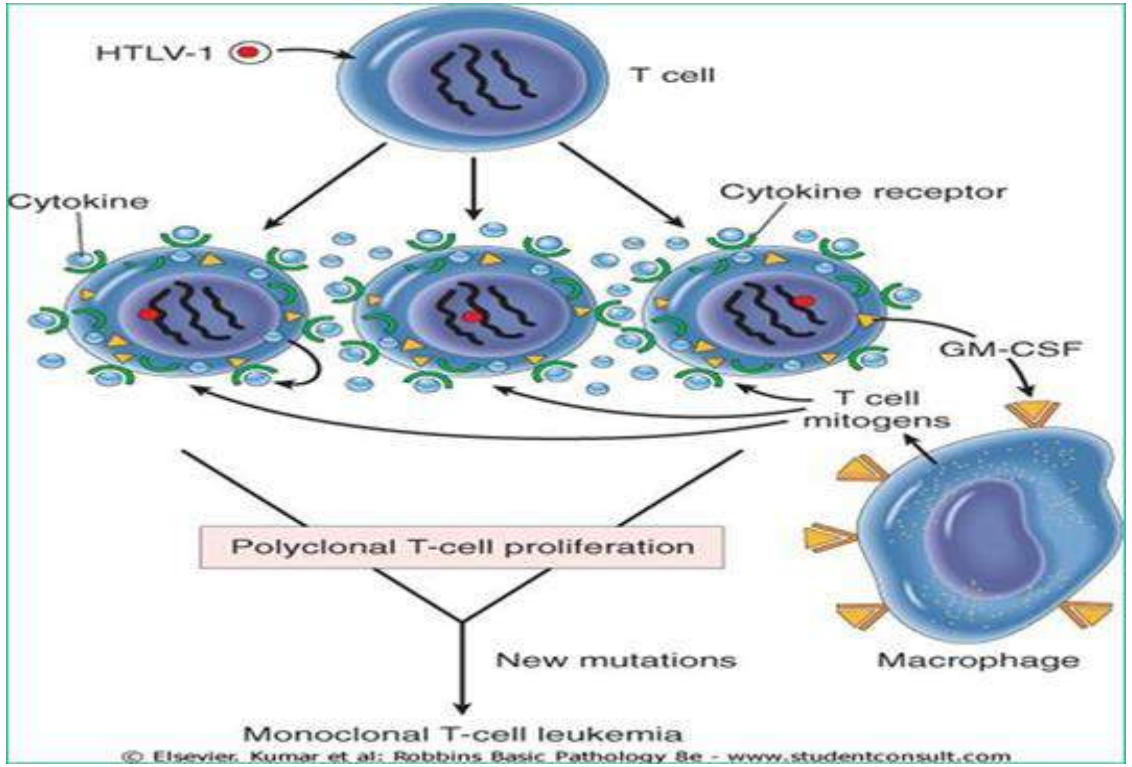
- Transmitted sexually, blood or breast milk.

Mode of action:

hotel تشه (HTLV)

Virus **TAX** gene--- TAX protein which:

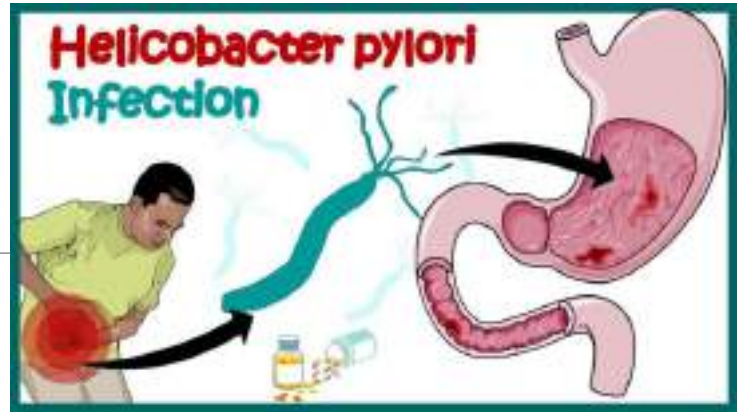
- Increased survival and growth of infected cells.
- Suppresses action of TP53 & CDKI
- Increased genomic instability.



POLYCLONAL→ MONOCLONAL → LEUKEMIA (3-5% of cases - latent period 40-60 yrs).

neoplastic تعبي حتى
— Polyclonal → reactive

5- Helicobacter pylori: البكتيريا الحلزونية



- First described as a cause for peptic ulcer.

- Multifactorial etiology in **gastric carcinoma** & **gastric lymphoma**

Carcinoma:

→ It infect gastric epithelial cells

Chronic gastritis → atrophy → intestinal metaplasia → dysplasia → Gastric Carcinoma

- This sequence occurs in only 3% after a long latent period

- **In adenocarcinoma**, H. pylori contains Cytotoxic Associated gene A (***Cag A***) → Cell proliferation

Lymphoma:

Chronic gastritis → mucosal lymphoid follicles → reactive polyclonal B cells → monoclonal B cells → MALT lymphoma

proliferation لي بيعد ت لهم

- Early in the course of the disease, eradicating *H. pylori* with antibiotics causes regression of the lymphoma by removing the antigenic stimulus for T cells.

* علاج (H Pylori) بيمنع تكون ال Lymphoma اجمالي لو كان في مراحله الاولى

Carcinogenesis (Cancer) تكوين ال

Molecular basis of cancer

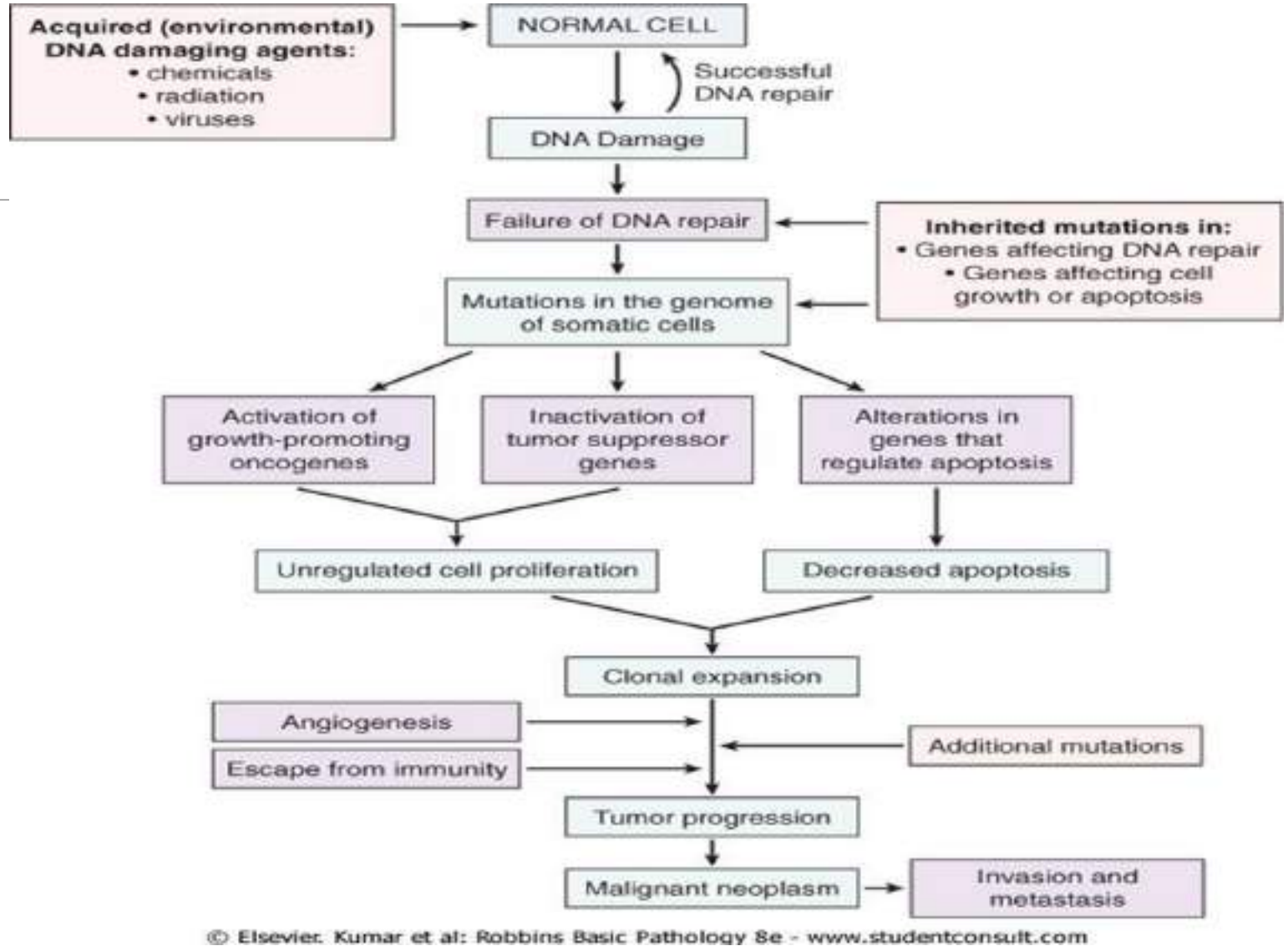
Neoplasms arising from a single clone of cells

Monoclonal proliferation

Cells that are genetically identical to the unit from which they were derived

- Non-lethal (non-killing) genetic damage (or mutation) lies at the heart of carcinogenesis

- Tumors arise from clonal growth of transformed cells that have developed mutations in several classes of genes:
  - Growth promoting proto-oncogenes
  - Growth inhibiting tumor suppressor genes
  - Genes regulating apoptosis
  - Genes involved in DNA repair



Revision

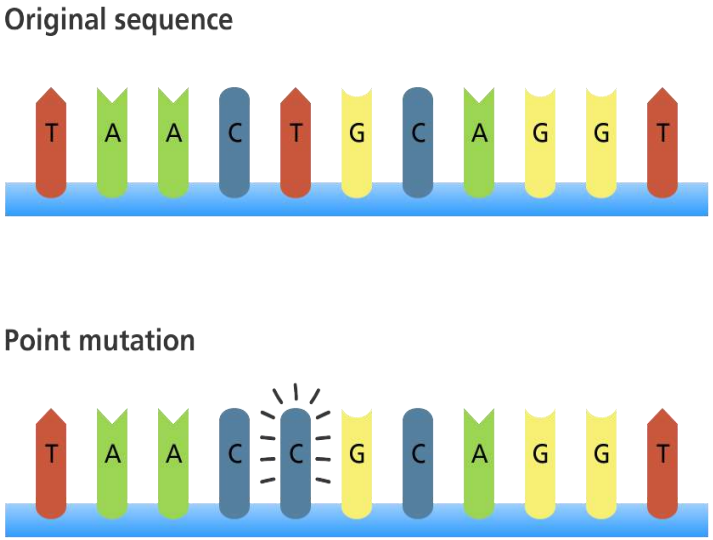
Genetic Lesions in Tumors

1. Point mutation:

-Change in a single base in a nucleotide sequence (altering amino acid residues) may activate an oncogene or inactivate a tumor suppressor.

e.g. RAS oncogene.

TP53, tumor suppressor gene.

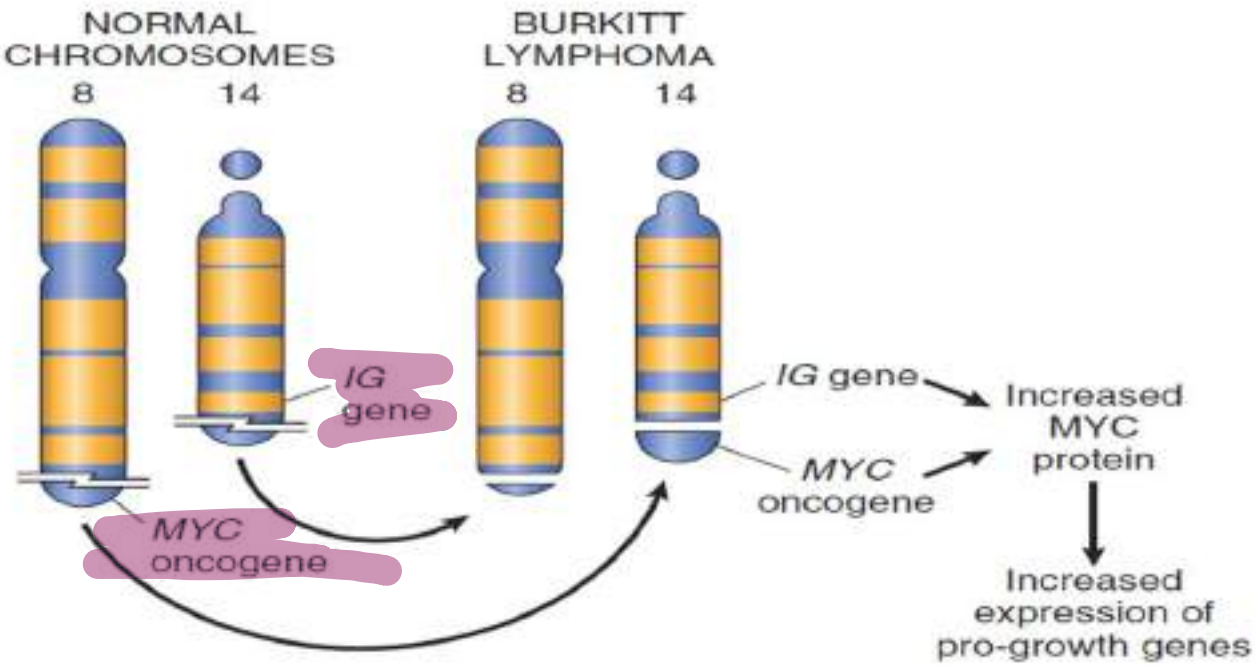


2. Translocation: تبديل الموقع

These rearrangements can activate proto-oncogenes in two ways:

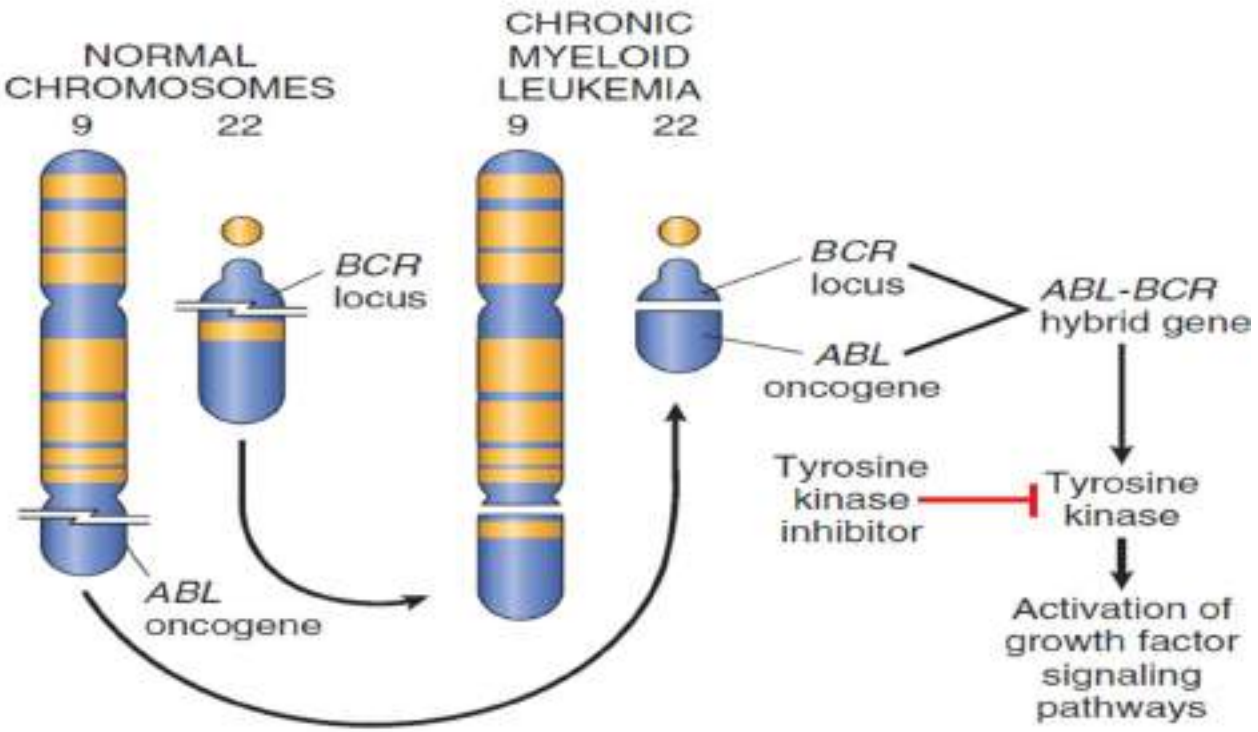
1. Result in overexpression of proto-oncogenes by removing them from their normal regulatory elements and placing them under the control of an inappropriate, highly active promoter or enhancer

- **Burkitt Lymphoma : t (8;14)**



2. Other oncogenic gene rearrangements create fusion genes encoding novel chimeric proteins.

- **Chronic myeloid leukemia :t(9;22)(PHILADELPHIA Chromosome)** ➞ Fusion Gene is produced: **BCR-ABL** (tyrosine kinase activity)



3. Chromosomal deletions:

-Deletion of specific regions of chromosomes may result in the loss of particular tumor suppressor genes.

e.g. Retinoblastoma, RB gene ch13

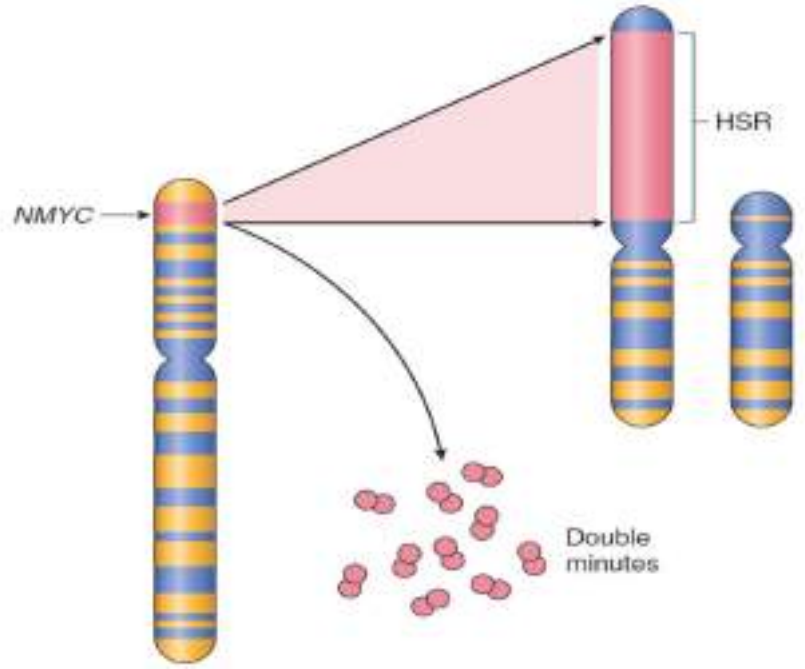
4. Gene amplification:

- Gene amplification, with consequent overexpression and hyperactivity of otherwise normal proteins.
- Such amplification may produce several hundred copies of the gene.

Two mutually exclusive patterns are seen:

- Double minutes: Small fragments of extrachromosomal DNA

- Homogenous staining regions produced by chromosomal segments with various lengths and uniform staining intensity.



Examples:-

- Neuroblastoma: N-MYC
- Breast carcinoma: HER2/Neu

5. Chromosomes loss or gain:

- Change from the normal multiples of **23** (Aneuploidy).

6. Epigenetic changes:

-Reversible, heritable changes in gene expression that occur without mutation.

- Involves posttranslational **modifications of histones and DNA methylation**

- This may silence tumor suppressor genes & repair genes, leading to carcinogenesis