Pathology

Subject :

Lec no : 24

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وقل رب زدني علماً

NEOPLASIA

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2- Radiation and Physical Carcinogens:

- Sources: أي لشعاع هـ

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

U-V light:

الناس البيض لما تتعرض لل UV
بكون خطر أكتر لل Cancer & نه نسبة
الميلانين أقل

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

Skin Cancers, including:

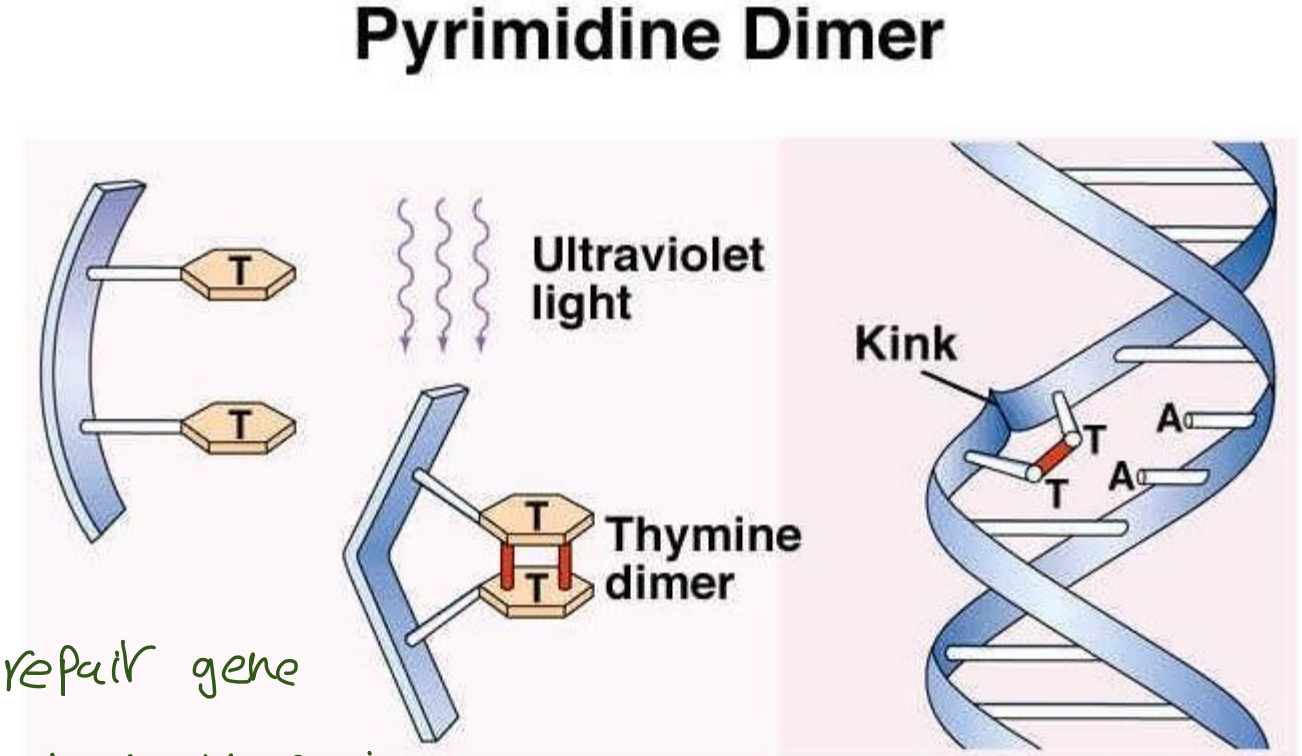
*Squamous Cell CA

*Basal Cell CA

*Melanoma

بيجي ال UV light على ال strand بتعمل DNA روابط بين القواعد اللي موجودة على نفسه

- 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.

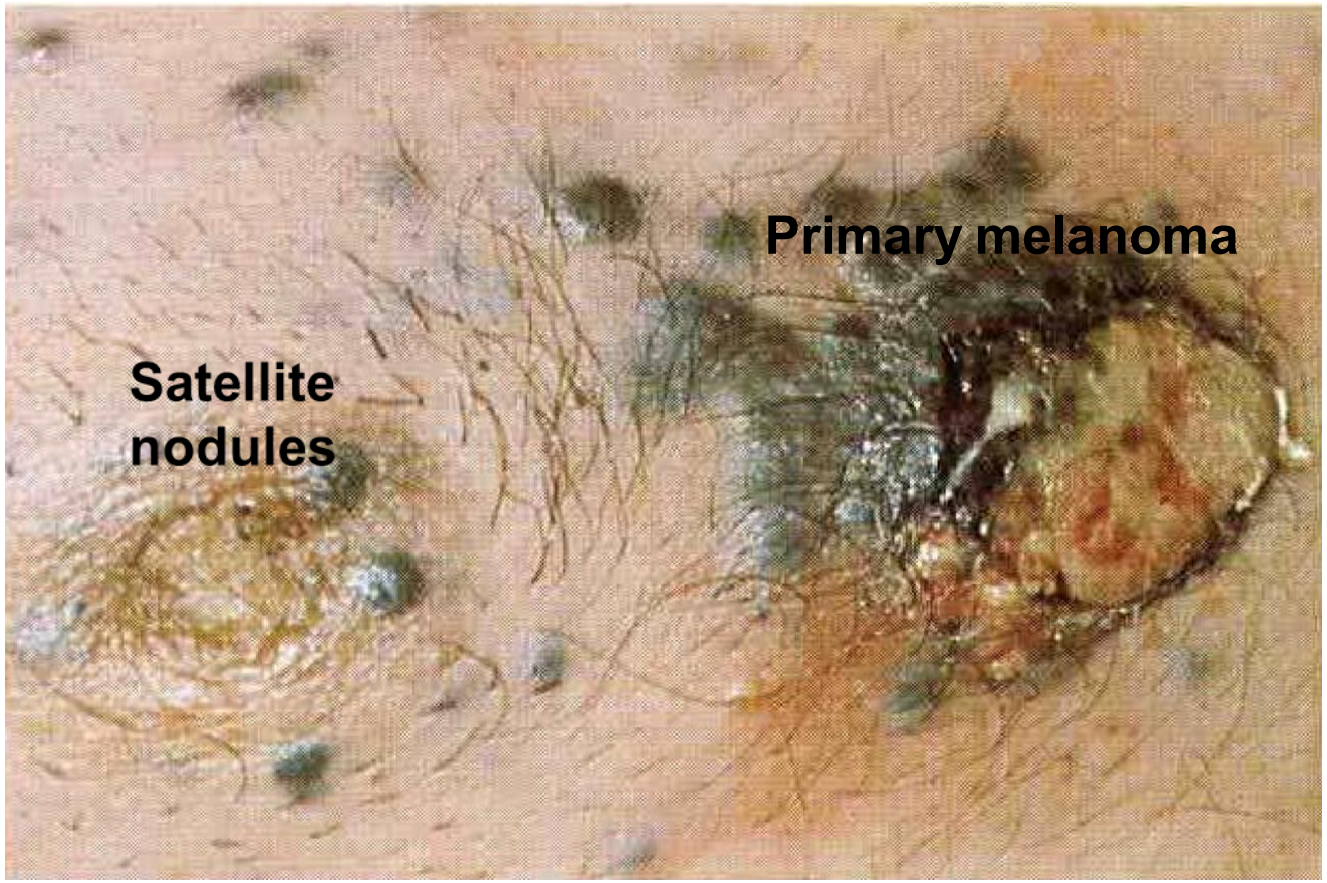


Nucleotide excision repair pathway = repair gene

بعمل repair لكن هاد ال repair gene بتصرف لما يكون high intensity بيطلع ملحوظ وبعمل mutation أكتر damage

black لونها
nodule وحولها

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 (bacteria)

1- HPV-Human Papilloma Virus:

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

Mode of action:

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

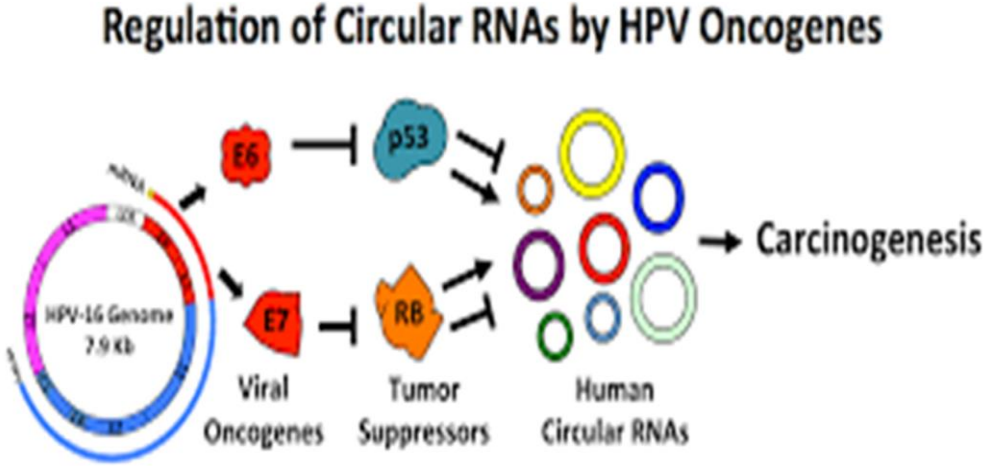
E6 protein binds & degrades **p53** → no apoptosis

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

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

- 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.

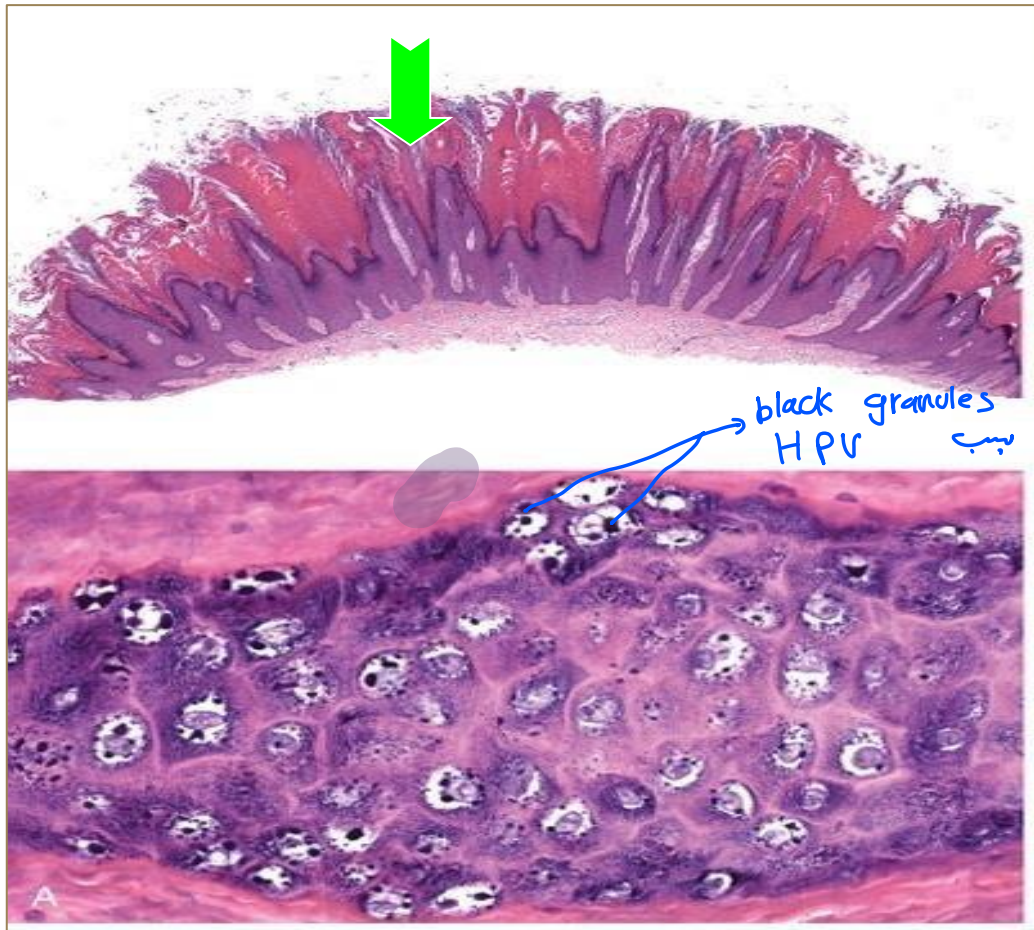
- Integration interrupts a negative regulatory region in the viral DNA, resulting in overexpression of the E6 and E7 oncoproteins → Cell proliferation.

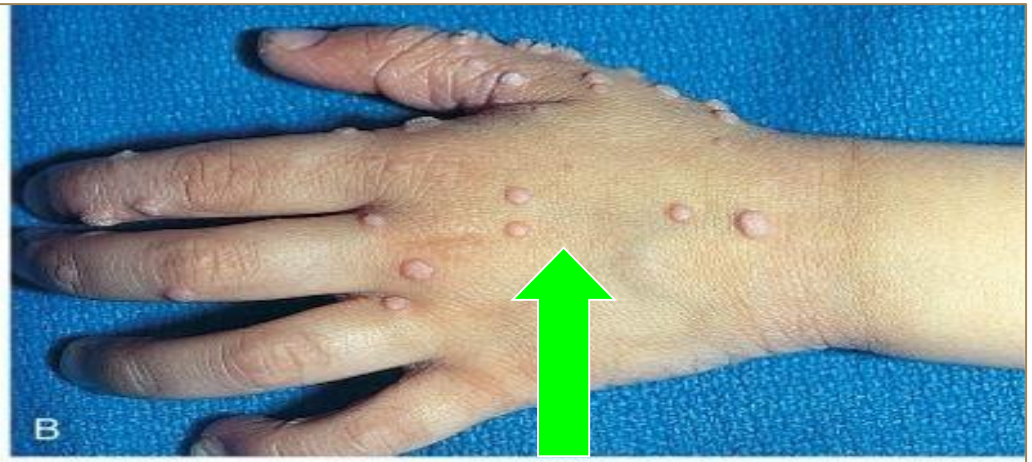


A: Squamous papilloma: finger like projection

Symmetrical papillary epidermal proliferation(top).

Histology shows nuclear pallor, prominent keratohyalin granules





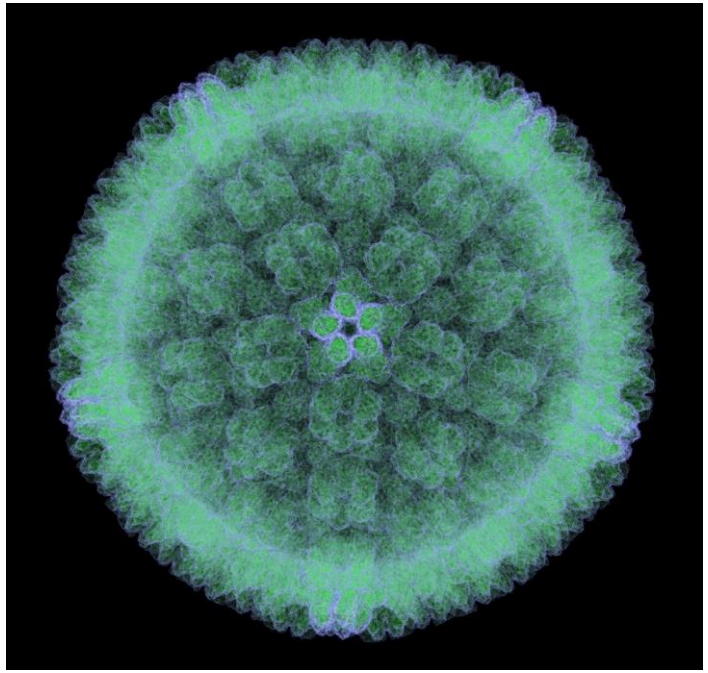
B: Squamous papilloma: Multiple papules with rough, pebble-like surfaces at infection sites

2- EBV - Epstein Barr Virus

- A member of the herpesvirus family.

Associated with:

- Burkitt Lymphoma
- Other B-cell Lymphoma
- Hodgkin lymphoma (Subset)
- Nasopharyngeal Carcinoma



Mode of action in Burkitt lymphoma:

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

LMP1 هاد الجين بحفز proliferation B lymphocyte وبدخل لك داخلها بكون عنده oncogene فبيزيد عدد الخلايا المصابة بالفيروس كبيرة فتتدخل خلايا المناعة (T cell) وتحاول تقضي على الفيروس لذا أغلب الناس المصابة بتكون asymptomatic

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

Induces B cell proliferation

Prevents apoptosis by activating BCL2.

↓

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

and the affected patient either remains Asymptomatic.

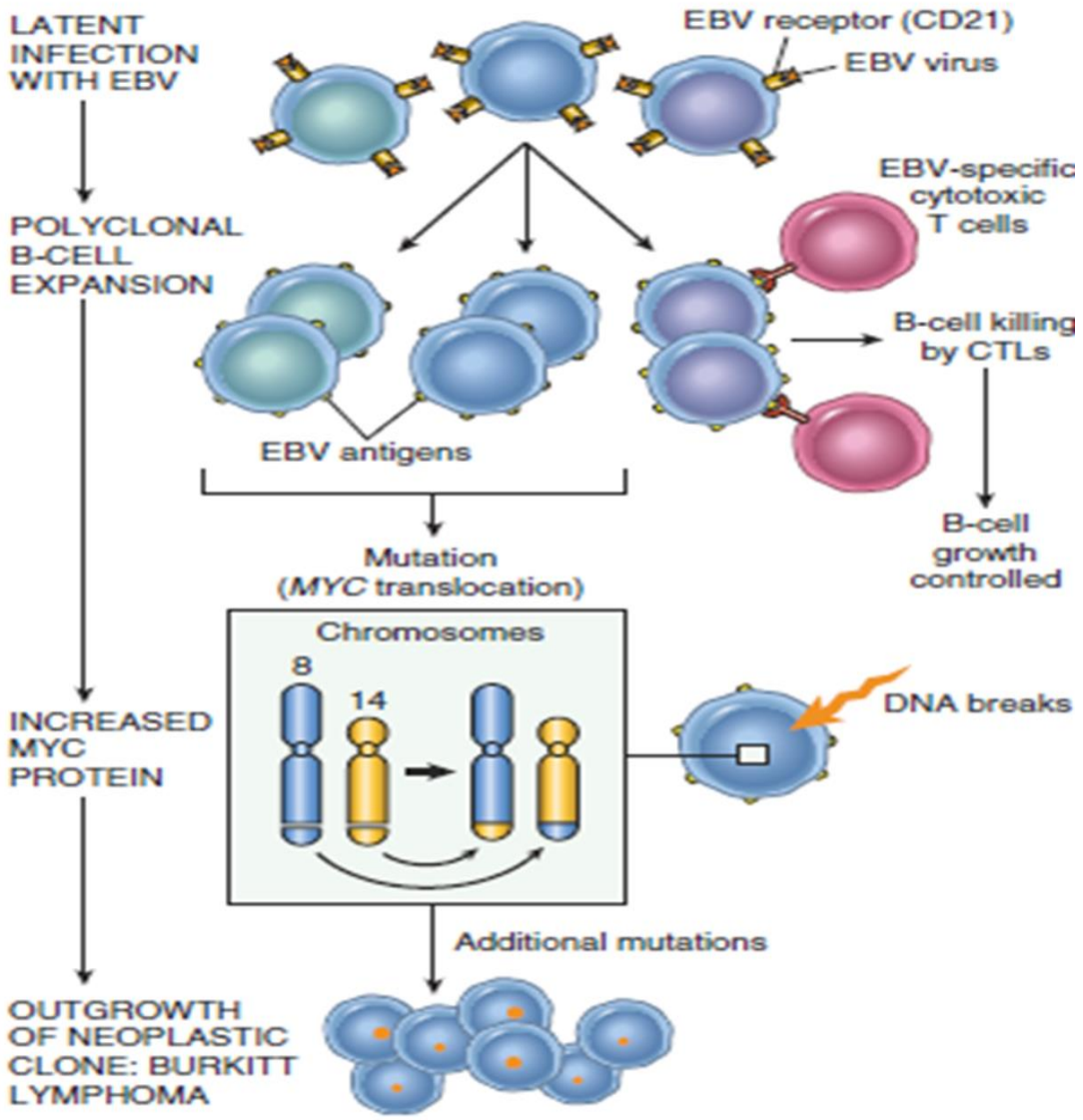


Fig. 6.34 Possible evolution of EBV-induced Burkitt lymphoma.

But…

في أحيانا حالات بتقل ال immunity بالتالي ما رح نقضي على EBV infected B-cell

-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

Malignant tumor of epithelium

In nasopharyngeal carcinoma:

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

(EBV) بعمل infection لل epithelial cell و بعملها proliferation بالزيادة بطلع لل cancer

- 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

كيف بيعمل Cancer !؟

effect for HBV/HCV by immunologically* mediated chronic inflammation → injury → death → regeneration → proliferation → mutation → cancer

- 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.

The oncogenic effect of HBV seems to be:

(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 contains HBx gene, may more directly promote the development of cancer:

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

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

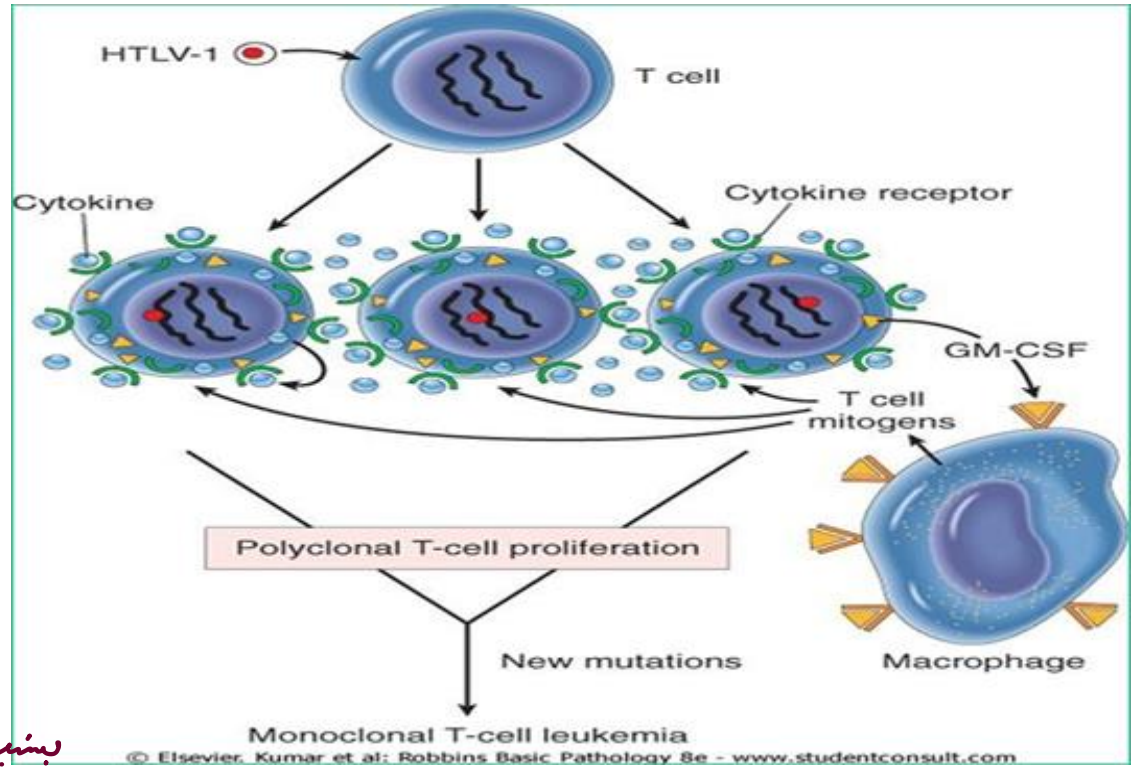
4- Oncogenic RNA Viruses:

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

- 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:

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

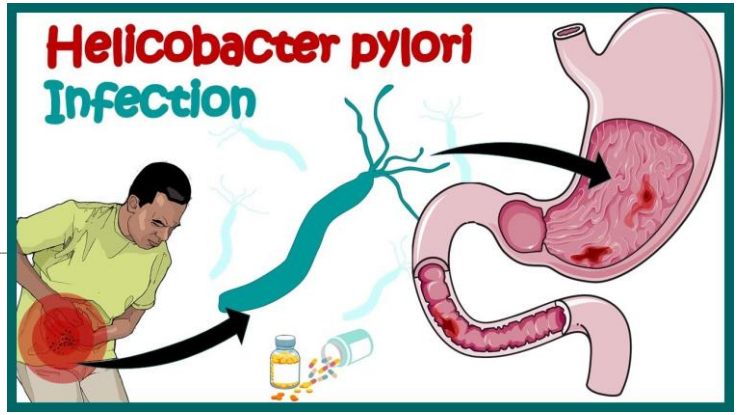
- Increased survival and growth of infected cells.
- Suppresses action of TP53 & CDKI
- Increased genomic instability.

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

بكتيريا حلزونية تسبب قرحة المعدة (جرثومة المعدة)

5- Helicobacter pylori:

من الأكل عادة تنتقل



- First described as a cause for peptic ulcer.

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

Carcinoma:

تقريبًا (Hepatitis C/B) نفس الطريقة

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

إذا ما تعالجت

intestinal mucosa إلى gastric mucosa تتحول الـ

↓ differentiation

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

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

هاد الجين بساعد بـ ((proliferation)) لـ Carcinoma وبالتالي ↑

adenocarcinoma

Lymphoma:

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

- 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.

Cancer cell يكون ال Cancer عن طريق مرفة خطا نفس

Carcinogenesis

Molecular basis of cancer

Neoplasms arising from a single clone of cells

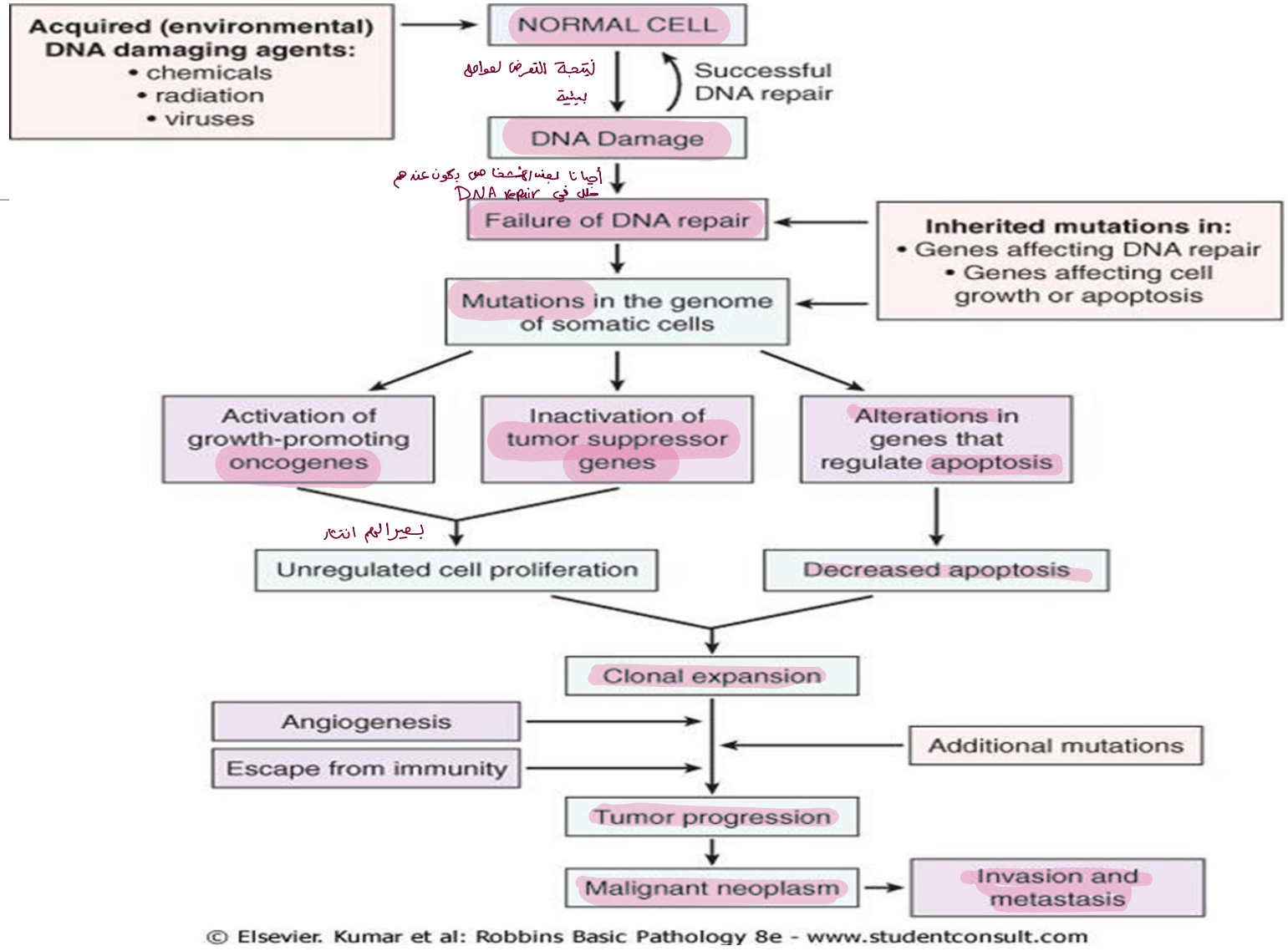
Monoclonal proliferation

كل الخلايا الموجودة في ال clon بكونوا شبه ال original cell اللي صارلها 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



Genetic Lesions in Tumors

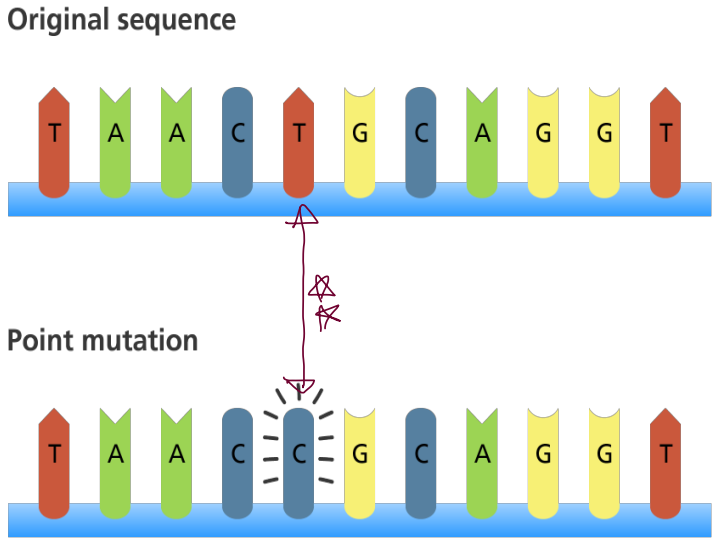
1. Point mutation:

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

يمكن هاد الجين اللي تحول يكون عنده عن tumor suppressor

e.g. RAS oncogene.

TP53, tumor suppressor gene.



2. Translocation:

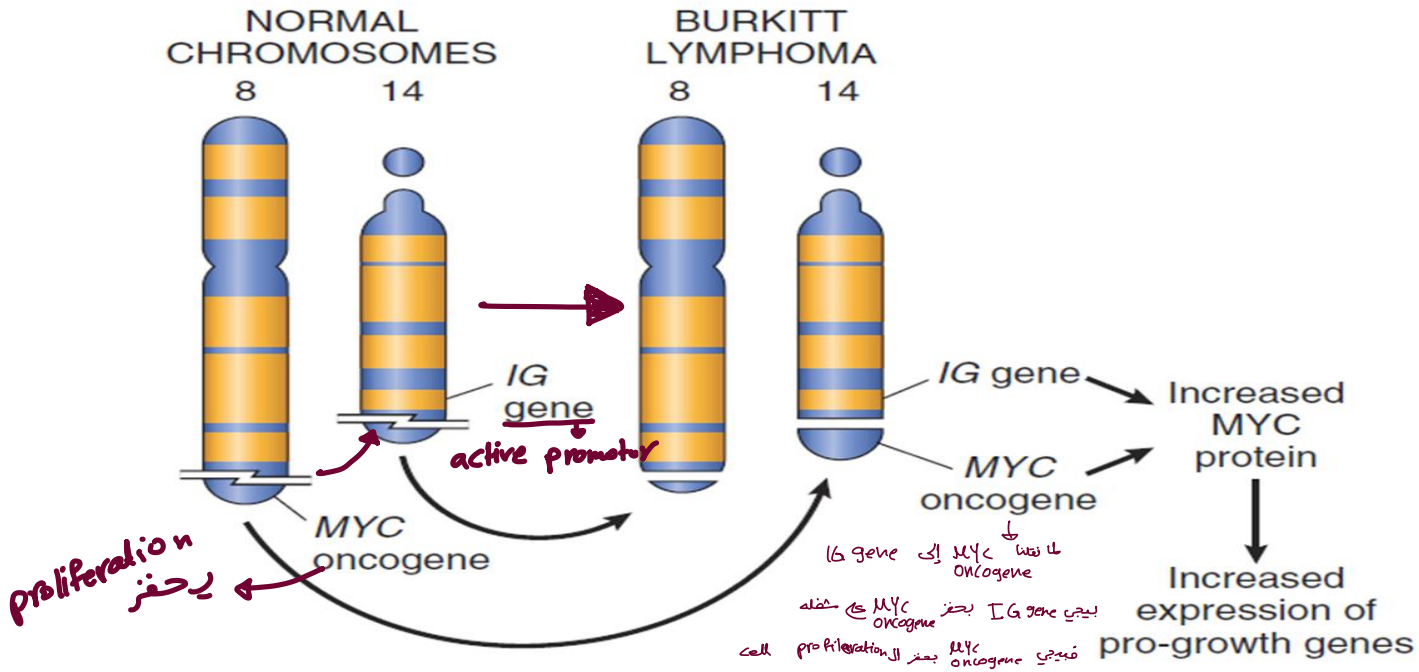
تغير أماكن بين الكروموسومات

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)**

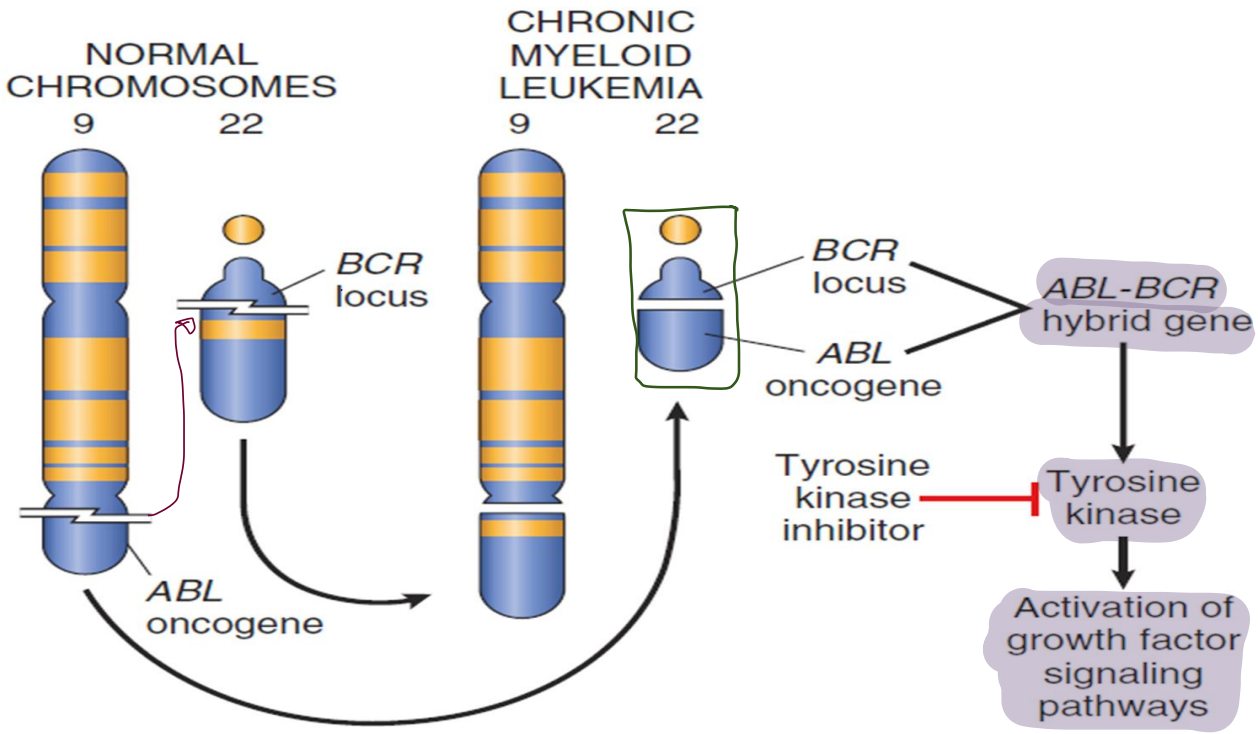
هنا صار تحول من chromosome 8 إلى chromosome 14



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

تبديل بين كرموسوم (9) و(12) بكونوا مرتبطين مع Myloid leukemia

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



بروح لعند (BCR) و بند مجو الاثنين يلي ABL oncogene

مع بعض وبنتج عنه (higher activity) و (Tyrosine kinase activity) تعمل

activation of growth factor signaling pathways

3. Chromosomal deletions:

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

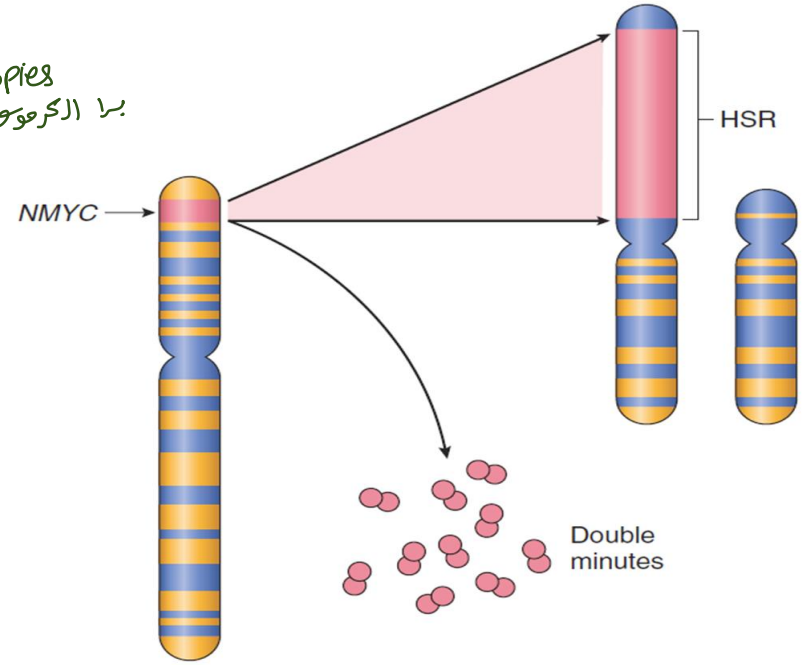
e.g. Retinoblastoma, RB gene ch13

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).

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6. Epigenetic changes:

حدث بعد ما يصير translation للبروتين بنعمل له modification فيمكن هاي التعديلات تأثر على function الـ أو تفقده الـ function

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

- Involves posttranslational **modifications of histones and DNA methylation** → يا بنوخذ أو بنعطي لـ DNA methyl group

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

وبه تالله
بالتوفيق