تفريغ بطين زعاديد

الأورام السرطانية (Tumor)

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- Connective tissue
  - benign
    - ↓
    - tissue + oma
  - malignant
    - ↓
    - origin + sarcoma
- epithelial tissue
  - Malignant
    - ↓
    - carcinoma + origin tumor
  - (oma) benign
    - Adenoma
      - ↓
      - gland
      - Lack a glandular growth pattern.
    - papilloma
      - ↓
      - projection
      - finger-like fronds
    - polyp
      - ↓
      - projection from hollow organs

oma = bengin

لهذا هيدول بنعتبرو ب oma بكونوا malignant

هام جدًا

سؤال بالإمتحان

Exceptions (these are malignant, but end with oma)

- Leukemia, Lymphoma
- Glioma → Malignant Neuron tissue
- Melanoma → Melono cell
- Mesothelioma → Mesothelium cell
- Retinoblastoma → Retinia (eye)
- Seminoma... → Testis

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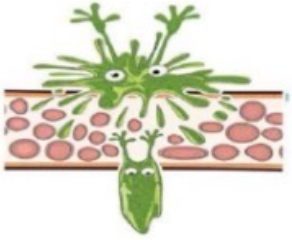
4- Metastasis:

أهم حاجة عن أي malignant



انتشار الورم لمكان بعيد

- Spread of malignant tumors to distant sites that are physically discontinuous with the primary tumor and unequivocally marks a tumor as malignant.
- Proportionate to the size and differentiation of the primary tumor
- **Most important factor in the diagnosis of malignancy** ***
- All tumors can potentially metastasize except BASAL CELL CARCINOMA (A) & most 1ry brain tumors (glioma) (B) ***

skin

كل الـ malignant tumor بعملو metastases عدا

أكيد، ما أحلاه وهو الجلد والدماغ أجزاءهم بتتحرك

- Prostatic CA ---- High in USA
- Colorectal CA ----High in USA
- Breast CA ---- High in USA
- Gastric CA ---High in Japan
- Skin CA----High in New Zealand
- Hepatocellular CA --- High in Africa & China
- Nasopharyngeal CA --- Far East
- Burkitt Lymphoma --- Africa

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ما حفظتهم اخ

- However, certain cancers occur more in children:

Acute Leukemia

Some Lymphomas

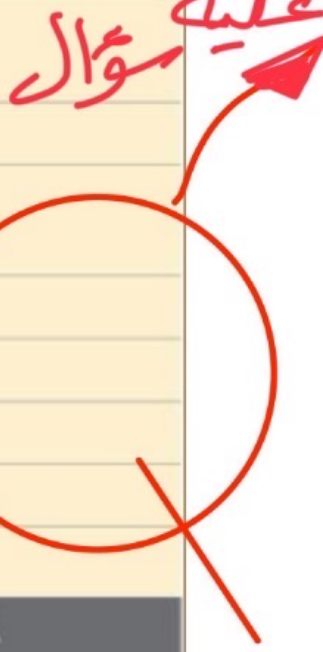
Some CNS Tumors

Blastomas → Retinoblastoma, Nephroblastoma

3. Heredity (5%-10% of cancers are familial)

Table 6.4 Inherited Predisposition to Cancer

Inherited Predisposition	Gene(s)
Autosomal Dominant Cancer Syndromes	
Retinoblastoma	*RB*
Li-Fraumeni syndrome (various tumors)	*TP53*
Melanoma	*CDKN2A*
Familial adenomatous polyposis/colon cancer	*APC*
Neurofibromatosis 1 and 2	*NF1, NF2*
Breast and ovarian tumors	*BRCA1, BRCA2*
Multiple endocrine neoplasia 1 and 2	*MEN1, RET*
Hereditary nonpolyposis colon cancer	*MSH2, MLH1, MSH6*
Nevoid basal cell carcinoma syndrome	*PTCH1*
Autosomal Recessive Syndromes of Defective DNA Repair	
Xeroderma pigmentosum	Diverse genes involved in nucleotide excision repair
Ataxia-telangiectasia	*ATM*
Bloom syndrome	*BLM*
Fanconi anemia	Diverse genes involved in repair of DNA cross-links



هذول الثلاثة اعرفوا فقط اسمهم وانهم Autosomal recessive.

Major types of chemical carcinogens:

1- **Alkylating Agents:** Direct, used in chemotherapy of cancer - may induce Leukemia.

2- **Polycyclic Hydrocarbons:** Indirect & very strong - include benzopyrene in cigarette smoke → CA Lung

3- **Aromatic Amines & Azo dyes:** Indirect -Rubber & Food Industry e.g. β-naphthylamine → Bladder CA

4- **Natural plant and microbial products:** includes Aflatoxin B1 produced by the fungus Aspergillus flavus (a mold that grows on improperly stored grains and nuts). → Hepatocellular CA.

5- **Nitrosamines:** Endogenous or food preservatives cause Gastric & Colon CA

1- HPV-Human Papilloma Virus:

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- 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.

2- EBV - Epstein Barr Virus

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- A member of the herpesvirus family.

Associated with:

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

LMP1 هذا oncogene وبدخل لك داخلها بكون عنده B lymphocyte infection بعد (EBV)
هاد الجين بحفز B lymphocyte proliferation فبيصير عدد الخلايا المصابة بالفيروس كبيرة فتتجي خلايا المناعة (T cell) وتحاول تقضي عالفيروس لكن اغلب الخلايا المصابة بتكون asymptomatic

Cancer بعملهم proliferation و epithelial cell بعد infection (EBV)

- LMP1 is expressed on epithelial cells activating cell proliferation

1. Self-sufficiency in growth signals

↳ mutation → gain function

- **Gain of function mutation in Genes coding for growth: Classified by the site of action**

- Proto-oncogenes: Normal.
- Oncogenes: Mutant/overexpressed
- oncogenes ⟹ oncoproteins (promote cell growth, even without normal growth-promoting Signals).
- They include genes coding:

1. Growth factors
2. Cell surface receptors
3. Signal transduction proteins (RAS/ABL)
4. Nuclear transcription factors
5. Cell cycle proteins
6. Inhibitors of apoptosis

activate receptors

sends signals inside cells

into the nucleus to activate the transcription of the genes

Control of Cyclins → control of cell cycle (↑ proliferation)

expression of proteins

can either → inhibit apoptosis / tumor suppressor genes

→ over expression of proto-oncogenes

- Selective or nonselective inhibition.
  - work on a specific one

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- Examples: p21, p27 & p57 inhibit all CDKs while INK4 Inhibitors (p15, p16, p18 & p19) inhibit CDK4 & CDK6.

(non-selective الباقي)

- The tumor suppressor protein p53 controls expression of p21.

Mode of activation & action:

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- p53 senses DNA damage or other stresses through various sensors, like protein kinases e.g. Ataxia telangiectasia mutated (ATM) protein → phosphorylates p53 → prevent degradation by MDM2
- p53 released from MDM2 & activated with longer half-life →
  - Transcription of CDKI gene *CDKN1A* (p21) → cell cycle arrest at G1 (Quiescence) --- Result: more time for repair --- Normal (inactive)

OR

→ GADD45 / PCNA → for repair

- If repair fails ----Senescence (permanent cell cycle arrest) or Apoptosis(p53 is a positive regulator of apoptosis (*BAX* & *PUMA*). (Bak
- **OR** *Fixed mutation* --- ***NEOPLASIA***

2.Insensitivity to growth-inhibitory signals

- **Disruption in Cancer Suppressor Genes**

- Growth inhibitory pathway by:

RB gene: Regulate cell cycle

TP53 gene: Regulate cycle & apoptosis

TGF- β: Block GF signals → Anti proliferative action

APC gene: regulates β –catenin

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APC + β-catenin + E-Cadherin → **Destruction Complex**

WNT → activates cell proliferation

Angiogenic factors:

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- Controlled by HYPOXIA which induces angiogenic factors by tumor cells ➡ Hypoxia-Inducible Factor **(HIF-1α)**→**VEGF** ⟶ stimulates the proliferation of endothelial cells and guides the growth of new vessels toward the tumor.

HIF-1α

تعني Hypoxia-Inducible Factor 1 Alpha، وهو بروتين يلعب دورًا رئيسيًا في استجابة الخلايا لل (hypoxia)

VEGF : vascular endothelial GF

- Gain-of-function mutations in *RAS* or *MYC* upregulate the production of VEGF:↑ VEGF

- Proteases from tumor or stroma can release the basic angiogenic **FGF** stored in the ECM

fibroblast GF

❖ Anti- angiogenesis:

Thrombospondin:"

يشير إلى الدم وعمليات التخثر "Thrombo"

ال "Spondin" يأتي من الكلمة اليونانية "Spondylos" وتعني فقرة، وتشير إلى القدرة على التأثير على العمود الفقري أو التماثل النسيجي.-

1:يشير إلى الرقم 1 ويُستخدم لتمييز هذا النوع من البروتينات عن غيرها في عائلة Thrombospondin.

1. **Thrombospondin1**(TSP-1) induced by P53

- Thus, loss of p53 in tumor cells provides a more permissive environment for angiogenesis

2. **VHL** protein destroys HIF-1 α → No VEGF بالسلايد قادم

- Germline mutation of VHL → von Hippel-Lindau Syndrome → hereditary renal CA, CNS hemangiomas.

benign tumor of blood vessels,

in syndrome : inactivate VHL ➡

hemorrhagic ➡ due to build vessels

3. Angiogenesis inhibitors:

Angiostatin, Endostatin, Vasculostatin from stromal cells in ECM.

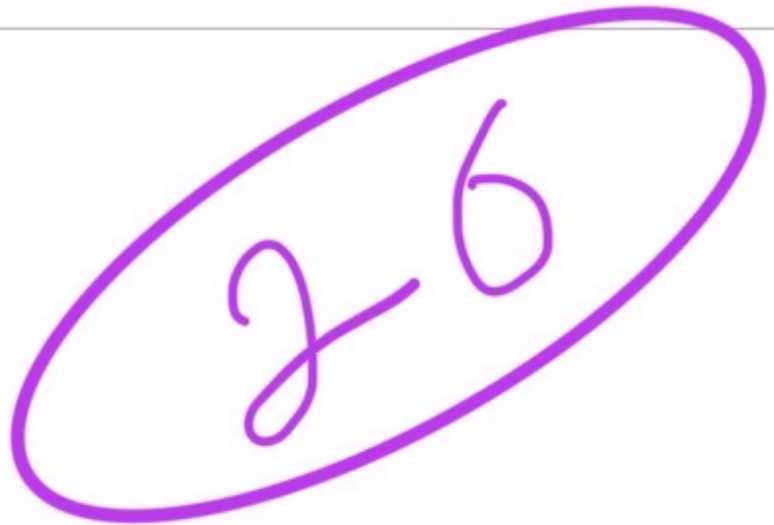
↑ vascular density = Poor prognosis

Statin" : يشير إلى مثبط

TUMOR IMMUNITY: Host Defense Against Tumors:

Host defenses

- CTLs (CD8+ T-Cells)
- NK cells
- T helper cells
- Macrophages
- Humoral (Antibodies)



Genomic Instability as an Enabler of Malignancy:

2-6

- Individuals born with inherited **defects in DNA repair genes** are at greatly **increased risk for the development of cancer.**

- Includes:

- **Mismatch repair** repair errors in the pairing of nucleotides during cell division (HNPCC – Hereditary Nonpolyposis Colonic Ca. syndrome):
- **Nucleotide excision repair** **Defective in Xeroderma Pigmentosum:**
- **Recombination repair**

DNA Repair by Homologous Recombination:

Bloom syndrome, ataxia-telangiectasia, and Fanconi anemia

BRCA-1 & BRCA-2: **50% of familial breast cancers & ovarian CA**

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Examples of paraneoplastic syndromes:

Commonest 3 syndromes reported:

1. Cushing syndrome

2. Thrombotic endocarditis (caused by hypercoagulability of blood.

3. Hypercalcemia.

exposure to high levels of cortisol, a hormone produced by the adrenal glands

- **Note: Hypercalcemia due to skeletal metastasis is not a paraneoplastic syndrome!**

ولو كانت ليست بسبب metastases بتكون...Para

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- **Hepatic & Renal CA** → **Polycythemia** (Erythropoietin)

هي حالة تتسم بارتفاع في عدد خلايا الدم الحمراء في الدم.لوجود ورم يفرز هرمون الأريثروبويتين الذي يحفز إنتاج الخلايا الحمراء

Poly- (بولي): يعني "كثير" أو "كثافة".
-cythemia (سيثيميا): يعني "خلايا الدم".
Erythro- (إريثرو): يعني "اللون الأحمر" ويشير إلى خلايا الدم الحمراء.
-poietin (-بويتين): يعني "المنشئ" أو "المنتج".

- **Advanced Cancers** → Nonbacterial thrombotic endocarditis.

- **Fibrosarcoma** → **Hypoglycemia** (Insulin-like substance)

اعرفوا شو نوع السرطان المرتبط بكل عرض

Types of tumor markers

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1- Hormones:

- Human Chorionic Gonadotrophic Hormone (β-HCG)
  - Elevated levels are seen in Pregnancy & Gestational Trophoblastic Disease (Choriocarcinoma)
  - Also high in some testicular tumors

2- Oncofetal Antigens: اعرفناه من قبل

- Carcinoembryonic Antigen (CEA):
  - In fetal tissue & some malignancies – Colorectal CA
- Alpha-Fetoprotein (AFP):
  - Cirrhosis: Elevated
  - Hepatocellular carcinoma: Extremely high

3- Isoenzymes:

- Prostatic Acid Phosphatase (PAP)

↑ levels are seen in prostatic CA

4- Specific Proteins:

- Immunoglobulins secreted in Multiple Myeloma
- Prostate-specific antigen (PSA): Present in epithelium of prostatic ducts.
  * ↑ Prostatic hyperplasia
  * ↑↑↑ in Prostatic CA

5- Several mucins

- MUC-1 in breast CA
- CA-125 in ovarian CA
- CA-19.9 in colon ca


كتائب
القسام
الناطق العسكري
Aymantoon