النادي الطبي MC

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لا تنسونا من دعائكم بالتوفيق

تفريغ عود

Radiation, hypoxia, free radicals and chemical agents as chemotherapy produce DNA damage → Activation of p53

Activation off p21 (if the damage is small) → Inhibition of CDKs (Important to move from one phase to another) → So the damage can be repaired and then move to the next phase

activate the apoptotic pathway through activation of the apoptotic gene i.e. Bax gene (if the damage is significant)

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آخر جزئية من المحاضرة في موضوع cancer عن الفيروس لما يدخل الخلية ويسبب حاطوا افهموه واحفظوه صح

G1 CHECKPOINT: DNA DAMAGE

- In normal cells, both **Bax** and **Bcl-2** are present in balance **(the ratio of apoptosis inhibitors to apoptosis stimulators makes death decision)**.

Induction of apoptosis ⟶ ↑Bax

Inhibition of apoptosis ⟶ ↑Bcl-2

I. Point mutation in proto-oncogene

تفريغ محمود

Ras protein is a class of G protein and is found in all nucleated cells

RAS Proto-oncogene → (Mutation) → RAS Oncogene

RAS Proto-oncogene ↓ Normal RAS protein (GTP to GDP+p)

RAS Oncogene ↓ Mutated RAS protein (Decrease GTPase activity) → doesn't have a strong GTPase activity as the normal RAS protein (it has very low efficacy for GTPase) accumulation of GTP → uncontrolled growth

↓ GTP will increase in the cell

RAS protooncogene ⟵ RAS protein ⟵ يكون مرتبط بشكل طبيعي بـ(guanin GTP) وعندما تكون مرتبطة بـ GTP تكون on ولكنها لا تبقى هكذا دائماً بسبب امتلاكها GTPase activity تقوم بتحويل GTP → GDP (بعد إنهاء عملها مثلاً: عندما ينفصل receptor عن GF)

(GTP: active form, GDP: inactive form) → off رح تصير

(on ⟸ مرتبط بـGTP, off ⟸ مرتبط بـGDP)

(on: تنقل الsignal من خارج الخلية إلى داخلها)

mutation

RAS oncogene (with reduced GTPase activity) ⟵ Mutated RAS protein ⟵ ما رح يقدر يحول GTP → GDP عند إنها العمل (عند انفصال GF عن receptor) بالتالي رح يستمر بنقل signals وكأنه GF رابط بـreceptor حتى بعد ما انفصل. → رح يظل on

This mutation is observed in about 15% of cancers.

In summary: mutated Ras **remains in the active form** (Ras GTP complex) as this point mutation dramatically **reduces the GTPase activity** of the Ras proteins.

- So mutated Ras acts as a growth promoting signal even in the absence of growth factors.

II. Chromosomal Translocations

1. Placing the **normal proto-oncogene** near the promotor (stimulate transcription) of another gene with subsequent overexpression of this proto-oncogene.

e.g. c-MYC in lymphoid tumors (Burkitt lymphoma).

هذا النوع الدكتورة عادته بالمحاضرة جاي والي بعدها كتير

MYC is **located on chromosome 8**

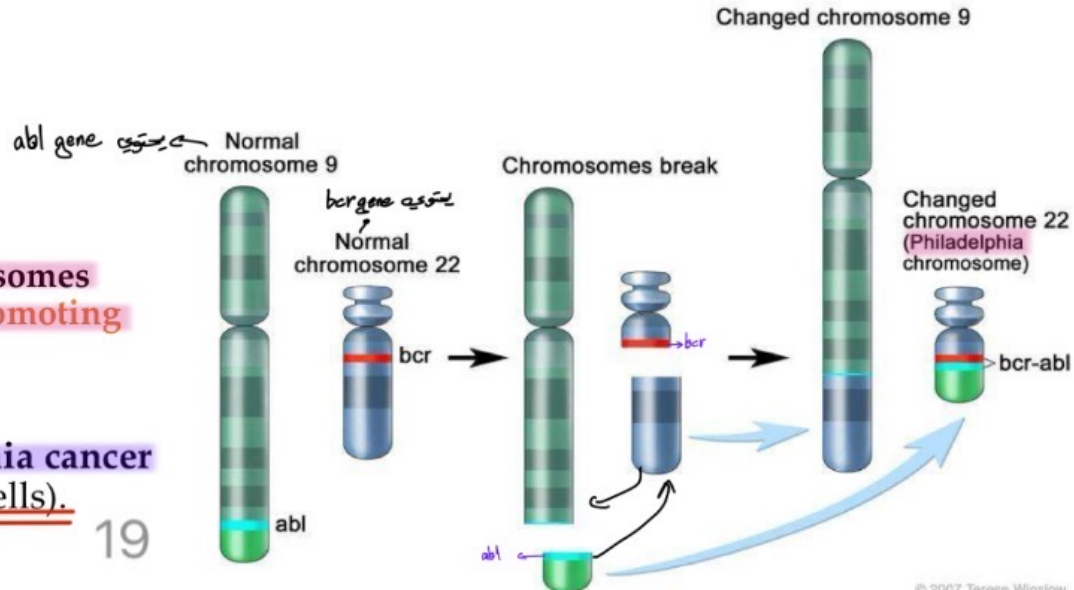
الدكتورة قالت هو نه مهم

A tyrosine kinase signaling protein that is "always on", causing the cell to divide uncontrollably.

يحصل على

2. Placing **normal unaltered genes** from **two different chromosomes** to **recombine** and form hybrid genes that **encode growth promoting** (chimeric) **proteins.**
   - e.g. Philadelphia chromosome.

specific **genetic abnormality in chromosome 22 of leukemia cancer cells** (particularly chronic myelogenous leukemia (CML) cells).



2. Tumour suppressor genes

Retinoblastoma (Rb) gene

- Under normal conditions the retinoblastoma protein oscillates between the hypo/unphosphorylated (active) and phosphorylated (inactive) forms.
  - i.e. there will be a brake followed by an acceleration of the cell cycle.

- If the Rb gene is deleted or mutated → the molecular brakes on the cell cycle are released
  - **the cell proliferation is uncontrolled**, and cancer will result (Rb gene is a protective gene against cancer development).

- The main tumors in which inactivation of pRb is an important cause include **tumors of the retina** (**retinoblastoma**)-a rare childhood tumor of the retina- , **lung cancers**, adenocarcinoma of prostate and tumors of bone and connective tissues.

in Normal cells → P53 binds with MDMZ

DNA damage

P53 separates from MDMZ
(activation of P53)

DNA damage عند حدوث
activation of ATM and ATR يحدث

phosphorylation of P53 يعملوا
P53 و MDMZ لحتى نمنع إعادة ارتباط

has a very short half life,

- Located on chromosome 17.

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P53 act as transcription factor → P21 gene → P21 → inhibition of CDK4 or CDK6

E2F transcription factor يتم انتاجها من طريق

inhibition of produce cyclinE_CDK2 complex

+

↓

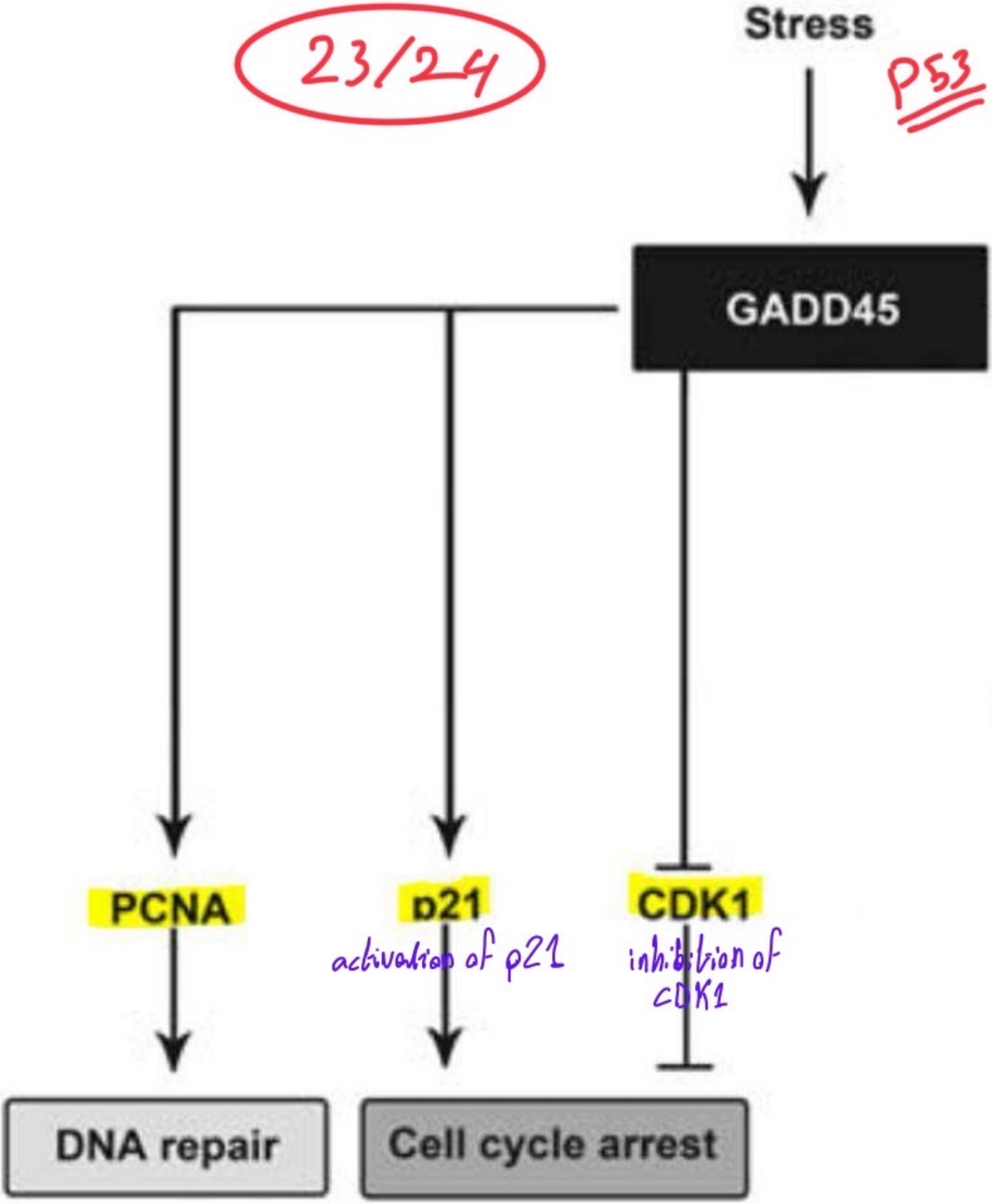
can't phosphorylation of RB

P53 Gene

- Has been described as the guardian of the genome (the **policeman** of the cell)
  → **prevents** the propagation of genetically damaged cells. → Why؟ شوف العودة فوق damage قوة نشر

mutation or deletion of two allels يعني لازم لحتى P53 نفقد وظيفته

- To lose functions as a tumor suppressor gene, the two alleles of p53 gene on the two loci of chromosome 17 must be affected by mutation or deletion.


23/24
Stress
P53
GADD45
PCNA
p21
activation of p21
CDK1
inhibition of CDK1
DNA repair
Cell cycle arrest

Li–Fraumeni syndrome

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- Is a rare, autosomal dominant, hereditary disorder that predisposes carriers to cancer development
- The syndrome is linked to mutations of the p53 tumor suppressor gene
- Li–Fraumeni syndrome is characterized by **early onset of cancer**, a wide variety of types of cancers
- The classical LFS malignancies: sarcoma, cancers of the breast, brain, and adrenal glands—comprise about 80% of all cancers that occur in this syndrome

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- **INK4** Inhibitors are p15, p16, p18, and p19, specifically inhibits CDK4 and CDK6 activity

- **CIP/KIP** Inhibitors are consisting of p21, p27, and p57, inhibits other cyclin-CDK complexes

Nondisjunction is the failure of homologous chromosomes (in meiosis I) or sister chromatids to separate properly (meiosis II and mitosis) during cell division.

If either of these gametes unites with another during fertilization, the result is aneuploidy

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in females ←

- **D. XO (Monosomy X)** also called **Turner's syndrome**: 1:5000 live births; **the only viable monosomy in humans** -women with Turner's have only 45 chromosomes!!! XO individuals are genetically female, however, they do not mature sexually during puberty and are sterile. Short stature and normal intelligence.

Approximately 99% of pregnancies affected with Turner syndrome are miscarried.

٩٩٪ من الحوامل
أصلاً حيهيي معهم
abortion
حالات قليله اللي رح
تشوفهم عايشين

Chromosome structural changes

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Deletions

In humans, **cri-du-chat syndrome**, also known as chromosome 5p deletion syndrome, is a rare genetic disorder due to a missing part (deletion) of the short arm of chromosome 5. The symptoms of this deletion, include severe mental retardation and an abnormally small head.

Duplications

Fragile X syndrome is a genetic disorder which occurs as a result of a **mutation of the fragile x mental retardation 1 (FMR1) gene on the X chromosome**, most commonly an increase in the number of CGG trinucleotide repeats in the 5' untranslated region of FMR1

CAUSE
Trinuoleotide repeat in the FMR-1 gene on the X chromosone

APPEARANCE
Portion of chromosone X appears fragile and about to break

* ملخص صعيب :-
بسبب الـ Constriction هو الـ methylation
وسبب الـ methylation انه وغريا العادة اكام اللي
هيه الـ Cytosin كيف وغرناها صارت طفرة زادت CGG
وين صارت بالـ Long arm للكروموسوم X
شو صار ؟ بطل يطلع البروتين صار Mental reterdation
والـ Females ← Sterile

Inversions

هش كيتر مهم ماعليه أسئلة كيتر
ومعناه انه تاخذ قطعة من الكروموسوم وتقلبها

Translocations

تبديل جينات بين كروموسومين ومنه أشكاله :

* مثال الـ philadelphia Chromosomes
اللي لهمة بصيروا بين كروموسوم ٩ و ٢٢

Acute promyelocytic leukemia **(APL)** is caused by translocation. بين كروموسوم 15 و 17

حسب المشكلة هل هيه نتيجة خلل بالميتوكندريا نفسها
ولا خلل ببروتينات تانية بتحتاجهم الميتوكندريا لكن انتاجهم من النواة

- Mitochondrial diseases are inherited from 2 types of genetic material:

- Mitochondrial DNA, which are passed on from the mother to all children

- Nuclear DNA, which is passed on from both parents. Therefore ,mitochondrial disease can be inherited as:

Heteroplasmy : *the presence of more than one type of organellar genome within a cell or individual. It is an important factor in considering the severity of mitochondrial diseases.*


محمد رسو الله
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