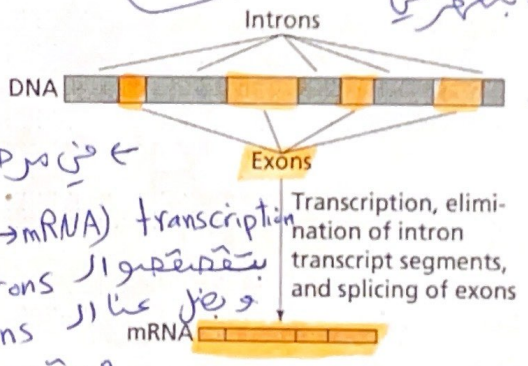
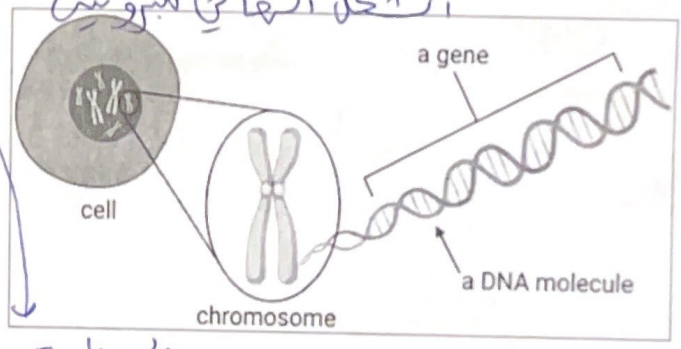
GENES

- Genes are regions of DNA that control a discrete heritable characteristic, usually corresponding to a single protein or RNA.
- In eukaryotic cells, genes are composed of coding regions, called exons, separated by non-coding regions, called introns.





MUTATIONS

- A mutation is a change in the DNA sequence of an organism.
- Mutations can result from errors in DNA replication during cell division (1), exposure to mutagens (2) or a viral infection (3).
- Germline mutations (that occur in eggs and sperm) can be passed on to offspring, while somatic mutations (that occur in body cells) are not passed on.

* هل توّرث ال mutations ؟ صح صارت على اي مستوى , من حال صارت على مستوى germline cells يلي هم ال egg و sperm , ماتكون البويضة المخصّبة وبصير إلها انقسام متساوي وتكاثر وتكون كل خلايا الجسم وبعدين تصير mutation وتتحول إلى أعضاء الجسم , فإذا صارت الـ mutation بعدين deffrientiation مستوى germline cells راح تقدر تنتقل الأولاد , لكن لو صارت الـ mutation على مستوى body cells مثلاً أخذوا معين أو تعرّض لـ radiation مثلاً مبارة ذرة مثلاً في خلايا العدة (مش كل خلايا الجسم) هاي الـ mutation لا تورّث إلى الأولاد

MUTATIONS – Mutagenic Agents

- Mutations can be **spontaneous** or **induced** by mutagenic agents.
- The main mutagenic agents are:
  1. Chemical agents,
  2. Physical agents and
  3. Viruses

base pairs بدخشو حالهم بين molecules هاي ال : interlayer ②
وممكن تعمل errors ومشاكل بالتالي mRNA ثم البروتين الناتج
عن translation ممكن يتغير

CHEMICAL AGENTS

بتفاعلو chemically مع ال DNA strand

- Chemical mutagens agents are chemical compounds that cause local changes in the nucleotide sequence. They are classified according to their mode of action into:

1. Base analogues or tautomer of nitrogenous bases: these are isomers of nitrogenous bases that differ in the position of the functional group. They are incorporated into DNA during replication in place of the corresponding base. For example, 5-bromouracil instead of thymine or 2-aminopurine instead of adenine.
2. Interlayer agents: These are flat molecules that insert between two base pairs of DNAs, separating them from each other. During replication, they can cause insertions or deletions in DNA, leading to mutations by changing the reading pattern. Examples: acridine (acridine orange), benzopyrene, ethidium bromide and proflavine.
3. Modification of nitrogenous bases: they remove or add groups to nitrogenous bases. For example, nitrous acid causes the removal of the amino group from bases, and mustard gas adds methyl or ethyl groups to bases.

base pairs بدخشو حالهم بين ←
← هدول ممكن نلاقيهم بالجو ، بالأكل ، بالأدوية by product

① base analogues ← بشبه الستركشر تاع nitrogenous bases
وهو ال DNA عم يصير له replication بدل م يجي يركب
مثلاً بجي اشي بشبهو مثل adenin يجي 2-aminopurine (ممكن
الخلية تقدر تعالجه repair وممكن لا)
← طبعاً الانزيمات المسؤولة عن repair موجودة بكل خلايا
جسمنا لانه كل الخلايا تتجدد ويصير إلها replication

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PHYSICAL AGENTS

- Physical agents that cause mutations are radiation, both ionising and non-ionising, and heat.

① ② ③

1. Ionising radiation, such as X-rays, gamma rays, alpha radiation, and beta radiation, cause the loss of electrons from some DNA atoms in the form of highly reactive ions. They can lead to base modifications and can also cause structural chromosomal alterations, such as chromosome breaks and translocations. Non-ionising radiation, mainly ultraviolet radiation, causes point mutations.
2. Thermal fluctuations, such as exposure to temperatures above 37°C, cause point mutations in DNA, such as the loss of purine bases (depurination), or the loss of amino groups from bases (deamination).

طاقة عالية
في أماكن صغيرة ومحددة

① هدول ال ionising radiation ما بخترقو الغلاف الجوي بسبب طبقة الأوزون ، طيب عين بتعرض الهم ؟ بالمستشفيات ، تصوير الأشعة
② هدول ال ionising طاقتهم عالية بعملو damage أكتر من ال nonionising
أماكن التضيع وهيك
(مثل UV) ،

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تابع

③ هيا الـ ionising هو بضرب في مكان معين وبسبب طاقته العالية بوخد من جزيء الـ DNA إلكترونات فبنكسر وبصير مثل جذور حرّة (reactive species) وممكن هاي الجذور الحرّة يصيرو يها جمو أماكن أخرى في جزيء DNA, فممكن الـ effect تاعهم

VIRUSES

ينتشر ويصير يأثر على أماكن مجاورة للـ DNA strand كمان يصير mutation على مستوى الكروموسوم

- Viruses are also mutagenic agents. In humans, infection with several viruses has been linked to the development of some types of cancer. They are referred to as ongenic viruses or oncoviruses. There are six major families of oncogenic viruses. Five of these families are DNA viruses (Polyomavirus, Adenovirus, Hepatitis B, Herpesvirus-EBV and Papillomavirus); while the sixth family (Retroviruses) have RNA as their genetic material.

- Retroviruses or RNA viruses can insert their genome at a place close to an oncogene, resulting in a change in its function.
- DNA viruses promote cancer by producing proteins that hijack and inactivate tumor suppressor genes like p53 and retinoblastoma protein, leading to uncontrolled cell growth, genomic instability, and the potential for tumor formation.

← عنا جينات في هلايا الانسان مثل p53 و هيا هدول وظيفتهم انه يمنعو السرطان (by Controling mutations) هيا الـ DNA viruses, بتنتج بروتينات تعمل hijack على هاي الجينات (يعني تثبط أو تمنع شغلها)

TYPES OF MUTATIONS

- There are many ways to classify the types of mutations, such as by how they are produced, what they affect, the effect they produce, or by the amount of material affected.

① According to their production method (Spontaneous vs. Induced by a mutagenic agent) ← له علاقة بوظائف الخلية وال

② According to which genetic material they affect (Structural chromosomal mutations vs. Gene mutations)

* Structural chromosomal mutations: these affect fragments of the chromosomes. Translocations, duplications, inversions, insertions and deletions can occur.
* Gene mutations; may or may not cause a change in the reading pattern of genes. They can be substitutions, insertions, or deletions.
  - Insertions, or deletions generally cause a change in the reading frame of the gene, resulting in the generation of a different polypeptide chain from the insertion point.
  - The substitutions are replacements of one nucleotide for another, which can lead to a change in the amino acid they encode. The substitutions that do not result in amino acid changes are called synonymous substitutions.

← مرضيتهم أكبر للتغير لانه بتحذف اشي كامل deletions/ insertion, اما الـ substitution في فرصة يتم تبديله بإشي مكافئ

TYPES OF MUTATIONS

3. According to their effect

- Not all nucleotide sequence changes lead to changes in the amino acid sequence or function of the proteins encoded by the affected genes.

1. Silent Mutations – the nucleotide sequence change does not result in an amino acid change in the protein.
2. Missense mutations – cause a change of one amino acid to another.
3. nonsense mutations – cause a change from a coding codon to a stop codon.

initiation
elongation
termination →

* nonsense mutations ← translation صبا بعملية ال بصير

كيف بتصير؟
لازم يكون في نهاية mRNA
stop codone بحكي للرايبوسوم
mutation صارلنا / فإذا
انه خلص لهون
سبب تحول
Coding codon to stop codone
(بيطل يعمل ال function اللي المفروض)

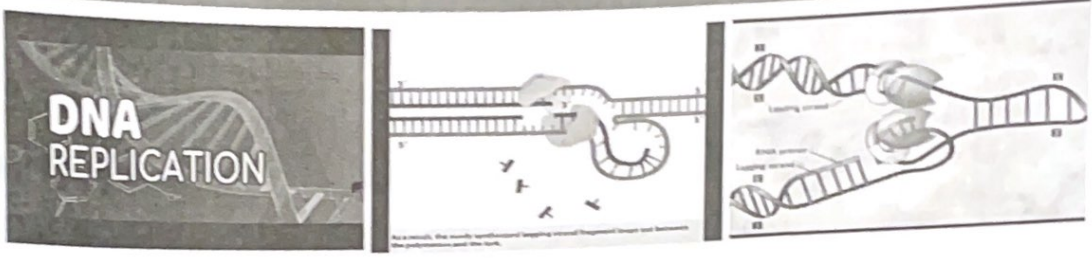
TYPES OF MUTATIONS

4. According to the affected cells

- Mutations that are located only in the DNA of somatic cells are called somatic mutations. Somatic mutations usually occur in tumour cells and may be associated with tumour aggressiveness or response to a particular therapy.
- A mutation can also originate randomly in germline cells of an individual. It can therefore be passed on to descendants. Thus, this inherited mutation will be present in all cells of the individual's body. These types of mutations are called germline mutations. Germline mutations can predispose a carrier individual to the development of cancer.

هاد الموضوع ما إله ريكورد
بس أكيد شرحته

DNA Replication



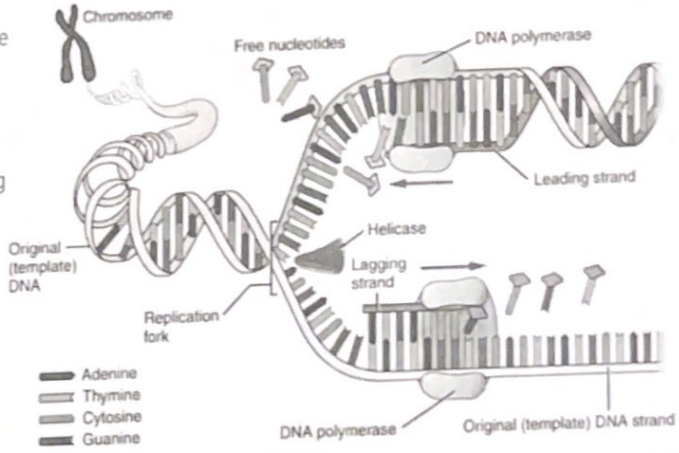
https://www.youtube.com/watch?v=TEQMeP9GG6M&t=40s

https://youtu.be/WCIiyI4_cM

https://youtu.be/2_-jSoSaaTA

DNA Replication

- **Replication Process**: The duplication of the DNA molecule before cell division
- Carried out by a series of enzymes
- **Directionality**: Replication is always in the 5' to 3' direction, with leading and lagging strand synthesis.
- because the two strands are anti-parallel (they run in opposite directions) the two new strands are synthesised in opposite directions.
- The point where the two strands are split is called the *replication fork*.



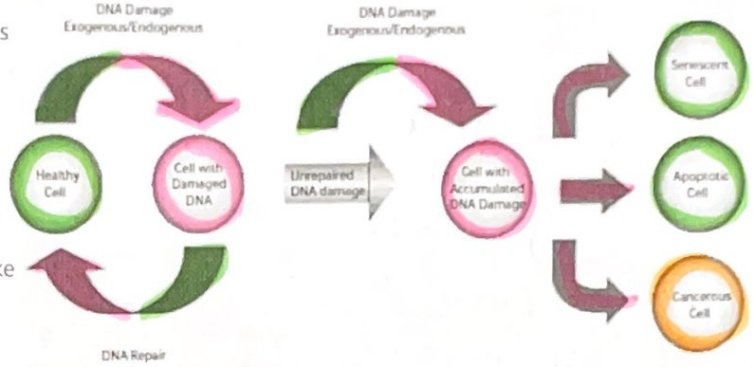
عشان هيك هاد الموضوع مهم لانه باعد في تصنيع أدوية مناسبة، مثلاً الخلايا السرطانية بكون جزء من شغال repair system وجزء لا، فأحنا لازم نعرف شو الشغال عشان نعمل إلهم targeting بالأدوية (بنحاول بالأدوية نخلي الخلية توصل لل(apoptosis) (يعني فوق مهي أحلا كنه ما جزء خربان من بدي آخرب كمان الجزء الشغال منه)

repair system

DNA Repair

Dr Ala Abuhammad, PhD

- DNA is constantly **exposed to damage** (UV light, chemicals, replication errors). Repair is essential to maintain genome stability.
- To compensate for the degree and types of DNA damage that occur, cells have developed multiple repair processes.
- Cells may have evolved to proceed into apoptosis or senescence if overwhelming damage occurs rather than expend energy to effectively repair the damage.
- The rate at which a cell is able to make repairs is contingent on factors including cell type and cell age.



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Oct-24

مكينا انه الخلية استجابة لهاي الأخطاء المتكررة لأسباب سواء من داخل أو خارج الخلية، فكينا mechanism فالخلية لتصليح هاي الأخطاء (ليس طبيعي انها تصير)، لكن وين بتصير المشكلة لما تصير الأخطاء هاي أكثر من قدرة الخلية على تصليحها وينتج عنا تراكم accumlation للـ errors وبالتالي بتأثر على الـ genetic material للخلية وبالتالي وظيفتها وغالباً بتصير Cancer cells أو بتعمل الخلية apoptosis (cell death)

DNA Repair

① تصليح الأخطاء
② تكوين خلايا سرطانية
③ في حال كان damage كتير كبير ومكلف للخلية انها تعمل تصليح تلجأ الى apoptosis

The Nobel Prize in Chemistry 2015

Tomas Lindahl, **Paul Modrich** and **Aziz Sancar** were awarded the Nobel Prize in Chemistry 2015 for having mapped and explained how the cell repairs its DNA and safeguards the genetic information.

The Nobel Prize in Chemistry 2015 was awarded jointly to Tomas Lindahl, Paul Modrich and Aziz Sancar "for mechanistic studies of DNA repair"

The 2015 Nobel Prize in Chemistry The Discovery of Essential Mechanisms that Repair DNA Damage - PubMed (nih.gov)

The Nobel Prize in Chemistry 2015 - Popular information - NobelPrize.org

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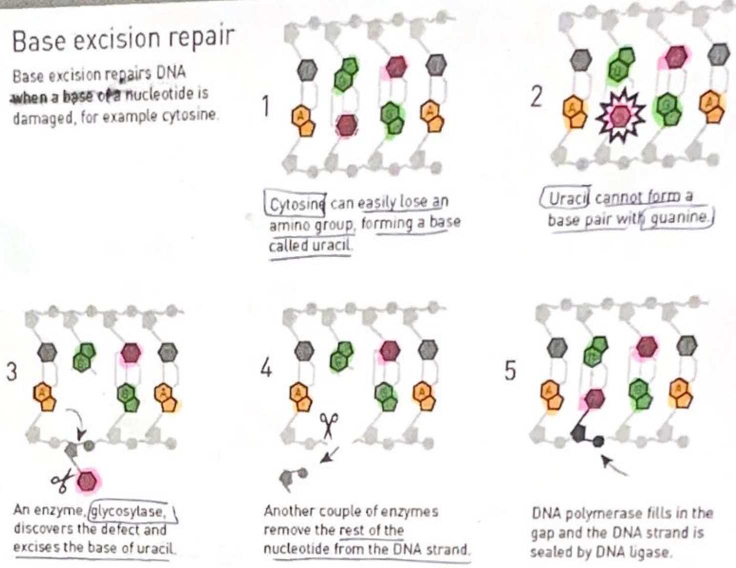
DNA Repair Mechanisms

1. Base Excision Repair (BER):

- Repairs small, non-helix-distorting base lesions.
- Damaged base removal and replacement.



Base excision repair
Base excision repairs DNA when a base of a nucleotide is damaged, for example cytosine.
1
Cytosine can easily lose an amino group, forming a base called uracil.
2
Uracil cannot form a base pair with guanine.
3
An enzyme, glycosylase, discovers the defect and excises the base of uracil.
4
Another couple of enzymes remove the rest of the nucleotide from the DNA strand.
5
DNA polymerase fills in the gap and the DNA strand is sealed by DNA ligase.

← الخلية لما تشوف انه عندها defect على مستوى neutrogenous base مثلاً Cytosin (بفقد amino acid ويتحول إلى uracil)، فوراً هاي ال mech تشتغل لتعادل الخطأ، بيجي إنزيم اسمه glycosylase بكتشف الخطأ وبروح بقص ال uracil، وبظل عنا بقايا ال nucleotide (phosphate + ribose) تاني وبشيلهم بيجي انزيم وبعدين

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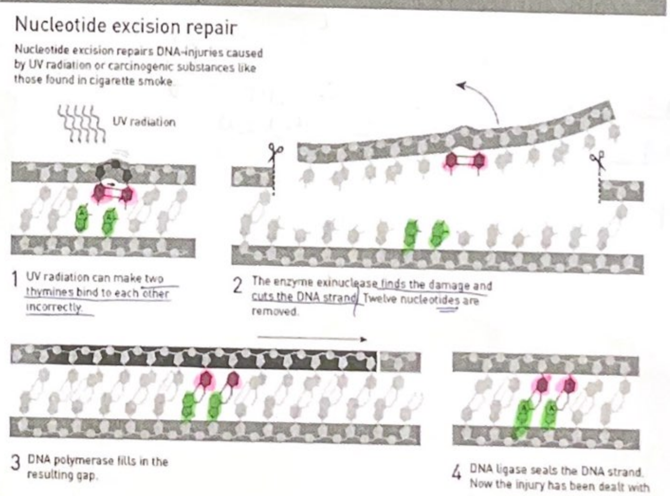
DNA Repair Mechanisms

2. Nucleotide Excision Repair (NER):

- Removes bulky lesions, such as UV-induced thymine dimers.
- Example: Xeroderma pigmentosum (a genetic disorder caused by NER defects).

لازم بتقص 12 nuclotide

بتحسسو كثير من أشعة الشمس



Nucleotide excision repair
Nucleotide excision repairs DNA-injuries caused by UV radiation or carcinogenic substances like those found in cigarette smoke.
UV radiation
1 UV radiation can make two thymines bind to each other incorrectly.
2 The enzyme exinuclease finds the damage and cuts the DNA strand. Twelve nucleotides are removed.
3 DNA polymerase fills in the resulting gap.
4 DNA ligase seals the DNA strand. Now the injury has been dealt with

* هاي ال mechanism بتصير لما ال error يلي بلزمه هاد ال repair يكون بسبب تعرض الخلايا (DNA) إلى UV radiation that induce interaction between two thymine groups → وهاد الشي مومقبول بروح انزيم اسمه exinuclease بكتشف الخطأ وبقص 12 nucleotide (بغض النظر عن يلي جنب الخطأ)

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3. Mismatch Repair (MMR):

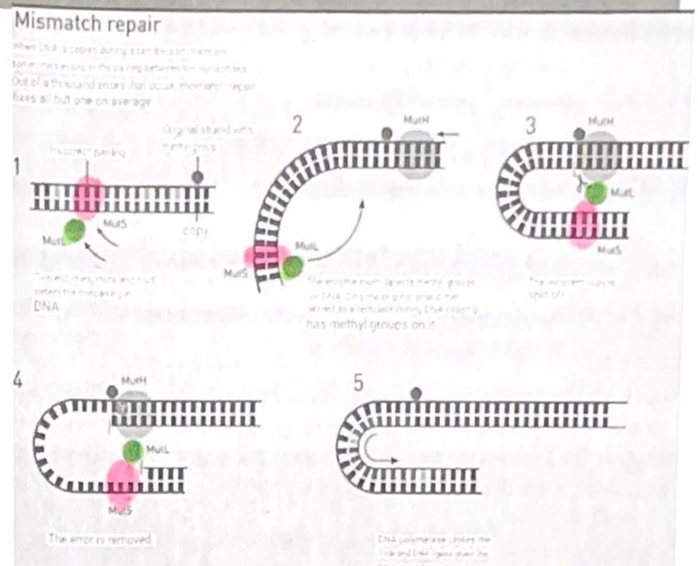
- Fixes replication errors, such as misincorporated bases.
- Example: Mismatch repair defects lead to Lynch syndrome (hereditary cancer risk).

(العلاقة بالقولون)

← يكون الـ two neoclotide يلي مقابلين بعض mismatch ; يعني مثلاً يكون Cytosin مقابل adenine ,

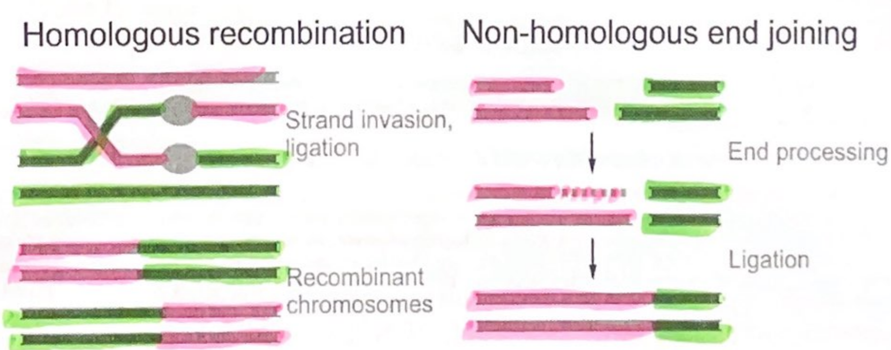
بتروح الخلية بتعمل لا Cutting region around mismatch

بس لازم يكون عنا refrence point يلي هي الـ methyl group قريبة من الـ mismatch يلي صار، بتروح الانزيم بتقص من عند methyl لغاية ما يوصل لل mismatch ثم



4. Homologous Recombination (HR) and Non-Homologous End Joining (NHEJ):

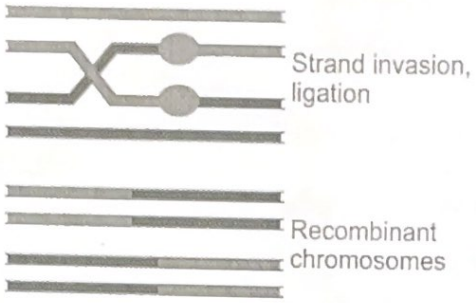
- Repair of double-strand breaks.
- HR uses a sister chromatid for repair; NHEJ directly ligates the broken ends.



← بشتغلو على الـ errors يلي بتسبب breakage كامل أو جزئي لل DNA strand

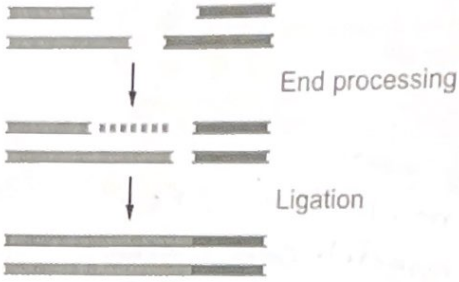
DNA Repair Mechanisms –(HR) and (NHEJ):

Homologous recombination



- Uses a sister chromatid (a similar or identical DNA strand) as a template to accurately repair the break.
- This method is precise because it copies the correct sequence from the undamaged DNA strand.

Non-homologous end joining



- **Directly joins the broken ends** of DNA without using a template.
- Faster but can be more **error-prone** because it sometimes leads to small insertions or deletions at the repair site.

غالباً هاي الأخطاء بتصير خلال replication, breakage بتستعين الـ strand اللي بعيد منها اللي (identical or similar) sister strand as a template عشان تصلح الـ breakage اللي صار، لذلك نوعاً ما عملية التصحيح بتكون دقيقة لأنه في مرجع

(هذه هي سولفتة كيش هون بس ما فهمت اشي)

Defects In The Repair Systems Cause Cancer

- Besides base excision repair, nucleotide excision repair, and mismatch repair, there are several other mechanisms that maintain our DNA.
- Every day, they fix thousands of occurrences of DNA damage caused by the sun, cigarette smoke or other genotoxic substances; they continuously counteract spontaneous alterations to DNA and, for each cell division, mismatch repair corrects some thousand mismatches.
- Our genome would collapse without these repair mechanisms. If just one component fails, the genetic information changes rapidly and the risk of cancer increases.
- Congenital damage to the nucleotide excision repair process causes the disease *xeroderma pigmentosum;* individuals who suffer from this disease are extremely sensitive to UV radiation and develop skin cancer after exposure to the sun.
- Defects in DNA mismatch repair **increase the risk of developing hereditary** colon cancer, for instance.
- In fact, in many forms of cancer, one or more of these repair systems have been entirely or partially switched off. This makes the cancer cells' DNA unstable, which is one reason why cancer cells often mutate and become resistant to chemotherapy. At the same time, these sick cells are even more dependent on the repair systems that are still functioning; without these, their DNA will become too damaged and the cells will die. Researchers are attempting to utilise this weakness in the development of new cancer drugs. Inhibiting a remaining repair system allows them to slow down or completely stop the growth of the cancer.
- One example of a pharmaceutical that inhibits a repair system in cancer cells is ***olaparib (PARP inhibitor).***

DNA Repair – Pharmaceutical Applications

- Significance in Drug Development
  - **Cancer Treatment**: Many cancer therapies (e.g., radiation, chemotherapy) work by inducing DNA damage. Understanding repair mechanisms allows for the development of drugs that inhibit these processes in cancer cells.
    - Example: **PARP Inhibitors** for BRCA-mutated cancers (affecting DNA repair via homologous recombination).
  - **Targeting DNA Repair Pathways**:
    - Drugs that block repair pathways (e.g., Mismatch Repair) increase the efficacy of treatments that induce DNA damage.
    - Example: Tumor cells with defective MMR are more sensitive to immunotherapy.

Personalized Medicine And DNA Repair

- **Pharmacogenomics**: Tailoring treatments based on a patient's DNA repair capacity.
- Pharmacogenomics involves designing treatments based on an individual's genetic makeup, particularly their ability to repair DNA damage. Some people may have mutations in genes involved in DNA repair, such as BRCA1 or BRCA2, which affect how their cells respond to DNA damage.
- **BRCA1 and BRCA2** are breast cancer genes that play a key role in repairing damaged DNA, specifically through **Homologous Recombination (HR)**. These genes help prevent mutations that could lead to cancer.
- Genetic mutations in DNA repair genes (like BRCA1/BRCA2) inform the selection of therapies, particularly in oncology.
- For example, mutations in BRCA1/BRCA2 are associated with defective HR repair, making those patients more vulnerable to certain cancers (e.g., breast or ovarian cancer).Treatments like PARP (Poly (ADP-ribose) Polymerase) inhibitors are designed for patients with these mutations because they block alternative repair mechanisms, forcing cancer cells to die when they cannot repair their DNA. Understanding whether a patient's cancer involves defective HR or reliance on NHEJ helps oncologists choose therapies that specifically exploit these weaknesses in cancer cells.

على الرغم من انهم عندهم repair mechanism ضعيف
من غيرهم الا انهم
قادرين يلاقوا طرق عشان يكونوا more aggressive و استجابتهم للـ
chemotherapy أقل من غيرهم، بنعمل targeting لـ repair system (لانها أصلا بتعاني منه)