



Genetics

***Subject* : Genetics**

***Lec no* : 20**

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وَقُلْ رَبِّ زِدْنِي عِلْمًا

* يوجد أكثر من طريقة لـ repair لأنه يوجد أكثر من شكل لـ damage

في هذه mechanism أنا بطلع
ad damage اللي يكون صيني بشكل
عكس chemical modification

deamination of cytosine to uracil

Base-Excision Repair

• Every cell has a class of enzymes called **DNA glycosylases** that recognize particularly common DNA lesions and remove the affected base by cleaving the **N-glycosyl bond**.

• Lesions such as the products of cytosine and adenine deamination.

DNA glycosylase -
يعتبر (تصرف) مكات
cleavage of glycosidic bond
الربطة بين sugar phosphat and abnormal bases
backbone

• **First step** involves only the removal of the base rather than an entire nucleotide.

apurinic or apyrimidinic site (AB site) (abasic site) فتح

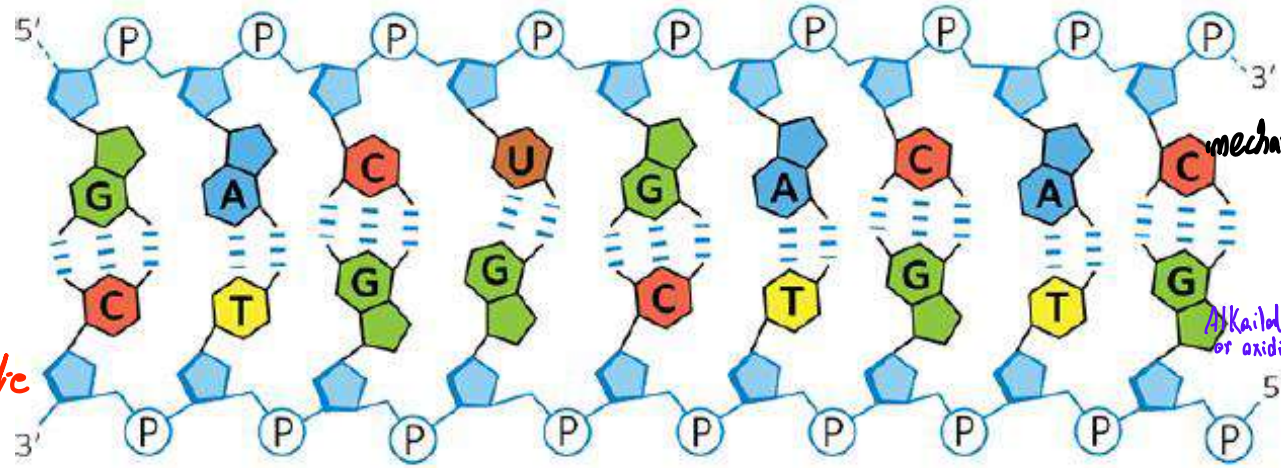
• The cleavage creates an **apurinic or apyrimidinic site** in the DNA, commonly referred to as an AP site or abasic site.

lesion specific لـ DNA glycosylase يكون

• Each DNA glycosylase is generally **specific** for one type of lesion.

deamination of
 guanine to xanthine ← DNA glycosylase
 adenine to hypoxanthine ← DNA glycosylase
 cytosine to uracil ← DNA glycosylase

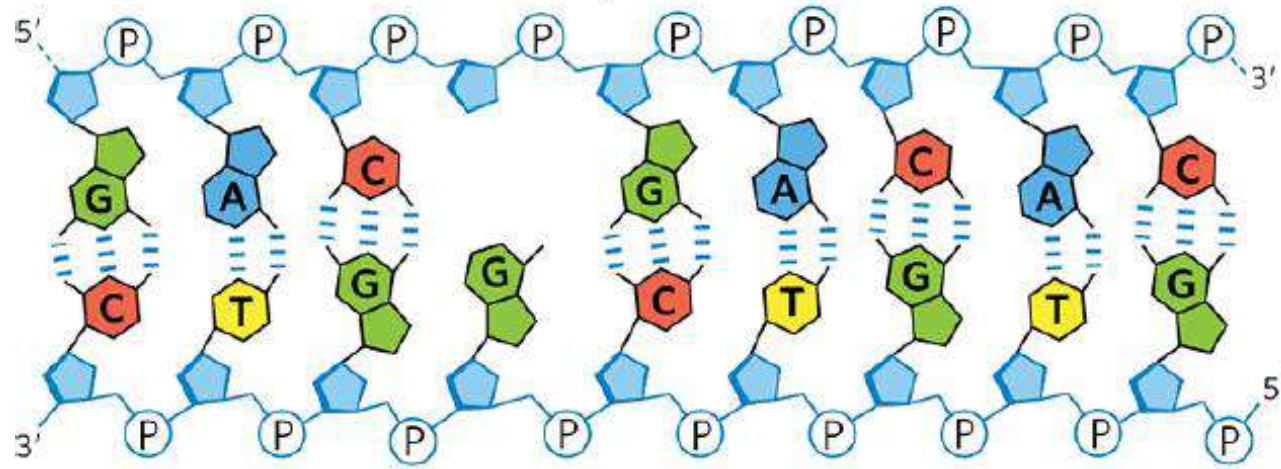
DNA glycosylase will cleavage the glycosidic bond between uracil base and sugar phosphate backbone.



Base-excision repair

Hydrolysis of the glycosidic bond
 لانه انا قاعدتين بشي base في mechanism
 وهذه mechanism تصلي على single base
 تكون chemically modified
 الحماض تكون Alkylated, deaminated or oxidised.

DNA glycosylase (uracil glycosylase) → U ① First step remove the abnormal uracil base



Base-Excision Repair

The second step:

- Once an AP site has been formed by a DNA glycosylase, another type of enzyme must repair it.

abnormal bases إزالة nucleotides من sequence بعد

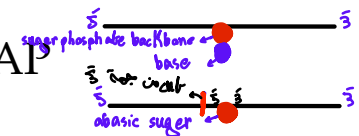
- The deoxyribose 5'-phosphate left behind is removed and replaced with a new nucleotide.

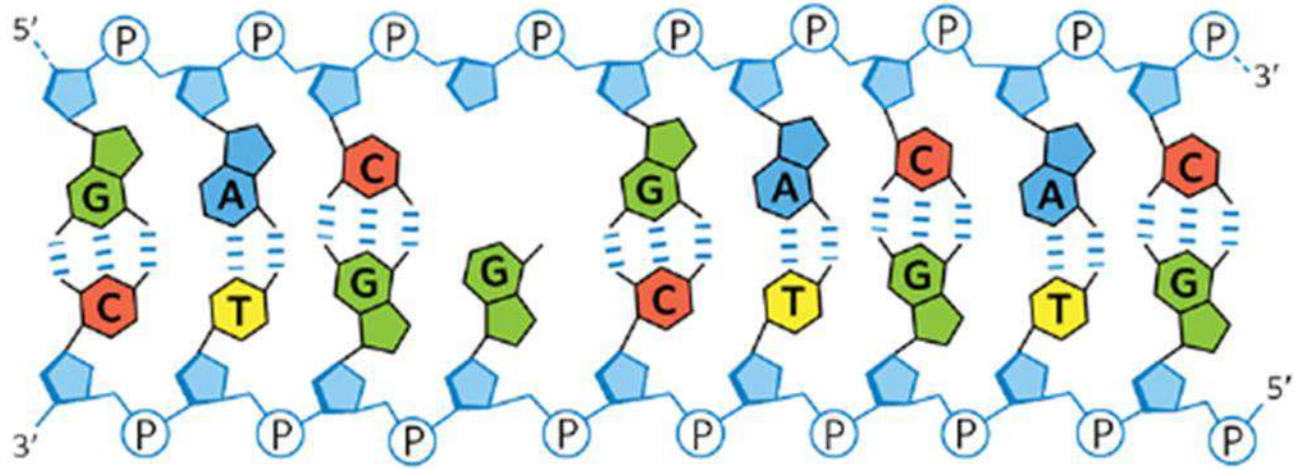
- This process begins with one of the AP endonucleases, enzymes that cut the DNA strand containing the AP site.

bases sequence إلى مشهور من bases

cut DNA on the 5' side of abasic sugar. sugar phosphate backbone base cut create abasic sugar

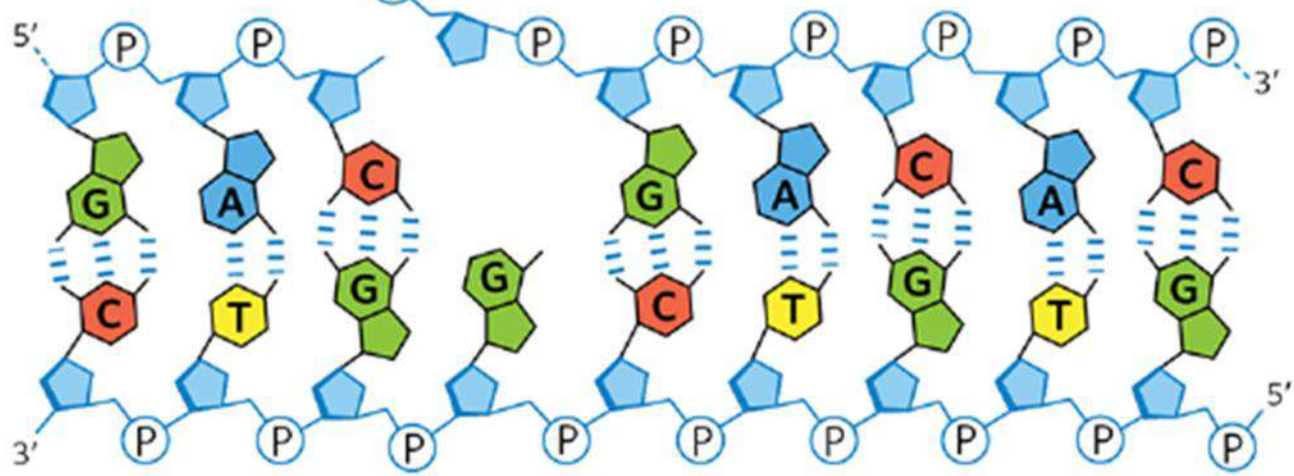
- The position of the incision relative to the AP site (5' or 3' to the site) depends on the type of AP endonuclease.





5' of abasic sugar not cut \rightarrow 5'

AP endonuclease 2



Base-Excision Repair

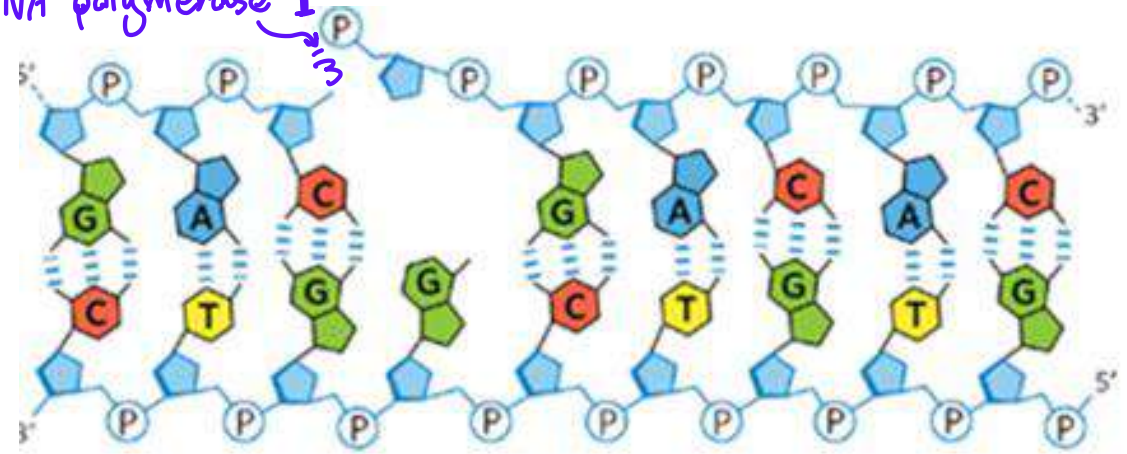
The third step:

DNA polymerase I initiates repair synthesis from the free 3' hydroxyl at the nick, removing (with its 5' → 3' exonuclease activity) and replacing a portion of the damaged strand.

of adjacent nucleotide

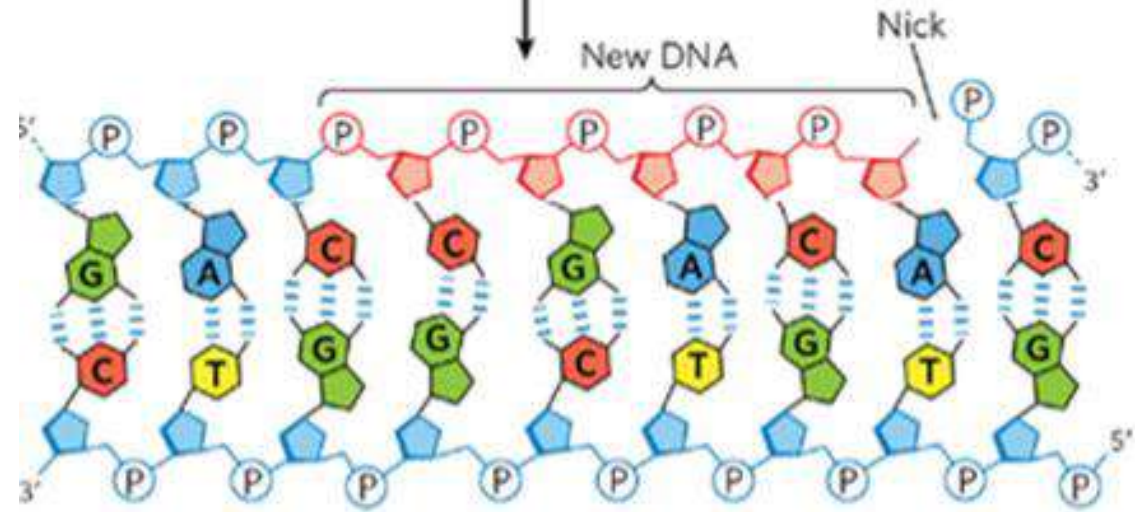
بجيت انه كان رح يمشي جزء من normal nucleotides بالإضافة الى
deoxyribose 5-phosphate

DNA polymerase I



DNA polymerase I → NTPs → Deoxyribose phosphate + dNMPs

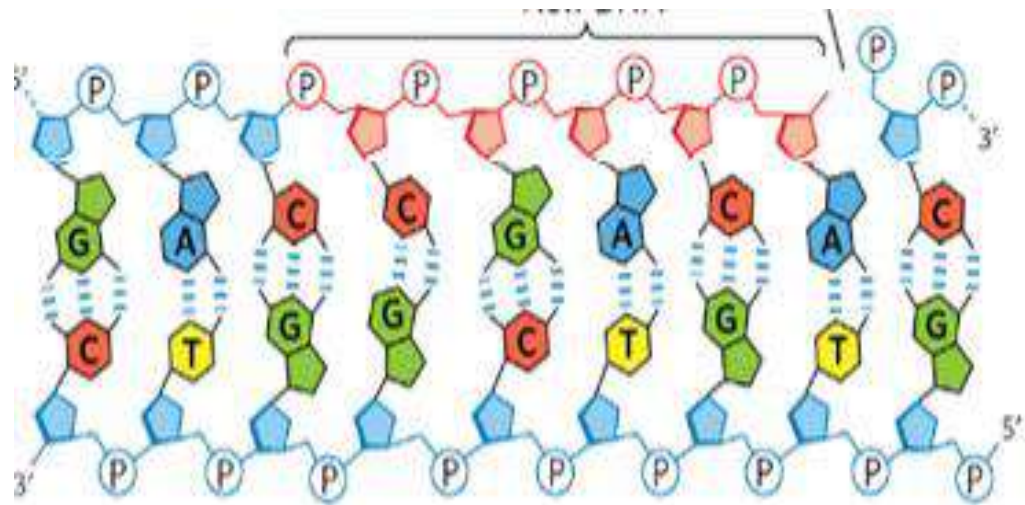
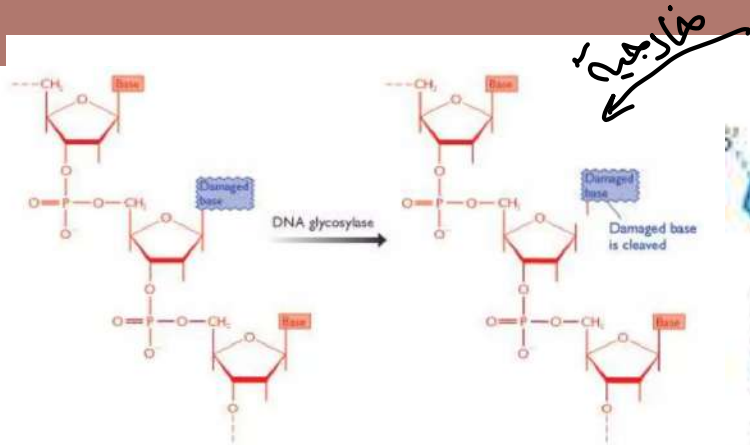
3 → Nucleotides triphosphate.



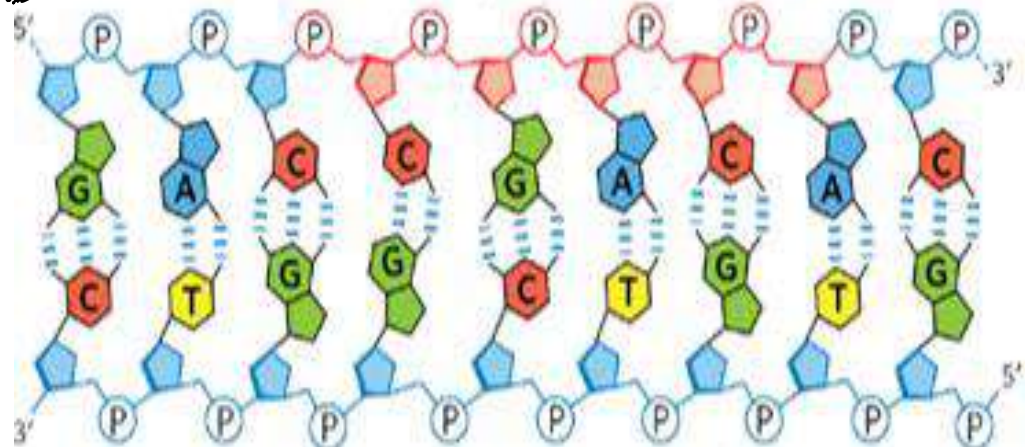
Base-Excision Repair

The fourth step:

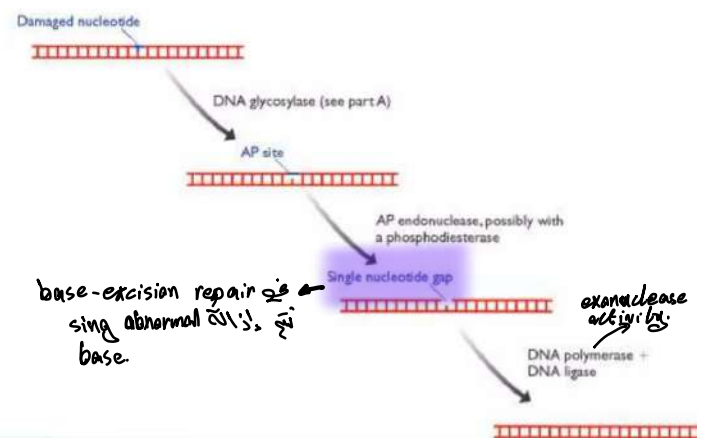
- The nick remaining after DNA polymerase I has dissociated is sealed by DNA ligase.



DNA ligase ④



(B) Outline of the pathway



Handwritten: base-excision repair of sing abnormal nucleotide base.

Handwritten: exonuclease activity

مراجعة

Base Excision Repair and Nucleotide Excision Repair are the two major pathways for repairing DNA damage

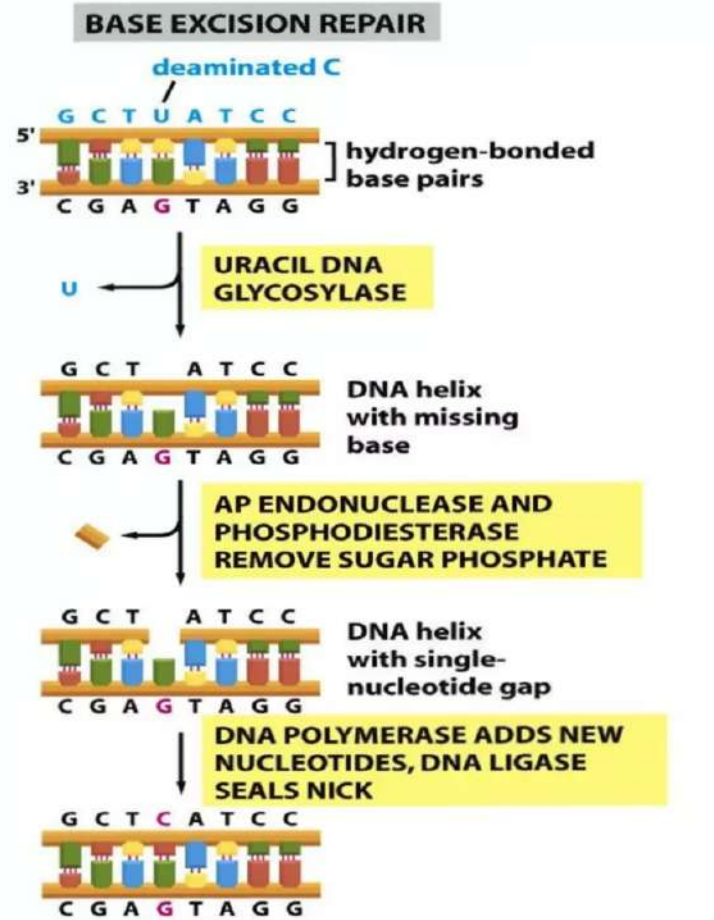


Figure 5-48a Molecular Biology of the Cell 5/e (© Garland Science 2008)

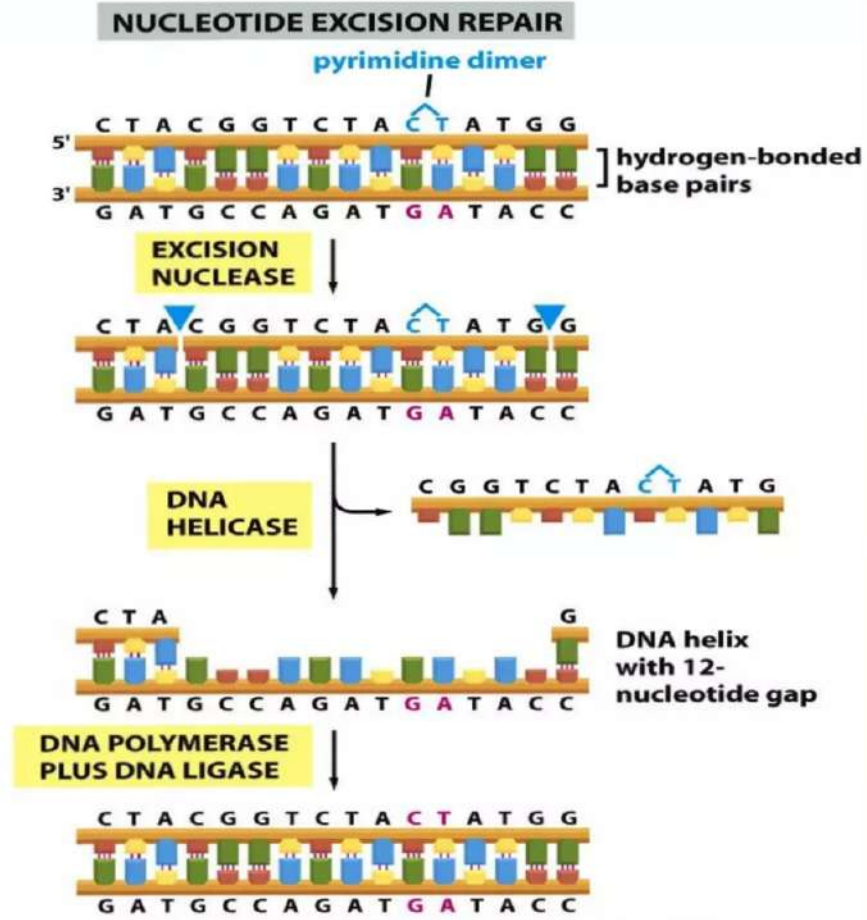


Figure 5-48b Molecular Biology of the Cell 5/e (© Garland Science 2008)

one base's chemical modification من نتيجة damage في حالة In Base-excision repair mechanism → removal of one base occurs.
dimers نتيجة UV radiation من نتيجة damage في حالة In nucleotide-excision repair mechanism → removal of multiple nucleotides occurs.

Nucleotide-Excision Repair

- DNA lesions that cause large distortions in the helical structure of DNA generally are repaired by the **nucleotide-excision system**; a repair pathway critical to the survival of all free-living organisms.
- This mechanism is used to replace several damaged bases, up to 30 bases.

eukaryotic and prokaryotic ← غير مهمات لانهم يختلفوا بيت
عدد Nucleotides في الـ fragment الناتجة
و specific side of excision

Nucleotide-Excision Repair

- In nucleotide-excision repair, a multisubunit enzyme (excinuclease) hydrolyzes **two phosphodiester bonds**, one on either side of the distortion caused by the lesion.
- In humans and other eukaryotes, the enzyme system hydrolyzes **the sixth phosphodiester bond on the 3' side** and the **twenty-second phosphodiester bond on the 5' side**, producing a fragment of 27 to 29 nucleotides.
- The DNA segment — of 13 nucleotides or 29 nucleotides — **is removed with the aid of a helicase.**

hydrolysis of two phosphodiester bonds → release of fragment
لـ الناتجة من

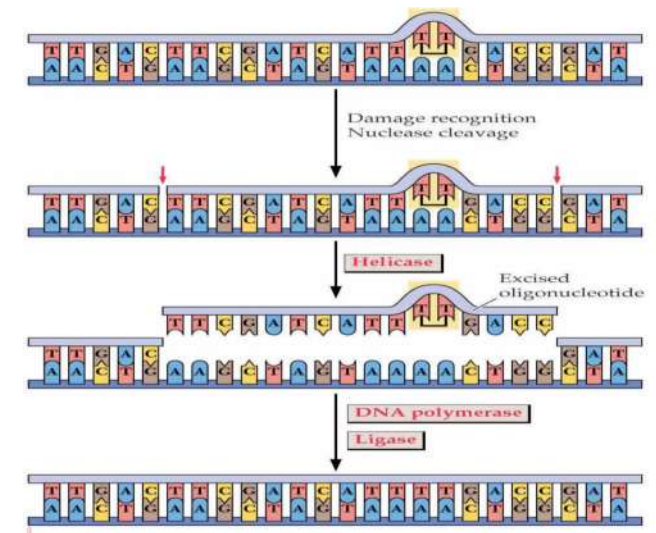
Nucleotide-Excision Repair

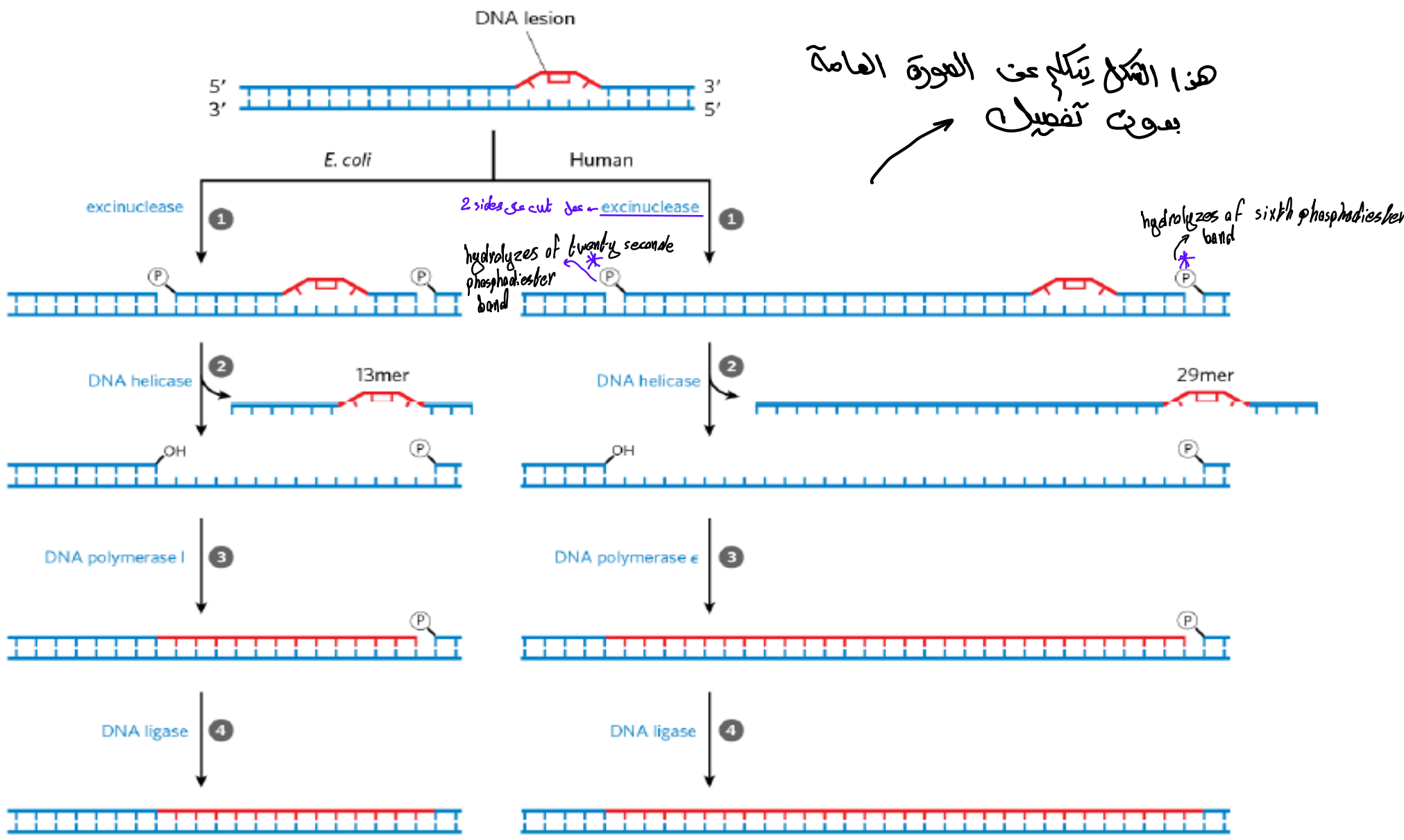
- Following the dual incision, the excised oligonucleotides are released from the duplex and the resulting gap is filled — by DNA polymerase I in *E. coli* and DNA polymerase ϵ in humans.
- DNA ligase seals the nick.

by excinuclease

by helicase

by → DNA polymerase I (in human)
by → DNA polymerase ϵ (in *E. coli*)





هذا الشكل يتكلم عن التورق العامة
 بدون تفصيل

2 sides cut — excinuclease
 hydrolyzes of twenty seconds
 phosphodiester bond

hydrolyzes of six phosphodiester
 bond

Nucleotide-Excision Repair

الناتج عن طريق UV radiation

recognise the DNA damage

The key enzymatic complex is the ABC excinuclease, which has three protein components, (UvrA, UvrB, and UvrC)

Ultraviolet light → repair

UV light damage

من غير مفتوح

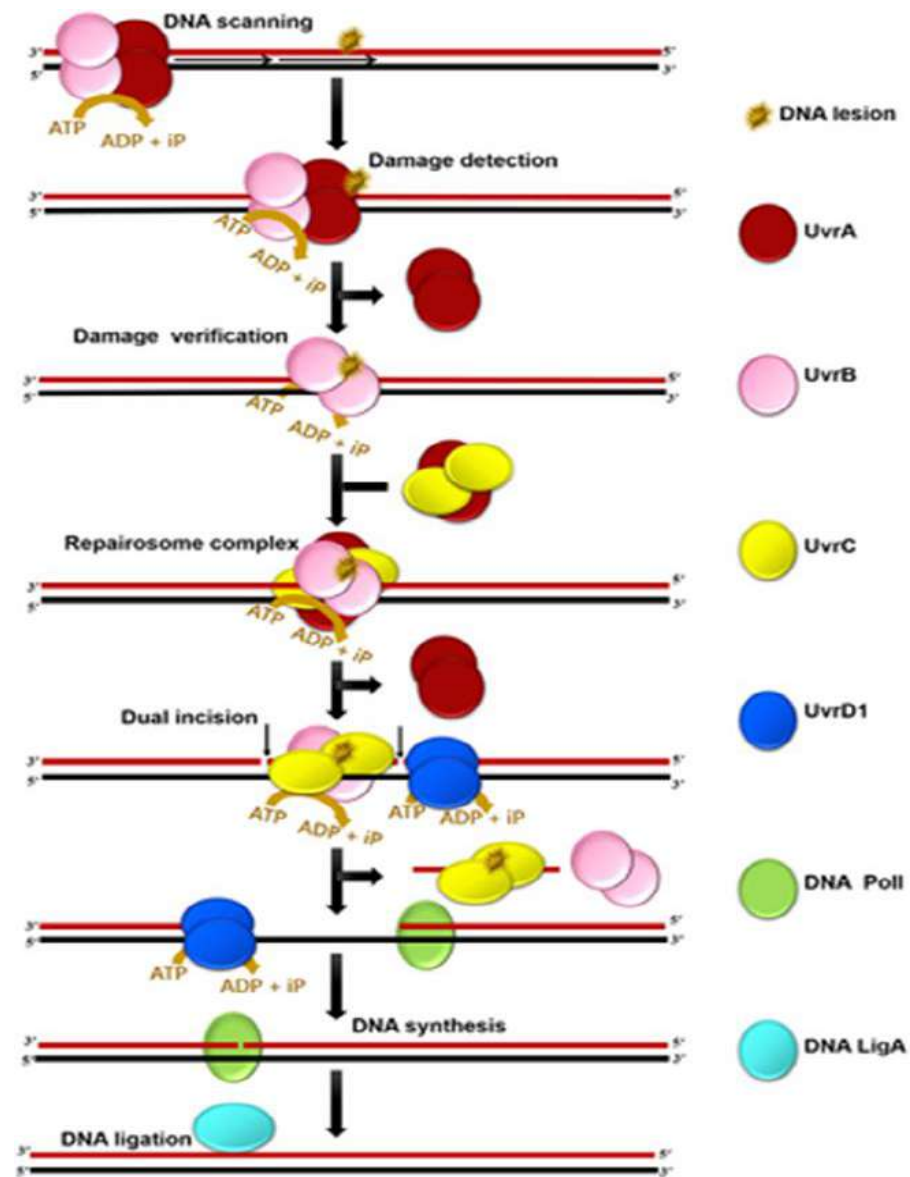
هذه البروتينات تعمل على إصلاح ناتج عن UV light و الأجاب اخرى

- Uvr stands for ultraviolet light repair of pyrimidine dimers and can be used to repair other types of damage (exposure to cigarette smoke).

The term “excinuclease” is used to describe the unique capacity of this enzyme complex to catalyze two specific endonucleolytic cleavages, distinguishing this activity from that of standard endonucleases.

يشي على DNA وسهل scan وعندما يجد lesion يرتبط عنده

1. The dimeric UvrA protein (an ATPase) scans the DNA and binds to the site of a lesion.
فهي روايات يتحركه انا UvrB. يكون مرتبط مع UvrA اثنان ما يجمع scan وروايات اخرى يتحركه انه يرتبط بـ UvrA بعد ما يرتبط بـ lesion
2. A UvrB protein can bind to UvrA either before or after an encounter with the lesion.
3. At the lesion, the UvrA dimer dissociates, leaving a tight UvrB-DNA complex.
4. UvrC protein then binds to UvrB, and UvrB makes an incision at the fifth phosphodiester bond on the 3' side of the lesion.
5. This is followed by a UvrC-mediated incision at the eighth phosphodiester bond on the 5' side.
6. The resulting fragment, consisting of 12 to 13 nucleotides, is removed by UvrD helicase.
7. The short gap thus created is filled in by DNA polymerase I and DNA ligase.

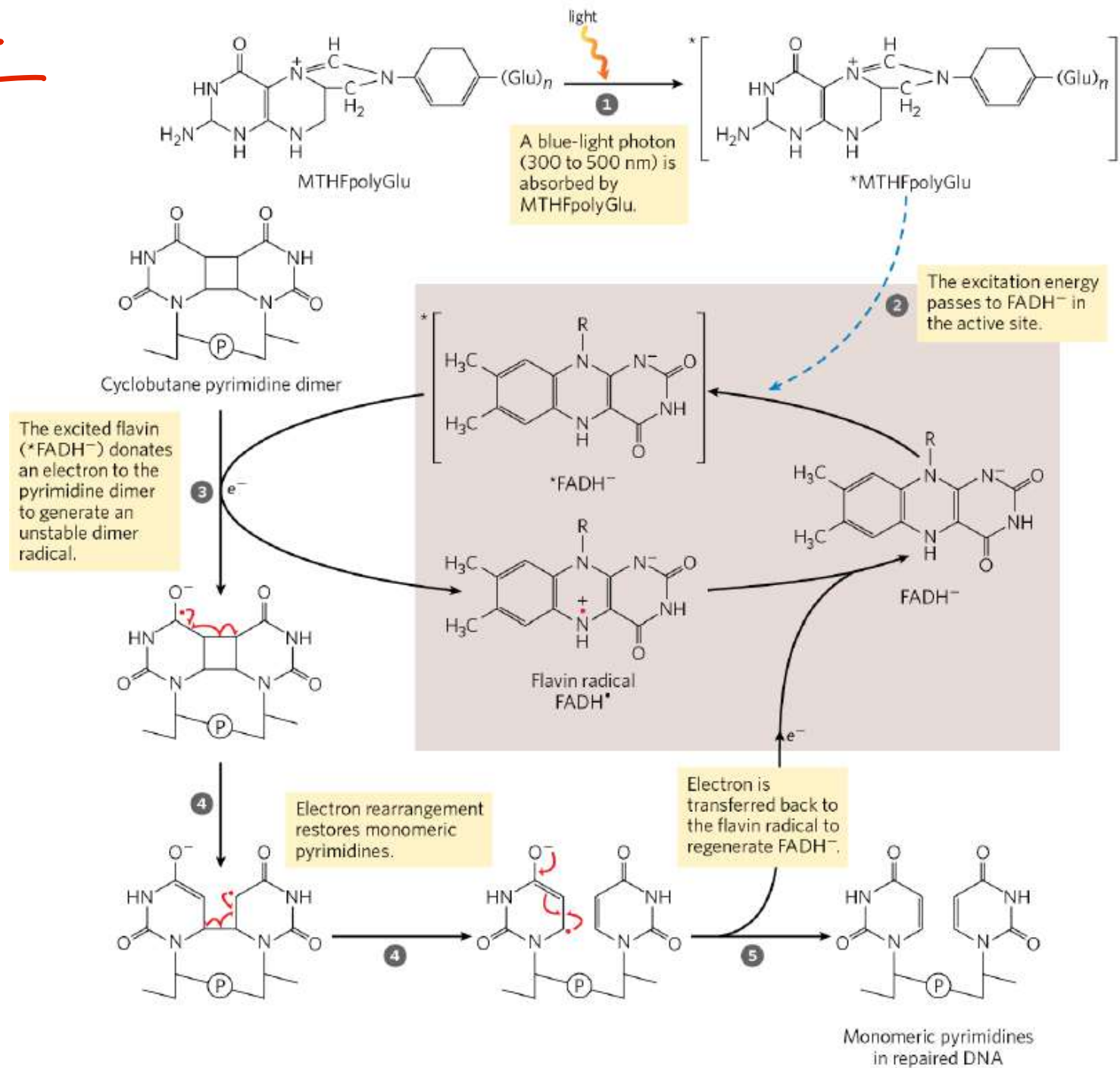


Direct Repair

ما بصير فيه ازالة د Bases او nucleotides

- Several types of damage are repaired without removing a base or nucleotide.
- The best-characterized example is **direct photoreactivation of cyclobutane pyrimidine dimers**, a reaction promoted by **DNA photolyases**. Pyrimidine dimers result from a UV-induced reaction. *enzymes بتستخدم energy ممتصة من light وبتقدر تعمل reversal د damage*
- Photolyases use energy derived from absorbed light to reverse the damage. Photolyases generally contain two cofactors that serve as light-absorbing agents, or chromophores: in all organisms, one is **FADH₂**; in *E. coli* and *yeast*, the other is a **folate**.

غير مطلوبه





Diseases caused by defective DNA repair

Hereditary non polyposis colon cancer (HNPCC)

- This is one of the most common inherited cancers. It results from a mutation in a gene involved in mismatch repair.

* يوجد damage ← repair لأنه يكون عن طريق mismatch repair ولكن يوجد mutation في gene التي يسمي product هذه mechanism فما يصير repair وينزل damage

Xeroderma pigmentosum

- This is an autosomal recessive disease characterized by sensitivity to ultraviolet light, leading to skin damage, pigmentation, and multiple skin cancers. It is caused by defective thymine-thymine dimer repair (nucleotide excision repair).

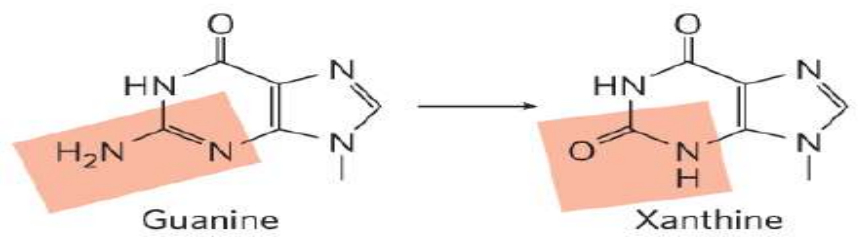
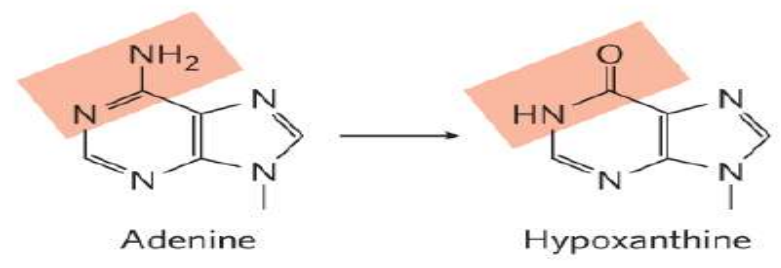
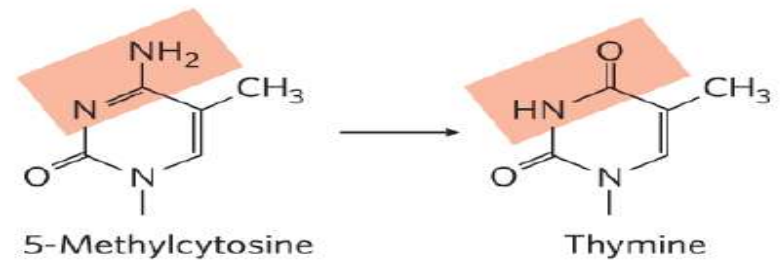
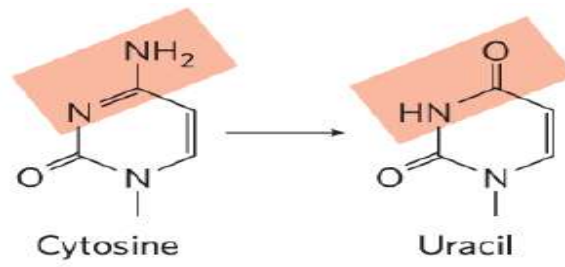
في حالة dimer يكون repair عن طريق Nucleotide excision repair
لأنه ولكن يوجد مشكلة في هذه mechanism

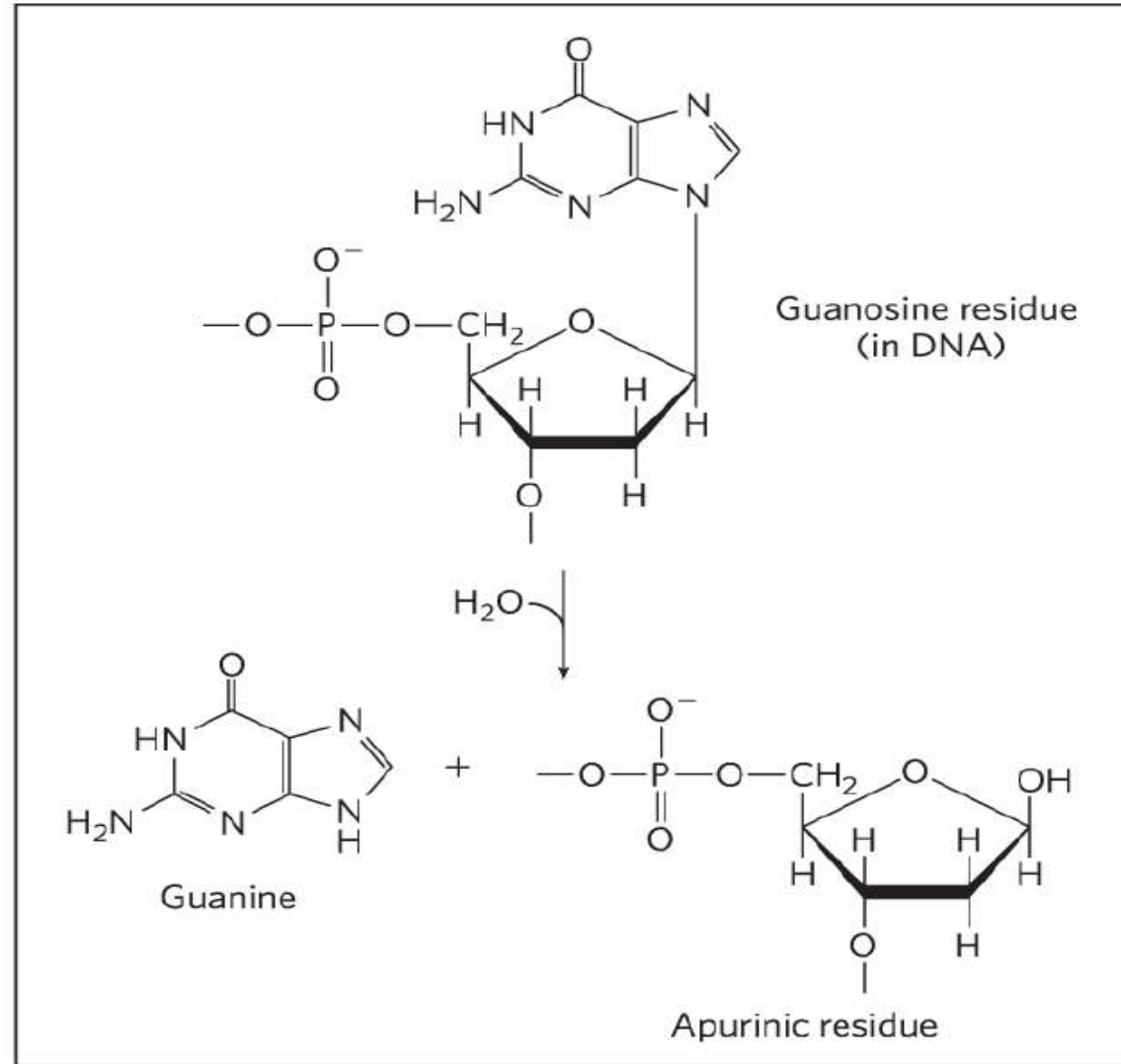
Xeroderma pigmentosum

UV light بحساسية عالية ←



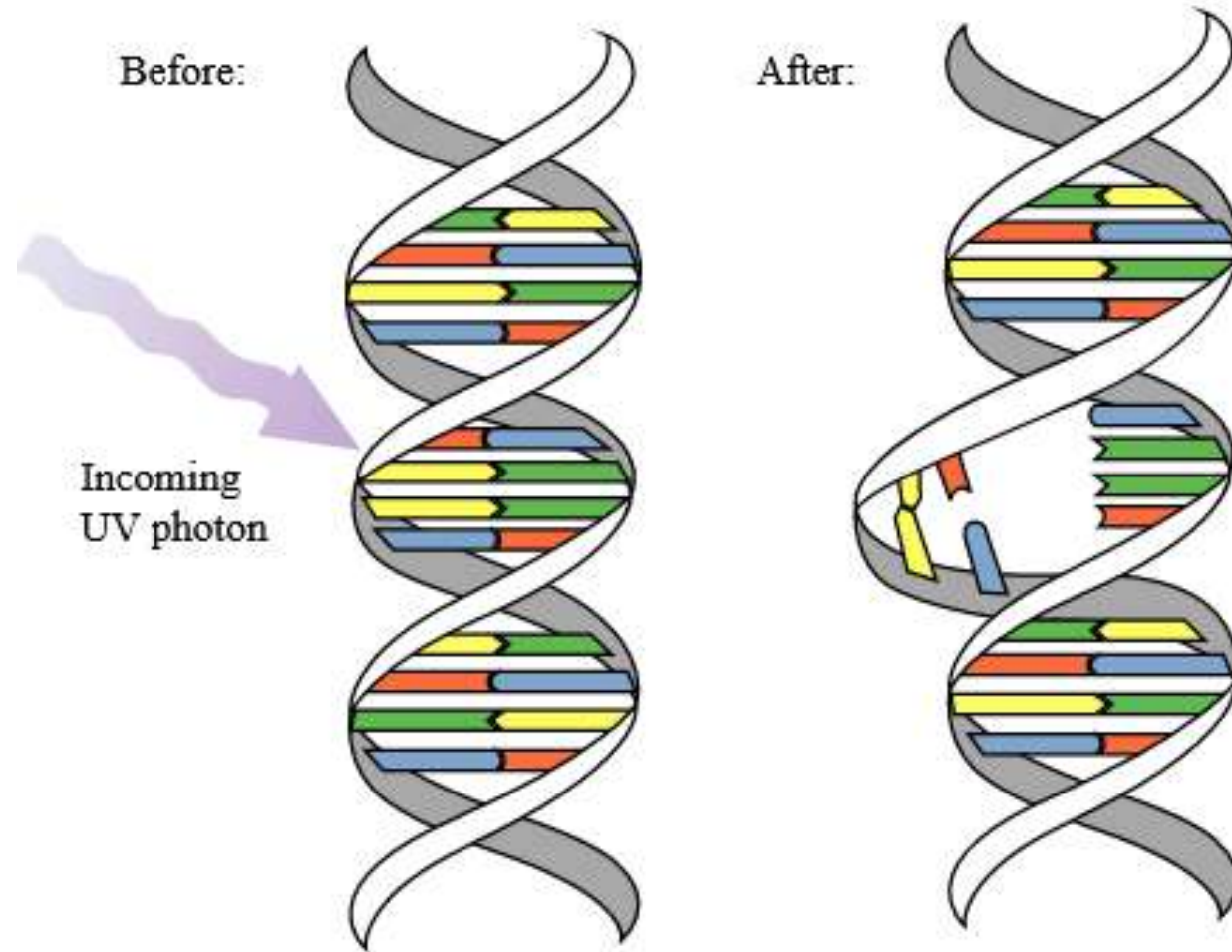
للفائدة فقط



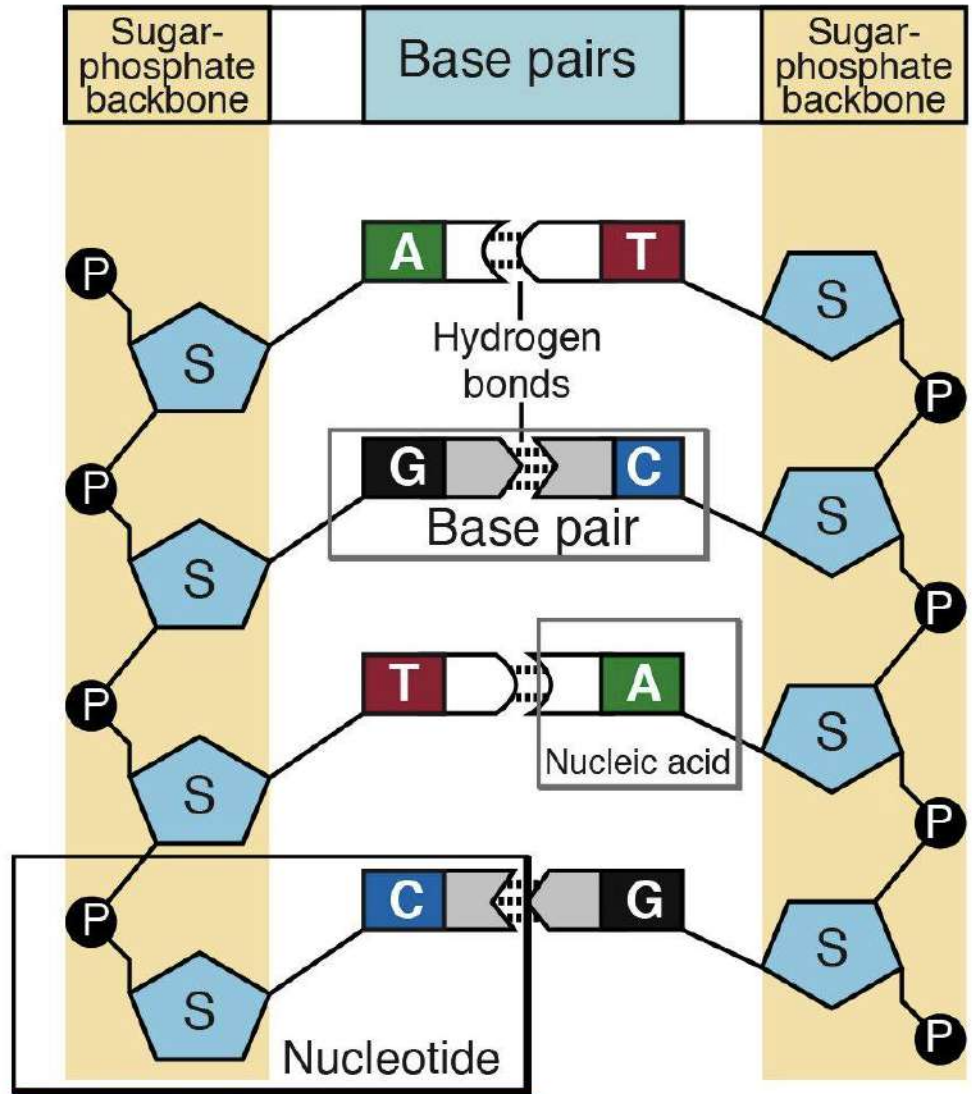


(b) Depurination

Pyrimidine dimers



Deoxyribonucleic Acid (DNA)



- A** Adenine
- T** Thymine
- C** Cytosine
- G** Guanine