Lec4 \ DNA Damage and Repair

DNA Damage

DNA damage is an alteration in the chemical structure of DNA, such as a break in a strand of DNA, a nucleobase missing from the backbone of DNA, or a chemically changed base such as 8-OHdG.

Sources of DNA damage

- naturally
- Environmental
- Radiation
- Carcinogens
- Mistakes in replication

DNA Repair

Depending on the type of defect found in the DNA, there are several batteries to activate the DNA, which can be explained as follows

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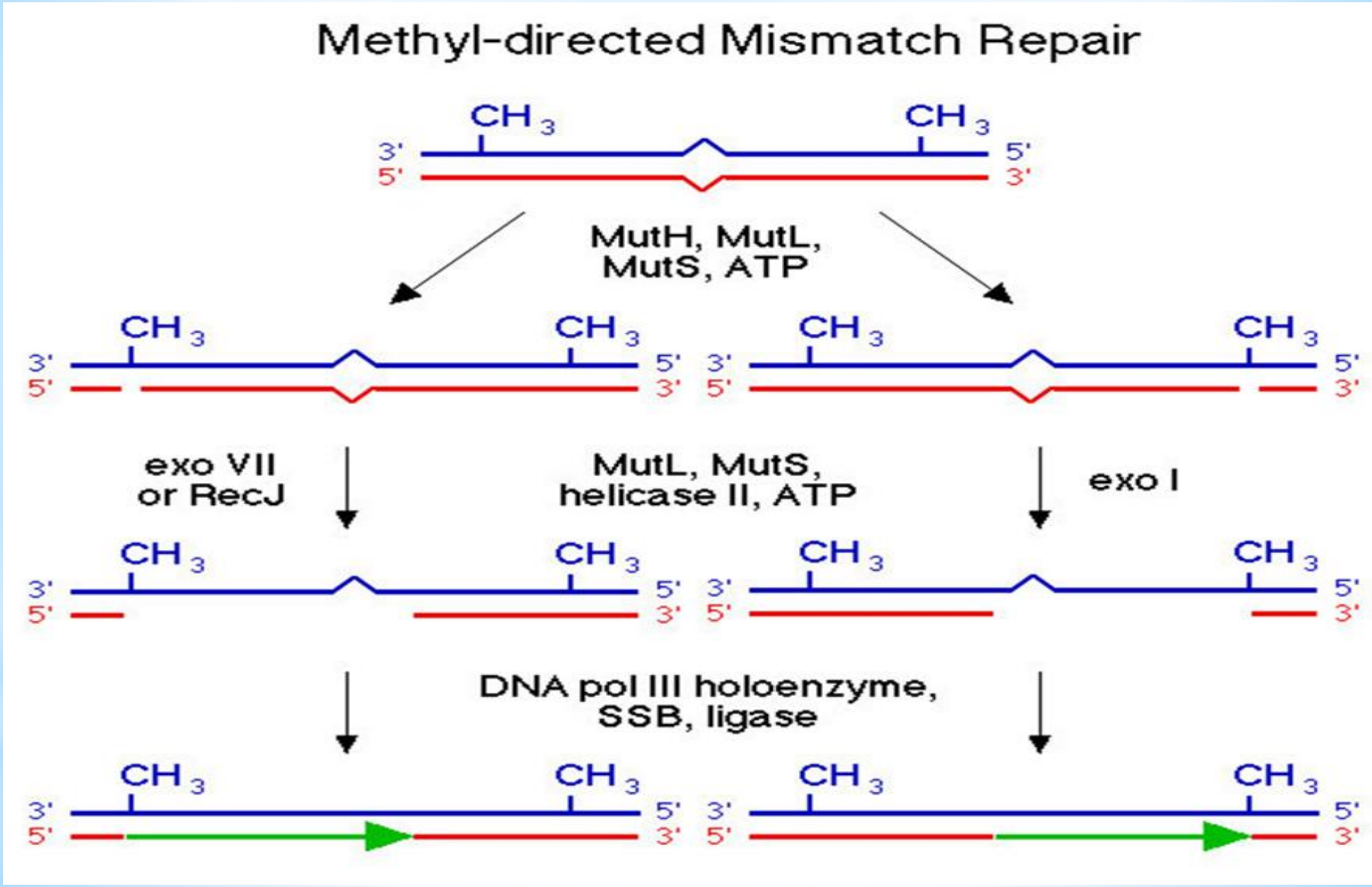
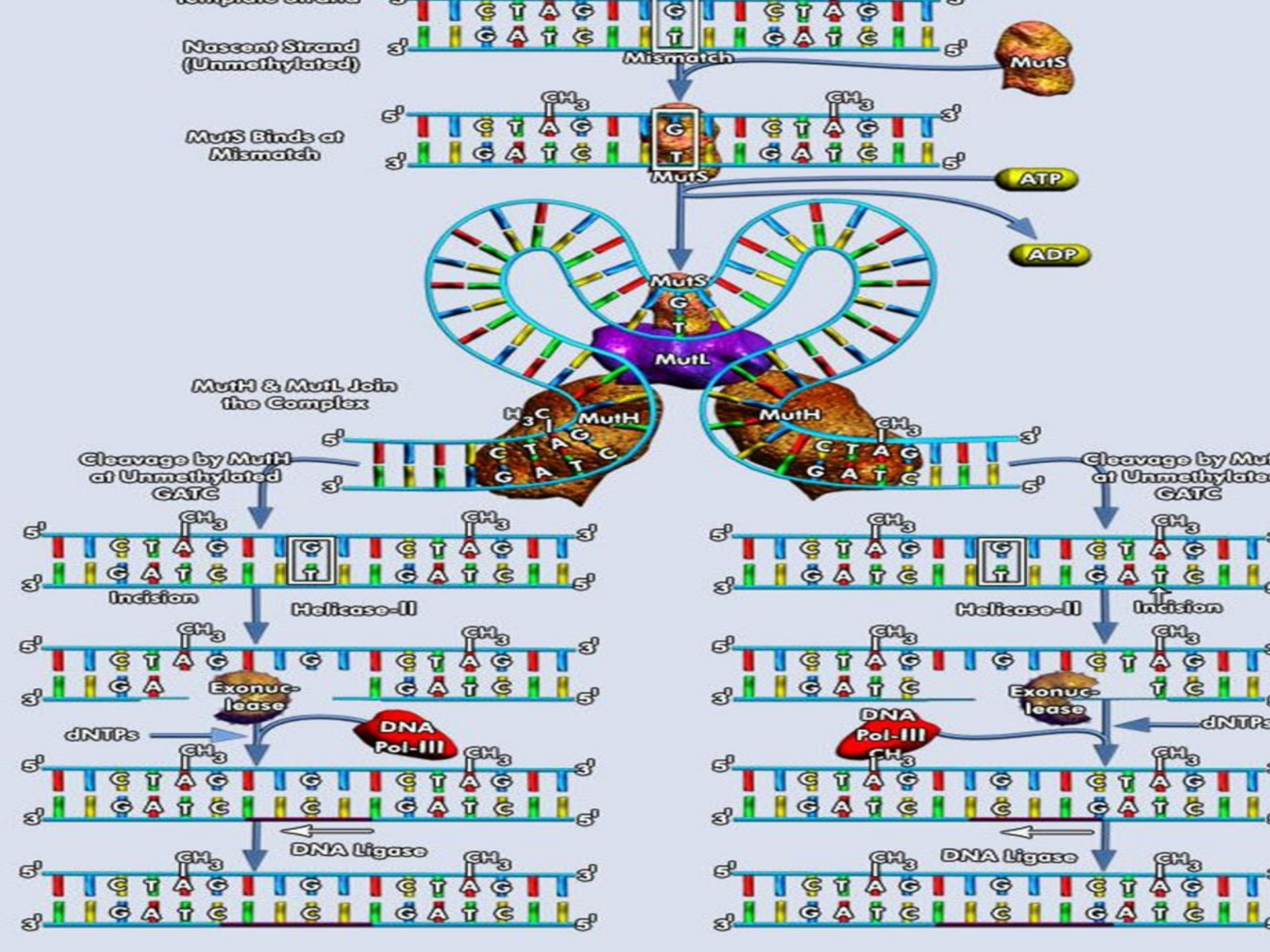
1-Mismatch Repair
2- Nucleotide Excision Repair
3-Base Excision Repair
4-Direct Photoreactivation Repair

1- Mismatch Repair (MMR):

* This mechanism is used to break the incorrect connection that occurs between incompatible bases, especially the wrong connection that occurs between Adenine and other incompatible bases.
This mechanism is used to repair the wrong association that occurs as a result of point mutations and frameshift mutations, meaning this mechanism is used to repair Simple lesions and Bulky lesions..


Methyl-directed Mismatch Repair
CH 3
CH 3
3'
5'
5'
3'
MutH, MutL,
MutS, ATP
exo VII
or RecJ
MutL, MutS,
helicase II, ATP
exo I
DNA pol III holoenzyme,
SSB, ligase


Nascent Strand (Unmethylated)
Mismatch
MutS
MutS Binds at Mismatch
MutS
ATP
ADP
MutS
MutL
MutH & MutL Join the Complex
MutH
MutH
Cleavage by MutH at Unmethylated GATC
Cleavage by Mut at Unmethylate GATC
Incision
Helicase-II
Helicase-II
Incision
Exonuc-lease
Exonuc-lease
dNTPs
DNA Poi-III
DNA Poi-III
dNTPs
DNA Ligase
DNA Ligase

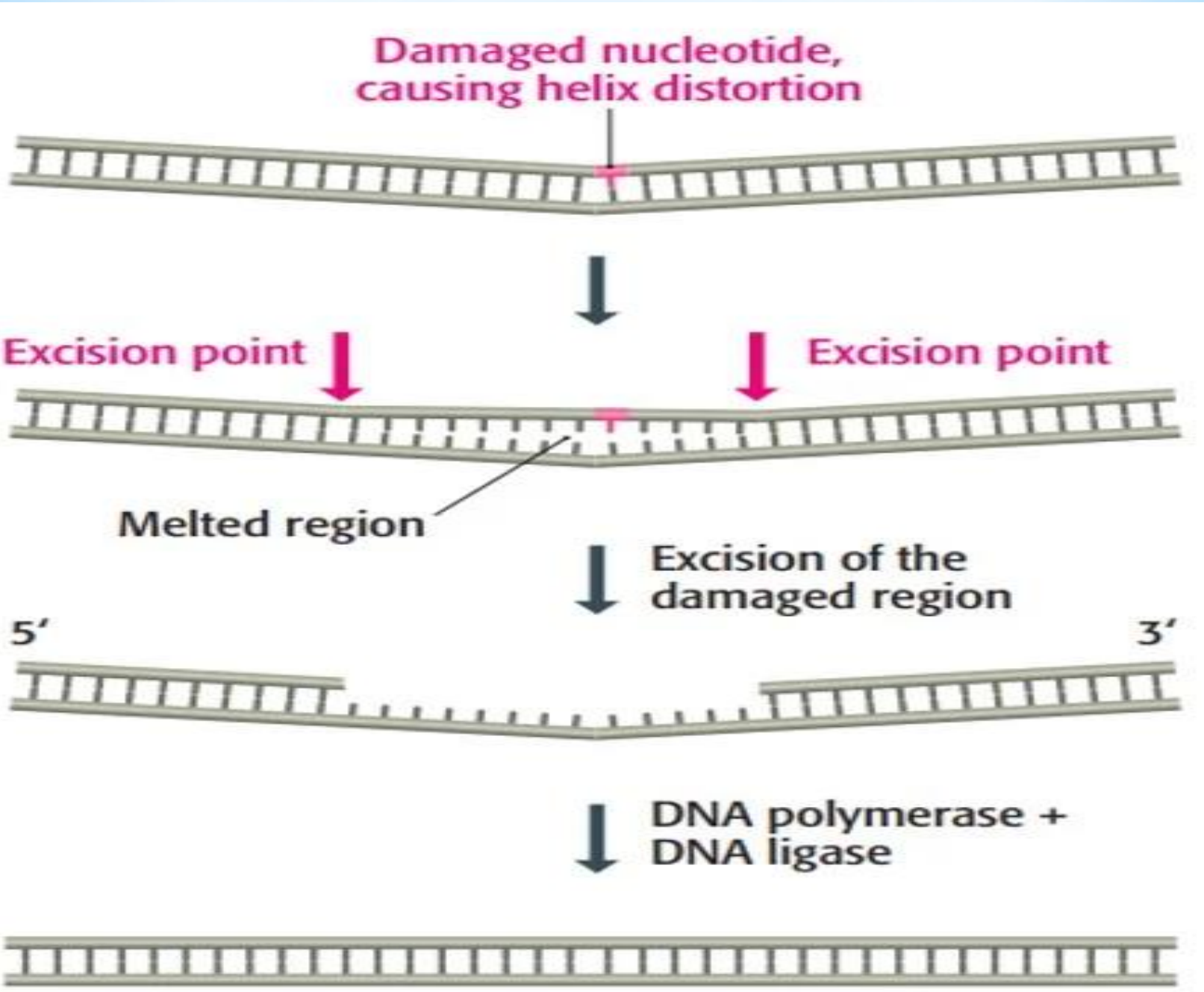
2- Nucleotide excision repair (NER) *

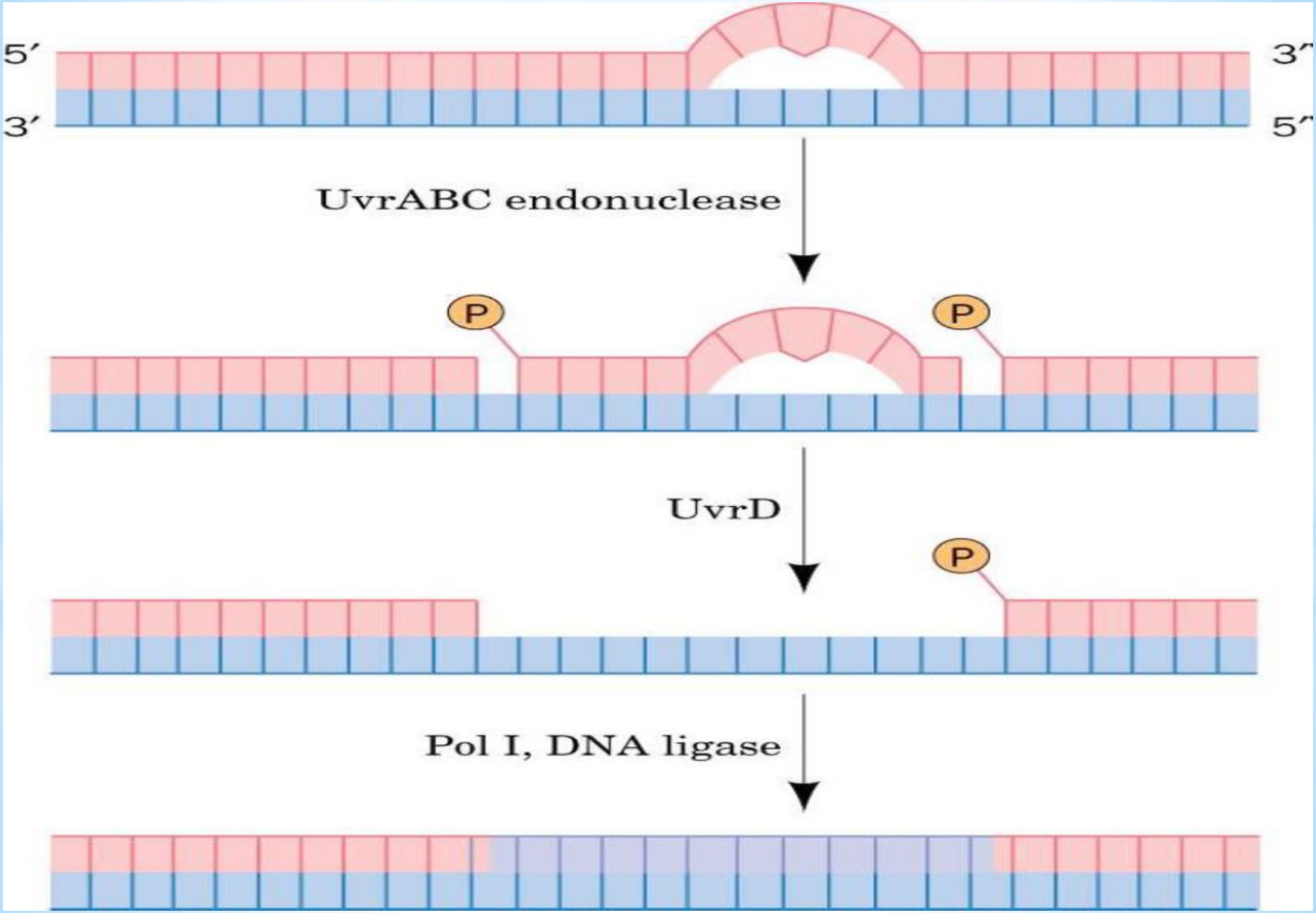
nucleotide excision repair (NER) This mechanism is used to repair bulky lesions that occur in more than one base and lead to a defect in the double helix, such as the Thymine Dimer, as follows:

deals with bulky adducts and cross-linking lesions caused by UV radiation or chemical exposure.

NER removes a fragment of nucleotides containing the damaged lesion and synthesizes a new DNA strand using the undamaged strand as a template.

Global Genome NER (GG-NER) repairs bulky damages throughout the entire genome, including regions that are not actively transcribed. Transcription-Coupled NER (TC-NER repairs damage that occurs on the transcribed DNA strand.

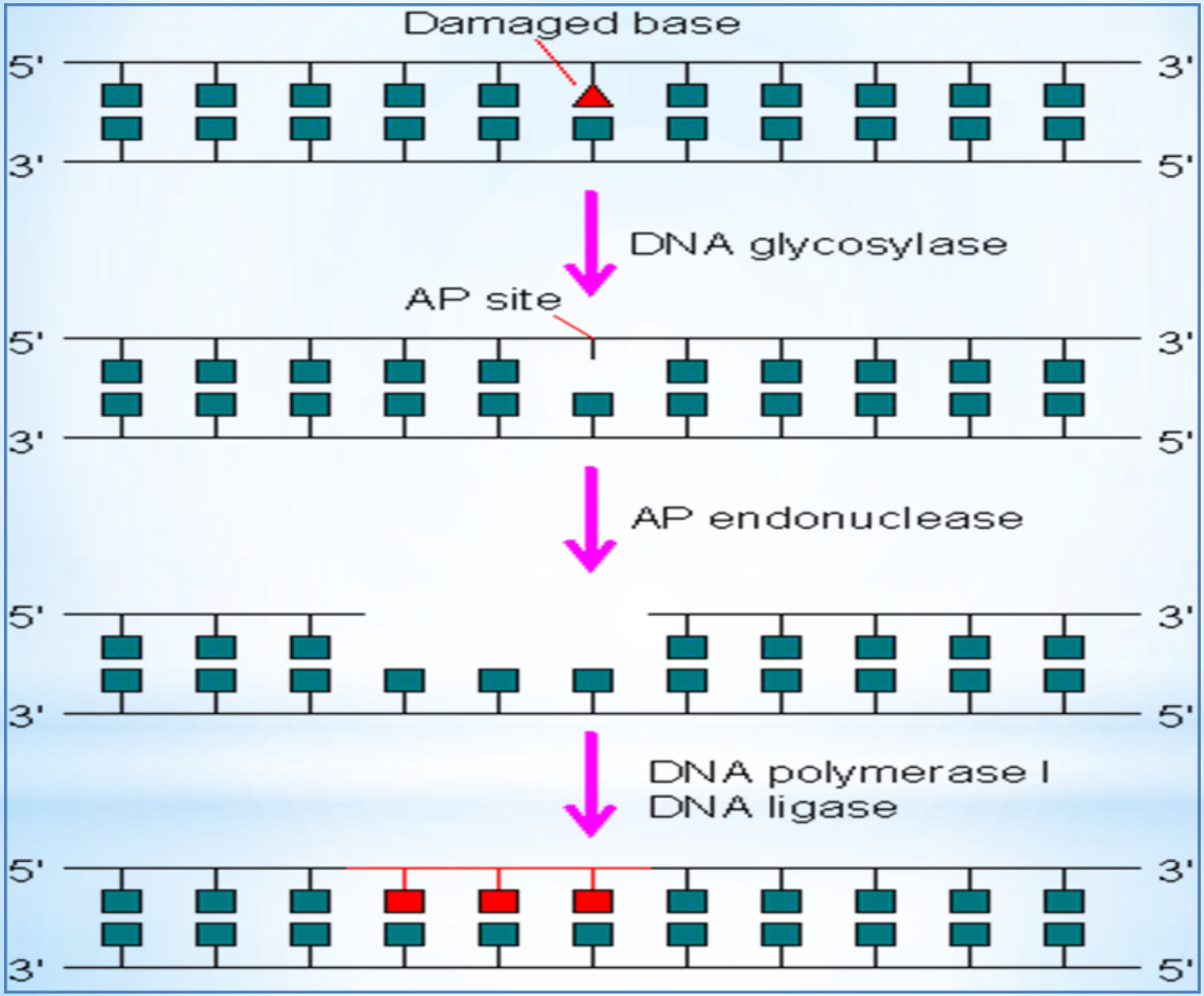

Damaged nucleotide,
causing helix distortion
Excision point
Excision point
Melted region
Excision of the
damaged region
5′
3′
DNA polymerase +
DNA ligase


5′
3′
3′
5′
UvrABC endonuclease
P
P
UvrD
P
Pol I, DNA ligase

3-Base Excision Repair (BER)*

This mechanism is used to repair non-bulky lesions that occur in only one base and do not lead to a defect in the double helix. An example is the damage that occurs in DNA as a result of:

deamination,
oxidation,
and alkylation processes.

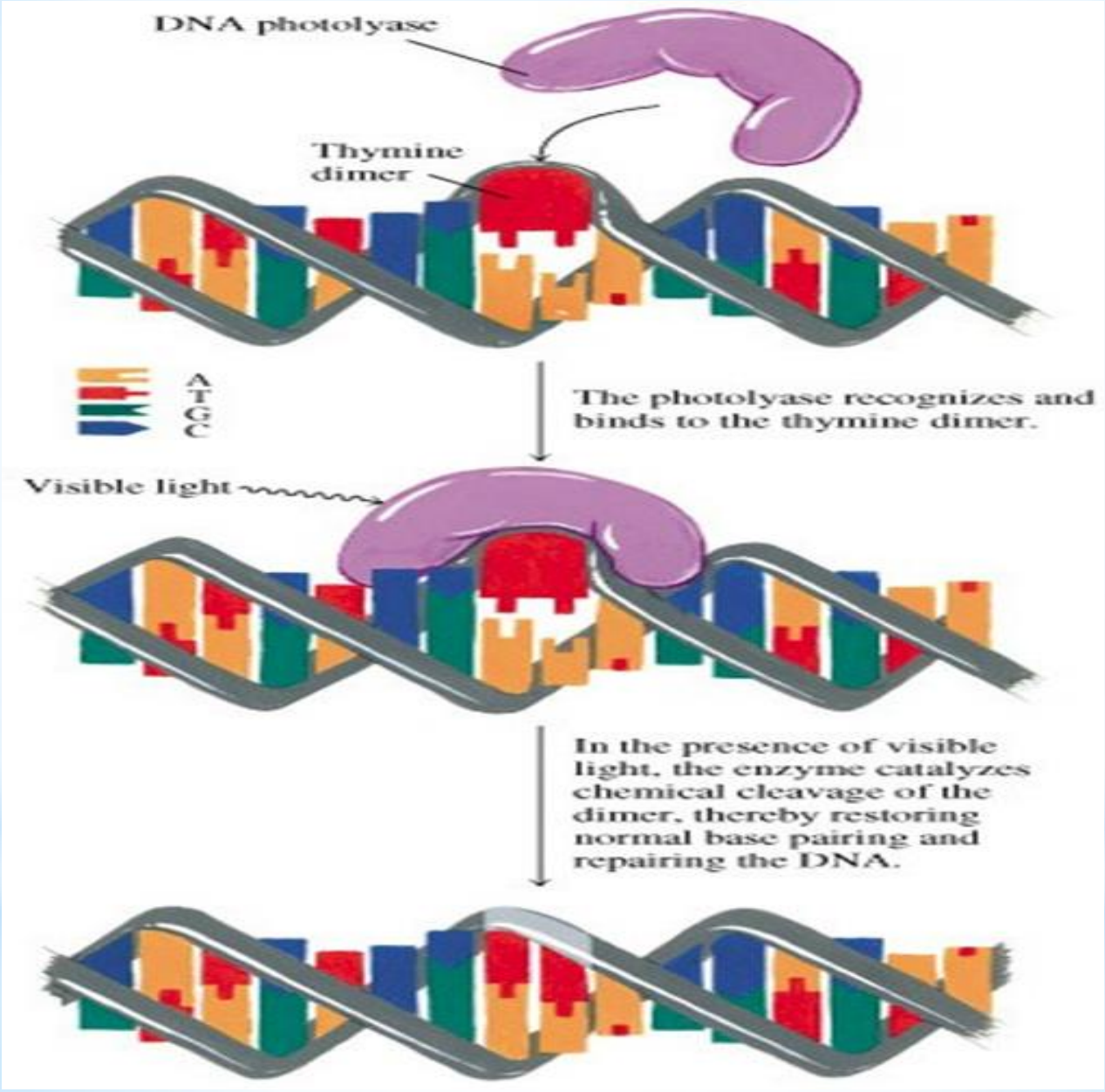

Damaged base
5'
3'
3'
5'
DNA glycosylase
AP site
5'
3'
3'
5'
AP endonuclease
5'
3'
3'
5'
DNA polymerase I
DNA ligase
5'
3'
3'
5'

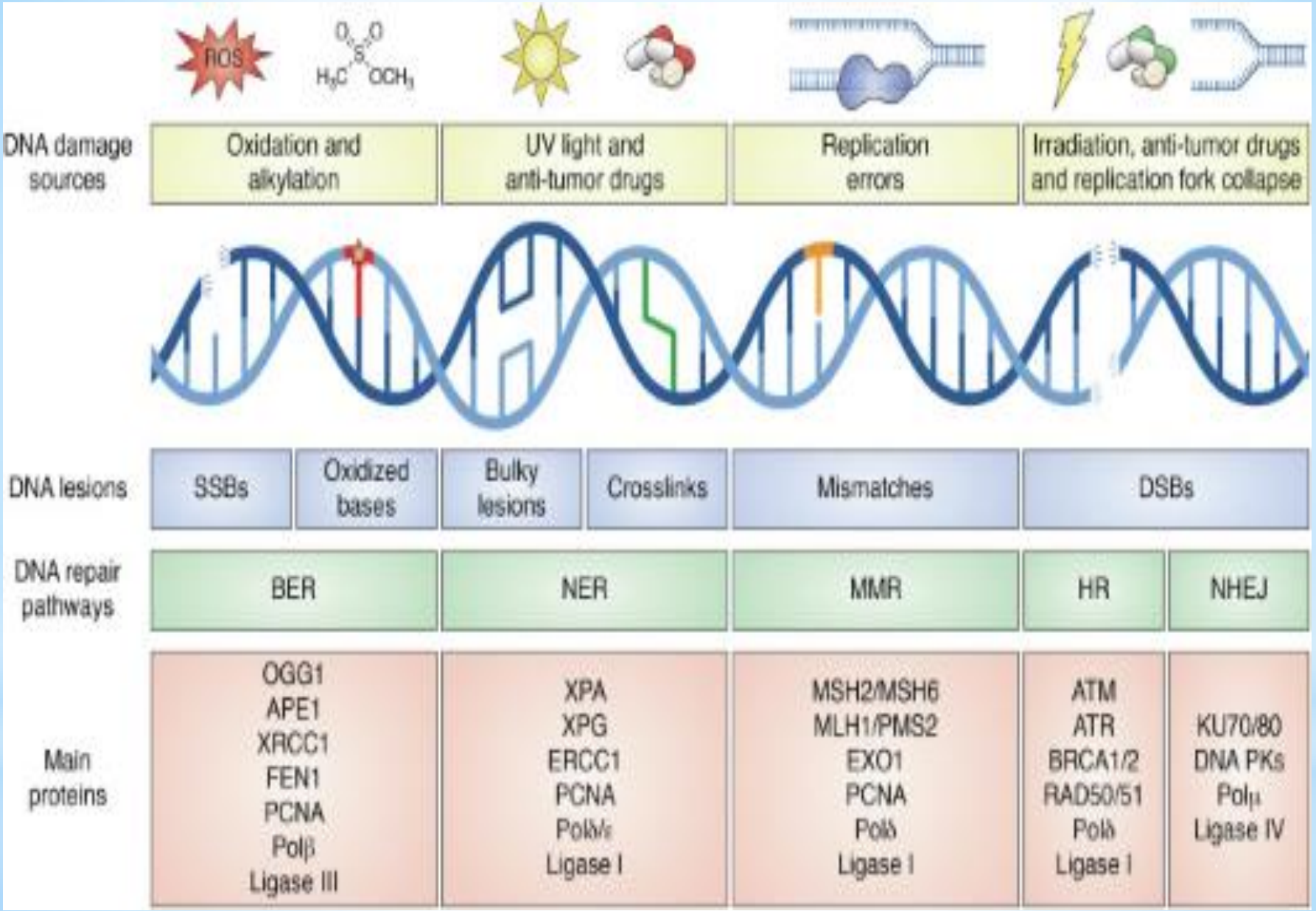
4- Direct Photoreactivation Repair *

It is the mechanism that is used to repair DNA damage resulting from UV-B and UV-C rays, which lead to the formation of photoproducts, such as Thymine Dimer.

This mechanism is summarized as follows:

The photolyase enzyme absorbs visible light and transfers electrons to FADH and from there to the Thymine Dimer, which leads to the dissolution of the Thymine Dimer.


DNA photolyase
Thymine dimer
A
T
G
C
The photolyase recognizes and binds to the thymine dimer.
Visible light
In the presence of visible light, the enzyme catalyzes chemical cleavage of the dimer, thereby restoring normal base pairing and repairing the DNA.


ROS
DNA damage sources
Oxidation and alkylation
UV light and anti-tumor drugs
Replication errors
Irradiation, anti-tumor drugs and replication fork collapse
DNA lesions
SSBs
Oxidized bases
Bulky lesions
Crosslinks
Mismatches
DSBs
DNA repair pathways
BER
NER
MMR
HR
NHEJ
Main proteins
OGG1
APE1
XRCC1
FEN1
PCNA
Polβ
Ligase III
XPA
XPG
ERCC1
PCNA
Polδ/ε
Ligase I
MSH2/MSH6
MLH1/PMS2
EXO1
PCNA
Polδ
Ligase I
ATM
ATR
BRCA1/2
RAD50/51
Polδ
Ligase I
KU70/80
DNA PKs
Polμ
Ligase IV