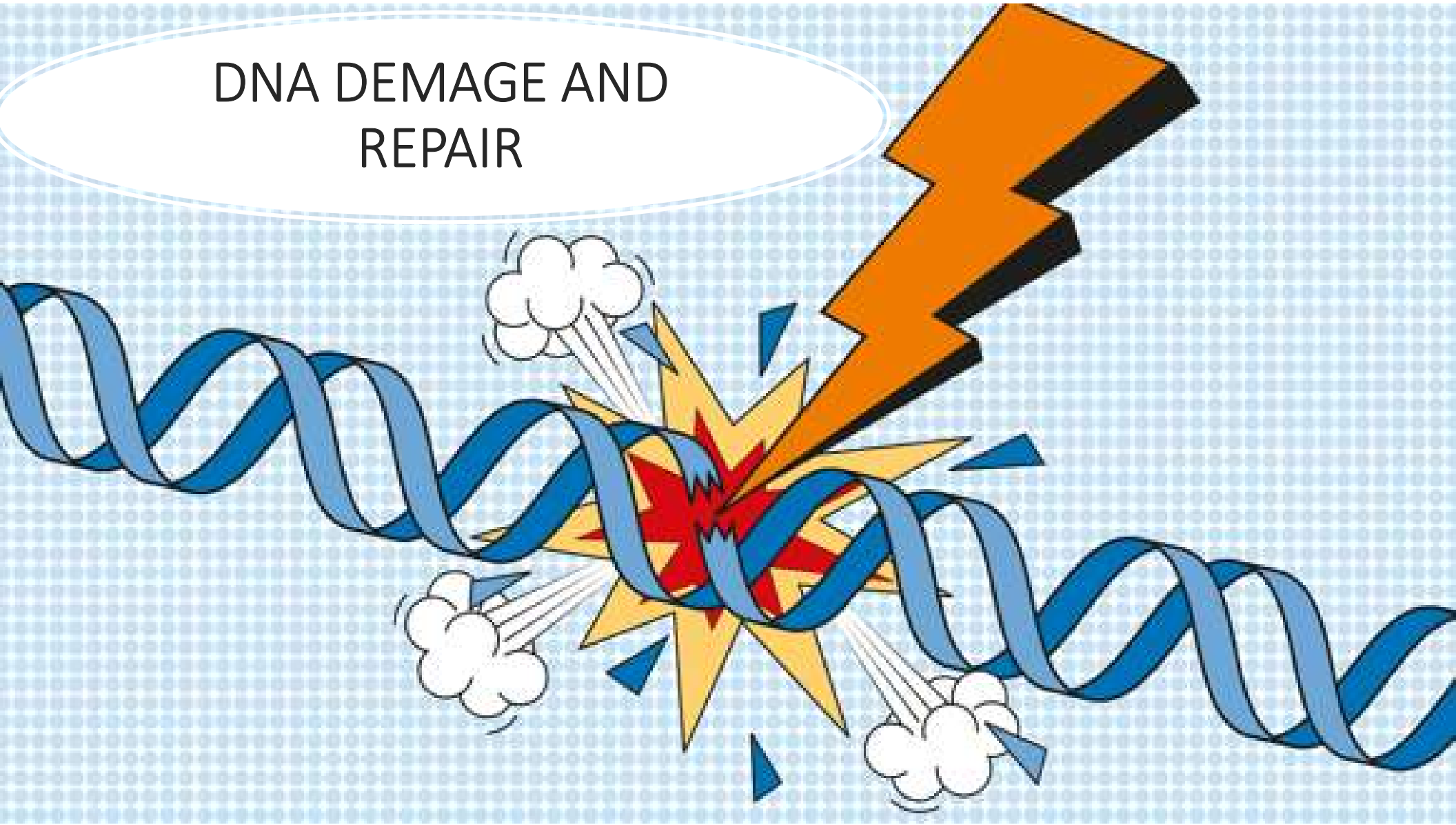
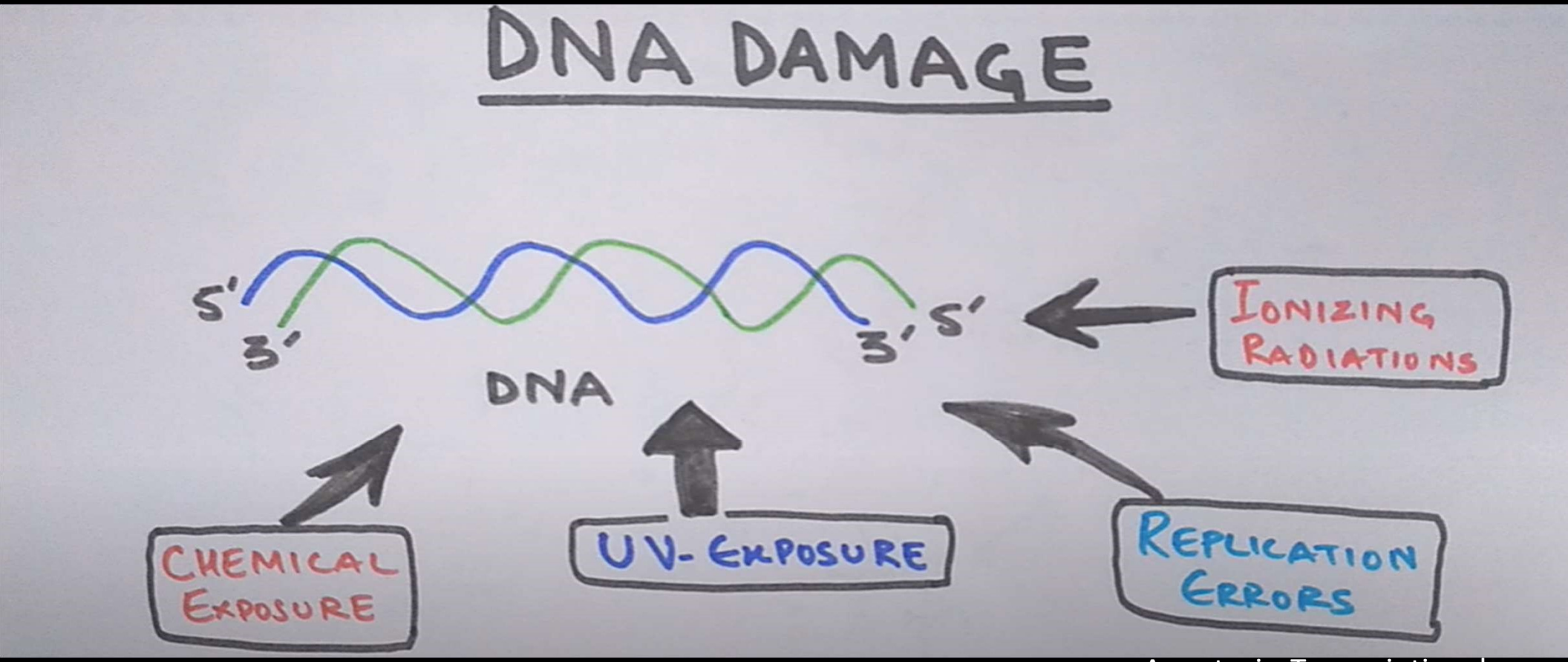
DNA DEMAGE AND REPAIR

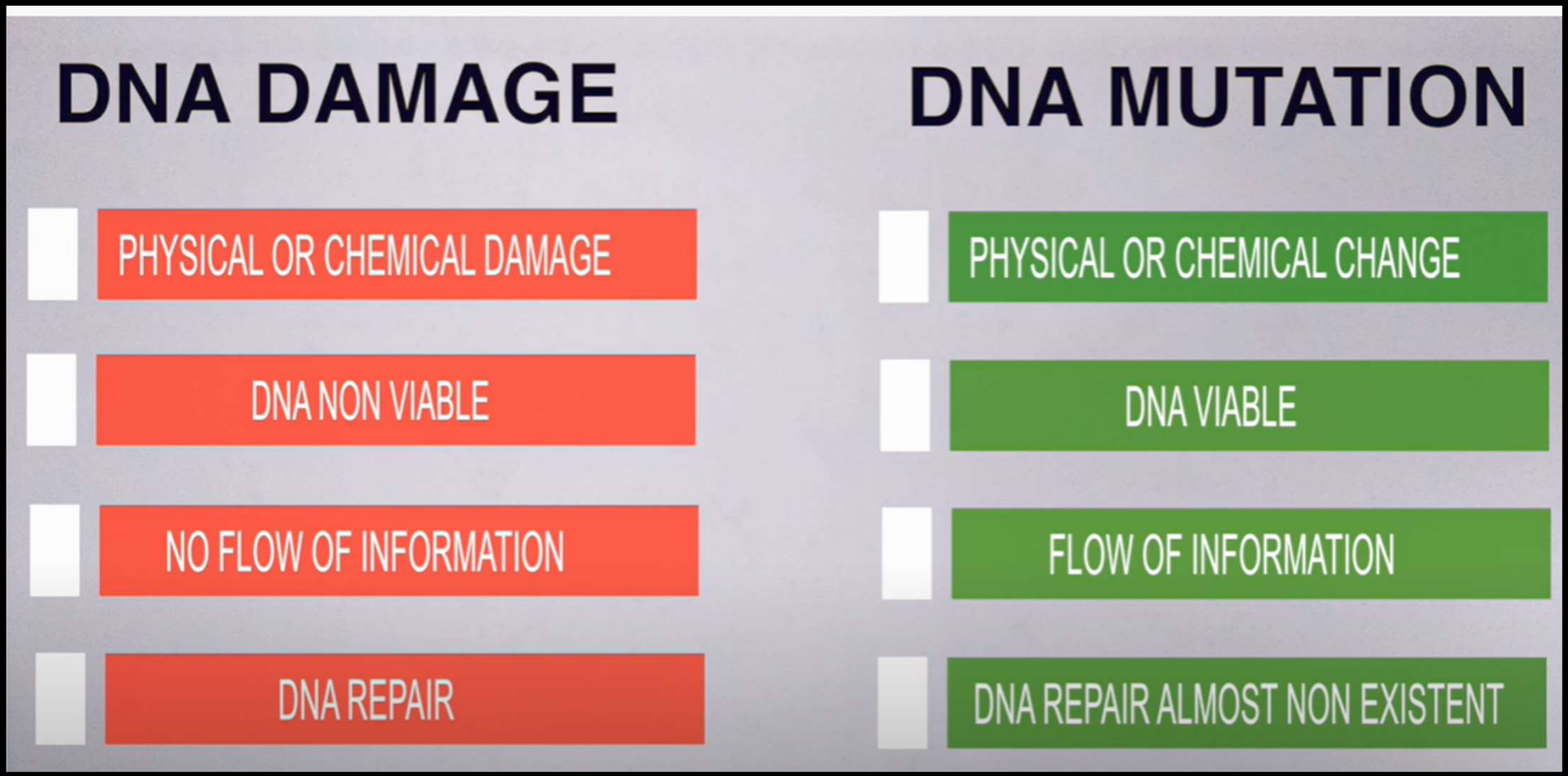




Apoptosis, Transcriptional program activation, Cell cycle check point activation

DNA DAMAGE VERSUS MUTATION

DNA DAMAGE	MUTATION
Injuries to DNA that introduce deviations from its normal, intact structure and which may if left unrepaired, result in a mutation or a block of DNA replication	Permanent alteration of the nucleotide sequence of the genome of an organism, virus, or extrachromosomal DNA or other genetic elements
A structural change in DNA	An alteration of the nucleotide sequence in DNA
Most damages are repaired by cellular mechanisms	Permanent changes in DNA
Un-repaired DNA damages become mutations in replicating cells	Pass over generations
Caused by compounds released during metabolism and environmental factors	Caused by the errors in DNA replication and recombination
Three types are chemical changes of nitrogenous bases, missing of bases, and breaks in DNA strands	Three types are substitutions, deletions, and insertions
Prevent the proceeding of DNA replication	Change the genetic information encoded by DNA


DNA DAMAGE
PHYSICAL OR CHEMICAL DAMAGE
DNA NON VIABLE
NO FLOW OF INFORMATION
DNA REPAIR
DNA MUTATION
PHYSICAL OR CHEMICAL CHANGE
DNA VIABLE
FLOW OF INFORMATION
DNA REPAIR ALMOST NON EXISTENT

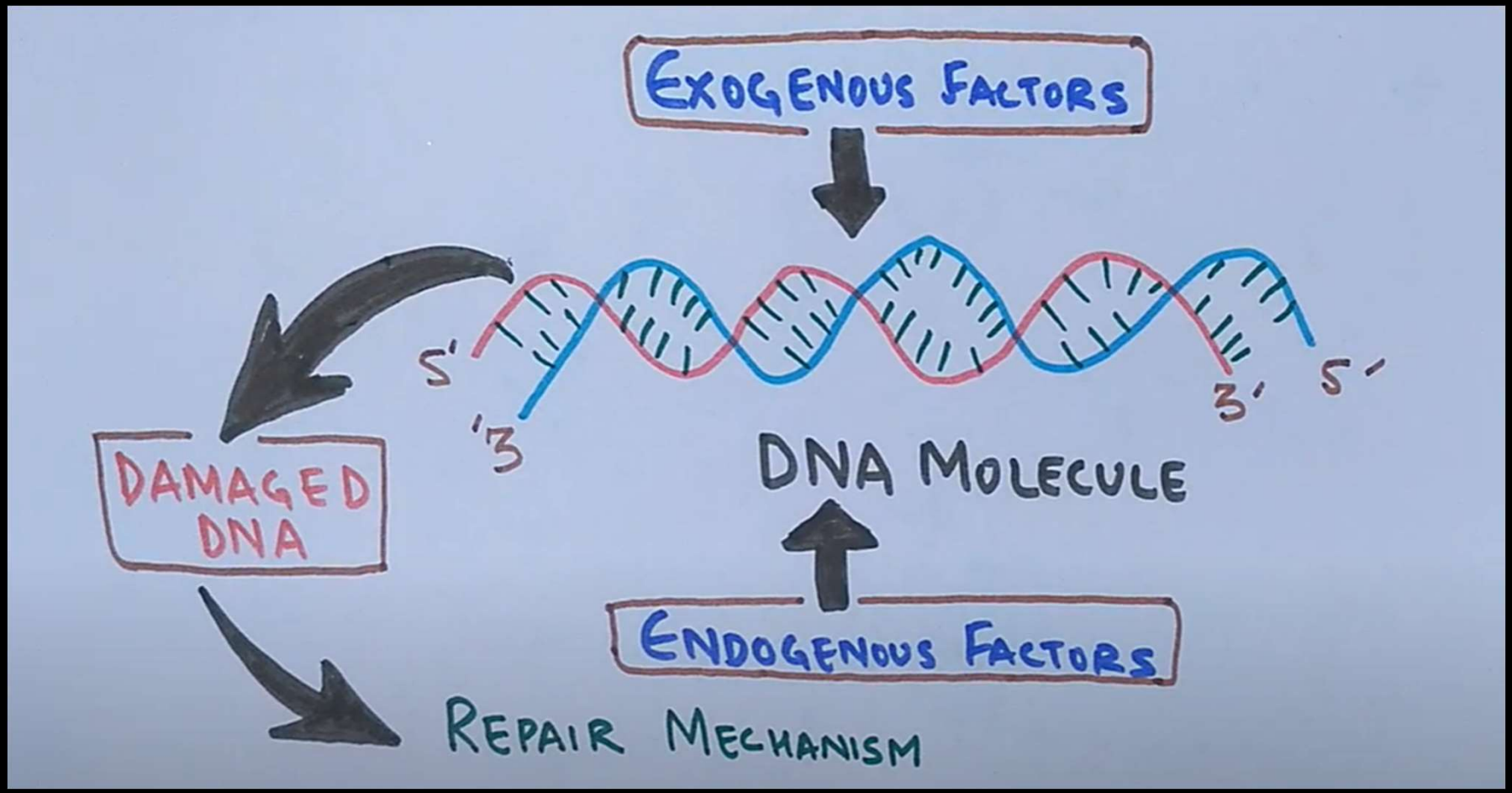
Sources of DNA Damage

- ROS: Reactive O_2 Species
- Replication Error
- Poor Repair System

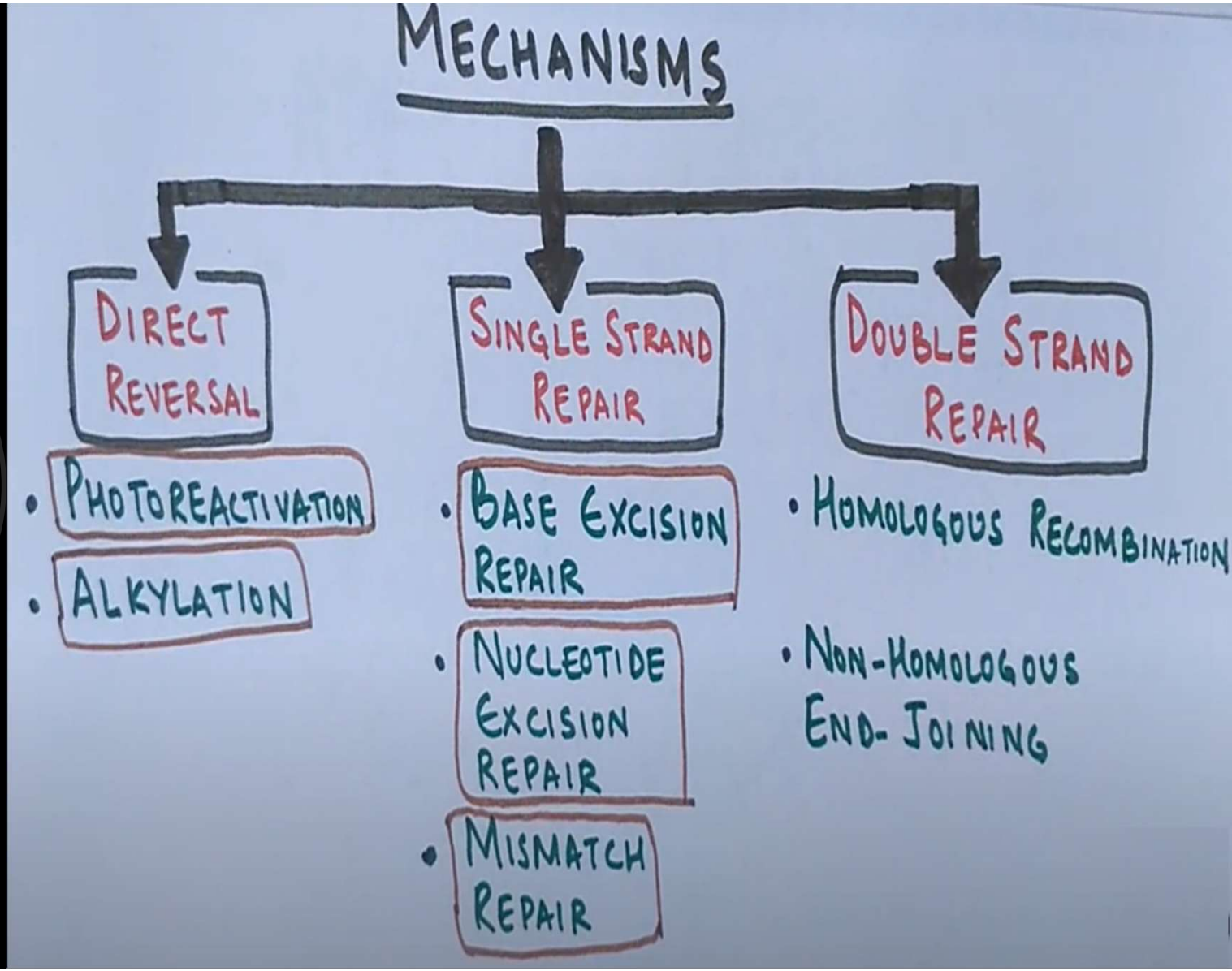
- UV Radiations
- X-Rays, Gamma Rays.
- Hydrolysis or Thermal Disruption
- Interclating Agents

Type of Damage

- Oxidation of Bases
- Alkylation of Bases.
- Hydrolysis
- Mismatch Bases
- Bulky Adduct Formation
- DNA Strand Breaks : By UV

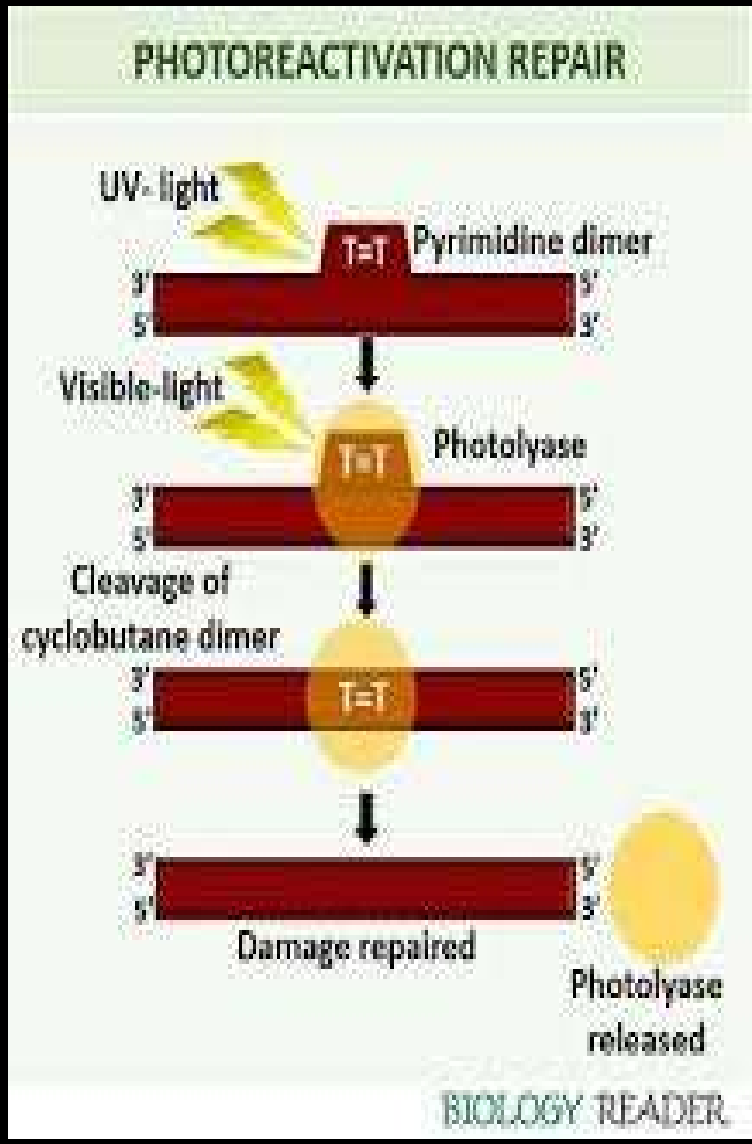

EXOGENOUS FACTORS
5'
3'
3'
5'
DAMAGED DNA
DNA MOLECULE
ENDOGENOUS FACTORS
REPAIR MECHANISM

DNA REPAIR


MECHANISMS
DIRECT REVERSAL
SINGLE STRAND REPAIR
DOUBLE STRAND REPAIR
• PHOTOREACTIVATION
• ALKYLATION
• BASE EXCISION REPAIR
• NUCLEOTIDE EXCISION REPAIR
• MISMATCH REPAIR
• HOMOLOGOUS RECOMBINATION
• NON-HOMOLOGOUS END-JOINING

Photoreactivation

- It is a type of DNA **repair mechanism** present in prokaryotes, archaea and in many eukaryotes. (bacteria, yeast, some vertebrates - not humans) ... In this DNA **repair** method cells recovers its DNA after UV exposure induced damages. The UV light is lethal to cellular DNA since it induces structural lesions in the DNA by the formation of pyrimidine dimer.
- Two thymines connected together by UV light.
- The photoreactivation process directly reverses this damage by the action of the enzyme photolyase, whose activation is obligately dependent on energy absorbed from blue/UV light (300–500 nm wavelength) to promote catalysis

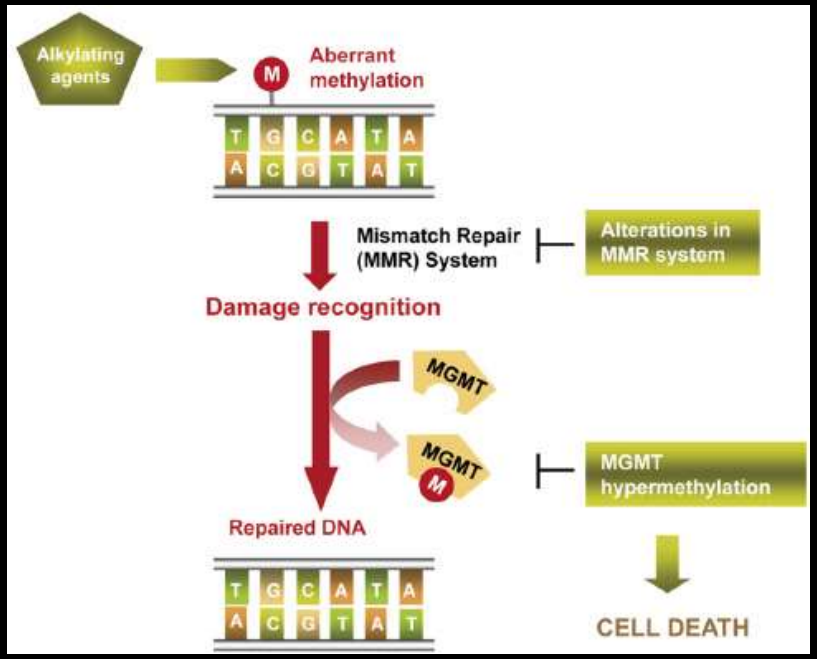


Alkylation damage repair

It involves multiple partially redundant pathways, which include direct reversal by MGMT, the ALKB family of demethylases, and base excision **repair**.

Transfer of alkyl gp (methyl/ethyl) to reactive site on base or phosphate group

Damage is removed by O6 Methyl guanine methyl transferase



Excision Repair

- Conserved throughout evolution, found in all prokaryotic and eukaryotic organisms

- Three step process:
  - 1. Error is recognized and enzymatically clipped out by a nuclease that cleaves the phosphodiester bonds (uvr gene products operate at this step)

  - 2. DNA Polymerase I fills in the gap by inserting the appropriate nucleotides

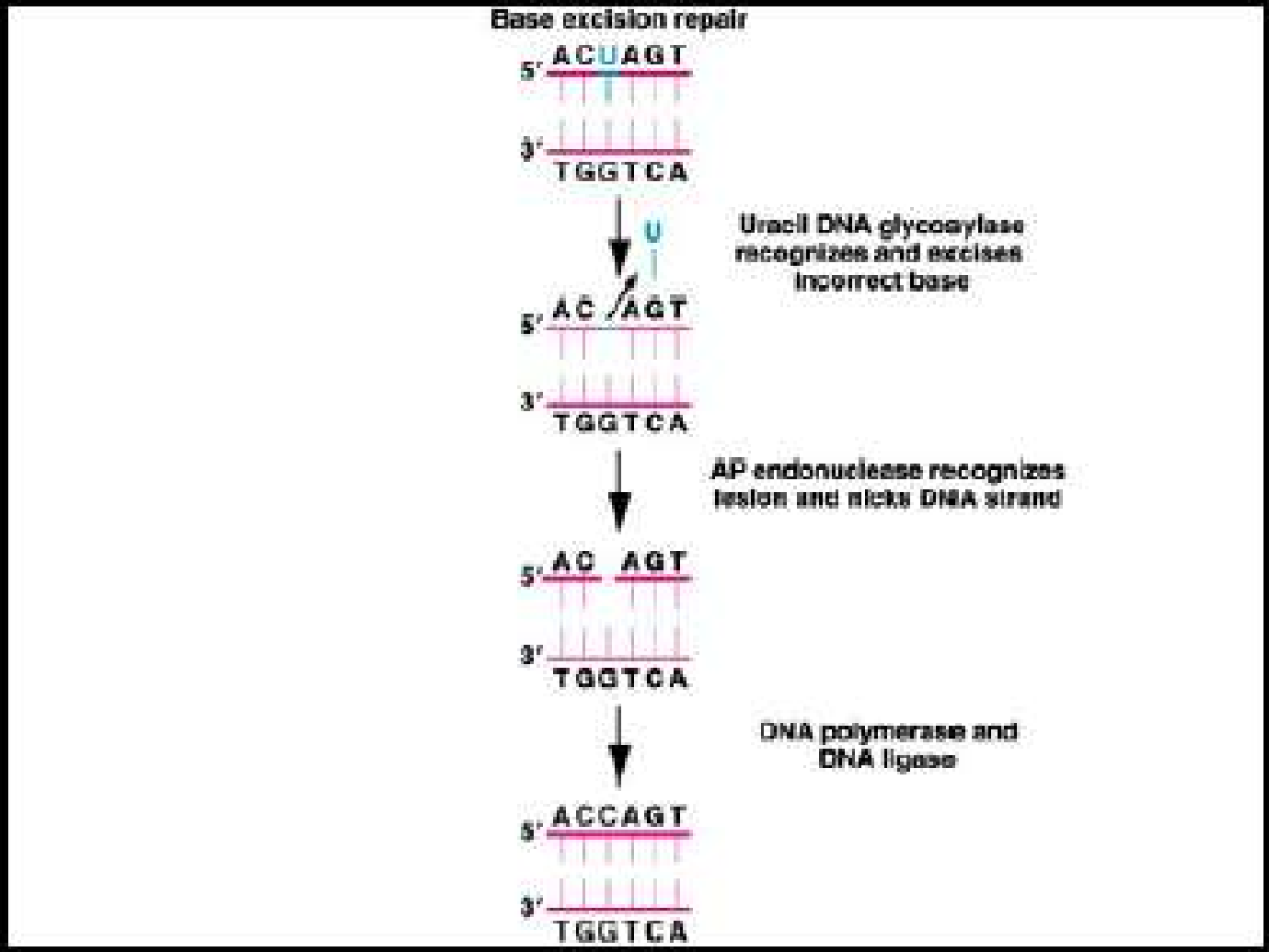
  - 3. DNA Ligase seals the gap

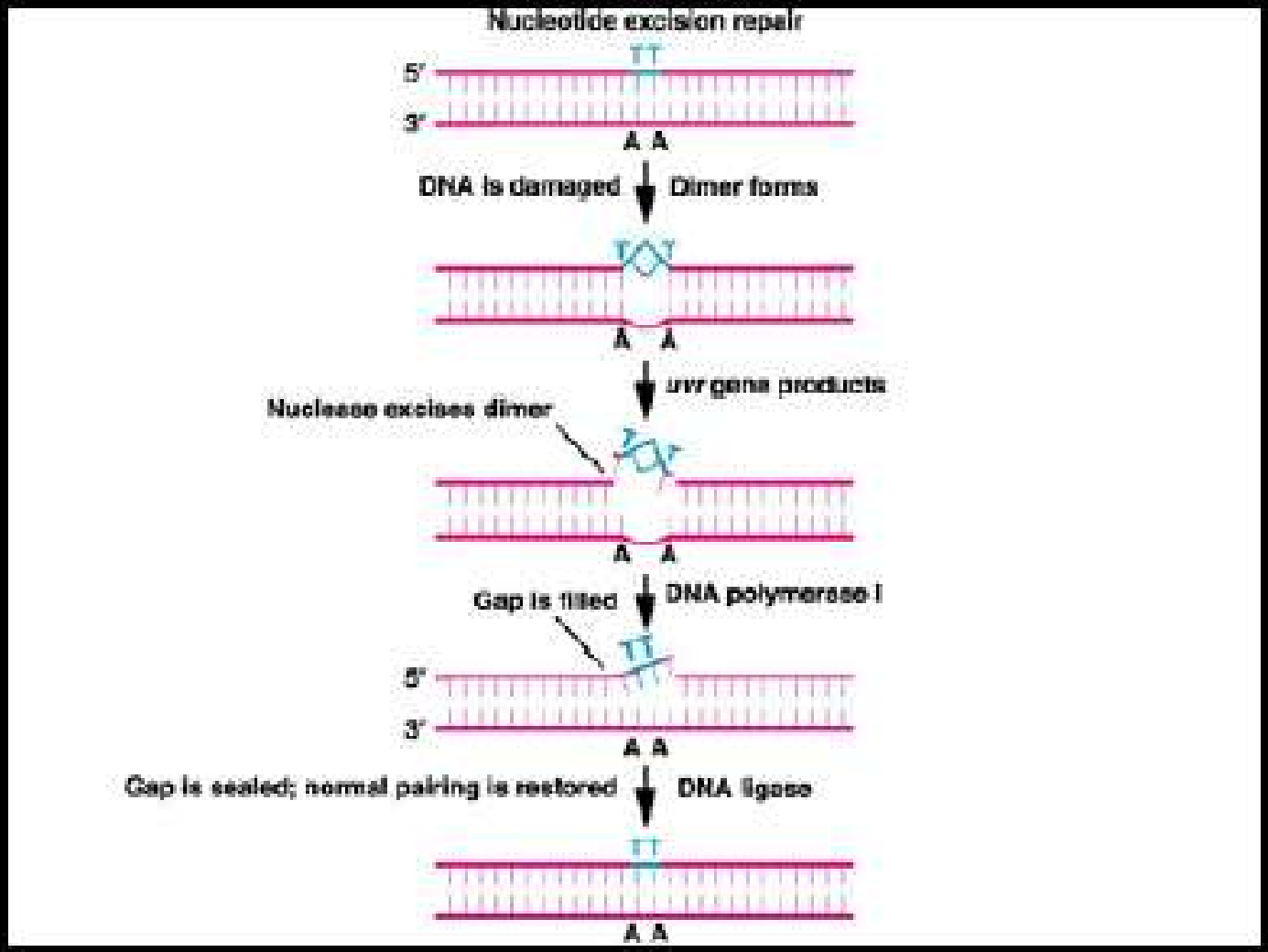
Excision Repair

• Two know types of excision repair

– **Base excision repair (BER)**
• corrects damage to nitrogenous bases created by the spontaneous hydrolysis of DNA bases as well as the hydrolysis of DNA bases caused by agents that chemically alter them

– **Nucleotide excision repair (NER)**
• Repairs "bulky" lesions in DNA that alter or distort the regular DNA double helix
• Group of genes (uvr) involved in recognizing and clipping out the lesions in the DNA
• Repair is completed by DNA pol I and DNA ligase


Base excision repair
5′ ACUAGT
3′ TGGTCA
U
Uracil DNA glycosylase recognizes and excises incorrect base
5′ AC AGT
3′ TGGTCA
AP endonuclease recognizes lesion and nicks DNA strand
5′ AC AGT
3′ TGGTCA
DNA polymerase and DNA ligase
5′ ACCAGT
3′ TGGTCA


Nucleotide excision repair
5′
3′
A A
DNA is damaged
Dimer forms
A A
uvr gene products
Nuclease excises dimer
A A
Gap is filled
DNA polymerase I
5′
3′
A A
Gap is sealed; normal pairing is restored
DNA ligase
A A

Proofreading and Mismatch Repair

• In bacterial systems, proofreading decreases the error rate in DNA replication by two orders of magnitude
– from 1 mismatch in every 105 nucleotide pairs to 1 in every 107 base pairs

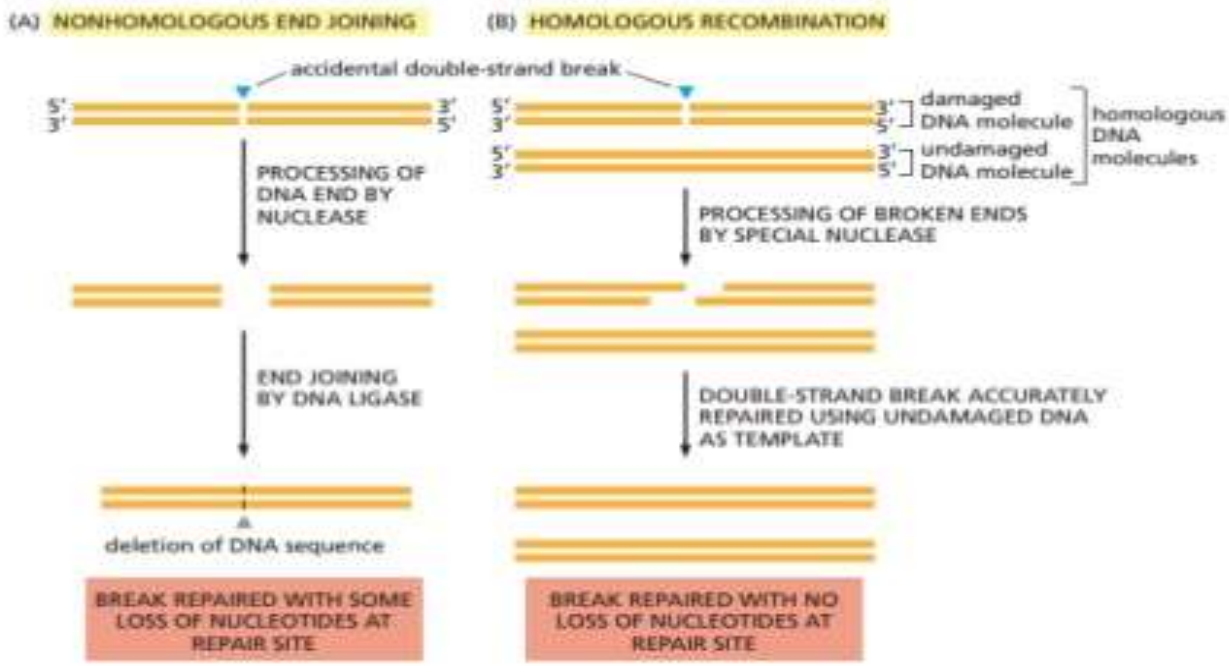
• **Mismatch repair** is another mechanism by which mismatches can be fixed in the DNA strand

• In bacteria, mismatch repair is based on the process of DNA Methylation, which labels one strand, providing a basis for the mismatch repair.

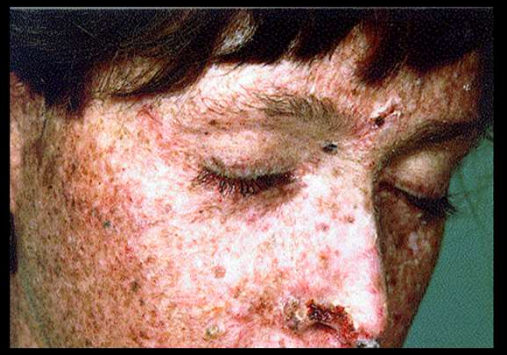
Repair of double stranded break

- Double stranded breaks are caused by the high energy radiation or oxidative free radicals.
- Such breaks occur naturally during gene rearrangements.
- It can't be corrected by any of the above mentioned strategies.
- But, can be repaired either by:
  - **1. Non-homologous end-joining repair.**
  - **2. Homologous recombination repair.**

Double stranded DNA repair break



Diseases in which DNA repair is damage



- **Xeroderma pigmentosum** (XP): Patients are hypersensitive to UV light; patients often develop malignancies of the skin.

- Severe sunburn.
- Development of many freckles at an early age.
- Rough-surfaced growths (solar keratoses), and skin cancers.
- Eyes that are painfully sensitive to the sun and may easily become irritated, bloodshot and clouded.
- Blistering or freckling on minimum sun exposure.

Fanconi's anemia:

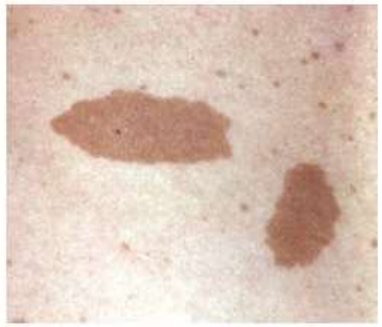
Rare, 10-20 case every year

Patients demonstrate aplastic anemia, growth retardation, and congenital anomalies; related to a deficiency in repair of DNA cross-links.

Fanconi Anemia - Clinical Description

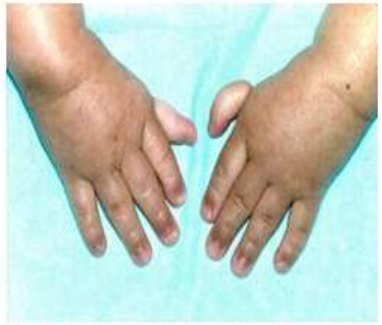
Congenital malformations

- Short stature
- Microcephaly (small head)
- Micropthalmia (small eyes)
- Hypo/hyperpigmentation
- Abnormal thumbs



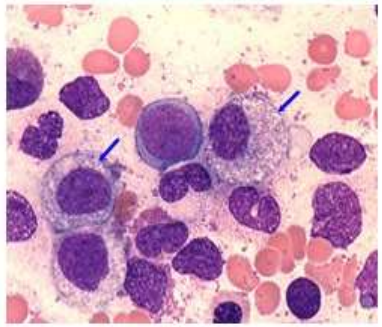
Hematological abnormalities

- Bone marrow failure
- Acute myeloid leukemia (x800)



Non-Hematological abnormalities

- Head and neck squamous cell carcinomas (x2000)
- Gynecologic squamous cell carcinomas (x4000)
- Benign and malignant liver, brain and renal tumors



Ataxia telangiectasia (AT): Patients are sensitive to gamma irradiation; patients develop neurological and skin lesions.