Molecular Repair of DNA Damage

Faculty of Applied Science- Department of Radiology

Course Name: Radiobiology Course Code: MTR 211

Second Grade/ Fall Semester 2025-2026

Lecture 4/ 23rd November 2025

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Outlines

- Why DNA Repair Matters?
- Sources of DNA Damage.
- Types of DNA Damage.
- Radiation-Induced DNA Damage.
- DNA Repair Pathways.
- Why DSBs are Dangerous?
- DSBs Repair Pathways.
- Cell Cycle Influence on DNA Repair.
- Oxygen Effect.
- Chromatin Structure and DNA Repair.
- Radiation Dose Rate.
- Misrepair Outcomes.

Learning Outcomes

By the end of the lecture, students should be able to:

- Identify major types of radiation-induced DNA damage
- Describe key DNA repair pathways
- Differentiate error-free vs error-prone mechanisms
- Explain how cell cycle phase and oxygen influence repair
- Relate misrepair to mutations, carcinogenesis, and radiosensitivity

Why DNA Repair Matters?

Cells experience DNA damage all the time, from **normal metabolism** and from **radiation**. The way a cell repairs this damage determines what happens to it.

1. Repair = Survival

- If the cell can fix the DNA damage correctly, it continues working normally.
- **Good repair → cell survives**.

2. Too Much Damage = Cell Death

- If the damage is **too severe** or **cannot be fixed**, the cell will:
- Undergo **apoptosis** (a clean, programmed death), or
- Die by **necrosis** (uncontrolled death after heavy damage).

Why DNA Repair Matters?

3. Incorrect Repair = Mutations

If the cell repairs DNA incorrectly:

- Mistakes can be left behind.
- Chromosomes can be misjoined.

These mistakes may lead to **mutations** and can eventually cause **cancer**.

4. Repair Determines Radiosensitivity

A cell's ability to repair DNA affects how sensitive it is to radiation:

- Good repair systems → **more resistant** to radiation.
- Weak or faulty repair → **more sensitive** to radiation.

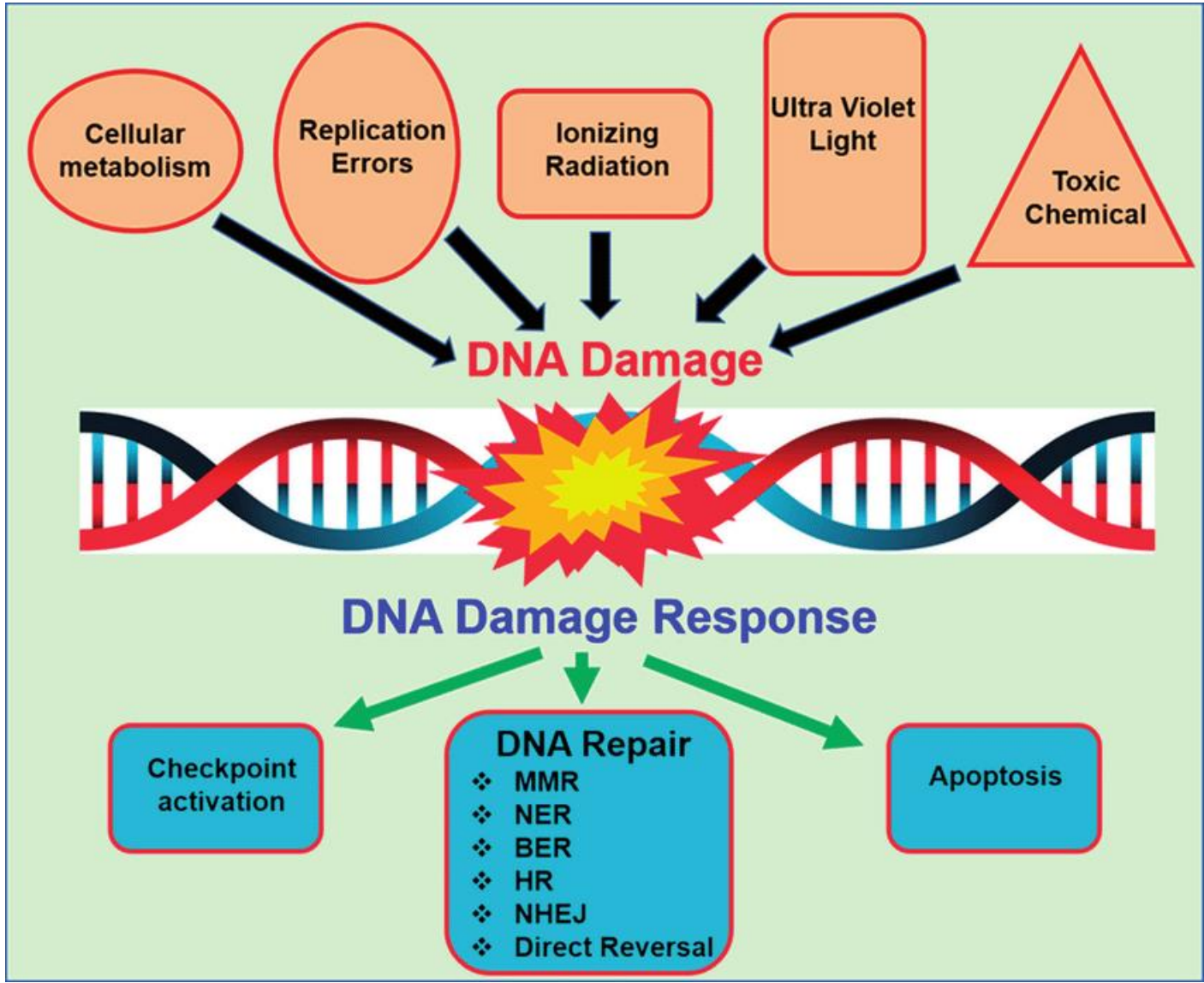
Sources of DNA Damage

Endogenous:

- ROS from metabolism
- Replication mistakes

Exogenous:

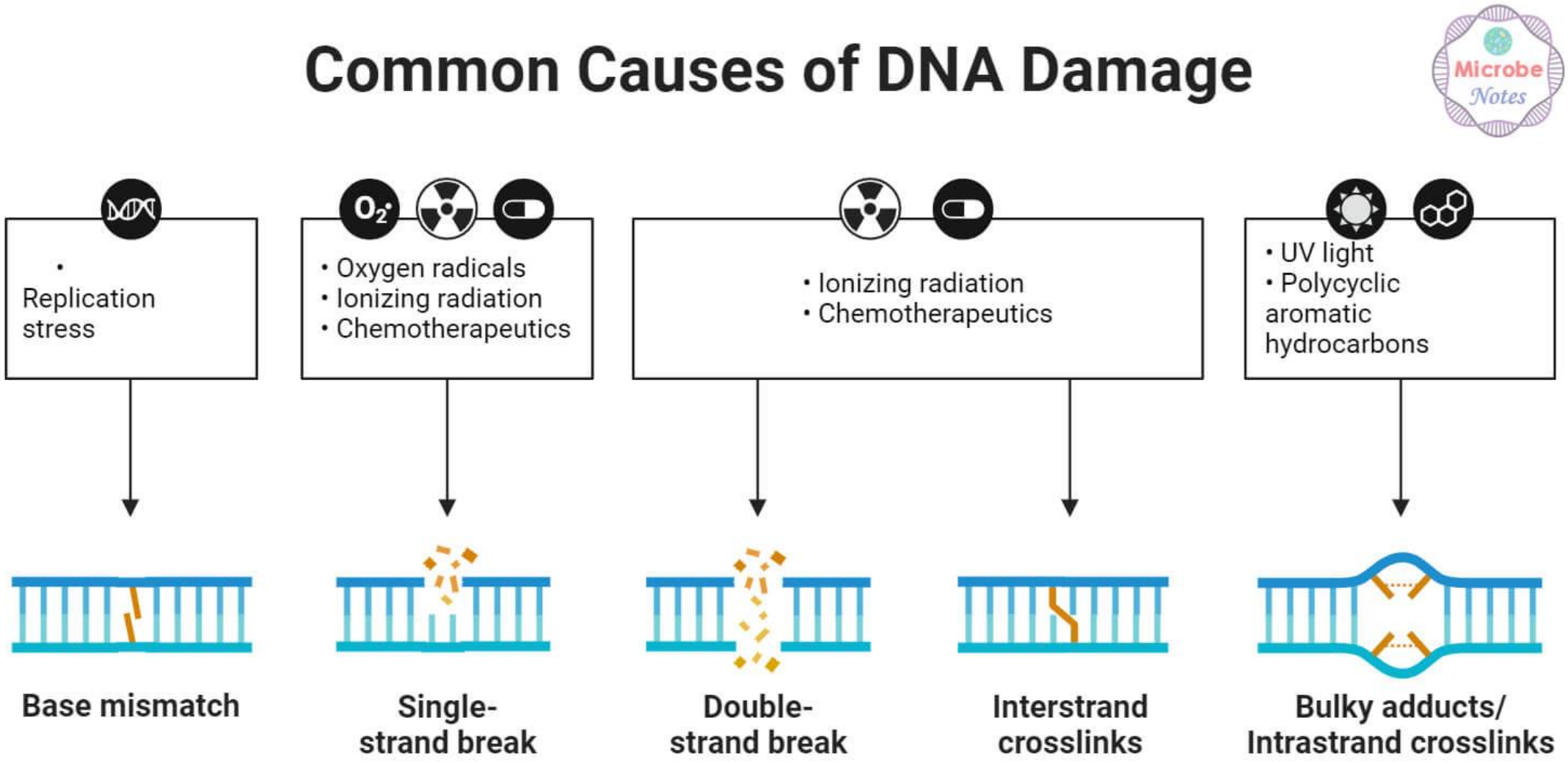
- Ionizing radiation
- UV light
- Chemicals



Types of DNA Damage

- **Single-Strand Breaks (SSBs):** A break in **one DNA strand**; usually repaired quickly because the opposite strand is still intact.
- **Double-Strand Breaks (DSBs):** Both **strands are broken**, leaving no template for accurate repair and increasing the risk of mutations or cell death.
- **Base Damage:** Individual bases are **chemically altered**; if not fixed, they can mispair during replication and cause point mutations.
- **Crosslinks:** Two DNA strands become **chemically bonded together**, preventing the helix from opening and blocking replication and transcription.
- **DNA–Protein Crosslinks:** **DNA is stuck to proteins**, physically obstructing essential DNA-processing enzymes.
- **Clustered Lesions:** **Several different damages** occur very close together, making repair difficult and often resulting in errors or conversion to DSBs.

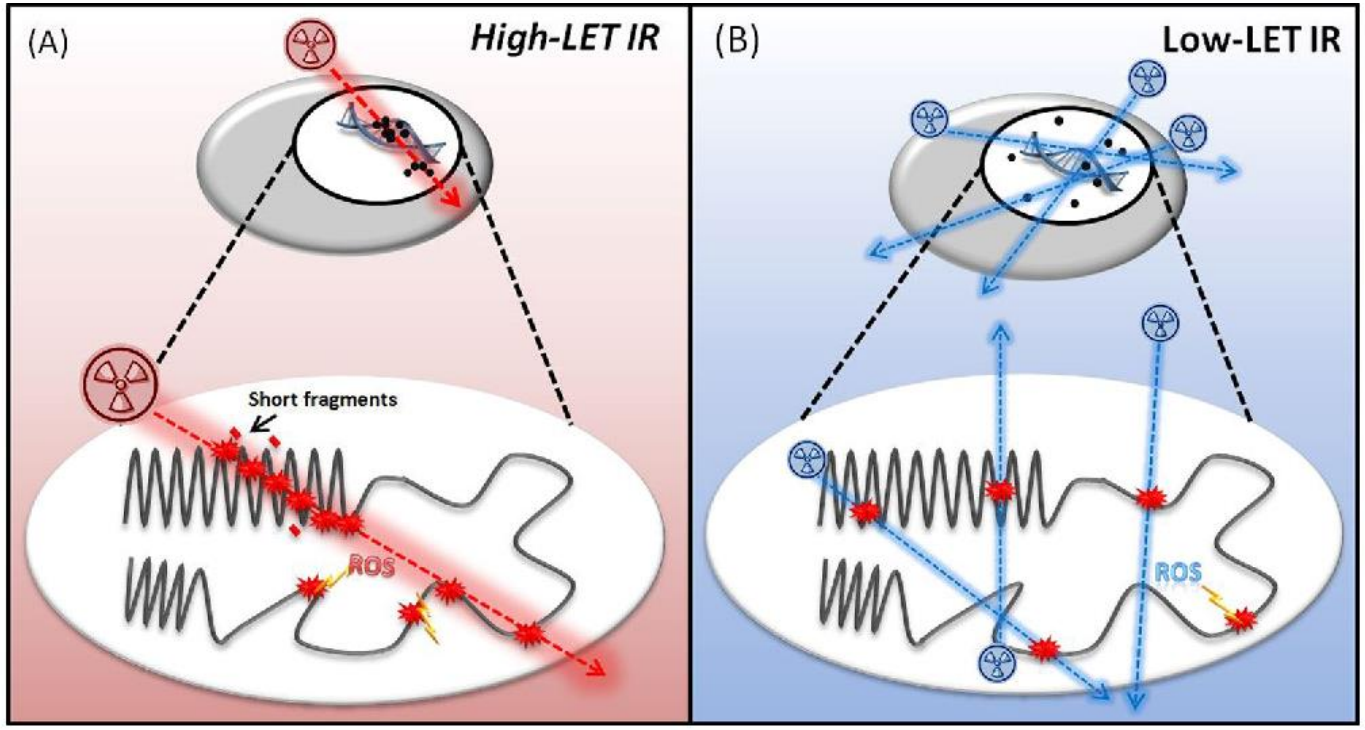
Types of DNA Damage



Radiation-Induced DNA Damage

- **Low-LET radiation** (e.g., **X-rays, gamma rays**): produces sparse, isolated DNA damage that is **easier for the cell to repair**.

- **High-LET radiation** (e.g., **alpha particles, neutrons**) creates dense, clustered damage, including multiple breaks close together, which is much **harder to repair**.



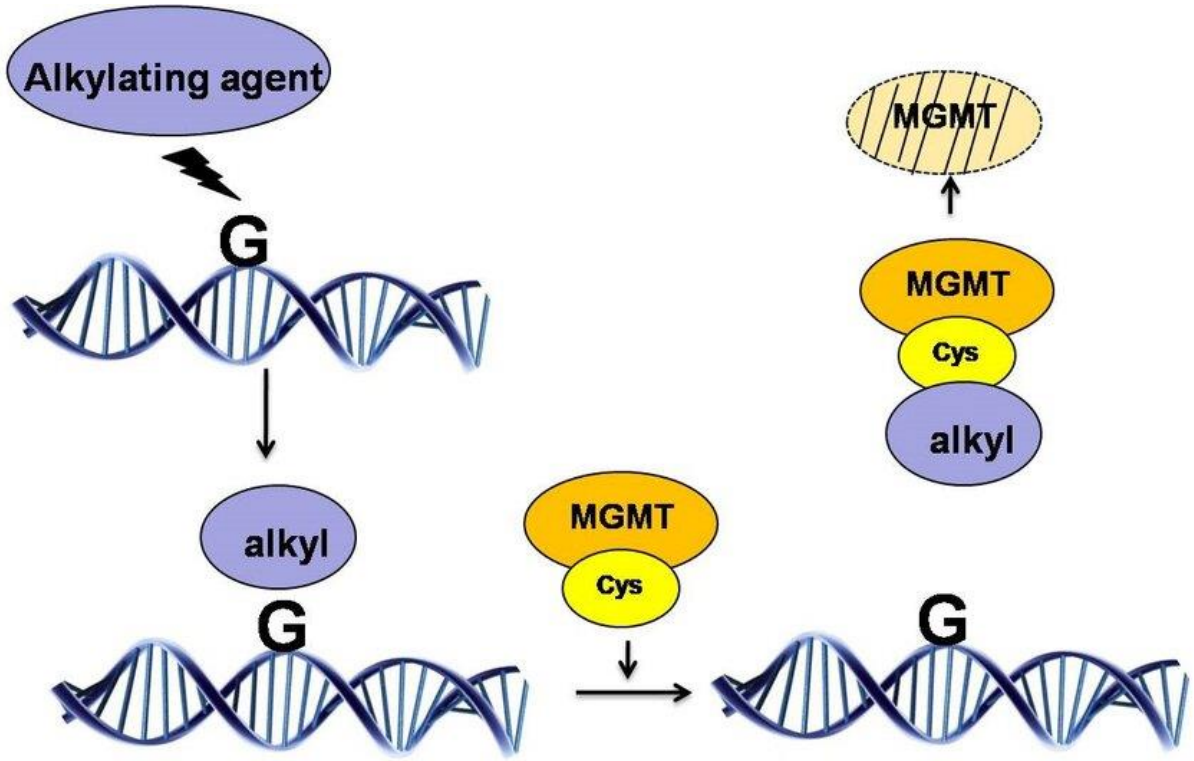
DNA Repair Pathways

Cells have multiple repair systems depending on the type of DNA damage:

1. **Direct Repair:** Fixes certain lesions without removing DNA bases.
2. **Base Excision Repair (BER):** Repairs small, simple base changes and single-strand breaks.
3. **Nucleotide Excision Repair (NER):** Removes bulky, helix-distorting lesions like UV-induced dimers.
4. **Mismatch Repair (MMR):** Corrects errors from DNA replication (wrong bases or small insertions/deletions).
5. **Double-Strand Break Repair:**
   - **Non-Homologous End Joining (NHEJ):** Fast, error-prone repair.
   - **Homologous Recombination (HR):** Accurate repair using a sister chromatid.
   - **Alternative End Joining (alt-EJ):** Backup, very error-prone pathway.

Direct Repair

- Some DNA lesions can be repaired directly, **without removing bases or cutting the DNA**.
- **Example:** MGMT removes harmful alkyl groups from guanine.
- Fast and accurate, but **only works for a limited set of DNA damages**.
- Photolyase can reverse UV-induced pyrimidine dimers in bacteria (not in humans).



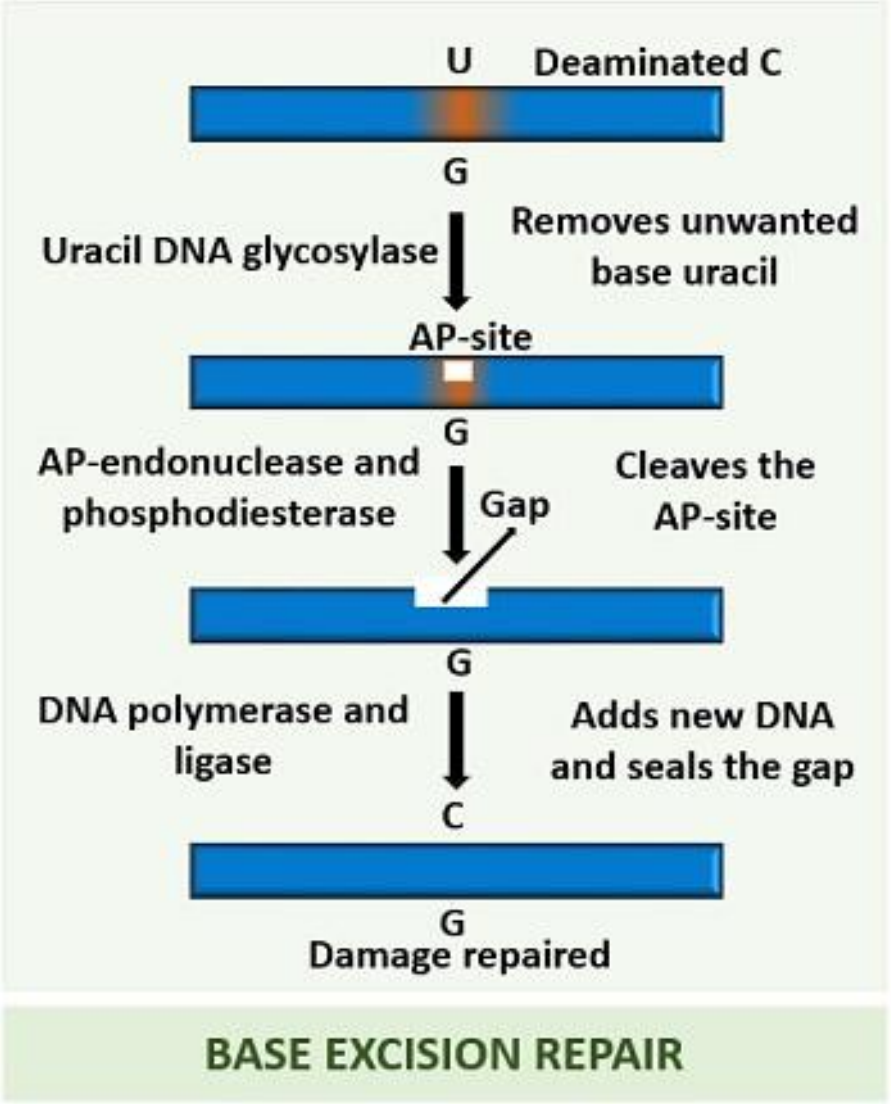
Base Excision Repair (BER)

- Repairs small, simple DNA lesions like oxidized or alkylated bases and single-strand breaks.

Steps:

1. **DNA glycosylase** removes the damaged base.
2. **AP endonuclease** cuts the DNA backbone.
3. **DNA polymerase** inserts the correct base.
4. **DNA ligase** seals the strand.

- Quick and accurate, keeps DNA stable and prevents mutations.



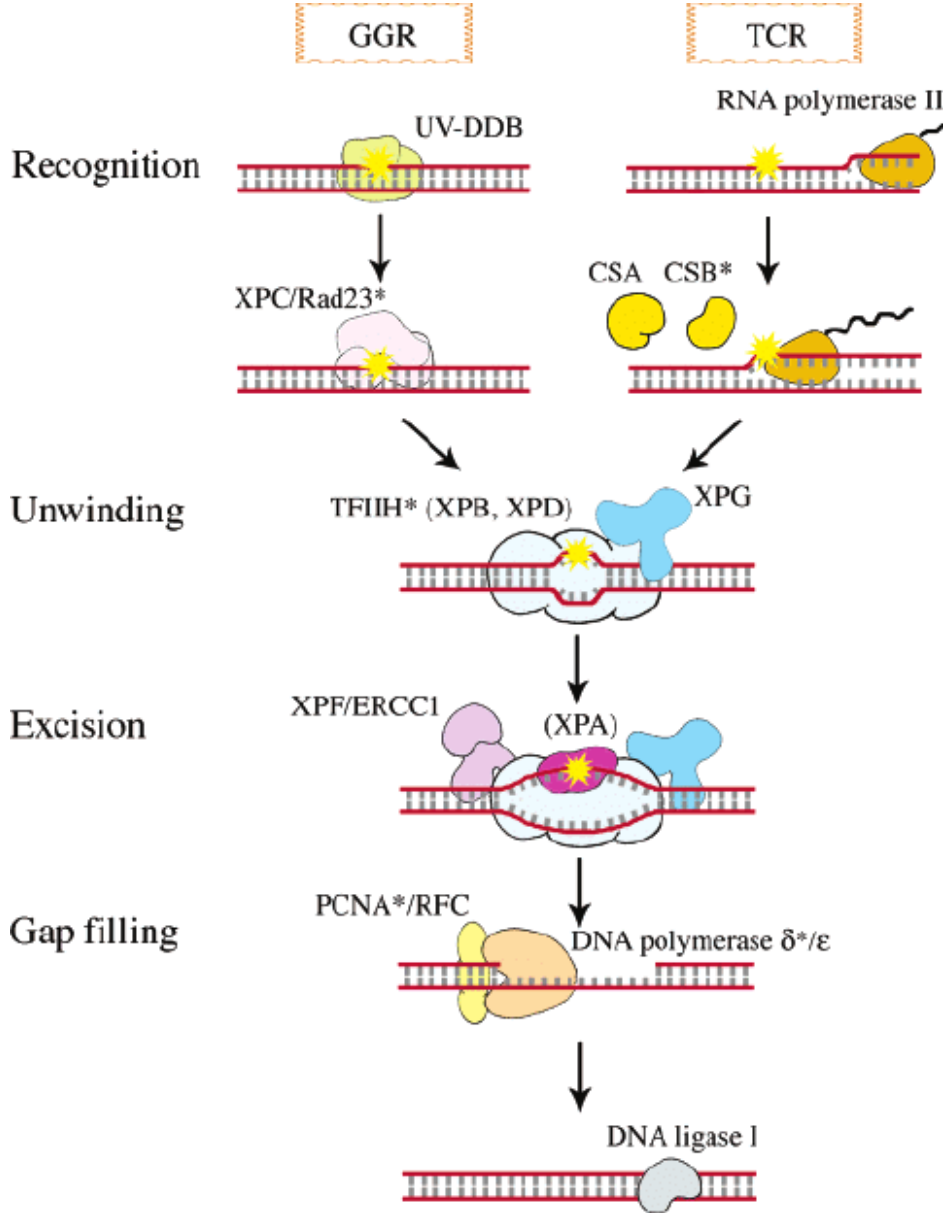
Nucleotide Excision Repair (NER)

- Repairs bulky DNA lesions that distort the DNA helix, like UV-induced pyrimidine dimers or chemical adducts.

Two types:

1. **Global Genome NER (GG-NER):** scans the whole genome for damage.
2. **Transcription-Coupled NER (TC-NER):** fixes damage on actively transcribed genes.

- Defects in NER cause Xeroderma Pigmentosum (XP), making cells extremely sensitive to UV light.

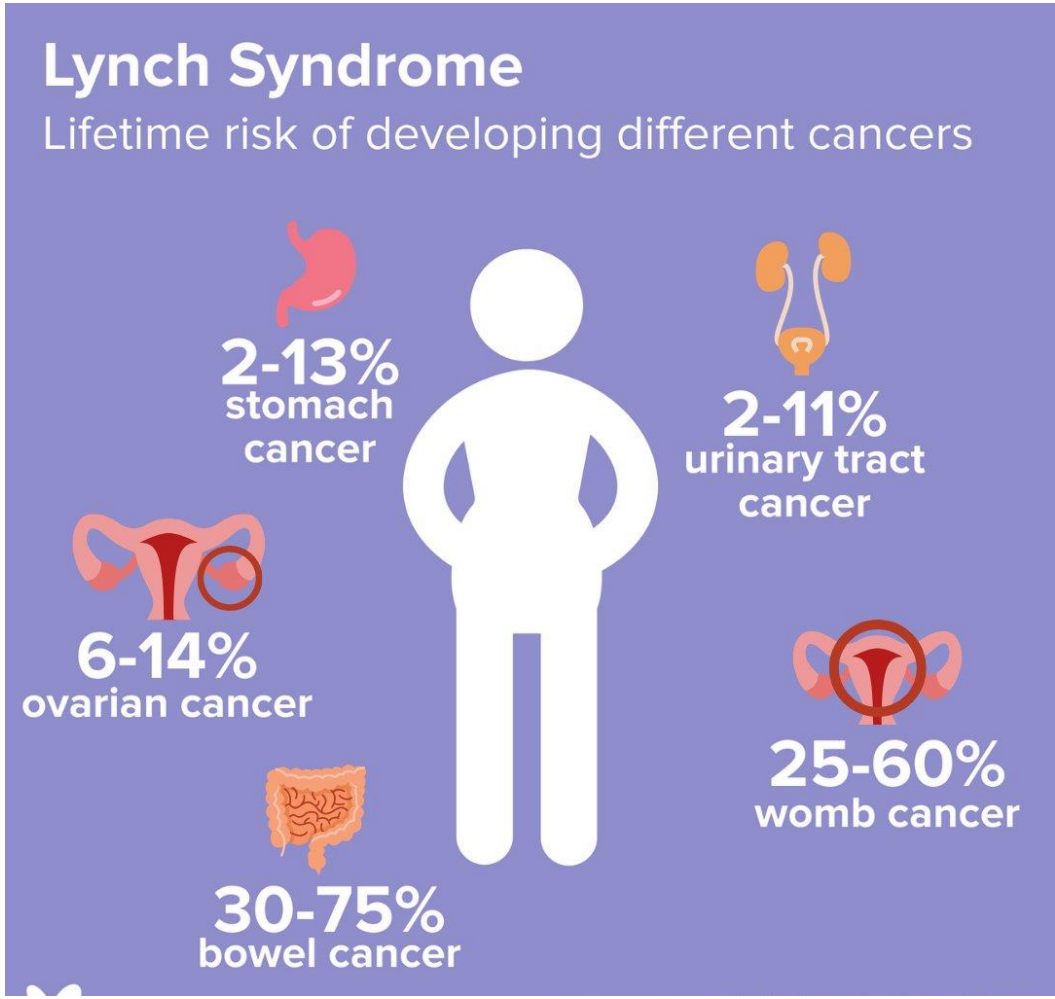


Mismatch Repair (MMR)

Fixes errors that occur during DNA replication, such as:

1. **Wrong base pairs** (e.g., A paired with C)
2. **Small insertions** or **deletions**

- *Prevents mutations from being passed on during cell division*.
- Defects in MMR cause **microsatellite instability** and **increase cancer risk**, such as in **Lynch syndrome**.



Why Double-Strand Breaks (DSBs) Are Dangerous?

- DSBs involve breaks in **both DNA strands** at the **same location**.
- They are the **most lethal type of DNA damage** because **there is no intact strand to guide repair**.

If unrepaired or repaired incorrectly, they can cause:

1. **Mutations**
2. **Chromosomal rearrangements**
3. **Cell death**

DSBs are the main reason radiation can kill cells.

Double-Strand Break (DSB) Repair Pathways

Cells use **two main pathways** to repair double-strand breaks:

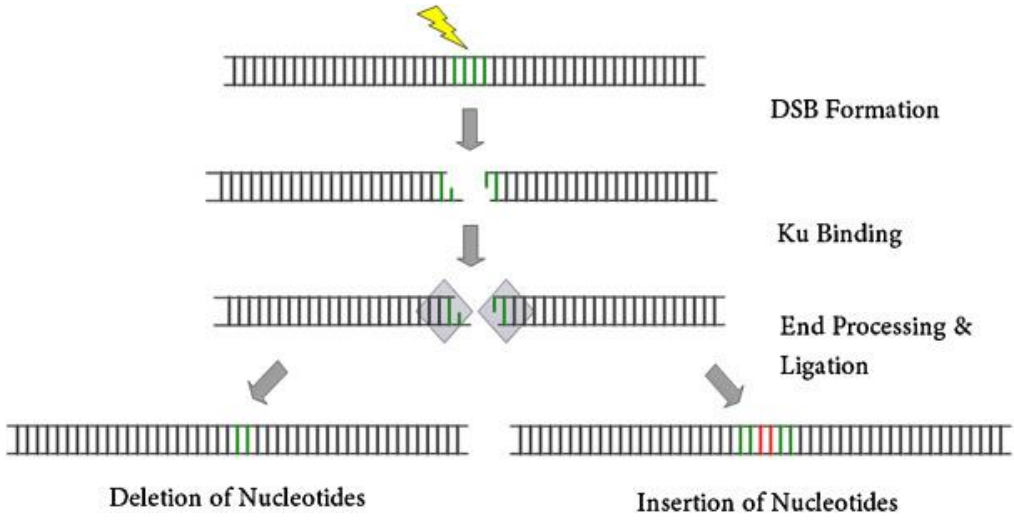
1. **Non-Homologous End Joining (NHEJ)**
    1. Fast and works throughout the cell cycle.
    2. Does **not need a template**, but is **error-prone** (can cause small insertions/deletions).

2. **Homologous Recombination (HR)**
    1. Accurate repair using a **sister chromatid as a template**.
    2. Works mainly in **S and G2 phases** of the cell cycle.

3. There is also **Alternative End Joining (alt-EJ)**, a backup, **very error-prone** pathway.

Non-Homologous End Joining (NHEJ)

- Repairs double-strand breaks **quickly without using a template**.
- Dominant in **G0 and G1 phases** of the cell cycle.



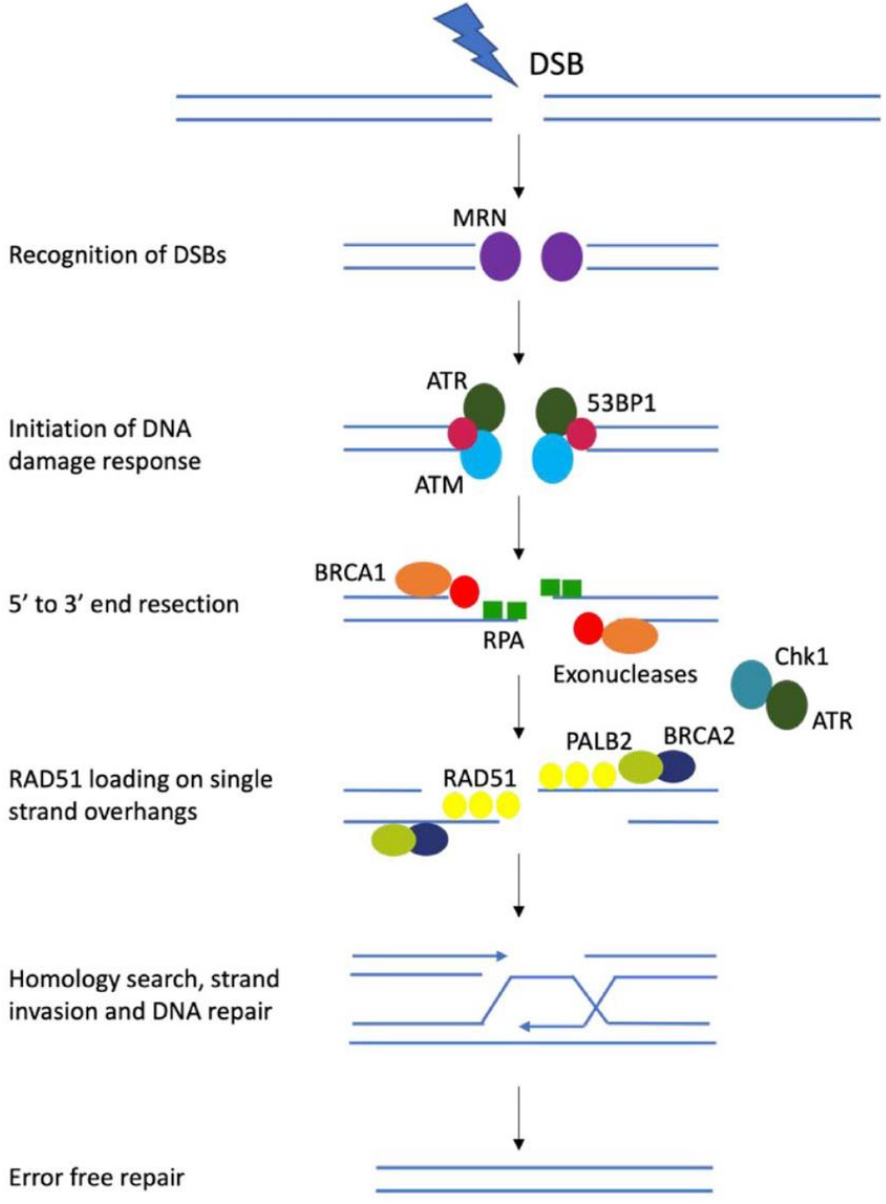
Steps:

1. Ku70/Ku80 proteins bind to DNA ends.
2. DNA-PKcs and Artemis process the ends.
3. DNA ligase IV joins the ends.

- **Fast but error-prone** → may introduce small insertions or deletions.

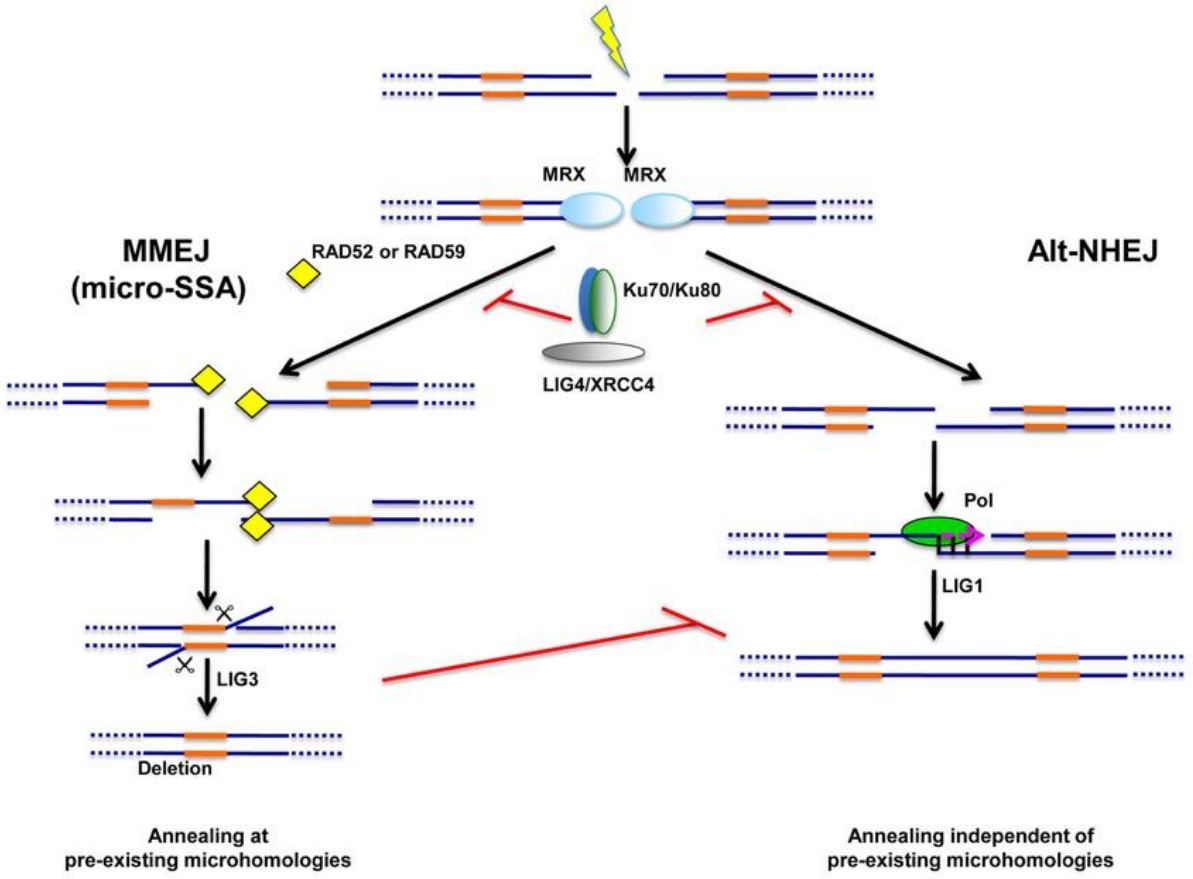
Homologous Recombination (HR)

- Repairs **double-strand breaks accurately** using a **sister chromatid as a template**.
- Active mainly in **S and G2 phases** of the cell cycle.
- Key proteins: **BRCA1, BRCA2, RAD51**.
- **Very accurate**, but slower than NHEJ.
- Defects in HR (e.g., BRCA mutations) increase **genomic instability** and **cancer risk**.



Alternative End Joining (alt-EJ)

- A **backup pathway** for repairing double-strand breaks when NHEJ fails.
- Uses **short microhomology sequences** to join DNA ends.
- **Slower and very error-prone**, often introducing deletions or rearrangements.
- It can contribute to **genomic instability** and **mutations**.

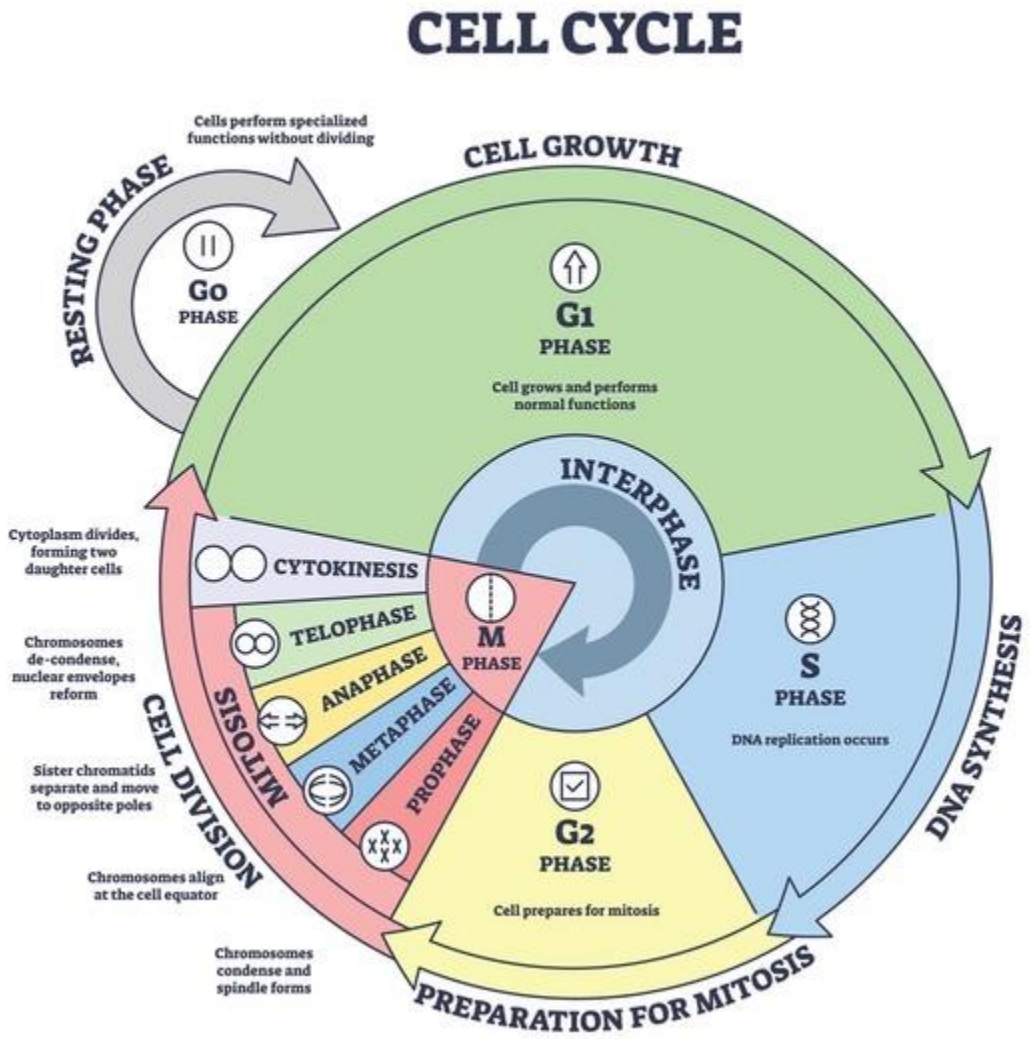


Cell Cycle Influence on DNA Repair

- The **cell cycle stage** affects which repair pathway is used and repair efficiency.

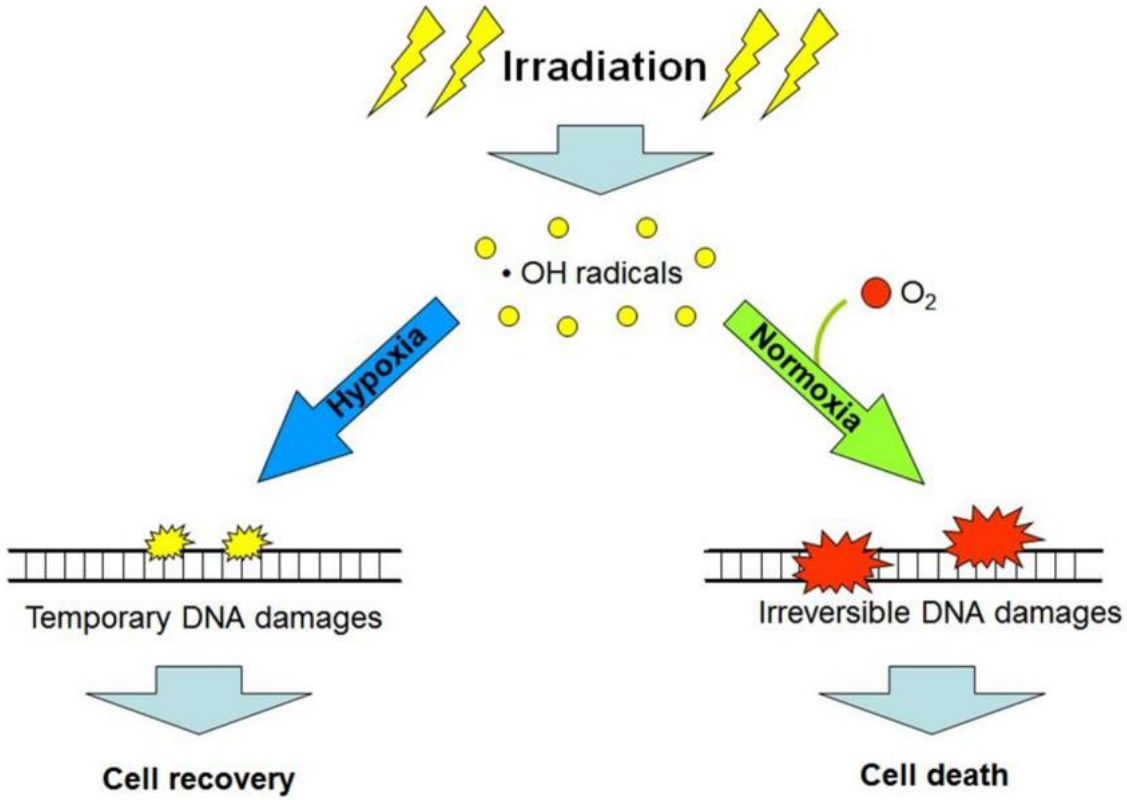
1. **G1 phase:** NHEJ is dominant (fast, works without a template).
2. **S and G2 phases:** HR becomes active (accurate, needs sister chromatid).
3. **M phase:** Repair is largely suppressed → cells are highly **radiosensitive**.

- Understanding this helps explain why cells respond differently to radiation at different stages.



Oxygen Effect

- Oxygen makes radiation damage **permanent** by reacting with DNA radicals ("oxygen fixation").
- **Well-oxygenated cells** → more damage → **more radiosensitive**.
- **Hypoxic cells** (low oxygen, often in tumors) → damage is more easily repaired → **more radioresistant**.
- This is important in **radiotherapy**, as oxygen levels influence treatment effectiveness.

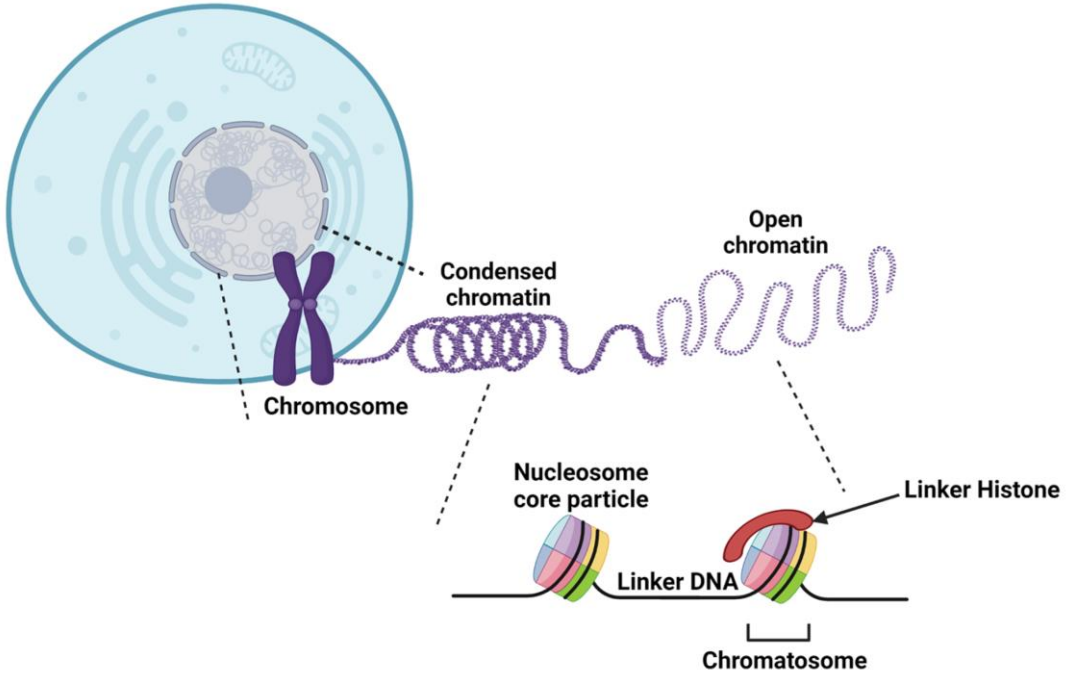


Chromatin Structure and DNA Repair

- DNA is packed into **chromatin**, which affects repair efficiency.

1. **Euchromatin** (loosely packed) → repair proteins can access damage **quickly**.
2. **Heterochromatin** (tightly packed) → repair is **slower and more complex**.

- Chromatin remodeling is often needed before repair can occur, influencing **radiosensitivity**.

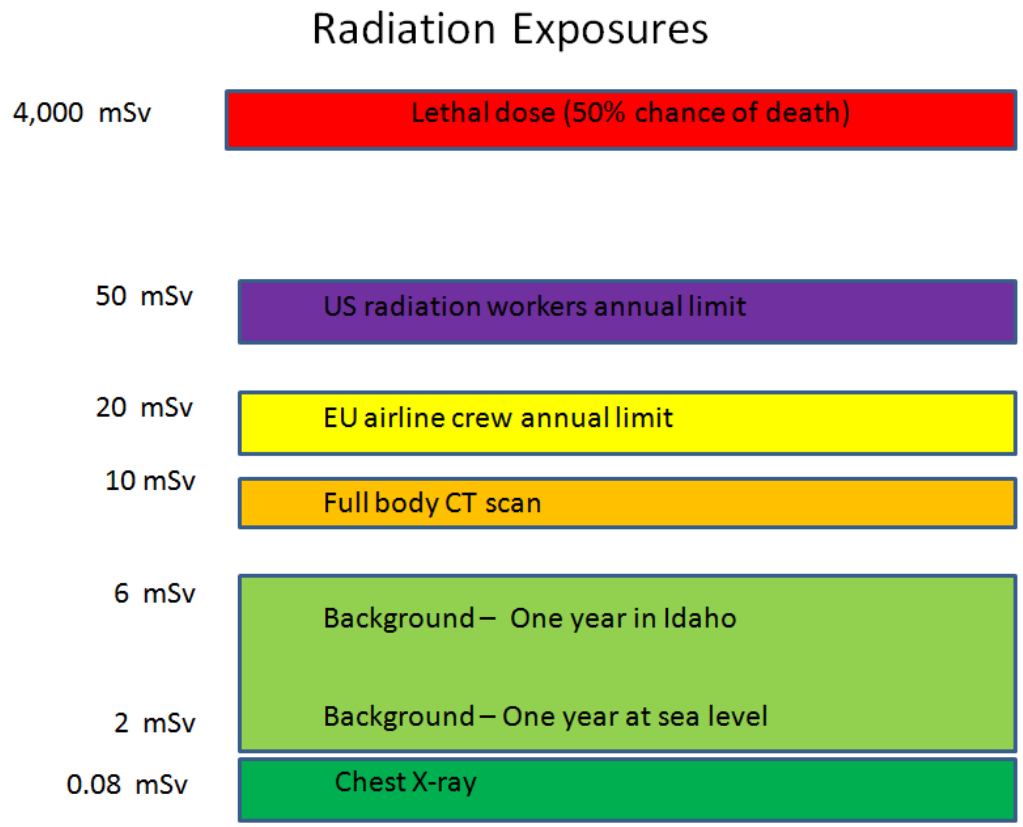


Radiation Dose Rate

- The **rate at which radiation is delivered** affects DNA repair and cell survival.

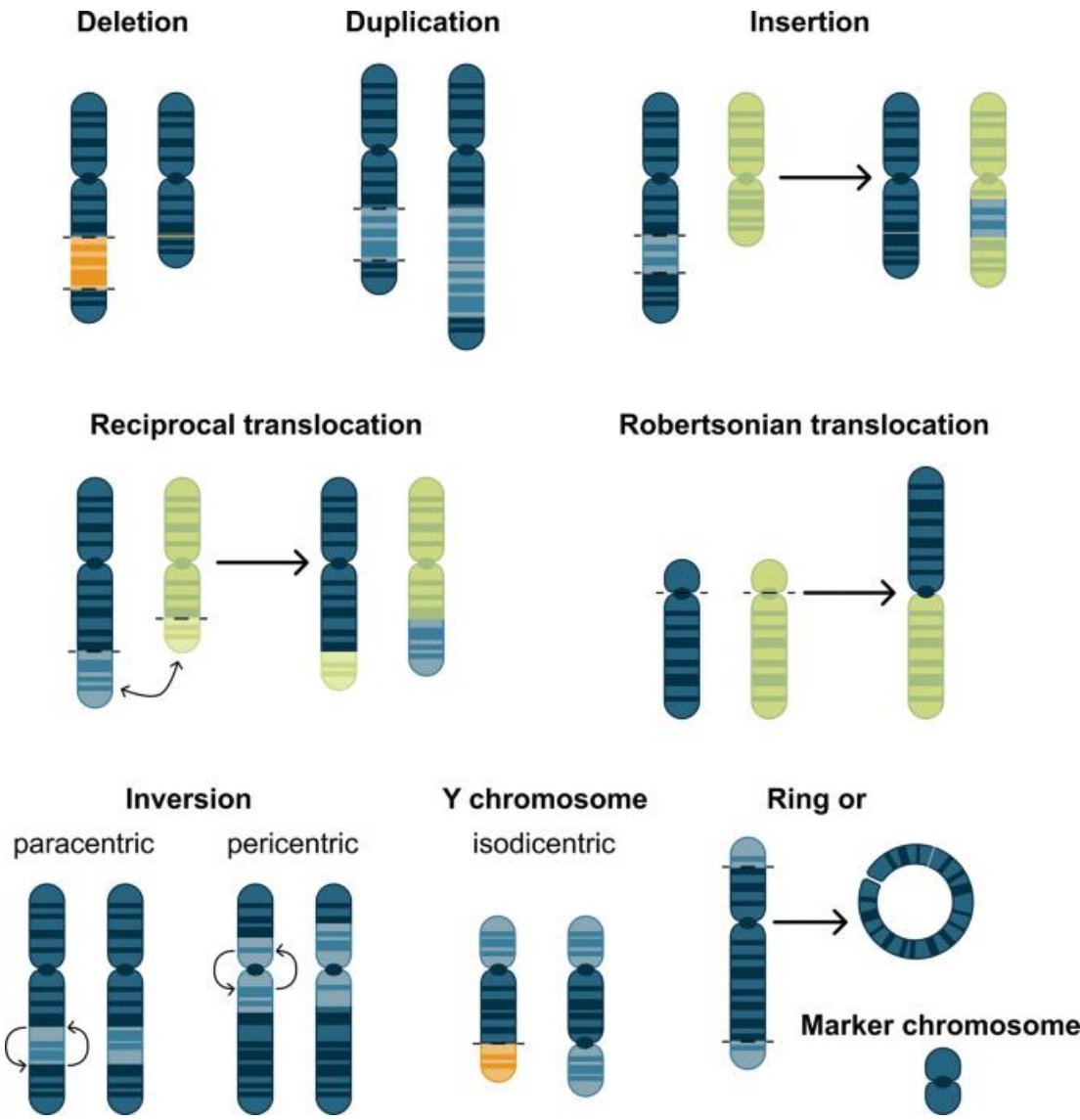
1. **Low dose rate:** gives cells more time to repair damage → **less cell killing**.
2. **High dose rate:** overwhelms repair systems → **more cell death and mutations**.

- This principle is important in **radiotherapy planning** and radiation protection.



Misrepair Outcomes

- When DNA repair goes wrong, it can cause **mutations** or **chromosomal changes**.
- **Examples:** point mutations, deletions, translocations, dicentrics, or ring chromosomes.
- Misrepair can lead to **genomic instability** and increase the risk of **cancer**.
- Accurate repair is therefore critical for **cell survival and genome integrity**.



Questions? Comments?

Thank you!