The Effect of Radiation on Cells

Faculty of Applied Science- Department of Radiology

Course Name: Radiobiology Course Code: MTR 211

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Outlines

- Introduction: How Radiation Affects the Cell.
- Major Cellular Targets of Radiation.
- Possible Cellular Outcomes: Survival, Mutation, Death.
- Modulating Factors of Cellular Outcomes.
- Mechanisms of Radiation Action.
- The Oxygen Effect and Its Role in Cellular Radiosensitivity.
- Radiosensitizers: Agents That Enhance Radiation Effects.
- Radioprotectors: Agents That Protect Cells from Radiation Damage.
- Irradiation-Induced Cellular Damage.
- Molecular Sensors of Radiation-Induced DNA Damage.
- DNA Damage Response (DDR): Detection and Coordination of Repair.
- Clinical Implications: Oxygen Effect & Radiosensitizers in Radiotherapy.
- Clinical Use of Radioprotectors to Protect Normal Tissues.

Learning Outcomes

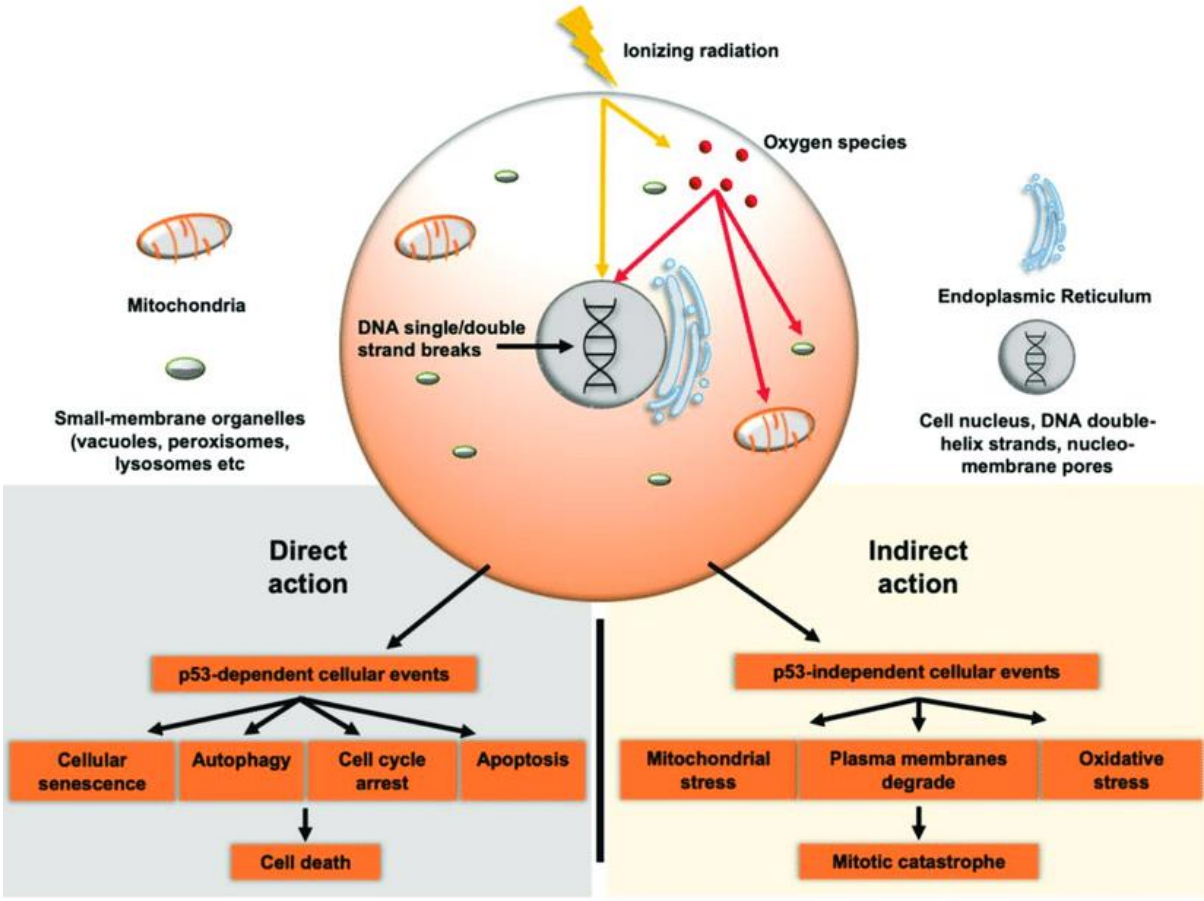
By the end of the lecture, students should be able to:

- Explain how ionizing radiation interacts with cellular components.
- Describe the oxygen effect and its role in radiosensitivity.
- Distinguish between radiosensitizers and radioprotectors.
- Identify types of radiation-induced damage in cells.
- Outline the mechanisms of DNA damage response and sensors of damage.

Introduction: How Radiation Affects the Cell

Ionizing Radiation → Atomic & Molecular Interactions → Biological Damage

- When a cell is exposed to ionizing radiation (X-rays, γ-rays, electrons, heavy ions, etc.), energy is deposited along the path of radiation by **ionizations** and **excitations** of atoms and molecules in cellular water and biomolecules.
- These ionizations produce **free radicals** (especially ·OH, H·, $O_2^{\cdot -}$) via radiolysis of water (**since the cell is ~70-80% water**).
- These radicals diffuse and react with nearby molecules (**DNA, proteins, lipids**).
- Some fraction of the damage is due to **direct interactions** (radiation directly ionizes the DNA or other biomolecule), and some is **indirect** via radical chemistry.



Major Cellular Targets of Radiation

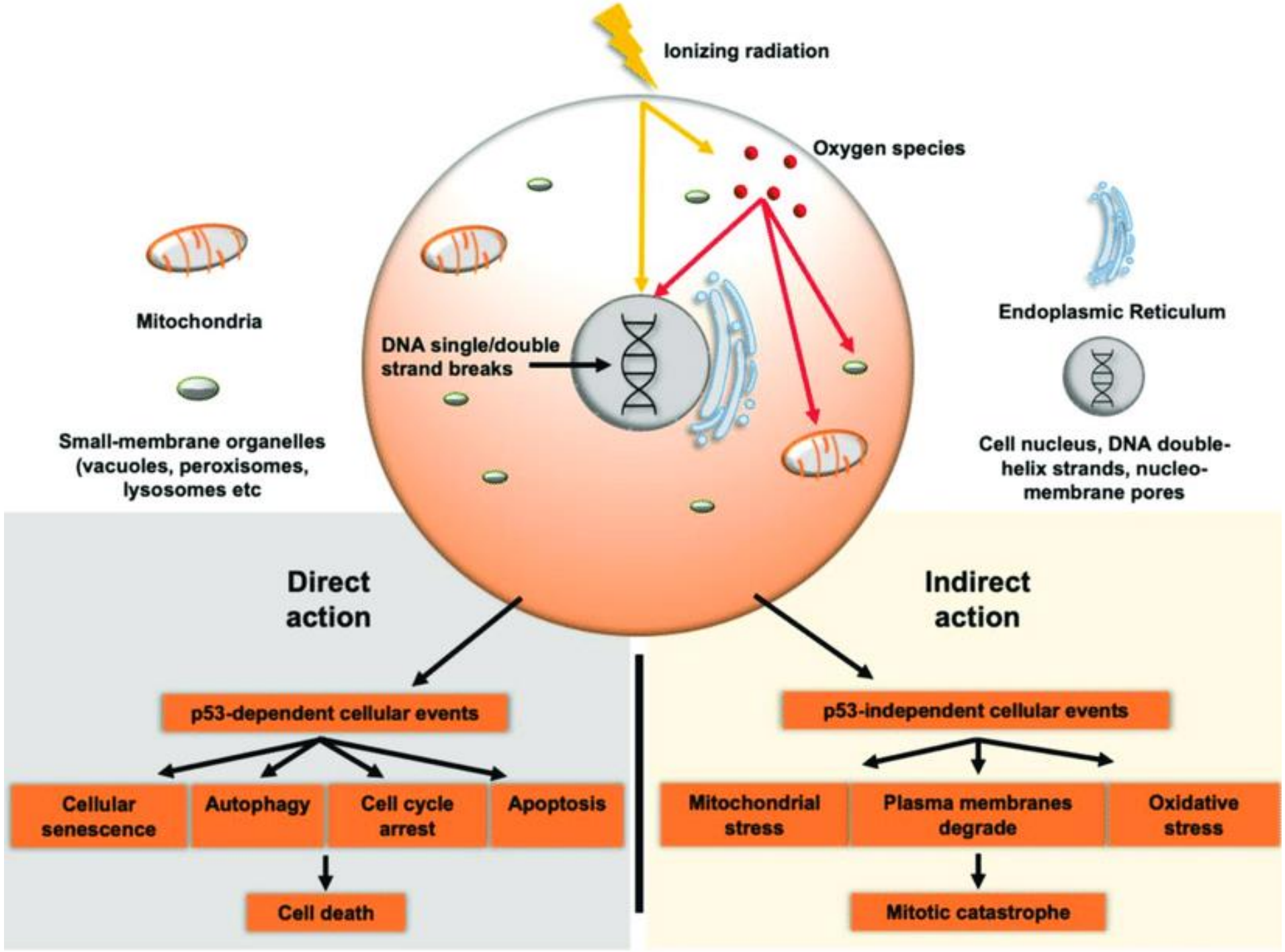
Cellular Target	How Radiation Affects It & Consequences
DNA (nuclear & mitochondrial)	Breakage of chemical bonds, base damage, cross-links, strand breaks (single or double): these are often the critical lesions that determine cell fate.
Cell Membrane / Lipids	Free radical attack → lipid peroxidation, changes in membrane permeability, altered transport, loss of membrane integrity
Proteins / Enzymes	Oxidation or modification of amino acids, loss of enzyme activity, disruption of signaling or structural proteins
Mitochondria	Damage to mitochondrial DNA, membranes → increased reactive oxygen species (ROS), loss of membrane potential, triggering apoptosis pathways

Possible Cellular Outcomes: Survival, Mutation, Death

After irradiation, a cell's fate is determined by the extent and type of damage, the efficiency of repair systems, and the cellular context (cell cycle stage, presence of checkpoints, metabolic state).

- **Cell Survival (correct repair):** If damage is **modest and reparable**, the cell may successfully repair the lesions (**using DNA repair pathways**) and continue to survive, divide, and **function normally**.
- **Mutation or Transformation:** If repair is error-prone or incomplete, residual lesions or misrepaired DNA can lead to **mutations, chromosomal aberrations, or genomic instability**. Over time, these changes may contribute to **carcinogenesis**.
- **Cell Death:** If damage is too extensive or repair fails, the cell may be eliminated by different death pathways, such as:

1. **Mitotic (reproductive) death:** The cell attempts division with damaged chromosomes → lethal chromosome aberrations → inability to proliferate.
2. **Apoptosis (programmed cell death):** Activation of cell death pathways when damage is sensed (often via p53).
3. **Necrosis** or other forms of death (especially at very high doses, or in non-dividing cells).


Ionizing radiation
Oxygen species
Mitochondria
Small-membrane organelles (vacuoles, peroxisomes, lysosomes etc
DNA single/double strand breaks
Endoplasmic Reticulum
Cell nucleus, DNA double-helix strands, nucleo-membrane pores
Direct action
Indirect action
p53-dependent cellular events
Cellular senescence
Autophagy
Cell cycle arrest
Apoptosis
Cell death
p53-independent cellular events
Mitochondrial stress
Plasma membranes degrade
Oxidative stress
Mitotic catastrophe

Modulating Factors of Cellular Outcomes

- **Dose and dose rate:** Higher doses produce more complex, clustered damage. Lower dose rate allows repair to keep up.

- **Radiation quality / LET (Linear Energy Transfer):** High-LET radiation (e.g. α-particles) produces dense clusters of damage that are more lethal and less reparable.

- **Cell cycle phase:** Cells in **G_2/M** are more radiosensitive; **S phase** is often more resistant due to active repair and replication-associated protection.

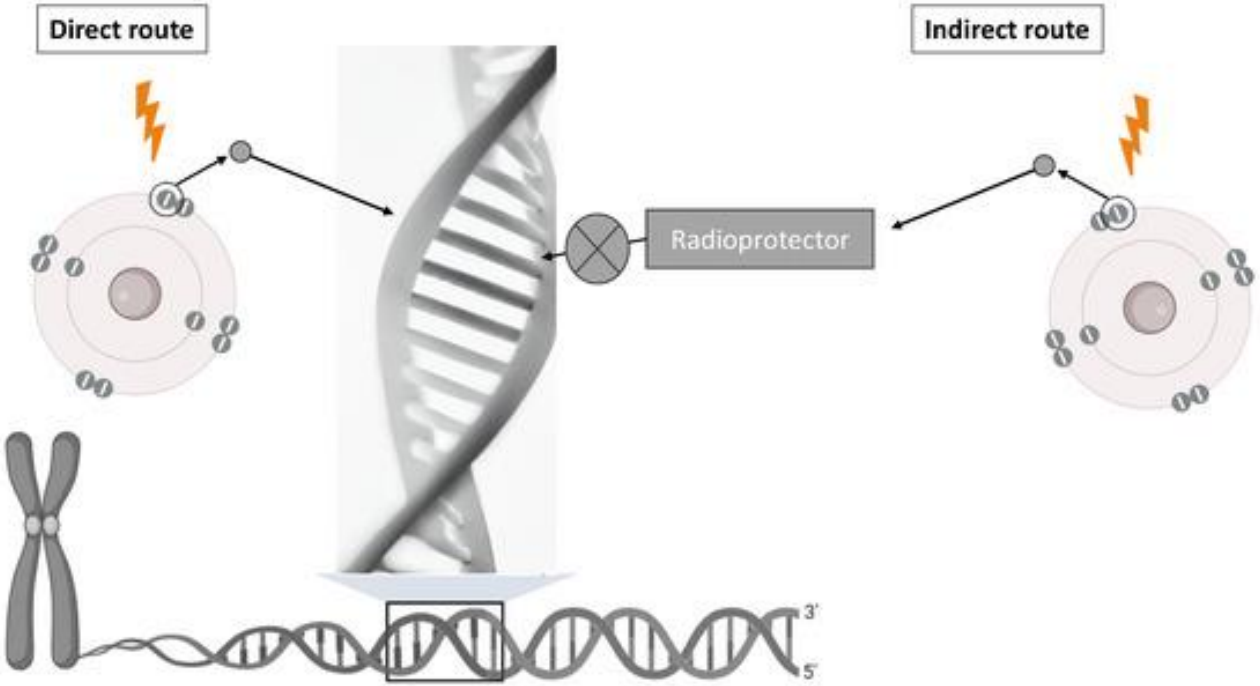
- **Repair capacity/genetic background:** Cells with **efficient DNA repair** (e.g., proficient homologous recombination, non-homologous end joining) are more resistant; cells with **DNA repair defects** are radiosensitive (e.g., in Ataxia–telangiectasia).

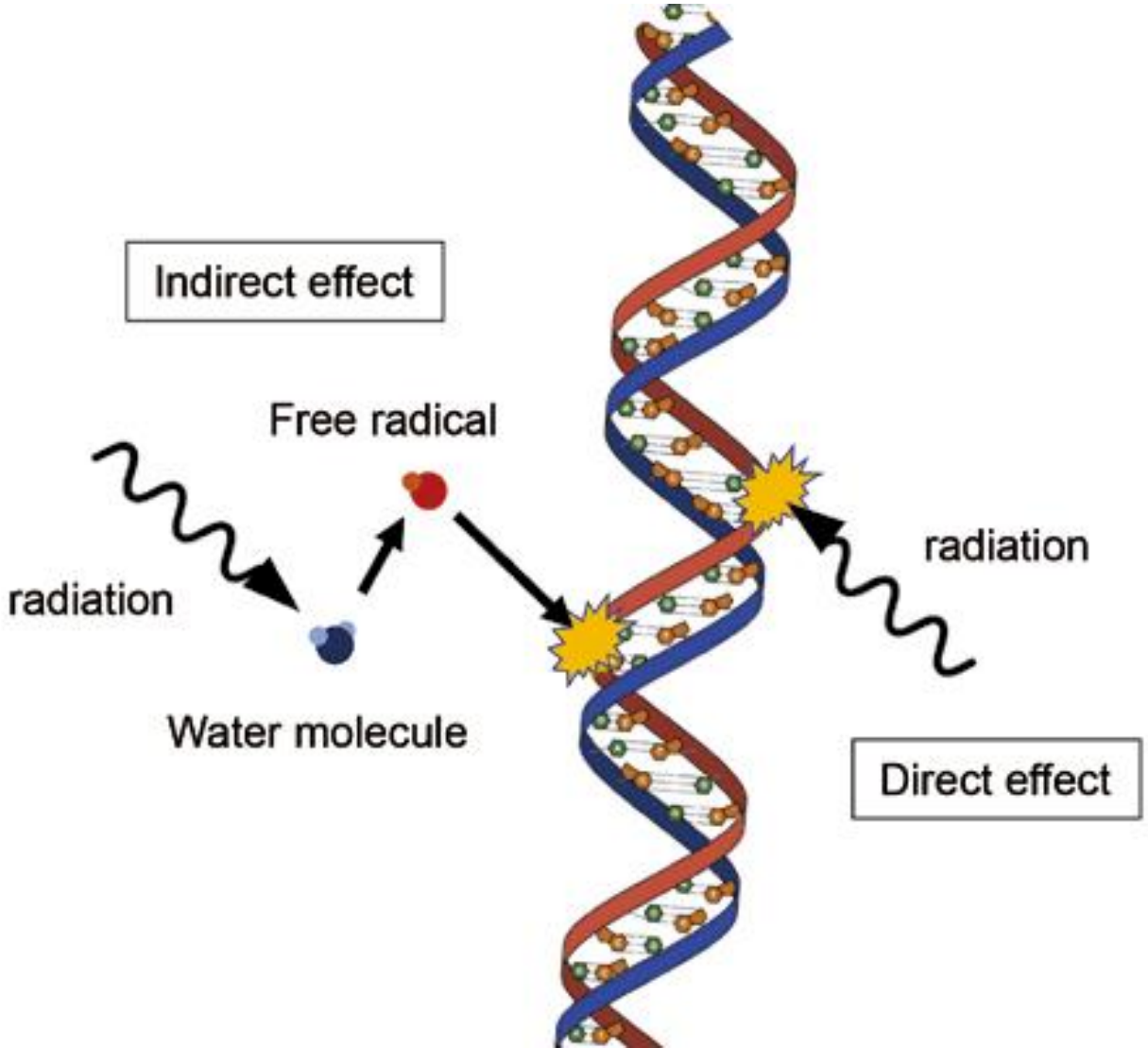
Modulating Factors of Cellular Outcomes

- **Oxygenation, microenvironmental factors:** **Presence of oxygen** “fixes” radical damage, making it permanent (oxygen effect).

- **Checkpoint activation/signaling networks**: Good cell cycle checkpoints can allow repair time; defective checkpoints may push cells into lethal mitosis or apoptosis.

Mechanisms of Radiation Action





The Oxygen Effect and Its Role in Cellular Radiosensitivity

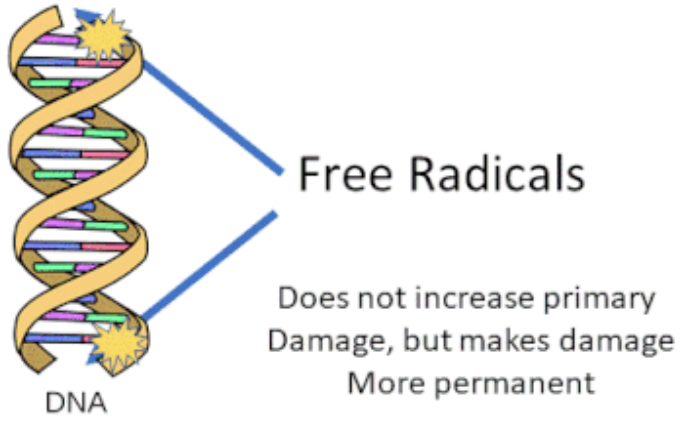
- The **Oxygen Effect** describes the phenomenon in which the **presence of oxygen** during **irradiation** enhances the biological damage produced by ionizing radiation.
- Oxygen increases the **fixation of radiation-induced damage**, making it permanent and non-repairable.
- Cells irradiated in oxygen-rich (aerobic) conditions are **2–3 times more radiosensitive** than those in oxygen-deficient (hypoxic) conditions.

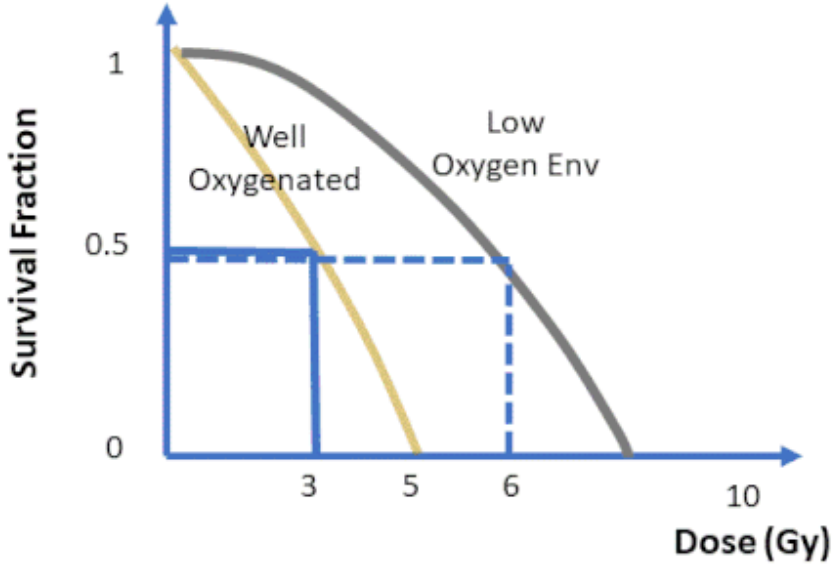
Typical OER values:

1. ~3.0 for low-LET radiations (X-rays, γ-rays).
2. ~1.0–1.5 for high-LET radiations (α-particles, neutrons).

The Oxygen Effect and Its Role in Cellular Radiosensitivity

- **Without Oxygen (Hypoxic Conditions):** $R\bullet + H\bullet \rightarrow RH$ (Damage repaired).
- **With Oxygen (Aerobic Conditions):** $R\bullet + O2 \rightarrow ROO\bullet$ (Damage fixed – permanent).
- The **Oxygen Enhancement Ratio (OER)** quantifies this effect:





$$OER = \frac{Dose\ without\ Oxygen}{Dose\ with\ Oxygen} = \frac{Dose\ in\ hypoxia}{Dose\ in\ air}$$

Takeaway More O_2 -> Less Repair -> More Damage

Radiosensitizers: Agents That Enhance Radiation Effects

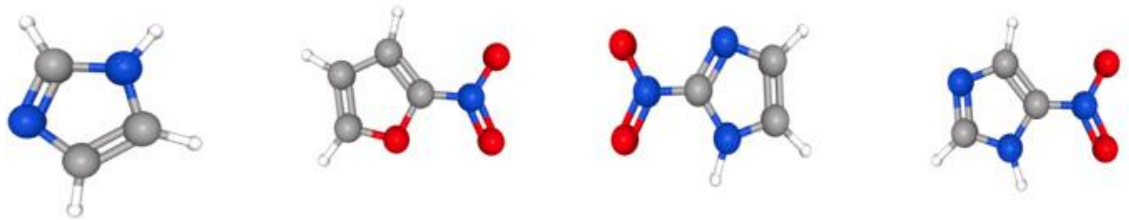
- Radiosensitizers are chemical or biological agents that increase the sensitivity of cells or tissues to ionizing radiation.
- They act by enhancing radiation-induced DNA damage or inhibiting repair processes, making cells more likely to die after irradiation.

Mechanisms of Action:

1. **Oxygen Mimicry:**
   - Mimic oxygen's role in "fixing" radiation damage.
   - Example: Nitroimidazoles.

2. **Inhibition of DNA Repair:**
   - Block cellular mechanisms that fix DNA breaks.
   - Example: PARP inhibitors.

(a) Oxygen mimics radiosensitizers



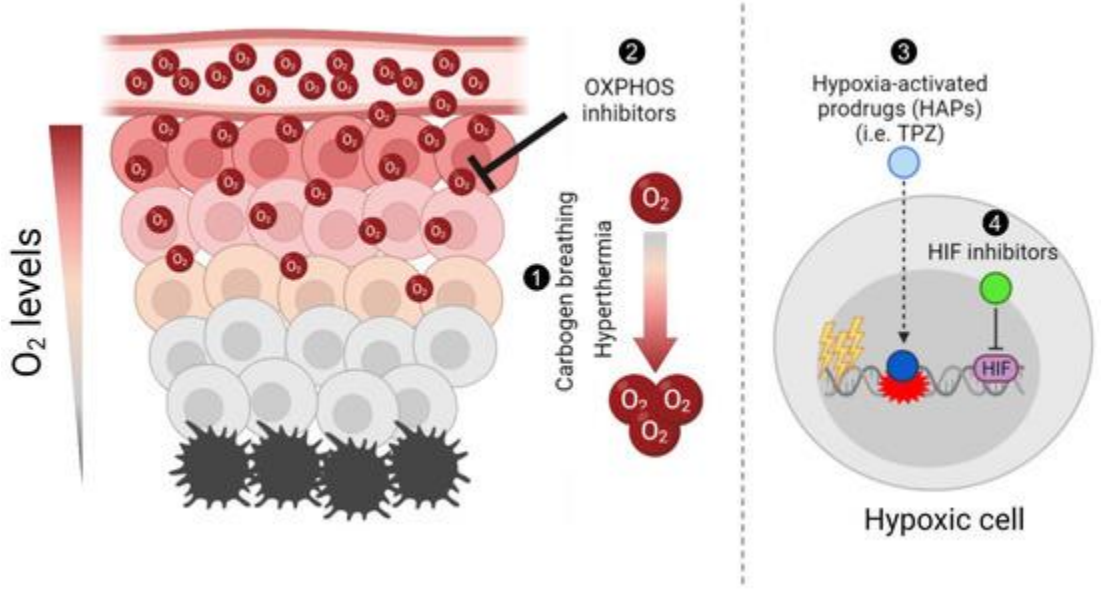
Imidazole ($C_3H_4N_2$) | 2-Nitrofuran ($C_4H_3NO_3$) | 2-Nitroimidazole ($C_3H_3N_3O_2$) | 4(5)- Nitroimidazole ($C_3H_3N_3O_2$)

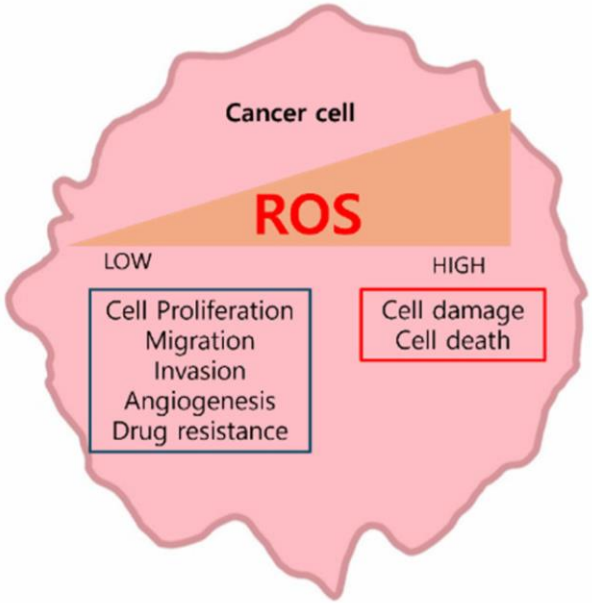
Radiosensitizers: Agents That Enhance Radiation Effects

3. **Cell Cycle Modulation:**
   - Arrest cells in radiosensitive phases (**G_2/M**).
   - Example: Taxanes, Hydroxyurea.

4. **Bioreductive Activation in Hypoxia:**
   - Selectively activated in low-oxygen tumor areas.
   - Example: Tirapazamine.

5. **Increased ROS Generation:**
   - Promote formation of reactive oxygen species → more oxidative stress.





Classes / Examples of Radiosensitizers

Class	Examples	Mechanism
Oxygen mimetics	Misonidazole, Etanidazole	Imitate oxygen’s fixation of damage
Chemotherapeutic agents	Cisplatin,	Interfere with DNA repair and replication
Biological agents	EGFR inhibitors	Inhibit survival signaling pathways
Targeted drugs	PARP inhibitors	Block DNA damage repair
Nanoparticles / others	Gold nanoparticles	Amplify local dose deposition

Radioprotectors: Agents That Protect Cells from Radiation Damage

- **Radioprotectors** are natural or synthetic compounds that reduce the harmful effects of ionizing radiation on normal (non-cancerous) tissues by **limiting free radical damage**, **enhancing repair**, or **stabilizing cellular structures**.

Mechanisms of Action:

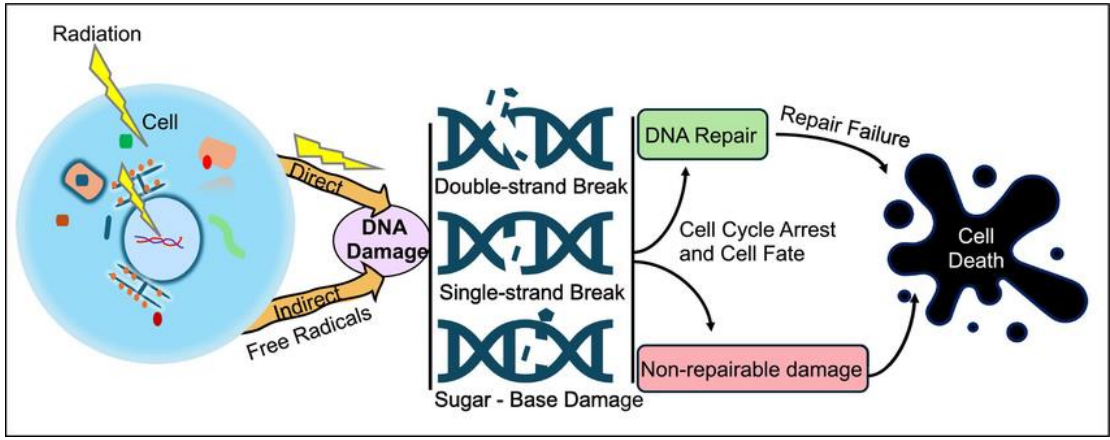
1. **Free Radical Scavenging:**
   - Donate hydrogen atoms or electrons to neutralize radicals (•OH, H•).
   - Example: *Cysteine*.
2. **Enhancement of DNA Repair:**
   - Stimulate repair enzymes and antioxidant pathways.
   - Example: *Vitamin E*, *Melatonin*.
3. **Chemical Binding of Toxic Products:**
   - Prevent lipid peroxidation and membrane damage.
4. **Induction of Hypoxia in Normal Tissues:**
   - Reduce oxygen availability → temporary radio-resistance.

Examples of Radioprotectors:

Type	Examples	Mechanism / Use
Thiol compounds	Amifostine, Cysteamine	Scavenge free radicals; donate hydrogen atoms
Antioxidants	Vitamin E, Vitamin C, Melatonin	Neutralize ROS; reduce oxidative stress
Cytokines / Growth factors	Interleukin-1	Promote recovery of irradiated tissues
Plant-derived agents	Curcumin	Antioxidant and anti-inflammatory actions

Irradiation-Induced Cellular Damage

- When **ionizing radiation** interacts with **cellular atoms and molecules**, it produces ionizations and excitations that lead to chemical alterations in critical biomolecules: primarily **DNA**, **membranes**, and **proteins**.
- These alterations can cause **molecular**, **structural**, and **functional** damage, ultimately determining cell fate (repair, mutation, or death).



Types of Radiation-Induced Cellular Damage:

1. DNA Damage (Critical Target)

- **Single-Strand Breaks (SSBs)** – usually repairable.
- **Double-Strand Breaks (DSBs)** – difficult to repair; may lead to cell death or mutation.
- **Base damage and cross-linking** – interfere with replication and transcription.

Irradiation-Induced Cellular Damage

2. Membrane Damage

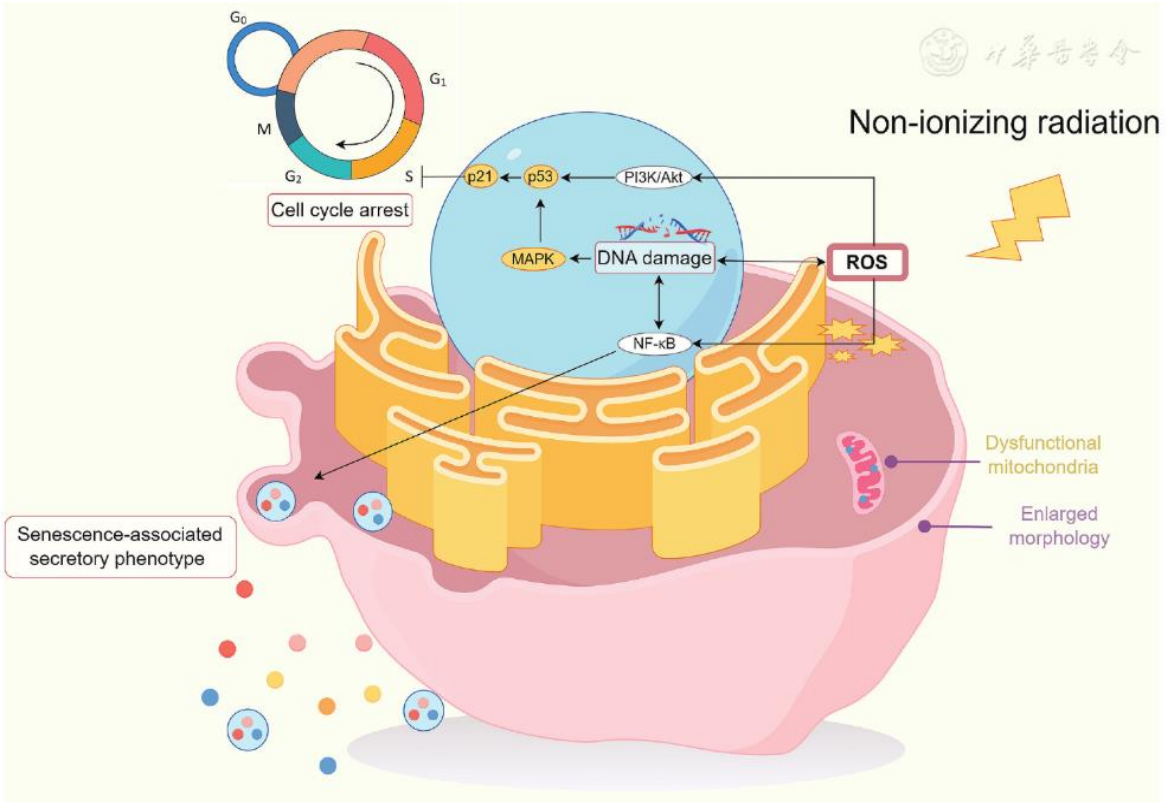
- Lipid peroxidation alters membrane permeability.
- Disruption of receptor and ion channel functions.
- Leads to loss of homeostasis and cell signaling failure.

3. Protein and Enzyme Damage

- Oxidation and fragmentation of structural proteins.
- Enzyme inactivation → metabolic imbalance.

4. Organelle Damage

- **Mitochondria:** impaired ATP production, excess ROS.
- **Nucleus:** chromatin condensation, apoptosis initiation.
- **Endoplasmic reticulum:** stress response activation (UPR).



Molecular Sensors of Radiation-Induced DNA Damage

MRN Complex (Mre11-Rad50-Nbs1)

- Detects **double-strand breaks (DSBs)**.
- Recruits and activates **ATM kinase**.
- Bridges broken DNA ends for repair.

PARP-1 (Poly ADP-ribose Polymerase-1)

- Detects **single-strand breaks (SSBs)**.
- Catalyzes **poly(ADP-ribosyl)ation**, recruiting repair proteins.
- Rapidly responds within seconds to DNA damage.

RPA (Replication Protein A)

- Binds **single-stranded DNA (ssDNA)** at stalled replication forks.
- Activates **ATR kinase** signaling for checkpoint control.

Molecular Sensors of Radiation-Induced DNA Damage

γ-H2AX (Phosphorylated H2AX)

- Histone H2AX becomes phosphorylated at DSB sites.
- Forms **foci visible by immunofluorescence**, marking DNA damage.
- Serves as a **sensitive biomarker for radiation-induced DSBs**.

53BP1 and MDC1

- Scaffold proteins recruited to DSBs.
- Facilitate recruitment of repair complexes (NHEJ and HRR).

DNA Damage Response (DDR): Detection and Coordination of Repair

- The DNA Damage Response (DDR) is a complex cellular network that detects DNA damage, signals its presence, and coordinates repair, cell cycle arrest, or apoptosis.
- It determines whether a cell survives, mutates, or dies after irradiation.

1. Damage Detection (Sensors):

- **MRN Complex (Mre11–Rad50–Nbs1):** Recognizes DNA double-strand breaks (DSBs).
- **RPA (Replication Protein A):** Detects single-stranded DNA regions.
- **PARP-1 (Poly ADP-ribose polymerase):** Binds to single-strand breaks (SSBs).

2. Signal Transduction (Transducers):

- **ATM (Ataxia Telangiectasia Mutated):** Activated by DSBs → phosphorylates downstream targets.
- **ATR (ATM and Rad3-related):** Activated by replication stress or SSBs.
- **DNA-PKcs (DNA-dependent protein kinase catalytic subunit):** Facilitates repair in non-homologous end joining (NHEJ).

DNA Damage Response (DDR): Detection and Coordination of Repair

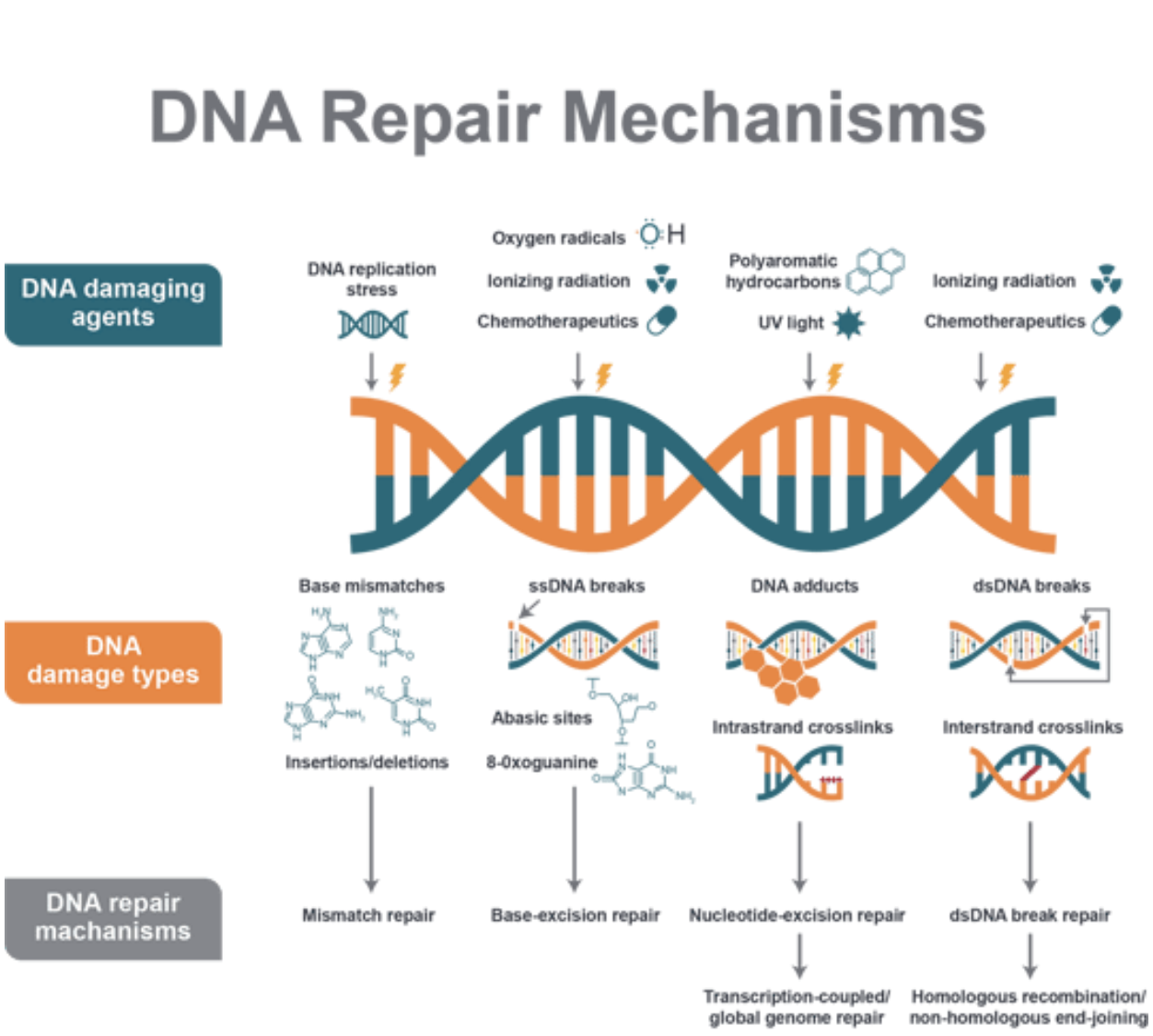
3. Effector Proteins (Responses):

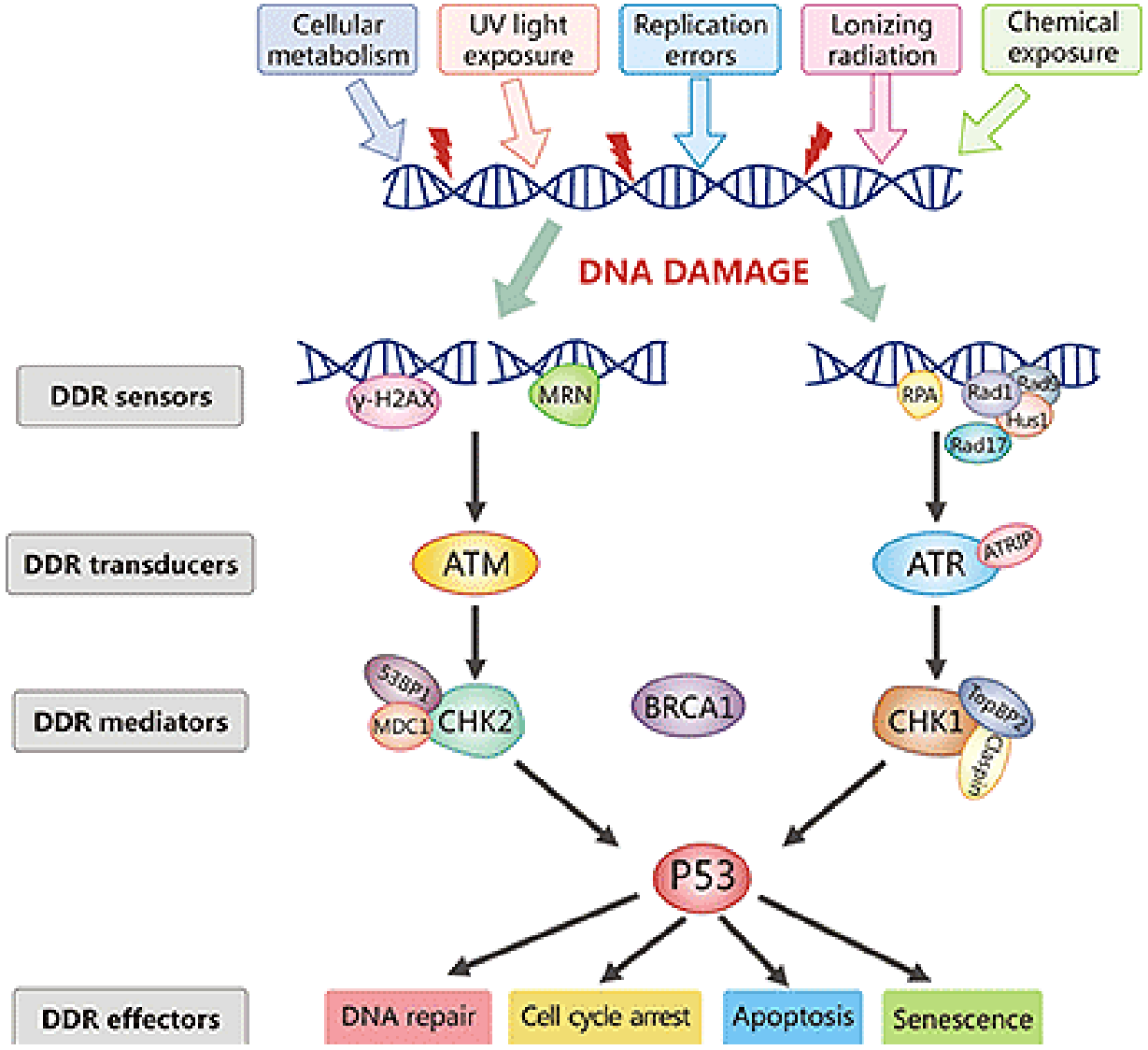
- **p53:** Induces cell cycle arrest (via p21) or apoptosis.
- **Chk1 / Chk2:** Enforce G1/S and G2/M checkpoints.
- **BRCA1 / BRCA2:** Direct homologous recombination repair.
- **Ku70/80:** Bind DNA ends in the NHEJ pathway.

4. Cellular Outcomes:

Outcome	Mechanism / Pathway	Result
DNA Repair	NHEJ or HR pathways	Cell survival
Cell Cycle Arrest	p53 → p21; Chk1/Chk2 → Cdc25 inhibition	Time for repair
Apoptosis / Senescence	Persistent or irreparable damage	Cell death or permanent arrest

DNA Damage Response (DDR): Detection and Coordination of Repair





Clinical Implications: Oxygen Effect & Radiosensitizers in Radiotherapy

1- Tumor Hypoxia & Radioresistance:

- Poorly vascularized tumor regions are **hypoxic**, reducing radiation effectiveness.
- OER indicates hypoxic cells may require **2–3 times higher dose** for the same tumor control.

2- Exploiting Oxygen Effect:

- **Hyperbaric oxygen therapy (HBO):** Patient breathes pure oxygen during irradiation → temporarily increases tumor oxygenation.
- **Fractionated radiotherapy:** Allows reoxygenation between fractions → improved tumor control.

3- Use of Radiosensitizers:

- **Chemical radiosensitizers** mimic oxygen or inhibit DNA repair.

Example: *Misonidazole* targets hypoxic tumor cells.

- **Molecular targeted agents** enhance tumor radiosensitivity.

Example: *PARP inhibitors*, *EGFR inhibitors*.

Clinical Use of Radioprotectors to Protect Normal Tissues

1- Purpose of Radioprotectors:

- Reduce radiation-induced damage in **normal tissues** without protecting tumor cells.
- Allow **higher tumor doses** and **better therapeutic ratio**.

2- Clinical Applications:

- **Head and Neck Cancer:** Amifostine reduces **xerostomia**.
- **Bone Marrow Protection:** Cytokines support hematopoietic recovery during chemo-radiotherapy.
- **Radiation Emergencies:** Antioxidants and thiol compounds for accidental or occupational exposure.

Clinical Use of Radioprotectors to Protect Normal Tissues

3- Examples of Clinically Used Radioprotectors:

Agent	Mechanism / Use
Amifostine (WR-2721)	Thiol prodrug; scavenges free radicals; protects salivary glands in head & neck radiotherapy
Vitamin E, Melatonin	Antioxidants; reduce oxidative stress and inflammation
Cytokines / Growth Factors	Promote tissue repair and recovery (e.g., GM-CSF, IL-1)

Questions? Comments?

Thank you!