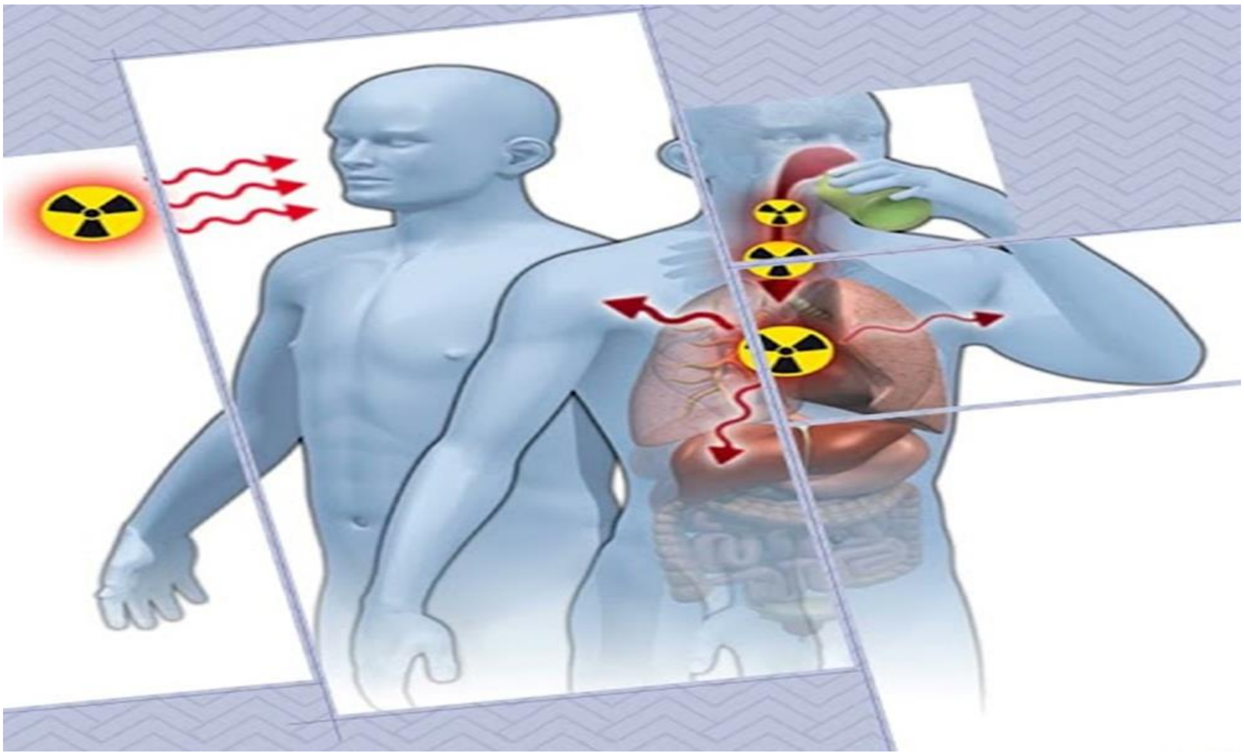
Biological factors influencing radiosensitivity
2nd Lecture



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Teaching of Biological Radiation hazards

College of Technology & Health Sciences

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Biological factors influencing radiosensitivity

The presence of chemical agents (radiosensitizers and radioprotectors) that can change the cellular response to radiation; age, as older cells may have impaired DNA repair capabilities; the ability of cells to repair themselves and repopulate after irradiation; the presence of oxygen, which intensifies radiation damage; and hormesis, a theory where low-dose radiation may have positive effects, are biological factors that influence radio-sensitivity.

1. Oxygen Effect

- **Mechanism:**

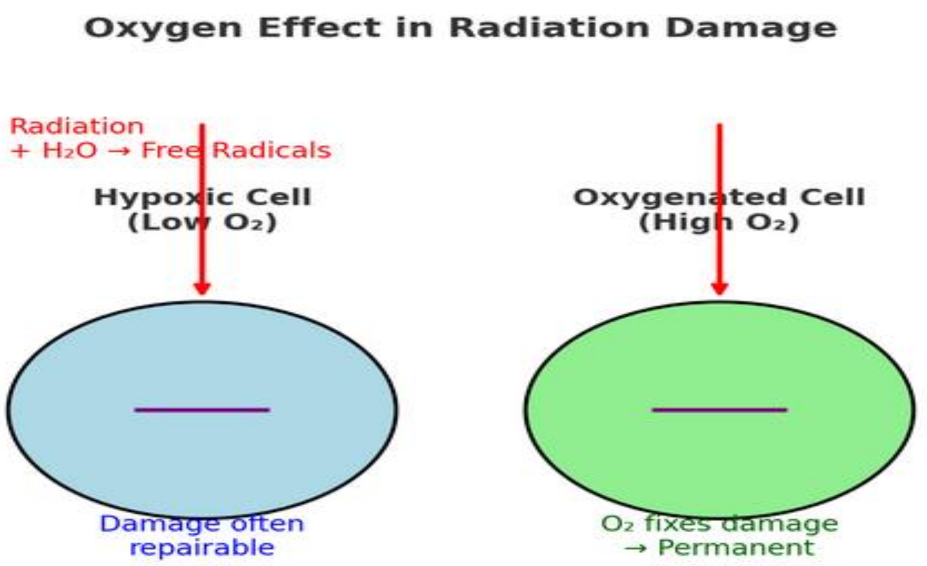
Radiation damages cells mainly by producing **free radicals** (especially hydroxyl radicals) from the radiolysis of water. These radicals are highly reactive and can break DNA strands.

- **Without oxygen:** Many of these free radical–induced DNA breaks can be repaired by the cell before they become permanent.
- **With oxygen present:** Oxygen reacts with the DNA radicals to form **peroxides**, which "fix" the damage and make it permanent and irreparable.

This is why tissues with good oxygen supply (well-oxygenated) are **more radiosensitive**, while tissues or tumors with poor oxygen supply (hypoxic) are **more radioresistant**.

This concept is expressed as the **Oxygen Enhancement Ratio (OER)**, which is typically about **2.5–3.0** for low-LET radiation (like X-rays and gamma rays). It means radiation is 2–3 times more effective at causing cell death when oxygen is present compared to hypoxic conditions.

Oxygen makes radiation-induced DNA damage permanent, reducing repair and increasing radiosensitivity.



- In hypoxic cells (low O_2), radiation-induced damage is often repairable.
- In oxygenated cells (high O_2), oxygen reacts with radicals and makes the DNA damage **permanent**.

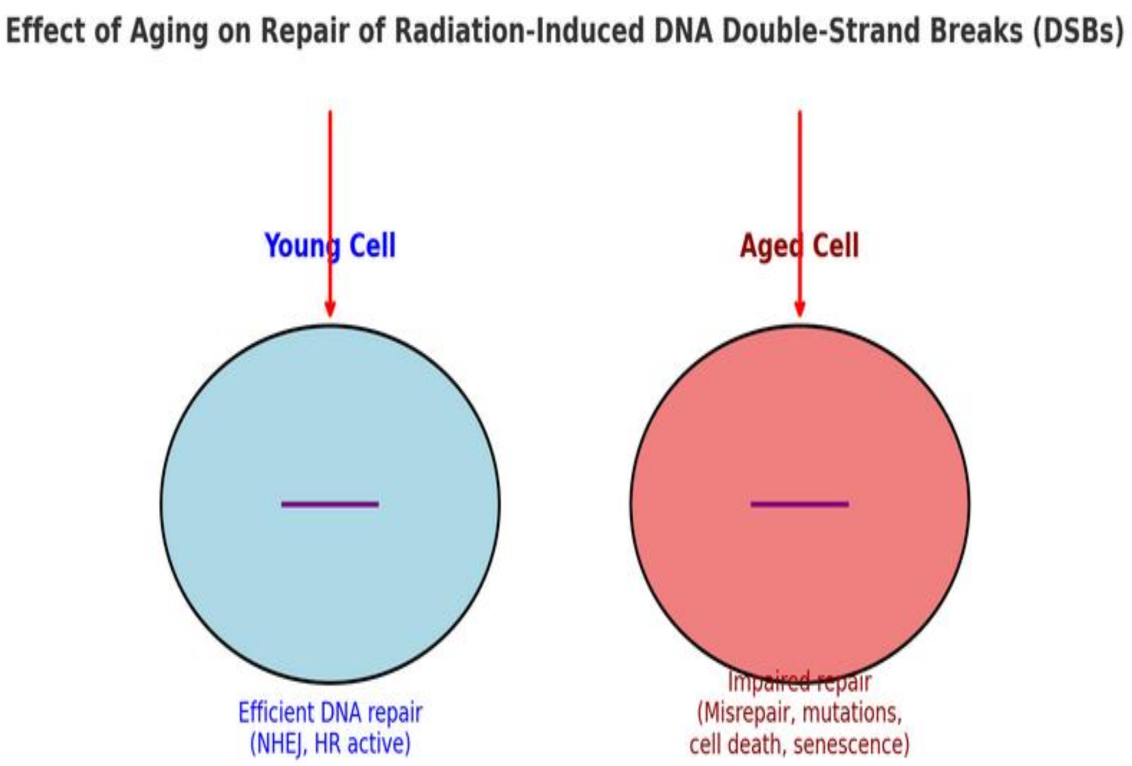
2. Age

Aging reduces the efficiency and fidelity of DNA repair systems, which makes cells more vulnerable to radiation damage, especially **double-strand breaks (DSBs)**—the most lethal form of DNA damage. Here's how:

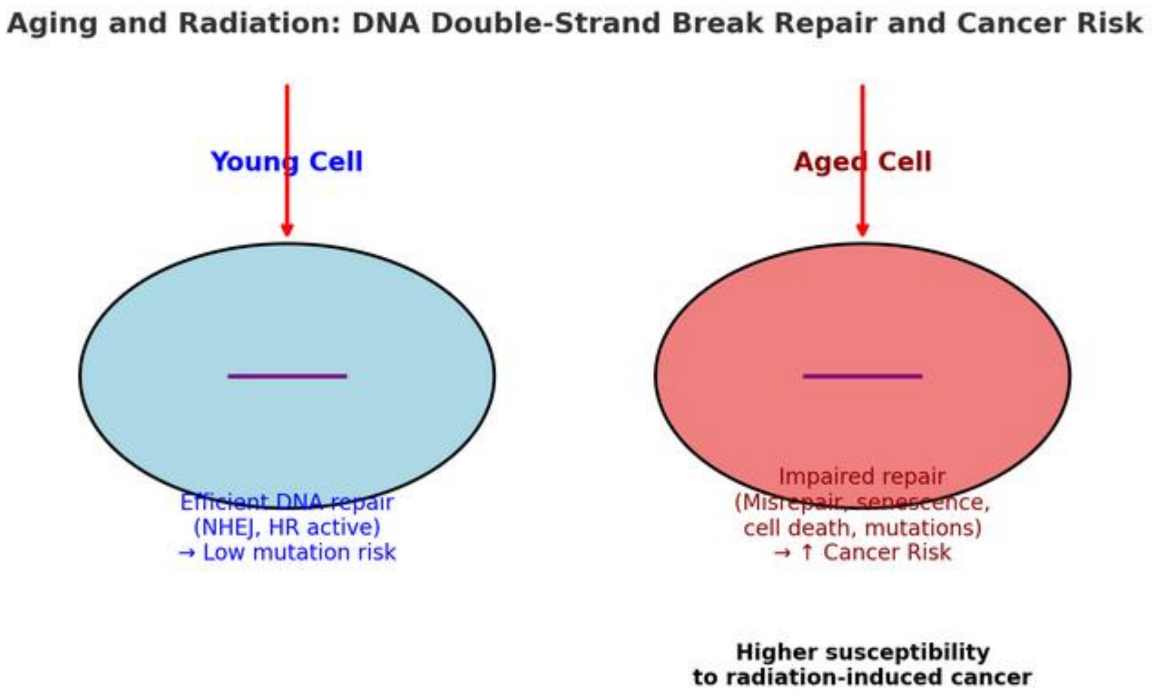
1. **Decline in DNA repair pathways**
   - The **non-homologous end joining (NHEJ)** pathway becomes less accurate with age, introducing mutations.
   - The **homologous recombination (HR)** pathway, which is error-free, is also downregulated in older cells.
2. **Accumulation of DNA damage**
   - Over time, unrepaired or misrepaired DSBs accumulate, leading to genomic instability.
   - This contributes to aging phenotypes and age-related diseases, such as cancer.

3. **Mitochondrial dysfunction & oxidative stress**
   - Aging cells have higher levels of **reactive oxygen species (ROS)**, which create more DNA breaks.
   - Combined with impaired repair, this amplifies damage.
4. **Cell fate after DSBs**
   - In younger cells: repair → survival.
   - In older cells: misrepair or failure → apoptosis, senescence, or malignant transformation.

Aging weakens the cell's ability to repair DSBs, making radiation more harmful and increasing the risk of mutations, cell death, or cancer.



- **Young cell** → Radiation-induced DSBs are efficiently repaired (via NHEJ and HR).
- **Aged cell** → Repair is impaired, leading to misrepair, mutations, cell death, or senescence.



- **Young cells**: Efficient repair → low mutation risk.
- **Aged cells**: Impaired repair → misrepair, senescence, cell death, and **increased cancer risk** after radiation exposure.

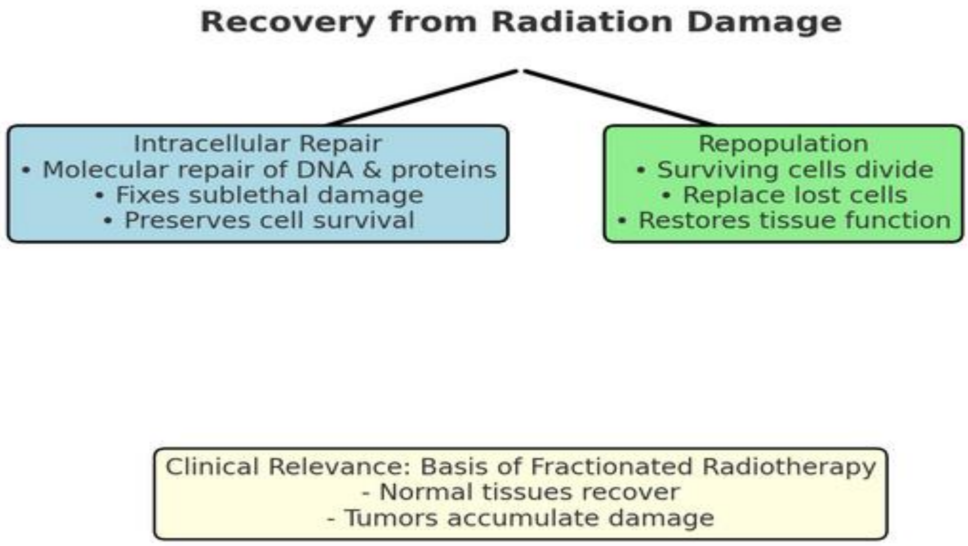
3. Recovery

Recovery from Radiation Damage

1. **Intracellular Repair**
   - Cells possess molecular repair mechanisms that fix sublethal damage to DNA, proteins, and membranes.
   - Example: DNA double-strand breaks can be repaired through **NHEJ** or **HR pathways**.
   - This repair reduces long-term radiation injury if damage is not too severe.
2. **Repopulation (Cell Division)**
   - Surviving cells in tissues can **divide and replace** cells that were killed by radiation.
   - Particularly important in tissues with **high proliferative capacity** (e.g., skin, intestinal lining, bone marrow).
   - Contributes to the **healing of tissue function** after radiation.

3. **Clinical Importance**
   - Basis for **fractionated radiotherapy**:
     - Small daily doses allow normal tissues to **recover** between sessions.
     - Tumor cells, with poorer repair mechanisms, accumulate damage.

Recovery = Intracellular repair + Repopulation, helping tissues restore structure and function after radiation exposure.

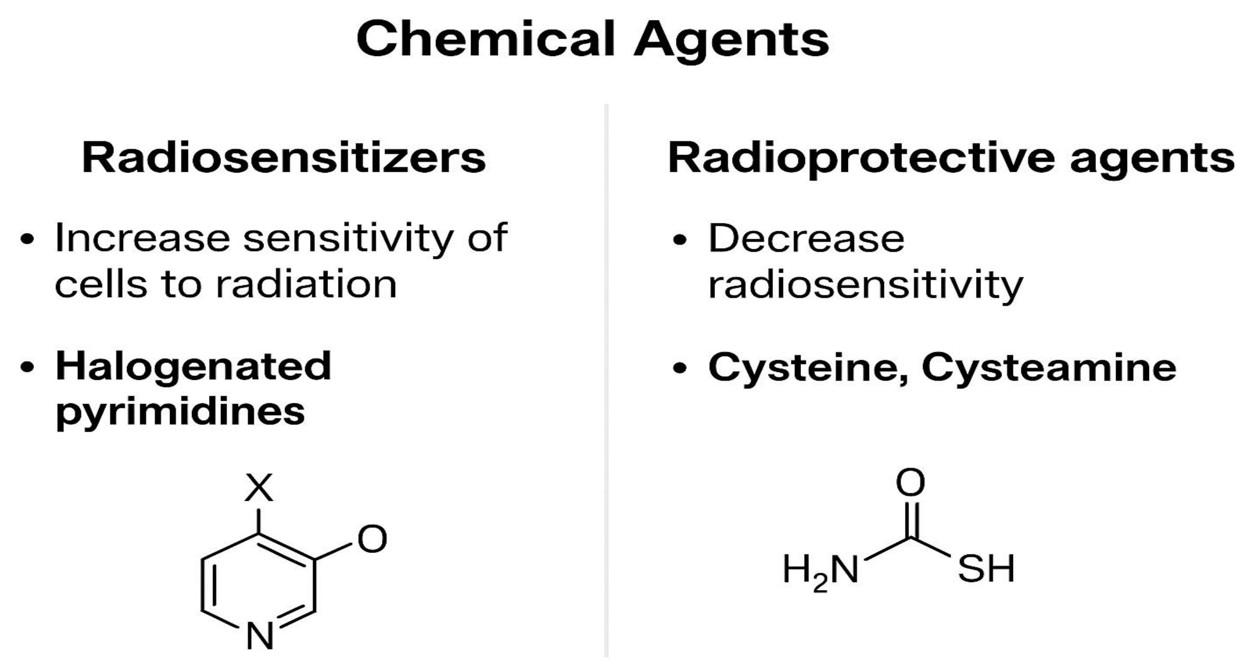


- **Intracellular Repair** → fixes sublethal molecular damage.
- **Repopulation** → surviving cells divide to restore tissue function.

4. Chemical Agents

1. **Radiosensitizers**
   - Definition: Compounds that increase the sensitivity of cells to radiation.
   - Mechanism: They enhance radiation-induced damage, making cancer cells more vulnerable to treatment.
   - Example: **Halogenated pyrimidines** (incorporated into DNA, making it more prone to radiation-induced breaks).

2. **Radioprotective Agents**
    - Definition: Substances that protect normal tissues and cells from radiation injury.
    - Mechanism: They act by scavenging free radicals or repairing damage, thereby **decreasing radiosensitivity**.
    - Examples: **Cysteine, Cysteamine** (contain sulfhydryl groups that neutralize free radicals).



5. Hormesis

The **hormesis principle** in the context of radiation biology is the idea that **low doses of a potentially harmful agent, like ionizing radiation, may actually have positive effects on organisms**. This seems counterintuitive because radiation is usually considered harmful, but at very low levels, it can trigger protective mechanisms.

Here's how it works:

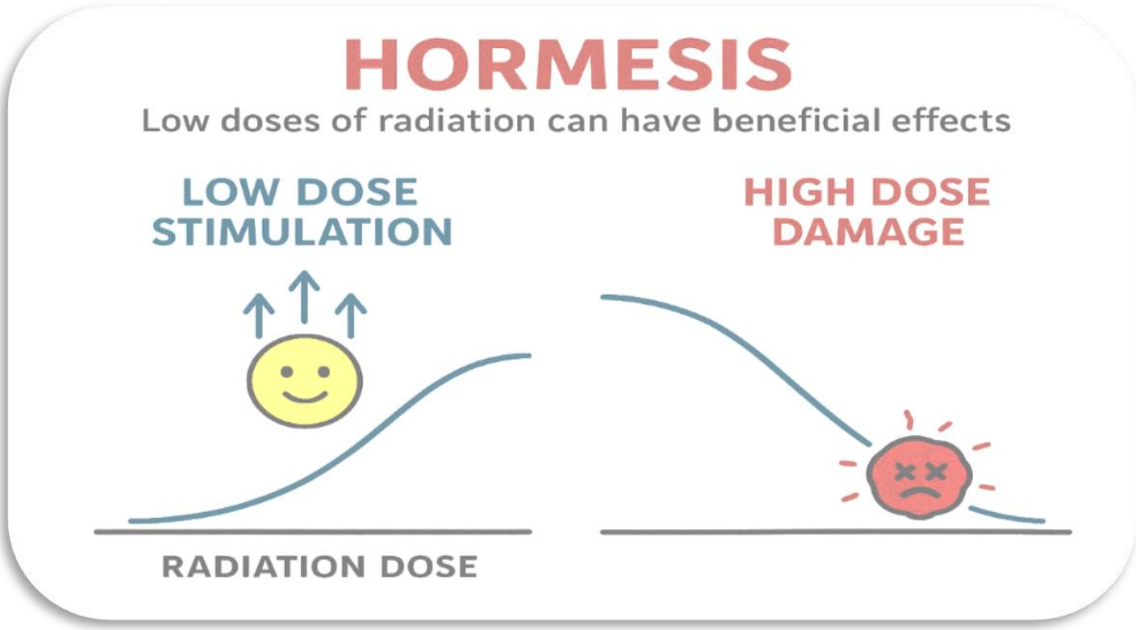
1. **Low-dose exposure triggers adaptive responses**
    - Cells exposed to small amounts of radiation may activate repair systems more efficiently.

- DNA repair enzymes, antioxidant production, and stress-response proteins increase, helping the cell cope with damage.

2. **Strengthening biological defenses**
   - These mild stress responses "train" cells to handle future stress better, similar to how vaccination primes the immune system.
   - This can lead to improved resilience against oxidative stress, DNA damage, or other harmful agents.

3. **Potential beneficial effects**
   - Some studies suggest low-dose radiation might enhance immune function, promote cellular repair, or reduce the incidence of certain diseases.
   - The effect is **dose-dependent**: too little may have no effect, while too much causes damage.
   - Hormesis is not an excuse to expose people to radiation recklessly; it occurs **only at very low, carefully controlled doses**. At higher doses, radiation is overwhelmingly harmful.

hormesis is like a "biological workout": a tiny bit of stress pushes the body to strengthen itself.



Biological Factors Influencing Radiosensitivity – MCQs

1. Which of the following increases the radiosensitivity of cells?
   a) Hypoxia
   b) **Presence of oxygen**
   c) Low mitotic activity
   d) Radioprotectors
   e) Hormesis
2. The Oxygen Enhancement Ratio (OER) typically for low-LET radiation is approximately:
   a) 1
   b) 1.5
   c) **2.5–3.0**
   d) 4–5
   e) 5–6
3. What is the main mechanism by which oxygen increases radiosensitivity?
   a) Reducing free radicals
   b) Promoting apoptosis
   c) **Fixing DNA damage caused by free radicals**
   d) Enhancing cell division
   e) Preventing radiation entry into cells
4. Hypoxic cells are generally:
   a) More radiosensitive
   b) Equally sensitive as oxygenated cells
   c) **More radioresistant**
   d) Unable to repair DNA
   e) Undergoing hormesis
5. Free radicals formed during radiolysis of water are mainly:
   a) Superoxide ions
   b) Hydrogen peroxide
   c) **Hydroxyl radicals**
   d) Nitric oxide
   e) Singlet oxygen
6. Aging affects radiosensitivity primarily by:
   a) Increasing oxygen levels in tissues
   b) **Reducing DNA repair efficiency**
   c) Promoting radiosensitizers
   d) Increasing repopulation
   e) Triggering hormesis
7. Which DNA repair pathway becomes less accurate with age?
   a) Homologous recombination
   b) **Non-homologous end joining (NHEJ)**
   c) Base excision repair
   d) Mismatch repair
   e) Nucleotide excision repair
8. Which pathway is error-free but downregulated in older cells?
   a) NHEJ
   b) Base excision repair

c) **Homologous recombination (HR)**
d) Mismatch repair
e) SOS repair

9. Accumulation of unrepaired DNA damage in aged cells leads to:
   a) Improved repair
   b) Hormesis
   c) **Genomic instability**
   d) Decreased radiosensitivity
   e) Increased radioprotection
10. In younger cells, radiation-induced double-strand breaks (DSBs) are:
   a) Mostly lethal
   b) **Efficiently repaired**
   c) Always misrepaired
   d) Ignored by the cell
   e) Enhanced by radioprotectors
11. Aging increases radiation-induced cancer risk by:
   a) Increasing NHEJ fidelity
   b) Decreasing ROS
   c) **Impairing DNA repair mechanisms**
   d) Increasing repopulation
   e) Reducing radiosensitivity
12. Recovery from radiation damage includes:
   a) Hormesis only
   b) Radiosensitizers
   c) Oxygen effect
   d) **Intracellular repair and repopulation**
   e) Hypoxia
13. Intracellular repair mechanisms fix:
   a) Only proteins
   b) Only membranes
   c) Only DNA
   d) **DNA, proteins, and membranes**
   e) Only RNA
14. Repopulation after radiation is most important in tissues with:
   a) Low proliferative capacity
   b) **High proliferative capacity**
   c) No stem cells
   d) Mostly necrotic cells
   e) Hypoxic zones
15. Fractionated radiotherapy is based on:
   a) Hormesis
   b) Radiosensitizers
   c) **Recovery of normal tissues between doses**
   d) Hypoxia induction
   e) High-dose single fractions
16. Radiosensitizers function by:
   a) Reducing radiation effects

b) Protecting normal tissue
c) **Increasing cellular sensitivity to radiation**
d) Promoting repopulation
e) Reducing oxygen levels

17. An example of a radiosensitizer is:
a) Cysteine
b) Cysteamine
c) **Halogenated pyrimidines**
d) Antioxidants
e) Mitochondrial ROS

18. Radioprotective agents act by:
a) Generating free radicals
b) **Scavenging free radicals**
c) Blocking DNA replication
d) Increasing oxygen supply
e) Inhibiting NHEJ

19. Examples of radioprotective agents include:
a) Halogenated pyrimidines
b) **Cysteine and cysteamine**
c) ROS
d) Hydrogen peroxide
e) Ionizing radiation

20. The hormesis principle suggests:
a) High-dose radiation is beneficial
b) Radiation is always harmful
c) **Low-dose radiation may have positive effects**
d) Oxygen decreases radiosensitivity
e) Recovery is unnecessary

21. Hormesis can improve:
a) DNA damage permanently
b) **Adaptive responses and stress resistance**
c) Hypoxia
d) Radiosensitivity of tumors
e) NHEJ accuracy

22. Low-dose radiation in hormesis:
a) Damages DNA irreversibly
b) **Triggers cellular repair systems**
c) Prevents oxygen interaction
d) Reduces ROS
e) Induces apoptosis only

23. Which effect is dose-dependent in hormesis?
a) Radiosensitizer effect
b) Oxygen fixation
c) **Beneficial or harmful outcomes**
d) Recovery speed
e) Intracellular repair

24. High-dose radiation in hormesis:
    a) Enhances repair
    b) **Overwhelmingly harmful**
    c) Improves repopulation
    d) Protects normal tissue
    e) Activates antioxidants only
25. Aging cells have higher levels of:
    a) Radiosensitizers
    b) **Reactive oxygen species (ROS)**
    c) Radioprotectors
    d) Oxygen
    e) Antioxidants
26. ROS contribute to:
    a) DNA repair
    b) **DNA breaks**
    c) Hormesis
    d) Radioprotection
    e) Cell division
27. NHEJ and HR pathways are important for repairing:
    a) Single-strand breaks
    b) Protein damage
    c) Membrane damage
    d) **Double-strand breaks (DSBs)**
    e) Free radicals
28. Radiosensitivity increases when cells:
    a) Are hypoxic
    b) **Have high oxygen levels**
    c) Have low proliferative capacity
    d) Are protected by cysteine
    e) Are aged
29. Which factor does **not** influence radiosensitivity?
    a) Age
    b) Hormesis
    c) Oxygen
    d) **Hair color**
    e) Chemical agents
30. In hypoxic conditions, radiation-induced DNA damage is:
    a) Permanent
    b) **Often repairable**
    c) Exponentially lethal
    d) Enhanced by radiosensitizers
    e) Fixed by oxygen
31. Fractionated doses allow normal tissues to:
    a) Accumulate damage
    b) Become hypoxic
    c) **Recover between sessions**

d) Lose repair ability
e) Mutate faster

32. Halogenated pyrimidines are incorporated into:
a) Proteins
b) Membranes
c) **DNA**
d) RNA
e) Mitochondria

33. Cysteamine protects cells by:
a) Increasing DSBs
b) **Neutralizing free radicals**
c) Enhancing radiosensitivity
d) Reducing repair
e) Decreasing oxygen

34. Aging leads to misrepair of DSBs, causing:
a) Efficient recovery
b) **Mutations, senescence, or apoptosis**
c) Radiosensitization only
d) Hormesis
e) Oxygen fixation

35. Recovery mechanisms are crucial for:
a) Increasing radiation dose
b) Reducing radiosensitizers
c) **Restoring tissue structure and function**
d) Promoting hypoxia
e) Aging tissues

36. Oxygen "fixes" DNA damage by:
a) Scavenging free radicals
b) **Reacting with DNA radicals to form peroxides**
c) Reducing ROS
d) Enhancing repair
e) Blocking radiosensitizers

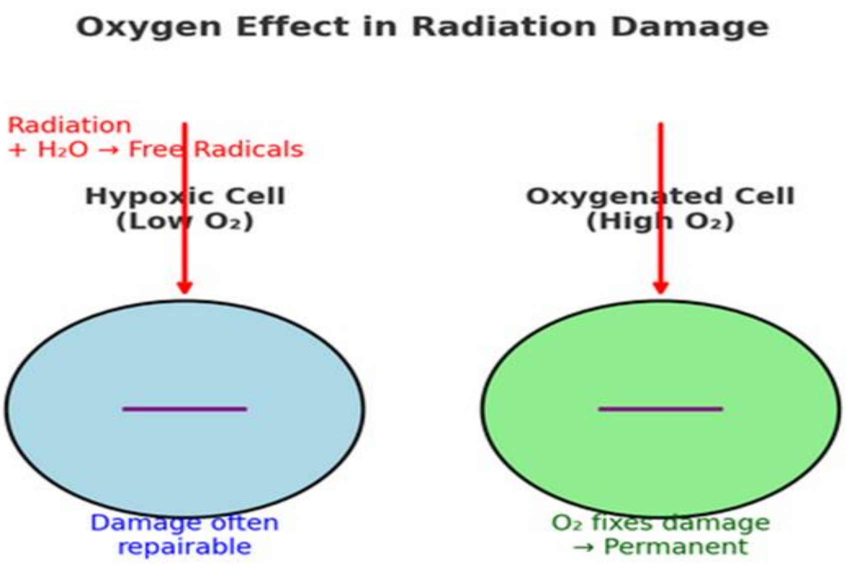
37. Which is a hallmark of hormesis?
a) High-dose toxicity
b) **Low-dose adaptive response**
c) Permanent DNA damage
d) Increased hypoxia
e) Reduced recovery

38. Young cells exposed to radiation typically:
a) Die immediately
b) **Repair DSBs efficiently**
c) Become hypoxic
d) Accumulate mutations rapidly
e) Show impaired HR

39. Repopulation after radiation is least important in:
a) Skin
b) Bone marrow

c) Intestinal lining
d) **Cartilage**
e) Liver (hepatocytes have moderate capacity)

40. Radiosensitizers are mainly used to:
a) Protect normal tissue
b) **Enhance cancer cell kill**
c) Promote hormesis
d) Repair DNA
e) Reduce oxygen effect



1. What happens when radiation interacts with water in cells?
a) Produces oxygen molecules
b) Produces carbon dioxide
c) Produces ATP
d) Produces glucose
e) **Produces free radicals**

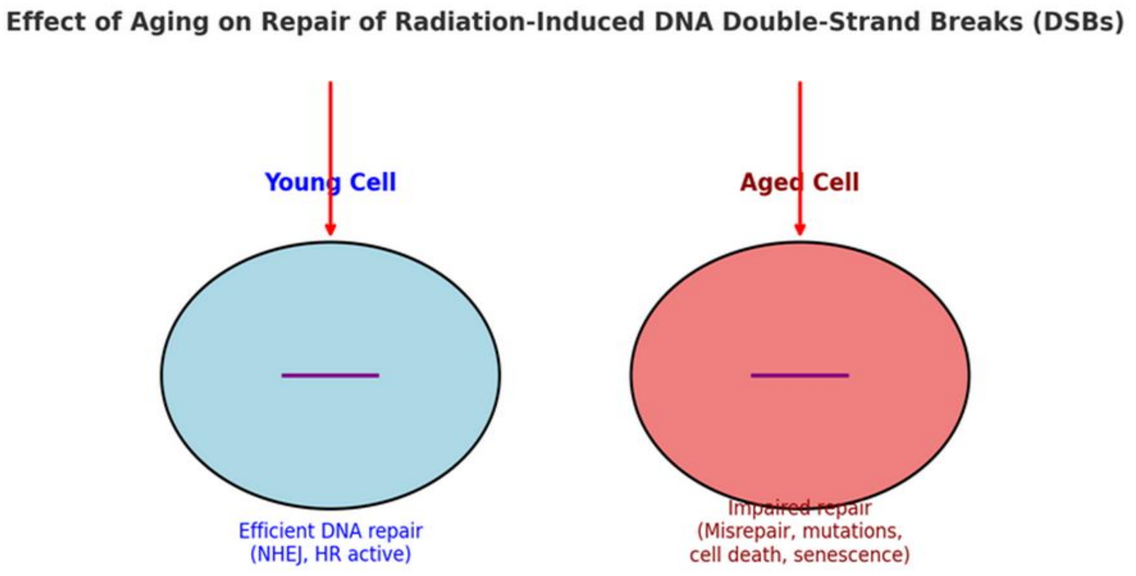
2. In hypoxic cells (low O_2), radiation damage is:
a) Always permanent
b) **Often repairable**
c) Irreversible

d) Not caused at all
e) Increased

3. In oxygenated cells (high O_2), the role of oxygen is to:
a) Prevent free radical formation
b) Repair damaged DNA directly
c) Neutralize radiation
d) **Fix the damage and make it permanent**
e) Decrease radiosensitivity

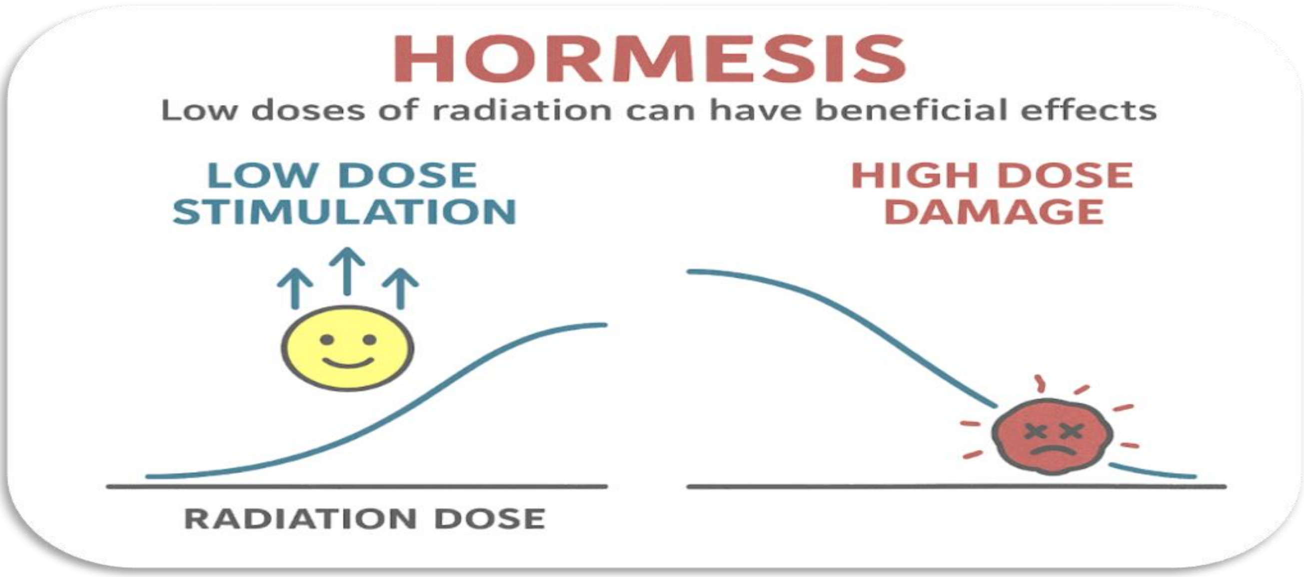
4. Which statement best explains the oxygen effect in radiation damage?
a) Oxygen reduces the effect of radiation on cells
b) **Oxygen increases radiation damage by fixing free radical damage permanently**
c) Hypoxic cells are more radiosensitive than oxygenated cells
d) Free radicals cannot exist without oxygen
e) Oxygen protects cells from radiation

5. The higher radiosensitivity of oxygenated cells is mainly due to:
a) Increased energy absorption
b) **Oxygen fixation of radiation-induced damage**
c) Lack of DNA repair mechanisms
d) Reduced water content in cells
e) Higher production of ATP



1. **What is the primary difference in DNA repair between a young cell and an aged cell?**
   a) Both cells repair DNA with the same efficiency
   b) Young cells have impaired DNA repair
   c) **Young cells have efficient DNA repair, while aged cells have impaired repair**
   d) Aged cells repair DNA faster
   e) Both cells do not repair DNA
2. **What is the outcome of impaired DNA repair in aged cells?**
   a) Enhanced cell growth
   b) **Misrepair, mutations, cell death, and senescence**
   c) Increased cell regeneration
   d) DNA repair is unimpeded
   e) No observable effect
3. **Which of the following DNA repair mechanisms are active in young cells according to the image?**
   a) NHEJ only
   b) **NHEJ and HR**
   c) HR only
   d) Only base excision repair
   e) None of the above
4. **Which type of cells has a higher risk of mutations due to DNA repair impairment?**
   a) Immature cells
   b) **Aged cells**
   c) Highly active cells
   d) Cells with no DNA damage
   e) Healthy cells

5. **What is one of the consequences of the impaired DNA repair in aged cells?**
   a) Enhanced mutation correction
   b) **Cell death**
   c) Faster cell division
   d) More efficient repair mechanisms
   e) Lower mutation rate



1. What does the concept of hormesis suggest about low doses of radiation?

a) They are always harmful
b) They can have beneficial effects
c) They are neutral and have no effect
d) They accumulate and cause cancer immediately
e) They cause genetic mutations

2. According to the image, what is the response to a low dose of radiation?

a) Cell death
b) DNA damage
c) Stimulation or beneficial response
d) Mutation
e) No change

3. What happens at high doses of radiation according to the hormesis curve?

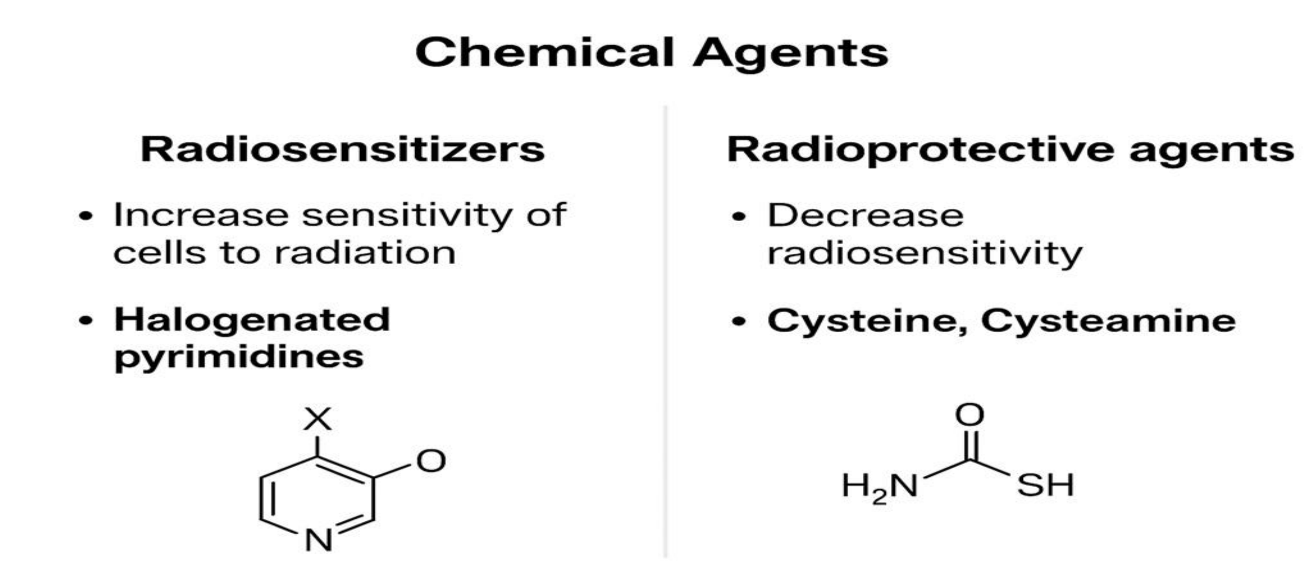
a) Increased stimulation
b) No effect
c) Immortality of cells
d) Damage to the organism
e) Enhanced healing

4. How is the relationship between radiation dose and effect represented in the image?

a) Linear increase
b) Constant level
c) Inverted U-shape
d) S-shaped curve
e) Exponential growth

5. What is the emotional representation of the effect of high radiation dose in the image?

a) Smiling face
b) Laughing emoji
c) Winking face
d) Sad and crossed-out face
e) Sleeping emoji



1. What is the primary function of radiosensitizers?

a) Protect cells from radiation
b) Repair damaged DNA
c) Increase sensitivity of cells to radiation

d) Neutralize radiation completely
e) Block cell division

2. Which of the following is listed as a radiosensitizer in the image?

a) Cysteine
b) Cysteamine
c) Benzene
d) Halogenated pyrimidines
e) Thymine

3. Radioprotective agents primarily work by:

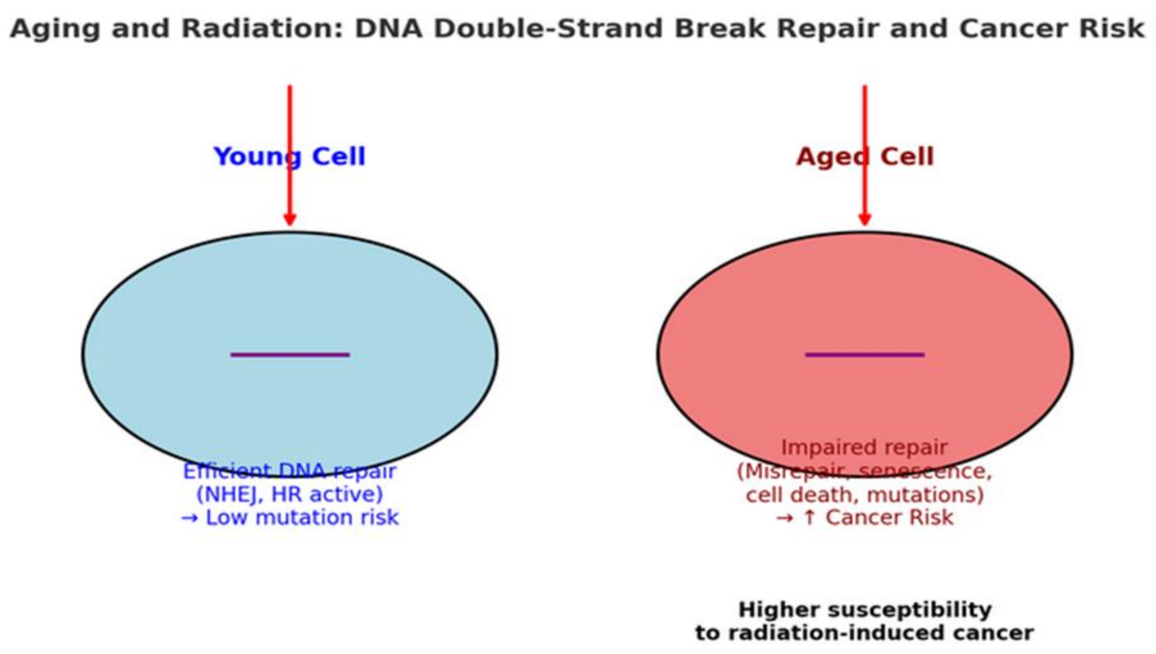
a) Decreasing radiosensitivity
b) Increasing radiosensitivity
c) Binding radiation directly
d) Stimulating apoptosis
e) Enhancing DNA mutation

4. Which of the following is an example of a radioprotective agent shown in the image?

a) Halogenated purines
b) Uracil
c) Cysteine
d) Thymidine
e) Cytosine

5. What chemical group is present in the radioprotective molecule shown at the bottom right?

a) Nitrate
b) Hydroxyl
c) Alkene
d) Thiol (-SH)
e) Ether



1. **What is the key factor differentiating DNA repair efficiency in young versus aged cells?**
   a) The presence of radiation
   b) The efficiency of the NHEJ and HR repair mechanisms
   c) Efficient DNA repair in young cells
   d) Higher mutation risk in young cells
   e) None of the above
2. **In aged cells, what typically happens to the DNA repair process?**
   a) It becomes more efficient than in young cells
   b) It leads to reduced mutation risk
   c) It becomes impaired, leading to higher cancer risk
   d) It remains unaffected by aging
   e) The cell does not repair DNA breaks at all
3. **Which of the following is a consequence of impaired DNA repair in aged cells?**
   a) Improved cell regeneration
   b) Lower cancer risk
   c) Decreased cell death
   d) Increased susceptibility to radiation-induced cancer
   e) Increased DNA repair efficiency
4. **What does the "NHEJ" repair mechanism contribute to in young cells?**
   a) Promoting cell death
   b) Reducing cancer risk by repairing DNA breaks
   c) Efficient DNA repair and low mutation risk
   d) Causing mutations in the DNA
   e) Accelerating aging

5. **Which of the following conditions is more likely to occur in aged cells due to impaired DNA repair?**
   a) Decreased mutations
   b) Lower cancer risk
   c) Cell death, mutations, and higher cancer risk
   d) Efficient repair of double-strand breaks
   e) No impact on cancer risk
