College of Health and Medical Technologies

Department of Radiology Technologies

Radiobiology

The first stage

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Lecture No.2

Indirect action of cell damage by radiation

In indirect action the radiation interacts with other molecules and atoms (mainly **water**, since 80% of a cell is composed of water) within the cell to produce free radicals that can, through diffusion in the cell, damage the critical target within the cell.

In interactions of radiation with water short-lived yet extremely reactive free radicals such as H_2O^+ (water ion) and **OH•** (hydroxyl radical) are produced. **The free radicals** in turn can cause damage to the target within the cell.

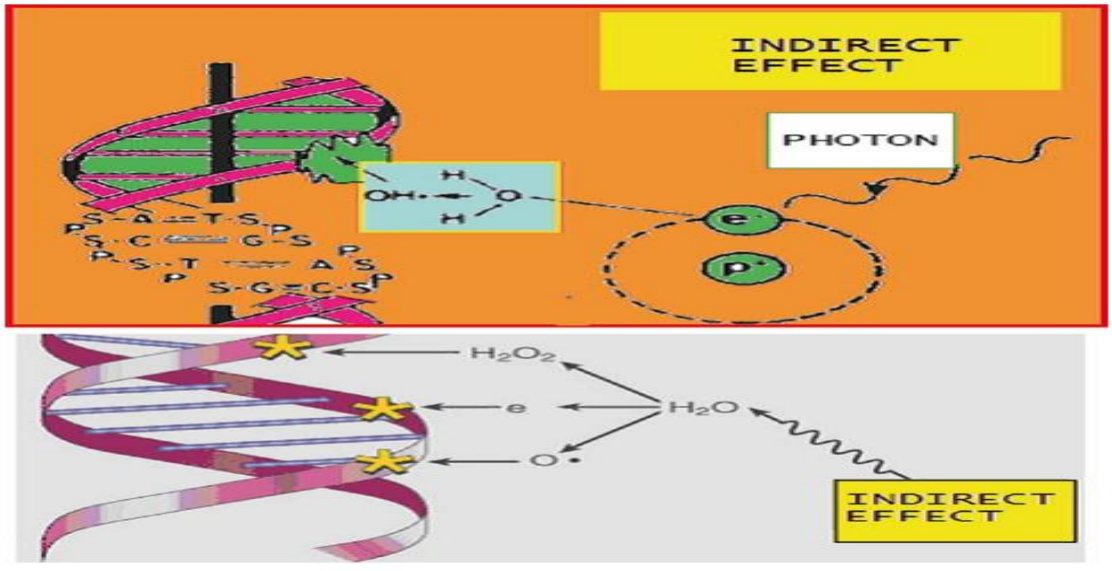
- **The free radicals** that break the chemical bonds and produce chemical changes that lead to biological damage are **highly** reactive molecules because they have an unpaired valence electron.
- About two thirds of the biological damage by **low LET** radiations , such as **x-rays** or **electrons**, is due to **indirect action**.
- **The indirect** action can be modified by chemical **sensitisers** or radiation **pro-tectors.**
- For the **indirec**t action of **x-rays** the steps involved in producing biological damage are as follows:

Step 1: Primary photon interaction (photoelectric effect, Compton effect, pair production) produces a **high** energy electron.

Step 2: The **high-energy** electron in moving through tissue produces **free radicals** in water.

Step 3: **The free radicals** may produce changes in **DNA** from breakage of chemical bonds.

Step 4: The changes in chemical bonds result in biological effects.



Fate of irradiated cells

Irradiation of a cell will result in one of the following four possible outcomes:

(1) **No effect**

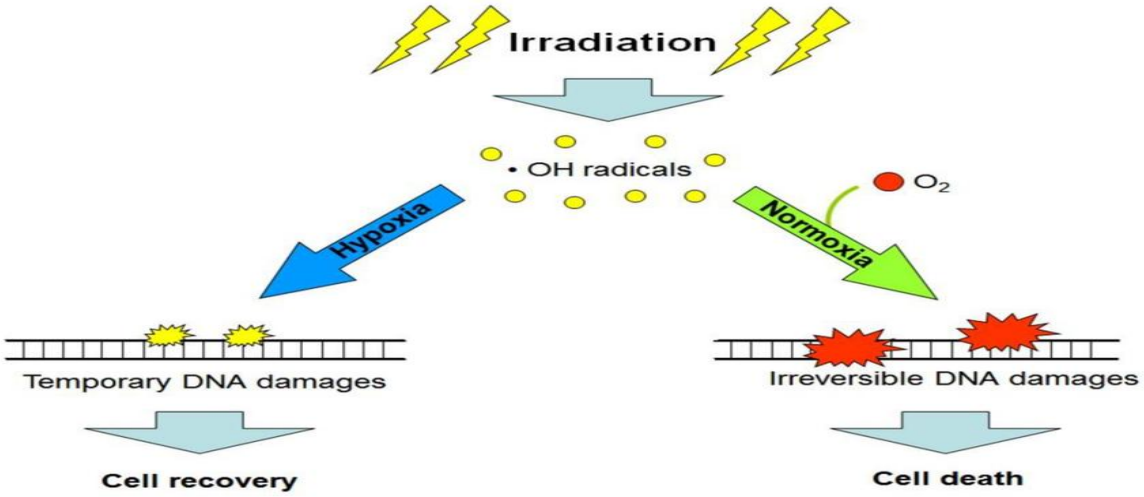
(2) **Division delay**: the cell is delayed from going through division.

(3) **Apoptosis**: the cell dies before it can divide or afterwards by fragmentation into smaller bodies which are taken up by neighboring cells.

(4) **Reproductive failure**: the cell dies when attempting the first or subsequent mitosis.

The oxygen enhancement ratio (OER) or oxygen enhancement effect

- ❖ In the field of radiobiology describes how the presence of **oxygen** can amplify the therapeutic or harmful impact of ionizing radiation.
- ❖ This phenomenon, known as the **oxygen effect**, is particularly significant when cells are exposed to doses of ionizing radiation.



- ❖ Traditionally, the **OER** is defined as the ratio of radiation doses required to produce the same **biological effect** under conditions of **oxygen** deprivation compared to normal **oxygen** levels.
- ❖ However, the numerical value of this ratio can vary depending on the specific **biological effect** being studied.
- ❖ Moreover, the presentation of **OER** may incorporate considerations of hyperoxic environments or altered **oxygen** baselines, adding complexity to its interpretation.
- ✓ The maximum **OER** primarily hinges on the ionizing density, also known as linear energy transfer (**LET**), of the radiation.
- ✓ Radiation with **higher LET** and greater relative biological effectiveness (**RBE**) typically exhibits a **lower OER** in mammalian cell tissues.
- ✓ The **maximum OER** value varies, generally falling within the range of **1 to 4.**
- ✓ For **low-LET** radiations like **X-rays**, **beta particles**, and **gamma rays**.
- ✓ **High-LET** radiations such as **low-energy alpha** particles typically have an OER of **1**.

Explanation of the Oxygen Effect

- The best known explanation of the **oxygen** effect is the oxygen fixation hypothesis which postulates that oxygen permanently fixes radical-induced **DNA** damage so it becomes permanent.
- Recently, it has been posited that the **oxygen** effect involves radiation exposures of cells causing their **mitochondria** to produce greater amounts of reactive oxygen species (**ROS**).

Radio sensitizers and Radio protectors

Radiosensitizers are agents that increase the effects of radiation.

- To be useful clinically, a **radio sensitizer** must show a therapeutic gain for tumors versus normal tissues.
- Examples of **radiosensitizers** currently in use are **cisplatin** and **gemcitabine**,

Radioprotectors are agents that protect cells (organs, organisms) from the damaging effects of ionizing radiation.

- These agents reduce the effective dose of the radiation, measured in terms of the dose reduction factor (DRF).
- Sulfhydryl compounds (e.g., amifostine) are radioprotectors that contain free SH groups, which interrupt the chain of events that utilizes free radicals to **indirectly** damage target molecules (i.e., free radical scavengers).

The DNA damage response (DDR)

Comprising **DNA** repair and cell-cycle checkpoint pathways, is an attractive target for cancer therapy. **DDR** inhibitors have been developed to

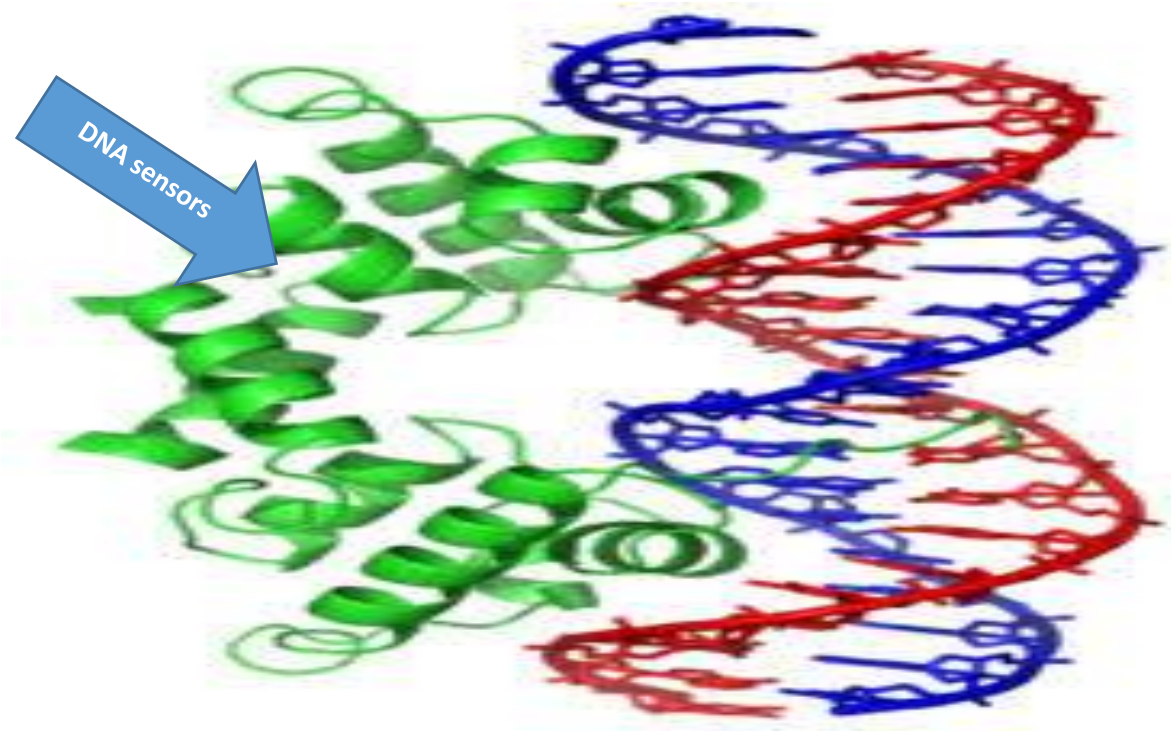
(i) Overcome **DDR**-mediated resistance to **DNA**-damaging anticancer therapy.

(ii) Exploit **DDR** dysfunction in cancer by targeting complementary pathways.

The DNA damage response (**DDR**) involves a complex network of genes responsible for sensing and responding to specific types of **DNA** damage, encompassing specific machineries:

1. **mediating DNA repair**
2. **cell cycle regulation**
3. **Replication stress responses and apoptosis.**

DNA sensors are DNA-binding proteins that are component of the innate immune system which are capable of detecting perturbations in **DNA** homeostasis of the cell and activate the intracellular signaling cascades of the innate immune system as a response



1. **What percentage of a cell is composed of water?

   a) 50%

   b) 60%

   c) 70%

   d) 80%

   e) 90%

2. **Which type of molecule is primarily involved in indirect action damage by radiation?**

   a) Proteins

   b) Carbohydrates

   c) Lipids

   d) Water

   e) DNA

3. **Which free radical is produced by the interaction of radiation with water?**

   a) OH•

b) H_2O^+

c) O_2^-

d) H_2O_2

e) Both a and b

4. **What is the main cause of the biological damage from low LET radiations like x-rays?**

a) Direct action

b) Indirect action

c) Absorption by lipids

d) Interaction with proteins

e) None of the above

5. **What proportion of biological damage from low LET radiations is due to indirect action?**

a) One third

b) One half

c) Two thirds

d) Three quarters

e) All

6. **Which of the following can modify the indirect action of radiation?**

a) Temperature

b) Chemical sensitisers

c) Light

d) Pressure

e) None of the above

7. **What is the first step in producing biological damage by x-rays?**

a) Free radical formation

b) DNA damage

c) High energy electron production

d) Chemical bond breakage

e) Biological effect manifestation

8. **Which of the following is a potential outcome of cell irradiation?**

a) Increased metabolism

b) Enhanced growth

c) Apoptosis

d) Differentiation

e) All of the above

9. **What is apoptosis?**

a) Cell growth

b) Cell division

c) Programmed cell death

d) DNA replication

e) Protein synthesis

10. **What does the Oxygen Enhancement Ratio (OER) describe?**

a) The effect of light on radiation

b) How oxygen amplifies the impact of ionizing radiation

c) The effect of temperature on radiation

d) The effect of pressure on radiation

e) None of the above

11. **The maximum OER primarily depends on what factor?**

a) Radiation frequency

b) Radiation wavelength

c) Linear energy transfer (LET)

d) Radiation duration

e) Cell type

12. **What is the typical OER range for low-LET radiations like x-rays?**

a) 0.5 to 1.5

b) 1 to 2

c) 2 to 3

d) 1 to 4

e) 3 to 5

13. **What hypothesis explains the oxygen effect?**

a) Oxygen suppression hypothesis

b) Oxygen fixation hypothesis

c) Oxygen amplification hypothesis

d) Oxygen induction hypothesis

e) None of the above

14. **Radiosensitizers are agents that:**

a) Protect cells from radiation

b) Increase the effects of radiation

c) Neutralize radiation

d) Block radiation

e) None of the above

15. **Which of the following is an example of a radiosensitizer?**

a) Amifostine

b) Vitamin C

c) Cisplatin

d) Water

e) Glucose

16. **Radioprotectors are agents that:**

a) Increase the damage from radiation

b) Protect cells from the damaging effects of radiation

c) Sensitize cells to radiation

d) Block cell division

e) None of the above

17. **Which of the following is a radioprotector?**

a) Cisplatin

b) Gemcitabine

c) Amifostine

d) Hydrogen peroxide

e) Sodium chloride

18. **What is the role of sulfhydryl compounds in radiation protection?**

a) Enhance radiation effects

b) Repair DNA damage

c) Act as free radical scavengers

d) Increase cell proliferation

e) None of the above

19. **Which statement about DNA damage response (DDR) is correct?**

a) DDR only involves cell cycle regulation

b) DDR includes DNA repair and apoptosis pathways

c) DDR is unrelated to cancer therapy

d) DDR is not affected by radiation

e) DDR is a simple, single-pathway process

20. **What are DNA sensors responsible for?**

a) Protein synthesis

b) Detecting perturbations in DNA homeostasis

c) Increasing cell metabolism

d) Decreasing cell proliferation

e) All of the above

21. **Which step in the indirect action of x-rays involves high-energy electron production?**

a) Step 1

b) Step 2

c) Step 3

d) Step 4

e) Step 5

22. **Which type of radiation typically has an OER of 1?**

a) X-rays

b) Beta particles

c) Gamma rays

d) Low-energy alpha particles

e) High-energy electrons

23. **What is the purpose of DDR inhibitors in cancer therapy?**

a) To repair DNA

b) To overcome DDR-mediated resistance

c) To increase cell division

d) To protect normal cells

e) None of the above

24. **Which free radical is not commonly produced by radiation interaction with water?**

a) OH•

b) H_2O^+

c) O_2^-

d) H_2O_2

e) All are commonly produced

25. **What does the dose reduction factor (DRF) measure?**

a) Increased radiation dose

b) Decreased radiation dose

c) Effective dose reduction by radioprotectors

d) Radiation absorption rate

e) Cell division rate

26. **Which outcome is not one of the four possible outcomes of irradiated cells?**

a) No effect

b) Division delay

c) Apoptosis

d) Reproductive success

e) Reproductive failure

27. **What is the primary target for indirect action damage in the cell?**

a) Lipids

b) Proteins

c) Carbohydrates

d) DNA

e) RNA

28. **Which of the following is not a free radical produced by radiation interaction with water?**

a) OH•

b) H_2O^+

c) O_2^-

d) CO_2

e) H_2O_2

29. **What is the significance of free radicals in radiation damage?**

a) They stabilize DNA

b) They repair cell membranes

c) They break chemical bonds and produce biological damage

d) They enhance cell division

e) None of the above

30. **Which biological effect is not caused by radiation-induced DNA changes?**

a) Cell death

b) Mutation

c) Cancer

d) Infection

e) Apoptosis

31. **The term 'radio protectors' refers to agents that:**

a) Enhance the effects of radiation on tumors

b) Protect normal tissues from radiation damage

c) Increase radiation dose required for an effect

d) Block all effects of radiation

e) None of the above

32. **Which of the following is not an outcome of the oxygen effect?**

a) Increased effectiveness of radiation

b) Increased production of reactive oxygen species

c) Decreased effectiveness of radiation

d) Permanent fixation of DNA damage

e) Increased cellular response to radiation

33. **How do chemical sensitizers affect indirect radiation action?**

a) They decrease radiation damage

b) They increase radiation damage

c) They neutralize free radicals

d) They repair DNA

e) None of the above

34. **Which molecule is not directly involved in the production of free radicals during indirect action?**

a) H2O

b) DNA

c) H2O+

d) OH•

e) O2-

35. **What is the main cause of reproductive failure in irradiated cells?**

a) Enhanced DNA repair

b) Increased cell metabolism

c) DNA damage preventing successful cell division

d) Increased protein synthesis

e) None of the above

36. **Which statement about high-LET radiation is true?**

a) It has a higher OER than low-LET radiation

b) It produces less biological damage than low-LET radiation

c) It typically has an OER of 1

d) It is less effective in damaging DNA

e) It does not produce free radicals

37. **Which factor does not influence the numerical value of the OER?**

a) Specific biological effect being studied

b) Type of cell

c) LET of radiation

d) Environmental oxygen levels

e) Temperature

38. **Which of the following describes the oxygen fixation hypothesis?**

a) Oxygen increases free radical production

b)

Oxygen decreases DNA damage

c) Oxygen permanently fixes radical-induced DNA damage

d) Oxygen blocks radiation effects

e) Oxygen neutralizes free radicals

39. **Which component is not part of the DNA damage response (DDR)?**

a) DNA repair

b) Cell cycle regulation

c) Protein synthesis

d) Replication stress responses

e) Apoptosis

40. **The maximum OER value is generally within which range?**

a) 1 to 2

b) 2 to 3

c) 3 to 4

d) 1 to 4

e) 4 to 5