



**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 $\mathbf{H_2O^+}$ (water ion) and **OH•** (hydroxyl radical) are produced. **The free radicals** in turn can cause damage to the target within the cell.

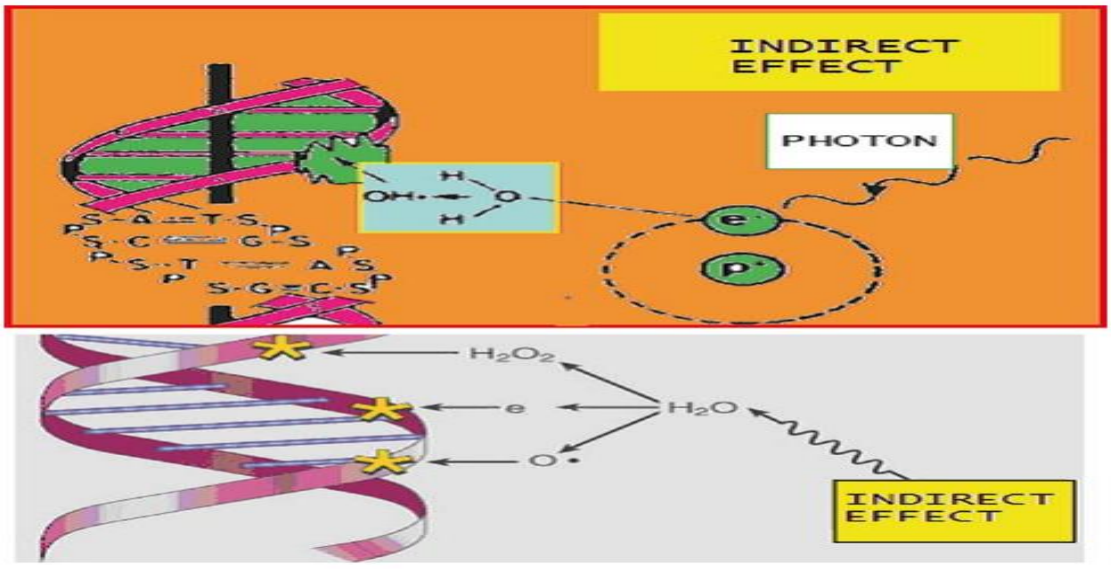
- **The free radicals** that break the chemical bonds and produce chemical changes that lead to biological damage are **highly** reactive molecules because they have an unpaired valence electron.
- About two thirds of the biological damage by **low LET** radiations , such as **x-rays** or **electrons**,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

## Radiosensitizers 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