Effects of radiation on normal tissue

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Radiobiology

Science which combines the basic principles of physics and biology and is concerned with the action of ionizing radiation on biological tissues and living organisms.

The study of basic radiobiological mechanisms deals with biological effects produced by energy absorption in small volumes corresponding to single cells or parts of cells.

Basic principles:

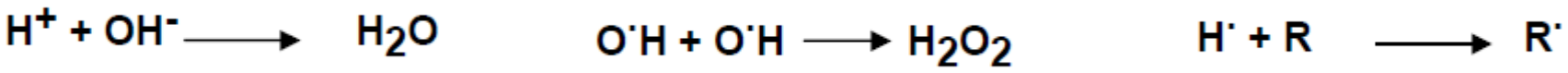
- The interaction of radiation with the cells is a **probability function**. The interaction may occur or not, and where it occurs, it could or not to produce damages.
- Absorption and energy deposit occurs **very quickly**, in about 10^{-17} sec.
- The interaction **is not selective**. The energy of the radiation can deposit anywhere, because there is no greater affinity for any structure.
- The lesions that appear **are not specific**, other agents can also cause them.
- Biological changes resulting require a time until its clinical manifestation (**latency**), which depends on the absorbed dose, and can vary from hours (acute effects) to years (late effects).
- Radiation always cause **injury** on cell/tissue, larger or smaller according to the radiosensitivity.

Ionizing Radiations

Ionizing radiations (rays X and gamma, neutrons, protons, α and ß particles) after its cellular absorption cause processes of excitation, ionization and radiolysis, either in the genetic material (DNA), or in cytoplasm (a liquid solution), causing injury in the tissues directly (*direct action*) or by secondary reactions (*indirect action*).

X-rays for example, have a special interest in the medical field, because they are used both in radiodiagnosis as in treatment (radiotherapy).

- **Direct action**: transfer of energy to macromolecules such as DNA, RNA. Damage is produced by ionization and excitation of key molecules for survival and cellular function.
- **Indirect action**: energy absorption by intracellular medium, mainly water, causing the radiolysis, and as a result are released ions H^+ and free radicals (H•, OH•). They can through diffusion in the cell form chain reactions. Some examples:



Ionizing Radiations

The effect of free radicals depends on the affected structure:

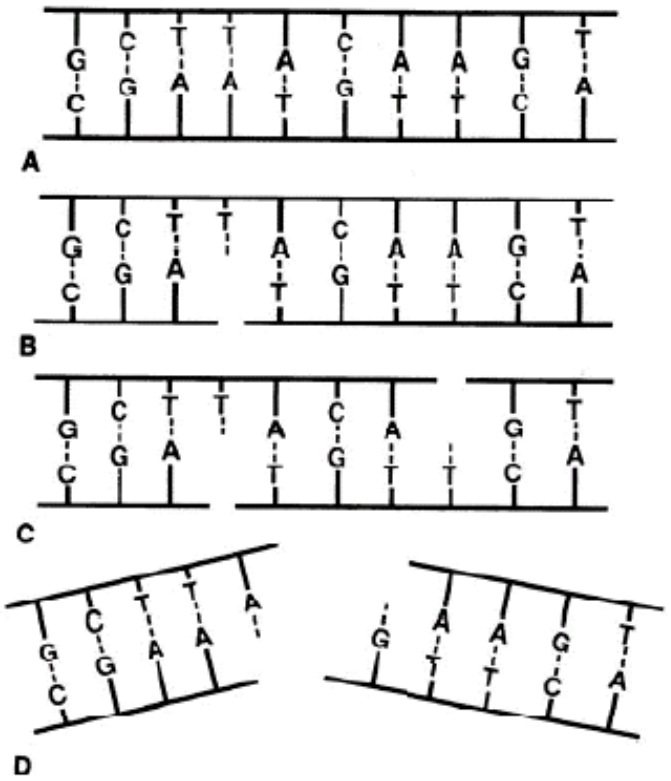
- Non-essential molecules (carbohydrates, lipids or proteins). These structures are rapidly synthesized in the metabolism, so there aren't significant effects.

- DNA. May appear:
  - Strand breaks (single or double).
  - Damaged nitrogenous bases (hydroxylation, deamination, loss…)
  - Damaged sugars.
  - Dimers (e.g. , pyrimidine).
  - Multiple localized damage.

Mutations

The changes that occur in the DNA, <u>if they are not repaired</u>, can lead to **mutations**.

(1)*



Normal DNA

Single-strand break

Single break in both strands

Double-strand break

Mutations

When the DNA damage is fully repaired there is no impact. On the contrary, if the lesion is not repaired mutations appear.

Basic principles:

1) Mutations can affect both the germ and somatic cells, and therefore transmitted to the offspring (with recessive character. They can remain hidden for generations).
2) Mutations appear in all organisms. Radiation induced mutations are not specific, but the radiation increases their frequency, overloading the repair mechanisms.
3) They have no threshold dose. A single impact may cause an injury.
4) Its frequency of occurrence increases with the dose of radiation absorbed, which confirms the cumulative effect of the radiation.

Stochastic Effects Vs Deterministic Effects

Effects of the radiation:

- ***Stochastic Effects.*** The irradiated cell has not been repaired completely, but enough to be viable in spite of their chromosomal alterations, which are likely to be transmitted to the offspring. Associated with the development of long-term carcinogenicity.

- ***Deterministic Effects***. The irradiated cell is not viable, so that cell death occurs. This gives rise to acute toxicity or late complications, according to the number of affected cells and the time of manifestation of damage.

Stochastic Effects Vs Deterministic Effects

	Stochastic	Deterministic
	The **probability** of occurrence increases with increasing dose	Increases in **severity** with increasing dose
Mechanism	Sublethal damage on a single cell	Lethal damage on many cells
Nature	Somatic and germinal	Somatic
Threshold dose	No. Any dose can produce the effect	Yes. If it does not exceed the threshold dose, the effect will not take place
Presentation	Late	Immediate/late

Cellular Radiosensitivity

The effects of radiation on the nucleus or cytoplasm depend on the type of cell on which the radiation reaches. There are a few more susceptible to radiation than others.

In 1906, Bergonie and Tribondeau (2)* formulated laws about the radio-sensitivity cellular. X rays cause more damage to the cells:

I. Greater is their reproductive activity.
II. More divisions required to adopt its final form and function.
III. Less differentiated have their morphology and their functions. An undifferentiated cell is an immature cell, whose main function is to divide to keep its own population and to replace lost mature cells. They are considered the precursor cells or stem cells from a population.

*One exception is the **lymphocyte**, the most radio-sensitive cell despite not having any of this characteristics.

Cellular Radiosensitivity

Factors affecting cell radiosensitivity (1):

- ***Types of radiation and energy deposition:*** ionizing radiations with high LET (linear energy transfer), for example α particles, cause greater number of ionizations and more grouped. Therefore lower cellular survival.

- ***Dose***: with more radiation, higher number of strand breaks, and therefore lower cellular survival.

- ***Dose rates/fractionation rates***: If the dose is administered acutely or at a rapid pace, cellular survival will be less, because the repair mechanisms will be less effective.

- ***Radioprotectors*** (nucleotides, vitamins, cysteine, glutathione...) ***or Radiosensitizers*** (O_2). Their presence decreases or increases the response to radiation, and therefore increase or decrease cellular survival, respectively.

Cellular Radiosensitivity

Factors affecting cell radiosensitivity (2):

- ***Phase of the cell cycle.*** If the radiation is applied in G2 phase, cellular survival will be less, because this is the phase where the cells are more radio-sensitive. Opposite situation if the radiation is applied in S phase (there will be more survival).

- ***Repair mechanisms***. The enzymatic mechanisms responsible for repairing the damage will be more or less effective depending on: cell type and its tolerance to damage, repair capability, phase of the cell cycle and dose rate (if the rate is high, the mechanisms are not the fast enough, and before repairing the first strand break, the second appears).

- ***Activation of cell death routes***. According to the dose of radiation used, will activate a route of cell death or another.

- ***Cellular microenvironment.***

Bibliography

http://sisbib.unmsm.edu.pe/bibvirtualdata/tesis/basic/bernui_vm/Cap4.PDF (1)

http://samclaret.260mb.com/documentos%20proteccion%20radiologica/efectos%20biologicos.pdf (2)

http://www.irsn.fr/FR/professionnels_sante/documentation/Documents/basic_radiobiology.pdf

http://www-rayos.medicina.uma.es/rmf/radiobiologia/revista/numeros/RB3(2003)44-46.pdf