NATURE OF RADIATION AND DNA DAMAGE

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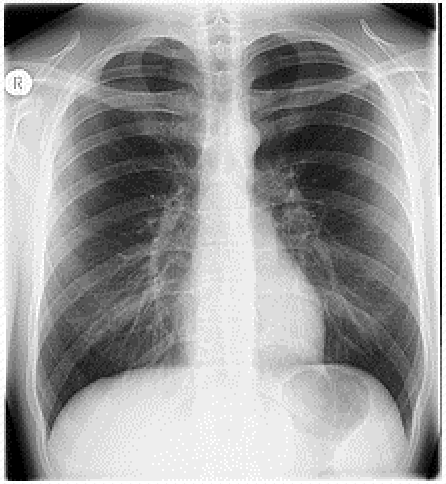
What is radiation?



All energy that spreads wave like through space

Depending on their nature:

→Electromagnetic radiation

→Corpuscular radiation

Depending on their effect:

→Ionizing or high energy radiation

→Non-ionizing or low energy radiation

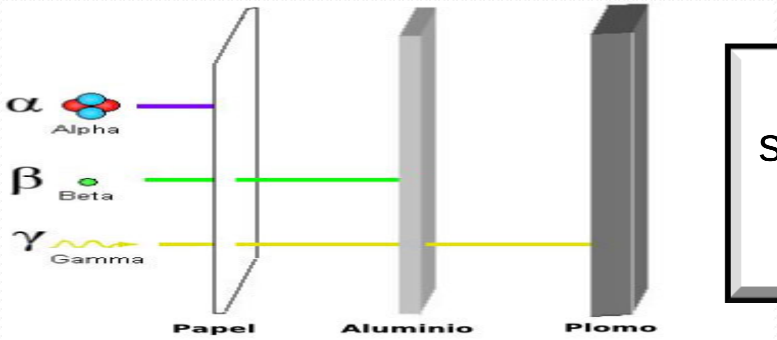
Nature of radiation

Electromagnetic radiation[1]: wave propagation of electric and magnetic energy

- Ionizing radiation.
- Non-ionizing radiation

Corpuscular radiation: because of propagation of subatomic particles

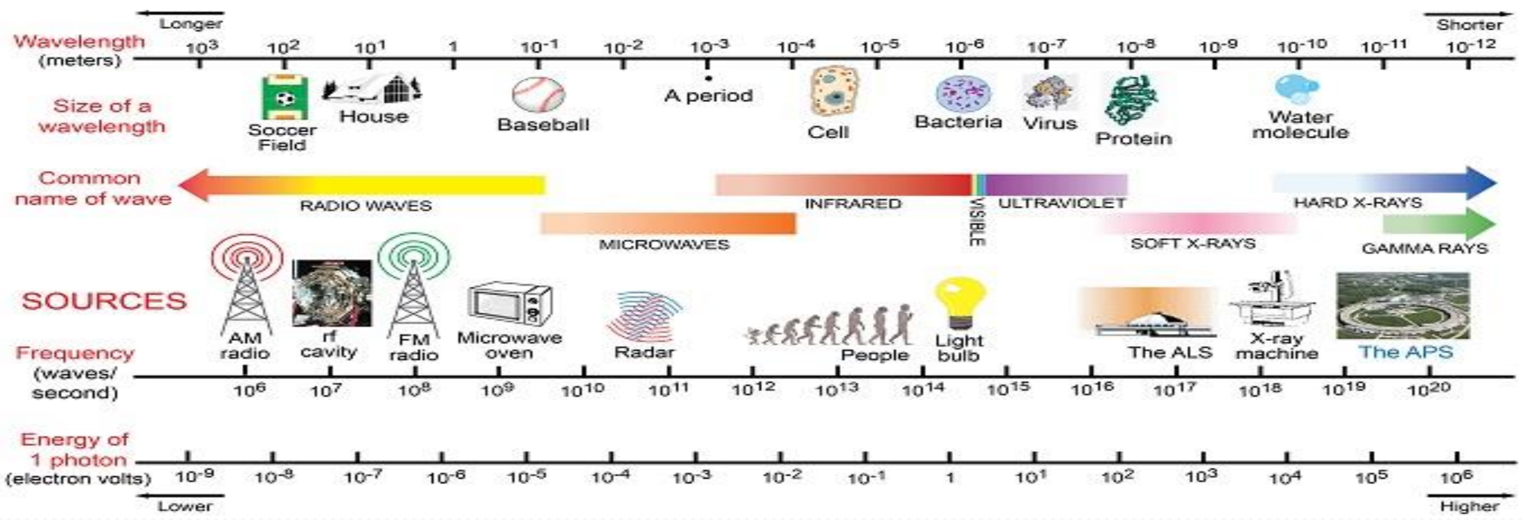
- It includes alpha particles (helium nuclei), beta (electrons and high-energy positrons), protons, neutrons
- And other particles that are produced only by cosmic rays or high energy accelerators such as pions or muons.



An alpha particle doesn't penetrate a sheet of paper, a beta doesn't penetrate metal and a photon penetrates even very thick metal

Electromagnetic spectrum

It is the energy distribution of all the electromagnetic waves



- Ionizing radiation[1] :gamma rays and X-rays
- Non-ionizing radiation: ultraviolet, visible, infrared light, microwaves and radio waves

The time-scale of effects in radiation biology [2]

Duración	Etapa	Proceso
Physical phase	10^{-15} seconds	Energy absorption, energy ionization
Chemical phase	Seconds	Free radicals interact with molecules, cells and DNA
Biological phase	Tens of minutes to tens of years	Cell death, change of genetic information in the cells, mutations

Mechanisms of action of radiation

The action of ionizing radiation on cells, tissues and organs is determined by processes of excitation, ionization and radiolysis, either in the genetic material (DNA) or in the medium in which are cellular organelles (mainly water) [3]

The mechanisms of action of radiation to cause effects in the cell can be classified into two types:

Indirect action	• Absorbing the energy dissipated in intracellular media, mainly water. • The absorption of radiation energy can lead to the formation of free radicals.
Direct action	• A photon interacts with a biological molecule to give it energy→ionization of molecules→radiolysis/transformation of the impacted molecules.

DNA as radiation target

lines of evidence suggest that DNA damage is a critical component of cell death [3]

√ Thymidine analogues change the radiosensitivity when they are incorporated into chromatin.

√ Micro-irradiation studies show that killing a cell requires more doses if the cytoplasm is the only one irradiatied vs if it is the core the only one irradiated

√ The incidence of DSB doesn't result in cell death, while the incidence of chromosomal aberrations and DSB is associated with cell death.

√ Isotopes with short-range emission produce efficient death when they are incorporated directly into DNA

DNA as radiation target

The reservoir of energy is not uniform:

"SPUR": diameter of 4 nm (2xDNA diameter), 100 eV energy deposited, 3 pairs of ions. X-rays deposit 95% of the energy way spur.

"**BLOB":** diameter of 7 nm, 100-500 eV energy deposited, 12 pairs of ions. Neutrons and alpha particules deposit much of their energy way blob. Because of the high number of ions generated, the DNA damage can be much more severe than Spur.

DNA damage

Nitrogenous bases damage

- For each 1G, 800/1000 nitrogenous bases damage T>C>>A>G

Single-strand break

- It happens in the phosphodiester bond. It is the most common damage after radiation. It happens with each 1 Gy, 500/1000 SSB repaired (without biological consequences) and not repaired (mutations).
- In well-oxygenated cells (rather than hypoxic one) in 1 or 2 strands of DNA. Sublethal damage.

Double strand break

- For each 1Gy, 40 DSB. It is hard to repair: mutation, death or carcinogenicity. Lethal injury.

Multiple localized damage

- In one area a combination of one or more double strand breaks with a varying number of single strand breaks, base and sugar damage are located. It is very difficult to repair.

DNA repair pathways

Base Excision Repair (BER)	Nucleotide excision repair (NER)
• If there is a base mutation, it is removed by a glycosylase/DNA lyase. This is followed by the removal of the sugar residue by an AP endonuclease, then replacement with the correct nucleotide by DNA polymerase beta and completed by DNA ligase mediated ligation.	• Removes bulky adducts in the DNA, such as pyrimidine dimers. The steps in this pathway are: damage recognition, DNA incisions that bracket the lesion, removal of the region containing the adducts, repair synthesis to fill in the gap region and DNA ligation.

DNA repair pathways

Repair of double strand breaks by two mechanisms [4]

Nonhomologous End Joining (NHEJ)

Four steps:

1. End recognition
2. End processing
3. Fill in sythesis, or end bridging
4. Ligation

It does not require sequence homology

5 of these gens are at least involved: Ku70, Ku80, DNA- PCK, ligasa IV, Xrcc4. In addition, other proteins such as ATM and ATR, BRCA1 and BRCA2. It is not a high fidelity mechanism .

Homologous Recombination Repair (HRR)

HRR requires physical contact with an undamaged chromatid or chromosome for repair to occur

HRR is activated when the damage involves loss of genetic material

High fidelity mechanism of repairing DNA double strand breaks. Minor repair mechanism.

Processing of DNA damage

- ✓Correct union (repair)
- ✓Nonunion (delection)
- ✓Incorrect union (chromosomal aberration)

Unstable aberration	Cell death	Dicentric rings	Acentric fragments	Centric rings
Stable aberration	They allow survival	Reciprocal translocations	Terminal deletion/internal deletion	Peri-paracentric inversion.
Chromosomal aberration	It depends on the stage of the cycle:	Irradiation in G1 and S: chromosomal aberration	Irradiation in S and G2: chromatid aberrations	

Bibliography

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