**Biological Molecular and Cellular Effects of Ionizing Radiation**

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**Abstract**

X-rays are a form of electromagnetic radiation with wavelengths ranging from 0.01 to 10 nanometers. In the setting of diagnostic radiology, X-rays have long enjoyed use in the imaging of body tissues and aid in the diagnosis of disease. Simply understood, the generation of X-rays occurs when electrons are accelerated under a potential difference and turned into electromagnetic radiation. An X-ray tube, with its respective components placed in a vacuum, and a generator, make up the basic components of X-ray production

**I. INTRODUCTION**

Radiobiology = Radiation Biology is the study of action of ionizing radiation on living organisms Physics & Biology Different types of ionizing radiation: non-ionizing & ionizing radiation. Ionizing radiation: Directly ionizing radiation deposit dose straight away (charged particles): electrons, protons, alpha particles, heavy ions Indirectly ionizing radiation interact with matter and cause ionization (neutral particles): photons, neutrons Energy absorption at the atomic and molecular level à biological damage Radiobiological principles used in Radiotherapy aim to treat cancer by having minimal damage in healthy tissues

**Basic concepts of radiation biophysics**

The DNA Double Strand Break (DSB) is considered the type of lesion most directly related to cell killing different radiation qualities produce the same spectrum of DNA lesions BUT the distribution of lesions inside the target can be very different The Effects of Radiation on the Cell at the Molecular Level

When radiation interacts with target atoms, energy is deposited, resulting in ionization or excitation. The absorption of energy from ionizing radiation produces damage to molecules by direct and indirect actions. For direct action, damage occurs as a result of the ionization of atoms on key molecules in the biological system. This causes inactivation or functional alteration of the molecule. Indirect action involves the production of reactive free radicals whose toxic damage to the key molecule results in a biological effect.

**Direct Effects**

Direct ionization of atoms in molecules is a result of the absorption of energy by photoelectric and Compton interactions. Ionization occurs at all radiation qualities but is the predominant cause of damage in reactions involving high LET radiations. Absorption of energy sufficient to remove an electron can result in bond breaks.

Ionizing Radiation R- + H+

**Indirect Action**

These are effects mediated by free radicals. A free radical is an electrically neutral atom with an unshared electron in the orbital position. The radical is electrophilic and highly reactive. Since the predominant molecule in biological systems is water, it is usually the intermediary of radical formation and propagation.

**Indirect Action- Radiolysis of Water**

H-O-H ® H+ + OH- (Ionization)

H-O-H ® H0+OH0 (Free radicals)

Free radicals readily recombine to electronic and orbital neutrality. However, when many exist, as in high radiation fluence, orbital neutrality can be achieved by:

1. Hydrogen radical dimerization (H2)

2. The formation of toxic hydrogen peroxide (H2O2).

3. The radical can also be transferred to an organic molecule in the cell.

**Indirect Action - The Lifetimes of Free Radicals**

The lifetimes of simple free radicals (H0 or OH0) are very short, on the order of 10-10 sec. While generally highly reactive they do not exist long enough to migrate from the site of formation to the cell nucleus. However, the oxygen-derived species such as hydroperoxy free radical does not readily recombine into neutral forms. These more stable forms have a lifetime long enough to migrate to the nucleus where serious damage can occur.

**Indirect Action- Free Radicals**

The transfer of the free radical to a biological molecule can be sufficiently damaging to cause bond breakage or inactivation of key functions. The organic peroxy free radical can transfer the radical from molecule to molecule causing damage at each encounter. Thus, a cumulative effect can occur, greater than a single ionization or broken bond.

**Biochemical Reactions with Ionizing Radiation**

DNA is the most important material making up the chromosomes and serves as the master blueprint for the cell. It determines what types of RNA are produced which, in turn, determines the types of protein that are produced. The DNA molecule takes the form of a twisted ladder or double helix. The sides of the ladder are strands of alternating sugar and phosphate groups. Branching off from each sugar group is one of four nitrogenous bases: cytosine, thymine, adenine, and guanine.

**Biochemical Reactions with Ionizing Radiation-DNA Damage**

There is considerable evidence suggesting that DNA is the primary target for cell damage from ionizing radiation. Toxic effects at low to moderate doses (cell killing, mutagenesis, and malignant transformation) appear to result from damage to cellular DNA. Thus, ionizing radiation is a classical genotoxic agent.

**Biochemical Reactions with Ionizing Radiation-DNA Damage**

Active enzymatic repair processes exist for the repair of both DNA base damage and strand breaks. In many cases breaks in the double-strand DNA can be repaired by the enzymes, DNA polymerase, and DNA ligase. The repair of double strand breaks is a complex process involving recombinational events, depending upon the nature of the initial break.

**Radiation Induced Chromosome Damage**

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**Radiation Induced Chromosome Damage**

After irradiation, chromosomes may appear to be "sticky" with the formation of temporary or permanent intrachromosomal bridges preventing normal chromosome separation during mitosis and transcription of genetic information. In addition, radiation can cause structural aberrations with pieces of the chromosomes breaking and forming aberrant shapes. Unequal division of nuclear chromatin material between daughter cells may result in the production of nonviable, abnormal nuclei.

**Radiation Induced Membrane Damage**

Biological membranes serve as highly specific mediators between the cell (or its organelles) and the environment. Alterations in the proteins that form part of a membrane’s structure can cause changes in its permeability to various molecules, i.e., electrolytes. In the case of nerve cells, this would affect their ability to conduct electrical impulses. In the case of lysosomes, the unregulated release of its catabolic enzymes into the cell could be disastrous. Ionizing radiation has been suggested as playing a role in plasma membrane damage, which may be an important factor in cell death (interphase death)

**Cell Cycle**

Undifferentiated cells that are growing are destined to divide. The generation time from one cell division to the next, known as the cell cycle, is dependent on species, tissue type, age, and environmental influences. Mitosis occurs with division of the cell. The cell cycle can be divided into phases: G1 (gap), S (synthesis), G2 (gap), and M (mitosis). Cells not actively growing occupy a fifth phase known as G0. The cell in G0 can often be stimulated to enter the active cycle by environmental stresses.

Cells in G0, G1, S and G2 phases of the cell cycle occupy what is called the interphase period. During mitosis (M phase) chromosomes condense (prophase) and become aligned on the equatorial plane (metaphase). Pairs separate (anaphase) and condense at the poles of dividing cell (telophase), and the new nucleus forms in each cell.

Cells are most sensitive to cell killing during the period shortly before M phase at late interphase (G2), and during M phase. Higher resistance is seen in cells in S phase and late G1 phase as well as all cells in G0 phase. Resistance in S phase may be due to the presence of synthetic enzymes capable of prompt repair of DNA breaks. However, mutation frequency increases in cells in or just before S phase.

Irradiation of the cell causes cell death at mitosis as a result of the inability to divide. (Mitotic death) RNA and protein synthesis do not halt in the sterilized cell. The result is the production of the giant cell, whose unbalanced growth eventually proves lethal to the cell.

**Bergonié-Tribondeau Low**

According to these early radiobiologists (1906), radiation response in tissue was a function of

1. a high number of undifferentiated cells in the tissue,

2. a high number of actively mitotic cells

3. the length of time the cells remain in active proliferation.

**Radiosensitivity**

* High-dose radiotherapy is ineffective for tumor control and has serious side effects.
* The basis of fractionation is rooted in five primary biological factors that affect the responses of normal and tumor tissues in fractionated radiotherapy called the five Rs of radiotherapy
* **Repopulation:**
	1. Both tumor and healthy normal cells continue to proliferate even when they are exposed to radiation.
	2. This repopulation enables tumor cells to partially resist the lethal effects of radiotherapy. The time required for the tumor cell number to double is known as the “tumor doubling time,” Tp and can also be considered the repopulation time.
	3. Repopulation is slow at the beginning of radiotherapy, but it speeds up after the first doses of radiation therapy. This increase in repopulation rate is termed “accelerated repopulation,” and the time taken for it to begin is termed the “kick-off time” (Tk).
	4. Repopulation must be taken into account when protracting radiation e.g. due to scheduled (or unscheduled) breaks such as holidays.
	5. Normal tissue also repopulate during radiotherapy, this is an important mechanism to reduce acute side effects. e.g. the irradiation of skin or mucosa.
* **Repair:**
	1. Radiotherapy causes lethal damage to tumor cells and Sublethel Damage in normal tissues. The application of radiotherapy in fractionated doses allows normal tissues to repair sublethel damage.
	2. t1/2  is the parameter used in this effect which defines that half the time required for cell repair after radiation damage (t1/2) and the value of this parameter can be minutes to hours.
	3. Therefore, interfraction intervals should be at least 6 h in order to allow normal tissue cells to repair radiation damage prior to giving another fraction of radiation.

 

* **Redistribution:**
	1. Redistribution is the selective killing of cells in the certain phase of cell cycle
	2. The radiosensitivities of cells vary with the phase of the cell cycle.
	3. The most sensitive phases are M and G2, while the most resistant is the S phase. Cells in resistant phases of the cell cycle may progress into a sensitive phase during the next dose fraction.Therefore, the probability that tumor cells will be exposed to radiation during a sensitive phase increases.

 

* **Re-Oyxgenation:**
	1. Oxygen is an important enhancement for radiation effects
	2. As the tumor volume increases through the proliferation of tumor cells, the vascularity of the tumor tissue becomes insufficient and hypoxic regions occur within the tumor cell. Therefore hypoxic cells are more resistant to radiation.
	3. During the course of fractionated radiotherapy, the hypoxic cells gradually obtain much better vascularity and oxygenation, and their radiosensitivity’s increases.



* **Radiosensitivity:**
	1. The term “radiosensitivity” was first defined by Bergonie and Tribendau, they suggested that radiosensitivity was directly proportional to mitosis and inversely proportional to differentiation.
	2. The damage depends on: i.) Type of cell irradiated, ii) volume of tissue irradiated, iii.) Dose received
	3. Radiosensitivity may be affected by environmental conditions.
	4. The term SF2 was introduced, (SF2 = surviving cell fraction after a radiation dose of 2 Gy). As SF2 increases, radiosentivity decreases. Radiosensitizers are used to decrease SF2.

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