

Ionizing Radiation-induced Cell Death

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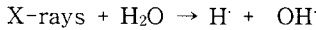
Modes of Radiation Injury

Low LET radiations (X- and γ -rays):
free radicals \Rightarrow indirect action

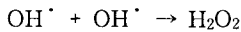
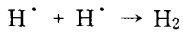
High LET radiations (protons and α particles):
ionization \Rightarrow direct action

A. Free Radicals: neutral atoms or molecules having an unpaired electron

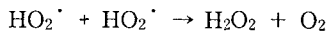
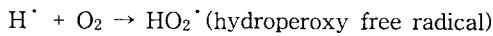
Two types of free radicals in case of X-rays
by interaction with water



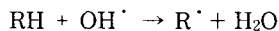
Recombination of free radicals



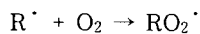
Formation of additional free radicals in the
presence of an excess of oxygen



Formation of organic free radicals in the
presence of organic molecules



Formation of peroxy free radicals: O_2 fixation
phenomenon



※ Two free radicals, in the presence of excess
oxygen, accounting for the increased radiation
damage: $\text{HO}_2\cdot$ (hydroperoxy) and $\text{RO}_2\cdot$ (peroxy)

(Lifetime of free radicals)

- very short-lived and very reactive:

less than 10^{-10} sec

- some free radicals from complex organic substances: stable and less reactive
- (Reactivity of free radicals)
- oxidize or reduce the biological molecules within the cells
 - damage DNA, RNA, and protein as well as membranes
 - implicated in the etiology of cancer and in neurodegenerative diseases

Time domains of radiation action in biological systems

Physical stage:

10^{-18} to 10^{-17} s	Fast particle traverses small atom or molecule
10^{-16}	Ionization $\text{H}_2\text{O} \rightarrow \text{H}_2\text{O}^+ + \text{e}^-$
10^{-15}	Electronic excitation $\text{H}_2\text{O} \rightarrow \text{H}_2\text{O}^*$
10^{-13}	Molecular vibrations and dissociation
10^{-12}	Rotation, relaxation and solvation of the electron in water

Chemical stage:

10^{-10} to 10^{-7} s	Reactions of e-eq and other free radicals with solutes in radiation tracks and spurs
10^{-7}	Homogeneous distribution of free radicals
10^{-3}	Free-radical reactions largely complete
Seconds, minutes, hours	Biochemical changes (enzyme reactions)

Cellular and tissue stages:

Hours	Cell division inhibited in microorganisms and mammalian cells; reproductive death
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Days	Damage to gastrointestinal tract (and central nervous system at high doses)
Months	Haemopoietic death; acute damage to skin and other organs; late normal-tissue morbidity
Years	Carcinogenesis and expression of genetic damage in offspring.

division & also it occurs in non-cycling cells.

- Disappearance of microvilli, appearance of smooth surface or of extensive changes to blistered surface, alterations in membrane permeability, reduction of cell volume, condensation of cytoplasm & chromatin, internucleosomal cleavage of DNA

B. Radiation 'target'

critical target : DNA

membrane damage : interactions between the nucleus and the plasma membrane

C. Definitions

Reproductive death(Mitotic death) :

- It happens one or even several divisions after irradiation and is characteristic of actively proliferating cells. It is considered to be due to radiation-induced DNA lesions and chromosomal damage
- based on the ability of individual cells to divide and form recognizable colonies in a plastic dish

Plating efficiency(PE) : percentage of cells that are able to form visible colonies. not 100% plating efficiency, due to trauma associated with suspension, dilution, and plating

Interphase death

- Impairment of cellular metabolism and disintegration of cells before entering mitosis Loss of dye exclusion capacity is the usually applied end point
- Radiosensitive thymocytes, T-cell leukemia cell, neonatal kidney cells, serous acinar cells of salivary & lacrimal glands, some murine tumor cells → rapid death after relatively low dose of irradiation.
- It occurs before the entry of cells into next

Necrosis vs. apoptosis

Characteristics	Necrosis	Apoptosis
DNA electrophoresis	smear	'ladder'
Transglutaminase activity	unchanged	increased
Cell borders	indistinct	sharply delineated
Cytoplasm	eosinophilic	eosinophilic or poorly stained
Nucleus	dots of shrunken chromatin	shrunken or fragmented nucleus with sharply compacted chromatin
Mitochondria	swollen	unchanged
Cell size	unchanged or swollen	shrunken
Inflammation in surrounding cells	yes	no
Distribution	groups of cells	isolated cells

D. Types of Cellular Injury

- Extent of radiation damage of a given cell type depends on;
 - (1) total dose
 - (2) dose rate
 - (3) type of radiation ; high LET vs low LET
 - (4) mode of radiation delivery; single vs fractionation
 - (5) environmental condition of the medium

Types of cellular damage in relation to approximate dose

Dose(rads)	Type of Damage	Comments
1-5	Mutation(chromosomal aberration, gene damage)	Irreversible chromosome breaks, may repair
100	Mitotic delay, impaired cell function	Reversible
300	Permanent mitotic inhibition, impaired cell function, activation and deactivation of cellular genes, and oncogenes	Certain functions may repair; one or more divisions may occur
>400-1000	Interphase death	No division
50,000	Instant death	Proteins coagulate