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- Target Theory
- Cell Survival Kinetics
- Single-Target, Single-Hit Model
- Multitarget, Single-Hit Model
- Recovery

Radiation Interaction
- Initial interaction between radiation & tissue occurs at electron level
- Observable human injury results from changes at molecular level
- Separated into effects on:
  1. Macromolecules
  2. Water

Irradiation of Macromolecules
- In-Vitro Irradiation
  - Macromolecules irradiated outside of body or cells
- In-Vivo Irradiation
  - Macromolecules irradiated inside a living cell

Irradiation of Macromolecules
- When irradiated in-vitro, the following occur:
  1. Main-chain scission
  2. Cross-linking
  3. Point lesions
When irradiated in-vitro, the following occur:

1. Main-chain scission
2. Cross-linking
3. Point lesions

At low dose, point lesions are the cellular damage resulting in the late effects observed at whole body level.

Function of a normal cell:
- Catabolism, Anabolism, & Synthesis
- Synthesis of protein & nucleic acid is critical for cell survival
- DNA is the most radiosensitive macromolecule

DNA Synthesis
- DNA is the most radiosensitive macromolecule

Radiation Effects on DNA
- DNA is the most important molecule in the human body
Irradiation of Macromolecules

Radiation Response of DNA

1. Main-chain scission with one side rail severed
2. Main-chain scission with both sides rail severed
3. Main-chain scission and subsequent cross-linkage
4. Change or loss of base molecular lesion (Point Mutation)

Radiolysis of Water

- Human body is 80% water
- Irradiation of water represents principle radiation interaction
- Dissociation into other molecules
  - Radiolysis of water

Radiolysis of Water

- Irradiation causes ionization
- Dissociates into two ion pairs

Radiolysis of Water

- After initial ionization
- May rejoin into stabilize water molecule
- May attach to another water molecule

Radiolysis of Water

- HOH⁺ & HOH⁻ are unstable
- Dissociate into smaller molecules
- Free-radicals:
  - Uncharged, contain single unpaired electron in outermost shell

Radiolysis of Water
Free Radicals

- Highly Active
- Unstable (~1ms)
- Diffuse through cell & interact at distance site
- Excess energy transferred to other molecules, disrupting bonds, causing point lesions
- Can also produce toxins

Free Radicals

- Hydrogen Peroxide Formation

\[ \bullet + \text{O}_2 \rightarrow \text{H}_2\text{O}_2 \]

- Hydroperoxyl Formation

\[ \bullet + \text{O}_2 \rightarrow \bullet \text{O}_2 \]

Direct & Indirect Effects

Direct Effect
- Initial ionizing event occurs on the most radiosensitive molecule, DNA

Indirect Effect
- Initial ionizing event occurs on any other molecule (usually water) which transfers energy to the DNA

Principle effect in humans is indirect

Target Theory

- Some abundant molecules
  - Damage causes no noticeable effect
- Some molecules are vital & scarce
  - Damage causes severe effects
- Target theory
  - For a cell to die, target molecule must be inactivated
- Radiation interaction that inactivates target molecule is called a ‘Hit’

Measuring lethal effects of radiation on cells

- Mathematical extension of target theory
- Produces TWO models of cell survival
- Radiation dose-response for single cell

1. Single-Target, Single-Single Hit Model
2. Multitarget, Single-Hit Model
Single-Target, Single-Hit Model

Simple Analogy
- 100 paving slabs
- Each represents a cell
- It Starts to Rain!
- A slab is considered wet when ONE raindrop has hit it

Single-Target, Single-Hit Model

Simple Analogy
- First raindrop falls
- One Slab WILL be wet
- 1/100 of slabs are wet
- Second raindrop falls
- It will probably hit a dry slab
- Two slabs will be wet
- 2/100 of slabs are wet

Single-Target, Single-Hit Model

Simple Analogy
- As the number of raindrops increases it becomes more probably that a square will be hit by more than one drop
- Raindrops are falling RANDOMLY
- Probability that a given slab will become wet governed by Poisson Statistics

Single-Target, Single-Hit Model

Poisson Statistics
- When 100 raindrops have fallen:
  - 63% slabs will be wet; 37% slabs dry
  - If rain fell uniformly: 100% wet
- 200 raindrops fallen:
  - 0.37x0.37 (14%) dry slabs
- 300 raindrops fallen:
  - 0.37x0.37x0.37 (5%) dry slabs
- And So On...

Single-Target, Single-Hit Model

Extend Analogy to Cells
- A large sample of cells
- Each cell contains ONE target molecule
- D_{37} : Dose required to kill 63% of cells
- If radiation interacted uniformly (no wasted hits)
  - D_{37} would kill 100% cells
- Lower D_{37}, higher radiosensitivity

Single-Target, Single-Hit Model

Single-Target, Single-Hit Model

SS = Surviving fraction
NN = Number of surviving cells
NN_0 = Initial number of cells
DD_{37} = Constant dose related to radiosensitivity
DD = Dose

$$S = \frac{N}{N_0} = e^{-D/D_{37}}$$

Percentage of Surviving Cells

Radiation Dose (Gy)
Multitarget, Single-Hit Model

Simple Analogy

- 100 paving slabs
- Slabs divided into TWO
- I.e. cells with TWO target molecules

- It Starts to Rain!
- A slab is only considered wet when both halves are wet
- Many drop must fall before a square is wet
- Threshold

Simple Analogy

- First few raindrops
  - Only one half of any slab is wet
  - All considered dry

- More raindrops fall
  - Some slabs will have both halves wet
  - Considered wet

- Many rain drops have fallen
  - Most slabs have one wet half
  - Each additional hit causes a wet slab

Simple Analogy

- First few raindrops
  - Only one half of any slab is wet
  - All considered dry

- More raindrops fall
  - Some slabs will have both halves wet
  - Considered wet

- Many rain drops have fallen
  - Most slabs have one wet half
  - Each additional hit causes a wet slab

Extend Analogy to cells

- Low Dose - Below Threshold ($D_0$)
  - Only one target molecule hit
  - All cells alive

- Intermediate Dose
  - Some cells have both target molecules hit
  - Some dead cells

- High Dose
  - Most cells have received one hit
  - Each additional hit causes death

- High $D_0$ indicates cell can readily recover

Fraction of Surviving Cells ($N/N_0$) vs. Radiation Dose (Gy)

Surviving fraction

$S = N/N_0 = 1 - (1 - e^{-D/D_0})^n$

$S$ = Surviving fraction
$N$ = Number of surviving cells
$N_0$ = Initial number of cells
$D_0$ = Mean Lethal Dose
$D$ = Dose required to reduce survival by 37% after threshold region
$n$ = Exponential number

Fraction of Surviving Cells ($N/N_0$) vs. Radiation Dose (Gy)
Multitarget, Single-Hit Model

\[ S = \frac{N}{N_0} = 1 - (1 - e^{-D/D_0})^n \]

- **S**: Surviving fraction
- **N**: Number of surviving cells
- **N_0**: Initial number of cells
- **D_0**: Mean Lethal Dose
  - Dose required to reduce survival by 37% after threshold region
- **D**: Dose
- **n**: Extrapolation number
  - \( (N_{\text{of target molecules}}) \)

Example

- Blood cells have a radiation response that follows the multi-target single-hit model with 3 target molecules.
- An average dose of 5 mGy is required to kill 63% of the cell population beyond the threshold dose.
- What fraction of the cell population would survive a dose of 10 mGy?

Recovery

- Shoulder of the graph show that some damage must accumulate before a cell dies
  - **Sublethal Damage**
- Wider shoulder, more sublethal damage can be sustained

Recovery

- New population used for 2nd cell survival experiment
- Surviving cells subjected to another dose
- Generate another response curve
- Precisely the same shape as the original curve
- Same extrapolation number
- Separated along dose axis by \( D_0 \)
- \( D_0 \) is not only a measure of a cells capacity to accumulate sublethal dose
- Also a measure of cell ability to recover

Summary

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