Cell Death After Irradiation

Faculty of Applied Science- Department of Radiology

Course Name: Radiobiology Course Code: MTR 211

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Outlines

- Introduction: Radiation and Cell Fate.
- Overview of Cell Death Pathways.
- Programmed Cell Death.
- Apoptosis: Mechanism, Morphological Features and Examples.
- Autophagy and Radiation.
- Necrosis and Radiation.
- Senescence: Definition, Mechanism, and Biological Significance.
- Mitotic Catastrophe: Overview and Mechanism.
- Factors Influencing Cell Death Type.
- Biological and Clinical Relevance.

Learning Outcomes

By the end of the lecture, students should be able to:

- Describe the major types of cell death after radiation exposure.
- Distinguish between apoptosis, autophagy, necrosis, senescence, and mitotic catastrophe.
- Explain molecular mechanisms underlying each type.
- Relate radiation dose and cell cycle phase to death mode.
- Understand biological and clinical relevance in radiotherapy.

Introduction: Radiation and Cell Fate

Ionizing radiation damages

- Mainly DNA, but also cell membranes and organelles (especially mitochondria).
- Damage is caused directly by energy deposition or indirectly through free radicals.

How cells respond

- **Repair:** If damage is small, the cell activates repair systems and survives.
- **Cell cycle arrest:** The cell temporarily stops dividing to allow repair.
- **Programmed death:** If damage is too great, the cell activates death pathways (apoptosis, autophagy, etc.) to prevent mutation spread.

Outcome depends on

- Radiation type and dose
- Cell type
- Microenvironment

Overview of Cell Death Pathways

After radiation exposure, cells may:

- **Survive and repair** → continue normal division.
- Die through several possible pathways, depending on the type and extent of damage.

Main types of cell death after irradiation

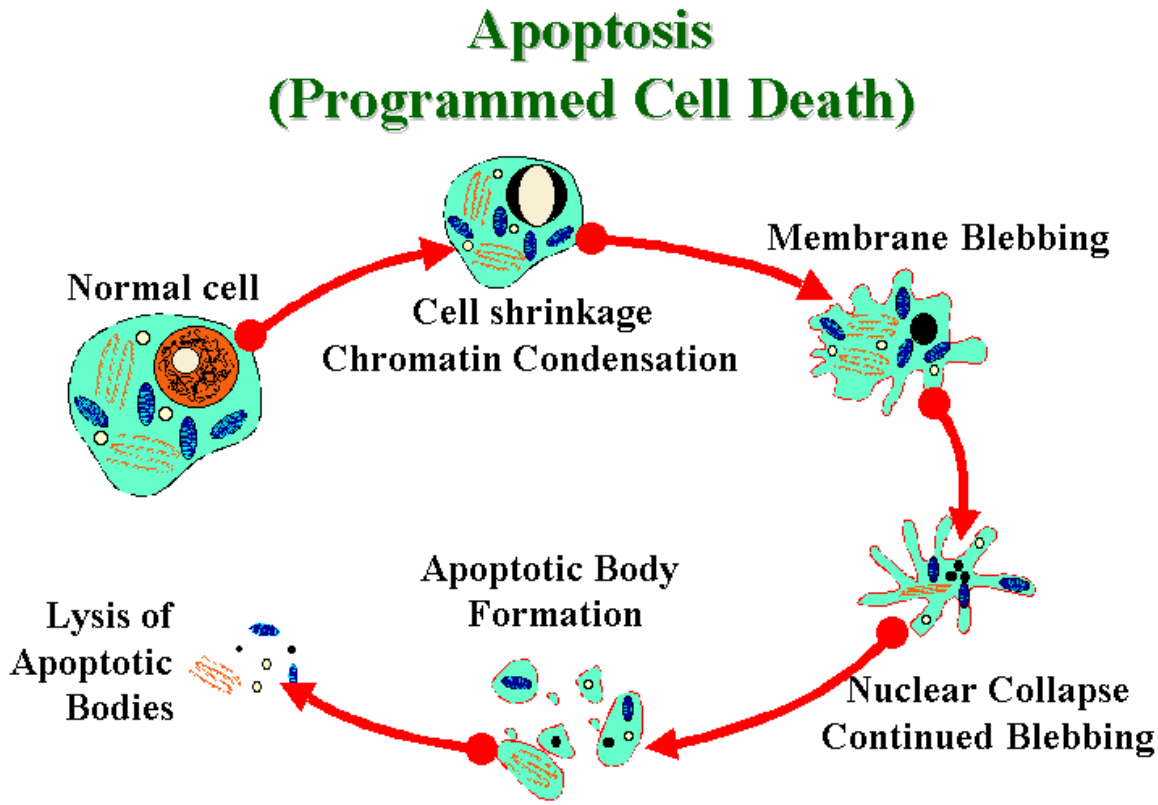
- **Apoptosis** → programmed, clean cell death.
- **Autophagy** → self-digestion of damaged parts; may lead to death or survival.
- **Necrosis** → uncontrolled, messy cell death causing inflammation.
- **Senescence** → permanent stop in cell division, but cell remains alive.
- **Mitotic catastrophe** → abnormal division leading to giant or multinucleated cells that eventually die.

Programmed Cell Death (PCD)

- It’s a **controlled**, **energy-dependent** process by which cells *deliberately die*.
- Unlike necrosis, it’s **orderly and regulated** — the cell “decides” to die to protect the tissue.

Why does it happen after irradiation?

- Radiation damages **DNA** and other **vital structures**.
- If repair fails, the cell activates programmed death to prevent passing mutations to new cells.
- This is a **protective mechanism for the body**.



Main forms of PCD

- Apoptosis.
- Autophagy-associated death.

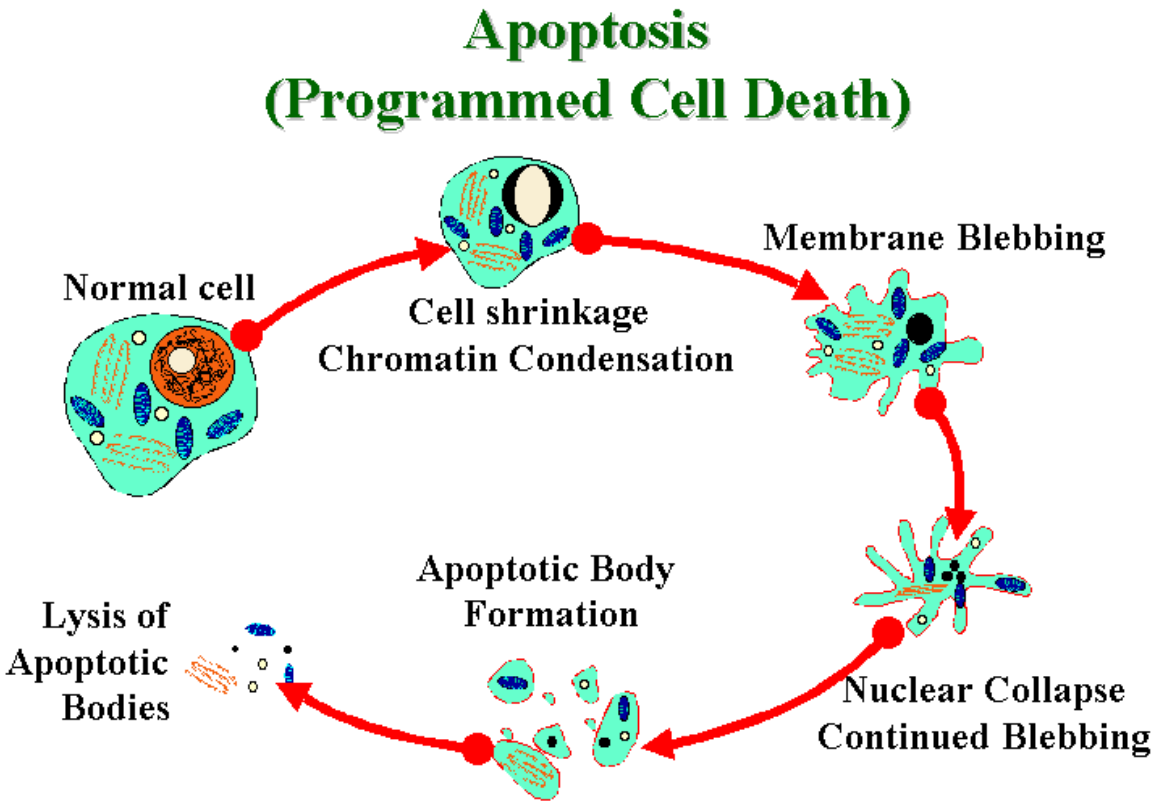
Apoptosis: Overview

What is apoptosis?

- A programmed cell death mechanism; clean, orderly, and energy-dependent.
- The cell **shrinks** and **fragments** without causing inflammation.
- Often called “cellular suicide”.

Why does it occur after irradiation?

- DNA damage from radiation activates control proteins (like **p53**).
- If damage is beyond repair, these proteins trigger apoptosis to remove the damaged cell.



Apoptosis: Mechanisms

Key characteristics

- Affects **individual cells**, not large groups.
- **Does not harm neighboring cells**.
- Important in maintaining **tissue health** and **preventing cancer**.

Two main pathways

1. Intrinsic (Mitochondrial pathway):

- Triggered by DNA damage from radiation.
- The cell activates p53, which increases BAX/BAK proteins.
- These proteins make holes in the mitochondria, releasing cytochrome c.
- Cytochrome c activates caspases (special enzymes) that break down the cell.

Apoptosis: Mechanisms

2- Extrinsic (Death receptor pathway):

- Starts outside the cell.
- Death signals bind to receptors on the cell surface (like Fas or TNF receptors).
- This activates caspase-8, which triggers the same caspase cascade to destroy the cell.

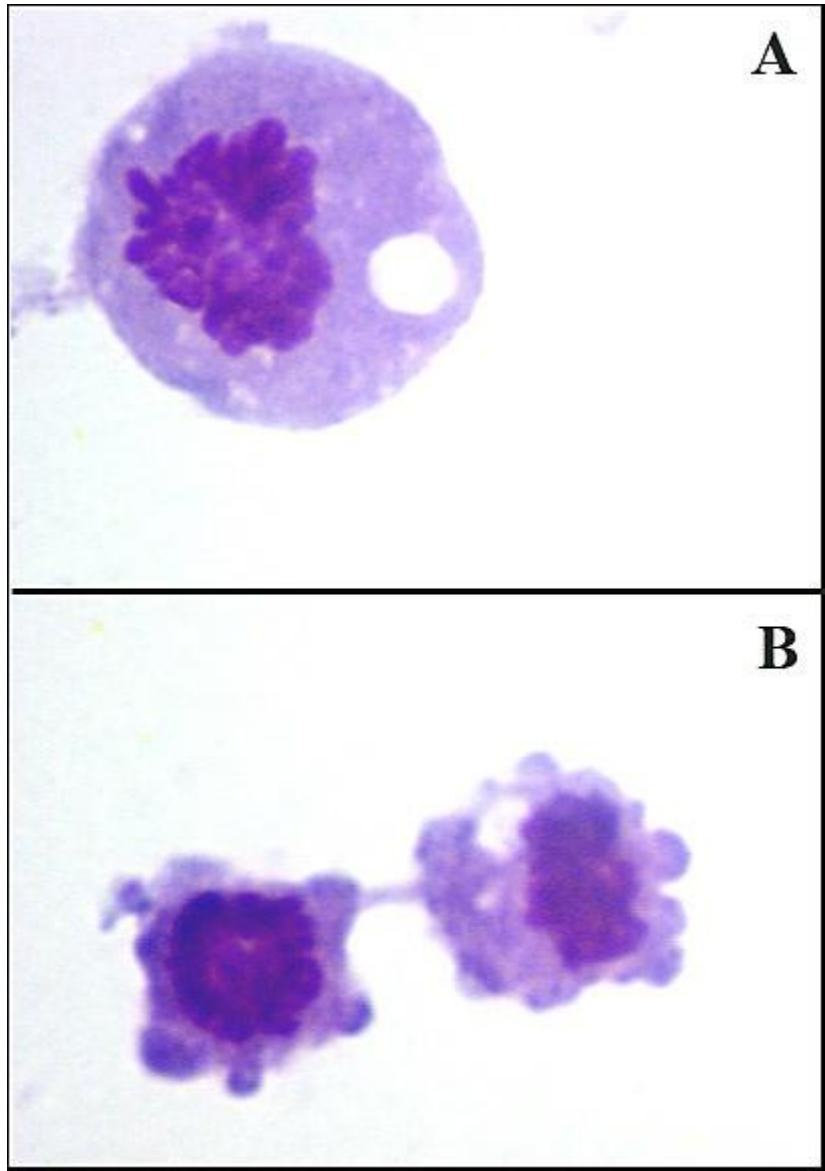
Result

- Caspases cut up **proteins** and **DNA**.
- The cell breaks into **small pieces** (apoptotic bodies) that **are removed by other cells**.

Apoptosis: Morphological Features

What happens to the cell?

1. **Cell shrinkage:** The cell gets smaller and more compact.
2. **Chromatin condensation:** The nucleus becomes dense and dark under the microscope.
3. **Membrane blebbing:** The outer membrane forms small bubble-like protrusions.
4. **Fragmentation:** The cell breaks apart into tiny sealed pieces called apoptotic bodies.
5. **Phagocytosis:** Neighboring cells or macrophages quickly remove these pieces; *no inflammation occurs*.



Apoptosis: Radiation Examples

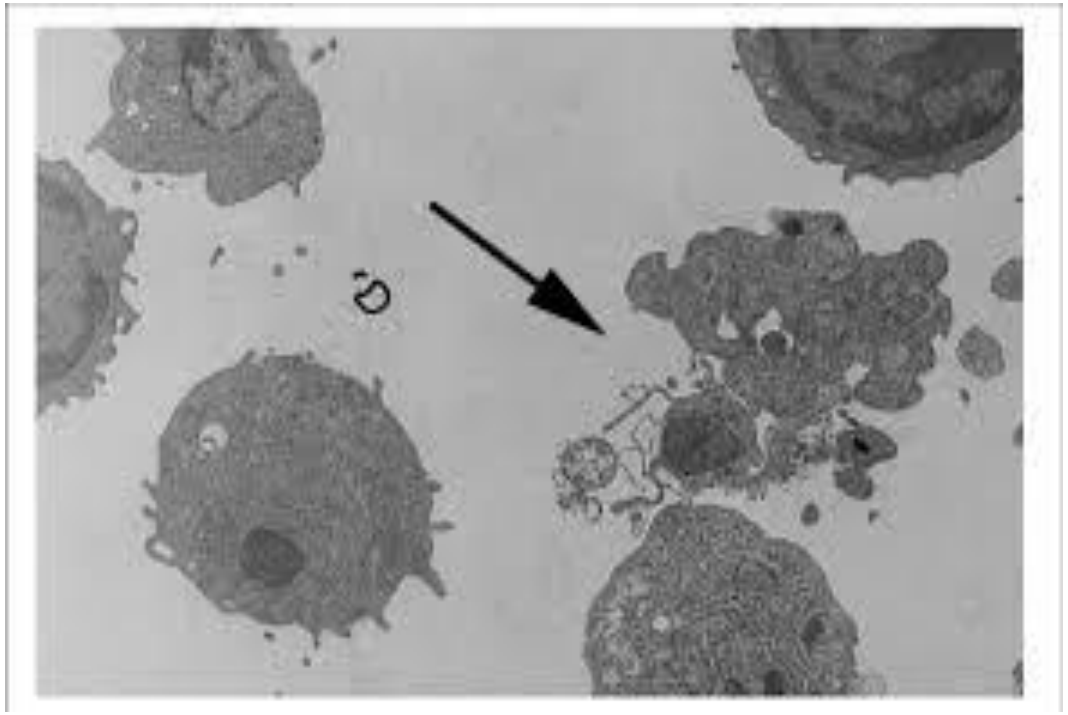
Cells that show a strong apoptotic response

1- Lymphocytes and thymocytes:

- Extremely sensitive to radiation.
- Undergo apoptosis even at low doses.
- Death occurs within a few hours after exposure.

2- Intestinal crypt cells and germ cells:

- Shows rapid apoptosis due to high cell turnover.



Why these cells?

- They are actively dividing and have strong p53 activity, so they respond quickly to DNA damage.
- Apoptosis prevents damaged cells from multiplying and forming mutations.

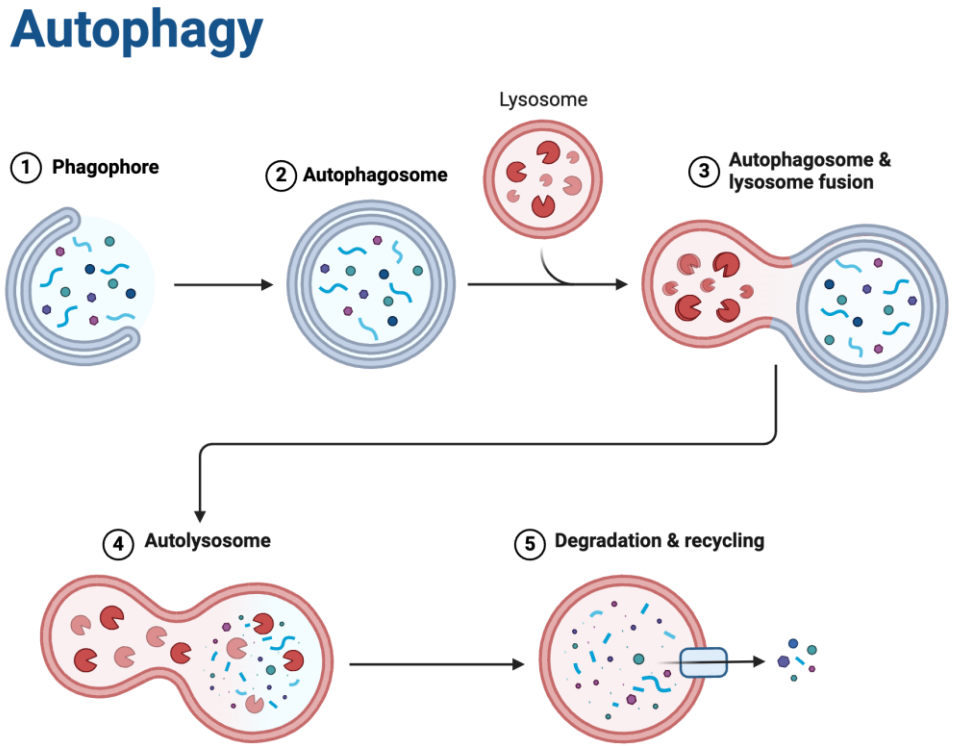
Autophagy: Definition

What is autophagy?

- The word means "**self-eating**."
- It's a process where the cell digests its **own damaged parts** (like proteins or organelles) inside special vesicles called **autophagosomes**.
- These vesicles then fuse with **lysosomes**, where the contents are broken down and recycled.

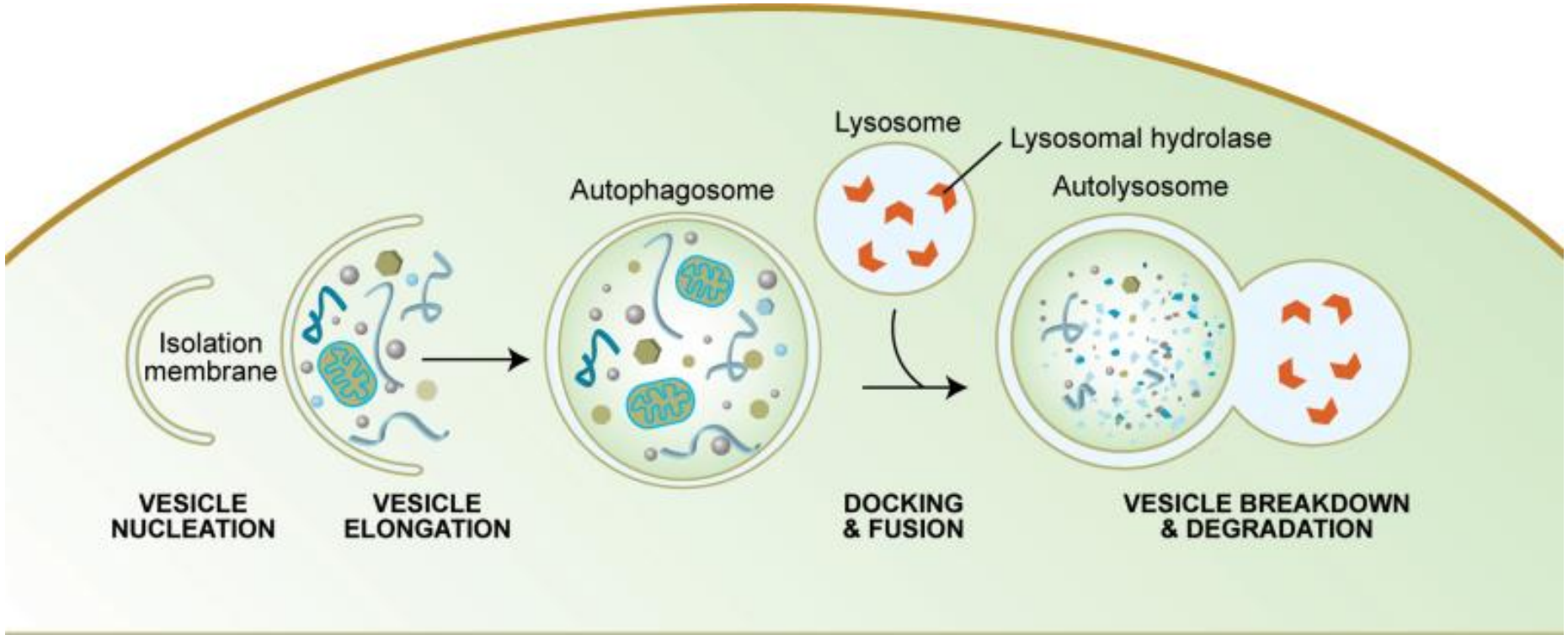
Why does it happen after irradiation?

- Radiation causes **stress** and damage to cell components (especially mitochondria).
- The cell activates autophagy to **remove damaged parts** and survive.
- If the process continues too long or becomes excessive → it can lead to **cell death**.



Autophagy: Mechanism

1. **Initiation:** The cell senses stress or damage and forms a small membrane called a **phagophore**.
2. **Elongation:** The phagophore expands and engulfs damaged organelles or proteins, forming an **autophagosome**.
3. **Fusion:** The autophagosome fuses with a **lysosome** to form an **autolysosome**.
4. **Degradation:** The lysosomal enzymes break down the contents, recycling nutrients back to the cell.



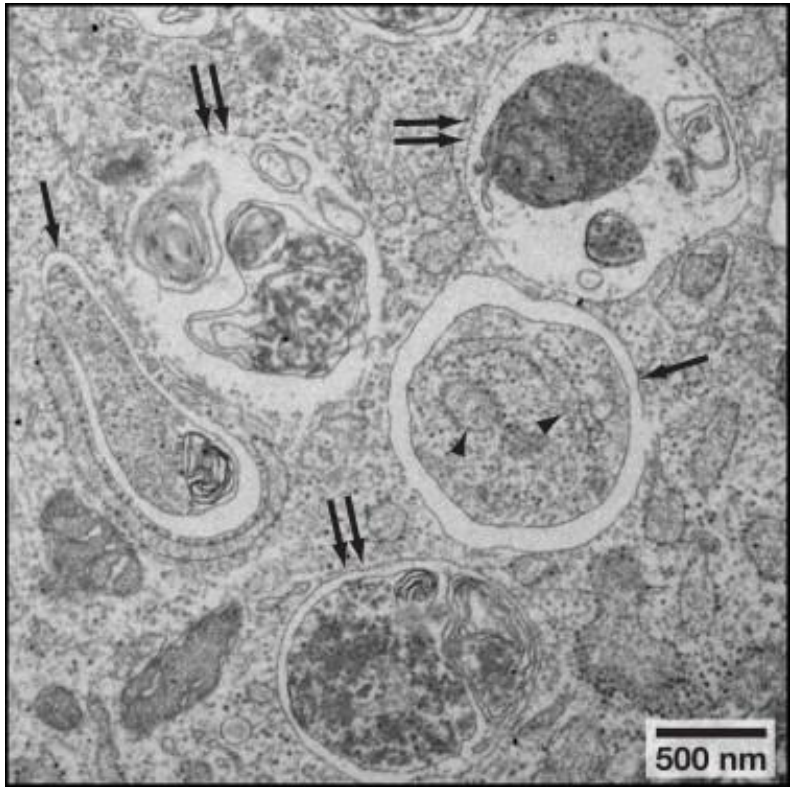
Autophagy and Radiation

What happens after radiation?

- **Moderate radiation:**
  - Activates autophagy as a **protective mechanism**.
  - The cell removes damaged organelles and proteins to survive.
- **Excessive or prolonged radiation:**
  - Autophagy can become **too active** → leading to **cell death**.

Examples

- Tumor cells resistant to apoptosis often rely on autophagy.
- Targeting autophagy can **increase radiosensitivity** in cancer therapy.



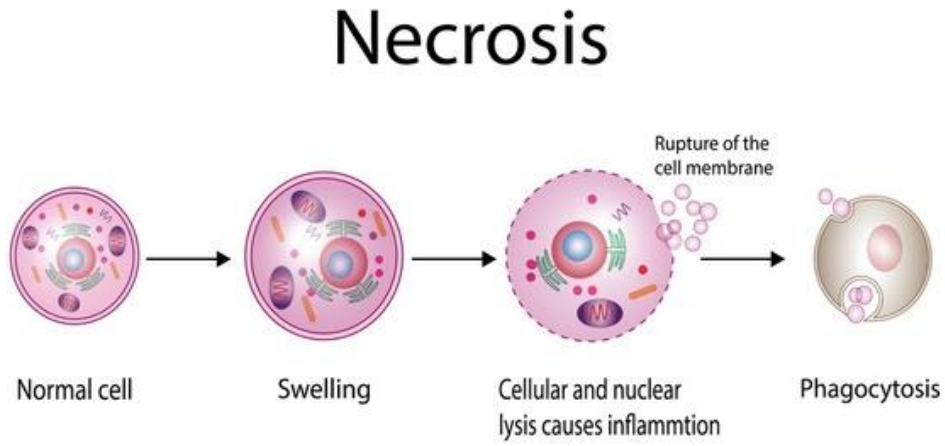
Necrosis: Overview

What is necrosis?

- **Uncontrolled cell death** caused by severe damage.
- Occurs **suddenly** when the cell cannot maintain energy or structural integrity.
- Unlike apoptosis, it is **messy** and triggers **inflammation** in surrounding tissue.

Morphological features

- **Cell swelling** → the cell enlarges.
- **Organelle breakdown** → mitochondria and other organelles fail.
- **Plasma membrane rupture** → contents leak out.
- **Inflammatory response** → attracts immune cells.



Necrosis and Radiation

When does necrosis occur?

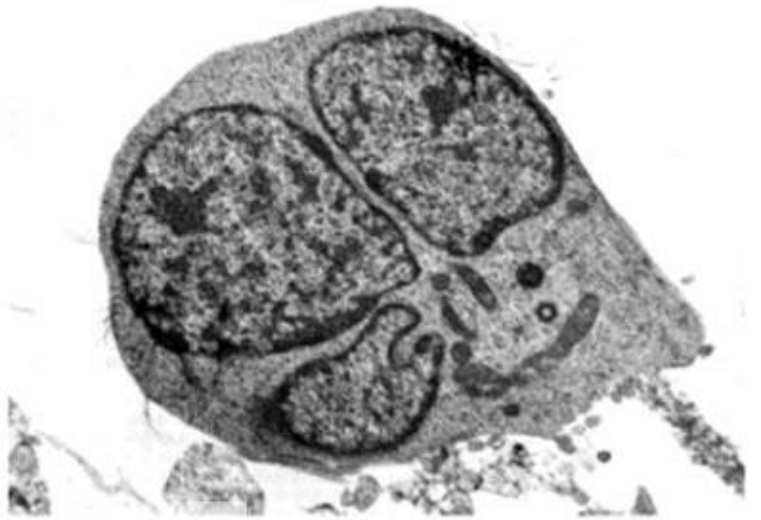
- Usually after **high doses of radiation**.
- Common in cells/tissues that **cannot repair damage quickly**, or have poor blood supply.

Examples

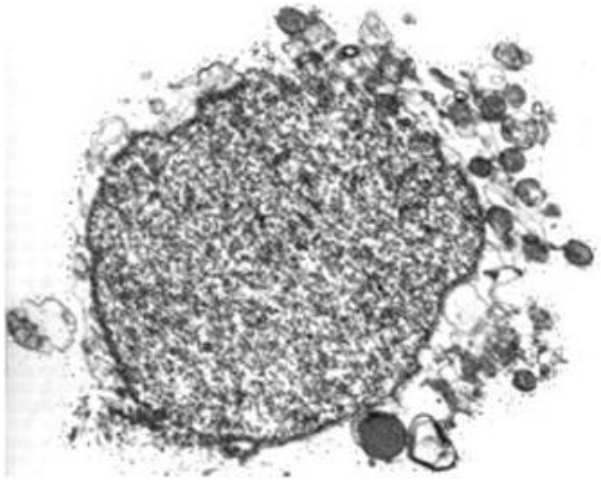
- Brain tissue, spinal cord, or other late-responding tissues can develop necrosis after radiotherapy.
- Contributes to **late radiation injury**, such as fibrosis and tissue loss.

Key points

- Necrosis is **uncontrolled and inflammatory**, unlike apoptosis.
- It is more common in **normal tissues** exposed to very high doses rather than in rapidly dividing tumor cells at therapeutic doses.



apoptosis



necrosis

Ueda, etal., 2007
PMID: 17353361

Senescence: Definition

What is senescence?

- Permanent cell cycle arrest — the cell stops dividing but **remains alive and metabolically active**.
- It is a **protective mechanism** to prevent damaged cells from proliferating.

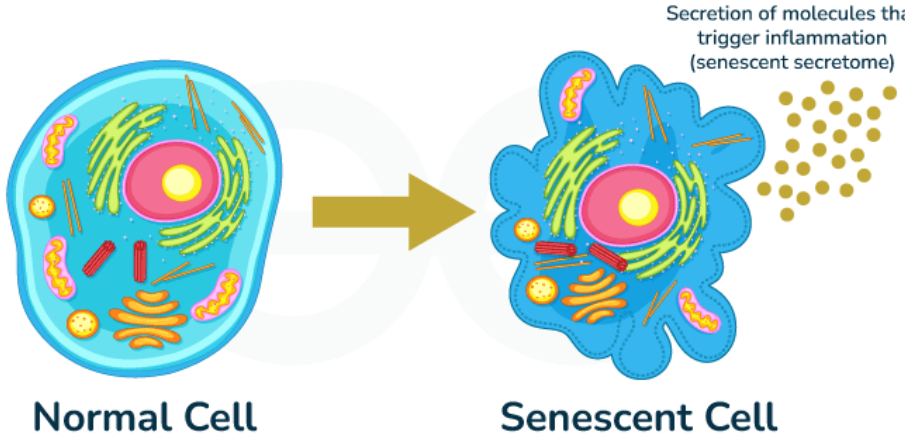
Why does it happen after radiation?

- Radiation causes **DNA damage** or telomere shortening.
- The cell activates **p53/p21** or **p16 pathways** to stop division permanently.
- Damaged cells remain in the tissue without dividing.

Key points

- Senescent cells are alive but **cannot replicate**.
- They can affect surrounding tissue through secreted factors called **SASP (Senescence-Associated Secretory Phenotype)**.

Senescence: Mechanism



How does senescence occur after radiation?

1. **DNA damage detection:**
    1. Radiation causes double-strand breaks or other severe damage.
    2. **p53** is activated.
2. **Cell cycle arrest:**
    1. p53 → p21 → blocks cyclin-dependent kinases → **G1/S arrest**.
    2. **p16INK4a** can also reinforce permanent arrest.
3. **Metabolic activity continues:**
    1. The cell stays alive but **cannot divide**.
4. **SASP activation:**
    1. Senescent cells secrete **cytokines, growth factors, and proteases**.
    2. Can influence nearby cells, sometimes promoting inflammation or tissue remodeling.

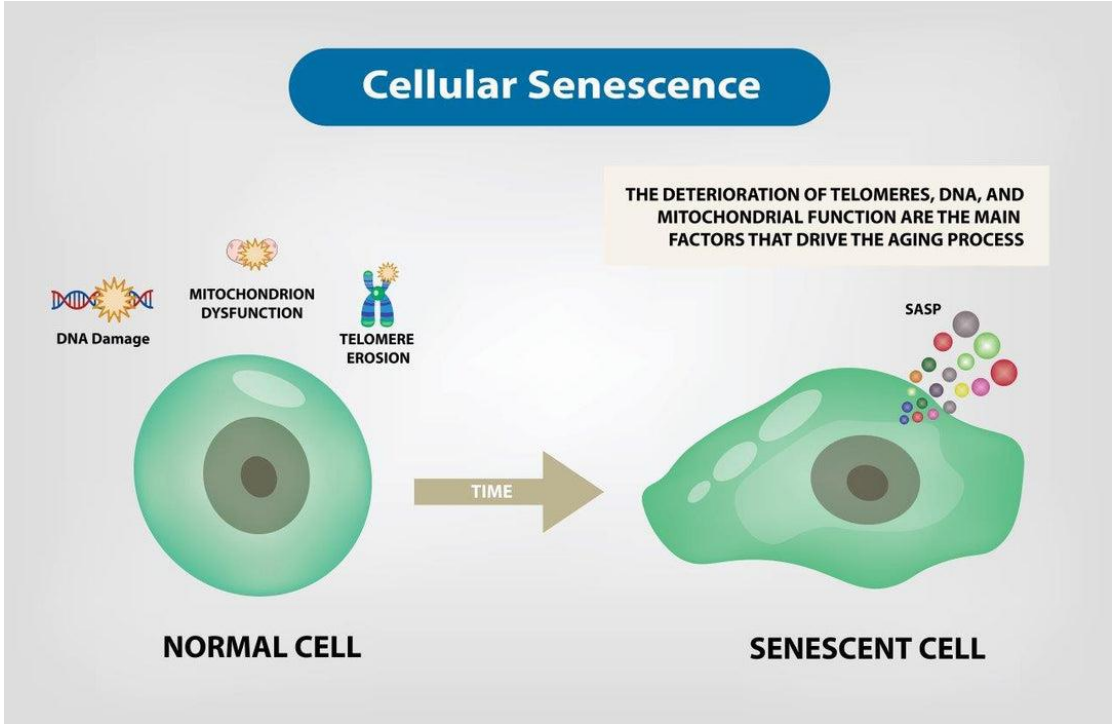
Senescence: Biological Significance

Protective roles

- Prevents **damaged or mutated cells** from dividing → reduces cancer risk.
- Acts as a **tumor-suppressor mechanism** in tissues exposed to radiation.

Potential drawbacks

- Senescent cells remain metabolically active.
- Secrete **SASP factors** → cytokines, growth factors, proteases.
- Can cause **chronic inflammation**, tissue remodeling, or promote aging in nearby cells.



Mitotic Catastrophe: Overview

What is mitotic catastrophe?

- A form of **cell death caused by abnormal mitosis**.
- Happens when cells enter **mitosis with damaged DNA** or defective checkpoints.
- Results in **giant or multinucleated cells** that eventually die.

When does it occur?

- Typically, in rapidly dividing cells exposed to radiation.
- Happens when DNA damage **cannot be repaired** before mitosis.

Key point

- Mitotic catastrophe is **not a separate type of death** — it usually leads to **apoptosis or necrosis** after defective mitosis.

Mitotic Catastrophe: Mechanism

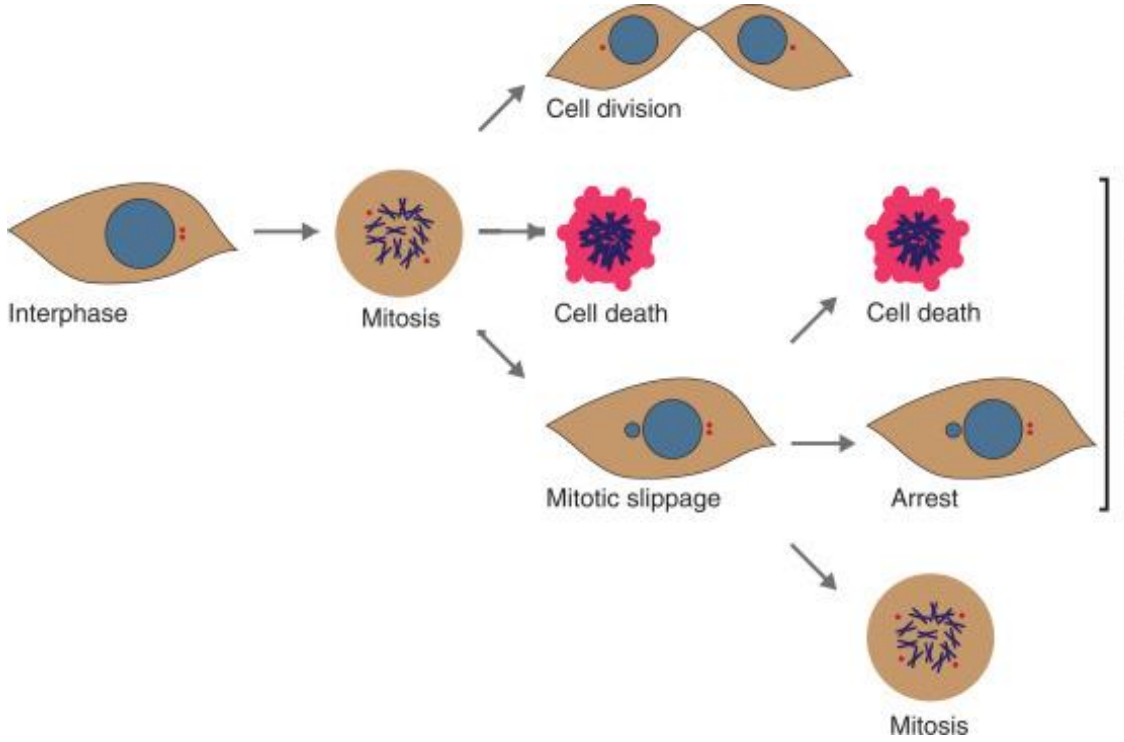
How does it happen?

1. **DNA damage from radiation** → chromosomes are broken or mis-repaired.

2. **Checkpoint failure** → cell enters mitosis despite the damage.

3. **Abnormal mitosis:**
    1. Chromosomes do not segregate properly.
    2. Spindle defects occur.

4. **Cellular outcome:**
    1. Formation of **giant cells** or **multinucleated cells**.
    2. Cell eventually dies via **apoptosis** or **necrosis**.



Factors Influencing Cell Death Type

1. Radiation dose and type

- **Low doses / low-LET radiation** → DNA damage may be repairable → apoptosis is more common.
- **High doses / high-LET radiation** → severe, clustered damage → necrosis or mitotic catastrophe.

2. Cell cycle phase

- **G2/M phase** → most radiosensitive.
- **S phase** → most resistant to radiation-induced death.

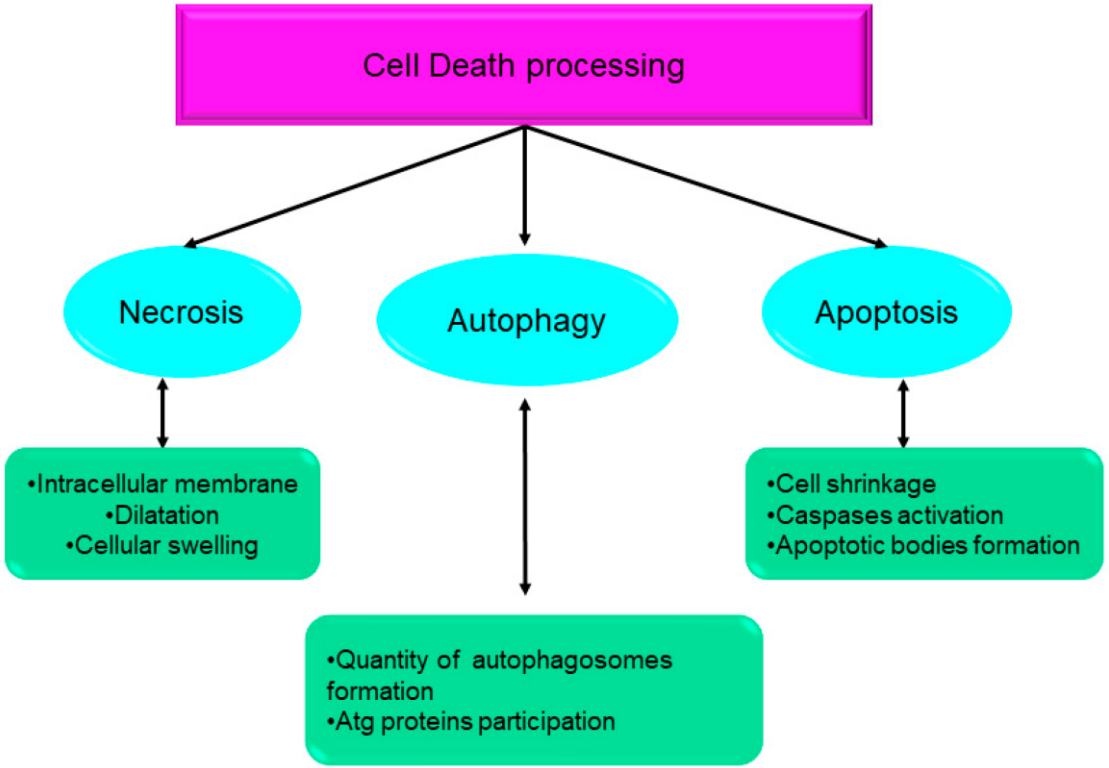
3. Cell type

- Rapidly dividing cells (e.g., lymphocytes, intestinal crypts) → high apoptosis.
- Slowly dividing or differentiated cells (e.g., neurons, fibroblasts) → senescence or necrosis.

Factors Influencing Cell Death Type

4. Microenvironment

- **Oxygen:** enhances DNA damage → increases apoptosis.
- **Hypoxia:** reduces effectiveness of radiation → survival or autophagy.
- **Nutrients and stress:** can shift response toward autophagy or survival pathways.



Biological and Clinical Relevance

Why does it matter?

- Determines **tumor response** to radiotherapy.
- Helps predict **radiosensitivity** of normal tissues.
- Guides development of **radiosensitizers** (make tumor cells more sensitive) and **radioprotectors** (protect normal tissue).

Clinical examples

- **Rapidly dividing tumor cells** → apoptosis and mitotic catastrophe → treatment success.
- **Normal tissue exposed to high doses** → necrosis or senescence → late side effects (fibrosis, inflammation).
- Targeting autophagy in resistant tumor cells can **improve therapy outcomes**.

Questions? Comments?

Thank you!