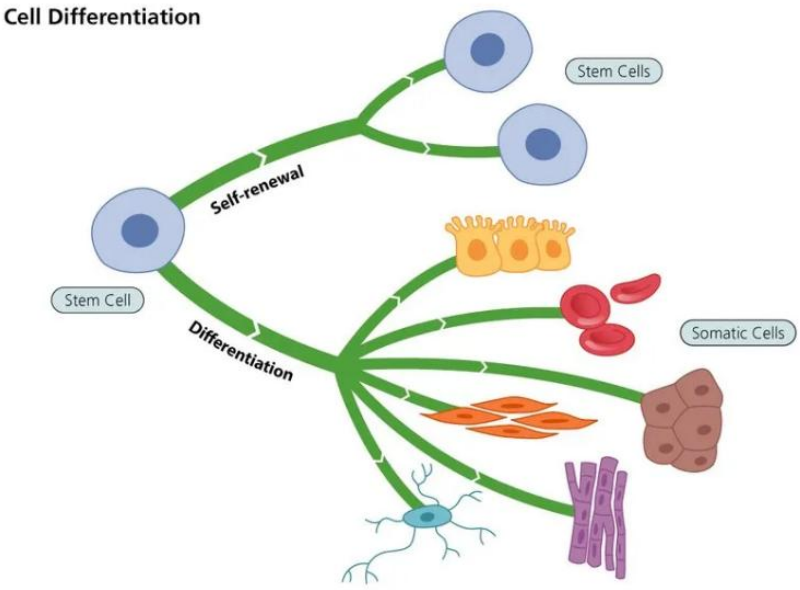
CELL RENEWAL

Cell renewal refers to the process of regenerating mature functional tissue in rapidly regenerating tissues, such as the epidermis of the human skin, through the self-renewal ability of stem cells and their progeny, regulated by both intrinsic properties and extrinsic factors from the local environment

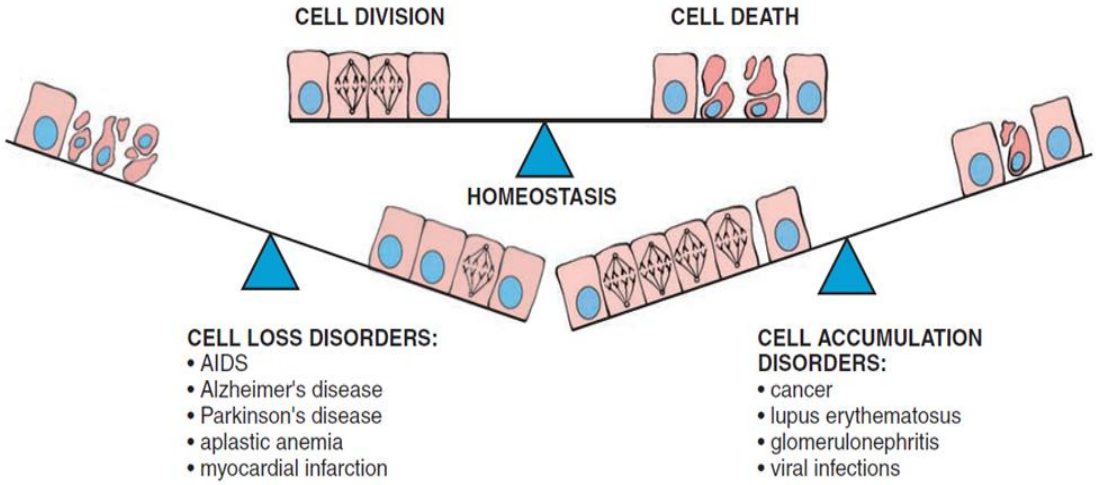


Somatic cells in the adult organism may be classified according to their mitotic activity as:

1. **Static cell populations (***terminally differentiated***)** consist of cells that no longer divide (meaning that renewed cycling cannot occur and the specialized cells exist from cell cycle), such as cells of the central nervous system and cardiac muscle cells. Under certain circumstances some of these cells (i.e., cardiac myocytes) may enter mitotic division.
2. **Stable cell populations** consist of cells that divide episodically and slowly to maintain tissue integrity. Such as most connective tissues, smooth muscle, and the cells lining blood vessels.
3. **Renewing cell populations** may be slowly or rapidly renewing but display regular mitotic activity. Division of such cells usually results in two daughter cells that differentiate both morphologically and functionally or two cells that remain as stem cells. Daughter cells may divide one or more times before their mature state is reached. The differentiated cell may ultimately be lost from the body.
   - **A. Slowly renewing populations** include smooth muscle cells of most hollow organs, fibroblasts of the uterine wall, and epithelial cells of the lens of the eye. Slowly renewing populations may actually slowly increase in size during life, as do the smooth muscle cells of the gastrointestinal tract and the epithelial cells of the lens.
   - **B. Rapidly renewing populations** include blood cells, epithelial cells and dermal fibroblasts of the skin, and the epithelial cells and subepithelial fibroblasts of the mucosal lining of the alimentary tract.

CELL DEATH

In humans, as in all other multicellular organisms, the rates of cell proliferation and cell death determine the net cell production.
An abnormality in any of these rates can cause **disorders of cell accumulation** (e.g., hyperplasia, cancer, autoimmune diseases) or **disorders of cell loss** (atrophy, degenerative diseases, AIDS, ischemic injury). Therefore, the balance (homeostasis) between cell production and cell death must be carefully maintained.



Schematic diagram shows the relationship between cell death and cell division.

Cell death may occur as a result of acute cell injury or an internally encoded suicide program.

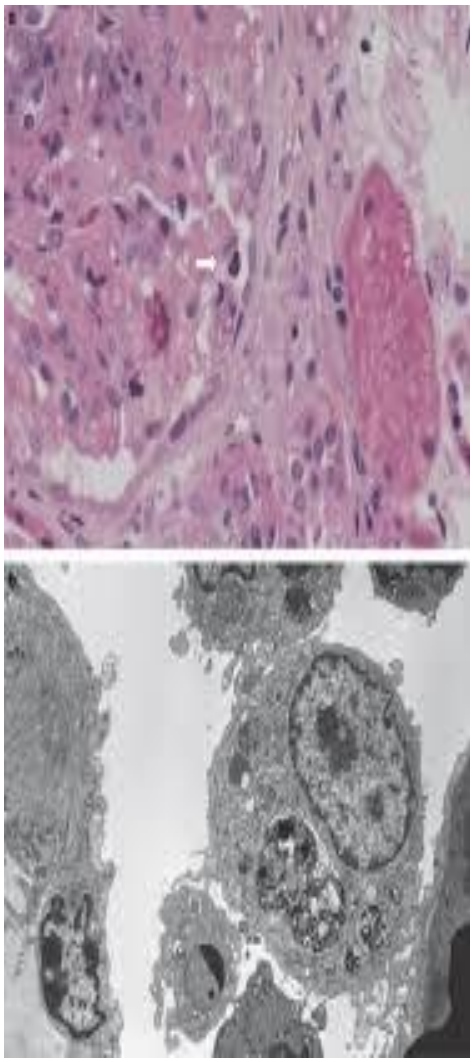
The major two different mechanisms of cell death are necrosis and apoptosis.

Necrosis or accidental cell death:

1. It is a pathologic process.
2. It occurs when cells are exposed to an unfavorable physical or chemical environment (e.g., hypothermia, hypoxia, radiation, low pH, cell trauma) that causes acute cellular injury and damage to the plasma membrane. Under physiologic conditions, damage to the plasma membrane may also be initiated by viruses.
3. Rapid cell swelling and lysis are two characteristic features of this process.
4. Damage to the cell membrane leads to an influx of water and extracellular ions.
5. Intracellular organelles such as the mitochondria, rER, and nucleus undergo irreversible changes that are caused by cell swelling and cell membrane rupture (cell lysis).
6. As a result of the ultimate breakdown of the plasma membrane, the cytoplasmic contents, including lysosomal enzymes, are released into the extracellular space.
7. Therefore, necrotic cell death is often associated with extensive surrounding tissue damage and an intense inflammatory response.

Apoptosis *[Gr. apo,* off + *ptosis,* a falling*]*

- It is a series of molecular steps in a cell lead to its death. This is one method the body uses to get rid of unneeded or abnormal cells.
- Apoptosis occurs under normal physiologic conditions.
- Apoptosis was first discovered as **programmed cell death** in embryos, where it plays an essential part in shaping various developing organs or body regions, such as the free spaces between embryonic fingers and toes. Apoptosis also plays an important role in the final development of the central nervous system. In the ovary, apoptosis is the mechanism for both the monthly loss of luteal cells and the removal of excess oocytes and their follicles.
- Apoptosis is characterized by controlled **autodigestion**, which maintains cell membrane integrity; thus, the cell dies with dignity without spilling its contents and damaging its neighbors.
- Cells undergoing apoptosis show the following characteristic **morphologic features:**



Light microscopy has identified the various morphological changes that occur during the early process of apoptosis:

1. Cell shrinkage
2. Cells are smaller in size
3. The cytoplasm is dense
4. The organelles are more tightly packed.
5. Pyknosis is the result of chromatin condensation and this is the most characteristic feature of apoptosis.

On histologic examination with hematoxylin and eosin stain, apoptosis involves single cells or small clusters of cells. The apoptotic cell appears as a round or oval mass with dark eosinophilic cytoplasm and dense purple nuclear chromatin fragments.

Electron microscopy can better define the subcellular changes. Early during the chromatin condensation phase, the electron-dense nuclear material characteristically aggregates peripherally under the nuclear membrane although there can also be uniformly dense nuclei.

Extensive plasma membrane blebbing occurs followed by separation of cell fragments into **apoptotic bodies** during a process called **"budding."**

- ✓ Apoptotic bodies consist of cytoplasm with tightly packed organelles with or without a nuclear fragment.

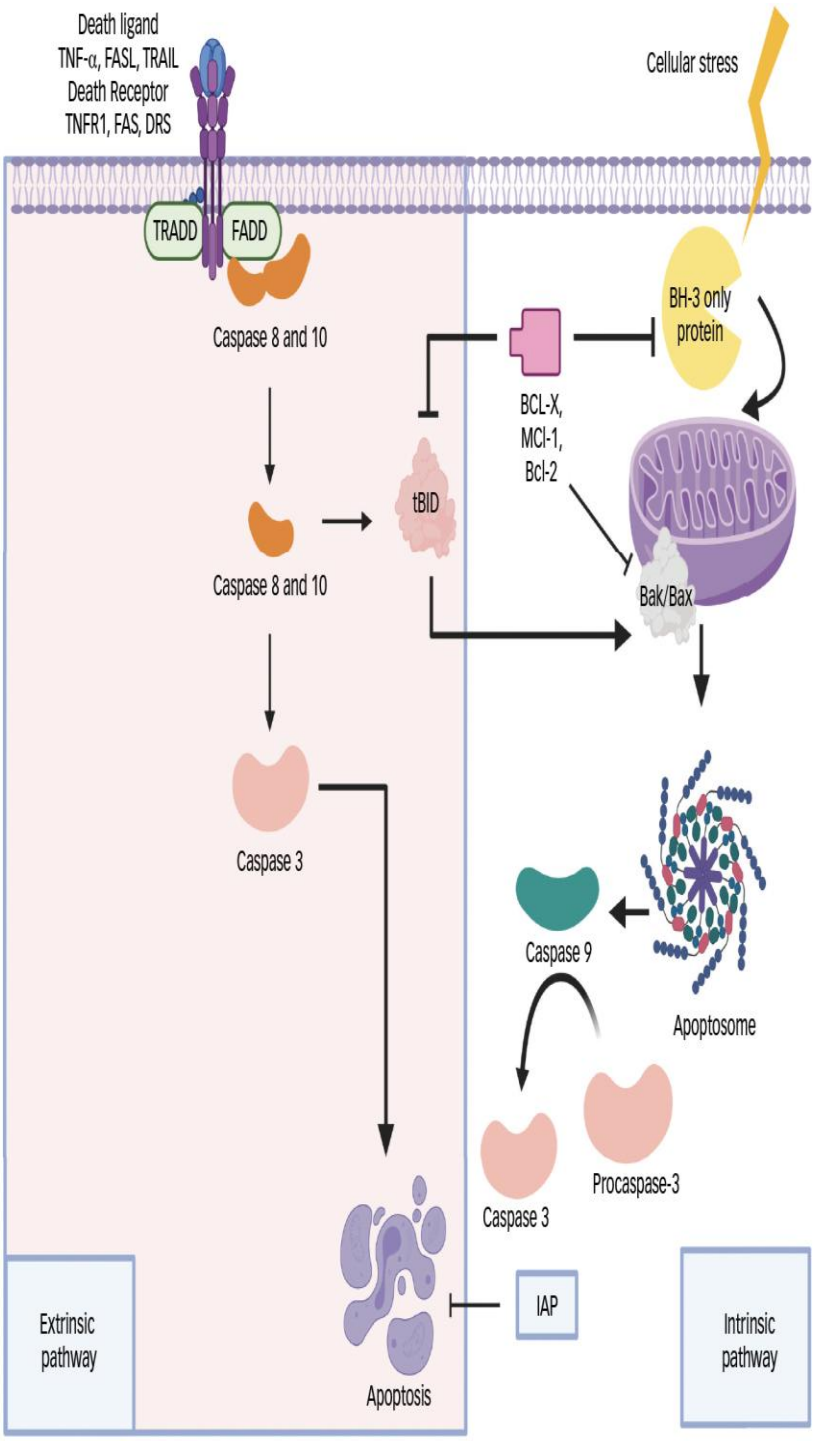
The organelle integrity is still maintained and all of this is enclosed within an intact plasma membrane. These bodies are subsequently phagocytosed by macrophages and degraded within phagolysosomes. There is essentially no inflammatory reaction associated with the process of apoptosis nor with the removal of apoptotic cells because:
(1) apoptotic cells do not release their cellular constituents into the surrounding interstitial tissue
(2) They are quickly phagocytosed by surrounding cells thus likely preventing secondary necrosis
(3) The engulfing cells do not produce anti-inflammatory cytokines.

Apoptotic processes can be activated by a variety of internal and external stimuli called the intrinsic pathway of apoptosis and the extrinsic pathway of apoptosis.

In both the intrinsic and extrinsic pathway of apoptosis events controlled by the **Bcl-2 family of proteins** regulating the release of death-promoting factors from mitochondria. Signaling results in the activation of a family of Cys (Cysteine) proteases, named **caspases** that acts in a proteolytic cascade which degrade proteins of the cytosol, cytoskeleton, and cell membrane. Also **endonucleases** are activated, which degrade all nuclear DNA.

1. **The extrinsic or death receptor pathway of apoptosis** begins outside a cell, when conditions in the extracellular environment determine that a cell must die. Death Receptors (DRs) are cell surface receptors that transmit apoptotic signals initiated by specific ligands and play a central role in instructive apoptosis. These receptors activate Death Caspases (DCs) within seconds of ligand binding, causing an apoptotic demise of the cell within hours.
2. **The intrinsic or mitochondrial pathway of apoptosis** pathway begins when mitochondrial outer membrane permeabilisation or MOMP. Following MOMP, mitochondrial intermembrane space proteins, notably cytochrome *c*, are released into the cytosol whereupon they activate caspases. However, once released from mitochondria, cytochrome *c* adopts a lethal function that is essential for caspase activation. This leads to extensive cytoplasmic conformational changes form a heptameric structure called the apoptosome. The apoptosome activates pro-caspase-9 that in turn cleaves and activates caspases-3

The extrinsic and intrinsic pathways converge on the same terminal pathway. This pathway is initiated by the cleavage of caspase-3 and results in DNA fragmentation, degradation of cytoskeletal and nuclear proteins, cross-linking of proteins, formation of apoptotic bodies, expression of ligands for phagocytic cell receptors and finally uptake by phagocytic cells.


Death ligand
TNF-α, FASL, TRAIL
Death Receptor
TNFR1, FAS, DRS
Cellular stress
TRADD
FADD
Caspase 8 and 10
BH-3 only protein
BCL-X, MCl-1, Bcl-2
tBID
Caspase 8 and 10
Bak/Bax
Caspase 3
Caspase 9
Apoptosome
Procaspase-3
Caspase 3
Extrinsic pathway
IAP
Intrinsic pathway
Apoptosis

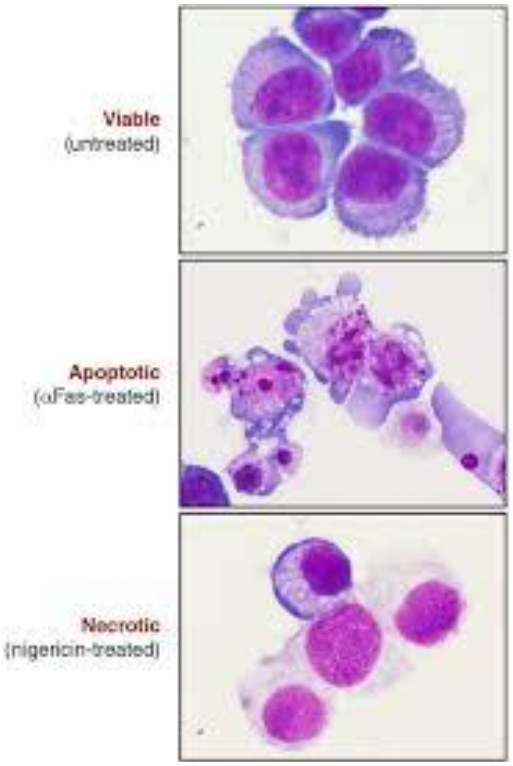


TABLE Overview of Characteristic Features Distinguishing Necrosis from Apoptosis

Features of Dying Cells	Necrosis	Apoptosis
Cell swelling	+++	–
Cell shrinkage	–	+++
Damage to the plasma membrane	+++	–
Plasma membrane blebbing	–	+++
Aggregation of chromatin	–	+++
Fragmentation of the nucleus	–	+++

Necrosis and apoptosis compared