CELL RENEWAL, CELL DEATH & CELL SENESCENCE

Cell Renewal

Cell populations may be classified as:

- **Static cell populations**: consist of cells that no longer divide (**postmitotic cells, G_o cells**), such as cells of the central nervous system and skeletal or cardiac muscle cells. *Under certain circumstances, some of these cells (e.g., skeletal myocytes) may enter mitotic division*.
- **Stable cell populations**: consist of cells that divide periodically and slowly to maintain normal tissue or organ structure. These cells may be stimulated by injury to become more mitotically active. Examples of such cells include Periosteal and perichondrial cells, smooth muscle cells, endothelial cells of blood vessels, and fibroblasts of the connective tissue.
- **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.
  - **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.
  - **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.

*Cells identified as **reserve stem cells** may be thought of as **G_o** cells that may be induced to re-enter the cell cycle in response to injury of cells within the tissues of the body. Activation of these cells may occur in normal wound healing and during regeneration of an organ, such as the liver, after removal of a major portion. If damage is too severe, even the reserve stem cells die, and there is no potential for regeneration.*

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.*

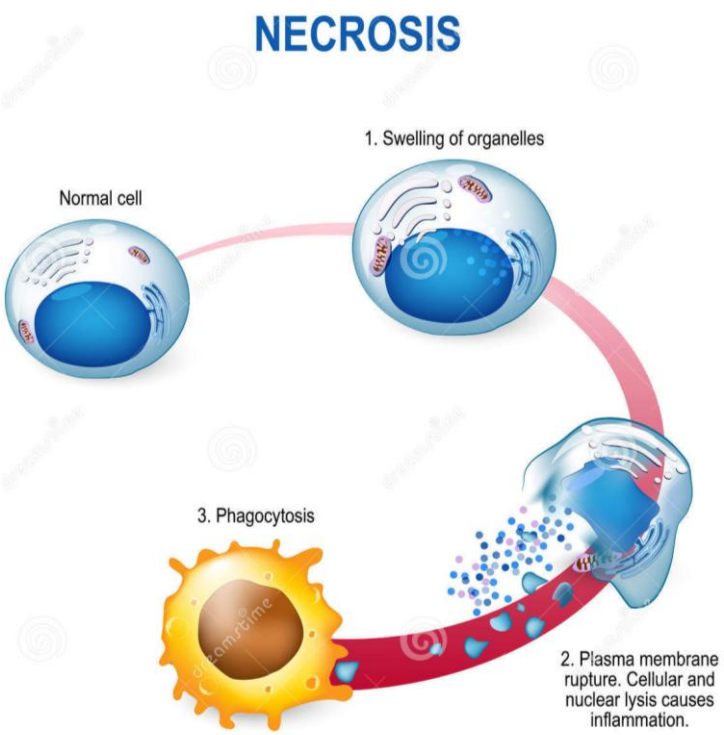
Cell death may result from accidental cell injury or mechanisms that cause cells to self-destruct (an internally encoded suicide program).

The major two different mechanisms of cell death are:

1. **Necrosis** (or accidental cell death), represents a pathologic process. It occurs when cells are exposed to an unfavourable physical or chemical environment (e.g., hypothermia, hypoxia, radiation, low pH, cell trauma) that causes acute cellular injury and damage to the plasma membrane. Damage to the plasma membrane may also be initiated by viruses, or proteins called *perforins*. Rapid **cell swelling,** and **lysis** are two characteristic features of this process.
2. **Apoptosis** *(Gr., falling off*) was referred to in the past as **programmed cell death**. Today, the term *programmed cell death* is applied more broadly to any kind of cell death mediated by an intracellular death program, irrespective of the trigger mechanism. Apoptosis represents a physiologic process. During apoptosis, cells that are no longer needed are eliminated from the organism. This process may occur during normal embryologic development or other normal physiologic processes. Cells can initiate their own death through activation of an internally encoded suicide program. Apoptosis is characterized by controlled **autodigestion**, which maintains cell membrane integrity; thus, the cell "dies with dignity" without spilling its contents and damaging its neighbours.

Mechanism of Necrosis

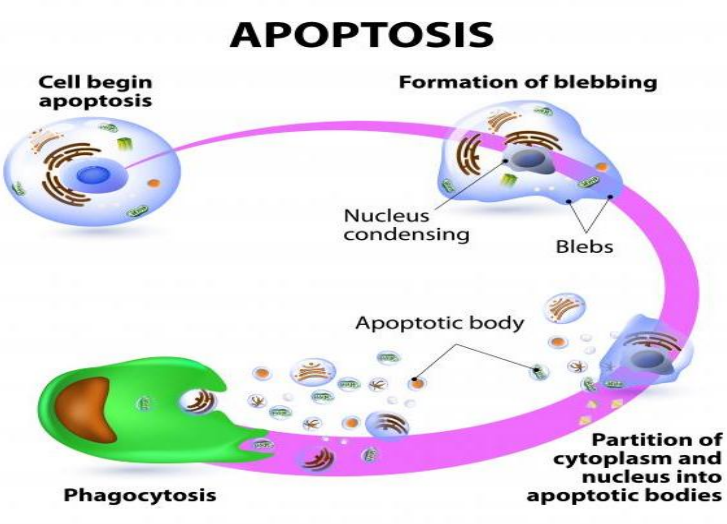
⊕ **Necrosis** begins with impairment of the cell's ability to maintain homeostasis**.**



- As a result of cell injury, damage to the cell membrane leads to an influx of water and extracellular ions.
- Intracellular organelles (such as the mitochondria, and rER) and nucleus undergo irreversible changes that are caused by cell swelling and cell membrane rupture (**cell lysis**).
- As a result of the ultimate breakdown of the plasma membrane, the cytoplasmic contents, including lysosomal enzymes, are released into the extracellular space.
- Therefore, necrotic cell death is often associated with extensive surrounding tissue damage and an **intense inflammatory response**.

Mechanism of Apoptosis

- In apoptosis, the cell is an active participant in its own death ("cellular suicide").
- This process is activated by a variety of extrinsic and intrinsic signals.
- Cells undergoing apoptosis show the following characteristic morphologic and biochemical features:
  - **DNA fragmentation** occurs in the nucleus and is an irreversible event that commits the cell to die. Nuclear chromatin then aggregates, and the nucleus may divide into several discrete fragments bounded by the nuclear envelope.
  - **Decrease in cell volume** is achieved by shrinking of the



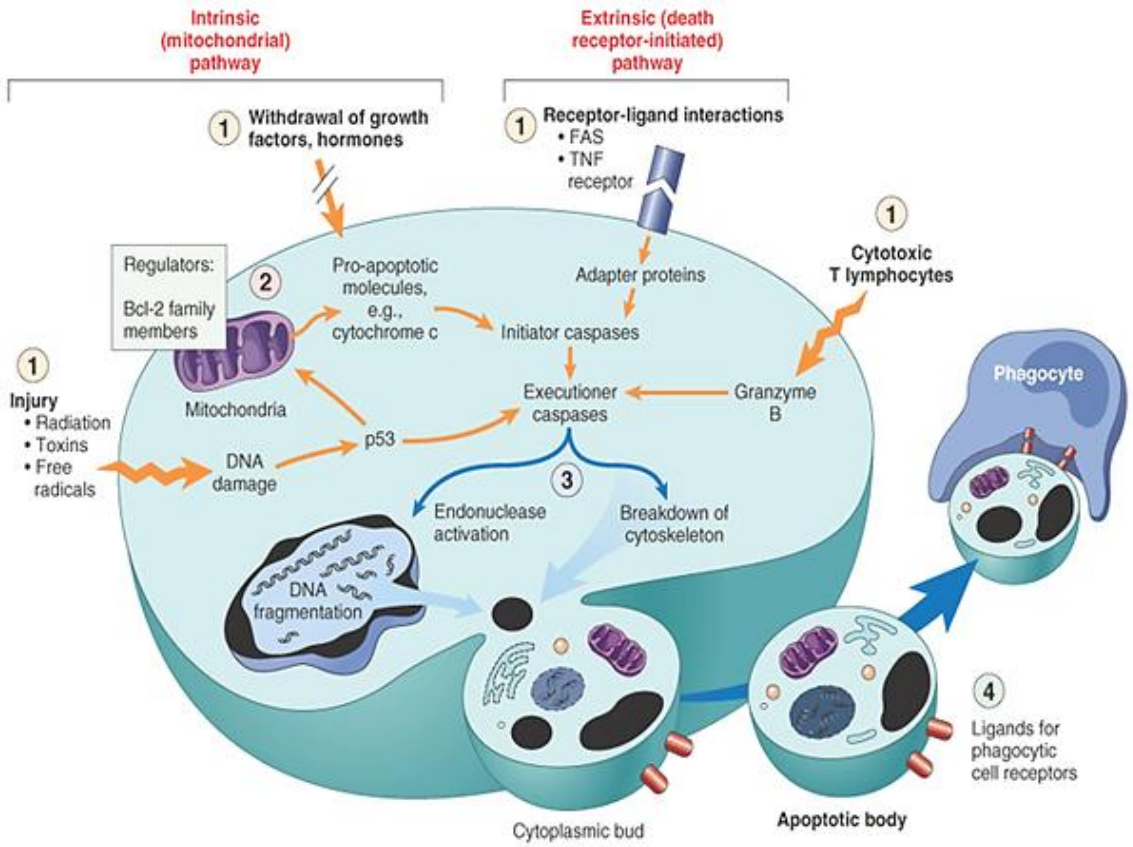
cytoplasm. The cytoskeletal elements become reorganized in bundles parallel to the cell surface.

- **Loss of mitochondrial function** is caused by changes in the permeability of the mitochondrial membrane channels. The integrity of the mitochondrion is breached, and mitochondrial proteins are released into the cytoplasm to activate a cascade of proteolytic enzymes called **caspases** that are responsible for pulling the cell to pieces.
- **Membrane blebbing** results from cell membrane alterations.
- **Formation of apoptotic bodies** which is, the final step of apoptosis, results in cell breakage. These membrane-bounded vesicles originate from the cytoplasmic bleb containing organelles and nuclear material. They are rapidly removed without a trace by phagocytotic cells. The removal of apoptotic bodies is so efficient that no inflammatory response is elicited.

- Apoptosis occurs more than 20 times faster than mitosis; therefore, it is challenging to find apoptotic cells in a routine H&E preparation.

Regulation of Apoptosis

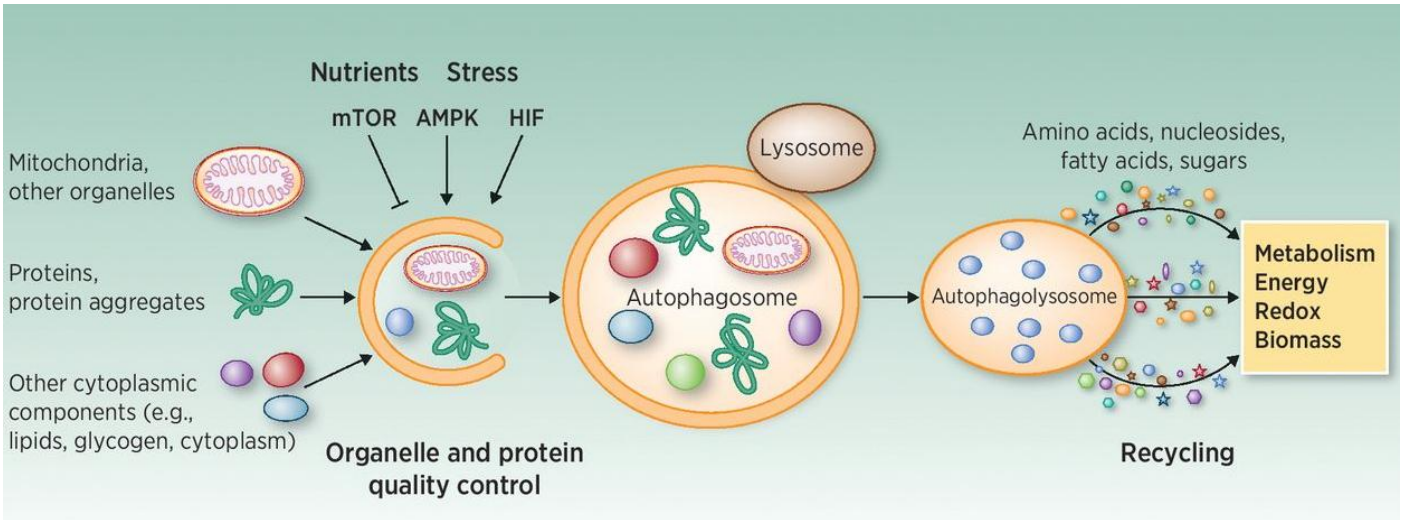
- **Apoptotic processes** can be activated by a variety of external and internal stimuli.
- External activators of apoptosis include free radicals, oxidants, and UV and ionizing radiation.
- Internal activators of apoptosis include **oncogenes** (tumor forming gene), **tumor suppressors (**such as p53), and **nutrient-deprivation antimetabolites** (*An antimetabolite is a chemical that inhibits the use of a metabolite, which is another chemical that is part of normal metabolism*). Apoptotic pathways are also activated by the events leading to mitotic catastrophe.
- Apoptosis can also be inhibited by signals from other cells and the surrounding environment via so-called ***survival factors***. These include growth factors, hormones such as estrogen and androgens, and interactions with extracellular matrix proteins.



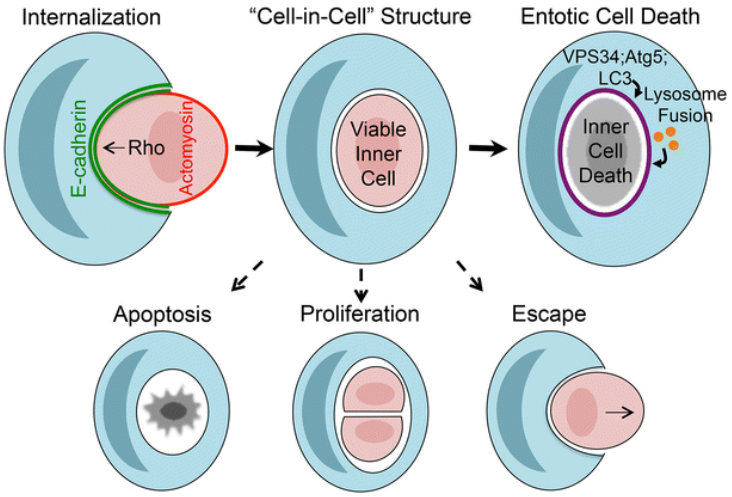
Other Forms of Programmed Cell Death

There are several different forms of programmed cell death that do not fit into the classical apoptosis or necrosis scheme. They include the following:

- **Autophagy:** is a regulated cellular process that enables cells to turn over their contents by lysosomal degradation of their own components. It starts when an intracellular membrane wraps around an organelle or portion of cytoplasm, forming a closed double membrane–bound vacuole. This vacuole, called an **autophagosome**, initially devoid of any lysosomal enzymes, fuses with lysosomes and initiates digestion of its contents.

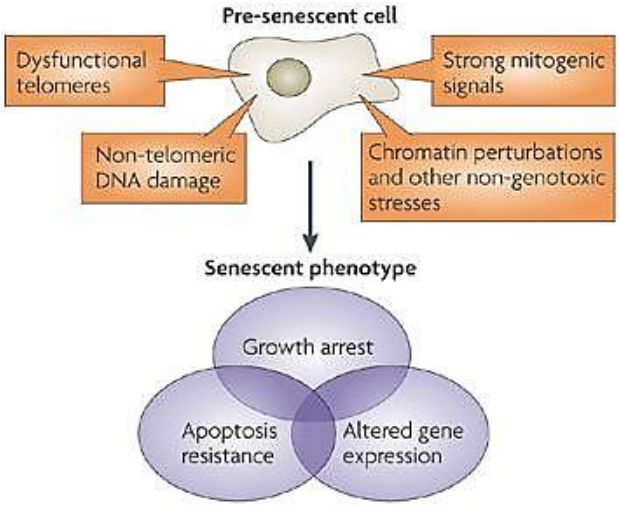


- **Mitotic catastrophe**: is a type of cell death that occurs during mitosis. It results from a combination of cellular damage and malfunction of several cell-cycle checkpoints. Failure to arrest the cell cycle before mitosis occurs causes problems with chromosome separation, which triggers the apoptotic pathway and cell death.
- **Paraptosis** is an alternative, nonapoptotic cell death that may be induced by growth factor receptors.
- **Pyroptosis** is a form of cell death induced by infection with certain microorganisms that generate intense inflammatory reactions.
- **Entosis** (*Gr., inside*) is a nonapoptotic cell death process in which one cell can actively internalize a similar cell that became detached from the extracellular matrix. After internalization, the "swallowed" cell remains alive within the host cell until it is either degraded by the **lysosomal mechanism** or released.



AGEING & CELLULAR SENESCENCE

- **Ageing** is a universal feature of biological organisms, defined by a gradual decline over time in cell and tissue function that often, but not always, decreases the longevity of an individual.
- **Cellular senescence** is defined by an irreversible arrest in cell proliferation when cells experience DNA damage at telomeres and a decrease in mitogenic signaling.
- In contrast to reversibly arrested quiescent cells in **G_o** of the cell cycle, senescent growth arrest is irreversible; cells in this state cannot be stimulated to proliferate by known stimuli and cannot be prompted to re-enter the cell cycle by physiological mechanisms.



- Senescent cells can cause or foster **degenerative diseases**. In old age, cellular senescence in humans determines typical pathologies, including atherosclerosis leading to stroke, osteoporosis, macular degeneration, cardiopulmonary and renal failure, and neurodegenerative diseases such as Alzheimer's and Parkinson's disease.
- Senescent cells undergo changes in gene expression, which result in the secretion of proinflammatory cytokines, growth factors and proteases, activities that collectively define a senescence-associated secretory phenotype capable of triggering angiogenesis, inflammatory responses, and which may also determine resistance to cancer chemotherapy.
- Cellular senescence can be caused by a disruption of metabolic signaling pathways, derived from mitogens and proliferation factors, and the activation of tumor suppressors, combined with telomere shortening and genomic damage.

Telomeres

- Most types of differentiated cells can divide only a limited number of times (about 50 to 60 times).
- One factor that may control the number of cell divisions is the length of the **telomeres** at the ends of chromosomes.
- Telomeres protect the ends of chromosomes from deteriorating or fusing with other chromosomes.
- Each time a cell divides, the telomeres normally shorten, and cells with shorter telomeres tend to undergo fewer divisions.
- Some cells, such as stem cells, possess an enzyme called **telomerase**, which refills the length of the telomeres, effectively making stem cells immortal.
- Cancer cells, which behave in a similar manner to stem cells, frequently possess an active telomerase enzyme, which allows them to replicate continuously.

- Studies using stem cells and cancer cells have begun to close in on the genetic factors that cause cellular aging. For example, in 2012 researchers used ***gene therapy*** to introduce an active telomerase enzyme into mice, thus slowing the aging process.