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The Dance of Life and Death: A Review of Programmed and Non-Programmed Cell Death

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ABSTRACT:

Background: *Multicellular organisms are composed of individual cells acting in tightly regulated cooperation. The health and homeostasis of multicellular organisms depend on the tight balance between cell proliferation and cell death. Cell death was divided into three main types according to morphological changes that occur: Type I cell death (apoptosis), Type II cell death (autophagy), and Type III cell death (necrosis). Recently, cell death types can be categorized into programmed and non-programmed cell death based on their signal dependency.*

Objective of the study: *This review will focus primarily on programmed regulated cell death. It will also discuss non-programmed cell death and different signaling pathways.*

KEYWORDS:

Cell death, apoptosis, necrosis, autophagy.

1. Introduction

Cell proliferation is an important intracellular process in which nearly all of the billions of cells in our body undergo in a strictly regulated manner. It allows cell populations to increase through cell growth and division. (1)

Proper regulation of the cell cycle is crucial for ensuring effective DNA repair and preventing the transmission of damaged genetic material. When cellular damage becomes irreparable, programmed cell death eliminates defective cells. Thus, multicellular organisms depend on a precise balance between cell proliferation and Death to preserve tissue integrity and overall homeostasis. (2)

While cell death is a normal physiological process, with millions of cells dying and being replaced every second, dysregulation of cell death can contribute to diseases like cancer (where cell death is suppressed) and neurodegenerative disorders (where cell death is excessive). Therefore, cell death plays a critical role in both normal function and disease pathology. (3)

2. Historical background and Classifications

Cell death historically was divided into three main types according to morphological changes that occur: Type I cell death (apoptosis), Type II cell death (autophagy), and Type III cell death (necrosis). All three can be executed through distinct, and sometimes overlapping, signaling pathways engaged in response to specific stimuli. (4) (Figure 1)

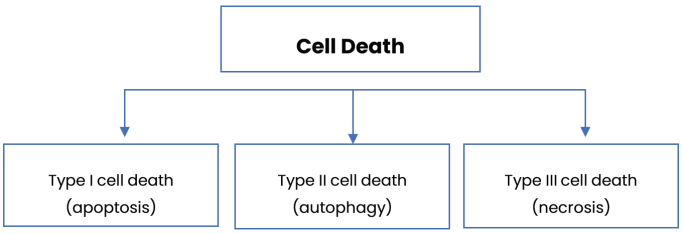

Figure 1:Classification of cell death based on its morphological dependency. (4)

The study of regulated cell death (RCD) began in 1842 when Karl Vogt observed dying cells in toads. However, research into RCD didn't really take off until the term "apoptosis" was introduced in 1972 by John Kerr, Andrew Wyllie, and Alastair Currie. (5)

Cell death can be classified into two main categories: programmed cell death (PCD) and

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non-programmed cell death. PCD is controlled by specific signals within the cell, while non-programmed cell death is caused by unexpected damage. (6) (Figure 2)

Accidental cell death is uncontrolled and occurs due to severe damage, such as from chemicals or physical injury. Regulated cell death, on the other hand, is a controlled process that can occur physiologically or in response to different types of stress. (7)

Given the morphological characteristics and molecular mechanisms, PCD can be further categorized into apoptotic cell death and nonapoptotic cell death. Apoptosis retains cell membrane integrity and occurs in a caspase-dependent manner. By contrast, nonapoptotic cell death is mostly characterized by caspase independence. (7) The recent classification is based on both morphological and signal dependency of cell death. On the other hand, the necrotic cell death can be further divided into a regulated and a non-regulated form of cell death. (8, 9) (Figure 3)

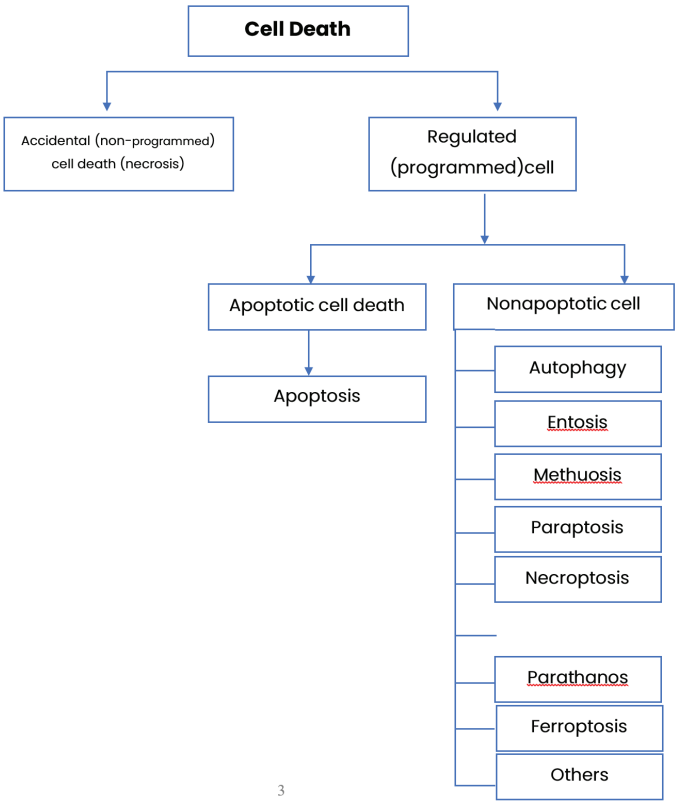

Figure 2:Classification of cell death based on its signal dependency. (10)

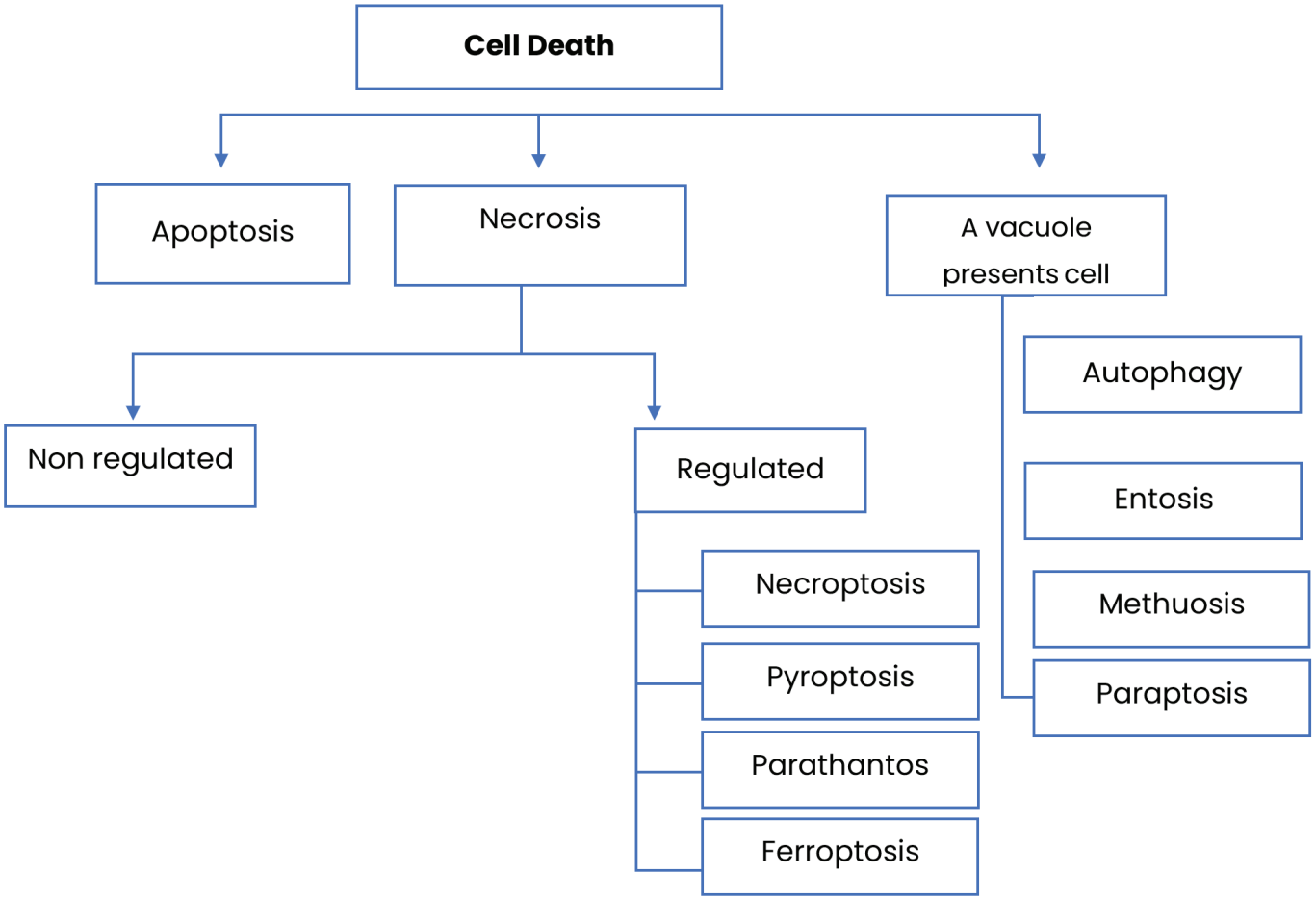

Figure 3: Classification of cell death based on its morphological and signal dependency. (9)

3. Apoptosis

Apoptosis, derived from Greek words meaning "falling off" like petals from a flower or leaves from a tree, refers to a genetically programmed form of cell death. This controlled process involves a specific sequence of cellular events and has a distinct microscopic appearance, differentiating it from other cell death mechanisms. (11)

Apoptosis is a normal biological process. All cells can undergo apoptosis, which is a way to remove unnecessary, damaged, or unwanted cells without harming nearby cells. The human body has around 100 trillion cells. Every day, billions of new cells are created through mitosis, and a similar number die through apoptosis to keep tissues healthy. (12)

Also, toxic insults, in particular by agents that damage DNA, can induce apoptosis. The low doses of stimuli can induce apoptosis, but these same stimuli can result in necrosis at higher doses. (13, 14). During apoptosis, cells maintain their outer membrane integrity and metabolic activity (to some degree) as the process proceeds to completion, which—in vivo— allows for the rapid clearance. (15)

To maintain genomic integrity, cells rigorously monitor their DNA and the machinery involved in mitosis. When damage or errors are detected at key checkpoints—such as the DNA damage checkpoint or the mitotic spindle checkpoint—the cell cycle is halted, and apoptosis is activated to prevent the propagation of defective cells. Failure of these checkpoints or the apoptotic machinery allows abnormal cells to continue dividing, contributing to tumor development. Beyond cancer, dysregulation of apoptosis has broader pathological implications: insufficient apoptosis is associated with cancer, viral infections, and autoimmune disorders, whereas excessive or premature apoptosis underlies many neurodegenerative diseases, including Alzheimer's and Parkinson's disease, as well as certain cardiovascular conditions and infections such as AIDS.(16)

Importance of apoptosis

During embryonic development, the signaling molecule Sonic hedgehog (Shh) is released from the notochord in a gradient to guide the patterning of cells in the neural tube. Cells in the neural tube express Patched 1 (Ptc1), the receptor for Shh. When Shh binds to Ptc1, it promotes the survival of the target cells. However, in the absence of Shh, cells that express Ptc1 undergo apoptosis. (17, 18)

In mammalian embryos, apoptosis occurs during cavitation and plays an essential role in shaping the developing embryo. (19) It is now widely recognized that appropriate apoptosis is crucial for normal development, as defects in the molecules that regulate apoptosis can lead to embryonic Death or severe malformations. (20) In contrast, other forms of cell death are not necessary during the developmental process. (21)

During human development, structures like the branchial arches, embryonic tails, and webbed fingers disappear before birth due to programmed cell death. (22) In a developing fetus, the hand initially appears webbed. Extra cells die through apoptosis to form fingers. Similarly, in a developing nervous system, more than half of the nerve cells die soon after they are created. (23)

1. Tissue homeostasis: The number of cells is kept relatively constant as a result of a balance between cell division and cell death. When cells are damaged or nonfunctioning, they must be replaced. Generation of new cells must be offset by cell death to maintain a stable baseline population. (23)

2. Aging can also be considered to be a physiological cell death process. For most animals, lifespan is genetically predetermined. (12)

3. It plays an important role in the immune system by removing self-reactive T cells through negative selection. Lymphocytes can induce apoptosis in target cells. (24)

4. Apoptosis happens as a cellular response to growth factors and hormones. Withdrawal of hormones results in atrophy of the hormone-dependent tissue, and apoptosis has been found to be responsible for this phenomenon in the prostate, adrenal cortex, endometrium, and mammary glands. (25, 26)

5. It may also be used to minimize the risk in cells frequently exposed to mutagenic chemicals or radiation. Diverse chemotherapeutic agents kill sensitive cells by apoptosis. (27)

6. Apoptosis prevents malignant transformation, whereas abnormal apoptosis can predispose to cancer. (28)

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2.2 Morphological and molecular events in apoptosis

Apoptosis progresses through several stages: The earliest stage recognizable by electron microscopy, apoptotic cell death is characterized by a distinct nuclear behavior involving progressive chromatin margination and compaction. Chromatin margination is first limited to thin electron-dense areas underlying the nuclear envelope. These electron-dense areas are then organized in cap-shaped compact structures. (29) These compacting areas of chromatin are rearranged due to DNA fragmentation. (30)(Figure 4)

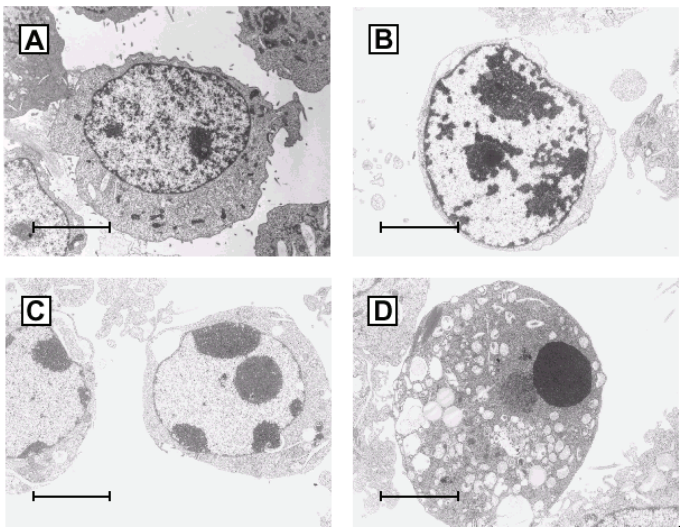

Figure 4: Electron microscopy of uninfected (A) and reovirus strain-infected (B, C, and D) A. Uninfected cells B. Initial condensation of chromatin. Margination of chromatin at the nuclear membrane. Complete condensation of the nucleus. (31)

During chromatin margination, plasma membrane blebs appear on the cell surface, and specialized surface elements such as microvilli have disappeared. (32) The membrane blebbing causes the nucleus to break (karyorrhexis). This process represents another morphological hallmark of in vitro and in vivo apoptosis, and it is controlled by actomyosin contraction. (33)

During apoptosis, nuclear fragmentation becomes evident through nuclear splitting and the frequent appearance of micronuclei, while cytoplasmic condensation leads to the breakdown of cell–cell interactions. Classically, it is understood that microtubules and intermediate filaments become disorganized at the onset of the execution phase, whereas the actin cytoskeleton drives the characteristic remodeling of the cell. In later stages, microtubules reorganize to form the apoptotic microtubule network, a specialized structure that supports apoptotic cell morphology, preserves plasma membrane integrity, and contributes to the orderly dispersion of cellular and nuclear fragments. (34, 35)

Finally, the splitting of the cellular content into distinct membrane-enclosed vesicles, termed apoptotic bodies, containing portions of the fragmented nucleus and an array of intact organelles. (32) The apoptotic cell removal by phagocytes is very rapid; therefore, the presence of apoptotic bodies (ApoBDs) is very limited in vivo. (36)

One of the critical properties of the fragmentation process is that the cytoplasm and organelles are essentially repackaged without the leakage of any potentially harmful cellular components into the extracellular space or bloodstream. (37)

Finally, the release of cell surface markers (phosphatidylserine) from the cell membrane facilitates phagocytosis by cells such as macrophages and parenchymal cells for further degradation, thereby preventing secondary necrosis. (32)

2.3 Apoptotic Bodies

Dying cells produce vesicular apoptotic bodies that are variable in size, structure, and composition. Apoptotic bodies appear after the disassembly of an apoptotic cell into subcellular fragments. The formation of ApoBDs is an important process downstream of apoptotic cell death, considered a hallmark of apoptosis. (38)

In fact, they may contain a wide variety of cellular components: micronuclei, chromatin remnants, cytosol portions, degraded proteins, DNA fragments, or even intact organelles. Reports describe that an apoptotic body contains a large amount of RNA.(39)

Apoptosis does not trigger an inflammatory reaction because apoptotic cells retain their intracellular contents and do not release them into the surrounding tissue; their apoptotic bodies are rapidly phagocytosed by neighboring cells—preventing secondary necrosis—and the cells responsible for engulfing these fragments do not produce inflammatory cytokines. (40)

Furthermore, the phagocytosis of apoptotic cells and apoptotic bodies is precisely coordinated

during the early stages of apoptosis, and a membrane lipid rearrangement occurs, which involves phosphatidylserine (PS) translocation from the inner to the outer leaflet. (41)Thus, PS, a phospholipid normally localized in the inner leaflet of the plasma membrane, is remodeled and is exposed onto the outer leaflet, which is believed to act as an "eat me" signal that facilitates the recognition and uptake of apoptotic cells by phagocytes. (42)

The formation of ApoBDs can promote efficient removal of cell debris by means of the surrounding phagocytes. Additionally, ApoBDs can harbor biomolecules, including microRNA and DNA, to regulate intercellular communication. (43)

Depending on the mechanism used by a particular cell type undergoing apoptotic cell disassembly, a different quantity and quality of ApoBDs will be generated. However, it is not yet clear why different cell types need to disassemble differently and the functional significance of such diversity. In autoimmune diseases, a defect in the clearance of ApoBD formation may contribute to the development of autoimmune disease. (44)

2.4 The clearance of dying cells (efferocytosis)

Cellular turnover is continuous in adult tissues, and rapid clearance of dying cells is essential to avoid inflammation and immune activation. This process is carried out by professional phagocytes—such as Kupffer cells, alveolar macrophages, and microglia—as well as non-professional phagocytes like epithelial cells and fibroblasts. (45)

Efferocytosis is an active, highly regulated process designed to efficiently eliminate dying cells and promote immunological tolerance. It involves a series of coordinated steps in which dying cells release "find-me" signals to attract phagocytes, which then recognize and bind to "eat-me" signals on the cell surface. The phagocyte subsequently engulfs the cellular corpse, processes and degrades it, and finally generates an appropriate immune response to the ingested material. (40)(Figure 5)

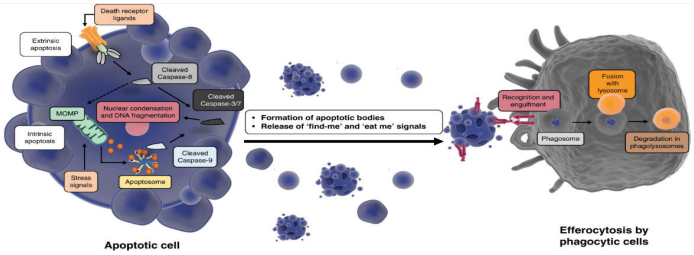

Figure 5: Clearance of dying cells. (46)

Recruitment of phagocytes to sites of cell death occurs before the completion of apoptosis, indicating that one of the first acts of a dying cell is to prepare for its own elimination. (47) During this process, apoptotic cells release 'find-me' signals, distinct molecules that establish a chemotactic gradient to attract phagocytic cells. (48)

Find-me' signals are often released in an active, caspase-dependent manner, yet these molecules are also released (in greater quantities) during other forms of cell death, such as necrosis or necroptosis. (49)

Just as dying cells must recruit phagocytes, they must also transform themselves into targets for engulfment, displaying distinct signals that differentiate them from viable cells. Thus, the simultaneous presence of 'don't eat me' signals, such as CD31, CD47, and CD61, on viable cells, may negatively regulate phagocytosis. (15)

Acidic proteases and nucleases in mature phagolysosomal compartments degrade dying cells into their basic cellular components, including fats, sterols, peptides, and nucleotides. (50)

2.5 Apoptosis pathways

Apoptosis is a multi-pathway mode of cell death that leads to cellular destruction, with the nucleus playing a crucial role in this process. (51)

Apoptosis requires energy input and thus is an active process. In more detail, apoptosis is initiated by either internal or external stimuli and mediated via two distinct pathways: the intrinsic pathway (mitochondria-mediated pathway) and the extrinsic pathway (death receptor-mediated pathway). (52)

Its induction is dependent on the presence of a wild-type p53 gene, which is a tumor suppressor protein that plays a role when DNA is damaged. P53 is a key element in apoptosis induction in cells in response to DNA damage. It becomes phosphorylated, stabilized, and activated. (53)

Cellular stress, including that induced by chemotherapy or irradiation, activates p53 either directly or indirectly. P53 can also move directly to the mitochondria, where it exerts proapoptotic activity. (54) Its transactivation can contribute to the induction of apoptosis in some cell types, and a number of genes transactivated by p53

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have been implicated in the apoptosis response. (55, 56)

Many genes involved in cell cycle regulation are also involved in the regulation of apoptosis (e.g., c-myc, c-fos, c-jun, and p53). Thus, signals that promote proliferation can also promote apoptosis. If apoptosis is blocked by survival signals, an increase in cell numbers occurs, which can manifest in cancer. For example, c-myc plus bcl-2 leads to proliferation, and c-myc plus p53 leads to apoptosis. (54)

➢ **Intrinsic apoptotic pathway (Figure 6)**

Intrinsic apoptosis is a form of RCD initiated by a variety of microenvironmental perturbations, including, but not limited to, the following:(57)

- Growth factor withdrawal.
- DNA damage (chemotherapeutic drugs).
- Endoplasmic reticulum (ER) stress.
- Reactive oxygen species (ROS) overload.
- Microtubular alterations.
- Mitotic defects.

The key to the regulation and execution of intrinsic apoptosis lies in the BCL-2 family of proteins, which includes both proapoptotic (promote apoptosis) and antiapoptotic (inhibit apoptosis) members. The careful modulation of the balance between these two groups of BCL-2 proteins can largely determine cell fate decisions between life and Death. (52) Bcl-2 contains four so-called Bcl-2 homology domains (BH1–BH4), which are absolutely required for its survival functions. (58) (Table 1)

Table 1: Bcl2 family (58)

Genes	Role of apoptosis	Functions
Bcl2 (B-cell lymphoma-2)	Inhibits apoptosis	Prevent apoptosis by inactivating (Bax and Bak proteins).
Bcl-xl (B-cell lymphoma-xl)	Inhibits apoptosis	Prevent apoptosis by rendering mitochondrial pores impermeable.
BAX (Bcl2-associated X protein)	Promotes apoptosis	Oppose Bcl2 Forms pores in the outer mitochondrial membrane (OMM). Cytochrome c release.
BAK (Bcl-2 antagonist killer	Promotes apoptosis	Same as BAX
BAD (Bcl-2 associated death promoter)	Phosphorylated BAD Antiapoptotic	No interaction with bcl2
	DE-phosphorylated BAD proapoptotic	Inactivate BCL2 so Bax is activated
BID	proapoptotic	Insertion of BAX into OMM
(Bik, Bim) other Bcl-2 death promoters		

In physiological conditions, the proapoptotic Bcl-2 protein Bax is predominantly found in the cytosol of nonapoptotic cells and is commonly thought to translocate to mitochondria following an apoptotic stimulus, initiating mitochondrial targeting and outer-membrane permeabilization. In contrast, BAK constitutively resides at the OMM.(59)

In response to apoptotic stimuli, MOMP is mediated by BAX and BAK. BAX and BAK are the only BCL2 family members characterized so far in mammalian cells for their ability to form pores across the outer mitochondrial membrane (OMM) and possibly other intracellular membranes. (60)

The critical step for intrinsic apoptosis, which is irreversible, is mitochondrial outer membrane

permeabilization (MOMP). It is controlled by proapoptotic and antiapoptotic members of the BCL2. (61)

Active BAX and BAK have also been proposed to permeabilize ER membranes, especially in response to reticular stress, resulting in the cytosolic leak of Ca2+ ions from ER and consequent mitochondrial Ca2+ uptake. (62)

This process further leads to the release of proapoptotic proteins through the intermembrane space into the cytosol. The presence of cytochrome c in the cytosol binds Apaf-1 (apoptotic protease activating factor) and caspase 9 to form a complex called "apoptosome".(63)

Activated CASP9 can catalyze the proteolytic activation of CASP3 and CASP7, which are widely perceived as the enzymes responsible for cell demolition during intrinsic (and extrinsic) apoptosis in mammalian cells. (64)

XIAP(X-linked inhibitor of apoptosis protein) is the only IAP(Inhibitor of Apoptotic protein) protein family member that counteracts the apoptotic cascade by stably binding to and hence physically blocking caspases. (65) IAPs are negatively regulated by IAP-antagonist proteins such as Smac/Diablo.(66, 67)

➢ **Extrinsic apoptotic pathway (Figure 6)**

The extrinsic pathway of apoptosis is a process whereby cells initiate programmed cell death in response to external signals, such as those from neighboring cells or the immune system. (68)

The external program that stimulates apoptosis occurs via death receptors that are members of the tumor necrosis factor receptor (TNFR) gene superfamily. Individual members of this family recognize specific ligands, but not all members of the TNF family initiate cell death. Those who initiate cell death possess a homologous cytoplasmic sequence termed death domain(DD). (68) This death domain is essential for the transmission of the death signal from the cell surface to intracellular signaling pathways. (68)

The binding of the death domain /adapter protein to the receptor ligand complex allows the binding of an initiator caspase 8 or 10 through its death effector domain (DED) to form an activated complex called the death-inducing signaling complex (DISC). Furthermore, the binding and activation allow caspase 8 to relay the death signal to an execution caspase to bring about apoptosis. (69)

Insufficient activation of caspase-3 leads to caspase-8 cleaving BID to generate its activated form: (tBID). TBID stimulates the intrinsic apoptotic pathway by binding directly to Bax/Bak, inducing MOMP.(70)

➢ **Granzyme-mediated apoptosis**

Cytotoxic lymphoid cells (predominantly NK cells and cytotoxic T cells) can induce cell death via death receptor ligands or the granzyme/perforin system. After recognition of transformed or infected cells, cytotoxic cells release secretory granules that contain perforin and granzyme B. These secreted factors are taken up by endocytosis and released into the cytosol by the perforin-dependent or -independent pathways. Once released to the cytosol, granzyme B cleaves caspases and Bid, activating apoptotic pathways. (71) (Figure 6)

The insertion of perforins into the target cell plasma membrane creates pores through which granzymes and toxins pass into the interior of the target cell. The granzymes are serine esterases that cleave and activate proteases. These enzymes have the capacity to induce DNA fragmentation and apoptosis of the target cells. (72)

2.6 Caspase family

Caspases are protease enzymes and key mediators of apoptosis, produced as inactive zymogens that are rapidly activated when needed. Fourteen caspases have been identified, with the major ones classified as initiators (caspase 2, 8, 9, 10), executioners (caspase-3, 6, 7), and inflammatory caspases (caspase 1, 4, 5). Additional members include caspase 11, involved in apoptosis and cytokine maturation during septic shock; caspase 12, linked to ER-stress-induced apoptosis; caspase 13, considered bovine-specific; and caspase 14, expressed mainly in embryonic tissues. (14, 73, 74)

Apoptosis proceeds through a caspase cascade in which initiator caspases, activated by the apoptosome (caspase 9), death receptors (caspase 8 and 10), or granzyme B (activating caspase 3 and 7), trigger downstream executioners. These caspases cleave nuclear

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and cytoplasmic substrates, activating endonucleases that fragment DNA—a hallmark of apoptosis—and promoting phosphatidylserine exposure on the cell surface. (75)

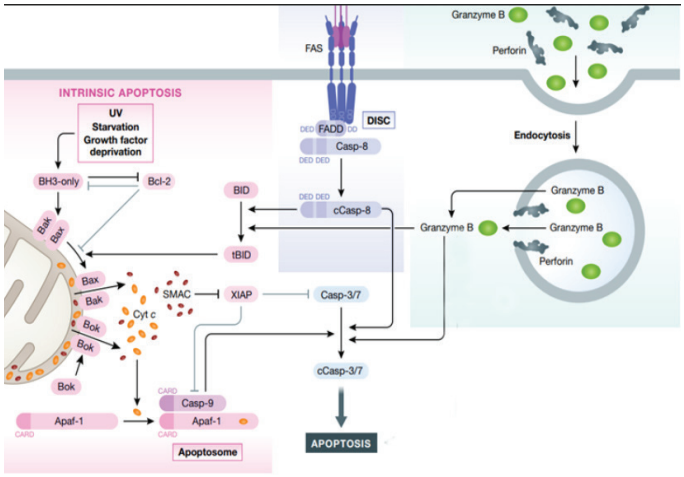

Figure 6: Apoptotic pathways and granzyme-mediated apoptosis. (70)

2.7 Anoikis

Anoikis is a programmed cell death occurring upon cell detachment from the correct extracellular matrix by disrupting integrin ligation. It is a critical mechanism in preventing dysplastic cell growth or attachment to an inappropriate matrix. Anoikis prevents detached epithelial cells from colonizing elsewhere and is thus essential for tissue homeostasis and development. (76)

It has become clear that the integrin-α6β4, a major component of hemidesmosomes, is able to transduce signals from the extracellular matrix to the interior of the cell, which critically modulates the organization of the cytoskeleton, proliferation, apoptosis, and differentiation. Maintenance of cell–cell contact is therefore important for preservation of normal epithelial structure and function. (77)

2.8 Methods of apoptosis detection

I. Morphological features

a. Light microscopy reveals the shrinking, rounding, and shedding of nuclei, chromatin morphology, and apoptotic bodies of the cells. (78)

b. Transmission electron microscopy: A common method used to assay the cellular state. It is used to detect vacuolations, chromatin condensation, and margination within the cell. Also, the cell nuclei fragmentations, apoptotic bodies, and changes in cell organelles. (78)

c. Image Cytometry: it uses a Cell Analysis Systems platform to quantify cell proliferation and apoptosis, with apoptosis measured as the percentage of epithelial cells showing characteristic apoptotic morphology under the light microscope. (79)

II. Biochemical characterization of apoptosis

a. DNA gel electrophoresis: This method is characterized by the formation of ladder-like DNA bands to detect apoptosis. (80) DNA laddering is a distinctive feature of DNA degraded by caspase-activated DNase. It can only be used for the semi-quantitative detection of apoptosis. It is also not suitable for detecting minor damage to the DNA.(81)

b. Real-time quantitative polymerase chain reaction (RT-qPCR): It is one of the most widely used methods of gene quantification. It is used to measure the mRNA expression of apoptosis-related genes. (82)

c. Analysis of mitochondrial membrane potential: Mitochondrial membrane potential, an early marker of mitochondrial apoptosis, is assessed using fluorescent cationic dyes, where high potential produces red fluorescence due to dye accumulation, and low potential yields green fluorescence as the dye fails to accumulate. (83)

III. Immunological characteristics of apoptosis

a. Western blotting: It is a laboratory technique used for the measurement of Cyto-C and the expression of apoptotic proteins. (84) The method involves using gel electrophoresis to separate the sample's proteins. The separated proteins are then exposed to an antibody specific to the target protein. The binding of the antibody is detected using a radioactive or chemical tag. This is one of the earliest detections of apoptosis. (85)

b. Immunolabeling technology: This refers to the antigen-antibody reaction of labeling antigens or antibodies with fluorescein, radioisotopes, enzymes, or electron-dense substances. (78)

c. Flow cytometry: This method is used to detect apoptotic cells after Annexin V/propidine iodine (PI) staining. Annexin V is used as a fluorescent probe to label the exposed

phosphatidylserine (PS) on the outer cell membrane. (86)This method is used to detect the level of apoptotic cells during apoptosis, as well as in necrosis. (78) Intracellular Ca2+ is labeled using fluorescent probes and then qualitatively and quantitatively analyzed by flow cytometry. (87)

d. Fluorescent ELISA: It is an immunological assay commonly used to measure the levels of apoptotic proteins in biological samples. An ELISA is a highly sensitive, quantitative method for detecting apoptosis. It is suitable for the method of detecting apoptosis at different stages. (86) The activity of caspases and Cyto-C decreases during the late stage of apoptosis. (78)

4. Necrosis

4.1 Non-regulated necrosis

Necrosis is an irreversible and unregulated form of cell death that arises from pathological injury. It is characterised by swelling of organelles, rupture of the plasma membrane, and the release of intracellular contents, resulting in tissue damage and inflammation. (88)

Necrosis occurs when cells are exposed to severe external insults and is almost always accompanied by an inflammatory response. Unlike apoptosis, it does not involve caspase activation and is not part of normal developmental processes. (89)

The main causes of necrosis include hypoxia, such as that resulting from ischaemia, shock, or respiratory failure; physical agents like trauma, extreme temperatures, radiation, electrical injury, or chemical burns; toxic chemical exposures, including poisons and harmful drugs; and biological agents such as bacteria, viruses, and fungi. (88)

➢ **Cellular mechanisms**

There are three events leading to cell rupture in necrosis:(90)(Figure 7)

1. Loss of selective plasma membrane permeability.
2. Loss of calcium homeostasis.
3. Failure of membrane ion pumps.

These three are interlinked. Any one event often leads on to another, allowing fluid and ions into the cell. This process spirals out of control: a vicious circle occurs, and the cell swells up until it finally ruptures. (90)

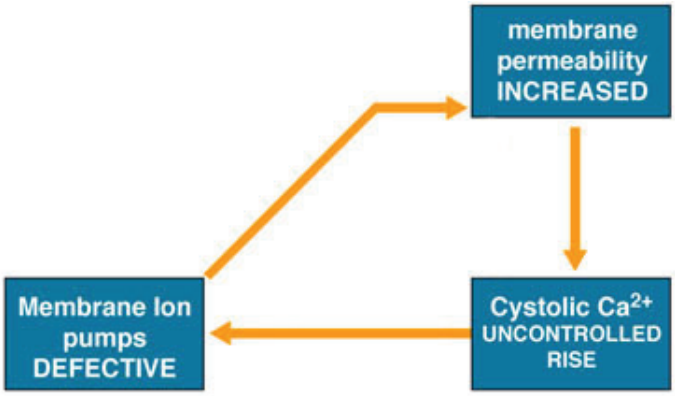

Figure 7: Events of necrosis

In necrosis, there is an important relation between ATP levels and membrane permeability. In injured cells, there is a lack of oxygen supply, leading to decreased ATP production. (91)

This lack of ATP results in the failure of the energy-dependent sodium pump in the plasma membrane, causing an influx of calcium and water, leading to cell swelling and detachment of ribosomes from the endoplasmic reticulum. Increased cytosolic calcium and oxidative stress lead to mitochondrial damage. Cytosolic calcium can also lead to the activation of several cytosolic enzymes, including phospholipases, which can attack lipids in the plasma membrane, and proteases, which lead to the breakdown of proteins. (91)

Loss of cell membrane integrity as a result of exposure to a noxious stimulus allows extracellular ions to move inside the cell, calcium ions accumulate, and flux leads to calcium matrix density formation in the mitochondria. (92)

The disruption of the lysosomal membrane leads to the release of proteolytic enzymes into the cell, such as proteases, RNAases, DNAases, and phosphatases. These, when activated in the cytosol, lead to damage to DNA, RNA, and proteins. These enzymes cause the digestion of the cellular components, causing cell destruction. These mechanisms lead to disruption of the plasma membrane, leading to the spilling of intracellular contents into the surrounding tissue. (90)

Cells undergoing necrosis release Damage-associated molecular patterns (DAMPs). DAMPs

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are molecules within living cells that are released when cell membranes are ruptured. Although DAMPs have physiological functions inside the cell, once DAMPs are released extracellularly, they elicit various biological responses, including inflammation, proliferation, tissue damage, and tissue repair, in a context-dependent manner. (93)

➢ **Primary and secondary necrosis (Figure 8)**

Unregulated cell death (usually termed "accidental" or "primary necrosis") is the response to extreme exogenous stress (e.g., burns, frost bites, strong mechanical stress), which prompts an immediate rupture of the cell membrane and release of intracellular molecules. (94)

In apoptosis, when apoptotic cells are not cleared in a timely manner, they progress to late apoptosis, which is characterized by a disrupted cell membrane and loss of cell integrity. This autolysis was termed "secondary necrosis" (95)

Progression of apoptosis to secondary necrosis occurs in vivo in physiological situations where apoptotic cells are shed into areas without phagocytes (e.g., in the gut or airways lumen) and the complete apoptotic program can fully progress. Secondary necrosis can also be observed in tissues with excessive apoptosis, which overwhelms the clearance capacity of phagocytes or when the clearance capacity itself is reduced. (96)

In the case of necrosis, intracellular damage-associated molecular patterns (DAMPs) leak out of the damaged cell, activating innate immune cells. Interestingly, microparticles released from apoptotic cells (often referred to as "apoptotic bodies" when they lose their cell membrane integrity and are quickly removed) result in a limited secretion of DAMPs into the microenvironment, which attracts phagocytes for efficient elimination. (96)

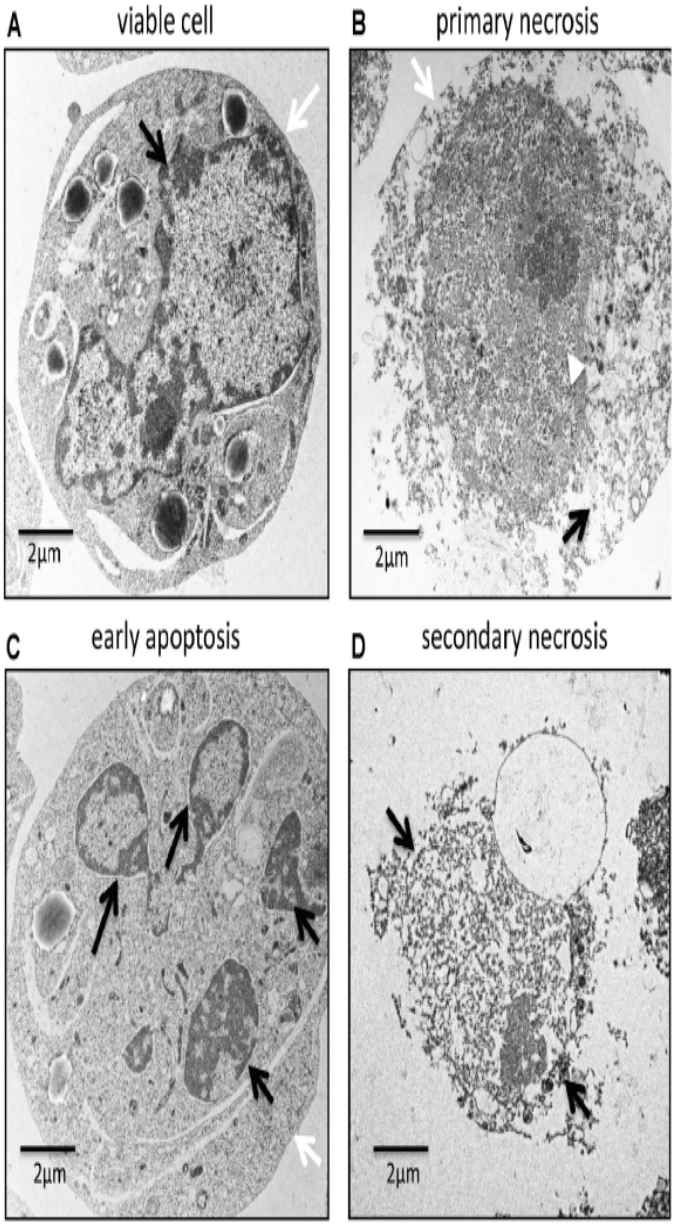

Figure 8: Transmission electron microscopic images of viable, primary necrotic, early apoptotic, and secondary necrotic cells. Human cells were cultured, and cell death (primary necrosis and apoptosis) was induced. A Viable cell with a normal morphology, including an intact cell membrane (white arrow) and nuclear membrane (black arrow). B Primary necrotic showing the loss of membrane integrity (white arrow) and low cytoplasm density (black arrow). A high DNA content can still be observed (white arrowhead). C Apoptotic cell marked by chromatin condensation and karyorrhexis (black arrows) and intact plasma membrane (white arrow). D Secondary necrosis showing a disintegrated cell membrane (black arrows) and loss of chromatin. Black bar 2 µm. (96)

4.2 Regulated necrosis

a. Necroptosis

Necroptosis has been discovered to be a novel form of programmed necrotic cell death, mechanically resembling apoptosis, while

morphologically similar to necrosis. (97)

Both apoptosis and programmed necrosis (necroptosis) are initiated by the same stimulants and activation of death receptors. However, the strength of the exposure will lead the cell toward necrosis or apoptosis. (98) The necroptosis pathway has been implicated as both an adaptive and pathogenic component of many human pathologies that involve inflammatory processes, including atherosclerosis, reperfusion injury, sepsis, inflammatory bowel disease, neurodegenerative disease, and pathological cell damage (viral infection). (99)

Necroptosis also acts as an alternative "fail-safe" cell death pathway in cases where cells are unable to undergo apoptosis, such as during viral infection, in which apoptosis signaling proteins are blocked by the virus. (100)

The most evident difference between necroptosis and apoptosis is the local inflammation caused by the release of the cell contents. The inflammation in necroptosis mainly presents as a large amount of inflammatory cell invasion and activation. (101)

The signaling pathway responsible for carrying out necroptosis is generally understood. Necroptosis is triggered by TNFR1 through interaction with the death domain (DD) that forms TRADD (Tumor Necrosis Factor Receptor Associated Death Domain). Then, RIPK1 was attracted, which recruits RIPK3, forming the necrosome. Phosphorylation of MLKL by the necrosome drives oligomerization of MLKL, allowing MLKL to insert into and permeabilize plasma membranes and organelles. (102)

Integration of MLKL leads to the inflammatory phenotype and release of damage-associated molecular patterns (DAMPs), which elicit immune responses. (102)

As in all forms of necrotic cell death, cells undergoing necroptosis rupture and leak their contents into the intercellular space. Unlike in necrosis, permeabilization of the cell membrane during necroptosis is tightly regulated. (103)

b. Pyroptosis

It is a regulated inflammatory form of programmed cell death that commonly occurs upon the recognition of intracellular pathogens. Pyroptosis can be triggered by bacteria, pathogens, or their endotoxins. (104)

The inflammation sensors of infected macrophage recognize the flagellin components of pathogens and initiate the formation of a multi-protein complex, the inflammasomes, which subsequently activate caspase1. (104) All inflammasomes require the adapter protein apoptosis-associated speck-like protein containing a CARD (ASC) for the activation of caspase 1. (105)

Caspase-1 is activated after the inflammasomes are formed. The inflammasome, which is a large supramolecular complex, subsequently mediates the maturation and secretion of interleukin-1 beta and interleukin-18. (106)

The morphological characteristics of pyroptosis include rupture of the cell membrane and release of its intracellular contents. This event provides a localized pool of potential proinflammatory molecules that include both direct activators of immune cells, such as cytokines and chemokines, as well as other signaling molecules or so-called "danger signals" able to trigger the production of inflammatory molecules from a variety of cell types. (107)

Inflammatory caspases activate Gasdermin D (GSDMD). Then, activated GSDMD translocates to the plasma membrane, where it binds to membrane phospholipids and initiates pore formation, resulting in loss of membrane integrity (as rupture of the cell membrane), cytosolic swelling, and release of cellular contents leading to cell death. The process is also accompanied by DNA condensation and fragmentation. (108)

c. Parthanatos

Parthanatos, a kind of new programmed death mode, indicates a caspase-independent cell death subroutine that critically relies on the hyper-activation of poly (ADP-ribose) polymerase 1 (PARP1). PARP-1 is important for DNA repair, genomic stability, and transcription. (109)

Cell demise from PARP-1 over-activation has been attributed to depletion of cellular energy, release of the death effector apoptosis-inducing factor (AIF) from the mitochondria, and production of excess poly-ADP ribose (PAR) polymer, a novel death signal. (109)

Upon PARP-1 overactivation, excess PAR, free or bound, shuttles outside of the nucleus and binds to specific cytosolic or mitochondrial proteins.

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PAR binding to these proteins ultimately leads to AIF release from the mitochondria. (110)

Mitochondria have been reported to contain the caspase-independent death effectors, apoptosis-inducing factor (AIF). AIF induces chromatin condensation and large-scale DNA fragmentation when released into the cytosol. (111)

Translocation of AIF into the nucleus, and not its loss from the mitochondria, kills cells. AIF translocation to the nucleus has been observed in different cell types induced to die. (109)

Parthanatos shares cytological and morphological features of apoptosis and necrosis, but is the result of a distinct molecular mechanism. Parthanatos is caspase-independent and does not involve the formation of apoptotic bodies. (112)

Nuclear mitochondrial crosstalk in parthanatos is triggered by DNA-damaging stimuli, activating PARP1. PAR, synthesized in response to DNA breaks, travels to the mitochondria and induces liberation of AIF. In turn, AIF interacts with MIF, and the latter degrades DNA.(113) AIF may recruit nucleases that induce chromatinolysis. (114)

d. Ferroptosis

Ferroptosis is an intracellular iron-dependent form of cell death that is distinct from apoptosis, necrosis, and autophagy. (115) It is characterized by the accumulation of lipid peroxide (polyunsaturated fatty acids) due to an increase in reactive oxygen species (ROS). Cellular iron is also recognized as a key factor in ferroptosis. Excess of active iron generation facilitates ROS production, which promotes lipid peroxidation and ferroptosis. (116)

Iron, which is involved in many biological functions, is a pro-oxidant agent that is able to react with hydrogen peroxide to produce reactive oxygen species (ROS). When the antioxidant system is saturated, an excess of ROS may cause cellular changes, such as damage to the plasma membrane and intracellular organelles, leading to cell death. (117) There is a role of iron in ferroptosis, but the exact mechanisms of its involvement are not clear. (118, 119)

Glutathione serves as a substrate for glutathione peroxidase (GPX4)(an antioxidant enzyme), which protects cells against oxidative stress by converting hydrogen peroxide to water. Additionally, GPX4 converts toxic lipid peroxides to nontoxic lipid alcohols. (58)

Biochemically, in ferroptosis, there is intracellular glutathione (GSH) depletion and decreased activity of glutathione peroxidase 4 (GPX4); lipid peroxides cannot be metabolized by the GPX4-catalyzed reduction reaction, and Fe^{2+} oxidizes lipids, resulting in a large amount of ROS, which promotes ferroptosis. (120)

Morphologically, ferroptosis occurs mainly in cells as reduced mitochondrial volume, increased bilayer membrane density, and reduction or disappearance of mitochondrial cristae, but the cell membrane remains intact, the nucleus is normal in size, and there is no condensation of chromatin. (116)

5. Vacuolepresenting cell death

a. Autophagy

Autophagy is an intracellular lysosomal (vacuolar) degradation process that is characterized by the formation of double-membrane vesicles (appearance of large intracellular vesicles) known as autophagosomes, which sequester in the cytoplasm. (121)

Autophagy has been described both as a means to resist starvation and as part of cellular remodeling during differentiation, metamorphosis, aging, cell transformation, physiological whole-organ changes, as well as in the removal of anomalous cellular components that accumulate following toxic insults or during cell death. (122)Autophagy is also initiated upon cellular stress as a protective response. Once the cellular stress is irreversible, the cell will be committed to Death, also through excessive levels of autophagy. (123)

Cells in the early stages of autophagy contain several autophagic vacuoles, although the nuclear structure still appears normal. Mitochondria and the endoplasmic reticulum are sometimes dilated, and the Golgi apparatus is often enlarged. The plasma membrane loses specializations such as microvilli and junctional complexes, and blebbing can occur. (121)

During late stages, both the number and size of vacuoli increase, and many of them are filled with lipids, which appear as pale gray inclusions in the cytoplasm. The nucleus of a cell undergoing

autophagic cell death can become pyknotic and identifiable. (124)

There are three defined types of autophagy: macro-autophagy, micro-autophagy, and chaperone-mediated autophagy, all of which promote proteolytic degradation of cytosolic components at the lysosome. Macro-autophagy delivers cytoplasmic cargo to the lysosome through the intermediary of a double membrane-bound vesicle, referred to as an autophagosome, that fuses with the lysosome to form an autolysosome. (125)

In micro-autophagy, by contrast, cytosolic components are directly taken up by the lysosome itself through invagination of the lysosomal membrane. Both macro-and micro-autophagy are able to engulf large structures through both selective and non-selective mechanisms. In chaperone-mediated autophagy (CMA), targeted proteins are translocated across the lysosomal membrane in a complex with chaperone proteins that are recognized by the lysosomal membrane receptor, resulting in their unfolding and degradation. (126)

➢ **The interplay of autophagy and apoptosis**

Autophagy and apoptosis often occur in the same cell, mostly in a sequence in which autophagy precedes apoptosis. This is because stress often stimulates an autophagic response, especially if the level of stress is not lethal. Apoptotic lethal programmer is activated when stress exceeds a critical duration or an intensity threshold. Nonetheless, if the cell commences apoptosis, autophagy can be inactivated, in part owing to the caspase-mediated cleavage of essential autophagy proteins, resulting in the inactivation of the autophagic programmed cell death. (127)

Autophagy induction is exacerbated if apoptosis is suppressed, for instance, by removing proapoptotic proteins such as BCL-2-associated X protein (BAX) and BCL-2 antagonist or killer (BAK) or by adding caspase inhibitors. (128)

The fact that many signal transduction pathways that are elicited by cell-intrinsic stress regulate both autophagy and apoptosis might explain the sequential activation of both processes. p53 is usually present in the cytosol but translocates to the nucleus upon DNA damage following its phosphorylation by a number of distinct stress-activated kinases. The available evidence indicates that the cytosolic pool of p53 represses autophagy and that the nuclear translocation of p53 leads to a decrease in this p53 pool, thereby facilitating the induction of autophagy. (127)

b. Entosis

It is a unique form of cell death characterized by the invasion of one living cell into another of the same type, a process that requires adhesion molecules, actin cytoskeleton remodelling, and energy expenditure. Once internalised, entotic cells may undergo regulated cell death within the entotic vacuole (entosome), via a specific autophagy-related process. (129) Interestingly, sometimes an entrapped inner cell stays viable for some time and is even able to divide inside the host cell or escape outside. (130, 131)

Entosis is believed to be triggered by integrinextracellular matrix (ECM) detachment. Subsequently, the cell produces adherens junctions with the neighboring cell and actively penetrates it, creating a cell-in-cell structure (CIC). Upon initiation of entosis, E-cadherin and β-catenin accumulate at the surface of the internalizing cells. (131)

Cytoskeleton dynamics plays a main role in entosis, linking adhesion sites and acts as an active signaling hub. A multi-molecular complex termed the mechanical ring (MR) is positioned between the invading and the engulfing cells. MR links adherens junctions with contractile actomyosin, coordinating their actions and promoting entosis. The entry of the inner cell is obviously dependent on actin filaments and actomyosin contractility. (132)

c. Methuosis

Methuosis is a distinct form of nonapoptotic cell death characterized by the massive accumulation of large fluid-filled single membrane vacuoles derived from macropinosomes. (133)

The consequent morphology resembles necrosis in the manner of cell swelling and plasma membrane integrity loss. The process begins with the abnormal fusion of nascent macropinosomes, resulting in osmotic cytoplasmic vacuolization. These enlarged vacuoles, which fail to undergo recycling or fusion with lysosomes, ultimately lead to cell death. (134)

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d. Paraptosis

The hallmark of paraptosis is the extensive cytoplasmic vacuolization originating from the dilated endoplasmic reticulum (ER) and the mitochondria. Several studies have shown that paraptosis is associated with reactive oxygen species (ROS) generation and the accumulation of misfolded proteins in the ER, as well as mitochondrial Ca2+ overload. Unlike apoptosis, Paraptosis lacks apoptotic features (e.g., DNA condensation and fragmentation, membrane blebbing, and apoptotic bodies), and unlike necrosis, cell membrane integrity is preserved in paraptosis (135, 136)

e. Ghost messages: cell death signals spread

Ghost messages refer to information transmitted from dying or dead cells to viable and healthy cells in the local or distant microenvironment, influencing their biological functions. To maintain body homeostasis, cells communicate through signaling molecules, including cell death signals. (137)

Cell death is classified as lytic or nonlytic. (138) Lytic forms—such as necrosis, necroptosis, pyroptosis, and ferroptosis—are characterized by the loss of membrane integrity and the release of damage-associated molecular patterns (DAMPs), proinflammatory cytokines, and other intracellular components into the extracellular space. (139)

In contrast, nonlytic cell death maintains membrane integrity and usually avoids triggering inflammation. Evidence indicates that dying cells can regulate inflammation, tissue repair, regeneration, and tumorigenesis through signaling to neighboring cells. (140)

Forms of ghost messages

Regardless of the death type, dying cells release various molecules and **extracellular vesicles (EVs)** that act as intercellular signals. These components influence recipient cells through receptor binding or internalization. (Figure 9)

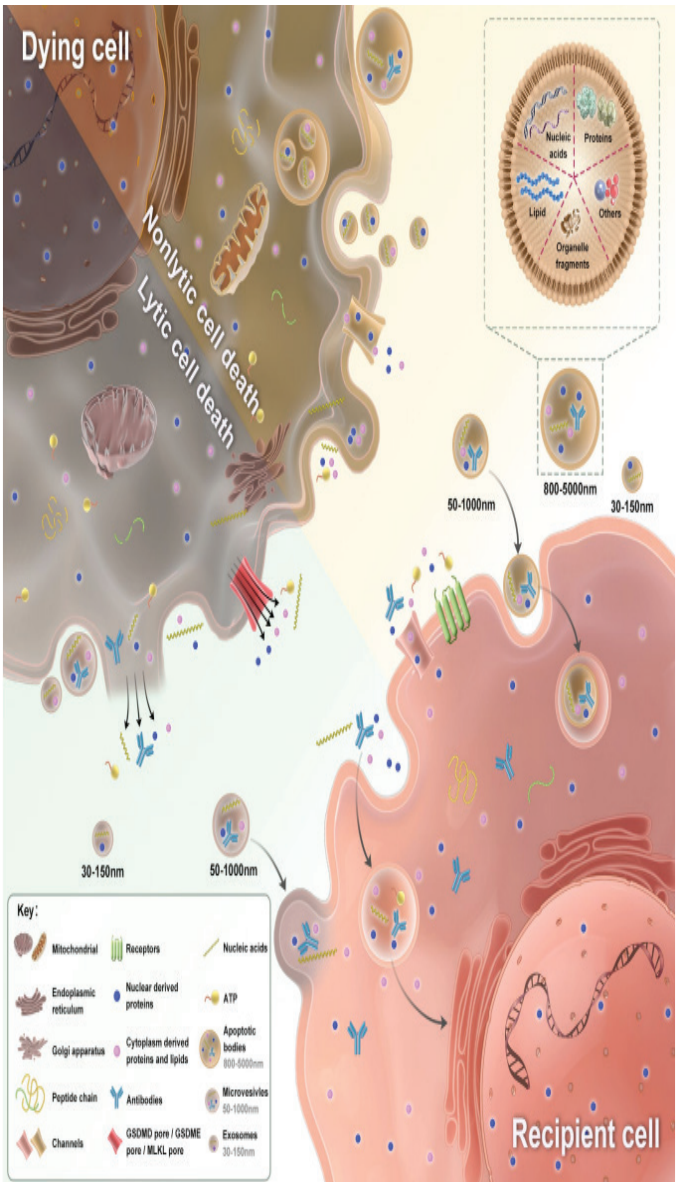

Figure 9: Ghost messages from dying cells to recipient cells(141)

1. Extracellular vesicles

Extracellular vesicles (EVs) are cell-derived lipid bilayer-enclosed membranous structures that consist of ApoBDs, exosomes, and microvesicles carrying biomolecules such as nucleic acids, proteins, and lipids. (142) It is now recognized that these vesicles can mediate intercellular communication. Vesicle secretion is a constitutive physiological process of healthy cells, but dying cells also release EVs.(143) Several studies have shown that cells undergoing nonapoptotic cell death generate a larger number of EVs compared with viable and apoptotic cells. (144)

- **Apoptotic bodies (ApoBDs)**

Large vesicles (800–5000 nm) formed during apoptosis; they are phagocytosed to prevent inflammation. Dying cells release "find-me" signals to attract phagocytes for debris clearance. (145, 146)

- **Exosomes and microvesicles**

Exosomes (30–150 nm) and microvesicles (50–1000 nm) mediate local and distant communication by transferring bioactive cargo. (146) Caspase activation during apoptosis can induce apoptotic exosome-like vesicles, which differ from classical exosomes in protein composition. (147)

The presence of microvesicles may preserve the integrity of the parent cells by eliminating complement and the risk of cytolysis. Release of microvesicles may rid the cell of toxic substances, but may also induce repair in neighboring cells. (148)

2. Soluble factors

A variety of soluble factors secreted by viable cells, such as cytokines, growth factors, receptors, hormones, and metabolites, can affect specific target cells via autocrine, paracrine, and endocrine signals. (149)Dying cells transmit messages through active secretion of some factors or passive release of intracellular contents following loss of membrane integrity. (149)

➢ **Target cells involved in ghost messages in biological processes:**

a. Immune cells

Immune cells are the first to respond to dying cells by engulfing debris and presenting antigens. Apoptosis is generally immunologically silent and promotes anti-inflammatory responses through **TGF-β** and **IL-10** secretion. (150)

TNF-α has been shown to reduce the capacity for dead cell engulfment, which exacerbates the inflammatory response. A defective clearance of apoptotic cells and dsDNAAb(double-stranded DNA antibodies)has been reported in systemic disease. (151)

During apoptosis, caspase activation opens Pannexin 1 channels, leading to (adenosine monophosphate) AMP release. As a "calm down" signal, AMP is converted to adenosine on macrophages, which activate anti-inflammatory genes. (150)

Nonapoptotic cell death released DAMPs also activate dendritic cells (DCs) and initiate adaptive T-cell immune responses. Insufficient autophagy of deteriorated organelles leads to the massive release of DAMPs, which exacerbates the inflammatory response. (152)

b. Stem and progenitor cells

Stem and progenitor cells possess self-renewal and differentiation capacity. After injury, apoptotic cells release growth factors such as **BMP**, **TGF-β**, **EGF**, **FGF**, and **IGF-1**, which recruit and activate these cells for tissue repair. (153)

PS externalization also influences cell differentiation. For example, mesenchymal stem cells (MSCs) that engulf apoptotic cells show enhanced osteogenic differentiation. (154)

c. Stromal cells and resident tissue cells

Stromal cells and resident tissue cells are a population of important functional cells that induce tissue regeneration and fibrosis. This process is essential for tissue repair after injury, but the role of ghost messages depends on the context. Active communication between apoptotic cells and healthy cells promotes surrounding cells' proliferation and maintenance of tissue homeostasis through what is commonly called apoptosis-induced compensatory proliferation. (155)

4. Conclusion

Cell death is essential for development, tissue renewal, and the preservation of homeostasis. This review highlights the major forms of programmed and non-programmed cell death, each defined by distinct molecular pathways and biological outcomes. Dysregulation of these pathways contributes to a wide range of diseases, from cancer to neurodegeneration and inflammatory disorders. Importantly, dying cells actively influence their microenvironment through signals and extracellular vesicles, affecting immunity, repair, and regeneration. A deeper understanding of these mechanisms offers promising avenues for future therapeutic strategies aimed at either promoting or preventing specific modes of cell death.

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References

1. Lee EJ. Cell Proliferation and Apoptosis in ADPKD. In: Cystogenesis. Springer Singapore; 2016. p. 25–34.

2. Kopeina GS, Efimenko AYu, Tkachuk VA, Zhivotovsky B. Programmed cell death and tissue regeneration: a link that should be resolved. Physiol Rev. 2025 Oct 1;105(4):2377–412.

3. Damiescu R, Efferth T, Dawood M. Dysregulation of different modes of programmed cell death by epigenetic modifications and their role in cancer. Cancer Lett. 2024 Mar;584:216623.

4. Yan G, Elbadawi M, Efferth T. Multiple cell death modalities and their key features (Review). World Acad Sci J. 2020 Mar 11;

5. Tang D, Kang R, Berghe T Vanden, Vandenabeele P, Kroemer G. The molecular machinery of regulated cell death. Cell Res. 2019 May 4;29(5):347–64.

6. Saiyad S, Patel U. PHYSIOLOGICAL CELL DEATH: APOPTOSIS. Int J Basic Appl Physiol. 2022;11(1).

7. Tang D, Kang R. Cell death. In: Mechanisms of Cell Death and Opportunities for Therapeutic Development. Elsevier; 2022. p. 47–64.

8. Tonnus W, Belavgeni A, Beuschlein F, Eisenhofer G, Fassnacht M, Kroiss M, et al. The role of regulated necrosis in endocrine diseases. Nat Rev Endocrinol. 2021 Aug 16;17(8):497–510.

9. Yan G, Elbadawi M, Efferth T. Multiple cell death modalities and their key features (Review). World Acad Sci J. 2020 Mar 11;

10. Tang D, Kang R. Cell death. In: Mechanisms of Cell Death and Opportunities for Therapeutic Development. Elsevier; 2022. p. 47–64.

11. Lossi L. The concept of intrinsic versus extrinsic apoptosis. Biochemical Journal. 2022 Feb 11;479(3):357–84.

12. Singh N. Apoptosis in health and disease and modulation of apoptosis for therapy: An overview. Indian Journal of Clinical Biochemistry. 2007 Sep;22(2):6–16.

13. Malhi H, Gores GJ, Lemasters JJ. Apoptosis and Necrosis in the Liver: A Tale of Two Deaths? Hepatology. 2006 Feb;43(Supplement 1):S31–44.

14. Elmore S. Apoptosis: A Review of Programmed Cell Death. Toxicol Pathol. 2007 Jun 1;35(4):495–516.

15. Green DR, Oguin TH, Martinez J. The clearance of dying cells: table for two. Cell Death Differ. 2016 Jun 18;23(6):915–26.

16. Song G, Liu J, Tang X, Zhong J, Zeng Y, Zhang X, et al. Cell cycle checkpoint revolution: targeted therapies in the fight against malignant tumors. Front Pharmacol. 2024 Oct 11;15.

17. Jeong J, McMahon AP. Growth and pattern of the mammalian neural tube are governed by partially overlapping feedback activities of the hedgehog antagonists patched 1 and Hhip1. Development. 2005 Jan 1;132(1):143–54.

18. Guerrero I, Ruiz i Altaba A. Longing for Ligand: Hedgehog, Patched, and Cell Death. Science (1979). 2003 Aug 8;301(5634):774–6.

19. Penaloza C, Lin L, Lockshin RA, Zakeri Z. Cell death in development: shaping the embryo. Histochem Cell Biol. 2006 Aug 1;126(2):149–58.

20. McIlwain DR, Berger T, Mak TW. Caspase Functions in Cell Death and Disease. Cold Spring Harb Perspect Biol. 2013 Apr 1;5(4):a008656–a008656.

21. Oberst A, Dillon CP, Weinlich R, McCormick LL, Fitzgerald P, Pop C, et al. Catalytic activity of the caspase-8–FLIPL complex inhibits RIPK3-dependent necrosis. Nature. 2011 Mar 17;471(7338):363–7.

22. Santos C, Marshall AR, Murray A, Metcalfe K, Narayan P, de Castro SC, et al. Spinal neural tube formation and tail development in human embryos. Elife. 2024 Dec 5;12.

23. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. Programmed Cell Death (Apoptosis). Molecular Biology of the Cell 4th edition. Garland Science; 2002.

24. Gravano DM, Hoyer KK. Promotion and prevention of autoimmune disease by CD8+ T cells. J Autoimmun. 2013 Sep;45:68–79.

25. Reznikov A. Hormonal impact on tumor growth and progression. Exp Oncol. 2015 Feb;37:162–72.

26. L. Miller W, Flück CE, Breault DT, Feldman BJ. The Adrenal Cortex and Its Disorders. In: Sperling Pediatric Endocrinology. Elsevier; 2021. p. 425–90.

27. Li SY, Sun R, Wang HX, Shen S, Liu Y, Du XJ, et al. Combination therapy with epigenetic-targeted and chemotherapeutic drugs delivered by nanoparticles to enhance the chemotherapy response and overcome resistance by breast cancer stem cells. Journal of Controlled Release. 2015 May;205:7–14.

28. Wong RS. Apoptosis in cancer: from pathogenesis to treatment. Journal of Experimental & Clinical Cancer Research. 2011 Dec 26;30(1):1–14.

29. Xu X, Lai Y, Hua ZC. Apoptosis and apoptotic body: disease message and therapeutic target potentials. Biosci Rep. 2019 Jan 31;39(1).

30. Burattini S, Ferri P, Battistelli M, D'emilio A, Biagiotti L, Sestili P, et al. Apoptotic DNA fragmentation can be revealed in situ: An ultrastructural approach. Microsc Res Tech. 2009 Dec 29;72(12):913–23.

31. Clarke P, DeBiasi RL, Goody R, Hoyt CC, Richardson-Burns S, Tyler KL. Mechanisms of Reovirus-Induced Cell Death and Tissue Injury: Role of Apoptosis and Virus-Induced Perturbation of Host-Cell Signaling and Transcription Factor Activation. Viral Immunol. 2005 Mar;18(1):89–115.

32. Obeng E. Apoptosis (programmed cell death) and its signals - A review. Brazilian Journal of Biology. 2021 Dec;81(4):1133–43.

33. Charras GT, Yarrow JC, Horton MA, MahadevanL,MitchisonTJ.Non-equilibration of hydrostatic pressure in blebbing cells. Nature. 2005 May;435(7040):365–9.

34. Ávila MO, Vega AF, Maraver JG, Paz MV, De Lavera I, De La Mata M, et al. The Apoptotic Microtubule Network During the Execution Phase of Apoptosis. In: Cell Death - Autophagy, Apoptosis and Necrosis. InTech; 2015.

35. Kiraly G, Simonyi AS, Turani M, Juhasz I, Nagy G, Banfalvi G. Micronucleus formation during chromatin condensation and under apoptotic conditions. Apoptosis. 2017 Feb 25;22(2):207–19.

36. Akers JC, Gonda D, Kim R, Carter BS, Chen CC. Biogenesis of extracellular vesicles (EV): exosomes, microvesicles, retrovirus-like vesicles, and apoptotic bodies. J Neurooncol. 2013 May 2;113(1):1–11.

37. Zahri S, Razavi SM, Niri FH, Mohammadi S. Induction of programmed cell death by Prangos uloptera, a medicinal plant. Biol Res. 2009;42:517–22.

38. Battistelli M, Falcieri E. Apoptotic Bodies: Particular Extracellular Vesicles Involved in Intercellular Communication. Biology (Basel). 2020 Jan 20;9(1):21.

39. Bayraktar R, Van Roosbroeck K, Calin GA. Cell-to-cell communication: microRNAs as hormones. Mol Oncol. 2017 Dec 26;11(12):1673–86.

40. Poon IKH, Lucas CD, Rossi AG, Ravichandran KS. Apoptotic cell clearance: basic biology and therapeutic potential. Nat Rev Immunol. 2014 Mar 31;14(3):166–80.

41. Rysavy NM, Shimoda LMN, Dixon AM, Speck M, Stokes AJ, Turner H, et al. Beyond apoptosis: The mechanism and function of phosphatidylserine asymmetry in the membrane of activating mast cells. Bioarchitecture. 2015 Feb;4:127–37.

42. Depraetere V. "Eat me"signals of apoptotic bodies. Nat Cell Biol. 2000 Jun;2(6):E104–E104.

43. Zernecke A, Bidzhekov K, Noels H, Shagdarsuren E, Gan L, Denecke B, et al. Delivery of MicroRNA-126 by Apoptotic Bodies Induces CXCL12-Dependent Vascular Protection. Sci Signal. 2009 Dec 8;2(100).

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2026.06.1.1809

44. Schiller M, Parcina M, Heyder P, Foermer S, Ostrop J, Leo A, et al. Induction of Type I IFN Is a Physiological Immune Reaction to Apoptotic Cell-Derived Membrane Microparticles. The Journal of Immunology. 2012 Aug 15;189(4):1747–56.

45. Arandjelovic S, Ravichandran KS. Phagocytosis of apoptotic cells in homeostasis. Nat Immunol. 2015 Sep 19;16(9):907–17.

46. Nössing C, Ryan KM. 50 years on and still very much alive: 'Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics.' Br J Cancer. 2023 Feb 2;128(3):426–31.

47. Reddien PW, Horvitz HR. CED-2/CrkII and CED-10/Rac control phagocytosis and cell migration in Caenorhabditis elegans. Nat Cell Biol. 2000 Mar 2;2(3):131–6.

48. Hochreiter-Hufford A, Ravichandran KS. Clearing the Dead: Apoptotic Cell Sensing, Recognition, Engulfment, and Digestion. Cold Spring Harb Perspect Biol. 2013 Jan 1;5(1):a008748–a008748.

49. Iyer SS, Pulskens WP, Sadler JJ, Butter LM, Teske GJ, Ulland TK, et al. Necrotic cells trigger a sterile inflammatory response through the Nlrp3 inflammasome. Proceedings of the National Academy of Sciences. 2009 Dec;106(48):20388–93.

50. Kawane K, Ohtani M, Miwa K, Kizawa T, Kanbara Y, Yoshioka Y, et al. Chronic polyarthritis caused by mammalian DNA that escapes from degradation in macrophages. Nature. 2006 Oct 26;443(7114):998–1002.

51. Frolova AS, Chepikova OE, Deviataikina AS, Solonkina AD, Zamyatnin AA. New Perspectives on the Role of Nuclear Proteases in Cell Death Pathways. Biology (Basel). 2023 May 31;12(6):797.

52. Singh R, Letai A, Sarosiek K. Regulation of apoptosis in health and disease: the balancing act of BCL-2 family proteins. Nat Rev Mol Cell Biol. 2019 Mar 17;20(3):175–93.

53. Yogosawa S, Yoshida K. Tumor suppressive role for kinases phosphorylating p53 in <scp>DNA</scp> damage-induced apoptosis. Cancer Sci. 2018 Nov 6;109(11):3376–82.

54. Lawen A. Apoptosis—an introduction. BioEssays. 2003 Sep 18;25(9):888–96.

55. Fridman JS, Lowe SW. Control of apoptosis by p53. Oncogene. 2003 Dec 8;22(56):9030–40.

56. Manohar S, Leung N. Cisplatin nephrotoxicity: a review of the literature. J Nephrol. 2018 Feb 5;31(1):15–25.

57. Czabotar PE, Lessene G, Strasser A, Adams JM. Control of apoptosis by the BCL-2 protein family: implications for physiology and therapy. Nat Rev Mol Cell Biol. 2014 Jan 20;15(1):49–63.

58. RK G, S T. Ozone: A new face of dentistry. 2009 Feb;7.

59. Schellenberg B, Wang P, Keeble JA, Rodriguez-Enriquez R, Walker S, Owens TW, et al. Bax Exists in a Dynamic Equilibrium between the Cytosol and Mitochondria to Control Apoptotic Priming. Mol Cell. 2013 Mar;49(5):959–71.

60. Moldoveanu T, Follis AV, Kriwacki RW, Green DR. Many players in BCL-2 family affairs. Trends Biochem Sci. 2014 Mar;39(3):101–11.

61. Bock FJ, Tait SWG. Mitochondria as multifaceted regulators of cell death. Nat Rev Mol Cell Biol. 2020 Feb 21;21(2):85–100.

62. Oakes SA, Scorrano L, Opferman JT, Bassik MC, Nishino M, Pozzan T, et al. Proapoptotic BAX and BAK regulate the type 1 inositol trisphosphate receptor and calcium leak from the endoplasmic reticulum. Proceedings of the National Academy of Sciences. 2005 Jan 4;102(1):105–10.

63. Xu W, Jing L, Wang Q, Lin CC, Chen X, Diao J, et al. Bax-PGAM5L-Drp1 complex is required for intrinsic apoptosis execution. Oncotarget. 2015 Oct 6;6(30):30017–34.

64. Julien O, Wells JA. Caspases and their substrates. Cell Death Differ. 2017 Aug 12;24(8):1380–9.

65. Eckelman BP, Salvesen GS. The Human Anti-apoptotic Proteins cIAP1 and cIAP2 Bind but Do Not Inhibit Caspases. Journal of Biological Chemistry. 2006 Feb;281(6):3254–60.

66. Abbas R, Larisch S. Targeting XIAP for Promoting Cancer Cell Death—The Story of ARTS and SMAC. Cells. 2020 Mar 9;9(3):663.

67. Hamacher-Brady A, Brady NR. Bax/Bak-dependent, Drp1-independent Targeting of X-linked Inhibitor of Apoptosis Protein (XIAP) into Inner Mitochondrial Compartments Counteracts Smac/DIABLO-dependent Effector Caspase Activation. Journal of Biological Chemistry. 2015 Sep;290(36):22005–18.

68. Yanumula A, Cusick JK. Biochemistry, Extrinsic Pathway of Apoptosis. StatPearls Publishing; 2020.

69. Guicciardi ME, Gores GJ. Life and death by death receptors. The FASEB Journal. 2009 Jun 13;23(6):1625–37.

70. Kist M, Vucic D. Cell death pathways: intricate connections and disease implications. EMBO J. 2021 Mar 13;40(5).

71. Voskoboinik I, Whisstock JC, Trapani JA. Perforin and granzymes: function, dysfunction and human pathology. Nat Rev Immunol. 2015 Jun 22;15(6):388–400.

72. Garant PR. Oral Cells and Tissues. Quintessence Publishing (IL); 2003.

73. Yan J, Xie Y, Si J, Gan L, Li H, Sun C, et al. Crosstalk of the Caspase Family and Mammalian Target of Rapamycin Signaling. Int J Mol Sci. 2021 Jan 15;22(2):817.

74. Rai NK, Tripathi K, Sharma D, Shukla VK. Apoptosis: A Basic Physiologic Process in Wound Healing. Int J Low Extrem Wounds. 2005 Sep 1;4(3):138–44.

75. Suzuki J, Imanishi E, Nagata S. Xkr8 phospholipid scrambling complex in apoptotic phosphatidylserine exposure. Proceedings of the National Academy of Sciences. 2016 Aug 23;113(34):9509–14.

76. Taddei M, Giannoni E, Fiaschi T, Chiarugi P. Anoikis: an emerging hallmark in health and diseases. J Pathol. 2012 Jan;226(2):380–93.

77. Loro L, Vintermyr O, Johannessen A. Apoptosis in normal and diseased oral tissues. Oral Dis. 2005 Sep 25;11(5):274–87.

78. Guo M, Lu B, Gan J, Wang S, Jiang X, Li H. Apoptosis detection: a purpose-dependent approach selection. Cell Cycle. 2021 Jun 3;20(11):1033–40.

79. Sgonc R, Gruber J. Apoptosis detection: an overview. Exp Gerontol. 1998 Sep;33(6):525–33.

80. Kari S, Subramanian K, Altomonte IA, Murugesan A, Yli-Harja O, Kandhavelu M. Programmed cell death detection methods: a systematic review and a categorical comparison. Apoptosis. 2022 Aug 17;27(7–8):482–508.

81. Ansari SM, Saquib Q, Attia SM, Abdel-Salam EM, Alwathnani HA, Faisal M, et al. Pendimethalin induces oxidative stress, DNA damage, and mitochondrial dysfunction to trigger apoptosis in human lymphocytes and rat bone-marrow cells. Histochem Cell Biol. 2018 Feb 18;149(2):127–41.

82. Lugli E, Troiano L, Ferraresi R, Roat E, Prada N, Nasi M, et al. Characterization of cells with different mitochondrial membrane potential during apoptosis. Cytometry Part A. 2005 Nov 19;68A(1):28–35.

83. Heisler-Taylor T, Kim B, Reese AY, Hamadmad S, Kusibati R, Fischer AJ, et al. A new multichannel method quantitating TUNEL in detached photoreceptor nuclei. Exp Eye Res. 2018 Nov;176:121–9.

84. da Fonseca RR, Kosiol C, Vinař T, Siepel A, Nielsen R. Positive selection on apoptosis related genes. FEBS Lett. 2010 Feb 5;584(3):469–76.

85. Martinez MM, Reif RD, Pappas D. Detection of apoptosis: A review of conventional and novel techniques. Analytical Methods. 2010;2(8):996.

86. Wlodkowic D, Skommer J, Darzynkiewicz Z. Flow Cytometry-Based Apoptosis Detection. In 2009. p. 19–32.

87. Vogler M, Hamali HA, Sun XM, Bampton ETW, Dinsdale D, Snowden RT, et al. BCL2/BCL-XL inhibition induces apoptosis, disrupts cellular calcium homeostasis, and prevents platelet activation. Blood. 2011 Jun 30;117(26):7145–54.

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2026.06.1.1809

88. Khalid N, Azimpouran M. Necrosis. StatPearls Publishing; 2023.

89. Festjens N, Vanden Berghe T, Vandenabeele P. Necrosis, a well-orchestrated form of cell demise: Signalling cascades, important mediators and concomitant immune response. Biochimica et Biophysica Acta (BBA) - Bioenergetics. 2006 Sep;1757(9–10):1371–87.

90. Sarhan M, Land WG, Tonnus W, Hugo CP, Linkermann A. Origin and Consequences of Necroinflammation. Physiol Rev. 2018 Apr 1;98(2):727–80.

91. guicciardi maria eugenia, Gores GJ. Complete lysosomal disruption: A route to necrosis, not to the inflammasome. Cell Cycle. 2013 Jul 31;12(13):1995–1995.

92. Wojtczak L, Zabłocki K. Basic Mitochondrial Physiology in Cell Viability and Death. In: Drug-Induced Mitochondrial Dysfunction. Wiley; 2008. p. 1–35.

93. Nakano H, Murai S, Moriwaki K. Regulation of the release of damage-associated molecular patterns from necroptotic cells. Biochemical Journal. 2022 Mar 18;479(5):677–85.

94. Priante G, Gianesello L, Ceol M, Del Prete D, Anglani F. Cell Death in the Kidney. Int J Mol Sci. 2019 Jul 23;20(14):3598.

95. Gao Y, Jiao Y, Gong X, Liu J, Xiao H, Zheng Q. Role of transcription factors in apoptotic cells clearance. Front Cell Dev Biol. 2023 Jan 19;11.

96. Sachet M, Liang YY, Oehler R. The immune response to secondary necrotic cells. Apoptosis. 2017 Oct 31;22(10):1189–204.

97. Ye H, Lu M, Tu C, Min L. Necroptosis in the sarcoma immune microenvironment: From biology to therapy. Int Immunopharmacol. 2023 Sep;122:110603.

98. Mozaffari S, Abdollahi M. Mitochondrial contribution to cell death. In: Mitochondrial Metabolism. Elsevier; p. 2021.

99. Choi ME, Price DR, Ryter SW, Choi AMK. Necroptosis: a crucial pathogenic mediator of human disease. JCI Insight. 2019 Aug 8;4(15).

100. Gong Y, Fan Z, Luo G, Yang C, Huang Q, Fan K, et al. The role of necroptosis in cancer biology and therapy. Mol Cancer. 2019 Dec 23;18(1):1–17.

101. Liu C, Zhang K, Shen H, Yao X, Sun Q, Chen G. Necroptosis: A novel manner of cell death, associated with stroke (Review). Int J Mol Med. 2017 Nov 22;

102. Cho S, Pronko A, Stout-Delgado H. Crosstalk between necroptosis and the inflammasome. In: Inflammasome Biology. Elsevier; 2023.

103. Purnama CA, Meiliana A, Barliana MI, Lestari K. Update of cellular responses to the efferocytosis of necroptosis and pyroptosis. Cell Div. 2023 Apr 9;18(1):5.

104. Miller DR, Cramer SD, Thorburn A. The interplay of autophagy and non-apoptotic cell death pathways. In: International review of cell and molecular biology. 2020. p. 159–87.

105. Stutz A, Horvath GL, Monks BG, Latz E. ASC Speck Formation as a Readout for Inflammasome Activation. In 2013. p. 91–101.

106. Li Y, Fan J, Ju D. Neurotoxicity concern about the brain targeting delivery systems. In: Brain Targeted Drug Delivery System. Elsevier; 2019. p. 377–408.

107. Firestein G, Budd R, Gabriel S, McInnes I, O'Dell J. Firestein & kelley's textbook of rheumatology-E-book. Elsevier Health Sciences; 2020.

108. Iorga A, Dara L. Cell death in drug-induced liver injury. In: Advances in Pharmacology. 2019. p. 31–74.

109. David KK, Andrabi SA, Dawson TM, Dawson VL. Parthanatos, a messenger of death. Frontiers in Bioscience. 2009;Volume(14):1116.

110. David KK, Andrabi SA, Dawson TM, Dawson VL. Parthanatos, a messenger of death. Frontiers in Bioscience. 2009;Volume(14):1116.

111. Nguyen TNA, Lai HT, Fernandes R, Dall'Olio FG, Blériot C, Ha-Duong T, et al. Apoptosis-inducing factor (AIF) at the crossroad of cell survival and cell death: implications for cancer and mitochondrial diseases. Cell Communication and Signaling. 2025 Jun 4;23(1):264.

112. Fatokun AA, Dawson VL, Dawson TM. Parthanatos: mitochondrial-linked mechanisms and therapeutic opportunities. Br J Pharmacol. 2014 Apr 28;171(8):2000–16.

113. Robinson N, Ganesan R, Hegedűs C, Kovács K, Kufer TA, Virág L. Programmed necrotic cell death of macrophages: Focus on pyroptosis, necroptosis, and parthanatos. Redox Biol. 2019 Sep;26:101239.

114. Novo N, Romero-Tamayo S, Marcuello C, Boneta S, Blasco-Machin I, Velázquez-Campoy A, et al. Beyond a platform protein for the degradosome assembly: The Apoptosis-Inducing Factor as an efficient nuclease involved in chromatinolysis. PNAS Nexus. 2023 Feb 3;2(2).

115. Zhang C, Liu X, Jin S, Chen Y, Guo R. Ferroptosis in cancer therapy: a novel approach to reversing drug resistance. Mol Cancer. 2022 Dec 12;21(1):47.

116. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, et al. Ferroptosis: An Iron-Dependent Form of Nonapoptotic Cell Death. Cell. 2012 May;149(5):1060–72.

117. Sousa L, Oliveira MM, Pessôa MTC, Barbosa LA. Iron overload: Effects on cellular biochemistry. Clinica Chimica Acta. 2020 May;504:180–9.

118. Kim-Campbell N, Gomez H, Bayir H. Cell Death Pathways. In: Critical Care Nephrology. Elsevier; 2019. p. 113-121.e2.

119. Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. Nat Rev Mol Cell Biol. 2021 Apr 25;22(4):266–82.

120. Flores-Romero H, Ros U, García-Sáez AJ. A lipid perspective on regulated cell death. In: International review of cell and molecular biology. 2020. p. 197–236.

121. Chen Y, Klionsky DJ. The regulation of autophagy – unanswered questions. J Cell Sci. 2011 Jan 15;124(2):161–70.

122. Wang L, Ye X, Zhao T. The physiological roles of autophagy in the mammalian life cycle. Biological Reviews. 2019 Apr 21;94(2):503–16.

123. Ravanan P, Srikumar IF, Talwar P. Autophagy: The spotlight for cellular stress responses. Life Sci. 2017 Nov;188:53–67.

124. Chen Y, Li X, Yang M, Liu SB. Research progress on morphology and mechanism of programmed cell death. Cell Death Dis. 2024 May 10;15(5):327.

125. Glick D, Barth S, Macleod KF. Autophagy: cellular and molecular mechanisms. J Pathol. 2010 May;221(1):3–12.

126. Mizushima N. A brief history of autophagy from cell biology to physiology and disease. Nat Cell Biol. 2018 May 23;20(5):521–7.

127. Mariño G, Niso-Santano M, Baehrecke EH, Kroemer G. Self-consumption: the interplay of autophagy and apoptosis. Nat Rev Mol Cell Biol. 2014 Feb 8;15(2):81–94.

128. Yu L, Alva A, Su H, Dutt P, Freundt E, Welsh S, et al. Regulation of an ATG7- beclin 1 Program of Autophagic Cell Death by Caspase-8. Science (1979). 2004 Jun 4;304(5676):1500–2.

129. White E. Entosis: It's a Cell-Eat-Cell World. Cell. 2007 Nov;131(5):840–2.

130. Kianfar M, Balcerak A, Chmielarczyk M, Tarnowski L, Grzybowska EA. Cell Death by Entosis: Triggers, Molecular Mechanisms and Clinical Significance. Int J Mol Sci. 2022 Apr 30;23(9):4985.

131. Mlynarczuk-Bialy I, Dziuba I, Sarnecka A, Platos E, Kowalczyk M, Pels KK, et al. Entosis: From Cell Biology to Clinical Cancer Pathology. Cancers (Basel). 2020 Sep 1;12(9):2481.

132. Wan Q, Liu J, Zheng Z, Zhu H, Chu X, Dong Z, et al. Regulation of myosin activation during cell–cell contact formation by Par3-Lgl antagonism: entosis without matrix detachment. Mol Biol Cell. 2012 Jun;23(11):2076–91.

133. Maltese WA, Overmeyer JH. Methuosis. Am J Pathol. 2014 Jun;184(6):1630–42.

134. Silva-Pavez E, Villar P, Trigo C, Caamaño E, Niechi I, Pérez P, et al. CK2 inhibition with silmitasertib promotes methuosis-like cell death associated to catastrophic massive vacuolization of colorectal cancer cells. Cell Death Dis. 2019 Jan 25;10(2):73.

135. Kim E, Lee DM, Seo MJ, Lee HJ, Choi KS. Intracellular Ca2 + Imbalance Critically Contributes to Paraptosis. Front Cell Dev

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2026.06.1.1809

Biol. 2021 Jan 12;8.

136. Hanson S, Dharan A, P. V. J, Pal S, Nair BG, Kar R, et al. Paraptosis: a unique cell death mode for targeting cancer. Front Pharmacol. 2023 Jun 15;14.

137. Zhang M, Lin Y, Chen R, Yu H, Li Y, Chen M, et al. Ghost messages: cell death signals spread. Cell Communication and Signaling. 2023 Jan 9;21(1):6.

138. Vicar T, Raudenska M, Gumulec J, Balvan J. The Quantitative-Phase Dynamics of Apoptosis and Lytic Cell Death. Sci Rep. 2020 Jan 31;10(1):1566.

139. Berghe T Vanden, Vanlangenakker N, Parthoens E, Deckers W, Devos M, Festjens N, et al. Necroptosis, necrosis and secondary necrosis converge on similar cellular disintegration features. Cell Death Differ. 2010 Jun 11;17(6):922–30.

140. Levine B, Kroemer G. Biological Functions of Autophagy Genes: A Disease Perspective. Cell. 2019 Jan;176(1–2):11–42.

141. Zhang M, Lin Y, Chen R, Yu H, Li Y, Chen M, et al. Ghost messages: cell death signals spread. Cell Communication and Signaling. 2023 Jan 9;21(1):6.

142. van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. Nat Rev Mol Cell Biol. 2018 Apr 17;19(4):213–28.

143. Li M, Liao L, Tian W. Extracellular Vesicles Derived From Apoptotic Cells: An Essential Link Between Death and Regeneration. Front Cell Dev Biol. 2020 Oct 2;8.

144. Baxter AA, Phan TK, Hanssen E, Liem M, Hulett MD, Mathivanan S, et al. Analysis of extracellular vesicles generated from monocytes under conditions of lytic cell death. Sci Rep. 2019 May 17;9(1):7538.

145. Kang M, Jordan V, Blenkiron C, Chamley LW. Biodistribution of extracellular vesicles following administration into animals: A systematic review. J Extracell Vesicles. 2021 Jun 24;10(8).

146. Chekeni FB, Elliott MR, Sandilos JK, Walk SF, Kinchen JM, Lazarowski ER, et al. Pannexin 1 channels mediate 'find-me' signal release and membrane permeability during apoptosis. Nature. 2010 Oct 13;467(7317):863–7.

147. Liu ML, Williams KJ, Werth VP. Microvesicles in Autoimmune Diseases. In: dvances in clinical chemistry. 2016. p. 125–75.

148. Ståhl A lie, Johansson K, Mossberg M, Kahn R, Karpman D. Exosomes and microvesicles in normal physiology, pathophysiology, and renal diseases. Pediatric Nephrology. 2019 Jan 27;34(1):11–30.

149. Mitchell R, Mellows B, Sheard J, Antonioli M, Kretz O, Chambers D, et al. Secretome of adipose-derived mesenchymal stem cells promotes skeletal muscle regeneration through synergistic action of extracellular vesicle cargo and soluble proteins. Stem Cell Res Ther. 2019 Dec 5;10(1):116.

150. Yamaguchi H, Maruyama T, Urade Y, Nagata S. Immunosuppression via adenosine receptor activation by adenosine monophosphate released from apoptotic cells. Elife. 2014 Mar 25;3.

151. Schulze C, Munoz LE, Franz S, Sarter K, Chaurio RA, Gaipl US, et al. Clearance deficiency—A potential link between infections and autoimmunity. Autoimmun Rev. 2008 Oct;8(1):5–8.

152. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature. 2010 Mar;464(7285):104–7.

153. Amcheslavsky A, Wang S, Fogarty CE, Lindblad JL, Fan Y, Bergmann A. Plasma Membrane Localization of Apoptotic Caspases for Non-apoptotic Functions. Dev Cell. 2018 May;45(4):450-464.e3.

154. Verma SK, Leikina E, Melikov K, Gebert C, Kram V, Young MF, et al. Cell-surface phosphatidylserine regulates osteoclast precursor fusion. Journal of Biological Chemistry. 2018 Jan;293(1):254–70.

155. Tso GHW, Law HKW, Tu W, Chan GCF, Lau YL. Phagocytosis of Apoptotic Cells Modulates Mesenchymal Stem Cells Osteogenic Differentiation to Enhance IL-17 and RANKL Expression on CD4+ T Cells. Stem Cells. 2010 May 1;28(5):939–54.