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Review Article

Apoptosis: Mechanisms of Programmed Cell Death and its Biological Significance

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ABSTRACT

Apoptosis is a highly regulated, genetically programmed form of cell death essential for maintaining homeostasis in multicellular organisms. Unlike necrosis, which involves cell swelling and inflammatory rupture, apoptosis is characterized by distinct morphological features, including cell shrinkage, chromatin condensation, nuclear fragmentation, and the formation of membrane-bound apoptotic bodies. This process is primarily orchestrated through the intrinsic and extrinsic pathways, both of which culminate in a proteolytic cascade involving initiator and executioner caspases. The biological significance of apoptosis spans embryonic development, immune system regulation, and the elimination of damaged or virus-infected cells. Efficient phagocytosis of apoptotic remains, or efferocytosis, ensures tissue renewal without an inflammatory response. Dysregulation of these pathways is central to various pathologies, including cancer, autoimmune disorders, and neurodegenerative diseases. This review summarizes the morphological and biochemical mechanisms of the intrinsic and extrinsic pathways and evaluates their biological significance for tissue homeostasis and disease pathology.

Keywords: Apoptosis, Caspases, Extrinsic Pathway, Homeostasis, Intrinsic Pathway.

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INTRODUCTION

In multicellular organisms, homeostasis is maintained by a balance between cell proliferation and cell death. Cell death is an irreversible injury that may occur in the living body as a local or focal change, such as autolysis (self-digestion), necrosis (uncontrolled cell breakdown), and apoptosis (programmed cell death).[1] In 1972, Kerr, Wyllie, and Currie first used the term "apoptosis" to describe a morphologically distinct form of cell death.[2]

Unlike accidental cell death caused by injury (necrosis), apoptosis is a regulated form of cell death where cells actively participate in their own elimination in an orderly, controlled, and regulated manner.[3] This mechanism is essential for development, immune regulation, and the removal of damaged or abnormal cells. It primarily occurs through the intrinsic (mitochondrial), extrinsic (death receptor), and cytotoxic CD8+ T-cell mediated pathways.[4] Ultimately, apoptosis is an essential process for maintaining tissue homeostasis and organismal health by eliminating superfluous cells.[3,5] The objective of this review is to examine the morphological and biochemical mechanisms of programmed cell death, specifically the intrinsic and extrinsic pathways and to evaluate its biological significance in tissue homeostasis and disease pathology.

Cell Death

Cell death is a fundamental process for development, tissue maintenance, and physiological balance in multicellular organisms. It facilitates the removal of unwanted cells during embryogenesis, metamorphosis, and tissue turnover, as well as in response to pathogenic threats. Programmed cell death (apoptosis) and necrosis are the two primary mechanisms.[3] The common types of cell death are depicted in Figure 1.

Apoptosis

Apoptosis is a genetically regulated self-destruction process triggered by extracellular or intracellular signals, including internal factors like Bax, Bak, and cytochrome C. It is essential for maintaining tissue homeostasis.[3]

Necrosis

In contrast to the regulated nature of apoptosis, necrosis is traditionally viewed as a chaotic, uncontrolled response to severe

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injury, characterized by cell enlargement, membrane breakdown, and the spilling of cellular material, which often triggers an inflammatory response.[6]

Non-Apoptotic Programmed Cell Death

Recent research distinguishes apoptosis from other forms of programmed cell death, including autophagic cell death and necroptosis. Autophagic cell death, also known as type II cell death, is a self-degradative process prevalent in invertebrate tissues that plays a significant role in degrading cellular components within dying cells. Necroptosis, on the other hand, is a programmed form of necrotic death initiated by the same death signals that induce apoptosis, occurring in response to physical traumas, infections, and various forms of neurodegeneration. This process is characterized by both apoptotic and necrotic features and specifically requires the protein RIPK3 (Receptor-Interacting Protein Kinase-3) and its substrate MLKL (Mixed Lineage Kinase Domain-Like Pseudokinase), while being influenced by factors such as Toll-like receptors, death receptors, and interferons.[3,7,8]

MECHANISMS OF APOPTOSIS

Apoptosis occurs through complex molecular pathways that lead to the systematic destruction of a cell. Apoptosis occurs through complex molecular pathways that lead to the systematic destruction of a cell. The intrinsic (mitochondrial) pathway and extrinsic (death receptor) pathway are the two main signaling pathways that regulate apoptosis. The intrinsic apoptosis pathway begins when there is an injury within the cell, and the extrinsic apoptosis pathway begins outside a cell, when situations in the extracellular environment dictate that a cell must die. Generally, several hours are required from the initiation of cell death to the final cellular fragmentation.[9] Generally, several hours are required from the initiation of cell death to final cellular fragmentation, depending on the cell type and the specific pathway activated.[9]

Intrinsic apoptosis pathway

The intrinsic pathway is triggered by internal cellular stress such as DNA (Deoxyribonucleic Acid) damage, oxidative stress, oncogene activation, hypoxia, or the absence of growth factors. These stress signals activate regulatory proteins from the Bcl-2 family, which control mitochondrial integrity. Biochemically, pro-apoptotic members (BAX/BAK) of this family increase the permeability of the mitochondrial membrane, leading to the release of Cytochrome C into the cytoplasm. Once released, Cytochrome C forms a complex called the apoptosome, which subsequently activates a group of proteolytic enzymes known as Caspases. These caspases degrade key cellular proteins and fragment DNA, ensuring cells with severe internal damage are eliminated.[3,10]

Extrinsic signaling pathways

The extrinsic signaling pathway is initiated via death receptors that are members of the Tumor Necrosis Factor (TNF) receptor gene superfamily (e.g., FasL/FasR, TNF-α/TNFR1). These receptors possess a cytoplasmic "death domain" of about 80 amino acids that plays a critical role in transmitting signals from the cell surface to intracellular pathways.[11] When ligands engage these receptors, they trigger the biochemical assembly of the Death-Inducing Signaling Complex (DISC). This scaffold facilitates the autocatalytic activation of initiator caspase-8. Once

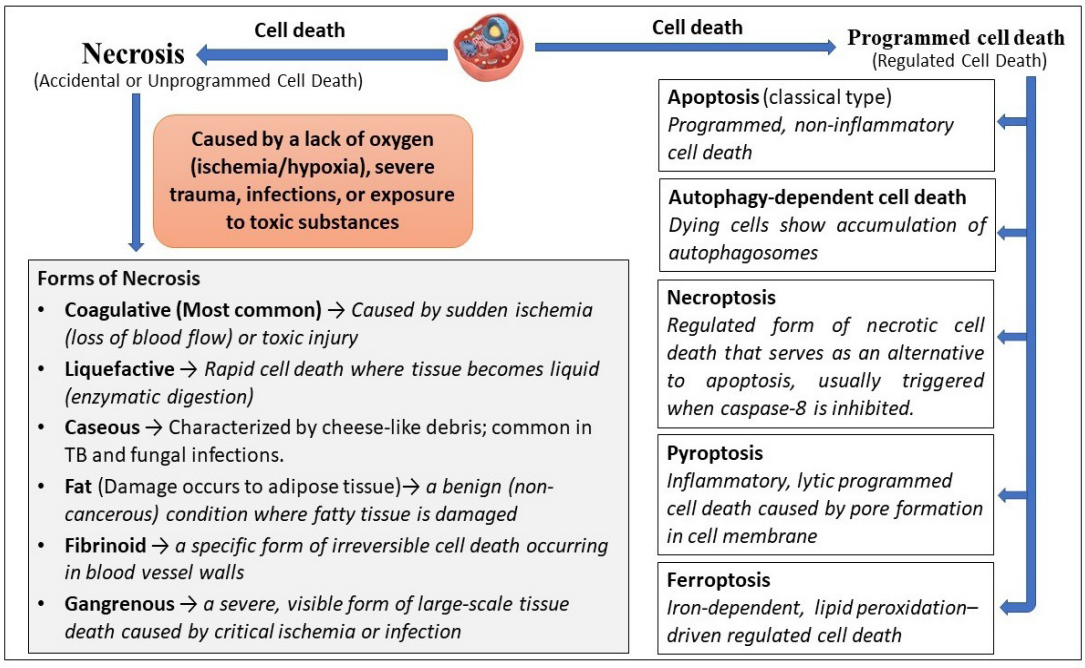

Figure 1: The common types of cell death.

active, these enzymes can directly trigger executioner caspases or cleave BID (a Bcl-2 member) to engage the mitochondrial pathway, providing a link between the two signaling routes.[12,13] This pathway is critical for the immune system to eliminate infected or abnormal cells.

The Execution Phase and Caspase Regulation

The main regulators of apoptosis are caspases that can be divided into two classes: initiator caspases (e.g., caspase-8 and -9) and effector/executioner caspases (e.g., caspase-3). This cascade is strictly regulated by the Bcl-2 protein family, which contains both pro-apoptotic and anti-apoptotic (pro-survival) members.[14] The activation of effector caspases leads to the final phase of Programmed Cell Death (PCD), characterized by specific biochemical alterations: internucleosomal DNA fragmentation, the proteolytic cleavage of the nuclear scaffold (PARP), and the externalization of phosphatidylserine on the plasma membrane.[15-17] These molecular events ensure the cell is efficiently decommissioned and prepared for phagocytic removal.

MORPHOLOGICAL CHANGES DURING APOPTOSIS

The morphological changes during apoptosis are a sequence of highly orchestrated events designed to dismantle the cell from within while keeping its outer membrane intact. This process ensures that the cell "disappears" without triggering an inflammatory response, which would occur if the cell simply burst (necrosis).[18] Cells undergoing apoptosis show distinct structural changes:

Cell shrinkage

Unlike cells dying from injury, which swell and burst, apoptotic cells lose water and ions, causing the cytoplasm to become dense and the overall cell volume to decrease. The organelles remain tightly packed but relatively intact during this initial phase.[2]

Chromatin condensation (Pyknosis)

This is the most characteristic feature of apoptosis. The chromatin (the mixture of DNA and proteins in the nucleus) aggregates and packs very tightly against the nuclear envelope. This dense packing is a visible sign that the cell's genetic "instruction manual" is being permanently closed and decommissioned.[19]

Nuclear fragmentation (Karyorrhexis)

As the process continues, the nucleus itself breaks apart. The nuclear envelope becomes discontinuous, and the DNA is cleaved by specific enzymes (endonucleases) into regular, small fragments. This prevents any viral or damaged genetic material from being functional or integrated elsewhere.[2]

Formation of membrane-bound apoptotic bodies

The cell surface begins to undergo "blebbing", a process where the plasma membrane bubbles outward. Eventually, the entire cell breaks into several small, membrane-wrapped fragments called apoptotic bodies. Because these bodies are sealed, the toxic enzymes and chemicals inside the cell do not leak out to damage the neighbors.[20]

Phagocytosis by neighboring cells without inflammation

Healthy cells usually have a lipid called phosphatidylserine on the inside of their membrane. During apoptosis, this lipid flips to the outside. This acts as an "eat-me" signal. Professional scavenger cells (macrophages) or neighboring cells recognize this signal and swallow the apoptotic bodies, a process often referred to as efferocytosis.[21]

BIOLOGICAL SIGNIFICANCE OF APOPTOSIS

Embryonic Development

Apoptosis plays a crucial role during development by removing unnecessary cells. Unlike necrosis, which involves tissue-wide swelling and membrane rupture due to injury, developmental cell death is characterized by pyknosis and the packaging of cellular components into membrane-enclosed vesicles for phagocytosis.[22] It drives the rearrangement of fetal membrane architecture *via* Fas-mediated signaling and regulates human trophoblast turnover through the Bcl-2 gene and Fas receptor.[23] A classic morphological example is limb morphogenesis, where apoptosis of interdigital cells facilitates the separation of fingers and toes.

Beyond mammalian development, apoptosis is the primary driver of large-scale body plan transitions in other species, such as the resorption of the tadpole tail during amphibian metamorphosis, a process synchronized by thyroid hormone triggers.[24] In humans, a similar large-scale physiological event occurs during the menstrual cycle; the shedding of the endometrial lining represents a massive wave of apoptosis triggered by the withdrawal of progesterone, demonstrating the mechanism's essential role in routine adult tissue remodeling and structural maintenance.[25]

Maintenance of Tissue Homeostasis

Apoptosis plays a central role in organ development and homeostasis by maintaining physiological balance through the controlled elimination of superfluous, damaged, or abnormal cells. This genetically regulated process ensures that cell proliferation is balanced by cell elimination, which is crucial for the overall health of multicellular organisms. Apoptosis is important in adult tissue turnover and for the removal of unwanted cells when a pathogen poses a threat.[26] Regardless of how a cell dies, for the organ to continue functioning normally, the cell must be removed before it can be replaced; phagocytosis by professional phagocytes must occur, and professional phagocytes have to generate ligands that

allow them to distinguish living cells from dying ones, and they also have to identify cells through the loss of inhibitory signals.[27] To distinguish this particular process, the term "efferocytosis" (from effero, "to carry to the grave") is used to describe the uptake of cells undergoing programmed or other forms of cell death, involving specific receptors and rapid intracellular digestion.[27]

In the context of aging, the precision of this homeostatic balance often shifts; when cells incur DNA damage, they may bypass apoptosis and enter a state of cellular senescence. Unlike apoptotic cells, which are cleanly removed via efferocytosis, senescent cells remain in the tissue and secrete pro-inflammatory cytokines, a state known as the Senescence-Associated Secretory Phenotype (SASP). This failure of the apoptotic program contributes to the chronic "inflammaging" and tissue dysfunction seen in older organisms.[28-30] Furthermore, the interaction between stem cells, particularly Mesenchymal Stem Cells (MSCs), and apoptosis further promotes the maintenance of homeostasis. MSCs contribute to homeostasis and tissue maintenance due to their ability to differentiate into various cell types, such as osteogenic, adipogenic, and chondrogenic lineages. Furthermore, these cells play a strategic role in local immunomodulation, which is vital for maintaining the stability of the cellular environment and counteracting adverse reactions during tissue regeneration.[26]

Impaired regulation of apoptosis disrupts this homeostatic balance, often leading to the onset of several human diseases, including developmental disorders, cancer, and autoimmune conditions. When the rate of apoptosis decreases, enhanced cell survival can lead to tumor proliferation, whereas excessive apoptosis can result in tissue degradation or neurodegeneration. Ultimately, the systematic destruction and phagocytosis of apoptotic bodies by surrounding cells allow for tissue remodeling and renewal without triggering an inflammatory response, thereby preserving the functional integrity of the organism.[26]

Immune System Regulation

Apoptosis is a physiological process of cell death that occurs as part of normal development and in response to a variety of physiological and pathophysiological stimuli. The effector mechanisms which carry out the death program are well preserved across species and evolution. Apoptosis is especially important in the immune system, where it plays significant roles in the control of the immune response, the deletion of immune cells recognizing self-antigens, and cytotoxic killing.[31]

This process is essential for all fundamental immune processes in T and B lymphocytes, acting as a mechanism to regulate the course of immune responses and to establish immunological memory, as well as central and peripheral tolerance. A critical quality-control checkpoint in this system is negative selection in the thymus; during T-cell maturation, any developing thymocytes that react too strongly to self-antigens are forced into apoptosis.[32] This serves as the primary safeguard against the survival of self-reactive lymphocytes that would otherwise cause systemic autoimmune destruction.[33] Consequently, apoptosis is tightly regulated by specific gene products that either induce or block cell death. Understanding the molecular basis for sensitivity and resistance to apoptosis is critical for elucidating the development of the immune system and the pathogenesis of diseases such as autoimmune disorders, AIDS, and cancer.[34] Ultimately, by eliminating infected or autoreactive immune cells, apoptosis prevents autoimmune diseases and maintains immune tolerance.

Cancer Prevention

Apoptosis serves as a critical defense mechanism against malignancy. Upon detection of DNA damage, the tumor suppressor protein p53 initiates programmed cell death to halt the proliferation of mutated cells. Consequently, the failure of these apoptotic pathways leads to uncontrolled cell growth and tumor formation. These hallmarks, uncontrolled growth, angiogenesis, and apoptosis evasion, are characteristic of all malignant cells. While the primary function of apoptosis is to eliminate damaged cells, the loss of this regulatory control allows mutated cells to persist. This extended lifespan facilitates the accumulation of further mutations that drive invasiveness and deregulate proliferation. By inhibiting caspase function or disabling apoptotic triggers, cancer cells achieve a universal hallmark of the disease. Therefore, targeting these pathways to either stimulate proapoptotic molecules or inhibit antiapoptotic ones remains a premier strategy for non-surgical cancer treatment.[35]

Current research focuses on B-cell Lymphoma 2 (BCL-2) inhibitors to restore the function of BAX and BAK, the core regulators of the intrinsic apoptotic pathway.[36] The Inhibitor of Apoptosis (IAP) family of proteins suppresses cell death by neutralizing both initiator and effector caspases. Specifically, the X-linked inhibitor of Apoptosis (XIAP) directly inhibits caspases-3, -7, and -9, thereby preventing the completion of the apoptotic cascade.[37] Additionally, alkylphospholipid analogs are under investigation for their ability to act as direct apoptotic signals by disrupting membrane integrity and signaling scaffolds. Identifying the most effective molecular targets among these diverse mechanisms remains the primary goal of clinical oncology research.[35]

Removal of Virus-Infected Cells

In a controlled and organized fashion, the body's immune system instigates apoptosis, which kills the virus-infected cell, so that the virus does not spread to other healthy cells.[4] Apoptosis is initiated in virus-infected cells before the virus has a chance to replicate, through either intrinsic (internal cell damage) or extrinsic (delivery of a signal by cytotoxic T lymphocytes that secrete caspase) mechanisms.[38] Once initiated, the cell breaks down into many small, separate fragments; subsequent to the death of the cell, phagocytic cells remove all of the cell's debris and do not cause inflammation, thereby neutralizing the threat and stabilizing the tissues.

Diseases Associated with Apoptosis Dysregulation

Dysregulation of programmed cell death is a primary driver in several pathological conditions. Excessive amounts of cell death (apoptosis) can cause the damage and eventual death of neurons associated with many neurodegenerative disorders like Alzheimer's and Parkinson's.[39] Conversely, when the process is inhibited or insufficient, abnormal cells can evade destruction, potentially resulting in the development of cancers, autoimmune diseases, or chronic viral persistence. Consequently, mapping these apoptotic pathways is a critical focus for designing targeted therapeutic interventions.[40,41]

Clinical Significance and Disease Pathology

Apoptosis is considered to be the "disease paragon" that maintains physiological homeostasis by regulating both cellular creation through division and cellular loss because of death, managing the constant generation of intestinal cells and the reduction in size of tissues, such as in the mammary gland, thymus, and adrenal glands. This process is essential for quality control during development, ensuring only cells with functional connections in the nervous system or specificities in the immune system survive. When functioning correctly, it serves as a critical defense mechanism by eliminating intracellular pathogens and newly developed cancer cells. Dying cells release antigens and signaling molecules that allow macrophages and dendritic cells to prime T-lymphocytes and B-cells for a targeted immune response. However, the organism's biological equilibrium is entirely dependent on the precision of this programmed cell death. As the body ages, the accuracy of apoptotic responses to DNA damage declines, increasing susceptibility to various pathologies. Cancer cells often evolve to evade this process through mutations, such as the overexpression of anti-apoptotic proteins like Bcl-2 or the inactivation of tumor suppressors like p53 by viruses such as HPV.[42] This decreased apoptosis rate enhances cell survival unnaturally, fostering tumor growth, cellular immortality, and autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis.

Excessive or uncontrolled apoptosis typically leads to systemic decay associated with the loss of essential cells. This overactivity is a hallmark of neurodegenerative disorders, including Alzheimer's, Parkinson's, Huntington's disease, and Amyotrophic Lateral Sclerosis (ALS). It also contributes to the depletion of immune cells in HIV and significant tissue damage in cardiovascular disorders, such as heart failure, stroke, and acute ischemic injuries triggered by the disruption of oxygen and nutrient delivery.[42,43] Overall, the health of an organism is represented by a fine-tuned state of dynamic equilibrium. A lack of apoptosis promotes malignancy, whereas an overabundance of apoptosis causes degeneration and loss of tissue. An organism will maintain biological integrity only when sufficient apoptosis is present to constrain malignant growth and allow for cellular immortality; however, excess programmed cell death can activate systemic decay and degeneration of tissue.

CONCLUSION

Apoptosis acts as a critical regulating factor that is necessary for proper embryonic development, maintaining tissue homeostasis, and removing injured or damaged cells. By utilizing distinct intrinsic and extrinsic signaling pathways, the body executes a programmed self-destruct mechanism, referred to as apoptosis, to remove unnecessary or risk-prone cells. The failure of either of these pathways continues to be a leading cause of various pathologies; thus, understanding the mechanism behind apoptosis is one of the major priorities of current cellular biology and clinical research.

ABBREVIATIONS

CD8+ T cells: Cytotoxic T lymphocytes; **MLKL:** Mixed lineage kinase domain-like pseudokinase; **RIPK3:** Receptor-interacting protein kinase-3; **BAX:** Bcl-2-associated X protein; **BAK:** Bcl-2 homologues antagonist/killer; **DNA:** Deoxyribonucleic acid; **TNF:** Tumor necrosis factor; **DISC:** Death-inducing signaling complex; **BID:** BH3-interacting domain death agonist; **PCD:** Programmed cell death; **PARP:** Proteolytic cleavage of the nuclear scaffold; **SASP:** Senescence-associated secretory phenotype; **IAP:** Inhibitor of apoptosis; **ALS:** Amyotrophic lateral sclerosis.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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