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Review Article

Apoptosis: A Symphony of Cellular Self-Destruction on Development and Disease

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Abstract

Apoptosis is a biological process that spontaneously removes unwanted cells from an organism during its early stages of development. It is triggered by several mechanisms, including as endoplasmic reticulum-mediated, mitochondrial-initiated, and extrinsic or cell surface death receptor mediated. Apoptosis can happen in pathological and physiological circumstances & as a result of infections, damaging stimuli, misfolded proteins, and DNA damage. It is necessary for the body to operate correctly and can be brought on by host immunological reactions or infections. Phagocytosis, DNA fragmentation, and protein digestion are all components of apoptosis biochemistry. This article provides an overview of apoptosis, a highly regulated cell death process that plays a crucial role in normal development, tissue homeostasis, and immune response. The article first defines apoptosis and discusses its importance in various physiological and pathological contexts. It then describes the different types of apoptosis, including intrinsic and extrinsic pathways, highlighting their specific mechanisms of activation and execution. The article also explores the intricate network of signalling molecules, such as caspases, Bcl-2 family proteins, and death receptors, that regulate apoptosis. Overall, this article aims to provide a comprehensive understanding of the intricate mechanisms and potential therapeutic approaches related to apoptosis.

Key words: dna damage; biological process; early stages; apoptosis; infection; immune response; normal development; cell death; cancer

1.Introduction

Apoptosis serves several important functions in the body. It is involved in embryonic development, helping to shape organs and structures by eliminating excessive or unnecessary cells. It is also crucial for maintaining tissue homeostasis, as it helps to remove damaged or abnormal cells that could potentially harm the overall tissue or organism. Additionally, apoptosis plays a role in the immune system, eliminating infected or cancerous cells, and in the regulation of cell populations in various physiological processes. Dysregulation of apoptosis can have serious consequences and is associated with numerous diseases. Insufficient apoptosis can result in uncontrolled cell growth and contribute to the development of cancer. On the other hand, excessive apoptosis can lead to degenerative diseases characterized by excessive cell death, such as neurodegenerative disorders. In summary, apoptosis is a highly regulated process that plays a essential role in maintaining the health and proper functioning of multicellular organisms. By eliminating damaged or harmful cells, apoptosis ensures the overall well-being and integrity of tissues and organs.

2.Definition of Apoptosis:

Apoptosis is a natural biological process that occurs in all multicellular organisms, including plants and animals, to remove unwanted cells from the body. It plays a crucial role in human development and maintaining a healthy immune system. On average, 50-80 billion cells die daily in a human adult due to apoptosis, eliminating infected, pre-cancerous, and cancer cells, and maintaining cell balance. [1,2]

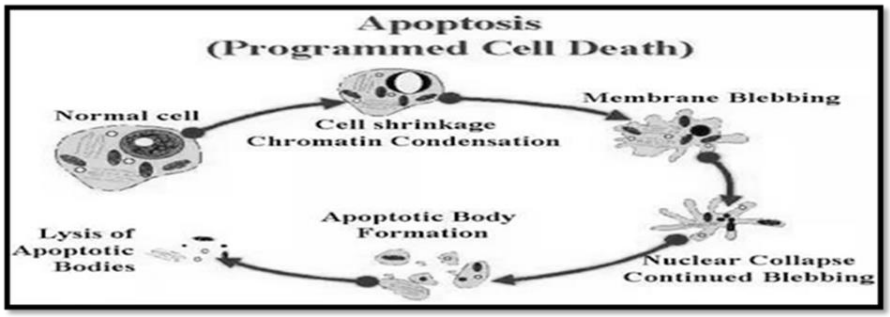

Figure 1: Apoptosis Process [5]

3. Characteristics of Apoptosis:

Induction of Apoptosis:

Extrinsic or cell surface death receptor mediated pathway. Mitochondrial –initiated pathway(intrinsic). Endoplasmic reticulum (intrinsic) [3]

Morphology of Apoptosis:

Shrinkage of cells. The most defining property is chromatin condensation. Development of apoptotic structures and cytoplasmic blebs. Macrophages' phagocytosis of apoptotic cells or cell bodies. The plasma membrane is unbroken until the very end. Inflammation is not induced by apoptosis [4]

4.Causes of Apoptosis:

4.1Apoptosis in Physiological situations:

Apoptosis occurs in physiological situations, including development and embryogenesis, endometrial cell loss, nursing breast regression, intestinal crypt epithelia, lymphocytes and neutrophils, and cytotoxic T-cell-induced cell death. It is necessary for normal cell and tissue formation, hormone-dependent tissue, and defense against viruses and tumors.[6]

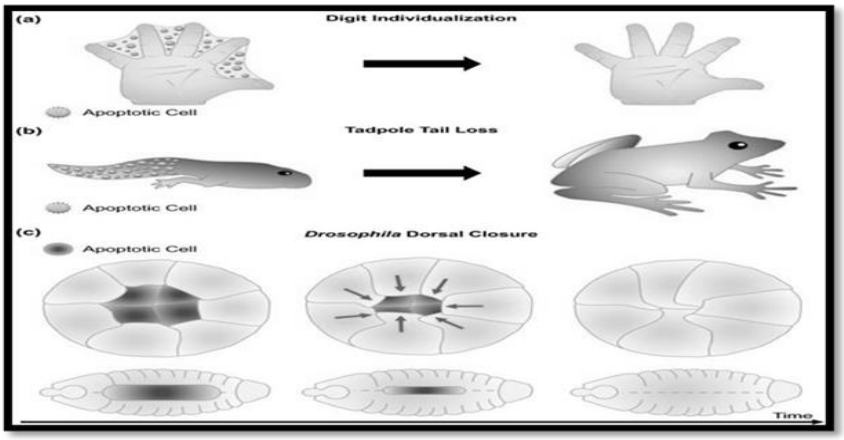

Figure 2: Physiological Apoptosis [7]

4.2Apoptosis Pathologic Conditions:

DNA damage:

Radiation, cytotoxic medications, temperature extremes, and hypoxia can damage DNA, leading to necrotic cell death. If repair mechanisms fail, cell apoptosis may occur, potentially causing malignant transformation, requiring cell elimination. [6]

Accumulation of Misfolded Protein:

Improperly folded proteins can arise from mutations in the genes encoding these proteins or from extrinsic factors such as free radical damage. Excessive accumulation of these proteins in the ER causes a condition known as ER stress, which culminates in apoptosis of cells. [6]

Cell Injury in certain Infections, particularly Viral Infections:

• Loss of infected cells is largely due to apoptotic death • That may be induced by the virus (As in Adenovirus & Human Immunodeficiency virus infections) • Or By the host Immune response (as in Viral Hepatitis) [6]

5.Apoptosis Biochemistry:

Protein Digestion (Caspases):

Protein-protein cross-linking, cytoskeletal protein proteolysis, DNA breakdown, nuclear chromatin fragmentation, and phagocytosis are key processes in apoptosis, allowing macrophages to recognize and initiate inflammatory cell responses. [7]

Steps involved in the programmed cell death:

Enzymes in cells consume proteins, rounding the cell, splitting DNA, and contracting the nuclear membrane, leading to apoptosis and the degeneration of the cell's nuclear membrane.[7]

6.Types of Apoptosis:

6.1 Intrinsic Pathway:

Cells undergo intrinsic apoptotic pathway when exposed to stressors like low oxygen levels, elevated ROS, or DNA damage. This leads to the cleavage of initiator caspases in mitochondria and endoplasmic reticulum, activating downstream effector caspases, ultimately causing cell death. [8]

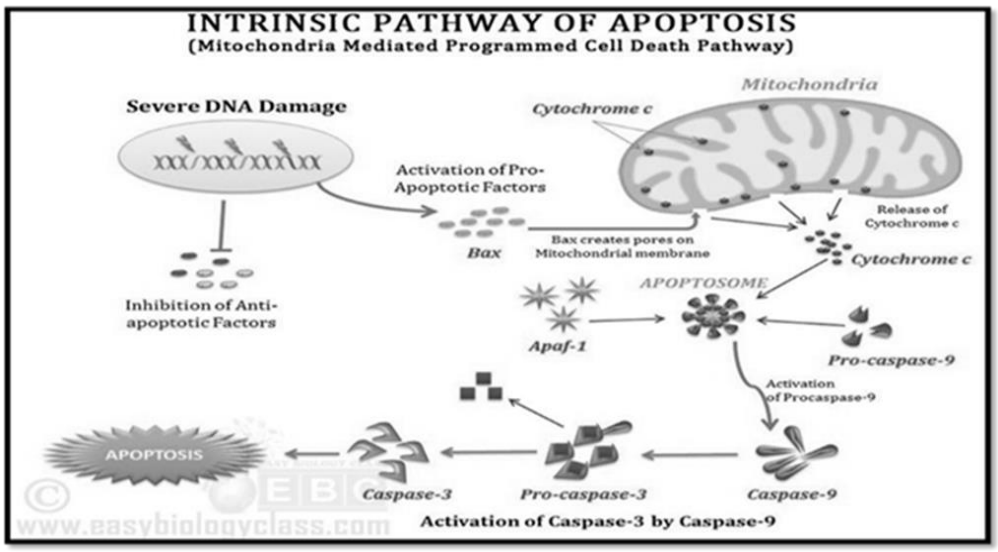

Figure 3: Intrinsic pathway of apoptosis [8]

6.2 Extrinsic Pathway:

The binding of a death ligand to a death receptor on the cell membrane initiates the extrinsic pathway of apoptosis. FAS and TNF receptors are death receptors that are triggered by FAS or TNF ligands. Initiator caspases within the cytoplasm are cleaved upon activation of these receptors. Cell death results from this activating downstream effector caspases. [8]

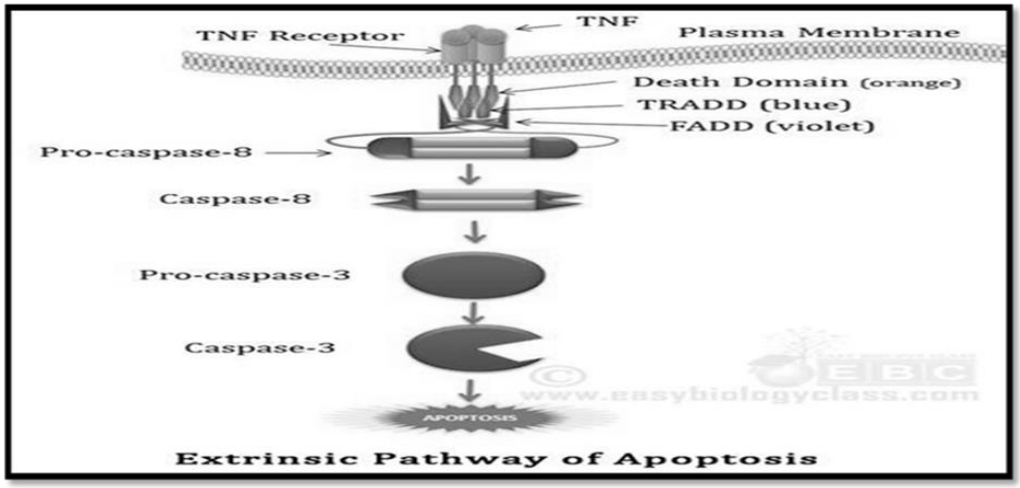

Figure 4: Extrinsic Pathway of Apoptosis [8]

6.3 Steps involved in the programmed cell death:

When the required enzymes begin to function in the cell, they consume the proteins, causing the cell to round out. The DNA inside the nucleus begins to split and finally contracts.The nuclear membrane that surrounds the nucleus of a cell degrades and becomes detached from it when apoptosis begins. [7]

7.Caspases:

A stands for aspartic acid, and C for cysteine. ASE for the Enzyme-Protease name. A class of proteolytic or protein-splitting enzymes known as caspases function. The key player in the transduction of apoptotic signals is caspases. Two varieties of caspases exist: 8, 10, 9, 2, and effector caspases caspase [3, 7, 6.] When initiator caspases bind to a particular oligometric adaptor protein, they become active. These initiator caspases then cleave proteins to activate effector caspases. The cell death program is then carried out.[8]

8.Mechanism of Apoptosis:

The apoptosis consists of 3 steps:

8.1 Initiation of Apoptosis:

Apoptosis Including Factor (AIF) triggers apoptosis by acting either extracellularly or intracellularly on the cell membrane, thereby initiating the intrinsic and extrinsic pathways. The AIF are as follows:

Retraction of signals necessary for regular cell survival (e.g., lack of growth hormone, cytokines) Retraction of extracellular signals: FAS receptor activation associated with TNF-R family. Intracellular Stimuli: primarily DNA damage, heat, radiation, and hypoxia. [9]

8.2 Process of Programmed cell death:

Once the cell switched on to self-destruct mode, the programme in-built in the cell will activated:

8.2.1Caspases activation:

Caspases are a class of proteolytic enzymes that act on proteins found in organelles and nuclear proteins. [9]

8.2.2 Death Receptor Activation:

Activation of caspases activates FAS receptor (CD95), a cell surface receptor found on cytotoxic CD8+ T cells that is a member of the TNF-R (tumor necrosis factor receptors) family.

FAS is also referred to as the "death receptor" because it activates particular growth-regulating genes, such as Bcl-2 and P52, when it comes into contact with a particular AIF. (Thus, the Death receptor pathway is the one that develops from FAS activation.). [9]

8.2.3 Activation of Development Regulating pathways of gene/cell death: Pathway of Death Receptor (Extrinsic Pathway):

o TNF-R and CD95 members' stimulation, which further activates caspase 8. Caspases 3 and the effector stage of apoptosis are triggered by this.

Mitochondrial pathway (Intrinsic Pathway):

Triggered by endogenous factors like DNA damage, which subsequently leads to p53 protein transcription and activation of the Bcl-2 gene family (found in the outer membrane of mitochondria). Bcl-2 contains both pro-apoptic members (like BASX, BAK, and BAD) and inhibitors of apoptosis (like BCL-XL), which prevent apoptosis from occurring. The final step involves the release of mitochondrial cytochrome C, which then combines with protein Apaf-1 to form an Apoptosome.

This combination of proteins—Procaspase 9, cytochrome C, and Apoptotic protease act6ivating factor -1<Apaf-1>—activates caspase 9, which in turn activates caspase 3 and starts the effect stage of apoptosis. P53 has the ability to induce apoptosis in itself. [9]

Cell Death (Effector Stage):

Degradation of the cytoskeleton, disruption of the endoplasmic reticulum, disruption of the nucleus, mitochondrial damage, and disruption of the cell membrane will all occur.

8.3 Phagocytosis:

The dead apoptotic cells develop membrane changes which promote their phagocytosis. Phosphatidylserine & Thrombospondin molecules will appear on the outer surface of the cells in apoptosis which facilitate their identification by adjacent phagocytes. So, it will not initiate any inflammatory response. [19]

9.Significance of Apoptosis:

It aids in keeping multicellular organisms' homeostasis intact. Apoptosis keeps the body at the appropriate size.

In an organism, apoptosis keeps the number of cells constant. The process of apoptosis rids the body of the undesirable cells. Apoptosis eliminates the harmful T-lymphocytes. Cell development depends on programmed cell death. [10]

10.Role of Apoptosis

Apoptosis is the cause of the fingers splitting apart during fetal development. The dorsal portion of the neural tube closes as a result. The immune system depends on apoptosis, which is crucial for immune response regulation, immune cell recognition of self-antigen elimination, and cytotoxic killing. Cell death eliminates the Wolffian ducts during the fetal sex determination process. Apoptosis in the uterus permits the excision of tissues unnecessary to the bladder and umbilicus. [10]

11.Implication in disease

11.1 Faulty routes

There are numerous distinct biochemical components found in the various forms of apoptotic pathways, many of which are still unknown.[11]

Altering apoptotic pathways can cause diseases or disorders, as seen in lung cancer NCI-H460. While discussing every disease caused by altered pathways is impractical, the general idea remains. [12]

The H460 cell line overexpresses X-linked inhibitor of apoptosis protein (XIAP), reducing proapoptotic agonists and causing cells to proliferate. Abnormalities in apoptosis regulation in cancer cells, such as NF-κB, alter transcriptional regulation and response to apoptotic signals, potentially facilitating cancer spread..[13]

11.1.1 Dysregulation of p53

Dysregulation of p53, a tumor-suppressor protein, can lead to cancer cell apoptosis and impaired apoptosis.[13] This is triggered by alpha- and beta-interferons, which stimulate p53 gene transcription and increase protein levels. Interference with p53 or interferon genes can cause tumor formation.[14])

11.1.2` Inhibition

Inhibition of apoptosis can lead to various cancers, inflammatory illnesses, and viral infections. Cell accumulation is caused by decreased cell death, not increasing cellular proliferation. Cancer is a common example, characterized by overexpression of IAP family members and mutations in cycle-regulating genes, causing abnormal cell responses to apoptosis. [15]. The "Warburg hypothesis" suggests a link between cancer cell apoptosis pathological inactivation and frequent respiratory metabolic shifts towards glycolysis. [16]

11.2 HeLa cell

HeLa cells produce inhibitory proteins that target tumor-suppressive proteins in retinoblastoma. [36] These proteins, expressed by the human papillomavirus (HPV), cause cervical tumors. [18,19]. HPV E6 and E7 disrupt p53, causing cell cycle regulator p53 to become dormant, and preventing apoptosis, thereby preserving HeLa cell immortality [20].

11.2.1Treatments

MiCK test

The MiCK test is a tool used to assess the susceptibility of diseased cells to apoptosis, which is the main treatment strategy for signaling-related diseases. Therapies can increase or decrease apoptosis susceptibility, depending on the cause. Examples include increasing death receptor ligands, blocking anti-apoptotic pathways, and introducing Smac mimetics.[21] Apoptosis is a multi-step process in the body, and cancer treatment primarily targets cells through apoptosis.[22].

11.3 Hyperactive apoptosis

However, loss of control over cell death (excess apoptosis) can result in tissue damage, hematologic disorders, and neurodegenerative diseases. In neurodegenerative diseases like Alzheimer's and Parkinson's, neurons that depend on mitochondrial respiration die a phenomenon called the "Inverse Warburg hypothesis"[23][25]. Moreover, eurodegenerative illnesses and cancer have an inverse epidemiological comorbidity [24]. Excessive apoptosis in HIV-positive patients is linked to abnormal signaling pathways controlling the Bcl-2 family of proteins. This leads to

increased expression of apoptotic proteins like BIM, resulting in cell death and various pathologies. Cancer cells can evade apoptosis by inhibiting BIM expression or increasing proteolysis, thereby affecting the progression of HIV.

11.3.1Treatments

HIV progression

HIV progression into AIDS is primarily due to the rapid depletion of CD4+ T-helper lymphocytes, leading to a compromised immune system[26]]. Apoptosis is a key mechanism, triggered by various biochemical pathways. HIV enzymes make cells anti-apoptotic, preparing them for apoptosis [29]. HIV proteins reduce the CD4 glycoprotein marker on cell membranes, and viral particles can cause "bystander" T helper cells to undergo apoptosis.[27]

Researchers from Kumamoto University have developed a new method called "Lock-in and apoptosis" to eradicate HIV in viral reservoir cells. However, this approach is not yet available to HIV patients, as further research is needed to combine existing drug therapy with this approach[28].

11.4Viral infection

A virus infects living cells, causing apoptosis through viral induction, which is crucial for normal cell development, cycle maturation, and maintaining cell operations.

•Viral infections can cause infected cells to undergo apoptosis through a variety of mechanisms, such as:

Binding of receptors

Protein kinase R (PKR) activation;

11.4.1 P53 interaction

The canine distemper virus (CDV) induces apoptosis in both in vivo and in vitro central nervous systems and lymphoid tissue of infected dogs through the extrinsic pathway, which triggers caspases that impair cellular function and ultimately result in cell death [30,31]. The Oropouche virus (OROV) is a zoonotic arbovirus that disrupts cultured cells, such as HeLa cells, and requires viral uncoating, viral internalization, and cell replication. Proteins that can prevent apoptosis are encoded by numerous viruses, such as Bcl-2 homologs, caspase inhibitors, and p53 inhibitors [32]. These proteins bind to p53 and prevent its transcriptional transactivation activity, preventing the production of proapoptotic protein [33]. s However, viruses can survive apoptosis, especially in the latter phases of infection, as phagocytes consume apoptotic bodies that separate from the dying cell's surface, preventing the host response from starting and encouraging the infection to propagate. Neurons may also undergo apoptosis due to prions[34,35].

Apoptosis in OROV requires viral uncoating, internalisation, and cell replication. Some viruses respond to external stimuli, while others activate it via intracellular cues and mitochondria[33]. Many viruses encode proteins that prevent apoptosis, such as Bcl-2 homologs, caspase inhibitors, and p53 inhibitors[36,37]. These proteins block proapoptotic proteins, such as BAK and BAX, and prevent TNF and Fas from triggering reactions[38]. Viruses can survive apoptosis, especially in the latter phases of infection, by exporting apoptotic bodies and phagocytes. Neurons may also undergo apoptosis due to prions. [39]

11.5 Plants

Caspase inhibitors enable the assessment of biological processes containing active caspases. In the absence of caspase activation, cells can still have apoptotic morphology. This behavior is linked to mitochondrial release of AIF and its NLS-mediated translocation into the nucleus. [40]

12. Conclusion

In conclusion, apoptosis is a highly regulated and crucial process in maintaining cellular balance and homeostasis. It plays a fundamental role in embryonic development, tissue remodelling, and immune system regulation. Through various signalling pathways and cellular mechanisms, apoptosis ensures the removal of unwanted or damaged cells, preventing the accumulation of potentially harmful substances, in this article Intrinsic & Extrinsic pathway are also explained details with proper figures. This article is involves with the discussion of cause, biochemistry, types, significance, role, implication in disease of apoptosis. Besides this, apoptosis acts as a defense mechanism against the development of cancer, as it eliminates cells with DNA damage or unrestrained proliferation. The dysregulation of apoptosis can lead to severe health implications, such as autoimmune diseases, neurodegenerative disorders, and cancer. Thus, a comprehensive understanding of the apoptotic process is essential for therapeutic advancements and medical interventions aimed at modulating cell death to alleviate diseases. Further research into apoptosis and its intricate mechanisms holds promise for improved treatments and potential breakthroughs in combating various illnesses.

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