Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)
www.ajprd.com
ISSN 2320-4850

Review Article

# A BRIEF REVIEW ON APOPTOSIS

**ANKIT*, RANU SHARMA, SURYA PRATAP SINGH, M. P. KHINCHI**

Department of Pharmacology, Kota College of Pharmacy, Kota, Rajasthan, India

***ABSTRACT***

*Apoptosis is a cell death mechanism characterized by depolymerization of cytoskeleton, cell shrinkage, chromatin condensation, nuclear fragmentation and translocation of phosphatidylserine to the cell surface. This process is therefore called programmed cell death. Between 50 and 70 billion cells die each day due to apoptosis in the average human adult. Apoptosis and necrosis are considered to be distinct modes of cell death; however, apoptosis can progress to secondary necrosis if apoptotic cells are not efficiently removed by phagocytic cells. During the last decade, exceptional for the basic research, the apoptosis have attracted many attentions due to its potential application in therapying the various human diseases. . In diseases caused by deficient apoptosis, such as cancer, viral latency and autoimmunity, methods of producing selective apoptosis are being sought*

***Keywords:*** *depolymerisation, cytoskeleton, chromatin condensation, necrosis, phagocytic cell.*

## INTRODUCTION

Apoptosis is a cell death mechanism characterized by depolymerization of cytoskeleton, cell shrinkage, chromatin condensation, nuclear fragmentation and translocation of phosphatidylserine to the cell surface. Apoptosis arises from a number of stimuli that initiate multiple signaling pathways which lead to caspase cascade activation and cell death. Increases in apoptotic activity are hallmarks of several disease states including AIDS, neurodegenerative disorders, insulin-dependent diabetes, myocardial infarction and atherosclerosis. .[1]

***Corresponding author***
***Ankit Sharma***
*Kota College of Pharmacy,*
*Kota, Rajasthan*
*E mail: ankitsharmanik2012@gmail.com*
*Mobile – 7597306841*

The cells of a multicellular organism are members of a highly organized community. The number of cells in this community is tightly regulated—not simply by controlling the rate of cell division, but also by controlling the rate of cell death. If cells are no longer needed, they commit suicide by activating an intracellular death program. This process is therefore called programmed cell death.[2] Unlike necrosis, apoptosis produces cell fragments called apoptotic bodies that phagocytic cells are able to engulf and quickly remove before the contents of the cell can spill out onto surrounding cells and cause damage to the neighbouring cells.[3] Between 50 and 70 billion cells die each day due to apoptosis in the average human adult. For an average child between the ages of 8 and 14, approximately 20 billion to 30 billion cells die a day.[4] Research on apoptosis has increased substantially since the early 1990s. In addition to its importance as a

biological phenomenon, defective apoptotic variety of diseases. Excessive apoptosis causes atrophy, whereas an insufficient amount results in uncontrolled cell proliferation, such as cancer. Some factors like Fas receptors and caspases promote apoptosis, while some members of the Bcl-2 family of proteins inhibit apoptosis. Because apoptosis cannot stop once it has begun, it is a highly regulated process. Apoptosis can be initiated through one of two pathways. In the intrinsic pathway the cell kills itself because it senses cell stress, while in the extrinsic pathway the cell kills itself because of signals from other cells. Both pathways induce cell death by activating caspases, which are proteases, or enzymes that degrade proteins. The two pathways both activate initiator caspases, which then activate executioner caspases, which then kill the cell by degrading proteins indiscriminately.

Apoptosis and necrosis are considered to be distinct modes of cell death; however, apoptosis can progress to secondary necrosis if apoptotic cells are not efficiently removed by phagocytic cells.In contrast to necrosis, which is a form of traumatic cell death that results from acute cellular injury, apoptosis is a highly regulated and controlled process that confers advantages during an organism's lifecycle. For processes have been implicated in a wide example, the separation of fingers and toes in a developing human embryo occurs because cells between the digits undergo apoptosis.[5]

## PATHWAYS

The mechanisms of apoptosis are highly complex and sophisticated, involving an energy-dependent cascade of molecular events. To date, research indicates that there are two main apoptotic pathways: the extrinsic or death receptor pathway and the intrinsic or mitochondrial pathway. However, there is now evidence that the two pathways are linked and that molecules in one pathway can influence the other. There is an additional pathway that involves T-cell mediated cytotoxicity and perforin-granzyme-dependent killing of the cell. The perforin/granzyme pathway can induce apoptosis via either granzyme B or granzyme A. The extrinsic, intrinsic, and granzyme B pathways converge on the same terminal, or execution pathway. This pathway is initiated by the cleavage of caspase-3 and results in DNA fragmentation, degradation of cytoskeletal and nuclear proteins, cross-linking of proteins, formation of apoptotic bodies, expression of ligands for phagocytic cell receptors and finally uptake by phagocytic cells. The granzyme A pathway activates a parallel, caspase-independent cell death pathway via single stranded DNA damage.[6]

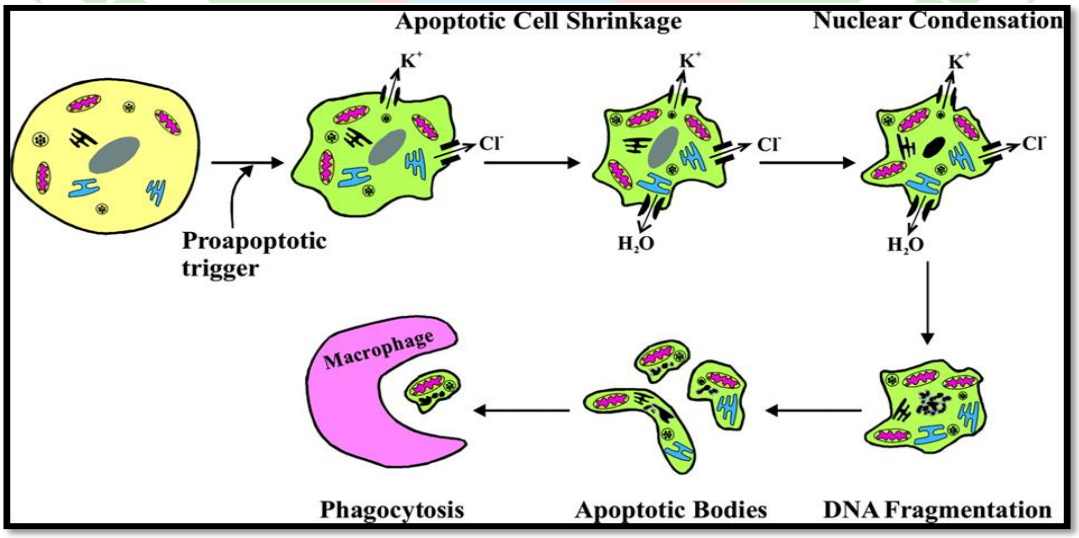


**Fig.1 Normal apoptosis process**

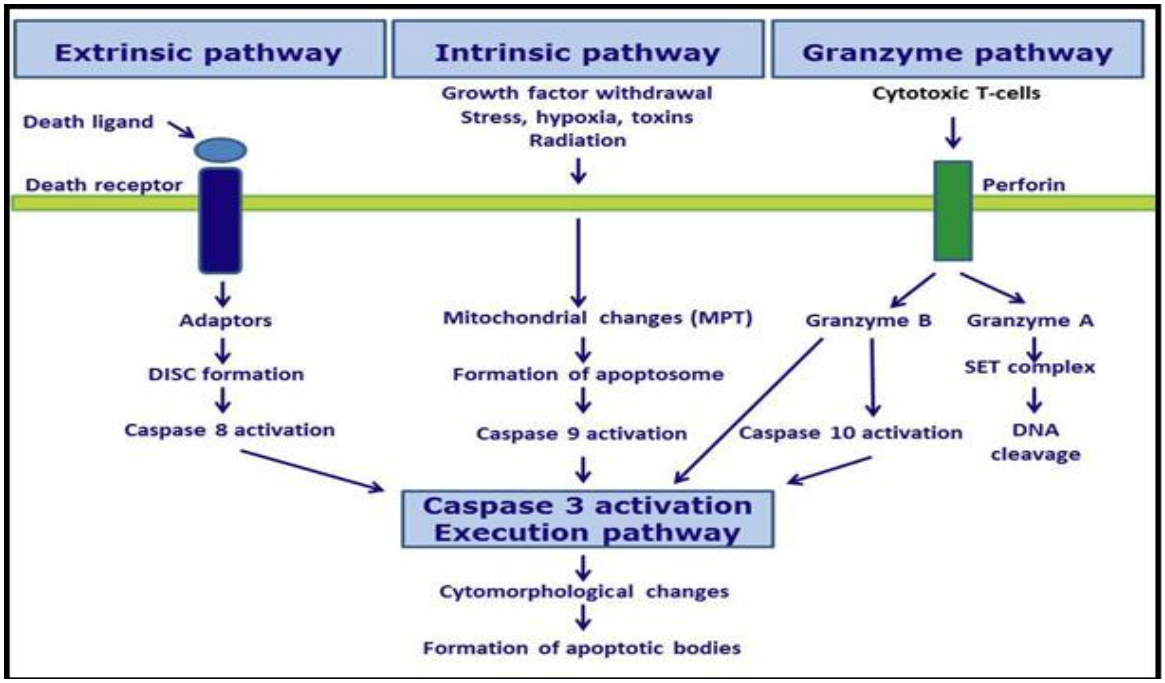


**Figure 2 : Apoptotic Pathway By Different Pathways**

- **Intrinsic Pathway**

The intrinsic signaling pathways that initiate apoptosis involve a diverse array of non-receptor-mediated stimuli that produce intracellular signals that act directly on targets within the cell and are mitochondrial-initiated events. The stimuli that initiate the intrinsic pathway produce intracellular signals that may act in either a positive or negative fashion. Negative signals involve the absence of certain growth factors, hormones and cytokines that can lead to failure of suppression of death programs, thereby triggering apoptosis. In other words, there is the withdrawal of factors, loss of apoptotic suppression, and subsequent activation of apoptosis. Other stimuli that act in a positive fashion include, but are not limited to, radiation, toxins, hypoxia, hyperthermia, viral infections, and free radicals. The mitochondria are essential to multicellular life. Without them, a cell ceases to respire aerobically and quickly dies. This fact forms the basis for some apoptotic pathways. Apoptotic proteins that target mitochondria affect them in different ways. They may cause mitochondrial swelling through the formation of membrane pores, or they may increase the permeability of the mitochondrial membrane and cause apoptotic effectors to leak out.[7][8]

- ***Extrinsic Pathway***

Two theories of the direct initiation of apoptotic mechanisms in mammals have been suggested: the TNF-induced (tumor necrosis factor) model and the Fas-Fas ligand-mediated model, both involving receptors of the TNF receptor (TNFR) family[9] coupled to extrinsic signals.

- **TNF path**

TNF-alpha is a cytokine produced mainly by activated macrophages, and is the major extrinsic mediator of apoptosis. Most cells in the human body have two receptors for TNF-alpha: TNFR1 and TNFR2. The binding of TNF-alpha to TNFR1 has been shown to initiate the pathway that leads to caspase activation via the intermediate membrane proteins TNF receptor-associated death domain (TRADD) and Fas-associated death domain protein (FADD). cIAP1/2 can inhibit TNF-α signaling by binding to TRAF2. FLIP inhibits the activation of caspase-8.[10] Binding of this receptor can also indirectly lead to the activation of transcription factors involved in cell survival and inflammatory responses. However, signalling through TNFR1 might also induce apoptosis in a caspase-independent manner.[35]The link

between TNF-alpha and apoptosis shows why an abnormal production of TNF-alpha plays a fundamental role in several human diseases, especially in autoimmune diseases.

- **Fas path**

The fas receptor (First apoptosis signal) – (also known as Apo-1 or CD95) is a transmembrane protein of the TNF family which binds the Fas ligand (FasL). The interaction between Fas and FasL results in the formation of the death-inducing signaling complex (DISC), which contains the FADD, caspase-8 and caspase-10. In some types of cells (type I), processed caspase-8 directly activates other members of the caspase family, and triggers the execution of apoptosis of the cell. In other types of cells (type II), the Fas-DISC starts a feedback loop that spirals into increasing release of proapoptotic factors from mitochondria and the amplified activation of caspase-8.[10]

- ***Perforin/granzyme Pathway***

T-cell mediated cytotoxicity is a variant of type IV hypersensitivity where sensitized CD8+ cells kill antigen-bearing cells. These cytotoxic T lymphocytes (CTLs) are able to kill target cells via the extrinsic pathway and the FasL/FasR interaction is the predominant method of CTL-induced apoptosis. However, they are also able to exert their cytotoxic effects on tumor cells and virus-infected cells via a novel pathway that involves secretion of the transmembrane pore-forming molecule perforin with a subsequent exophytic release of cytoplasmic granules through the pore and into the target cell. The serine proteases granzyme A and granzyme B are the most important component within the granules .

Granzyme B will cleave proteins at aspartate residues and will therefore activate procaspase-10 and can cleave factors like ICAD (Inhibitor of Caspase Activated DNAse) . Reports have also shown that granzyme B can utilize the mitochondrial pathway for amplification of the death signal by specific cleavage of Bid and induction of cytochrome *c* release. However, granzyme B can also directly activate caspase-3. In this way, the upstream signaling pathways are bypassed and there is direct induction of the execution phase of apoptosis.

- **Execution Pathway**

The extrinsic and intrinsic pathways both end at the point of the execution phase, considered the final pathway of apoptosis. It is the activation of the execution caspases that begins this phase of apoptosis. Execution caspases activate cytoplasmic endonuclease, which degrades nuclear material, and proteases that degrade the nuclear and cytoskeletal proteins. Caspase-3, caspase-6, and caspase-7 function as effector or "executioner" caspases, cleaving various substrates including cytokeratins, PARP, the plasma membrane cytoskeletal protein alpha fodrin, the nuclear protein NuMA and others, that ultimately cause the morphological and biochemical changes seen in apoptosis.

Caspase-3 is considered to be the most important of the executioner caspases and is activated by any of the initiator caspases (caspase-8, caspase-9, or caspase-10). Caspase-3 specifically activates the endonuclease CAD. In proliferating cells CAD is complexed with its inhibitor, ICAD. In apoptotic cells, activated caspase-3 cleaves ICAD to release CAD. CAD then degrades chromosomal DNA within the nuclei and causes chromatin condensation. Caspase-3 also induces cytoskeletal reorganization and disintegration of the cell into apoptotic bodies. Gelsolin, an actin binding protein, has been identified as one of the key substrates of activated caspase-3.

## *BIOCHEMICAL FEATURES*

Apoptotic cells exhibit several biochemical modifications such as protein cleavage, protein cross-linking, DNA breakdown, and phagocytic recognition that together result in the distinctive structural pathology described previously.[11] Caspases are widely expressed in an inactive proenzyme form in most cells and once activated can often activate other procaspases, allowing initiation of a protease cascade. Some procaspases can also aggregate and autoactivate. This proteolytic cascade, in which one caspase can activate other caspases, amplifies the apoptotic signaling pathway and thus leads to rapid cell death.

Caspases have proteolytic activity and are able to cleave proteins at aspartic acid residues, although different caspases have different specificities involving recognition of neighboring amino acids. Once caspases are initially activated, there seems to be an irreversible commitment towards cell death. To date, ten major caspases have been identified and broadly categorized into initiators (caspase-2,-8,-9,-10). effectors or executioners (caspase-3,-6,-7) and inflammatory caspases (caspase-1,-4,-5). The other caspases that have been identified include caspase-11, which is reported to regulate apoptosis and cytokine maturation during septic shock, caspase-12, which mediates endoplasmic-specific apoptosis and cytotoxicity by amyloid-*β*, caspase-13, which is suggested to be a bovine gene, and caspase-14, which is highly expressed in embryonic tissues but not in adult tissues

Extensive protein cross-linking is another characteristic of apoptotic cells and is achieved through the expression and activation of tissue transglutaminase . DNA breakdown by $Ca^{2+}$-and $Mg^{2+}$-dependent endonucleases also occurs, resulting in DNA fragments of 180 to 200 base pairs. A characteristic "DNA ladder" can be visualized by agarose gel electrophoresis with an ethidium bromide stain and ultraviolet illumination.

Another biochemical feature is the expression of cell surface markers that result in the early phagocytic recognition of apoptotic cells by adjacent cells, permitting quick phagocytosis with minimal compromise to the surrounding tissue. This is achieved by the movement of the normal inward-facing phosphatidyl serine of the cell's lipid bilayer to expression on the outer layers of the plasma membrane. Although externalization of phosphatidyl serine is a well-known recognition ligand for phagocytes on the surface of the apoptotic cell, recent studies have shown that other proteins are also be exposed on the cell surface during apoptotic cell clearance. These include Annexin I and calreticulin.

Annexin V is a recombinant phosphatidylserine-binding protein that interacts strongly and specifically with phosphatidylserine residues and can be used for the detection of apoptosis. Calreticulin is a protein that binds to an LDL-receptor related protein on the engulfing cell and is suggested to cooperate with phosphatidylserine as a recognition signal.[12] The adhesive glycoprotein, thrombospondin-1, can be expressed on the outer surface of activated microvascular endothelial cells and, in conjunction with CD36, caspase-3-like proteases and other proteins, induce receptor-mediated apoptosis.

## PROTEOLYTIC CASPASE CASCADE

Many pathways and signals lead to apoptosis, but these converge on a single mechanism that actually causes the death of the cell. After a cell receives stimulus, it undergoes organized degradation of cellular organelles by activated proteolytic caspases. In addition to the destruction of cellular organelles, mRNA is rapidly and globally degraded by a mechanism that is not yet fully characterized[13]. mRNA decay is triggered very early in apoptosis. A cell undergoing apoptosis shows a characteristic morphology:

- Cell shrinkage and rounding are shown because of the breakdown of the proteinaceous cytoskeleton by caspases.
- The cytoplasm appears dense, and the organelles appear tightly packed.
- Chromatin undergoes condensation into compact patches against the nuclear envelope (also known as the perinuclear envelope) in a process known as pyknosis, a hallmark of apoptosis.
- The nuclear envelope becomes discontinuous and the DNA inside it is fragmented in a process referred to as karyorrhexis. The nucleus breaks into several discrete *chromatin bodies* or *nucleosomal units* due to the degradation of DNA.
- The cell membrane shows irregular buds known as blebs.
- The cell breaks apart into multiple vesicles called *apoptotic bodies*, which are then phagocytosed.

Apoptosis progresses quickly and its products are quickly removed, making it difficult to detect or visualize. During karyorrhexis,

endonuclease activation leaves short DNA fragments, regularly spaced in size. These give a characteristic "laddered" appearance on agar gel after electrophoresis[14] Tests for DNA laddering differentiate apoptosis from ischemic or toxic cell death.

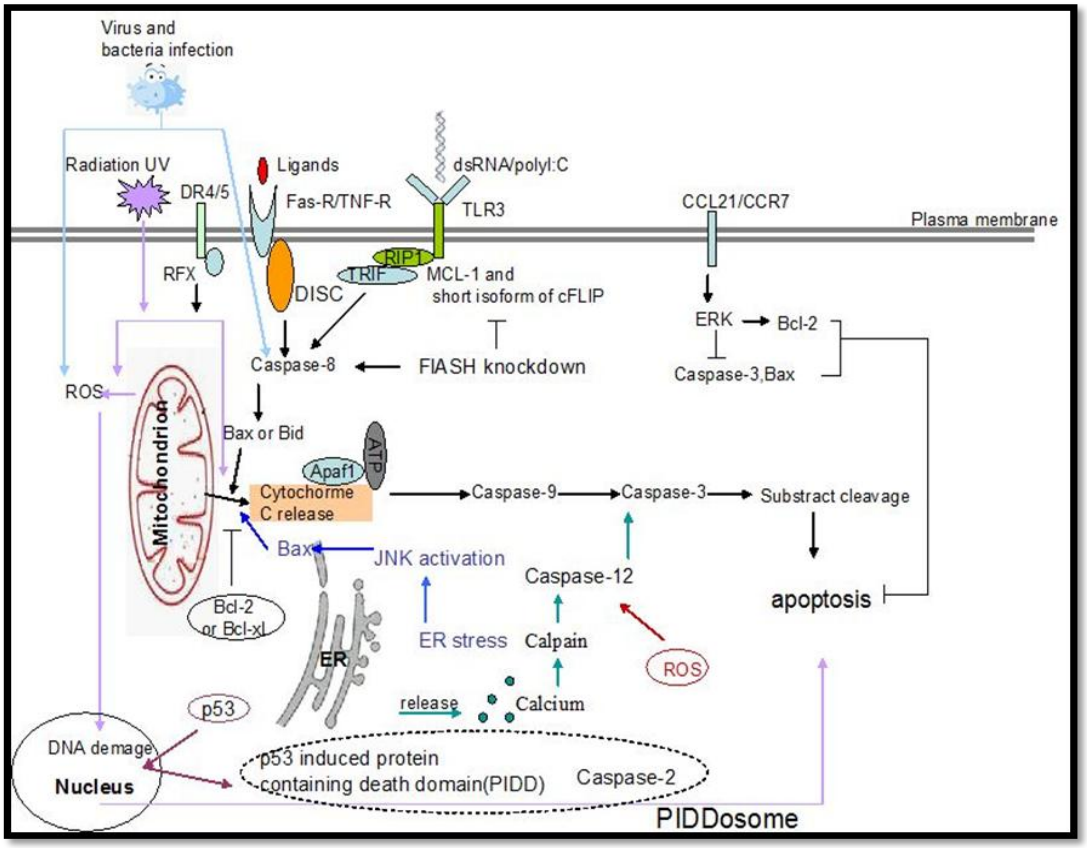


**Fig 3 : Degradation of cellular organelles by activated proteolytic caspases**

***Methods for Distinguishing Apoptotic From Necrotic Cells***

In order to perform analysis of apoptotic versus necrotic (necroptotic) cells, one can do analysis of morphology by time-lapse microscopy[15], flow fluorocytometry, and transmission electron microscopy. There are also various biochemical techniques for analysis of cell surface markers (phosphatidylserine exposure versus cell permeability by flow fluorocytometry), cellular markers such as DNA fragmentation[55] (flow cytometry), caspase activation, Bid cleavage, and cytochrome c release (Western blotting). It is important to know how primary and secondary necrotic cells can be distinguished by analysis of supernatant for caspases, HMGB1, and release of cytokeratin 18. However, no distinct surface or biochemical markers of necrotic cell death have been identified yet, and only negative markers are available. These include absence of apoptotic markers (caspase activation, cytochrome c release, and oligonucleosomal DNA fragmentation) and differential kinetics of cell death markers (phosphatidylserine exposure and cell membrane permeabilization).

***Trigger Apoptosis Ligands and Cell Environment Materials***

Apoptosis, as a major cell death procession for healthy, play an important role in homeostasis of whole life. In the period of fetation, apoptosis happened, as the essential affair for the finger and toe formation. due the cells between fingers occured apoptosis, we can form five fingers per hand. Apoptosis also can enhance embryonic stem

cell survival during stress by increased expression Bcl-2 protein which significantly weaken the apoptosis and help colony formation ,Apoptosis also take part in some tissues regeneration and homeostasis.[16]

## EXTRINSIC CELL MATERIALS

- **Cytokines**

TNF-alpha plus z-VAD can trigger cell apoptosis, and this method is well-known in creating cell apoptosis model. TNF-alpha can bind to extracellular domain of TNF-alpha receptor, and the cytoplasm domain can aggregate FADD and FLICE which can initiated the apoptosis; Another famous cytokine, IFN—γ ,which can induce the macrophage apoptosis, plays a key role in clearance of the mycobacterium tuberculosis by inducing host cell apoptosis depended by the nitric oxide(NO).[17]

- **Drugs**

Some cytotoxic drugs (Cisplatin, Gemcitabin Tooitecan, and paclitaxel) can trigger apoptosis; Didymin induce apoptosis by preventing N-Myc protein expression and make the cell G2/M arrest, which may be a novel mechanism to anti-neuroblastoma.[18] apart from this anti-neuroblastoma properties, didymin have an anti-no small cell lung cancer ability by induced the Fas-mediated apoptosis, it may be a novel new chemotherapeutic agent to treat the lung cancer.

- **Hormone**

Apoptosis occurs in the embryonic development and during the formation of organs, Hormones is usually a peptide or steroid, produced by one tissue and conveyed by the bloodstream to another place to affect physiological activity, such as growth, proliferation, metabolism. Some researchers also found that hormones can regulate the apoptosis, and through this way hormone can control the metabolism of tissues or organs. For example, the leptin is one hormone produced by adipocytes, and it has been found as a inhibitor of apoptosis, leptin can down-regulate cleaved caspase-3 and Bcl-2 associated X protein and up-regulate Bcl-2 protein, if this hormone level is normal, there will be no apoptosis, however, if the hormone level decreased, the apoptosis will happen[19], this is one mechanism by which the hormone act as inhibitor of apoptosis, the other mechanism is that hormone act as an inducer of apoptosis

- **Pathogen Effectors**

During the fight between host and pathogen, there are many roads that benefit the cell survival. There is the proverb “Survival of the fittest”. If failing to defense the pathogen, host will be ill, and give the phenomenon of inflammation or cell death（apoptosis, necrosis, auto-phage, pyropt osis）. In this part, we will give the conclusion about host cell apoptosis which can be triggered by some pathogens, If cell occured apoptosis, the pathogen can not survival either, so through this way, host cells can clear the pathogen with little bad effects.

- **Native Activities Compounds**

Although apoptosis is the programmed cell death and can be recognized as the normal cell death by the immune system; and apoptosis have many important functions in the tissue development. While everything have two sides, in some cases, apoptosis also have the damage and negative effect to the life healthy. Recently, food scientists and biologist found that some native compounds from the daily life dietary can block or hamper apoptosis, and through this way, these native compounds can help to keep the body healthy.

### *Intrinsic Cell Apoptosis Signal Materials*

- **Oxidative Stress (Ros; No; Gsh)**

Keratin is a cytoskeleton protein which have some abilities to maintain the cell shape, Guo-Zhong Tao group found that keratin can modulate the shape of mitochondria and contribute to hepatocyte predisposition to apoptosis and oxidative injury[20]. Depletion the mitochondria GSH in the human B lymphoma cell line by treatment with L-buthionine sulfoximine can induce caspase-3 activation and apoptosis, and indicating that GSH may be the potential early activator of apoptotic signal. ROS is a type of toxic compound and usually detoxified by cells

GSH, when the oxidative stress occur, the ROS detoxify will be failed, and ROS will participate in apoptosis through redox-sensitive death pathway.

- **Cytochrome C**

Cytochrome C, as a proapoptotic protein, plays an important role in triggering programmed cell death, The activation of cytochrome C is related with the changes of Bak/Bax ratio. The latest researches shown that the interactions of heterotypic mitochondrial membrane will change the lipid milieu, in the end, mitochondrial membrane will be permeatable and cytochrome c will release.; Apart the changes of lipid milieu, arachidonic acid, triiodothyronine (T3), or 6-hydroxdopamine can also effect the permeability of mitochondrial membrane and release $Ca^{2+}$ and cytochrome c. Cytochrome c can thrigger caspase activation via oligomerization of APAF1 protein. Caspase activation can catalyze the PARP-1, Finally, the apoptosis will happen. In short, cytochrome C is the one of major intrinsic cell apoptosis signal molecules.

- **Calcium Iron**

The concentration of calcium in vivo is the key role in maintain the permeatability of mitochondrial membrane. The increased intra-mitochondrial calcium can result in enhanced ROS, Furthermore, cytochrome c will be stimulated to release.[21] And calcium also trigger the ER stress, and then activate JNK pathway, afterwards, JNK activation can stimulate Bax activation;Moreover,calcuim can regulate the cysteine protease calpain, It's well known that calpain participate in the cell proliferation, cell cycle, and apoptosis

- **Endoplasmic Reticulum (Er) Stress**

As the apoptogenic factor, the permeabilization of lysosomal membrane can induce apoptosis by both caspase-dependent and caspase-independent pathway;[22] Tackled with the unfolded proteins is the one of the important ER functions, cell can regulate the unfolded proteins in ER according to metabolically needed, while if numerous unfolded proteins stimulate the ER and make the ER overload stress, the cells which have lots of unfolded proteins will apoptosis, Differing from the ER stress, chaperons will protect this cell death.

***Implication of Apoptosis***

During the last decade, exceptional for the basic research, the apoptosis have attracted many attentions due to its potential application in therapying the various human diseases. In order to maintain the function of whole organism, millions of cells will die and proliferate every day, cell death like apoptosis is the essential for the regulation of organism growth and maintenance the tissue homeostasis. If the cell death and proliferation go to imbalance, many diseases will happen. Such as: some acute pathologies (stroke, heart attack, liver failure) ; cancer; neurodegenerative syndromes; diabetes and so on. Due to its no lethal effect to the body, Apoptosis play a fundamental role in organism development and tissue homeostasis, while if apoptosis was not under controlled, a variety of diseases will occur.

***Therapeutic Possibilities and Future Directions***

The widespread involvement of apoptosis in the pathophysiology of disease lends itself to therapeutic intervention. In diseases caused by increased cell loss, such as viral hepatitis and neurodegenerative disease, the aim will Anaesthesia, be to minimise apoptosis by modifying the signals which trigger the response (e.g. Ca21, ROS) or interfering with the effectors (e.g. caspases and endonucleases). However, inhibition of apoptosis may be deleterious because new tumours may arise when damaged cells are prevented from committing suicide. In diseases caused by deficient apoptosis, such as cancer, viral latency and autoimmunity, methods of producing selective apoptosis are being sought. Agents targeting receptors or regulatory molecules and agents targeting the final common pathway are attractive possibilities.

Agents targeting receptors or regulatory molecules and agents targeting the final common pathway are attractive possibilities. The soluble form of Fas could prove useful for increasing apoptosis (e.g. in

tumours). Antibodies to Fas or Fas ligand may be useful in preventing apoptosis (e.g. in neurodegenerative disease). Preliminary successes in treating chronic inflammatory diseases, such as rheumatoid arthritis and ulcerative colitis, with TNF-α inhibitors have been reported, but these therapies have proved disappointing in sepsis [23]

## CONCLUSION

Apoptosis is regarded as a carefully regulated energy-dependent process, characterized by specific morphological and biochemical features in which caspase activation plays a central role. Although many of the key apoptotic proteins that are activated or inactivated in the apoptotic pathways have been identified, the molecular mechanisms of action or activation of these proteins are not fully understood and are the focus of continued research. The importance of understanding the mechanistic machinery of apoptosis is vital because programmed cell death is a component of both health and disease, being initiated by various physiologic and pathologic stimuli. Moreover, the widespread involvement of apoptosis in the pathophysiology of disease lends itself to therapeutic intervention at many different checkpoints. Understanding the mechanisms of apoptosis, and other variants of programmed cell death, at the molecular level provides deeper insight into various disease processes and may thus influence therapeutic strategy.

## REFERENCES


1. *https://www.novusbio.com/apoptosis-pathway.html*
2. *https://www.ncbi.nlm.nih.gov/books/NBK26873/*
3. *Alberts, Bruce; Johnson, Alexander; Lewis, Julian; Raff, Martin; Roberts, Keith; Walter, Peter (2008). "Chapter 18 Apoptosis: Programmed Cell Death Eliminates Unwanted Cells". Molecular Biology of the Cell (textbook) (5th ed.). Garland Science. p. 1115.*
4. *Karam, Jose A. (2009). Apoptosis in Carcinogenesis and Chemotherapy. Netherlands: Springer.*
5. *Paulina Strzyz (2017) Nature Reviews Molecular Cell Biology*
6. *Susan Elmore(2007)Apoptosis: A Review of Programmed Cell Death,sage journals*
7. *Cotran, Ramzi, S.; Kumar, Collins (1998). Robbins Pathologic Basis of Disease. Philadelphia: W.B Saunders Company.*
8. *D. González, I. Bejarano, C. Barriga, A.B. Rodríguez, J.A. Pariente (2010). "Oxidative Stress-Induced Caspases are Regulated in Human Myeloid HL-60 Cells by Calcium Signal". Current Signal Transduction Therapy.*
9. *Wajant H (2002). "The Fas signaling pathway: more than a paradigm". Science*
10. *Wajant, H. "Connection Map for Fas Signaling Pathway". Science*
11. *Hengartner et al.(2000) The biochemistry of apoptosis.Nature.*
12. *Michalak M, Henson PM( 2005) Cell-surface calreticulin initiates clearance of viable or apoptotic cells through trans-activation of LRP on the phagocyte.*
13. *Thomas, M. P.; Liu, X; Whangbo, J; McCrossan, G; Sanborn, K. B.; Basar, E; Walch, M; Lieberman, J (2015). "Apoptosis Triggers Specific, Rapid, and Global mRNA Decay with 3' Uridylated Intermediates Degraded by DIS3L2". Cell Reports.*
14. *Gong JP, Traganos F, Darzynkiewicz Z. (1994) A selective procedure for DNA extraction from apoptotic cells applicable for gel electrophoresis and flow cytome*
15. *http://www.ecdo.eu/research.html*
16. *Z. Zhang, et al.2012 The protection of MSCs from apoptosis in nerve regeneration by TGFβ1 through reducing inflammation and promoting VEGF-dependent angiogenesis.*
17. *Bianca E.Schneider.Interferon Gamma Activated Macrophage by Nitric Oxide Induced Apoptosis.*
18. *R. Vitsyayan, et al. 2012 Didymin Induced Apoptosis by Inhibiting N-Myc and Up-regulating RKIP in Neuroblastoma.*
19. *C. Peyronel,2011 Effects of leptin on lipopolysaccharide-induced myometrial apoptosis in an in vitro human model of chorioamnionitis.*
20. *M. Looi, etal. Toivola,2011 Keratins modulate the shape and function of hepatocyte mitochondria: a mechanism for protection from apoptosis.*
21. *S. L. Sitasawad,2012 glucose-induced. High, Ca (2, overload, stress. oxidative, to. contribute, of. apoptosis, cells. cardiac, mitochondrial. through, dependent, pathways. independent, Biochim Biophys Acta.*
22. *Pupyshev AB2011.Lysosomal membrane permeabilization as apoptogenic factor.*
23. *Natanson C, Hoffman WD, Suffredini AF, Eichacker PQ & Danner RL. Selected treatment strategies for septic shock based on proposed mechanisms of pathogenesis.*