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AN INSIGHT ON HOMOLOGY MODELING OF FAP1 & SURVIVIN

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Abstract

Apoptosis is a programmed cell death in multi cellular organisms which involves a series of biochemical events which leads to change in cell morphology. This paper discusses brief over view on homology modelling of FAP1 & SURVIVIN. In this paper, review has been carried out on very important aspects of Apoptosis, related molecular mechanism and possible targets for future drug designing to develop anticancer drugs. Various aspects such as components of Apoptosis, Apoptosis execution, Apoptosis pathway and signaling.

1. Introduction

Apoptosis has significant responsibility towards the development and homeostasis of metazoans. Research studies are being carried out related to apoptosis for the past two decades and it has led to the recognition of several of genes that govern the initiation, execution, and regulation of apoptosis. An earlier investigation on the genetic and cell biological characterization was complemented by systematic bio-chemical and structural investigation, gives rise to an unprecedented level of maturity and clarity and importance in many aspects of apoptosis. It is attempted to understand on the molecular mechanisms of apoptosis, the interacting ligands to death receptors, actions of the IAP family or field of proteins, and caspase activation, inhibition, and removal of inhibition and the predict the structures for Fap 1 and Survivin [1-4].

2.0. Review of Literature [1-10]

In this paper, review has been carried out on very important aspects of Apoptosis, related molecular mechanism and possible targets for future drug designing to develop anticancer drugs.

2. 1. Apoptosis

Apoptosis is a form of programmed cell death in multicellular organisms. It is one of the important types or varieties of Programmed Cell Death (PCD) and involves a series of biochemical events or occurrences leading or resulting to a characteristic cell morphology and death, a series of biochemical events that lead to a variety of morphological changesalong with blebbing, changes to the cell membrane, namely, such as loss of membrane asymmetry and attachment, nuclear fragmentation, cell shrinkage, chromatin condensation, and chromosomal DNA fragmentation. This concept of cell suicide has gained increased interest in cytology and pathology. Excessive apoptotic cell death may cause organ atrophy and organ failure and for neurodegenerative diseases and viral hepatitis. Inefficient elimination of malignant, auto reactive, infected, or redundant cells will lead to the development of neoplasia, autoimmunity, viral persistence, and congenital malformations. Cells die in two ways: they are killed by injurious agents and are induced to commit suicide. Cells that are damaged by injury, such as by mechanical damage and exposure to toxic chemicals undergo a characteristic series of changes like they swell, because the ability of the plasma membrane to control the passage of ions and water is disrupted. The cell contents leak out, leading to inflammation of surrounding tissues. Cells that are induced to commit suicide: shrink, develop bubble-like blebs on their surface; the chromatin (DNA and protein) in their nucleus degrade; mitochondria break down with the release of cytochrome c; break into small, membrane-wrapped, fragments. The phospholipid phosphatidylserine, which is generally hidden within the plasma membrane, will be exposed on the surface. This is limited or bound by receptors on phagocytic cells like macrophages and dendritic cells which then engulf the cell fragments. The phagocytic cells secrete cytokines that **i**nhibit inflammation e.g., IL-10 and TGF-β. The pattern of events in death by suicide is often called Programmed Cell Death or PCD.

2. 2.Components of Apoptosis

Apoptosis mediated by death receptors that are belonging to the tumor-necrosis factor (TNF) receptor superfamily is the best-studied pathway in cells. Members of the TNF receptor family, TNF, Fas (Apo-1, CD95) and TRAIL (TNF-related apoptosis-inducing ligand)-R sharing a common internal domain, the so-called death domain. These receptors are activated by their natural ligands TNFα, FasL, and TRAIL, respectively and also the recruitment of FADD and TRADD.

2. 2. 1. Fap-1

Fas-associated phosphatase-1 (FAP-1) is a non-receptor protein tyrosine phosphatase. It has been proved and verified that FAP-1 can block the function of Fas by proper interaction with its carboxy-terminal three amino acids. Cell lines resistant to Fas-mediated apoptosis strongly overexpressed FAP-1 and also it was highly expressed in tumor cells in pancreatic carcinoma tissues

2. 2. 2. Bcl-2 FAMILY

It is found in the literature that the Bcl-2 family is the better-characterized group of apoptosis-mediating factors which can be divided into two significant groups as per their functional properties; anti-apoptotic proteins, namely, Bcl-x_L and Bcl-2 and pro-apoptotic proteins, namely, Bak, Bax and Bad. Bcl-2 proteins interact with other molecules through an α-helical domain termed BH-3 domain. This interaction is believed to be important for regulation of apoptosis .

2. 2. 3. CASPASES

The central component of apoptosis is a proteolytic system that involving a family of cysteine proteases termed as caspases. In general, caspases initiate and execute cell death by inactivating anti-apoptotic proteins, shutting down DNA replication and repair, reorganization of the cytoskeleton and disruption of the nuclear lamina. Caspases involved in apoptotic pathways include.Caspase 1, Caspase 3, Caspase 7, Caspase 6, Caspase 8, and Caspase 9.

2.2.4. IAP FAMILY

The inhibitor of apoptosis proteins (IAPs) are a family of antiapoptotic proteins which bind and inhibit caspases 3, 7, and/or 9, but not caspase 8. IAPs also modulate cell division, cell cycle progression, and signal transduction pathways. , IAPs are attractive therapeutic targets, and efforts are under way to generate antisense and chemical IAP inhibitors that may be useful for the treatment of a variety of malignancies. The inhibitor of apoptosis (IAP) family including cIAPs, XIAP and Survivin can block apoptosis through interaction with members of the caspase family.

SURVIVIN

Survivin was identified as a new member of the inhibitor of apoptosis (IAP) family. Survivin is generally expressed in the G_2/M phase of the cell cycle in a cycle-regulated manner. It will directly bind to and inhibits both caspase-3 and caspase-7 activity leading to arrest of apoptosis. It is highly expressed in wide range of cancer tissues that including neuroblastoma, colorectal and stomach carcinoma.

SMAC/DIABLO

The inhibitor of apoptosis are inhibited by a protein, namely, Second mitochondria-derived activator of caspase/direct IAP binding protein with low pI (SMAC/DIABLO). SMAC/DIABLO may generally have a therapeutic application in increasing the effect of chemotherapeutics by binding IAPs that are overexpressed in a wide variety of carcinoma cells including pancreatic cancer.

GROWTH FACTORS

Growth factors include, Insulin-like growth factor (IGF) and the receptors, Insulin-like growth factor (IGF-1) receptor (IGF-1R) and IGF-2 receptor, epidermal growth factor (EGF), EGF receptor (EGFR) and ErbB2, transforming growth factor-α (TGF-α), and transforming growth factor-β (TGF-β), fibroblast growth factor (FGF), vascular endothelial growth factors (VEGF) and their receptors.

OTHER FACTORS AND SIGNALING PATHWAYS

Nuclear factor of κB (NF-κB)

Survival signaling through PI3K/AKT

PKCμ

p53

The p53 pathway indicates the molecular connection between the cell cycle and apoptosis. The p53 gene encodes a 53-kDa nuclear phosphoprotein. p53 generally inhibits cell growth through activation of cell cycle arrest and apoptosis

2.3 Apoptosis Execution

When it comes to the successful eradication of cancer cells by nonsurgical means, ultimately, all roads lead to apoptosis. All cytotoxic anticancer drugs currently in clinical use induce apoptosis of malignant cells. Microtubule binding drugs, DNA-damaging agents, and nucleosides are important weapons in the treatment of cancer, but a new class of targeted therapeutics may soon be forthcoming based on strategies that have emerged from a deeper understanding of the molecular mechanisms that underlie the phenomenon of apoptosis.

Cells commit suicide by 3 two different mechanisms. By signals arising within the cell, by death activators binding to receptors at the cell surface like TNF-α , Lymphotoxin & Fas ligand (**FasL**) and by dangerous reactive oxygen species.

2. 3. 1. Intrinsic Pathway

Apoptosis triggered by internal signals: the intrinsic or mitochondrial pathway. In a healthy cell, the outer membranes of its mitochondria display the protein Bcl-2 on their surface. Bcl-2 inhibits apoptosis. Internal damage to the cell causes related proteins, Bad and Bax, to migrate to the surface of the mitochondrion where they bind to Bcl-2 blocking its protective effect and punch holes in the outer mitochondrial membrane, causing cytochrome c to leak out. The released cytochrome c binds to the protein Apaf-1. Using the energy provided by ATP, these complexes aggregate to form apoptosomes. The apoptosomes bind to and activate caspase-9. Caspase-9 is one of a family of over a dozen caspases. They are all proteases. They get their name because they cleave proteins mostly each other at aspartic acid (Asp) residues). Caspase-9 cleaves and, in so doing, activates other caspases (caspase-3 and -7). The activation of these "executioner" caspases creates an expanding cascade of proteolytic activity (rather like that in blood clotting and complement activation) which leads to digestion of structural proteins in the cytoplasm, degradation of chromosomal DNA, and phagocytosis of the cell.

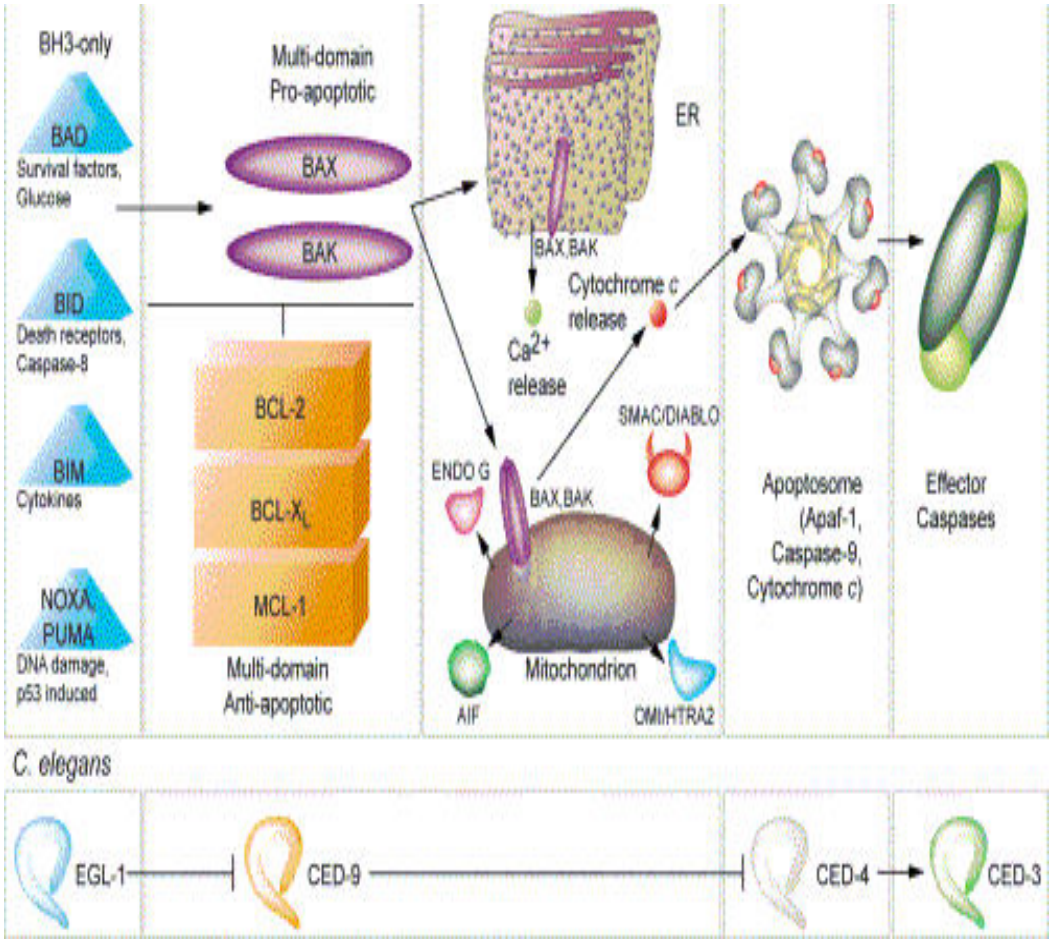

Figure No.1 Intrinsic Apoptotic Pathway.

2. 3. 2. Extrinsic Pathway

Apoptosis triggered by external signals: the extrinsic or death receptor pathway.

Fas and the TNF receptor are integral membrane proteins with their receptor domains exposed at the surface of the cell. They bind to the complementary death activator (FasL and TNF respectively) and transmit a signal to the cytoplasm that leads to activation of caspase 8. Caspase 8 initiates a cascade of caspase activation leading to phagocytosis of the cell.

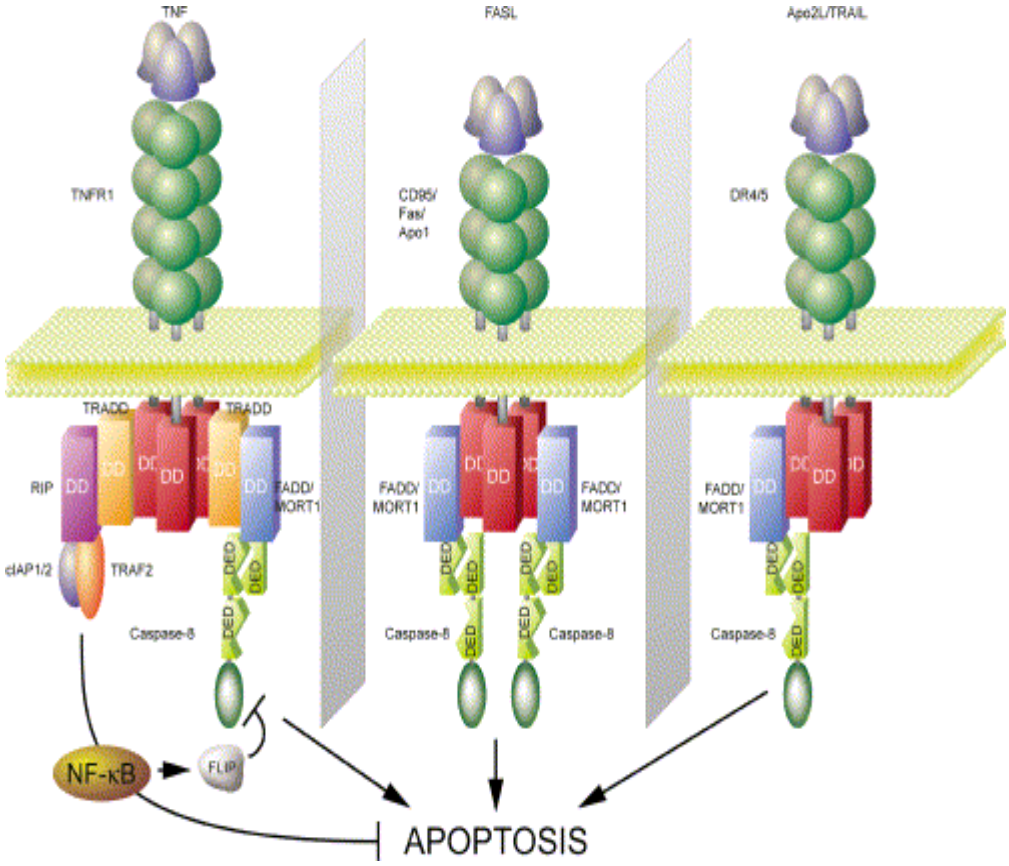

Figure No. 2 Extrinsic Pathway.

Courtesy: Extrinsic Death Receptor PathwaysThe distinct composition of the *D*eath-*I*nducing-*S*ignaling *C*omplex (DISC) downstream of the various death receptors TNFR1, CD95, and DR4/5 is illustrated.

2. 3. 3. Apoptosis-Inducing Factor (AIF)

Apoptosis-inducing factor (**AIF**) is a protein that is normally located in the intermembrane space of mitochondria. AIF is released from the mitochondria and migrates into the nucleus; binds to DNA, which triggers the destruction of the DNA and cell death.

2.4. Apoptosis Pathway & Signaling

Apoptosis is a regulated cellular suicide mechanism characterized by nuclear condensation, cell shrinkage, membrane blebbing and DNA fragmentation. Caspases, a family of cysteine proteases, are the central regulators of apoptosis. Initiator caspases including caspase-2, -8, -9, -10, -11 and -12 are closely coupled to pro-apoptotic signals. These caspases cleave and activate downstream effector caspases including caspase-3, -6 and -7, which in turn execute apoptosis by cleaving cellular proteins following specific Asp residues. In general, activation of Fas and TNFR by FasL and TNF, respectively, leads to the activation of caspase-8 and -10. DNA damage produces the expression of PIDD that binds to RAIDD and caspase-2 and will lead to the activation of caspase-2. Cytochrome c released from damaged mitochondria is integrated to the activation of caspase-9. XIAP inhibits caspase-3, -7 and -9. Mitochondria release multiple pro-apoptotic molecules, namely, Smac/Diablo, AIF, HtrA2 and endoG, in addition to cytochrome c. Smac/Diablo binds to XIAP that prevents it from inhibiting caspases. Caspase-11 is induced and activated by pathological proinflammatory and pro-apoptotic stimuli and leads to the activation of caspase-1 to promote inflammatory response and apoptosis by directly generating caspase-3. Caspase-12 and caspase-7 will be activated under ER stress conditions. Anti-apoptotic ligands including growth factors and cytokines activate Akt and p90RSK. Akt inhibits Bad by direct phosphorylation and will prevent the expression of Bim by phosphorylating and inhibiting the Forkhead family of transcriptional factors FKHR. FKHR promotes apoptosis by upregulating proapoptotic molecules such as FasL and Bim.

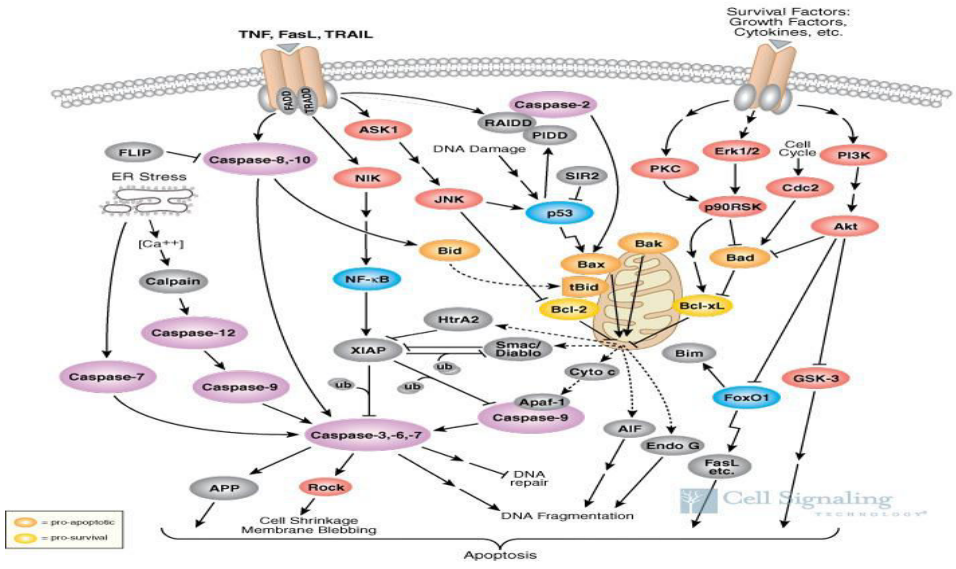

Fig.No.3 Apoptosis Pathway & Signaling.

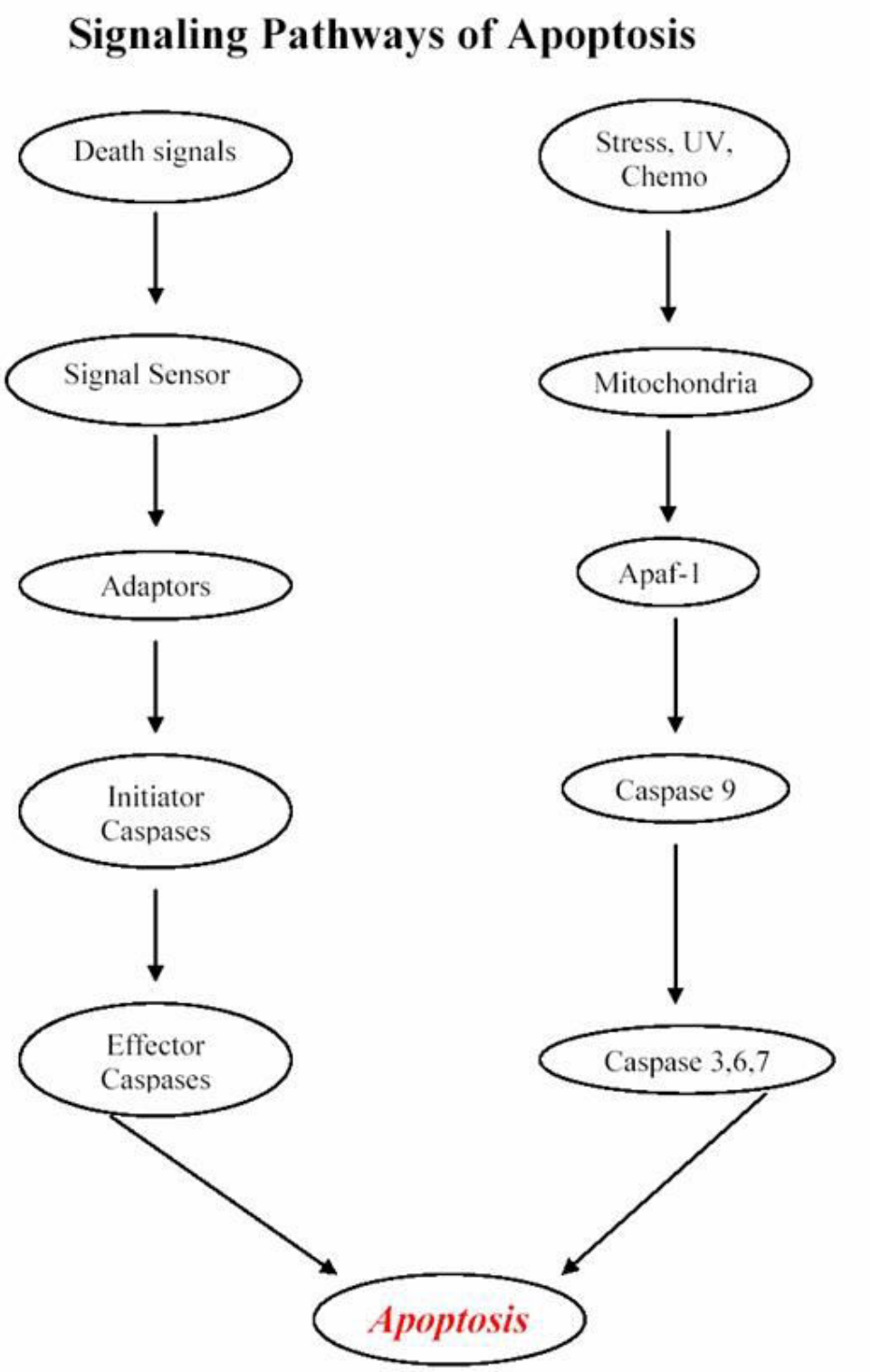

Figure No.4 Signaling Pathway of Apoptis.

2. 5. Important Functions of Apoptosis

- Programmed cell death is as needed for proper development as mitosis is.
- Programmed cell death is needed to destroy cells that represent a threat to the integrity of the organism.
- To maintain Homeostasis between the withdrawal of positive signals and receipt of negative signals.

3.0. Summary

This paper presents over view on homology modelling of FAP1 & SURVIVIN. In this paper, review has been carried out on very important aspects of Apoptosis, related molecular mechanism and possible targets for future drug designing to develop anticancer drugs. Various aspects such as components of Apoptosis, Apoptosis execution, Apoptosis pathway and signaling. It is noted that Apoptosis is a programmed cell death in multi cellular organisms which involves a series of biochemical events which leads to change in cell morphology.

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