PHYSIOLOGICAL CELL DEATH: APOPTOSIS

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Abstract: Apoptosis is normal physiological programmed cell death. It plays key role in maintenance of normal homeostasis of the body. It is characterised by formation of apoptotic bodies in the cell and condensation of chromatin and finally fragmentation of cell. It is required during intrauterine development and throughout life for tissue homeostasis. Impaired apoptosis can lead to various pathological implications.

Key words: Cell death, apoptosis, physiological, pathological apoptosis, hoemostasis.

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Introduction:

Nothing is permanent in this creation on earth. All cells in body constantly undergo process of degeneration and regeneration which is a physiological phenomenon. 'Apoptosis' is derived from Latin meaning "to fall off". It is a type of cell death, sometimes also referred as 'suicide by cell'.

There are two types of cell death- Apoptosis and Necrosis. Apoptosis is normal physiological cell death, whereas necrosis is pathological cell death. Apoptosis is considered as physiological process leading to programmed cell death useful to remove unwanted cells by process of phagocytosis without inflammation, while necrosis is pathological phenomenon to remove damaged cell with inflammatory reaction.

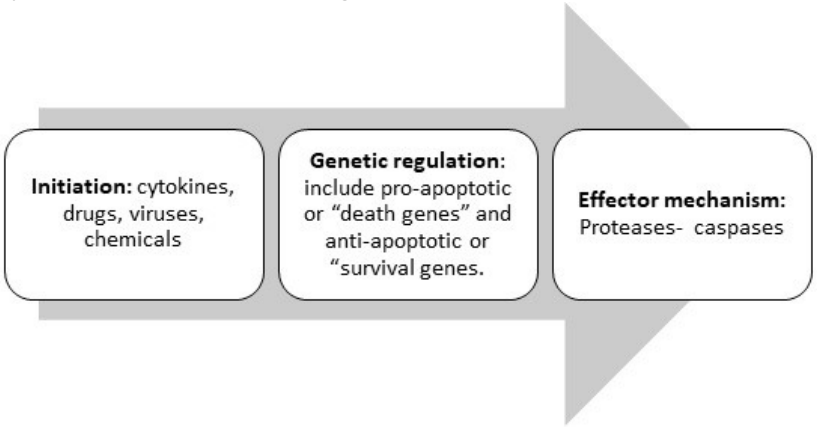
Apoptosis is also called programmed cell death as specific proteins responsible for it are encoded in the cell itself. It plays a vital role in tissue homeostasis. It is a physiological process of cell death by which a single cell may be eliminated from the living tissue. Since the process is mediated by specific proteins encoded in the host's genome, it is also a programmed cell death.

During apoptosis, there is condensation of chromatin and cytoplasm and fragmentation of the cell into membrane bound particles called as apoptotic bodies[1]. It is characterized by shrinkage of cell, condensation of dense chromatin, budding and fragmentation followed by phagocytosis of nearby cells and DNA fragmentation into 200 units of base pairs[2]. These changes during apoptosis were described by Kerr in 1972[3]. During apoptosis, membrane integrity is maintained which prevents release of toxic substances from cytoplasm, thus preventing inflammation of surrounding tissues. Apoptotic bodies are later phagocytised by phagocytic cells and surrounding epithelial cells.

Mechanism of apoptosis:

There are three stages of apoptosis: Initiation, genetic regulation, effector mechanism[4].

Figure 1: Stages of apoptosis.



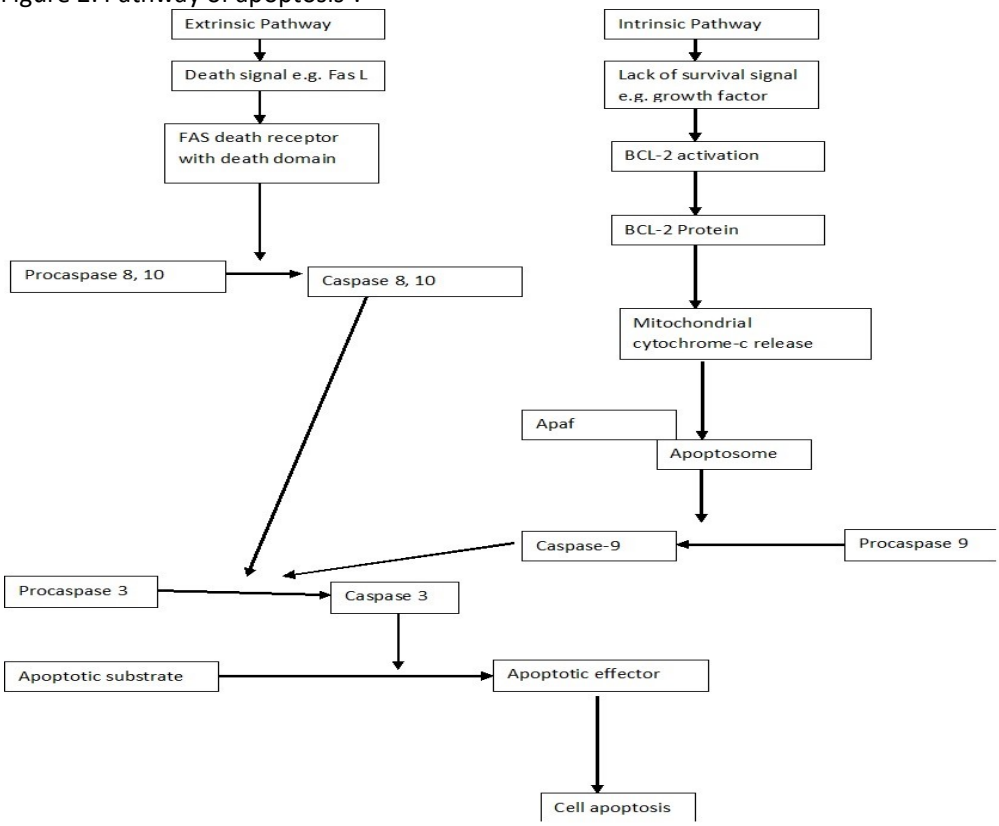
Two important biochemical representation of initiation process of apoptosis areappperance of excess sterols at plasma membrane and migration of phosphatidylserine from inner to outer leaflet of plasma membrane[5].

There are two main pathway of apoptosis-

1) Exrinsic pathway :The extrinsic pathway of apoptosis is initiated when environment outside a cell are not favorable to survive leading to death of the cell eg. lack of survival signal & growth factors, presence of death signals in the form of Fas,TNF -α

2) The intrinsic pathway of apoptosis pathway isstimulated when an injury occurs within the cell like DNA damage, hypoxia, and survival factor deprivation.

Figure 2: Pathway of apoptosis[6].



In both the intrinsic and extrinsic pathway of apoptosis, there is activation of Cysteine,aspartate proteases, also known as caspases, that act in a proteolytic cascade to dismantle and remove the dying cell. Caspases are proteolytic enzymes which hydrolyze specific bond at aspartate aminoacid residue site in the proteins. This leads to cleavage of vital proteins resulting in death and removal of cell. Apoptosis causes changes in the plasma membrane phospholipid orientation, modifications of intracellular ion homeostasis, activation of proteases and endonucleases, cleavage of proteins and DNA, intracellular generation of ceramide via spngomyelinase an activation of transglutaminase[7].

Importance of apoptosis:

Apoptosis is required for tissue remodelling and for normal tissue turnover.

* Physiological role of apoptosis:

During intrauterine development, apoptosis helps to give shape to organ and helps in carving out the interdigital webs of fingers and toes[4]. In intrauterine life, the hand of fetus is like duck paddle foot having webs between the fingers. The extra cells apoptose giving shape to fingers. Failure of apoptosis in fetal life can lead to various fetal abnormalities.

Throughout life, old cells die via apoptosis and new cells are formed. The cells which get damaged beyond repair get eliminated by apoptosis. Apoptosis causes cell death which is a highly conserved evolutionary process for

deletion of old, damaged, redundant and harmful cells from the body[7]. Also, rate of apoptosis is paired with rate of mitosis for maintenance of homeostasis. Apoptosis helps in prevention of carcinoma.

Apoptosis also play an important role in maintenance of normal homeostasis of immune system of the body and immune tolerance by removal of harmful and toxic cells.

Primary role of apoptosis in animal virus infection is to facilitate dying cells to be phagocytosed by macrophages, thus preventing dysregulated inflammatory reactions at site of virus infection[8].

* Abnormal apoptosis:

Dysregulation of apoptosis can lead to disturbances in cellular homeostasis.

Inhibition of apoptosis can result in tissue hyperplasia, malignancies, autoimmune disorders, viral infections. In autoimmune disorder, rheumatoid arthritis, impaired apoptosis leads to hyperplasia of synovial tissuesor increased apoptopic cell death of osteoblasts results in bone loss[9]. Salivary gland cell apoptosis occurs in Sjogren's syndrome.

Potentiation of apoptosis can result in tissue atrophy leading to tissue dysfunction, neurodegenerative diseases like Alzheimer's, Parkinsonism.

Failure of apoptosis to delete genetically changed cells can lead to malignant transformation[7].

*Therapeutic uses of apoptosis[4]:

Modulating apoptosis can be used for management of certain disease processes. Many drugs like non steroidal anti inflammatory drugs act by modifying apoptosis. Cytotoxic drugs, radiotherapy induce apoptosis in tumour cells. Caspase inhibitors can be used for management of parkinsonism, amyotropic lateral sclerosis. Apoptosis gives potential for prevention and therapeutic modulation of many disorders[10].

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