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APOPTOSIS

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ABSTRACT

Apoptosis is a form of cell death that occurs when a cascade of molecular events in a cell causes it to die. The process of planned cell death, which occurs on a regular basis to maintain a homeostatic balance between the rates of cell production and cellular damage. Apoptosis is distinguished by different phenotypic traits and an energy-dependent metabolic process. This review focuses on the primary apoptotic signaling pathways as well as the molecular components engaged. Defects can develop at any point along these pathways, resulting in malignant transformation of the afflicted cell, tumor spread, and medication tolerance.

KEYWORDS: Apoptosis, Programmed Cell Death, Extrinsic and Intrinsic Pathway.

INTRODUCTION

Prior to the concept that cell death does not happen inadvertently, the mechanism of sequential sequence of cell death known as apoptosis was first discovered in 1964. (Lockshin and Williams, 1964). The phenomena was discovered in 1842 by German scientist and philosopher Carl Vogt, who undertook little more investigation into it after seeing that cells within the notochord vanished but were later regenerated throughout growth. Glucksmann proposed in 1951 that cell death was necessary for both the growth and demise of an organism. Apoptosis, which was initially described as a morphological process of unique cell death and was coined from the Greek term "a-po-toe-sis," which literally means dropping, was later noted by Kerr, Wyllie, and Currie in their study (Paweletz and Walther, 2001).

There are around 1014 cells in an adult human body. Mitosis is outpaced by apoptosis by a factor of nearly 20. Between 50 and 70 billion cells each day in an average adult person perish through apoptosis. About 20 billion to 30 billion cells every day for an average youngster between the ages of 8 and 14 die. Numerous studies have demonstrated how important this mechanism is for growth and homeostasis (Hassan et al. 2014).

Morphological Changes in Apoptosis

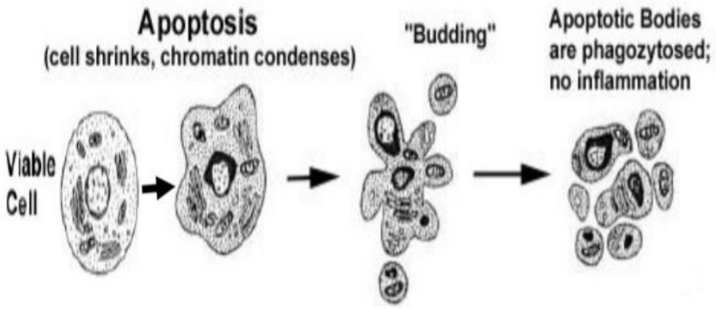

Fig.1.Mophological features of apoptotic cell: Cellular shrinking, chromatin condensation and marginalization, formation of membrane-bound apoptotic bodies, cytosol and nuclear fragmentations.

The morphological changes that take place throughout apoptosis have been detected by electronic microscopic research, including chromatin condensation, cytoplasmic shrinkage, and plasma membrane blabbing. Chromatin precipitation begins near the nuclear membrane's edge, generating a ring- or crescent-shaped formation.

These circumstances are followed by the plasma membrane blabbing, which causes the nucleus to rupture (karyorrhexis). The cell separates from the tissue around it, and its outlines swell and take on extensions. "Budding" is the process of cell fragmentation into apoptotic bodies. The cytoplasm of apoptotic entities contains densely compacted organelles, either with or without a nuclear fragment. The cellular coherence is still present, and the plasma membrane that encloses it is unharmed. Last but not least, the discharge of cell surface indicators (phosphatidylserine) from the cell membrane encourages certain cells, notably macrophages and parenchyma, to phagocytose these entities for subsequent destruction. Secondary necrosis is the name for the process of deterioration that occurs when the remains of apoptotic cells are not phagocytosed, as may happen in an artificial cell culture environment.

Mechanism of Apoptosis

The effective and strictly controlled cell killing process known as apoptosis involves a number of variables. Apoptosis may be genetically predetermined or triggered by cellular or environmental factors. Apoptosis is characterised by three factors: nuclear DNA breakdown, protein breakage or hydrolysis, and phagocytic cell identification of the apoptotic cell. Proteins are predominantly broken down by a class of cysteine proteases known as caspases (Cysteine ASPartate-Specific ProteASEs). As the innovators and executors of apoptosis, caspases are essential to the process. Three different mechanisms can activate caspases. The intrinsic (or mitochondrial) and extrinsic (or death receptor) routes of apoptosis are the two usually mentioned starting processes. Extrinsic and intrinsic routes meet within the same processing pathway or terminal. Intrinsic endoplasmic reticulum route is the name of the third, less popular starting pathway (Rebbeca, 2011).

Extrinsic (DR) Pathway

Beginning with pro-apoptotic receptors on the cell's surface that have been triggered bya pro-apoptotic chemical or receptor-specific ligands, this route (see Figure 1) is extrinsic. Tumor necrosis factor (TNF) ligand, TNF-related apoptosis inducing ligand (TRAIL ligand), DR4 and DR5 receptors, or the FasL ligand bind to the TNF, TRAIL, or Fas receptors, respectively, to begin the apoptosis process. These death receptors feature an intracellular death domain that attracts adaptor proteins including TNF receptor-associated death domain (TRADD) and Fas-associated death domain (FADD), in addition to cysteine proteases like caspase.[8] The death-inducing signalling complex (DISC) is made up of the death ligand, the death receptor, and any adaptor proteins that are formed as a result of their binding to one another. causing procaspase-8 to be activated auto-catalytically (Kischkel et al., 1995). Caspase 8 is an enzyme that, when activated, acts as an initiator caspase, causing other downstream or executioner caspases to cleave in order to start the apoptotic process.

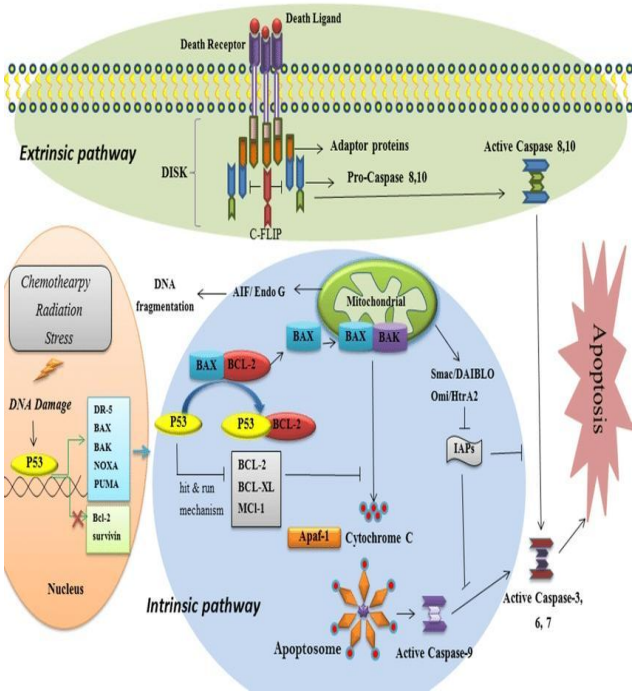

Fig.2: Schematic diagram of extrinsic and intrinsic pathway.

Intrinsic Mitochondrial Pathway

In response to internal cellular stressors such DNA damage, ROS, radiation, lack of hormones or growth factors, chemotherapy, cytokines, and glucocorticoids, the intrinsic mitochondrial pathway (see Figure 1) is activated. The intrinsic mechanism of apoptosis is mediated by Bax/Bak insertion into mitochondrial membrane, with cytochrome c being released from the mitochondrial intermembrane gap into the cytosol. Anti-apoptotic molecules, including as Bcl-2, Bcl-xL, and Mcl-1, are neutralised when they are combined with pro-apoptotic molecules. The pro-apoptotic proteins (such as Bax, theak, Bad, Bcl-Xs, Bid, Bik, Bim, and Hrk) and the anti-apoptotic proteins (such as Bcl-2, Bcl-XL, Bcl-W, Bfl-1, and Mcl-1) are the two main families of the Bcl-2 proteins. Pro-apoptotic proteins work by encouraging the release of cytochrome-c from the mitochondria, whereas anti-apoptotic proteins control apoptosis by inhibiting this release. (Apaf-1 and procaspase-9 work together with cytochrome c to form an apoptosome. The caspase-9 and caspase-3 signalling caspases are activated by the multiproteinapoptosome, which has seven spokes and is formed like a ring. This results in the destruction of cells and the onset of apoptosis. The secondary mitochondria-derived activation of caspase (Smac), straight IAP protein complex with low pI (DIABLO), Omi/high temperature requirement protein A, and apoptosis inducing factor are additional apoptotic factors that are released from the mitochondrial intermembrane gap into the cytoplasm (HtrA2).

Exception Pathway /Common pathway

Pathways that are intrinsic and extrinsic converge at the same location (execution phase). The term "execution phase" describes the last stage of apoptosis. The execution stage of apoptosis results in the activation of several caspases. The upstream caspase for the intrinsic route is caspase 9, whereas the upstream caspase for the extrinsic pathway is caspase 8. To reach caspase 3, the intrinsic and extrinsic routes converge. ICAD is broken down by activated caspase-3, releasing CAD (Sakahira et al., 1998). CAD then results in chromatin condensing and the degradation of chromosomal DNA inside the nucleus. is in charge of nuclear apoptosis. Additionally, downstream caspases cause the cleavage of inhibitory components of the endonuclease family, cytoskeletal proteins, DNA repair proteins, and protein kinases. Cytoplasmic endonuclease is activated by executor caspases, which results in chromatin condensation, the development of cytoplasm blebs, and the production of apoptotic bodies. .

MALFUNCTIONING OF APOPTOSIS AND PATHOGENESIS

Numerous human illnesses, including cancer, neurological disorders, and several autoimmune disorders, may be brought on by improper apoptosis or dysfunction of specific apoptotic machinery (Figure 2). It has been discovered that conditions including Alzheimer's disease, Parkinson's disease, and Huntington's disease are linked to unneeded cell death and improper caspase activity control.

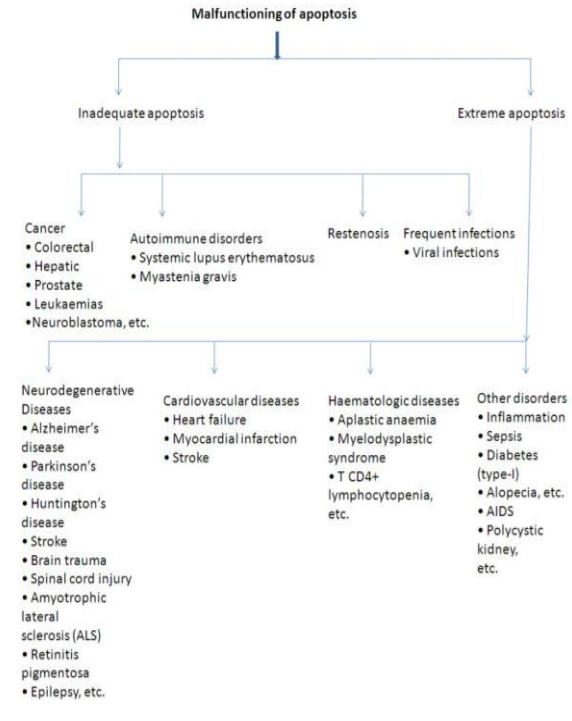

Fig.3.Some common diseases associated with malfunctioning of apoptosis or PCD.

Apoptosis in Cancer

Changes in apoptosis are crucial to the development of cancer. Defects in the apoptotic pathway are also to blame for resistance to treatment, and new therapeutic techniques aim to circumvent the block and reactivate these processes. One way that p53 and its management of apoptosis help to maintain normal cellular numbers is. Overexpression or underexpression of specific genes has been found to contribute to carcinogenesis by reducing apoptosis in cancer cells. Deficiencies in p53 can result in reduced apoptosis and tumour development.

In general, there are three main ways that apoptosis can be avoided:

1. A disrupted balance of pro- and anti-apoptotic proteins.
2. Decreased caspase activity.
3. A dysfunction in death receptor signalling.

Regulation Of Apoptosis

A cascade of intricate processes known as apoptosis involves the execution of apoptosis by proteases and endonucleases as well as the transmission of external signals through specific receptor complexes. Positive and negative genetic and environmental regulators can influence whether the pro- or anti-apoptotic pathway is selected. Cell death results from pro-apoptotic gene activation, whereas gene inactivation prevents apoptotic processes. The anti-apoptotic members work by preventing the intrinsic release of cytochrome c and maintaining the integrity of the outer mitochondrial membrane. IAP (inhibitors of apoptosis proteins) family protein stimulation, caspase inhibition, PARP (poly [ADP-ribose] polymerase) suppression, stimulation of the PKB/Akt (protein kinase B) pathway, and inhibition of Bcl-2 proteins are a few examples of possible anti-apoptotic therapeutic techniques. A cell that has begun or is on the death route may receive a survival signal that prevents apoptosis. The p53 tumour suppressor gene, the caspase family, the c-Myc gene family, and DRs are examples of genetic regulators (mainly pro-apoptotic). The c-Myc gene controls apoptosis and cell growth.

CONCLUSION

The best kind of planned cell death is apoptosis. and a preserved shape via evolution. Different routes that lead to cell death are constantly regulated by nearby stresses, growth factors, and local cellular events. Both extrinsic and intrinsic cell death can be started by activating caspase-8 with death ligands (such as TRAIL and fasL) and caspase-9 with DNA damage. Therefore, it can be inferred from this analysis that apoptotic cell death plays a crucial part in both normal cell formation and function as well as in diseases brought on by

these cells' defects. The apoptotic route is revealed to play a crucial part in cargogenesis, per the findings.

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