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Comprehending Apoptotic Pathways and Apoptosis Targeted Cancer Treatments.

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ABSTARCT:

Apoptosis is a type of cell death that happens when a cell dies as a result of a series of molecular events. the frequent occurrence of intentional cell death, which keeps the rates of cell creation and cellular damage in a homeostatic balance. Different phenotypic characteristics and an energy-dependent metabolic process are characteristics that set apoptosis apart. The main apoptotic signalling routes and the chemical elements involved are the main topics of this review. Anywhere along these pathways, defects may arise, leading to drug tolerance, tumour growth, and the malignant transformation of the affected cell.

Key words :- Apoptosis: - Programmed Cell death, extrinsic and intrinsic pathway, disease, regulation.

Introduction:

The mechanism of apoptosis, a systematic series of cell death, was initially identified in 1964, before the idea that cell death did not occur accidentally. Williams and Lockshin, 1964. When German scientist and philosopher Carl Vogt noticed that cells within the notochord disappeared but later regenerated throughout growth, he conducted a little further research into the phenomenon and found it in 1842. In 1951, Glucksmann postulated that an organism's ability to grow and die depended on its cells dying. Kerr, Wyllie, and Currie later identified apoptosis in their study (Paweletz and Walther, 2001). Originally defined as a morphological process of distinct cell death, the phrase was derived from the Greek word "a-po-toe-sis," which literally means dropping.(1). There are around 1014 cells in an adult human body. (2) Apoptosis outpaces mitosis by over a factor of 20. In an ordinary adult, apoptosis causes between 50 and 70 billion cells to die every day. On average, between the ages of 8 and 14, 20 billion to 30 billion cells every day die. 7.(2) The significance of this pathway for growth and homeostasis has been shown in numerous studies (Hassan et al. 2014).(1)

Apoptosis morphological changes:

Electronic microscopy studies have identified the morphological alterations that occur during apoptosis, such as chromatin condensation, cytoplasmic shrinkage, and plasma membrane blebbing. (9) Chromatin precipitation starts close to the margin of the nuclear membrane and forms a crescent or ring (7).
The plasma membrane blebbing occurs after these conditions.

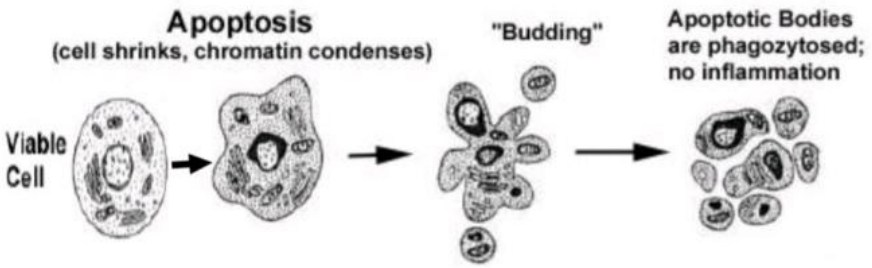


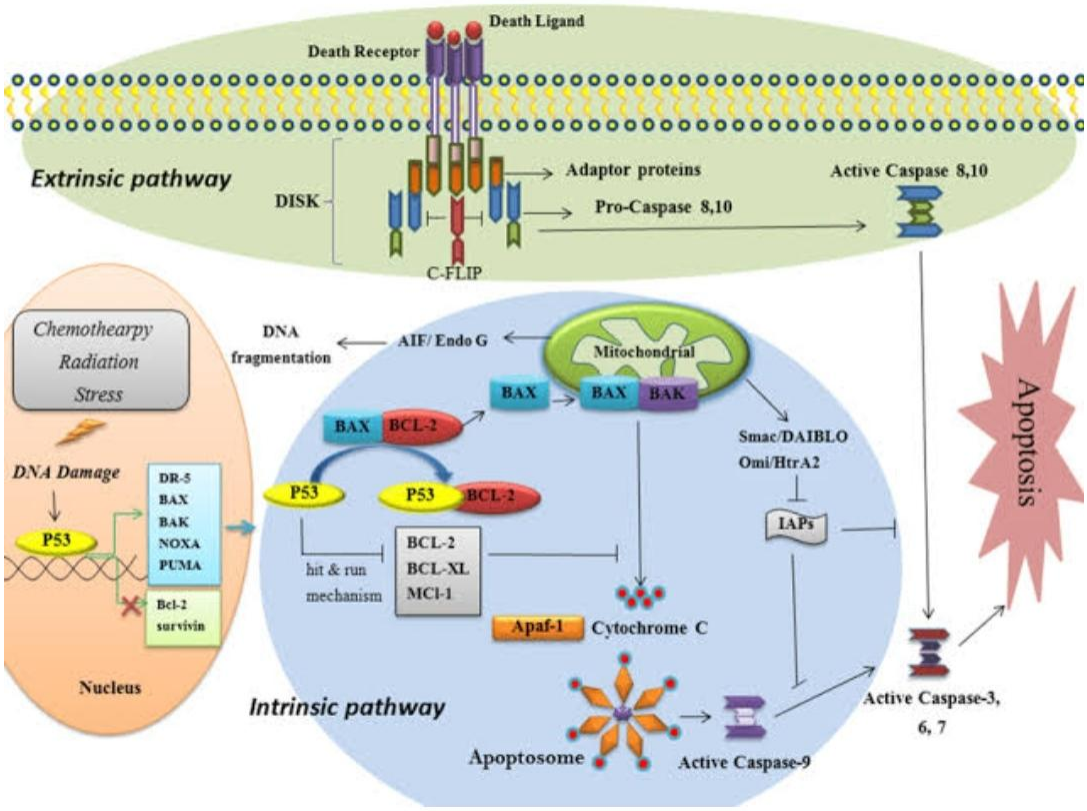
Fig.1.Mophological features of apoptotic cell: Cellular shrinking, chromatin condensation and marginalization, formation of membrane-bound apoptotic bodies, cytosol and nuclear fragmentations.

ultimately results in karyorrhexis, or the rupture of the nucleus. (1). The cell's outlines swell and take on extensions as it separates from the surrounding tissue. (2). It is called "budding" when cells break apart into apoptotic bodies. Densely packed organelles, with or without a nuclear fragment, are found in the cytoplasm of apoptotic entities (3). The plasma membrane that surrounds the cell remains intact, as does the cellular coherence. (3). Finally, when cell surface markers (phosphatidylserine) are released from the cell membrane, some cells, such as macrophages and parenchyma, are prompted to phagocytose these substances for eventual elimination (1). The process of deterioration known as secondary necrosis happens when the remnants of apoptotic cells are not phagocytosed, which can happen in an artificial The process of deterioration known as secondary necrosis happens when the remnants of apoptotic cells are not phagocytosed, which can happen in an artificial cell culture setting. (7)

Mechanism of apoptosis:

Apoptosis, the efficient and tightly regulated process of cell death, is dependent on several factors. (2). Genetic predispositions or environmental or cellular conditions can cause apoptosis. Nuclear DNA degradation, protein hydrolysis or breaking, and phagocytic cell recognition of the apoptotic cell are the three characteristics that define apoptosis. Caspases (Cysteine ASPartate-Specific ProteASEs) are a type of cysteine proteases that mostly break down proteins (10). Caspases play a crucial role in apoptosis as its initiators and executors. 7. Caspases can be activated by three distinct ways. (2). The two beginning mechanisms of apoptosis that are typically mentioned are the intrinsic (or mitochondrial) and extrinsic (or death receptor) approaches. 7. The same processing pathway or terminal is where intrinsic and extrinsic routes converge. (3). The third, less well-known initial approach is called the intrinsic endoplasmic reticulum route (Rebbeca, 2011). (2).

Schematic diagram of extrinsic and intrinsic pathway (4)



Extrinsic (DR) pathway:

This pathway is extrinsic and starts with pro-apoptotic receptors on the cell surface that have been activated by hormones that promote cell death or receptor-specific ligands (see Figure 1). (10). The apoptosis process is initiated by the binding of tumour necrosis factor (TNF) ligand, TNF-related apoptosis inducing ligand (TRAIL ligand), DR4 and DR5 receptors, or the FasL ligand to the corresponding TNF, TRAIL, or Fas receptors. (8). In addition to cysteine proteases like caspase 8, these death receptors have an intracellular death domain that draws adaptor proteins like TNF receptor-associated death domain (TRADD) and Fas-associated death domain (FADD) (7). The death ligand, death receptor, and any adaptor proteins that are created when they bind to each other comprise the death-inducing signalling complex (DISC) (2). resulting in the auto-catalytic activation of procaspase-8 (Kischkel et al., 1995). (3). When activated, the enzyme caspase 8 functions as an initiator caspase, triggering the cleavage of other downstream or executioner caspases to initiate the apoptotic process.(7)

Intrinsic mitochondrial pathway:

The intrinsic mitochondrial pathway (see Figure 1) is triggered in response to internal cellular stresses like radiation, ROS, DNA damage, cytokines, glucocorticoids, chemotherapy, and a lack of hormones or growth factors. (10). Cytochrome c is released from the mitochondrial intermembrane gap into the cytosol as a result of Bax/Bak insertion into the mitochondrial membrane, which mediates the intrinsic mechanism of apoptosis. (6). Combining anti-apoptotic molecules with pro-apoptotic ones neutralises them, such as Bcl-2, Bcl-xL, and Mcl-1. (8). The two primary families of Bcl-2 proteins are pro-apoptotic proteins (Bax, theak, Bad, Bcl-Xs, Bid, Bik, Bim, and Hrk) and anti-apoptotic proteins (Bcl-2, Bcl-XL, Bcl-W, Bfl-1, and Mcl-1). Anti-apoptotic proteins regulate apoptosis by preventing the release of cytochrome-c from the mitochondria, while pro-apoptotic proteins promote this release. 7. Apaf-1, procaspase-9, and cytochrome c combine to produce an apoptosome. The caspase-9 and caspase-3 signalling caspases are activated by the seven-spoken, ring-shaped multiprotein apoptosome. As a result, apoptosis starts and cells are killed. Apoptosis inducing factor, Omi/high temperature requirement protein A, straight IAP protein complex with low pI (DIABLO), and secondary mitochondria-derived activation of caspase (Smac) (HtrA2) are additional apoptotic factors that are released from the mitochondrial intermembrane gap into the cytoplasm. (2)

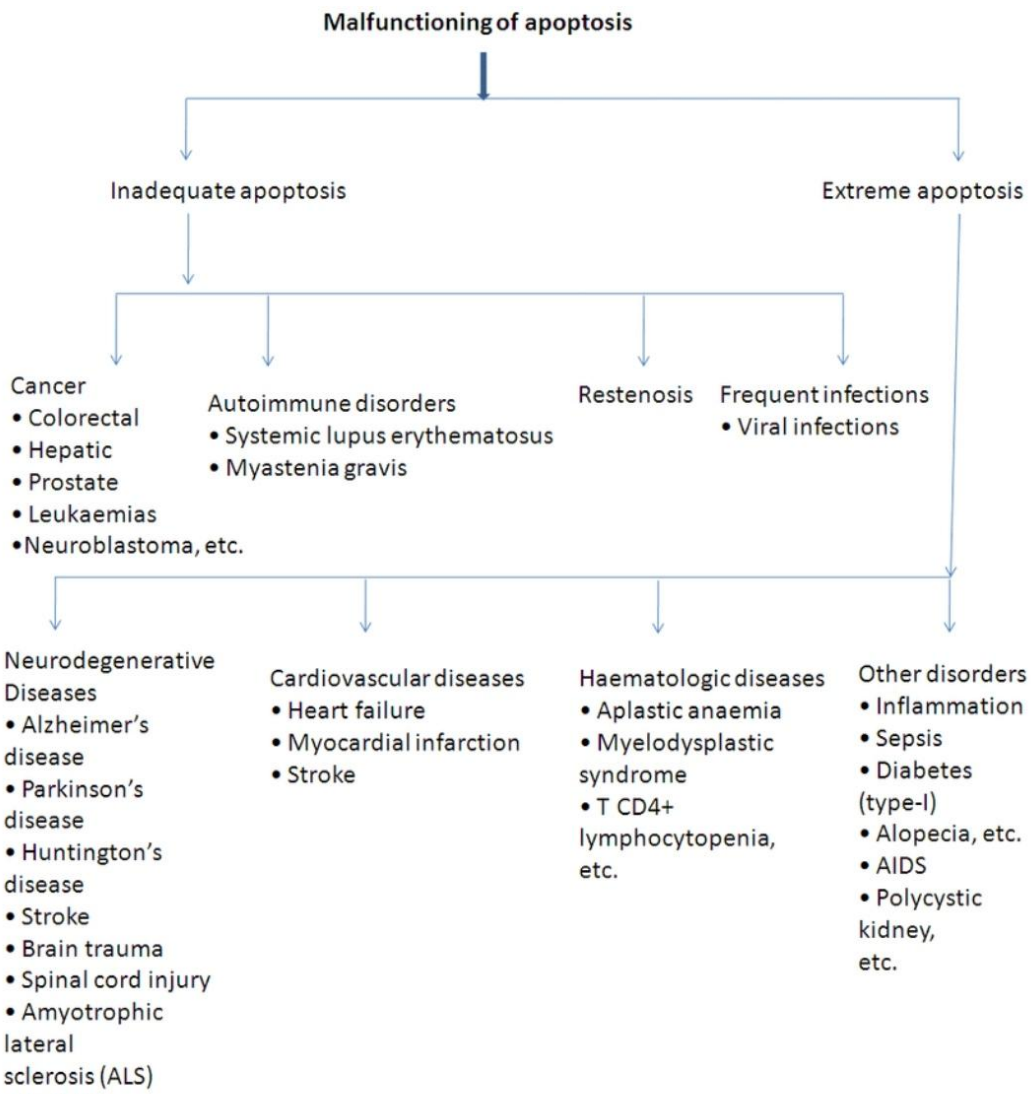
Common pathway or exception pathway:

intrinsic and extrinsic pathways converge at the same point (execution phase). Apoptosis' final stage is referred to as the "execution phase". (6). Several caspases are activated during the apoptotic execution step. While caspase 8 is the upstream caspase for the extrinsic pathway, caspase 9 is the upstream caspase for the intrinsic route. (2) The extrinsic and intrinsic pathways converge to reach caspase 3. 7. Activated caspase-3 releases CAD by breaking down ICAD (Sakahira et al., 1998). Inside the nucleus, chromatin condensing and chromosomal DNA destruction follow CAD. (3). is responsible for nuclear death. 7. Furthermore, cytoskeletal proteins, DNA repair proteins, protein kinases, and inhibitory elements of the endonuclease family are cleaved by downstream caspases. (2). Executor caspases activate cytoplasmic endonuclease, which causes chromatin condensation, cytoplasmic bleb formation, and apoptotic body formation. (6).

Pathogenesis and apoptosis malfunction:

Improper apoptosis or malfunction of certain apoptotic machinery can cause a variety of human diseases, such as cancer, neurological problems, and various autoimmune disorders (Figure 2). It has been found that disorders such as Huntington's disease, Parkinson's disease, and Alzheimer's disease are associated with inappropriate caspase activity regulation and unnecessary cell death. (2)

Fig.2.Some common diseases associated with malfunctioning of apoptosis or PCD



Apoptosis in cancer:

Apoptosis alterations are essential for the emergence of cancer. New therapeutic approaches seek to get around the block and revive these processes because apoptotic pathway defects are also the cause of treatment resistance. (5). Maintaining normal cell counts is facilitated by p53 and its control of apoptosis. By lowering apoptosis in cancer cells, overexpression or underexpression of particular genes has been shown to contribute to carcinogenesis. Reduced apoptosis and cancer growth may be the outcome of p53 deficiencies (10). In general, apoptosis can be prevented in two major ways: 1) an imbalance between proteins that promote and inhibit apoptosis.2) Reduced activity of caspase. 3) a malfunction in the signalling of death receptors.(7).

Regulation of Apoptosis:

Proteases and endonucleases carry out apoptosis, and some receptor complexes transmit external signals as part of a complicated series of activities known as apoptosis. (2). The selection of the pro- or anti-apoptotic pathway can be influenced by both positive and negative genetic and environmental factors. While gene inactivation stops apoptotic processes, pro-apoptotic gene activation causes cell death. (10). By stopping the intrinsic release of cytochrome c and preserving the integrity of the outer mitochondrial membrane, the anti-apoptotic members function. (11). Examples of potential anti-apoptotic therapy approaches include caspase inhibition, PARP (poly [ADP-ribose] polymerase) suppression, stimulation of the PKB/Akt (protein kinase B) pathway, inhibition of Bcl-2 proteins, and IAP (inhibitors of apoptosis proteins) family protein stimulation. (3). A survival signal can stop apoptosis in a cell that has started or is headed towards death. Genetic regulators (mostly pro-apoptotic) include the p53 tumour suppressor gene, the caspase family, the c-Myc gene family, and DRs. Cell development and death are regulated by the c-Myc gene (10).

Conclusion:

Apoptosis is the best type of intentional cell death, and evolution has retained its structure. Nearby stressors, growth factors, and local cellular events continuously regulate the various pathways that result in cell death. Activating caspase-8 with death ligands (like TRAIL and fasL) and caspase-9 with DNA damage can initiate both intrinsic and extrinsic cell death. Thus, this data suggests that apoptotic cell death is important for normal cell production and function as well as diseases caused by abnormalities in these cells. The results show that the apoptotic pathway is essential for cargogenesis.

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