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Review Article

The Vital Phenomena of Apoptosis: A Review

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Abstract: Apoptosis is a programmed cell death when the cell intentionally decides to die. It occurs due to the biochemical instruction from the DNA of cells. It is different from necrosis wherein a cell dies due to outside insult or deprivation. It is a complex process and is triggered by the signal molecules that tell the cell it's time, to commit cellular suicide. It is an important evolutionary adaptation to destroy its cells when they are no more useful to the organism. The apoptosis is a Greek word which means "falling off" as leaves do in autumn. Apoptosis is characterized by cell shrinkage, blabbing of plasma membrane maintenance of organelle integrity, condensation, and fragmentation of DNA, followed by removal of the apoptotic cell by phagocytosis. The South-African born biologist Sydney Brenner, American biologist H. Robert Horvitz and British biologist John E. Sulston shared the Nobel Prize in Physiology or Medicine in 2002 for their work on apoptosis.

Keywords: Apoptosis, Programmed cell death, Necrosis, Apoptotic signalling pathways, intrinsic pathway, extrinsic pathway.

INTRODUCTION

Cell death is an essential part of the normal development and maturation cycle [1]. Cell deprived of survival factor activate an intracellular suicide program and die by a process of programmed cell death, called apoptosis. It is essential to maintain a balance between cell proliferations, death and to carry out a normal physiological process. It is an active, normal physiological process that removes individual cells without damaging the neighbouring cells or inducing inflammation.

The mechanism of planned apoptosis became apparent to the scientists in 1840s when they realize that the development from fertilized egg to adult is not a linear process. It was intriguing to note that the initial structure such as tadpole's tail is replaced by an entirely different and distinct adult system, such as frog's leg. The medical significance of cell death was recognized by Australian researcher John Foxton R. Kerr and Scottish scientists Andrew H. Wyllie and Alastair Currie in the 20th century. In a paper published in 1972, they used the term apoptosis to describe the occurrence of apoptotic cells in human tissues. It is a Greek term which means "falling off" as leaves do in autumn [2]. South African-born biologist Sydney Brenner, American biologist H. Robert Horvitz, and British biologist John E. Sulston shared the Nobel Prize in Physiology or Medicine in 2002 for their discoveries about how genes regulate tissue and organ development via a key mechanism called programmed cell death, or apoptosis. Apoptosis is characterized by cell shrinkage, blabbing of plasma membrane maintenance of organelle integrity, condensation, and fragmentation of DNA, followed by removal of the apoptotic cell by phagocytosis [3].

Apoptosis-Pathways

The detailed understanding of Apoptotic signalling pathways are incomplete, but it is known that the process is controlled by several complex proteins, which are activated by various triggers. Apoptosis occurs through two main pathways. The first referred to as the intrinsic or mitochondrial pathway, that, when stimulated leads to the release of Cytochrome-c from the mitochondria and activation of death signals [4]. The second pathway is extrinsic or cytoplasmic pathway is triggered by the FAS death receptors, a member of the tumor necrosis factor (TNF) receptor super family [5].

Both pathways converge to a final pathway involving the activation of a cascade of proteases called Caspase that cleaves regulatory and structural molecules culminating in the death of the cell. The pathways are linked also. The over-expression of BCL-2 in

the intrinsic pathway may lead to inhibition of extrinsic mediated apoptosis, conversely, TNF-α may increase the expression of NFκB and stimulate antiapoptotic members of the BCL-2 family proteins.

The Intrinsic Pathway

Internal cell death program is initiated if irreparable damage to DNA and cellular component has occurred. The pro-apoptotic protein BAX is induced and inserted into the mitochondrial membrane. They form channels in the mitochondrial membrane. The Cytochrome –c exits from the mitochondria. It triggers the formation of the apoptosome, which is a large protein complex. It requires ATP for this process to occur. Apaf-1 is an adapter protein which is activated in the presence of dATP/ATP. There is self oligomerization to form Apaf-1 multimer. Procaspase is formed via interaction between specialized CARDS (Caspase recruitment domains) at the NH2 termini of Apaf-1 and procaspase-9.

Apoptosome is a complex protein which brings several molecules of procaspase-9 into proximity and by doing so, promotes its self-processing. Active caspase-9 then recruits and cleaves procaspase-3 which, when released in the cytosol, causes proteolytic degradation of its target substrate. The release of Cytochrome-c and its activity are under strict regulation by several mechanisms. They are broadly classified as upstream and downstream regulators. From the damage of cells to release of Cytochrome-c, is controlled by upstream regulators while the downstream regulator causes the release of Cytochrome-c and it functions, till the death of cells.

Upstream Regulators

The family of BCL-2 proteins is the upstream regulators. They are in two categories. The proapoptotic proteins consist of Bax, Bak, Bad, Bid, Bik, Bim, HrK, and Bcl-Xs, etc. The antiapoptotic proteins are BcL-2, BcL-W, BfL-1, McL-1 BcL-Xl, etc. It is the relative amount of pro and anti-apoptotic proteins that determine the cellular damage and also determines whether the cell will die or remain alive. All members of BcL-2 family contain at least one of the four so-called BH domains (BH-1 to BH4). In some proapoptotic protein members like Bad, contains only BH3 domain. The BH3 domain mediates the interaction between various members of BcL-2 family to generate several hetero and homodimers. BH3 only proteins e.g. Bid function to facilitate the activity of pro-apoptotic family members such as Bax and Bak and represent the target for the antiapoptotic function of Bcl-2 and BcL-Xl [6, 7]. Because of Bax mediated release of Cytochrome-c there is the formation of pores in the outer mitochondrial membrane through which Cytochrome-c and other apoptosis-inducing factors are released in the cytosol.

Downstream Regulators

In the cell, Apaf-1 is activated by Cytochrome-c after it is released by mitochondria. Apaf-1 proteins then form a multi sub-unit complex with caspase-9, termed, apoptosome in which caspase-9 becomes proteolytically active. Caspase-9 then cleaves and activates many proteins within the cells, including iCAD, an inhibitor of an endonuclease (CAD) that cleaves the cell DNA [8]. Which can be detected as, classical ladder pattern by electrophoresis [9].

Extrinsic Pathways

This pathway comprises several protein members including the death receptors, the membrane-bound Fas ligand, and the Fas complex, the associated death domain and Caspase 8 and 10, which ultimately activates the rest of the downstream Caspase leading to apoptosis. Activation of the extrinsic pathway is initiated with the ligation of cell surface receptors called death receptors (DRs). Fas, are a member of the tumor necrosis factor (TNF) receptor super-family and is also called Apo-1 or CD 95. Other TNF receptors include TNF-R, DR-3(Apo-2), DR4 or TRAIL-R-1 (Tumour necrosis factor-related apoptosis-inducing ligand receptor-1), DR5 (TRAIL-R-2), and DR6. These receptors are ligated on the surface of cell destined to die. It results in the recruitment of several intracellular proteins, including certain procaspase, to the cytosolic domains of these receptors, forming a “death-inducing signalling complex” (DISC) that triggers Caspase activation. This sequence of events is called extrinsic pathways for apoptosis [10]. The caspase-8 and in some cases, caspase-10 is the specific Caspases, summoned to the DISC. These caspases contain so-called death effecter domains (DEDs) in their N-terminal pro-domain that binds to a corresponding DED in the adaptor protein, FAAD, thus linking them to TNF family receptor complexes.

The third pathway for apoptosis induction is specific to CTL and NK cells, which spray apoptosis-inducing protease, Granzyme B (GraB), onto the target cells. GraB then piggybacks into cells via mannose-6-phosphate receptors (IGFR2) and enters effective cellular compartments via perforin channels [11]. GraB is a serine protease but, similar to caspases it cleaves substrate at Asp residues, including several caspases and some Caspase substrates.

The fourth pathway is a Caspase activation pathway. This pathway is proposed to be linked with the endoplasmic reticulum (ER/Golgi stress) but the details are lacking [12].

The fifth and final pathway is the nuclear pathway. This pathway depends upon the discrete nuclear organelle, called Pml Oncogene domains (PODs) or nuclear bodies (NBs). Ablation of Pml gene in mice results in general resistance to apoptosis through unknown mechanisms. Several proteins that can promote apoptosis have been localized to PODs, including Daax, Zip kinase, and

Par4, and defects in the assembly of these nuclear structures are documented in cancers. How PODs are linked to Caspase activation pathway is unknown, but dysregulation of their expression in function in cancers have been obtained [13].

The apoptosis is a normal physiological mechanism that occurs during normal development and aging as a homeostatic mechanism to maintain the cell population in the tissue. It can also occur as an immune reaction or in response to cell damage due to disease or noxious agents [14]. There are a wide variety of stimuli and conditions, both physiological and pathological that can trigger apoptosis, like irradiation, drugs hormones, etc although not all cells will necessarily die in response to the same stimulus.

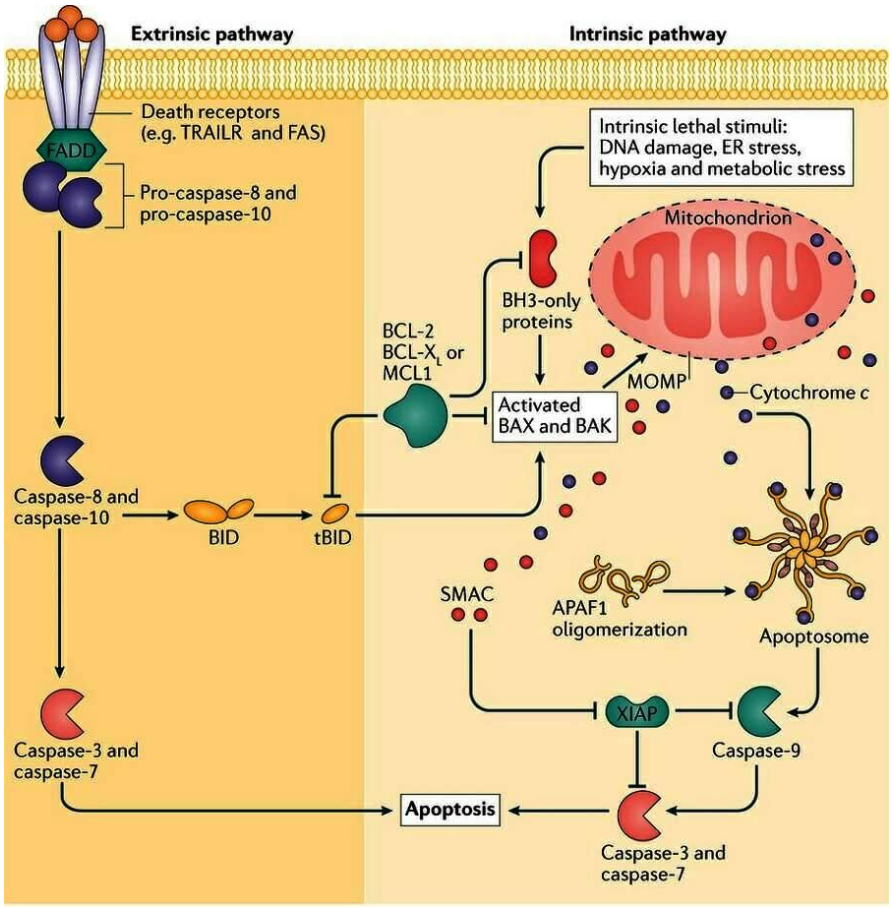

Fig-1: The Extrinsic and Intrinsic pathways of Apoptosis

The Apoptosis as a Physiological Process

Apoptosis is critically important during various developmental processes. The burning example is the nervous system and the immune system where there is an overproduction of cells. This initial overproduction is then followed by the death of those cells that fail to establish functional synaptic connections or productive antigen specificities, respectively [15, 16]. It is a vital component of wound healing where apoptosis causes the removal of inflammatory cells and the evolution of granulation tissue into scar tissue [17]. The dysregulation of apoptosis during wound healing can lead to pathologic forms of healing such as excessive scarring and fibrosis. Apoptosis is also needed to eliminate activated or auto-aggressive immune cells either during maturation in the central lymphoid organs (bone marrow and thymus) or in peripheral tissues [18]. As the organism grow older, some cells begin to deteriorate at a faster rate and are eliminated via apoptosis. The oxidative stress plays a primary role in the pathophysiology of age-induced apoptosis via accumulated free-radical damage to mitochondrial DNA [19, 20]. It is a tightly regulated phenomenon since too little or too much cell death may lead to pathology, including developmental defects, autoimmune diseases, neurodegeneration, or cancer.

Apoptosis as A Pathological Process

Regulation of cell death may become abnormal in many diseased conditions. The examples are cancers, autoimmune lymphoproliferative syndrome, AIDS, ischemia and neurodegenerative disorders like Parkinson's disease, Alzheimer's disease, Huntington's disease, etc. The disease may be characterized by either excessive apoptosis or less of it. Malignancies are an example where the normal mechanisms of cell cycle regulation are dysfunctional, with either an over-proliferation of cells and/or decreased removal of cells [21]. It has been established that suppression of apoptosis during carcinogenesis is thought to play a central role in the development and progression of some cancers [22]. Alterations of various cell signalling pathways can result in dysregulation of apoptosis and lead to cancer. The p53 tumor suppressor gene is a transcription factor that regulates the cell cycle and is the most widely mutated gene in human tumorogenesis [23]. Too little apoptosis can also result in diseases such as autoimmune

lymphoproliferative syndrome (ALPS) [24]. This is the result of insufficient apoptosis of auto-aggressive T cells, resulting in multiple autoimmune diseases. An over-proliferation of B cells occurs as well, resulting in excess immunoglobulin production, leading to autoimmunity. Some of the common diseases of ALPS include haemolytic anaemia, immune-mediated thrombocytopenia, and autoimmune neutropenia.

Excessive apoptosis may also be a feature of some conditions such as autoimmune diseases, neurodegenerative diseases, and ischemia-associated injury. Autoimmune deficiency syndrome (AIDS) is an example of an autoimmune disease that results from infection with the human immunodeficiency virus (HIV) [25]. This virus infects CD4+ T cells by binding to the CD4 receptor. It causes excessive apoptosis of T lymphocytes. Alzheimer's disease is a neurodegenerative condition which is characterized by excessive apoptosis in neurons and glia. Excessive apoptosis is also thought to play an important role in various ischemia-associated injuries. One example is myocardial ischemia, the over-expression of BAX has been detected in ischemic myocardial tissue and therapy aimed at reducing apoptosis has shown some success in reducing the degree of tissue damage [26].

CONCLUSION

The programmed cell death or apoptosis is as vital as the cell division and development. It is an essential evolutionary process which ensures the survival of the fittest. When it becomes pathological it can give rise to many diseases. Manipulating apoptosis is one avenue through which scientists can address several vexing medical problems. In the malignancies, there is the growth of abnormal cells which do not follow the usual rule of cell division. Restoring effective surveillance of abnormal cells and help those to commit suicide can contribute dramatically to the cancer eradication. In the inflammatory process enhancing the destruction of infected cells by mimicking apoptotic process may help in resolving infection by disposing of the infected cells. Inhibition of apoptosis has the potential to substantially reduce the damage to cardiac and neural tissues by ischemia. The selective control of apoptosis may substantially improve the outcome in Diabetes mellitus, AIDS and neurodegenerative disorders. Our knowledge about the apoptosis is still very limited and its scientific exploration will go a long way in understanding many disease processes and to find out its effective cure.

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