Iran. J. Ichthyol. (Special Issue 2023): 209-218

P-ISSN: 2383-1561; E-ISSN: 2383-0964
http://www.ijichthyol.org

Role of Apoptotic signaling pathways in the immune system

Ali B. ALDEEWAN*, Basil A. ABBAS, Nawres N. JABER, Mohammed H. KHUDOR

College of Veterinary Medicine, University of Basrah, Basrah, Iraq.
**Email: ali.dewan@uobasrah.edu.iq*

Abstract: Cell death is an essential element of life in multicellular organisms, playing roles in development, defense, and homeostasis. Apoptosis is the most common mode of cell death in animals, especially when it occurs as part of normal physiology. In the past, apoptosis was focused on the caspase, a family of cysteine proteases. Now, apoptosis is classified into types I, II, and III PCD: type I PCD is the classic apoptosis, the well know caspase-dependent apoptosis; type II PCD's morphology characters are the appearance of the autophagic and double membrane of vacuole; type III PCD occurs without the condensate chromatin and has not been well-known. Type II and type III PCD are caspase-independent apoptosis. This review will focus on the apoptosis signal pathway and some ligands that have been linked to apoptosis, with a focus on concluding apoptosis from two perspectives, in vivo, and in vitro cells, so that we can better understand the network of cell death and provide the results of the most recent research. On the other hand, this review focuses on apoptosis in immune system physiology. Aspects of apoptotic signal transduction, as well as the role of apoptosis in immunological development, are discussed in the various reviews.

Keywords: Physiology, Immune system, Development.
Citation: Aldeewan, A.B.; Abbas, B.A.; Jaber, N.N & Khudor, M.H. 2023. I Role of Apoptotic signaling pathways in the immune system. Iranian Journal of Ichthyology (Special Issue 1): 209-218.

Introduction

Apoptosis is a programmed cell death (PCD) required for normal cell function. The word "apoptosis" comes from the Greek language meaning "falling off" or "dropping off" of petals from flowers or leaves from trees in the autumn. Following the apoptosis research came in the third period in recent years; scientists began to research the molecular mechanism of apoptosis and to use this cell death for clinical treatment. Some key proteins in the procession of apoptosis have been found, such as Bcl-2 family protein, caspase-3, caspase-8, caspase-9, Bid, and Bax. This review will focus on the apoptosis signal pathway and some ligands that have been linked to apoptosis, with a focus on concluding apoptosis from two perspectives, *in vivo* and *in vitro* cells, so that we can better understand the network of cell death and provide the results of the most recent research i.e. it focuses on apoptosis in immune system physiology.

Apoptosis research timeline: Cell death is necessary for body homeostasis; necrosis, apoptosis, and pyroptosis are the three types of cell death currently studied. The term apoptosis was originally used in 1972, and some years ago, pyroptosis was known by the symbol of a hole in the cell membrane that released inflammatory chemicals. The study of apoptosis began in the nineteenth century. Sydney Brenner, Horvitz, and John E Suston were awarded the Nobel Prize in Medicine in 2002 for their contributions to apoptosis research. They are pioneers in organ development and genetic and systemic regulation-programmed cell death research. Sydney Brenner's contribution is the creation of a *C. elegans* nematode model. Suston then discovered the *C. elegans* cell lineage and the first gene (Nuc-1) associated with apoptosis. *Caenorhabditis elegans* is still the standard model

for studying apoptosis and organ development today. Now that apoptosis has been discovered in tumor development, and it is known that apoptotic pathway change is a typical hallmark of malignancies, allowing cancer cells to survive chemotherapeutic interventions, apoptosis signal pathway molecules have become interesting targets in cancer therapy. Apoptosis has been discovered in various disorders, including neurological diseases, diabetes, stroke, and so on, in addition to tumor growth. The essential apoptotic pathways are reviewed, and the role of apoptotic signaling pathways in the immune system is described.

Apoptosis signal pathway: Multi-signal pathways initiate apoptosis, regulated by a complex set of extrinsic and intrinsic ligands. The apoptosis process is regulated by the diverse cell signaling pathway and is important in determining whether a cell will die or live. There are two primary apoptosis mechanisms depending on whether or not caspases are involved. As cross-talk organelles, mitochondria can connect the many apoptosis pathways. Apoptosis is scientifically defined by the physical characteristics of the dying cell (Wyllie et al. 1980), particularly the condensation of chromatin, which is frequently followed by nucleus fragmentation. The plasma membrane frequently forms 'blebs,' and the cell may split into distinct membrane-bound apoptotic entities. Phagocytic cells quickly eliminate the apoptotic cell and any apoptotic bodies, and cell death does not trigger an inflammatory response. Although all cell death with these characteristics is apoptosis by definition, scientists often analyze molecular events in dying cells to further identify the process. However, characterization is not always as straightforward as it appears. Apoptosis is a mechanism for removing cells. This removal could be due to infection or injury, an overabundance, a developmental 'test' failure, or their existence is no longer required for physiological activity. Apoptosis occurs in the immune system when cells are stressed or deprived of growth factors, when developing cells fail to properly rearrange an antigen receptor or express one that fails negative or positive selection, or when cells have expanded in response to an antigenic stimulus and are now in excess, to name a few examples.

The idea of clonal deletion, in which lymphocytes with randomly produced antigen receptors are deleted from the system if they engage their unique antigen early in their (the cells') development, foreshadowed the relevance of apoptosis in the immune system. If the antigen is always present in the body, this process, now known as 'negative selection,' ensures that the specific cells do not mature. The immune system is able to function because one tier of the illusion of self/non-self-differentiation is generated (What is the 'illusion' here? Anything can be ‘self' since it is mechanistically defined in the system by the constant presence of an antigen. Fortunately, our own molecules are generally involved, which is why the system works). However, even after a cell has died, its impact on the immune system may continue. As previously stated, phagocytes clear apoptotic cells quickly, and among these are dendritic cells, the immune system's main antigen-presenting cells. The uptake of antigens from apoptotic cells can change the presentation process, affecting immune regulation. The full scope of this regulation's causes and repercussions is unknown. The caspases, a group of proteases in the cell, are responsible for orchestrating apoptosis (cysteine proteinases with specificity for aspartate residues).

Caspase-dependent pathway: Caspase-dependent apoptosis is the classic programmed cell death pathway, the capase-8, caspase-9, caspase-12, caspase-7, and caspase-3 cascades are frequently involved in this form of the apoptosis pathway. A variety of receptors are involved in this type of apoptosis pathway, including the TNF-alpha receptor, FasL receptor, TLR, death receptor, and so on. Some iron channels may have a role in the apoptotic process. The calcium channel is the most common iron channel. Because calcium

concentration in the cytosol regulates signal transduction and plays a role in cell proliferation and death, cell fate can be controlled by the calcium channel opening or closing.

The TNF-alpha-induced caspase-8-dependent pathway uses the TNF-alpha receptor to activate caspase-8 through the death complex, which then activates the Bcl-2 protein. Bcl-2 family protein activation may cause the mitochondria membrane to alter and drive the release of cytochrome c. Cytochrome c is a proapoptosis signaling molecule that stimulates the caspase cascade process, resulting in apoptosis. Radiation such as UV or X-rays can cause mitochondrial depolarization and membrane permeabilization, resulting in an increase in ROS, the release of cytochrome c, and the activation of caspase-9 and caspase-3. Finally, activation caspases will cleave the substrates, and cells will undergo apoptosis; some pathogen infection-induced apoptosis may also involve a caspase-8-dependent process.

The FasL receptor can identify alien pathogens and recruit FADD and caspase-8. For example, the intracellular pathogen herpesvirus infection can trigger caspase-8-dependent death. Some infections can induce alternative caspase-dependent apoptosis pathways in addition to caspase-8-dependent apoptosis. Mycobacterium TB, for example, can cause programmed cell death in macrophages, and this apoptosis pathway is dependent on caspase-12. NO and ROS generation, which is induced by ER stress, is also involved in Mycobacterium tuberculosis-induced apoptosis (Lim et al. 2011). Aside from bacteria, viruses can also cause apoptosis. An alternate Kaposi's sarcoma-associated herpesvirus replication can cause caspase-dependent host cell death (Prasad et al. 2012). Apart from bacteria and viruses, RNA fragments and DNA can also cause caspase-dependent apoptosis, as evidenced by the RNA fragment produced by *Mycobacterium tuberculosis*, which can activate caspase-8 dependent apoptosis during early log-phase growth (Obregón-Henao et al. 2012); In vivo, DNA damage can cause apoptosis by increasing ROS levels and changing mitochondria membrane permeability; many proteins or peptides can also cause cell death; amyloid peptide cytotoxicity can cause intracellular calcium disturbance, and then calpain is activated as a result of the calcium imbalance. While calpain may activate caspase-12, which is found in the ER and can inactivate Bcl-Xl, this is a new caspase-12-dependent death pathway (Nakagawaa & Yuana 2000). The mitochondria can employ this pathway to connect to other cell death pathways. Above all, viruses, RNA or DNA, proteins or peptides, some chemical substances, or natural chemicals can all cause caspase-dependent apoptosis. They could have various receptors and cause cell death by using different caspases as a transducer to transmit downstream signals. This was the host's method of defending against hazardous elements and maintaining a healthy physiological condition. It is clearly known that the different ligands and receptors are involved in this type of apoptosis, and this picture will give us a direct impression of this type of apoptosis.

Caspases cleave certain substrates, either activating or inactivating them, when they are active. The morphologic and phagocytic alterations associated with apoptosis are caused by these. They also supply us with markers of apoptosis, either directly or indirectly. Caspase assays or antibodies to the cleaved form of the caspases can be used to detect cells with activated caspases. Furthermore, caspases activate enzymes that cause clearly detectable cellular alterations, such as DNA fragmentation (detected by TUNEL (terminal-deoxynucleotidyl-transferasemediated dUTP–digoxigenin nick end labelling) or subdiploid tests) and phosphatidylserine externalization on the plasma membrane) (detected by the binding of annexin V) While all of them are helpful, it's vital to realize that none of them formally define apoptosis; yet, they do help to characterize cell death in useful and practical ways. Caspases engaged in apoptosis fall into two groups, which are characterized by

their chemistry and functions.

In their preforms, the 'executioner' caspases (caspases-3, -6, and -7 in vertebrates) exist as inactive dimers that primarily dwell in the cytosol. They are activated by cleavage at specified places in the mature enzymes' large and small subunits, and it appears that this is the only way they can be activated (Boatright et al. 2003). Granzyme B, a serine protease, is one enzyme capable of cleaving and activating the executioner caspases. It is found in cytotoxic lymphocyte granules and is delivered to target cells during the killing process. Granzyme B can (at least in theory) circumvent several possible regulatory areas that intracellular parasites could exploit by directly targeting executioner caspases. Another group of caspases known as 'initiator' or 'apical' caspases (the major enzymes) is responsible for cleaving and activating the executioner caspases. The initiator caspases, unlike the executioner caspases, are not activated by cleavage (cleavage does occur, but it does not result in the development of an active site (Boatright et al. 2003). The initiator caspases are monomers in their preforms, and it appears that only their forced dimerization can activate them. Adapter molecules attach to protein-interaction domains near the initiator caspases' N-terminal prodomains, causing them to activate. The executioner caspases' prodomains are substantially shorter and lack such protein-interaction domains.

Apoptotic caspase activation and cell death are defined by the initiator caspases and the adapter molecules that bind and oligomerize them. The death receptor pathway and the mitochondrial pathway (sometimes known as the 'extrinsic' and 'intrinsic' pathways, respectively) are the two pathways in vertebrates. The routes are useful for a first look at apoptotic signaling, even if the distinctions are rather arbitrary. Death receptors are a subset of the tumor necrosis factor (TNF) receptor family, including TNFR1, Fas, DR3/TNF receptor apoptosis-mediating protein, and the TNF-related apoptosis-inducing ligand receptors.

A protein-interaction region called a death domain is present in these trimeric receptors (DD). The DDs of these receptors attach to a comparable DD on the adapter molecule, Fas-associated DD (FADD), after binding their ligands (an exception is TNFR1, which binds to a different adapter, TRADD, which in turn binds to FADD). FADD features another protein-interaction domain called a death effector domain in addition to a DD (DED). The DD and DED are structurally similar, forming a so-called "death fold." FADD's DED attaches to a DED in the prodomains of caspase-8 and caspase-10, the initiator caspases (the latter is present in humans, but apparently not in rodents). A death-inducing signaling complex is created by the ligated death receptors, FADD, and caspases, and resulting in the dimerization and activation of the initiator caspases. The other well-known method of initiator caspase activation is the mitochondrial pathway. The initiator caspase in this situation is caspase-9, which is activated when its death-fold caspase recruitment domain (CARD) binds to the CARD of the other caspase.

Apoptotic protease-activating factor-1 is an adapter molecule (APAF-1). In the cytoplasm of live cells, APAF-1 resides as a monomer, but when activated, it forms an oligomer (apoptosome) that exposes its CARD domain. Caspase-9 dimerizes and is activated as a result of this action. Holocytochrome is the only known chemical that can activate vertebrate APAF-1. Holocytochrome c is normally isolated from APAF-1 and sequestered in the mitochondrial intermembrane gap, where it plays an important role in electron transport. During apoptosis, however, mitochondrial outer membrane permeabilization (MOMP) occurs, releasing intermembrane space proteins, and allowing cytochrome c to activate APAF-1 for apoptosis to proceed. MOMP is a tightly regulated mechanism that is governed by Bcl-2 family members. (It is not just 'damage' to the mitochondria, which is a common description in this context, but it suggests that a range of substances that directly attack the mitochondria might cause MOMP). This does not

appear to be the case. Anti-apoptotic Bcl-2 family members (Bcl-2, Bcl-xL, A1, Bcl-w, Mcl-1) inhibit MOMP, preventing cytochrome c release and APAF-1 activation. There are two types of pro-apoptotic Bcl-2 family members. Some proteins are classified as 'multidomain' or 'BH123' because they share three Bcl-2 homology domains (BH1, BH2, and BH3). Bax, Bak, and Bok are some of these proteins. Recent research suggests that if activated, they are both essential (Wei et al. 2001) and sufficient (Kuwana et al. 2002) for permeabilizing the mitochondrial outer membrane. Another set of proapoptotic Bcl-2 family members that share only the BH3 domain and are hence referred to as 'BH3-only' proteins activates the BH123 proteins. Bim, Bid, Bad, Bmf, BNIP-3, Puma, Noxa, and others are only a few examples (Puthalakath & Strasser 2002).

Caspase independent pathway: Apoptosis is mediated by a variety of mechanisms. It has multiple signal transduction pathways and can be triggered by *in vitro* and *in vivo* cell ligands. Apoptosis pathways are now divided into two categories: caspase-dependent and caspase-independent. The caspase-dependent pathway, which is characterized by the participation of caspase in this sort of cell death process, is described and concluded in the preceding sections.

Caspase does not engage in this type of process. Many researchers have discovered this type of apoptosis, and the research data provide us with a wealth of information that can aid in our understanding of the apoptosis complex mechanism. In addition to mechanisms, many works have discovered complicated ligands that can cause this type of cell death. We will go over some specifics of caspase-independent apoptosis in the next sections many ligands can cause a change in mitochondria membrane potential in the cell; mitochondrial damage will be the initial step in apoptosis, followed by an increase in ROS generation, and ROS may be the key contributor in caspase-independent apoptosis. Denis Martinvalet discovered that granzyme A can cause an increase in reactive oxygen species (ROS) and mitochondrial damage without the use of caspases. Then the granzyme A target, the ER-associated complex (SET complex), translocates to the nuclear and contributes to apoptosis (Martinvalet et al. 2005).

AIF has been discovered as a major important caspase-independent pro-apoptosis factor, which can release from the mitochondria and translocate to the nuclear to cleave the DNA, and apoptosis will occur if the DNA damage is not repaired by the cells. Simvastatin, staurosporine, cadmium, and other chemicals that can accompany AIF synthesis and promote cell death. These substances produced caspase-independent PCD, which matched the organism's needs; in addition to AIF, ROS also plays a role in this form of cell death. ROS can activate the poly (ADP-ribose) polymerase-1 (PARP-1) enzyme, which is required for AIF release from mitochondria. As a result, ROS plays a role in cell death networks (Kang et al. 2004). ROS, on the other hand, was involved in the caspase-dependent apoptosis pathway. ROS may serve as a crucial link between two forms of apoptosis in vivo. Because mitochondria produce the majority of ROS, they play an important role in the crosstalk between apoptotic pathways. And the ligands frequently produce complex responses, such as AIF nuclear translocation, an increase in reactive oxygen species (ROS), and mitochondrial malfunction, all of which can disrupt the caspase-independent apoptosis pathway. For example, Cyclohexyl analogues of Ethylene diamine Dipropanoic Acid, a chemical that can cause apoptosis in both healthy and leukemic peripheral blood mononuclear cells by activating several apoptogenic proteins, can induce apoptosis in both healthy and leukemic patients such as AIF nuclear translocation, ROS increase and mitochondrial dysfunction networks (Misirlic Dencic et al. 2012). In terms of ROS, we believe that GSH, NO, or other free radical groups may also be involved in this form of cell death. GSH and NO can block some active thiol groups, causing the protein to undergo S-glutathionylation or

Snitrosylation alteration, and so may play a role in the apoptotic cascade. These modifications may have an effect on the function of the protein, causing the cell to apoptose. However apart from AIF and ROS, many other ligands and signal molecular from vitro or vivo cells act as apoptogenic factors in the caspase-independent apoptosis pathway, such as lysosomal membrane permeabilization; some virus's protein; drugs; p53 suppression tumor factors, or a variety of other unknown compounds. Until now, the caspase-independent apoptosis mechanism has remained unclear.

Although some researchers have discovered that AIF, ROS, and other ligands can activate this sort of PCD, the signal pathway is still in the experimental stage, and we need to dive deeper into the mechanism. Regardless of which sort of apoptosis occurs, this type of cell death has critical tasks that warrant further investigation. Caspase-independent apoptosis was observed in a number of species and played a critical role in cell development, proliferation, and death. Caspases family members were not involved in this kind of apoptosis, and caspase inhibitors such as z-VAD-FMK, quinolyl valyl-o methylaspartyl [2,6-difluorophenoxy]-methyl ketone(Q-VD-OPH), Ac-DEVD-FMK, and others could not stop it. Some components and processes in the cells, such as AIF, ROS, Ca2+, NAD+, and ATP; protein misfolding and modification; and caspase-independent apoptosis, can trigger caspase-independent apoptosis.

Mitochondria dynamics and apoptosis: Mitochondria, as a semiautonomous organelle in cells, play a crucial function in energy metabolism in addition to containing their own genetic material. It manufactures ATP to maintain cell life activity and is known as a cell energy company. Mitochondria are the sites of several biological reaction mechanisms, including ROS generation, apoptosis, and aging regulation (Marchi et al. 2012). Mitochondrial malfunction has been linked to a variety of disorders (Alzheimer's, Parkinson's, cancer, and diabetes) (Kwong et al. 2006; Reddy et al. 2009). These disorders have been linked to apoptosis, and ROS produced by mitochondria has been recognized as one of the most essential components in apoptosis. When a pathogen infects a cell, the production of reactive oxygen species (ROS) increases. ROS can cause apoptosis, which causes pathogens to lose their ideal living habitat, allowing the host to defend against the infection's spread. Because of these functions, mitochondria may be a good therapeutic target for disorders involving this kind of cell death (Moreira et al. 2010).

Mitochondria can change their form and structure in response to various stimuli and metabolic demands of cells. According to the most recent biochemistry and cell biology studies, the changes in mitochondrial shape between fusion and fission play a critical role in apoptosis regulation (Sheridan et al. 2008; Karbowski 2010;). There were also disagreements concerning whether apoptosis occurred as a result of mitochondrial fission. These disputes centered on which process came first: apoptosis or mitochondrial fission and fragmentation as a result of apoptosis, or the mitochondrial fission and fragmentation as a result of apoptosis as a follow-up event. According to recent studies, it is certain that dynamic changes in mitochondrial structure are linked to apoptosis: Calcium irons operate as an upstream trigger that can stimulate cellular mitochondrial fission. As the calcium level in the intracellular increases, the mitochondrial fragmentation rate increases. If the calcium level is raised for an extended period of time, mitochondrial fragmentation will become irreversible, leading to apoptosis. As a result, calcium was involved in mitochondrial morphology and apoptotic processing (Hom et al. 2007). Some mitochondrial membrane proteins control mitochondrial morphology, such as the Bcl-2 protein, which resides in the outer mitochondrial membrane and acts as a central regulator of the intrinsic apoptotic cascade; while other toxins or

proteins can also regulate mitochondrial fission/fusion, and these variations in mitochondrial shapes have been linked to some diseases. For example, Parkinson's disease has been linked to abnormalities in mitochondrial morphology. Two toxin proteins, parkin and PINK1 play a role in mitochondrial homeostasis by targeting mitochondria and regulating mitochondrial dynamics (Van Laar & Berman 2009) [20]. In mammalian cells, there is DRP1-dependent division and FZO1-dependent fusion response, and mitochondrial division is associated with apoptosis. If mitochondrial fission/fusion dynamics lose balance, it can lead to neurodegenerative disorders. In conclusion, mitochondria play a crucial role in maintaining cell health. Cytochrome C, a mitochondrial iron transporter, plays a key function in apoptosis. It connects to the caspase cascade reaction as a bridge. When mitochondrial cytochrome C is released into the cytoplasm in response to some intrinsic or extrinsic ligands, it can activate downstream caspases and cause intrinsic apoptosis. Therefore, mitochondria may also govern the intrinsic apoptotic pathway via cytochrome C, calcium, morphological changes (fission/fusion), or an imbalance in the expression of membrane proteins (Bcl-2).

Another set of proapoptotic Bcl-2 family members that share only the BH3 domain and are hence referred to as 'BH3-only' proteins activates the BH123 proteins. Bim, Bid, Bad, Bmf, BNIP-3, Puma, Noxa, and others are only a few examples (Puthalakath, H. & Strasser 2002). These proteins are regulated in a variety of ways, and they are thought to be linked to different signaling pathways in the MOMP process (and apoptosis). Phosphorylation activates Bad, proteolytic cleavage activates Bid, and cytoskeleton release activates Bim and Bmf. MOMP causes the release of proteins that regulate cell death and survival in addition to cytochrome c. EndoG and AIF, apoptosis-inducing factor, are two of these proteins that may trigger cell death without caspase activation.

Smac/ DIABLO, second mitochondria-derived activator of caspase/direct inhibitor of apoptosis protein (IAP)-binding protein with low pI, and Omi/Htra2 are two other proteins that regulate caspase activation via binding to IAPs. Smac/DIABLO and Omi/Htra2 enhance caspase activation by interfering with IAP function, as IAPs bind to and inhibit active caspases. The death receptor, granzyme B, and mitochondrial pathways are beginning to converge. IAPs may be present in the cell to block caspases, despite the fact that death receptors and granzyme B can directly activate caspases without the involvement of mitochondria. Caspase-8 and granzyme B, on the other hand, can cleave and activate the BH3-only protein Bid, which then activates Bax and Bak, resulting in MOMP. As a result, Smac and Omi can be released, preventing IAP-mediated caspase inhibition and therefore encouraging death. If MOMP has happened, death may occur even if caspases are stopped.

As previously stated, mitochondria release AIF and EndoG, which can cause death without the use of caspases (caspase-independent death). Omi has also been proven to have the ability to destroy cells without the need of caspases. Furthermore, mitochondria that have been subjected to MOMP gradually lose their function, which may result in a cell's death. There are likely a number of alternative avenues to caspase activation and apoptosis that are less well-known. In some cells, one initiator caspase, caspase-2, has been proposed to be required for the initiation of apoptosis upstream of mitochondria (Lassus et al. 2001). While a CARD-containing adaptor molecule (RAIDD) for this caspase has been found, it is unknown how, when, or whether (or not) it activates the caspase, as well as the downstream stages in this pathway. Some caspases are involved in cytokine processing (for example, caspases-1 and-5 are involved in interleukins-1b and -18 processing), and these caspases appear to be activated by the creation of an inflammasome (Martinon et al. 2002). This pathway's ability to activate executioner caspases

and cause apoptosis is unknown. Another mechanism appears to involve DED-containing adaptor molecules termed Hip-1 and Hippi, which appear to activate caspase-8 in cells where polyglutamate proteins have formed aggregates (as seen in numerous types of neurodegenerative disorders) (Gervais et al. 2002). Finally, stress-induced apoptosis in the endoplasmic reticulum involves mechanisms other than those outlined here, such as caspase-8 (Breckenridge et al. 2002) or caspase-12 (Nakagawa et al. 2000) in rodents (humans do not appear to express caspase-1 (Fischer et al. 2002). These or other routes could work in lymphocytes, especially as lymphocytes lacking APAF-1 or caspase-9 can still activate caspases and undergo apoptosis (Hara et al. 2002; Marsden et al. 2002).

Trigger apoptosis ligands and cell environment materials: Apoptosis is a significant cell death mechanism that plays a crucial part in maintaining life's equilibrium. Apoptosis occurred during fetal development, and it was necessary for the production of the fingers and toes. We can produce five fingers per hand because to apoptosis in the cells between the fingers. Apoptosis can also help embryonic stem cells survive during stress by increasing the production of the Bcl-2 protein, which weakens apoptosis and aids colony formation (Ardehali et al. 2011). Apoptosis is also involved in the regeneration and homeostasis of some tissues (Bergmann & Steller 2010; Luo et al. 2012). Apoptosis, in addition to the functions listed above, can also reduce inflammation and hinder pathogen persistence, particularly by interfering with intracellular parasite diffusion. Finally, apoptosis is beneficial to people's health in a multitude of ways, and it has recently become a study focus. Several ligands can either activate or suppress apoptosis, based on current studies. By deduction, we divided these ligands into two groups: Extrinsic signal ligands are a type of extrinsic signal ligand. Intrinsic ligands are ligands that are found naturally in the body. Extrinsic cell materials: Materials for cytokines, drugs, hormones, pathogen effectors, native activities compounds, and intrinsic cell apoptosis signaling included: Endoplasmic reticulum (ER) stress, oxidative stress (ROS; NO; GSH), Cytochrome C, Calcium iron.

Cytokines: TNF-alpha with z-VAD can cause cell death, and this approach is often used to create cell death models. TNF-alpha can bind to the extracellular domain of the TNF-alpha receptor, and the cytoplasm domain can aggregate FADD and FLICE, which can initiate apoptosis; another well-known cytokine, IFN-γ, which can induce macrophage apoptosis, plays a key role in mycobacterium tuberculosis clearance by inducing nitric oxide-dependent host cell apoptosis (NO) (Herbst et al. 2011). TGF-1-β1 is a chemoattractant that is critical for the immune response; nevertheless, this cytokine also has a suppressive role, limiting cell proliferation and driving B cells to apoptosis (Lebman & Edmiston 1999).

Cytokines are a positive apoptosis inducer. Another mechanism of cytokine-related apoptosis discovered by the researchers is negative induction caused by the loss of suppressive signal. Many cells' vitality depends on the continual or intermittent flow of cytokines or growth factors; without these, the cell will go into apoptosis. These cytokines or growth factors operate as apoptosis suppressors in this situation. For example, when culturing hematopoietic cells, colony-stimulating factors and IL-3 should be added; also, IL-12 is necessary to sustain the viability of activated T cells in in vitro culture systems; and neurorophic cells require nerve growth factor (NGF) to survive. Furthermore, several additional cytokines and growth factors, such as epidermal growth factor, platelet-derived growth factor, and insulin-like growth factor-I, operate as apoptosis suppressors. They also operate as survival factors, inhibiting apoptosis, whereas blocking or removing these factors causes the associated cells to undergo apoptosis. Cytokines can act as an inducer or suppressor in the apoptotic pathway.

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