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Apoptosis: An essential biological phenomenon

Kajal Nayan Majumdar
Post Graduate Department of Zoology, Midnapore College (Autonomous), P.O. Midnapore,
Dist. Paschim Medinipur, West Bengal, INDIA, PIN-721101.
E-mail: *kajalnm@gmail.com*

Abstract

Apoptosis or "programmed cell death" is a normal cellular process by which cells in a multi-cellular organism commit suicide by distinctively ordered metabolic changes through normal development as well as during environmental stress or pathogen attack to attain and maintain homeostasis, to control cell number and to remove cells that threaten the animal's survival. Apoptosis is a pervasive, organized and rational type of cell death in which the cell employs special cellular machinery to kill itself without causing any inflammatory response. Apoptotic cell death is characterized by a number of distinct cellular changes like cell shrinkage, irregularities in cell shape, membrane blebbing, externalization of phosphatidylserine in cell membrane, chromatin condensation, and inter-nucleosomal DNA fragmentation, increased mitochondrial membrane permeability leading to the release of cytochrome c in the cytoplasm and subsequent formation of "apoptotic bodies" which are then phagocytosed by neighboring cells. Apoptosis plays an important role both in embryonic development and in adult tissue homeostasis to maintain the integrity of multi-cellular organisms. Moreover, it is an essential biological phenomenon as defective apoptotic processes have been associated with an extensive variety of diseases. Too much apoptosis causes hypotrophy, like in ischemic damage, alternatively an inadequate amount results in uncontrolled cell proliferation, such as cancer. Therefore apoptosis is very much essential for living organisms to preserve homeostasis as well as to maintain their internal states within certain limits.

Keywords: Apoptosis, Cancer, Caspase, Cell Death, Homeostasis, Necrosis.

Introduction

The structural and functional unit of all living organisms is a cell. From the initial stages of embryonic development, the shape and architecture of all organs are well-defined by a tightly controlled balance between proliferation, differentiation and cell death. The cell numbers are kept relatively constant through the mechanism of cell death and division in an adult organism. When cells become diseased or malfunctioning, they must be replaced; but proliferation must be compensated by cell death (*Thompson, 1995*). This harmonizing process is part of the homeostasis necessary for living organisms to maintain their internal states within certain limits. When the rate of mitosis (cell proliferation) in the tissue is balanced by cell death, homeostasis is achieved. If this equilibrium is disturbed, one of the two potentially fatal disorders occurs: (I) if the cells divide faster than they die effectively develops a tumor, (II) if the cells divide slower than they die results in a disorder of cell loss. The organism must orchestrate a complex series of controls to keep homeostasis tightly controlled, a process which is ongoing for the life of the organisms. Impairment of any one of these controls leads to a diseased state.

Apoptosis: A biological event

Death is an unavoidable fact of life for organisms. And for every cell there is a time to live and time to die. As all cells have a finite lifespan, biologists have come to realize gradually that death is also, in many cases, an important and predestined fate of individual cells of organisms. In a mature organism, the number of cells is kept relatively constant through cell death and division. Therefore, it has been emphasized that the death of living matter is an integral and necessary part of the life cycle of organisms. Cell can die in two ways: by damaging their cell membrane and then undergoing necrosis or by shrinking and blebbing the intact cell membrane, which leads to apoptosis (*Oberholzer et al., 2001*).

More than 100 years back, scientists have discovered that cell death is a completely normal process in living organisms. Since the mid-nineteenth century, many observations have showed that cell death plays crucial role during physiological processes of multicellular organisms, primarily during embryogenesis and metamorphosis (*Glucksmann, 1951*). In 1964, the term programmed cell death was introduced, suggesting that cell death in the period of development is not of accidental nature but follows a sequence of orderly steps leading to locally and temporally defined self-destruction (*Lockshin, 1964*). Eventually, the term apoptosis had been coined to describe the morphological processes leading to controlled cellular self-destruction was first described by Kerr, Wyllie and Currie (*Kerr et al., 1972* and *Sankari et al., 2015*). Apoptosis (Greek: *apo* - from, *ptosis* - falling; commonly pronounced with a silent second p) is of greek origin, that means "falling off or dropping off", in analogy to leaves falling off trees or petals dropping off flowers.

In cellular terms, apoptosis is a pervasive, organized, rational type of cell death in which the cell uses special cellular machinery to kill itself. Apoptosis is a normal cellular process by which cells in a multicellular organism commit suicide by specifically ordered metabolic changes during normal development, environmental stress or pathogen attack to achieve and maintain homeostasis, to control cell number and to eliminate cells that threaten the animal's survival. Using an elaborate arsenal of cellular and molecular machinery a cell itself initiates, regulates, and executes the apoptotic process. The apoptotic cell death tends to follow a morphologically similar pattern as well as it involves an orchestrated series of biochemical events leading to characteristic cell morphology and death. Apoptosis is characterized by a number of distinct cellular changes such as cell shrinkage, irregularities in cell shape, membrane blebbing, externalization of phosphatidylserine in cell membrane, chromatin condensation, and internucleosomal DNA fragmentation, increased mitochondrial membrane permeability leading to the release of proapoptotic proteins (like cytochrome c) in the cytoplasm and subsequent formation of "apoptotic bodies" (several membrane-enclosed vesicles containing intracellular materials inside). In fact, apoptotic process is functionally conserved and physiological forms of this type of cell death are genetically programmed (*Lockshin and Zakeri, 2001*). Therefore, the term apoptosis is often used interchangeably with the term "programmed cell death," or PCD (although technically, apoptosis is but one particular form of programmed cell death).

Apoptosis is essential in the homeostasis of normal tissues of the body, especially those of the gastrointestinal tract, immune system and skin (*Bold et al., 1997*). Apoptosis plays an important role both in embryonic development and in adult tissue homeostasis to maintain the integrity of multicellular organisms (*Kerr et al., 1972*). Cells may also undergo apoptotic death in times of distress, for the good of the organism as a whole. Apoptosis occur during a number of events such as when a cell is damaged beyond repair, infected with a virus, or undergoing stress conditions like starvation. In these cases, to prevent the cell from sapping further nutrients from the organism or to prevent the spread of viral infections, removal of the damaged cell occurs through apoptosis. Apoptosis is the most common mechanism by which the body eliminates damaged or unneeded cells without local inflammation from leakage of cell contents as well as the process is carried out in such a way as to carefully dispose of cell corpses and fragments. Additionally it is an important biological phenomenon as defective apoptotic processes have been implicated in an extensive variety of diseases. Too much apoptosis causes hypotrophy, like in ischemic damage, alternatively an insufficient amount results in uncontrolled cell proliferation, such as cancer. Apoptosis also has a preventing role in cancer; if a cell is not able to undergo apoptosis, due to mutation or biochemical inhibition, it starts to divide continuously and develop into a tumor. Therefore apoptosis is very much essential for living organisms to preserve homeostasis as well as to maintain their internal states within certain limits.

Morphological characteristics of apoptosis

Apoptosis involves a series of organized biochemical events which results in a distinctive cellular morphology. During apoptotic cell death, a cell shows a characteristic morphology that can be observed with a microscope:

1. Cell shrinks and become roughly round in shape, due to the breakdown of the proteinaceous cytoskeleton by caspases.
2. The cytoplasm appears dense, the organelles found tightly packed and endoplasmic reticulum becomes dilated.
3. Chromatin condensation occurs into compact patches against the nuclear envelope through the process known as pyknosis, a hallmark of apoptosis.
4. Karyorrhexis takes place, a process where the nuclear envelope becomes discontinuous and the DNA inside it is fragmented. The nucleus breaks into several discrete chromatin bodies or nucleosomal units due to the degradation of DNA.
5. The cell membrane develops irregular buds known as blebs.
6. The cell breaks apart into several membrane-enclosed vesicles called "apoptotic bodies" containing intracellular materials in it, which are then phagocytosed.

In contrast to apoptosis, the necrotic mode of cell death represents a passive consequence of mechanical damage or exposure of the cells to toxins. This type of cell death results from acute cellular injury in which cells suffer a major insult, resulting in a loss of membrane integrity, cellular swelling, organelle dysfunction, mitochondrial collapse and ultimately cellular disintegration. During necrosis, the abandoned release of cellular contents into the extracellular environment consequences in the damage of neighboring cells and a strong inflammatory response in the corresponding tissue. The differences between apoptosis and necrosis are summarized in Figure 1 and Table 1.

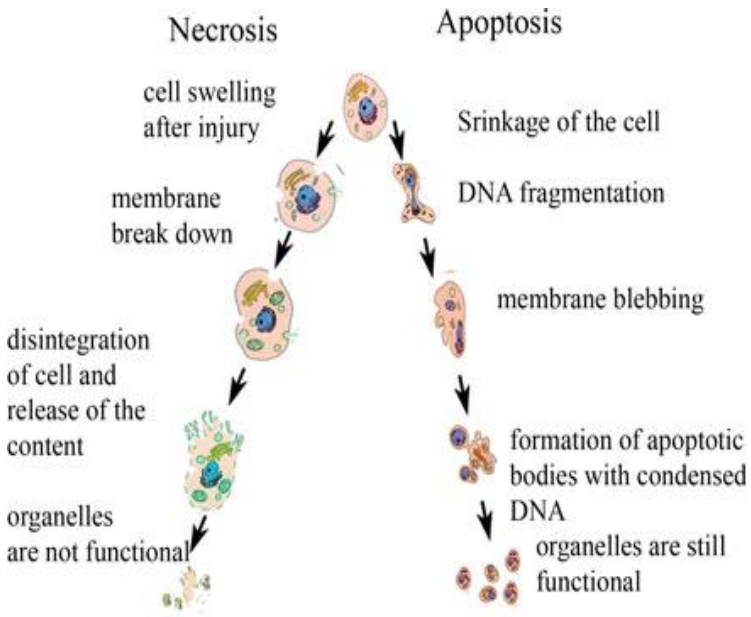

Figure 1. Schematic representation of necrotic and apoptotic cell morphology. (Buttino *et al.*, 2011 Apoptosis to predict …. future perspectives. Hydrobiologia 666:257–264)

Table1: Comparison of apoptosis with necrosis.

	Apoptosis	Necrosis
Etiology	Physiological or pathological.	Accidental, always pathological.
Regulation	Susceptibility tightly regulated.	Unregulated or poorly regulated.
Inflammation	No leakage of cell content, no inflammatory response.	Leakage of cell content, significant inflammatory response.
Morphological and biochemical characters	Cell shrinkage, cytoplasm appears dense, chromatin condensation (pyknosis), regular DNA fragmentation leading to nuclear fragmentation (karyorrhexis), loss of membrane asymmetry early, membrane blebbing but integrity maintained, plasma membranes near to intact until late stage, increased mitochondrial membrane permeability leading to the release of proapoptotic proteins and subsequent formation of apoptotic bodies.	Cell swelling, swelling of the entire cytoplasm, random degradation of DNA, plasma membranes destroyed early, loss of membrane integrity, organelle swelling as well as lysosomal leakage, and swelling of mitochondria.
Effectiveness	Affects single cell.	Affects groups of neighboring cells.
Removal of dead cells	Apoptotic bodies ingested by neighboring cells.	Lysed cells ingested by macrophages.

Process of apoptosis

Apoptosis is a strongly regulated and at the same time very much competent cell death program which necessitates the interplay of a multitude of factors. For apoptotic cell death, the components of the signaling network are genetically encoded and are believed to be usually in place in a nucleated cell ready to be activated by death-stimuli. In general, the activation of apoptosis is observed to occur when a cell encounters a particular death-inducing signal (withdrawal of positive signals like growth factors, those are needed for continued survival or receipt of negative signals like DNA damage, environmental stress and pathogen attack which causes cell death) or when cells are treated with a cytotoxic drugs.

Apoptosis can be triggered by a wide variety of extracellularly (extrinsic inducers) or intracellularly (intrinsic inducers) originated stimuli, e.g. by ligation of cell surface receptors to certain death factors, by DNA damage as a result of defects in DNA repair mechanisms, by a lack of survival signals, by development of death signals, contradictory cell cycle signaling, treatment with cytotoxic drugs or irradiation. Intracellular apoptotic signalling is a response initiated by a cell in response to stress; which ultimately results in cell suicide. In a damaged cell, several factors such as binding of nuclear receptors with glucocorticoids, heat, radiation, nutrient deprivation, viral infection and hypoxia can lead to the release of intracellular apoptotic signals (*Cotran et al., 2004*). On the other hand, extracellular signals include hormones, growth factors, nitric oxide or cytokines which must either cross the plasma membrane or transduce through it to generate a response. Death signals of such diverse origin however appear to eventually activate a common cell death machinery leading to apoptosis. Before the actual death process of cell is carried out by enzymes, apoptotic signals necessarily are connected to the respective death pathway by way of regulatory proteins. This step permits apoptotic signals to either terminate in cell death, or be aborted, keeping the cell no longer necessity to die. A number of regulatory proteins are involved, however two main methods of attaining regulation have been identified; targeting mitochondria functionality, or straightly transducing the signal through adapter proteins to the apoptotic mechanisms. Generally, the genetic design of apoptosis involves the activation of a complex array

of cysteine aspartate proteases (caspases) either through death-receptors mediated extrinsic pathway or mitochondria mediated intrinsic pathway (*Hussein et al., 2003*). However, these two main pathways converge to a common execution phase of apoptosis.

I. The death receptor mediated extrinsic apoptotic pathway:

The extrinsic apoptotic pathway is typically engaged in cellular immunity to delete activated T-cells at the end of an immune response, but also be implicated in the response of cancer cells to drug therapy. This pathway is initiated by the binding of death factors like TNFα, TRAIL (TNF-related apoptosis-inducing ligand) or FasL (Fas Ligand) with their cognate death-receptor superfamily. This binding induces the trimerization and activation of the receptor. Once activated, the cytoplasmatic domain of the receptor (namely, the 'death domain') binds a series of adaptor proteins, DED (death effector domain) that in turn recruit the inactive proforms of procaspase 8 (previously called FLICE) resulting in the formation of multimeric death-inducing signaling complex (DISC). The complex brings multiple pro-caspase 8 molecules in close proximity, resulting in the activation of caspase 8 through 'induced proximity' and by autoproteolysis (the aggregation molecules results in their cross-activation). After that activated caspase-8 (a heterotetramer) is released from DISC into the cytoplasm, where it functions as an initiator caspase, activating downstream executioner caspase, primarily via procaspase-3 (*Soengas et al., 2003*).

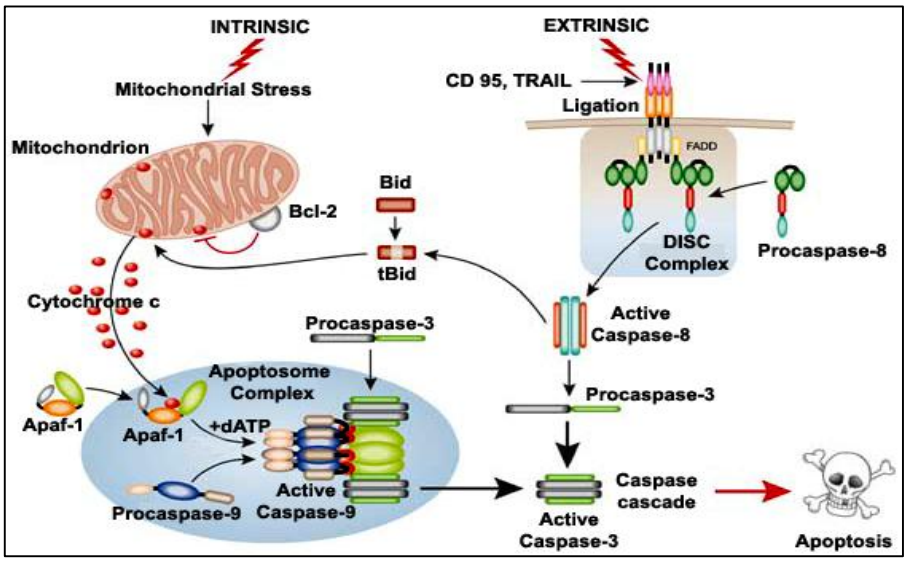

Figure 2: The 'extrinsic' and 'intrinsic' pathways of caspase activation during apoptotic cell death. [Marion MacFarlane and Ann C Williams EMBO Rep. (2004)5:674-678]

II. The mitochondria mediated intrinsic apoptotic pathway:

Besides amplifying and mediating extrinsic apoptotic pathways, mitochondria also actively participate in the integration and propagation of death signals which originate inside the cell (*Wang, 2001*). The mitochondrial pathway is usually activated in response to lethal stimuli such as DNA damage, growth factor deprivation, cell-cell detachment (anoikis), oxidative stress and low oxygen (hypoxia) (*Rich et al., 2000*). During apoptosis, mitochondria targeting proteins affect them in different ways; they may cause swelling of mitochondria through the formation of membrane pores or they may increase the permeability of the mitochondrial membrane and cause apoptotic effectors to leak out (*Cotran et al., 2004*).

Mitochondria contain a number of proapoptotic factors such as cytochrome c and apoptosis inducing factors (AIF). These proteins are harmless and safely impounded within the mitochondria but when stimulated with death stimuli they released into the cytoplasm. Upon stimulation with death signals, like DNA damage or oxidative stress cytochrome c releases from mitochondria due to increased permeability of the outer mitochondrial membrane and serves as a critical inducer of programmed cell death (*Cotran et al., 2004*). Once released into the cytosol, cytochrome c binds the apoptotic activator 1(Apaf-1)

and in the presence of ATP coordinates a series of conformational changes that allow the oligomerization of Apaf-1 into a ring-like complex with a sevenfold symmetry referred to as the 'apoptosome'. The apoptosome binds and activates caspase 9, which in turn recruits and activates caspases 3 and/or -6 and -7 and engages a series of proteolytic events that will culminate in a coordinated disintegration of the cell (*Soengas et al., 2003*).

The regulation of the mitochondrial pathway is complex. A main sensor in this pathway is the 'guardian of the genome' p53. Once activated, p53 will induce the expression of multiple transcriptional targets, including proapoptotic members of the Bcl-2 (B cell lymphoma 2) family such as Bax (Bcl-2-associated X protein), Puma (p53-upregulated modulator of apoptosis) and Noxa (PMA-induced protein). These factors contribute to changes in mitochondrial physiology that favour the release of cytochrome c. Some antiapoptotic Bcl-2 family members like Bcl-2, Bcl-X_L (Long isoform) and Mcl-1 (Induced myeloid leukaemia cell differentiation protein) control the release of cytochrome c into the cytosol (*Adams and Cory, 1998*). Formation of the apoptosome and activation of the downstream caspases is also controlled by a family of IAPs (inhibitor of apoptosis proteins), which in turn are inactivated by yet other proapoptotic factors released from the mitochondria, the Smac (second mitochondria-derived activator of caspase)/Diablo and Omi/OtrA (*Wang, 2001; Soengas et al., 2003*).

The Executioner stage of apoptosis:

Although many pathways and signals lead to apoptosis, there is only one mechanism which actually causes the death of the cell in this process; after the appropriate stimulus has been sensed by the cell and the essential controls exerted, then the cell undergoes the organized degradation of cellular organelles by activated proteolytic caspases. Therefore, final phase of apoptosis execution that includes activation of executioner caspases (e.g. Caspase 3) is shared by both these pathways (*Cryns and Yuan, 1998*). Thus, the mitochondrial and the death receptor mediated pathways meet at this point. Stimulation of the 'initiator' caspases (-8, -9,-10) results in activation of the 'executioner' caspases (-3,-6,-7), which then cleave vital substrate/cellular death substrates ultimately leading to the demise of the cell.

Removal of dead cells by phagocytosis:

Dying cells that undergo the final stages of apoptosis exhibit phagocytotic molecules, such as phosphatidylserine, on their cell surface (*Li et al., 2003*). Normally phosphatidylserine remain present on the cytosolic surface of the plasma membrane, but during apoptosis is redistributed to the extracellular surface by a hypothetical protein known as scramblase (Wang *et al.*, 2003). These molecules mark the cell for phagocytosis (eat me signal) by cells possessing the appropriate receptors, such as macrophages (*Savill et al., 2003*). During recognition, the phagocytes identify its cytoskeleton for engulfment of the cell. The removal of dying cells by professional (e.g. macrophage) or semi-professional phagocytes (e.g. neighbouring cells) occurs in an orderly manner without eliciting an inflammatory response.

The role of caspases in apoptosis

A biochemical hallmark of apoptotic cell death which increasingly appears general is the activation of caspases, which are cysteine-dependent aspartate-specific protease related to *ced-3*, the "death gene" of the nematode *Caenorhabditis elegans*. The proteolytic activity of these enzymes is characterized by their unusual ability to cleave their substrate proteins at aspartic acid residues. Although different caspases have different fine specificities involving recognition of neighboring amino acids, their catalytical activity depends on a critical cysteine residue within a highly conserved active-site pentapeptide QACRG.

The different members of this protease family differ in primary structure and substrate specificity but share several common features. First, each caspase cleaves on the carboxyl side of aspartate residues. Second, each active caspase is a tetramer composed of two identical large subunits and two identical small subunits. Again, in the cell, each caspase is synthesized as an inactive zymogen, the so called procaspase that contains an N-terminal prodomain, a large subunit and a small subunit which sometimes are separated by a linker peptide. Finally, proteolytic cleavage to liberate each caspase involves sequential cleavages at two or more aspartate residues, thereby separating the large and small subunits from one another and from the prodomain. The prodomain is normally but not essentially removed at the time of the activation process. A heterotetramer consisting of two small and two large subunits each then forms an active

caspase. There are two concepts about caspase activation; caspase activation might involve either a proteolytic cascade or an auto-activation process. Both of these ideas have subsequently proven correct (*Kaufmann et al., 2000*). Active caspases can often activate other pro-caspases, allowing initiation of a protease cascade.

According to a unified nomenclature, the caspases are referred to in the order of their publication: the first protease in this class (caspase-1) is Interleukin-1ß-Converting Enzyme (ICE). At present, 14 different caspases have been identified in mammals that differ in specificity of tissue expression, substrate proteolysis and possible triggers of activation. Of the twelve known human caspases, caspases -2, -3, -6, -7, -8, -9, and -10 have been recognized to play an important role in the apoptotic signaling machinery and are definitely involved in apoptosis in various model systems (*Kaufmann et al., 2000*). One current classification scheme divides these apoptotic caspases into two classes, effector ("executioner" or "downstream") caspases, which are responsible for most of the cleavages that disassemble the cell, and initiator (or "upstream") caspases, which initiate the proteolytic cascade. Caspases-2, -8, -9 and -10 are the initiator caspases identified to date. Zymogen forms of these enzymes display low but detectable protease activity (*Earnshaw et al., 1999*). This activity increases when the prodomains of these zymogens interact with certain binding partners. Upon activation, caspase-8 and -9 acquire the ability to cleave and activate effector caspases.

Caspases-3, -6, and -7 are the major effector caspases characterized so far and upon activation, these enzymes are proficient of cleaving the vast majority of polypeptides that undergo proteolysis in apoptotic cells (*Earnshaw et al., 1999*). Interestingly, over-expression of the zymogen forms of these caspases in mammalian cells is relatively non-toxic, suggesting that these precursors have limited capacity for autoactivation. Instead, effector caspases are usually activated by other proteases.

Depending on the signal, different caspases are activated, leading to apoptosis. In case of extrinsic apoptotic pathway, when ligand binding occurs (FasL, TNF-α etc.) to their death receptors, procaspase-8 is recruited by its death-effector domains (DEDs) to a membrane receptor complex, the death-inducing signaling complex (DISC) and in turn activated as caspase-8. When bound to the DISC, numerous procaspase-8 molecules come in close proximity to each other and therefore are assumed to activate each other by auto proteolysis (*Denault and Salvesen, 2002*).

On the other hand, in intrinsic apoptosis pathway caspase-9 is activated in response to lethal stimuli such as DNA damage, oxidative stress and hypoxia. Caspase-9 is activated downstream of mitochondrial proapoptotic events at the so-called apoptosome. Activation of caspase-9 in turn engages and activates caspases -3 and/or - 6 and -7 as well as initiates a series of proteolytic events that terminates in a coordinated disintegration of the cell.

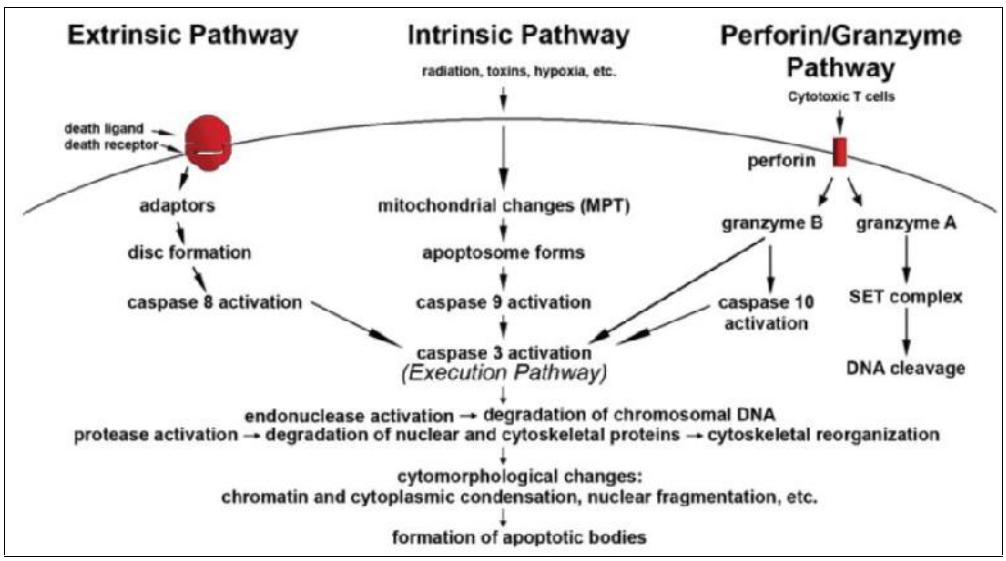

Figure 3. An overview of apoptosis execution pathway. (Elmore, S. 2007)

Promoting apoptosis: a strategy for cancer therapy

The treatment providing for cancer is greatly variable and dependents on numerous factors including the type, location, and acuteness of disease and the health status of the patients. Chemotherapy is one of the most common treatments for cancer and has been used for several years. While chemotherapy can be relatively efficient in treating certain cancer, chemotherapy drugs reach not just the cancer cells but all parts of the body. Because of this, there may be side effects during the cancer treatment. Chemotherapeutic drugs could theoretically target all metastatic sites, but current treatments do not provide a significant therapeutic benefit (*Soengas et al., 2003*). One of the main causes of failure in the treatment of cancer is the development of drug resistance by the cancer cells (*Johnstone et al, 2002*). Those cells are resistant will survive and multiply resulting in the re-growth of tumor that is not sensitive to the original drug. This is a very serious problem that may lead to reappearance of disease or even death.

Resistance to chemotherapy may arise from alterations of the apoptotic pathway in tumor cells. Exclusively, failure of apoptosis is a 'hallmark of cancer', an obligate procedure in the malignant transformation of normal cells. By inactivating apoptosis, cancer cells become double winners: they enhance their chances of survival and increase their resistance to chemotherapeutic agents (*Soengas et al., 2003; Johnstone et al., 2002*). It has been observed that mutations in p53 fail to detect DNA damage and subsequent induction of apoptosis (*Ko and Prives, 1996*). Alterations in the essential genes of the apoptotic pathway also may confer resistance to standard therapeutic regimens. In addition, mutation or deletion of the proapoptotic bax gene has been related with resistance to chemotherapy in patients with colon cancer (*Rampino et al., 1997*). Indeed, proteins that control the apoptotic process hold big promise as drug targets for multiple tumor types. Therefore, a better understanding of the interplay of chemotherapy and apoptosis will lead to the avoidance of ineffective treatment regimens as well as possibly an increase in efficacy through the modulation of the apoptotic pathway (*Soengas et al., 2003*).

The development and maintenance of multicellular biological systems depends on a sophisticated interplay between the cells forming the organism. In general, cells grow and divide to form new one as the body requires them. After becoming old, cells die, and new cells take their place. At the same time, during development numerous cells are produced in excess which ultimately undergo programmed cell death and thus contribute to sculpturing many organs and tissues (*Meier, 2000*). Sometimes these orderly processes go wrong. New cells produced while the body does not need them, and old cells do not die as they should. These extra cells may form a mass of tissue called a growth or tumor. It has become evident that alterations or failure in the apoptotic pathways are intimately involved in a variety of potentially fatal diseases including, cancer. Cancers are diseases in which uninterrupted clonal expansion of somatic cells kill neighboring normal cells by invading, subverting and eroding normal tissues (*Evan et al., 2001*).

The primary abnormality resulting in the development of cancer is the continual unregulated proliferation of cancer cells. Rather than responding to proliferation check points, a transformed cell gives rise to a clone of cells that can enlarge to a substantial size, producing a tumor or neoplasm - a persistently growing mass of abnormal cells. Not all tumors are cancer. As long as the neoplastic cells remain clustered together in a single mass, the tumor is called benign. A tumor is considered malignant if its cells attain metastatic property. Metastasis denotes the ability of transformed cells to break-loose, enter the blood stream or lymphatic vessels and form secondary tumors at other sites of the body. Malignant tumors are generally more serious and are properly referred as cancers. Malignant tumors may be life threatening as cells from this type of tumor can invade and damage as well as metastasize nearby tissues or organs spreading cancer from one part to another (*Evan et al., 2001*). Cancer is formed due to abnormal proliferation of any of the different kinds of cells of the body; as a result there are more than a hundred distinct types of cancer, which can vary substantially in their behaviors and responses to treatment. Generally, cancers are classified according to the embryonic origin of the tissue from which the tumor is derived.

Apoptosis is essential to achieve and maintain homeostasis of normal tissues of the body, to control cell number and to eliminate cells that threaten the animal’s survival. Apoptosis is the most familiar mechanism by which the body removes damaged or unneeded cells. Cells may also be eliminated by other alternative mechanisms including necrosis. During necrosis, the free release of the cellular contents into the extracellular milieu produces a profound host inflammatory reaction and causes damage to

surrounding cells and tissues (*Kroemer et al., 1998*), whereas the apoptosis leads to little, if any, activation of the host immune system (*Bold et al., 1997*). At the same time, apoptosis is associated with the rapid engulfment and removal of cell corpses by phagocytes without causing local inflammation. This basic difference between these two processes of cell death underscores the reason why apoptosis, and not necrosis, represents the most useful target mechanism for the induction of tumor cell death. There is increasing evidence that the processes of neoplastic transformation, progression and metastasis involve alterations in the normal apoptotic pathways (*Bold et al., 1997*). Apoptosis plays an important role in the deletion of pre-neoplastic cells, in consequence preventing the progress of the disease. The importance of apoptosis in the treatment of tumors has already been established as well as is based on the observation that the majority of chemotherapeutic agents and ionizing radiation utilize the endogenous apoptotic mechanisms to induce cancer cell death (*Potten et al., 1994*). In an addition, apoptotic cell death is the outcome of a series of precisely regulated events that are frequently altered in tumor cells. Furthermore, resistance to standard chemotherapies also seems to be determined by alterations in the apoptotic pathways of cancer cells (*Bold et al., 1997*). Therefore, all aspects of apoptosis are now under intense investigation to bring about the death of the tumor cell without damaging normal cells.

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