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Apoptosis – Journey of a Cell in Life

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Abstract:

Apoptosis is one of the key biological events that has versatile physiological significance starting from the development of an organism, to its differentiation, proliferation and proceeds till the last stage of removal of defective and harmful cells. The cascade of events in apoptosis spans through the entire cellular plethora with morphological and functional changes occurring in all the organelles from nucleus to the cell membrane. Apoptosis and necrosis form the two ends of a spectrum with marked differences in their triggering factors and the sequence of cellular events. The physiological apoptosis becomes pathological if it gets disrupted by mutation resulting in a variety of diseases starting from neurodegenerative disorders to cancer . This review article emphasize the life time journey of cell

Key Words : Apoptosis, Cell Death, Exfoliation, caspase enzyme.

INTRODUCTION:

The word apoptosis came from the Greek origin meaning " falling off or dropping off". It resembles leaves falling off trees or petals dropping off flowers. This analogy emphasizes that the death of living matter is an integral and a naturally evolving part of life cycle of the organism[1] The apoptosis (a-po-toe-sis) was first used in a now classic paper by Kerr, Wyllie, and Currie in 1972 to describe a morphologically distinct form of cell death, although certain components of the apotosis concept had been explicitly described many years ago[2]. Apoptosis is a kind of programmed cell death that plays an important part in the early development and growth of tissue and metamorphosis [3,4.]Apoptosis is mostly synonymous with the suicide of the cell and it also refers to the controlled regulation of the cycle and removal of superfluous cells at appropriate times without causing surrounding tissue damage [3]. Apoptosis is controlled by genes reveals its clinical relevance. Apoptosis disrupted by mutation results in a variety of disease states including neurodegenerative diseases and cancer respectively [5].

Apoptosis occurs during the normal development of a multicellular organism and is continuous throughout life. It brings about a homeostatic mechanism in the number of cell population in a tissue. The combination of apoptosis and cell proliferation is responsible for shaping tissues and organs in the developing embryo [6]. Apoptosis also act as a defense mechanism such as immune reactions or when cells are damaged by a disease or noxious agents[7]. In the past decades, programmed cell death was held synonymous with apoptosis, a death process characterized by morphological changes such as shrinkage of the cell, condensation of chromatin, and disintegration of the cell into small fragments (so called apoptotic bodies) that can be removed by phagocytosis without inflammation[8].

As apoptosis was introduced as a term describing the specific morphology of cell death, it should not be used synonymously with the term programmed cell death which usually occurs via apoptosis. The term programmed cell death refers to time and position programmed cell death during development of an organism. However, apoptosis can be induced by anti cancer drugs. In such instances the cell death process is initiated, but without treatment the cells would not die . Apoptosis is over 20 times faster than mitosis. Sighting of dying cells in vivo is therefore rare. If mitosis proceeded without cell death ,an 80 years old person would have 2 tons of bone marrow and lymph nodes and a gut of 16 km length [9] .

THE SIGNIFCANCE OF APOPTOSIS:

Apoptotic process are of widespread biological significance being involved in development,differentiation,proliferation,homeostasis,regulation and function of the immune system and in the removal of defective and harmful cells.

The majority of the developing lymphocytes die either during genetic rearrangement events in the formation of the antigen receptor, during negative selection or in the periphery, thereby tightly controlling the pool of highly efficient and functional but not self reactive immune cells and at the same time keeping the lymphocyte numbers relatively constant[10]. Thus dysfunction or dysregulation of the apoptotic program is implicated in a variety of pathological conditions.

Defects in apoptosis results in malignancies, autoimmune diseases, spreading of viral infection and neurodegenerative disorders while excessive apoptosis occurs in AIDS and ischemic diseases.[11]

MORPHOLOGY OF APOPTOSIS:

The various morphological changes that occur during apoptosis are studied under light and electron microscopy. [12] During the early process of apoptosis, cell shrinkage and pyknosis is visible by light microscopy.[13]

NUCLEUS:

Morphological hallmarks of apoptosis in the nucleus are chromatin condensation and nuclear fragmentation.The condensation starts peripherally along the nuclear membrane, forming a crescent or ring like structure and during later stages of apoptosis, the nucleus further condenses and finally breaks up inside the cell with an intact cell membrane, a feature described as Karyorrhexis.[14]

The chromatin condensation is readily visible by fluorescence microscopy after staining with 4, 6-diamino 2-phenylindole. DNA strand break can also be detected morphologically by using the incorporation of labeled dUTP by enzyme terminal deoxynucleotide transferase nick end labeling (TUNEL) method.[15] These morphological features can be initiated by caspases which cause the cleavage of various proteins. Lamin and nuclear mitotic apparatus proteins are cleaved by activated caspase 3 and 6.[16] A major hallmark of apoptosis in the nucleus is the inter nucleosomal fragmentation of double stranded DNA into fragments of 180 to200 bp length, which is caused by number of caspase substrates that are involved in DNA repair and replication. Examples are DNA fragmentation factor [DFF] 40 and caspase –activated DNase[CAD].

These proteins are constitutively present as hetrodimers with inhibitor proteins DFF45 and inhibitor of CAD [ICAD]. On activation, DFF40 and CAD were able to fragment DNA together with a large number of other endonucleases that are suggested to be involved in apoptosis.[16] Other proteins that are cleaved and inactivated during apotosis, are poly ADP-ribose polymerase and DNA –dependent protein kinase.These proteins are involved in DNA repair mechanism.

CELL MEMBRANE AND CYTOSOL:

Early during the initiation of apoptosis, cell loses contact with the neighboring cells membrane.[17] The cell shrinks, and finally the blebs separate , forming apoptotic bodies densely packed with cellular organelles and nuclear fragments that were engulfed by phagocytosis of the surrounding cells.[18]

Morphologically these ingested apoptotic bodies can be observed for some time, but eventually they will degrade and no traces will be left. Apoptosis occurs without associated inflammation due to the containment of the cellular constituents by an intact membrane and the subsequent engulfment of apoptotic bodies. However, if the remnants of apoptotic cells are not phagocytosed they will undergo degradation that resembles necrosis and is called secondary necrosis

The shrinkage of cells blebbing, and formation of apoptotic bodies can be observed by using light and electron microscopy. One of the earliest signs of apoptosis is the externalization of phosphatidylserine , providing an ‘ eat –me’ signal for phagocytosis cells.[19] This can be employed in vitro as a marker for the detection of apotosis because annexin V binds to phosphatidylserine , with a high affinity. Annexin V is a 35 kDa Ca2 + - binding protein that is available conjugated to fluorochromes for use in fluorescence microscopy and coupled to other markers suitable for light and electron microscopy.

Another combined morphological enzymatic assay for detection of apoptotic cells is the turnover of membrane –permeable, fluorescently quenched substrates for caspase. phiphiLux is one of these substrates that get cleaved by caspase 3, resulting in a bright fluorescent product that can be detected in unfixed cells by light microscopy.

A number of structural proteins are processed on initiation of the apoptotic cascades and one of the most prominent protein is actin.[20] Actin forms microfilaments and regulates the cell shape in the cortical cytoskeleton. Examples of other proteins that are cleaved by caspase during apoptosis are spectrin , fordin, β- catenin,gelsolin, growth arrest –specific 2, and p 21 –activated kinase2. These proteins are involved in the maintainence, organization, and attachment of the cytoskeleton.

MITOCHONDRIA:

Alterations in cellular stress responses and bio energetic states play an important role in the initiation of apoptosis. Both events are continuously monitored by mitochondria that integrate multiple pro apoptotic signals into common apoptotic degradation cascades. [5] The mitochondrial membrane permeabilization has a central role during this process.

Pro apoptotic members of the Bcl2 family appear to be central during the initiation of the mitochondrial membrane permeabilization, whereas anti apoptotic members of the Bcl2 family inhibits this process. A number of proteins are released, including cytochrome c, AIF, Smac /DIABLO, and others when mitochondrial members are permeabilized . A complex called the apoptosome is formed by interaction of cytochrome c with Apaf -1, which results in Apaf-1 oligomerization and binding as well as activation of caspase -9. Smac/DIABLO facilitates the activation of caspase by binding to a family of proteins called inhibitor of apoptosis proteins. AIF, in contrast to the caspase –activating proteins, translocates to the nucleus and induces chromatin condensation and DNA fragmentation. Despite the importance of the mitochondria, their light and electron microscopic appearances are largely unaffected until late in the process of apoptosis, when they swell like other organelles. [21]

DISTINGUISHING APOTOSIS FROM NECROSIS:

The alternative to apoptotic cell death is necrosis, which is considered to be a toxic process where the cell is a passive victim and follows energy – independent mode of death. But since necrosis refers to the degradative processes that occur after, it is considered by some to be an inappropriate term to describe a mechanism of cell death. [14]

Oncosis is therefore used to describe a process that leads to necrosis with karyolysis and cell swelling where as apoptosis leads to cell death with cell shrinkage, pyknosis, and karyorrhexis. Therefore the terms “oncotic cell death” and “ oncotic necrosis” have been proposed as alternative to describe cell death that is accompanied by cell swelling, but these terms are not used at this time.

Although the mechanisms and morphologies of apoptosis and necrosis differ, there is overlap between these two processes. Evidence indicates that apoptosis and necrosis represent morphologic expressions of a shared biochemical network described as the “ apoptosis- necrosis continuum.” [22] For example, two factors that will convert an ongoing apoptotic process in to a necrotic process include a decrease in the availability of caspases and intra cellular ATP.

Whether a cell dies by necrosis or apoptosis depends in part on the nature of the cell death signal, the tissue type, the developmental stage of the tissue and the physiologic milieu.Some of the major morphological differences are included in the Table.1.

Table 1.General differences between apoptosis and necrosis

Characteristics	Apoptosis	Necrosis
Stimulus	Physiological	Pathological (Due to Injury)
Appearance	Individual Cells	Cellular Groups
Reversibility	No (After Morphological Changes)	Yes (Until Irreversible Changes)
Adhesions between cells and to Basement Membrane	Disappears at an Early Period	Disappears at a Late Period
Cytoplasmic Organelles	Swells at a Late Period	Swells at an Early Period
Lysosomal Enzyme Release	Absent	Present
Nucleus	Disintegrates (Karyorrhexis)	Disappears (Karyolysis)
Nuclear Chromatin	They are collected together in similar clusters	They are clustered with ill defined borders
DNA Fragmentation	Inter nucleosomal	Random
Cell	Apoptotic bodies form	Swells and bursts at a late stage
Phagocytosis by other cells	Present	Absent
Exudative inflammation	Absent	Present
Scar formation	Absent	Present

[71]Apoptosis signal pathway:

Apoptosis is triggered by multi-signal pathways and regulated by multi-complicated extrinsic and intrinsic ligands. There are two major apoptosis pathways distinguished according to whether caspases are involved or not. The mitochondria as the cross-talk organelle, can connect the different apoptotic pathways.

Caspase dependent pathway

Caspase-dependent apoptosis is the classic programmed cell death pathway, in which the caspases-8, 9, 12, 7, and3 cascades usually participate. Variety of receptors take part in this type of apoptosis pathway such as, the TNF-alpha receptor, FasL receptor, TLDR and among the various ion channels, calcium ion channel is mainly involved, because calcium's concentration in the cytosol plays an important role in the signal transduction regulation and participates in both the cell proliferation and death.

TNF-alpha induced caspase-8-dependent pathway relies on the TNF-alpha receptor and activates the caspase-8 through the death complex. Later the Bcl-2 protein is activated and may induce changes in the mitochondrial membrane and hence stimulating the release of cytochrome c. Cytochrome c is the proapoptotic signal molecule which can activate the caspase cascade reaction and induce the apoptosis at the end.

Other factors that activate caspase dependent apoptotic pathway include radiation such as UV or X-rays, pathogenic infections, DNA and RNA fragments, proteins or peptides and chemical compounds. The latest research showed that an alternative Kaposi's sarcoma-associated herpes virus replication can trigger host cell apoptosis in a caspase dependent manner. [23] Research also showed that RNA fragments and DNA can also trigger caspase dependent apoptosis such as, RNA fragments produced by mycobacterium tuberculosis which in the early log-phase growth can trigger caspase-8 dependent apoptosis. [24]

In vivo, DNA damage can trigger apoptosis through enhancing ROS level and changing the mitochondrial membrane permeability.

Many proteins or peptides will also make cell apoptosis, amyloid β peptide cytotoxicity can induce the intracellular calcium disturbance, and then the calpain will be activated by imbalanced calcium storage, While the calpain can activate caspase-12 which is located in ER to inactivate the Bcl-Xl, which is a novel caspase-12 dependent apoptosis pathway. [25] Fig 2.,summarize the caspase dependent pathway transduction,ligands and receptors involved in it.

Caspase independent pathway

In the cell, numerous ligands can induce mitochondrial membrane potential changes and the mitochondrial damage will be the first step of the apoptosis, followed by ROS production increase.ROS is the main factor to induce caspase independent apoptosis. For an instance, it is found that granzyme A can directly induce the ROS increase and caspase independent mitochondrial damage. The target of granzyme A,(ER associated complex (SET complex)) will be translocated to the nucleus and contributed to apoptosis.[26].

AIF has been found to be the major caspase-indenpendent pro-apoptotic factor, which is released from the mitochondria and translocated in-to the nucleus to cleave the DNA .At the end, if the DNA damage has not been repaired by cells, and then apoptosis will happen. Recently, researchers found some compounds which can accompany with AIF production and induce cell death, such as simvastatin, staurosporine, cadmium and others. These factors triggered caspase-independent PCD, and Besides AIF triggered caspase-independent PCD, ROS also participates in this type of cell death. ROS can mediate poly (ADP-ribose) polymerase-1 (PARP-1) activation, and this is necessary for AIF release from mitochondria, hence ROS is also involved in this type of cell death networks. [27] However, ROS also participated in the caspase dependent apoptotic pathway.

Consequently, ROS might be the important bridge to connect two types of apoptosis in vivo and it mainly comes from mitochondria, so mitochondria play an important role in apoptotic pathways crosstalk and the ligands usually trigger complicated reactions, including that of AIF nuclear translocation, ROS increase and mitochondrial dysfunctions. These changes produce the caspase independent apoptotic pathway.

Besides the AIF and ROS, there are many other ligands and signal molecules from the vitro or vivo cells, as apoptogenic factors involved in the caspase independent apoptosis pathway.They are lysosomal membrane permeabilization, some virus's protein, drugs, p53 suppression tumor factors and many other unknown compounds which deserves to be researched deeply.
Fig 3, summarize the caspase Independent apoptosis pathway.

Mitochondria dynamics and apoptosis:

Mitochondria are a semiautonomous organelle in the cell containing genetic material, and it is the site of ATP synthesis activity, ROS production ,apoptosis and regulation of aging,etc.[28]

Mitochondria's dysfunction has the relation with many diseases such as Alzheimer's disease; Parkinson's disease, cancer and diabetes which in turn have been identified to have some relation with the apoptosis.[29,30] ROS produced by mitochondria have been regarded as one of the important factors of apoptosis.

As a dynamic organelle, mitochondria can change their shape and structure constantly to respond to the different stimuli and metabolic demands of the cells. According to the latest researches, the mitochondrial shape changes between fusion and fission and play a very important role in the regulation of apoptosis.[31, 32]

Calcium ions act as the upstream stimulus which can activate the mitochondrial fission causing fragmentation rapidly depending upon the level of increased intracellular calcium ions. If the calcium level is increased protractedly, mitochondria's fragmentation will be non-reversible and leads to apoptosis.[33] Apart from the above,mitochondrial membrane protein Bcl-2 and cytochrome C acts as regulators in bringing about the apoptosis cascade.

Apoptotic ligands:

Various extrinsic and intrinsic ligands can trigger apoptosis.Extinsic ligands

Cytokines:

TNF-alpha plus z-VAD can trigger cell apoptosis and this method is well-known to create cell apoptosis model. TNF-alpha can bind to extracellular domain of TNF-alpha receptor , and the cytoplasm domain can aggregate FADD and FLICE which can initiate the apoptosis; Another famous cytokine IFN—γ, which can induce the macrophage apoptosis plays a key role in clearance of the mycobacterium tuberculosis by inducing host cell apoptosis dependent of nitric oxide(NO). [34] TGF-β1 acts as a chemo attractant which is very important for the immune response and this cytokine also plays a predominant suppressive role in inhibiting the cell proliferation and stimulating B cells to apoptosis.[35]

Drugs:

Some cytotoxic drugs (Cispkatin, Gemcitabin, Tooitecan, and paclitaxel) can trigger apoptosis; Didymin induces apoptosis by preventing N-Myc protein expression and makes the cell G2/M arrest, which may be a novel mechanism to anti-neuroblastoma. [36] Apart from this anti-neuroblastoma properties, didymin has an anti-no small cell lung cancer ability by inducing the Fas-mediated apoptosis which may be a novel new chemotherapeutic agent to treat the lung cancer. [37]

Gomisin N have anti-hepatotoxic, anti-oxidative and anti-inflammation abilities, while it also have anti-cancer activity by triggering the TRAIL-induced apoptosis.[38] Andrographolide as an anti-bacterial drug has been found to have anti-cancer activity. Andrographolide treated cancer cell can activate the p53 by increasing p53 phosphorylation and this p53 activation can increase DR4 protein expression which then triggers the TRAIL-induced apoptosis.[39] Ursolic acid can stimulate the ROS production and trigger JNK activation, which in turn can make the DR up expression and in the end TRAIL-induced apoptosis occurs in a p53 independent manner.[40]

Ciglitazone, as an anti-diabetic drug, has been found by Plissonnier ML group that it has antineoplastic effectiveness in a lot of cancer cell lines through up-regulation of soluble and membrane bound TRAIL, which activates caspase , death receptor signal pathways and induces Bid to be cleaved as response to TRAIL.These data gave the evidence that ciglitazone can down regulate the c-FLIP and surviving protein, and then triggered the TRAIL-induced apoptosis to kill the cancer cells.[41] These data provided the powerful evidence that triggering apoptosis may be a feasible method for clinical cure.

Hormones

Hormones are usually a peptide or steroid, produced by one tissue and conveyed by the

bloodstream to another place to affect physiological activities, such as growth, proliferation and metabolism. Studies found that hormones can regulate the apoptosis and through this way hormone can control the metabolism of tissues or organs.

The major relations between the hormone and apoptosis are concluded in table II and III.

Table II. Hormones as inhibitors f apoptosis

Known inhibitors of apoptosis	Apoptotic cell (Target)
Testosterone	Prostate[42]
Oestradiol	ovarian cells[43,44]
Growth hormone	Human monocytes or human promyelocytic leukaemia [34]
Leptin	myometrial cells[45]
Dihydrotestosterone	Prostate[42]

Table III Hormones as inducers of apoptosis

Glucocorticoids	Human small cell lung cancer[36]
Progesterone	human endometrial cell [37]
Thyroid hormones	Play an important role in amphibian organ remodeling during metamorphosis through inducing apoptosis [38]
Estrogen	Breast cancer cell [39]
Phytoestrogens	Breast cancer cell [40]

Pathogens

Mycobacterium can be cleared by macrophage's apoptosis which was induced by the NO and IFN-γ.[46] Chlamydia pneumoniae infection can induce the human T lymphocyte cell apoptosis and through this way, they could induce immunologic tolerance and would make pathogen persistence infection and inflammation. [47]

Dendritic cells (DC) are well known antigen-processing immune cells, and they can inhibit pathogen replication and diffusion by caspase-3 dependent apoptosis in an early stage of infection. For instance, *Legionella pneumophila* was unable to replicate in DC, because DC go to apoptosis when infected in the early stages.[48] Besides the bacterial infection induced apoptosis, some viruses were also found to be involved in the apoptosis. For

Example, transmissible gastroenteritis (viral infection) can up-regulate the FasL and

subsequently, the Bid protein can be cleaved and cytochrome c released. Hence, in the end, Caspase-8 can be activated and the host cell undergoes apoptosis. [49]

Native compounds:

Native compounds from the daily dietary life can block or hamper apoptosis, and through this way, these native compounds can help to keep the body healthy.Vitamin E(tocopherol) as an antioxidant, has an important role in redox balance. Recently, apart from its major role in antioxidant ability

, vitamin E can also block the reduction of the mitochondrial membrane potential and inhibit the activation of caspase-3.Vitamin E is conducive to cell viability through blocking the caspase-3 triggered apoptosis.[50] Purple sweet potato pigments can scavenge ROS and protect the murine thymocyte by inhibiting caspase-dependent apoptotic pathway.[51]

Lycopenes (rhodopurpurin) can be taken from the tomatoes, fruits and vegetables easily and they have an anti-prostate cancer activity; Apart from the anti-tumor properties, lycopene can inhibit ROS increase, DNA damage and apoptosis in gastric epithelial AGS cells which was induced by helicobacter pylori infection.[52]

Apart from these food derived natural compounds, there are many plant components which can trigger apoptosis, such as fisetin, wongonin, emodin and others. Fisetin is a natural flavonoid which can induce several types of cancer cells to apoptosis by dose and time dependent manner and can activate caspase-8/caspase-3 dependent apoptotic pathways. These pathway transducer molecules will be the candidates for cancer therapy; [53] Wongonin, as an O-methylated flavonoid, was detected to have anxiolytic activity and the ability to trigger apoptosis of some cancer cells. [54] Table IV summarizes other native compounds that can trigger a poptosis as well as elucidate the molecular mechanisms of these natural products and identify their targets.

Table IV:Native compound Caspase dependent apoptosis

Luteolin	Triggers mitochondrial - dependent apoptosis, and activates Bax, Bcl-xl, Bcl-2, Mcl-1, caspase-9, caspase-3, and PARP [41]
Apigenin	Induces cytochrome C release and ROS enhancement.[55]
Phytosphingosine	Leads to caspase-8 activation and mitochondrial-dependent cell death[46]

Intrinsic cell apoptosis signal materials

Oxidative stress (ROS; NO; GSH)

Keratin is a cytoskeletal protein which has some abilities to maintain the cell shape, modulate the shape of mitochondria and contribute to hepatocyte predisposition, apoptosis and oxidative injury .[56] Depletion of the mitochondrial GSH in the human B lymphoma cell line by treatment with L-buthionine sulfoximine can induce caspase-3 activation and apoptosis thereby indicating that GSH may be the early potential activator of apoptotic signals. [57]

ROS is a type of toxic compound which is usually detoxified by the cells GSH, but when the oxidative stress occurs, the ROS detoxification fails and ROS will participate in apoptosis through redox-sensitive death pathway.

Cytochrome C

Cytochrome C is a proapoptotic protein, which on activation changes the Bak/Bax ratio. Studies have shown that the interactions of heterotypic mitochondrial membrane will change the lipid milieu and in the end mitochondrial membrane will be permeable and cytochrome c will release.[58]

Apart from the changes of lipid milieu, arachidonic acid, triiodothyronine (T3), or 6-hydroxdopamine can also effect the permeability of mitochondrial membrane and release Ca2+ and cytochrome c. [59] Cytochrome c can trigger caspase activation via oligomerization of APAF1 protein and this Caspase activation can catalyze the PARP-1and thereby resulting in apoptosis.

Calcium ion:

The concentration of calcium in vivo plays the key role in maintaining the permeability of mitochondrial membrane. The increased intra-mitochondrial calcium can result in enhanced ROS and in turn will stimulate cytochrome c release .[60] Calcium also triggers the ER stress, and then activates JNK pathway, and later JNK activation can stimulate Bax activation. Moreover, calcuim can regulate the cysteine protease calpain and its well known that calpain participates in the cell proliferation, cell cycle and apoptosis. Calpain can cleave the N terminal of Bax and generate a proapoptotic fragment; .At the same time, the cells will enter the apoptosis. In a brief, calcium can trigger Bcl-2 independent cytochrome c release, and through regulating the activity of the calpain, calcium ions can play their role in modulating the apoptosis. [61]

Endoplasmic reticulum (ER) stress:

Tackling the unfolded proteins is one of the most important ER functions and a cell can regulate the unfolded proteins in ER according to the metabolic need. If numerous unfolded proteins stimulate the ER overload it with stress then these cells which have lots of unfolded proteins will undergo apoptosis.[62] Differing from the ER stress, chaperons will protect this cell death. For example, the HSP72 protein can hamper the apoptosis through down regulation of the unfolded protein signal response sensor (IRE1alpha). Some neurodegenerative diseases are usually accompanied with unfolded protein acceleration and ER stress, hence So it is meaningful to research the relationship between the ER stress and neurodegenerative diseases. This finding will determine the function of apoptosis in some neurodegenerative diseases. The intrinsic components which can trigger the apoptotic pathway can connect with each other by the vivo organelles.

Inhibition of Apoptosis

There are many pathological conditions that feature excessive apoptosis (neurodegenerativediseases, AIDS, ischemia, etc.) and they may benefit from artificially inhibiting apoptosis. A short list of potential methods of anti-apoptotic therapy includes stimulation of the IAP (inhibitors of apoptosis proteins) family of proteins, caspase inhibition, PARP (poly [ADP-ribose] polymerase) inhibition,PKB/Akt (protein kinase B) pathway, and inhibition of Bcl-2 proteins. The IAP families of proteins are perhaps the most important regulators of apoptosis, due to the fact that they regulate both the intrinsic and extrinsic pathways .[63]

Among eight human IAP proteins XIAP (X-linked mammalian inhibitor of apoptosis protein) and survivin remain the better-known members. Members of the IAP family have been investigated as therapeutic targets for the treatment of stroke, spinal cord injuries, multiple sclerosis and cancer. Specific inhibitors of caspase activity such as ICE inhibitors have been developed to treat rheumatoid arthritis and other inflammatory conditions via reduction of interleukin 1β and nonspecific caspase inhibitor

which includes z-VAD-fmk that has shown to reduce the severity of myocardial reperfusion injury in rat and mouse models of myocardial infarction.[64,65] Due to the dual role of PARP-1 in both DNA repair and apoptosis, the pharmacological and organ injury may be able to enhance the cytotoxicity of antitumor agents.[66]

Other Forms of Programmed Cell Death:

Various other forms of non-apoptotic programmed cell death should also be considered since this may have new insights into cell death programs and reveal their potentially unique roles in development, homeostasis, neoplasia and degeneration. "Aponecrosis" is a form of cell death that has certain morphological features of both necrosis and apoptosis.[67]

"Autophagy" represents another mechanism of programmed cell death which is similar to apoptosis, and has important roles in the developmental processes, human diseases and cellular responses to deprived nutrition.[68] Other terms used synonymously are "macroautophagy" and "autophagic type II cell death". Autophagic cell death is characterized by the sequestration of cytoplasm and organelles in a double or multimembrane vesicle along with the delivery to the cells own lysosomes for subsequent degradation.[69] This is considered to be the major inducible pathway for the general turnover of cytoplasmic components. A unique ubiquitin-like protein conjugation system and a protein complex that directs membrane docking and fusion at the lysosome or vacuole are important components of autophagy. In general, the process of autophagy includes: induction, formation of the autophagosome, fusion with the lysosome or vacuole, autophagic body breakdown and recycling. The regulation of this process occurs through various kinases, phosphatases and guanosine triphosphatases (GTPases). There are some settings where autophagy and apoptosis seem to be interconnected and the idea of "molecular switches" between these two processes has been introduced .[70]

Autophagy is considered the major cellular mechanism for disposing the long-lived proteins and cytoplasmic organelles however, the concept of autophagic cell death has been a matter of debate within the scientific community. Since there is a distinct advantage of increased autophagy in various physiological and stressful conditions, it has been suggested that autophagy represents an important adaptive mechanism that attempts to rescue the cells from death. In other words, the presence of auto-phagic vesicles in dying cells may reflect an adaptive response to maintain the cell survival under stressful conditions rather than a reflection of "autophagic cell death."

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