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Chapter 1

Extrinsic and Intrinsic Apoptosis Signal Pathway Review

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Additional information is available at the end of the chapter

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1. Introduction

Apoptosis, as a programmed cell death (PCD) is essential for normal cell mechanism. The word "Apoptosis" derives from Greek language "απόπτωσις" and means trees shedding their leaves in autumn, which describes the "dropping off" or "falling off" of petals from flowers, or leaves from trees. This language imaginarily described the cell death triggered by physiological and pathological stimulation. The apoptosis phenomena were first described by German Scientist Carl Vogt in 1842 year, while until 1972 year, apoptosis term was first used by John Foxton Ross Kerr group. They use apoptosis word to describe the tissue cell death. The above is the beginning of apoptosis researches and this period is the apoptosis formation; the second period about apoptosis is the biochemical level and apoptosis cell morphological changes research. In this age, people know that apoptosis accompany with cell membrane wrinkled, DNA fragmentation, cytosol calcium increased and form the apoptosis body which contain its own content so on. In this time the electron microscope play a vital role in the research. 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 the apoptosis have been found, such as Bcl-2 family protein, caspase-3, caspase-8, caspase-9, Bid, Bax and so on.

In the past, the apoptosis was focused on the caspase, a family of cysteine protease. While, using the caspase inhibitor to block the apoptosis pathway, the researchers found that the apoptosis still happen. So another pathway that is caspase-independent was found. Now, apoptosis is classified to type I, Type II, Type III PCD: type I PCD is the classic apoptosis, the well know caspase denpendent 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 IIand type III PCD are the caspase-independent apoptosis. For example, the apoptosis induce factor(AIF), a mitochondria intermembrane flavoprotein, that can be released from mitochondria to

translocate into the nuclear and cause many high molecular weight DNA fragmentation and chromatin condensation in cells, this type of apoptosis is in the caspase-independent manner. [65] No mater the typeI, Type II or type III PCD, the apoptosis will assist the host to defense the outer or inner aliens and toxic compounds and help the organism survive.

In this chapter, we will key on the apoptosis signal pathway and some ligands have the clue with apoptosis and mainly on concluded the apoptosis on two aspects, from in vivo and in vitro cells, and we can clarify the network of this cell death and give the conclusion of the latest research about this.

2. Apoptosis research time line

Cell death is essential for body homeostasis, currently years research, cell death can be classified as necrosis, apoptosis, pyroptosis. Necrosis is the first to be found, and then in the 1972 year, the apoptosis term began to be used; several years ago, pyroptosis was been known by the symbol of formation hole in cell membrane and released inflammatory factors. Apoptosis research started in the nineteen century. According to the past research, we collect and analyze the research of apoptosis and give the following summary of history and highlights about apoptosis in Table1

Year	Scientist	Research
1842	Carl Vogt	First describe the principle of apoptosis
1885	Walter Flemming	Give more precise description of PCD
1965	John Foxton Ross Kerr	Distinguish the apoptosis used by electronic microscopy
1972	John Foxton Ross Kerr	Initially used the apoptosis term
2002	Sydney Brenner, Horvitz and John E suston	Awarded to Nobel prize in medicine according they contribute in apoptosis research area.

Table 1. History and highlights about apoptosis research

In 2002 year, the Nobel Prize in medicine was awarded to the Sydney Brenner, Horvitz and John E suston, according they contribute to the apoptosis research. They make a stone research work in organ development research and genetic systemic regulation programme cell death. Sydney Brenner's contribution is the construction of nematode of C.elegan model. And subsequently, suston found the cell lineage of C.elegan and found the first gene(Nuc-1) related with apoptosis. Now the C.elegan is still the classic model to research apoptosis and organ development research, Now, apoptosis has been found in the tumor development, and it has been clear that alteration of apoptotic pathways is a common feature of tumors, enabling cancer cells to survive chemotherapeutic interventions, so apoptosis signal pathway molecular become attractive targets in cancer therapy. Beside involving in the tumor development, apoptosis have been found in many other diseases, such as neurodegenerative diseases, diabetes, stroke and so on. Here, we review the

fundamental apoptotic pathways and summarize many ligands that can trigger apoptosis and give some insights in the designing some drugs, plus, we also give the opinions that changes the dietary arable may be help to improve the people's healthy.

3. Apoptosis signal pathway

Apoptosis is triggered by multi-signal pathways and regulated by multi-complicated extrinsic and intrinsic ligands. The process of apoptosis is controlled by diversity cell signals pathway and involved in regulation of cell fate death or survival. There are two major apoptosis pathways distinguished according to whether caspases are involved or not. The mitochondria, as the cross-talk organelles, can connect the different apoptosis pathway.

3.1. Caspase dependent pathway

Caspase-dependent apoptosis is the classic programmed cell death pathway, the capase-8, caspase-9, caspase-12, caspase-7, caspase-3 cascade usually participate in this type of apoptosis pathway, Variety of receptors take part in this type of apoptosis pathway, such as the TNF-alpha receptor, FasL receptor, TLR, Death receptor and so on. Some iron channels may also be involved in apoptosis pathway. The typical iron channel is the calcium channel, Since calcium's concentration in the cytosol plays an important role in the signal transduction regulation and participates in the cell proliferation and cell death, the cell fate can be controlled by the calcium channel opening or closing. In this part, we will discuss the caspase-dependent apoptosis transduction and review the complex signal crosstalk in the cells.

TNF-alpha induced caspase-8-dependent pathway relies on the TNF-alpha receptor and activates the caspase-8 through the death complex, and then the Bcl-2 protein is activated, Bcl-2 family protein activation may induced the mitochondria membrane changed and stimulates the cytochrome c released. Cytochrome c is the proapoptosis signal molecular which can activates the caspase cascade reaction and induced the apoptosis in the end. Some radiation UV or X ray can make mitochondria depolarization and membrane permeabilization, subsequently, the ROS increased; cytochorme c released, and then trigger caspase-9, caspase-3 activation,, In the end, the substracts will be cleavaged by the activation caspases and the fate of cells will be apoptosis; Some pathogen infection induced the apoptosis may be also have the caspase-8 dependent pathway, The alien pathogens can be recognized by FasL receptor and recruit FADD and caspase-8, for example, the intracellular pathogen herpervirus infection can induced the caspase-8 dependent apoptosis. Beside caspase-8 dependent apoptosis, some pathogens can trigger others caspases dependent apoptosis pathway. For example, Mycobacterium tuberculosis can induce programmed cell death on macrophage, and this apoptosis pathway is the caspase-12 dependent. NO and ROS production, stimulated by ER stress, also take part in apoptosis triggered by Mycobacterium tuberculosis; [1] Exclude bacteria, virus also can induce the apoptosis. The latest research found that an alternative Kaposi's sarcoma-associated herpesvirus replication can trigger host cell apoptosis in caspase dependent manner. [2]. Apart

from the bacteria and virus, we found that many researchers' data show that RNA fragments and DNA can also trigger caspase dependent apoptosis, such as RNA fragment produced by mycobacterium tuberculosis which in the early log-phase growth can trigger caspase-8 dependent apoptosis[3]; In vivo, DNA damage can trigger apoptosis through enhancing ROS level and changing the mitochondria 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 can located in ER to inactivate the Bcl-Xl, this is a novel caspase-12 dependent apoptosis pathway[4]. This way can be used by the mitochondria to connect with other cell death pathway.

Above all, we can give the conclusion that pathogens, RNA or DNA, proteins or peptides, some chemical compounds or native compounds can all trigger caspase dependent apoptosis. They may have the different receptors and induce cell death through different caspase as the transducer to make the downstream signals transduction. The host used this way to defense the harmful factors and maintain the healthy physiological state. In the figure 1, we summarized the caspase dependent pathway transduction; we clearly known that the different ligands and receptors involved in this type of apoptosis, this picture will give us the direct impression about this type of apoptosis.

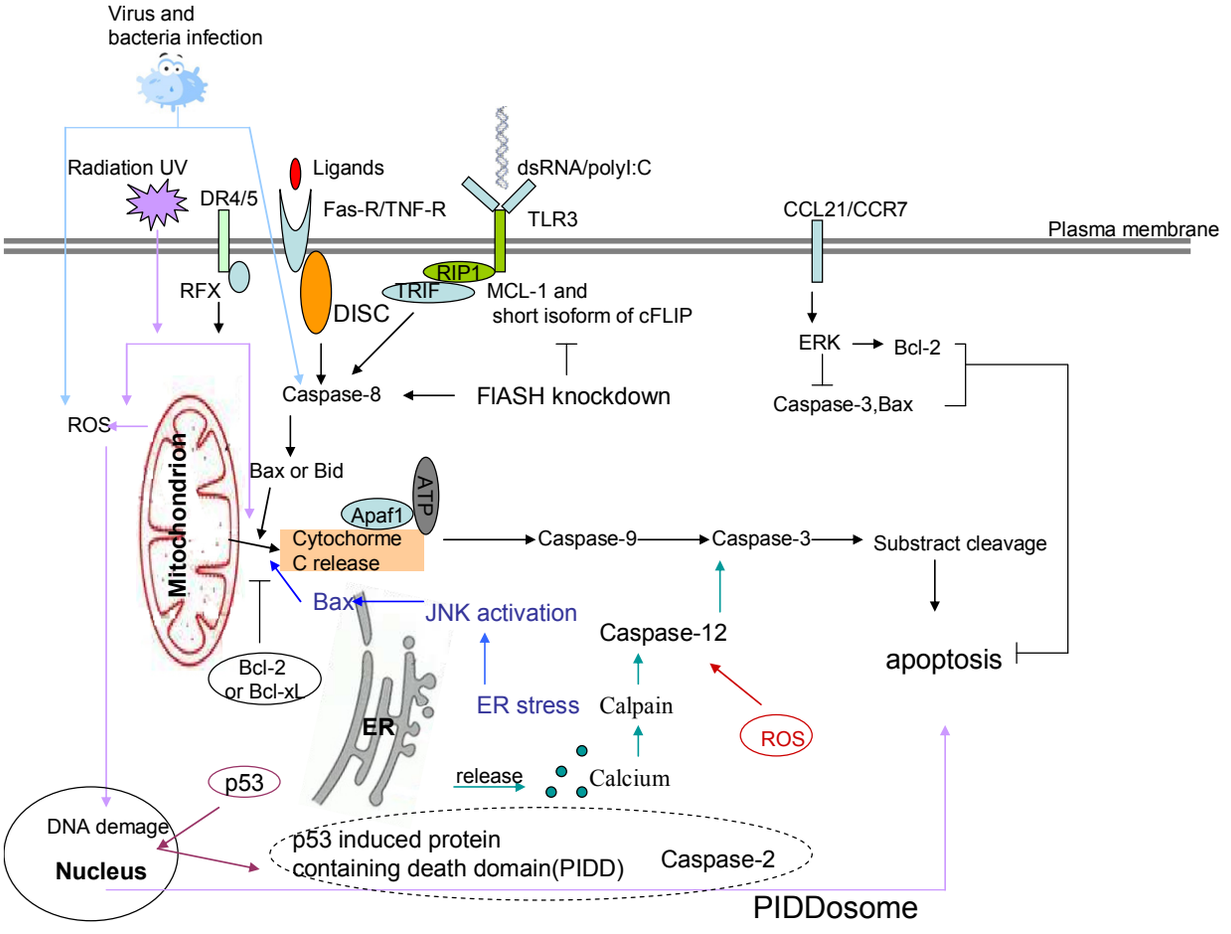

Figure 1. Summarize the caspase dependent apoptosis pathway

In this figure, we can clearly know that mitochondrion and nucleus organelles play the pivotal role in this type cell death and these organelles can connect different signals to induce the caspase activation, in this process period, ROS; Cytochorme C release; mitochondrion membrane potential change; Apart the mitochondrion pathway, some ligands can trigger MAPK pathway, such as activate ERK and then activate the caspase family which can be confluenced with apoptosis pathway.

3.2. Caspase independent pathway

Apoptosis have many mechanisms. It can be triggered by in vitro and in vivo cell ligands, and have different signal transduction pathways. Now, Apoptosis pathways are classified as caspase dependent pathway and caspase-independent pathway. In the above, we describe and conclude the caspase dependent pathway, which is characterized by the involvement of caspase in this type cell death process. In this paragraph, we will deep research the caspase independent apoptosis pathway. We will know that caspase does not participate in this type of process from the literally meaning. Up to now, this type of apoptosis has been founded by many researchers, and the research data give much information to us, this information can help us to understand the apoptosis complex mechanism, beside the mechanisms, the complicated ligands, which can induce this type of cell death, can also be found by many researchers. In the following, we will give some detailed contents about caspase independent apoptosis.

In the cell, a lot of ligands can induce mitochondria membrane potential change, the mitochondria damage will be the first step of the apoptosis, then ROS production increase, and ROS may the mainly factor to induce caspase independent apoptosis. For example, Denis Martinvalet found that granzyme A can directly induce the ROS increase and caspase independent mitochondria damage. Then the target of granzyme A, ER associated complex (SET complex), will translocated to nuclear and contributed to apoptosis [5]; AIF has been found the major important caspase-indenpendent pro-apoptosis factor, which can release from the mitochondria and translocate in the nuclear to cleavage the DNA, in the end, if the DNA damage have not been repaired by cells, the apoptosis will happen. Recently, many researchers found some compounds which can accompany with AIF production and induce cell death, such as simvastatin, staurosporine, cadmium and so on. These factors triggered caspase-independent PCD and fitted for the organism requirement; Beside AIF triggered caspase-independent PCD, ROS also participate in this type cell death. ROS can mediate poly (ADP-ribose) polymerase-1 (PARP-1) activation, and PARP-1 activation is necessary for AIF release from mitochondria. So ROS also involved in this type of cell death networks.[6].However, ROS participated in the caspase dependent apoptosis pathway also, Consequently, ROS might be the important bridge to connect two types of apoptosis in vivo. ROS mainly come from mitochondria, so mitochondria play important role in apoptosis pathways crosstalk. And the ligands usually trigger complicated reactions, including that AIF nuclear translocation, ROS increase and mitochondrial dysfunctions, these changes can cause to the caspase independent apoptosis pathway. For example, Cyclohexyl analogues of

Ethylenediamine Dipropanoic Acid, the compound that can induce peripheral blood mononuclear cells apoptosis of both healthy controls and leukemic patients through stimulating many apoptogenic factors activation(such as: AIF nuclear translocation, ROS increase and mitochondrial dysfunction). [7] Referring the ROS, we propose that the GSH , NO, or other free radical groups may also take part in this type cell death, By this way, the GSH or NO modification proteins may also take part in the apoptosis pathway, GSH and NO can block some active thiol group and make the protein S-glutathionylation or S-nitrosylation modification. These types modification may affect the protein's functions and make the cell to apoptosis result. Beside the AIF and ROS, there are many other ligands and signal molecular from the vitro or vivo cells as apoptogenic factors involving in caspase independent apoptosis pathway, such as lysosomal membrane permeabilization; some virus's protein; drugs; p53 suppression tumor factors or many other unknown compounds.

Up to now, the caspase independent apoptosis mechanism is still unknown clearly. Although some researchers have found AIF; ROS and other ligands can stimulate this type of PCD, the signal pathway still stay the phenomena stage and the deep mechanism should be dig out by us. No matter either apoptosis form, this type cell death has very important functions and deserves to be researched deeply. We collected a variety of information about this cell death and found that the caspase independent apoptosis existed in a mount of species and played indispensable role in cell growth, proliferation and death. In the figure 2, we give the outline about this type apoptosis pathway and the crosstalk manner between the different pathways, this picture will help us to know this type apoptosis well in the whole level.

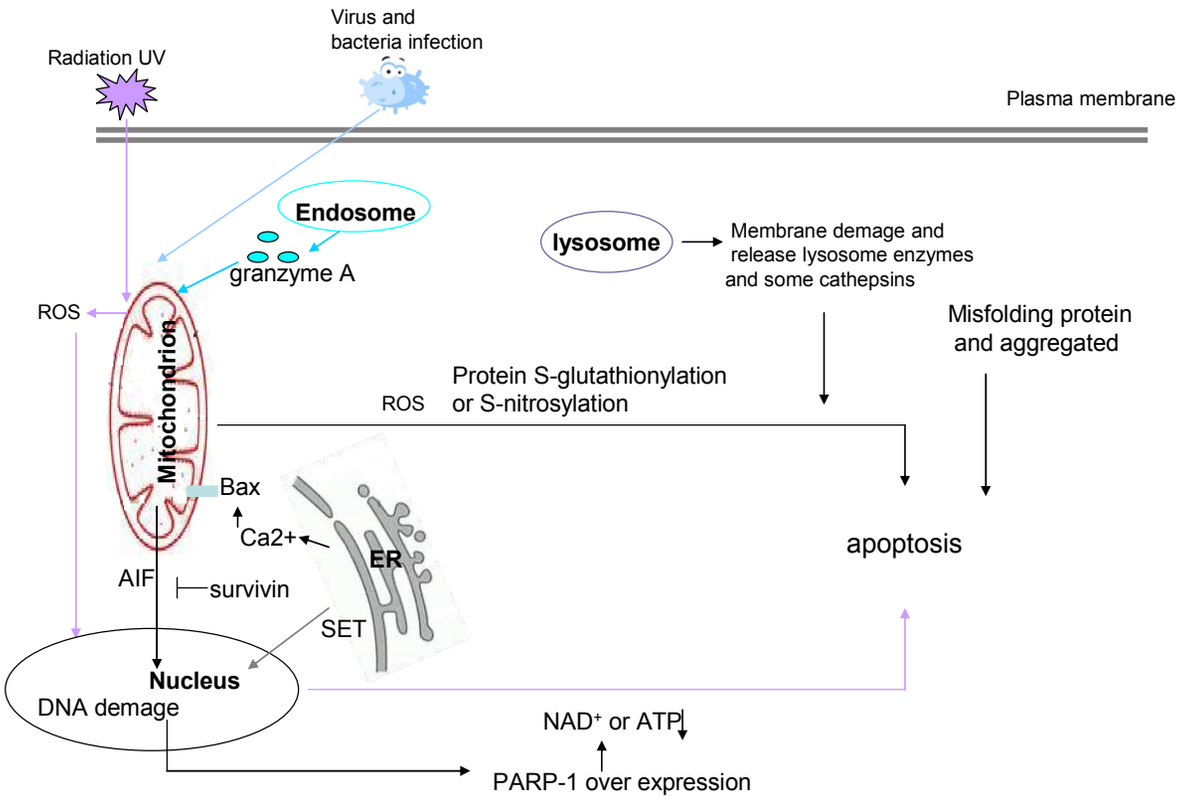

Figure 2. Caspase independent apoptosis pathway

In this type apoptosis, caspase family members did not involve in this cell death, and can not be inhibited by the caspase inhibitor {such as: the z-VAD-FMK; quinolyl valyl-o methylaspartyl[-2,6-difluorophenoxy]-methyl ketone(Q-VD-OPH);Ac-DEVD-FMK and so on}. In the cells, some components and events, such as the AIF; ROS; Ca^{2+}; NAD^{+} and ATP; protein misfolding and modification, can trigger the caspase independent apoptosis.

3.3. Mitochondria dynamics and apoptosis

Mitochondria, as a semiautonomous organelle in cells, apart from containing their own genetic material, play an important role in the energy metabolism. It can produce ATP to maintain the cell life activity and be known as an energy company in cells. Beside this major role, mitochondria are the places that the lot of biological reaction processes happened, such as ROS production, apoptosis, and regulation of aging [8] and so on. Mitochondria's dysfunction has the relation with many diseases (Alzheimer's disease; Parkinson's disease, cancer, diabetes) [9, 10]. These diseases have been identified to have some relation with the apoptosis; ROS produced by mitochondria have been regarded as one of important factors for apoptosis. Currently, many researches found the ROS produced increased when some pathogen infected, ROS can trigger apoptosis, through apoptosis, the pathogens may lost the perfect living environment, the host may defense the pathogen's diffusion by this manner. Due to these roles, mitochondria may be used as a proper therapeutic target to cure diseases related with this type cell death [11].

As a dynamic organelle, mitochondria can change their shape and structure constantly to respond to the different stimuli and metabolic demands of cells. According to the latest researches about biochemistry and cell biology, the mitochondrial shape changes between fusion and fission play a very important role in the regulation of apoptosis [12, 13]. There were some debates about the opinion that apoptosis occurred relating with the mitochondria fission. These debates focused on which process happened firstly, either apoptosis is the result of the mitochondria fission and fragmentation, or reversely, as a following up affair, the mitochondria's fission and fragmentation happened at the downstream of apoptosis. While, we can sure that mitochondria shape dynamic changes must be connected with apoptosis according to the follow latest researches:

Calcium irons act as the upstream stimulus which can activate the cellular mitochondrial fission, the mitochondrial became fragmentation rapidly depended by the increased calcium level in intracellular. If the calcium level increased protractedly, mitochondria's fragmentation will be non-reversible and lead to apoptosis. So Jennifer R. Hom group regarded that the calcium involved in mitochondria morphology and participated in the apoptosis processing;[14] some mitochondria membrane proteins also have been found to control mitochondrial morphology, for example, the Bcl-2 protein resides in the outer mitochondrial membrane, and this protein acts as a central regulator of the intrinsic apoptotic cascade; while some other toxins or proteins can also regulate the mitochondrial fission/fusion, and these variation shapes of mitochondria was found to have relation with some diseases, For instance, the PD(Parkinson's disease) have been found with the

mitochondrial morphology changes, there were two toxin proteins parkin and PINK1 which were detected to play a role in maintaining mitochondrial homeostasis through targeting the mitochondria and regulating the mitochondrial dynamics[15]; Fusion and fission often occur swiftly and are found to have relation with the mitochondria membrane potential changes .there are DRP1-dependent division and FZO1-dependent fusion reaction in mammalian cells, and division of mitochondria accompany with apoptosis., If mitochondrial fission/fusion dynamics losses balance, it will lead to some neurodegeneration diseases. So in brief, mitochondria act as the important role to keep cell healthy.

Mitochondrial iron transporter cytochrome C plays an classic role in apoptosis. As a bridge, it connect with caspase cascade reaction. When cytochrome C is released to the cytoplasm from the mitochondria as a result of response to some intrinsic or extrinsic ligands, it can trigger the downstream caspases and induce the intrinsic apoptosis. So mitochondria are not only the energy company of cell, but also have the ability to control the intrinsic apoptosis pathway through either cytochrome C, calcium, morphology changes(fission/fusion) or some membrane proteins expression imbalance(Bcl-2).

4. Trigger apoptosis ligands and cell environment materials

Apoptosis, as a major cell death procession for healthy, play an important role in homeostasis of whole life. In the period of fetation, apoptosis happened, as the essential affair for the finger and toe formation. due the cells between fingers occured apoptosis, we can form five fingers per hand. Apoptosis also can enhance embryonic stem cell survival during stress by increased expression Bcl-2 protein which significantly weaken the apoptosis and help colony formation [16];Apoptosis also take part in some tissues regeneration and homeostasis [17,18]; In addition to the function that we have described above, apoptosis can still anti-inflammation and hamper pathogens persistence infection, especially interfering the intracellular parasites diffusion; In conclusion, apoptosis are good for people's healthy in variety aspects, and apoptosis become research areas hotspots at present. Summarizing the currently researcher's data, we found that many ligands can trigger or inhibit apoptosis. We classified these ligands to two parts by its derivation: 1. extrinsic signal ligands. 2. Intrinsic ligands. The details about the ligands which can trigger the apoptosis will be described below:

4.1. Extrinsic cell materials

4.1.1. Cytokines

TNF-alpha plus z-VAD can trigger cell apoptosis, and this method is well-known in creating 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 initiated 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 depended by the nitric oxide(NO).[19] TGF-β1 acts as a chemo-attractant and is very important for the immune response, this cytokine also play a predominant suppressive role in inhibiting the cell proliferation and stimulating B cells to apoptosis. [20]

Above all, the cytokines are the positive inducer of apoptosis. The investigators also found another mechanism of cytokines related apoptosis which is negative induction by loss of suppressive signal. Many cells viability required supplying the constant or intermittent cytokines or growth factors, Lack of cytokine or growth factors, the cell will go to apoptosis. In this circumstance, these cytokines or growth factors act as the suppressors of apoptosis. For example, when we culture hematopoietic cells, we should add colony-stimulating factors and IL-3; In addition, IL-12 is required to maintain the viability of activated T cells in in vitro culture systerm; the neurorophic cells required the nerve growth factor (NGF) for survival. Moreover, there are many other cytokines and growth factors as the suppressors of apoptosis, such as: epidermal growth factor, platelet-derived growth factor and insulin like growth factor-I and so on. They are also act as the survival factors and inhibit the apoptosis, while if we block or remove these factors; the related cells will be in the procession of apoptosis. So in above all, we have known that cytokines may as inducer or suppressor to participate in apoptosis pathway.

4.1.2. Drugs

Some cytotoxic drugs (Cispkatin, Gemcitabin, Tooitecan, and paclitaxel) can trigger apoptosis; Didymin induce apoptosis by preventing N-Myc protein expression and make the cell G2/M arrest, which may be a novel mechanism to anti-neuroblastoma.[21]; apart from this anti-neuroblastoma properties, didymin have an anti-no small cell lung cancer ability by induced the Fas-mediated apoptosis, it may be a novel new chemotherapeutic agent to treat the lung cancer. [22] Gomisin N have anti-hepatotoxic, anti-oxidative and anti-inflammation abilities, while it also have anti-cancer activity through triggered the TRAIL-induced apoptosis.[23] Andrographolide as an anti-bacteria drug have been found having anti-cancer activity adrographolide treated cancer cell can activate the p53 by increasing p53 phosphorylation, p53 activation can make DR4 protein expression increased and then trigger the TRAIL-induced apoptosis.[24] Ursolic acid can stimulate the ROS production and trigger JNK activation, ROS and activated JNK can make the DR up expression, and in the end, TRAIL-induced apoptosis happened in p53 independent manner.[25] Ciglitazone, as an anti-diabetic drug, has been found by Plissonnier ML group that ciglitazone have antineoplastic effectiveness in a lot of cancer cell lines through up-regulation of soluble and membrane bound TRAIL, make caspase activation, death receptor signal pathway activation and induce 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 cell.[26] These data provided the powerful evidence that triggering apoptosis may be a feasible method for clinically cure.

4.1.3. Hormone

Apoptosis occurs in the embryonic development and during the formation of organs, Hormones is usually a peptide or steroid, produced by one tissue and conveyed by the bloodstream to another place to affect physiological activity, such as growth, proliferation, metabolism. Some researchers also found that hormones can regulate the apoptosis, and through this way hormone can control the metabolism of tissues or organs. For example, the leptin is one hormone produced by adipocytes, and it has been found as a inhibitor of apoptosis, leptin can down-regulate cleaved caspase-3 and Bcl-2 associated X protein and up-regulate Bcl-2 protein, if this hormone level is normal, there will be no apoptosis, however, if the hormone level decreased, the apoptosis will happen[27], this is one mechanism by which the hormone act as inhibitor of apoptosis, the other mechanism is that hormone act as an inducer of apoptosis. The majority relations between the hormone and apoptosis are concluded as below the table 2

Hormones	Apoptosis cell (Target)	Reference
Known inhibitors of apoptosis		
Testosterone	Prostate	51
Oestradiol	ovarian cells	53,52
Growth hormone	Human monocytes or human promyelocytic leukaemia	54
Leptin	myometrial cells	27
Dihydrotestosterone	Prostate	51
progeterone	cardiomyocytes	55
Act as inducers of apoptosis		
Glucocorticoids	Human small cell lung cancer	56
progeterone	human endometrial cell	57
Thyroid hormones	Play an important role in Amphibian organ remodeling during metamorphosis through inducing apoptosis	58
Estrogen	Breast cancer cell	59
Phytoestrogens	Breast cancer cell	60

Table 2. Involvement of hormones in apoptosis

4.1.4. Pathogen effectors

During the fight between host and pathogen, there are many roads that benefit the cell survival. There is the proverb “Survival of the fittest”. If failing to defense the pathogen, host will be ill, and give the phenomenon of inflammation or cell death (apoptosis, necrosis, auto-phage, pyroptosis). In this part, we will give the conclusion about host cell apoptosis which can be triggered by some pathogens, If cell occured apoptosis, the pathogen can not survival either, so through this way, host cells can clear the pathogen with little bad effects. The pathogen effectors, which possess the ability to trigger apoptosis, have been found as following below:

Mycobacterium can be cleared by macrophage's apoptosis which was induced by the NO and IFN-γ [28]; Chlamydia pneumoniae infection can induce the human T lymphocyte cell apoptosis, through this way, Chlamydia pneumonia could induce immunologic tolerance and would make pathogen persistence infection and inflammation[29]; Dendritic cells(DC) were well known immune cells, as an antigen-process cell, DC can inhibit pathogen replication and diffusion by caspase-3 dependent apoptosis in early infection stage, For instance, *Legionella pneumophila* was unable replicated in DC, because DC go to apoptosis when *Legionella pneumophila* infected these cells in the early stage.[30] Beside the bacteria infection induced the apoptosis, some virus also be found to involve in the apoptosis. For example, transmissible gastroenteritis virus infection can up-regulate the FasL; Subsequently, the Bid protein can be cleaved and cytochrome c release; in the end, Caspase-8 can be activated and the host cell happen apoptosis. [31] Through this way, the pathogens, especially the obligate intracellular parasites, will lost the suitable environment for their life and will die, however, the host will survival and suffer lowest bad effect.

From this part, we give the conclusion that apoptosis play the key role in host-pathogen confrontation. There are about two mechanisms in this confrontation, one mechanism is that pathogen's target cells can clear the pathogen and inhibit it persistence diffusion by itself apoptosis. Another is that pathogens infection didn't induce the targeted cell apoptosis but cause the related immune cells apoptosis. By this way, the host cells will fail to clear the pathogen. The loss function of host immune cells will benefit the pathogen's replication and help pathogen's diffusion persistence. There are always two sides to every thing, the apoptosis also have no exception..

4.1.5. Native activities compounds

Although apoptosis is the programmed cell death and can be recognized as the normal cell death by the immune system; and apoptosis have many important functions in the tissue development. While everything have two sides, in some cases, apoptosis also have the damage and negative effect to the life healthy. Recently, food scientists and biologist found that some native compounds from the daily life dietary can block or hamper apoptosis, and through this way, these native compounds can help to keep the body healthy.

Vitamin E, another name is tocopherol. As an antioxidant, Vitamin E has an important role in redox balance. Recently, apart it's major role in antioxidant ability, vitamin E can block the reduction of the mitochondrial membrane potential and inhibit the activation of caspase-3, in a brief, vitamin E is conducive to cell viability through blocking the caspase-3 triggered apoptosis. [32] Moreover, Purple Sweet Potato Pigments can scavenge ROS and protect the murine thymocyte by inhibiting caspase-dependent pathway apoptosis also [33]. Lycopene, another name is rhodopurpurin, Lycopene can be taken from the tomatoes, fruits and vegetables easily. As an antioxidant, Lycopene was been found that it contribute to body's heath. Nearly, researchers found that lycopene have anti-prostate cancer activity; Apart from the anti-tumor properties, it have anti-infection ability. For example, Jang SH' group gave the proof that lycopene can inhibit ROS increased, DNA damage and apoptosis in

gastric epithelial AGS cells induced by helicobactera pylori infection. [34]. Soy isoflavone also have been documented as dietary nutrients broadly, it was been classified as "natural agents" which play the important role in reducing the incidence of hormone-related cancers in Asian countries, and have shown inhibitory effects on cancer's development and progression in vitro and in vivo. [35] Beside this soy isoflavone, in recent years, dietary compounds which was from the bounties of nature have been paid any attentions, the latest researches data have shown that there are some associations between the consumption of some native dietary compounds and the reduced risk of several types of cancers, [36, 37] because there are lots of active compounds containing in the food which have some associations with the apoptosis, and due by apoptosis, these native compounds will inhibit cell abnormal proliferation.

Apart from these food derived natural compounds, there are many plant components which can be used by Chinese traditional medicine (TCM), these plant active components can also have trigger apoptosis, such as fisetin, wongonin, emodin and so on. Fisetin is a natural flavonoid which can induce several type cancer cells to apoptosis by dose and time dependent manner. Fisetin can activate caspase-8/caspase-3 dependent apoptosis pathway, and these pathway transducer molecular will be the candidates for cancer therapy; [38] Wongonin, as an O-methylated flavonoind, was detected to have anxiolytic activity, and also have the ability to trigger some cancer cells apoptosis. For instance, wongonin and fisetin can make PARP to be cleaved, then pro-caspase-3 will be activated in HL-60 cells, while they can induce the ROS decreased, so it is not the ROS dependent apoptosis pathway. Several compounds have the similar structural with flaconoids, including the luteolin, nobiletin, wogonin, baicalein, apigenin, myricetin and fisetin, they all have biological activities. Up to now, wogonin and fisetin have been found that they have the potential ability to trigger apoptosis through caspase-8 dependent manner[40,41]. Rheum palmatum is traditional Chinese medicines which have anti-bacteria; anti-inflammation; and improving microcirculation, emodin is an active component of Rheum palmatum and have apoptosis-inducing activity, Chen YC group found that the emodin can activate caspase-3 cascade and trigger HL-60 cell apoptosis independent of ROS production also. [41]

Some researches gave us many inspirations in the apoptosis research. We known that many tradition Chinese medicines (TCM) have some active constituents, these active components have anti-tumor activity through apoptosis, so combination the molecular biology to dig out the mechanism of drug functions will be effective and scientifical, Now, the functions of some tradition Chinese medicines are still stay the phenomena, we did not know the real mechanism of activity materials. Although TCM have not curative effect faster than western medicine, but the TCM have the lowest side effect and help for prognosis, so many patients choose TCM to defense the diseases in china. More and more investigators are focusing on elucidating the molecular mechanisms of these natural products and identifying its targets. Moreover, I think the researches of active components from TCM will be meaningful and broadly potential in the future. In the table 3, we summarized some other native compounds that can trigger apoptosis, I hope that these informations will guild us to research some active components in the drug.

Native compound	Caspase dependent apoptosis	Reference
luteolin	Trigger mitochondria- dependent apoptosis. And activate Bax, Bcl-xl, Bcl-2, Mcl-1, caspase-9, caspase-3, and PARP	61
Apigenin	Induce cytochrome C release and ROS enhance	62
phytosphingosine	Leading caspase-8 activation and mitochondria-dependent cell death	63
β-Lapachone	Leading ER stress and JNK activation and mitochondria mediate apoptosis	64

Table 3. Another native compounds which can trigger apoptosis apart from above paragraph's related

4.2. Intrinsic cell apoptosis signal materials

4.2.1. Oxidative stress (ROS; NO; GSH).

Keratin is a cytoskeleton protein which have some abilities to maintain the cell shape, Guo-Zhong Tao group found that keratin can modulate the shape of mitochondria and contribute to hepatocyte predisposition to apoptosis and oxidative injury [42].Depletion the mitochondria GSH in the human B lymphoma cell line by treatment with L-buthionine sulfoximine can induce caspase-3 activation and apoptosis, and indicating that GSH may be the potential early activator of apoptotic signal [43]. ROS is a type of toxic compound and usually detoxified by cells GSH, when the oxidative stress occur, the ROS detoxify will be failed, and ROS will participate in apoptosis through redox-sensitive death pathway.

4.2.2. Cytochrome C

Cytochrome C, as a proapoptotic protein, plays an important role in triggering programmed cell death, The activation of cytochrome C is related with the changes of Bak/Bax ratio. The latest researches shown that the interactions of heterotypic mitochondrial membrane will change the lipid milieu, in the end, mitochondrial membrane will be permeatable and cytochrome c will release. [44]; Apart the changes of lipid milieu, arachidonic acid, triiodothyronine (T3), or 6-hydroxdopamine can also effect the permeability of mitochondrial membrane and release Ca^{2+} and cytochrome c. [45] Cytochrome c can thrigger caspase activation via oligomerization of APAF1 protein. Caspase activation can catalyze the PARP-1, Finally, the apoptosis will happen. In short, cytochrome C is the one of major intrinsic cell apoptosis signal molecules.

4.2.3. Calcium iron

The concentration of calcium in vivo is the key role in maintain the permeatability of mitochondrial membrane. The increased intra-mitochondrial calcium can result in enhanced ROS, Furthermore, cytochrome c will be stimulated to release. [46] And calcium also trigger

the ER stress, and then activate JNK pathway, afterwards, JNK activation can stimulate Bax activation; Moreover, calcuim can regulate the cysteine protease calpain, It's well known that calpain participate in the cell proliferation, cell cycle, and apoptosis. Calpain can cleave the N terminal of Bax and generate a proapoptotic fragment, and in 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 iron can play its roles in modulating the apoptosis. [47]. Beside involving in the apoptosis, Cacium iron can take part in many other signal pathways by controlling the iron channel's open or close.

4.2.4. Endoplasmic reticulum (ER) stress

As the apoptogenic factor, the permeabilization of lysosomal membrane can induce apoptosis by both caspase-dependent and caspase-independent pathway [48]; Tackled with the unfolded proteins is the one of the important ER functions, cell can regulate the unfolded proteins in ER according to metabolically needed, while if numerous unfolded proteins stimulate the ER and make the ER overload stress, the cells which have lots of unfolded proteins will apoptosis[49]; Differing from the ER stress, chaperons will protect this cell death. For example, the HSP72 protein can hamper the apoptosis through down regulating the unfolded protein signal response sensor IRE1alpha. Some neurodegeneration diseases usually accompany with unfolded protein accelerated and ER stress. So it is meaningful to research the relationship between the ER stress and neurodegenration diseases, and by this way, we will well known the function of apoptosis in the some neurodegeration diseases.

The intrinsic components, which can trigger apoptosis pathway, can connect with each other by the vivo organelles. By this way, lots of materials in the cells will consisted in the network of apoptosis to feedback the vitro stimulus, This type cell death will mostly help for the body health.

5. Apoptosis and diseases

During the last decade, exceptional for the basic research, the apoptosis have attracted many attentions due to its potential application in therapying the various human diseases. In order to maintain the function of whole organism, millions of cells will die and proliferate every day, cell death like apoptosis is the essential for the regulation of organism growth and maintenance the tissue homeostasis. If the cell death and proliferation go to imbalance, many diseases will happen. Such as: some acute pathologies (stroke, heart attack, liver failure); cancer; neurodegenerative syndromes; diabetes and so on. Due to its no lethal effect to the body, Apoptosis play a fundamental role in organism development and tissue homeostasis, while if apoptosis was not under controlled, a variety of diseases will occur.

Some neurodegenerative diseases (Alzheimer's, Parkinson's and Huntington's diseases) usually have the phenomena of the ER dyshomeostasis, mitochondrial dysfunction, and unfolded protein accelerated. In these diseases, some neural cells occur to apoptosis and

brain tissue damage. In the ischemia/reperfusion injury tissue, the intracellular calcium and ROS level will increased, these factors all contribute to induce AIF to release and translocate to the nucleus, in the end, the caspase-independent apoptosis will happen, if we prevent this cell death, the prognosis of ischemia/reperfusion will be favorable. However, if we promote this cell death in cancer cells , the cancer cells will form several apoptotic body containing the cell content, and did not release the cytosol and will not lead to the fatal inflammation, in this way, the patient will have the least bad effect and help them to fight against the disease; Apoptosis occur accompanying with inflammation, inflammasome in the cells may be related with the caspase family, the tissues or organs may be existed the apoptosis and deduct the immune reaction which induced by the inflammation, we proposed that if the apoptosis do not happen in this case, the persistent proliferation and serious inflammation will be occurred in cancer cells, this is bad for the organism.

5.1. Drug design

Apoptosis is the normal cell death in order to maintain the balance of homeostasis. Unlikely the necrosis can induce inflammation. apoptosis can give little side effects. So as the therapy targets, apoptosis will be the reasonable way to cure some diseases. such as obesity [50], cancer, neuron-degeneration diseases and so on. Due to the genetic changes often existed in the human tumor cells and apoptosis have the little side effect in curing some diseases, ,it is not surprised that the antitumor drug have direct or indirect to target the apoptosis pathway molecular. The identification of the apoptosis signal pathways, and together with the increased knowledge about the apoptosis mechanisms, have given the great lots of evidences for the discovery of new drugs which can target to the apoptosis.

Above all, from the life beginning and during the whole life, apoptosis always existed to make our life healthy. Apoptosis can not release the intracellular content in the end, this cell process will not lead to inflammation, and therefore, apoptosis is the injury-limiting mode of cell disposal. Above all, it is necessary and meaningful to research the apoptosis mechanism, it will give the deep inside to guild the clinical treatment and drug design. Beside, in the nutrition research area, there are some native compounds which can be from the fruits, vegetables and some marine products can help for healthy through inducing or inhibiting apoptosis signal pathway, so knowing the mechanism of apoptosis deeply not only good for guiding people to use proper drug or balance dietary in daily life, but also far reaching impacts in design some new drugs.

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