Apoptosis

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Adapted from APOPTOSIS AND MEDICINE
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Published by InTech
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Apoptosis

- 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.

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

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:

- ***Caspase dependent pathway***

- ***Caspase independent pathway***

PCD

- Type I: the classic apoptosis, the well know caspase dependent apoptosis

- Type II: its morphology characters are the appearance of the autophagic and double membrane of vacuole

- Type III: occurs without the condensate chromatin and has not been well-known.

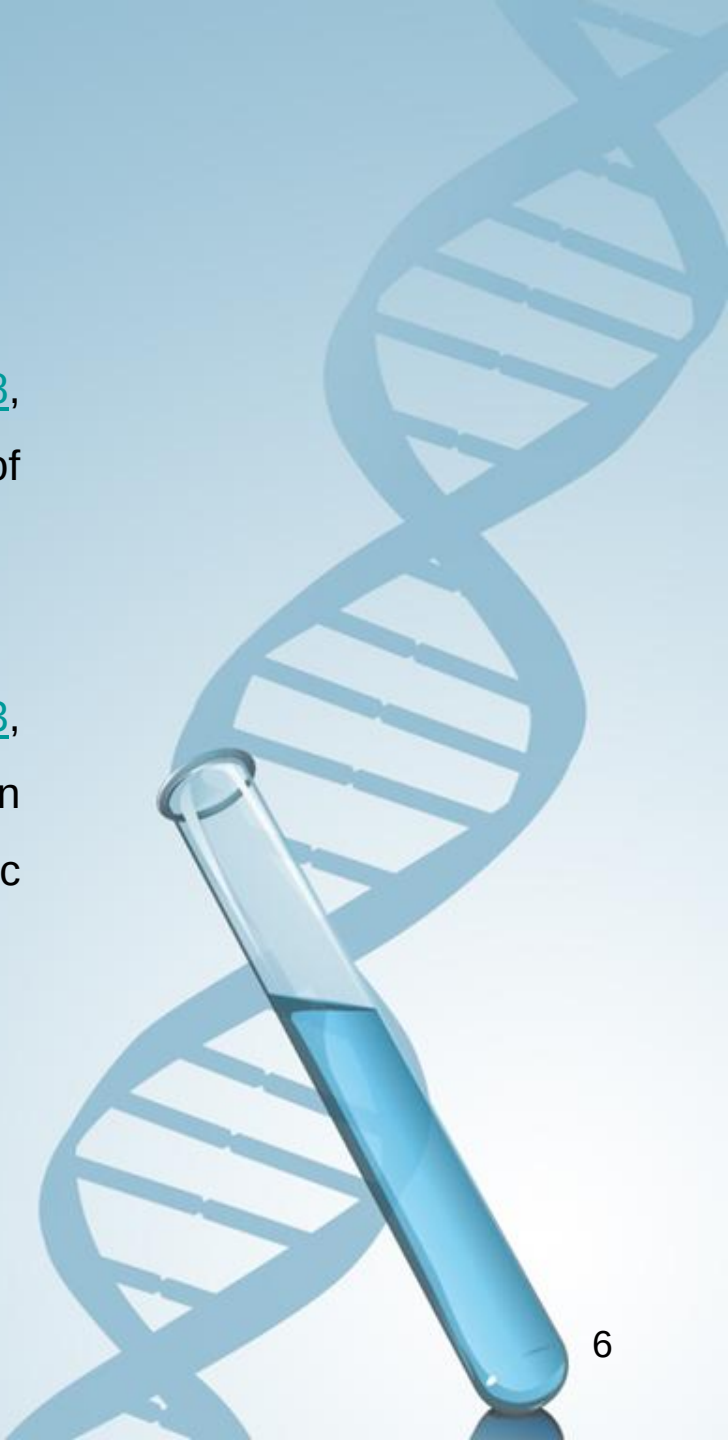
- Type II and type III PCD are the caspase-independent apoptosis.

Caspase

- Caspases, or cysteine-aspartic proteases or cysteine-dependent aspartate-directed proteases are a family of cysteine proteases that play essential roles in apoptosis (programmed cell death), necrosis, and inflammation.
- Caspases are essential in cells for apoptosis, or programmed cell death, in development and most other stages of adult life, and have been termed "executioner" proteins for their roles in the cell. Some caspases are also required in the immune system for the maturation of lymphocytes.

- Initiator (apical) caspases: (e.g., CASP2, CASP8, CASP9, and CASP10) cleave inactive pro-forms of effector caspases, thereby activating them.

- Effector (executioner) caspases: (e.g., CASP3, CASP6, CASP7) in turn cleave other protein substrates within the cell, to trigger the apoptotic process.



I. Caspase dependent pathway

- Caspase dependent apoptosis is the classic programmed cell death pathway

- Participants: the capase-8, caspase-9, caspase-12, caspase-7, caspase-3

- Receptors: the TNF-alpha receptor, FasL receptor, TLR, Death receptor and some iron channels

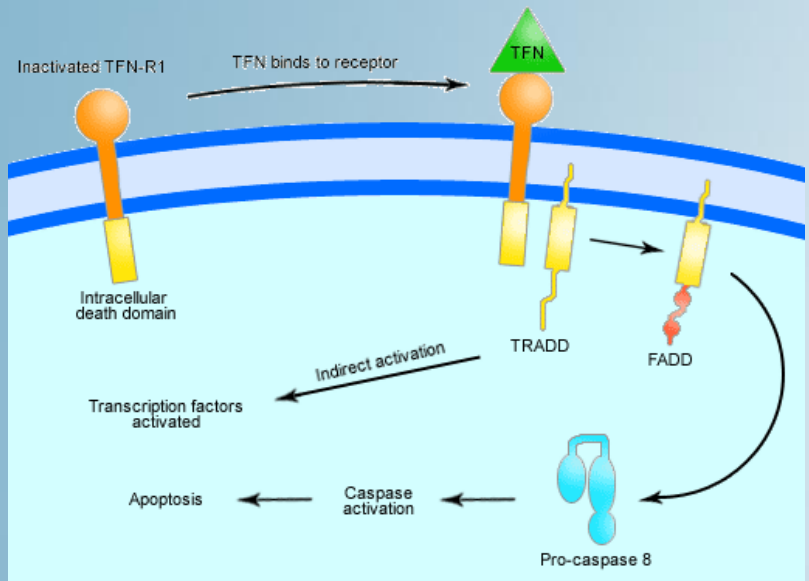
Caspase dependent pathway

- Inducing caspase-8 dependent pathway by TNF-α*
- Activating Bcl-2 protein
- Inducing the mitochondria membrane changes
- Releasing cytochrome C

- Cytochrome c is the proapoptosis signal molecular which can activates the caspase cascade reaction and induced the apoptosis in the end.

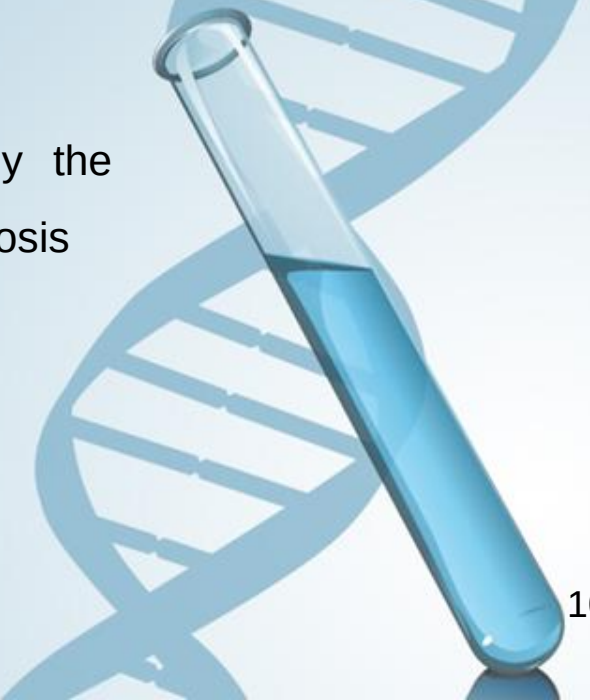
* TNF path

- TNF is a cytokine produced mainly by activated macrophages, and is the major extrinsic mediator of apoptosis. Most cells in the human body have two receptors for TNF: TNF-R1 and TNF-R2. The binding of TNF to TNF-R1 has been shown to initiate the pathway that leads to caspase activation via the intermediate membrane proteins TNF receptor-associated death domain (TRADD) and Fas-associated death domain protein cIAP1/2 inhibit TNF-α signaling by binding to TRAF2. FLIP inhibits the activation of caspase-8 (FADD). Binding of this receptor can also indirectly lead to the activation of transcription factors involved in cell survival and inflammatory responses. The link between TNF and apoptosis shows why an abnormal production of TNF plays a fundamental role in several human diseases, especially in autoimmune disease.



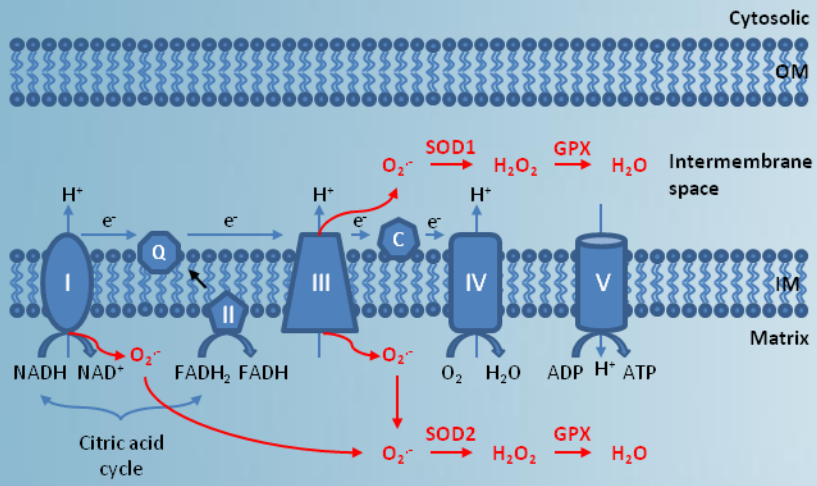
- Depolarization and membrane permeabilization of mitochondria by Some radiation UV or X ray:
- Increasing the ROS**
- Releasing cytochorme c
- and then triggering caspase-9, caspase-3 activation

- In the end, the substrates will be cleavaged by the activation caspases and the fate of cells will be apoptosis



** ROS

- Mitochondrial ROS (mtROS or mROS) are reactive oxygen species (ROS) that are produced by mitochondria. Generation of mitochondrial ROS mainly takes place at the electron transport chain located on the inner mitochondrial membrane during the process of oxidative phosphorylation (OXPHOS).
- High levels of mitochondrial ROS activate apoptosis pathways capable of inducing cell death.



Some pathogens can trigger others caspases dependent apoptosis pathway

1. Mycobacterium tuberculosis can induce programmed cell death on macrophage, and this apoptosis pathway is the caspase-12 dependent.
2. NO[1] and ROS production, stimulated by ER stress, also take part in apoptosis triggered by Mycobacterium tuberculosis
3. An alternative Kaposi's sarcoma-associated herpesvirus replication can trigger host cell apoptosis in caspase dependent manner

[1] Nitric oxide

4. 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
5. In vivo, DNA damage can trigger apoptosis through enhancing ROS level and changing the mitochondria membrane permeability
6. 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

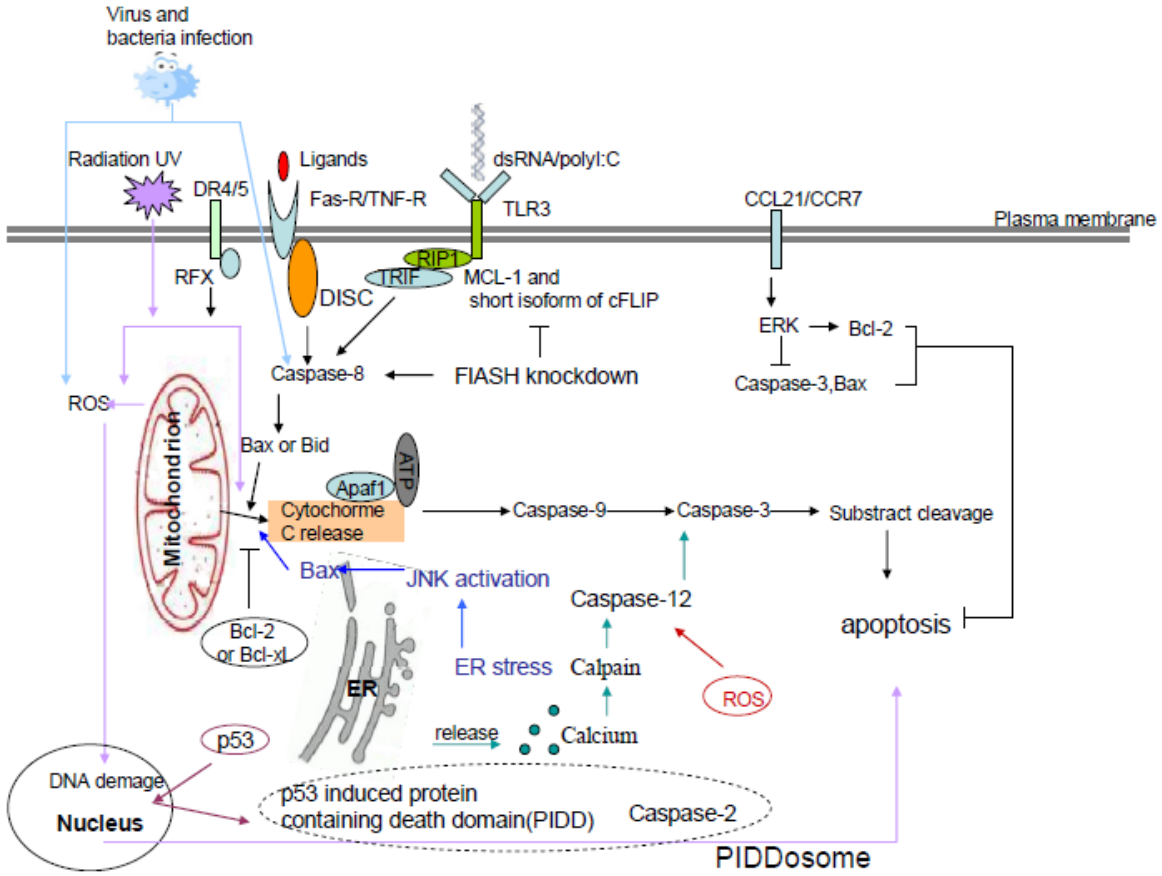
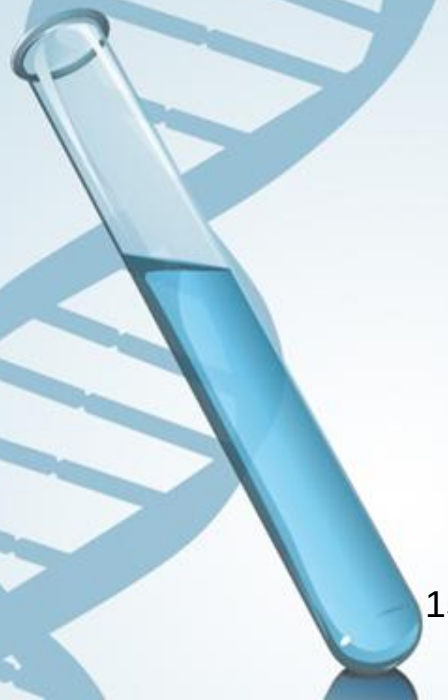


Figure 1. Summarize the caspase dependent apoptosis pathway

II. Caspase independent pathway

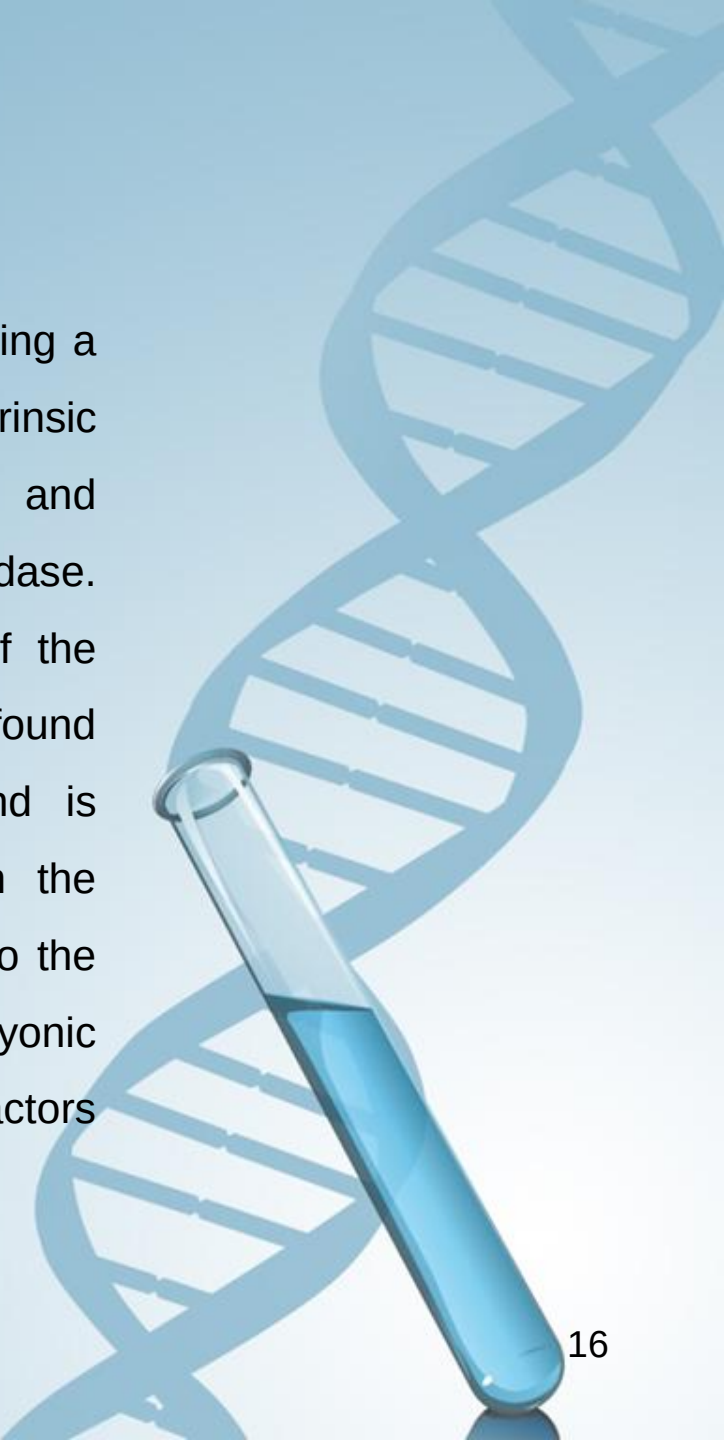
The mitochondria damage will be the first step of the apoptosis, then ROS production increase, and ROS may the mainly factor to induce caspase independent apoptosis.

1. 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
2. AIF*** has been found the major important caspase-indenpendent pro-apoptosis factor, which can release from the mitochondria and translocat in the nuclear to cleavage the DNA, in the end, if the DNA damage have not been repaired by cells, the apoptosis will happen.



*** AIF

Apoptosis inducing factor (a flavoprotein) is involved in initiating a caspase-independent pathway of apoptosis (positive intrinsic regulator of apoptosis) by causing DNA fragmentation and chromatin condensation. It also acts as an NADH oxidase. Another AIF function is to regulate the permeability of the mitochondrial membrane upon apoptosis. Normally it is found behind the outer membrane of the mitochondria and is therefore secluded from the nucleus. However, when the mitochondrion is damaged, it moves to the cytosol and to the nucleus. Inactivation of AIF leads to resistance of embryonic stem cells to death following the withdrawal of growth factors indicating that it is involved in apoptosis



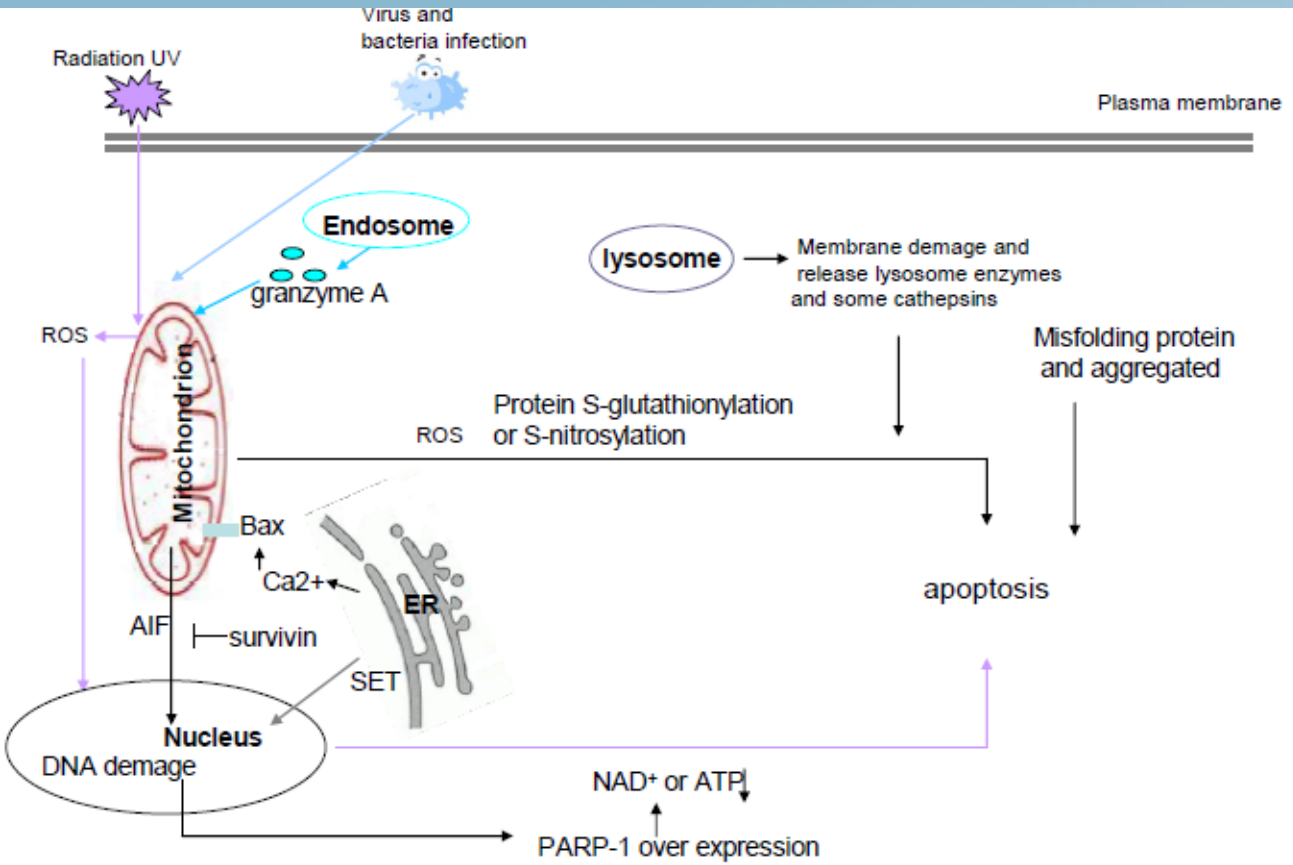
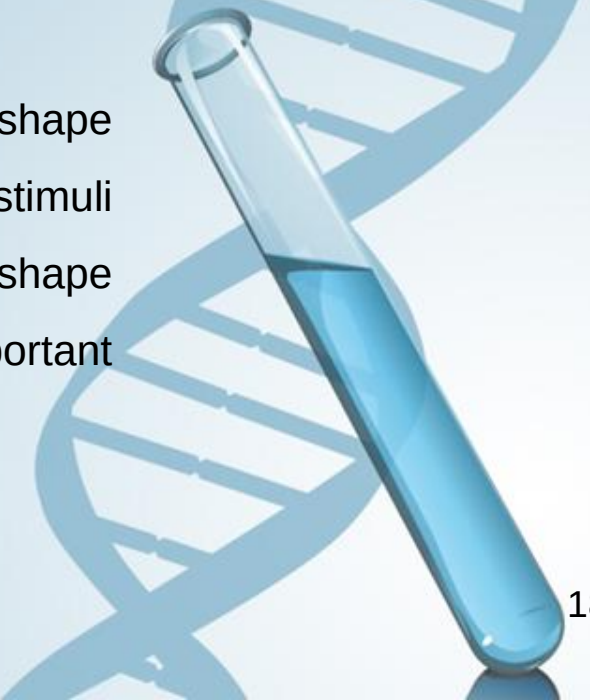


Figure 2. Caspase independent apoptosis pathway

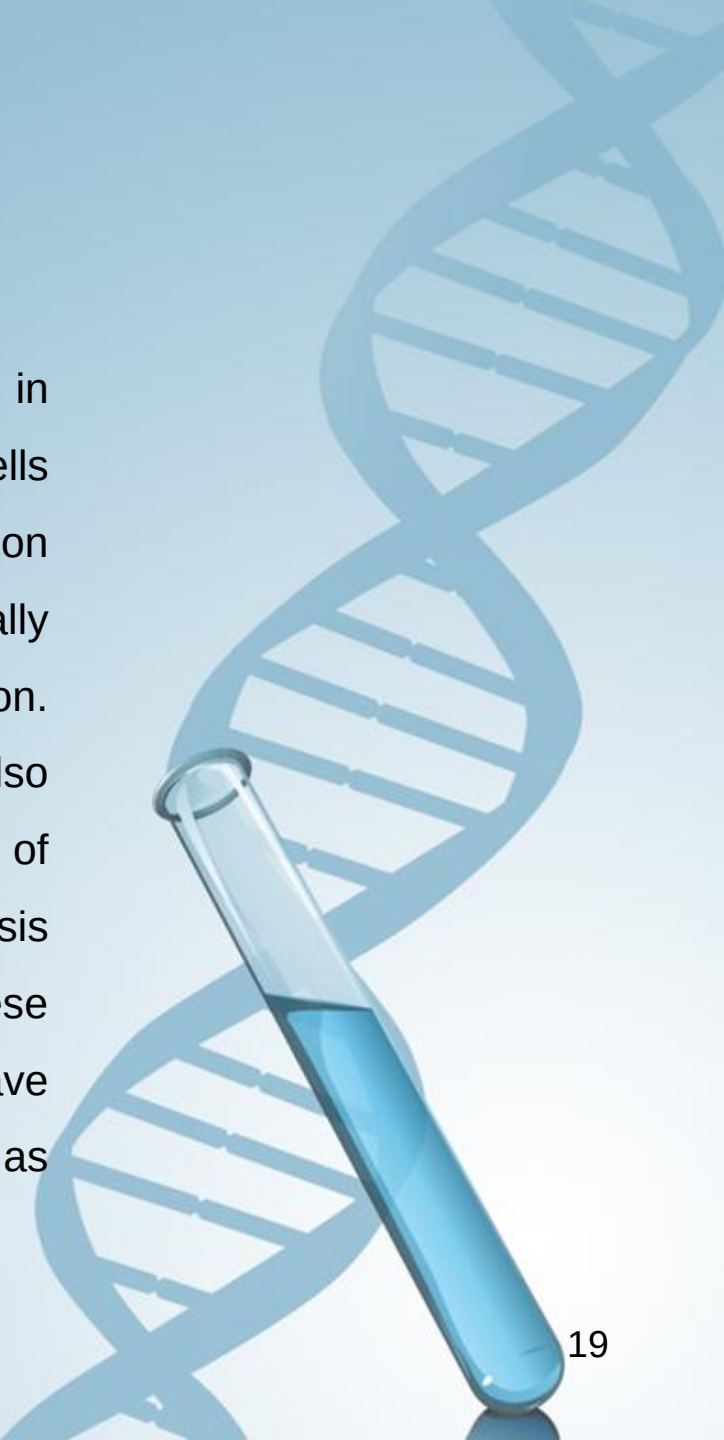
III. Mitochondria dynamics and apoptosis

Mitochondria's dysfunction has the relation with many diseases (Alzheimer's disease; Parkinson's disease, cancer, diabetes). 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.

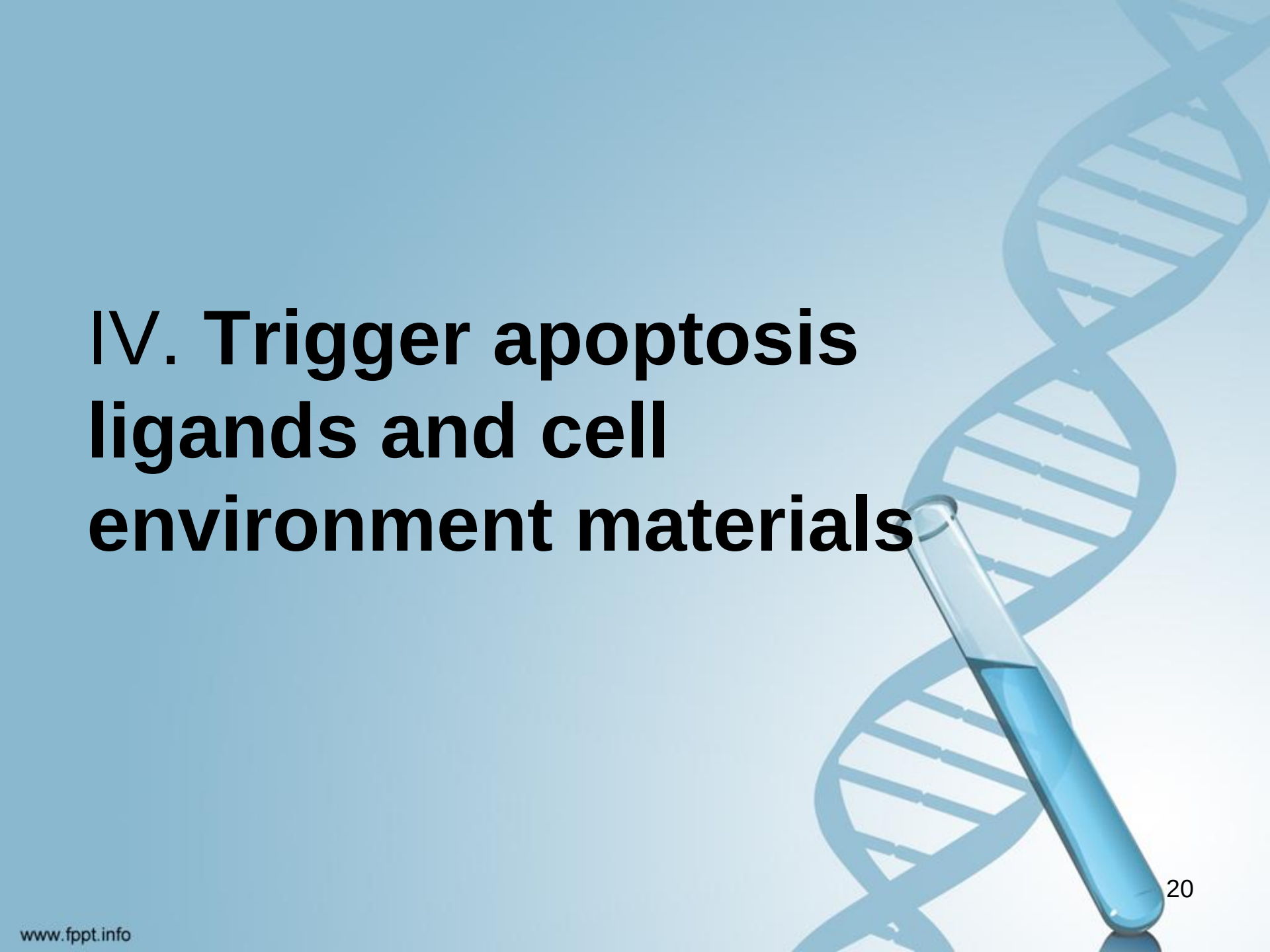
As a dynamic organelle, mitochondria can change their shape and structure constantly to respond to the different stimuli and metabolic demands of cells. The mitochondrial shape changes between **fusion** and **fission** play a very important role in the regulation of apoptosis



Mitochondrial fission and fusion play critical roles in maintaining functional mitochondria when cells experience metabolic or environmental stresses. Fusion helps mitigate stress by mixing the contents of partially damaged mitochondria as a form of complementation. Fission is needed to create new mitochondria, but it also contributes to quality control by enabling the removal of damaged mitochondria and can facilitate apoptosis during high levels of cellular stress. Disruptions in these processes affect normal development, and they have been implicated in neurodegenerative diseases, such as Parkinson's.



IV. **Trigger apoptosis ligands and cell environment materials**



1. Extrinsic cell materials

1.2. Cytokines

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

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)

TGF-β1 acts as a chemoattractant 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.

1.2. Drugs

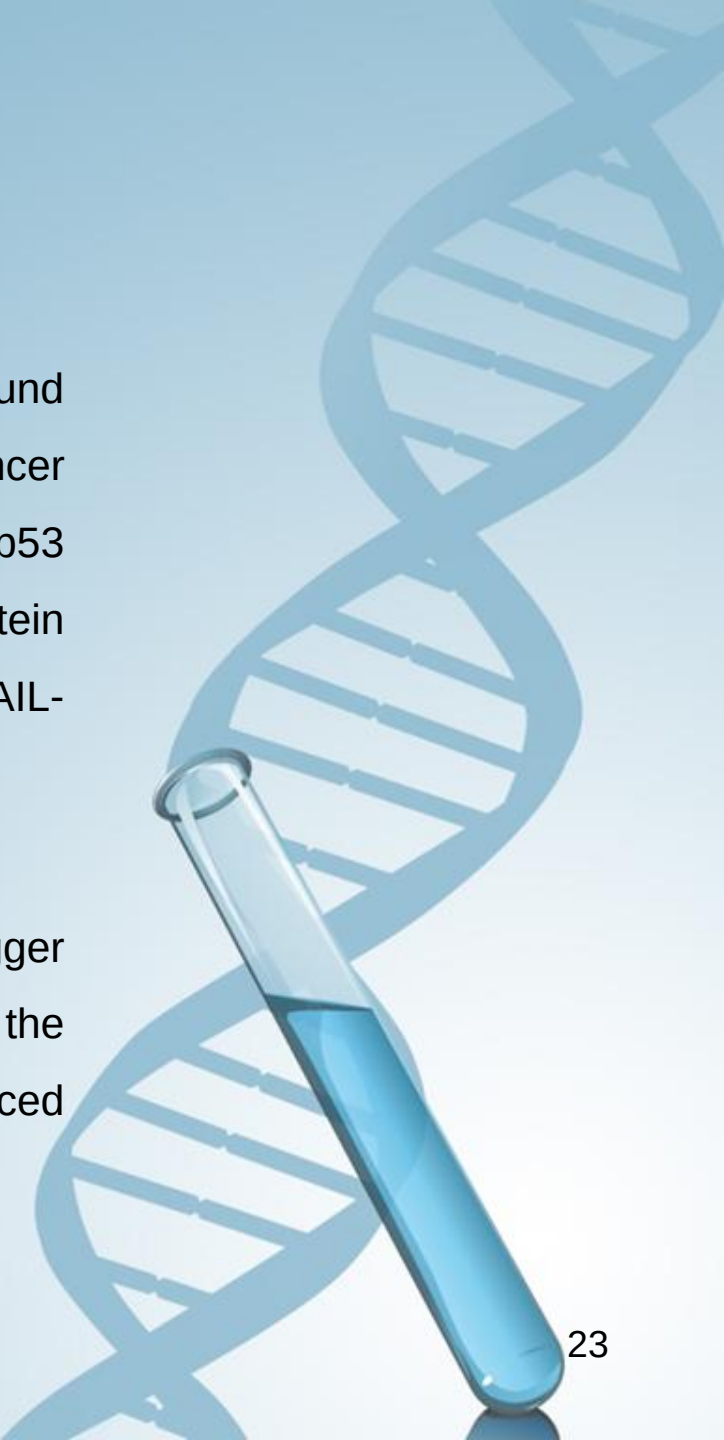
Some cytotoxic drugs (Cispkatin, Gemcitabin, Tooitecan, and paclitaxel) can trigger apoptosis

Didymin induce apoptosis by preventing N-Myc protein expression and make the cell G2/M arrest

Gomisin N have anti-hepatotoxic, anti-oxidative and anti-inflammation abilities, while it also have anti-cancer activity through triggered the TRAIL-induced apoptosis

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

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



1.3. Hormone

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

1.4. Pathogen effectors

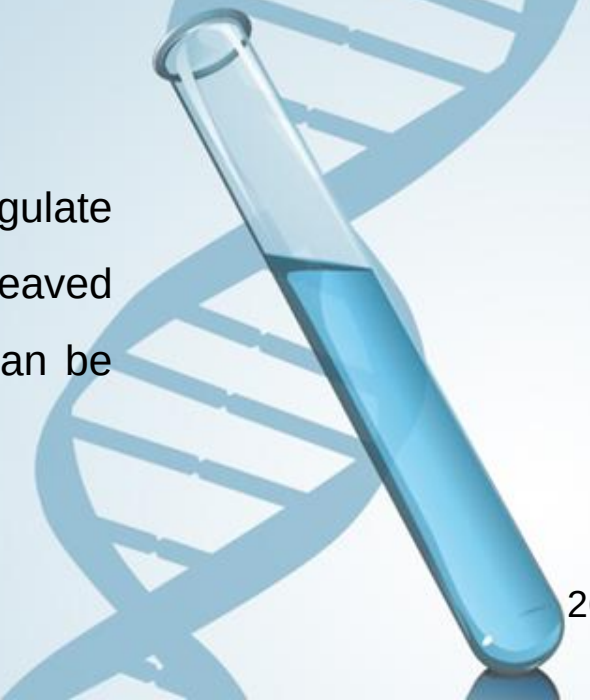
If failing to defense the pathogen, host will be ill, and give the phenomenon of inflammation or cell death (apoptosis, necrosis, auto-phage, pyroptosis).

Mycobacterium can be cleared by macrophage's apoptosis which was induced by the NO and IFN-γ

Chlamydia pneumoniae infection can induce the human T lymphocyte cell apoptosis, through inducing immunologic tolerance and would make pathogen persistence infection and inflammation

Dendritic cells(DC), an antigen-process cell, 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

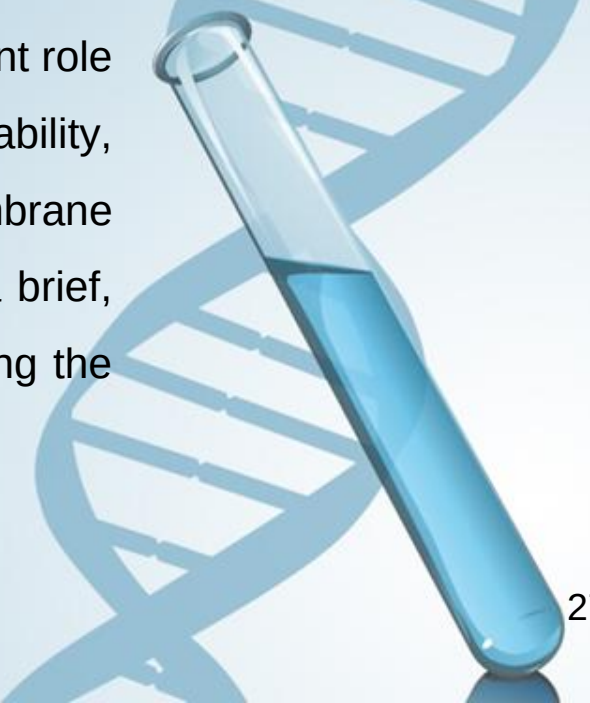
Transmissible gastroenteritis virus infection can up-regulate the FasL; Subsequently, the Bid protein can be cleaved and cytochrome c release; in the end, Caspase-8 can be activated and the host cell happen apoptosis



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.

Vitamin E (tocopherol), as an antioxidant, has an important role in redox balance. Apart it's major role in antioxidant ability, it 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.



Purple Sweet Potato Pigments can scavenge ROS and protect the murine thymocyte by inhibiting caspase-dependent pathway apoptosis

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, lycopene can inhibit ROS increased, DNA damage and apoptosisgastric epithelial AGS cells induced by helicobactera pylori infection.

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

2. Intrinsic cell apoptosis signal materials

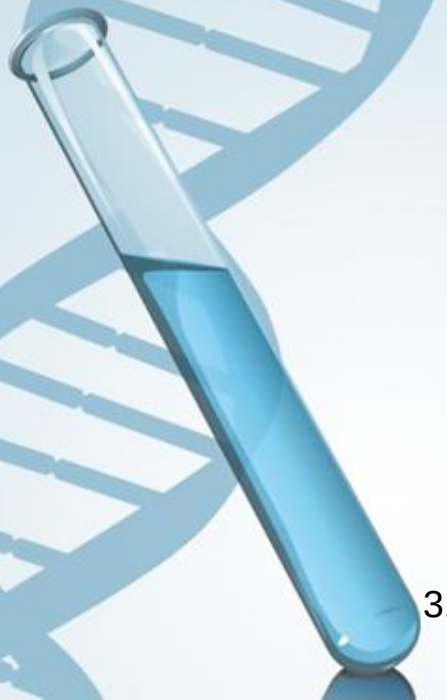
2.1. Oxidative stress

(ROS; NO; GSH)

Keratin is a cytoskeleton protein which have some abilities to maintain the cell shape. It can modulate the shape of mitochondria and contribute to hepatocyte predisposition to apoptosis and oxidative injury

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

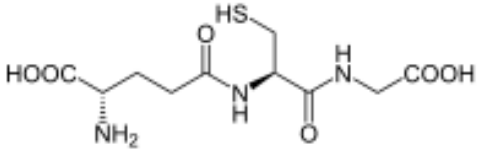
ROS is a type of toxic compound and usually detoxified by cells GSH, when the oxidative stress occur, the ROS detoxify will be failed, and ROS will participate in apoptosis through redox-sensitive death pathway

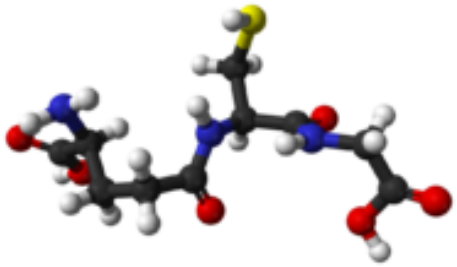


* GSH

Glutathione (GSH) is a tripeptide with a gamma peptide linkage between the amine group of cysteine (which is attached by normal peptide linkage to a glycine) and the carboxyl group of the glutamate side-chain. It is an antioxidant, preventing damage to important cellular components caused by ROS such as free radicals and peroxides.

Glutathione[1]





IUPAC name [hide]

(2*S*)-2-amino-4-{[(1*R*)-1-[(carboxymethyl) carbamoyl]-2-sulfanylethyl]carbamoyl}butanoic acid

Other names [hide]

γ-L-Glutamyl-L-cysteinylglycine
(2*S*)-2-Amino-5-[[(2*R*)-1-(carboxymethylamino)-1-oxo- 3-sulfanylpropan-2-yl]amino]-5-oxopentanoic acid

2.2. Cytochrome C

Cytochrome C, as a proapoptotic protein, plays an important role in triggering programmed cell death

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

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. 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