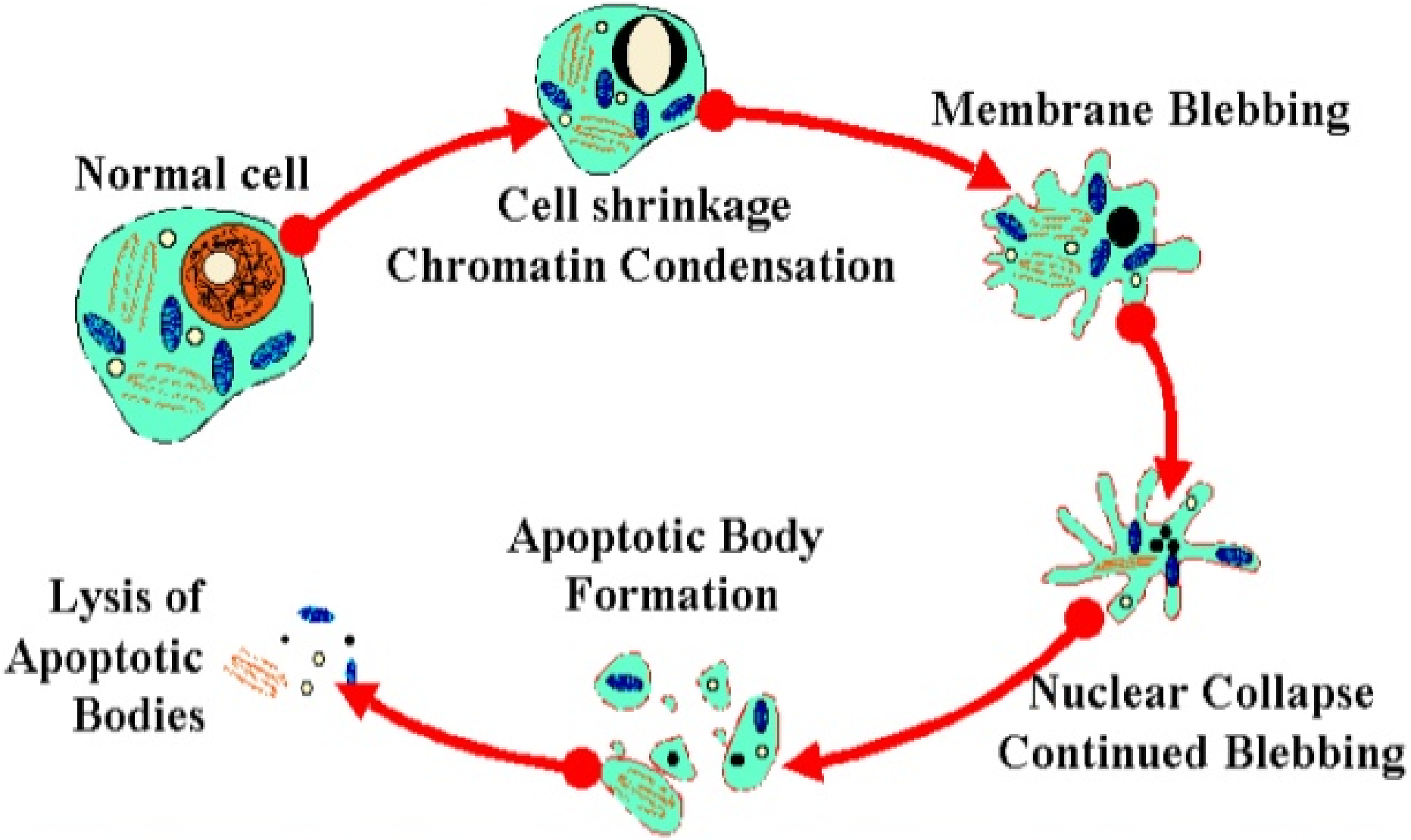
Introduction

- Apoptosis, or programmed cell death, is a highly regulated process that allows a cell to self-degrade in order for the body to eliminate unwanted or dysfunctional cells. During apoptosis, the genome of the cell will fracture, the cell will shrink and part of the cell will disintegrate into smaller apoptotic bodies.
- Between 50 and 70 billion cells die each day due to apoptosis in the average human adult. For an average child between the ages of 8 and 14, approximately 20 billion to 30 billion cells die a day.

Apoptosis
(Programmed Cell Death)



History

- German scientist Carl Vogt was first to describe the principle of apoptosis in 1842. In 1845, anatomist Walther Flemming delivered a more precise description of the process of programmed cell death.

- Kerr received the Paul Ehrlich and Ludwig Darmstaedter Prize on March 14, 2000, for his description of apoptosis. He shared the prize with Boston biologist Robert Horvitz.

- Walther Flemming – Process of programmed cell death (1845).

- The 2002 Nobel Prize in Medicine was awarded to Sydney Brenner, Horvitz and John E. Sulston for their work identifying genes that control apoptosis. The genes were identified by studies in the nematode *C. elegans* and these same genes function in humans for apoptosis.

- Apoptosis has since been recognized and accepted as a distinctive and important mode of "programmed" cell death, which involves the genetically determined elimination of cells.
- Apoptosis is essential to embryonic development and the maintenance of homeostasis in multicellular organisms. In humans, for example, the rate of cell growth and cell death is balanced to maintain the weight of the body. During fetal development, cell death helps sculpt body shape and making the right neuronal connections.

- Tissue homeostasis mainly depends on the balance between cell proliferation and cell death. Programmed cell death or apoptosis is an intrinsic death program that occurs in various physiological and pathological situations .
- Apoptosis or self destruction is necessary for normal development and homeostasis of multicellular organisms.

Apoptosis plays a major role in many diseases like

cancer,

AIDS and

neurodegenerative disorders.

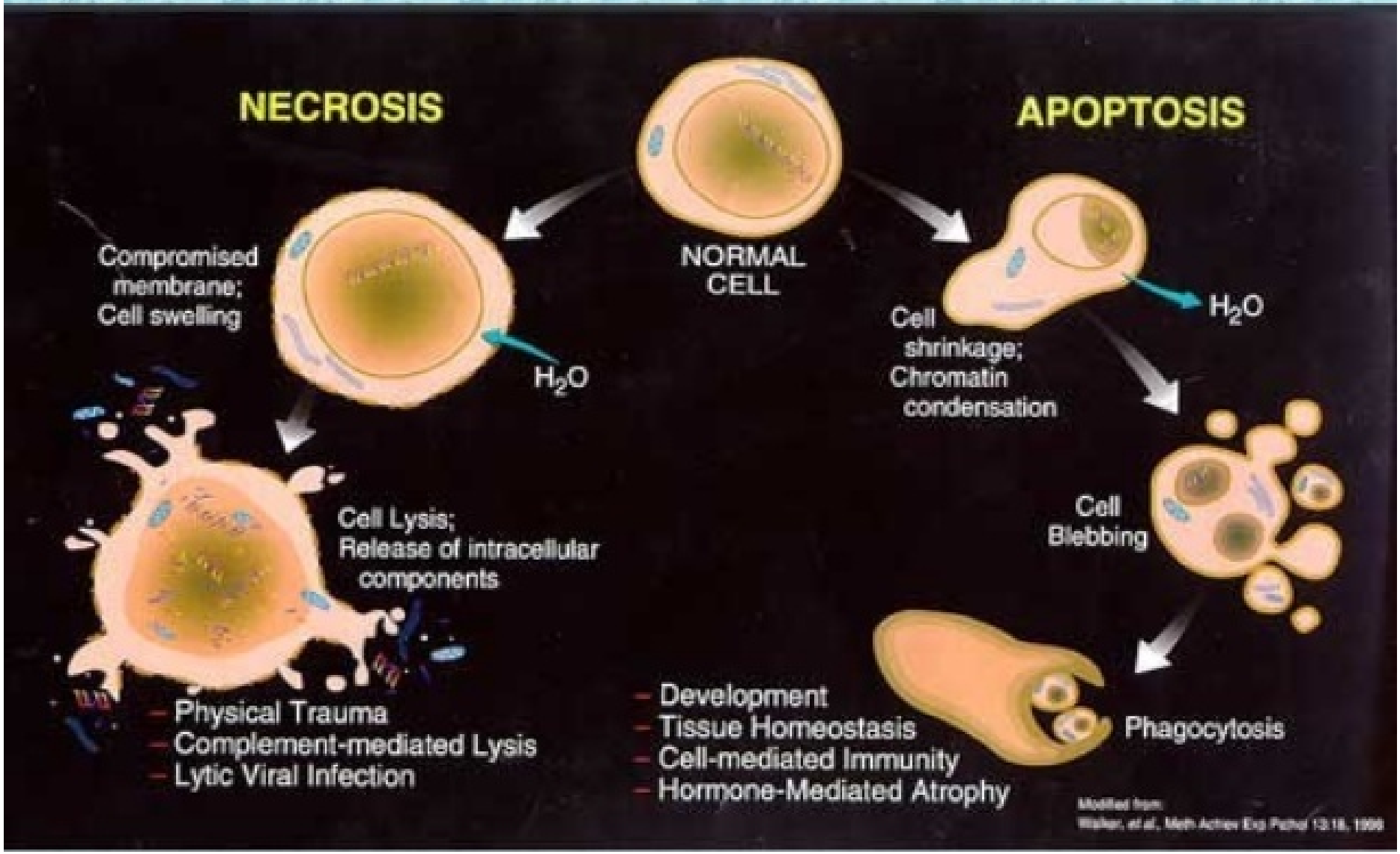
Cell death

- Cell die by one of two mechanisms-

  - **Necrosis - Death By Injury**
  - **Apoptosis - Death By Suicide**

- Apoptosis and necrosis have different characteristics

NECROSIS Vs APOPTOSIS



APOPTOSIS (Physiological cell death)	NECROSIS (Pathological cell death)
Functional form of cell death	Accidental form of cell death
Occurs under physiological conditions	Seen under pathological conditions
Energy (ATP)- dependent	No energy requirement
Cell shrinks and pulls away from its neighbours	Cell swelling in a defining features
Nucleus ruptures	Entire cell balloons and ruptures
Induced by physiological stimuli(lack of growth factor, changes in harmonal environment	Induced by non-physiological disturbances lytic viruses, hypothermia,hypoxia, ischaemia,metabolic poisons
No inflammation follows apoptosis	Necrosis is followed by inflammation

Need Of Apoptosis

- **Apoptosis is needed for proper development**

  Examples:

  The resorption of the tadpole tail

  The formation of the fingers and toes of the fetus

  The formation of the proper connections between neurons in the brain

- **Apoptosis is needed to destroy cells**

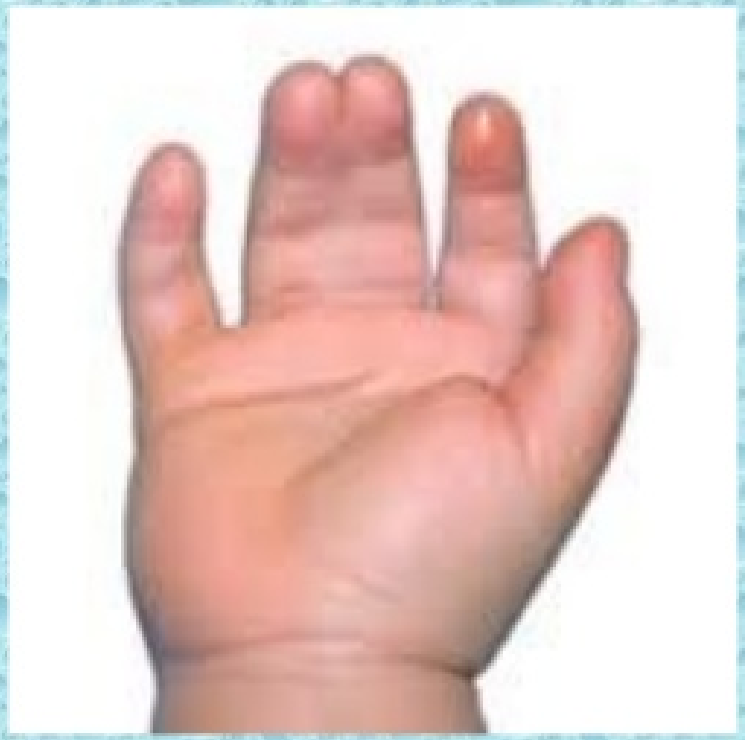
  Examples:

  Cells infected with viruses

  Cells with DNA damage

  Cancer cells

Incomplete differentiation due to lack of Apoptosis



FROG METAMORPHOSIS

Rana sp.

Reasons of apoptosis

- **Withdrawal of positive signals**

  examples :
  - growth factors for neurons
  - Interleukin-2 (IL-2)

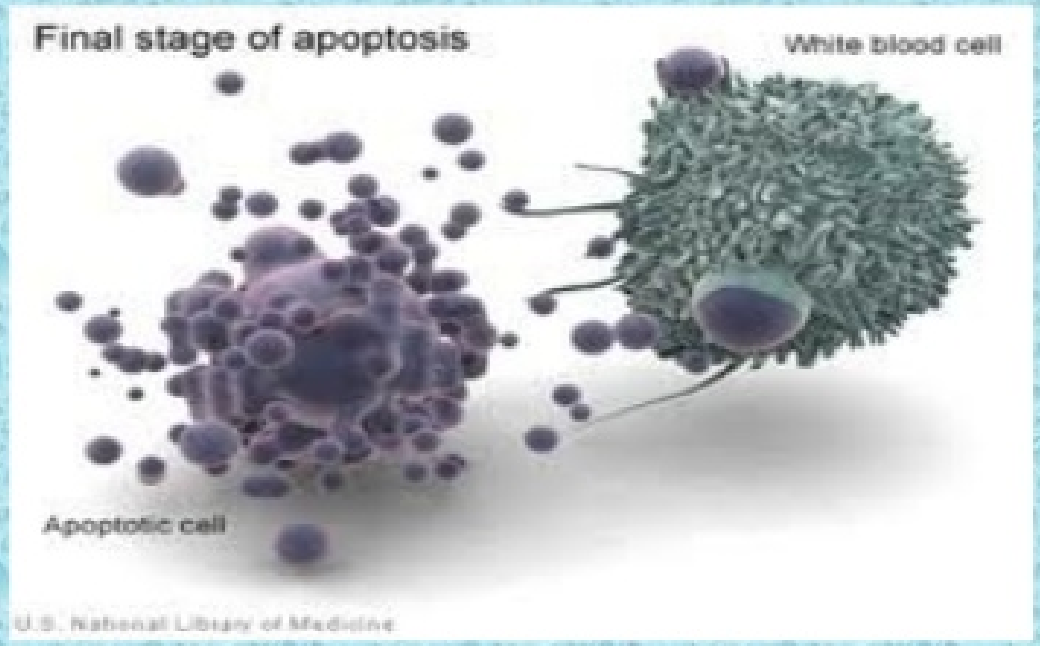
- **Receipt of negative signals**

  examples :
  - increased levels of oxidants within the cell
  - damage to DNA by oxidants
  - death activators :
    - Tumor necrosis factor alpha (TNF-α)
    - Lymphotoxin (TNF-β)
    - Fas ligand (FasL)

Inducers of Apoptosis

- TNF family
- Growth factor withdrawl
- Calcium
- Oncogenes
- Nutrient deprivation
- Toxins
- UV radiation
- Gamma radiation

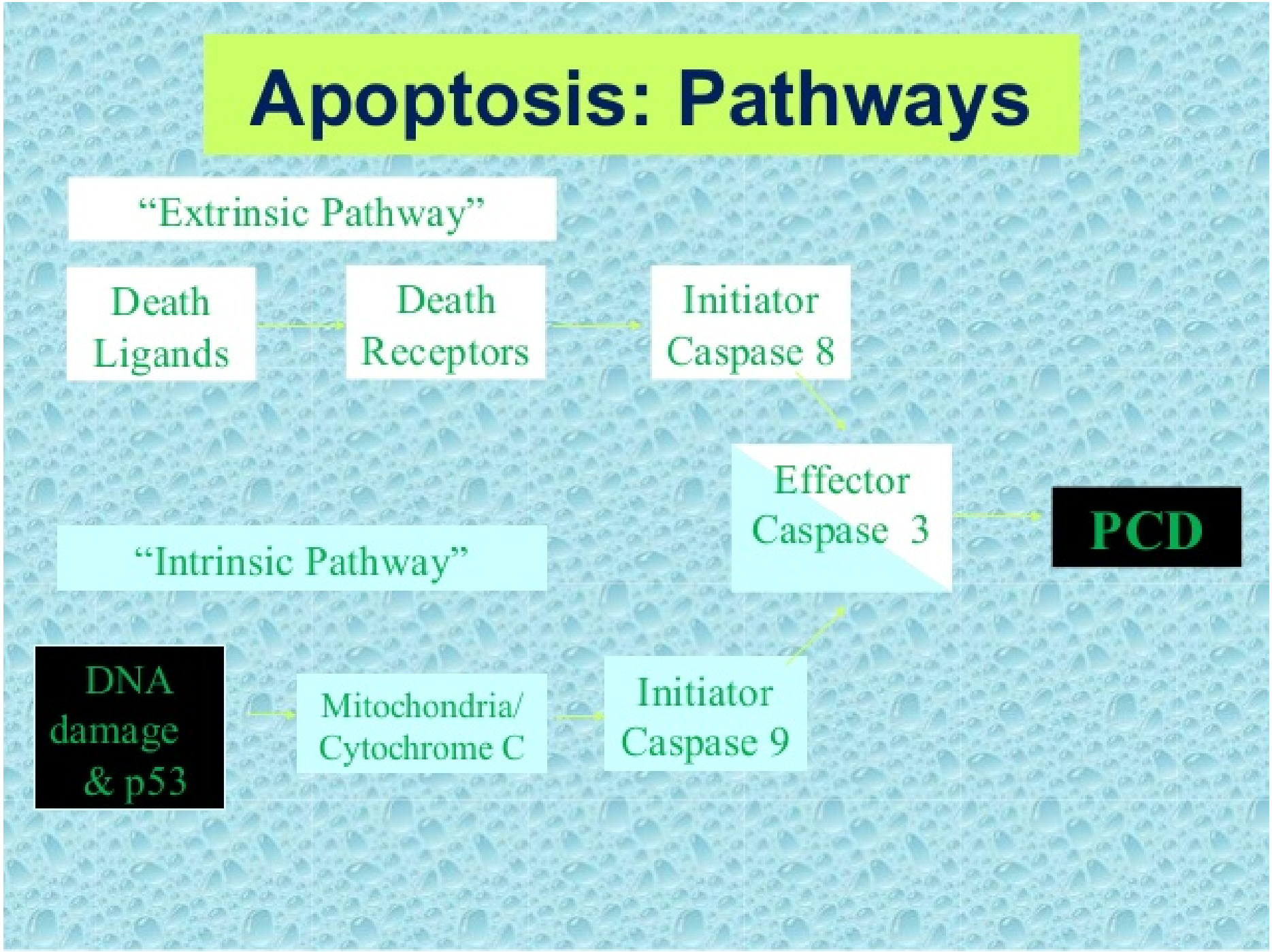
Apoptosis in physiological conditions

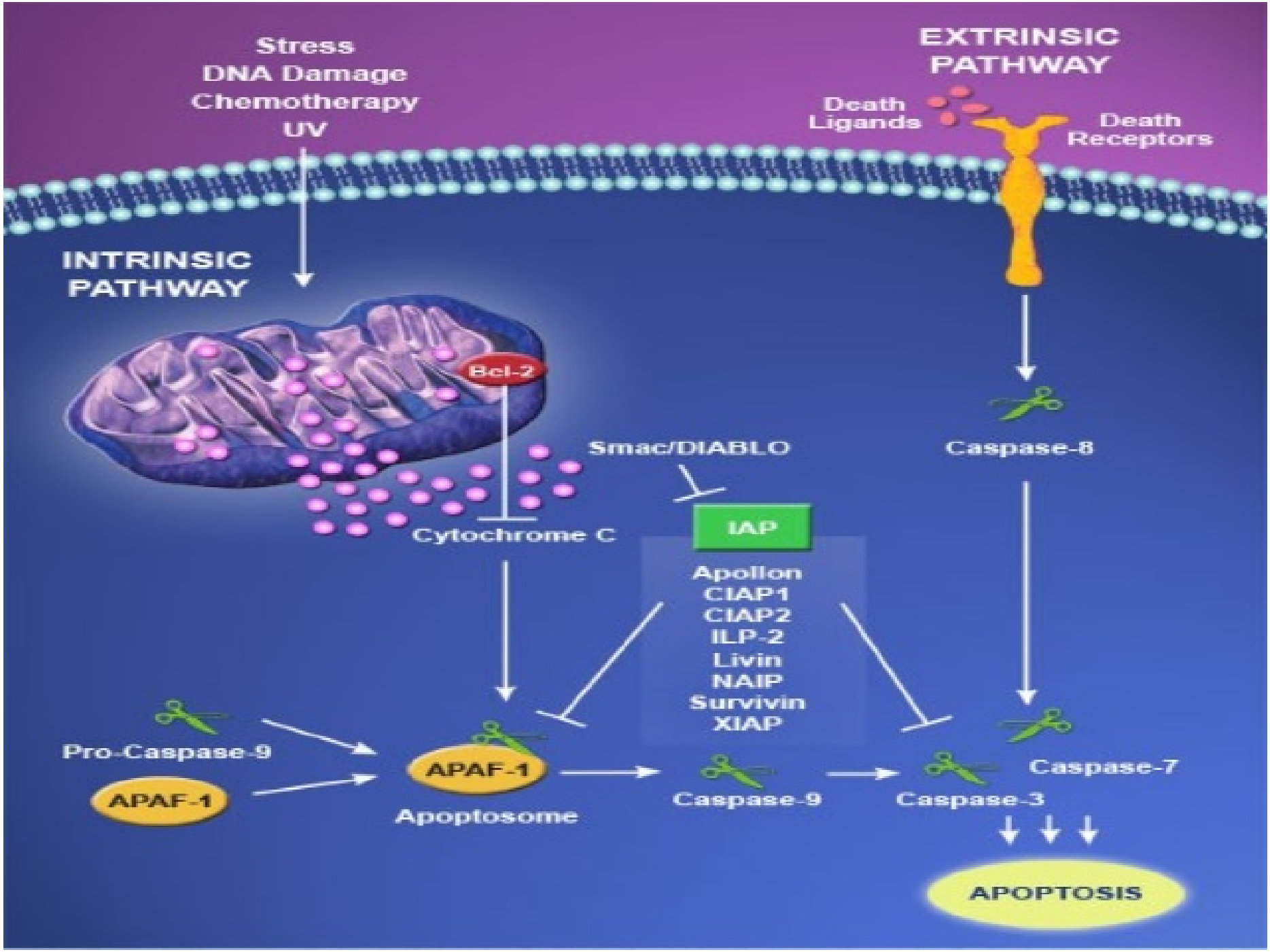


In human body about 100,000 cells are produced every second by mitosis and a similar no. die by apoptosis

- Important in normal physiology
  - **Development**: Immune systems maturation, Morphogenesis, Neural development
  - **Adult**: Immune privilege, DNA Damage and wound repair.
- Excess apoptosis
  - Neurodegenerative diseases
- Deficient apoptosis
  - Cancer
  - Autoimmunity

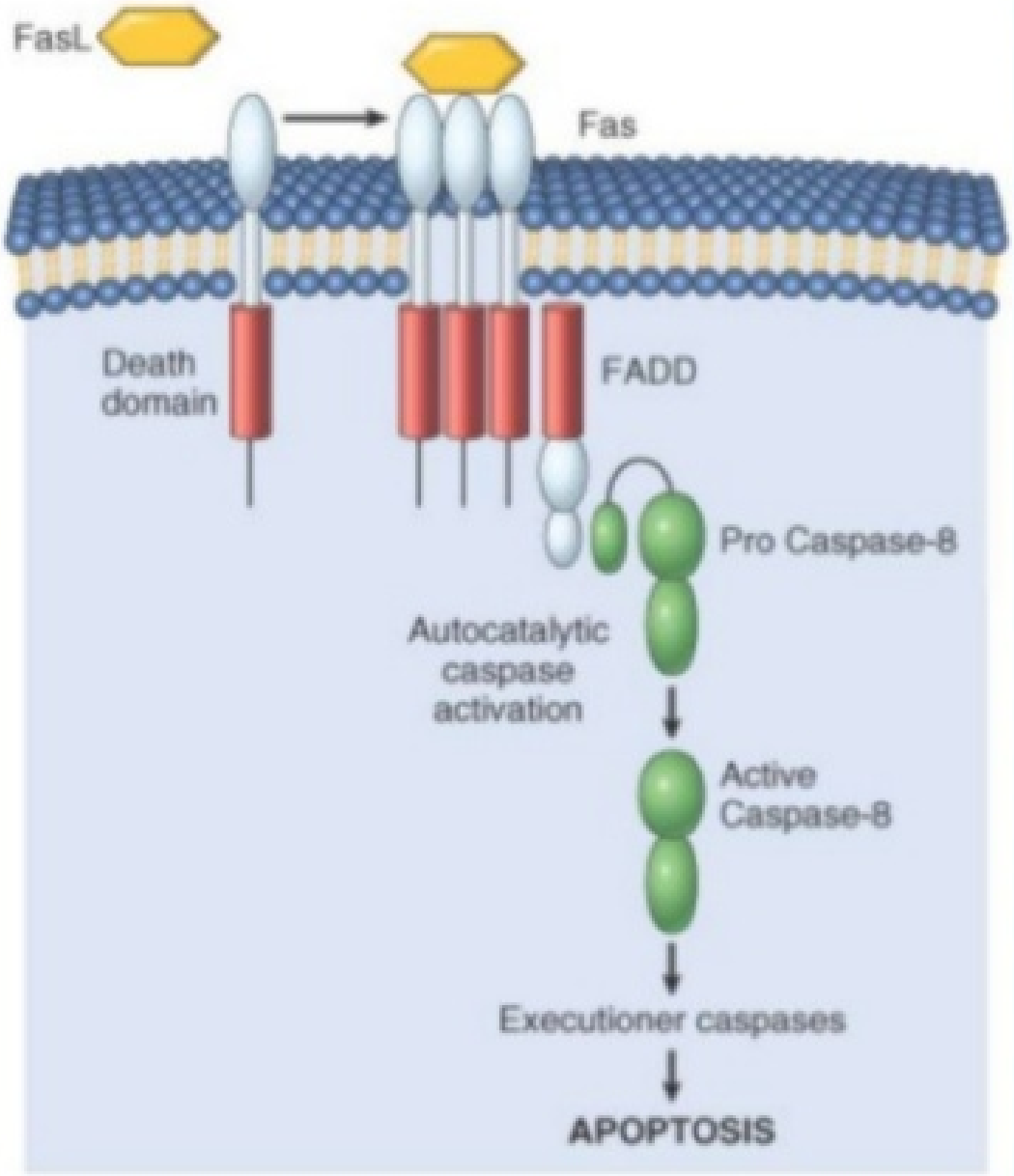
Apoptosis: Pathways

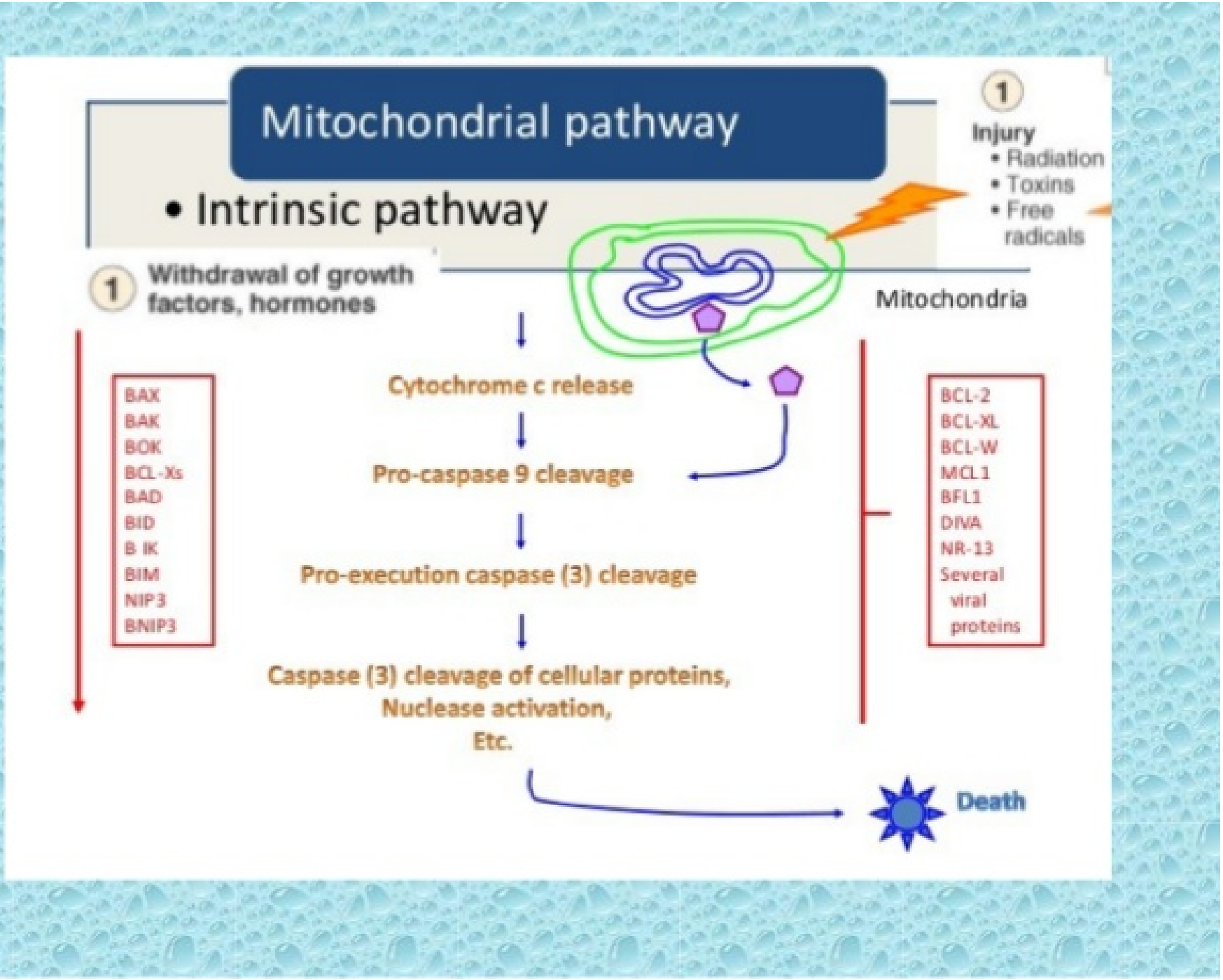



Stress
DNA Damage
Chemotherapy
UV
EXTRINSIC
PATHWAY
Death
Ligands
Death
Receptors
INTRINSIC
PATHWAY
Bcl-2
Smac/DIABLO
Caspase-8
IAP
Cytochrome C
Apollon
CIAP1
CIAP2
ILP-2
Livin
NAIP
Survivin
XIAP
Pro-Caspase-9
APAF-1
APAF-1
Apoptosome
Caspase-9
Caspase-3
Caspase-7
APOPTOSIS

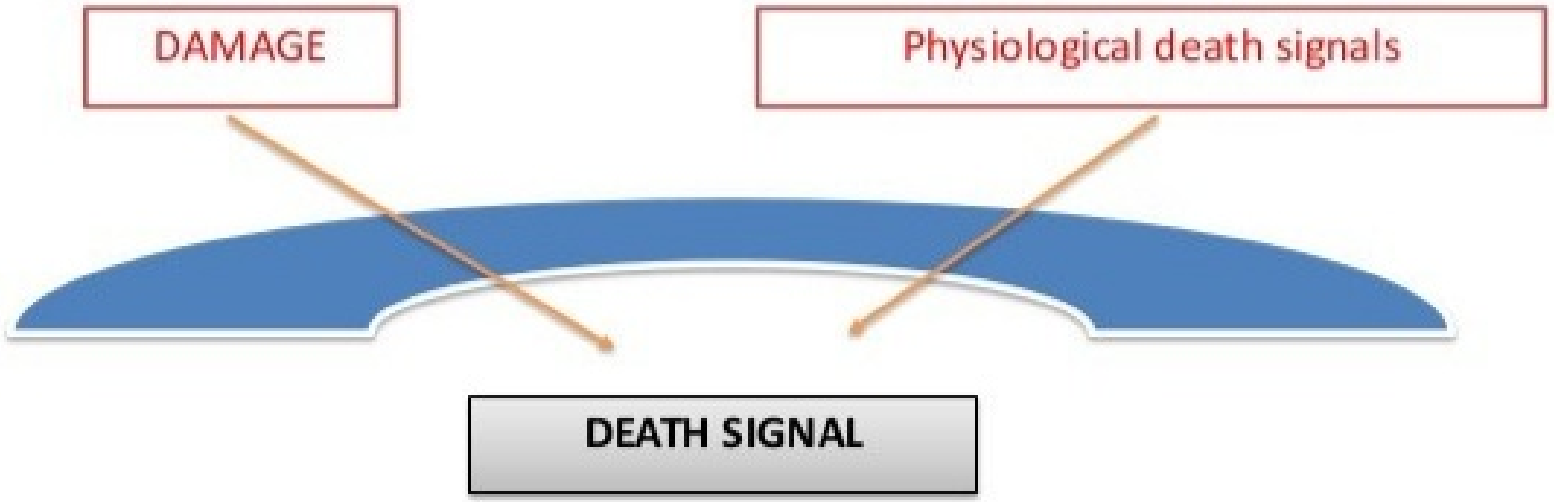
- Extrinsic pathway

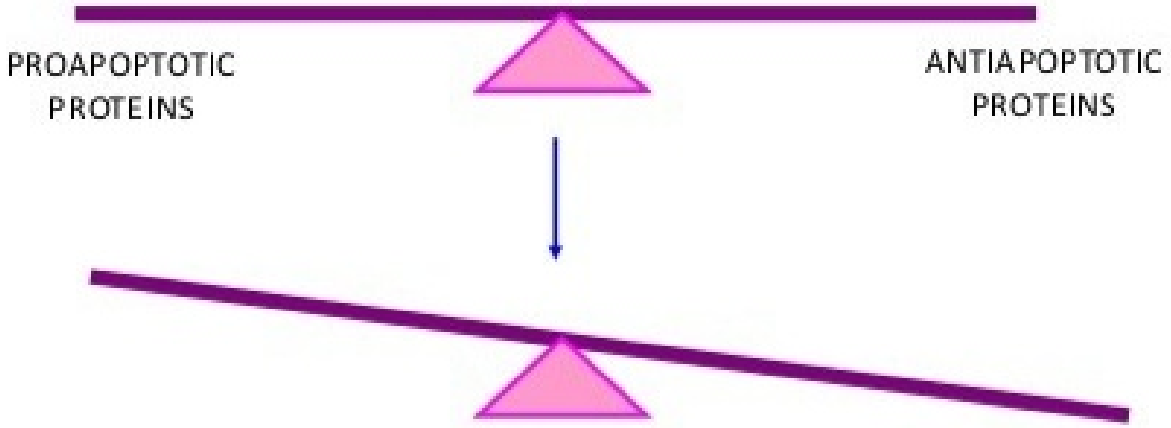
The death receptor pathway

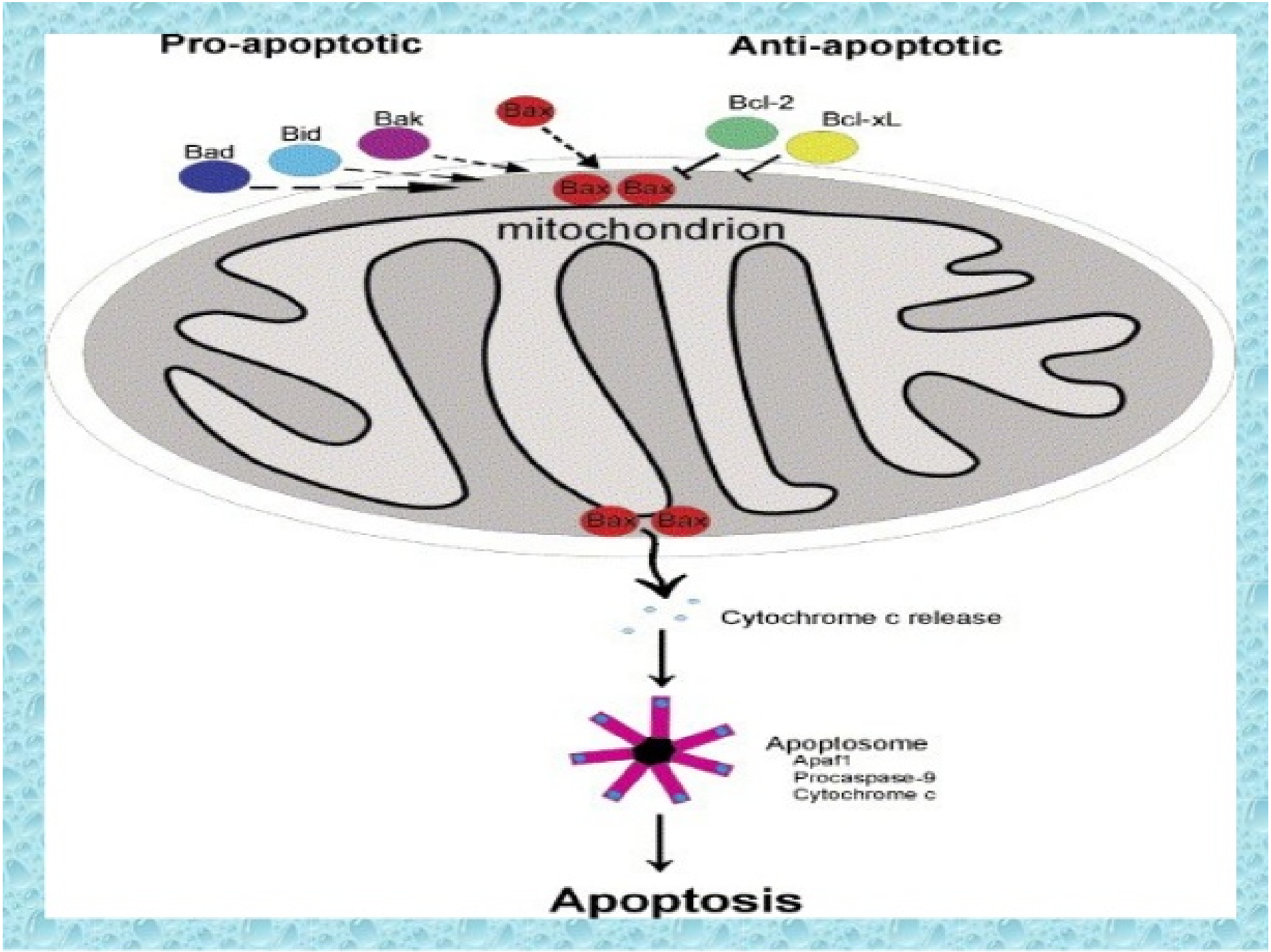



Mitochondrial pathway
• Intrinsic pathway
1
Injury
• Radiation
• Toxins
• Free radicals
1
Withdrawal of growth factors, hormones
Mitochondria
BAX
BAK
BOK
BCL-Xs
BAD
BID
B IK
BIM
NIP3
BNIP3
Cytochrome c release
Pro-caspase 9 cleavage
Pro-execution caspase (3) cleavage
Caspase (3) cleavage of cellular proteins,
Nuclease activation,
Etc.
BCL-2
BCL-XL
BCL-W
MCL1
BFL1
DIVA
NR-13
Several viral proteins
Death

CELLS ARE BALANCED BETWEEN LIFE AND DEATH






Pro-apoptotic
Anti-apoptotic
Bad
Bid
Bak
Bax
Bcl-2
Bcl-xL
Bax Bax
mitochondrion
Bax Bax
Cytochrome c release
Apoptosome
Apaf1
Procaspase-9
Cytochrome c
Apoptosis

Disorders where apoptosis is inhibited (decreased apoptosis,increase in cell survival)

1.Cancer

Colorectal cancer

Glioma

Liver

Lymphoid malignancies

Neuroblastoma

Prostate cancer

Follicular lymphomas

Carcinomas with p-53 mutations

2. Autoimmune disorders

Mysthenia gravis

Systemic lupus erythematous

3 Inflammatory disease

Bronchial asthma
Inflammattory bowel disease
Pumonary inflammation

4 Viral infections

Herpesviruses
Poxviruses
Adenoviruses
Baculovirus
Cowpox

Disorders where apoptosis is excessive
increase in cell death (Means hyperactive apoptosis).

1 AIDS

CD4+ cells

T- lymphocytes

2. Neurodegenerative disorders

Alzheimer's disease

Epilepsy

Parkinson's disease

Amyotrophic lateral sclerosis

Retinitis pigmentosa

Cerebellar degeneration

Role of Caspases in Alzheimer's Disease

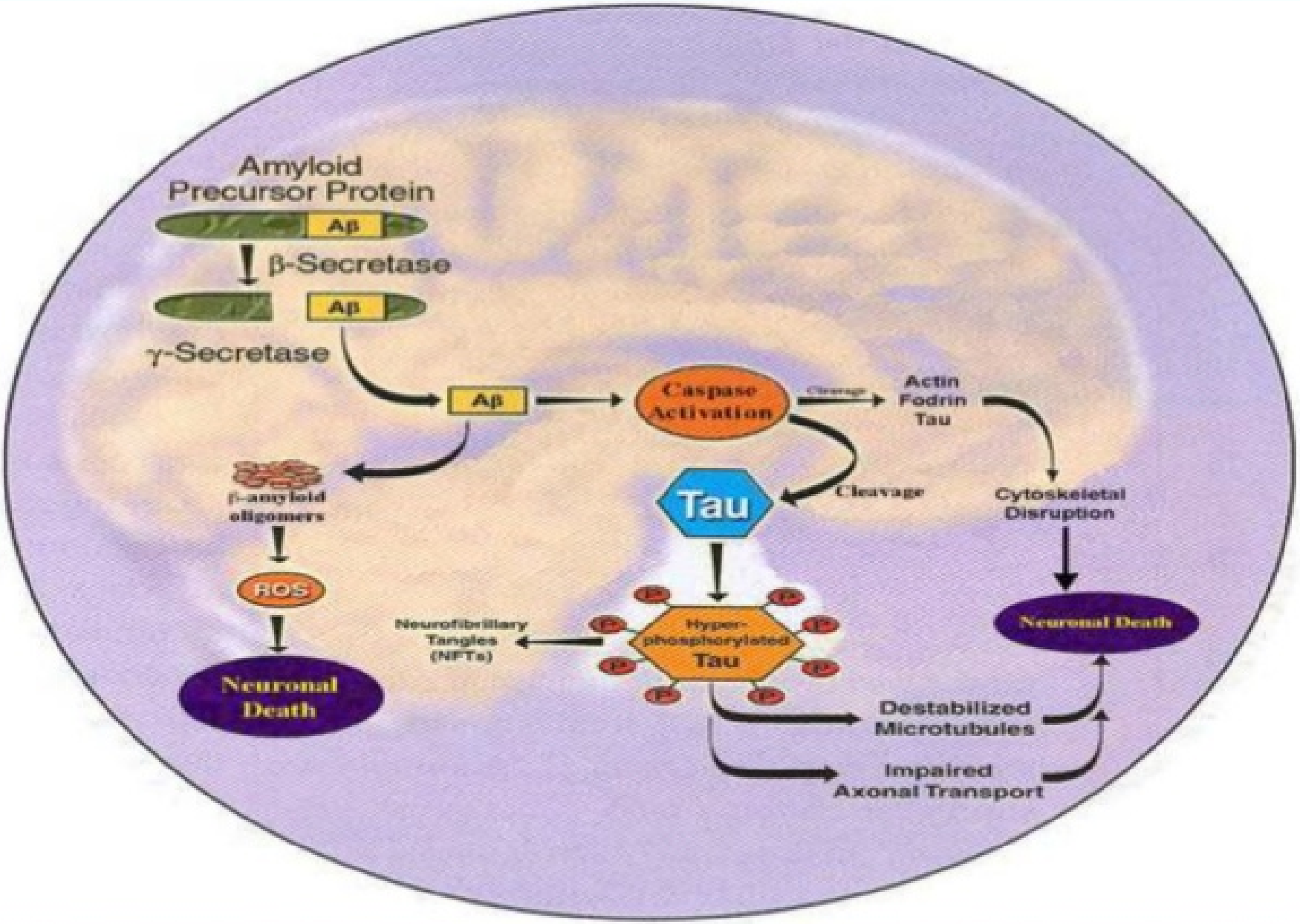


Table 2. Summary of caspases found to be activated in acute and chronic human neurological disease.

	CASPASE ACTIVATION
Parkinson's Disease	3?
Alzheimer's Disease	3
Huntington's Disease	1, 8
Amyotrphic Lateral Sclerosis	1, 3-like
Stroke	3
Brain/Spinal Cord Trauma	1, 3

Apoptosis: Role in Disease

Cancer

- Apoptosis eliminates damaged cells (damage => mutations => cancer

- Tumor suppressor p53 controls senescence and apoptosis responses to damage.

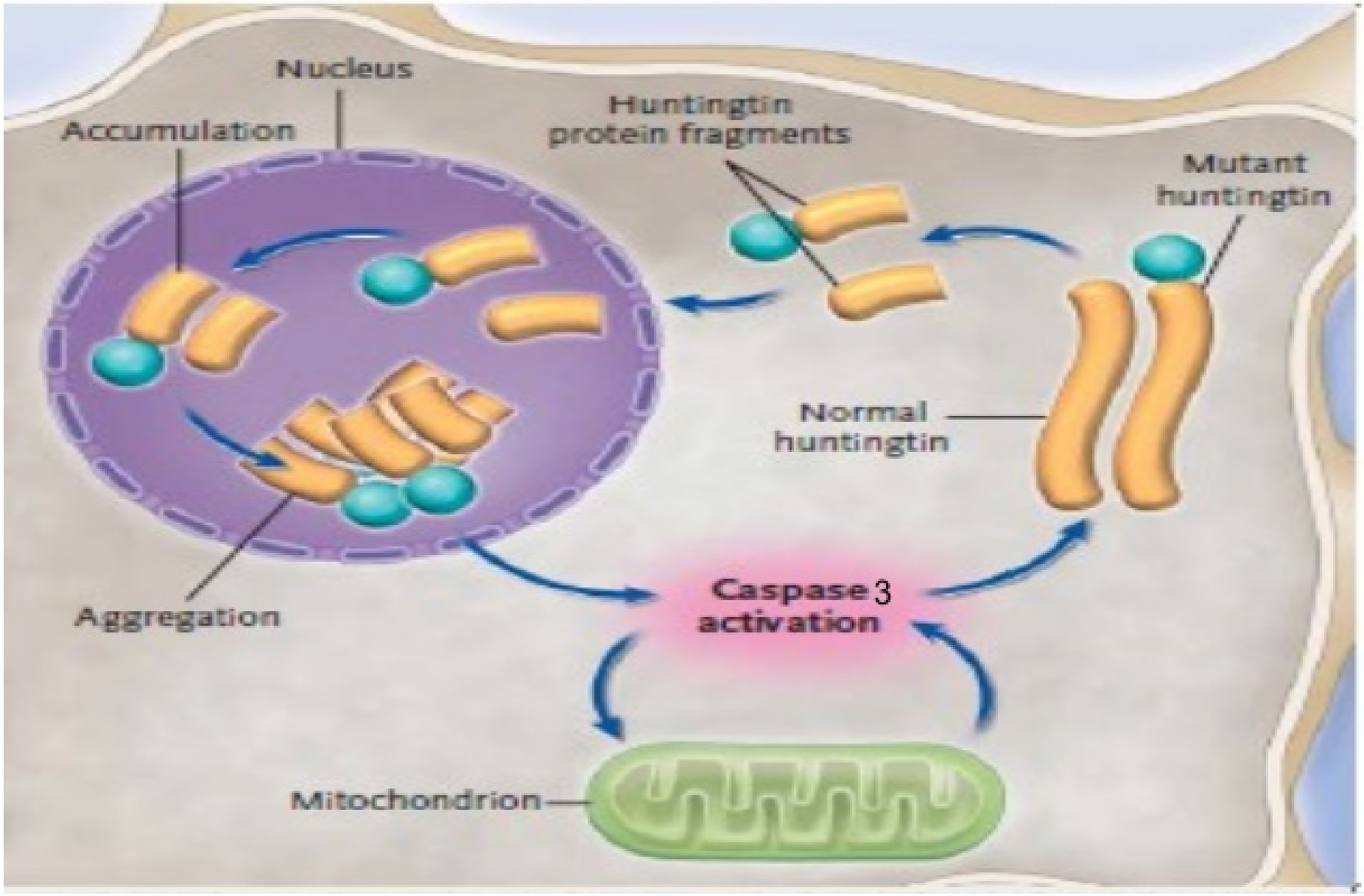
- Most cancer cells are defective in apoptotic response(damaged, mutant cells survive)

- High levels of anti-apoptotic proteins

  or

- Low levels of pro-apoptotic proteins ===> CANCER

Role of Caspases in HUNTINGTON DISEASE



AIDS

Autoimmune deficiency syndrome (AIDS) is an example of an autoimmune disease that results from infection with the human immunodeficiency virus (HIV) . This virus infects CD4+ T cells by binding to the CD4 receptor. The virus is subsequently internalized into the T cell where the HIV Tat protein is thought to increase the expression of the Fas receptor, resulting in excessive apoptosis of T cells .

So what kills so many uninfected CD4+ cells?
Answer is: Apoptosis.

There are several possibilities. One of them:
→ All T cells, both infected and **uninfected**, express **Fas**.
→ Expression of a HIV gene (called ***Nef***) in a HIV-infected cell causes
→ The cell to express high levels of **FasL** at its surface
→ While preventing an interaction with its own Fas from causing it to self-destruct.
→ However, when the infected T cell encounters an uninfected one (e.g. in a lymph node), the interaction of **FasL** with **Fas** on the uninfected cell kills it by apoptosis.

Recent advances

- **Caspase inhibitors** such as N-benzyloxycarbonyl-Val-Ala-Asp fluoromethyl-ketone (Z-VAD) were being investigated for the treatment of a number of **neurodegenerative disorders** including:-

✓ Alzheimer disease

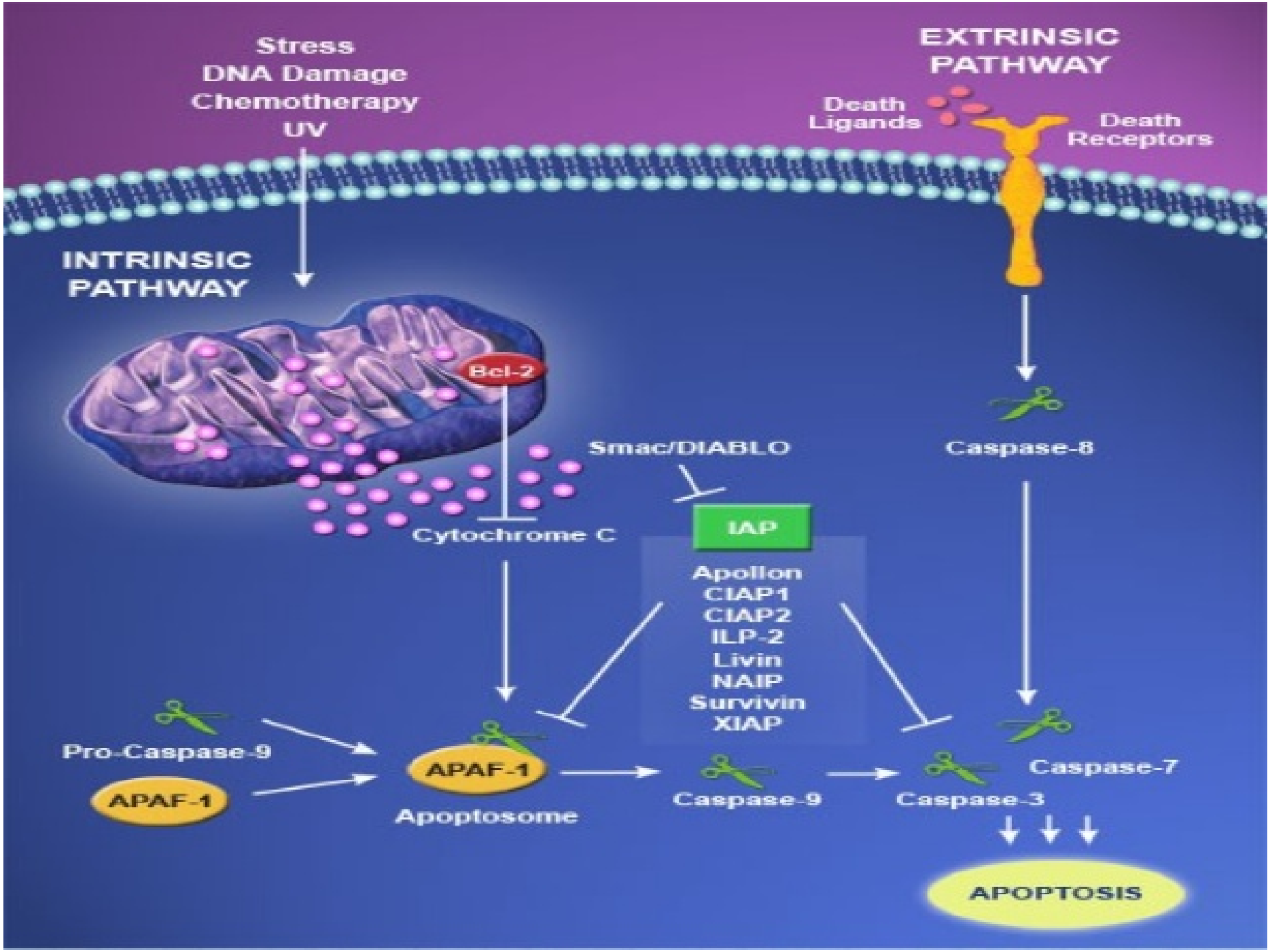
✓ amyotrophic lateral sclerosis (ALS)

✓ Huntington's disease

✓ Parkinson's disease (PD)

✓ and finally acute neurologic diseases including ischemia or traumatic injury .

Unfortunately, clinical development of Z-VAD was discontinued following the recognition that metabolism of Z-VAD produces liver damage following the production of the toxic compound**, fluoroacetate** .


Stress
DNA Damage
Chemotherapy
UV
EXTRINSIC
PATHWAY
Death
Ligands
Death
Receptors
INTRINSIC
PATHWAY
Bcl-2
Smac/DIABLO
Caspase-8
IAP
Cytochrome C
Apollon
CIAP1
CIAP2
ILP-2
Livin
NAIP
Survivin
XIAP
Pro-Caspase-9
APAF-1
APAF-1
Apoptosome
Caspase-9
Caspase-3
Caspase-7
APOPTOSIS

Thank You
So Much