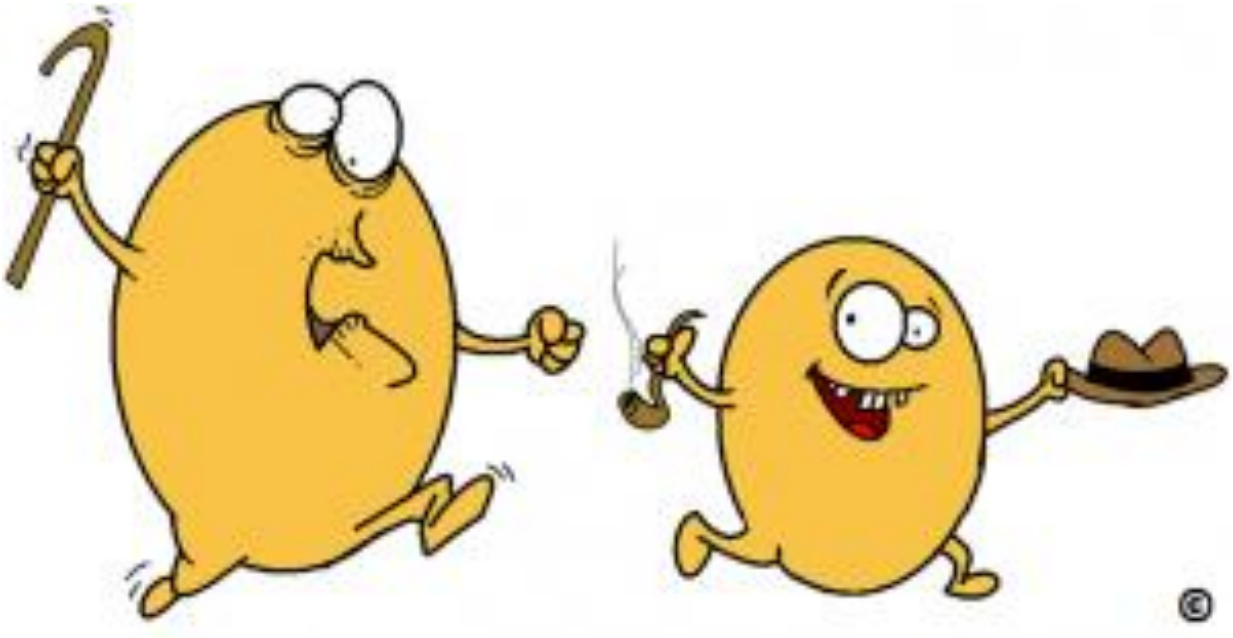
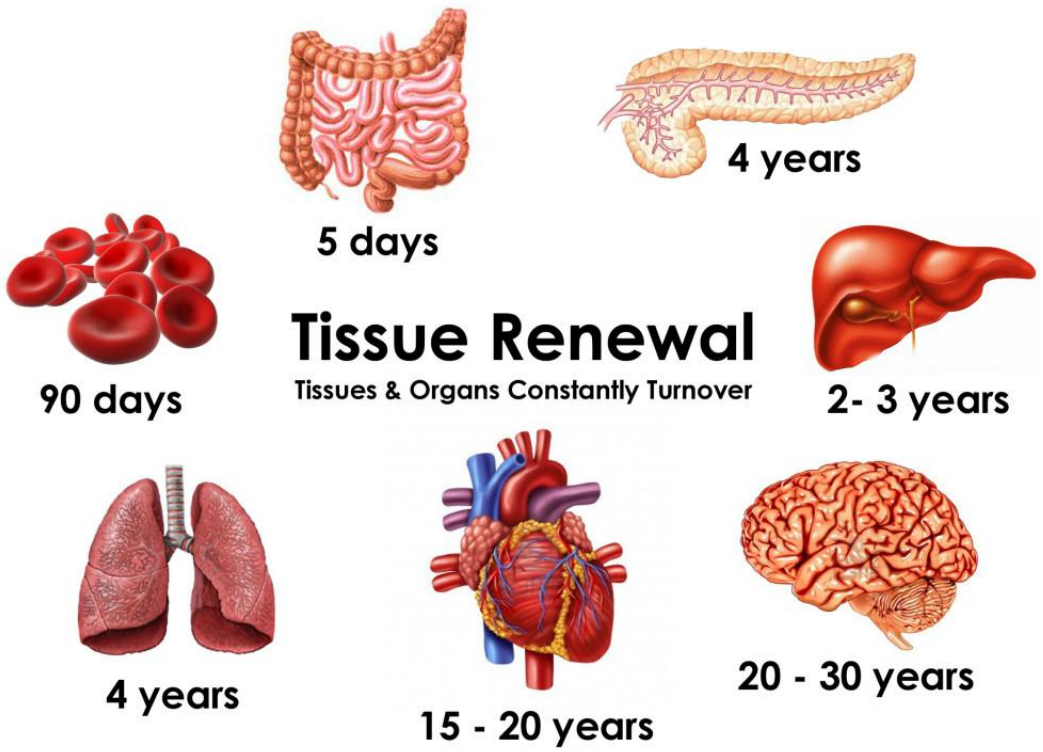
Cell ageing
and
cell death

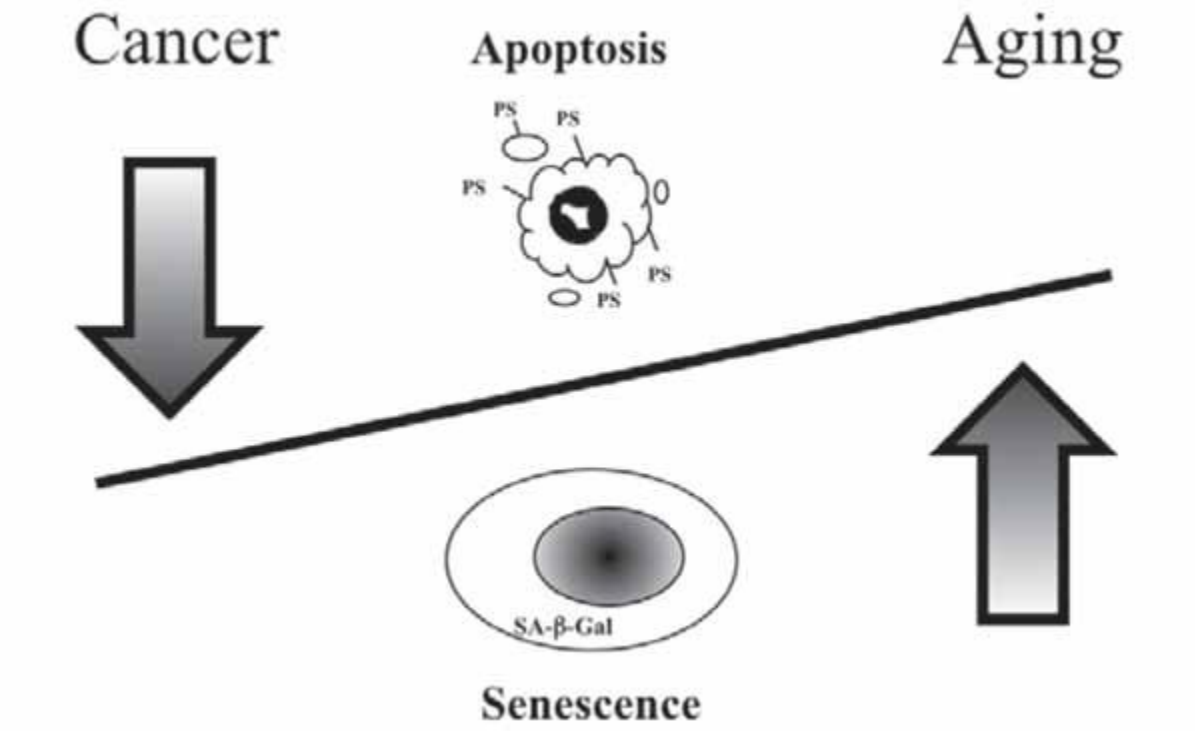


SENESCENCE AND APOPTOSIS



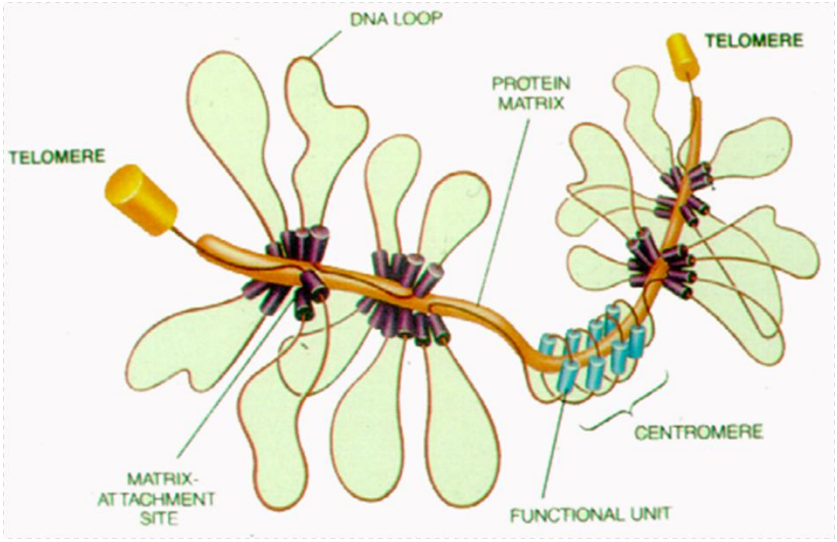
Tissue renewal is essential for the viability of complex multicellular organisms such as mammals, but cell proliferation is essential for tumorigenesis, and renewable tissues are at risk of developing cancer.

SENESCENCE AND APOPTOSIS



The danger that cancer posed to longevity was mitigated by the evolution of tumor-suppressor mechanisms. One of them is **cellular senescence**, which stops incipient cancer cells from proliferating, second is programmed cell death – **apoptosis**, which eliminates incipient cancer cells from organism

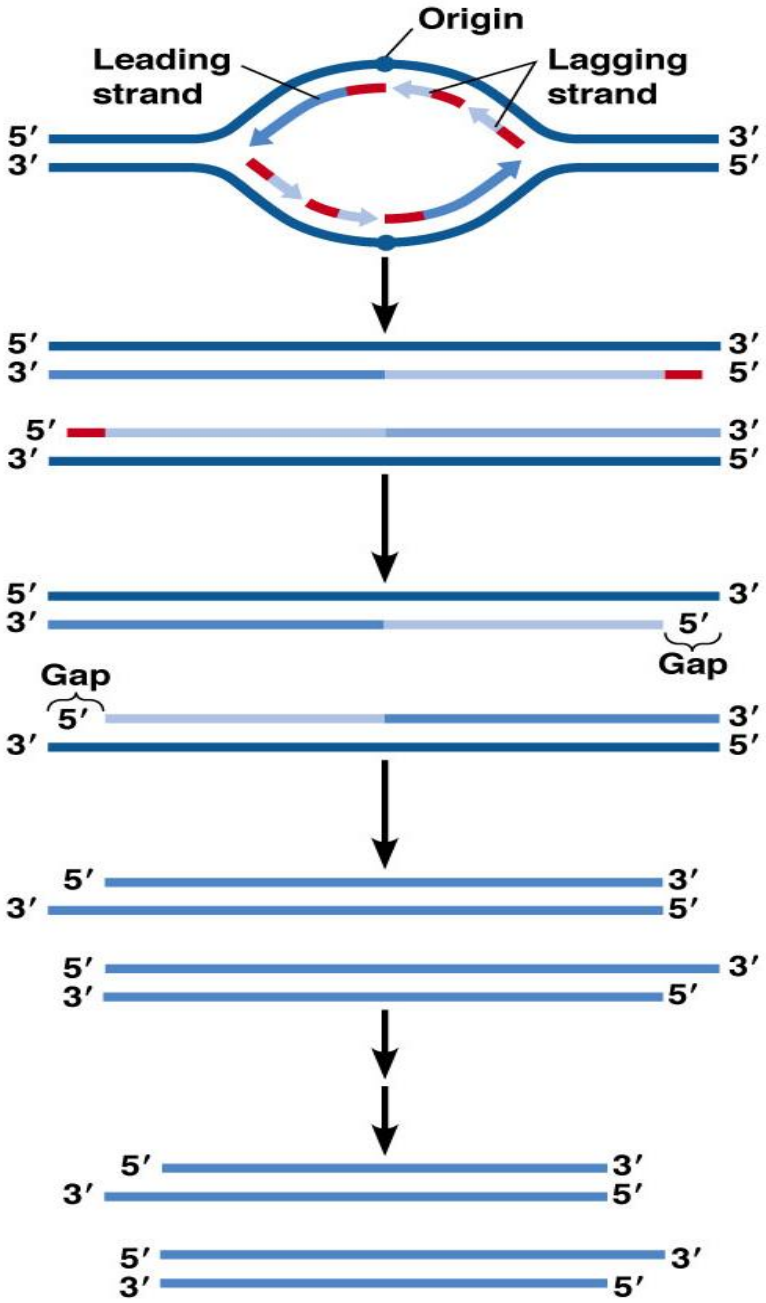
REPLICATIVE SENESCENCE



Telomere-dependent senescence involves shortening of telomeres

Telomeres are fragments of a repetitive noncoding DNA sequence (TTAGGG) and associated proteins that are located at the ends of chromosomes and protect them from lysis and fusion.
Human telomeres in the newborn have a length 25 000 bp.

CHROMOSOME STRUCTURE
Linear chromosomes are less stable than circular DNA, but determine the genetic diversity of living organisms (recombinations)

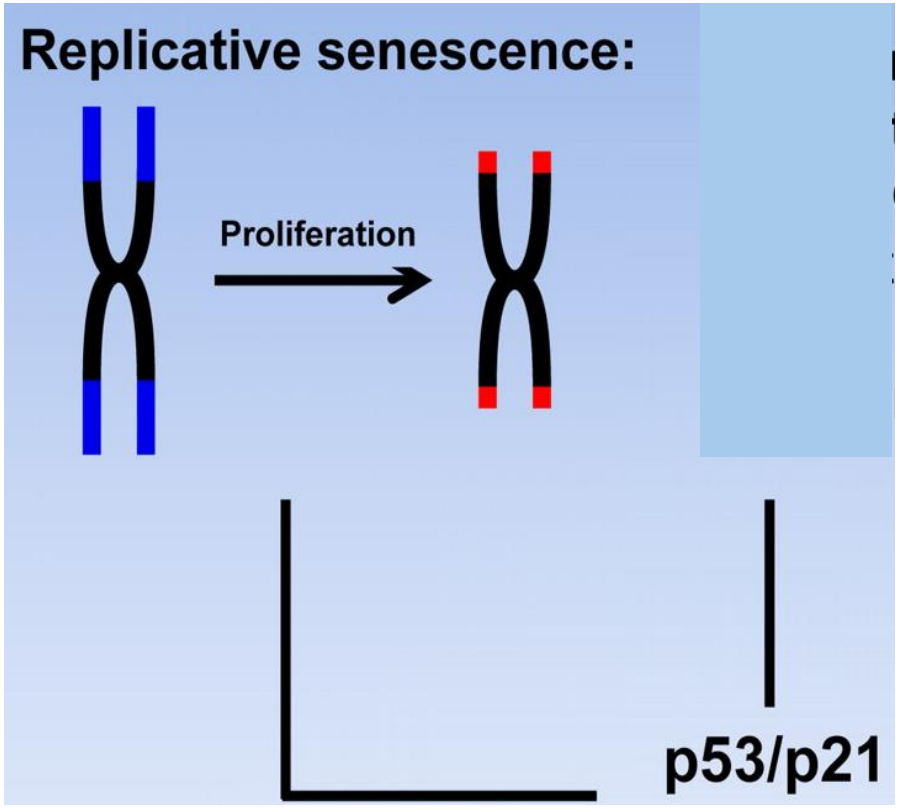


End replication problem - the shortening of telomeres during replication

The DNA polymerase can read and synthesize the new strand of DNA in one direction, starting with the primer. Because the synthesis of DNA requires primers attaching ahead on the DNA strand, human chromosomes lose some telomere DNA in each cell division.

REPLICATIVE SENESCENCE

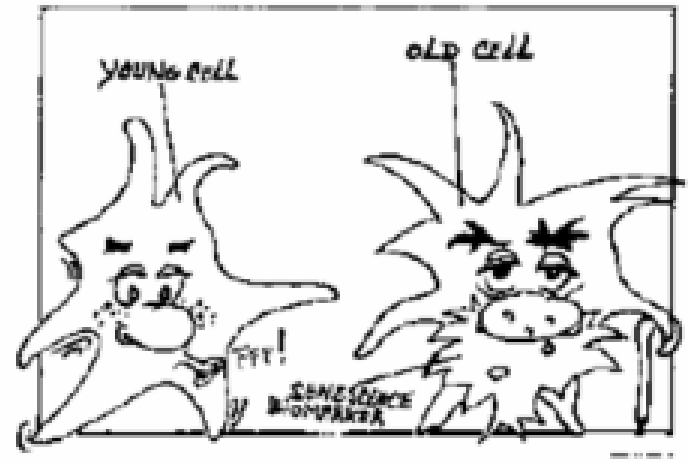
Dysfunctional, short telomeres trigger senescence or apoptosis through the p53 pathway.

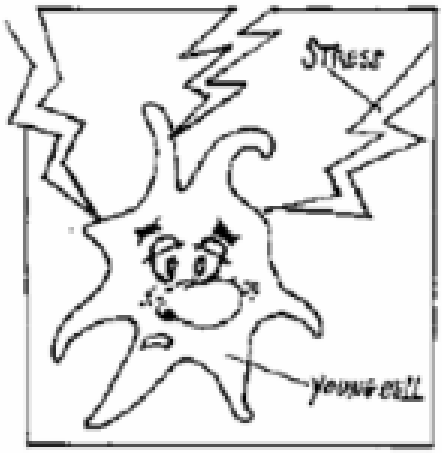


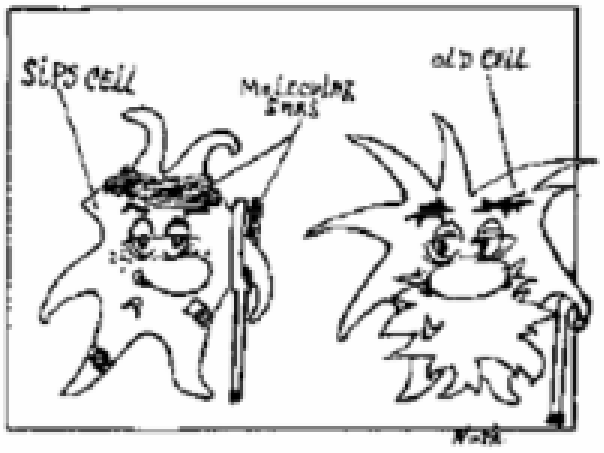
The senescence and apoptosis regulatory systems communicate probably through their common regulator, the p53.

REPLICATIVE SENESCENCE

Some cells undergo replicative senescence independently of telomere shortening. This senescence is due to stress (oxidative stress). It increases p16 (an inhibitor CDK4 and 6) expression and engages the p16–retinoblastoma protein (pRB) pathway. This response is termed stress-induced premature senescence (SIPS).







Senescent cell

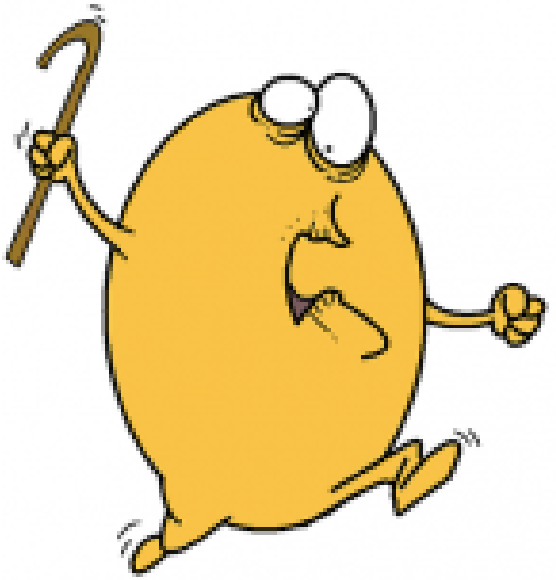
mitotic cell no longer capable of dividing but still alive and metabolically active.

Young cells express lysosomal β-galactosidase (optimum activity at pH 4.5).Senescent cells express a β-galactosidase, with optimum activity at pH 6 (sa-β- gal - senescence-associated β- gal).

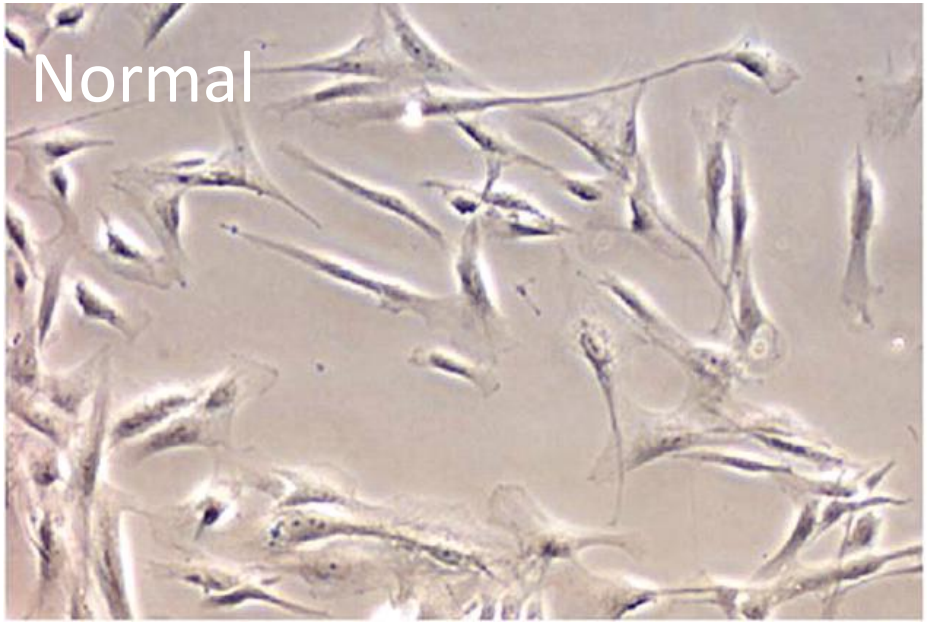
Change in the cell shape (hypertrophy)

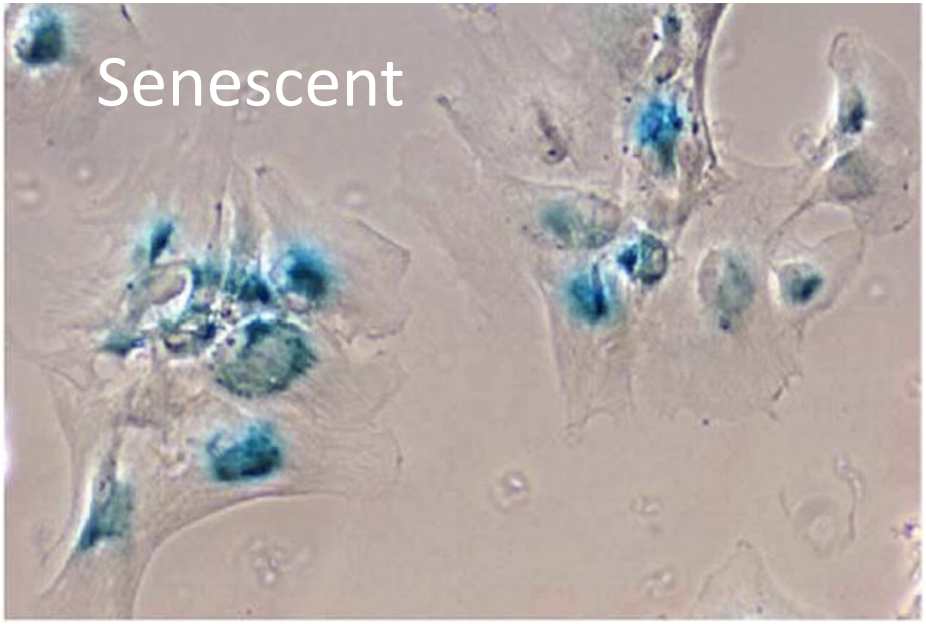
Senescence-associated secretory profile

Senescence Associated Heterochromatic Foci (SAHF)

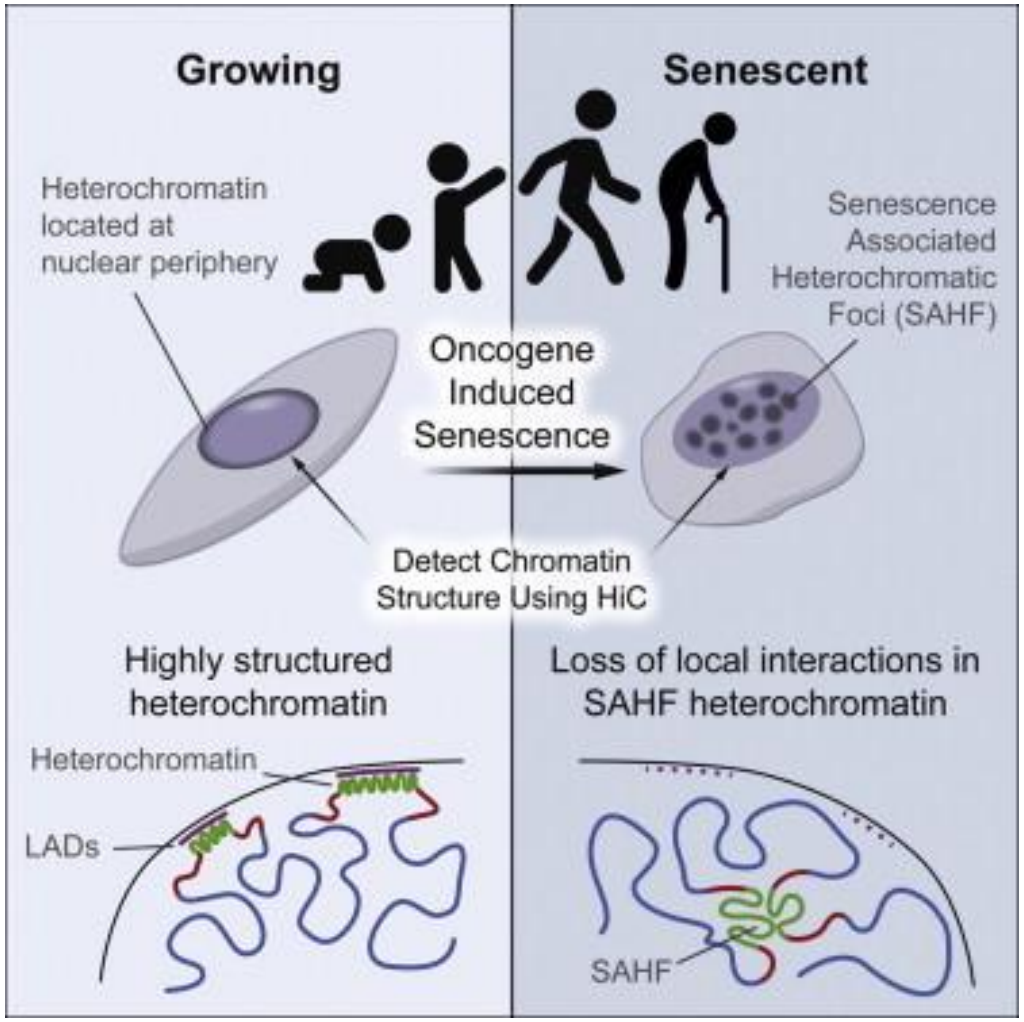


Smooth muscle cells in culture labeled for senescence-associated β-galactosidase (pH 6)





Senescence Associated Heterochromatic Foci (SAHF)



These foci are present in senescence but not in quiescent cells. SAHF embed genomic loci encoding pro-proliferative proteins into heterochromatin structures, thus preventing their transcription.

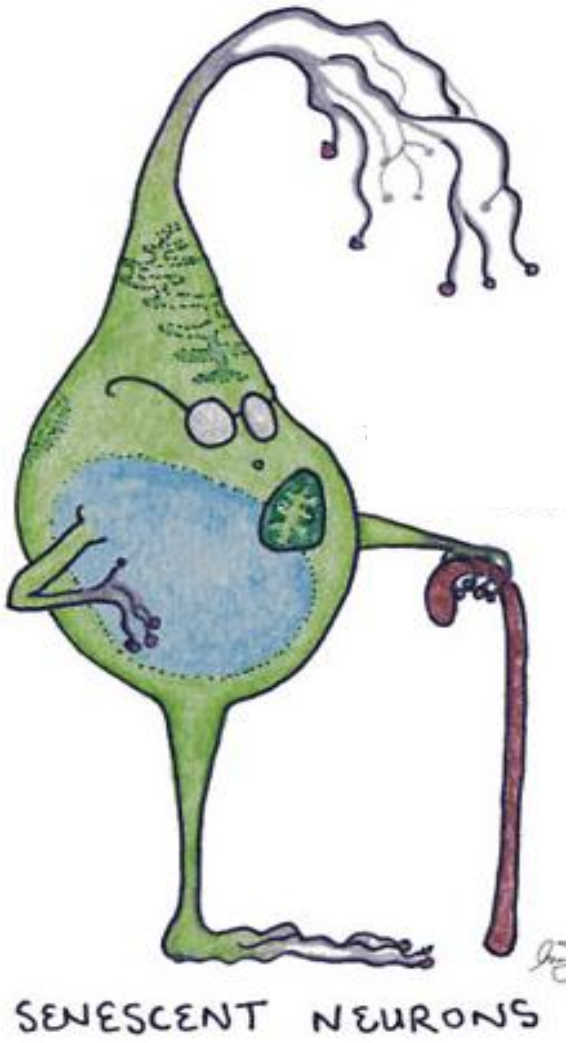
Senescence-associated secretory profile

SASP factors can be divided into the following categories: interleukins, chemokines, growth factors, proteases and ECM components.

These factors can affect surrounding cells by activating various cell-surface receptors and corresponding signal transduction pathways that may lead to multiple pathologies, including cancer, and can participate in degradation of ECM.

Senescent cells can modify the tissue microenvironment.

Terminally differentiated cells and senescence

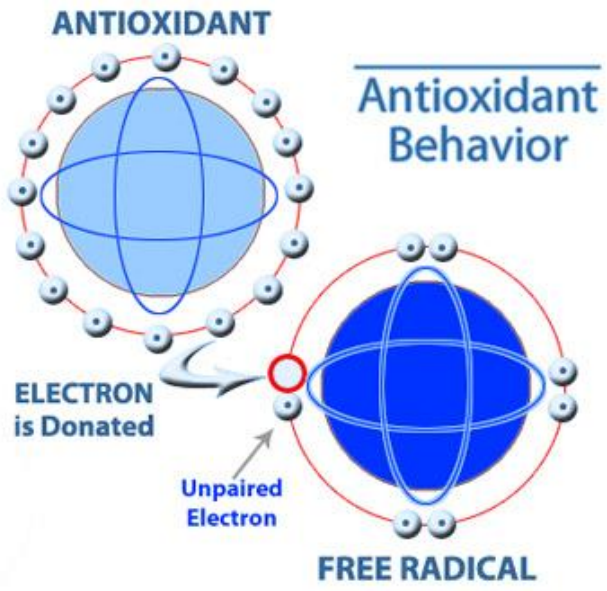


Neurons accumulate various forms of DNA and other macromolecules damage. (entropic ageing)

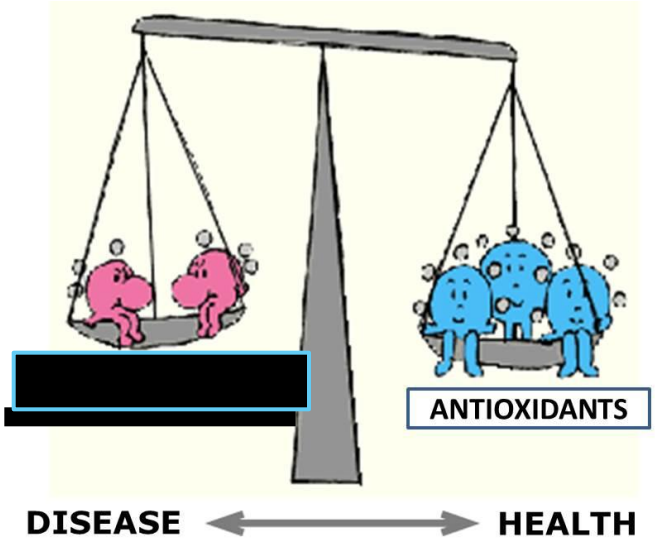
Senescsent neurons display SASP, sa-b-gal expression and SAHF.

The free radical theory of aging (FRTA)

Free radicals (O_2^- , OH^-, H_2O_2) - intracellular messengers (control the transcription factors and regulation of the activity of kinases and phosphatases, DNA methylation).



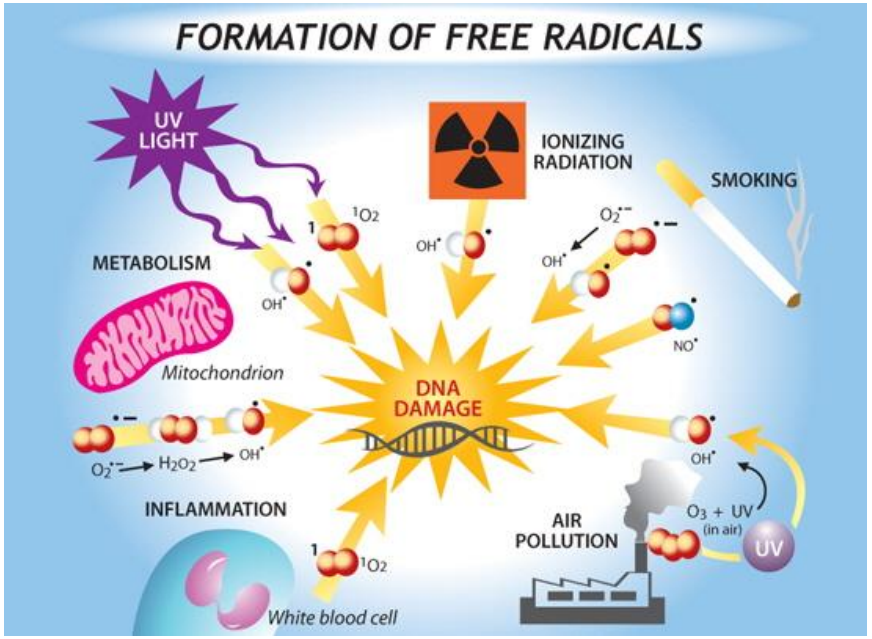
In young organisms free radicals are efficiently neutralized by antioxidants (superoxide dismutase (SOD), catalase, glutathione peroxidase, peroxiredoxin1, β-carotene, folate, uric acid, vitamin A, C, E).



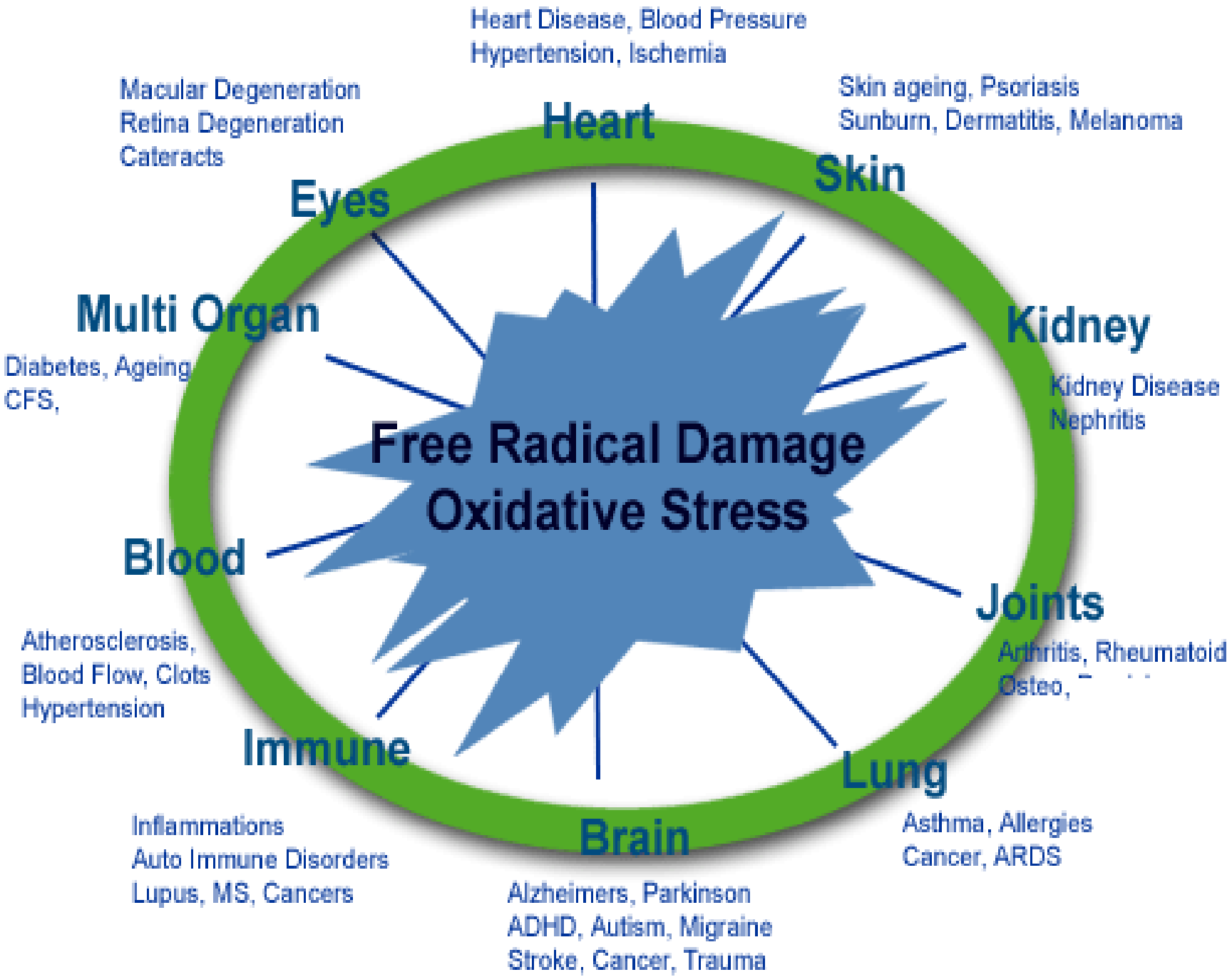
The free radical theory of aging (FRTA)

The activity and number of antioxidants decrease with age. This situation leads to an excess of free radicals in tissues and oxidative stress. It causes progressive aging and diseases associated with this process.

The increased concentration of free radicals with age interferes with their regulatory role leading to entropic aging.



Free radicals easily react with proteins, lipids and nucleic acids. The result is the carbonylation of proteins (the formation of the C = O), and oxidation of the SH groups, initial peroxidation of unsaturated fatty acids, and changes in the DNA molecules (oxidative stress).

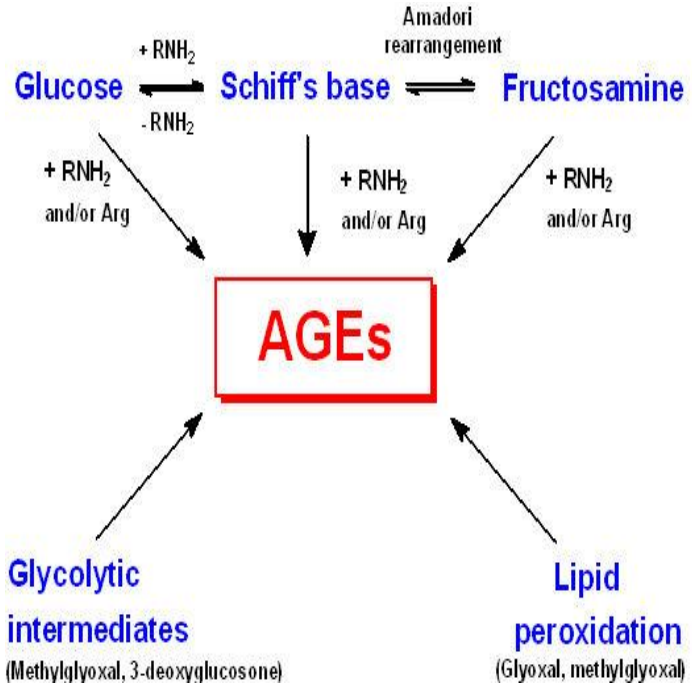

Heart Disease, Blood Pressure
Hypertension, Ischemia
Heart
Macular Degeneration
Retina Degeneration
Cateracts
Eyes
Skin ageing, Psoriasis
Sunburn, Dermatitis, Melanoma
Skin
Multi Organ
Diabetes, Ageing
CFS,
Free Radical Damage
Oxidative Stress
Kidney
Kidney Disease
Nephritis
Blood
Atherosclerosis,
Blood Flow, Clots
Hypertension
Joints
Arthritis, Rheumatoid
Osteo,
Immune
Inflammations
Auto Immune Disorders
Lupus, MS, Cancers
Brain
Alzheimers, Parkinson
ADHD, Autism, Migraine
Stroke, Cancer, Trauma
Lung
Asthma, Allergies
Cancer, ARDS

Glycation and senescence

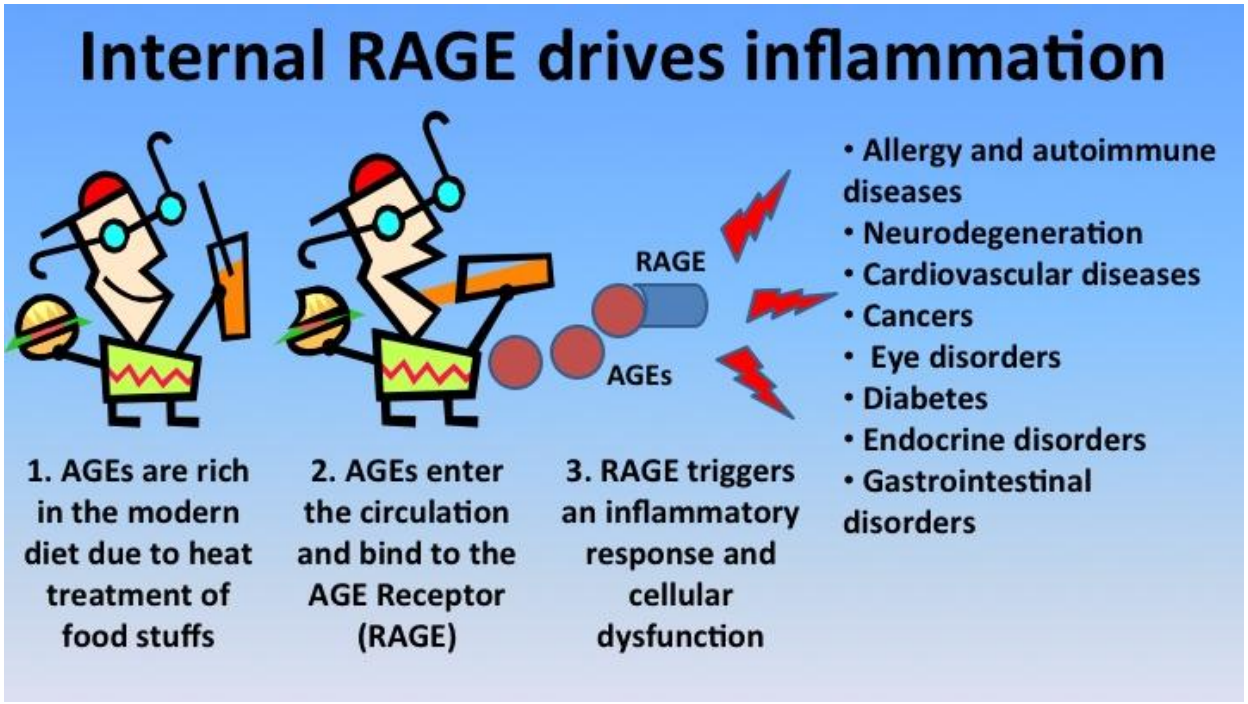
Glycation is the result of covalent binding of a protein, lipid or DNA molecule with a sugar molecule without the controlling action of an enzyme - a haphazard process that impairs the functioning of biomolecules.

Glycation leads to formation of advanced glycation endproducts (AGEs).

Some AGEs are benign, the others are implicated in many age-related diseases such as cardiovascular diseases, Alzheimer's disease, peripheral neuropathy and deafness



Glycation and senescence

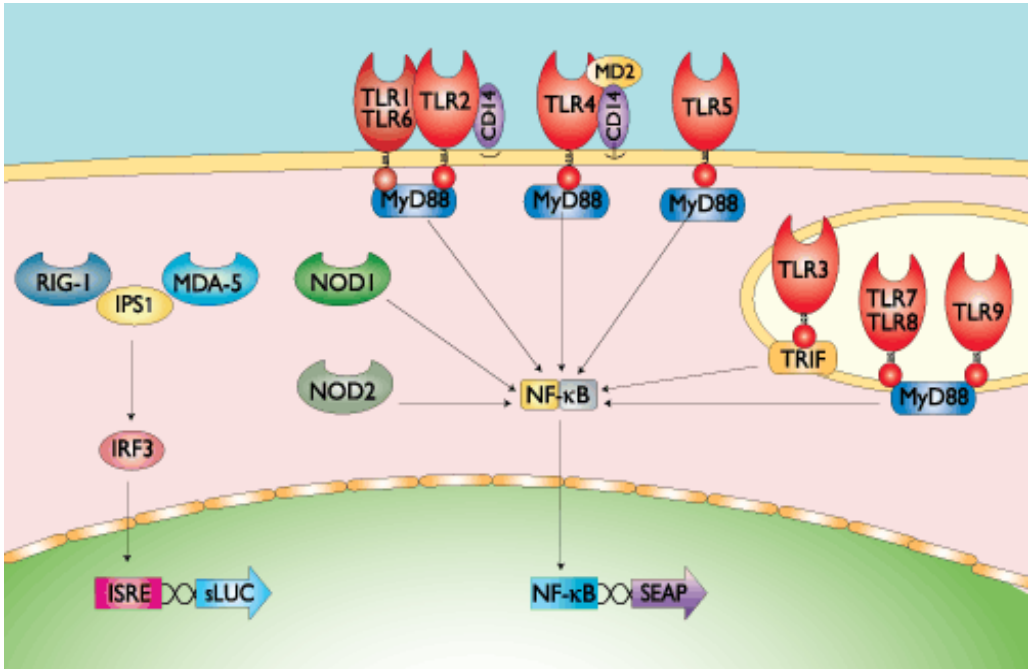


Some types of cells (endothelial cells, immunocompetent cells) possess receptors for AGE - RAGE. The number of RAGE increases with age and in the course of degenerative diseases and diabetes. AGEs accumulate in cells and stimulate the production of free radicals, activity of NFκB and inflammaging.

Toll- and NOD-like receptors

identify pathogen-associated molecular patterns (PAMPs), or damage-associated molecular patterns (DAMPs), which are associated with cell components released during cell damage.

Toll-like receptors (TLRs) transmembrane proteins. Interaction of TLRs with their specific PAMP induces NF-κB and therefore the secretion of pro-inflammatory cytokines.

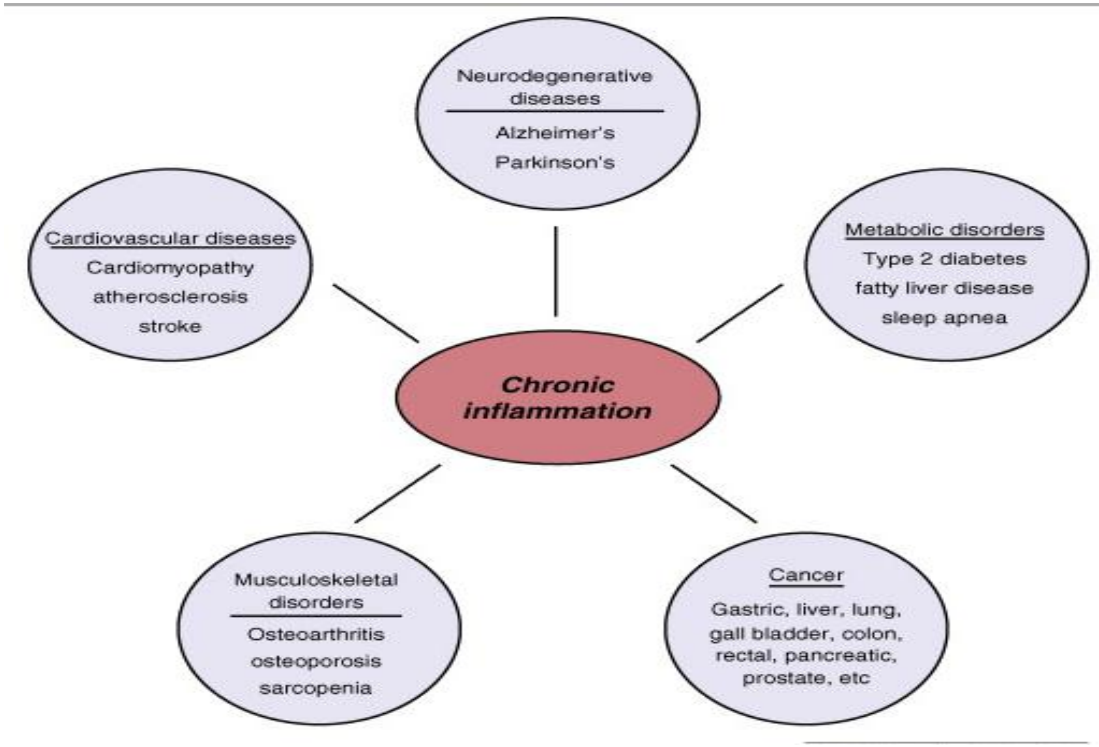


NOD-like receptors (NLRs) cytoplasmic proteins that regulate inflammatory and apoptotic responses. Some of these proteins recognize endogenous or microbial molecules activate the NF-κB signaling pathway to induce production of inflammatory molecules.

Inflammaging

defined as low-grade **chronic systemic inflammation** established during physiological aging

Increased level of pro-inflammatory cytokines (e.g., IL-6 and TNF), acute-phase reactants (C-reactive protein), and decreased level of anti-inflammatory cytokines (IL-10) impair the maintenance of immunological homeostasis. Overactivation NFκB.



Inflammaging is engaged in numerous age-related diseases.

Type I programmed cell death - APOPTOSIS

1842 – Vogt, 1885 – Flemming,

1965 – Kerr, 2002 - Brenner, Horvitz, Sulston - Nobel prize in medicine

Apoptosis

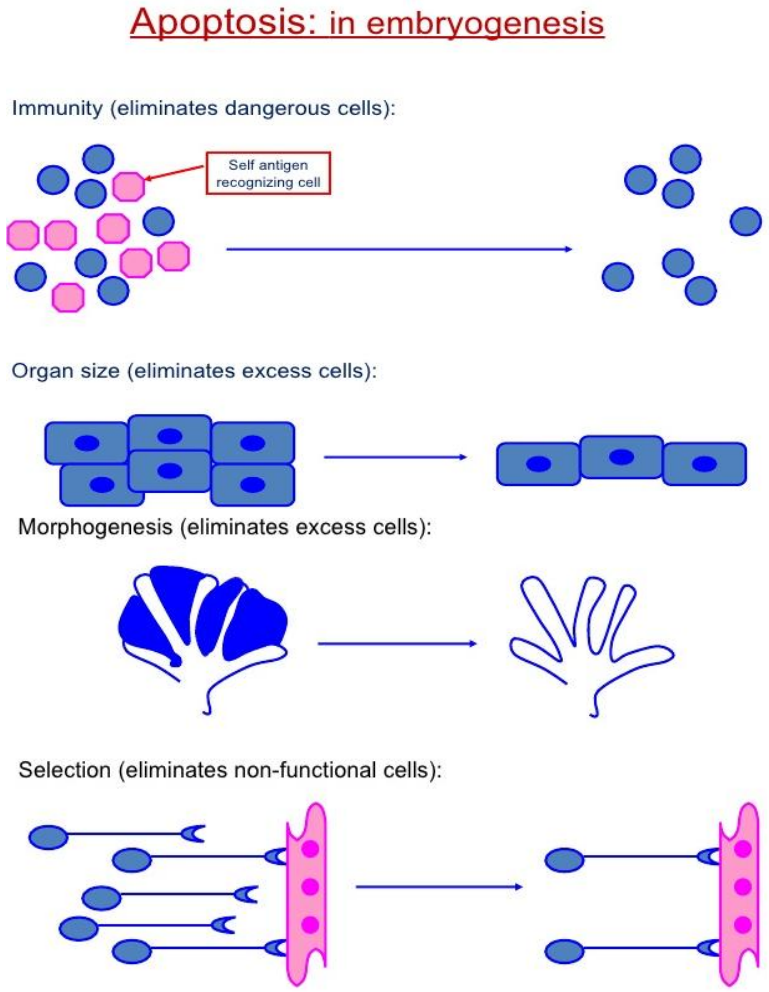
trees shedding their leaves in autumn, which describes the "dropping off" or "falling off„ leaves

Apoptosis participates in various biological processes such as development, maintenance of tissue homeostasis and elimination of cancer cells. Apoptosis requires the triggering of new biochemical pathways.

Apoptosis

During embryogenesis many cells are driven into apoptosis.
The differentiation of fingers and toes occurs because cells between the fingers undergo apoptosis; the result is that the digits are separate.

Also throughout the rest of life is necessary to maintain the balance between cell proliferation and cell death. About 50 to 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 to 30 billion cells die a day (e. g. within the bone marrow, digestive tract).

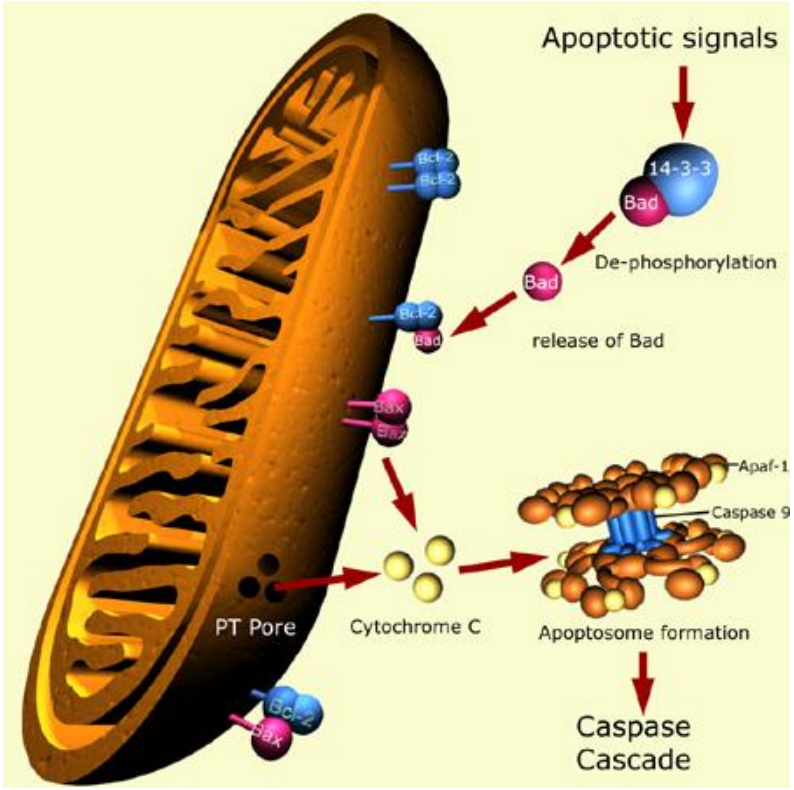


Apoptosis

is triggered by multi-signal pathways, regulated by extrinsic and intrinsic ligands

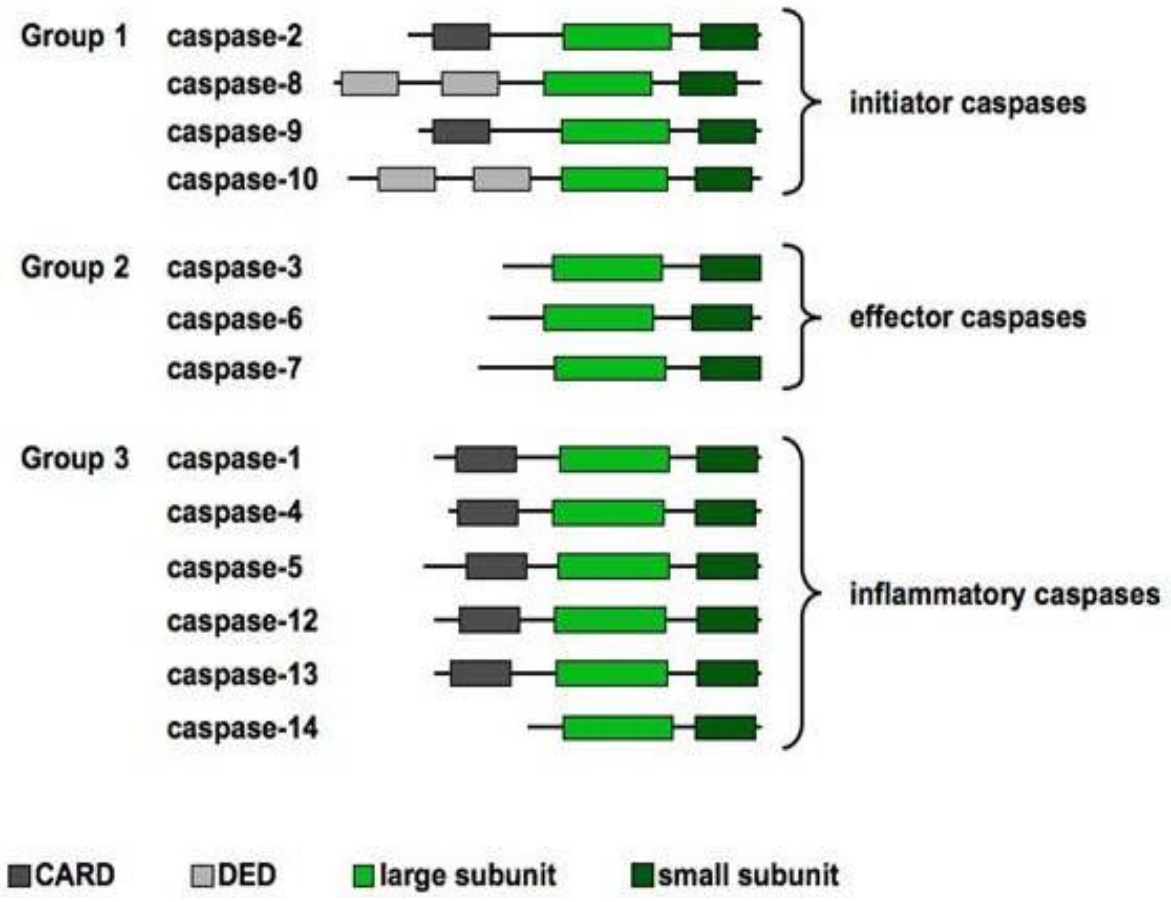
There are different apoptosis pathways distinguished according to whether caspases are involved or not.

The mitochondria, as the cross-talk organelles, connect the different apoptosis pathways.



Caspases

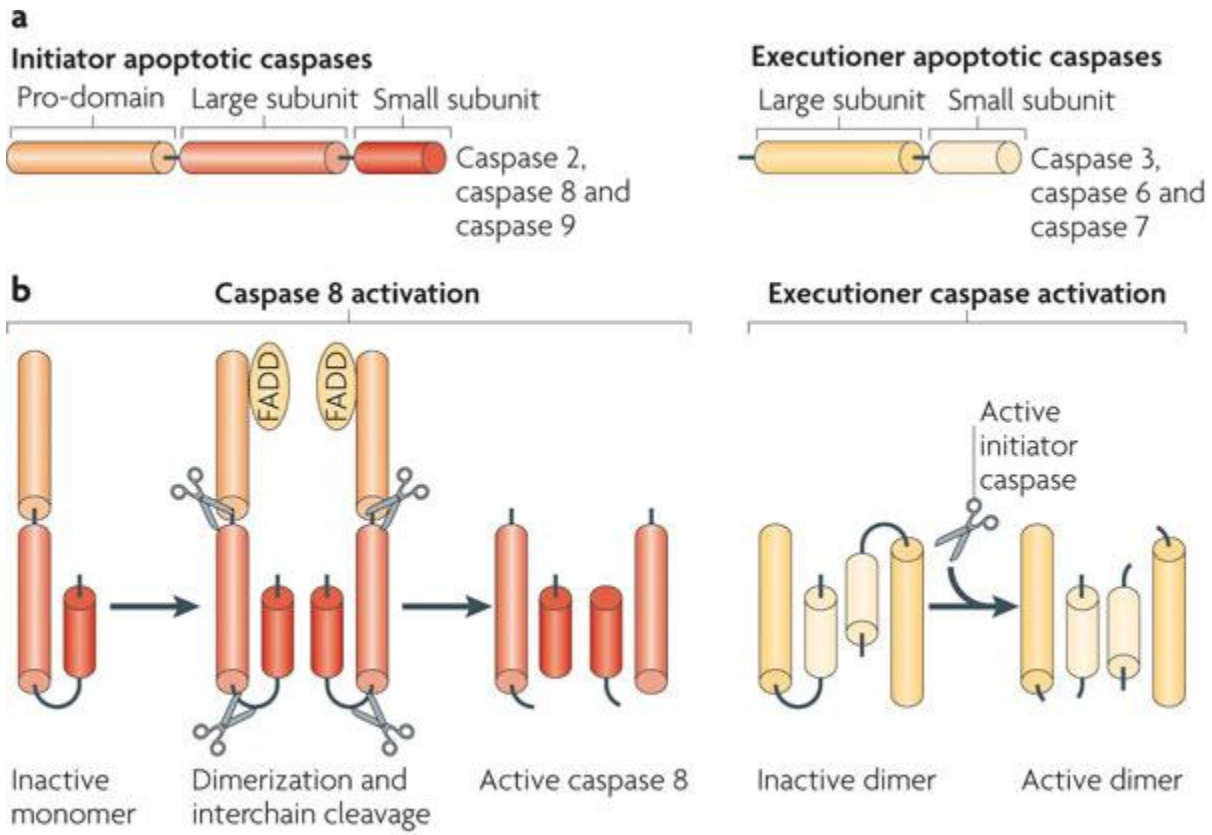
cysteine-aspartic proteases or cysteine-dependent aspartate-directed proteases



Caspases are endoproteases that have cysteine residues in their active sites and hydrolyze peptide bonds only after aspartic acid residues.

Caspases

Apoptotic caspases are divided into two classes: initiator and executioner caspases. Initiator caspases (caspase 2, 8, 9 and 10) and executioner caspase (caspase 3, 6 and 7)



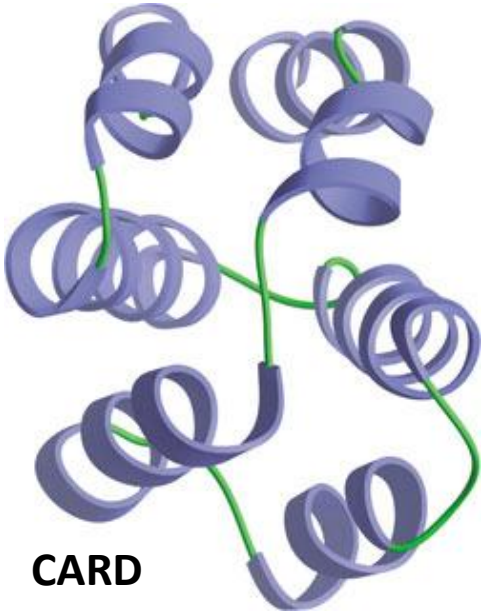
These enzymes are present in cytoplasm as inactive proenzymes, which are activated as a result of proteolysis and formation of active tetramers

Initiator caspases

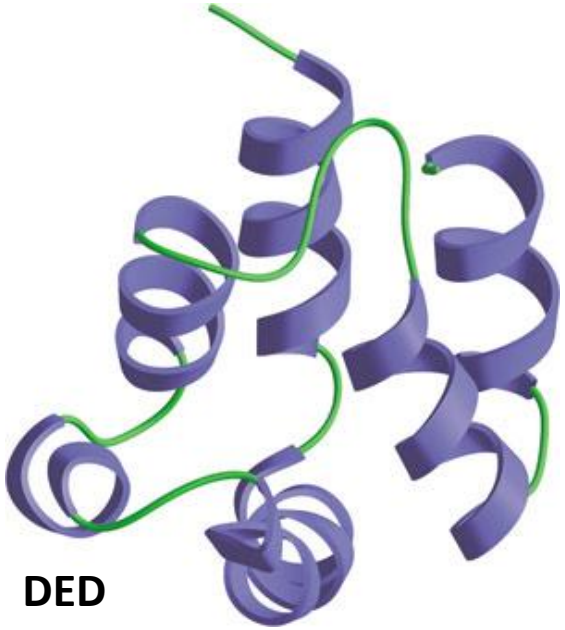
recruit executioner caspases

Initiator caspases of **intrinsic pathway** of apoptosis **2 and 9** possess caspase activation and recruitment domains (CARDs). The **CARD** domain typically associates with other CARD-containing proteins, forming either dimers or trimers.

Initiator caspases of **extrinsic pathway** of apoptosis **8 and 10** possess death-effector domains (DEDs). **DED** associates with other DED – containing proteins.



CARD



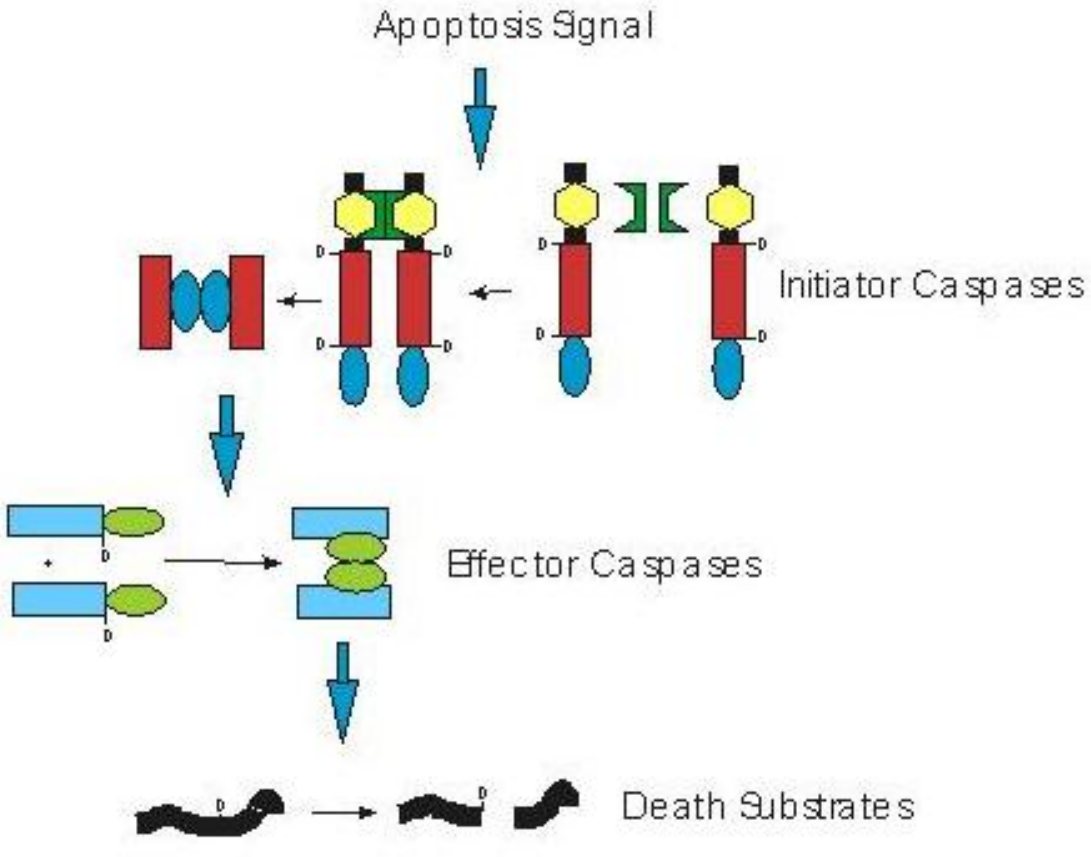
DED

Executioner caspases 3, 6, 7

coordinate the execution phase of apoptosis by cleaving multiple structural and repair proteins

Main executioner of apoptosis is caspase 3

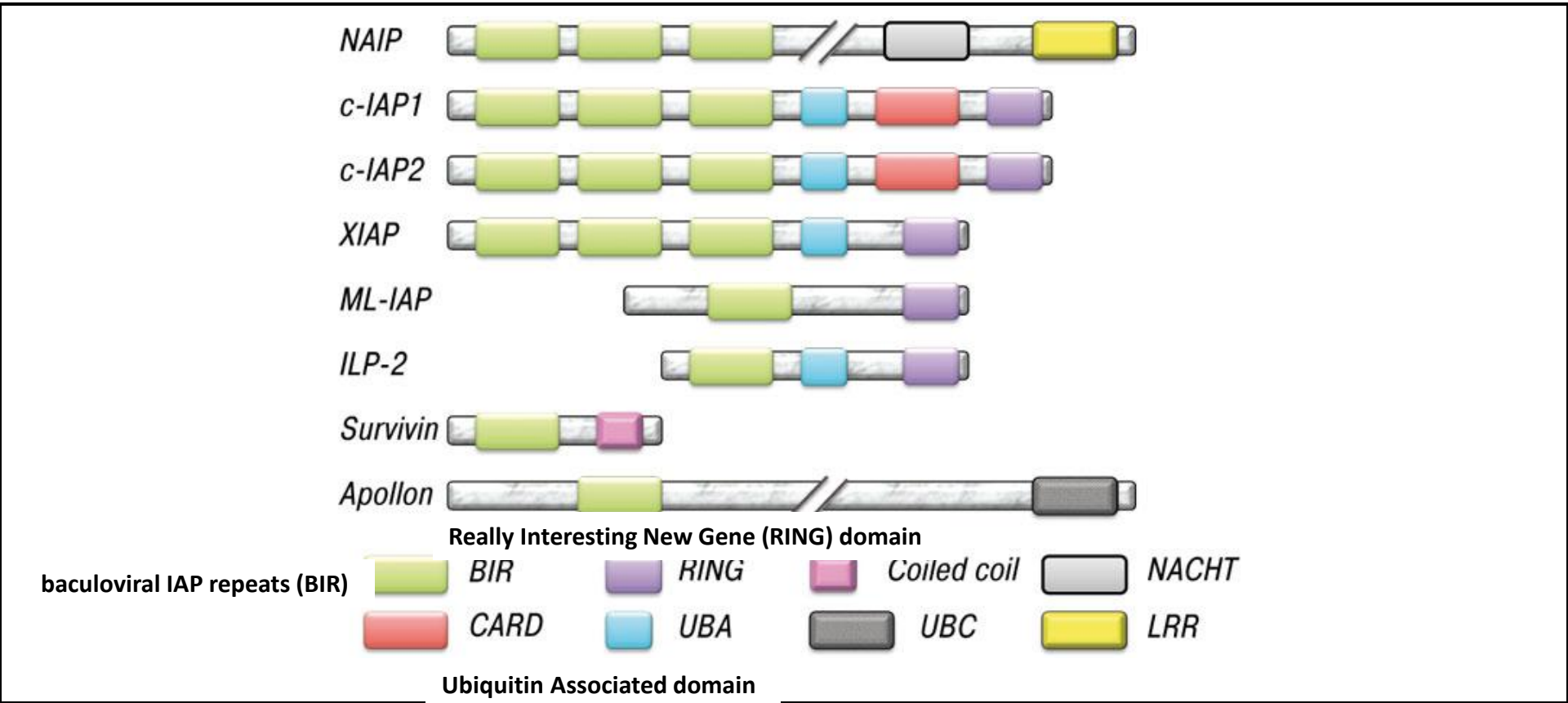
Substrats :
Numerous structural and regulatory proteins e. g.:
Gelsolin
Nuclear lamins
ICAD – inhibitor of caspase-activated DNA-se (CAD).
After activation CAD cut DNA.



Inhibitor of apoptosis proteins (IAP)

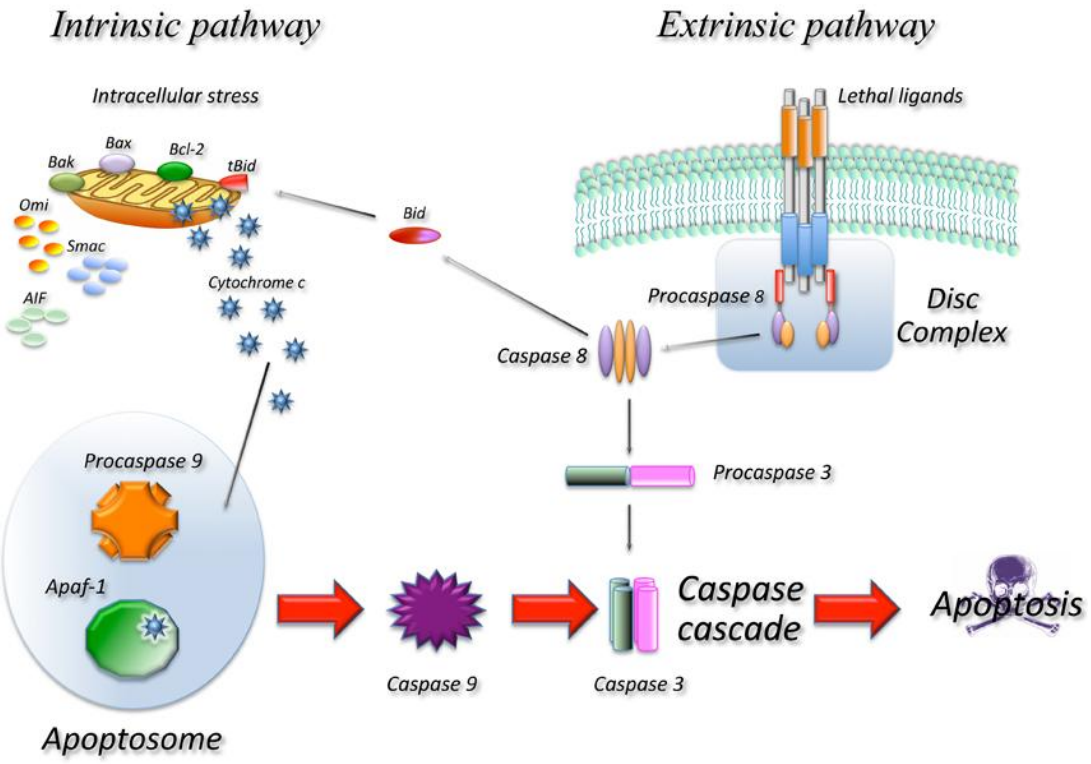
family of proteins that serve as caspase inhibitors

Some IAPs bind to and inhibit caspases. XIAP (X-linked inhibitor of apoptosis protein) binds caspase- 9, 3 and 7, thereby inhibiting their activation and preventing apoptosis.



Pathways of apoptosis

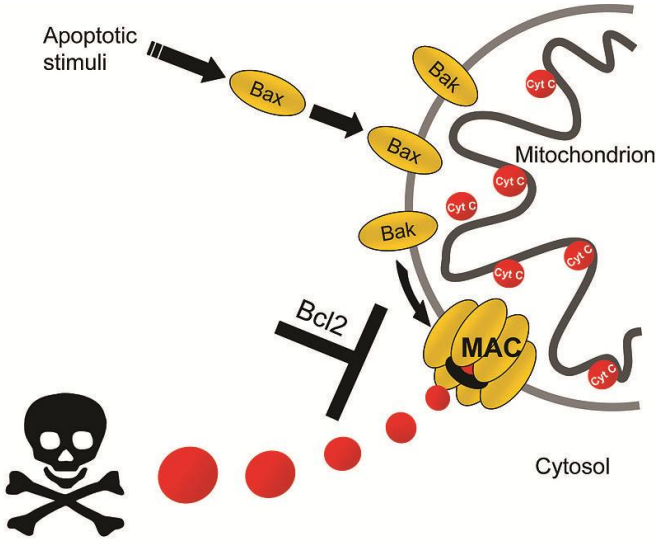
Intrinsic pathway
triggered by DNA damage, lack of trophic factors, lack of normal interactions with ECM.



Extrinsic pathway
triggered by action of other cells or their mediators – TNF, FAS-ligand (CD95L) and TRAIL (TNF-related apoptosis-inducing ligand)

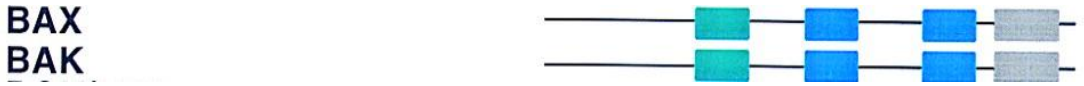
Intrinsic pathway of apoptosis

Apoptosis regulator Bcl-2 (B-cell lymphoma) protein family.These family comprises anti- and proapoptotic proteins



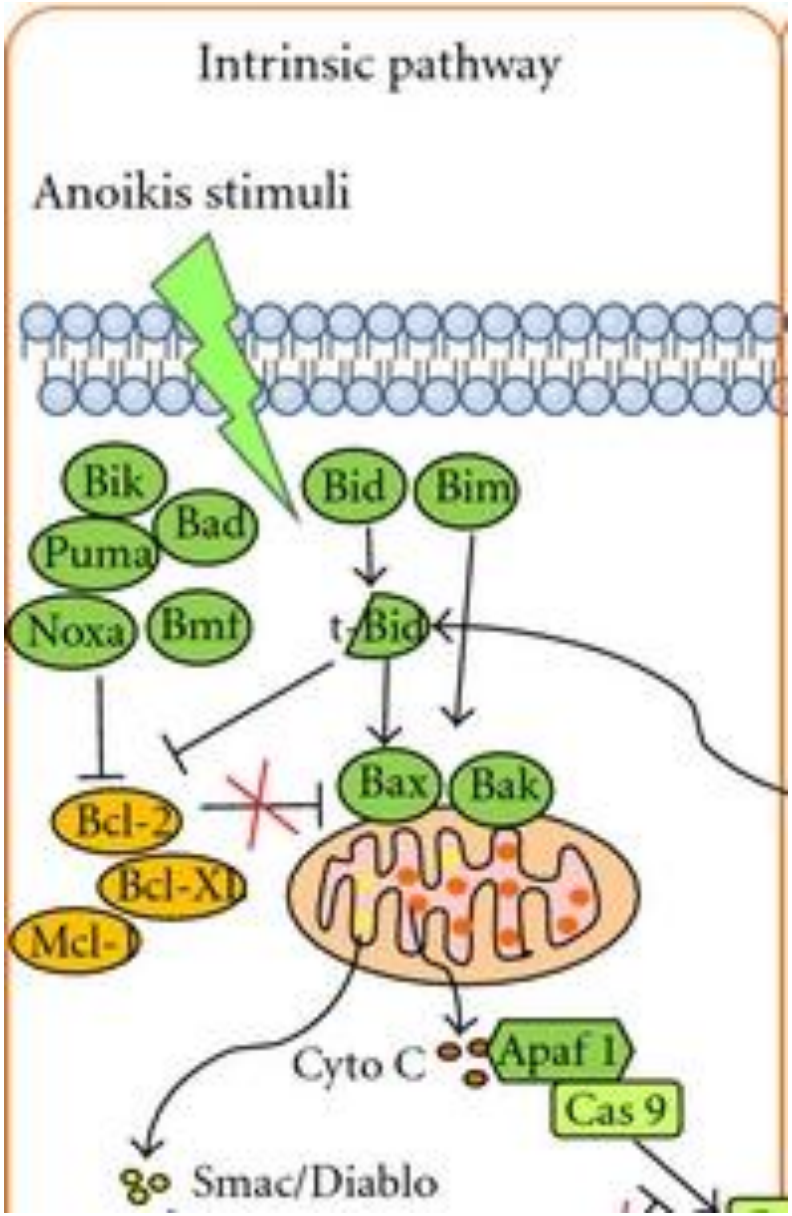
Antiapoptotic proteins: Bcl-2 and Bcl-XL (extra large). They inhibit the formation of mitochondrial apoptosis-induced channels in outer mitochondrial membrane and thus inhibit the release of proapoptotic factors from these organelles.

Proapoptotic proteins BAX (Bcl-2-associated X protein) and BAK (Bcl-2 homologous antagonist/killer) open mitochondrial channels.



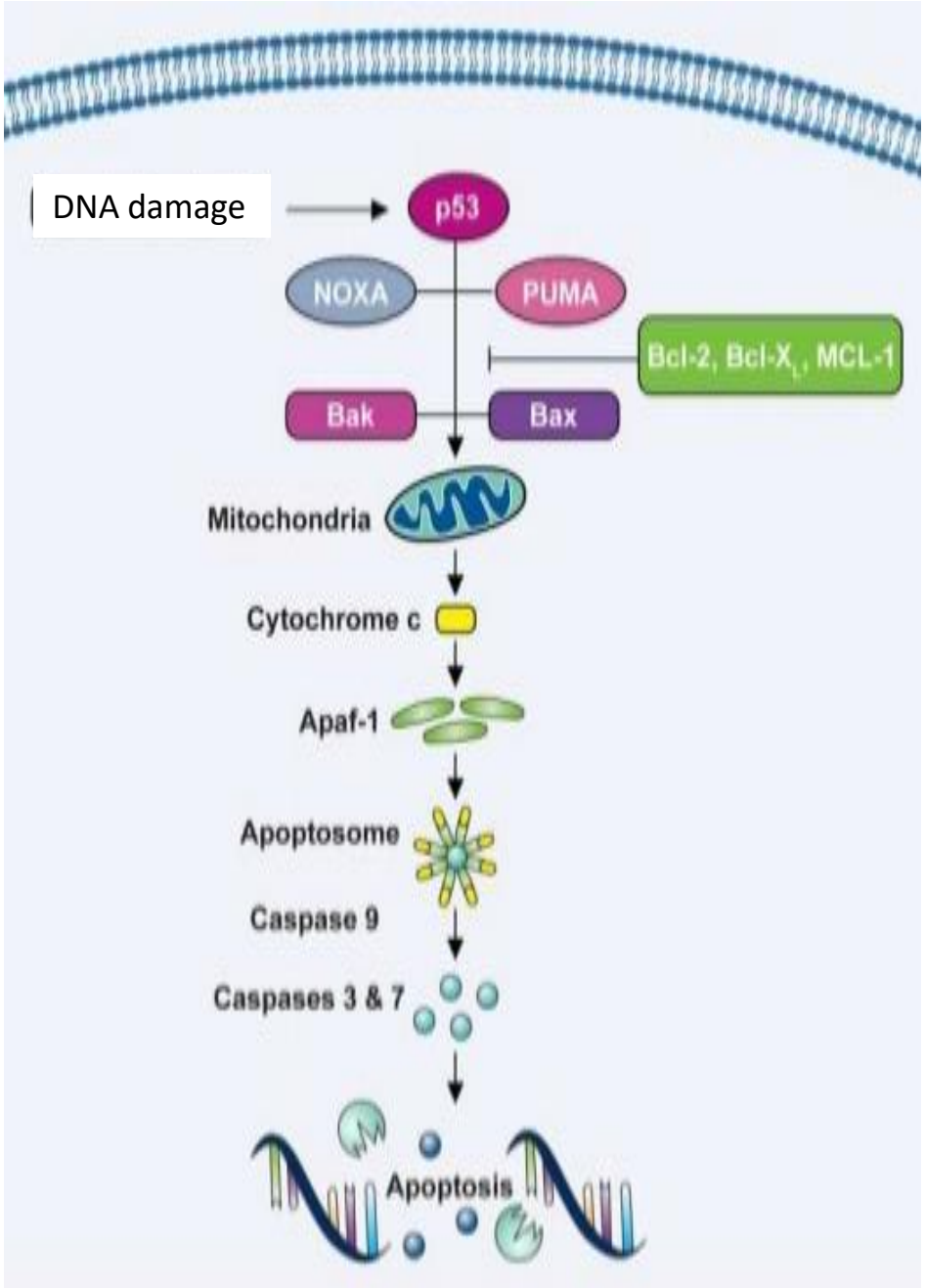
Intrinsic pathway of apoptosis

Incorrect interactions between cell and ECM results in releasing of Bim (Bcl-2L11) protein from cytoskeleton. Bim through interaction with Bcl-2 and Bcl-XL allows BAX and BAK to open the mitochondrial channels, which leads to the release of cytochrome c and Diablo factor (anoikis).



Intrinsic pathway of apoptosis

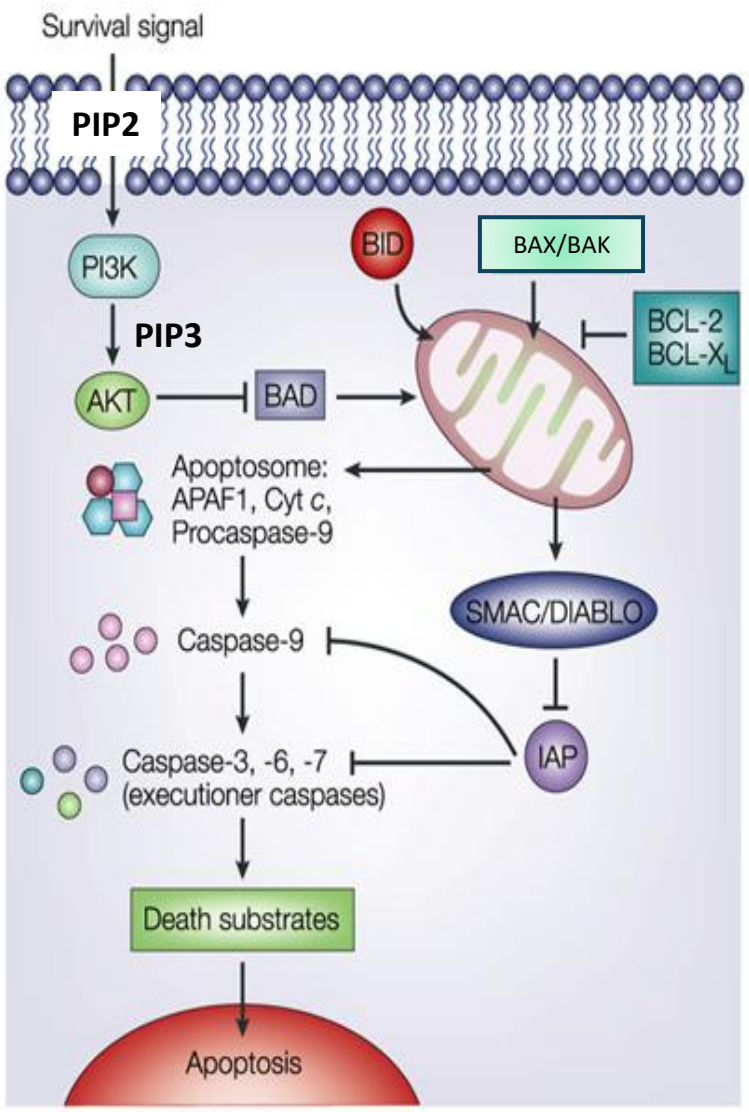
DNA damage results in activation of p53 protein, which (if the DNA repair is impossible) increases the expression of Puma (p53 upregulated modulator of apoptosis) or (and) Noxa (latin – damage). They act similarly to the Bim and cause the releasing cytochrome c and Diablo from mitochondria.



Intrinsic pathway of apoptosis

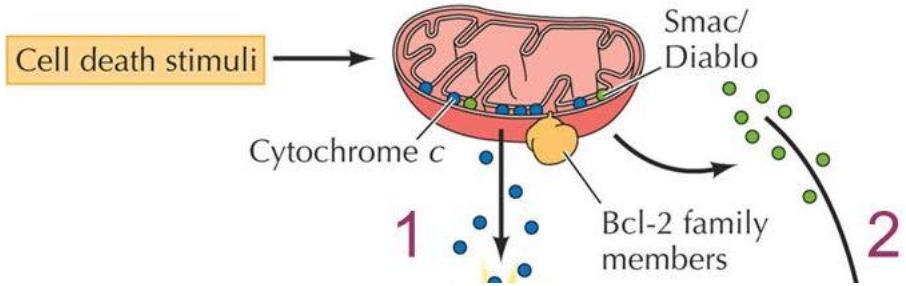
The lack of growth factors results in activation of BAD (Bcl-2-associated death promoter) which forms a heterodimer with Bcl-2 and Bcl-XL, inactivating them and thus allowing BAX/BAK-triggered apoptosis.

When BAD is phosphorylated by Akt/protein kinase B (triggered by PIP3), it is inactivated. This leaves Bcl-2 free to inhibit BAX-triggered apoptosis. BAD phosphorylation is thus anti-apoptotic, and BAD dephosphorylation is pro-apoptotic.



Intrinsic pathway of apoptosis

results in the release of cytochrome c and Smac/Diablo from inter-membrane space of mitochondrion.

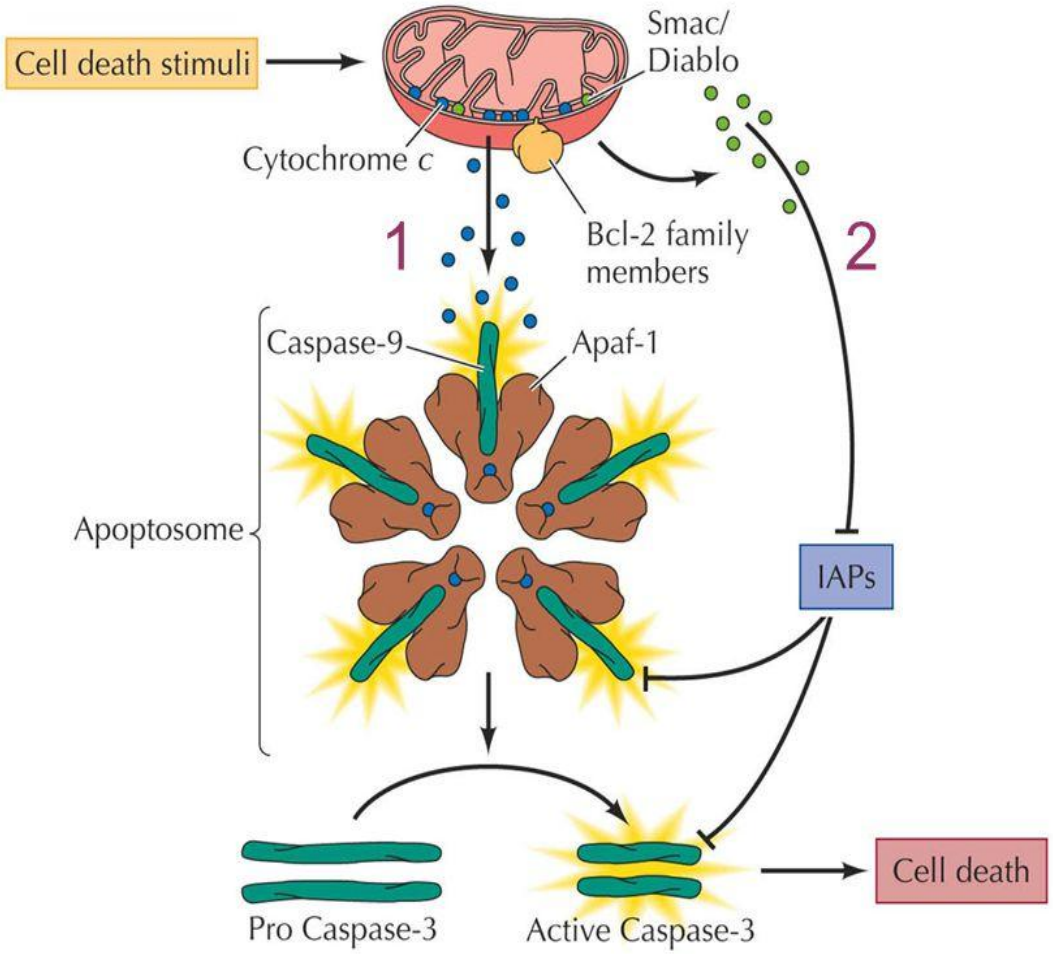


Cytochrome c is a hemoprotein connected with cardiolipin with the inner mitochondrial membrane. During the early phase of apoptosis, mitochondrial ROS production is stimulated, and cardiolipin is oxidized. The cyt c is then detached and can be extruded into the cytoplasm through pores in the outer membrane

DIABLO is a second mitochondria-derived activator of caspases or SMAC. This protein binds inhibitor of apoptosis proteins (IAPs), thus freeing caspases to activate apoptosis.

Intrinsic pathway of apoptosis

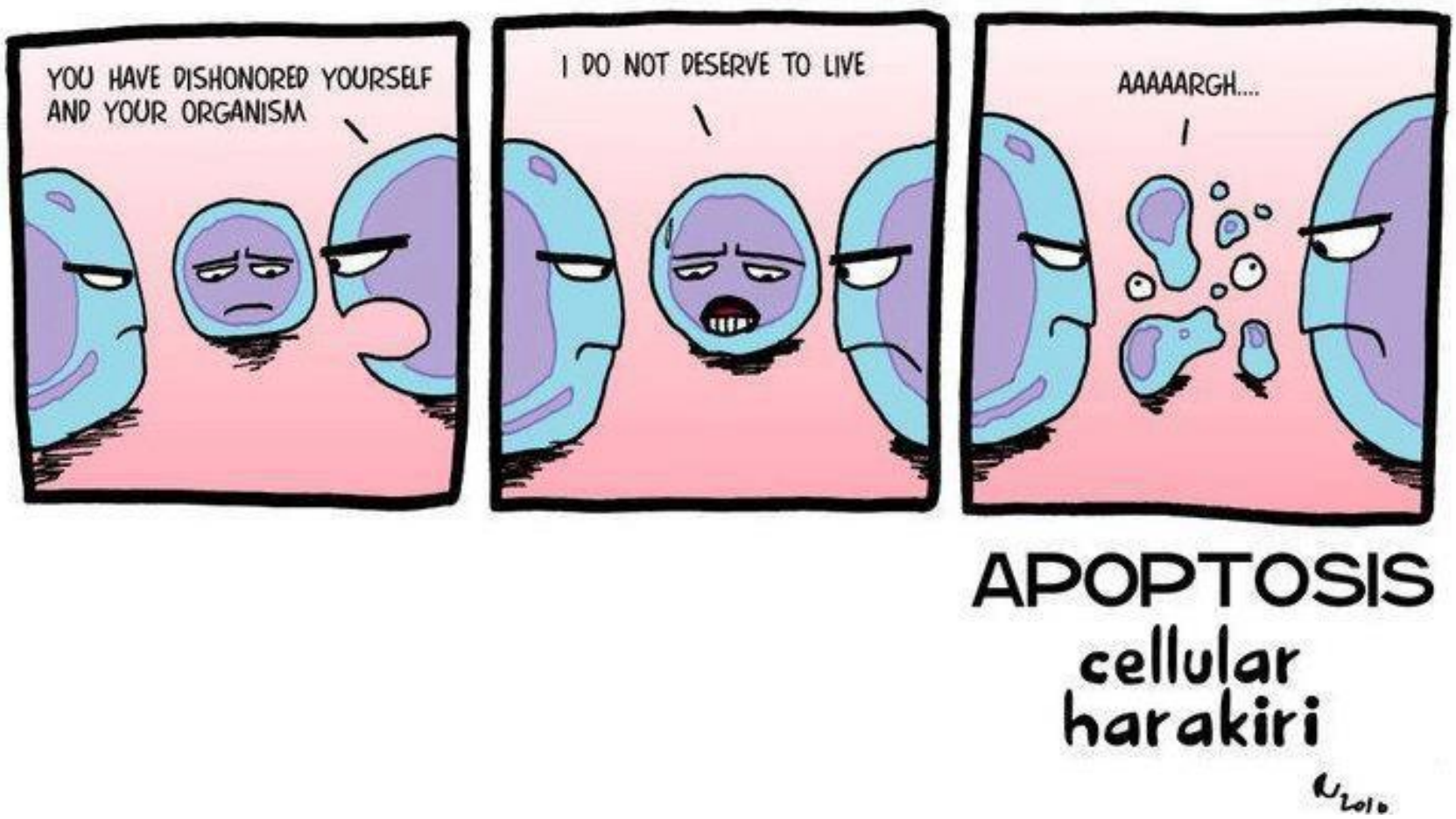
Cytochrome c binds to the cytoplasmic protein Apaf-1 (apoptotic protease activating factor-1) which possesses domain CARD



These complexes aggregate to form apoptosomes. The apoptosomes bind to and activate caspase-9. Caspase-9 cleaves and activates effector caspases. Diablo binds inhibitor apoptosis proteins.

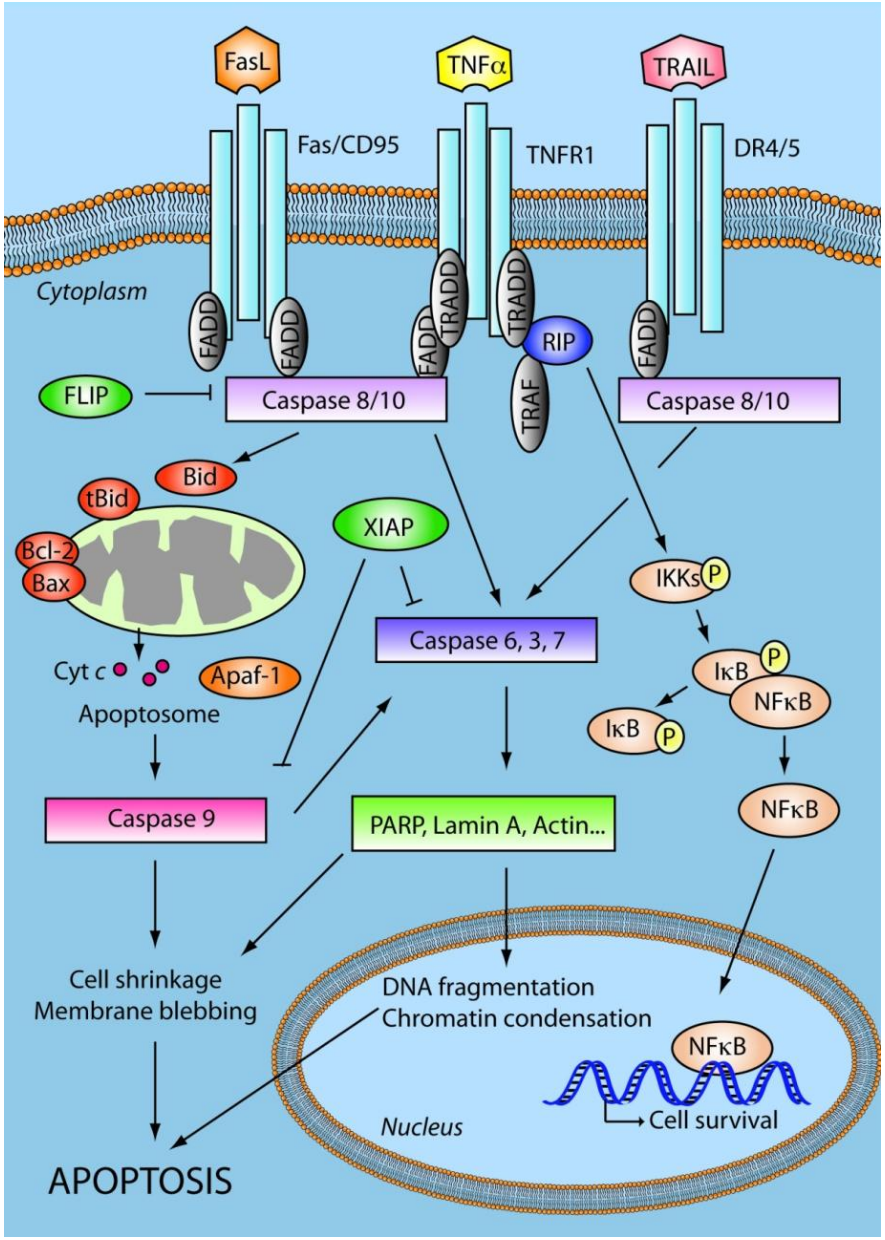
Extrinsic pathway of apoptosis

Activity of other cells



Extrinsic pathway of apoptosis

Activation of death receptors (DRs), which are members of TNFR family. Fas (CD95) binds Fas ligand, transmebrane protein expressed on cytotoxic T lymphocytes.
TNFR1 binds TNF.
Receptors for TRAIL bind TRAIL.
The cytoplasmic portion of DRs contains death domains – DDs. After binding of ligand DRs undergo trimerization and by DD bind DD of adapter proteins. Adapter proteins contain also death effector domains (DEDs) by which they recruit initiator caspases 8 or (and) 10 forming DISC (death-inducing signaling complex).



Extrinsic pathway of apoptosis

Adapter proteins with **DD** and **DED** domains:

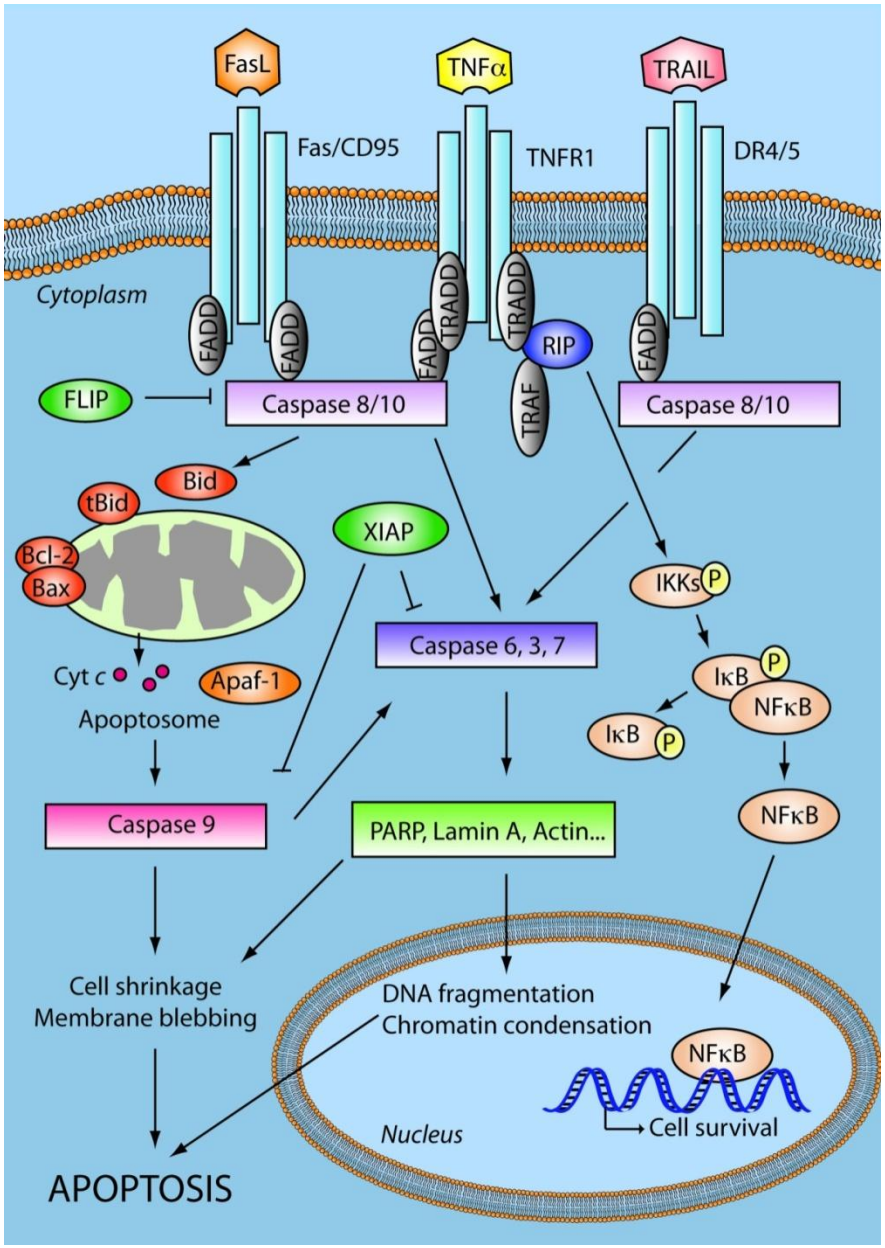
TRADD -Tumor necrosis factor receptor type 1-associated death domain protein

FADD -Fas-associated protein with death domain

Anti-apoptotic factors:

TRAF1 and 2 - TNF receptor associated factors, interacts with the IAPs and functions as a mediators of the anti-apoptotic signals.

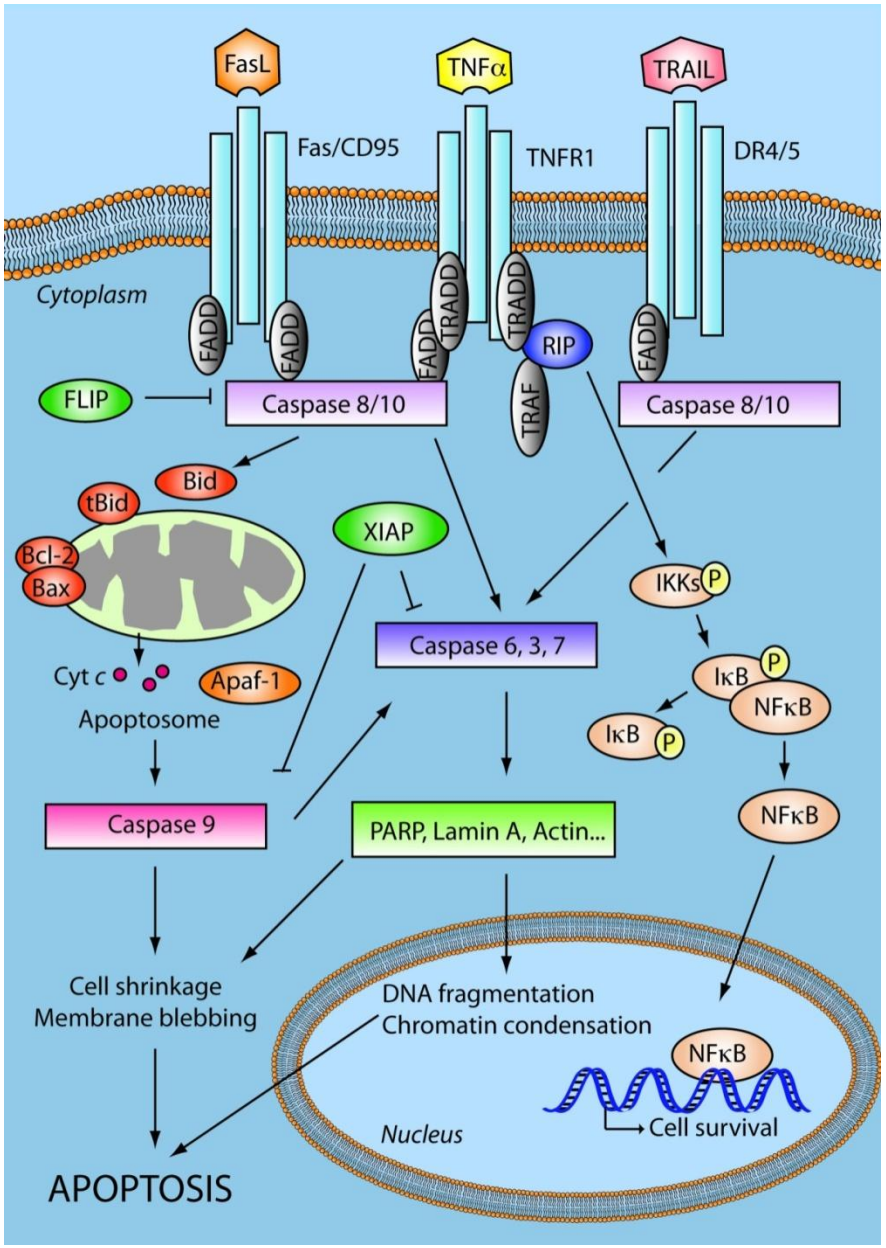
RIP1 kinase (DD domain) can interact with FADD, TRADD and TRAF2 promoting strong activation of NFκB, which induces IAP production and inhibits apoptosis



Extrinsic pathway of apoptosis

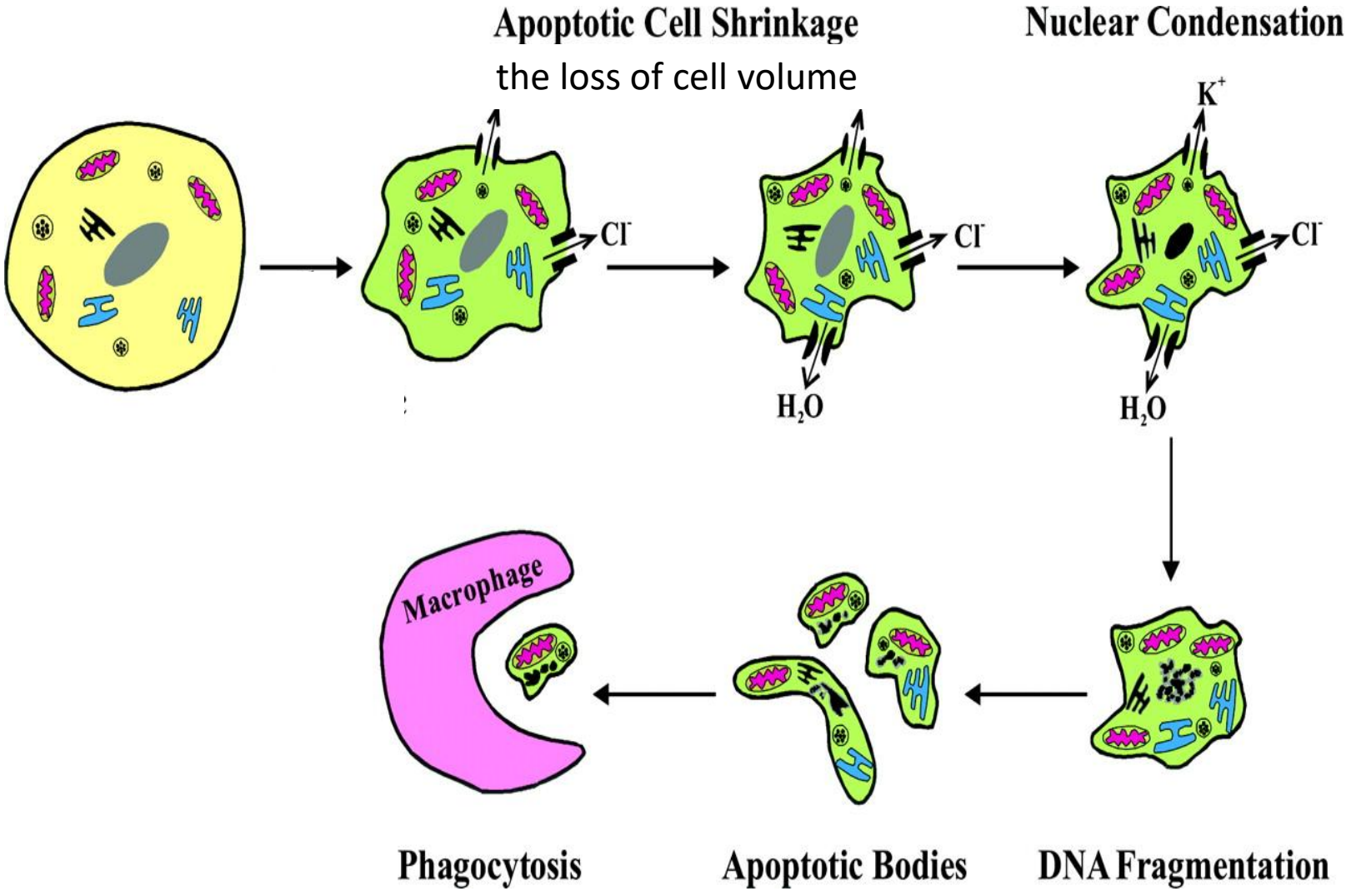
Death receptors after binding of ligand can also stimulate mitochondria to release cytochrome c and Diablo by protein BID (BH3 interacting-domain death agonist). BID facilitates the Bax to insert to outer mitochondrial membrane.

Decoy receptors compete for ligand with death receptors, but they are not able to transmit the signal.

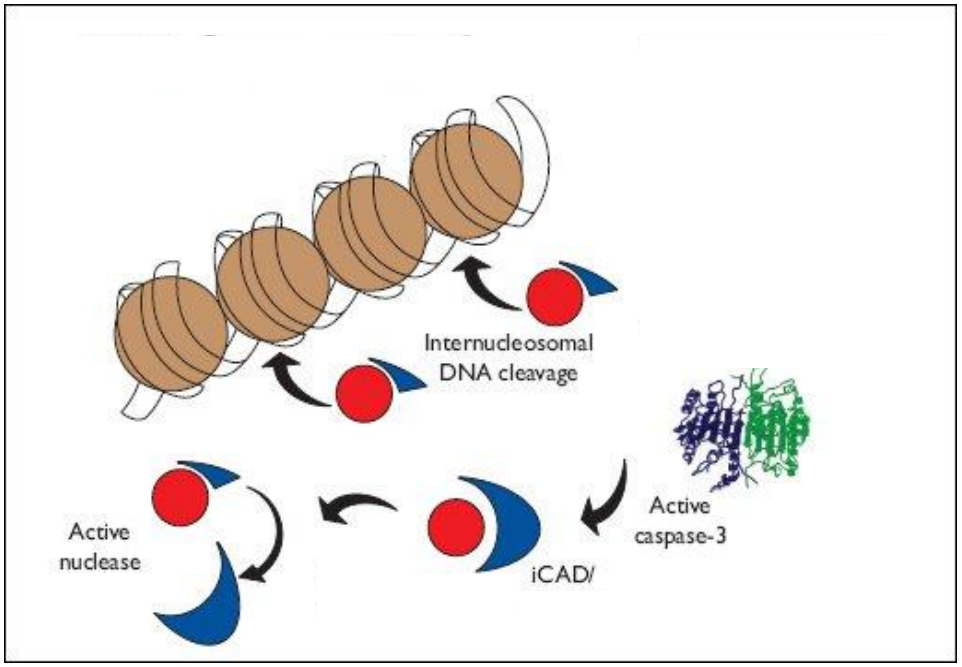


Apoptosis

Executioner caspases 3, 6, 7 coordinate the execution phase of apoptosis by cleaving multiple structural and rgulatory proteins (cascade of caspases).



DNA fragmentation during apoptosis

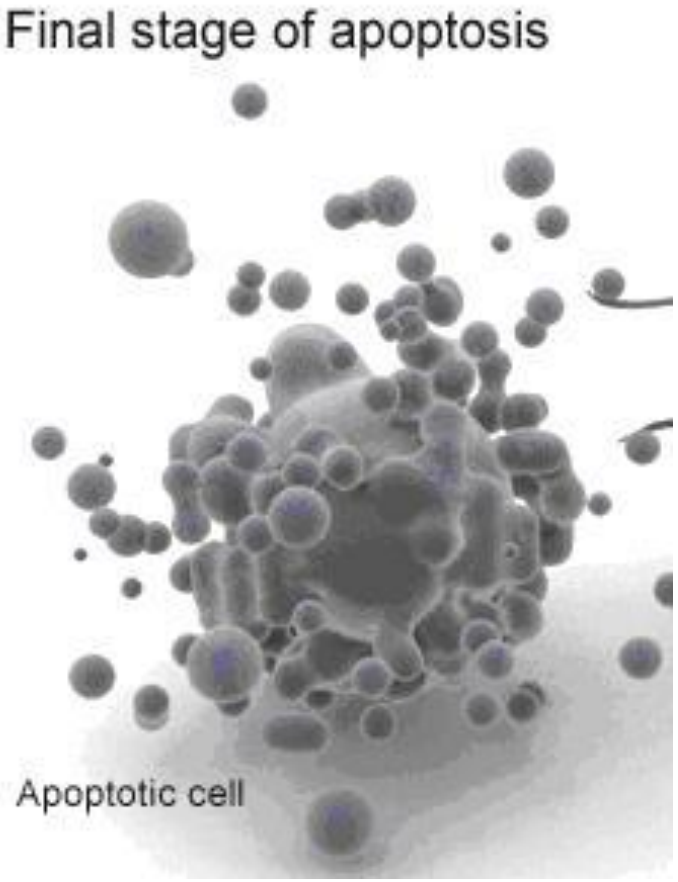


The enzyme responsible for DNA fragmentation is the caspase-activated DNase (CAD). CAD is normally inhibited by inhibitor - ICAD. During apoptosis caspase 3 cleaves ICAD and thus causes CAD to become activated.

CAD cleaves DNA at internucleosomal linker sites between nucleosomes, that occur at ~180-bp intervals. This is because the DNA is normally tightly wrapped around histones. The linker sites are the only parts that are exposed and accessible to CAD. Therefore the DNA fragments can comprise 180 or multiples of 180 bp (360, 540, 720 etc).

Apoptotic bodies formation

Apoptotic bodies - apobodies, are small membrane sealed vesicles. Because of the formation of apoptotic bodies the content of dead cells does not leak into the surrounding tissue.
This prevents exposure of tissue to enzymes, oxidants and prevents the contact of cellular content with immune system.

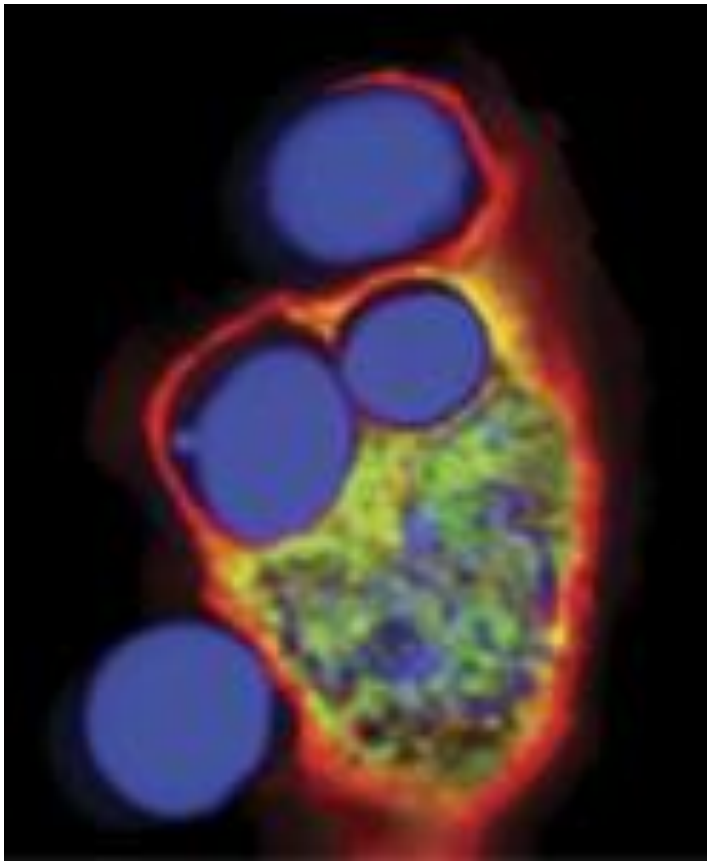


Phagocytosis - efferocytosis

(from efferre, Latin for 'to take to the grave', 'to bury'), process by which dying/dead cells are removed by phagocytic cells.

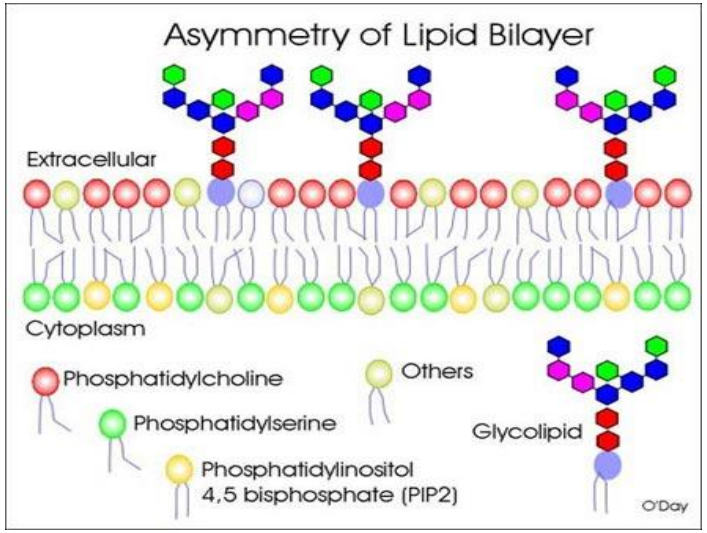
Efferocytosis is performed by macrophages, dendritic cells, epithelial cells and fibroblasts.

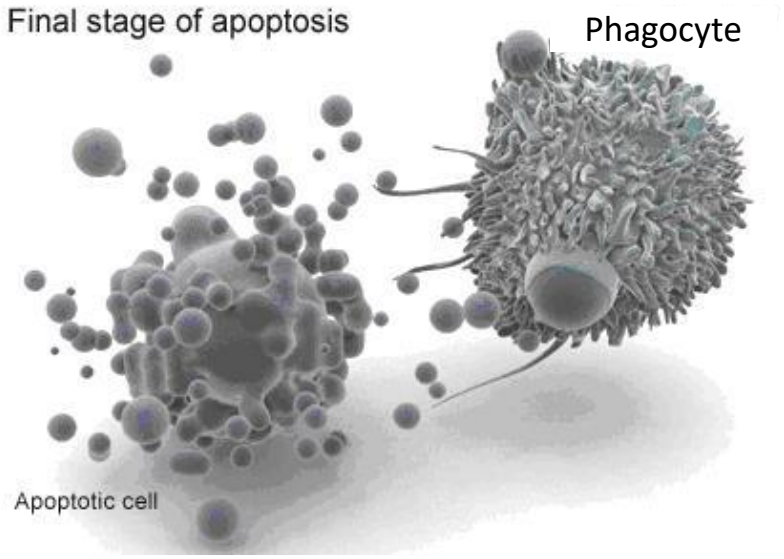
Phagocyte engulf the apoptotic bodies, forming a large fluid-filled vesicles. These ingested vesicles are called efferosomes.



Phagocytosis - efferocytosis

The apoptotic cells carry specific 'eat me' signal - the presence of phosphatidylserine in the outer leaflet of lipid bilayer. Normally phosphatidylserine is component of inner leaflet.





The enzyme - floppase transfers phosphatidylserine from inner to the outer leaflet (flip-flop).

The cells responsible for phagocytosis of apoptotic cells have receptors for phosphatidylserine.

SENOLYTICS

FOXO4-related peptides, Binding of FOXO4 to p53 protein prevents it from activating of apoptosis and promotes cellular senescence. A peptide that binds with FOXO4 disrupts the p53-FOXO4 interaction and triggering cell death.

Inhibitors of different members of the bcl-2 family of anti-apoptotic proteins. (fisetin and **quercetin**) induce apoptosis by inhibition of the anti-apoptotic protein Bcl-xL.
Src tyrosine kinase inhibitors: dasatinib with quercetin **clinical trial**

Senescence-specific killing compound 1: A gemcitabine (a cytotoxic chemotherapeutic) prodrug that is activated by sa lysosomal β-galactosidase

Inhibitors of the kidney-type glutaminase 1 (GLS1). Senescent cells have a low pH due to their high lysosomal content and leaking lysosomal membranes.
To neutralize low pH, these cells produce high levels of GLS1; inhibiting the activity of this enzyme exposes senescent cells to unsurvivably severe internal acidity, leading to cell death

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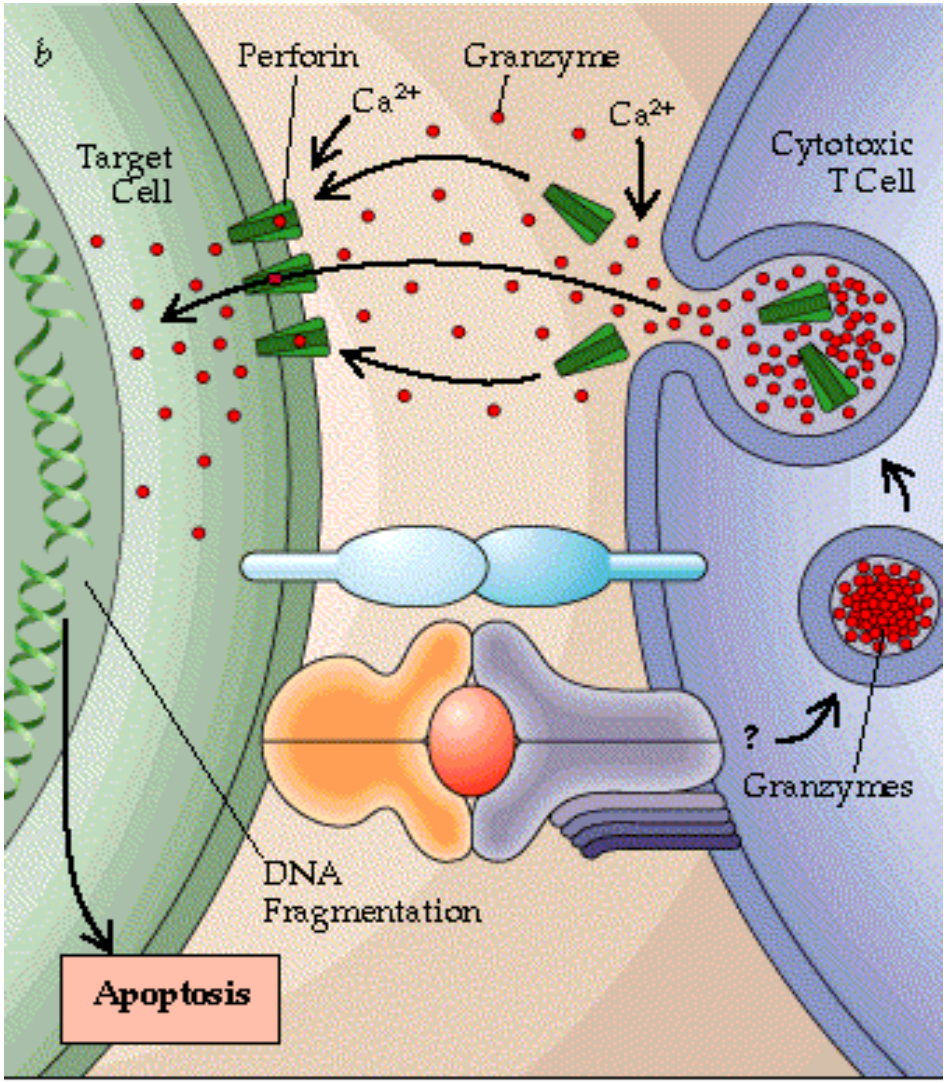
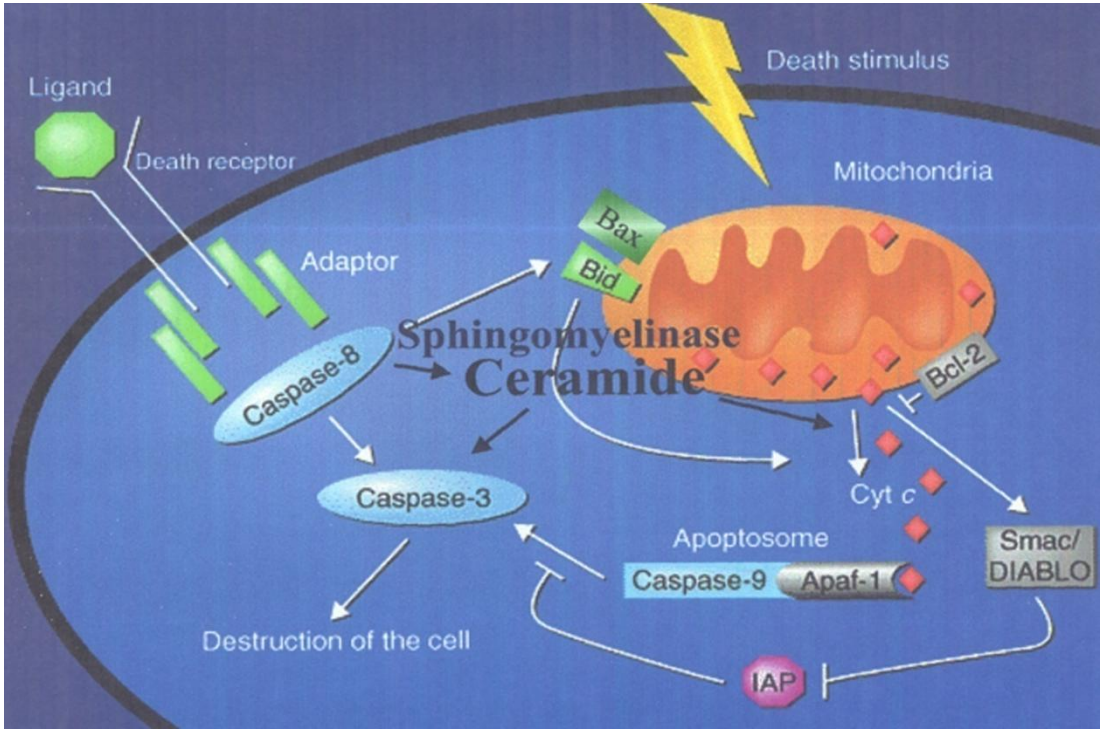
Perforin/granzyme pathway of apoptosis

Cytotoxic T cells and NK cells have granules, which contain perforin and granzymes



Upon degranulation, perforin binds to the target cell's plasma membrane, and oligomerises in a Ca^{2+} dependent manner to form pores on the target cell. The pores allow the passive diffusion of a family of pro-apoptotic serine proteases, known as the granzymes.

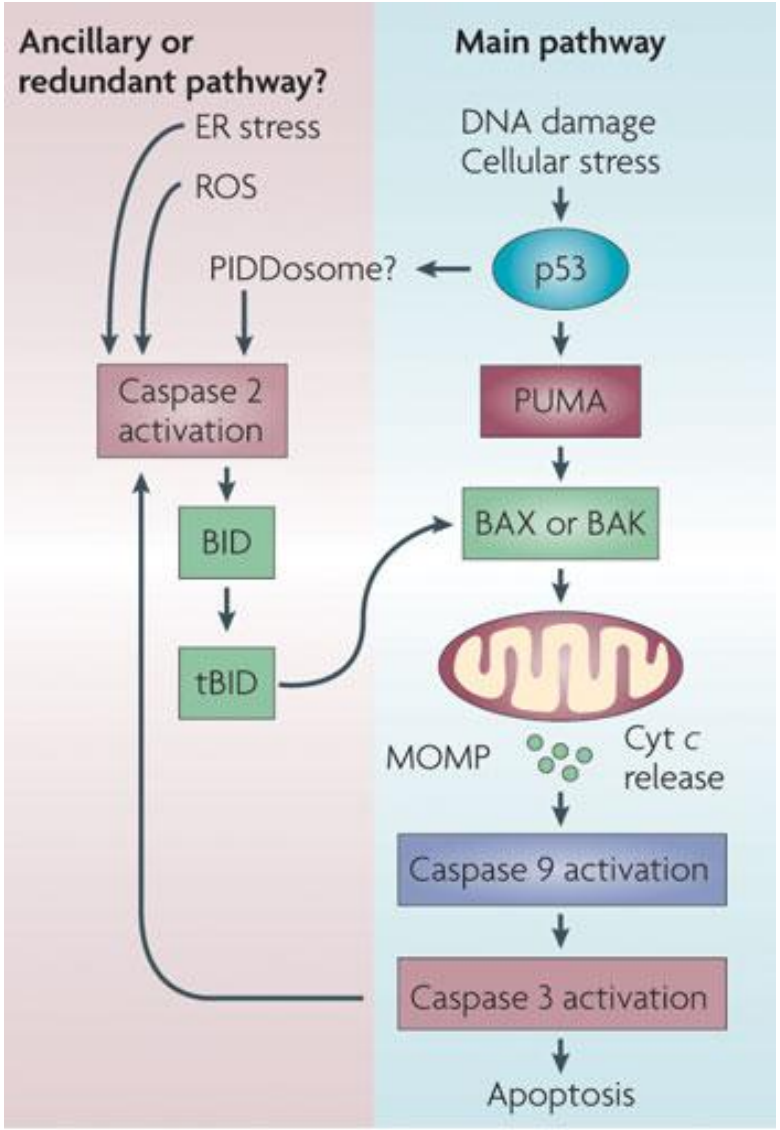
Granzyme B induces apoptosis by cleavage of caspases - initiator 8, 10, executioner 3, 7, BID protein and ICAD.



Sphingosine-ceramide pathway of apoptosis

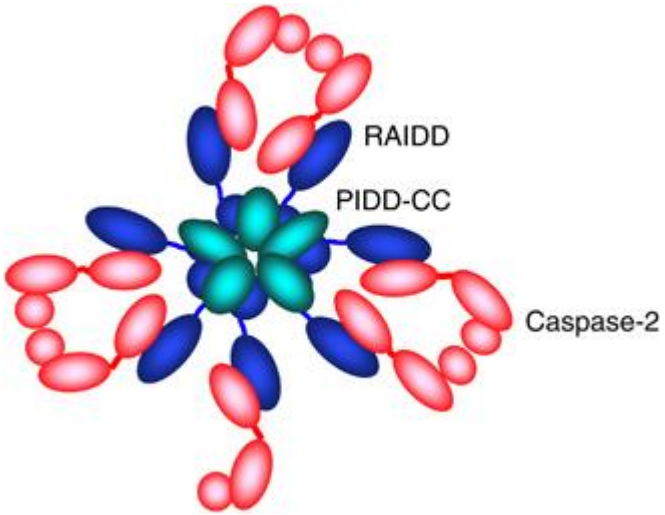
Sphingomyelin is a type of sphingolipid found in cell membranes. It usually consists of phosphocholine and ceramide. Upon stimulation with apoptotic stimuli such as Fas-ligand or TNF sphingomyelin is degraded by sphingomyelinase and ceramidase resulting in ceramide and sphingosine accumulation. Ceramide is also generated *de novo* by ceramide synthase. Sphingosine and ceramide have been shown to induce apoptosis in cells by the mitochondrial pathway (activation of Bid and Bad proteins)

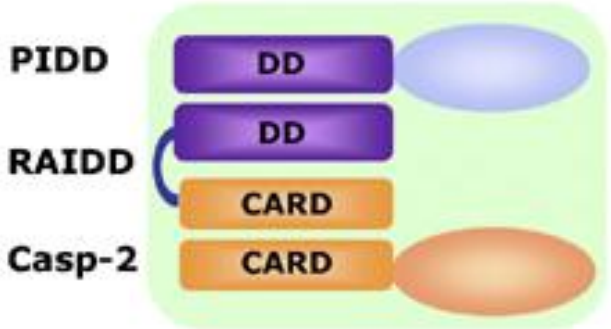
The caspase 2 pathway of apoptosis



In an alternative pathway p53 activates cell death by PIDD – the component of PIDDosome which activates caspase 2 (caspase 2 can be also activated by caspase 8). Caspase 2 activates BID (BH3 interacting-domain death agonist) and this causes cyt c release. Caspase 2 mediates also the apoptosis induced by ROS and ER stress. The caspase 2 pathway is therefore may function as an ancillary or backup mechanism of p53-dependent apoptosis.

The caspase 2 pathway of apoptosis



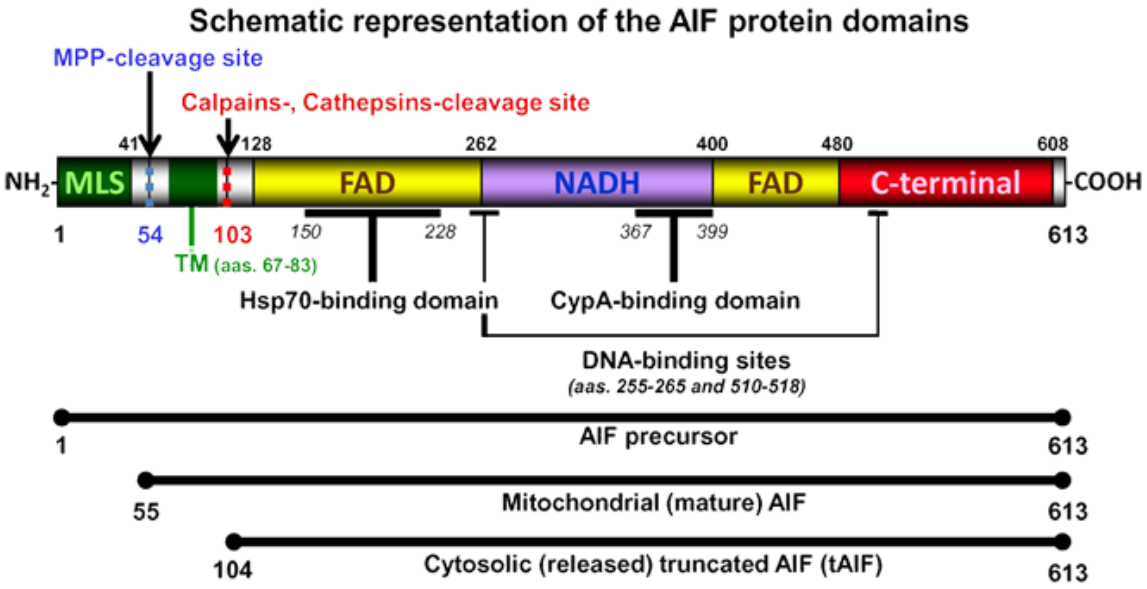


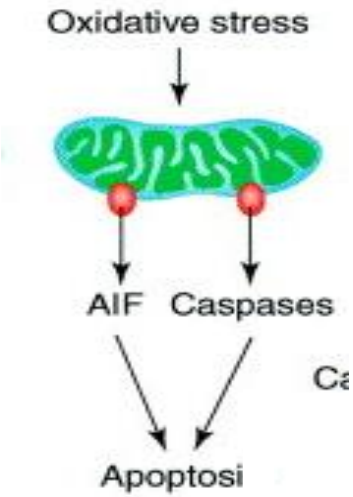
PIDDosome is the structure composed of PIDD, RAIDD and caspase 2. Piddosome particippates in caspase 2 activation.

PIDD - p53-induced protein with a death domain
RAIDD - RIP-associated Ich-1/Ced-3 homologous protein with a death domain. This protein has also CARD domain, similarly to caspase 2

Caspase-independent programmed cell death (CI-PCD)

Apoptosis-inducing factor (AIF) is a mitochondrion-localized flavoprotein with NADH oxidase activity. AIF translocates from mitochondria to the nucleus during apoptosis and induces chromatin condensation and 'large-scale' DNA fragmentation. AIF can be released from mitochondrion in caspase-independent or dependent pathway.

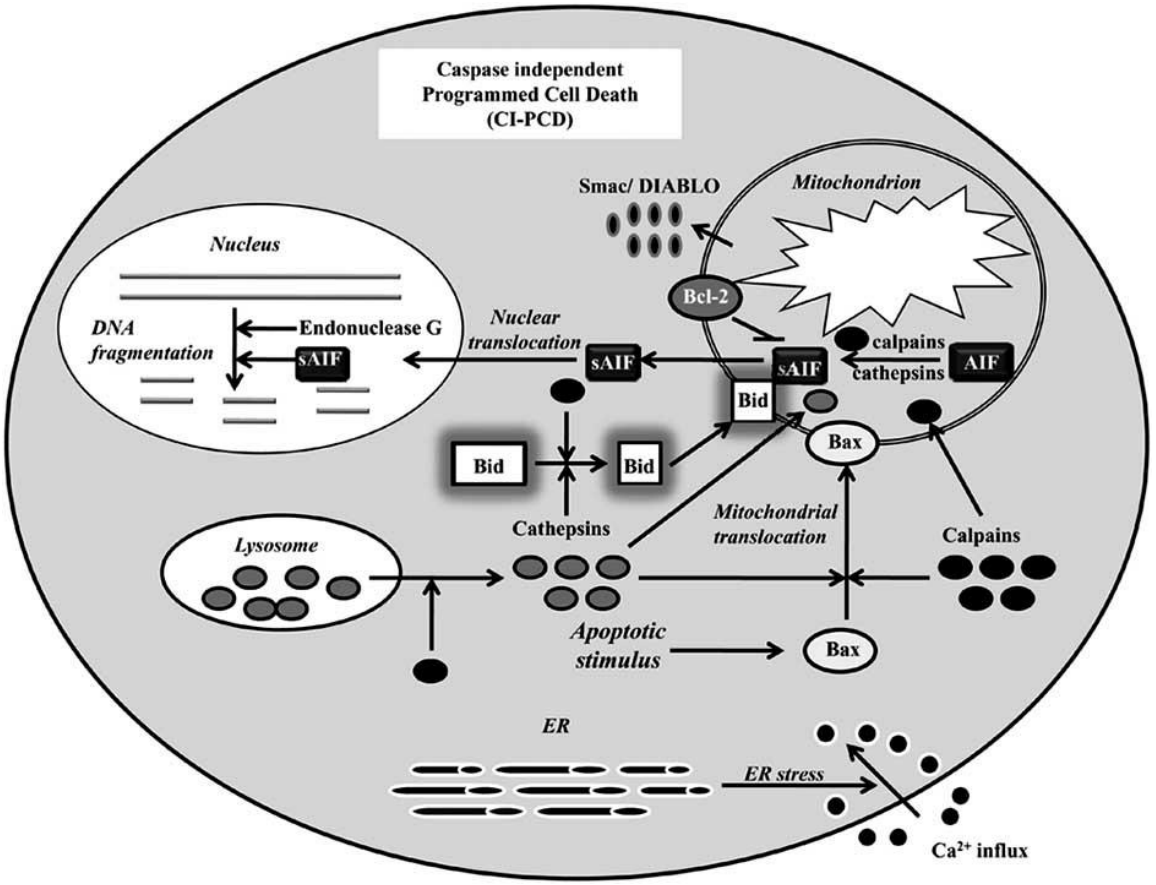




Caspase-independent programmed cell death (CI-PCD)

Executioners enzymes in CI-PCD are the cathepsins and the calpains. Cathepsins are released from the lysosomes and calpains are activated following Ca^{2+} influx in the cell triggered by ER stress.

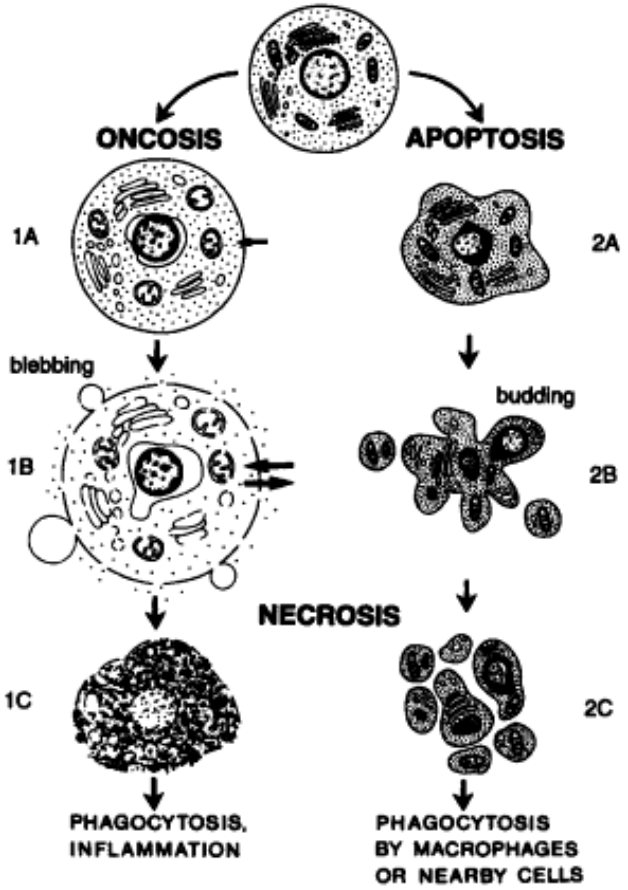
Cathepsins and calpains are involved in the cleavage and translocation of Bax to the mitochondrion and the cleavage of AIF. Proteins Bax and Bid cause the release of AIF from mitochondria. AIF induces DNA fragmentation.



Oncosis - ischemic cell death

passive or accidental cell death

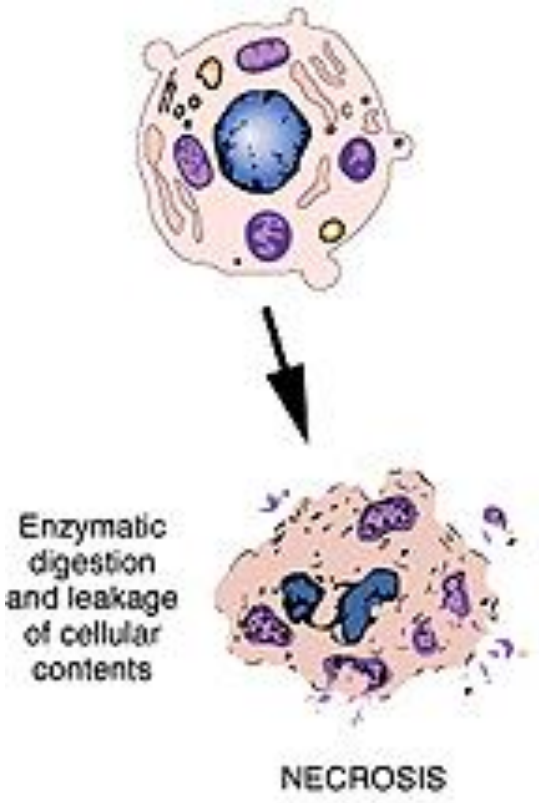
caused, typically, by ischemia, characterized by nuclear, cytoplasmic and mitochondrial swelling, vacuolization of cytoplasm, blebbing and increased membrane permeability – failure of the ionic pumps and karyolysis. The DNA is broken down in nonspecific fashion. This cell death is associated with inflammation.



Porimin (pro-oncosis receptor inducing membrane injury) a highly glycosylated protein, a member of mucin family is proposed to function as a cell surface receptor that mediates oncosis.

Necrosis

Necrosis (Greek death) - changes after death. These are the features of cell's cadaver whatever the mechanism of the cell's death was.
In necrosis cell or tissue destruction is due to **autolysis**, initiated by the cells' lysosomes releasing enzymes. These enzymes are however released due to the cessation of active processes in the cell, not as an active process. Though autolysis only resembles the active process of digestion of nutrients by live cells. The dead cells are not actively digesting themselves.



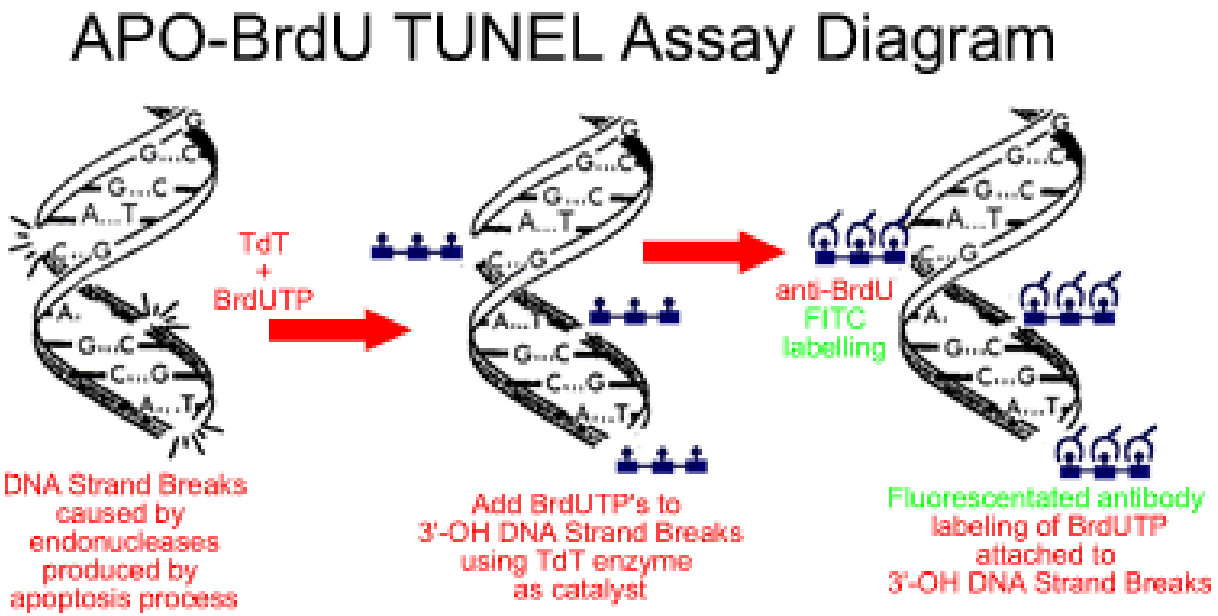
TUNEL ASSAY

(terminal deoxynucleotidyl transferase dependent nick end labeling)

common method for detecting DNA fragmentation in apoptosis.

The assay relies on the presence of nicks in the DNA which can be identified by terminal deoxynucleotidyl transferase - TdT, an enzyme that catalyzes the addition of labeled dUTPs (deoxyuridine 3-phosphate) or synthetic nucleoside BrdU, - bromodeoxyuridine (5-bromo-2'-deoxyuridine) to 3’-OH end of DNA strand breaks

Then cells are exposed to detection system.

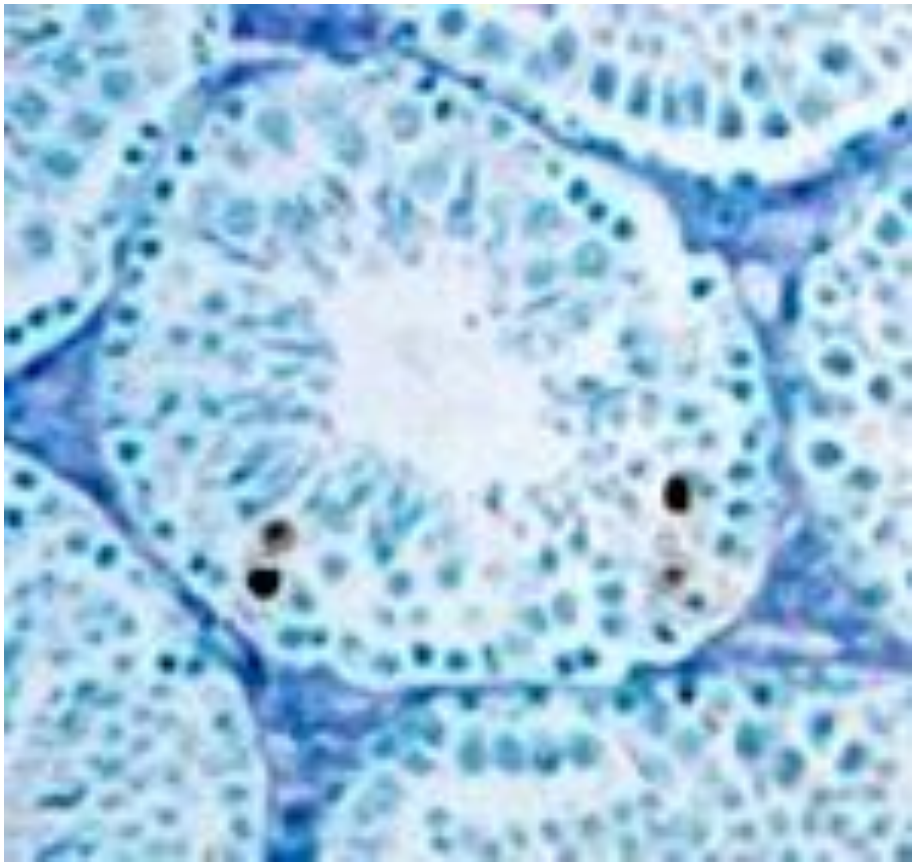


TUNEL

(terminal deoxynucleotide transferase nick-end labeling)

TUNEL staining is not limited to the detection of apoptotic cells. It can be used to detect DNA damage associated with non-apoptotic cell death and has also been reported to stain cells undergoing active DNA repair.

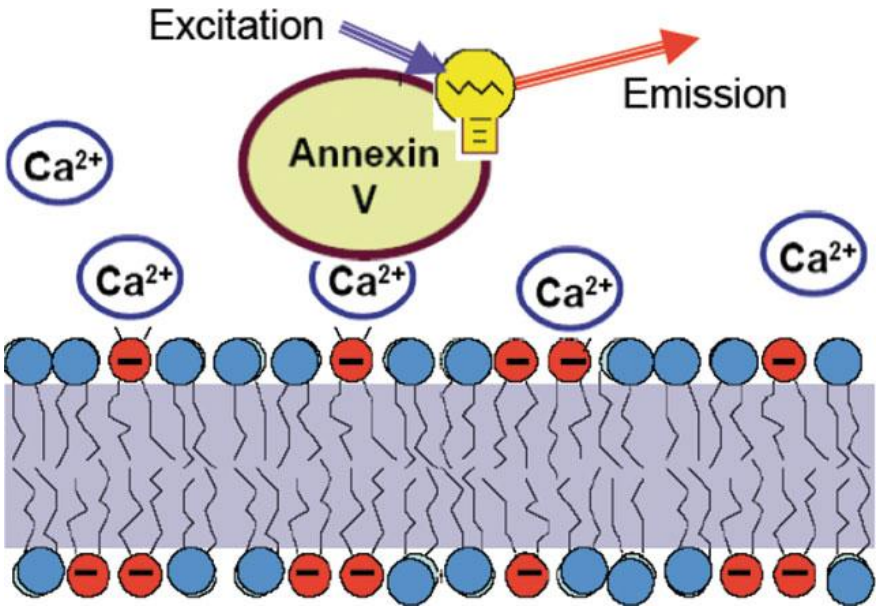
Therefore TUNEL staining may be considered generally as a method for the detection of DNA damage (DNA fragmentation).



Annexin V-binding assay

Annexin V is a protein which participates in the inhibition of blood coagulation by competing for phosphatidylserine (PS) binding sites with prothrombin.

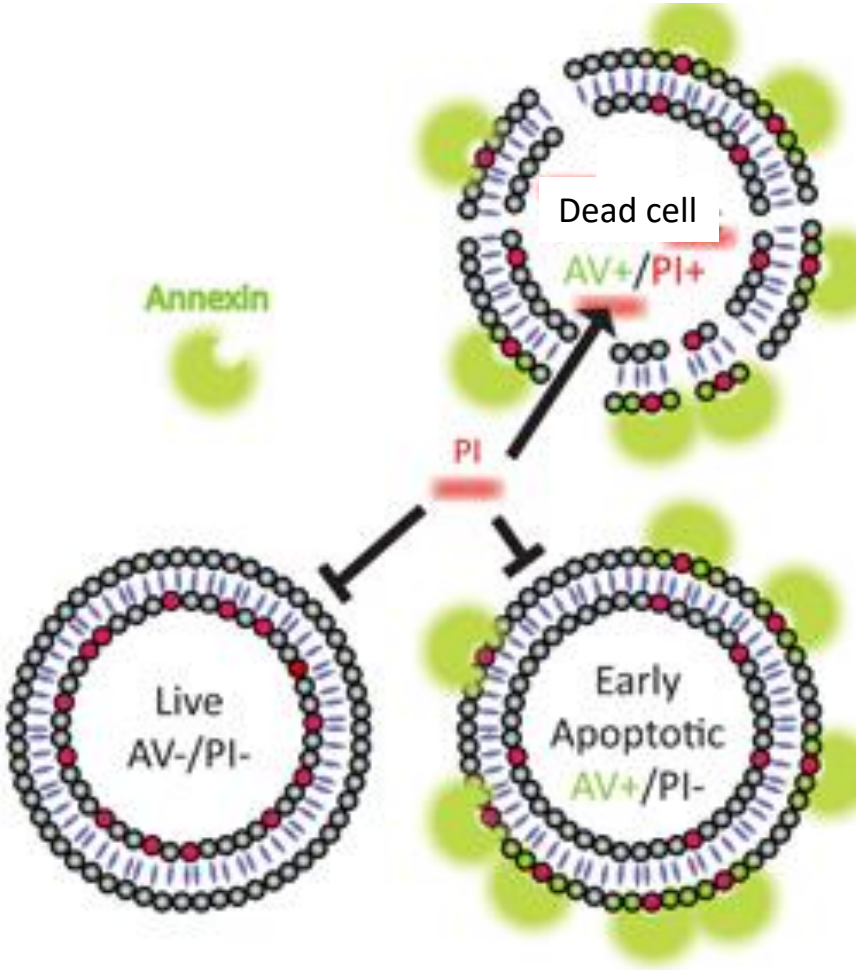
The annexin V binding assay is used for the detection of apoptotic cells *via* annexin V binding to PS at cell surface of apoptotic cells. One of features of apoptosic cells is the exposure of PS on the outer leaflets of the plasma membrane in contrary to normal cells.



Annexin V preferentially binds to PS in the presence of Ca^{2+}. Annexin V is labelled with a fluorochrome. After excitation of the dye by ultraviolet light apoptotic cells can be visible.

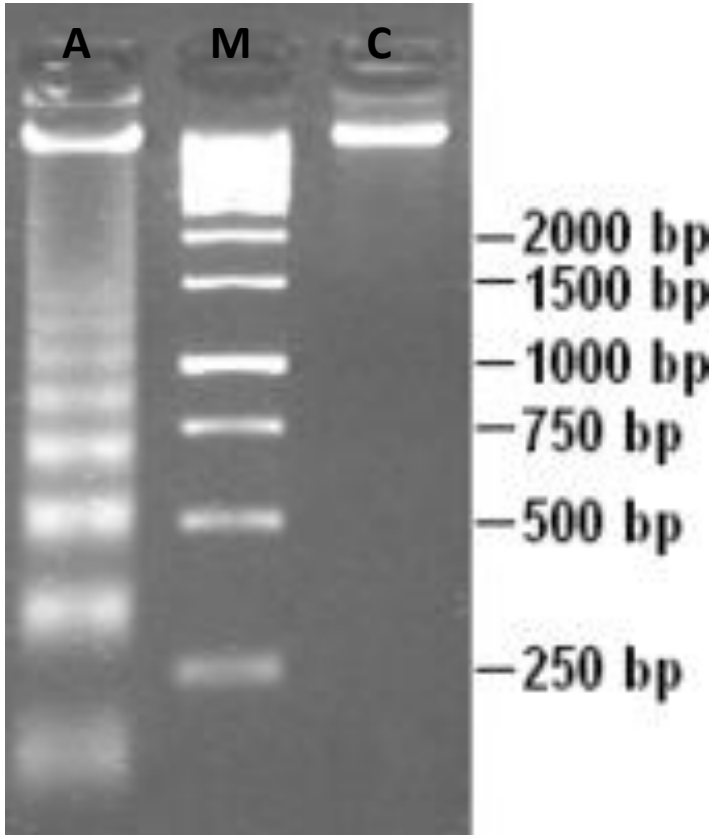
Annexin V-binding assay with propidium iodide

PS translocation accompanies cell death resulting from either apoptotic or other cell death processes.



Therefore, annexin V is used with a vital dye - propidium iodide (PI) for identification of apoptotic cells. Viable cells exclude PI, whereas dead and damaged cells don't. Therefore, viable cells are both annexin V and PI negative, while cells in apoptosis are annexin V positive and PI negative, and dead cells (with a discontinuous cell membrane) are both annexin V and PI positive.

Apoptotic DNA ladder assay

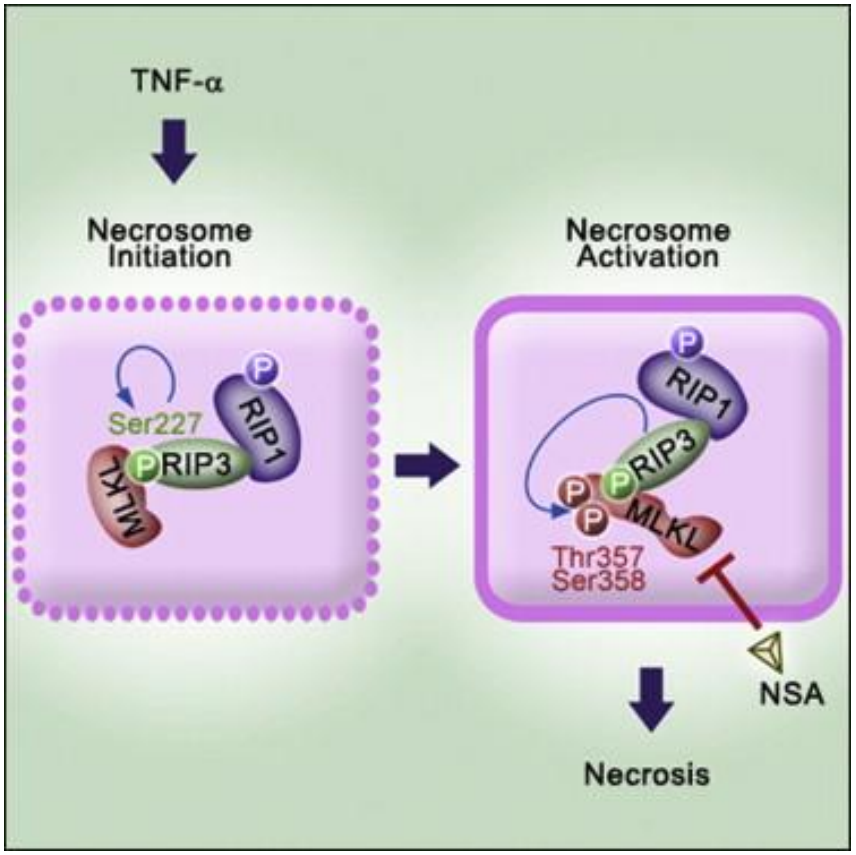


DNA ladder is observed when DNA fragments, resulting from apoptotic DNA fragmentation, are visualized after separation by gel electrophoresis.
DNA ladder is a distinctive feature of DNA degraded by caspase-activated DNase (CAD). CAD cleaves genomic DNA at internucleosomal linker regions, resulting in DNA fragments that are multiples of 180–185 base-pairs in length. Separation of the fragments by agarose gel electrophoresis and subsequent visualization, results in a characteristic "ladder" pattern

Necroptosis – programmed inflammatory cell death

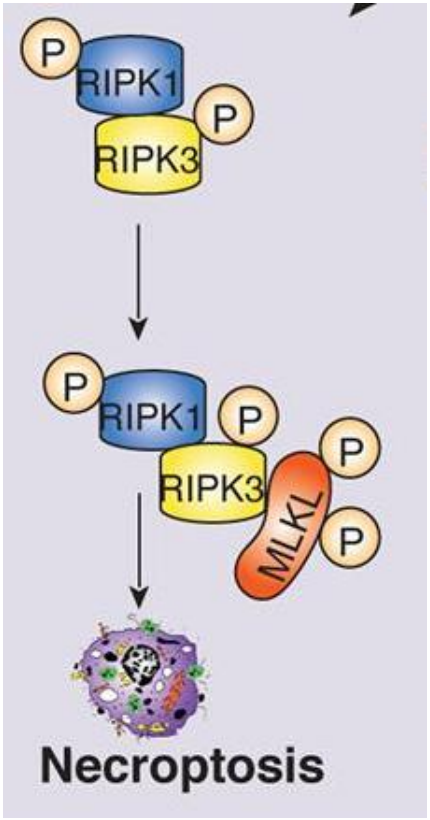
viral defense mechanism, allowing the cell to undergo “cellular suicide” in a caspase-independent fashion in the presence of viral caspase inhibitors.

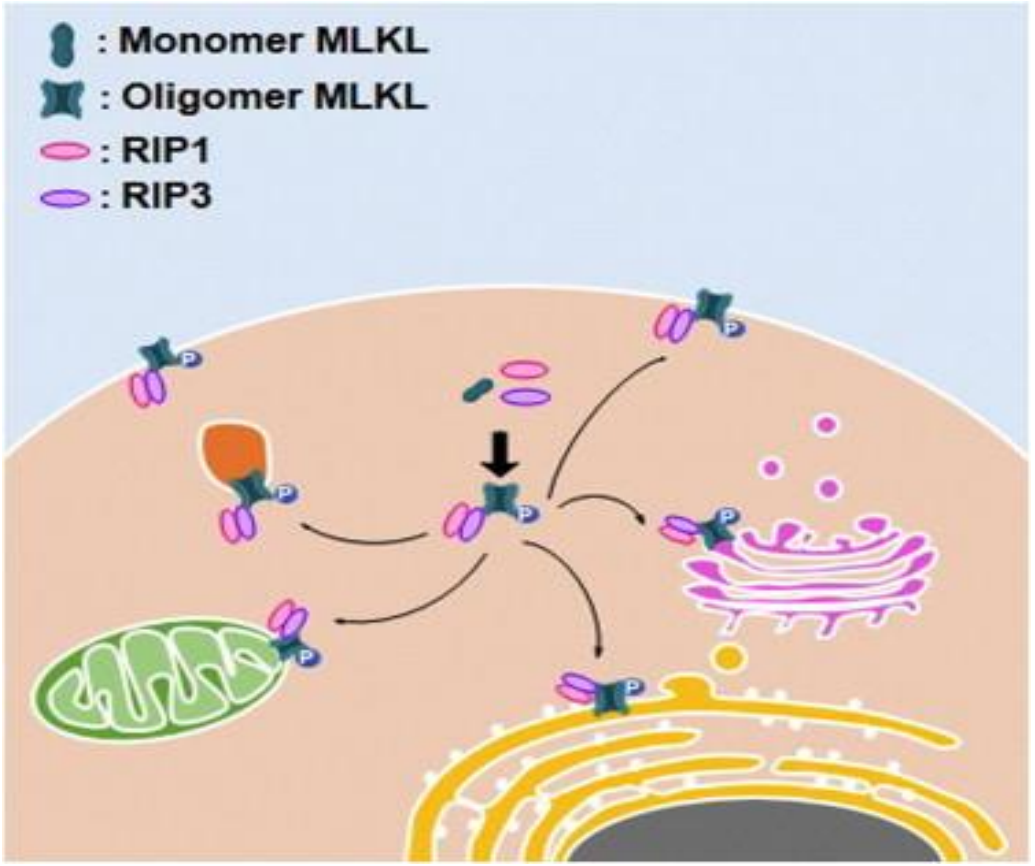
Production of TNF during viral infection leads to stimulation of its receptor TNFR1. The TNFR-associated TRADD signals to RIPK1 which recruits RIPK3. Necrosome contains RIPK1, RIPK2, MLKL (mixed lineage kinase domain-like).



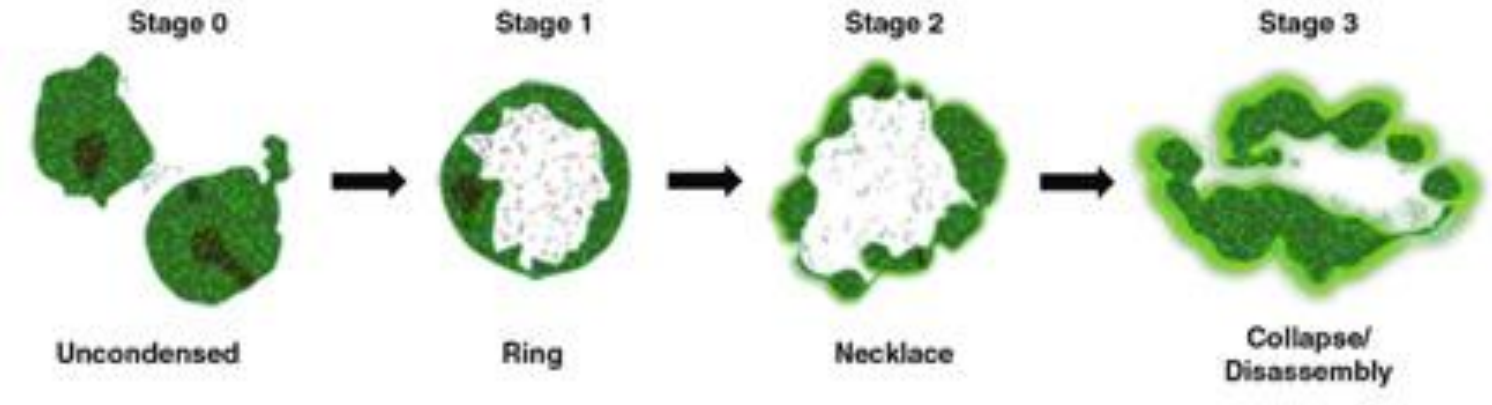
Necroptosis – programmed inflammatory cell death

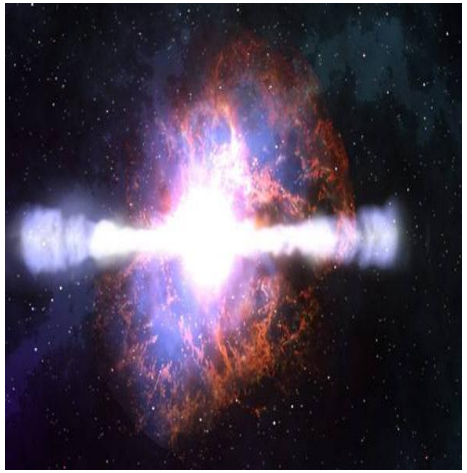
Phosphorylation of MLKL by RIPK3 drives oligomerization of MLKL, allowing MLKL to insert into and permeabilize plasma membranes and organelles. Integration of MLKL leads to the inflammatory phenotype and release of DAMPs, which elicits immune response.





Changes in cell nucleus during apoptosis





INDUCTION OF APOPTOSIS IN THERAPY

Tumor heterogeneity and evolutionary complexity may underlie treatment failure in spite of the development of many targeted agents. New strategy is based on using different ways to overcome tumor evolutionary complexity.

The majority of chemotherapeutic agents target mitotic cancer cells by inducing DNA damage pathways or altering cell cycle regulation. Chemotherapeutic agents induce apoptosis. Increased numbers studies have demonstrated that activation of apoptosis contributes to the cytotoxicity action of chemotherapeutic agents (intrinsic pathway p53)

INDUCTION OF APOPTOSIS IN THERAPY

Ionizing irradiation is able to cause cell death. DNA is the critical target, and the radiation generates both single and double-strand DNA breaks. The putative involvement of apoptosis in radiation-induced tumor growth inhibition has been controversial but it has recently generated significant interest among tumor biologists.

Recombinant, soluble TRAIL selectively induces apoptosis in transformed or stressed cells but not in most normal cells. In cancer patients, clinical trials using agonistic mAbs that engage the human TRAIL receptors DR4 and DR5 have also provided encouraging results. It is now evident that TRAIL suppresses autoimmune disease in various experimental animal models.

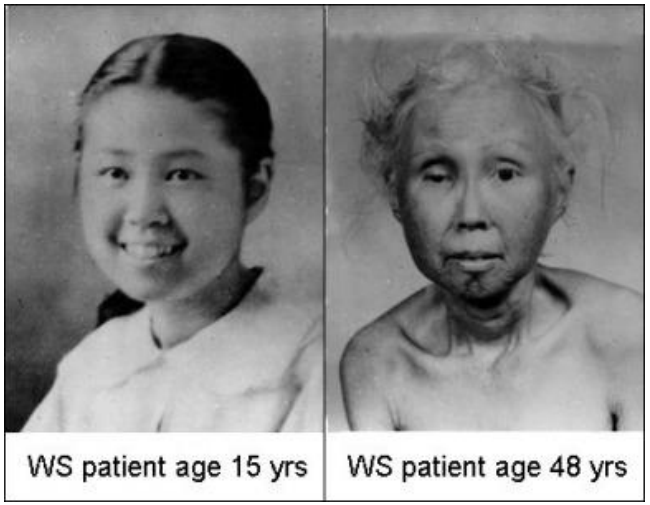
DNA mutations and senescence

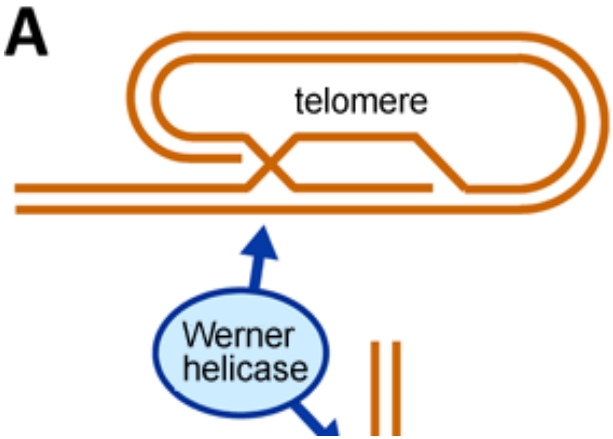
Unrepaired mutations, often in genes encoding DNA processing proteins, accumulate in cells and are responsible for process called entropic aging.

Embarrassing moments at gene parties

Werner Syndrome

Werner syndrome (WS), - adult progeria, autosomal recessive progeroid syndrome, characterized by the appearance of premature aging.

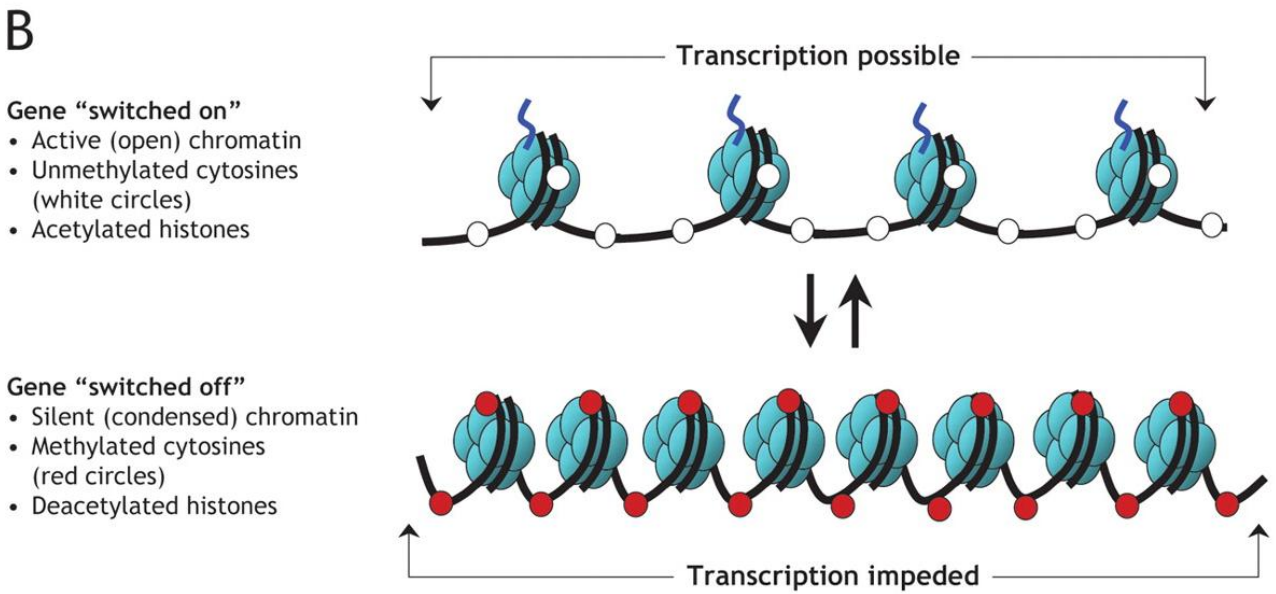




Different mutations in gene WRN, encoding, helicase, that functions in DNA repair of doubled stranded breaks.

WRNp interacts with several proteins involved in DNA processing: p53.

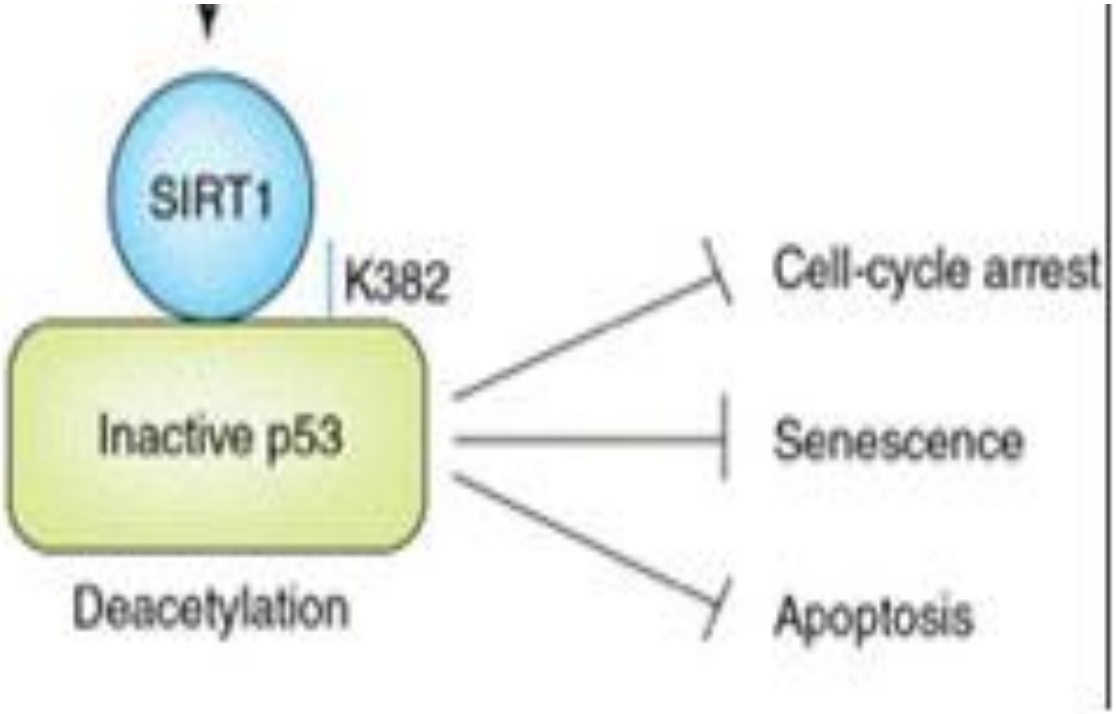
WRN helicase maintains telomeres length and stability. Thus, WRN helicase is important for preventing catastrophic telomere loss during DNA replication.



Epigenome and senescence

In aging people, simultaneously with the decrease in the DNA methylation, there are local points of hypermethylation of CpG islands, which are present in the promoters of genes. As a result the aging cells gradually lose the ability to express multiple genes (p53, transcription factors regulating the biogenesis of mitochondria, ATP production, antioxidants, NO synthase, lipoxygenase)

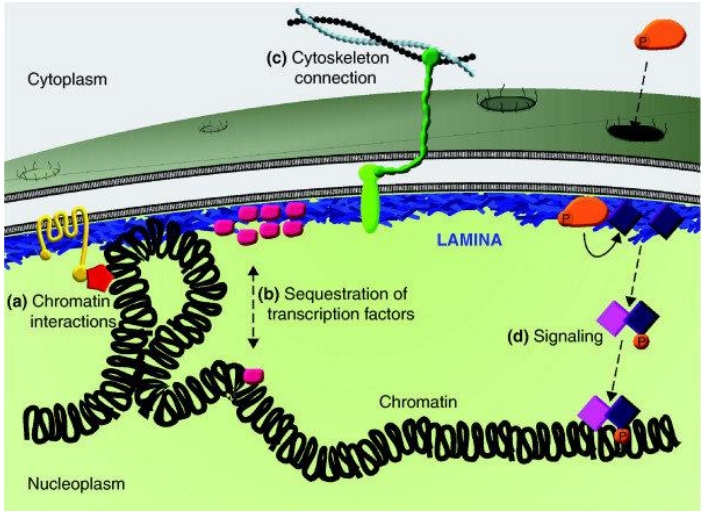
SIRT1 AND CELLULAR SENESCENCE



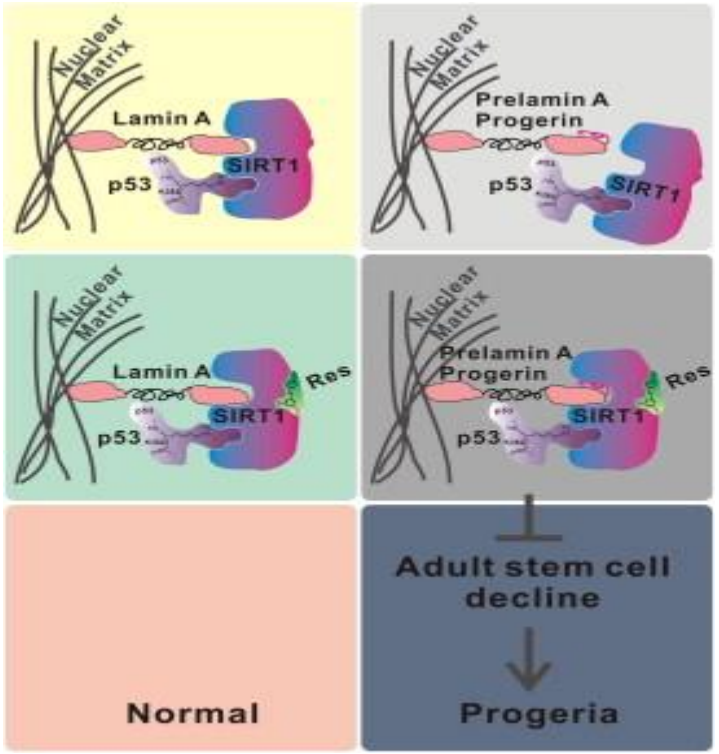
SIRT1 deacetylates p53. The deacetylated form of p53 has decreased transcriptional activity. SIRT1 promotes the survival of cells. It also deacetylates NF-κB and suppresses immune response and inflammaging.

ACTIVATORS OF SIRTUIN 1

Resveratrol - natural phenol, produced by plants in response to injury or to pathogens, present in the skin of grapes, blueberries. Resveratrol increases the expression of SIRT1 and enhances the binding between Sirtuin 1 and Lamin A.

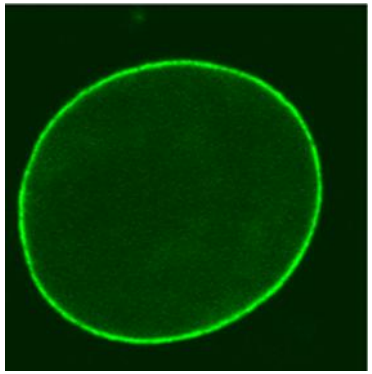


Lamin A

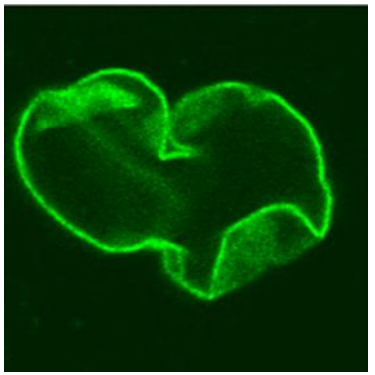


Hutchinson Gilford Progeria Syndrome

Genetic disease, which symptoms resemble aging. People born with progeria typically live to their mid teens and early twenties. Children with progeria usually develop the first symptoms during their first few months.



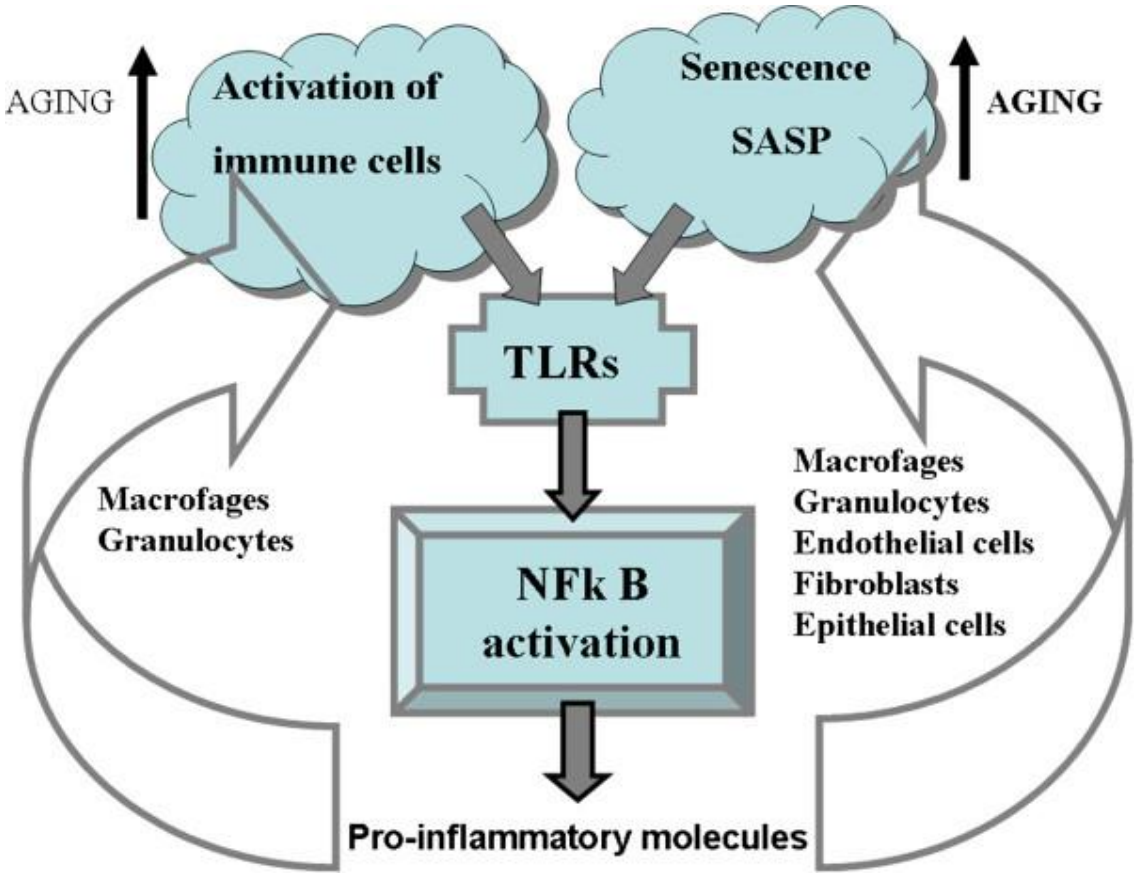
The cause of progeria - a point mutation in the LMNA gene - cytosine is replaced with thymine



Transcriptional factor NF-κB and aging

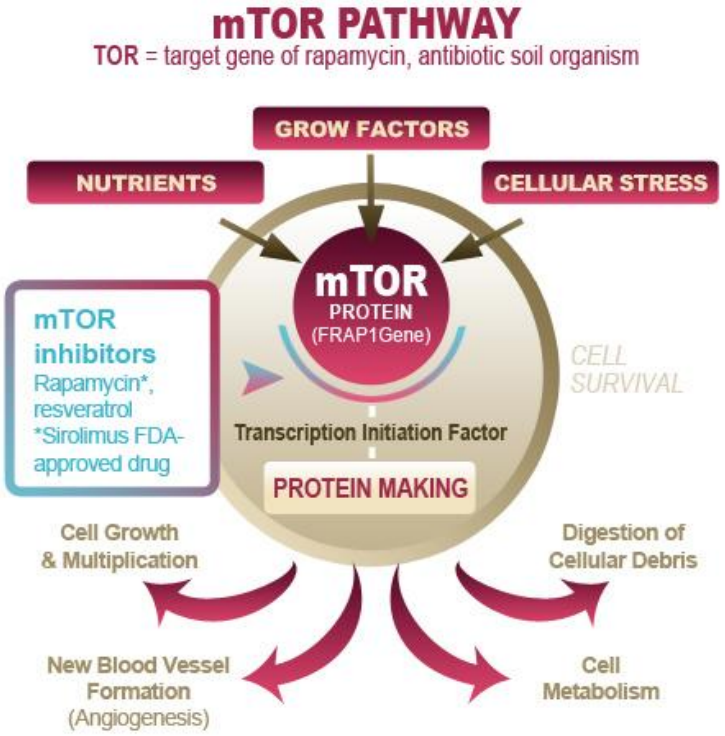
nuclear factor kappa-light-chain-enhancer of activated B cells
protein complex that controls cytokine production and cell survival.

NF-κB promotes the cell survival and regulates the immune response to infection. Incorrect regulation of NF-κB has been linked to cancer, inflammatory, and autoimmune diseases, and inflammaging.



mTOR and ageing

mechanistic target of rapamycin, also known as mammalian target of rapamycin



mTOR is a serine/threonine protein kinase that regulates cell survival and autophagy.

mTOR's role in aging

mTOR causes:

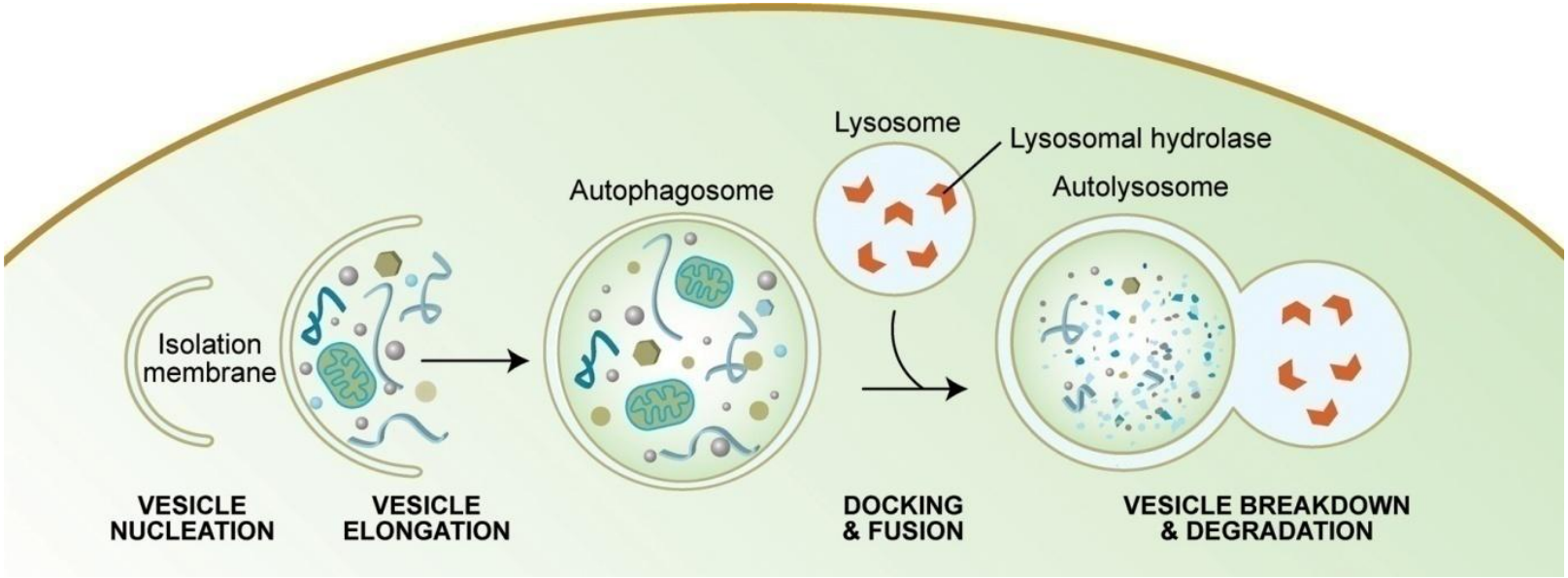
1.the accumulation of unfolded proteins in ER

2. increases production of ROS and oxidative damage to proteins, lipids and DNA

3. inhibits the autophagy and cell components renewal.

Autophagy

mechanism of degradation of cellular components through the actions of lysosomes

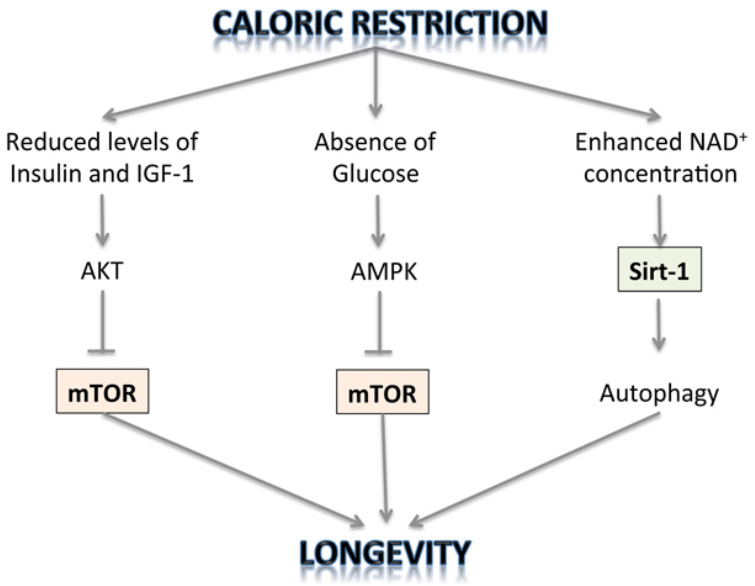


Autophagy promotes cellular survival during starvation and allows the degradation and recycling of cellular components.

Probably autophagy is required for the lifespan-prolonging effects of caloric restriction

Caloric restriction

dietary regimen that is based on low calorie intake.



Caloric restriction (CR) without malnutrition has been shown to decelerate the aging process, resulting in longer maintenance of youthful health and an increase in maximum lifespan of yeast, fish, rodents and dogs.

In humans the long-term health effects of moderate CR with sufficient nutrients are unknown.