Programmed and unprogrammed cell death

Programmed cell death

mediated by specific cells

signaling system beneficial for the organism

has been described in plants and animals

participation in ensuring homeostasis

participation in developmental processes

removal of damaged / infected cells

Unprogrammed cell death

arises unregulated from external causes (insults)

Types of cell death

apoptosis (mediated by **caspases** during development, aging, or in response to specific stimuli)

autophagy (degradation of cellular components in lysosomes)

excitotoxicity (al cell death due to excessive activation of receptors for neurotransmitters)

anoikis (result of the breakdown interactions that anchor cell in the matrix)

necrosis (trauma-induced nonspecific)

necroptosis (necrosis induced by specific stimuli, without the involvement of caspases)

Other types of cell death

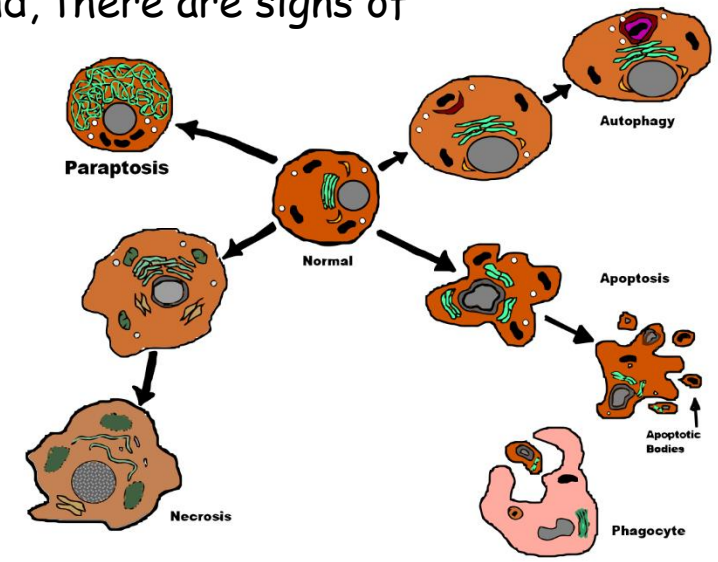
Aponecrosis

– does not occur completion of cell death, in the end, there are signs of necrosis

Paraptosis

– It has nothing to do with apoptosis

- striking vacuolation and swelling of mitochondria



Necroptosis

– Similarity to apoptosis

- Necrosis induced by external stimuli through death receptors, if apoptosis does not occur

Pyroptosis

- Programmed cell death associated with antimicrobial responses

Autophagy

– Catabolic mechanism for the degradation of the cell and recycling of cellular components

Mitotic catastrophe

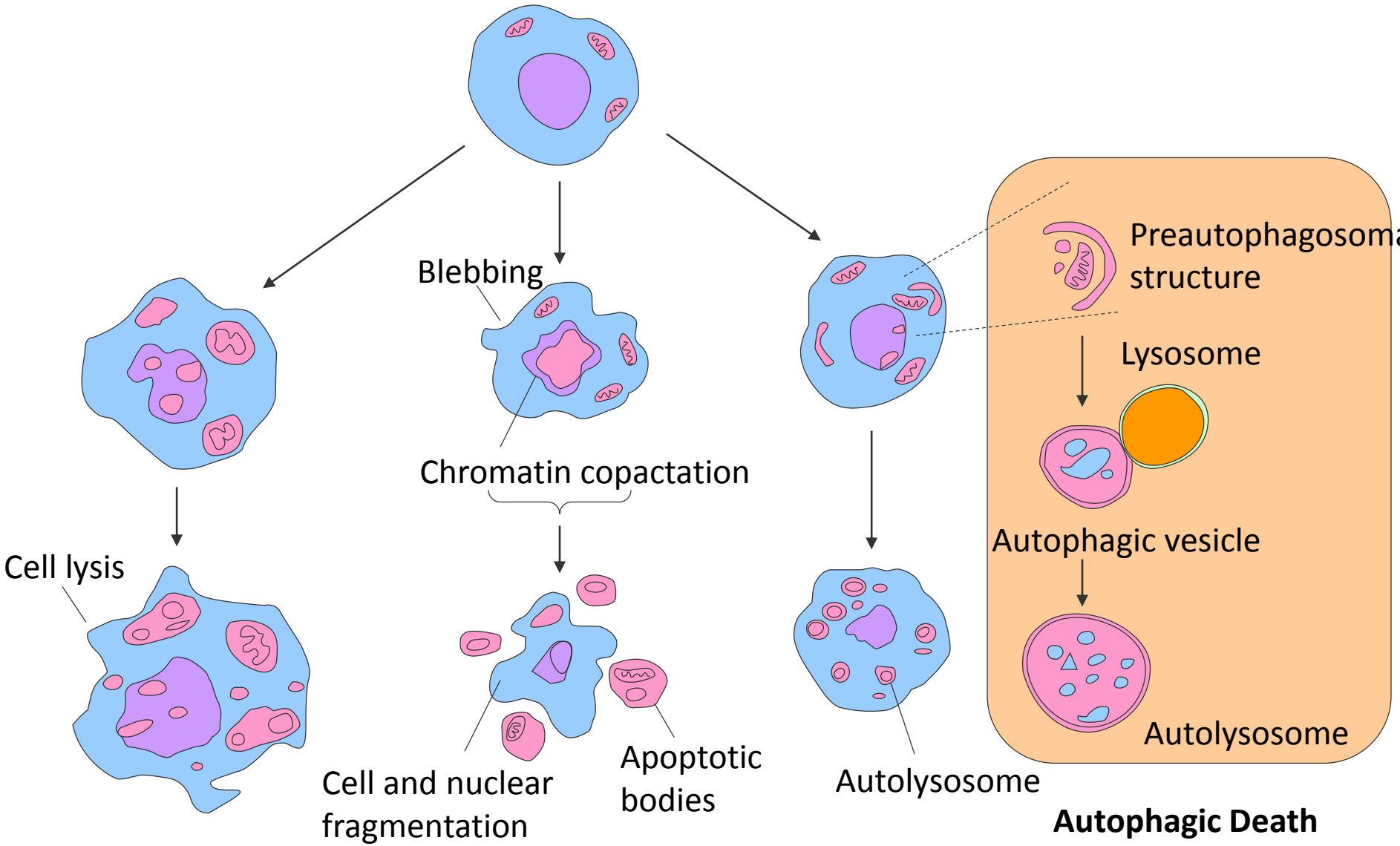
Cornification

Anoikis

– Programmed cell death caused by loss of contact

TEST

Different forms of cell death



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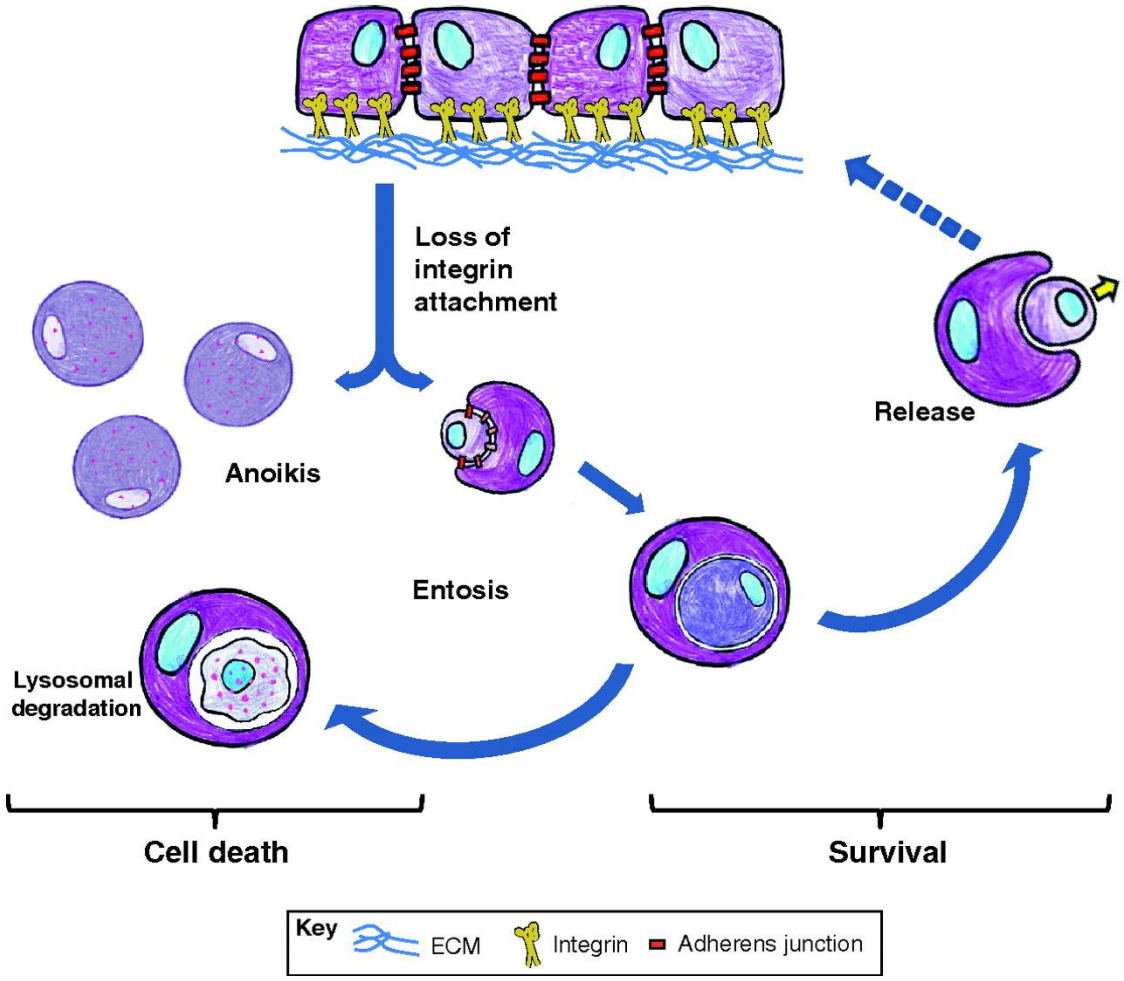
The potential dual role of **entosis.**

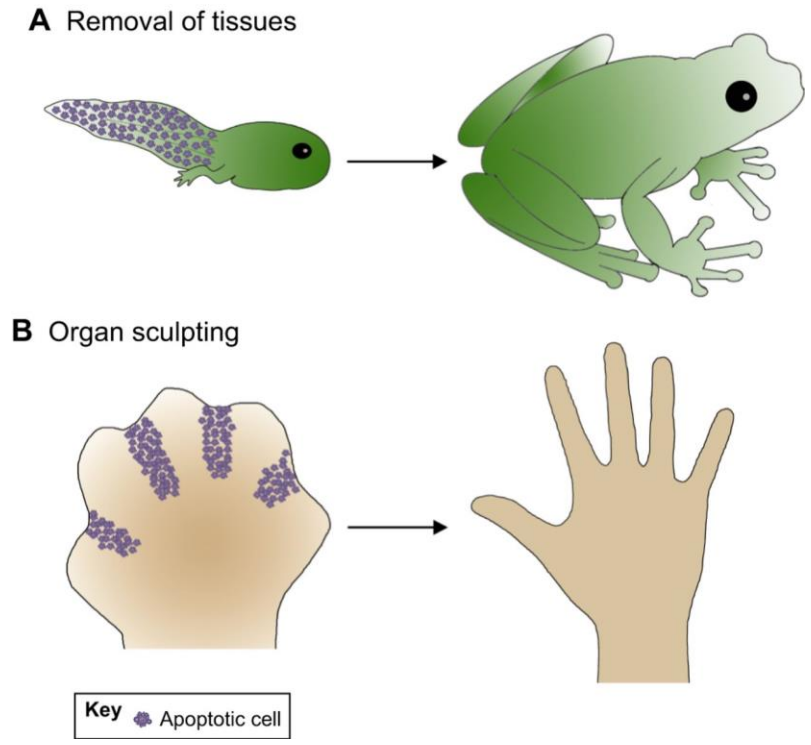
When epithelial cells lose their attachment to the ECM, cells can undergo, instead of anoikis, the process of entosis, which is favored by forces that are associated with adherens junctions. In this intermediate state, where one cell is inside another, an important decision can be made: the internalized cell can either die or be released from the host cell, and potentially reattach to ECM, pointing to a protective role of entosis.



APOPTOSIS

Physiological proces → regulation of cell homeostasis

(Counterpart to cell division)



Part of embryogenesis and organogenesis:

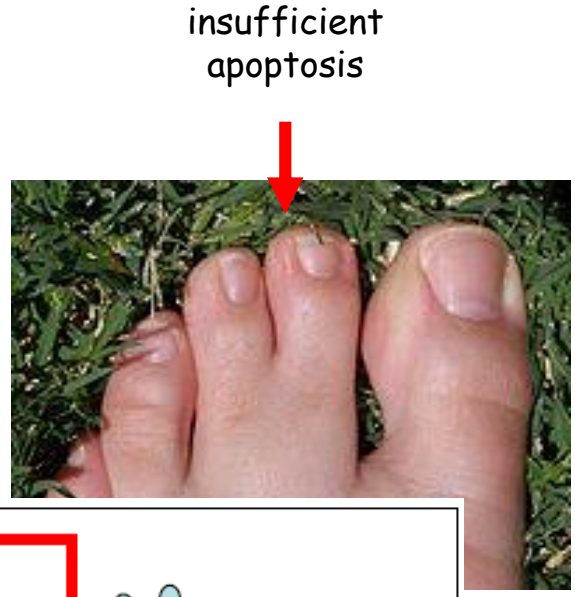
- It is necessary in the production of body cavities during morphogenesis of fingers and toes
- Neuronal death during the formation of the CNS
- Cell death during the development of limbs
- Hormonally regulated during the tadpole tail loss
- Atrophy - atrophy of the mammary gland in menopause, endometrial cell death during menstruation

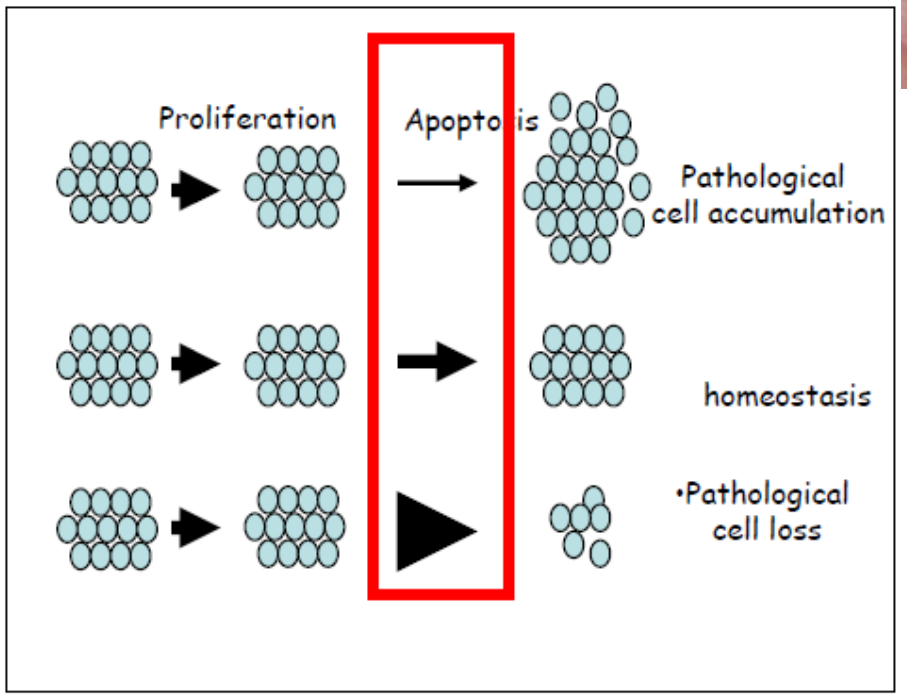
Apoptosis eliminates harmful cells:

- death of cells detected as cells infected by virus
- cells with damaged DNA

Apoptosis in pathology

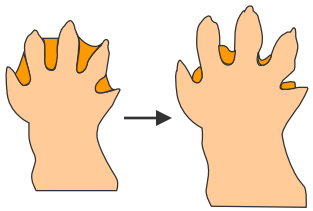
- **Insufficiency** can lead to malignancy, or autoimmune diseases; common are adhesions toes (fig.)
- Conversely, **excessive** apoptosis contributes to neurodegenerative diseases (Alzheimer, Parkinson, Huntington's disease), AIDS, certain autoimmune diseases, spinal muscular atrophy, multiple sclerosis ...



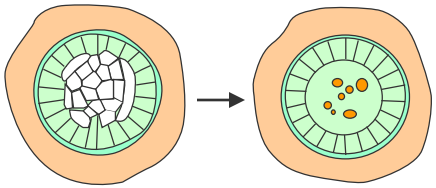


Programmed cell death during animal development

Sculpting

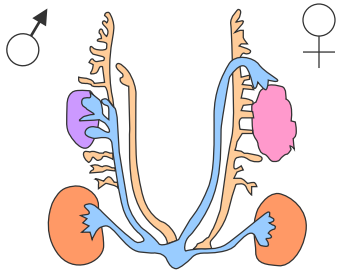


A

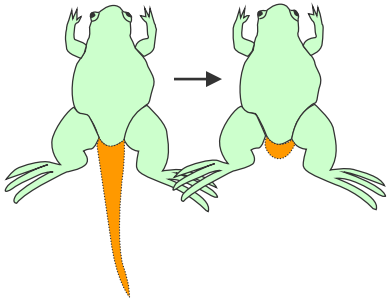


B

Deleting structures

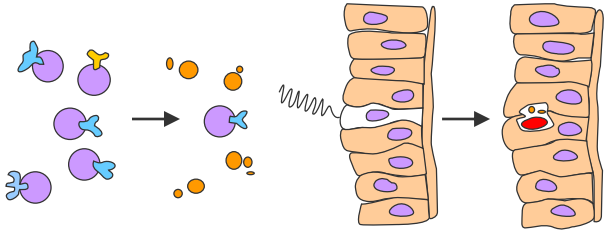


C



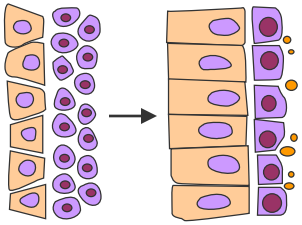
D

Eliminating dangerous or injured cells



E F

Adjusting cell numbers

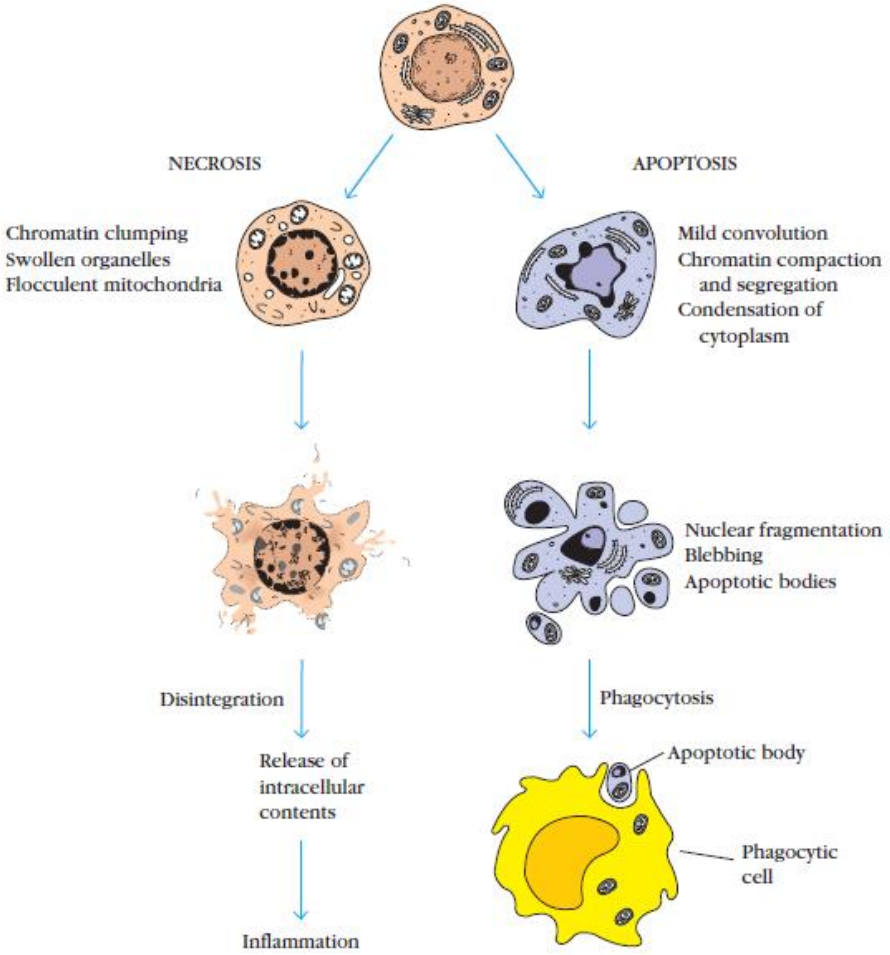


G

Apoptosis vs. necrosis

Apoptosis

- Programmed cell death
- It affects individual cells
- Induction by physiological stimuli
- No inflammatory reaction
- Active process - consumption of ATP



Necrosis

- It refers to a group of affected cells
- Caused by non-physiological injury (viral infections, hypoxia, metabolic poisons ...)
- inflammatory reaction

Apoptosis

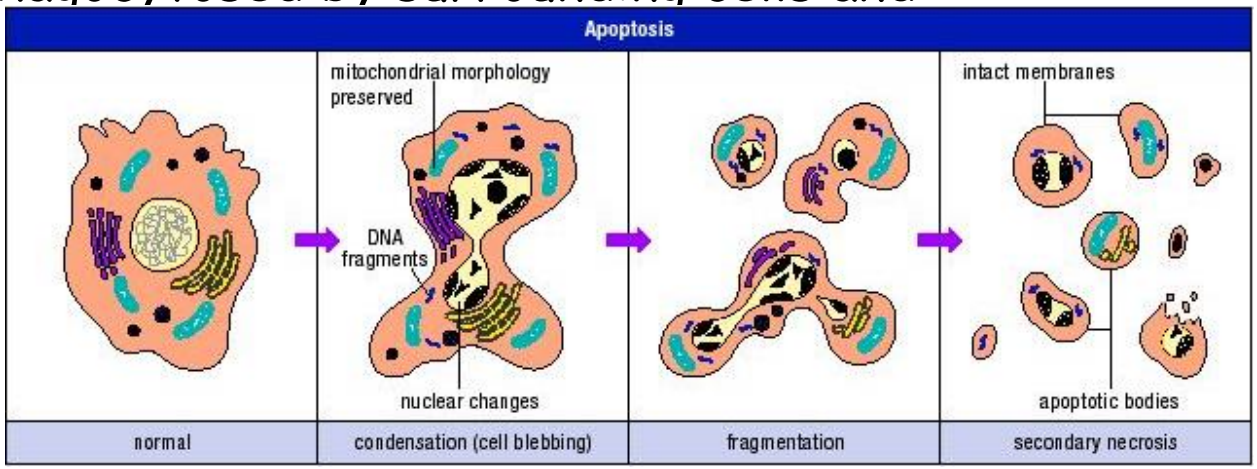
Morphological features:

Condensation of the cell and nucleus membrane pouch (,, blebbing ")

Condensation of chromatin, fragmentation of nuclei

Disintegration of cells to apoptotic bodies → membrane does not lose its integrity

Apoptotic bodies are phagocytosed by surrounding cells and macrophages



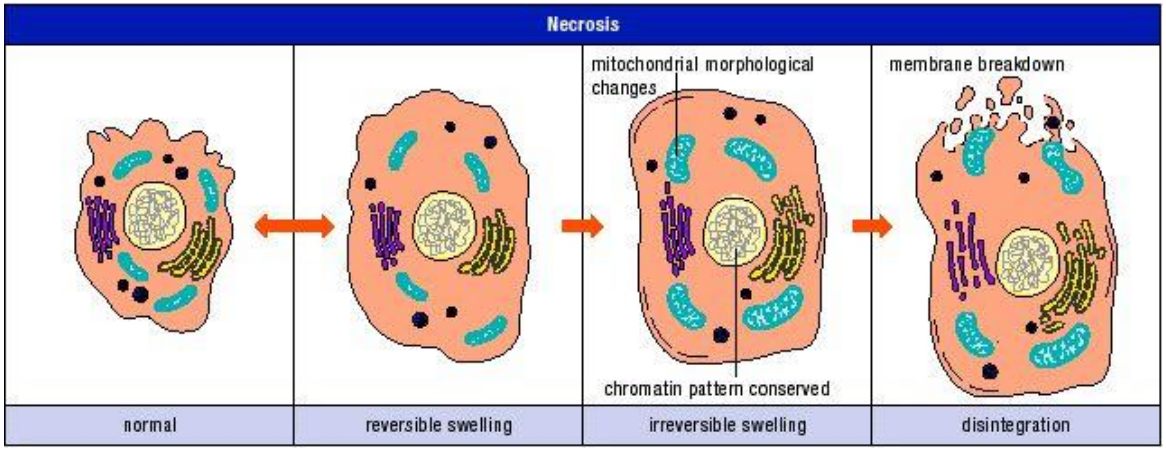
Biochemical features:

- Strictly regulated active process requiring energy
- Nonrandom DNA fragmentation (charts electrophoresis)
- Release of specific factors from the mitochondria into the cytoplasm
- activation of caspases

Necrosis

Morphological features :

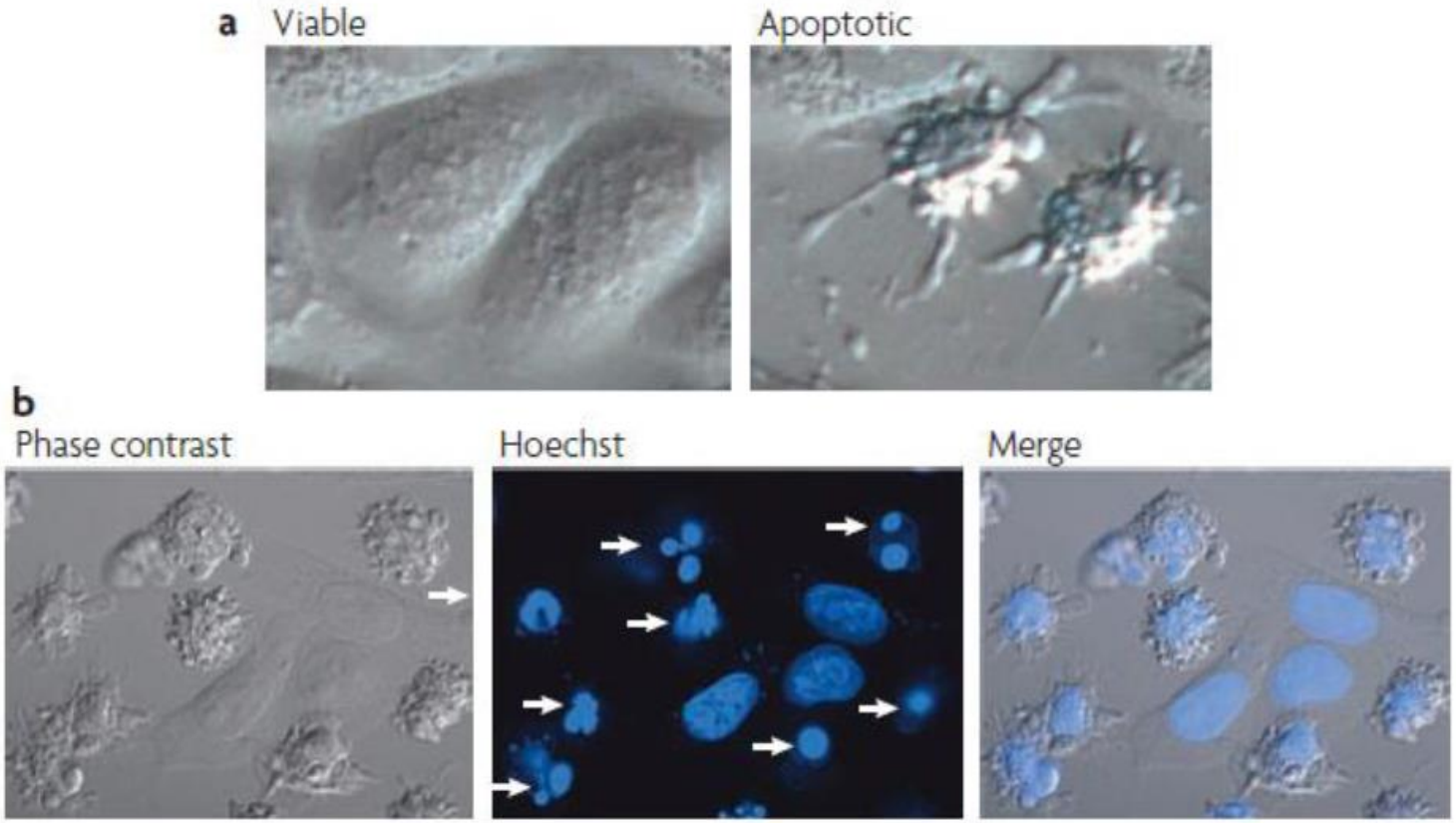
- It starts swelling cytoplasm and mitochondria
- Organelles disintegrate, they do not form vesicles
- Loss of integrity of the cell membrane
- Ends complete lysis



Biochemical features :

- Loss of homeostasis regulation
- Passive process (does not require energy)
- Random degradation and fragmentation of DNA

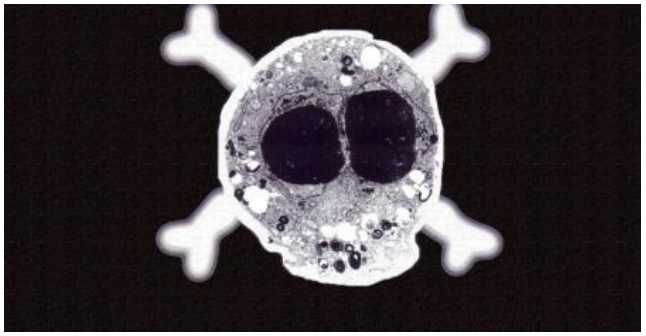
Apoptotic cells under microscope



(Taylor RC, Cullen P, Martin SJ, 2008)

Regulation of apoptosis

Apoptosis induced:
Loss of contact with the outside environment (anoikis)
irreparable damage
Simultaneous reception of signals for the division and apoptosis
Receiving death signals



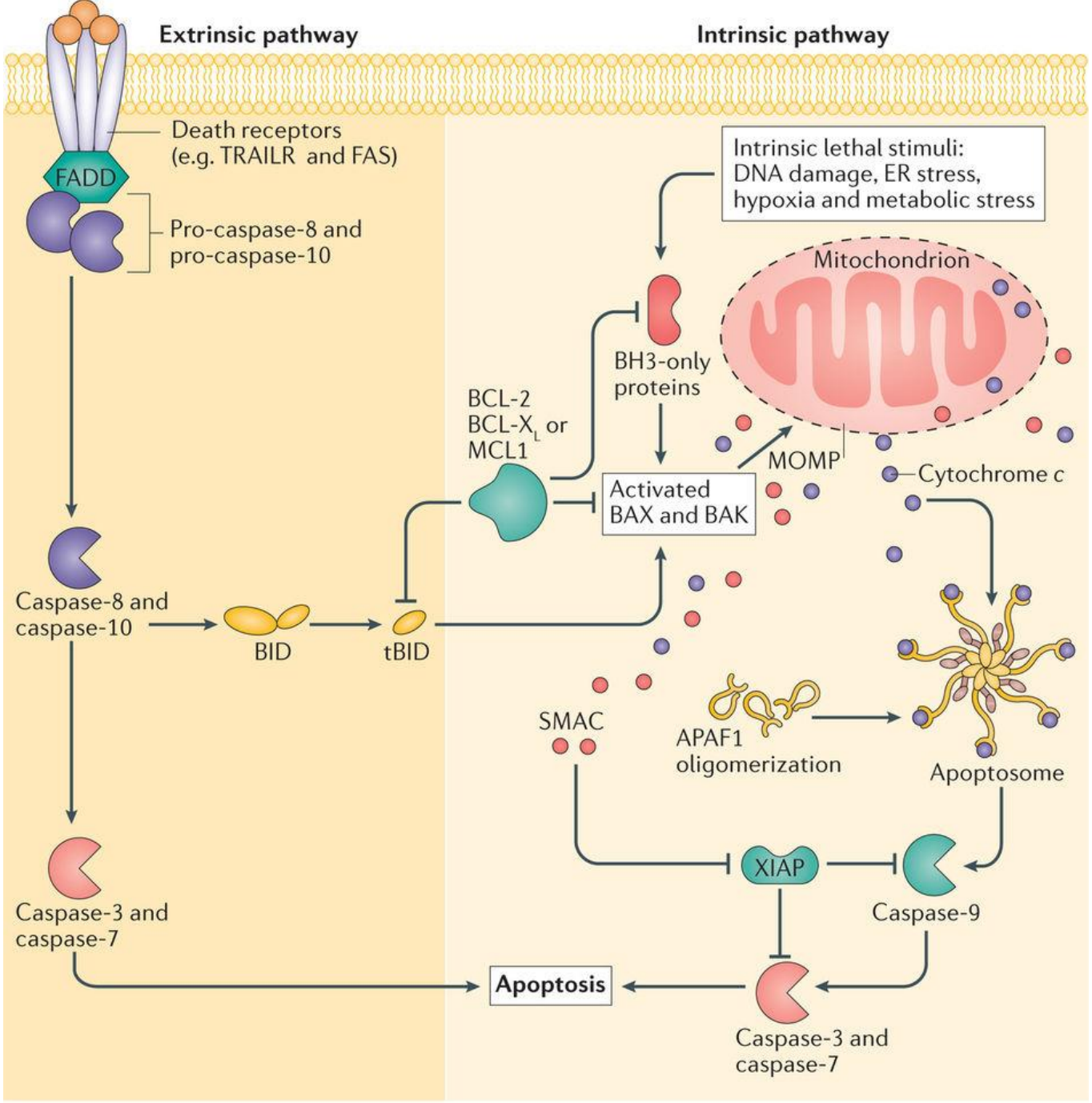
intrinsic
They come from their own cells
"Voluntary" death

extrinsic
They come from surrounding cells from the external environment

Main apoptotic pathway

Extrinsic receptor: ligand binds to the **death receptor** and proapoptotic signal is formed. This leads to the activation of death domain for the participation of other proteins. The goal is the activation of **procaspases 8**.

Intrinsic pathway: by signaling (e.g. via p53) is initiated apoptosis, whose component is the **Bcl-2/Bax**, key organelle is **mitochondria**, **apoptosome** complex is formed and the goal is the activation of **procaspases 9**.



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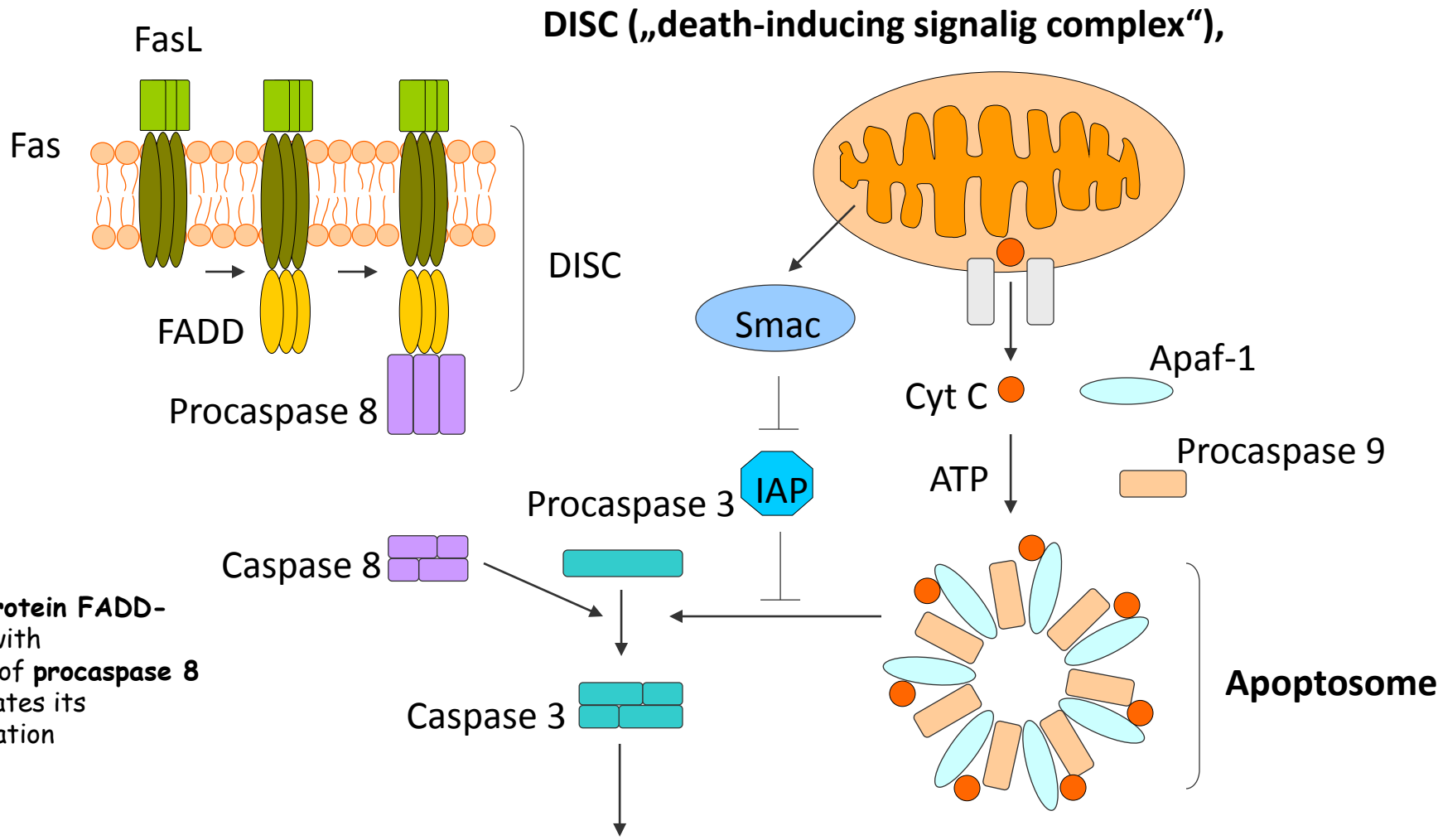
TEST

Caspase activation by the extrinsic and intrinsic pathways



adapter protein FADD- interacts with monomers of **procaspase 8** and stimulates its oligomerization

Cleavage of proteins leading to cell death

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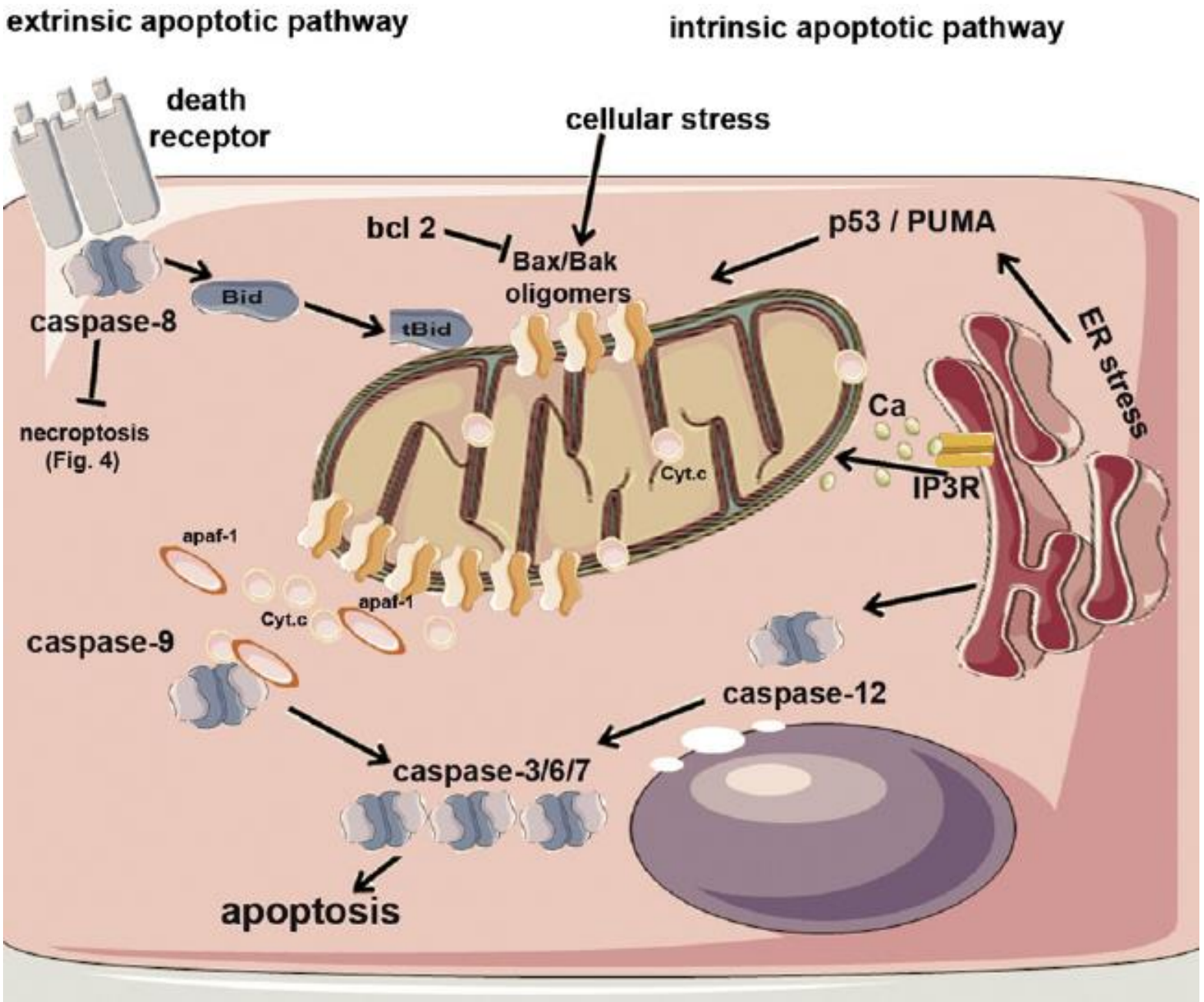

extrinsic apoptotic pathway
intrinsic apoptotic pathway
death receptor
cellular stress
bcl 2
Bax/Bak oligomers
p53 / PUMA
Bid
tBid
caspase-8
necroptosis (Fig. 4)
Cyt.c
Ca
IP3R
ER stress
apaf-1
apaf-1
Cyt.c
caspase-9
caspase-12
caspase-3/6/7
apoptosis

Extrinsic (the receptor) pathway of apoptosis

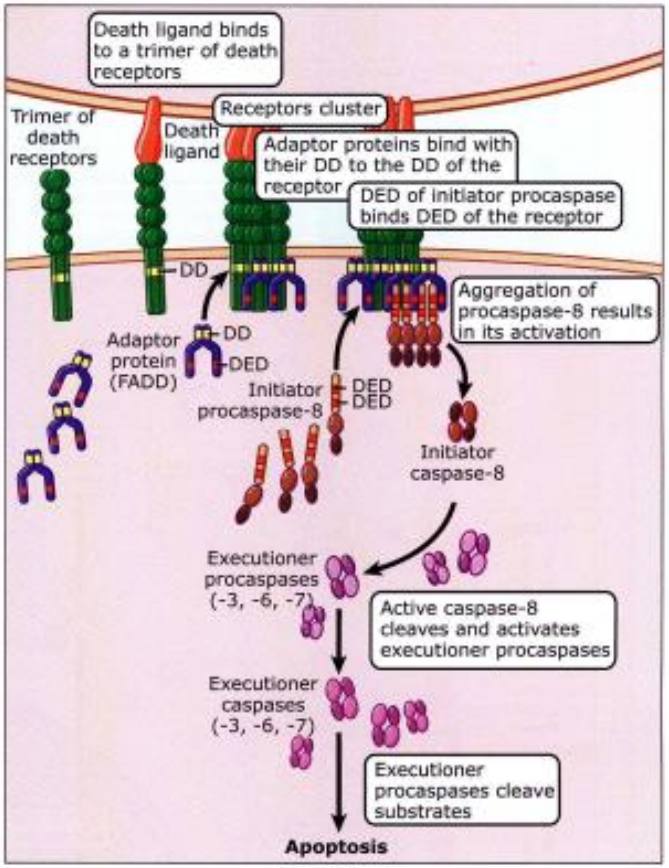
- activated by extrinsic **(„death") ligands**
- registration of ligand **by death receptors (TNF family) – Fas and TRAIL**
- receptors form trimers after activation
- 2 or 3 trimers are connected by ligands
- intracellular domain of death receptors are activated
- – they interact with other proteins – etc.

adapter protein FADD

- FADD interacts with

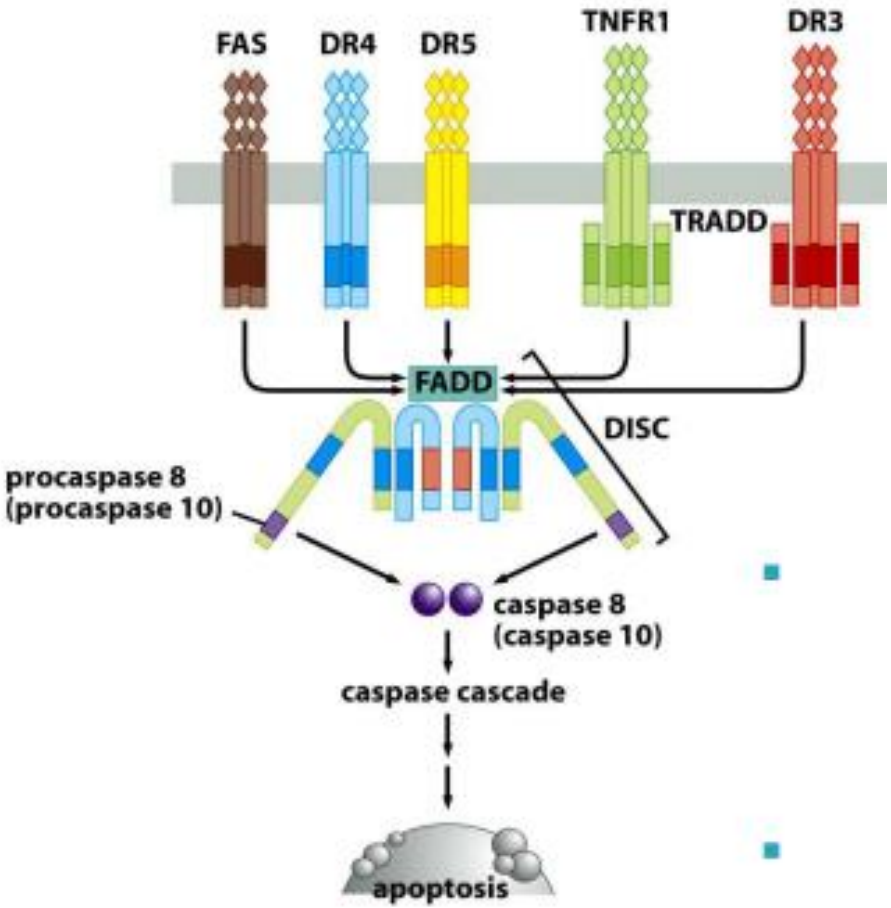
monomers of **procaspase 8** and stimulates its dimerization

dimerizatio **activates caspases 8,** which activates executioner caspases (procaspase-3).

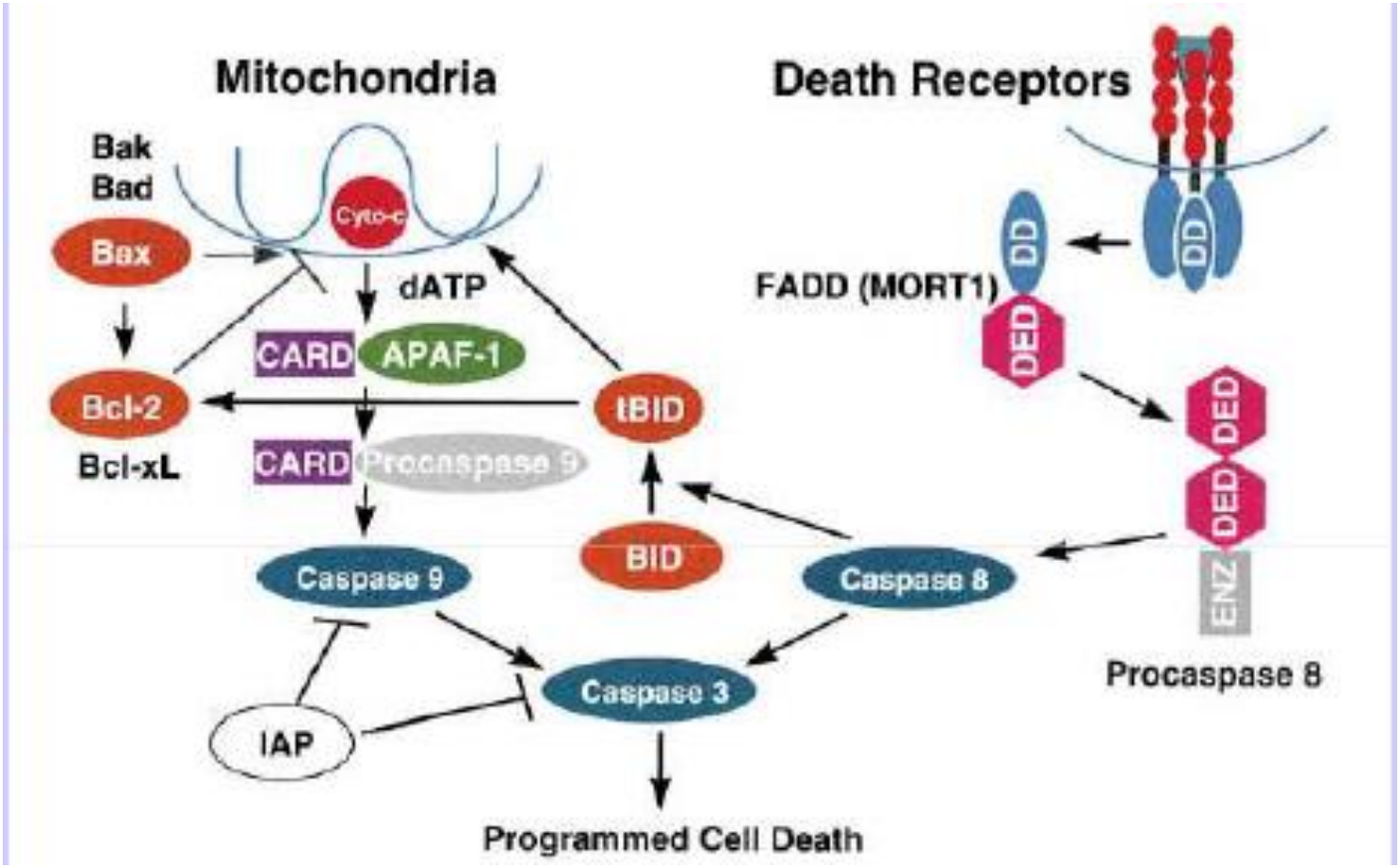


Death receptors

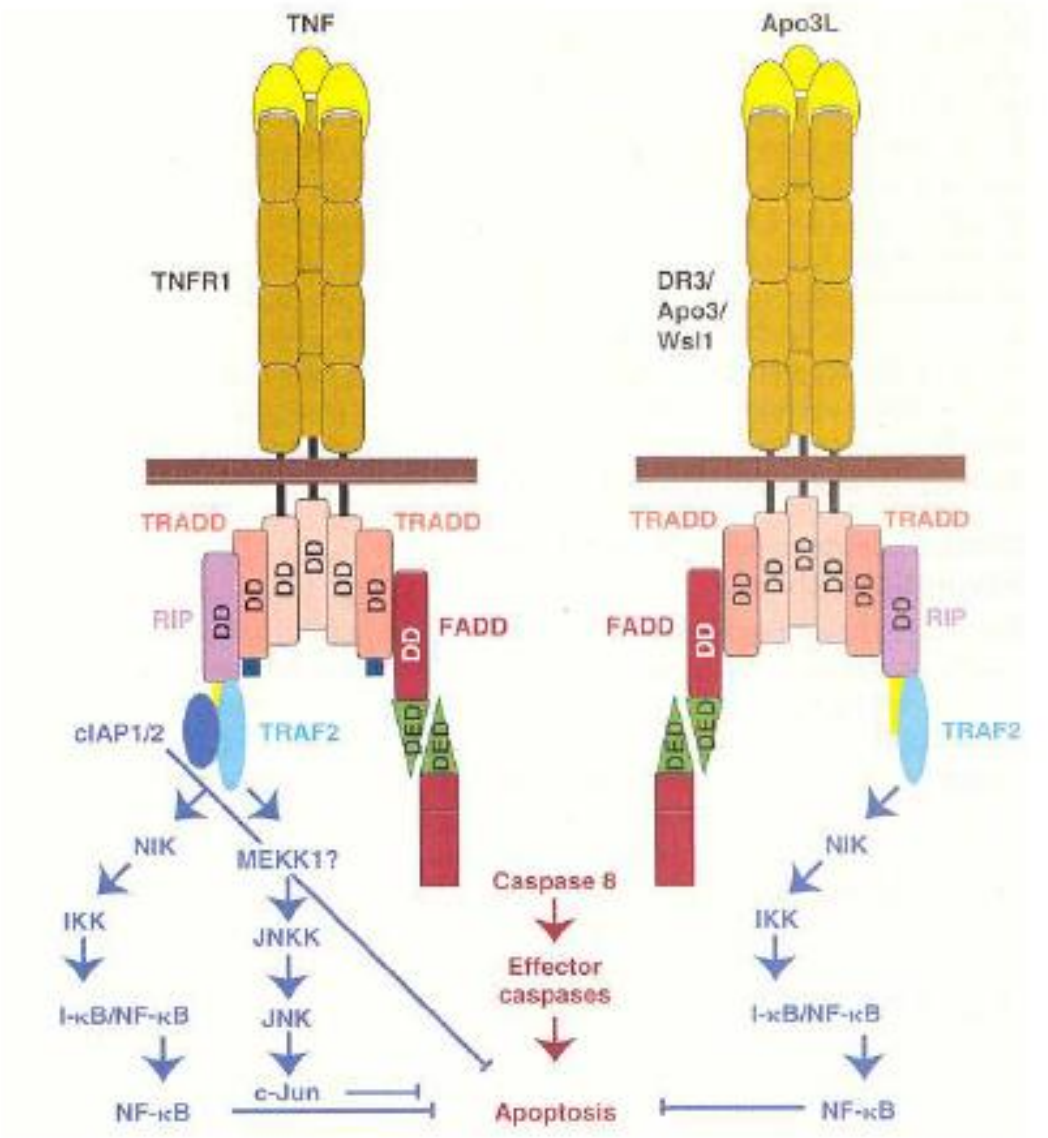
- transmembrane surface receptors
- transmits signals induced apoptotic death ligands they belong to the family of receptors **TNF** (tumor necrosis factor)
- They can activate caspases within seconds of ligands binding, causing removal of the cell within a few hours
- contain homologous cytoplasmic death domain, which allows them to directly interact with apoptotic apparatus
- extracellular cysteine-rich domains (in number of two to five copies)
- intracellular **death domain**



Signaling pathways in apoptosis

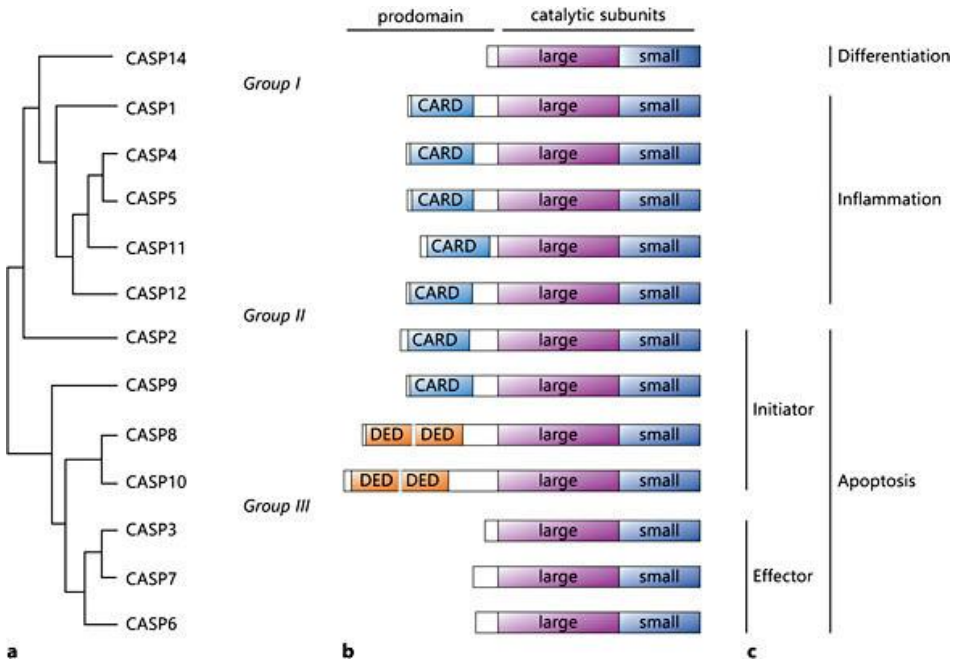


TNFR and DR3 signalization



Caspases

- group of proteins which function in initation and progress of apoptosis
- **cysteine proteases**
-specifically cleaves **aspartic acid** in their substrates
- synthesized in an inactive form as **zymogens**
- dividing by the physiological role: **inflammatory and apoptotic**
- division according apoptosis: the **initiator** and **effector**
-initiator **caspases are -2,-8,-9 and -10**
-effector **caspases** are **-3,-6 and -7**

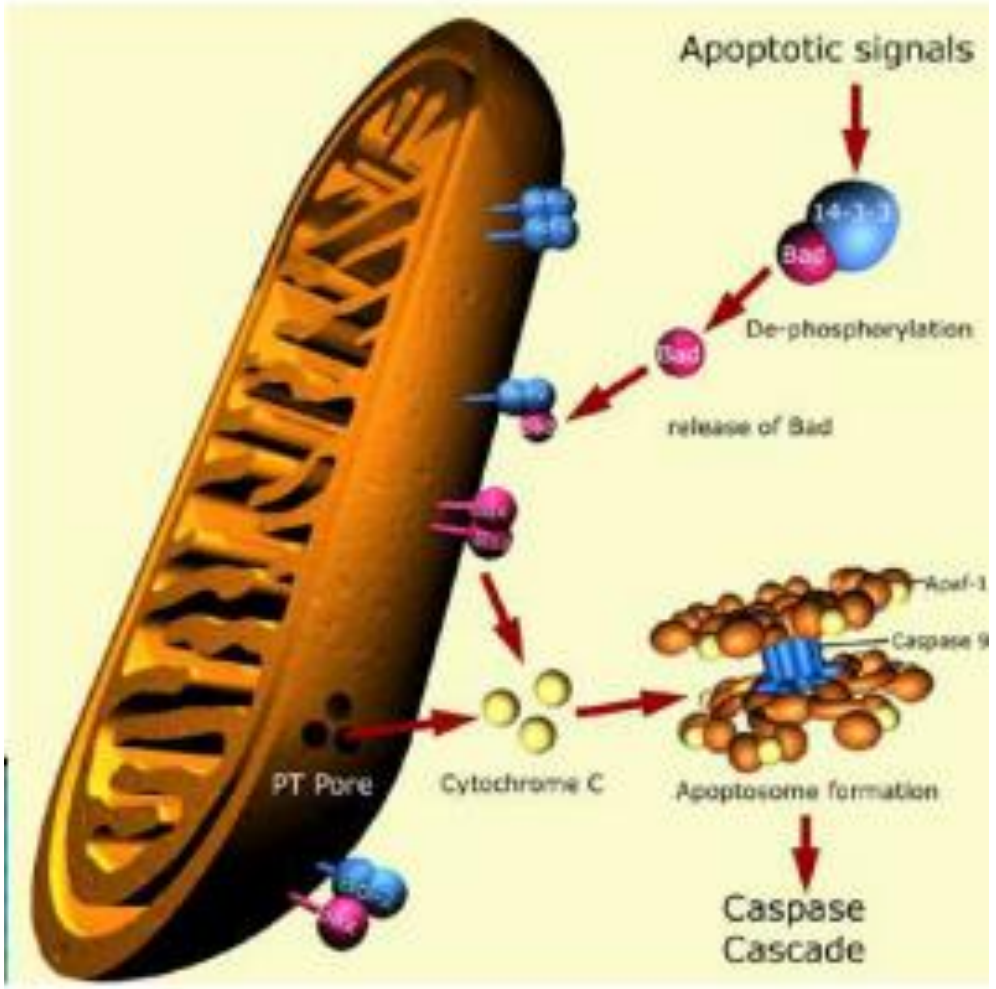


Intrinsic (mitochondrial) signal apoptosis pathway

The main elements are the mitochondria and cytochrome c in the space between the outer and inner membrane

translocation of cytochrome c into the cytosol
It is a critical event path

Bad
Cytochrome c
Apoptosome
caspases



cytochrome c

Cytochrome c is normally located in the space between the inner and outer membrane of mitochondria,
which is involved in electron transport in **oxidative phosphorylation**

permeabilized external mit. membrane diffuses into the intermembrane space cytosol

Cytochrome c binds to **Apaf-1**
("Apoptotic protease activating factor")

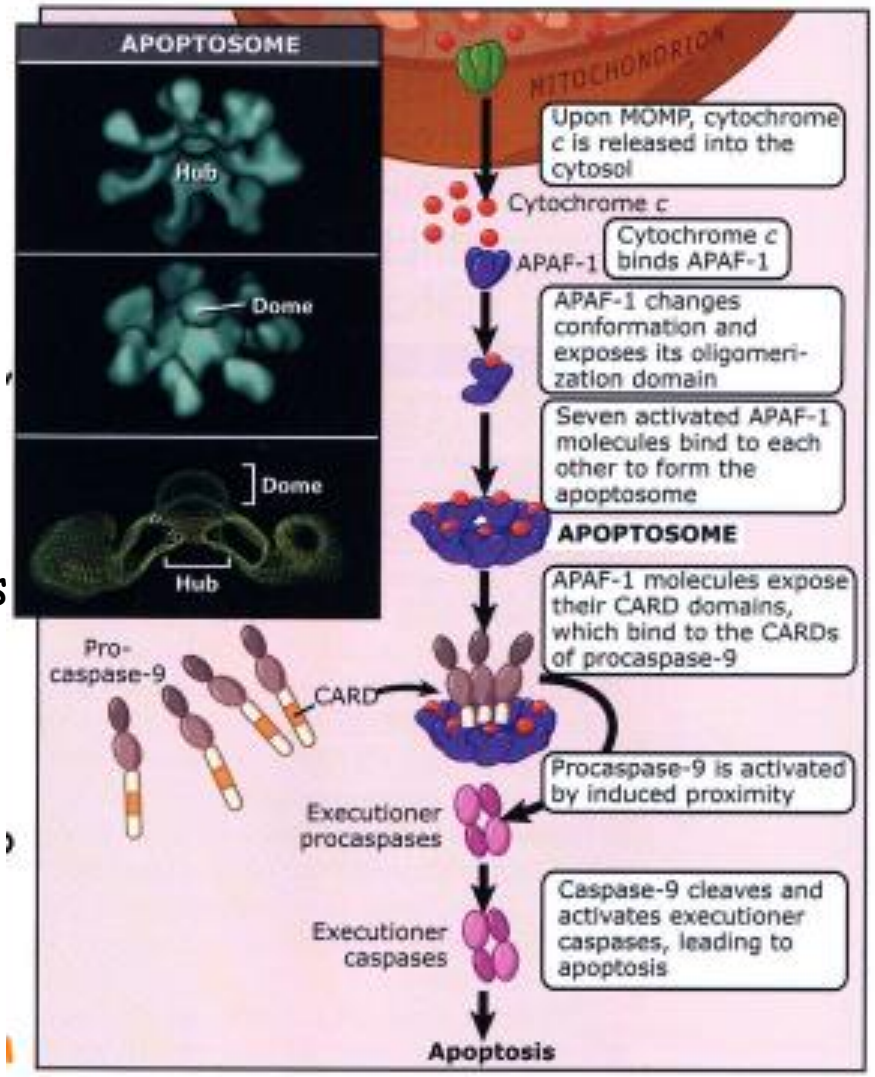
Apaf-1 alters the conformation-enable links dATP
bond dATP conformation with Apaf-1 below changes - baring oligomerization domain

7 molecules of Apaf-1-links formed **apoptosome**

apoptosome binds initiation **procaspases 9**

molecules procaspases 9 in apoptosome come in close proximity,
leading to their activation

caspase-9 activates the execution caspases (caspase 3 and 7



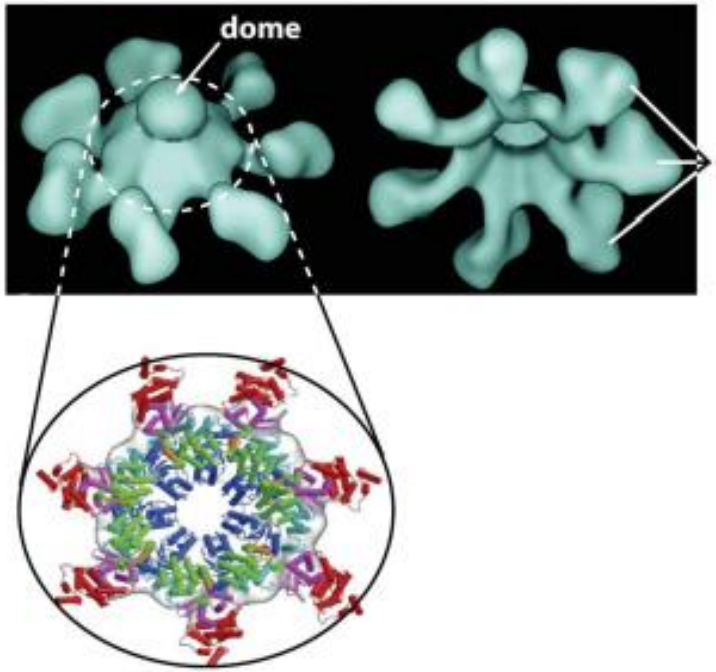
Apoptosome

cytochrome c released from the mitochondria into the cytosol binds to Apaf-1

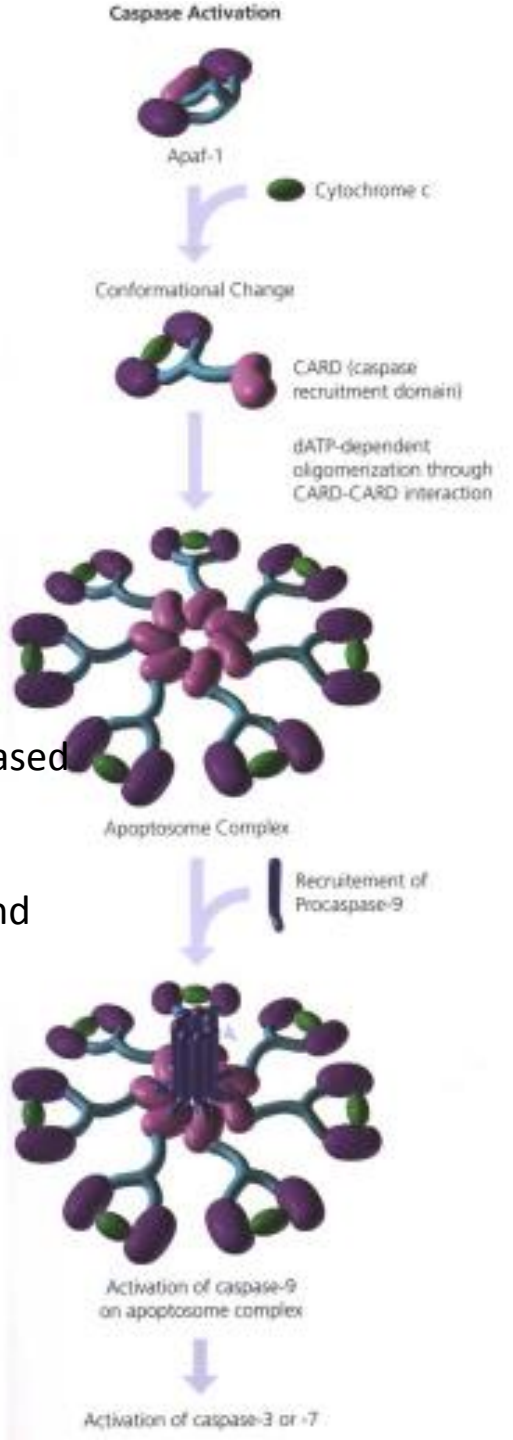
Apaf-1 alters the conformation and oligomerized

in the presence of dATP complex of cytochrome c/Apaf-1 binds and activates **procaspases 9** ("apoptosome")

activated caspase 9 activates another caspase responsible for apoptotic cell death (caspase 3 or 7)



Apoptosome is formed in Cytosol, Cytochrome C is released from mitochondria and associates with Apaf-1, So creates a seven-branched round wherein the arms are formed seven subunits Apaf-1 and their vertices form cytochrome C (red). This round attracted procaspases 9 which binds the middle/wheel axis (blue) and activated caspase 9



What decides the cytochrome c release?

proteins Bcl-2

the ratio of anti-apoptotic ("pro-survival") and pro-apoptotic proteins act mutually heterodimers and mitochondrial permeability

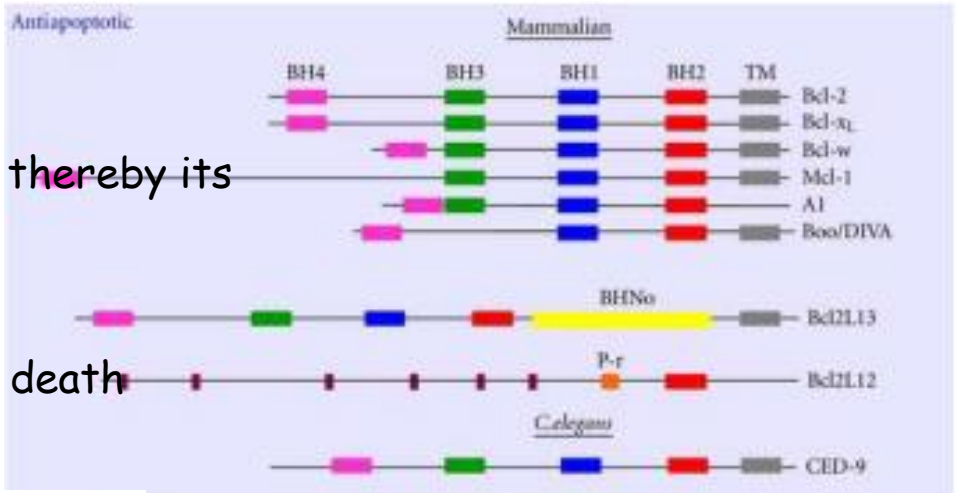
membrane cytochrome c

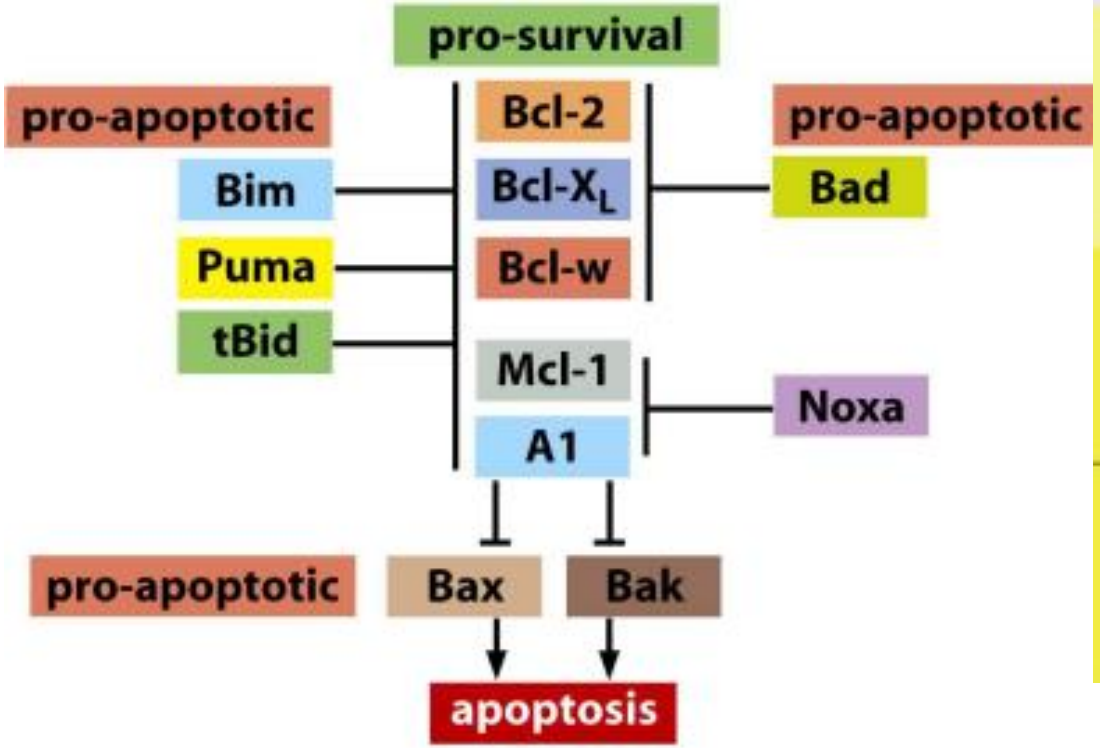
Table 4.1. Selected proteins in the Bcl-2 superfamily

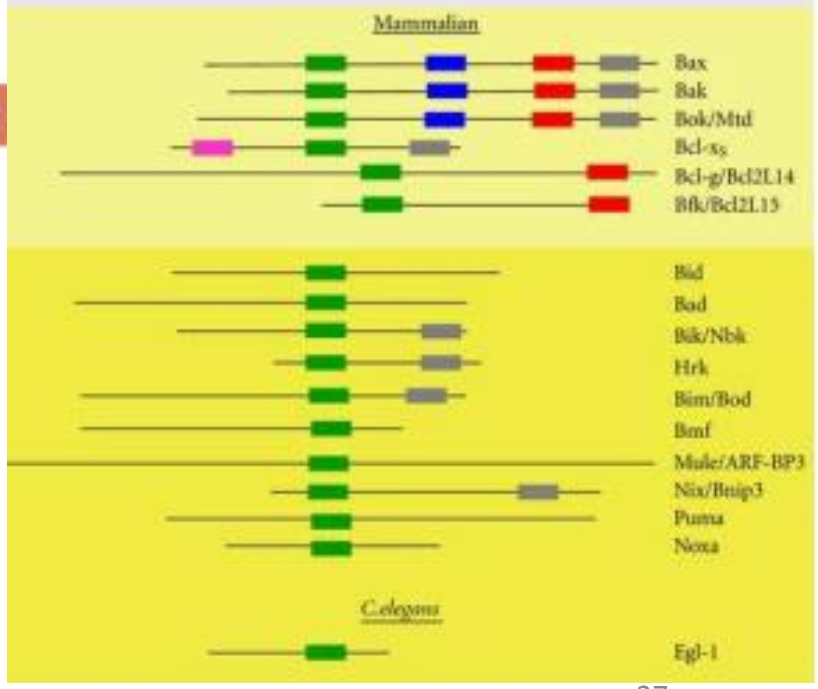
Pro-apoptotic	Anti-apoptotic
Bax	Bcl-2
Bak	Bcl-X_L
BOK	Bcl-W
BIM	MCL-1
BID	Bcl-B
BAD	+ viral homologs
NOXA	
PUMA	

Bcl-2 protein forms dimers

through BH3 domains or homodimers
heterodimers
homodimers Bax induce apoptosis
Bcl-2 constitutes a protein Bax heterodimer, thereby its
pro-
apoptotic activity inhibit
ratios factors "pro-death" and
"Pro-survival" Bcl-2 family decisions about cell death







Bcl-2 family

- pro-apoptotic signals causes **depolarization of the external mitochondrial membrane** and the assembly of such dimers of proteins Bcl-2,
which facilitate transfer membrane cytochrome c into the cytosol, where it combines with other proteins and initiates a cascade of reactions leading to apoptosis
  anti-apoptotic signals, leading to compiling such complexes Bcl-2 family that cytochrome c release outside mitochondria
do not allow