Pathology

Modified slides no.4

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- We have 2 types of cell death one is called apoptosis and the other one is called necrosis and they are different from each other .

Apoptosis and autophagy

cell injury and adaptations

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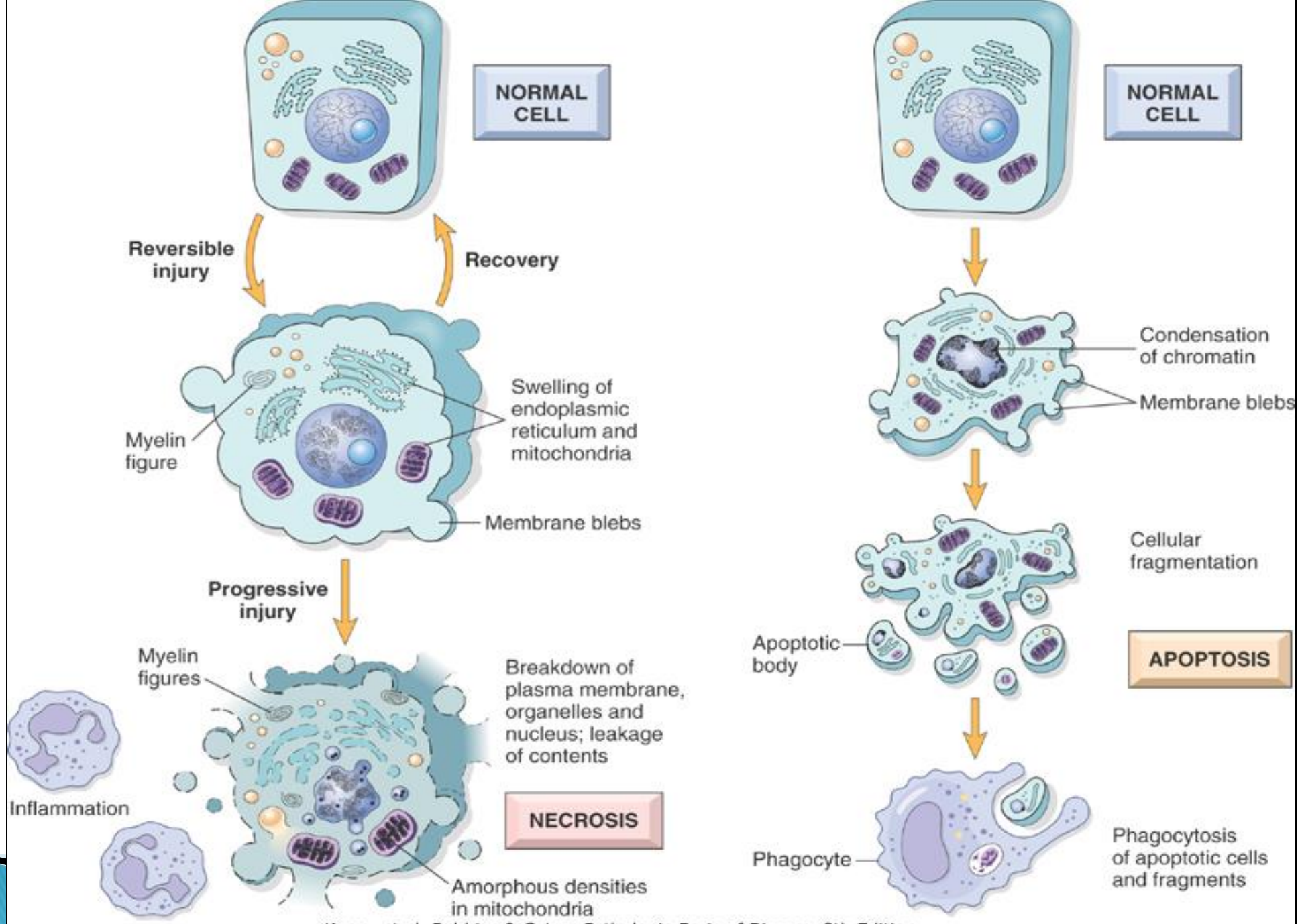
Definition

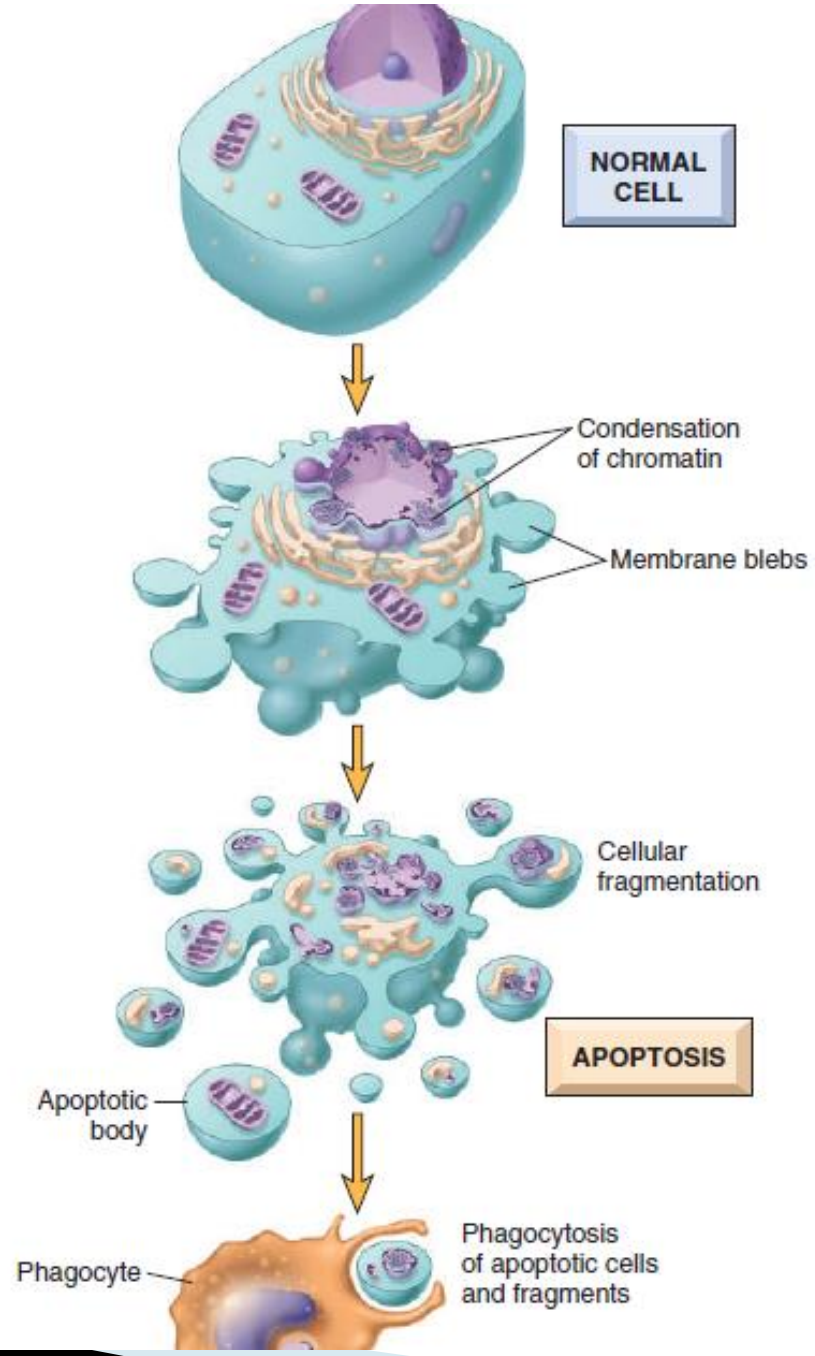
NOTE: we call it sometimes also cell suicide or the clean cell death

- **“Programmed cell death”**
- “a genetically determined process of cell self-destruction”
- “ this pathway of cell death is highly controlled in which cells activate enzymes that degrade the cells’ own nuclear DNA and nuclear and cytoplasmic proteins.”
- The dead cell and its fragments are cleared with little or no leakage of cellular contents, NO inflammatory reaction. (And this is one difference from necrosis)



- The complementing this slide: in apoptosis the cell went shrinking instead of swelling and we start to have many blebs of the cell membrane.
- Nuclear material starts to condensate the chromatin becomes darker under the LM and then it starts to fragment as we call it karyorrhexis.
- The cell membrane stays intact and the cell starts to fall off like (عنقود العنب)

A lot of these we have mentioned in Lec 2



- Now every part of cell membrane enclose some organelles and some cytoplasmic proteins and it separates from the main cell.
- These fragments or apoptotic bodies they give some signals to the phagocytes that will come to engulf them and get rid of them without eliciting an inflammatory reaction.

- So, to sum up the cell that goes apoptosis:
- – Shrinking in size
- – Start to fall off in the form of apoptotic bodies (membrane bound vesicles of the cell)
- – the nucleus also undergoes certain changes in the form of shrinkage then fragmentation of the nucleus
- – Every apoptotic body contains parts of the organelles, parts of cytoplasm, parts of proteins..
- The phagocytes will sense the presence of these apoptotic bodies and will eat them, clean the area without eliciting again an inflammatory reaction.
- that's why we call apoptosis Clean cell death.

NOTE: Not too many cells compared to necrosis

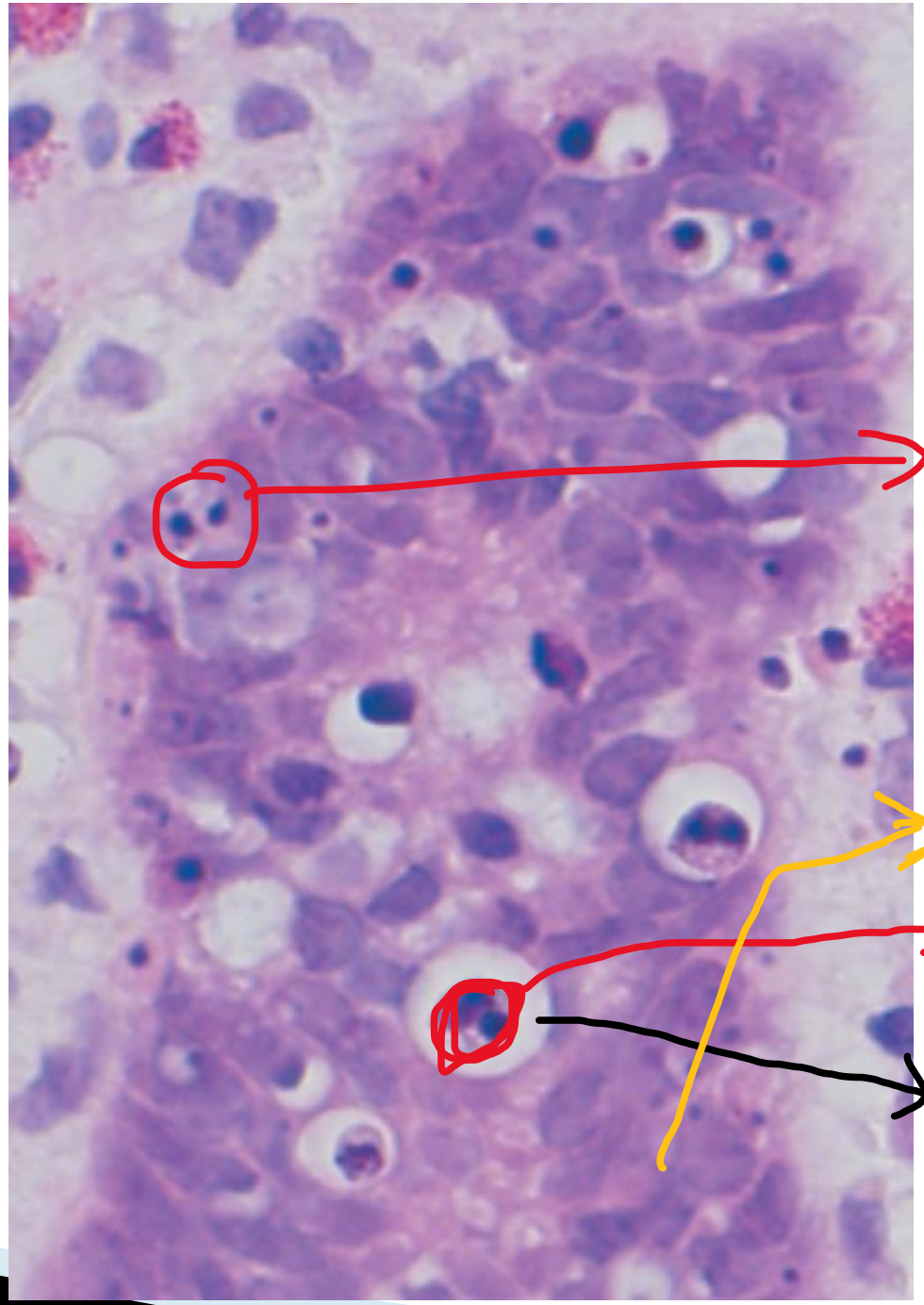
Feature	necrosis	Apoptosis
Cell size	Enlarged(swelling)	Reduced(shrinkage)
Nucleus	Pyknosis, Karyorrhexis, karyolysis	Fragmentation into nucleosome- size fragments
Plasma membrane	**Disrupted**	**Intact**, altered structure, especially orientation of lipids
Cellular content	Enzymatic digestion, may leak out of cell	Intact, may be released in apoptotic bodies.
Adjacent inflammation	**Frequent**	**No**
Physiologic or pathologic role	Invariably pathologic	often physiologic and may be pathologic

NOTE: Important difference

NOTE: in apoptosis we can say we have pyknosis then karyorrhexis then these karyorrhectic debris of the nucleus will start to separate in the apoptotic bodies and these apoptotic bodies will then be cleared by phagocytes

However, apoptosis and necrosis sometimes coexist, and apoptosis induced by some pathologic stimuli may progress to necrosis, like in ischemia.

- NOTE: the nucleur material is fragmented, it is condensed it is very dark in color
- H&E stain under LM
- No inflammatory reaction



- NOTE: Fragment DNA material
- NOTE: Normal cells
- NOTE: Shrunken cell
- NOTE: empty lacunae

Causes of apoptosis

- Physiologic apoptosis
- Apoptosis in pathologic conditions

Causes of Apoptosis

- **Physiologic**

- During embryogenesis
- Involution of tissues upon hormone deprivation (endometrium, lactating breast)
- Steady state population (Gut, Skin)
- End of function/life (neutrophils at end of inflammation)
- Self reacting lymphocytes

- The complementing this slide:
- During embryogenesis: in the uterus all the time during embryogonesis the new cells appear and old cells die and this death is usually occurs by means of apoptosis.
- **Involution of tissues upon hormone deprivation (endometrium, lactating breast):** in case of endometrium at the end of the menstrual cycle the endometrial glands are lost and then the shedding of the endometrium start this loss and this death usually occurs by means of apoptosis, Lactating breast after the sensation of lactation there will be deprivation of the hormons and the new glands which appeared of the onset of lactation will die by the process of apoptosis so this is mediated by the loss of hormonal stimulation.
- **Steady state population(Gut,Skin):** as you know these organs they have rabid turnover so new cells are made all the time and the old cells die by apoptois in a rapid regenration capacity process.
- **End of function/life (neutrophils at end of inflammation):** having done their job, Neutrophils don't go back to circulation. Instead, they die out in tissues by Apoptosis.
- **Self reacting lymphocytes:** There are certain lymphocytes produced within our body that are reactive to our own self-antigens which could increase the risk of Autoimmune diseases. To prevent that, the body gets rid of these cells by Apoptosis (in order not to have autoimmune diseases)

- NOTE: if this DNA damage is not repaired the cell will be directed to apoptosis .
- If the DNA damage cells continues to replicate we will have cancers at the end

- **Pathologic:** (damaged cells beyond repair) الخلية الي بقدرش الجسم يصلحها بقتلها

- DNA damage (Rx(Radiation) , ChemoTx(Chemotherapy), Temperature,UV (Ultraviolet light) due to sun exposure, Hypoxia)
- Accumulation of misfolded proteins. discussed in the mechanism of cell death Lec.
- Some infections (adenovirus, HIV, hepatitis viruses)

- These viruses can cause cell death even by necrosis or by apoptosis so you will find both of the processes taking place togther

Condition	Mechanism of Apoptosis
Physiologic	
During embryogenesis	Loss of growth factor signaling (presumed mechanism)
Turnover of proliferative tissues (e.g., intestinal epithelium, lymphocytes in bone marrow, and thymus)	Loss of growth factor signaling (presumed mechanism)
Involution of hormone-dependent tissues (e.g., endometrium)	Decreased hormone levels lead to reduced survival signals
Decline of leukocyte numbers at the end of immune and inflammatory responses	Loss of survival signals as stimulus for leukocyte activation is eliminated
Elimination of potentially harmful self-reactive lymphocytes	Strong recognition of self antigens induces apoptosis by both the mitochondrial and death receptor pathways
Pathologic	
DNA damage	Activation of proapoptotic proteins by BH3-only sensors
Accumulation of misfolded proteins	Activation of proapoptotic proteins by BH3-only sensors, possibly direct activation of caspases
Infections, especially certain viral infections	Activation of the mitochondrial pathway by viral proteins Killing of infected cells by cytotoxic T lymphocytes, which activate caspases

Mechanisms of Apoptosis

- **Activation of enzymes called caspases**
- Two distinct pathways can lead to caspase activation:
- 1) The mitochondrial pathway (Intrinsic pathway)
- 2) The death receptor pathway (Extrinsic pathway)

NOTE: Each of them has its own distinct properties but at the end, they overlap by the activation of exudative caspases

Mitochondrial (intrinsic)

- NOTE: It's called intrinsic because it starts at the level of mitochondria inside the cell

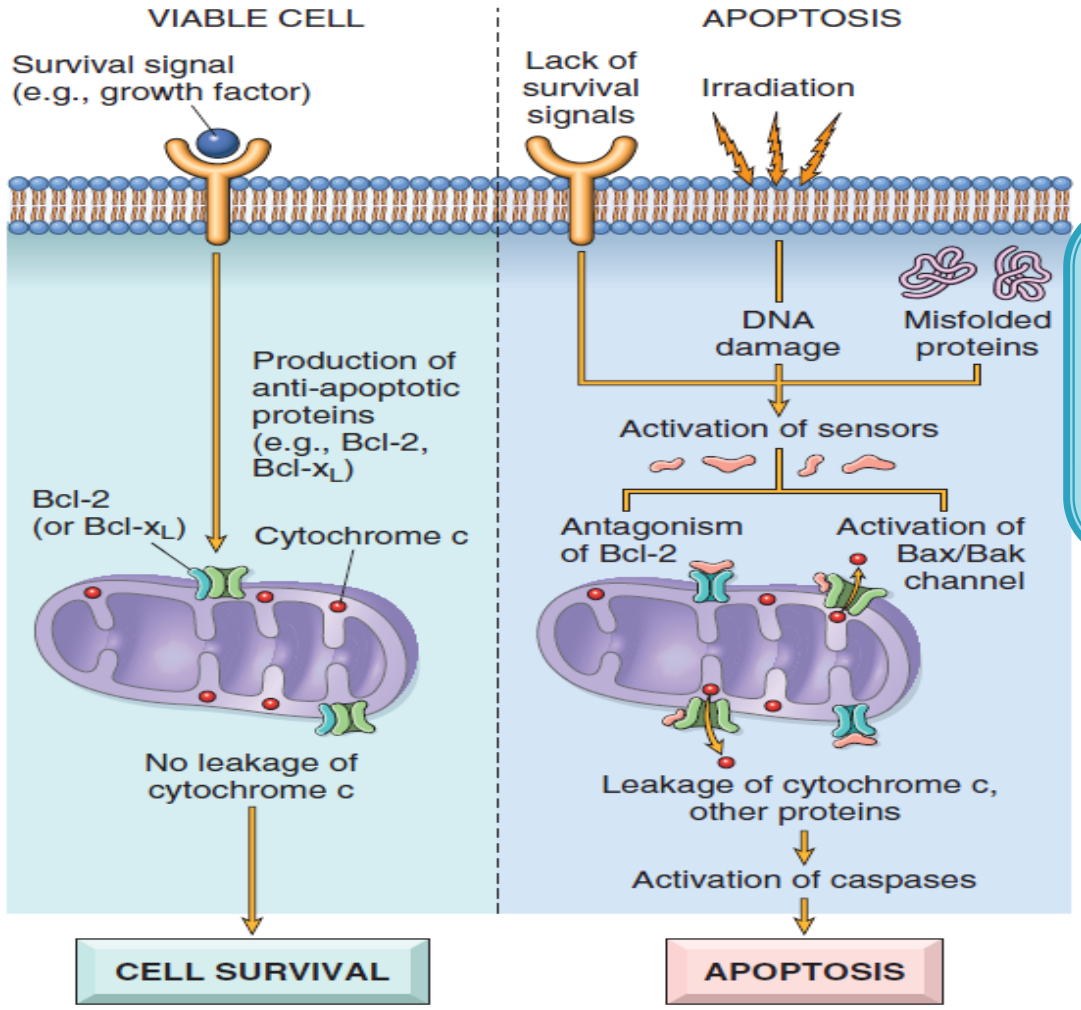
- NOTE: Because inside the mitochondria we have certain enzymes and molecules that will leak to the cytosol when the permeability increases, and that cause activation of caspases

Responsible for apoptosis <u>in most physiologic and pathologic situations</u>

Bcl2 family of proteins **control mitochondrial membrane permeability**

Bcl2 antiapoptotic
<u>Bax/Bak proapoptotic</u>
BH3 sensors in the cytosol

Cytochrome c activates caspase-9



: antiapoptotic means it prevents Apoptosis

- The complementing this slide: The most important molecule in the mitochondria is the cytochrome c, if it leaks outside the mitochondria, it'll cause apoptosis, so it should stay inside the mitochondria عشان تضل الخلية حية

- The complementing this slide: Bcl2 family includes antiapoptotic proteins (Bcl2 & BclxL), proapoptotic proteins (Bax & Bak) which all are in the mitochondria membrane, and the BH3 sensors in the cytoplasm which will sense any change that will lead to apoptosis

- The complementing this slide: FOLLOW THE PICTURE PLZ..
- In viable cell, survival signals keep reaching the cell (growth factors, hormones) and that will lead to the activation of antiapoptotic proteins
- Bcl2 has inhibitory effect on Bax and Bak (Green in picture) and that will inhibit the leakage of cyt.c to the cytoplasm
- Once the cells exposed to lack of survival signals (e.g. UV), DNA damage or proteins misfolding, all of them will activate BH3 sensors in cytoplasm, they'll inhibit Bcl2 proteins and activate Bax & Bak proteins
- When Bax and Bak are free from their inhibitor (Bcl2) they'll dimerize forming a channel, through which cyt.c will leak out and start series of caspases activation (caspase-9 mainly) and apoptosis.

Death receptor (extrinsic)

- TNF receptor family, cytoplasmic death domain
- Prototypes: Type 1 TNF receptor and Fas receptor
- Fas ligand on activated T lymphocytes
- Fas –FasL interaction(lock and key phenomena) activates death domain which in turn activates caspase 8(Cytoplasmic enzyme) which will activate series of caspases that will lead at the end to apoptosis.

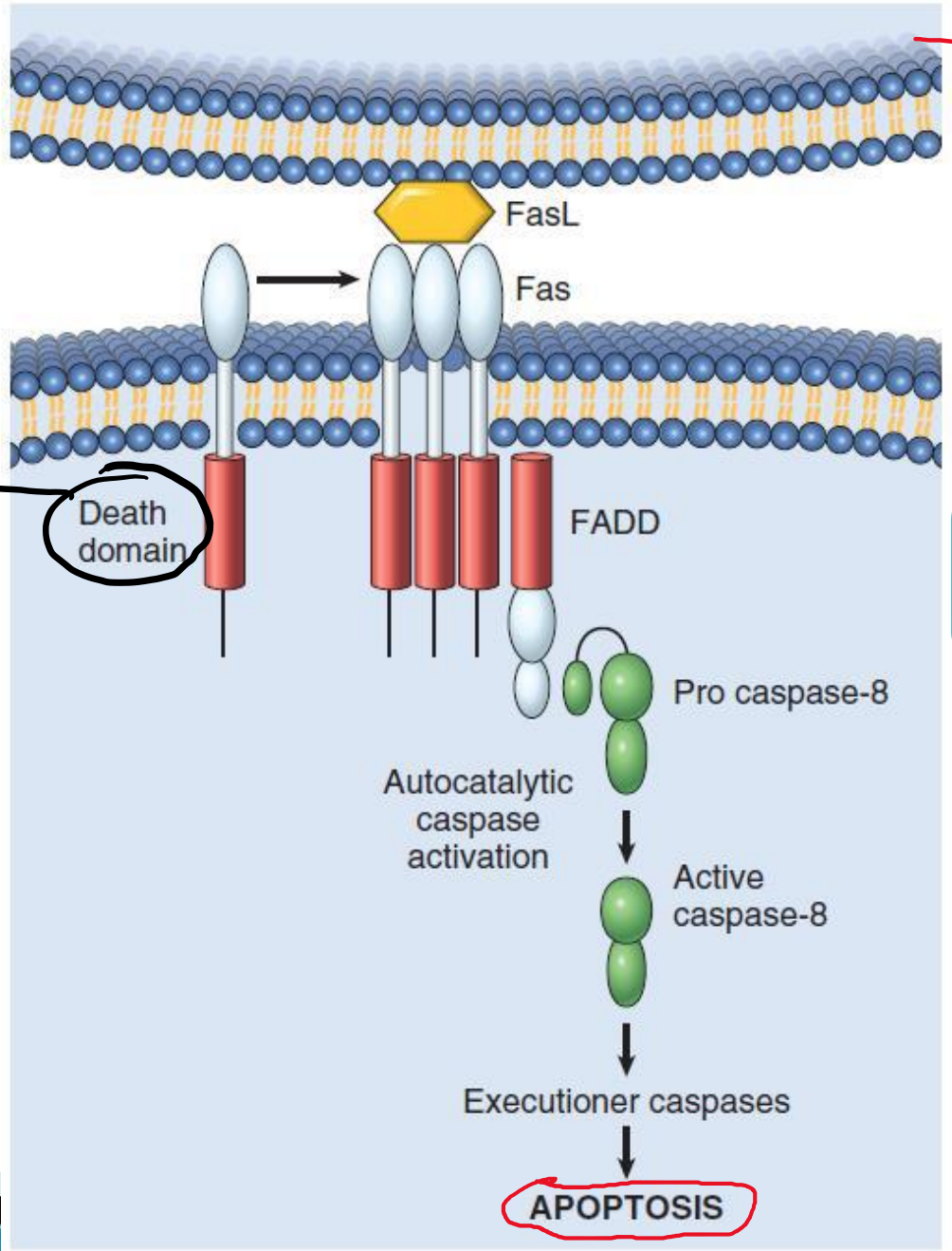
- **Used in:**
- Elimination of self-reactive lymphocytes
- killing of target cells by some cytotoxic T lymphocytes (CTLs)

NOTE: This is a receptor which is present in the plasma membrane, with cytoplasmic death domain, because it interact with proteins in the cytoplasm leading to the activation of caspases

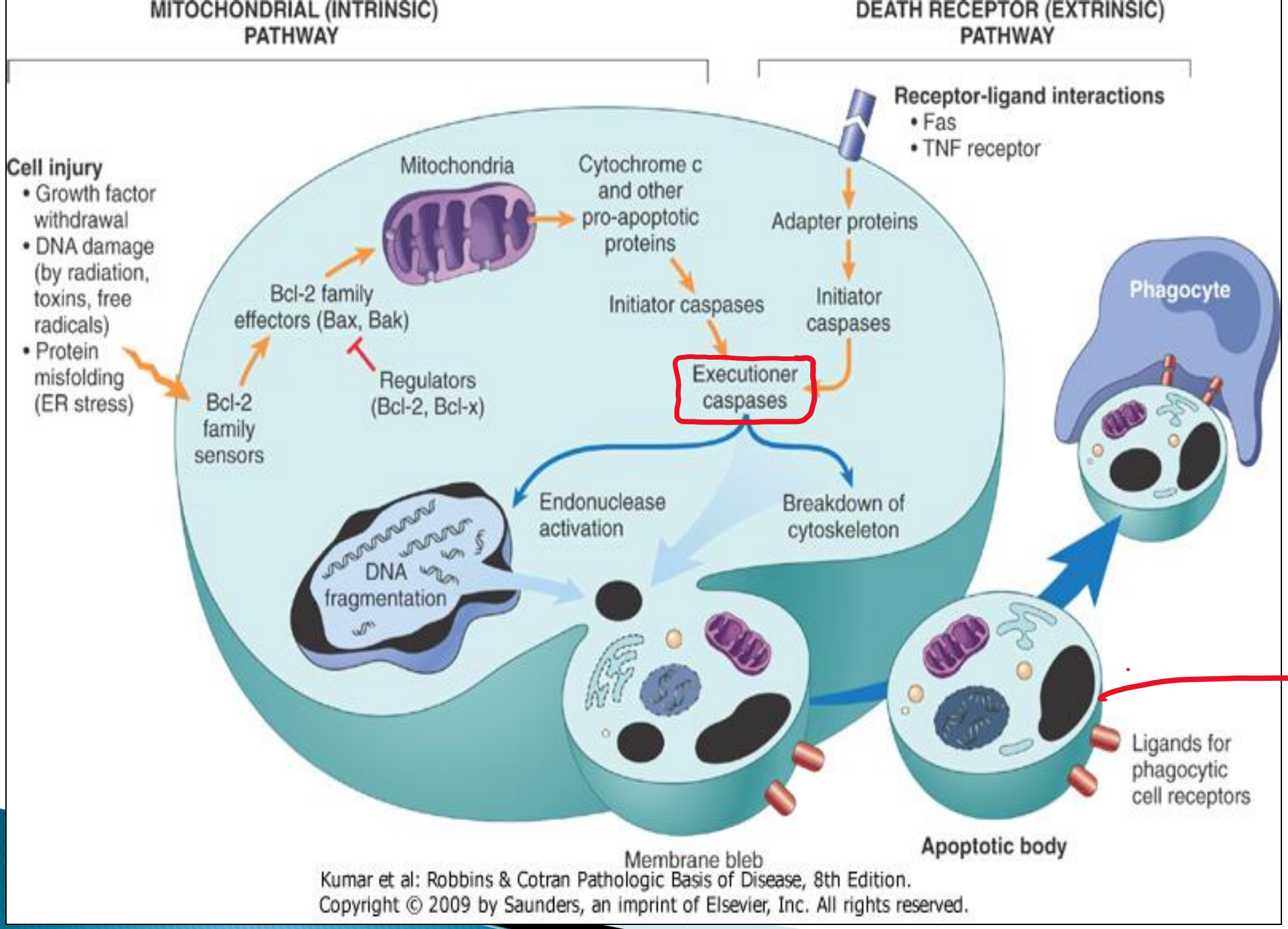
NOTE: Virally infected cells, tumor cells…

Additional information:
Elimination of self-reactive lymphocytes by apoptosis is mediated by which of the following molecules?
Ans: Fas-FasL interaction

- NOTE: if activated it will activate the caspases (caspase8 mainly) leading to apoptosis as we Mentioned earlier.



- NOTE: Fas receptor is present on the cell that will be directed to death



Read the picture important!!!!

- NOTE: Both pathways will link with exudative caspases activation

- NOTE: Apoptotic bodies have attractive process to make the phagocyte ingulf it

Autophagy

- NOTE: Autophagy is related somehow to apoptosis also related to adaptive mechanism called Atrophy
- The cell eats itself
- This is survival mechanism !
- And sometimes it is considered as an adaptive mechanism

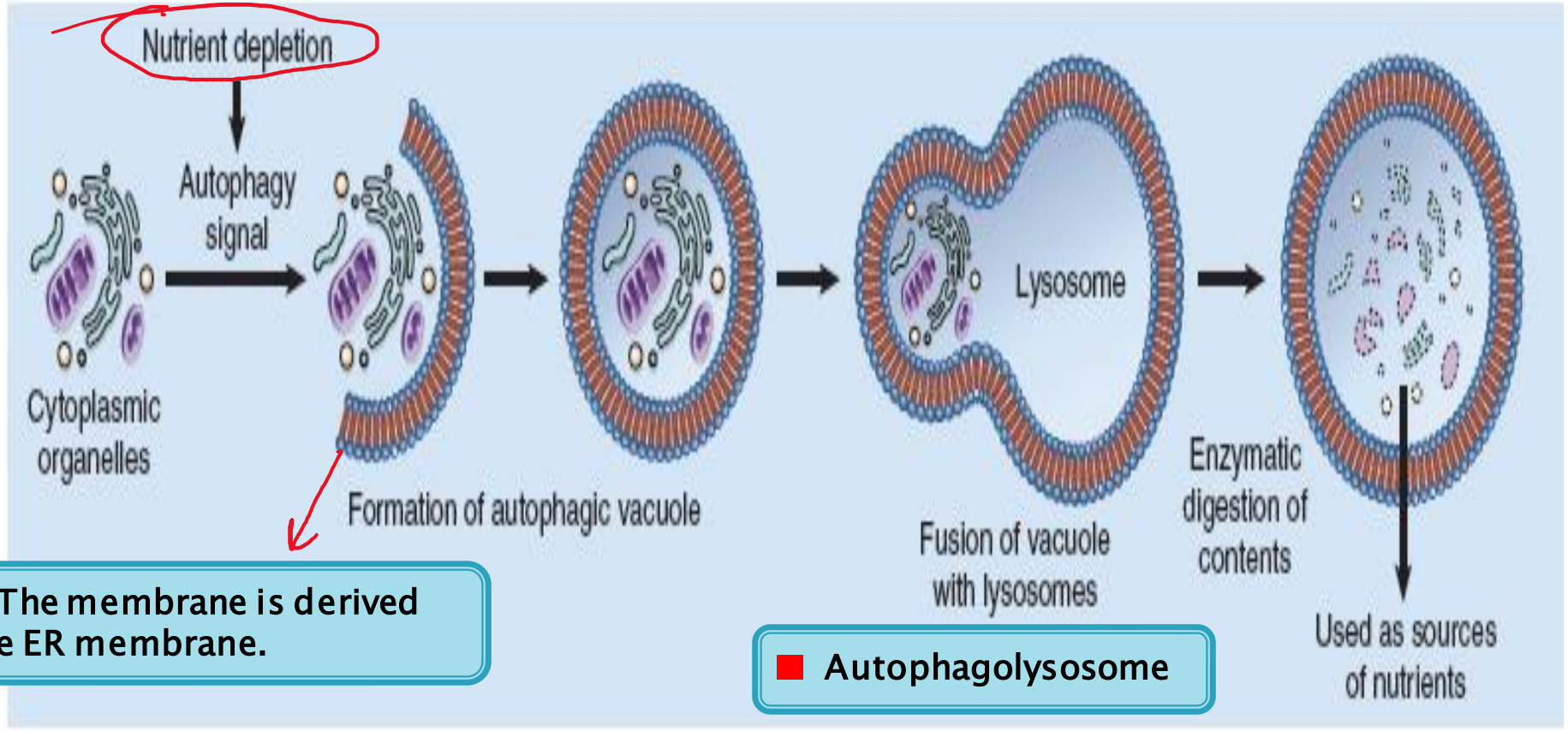
- Self-eating
- Lysosomal digestion of the cells own components
- Survival mechanism in times of nutrient deprivation.
- **Recycling cells contents to provide nutrients and energy in times of starvation.**

What happens in Autophagy:

- ER-derived autophagic vacuole
- Vacuole fuses with lysosome >>>autophagolysosome

- May lead to atrophy. Shrinkage of the cell
- Failure of adaptation >>>apoptosis

- NOTE: like longer starvation.



- NOTE: The membrane is derived from the ER membrane.

- Autophagolysosome