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PATHOLOGY

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• Apoptosis

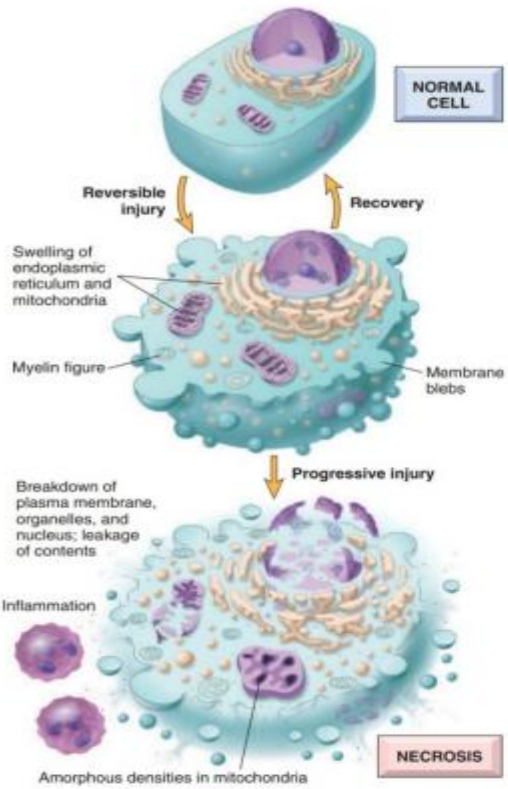
Apoptosis can be defined as :-

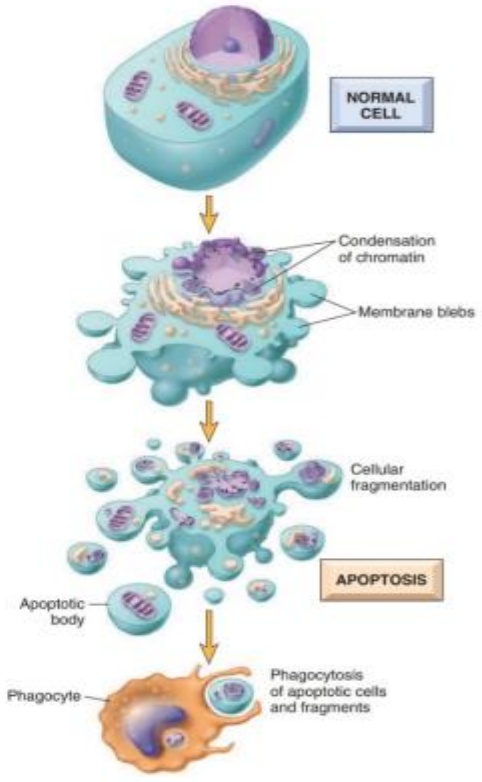
1- A pattern of cellular death which is tightly regulated hence being termed **cell-suicide or programmed cell death** due to it being genetically determined and highly controlled process of cellular death due to a **physiological or pathological condition**.

2- A pathway of cell death in which the cell activates its own enzymes that degrade the cells own nuclear DNA and cytoplasmic proteins.

The dead cells and its fragments are cleared with little leakage of the cellular contents to the surroundings and hence apoptosis is considered **non-inflammatory**.

This process of clearing dead cells is done by macrophages in a very innocent method and therefore there is no consequent inflammation contrary to necrosis which is frequently followed by an inflammatory response. For that reason, Apoptosis is called **Peaceful cell death**





Necrosis

Cellular contents swell (ER ,mitochondria),hence an increase in cell size.

Necrosis is mostly pathologic

Generally, the plasma membrane isn't intact and there is Enzymatic digestion as well as leakage of cellular contents

Apoptosis

Cells shrink, get smaller in size at the level of organelles (Condensation of chromatin).

The plasma membrane is intact (no enzymatic digestion). In other words, it won't undergo rapturing and therefore there is no leakage of cellular contents to the outside.

The contents of the apoptotic cell are enclosed by parts of the plasma membrane resulting the formation of **Apoptotic bodies** that will be subsequently released.

These apoptotic bodies are said to be edible which means they can be detected by phagocytes including macrophages that engulf them in a peaceful way hence No intense Inflammatory response.

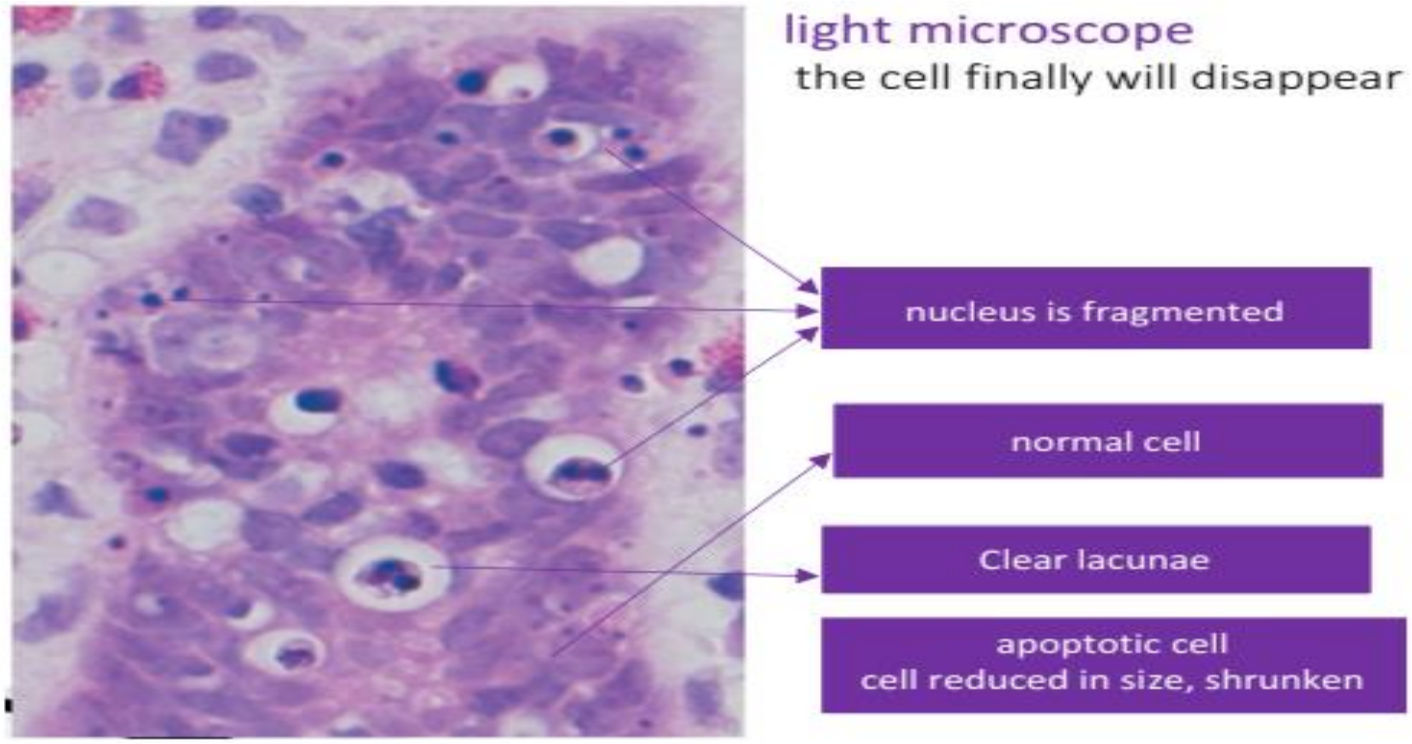
Apoptosis can be both physiological and pathological

To summarize the differences :-

Swelling accumulations of water

first condensation of the nucleus then fragmentation
it is similar somehow to karyorrhexis but the process is different

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



In the previous histological section :- Notice that those apoptotic cells are evidently shrunken in size inside Lacunae. It is also possible to identify fragmentation of cells as well as Chromatin condensation.

✓ Sometimes it is possible to have mixture between both apoptosis and necrosis which is the case for **Ischemia**. In cases of mild ischemia , cells start to die out by apoptosis. However, if it progresses severe ischemia, cells die out by Necrosis.

- ## Causes of apoptosis:

1) Physiological Apoptosis:-

1- **During embryogenesis** : during embryonic development in the uterus some structures temporarily appear and then they die out by apoptosis either **to serve a certain need** (For example: formation of fingers), or **they could be replaced by other larger, more complex structures**.

2- **Involution of tissues upon hormone deprivation (Endometrium, lactating breast):**

a- **In the case of endometrium**, following menopause, we are essentially having estrogen withdrawal, this may lead to atrophy while other cells might choose to die by apoptosis and therefore seen as Decrease in endometrium thickness.

b- **In the case of lactating breast**, after the cessation of lactation, the cells that have already gone through hyperplasia undergo apoptosis.

3- **Maintenance of Steady state population (Gut, skin):** This occurs in Rapidly proliferating cells (epithelial cells for instance) to maintain the normal number of cells in these layers by having some cells dying by apoptosis (old cells) and new cells will replace them.

4- **End of function and life (Neutrophils at the end of inflammation):** Having done their job, Neutrophils don't go back to circulation. Instead, they die out in tissues by Apoptosis.

5- **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.

2) Pathological Apoptosis: (Damaged cells beyond repair)

1- **DNA damage (Radiation, Chemotherapy, Temperature, Ultraviolet light due to sun exposure, Hypoxia):** After DNA damage, the cell activates p53 to repair the damage. However, if repairing is unsuccessful, the cell will die by apoptosis
2- **Accumulation of misfolded proteins.**
3- **Infections (Adenovirus, HIV ,Hepatitis virus)**

To summarize:-

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

- **Mechanisms of apoptosis:**

  All of which share the activation of enzymes known as **Caspases (8 or 9)**.

I. Mitochondrial (Intrinsic) pathway utilizing caspase 9:

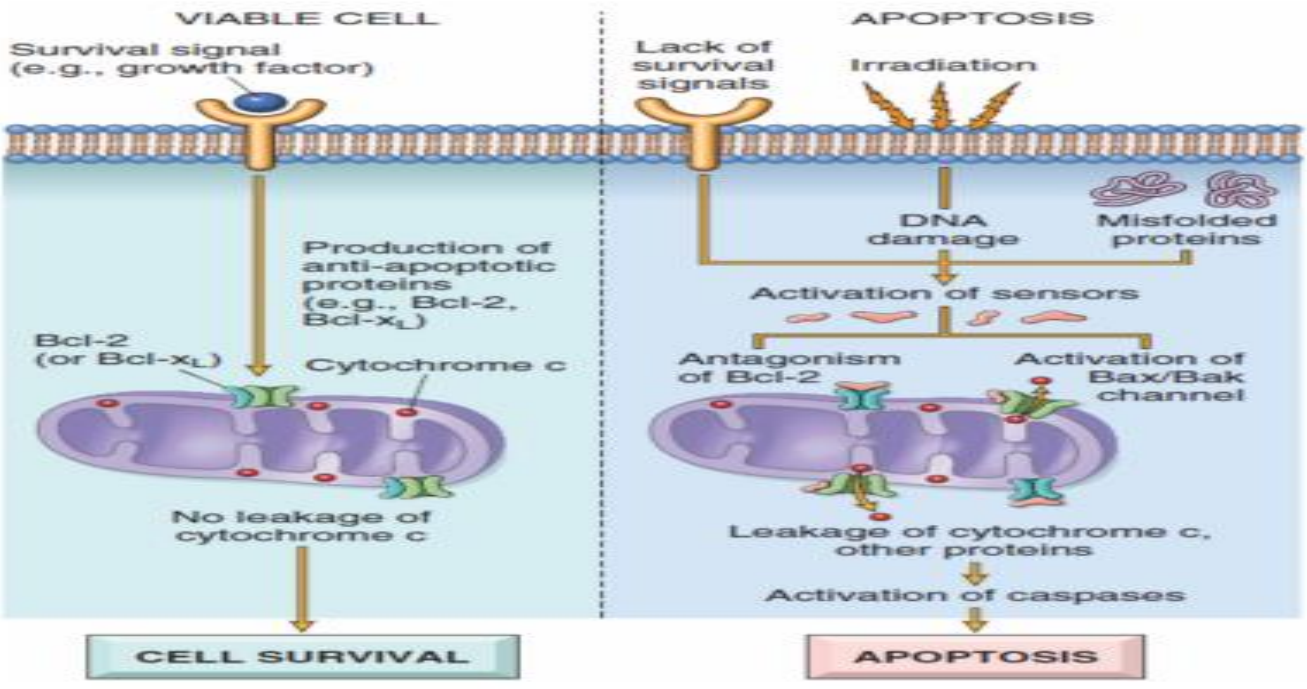
- Responsible for apoptosis in most physiological, pathological conditions.
- Its termed Intrinsic because the process starts from the mitochondria (inside the cell).
- This pathway is tightly regulated by the Bcl2 family of proteins (20 proteins) that control the mitochondrial membrane permeability by acting as channels. The significance of this lies the in fact that Mitochondria contains a substance, known as **Cytochrome C** which should be kept away from the cytoplasm as to prevent the activation of **Caspase 9** which in turn , activates Apoptosis

- **The Normal Scenario**:- Normally when cells are receiving Survival signals (Growth factor) and no hypoxia Ischemia and DNA damage), these signals improve The production of the **Anti-apoptotic proteins (Bcl-2 and Bcl-XL)**. Maintaining Cytochrome C inside mitochondria Facilitated by the action of Bcl2 family, more Specifically, the Bcl-XL ,Bcl-2 proteins. Thus acting as guardians of the mitochondrial membrane At which they reside and therefore preventing leakage of Cytochrome C = Prevention of apoptosis.

The Bcl2 family of proteins

This family of mitochondrial-membrane proteins is composed of :-

1- **Anti-apoptotic proteins**: Bcl-2 ,Bcl-XL , they prevent apoptosis
2- **Pro-apoptotic proteins**: Bak ,Bax
They stimulate apoptosis



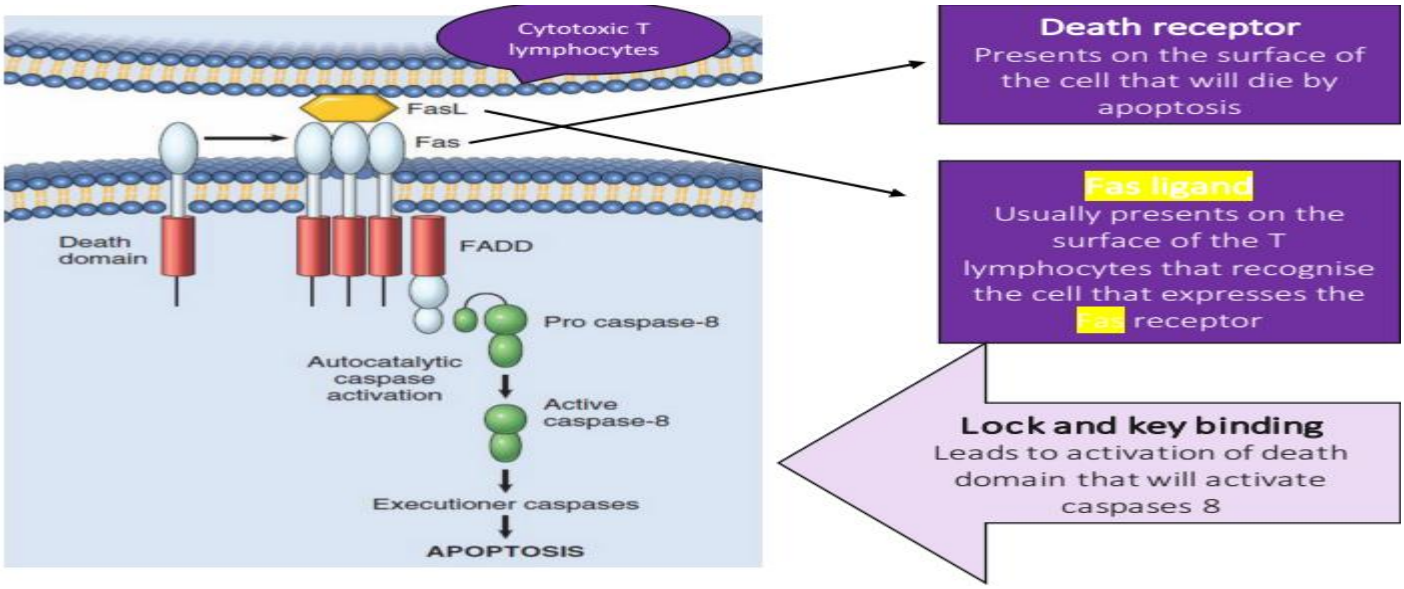
- **The abnormal scenario**: When cells are subject for instance to radiation, lack of or misfolded proteins, this will result in the activation of certain sensory in the cytoplasm known as BH3-sensor proteins that will either:
    1- Activation of the **Bax/Bak channel** and therefore causing the leakage of ***cytochrome C*** and hence Apoptosis.
    2- Antagonism of **Bcl-2** and therefore inhibiting their anti-apoptotic effect thus causing leakage of **Cytochrome C** and hence Apoptosis.

Either way, both cases result the release of cytochrome C that activates the Caspase-9 protein which starts a sequence of events leading to Apoptosis.

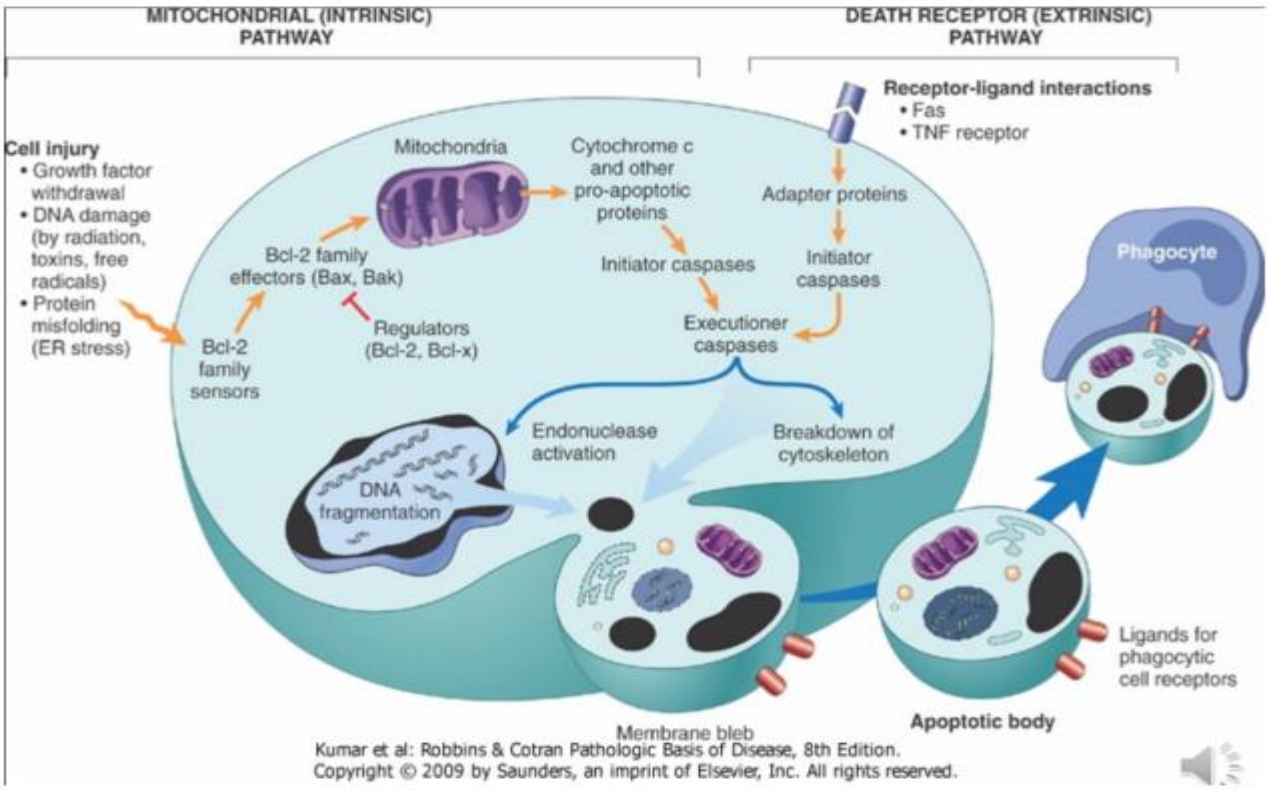
II. The Death Receptor pathway (Extrinsic pathway) utilizing Caspase 8

- It is called extrinsic because the process starts from outside at the surface of the cell.
- This pathway is utilized is certain scenarios whereby we are having the **elimination of self-reactive lymphocytes and killing of certain target cells** (Virally infected or cancerous) By some Cytotoxic T-lymphocytes.
- The death receptor includes a family of the tumour necrosis factor receptors TNF. These receptors have a cytoplasmic domain called the death domain [because it mediate process that will lead to cell death]
- The prototypes of these receptors are:
    1- **Type 1 tumor necrosis factor (TNF) receptors.**
    2- **The Fas receptors that usually bind to its ligand (Fas ligand) which is usually located on the surface of activated T lymphocytes.**

- **The scenario:-** When activated T-lymphocytes **Fas Ligand** binds with the cells that express the Fas-receptor on their surface (Cells that need to undergo apoptosis), The death domain of the receptor is activated thus activating the Cytoplasmic protein **Caspase-8** which will activate other subsequent Executioner caspases and steps that eventually lead to destruction of cellular proteins and therefore the falling of cells as apoptotic bodies.



✓ **In conclusion,** both pathways (Intrinsic or Extrinsic) converge at the end by the activation of executive caspases But the mechanism is different according to the cause of apoptosis.



• Autophagy (self-eating of cells):

- **Autophagy (self-eating of cells**) refers to self-lysosomal digestion of the cell components usually in periods of nutrient starvation as a survival adaptive mechanism done by recycling its own contents to provide nutrients and required energy of the cell.
- The process of autophagy involves the formation of Autophagic Vacuoles ,derived from the ER, that will later fuse with a lysosome therefore forming an **Auto phagolysosome**.
- Therefore, Autophagy is a mechanism of atrophy as a method of adaptation. However, if starvation is severe and the cell fails to adapt , the cell chooses to undergo apoptosis.

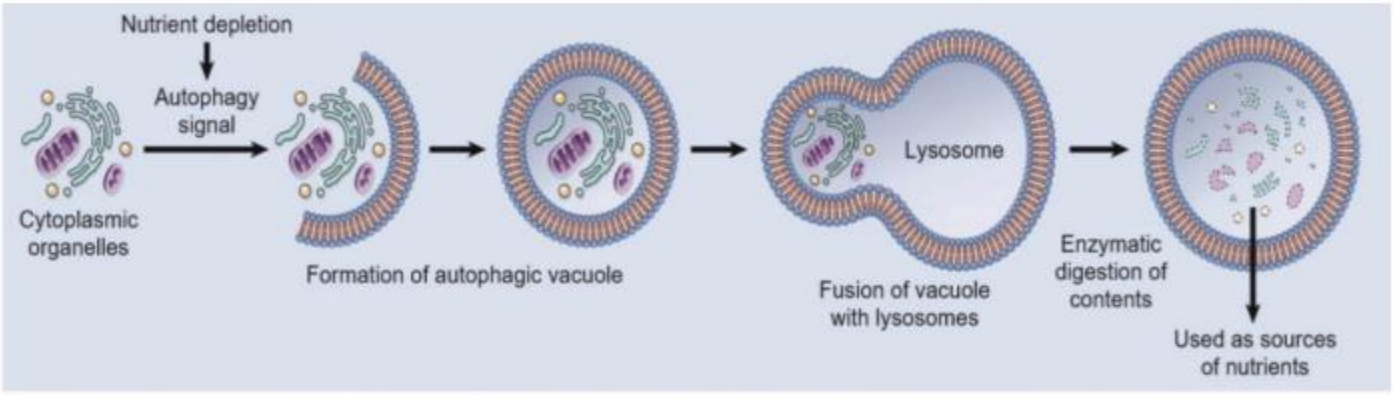


Fig. 2.14 Autophagy. Cellular stresses, such as nutrient deprivation, activate autophagy genes, which initiate the formation of membrane-bound vesicles in which cellular organelles are sequestered. These vesicles fuse with lysosomes, in which the organelles are digested, and the products are used to provide nutrients for the cell. The same process can trigger apoptosis by mechanisms that are not well defined.