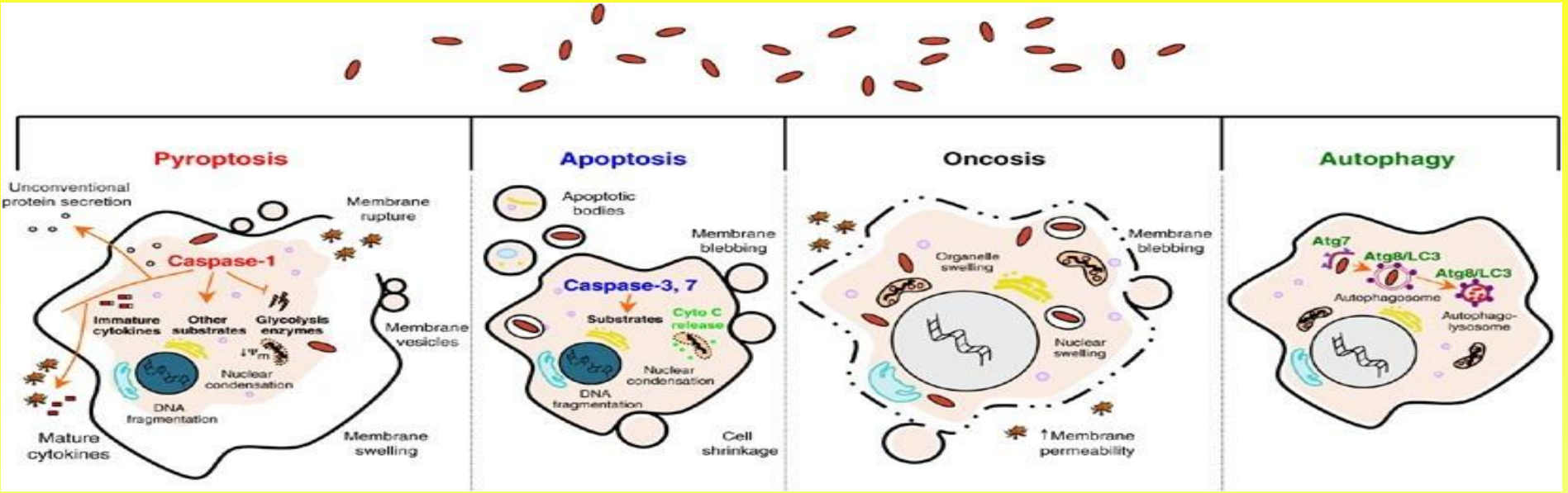
Cell Death Processes



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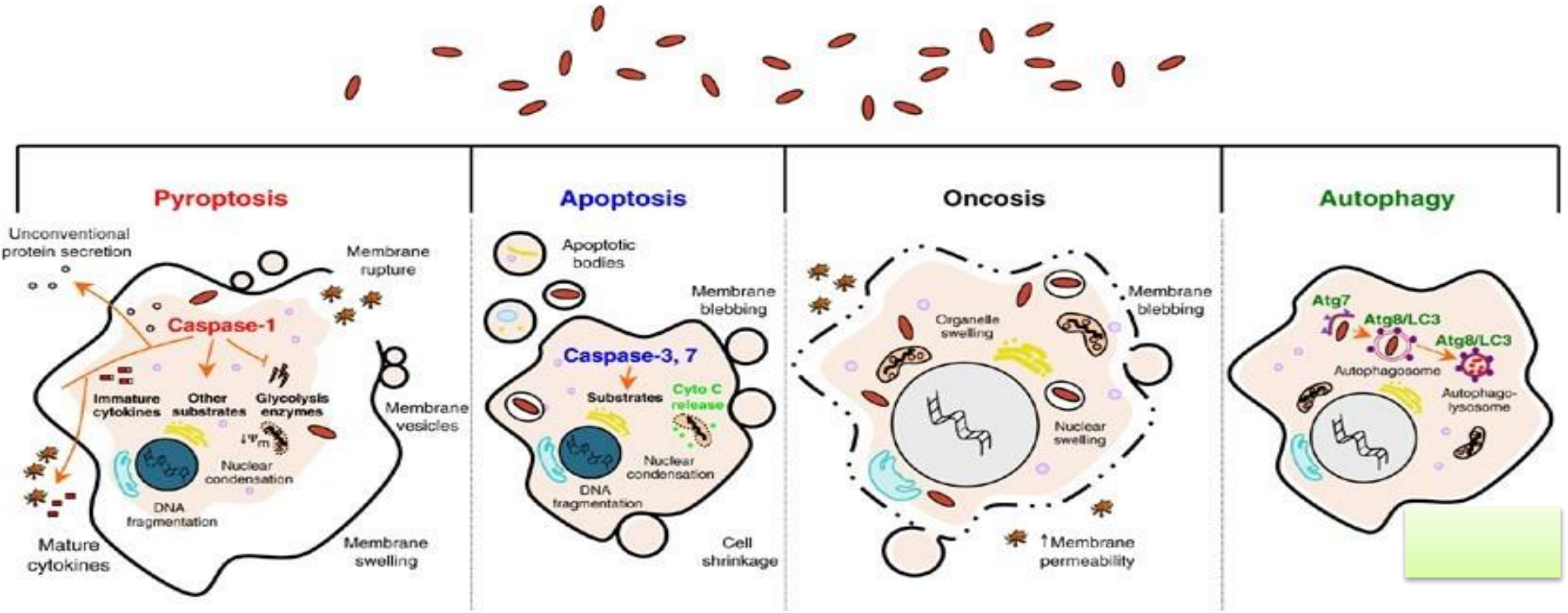
The cell death is essential for body homeostasis

Cell death can be classified as :

- Necrosis
- Apoptosis
- Autophagy
- Mitophagy
- Pyroptosis



Necrosis (Oncosis)

. Necrosis is caused by factors external to the cell or tissue, such as infection, or trauma which result in the unregulated digestion of cell components. It is an uncontrolled cell death that results in swelling of the cell organelles, plasma membrane rupture and eventual lysis of the cell, and spillage of intracellular contents into the surrounding tissue leading to tissue damage.

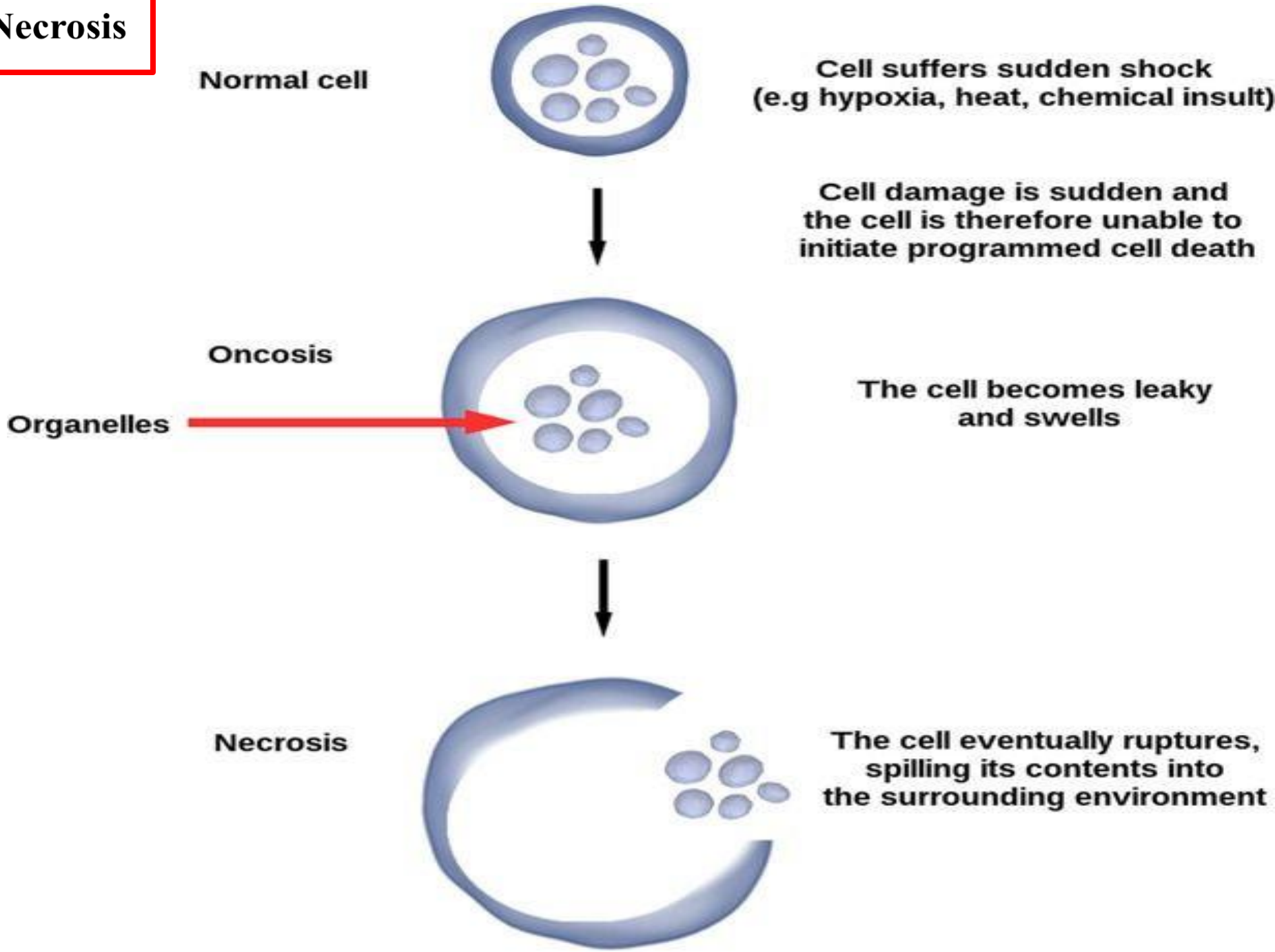
Necrosis occurs due to overwhelming harmful stimulus from outside the cell and is almost always associated with inflammatory responses due to the release of heat shock proteins, uric acid, ATP, DNA, and nuclear proteins, which cause inflammasome activation and secretion of proinflammatory cytokine interleukin-1 beta (IL1).

Cell injury can range from external injury to internal abnormalities. The most common causes of injurious stimulus include:

1. Hypoxia: This can occur due to ischemia, shock, or respiratory failure.
2. Physical agents: These include external injuries such as trauma extremes of temperature, radiation exposure, or electric shock
3. Chemical agents: These include poisons, occupational exposure, drug toxicities, or recreational drugs.
4. Biological agents: bacteria, viruses, or fungi
5. Immunologic reactions: autoimmune responses

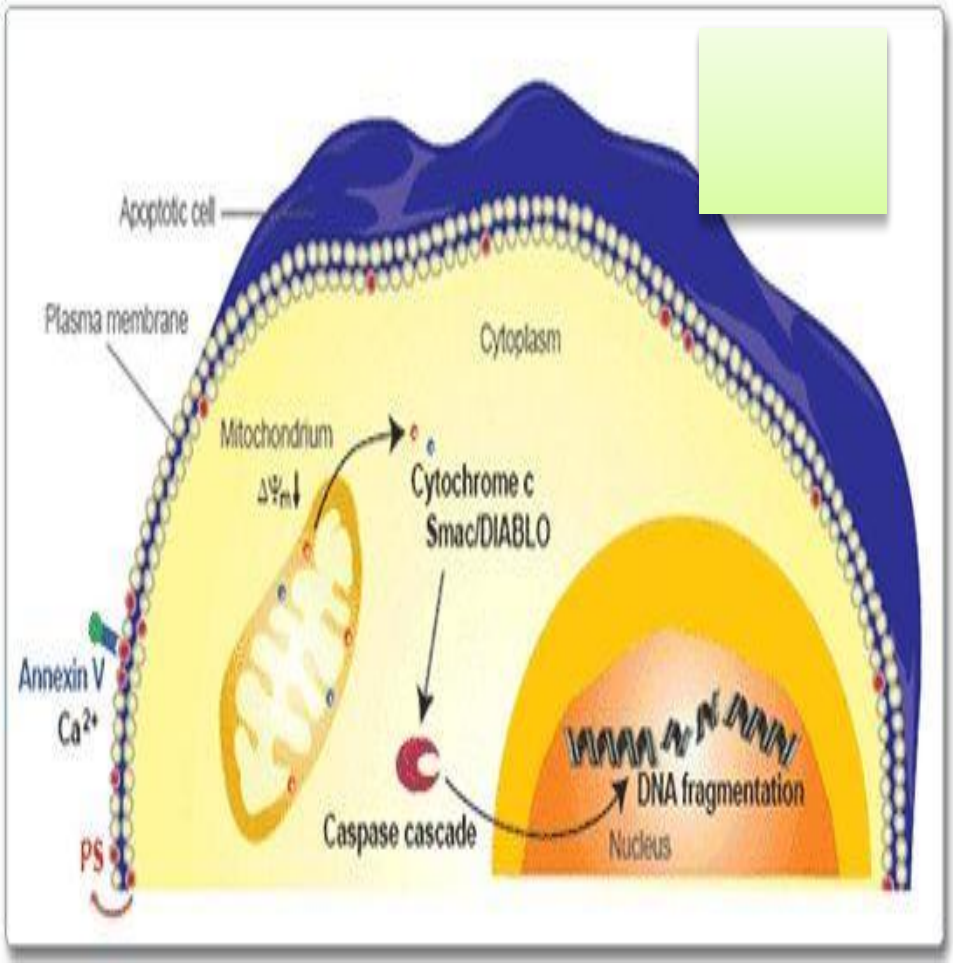
- Heat shock proteins (HSP) are a family of proteins that are produced by cells in response to exposure to stressful conditions.

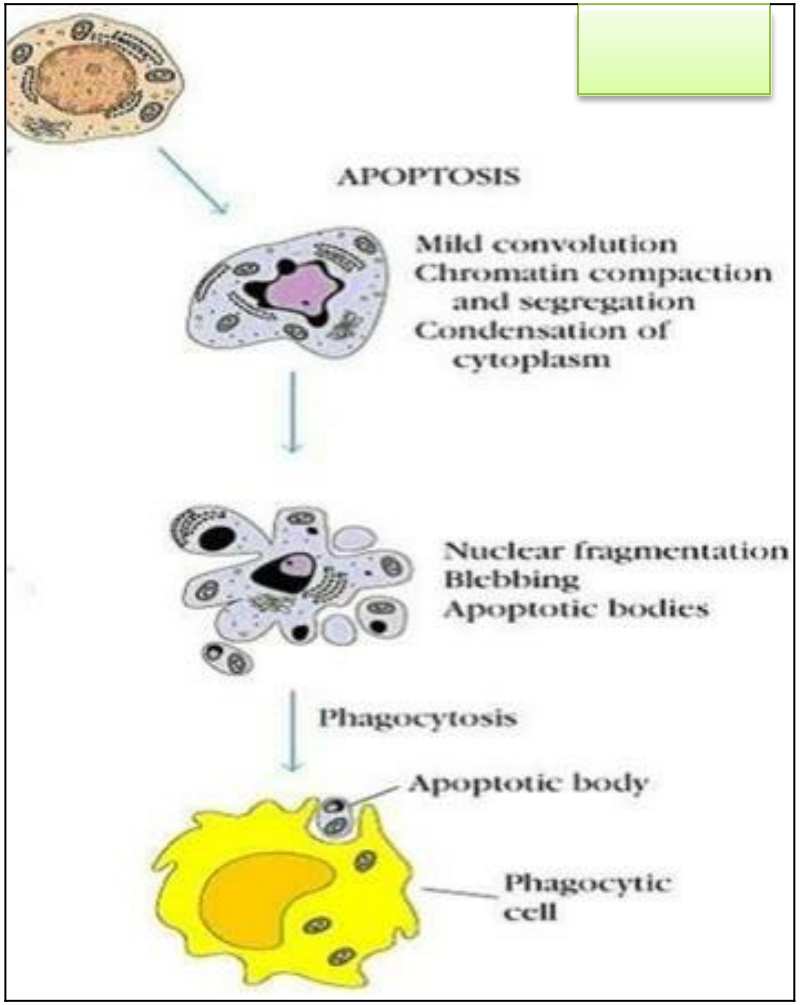
Necrosis


Normal cell
Cell suffers sudden shock
(e.g hypoxia, heat, chemical insult)
Cell damage is sudden and
the cell is therefore unable to
initiate programmed cell death
Oncosis
Organelles
The cell becomes leaky
and swells
Necrosis
The cell eventually ruptures,
spilling its contents into
the surrounding environment

Apoptosis

Apoptosis is the process of programmed cell death. Apoptosis is an ordered and arranged cellular process that occurs in physiological and pathological conditions. The cells undergoing apoptosis display blebbing, cell shrinkage, nuclear fragmentation, and DNA fragmentation.





Morphological apoptotic changes in cells

Cells undergoing apoptosis display blebbing, cell shrinkage, nuclear fragmentation, and DNA fragmentation.

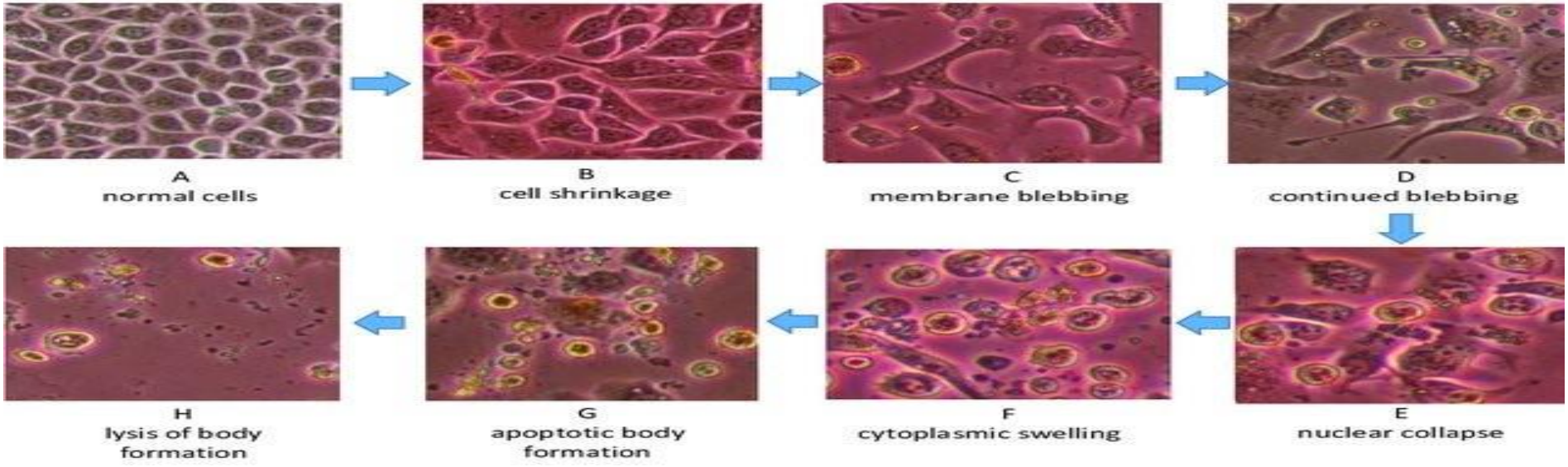
(A): Normal cells.

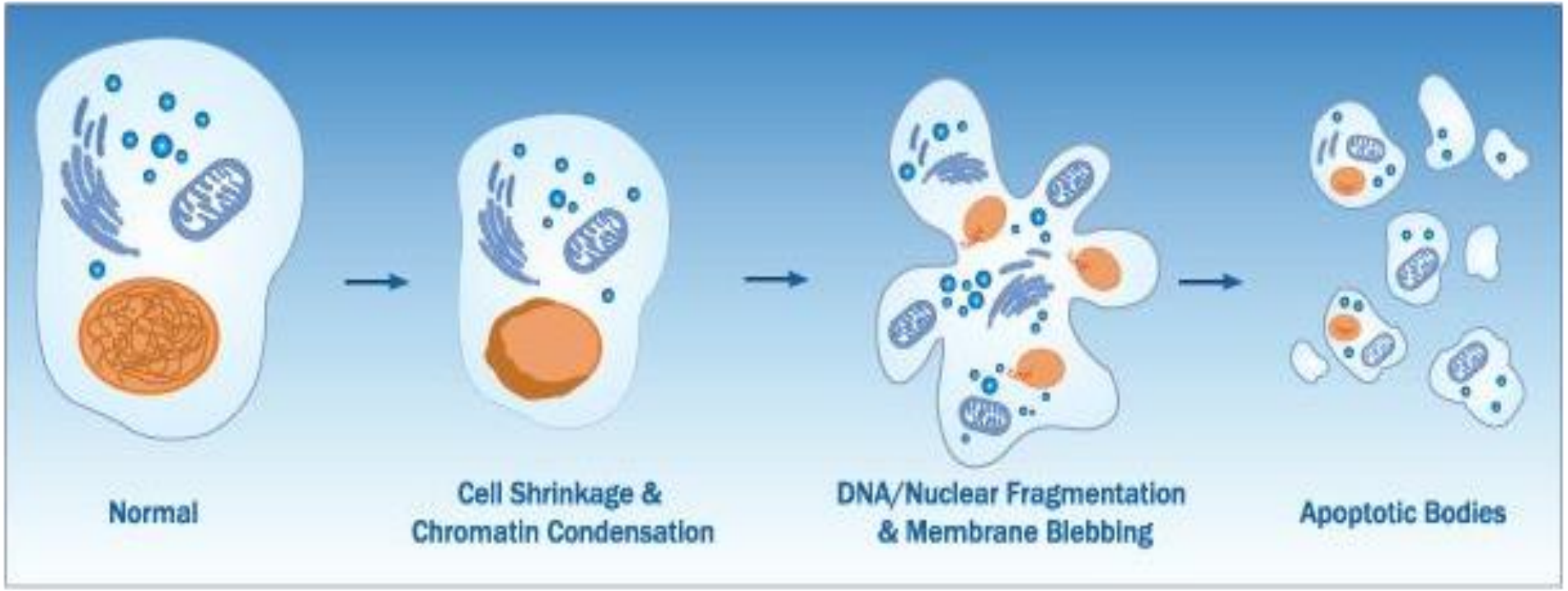
(B, C,D): cells underwent cell shrinkage and membrane blebbing (E): the cells exhibited cytoplasmic swelling.

(F): plasma membrane destruction.

(G): cell disruption and formation of apoptotic bodies.

(H): lysis of apoptotic bodies.





Mechanisms of Apoptosis

There are two major apoptosis pathways that involved in regulation of cell fate death or survival:

1) External Pathway (Extrinsic Pathway) or Caspase dependent pathway.

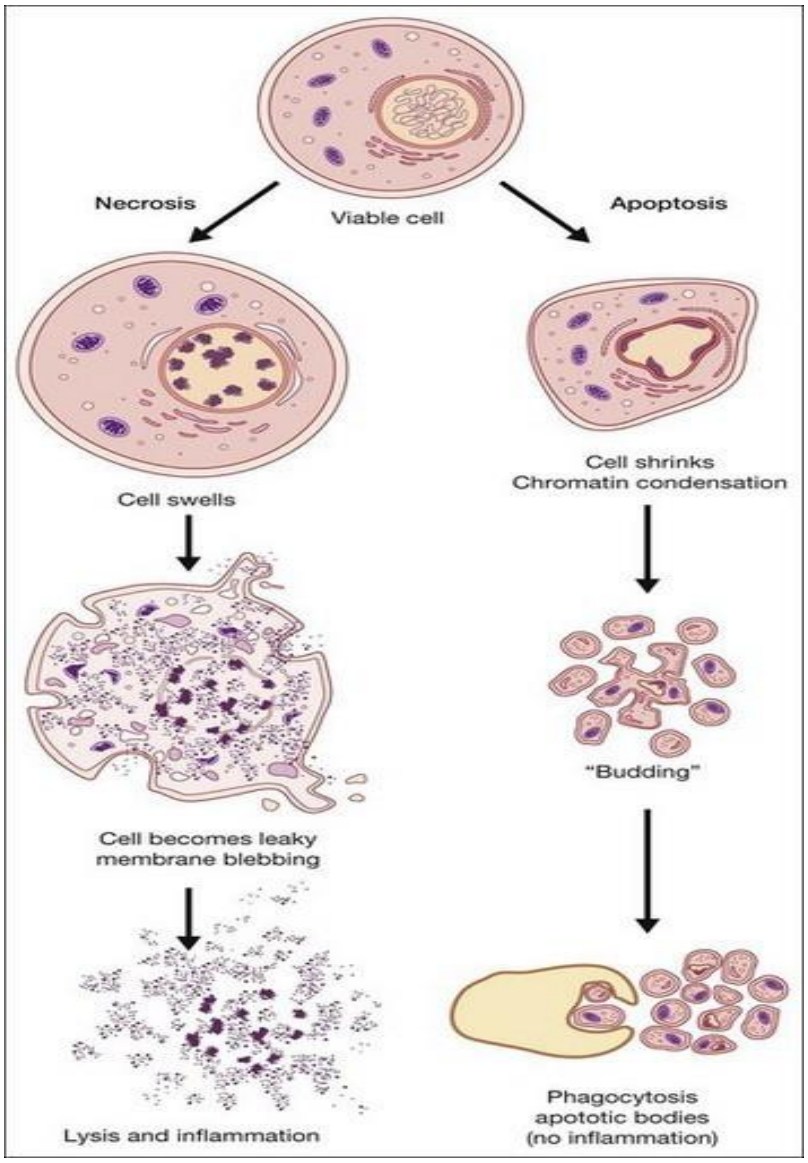
2) Internal Pathway (Intrinsic Pathway) or Caspase independent pathway in which the mitochondria, as the cross-talk organelles, can connect in this pathway.

Necrosis VS. Apoptosis

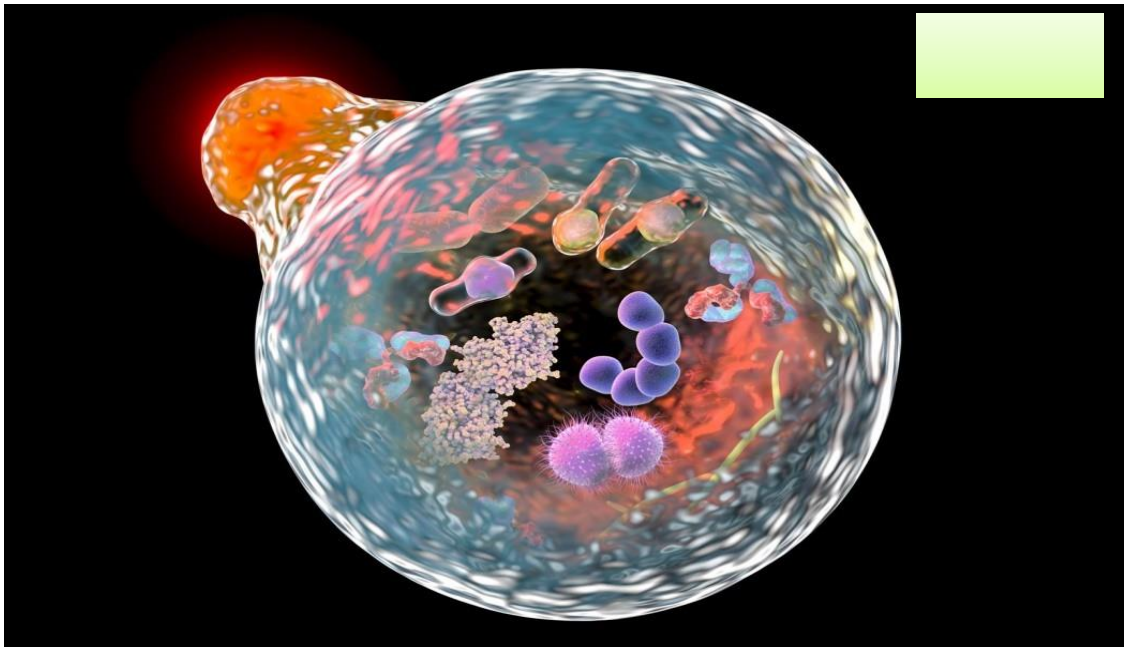
The big pathophysiological difference between necrosis and apoptosis is inflammation.

Necrosis culminates in the uncontrolled release of antigens due to the rupture of the plasma membrane which lead to activation of the immune system and inflammation.

Whereas in apoptosis cell-bound bodies are formed which are phagocytosed by neighboring cells and there is an absence of inflammation.



Autophagy (“self-eat”)



Autophagy can selectively degrade damaged or dysfunctional organelles, remove aggregated proteins and eliminate intracellular pathogens.

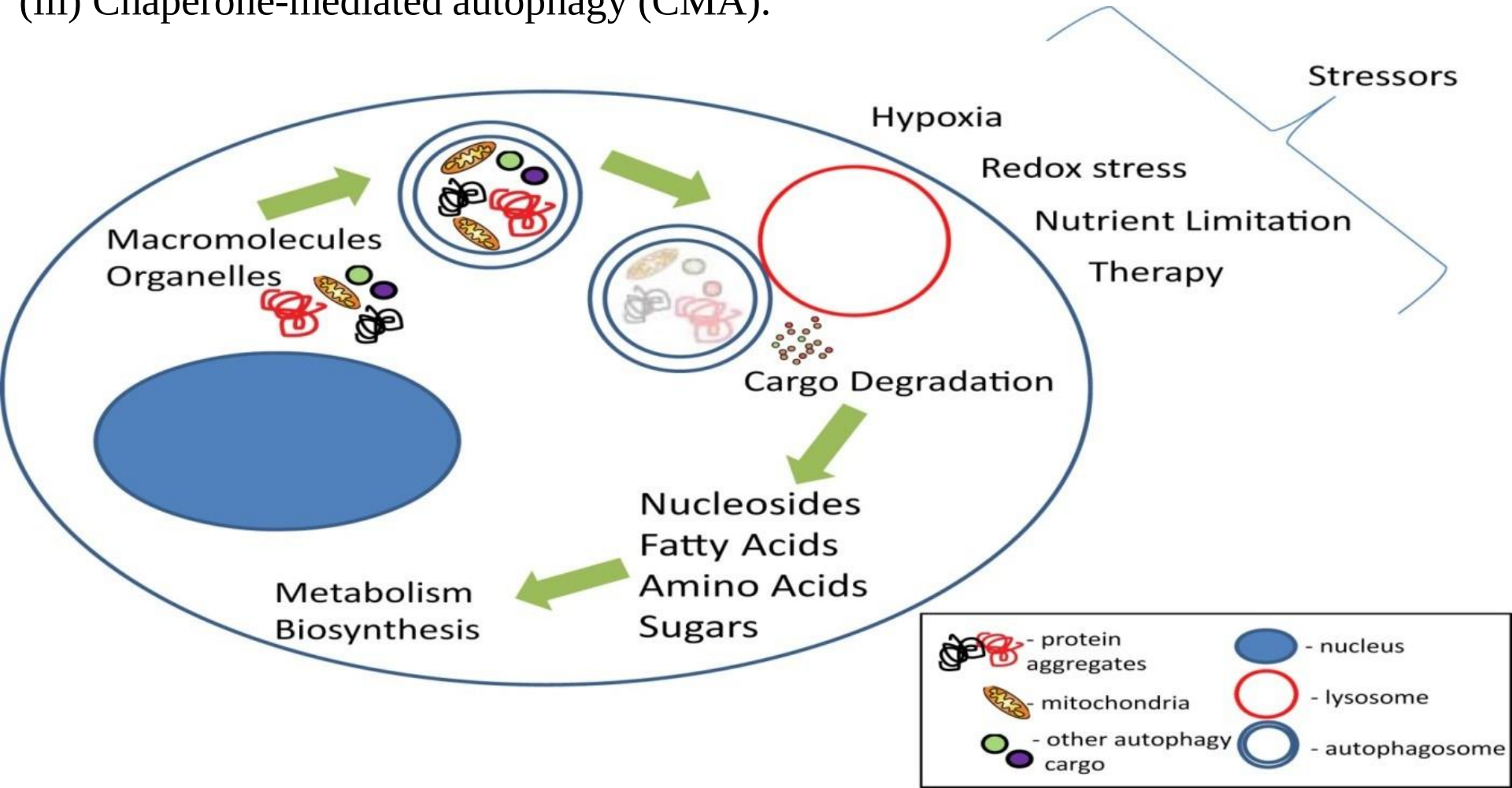
fusion of a lysosome (upper left) with an autophagosome during the process of autophagy.

Autophagy is a cellular process in which proteins and organelles become degraded through lysosomes in order to maintain an adequate cellular homeostasis. In mammals, three different types of autophagy pathways have been described,

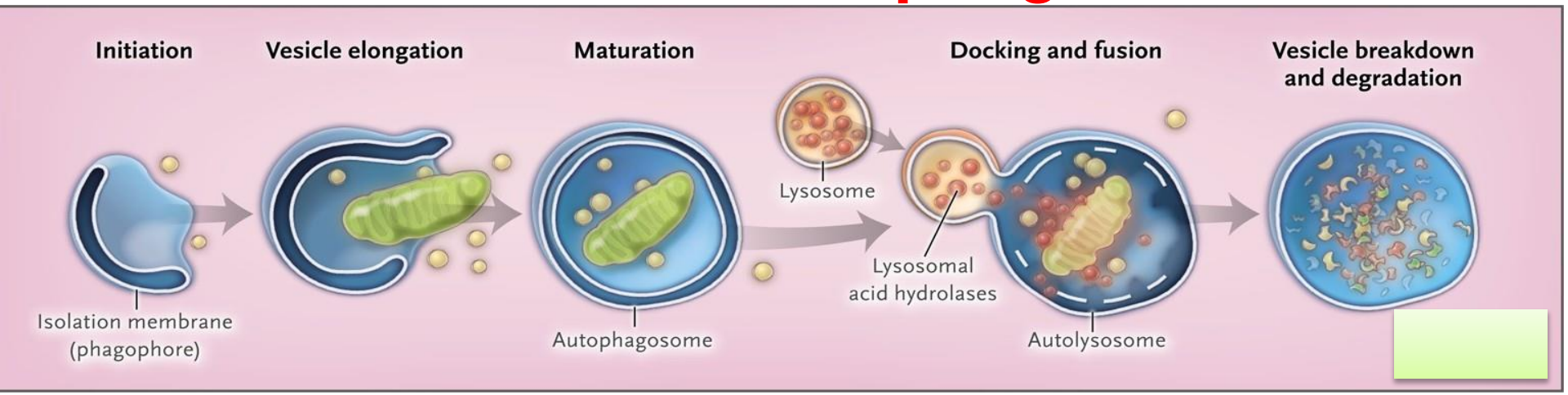
(i) Macroautophagy (mostly known as "autophagy").

(ii) Microautophagy.

(iii) Chaperone-mediated autophagy (CMA).



Phases of the Autophagic



The autophagic pathway proceeds through several phases, including:

1. **Initiation**: formation of double-membrane bound vesicles called phagophore.

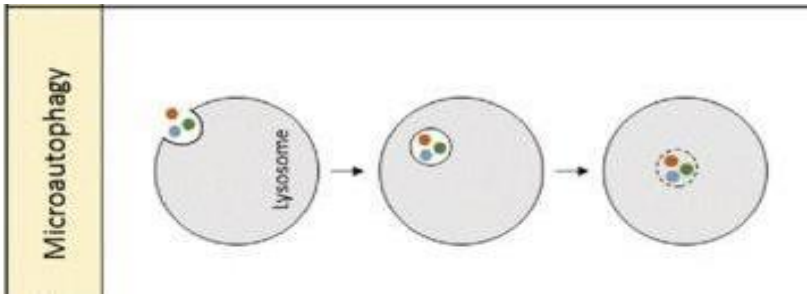
2. **Vesicle elongation** in which the isolation membrane or phagophore develops: this cytoplasmic sequestering structure is effectively an incomplete/unsealed autophagosome.

3. **Autophagosome** which grows, and ultimately seals to form a 3D structure with double membrane that is the completed autophagosome.

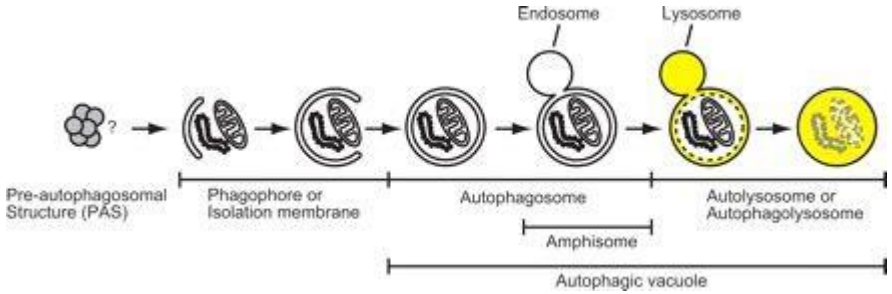
4. **Autolysosom**e in which autophagosome–lysosome are fused.

5. **Vesicle degredation** in which the autophagosomal contents (macromolecules are degraded into their constitutive building blocks by acidic hydrolases that are released back into the cytoplasm via specific retrograde pumps for metabolic recycling.

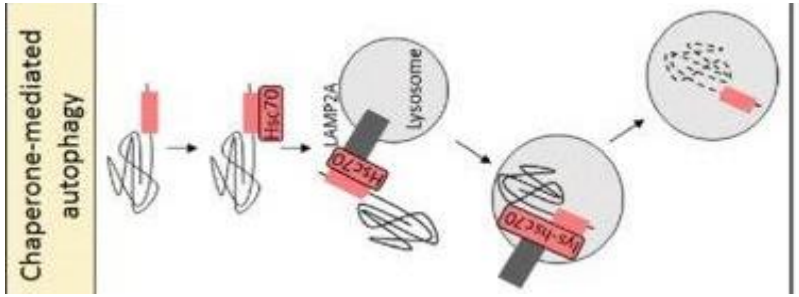
Types of autophagy



Microautophagy, the non-selective lysosomal degradative process, involves direct engulfment of cytoplasmic cargo at a boundary membrane by autophagic tubes, which mediate both invagination and vesicle scission into the lumen. With its constitutive characteristics, microautophagy of soluble substrates can be induced by nitrogen starvation or rapamycin via regulatory signaling complex pathways.

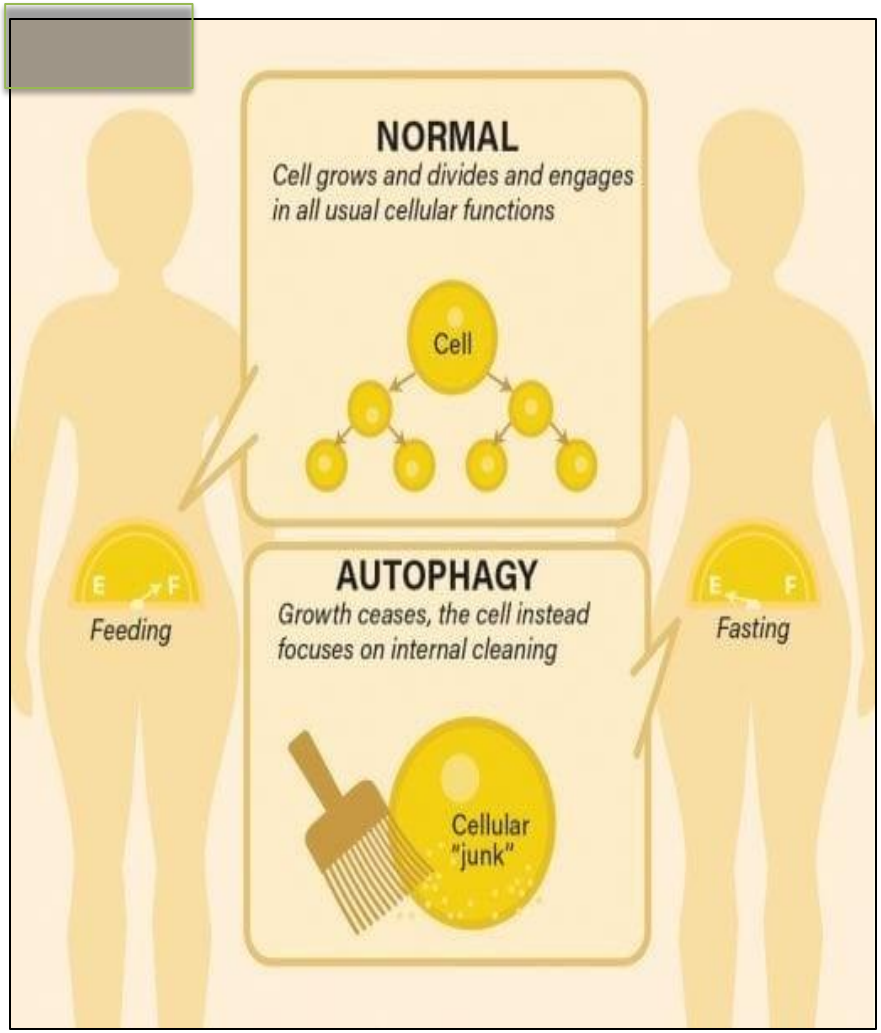


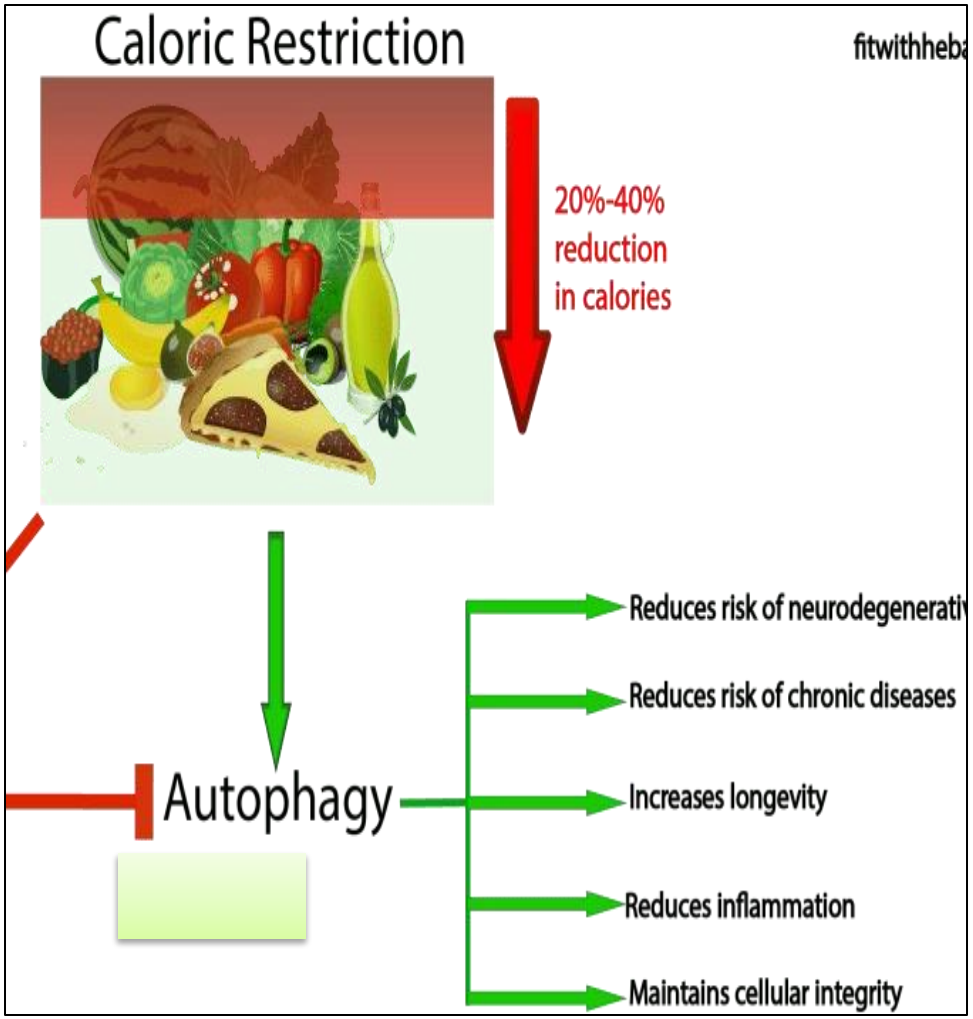
Macroautophagy: A portion of cytoplasm, including organelles, is enclosed by a phagophore or isolation membrane to form an autophagosome. The outer membrane of the autophagosome subsequently fuses with the endosome and then the lysosome, and the internal material is degraded. In yeast, autophagosomes are generated from the PAS, which has not yet been identified in mammalian cells. The nomenclature for various autophagic structures is indicated.



Chaperone-mediated autophagy (CMA) is a lysosomal-dependent protein degradation pathway. At least 30% of cytosolic proteins can be degraded by this process. The two major protein players of CMA are LAMP-2A and HSC70. While LAMP-2A works as a receptor for protein substrates at the lysosomal membrane, HSC70 specifically binds protein targets and takes them for CMA degradation. Because of the broad spectrum of proteins able to be degraded by CMA, this pathway has been involved in physiological and pathological processes such as lipid and carbohydrate metabolism, and neurodegenerative diseases, respectively.

autophagy has a greater variety of physiological and pathophysiological roles than expected, such as starvation adaptation, intracellular protein and organelle clearance, development, anti-aging, elimination of microorganisms, cell death, tumor suppression, and antigen presentation.

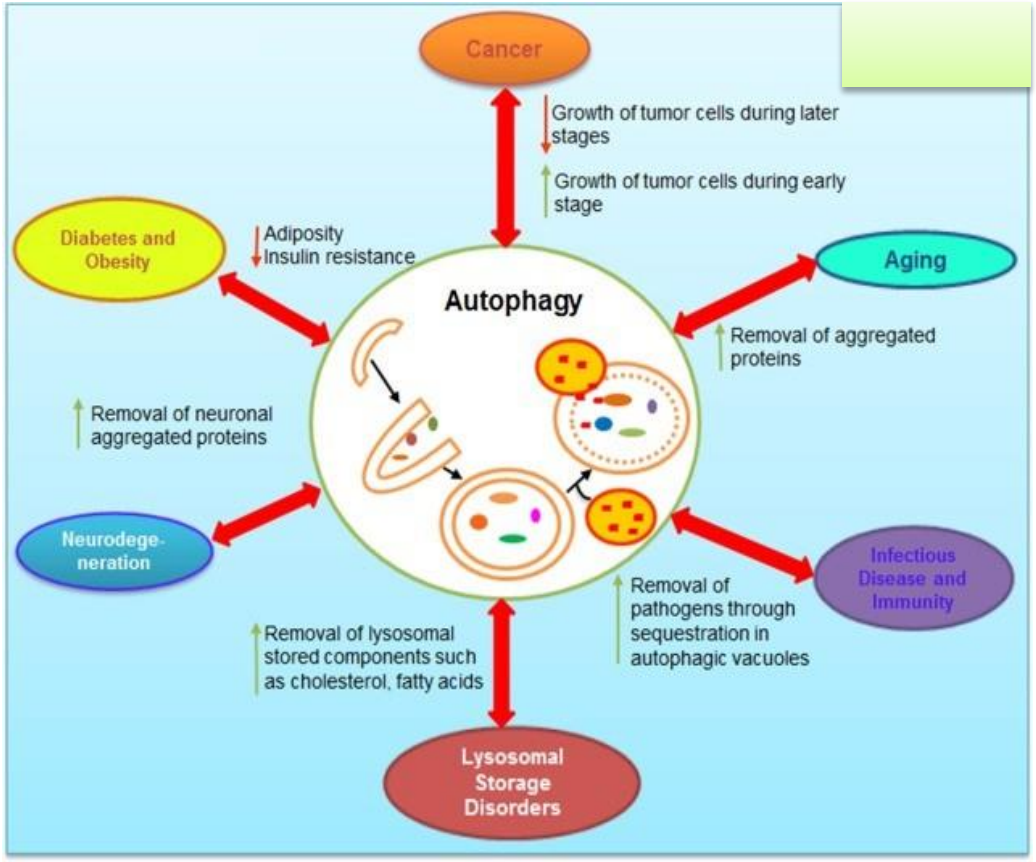




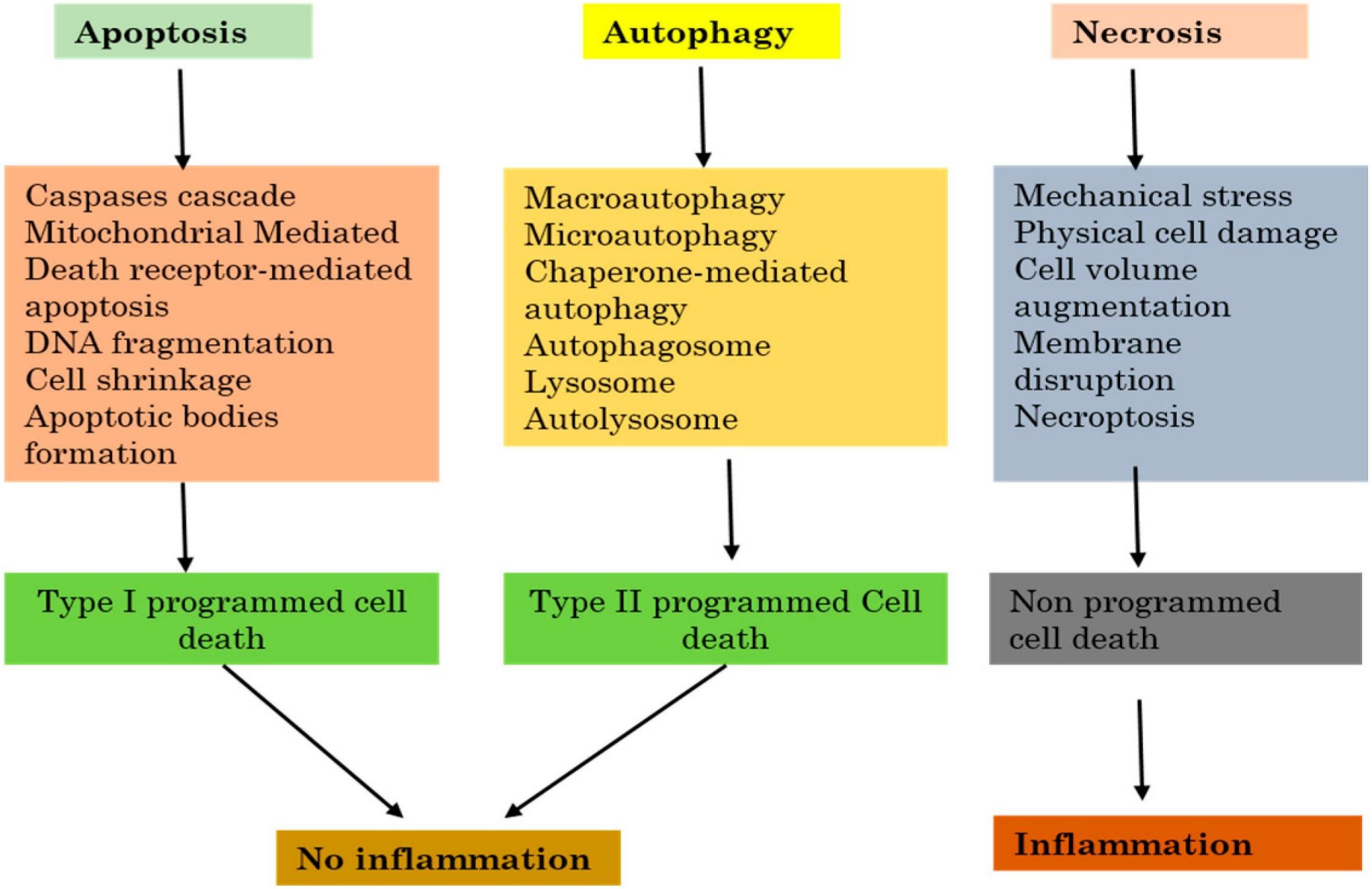
Autophagy and Diseases

The induced autophagy normally prevents stress responses that are leading for causing diseases. When autophagy inhibits this will implicate in a wide range of diseases:

- **Infectious diseases**, where autophagy is required to clear invading pathogens and contributes to the acquired immune response,
- **Degenerative diseases** (e.g, neurodegenerative conditions; heart disease; diabetes).
- **Aging**
- **Metabolism diseases**
- **Cancer**



Differences between Apotosis, Autophgay, and Necrosis



Any Question?
Thanks for Listening