APOPTOSIS

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INTRODUCTION & DEFINITION

- Coordinated and internally programmed cell death.
- Greek word meaning “falling off or droping off”.
- First introduced in 1972 and differ from necrosis by being a form of cell death which is controlled and regulated by rate of cell division,when the cell is not needed, pathway of cell death is activated(cell suicide).
- It is not accompanied by inflammation and collateral tissue damage.

APOPTOSIS IN BIOLOGIC PROCESSES

- *PHYSIOLOGICAL PROCESS*:

- Organised cell destruction in sculpting of tissue during development of embryo.
- Physiological involution of cells in hormone dependent tissues.
- Normal cell destruction followed by replacement proliferation like intestinal epithelium.
- Involution of thymus in early age.

- *PATHOLOGICAL PROCESS*:
- Cell death in tumours exposed to chemotherapeutic agents
- Cytotoxic t cell mediated cell death
- Depletion of CD4+ t cells in AIDS
- Cell death in viral infection
- Pathologic atrophy of organs and tissue on withdrawal of stimuli
- In response to certain injurious agent like radiation,hypoxia ,mild thermal injury etc.
- Degenerative disease of CNS.e.g. Alzheimer's disease,Parkinson's disease,Chronic infective dementias
- Heart diseasese.g. heart failure, acute MI.

PHASES OF APOPTOSIS

- Divided in to : initiation phase and execution phase.

a) Initiation phase: Apoptosis is initiated by two distinct pathways:

1)Intrinsic or mitochondrial pathway.

2) Extrinsic or death receptor pathway.

1)Intrinsic or mitochondrial pathway: activated by intracellular signals.

- ROLL OF MITOCHONDRIA IN APOPTOSIS:

- Mitochondrial damage is the major mechanism in a variety of physiological and pathological apoptosis.
- Mitochondria contain proteins capable of inducing apoptosis ,like cytochrome c and several proapoptotic proteins.
- Survival of apoptosis of cell is determined by permeability of mitochondria.
- Mitochondrial permeability is controlled by Bcl-2 family of more than 20 protein which is divided into proapoptotic and anti apoptotic proteins.

- Pro apoptotic proteins: Bax,Bak,Bid,Bad and Bik,BclxS(Stimulate)
- Anti apoptotic proteins: Bcl2,Bcl-xL(lower),Mcl-1

They prevent leakage of mitochondrial proteins that trigger apoptosis.Growth factors and survival signals stimulate production of anti apoptotic protein.

If the balance shifts to proapoptotic proteins the apoptotic cascade is activated.

- CAUSES OF MITOCHONDRIAL INJURY:

- Deprivation/ withdrawal of growth factor or survival signals.
- DNA damage by radiation, cytotoxic drugs,hypoxia either directly or through free radicals.
- Accumulation of excessive amount of misfolded proteins.
- Increased intracellular free calcium.

2) Extrinsic or death receptor pathway: Initiated by extracellular signals.

- Many cells express “death receptors” molecules on the surface of plasma membrane that trigger apoptosis.
- Death receptors are members of the TNF receptor family that contain death domain because it is essential for delivering apoptotic signals.
- It is activated by binding of fas ligand to CD95(Member of TNF receptor family) **or** binding of TRAIL(TNF related apoptosis inducing ligand) to death receptor DR4 and DR5.

- Functions of extrinsic pathway:Involve in eliminating-

-Self reactive lymphocytes thereby avoiding autoimmunity.

- Virus infected cells and tumour cells through cytotoxic T lymphocytes.

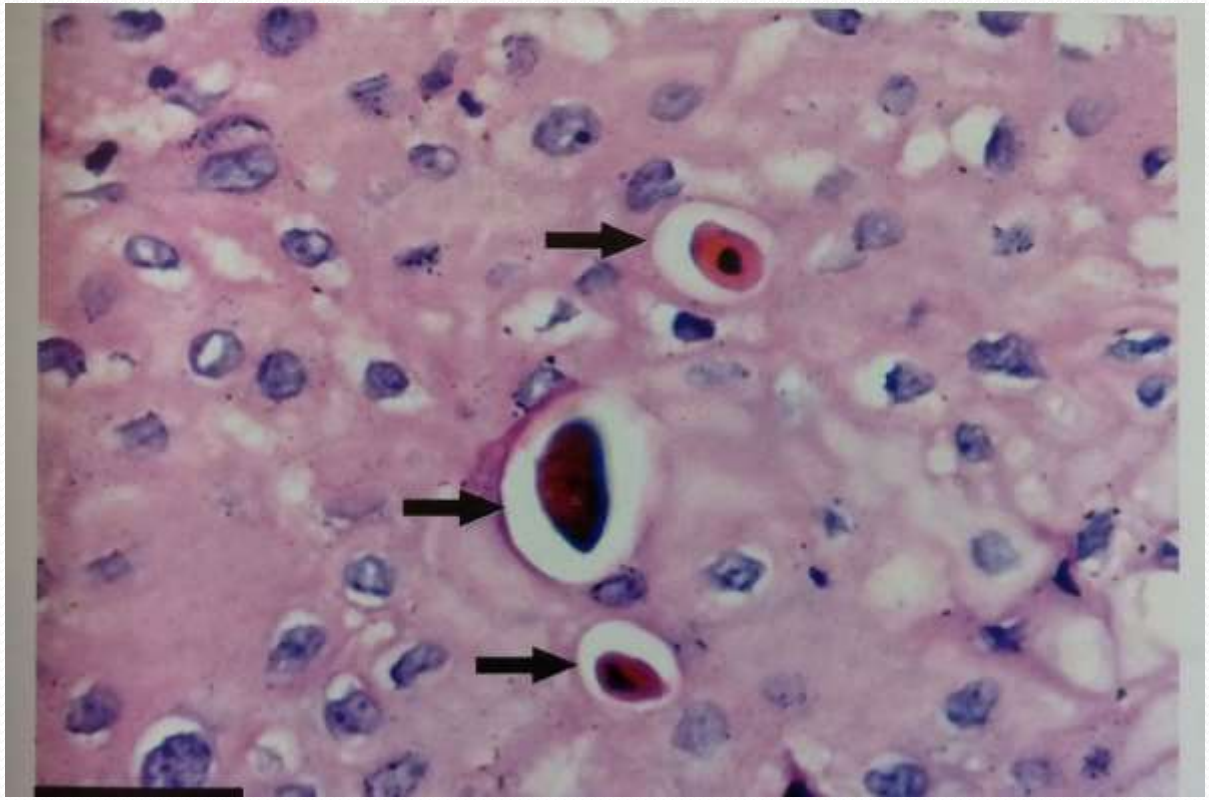
b) Execution phase of apoptosis:

- Executioner caspases act on many cellular components and activate Dnase,which induces fragmentation of nuclei.
- Caspases also degrade components of nuclear matrix and cytoskeleton resulting in fragmentation of involved cells.

MORPHOLOGICAL CHANGES

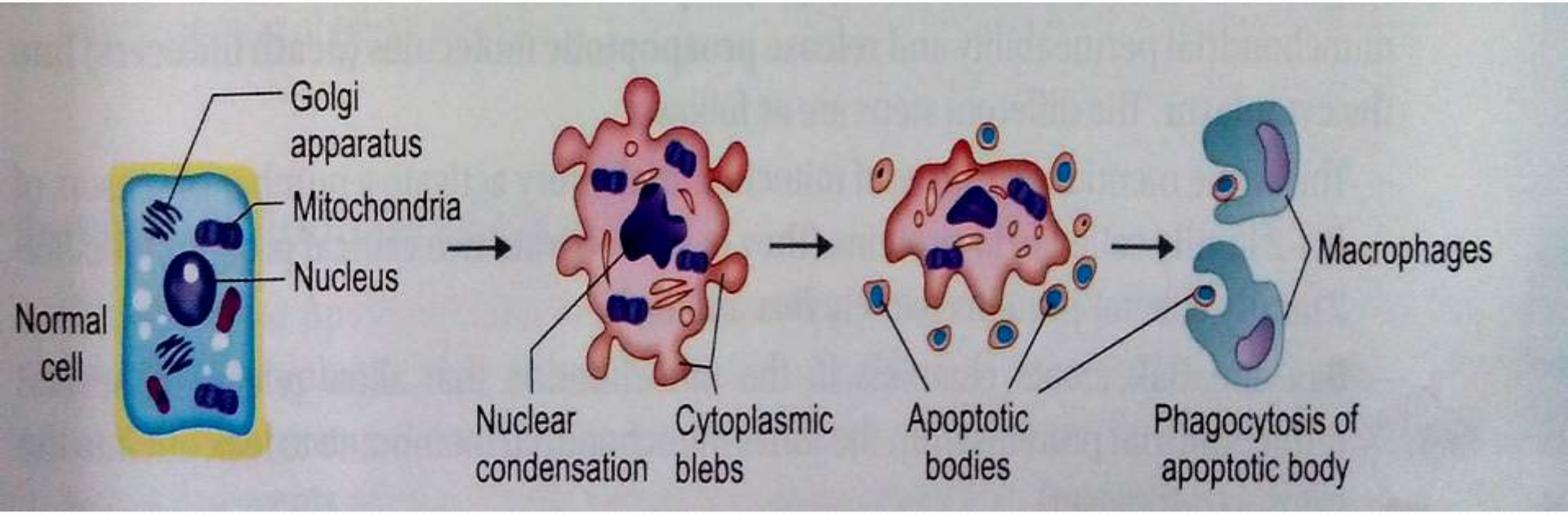
- LIGHT MICROSCOPY:

- The apoptotic cells appear as round or oval mass having intensly eosinophilic cytoplasm.
- Nuclei- appear as fragments of dense nuclear chromatin and shows pyknosis.



- ELECTRON MICROSCOPY:

- Cell shrinkage:cytoplasm becomes dense.
- Nuclear condensation and fragmentation: under nuclear membrane.
- Formation of cytoplasmic blebs and apoptotic bodies:apoptotic bodies are composed of cytoplasm and tightly packed organelles with or without nuclear fragments.
- Phagocytosis of apoptotic cells/bodies: ingested by phagocytes and degraded by lysosomal enzymes of phagocytes.


Golgi apparatus
Mitochondria
Nucleus
Normal cell
Nuclear condensation
Cytoplasmic blebs
Apoptotic bodies
Phagocytosis of apoptotic body
Macrophages

REMOVAL OF APOPTOTIC CELLS

- Phagocytosis: by phagocytic cells mainly macrophages within minutes.
- Factors faviring phagocytosis:

- Expression of phosphatidylserine: The cells undergoing apoptosis express phosphatidylserine on outer layer of membrane that is normally present on the inner leaflet of plasma memb..That help in easy recognition of cells by phagocytes.
- Secretion of soluble factors like thrombospondin that recruit phagocytes.
- Natural antibodies and proteins of the complement system may coat apoptotic bodies which aids in phagocytosis.

THANK YOU