Cell injury

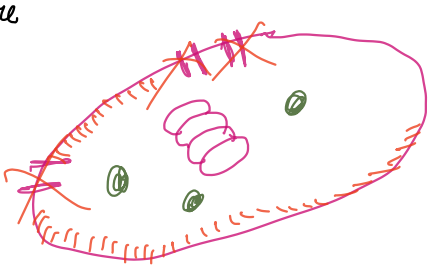
Reversible cellular injury

CI → Ischaemia
CI → hypoxia

Due to ↓ ATP

→ Ischaemia – Aerobic resp ↓ – glucose availability ↓ ∴ faster effects of CI

hypoxia – Anaerobic resp ↑ → CI less severe



pathogenesis :

i) Intracellular lactic acidosis : Nuclear clumping

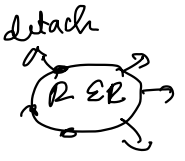
O_2 ↓ → aerobic resp by mt fails → anaerobic glycolytic pathway

Clumping nucleus ← lactic acidosis ← ↑ lactic & CPK ↓)

ii) Damage of plasma memb pumps

ATP ↓ → PL ↓ → ∴ repair of memb ↓ → damage to membrane pumps [Na-K & Ca]

iii) Reduced protein synthesis



Hypoxia → membranes of ER & golgi swells → ribosomes detach from RER & polysomes degranules to monosomes

Morphology :

Cell memb → blebs } plasma memb pumps.
ER → swollen (swell) } protein synth ↓
Ribosomes → dispersed
lysosomes → Autophagy
mc → swollen
nucleus → clumped } lactic ā

R C I

R → Ribosome detach ↓ protein ↓
C → cell memb repair ↓ due to ↓ PL due to ↓ ATP ∴ plasma memb pump ×
I → lactic acidosis ↓ nucleus clumping.

Irreversible CI

•) Ca influx (mitochondrial damage) → continued hypoxia → Ca accumulation in mc ↑ → disables mc

•) Activated phospholipases

Ca ↑ → activates PL → degradation of memb PL → ∴ memb degradation → ATPase activated-ATP ↓

•) Activated intracellular proteases (degrades proteins)

→ cytoskeleton, microtubules, filaments – damaged

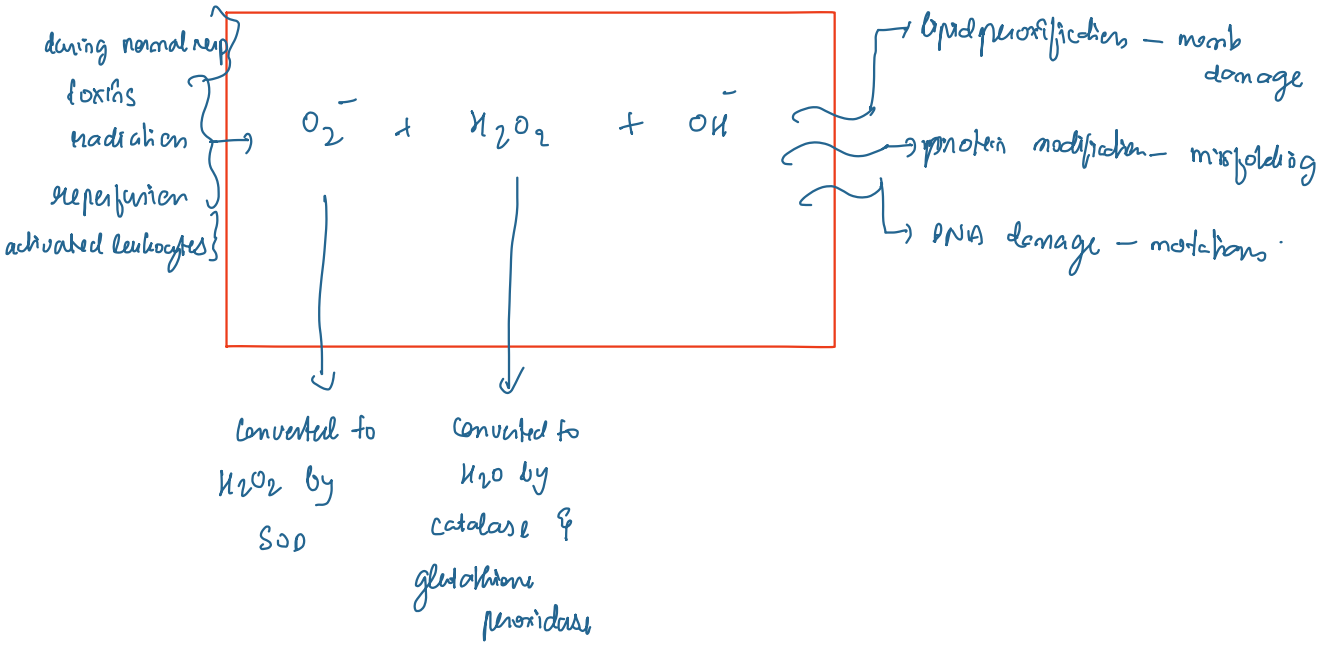
•) Activated endonucleases (nuclear damage)

Nucleoproteins damaged by activated endonuclease & proteases

•) lysosomal hydrolytic enzymes

- lysosome memb damage → escape of lysosomal hydrolytic enzymes → cell death

Free radical injury



Apoptosis

It is a type of cell death that is induced by tightly regulated suicidal program by the activation of intrinsic enzymes of the cell that degrade its own DNA content & proteins

- Imbalance b/w pro apoptotic & antiapoptotic
- results from activation of enzymes called caspases

Phases
- Initiation → Intrinsic (mitochondrial)
- Initiation → extrinsic (death receptor initiated)
- execution

} pathways

Intrinsic & INTRINSIC PATHWAYS

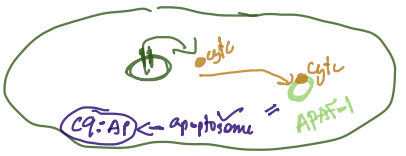
- mitochondrial damage : major mech of apoptosis
- mc contains proteins that are capable of inducing apoptosis . eg. cytc , proapoptotic proteins
- survival from apoptosis determined by the permeability of mc memb
  ↓
  permeability controlled by BCL2 family (oncogene of B-cell lymphoma)

BCL 2 family

- Proapoptotic: BAX , BAK
- Antiapoptotic: BCL-2, mCL-1, BCL-xL
  * prevents leakage of mc contents
  * GF & other signals help in the production of antiapoptotic proteins

o Causes of mc injury :
  * ↓ GF or survival signals (↓ antiapoptotic)
  * ↑ accumulation of Ca
  * ↑ misfolded proteins
  * DNA damage by radiation , cancer drugs or hypoxia

Steps in intrinsic pathway :



B

mc injury → activate no. of sensors of BCL2 family (BH3 proteins) → activate BAX & BAK (proapoptotic)

BAX & BAK create channels in the mc membrane

release of mc proteins from inner mitochondrial membrane to cytosol

cytochrome c binds to apoptosis-activating factor-1 (APAF-1)

cyto-APAF1

caspase-cascade activation (apoptosome) → this complex binds to caspase 9 (critical initiator)

cytoplasm of normal cells blocks the activation of caspase & functions as inhibitors of apoptosis (IAPs)

other mc proteins blocks the action of IAPs & initiate caspase-cascade

(BH3 proteins blocks the action of antiapoptotic proteins BAX & BAK)

Extrinsic (death receptor pathway)

* Initiated by extracellular signals
* many cells have death receptors on the plasma memb that triggers apoptosis
  - TNF family
  - contains a cytoplasmic domain called death domain
    - essential for giving apoptotic signals.

* extrinsic pathway gets activated when death receptors gets activated
* Death receptor (includes) — TNF-1 receptor & a related protein (Fas-CD95)
  - binding ligand of fas called fas-ligand (FasL-CD95L)

functions of extrinsic :

* self reacting lymphocytes elimination - ∴ prevent autoimmunity
* eliminates virus infected cells & tumor cells

STEPS :

* extrinsic pathways becomes activated when Fas/CD95 binds to the ligand FasL/CD95L

↓

FasL binds to the receptor (Fas), which cytoplasmic death domain gets binded to an adaptor protein (Fas-associated death domain - FADD)

↓

FADD binds to procaspase-8

↓

generates activate caspase-8 (initiator)

↓

activates another series of caspases (executioners) ie C3 & C6

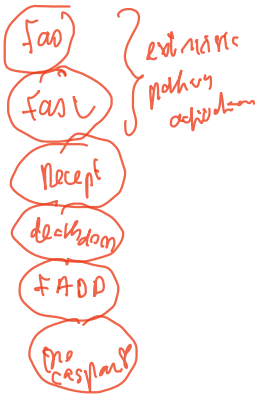
↓

C3 & C6 acts on many cellular components & activates DNAase

↓

fragmentation of nuclei

degrades the nuclear matrix & cytoskeleton



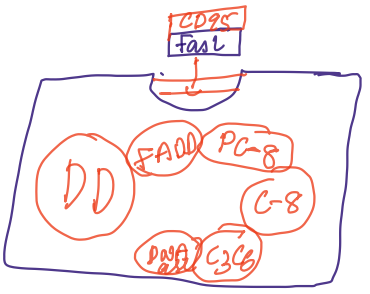
activates caspase-8

↓

C3 & C6

↓

DNAase



executioner phase

mediates final stage of apoptosis

Removal of apoptotic cells

* Phagocytosis : macrophages engulfs — disappear within minutes

↳ factors favouring phagocytosis

→ expression of phosphatidyl serine

→ secretion of soluble products (eg. thrombospondin)

→ Natural antibodies & proteins of the complement system

phosphatidyl serine

soluble products

- Disorders with Reed apoptosis :

  - Neurodegenerative disorders
  - Virus infected cells

TABLE 1.5: Differences between apoptosis and necrosis

Features	*Apoptosis*	*Necrosis*
Cause	Often physiological, means of eliminating unwanted cells; may also be pathological	Invariably pathological
Biochemical events	Energy-dependent fragmentation of DNA by endogenous endonucleases	Impairment or cessation of ion homeostasis
Lysosomes	Intact	Leak lytic enzymes
Morphology		
Extent	Single or small cluster of cells	Involves group of cells
Cell size	Cell reduced (shrinkage) and fragmentation to form apoptotic bodies with dense chromatin	Cell enlarged (swelling) and undergo lysis
Integrity of cell membrane	Maintained	Disrupted/lost
Nucleus	Fragmentation into nucleosome-size fragments	Pyknosis, karyorrhexis, karyolysis
Cellular contents	Intact; may be released in apoptotic bodies	Enzymatic digestion; may leak out of cell
Adjacent Inflammatory response	None	Usual
Fate of dead cells	Ingested (phagocytosed) by neighboring cells	Ingested (phagocytosed) by neutrophil polymorphs and macrophages
DNA electrophoresis	DNA laddering is seen	Shows smearing effect
TUNEL staining	Positive	Negative

Apoptosis : No inflammatory response from adjacent tissue.

Leakage of proteins from the necrotic cells into the circulation is useful for identifying the necrosis using blood and serum samples.

Necrosis

Necrosis is characterized by denaturation of cellular proteins, leakage of cellular contents through the damaged membranes, local inflammation & enzymatic digestion of lethally injured cell.

denaturation of cellular proteins → leakage of cellular contents → local inflammation
↓
enzymatic digestion of cell

MoA

Membrane damage
↓
leakage of cellular contents ie ATP & uric acid
(Damage associated molecular patterns, DAMPs)
↓
recognised by receptors on the macrophages
↓
trigger phagocytosis
↓

prodn of cytokines & induction of inflammation

↓

Release of proteolytic enzymes by inflammatory cells

↓

phagocytosis + enzymatic digestion of cells leads to clearance of necrotic cells

Morphology

* Red eosinophilia
* Glassy, homogenous (due to loss of glycogen particles)
* Dead cells are replaced by myelin figures (whorled phospholipid precipitates)
* Nuclear changes
  - Karyolysis (DNA loss)
  - Karyorrhexis (nucleus fragmentation)
  - Pyknosis (nucleus condenses, clumping of chromatin)

Types of necrosis

i) Coagulative necrosis

- Architecture of dead cell is retained for a span of some days
- Affected cells have firm texture
- Denaturation happens to both enzymes & proteins, ∴ blocks the proteolysis of the dead cells ⇒ Red eosinophilic
- Infiltrating leukocytes produces lysosomal enzymes which causes the breakdown of dead cells
- leukocytes also clean the necrotic cells by phagocytosis
- Area of necrosis ∴ infarct

  eg. Heart

2) Liquifactive necrosis.

- digestion of dead tissue, which leads to the transformation of the tissue to a viscous liquid.
- Seen in bacterial or fungal infections, because microbes stimulate the accumulation of leukocytes & liberation of enzymes these cells