Cell Adaptations:-

Types of cells: → continuously dividing

1.) **Labile cells** - those that continuously divide eg cells of intestinal lining, skin, duct epithelia, mucosa.

2.) **Stable cells** - after reaching adult size → do not divide further; but if any injury occurs - they divide
eg - Hepatocytes, renal cells

3.) **Permanent cells** - do not divide
eg - Cardiocytes, neurons
out of cell cycle

Adaptations:-

→ Reversible, structural responses to physiologic stress (eg. pregnancy) & pathologic stress.
→ during which new but altered steady states are achieved.
→ allowing the cell to survive & continue to function

5 types of adaptations:-

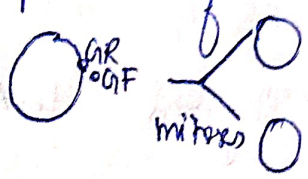
1) Atrophy
2) Hypertrophy
3) Hyperplasia
4) Metaplasia
5.) Dysplasia

1.) Hyperplasia -

↑ no. of cell, seen in tissue made up of labile & stable cells

Mech:-

↑ production of GF & GF receptors.



- **Physiological:-**
  1) female breast at puberty & lactation, pregnancy
  2) Enlarged size of uterus (hypertrophy)
  3) Proliferation of endometrium after normal menstrual cycle.

Pathological:-

1.) Endometrial hyperplasia following estrogen excess.
2.) Formation of sebaceous from hyperplasia of epidermis due to HPV.
3.) Compensatory hyperplasia

2.) HYPERTROPHY:-

↑ size of cells
⇒ only adaptation that can be done by permanent cell.

stress → ↑ adaptation → ↑ ↑ ↑

- **Mechanism:-**
  ↑ size is not due to cellular swelling, its due to more structural components/ cellular protein.

Physiological :-
Enlarged size of uterus in pregnancy.

- Pathology -
1) Hypertrophy of cardiac muscle in systemic hypertension or astic stenosis.
2) Hypertrophy in smooth muscles -
Cardiac achalasia (in oesophagus)
↳ LES doesn't relax
3) Hypertrophy of skeletal muscle -
athletes & manual labourers.

3) Atrophy :-
↓ in size & cell → still viable
Mechanism :- Reduction in cell organelle.

Physiological :-
1) Atrophy with lymphoid tissue with age.
2) Thymus → adult life.
3) Gonads → after menopause
4) ↓ in size of uterus after parturition
5) brain - ageing
6) Osteoporosis with ↓ in size of bony trabeculae due to ageing.

Pathologic -
1) Starvation Atrophy : cachexia - cancer
2) Ischaemic - atrophic kidney in atherosclerosis of RA.
3) Neuropathic atrophy - Poliomyelitis
4) Disuse Atrophy
5) Endocrine atrophy - hypopituitarism
↓ atrophy of
thyroid, adrenal, gonad
6) Pressure Atrophy - tumour
7) Idiopathic

4) Metaplasia :-
Reversible Δ of one type of mature adult cell by another mature adult cell.
2 types :- Epithelial :- Columnar, Squamous
Mesenchymal :- Osseous, Cartilaginous

(*) Mechanism :-
Reprogramming of stem cells that are known to exist in normal tissues

(*) Columnar Metaplasia :-
Ectocervix in vagina because of HPV inf.
LE because acid reflux in Barrett's oesophagus

(*) Squamous Metaplasia
→ Bronchus in chronic smokers.
→ endocervix of female in prolapse of uterus.
→ Gall bladder in cholelithiasis.
→ Prostate - Chronic prostatitis
→ Vitamin A def - squamous metaplasia in nose, bronchial, lacrimal & salivary glands.

5.) Dysplasia :-
disordered cellular development.
↑ no. of layers, disorderly arrangement, loss of basal polarity, pleomorphism,
↑ N/C ratio, nucleus hyperchromatism
↑ mitotic activity.

MORPHOLOGY OF REVERSIBLE CELL INJURY

1) Generalized swelling - cell membrane intact
2) Blebs
3) ER swelling
4) Dispersion of ribosomes
5) Mitochondrial swelling + small densities
6) Autophagy by lysosomes.
7) Nucleus - clumping

IRREVERSIBLE

1) Shrink
2) Defects in cell membrane; ruptured
3) Lysis of ER
4) Mitochondrial swelling + large densities
5) Rupture of lysosomes.
6) Nucleus - pyknosis - compaction
karyorrhexis - fragmentation
karyolysis - fading of basophilia
dissolution

Mechanism of cell injury:

5 mechanisms:

1) ATP depletn
2) Mitochondrial damage
3) Incr of calcium homeostasis
4) Defects in membrane permeability
5) Free radical injury

ATP depletn
- ↓ Na+ pump → ↑ influx of Ca++, Na+ & H2O; ↑ efflux of K+ → ER swelling
- ↓ Aerobic glycolysis → ↓ glycogen, ↑ lactic acid → ↓ pH → clumping of nuclear chromatin; cellular swelling; Incr of mitochondrial Ca++; Blebs
- detachment of ribosomes → ↓ protein synth

Mitochondrial Damage

↓ O2 supply / toxins / radiatn → mitochondrial damage → ↑ permeability → ↓ ATP generatn; ↑ production of ROS → multiple cellular abnormalities → Necrosis

↓ survival signals / DNA, protein damage → ↑ Pro-apoptotic prot; ↓ anti-apoptotic pro → leakage of mitochondrial proteins (cyto c) → apoptosis

3) Loss of calcium homeostasis :-

↑ cytosolic Ca^{2+}

- Activate cellular enzymes → ATPase
- ↑ mito permeability transition → ↓ ATP
- Phospholipase → ↓ phospholipids
- Protease → disrupt membrane & cytoskeletal proteins
- Endonucleases → nuclear damage

4) Defects in cell membrane :-

5) Free Radical Injury -

ROS generated within mitochondria.

$O_2 \rightarrow O_2^- \rightarrow OH^- \rightarrow H_2O_2$

Fenton Rxn :- $H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH^- + OH^-$

Haber Weiss → $H_2O_2 + O_2 \rightarrow 2OH^- + O_2$

Types :-

1) O_2^- ⇒ one e^-
2) H_2O_2 → 2 e^-
3) OH^- → 3 e^-

⇒ They react with & damage proteins, lipids, carbs & NA.

② Lipid peroxidation in cell membrane
③ Oxidation of AA & proteins resulting in fragmentation
④ Protein - protein cross linkages.

Removal :-

1) Superoxide dismutase
2) Glutathione peroxidase
3) Catalase
4) Vit E & C
5) transferrin, ferritin & ceruloplasmin

$O_2^- \xrightarrow{SOD} H_2O_2 \xrightarrow{Fenton} OH^{\cdot} + OH^-$

catalase → H_2O

GSH → GPx → GSSG → GR → GSH

Cell Injury

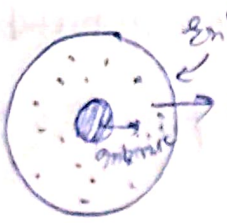
$O_2 \rightarrow O_2^- \xrightarrow{SOD} H_2O_2 \xrightarrow{GPx} OH^- \rightarrow H_2$

catalase → H_2O

Cell Death

- Apoptosis
- Necrosis

Pathway of cell death that is induced by a tightly regulated intracellular program in which cells destined to die activate enzymes (caspase) degrade the cells own nuclear DNA & cytoplasmic proteins



↓ no leakage ; no inflammatn

↓

phagocyte engulf apoptotic bodies

⇒ Apoptosis - generally involves single cell

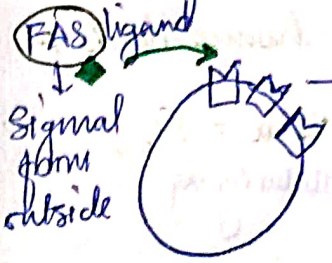
Apoptosis

Physiological
- Embryogenesis
- Elimination of potentially self-reacting lymphocytes
- Hormone dependent involution of uterus & breast
- Death of cells that have completed their functions

Pathological
- Cell death in tumour exposed to chemotherapeutic drugs
- Progressive depletion of CD4+ T cell in the pathogenesis of AIDS
- Cell death in viral infection eg - formation of councilman bodies in viral hepatitis.

Mechanism

- Extrinsic
  - IP
  - EP
- Intrinsic
  - IP
  - EP



Extrinsic :-

CFAS / CD95 receptor

↓

procaspase - (8) → Active caspase - (8)

Fas protein (CD95)

↓

Fas receptor (death receptor)

↓

Multiple Fas receptor come together

↓

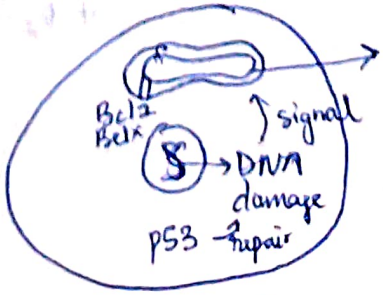
Cytoplasmic death domains combine to form FADD

↓

Activate procaspase - (8) to active caspase (8)

procaspase 8 → active caspase 8

Intrinsic - Initiation

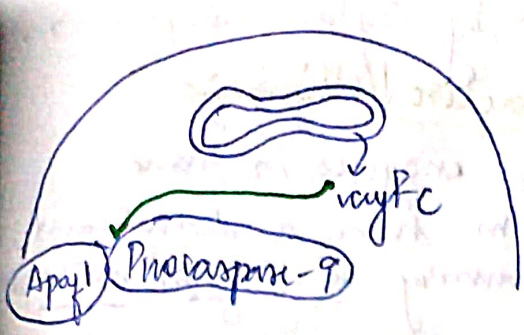


- Bcl-2
- Mcl
- Bclx

] Anti-apoptotic proteins

↓ replaced by

[Bax, Bak, Bim, Bad] Pro-Apoptotic gene proteins



cyt c takes apaf-1]

[Procaspase-9 → Caspase 9]

Stimuli

↓

[Anti-apoptotic molecules Bcl2 & Bclx are lost]

↓

[Replaced by pro-apoptotic molecules like Bak, Bax, Bim, Bad]

↓

(1) mitochondrial permeability

↓

Release to (cyt c) into cyto.

↓

Activates (Apaf1) along with procaspase-(9)

↓

[Activated caspase-9]

Execution Phase

Convergence point for both pathways.

EP → Caspase (8)

IP → Caspase (9)

[Activates caspase 3 & 7]

↓

Sequentially activates all other caspases

↓

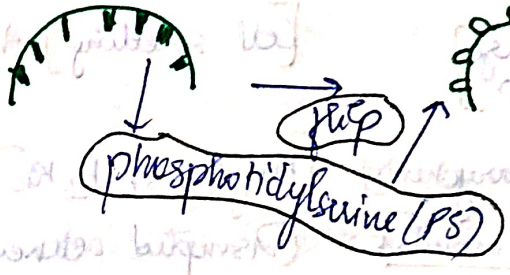
Caspases cleave cytoskeletal & nuclear matrix protein

↓

[Cell degenerate | apoptotic bodies formed]

Normally

During apoptosis



Morphological changes in Apoptosis

1.) Cellular shrinkage (earliest) eosinophilia

2.) Cellular organelles are tightly packed → eosinophilic

3.) Nuclear changes → Pyknosis - compact nucleus

Karyorrhexis - fragmentation (most characteristic features)

4.) Multiple surface blebs

5.) Apoptotic bodies

6.) Phagocytosis

plasma membrane intact

Diagnosis of Apoptosis

(1) Marker:- Annexin (5)

Apoptotic cells take up annexin V because it binds with phosphatidylserine → allow to bind

⑤ Agarose gel electrophoresis:-

Step ladder pattern - as DNA is in fragments by endonuclease.

Difference from necrosis:-

Apoptosis	Necrosis
Single or small clusters of cells.	Often contiguous cells.
Cell shrinkage Cromatin	Cell swelling
Pyknosis, karyorrhexis	Karyolysis, Pyknosis
Intact cell membrane	Disrupted cell membrane
Cytes retained in apoptotic bodies	Cytes released
No inflammation	Inflammation

NECROSIS (CCCFF)

1) Coagulative Necrosis :- m/c

→ architectural outlines persist but cellular & nuclear details are lost. (ghost cells) / tombstone appearance

→ type of tissue can be identified

Causes :- ① Ischemia (except brain) of any organ → liquefactive necrosis.

② mild burns

③ Zenker's degeneration necrosis.

Gross :-

pale, firm slightly swollen

Microscopy -

hallmark - tombstones - outlines of cells are retained & the cell type can be recognized but nuclear & cytoplasmic details are lost.

- Infiltration by inflammatory cells.

2.) Liquefactive / Colliquative

Hydrolytic enzymes in tissue degeneration have a dominant role in causing semifluid mass

Architectural, cyto, nuclear details all lost.

Causes :- Ischemia of brain

Pyogenic bacterial infections

Gross :-

Soft with liquified center containing necrotic debris

Cyst wall is formed - later

Micro :-

3.) Caseous (Cheese)

→ Dead tissue is converted into a homogenous granular mass resembling cottage cheese.

→ A, C, N - lost

→ Accumulation of amorphous debris within an area of necrosis.

Cause :- 1) TB 2) Syphilis 3) Histoplasma 4) Coccidioidomycosis.

Gross :- dry cheese, soft, granular yellowish

cheesy app → histotoxic effect of capsule of TB.

Microscopically :- Granuloma

4) Fat Necrosis - Omentum, Pancreas
Breast.
Trauma
Inflamm
Trauma

Gross :- yellowish white deposits
Only necrosis in which calcification occurs.
Formation of calcium soaps imparts the necrotic foci firmer & chalky white appearance.
Microscopically - Cloudy appearance surrounded by fatty cells.
→ calcium soaps.

5.) Fibrinoid Necrosis :-
deposits of fibrin-like.
In wall of blood vessel.

Causes - Immunologic injury of vessel wall → vasculitis

Microscopically :- brightly eosinophilic hyaline like deposition in vessel wall.

Gangrene
Necrosis of tissue associated with superadded putrefaction.

Types :- 1) Dry - no bact. superinf.
2) Wet - bact. superinf.
3) Gas

→ distal part of limb
→ due to ischemia of artery
→ line of separation
→ type of coagulative necrosis
Gross :- dry black, mummified
↓
due to liberation of haemoglobin

Wet :- liquefactive coagulative necrosis
→ moist tissue & organs - bowel, lung, mouth, cervix, vulva.
→ both veins & arterial blf
→ Rapid
→ no clear cut demarcation
eg - gangrene of bowel
diabetic foot

Gas :-
Clostria (gram positive anerobic bact.
Enters through contaminated wound.
Grossly :- swollen, edematous, painful & crepitant
Microscopically -
CN + LN
Capillary & venous thrombi - common

Pathologic Calcification

Deposition of calcium salts in tissues other than osteoid or enamel is called pathologic or heterotopic calcification.

Types :- 2 forms -
Dystrophic
Metastatic

D	M
• Ca deposits in dead & dying tissues.	• Ca deposits in normal tissues.
• Calcium metabolism normal	• Deranged Ca metabolism
Calcio - normal	• Hypercalcemia
Generally irreversible	• Reversible
• ↑ binding of phosphates with necrotic & degenerative tissue - binds to calcium forming Caphosphate.	↑ precipitation of Caphosphate due to hypercalcemia at certain sites (lungs, stomach, blood vessels, cornea)

Dystrophic Calcification :-
Encountered in dead & degenerated cell damaged ↓
Phospholipid is released ↓
Phosphatases within the phospholipid generate phosphate ions ↓
Ca binds to phosphate ions ↓
Forming calcium phosphate

Sites :
1) Caseation eg TB
2) Dead parasites like trichinosis, cysticercosis
3) Fat necrosis
4) Infarcts
5) Thrombi
6) Hematoma

Degenerative Tissues :-
1) Atherosclerosis - medial sclerosis
2) Damaged heart valves
3) Injected lymph nodes
4) Degenerating tumors.

Metastatic Calcification

Tissues → normal
Hypercalcemia.
Those organs that lose acid ↓
have an underlying alkaline compartment. ↓
Alkaline internal components susceptible to calcification

Sites :-
1) Basement membrane & tubular lamina of kidney
2) Pulmonary veins
3) Alveolar wall of lung
4) Cornea & conjunctiva
5) Synovium of the joint
6) Skeletal muscles.

Causes :- 1) hyperparathyroidism
2) hypervitaminosis D
3) Neoplasms

Gross - Pale chalky white
coarse gritty feel.

Micro :- Ca at salts → blue granules
on H & E.
Psammoma body.

Special stain :- Von Kossa - black
Alizarin Red S - Red.