Cell injury & adaptations.

Cell Adaptations: Reversible changes (neither normal/injured)
↓ on removal of stress
Normal - without loss of physiology

Types -
1) Hypertrophy
2) Hyperplasia.
3) Atrophy
4) Metaplasia.

1) **Atrophy** → Both size & number of cells ↓
→ associated with autophagy (performed by Lysosomes)
→ ↑ Risk of TB infection - macrophage associated gene deletion ATG1S-5.

Q. endometrial adenoCa associated with - atrophy & Hyperplasia
Hyperplasia - Type I endometrial adenoCa.
Atrophy - Type II (Type II postpartum sis)

2) **Hyperplasia** - Number of cells ↑; Size same.

3) **Hypertrophy** - Size of cell ↑; number same.

4) **metaplasia**: Adult cell replaced → another type of adult cell
→ Stem cell reprogramming - mechanism

Esophagus columnar → Squamous

Respiratory tract columnar → Squamous.

associated with which vitamin def Vitamin-A Def; ex

Barett's esophagus: Squamous → columnar.

Intestinal metaplasia Q - Hallmark of Barett's esopha

- Risk for oesophageal & Gastric Adenoca Q

mucin in barett's: acidic - pH 2.5

Stain used - Alcian blue.

Both Hyperplasia + Hypertrophy:-

Pregnant uterus - major - Hypertrophy

minor - Hyperplasia

Pregnant/pubertal Breast: Both hypertrophy + Hyperplasia

Q Lactating Breast - only Hypertrophy

CELL INJURY:

Q m/c Cause of cell injury - ischemia/Hypoxia.

Neurons → 3-4 mins.

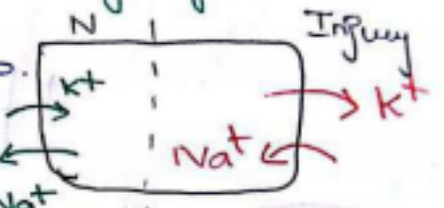
Cardiac Tissue → 20-40 mins.

most Resistant - Fibroblasts Q

↓ oxidative Phosphorylation.

↓ ATP (5-10% ↓ – cell injury)

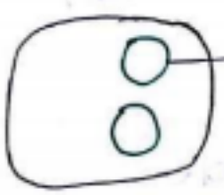
Failure of Na^+–K^+ pump.



I Cell Swelling – 1st Sign of cell injury.

eg – Ballooning degeneration of Hepatocytes

Q Except – Apoptosis. shrinkage 1st Sign

II  → water / Na^+ appear as vacuole due to insolubility

– Hydropic degeneration / cytoplasmic vacuoles /

cloudy Swelling (ATN)

III Ribosomal Degeneration – detachment due to swelling up of endoplasmic Reticulam:

* To diff. Reversible & Irreversible Injury Cell membrane damage

IV.  Small amorphous densities in mitochondria – Reversible

Flaccular large densities → Irreversible

→ ultrastructural findings.

V Nuclear change –  granular nuclear chromatin.

↓ change to

Disaggregation of granular nuclear chromatin

Most important Event in cell injury - Ca^{2+} cytosolic Rise

mild ↑ Severe ↑

Reversible injury Irreversible injury

↓

↑ phospholipase

↓

Damage to cell membrane of organelle

Concentric lamellated figure (phospholipase + Ca)

myelenoid bodies / myelin figures

→ Present in both Reversible, Irreversible

Irreversible > Reversible.

Irreversible Injury

Ca level ↑↑↑ - activates 3 enzymes

1) Phospholipase - myelin figures ↑↑ - maximum

Mitochondria - large amorphous flocculent densities

2) Protease - damage cytoskeletal protein damage.

↓

Loss of cell architecture.

eosinophilic - cytoplasm
nucleus - basophilic.

Damage of DNA / nucleus -

Pyknosis  clumping of chromatin.

↓

Karyorrhexis - fragmentation.

○○○ - pieces.

↓

Karyolysis - chromatin lysis → chromatin removed

↓ Basophilia of cell (chromatin dissolution)

Cell Death

- Events after cell death: Necrosis
- Apoptosis
- Necroptosis ®
- Pyroptosis ®

Necrosis:

- Denaturation of protein
  - ↓
  - Tissue architecture Normal / intact
  - ↓
  - Coagulative N
  - → m/c type
  - → m/c cause - Hypoxia.
  - m/c affecting - Heart (solid organs), Liver, kidney, spleen etc
- enzymatic actions.
  - ↓
  - Hydrolytic action
  - ↓
  - Tissue architecture - lost
  - ↓
  - Liquefactive N.
  - Bacterial / Brain infections

→ Solid organs Hard - collagen

Brain donot have - fibrous stroma - collagen

Hypoxia - all organs Coagulative necrosis

Brain - liquefactive

i) No collagen

ii) Rich in liquefactive enzymes.

m/c. Cause in Brain → Infections.

→ Thermal Burns - Coagulative.

Coagulative Necrosis -

TB

1st Coagulative necrosis

↓

Liquefactive necrosis.

Cheesy material - Caseous N

due to mycotic acid.

→ variant of coagulative N.

*Gangrene.

m/c site - lower limb.

Dry - default.

Tissue N → coagulative N

Architecture preserved.

Wet Liquefactive Necrosis.

Coag. Necrosis: TB < dry gangrene; TB > wet gagrene

Zenker's degeneration Necrosis - Prototype of Coagulative

Zenker's > Gangrene > TB > Wet gangrene

Necrosis

↑ Lysosomal Permeability
↓
↑ enzymes.
↓
* cell membrane damage
↓
Leakage of content
↓
* Inflammation

Physiological > pathological

Only pathological

Q. Programmed Cell Death.

Without Caspase activation
↓
Necroapoptosis.

Hybrid - Necrosis + Apoptosis
↓ cell membrane damage
Inflammation.
→ Variant of necrosis.
→ Both physiological & pathological.
Physiological - eg - mammalian growth plate formation.
Pathological -

Caspase
↓
Pyroptosis
- Neither apoptosis, nor necrosis.
Pyrogen Induced Apoptosis
(IL-1)
Inflammation (+)
cell membrane damage.

Apoptosis - Lateral - falling - off → Programmed cell Death

Active Process - due to usage of ATP from mitochondria.

Active process > Programmed cell Death

→ Apoptosis induced by loss of adhesion molecule → ANOIKIS

Physiological

→ Organogenesis.

- Cell deletion
- Cell deletion of auto reactive cells. protective against autoimmunity.

Pathological

Misfolding of proteins.
↓
stress.
↓
Apoptosis

eg. Familial Hypercholesterolemia
Parkinsons, Alzheimers
Huntingtons
Cystic fibrosis.
Tumor cell death.
GVHD → Salivary gland. duct

→ Chemotherapy + Radiotherapy - Necrosis / Apoptosis.
(eg. (Severe stimuli) → mild stimuli - only apoptosis to cell)

Glucocorticoid - induce apoptosis.

Pathological Apoptotic Body.
- Viral Hepatitis.

Morphology:-

1) earliest change → cell shrinkage.
2) M/characteristic: chromatin condensation > cell membrane intact
3) → No inflammation.
4) Cytoplasm — ↑eosinophilic.
5) 
Phosphatidyl Serine Receptors. (lipid Receptors) - facing inwards.
↓ Apoptosis.
Flip outside

Annexin V Dye - detects the flip :. marker of Apoptosis.
- stain used for Lipid

Lipid Stain - Oil Red stain.
Sudan IV / Black.
Osmium Tetraoxide

Glycogen → PAS.

6) 
- Cell membrane bleb
↓
Detach
Apoptotic Bodies
→ cell membrane bound structure with organelle, may/maynot have nuclear remnants.

End

Phagocytosis — Final Product of apoptosis.

Receptor mediated (∴ no inflammation)

Biochemistry of Apoptosis:

ProCaspase

Hallmark of Apoptosis

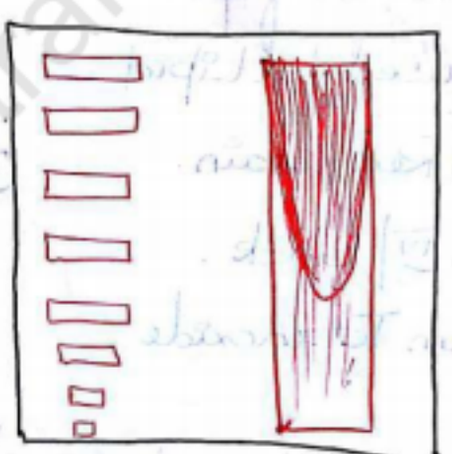
Caspase → endonuclease → DNA damage → Chromatin Condensation

⇒ DNA damage → Restricted fragment.

multiples of ×200 Base Pairs

Internucleosomal DNA damage

Agarose Gel Pattern -



Step Ladder Pattern — due to endonuclease.

Smeared Pattern

→ Seen in apoptosis & necrosis, But characteristic of Necrosis.

Apoptosis

→ Smearing Pattern - Necrosis.

1) Initiation Caspases.
   - a) Intrinsic - major pathway - Caspase-9
   - b) Extrinsic - Caspase-8 (animals), Caspase-10

↓ execution caspases.

↓ Caspase-3, 6, 7 — Cas-3 m/I.

↓ endonuclease

Protooncogenes

- Apoptotic
  - Bcl-X_S (stimulate)
  - BAX, BAK.
  - BH_3 Proteins.
- Anti-apoptotic
  - → Bcl-2
  - → Bcl-X_L (lowering)
  - MTCL-1 Q.

Drug Resitance -

P_{53} > MCL-1

(P_{53} m/c mutated in drug resistance)

P_{53} - Tumor suppressor.

MCL-1 Drug Resistance · protooncogene.

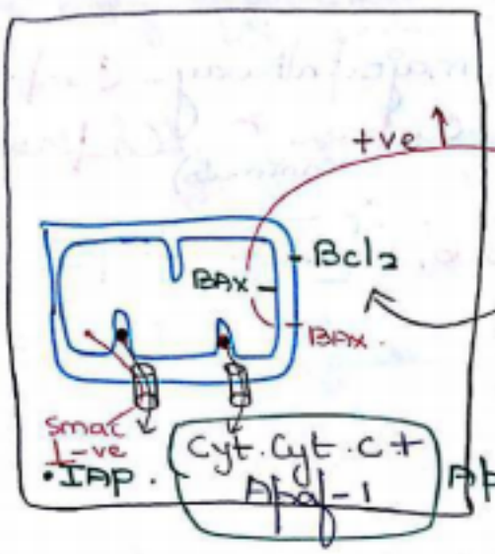
BH_3 Proteins. Stress Sensors.

- Bim
- Bad
- Bid.

→ PUMA Q

→ NOXA Q

a) Intrinsic Pathway (Mitochondrial Pathway)



Stress
↓
BH3
↓
Inhibited BAX expressed on outer membrane
↓
mitochondrial permeability channels
↓
↑ permeability / leakage of Proteins.

Cyt-C - mitochondria - ETC
cytosolic Cyt-C

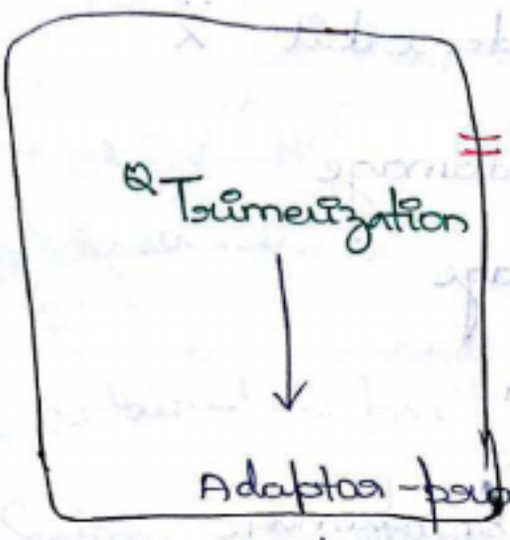
SMAC - DIABLO protein
↓
Inhibit
inhibitor of ~~anti~~ apoptosis

Cyt-C into cytosol + APAF1
↓
Apoptosome
↓
Initiate Caspase-9

Extrinsic Pathway — Death Receptor mediated.

TNF-R-1

FAS - CD-95



= Death Receptor + Ligaments.

↓ ← -ve Flip.

Procaspases 8, 10.

Flip protein - Inhibitor of extrinsic pathway In viruses, the

Final pathway

C-9 C-8, 10.

C, 3, 6, 7

↓

endonuclease → chromatin Condensation

Intrinsic & extrinsic pathway can occur independently.

→ Hallmark of Neuronal apoptosis — Apoptosis inducing factor

(No caspases)

Free - Radicals - Oxidative ROS

→ Produced normally

- unpaired electon in outer orbit ·×

→ oxidation - mechanism of damage

cell membrane damage

+

Cytoplasmic protein

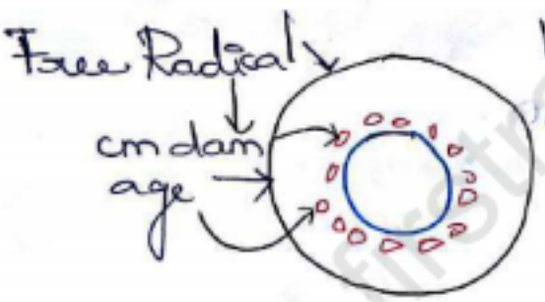
+

nuclear membrane damage

↓

DNA damage (Somatic damage)

most potent / most Reactive — OH·



Lipofuschin (Brown pigment)

i) Ageing

ii) malnutsition

iii) Cancu cachexia.

→ Tell tale sign of ageing / Free Radical injury

→ Brown atrophy of myocardium.

Carotroid Specimen brown - Lipofuschin.

Lipofuschin (m/c) > Hemosidein

Oil Red-O

Sudan Black.

Osmium Tetraoxide.

Annexin-V

Oil Red-O stain – best for oil – Frozen Section.

Perl's prussian blue stain

Ferrous ferrocyanide → Fe^{3+} ferricferrocyanide (insoluble & stained)
Fe^{2+}

Frozen Section – Intraoperative Biopsy.

→ Never confirm diagnosis immediately (confirm – 2 days)

Temp: −15 to −30°C

Δ – i) 15 – 20 minutes – ii) D – Benign/malignant.

Tentative Δ iii) can tell metastasis to sentinel lymph node

iv) Resection margin involvement.

i) Theory of Free Radical Damage for Ageing – most accepted theory.

ii) Increased crosslinking of collagen Theory for ageing

→ Anti-oxidant vitamins – Vitamin A, C, E.

→ Proteins – Transferrin, Ceruloplasmin Q.

→ Enzymes – Catalase, glutathione peroxidase, Superoxide Dismutase. } Q Peroxisomal enzymes

Vitreous of eye Vitamin D not present

→ Glutathione - peroxidase - most potent anti-oxidant in body

Peroxisomal enzymes - H_2O_2 production & degradation

Lysosomes - H_2O_2 production only

→ Brain protected from free radical injury SOD-1

Cu-Zinc SOD-1.

↓ mutation

AMTL (motor neuron disease)

Calcification

Abnormal Tissue - Death/degenerated

Dystrophic Calcification.

→ TB lymphnode.

→ RHD.

→ psammoma bodies

→ Aneurysm.

→ monckeberg's medial Sclerosis.

non-obstructive

Tissue normal / Ca ↑

metastatic Calcification

→ Hyperparathyroidism (m/c cause)

1° HPT

m/c - Parathyroid adenoma

→ Hypercalcemic Crisis.

Ca Breast > Ca lung.

Squamous + Small cell

→ Renal failure

→ Vitamin - A/D ↑

Vitamin D activate → Osteoclasts → lysis — Hypercalcemia

→ Parathyroid - not affected (calcified) / rarely affected

m/c affected alveoli (lung)

→ Calcification starts in mitochondria except kidney, Basement membrain

Special Stain for Calcium - 1) Von-Kossa [m/c, Best]

2) Alizarin-Red (most specific) for calcium.

3) Calcein

4) Tetracycline Labelling stain (Best for bone mineral

Melanin - Fontana-Masson.

Collagen → Connective Tissue - Masson Trichrome. Collagen - Blue

Fungal Hyphae - Silver methenamine.

Alzheimer's disease - Neurofibrillary tangles - Bielschowsky stain (Silver stain)

Ageing -

Telomeres - non coding areas at the end of chromosomes

Progressive size ↓ on further Replication

↓

No Telomeres.

↓

fusions / degradation

↓

Cellular ageing

→ Normal cells are capable of division of 60-70 times

Hayflick limit

Telomeres → Slowing Ageing

Telomere → lengthening - Carcinogenesis

Telomerase → RNA - depended DNA polymerase (Reverse Transcriptase

(responsible for lengthening)

↓

present in Germ cells > Stem cells.

→ Normal Somatic cell - no telomerase

most effective way of prolonging life span ↓ Calorie

↓

(small amt) Red wine → Sirtuins (+

↓ Apoptosis (+) Reduces free Radical damage

↑ glucose metabolism ii) ↑ insulin sensitivity

iii)

Werner Syndrome - MTEN I

Werner Syndrome — Premature aging.

defect in DNA Helicase.

(Repair)

Silver methamine Stain - Fungus - Black / Brown

Background green

Septate Branching / acute angle Branching - aspergillus

Immunofluorescence microscopy - Dichroic mirror (allows only a light)

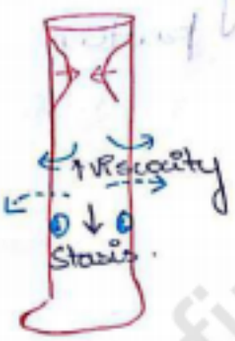
Background - Black.

Acanthamoeba - optically greenish white - cell wall
calcofluor white stain.

INFLAMMATION

- Acute inflammation -

I) Vascular events - - Ist Transient vasoconstriction
↓
Vasodilatation
↓
↑ Vascular Permeability - Hallmark of acute inflammat.
↓
Stasis (So that neutrophil can deviate to periphery).



Vascular Permeability)

1) Endothelial gap - (m/c - mechanism)
- at the level of venules. except lungs - capillaries.
- Immediate / Transient response.

2) Direct endothelial injury - Immediate & prolonged
mild endothelial injury - Sunburn / radiation,
↓
delayed & prolonged

Telomere → Shortening - Ageing

Telomere → lengthening - Carcinogenesis

Telomerase → RNA - depended DNA polymerase (Reverse Transcriptase)

(responsible for lengthening)

↓

present in Germ cells > Stem cells.

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↓

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