TOPIC 5: PATHOLOGY

TOPIC 6: IMMUNOLOGY

# BIOM20001

STUDY NOTES TOPICS 5&6

**85 (H1 First Class Honours)**

BACHELOR OF BIOMEDICINE | UNIVERSITY OF MELBOURNE (THE)

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# CAUSES OF CELL INJURY

**Principles of human pathology—**

- Cause, mechanism, response (acute inflammation & defence), resolution (regeneration/repair or chronic injury)

**Characteristics of disease—**

- Aetiology ⇒ cause of the disease
- Pathogenesis ⇒ mechanism causing disease
- Pathology ⇒ molecular & morphogenic changes to cells/tissues
- Clinical manifestations ⇒ functional consequence (signs/symptoms)
- Complications ⇒ secondary, systemic or remote consequences of disease
- Prognosis ⇒ anticipated course of disease
- Epidemiology ⇒ incidence, prevalence & distribution

**Adapt or die—**

- Normal cell homeostasis ⇒ increased demand/stress ⇒ adaptation
    - failure to adapt ⇒ **cell injury/death**
- Normal cell homeostasis ⇒ injury introducing stimulus ⇒ **cell injury/death**

**Injury inducing stimulus—**

- Gross physical trauma can be attributed to a single gene defect

*HYPOXIA:*

- Oxygen deficiency ⇒ interferes with aerobic oxidative respiration
    - pneumonia (inadequate oxygenation), blood loss anemia, CO poisoning, ischemia (loss of blood supply to tissue)

*CHEMICAL AGENTS:*

- Poisons, tobacco, alcohol, glucose & salt (alter osmotic imbalance)
    - alcohol causing cirrhosis of the liver
- Environmental agents ⇒ pollution, lead, mercury

*INFECTIOUS AGENTS:*

- Bacteria, viruses, fungi, parasites
- Prions ⇒ small proteinaceous infectious particles which are resistant to inactivation

**Cell injury-immunological reactions—**

- Immunologic reactions ⇒ immune imbalance, autoimmunity, hypersensitivities, graft rejection, immune deficiency

    - autoimmunity ⇒ rheumatoid arthritis
- Genetic defects ⇒ congenital malformations, single base mutations causing functional deficiency or protein misfolding
    - e.g. Tay-Sachs disease accumulation of GM2 gangliosides
- Nutritional imbalance ⇒ deficiency/malnutrition & excess
    - deficiency ⇒ rickets from vitamin-D deficiency
- Physical agents ⇒ mechanical trauma, thermal injury, electrical injury, ionising radiation & atmosphere
    - e.g. laceration, contusions, incised wounds & punctures

**Type of cell injury-aging—**

- Aging ⇒ progressive decline in cellular function/viability
    - genetic factors, exogenous influence

# ADAPTATION & INJURY

**Adaptation—**

- Normal myocyte ⇒ increased load ⇒ adapted myocyte (hypertrophy)
- Normal myocyte ⇒ cell injury ⇒ reversibly-injured myocyte
    - irreversible injury will result in **cell death**
- Physiological adaptation ⇒ cellular response to normal stimulation
    - hormones & endogenous chemicals
- Pathological adaptation ⇒ cellular response to stimulation secondary to underlying disease/to avoid injury

**NOTE: REVERSIBILITY IF STIMULUS REMOVED**

**Hypertrophy—**

- Increased work-load (physiological & pathological stimuli)
- Increased size of cells ⇒ increased organ size
    - no new cells ⇒ LARGER cells
        - e.g. body building & hypertension
- **Non-dividing cells** increase size (e.g. myocytes, skeletal cells)

**Hyperplasia—**

- Increase in number of cells in an organ/tissue
- Only in dividing cell populations
- Physiological & pathological response
    - **physiological** ⇒ hormonal (puberty), compensatory (liver resection), increased demand (low atmospheric oxygen increases erythrocytes)
    - **pathological** ⇒ hormonal (endometriosis), viral infection (skin warts), chronic stress (callous)

**Atrophy—**

- Reduced size of organ resulting from decrease in cell size & number
    - **physiological** ⇒ common during normal development (embryonic structures, uterus following pregnancy)
    - **pathologic** ⇒ depends on underlying cause
- Decreased amount of structural proteins & organelles due to decreased protein synthesis/increased protein degradation
    - e.g. decreased work load, loss of innervation, loss of blood supply, inadequate nutrition, loss of stimulation, aging etc.

**Metaplasia—**

- Replacement of one differentiated cell type with another
- Cells sensitive to stress replaced by a cell type better able to withstand stress
- Stem cell reprogramming
    - cigarette smoking ⇒ ciliated columnar to stratified squamous
    - chronic gastric reflux ⇒ stratified squamous to gastric columnar epithelial

**Normal vs. adaptation vs. injury—**

- Adaptation ⇒ response to stress/increased demand that maintains the steady state of the cell without compromising cellular function
- Reversible/sublethal injury ⇒ response to stress/stimuli that **compromises** cellular function
- Irreversible injury ⇒ response to stress/stimuli that **compromises** cellular function to the point that it cannot recover

**Recovery or death—**

*REVERSIBLE INJURY:*

- Cell function compromised
- Recovery if injury is removed
- May compromise organ function ⇒ reversibly injured myocytes (transient ischemia) may be transiently non-contractile which will affect heart functioning

*IRREVERSIBLE INJURY & CELL DEATH:*

- When the cell cannot recover & dies
- Two types of cell death which differ in morphology, cause & roles in disease
    - e.g. necrosis & apoptosis
- May have occurred before morphological changes become apparent

*WHEN INJURY CAUSES IRREVERSIBLE CHANGE:*

- Cell ⇒ genetics, adaptability, type, state
- Injury ⇒ type, duration, severity
    - short, LOW dose exposure vs. long, HIGH dose exposure to toxin/hypoxia

**Sequential development of changes seen in cell injury—**

- Cell may be non-functional but viable
- Cells may undergo biochemical changes & be non-viable (dead) before the appearance of ultrasound, microscopic & macroscopic changes are apparent

**Morphology—**

- Gross or microscopic appearance of cells/tissues
- Most cells are transparent ⇒ staining procedures make cells visible

*HAEMATOXYLIN & EOSIN STAIN:*

- Most popular staining method used in histology
- H&E contains two dyes
- Haematoxylin is considered a basic dye
    - stains acidic (or basophilic) structures a purplish-blue & stains nucleic acid
- Eosin is an acidic dye
    - stains basic (or basophilic) structures red/pink & most proteins

**Morphologic features of injury—**

- Withdrawal of acute stress ⇒ RECOVERY ⇒ NORMAL CELL
- Prolonged/severe injury ⇒ CELL DEATH ⇒ NECROSIS
    - **cell swelling is the first feature of most forms of cell injury**

**Reversible injury—**

- Features ⇒ swelling of ER & mitochondria, membrane blebs, clumping of chromatin
    - light microscope ⇒ cellular swelling, fatty change (lipid vacuoles in cytoplasm)
    - ultrastructural ⇒ plasma membrane blebbing, ER/mitochondrial changes, nuclear alterations

**Irreversible injury—**

- Features ⇒ fragmentation of cell membrane & nucleus, lysosome rupture, swollen mitochondria
    - inability to reverse mitochondrial dysfunction
    - disturbance of membrane function
- Membranes lose their structural integrity:
    - **lysosomal membranes** ⇒ contents leak into cell, nuclear/cytoplasmic components degraded
    - **plasma membrane** ⇒ loss of osmotic balance, cellular contents leak into EC space (inflammation)
    - **mitochondria membrane**

**Mechanisms of cell injury—**

- Complex, interconnected & tightly interwoven
- Abnormalities of essential cellular components
    - e.g. mitochondria, calcium homeostasis, plasma membrane, DNA & proteins

*DECREASED ATP:*

- Low $O_2$/nutrients, mitochondrial damage & toxins ⇒ decreased oxidative phos.
    - net gain of solute & osmotic gain of water ⇒ ER swelling, cellular swelling, blebs
        - malfunctioning ion channels

- cell with greater glycolytic capacity (i.e. liver) will survive longer than cells with limited capacity (i.e. brain) ⇒ decreased pH causes chromatin clumping
- protein misfolding, unfolded protein response, apoptosis

*DAMAGE TO MITOCHONDRIA:*

- Inefficient mitochondria ⇒ increased ROS production ⇒ loss of membrane potential (ETC halts)
- Cytoplasmic protein C becomes proapoptotic (death)
  - mitochondrial cytochrome C involved in ETC & ATP formation (survival)
  - formation of mitochondrial permeability transition pore

*INFLUX OF CALCIUM:*

- ATP dependent transport maintains **LOW** intracellular calcium
  - mitochondria & smooth ER are intracellular calcium stores
  - activation of cellular enzymes (phospholipase, protease, endonuclease, ATPase)
    - e.g. membrane damage, nuclear damage, decreased ATP stores
- Apoptosis ⇒ increased mitochondrial membrane permeability ⇒ activation of caspases

*ACCUMULATION OF ROS:*

- Free radical ⇒ chemical species with unpaired electron in outer orbital
  - unstable/reactive ⇒ attack nucleic acid, protein, lipids
  - damage to protein/nucleic acid ⇒ **apoptosis**
- ROS ⇒ oxygen derived free radical
  - by-product of respiration & produced by phagocytic leukocytes
  - removed by scavengers (antioxidants SOD, glutathione peroxidase, catalase)
    - oxidative stress ⇒ **HIGH** ROS or **LOW** scavengers

*MEMBRANE DAMAGE:*

- Important lipid membranes ⇒ plasma, mitochondria, lysosome
  - activated phospholipases & proteases contribute to membrane damage
  - rupture of lysosomes release pH-dependent hydrolytic enzymes
    - become active due to lowered internal pH of injured cell

**Hypoxia—**

- Oxygen deficiency & interferes with aerobic oxidative respiration
- Causes ⇒ ischemia, pneumonia, blood loss anemia, carbon monoxide poisoning
  - DECREASED aerobic respiration
    - **less ATP-dependent transport/macromolecule synthesis**
  - INCREASED anaerobic respiration
    - decreased pH & blood flow
- Inhibited synthesis/greater macromolecule digestion ⇒ **DECREASED** phospholipid/protein synthesis
  - i.e. cell membrane damage & cytoskeleton abnormalities
- Cell membrane damage

- plasma ⇒ loss of osmotic balance, ion influx
    - cell content leakage (i.e. inflammation)
- mitochondria ⇒ opening ion channels, release of apoptotic proteins
    - irreversibly damaged (cannot facilitate oxidative phos.)
- lysosome ⇒ leakage of enzymes
    - autolysis

*HYPOXIA OF THE HEART:*

- Increased staining with eosin ⇒ eosinophilia, protein denaturation, loss of basophilic RNA
- Reduced nuclei (less haematoxylin staining)
- Oedema & inflammatory cells
- Rupture of plasma membrane of myocytes as a consequence of irreversible injury ⇒ release of **cardiac proteins** (detectable by blood test)
    - i.e. cardiac isoform of creatine kinase, contractile protein troponin
- **Serum levels reflect tissue injury** ⇒ myocardial infarction (irreversible), angina (reversible)
    - angina ⇒ blood vessels narrowing (not occluded) & unable to provide sufficient blood to meet increased demand
    - myocardial infarction ⇒ prolonged occlusion of coronary vessel leading to irreversible cell injury of cardiac muscle cells (death of cells by ischemia)
- **Microscopic features of adaptation** ⇒ myocardiocytes are larger with enlarged nuclei
- **Macroscopic features of MI** ⇒ dark discoloured tissue is a region of haemorrhage, white areas of scarring and yellow/buttery appearance indicative of necrotic region
- **Microscopic features of MI** ⇒ remnants of anucleate cells (dead myocardiocytes) with intact architecture which will eventually be phagocytosed by infiltrating PMNs