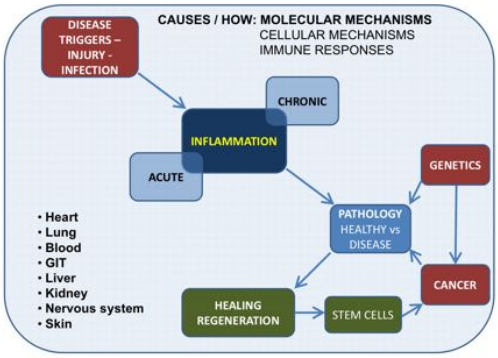
Pathology: Mechanisms of Disease

Lecture 1: Overview of Mechanisms Underlying Disease – Cell Death

Stages of the cellular response to stress and injurious stimuli

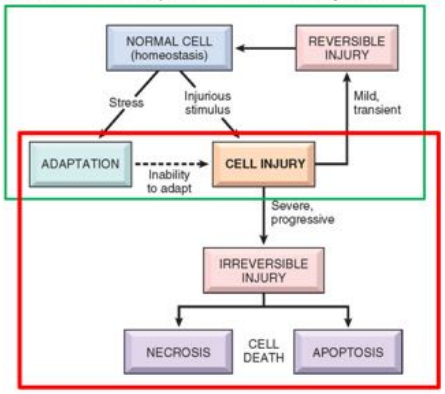


- The normal cell state is one of homeostasis, when something changes this (injury to cellular/tissue level)
- Adaptation can get one back to normal state
- If the insult is constant/ severe one off cells or tissue cannot return to normal state. This leads to;
    - Necrosis: quick and unregulated
        - Usually caused by injury
    - Apoptosis: programmed
        - Involves specific steps or factors

Pathogenesis of cell injury;

- Reduced ATP synthesis/ mitochondrial damage
- Loss of calcium homeostasis (trigger for cell death)
- Disrupted membrane permeability
- Free radicals (natural biological molecules that are released and cause damage)

Stages of the cellular response to stress and injurious stimuli



Robbins & Cotran, Pathologic Basis of Disease

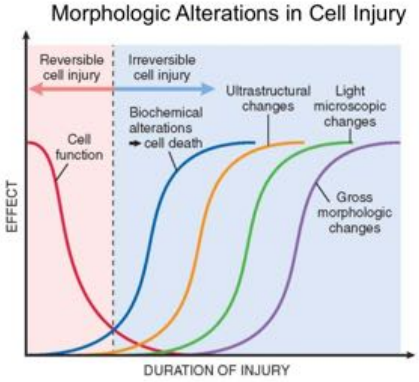
Study of cell death;

- Has evolved for many hundreds of years
- Long term process

Reversible/ Irreversible Cell Injury

- Time is a critical factor
    - Biochemistry changes occur quickly (ATP changes)
    - Ultra structural changes then occur – which can be seen by electron microscope
    - Light microscopy changes include cytoplasmic changes and nuclear changes
- There is a window of time where changes are occurring and metabolic pathways are ceasing, but the cell is still in a stage where it can switch back on.

Morphologic Alterations in Cell Injury



Morphological changes

- As injury progresses you begin to have gross morphological changes; changes in tubular structure to nuclear and membrane changes

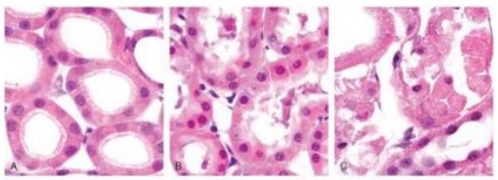


FIGURE 1-9 Morphologic changes in reversible cell injury and necrosis. A, Normal kidney tubules with viable epithelial cells. B, Early (reversible) ischemic injury showing surface blebs, increased eosinophilia of cytoplasm, and swelling of occasional cells. C, Necrosis (irreversible injury) of epithelial cells, with loss of nuclei, fragmentation of cells, and leakage of contents. The ultrastructural features of these stages of cell injury are shown in Figure 1-10. *(Courtesy of Drs. Neal Pinckard and M.A. Venkatachalam, University of Texas Health Sciences Center, San Antonio, TX.)*

Ischemia and Hypoxia

- **Ischemia: loss of blood flow that leads to hypoxia (biophysical phenomenon)**
    - Hypoxia- reduction to a critical level of oxygen
- Most common cell/tissue injury in clinical medicine

1. Injury is caused by an insufficiency of oxygen due to reduced blood supply → **reduction of ATP**
    - Metabolite substrates become limited and wastes accumulate
2. Effect of Ischaemia: dependent on balance between reversible and irreversible damage
    - Time dependent; if injury persists then damage increases and mitochondria are irreversibly damaged → no cellular energy

Irreversible damage = cells cannot recover (because cellular energy is so low and metabolic functions have reached a threshold they cannot return)

Types of insult – that lead to hypoxia

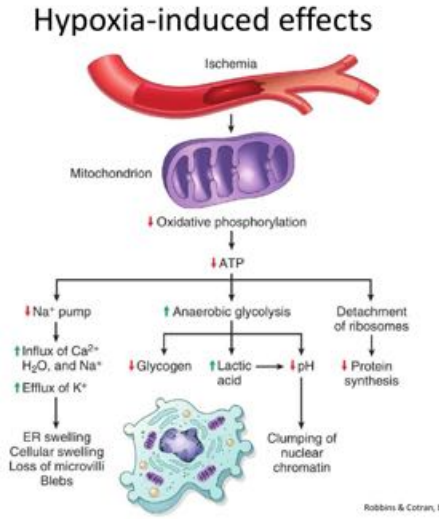
- Ischaemia
  - Local embolus (blood clot)
  - Systemic failure (cardiac failure/ heart attack)
- Hypoxemia – milder form
  - Oxygen problems (altitude)
  - Haemoglobin problems (anemia)
- Oxidative phosphorylation
  - Cyanide poisoning
    - Cause rapid decreases in oxygen

Recovery is possible after ischaemia as there is a window of opportunity for 'rescue'

- Varies between different cell/ tissue types and time

Reperfusion: restoration of blood flow

- Cells will recover if the oxygen and substrates are provided
- But, **reflow paradox** can occur; leading damage to be increased = reperfusion injury/ Ischemic – reperfusion injury

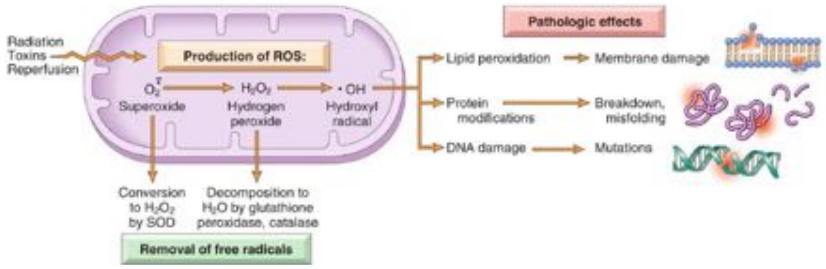


Hypoxia- induced effects

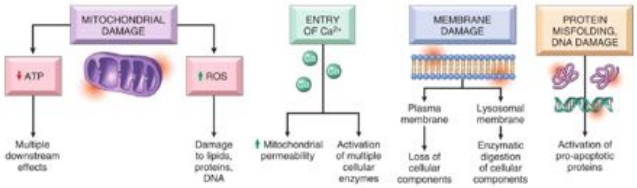
- Mitochondria is the most affected organelle
- Reduction in ATP leads to specific effects
- Reduction pH means the acidic environment leads to clumping of nuclear chromatin
  - This leads to DNA being affected → mRNA and proteins cannot be made
    - This is further affected by ribosomes detachment → affects translation

Free radicals;

- Highly reactive, unstable chemicals
- Associated with cell injury
  - Chemicals/ drugs, *reperfusion injury,* inflammation, irradiation, oxygen toxicity, carcinogenesis



Principle structural targets for cell damage;



- Mitochondrial damage
  - Reduction in ATP
    - Multiple downstream effects
  - Increase in ROS
    - Damage to lipids, proteins and DNA
- Entry of Calcium
  - Increased membrane permeability
  - Activation of multiple cellular enzymes
- Membrane damage
  - Plasma membrane
    - Loss of cellular components
  - Lysosomal membrane
    - Enzymatic digestion of cellular components
- Protein misfoldings, DNA damage
  - Activation or pro-apoptotic proteins