PATH30001

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Lecture 6- Disease triggers: Ischaemic and Reperfusion Injury: AMI

- AMI (macroscopic death of myocardium)- due to vascular insufficiency
- VI- myocardial ischemia, i.e. balance between supply/flow (perfusion) and demand for oxygenated blood

Aetiology/cause/trigger of the disease

AMI- major cause atherosclerosis (95%); other causes- spasm, drugs, trauma; risk factors- hypertension, diabetes, smoking, hypercholesterolemia, demography

- Atherosclerosis- chronic inflammatory and healing response of the arterial wall to endothelial injury
- Location, severity and rate of development of coronary obstructions due to atherosclerosis and thromboses; e.g. duration of occlusions, extent of collateral blood vessels

Molecules/pathways/genes involved

- Atherosclerosis- endothelial injury (increased vascular permeability, leucocyte adhesion, thrombosis) →accumulation of oxidised lipoproteins (LDL) in vessel wall→monocyte adhesion to endothelium, migration into intima, transformation into macrophages and foam cells→platelet adhesion (constrict flow of blood)→factor release from activated platelets, macrophages, vascular wall cells, SMC recruitment from media→SMC proliferation and ECM production→lipid accumulation extracellularly and within macrophages and SMCs
- Role of IL-1β- drives systemic inflammatory response and maintains a state of impaired cardiac function, impairs β-adrenergic receptor responsiveness (which play an important role in regulation of heart function)
- Inflammatory markers of AMI- myocyte proteins in MI (e.g. troponin I, C, T, CK-MB) leak out of plasma membrane from necrotic myocytes
- Ischaemic heart disease progression- coronary artery disease→myocardial ischemia/acute plaque change; coronary artery thrombosis→myocardial ischemia severe→MI→infarct healing/ventricular remodelling/ hypertrophy→CIHD→congestive heart failure (lose heart function, contractility, arrhythmia)→sudden cardiac death

Cell biology-structure/organelles/changes in cells-morphology metabolism

- Atherosclerosis- plaque stability issue; plaque weakness and inflammation around plaque→rupture, erosion, ulceration, haemorrhage→creates accelerated, acute inflammatory response→platelets activated→ abnormal thrombosis
- **Reversible injury**- until 20/30 minutes (ATP depletion, increased lactate)
- **Irreversible injury**- after 20-40mins
- AMI (progression of myocardial necrosis after coronary artery occlusion)- **irreversible injury**: first in sub-endocardial zone, extends/progresses transmurally (across whole thickness of cardia wall
    - 1. Cell death by necrosis/apoptosis rapidly post-ischemia (progressive and spreads)
    - 2. Reperfusion in <20 mins, myocytes survive infarct event
    - 3. No Reperfusion- necrosis complete in 6-12hrs
    - Day 1-normal, Day 3-4- monocyte infiltration, Day 7-10- phagocytosis of necrotic cells, Day 21- repair (collagen), Day >60- scar tissue
- Reperfusion- restoration of blood flow = rescue ischaemic muscle and limit infarct size
    - Reperfusion injury- reperfusing polymorphs→cytoplasmic xanthine oxidase activated→more ROS/FR, inhibitors of xanthine oxidase are protective

Tissue and organ changes-morphology/ECM/whole organ and effects on whole organism e.g. patient

- Atherosclerosis (pathogenesis of artery): normal artery→fatty streak→fibrofatty plaque→ advanced/vulnerable plaque→aneurysm and rupture→occlusion by thrombus→critical stenosis (narrowing)
- Complications of AMI- contractile dysfunction, arrhythmias, rupture, pericarditis, infarct expansion

Science/medicine tackle problem to inhibit/reverse disease progression

- Troponin assay- test for MI
- Modification of infarct (restoration of coronary blood flow)- thrombolysis, balloon angioplasty, coronary arterial bypass graft
- Inhibition of myocardial death- downregulation or inhibition of inflammasome components

Lecture 7- Pneumonias: Infectious & ARDS

- Normal lung structure- trachea, bronchus, bronchiole, alveoli
- Normal alveolar structure- type 1 pneumocytes (95%), type 2 cells synthesise surfactant, give rise to type 1 (repair of epithelium), resident macrophages (lamina propria), capillaries, rare monocytes/WBCs

Aetiology/cause/trigger of the disease

- Pneumonias- respiratory disorders involving acute inflammation of lung structure (alveoli and bronchioles)- affects people with **impaired host defences** e.g. loss of cough reflex (aspirate gastric contents), injury to muco-ciliary apparatus, accumulation of secretions, pulmonary congestion, interference with action of macrophages
    - Infectious- bacterial (common), viral, fungal
    - Non-infectious (usually cause **ALI**)- chemical (irritating substance), inhalation (aspiration)
    - Community acquired- usually Strep or viral pathogens
    - Hospital acquired- bacterial pathogens that are more resistant
- ARDS (severe **ALI**)- diffuse alveolar damage; causes-
    - Gastric aspiration, penetrating lung injury, ionising radiation, near drowning, inhalation injury, oxygen toxicity (SCUBA divers), reperfusion pulmonary oedema after lung collapse/transplant

Molecules/pathways/genes involved

- Acute inflammation- neutrophils fill alveolar spaces, blood vessels congested
- Chronic inflammation- chronic inflammatory cells, destruction of parenchyma/normal alveoli replaced by spaces lined by cuboidal epithelium, replacement by connective tissue (fibrosis)

Cell biology-structure/organelles/changes in cells-morphology metabolism

- Broncho or lobar pneumonia- both consolidation (liquid filled); host response (suppurative/fibrinous)
- Acute inflammation- time course
    - 1-2 days- lung heavy, full of blood-oedema, 2-4 days- red hepatisation (stasis and congestion), 4-8 days- grey hepatisation (full of fibrin, neutrophils, red cells disintegrate), >8 days- resolution (exudate breaks down, removed, fibrous masses)
- ARDS- always acute onset of respiratory failure- **bilateral infiltrate**
    - Exudative (acute): day 1- interstitial oedema, degenerative changes in type 1 cells, interstitial infiltrate (lymphocytes, macrophages, plasma cells), day 2- sloughing type 1 cells, hyaline membrane begins, day 4-5- peak of hyaline membrane formation, day 7- peak of infiltrate, type 2 proliferate, thrombi in alveolar capillaries/pulmonary arterioles
    - Organising (slower): interstitial inflammation, type 2 hyperplasia, macrophages break down hyaline membrane, > day 14- interstitial fibroblasts proliferate, produce collagen
- ARDS-possible outcomes
    - Resolution= complete recovery and restoration of normal lung function; collagen metabolised, epithelium restored, alveolar exudate/hyaline membrane resorbed, fibroblast proliferation ceases
        - Sodium pumps, ENaC, Aquaporins- important mechanisms in resolution
    - End-stage fibrosis- exudate associated with tissue destruction, hyaline membranes (scar tissue), lung architecture remodelled, honeycomb lung (cyst like spaces separated from each other by fibrous tissue), alveolar ends surrounded by fibrosis

Tissue and organ changes-morphology/ECM/whole organ and effects on whole organism e.g. patient

- Acute inflammation (lobar pneumonia complications)- pleurisy (spread of infection to pleural cavity), tissue destruction and necrosis, bacteria dissemination
    - Symptoms- fever, chills, cough, chest pain, ARDS

Science/medicine tackle problem to inhibit/reverse disease progression

- ARDS treatment- mechanical ventilation, inhalation of NO (vasodilator), surfactant therapy, anti-inflammatory drugs (glucocorticoids), stem cells?- factors produced from stem cells seem to help with recovery process

Lecture 8- Asthma: aetiology, pathogenesis and therapy

- COPD- emphysema, chronic bronchitis (not reversible), asthma (reversible)
    - Emphysema- irreversible enlargement of airspaces, lose elasticity of alveoli
    - Chronic bronchitis- persistent cough with sputum production, may progress to COPD, overlap with emphysema, hypersecretion of mucus, marked increase in goblet cells
    - Asthma- chronic disorder of conducting airways

Aetiology/cause/trigger of the disease

- Asthma- chronic disorder of conducting airways, caused by immunological reaction- marked by episodic bronchoconstriction
- **Atopic asthma**- triggered by environmental allergens (dust, pollen, foods); type 1 IgE-mediated hypersensitivity reaction; precipitating factors- bronchoconstriction, bronchial hyperesponsiveness/sensitivity
- **Non atopic asthma**- typically virus-induced inflammation
- Drug induced asthma (e.g. aspirin), occupational asthma (e.g. exposure to fumes)
- **Allergic asthma**- genetic predisposition to atopy (type 1 hypersensitivity), interplay between environmental and genetic factors, positive for skin prick allergy test, ADAM-33 polymorphisms (MMP involved in bronchial hyperesponsiveness), β_2-adrenergic receptor

- **Non-allergic asthma**- no evident family history

Molecules/pathways/genes involved

- **Atopic asthma-** Type 1 IgE-mediated hypersensitivity reaction- immediate
  - Allergen stimulates T_H2 response→B cells class switching-IgG to IgE→IgE binds to Fc receptors on mast cells→subsequent exposure to allergen=mast cell activation→release mediators (eosinophil/ neutrophil chemotactic factors, platelet-activating factor, histamines, membrane phospholipids→ vasodilation, vascular leakage) ; late phase reaction→cause inflammation

Cell biology-structure/organelles/changes in cells-morphology metabolism

- Airway in asthma- thickened basement membrane, increase mucus in bronchial lumen, goblet cell hyperplasia, hypertrophy of submucosal glands/smooth muscles

Tissue and organ changes-morphology/ECM/whole organ and effects on whole organism e.g. patient

- Asthma- persistent cough, wheezing, shortness of breath -use spirometry tests (FEV), methacholine challenge (causes bronchoconstriction, see how much you can expire)

Science/medicine tackle problem to inhibit/reverse disease progression

Management of asthma

- Short acting β_2 agonist, low dose inhaled corticosteroid (cause SM relaxation, counteract constriction)
  - With increasing severity, long acting β_2 agonist and high dose inhaled corticosteroid
  - 5% of asthma population to corticosteroid therapy
- General protection for chronic management- avoid cold air, tobacco fumes, crowds, mouldy places, etc

Experimental therapies- histone deacetylase inhibitors- shown potential anti-asthma effects (anti-inflammatory effects), act on both histone and non-histone proteins

Lecture 9- Toxic injury: alcohol-induced disease: Liver: acute and chronic inflammation

***use alcohol toxicity in liver as an example of mechanisms and outcomes of chemically induced cellular injury in acute and chronic inflammation**

Aetiology/cause/trigger of the disease

- Toxins- low dose xenobiotic metabolism works, high doses→toxicity
- Alcohol liver disease- due to chronic alcohol abuse→fatty liver (hepatic steatosis), alcoholic hepatitis, cirrhosis

Molecules/pathways/genes involved

- Ingestion of alcohol- absorbed directly via GIT→blood(mins)→metabolised by gastric mucosa (liver)→ excreted unchanged (5-10% air)
  - Blood enters lobules through branches of portal vein and hepatic artery→flows through sinusoids that are lined with hepatocytes→hepatocytes remove toxic substances from blood→blood exists through central vein [hepatocytes- respond to disease, long life spans, regenerate damaged hepatic tissue]
- **Metabolism of alcohol**- 3 different routes
  - Ethanol in cytosol to acetaldehyde (ADH enzyme) to acetic acid (ALDH enzyme) in mitochondria- MAJOR PATHWAY; acetaldehyde- major intermediate metabolic, extremely toxic
  - Ethanol goes through microsomes (CYP2E1/P450 enzyme- effective generator of ROS)- SECONDARY- when EtOH is high
  - Ethanol goes through peroxisomes (catalase enzyme)= MINOR

Cell biology-structure/organelles/changes in cells-morphology metabolism

- Acute effects of alcohol- CNS (powerful depressant, release excitatory pathways, affects cortex, limbic system, cerebellum, lower brain stem), party syndrome (euphoria, disordered cognitive and motor function)
  - Fatty liver/steatosis- small (microvesicular) lipid droplets in hepatocytes, **reversible**, FA metabolism altered, sponge-like appearance (exposure to alcohol)
    - Fat accumulates, increased FA synthesis, increased production of triglycerides, decreased apoproteins (more free FA), impaired release of lipoproteins (decrease FA transport proteins, more free FA)
  - Alcoholic hepatitis- severe exposure to alcohol, **potentially reversible**, hypoxic damage, misarrangement of sinusoids, slowdown of oxygenated blood, necrosis of hepatocytes, cytoplasmic hyaline inclusions (Mallory bodies), ECM damage long term, **symptoms** (fever, jaundice, liver tenderness), cytokines from Kupffer cells
- Chronic effects- metabolic derangement- accumulation of triglyceride
  - Cirrhosis-necrosis + inflammation + fibrosis + regeneration, **irreversible** scarring→portal hypertension, liver failure
    - Fatty liver/hepatitis usual precursor, induction of P450 (microsomes, ROS), mitochondrial function affected, disrupt membrane/cytoskeleton, active immune response

- Dark, green diffuse nodules on surface- nodular regeneration and scarring (bile stasis)

Tissue and organ changes-morphology/ECM/whole organ and effects on whole organism e.g. patient

- Other diseases/complications of ALD-
  - Acute gastritis (stomach)- acute, transient mucosal inflammatory process, erosion/sloughing of mucosa, epithelial layer, severe pain/inflammation/bleeding
  - Portal hypertension- elevation of BP due to resistance to normal blood flow to liver
  - Hepatic encephalopathy- brain abnormality due to liver's inability to remove toxins
  - Foetal alcohol syndrome- foetus intoxicated as alcohol crosses foetal-placental barrier, brain damage

Science/medicine tackle problem to inhibit/reverse disease progression

- Treatment and prognosis- abstinence from alcohol consumption; those who abstain, less severe fatty liver disease can be reversed in few weeks/resolution of hepatitis takes >6 months, more severe damage- corticosteroid treatment to reduce inflammatory response, liver transplant