Primary Cast Episode 23 - Pathology of Healing, Immunity and Neoplasia

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Inflammation - Tissue Response to injury

1. **Angiogenesis**
   What Is angiogenesis and when does it occur?
   - Branching and extension of existing vessels
   - Recruitment of endothelial progenitor cells
   - Occurs during wound healing, chronic inflammation, physiological processes such as endometrial proliferation and in tumour formation/growth

2. **Wound Healing**
   What are the sequence of events involved in wound healing?
   - Blood clot
   - Granulation tissue (angiogenesis, migration and proliferation of fibroblasts)
   - Cell proliferation and collagen deposition (of extracellular matrix)
   - Scar formation (blanching, type 3 collagen initially which is replaced by type 1)
   - Wound contraction via myofibroblasts
   - Connective tissue remodelling (ECM synthesis and degradation)
   - Recovery of tensile strength

   What is wound contraction?
   - A process that usually occurs in large surface wounds and helps to close the wound by decreasing the gap between its dermal edges.
   - This reduces the wound surface area and is an important feature of healing by secondary intention.
   - It is mediated by a network of myofibroblasts that form at the edge of the wound.

   How do skin wounds recover tensile strength?
   - Increase in collagen synthesis (type 1 collagen)
   - Reduction in collagen degradation for the first 2 months
   - Then structural modification of collagen with cross linking and increased fibre size

   What is the approximate timeframe for the recovery of tensile strength in skin wounds?
   - Skin wounds have 10% tensile strength at 1 week (usually when sutures are removed)
   - Improves for the first 3 weeks and plateaus at 3 months when tensile strength is 70-80% of the original
   - May never recover to 100%

3. **Scar formation and fibrosis**

What are the phases involved in scar formation?

- Inflammation
- Fibroblast migration and proliferation
- Angiogenesis
- Extracellular matrix deposition (usually collagen)
- Tissue remodelling
- Wound contraction

What factors influence scar formation?

- Tissue environment and extent of tissue damage
- Intensity and duration of stimulus
- Conditions that inhibit repair i.e. foreign body, infection or inadequate blood supply
- Systemic disease states i.e. diabetes, steroid use
- Nutritional status
- Genetic predisposition to scar formation i.e. keloid

4. **Fibrosis**

Describe the pathogenesis of fibrosis

- Fibrosis involves the excess deposition of collagen and extracellular matrix in chronic disease
- Usually a combination of healing and chronic inflammation
- Characterised by a persistent stimulus (infection, autoimmune, trauma)
- Macrophages are the key cells involved and the process is governed by growth factors which stimulate the proliferation and activity of fibroblasts

Please give some examples of fibrosis

- Cirrhosis
- Chronic pancreatitis
- Pulmonary fibrosis
- Constrictive pericarditis
- Glomerulonephritis

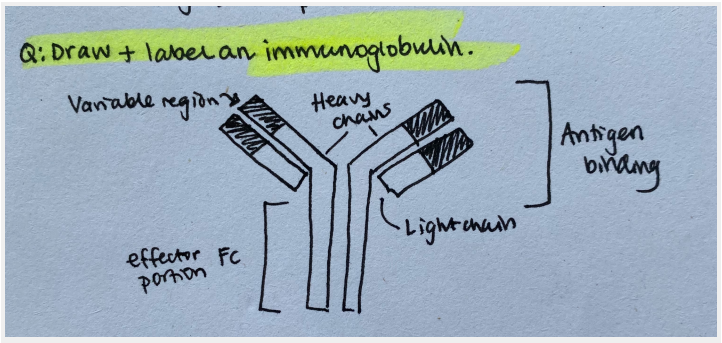
5. **Immunity - Immunoglobulins**

What are the types of immunoglobulins and their clinical significance?

- IgA - secretory
- IgD - antigen recognition by B cells
- IgE - important in anaphylaxis
- IgG - complement activation, infection fighting and immunity to past infections
- IgM - complement activation and is the first produced in acute infection

Draw and label a typical immunoglobulin

- Y shape
- Base of the Y has two parallel lines (the effector portion)
- The angled top parts of the Y each have two lines representing the heavy and light chains. This is the antigen binding portion
- The tips of the antigen binding portion (i.e. the most superior part of the arms of the 'Y') are known as the variable region, because they are different on different antibodies



What are the features of innate and acquired immunity?

Innate

- Early response
- Mediated by toll like receptors
- Bind common microbe sequence
- Defence mechanisms that are not specific i.e. interferons, phagocytosis

Acquired

- T cell mediators - antigen presenting cells, MHC markers, antigen presentation. T cells release cytokines and are responsible for orchestration of the immune response.
- B cells differentiate into plasma cells
- Memory cell formation, meaning secondary exposure leads to a magnified response.

6. **Type 1 Hypersensitivity**

Outline the immunological mechanisms leading to anaphylaxis

- Exposure to antigen
- Presentation of antigen to T helper cells by dendritic cells
- T helper cells differentiate into TH2 cells
- These release cytokines that act on B cells to produce IgE
- IgE binds to mast cells
- Repeat exposure to an antigen causes cross linking of IgE on mast cells leading to degranulation and release of vasoactive amines, lipid mediators and cytokines
- The action of these mediators on end organs results in clinical manifestations of anaphylaxis – vasodilation, vascular leakage and smooth muscle spasm

What are the clinical manifestations of anaphylaxis?

- Skin – rash, swelling
- Respiratory – wheeze, breathlessness, stridor
- GIT – diarrhoea and vomiting
- Cardiovascular – tachycardia, hypotension, shock and cardiovascular collapse

7. Type 2 Hypersensitivity

What is type 2 hypersensitivity?

Hypersensitivity caused by antibodies that react with antigens present on cell surfaces or in the extracellular matrix
Antigens can be intrinsic to the tissue or extrinsic i.e. drug metabolite

Describe the mechanisms involved and give examples of each mechanism

Opsonisation and phagocytosis
IgG antibodies opsonise cells, complement activation generates C3b and C4b which are recognised by phagocyte receptors resulting in phagocytosis and destruction of opsonised cells.
Examples: transfusion reactions, autoimmune haemolytic anaemia

Complement and Fc receptor mediated inflammation: antibodies bind to fixed tissue such as basement membranes and/or extracellular matrix which activates complement. The generation of C5a and C3a cause increased vascular permeability and activate inflammatory cells causing local tissue destruction.
Examples: glomerulonephritis, vasculitis, goodpastures syndrome

Antibody mediated cellular dysfunction: antibodies directed against cell surface receptors impair or dysregulate function without causing cell injury or inflammation
Examples: myasthenia gravis, graves disease, pernicious anaemia

8. Type 3 Hypersensitivity

Explain the pathogenesis of Type 3 Hypersensitivity

Antibodies bind antigen to form complexes, which are then deposited in tissues where they cause inflammation and tissue damage either directly or by activating complement.
3 phases involved in systemic diseases

- Formation of antigen/antibody complexes in the circulation
- Deposition of those immune complexes in various tissues
- Inflammatory reaction at the site of the deposition, causing tissue injury. This can take around 1o days to evolve.

What are some diseases caused by type 3 hypersensitivity?

Serum sickness, SLE. Post strep GN, reactive arthritis

What are some clinical features of type 3 HS?

Fever, urticarial, arthralgia, lymph node enlargement, proteinuria

9. Type 4 Hypersensitivity Reactions

Describe the sequence of events that lead to a type 4 hypersensitivity reaction.

- Initial injury
- Reaction is initiated by antigen-sensitised CD4+ or CD8+ T cells
- Antigen may be transported in the lymphatics of the damaged tissue
- Damage may occur via cytokines or via direct cell-mediated tissue injury

What are some examples of type 4 hypersensitivity reactions?

- Type 1 diabetes
- Multiple sclerosis
- Rheumatoid arthritis
- Inflammatory bowel disease
- Guillian Barre
- Contact dermatitis
- Tuberculin reaction
- Granulomatous disease
- Viral hepatitis

10. Neoplasia

What is a neoplasm?

- Abnormal growth of tissue that exceeds and is uncoordinated with that of the original tissue

How do cancer cells invade the extracellular matrix and then metastasise?

- Loosening of intercellular junctions
- Attachment to the basement membrane and interstitial connective tissue components
- Degradation of extracellular matrix via proteases, collagenases and other enzymes
- Migration of tumour cells via circulatory spread and/or embolization.
- Form metastatic deposits at other sites in the body

Why do some tumours metastasise to sites other than their natural blood and lymphatic drainage areas?

- Some organs/tissues have adhesion molecules to which tumour cells bind preferentially
- Some organs express chemokine receptors that attract cancer cells
- Downstream tissue may also be an environment that is not conducice to cancer cell growth i.e. skeletal muscle

11. Genetics of cancer

What is an oncogene?

A changed form of a gene that is usually involved in normal cell growth, resulting in a transformed phenotype when expressed in the cell.
The most common are H-Ras or K-Ras mutations which make up 30% of all human tumours.

How are oncogenes activated?

3 mechanisms - mutation, gene duplication or regulatory gene translocation
Before it becomes an oncogene through transformation, these genes are called proto-oncogenes.

12. Paraneoplastic syndromes

What is a paraneoplastic syndrome?

- A complex of symptoms that cannot be readily explained by the local or distant spread of a tumour or by elaboration of hormones from the tissue in which the tumour arose
- Occurs in around 10% of people with malignant disease

What are the main types of paraneoplastic syndromes?

Endocrinopathies

- Cushing's syndrome – release of ACTH by small cell lung Ca
- SIADH – release of ADH by small cell lung Ca or intracranial disease
- Hypercalcaemia – from parathyroid like hormones, seen in squamous cell lung Ca and breast cancer
- Carcinoid syndrome – from release of serotonin/bradykinin, seen in bronchial cancers, stomach and pancreatic Ca
- Polycythaemia – from EPO release, seen in renal tumours

Nerve and muscle syndromes

- Myasthenia – via immune mechanisms, seen in some bronchogenic carcinomas
- Other neurological syndromes can be seen with breast Ca

Dermatological

- Acanthosis nigricans, seen in gastric, lung and uterine Ca
- Dermatomyositis, seen in bronchogenic and breast Ca

What is the cause of cachexia in cancer?

- Poorly understood phenomenon
- Thought to be multifactorial – anorexia, elevated basal metabolic rate and humoral factors such as TNF/cytokines. Some possible influence of tumour produced factors.