Pathology - Topic 3 - Inflammation

General Features of Inflammation

- **Inflammation** is the response of vascularised living tissue to infection or injury.

Purpose and Main Features

- It brings protective cells and proteins to the affected site, removes harmful agents and dead tissue, and begins repair.
- The response can itself damage tissue when it is excessive, persistent or directed against normal body components.
    - The benefits and harmful effects therefore arise from many of the same protective mechanisms.
- Common stimuli include microbes, tissue necrosis, foreign material and immune reactions.
    - Inflammation does not always mean infection because sterile injury can activate the same response.

Acute and Chronic Responses

1. Acute Inflammation

- Acute inflammation begins rapidly and is characterised by vascular changes, fluid exudation and leukocyte recruitment.
    - Neutrophils often dominate early, but the cells present depend on the cause and the time of sampling.
- The response may resolve, form an abscess, heal by scarring or progress to chronic inflammation.

2. Chronic Inflammation

- Chronic inflammation is a prolonged response in which inflammation, tissue destruction and attempts at repair coexist.
    - Macrophages, lymphocytes and plasma cells are common, together with angiogenesis and fibrosis.
- A chronic response may follow unresolved acute inflammation or begin gradually without an obvious acute phase.

Cardinal Signs

- **Redness and warmth** mainly reflect increased local blood flow.
- **Swelling** results from fluid exudation and the accumulation of cells.
- **Pain** is promoted by mediators such as bradykinin and prostaglandins and by pressure within swollen tissue.
    - Loss of function may follow pain, tissue injury, swelling or subsequent scarring.

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Acute Inflammation

- Acute inflammation is an early inflammatory response characterised mainly by vascular changes, exudation and recruitment of neutrophils.

Recognition of Injury

- Resident macrophages, dendritic cells, mast cells and other cells recognise microbial products and molecules released by injured cells.
    - Pattern-recognition receptors help distinguish signals that require a protective response.
- Some danger signals activate the **inflammasome**, which promotes production of active interleukin-1 and can trigger inflammatory cell death.
    - The same mechanism contributes to sterile inflammation around crystals such as urate.

Vascular Events



1. Vasodilation and Stasis

- Arteriolar dilation increases blood flow and opens more of the local microcirculation.
    - Histamine and nitric oxide contribute to this early vascular response.
- Loss of plasma fluid into tissue concentrates the cells remaining in small vessels and slows the circulation.
    - This slowing, called **stasis**, promotes movement of leukocytes towards the endothelial surface.

2. Increased Vascular Permeability

A. Endothelial Contraction and Retraction

- Histamine produces rapid transient gaps, particularly in postcapillary venules, allowing protein-rich fluid to escape.
- Cytokine-induced cytoskeletal reorganisation produces a slower and potentially more sustained permeability change.

B. Direct and Leukocyte-Mediated Injury

- Severe burns and toxic injury can cause immediate persistent leakage through damaged endothelium.
- Adherent activated leukocytes can injure endothelial cells through oxidants and proteases.

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C. Leakage from New Vessels

- Newly formed vessels remain permeable while their junctions and supporting structures mature.
- Escaped proteins raise interstitial osmotic pressure and contribute to oedema.

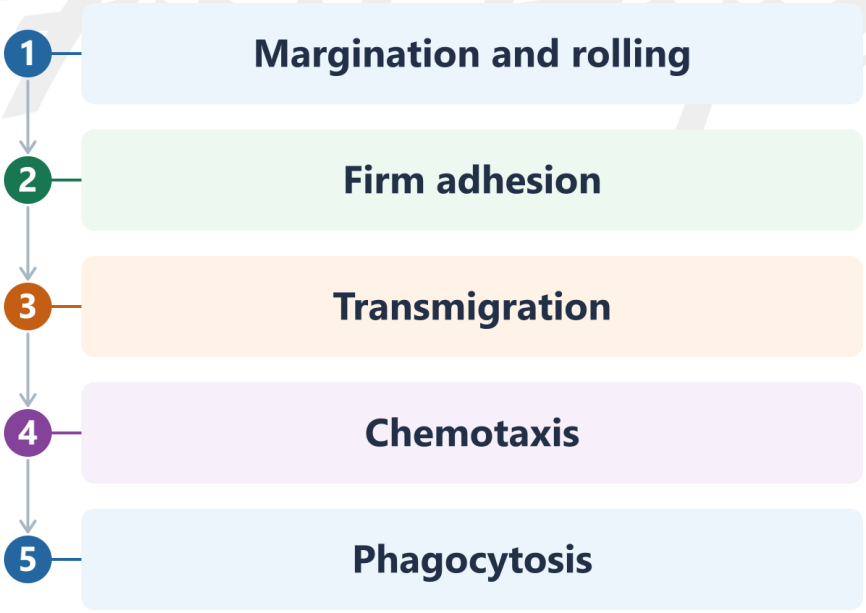
3. Exudate and Transudate

- An **exudate** is relatively protein-rich fluid produced mainly by increased vascular permeability.
  - It commonly contains inflammatory cells and cellular debris.
- A **transudate** is relatively protein-poor fluid caused mainly by an imbalance of hydrostatic and oncotic forces without primary inflammatory permeability change.
  - These terms describe mechanisms and fluid characteristics rather than one universal numerical protein cut-off.

4. Lymphatic Changes

- Lymph flow increases to remove excess interstitial fluid, proteins and organisms.
- Spread of infection through lymphatics may produce lymphangitis and reactive enlargement of regional lymph nodes.

Leukocyte Recruitment



1. Margination and Rolling

- Leukocytes move towards the vessel wall as blood flow slows.
  - Weak, repeated attachments then allow the cells to roll along the endothelial surface.
- **Selectins** on endothelium and leukocytes mediate many of these initial contacts.
- Endothelial E-selectin and P-selectin interact with carbohydrate ligands to produce the weak repeated attachments of rolling.

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2. Firm Adhesion

- Chemokines activate leukocyte integrins so that they bind strongly to endothelial adhesion molecules.
    - Tumour necrosis factor and interleukin-1 increase the endothelial expression of several required ligands.
- Defects in adhesion mechanisms can cause recurrent infection despite a high circulating neutrophil count.
- Activated leukocyte integrins bind endothelial ICAM-1 or VCAM-1 to create firm attachment.

3. Transmigration

- Adherent leukocytes pass between endothelial cells, mainly in postcapillary venules.
    - PECAM-1, also called CD31, participates in this passage across the endothelial barrier.
- The cells cross the basement membrane and enter the surrounding tissue.

4. Chemotaxis

- Leukocytes move along a chemical gradient towards the source of injury.
    - Important attractants include bacterial products, C5a, leukotriene B4 and chemokines such as CXCL8.
- Neutrophils often arrive before monocytes because they are numerous and respond rapidly to early signals.
    - Viral infections may favour lymphocytes, while allergic reactions and some parasites may recruit eosinophils.

Clinical Correlations of Defective Recruitment

- Defective integrin-dependent adhesion can cause recurrent bacterial infections with impaired pus formation and poor wound healing.
- Neutropenia can blunt the expected inflammatory cellular response even when infection is severe.

Phagocytosis and Microbial Killing

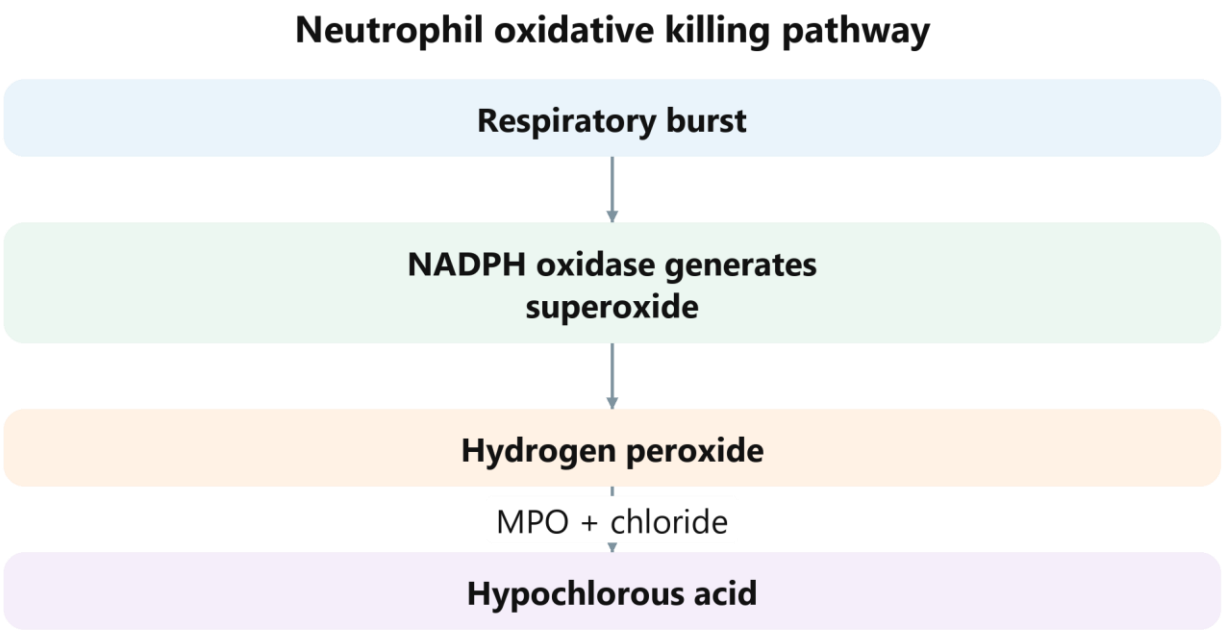
1. Recognition and Engulfment

- A phagocyte binds a target directly or through **opsonins**, which coat the target and improve recognition.
    - IgG and complement fragment C3b are important opsonins.
- The cell surrounds the target to form a phagosome, which fuses with lysosomes to form a phagolysosome.
- Fc and complement receptors on the phagocyte recognise the corresponding opsonins.

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2. Killing and Digestion

A. Oxygen-Dependent Mechanisms



- NADPH oxidase generates superoxide during the respiratory burst, and subsequent reactions produce hydrogen peroxide.
- Neutrophil myeloperoxidase uses hydrogen peroxide and chloride to form hypochlorous acid.
- A defect of NADPH oxidase causes chronic granulomatous disease with impaired killing of selected pathogens.
- Nitric oxide also contributes to microbial killing in activated macrophages.

B. Oxygen-Independent Mechanisms

- Lysosomal enzymes, defensins and other granule proteins damage or digest organisms within phagolysosomes.
- Failure of killing can allow infection to persist even when leukocyte recruitment is intact.

3. Extracellular Traps

- Neutrophils can release chromatin-associated antimicrobial proteins that trap organisms outside the cell.
- These traps may also promote thrombosis and injure host tissue.

4. Injury to the Host

- Activated leukocytes may release enzymes, oxidants and other mediators into surrounding tissue.
  - This occurs during persistent infection, frustrated phagocytosis of large targets and misdirected immune responses.

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