Microbiology 1

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Overview of Innate Immunity

- The innate immune system is the body's first line of defense, evolved as a complex system to detect and respond to pathogens through physical barriers, antimicrobial molecules, and cellular components. The major topics in innate immunity include:

- **Epithelial Barriers**:
  - ***Structure***: Intact epithelial layers (in skin, GI tract, respiratory, and genitourinary tracts) act as physical barriers.
  - ***Tight Junctions***: Maintain integrity of these barriers, preventing pathogen entry.
  - ***Mucus***: Contains antimicrobial enzymes (e.g., lysozyme), immunoglobulins, and glycoproteins, physically blocking pathogens and aiding removal through mechanisms like ciliary action.
  - ***Cystic Fibrosis:*** Defective CFTR proteins impair mucus secretion, leading to increased vulnerability to infections.
  - ***Primary Ciliary Dyskinesia:*** Impaired mucociliary clearance results in recurrent chest infections.
  - ***Eczema***: Skin barrier defects increase susceptibility to infections.

- **Antimicrobial Peptides (AMPs)**:
  - Types:
    - ✓ Defensins: Produced by epithelial cells and leukocytes, targeting bacterial cell membranes.
    - ✓ Cathelicidins: Produced by neutrophils and epithelial cells, providing bactericidal and immunomodulatory effects.
  - Mechanism: Positively charged AMPs interact with negatively charged bacterial membranes, disrupting them

- **Microbiota**:
  - The gut microbiota is essential for developing and maintaining the intestinal barrier, which helps prevent pathogen invasion.

- **Intraepithelial T Lymphocytes**:
  - Found within barrier epithelia, these cells often have γδ receptors and limited antigen receptor diversity. They recognize commonly encountered pathogens and operate independently of MHC presentation.

- **Leukocyte Migration into Tissues**
  - Leukocytes continuously circulate through blood and lymphoid organs, migrating to sites of infection or injury via a multi-step adhesion process:

  1. Recruitment and Inflammation:
     - ✓ Activated by cytokines from infected or injured tissue, endothelial cells at infection sites recruit leukocytes, initiating an inflammatory response.
  2. Adhesion Mechanisms:
     - ✓ *Selectins*: Carbohydrate-binding molecules on endothelial cells mediate initial, low-affinity leukocyte adhesion, which cytokines like IL-1 and TNF prompt within 1-2 hours.
     - ✓ *Integrins*: Heterodimeric proteins on leukocytes bind to endothelial ligands (e.g., ICAM-1) with high affinity after activation by chemokines, ensuring firm attachment for tissue migration.
  3. Chemokines:
     - ✓ Direct leukocyte migration by enhancing integrin binding and clustering on the endothelial cells, leading to precise movement into infection or injury sites.

- **Leukocyte Migration into Tissues and Chemokines**
  - Chemokines are critical in regulating leukocyte migration, guiding immune cells to infection or injury sites to initiate the immune response. Here are key points about chemokines and leukocyte migration:
  - Chemokine Families:
    - ✓ CC Chemokines: These chemokines have adjacent cysteine residues and primarily attract monocytes, eosinophils, and other leukocytes.
    - ✓ CXC Chemokines: These chemokines have a single amino acid separating their cysteine residues, and they primarily recruit neutrophils.
    - ✓ CX3C Chemokines: Less common, these chemokines play a role in recruiting both immune and non-immune cells.
    - ✓ XC Chemokines: A small subgroup involved in various immune responses.
  - Chemokine Receptors:
    - ✓ These receptors belong to the GPCR (G-protein coupled receptor) superfamily, which are seven transmembrane receptors activated by chemokines, enabling leukocyte migration.
  - Key Chemokines and Their Functions:
    - ✓ IL-8 (CXCL8): A CXC chemokine that primarily attracts neutrophils to the site of infection. It induces chemotaxis and promotes phagocytosis once neutrophils arrive.
    - ✓ Tumor Role: IL-8 is also co-opted by tumors for immunosuppressive purposes, reducing the immune system's ability to attack cancer cells.
    - ★ ***Question:*** Which chemokine family is responsible for recruiting neutrophils to infection or injury sites?
    - ☑ ***Answer:*** CXC chemokines
  - Clinical Correlate: Leukocyte Adhesion Deficiency (LAD):
    - ✓ LAD is an immunodeficiency disorder where leukocytes cannot migrate to infection sites due to a deficiency in adhesion molecules (e.g., LFA-1/Mac-1, CD18).
    - ✓ This results in inability to form pus, recurrent bacterial infections, and impaired inflammatory response.
  - Leukocyte Migration Process:
    - ✓ Endothelial Activation: Upon encountering microbes and cytokines, endothelial cells express selectins that slow down leukocytes in the bloodstream.
    - ✓ Chemokine Signaling: Chemokines bind to receptors on leukocytes, increasing their integrin affinity and allowing firm attachment to the endothelium.
    - ✓ Transmigration: Leukocytes then move through the endothelial barrier into tissues (paracellular transmigration).
  - Lymphocyte Chemotaxis:
    - ✓ Lymphocyte Movement: Lymphocytes travel through lymph nodes, and inflammation in peripheral tissues increases blood flow, leading to more T cells migrating into the lymph nodes for immune activation.
    - ✓ B Cell Homing: Like T cells, naive B cells also use similar mechanisms to enter secondary lymphoid tissues, aiding their ability to respond to antigens from different sites.
- In summary, chemokines and adhesion molecules are essential in guiding immune cells to infection or injury sites, and defects in these processes (e.g., in LAD) can result in significant immune deficiencies.

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