O Microbiology 1 2025-2024

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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:
 - ✓ <u>Defensins</u>: Produced by epithelial cells and leukocytes, targeting bacterial cell membranes.
 - <u>Cathelicidins</u>: 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 $\gamma\delta$ 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.
- ★ <u>Ouestion</u>: 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:

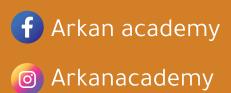
- Endothelial Activation: Upon encountering microbes and cytokines, endothelial cells express selectins that slow down leukocytes in the bloodstream.
- Chemokine Signaling: Chemokines bind to receptors on leukocytes, increasing their integrin affinity and allowing firm attachment to the endothelium.
- 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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