Chapter 15
Lymphocyte Migration and Inflammation

Lymphocyte Recirculation

I. Primary Lymphoid
II. Secondary
   - Lymph Nodes
   - Spleen
   - MALT

Leukocytes are constantly moving between sites where antigens may be encountered:
- Spleen
- Lymph nodes
- Other secondary lymphoid tissues
- Other tissues – especially skin and mucosal surfaces

Leukocytes accumulate at sites of inflammation

Lymphatic vessels
- Collect interstitial fluid and carry it (lymph), via a system of progressively larger vessels, into regional lymph nodes. (via afferent lymphatic vessels).
- Lymph leaves the lymph nodes via efferent lymphatic vessels, which eventually drain back into the circulatory system (via the thoracic duct).
1) If no antigen is present: lymphocytes routinely enter and leave secondary lymphoid tissues.
2) If antigen enters the secondary lymphoid tissue:
   Lymphocyte proliferation in response to antigen occurs within the lymphoid tissue.
   After several days, antigen-activated lymphocytes begin leaving the lymphoid tissue.

**CHOICES:**
- Antigen capture: (APC) or
- Macrophages: capture and process particulate antigens (via phagocytosis)
- Dendritic cells: capture and process non-particulate antigens (via endocytosis)
- B cells: capture and process antigens that bind to surface BCR (via endocytosis)

Dendritic cells: originate in bone marrow, capture antigen within tissues and transport antigen to secondary lymphoid tissue.

Lymphocytes can enter lymphoid tissues in two ways:
1) Direct entry into lymph nodes via afferent lymphatics
2) Entry from blood capillaries across specialized endothelial cells (high-walled endothelial cells) present in the postcapillary venules (High Endothelial Venules= HEV) within the secondary lymphoid tissue.

**Why?**
- For lymphocytes access to potential antigens.
- Migration of lymphocytes is determined by the pattern of expression of adhesion molecules on lymphocytes and on endothelial cells.
Cell-Adhesion Molecules (CAMs)

- Vascular endothelium in the blood vessels and posses CAMs that interact with leukocytes to allow **extravasation**.
- CAMs are either expressed **CONSTITUTIVELY** or in **INDUCED** by cytokines during inflammation.
- CAMs belong to **four families** of proteins:

1. **Selectins**
   - Bind to sialic acid residues on mucins.
   - L-selectin (lymphocytes)
   - E- and P-selectin (Endothelium)

2. **Mucins**: Heavily glycosylated proteins on the cell surface that contain sialic acid residues which bind to selectins
   - (GlyCAM-1, MAdCAM-1)

3. **Integrins**: Heterodimers consisting of a common β chain and a unique α chain.
   - (LFA-1, Mac-1, VLA-4)
   - Leukocyte integrins use the β2 chain:

4. **Integrins bind to ICAMs**.
   - Members of the Immunoglobulin Superfamily (ICAMs)
     - ICAM-1 (CD54)
     - ICAM-2 (CD102)
     - ICAM-3 (CD50)
     - VCAM (CD106)

Neutrophil Extravasation:

1. **Rolling**
2. **Activation**
3. **Arrest/adhesion**
4. **Transendothelial migration**

Remember: activation of the endothelial cells also caused by: MIP-1β, IL-8, platelet activating factor (PAF), C3a, C5a, TNF-alpha.
Lymphocyte Homing:

- Naïve lymphocytes re-circulate into secondary lymphoid tissue where they can be activated to become effector cells.
- Able to re-circulate into secondary lymphoid tissues through interaction with HEV
- Naïve lymphocytes express L-selectin (homing receptor) that interacts with GlyCAM-1 and CD34 on HEVs.
Steps in Extravasion of Naïve T cells to inflammatory sites

1) Inflammatory mediator (IL-8, MIP-1β, PAF, C3a, C5a) acts on the vascular endothelium
2) Vascular endothelium responds by expressing CAMs: GlyCAM-1, ICAM-1, (and E/P-selectins)
3) “Activated T cell” expresses LFA-1
4) From rolling to “tight” adhesion
5) The chemokine IL-8 acts on his receptor on the T cell
6) This interaction signals re-arrangement of LFA-1
7) LFA-1 on T cells interacts with ICAM-1 (tight adh.)
8) Extravasion and chemotaxis to inflammatory site

Chemokines

- A large family of small cytokines (90-130 amino acids - about 8-10 kD) that influence chemotaxis and activation of leukocytes.
- Over 50 chemokines have been identified to date.

Common features of chemokines:
- structural similarities
- the ability to attract leukocytes to infection sites
- regulate traffic of lymphocyte through peripheral lymphoid tissue

Examples of chemokines: IL-8, IP-10, MIP-1α, MIP-1β, MCP-1, MCP-2, MCP-3, eotaxin, RANTES 

Chemokine receptors:
- Chemokines mediate their effects by binding to surface receptors on responding cells.
- A significant number of chemokine receptors have been discovered.
- Two types: CXCR and CCR
- Most chemokine receptors bind more than one chemokine.
- Many chemokines can bind more than one receptor.

- Th1: CCR5, CXCR3
- Th2: CCR3, CCR4

Chemokines may have many different effects on cells:
- changes in cell shape
- changes in cell adhesiveness (by activation of leukocyte integrins)
- induction of the respiratory burst
- induction of degranulation
- other
In immunologic diseases and infections, chemokines influence the accumulation and activation of leukocytes in tissues.

The type of inflammatory infiltrate that characterizes a specific disease or infection is controlled, in part, by the subgroup of chemokines expressed in the diseased tissue.

**Examples:**
- Eotaxin - promotes eosinophil accumulation
- IL-8 – neutrophils
- MCP-1 - monocytes
- IP-10 - T cells

**Inflammation**

A rapid, nonspecific reaction triggered in response to tissue damage and/or infection.

**Inflammatory mediators**

Factors released by various cells during an inflammatory response which trigger or enhance the inflammatory response.

Include:
- Chemokines
- Plasma enzyme mediators of inflammation
- Lipid inflammatory mediators
- Cytokines

**Consists of three major events:**

1) **Vasodilation** - blood vessels at the site become dilated - results in redness at the site - allows increased blood flow to the area.
2) **Increase in capillary permeability** - results in swelling at the site - allows fluid to move from blood vessels into the tissues at the site
3) **Accumulation of cells of the immune system** - particularly neutrophils - at the site. These phagocytose bacteria and release lytic enzymes and other substances that damage BOTH invading microorganisms and the cells of the host at the site.

Excess fluid, dead cells and digested material forms pus at the site of infection.
II. Membrane phospholipids

Phospholipase

Anandamide
Cyclooxygenase
Prostaglandins
Leukotriene A4
Leukotriene B4
Prostacyclin

Thromboxane
Prostacyclin
Leukotrienes
Leupeptin
PLA2

Platelet aggregation
Vascular permeability
Other effects

Vasodilation
Increased vascular permeability
CAM vascular endothelium
Increased adhesion molecules
Increased mononuclear cell infiltration
Fibroblast proliferation
Platelet production
Chemokine induction (e.g., IL-8)
Induction of IL-6
T-cell activation
B-cell activation
Increased immunoglobulin synthesis

**TABLE 15-3** Redundant and pleiotropic effects of IL-1, TNF-α, and IL-6

<table>
<thead>
<tr>
<th>Effect</th>
<th>IL-1</th>
<th>TNF-α</th>
<th>IL-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endogenous pyrogen fever</td>
<td>+</td>
<td>+</td>
<td>*</td>
</tr>
<tr>
<td>Synthesis of acute-phase proteins by cells</td>
<td>+</td>
<td>+</td>
<td>*</td>
</tr>
<tr>
<td>Increased vascular permeability</td>
<td>+</td>
<td>+</td>
<td>*</td>
</tr>
<tr>
<td>Increased adhesion molecules on vascular endothelium</td>
<td>+</td>
<td>+</td>
<td>*</td>
</tr>
<tr>
<td>Fibroblast proliferation</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Platelet production</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Chemokine induction (e.g., IL-8)</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Induction of IL-6</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>T-cell activation</td>
<td>+</td>
<td>+</td>
<td>*</td>
</tr>
<tr>
<td>B-cell activation</td>
<td>+</td>
<td>+</td>
<td>*</td>
</tr>
<tr>
<td>Increased immunoglobulin synthesis</td>
<td>-</td>
<td>-</td>
<td>*</td>
</tr>
</tbody>
</table>

**TABLE 15-4** Chronic inflammatory diseases associated with NOS/NO production

<table>
<thead>
<tr>
<th>Disease</th>
<th>Affected organ</th>
<th>Thymus infiltration</th>
<th>Macrophage/CDC expression</th>
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<tbody>
<tr>
<td>Crohn's disease</td>
<td>Gut</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Diabetes mellitus</td>
<td>Pancreas</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>Joint</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Systemic lupus</td>
<td>Heart</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Lung</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Bone marrow</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Lymph node</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Leukemic cells</td>
<td>Bone marrow</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Includes iNOS, COX-2, iNOS inhibitors, and COX-2 inhibitors.