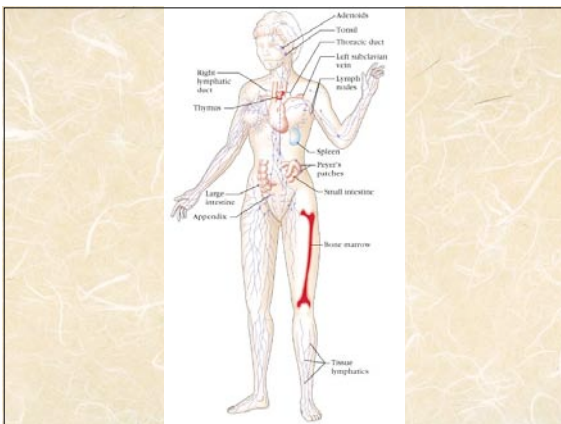


Leukocyte Migration

- Immune Cells are **MOBILE**, trafficking via the **LYMPH**
- This mobility contributes to **IMMUNE SURVEILLANCE** and **MEMORY**
- Migration is **NON-RANDOM**, and is regulated by distinct cell-surface and soluble molecules

What is Lymph?

- During blood circulation, roughly the whole blood volume leaks out of the capillaries and into the tissue each day.
- This fluid and protein is returned to the blood via a second vascular system-the **LYMPHATICS**



Lymph cont'd

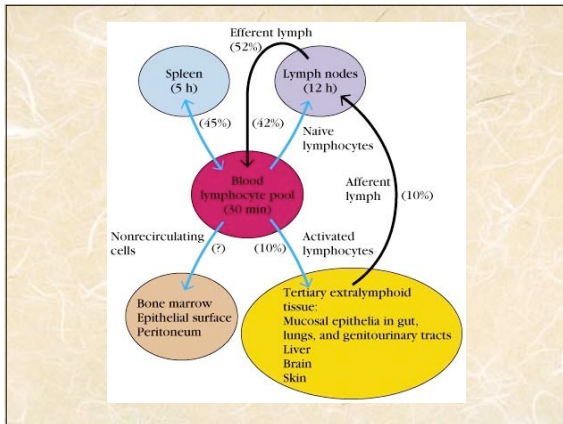
- Lymphatics begin as “afferent” blind-ended sacs, and lymph (tissue fluid and protein) enters by negative pressure (like a vacuum cleaner)
- Lymphatics eventually join, and re-enter the bloodstream via the THORACIC LYMPH DUCT

Immune Use of the Lymphatics

- 1) Lymph Nodes are interspersed at **pre-defined** places along the lymphatics, and filter the lymph for the presence of foreign antigen.
- 2) Leukocytes traffic between the blood and the tissues via the lymph (like a bypass).
 - Granulocytes, Macrophages, Dendritic Cells are retained within the lymph node
 - Lymphocytes can transit through the node, and return to the blood-RECIRCULATION.

How Important is Recirculation?

- In the average adult human:
 - 10^{12} lymphocytes total (3% total blood volume)
 - 10^{10} are in the blood at any time (1%)
 - 10^{11} are actively recirculating. (10%)



Non-Specific Migration

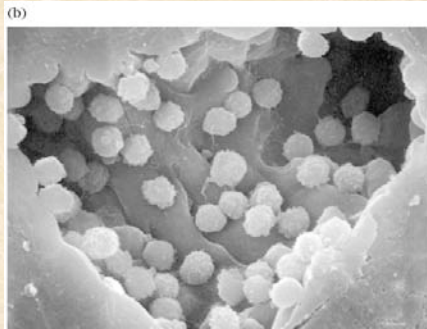
- Lymphocytes migrate NON-RANDOMLY through specific tissues (preferentially)
- MOST Lymphocytes recirculate through lymphoid tissue (LN) - 90%
- 10% of all lymphocytes migrate through non-lymphoid (tertiary) tissue

Organs of Preferential Migration

- At least 3 pools of lymphocytes exist, which migrate preferentially (repeatably) through
 - Lymph Nodes
 - Naïve T lymphocytes
 - Gut Tissue, Peyer's patches, lymph nodes
 - Memory T Lymphocytes stimulated in the gut
 - Skin
 - Memory T Lymphocytes stimulated in the skin

High Endothelial Venules

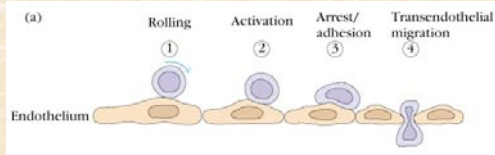
- “Plump, cuboidal” endothelial cells which line the post-capillary venules of lymph nodes in mice, humans.
 - Specialized “traffic” endothelium, the cause of this morphology is not understood.
- Endothelial cells which have been activated by local inflammation alter their structure to resemble HEV.



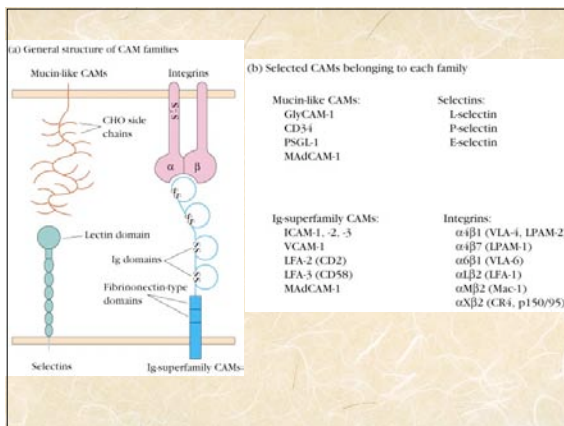
What is the Mechanism of Leukocyte Migration?

- The mechanism of migration is believed to be similar between all cells - only the molecules differ, which confers specificity.
- NEUTROPHILS are the most efficient cell at transendothelial migration, and current models are based on PMNs

4 Stages of Transmigration



1. Selectins 2. Chemokines 3. Integrins/ Ig Superfamily 4. Integrins



Selectins

- Regulate initial rolling - normally associated with SPECIFICITY or SELECTIVITY
- Known as CD62L, CD62E, CD62P
 - L-Selectin (Lymph Node Homing Receptor)
 - On Leukocytes
 - E-Selectin (Endothelial selectin)
 - On endothelial cells in skin, inflamed tissue
 - P-Selectin (Platelet selectin)
 - On platelets, endothelium in inflammation

Mucin-like Molecules

- A family of heavily glycosylated (sugar groups) proteins, which interact with the lectin domain of selectins
- SUGAR STRUCTURE determines specificity

Mucin-like Molecules cont' d

- GlyCAM -1 (Glycosylated Cell Adhesion Molecule 1)
 - On Endothelial Cells of Lymph Nodes, ligand for CD62L
- MadCAM-1 (Mucosal Addressin Cell Adhesion Molecule)
 - On Endothelial Cells of Gut, Peyer's patches
 - Ligand for CD62L, LPAM-1 ($\alpha 4\beta 7$ Integrin), VLA-4 ($\alpha 4\beta 1$ Integrin)

Mucins Cont' d

- PSGL-1 - (P Selectin Glycoprotein Ligand-1)
 - On neutrophils, binds to E and P-selectin on inflamed endothelium.
- CD34
 - A **specific form** of CD34, differing in sugar structure, which is found on lymph node traffic endothelium.

Integrins

- Integrins are a widespread family of **heterodimeric** proteins expressed by cells of the body which regulated adherence and cell-cell interactions
- Leukocytes use specific pairings of these α and β chains to regulate cell migration.

Integrins cont' d

- $\alpha 4\beta 1$ (VLA-4 - Very Late Antigen 4, CD49d)
 - On neutrophils, T cells, monocytes - binds to VCAM-1, MadCAM-1 on endothelial cells
 - Also binds fibronectin
- $\alpha 4\beta 7$ (LPAM-1 - Leukocyte Peyer's patch Adhesion Molecule)
 - On effector/memory T cells, monocytes - binds to MadCAM-1, VCAM-1 on endothelial cells.

Integrins cont' d

- LFA-1 ($\alpha L\beta 2$ Integrin, Leukocyte Function Associated Antigen 1)
 - Ligand for ICAM-1,2,3 on endothelial cells, APCs. General role in migration
- Other pairings regulate monocyte migration to inflammation (Mac-1), and T-progenitor migration to the thymus (VLA-6).

Immunoglobulin Superfamily

- Structure similar to antibody, T cell receptor
- Some important in T cell function, not critical to migration - LFA-2, LFA-3, ICAM-1,2,3.

Ig Superfamily

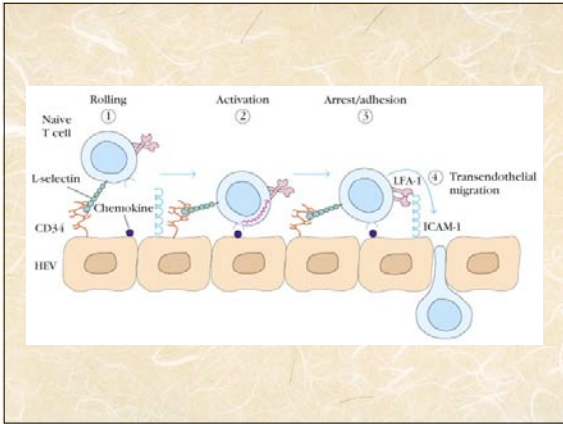
- MadCAM-1 - base structure is immunoglobulin, but specificity is denoted by sugars
- VCAM-1 (Vascular Cell Adhesion Molecule - 1;CD106)
 - Upregulated on inflamed endothelium - binds to the $\alpha 4$ integrins LPAM-1 and VLA-4, Mac-1.
- ICAM-1,2,3 - (Intracellular Adhesion Molecules 1,2,3)
 - On endothelium-general adhesion during migration.

TABLE 15-1 Some interactions between cell-adhesion molecules implicated in leukocyte extravasation*

Receptor on cells	Expression	Ligands on endothelium	Step involving interaction [†]	Main function
CLA or ESL-1	Effector T cells	E-selectin	Tethering/rolling	Homing to skin and migration into inflamed tissue
L-selectin	All leukocytes	GlyCAM-1, CD34, MAdCAM-1	Tethering/rolling	Lymphocyte recirculation via HEVs to peripheral lymph nodes and migration into inflamed tertiary sites
LFA-1 ($\alpha 4\beta 2$)	Leukocyte subsets	ICAM-1, 2, 3	Adhesion/arrest	General role in lymphocyte extravasation via HEVs and leukocyte migration into inflamed tissue
LPAM-1 ($\alpha 4\beta 7$)	Effector T cells, monocytes	MAdCAM-1, VCAM-1	Rolling/adhesion	Homing of T cells to gut via mucosal HEV; migration into inflamed tissue
Mac-1 ($\alpha M\beta 2$)	Monocytes	VCAM-1	—	Monocyte migration into inflamed tissue
PSGL-1	Neutrophils	E- and P-selectin	Tethering/rolling	Neutrophil migration into inflamed tissue
VLA-4 ($\alpha 4\beta 1$)	Neutrophils, T cells, monocytes	VCAM-1, MAdCAM-1, fibronectin	Rolling/adhesion	General role in leukocyte migration into inflamed tissue
VLA-6 ($\alpha 6\beta 1$)	T cells	Laminin	—	Homing of progenitor T cells to thymus; possible role in T cell homing to nonmucosal sites

*Most endothelial and leukocyte CAMs belong to four groups of proteins as shown in Figure 15-2. In general, molecules in the integrin family bind to Ig-superfamily CAMs, and molecules in the selectin family bind to mucin-like CAMs. Members of the selectin and mucin-like families can be expressed on both leukocytes and endothelial cells, whereas integrins are expressed only on leukocytes, and Ig-superfamily CAMs are expressed only on endothelium.

[†]See Figures 15-3a and 15-7 for an illustration of steps in the extravasation process.



Next Lecture

- Antigenicity/Immunogenicity.
 - Read Chapter 3, pp63-67.
- Web site address:
 - <http://biomicro.sdstate.edu/younga/>
