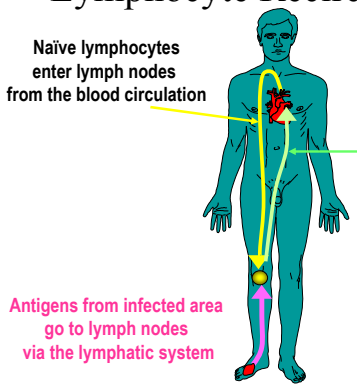
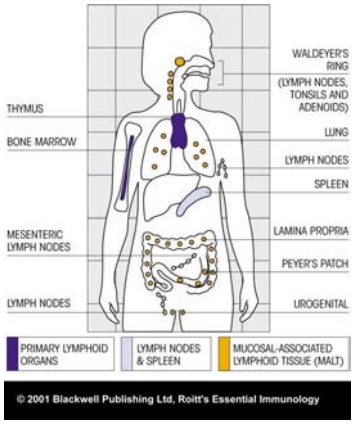
Chapter 15

Lymphocyte Migration and Inflammation

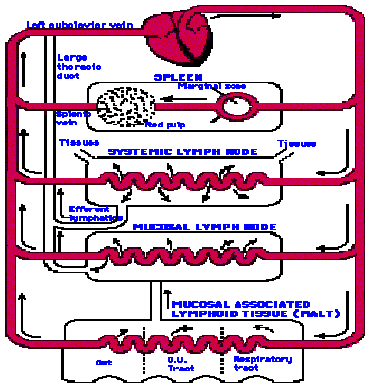
Lymphocyte Recirculation

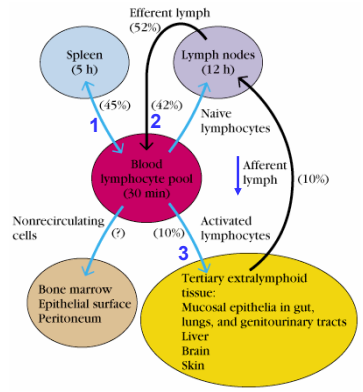




I. Primary Lymphoid

II. Secondary
- Lymph Nodes
- Spleen
- MALT

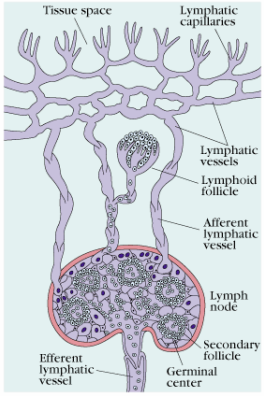




Leukocytes are constantly moving between sites where antigens may be encountered:

- 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).

CHOICES:

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.

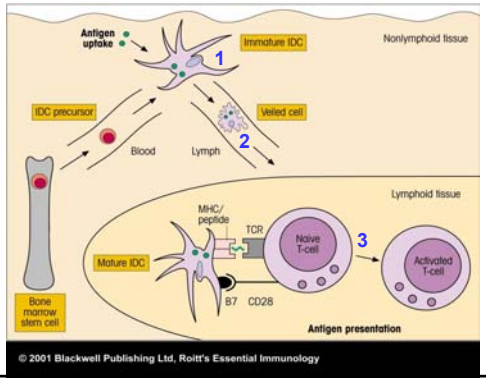
Antigen capture: (APC) or

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.



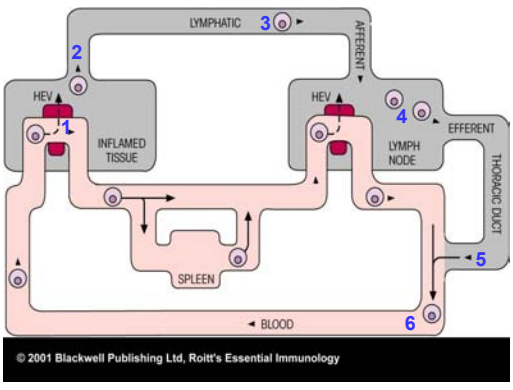
Lymphocytes can enter lymphoid tissues in two ways:

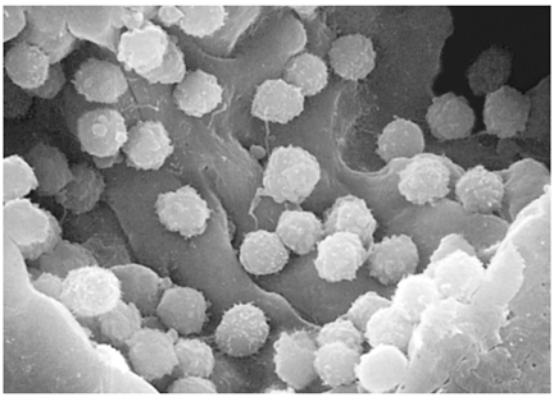
1) **Direct entry into lymph nodes via afferent lymphatics**

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?

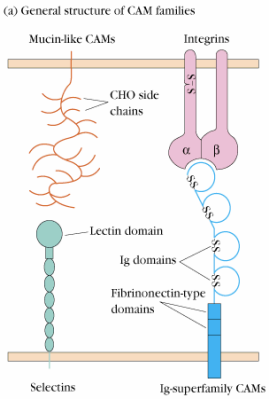
- **For lymphocytes access to potential antigens.**
- **Migration of lymphocytes is determined by the pattern of expression of adhesion molecules on lymphocytes and on endothelial cells.**





Cell-Adhesion Molecules (CAMs)

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



Expression of adhesion molecules controls leukocyte movement through tissues.

Four families of adhesion molecules

1) Mucins bind to 2) selectins.

3) Integrins bind to 4) ICAMs.

1. Selectins

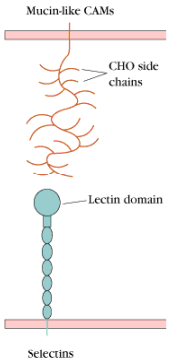
Bind to sialic acid residues on mucins.

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:

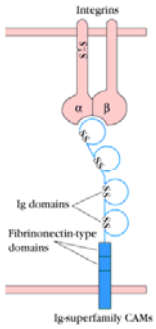
Heterodimers consisting of a common β chain and a unique α chain.

(LFA-1, Mac-1, VLA-4)

Leukocyte integrins use the β2 chain:

4. Integrins bind to ICAMs.

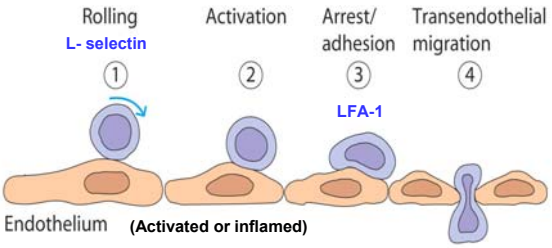
Members of the Immunoglobulin Superfamily (ICAMs)
ICAM-1 (CD54)
ICAM-2 (CD102)
ICAM-3 (CD50)
VCAM (CD106)



(b) Selected CAMs belonging to each family

Mucin-like CAMs:	Selectins:
*GlyCAM-1	* L-selectin
CD34	P-selectin
PSGL-1	E-selectin
*MAdCAM-1	
Ig-superfamily CAMs:	**Integrins:**
*ICAM-1, -2, -3	*α4β1 (VLA-4, LPAM-2)
*VCAM-1	α4β7 (LPAM-1)
*LFA-2 (CD2)	*α6β1 (VLA-6)
LFA-3 (CD58)	αLβ2 (LFA-1)
MAdCAM-1	αMβ2 (Mac-1)
	αXβ2 (CR4, p150/95)

Neutrophil Extravasion:



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

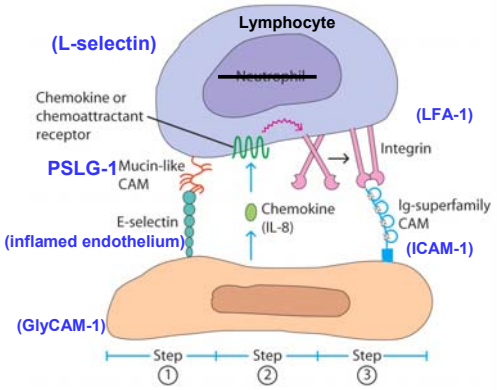
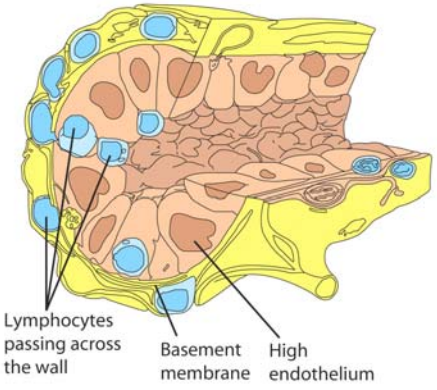


TABLE 15-1 Some Interactions between Cell-Adhesion Molecules Implicated in Leukocyte Extravasation*

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 ($\alpha_L\beta_2$)	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.

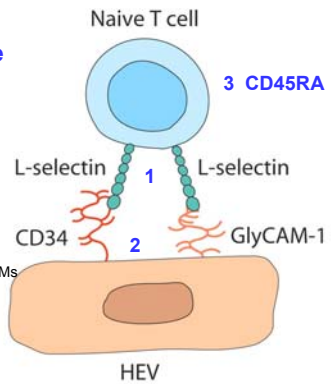


Lymphocyte Homing:

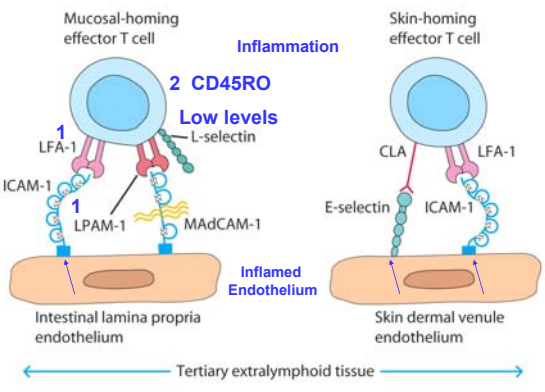
- Naïve lymphocytes re-circulate into secondary lymphoid tissue where they can be activated to become effector cells.
- Able to re-circulate into secondary lymphoid tissues through interaction with HEV
- Naïve lymphocytes express L-selectin (homing receptor) that interacts with GlyCAM-1 and CD34 on HEVs.

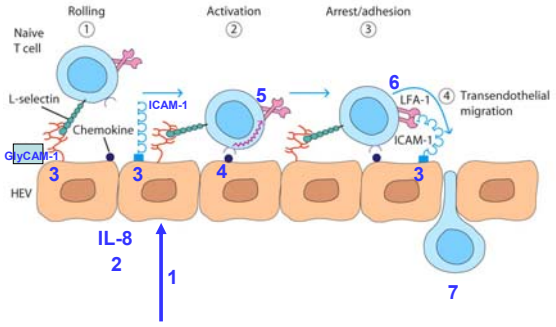
Naïve Lymphocyte "homing"

Remember= Constitutive expression



MUCINS-LIKE CAMs





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

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

Chemokine receptors	Chemokines bound by receptor
CXC subgroup	
CXCR1	IL-8, GCP-2
CXCR2	IL-8, Gro-α, Gro-β, Gro-γ, NAP-2, ENA-78
CXCR3	IP-10, Mig, I-TAC
CXCR4	SDF-1, PBSF
CXCR5	BCA-1
CC subgroup	
CCR1	MIP-1, RANTES, MCP-2, MIP-5
CCR2	MCP-1, MCP-2, MCP-3
CCR3	Eotaxin, RANTES, MCP-2, MCP-3, MCP-4, Eotaxin-2, MIP-5
CCR4	TARC, RANTES
CCR5	MIP-1α RANTES, MIP-1β
CCR6	Exodus-1
CCR7	ELC
CCR8	I-309
CCR10	MCP-1, MCP-2, MCP-3, RANTES
Both CC and CXC subgroups	
DARC (the Duffy antigen of RBCs)	Binds to a number of CC and CXC chemokines

Kuby Table 15-2

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.

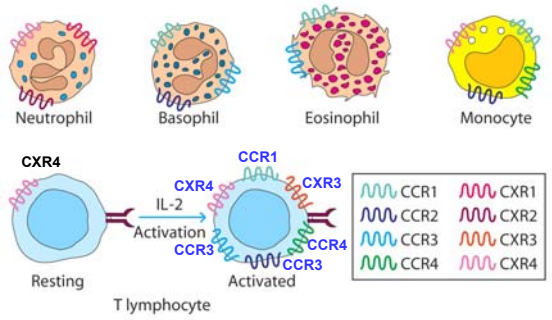
Examples:

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.

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.

Inflammatory mediators

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

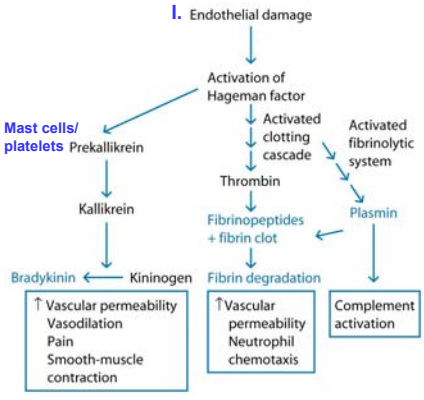
Include:

- Chemokines

- Plasma enzyme mediators of inflammation

- Lipid inflammatory mediators

- Cytokines



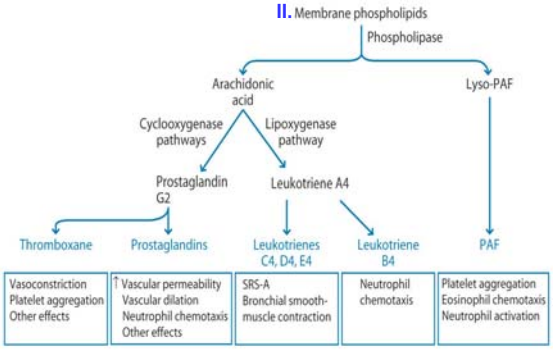
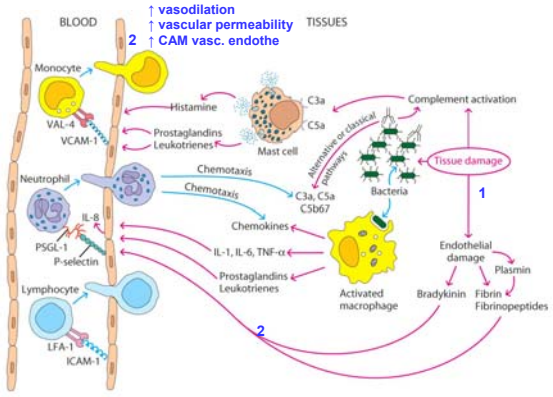


TABLE 15-3 Redundant and pleiotropic effects of IL-1, TNF-α, and IL-6

Effect	IL-1	TNF-α	IL-6
Endogenous pyrogen fever	+	+	+*
Synthesis of acute-phase proteins by liver	+	+	+*
Increased vascular permeability	+	+	+*
Increased adhesion molecules on vascular endothelium	+	+	–*
Fibroblast proliferation	+	+	–
Platelet production	+	–	+
Chemokine induction (e.g., IL-8)	+	+	–
Induction of IL-6	+	+	–
T-cell activation	+	+	+*
B-cell activation	+	+	+*
Increased immunoglobulin synthesis	–	–	+



Interferon-γ in chronic inflammation

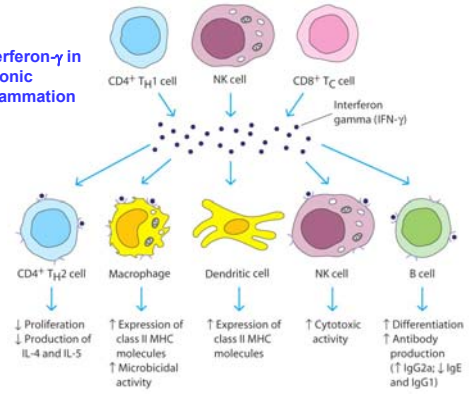


TABLE 15-4 Chronic inflammatory diseases associated with HEV-like vasculature

Disease	Affected organ	Plump endothelium	Mucin-like CAMs on endothelium*
Crohn's disease	Gut	+	+
Diabetes mellitus	Pancreas	+	+
Graves' disease	Thyroid	+	+
Hashimoto's thyroiditis	Thyroid	+	+
Rheumatoid arthritis	Synovium	+	+
Ulcerative colitis	Gut	+	+

*Includes GlyCAM-1, MAdCAM-1, and CD34.
SOURCE: Adapted from J. P. Girard and T. A. Springer, 1995, *Immunol. Today* **16**:449.