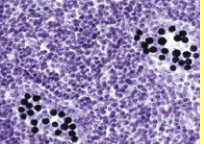
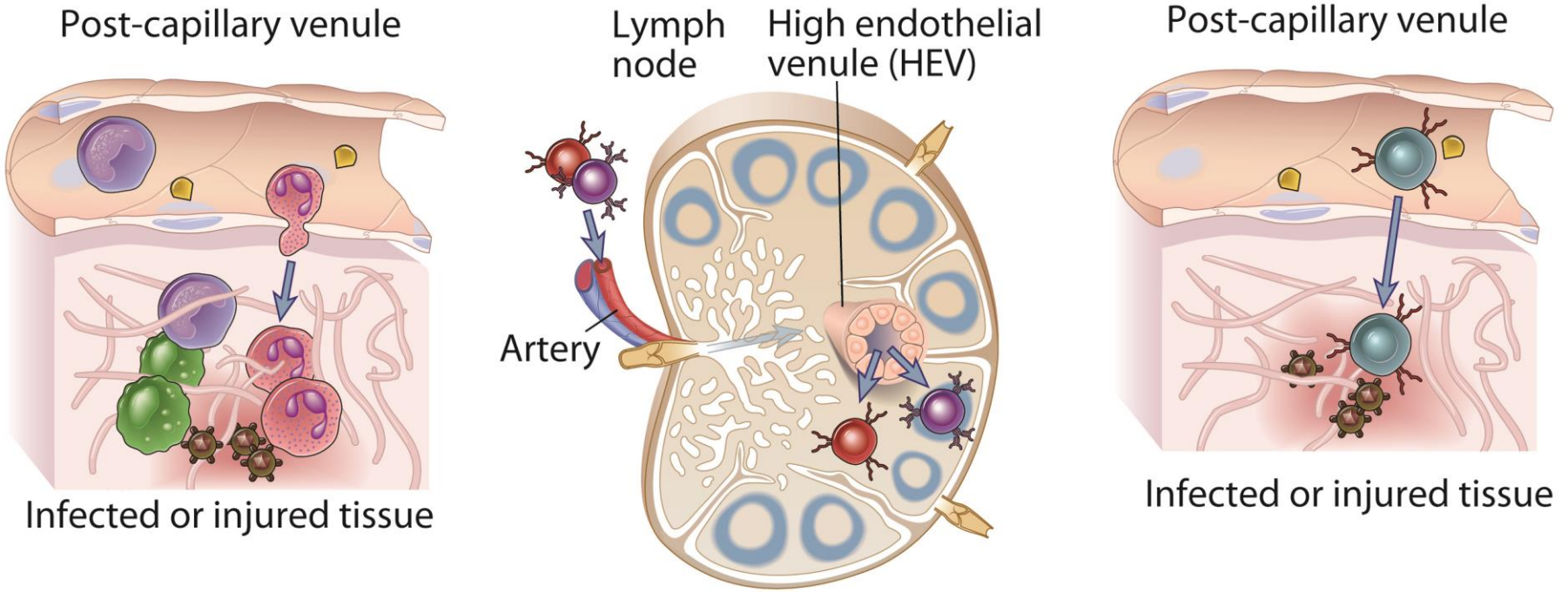


The migration of a particular type of leukocyte into a restricted type of tissue, or a tissue with an ongoing infection or injury, is often called leukocyte **homing**, and the general process of leukocyte movement from blood into tissues is called **recruitment**

The recruitment of leukocytes and plasma proteins from the blood to sites of infection and tissue injury is called **inflammation**

Inflammation = A complex reaction of vascularized tissue to infection, toxin exposure, or cell injury that involves extravascular accumulation of plasma proteins and leukocytes. Acute inflammation is a common result of innate immune responses, and local adaptive immune responses can also promote inflammation. Although inflammation serves a protective function in controlling infections and promoting tissue repair, it can also cause tissue damage and disease.

# Functions Served by Leukocyte Migration

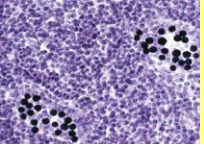



**Neutrophils and monocytes migrate to sites of infection and tissue injury: inflammation**

**Naive T and B cells migrate into secondary lymphoid tissues: initiation of adaptive immune responses**

**Effector and memory T cells migrate into sites of infection and tissue injury: cell-mediated immunity**

Fig. 3-1



Leukocyte recruitment from the blood into tissues depends first on adhesion of the leukocytes to the endothelial lining of postcapillary venules and then movement through the endothelium and underlying basement membrane into the extravascular tissue.

Selectins are plasma membrane carbohydrate-binding adhesion molecules that mediate an initial step of low-affinity adhesion of circulating leukocytes to endothelial cells lining postcapillary venules

**Integrins** are heterodimeric cell surface proteins composed of two non covalently linked polypeptide chains that mediate adhesion of cells to other cells or to extracellular matrix, through specific binding interactions with various ligands

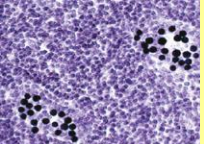


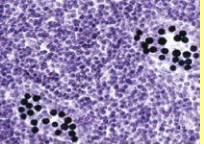
**TABLE 3–1 Major Leukocyte-Endothelial Adhesion Molecules**

| Family | Molecule | Distribution | Ligand (molecule; cell type) |
|---|---|---|---|
| Selectin | P-selectin (CD62P) | Endothelium activated by cytokines (TNF, IL-1), histamine, or thrombin | Sialyl Lewis X on PSGL-1 and other glycoproteins; neutrophils, monocytes, T cells (effector, memory) |
| | E-selectin (CD62E) | Endothelium activated by cytokines (TNF, IL-1) | Sialyl Lewis X (e.g., CLA-1) on glycoproteins; neutrophils, monocytes, T cells (effector, memory) |
| | L-selectin (CD62L) | Neutrophils, monocytes, T cells (naive and central memory), B cells (naive) | Sialyl Lewis X/PNAd on GlyCAM-1, CD34, MadCAM-1, others; endothelium (HEV) |

P=platelets (first found) is stored in cytoplasmic granules of endothelial cells and is rapidly redistributed to the surface in response to microbial products, cytokines, histamine from mast cells, and thrombin generated during blood coagulation

E= Endothelial  E-selectin is synthesized and expressed on the endothelial cell surface within 1 to 2 hours in response to the cytokines

L= Leucocyte  The ligands for L-selectin are sialomucins displayed on high endothelial venules, collectively called peripheral node addressin (PNAd). L-selectin on neutrophils serves to bind these cells to endothelial cells that are activated by IL-1, TNF, and other cytokines produced at sites of inflammation



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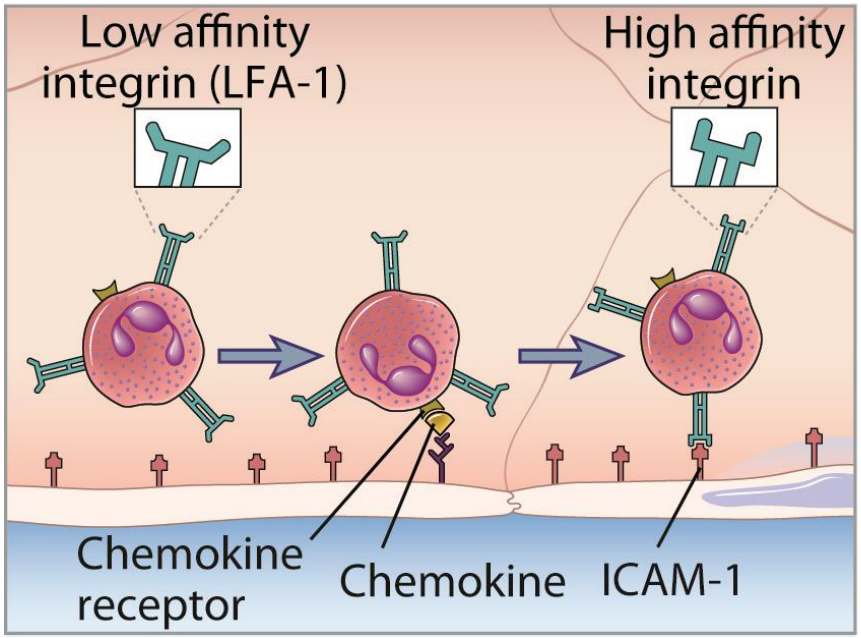
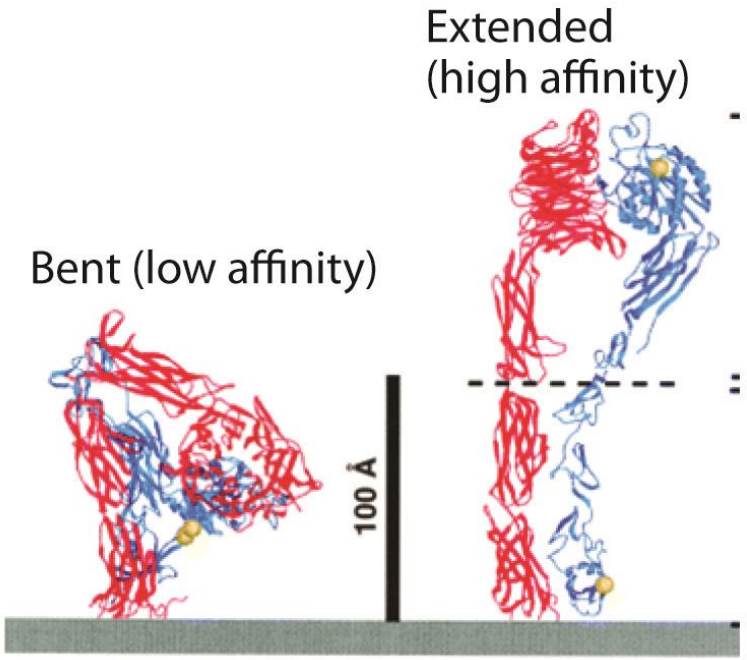
| | E-selectin (CD62E) | Endothelium activated by cytokines (TNF, IL-1) | Sialyl Lewis X (e.g., CLA-1) on glycoproteins; neutrophils, monocytes, T cells (effector, memory) |
| | L-selectin (CD62L) | Neutrophils, monocytes, T cells (naive and central memory), B cells (naive) | Sialyl Lewis X/PNAd on GlyCAM-1, CD34, MadCAM-1, others; endothelium (HEV) |
| Integrin | LFA-1 (CD11aCD18) | Neutrophils, monocytes, T cells (naive, effector, memory) | ICAM-1 (CD54), ICAM-2 (CD102); endothelium (upregulated when cytokine activated) |
| | Mac-1 (CD11bCD18) | Monocytes, dendritic cells | ICAM-1 (CD54), ICAM-2 (CD102); endothelium (upregulated when cytokine activated) |
| | VLA-4 (CD49aCD29) | Monocytes, T cells (naive, effector, memory) | VCAM-1 (CD106); endothelium (upregulated when cytokine activated) |
| | $\alpha_4\beta_7$ (CD49dCD29) | Monocytes, T cells (gut homing, naive, effector, memory) | VCAM-1 (CD106), MadCAM-1; endothelium in gut and gut-associated lymphoid tissues |

CLA-1, cutaneous lymphocyte antigen 1; GlyCAM-1, glycan-bearing cell adhesion molecule 1; HEV, high endothelial venule; ICAM-1, intracellular adhesion molecule 1; IL-1, interleukin-1; LFA-1, leukocyte function-associated antigen 1; MadCAM-1, mucosal addressin cell adhesion molecule 1; PNAd, peripheral node addressin; PSGL-1, P-selectin glycoprotein ligand 1; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule 1; VLA-4, very late antigen 4.

Intercellular adhesion molecule 1 (ICAM-1, CD54),

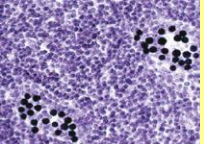
# Integrin Activation by Chemokines




***An important feature of integrins is their ability to respond to intracellular signals by rapidly increasing their affinity for their ligands***

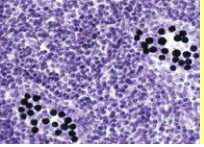
Fig. 3-2



***Chemokines are a large family of structurally homologous cytokines that stimulate leukocyte movement and regulate the migration of leukocytes from the blood to tissues.*** The name *chemokine* is a contraction of "chemotactic cytokine."

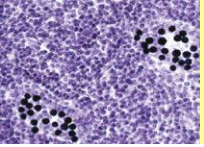
There are about 50 human chemokines, all of which are 8- to 12-kD polypeptides that contain two internal disulfide loops. The chemokines are classified into four families on the basis of the number and location of N-terminal cysteine residues. The two major families are the **CC** (also called β) chemokines, in which the cysteine residues are adjacent, and the **CXC** (or α) family, in which these residues are separated by one amino acid

***The receptors for chemokines belong to the seven-transmembrane, guanosine triphosphate (GTP)–binding (G) protein–coupled receptor (GPCR) superfamily.***



***The receptors for chemokines belong to the seven-transmembrane, guanosine triphosphate (GTP)–binding (G) protein–coupled receptor (GPCR) superfamily.***

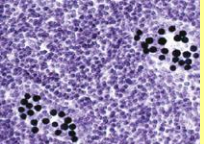
Occupancy of the receptor by ligand results in an exchange of GTP for GDP. The GTP-bound form of the G protein activates numerous cellular enzymes, including an isoform of phosphatidylinositol-specific phospholipase C that functions to increase intracellular calcium and activate protein kinase C. The G proteins stimulate cytoskeletal changes and polymerization of actin and myosin filaments, resulting in increased cell motility. These signals also change the conformation of cell surface integrins and increase the affinity of the integrins for their ligands



***Different combinations of more than 17 different chemokine receptors are expressed on different types of leukocytes, which results in distinct patterns of migration of the leukocytes.***

There are 10 distinct receptors for CC chemokines (called CCR1 through CCR10), six for CXC chemokines (called CXCR1 through CXCR6), and one for $CX_3CL1$ (called $CX_3CR1$)
Chemokine receptors are expressed on all leukocytes, with the greatest number and diversity seen on T cells

Relevance
Certain chemokine receptors, notably CCR5 and CXCR4, act as co-receptors for the human immunodeficiency virus (HIV)
Some activated T lymphocytes secrete chemokines that bind to CCR5 and block infection with HIV by competing with the virus.



*Some chemokines are produced by leukocytes and other cells in response to external stimuli and are involved in inflammatory reactions, and other chemokines are produced constitutively in tissues and play a role in tissue organization.*

*Chemokines are essential for the recruitment of circulating leukocytes from blood vessels into extravascular sites.*

*Extravascular chemokines stimulate movement of leukocytes and their migration toward the chemical gradient of the secreted protein, a process called chemokinesis.*

*Chemokines are involved in the development of lymphoid organs, and they regulate the traffic of lymphocytes and other leukocytes through peripheral lymphoid tissues.*

*Chemokines are required for the migration of dendritic cells from sites of infection into draining lymph nodes.*

# Leukocyte Recruitment Into Tissues

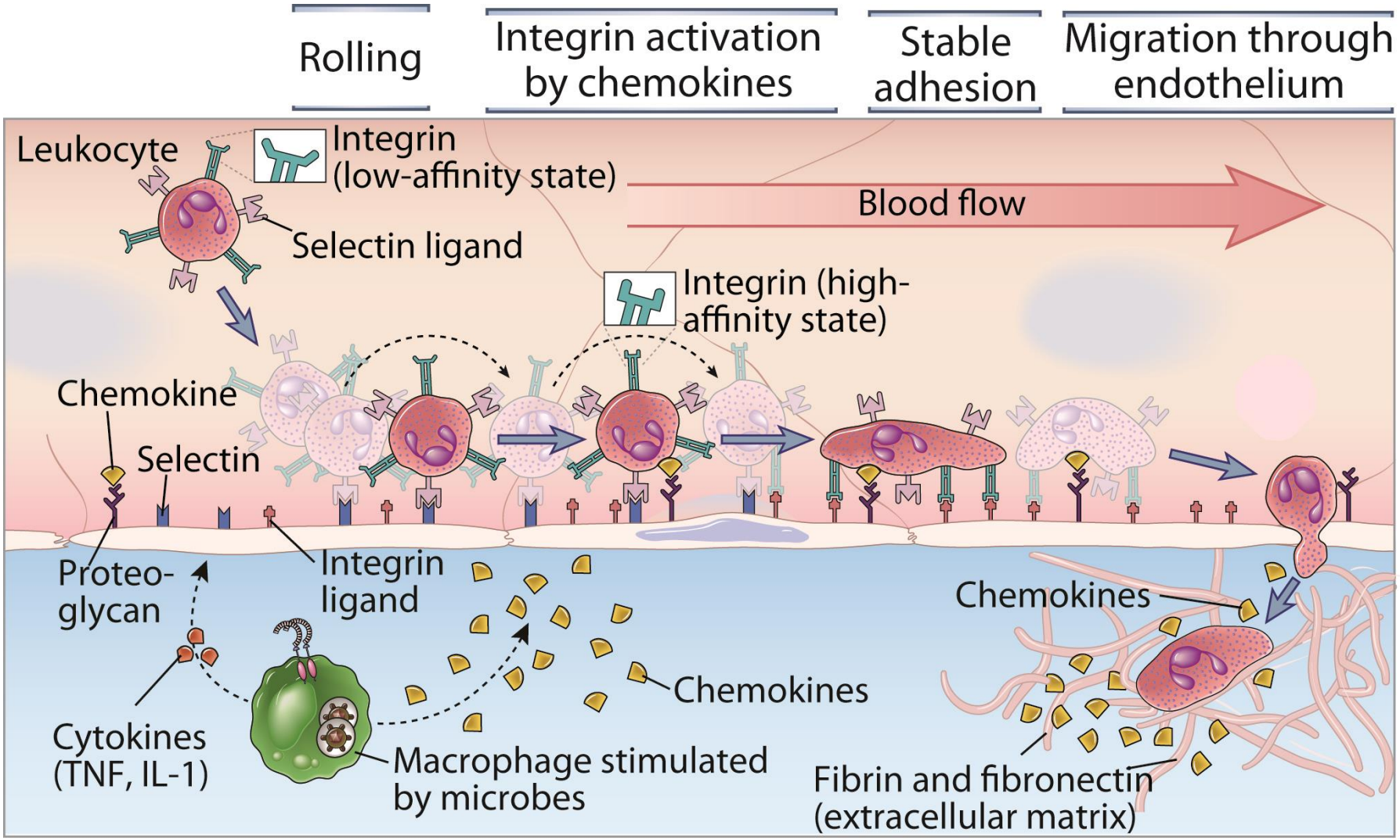
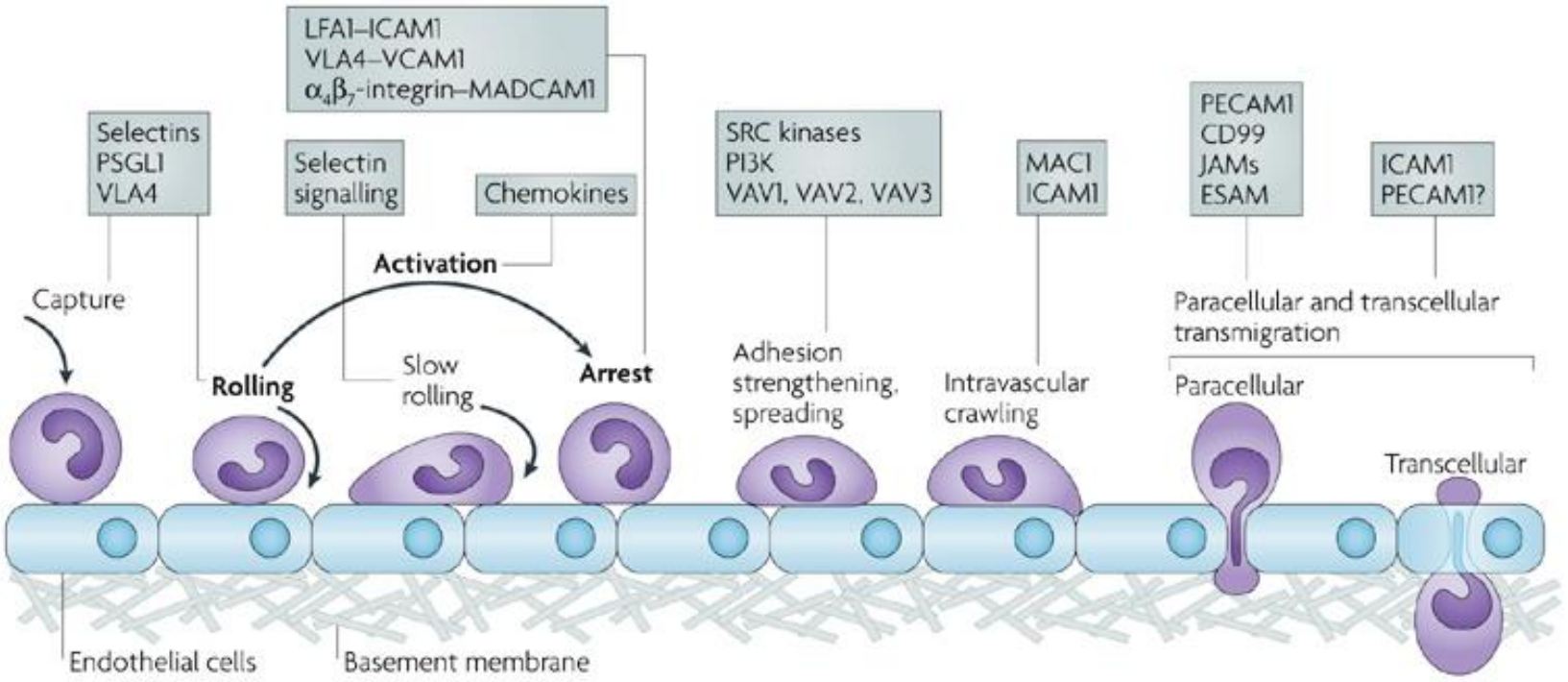



Fig. 3-3

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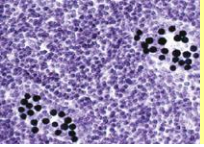
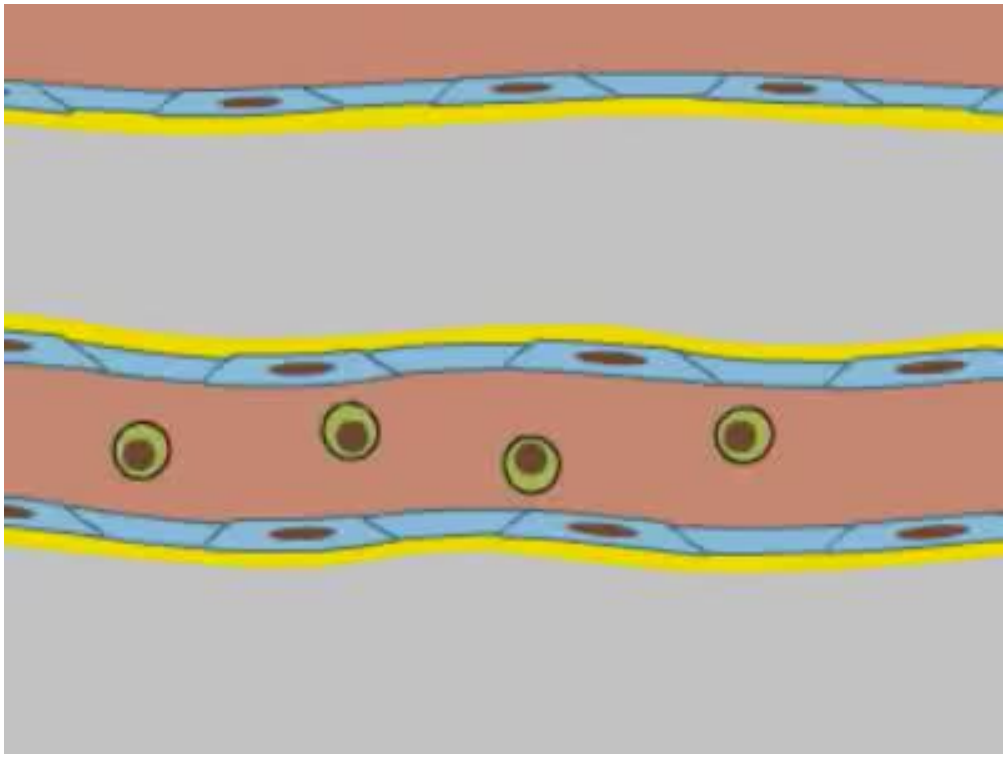
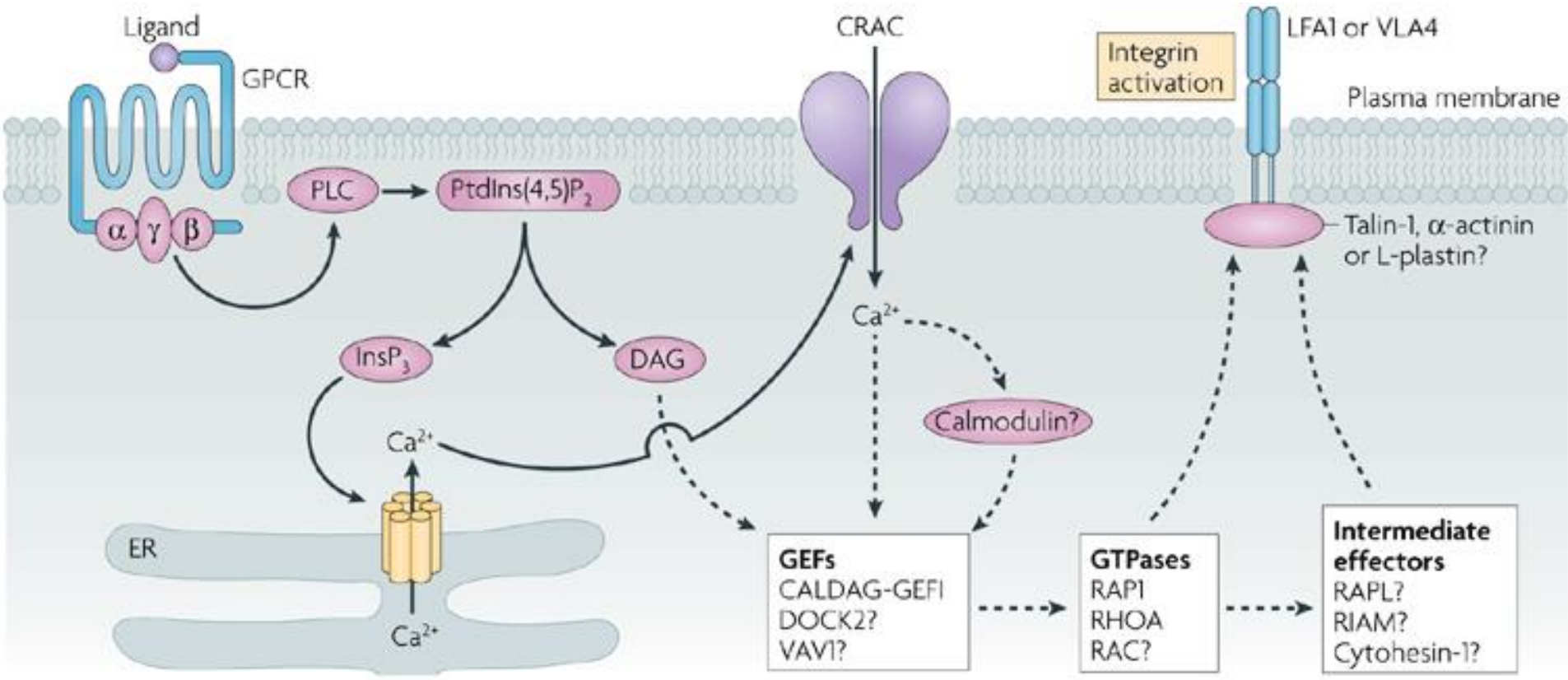
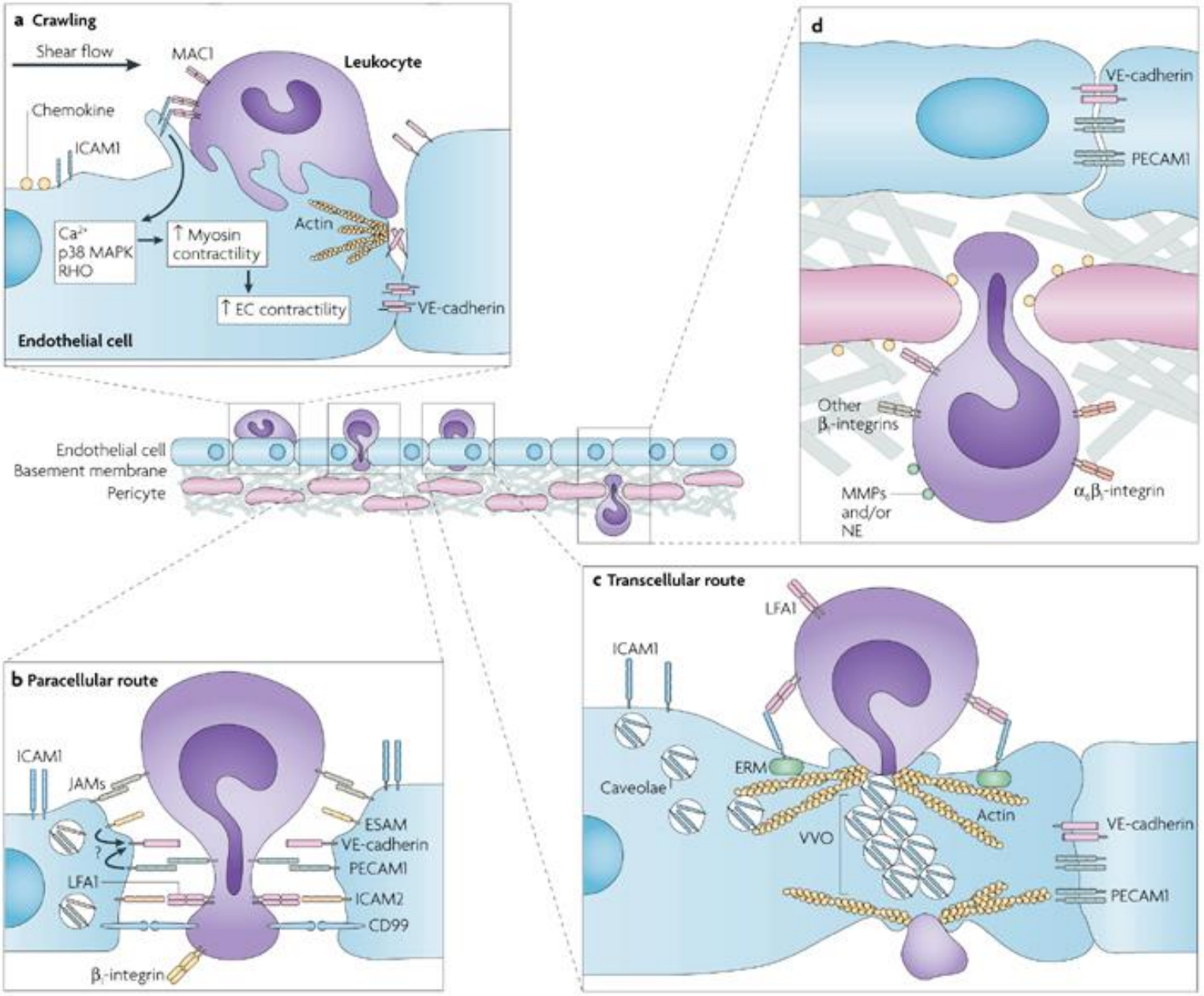


http://www.youtube.com/watch?v=WEGGMaRX8f0

http://www.youtube.com/watch?v=297HcgDxb7k




Ligand
GPCR
α
γ
β
PLC
PtdIns(4,5)P2
InsP3
DAG
Ca2+
ER
Ca2+
CRAC
Ca2+
Calmodulin?
Integrin activation
LFA1 or VLA4
Plasma membrane
Talin-1, α-actinin or L-plastin?
GEFs
CALDAG-GEFI
DOCK2?
VAV1?
GTPases
RAP1
RHOA
RAC?
Intermediate effectors
RAPL?
RIAM?
Cytohesin-1?


a Crawling
Shear flow
MAC1
Leukocyte
Chemokine
ICAM1
Ca2+
p38 MAPK
RHO
↑ Myosin contractility
Actin
↑ EC contractility
VE-cadherin
Endothelial cell
Endothelial cell
Basement membrane
Pericyte
d
VE-cadherin
PECAM1
Other β2-integrins
MMPs and/or NE
αLβ2-integrin
b Paracellular route
ICAM1
JAMs
ESAM
VE-cadherin
PECAM1
ICAM2
CD99
LFA1
β2-integrin
c Transcellular route
LFA1
ICAM1
ERM
Caveolae
Actin
VVO
VE-cadherin
PECAM1

Humans who lack one of the enzymes needed to express the carbohydrate ligands for E-selectin and P-selectin on neutrophils have similar problems, resulting in a syndrome called type 2 leukocyte adhesion deficiency (LAD-2). Similarly, an autosomal recessive inherited deficiency in the CD18 gene, which encodes the β subunit of LFA-1 and Mac-1, is the cause of an immune deficiency disease called type 1 leukocyte adhesion deficiency (LAD-1). Symptoms?

These disorders are characterized by recurrent bacterial and fungal infections, lack of neutrophil accumulation at sites of infection, and defects in adherence-dependent lymphocyte functions. Rare human mutations in the signaling pathways linking chemokine receptors to integrin activation also result in impaired leukocyte adhesion and recruitment into tissues and therefore ineffective leukocyte defense against infections.

# T lymphocyte Recirculation

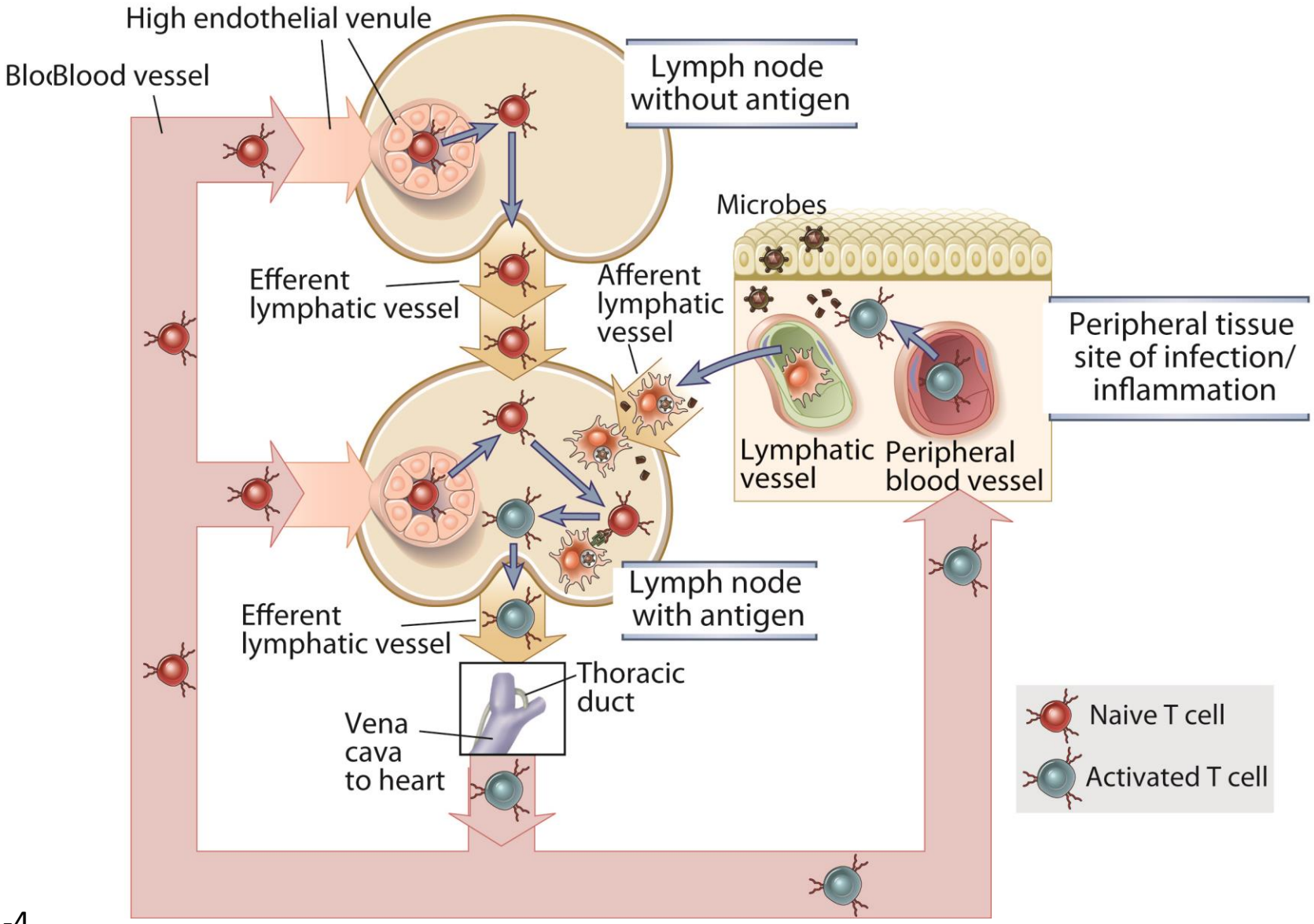



Fig. 3-4

# High Endothelial Venules (HEV 1)

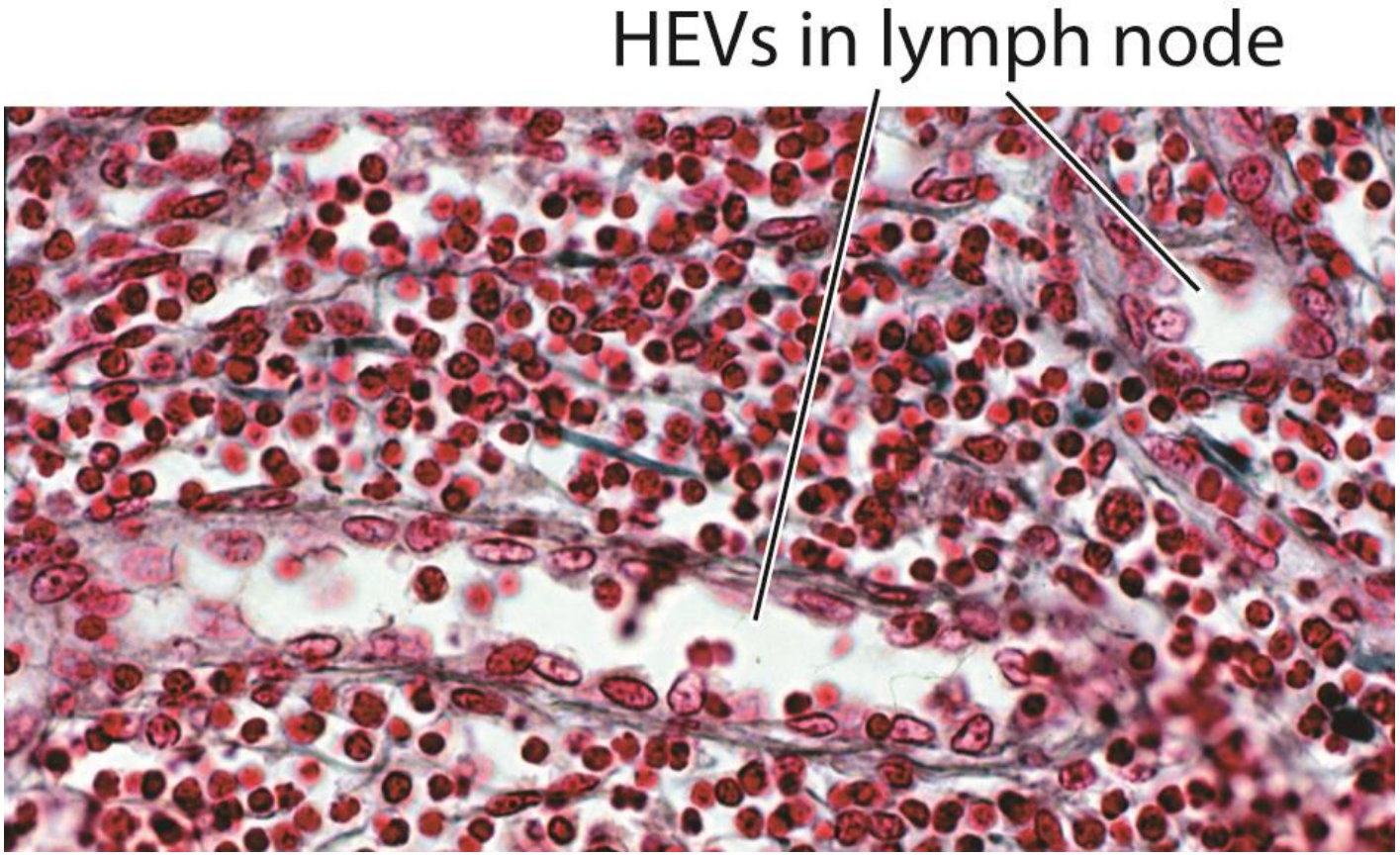



Fig. 3-5 A

# T Cells Binding to HEV

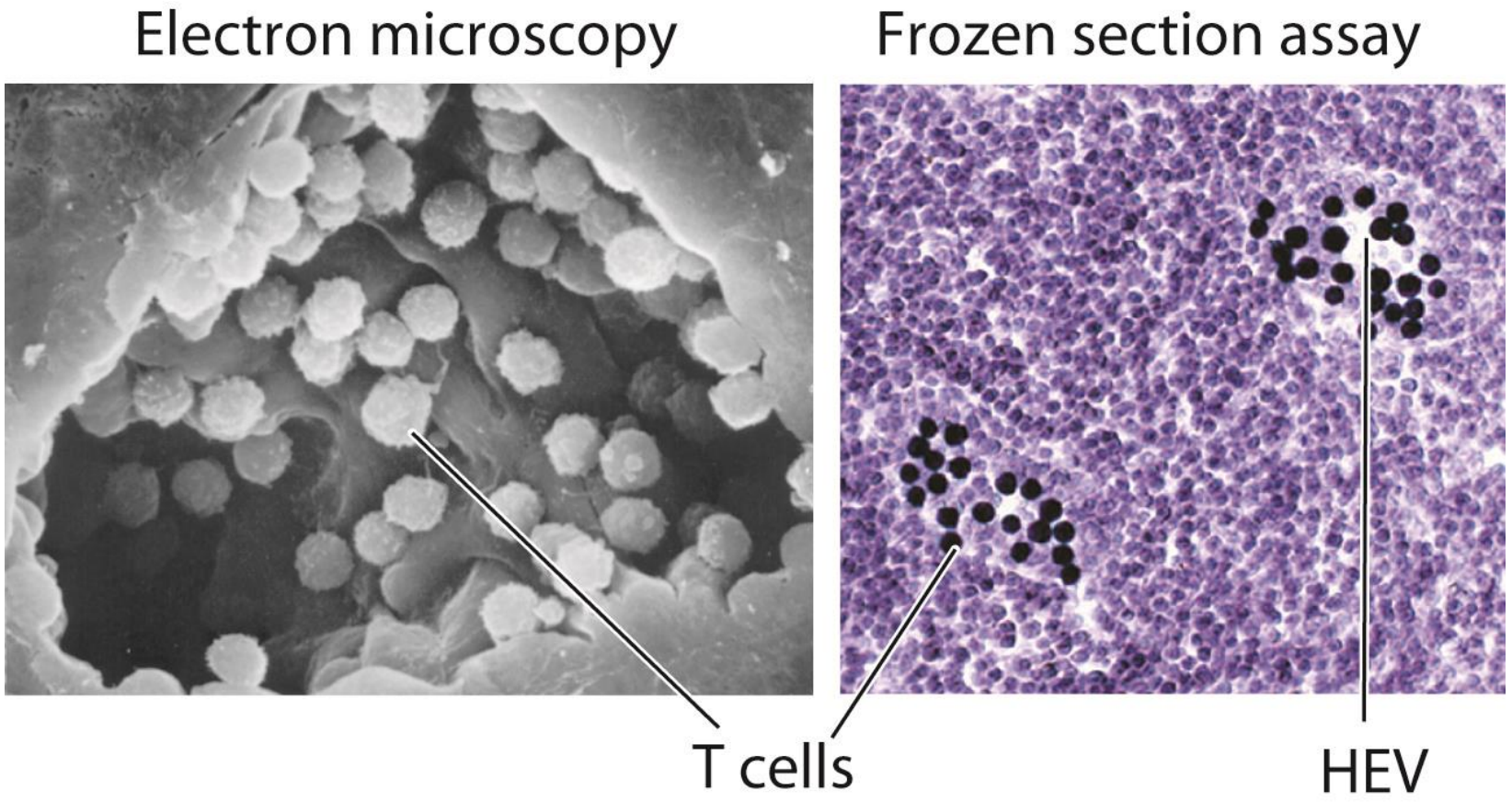
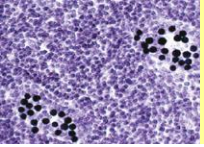



Fig. 3-5 C, D



***Lymphocytes are continuously moving through the blood stream, lymphatics, secondary lymphoid tissues, and peripheral nonlymphoid tissues, and functionally distinct populations of lymphocytes show different trafficking patterns through these sites***

***Homing of naive T cells into lymph nodes and mucosa-associated lymphoid tissues occurs through specialized postcapillary venules called high endothelial venules (HEVs) located in the T cell zones***
***Naive T cell migration out of the blood through the HEVs into the lymph node parenchyma is a multistep process consisting of selectin-mediated rolling of the cells, chemokine-induced integrin activation, integrin-mediated firm adhesion, and transmigration through the vessel wall***

# Migration of Naïve T Lymphocytes

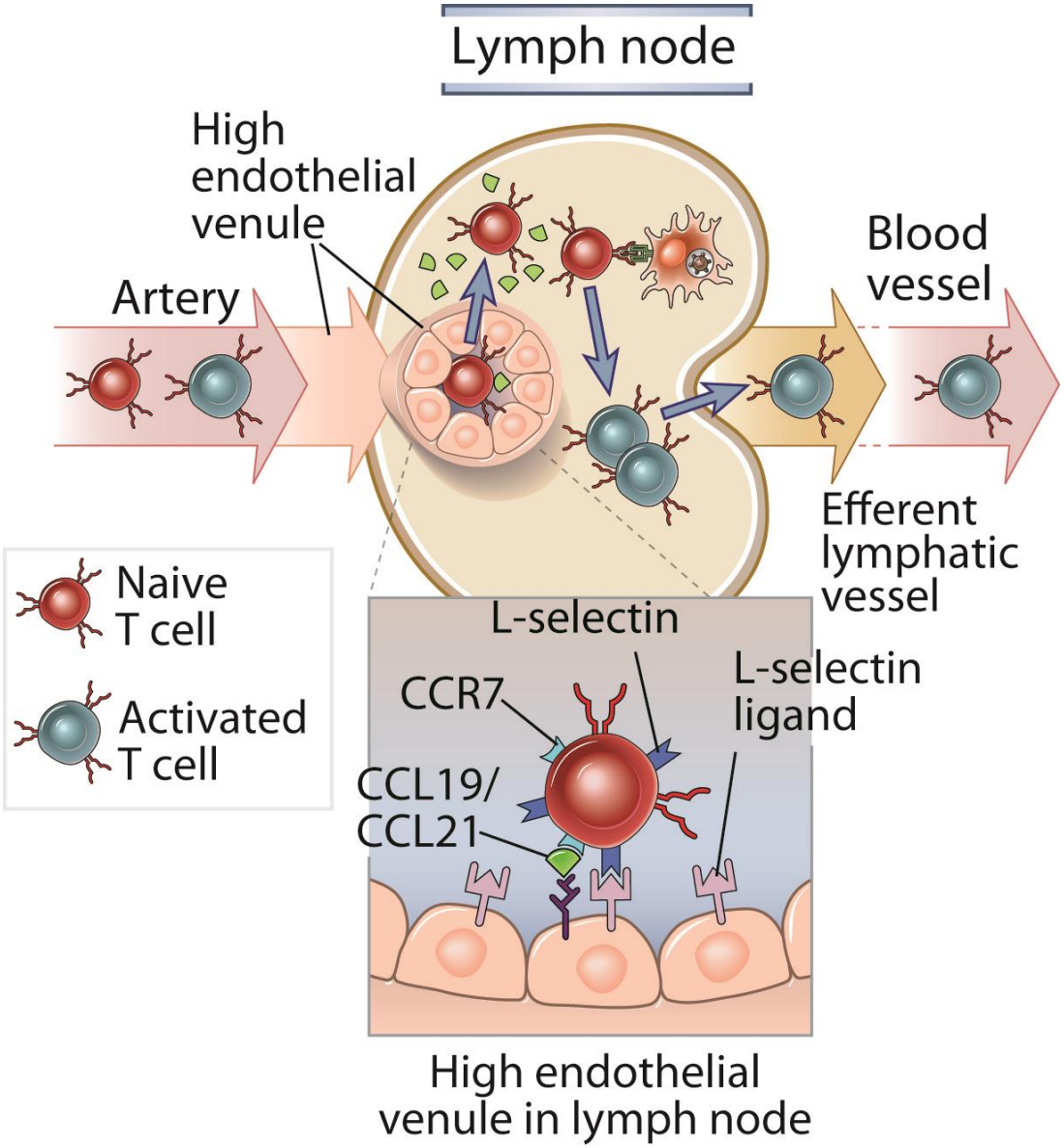



Fig. 3-6 A

# Migration of Effector T lymphocytes

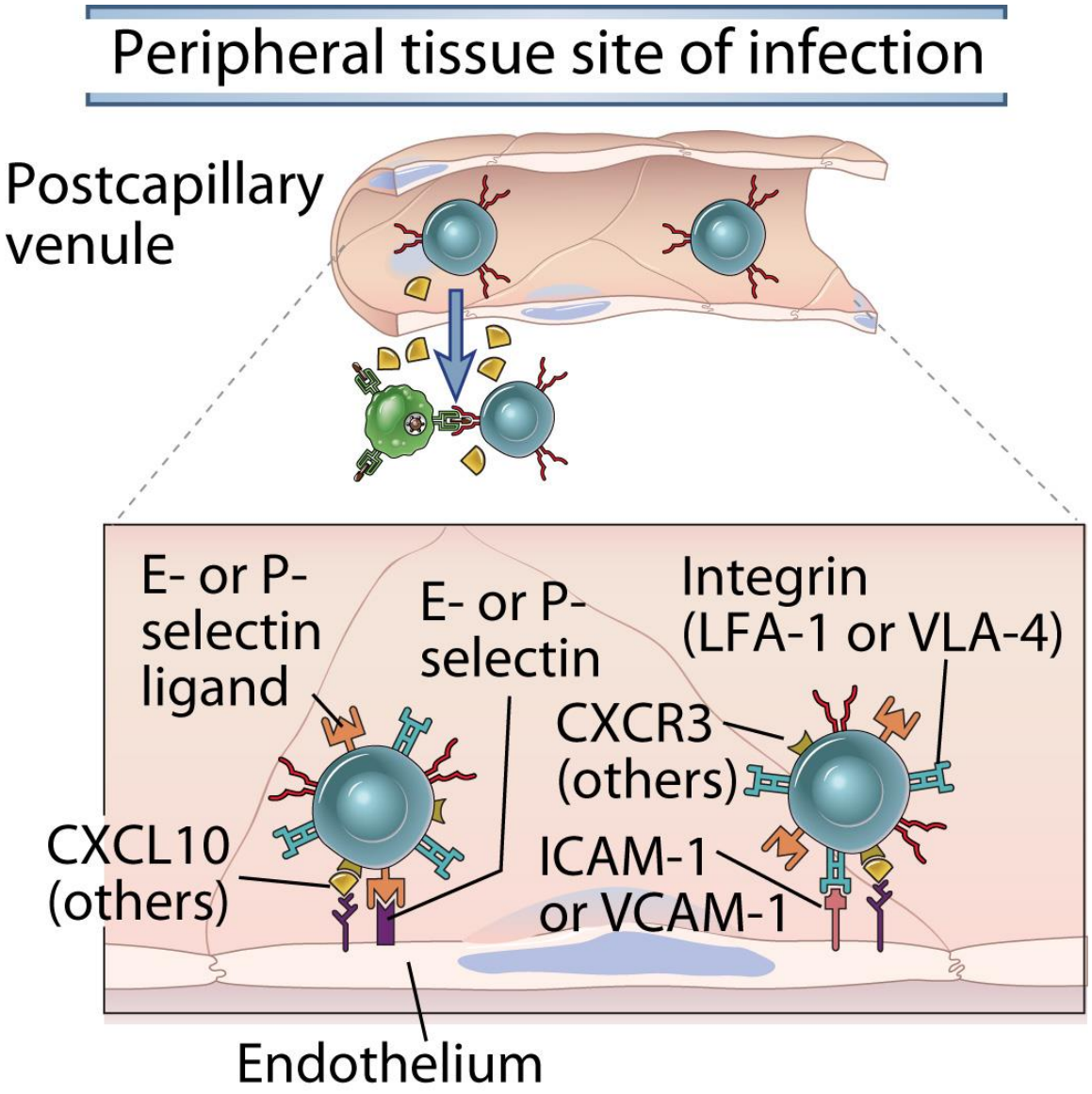
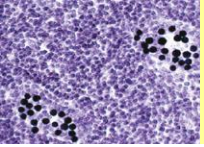



Fig. 3-6 A

# Molecular Mediators of T Cell Migration

| T cell homing receptor | Ligand on endothelial cell | Function of receptor: ligand pair |
|---|---|---|
| **Naive T cells** | | |
| L-selectin | L-selectin ligand | Initial weak adhesion of naive T cells to high endothelial venule in lymph node |
| CCR7 | CCL19 or CCL21 | Activation of integrins and chemokinesis |
| LFA-1 (β2-integrin) | ICAM-1 | Stable arrest on high endothelial venule in lymph node |
| **Activated (effector and memory) T cells** | | |
| E- and P-selectin ligand | E- or P-selectin | Initial weak adhesion of effector and memory T cells to cytokine activated endothelium at peripheral site of infection |
| CXCR3 | CXCL10 (others) | Activation of integrins and chemokinesis |
| CCR5 | CCL4 (others) | Activation of integrins and chemokinesis |
| LFA-1 (β2-integrin) or VLA-4 (β1 integrin) | ICAM-1 or VCAM-1 | Stable arrest on cytokine activated endothelium at peripheral site of infection |

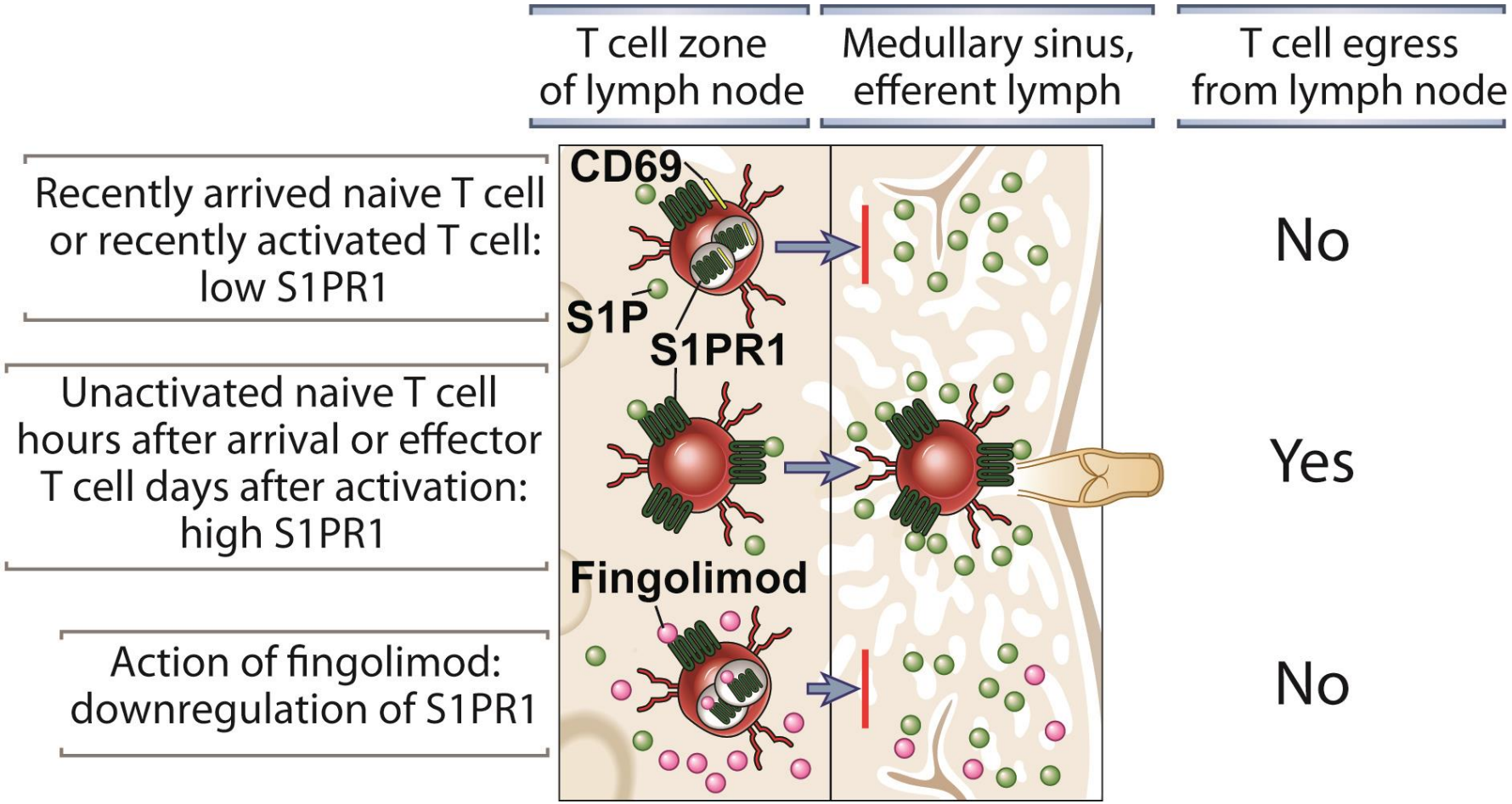
Fig. 3-6 B



***Naive T cells that have homed into lymph nodes but fail to recognize antigen and to become activated will eventually return to the blood stream.***

***The exit of naive T cells from lymph nodes is dependent on a lipid chemoattractant called sphingosine 1-phosphate (S1P), which binds to a signaling receptor on T cells called sphingosine 1-phosphate receptor 1 (S1PR1)***

# Egress of Lymphocytes from Lymph Node




Gilenya® is fingolimod (FTY720) to treat Multiple Sclerosis (MS)

Fig. 3-7