Leukocyte activation & Migration

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Lecture 9

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The Objectives

- Explain the following terms:
  - Cell Adhesion Molcules (CAMs) cell surface proteins mediate interaction bn cells, or bn cells and ECM
  - Neutrophil & Lymphocyte Extravasation
  - High-Endothelial Venules
  - Addressins
  - Homing of Lymphocytes
- Describe the steps involved in Neutrophil Extravasation
- Describe the location, structure and function of High Endothelial Venules

Leukocyte Migration

- Leukocyte Migration is a process of cells moving from the blood vasculature to peripheral tissues.

- This process is achieved by the following sequence events:
  1. Margining, Tethering and Rolling — low affinity interactions bn leukocytes and endothelial cells
  2. Activation — when detecting inflammatory mediators
  3. Adhesion — high affinity interactions
  4. Transmigration (diapedesis) — passage
  5. Chemotaxis

     the directed movement of cells in tissues

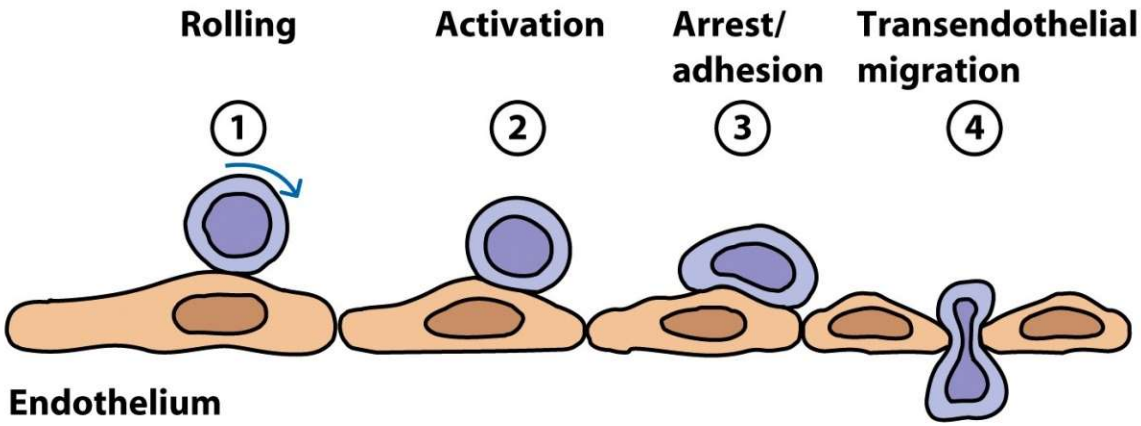


Figure 13-4
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Lymphocyte migration, activation & effector function depends on

cell-adhesion molecules

Cell-Adhesion Molecules

- A variety of **cell surface polypeptides (Receptors)**
- Ensure appropriate **cell-cell interactions.**
- **The adhesion molecules include:**
  1. Selectins
  2. Mucin-like CAMs (Addressins)
  3. Integrins
  4. Immunoglobulin Superfamily

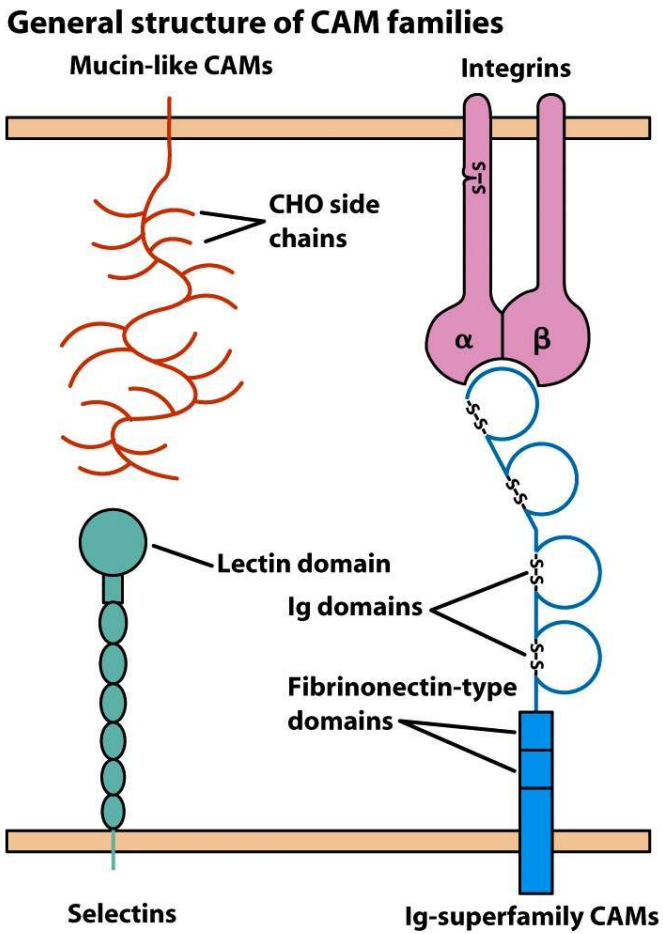
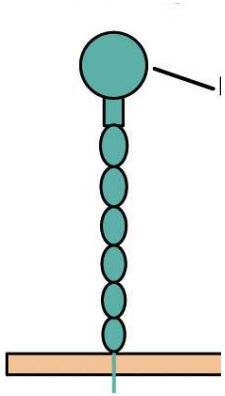


Figure 13-1a
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Selectins:

- E-selectin (on endothelium)
- P-selectin (on endothelium)
- L-selectin (on leukocytes)



Selectins

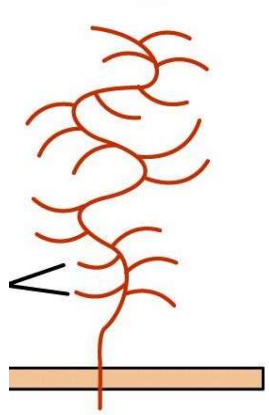
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Mucin-like CAMs (Addressin): group of serine and threonine rich proteins that bind selectins.

- CD34
- Glycam-1
- PSGL-1 P-Selectin Glycoprotein Ligand

– L-selectin on leukocyte binds to CD34 and Glycam-1 (mucin-like) on endothelial cells

– PSGL-1 (mucin-like) on Neutrophils binds E- or P- selectin on endothelium



Addressin

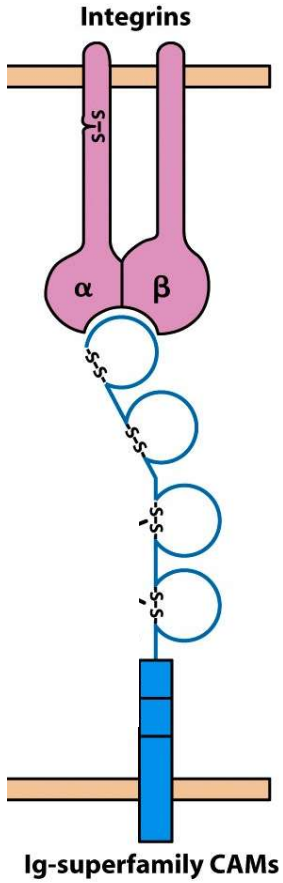
LFA: lymphocyte function associated antigen
MAC: Macrophage-1- Antigen
VLA: Very late antigen

Integrins:

- Heterodimeric protein consisting of an α and β chain

they bind to Ig-superfamily CAMs

For example: LFA-1, Mac-1, and VLA-4



Ig-superfamily CAMs (ICAMs):

Contain immunoglobulin-like domains

ICAMs are expressed on endothelial cells and bind to various integrin molecules

For example: ICAM-1, VCAM-1and PECAM –1

vascular

PECAM: platelet endothelial cell adhesion molecule, also known as CD31

1. Margination, Tethering and Rolling

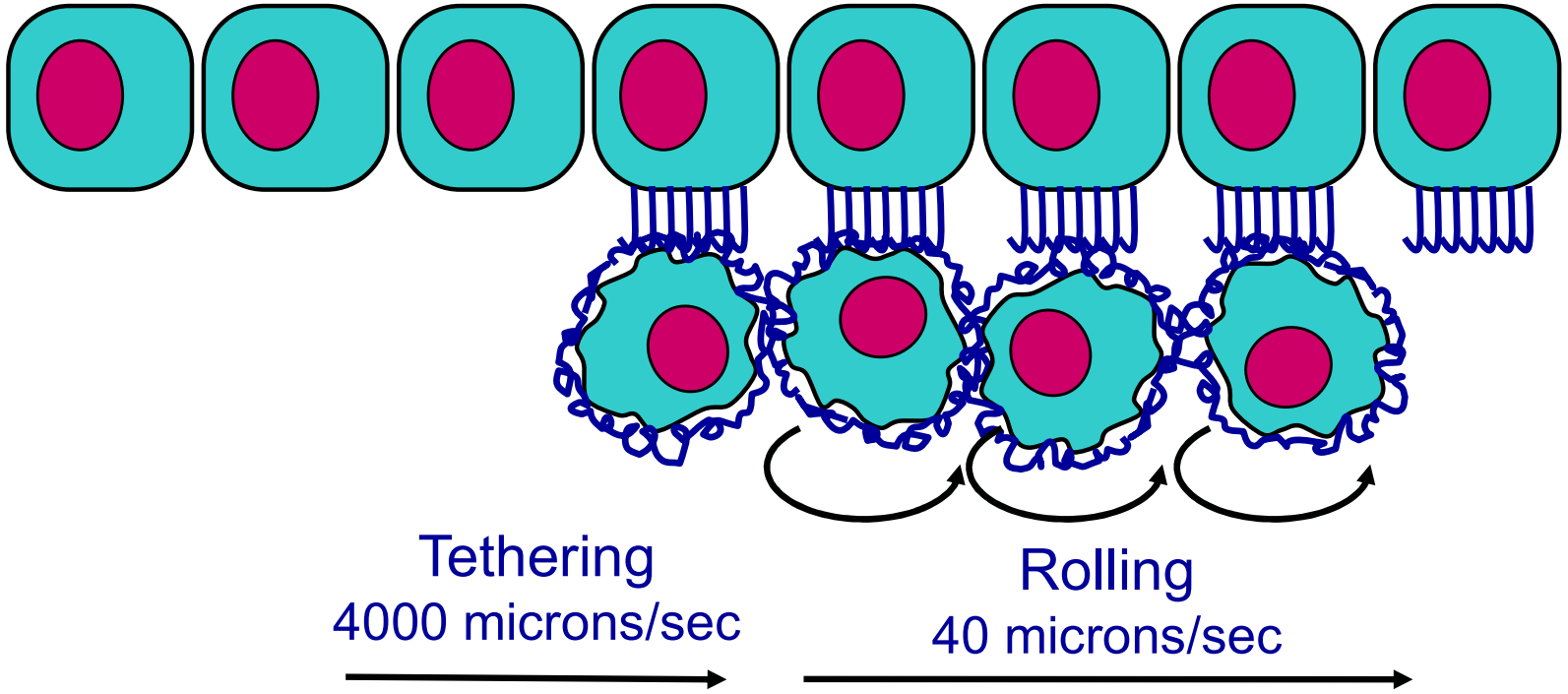
- With increased vascular permeability, fluid leaves the vessel causing
  - leukocytes to settle-out of the central flow column and "marginate" along the endothelial surface

- Endothelial cells and leukocytes have complementary surface adhesion molecules which briefly stick and release causing
  - leukocyte tethering then rolling along the endothelium like a tumbleweed until it eventually comes to a stop as mutual adhesion reaches a peak

  - Tethering and rolling is mediated by:
    Selectins binding to Mucin-like CAMs (addressins)

- L-selectin on leukocytes bind to Mucin like CAMs addressins on endothelium (CD34) that are upregulated on endothelium by cytokines (TNF, IL-1) at injury sites.

Cytokine activated endothelial cells express adhesion molecules
Leukcocytes ‘marginate’ from the peripheral pool to the marginal pool
And starts tethering and rolling along the edothelium.



2. Activation and 3. Adhesion

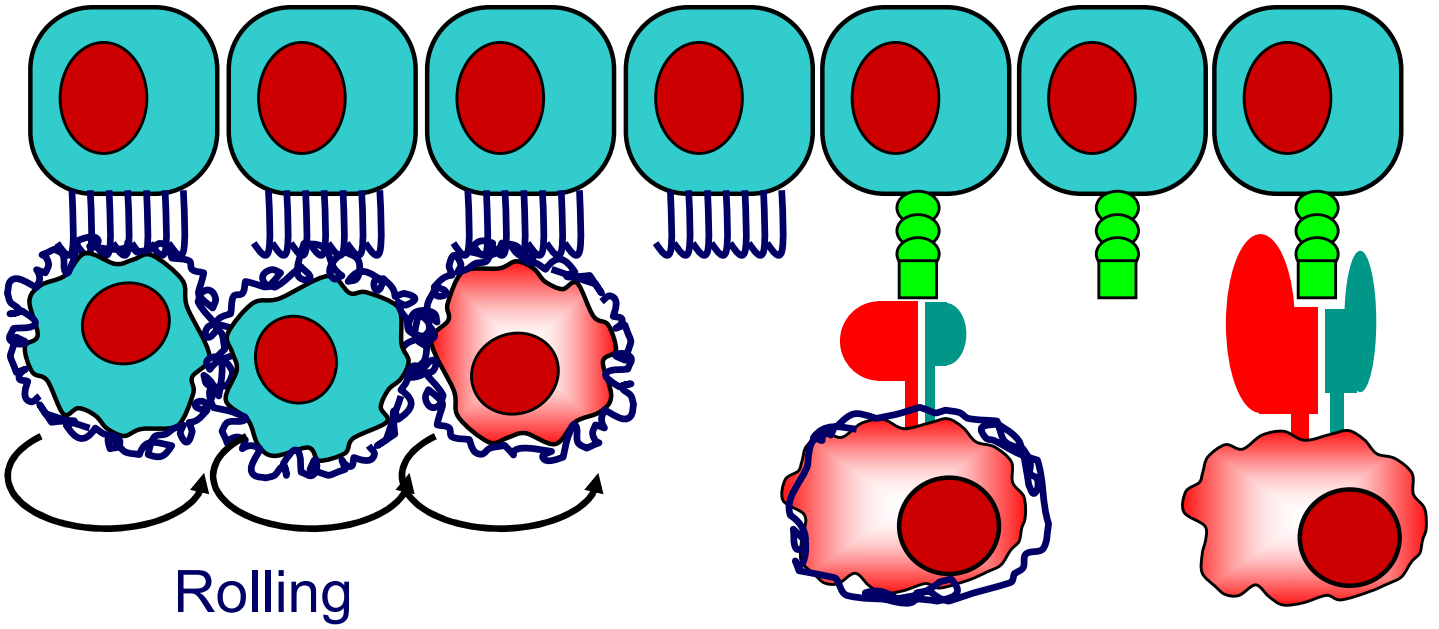
- Activation: During inflammation cytokines from epithelium activate and upregulate the expression of Intracellular integrin adhesion molecules

- Adhesion: Once rolling comes to a stop adhesion results by conformational changes to the integrin that allows the firm binding to Ig superfamily CAMs

- Adhesion molecules that participate in this are:
  - ICAM-1 and VCAM-1 (Ig-superfamily CAMs on Endothelial)
  - LFA-1 and VLA-4 (Integrins on Leukocyte)

  - ICAM-1 binds LFA-1
  - VCAM-1 binds VLA-4

2. Activation and 3. Adhesion cont'd



Rolling

Selectin is shed

INTEGRIN
(adhesion molecule)
has low affinity for
ICAM

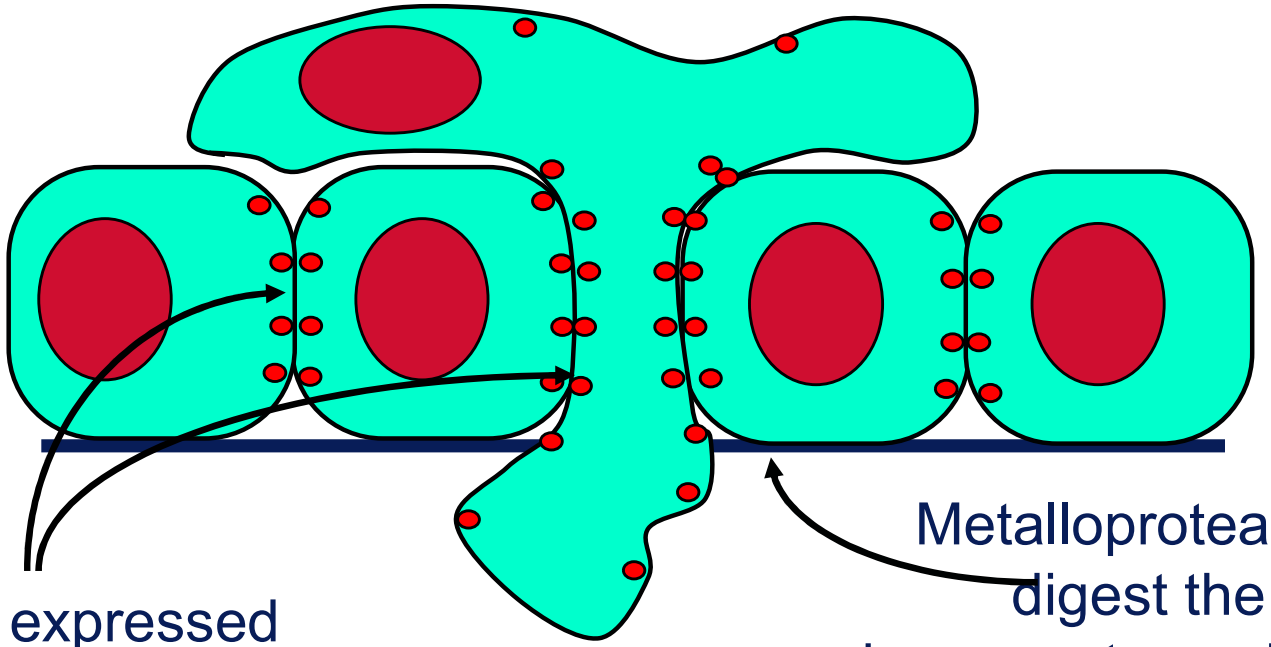
Cell activation
changes
integrin to
high affinity
format

4. Transmigration (diapedesis)

- Transmigration occurs after firm adhesion

- During transmigration cells must flatten and cross the endothelium basement membrane via
  - Collagenases
  - Ig-superfamily CAMs (PECAM –1)

4- Transmigration Diapedesis cont'd



PECAM expressed at intercellular junctions of endothelial cells and on the lymphocyte

Metalloproteases digest the basement membrane

5. Chemotaxis

- Leukocytes migrate towards the site of infection by following chemical gradient (chemokine) to site of injury.

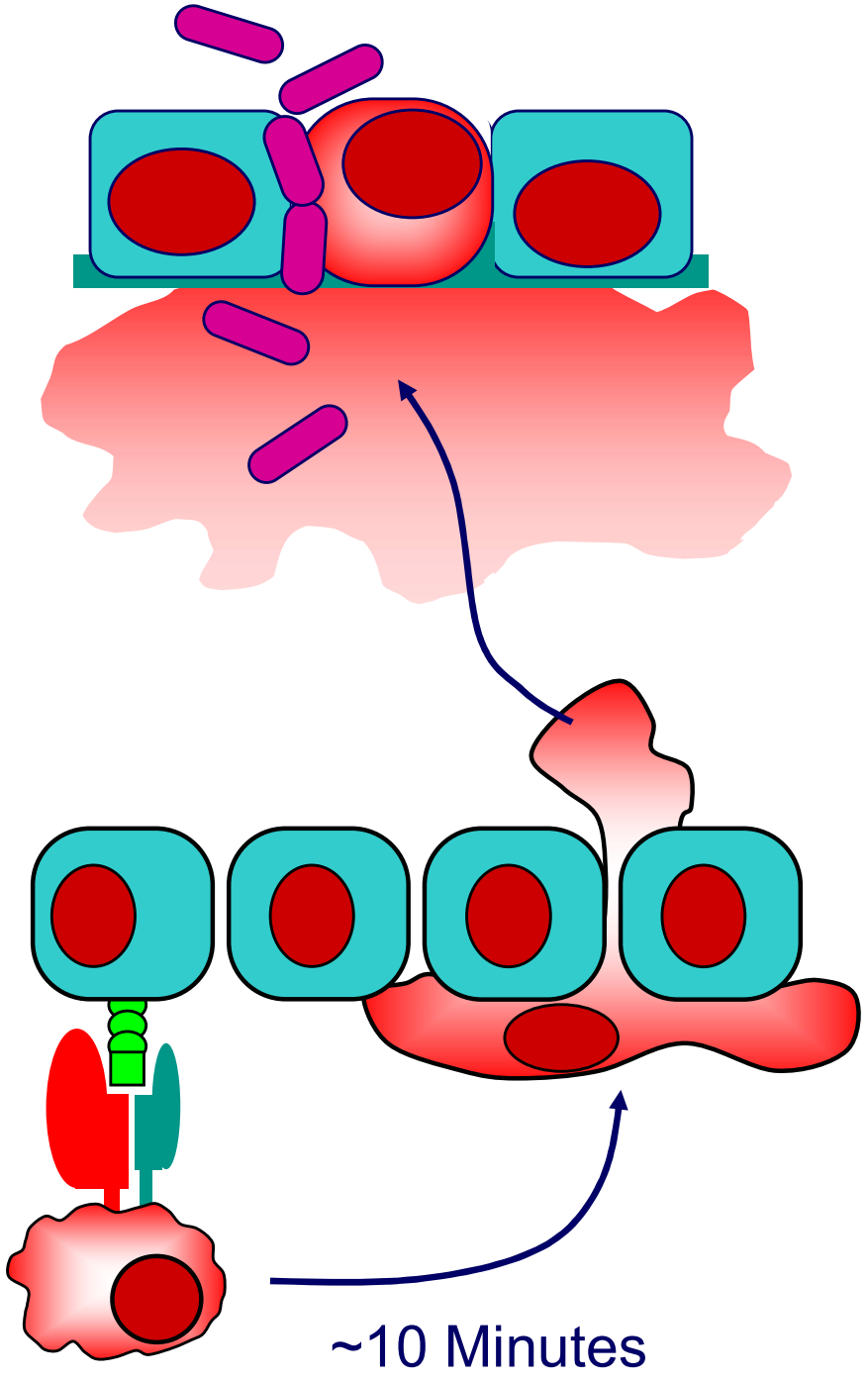
- Molecules that can cause chemotaxis include:

-Soluble bacterial products

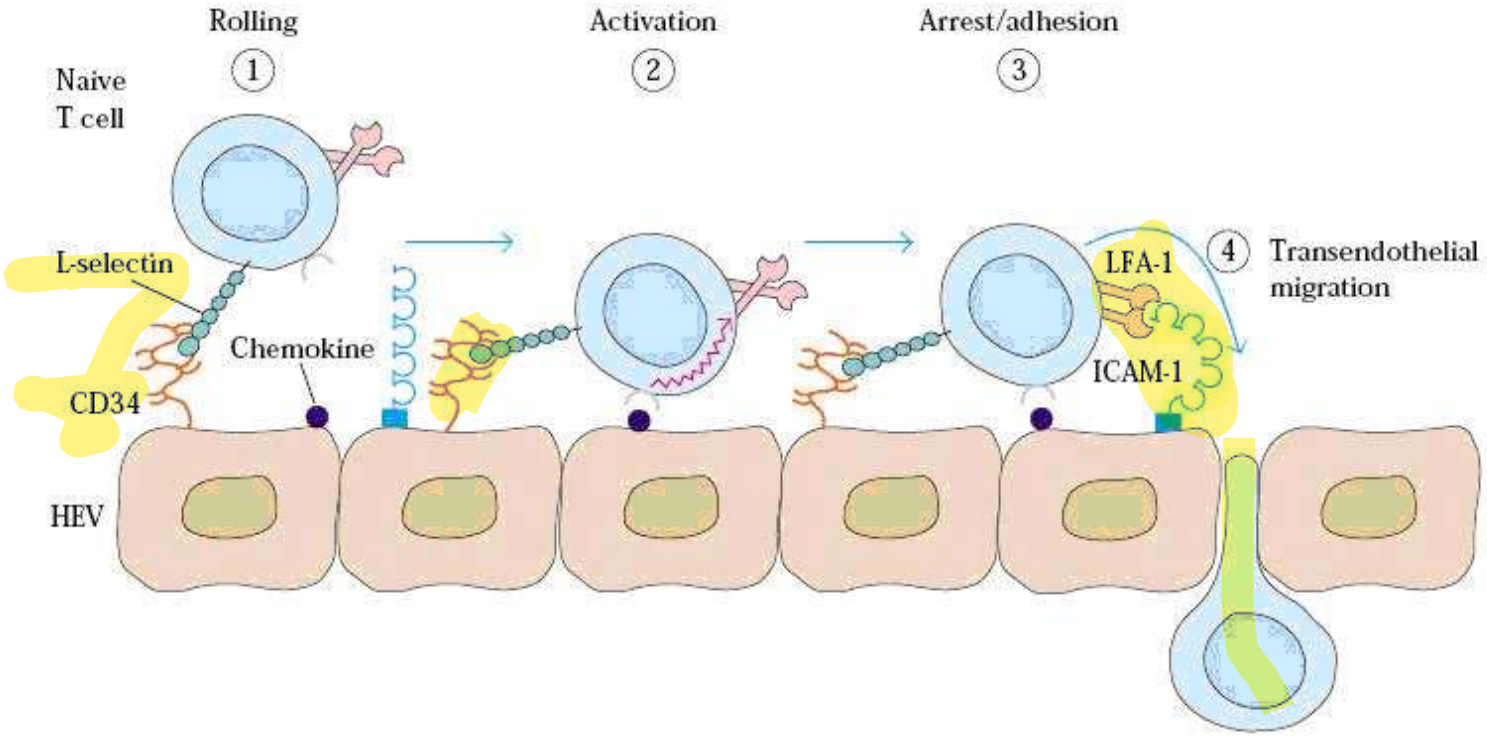
- Complement components (C3a, C4a and C5a)

- Cytokines (chemokine family **e.g.**, IL-8)

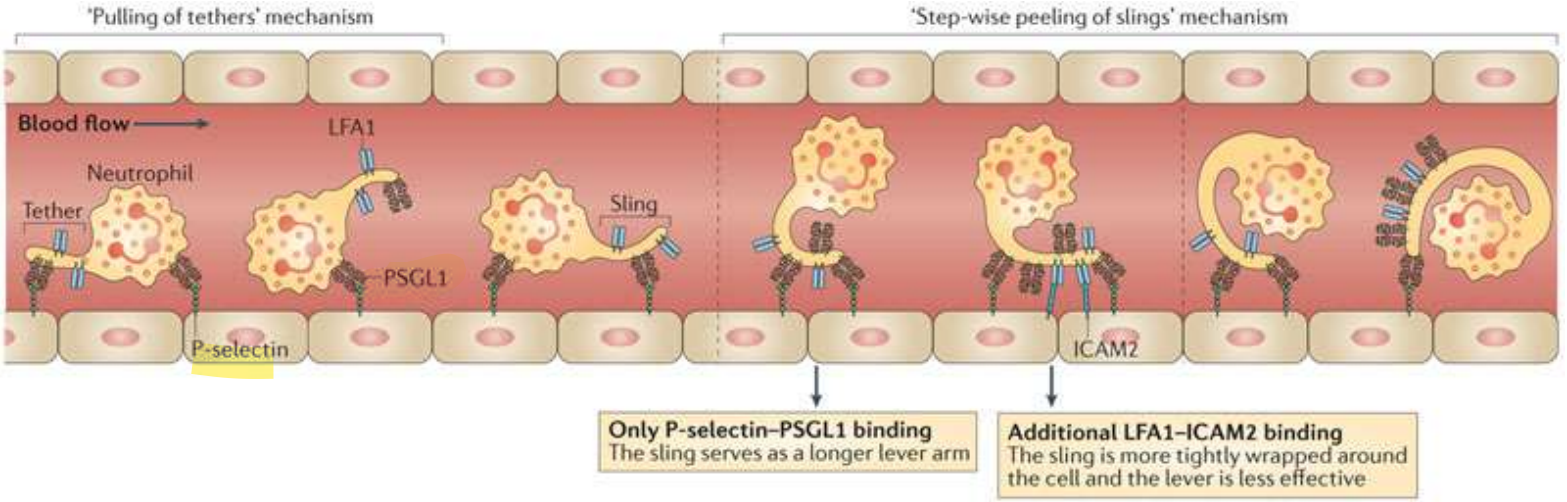
- Leukotrines (LTB_4)



Lymphocytes Migration

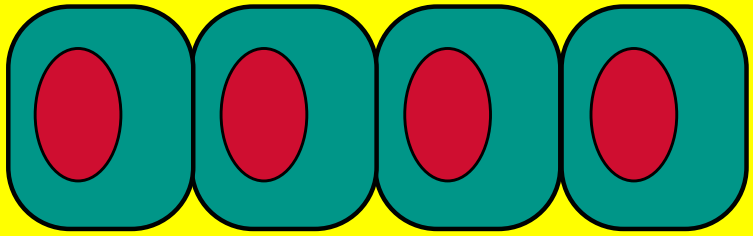


Neutrophils Migration



Role of endothelial cells in trafficking and recirculation

Endothelial cells are involved in:
vascular permeability, regulation of coagulation, immune modulation and lymphocyte extravasation



High endothelial venules: Region of Vascular Endothelium composed of specialized cells with a cuboidal shape
Found in Secondary Lymphoid organs like Lymph nodes but not spleen

Allow lymphocytes and nothing else into the lymph node from the circulation

Molecules expressed by endothelial cells regulate trafficking and recirculation through lymphoid and non-lymphoid tissues

Pathways & Mechanisms of Lymphocyte Recirculation & Homing

- **Naive lymphocytes** will move from the blood stream into lymph nodes & via lymphatics back into the blood stream many times, until they encounter an antigen they recognize within a lymph node

- This **traffic pattern of naive lymphocytes**, called **lymphocyte recirculation,**

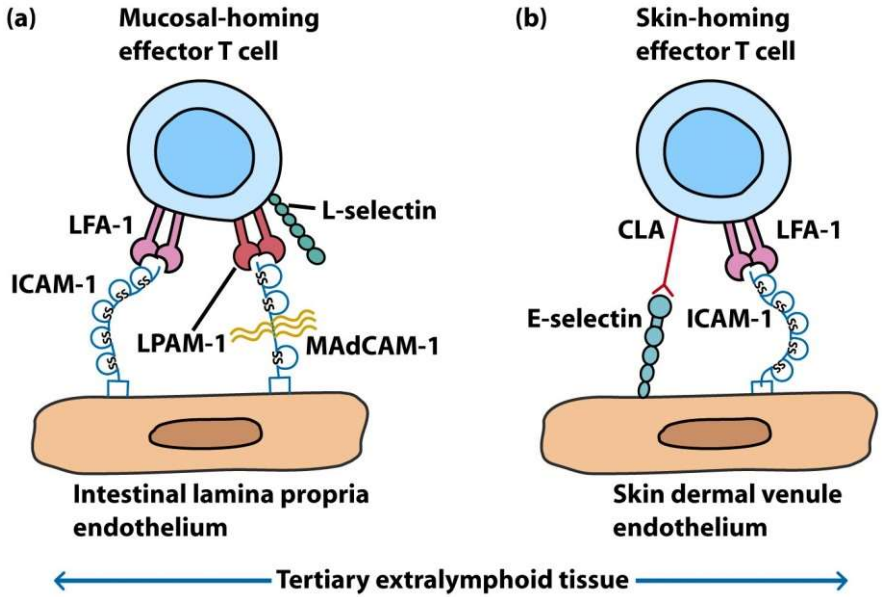
➢ Enables the limited number of naive lymphocytes that are specific for a particular foreign Ag to search for that Ag throughout the body

mature B and T cells are in constant motion
blood -- tissues -- lymphatics -- blood
increasing chance of encountering antigens

- Lymphocytes that have reacted to that antigen & differentiated into effector & memory cells within secondary lymphoid tissues may:

1. Move back into the blood stream
2. Then migrate into sites of infection and/or inflammation in peripheral (nonlymphoid) tissues

- Some effector lymphocyte subsets will preferentially migrate into a particular tissue, such as skin or gut, this is called **lymphocyte homing.**



homing: differential migration of lymphocytes to specific tissues, regulated by cell adhesion molecules

THANK YOU

ANY QUESTIONS??