Cellular events

Function of inflammation- deliver leukocytes at site of injury, activate them to perform functions in host defense

- Leukocyte extravasation
- Phagocytosis

Leukocyte extravasation

- In the lumen: margination, pavementing, rolling
- Emigration across endothelium
- Chemotaxis

In the lumen:

- **Margination**- Normally red and white cells flow intermingled in the center of the vessel separated from vessel wall by a clear cell-free plasmatic zone.

  - Due to slowing of the circulation, leucocytes fall out of the axial stream and come to periphery known as margination
- **Pavementing**- neutrophils close to vessel wall
- **Rolling**- neutrophils roll over endothelial cells
- **Adhesion**- binding to endothelial cells

Regulated by binding of complementary adhesion molecules on endothelial and leukocyte surfaces

Adhesion molecules

- Selectins

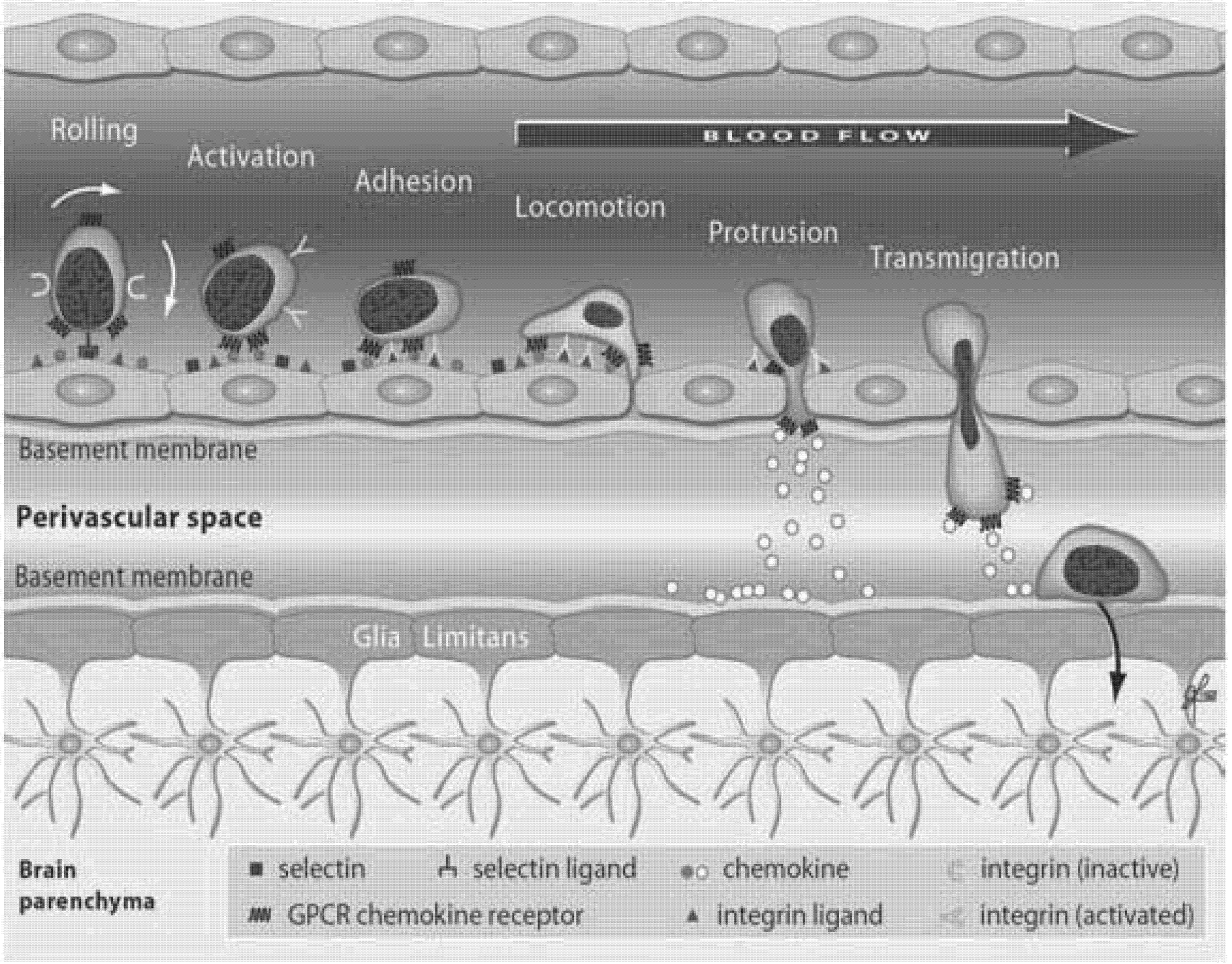
  E- selectin

  P- selectin

  L- selectin
- Immunoglobulins – ICAM-1, VCAM-1
- Integrins

Emigration

- neutrophils throw cytoplasmic pseudopods migrate through interendothelial spaces
- b/w endothelial cells & BM
- crosses BM by damaging it by collagenases
- escape of RBCs, diapedesis also occurs


Rolling
Activation
Adhesion
Locomotion
Protrusion
Transmigration
BLOOD FLOW
Basement membrane
Perivascular space
Basement membrane
Glia Limitans
Brain parenchyma
selectin
selectin ligand
chemokine
integrin (inactive)
GPCR chemokine receptor
integrin ligand
integrin (activated)

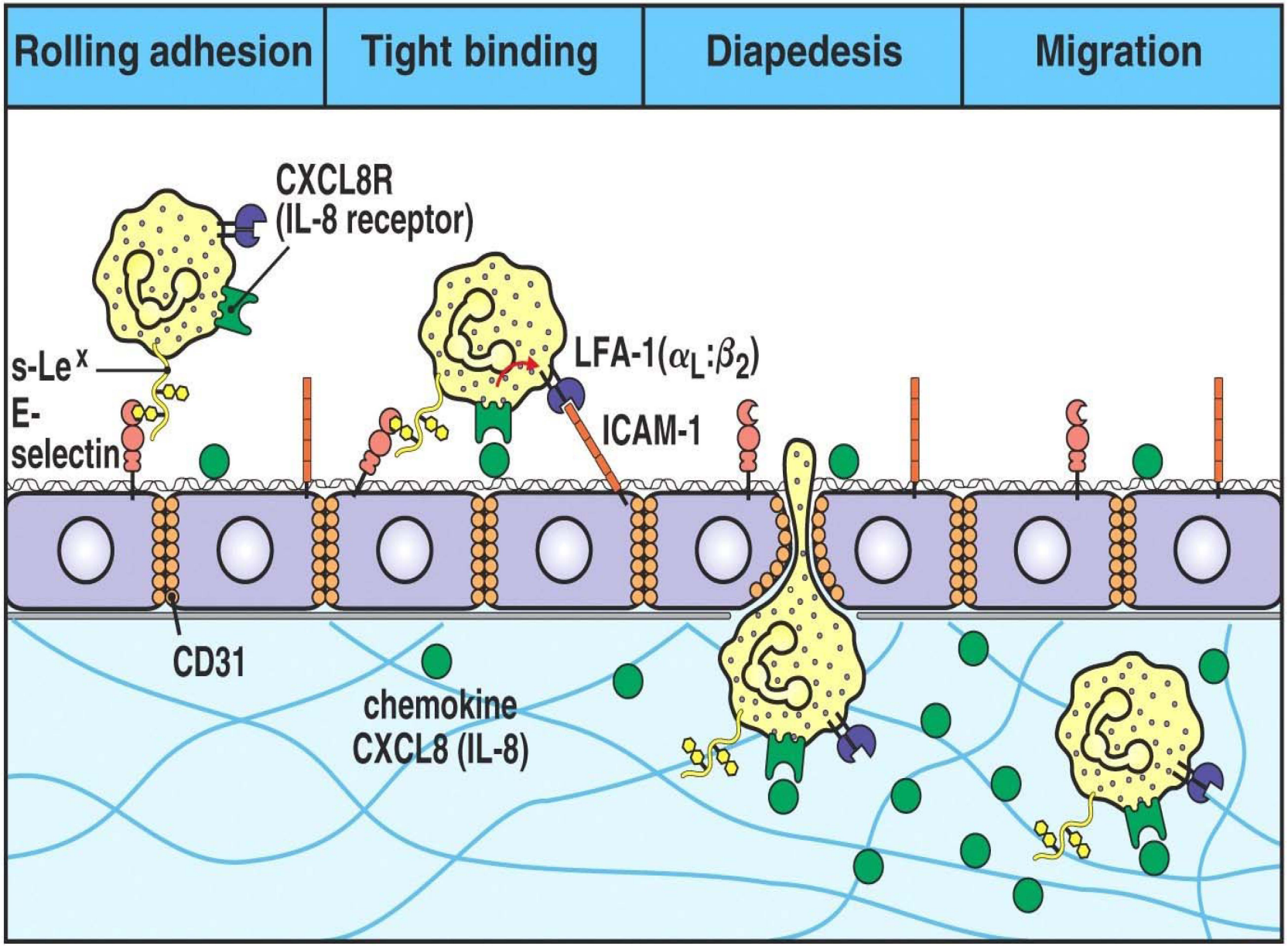


Figure 2-44 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)

Chemotaxis

- Leukocytes emigrate towards site of injury or chemical gradient
- Chemotactic agents:
  - exogenous – bacterial products
  - endogenous- complement system C5a, leukotrienes, cytokines
- Chemotactic agents bind to cell receptors on leukocytes→ ↑cytosolic Ca, phospholipases, activation of leukocytes
  - production of arachidonic acid metabolites
  - secretion of lysosomal enzymes
  - secretion of cytokines
  - modulation of leukocyte adhesion molecules

Phagocytosis

- Process of engulfment of solid particulate material by cells
- Polymorphs, macrophages
- 3 steps:

1. Recognition and attachment
2. Engulfment
3. Killing & degradation

Recognition & attachment

- Phagocytic cells attracted to bacteria by chemotactic factors released by bacteria & tissue proteins
- Microorganisms get coated by opsonins

  1) IgG opsonin is Fc fragment of IgG, naturally occuring Ab

  2) C3b opsonin- fragment of C3, generated by activation of complement pathway

  3) lectins- carbohydrate binding proteins

Engulfment

- opsonised particle ready for engulfment
- pseudopods due to activation of actin filaments
- phagocytic vacuole, breaks from cell membrane
- phagolysosome
- degranulation- preformed granule stored products are discharged

Killing or degradation

- Intracellular mechanisms

  i) Oxidative bactericidal mechanism: oxidative damage by production of reactive oxygen metabolites which are principal killers of bacteria – O_2, OH', HOCL, H_2O_2

  - A phase of ↑ O_2 consumption- (respiratory burst) requires presence of NADPH oxidase

  $NADPH + 2O_2 \rightarrow 2O'_2 + NADP + H^+$

  $2O'_2 + 2H \rightarrow H_2O_2$

- MPO dependent killing

$H_2O_2 \rightarrow HOCL + H_2O$

in presence of halides (cl', I', Br')

- MPO independent killing- macrophages lack MPO

$H_2O_{2\rightarrow}$ OH'

In presence of Fe or O_2

ii) Oxidative bactericidal mechanism by lysosomal granules: pre-formed granule stored products of neutrophils & macrophages are discharged into phagosomes

- lysosomal hydrolases: protease, trypsinase, alkaline phosphatase, phospholipase

iii) Non- oxidative bactericidal mechanism:

Nitric Oxide mechanism- NO produced by endothelial cells, macrophages