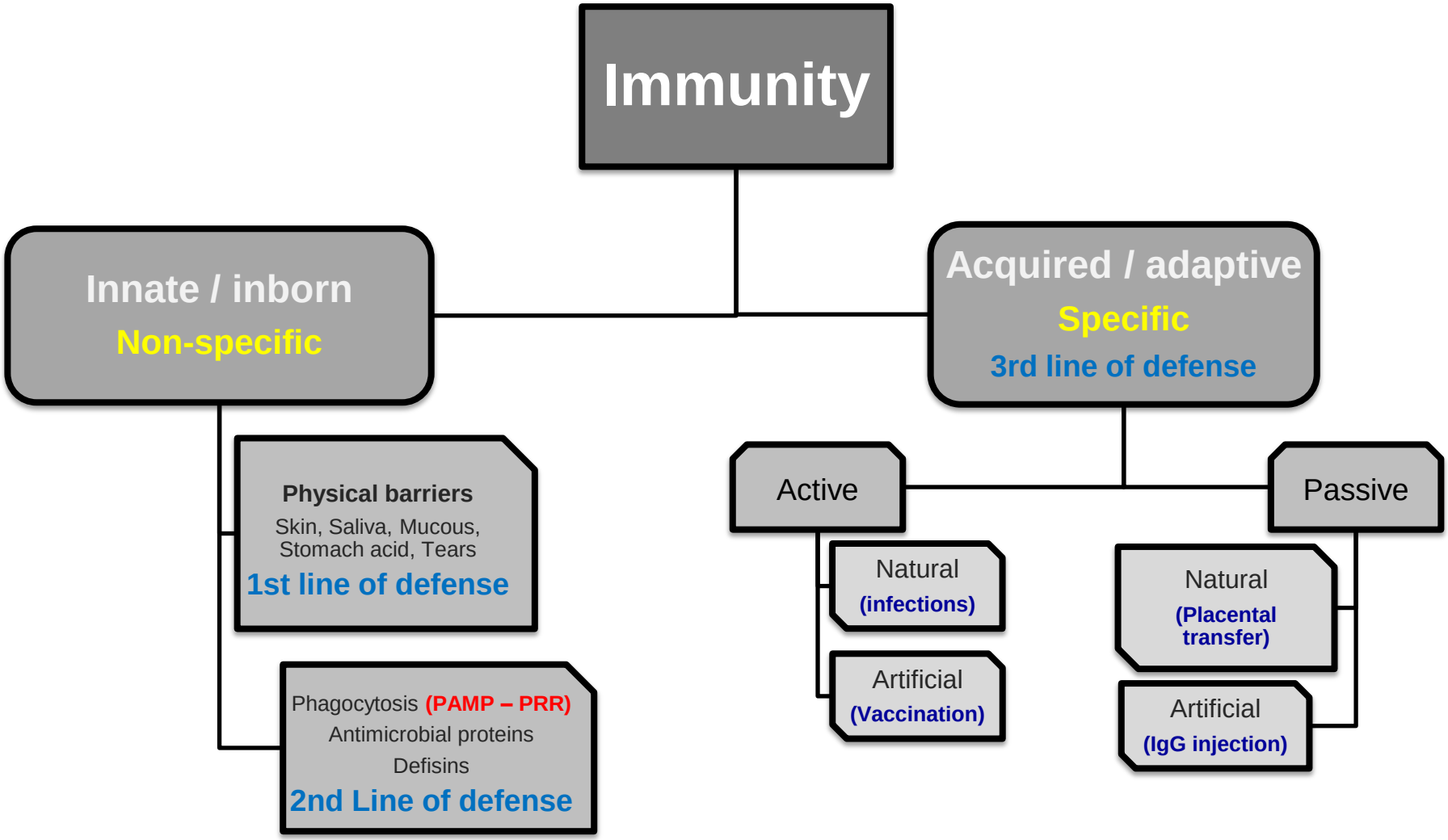
Innate Immunity

By
Dr. Gouse Mohiddin Shaik

Types of immunity



Innate immunity

- Innate immunity is non-specific arm of the immune system

Innate immunity

- Anatomical barriers
  - Mechanical factors
  - Chemical factors
  - Biological factors
- Cellular Components
  - Neutrophils, NK cells, Macrophages...
- Humoral Components
  - Complement – major one
  - Platelets, Cytokines..

Anatomical barriers

- Anatomical barriers - Mechanical

System/Organ	Cell type	Mechanism
Skin	Squamous epithelium	Physical barrier Desquamation
Mucous membranes	Non-ciliated epithelium (e.g. GI tract)	Peristalsis
	Ciliated epithelium (e.g. respiratory tract)	Mucociliary elevator
	Epithelium (e.g. nasopharynx)	Flushing action of tears, saliva, mucus, urine

Anatomical barriers

- Anatomical barriers - Chemical

System/Organ	Component	Mechanism
Skin	Sweat	Antimicrobial fatty acids
Mucous membranes	HCl (parietal cells), tears & saliva	Low pH Lysozyme phospholipase A
	Defensins (respiratory & GI tract)	Antimicrobial
	Surfactants (lung)	Opsonin

Opsonin enhances phagocytosis

Anatomical barriers

- Anatomical barriers - Biological

System/Organ	Component	Mechanism
Skin and mucous membranes	Normal flora	Antimicrobial substances Competition for nutrients and colonization

Humoral Components

Component	Mechanism
Complement	Lysis of bateria and some viruses Opsonin Increase in vascular permeability Recruitment and activation of phagocytic cells
Coagulation system	Increase vascular permeability Recruitment of phagocytic cells Beta-lysin from platelets – a cationic detergent
Lactoferrin and transferrin	Compete with bacteria for iron
Lysozyme	Breaks down bacterial cells walls
Cytokines	Various effects

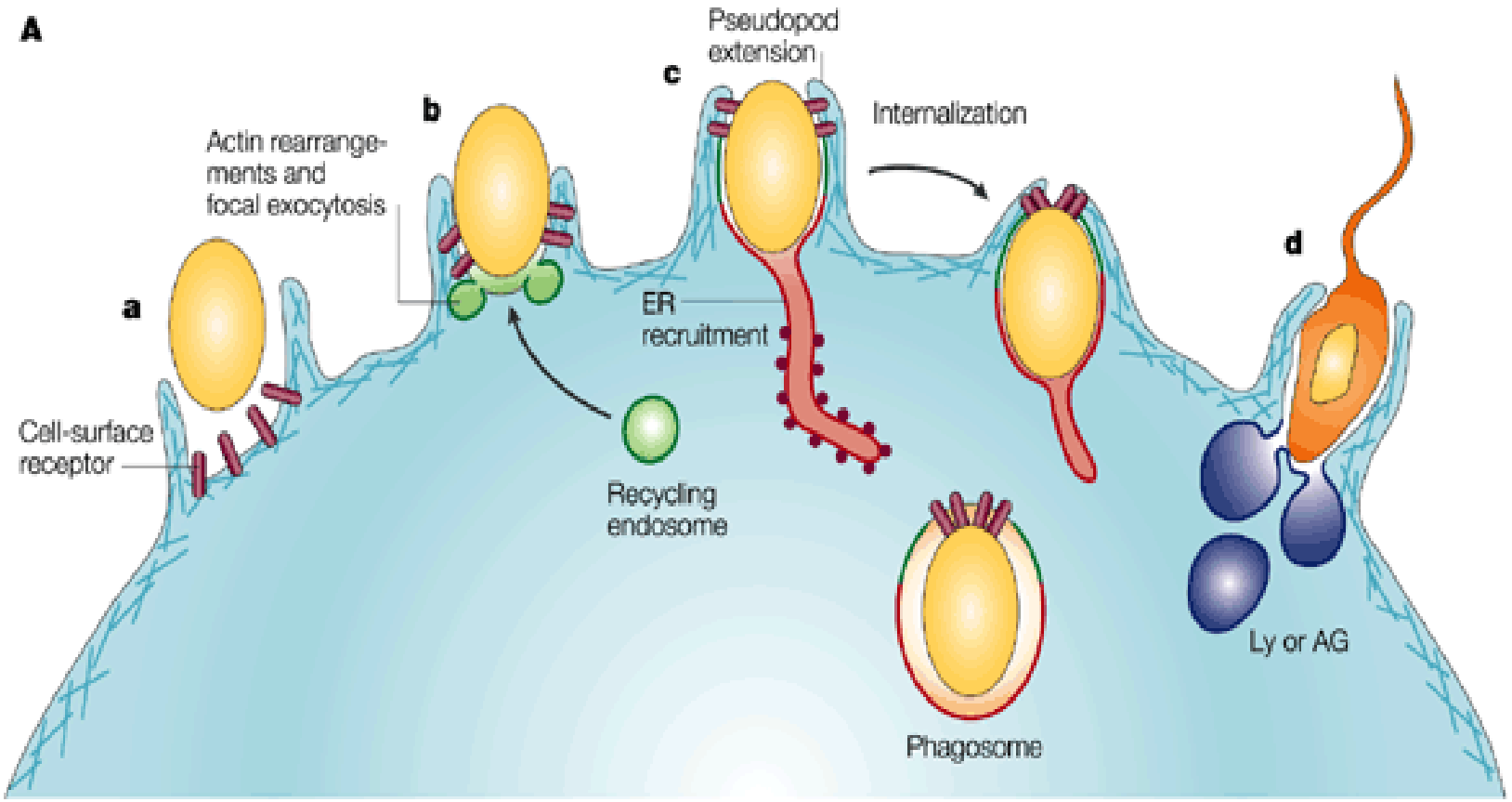
Cellular Components

Cell	Mechanism
Neutrophils	Phagocytosis and intracellular killing Inflammation and tissue damage
Macrophages	Phagocytosis and intracellular killing Extracellular killing of infected or altered self targets Tissue repair Antigen presentation for specific immune response
NK and LAK cells	Killing of virus-infected and altered self targets
Eosinophils	Killing of certain parasites

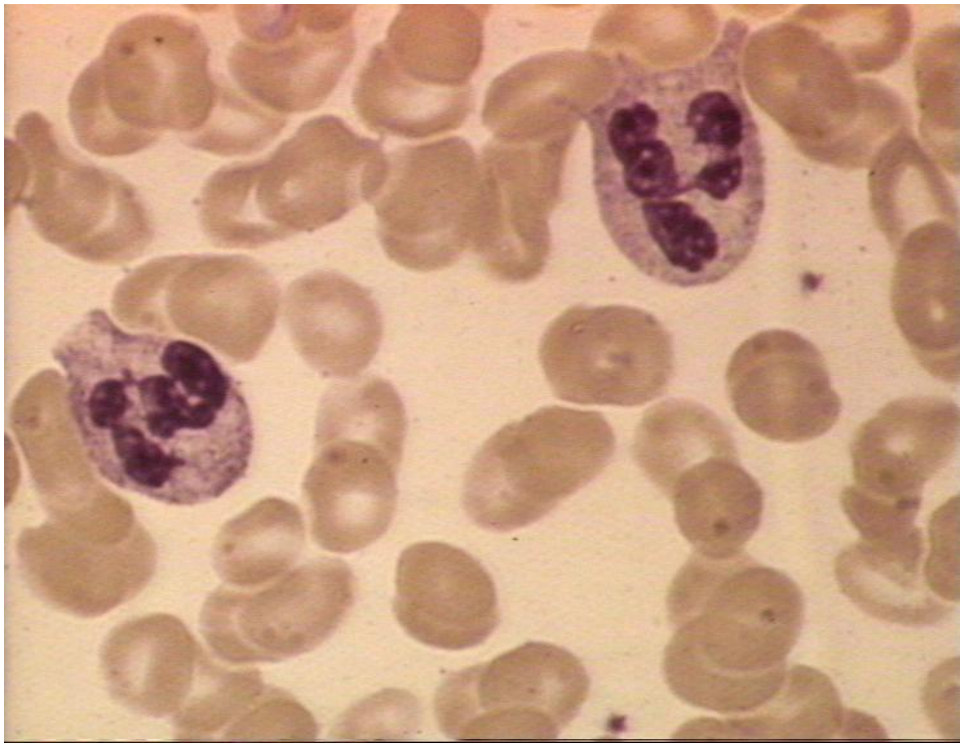
Phagocytosis

Phagocytosis and intracellular killing

Phagocytosis

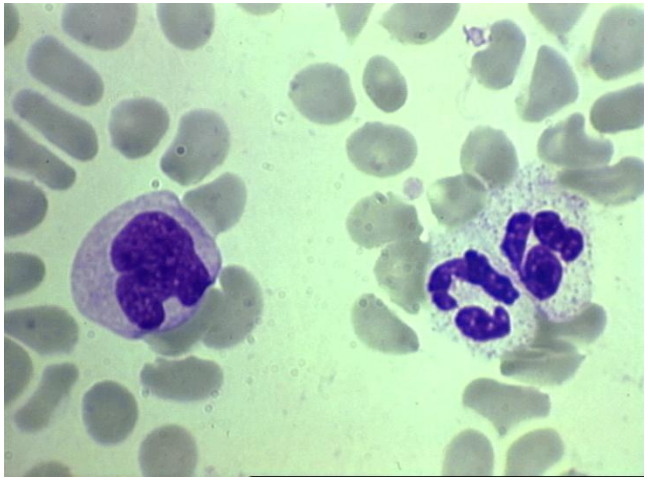


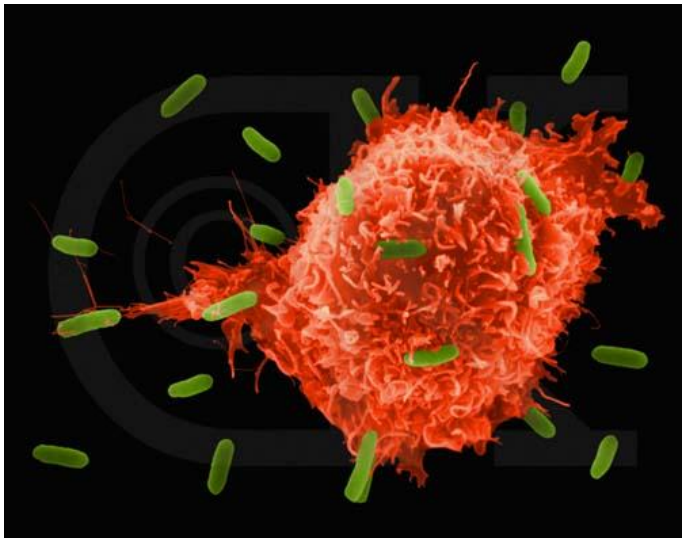
Neutrophils



- Azurophilic granules
- Granules – primary and secondary
- CD66 marker
- O2 dependent killing

Macrophages





- Kidney shaped nucleus
- Rich in lysosomes
- CD14 marker

Phagocytic response

- The SOS signals
  - N-formyl methionine-containing peptides
  - Clotting system peptides
  - Complement products
  - Cytokines released by tissue macrophages
- Phagocyte response
  - Vascular adherence
  - Diapedesis
  - Chemotaxis
  - Activation
  - Phagocytosis and killing

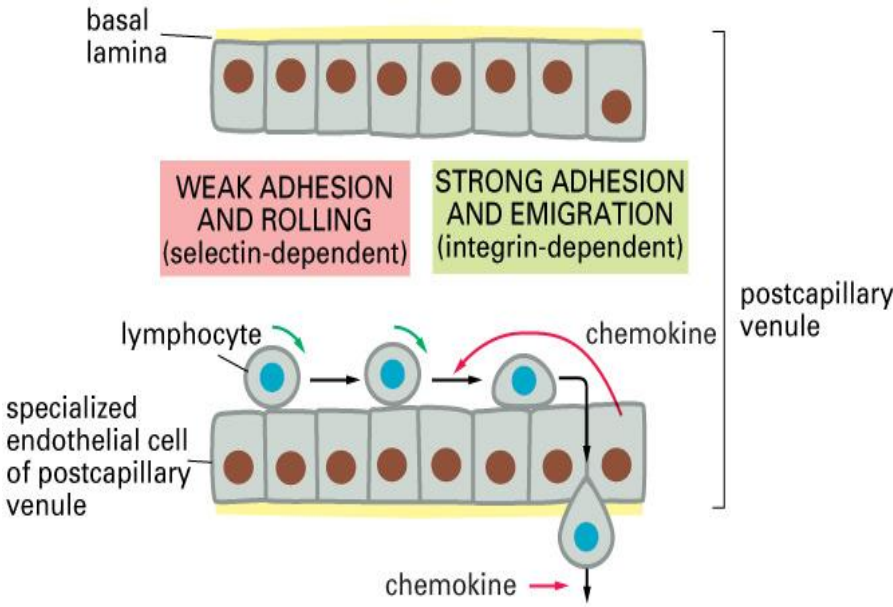
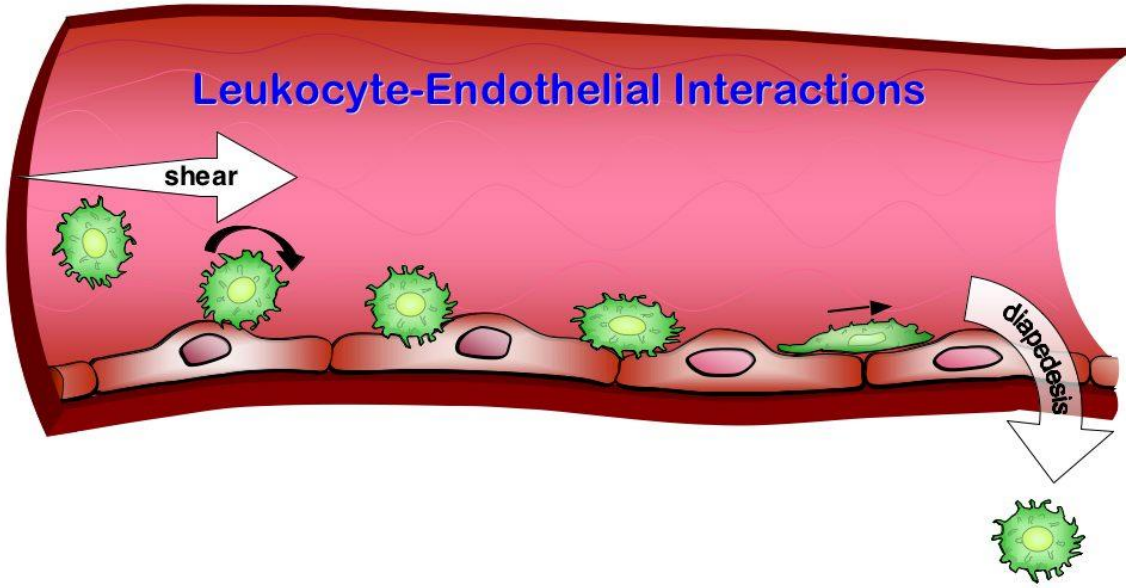


Figure 24–15. Molecular Biology of the Cell, 4th Edition.

Neutrophil extravasation



Neutrophil extravasation

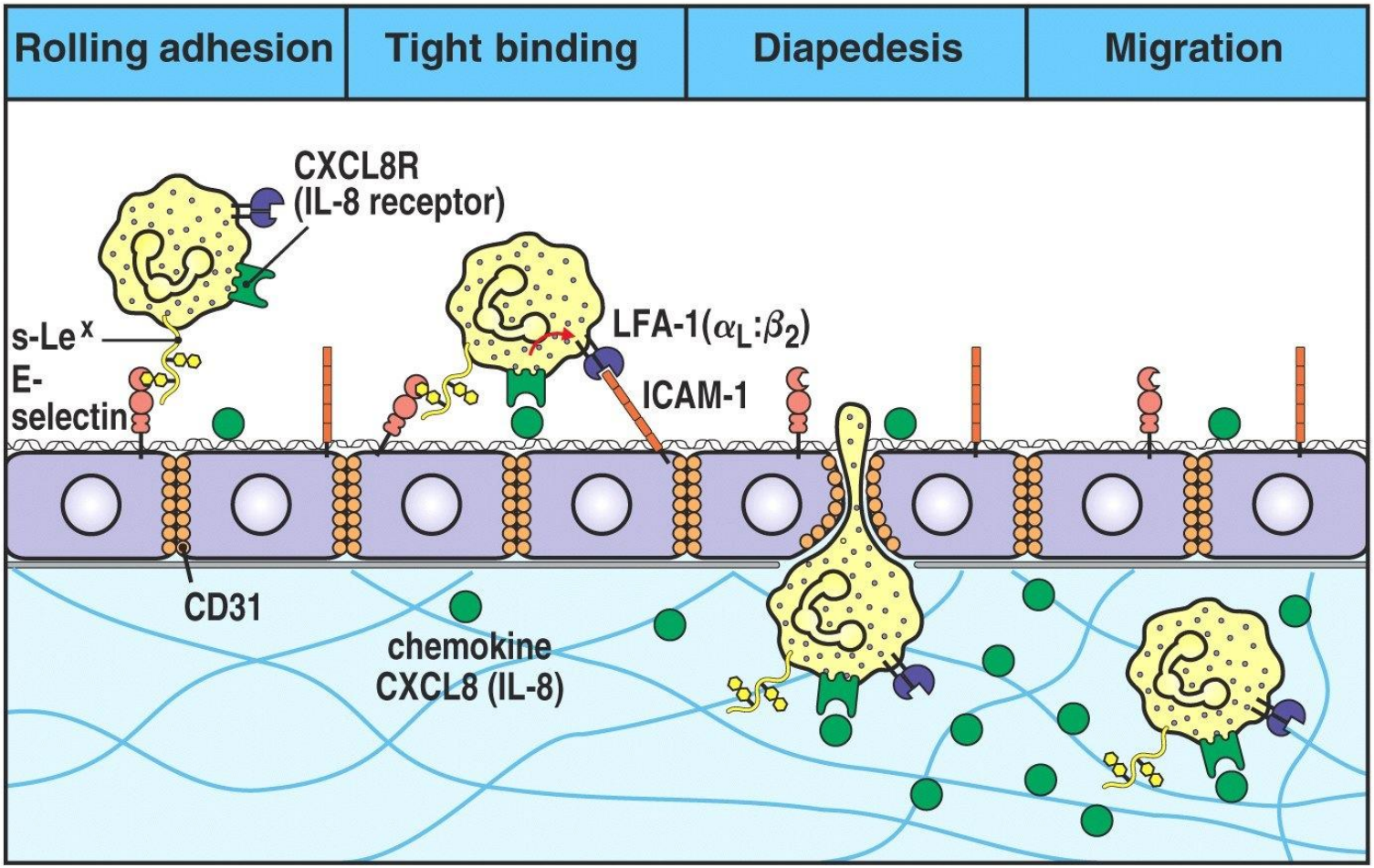
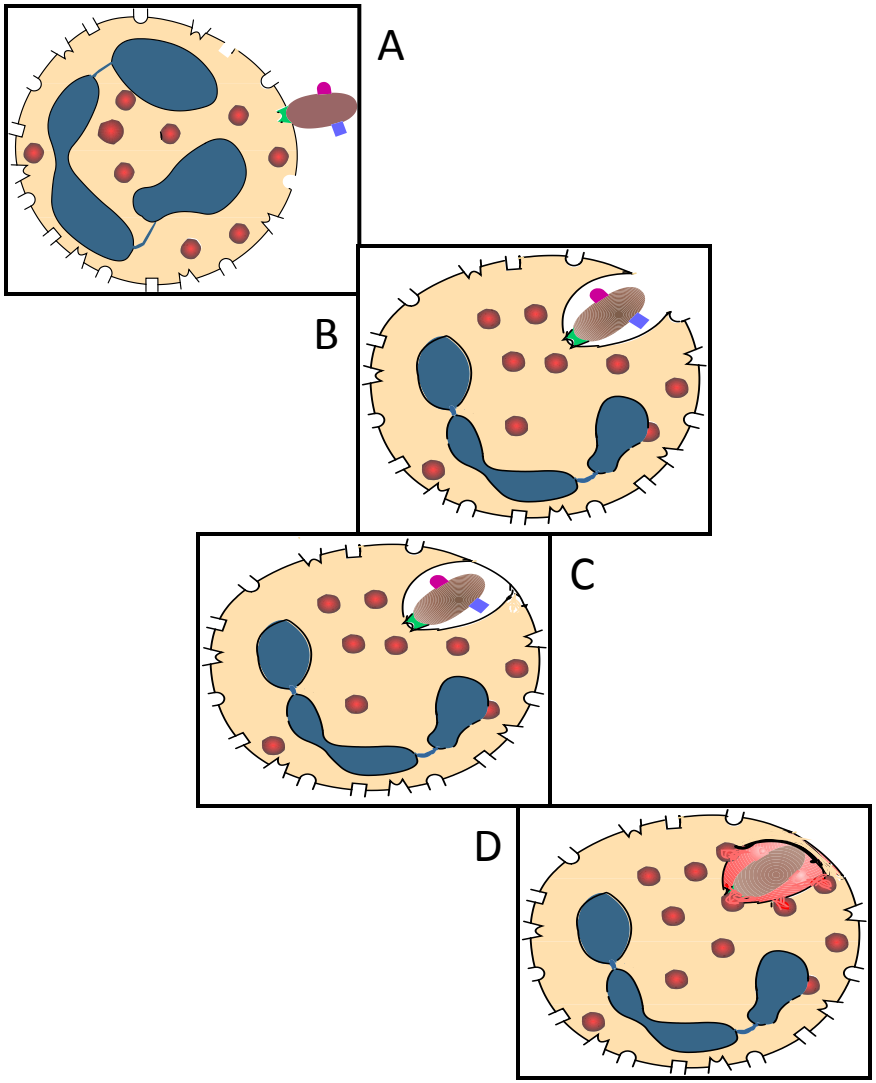


Figure 2-44 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)

Video

Initiation of Phagocytosis



- Attachment via receptors
  - FcR, complement R, scavenger R, Toll-like R
- Pseudopod extension
- Phagosome formation
- Granule fusion and Phagolysosome formation

Fc receptors

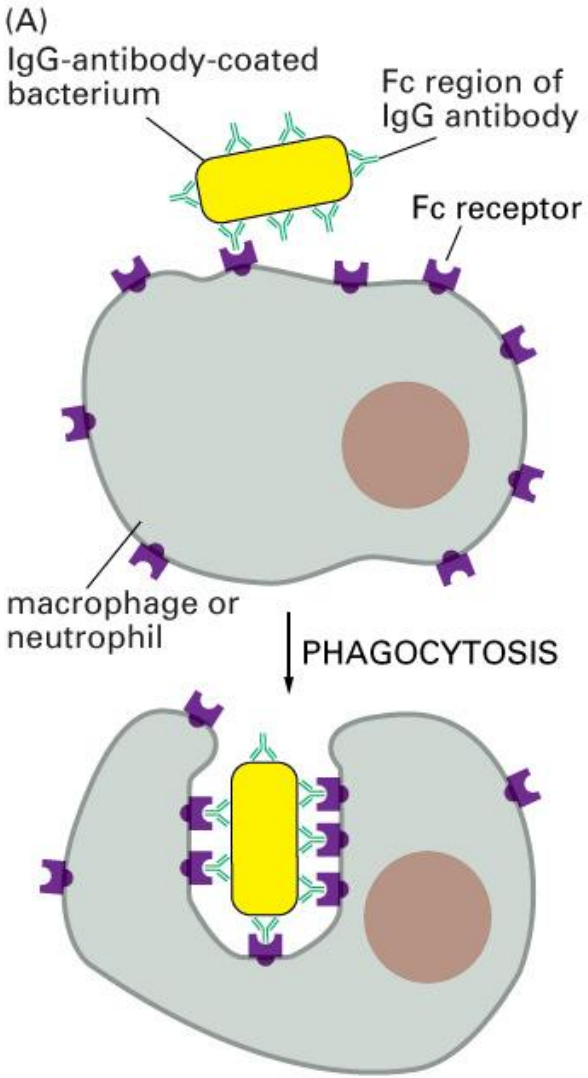
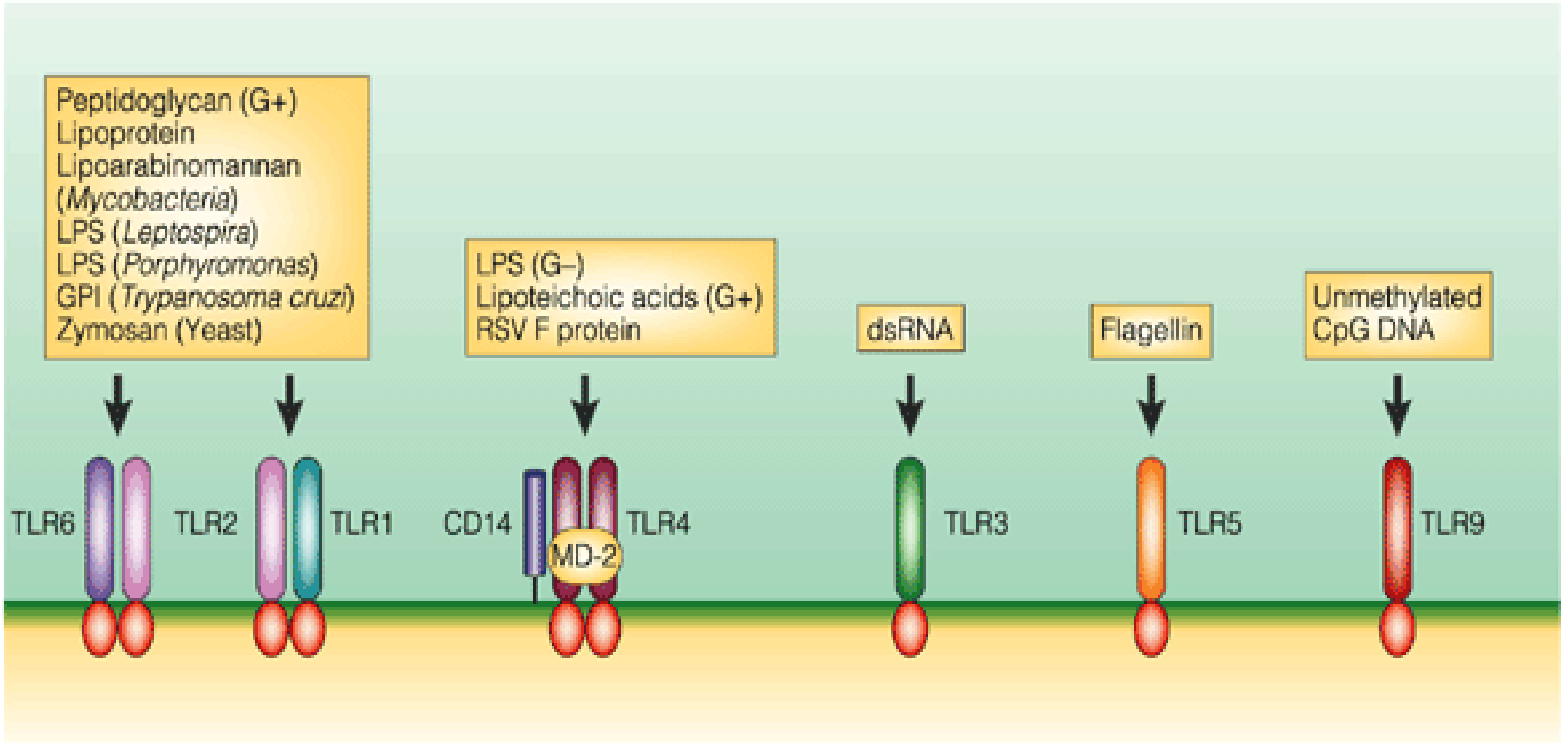


Figure 24–24 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Toll-like receptors



Major group of PRR

Toll-like receptors

- TLRs are transmembrane proteins
- “Toll” identified as essential molecule for embryonic patterning in *Drosphila*
- Evolutionary conserved among insects & humans
- 10 TLRs reported (1-10)
  - Expressed differentially on immune cells (low level)
  - Also expressed on other cell types (e.g., endothelial cells)
  - Respond to different stimuli
  - Expression modulated in response to stimuli – i.e., inducible

Respiratory Burst

OXIDATIVE (RESPIRATORY) BURST

- **Prodution of reactive oxygen compounds by the enzyme NADPH-oxidase**
- **Localized in the phagosome membrane and catalyses the reactions:**

  (surface) $O_2 \rightarrow O_2^-$ **(superoxide anion-radical)**

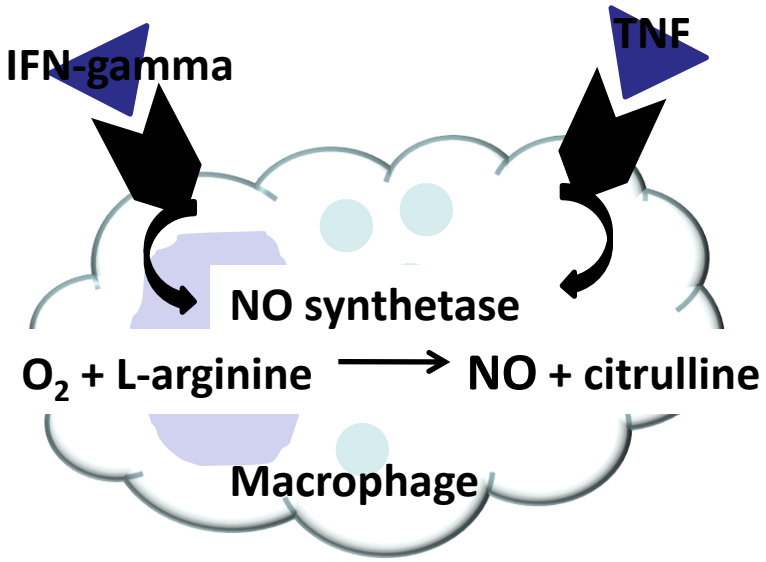
  (cytoplasm) $NADPH \rightarrow NADP^+ + H^+$

- **Superoxide reacts further to produce toxic compounds ("singlet oxygen", H_2O_2, ClO^-)**

O_2 independent killing

Effector molecule	Function
Cationic proteins (cathepsin)	Damage to microbial membranes
Lysozyme	Hydrolyses mucopeptides in the cell wall
lactoferrin	Deprives pathogens of iron
Hydrolytic enzymes (proteases)	Digests killed organisms

NO dependent killing



- Happens in macrophages
- Bacteria binds to macrophage
- Production of TNF-alpha
- Upregulates iNOS
- Release of NO

- NO is toxic to infected cells in the vicinity of macrophage

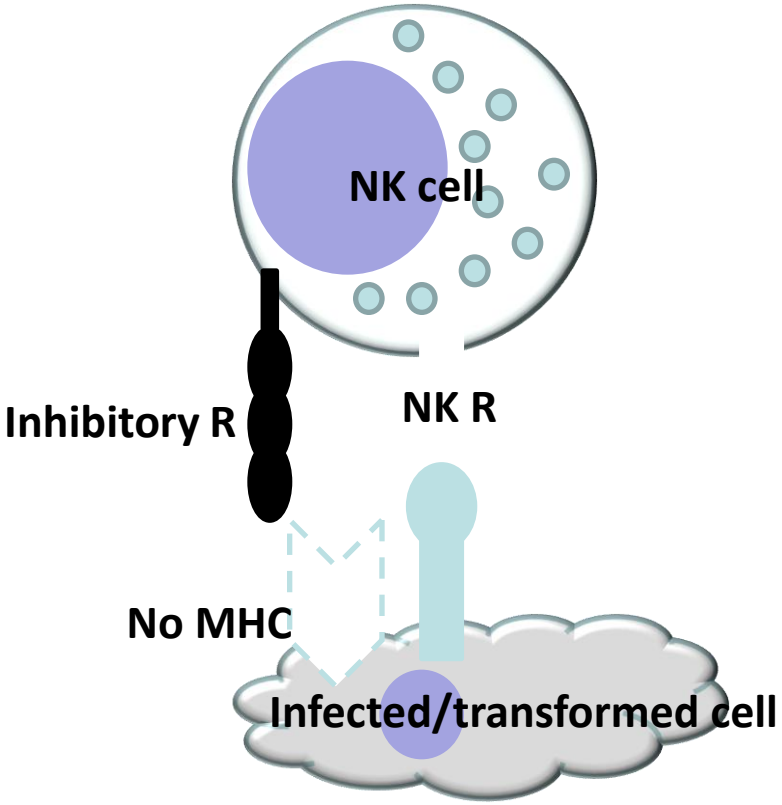
Extracellular killing

INF-gamma is product of adaptive immune system

NK cells

- Natural killer cells
  - Kills virus-infected or cancer cells
  - Has granules also
  - CD56 and CD16 and no CD3
  - Activated by IL2 and INF-gamma and becomes LAK (limphokine activated killer cells)

NK cell killing



- Infected or altered self (transformed) cell downregulated MHC
- NK does not receive inhibitory signal
- Signals kill infected cell

Killer inhibitory receptor (KIR)

How immune system is alerted ?

Hypothesis

- Stranger hypothesis (janeway 1989)
  - PRRs on immune cells detect strange patterns on microbes
    - TLR-5 recognizes flagellin
- Danger hypothesis (P. Metzenger 1994)
  - Alerted against tissue damage associated with microbial infection
    - Uric acid crystals activate Dendritic cells

Determinants involved in Innate immune system

- PAMPs- pathogen associated molecular patterns (Flagelling, LPS, pep.glycan, unmethylated CpG)
- PRRs- pattern recognition receptors
- DAMPs – Death or Damage or Danger associated molecular patterns (Heat shock proteins, chromatin complex, ATP, uric acid ….

Stranger model

Merits

- Explains the concept of tolerance to self
- Inline with induction of tolerance experiments
- Why xeno transplants are rejected
- Why tumors are not rejected

Problems

- Doesn’t explain why we are tolerant to commensal bacteria, fetus, hormones
- Why no immune response to inert foreign antigens and food we eat
- Why allo-transplants have high response then xeno
- Why autoimmunity

Stranger vs Danger model

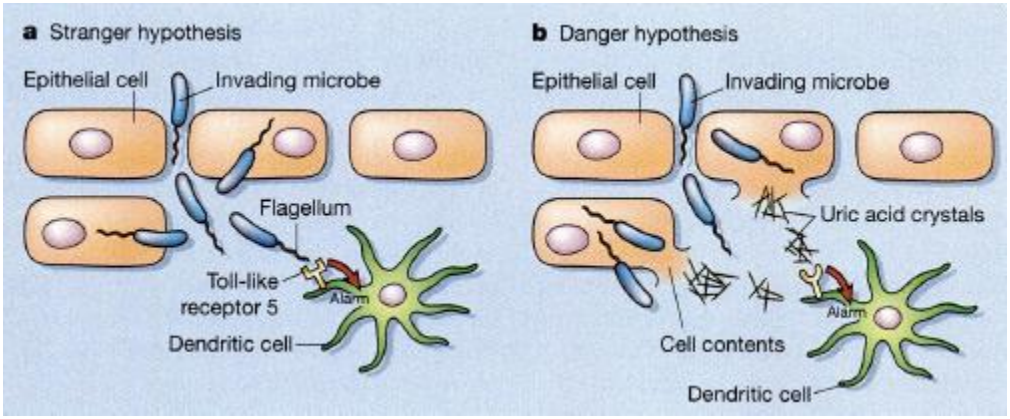
Problems with Stranger

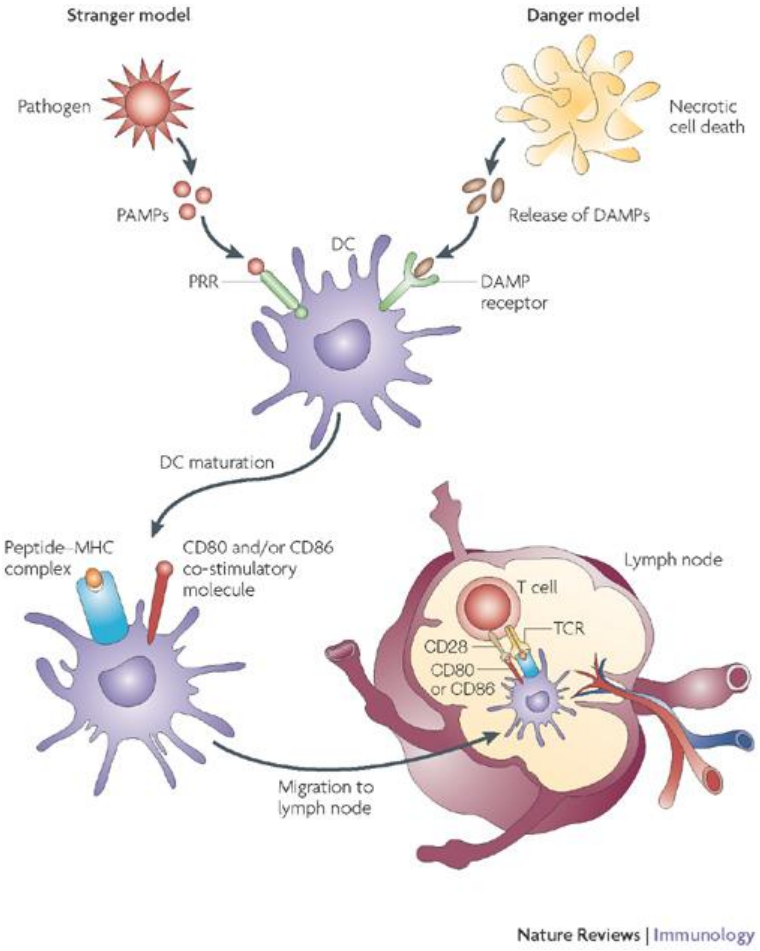
- Doesn't explain why we are tolerant to commensal bacteria, fetus, hormones
- Why no immune response to inert foreign antigens and food we eat
- Why allo-transplants have high response then xeno
- Why autoimmunity

Explanation of Danger

- No cell death in all these events
- If you add adjuvant, YES….
- DAMPs of allo-transplants are more reactive then xeno
- DAMPs activate APC

Stranger vs Danger





Stranger vs Danger model of alerting immune system

Determinants recognized by Innate immune system