Time course of immune response

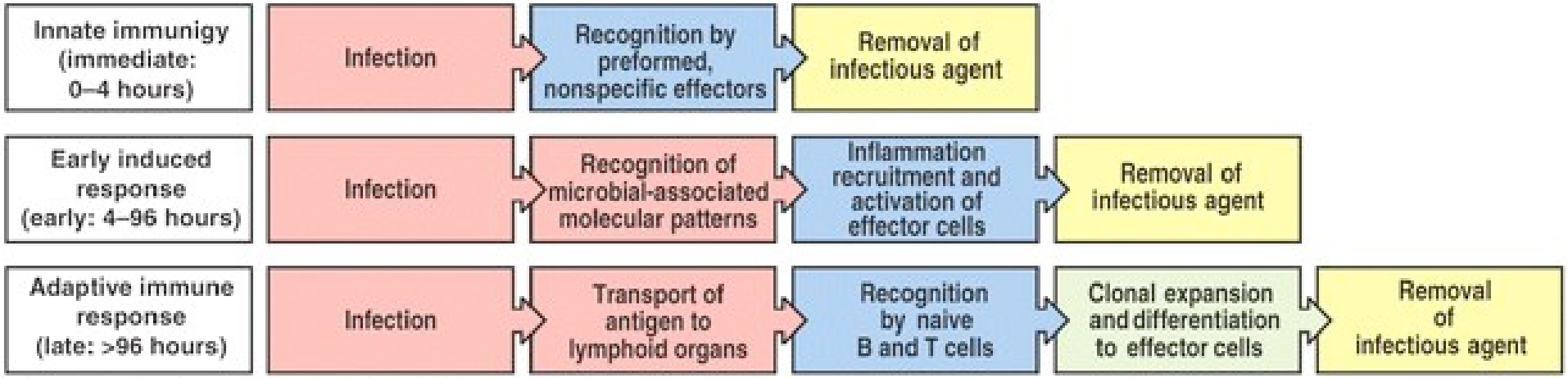
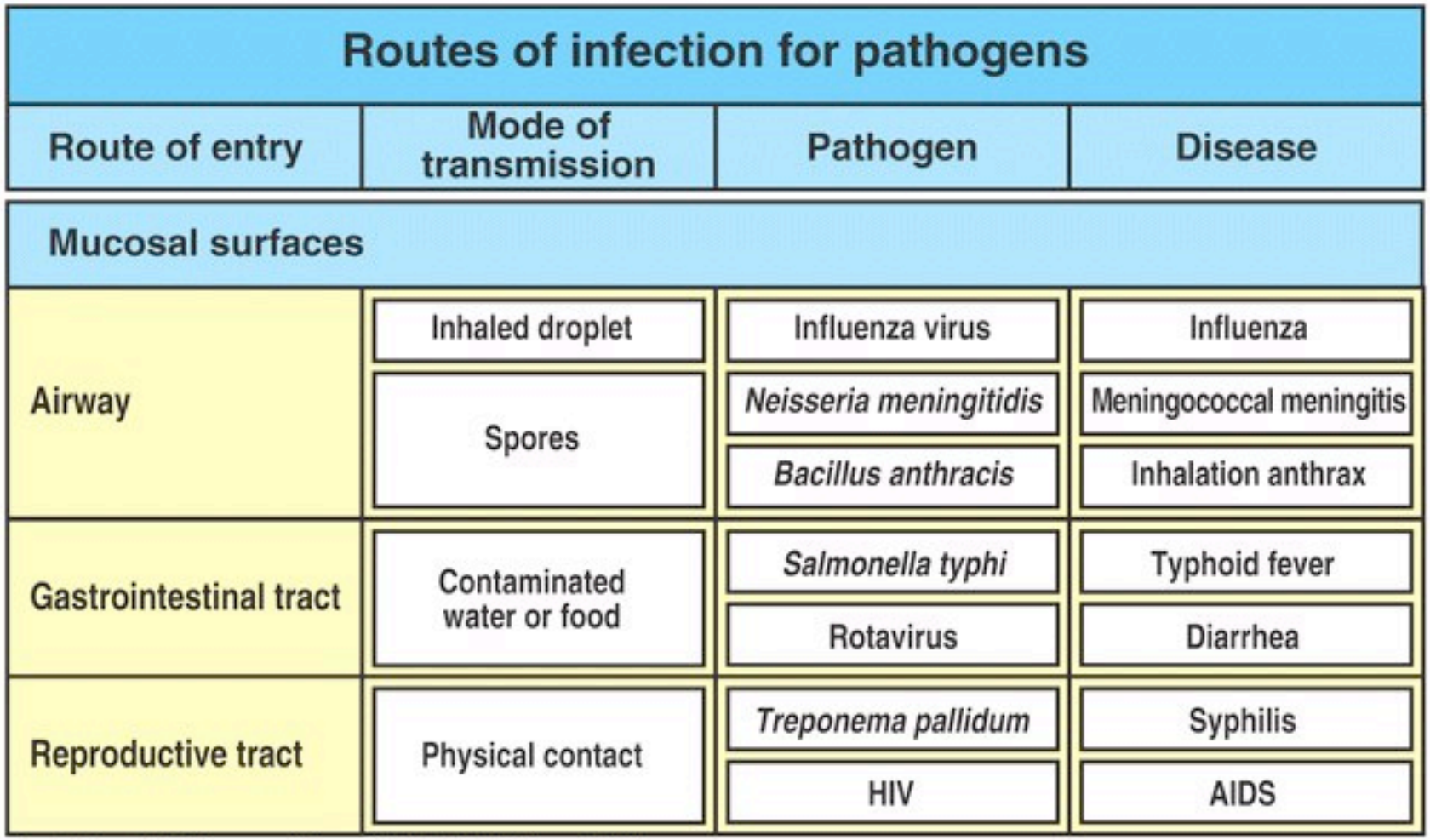


Figure 2-1 Immunobiology, 6/e. (© Garland Science 2005)

Route of entry



Routes of infection for pathogens			
Route of entry	**Mode of transmission**	**Pathogen**	**Disease**
Mucosal surfaces			
Airway	Inhaled droplet	Influenza virus	Influenza
	Spores	*Neisseria meningitidis*	Meningococcal meningitis
		Bacillus anthracis	Inhalation anthrax
Gastrointestinal tract	Contaminated water or food	*Salmonella typhi*	Typhoid fever
		Rotavirus	Diarrhea
Reproductive tract	Physical contact	*Treponema pallidum*	Syphilis
		HIV	AIDS

Figure 2-2 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Route of entry (cont.)

Routes of infection for pathogens			
Route of entry	**Mode of transmission**	**Pathogen**	**Disease**
External epithelia			
External surface	Physical contact	*Trichophyton*	Athlete's foot
Wounds and abrasions	Minor skin abrasions	*Bacillus anthracis*	Cutaneous anthrax
	Puncture wounds	*Clostridium tetani*	Tetanus
	Handling infected animals	*Francisella tularensis*	Tularemia
Insect bites	Mosquito bites (*Aedes aegypti*)	Flavivirus	Yellow fever
	Deer tick bites	*Borrelia burgdorferi*	Lyme disease
	Mosquito bites (*Anopheles*)	*Plasmodium* spp.	Malaria

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

Steps in infection

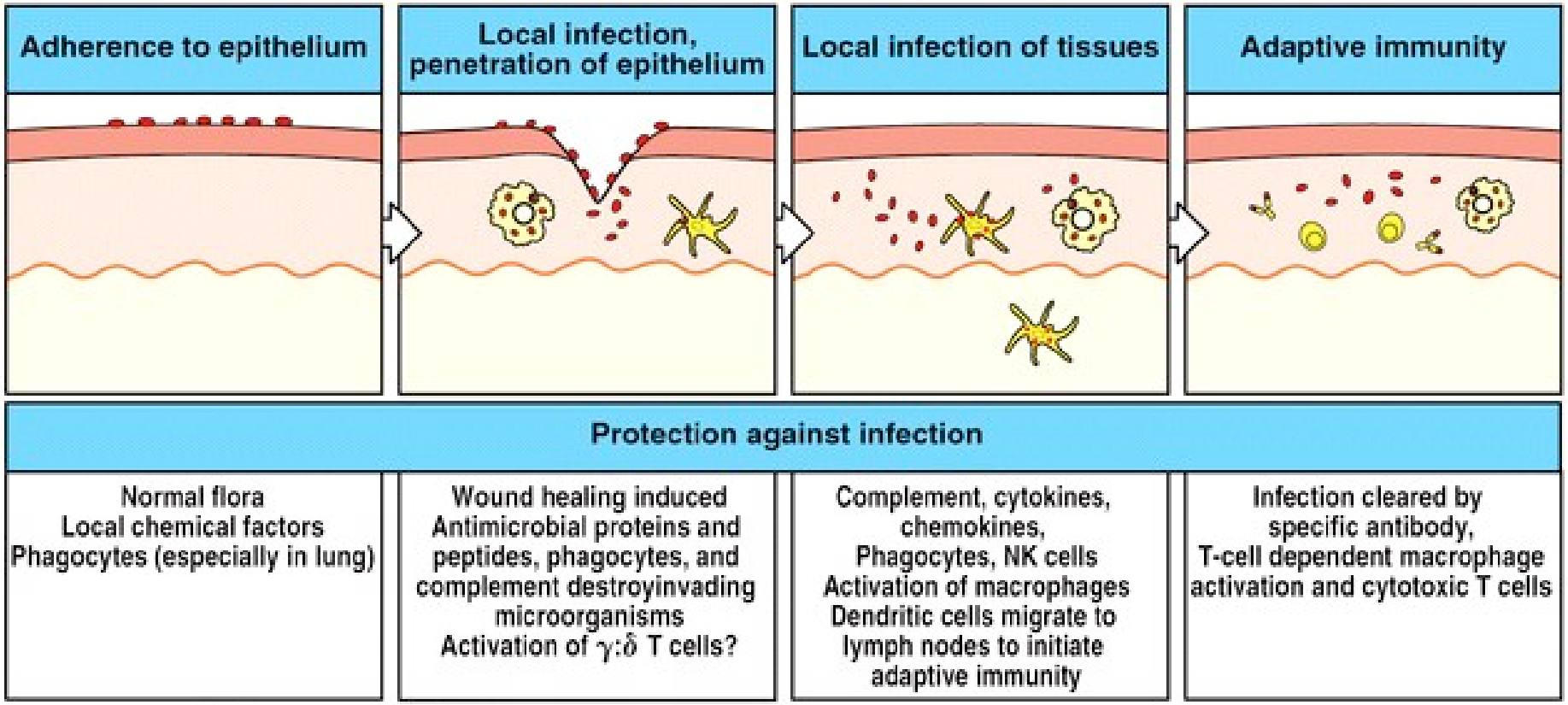


Figure 2-3 Immunobiology, 6/e. (© Garland Science 2005)

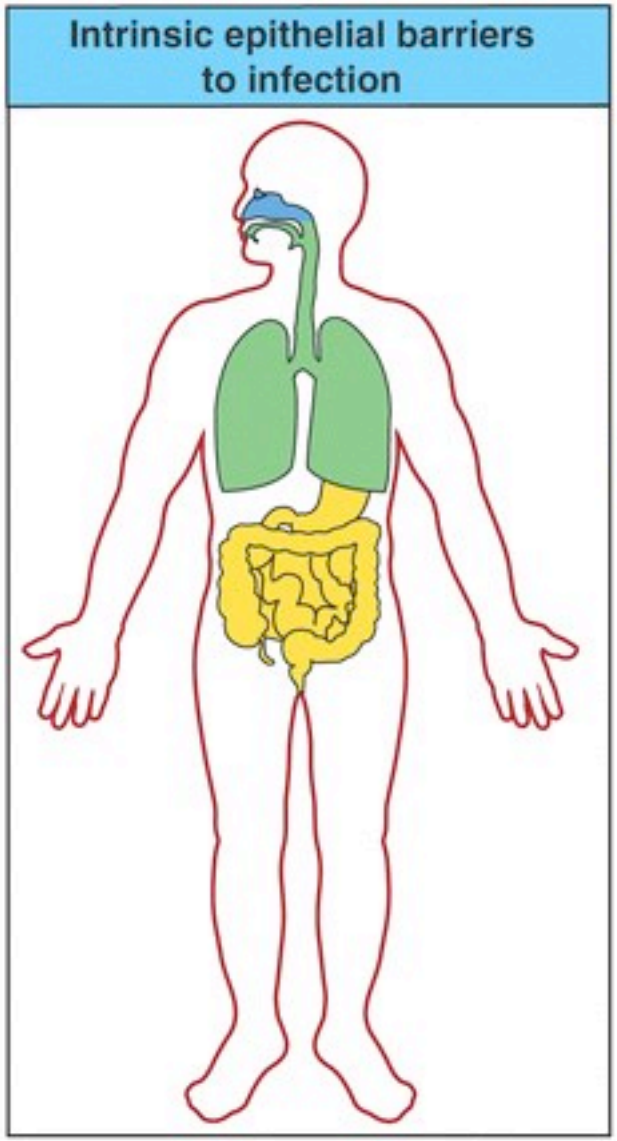


Figure 2-4 Immunobiology, 6/e. (© Garland Science 2005)

	Skin	Gut	Lungs	Eyes/nose
Mechanical	Epithelial cells joined by tight junctions			
	Longitudinal flow of air or fluid		Movement of mucus by cilia	
Chemical	Fatty acids	Low pH		Salivary enzymes (lysozyme)
		Enzymes (pepsin)		
	Antibacterial peptides			
Microbiological	Normal flora			

Barriers to infection

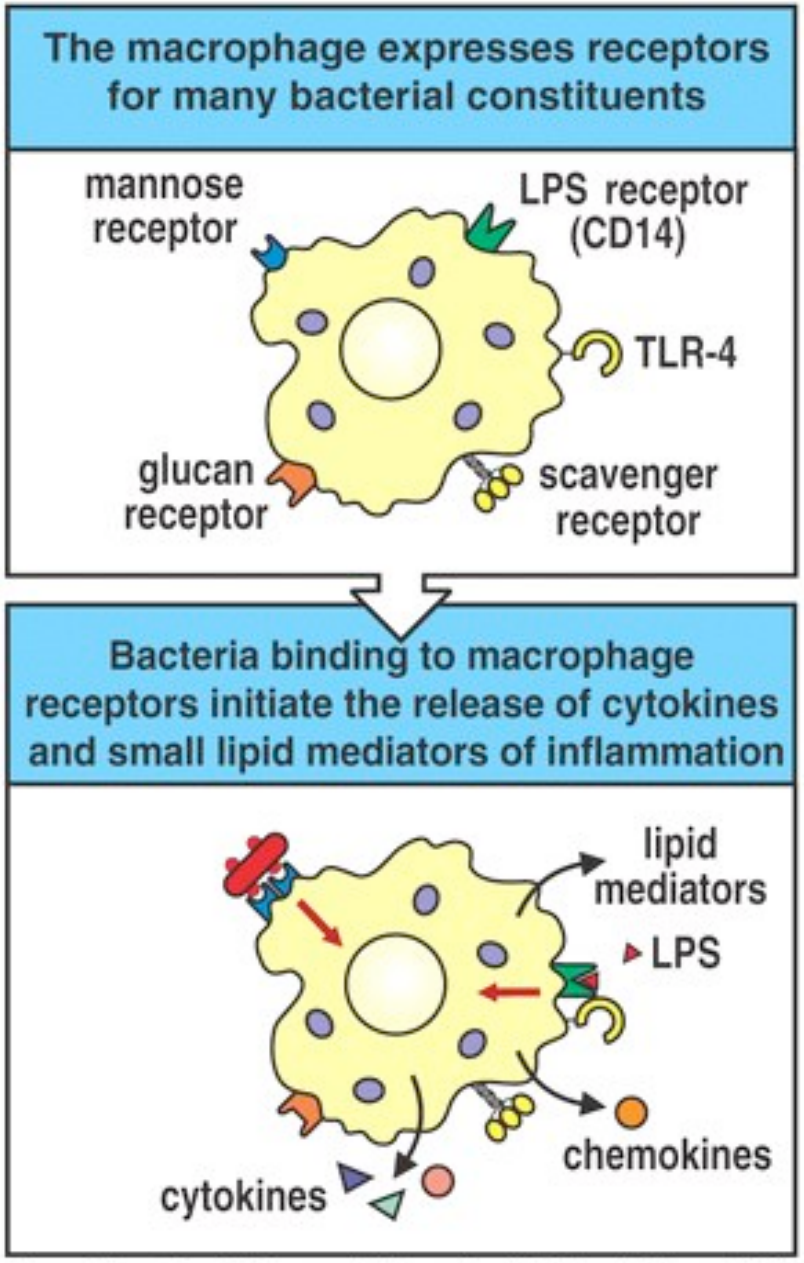


Figure 2-5 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

M receptors

- Facilitate engulfment
  - Glucan, mannose
  - Scavenger
  - CD11b/CD18
- Allows immediate response by lipid mediators
  - Leukotrienes
  - Prostaglandins
  - Platelet-activating factor
- Allows initiation of inflammatory response via cytokines
  - fMet-Leu-Phe receptor
  - Toll-like receptors (e.g. LPS receptor CD14)

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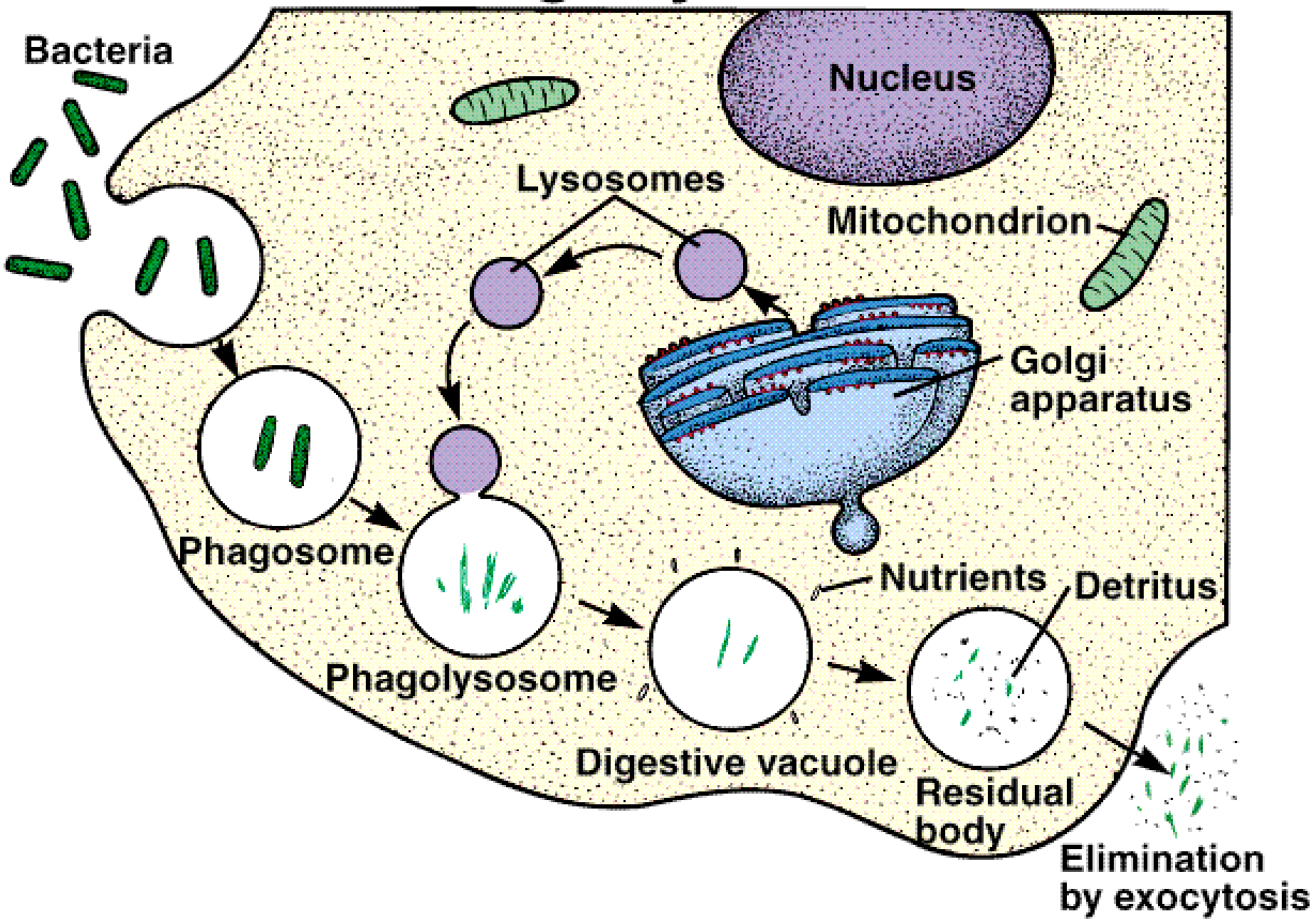
Phagocytosis



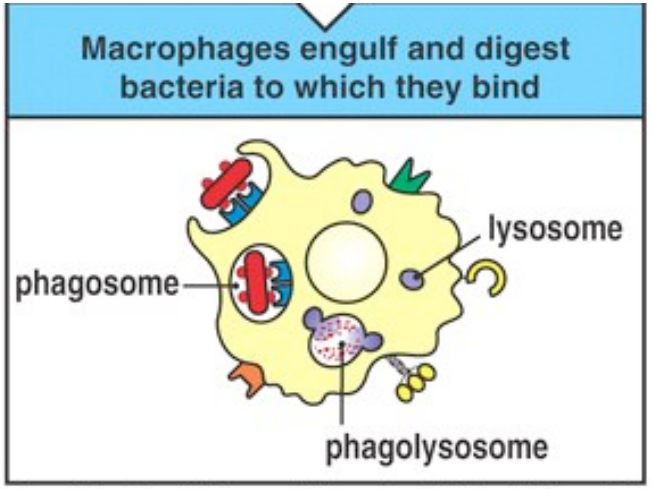


Figure 2-5 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

M□ functions

Class of mechanism	Specific products
Acidification	pH=~3.5–4.0, bacteriostatic or bactericidal
Toxic oxygen-derived products	Superoxide O_2^-, hydrogen peroxide H_2O_2, singlet oxygen $^1O_2^*$, hydroxyl radical OH^*, hypohalite OCl^-
Toxic nitrogen oxides	Nitric oxide NO
Antimicrobial peptides	Defensins and cationic proteins
Enzymes	Lysozyme—dissolves cell walls of some Gram-positive bacteria. Acid hydrolases—further digest bacteria
Competitors	Lactoferrin (binds Fe) and vitamin B_{12}-binding protein

Figure 2-6 Immunobiology, 6/e. (© Garland Science 2005)

LPS stimulation of M and inflammatory response

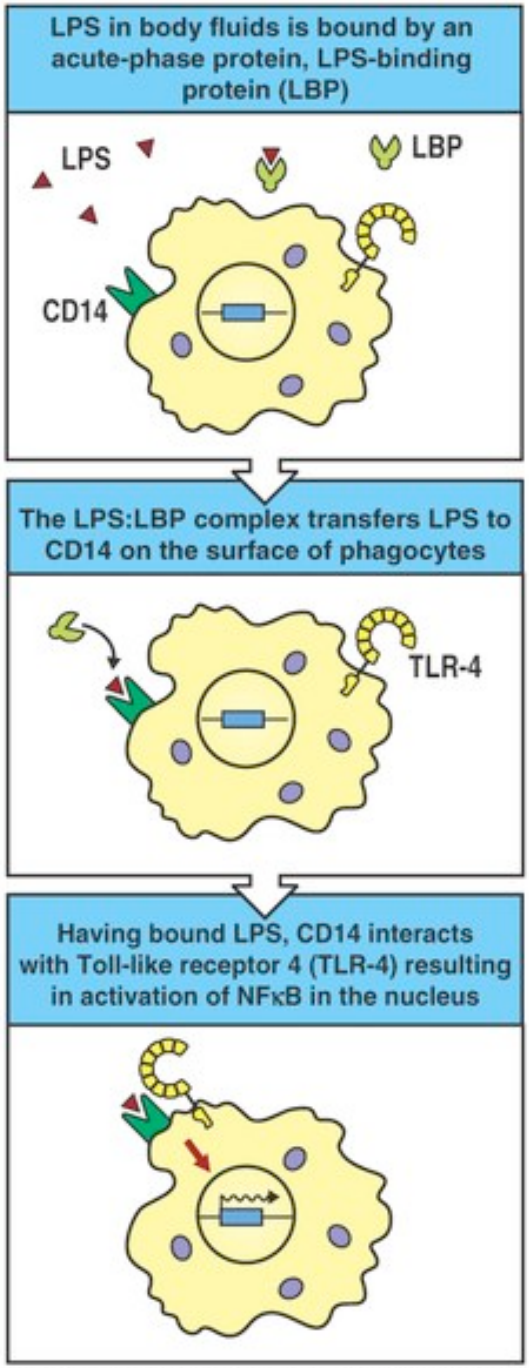


Figure 2-14 Immunobiology, 6/e. (© Garland Science 2005)

Signal transduction: LPS stimulation

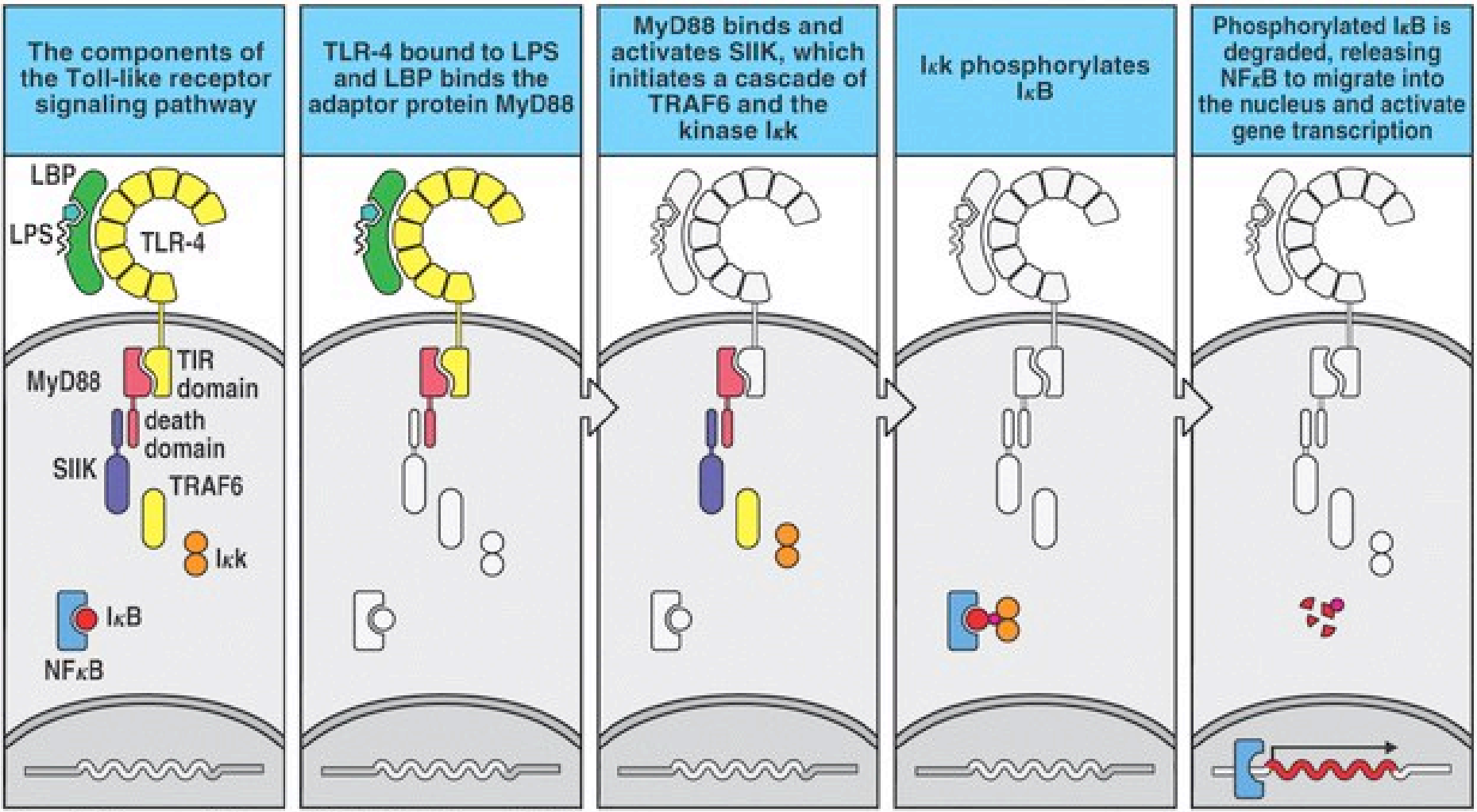


Figure 6-21 Immunobiology, 6/e. (© Garland Science 2005)

LPS stimulation of M□

- NF□B
  - Induces costimulatory molecules (B7.1, B7.2)
  - Increased MHC expression
  - Stimulates transcription of cytokines (IL-6, IL-12, IFN-□, IFN-□, TNF-□)

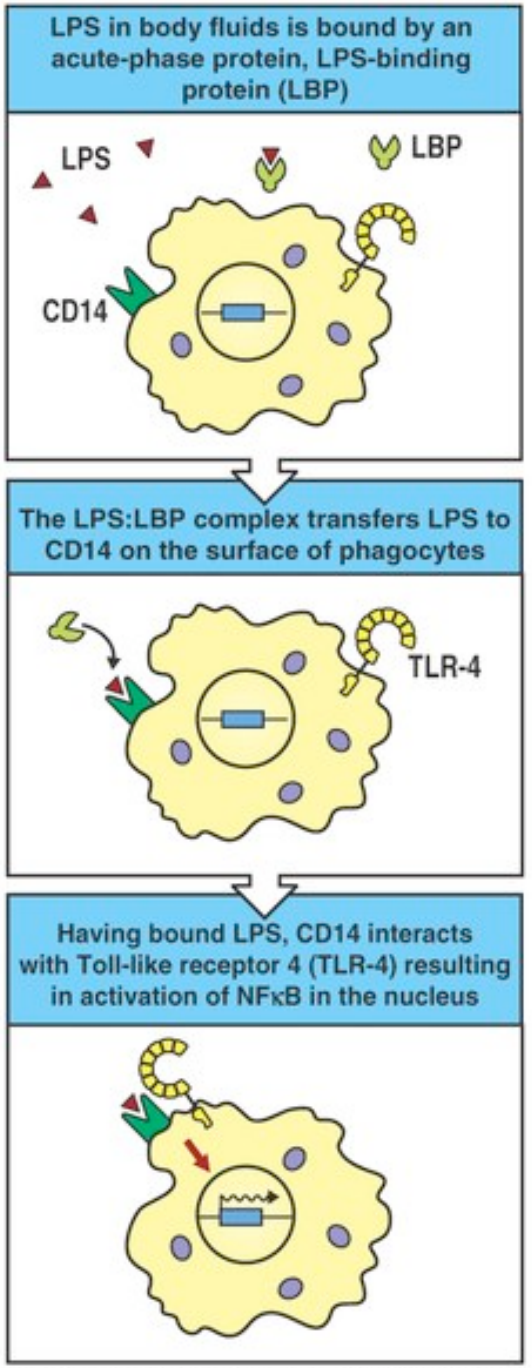


Figure 2-14 Immunobiology, 6/e. (© Garland Science 20

LPS stimulation of dendritic cells

- Resting to migrating cells
- Immature, in tissues:
  - Express many receptors
  - Highly phagocytic
  - Cannot stimulate T cells
- Mature, in lymph nodes:
  - No longer uptake Ag
  - Express costimulatory molecules
  - Activate T cells

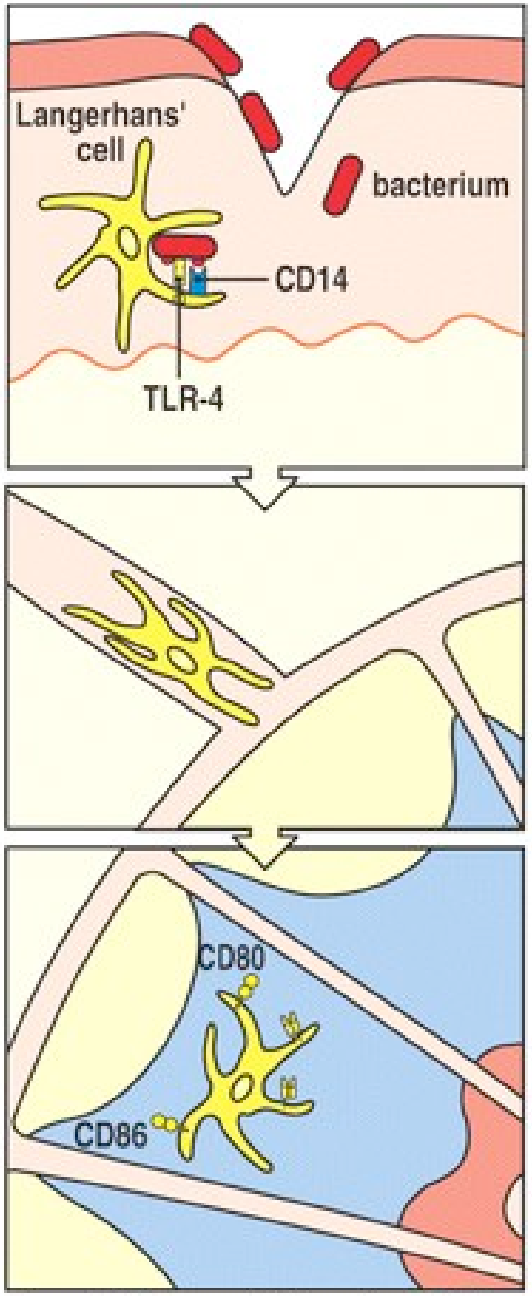


Figure 2-16 Immunobiology, 6/e. (© Garland Science 2005)

A conserved theme: Different Toll-like receptors (TLR) recognize various molecular patterns of pathogens

Innate immune recognition by Toll-like receptors	
Toll-like receptor	**Ligand**
TLR-1 dimer	Peptidoglycan Lipoproteins Lipoarabinomannan (mycobacteria) GPI (*T. cruzi*) Zymosan (yeast)
TLR-2/TLR-6 dimer	
TLR-3	dsRNA
TLR-4 dimer (plus CD14)	LPS (Gram-negative bacteria)
TLR-5	Flagellin
TLR-9	Unmethylated CpG DNA

Figure 2-12 Immunobiology, 6/e. (© Garland Science 2005)

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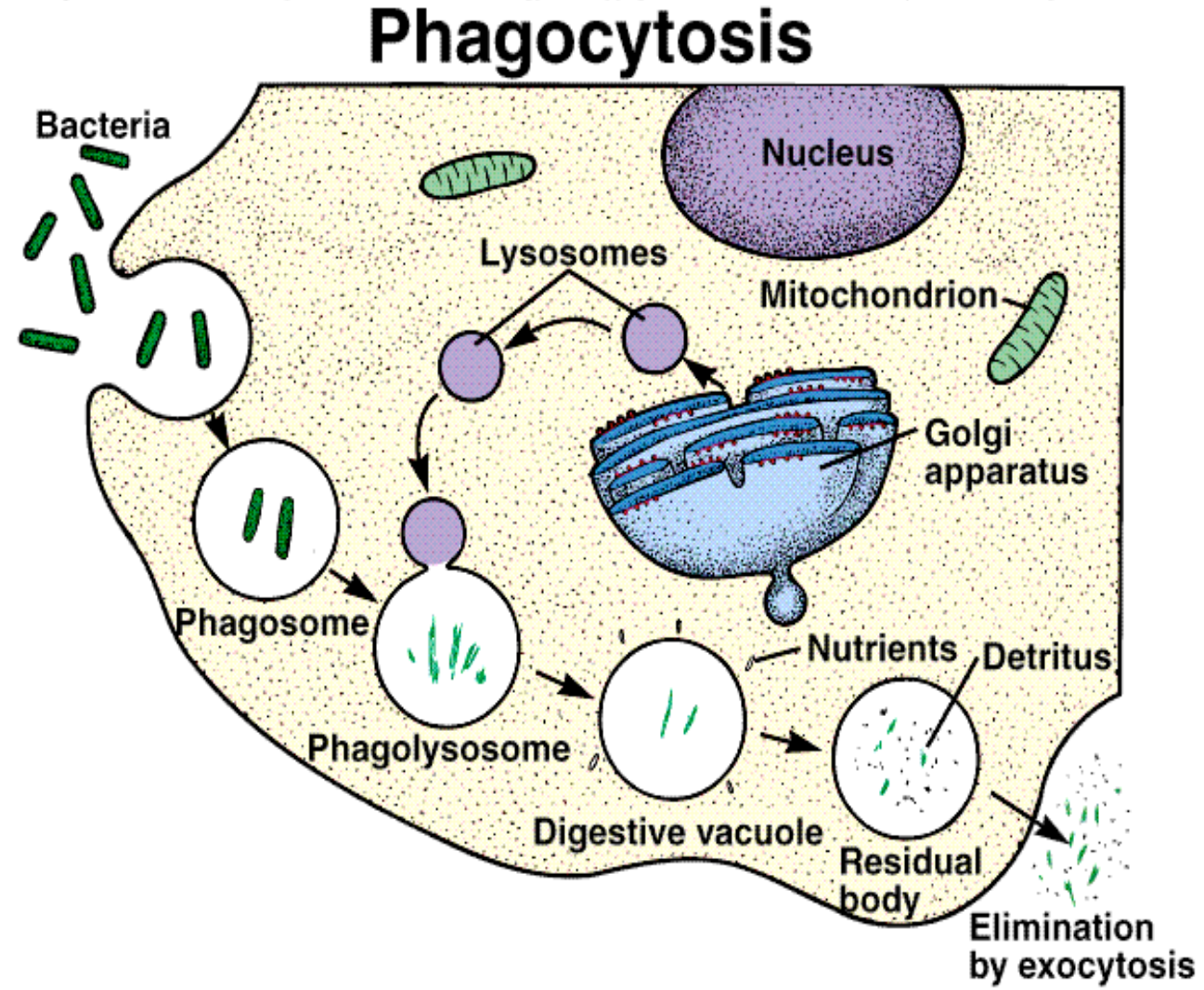
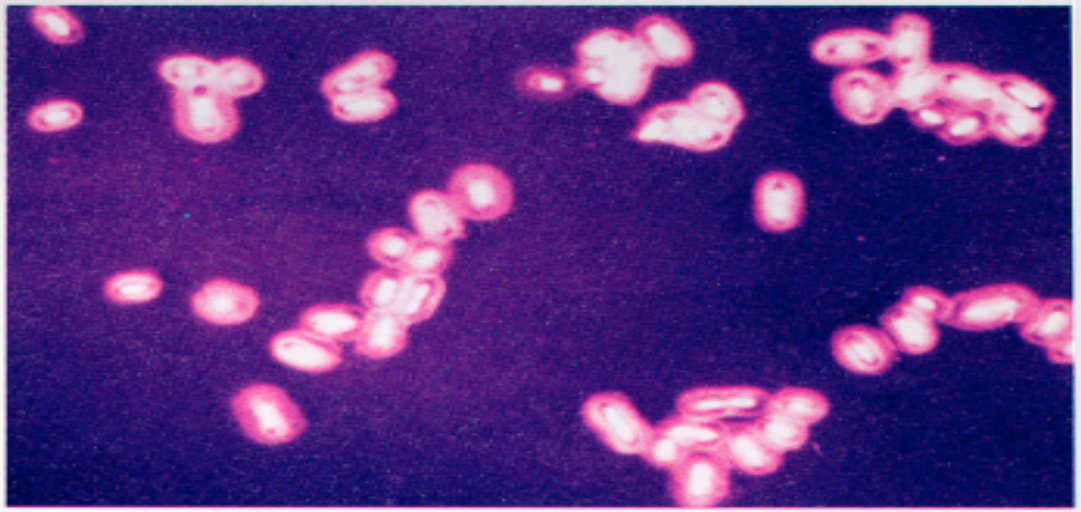


Pathogens work hard to evade phagocytosis!

Preventing engulfment: Capsule of *Klebsiella pneumoniae*

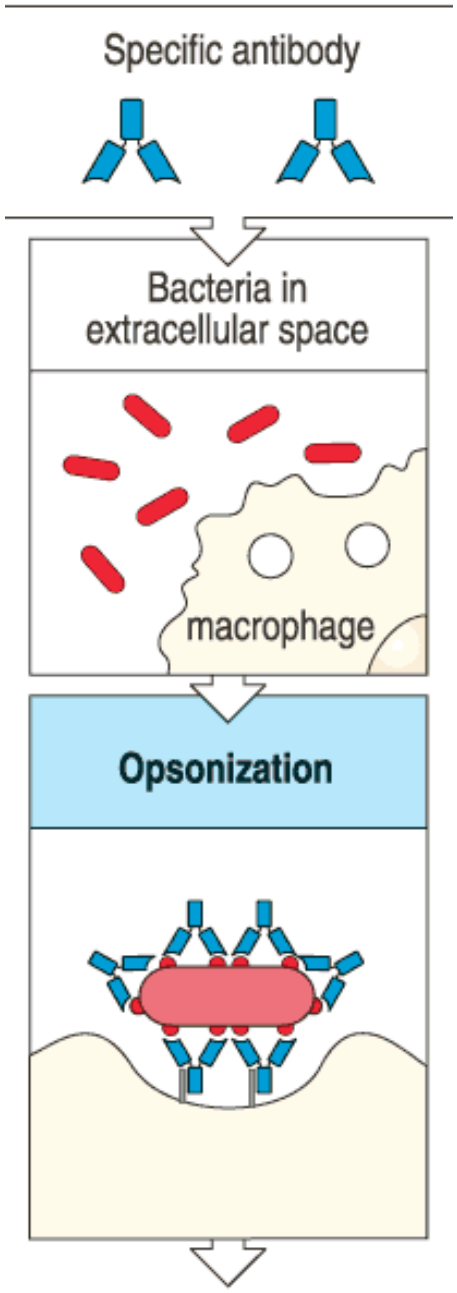


(a)

(b)

Figure 3.29 **Bacterial Capsules.** (*a*) *Klebsiella pneumoniae* with its capsule stained for observation in the light microscope (×1,500). (*b*) *Bacteroides* glycocalyx (gly), TEM (×71,250).

Inhibiting phagocytosis
via Fc receptor:
Protein A
of *Staphylococcus aureus*



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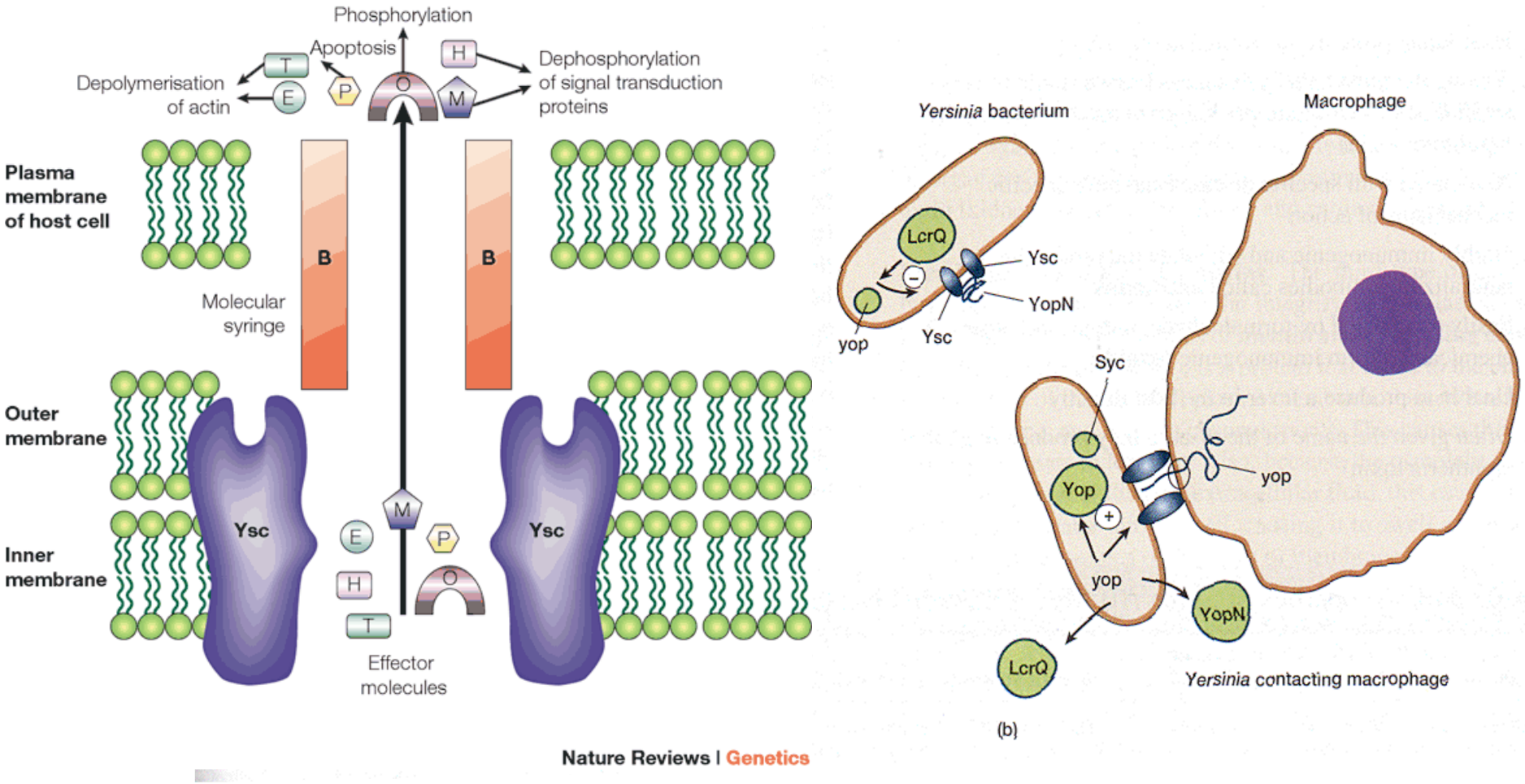
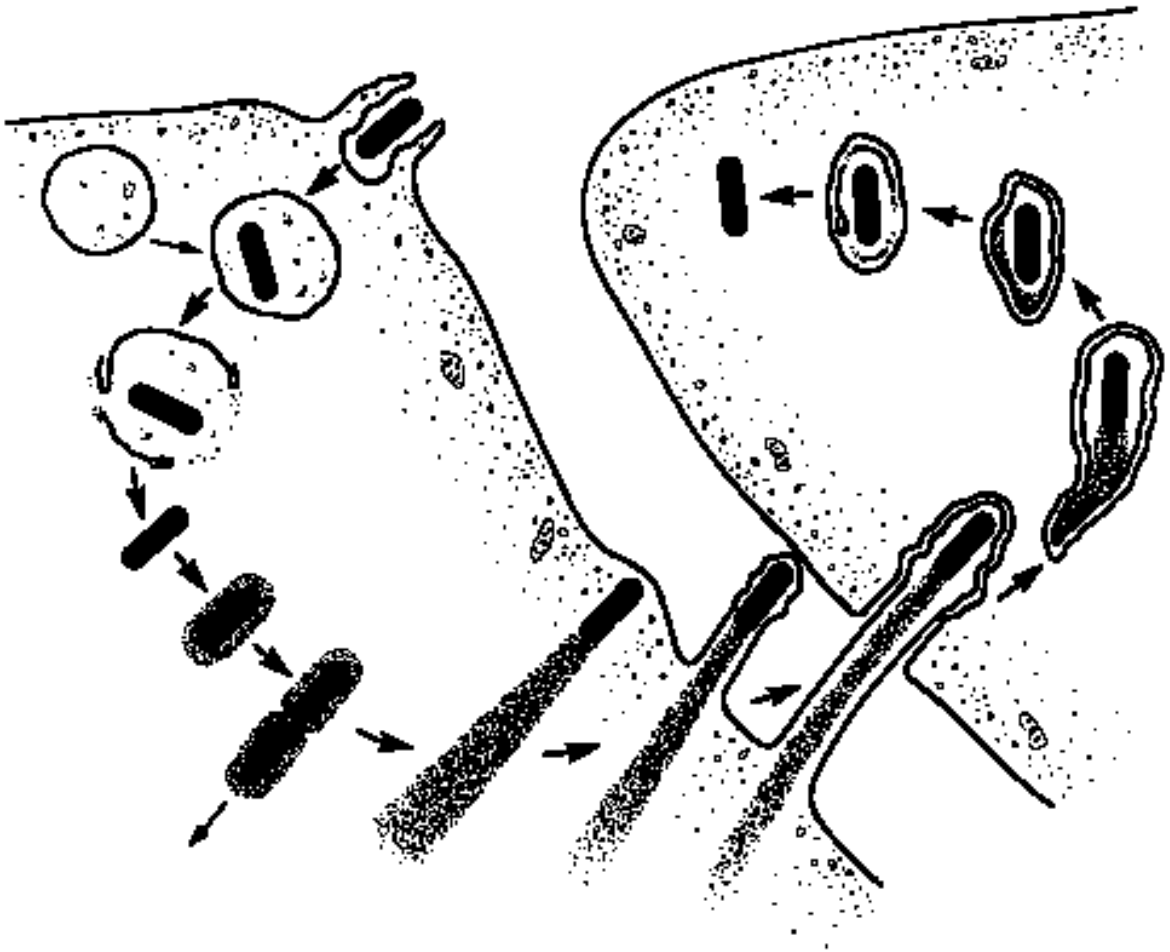
Preventing engulfment: Type III secretion of *Yersinia pestis*



Escape from the vacuole: *Listeria monocytogenes*



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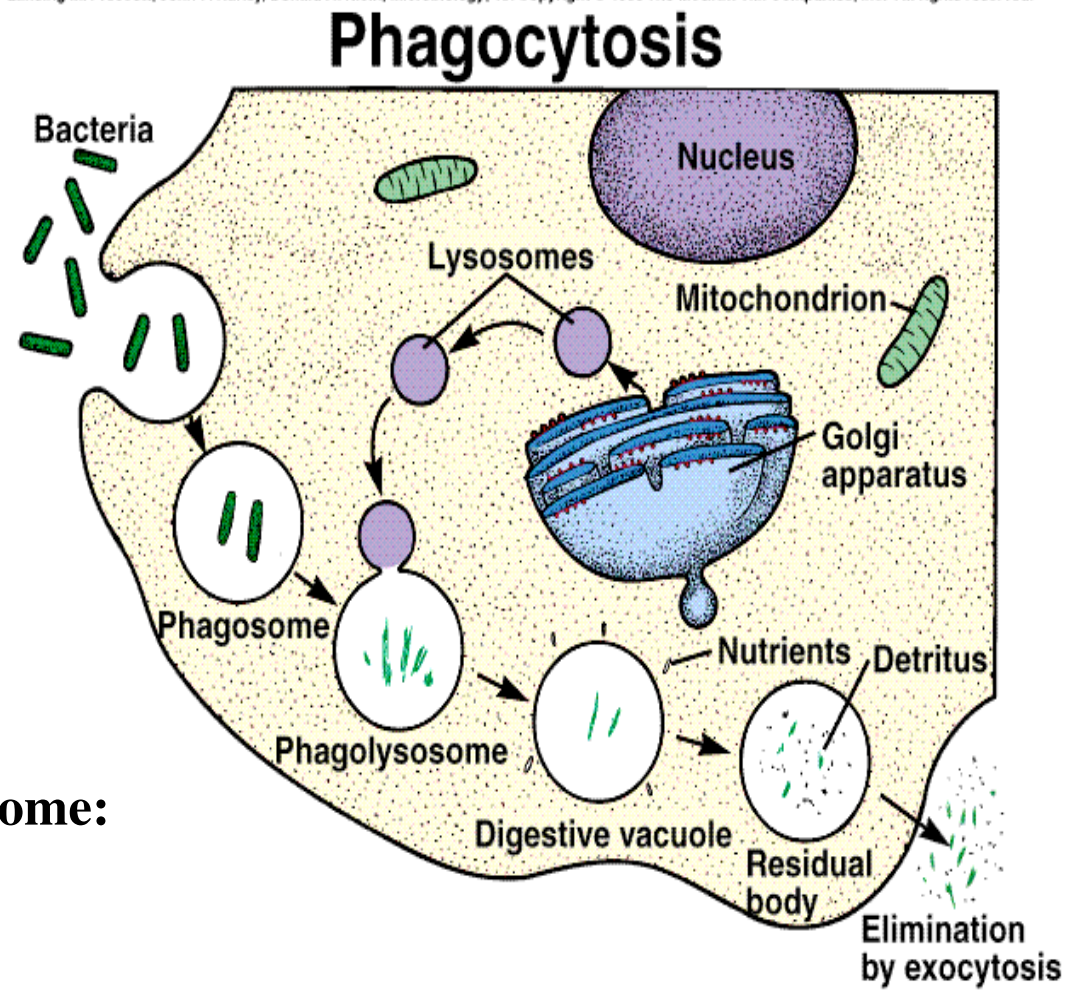


Prevent phagosome:lysosome fusion:
Legionella pneumophila
Mycobacterium tuberculosis

Survival in phagolysosome:
Mycobacterium leprae
Salmonella

Kill macrophage after engulfment:
Bacillus anthracis LF toxin

Inflammation

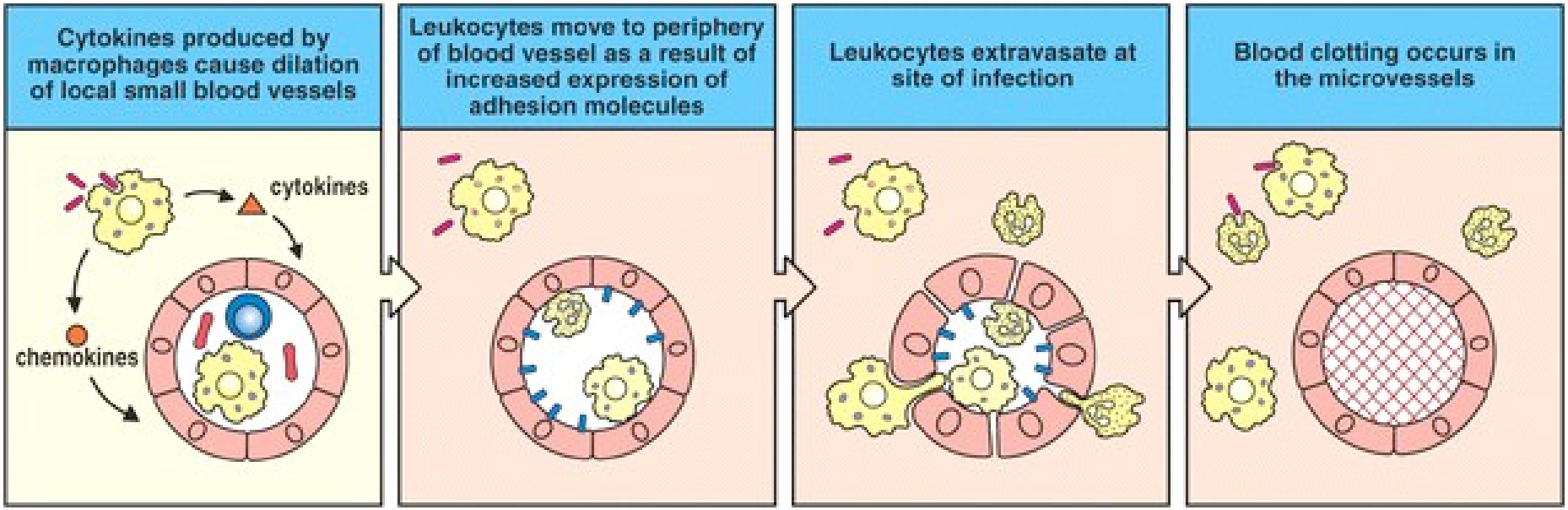


Figure 2-8 Immunobiology, 6/e. (© Garland Science 2005)

Cytokine properties

- Usually small ~25 kD
- Produced in response to an activating stimulus
- Function by binding to a specific receptor
- Usually soluble, but can be membrane associated
- Can work locally or at a distance

Main families of cytokines

- **Hematopoietins (Interleukins)**
- **Interferons (□, □, and □)**
- **TNF family (TNF-□)**
- **Chemokines (CXCL-8)**

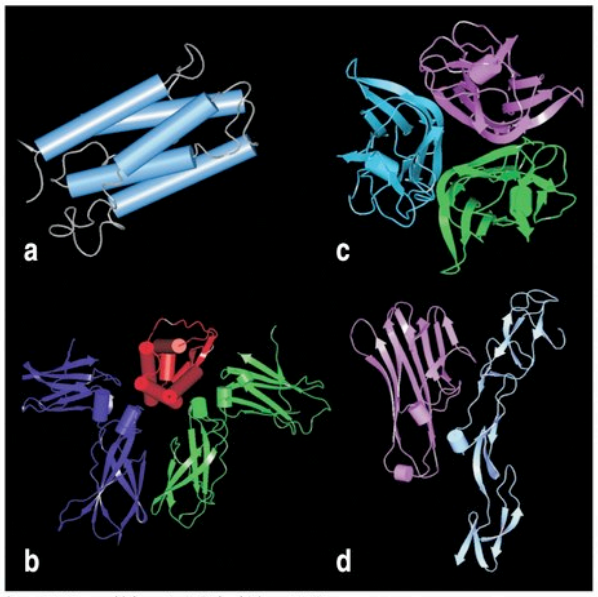


Figure 2-38 Immunobiology, 6/e. (© Garland Science 2005)

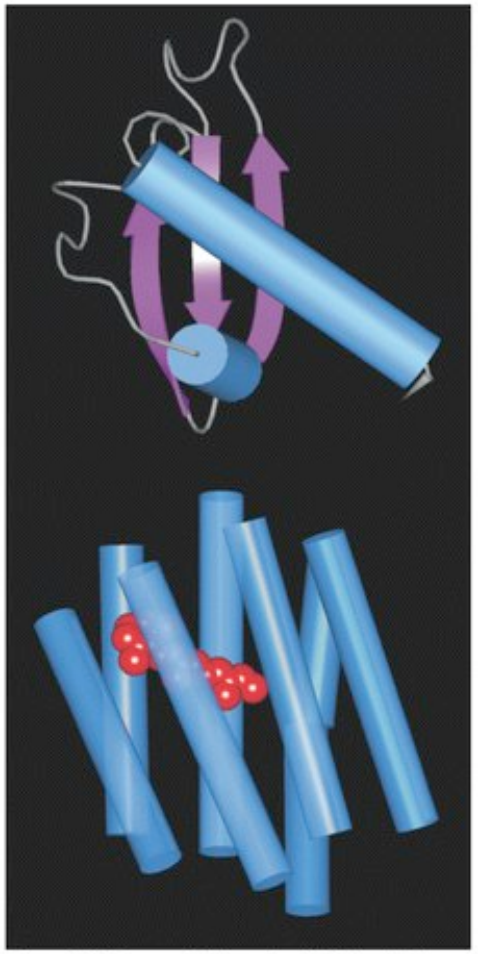


Figure 2-40 Immunobiology, 6/e. (© Garland Science 2005)

Activated M cytokines

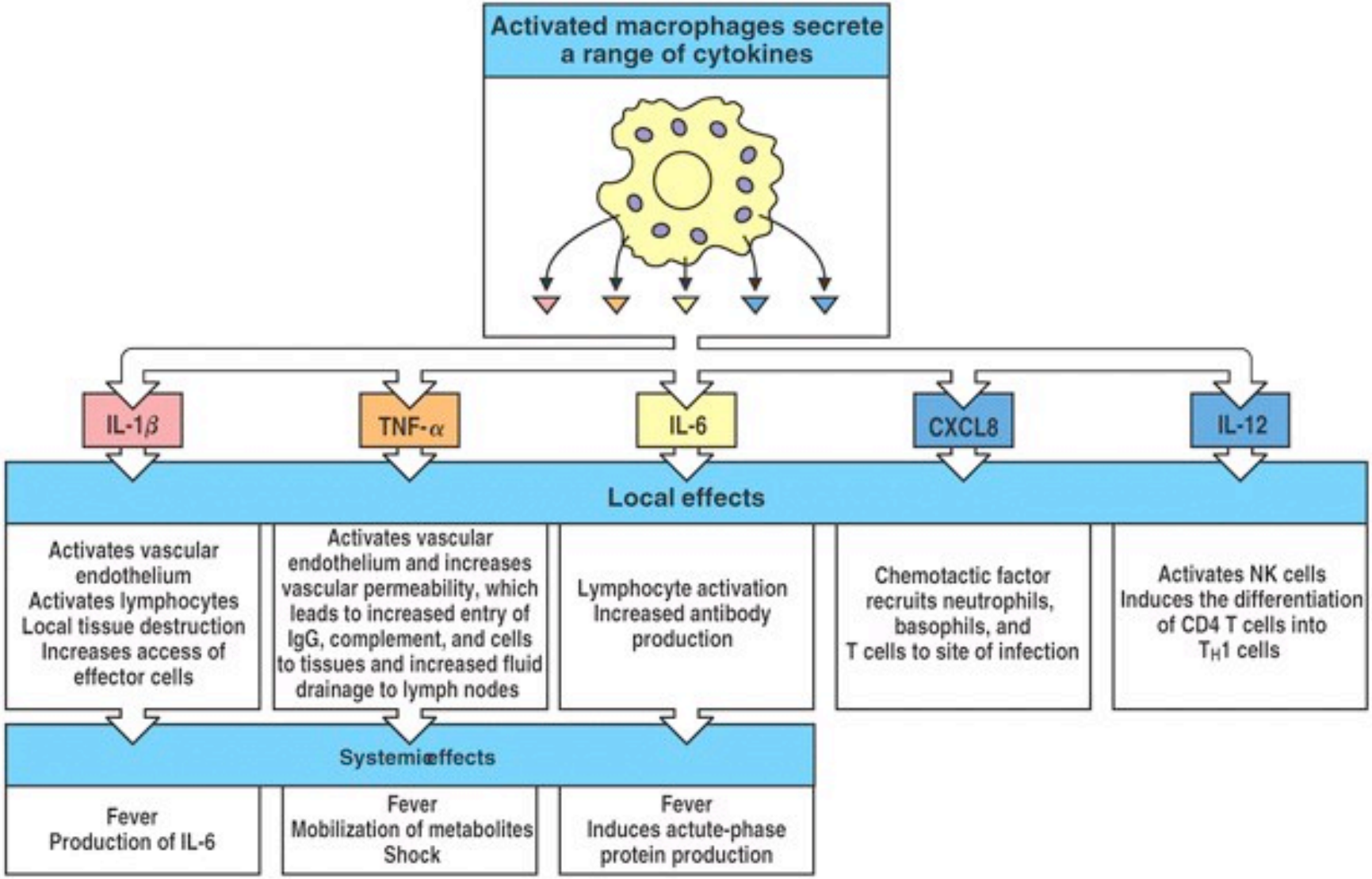
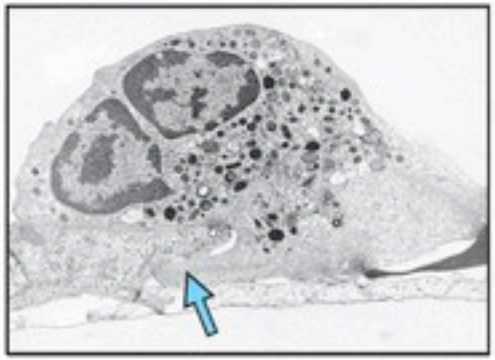
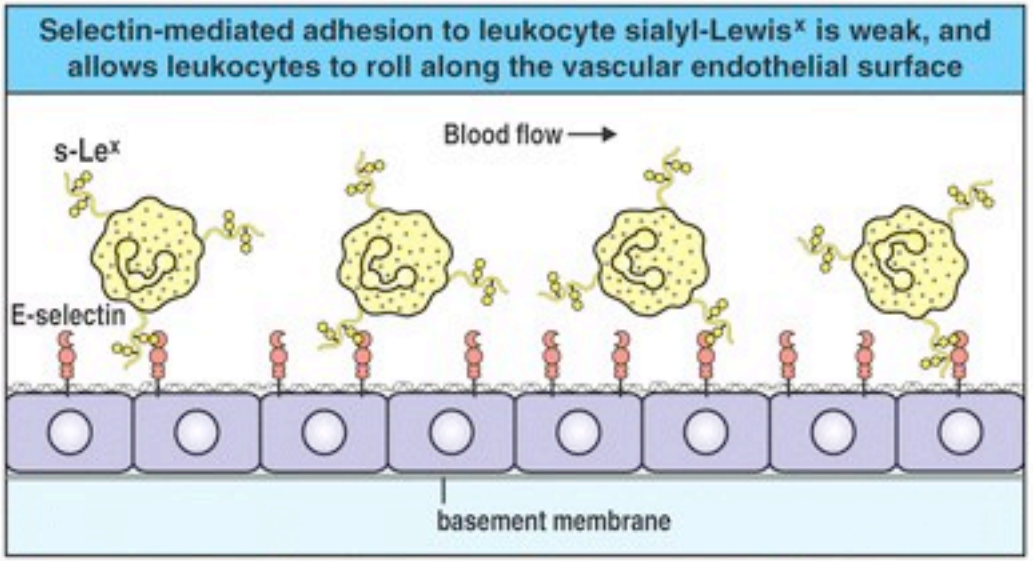


Figure 2-39 Immunobiology, 6/e. (© Garland Science 2005)

How to identify the site of infection





- Endothelium activation
  - Selectin binding to carbohydrates
  - ICAM binding to integrins
- Chemokine gradient

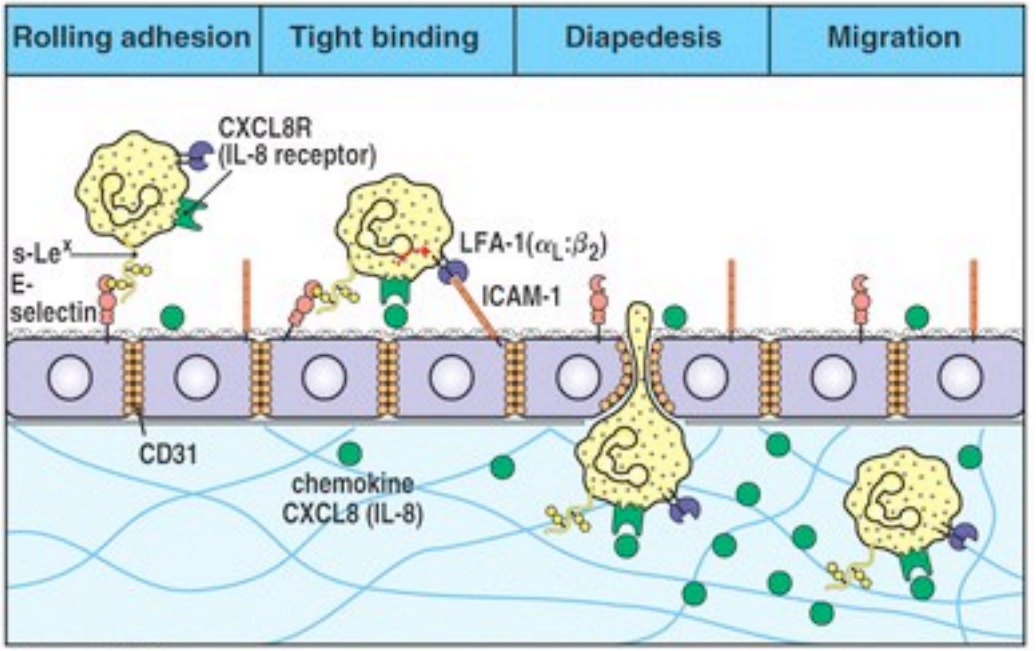


Figure 2-44 Immunobiology, 6/e. (© Garland Science 2005)

Selectins of endothelium bind to leukocyte surface carbohydrates

		Name	Tissue distribution	Ligand
Selectins	P-selectin	P-selectin (PADGEM, CD62P)	Activated endothelium and platelets	PSGL-1, sialyl-Lewis^x
Bind carbohydrates. Initiate leukocyte–endothelial interaction		E-selectin (ELAM-1, CD62E)	Activated endothelium	Sialyl-Lewis^x

Figure 2-42 part 1 of 3 Immunobiology, 6/e. (© Garland Science 2005)

Integrin:ICAM binding mediates higher affinity binding

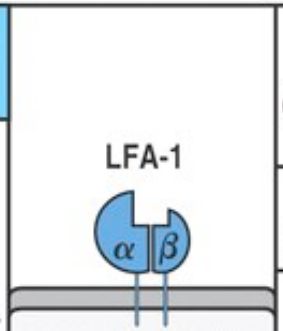
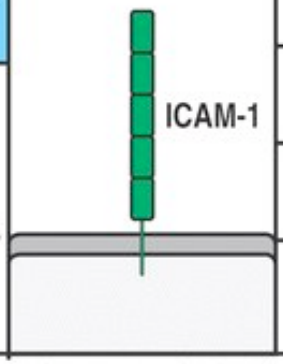
		Name	Tissue distribution	Ligand
Integrins		α_L:β_2 (LFA-1, CD11a/CD18)	Monocytes, T cells, macrophages, neutrophils, dendritic cells	ICAMs
Bind to cell-adhesion molecules and extracellular matrix. Strong adhesion		α_M:β_2 (CR3, Mac-1, CD11b/CD18)	Neutrophils, monocytes, macrophages	ICAM-1, iC3b, fibrinogen
		α_X:β_2 (CR4, p150.95, CD11c/CD18)	Dendritic cells, macrophages, neutrophils	iC3b
		α_5:β_1 (VLA-5, CD49d/CD29)	Monocytes, macrophages	Fibronectin

Figure 2-42 part 2 of 3 Immunobiology, 6/e. (© Garland Science 2005)

		Name	Tissue distribution	Ligand
Immunoglobulin superfamily		ICAM-1 (CD54)	Activated endothelium	LFA-1, Mac1
Various roles in cell adhesion. Ligand for integrins		ICAM-2 (CD102)	Resting endothelium, dendritic cells	LFA-1
		VCAM-1 (CD106)	Activated endothelium	VLA-4
		PECAM (CD31)	Activated leukocytes, endothelial cell–cell junctions	CD31

Integrin:ICAM tight binding allows extravasation

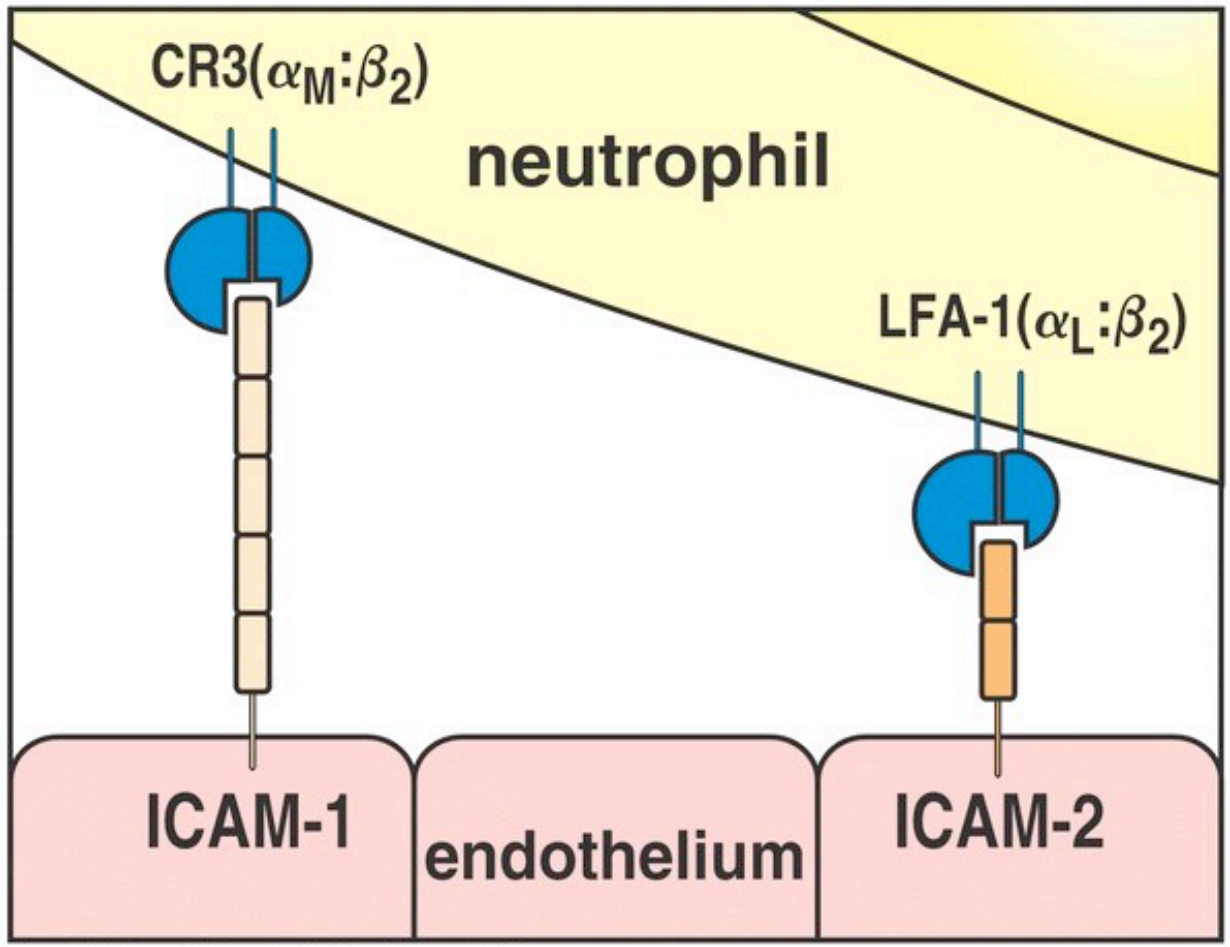
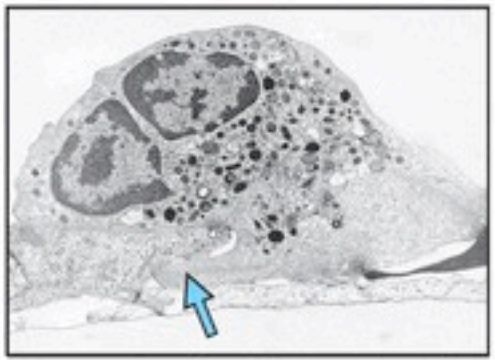


Figure 2-43 Immunobiology, 6/e. (© Garland Science 2005)



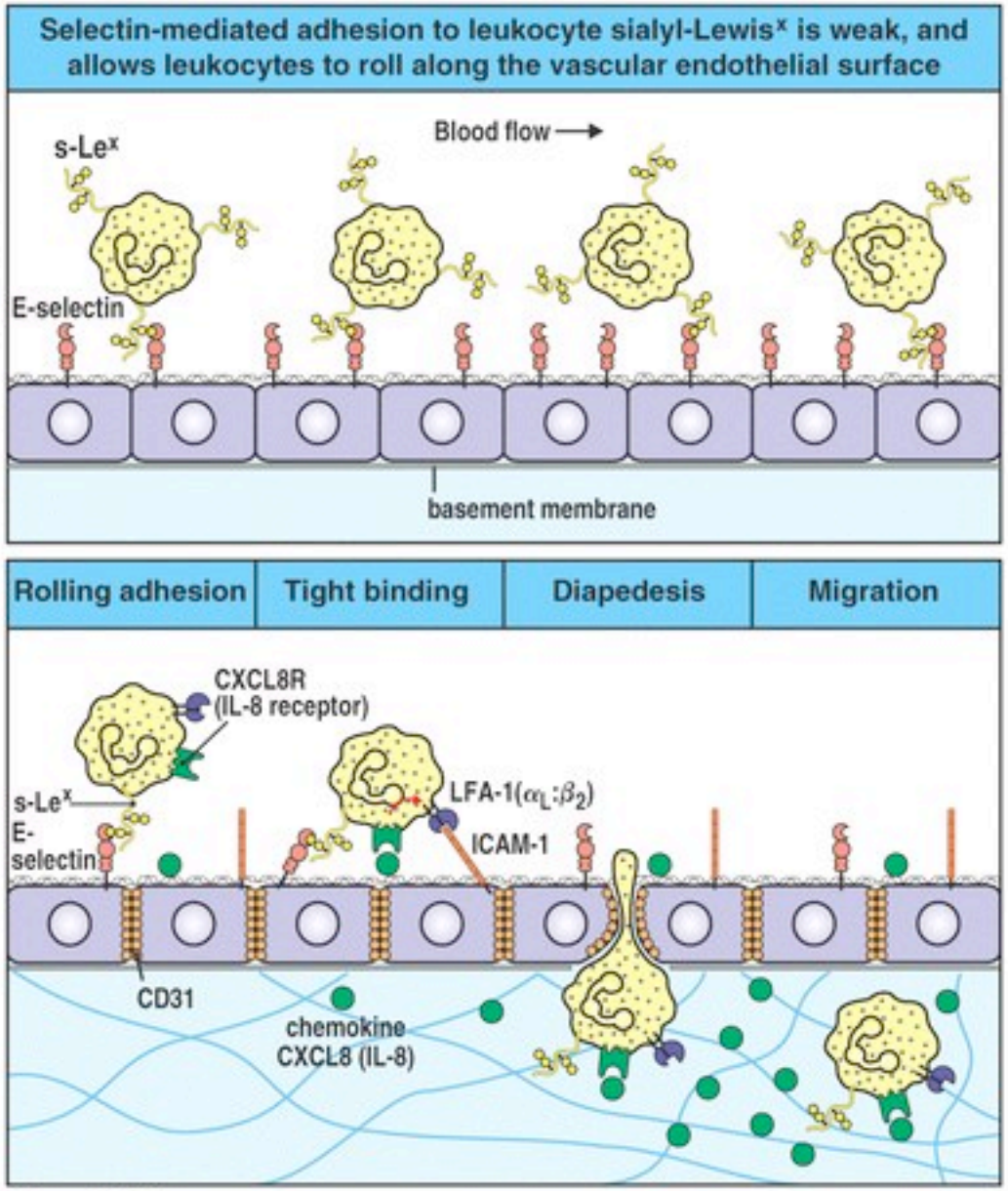


Figure 2-44 Immunobiology, 6/e. (© Garland Science 2005)

Similar proccesses mediate:

- Naïve T/B cell entry into lymphatic tissue from blood
- Homing of lymphocytes to site of infection at later time points

The good and the bad of TNF-□:

Inflammation vs. shock

Inflammation

Endotoxic shock

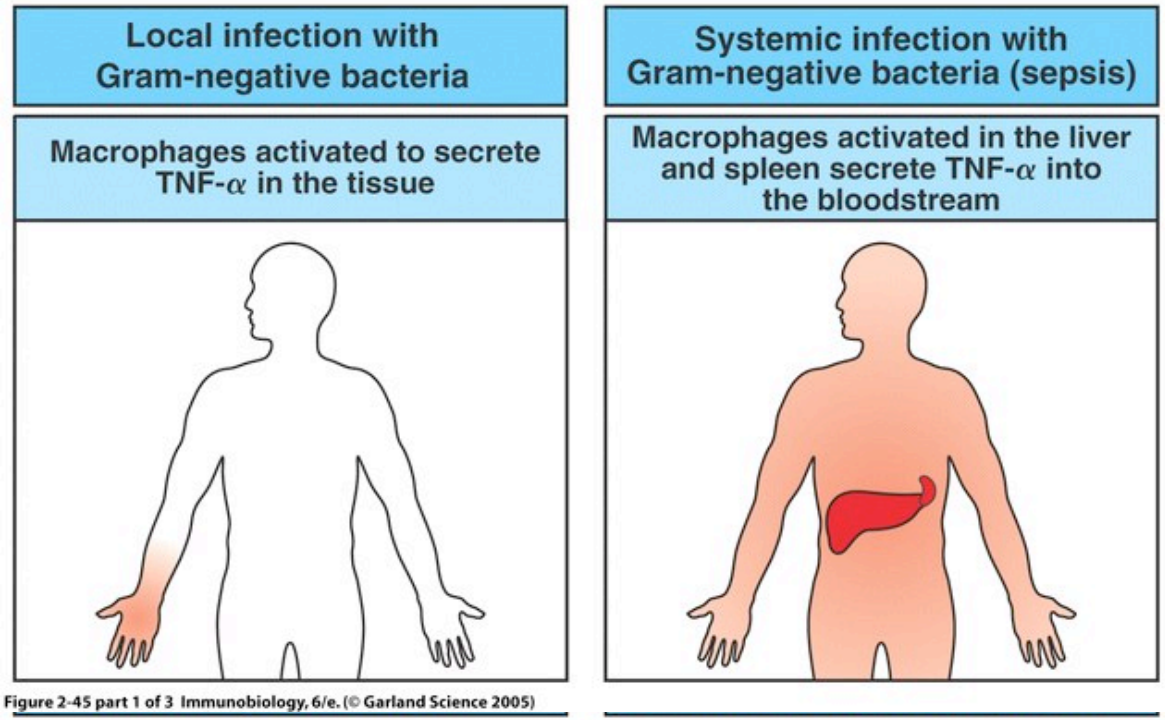


Figure 2-45 part 1 of 3 Immunobiology, 6/e. (© Garland Science 2005)

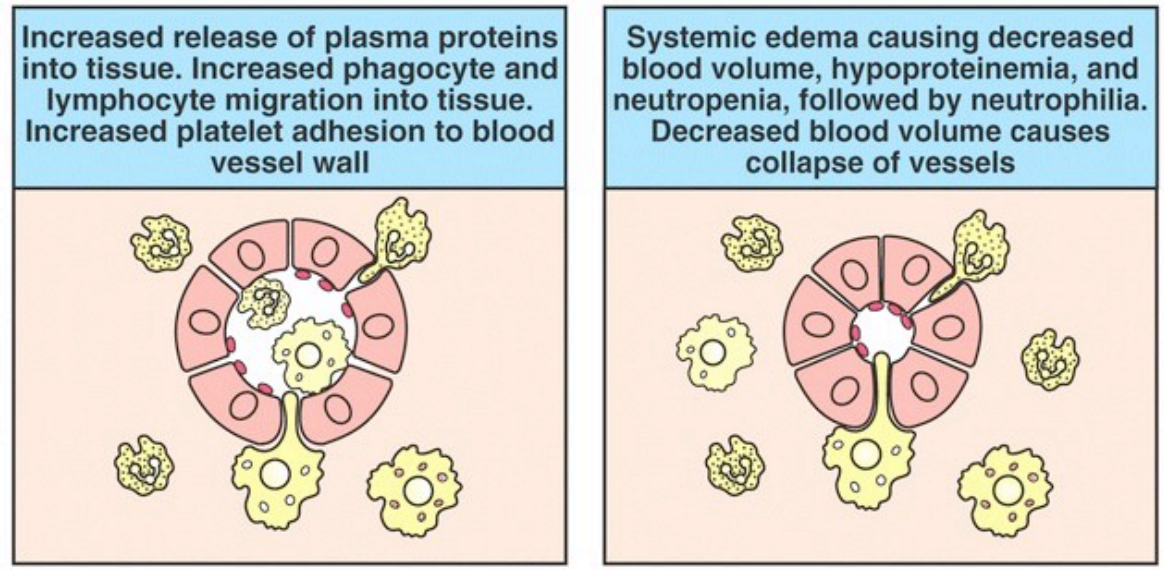


Figure 2-45 part 2 of 3 Immunobiology, 6/e. (© Garland Science 2005)

Inflammation Endotoxic shock

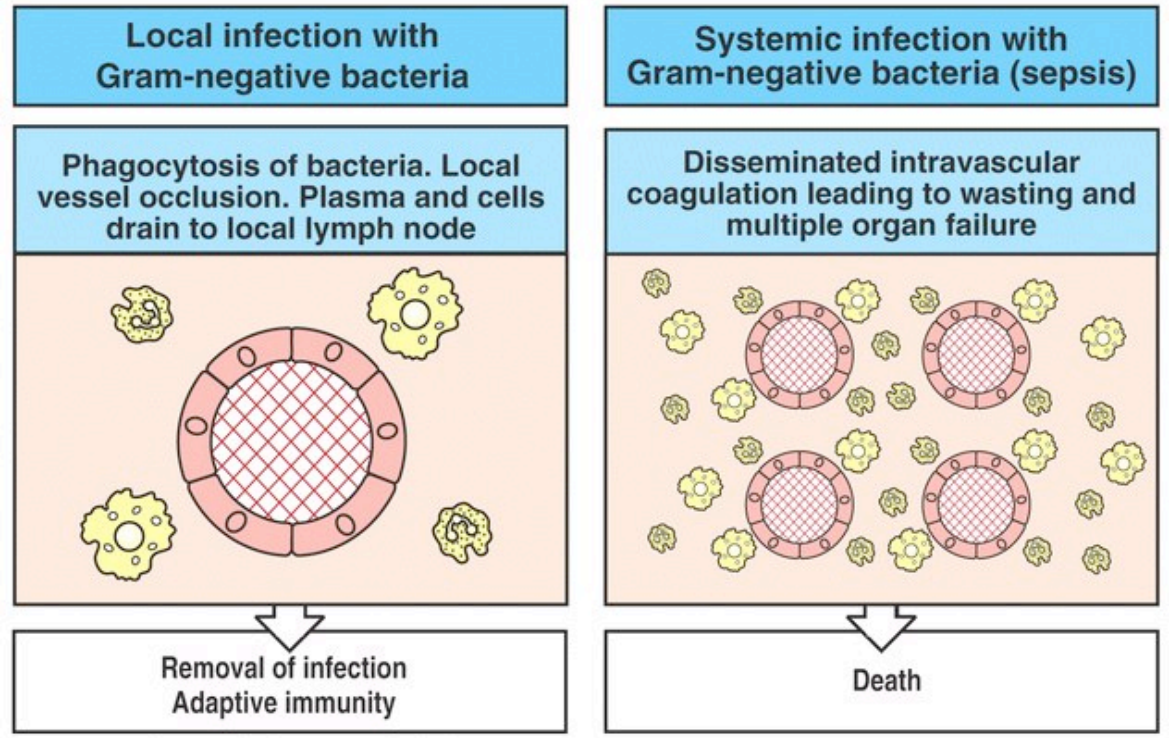


Figure 2-45 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)

Activated M cytokines

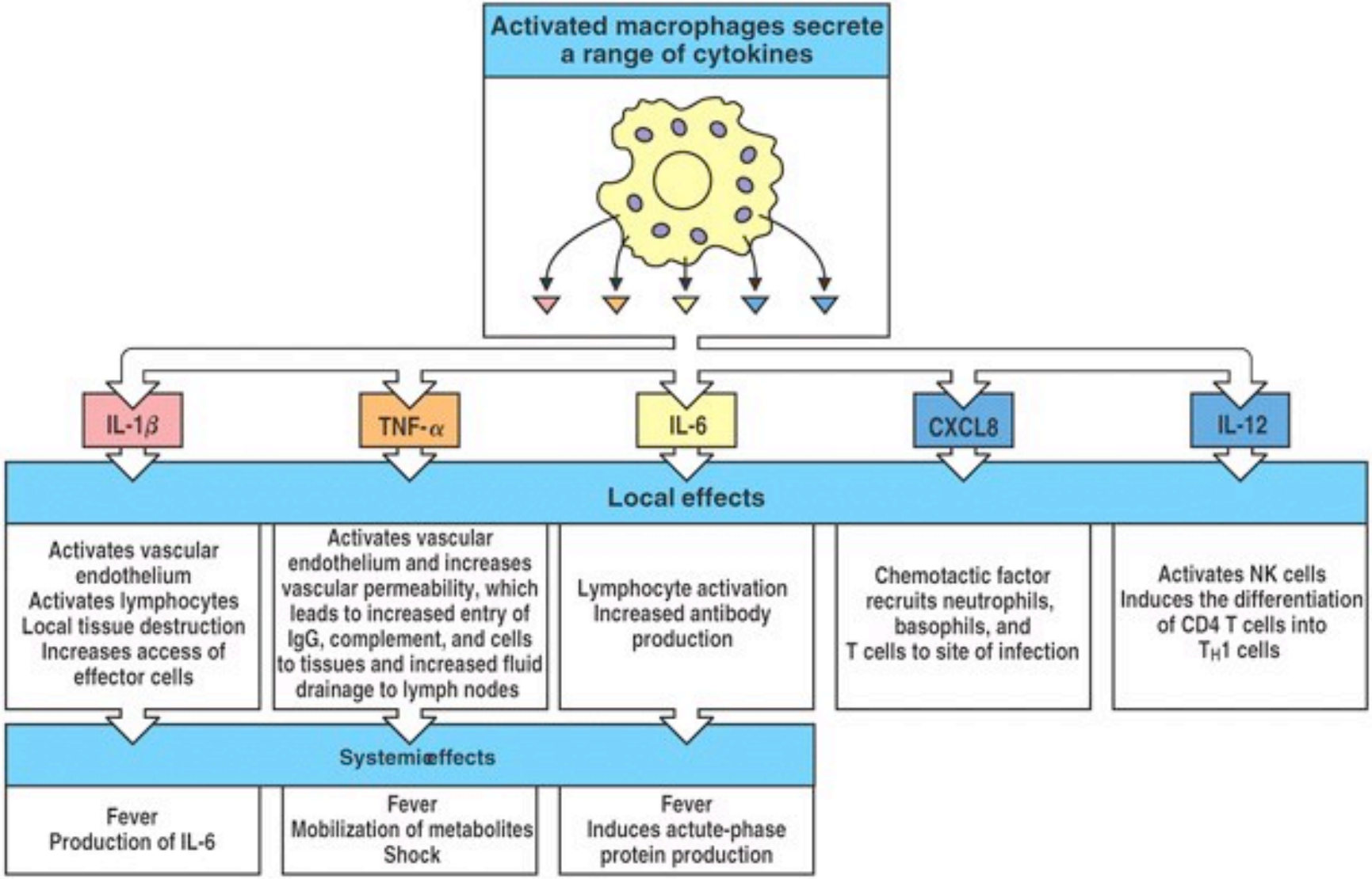


Figure 2-39 Immunobiology, 6/e. (© Garland Science 2005)

Complement pathways

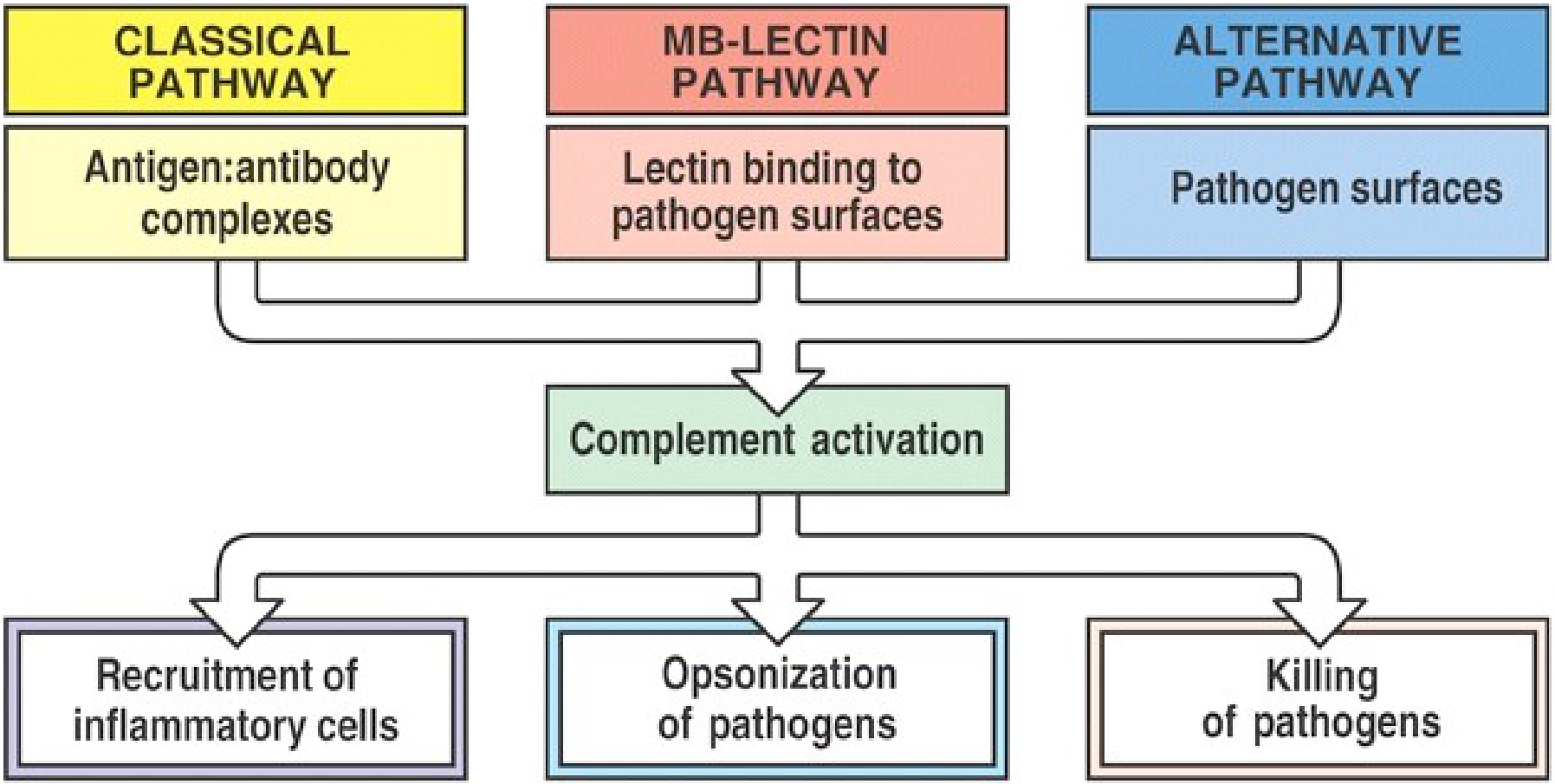


Figure 2-18 Immunobiology, 6/e. (© Garland Science 2005)

All roads lead to C3 convertase

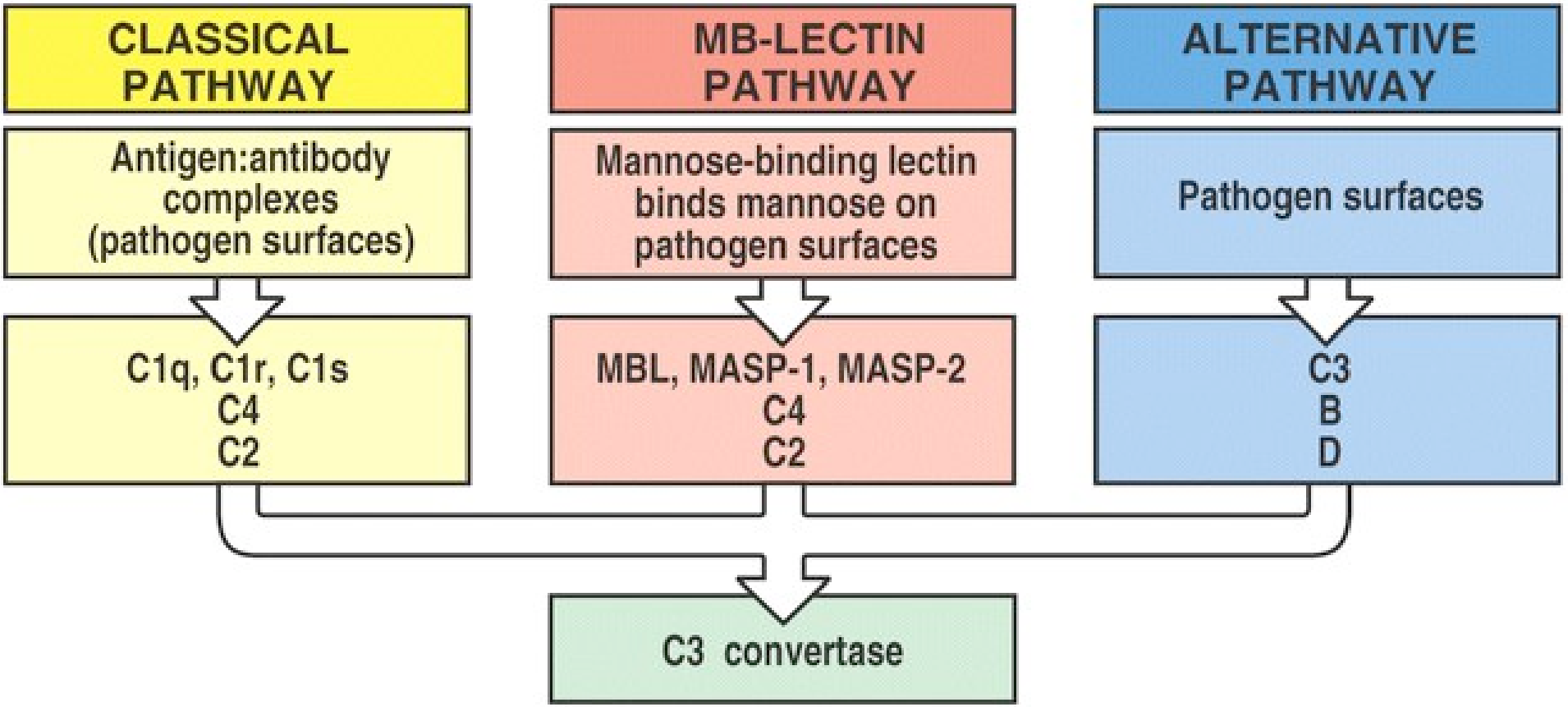


Figure 2-19 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

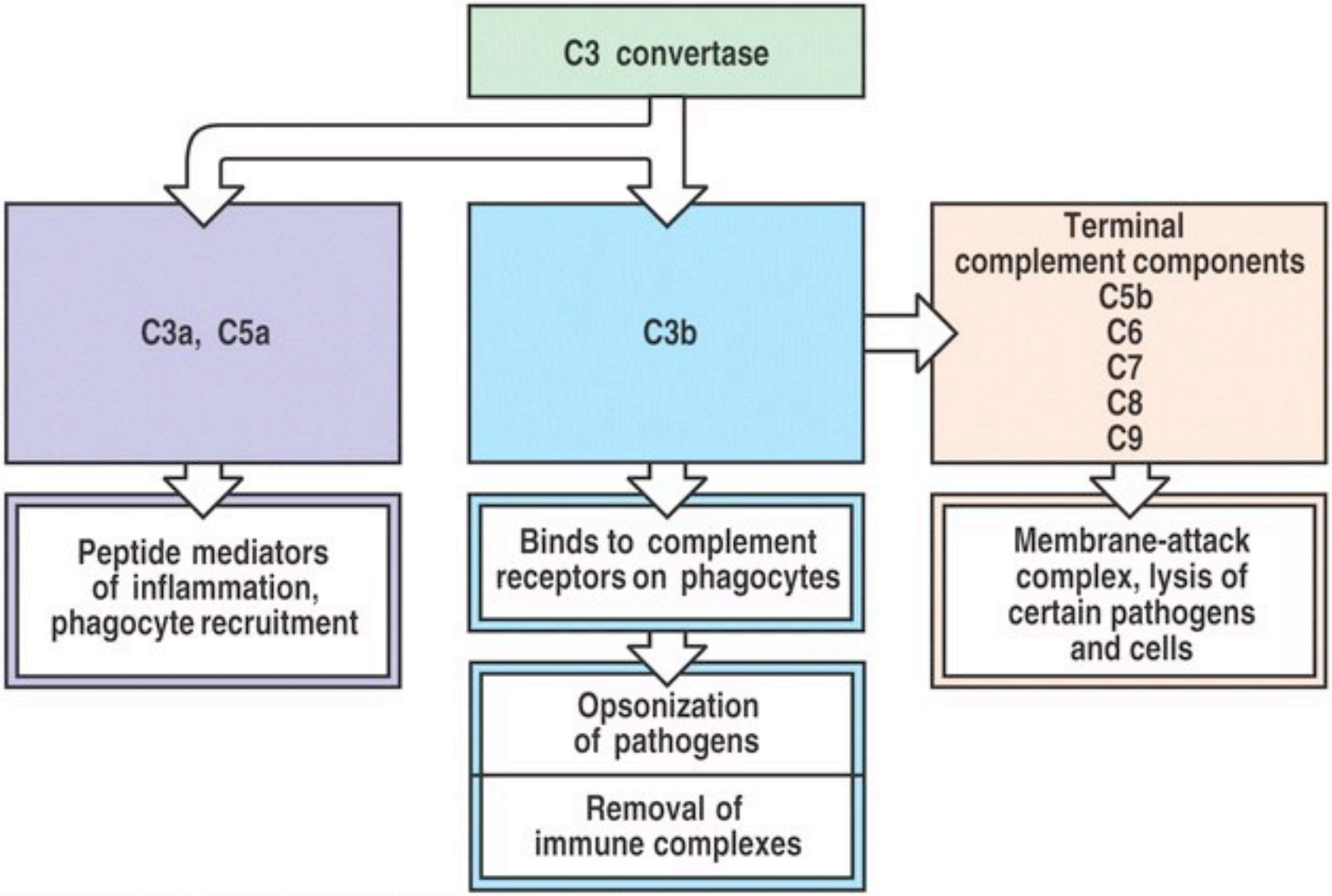


Figure 2-19 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Complement proteins

Functional protein classes in the complement system	
Binding to antigen:antibody complexes and pathogen surfaces	C1q
Binding to mannose on bacteria	MBL
Activating enzymes	C1r C1s C2b Bb D MASP-1 MASP-2
Membrane-binding proteins and opsonins	C4b C3b
Peptide mediators of inflammation	C5a C3a C4a

Functional protein classes in the complement system	
Membrane-attack proteins	C5b C6 C7 C8 C9
Complement receptors	CR1 CR2 CR3 CR4 C1qR
Complement-regulatory proteins	C1INH C4bp CR1 MCP DAF H I P CD59

Figure 2-20 Immunobiology, 6/e. (© Garland Science 2005)

C1q

- Initiates classical pathway
- Binds to Ab (Fc portion)
- Only binds to Ab bound to pathogen surface

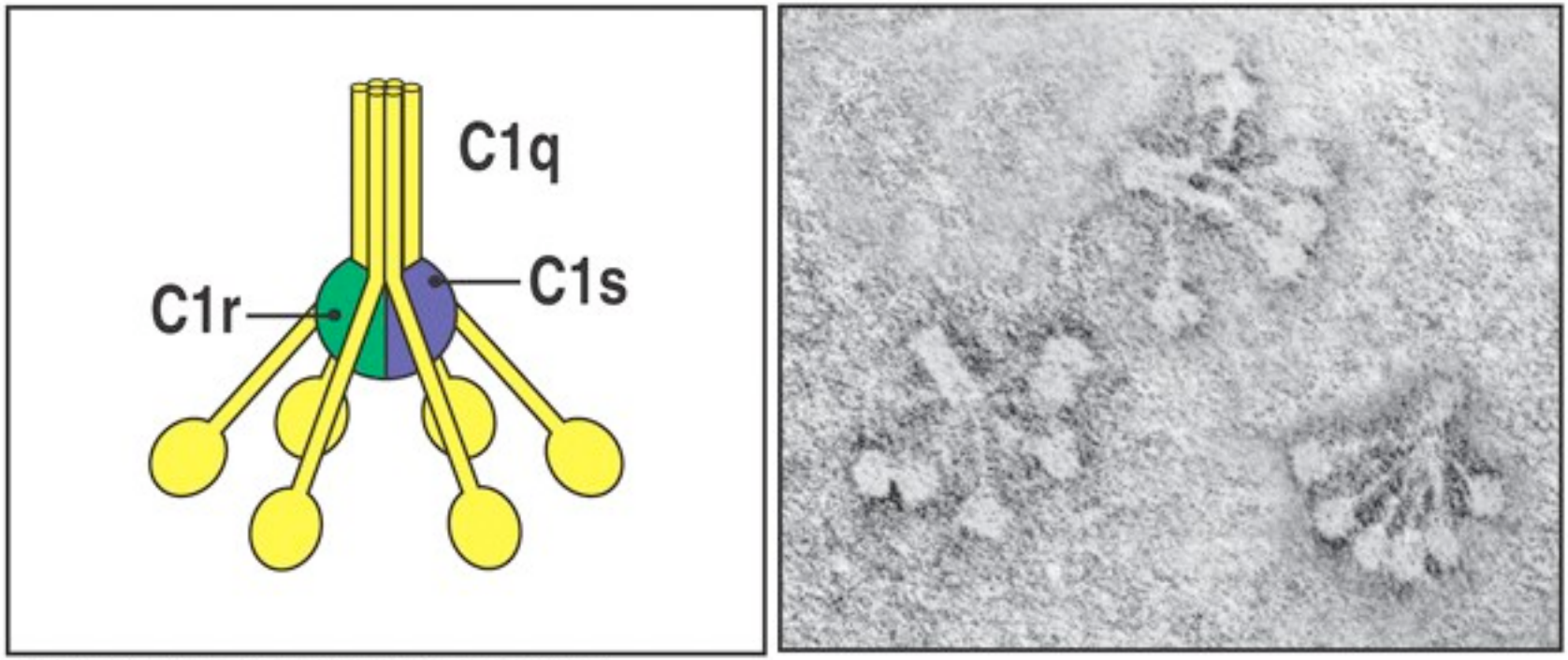


Figure 2-21 Immunobiology, 6/e. (© Garland Science 2005)

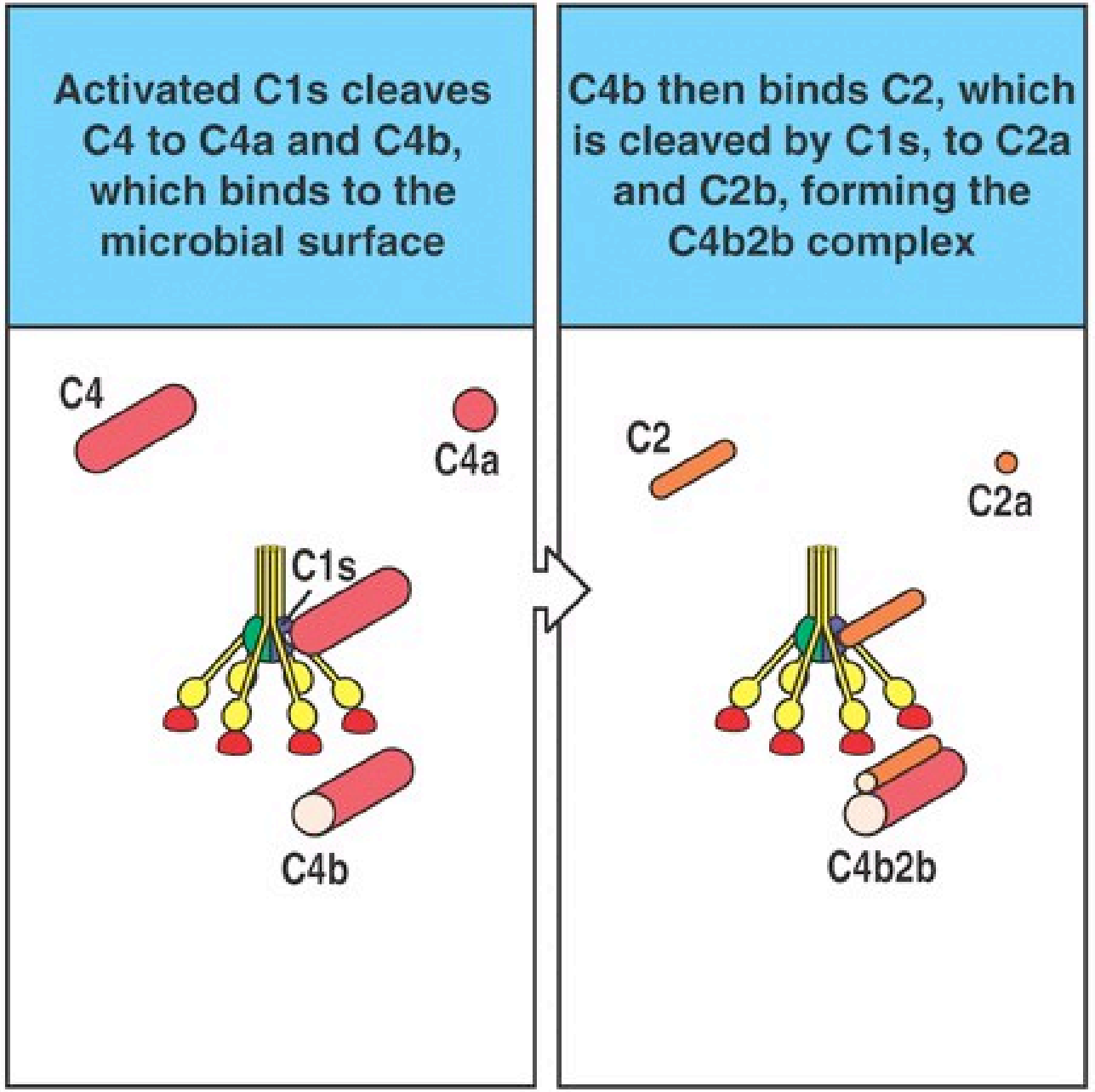


Figure 2-22 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

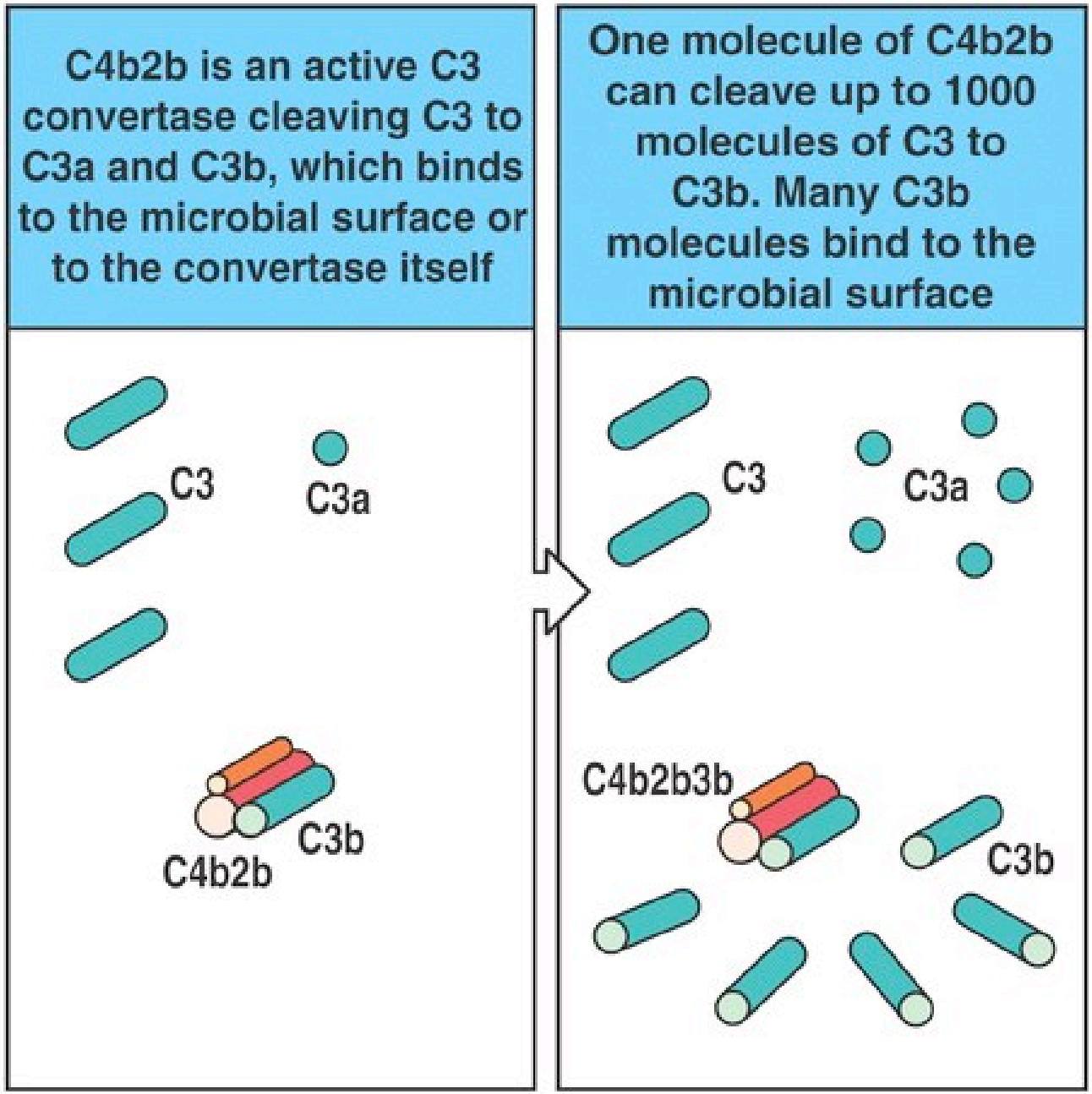


Figure 2-22 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

IL-6 and acute phase proteins

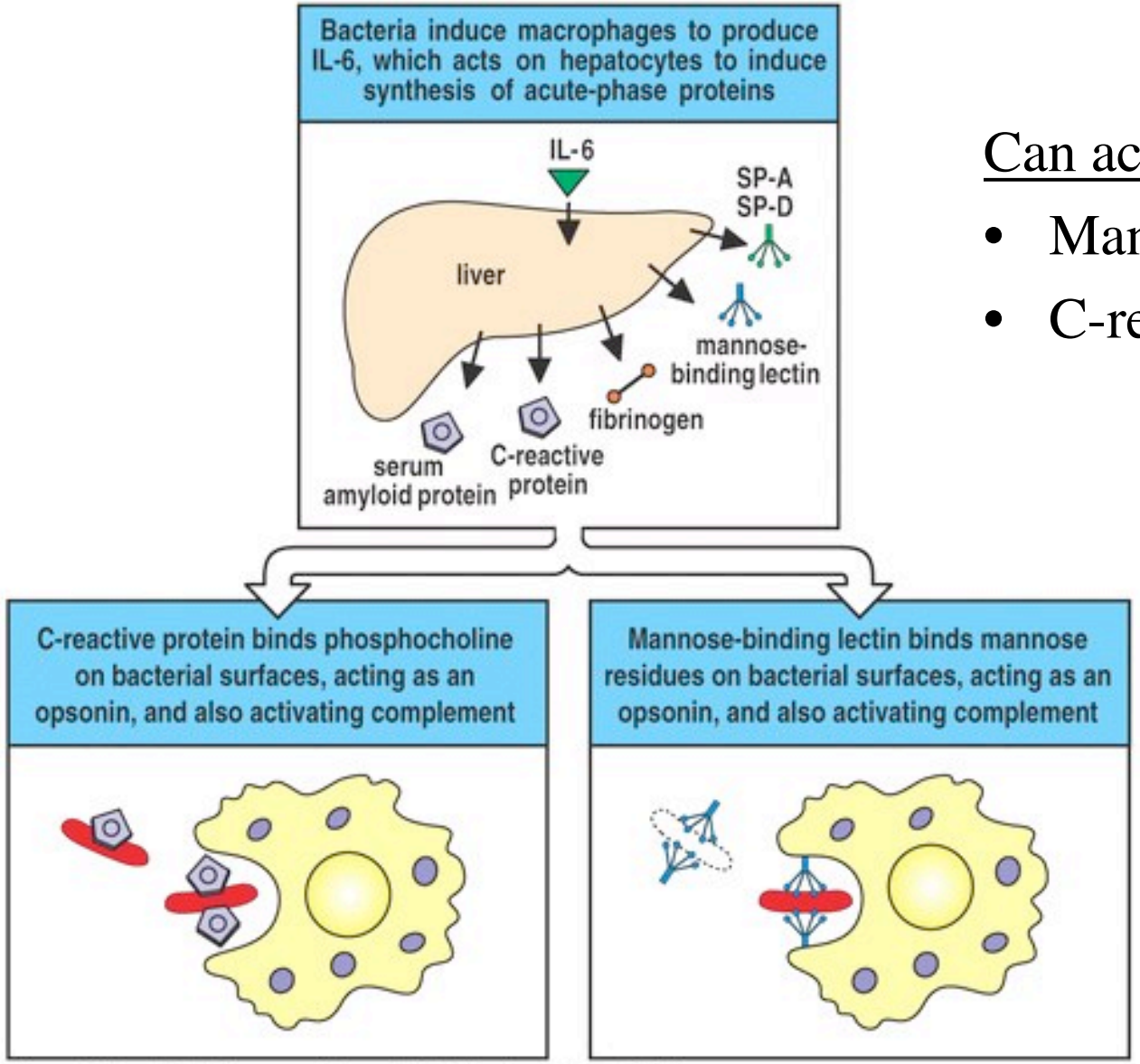


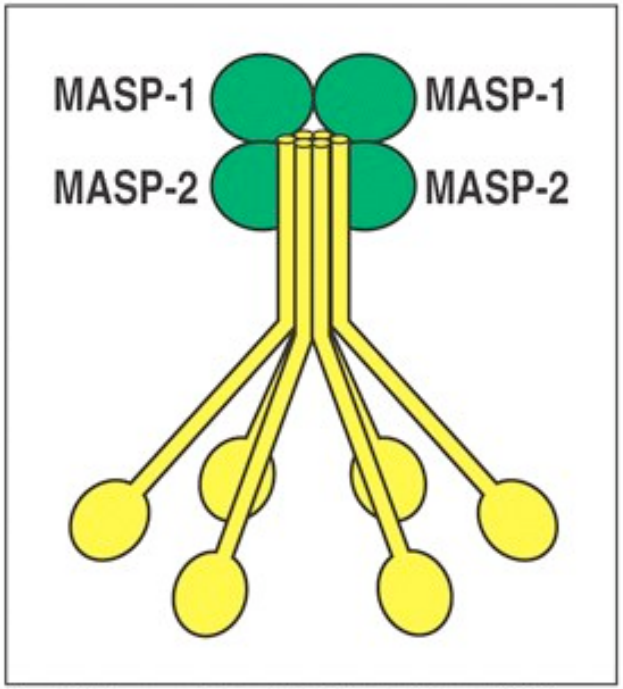
Figure 2-47 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

<u>Can activate complement</u>

- Mannan-binding lectin
- C-reactive protein

MB-Lectin pathway

- Mannan binding lectin binds to mannose
- MASP-1,-2 bind to bound MBL
- Mimics C1q
- Cleavage of C2 and C4 leads to C3 convertase



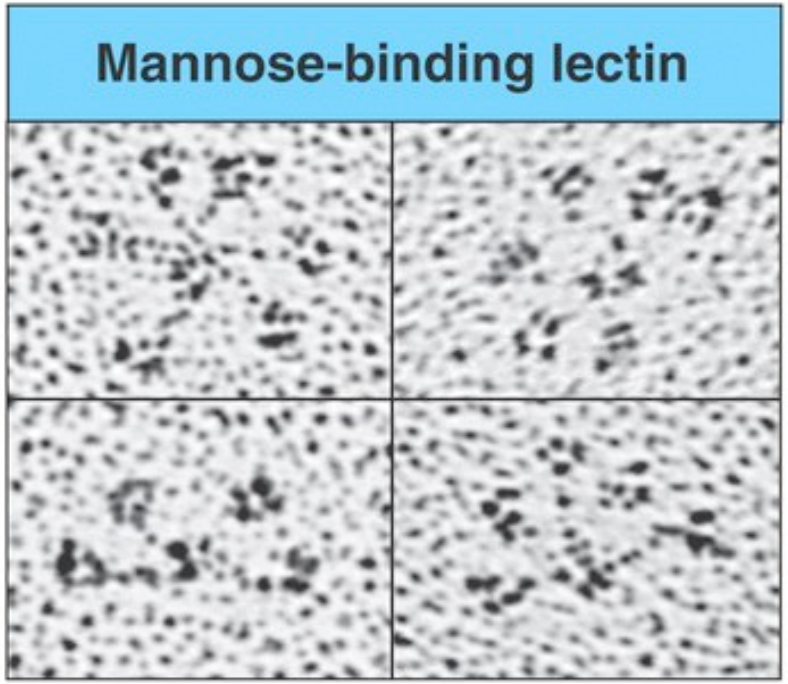


Figure 2-24 Immunobiology, 6/e. (© Garland Science 2005)

Alternative Pathway

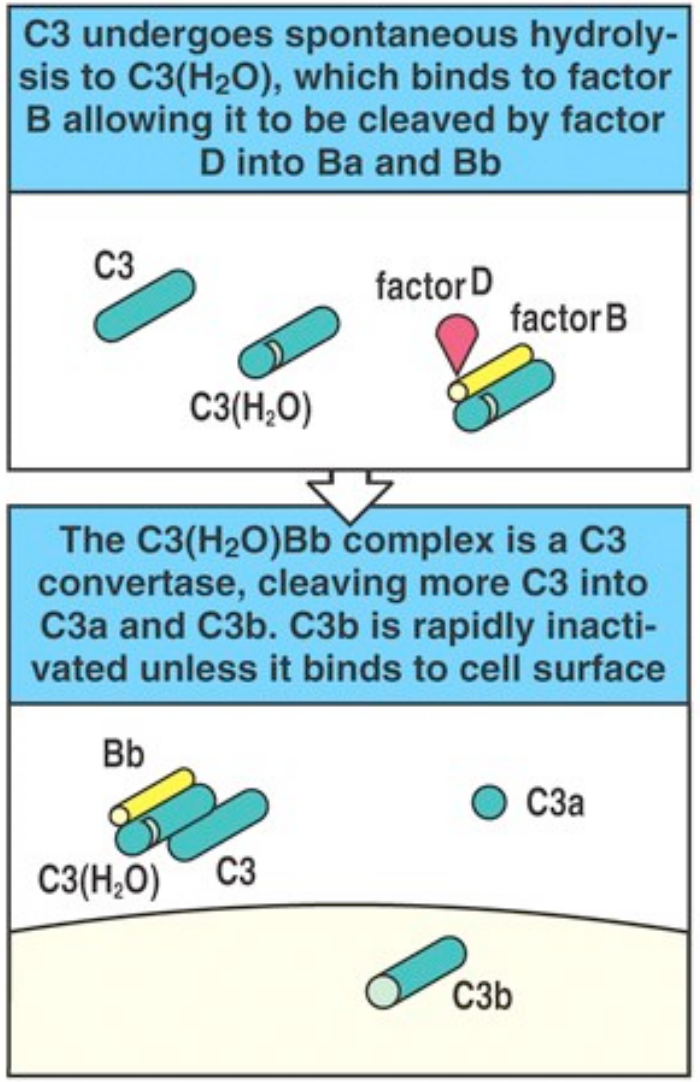


Figure 2-26 part 1 of 3 Immunobiology, 6/e. (© Garland Science 2005)

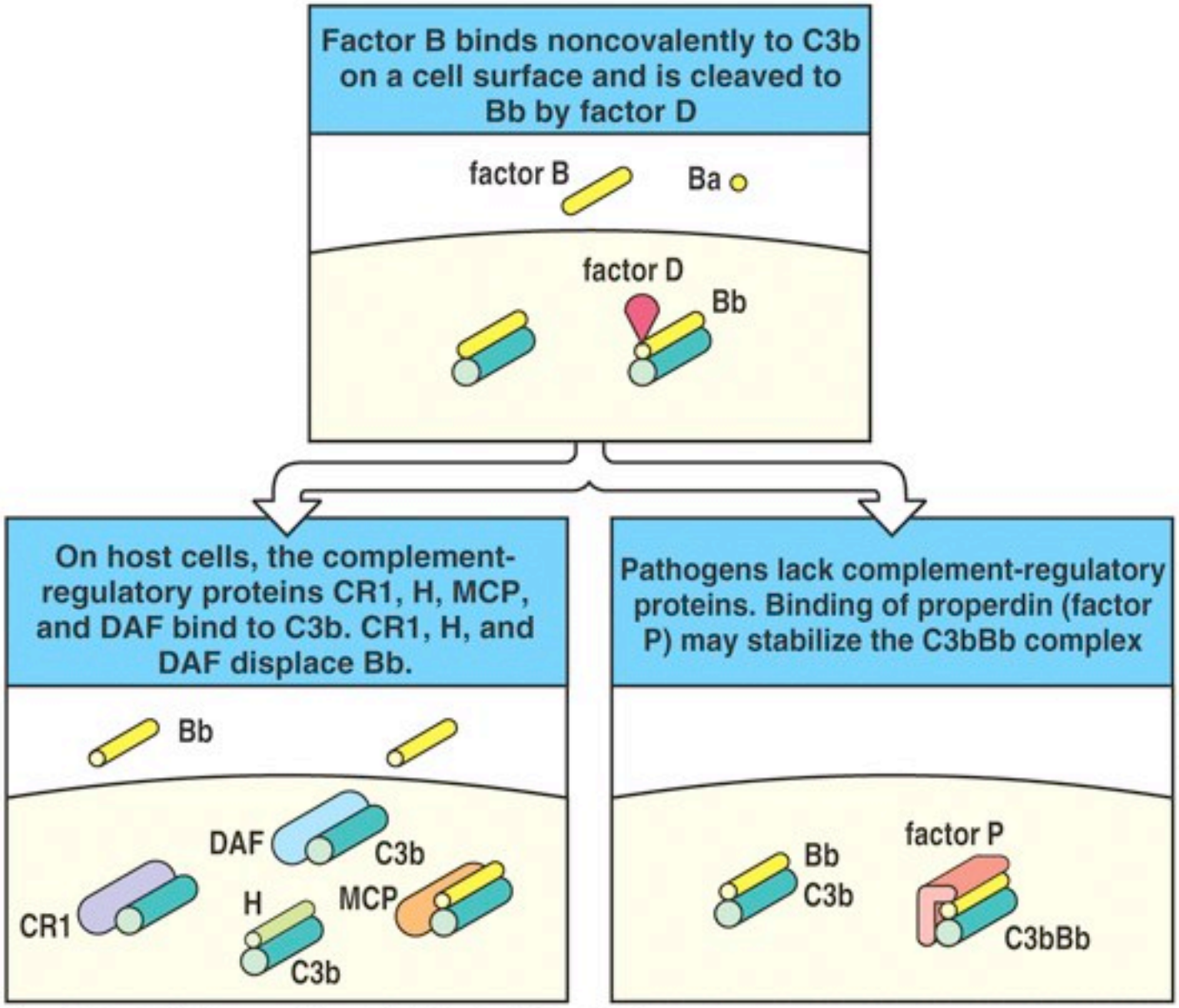


Figure 2-26 part 2 of 3 Immunobiology, 6/e. (© Garland Science 2005)

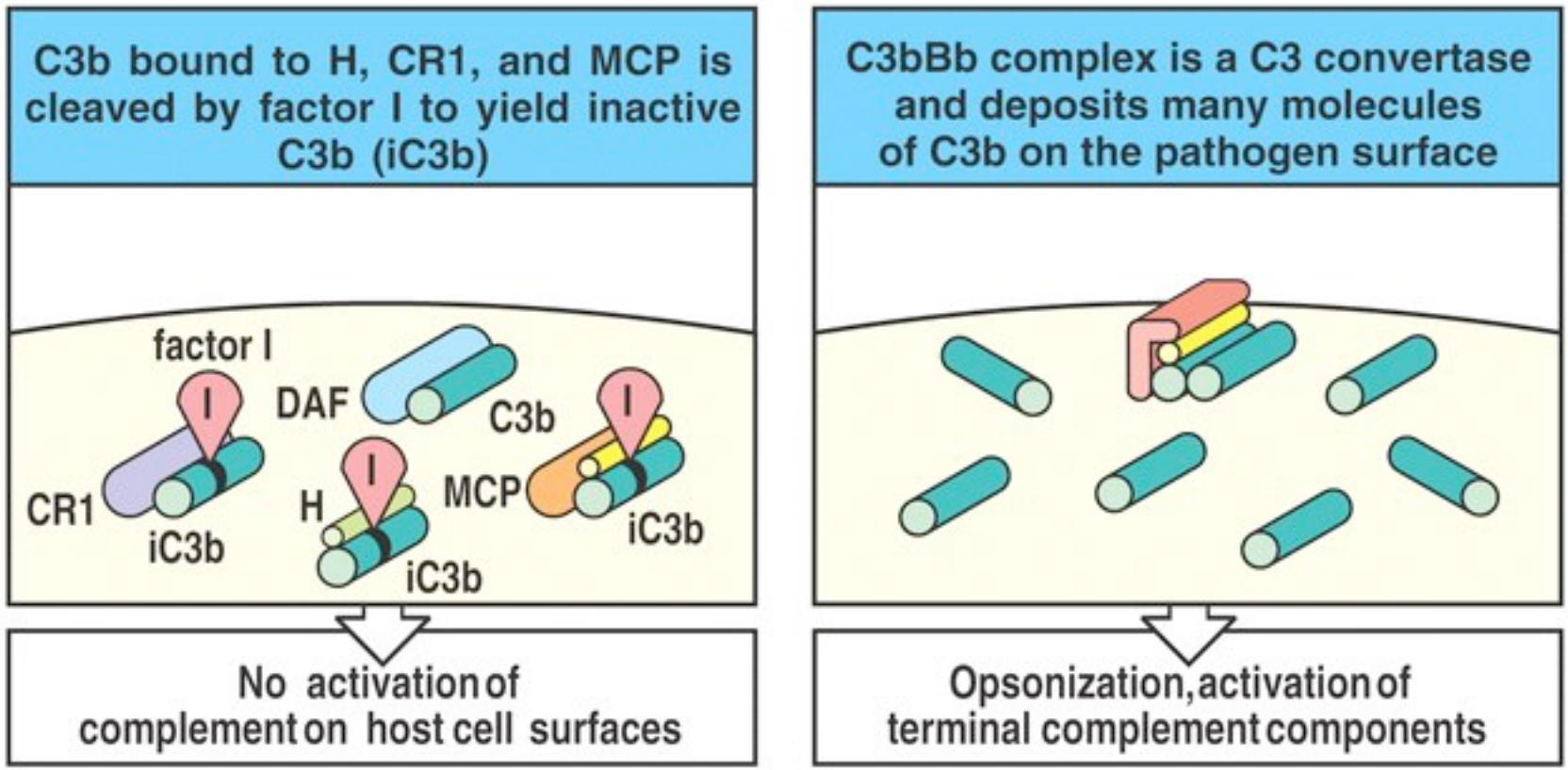


Figure 2-26 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)

Amplification of complement deposition by alternative pathway

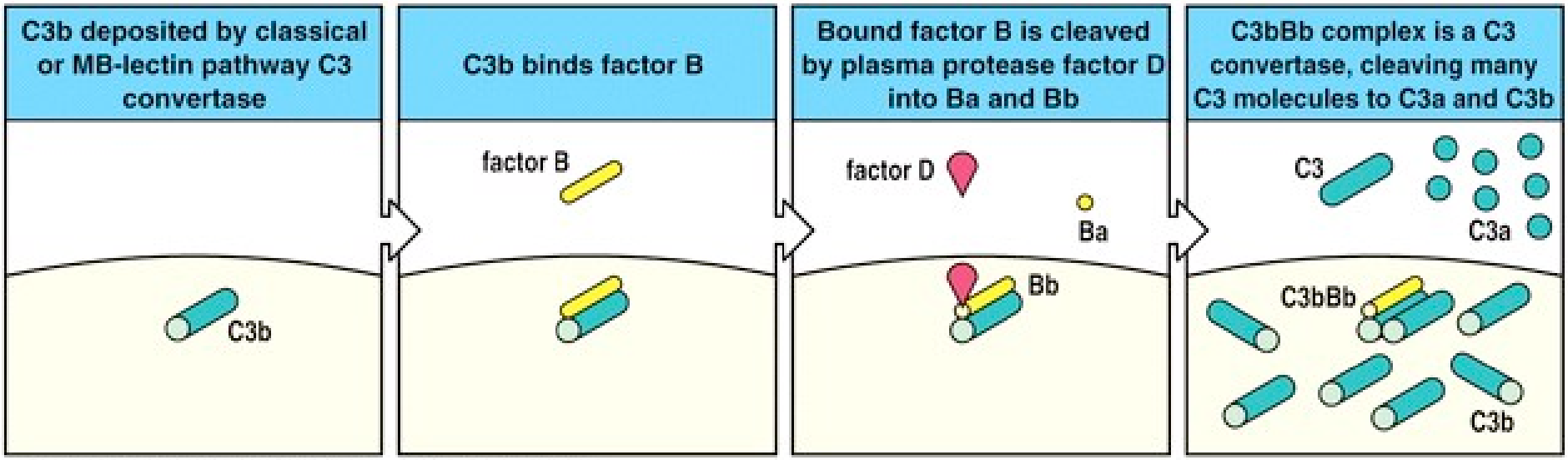


Figure 2-28 Immunobiology, 6/e. (© Garland Science 2005)

Complement receptors

- Enhance phagocytosis
- Respond to inflammatory mediators

Receptor	Specificity	Functions	Cell types
CR1 (CD35)	C3b, C4b iC3b	Promotes C3b and C4b decay Stimulates phagocytosis Erythrocyte transport of immune complexes	Erythrocytes, macrophages, monocytes, polymorphonuclear leukocytes, B cells, FDC
CR2 (CD21)	C3d, iC3b, C3dg Epstein–Barr virus	Part of B-cell co-receptor Epstein–Barr virus receptor	B cells, FDC
CR3 (Mac-1) (CD11b/ CD18)	iC3b	Stimulates phagocytosis	Macrophages, monocytes, polymorphonuclear leukocytes, FDC
CR4 (gp150,95) (CD11c/ CD18)	iC3b	Stimulates phagocytosis	Macrophages, monocytes, polymorphonuclear leukocytes, dendritic cells
C5a receptor	C5a	Binding of C5a activates G protein	Endothelial cells, mast cells, phagocytes
C3a receptor	C3a	Binding of C3a activates G protein	Endothelial cells, mast cells, phagocytes

Figure 2-31 Immunobiology, 6/e. (© Garland Science 2005)

C5 convertase

- Cleaves C5
- Composed of:
  - Classical/MBL pathway
    - C4b,C2b,C3b
  - Alternative pathway
    - $C3b_2/Bb$
- C5a required for efficient phagocytosis in absence of Ab

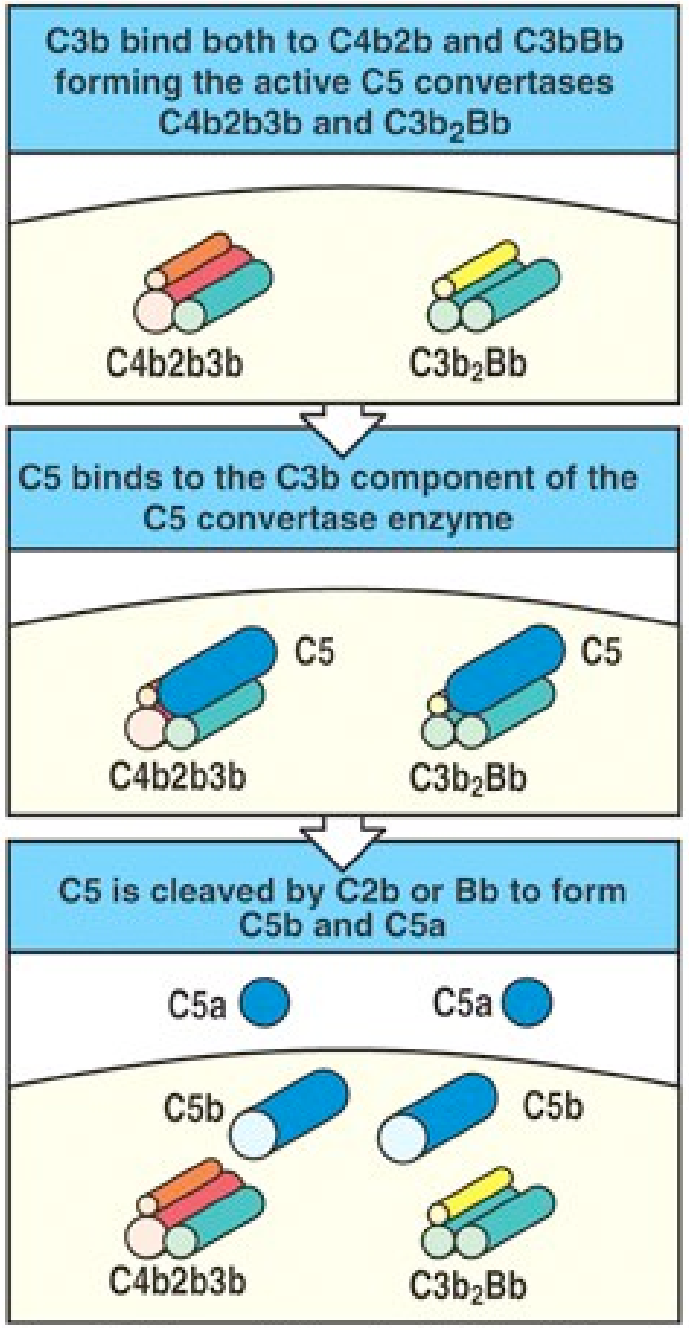


Figure 2-30 Immunobiology, 6/e. (© Garland Science 2005)

Complement mediated phagocytosis (no Ab)

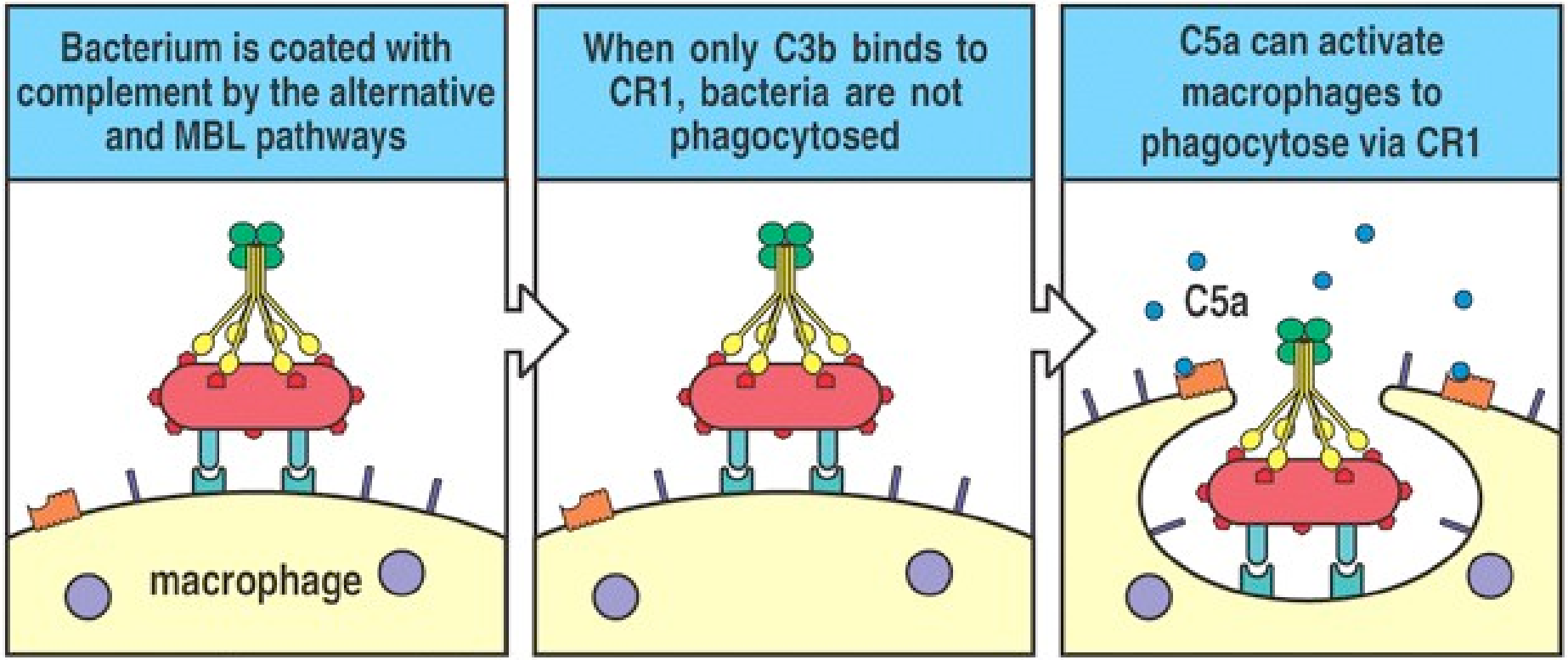


Figure 2-32 Immunobiology, 6/e. (© Garland Science 2005)

Complement mediated phagocytosis + Ab

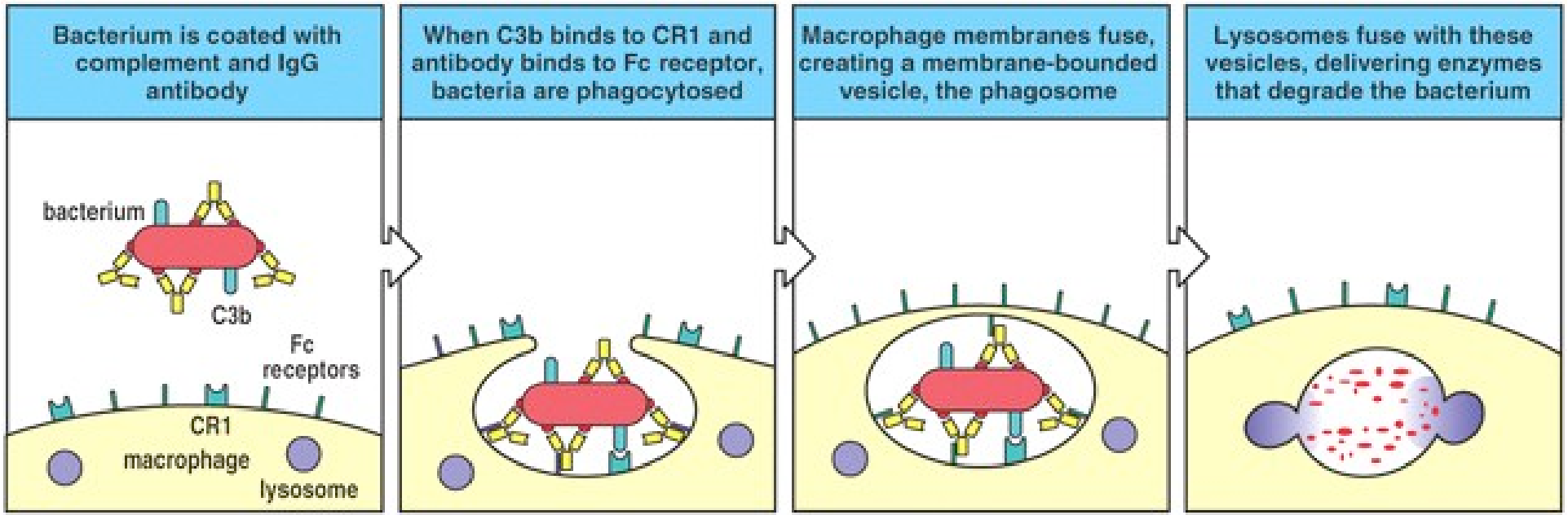


Figure 9-32 Immunobiology, 6/e. (© Garland Science 2005)

Complement as inflammatory mediators

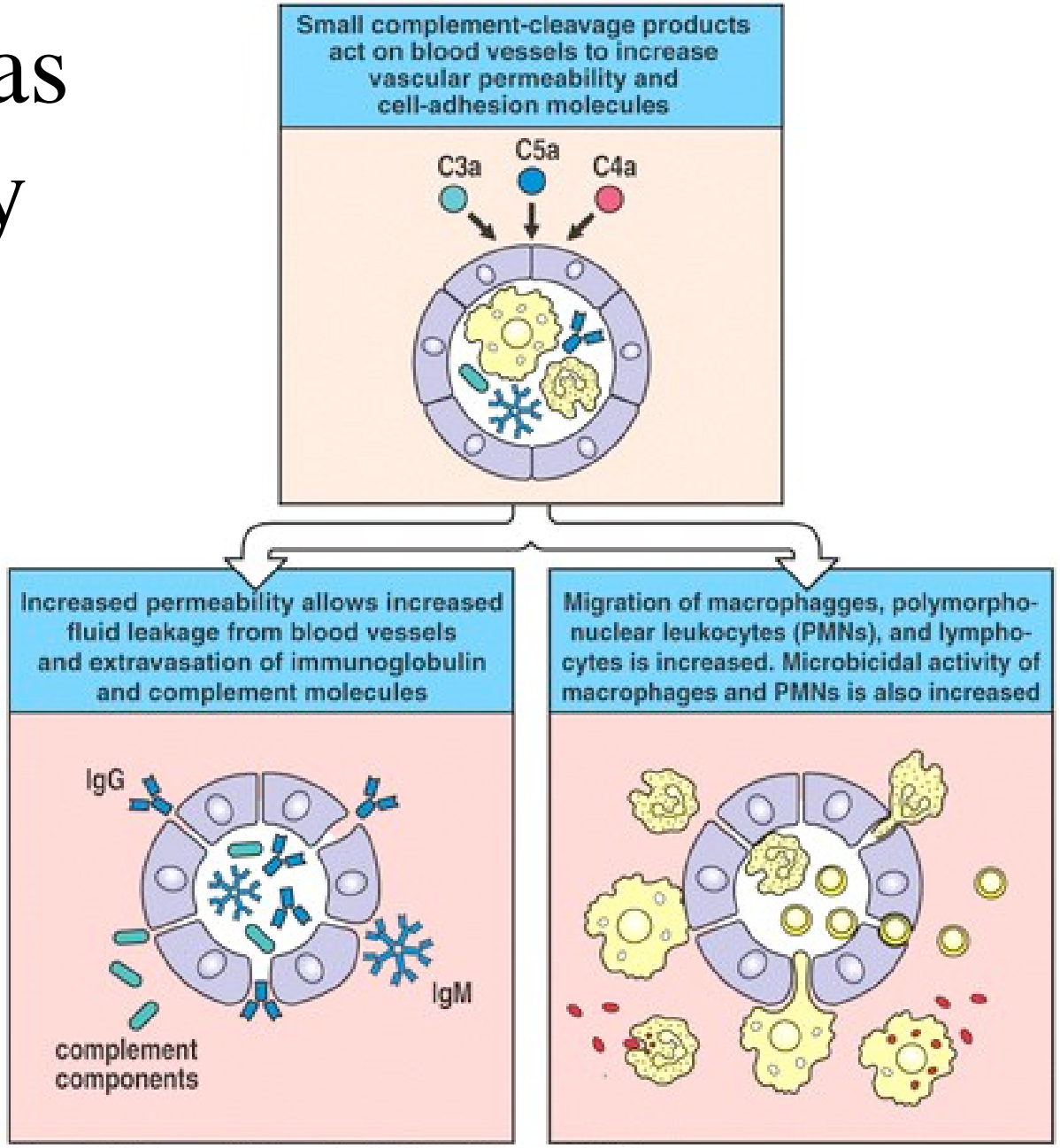


Figure 2-33 Immunobiology, 6/e. (© Garland Science 2005)

Terminal attack complex

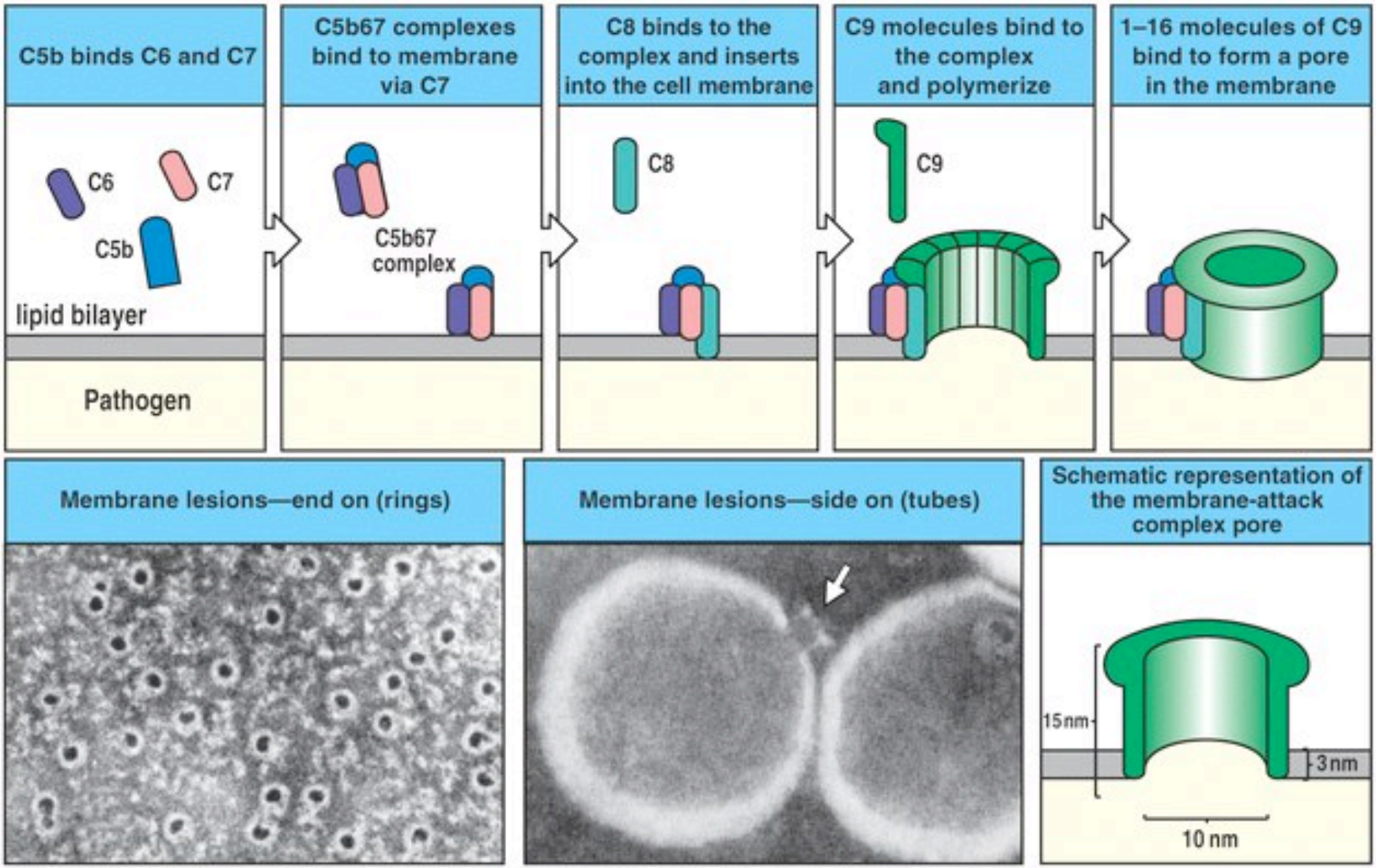


Figure 2-35 Immunobiology, 6/e. (© Garland Science 2005)

Complement regulatory proteins protect host cells

Regulatory proteins of the classical and alternative pathways

Name (symbol)	Role in the regulation of complement activation
C1 inhibitor (C1INH)	Binds to activated C1r, C1s, removing them from C1q
C4-binding protein (C4BP)	Binds C4b, displacing C2b; cofactor for C4b cleavage by I
Complement receptor 1 (CR1)	Binds C4b, displacing C2b, or C3b displacing Bb; cofactor for I
Factor H (H)	Binds C3b, displacing Bb; cofactor for I
Factor I (I)	Serine protease that cleaves C3b and C4b; aided by H, MCP, C4BP, or CR1
Decay-accelerating factor (DAF)	Membrane protein that displaces Bb from C3b and C2b from C4b
Membrane cofactor protein (MCP)	Membrane protein that promotes C3b and C4b inactivation by I
CD59 (protectin)	Prevents formation of membrane-attack complex on autologous or allogenic cells. Widely expressed on membranes

Figure 2-36 Immunobiology, 6/e. (© Garland Science 2005)

Interferons

□= leukocytes

□= fibroblasts

□= NK, T cells

□,□=

important in early viral infection

signal= dsRNA

□,□

- Inhibit viral replication
  - Endoribonuclease
  - Tranlation inhibition
- Increased MHC expression
- Activate NK cells 20-100-fold

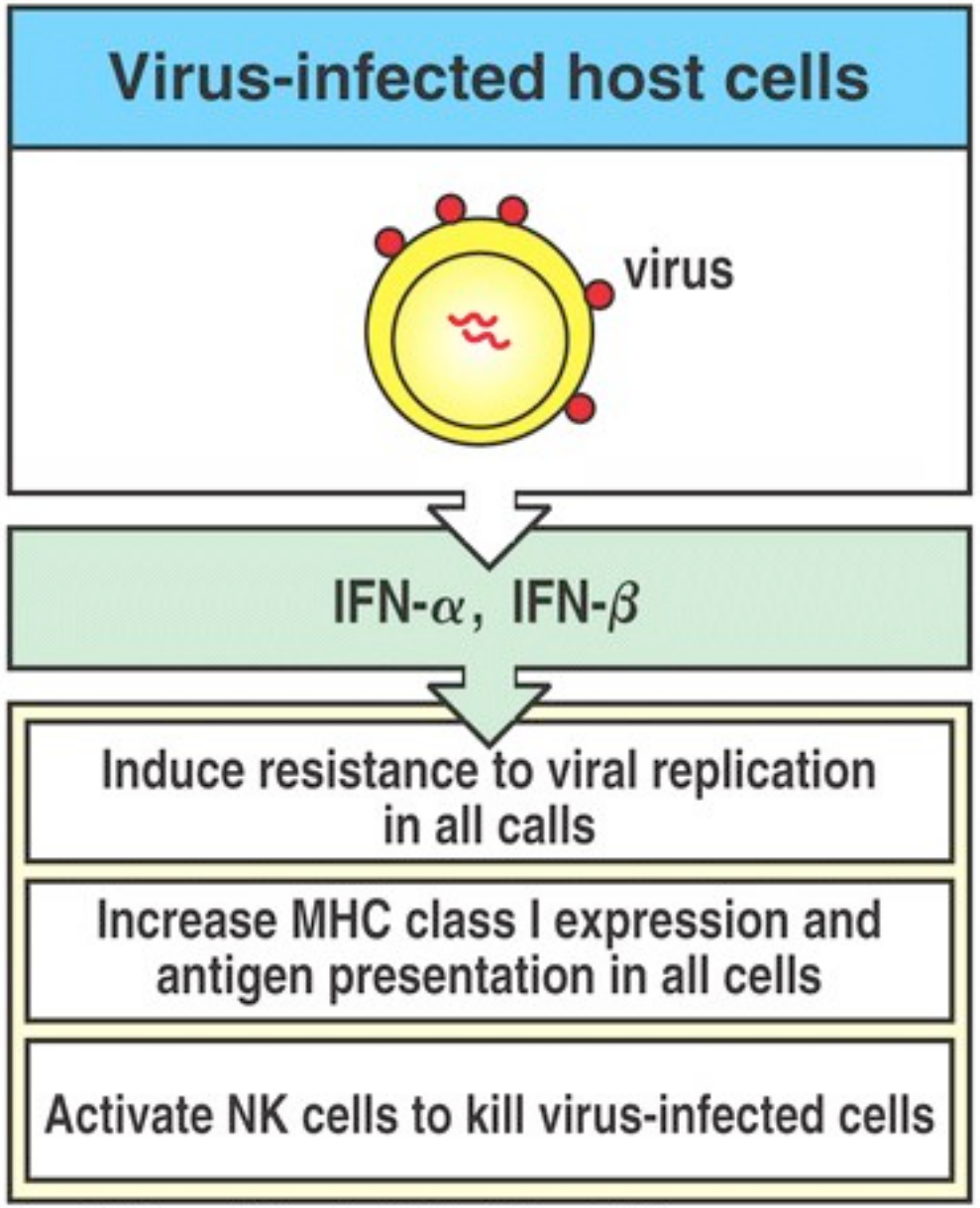


Figure 2-48 Immunobiology, 6/e. (© Garland Science 2005)

□,□ Interferons stimulate NK cell activity

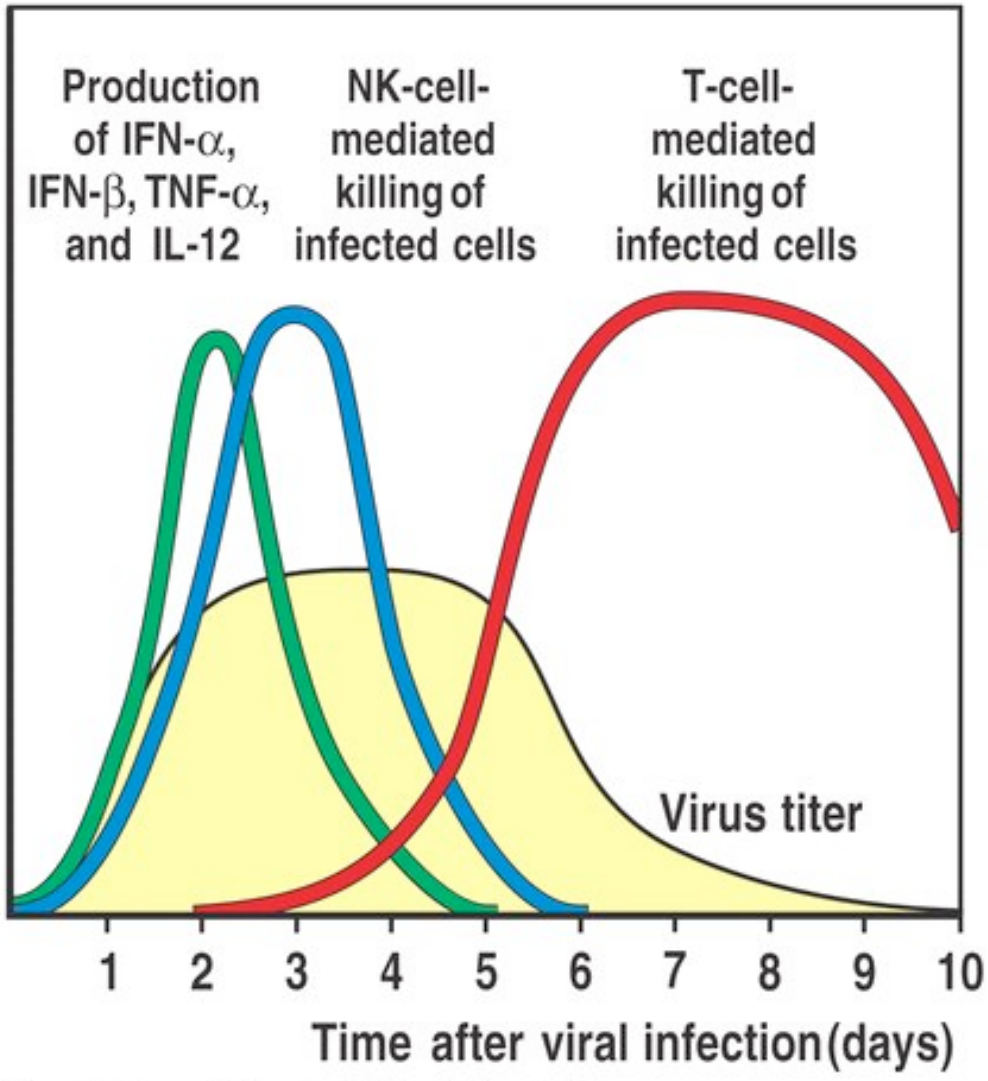


Figure 2-49 Immunobiology, 6/e. (© Garland Science 2005)

Natural Killer Cells

- Contain cytoplasmic granules
- Mechanism of killing similar to CTLs
  - Perforins
  - Induction of apotosis pathway in target cell
- NK cells produce γ-interferon after activation by α and β interferon

NK cell cytotoxicity

- Activating signal=
  - NK receptors bind to carbohydrates
- Inhibitory signal=
  - KIR/lectin molecules recognize MHC class I

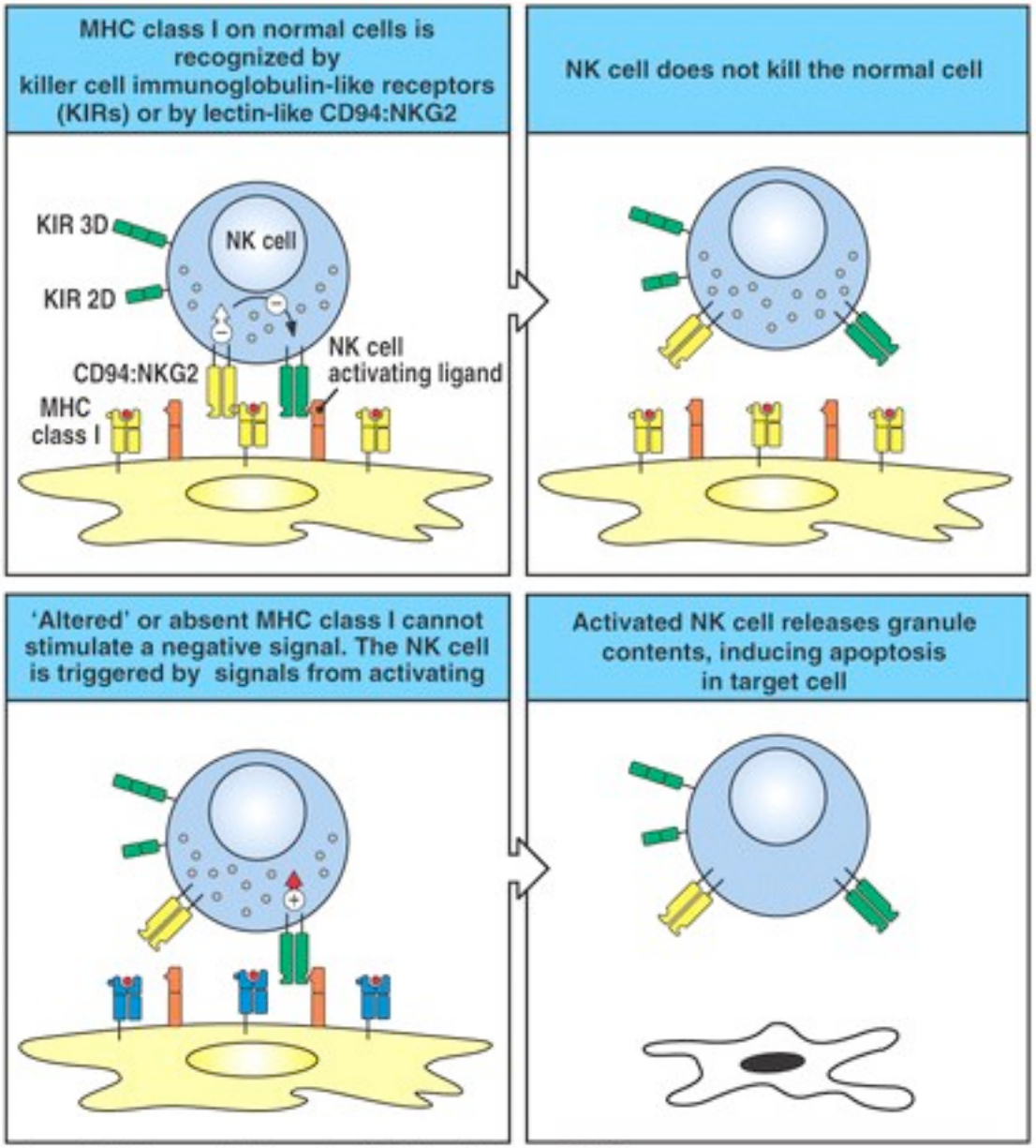


Figure 2-50 Immunobiology, 6/e. (© Garland Science 2005)

-interferon

- Activates macrophages
- Increased MHC expression
- Increased Ag processing components
- Isotype switching
- Supresses TH2 response

□□ T cells

- Found near epithelial surfaces
- Low diversity of TCR specificity
- Unknown ligand (something that changes upon infection?)
- Recognize Ag directly, not in MHC

B-1 B Cells

- Found in pleural/peritoneal cavities
- Low diversity of Ig specificity
- Commonly bind to polysaccharides
- Self-renewing in periphery

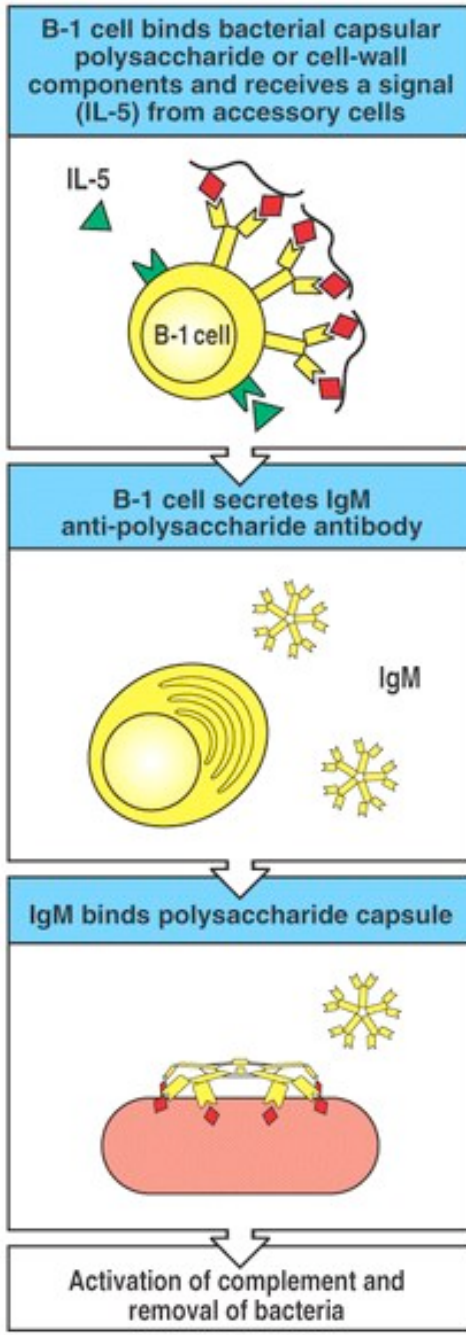


Figure 2-53 Immunobiology, 6/e. (© G

Innate immunity

- Barriers
- Phagocytosis (Neutrophils and M□)
  - M□ activation
  - Dendritic cell Ag presentation
  - M□ cytokines and effects
- Complement activation
  - Opsonization
  - Terminal attack complex
- Interferons
- NK cells
- B-1 B cells/□□ T cells