Innate immunity

J Ceuppens
Clinical Immunology
Katholieke Universiteit
Leuven

Innate immunity

- Primitive, less efficient defense system
- Barrier function
- Nonspecificity

Innate immunity

- Primitive less efficient defense system

  neutrophils, complement
  defensins, ….

- Barrier function

  epithelial surfaces

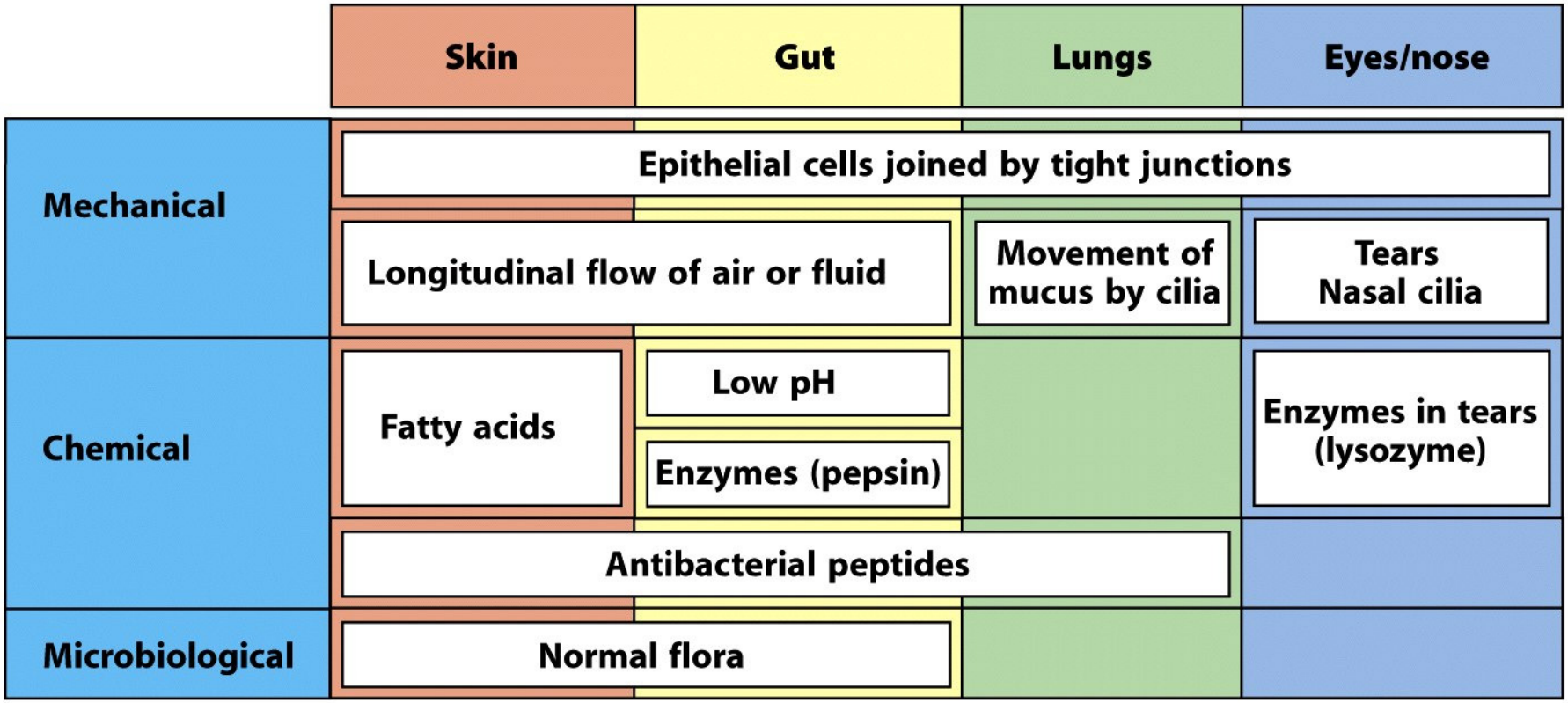


Figure 2-7 Immunobiology, 7ed. (© Garland Science 2008)

INNATE IMMUNITY = SENSOR for DANGER

- EPITHELIAL CELLS
- DENDRITIC CELLS
- MACROPHAGES

★ PAMS = PATTERN ASSOCIATED MOLECULAR PATTERNS

★ DAMS = DAMAGE ASSOCIATED MOLECULAR PATTERNS

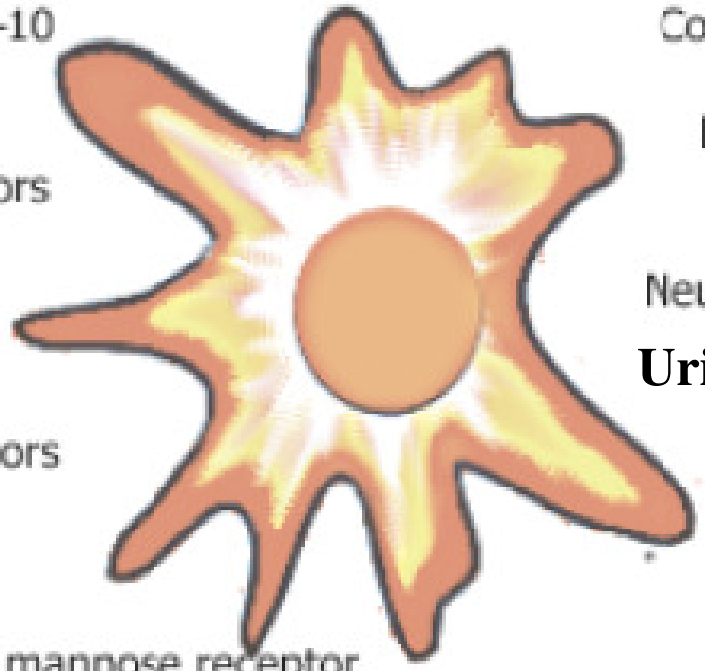
PAMP receptors

Toll-like receptor 1–10

Intracellular receptors
- NLRs
- TLR 7,9

C-type lectin receptors
- Dectin
- DEC 205
- BDCA-1
- Macrophage mannose receptor

RIG-like receptors



DAMP receptors

Complement receptors

Prostanoid receptors
DP1, EP4, IP

ATP

Neuropeptide receptors
NK1, CGRPR

Uric acid

Purinergic receptors
P2X, P2Y

Chromatin proteins

HMGB-1 receptor

RAGE

Receptors for heat shock proteins

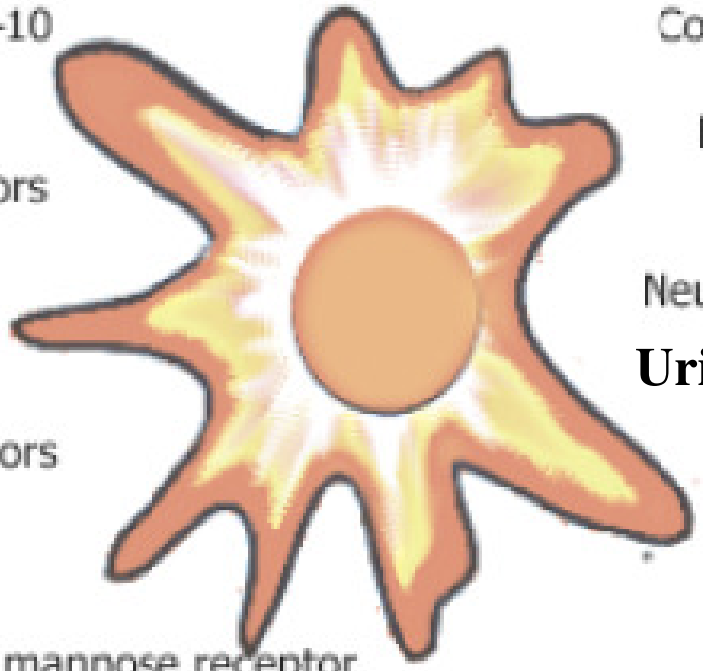
PAMP receptors

Toll-like receptor 1–10

Intracellular receptors
- NLRs
- TLR 7,9

C-type lectin receptors
- Dectin
- DEC 205
- BDCA-1
- Macrophage mannose receptor

RIG-like receptors



DAMP receptors

Complement receptors

Prostanoid receptors
DP1, EP4, IP

ATP

Neuropeptide receptors
NK1, CGRPR

Uric acid

Purinergic receptors
P2X, P2Y

Chromatin proteins

HMGB-1 receptor
RAGE

Receptors for heat shock proteins

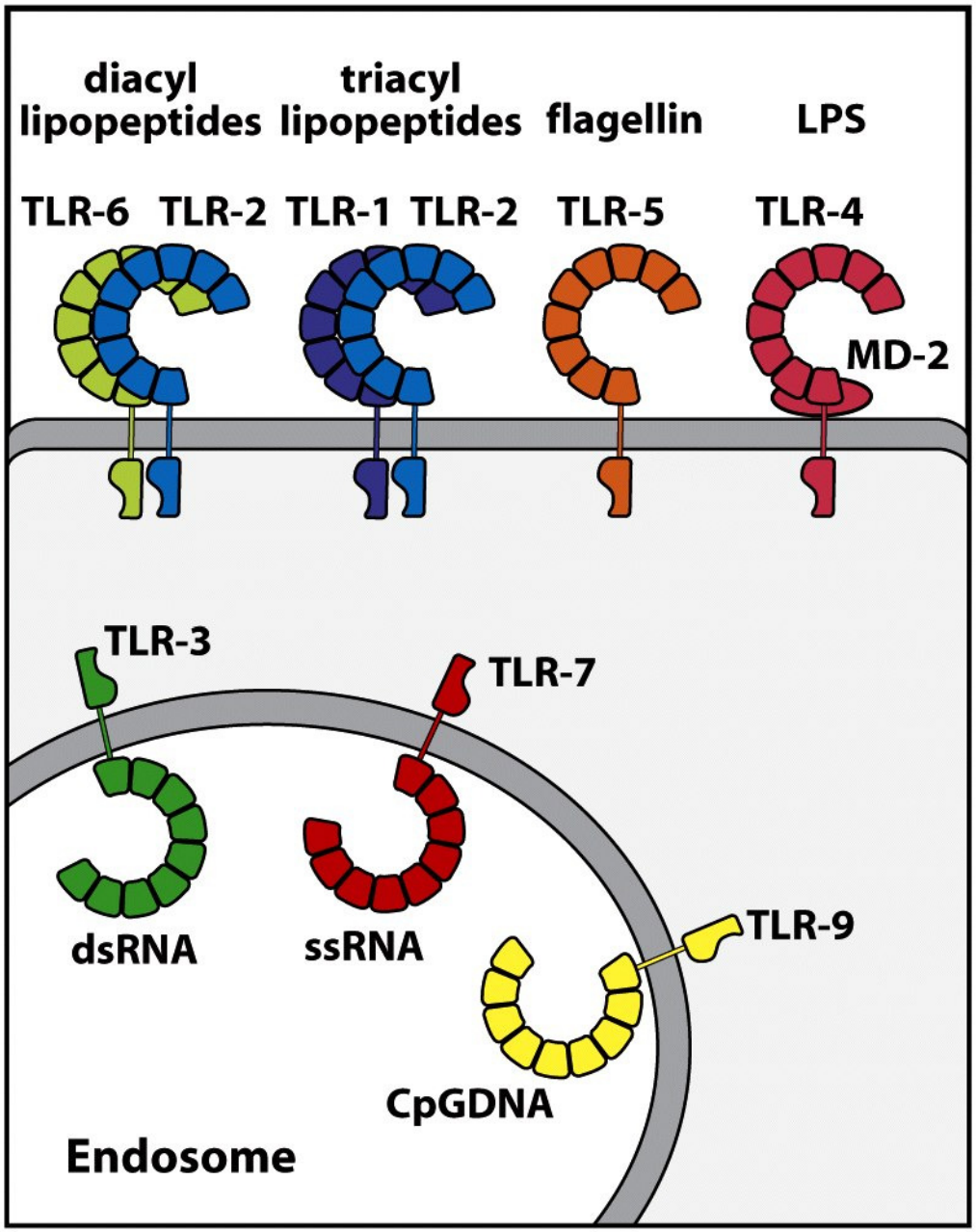


Figure 2-17 Immunobiology, 7ed. (© Garland Science 2008)

Innate immune recognition by Toll-like receptors	
Toll-like receptor	**Ligand**
TLR-1:TLR-2 heterodimer	Peptidoglycan Lipoproteins Lipoarabinomannan (mycobacteria) GPI (*T. cruzi*) Zymosan (yeast)
TLR-2:TLR-6 heterodimer	
TLR-3	dsRNA
TLR-4 dimer (plus MD-2 and CD14)	LPS (Gram-negative bacteria) Lipoteichoic acids (Gram-positive bacteria)
TLR-5	Flagellin
TLR-7	ssRNA
TLR-8	G-rich oligonucleotides
TLR-9	Unmethylated CpG DNA

Figure 2-16 Immunobiology, 7ed. (© Garland Science 2008)

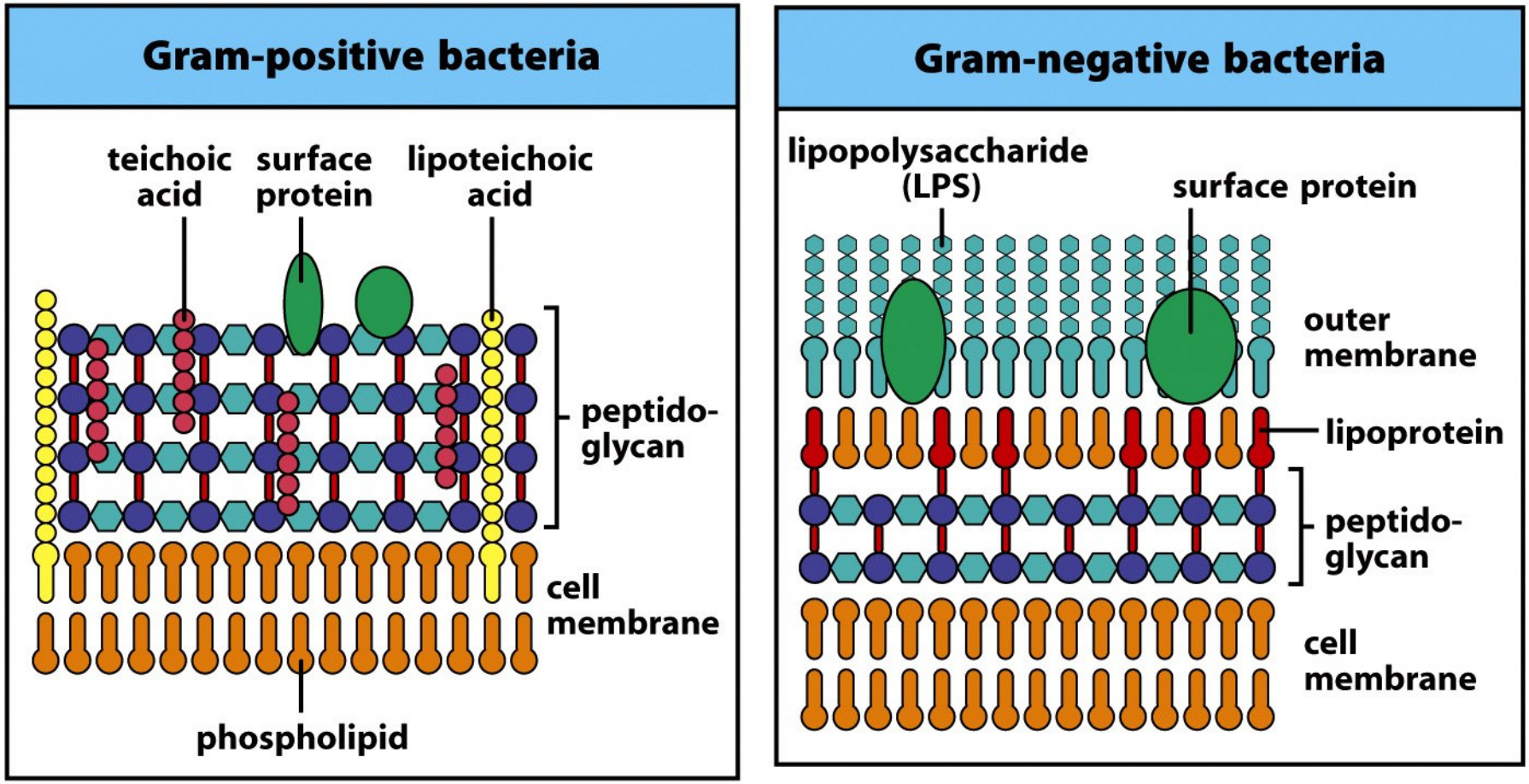


Figure 2-14 Immunobiology, 7ed. (© Garland Science 2008)

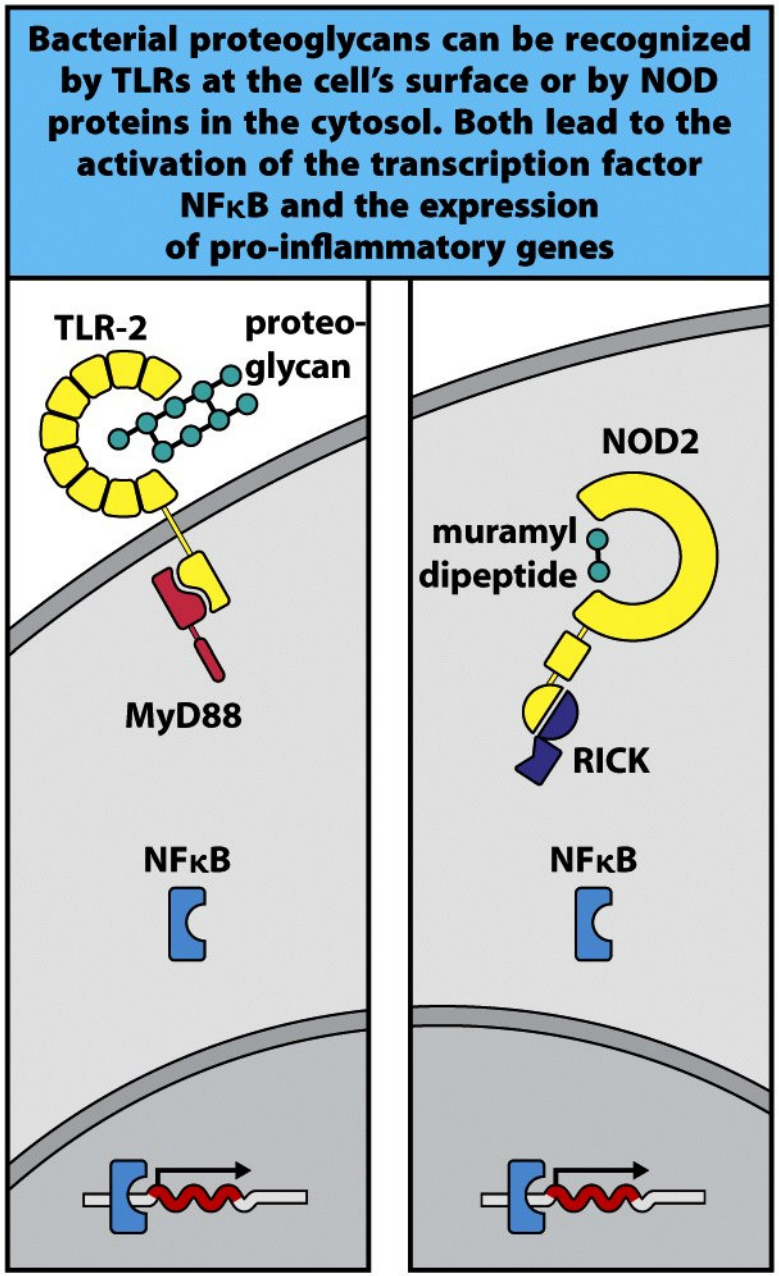


Figure 2-20 Immunobiology, 7ed. (© Garland Science 2008)

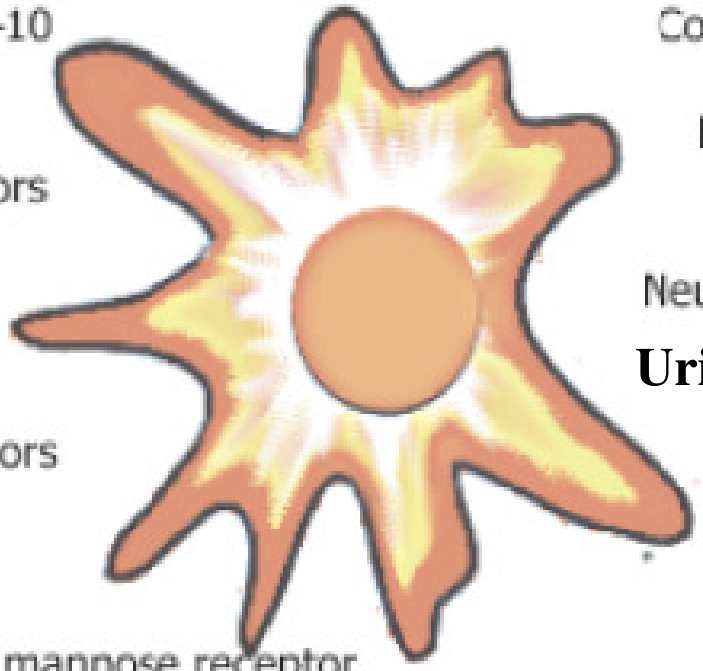
PAMP receptors

Toll-like receptor 1–10

Intracellular receptors
- NLRs
- TLR 7,9

C-type lectin receptors
- Dectin
- DEC 205
- BDCA-1
- Macrophage mannose receptor

RIG-like receptors



DAMP receptors

Complement receptors

Prostanoid receptors
DP1, EP4, IP

ATP

Neuropeptide receptors
NK1, CGRPR

Uric acid

Purinergic receptors
P2X, P2Y

Chromatin proteins

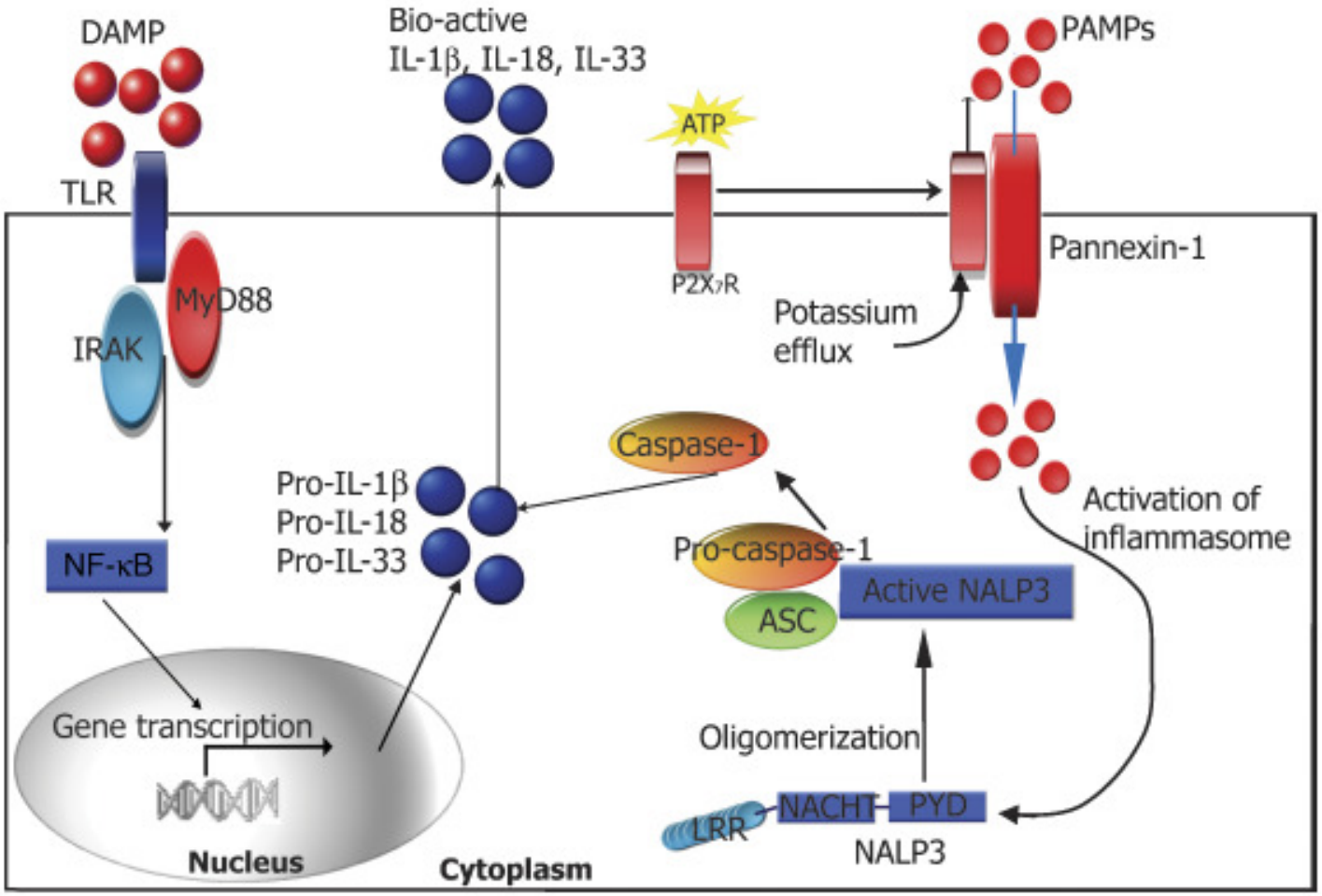
HMGB-1 receptor
RAGE

Receptors for heat shock proteins

PAMP and DAMP

ACTIVATE INNATE IMMUNE CELLS

- CYTOKINE SECRETION
- CHEMOKINE SECRETION
- UPREGULATION of SURFACE MOLECULES
  eg ADHESION MOLECULES
- MIGRATION
- PHAGOCYTOSIS and KILLING


DAMP
Bio-active
IL-1β, IL-18, IL-33
ATP
PAMPs
TLR
P2X7R
Pannexin-1
Potassium
efflux
MyD88
IRAK
Caspase-1
Pro-IL-1β
Pro-IL-18
Pro-IL-33
Activation of
inflammasome
NF-κB
Pro-caspase-1
Active NALP3
ASC
Gene transcription
Oligomerization
LRR
NACHT
PYD
NALP3
Nucleus
Cytoplasm

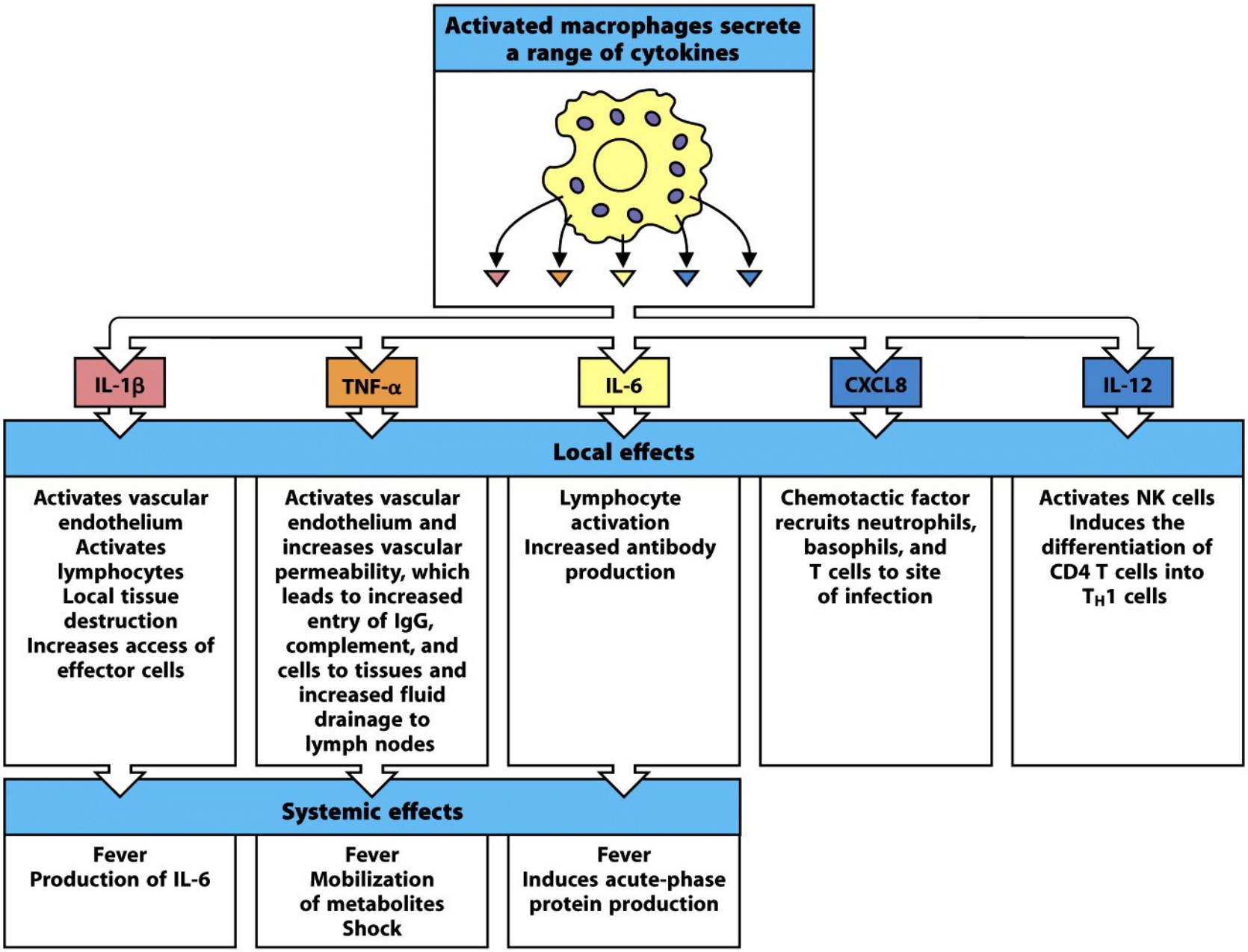


Figure 2-44 Immunobiology, 7ed. (© Garland Science 2008)

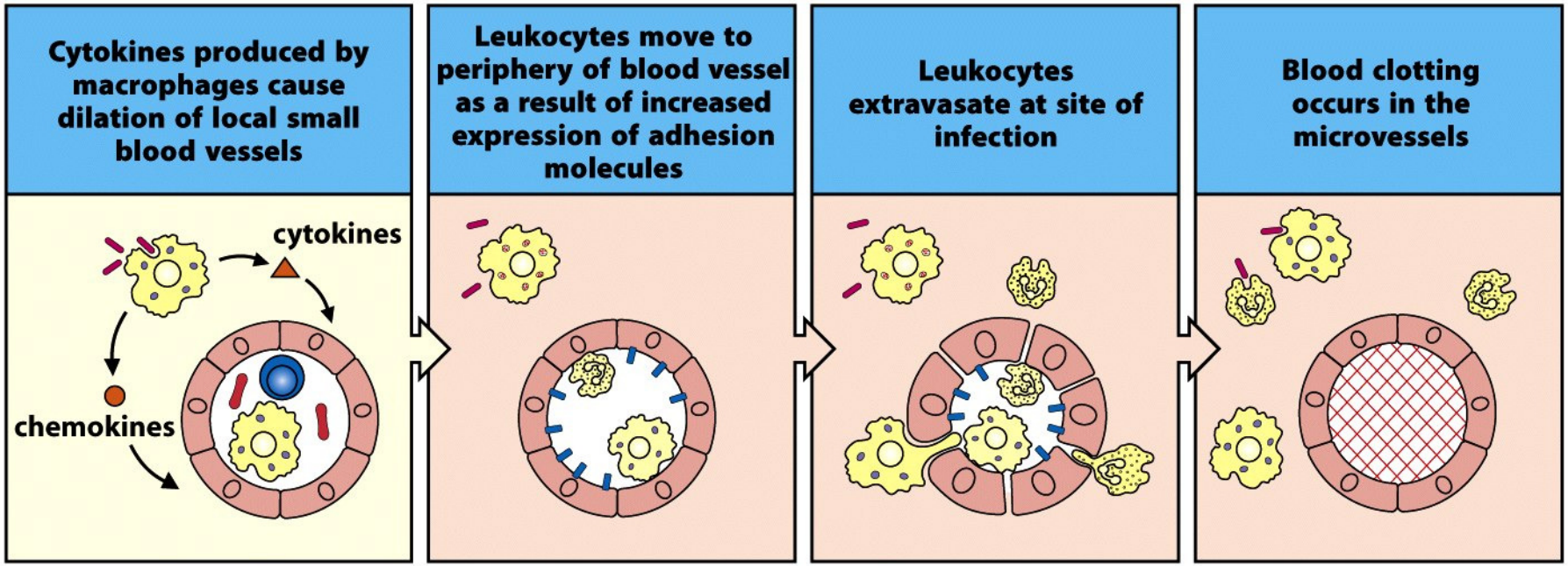


Figure 2-11 Immunobiology, 7ed. (© Garland Science 2008)

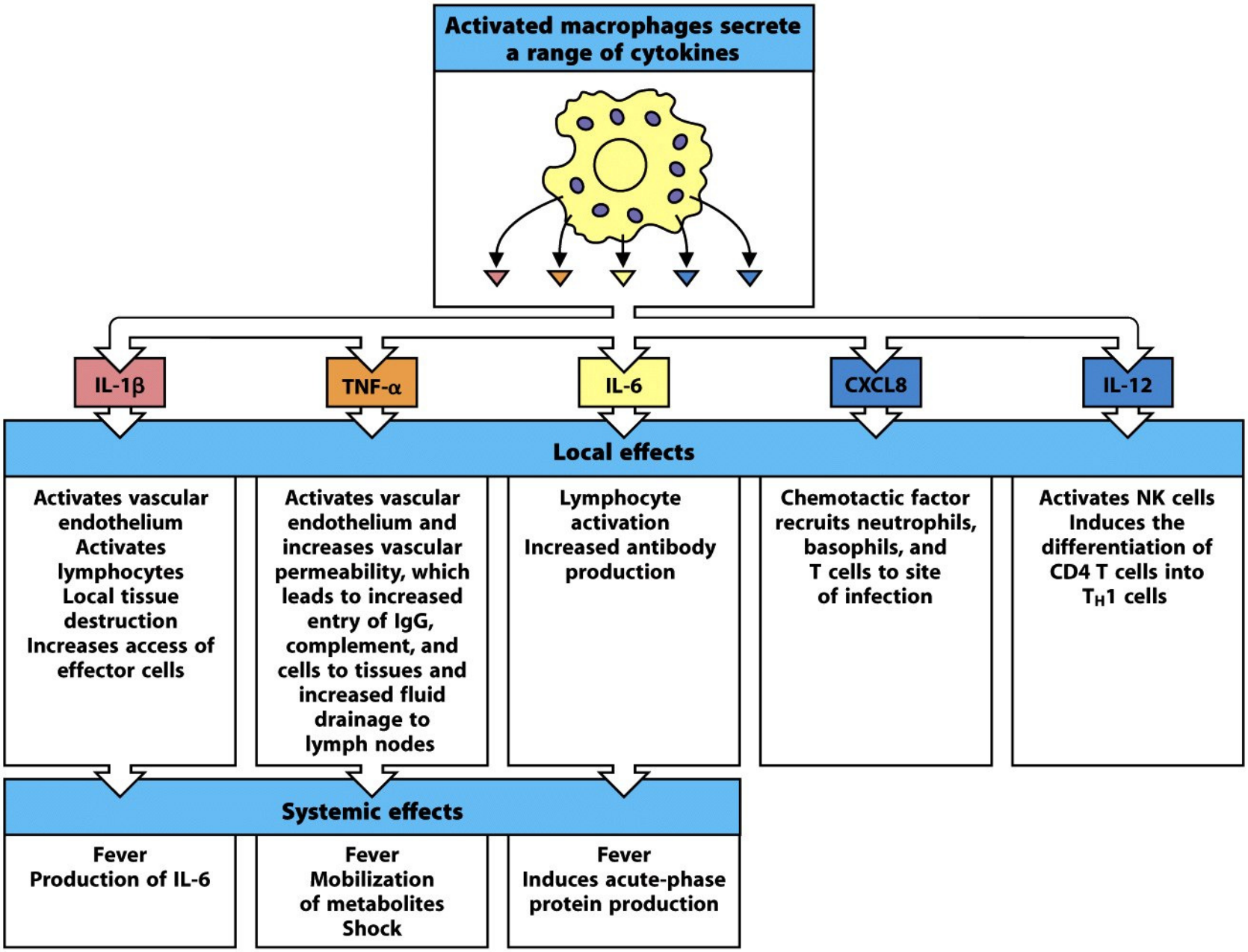


Figure 2-44 Immunobiology, 7ed. (© Garland Science 2008)

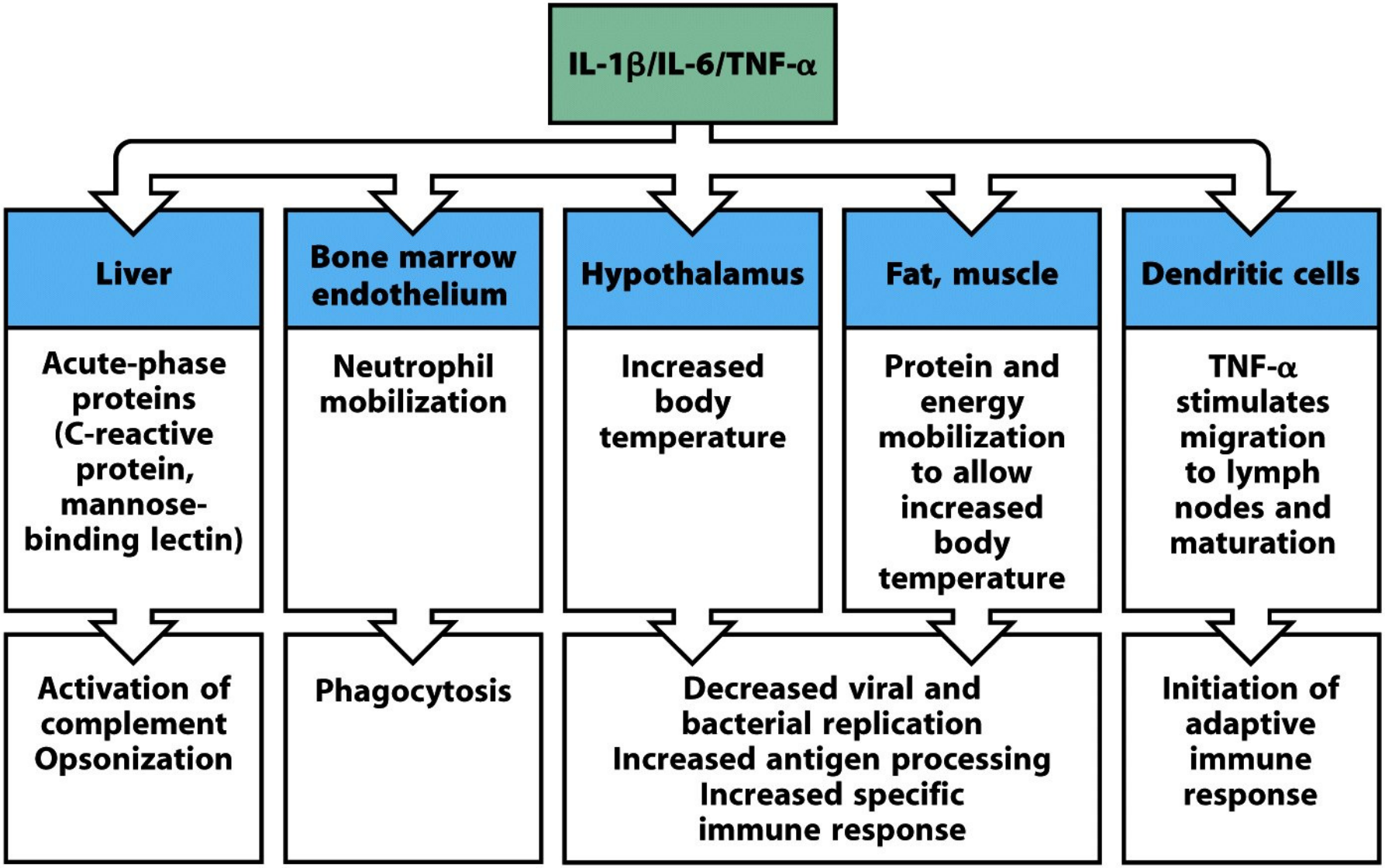
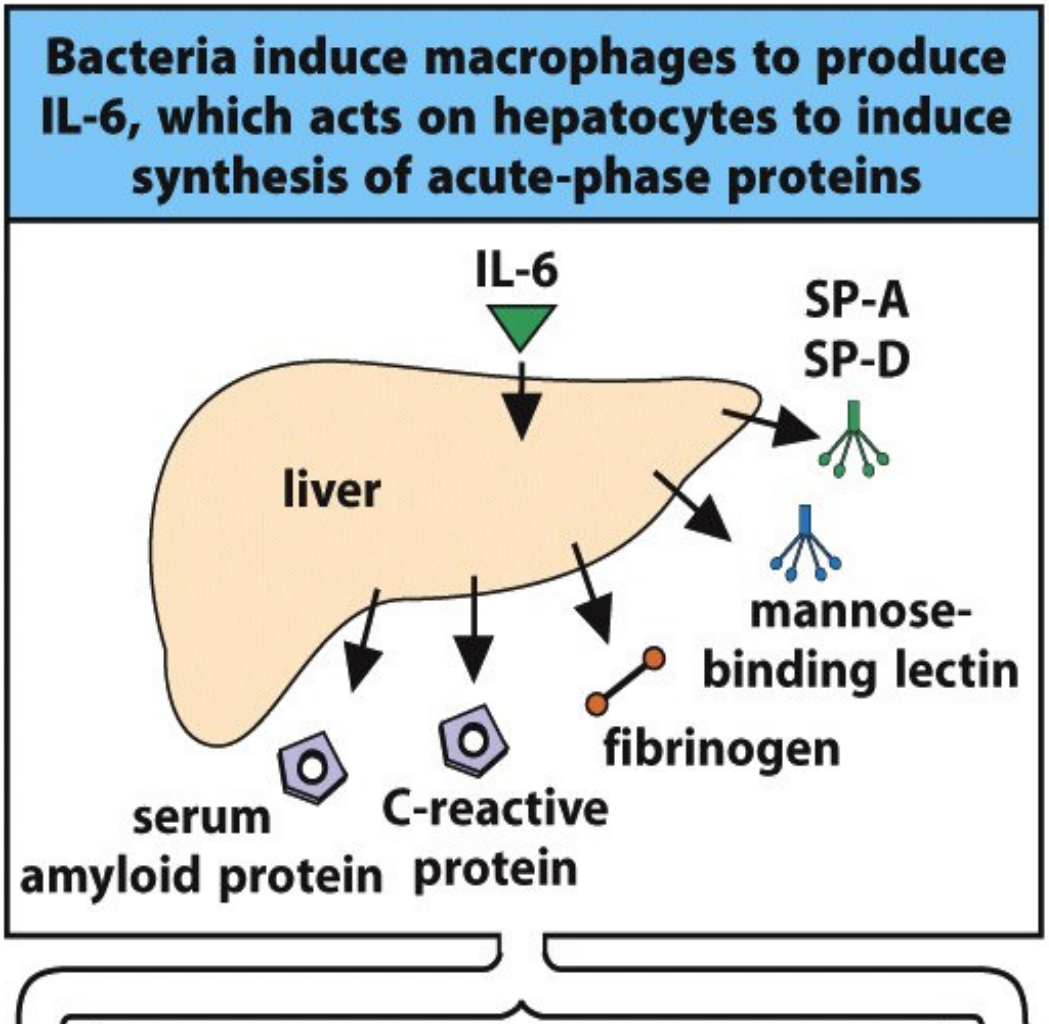


Figure 2-51 Immunobiology, 7ed. (© Garland Science 2008)


Bacteria induce macrophages to produce IL-6, which acts on hepatocytes to induce synthesis of acute-phase proteins
IL-6
SP-A
SP-D
liver
mannose-binding lectin
fibrinogen
serum amyloid protein
C-reactive protein

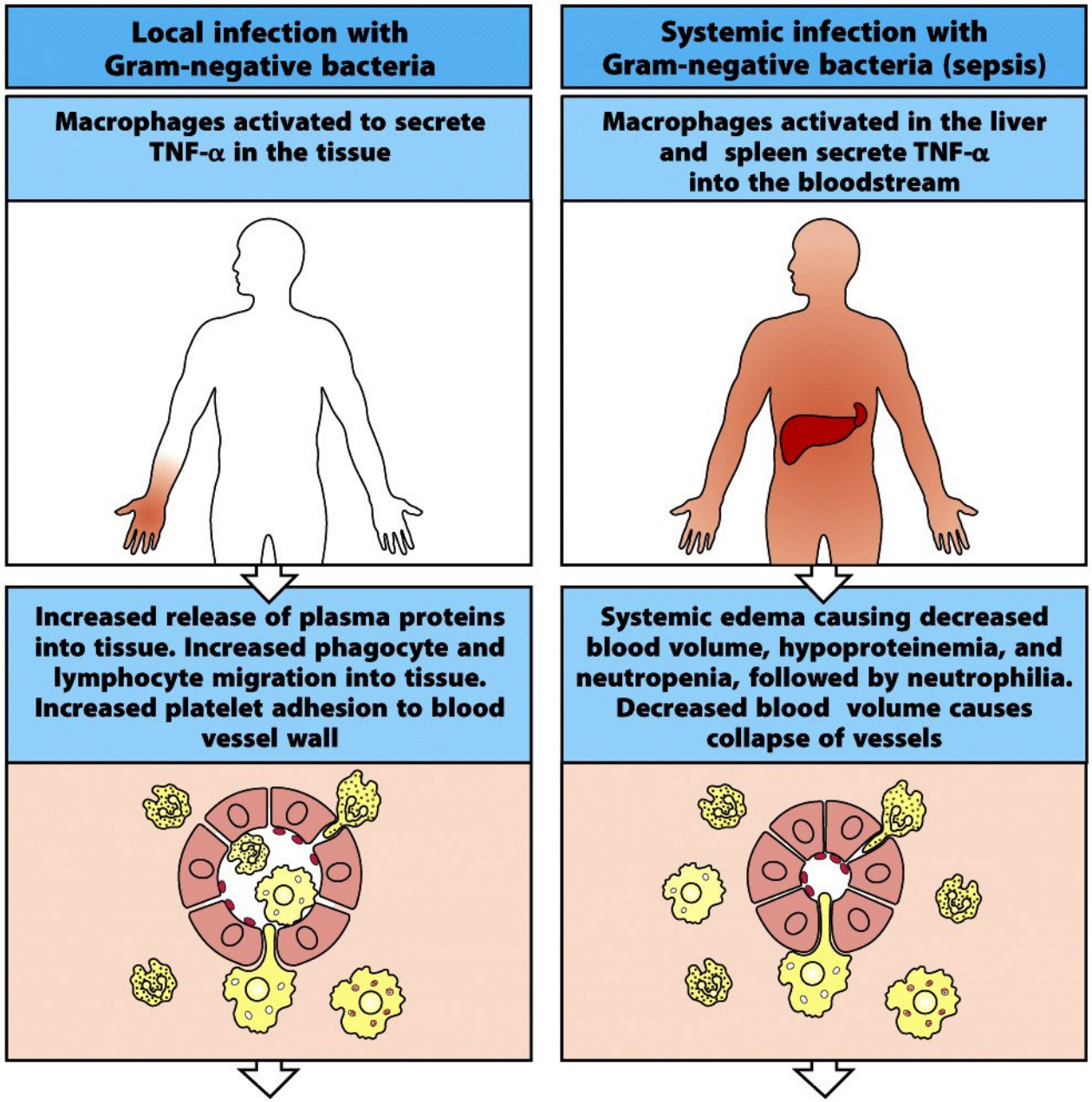


Figure 2-50 part 1 of 2 Immunobiology, 7ed. (© Garland Science 2008)

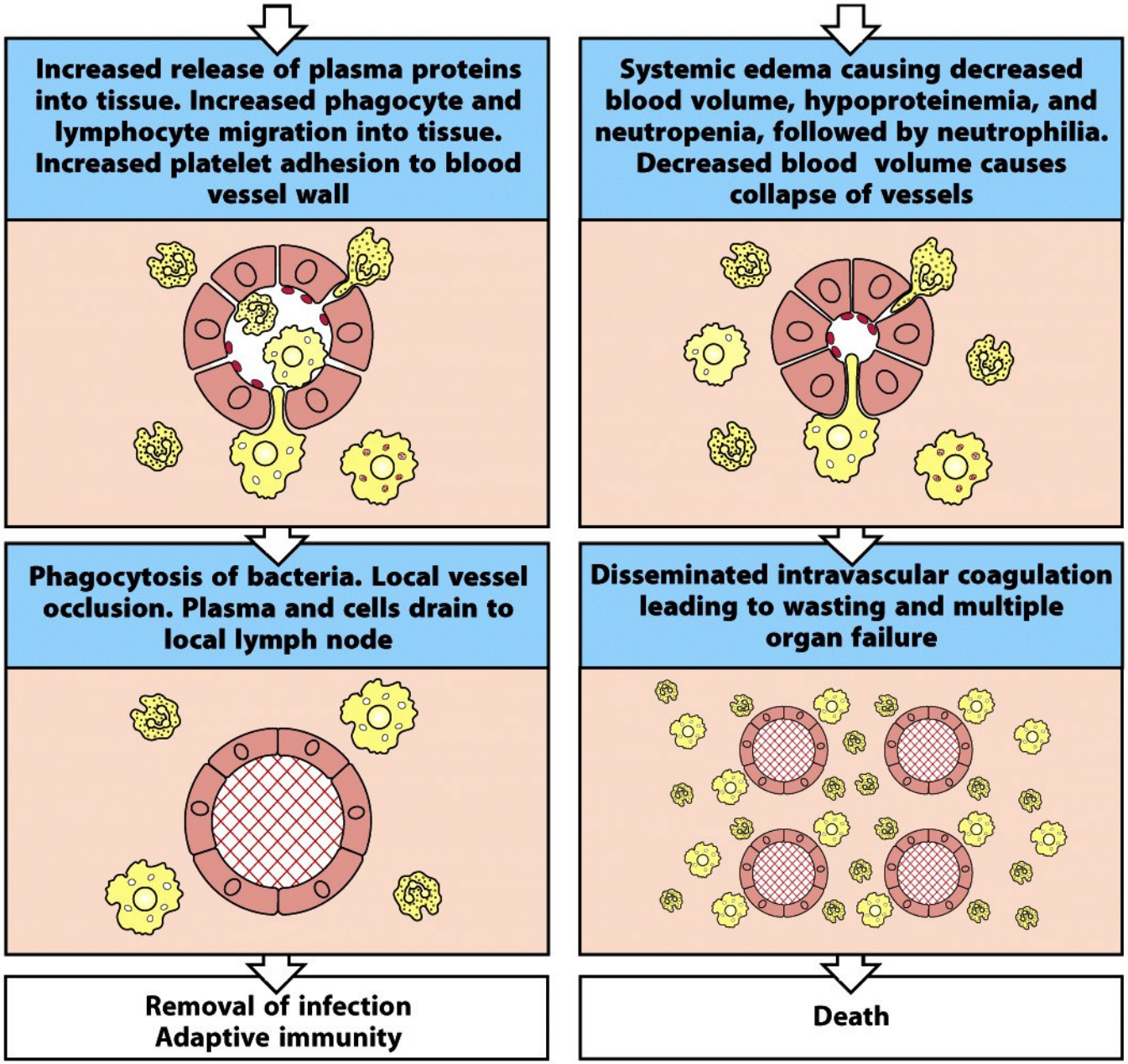


Figure 2-50 part 2 of 2 Immunobiology, 7ed. (© Garland Science 2008)

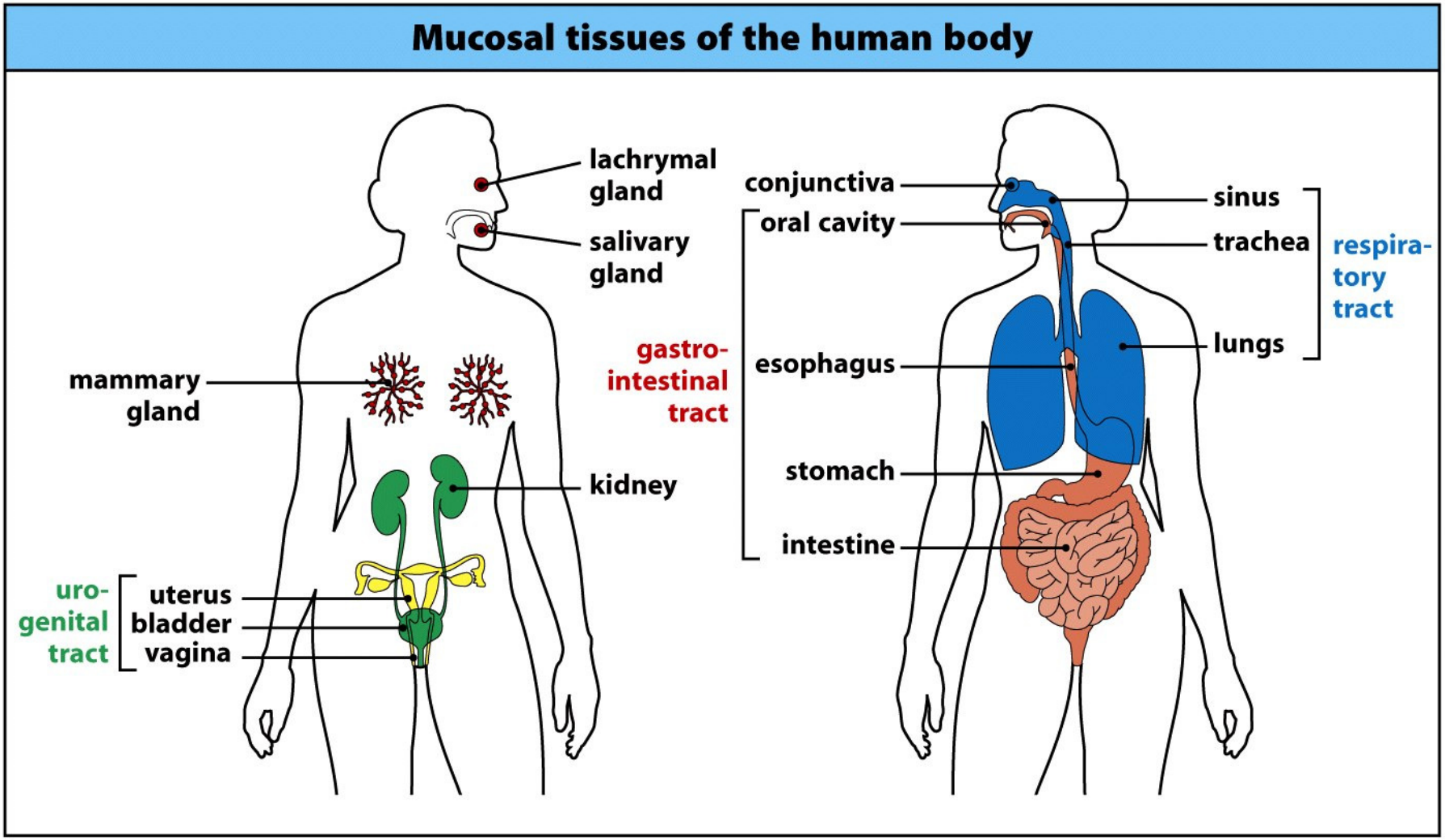


Figure 11-1 Immunobiology, 7ed. (© Garland Science 2008)

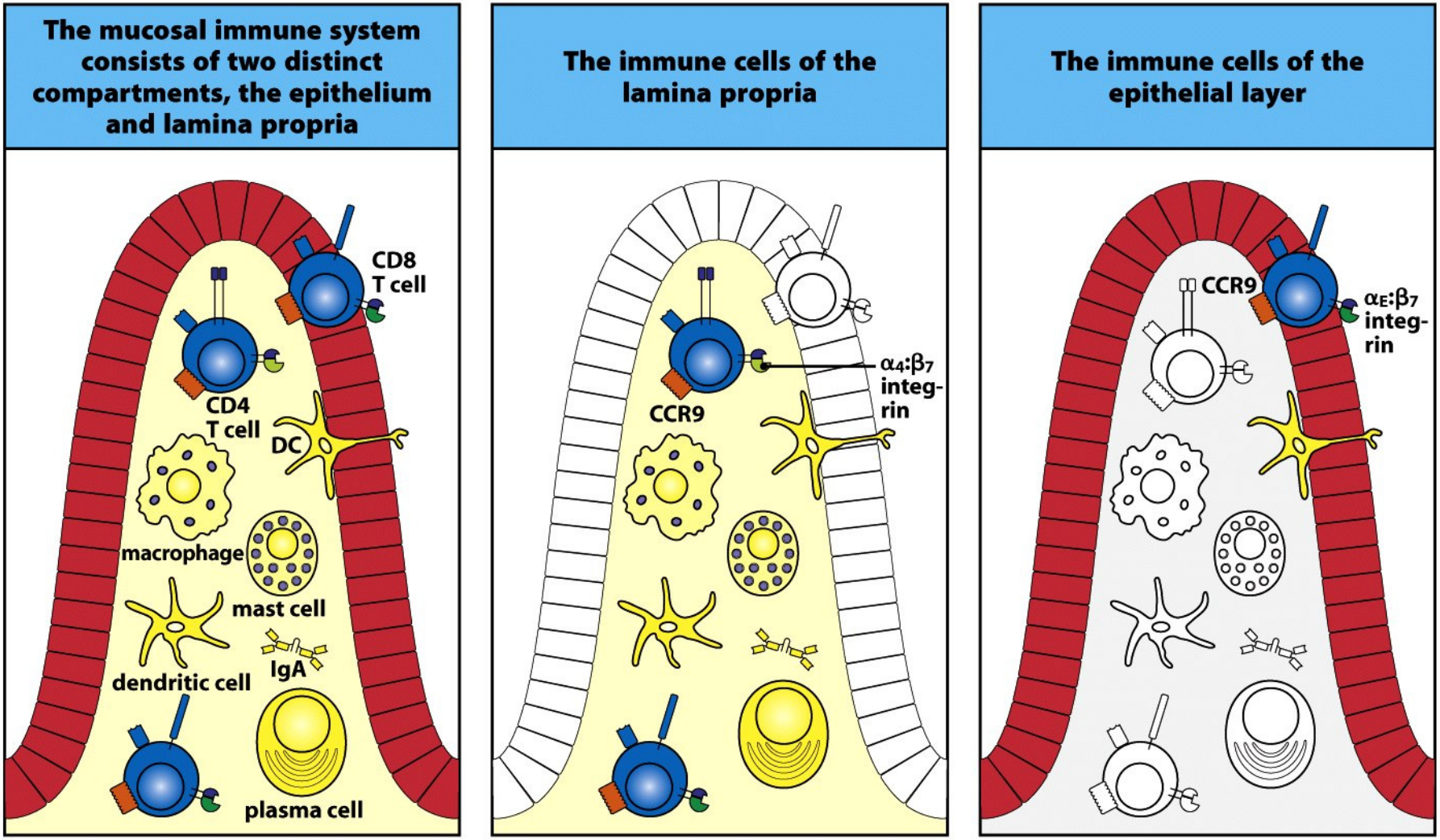
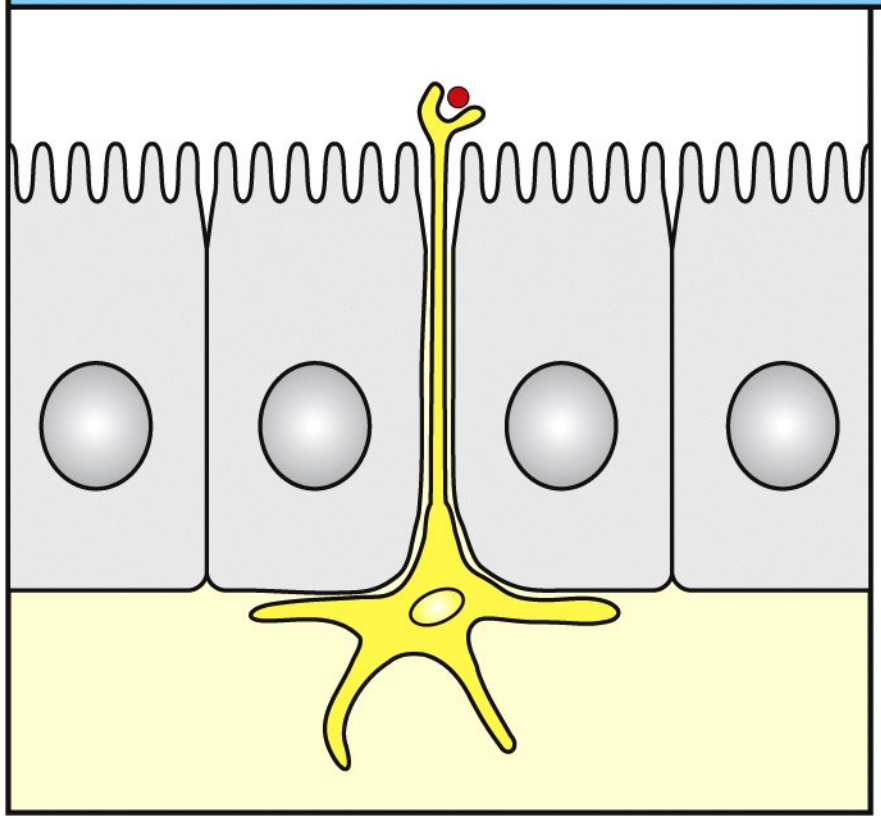


Figure 11-10 Immunobiology, 7ed. (© Garland Science 2008)

Dendritic cells can extend processes across the epithelial layer to capture antigen from the lumen of the gut



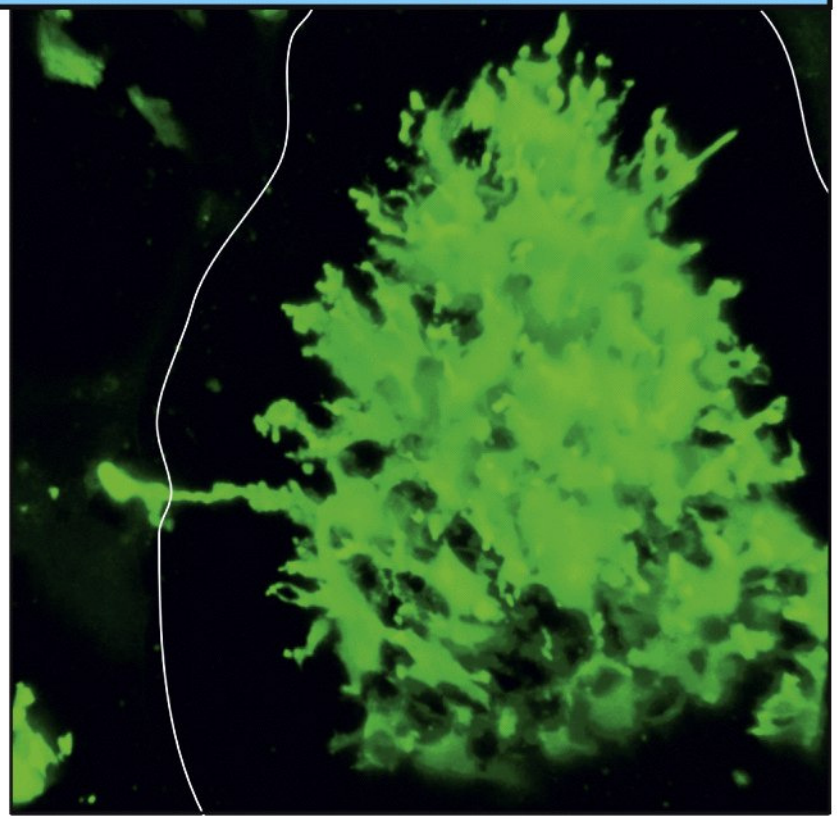
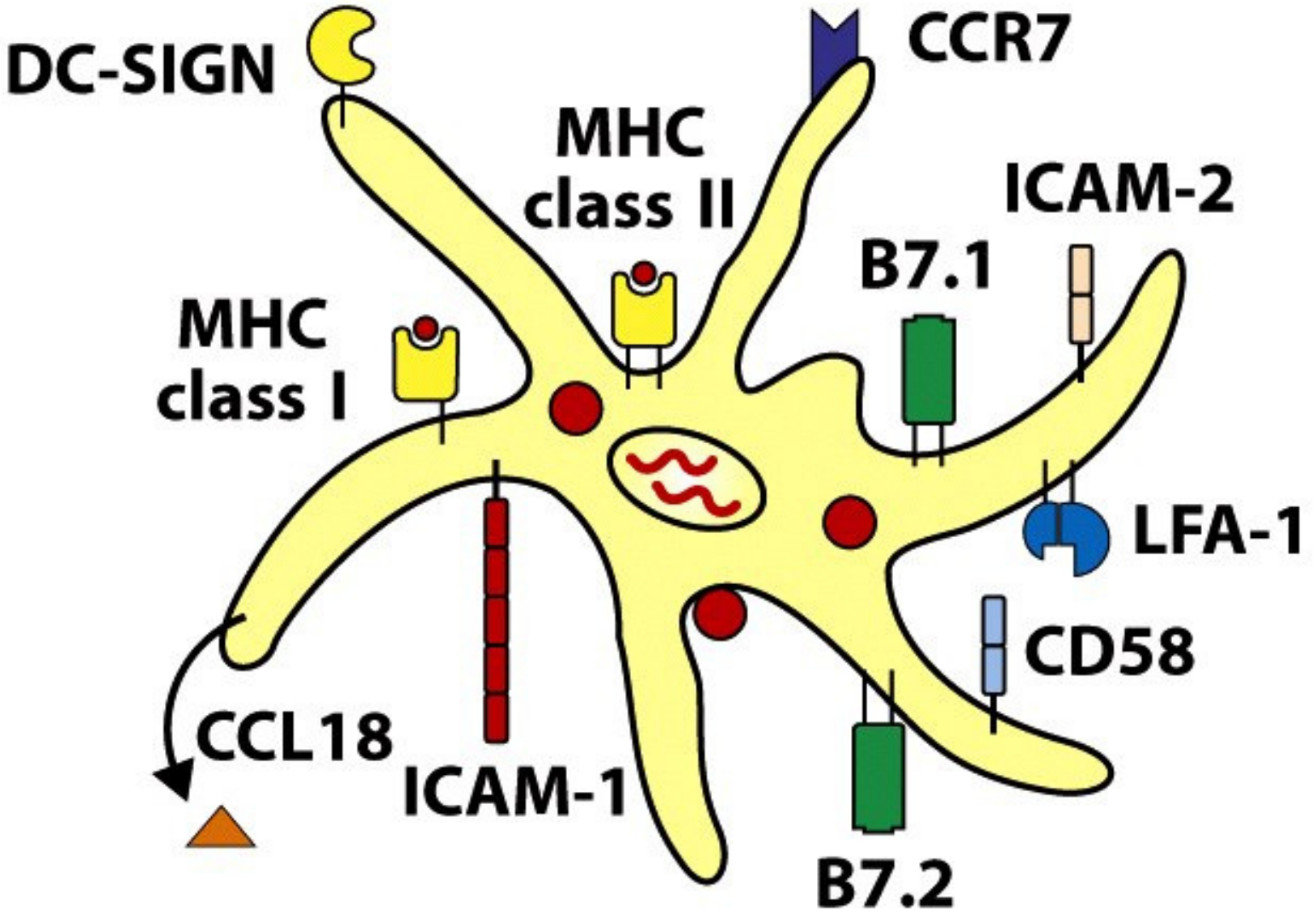


Figure 11-9 Immunobiology, 7ed. (© Garland Science 2008)

Conventional dendritic cell



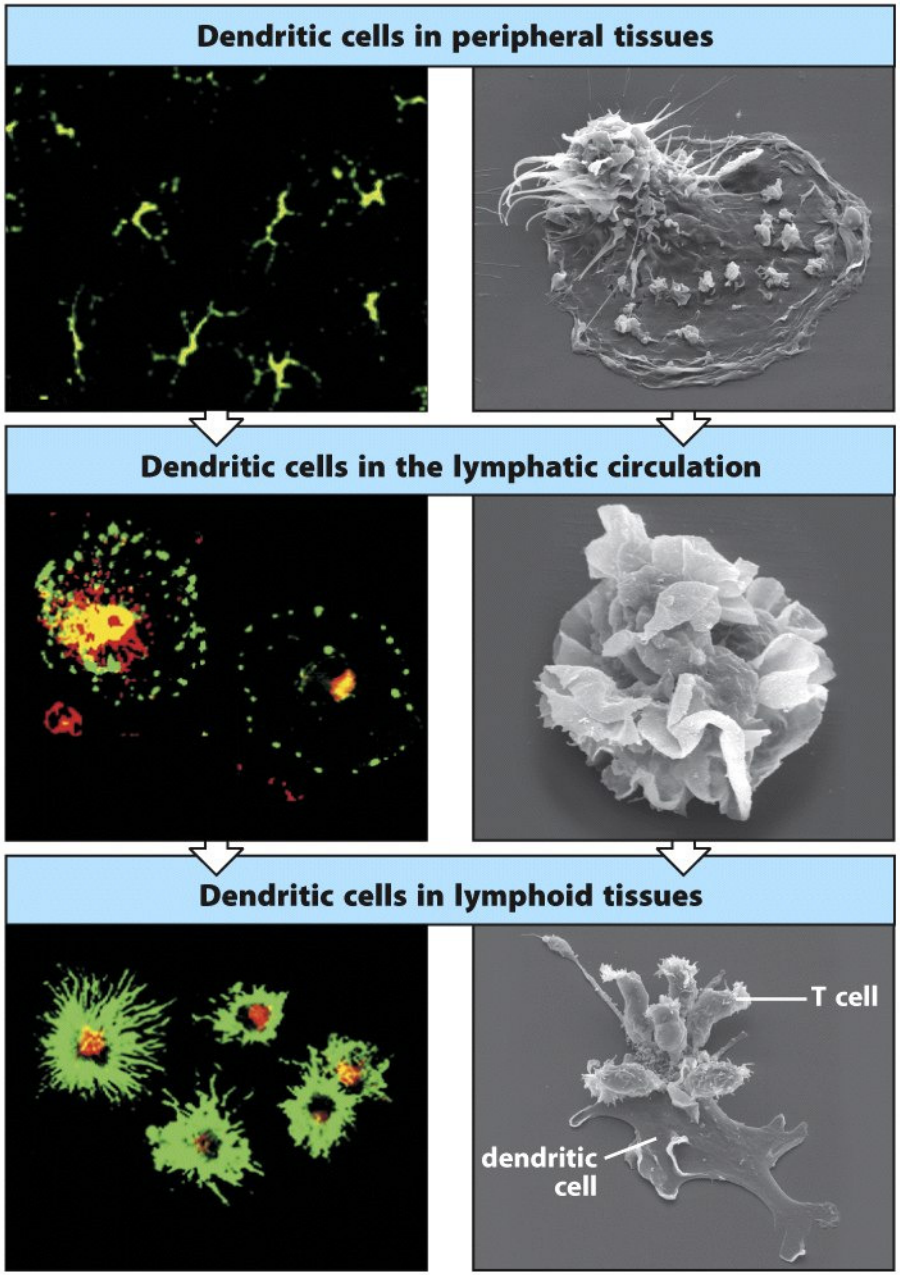


Figure 8-9 Immunobiology, 7ed. (© Garland Science 2008)

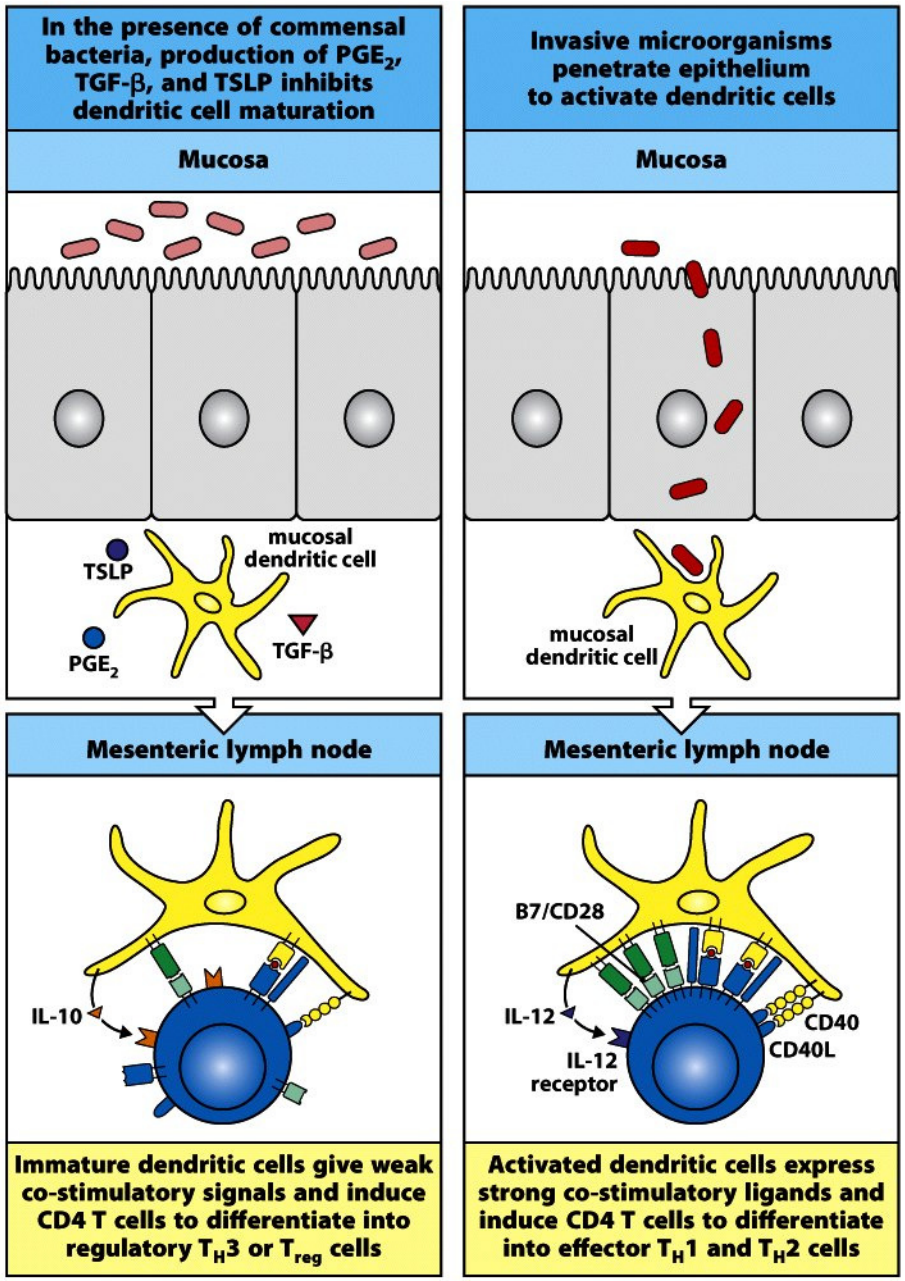
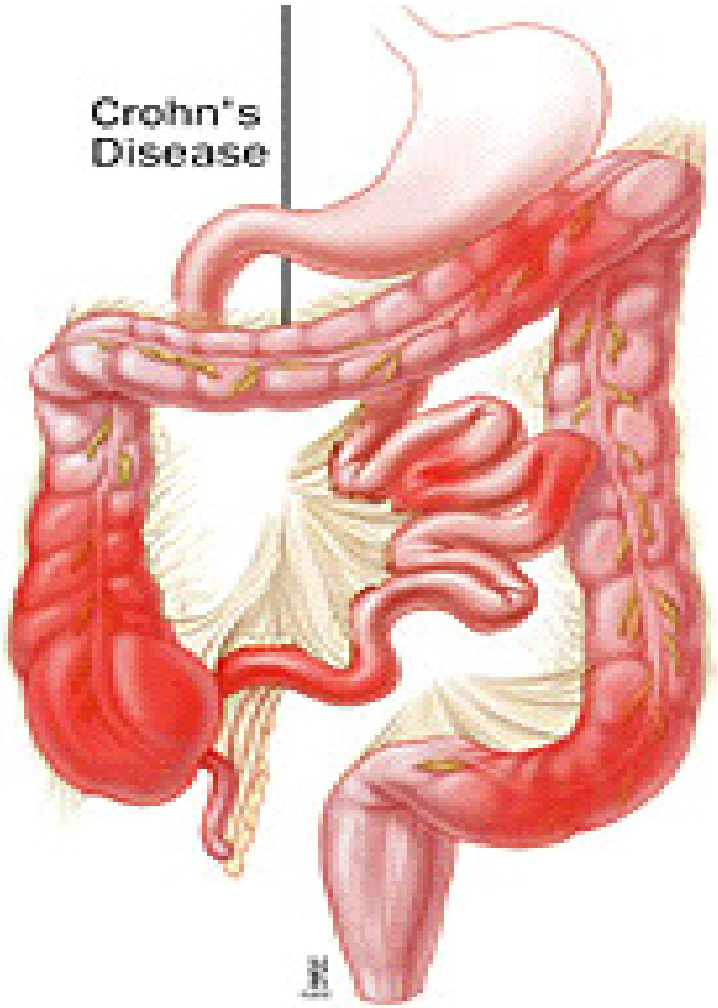


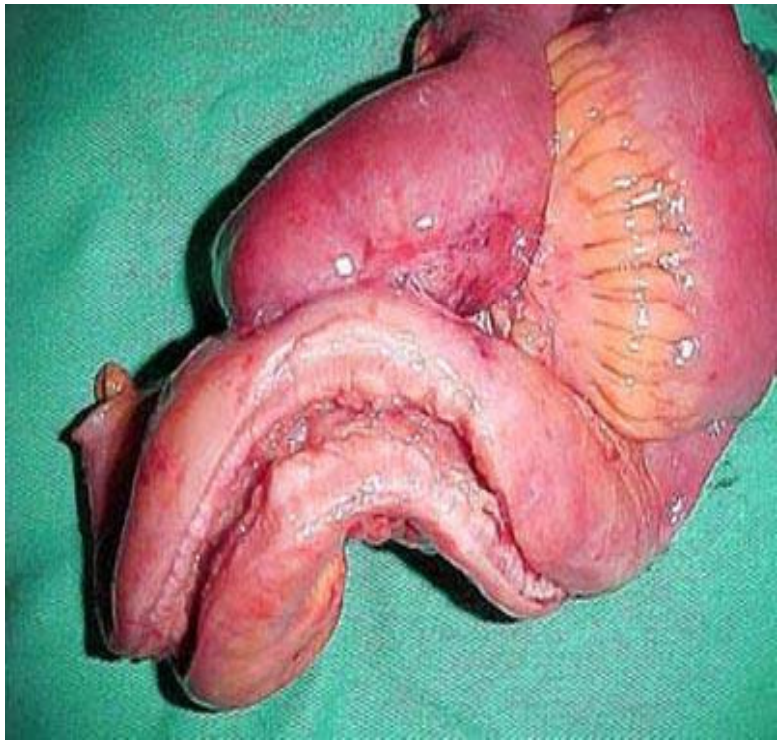
Figure 11-24 Immunobiology, 7ed. (© Garland Science 2008)

INFLAMMATORY DESEASES of THE MUCOSAL SYSTEM

- INFLAMMATORY BOWEL DISEASES
  - ★ Crohn's disease
  - ★ Ulcerative colitis
- CHRONIC AIRWAY DISEASES
  - ★ Rhinosinusitis
  - ★ Asthma
  - ★ COPD

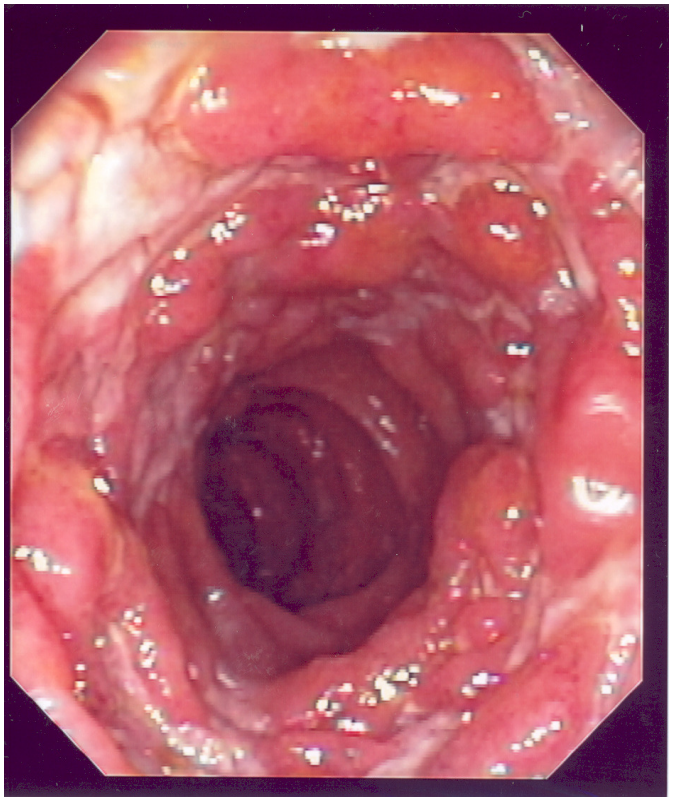
Crohn's disease





Any part of the bowel tract

Transmural



May 3rd 2002

May 3rd 2002

Etiopathogenesis of IBD: Present Hypothesis

IBD is caused by a loss of tolerance of the mucosal immune system to the commensal flora in the susceptible host triggered by as yet unknown environmental factors.

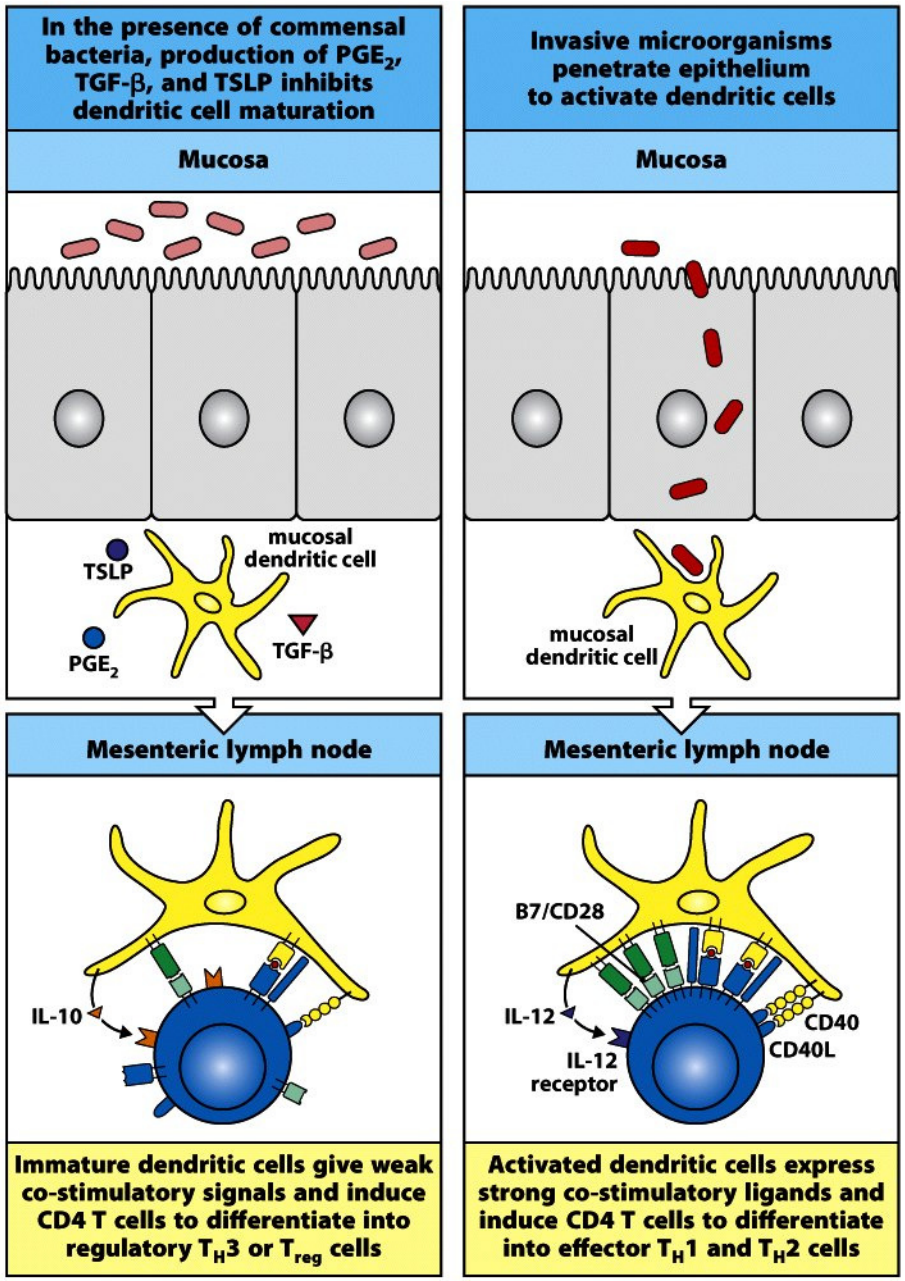
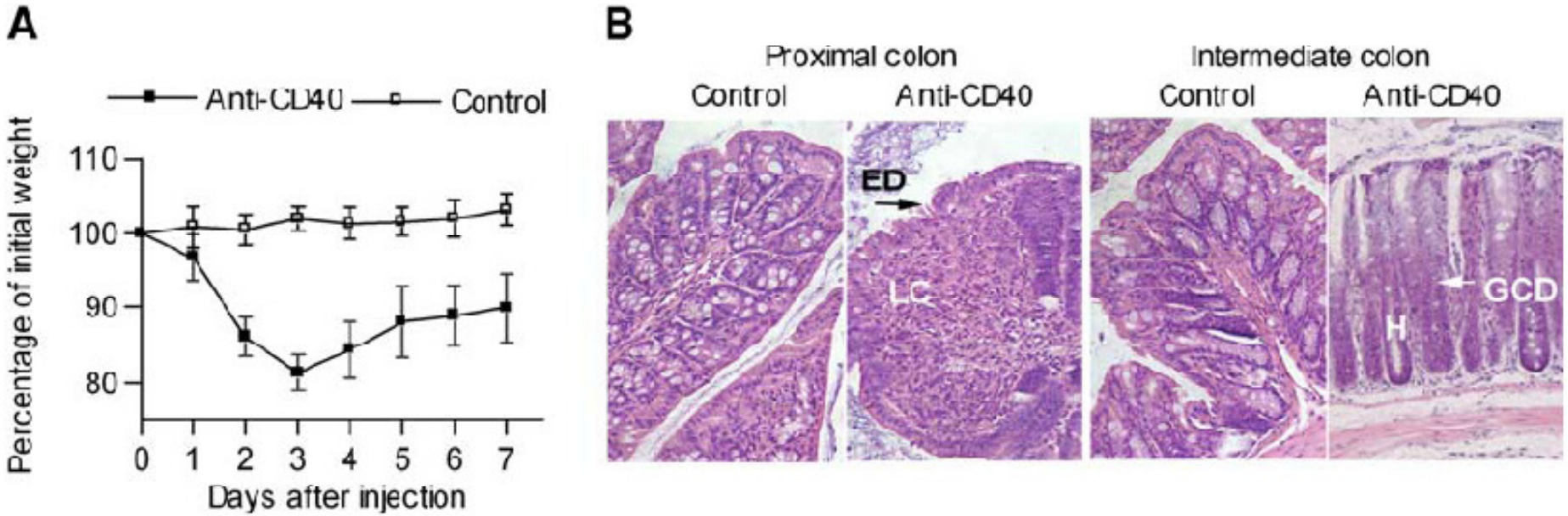
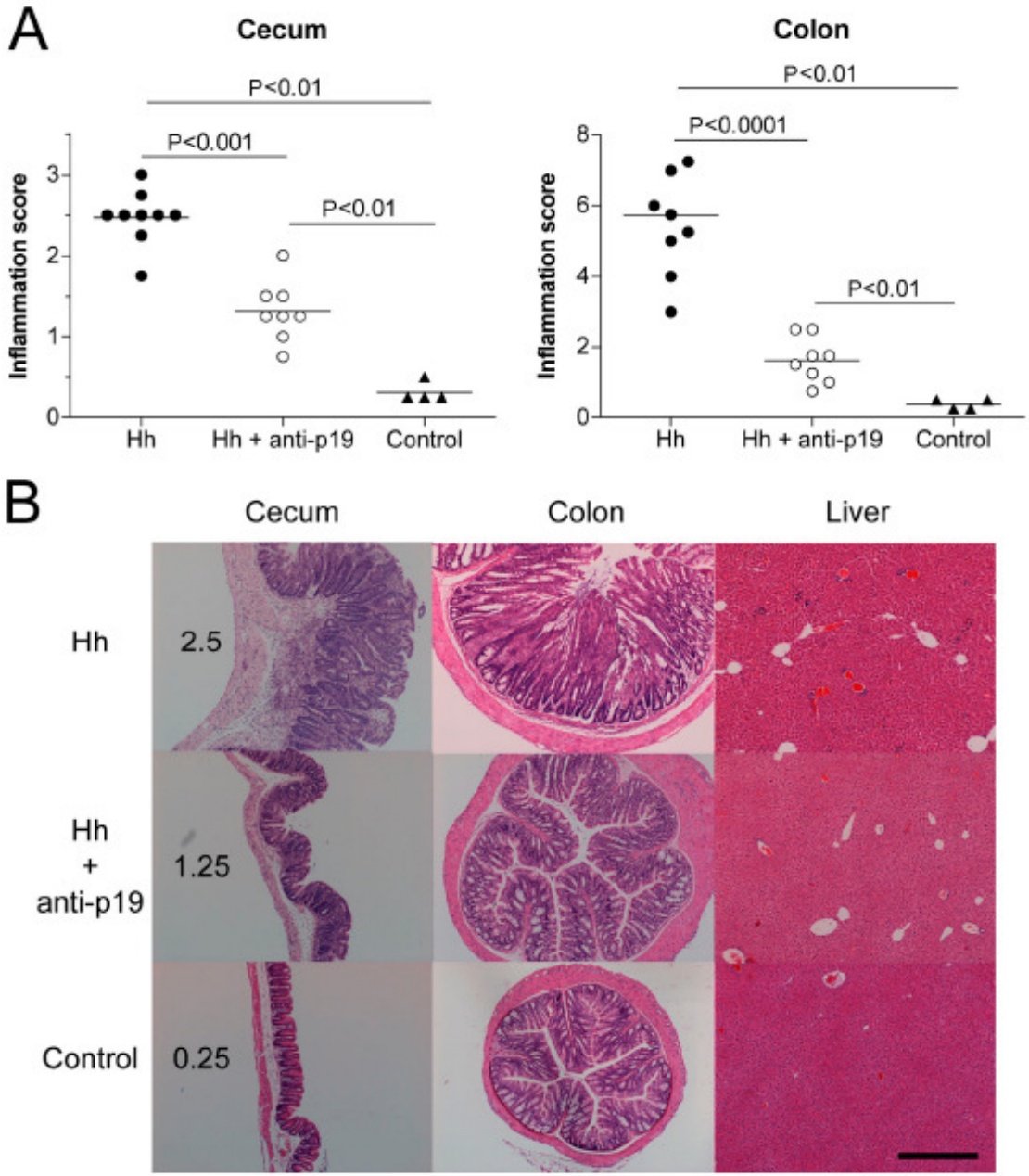


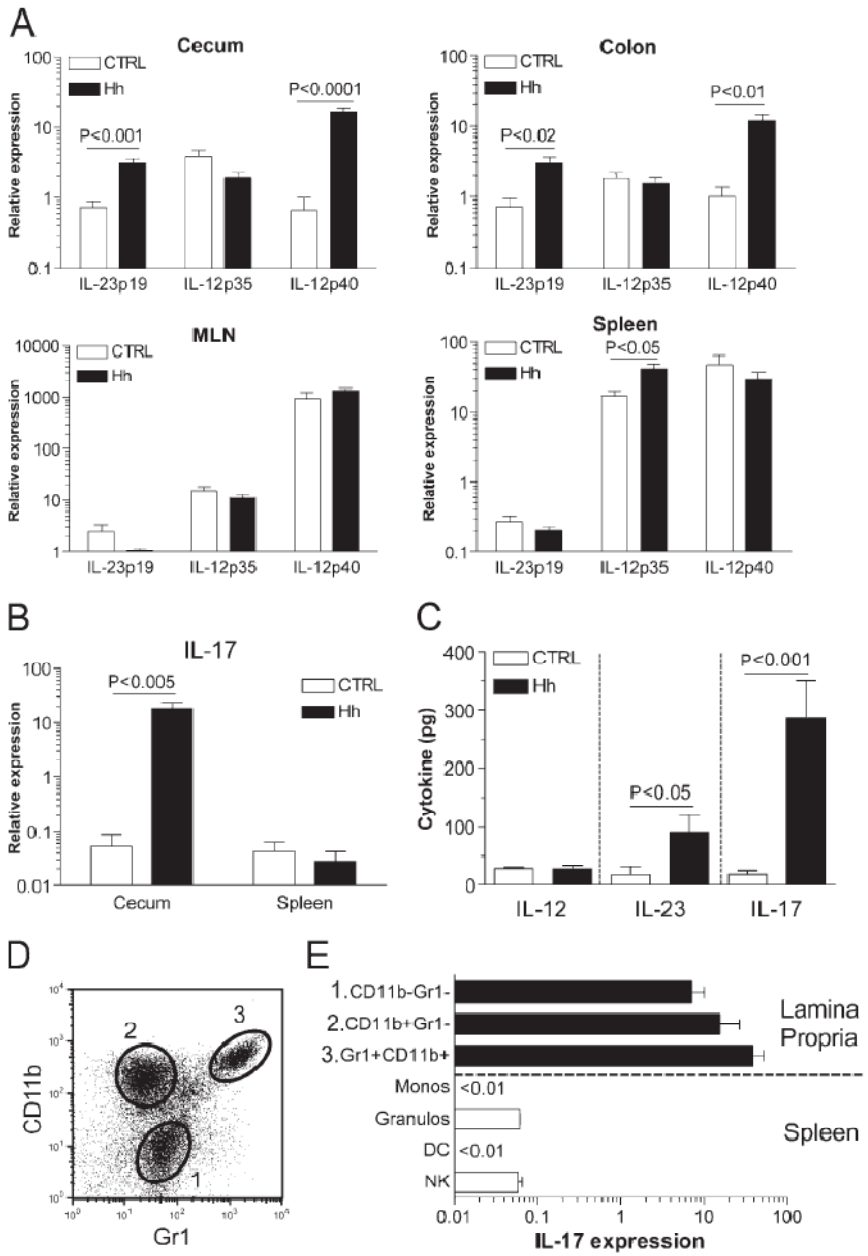
Figure 11-24 Immunobiology, 7ed. (© Garland Science 2008)



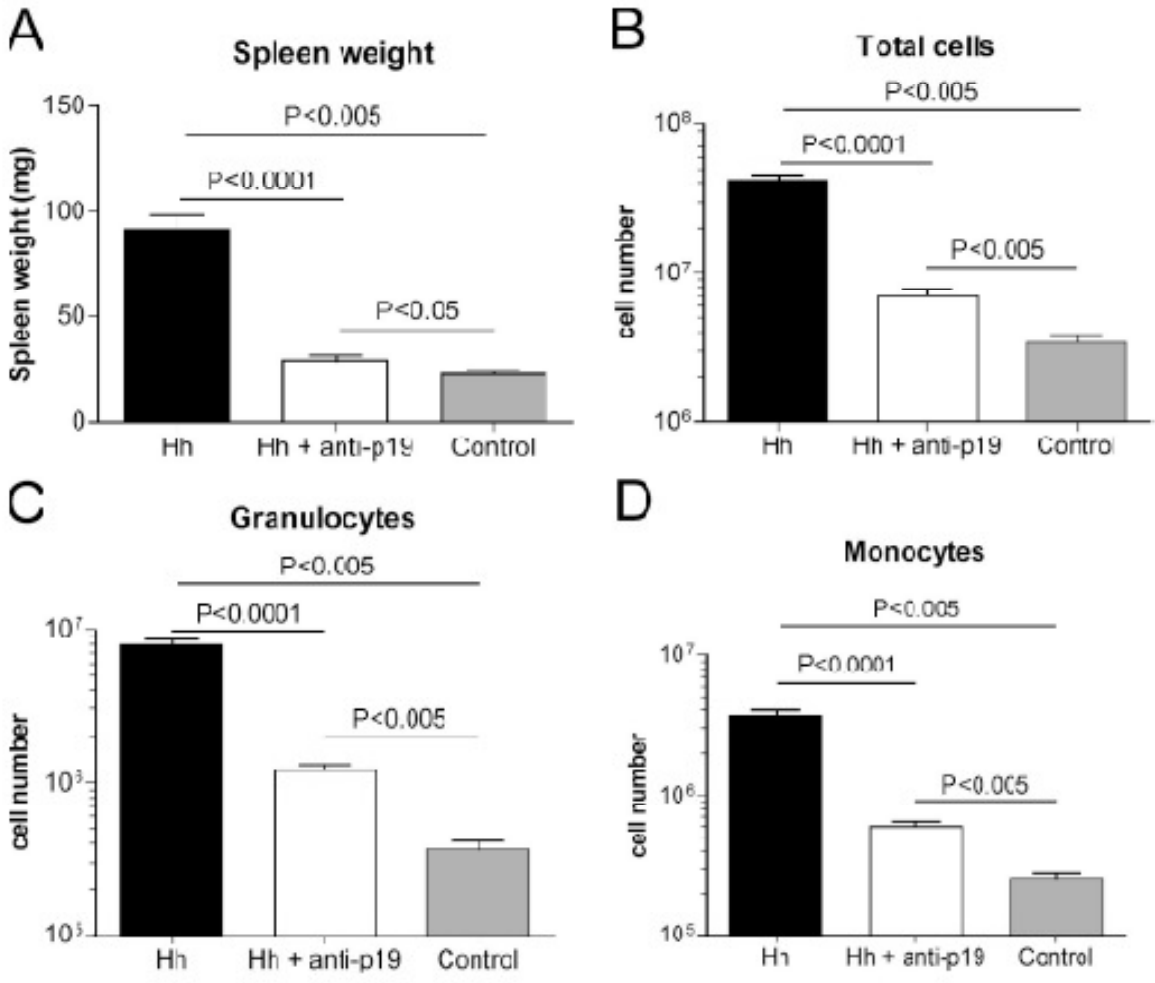
Uhlig et al 2006



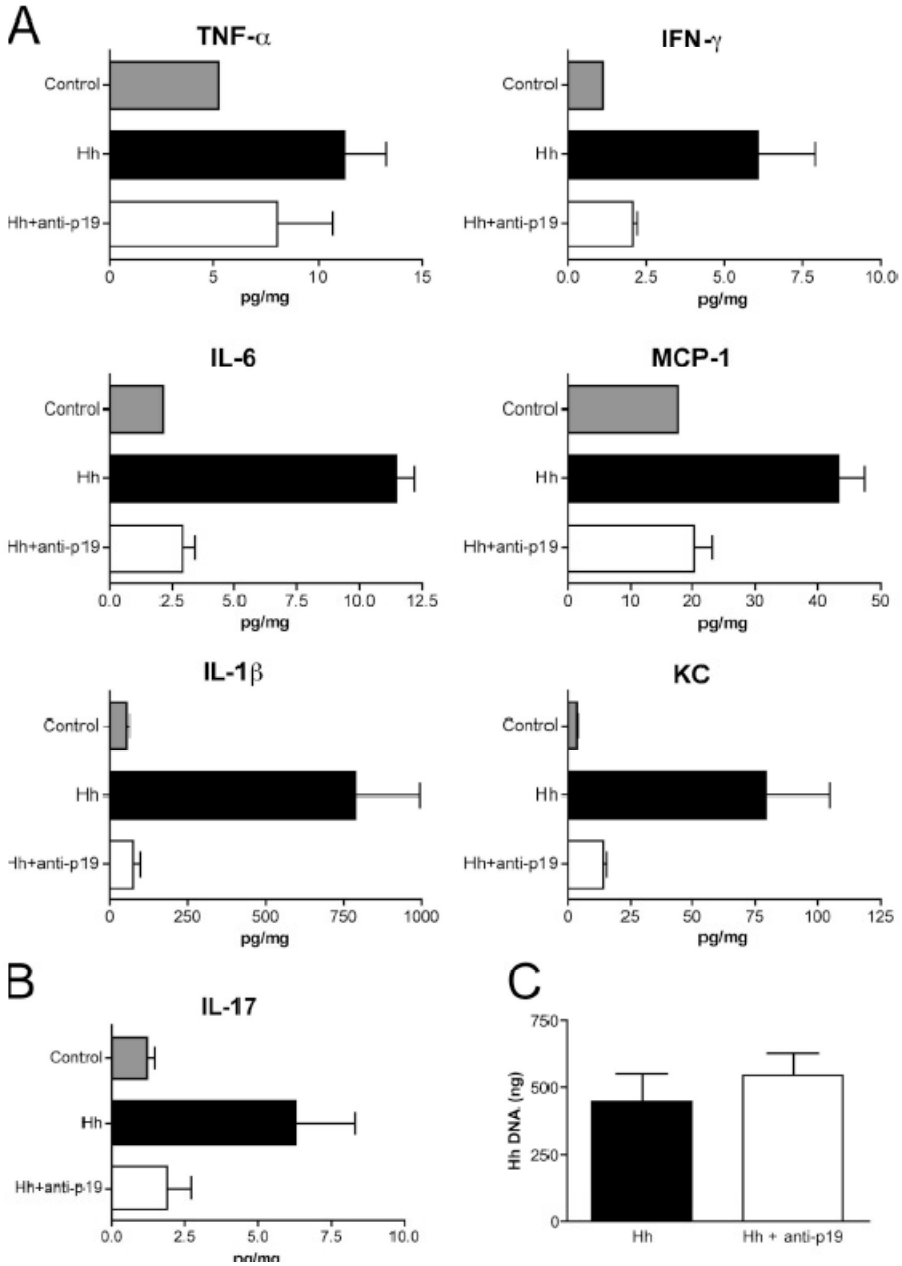
S. Hue et al – J Exp Med 2006



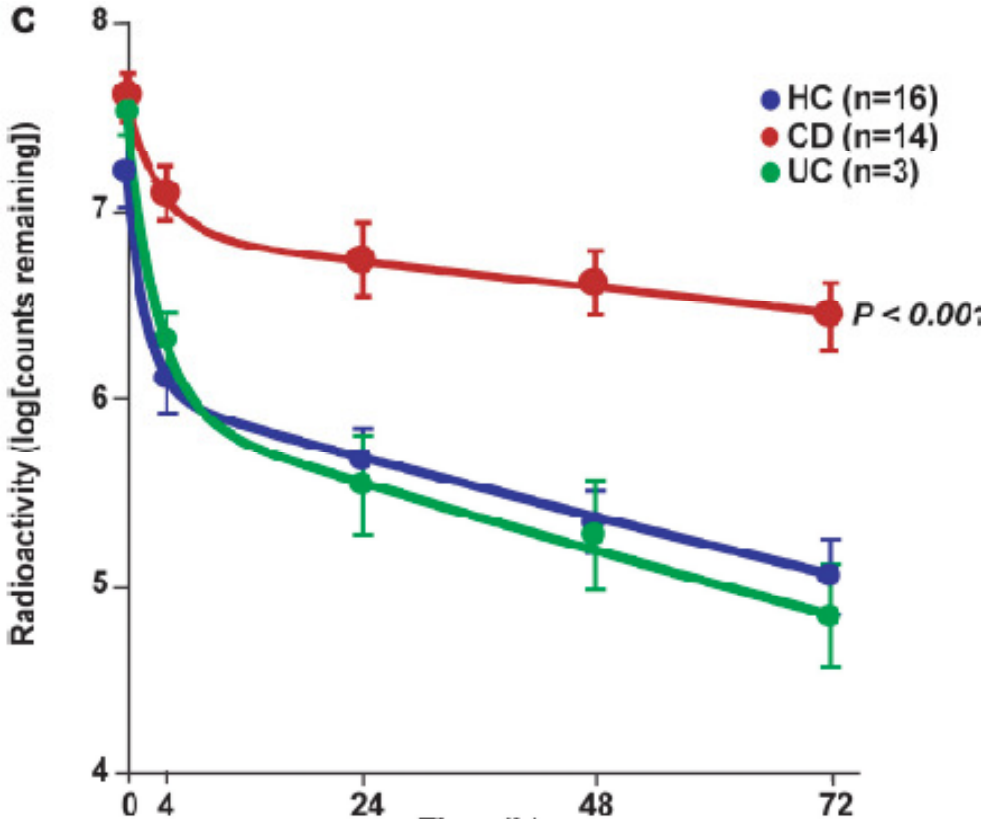
S. Hue et al – J Exp Med 2006



S. Hue et al – J Exp Med 2006



S. Hue et al – J Exp Med 2006

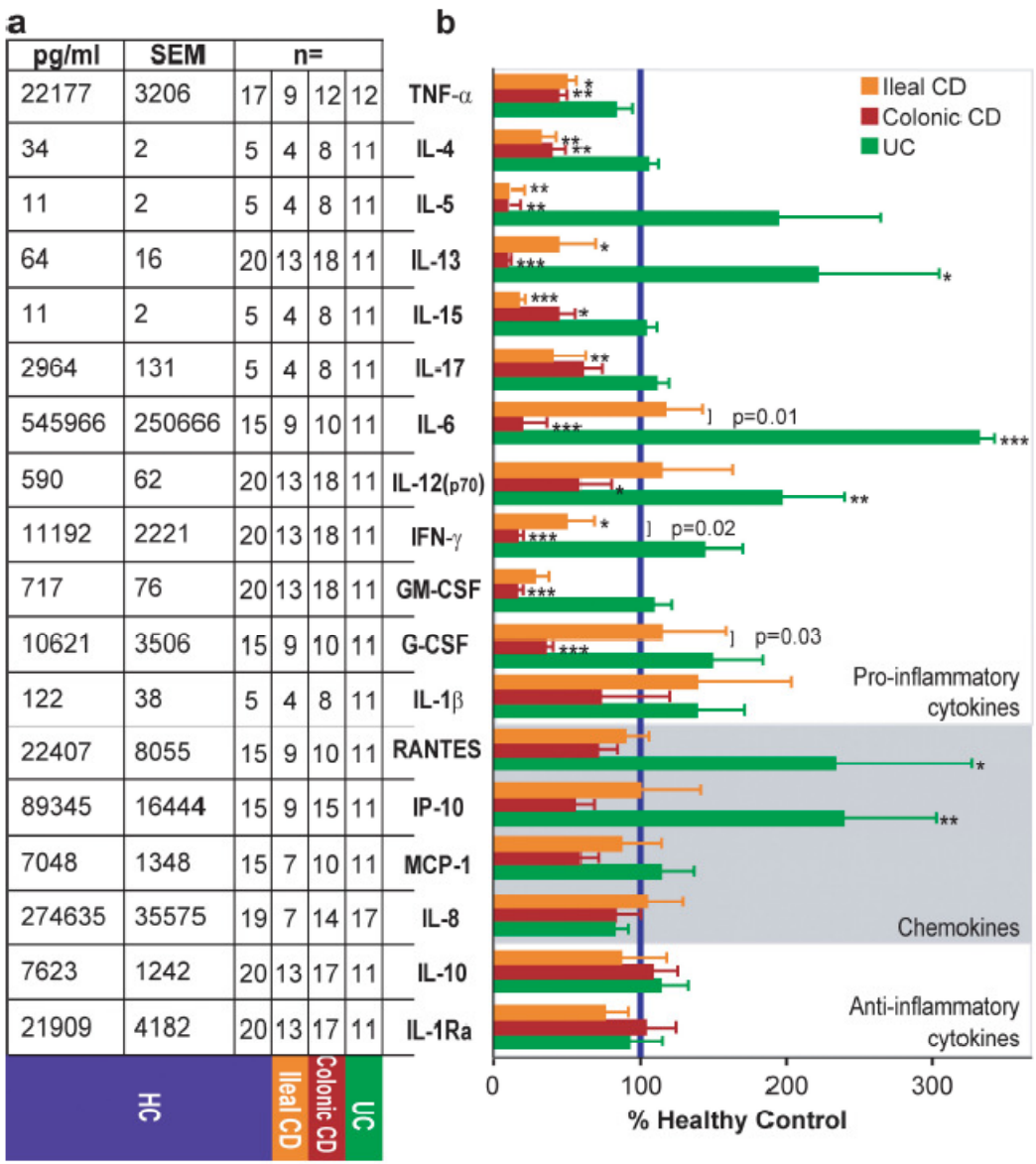


Bacterial clearance after S.C. injection of Hk E. Coli

Smith et Al J Exp Med 2009

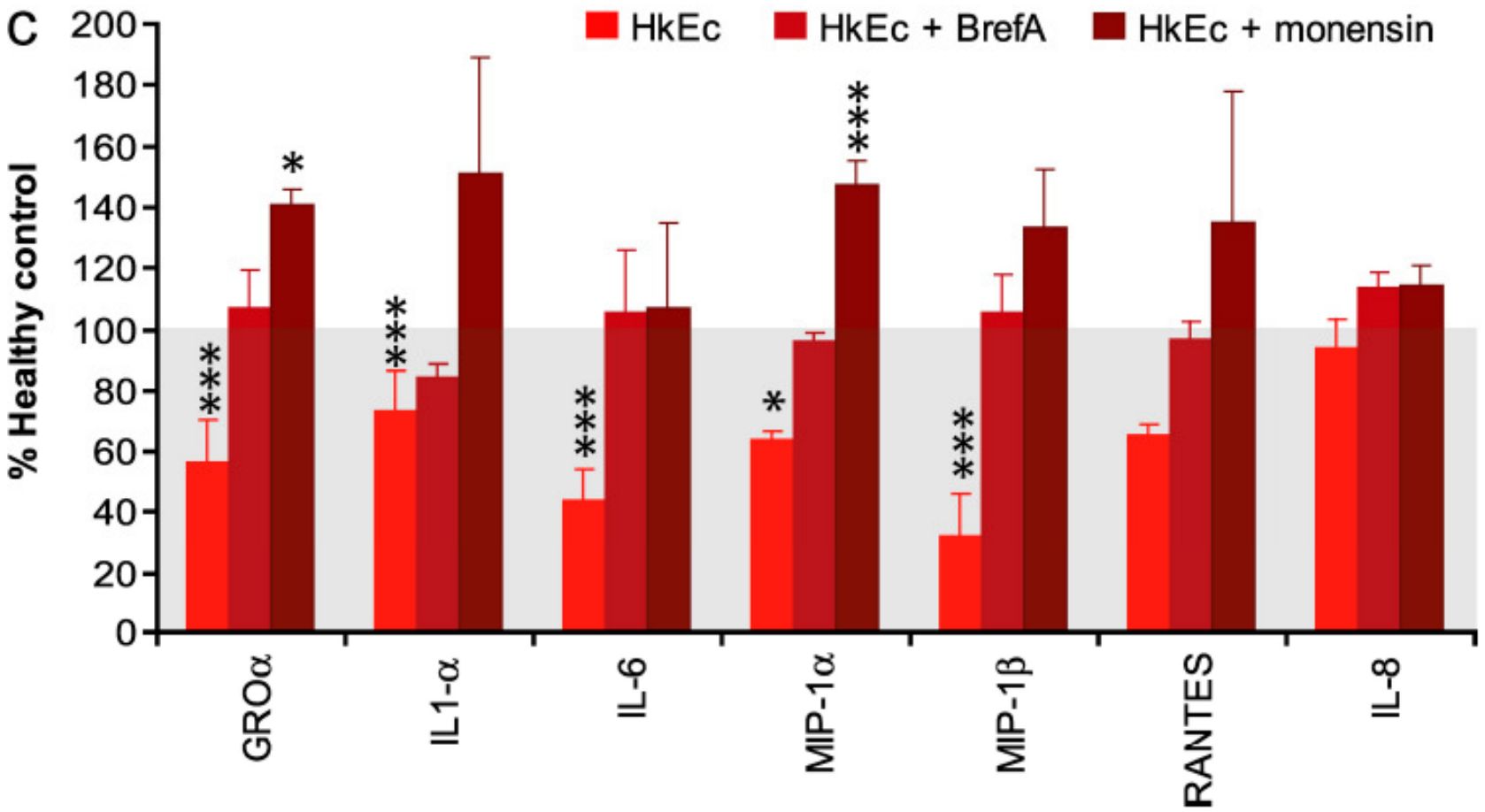
a

pg/ml	SEM	n=				
22177	3206	17	9	12	12	TNF-α
34	2	5	4	8	11	IL-4
11	2	5	4	8	11	IL-5
64	16	20	13	18	11	IL-13
11	2	5	4	8	11	IL-15
2964	131	5	4	8	11	IL-17
545966	250666	15	9	10	11	IL-6
590	62	20	13	18	11	IL-12(p70)
11192	2221	20	13	18	11	IFN-γ
717	76	20	13	18	11	GM-CSF
10621	3506	15	9	10	11	G-CSF
122	38	5	4	8	11	IL-1β
22407	8055	15	9	10	11	RANTES
89345	16444	15	9	15	11	IP-10
7048	1348	15	7	10	11	MCP-1
274635	35575	19	7	14	17	IL-8
7623	1242	20	13	17	11	IL-10
21909	4182	20	13	17	11	IL-1Ra



Blood monocyte derived Macrophages from CD patients produce <u>reduced</u> amounts of pro-inflammatory cytokines

Smith et Al J Exp Med 2009



Normalisation of intracellular cytokines in macrophages of CD patients after inhibition of vesicle trafficking or lysomal function

Smith et Al J Exp Med 2009

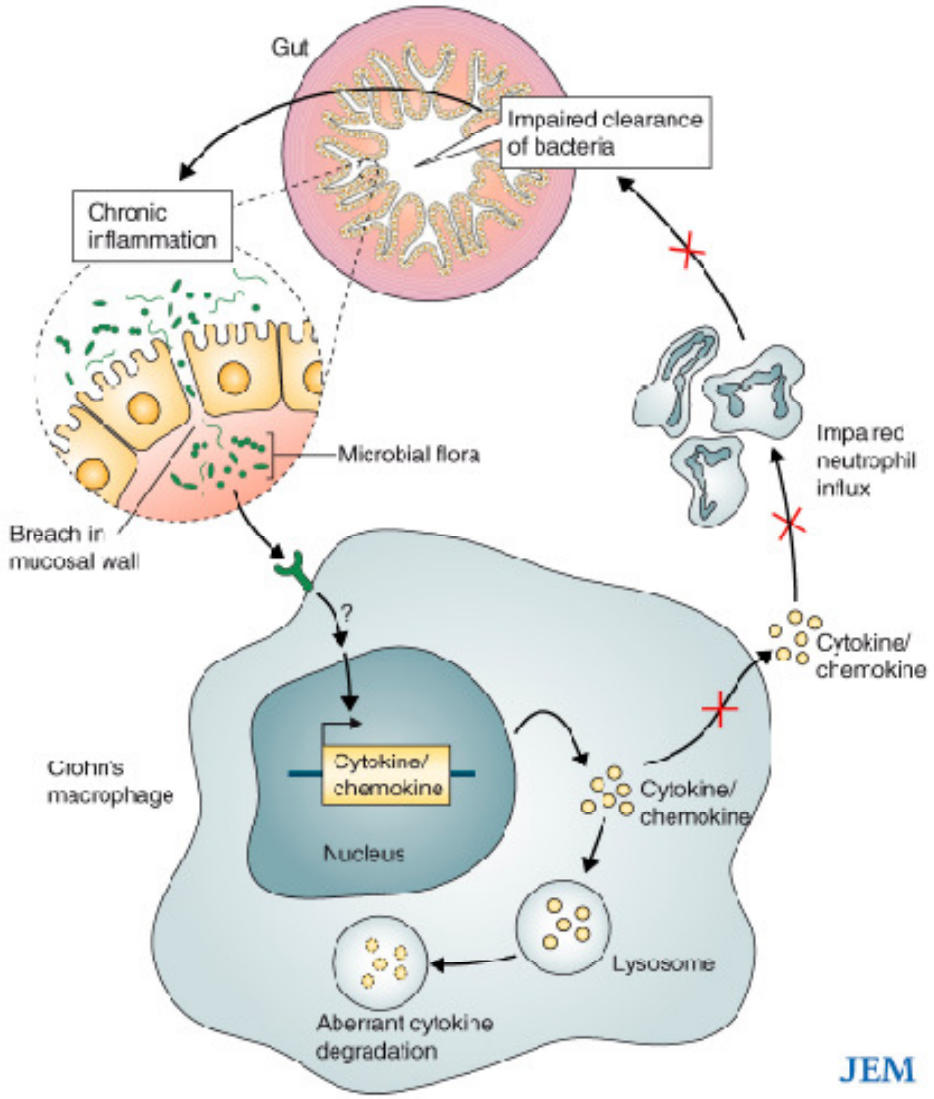
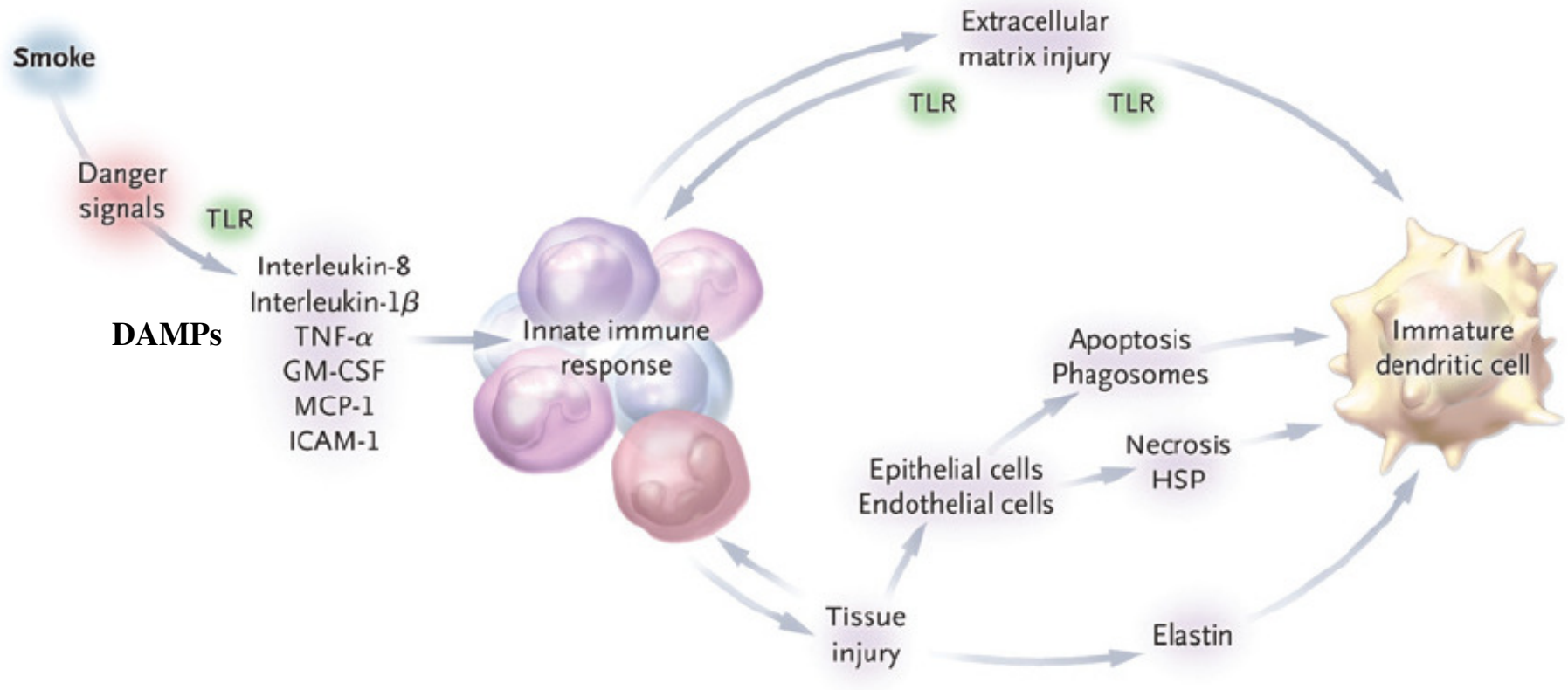


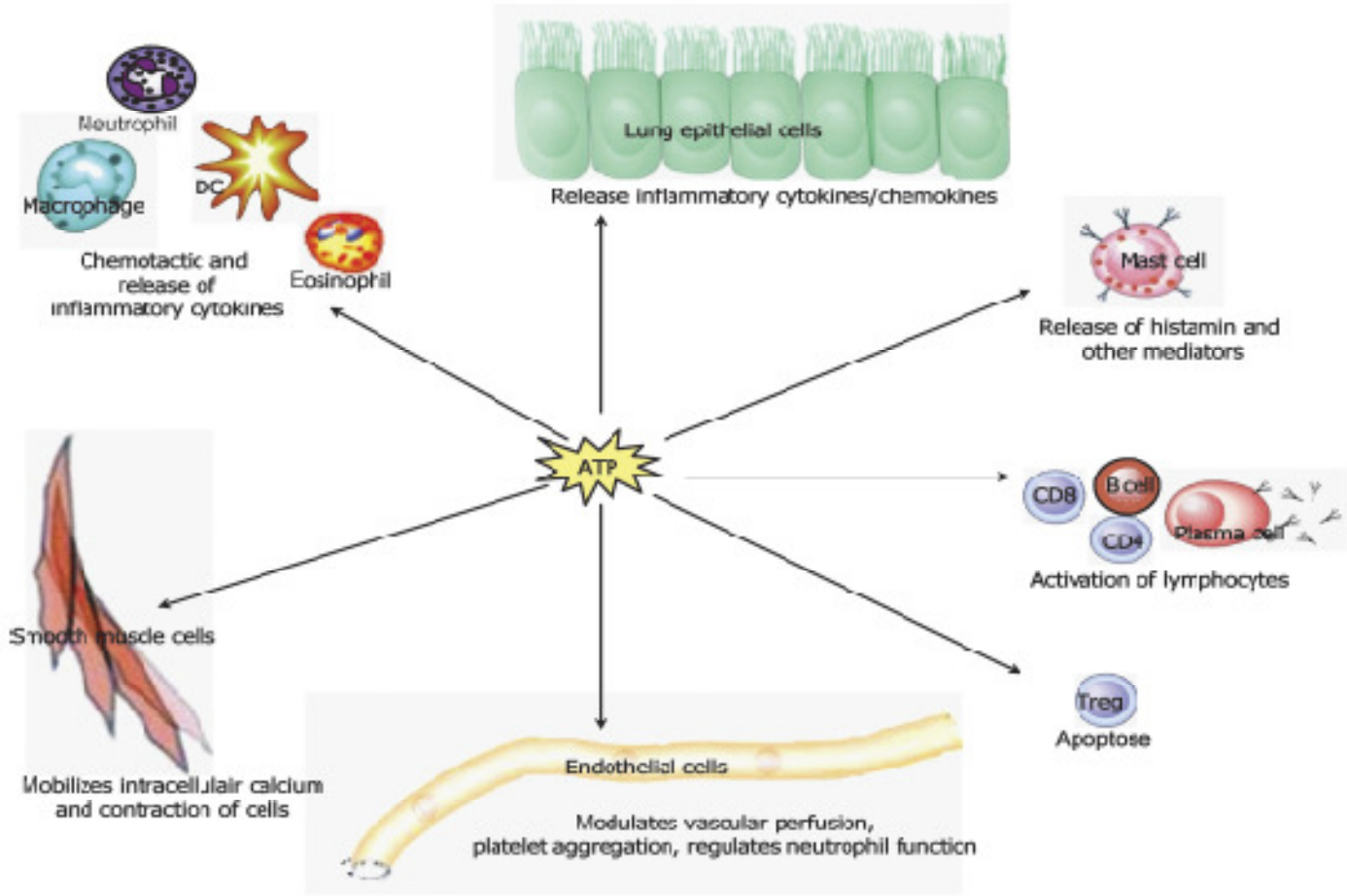
Figure1. A model of intestinal chronic inflammation caused by inborn errors of macrophages in patients with CD.

"Casanova and Abel, J Exp Med 2009"

INFLAMMATORY DESEASES of THE MUCOSAL SYSTEM

- INFLAMMATORY BOWEL DISEASES
  - ★ Crohn's disease
  - ★ Ulcerative colitis
- CHRONIC AIRWAY DISEASES
  - ★ Rhinosinusitis
  - ★ Asthma
  - ★ COPD


Smoke
Danger signals
TLR
DAMPs
Interleukin-8
Interleukin-1β
TNF-α
GM-CSF
MCP-1
ICAM-1
Innate immune response
Extracellular matrix injury
TLR
TLR
Apoptosis
Phagosomes
Necrosis
HSP
Epithelial cells
Endothelial cells
Tissue injury
Elastin
Immature dendritic cell


Neutrophil
Macrophage
DC
Eosinophil
Chemotactic and release of inflammatory cytokines
Lung epithelial cells
Release inflammatory cytokines/chemokines
Mast cell
Release of histamin and other mediators
ATP
CD8
B cell
CD4
Plasma cell
Activation of lymphocytes
Smooth muscle cells
Mobilizes intracellular calcium and contraction of cells
Treg
Apoptose
Endothelial cells
Modulates vascular perfusion, platelet aggregation, regulates neutrophil function

Innate immunity

Old view

- Primitive less efficient defense system
- Barrier function

New view

- Highly efficient defense system
- Sensing of DANGER directing adaptive immunity