Basic immunology

Lecture 4.

Innate immunity, inflammatory reaction

Timea Berki

Time kinetics of Innate and Adaptive Immunity

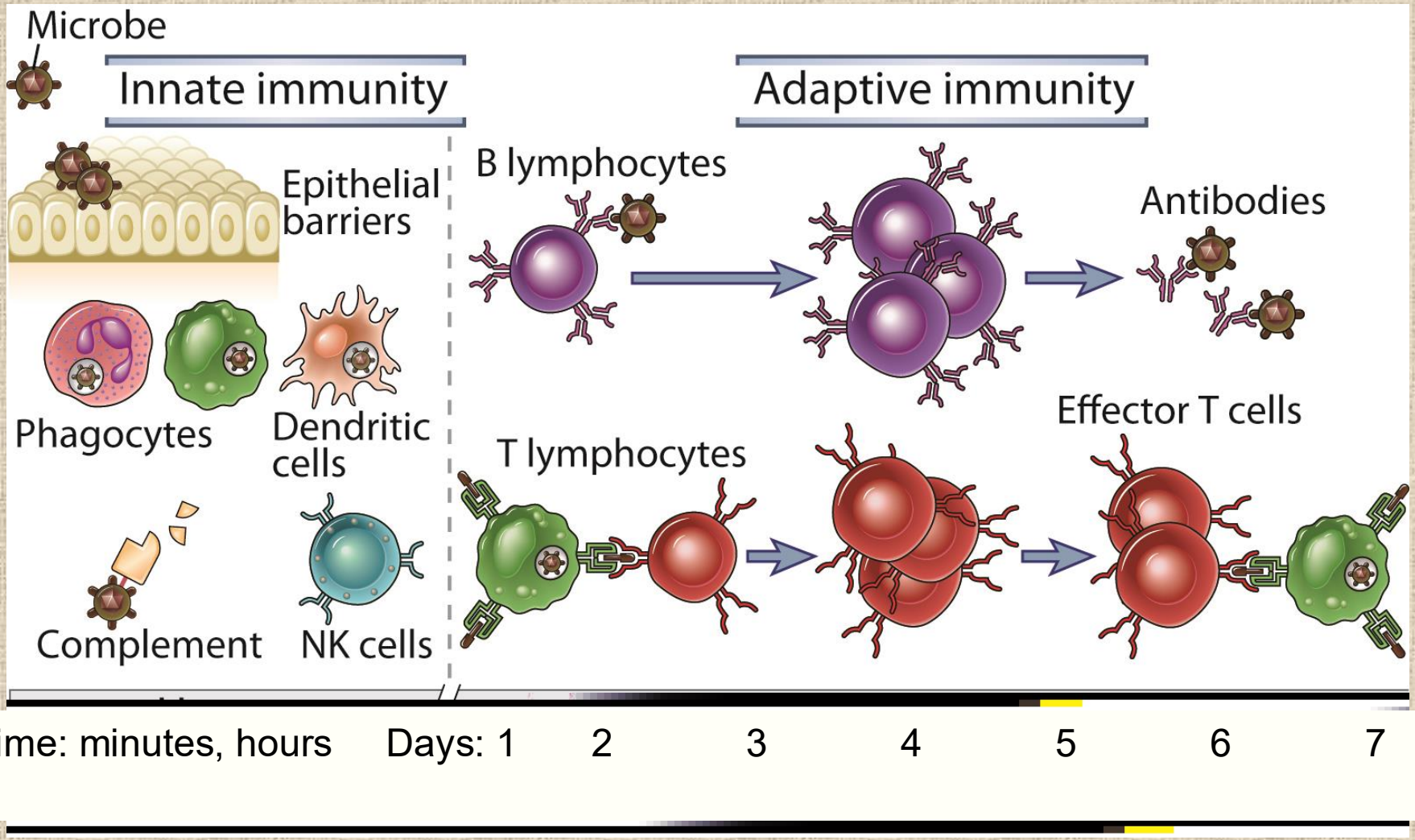


Fig. 1-1

Routes of Antigen Entry

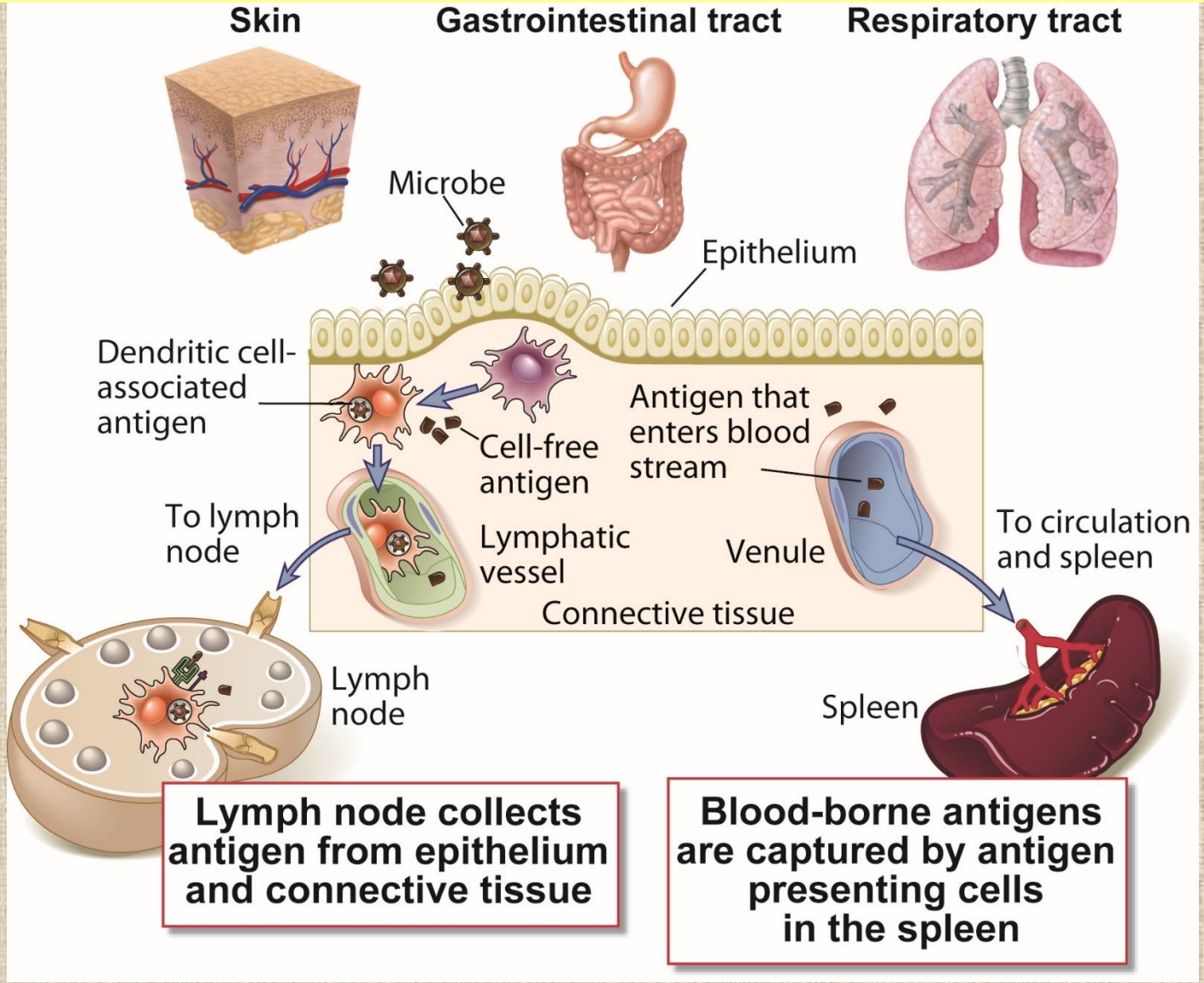


Fig. 6-3

INFLAMMATION

- **Acute inflammation < 2 weeks**
- **Chronic inflammation > 6 weeks**

- **LOCAL**
- **SYSTEMIC**

The causes or inducers of inflammation: exogenous and endogenous inducers

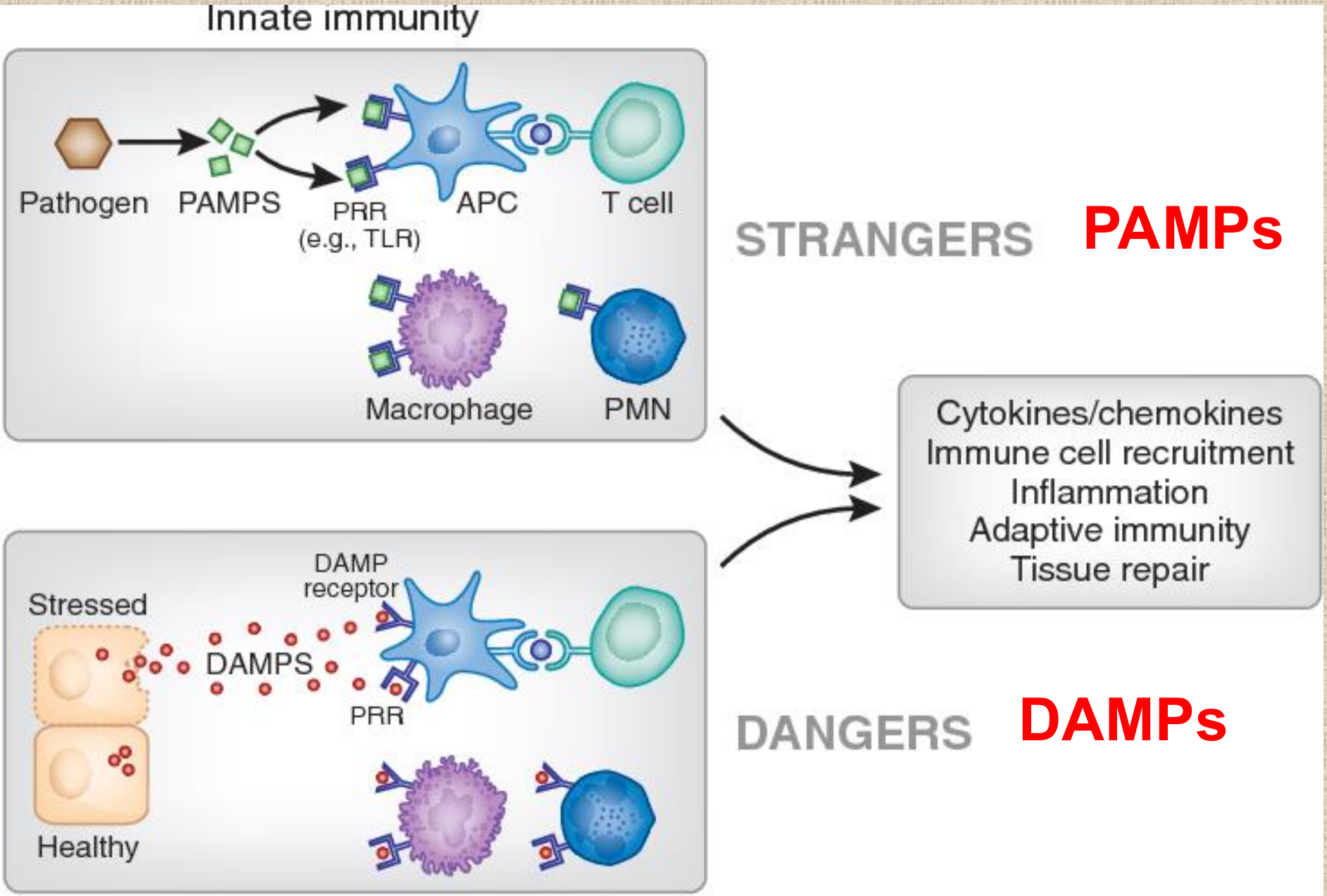
Microbial: **PAMPS** and Virulence factors (toxins)

Non-microbial: allergens, toxic compounds, irritants, and foreign bodies (silica)

DAMPS: Dead, damaged, malfunctioning or stressed cells, tissues release signals that induce inflammation

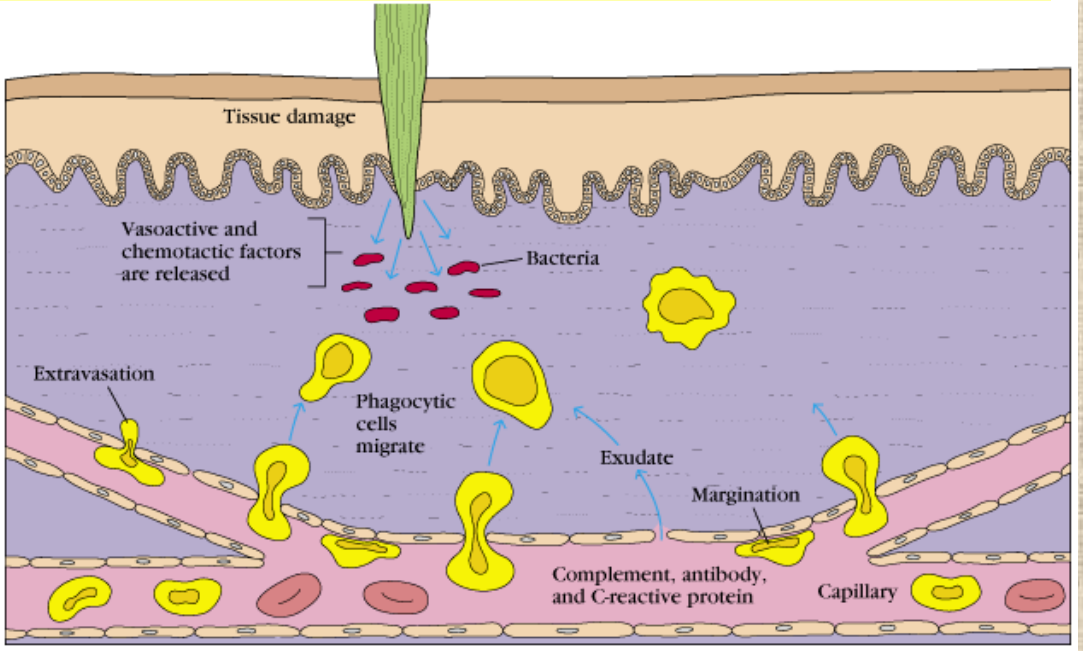
Alarm signals

- **PAMPs** (Pathogen-Associated Molecular Patterns) → microbial infection induced inflammation
- **DAMPs** (Damage-Associated Molecular Patterns) released from damaged host cells (like ATP, HMGB1, uric acid, histones, mitDNA) → sterile inflammation in response to injury, stress, or cancer,
- both activate immune cells via shared receptors (**PRRs**) to initiate healing


Innate immunity
Pathogen
PAMPS
PRR
(e.g., TLR)
APC
T cell
Macrophage
PMN
STRANGERS
PAMPs
Cytokines/chemokines
Immune cell recruitment
Inflammation
Adaptive immunity
Tissue repair
DAMP
receptor
Stressed
DAMPS
PRR
Healthy
DANGERS
DAMPs

Acute, local inflammation:

- Infection or tissue-injury initiate the cascade of non-specific reactions
- Immediate reaction
- Its role is to inhibit the spreading of infection and tissue injury



Celsus: 4 signs of inflammation: - rubor (red), calor (hot), dolor (painfull), tumor (swelling) + functio laesa (loss of function)

3 main events:
- Vasodilation – minutes
- Increased capillary permeability, fluid efflux, oedema
- Phagocytes migration: - hours

Goldsby RA, Kindt TJ, Osborne BA: Kuby Immunology 4th Edition, 2000.

Molecular mediators of inflammation

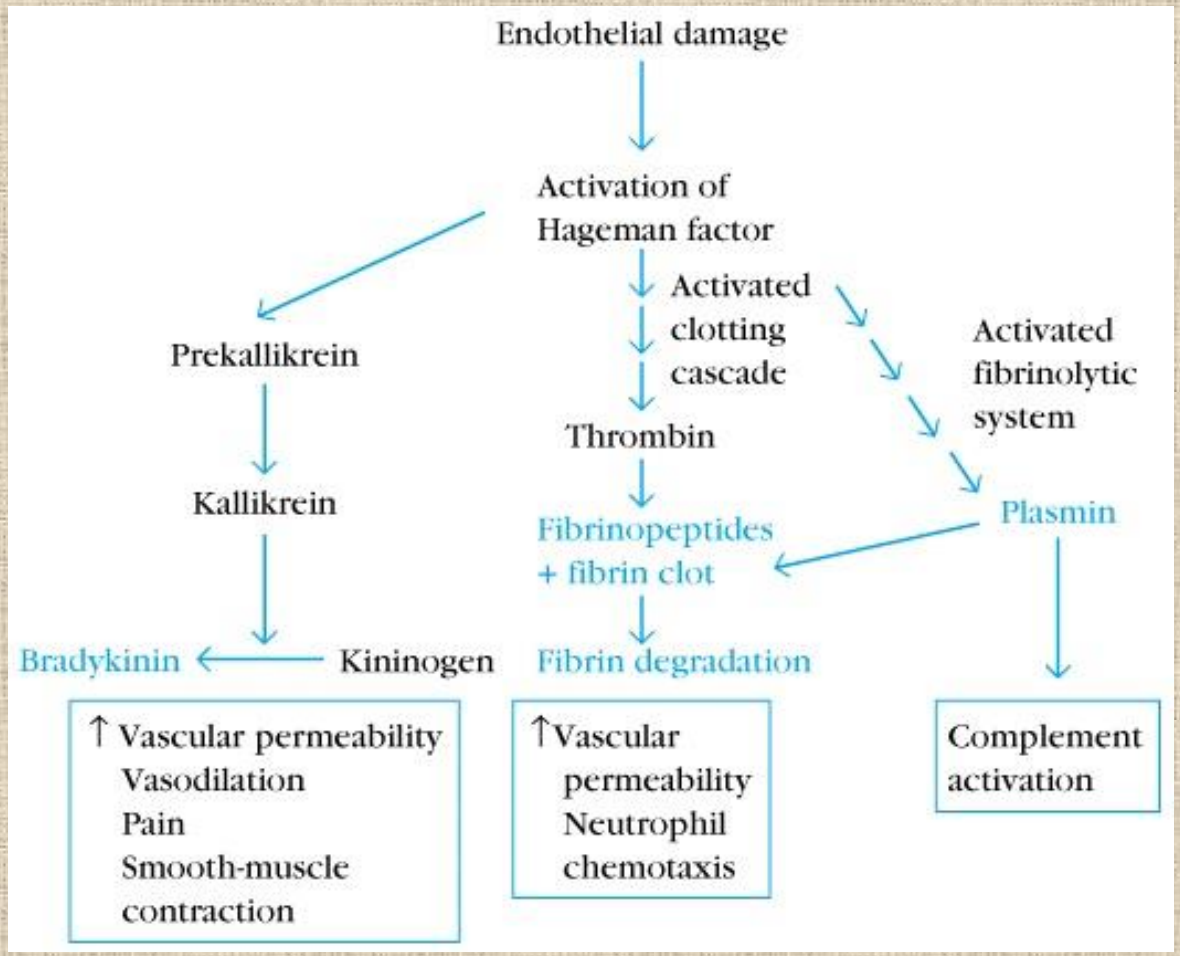
Plasma enzyme mediators:

- kinin kallikrein system
- Fibrinolytic system
- Complement cascade
- Clotting cascade

Lipid mediators:
leukotrienes,
prostaglandins (PGE)

Chemoattractants:
-Chemokines: IL-8
-Complement components
- PAF (platelet activating factor)

Inflammatory cytokines:
IL-1, IL-6, TNFalpha



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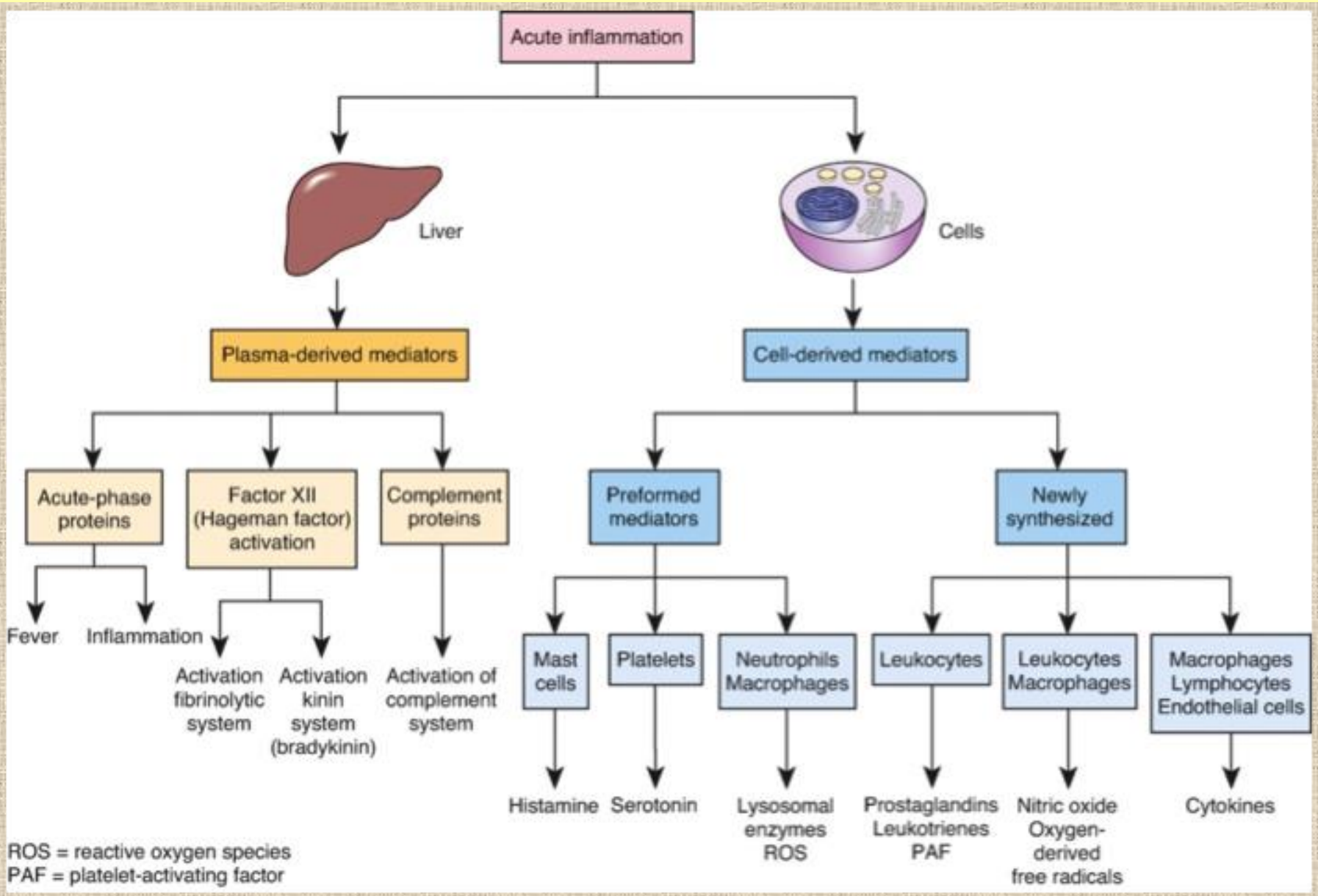
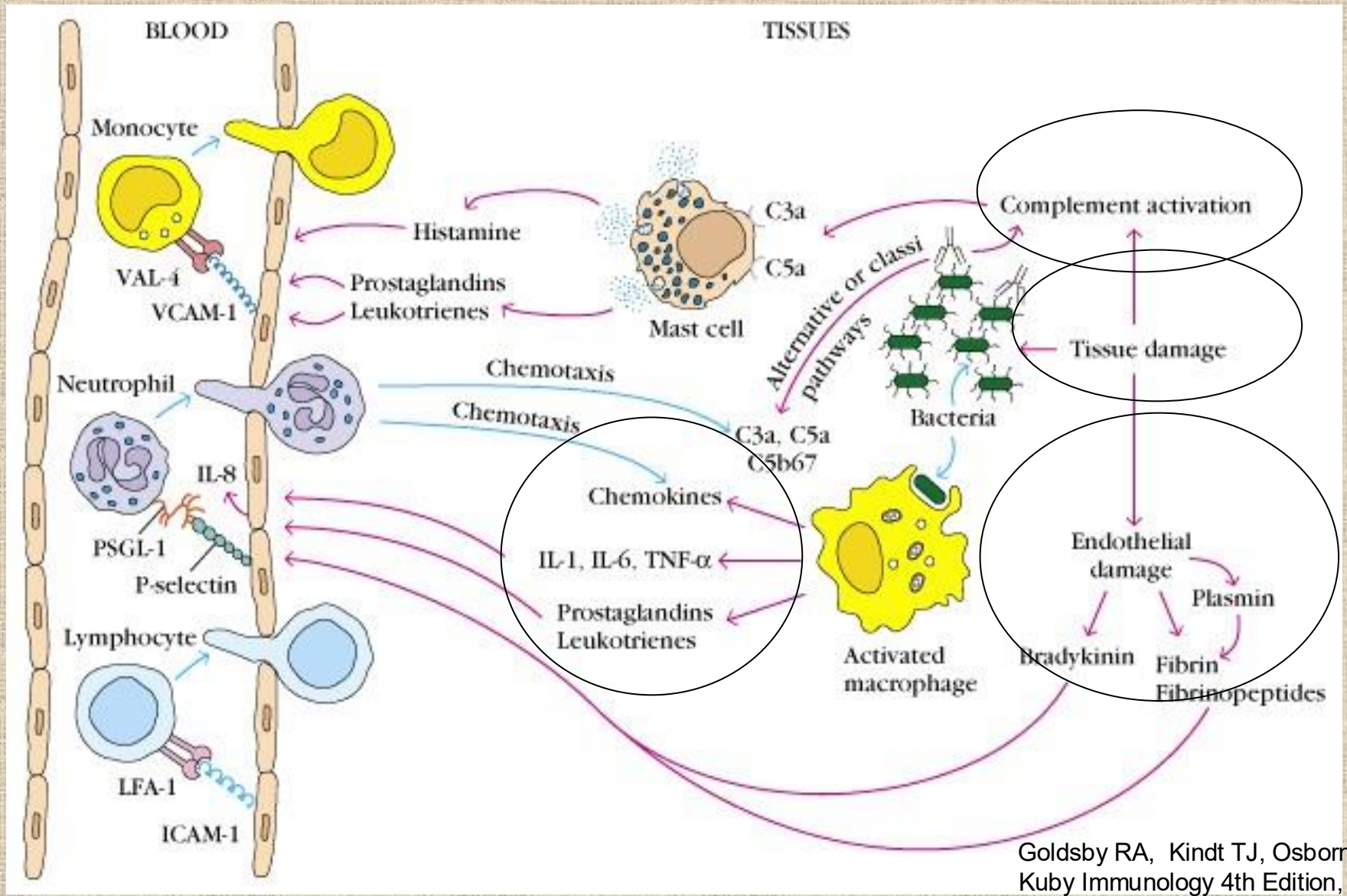
Kuby Immunology 4th Edition, 2000.

Production of mediators of inflammation



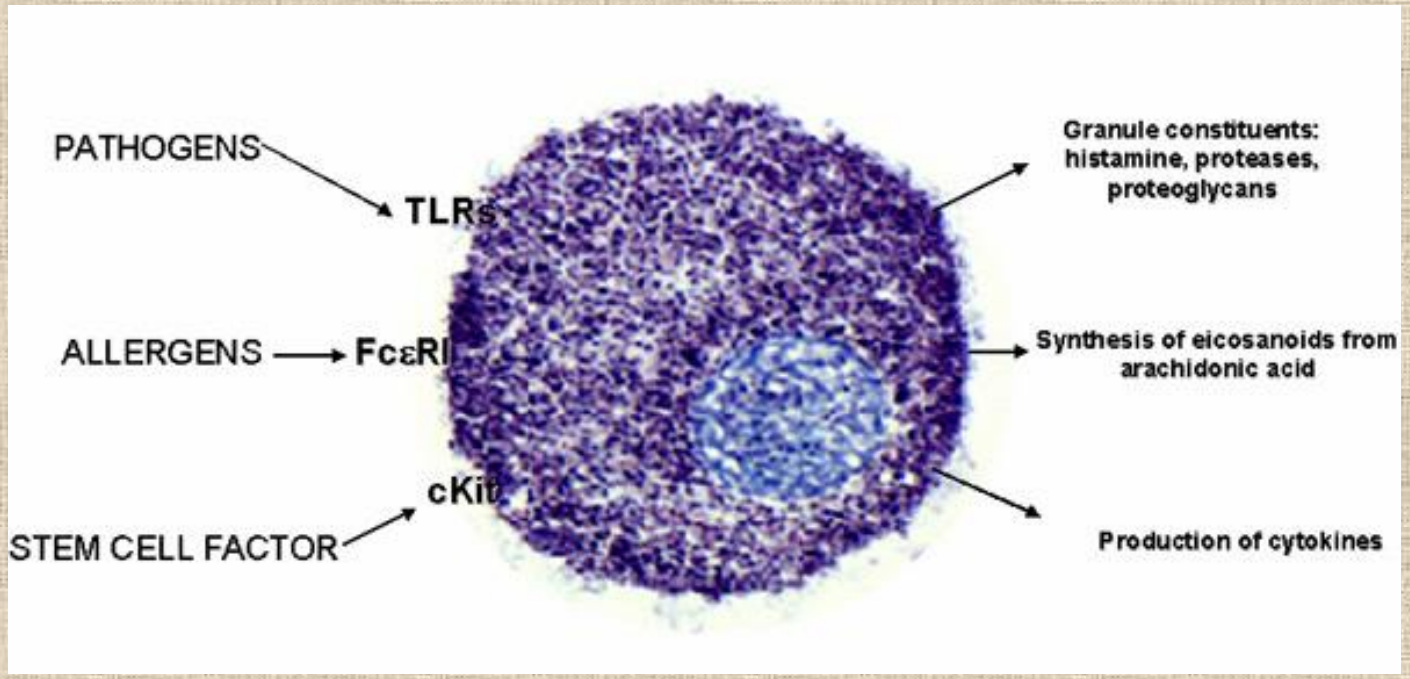
Initation of acute inflammation



Goldsby RA, Kindt TJ, Osborne BA: Kuby Immunology 4th Edition, 2000.

Mast cells and their activation

TLR4 – LPS →IL-1β, TNF-α, IL-6 and IL-13, without mast cell degranulation
TLR2 – peptidoglycan → mast cell degranulation and production of IL-4 and IL-5, IL-6, IL-13
TLR3,7,9 – Poly (I:C), CpG oligonucleotid → release of pro-infalmmatory cyítokines and chemokines



they express several hundred thousand high affinity receptors for IgE (FcεR1) and thus respond to IgE-directed antigens

express the pathogen-recognizing Toll-like receptors (TLRs) which probably account for the ability of mast cells to mount an effective innate immune response

Maturation of Macrophages and DCs

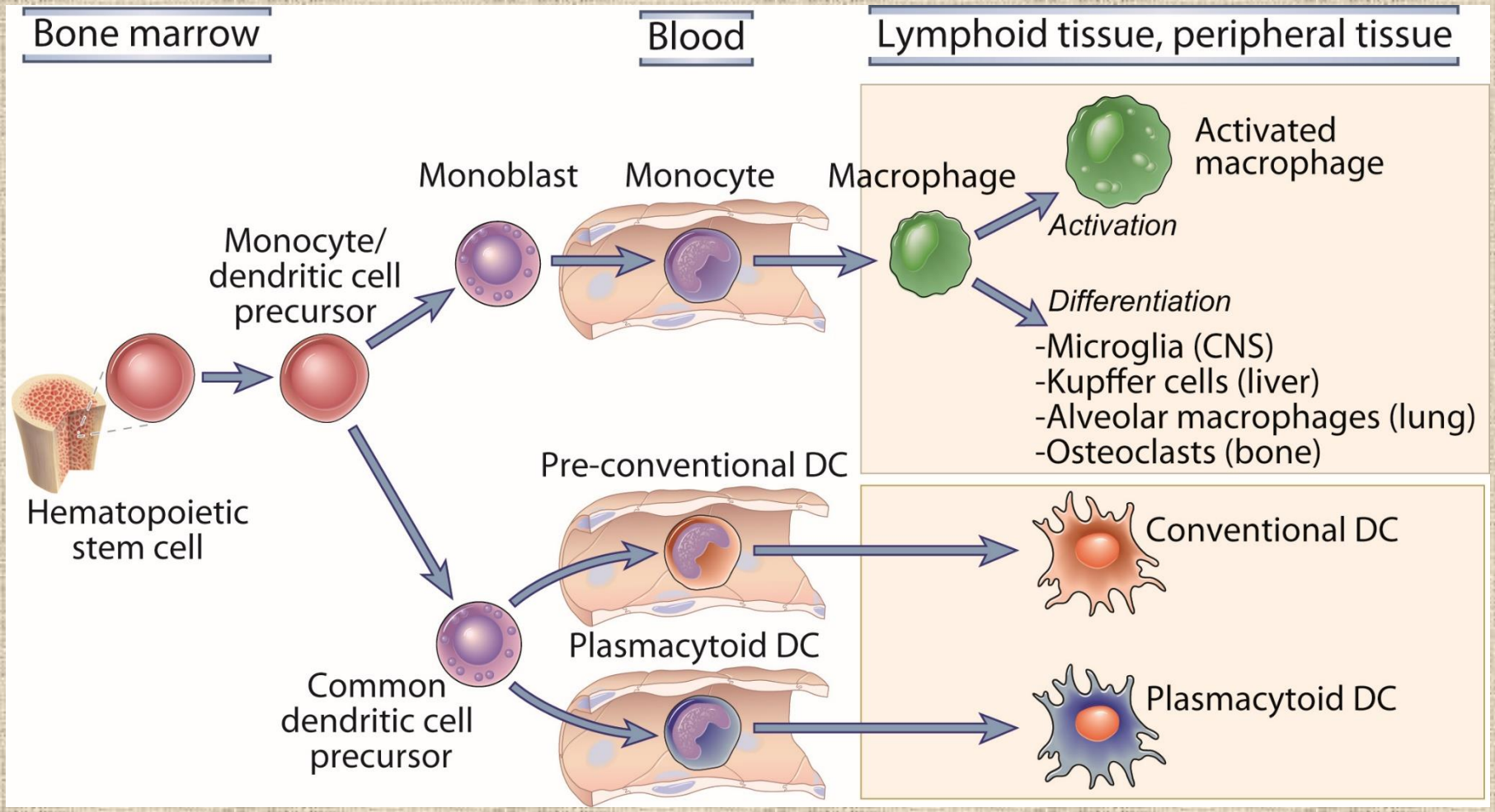
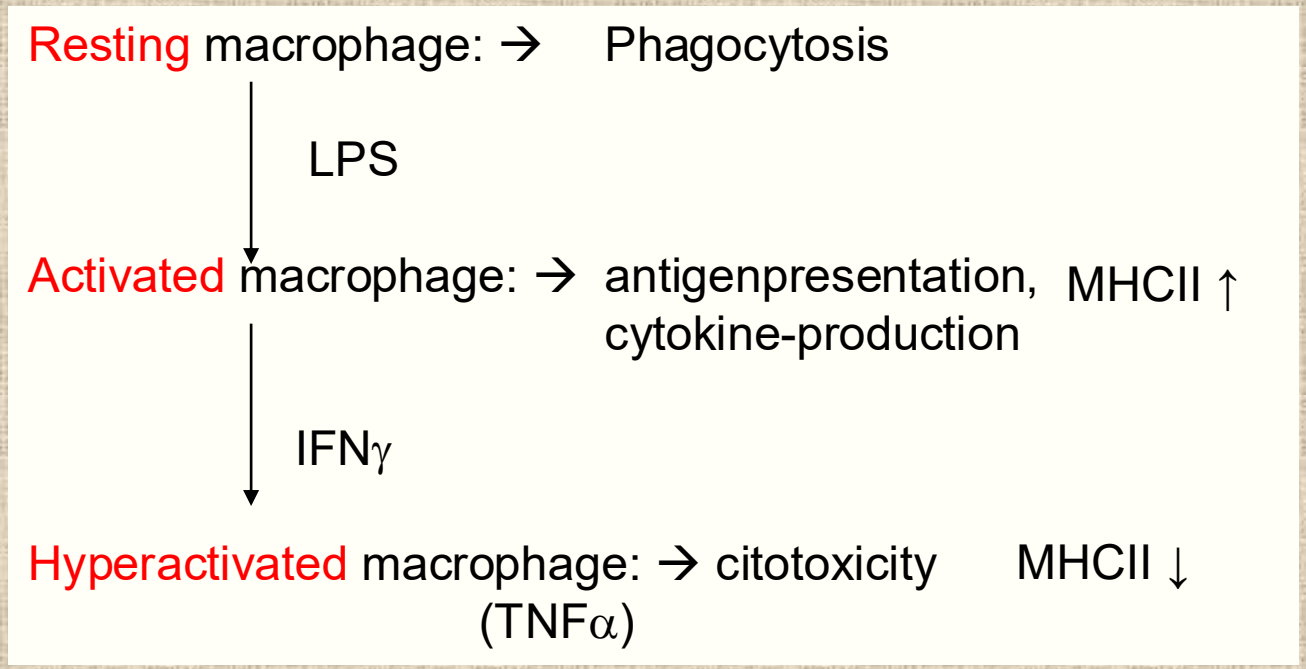


Fig. 2-2

Role of macrophages in acute inflammation: classical activation



Abbas, Lichtman, Pillai: Cellular and Molecular Immunology 7th Edition, 2012.

Janeway CA Jr, Travers P, Walport M, Shlomchik MJ. Immunobiology, 2005.

General characteristics of cytokines:

- Low molecular weight (10-40 kDa)
- Glycoproteins
- Isolated cells produce them due to activation signals
- They mediate cell-cell interactions:
  - sending information
  - regulation of the inflammation and immune response

Mode of action:

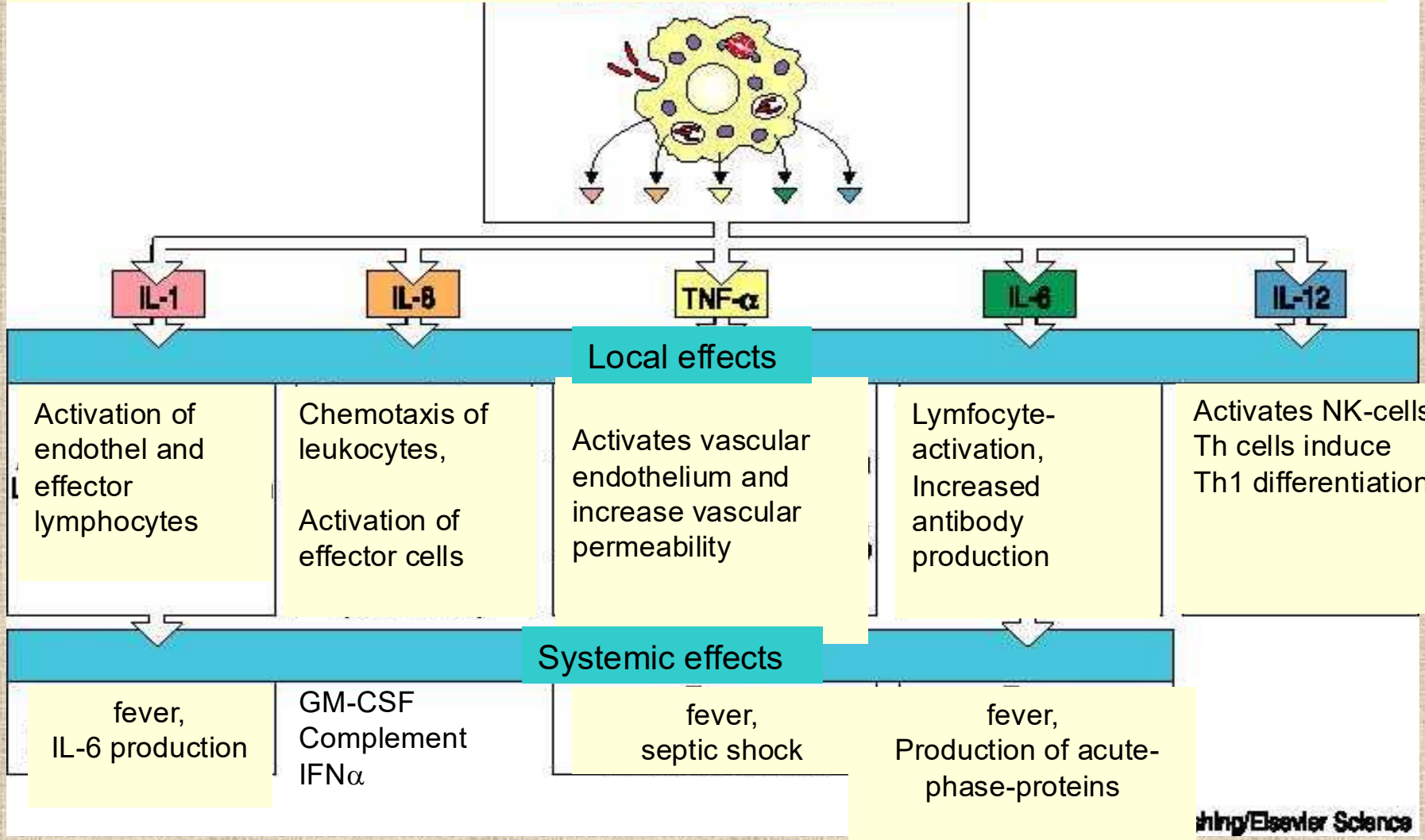
- products of transient gene activation
- they act through receptors
  - high affinity binding
  - low concentration, mostly local action

Functional groups of cytokines

I. Inflammatory cytokines	Anti-viral: IFNα, IFNβ Inflammatory:TNFα, IL-1α, IL-1β, IL-6, IL-17 Regulatory:IL-10, TGFβ, IL-35 Chemokines: CXCL8(IL-8), CCL3,4 (MCP, MIF)
II. Regulators of the specific immune response	Th1: IL-2,, INFγ, TNFβ, IL-12 Th2: IL-4, IL-5, IL-6, IL-13, Treg: IL-10, TGFβ, IL-35
III. Regulators of haematopoesis	SCF, GM-CSF, IL-3, IL-7

Activated macrophages produce infalmmatory cytokines

LPS originated from Gram – bacterium LPS activates the macrophages, those produce various cytokines



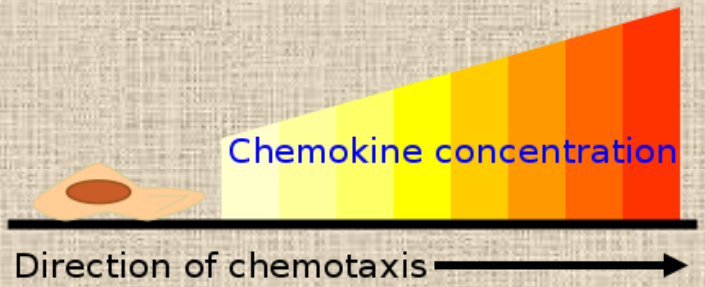
Janeway CA Jr, Travers P, Walport M, Shlomchik MJ. Immunobiology, 2005.

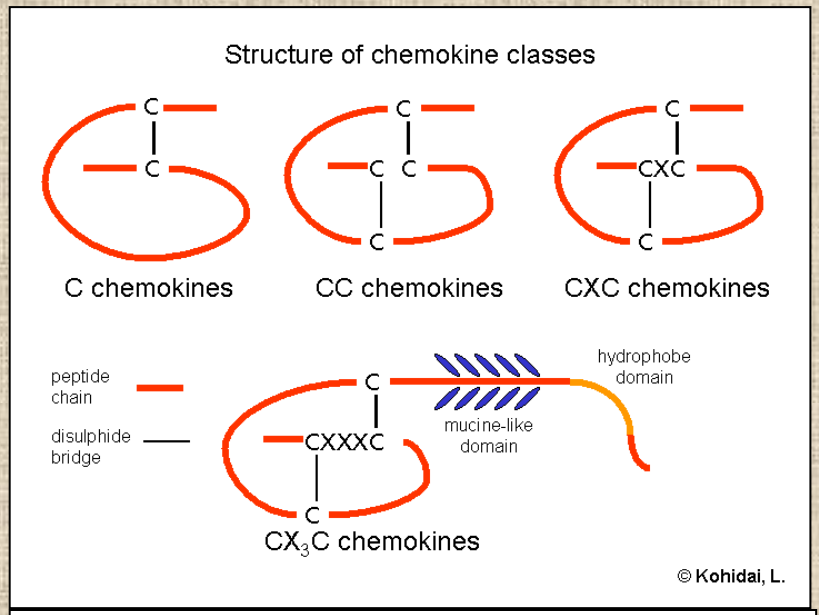
Chemokine action

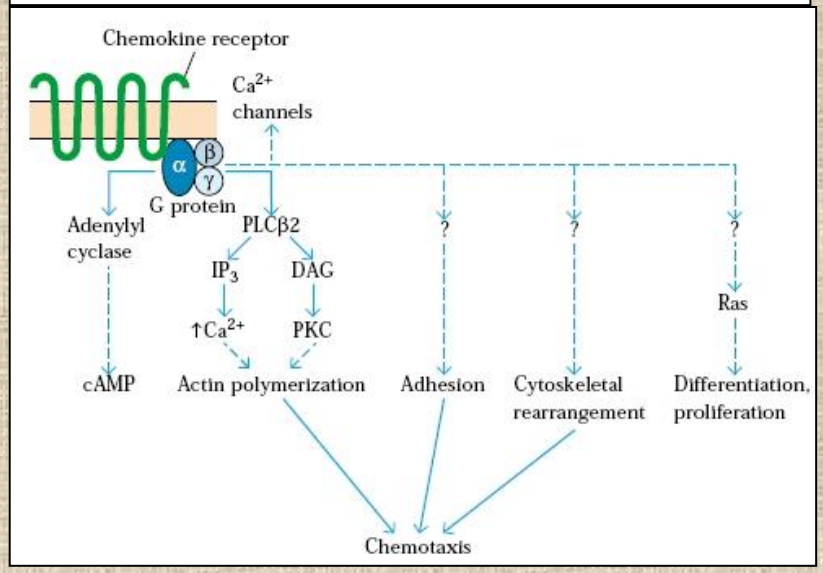
Chemokines are small molecular weight (8–10 kDa) cytokine proteins whose primary function is to control the migration (chemotaxis) of immune cells.

1. **Homeostatic chemokines**: These are produced continuously and are responsible for maintaining the normal functioning of the immune system (e.g., directing cells to lymph nodes).
2. **Inflammatory (inducible) chemokines**: These are released in response to infection or injury to recruit defense cells to the affected area.

Chemokines exert their effects through specific **G protein-coupled receptors**







Leukocyte Recruitment Into Tissues

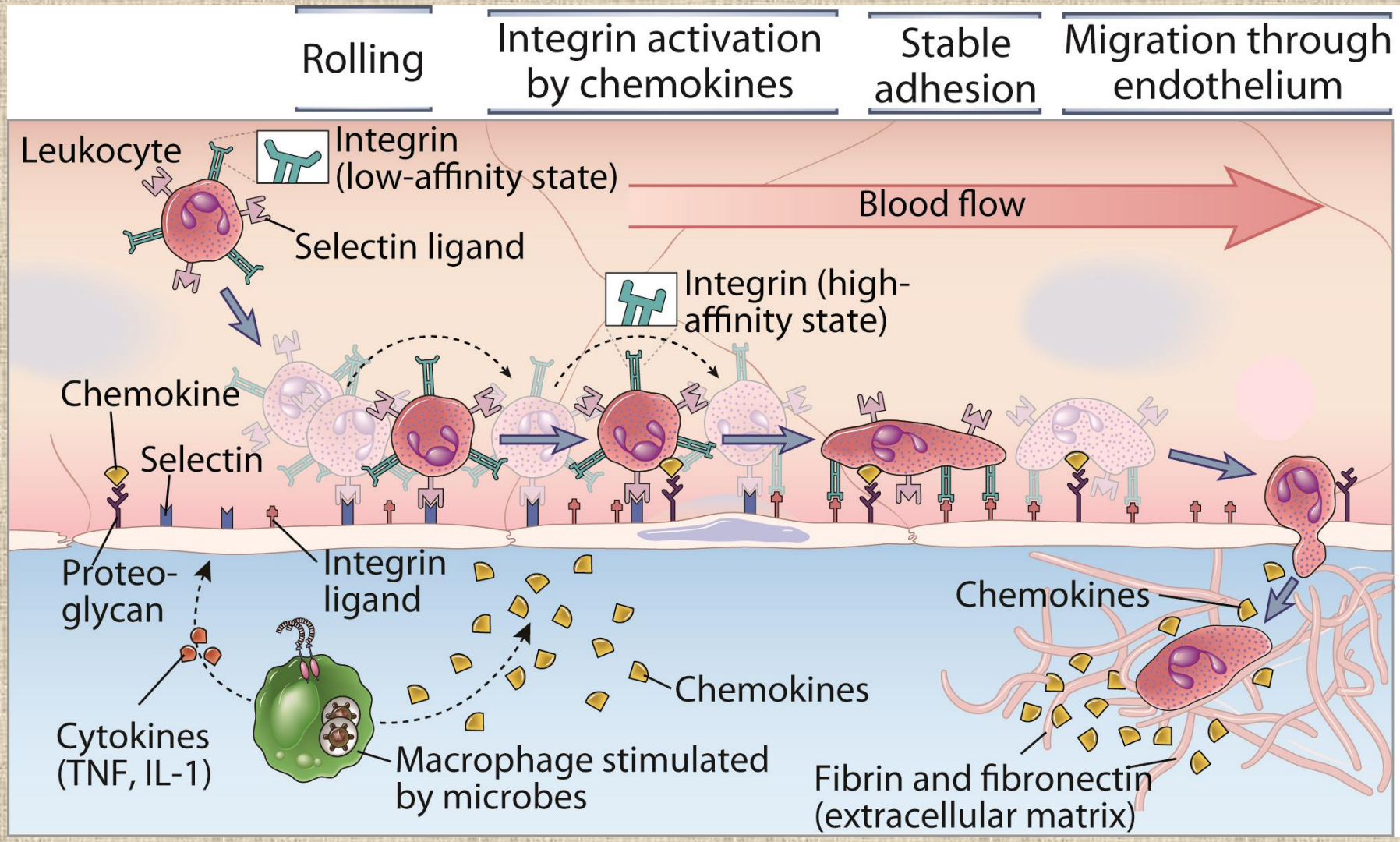
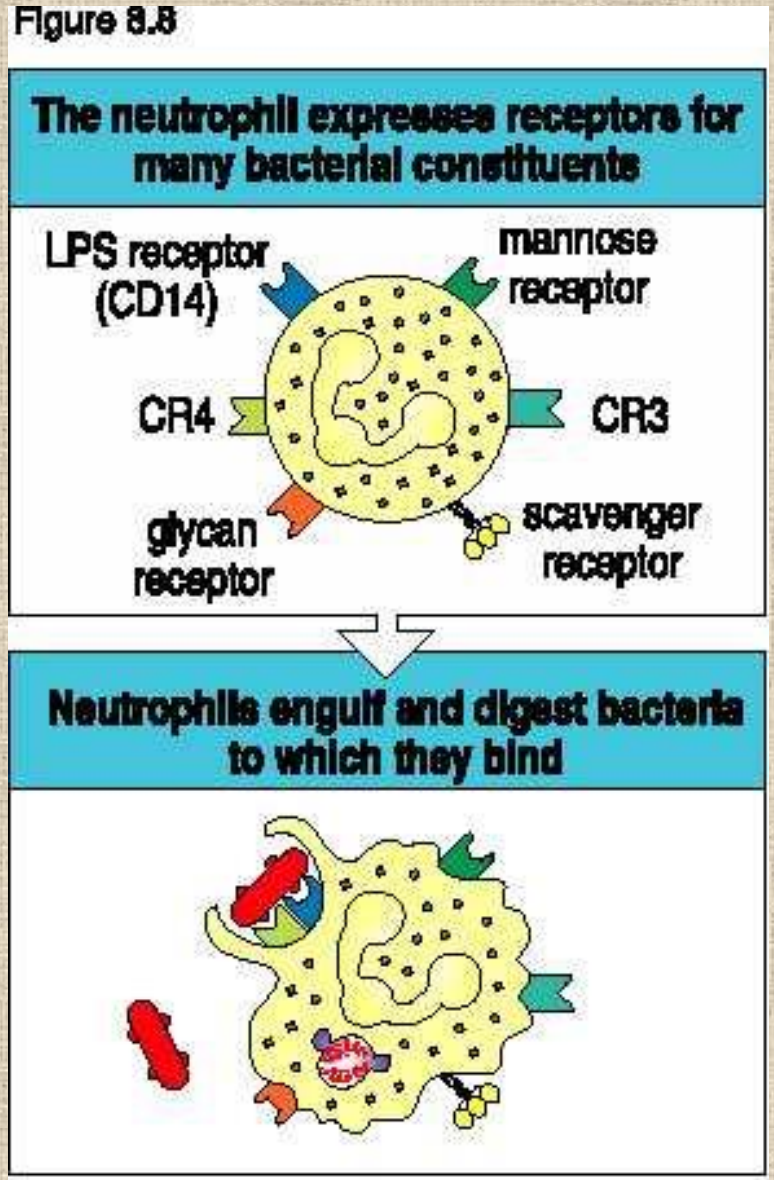


Fig. 3-3

Role of Neutrophils



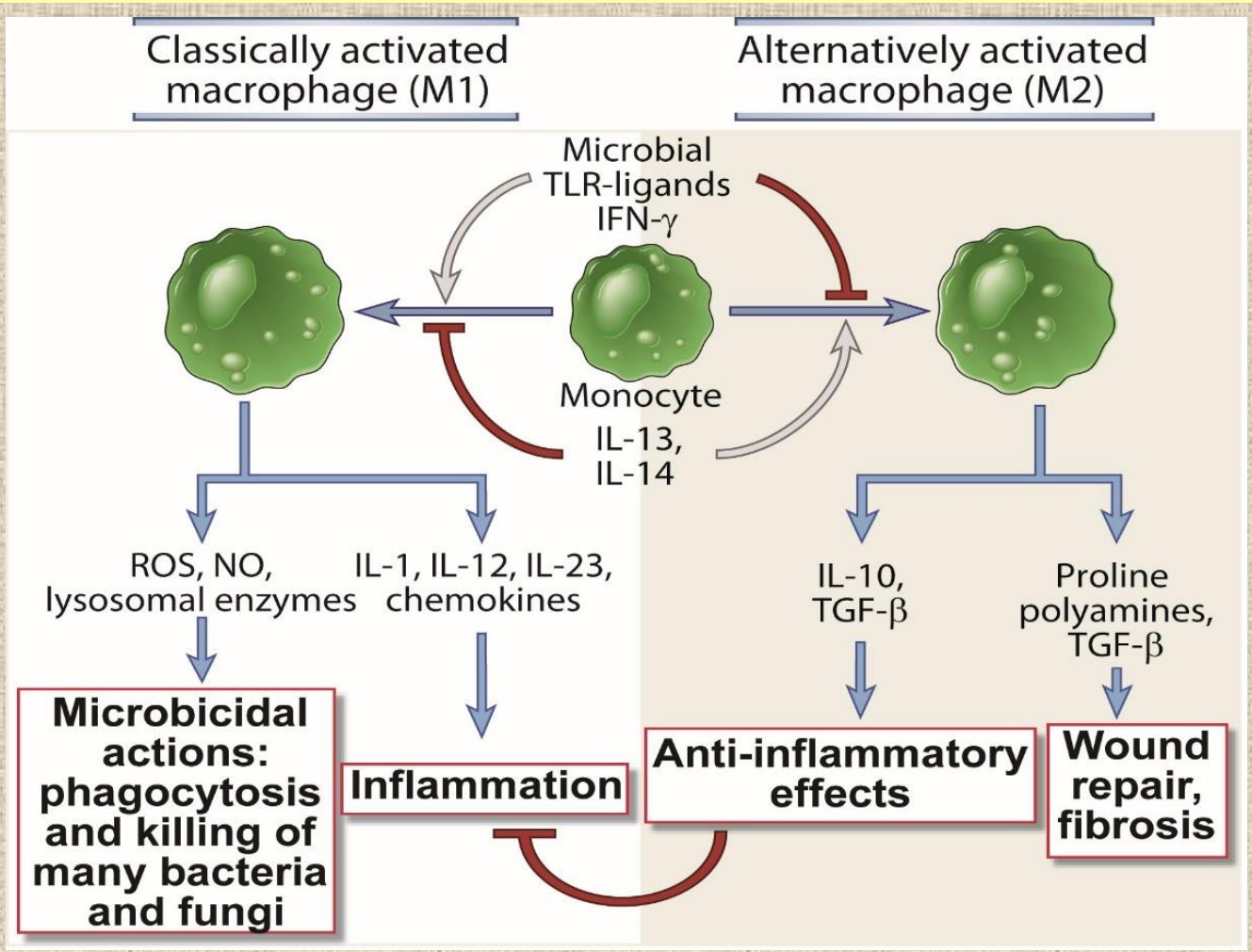
1. Phagocytosis / Receptor mediated endocytosis

2. Degranulation

3. NET formation

Janeway CA Jr, Travers P, Walport M, Shlomchik MJ. Immunobiology, 2005.

Polarization of macrophages



Abbas, Lichtman, Pillai: Cellular and Molecular Immunology 7th Edition, 2012.

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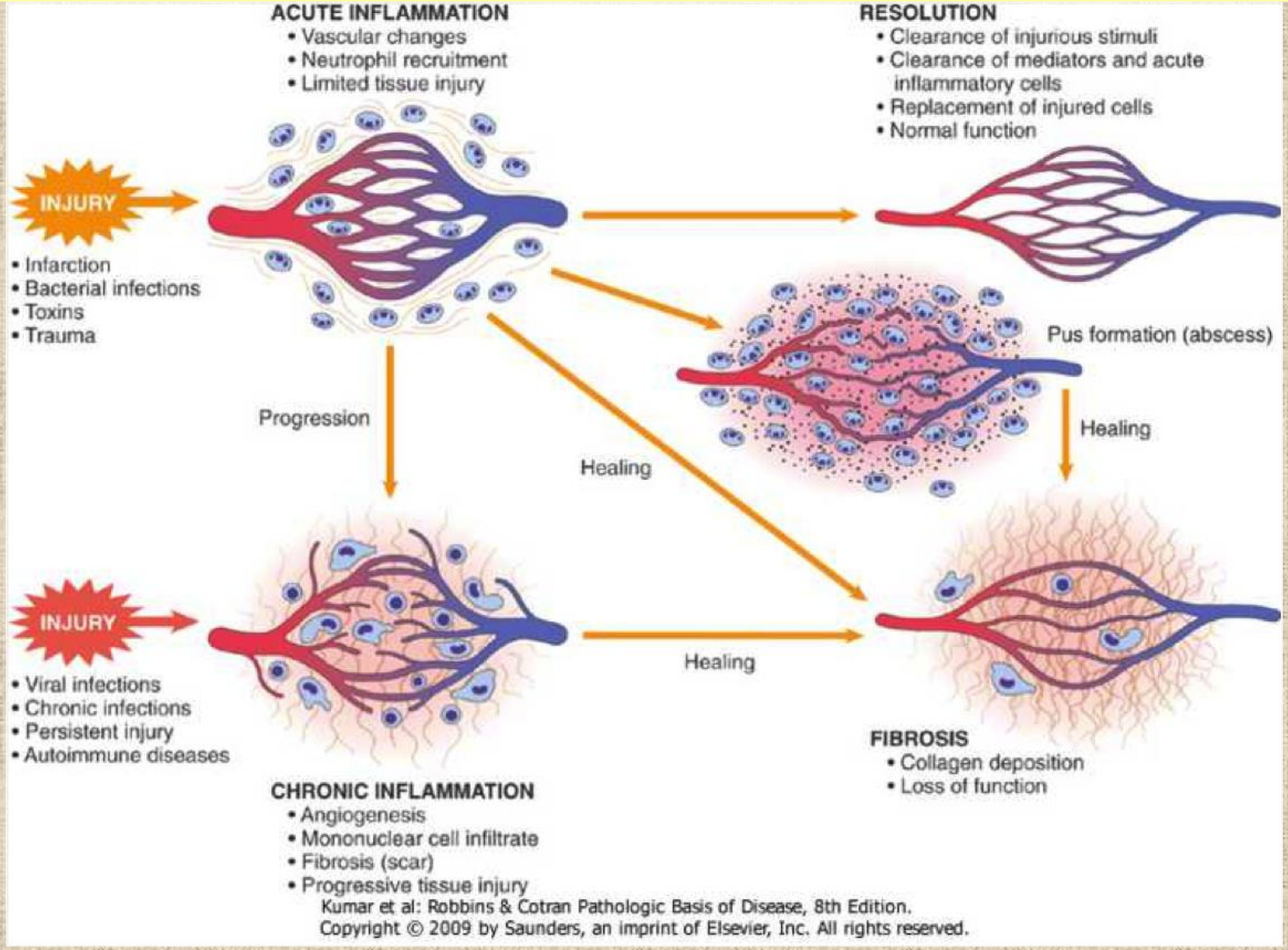
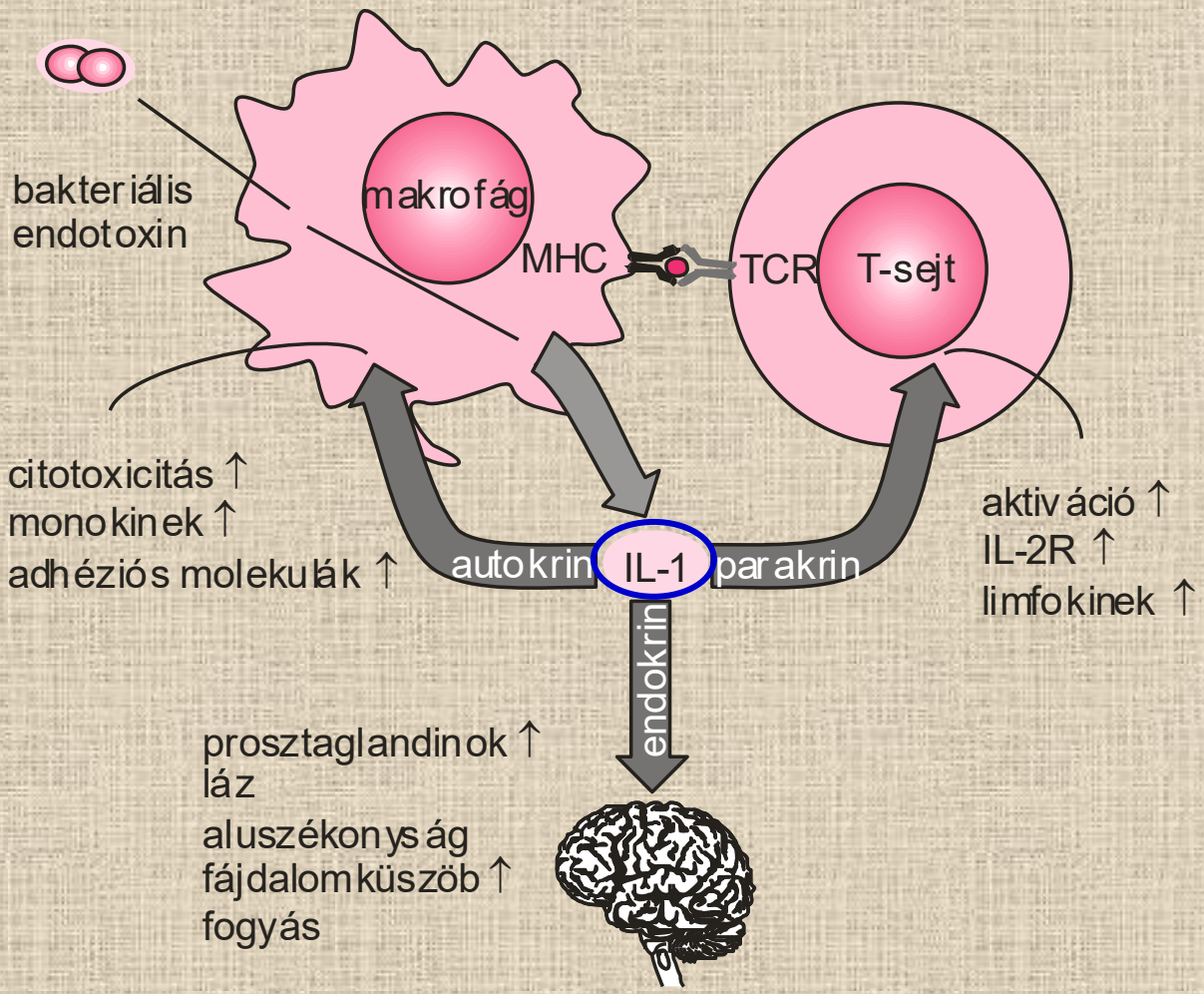
Outcomes of acute inflammation

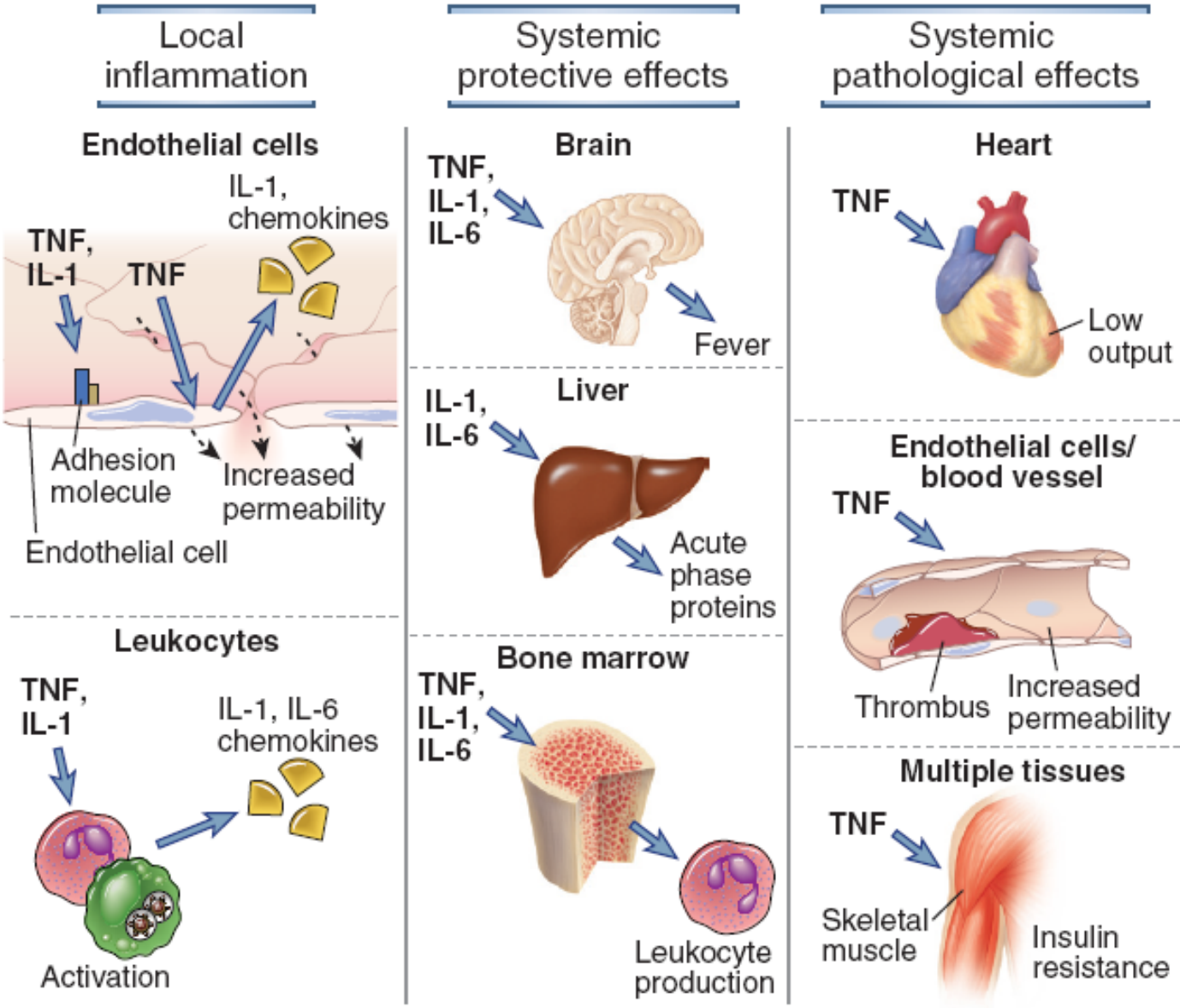


- **Systemic inflammation**

Autocrine, paracrine and endocrine effects of IL1



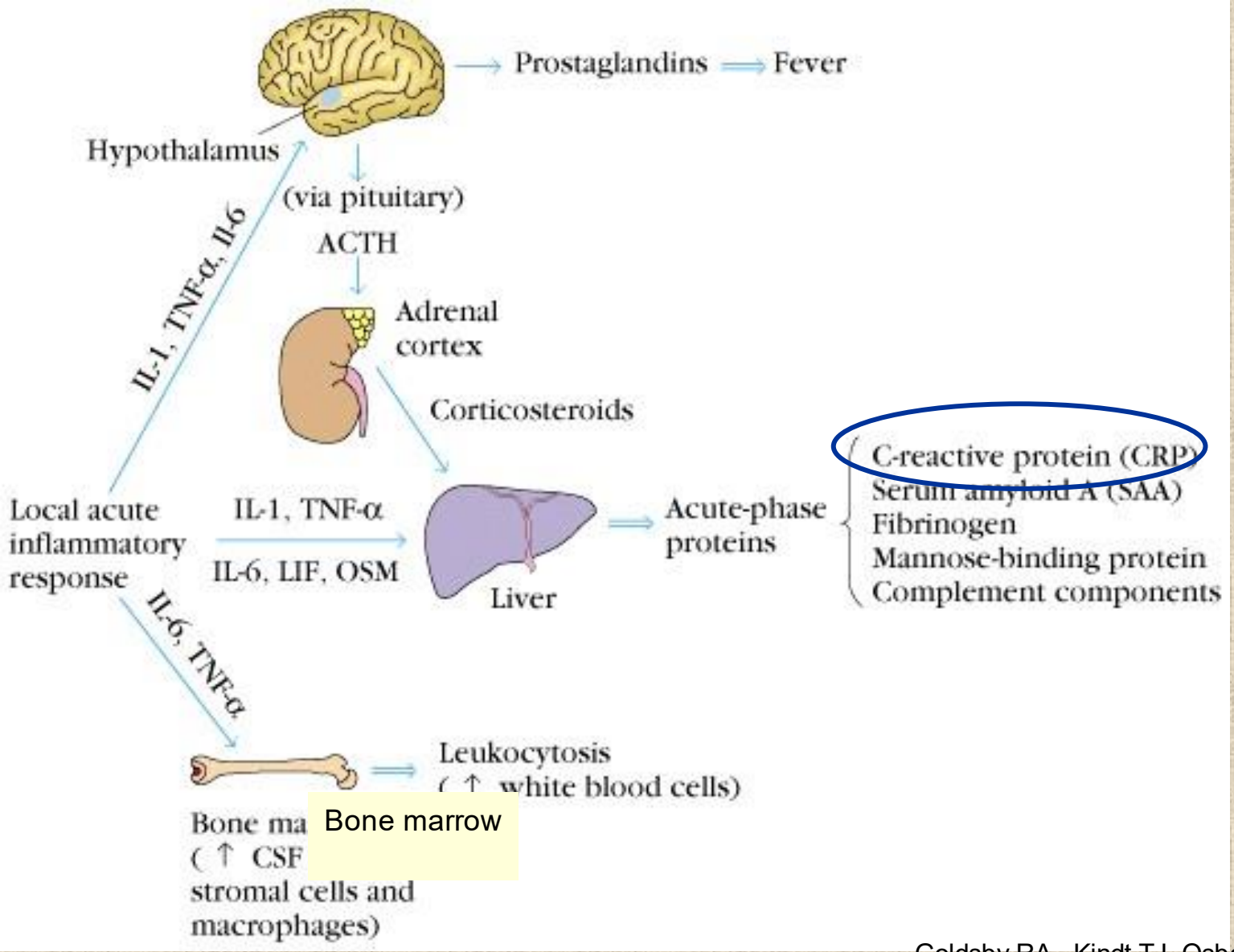
Local and systemic effects of TNF



TNF inhibitors, Steroids

Abbas, Lichtman, Pillai: Cellular and Molecular Immunology 7th Edition, 2012.

Systemic acute inflammation = acute phase reaction

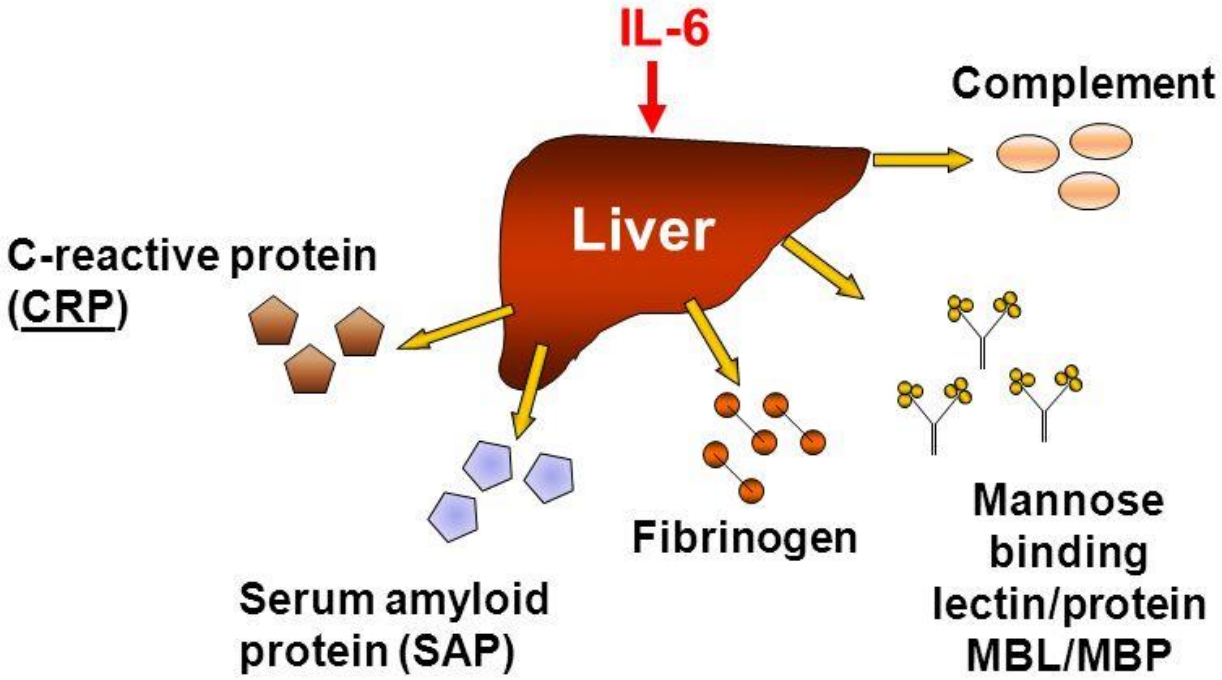


Goldsby RA, Kindt TJ, Osborne BA: Kuby Immunology 4th Edition, 2000.

Systemic effects of acute inflammation *acute phase response*

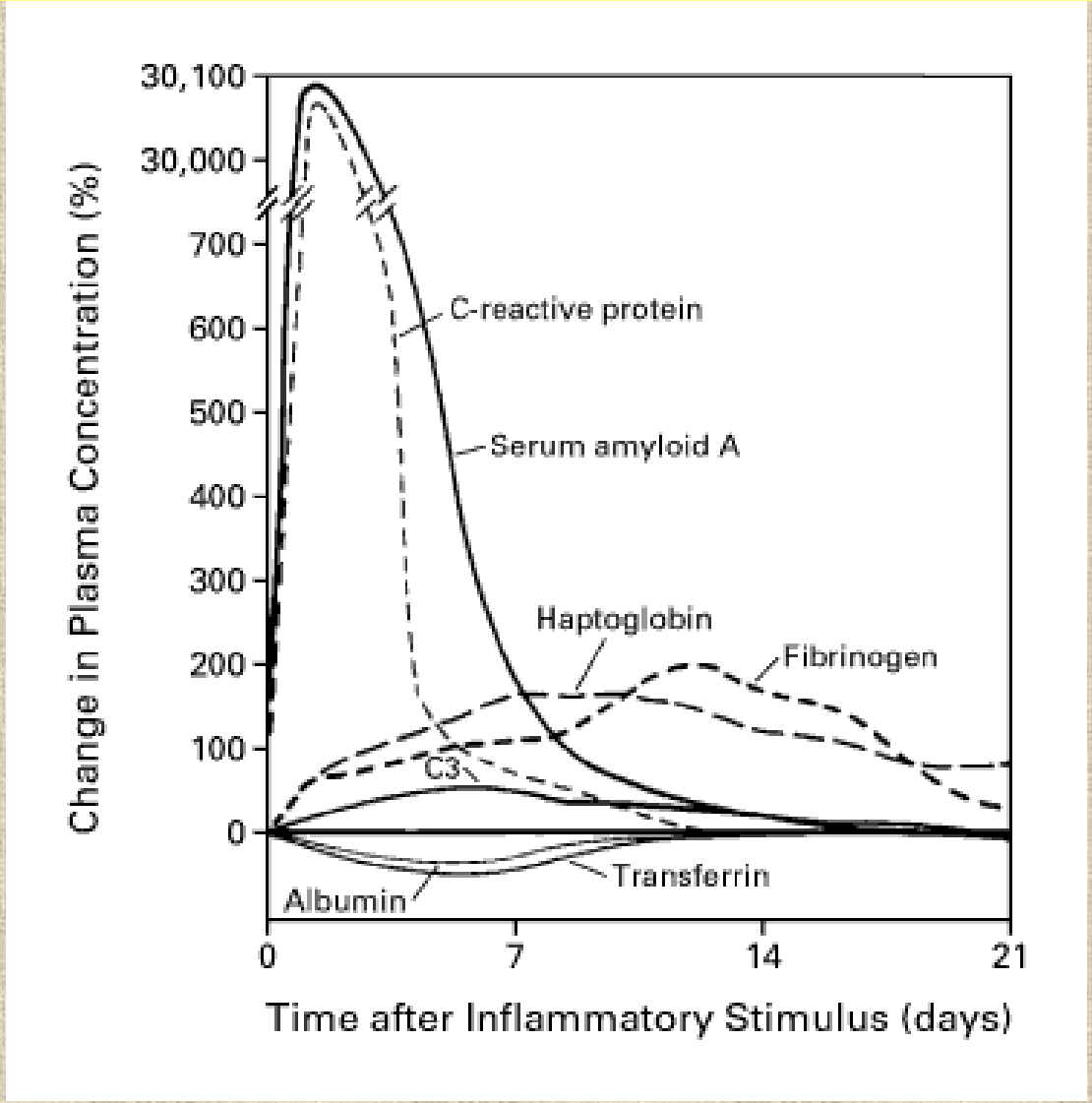
- Fever (temperature > 37.8°C or >100 F)
  - Increased pulse, blood pressure
  - Chills
  - Anorexia
- Leukocytosis
  - neutrophilia and left shift of neutrophils points to bacterial infection
  - Lymphocytosis points to viral infection
  - Eosinophilia point to allergy or parasitic infection
- Acute phase protein production in liver
  - fibrinogen, CRP,SAA leads to increased ESR

ACUTE PHASE REACTION



UNDER THE INFLUENCE OF IL-6 THE LIVER PRODUCES A BUNCH OF ACUTE-PHASE PROTEINS

Acute phase proteins in serum



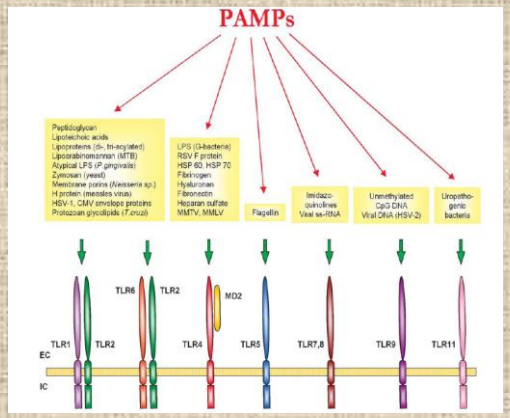
Causes of Chronic Inflammation

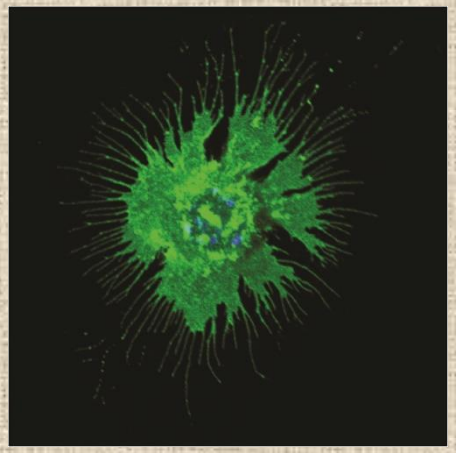
Unlike acute inflammation showing redness, swelling and pain, chronic inflammation can be invisible

Causes

- Autoimmune diseases e.g. such as rheumatoid arthritis, lupus
- Infectious agents e.g. H. pylori, viruses
- Atherosclerosis
- Environmental e.g. smoking
- Allergens
- Central adiposity: more macrophages localised in fat will thus produce more inflammatory mediators

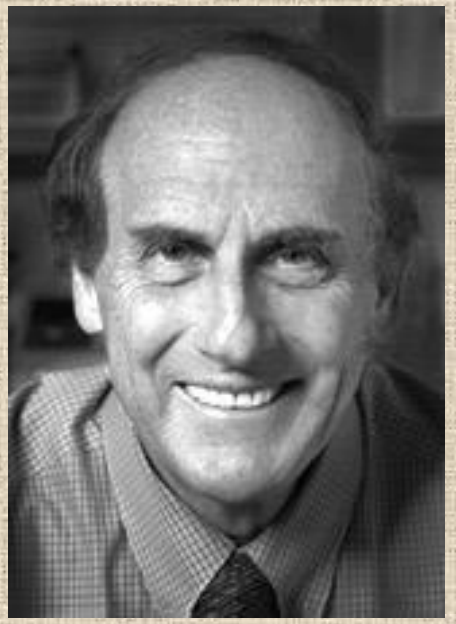
Nobel Laureates in 2011 for medicine and physiology





Jules A. Hoffmann

Bruce A. Beutler



Ralph M. Steinmann