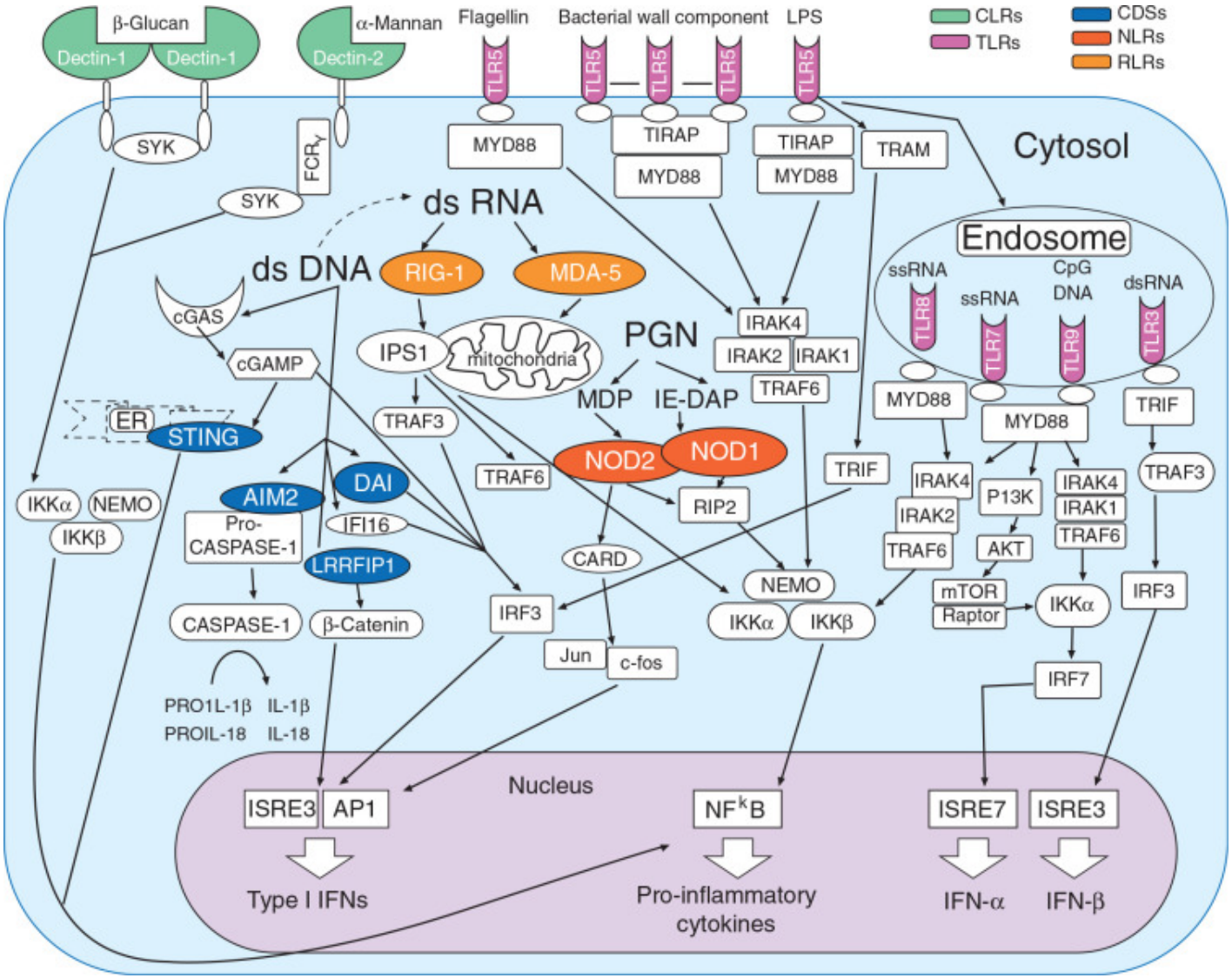
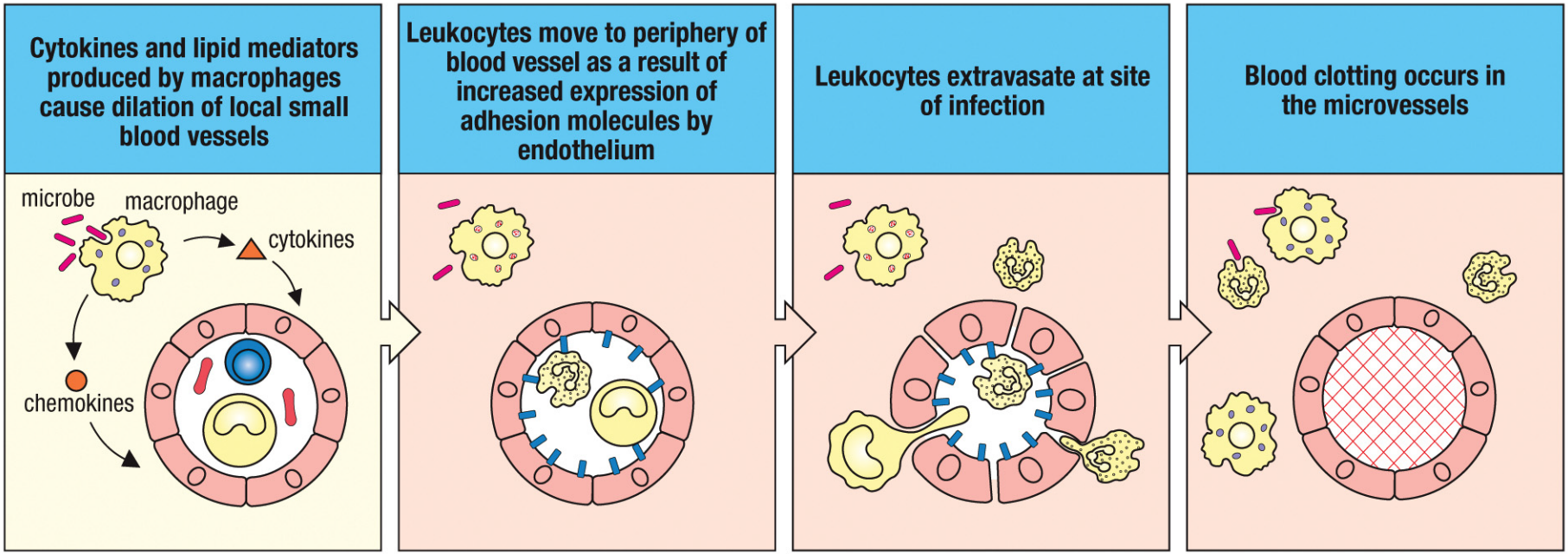
Pattern Recognition Receptors



C-type lectins receptors
Toll-like receptors
RIG 1 like receptors
NOD-like receptors
cytosolic DNA sensors

https://doi.org/10.1093/annonc/mdx179

Roles of Inflammation in Combating Infection



Outline

- Cytokines in innate immunity:

  Leukocyte recruitment
  Acute phase response
  Interferon
    Type I Interferon: antiviral response
    Interferon-γ: macrophage activation

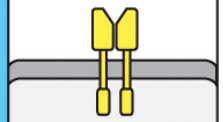
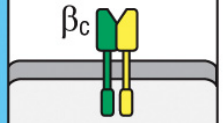
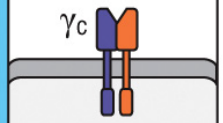
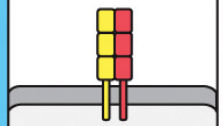
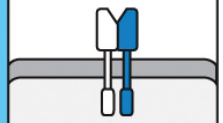
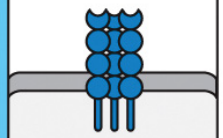
- NK cells

Definition

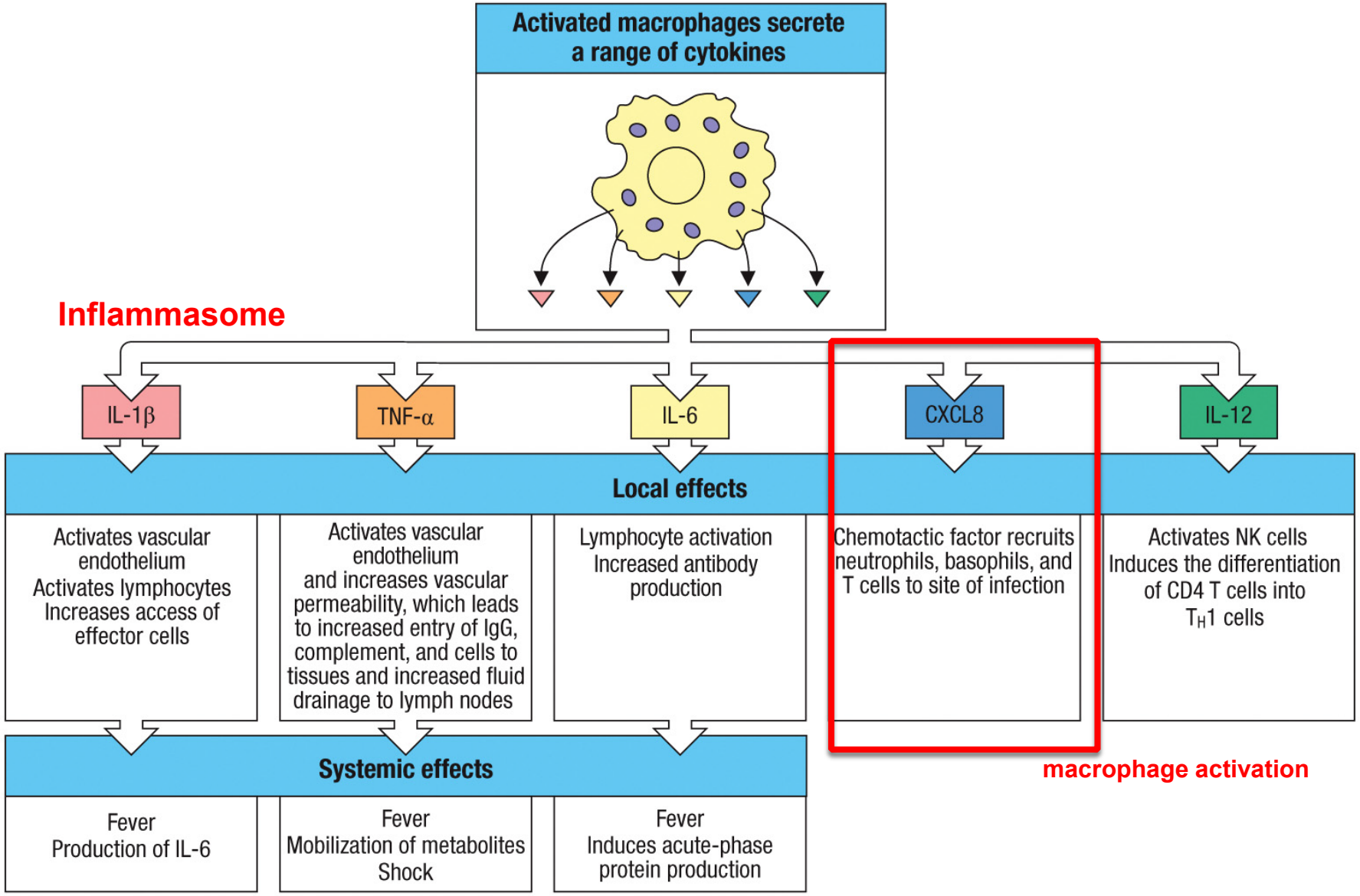
- Cytokine: broad and loose category of small proteins that are important in cell signaling. They are released by cells and affect the behavior of other cells.

- Chemokine: **chemo**tactic cyto**kines** that to induce directed chemotaxis in nearby responsive cells.

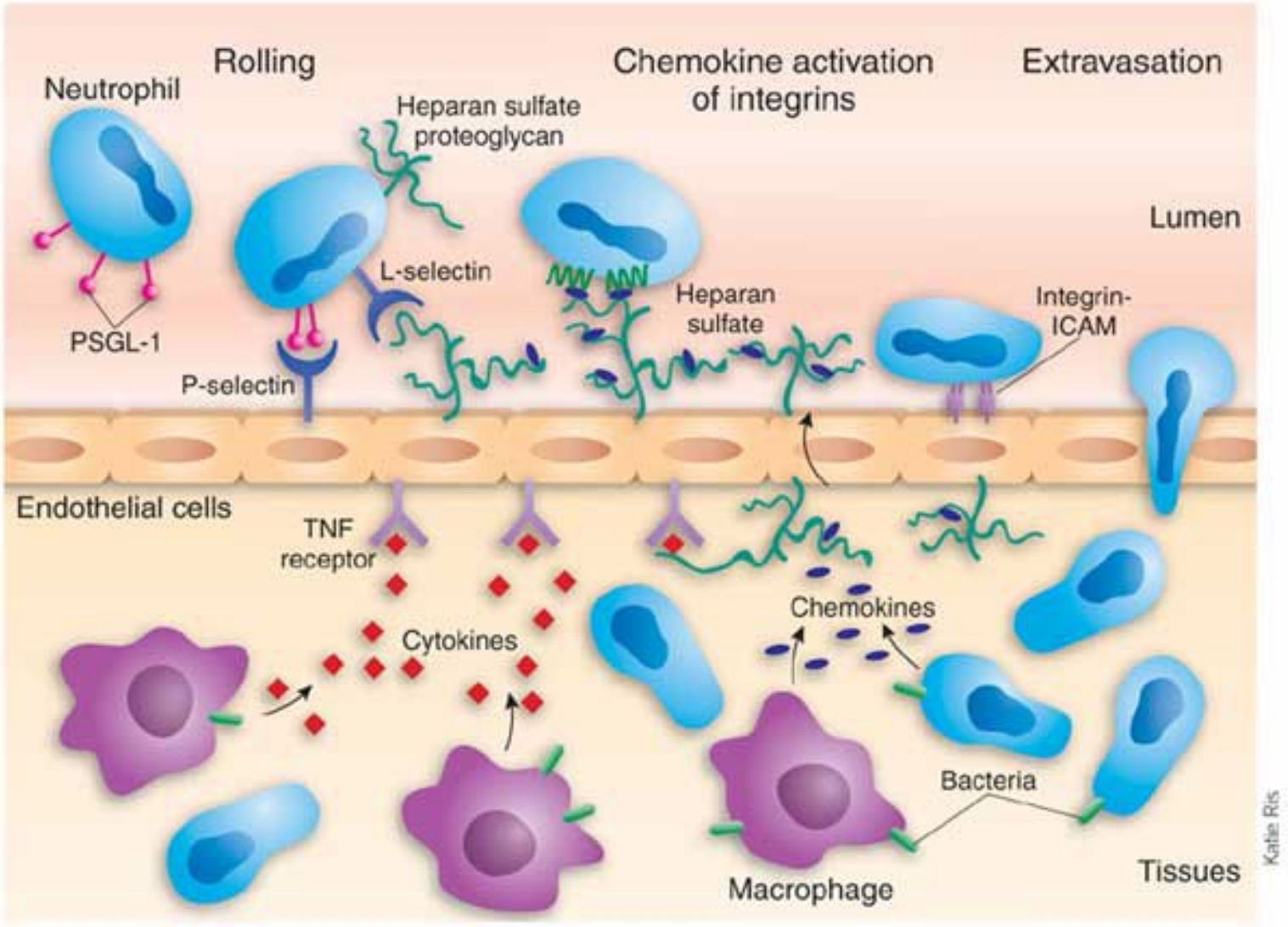
Cytokine Receptors

Homodimeric receptors		Receptors for erythropoietin and growth hormone
Heterodimeric receptors with a common chain		Receptors for IL-3, IL-5, GM-CSF share a common chain, CD131 or β_c (common β chain)
		Receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 share a common chain, CD132 or γ_c (common γ chain). IL-2 receptor also has a third chain, a high-affinity subunit IL-2Rα (CD25)
Heterodimeric receptors (no common chain)		IL-1 family receptors
		Receptors for IL-13, IFN-α, IFN-β, IFN-γ, IL-10
TNF receptor family		Tumor necrosis factor (TNF) receptors I and II, CD40, Fas (Apo1, CD95), CD30, CD27, nerve growth factor receptor
Chemokine receptor family		CCR1–10, CXCR1–5, XCR1, CX3CR1

Effects of Cytokine Secretion

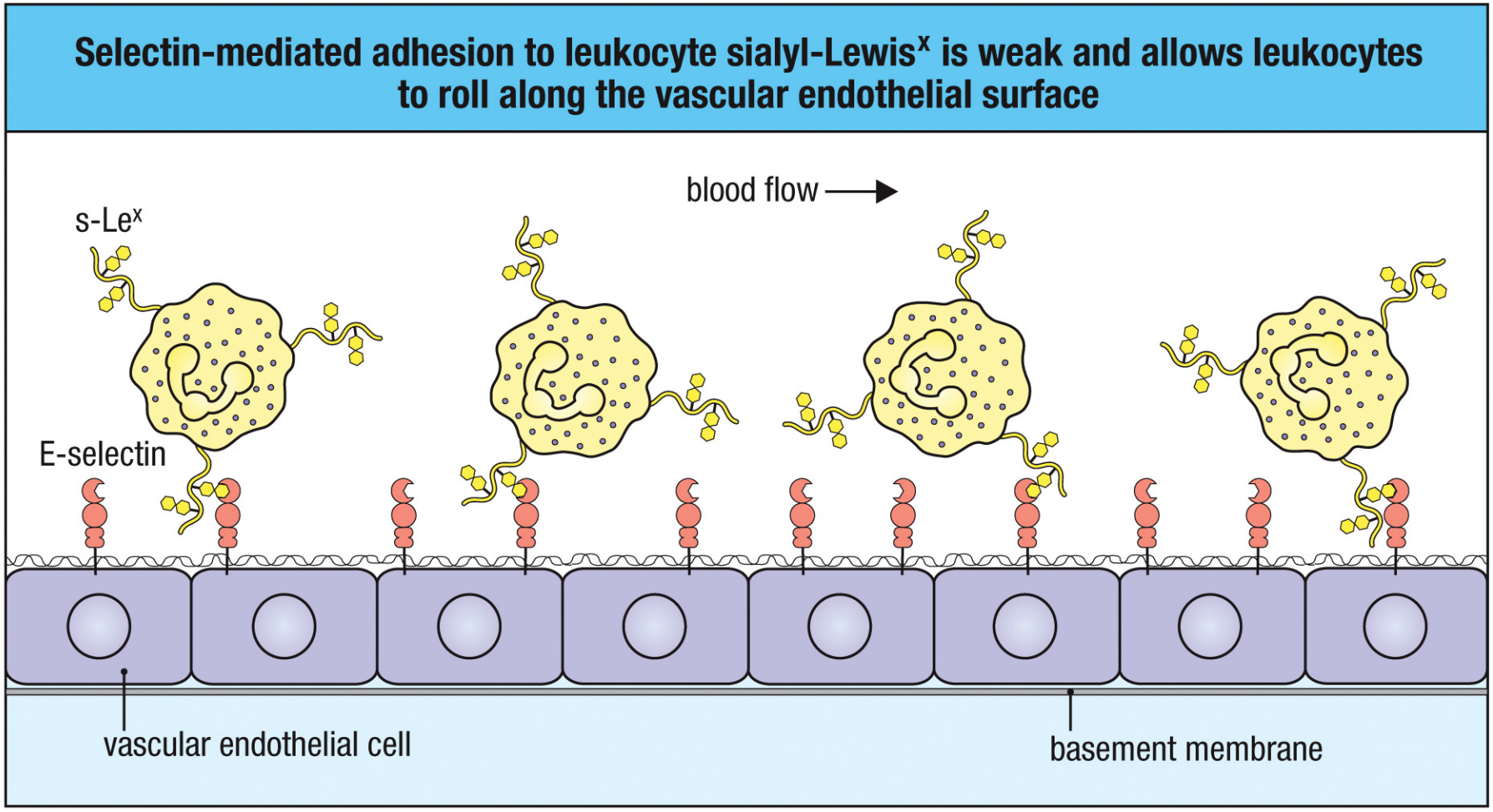


Cytokines Attract Leukocytes to Sites of Infection



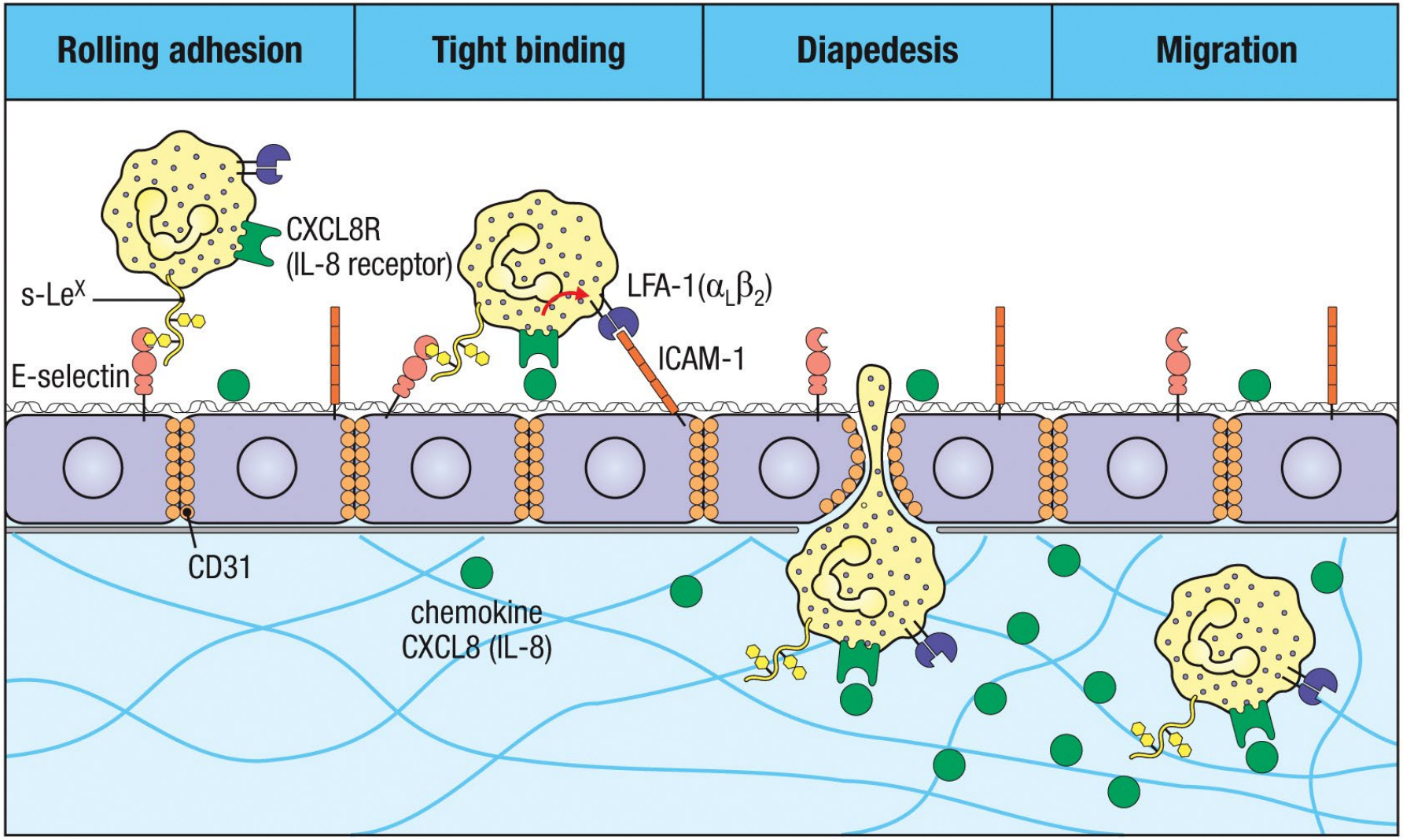
http://www.nature.com/ni/journal/v6/n9/fig_tab/ni0905-861_F1.html

Extravasation: Rolling

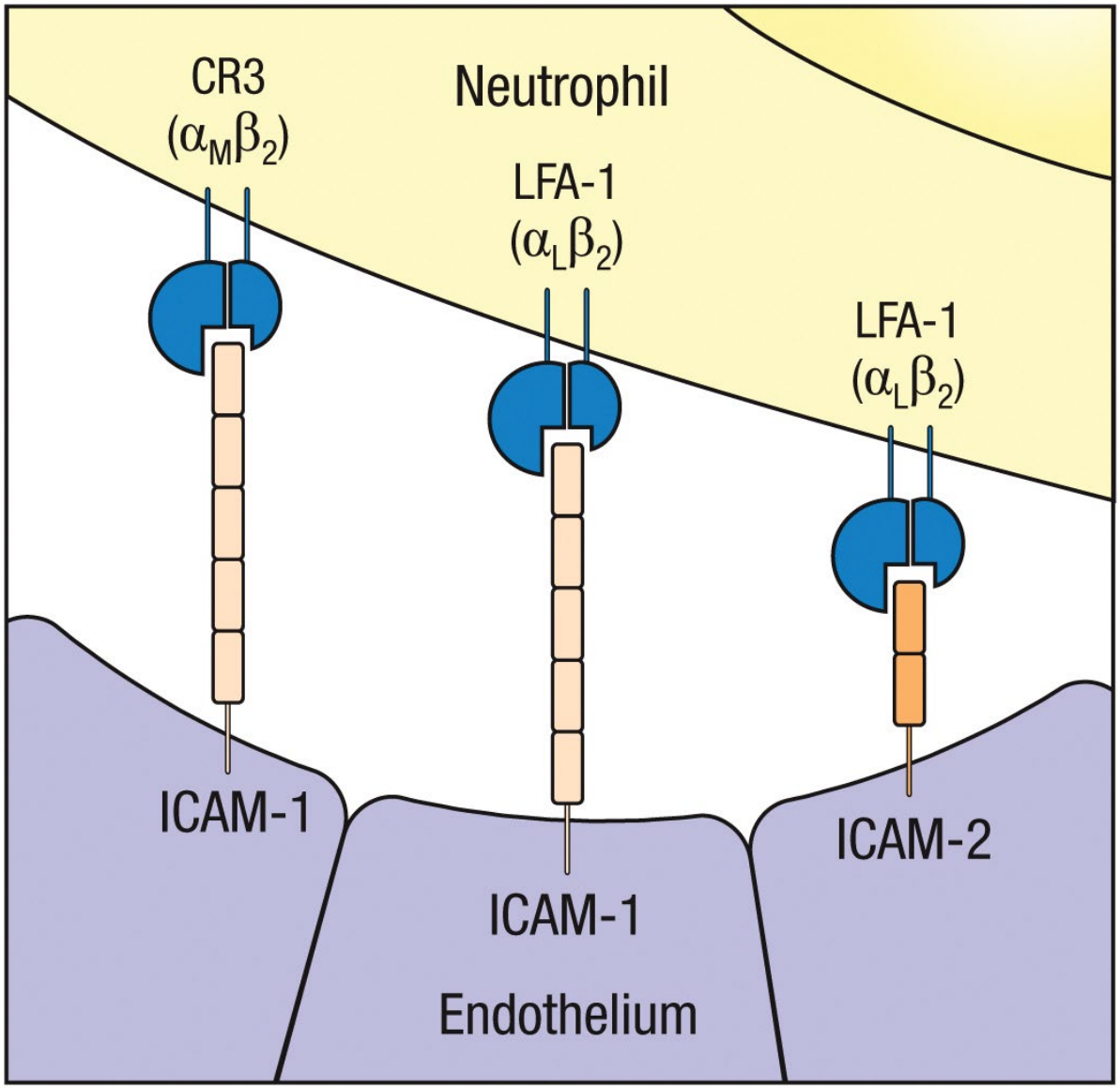


sialyl-Lewis^X moiety (s-Le^X)

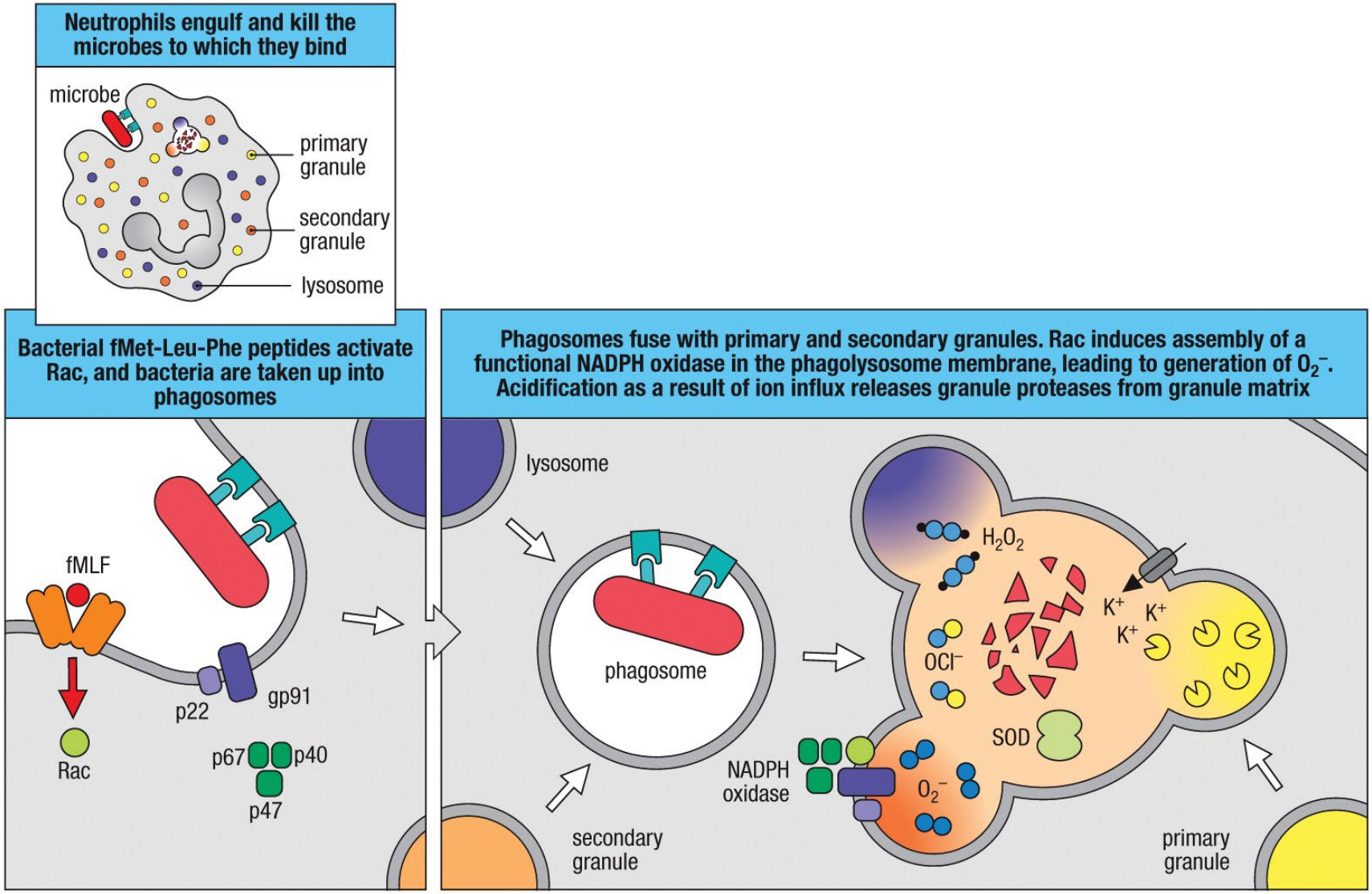
Extravasation: Diapedesis



Phagocyte Adhesion to Endothelium



Neutrophil ROS



Neutrophil Extracellular Trap

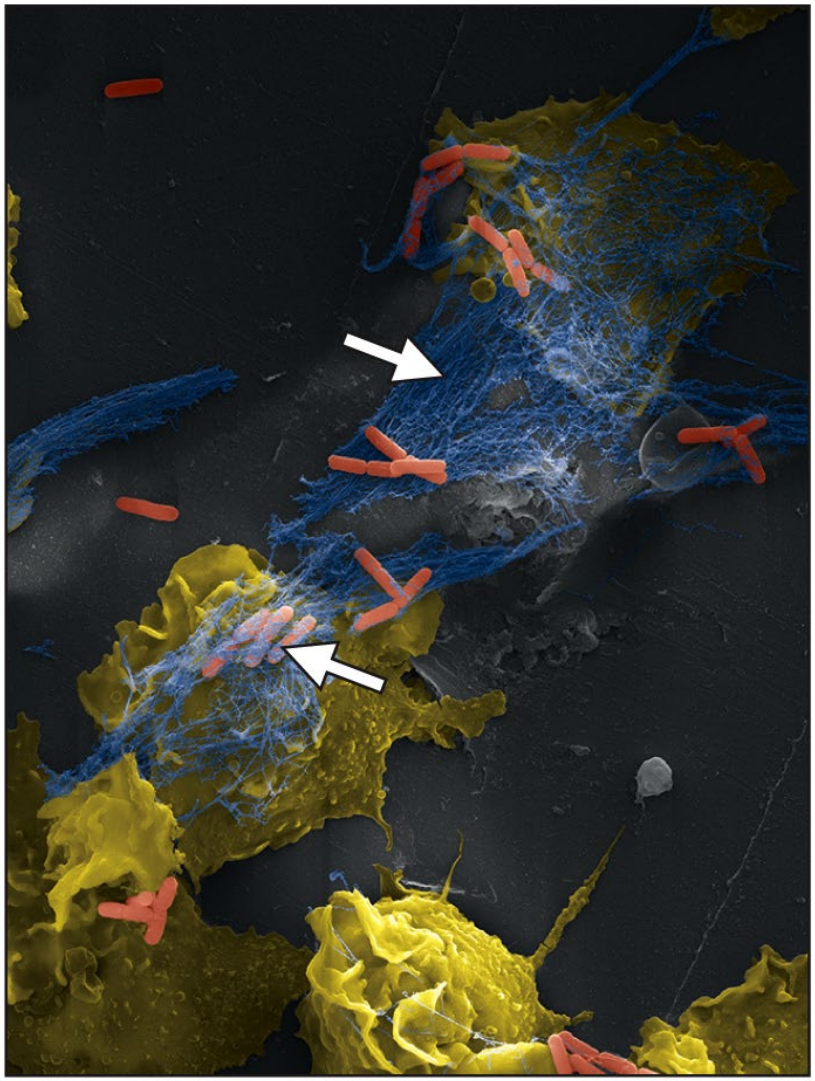
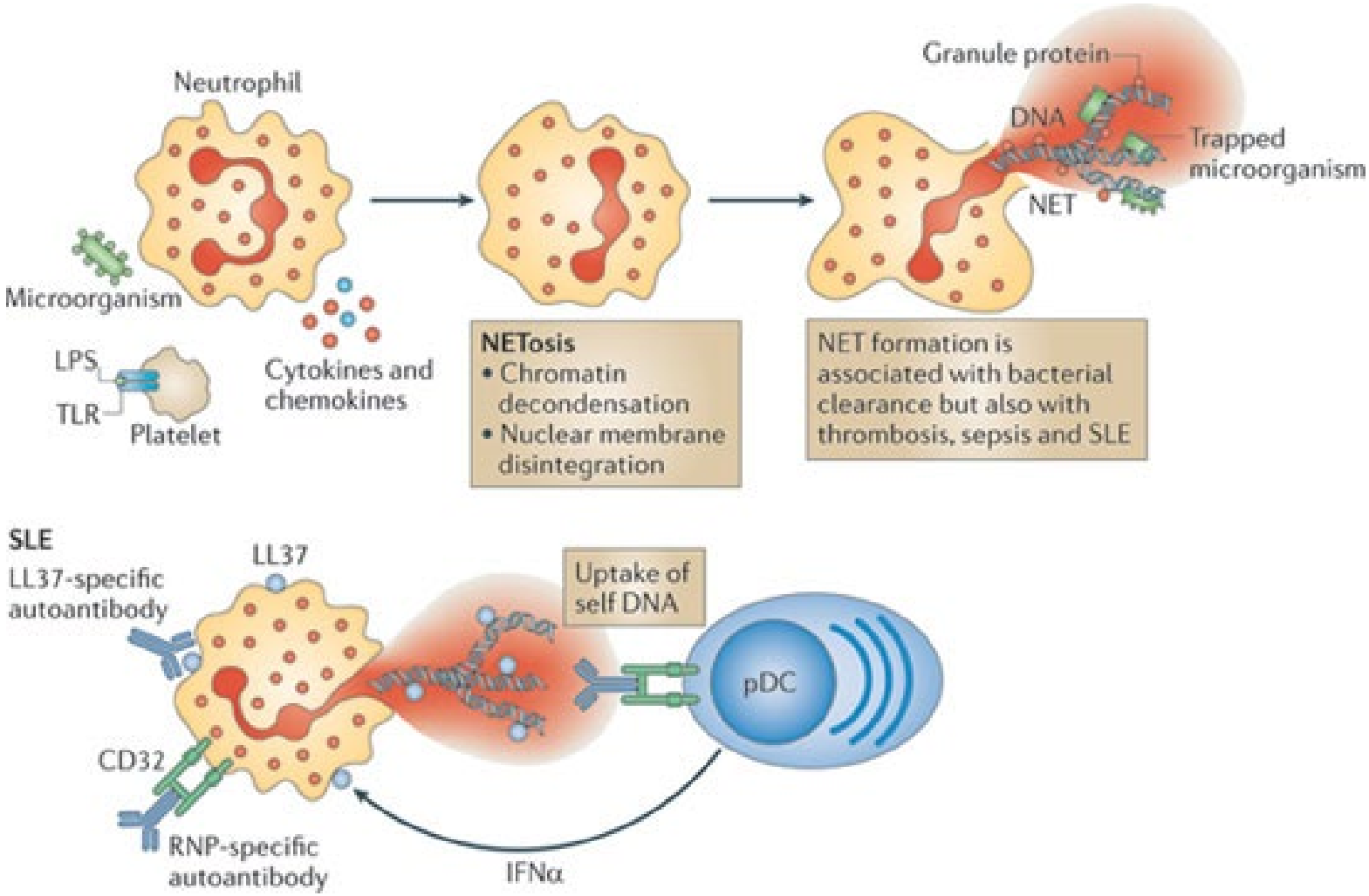


Figure 3.6 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

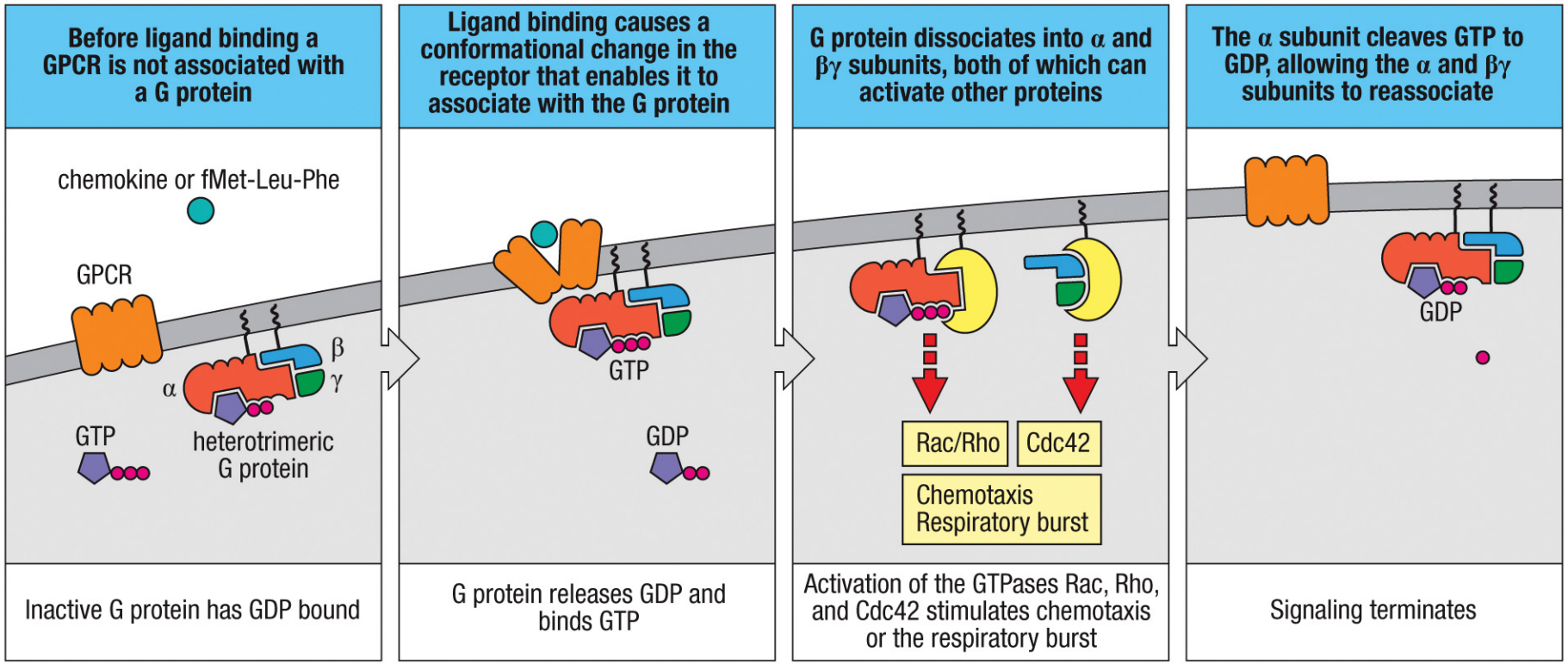
CXCR2: a neutrophil receptor that can trigger NET formation

Neutrophil Extracellular Trap

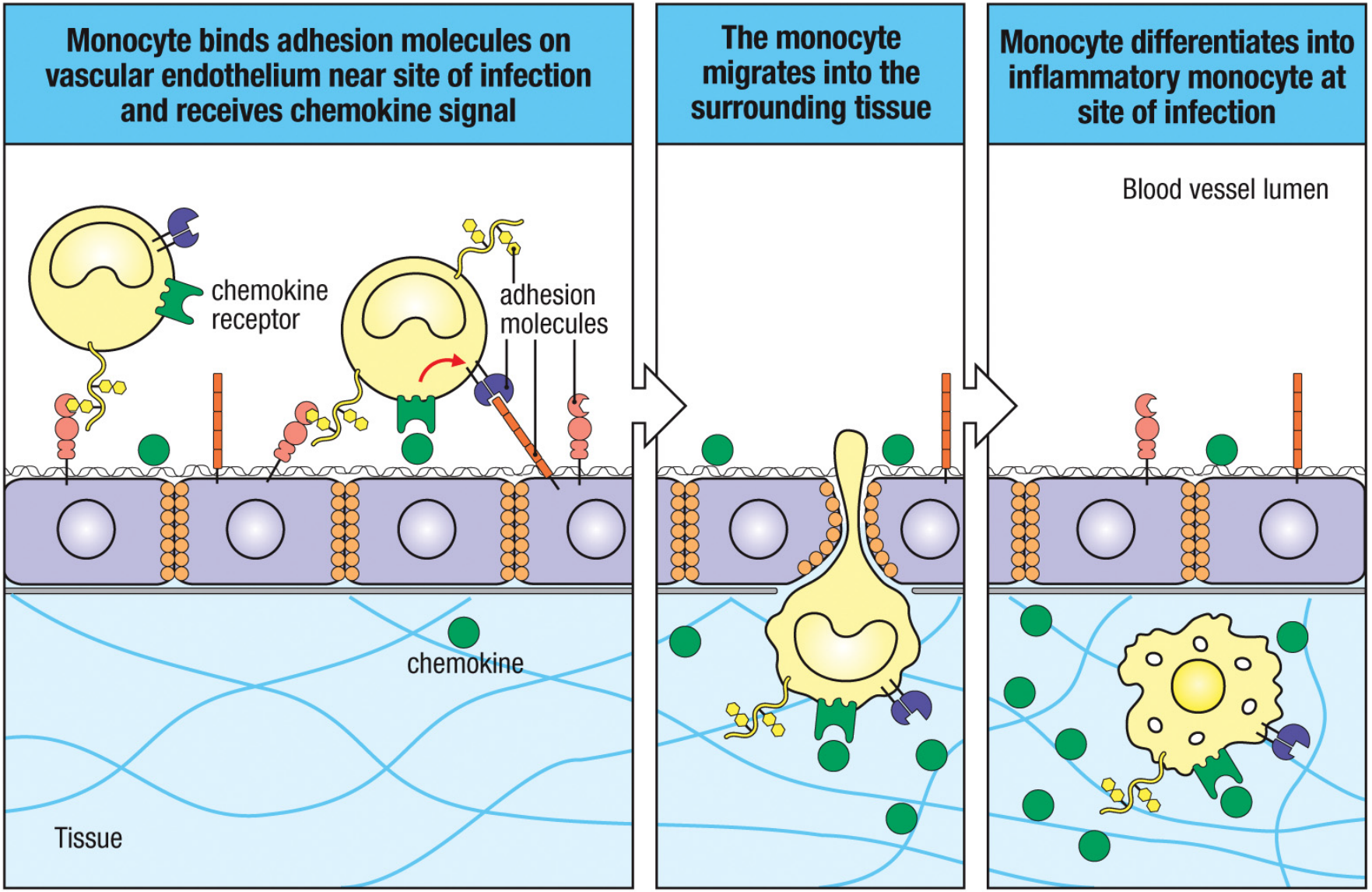


http://www.nature.com/nri/journal/v11/n8/full/nri3024.html

Chemokine Receptor Signalling



Monocytes Extravasation



Different Chemokines for Different Cells

Class	Chemokine	Produced by	Receptors	Cells attracted	Major effects
CXC	CXCL8 (IL-8)	Monocytes Macrophages Fibroblasts Epithelial cells Endothelial cells	CXCR1 CXCR2	Neutrophils Naive T cells	Mobilizes, activates, and degranulates neutrophils Angiogenesis
	CXCL7 (PBP, β-TG, NAP-2)	Platelets	CXCR2	Neutrophils	Activates neutrophils Clot resorption Angiogenesis
	CXCL1 (GROα) CXCL2 (GROβ) CXCL3 (GROγ)	Monocytes Fibroblasts Endothelium	CXCR2	Neutrophils Naive T cells Fibroblasts	Activates neutrophils Fibroplasia Angiogenesis
CC	CCL3 (MIP-1α)	Monocytes T cells Mast cells Fibroblasts	CCR1, 3, 5	Monocytes NK and T cells Basophils Dendritic cells	Competes with HIV-1 Antiviral defense Promotes T_H1 immunity
	CCL4 (MIP-1β)	Monocytes Macrophages Neutrophils Endothelium	CCR1, 3, 5	Monocytes NK and T cells Dendritic cells	Competes with HIV-1
	CCL2 (MCP-1)	Monocytes Macrophages Fibroblasts Keratinocytes	CCR2B	Monocytes NK and T cells Basophils Dendritic cells	Activates macrophages Basophil histamine release Promotes T_H2 immunity
	CCL5 (RANTES)	T cells Endothelium Platelets	CCR1, 3, 5	Monocytes NK and T cells Basophils Eosinophils Dendritic cells	Degranulates basophils Activates T cells Chronic inflammation
CXXXC (CX_3C)	CX3CL1 (Fractalkine)	Monocytes Endothelium Microglial cells	CX_3CR1	Monocytes T cells	Leukocyte–endothelial adhesion Brain inflammation

Cell Adhesion Molecules: Effects On Homing

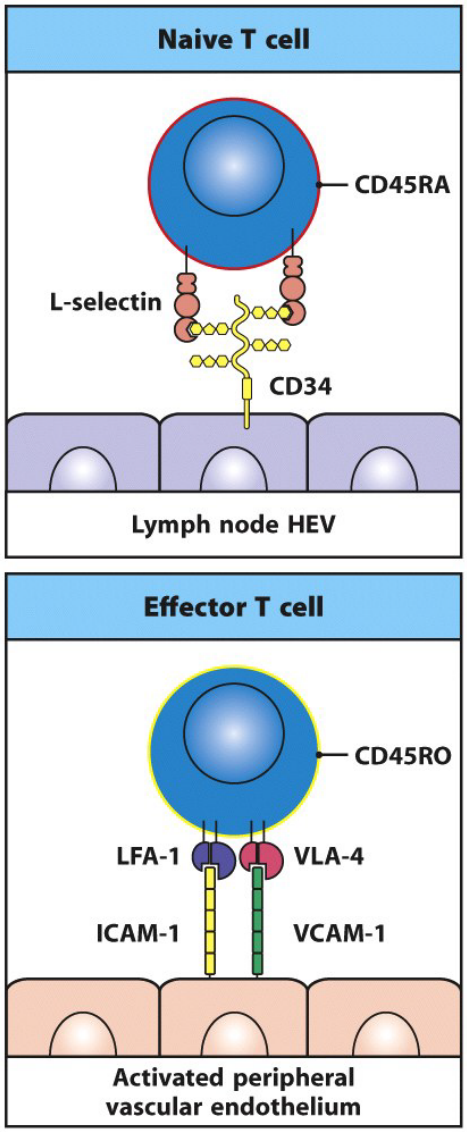


Figure 11.9 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Question

- How are immune cells recruited to sites of inflammation? What are the four steps and which molecules are involved?

Outline

- Cytokines in innate immunity:

  Leukocyte recruitment

  Acute phase response

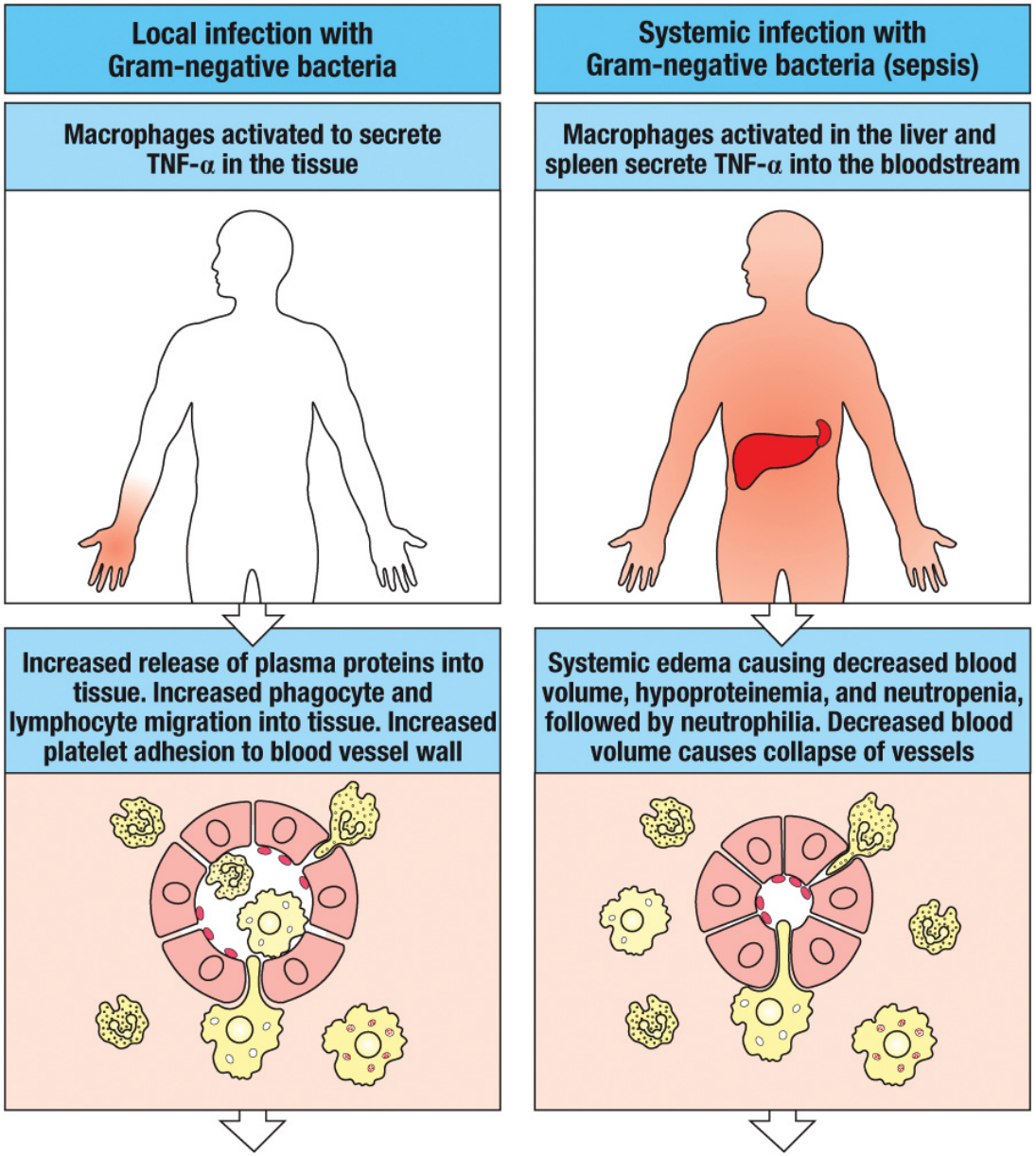
  Interferon

    Type I Interferon: antiviral response

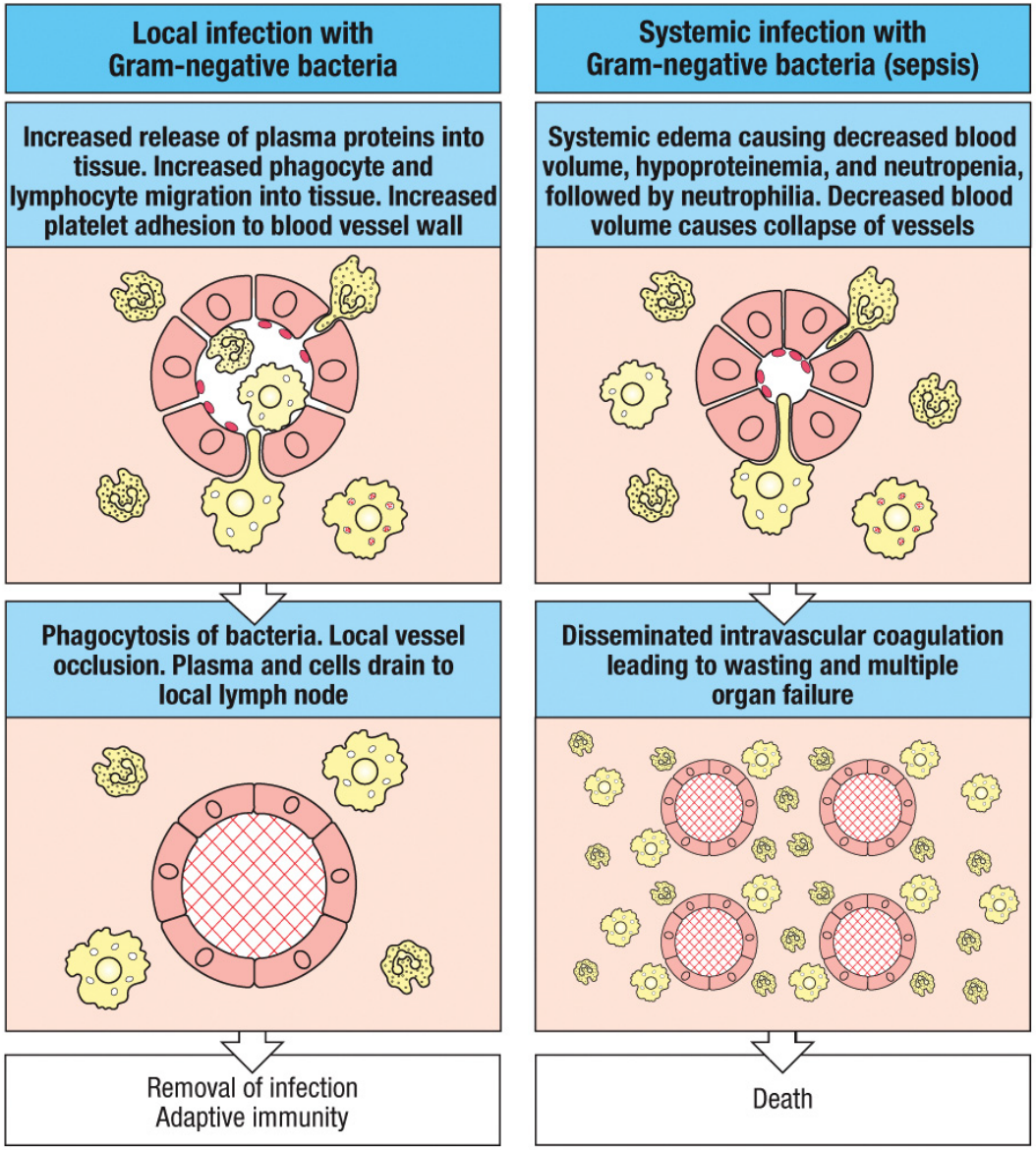
    Interferon-γ: macrophage activation

- NK cells

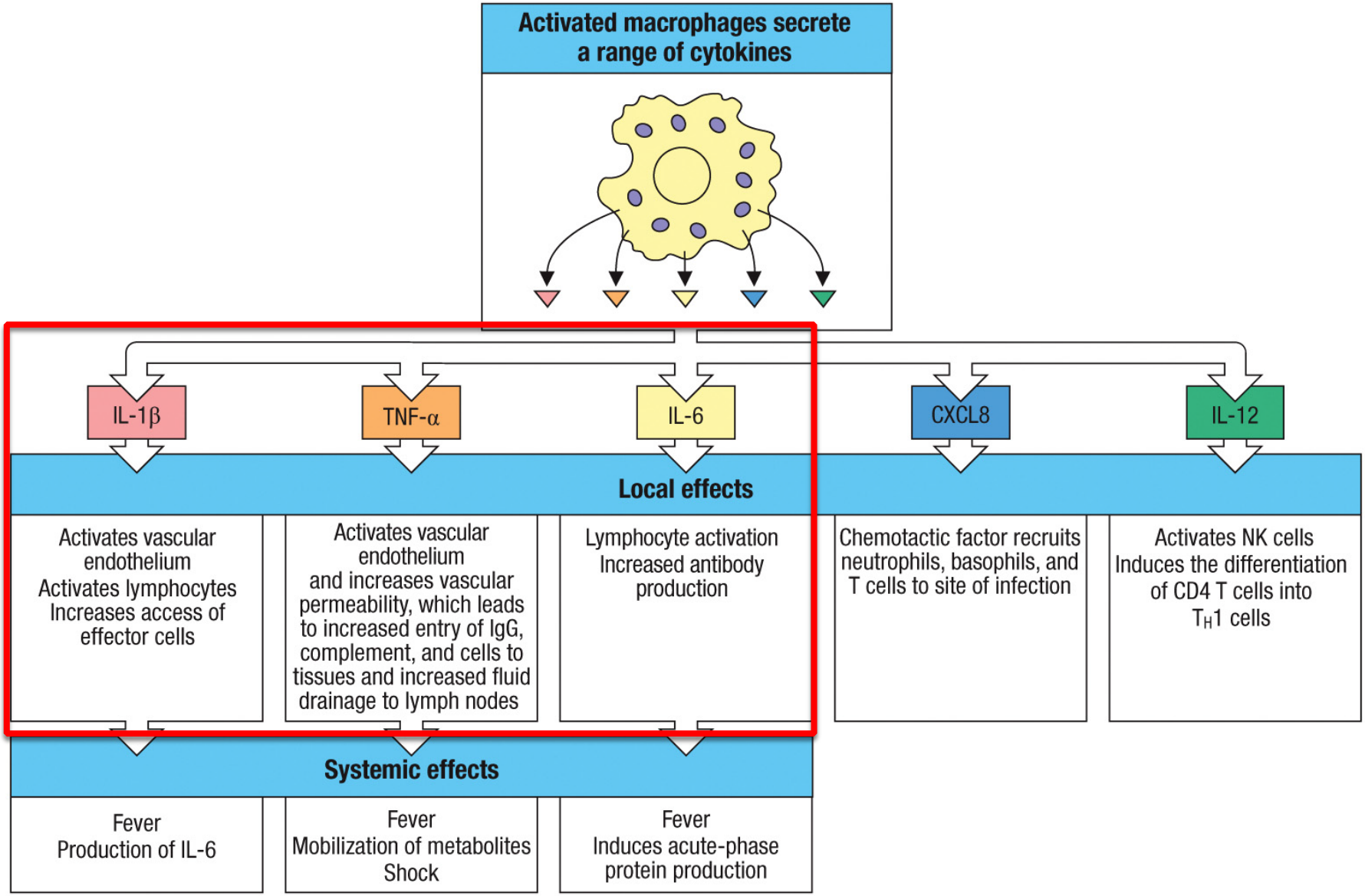
TNFα Contains Local Infection, But Leads to Septic Shock



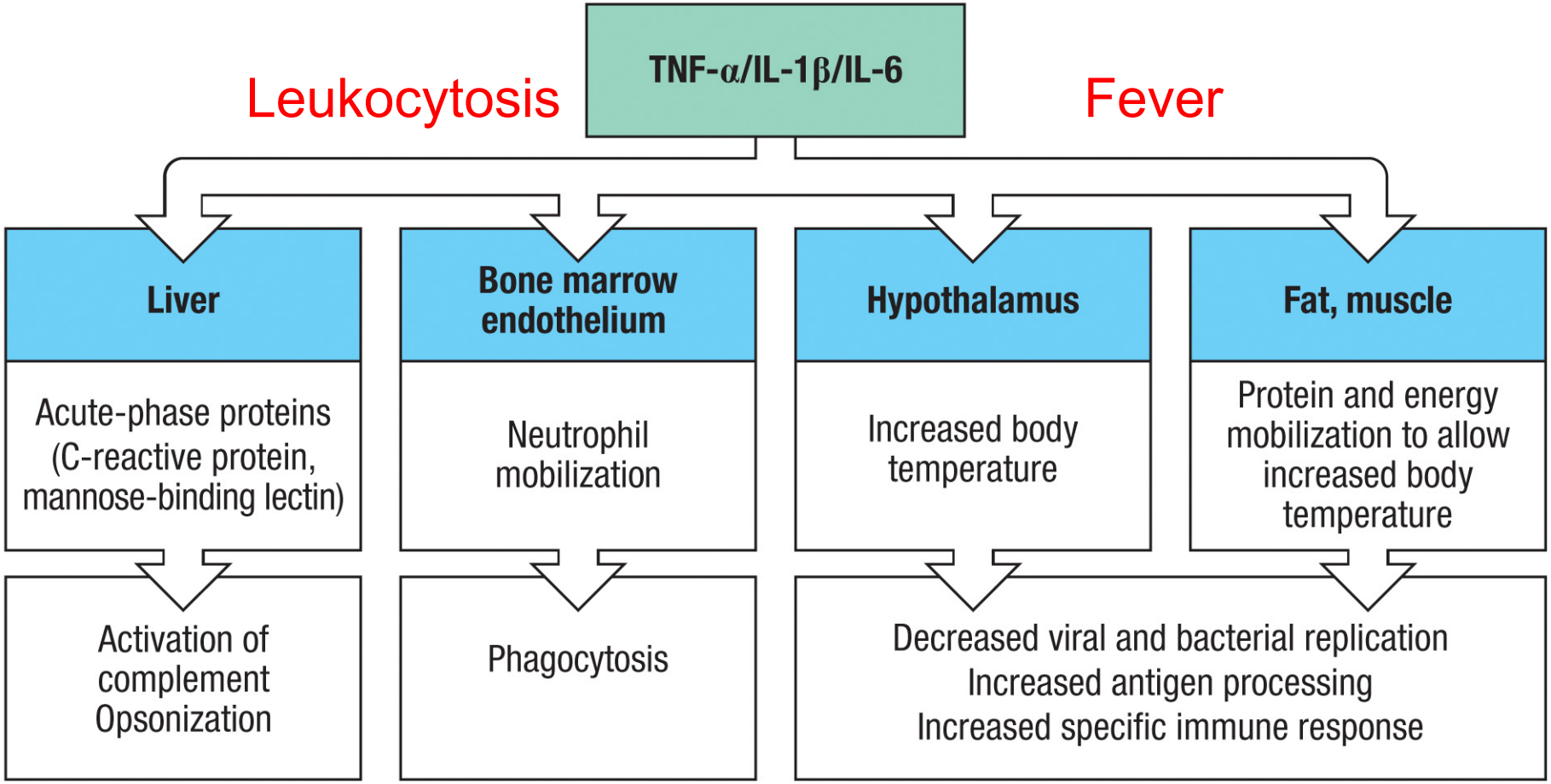
TNFα Contains Local Infection, But Leads to Septic Shock



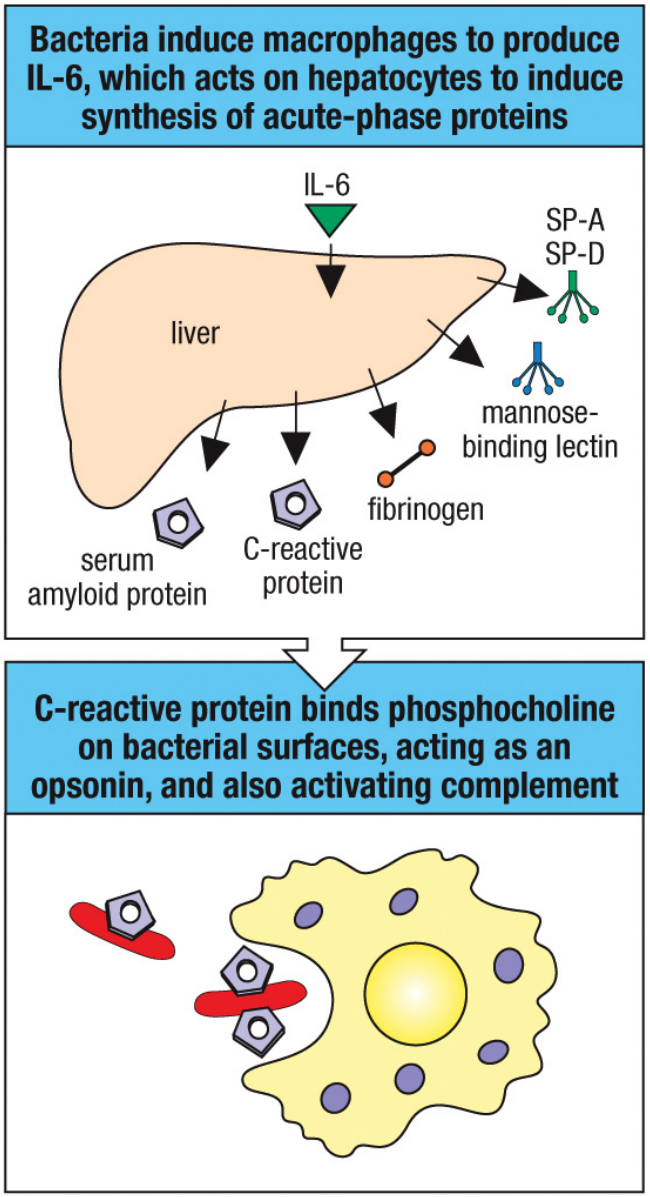
Effects of Cytokine Secretion



Cytokines Coordinate Body's Response to Infection

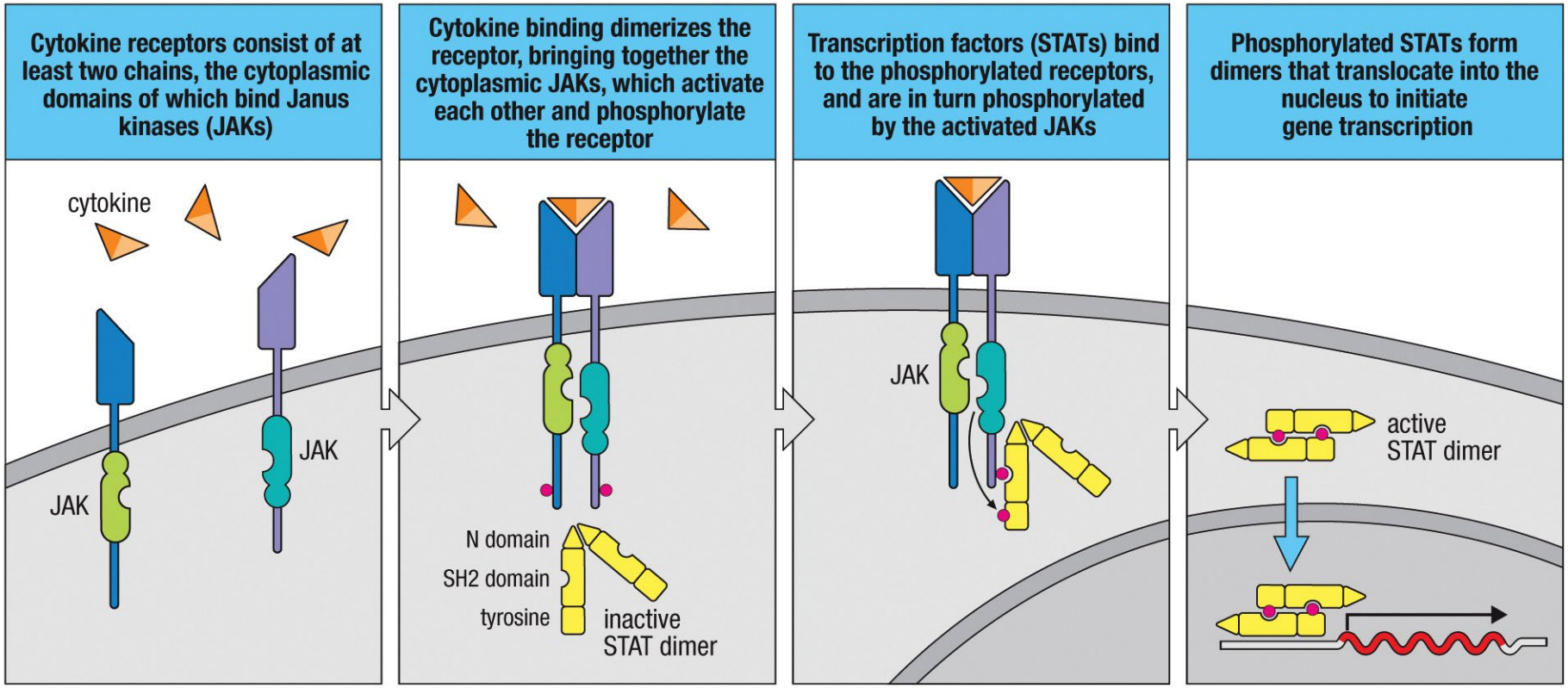


Acute-Phase Response



CRP is a general indicator of systemic inflammation

Cytokine Receptor Signalling



Question

- How do TNFalpha/IL-6/IL-1beta work? Explain their effects on liver and endothelium.

Outline

- Cytokines in innate immunity:

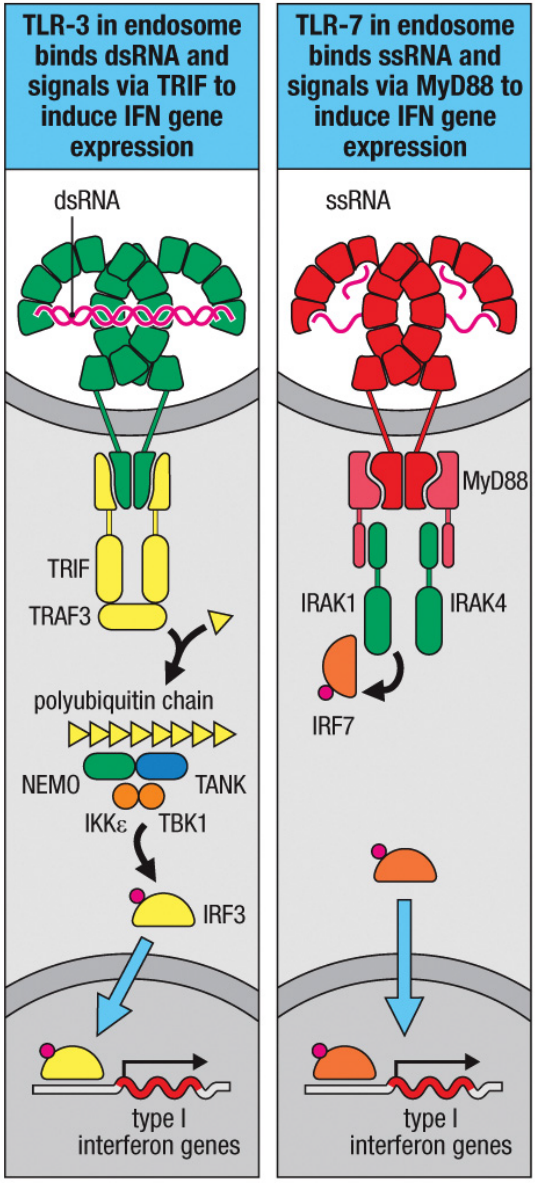
  Leukocyte recruitment
  Acute phase response
  Interferon
    Type I Interferon: antiviral response
    Interferon-γ: macrophage activation

- NK cells

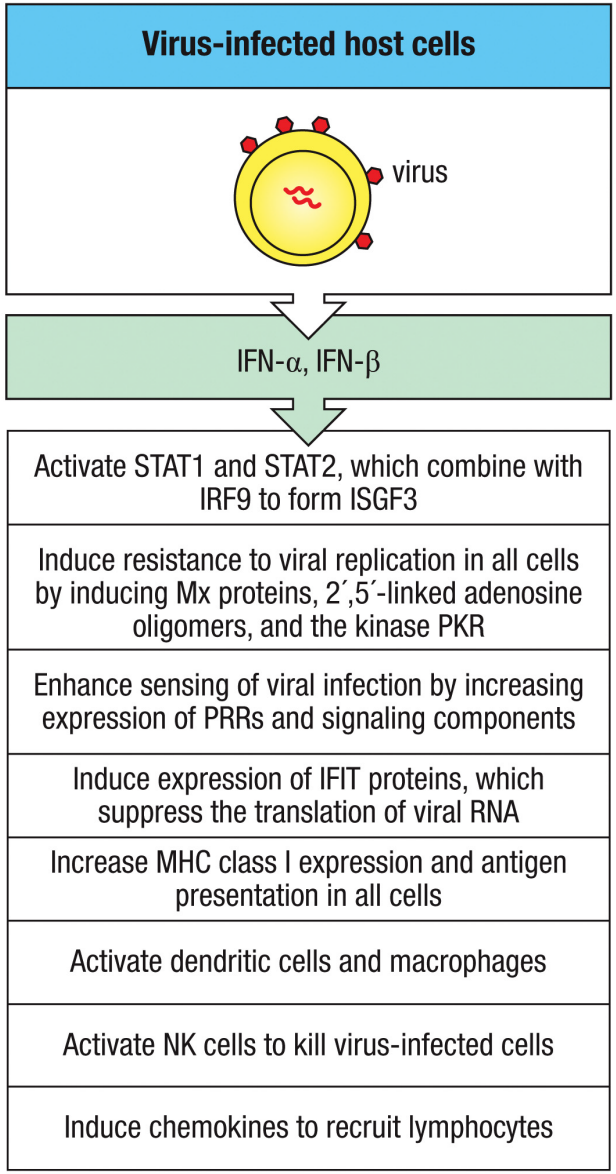
Interferons

- Interfere with viral replication in previously uninfected tissue culture cells.
- Restrict viral spreading
- Act on both infected and neighboring cells
- Type I interferon: Interferon-α and β

Intracellular TLRs Activate IFN Pathway

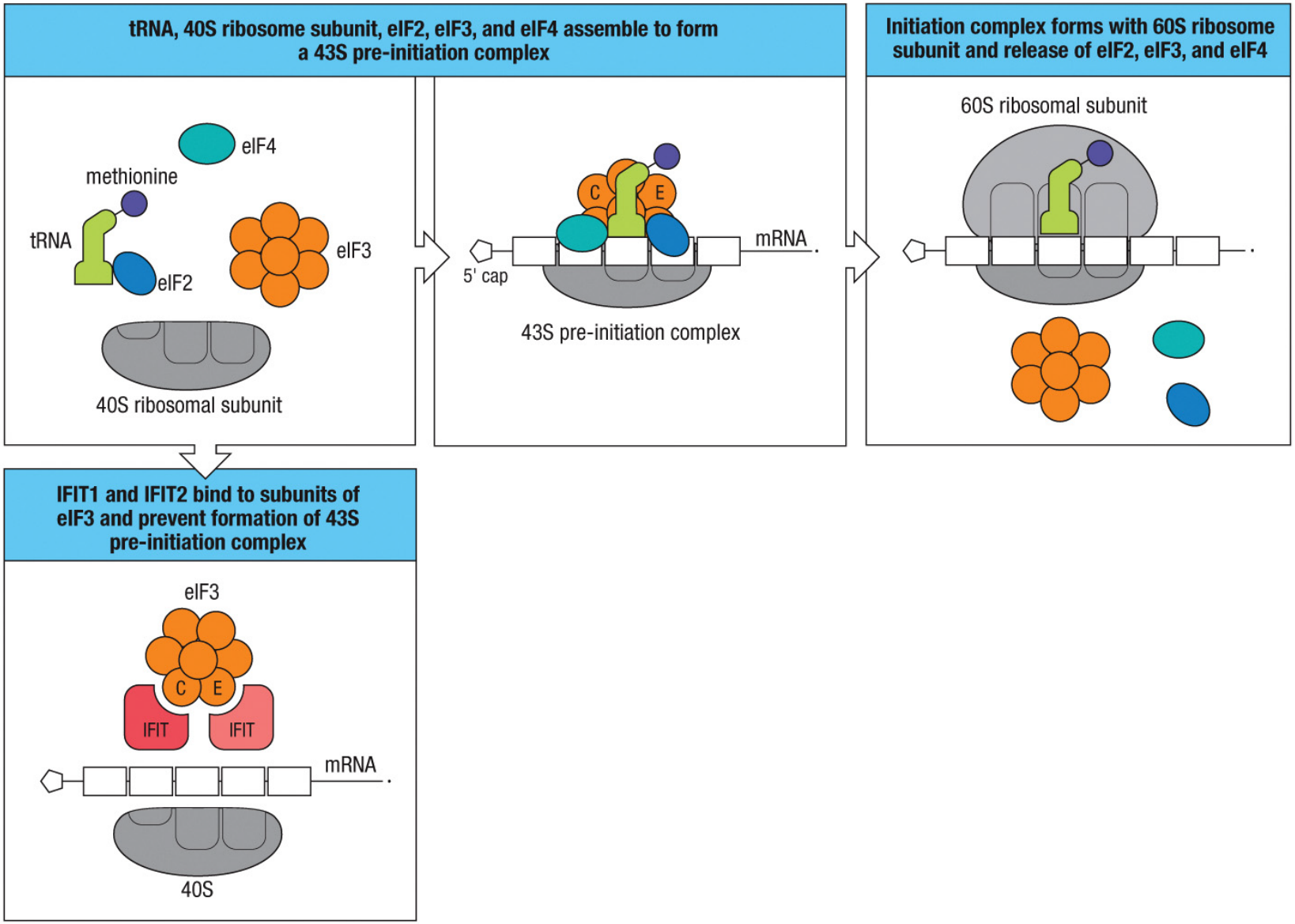


Interferons Induce Anti-Viral Responses



MX, unkown but very important
AO: Degrade viral RNA
PKR: Inhibiting translation

Inhibiting RNA Translation



IFN-γ Activates Macrophage

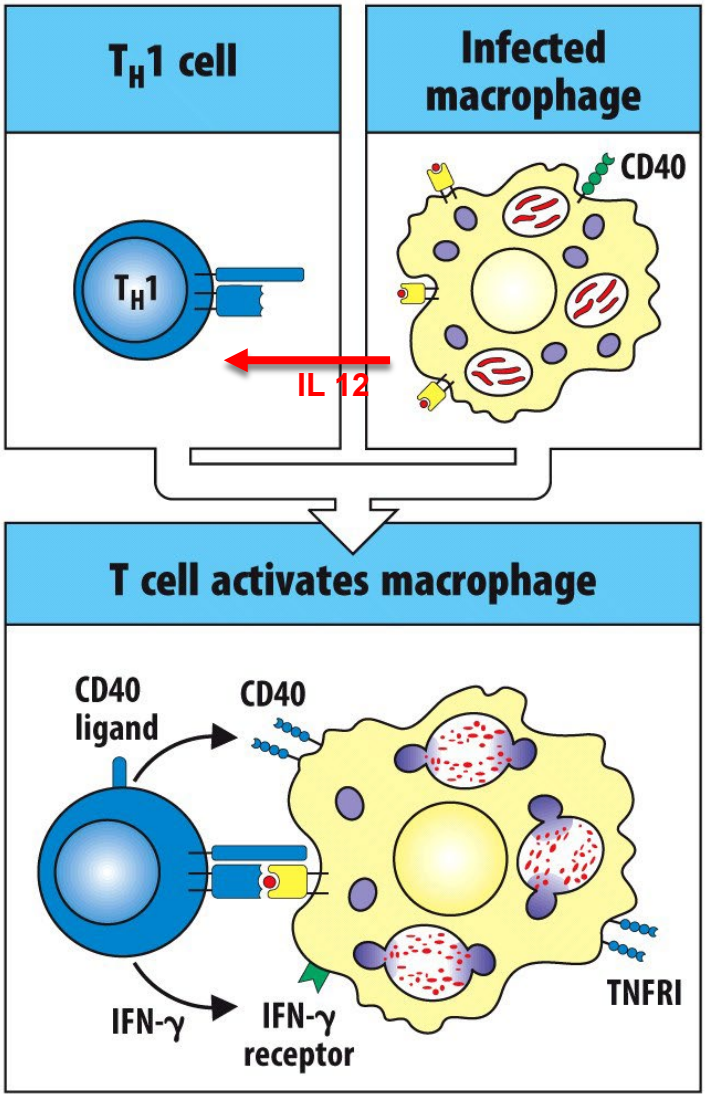


Figure 24.2 Case Studies in Immunology, 6ed. (© Garland Science 2012)

Question

- What are the major cytokines that defend against viral infection?
- How do these cytokines work?

Outline

- Cytokines in innate immunity:

  Leukocyte recruitment
  Acute phase response
  Interferon
    Type I Interferon: antiviral response
    Interferon-γ: macrophage activation

- NK cells

NK cells

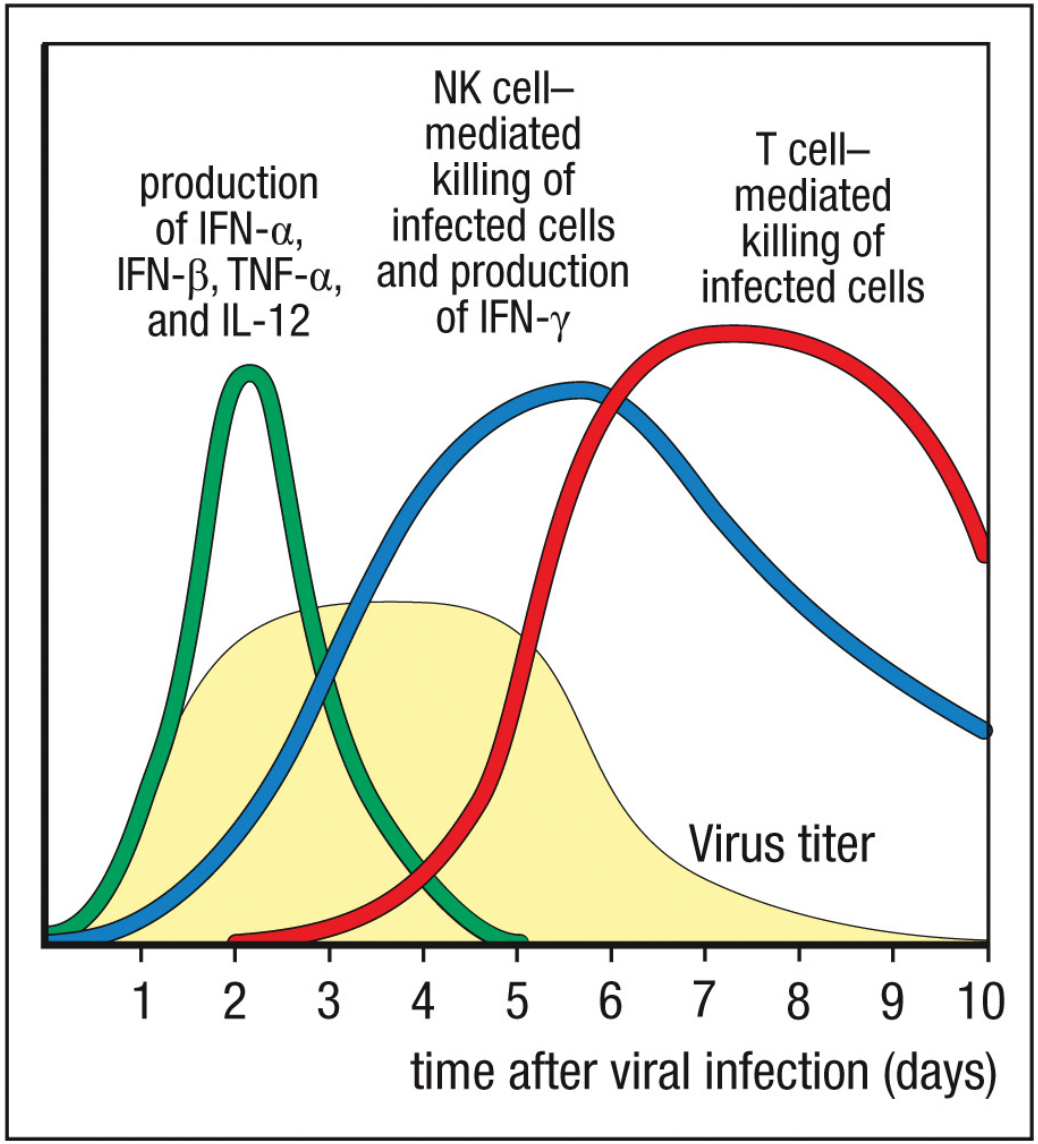
- Lymphoid progenitor
- Kill tumor cell lines in vitro
- Invariant surface receptor

NK Cells Kill Stressed Cells

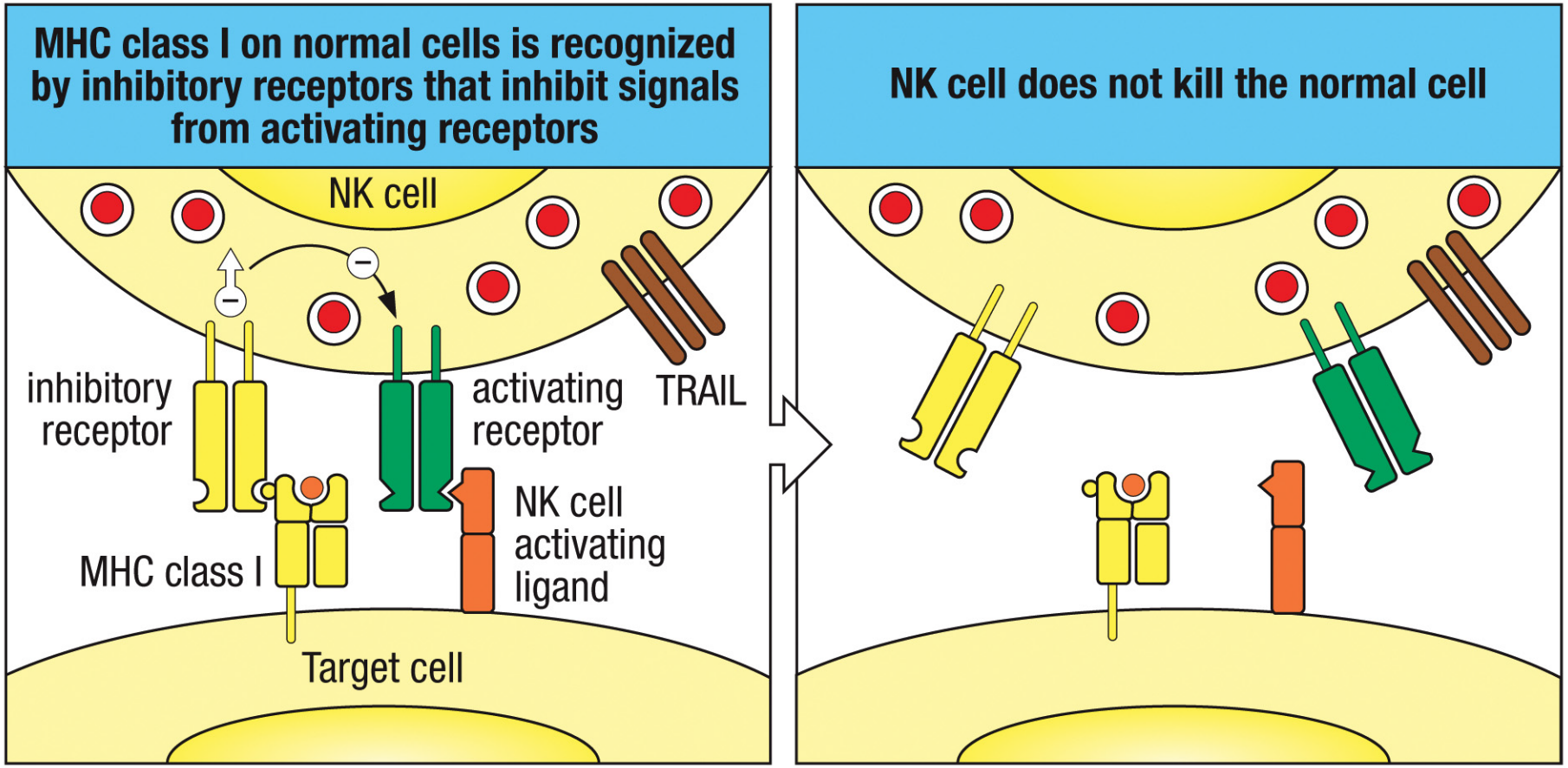
https://www.youtube.com/watch?v=HNP1EAYLhOs

https://www.youtube.com/watch?v=Va1jaBGwoT8

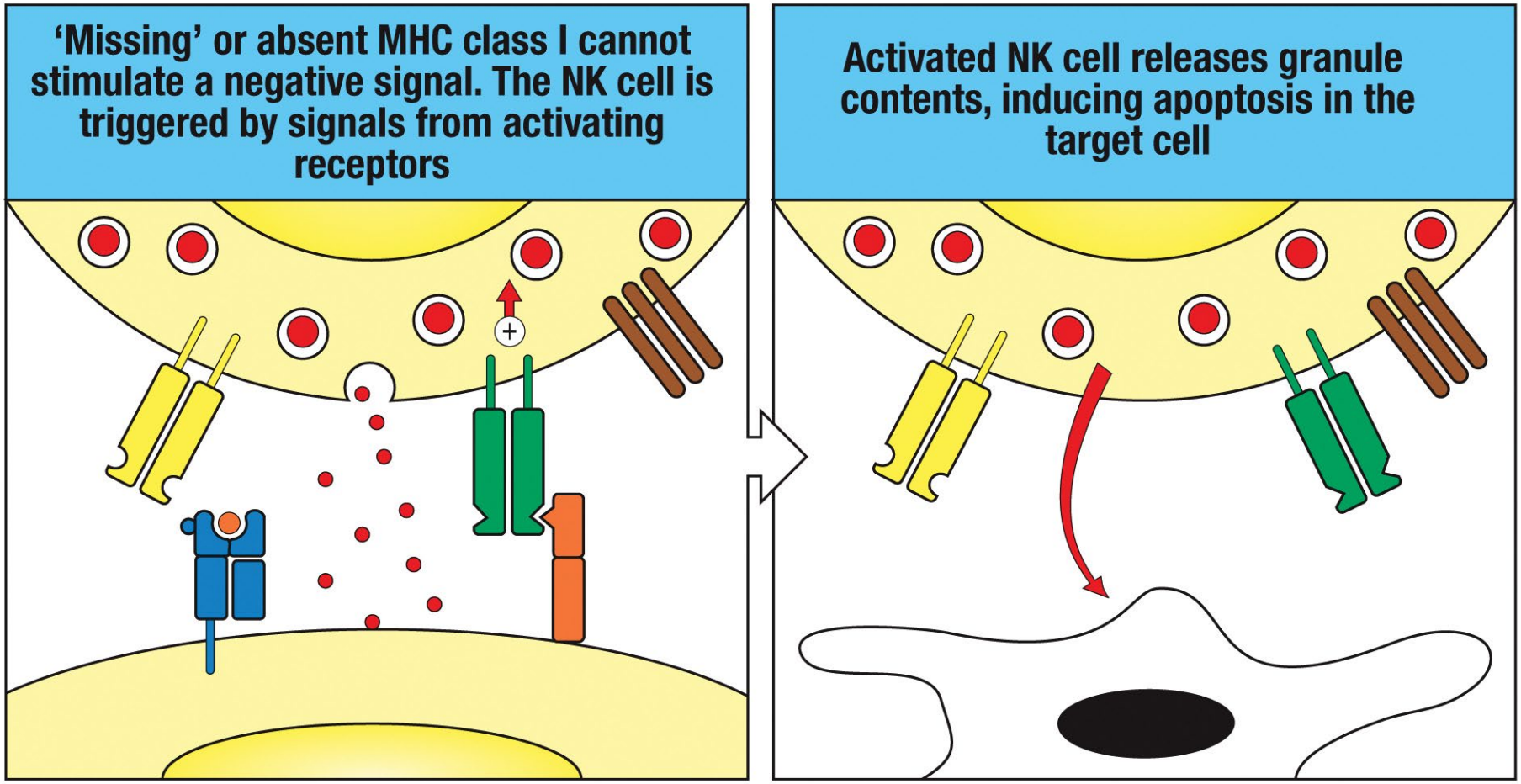
NK cells Kill Infected Cells



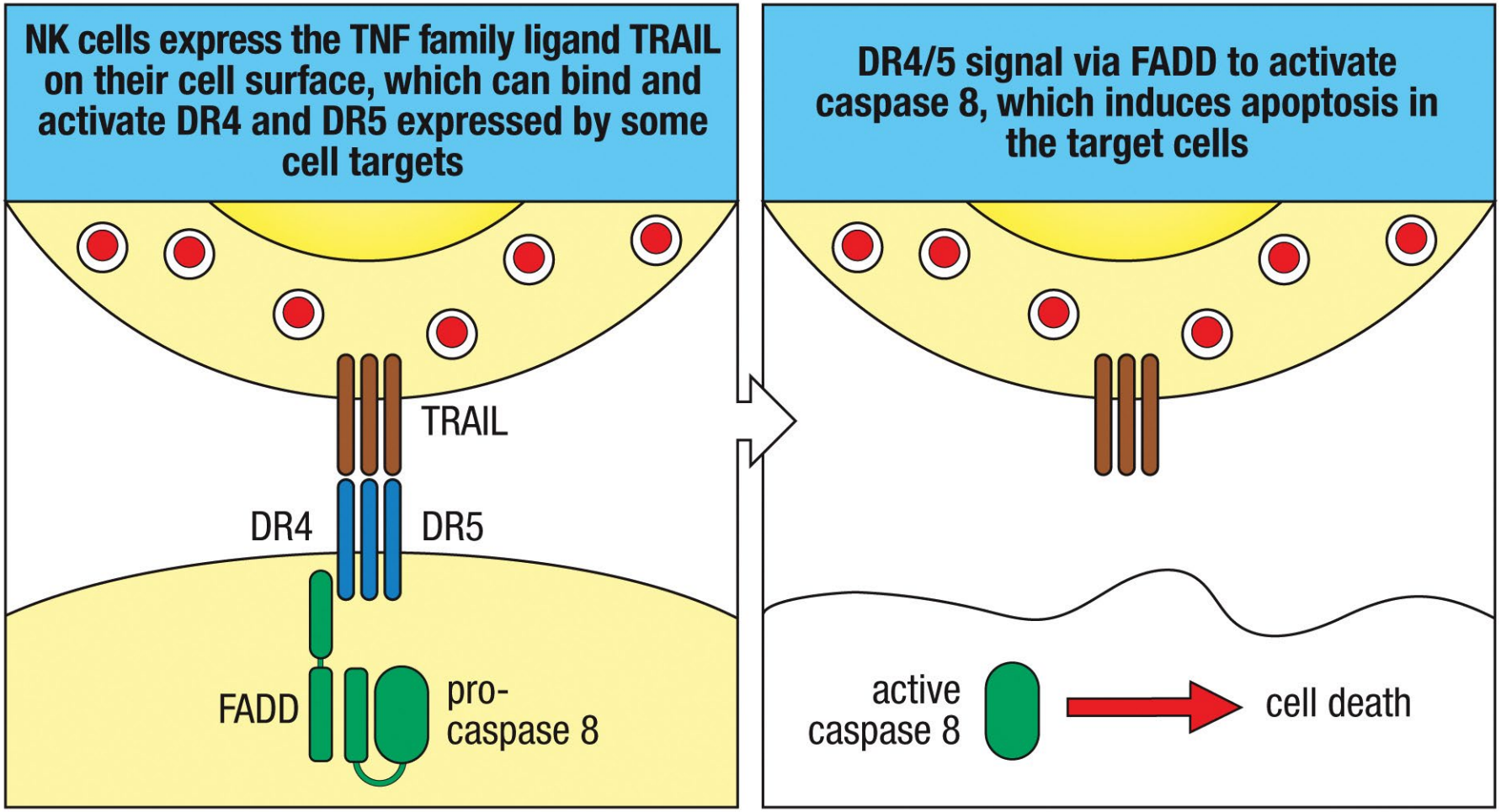
NK Cells Do Not Kill Normal Cells



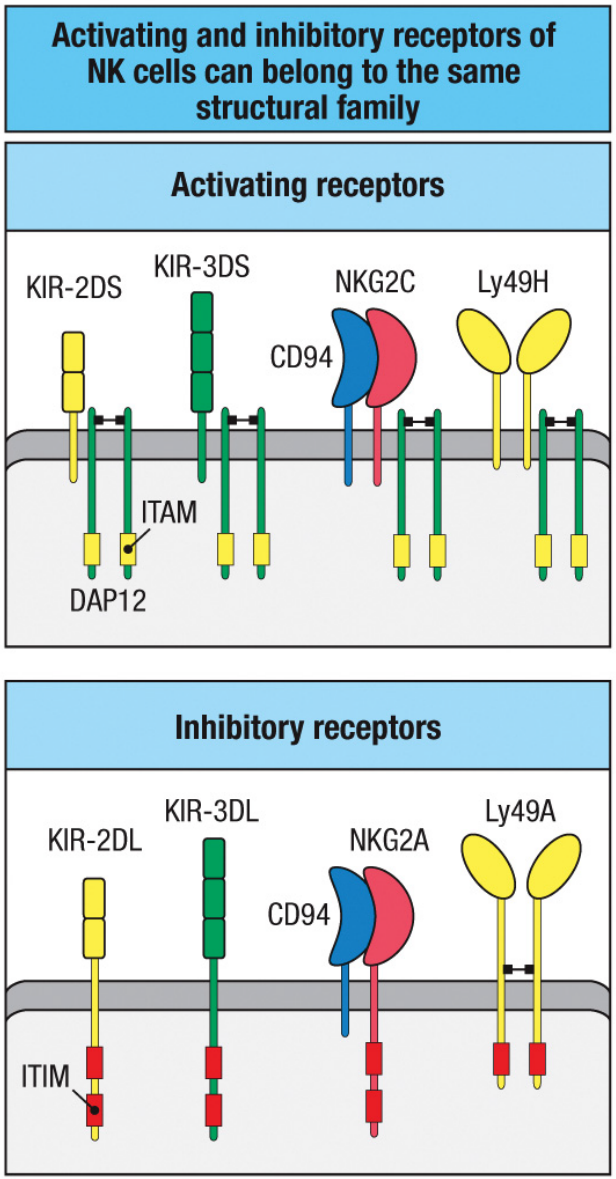
NK Cells Kill Abnormal Cells



NK Cells Kill Abnormal Cells



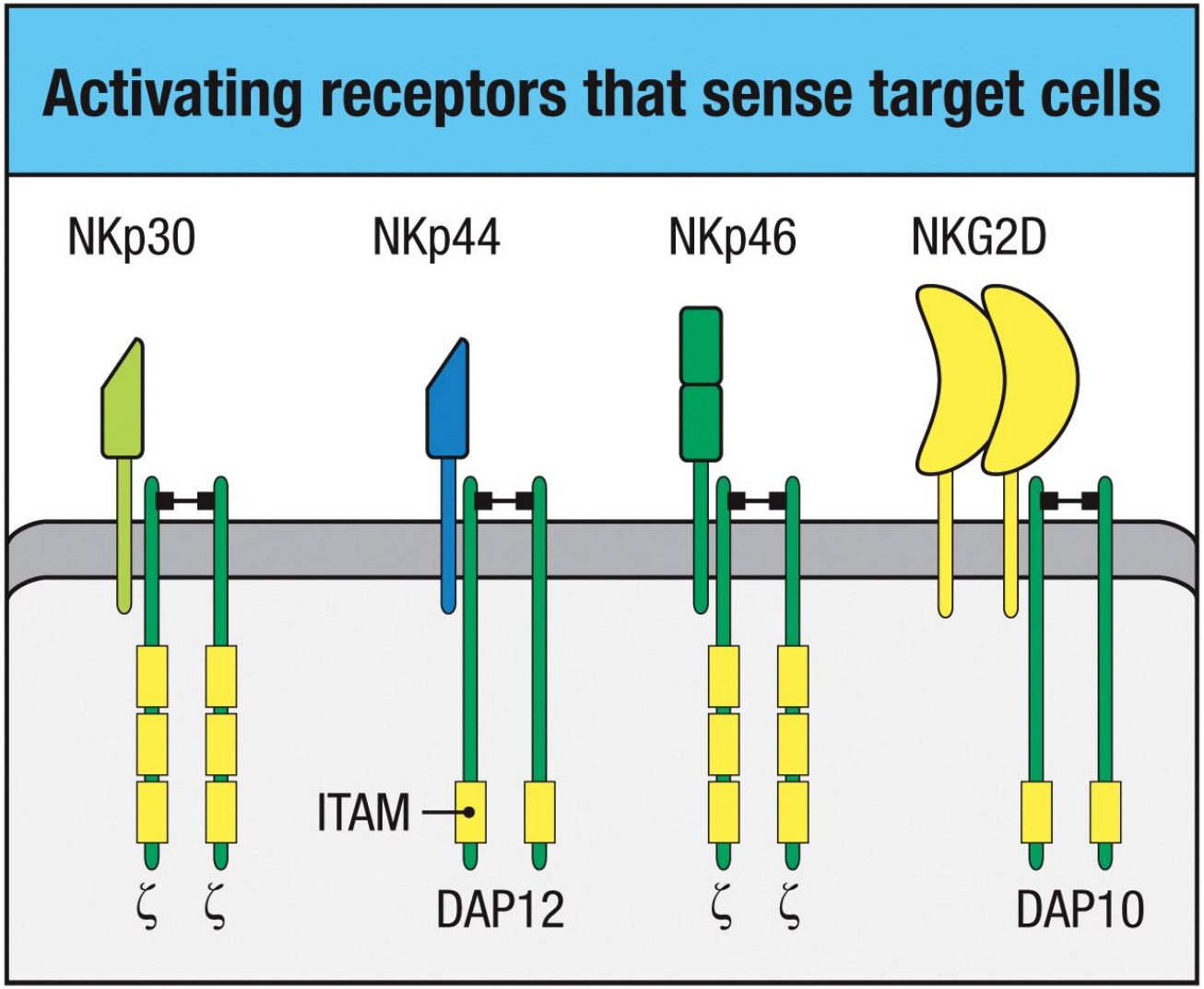
Two Types of Receptors



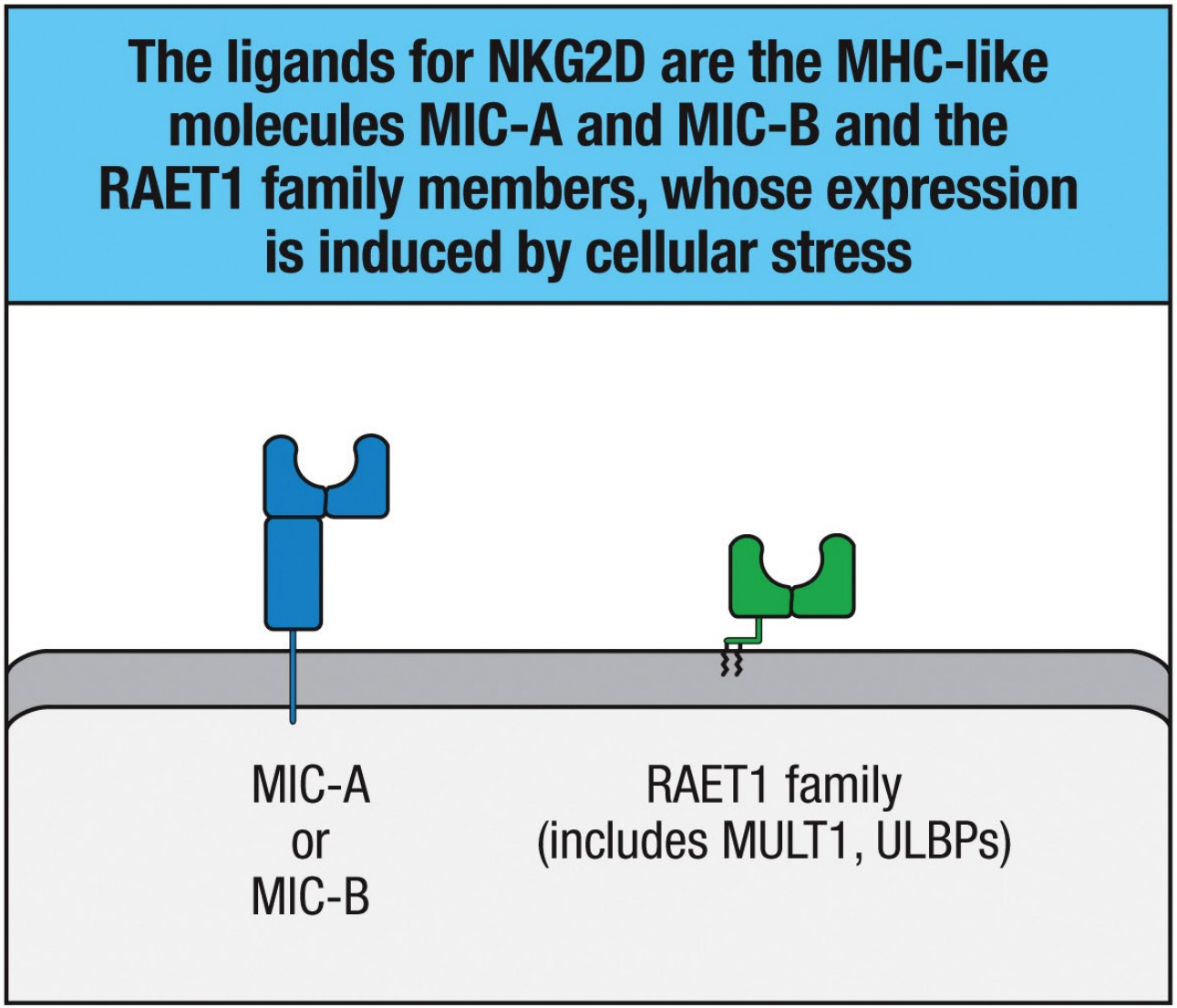
killer cell immunoglobulin-like receptors (KIRs)

killer cell lectin-like receptors (KLRs and Ly49 receptors)

Activating Receptors



Activating Ligands



Question

- What is NOT the function of cytokines?
- A) guide immune cell migration
- B) activate intracellular signaling
- C) activate innate immune cells
- D) activate adaptive immune cells
- E) none of the above

Case Studies

- Leukocyte Adhesion Deficiency
- Interferon-γ Receptor Deficiency

Leukocyte Adhesion Deficiency

Patient:

- 4-week-old female
- Fever 39°C,
- Redness and swelling around umbilical cord stump
- WBC count 20,000 cells/microliter (normal range 5,000-10,000)
- Skin culture positive for E.coli and S.aureus.

Family history:

- A brother died at 1 year of age due to Staphylococcal pneumonia infection

Diagnosis:

- Rebuck skin window-monitor the migration of immune cells into the damaged skin.
- No white cells

Treatment :

- Bone marrow transplantation

Deficient of Surface LFA

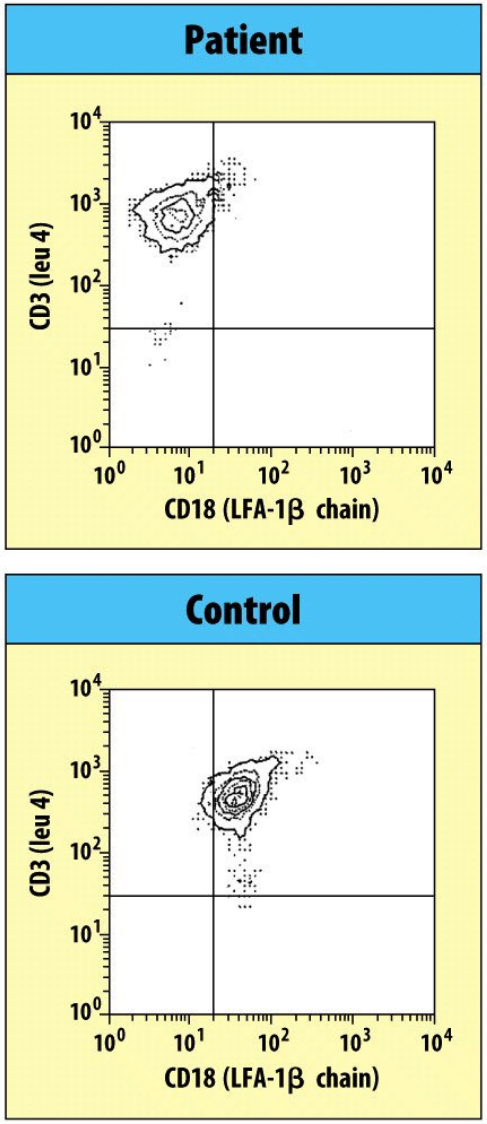


Figure 27.5 Case Studies in Immunology, 6ed. (© Garland Science 2012)

LFA-1

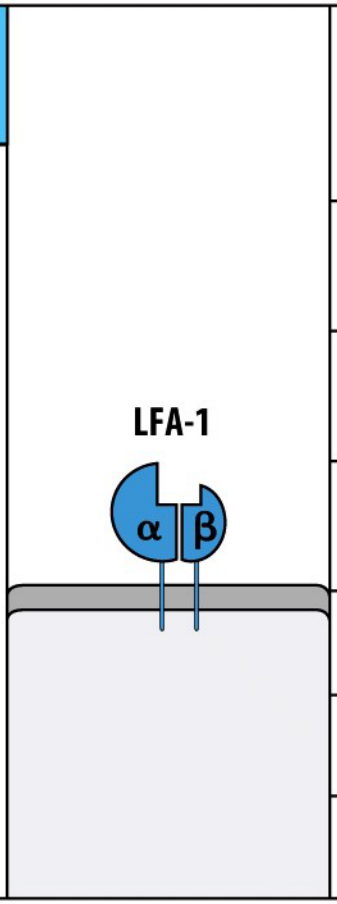
Integrins		Name	Tissue distribution	Ligand
Bind to cell-adhesion molecules and extracellular matrix. Strong adhesion		α_L:β_2 (LFA-1, CD11a/CD18)	Monocytes, T cells, macrophages, neutrophils, dendritic cells	ICAMs
		α_M:β_2 (Mac-1, CR3, CD11b/CD18)	Neutrophils, monocytes, macrophages	ICAM-1, iC3b, fibrinogen
		α_X:β_2 (CR4, p150-95, CD11c/CD18)	Dendritic cells, macrophages, neutrophils	iC3b
		α_4:β_1 (VLA-4, LPAM-2, CD49d/CD29)	Lymphocytes, monocytes, macrophages	VCAM-1 Fibronectin
		α_5:β_1 (VLA-5, CD49d/CD29)	Monocytes, macrophages	Fibronectin
		α_4:β_7 (LPAM-1)	Lymphocytes	MAdCAM-1
		α_E:β_7	Intraepithelial lymphocytes	E-cadherin

Figure 27.3 part 3 of 4 Case Studies in Immunology, 6ed. (© Garland Science 2012)

LFA-1 is Required for Leukocyte Infiltration

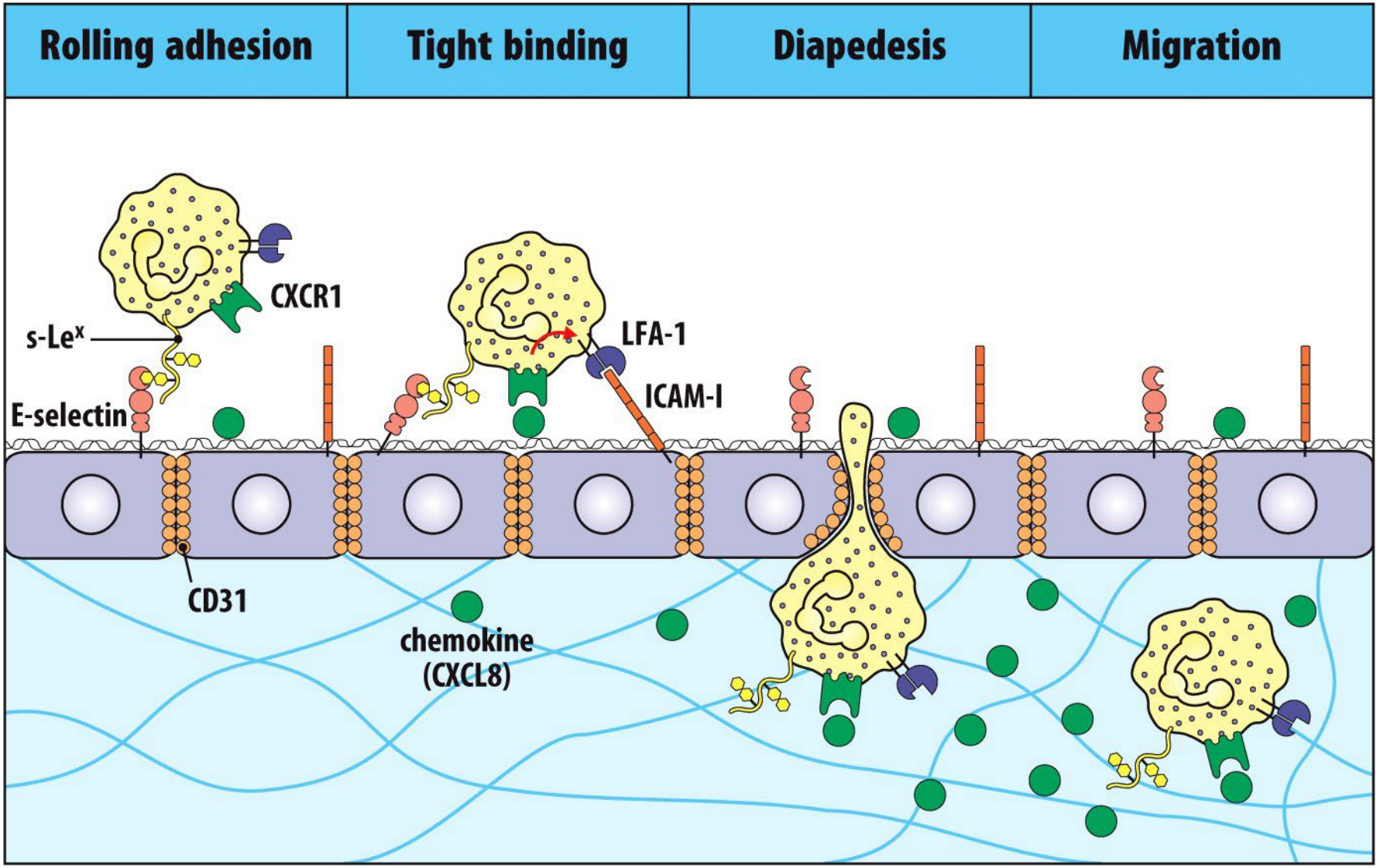


Figure 27.1 part 2 of 2 Case Studies in Immunology, 6ed. (© Garland Science 2012)

LFA-1 is Required for T Cell Activation

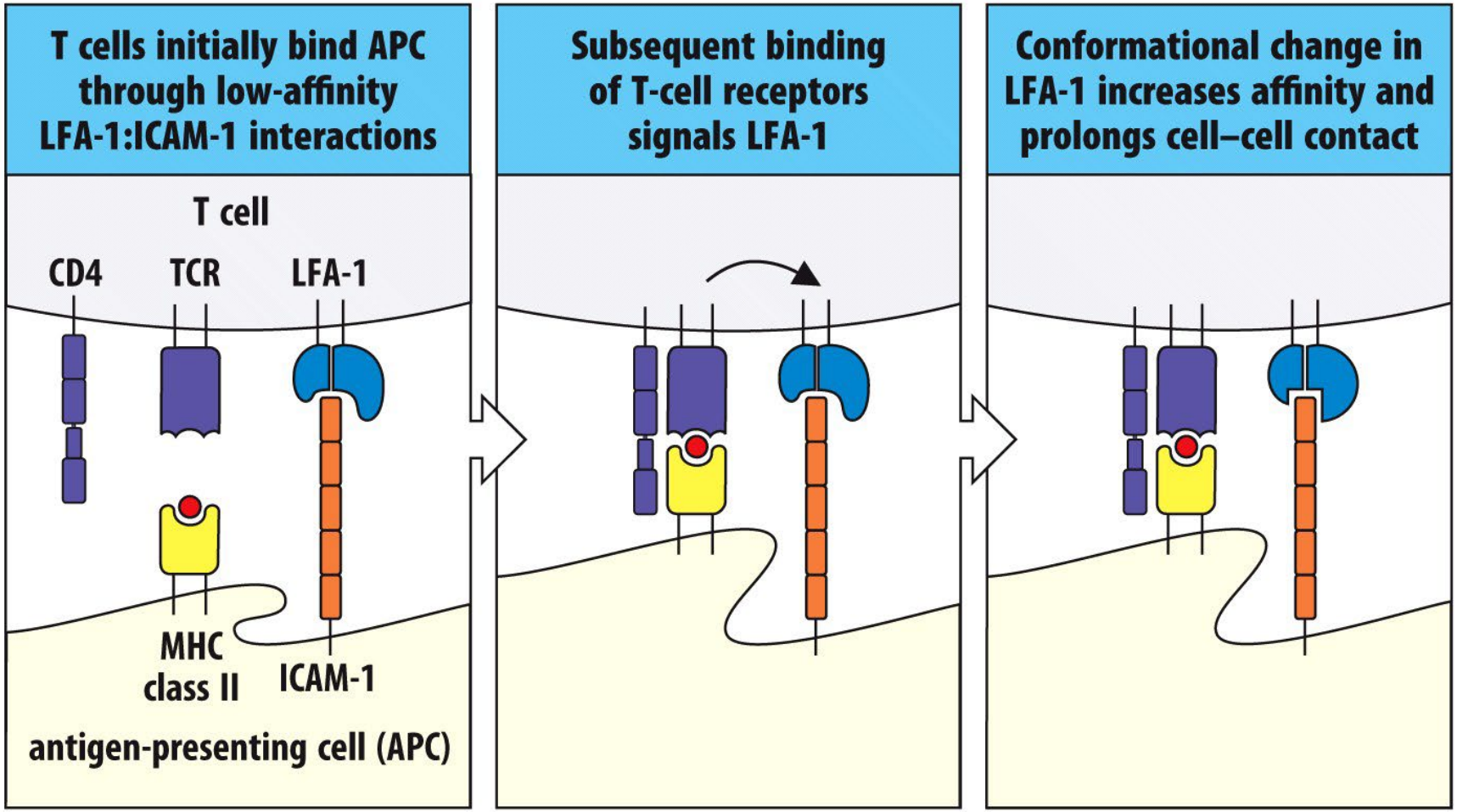


Figure 27.4 Case Studies in Immunology, 6ed. (© Garland Science 2012)

What's Wrong with the Patient?

- LFA-1 defect leads to impair recruitment of leukocytes to infected tissue.
- Poor T cell activation

- Severe immune deficiency

- Poor wound healing
  - Mechanism not understood.

Interferon-γ Receptor Deficiency

Patient:

- 2 1/2-year-old female
- enlarged lymph nodes
- Normal number of leukocytes and Ig levels

Family history:

- Distantly related

Diagnosis:

- Lymph nodes positive for Mycrobacterium avium

Treatment :

- Antibiotics

Outcome:

- Died after recurrent infection

IFN-γ Activates Macrophage

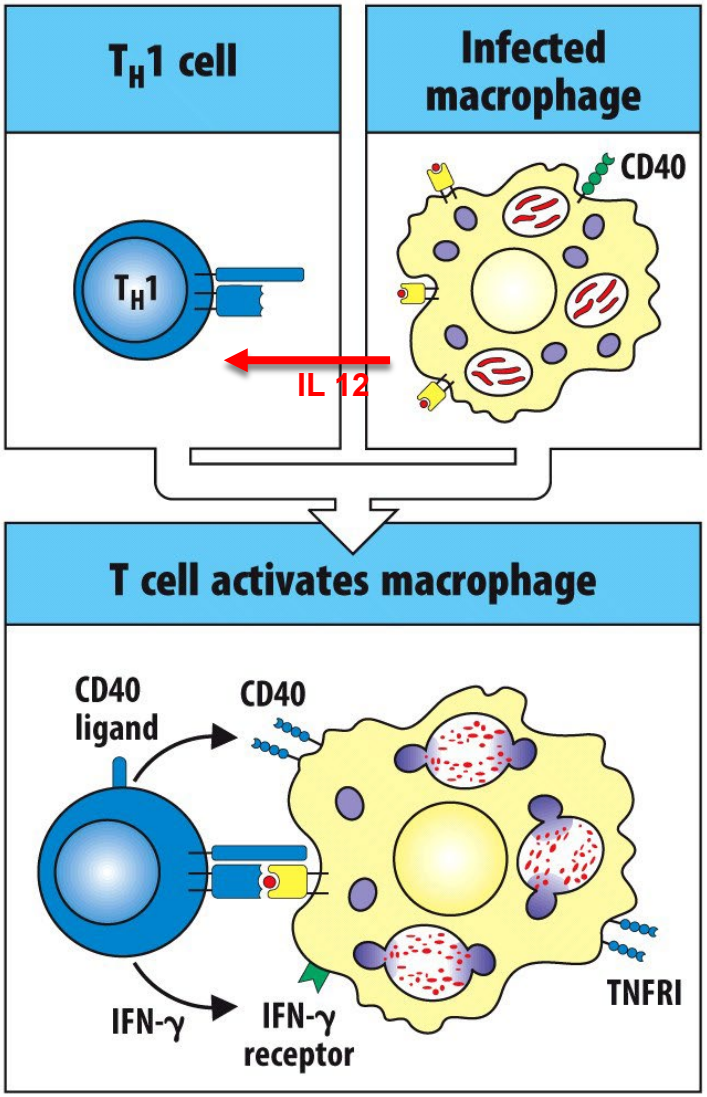


Figure 24.2 Case Studies in Immunology, 6ed. (© Garland Science 2012)

IFN-γ Signaling

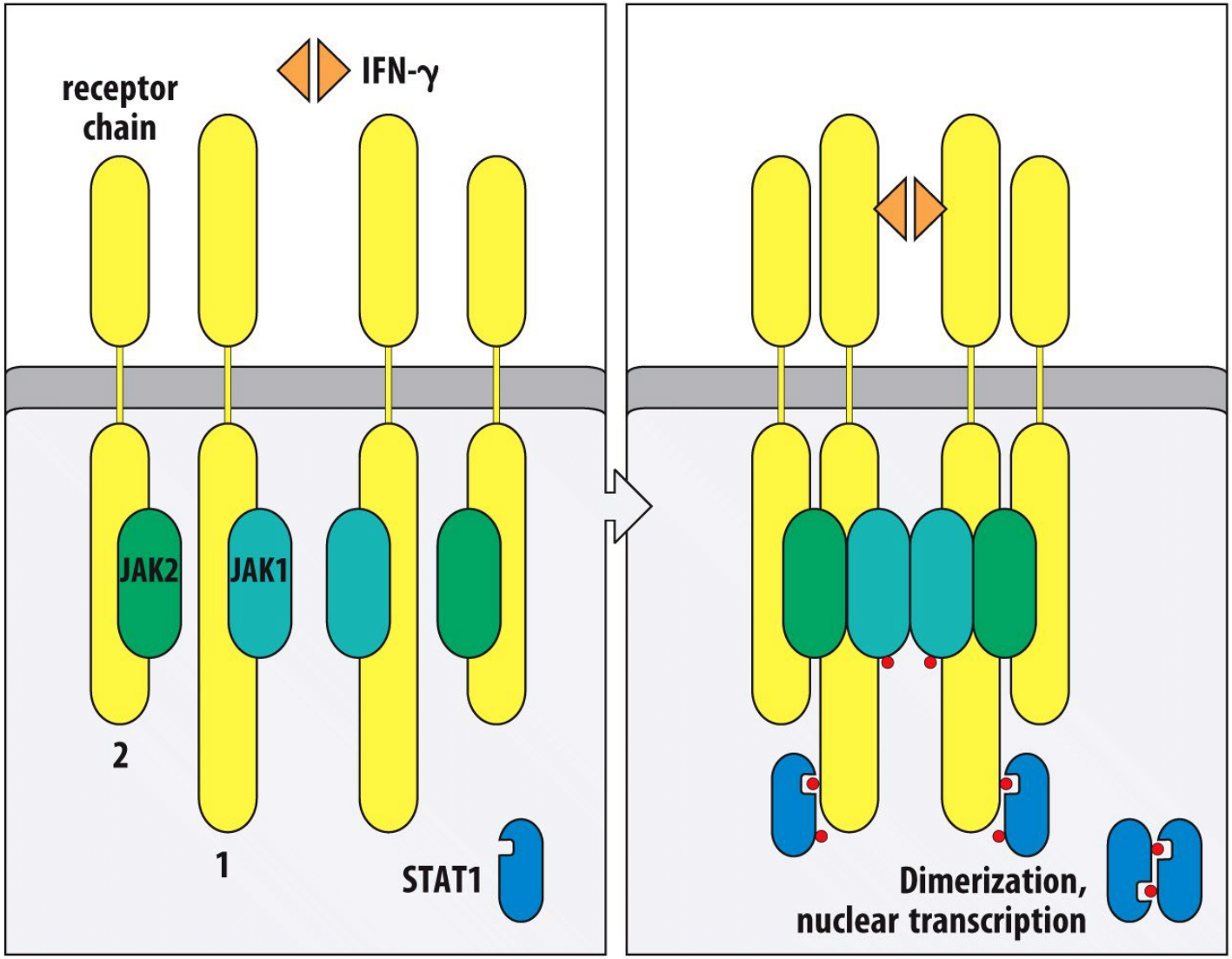


Figure 24.3 Case Studies in Immunology, 6ed. (© Garland Science 2012)

What's Wrong with the Patient?

- Defect in IFN-γ signaling
- Unable to activate infected macrophages
- Susceptible to intracellular bacterial infection