Innate Immunity & Inflammation

November 20, 2006

Ch. 22, Ch. 23

Cells & organs of immune system

Innate immune response

Signals (chemokines, cytokines)

Inflammation

Adaptive immune response

Cells of the Immune System

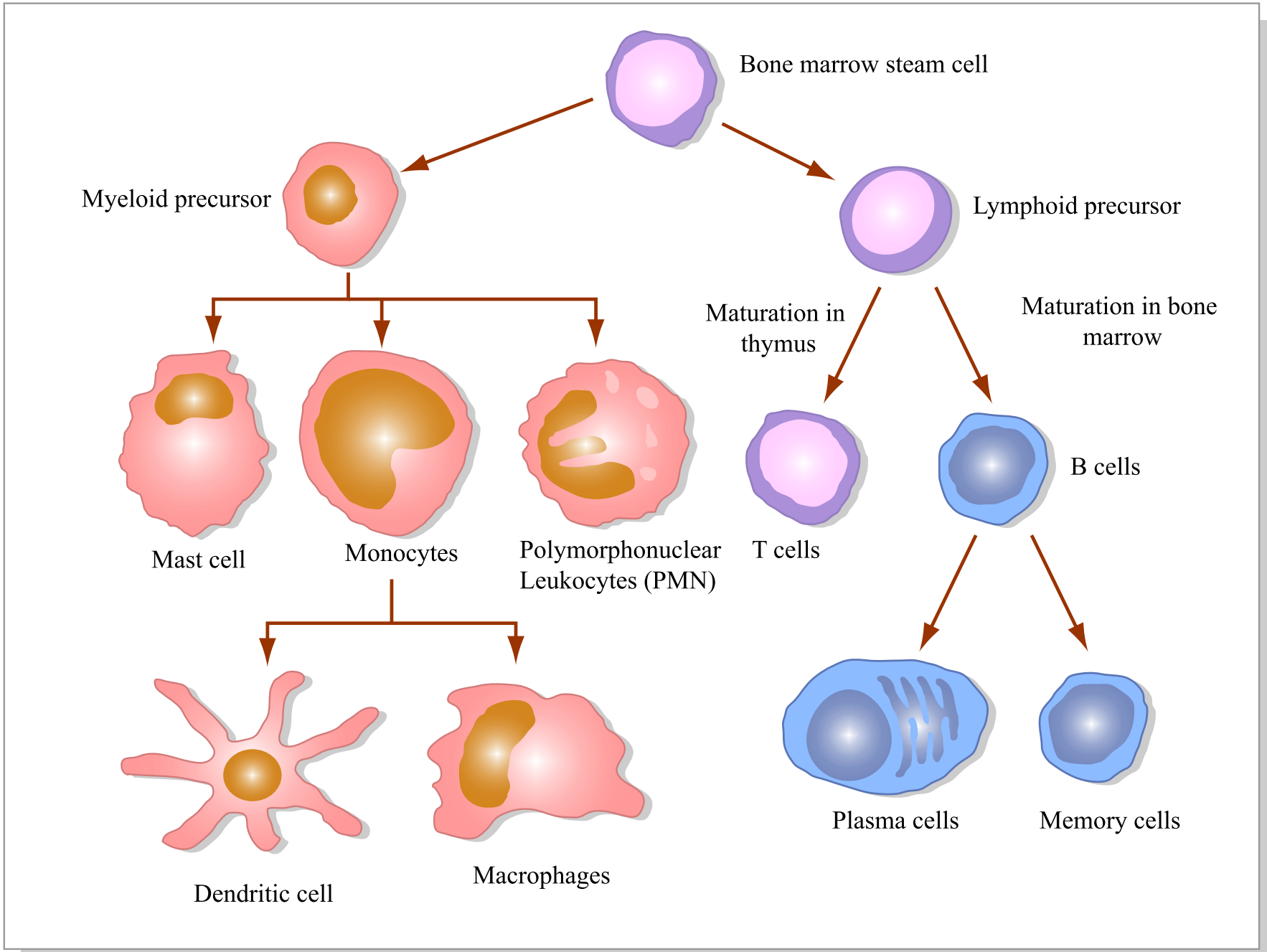


Figure by MIT OCW.

NEUTROPHIL
Common phagocytic cell

EOSINOPHIL
Allergic conditions and parasites

BASOPHIL
Synthesize-store heparin/histamine

Image showing neutrophils, eosinophils, basophils, monocytes, B lymphocytes, and T lymphocytes removed due to copyright restrictions.

MONOCYTE
A large phagocyte

B LYMPHOCYTE
Antibody production

T LYMPHOCYTE
Destroy targets (viruses and cancer cells)

Lymphatic System

Diagrams of the human lymphatic system removed due to copyright restrictions.
See Figures 22-2a and 22-2c in Madigan, Michael, and John Martinko. *Brock Biology of Microorganisms.* 11th ed. Upper Saddle River, NJ: Pearson Prentice Hall, 2006. ISBN: 0131443291

Immune Responses

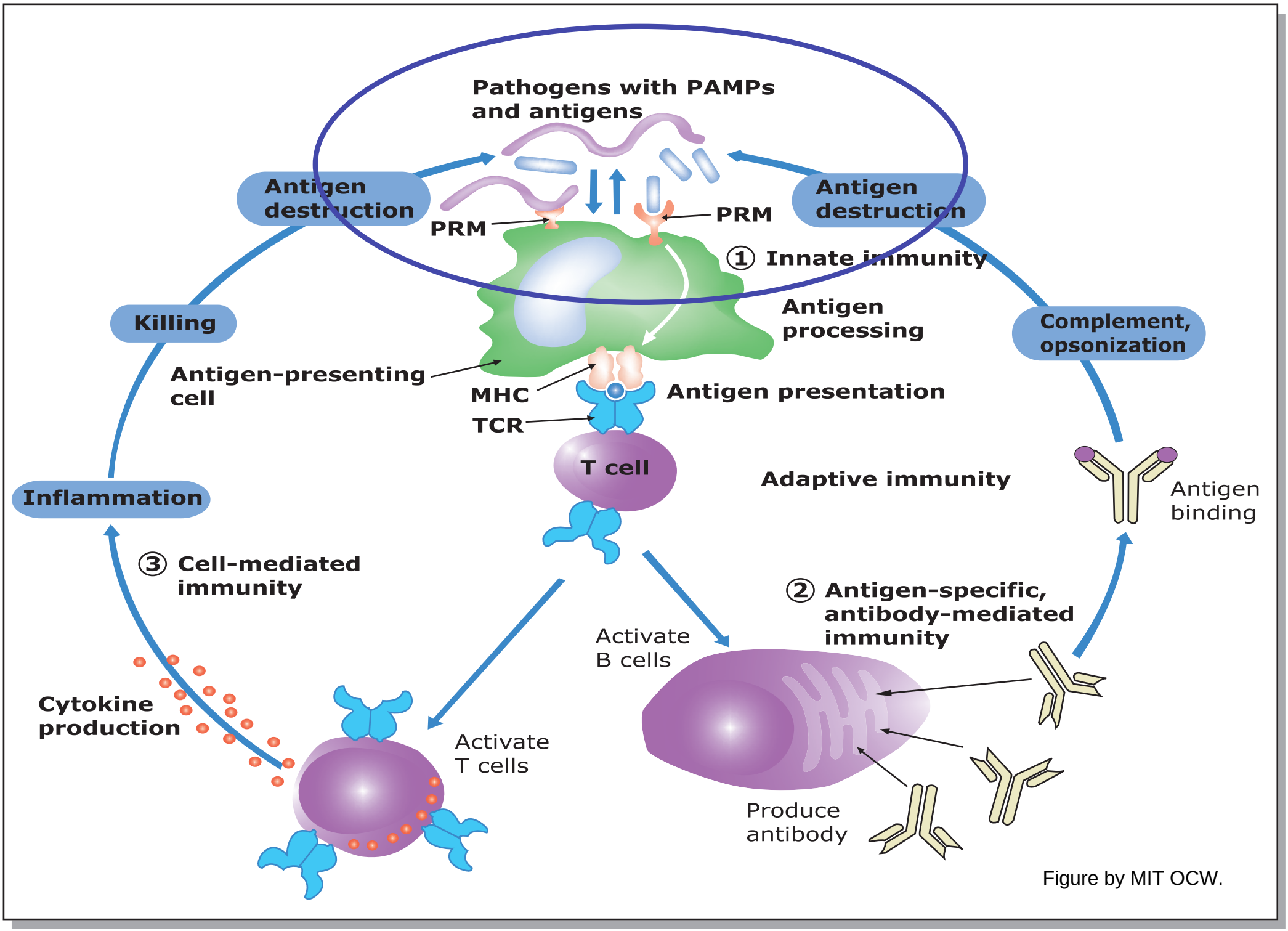


Figure by MIT OCW.

Cell Characteristics

PMN (**neutrophils**, basophils, eosinophils)

Monocytes (**macrophages**, dendritic cells)

- Phagocytic
- Attracted to the site of an active infection or tissue injury by soluble chemoattractants called **chemokines**
- Recognize **pathogen-associated molecular patterns (PAMPs)** via a family of membrane-bound **pattern-recognition receptors (PRRs)**

Activation of Phagocytes

PRRs

- Present before infection
- Evolved to recognize microbes
- PRRs interact with PAMPS shared by a variety of pathogens, activating complement and phagocyte effector mechanisms to target and destroy pathogens
- Activation of signaling cascade leads to production of chemokines and cytokine
- First discovered as the Toll receptors in *Drosophila* (the fruit fly), the evolutionarily and functionally related transmembrane proteins are called **Toll-like receptors (TLRs)** in mammals

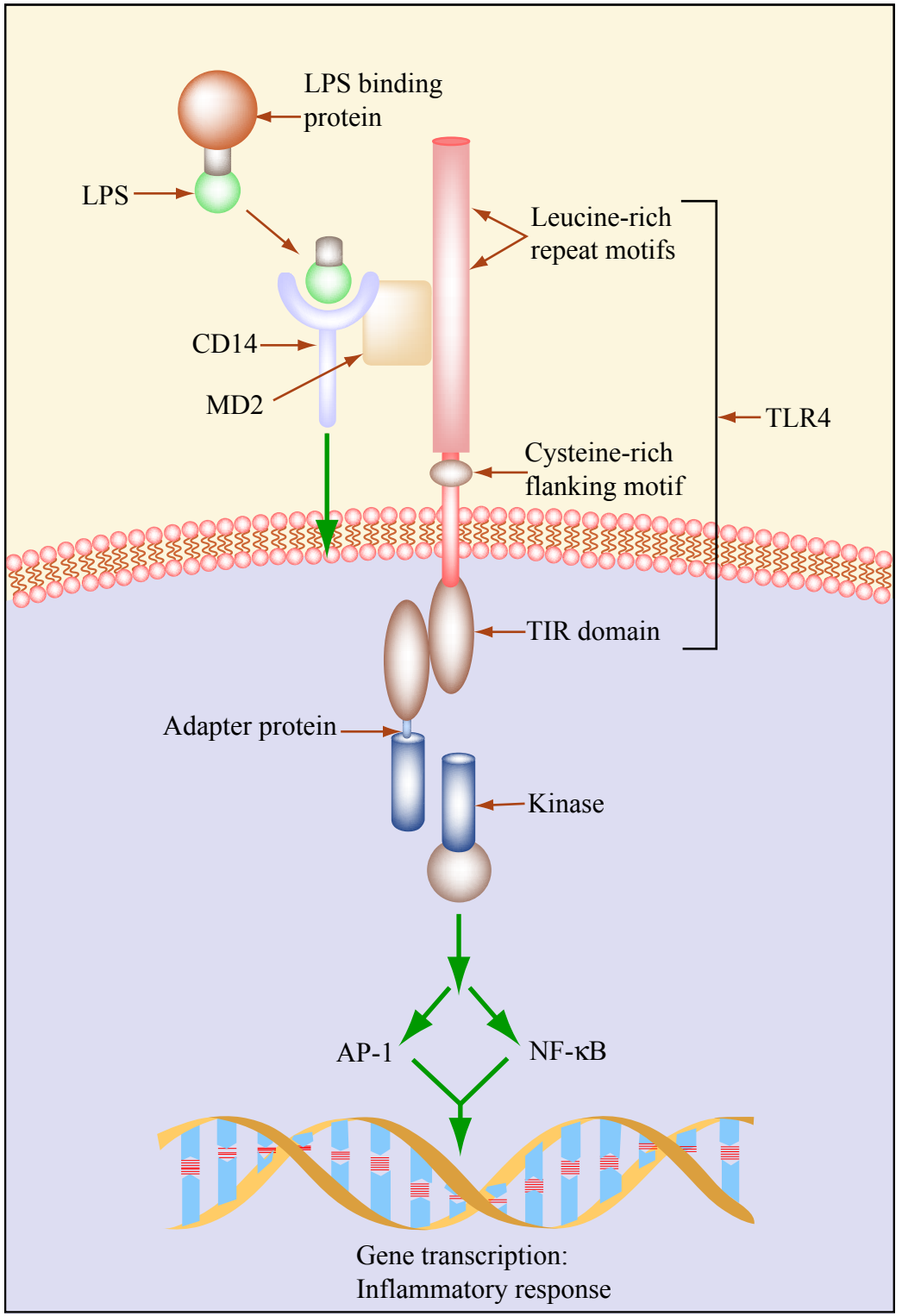
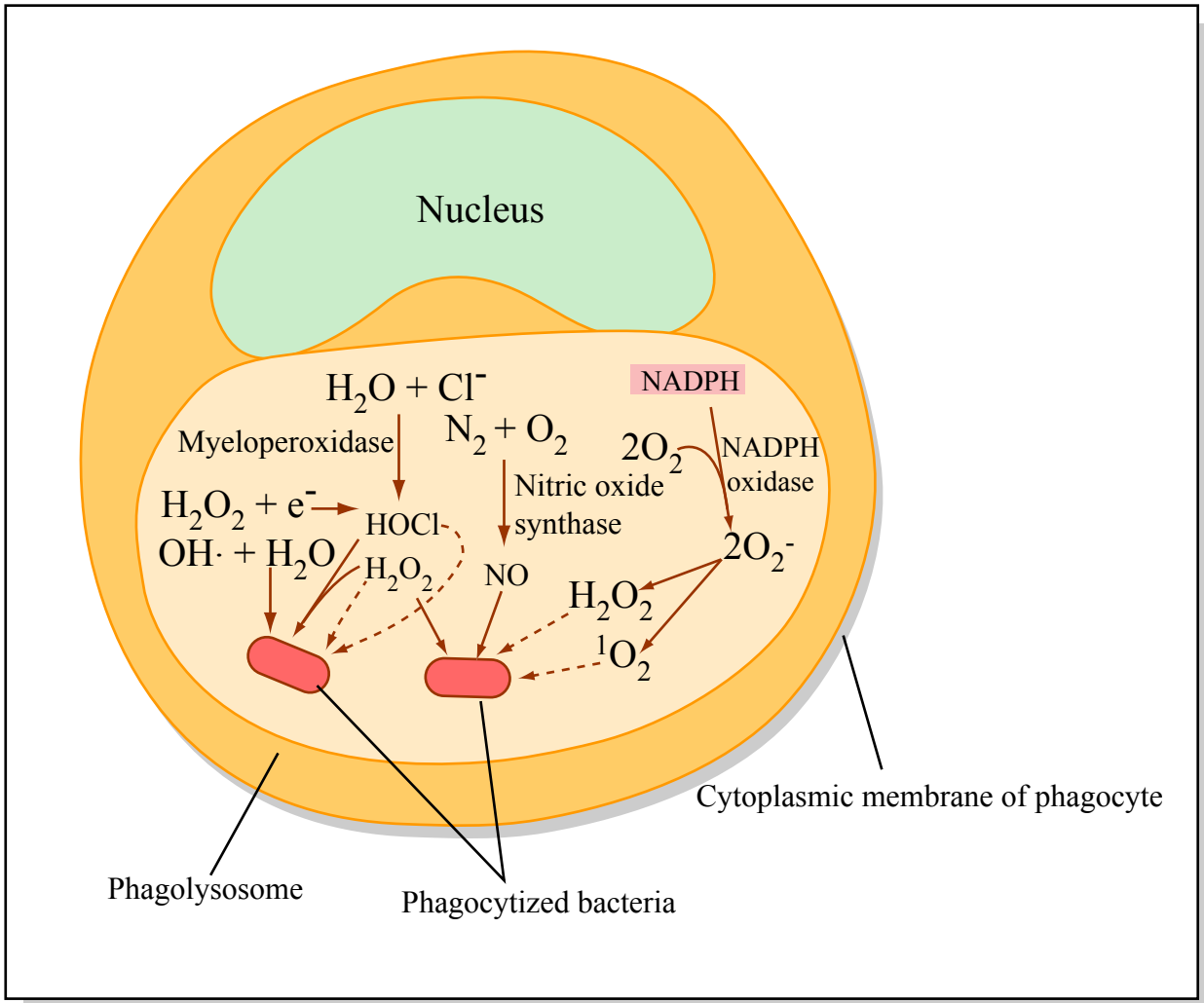


Figure by MIT OCW.

Table of receptors and targets in the innate immune response removed due to copyright restrictions. See Table 23-1 in Madigan, Michael, and John Martinko. *Brock Biology of Microorganisms*. 11th ed. Upper Saddle River, NJ: Pearson Prentice Hall, 2006. ISBN: 0131443291.

Phagocytosis



- Phagocytosis stimulates respiratory burst
- NADPH or phagocyte oxidase (Phox)
- PMNs produce myeloperoxidase that converts H_2O_2 to HOCl
- Efficient killing

Figure by MIT OCW.

Chemokines & Cytokines

Chemokines are potent chemoattractants

- CXC (alpha) act mostly on PMNs (IL-8)
- CC (beta) act on other phagocytes (MCP-1, MIP-1a)
- C (lymphotactin) and CX_3C (fractalkine)

Cytokines are activator molecules

- Acute phase response, septic shock
- Produced by leukocytes (interleukins [IL], IFN-γ, TNF-α)

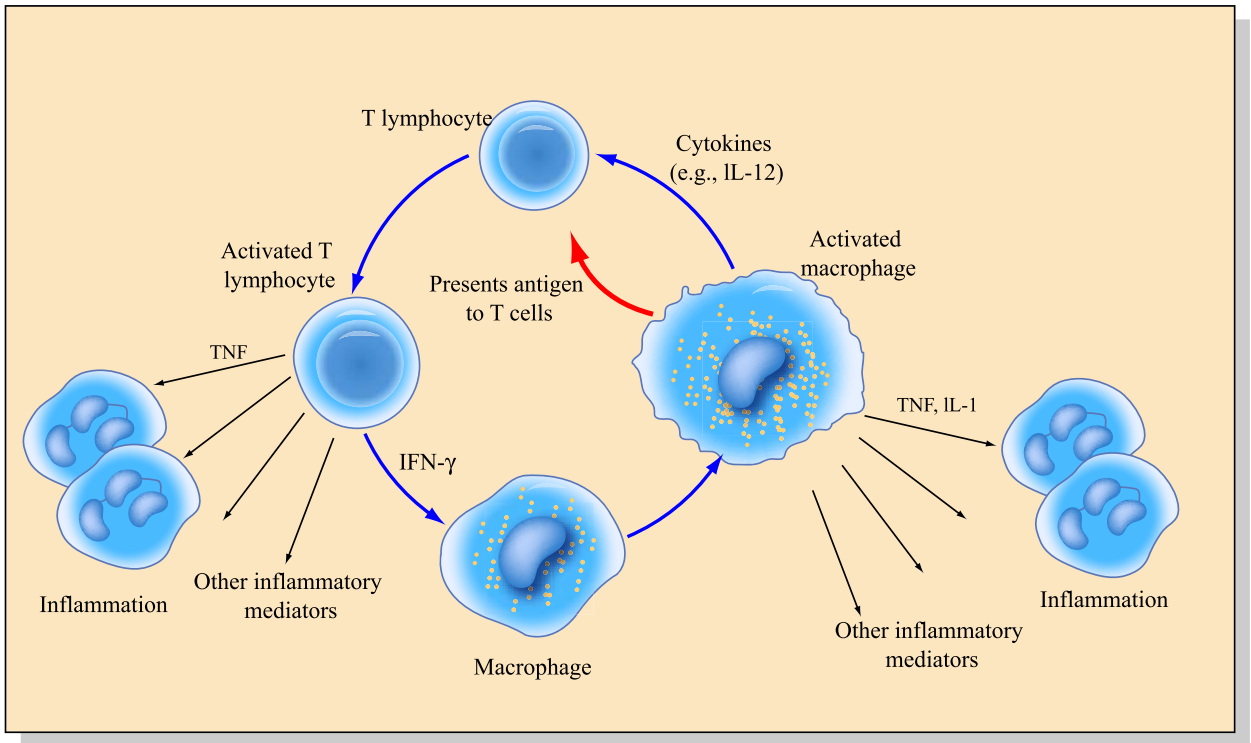


Figure by MIT OCW.

Inflammation

Redness

Swelling

Heat

Pain

- Reaction of blood vessels leading to the accumulation of fluid and leukocytes (white blood cells) in extravascular tissues
- Inflammation is a process, more than a state, and is closely linked to repair (regeneration and/or fibrosis)
- Although fundamentally protective, some instances of inflammation are harmful to the individual (hypersensitivity, chronic diseases, scarring)

Acute inflammation (vascular events)

1. Increased blood flow
   - After an initial vasoconstriction, there is vasodilation of arterioles, leading to increased blood flow (heat, redness)
2. Increased permeability
   - Structural changes in the microvasculature that permit plasma proteins and leukocytes to leave circulation
   - Loss of protein from plasma results in decreased osmotic pressure relative to the interstitial fluid
   - Combined with increased hydrostatic pressure from vasodilation, this results in outflow of fluid into the interstitial tissue (edema)
   - Slowing of circulation due to increased permeability of the microvasculature, increased viscosity and stasis
3. Emigration of leukocytes from the microcirculation and their accumulation at the site of injury
   - With stasis, margination of leukocytes, followed by rolling, then sticking (pavementing), then diapedesis

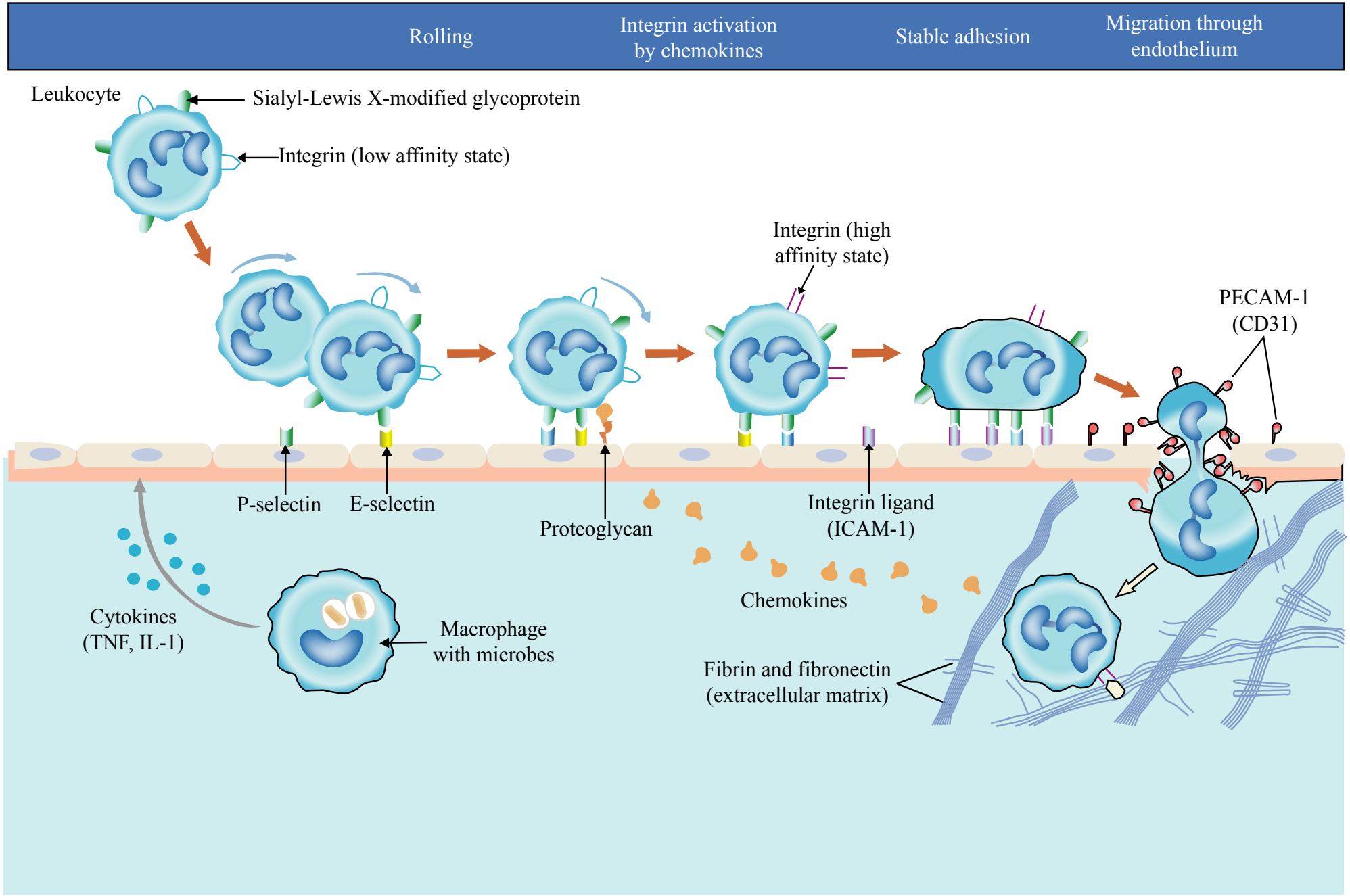
Mechanisms of vascular leakage

1. Endothelial gap formation (rapid, reversible, short-lived) occurs in post-capillary venules (20-60 μm in diameter)
2. Cytoskeletal reorganization (delayed, longer lasting)
3. Increased trancytosis (channels)
4. Direct endothelial injury (necrosis of endothelial cells, leading to thrombosis)
5. Delayed prolonged leakage (after a delay of 2-12 hours, lasting hours-days)
6. Leukocyte-mediated endothelial injury

Leukocyte extravasation

1. Margination, rolling, adhesion
   - E-selectin, P-selectin, and L-selectin
   - ICAM-1, VCAM-1, and integrins LFA-1, MAC-1, $\alpha_4\beta_1$, and $\alpha_4\beta_7$
2. Transmigration across the endothelium (diapedesis)
3. Migration in interstitial tissues towards a chemotactic stimulus (chemokines)

Leukocyte extravasation



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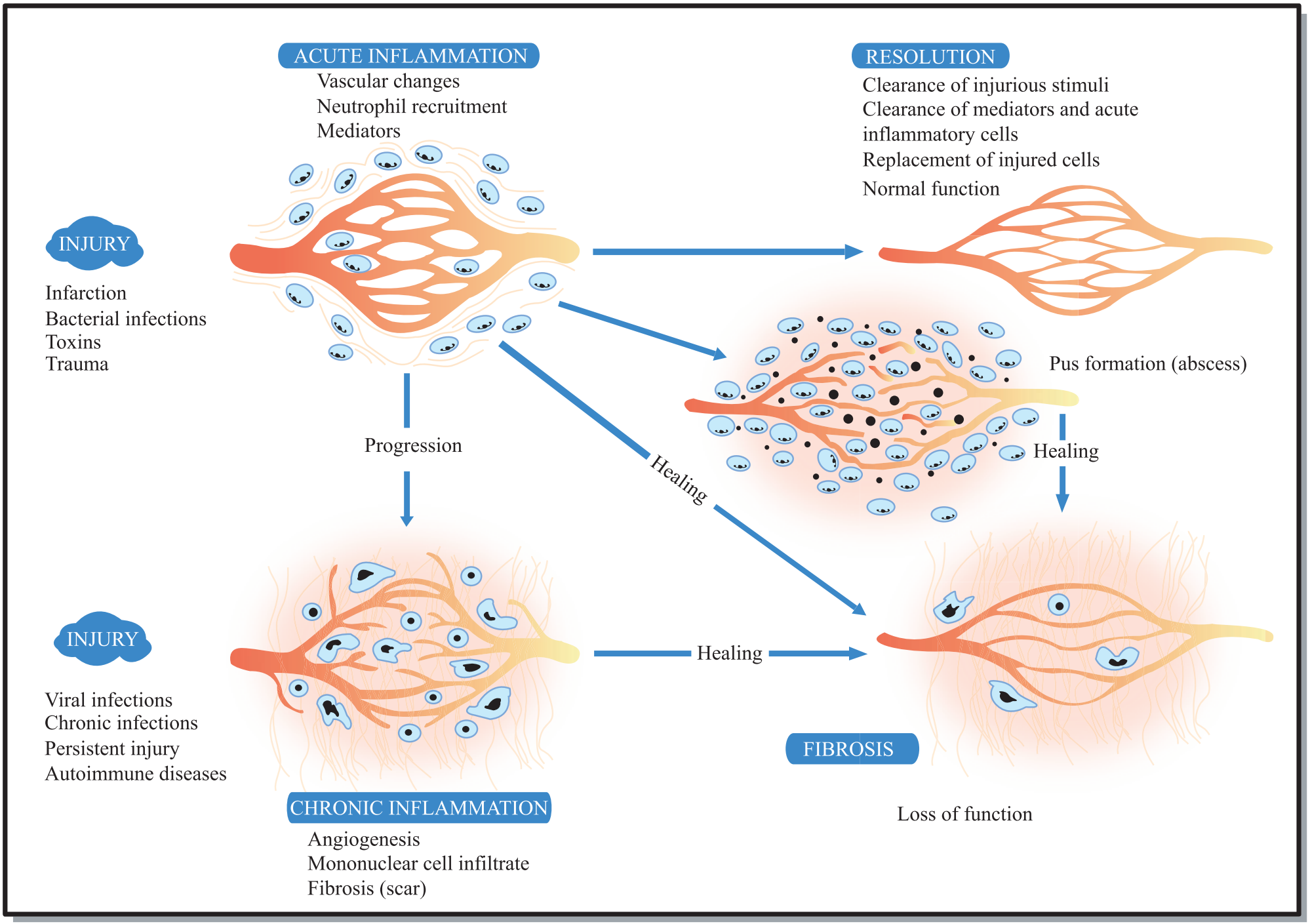

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Immune Response

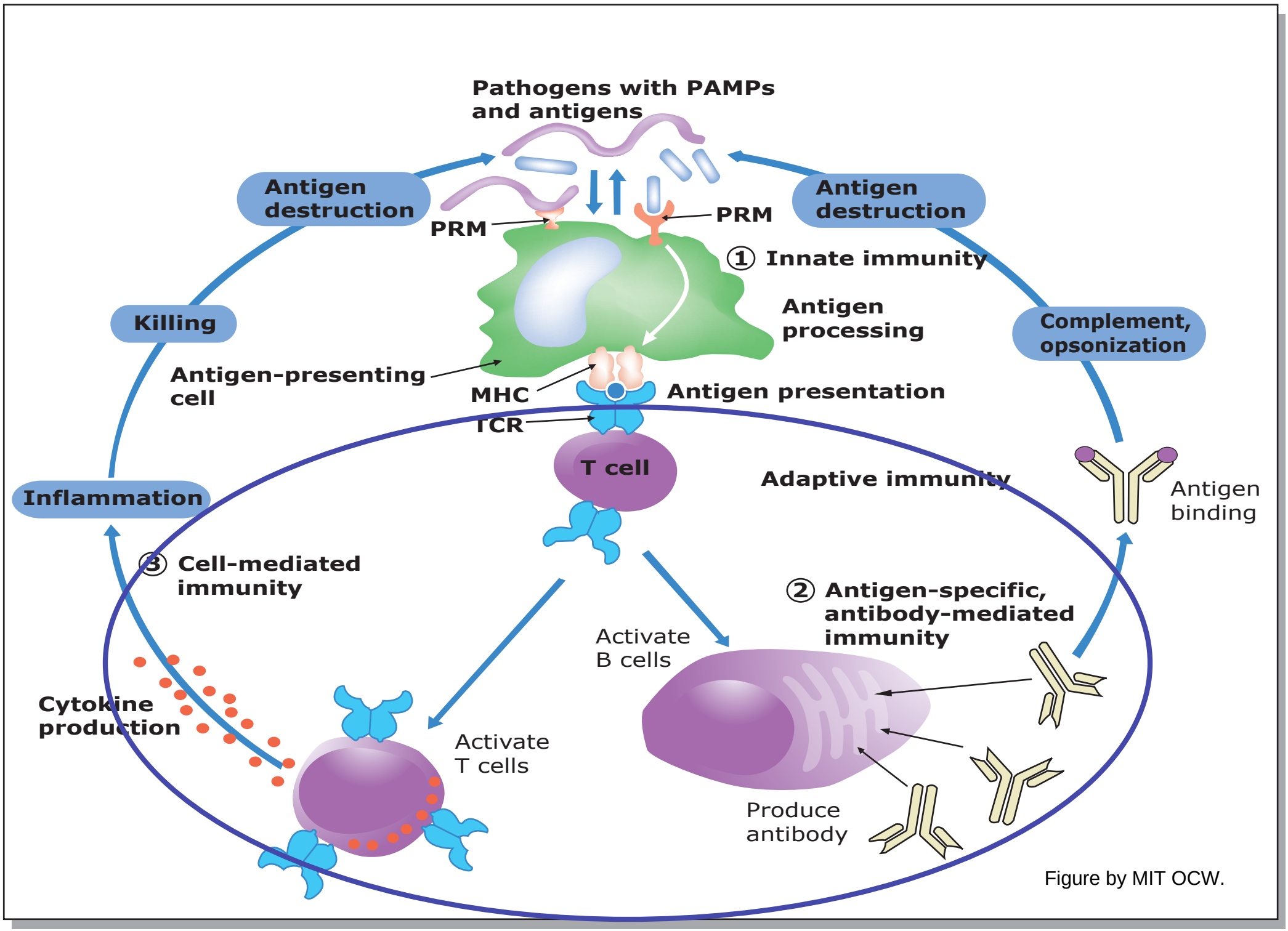
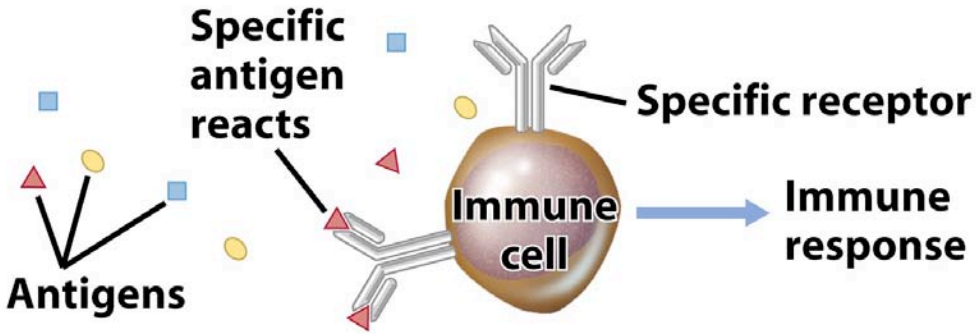


Figure by MIT OCW.

Adaptive Immunity

- nonspecific phagocytes present antigen to specific **T cells**
  - triggers the production of effector T cells and antibodies
  - T cells and antibodies react directly or indirectly to neutralize or destroy the antigen
- characterized by
  - **specificity** for the antigen
  - ability to respond more vigorously when reexposed to the same antigen (**memory**)
  - discriminate self antigens from nonself antigens (**tolerance**)



Specificity: Immune cells recognize and react with individual molecules (antigens) via direct molecular interactions.

Figure 22-8 part 1 Brock Biology of Microorganisms 11/e

Types of Adaptive Responses

Antibody-mediated immunity

particularly effective against pathogens such as viruses and bacteria in the blood or lymph and also against soluble pathogen products such as toxins

Cell-mediated immunity

leads to killing of pathogen-infected cells through recognition of pathogen antigens found on infected host cells