OLLI SG 492
Human Immune System

Session 6 - April 13, 2022

Today’s Meeting

- Recap last week’s session on cytokines.
- Grand Tour of the Immune System.
- Q&A on the Immune System.

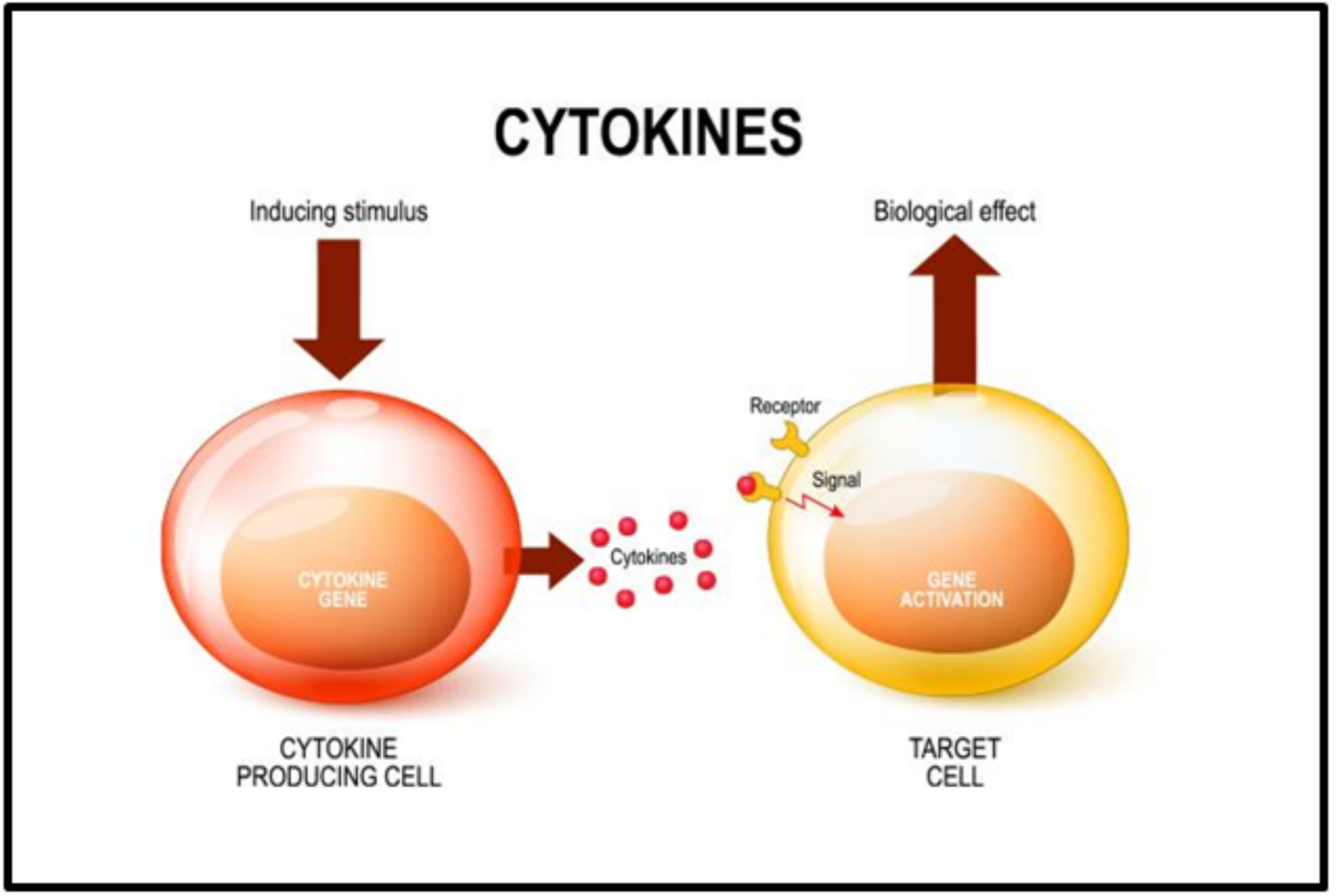
Basics of the Immune System

Cytokines

- Important in cell signaling.
- Small proteins, released by various cells in the body in response to an activating stimulus, e.g., detection by a macrophage of a pathogen.
- Cytokines can affect the releasing cell, nearby adjacent cells, and distant cells, e.g., cells of the hypothalamus which release hormones.
- Cytokines include: chemokines, interferons, interleukins, and tumor necrosis factors, among others.
- Cytokines act through cell surface receptors. They have important local and systemic (i.e., widespread) effects that contribute to both the innate and adaptive immunity.
- They “orchestrate” the immune system, and the immune response.

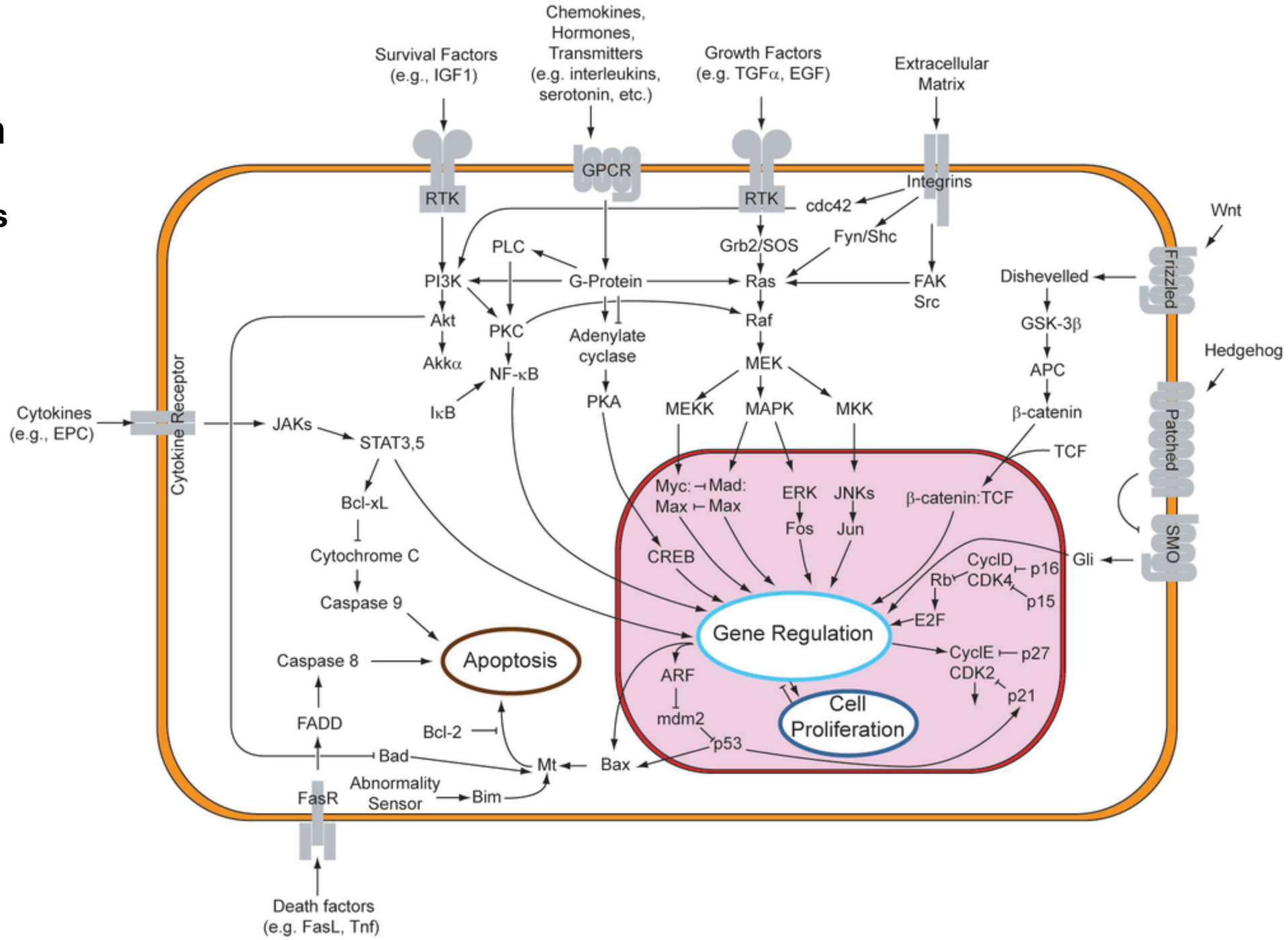
Basics of the Immune System

Cytokines



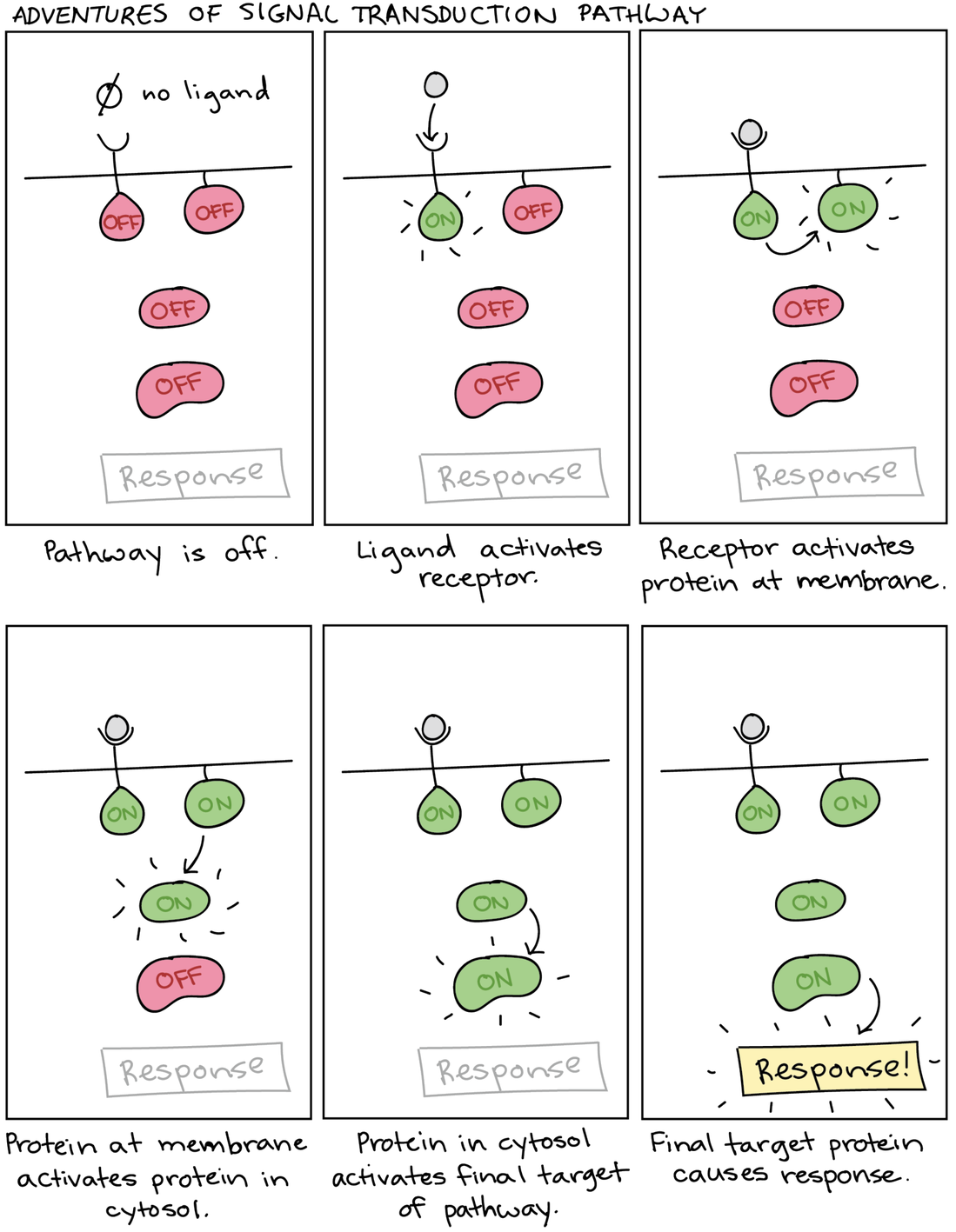
Basics of the Immune System

Intracellular Signaling Pathways



Basics of the Immune System

Intracellular Signaling Pathways



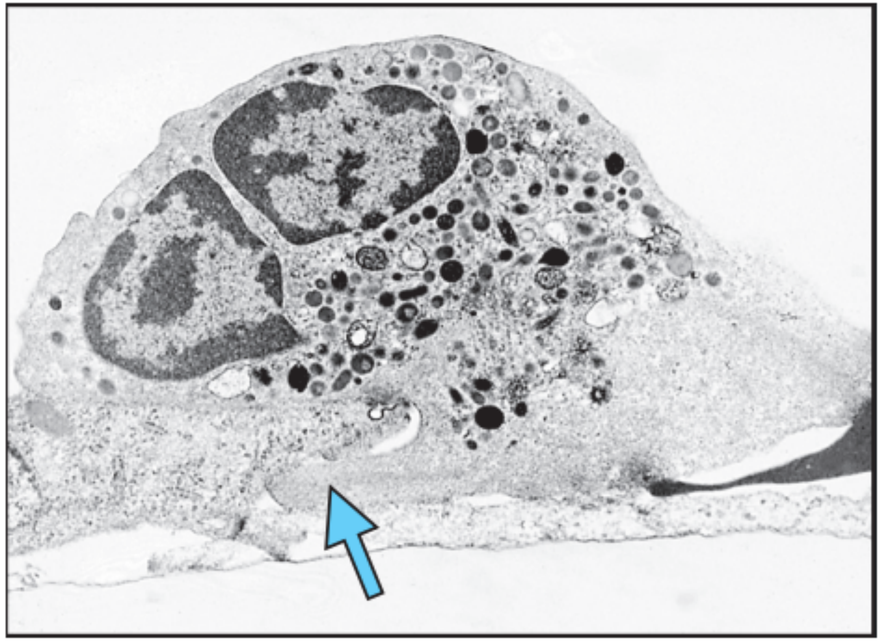
Basics of the Immune System

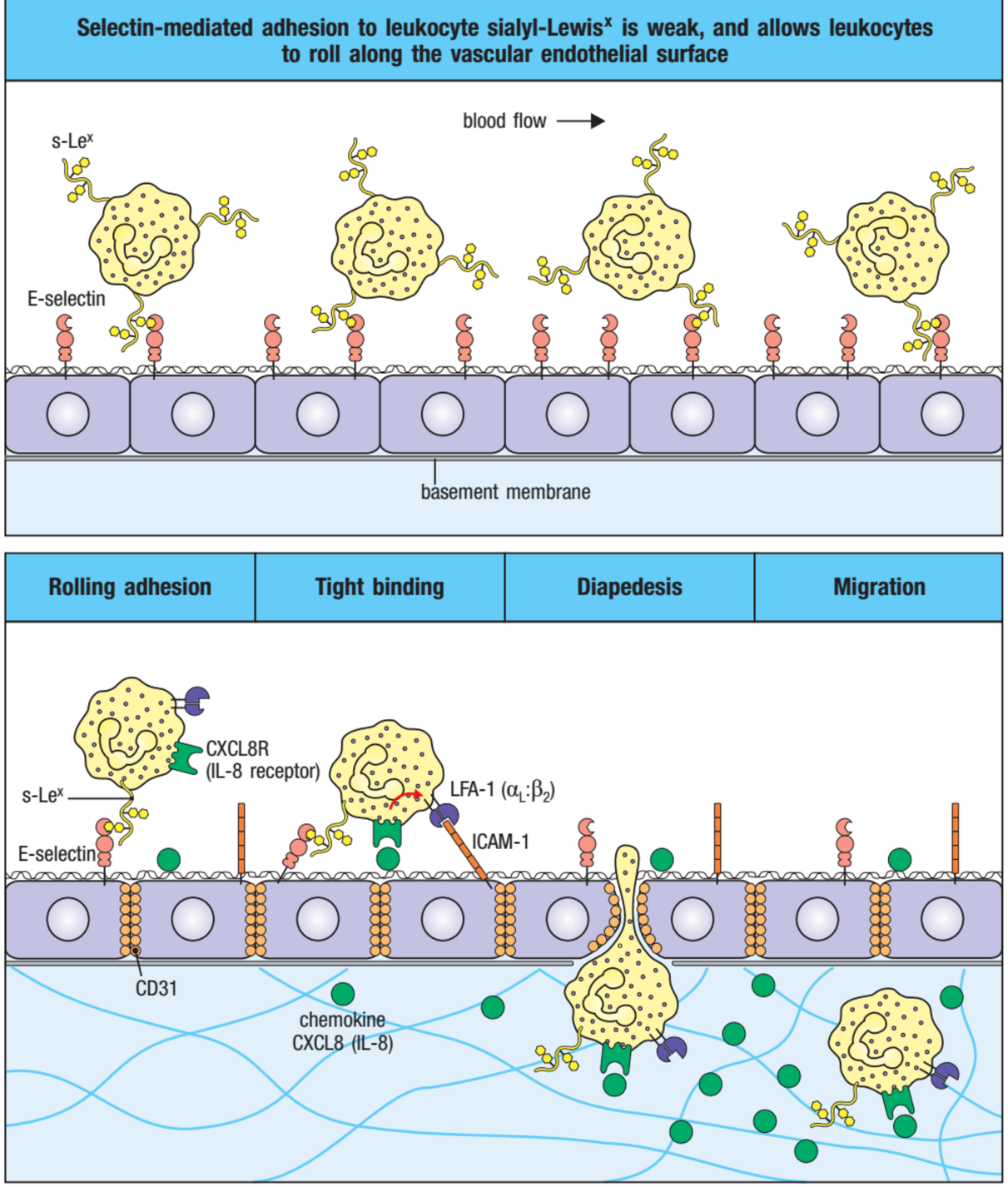
Cytokines

- Fever:
  - The cytokines TNF-alpha, IL-1beta, and IL-6 are termed endogenous pyrogens and cause fever.
  - These cytokines induce cells to produce the hormone prostaglandin E2, which acts on the hypothalamus, producing other hormones.
  - This results in increased heat production through the metabolism of “brown fat”, and heat retention through vasoconstriction.
  - Fever is generally beneficial - elevated heat inhibits activity of pathogens, increases adaptive immune activity.

Basics of the Immune System

Cytokines





Basics of the Immune System

Cytokines

- Septic Shock:
  - After pathogens (bacteria) have entered the bloodstream (sepsis), there is a massive release of soluble version of TNF, from macrophages in the liver and spleen, into the bloodstream.
  - This “systemic” release causes vasodilation, leading to loss of blood pressure and increased vascular permeability….
  - Which leads to loss of plasma volume and septic shock.
  - The TNF also causes blood clotting in small vessels throughout the body, reducing clotting proteins, and preventing clotting in other parts of the body.
  - Widespread coagulation frequently leads to organ failure of vital organs.
  - Septic shock has a very high mortality rate.

Immune System - Highlights

A Function of the Immune System

- Fighting infections:
  - Innate immune system components have generalized receptors that are fixed and can detect molecules associated with pathogens - non-self.
  - Innate immune system consists of both cells (macrophage, neutrophils, dendritic cells, etc.) and degradative enzymes and toxins (Complement, etc.)
  - Innate immune system cells initiate an inflammatory response on detection of pathogens by releasing cytokines, and attack and destroy pathogens.
  - Innate immune cells recruit other immune system cells, both adaptive and innate cells, to the site of infection.

Immune System - Highlights

Pattern Recognition Receptors

TLR - Toll Like Receptors
RLR - RIG-1 Like Receptor
NLR - NOD-like Receptors
CLR - C-type Lectin Receptors

Table 1. PRRs and Their Ligands

PRRs	Localization	Ligand	Origin of the Ligand
TLR			
TLR1	Plasma membrane	Triacyl lipoprotein	Bacteria
TLR2	Plasma membrane	Lipoprotein	Bacteria, viruses, parasites, self
TLR3	Endolysosome	dsRNA	Virus
TLR4	Plasma membrane	LPS	Bacteria, viruses, self
TLR5	Plasma membrane	Flagellin	Bacteria
TLR6	Plasma membrane	Diacyl lipoprotein	Bacteria, viruses
TLR7 (human TLR8)	Endolysosome	ssRNA	Virus, bacteria, self
TLR9	Endolysosome	CpG-DNA	Virus, bacteria, protozoa, self
TLR10	Endolysosome	Unknown	Unknown
TLR11	Plasma membrane	Profilin-like molecule	Protozoa
RLR			
RIG-I	Cytoplasm	Short dsRNA, 5′triphosphate dsRNA	RNA viruses, DNA virus
MDA5	Cytoplasm	Long dsRNA	RNA viruses (Picornaviridae)
LGP2	Cytoplasm	Unknown	RNA viruses
NLR			
NOD1	Cytoplasm	iE-DAP	Bacteria
NOD2	Cytoplasm	MDP	Bacteria
CLR			
Dectin-1	Plasma membrane	β-Glucan	Fungi
Dectin-2	Plasma membrane	β-Glucan	Fungi
MINCLE	Plasma membrane	SAP130	Self, fungi

Immune System - Highlights

A Function of the Immune System

- Fighting infections:
  - Adaptive immune system cells (B and T cells) have randomly generated receptors that are specific to an antigen.
  - B cells are active in the extracellular environment. The B cell receptor (BCR) is the same shape and has the same proteins as the antibodies it produces.
  - T cells are active in both the intracellular and extracellular environment. The T cell receptor can lock onto antigens presented by infected cells as well as by pathogens.

Immune System - Highlights

Phases of the Immune Response

Phases of the immune response			
Response		**Typical time after infection to start of response**	**Duration of response**
Innate immune response	Inflammation, complement activation, phagocytosis, and destruction of pathogen	Minutes	Days
Adaptive immune response	Interaction between antigen-presenting dendritic cells and antigen-specific T cells: recognition of antigen, adhesion, co-stimulation, T-cell proliferation and differentiation	Hours	Days
	Activation of antigen-specific B cells	Hours	Days
	Formation of effector and memory T cells	Days	Weeks
	Interaction of T cells with B cells, formation of germinal centers. Formation of effector B cells (plasma cells) and memory B cells. Production of antibody	Days	Weeks
	Emigration of effector lymphocytes from peripheral lymphoid organs	A few days	Weeks
	Elimination of pathogen by effector cells and antibody	A few days	Weeks
Immunological memory	Maintenance of memory B cells and T cells and high serum or mucosal antibody levels. Protection against reinfection	Days to weeks	Can be lifelong

Immune System - Highlights

Immune Response Scenario

- When the PRRs of macrophage or dendritic cells detect molecules associated with pathogens (e.g., LPS), an immune response is initiated.
- The macrophage (primarily) and dendritic cells release cytokines which:
  - Recruit other immune cells to the site of infection.
  - Change the environment of the infection to facilitate easier access to the infection site and create inflammation.
  - Facilitate the initiation of fever.
- The macrophage and dendritic cells attack and destroy the pathogens.
- Neutrophils and other immune cells enter the site of the infection and also attack and destroy pathogens.

Immune System - Highlights

Inflammatory Response

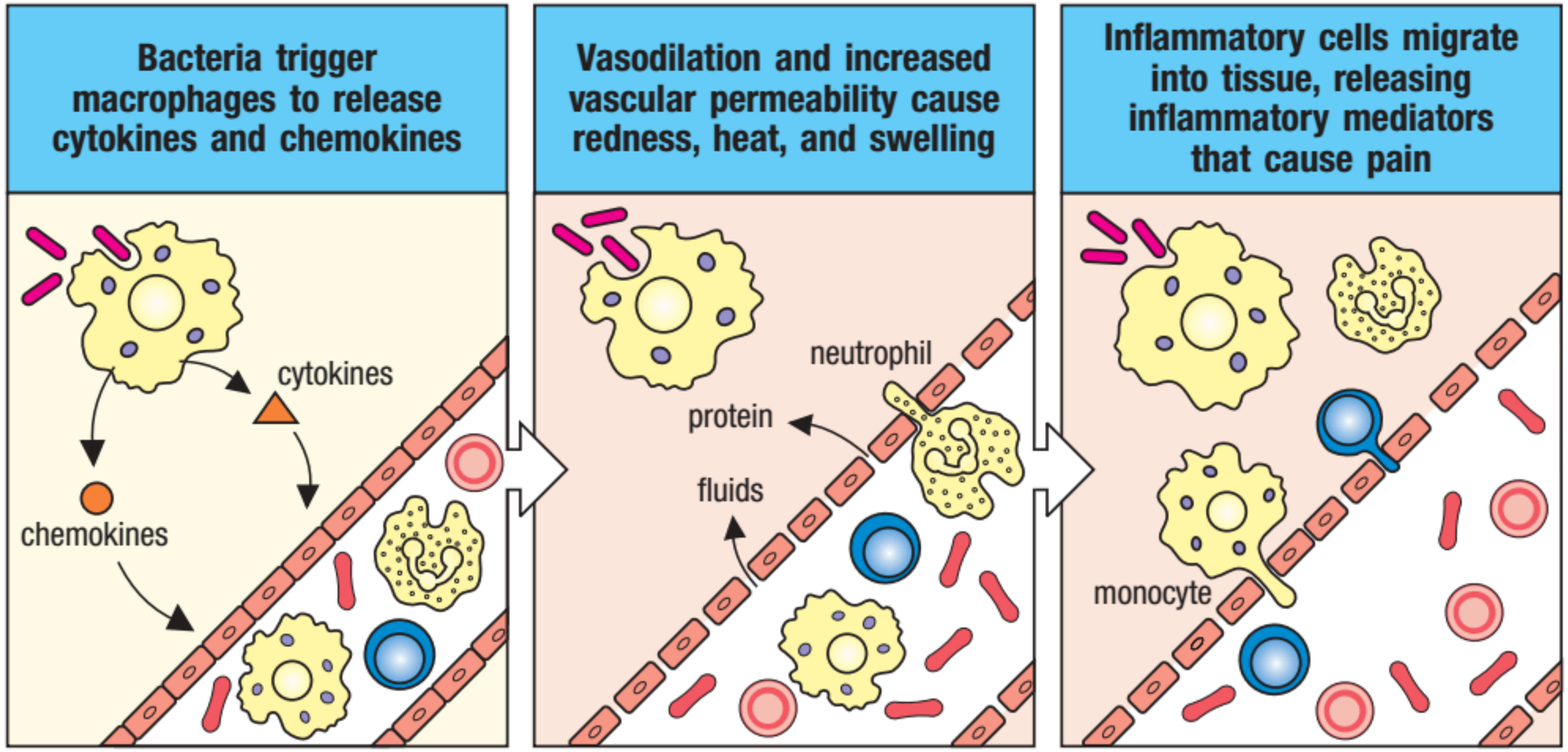
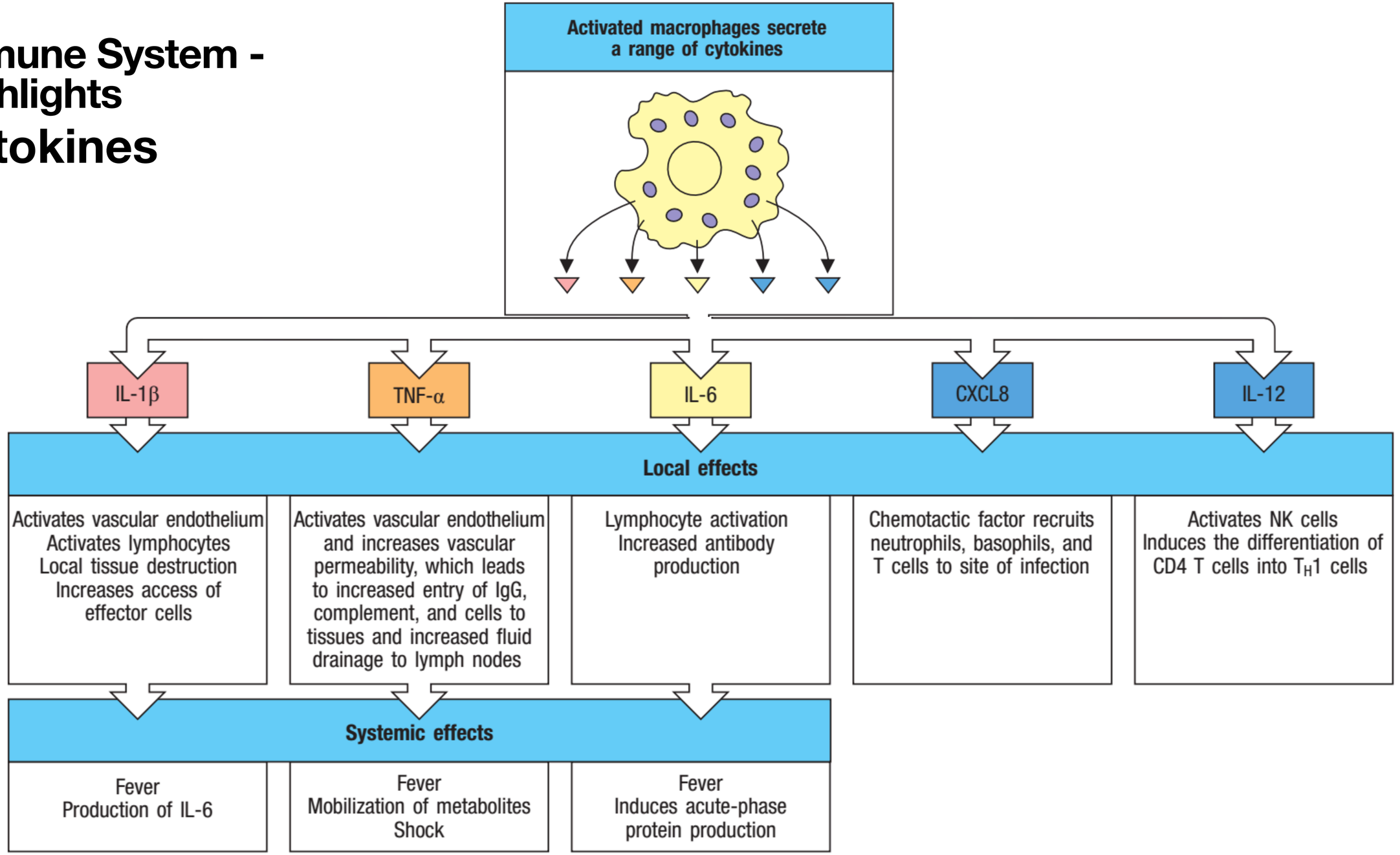


Fig. 1.10 Infection triggers an inflammatory response. Macrophages encountering bacteria or other types of microorganisms in tissues are triggered to release cytokines (left panel) that increase the permeability of blood vessels, allowing fluid and proteins to pass into the tissues (center panel). Macrophages also produce chemokines, which direct the migration of neutrophils to the site of infection. The stickiness of the endothelial cells of the blood vessel wall is also changed, so that circulating cells of the immune system adhere to the wall and are able to crawl through it; first neutrophils and then monocytes are shown entering the tissue from a blood vessel (right panel). The accumulation of fluid and cells at the site of infection causes the redness, swelling, heat, and pain known collectively as inflammation. Neutrophils and macrophages are the principal inflammatory cells. Later in an immune response, activated lymphocytes can also contribute to inflammation.

Immune System - Highlights

Cytokines



Immune System - Highlights

Immune Response Scenario

- The activation of the PRR of the dendritic cell and the subsequent destruction of the pathogen result in the expression of the genes for the **co-stimulatory** proteins on the surface of the dendritic cell.

- Segments of the destroyed pathogen are picked up by MHC proteins and migrate to the surface of the dendritic cell.

- Some segments will be picked up by MHC class 1 (MHC I), and others by MHC class 2 (MHC II) proteins.

- The dendritic cell then makes a beeline to the nearest lymphatic tissue, typically a lymph node.

Immune System - Highlights

Immune Response Scenario

- The dendritic cell is an antigen presenting cell (APC). The antigen peptide is held above the membrane surface of the dendritic cell by a MHC protein.
- Unactivated T cells (naive T cells) examine the antigen peptide presented by the dendritic cell.
- If the antigen receptor of the T cell locks onto the antigen peptide. and other receptors sense the **co-stimulatory** protein, activation of the T cell occurs.
- The membranes of naive T cells are also coated with other proteins, two of which function as **co-receptors**, namely CD8 and CD4.

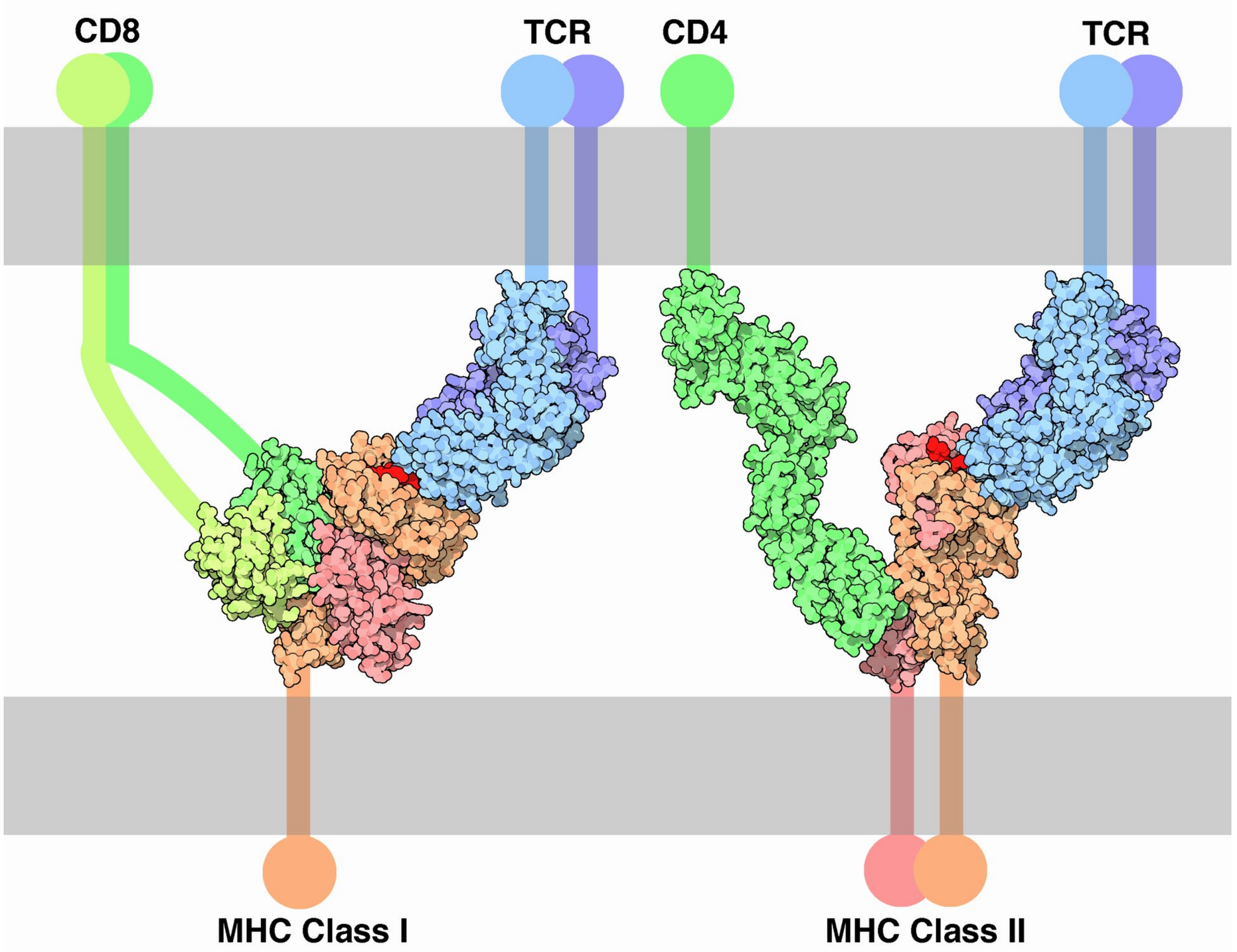
Immune System - Highlights

Immune Response Scenario

- If the MHC protein is class 1, and the T cell co-receptor is CD8, the T cell becomes a cytotoxic T cell (killer T cell).
- If the MHC protein is class 2, and the T cell co-receptor is CD4, the T cell becomes a helper T cell. Helper T cells mediate the activity of B cells and T cells during an immune response.
- After activation, the T cells, both cytotoxic and helper T cells, proliferate through cloning.
- Some T cells become regulatory T cells, whose function is to suppress the immune response of other immune cells after the infection has been eliminated.

Immune System - Highlights

Antigen-Specific Receptors



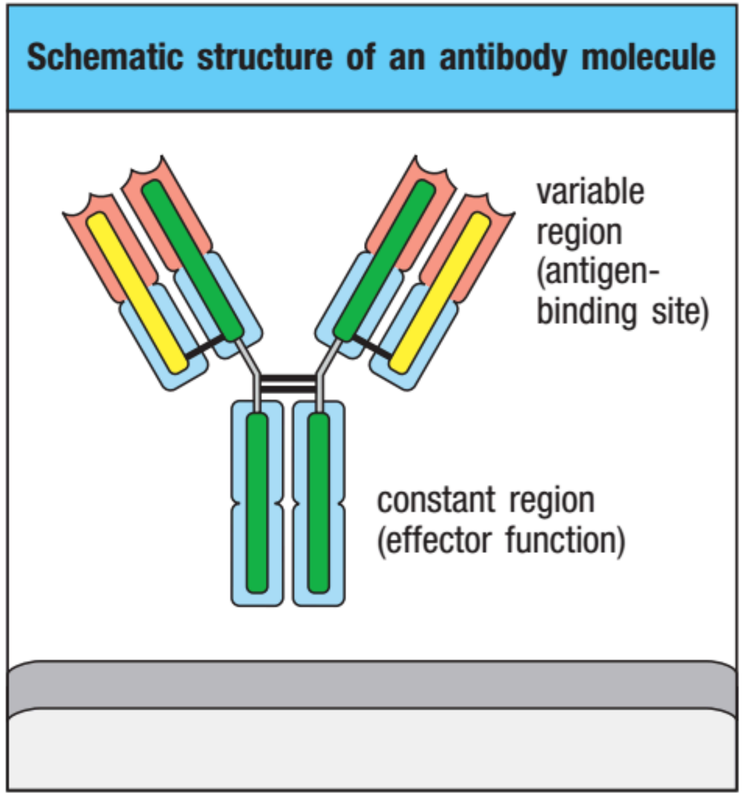
Immune System - Highlights

Immune Response Scenario

- B cell receptors (BCR) are a Y-shaped complex of proteins, produced by the same genes that produce antibodies.
- When the BCR is presented with an antigen fragment that matches the receptor, the B cell becomes activated.
- Upon activation, the B cell proliferates via cloning.
- All of the T cell types, and B cells, migrate to the site of the infection.
- At the site of infection, these immune cells take up their specific functions.

Immune System - Highlights

Antigen Receptors



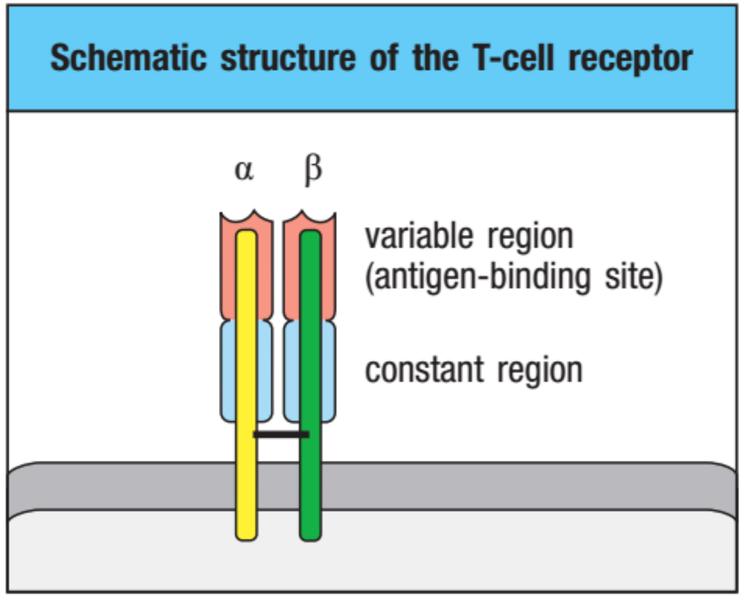


Fig. 1.13 Schematic structure of antigen receptors. Upper panel: an antibody molecule, which is secreted by activated B cells as an antigen-binding effector molecule. A membrane-bound version of this molecule acts as the B-cell antigen receptor (not shown). An antibody is composed of two identical heavy chains (green) and two identical light chains (yellow). Each chain has a constant part (shaded blue) and a variable part (shaded red). Each arm of the antibody molecule is formed by a light chain and a heavy chain, with the variable parts of the two chains coming together to create a variable region that contains the antigen-binding site. The stem is formed from the constant parts of the heavy chains and takes a limited number of forms. This constant region is involved in the elimination of the bound antigen. Lower panel: a T-cell antigen receptor. This is also composed of two chains, an α chain (yellow) and a β chain (green), each of which has a variable and a constant part. As with the antibody molecule, the variable parts of the two chains create a variable region, which forms the antigen-binding site. The T-cell receptor is not produced in a secreted form.

Immune System - Highlights

Immune Response Scenario

- When a cell is infected intracellularly, MHC proteins pick up fragments of pathogen proteins and transport them to the cell membrane. These fragments are “presented” on the surface of the infected cell.

- Cytotoxic T cells inspect cells at the site of the infection, and if they lock onto the pathogen antigen, they attach to the membrane of the infected cell, open a passage through the membrane, and inject toxic enzymes and molecules into the infected cell, killing it.

- Cytotoxic T cells also hunt for pathogens extracellularly. When they encounter an extracellular pathogen, they recruit phagocytic immune cells to engulf and kill the pathogen.

Immune System - Highlights

Immune Response Scenario

- Helper T cells activate the B cells at the site of an infection.
- B cells differentiate into plasma cells, and release quantities of antibodies which attach to the pathogens.
- This marks the pathogen for destruction by phagocytic immune cells.
- The presence of antibodies also recruits Complement proteins (enzymes). Some of the proteins can degrade the pathogen, killing it; other Complement proteins coat the pathogen making it more visible to phagocytic immune cells.
- Regulatory T cells signal other immune cells to stop after the infection has been eliminated.

Immune System - Highlights

Action of Antibodies

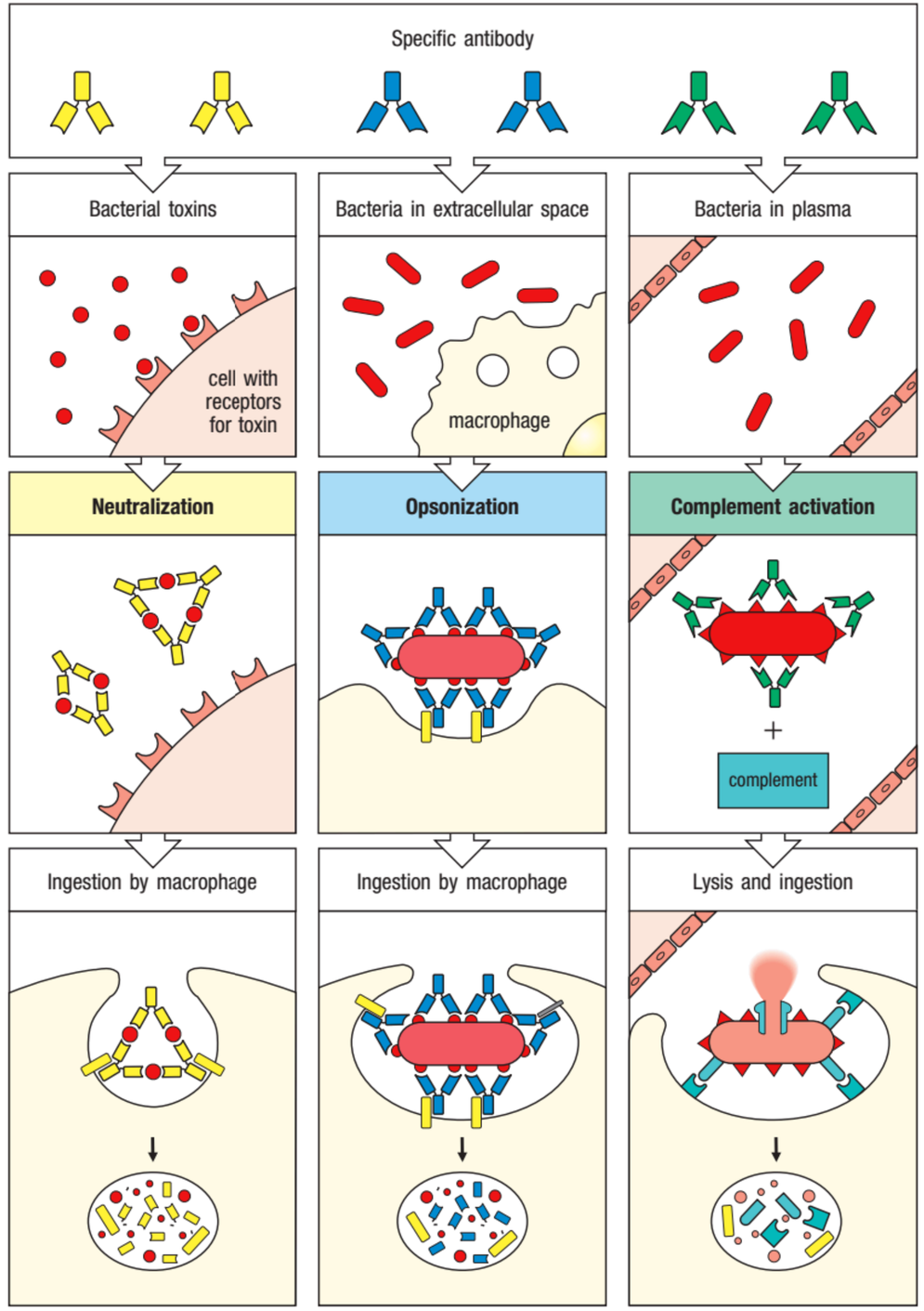


Fig. 1.28 Antibodies can participate in host defense in three main ways. The left panels show antibodies binding to and neutralizing a bacterial toxin, thus preventing it from interacting with host cells and causing pathology. Unbound toxin can react with receptors on the host cell, whereas the toxin:antibody complex cannot. Antibodies also neutralize complete virus particles and bacterial cells by binding and inactivating them. The antigen:antibody complex is eventually scavenged and degraded by macrophages. Antibodies coating an antigen render it recognizable as foreign by phagocytes (macrophages and neutrophils), which then ingest and destroy it; this is called opsonization. The center panels show opsonization and phagocytosis of a bacterial cell. Antibody first binds to antigens (red) on the bacterial cell through the variable regions. Then the antibody's Fc region binds to Fc receptors (yellow) expressed by macrophages and other phagocytes, facilitating phagocytosis. The right panels show activation of the complement system by antibodies coating a bacterial cell. Bound antibodies form a platform that activates the first protein in the complement system, which deposits complement proteins (blue) on the surface of the bacterium. This can lead in some cases to formation of a pore that lyses the bacterium directly. More generally, complement proteins on the bacterium can be recognized by complement receptors on phagocytes; this stimulates the phagocytes to ingest and destroy the bacterium. Thus, antibodies target pathogens and their toxic products for disposal by phagocytes.

Next Up

- The effects of stress, and time on the immune system.
- Read Chapter 5: Fever, Sress and the Power of the Mind, and…
- Read Chapter 6: Time and Space.