OLLI SG 492
Human Immune System

Session 5 - April 6, 2022

Basics of the Immune System

Nomenclature

"In an attempt to develop a standardized nomenclature for molecules secreted by, and acting on, leukocytes, many cytokines are called by the name interleukin (IL) followed by a number (for example, IL-1 or IL-2). However, not all cytokines are included in this system; thus **students of immunology are still faced with a somewhat confusing and difficult task**."

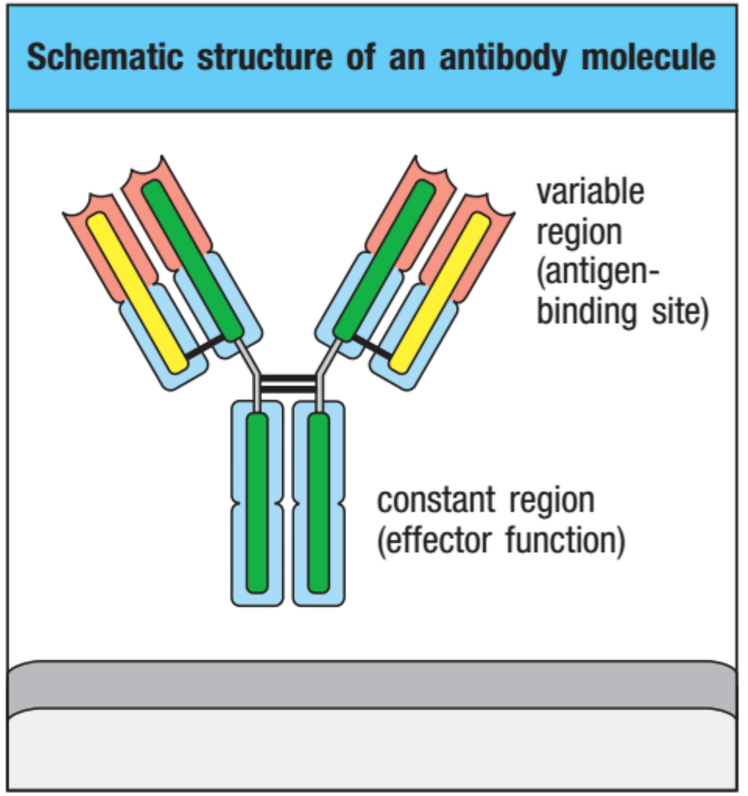
[From *Janeway's Immunobiology*]

Today’s Meeting

- Recap of our last meeting
- Overview of Cytokines
  - What are they?
  - Some of the major families.
  - Focus on their role in the initial inflammatory response.
- Clarifying comments on the use of interferon and other cytokines in treating cancer.
- The discovery of antibodies to block the action of cytokines in autoimmune diseases.

Basics of the Immune System

Antigen Receptors



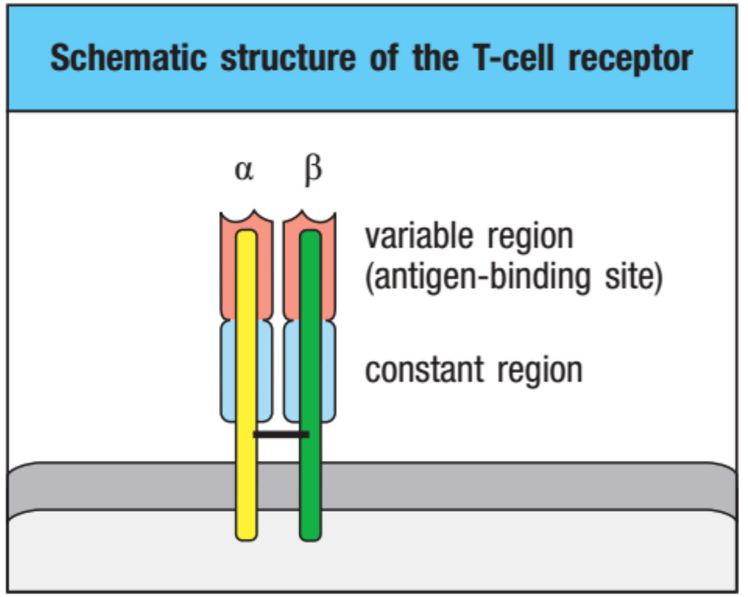


Fig. 1.13 Schematic structure of antigen receptors. Upper panel: an antibody molecule, which is secreted by activated B cells as an antigen-binding effector molecule. A membrane-bound version of this molecule acts as the B-cell antigen receptor (not shown). An antibody is composed of two identical heavy 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.

Basics of the Immune System

Antigen Receptors

- B cell receptors (BCR) are formed from the same genes that encode antibodies (AKA immunoglobulins).
- B cells are activated by both dendritic cells and helper T cells - APC cells.
- After antigen bind to a BCR, the B cell proliferates and differentiates into plasma cells which secrete antibodies that have the same antigen specificity as the BCR.
- After a T cell encounters an antigen its receptor can bind to, it proliferates and differentiates into several types of “effector” T cells, each with specific types of activity.

Basics of the Immune System

Antigen Receptors

- Differentiated T cells:
  - Cytotoxic T cells kill cells infected with viruses or other intracellular pathogens.
  - Helper T cells provide signals (by producing specific cytokines) that activate other cells, such as the B cell production of antibodies and macrophage killing of engulfed pathogens.
  - Regulatory (AKA Suppressor) T cells suppress the activity of other lymphocytes, limiting damage to uninfected cells.

Basics of the Immune System

Action of Antibodies

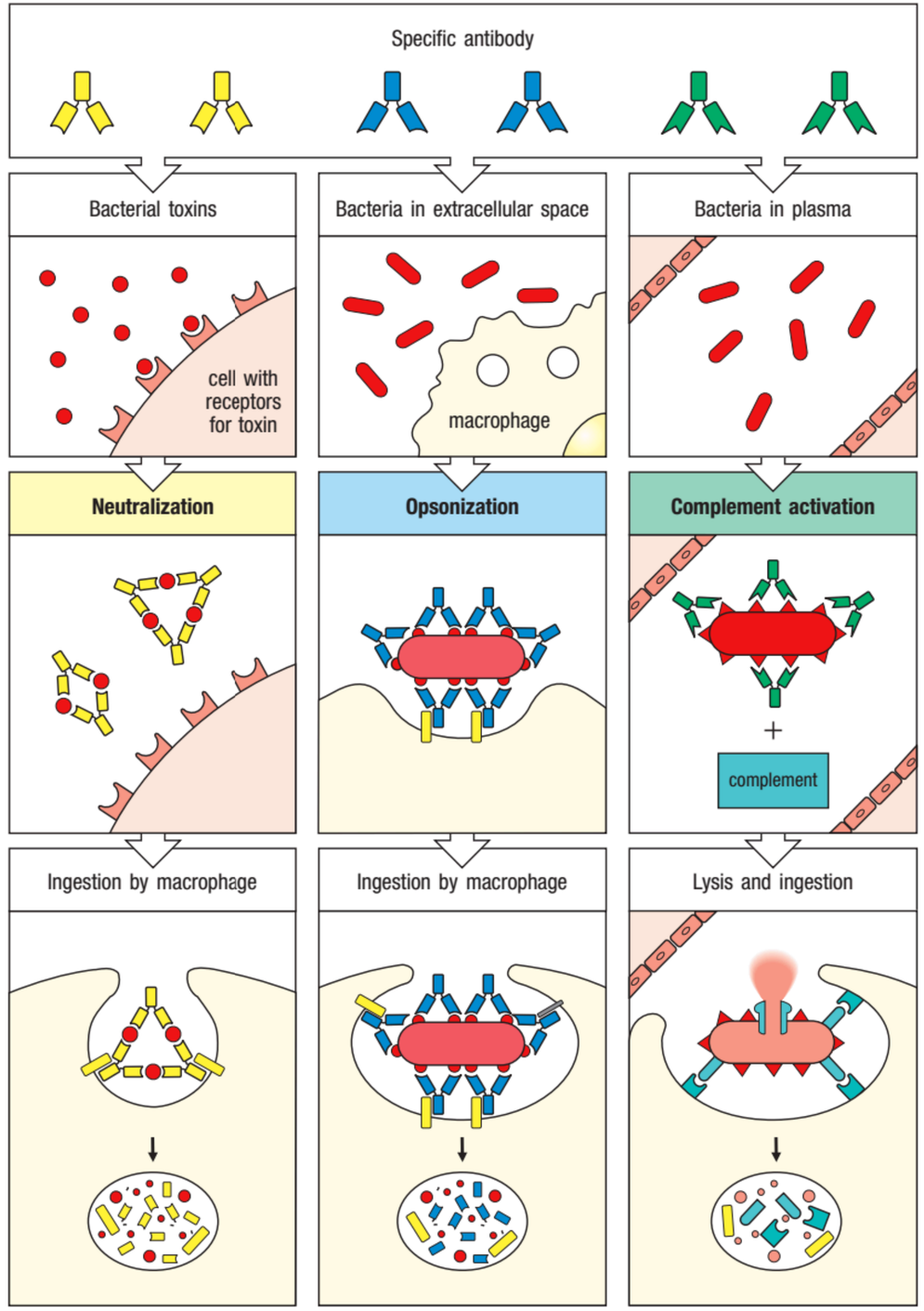
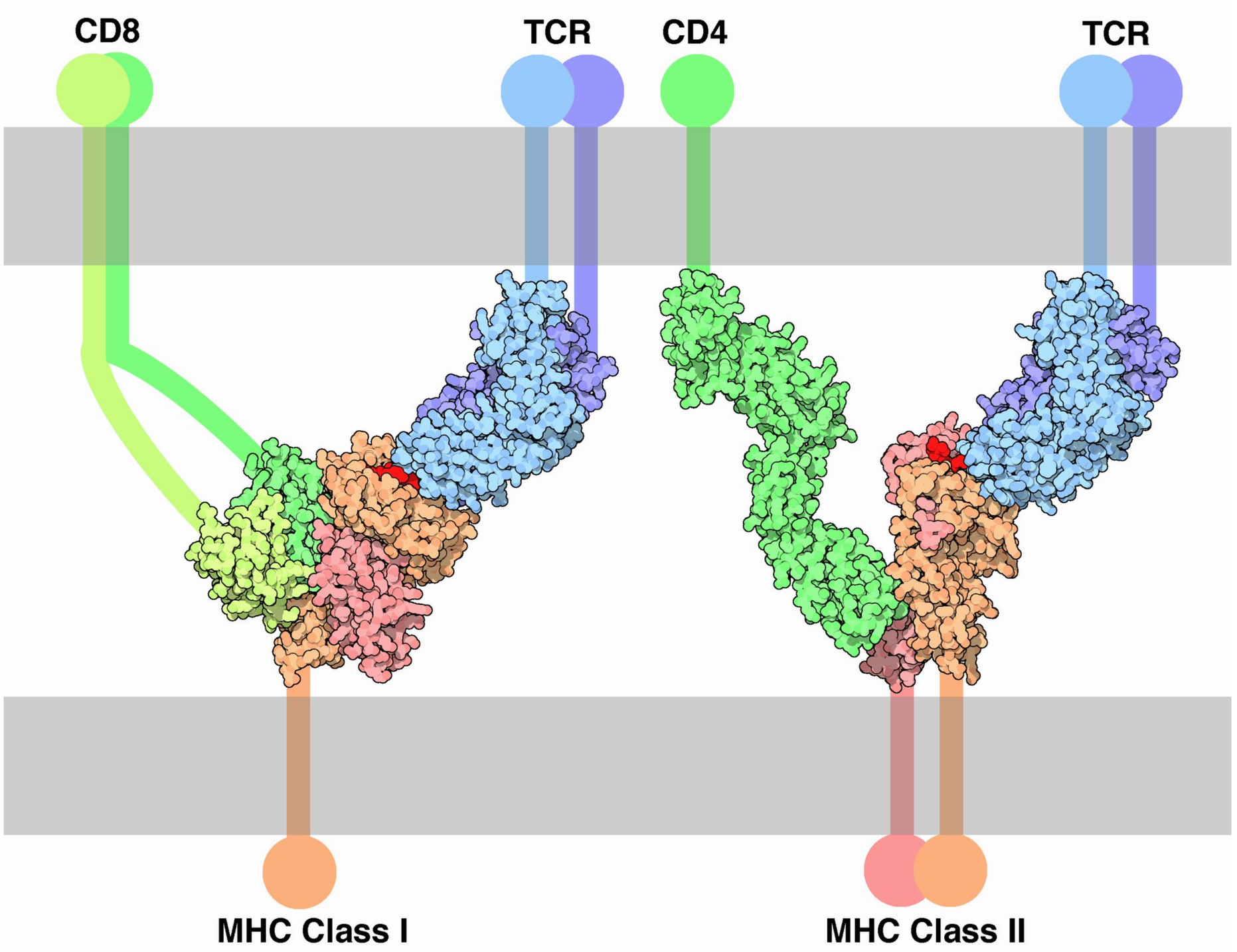


Fig. 1.28 Antibodies can participate in host defense in three main ways. The left panels show antibodies binding to and neutralizing a bacterial toxin, thus preventing it from interacting with host cells and causing pathology. Unbound toxin can react with receptors on the host cell, whereas the toxin:antibody 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.

Basics of the Immune System

Antigen-Specific Receptors



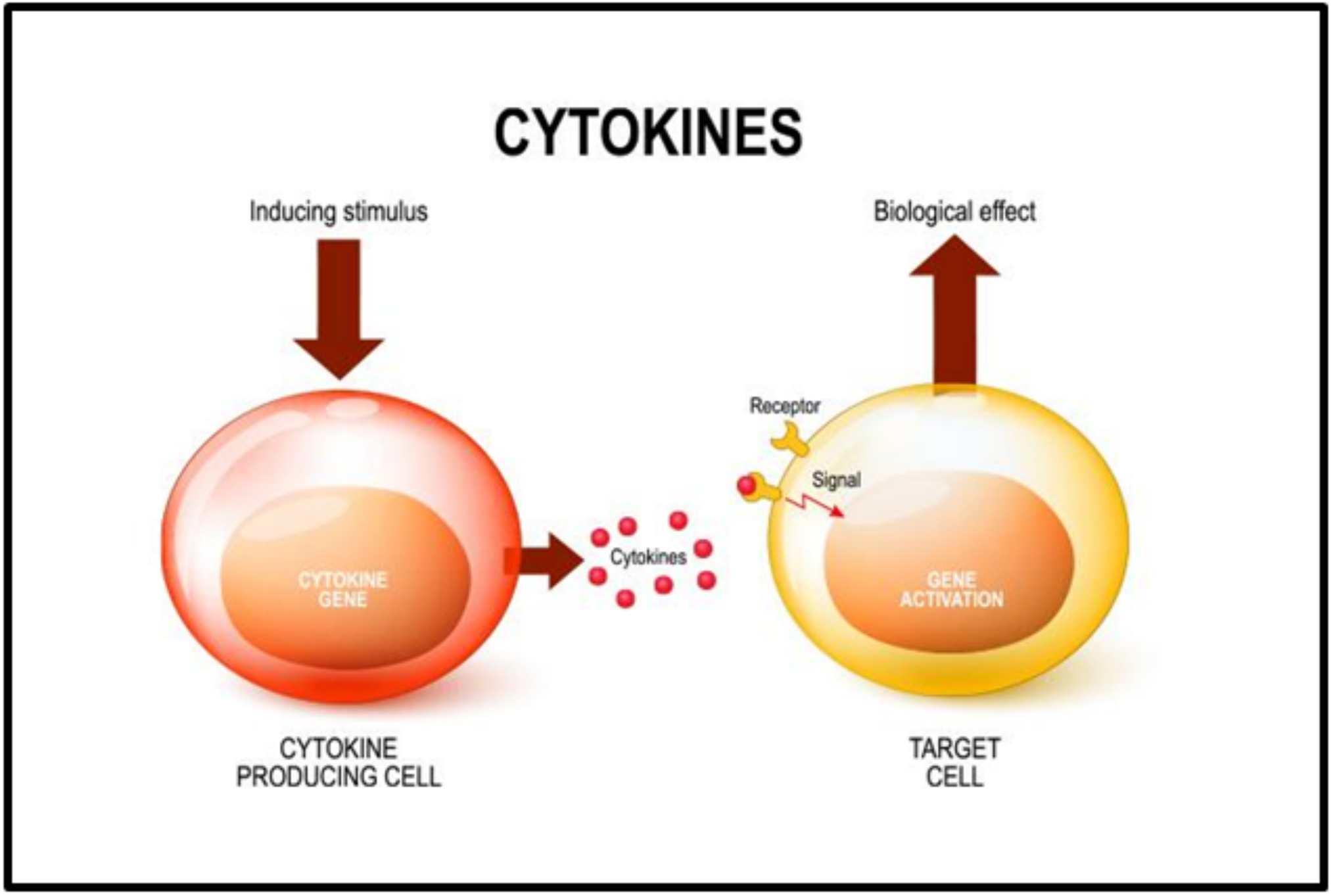
Basics of the Immune System

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.

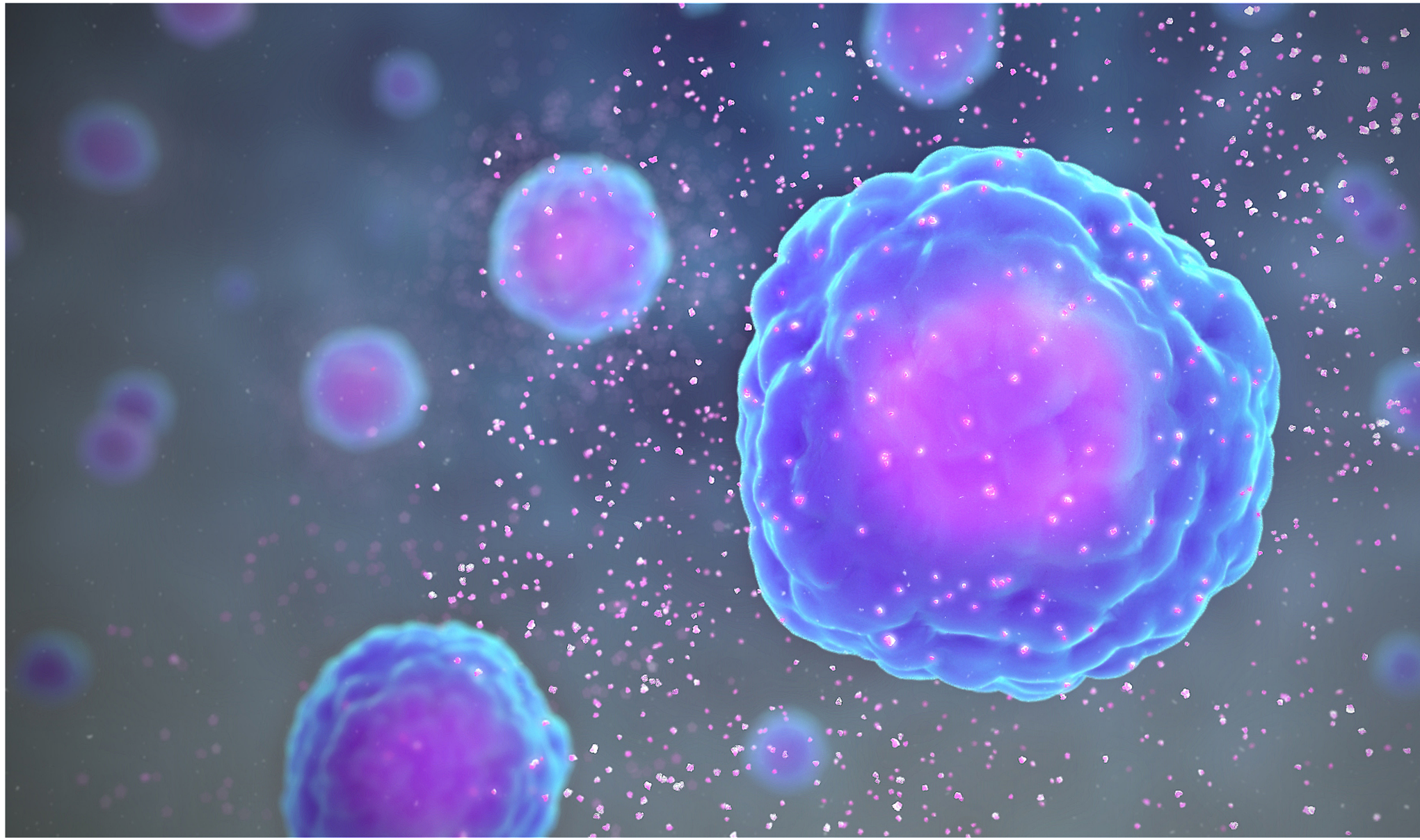
Basics of the Immune System

Cytokines



Basics of the Immune System

Cytokine Release



Basics of the Immune System

Cytokines

- Release of cytokines by a macrophage - Video

Basics of the Immune System

Cytokines

- Chemokines
  - “Chemoattractant” cytokines.
  - Change the shape of adhesion molecules on the surface of endothelial cells to facilitate stronger binding of passing immune cells.
  - Direct the migration of immune cells to the site of an infection by means of chemokine concentration gradients in the extracellular environment and on the surface of endothelial cells.

Basics of the Immune System

Cytokines

- TNF (Tumor Necrosis Factor)
  - Increases adhesion molecules on surface of endothelial cells.
  - Stimulate endothelial cells to trigger blood clotting, preventing pathogens from entering the blood stream.
  - Aids the entrance of immune cells into the infection site across the endothelial blood vessel wall (extravasation).
  - In conjunction with other cytokines, induces fever in the body.

Basics of the Immune System

Cytokines

- Interferons:
  - Stimulate certain genes to produce enzymes that degrade viral RNA, that suppress viral protein translation which contributes to suppressing viral replication, and that interfere with the fusion of viral membranes with the membranes of host organelles thus thwarting the entrance of the virus into a cell.
  - Stimulate production of chemokines that recruit lymphocytes to sites of infection.
  - Increase expression of MHC class I molecules, promoting the recognition of infected cells.

Basics of the Immune System

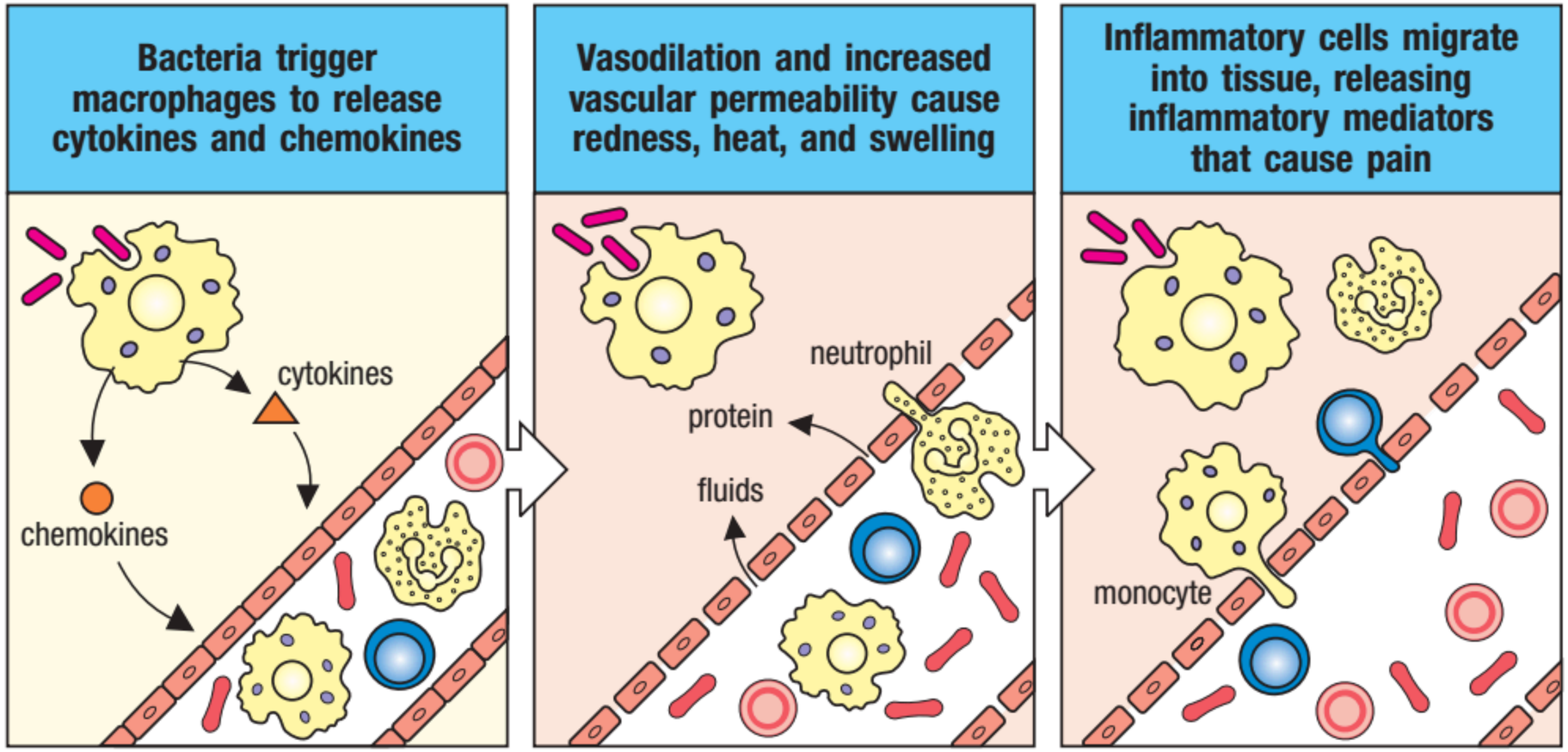
Cytokines

- 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

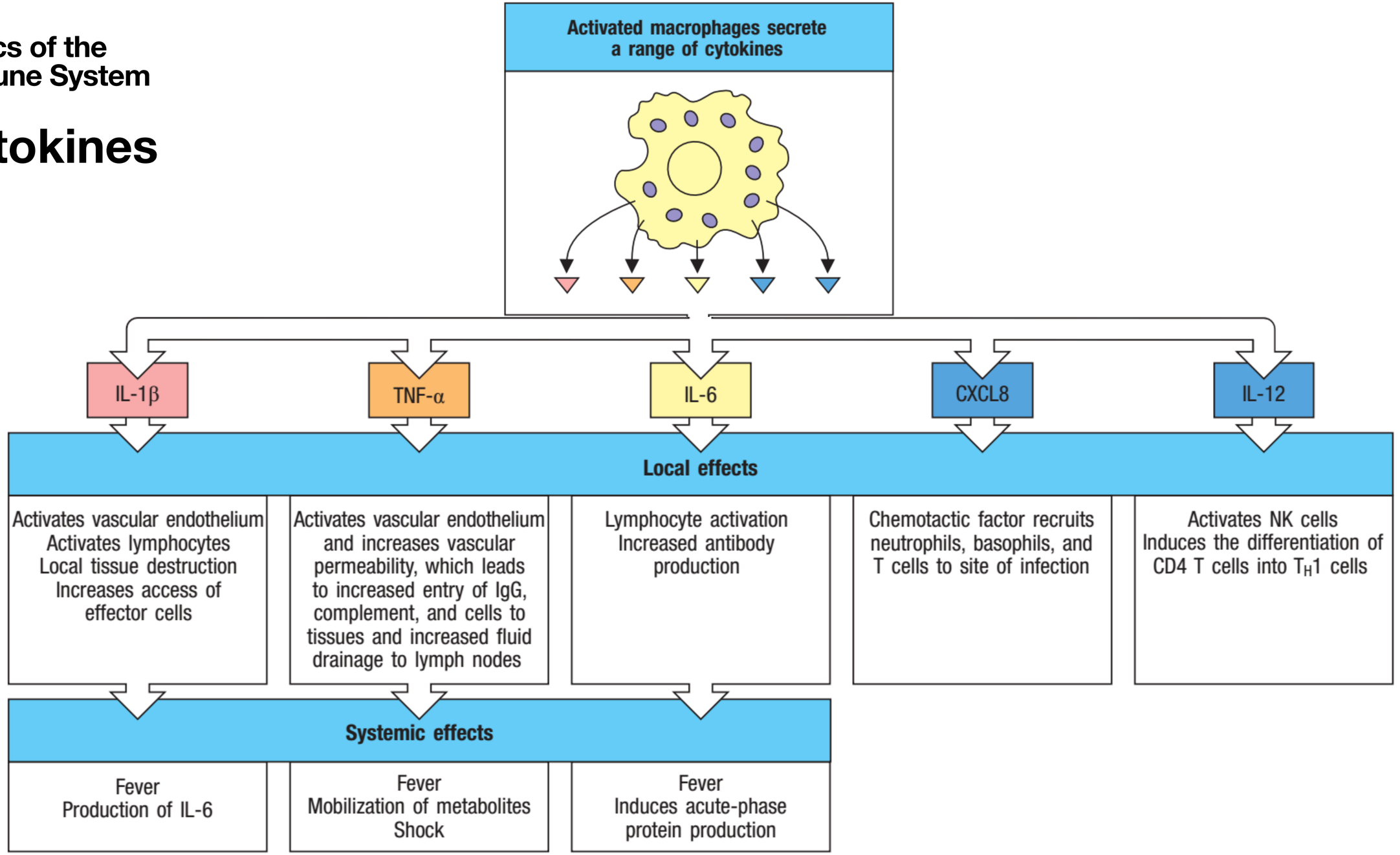
Inflammatory Response

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.



Basics of the Immune System

Cytokines



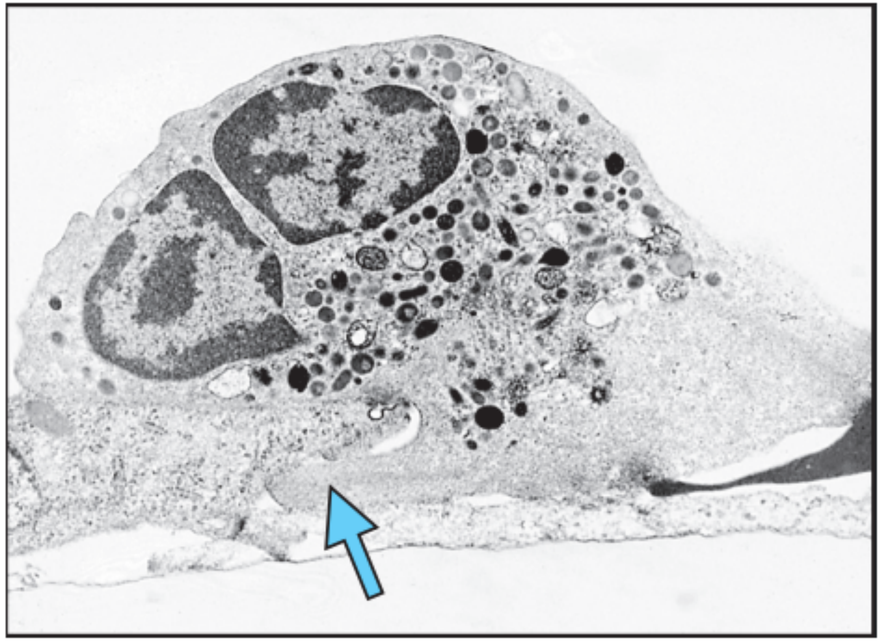
Basics of the Immune System

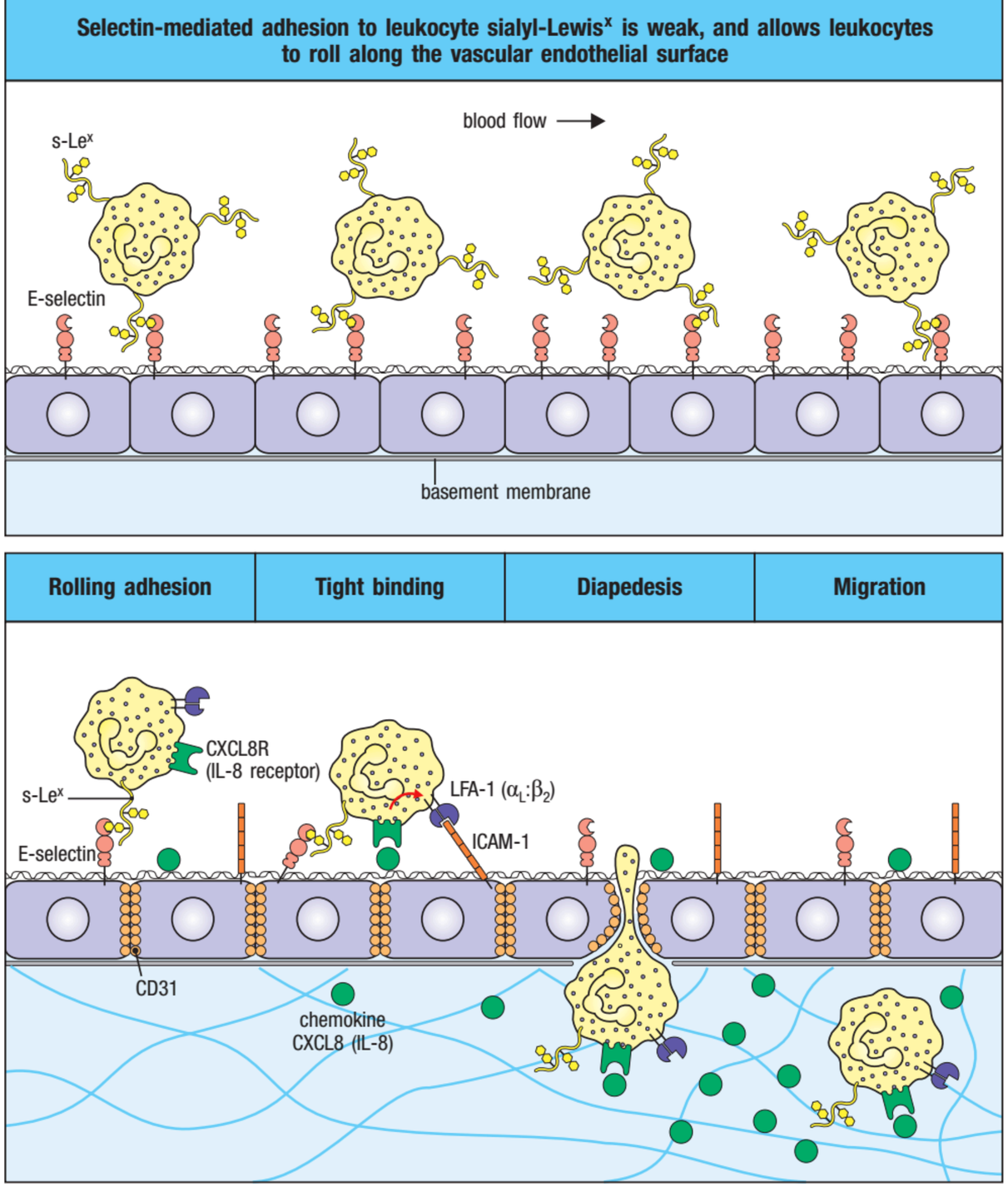
Cytokines

Fig. 3.27 Important cytokines and chemokines secreted by dendritic cells and macrophages in response to bacterial products include IL-1β, IL-6, CXCL8, IL-12, and TNF-α. TNF-α is an inducer of a local inflammatory response that helps to contain infections. It also has systemic effects, many of which are harmful (discussed in Section 3-20). The chemokine CXCL8 is also involved in the local inflammatory response, helping to attract neutrophils to the site of infection. IL-1β, IL-6, and TNF-α have a crucial role in inducing the acute-phase response in the liver and inducing fever, which favors effective host defense in various ways. IL-12 activates natural killer (NK) cells and favors the differentiation of CD4 T cells into the T_H1 subset in adaptive immunity.

Basics of the Immune System

Cytokines





Basics of the Immune System

Cytokines

Fig. 3.31 Neutrophils leave the blood and migrate to sites of infection in a multi-step process involving adhesive interactions that are regulated by macrophage-derived cytokines and chemokines. Top panel: the first step involves the reversible binding of a neutrophil to vascular endothelium through interactions between selectins induced on the endothelium and their carbohydrate ligands on the neutrophil, shown here for E-selectin and its ligand, the sialyl-Lewis^X moiety (s-Le^x). This interaction cannot anchor the cells against the shearing force of the flow of blood, and thus they roll along the endothelium, continually making and breaking contact. Bottom panel: the binding does, however, eventually trigger stronger interactions, which result only when binding of a chemokine such as CXCL8 to its specific receptor on the neutrophil triggers the activation of the integrins LFA-1 and CR3 (Mac-1; not shown). Inflammatory cytokines such as TNF-α are also necessary to induce the expression of adhesion molecules such as ICAM-1 and ICAM-2, the ligands for these integrins, on the vascular endothelium. Tight binding between ICAM-1 and the integrins arrests the rolling and allows the neutrophil to squeeze between the endothelial cells forming the wall of the blood vessel (i.e., to extravasate). The leukocyte integrins LFA-1 and CR3 are required for extravasation and for migration toward chemoattractants. Adhesion between molecules of CD31, expressed on both the neutrophil and the junction of the endothelial cells, is also thought to contribute to extravasation. The neutrophil also needs to traverse the basement membrane; it penetrates this with the aid of a matrix metalloproteinase enzyme, MMP-9, that it expresses at the cell surface. Finally, the neutrophil migrates along a concentration gradient of chemokines (shown here as CXCL8) secreted by cells at the site of infection. The electron micrograph shows a neutrophil extravasating between endothelial cells. The blue arrow indicates the pseudopod that the neutrophil is inserting between the endothelial cells. Photograph (×5500) courtesy of I. Bird and J. Spragg.

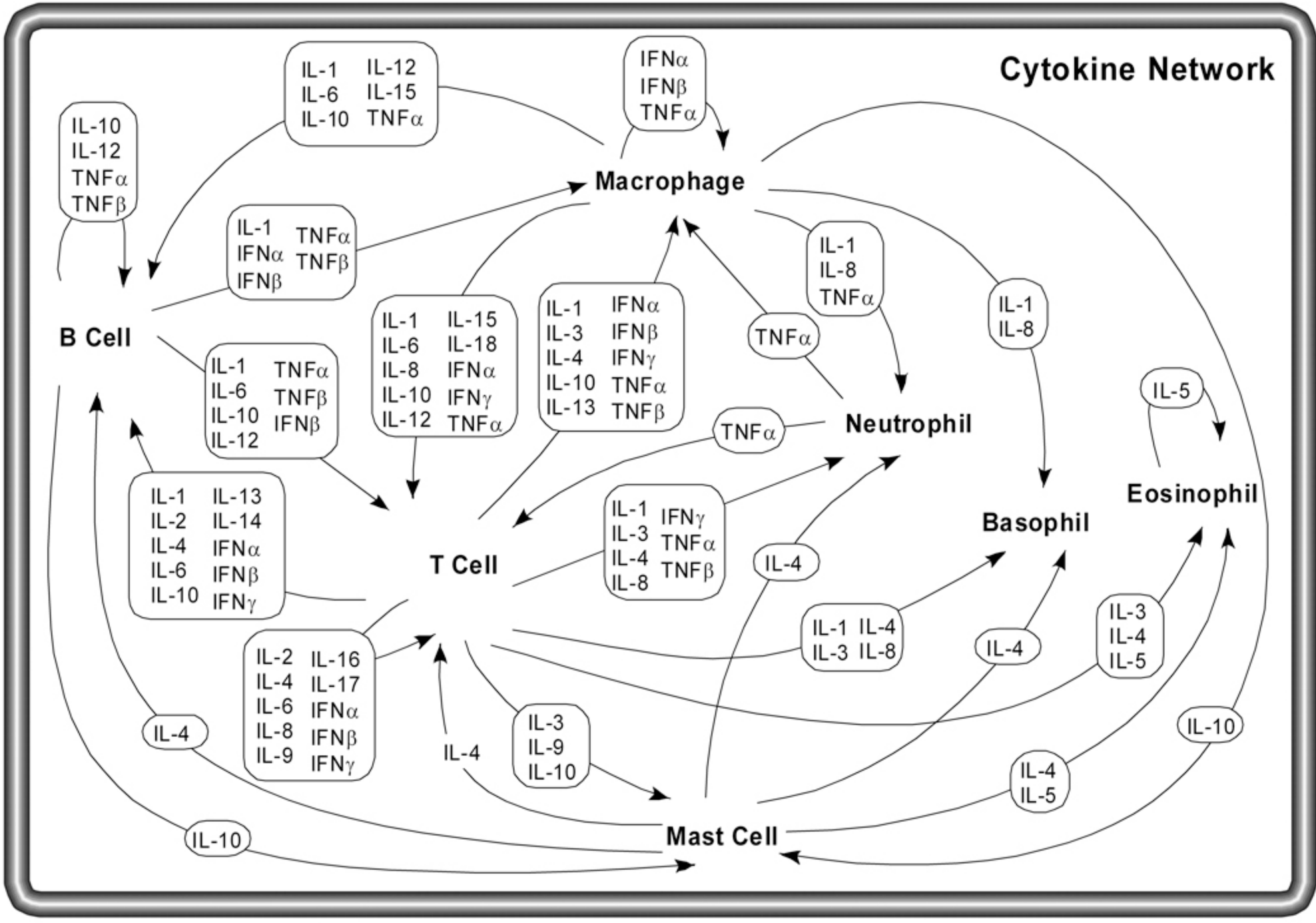
Basics of the Immune System

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.

Basics of the Immune System

Cytokines



Basics of the Immune System

Cytokines

- Other Activities:
  - Involved in the activation of B cells.
  - Coordinates activities among multiple immune cells.
  - Increases activity of immune cells.
  - Suppresses activity of immune cells.

Control and Restraint

From Discovery to Cancer Therapies

- Interferon belongs to a family of proteins, cytokines, whose purpose is communications between cells and tissues, and coordination of the immune system.
- There are at least 17 types of interferon, produced by different cells of the body.
- Many of the cytokines discovered after interferon are called interleukins (IL). There at least 37 different interleukins.
- Some interleukins boost and prolong the activity of immune cells like neutrophils and NK cells.
- Some turn off the immune response.

Control and Restraint

From Discovery to Cancer Therapies

- This knowledge about the different roles of cytokines has led to new approaches for therapies by manipulating their levels in the body.
- Example of Steven Rosenberg at the NIH National Cancer Institute. He used IL-2 (Interleukin-2) to boost a patients own immune system to fight cancer.
- But again, large trials proved disappointing. IL-2 seems to work for only some types of cancer.

Cytokines and Autoimmune Diseases

Rheumatoid Arthritis

- Marc Feldmann hypothesized that immune cells might activate each other through their cytokine secretions to such an extent that the activation becomes self-perpetuating, creating a vicious circle that overstimulates the immune system and causes it to harm the body.

- The medical implication of this hypothesis is that blocking a cytokine might stop immune cells from driving each other on and thus prevent autoimmune disease.

- Feldmann decided to focus on rheumatoid arthritis.

- Feldmann partnered with the clinician Ravinder Maini in London. This partnership combined the lab with the clinic.

Cytokines and Autoimmune Diseases

Rheumatoid Arthritis

- The Feldmann/Maini team found that “tumor necrosis factor” (TNF - a cytokine) was especially abundant in the joints of patients suffering from rheumatoid arthritis.
- This led the team to look for an “anti-cytokine” to block TNF.
- Enter Jan Vilcek. Using samples of TNF, he immunized mice with it, and isolated B cells from their spleen which would contain antibodies against TNF.
- The anti-TNF antibody had medical applications, including protection from sepsis.
- The biotech company Centocor attempted to use the anti-TNF antibody as a treatment for sepsis.

Cytokines and Autoimmune Diseases

Rheumatoid Arthritis

- The use of this antibody against sepsis failed, but Feldmann “convinced” Centocor to use it against rheumatoid arthritis.
- Ultimately, it was found that this antibody alleviated the symptoms, but was not a cure. It was a treatment for a chronic condition.
- Other approaches were taken up by other companies, and several therapeutic drugs were developed for rheumatoid arthritis.
- This showed the importance of controlling the action of cytokines as a therapy for autoimmune diseases and other diseases.

Cytokines and Autoimmune Diseases

Rheumatoid Arthritis

- But there are problems with this approach:
  - It weakens our defense against infections.
  - Given the genetic and environmental diversity behind each patient's condition, it does not provide a universal solution.
  - It is a treatment, not a cure.
- The use of antibodies as a treatment extends beyond rheumatoid arthritis, e.g. rituximab for treating cancer.
- But the use of antibodies as a therapy must be used cautiously because it can result in over-stimulation of the immune system and attacks on healthy cells.

Up Next

- No readings for next time.
- More on role and activity of cytokines.
- Wrap up first part of this study group - summary and overview of the significant features of the immune system - scenario of an immune response.
- Transition from the scientific discoveries to the therapies and practical applications.