OLLI SG 492
Human Immune System

Session 4 - March 30, 2022

Today’s Meeting

- Recap of our last meeting
- More on the innate immune cells
- Overview of lymphocytes - T cells and B cells
- Action of antibodies
- Presentation of antigens to lymphocytes
- Overview of the discovery of interferon and its use as a cancer therapy

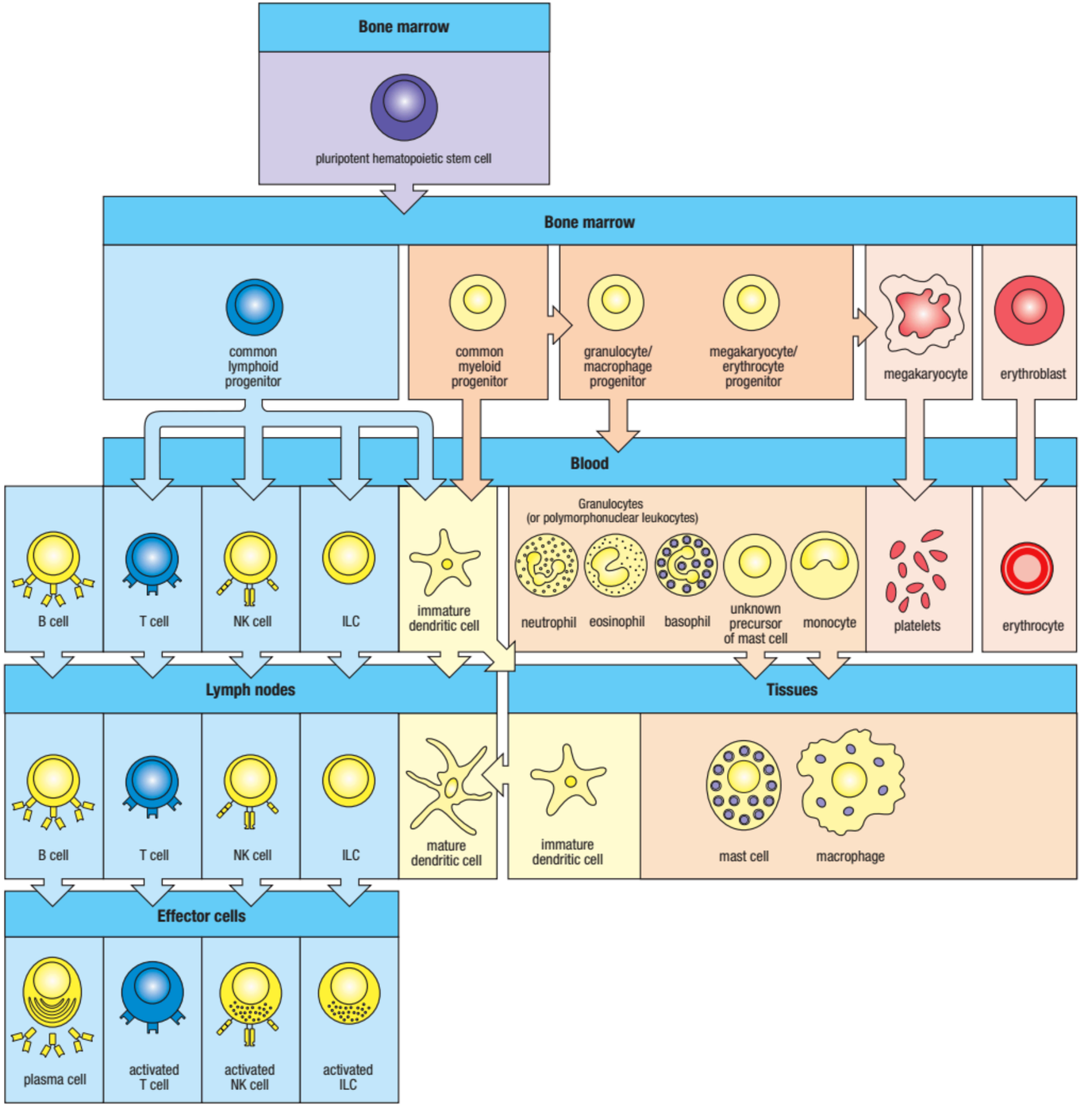
Recap

- Expanded the concept of “First Line of Defense” to include antimicrobial molecules, and systems like Complement.
- Clarified the types of infection - extracellular and intracellular.
- Described the inflammatory response.
- Reviewed the phases on an immune response.
- Presented an overview of two important cells of the innate immune system - macrophages and neutrophils.
- Reviewed the discovery of the dendritic cell by Ralph Steinman, and the subsequent discovery of it functions.

Cells of the Immune System

Fig. 1.3 All the cellular elements of the blood, including the cells of the immune system, arise from pluripotent hematopoietic stem cells in the bone marrow. These pluripotent cells divide to produce two types of stem cells. A common lymphoid progenitor gives rise to the lymphoid lineage (blue background) of white blood cells or leukocytes—the innate lymphoid cells (ILCs) and natural killer (NK) cells and the T and B lymphocytes. A common myeloid progenitor gives rise to the myeloid lineage (pink and yellow backgrounds), which comprises the rest of the leukocytes, the erythrocytes (red blood cells), and the megakaryocytes that produce platelets important in blood clotting. T and B lymphocytes are distinguished from the other leukocytes by having antigen receptors and from each other by their sites of differentiation—the thymus and bone marrow, respectively. After encounter with antigen, B cells differentiate into antibody-secreting plasma cells, while

T cells differentiate into effector T cells with a variety of functions. Unlike T and B cells, ILCs and NK cells lack antigen specificity. The remaining leukocytes are the monocytes, the dendritic cells, and the neutrophils, eosinophils, and basophils. The last three of these circulate in the blood and are termed granulocytes, because of the cytoplasmic granules whose staining gives these cells a distinctive appearance in blood smears, or polymorphonuclear leukocytes, because of their irregularly shaped nuclei. Immature dendritic cells (yellow background) are phagocytic cells that enter the tissues; they mature after they have encountered a potential pathogen. The majority of dendritic cells are derived from the common myeloid progenitor cells, but some may also arise from the common lymphoid progenitor. Monocytes enter tissues, where they differentiate into phagocytic macrophages or dendritic cells. Mast cells also enter tissues and complete their maturation there.



Basics of the Immune System

Other Cells of the Innate Immune System

- Eosinophils and Basophils
  - Granulocytes - contain cytoplasmic granules of enzymes and toxic proteins.
  - Phagocytic.
  - Important in defense against parasites.
- Mast Cells
  - Mature in peripheral tissue - skin, intestines, and airway mucosa.
  - Granulocytes - Ganules contain inflammatory mediators, which protect internal surfaces from pathogens.

Basics of the Immune System

Other Cells of the Innate Immune System

- Natural Killer (NK) Cells
  - Large lymphocyte-like cells with granular cytoplasm.
  - Adept at killing tumor cells and cells infected with herpesvirus.
  - Play an important role in the early immune response to viral infections.
- Innate Lymphoid Cells (ILCs)
  - Reside in peripheral tissue like the intestine.
  - Sources of mediators of inflammatory responses.

T and B Cells and Their Interaction With Dendritic Cells

- Lymphocytes and Dendritic Cells Video
- T Cells and B Cells Video
- Kurzgesagt on the Immune System

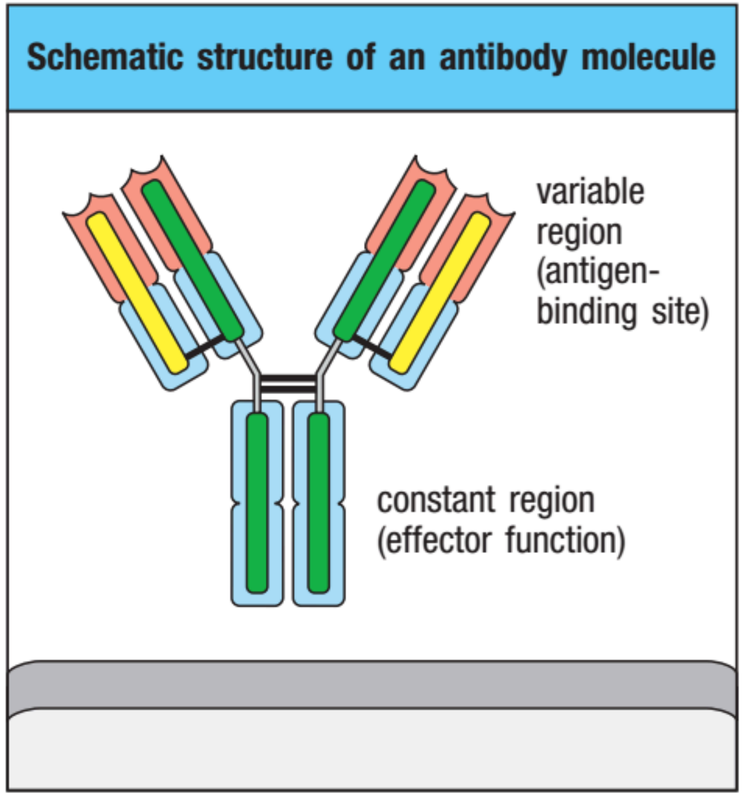
Basics of the Immune System

Adaptive Immune System Lymphocytes - T Cells and B Cells

- Produced in the billions in bone marrow
  - T cells migrate via bloodstream to the thymus where they mature, and are tested and selected.
  - B cells mature in the bone marrow.
  - Both eventually migrate to lymphatic organs, especially the lymph nodes.
  - Both show little functional activity until they encounter a specific antigen.
- Lymphocytes that have not been activated by antigen are “naive.”
- Upon activation, lymphocytes differentiate into “effector” cells.

Basics of the Immune System

Antigen Receptors



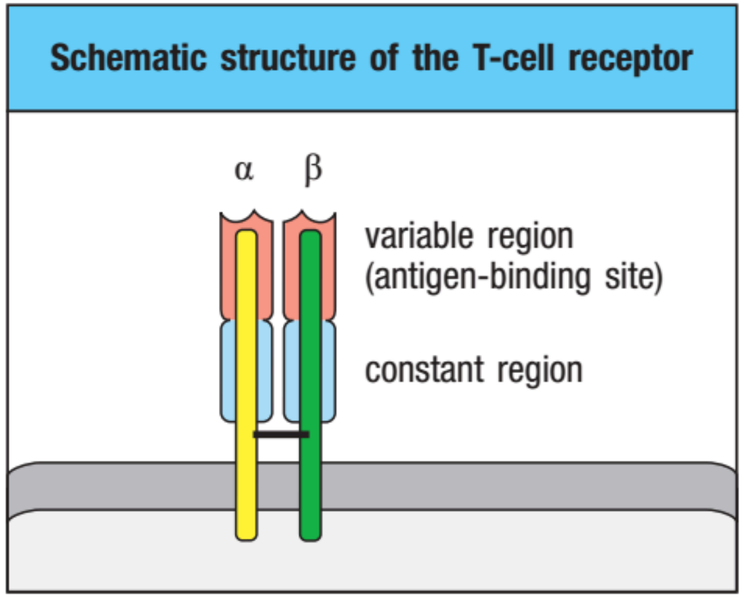


Fig. 1.13 Schematic structure of antigen receptors. Upper panel: an antibody molecule, which is secreted by activated B cells as an antigen-binding effector molecule. A membrane-bound version of this molecule acts as the B-cell antigen receptor (not shown). An antibody is composed of two identical heavy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

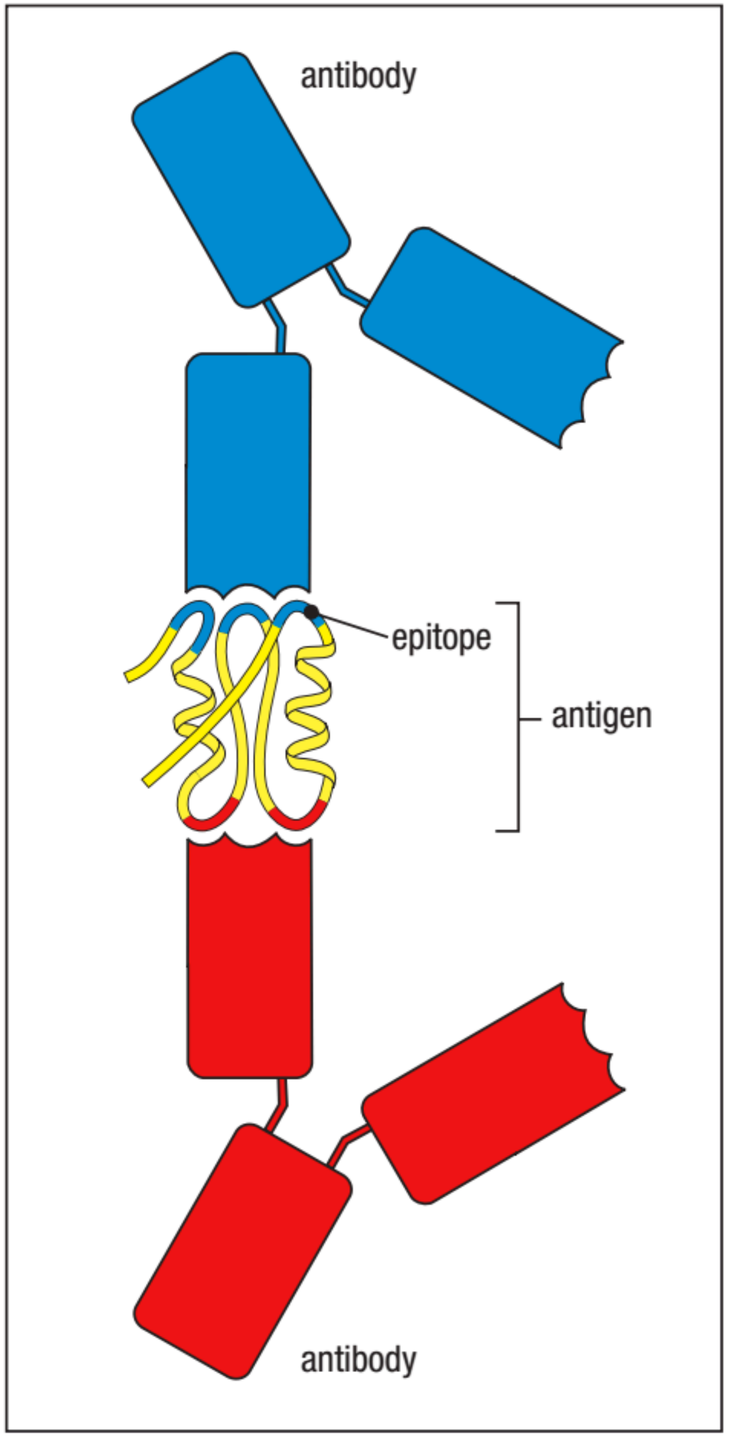
Antigen Receptors

- 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

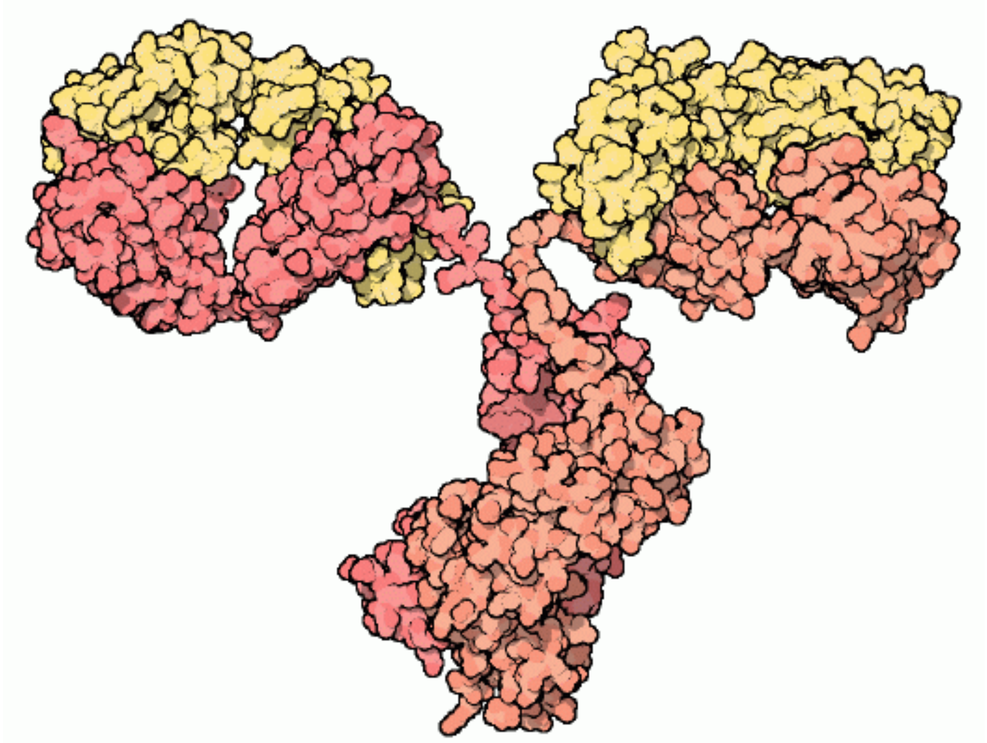
Antigen Receptors

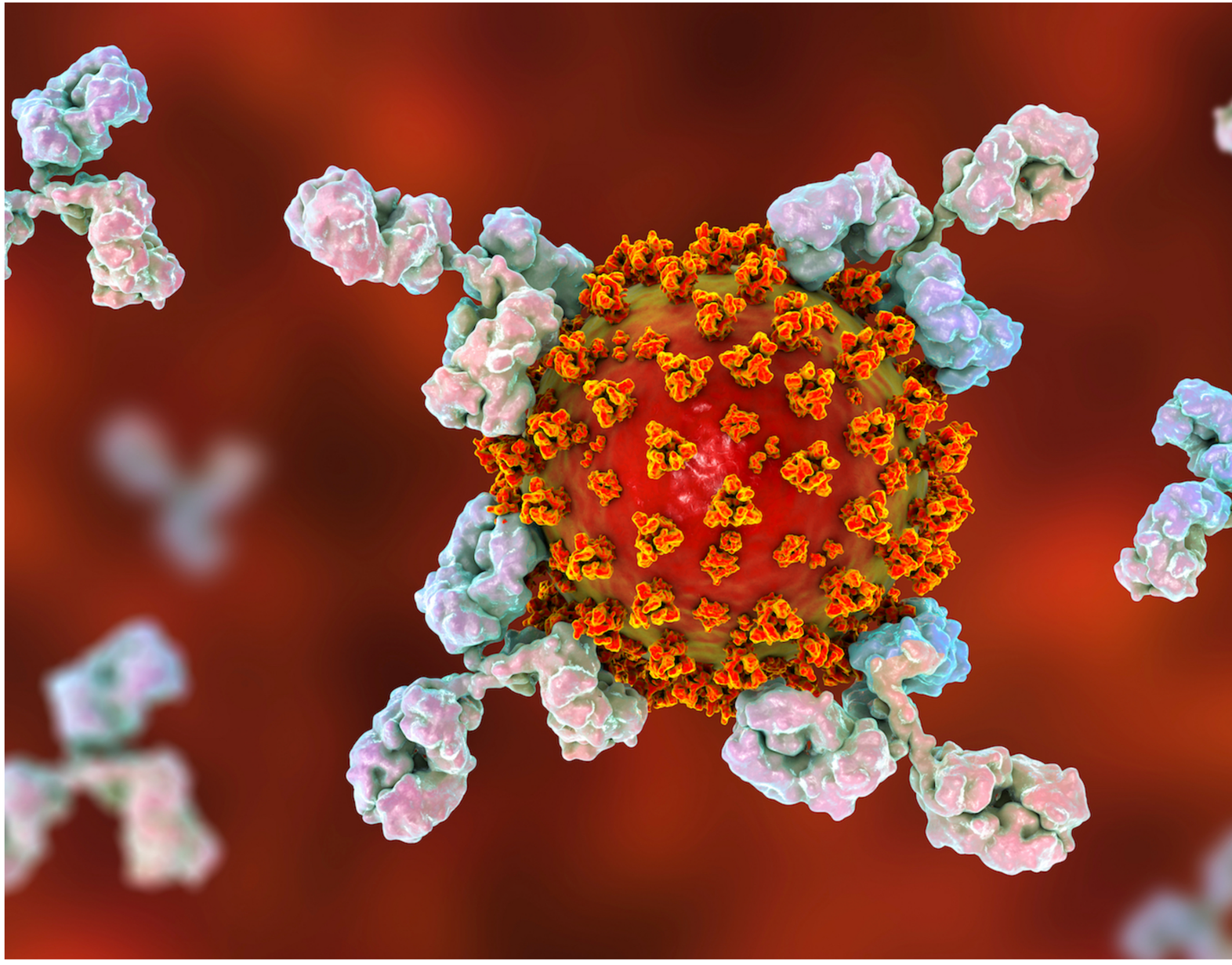
Fig. 1.14 Antigens are the molecules recognized by the immune response, while epitopes are sites within antigens to which antigen receptors bind.
Antigens can be complex macromolecules such as proteins, as shown in yellow. Most antigens are larger than the sites on the antibody or antigen receptor to which they bind, and the actual portion of the antigen that is bound is known as the antigenic determinant, or epitope, for that receptor. Large antigens such as proteins can contain more than one epitope (indicated in red and blue) and thus may bind different antibodies (shown here in the same color as the epitopes they bind). Antibodies generally recognize epitopes on the surface of the antigen.



Basics of the Immune System

Antibody Structure





Basics of the Immune System

Antigen Receptors

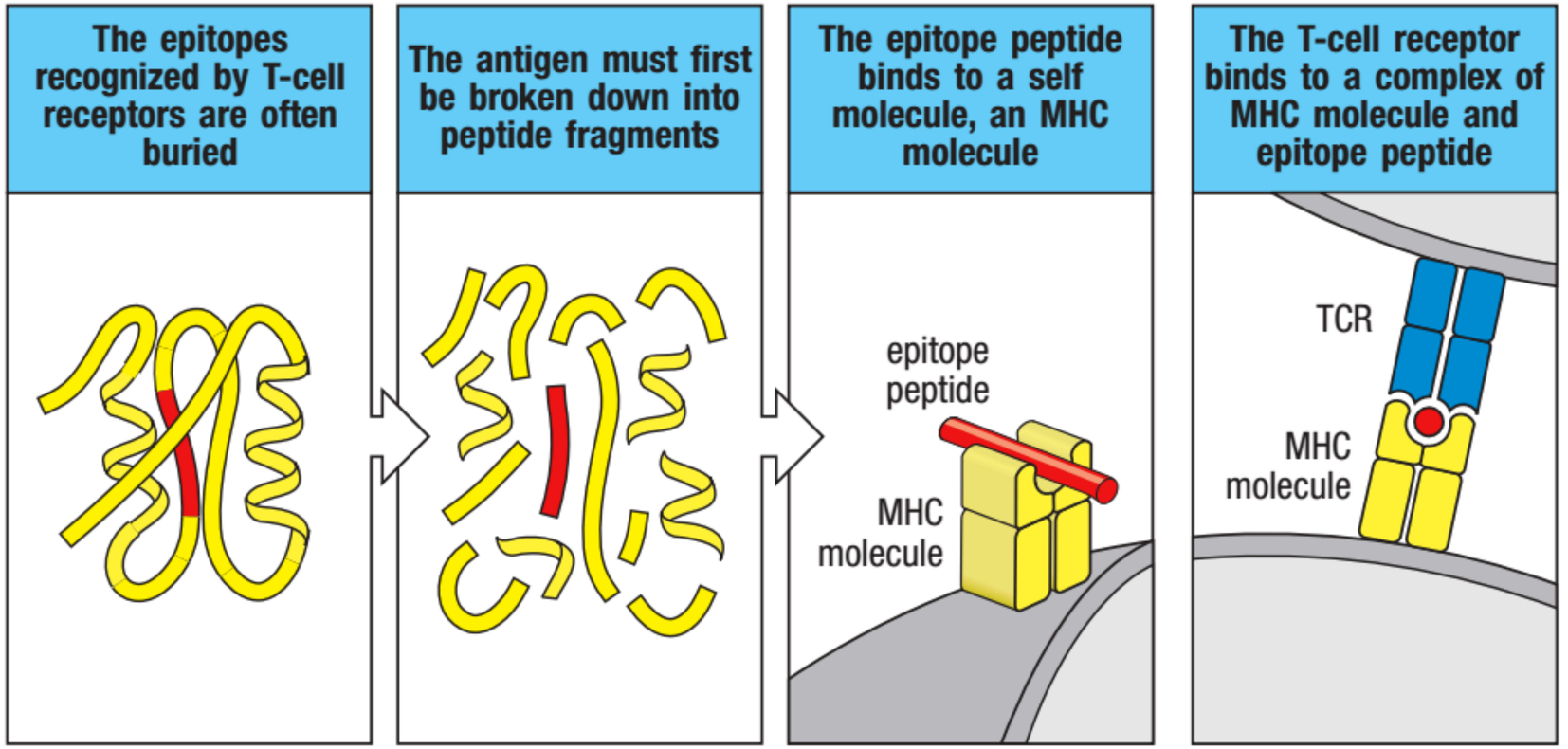


Fig. 1.15 T-cell receptors bind a complex of an antigen fragment and a self molecule. Unlike most antibodies, T-cell receptors can recognize epitopes that are buried within antigens (first panel). These antigens must first be degraded by proteases (second panel) and the peptide epitope delivered to a self molecule, called an MHC molecule (third panel). It is in this form, as a complex of peptide and MHC molecule, that antigens are recognized by T-cell receptors (TCRs; fourth panel).

Basics of the Immune System

Action of Antibodies

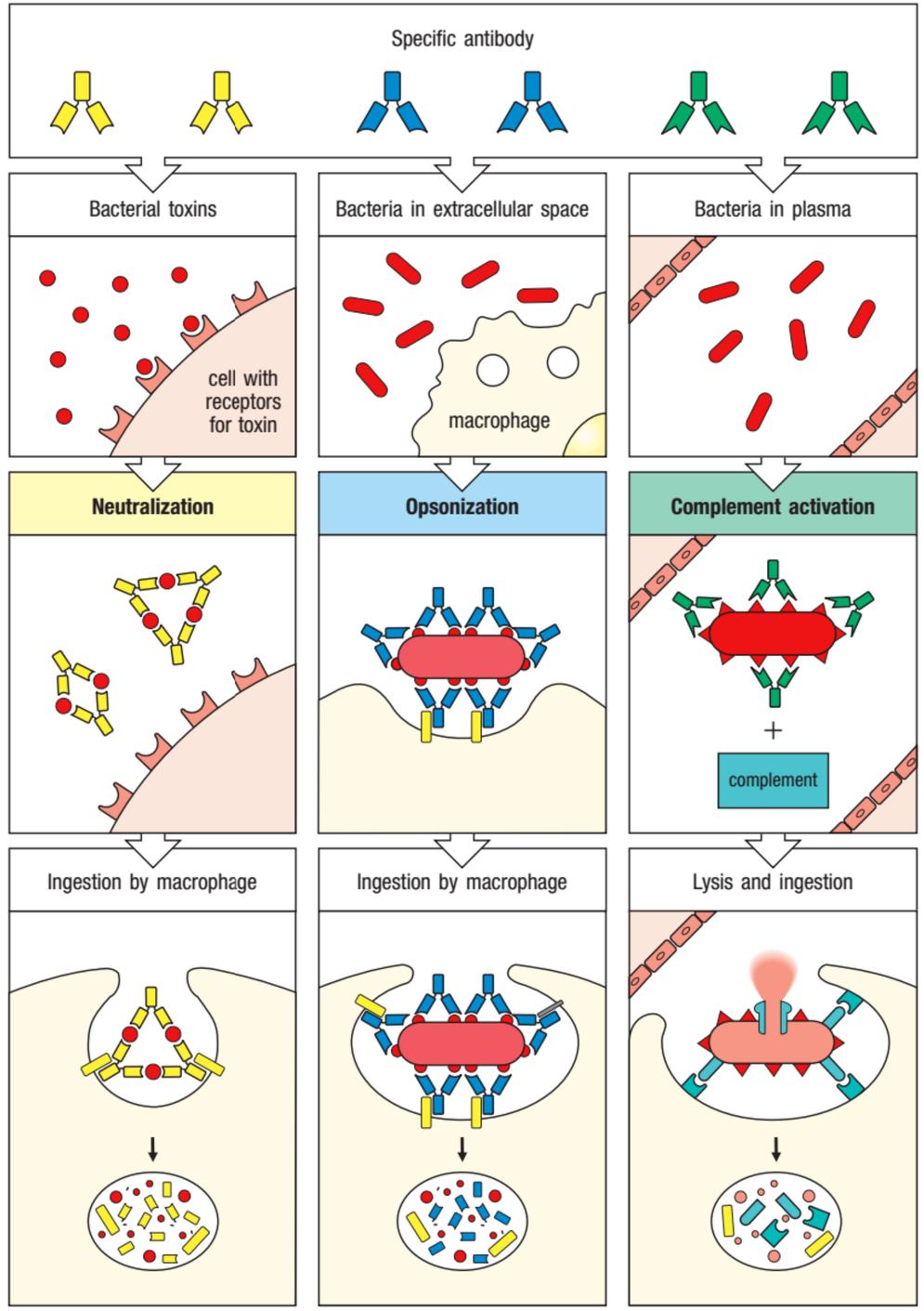
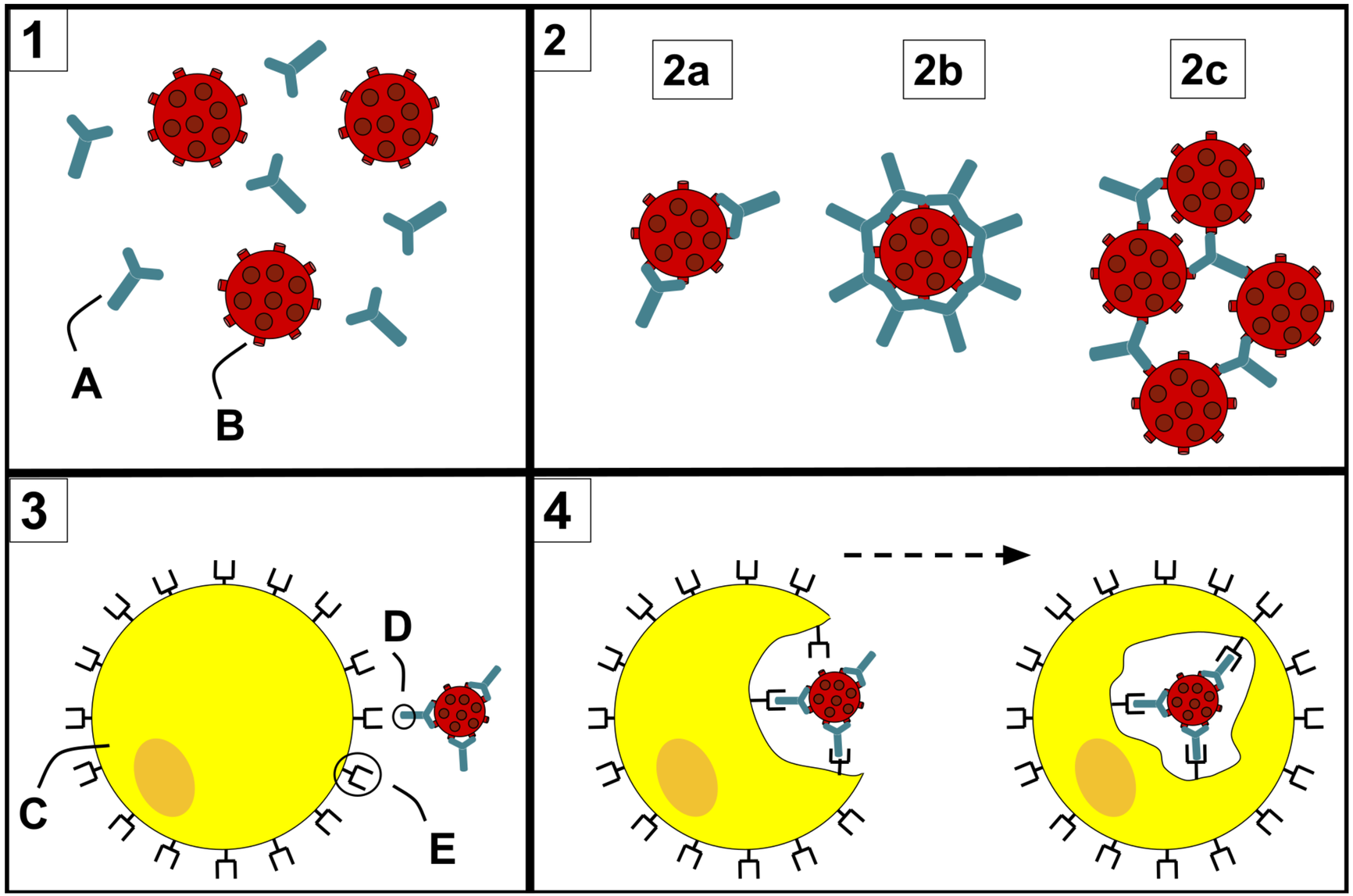


Fig. 1.28 Antibodies can participate in host defense in three main ways. The left panels show antibodies binding to and neutralizing a bacterial toxin, thus preventing it from interacting with host cells and causing pathology. Unbound toxin can react with receptors on the host cell, whereas the toxin:antibody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

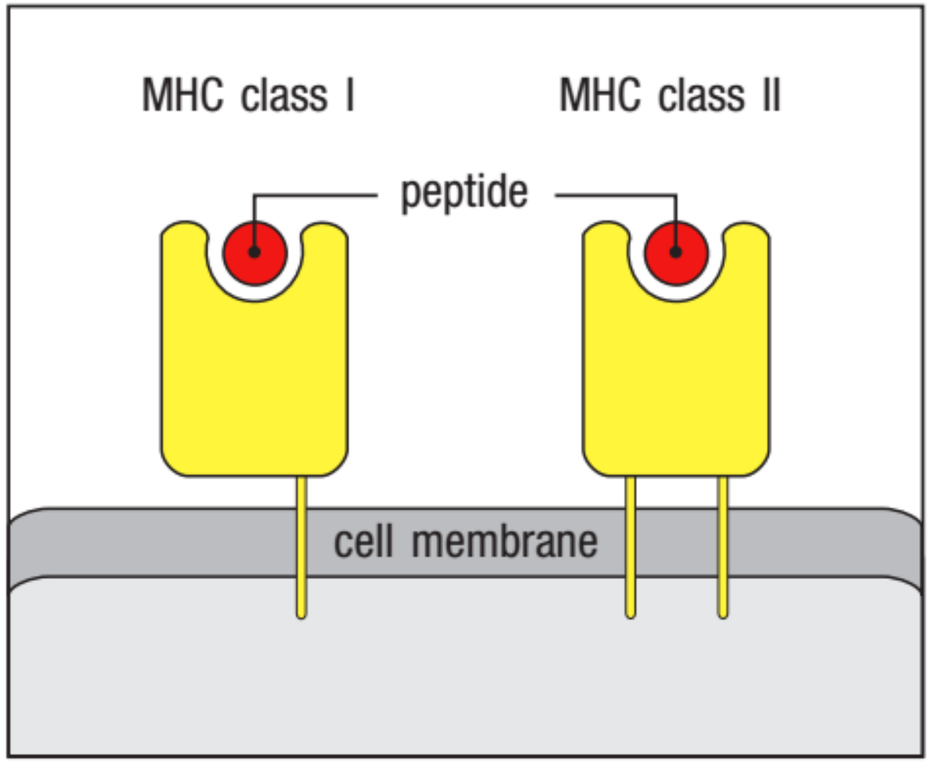
1) Antibodies (A) and pathogens (B) free roam in the blood. 2) The antibodies bind to pathogens, and can do so in different formations such as: opsonization (2a), neutralisation (2b), and agglutination (2c). 3) A phagocyte (C) approaches the pathogen, and the Fc region (D) of the antibody binds to one of the Fc receptors (E) of the phagocyte. 4) Phagocytosis occurs as the pathogen is ingested.



Basics of the Immune System

Antigen-Specific Receptors

Fig. 1.29 MHC molecules on the cell surface display peptide fragments of antigens. MHC molecules are membrane proteins whose outer extracellular domains form a cleft in which a peptide fragment is bound. These fragments are derived from proteins degraded inside the cell and include both self and foreign protein antigens. The peptides are bound by the newly synthesized MHC molecule before it reaches the cell surface. There are two kinds of MHC molecules, MHC class I and MHC class II; they have related but distinct structures and functions. Although not shown here for simplicity, both MHC class I and MHC class II molecules are trimers of two protein chains and the bound self or nonself peptide.



Basics of the Immune System

Antigen-Specific Receptors

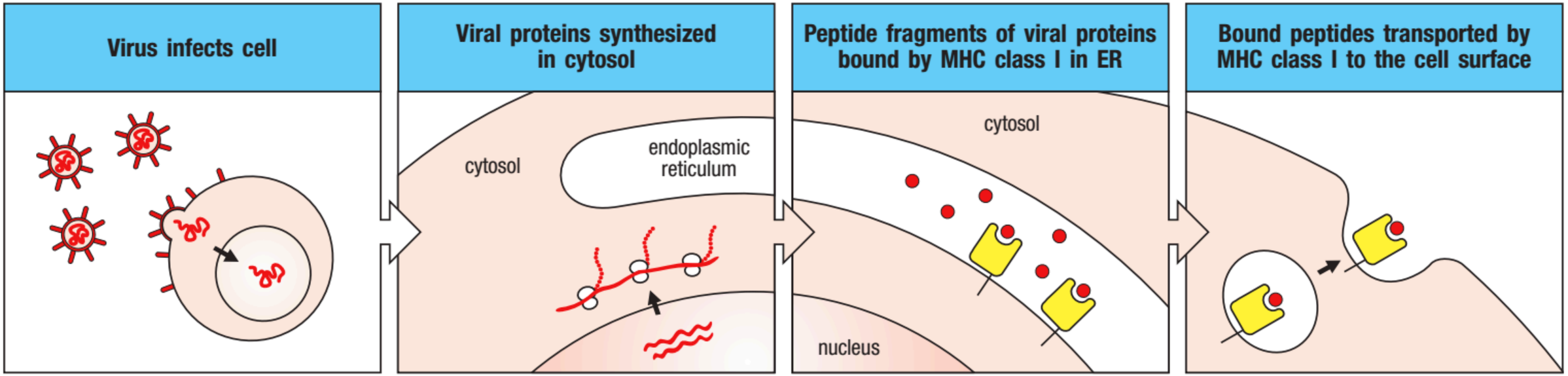
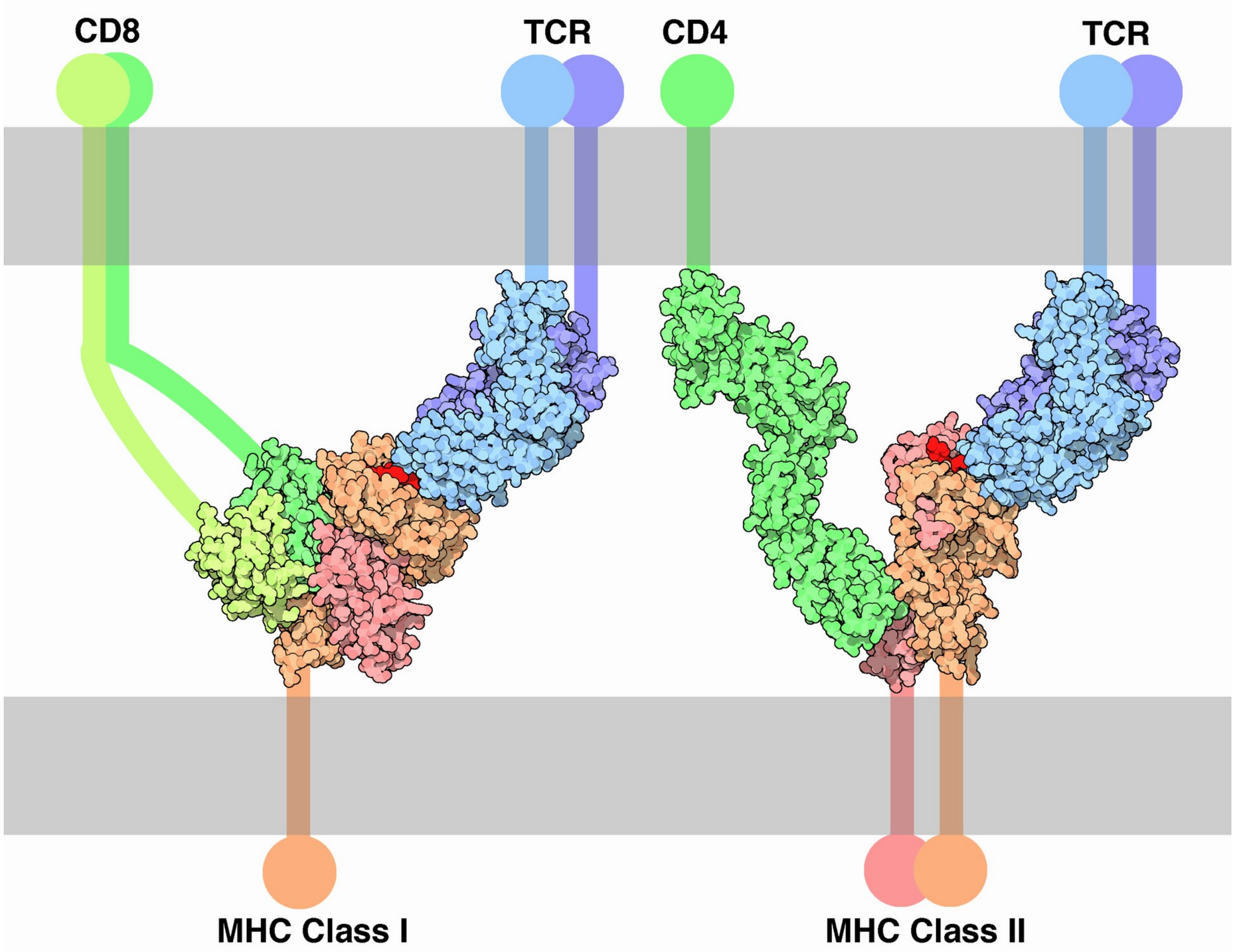


Fig. 1.30 MHC class I molecules present antigen derived from proteins in the cytosol. In cells infected with viruses, viral proteins are synthesized in the cytosol. Peptide fragments of viral proteins are transported into the endoplasmic reticulum (ER), where they are bound by MHC class I molecules, which then deliver the peptides to the cell surface.

Basics of the Immune System

Antigen-Specific Receptors



Control and Restraint

Discovery of Interferon

- Alick Isaacs and Jean Lindenmann during the summer of 1956 started to pursue a solution to a mystery, namely why the presence of one virus seems to block the growth of another.

- After one failed attempt, they modified their experimental setup and found that something in the liquid in which was suspended both a virus and membranes blocked the growth of other viruses.

- They named that substance interferon and began the laborious task of isolating and purifying it. (It subsequently took 15 years to do so.)

- After they published their findings, they were met with much skepticism. Their careers and personal lives went downhill from there.

Control and Restraint

From Discovery to Cancer Therapies

- In 1969, Ion Gresser published findings from his experiments with interferon and cancers in mice that showed, at least in mice, interferon could cure cancer.
- During the time Gresser was conducting his experiments, Kari Kantell in Finland had found a way to isolate and purify interferon.
- His process was so complex and difficult, that for a long time, he had a monopoly on the production and supply of interferon.
- The supply was always limited, and thus trials of interferon as a cure for cancer were always small. The trials that succeeded in acquiring interferon had some positive results.

Control and Restraint

From Discovery to Cancer Therapies

- This situation began to change in March 1978. Charles Weissmann from the Univ. of Zurich (and a co-founder of the U.S. biotech company Biogen) convinced Cantell to allow him to use genetic engineering techniques to produce larger quantities of interferon.

- Weissmann and Biogen succeeded. Increased availability of interferon led to more and larger trials. But the results were disappointing. Interferon was not going to be a cure for cancer.

- Interferon remains an important part of the treatment of melanoma and some types of leukemia.

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.

Up Next

- More on the adaptive immune system.
- Cytokines - their family tree and their role in “orchestrating” the immune system.
- Read Chapter 4: A Multibillion-Dollar Blockbuster.