Non-specific host defenses

Lecture 20/21 - Chapter 14

Topics

- Defense Mechanisms
- Components of immunity
- **Non-specific immunity**

Defense Mechanisms

- **Innate and nonspecific immunity**
  - First line of defense
  - Second line of defense
- **Acquired and specific immunity**
  - Third line of defense

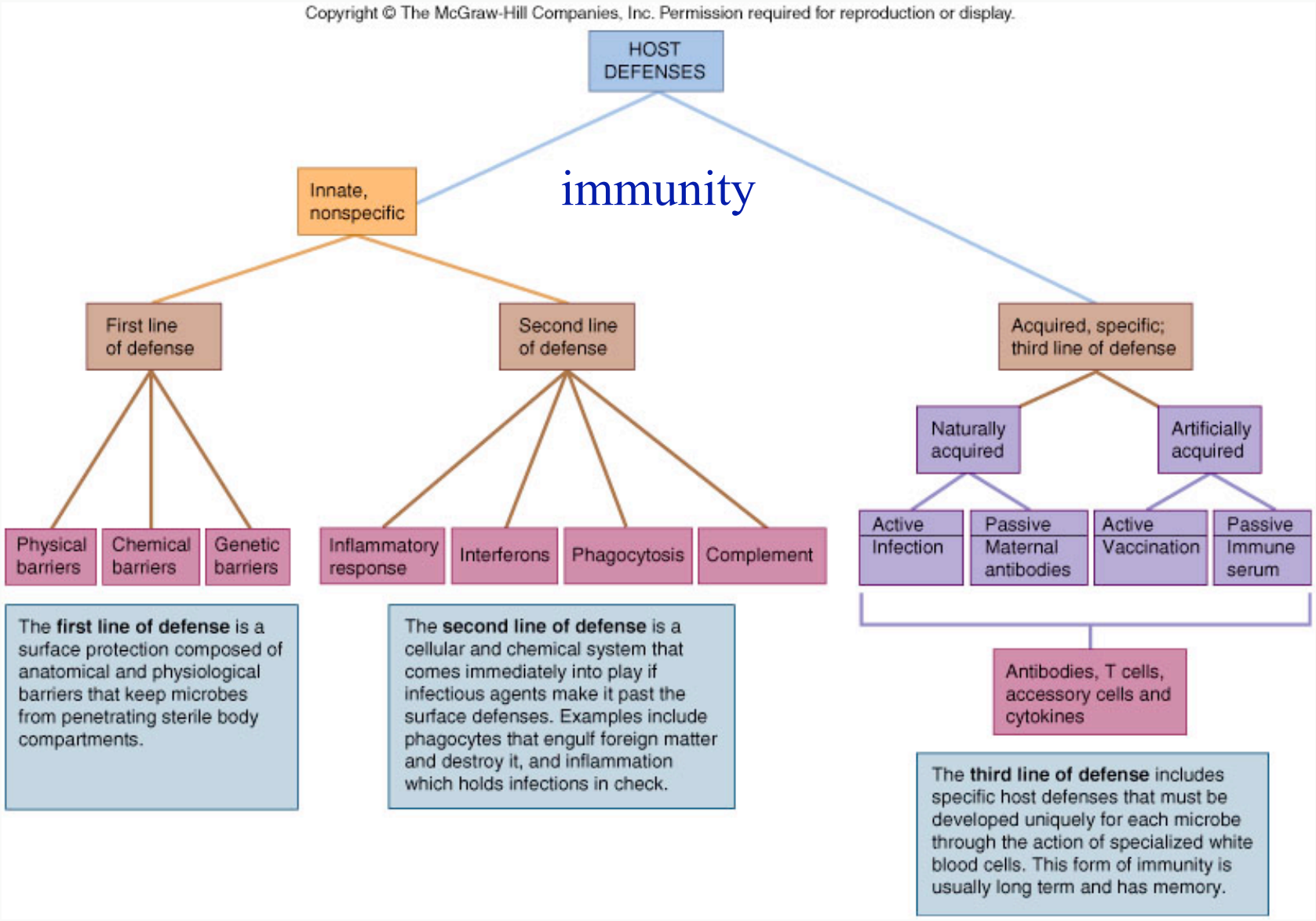


Fig. 14.1 Flowchart summarizing the major components of the host defenses.

Immunology

- **Study of immunity** - the host's resistance to infectious agents of disease

Immunity

- Involves nonspecific and specific components
- Has fluid-based (humoral) and cellular (white blood cells [wbc] = leukocytes) components
  - Surveillance of the host body
  - Recognition of foreign agents or material
  - Destruction of foreign agents or material

Non-specific Immunity

- Inflammation
- Phagocytosis
- Cytokines (i.e., Interferon)
- Complement

Inflammation

- Five major symptoms
  - Redness (Rubor)
  - Warmth (Calor)
  - Swelling (Tumor)
  - Pain (Dolor)
  - Loss of function

Inflammation - Causes

- Trauma
- Tissue injury due to physical or chemical agents
- Specific immune reactions

Inflammation - Function

- Mobilize and attract immune components to the site of injury (second line of defense)

- Localized and remove harmful substances
- Destroy microbes and block their invasion

- Aid in the repair of tissue damage

Phagocytosis

- Neutrophils
- Macrophages & Dendritic Cells

Mechanism of phagocytosis

- Chemotaxis (Peptidoglycan, LPS, foreign debris))
- Ingestion (Phagocytes enclose the pathogen or foreign material, form a phagosome)
- Phagolysosome (Phagosomes fuse with the Lysosome forming the the Phagolysosome, where antimicrobial chemicals are released
- Destruction (Enzymes: Oxidative burst; Nitrosative burst

A summary of the mechanism of phagocytosis.

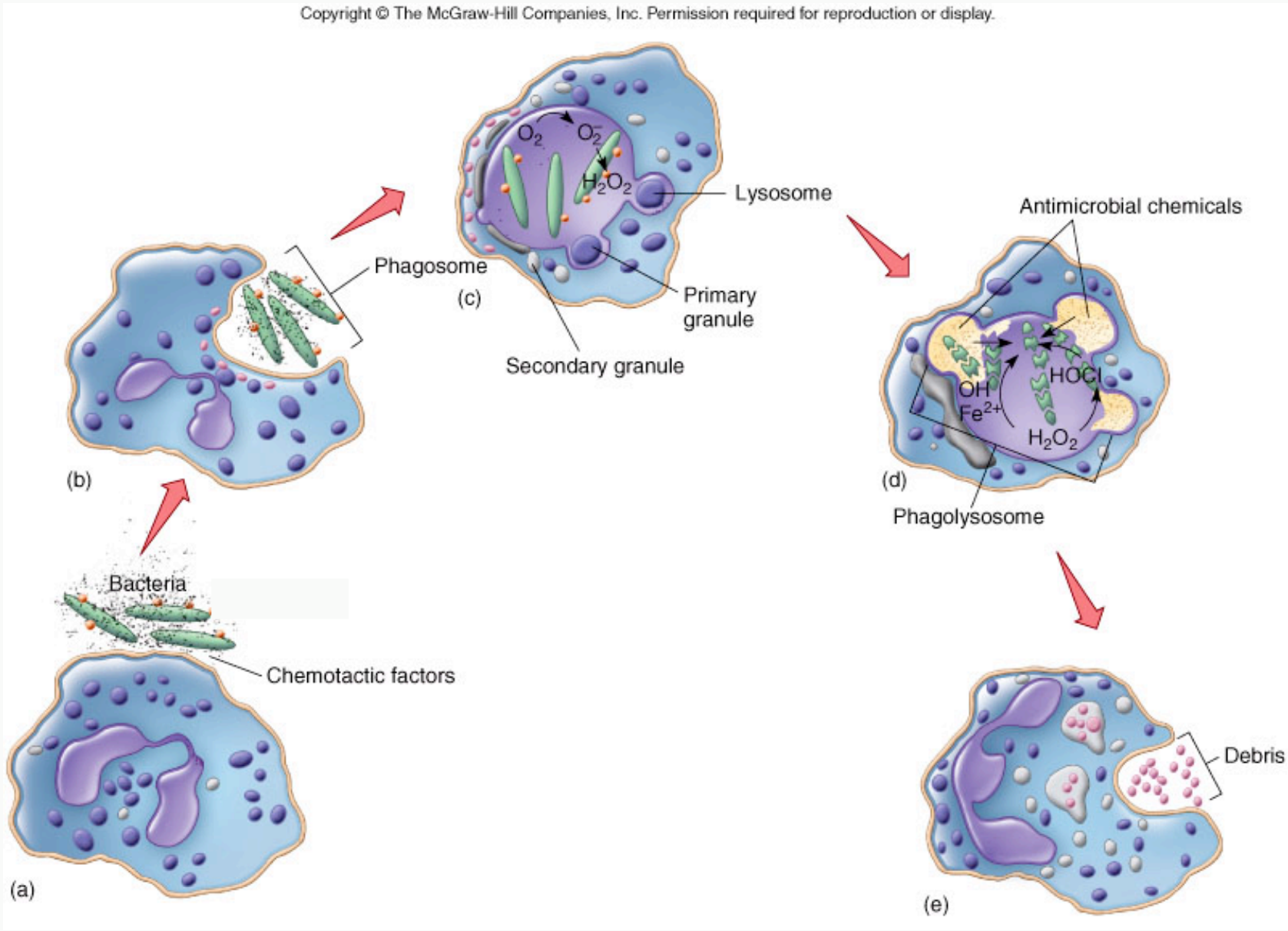


Fig. 14.19 The phases in phagocytosis

Interferon

- Synthesis: in WBCs & Tissue cells
- Produced in response to viral infections, microbe infections and other antigens, increased nucleic acid contents, immune products

Classes

- Interferon alpha
  - Product of lymphocytes and macrophages
- Interferon beta
  - Product of fibroblasts and epithelial cells
- Interferon gamma
  - Product of T lymphocytes

Activity

- A signal (induced by virus-cell interaction) is sent to the nucleus to synthesize (transcription and translation) interferon
- Interferon is secreted from cell
- Interferon binds to other host cells and induces production antiviral proteins (leads to inhibition of viral multiplication; I.e., by inhibition of translation)

Interferon is produced, released, and taken-up by a near-by cell, where by original cell is not protected but the recipient cell is protected.

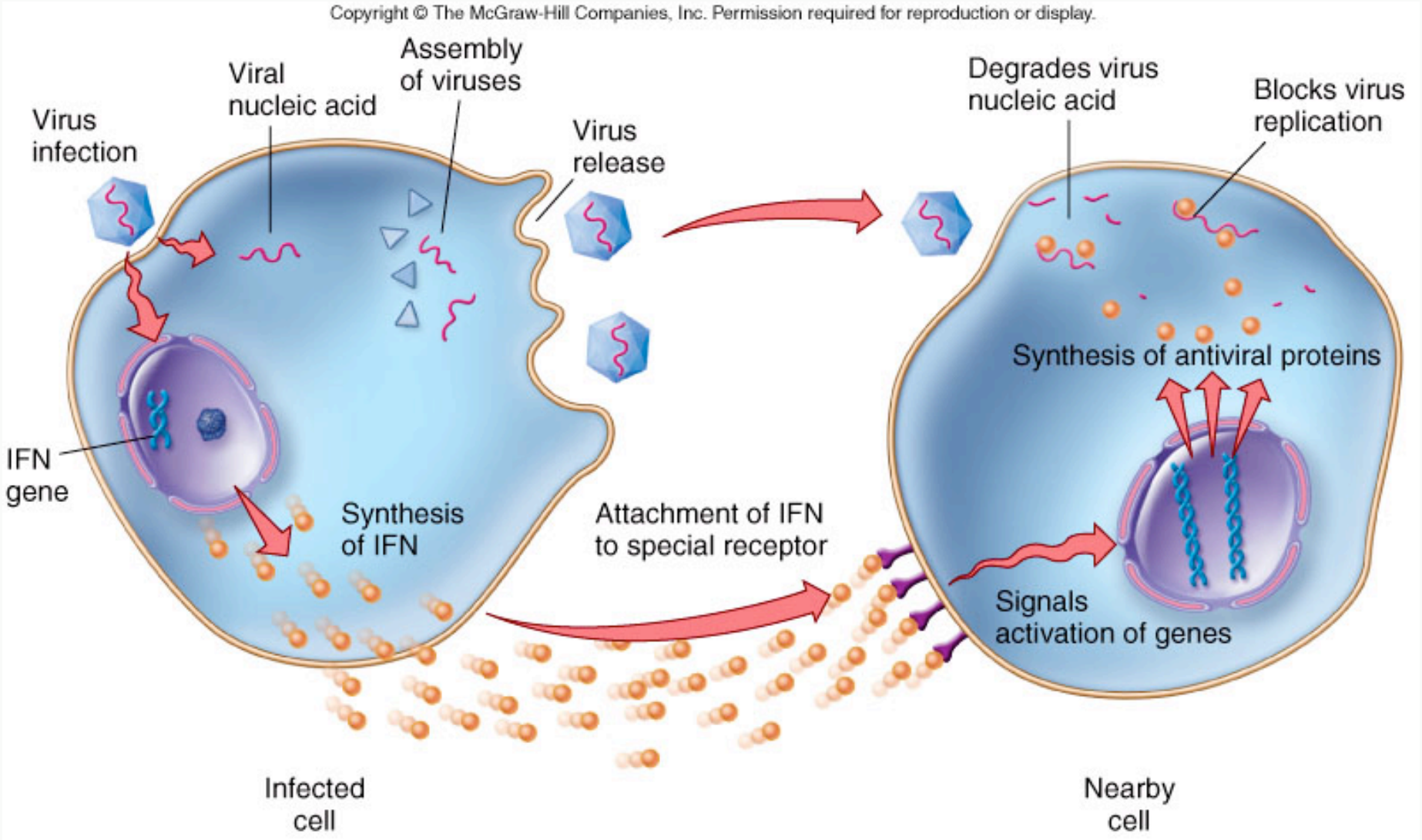


Fig. 14.20 The antiviral activity of interferon.

Other Roles of Interferon

- Activates and instructs T and B cell development
- Activates macrophages
- Inhibits tumor cell growth

Complement

- Consist of 26 blood proteins
- Produced by liver hepatocytes, lymphocytes, and monocytes

Pathways

- Classical
  - activated by the presence of antibody bound to microbes
- Lectin
  - activated when a host serum protein binds a particular sugar in the wall of fungi and other microbes
- Alternative
  - activated when complement proteins bind to cell wall or surface components of microbes

The three complement pathways, their activators, and the complement proteins involved.

TABLE 14.1 Complement Pathways

Pathway	Activators	Host Components That Initially Bind	Complement Proteins Involved
Classical (Rapid, efficient)	Complement-fixing antibodies (IgG, IgM) (sometimes microbe surface components)	C1 complex	C1 complex C4 C2 C3
Lectin	Mannans	Mannose-binding lectin	C5 C6 C7 C8 C9 Membrane Attack Complex
Alternative (Slower, less efficient)	Bacterial or fungal cell wall Viruses Parasite surfaces	C3	C3 Factor B Factor D Properdin

Table 14.1 Complement pathways

Stages

- Initiation
- Amplification and cascade
- Polymerization
- Membrane attack

The classical pathway begins with C1 components binding to antibodies, and ends by puncturing small pores through the membrane, leading to lysis.

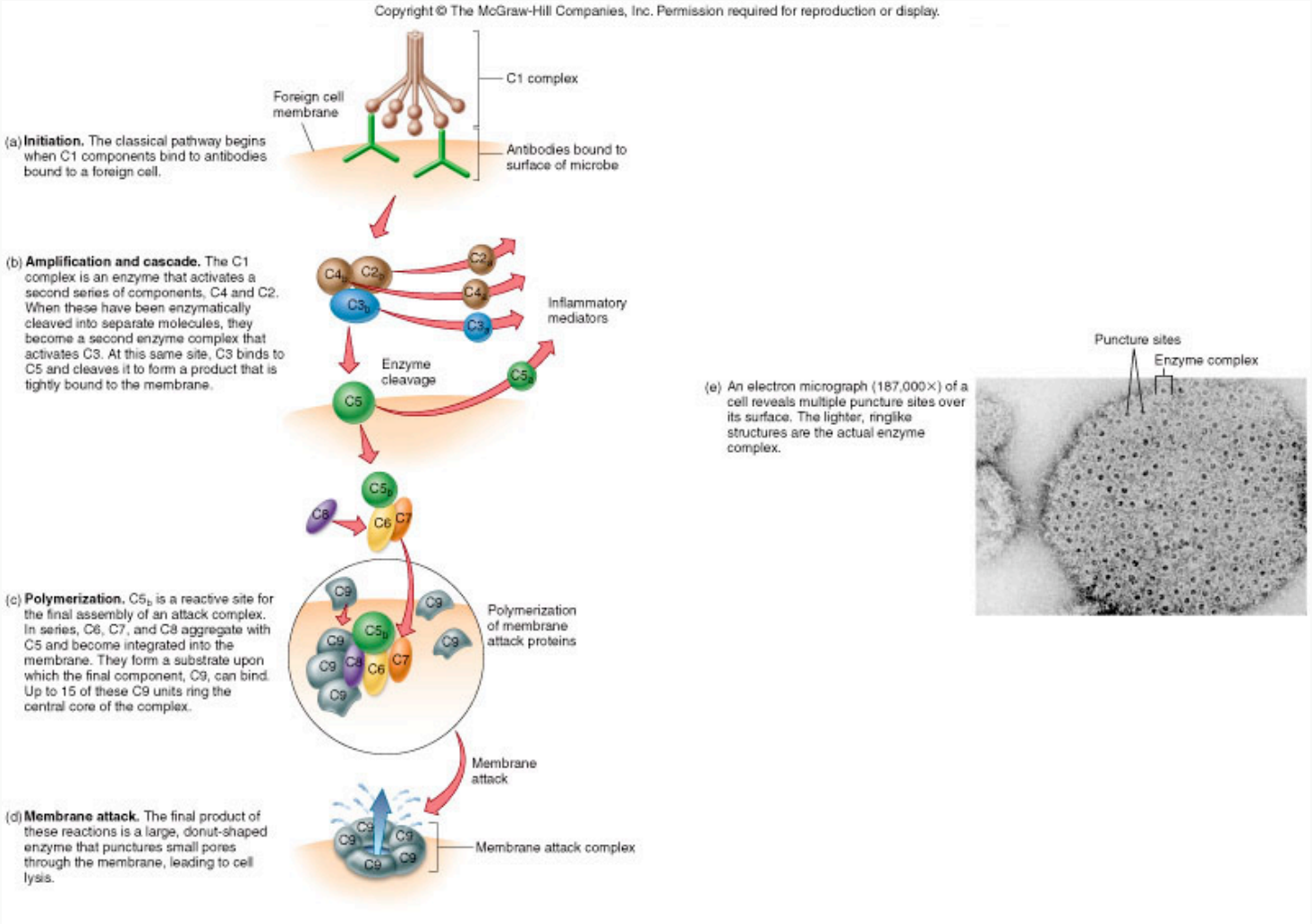


Fig. 14.21 Steps in the classical complement pathway at a single site.

Summary: Complement

- Different activators
- Different inflammatory mediators
- Formation of membrane attack complex
- Perforation and lysis of cells

Lecture 21 & 22 - Chapter 15

Third line of Defense

(Specific immunity is a complex system of immune cells interacting against antigens)

Adaptive immunity (IR)

(mediated by B- & T-lymphocytes)

- Specificity
- Tolerance
- Memory

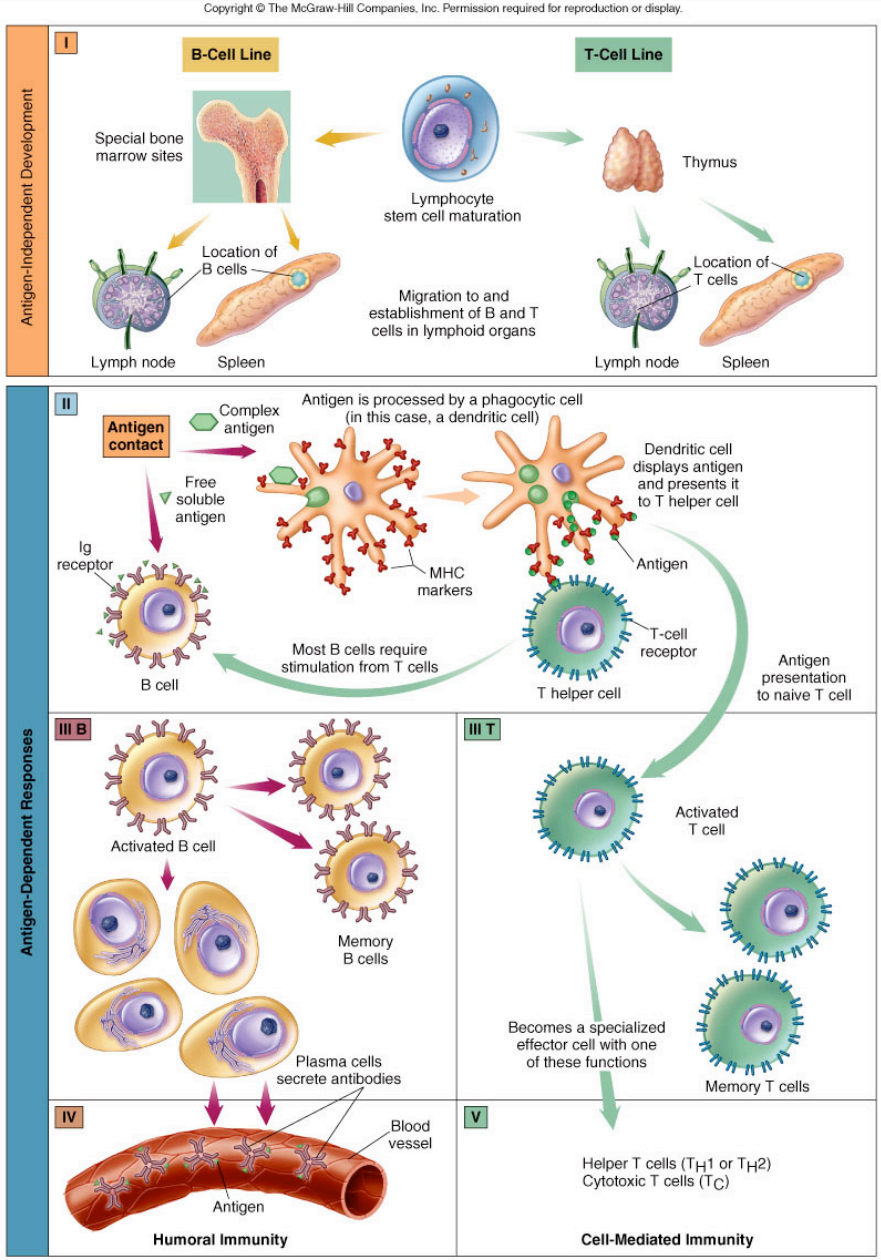


Fig. 15.1 Overview of the stages of lymphocyte development

Markers

- Host cells surface proteins (glycoproteins) confer **specificity** and **tolerance**
- Role – aid in detection, recognition, and communication
- Lymphocyte cells use receptors to distinguish between host cell surface proteins that display “self” and “non-self” in various ways.

Mature T and B cells migrate to the lymphoid tissue, where they encounter antigens.

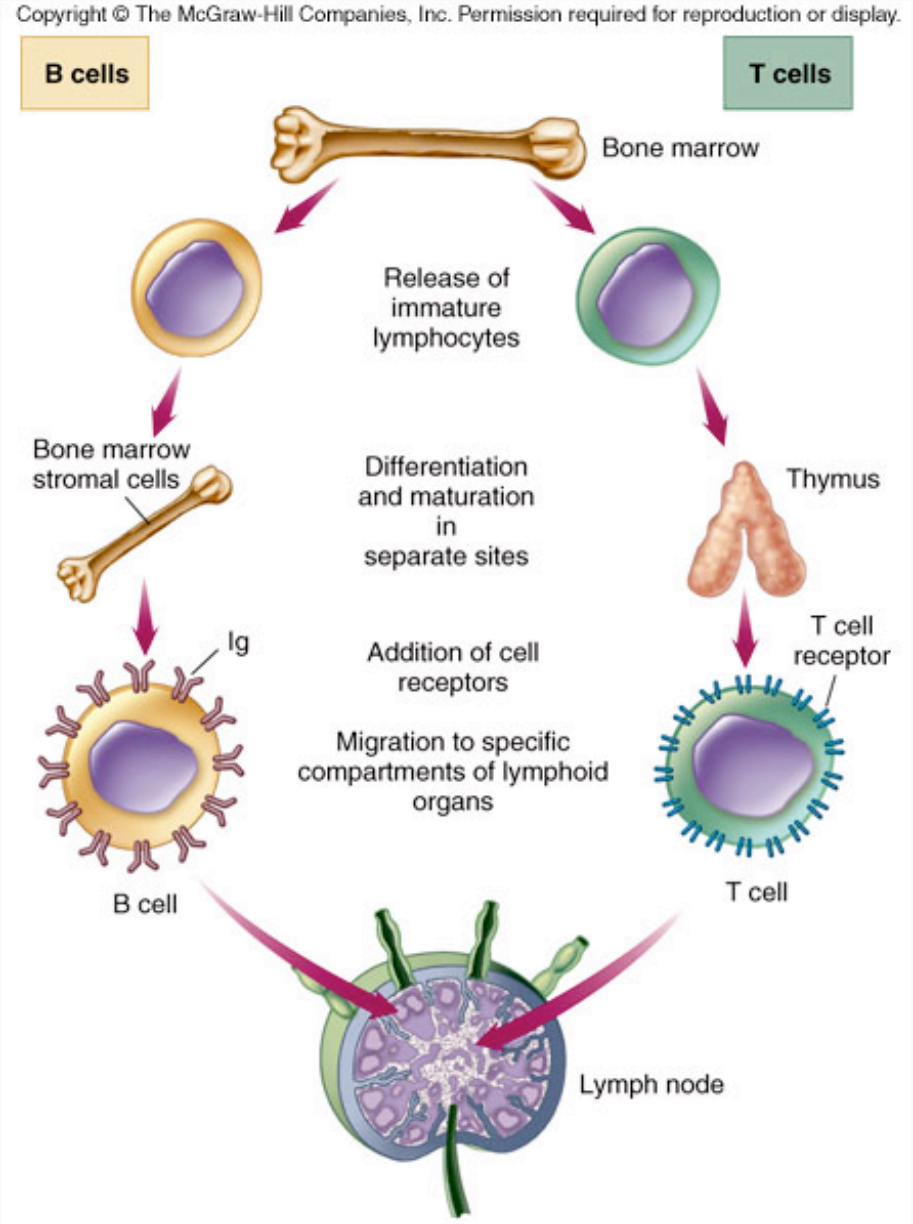


Fig. 15.4 Major stages in the development of B and T cells.

Lymphocyte Receptors

- Present on B and T cells
  - Have Variable & Constant regions
  - Act as dimers
- **B cell receptors:** Immunoglobulins
  - Light chain & Heavy chain
  - Secreted immunoglobulins (Igs) are called antibodies
- **T cell receptors:** only dimer of one chain

The structure of a receptor on B cells.

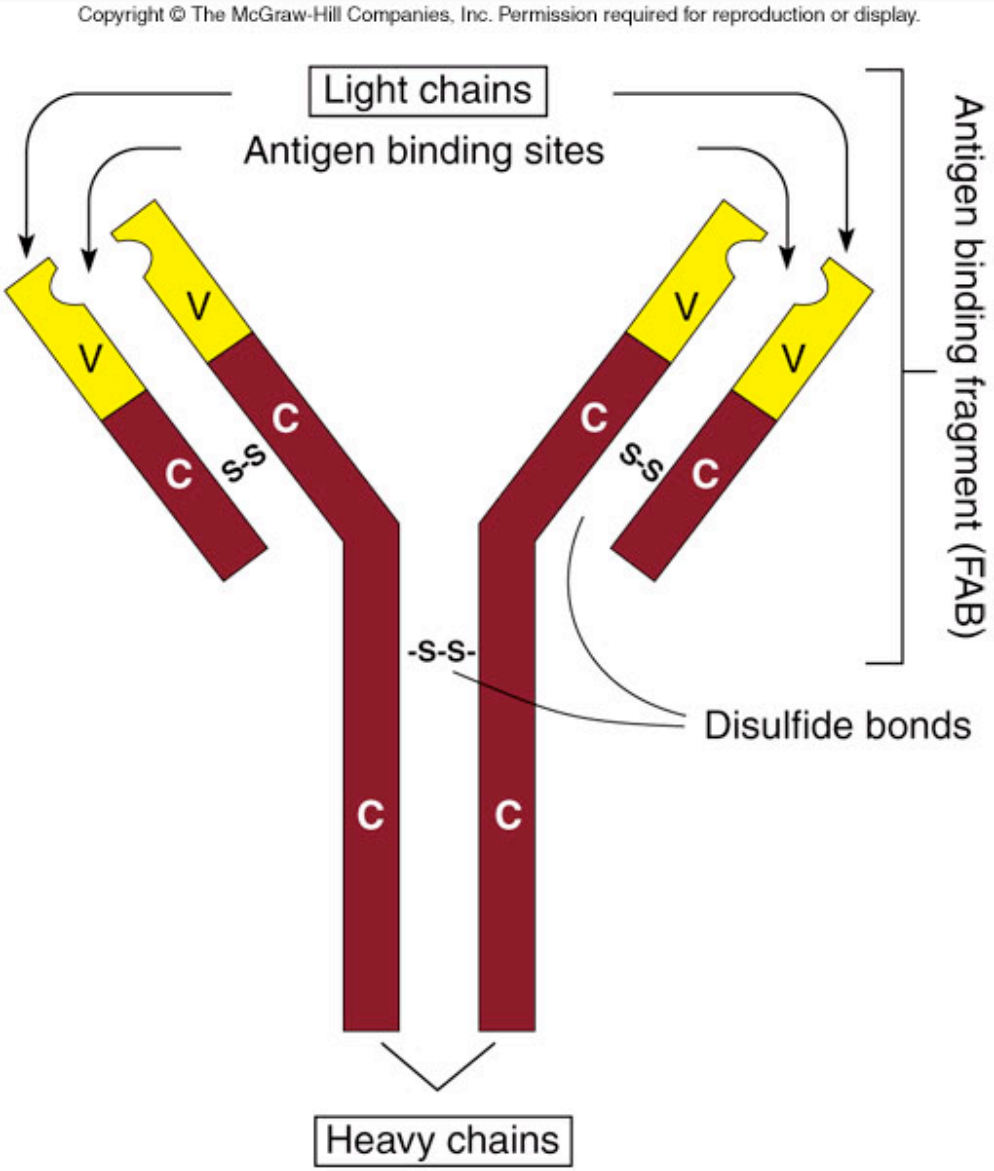


Fig. 15.5 Simplified structure of an immunoglobulin molecule on the surface of B cells.

The structure of the receptor on T cells.

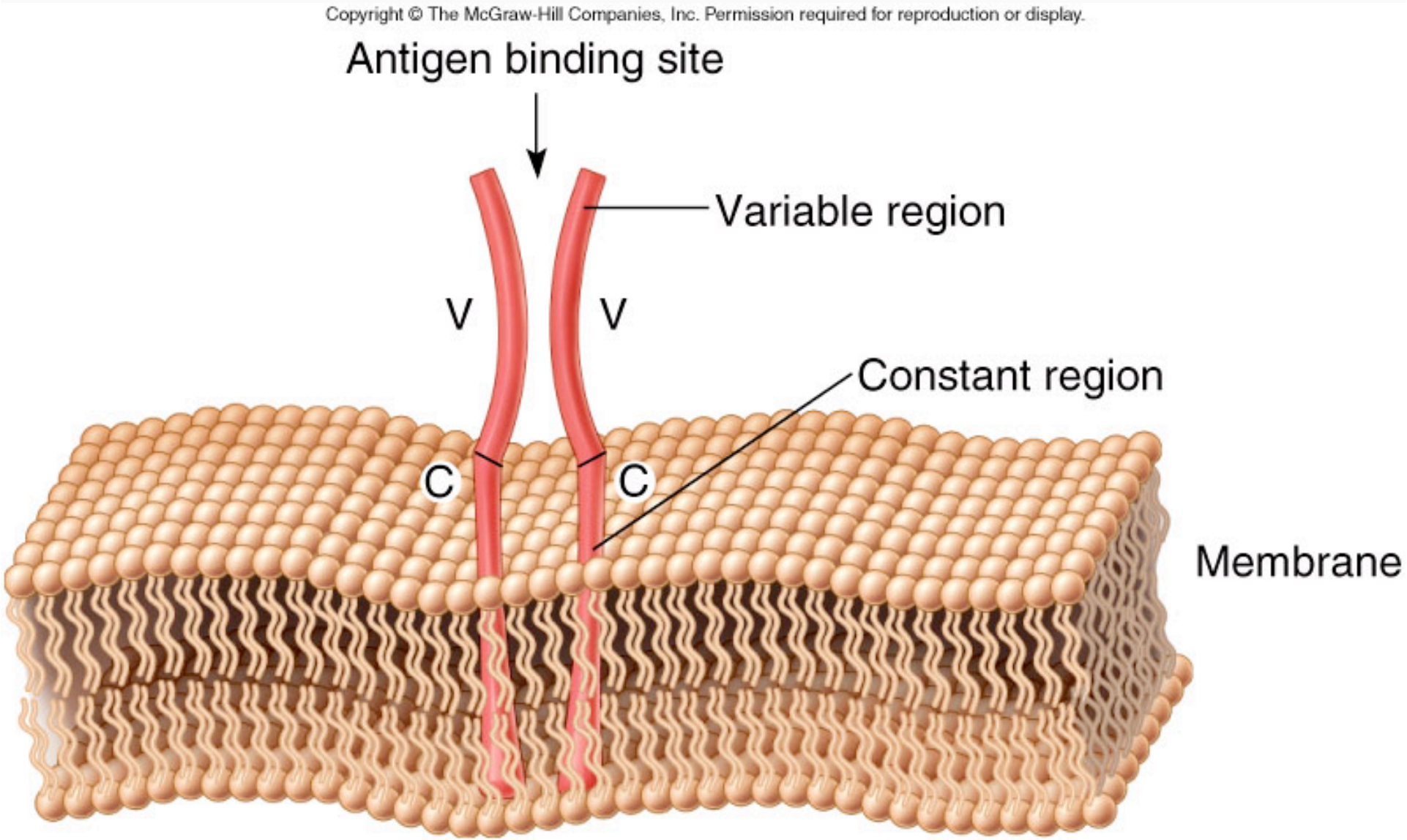


Fig. 15.6 Proposed structure of the T cell receptor for antigen.

Major histocompatibility complex (MHC)

- Glycoproteins (surface proteins)
- In humans – “Human leukocyte antigen” (HLA) is an old term for the MHC
- 3 Classes of MHC

Classes of MHC

- Each individual has a unique MHC profile
  - because of the expression of a particular combination of MHC genes
- **Class I** – all nucleated host cells
- **Class II** – only antigen-presenting cells (macrophages, dendritic cells, B-cells)

Antigen presenting cells (APC)

- Macrophages, dendritic cells and B -cells
  - process and present antigen in association with MHC (class) II
  - Interact with T-cell TCR/CD4 receptor complex, which recognizes antigen/MHC II

The Class I and II MHC of humans are surface glycoproteins.

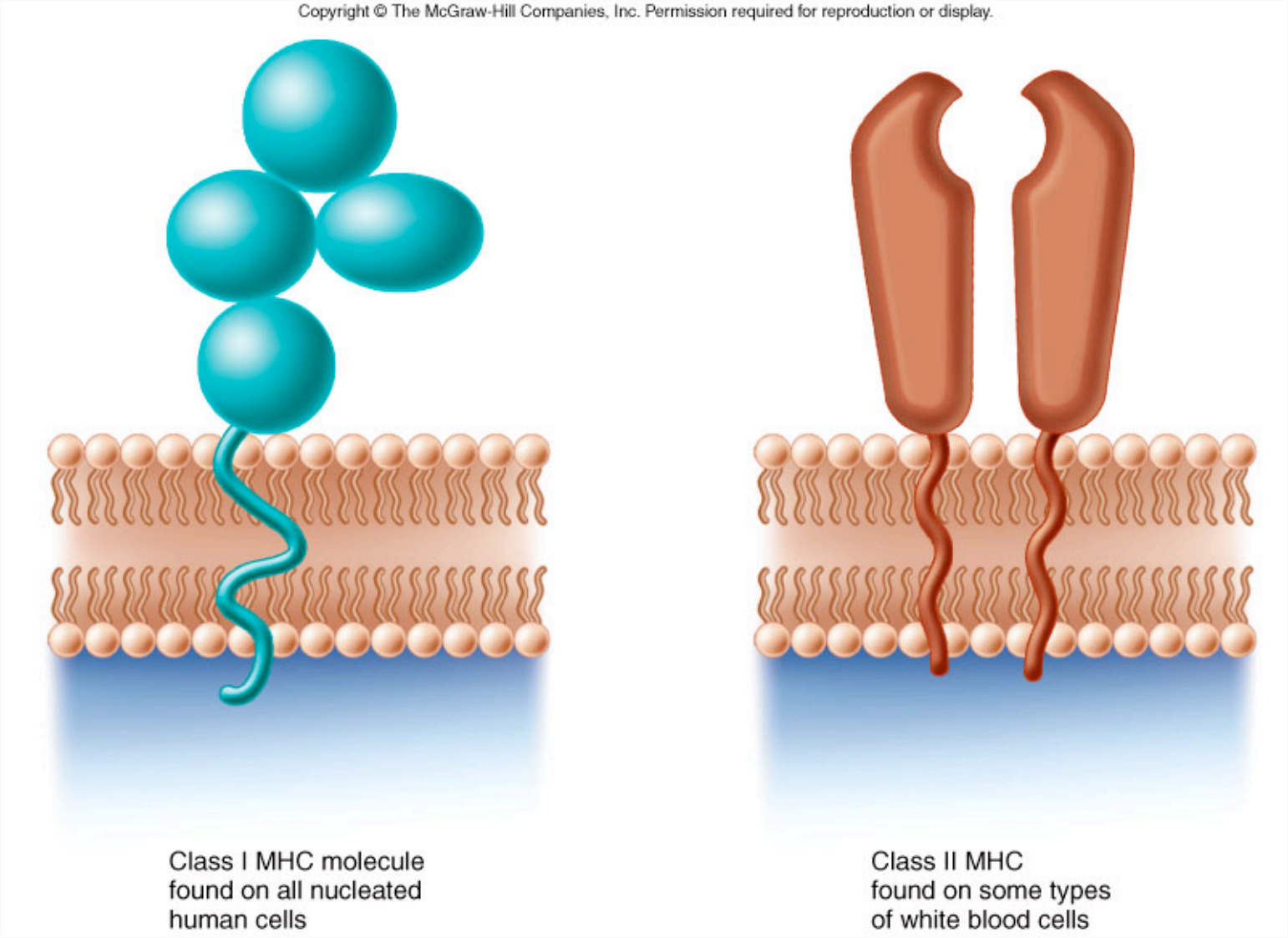


Fig. 15.2 The human major histocompatibility complex, MHC.

Antigens

- Foreign material
- Size and shape
- Alloantigens
- Superantigens

Foreign material

- Proteins and polypeptides
  - enzymes, cell surface proteins, hormones, exotoxins
- Glycoproteins
  - blood cell markers
- Nucleoproteins
  - DNA complexed to proteins
- Lipids
  - cell membranes
- Polysaccharides
  - capsules, LPS

Size and shape

- **Antigen** is called an **Immunogen** when IR elicited (means size is usually greater than 1000 daltons)
- **Antigen** is not called an **Immunogen** when no IR elicited (means size is usually less than1000 daltons)
- Proteins are better immunogens than polysaccharides
- **Epitope**
  - portion of the antigen (including immunogen) recognized by receptor molecule (Ig).
- **Hapten**
  - antigens that are too small to elicit an IR but can do so when they associate with a carrier protein molecule

A hapten can complex with a larger carrier protein in order to stimulate an immune response.

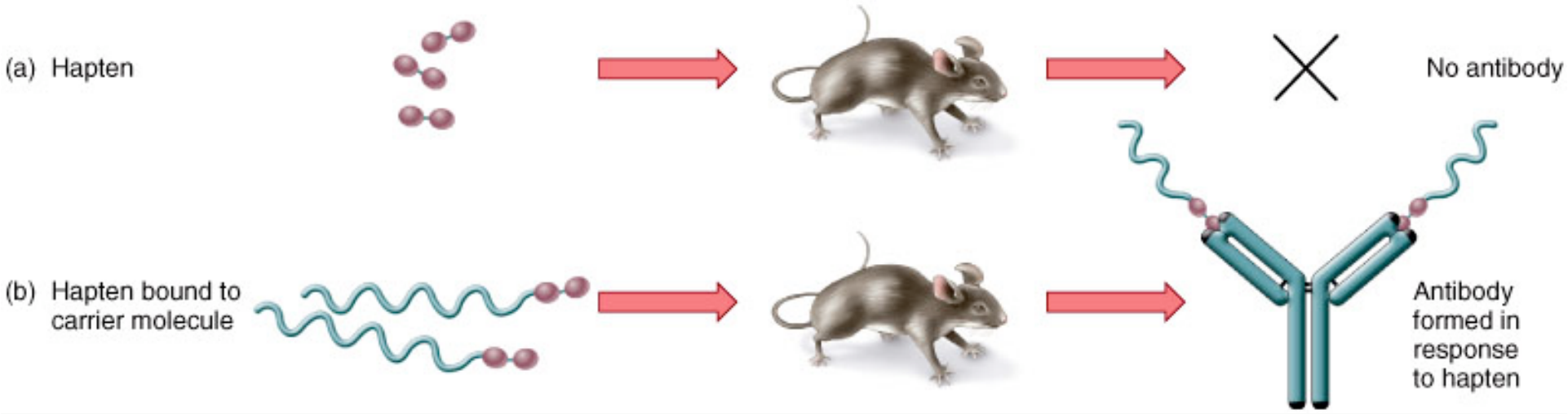


Fig. 15.8 The hapten-carrier phenomenon.

Alloantigens

- Cell surface markers that occur in some members of the same species
  - Blood typing (important for transfusion)
  - MHC profile (important for organ grafting)

Superantigen

(bind to MHC II and TCR in specific way and bypass the stepwise activation of T cells)

- Bacterial toxins (i.e., TSST)
- T-cell activation is much greater than by normal antigens
- Massive release of cytokines
- Results in toxic shock syndrome and some autoimmune diseases

Antibody (soluble B-cell receptor)

- Activated B cells (plasma cell) produce
  Immunoglobulin (Ig) or antibody
- Structure
  - Four polypeptides
  - Connected by disulfide bonds
  - Antigen binding fragment (Fabs)
  - Crystallizable fragment (Fc)
- Classes

Fab (function: antigen-binding)

- Variable (N-terminal of the heavy and light chains)
- Binds to the antigenic determinant
- Swiveling enables more efficient
- Held together by disulfide bonds

Fc (function: constant)

- Constant (C-terminal of heavy chain)
- Recognized by macrophages
- Anchors memnrane-bound Ig to lymphocyte
- Held together by disulfide bonds
- Responsible for **class** identification

The complete structure of an antibody “monomer.”

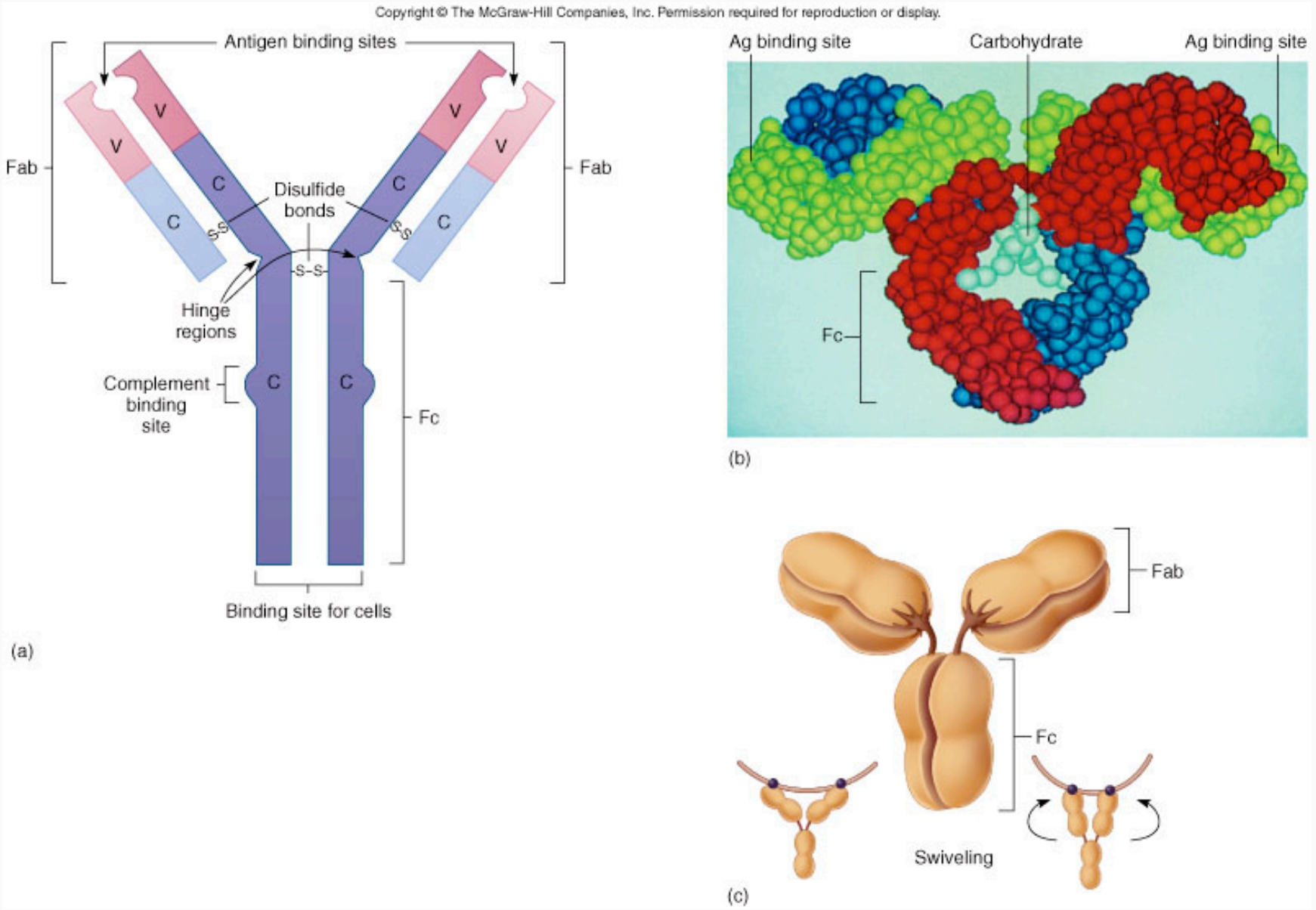


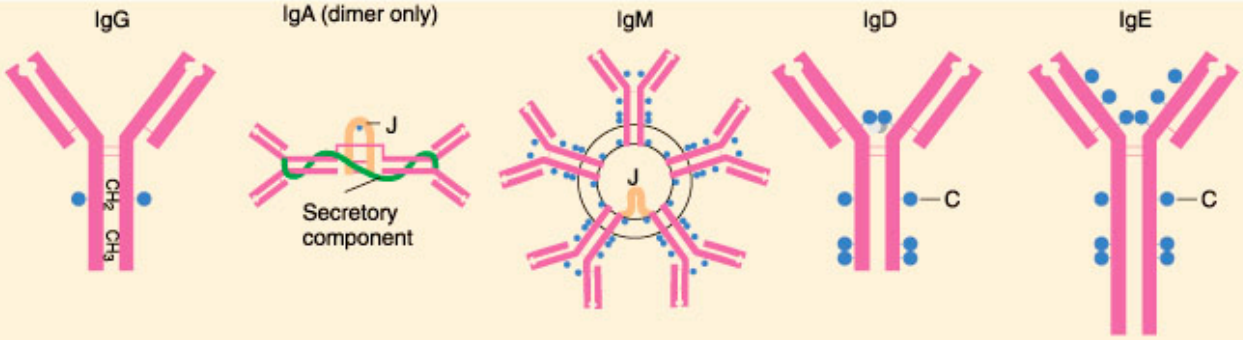
Fig. 15.11 Working models of antibody structure.

5 Classes of Igs

- based on the Fc fragment of Ig
  - IgM
  - IgG
  - IgD
  - IgA
  - IgE

The characteristics of the different immunoglobulin classes.

TABLE 15.2 Characteristics of the Immunoglobulin (Ig) Classes



	Monomer	Dimer, Monomer	Pentamer	Monomer	Monomer
Number of Antigen Binding Sites	2	4 2	10	2	2
Molecular Weight	150,000	170,000–385,000	900,000	180,000	200,000
Percent of Total Antibody in Serum	80%	13%	6%	1%	0.002%
Average Life in Serum (Days)	23	6	5	3	2.5
Crosses Placenta?	Yes	No	No	No	No
Fixes Complement?	Yes	No	Yes	No	No
Fc Binds To	Phagocytes				Mast cells and basophils
Biological Function	Long-term immunity; memory antibodies	Secretory antibody; on mucous membranes	Produced at first response to antigen; can serve as B-cell receptor	Receptor on B cells	Antibody of allergy; worm infections

C = carbohydrate.
J = J chain.

Table 15.2 Characteristics of the immunoglobulin classes.

IgM - first circulatory Ig

- Receptor for antigens on B cells
- **First to be synthesized** during primary immune response
- Circulates in the blood
- **Five monomers**, held together by a J chain
- Associated with complement fixation and opsonization

IgG - major circulatory Ig

- **Monomer**
- **Primary response** antibody
- Memory cell response
- **Most prevalent** in tissue fluid and blood

IgD - minor circulatory Ig

- Receptor for antigens on B cells
- Monomer
- **Small amounts** in the serum

IgA - secreted Ig

- Monomer or dimer (secretory IgA)
- Dimer – held together by a J chain
- Secretory IgA (mucous and serous secretions)
  - Local immunity
  - Salivary glands, intestine, nasal membrane, breast, lung, genitourinary tract
- Protection for newborns

IgE - allergic Ig

- Allergies
- Parasite infections
- Fc portion binds to basophils and mast cells
  - release of chemical mediators that aid in inflammation

Antibody-antigen interactions

- Opsonization
- Agglutination
- Neutralization
- Complement fixation

A complementary fit between an antibody and antigen involves hydrogen bonds and electrostatic attractions.

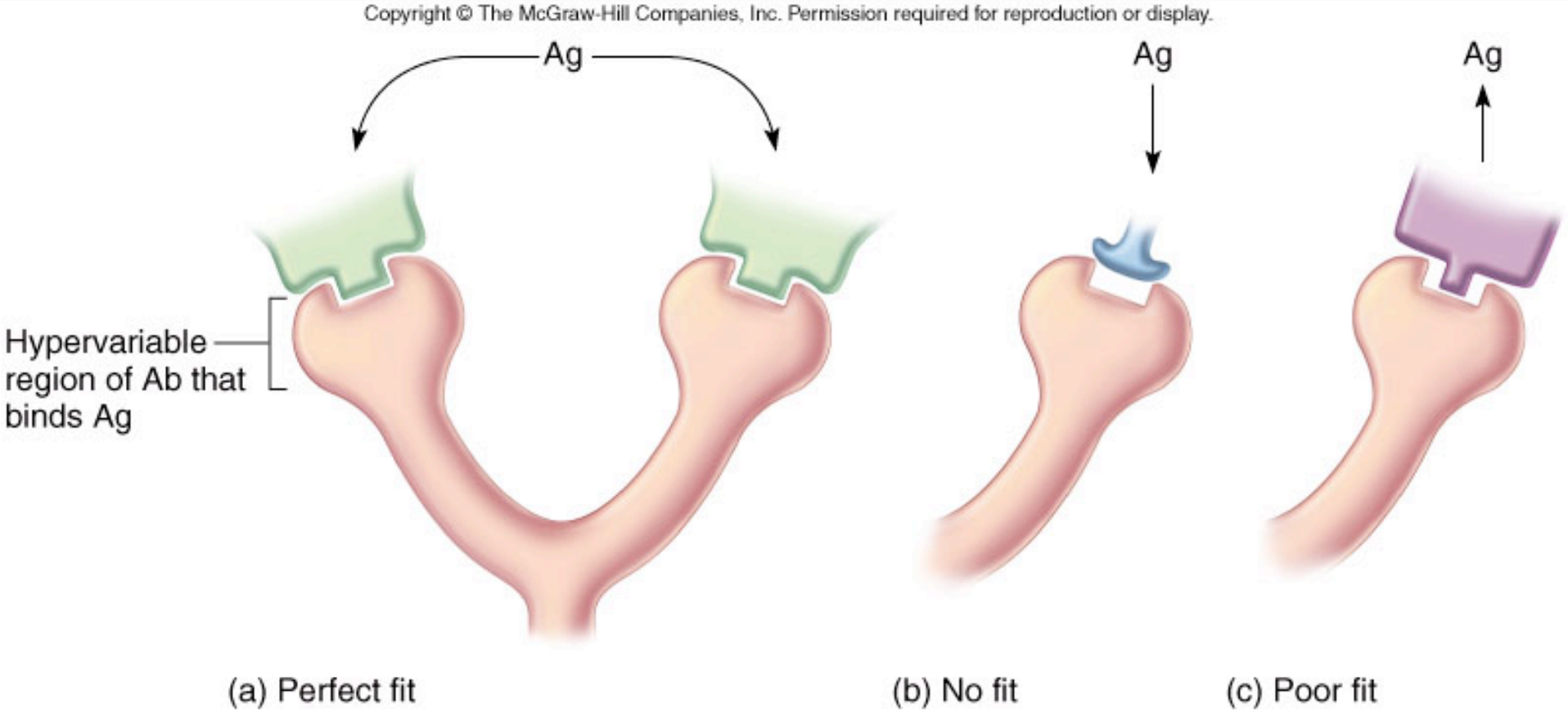


Fig. 15.12 Antigen-antibody binding

Opsonization

- Microbes or particles coated with antibodies
- Enables macrophages to recognize and phagocytoze microbe or particle

Agglutination

- Antibodies cross-link cells or particles into clumps
- Renders microbes immobile
- Enhances phagocytosis
- Principle for certain immune tests (RBC typing)

Neutralization

- Antibody binds to
  - The microbe or virus receptor
  - Antigenic site of a molecule (Eg. Exotoxin)

- Prevents further binding of microbe or toxin

Complement fixation

- Antibodies interaction with complement proteins (Eg. Classical pathway) thereby delivering the compliment to antigen.

- Lysis of microbial cell

The different functions of antibodies.

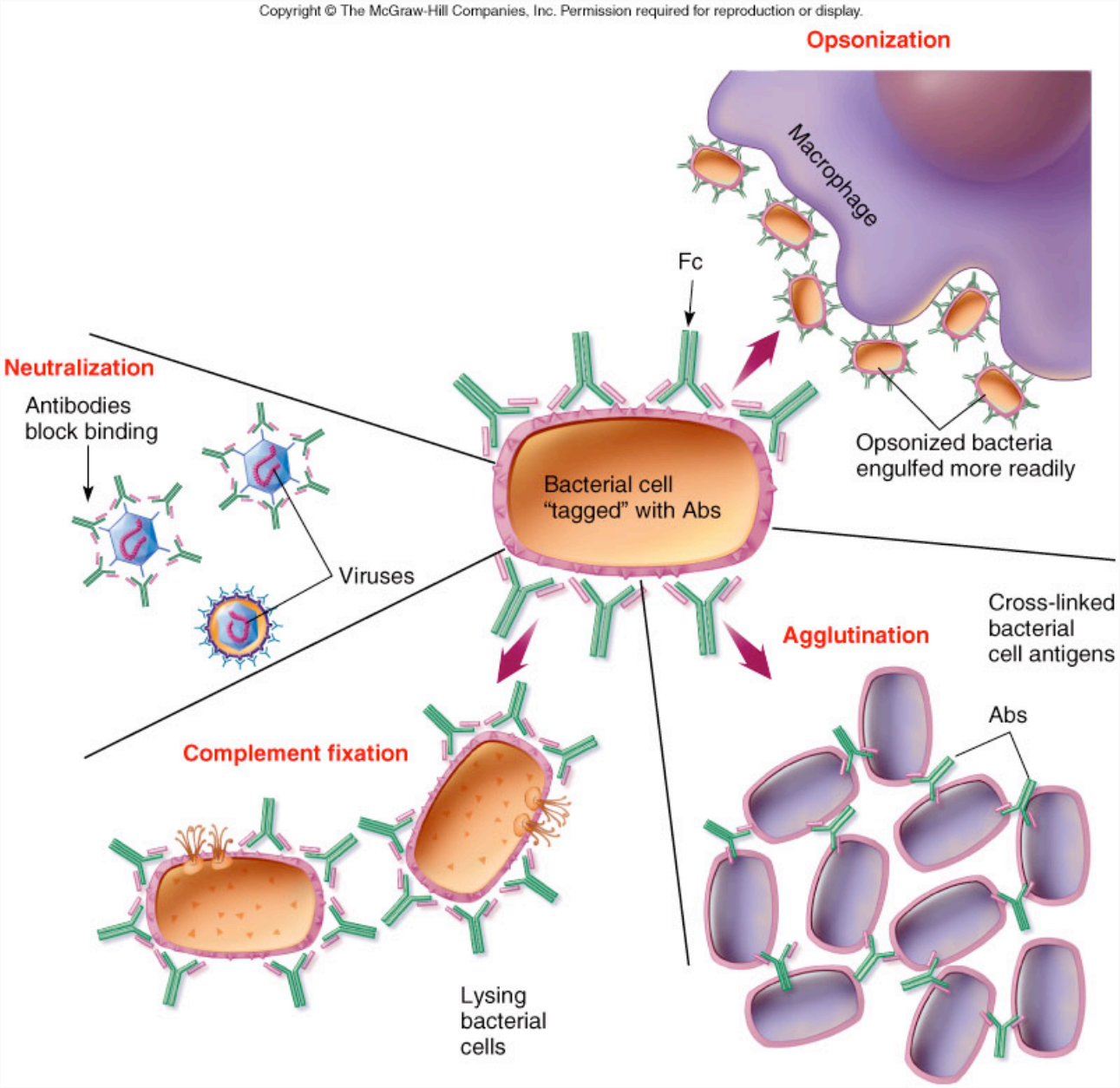
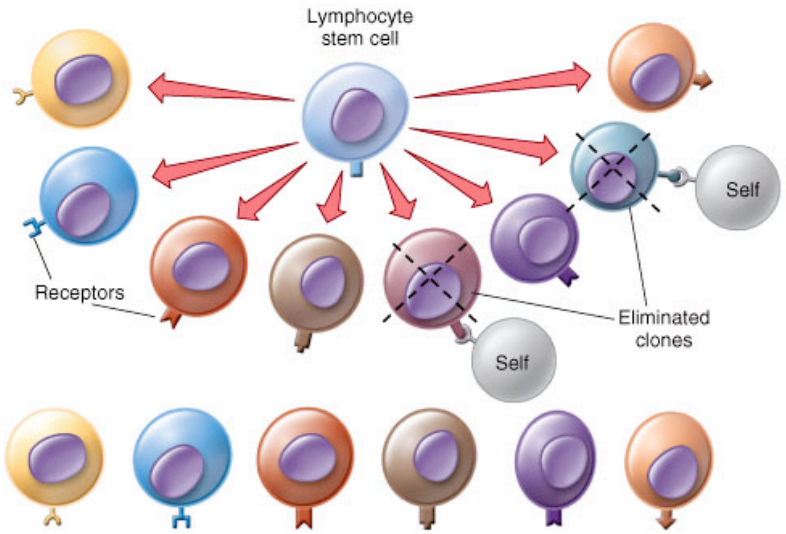


Fig. 15.13 Summary of antibody functions

Clonal selection

- The synthesis of varied receptor types
  - approximately 500 genes can undergo rearrangement
  - Not all individuals have all possible antigen-specificities (~10^{14})at any given time
  - eventually one clone recognizes an antigen and expands (proliferates)
- Clone
  - each mature lymphocyte possesses a single combination or receptor specificity
- Expansion
  - a single cell is stimulated by antigen recognition
- Clonal deletion
  - cells that recognize “self” are removed



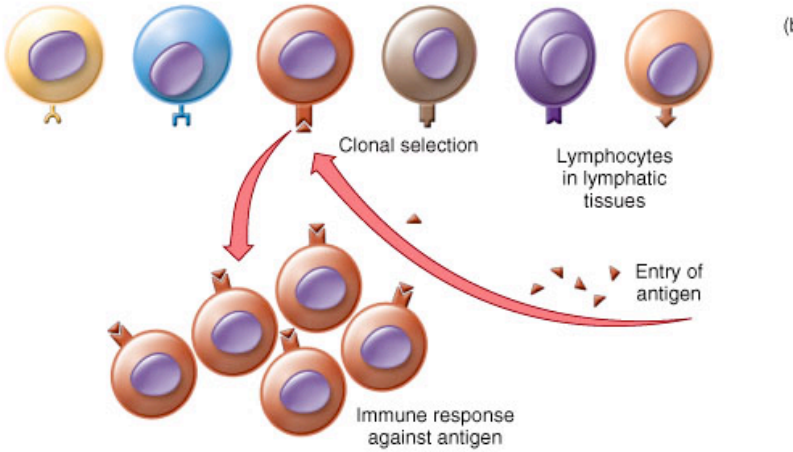
(a) **Antigen-Independent Period**

1. During development of early lymphocytes from stem cells, a given stem cell undergoes rapid cell division to form numerous progeny.

During this period of cell differentiation, random rearrangements of the genes that code for cell surface protein receptors occur. The result is a large array of genetically distinct cells, called clones, each clone bearing a different receptor that is specific to react with only a single type of foreign molecule or antigen.

2. At this same time, any lymphocyte clones that develop a specificity for self molecules and could be harmful are eliminated from the pool of diversity. This is called immune tolerance.

3. The specificity for a single antigen molecule is programmed into the lymphocyte and is set for the life of a given clone. The end result is an enormous pool of mature but naive lymphocytes that are ready to further differentiate under the influence of certain organs and immune stimuli.



(b) **Antigen-Dependent Period**

4. Lymphocytes come to populate the lymphatic organs, where they will finally encounter antigens. These antigens will become the stimulus for the lymphocytes' final activation and immune function. Entry of a specific antigen selects only the lymphocyte clone or clones that carries matching surface receptors. This will trigger an immune response, which varies according to the type of lymphocyte involved.

Fig. 15.3 Overview of the clonal selection theory of lymphocyte development and diversity.

T-cell development

- Occurs in Thymus gland (later bone in marrow)
- 2 steps of selection:
  - Positive selection: Specificity (TCR-CD4/8 and MHC I/II;)
  - Negative selection: Tolerance (TCR - self-MHC)
- Mature tolerant T-cells released into blood and lymph systems

B-cell development

- Have Igs as B-cell receptors (IgM, IgD)
  - **Specificity**
- Need to be activated by receptor-antigen interaction (equal to antibody-antigen interaction) to:
  - produce soluble Igs
  - establish **Memory**

B-cell clones

- Process of **activation** is selection and propagation of a single B-cell (then called a **clone**) to develop into a mature Plasma Cell for the synthesis of antibodies. If only one B-cell is selected, monoclonal antibodies are produced.
- A monoclonal antibody possess only one single specificity for a given antigen

B-cell Activation

- B-cell encounters and binds antigen
- B-cell processes antigen, presents it with MHC I & II
- MHC II interacts with TCR + CD4, followed by instruction by chemical mediators (interleukins)
- Transmission of signal to the nucleus
- B cell changes into an active cell called plasma cell (lots of ribosomes, enhanced cell division)
- Clonal expansion and memory cell formation
- Antibody production and secretion

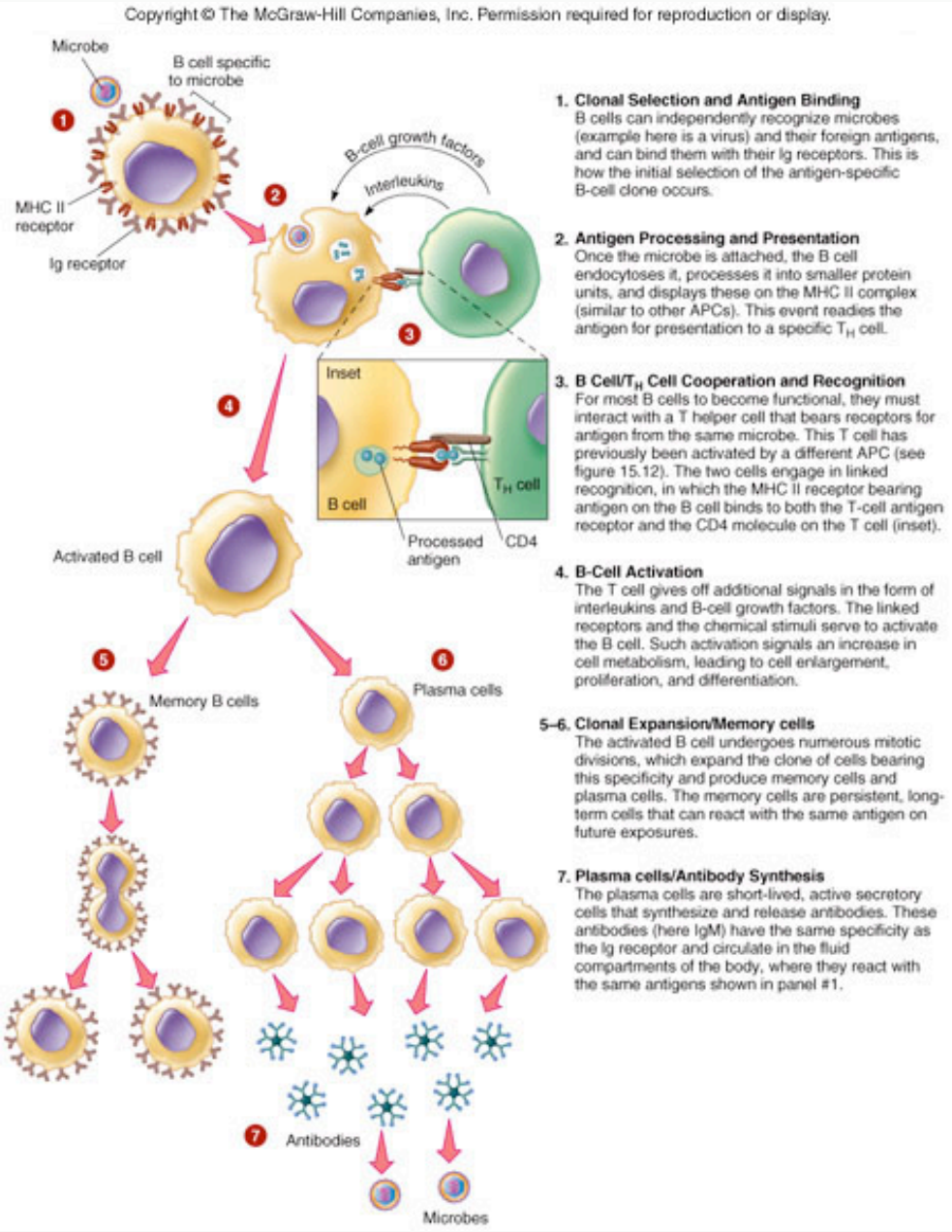


Fig. 15.10 Events in B-cell activation and antibody synthesis.

Responses to antigens

We distinguish 2 responses to antigens

- Primary
- Secondary

Primary Response

- First exposure to antigen
  - Latent period
    - Lack of antibody synthesis
  - Synthesis of antibodies
    - Level of antibodies (titer)
    - IgM first
    - Followed by IgG, and some IgA and IgM

Secondary Response

- Re-exposure to the same antigen (Anamnestic response)
- Antibody synthesis, titer, and length of antibody persistence is rapid and amplified
  - Primarily due to memory cells

If used for medical purposes, what is this called?

The stages of primary and secondary responses to antigens.

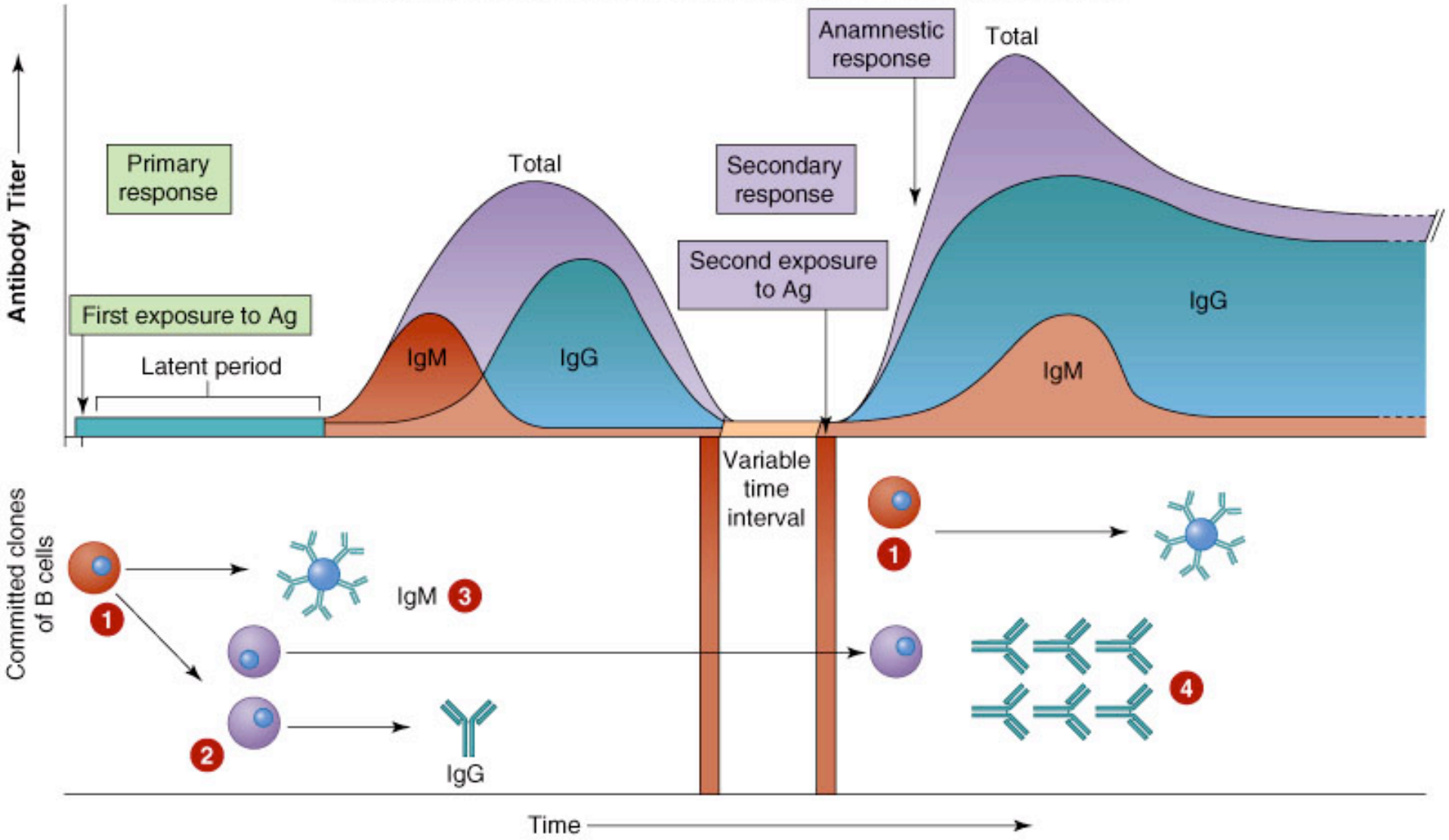


Fig. 15.15 Primary and secondary responses to antigens.

T cell clones

- Activation
- Types

Cell-mediated immunity

- Direct involvement of T cells
- Produce and react to cytokines
- Activated simultaneously with B cell activation
- Subset of T cells have unique CD receptors (CD4, CD8)

Activation

- Activated T cells prepare for mitosis
- Effector cells or types (T_H; T_C) are being produced
- Memory cells are produced
- Armed effector cells are produced

Types

- Helper T cells (T_H)
- Cytotoxic T cells (T_C)

T_H

- Regulate immune reactions to antigens by releasing cytokines
- TCR-CD4 co-receptor complex
- Type of cytokine will determine subset of T_H
  - T_{H1} (inflammatory T cells, delayed type hypersensitivity)
  - T_{H2} (Helper cells involved in B cell differentiation)
- Cytokines also activate macrophages
- Most prevalent in the blood

T_C

- Binds and lyses cells
  - virus or microbe-infected cells, foreign cells, cancer cells
- TCR-CD8 co-receptor complex
- “Perforins” – punch holes in the membrane
- “Granzymes” – degrade proteins
- Natural killer (NK) cells
  - related to T_C
  - attack only virus infected cells and cancer cells

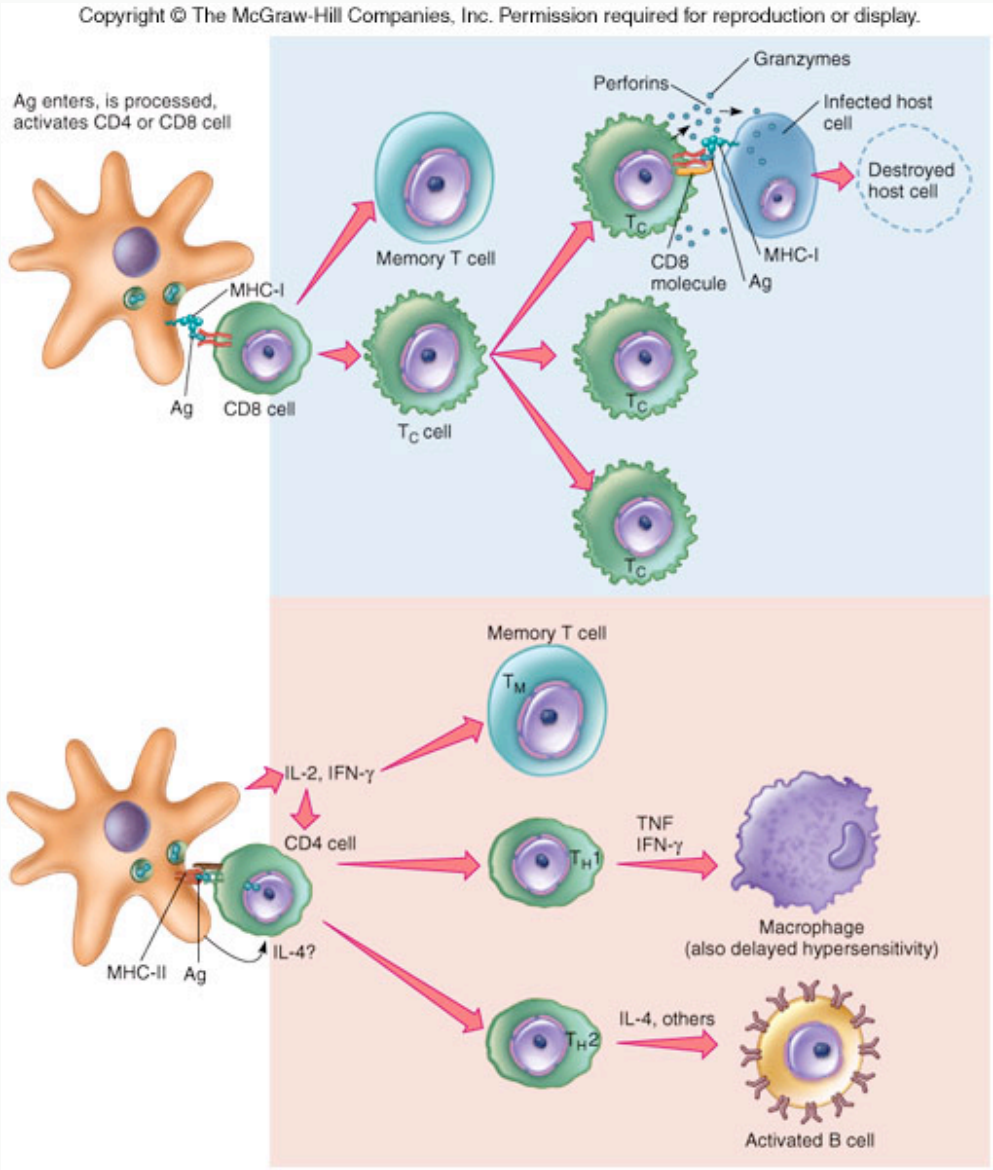


Fig. 15.16 Overall scheme of T-cell activation and differentiation into different types of T cells.

TABLE 15.3 Characteristics of Subsets of T Cells

Types	Primary Receptors on T Cell	Functions/Important Features
T helper cell 1 (T_H1)	CD4	Activates the cell-mediated immunity pathway, secrete tumor necrosis factor and interferon gamma, also responsible for delayed hypersensitivity (allergy occurring several hours or days after contact)
T helper cell 2 (T_H2)	CD4	Drives B-cell proliferation, secrete IL-4, IL-5, IL-6, IL-10; can dampen T_H1 activity
T cytotoxic cell (T_C)	CD8	Destroys a target foreign cell by lysis; important in destruction of complex microbes, cancer cells, virus-infected cells; graft rejection; requires MHC I for function

Table 15.3 Characteristic of subsets of T cells.