The Immune Response and immune system

The immune system (IS) maintains the integrity of the organism; recognizes harmful from harmless and protects the organism from ex- and endogenous harmful substances. It belongs together with the nervous system and the endocrine system between the regulatory systems.

Basic concepts:

- Immunity: protect the organism against pathogenic microorganisms and their toxins.
- Auto-tolerance: recognizes its own tissue.
- Immune surveillance: recognizes internal pollutants; removes old, damaged, mutated cells.
- Antigens (Ag): substances that the IS recognizes and reacts to.

Communication within the immune system

Communication between cells of the immune system occurs through signaling molecules:

- as direct interactions of molecules in membranes,
- through secreted molecules, including:
  - cytokines - protein molecules,
  - arachidonic acid derivatives (eicosanoids) - prostaglandins, leukotrienes, thromboxanes,
  - NO,
  - and oth.

Typical properties of the immune system

- Individual signals usually does not respond (is necessary the presence of costimulatory signals, otherwise usually leads to attenuation)
- Signal amplification (the signal is amplified over the signal path)
- The presence of signal transduction systems (termination of the immune response)
- Cell proliferation (cell number changes as needed)
- Diffusion arrangement (high probability of encountering a stimulus) + cell migration (which allows targeted response at the site where it is needed)

Local specificity of the immune response

Immune reactions occur mainly in mesenchymal tissues. Each reaction is associated with damage to your own structures! If there is a stimulus on the mucosa, it will usually be attenuated. If something goes into the sub-ligament, it will probably be pathogenic and the response will take place (see mucosal immune system).

Immune-privileged areas are areas where some immune mechanisms are missing. Immune reactions always damage their own structures, so they are areas with low tissue regeneration capabilities (eg, CNS).

Non-specific immunity

- It recognizes dangerous from harmless by Pathogen-Associated Molecular Pattern (PAMP) - phylogenetically conserved molecules that are typical for pathogens (eg viral RNA, lipopolysaccharide).
- It works with specific immunity (it gives information about what is dangerous).

Specific immunity

- T-lymphocytes recognize only linear peptide fragments processed and presented by antigen-presenting cell (APC), in particular dendritic cells in the presence of costimulatory signals. They help cells with nonspecific immunity in killing pathogens.
- B-lymphocytes recognize native antigen and receive costimulation from T-lymphocytes.
- Autoreactive lymphocytes are eliminated.
- It responds only against dangerous stimuli (this gives information non-specific immunity and apparently tissue that is pathogen-damaged).
- It has an immunological memory (use in active immunization).

Identification of Pathogenic Patterns

Pathogens are identified based on the presence of PAMP (Pathogen-Associated Molecular Pattern) - phylogenetically highly conserved structures. Their carriers are only microorganisms and are essential for their survival. Is part of them:

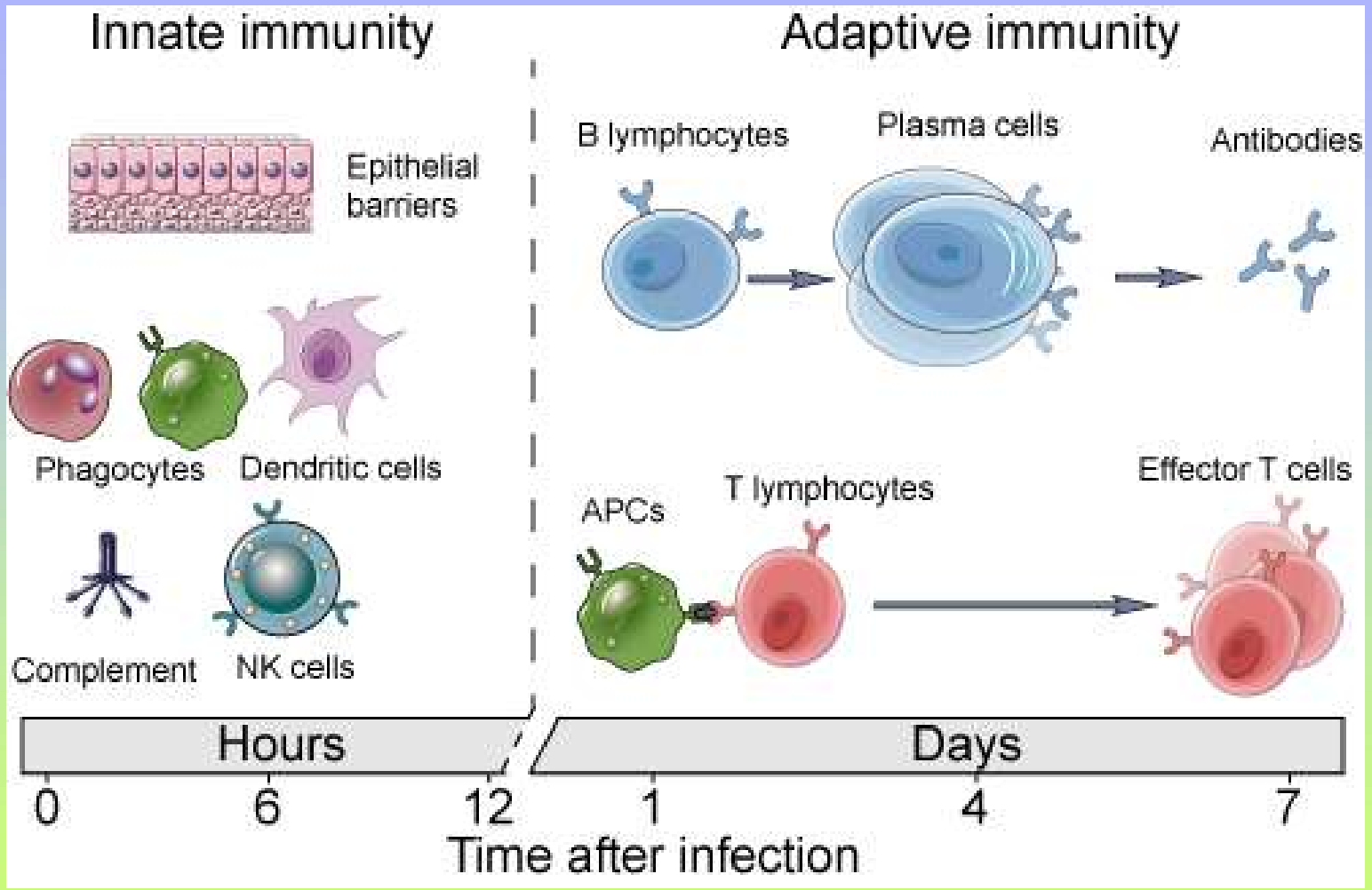
- bacterial wall - peptidoglycan, lipoteic acid, lipopolysaccharide,
- bacterial DNA - many cytosine and guanine, without methylation,
- dsRNA - viral.

- These patterns are recognized by PTH (Pathogen Pattern Receptor) = PRR (Pathogen Recognition Receptor) receptors. There are the following types:
  - secreted - opsonins (e.g., MBL) complement activation,
  - endocytic - on phagocytes, mediate phagocytosis (eg MMR), MSR (macrophage scavenger receptor) - cleans up bacterial residues),
  - signaling - activate the signaling pathway leading to cytokine production (e.g., Toll-like receptor (TLR).
- Identification of endogenous patterns

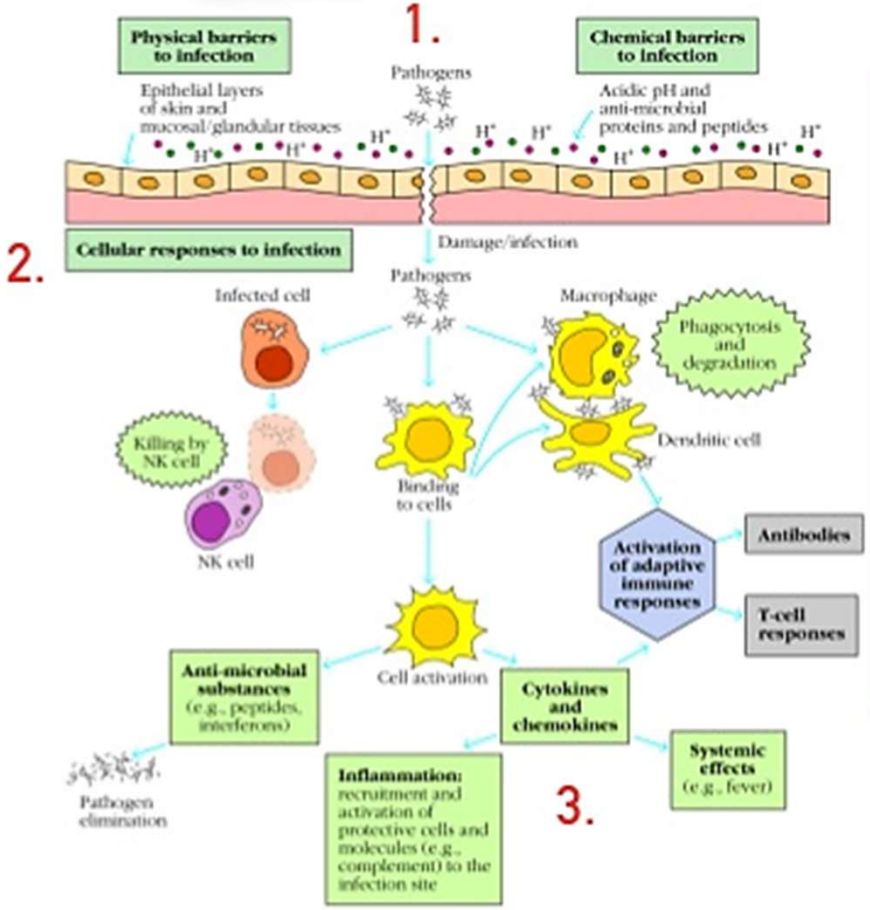
  In connection with apoptosis, APOP (Apoptotic Cell Associated Molecular Pattern) patterns, such as the phospholipids of the inner membrane of the cell membrane, are exhibited. Apoptotic Cell Receptor (ACR) receptors are recognized, producing rather anti-inflammatory cytokines.
- Antigen presentation

  Antigen Presenting Cells (APCs) absorb antigens, process them in lysosomes and present on HLA II molecules. class. Thus treated, antigens (or antigenic epitopes) are presented along with costimulatory signals to T lymphocytes.

  Note: If any cell, not just antigen presenting, is infected with an intracellular parasite, the antigen is presented on HLA class I.

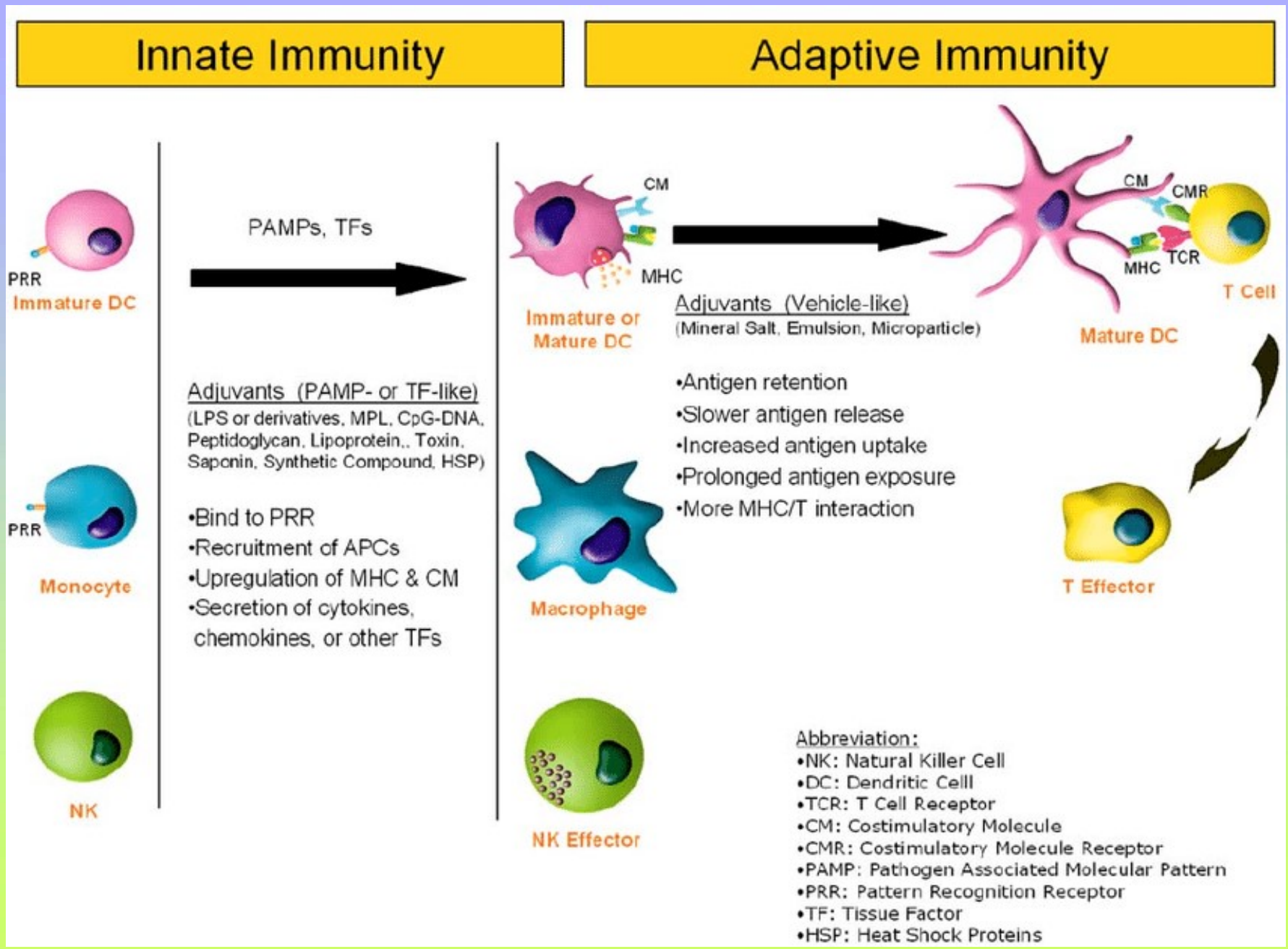

Innate immunity
Adaptive immunity
Epithelial barriers
B lymphocytes
Plasma cells
Antibodies
Phagocytes
Dendritic cells
APCs
T lymphocytes
Effector T cells
Complement
NK cells
Hours
Days
0
6
12
1
4
7
Time after infection

Component of innate immunity

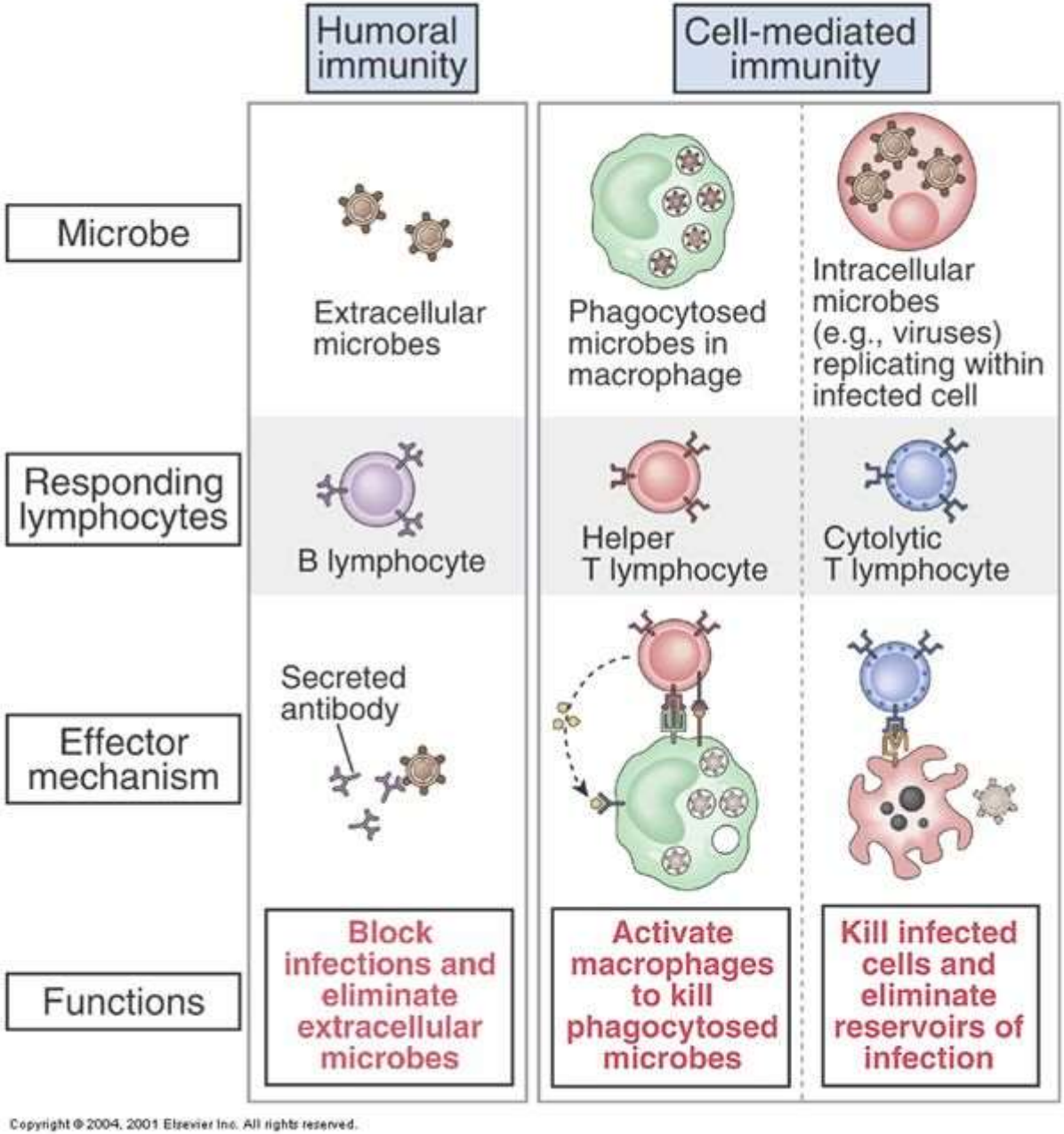


1. Anatomical barrier
   - Physical barriers
   - Chemical barriers
2. Cell
   - Phagocytic cells
   - Dendritic cell
   - NK cells, ILC
3. Soluble proteins
   - Complement
   - Cytokines, Chemokines
   - Anti-microbial substances

Kuby Immunology 7th edition.


Innate Immunity
Adaptive Immunity
PRR
Immature DC
PAMPs, TFs
CM
MHC
Immature or
Mature DC
CM
CMR
MHC
TCR
T Cell
Mature DC
Adjuvants (Vehicle-like)
(Mineral Salt, Emulsion, Microparticle)
Adjuvants (PAMP- or TF-like)
(LPS or derivatives, MPL, CpG-DNA,
Peptidoglycan, Lipoprotein,, Toxin,
Saponin, Synthetic Compound, HSP)
•Antigen retention
•Slower antigen release
•Increased antigen uptake
•Prolonged antigen exposure
•More MHC/T interaction
PRR
Monocyte
•Bind to PRR
•Recruitment of APCs
•Upregulation of MHC & CM
•Secretion of cytokines,
chemokines, or other TFs
Macrophage
T Effector
NK
NK Effector
Abbreviation:
•NK: Natural Killer Cell
•DC: Dendritic Celll
•TCR: T Cell Receptor
•CM: Costimulatory Molecule
•CMR: Costimulatory Molecule Receptor
•PAMP: Pathogen Associated Molecular Pattern
•PRR: Pattern Recognition Receptor
•TF: Tissue Factor
•HSP: Heat Shock Proteins

Types of Adaptive Immunity



The main components of the immune system

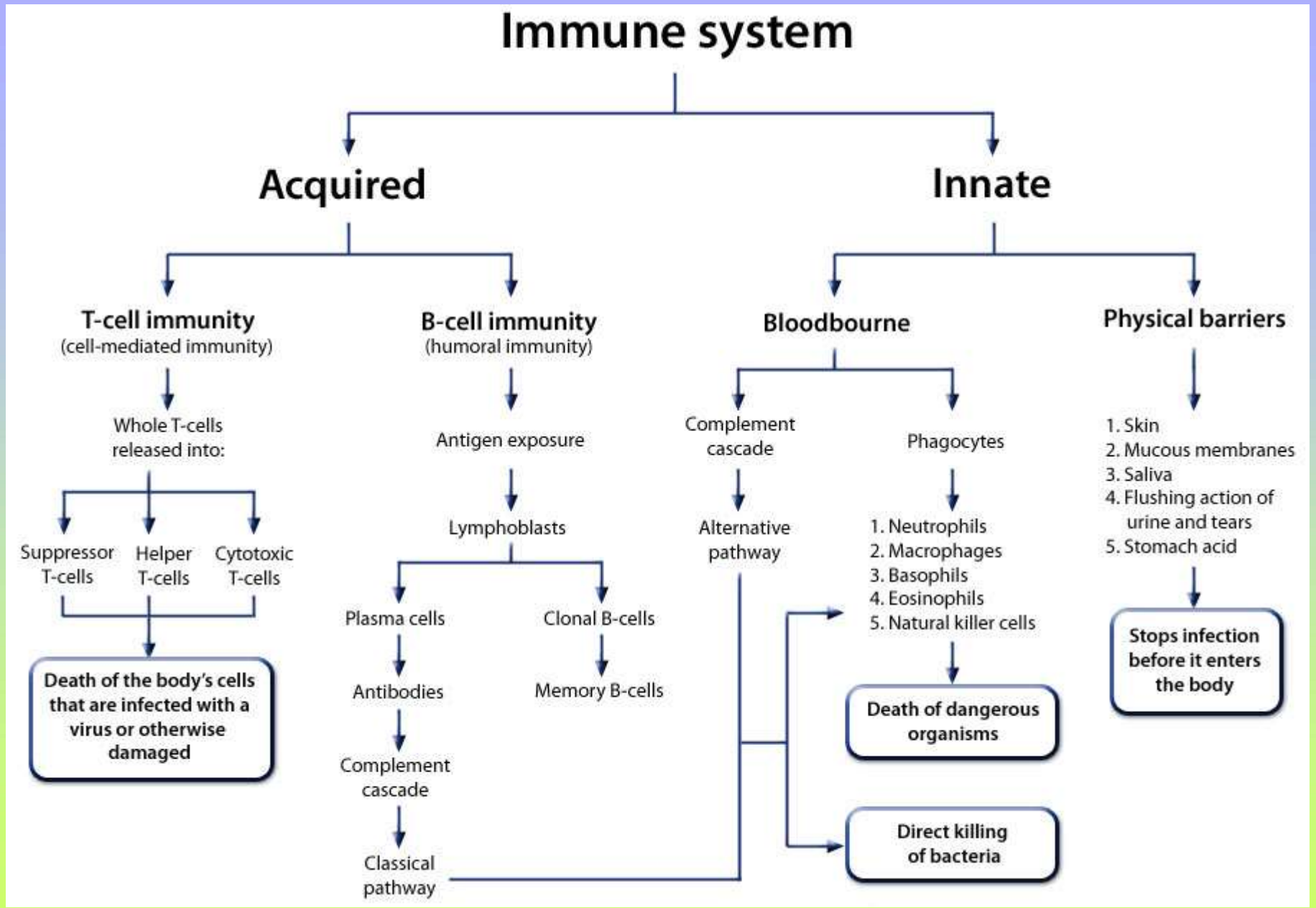
Immune reactions are ensured by different kinds of cells and molecules and their interactions.
IS cells + connective tissue cells → lymphatic tissue, lymphatic organs.
Immune system cells

Myeloid

- Monocytes (macrophages), neutrophils, basophils (mast cells), eosinophils, dendritic cells → non-specific IS component; phagocytosis, cytokine producers, soluble mediators.
- Dendritic cells, monocytes and macrophages = antigen presenting cells (APC); the basis of the antigen-specific part of IS.
- Myocytes also include erythrocytes and thrombocytes.

Lymphoid

- NK cells, lymphocytes B and T.
- The development of B-lymphocytes takes place in the bone marrow and is completed after encountering Ag in secondary lymphatic organs; the final stage is the antibody-producing plasma cells.
- Development of T-lymphocytes occurs mainly in thymus; 2 major phenotypically different subpopulations: precursors of helper cells (on CD4 receptor surface), cytotoxic cell precursors (CD8): upon aging with Ag on the surface of suitable APCs differentiate into mature effector T lymphocytes.
- The part of T and B lymphocytes, after meeting Ag, is differentiated in a memory cell responsible for immunological memory.


Immune system
Acquired
Innate
T-cell immunity
(cell-mediated immunity)
B-cell immunity
(humoral immunity)
Bloodbourne
Physical barriers
Whole T-cells released into:
Antigen exposure
Complement cascade
Phagocytes
1. Skin
2. Mucous membranes
3. Saliva
4. Flushing action of urine and tears
5. Stomach acid
Suppressor T-cells
Helper T-cells
Cytotoxic T-cells
Lymphoblasts
Alternative pathway
1. Neutrophils
2. Macrophages
3. Basophils
4. Eosinophils
5. Natural killer cells
Plasma cells
Clonal B-cells
Antibodies
Memory B-cells
Complement cascade
Classical pathway
Death of the body's cells that are infected with a virus or otherwise damaged
Death of dangerous organisms
Direct killing of bacteria
Stops infection before it enters the body

Basic molecules of the immune system

- TCR, BCR (antigen-specific receptors on the surface of T and B lymphocytes);
- MHC I, II. (HLA molecule);
- Fc receptors (bind Fc parts of immunoglobulin molecules);
- adhesive and costimulatory molecules;
- immunoglobulins;
- cytokines;
- components of the complement system.

The Immune System is the Third Line of Defense Against Infection

Nonspecific defense mechanisms		Specific defense mechanisms (immune system)
First line of defense	Second line of defense	Third line of defense
• Skin • Mucous membranes • Secretions of skin and mucous membranes	• Phagocytic white blood cells • Antimicrobial proteins • The inflammatory response	• Lymphocytes • Antibodies

Barrier Defenses

- Barrier defenses include the skin and mucous membranes of the respiratory, urinary, and reproductive tracts
- Mucus traps and allows for the removal of microbes
- Many body fluids including saliva, mucus, and tears are hostile to many microbes
- The low pH of skin and the digestive system prevents growth of many bacteria

Mucosal immune system

The mucosal immune system, or MALT mucosa associated lymphoid tissue (in GIT called GALT (gut), BALT (bronchus)) is the lymphatic tissue in the mucosal or sub-lymphatic ligament.

Peyer's plaques in the distal section of the ilea, histological specimen

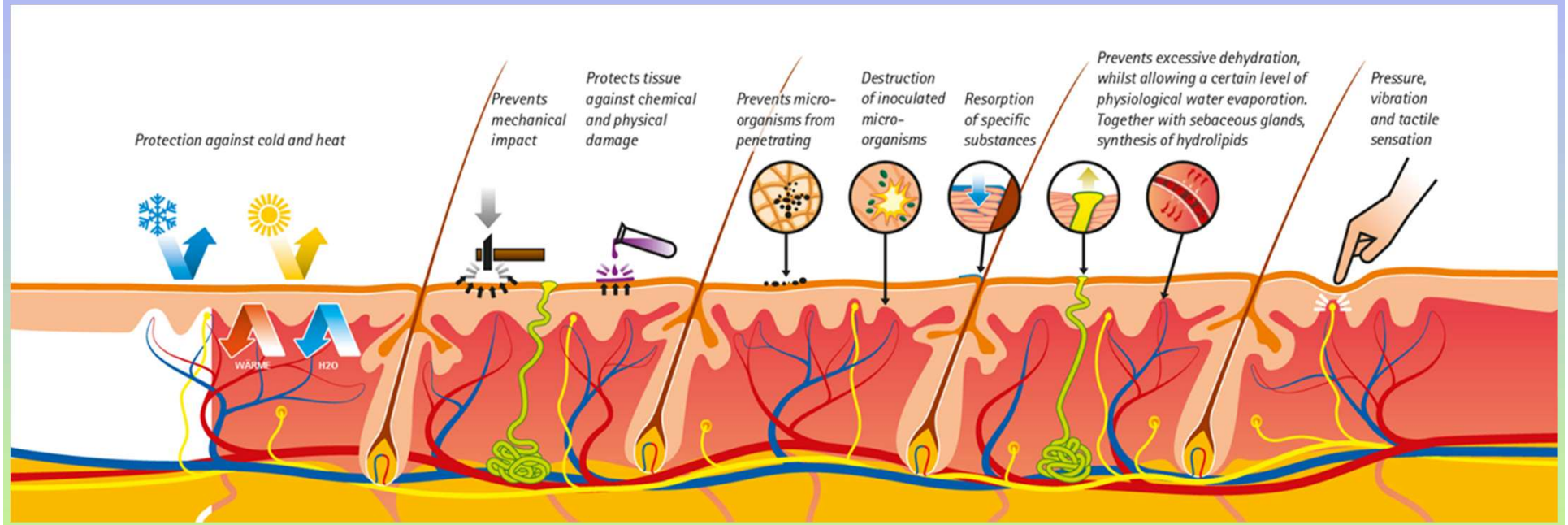
d-MALT - diffuse lymphatic tissue (cells are dispersed in the mucosa or submucosa)

o-MALT - Organized lymphatic tissue (cells are arranged in lymphatic follicles that can be isolated (*folliculi lymphatici aggregati*) or associated with so-called follicular lymphatic aggregates.

Over the lymphatic follicles, the intestinal wall is covered with FAE (epithelium associated with follicles), which contains a large number of M-cells (membrane cells - from the intestinal lumen endocytopes the antigens and transmit it to lymphocytes).

The First Line of Defense
~Skin~

- The dead, outer layer of skin, known as the **epidermis**, forms a shield against invaders and secretes chemicals that kill potential invaders
- You shed between 40 – 50 thousand skin cells every day!


Protection against cold and heat
WÄRME
H2O
Prevents mechanical impact
Protects tissue against chemical and physical damage
Prevents micro-organisms from penetrating
Destruction of inoculated micro-organisms
Resorption of specific substances
Prevents excessive dehydration, whilst allowing a certain level of physiological water evaporation. Together with sebaceous glands, synthesis of hydrolipids
Pressure, vibration and tactile sensation

Immune function of GIT

- Large surface
- The significance of intact gastrointestinal mucosa
- Mucosal barrier - mucus, lysozymes, phagocytes, pH of environment, humoral factors
- The immune system of the digestive tract:
  - Peyer plaques - lymphoid follicles, antibody production
  - Immune cells - intraepithelial lymphocytes, the lymphocytes in the lamina propria - immunoglobulin production
  - Drainage system of portal blood and lymph

The First Line of Defense
~Saliva~

What's the first thing you do when you cut your finger?

- **Saliva** contains many chemicals that break down bacteria
- Thousands of different types of bacteria can survive these chemicals, however

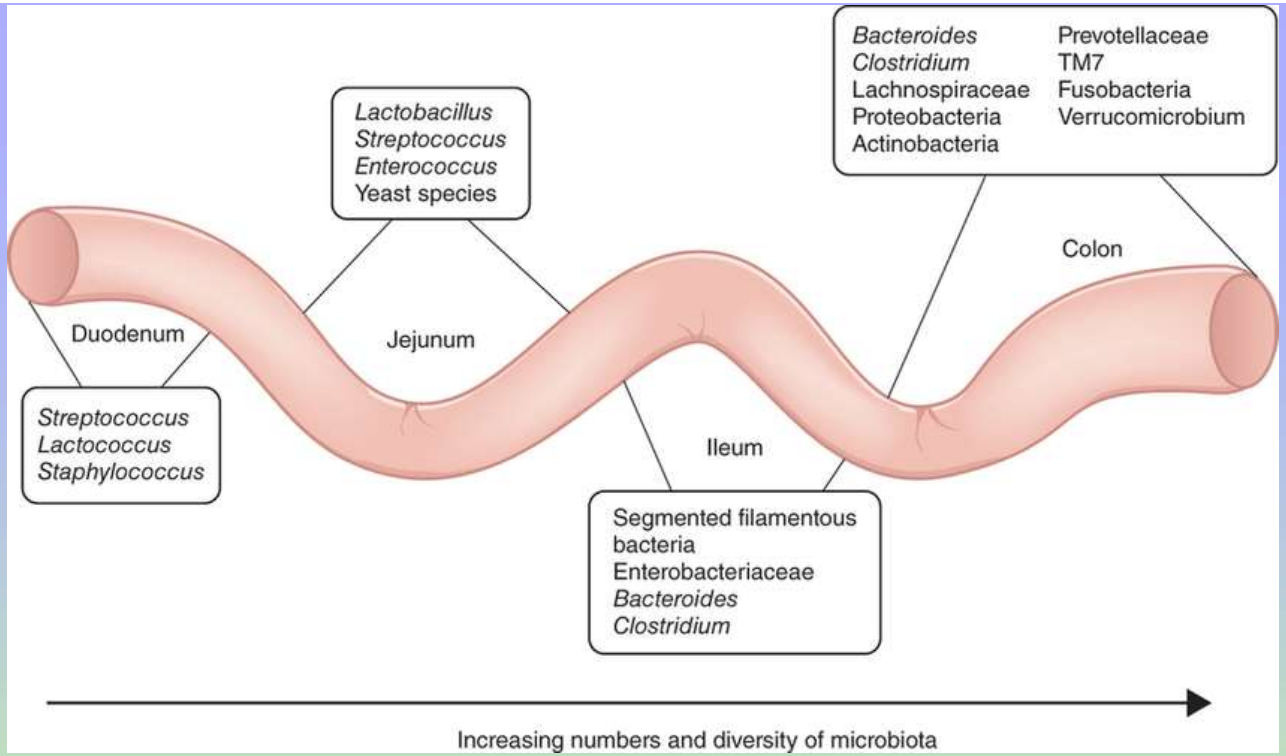
Parameter	Characteristics
Volume	600-1000ml/day
Electrolytes	Na+, K+, Cl-, Ca2+, Mg2+and F-
Secretory proteins/peptides	Amylase, proline-rich proteins, mucins, histatin, cystatin, peroxidase, lysozyme, lactoferrin and defensis.
Immunoglobulins	Secretory immunoglobulins A, immunoglobulins G and M
Small organic	Glucose, amino acids, urea, uric acid, and lipid molecules
Other components	Epidermal growth factor, insulin, cyclic adenosine monophosphate-binding proteins, and serum albumin

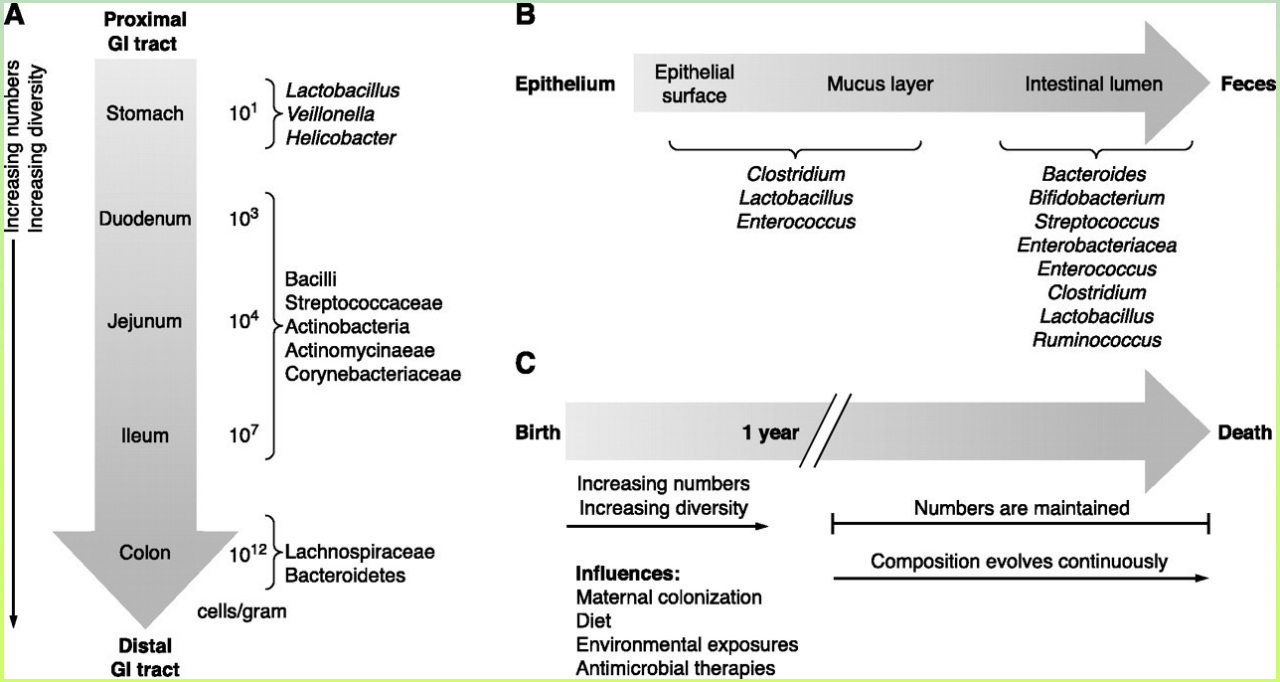
Table 1. Saliva components and functions (4).

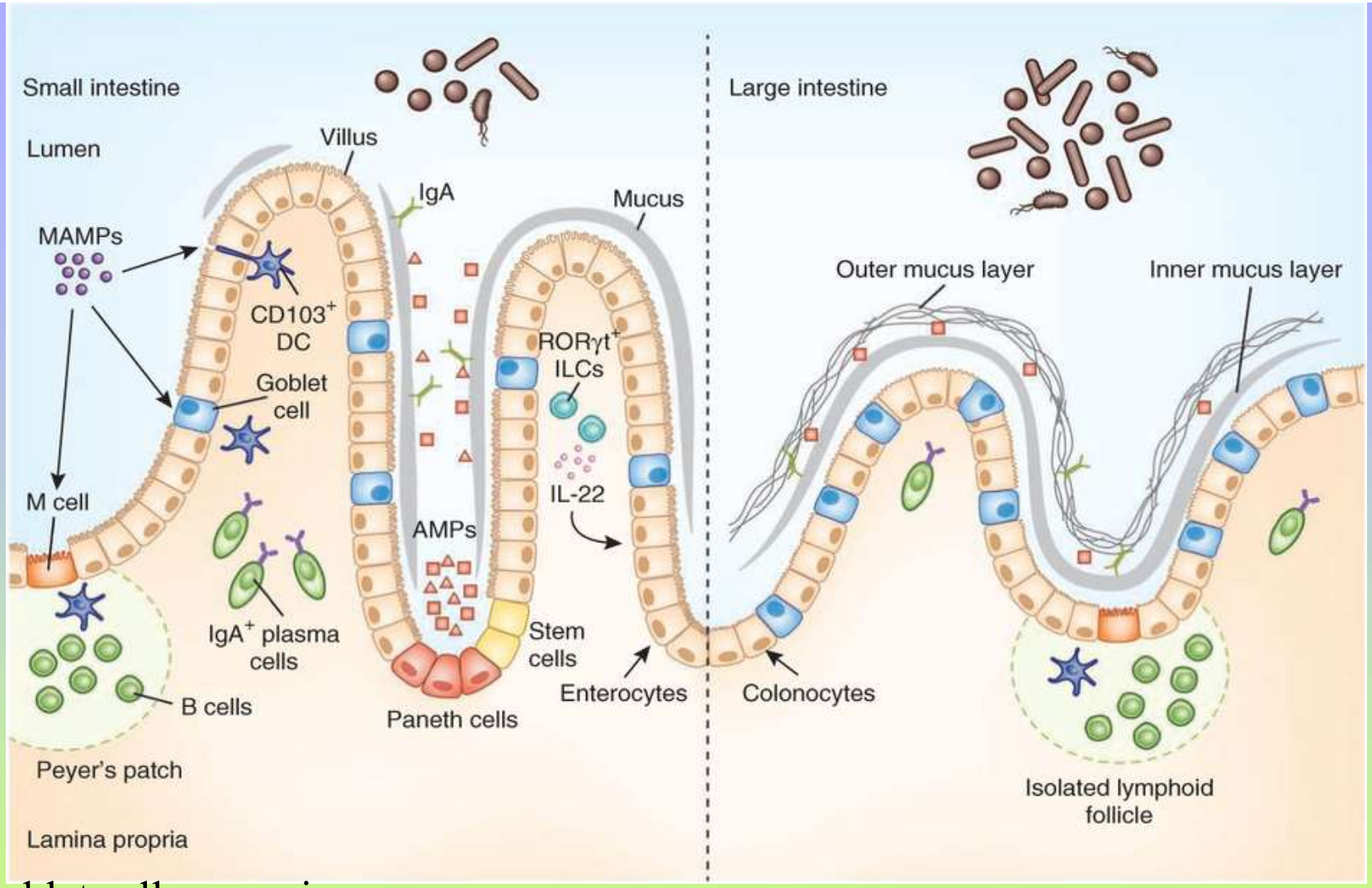
Functions	Components
Lubrication	Mucin, proline-rich glycoproteins, water
Antimicrobial action	Lysozyme, lactoferrin, lactoperoxides, mucins, cystins, histatins, immunoglobulins, proline-rich glycoproteins, IgA
Maintaining mucosa integrity	Mucins, electrolytes, water
Cleansing	Water
Buffer capacity and remineralisation	Bicarbonate, phosphate, calcium, staterin, proline-rich anionic proteins, fluoride
Preparing food for swallowing	Water, mucins
Digestion	Amylase, lipase, ribonucleases, proteases, water, mucins
Taste	Water, gustin
Phonation	Water, mucin

The First Line of Defense
~Stomach Acid~

- Swallowed bacteria are broken down by HCl in the stomach
- The stomach must produce a coating of special mucus or this acid would eat through the stomach!


Bacteroides
Clostridium
Lachnospiraceae
Proteobacteria
Actinobacteria
Prevotellaceae
TM7
Fusobacteria
Verrucomicrobium
Lactobacillus
Streptococcus
Enterococcus
Yeast species
Colon
Duodenum
Jejunum
Ileum
Streptococcus
Lactococcus
Staphylococcus
Segmented filamentous bacteria
Enterobacteriaceae
Bacteroides
Clostridium
Increasing numbers and diversity of microbiota


A
Proximal GI tract
Increasing numbers
Increasing diversity
Stomach
Duodenum
Jejunum
Ileum
Colon
Distal GI tract
10^1
10^3
10^4
10^7
10^12
cells/gram
Lactobacillus
Veillonella
Helicobacter
Bacilli
Streptococcaceae
Actinobacteria
Actinomycinaeae
Corynebacteriaceae
Lachnospiraceae
Bacteroidetes
B
Epithelium
Epithelial surface
Mucus layer
Intestinal lumen
Feces
Clostridium
Lactobacillus
Enterococcus
Bacteroides
Bifidobacterium
Streptococcus
Enterobacteriacea
Enterococcus
Clostridium
Lactobacillus
Ruminococcus
C
Birth
1 year
Death
Increasing numbers
Increasing diversity
Numbers are maintained
Composition evolves continuously
Influences:
Maternal colonization
Diet
Environmental exposures
Antimicrobial therapies



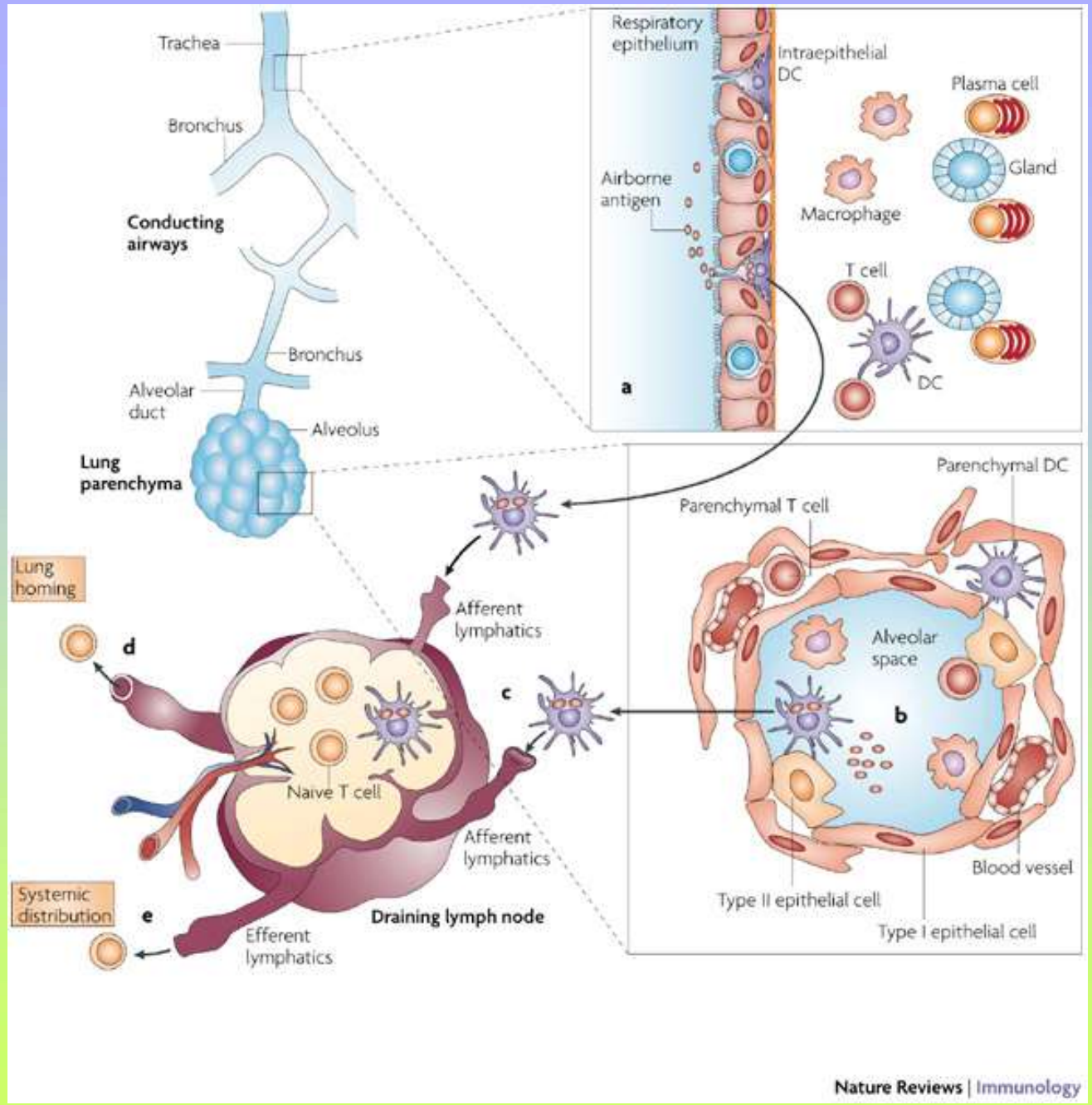
- Goblet cells – mucins
- M cells - ability to take up antigen from the lumen via endocytosis, phagocytosis, or transcytosis to antigen presenting cells, such as dendritic cells, and lymphocytes
- Paneth cells - synthesize and secrete substantial quantities of antimicrobial peptides and proteins

Lungs and immunity

Table 27-1 Surfactant Apoproteins

Apoprotein	Solubility	Role
SP-A	Water	Innate immunity Formation of tubular myelin
SP-B	Lipid	Speeds formation of monolayer Formation of tubular myelin
SP-C	Lipid	Speeds formation of monolayer
SP-D	Water	Innate immunity Metabolism of surfactant?

= opsonins to coat bacteria and viruses, thereby promoting phagocytosis by macrophages resident in the alveoli


Trachea
Bronchus
Conducting airways
Bronchus
Alveolar duct
Alveolus
Lung parenchyma
Respiratory epithelium
Intraepithelial DC
Plasma cell
Gland
Airborne antigen
Macrophage
T cell
DC
a
Parenchymal DC
Parenchymal T cell
Alveolar space
b
Blood vessel
Type II epithelial cell
Type I epithelial cell
Lung homing
d
Afferent lymphatics
c
Naive T cell
Afferent lymphatics
Systemic distribution
e
Efferent lymphatics
Draining lymph node
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Innate or Genetic Immunity: Immunity an organism is born with.

- **Genetically determined.**
- **May be due to lack of receptors or other molecules required for infection.**
  - **Innate human immunity to canine distemper.**
  - **Immunity of mice to poliovirus.**

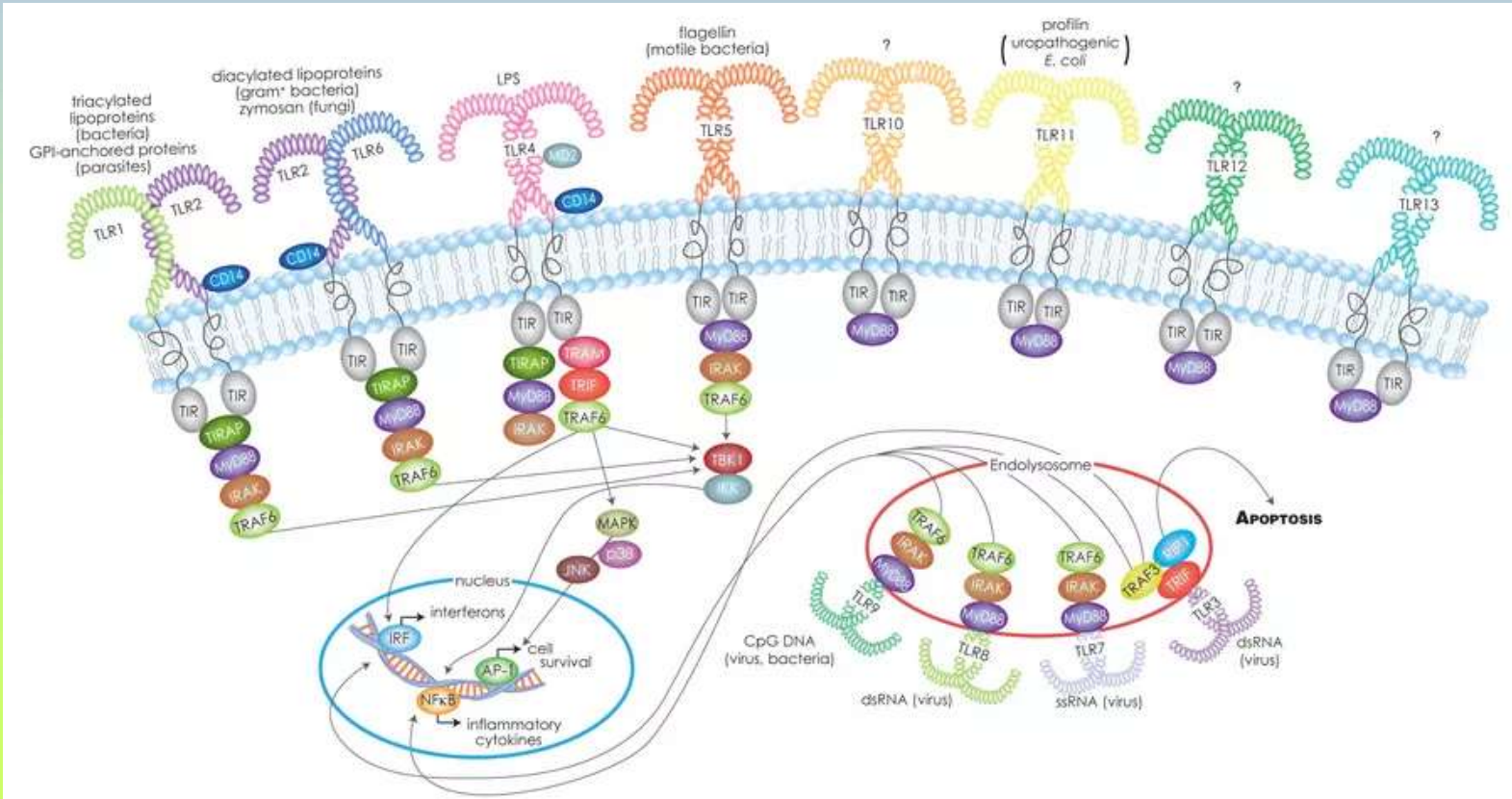
Acquired Immunity:Immunity that an organism *develops* during lifetime.

- **Not genetically determined.**
- **May be acquired naturally or artificially.**
  - **Development of immunity to measles in response to infection or vaccination.**

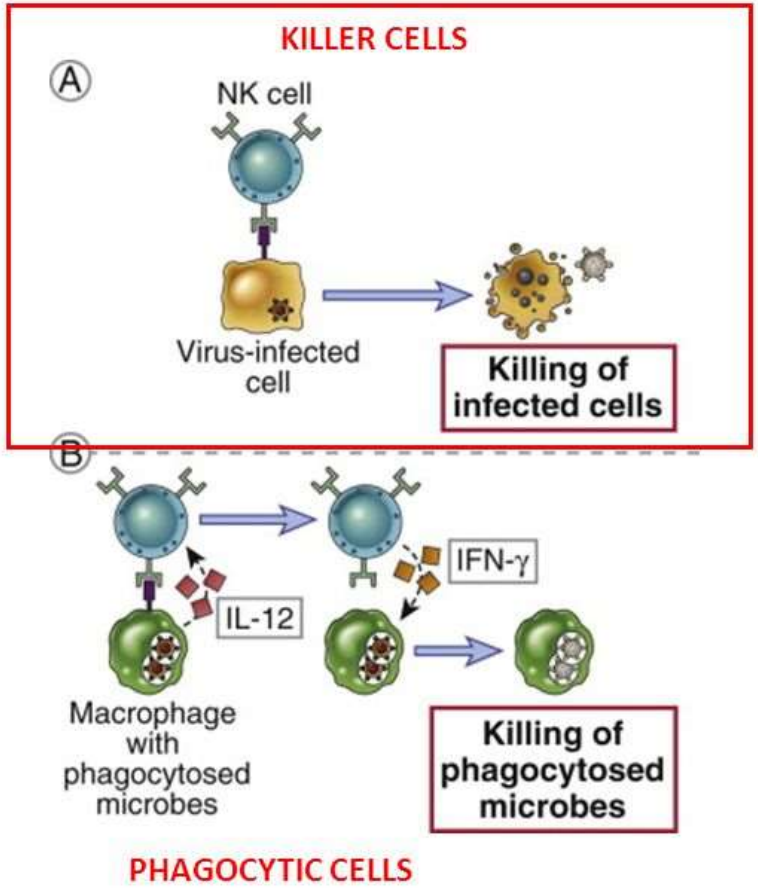
Innate versus acquired immunity

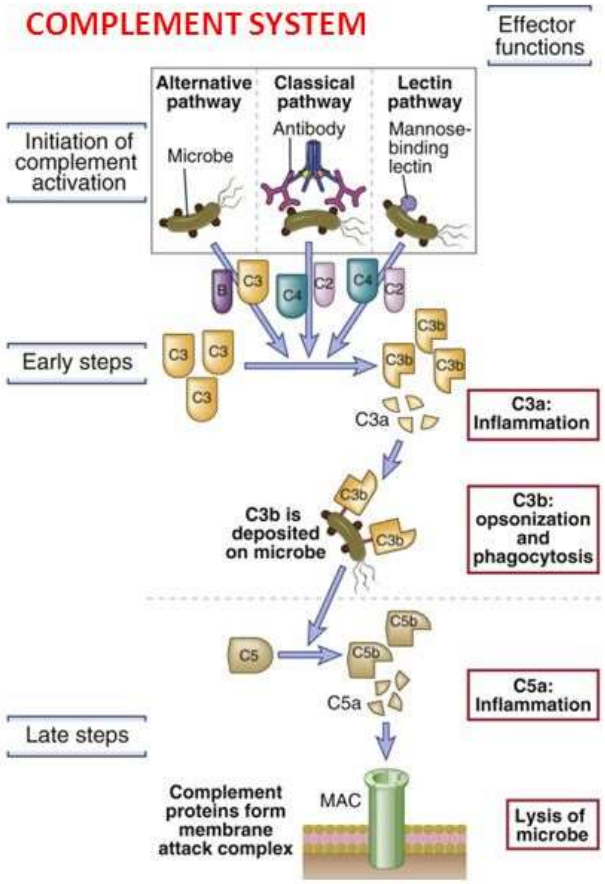
Innate immunity

- neutrophils, macrophages, NK cells
- Toll and toll-like receptors = affinity to bacterial lipopolysaccharides, lipoproteins, peptidoglycans, DNA = molecular patterns expressed by pathogens



EFFECTOR MECHANISMS OF INNATE IMMUNITY





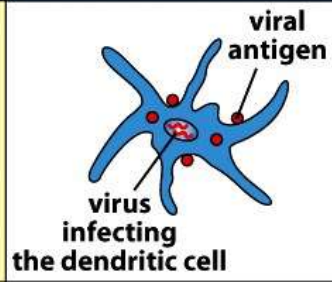
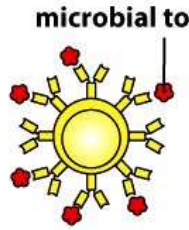
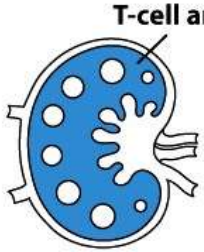
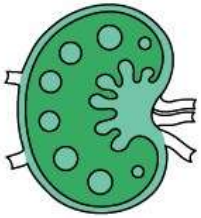
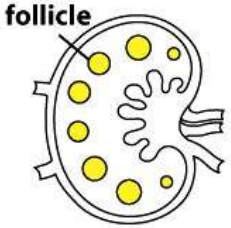
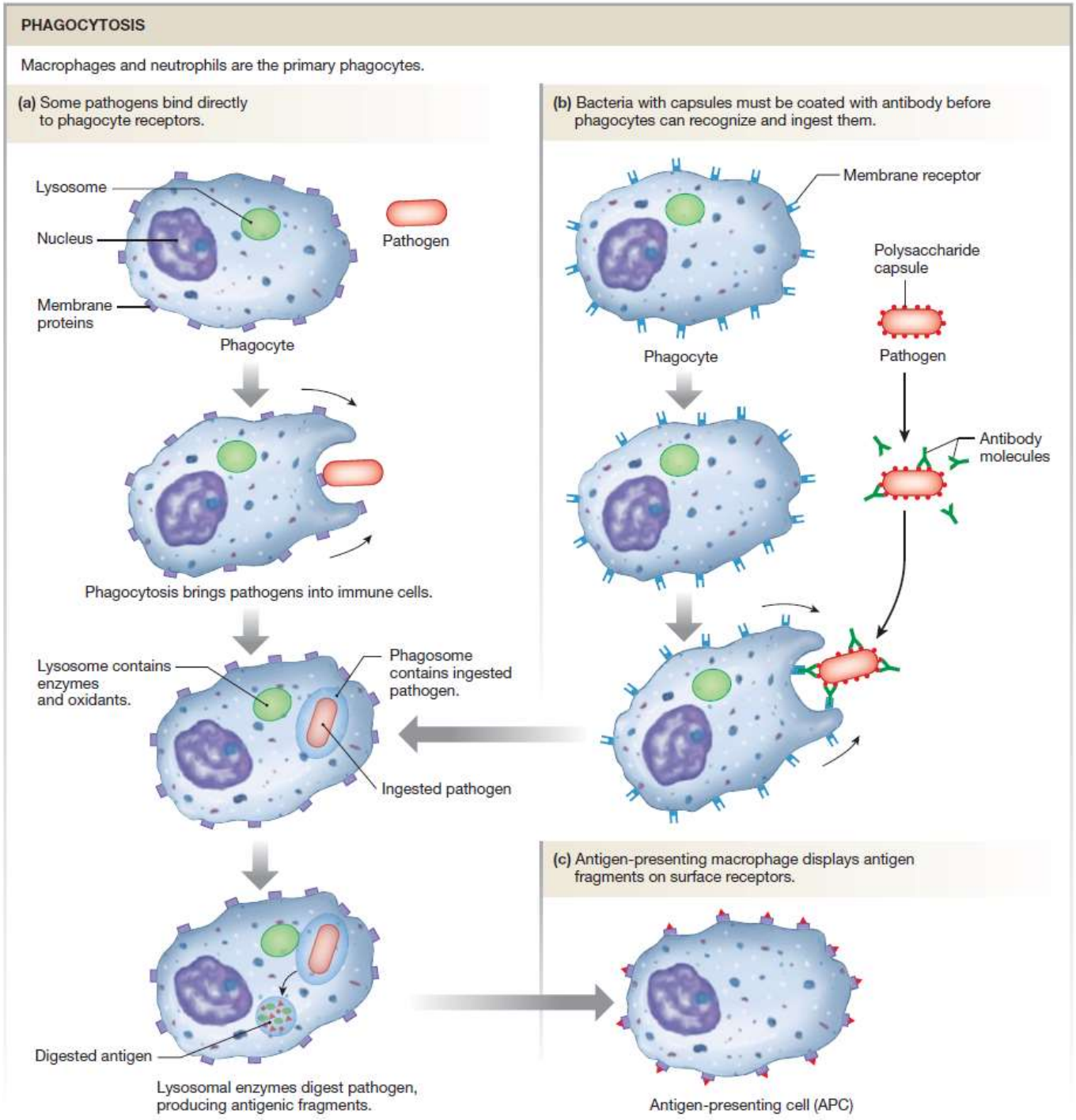
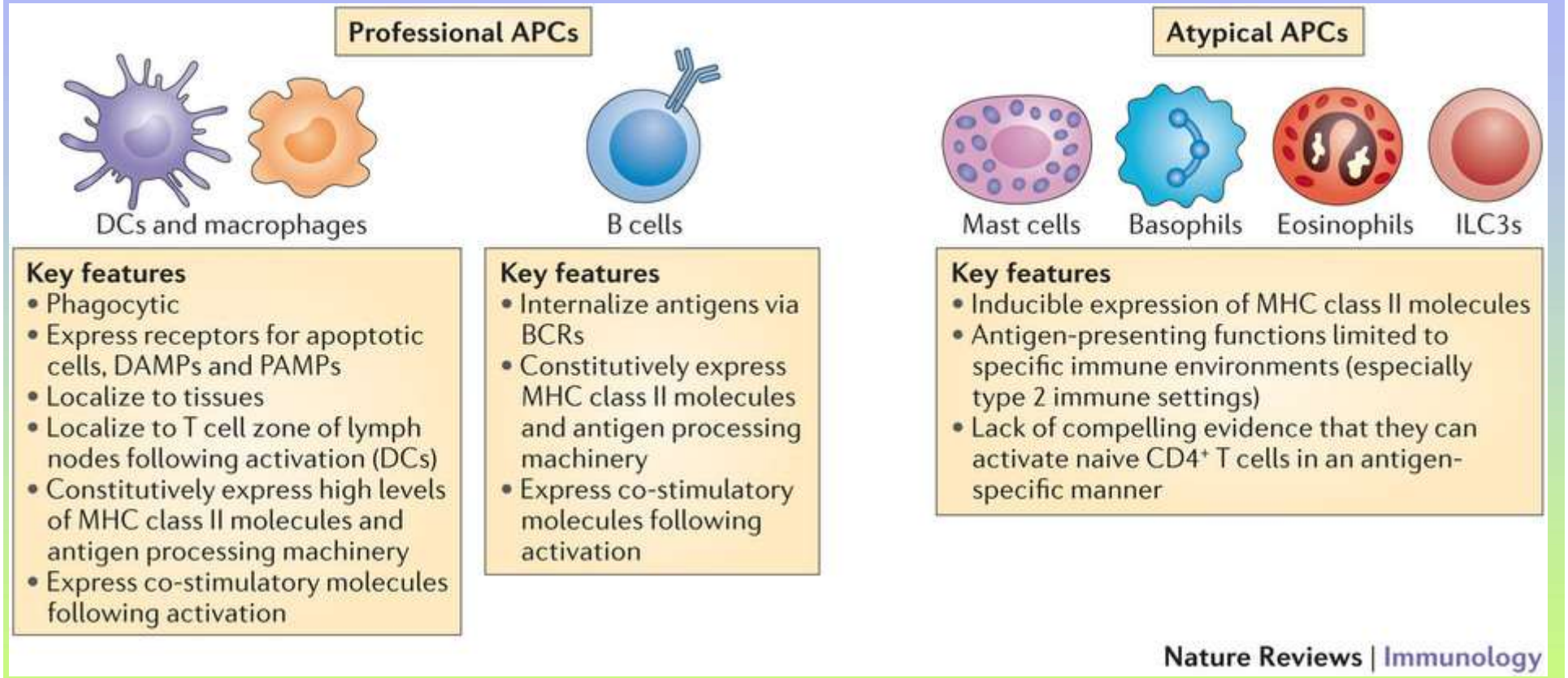
	Professional antigen-presenting cells		
	Dendritic cell	**Macrophage**	**B cell**
Cell type			
Location in lymph node			
Antigen uptake	+++ Macropinocytosis and phagocytosis by tissue dendritic cells Viral infection	Phagocytosis +++	Antigen-specific receptor (Ig) ++++
MHC expression	Low on tissue dendritic cells High on dendritic cells in lymphoid tissues	Inducible by bacteria and cytokines – to +++	Constitutive Increases on activation +++ to ++++
Co-stimulator delivery	Constitutive by mature, nonphagocytic lymphoid dendritic cells ++++	Inducible – to +++	Inducible – to +++
Antigen presented	Peptides Viral antigens Allergens	Particulate antigens Intracellular and extracellular pathogens	Soluble antigens Toxins Viruses
Location	Ubiquitous throughout the body	Lymphoid tissue Connective tissue Body cavities	Lymphoid tissue Peripheral blood

Figure 8.11 The Immune System, 3ed. (© Garland Science 2009)


PHAGOCYTOSIS
Macrophages and neutrophils are the primary phagocytes.
(a) Some pathogens bind directly to phagocyte receptors.
(b) Bacteria with capsules must be coated with antibody before phagocytes can recognize and ingest them.
Lysosome
Nucleus
Membrane proteins
Pathogen
Phagocyte
Phagocytosis brings pathogens into immune cells.
Membrane receptor
Polysaccharide capsule
Pathogen
Phagocyte
Antibody molecules
Lysosome contains enzymes and oxidants.
Phagosome contains ingested pathogen.
Ingested pathogen
Digested antigen
Lysosomal enzymes digest pathogen, producing antigenic fragments.
(c) Antigen-presenting macrophage displays antigen fragments on surface receptors.
Antigen-presenting cell (APC)


Professional APCs
Atypical APCs
DCs and macrophages
B cells
Mast cells
Basophils
Eosinophils
ILC3s
Key features
• Phagocytic
• Express receptors for apoptotic cells, DAMPs and PAMPs
• Localize to tissues
• Localize to T cell zone of lymph nodes following activation (DCs)
• Constitutively express high levels of MHC class II molecules and antigen processing machinery
• Express co-stimulatory molecules following activation
Key features
• Internalize antigens via BCRs
• Constitutively express MHC class II molecules and antigen processing machinery
• Express co-stimulatory molecules following activation
Key features
• Inducible expression of MHC class II molecules
• Antigen-presenting functions limited to specific immune environments (especially type 2 immune settings)
• Lack of compelling evidence that they can activate naive CD4+ T cells in an antigen-specific manner
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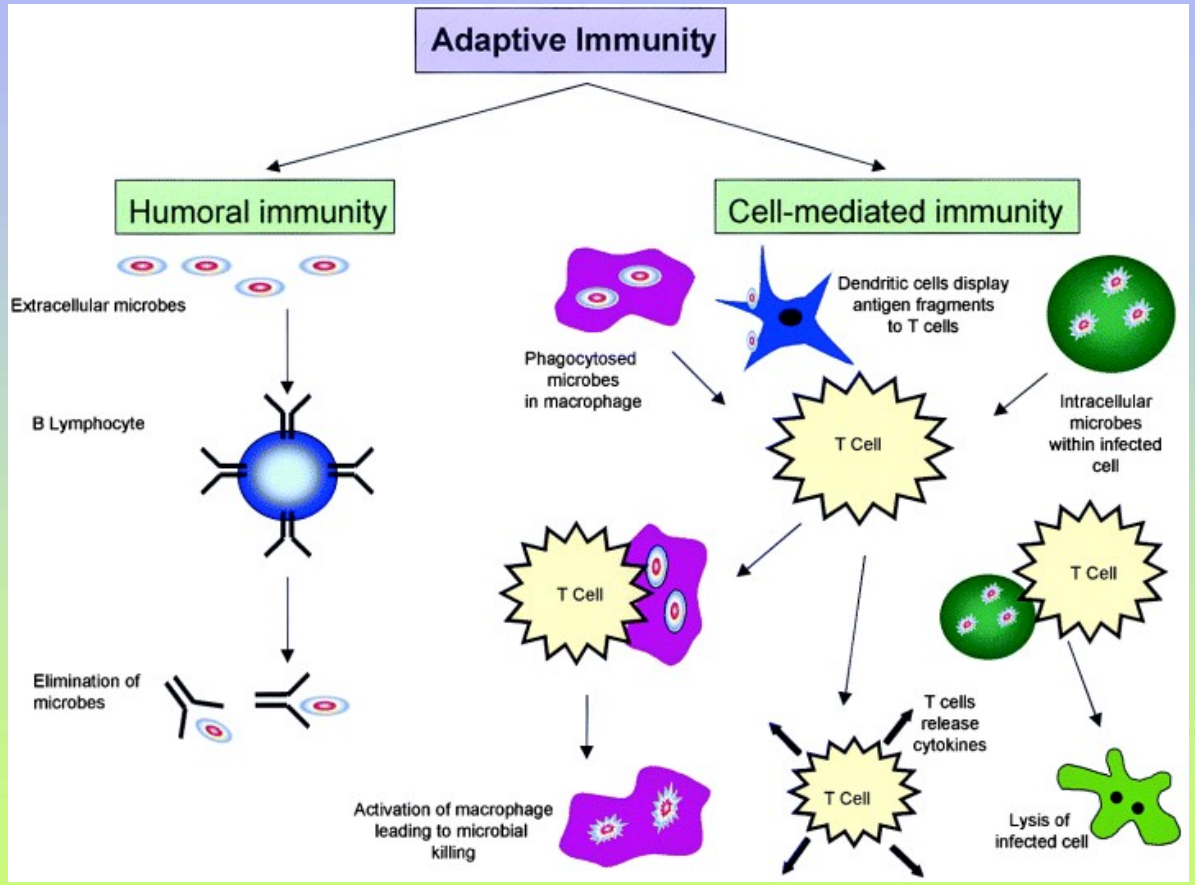
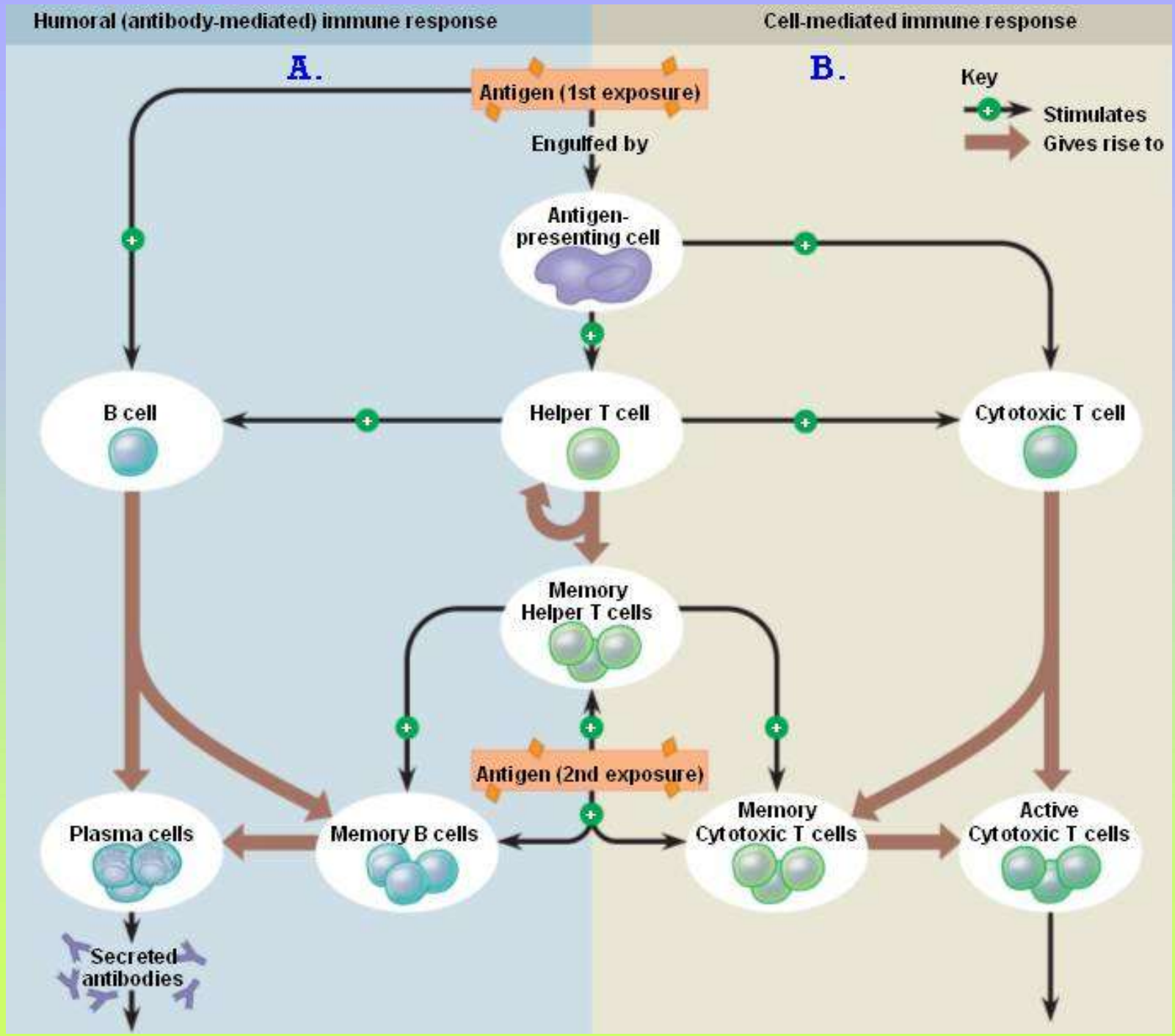
Innate versus acquired immunity

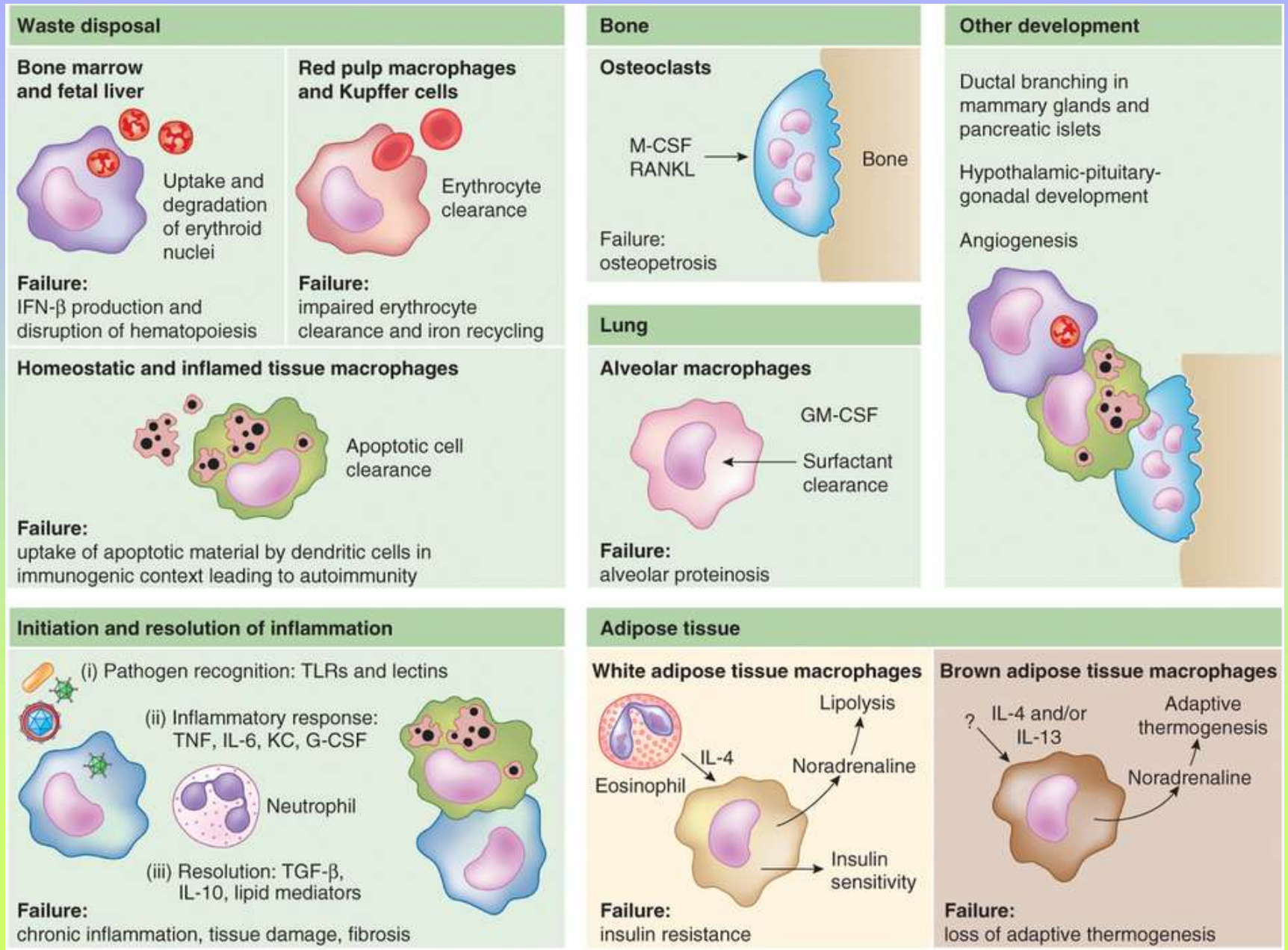
Acquired immunity

- Ability of lymphocytes to produce antibodies (B cells) or cell-surface receptors (T cells) = specific!
- Antigens (proteins, polypeptides, nucleic acids, lipids)
- Humoral immunity – circulating antibodies (plasma cells, activation of complement system, bacterial infection)
- Cellular immunity – T-lymphocytes




Humoral (antibody-mediated) immune response
Cell-mediated immune response
A.
B.
Key
Stimulates
Gives rise to
Antigen (1st exposure)
Engulfed by
Antigen-presenting cell
B cell
Helper T cell
Cytotoxic T cell
Memory Helper T cells
Antigen (2nd exposure)
Plasma cells
Memory B cells
Memory Cytotoxic T cells
Active Cytotoxic T cells
Secreted antibodies

Reticuloendothelial system – tissue macrophage system



Macrophages (MΦ)	Tissue	Functions	Pathology
Microglia	Brain	Brian development (121), immune surveillance, synaptic remodeling (122)	Neurodegeneration (123)
Osteoclasts	Bone	Bone modeling and remodeling, bone resorption (124), support to hematopoiesis (125)	Osteoporosis, osteopetrosis, arthritis (126)
Heart MΦ	Heart and vasculature	Surveillance	Atherosclerosis (127)
Kupffer cells	Liver	Toxin removal, lipid metabolism, iron recycling, erythrocyte clearance, clearance of microbes, and cell debris from blood (128, 129)	Fibrosis (130), impaired erythrocyte clearance (131)
Alveolar MΦ	Lung	Surfactant clearance, surveillance for inhaled pathogens (132)	Alveolar proteinosis (133)
Adipose tissue-associated MΦ	Adipose tissue	Metabolism, adipogenesis, adaptive thermogenesis (134)	Obesity, diabetes, insulin resistance, loss of adaptive thermogenesis (131)
Bone marrow MΦ	Bone marrow	Reservoir of monocytes, waste disposal (131)	Disruption of hematopoiesis (131)
Intestinal MΦ	Gut	Tolerance to microbiota, defense against pathogens, intestinal homeostasis (135)	Inflammatory bowel disease (136)
Langerhans cells	Skin	Immune surveillance (137)	Insufficient healing, fibrosis (138)
Marginal zone MΦ, red pulp MΦ	Spleen	Erythrocyte clearance, iron processing, capture of microbes from blood (139)	Impaired iron recycling and erythrocyte clearance (140)
Inflammatory MΦ[a]	All tissues	Defense against pathogens, protection against dangerous stimuli (141)	Chronic inflammation, tissue damage, autoimmunity (91)
Healing MΦ[b]	All tissues	Branched morphology, angiogenesis (142)	Cancer, fibrosis, epithelial hyperplasia (91)

[a] *Also known as inflammatory macrophages or M1 macrophages.*

[b] *Also known as deactivated or M2 macrophages.*

Types of Acquired Immunity

I. Naturally Acquired Immunity: Obtained in the course of daily life.

A. Naturally Acquired Active Immunity:

- ***Antigens*** **or pathogens enter body naturally.**
- **Body generates an immune response to antigens.**
- **Immunity may be lifelong (chickenpox or mumps) or temporary (influenza or intestinal infections).**

B. Naturally Acquired Passive Immunity:

- ***Antibodies*** **pass from mother to fetus via placenta or breast feeding (colostrum).**
- **No immune response to antigens.**
- **Immunity is usually short-lived (weeks to months).**
- **Protection until child's immune system develops.**

Types of Acquired Immunity (Continued)

II. Artificially Acquired Immunity: Obtained by receiving a vaccine or immune serum.

1. Artificially Acquired Active Immunity:

- *Antigens* are introduced in vaccines (immunization).
- Body generates an immune response to antigens.
- Immunity can be lifelong (oral polio vaccine) or temporary (tetanus toxoid).

2. Artificially Acquired Passive Immunity:

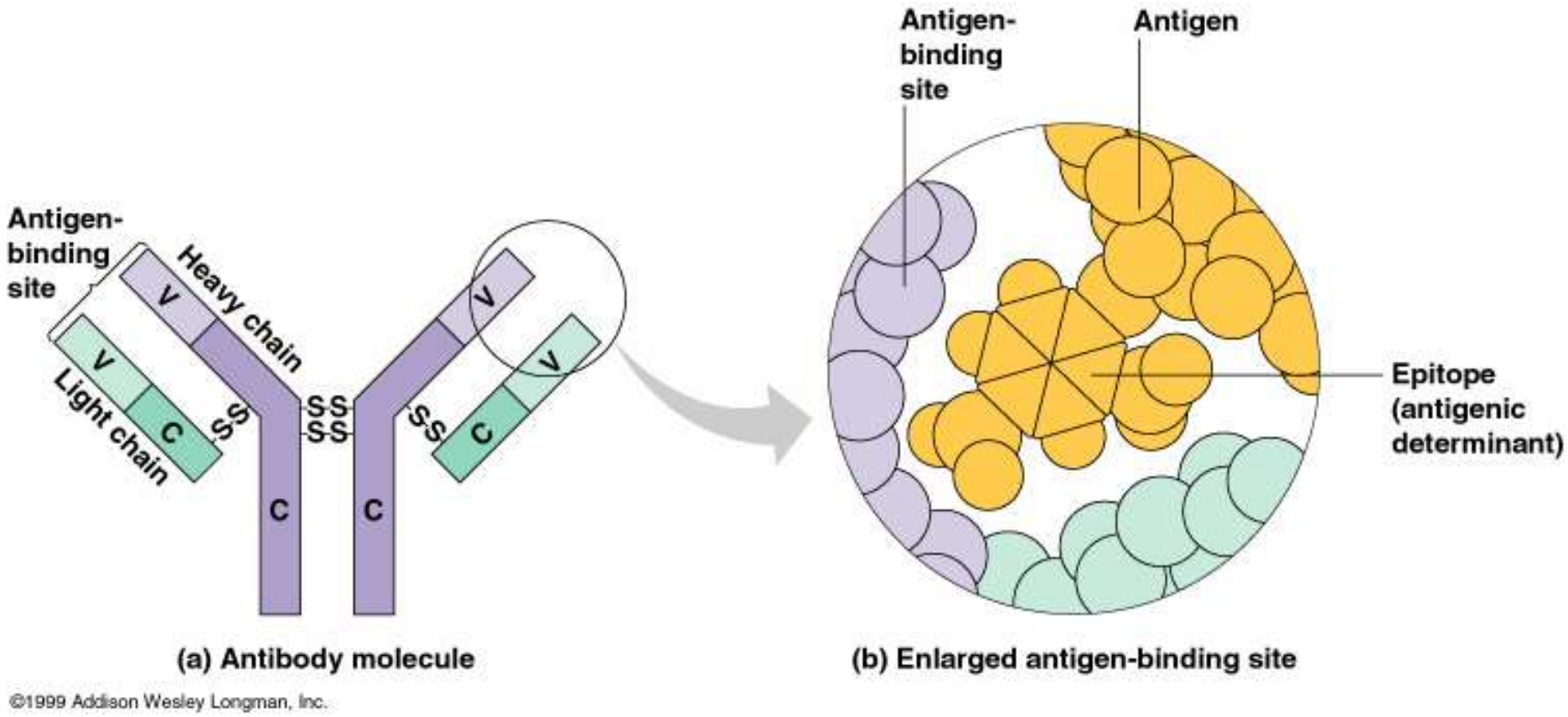
- Preformed *antibodies* (antiserum) are introduced into body by injection.
  - Snake antivenom injection from horses or rabbits.
- Immunity is short lived (half life three weeks).
- Host immune system does not respond to antigens.

Duality of Immune System

I. Humoral (Antibody-Mediated) Immunity

- **Involves production of antibodies against foreign antigens.**
- **Antibodies are produced by a subset of lymphocytes called B cells.**
- **B cells that are stimulated will actively secrete antibodies and are called *plasma cells*.**
- **Antibodies are found in extracellular fluids (blood plasma, lymph, mucus, etc.) and the surface of B cells.**
- **Defense against bacteria, bacterial toxins, and viruses that circulate freely in body fluids, *before* they enter cells.**
- **Also cause certain reactions against transplanted tissue.**

Antibodies are Proteins that Recognize Specific Antigens



Duality of Immune System II. Cell Mediated Immunity

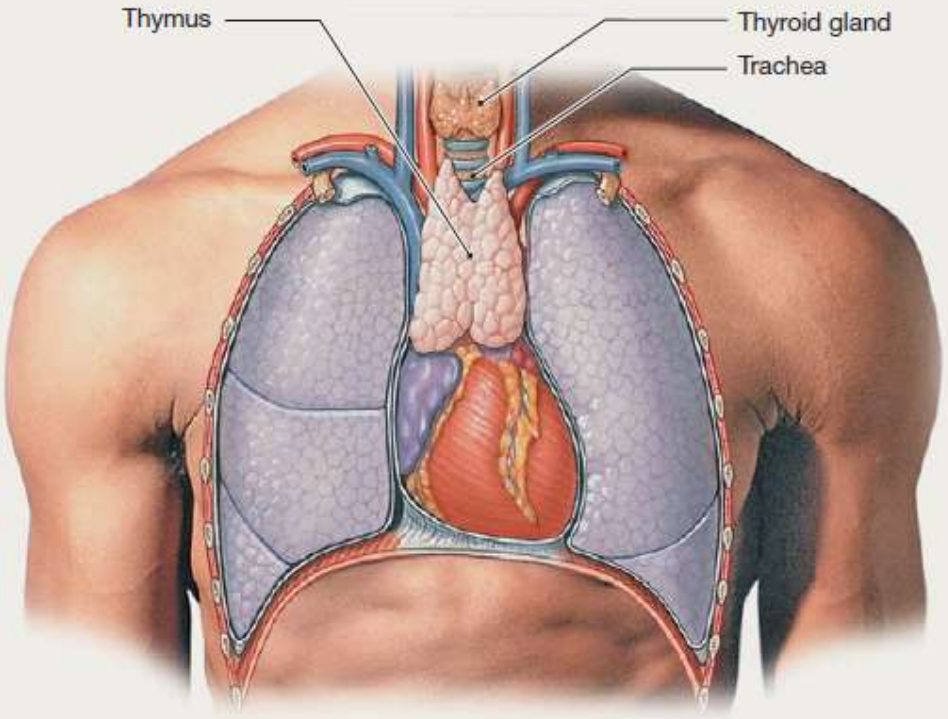
- Involves specialized set of lymphocytes called T cells that recognize foreign antigens on the surface of cells, organisms, or tissues:
  - Helper T cells
  - Cytotoxic T cells
- T cells regulate proliferation and activity of other cells of the immune system: B cells, macrophages, neutrophils, etc.
- Defense against:
  - Bacteria and viruses that are inside host cells and are inaccessible to antibodies.
  - Fungi, protozoa, and helminths
  - Cancer cells
  - Transplanted tissue

The Thymus Gland

The thymus gland is a two-lobed organ located in the thorax just above the heart.

The thymus gland reaches its greatest size during adolescence.Then it shrinks and is largely replaced by adipose tissue as a person ages.

During development in the thymus, those cells that would be self-reactive are eliminated. Those that do not react with "self" tissues multiply to form clones.

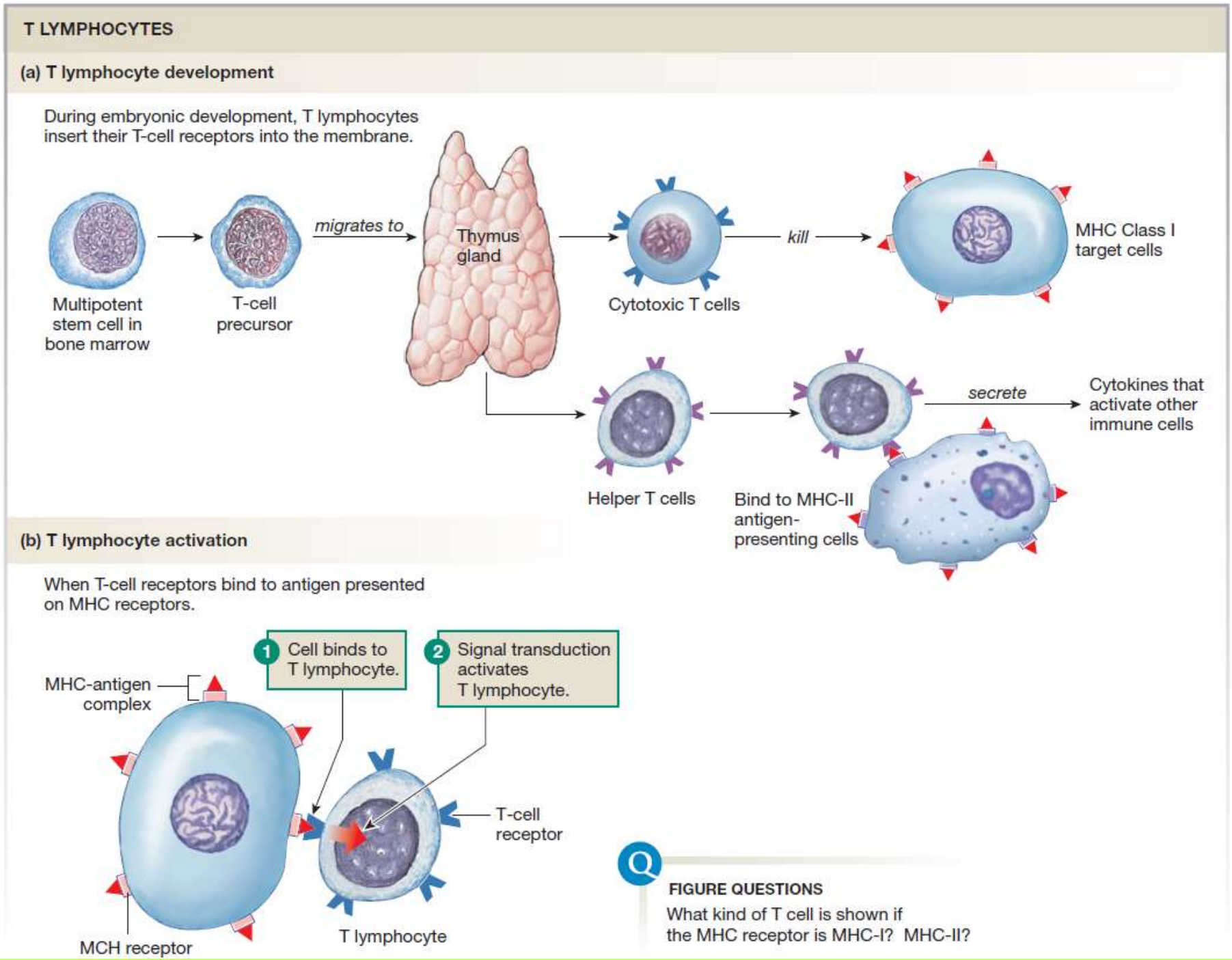


The thymus gland produces:

- T lymphocytes
- Peptides
  thymosin
  thymopoietin
  thymulin

FIGURE QUESTION

New T lymphocyte production in the thymus is low in adults, but the number of T lymphocytes in the blood does not decrease. What conclusion(s) about T lymphocytes can you draw from this information?


T LYMPHOCYTES
(a) T lymphocyte development
During embryonic development, T lymphocytes insert their T-cell receptors into the membrane.
Multipotent stem cell in bone marrow
T-cell precursor
migrates to
Thymus gland
Cytotoxic T cells
kill
MHC Class I target cells
Helper T cells
secrete
Cytokines that activate other immune cells
Bind to MHC-II antigen-presenting cells
(b) T lymphocyte activation
When T-cell receptors bind to antigen presented on MHC receptors.
1 Cell binds to T lymphocyte.
2 Signal transduction activates T lymphocyte.
MHC-antigen complex
T-cell receptor
MCH receptor
T lymphocyte
FIGURE QUESTIONS
What kind of T cell is shown if the MHC receptor is MHC-I? MHC-II?

Antigens

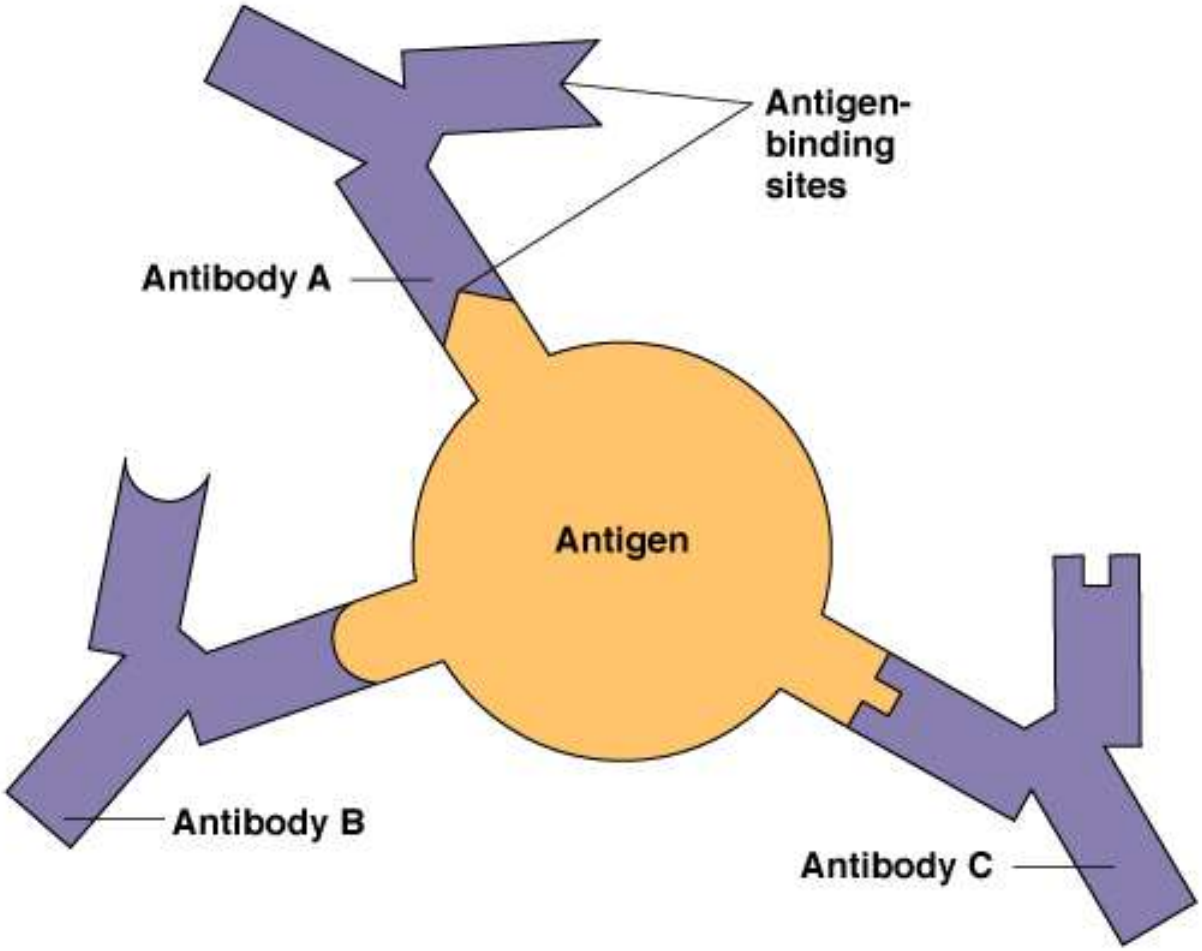
- Most are proteins or large polysaccharides from a foreign organism.
  - Microbes: Capsules, cell walls, toxins, viral capsids, flagella, etc.
  - Nonmicrobes: Pollen, egg white , red blood cell surface molecules, serum proteins, and surface molecules from transplanted tissue.
- Lipids and nucleic acids are only antigenic when combined with proteins or polysaccharides.
- Molecular weight of 10,000 or higher.
  - Hapten: Small foreign molecule that is not antigenic. Must be coupled to a carrier molecule to be antigenic. Once antibodies are formed they will recognize hapten.

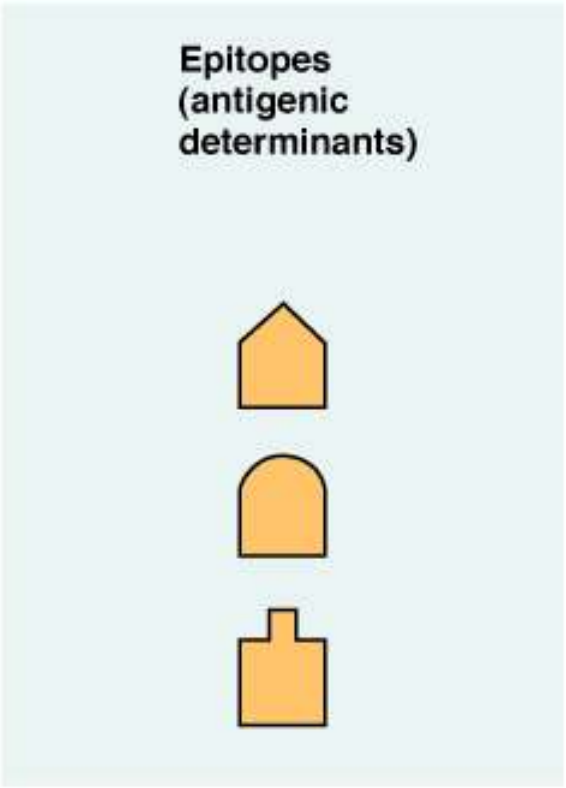
Antigens

Epitope:

- **Small part of an antigen that interacts with an antibody.**
- **Any given antigen may have several epitopes.**
- **Each epitope is recognized by a different antibody.**

Epitopes: Antigen Regions that Interact with Antibodies





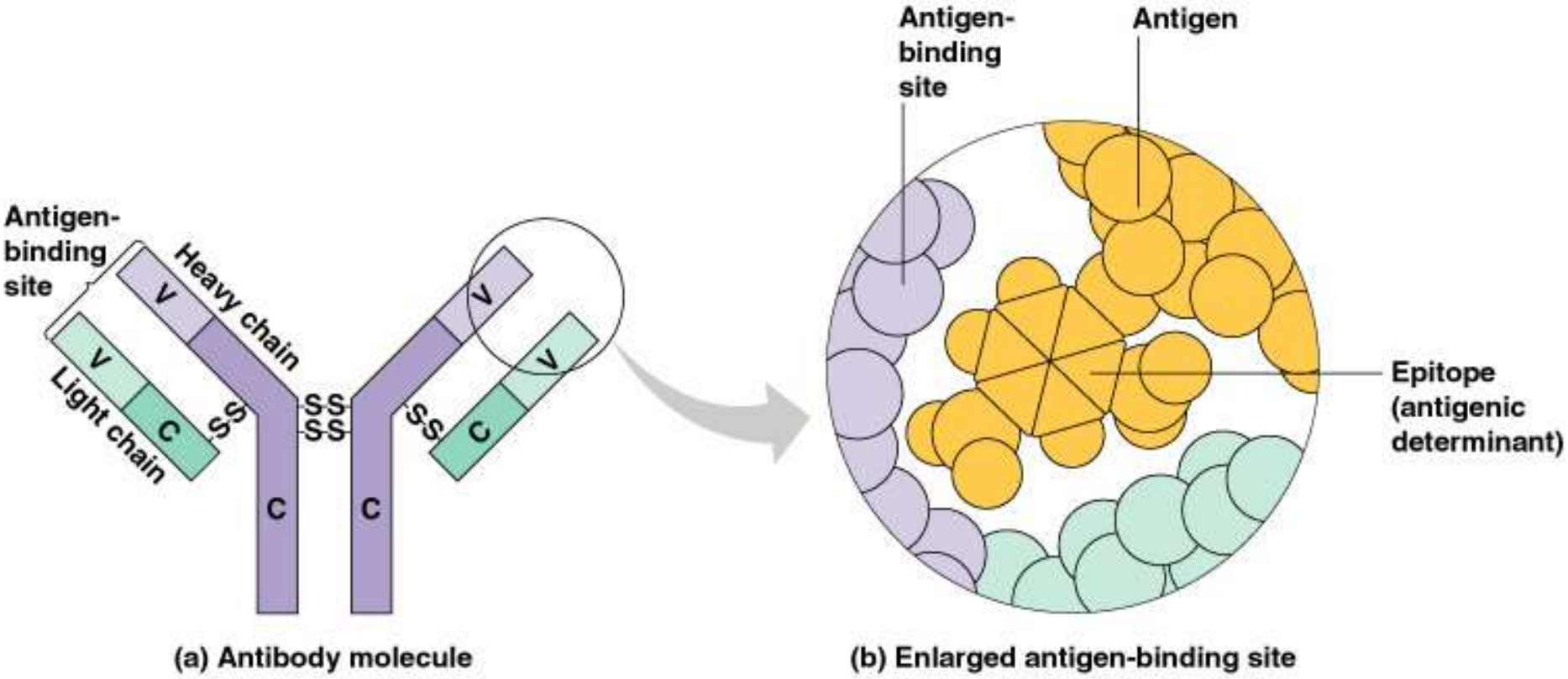
Antibodies

- **Proteins that recognize and bind to a particular antigen with very high *specificity*.**
- **Made in response to exposure to the antigen.**
- **One virus or microbe may have several *antigenic determinant sites*, to which different antibodies may bind.**
- **Each antibody has at least two identical sites that bind antigen: *Antigen binding sites*.**
- **Valence of an antibody: Number of antigen binding sites. Most are bivalent.**
- **Belong to a group of serum proteins called immunoglobulins (IGs).**

Antibody Structure

- **Monomer: A flexible Y-shaped molecule with four protein chains:**
  - **2 identical *light* chains**
  - **2 identical *heavy* chains**
- **Variable Regions: Two sections at the end of Y's arms. Contain the antigen binding sites (Fab). Identical on the same antibody, but vary from one antibody to another.**
- **Constant Regions: Stem of monomer and lower parts of Y arms.**
- **Fc region: Stem of monomer only. Important because they can bind to complement or cells.**

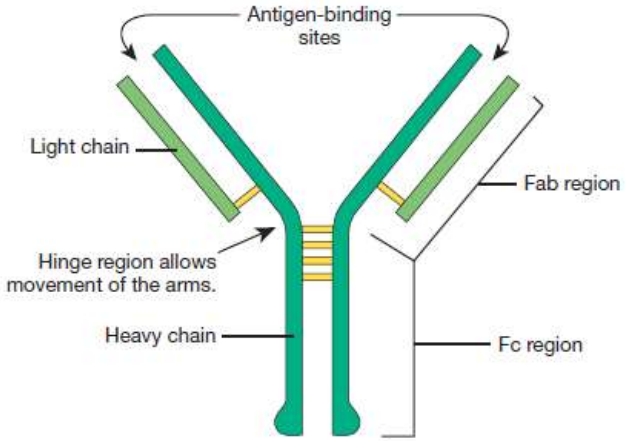
Antibody Structure



ANTIBODIES

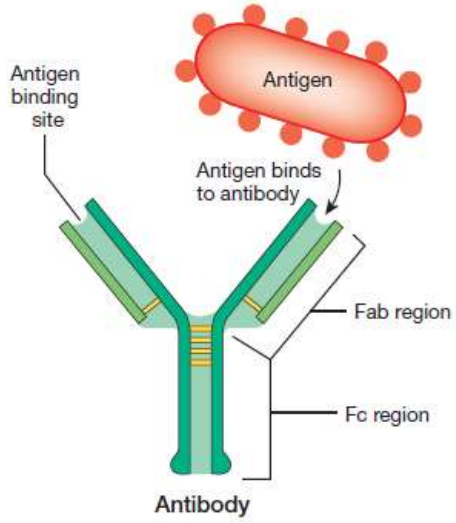
(a) Antibody structure

An antibody molecule is composed of two identical light chains and two identical heavy chains, linked by disulfide bonds.

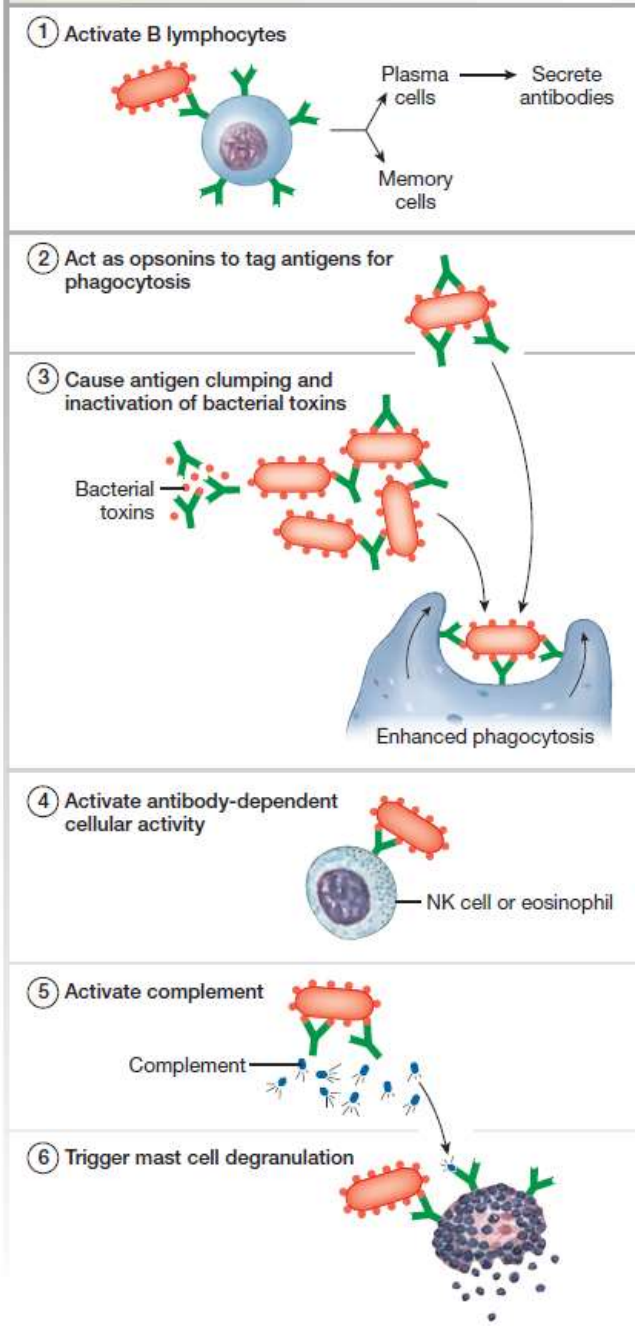


(b) Antigen binding

Antibodies have antigen-binding sites on the Fab regions.



(c) Antibody functions



Immunoglobulin Classes

I. IgG

- **Structure: Monomer**
- **Percentage serum antibodies: 80%**
- **Location: Blood, lymph, intestine**
- **Half-life in serum: 23 days**
- **Complement Fixation: Yes**
- **Placental Transfer: Yes**
- **Known Functions: Enhances phagocytosis, neutralizes toxins and viruses, protects fetus and newborn.**

Immunoglobulin Classes

II. IgM

- **Structure: Pentamer**
- **Percentage serum antibodies: 5-10%**
- **Location: Blood, lymph, B cell surface (monomer)**
- **Half-life in serum: 5 days**
- **Complement Fixation: Yes**
- **Placental Transfer: No**
- **Known Functions: First antibodies produced during an infection. Effective against microbes and agglutinating antigens.**

Immunoglobulin Classes

III. IgA

- **Structure: Dimer**
- **Percentage serum antibodies: 10-15%**
- **Location: Secretions (tears, saliva, intestine, milk), blood and lymph.**
- **Half-life in serum: 6 days**
- **Complement Fixation: No**
- **Placental Transfer: No**
- **Known Functions: Localized protection of *mucosal* surfaces. Provides immunity to infant digestive tract.**

Immunoglobulin Classes

IV. IgD

- **Structure: Monomer**
- **Percentage serum antibodies: 0.2%**
- **Location: B-cell surface, blood, and lymph**
- **Half-life in serum: 3 days**
- **Complement Fixation: No**
- **Placental Transfer: No**
- **Known Functions: In serum function is unknown. On B cell surface, initiate immune response.**

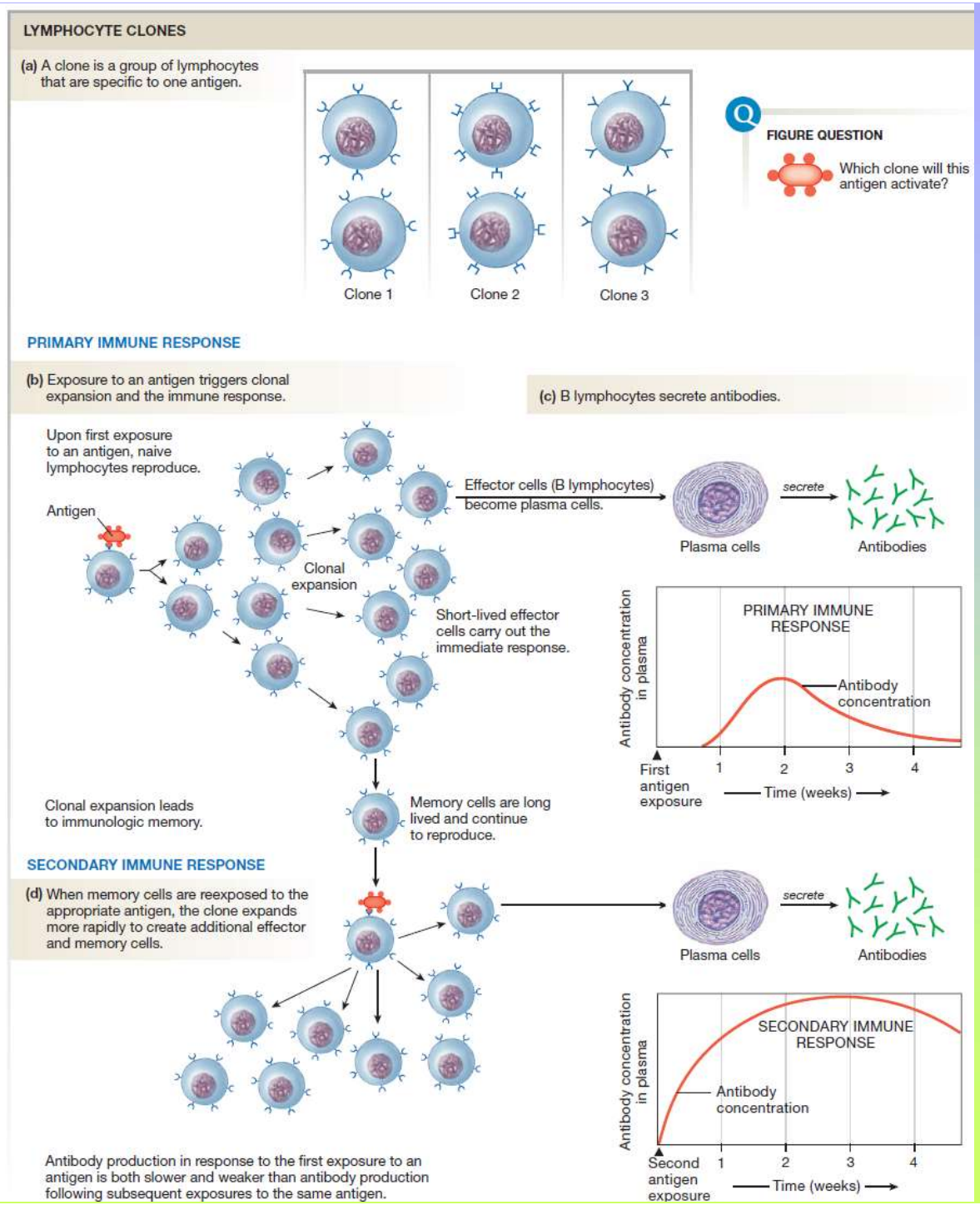
Immunoglobulin Classes

V. IgE

- **Structure: Monomer**
- **Percentage serum antibodies: 0.002%**
- **Location: Bound to mast cells and basophils throughout body. Blood.**
- **Half-life in serum: 2 days**
- **Complement Fixation: No**
- **Placental Transfer: No**
- **Known Functions: Allergic reactions. Possibly lysis of worms.**

How Do B Cells Produce Antibodies?

- B cells develop from stem cells in the bone marrow of adults (liver of fetuses).
- After maturation B cells migrate to lymphoid organs (lymph node or spleen).
- Clonal Selection: When a B cell encounters an antigen it recognizes, it is stimulated and divides into many clones called plasma cells, which actively secrete antibodies.
- Each B cell produces antibodies that will recognize only one antigenic determinant.


LYMPHOCYTE CLONES
(a) A clone is a group of lymphocytes that are specific to one antigen.
Clone 1
Clone 2
Clone 3
FIGURE QUESTION
Which clone will this antigen activate?
PRIMARY IMMUNE RESPONSE
(b) Exposure to an antigen triggers clonal expansion and the immune response.
(c) B lymphocytes secrete antibodies.
Upon first exposure to an antigen, naive lymphocytes reproduce.
Antigen
Clonal expansion
Effector cells (B lymphocytes) become plasma cells.
Plasma cells
secrete
Antibodies
Short-lived effector cells carry out the immediate response.
Clonal expansion leads to immunologic memory.
Memory cells are long lived and continue to reproduce.
PRIMARY IMMUNE RESPONSE
Antibody concentration in plasma
Antibody concentration
First antigen exposure
1
2
3
4
Time (weeks)
SECONDARY IMMUNE RESPONSE
(d) When memory cells are reexposed to the appropriate antigen, the clone expands more rapidly to create additional effector and memory cells.
Plasma cells
secrete
Antibodies
SECONDARY IMMUNE RESPONSE
Antibody concentration in plasma
Antibody concentration
Second antigen exposure
1
2
3
4
Time (weeks)
Antibody production in response to the first exposure to an antigen is both slower and weaker than antibody production following subsequent exposures to the same antigen.

Humoral Immunity

Apoptosis

- Programmed cell death ("Falling away").
- Human body makes 100 million lymphocytes every day. If an equivalent number doesn't die, will develop leukemia.
- B cells that do not encounter stimulating antigen will self-destruct and send signals to phagocytes to dispose of their remains.
- Many virus infected cells will undergo apoptosis, to help prevent spread of the infection.

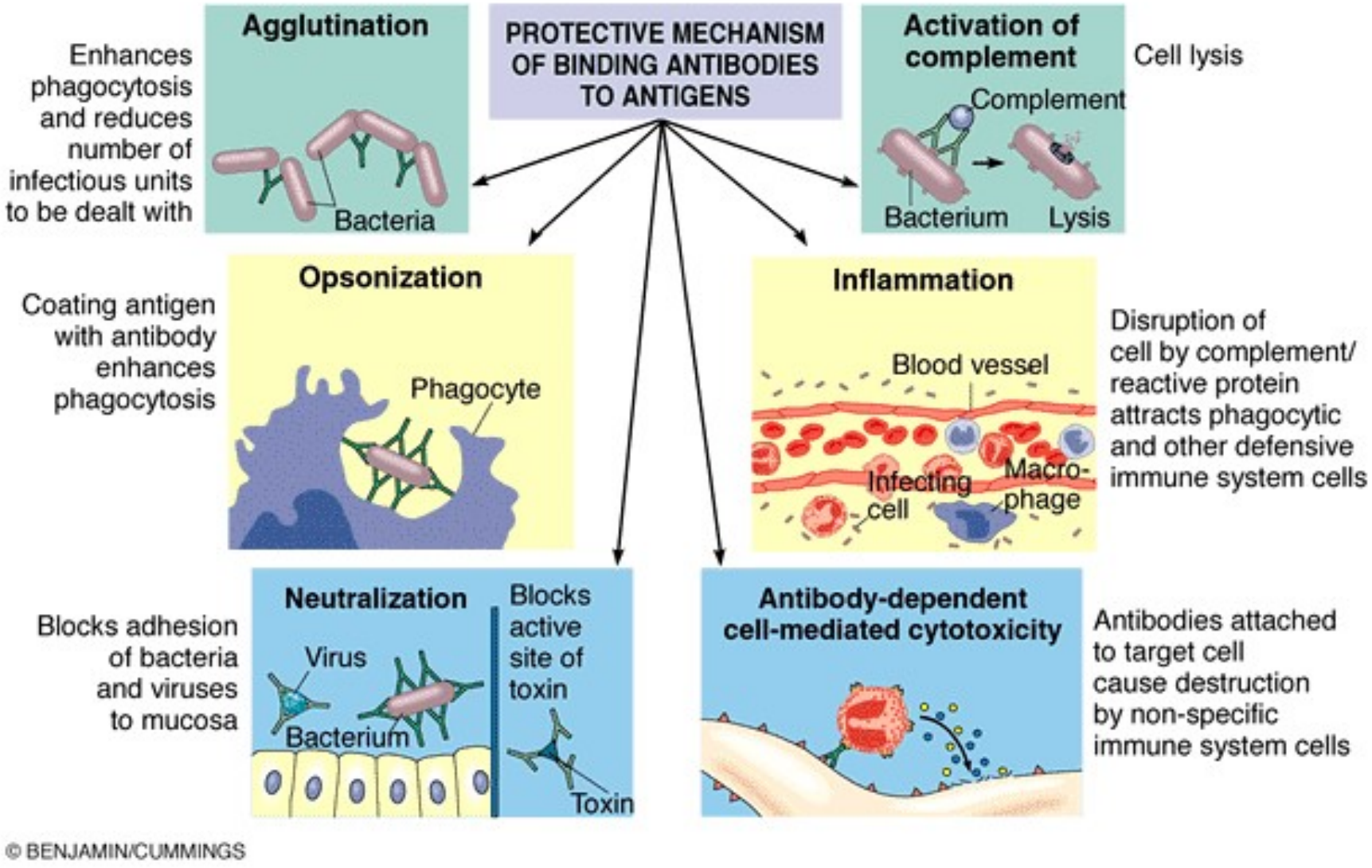
Consequences of Antigen-Antibody Binding

Antigen-Antibody Complex: Formed when an antibody binds to an antigen it recognizes.

Affinity: A measure of binding strength.

1. **Agglutination: Antibodies cause antigens (microbes) to clump together.**
   - **IgM (decavalent) is more effective that IgG (bivalent).**
   - **Hemagglutination: Agglutination of red blood cells. Used to determine ABO blood types and to detect influenza and measles viruses.**
2. **Opsonization: Antigen (microbe) is covered with antibodies that enhances its ingestion and lysis by phagocytic cells.**

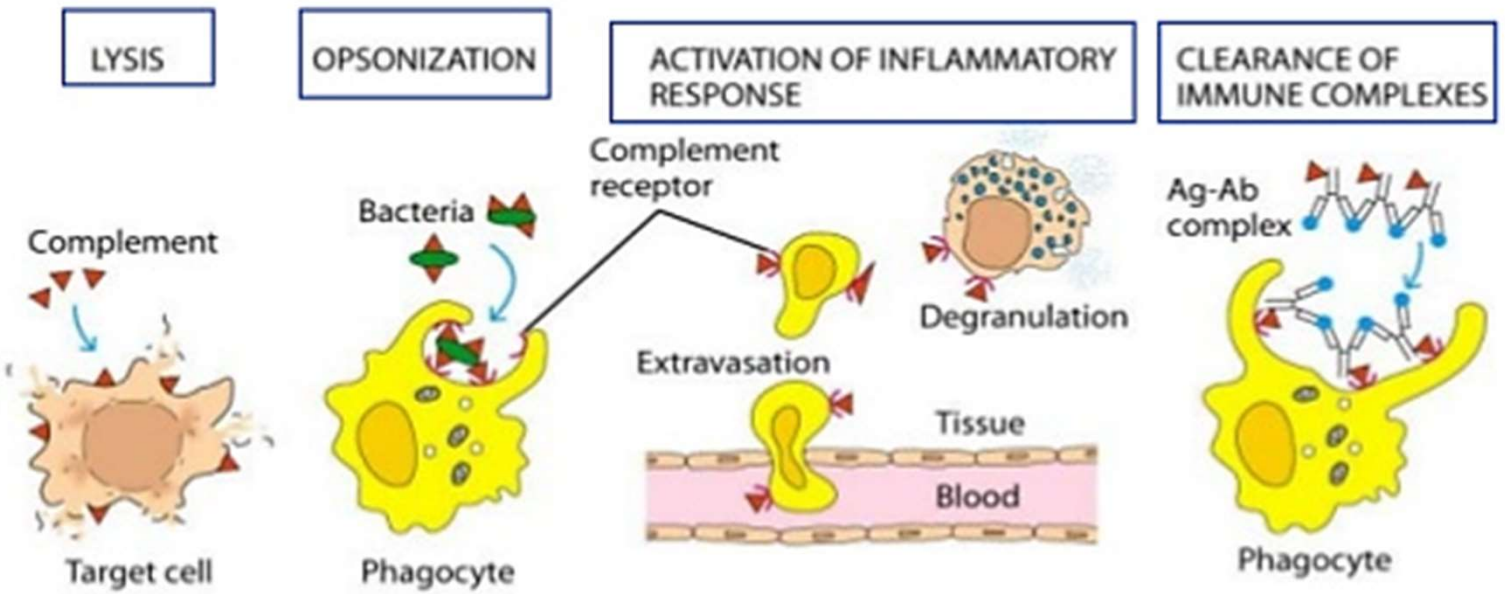
Consequences of Antibody Binding



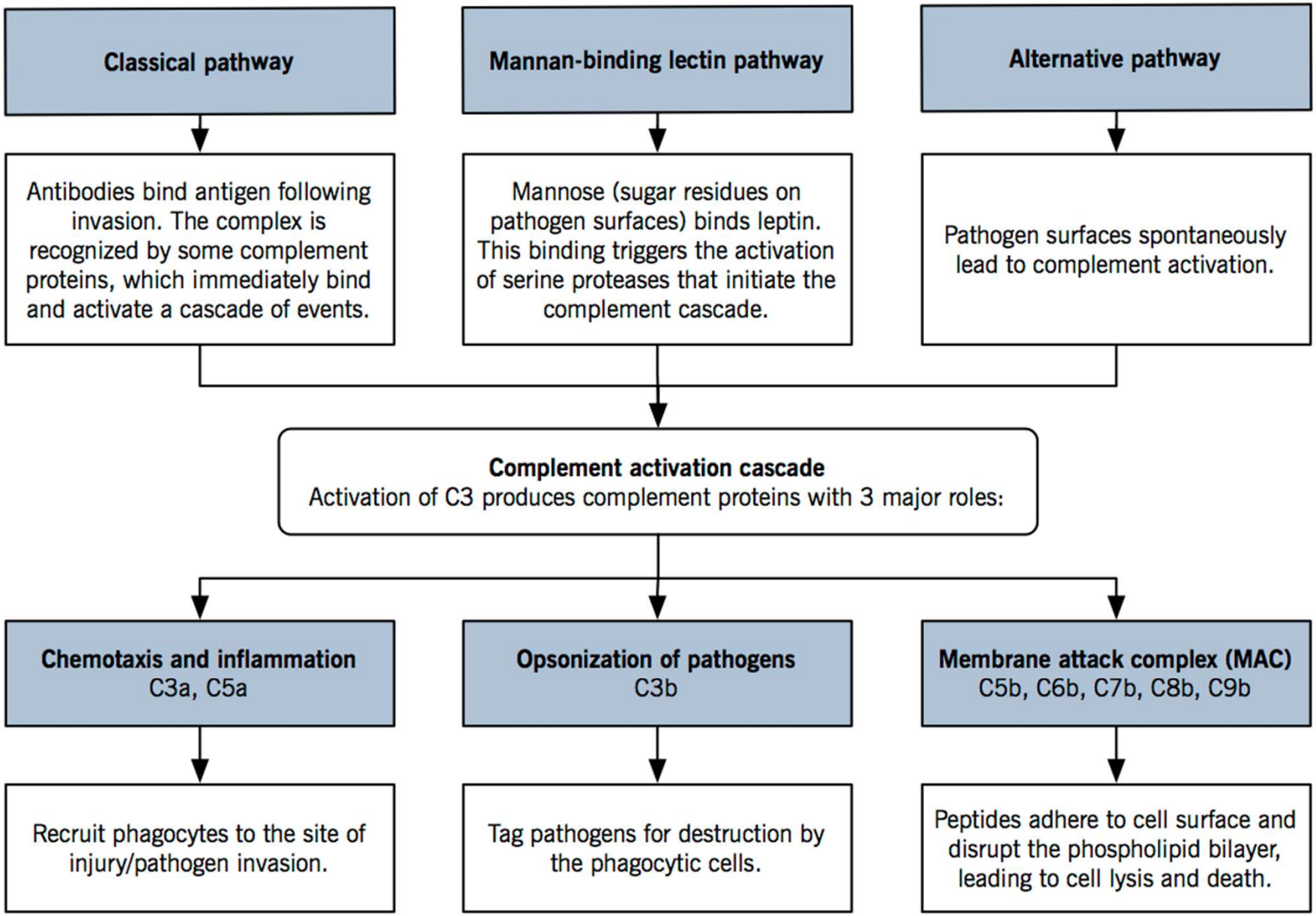
Humoral Immunity

3. Neutralization: IgG inactivates viruses by binding to their surface and neutralize toxins by blocking their active sites.
4. Antibody-dependent cell-mediated cytotoxicity: Used to destroy large organisms (e.g.: worms). Target organism is coated with antibodies and bombarded with chemicals from nonspecific immune cells.
5. Complement Activation: Both IgG and IgM trigger the complement system which results in cell lysis and inflammation.

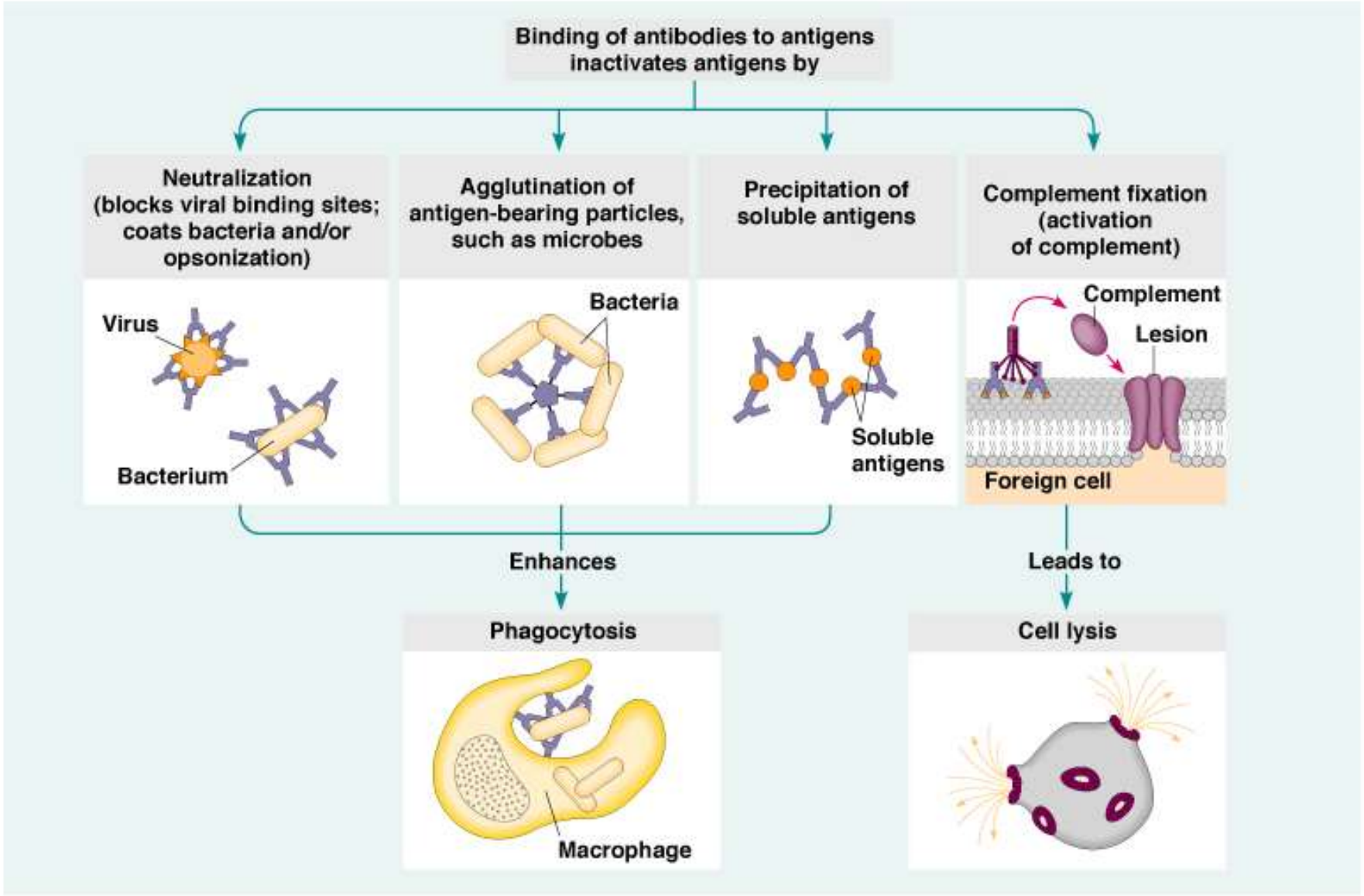
The multiple activities of the complement system.



Complement pathways



Consequences of Antibody Binding



Immunological Memory

Antibody Titer: The amount of antibody in the serum.

Pattern of Antibody Levels During Infection

Primary Response:

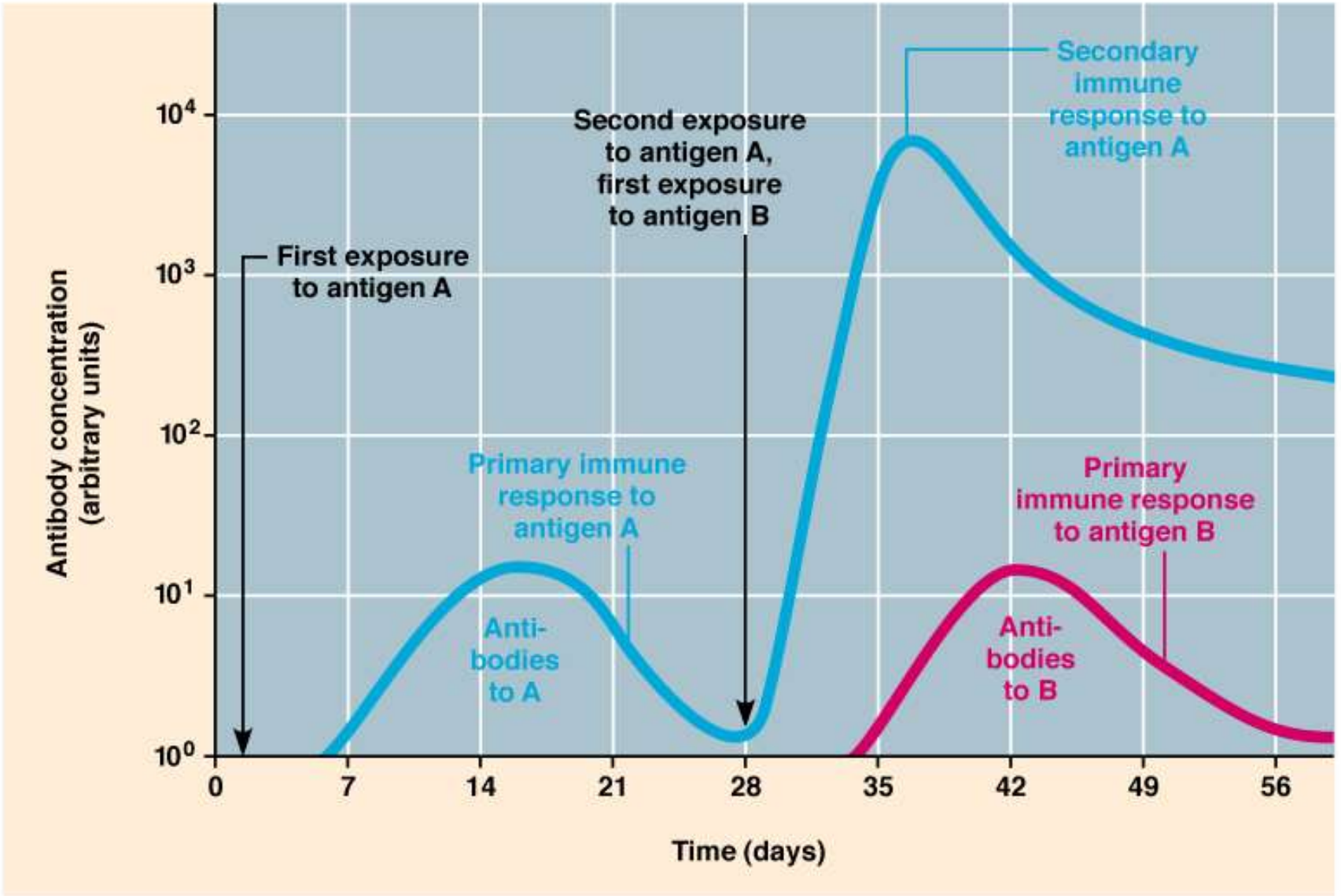
- **After *initial* exposure to antigen, no antibodies are found in serum for several days.**
- **A gradual increase in titer, first of IgM and then of IgG is observed.**
- **Most B cells become plasma cells, but some B cells become long living *memory cells*.**
- **Gradual decline of antibodies follows.**

Immunological Memory (Continued)

Secondary Response:

- **Subsequent exposure to the same antigen displays a faster and more intense antibody response.**
- **Increased antibody response is due to the existence of memory cells, which rapidly produce plasma cells upon antigen stimulation.**

Antibody Response After Exposure to Antigen



T Cells and Cell Mediated Immunity

Antigens that stimulate this response are mainly *intracellular*.

Requires constant presence of antigen to remain effective.

Unlike humoral immunity, cell mediated immunity is not transferred to the fetus.

Cytokines: Chemical messengers of immune cells.

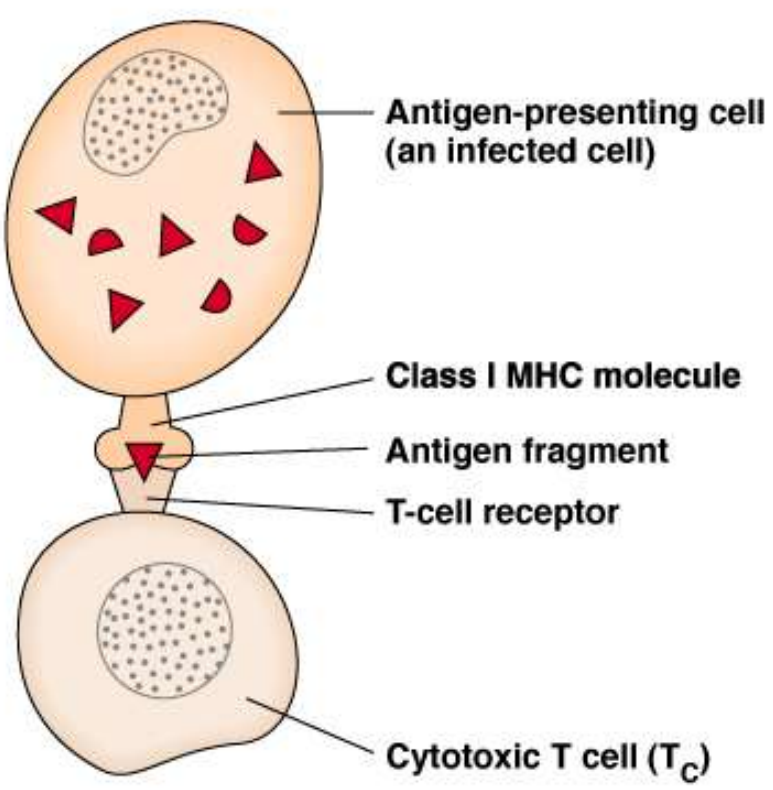
- **Over 100 have been identified.**
- **Stimulate and/or regulate immune responses.**
  - **Interleukins: Communication between WBCs.**
  - **Interferons: Protect against viral infections.**
  - **Chemokines: Attract WBCs to infected areas.**

T Cells and Cell Mediated Immunity

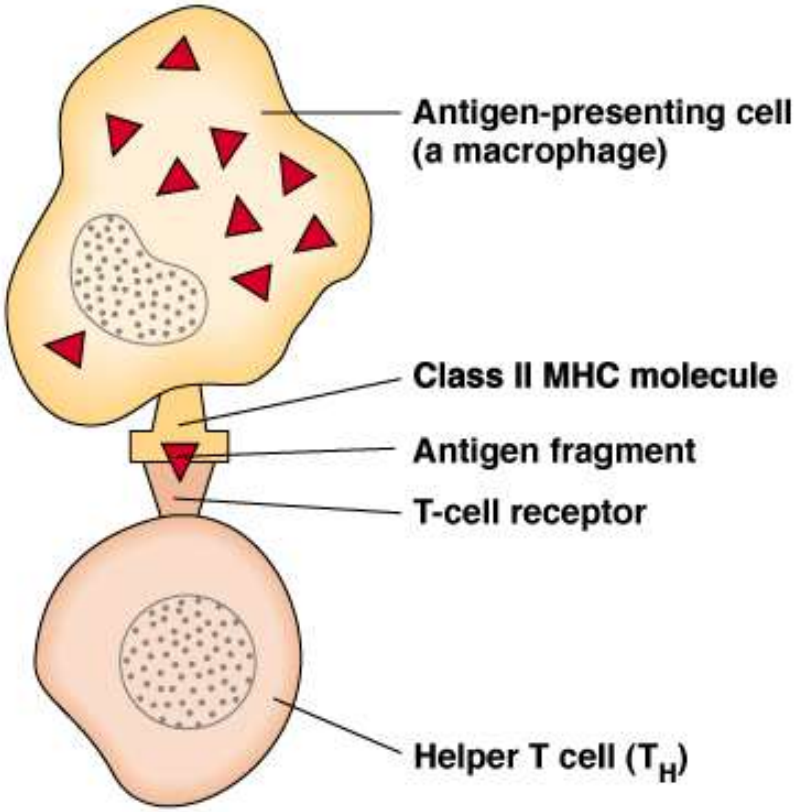
Cellular Components of Immunity:

- **T cells are key cellular component of immunity.**
- **T cells have an antigen receptor that recognizes and reacts to a specific antigen (T cell receptor).**
- **T cell receptor only recognize antigens combined with major histocompatability (MHC) proteins on the surface of cells.**
  - **MHC Class I: Found on all cells.**
  - **MHC Class II: Found on phagocytes.**
- **Clonal selection increases number of T cells.**

T Cells Only Recognize Antigen Associated with MHC Molecules on Cell Surfaces



(a)



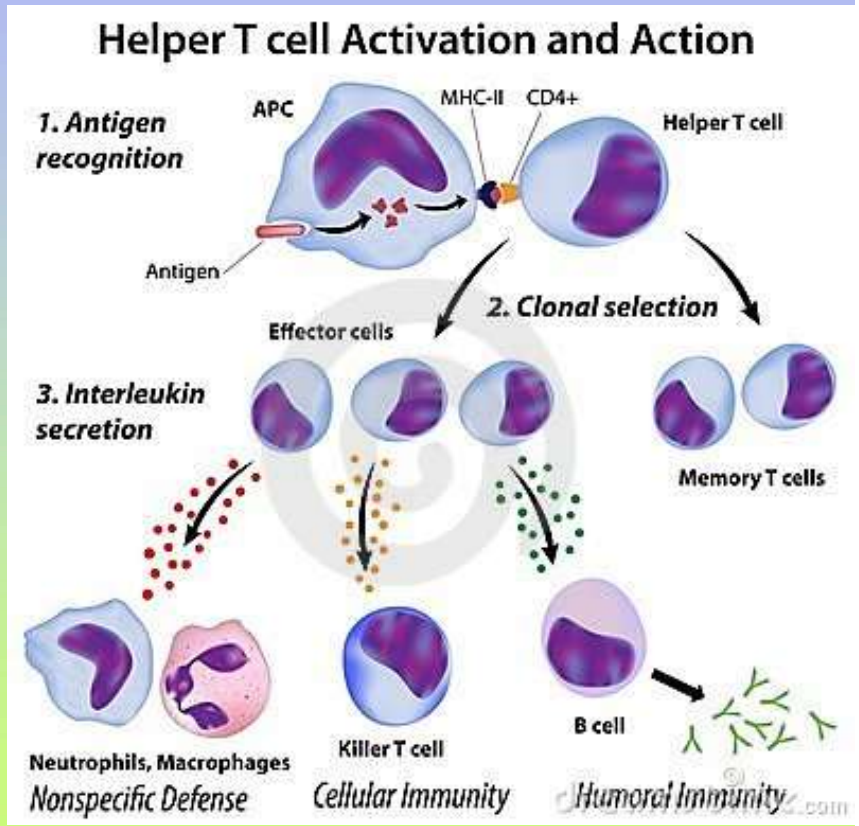
(b)

T Cells and Cell Mediated Immunity

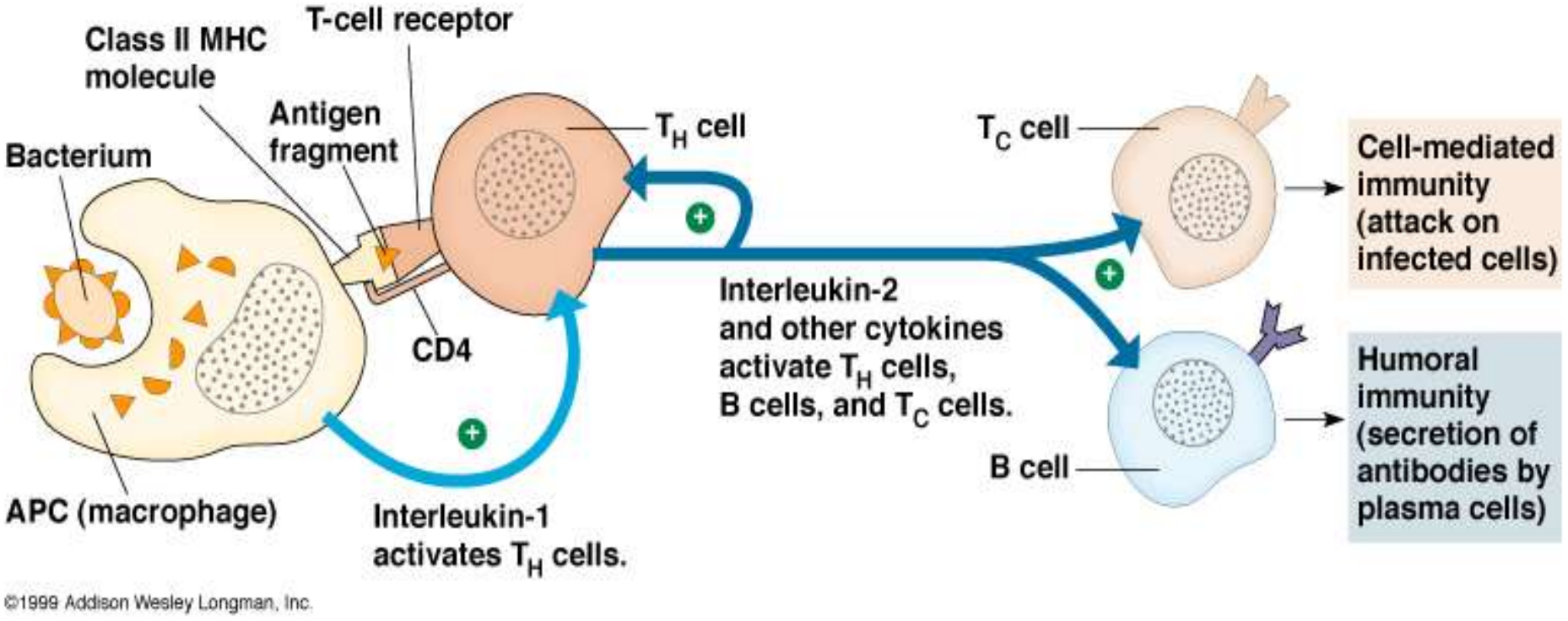
Types of T cells

1. T Helper (T_H) Cells: Central role in immune response.

- Most are $CD4^+$
- Recognize antigen on the surface of antigen presenting cells (e.g.: macrophage).
- Activate macrophages
- Induce formation of cytotoxic T cells
- Stimulate B cells to produce antibodies.



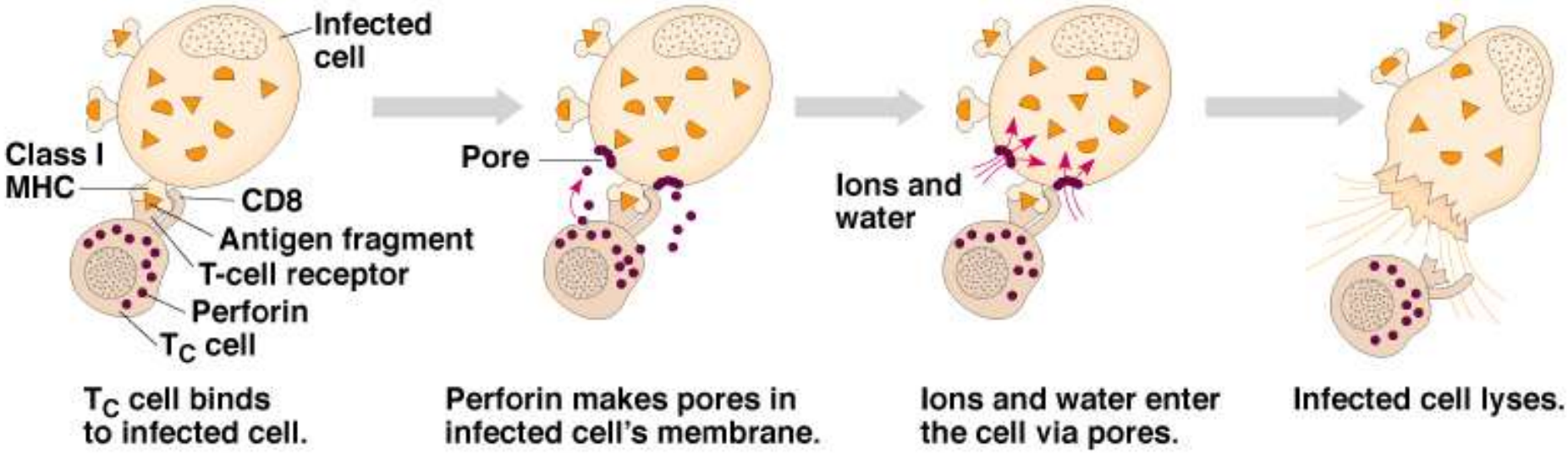
Central Role of Helper T Cells



Types of T cells (Continued)

2. **Cytotoxic T (Tc) Cells: Destroy target cells.**
   - **Most are CD4 negative ($CD4^-$).**
   - **Recognize antigens on the surface of all cells:**
     - **Kill host cells that are infected with viruses or bacteria.**
     - **Recognize and kill cancer cells.**
     - **Recognize and destroy transplanted tissue.**
   - **Release protein called *perforin* which forms a pore in target cell, causing lysis of infected cells.**
   - **Undergo apoptosis when stimulating antigen is gone.**

Cytotoxic T Cells Lyse Infected Cells

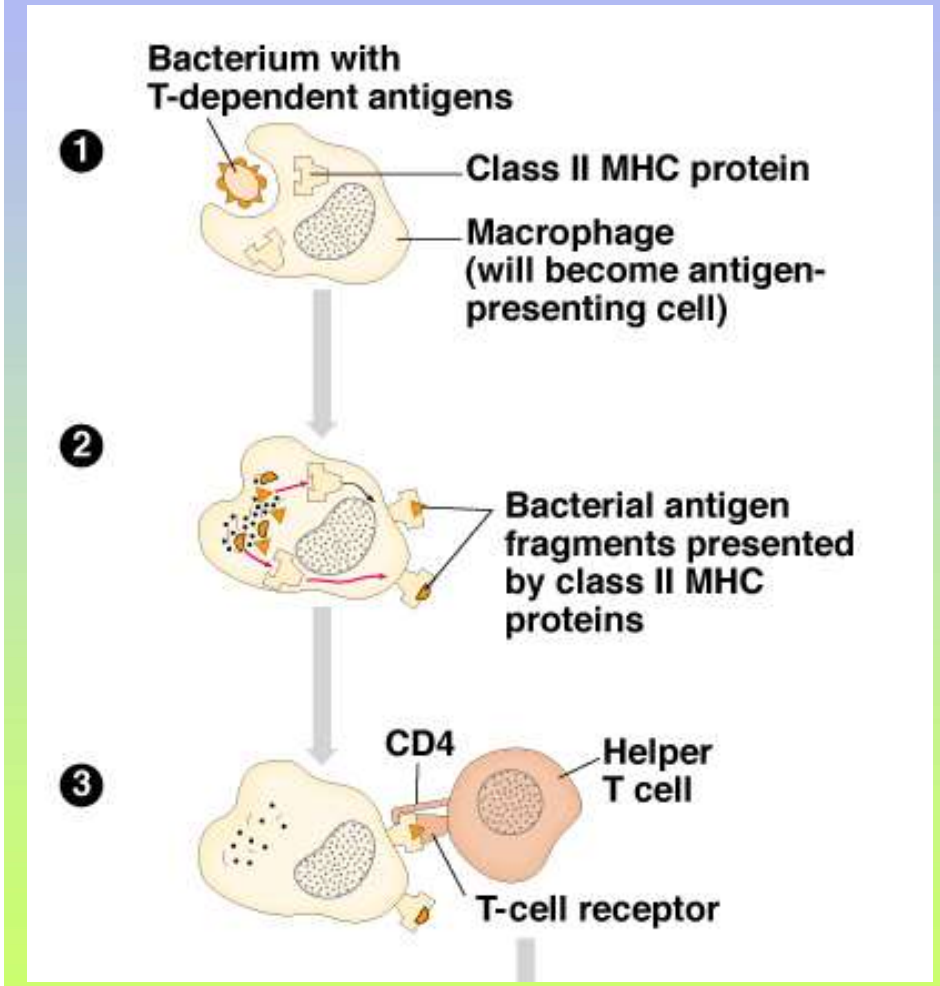


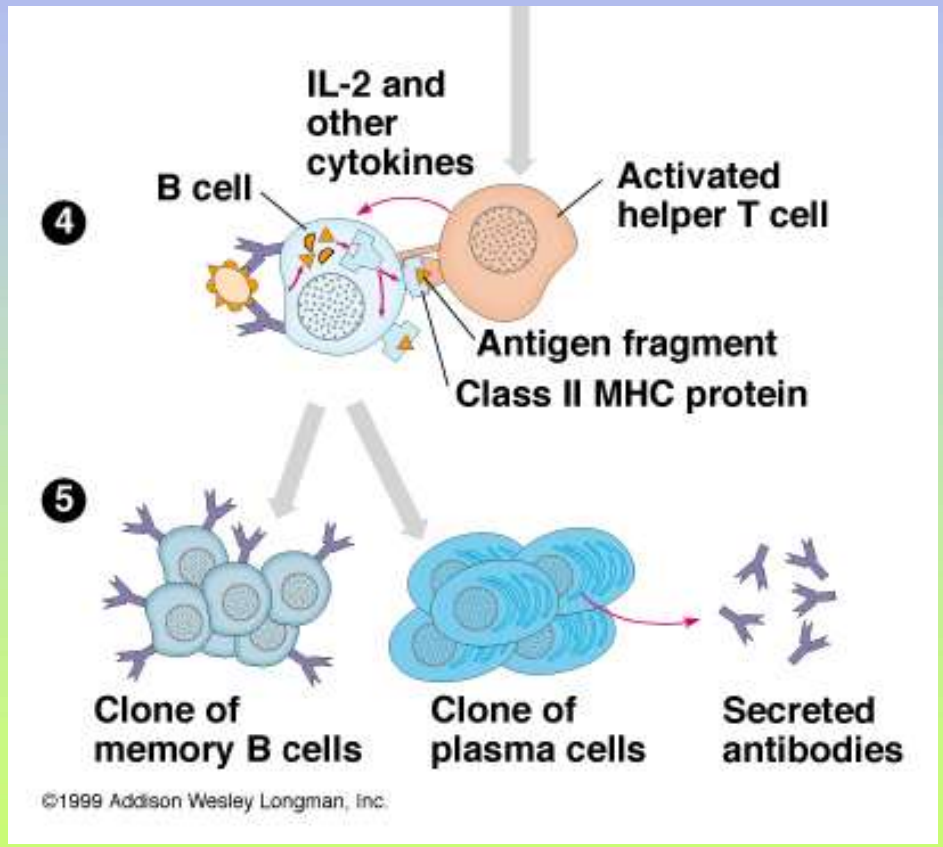
(a)

Types of T cells (Continued)

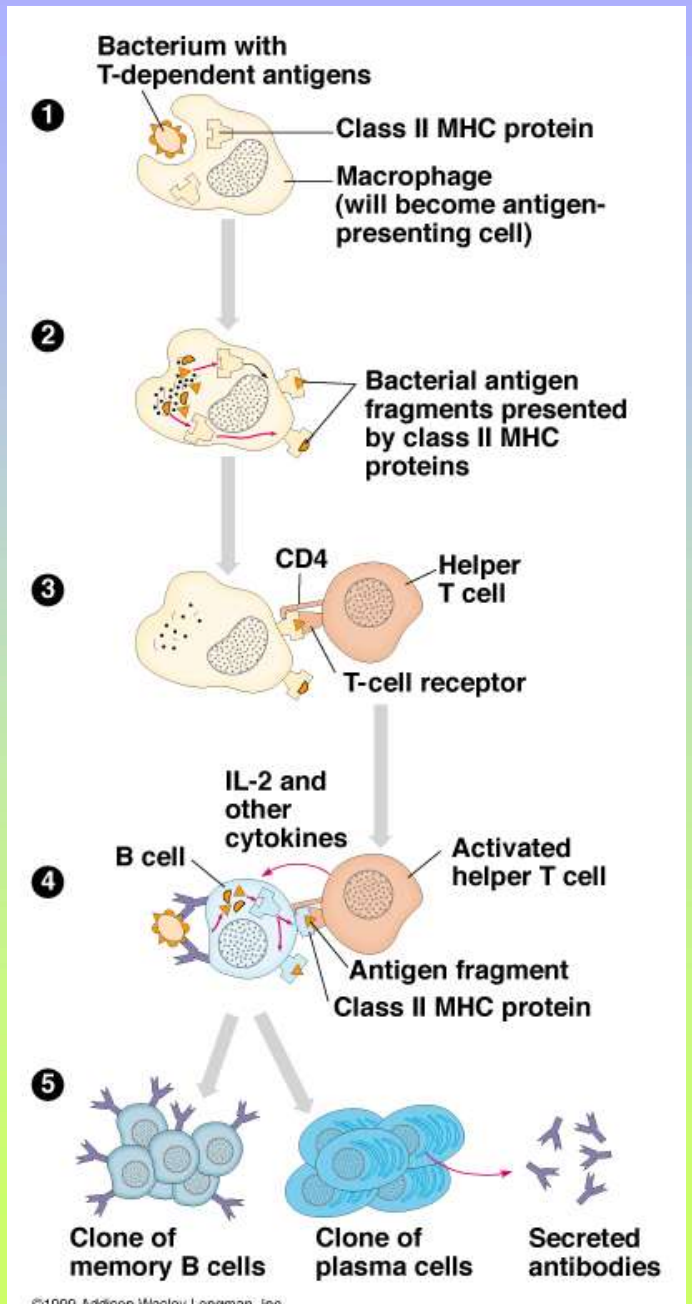
3. **Delayed Hypersensitivity T (T_D) Cells: Mostly T helper and a few cytotoxic T cells that are involved in some allergic reactions (poison ivy) and rejection of transplanted tissue.**
4. **T Suppressor (Ts) Cells: May shut down immune response.**

Humoral Response to T Dependent Antigens





Humoral Response to T Dependent Antigens

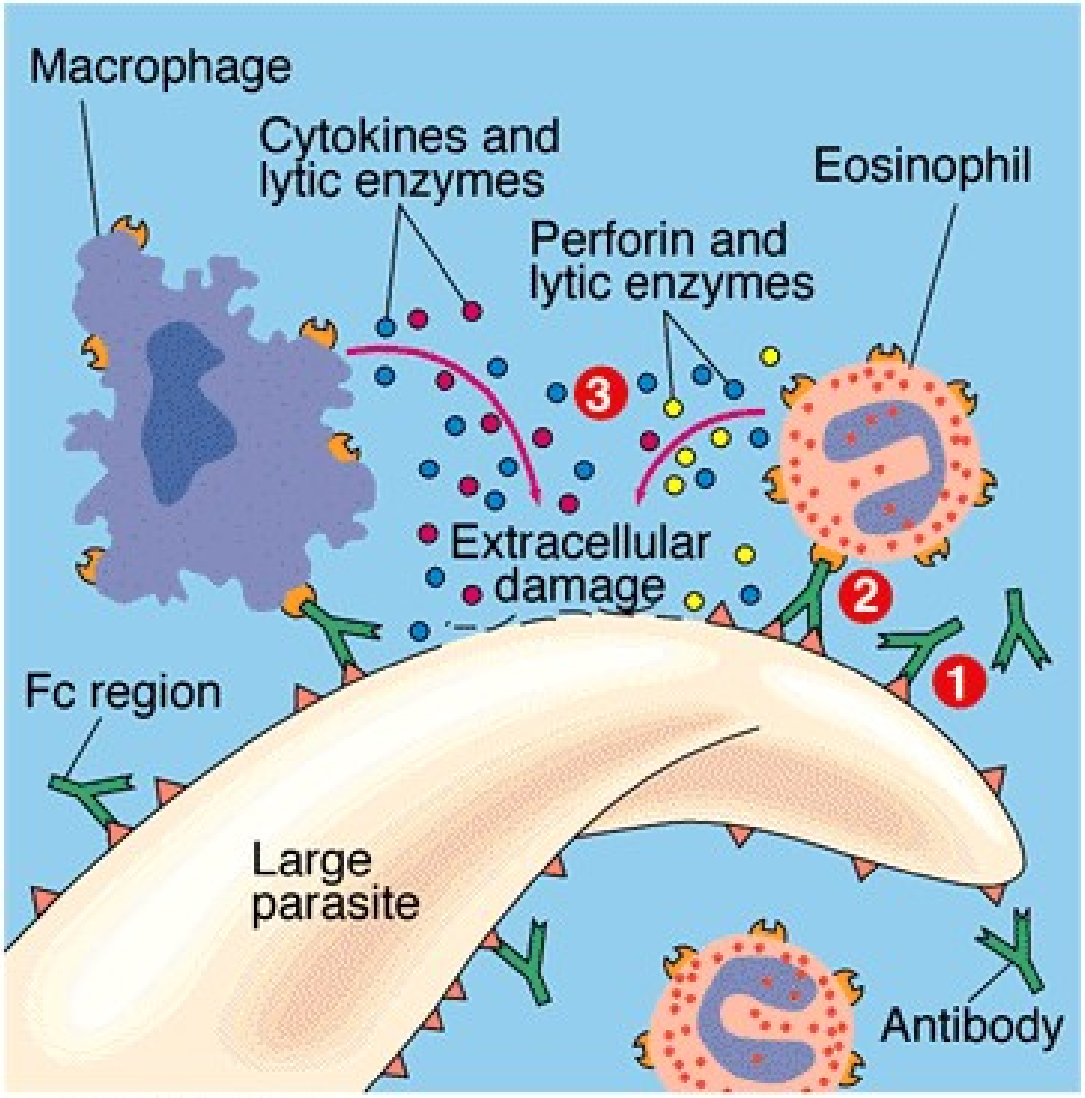


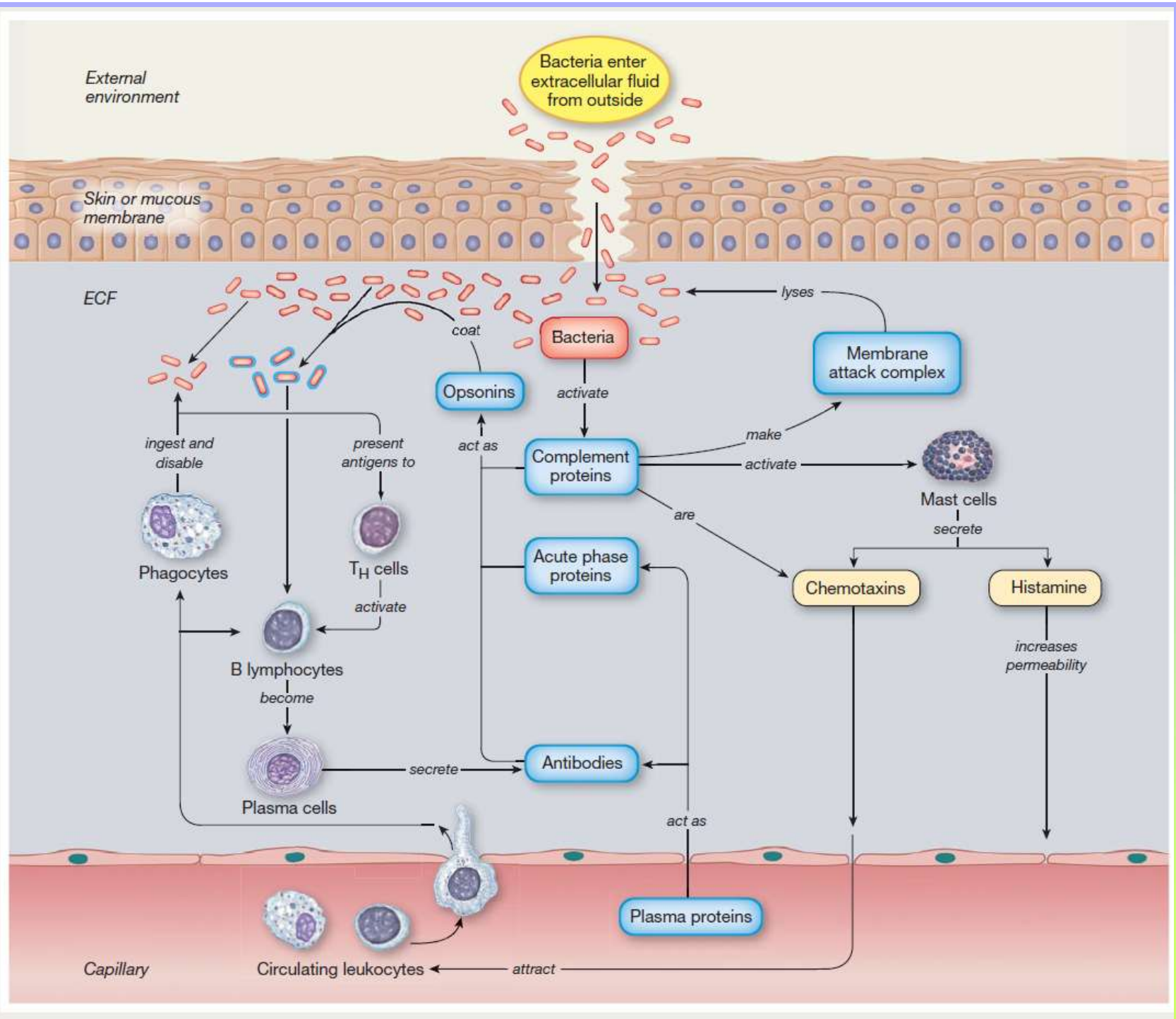
Relationship Between Cell-Mediated and Humoral Immunity

2. Antibody Dependent Cell Mediated Cytotoxicity (ADCC)

- Target cell is covered with antibodies, leaving Fc portion sticking outwards.
- Natural killer and other nonspecific cells that have receptors for Fc region are stimulated to kill targeted cells.
- Target organism is lysed by substances secreted by attacking cells.
- Used to destroy large organisms that cannot be phagocytosed.

Destruction of Large Parasites by ADCC




External environment
Bacteria enter extracellular fluid from outside
Skin or mucous membrane
ECF
Bacteria
coat
lyses
Membrane attack complex
Opsonins
activate
act as
make
Complement proteins
activate
Mast cells
ingest and disable
present antigens to
Phagocytes
TH cells
are
secrete
Acute phase proteins
Chemotaxins
Histamine
activate
B lymphocytes
increases permeability
become
Antibodies
secrete
Plasma cells
act as
Plasma proteins
Capillary
Circulating leukocytes
attract

Immune Responses to Viruses

This figure assumes prior exposure to the virus and preexisting antibodies.

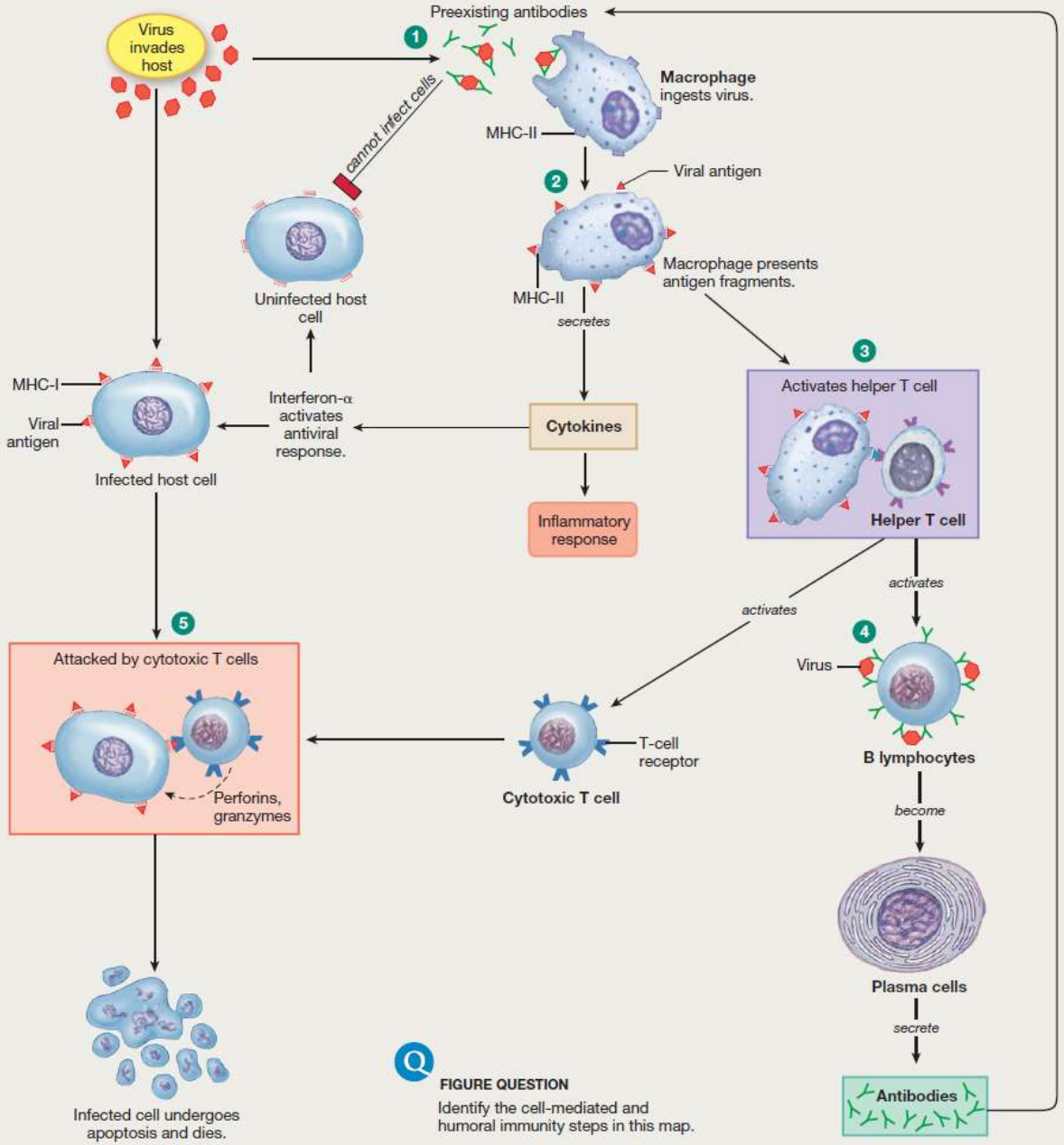
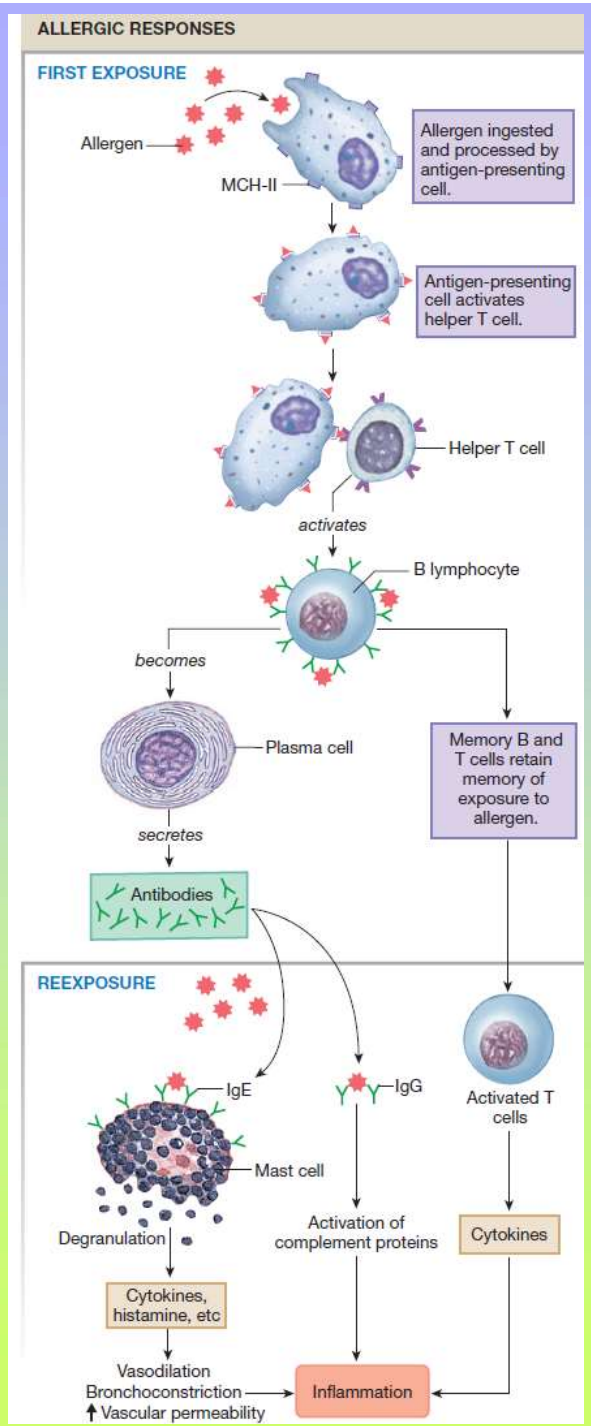


FIGURE QUESTION

Identify the cell-mediated and humoral immunity steps in this map.


ALLERGIC RESPONSES
FIRST EXPOSURE
Allergen
MCH-II
Allergen ingested and processed by antigen-presenting cell.
Antigen-presenting cell activates helper T cell.
Helper T cell
activates
B lymphocyte
becomes
Plasma cell
Memory B and T cells retain memory of exposure to allergen.
secretes
Antibodies
REEXPOSURE
IgE
IgG
Activated T cells
Mast cell
Degranulation
Activation of complement proteins
Cytokines
Cytokines, histamine, etc
Vasodilation
Bronchoconstriction
↑ Vascular permeability
Inflammation