The Immune Response and immune system

The Immune Response

Immunity: "Free from burden". Ability of an organism to recognize and defend itself against *specific* pathogens or antigens.

Immune Response: Third line of defense. Involves production of antibodies and generation of specialized lymphocytes against specific antigens.

Antigen: Molecules from a pathogen or foreign organism that provoke a specific immune response.

The Immune System is the Third Line of Defense Against Infection

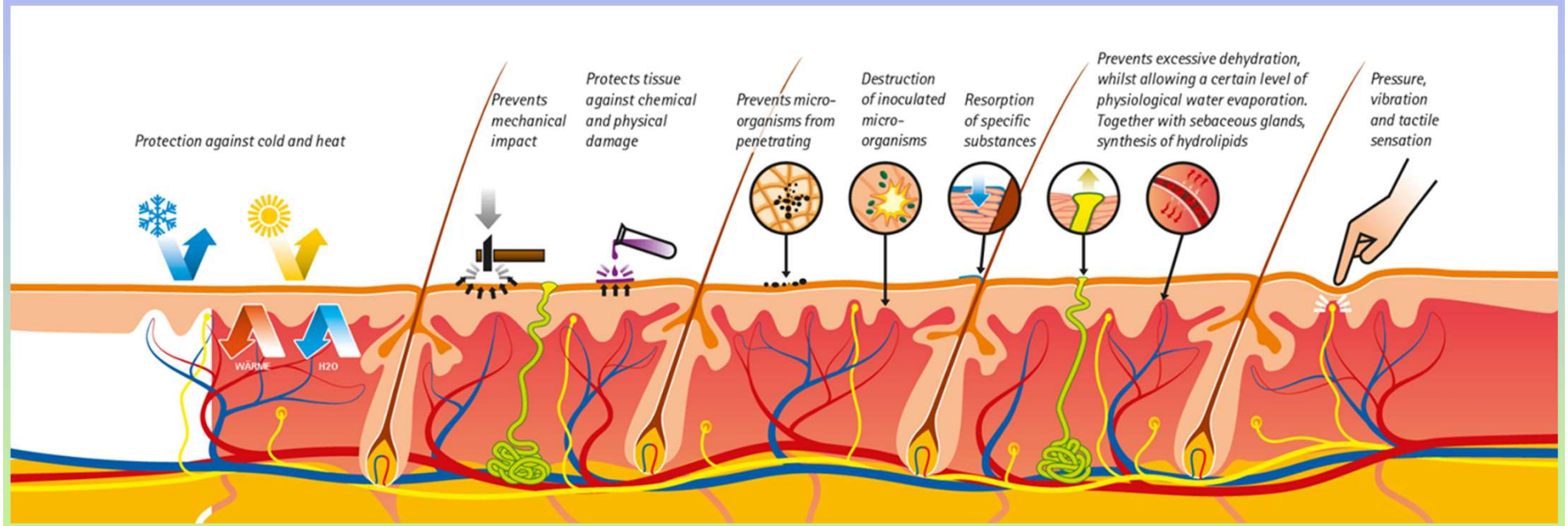
Nonspecific defense mechanisms		Specific defense mechanisms (immune system)
First line of defense	Second line of defense	Third line of defense
• Skin • Mucous membranes • Secretions of skin and mucous membranes	• Phagocytic white blood cells • Antimicrobial proteins • The inflammatory response	• Lymphocytes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

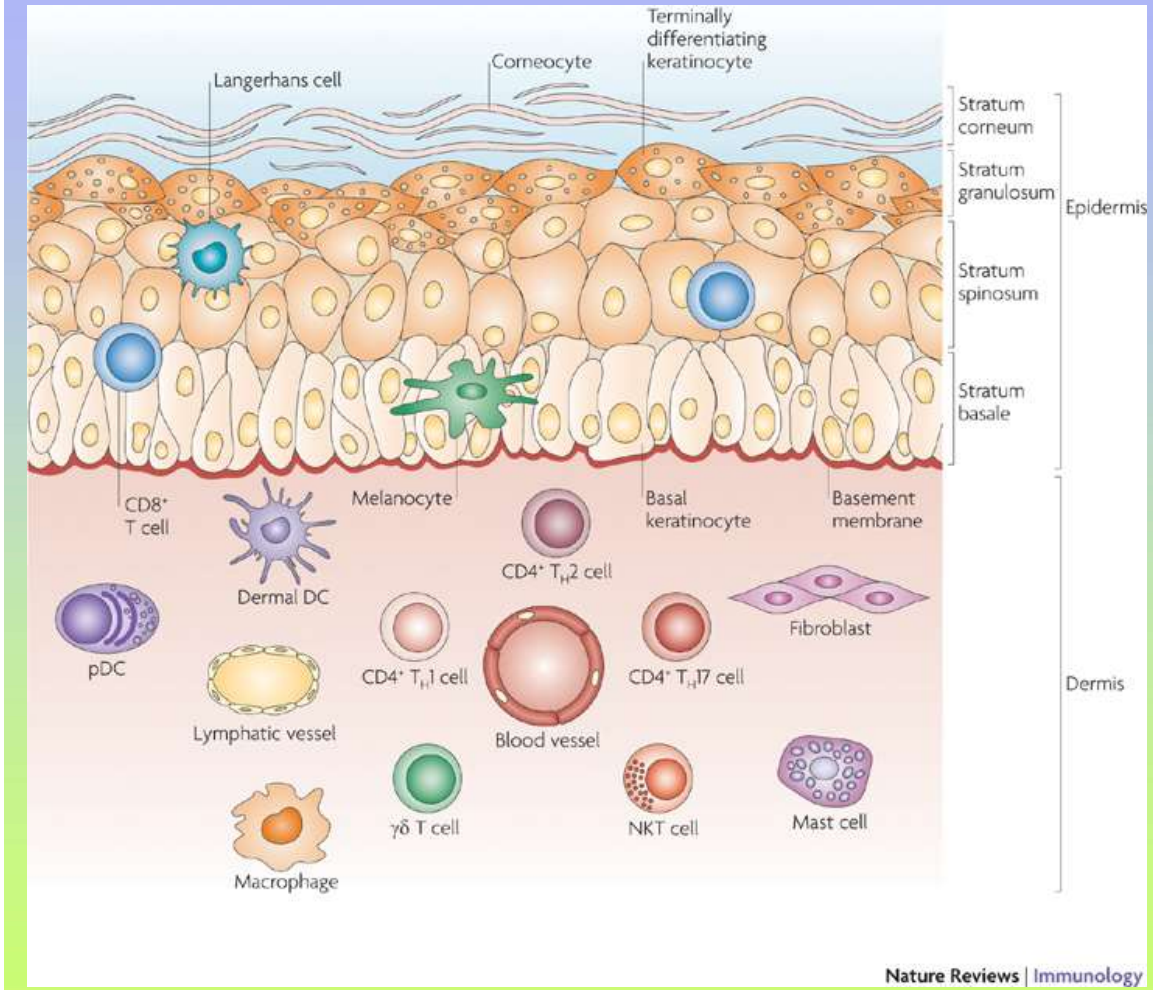
Barrier Defenses

- 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

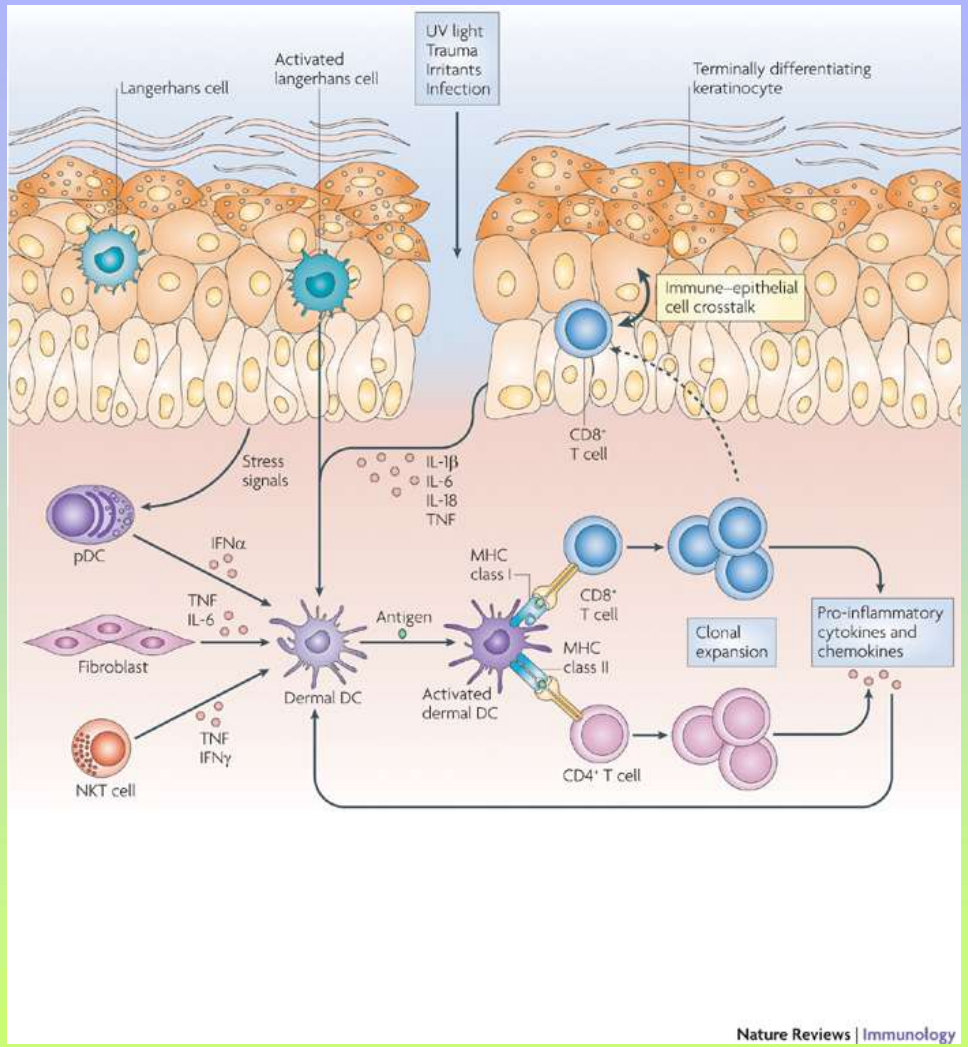
The First Line of Defense
~Skin~

- 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!

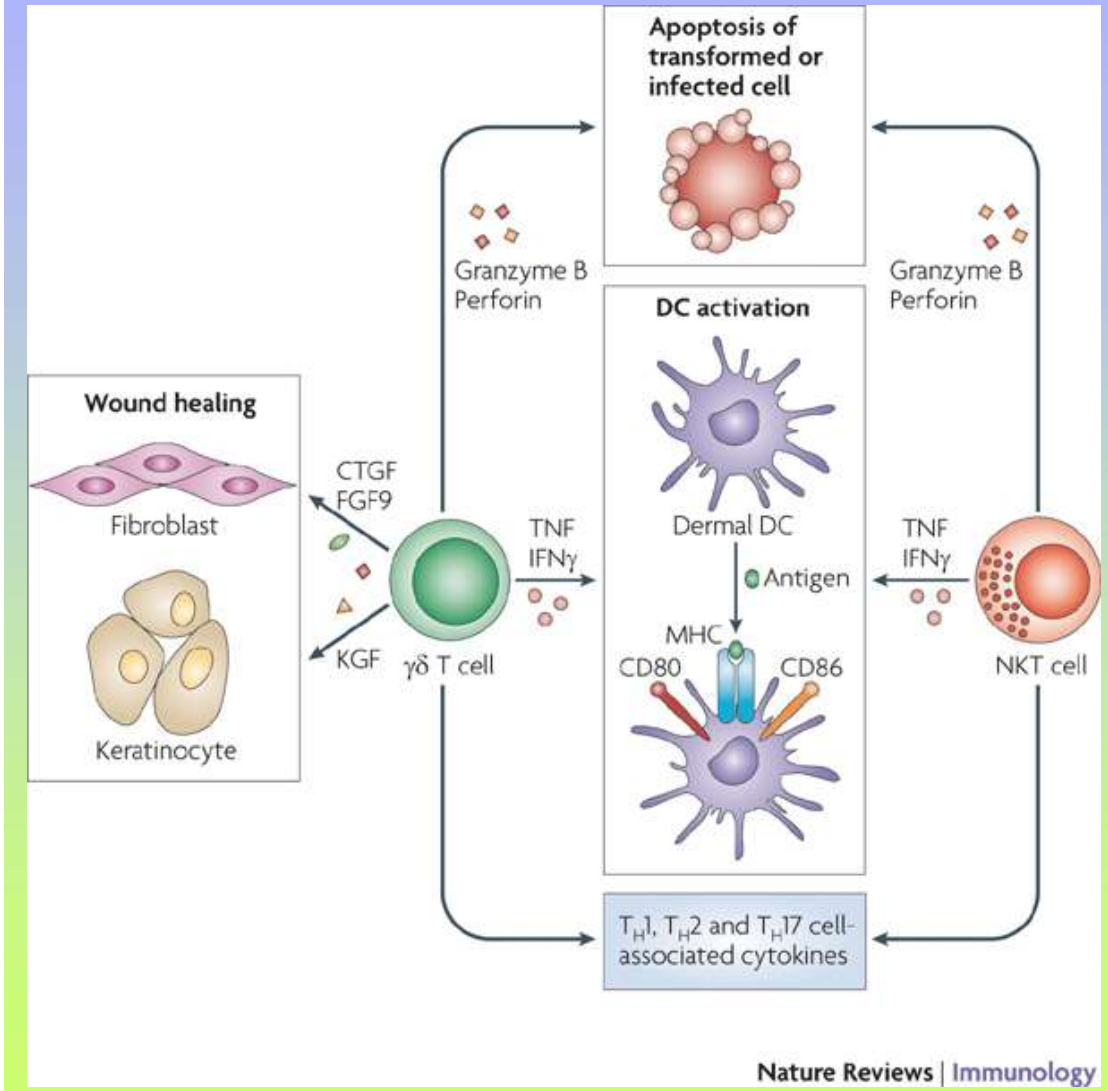

Protection against cold and heat
WÄRME
H2O
Prevents mechanical impact
Protects tissue against chemical and physical damage
Prevents micro-organisms from penetrating
Destruction of inoculated micro-organisms
Resorption of specific substances
Prevents excessive dehydration, whilst allowing a certain level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



The structure of the skin reflects the complexity of its functions as a protective barrier, in maintaining the body temperature, in gathering sensory information from the environment and in having an active role in the immune system. The epidermis contains the stratum basale, the stratum spinosum, the stratum granulosum and the outermost layer, the stratum corneum, which is responsible for the vital barrier function of the skin. Specialized cells in the epidermis include melanocytes, which produce pigment (melanin), and Langerhans cells. Rare T cells, mainly $CD8^+$ cytotoxic T cells, can be found in the stratum basale and stratum spinosum. The dermis is composed of collagen, elastic tissue and reticular fibres. It contains many specialized cells, such as dendritic cell (DC) subsets, including dermal DCs and plasmacytoid DCs (pDCs), and T cell subsets, including $CD4^+$ T helper 1 (T_H1), T_H2 and T_H17 cells, γδ T cells and natural killer T (NKT) cells. In addition, macrophages, mast cells and fibroblasts are present. Blood and lymphatic vessels and nerves (not shown) are also present throughout the dermis.



Ultraviolet (UV) light, trauma, irritants or infection (essentially any type of barrier disruption) triggers a coordinated immune response to maintain skin homeostasis. Skin-resident immune cells are key sentinels for restoring homeostasis but can also be effector cells during tissue pathology. Epidermal Langerhans cells are key immunological sentinels. Keratinocytes sense and react to noxious stimuli by producing pro-inflammatory cytokines (such as interleukin-1β (IL-1β), IL-6, IL-18 and tumour necrosis factor (TNF)), which in turn activate dermal dendritic cells (DCs) in the presence or absence of antigen encounter. Innate immune cells, such as plasmacytoid DCs (pDCs), activated by stress signals derived from keratinocytes, can also contribute to dermal DC activation by releasing interferon-α (IFNα). Fibroblasts can produce TNF and IL-6 and natural killer T (NKT) cells can produce TNF and IFNγ, thereby contributing to the local inflammatory response. Dermal DCs activate and promote the clonal expansion of skin-resident memory $CD4^+$ or $CD8^+$ T cells. T cell-derived pro-inflammatory cytokines and chemokines in turn can further stimulate epithelial and mesenchymal cells, including keratinocytes and fibroblasts, thus amplifying the inflammatory reaction. Moreover, skin-resident T cells can migrate into the epidermis, engaging in an immune–epithelial cell crosstalk.



Nonconventional T cells, such as γδ T cells and natural killer T (NKT) cells, are involved in skin immunosurveillance. Both γδ T cells and NKT cells are cytolytic and release granzyme B and perforin and cause apoptosis of transformed or infected cells. They activate dermal dendritic cells (DCs) by producing tumour necrosis factor (TNF) and interferon-γ (IFNγ). Moreover, γδ T cells produce growth factors that are essential for wound healing, such as connective tissue growth factor (CTGF), fibroblast growth factor 9 (FGF9; also known as GAF) and keratinocyte growth factor (KGF). Finally, both γδ T cells and NKT cells produce cytokines that are usually associated with T helper 1 (T_H1), T_H2 and T_H17 cells.

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!

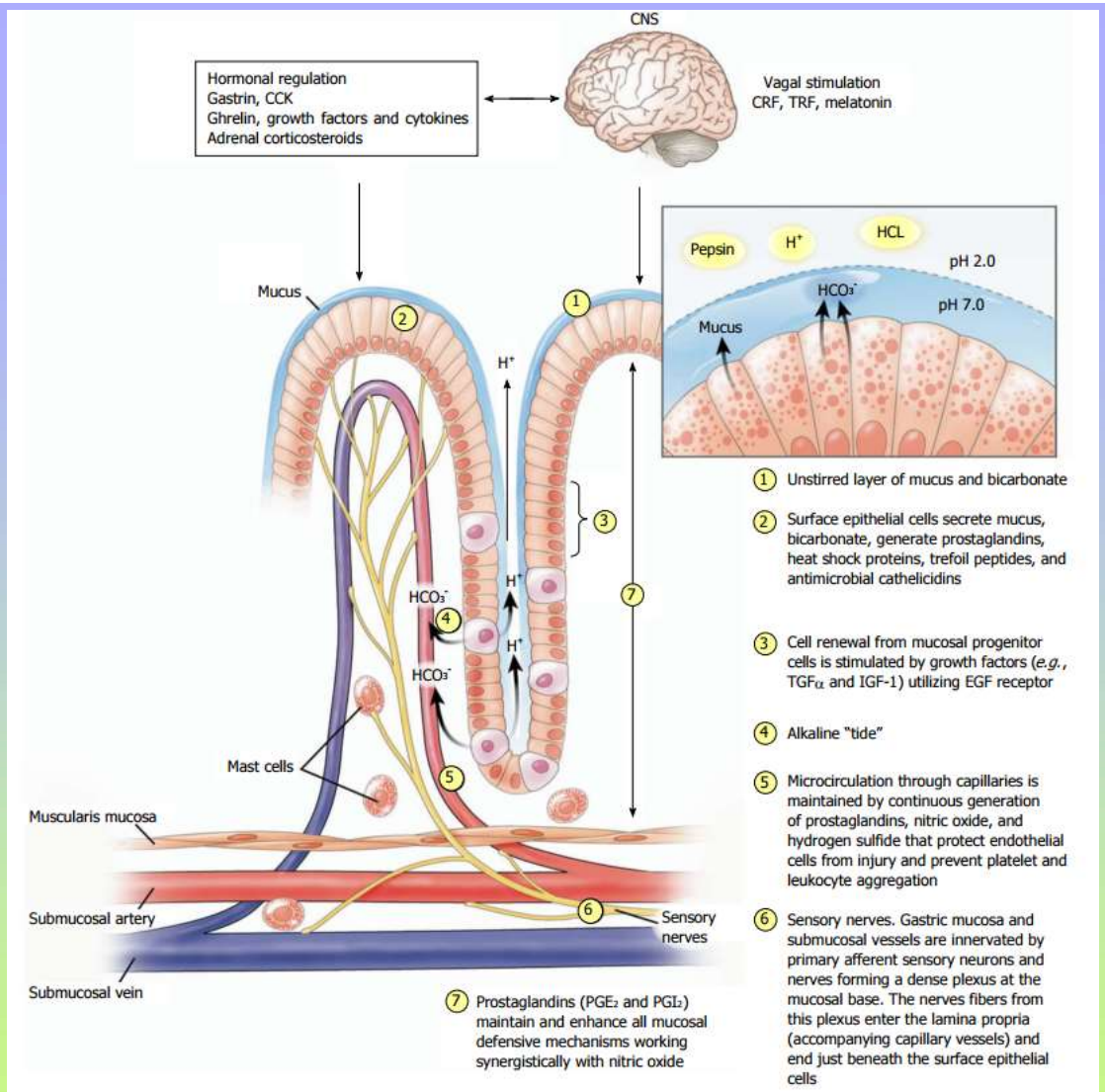


Figure 2 Gastric mucosal defense. Schematic representation of gastric mucosal defense mechanisms. Reproduced with permission from Laine, Takeuchi and Tarnawski[4]. (1) "Unstirred" layer of mucus/bicarbonate/phospholipids above surface epithelial cells constitutes the first line of defense. It maintains a pH of approximation 7.0 (close to the physiological cell pH) at the surface epithelial cells, while pH in the lumen is about 1.0-3.0; (2) the surface epithelial cells secrete mucus, bicarbonate and synthesize prostaglandins and heat shock proteins; (3) mucosal cell renewal from mucosal progenitor cells is driven by growth factors (transforming growth factor α and insulin like growth factor-1α) utilizing the epidermal growth factor receptors). Expression of survivin in epithelial progenitor cells prevents apoptosis and is the key for "immortality" of these cells under normal conditions; (4) "Alkaline tide"-parietal cells secreting HCl into the gastric gland lumen concurrently secrete bicarbonate into the lumen of adjacent capillary blood vessels. Bicarbonate is transported to the surface and contributes to the first line of defense; (5) mucosal microcirculation through the capillary microvessels is essential for delivery of oxygen and nutrients. Endothelial cells of microvessels generate prostaglandins, mainly PGI_2 (prostacyclin) and nitric oxide, which exert vascular and mucosal protective actions; (6) sensory nerve stimulation by H^+-ion or other irritants causes release of neurotransmitters such as calcitonin gene related peptide (CGRP) and substance P in nerve terminals, which induce vasodilatation and enhance mucosal blood flow; and (7) continuous generation of prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2) by the gastric mucosal cells is crucial for the maintenance of mucosal integrity. Almost all of the above (1-6) mucosal defense mechanisms are stimulated or facilitated by endogenous or exogenous prostaglandins. CRF: Corticotrophin-releasing factor; TRF: Thyrotropin-releasing factor; CCK: Cholecystokinin.

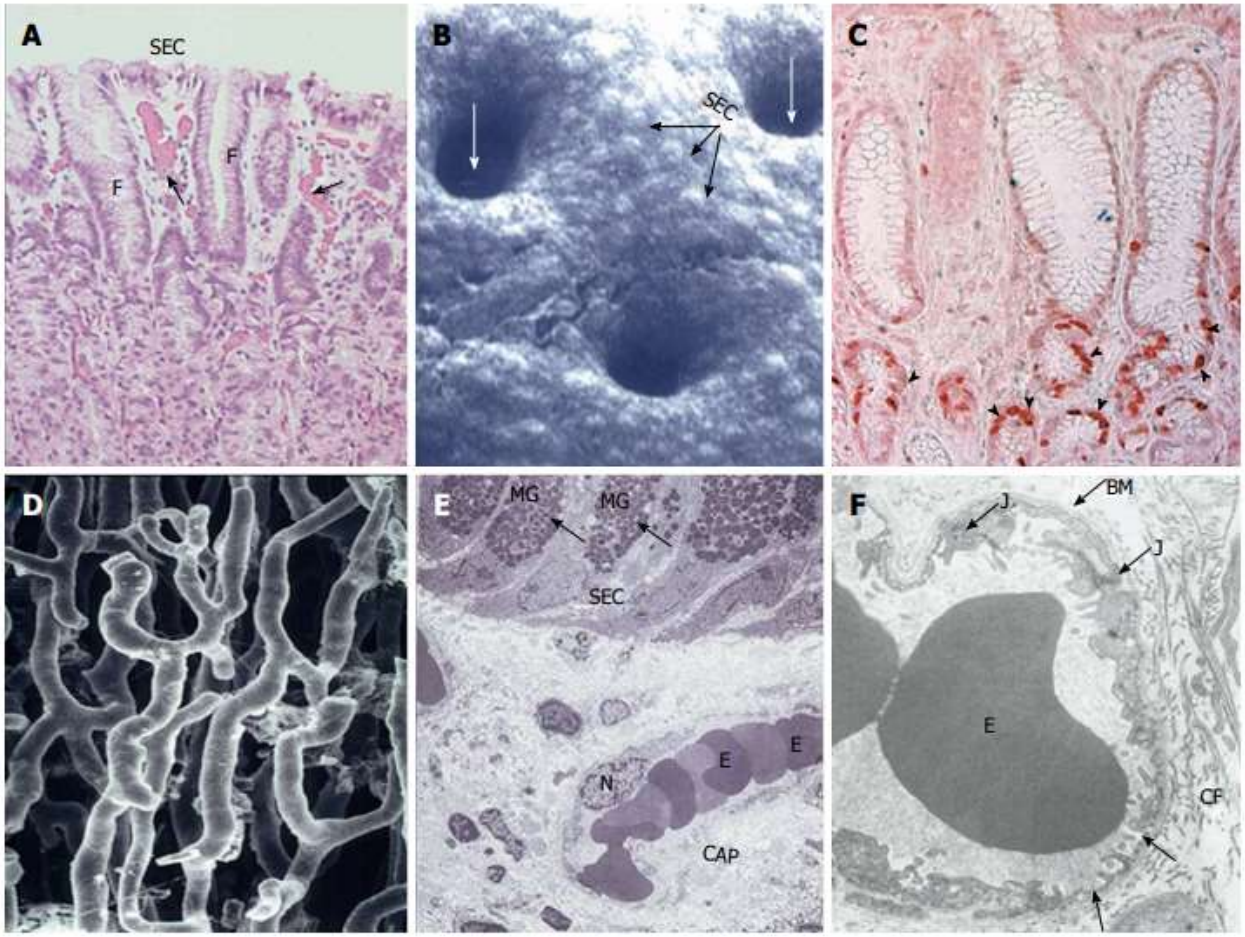
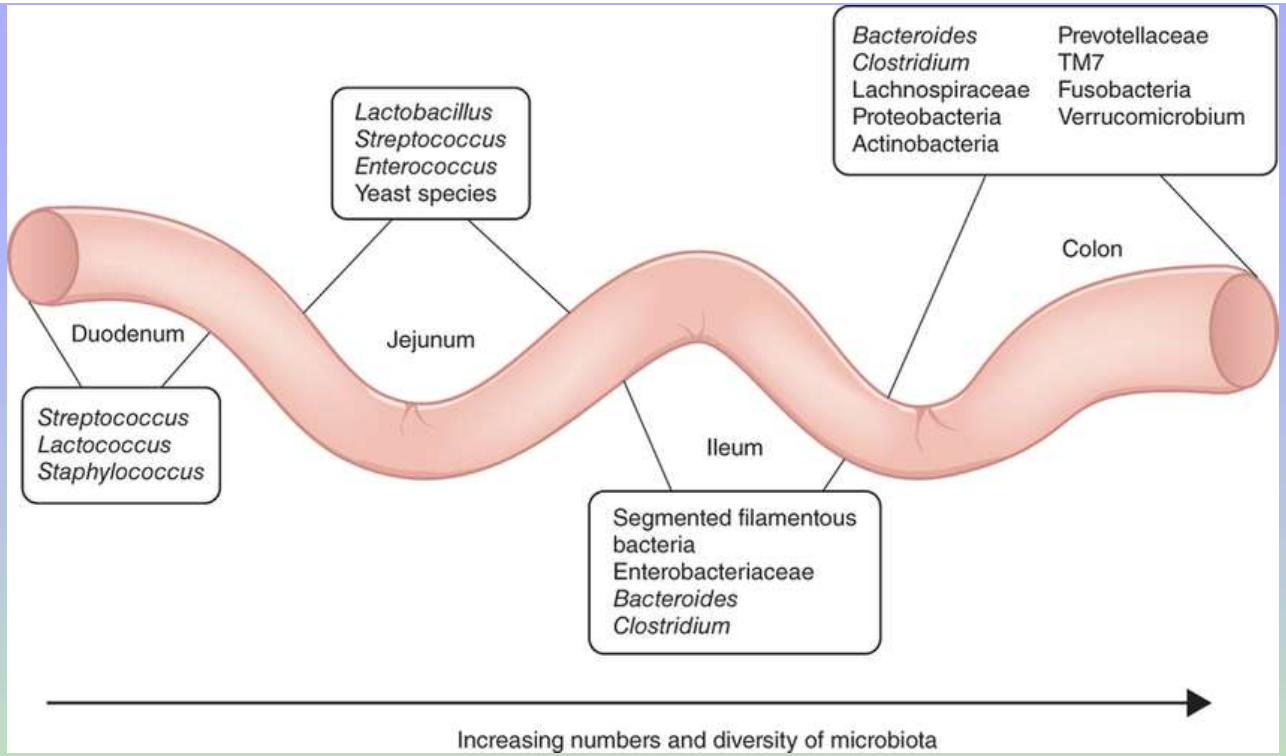
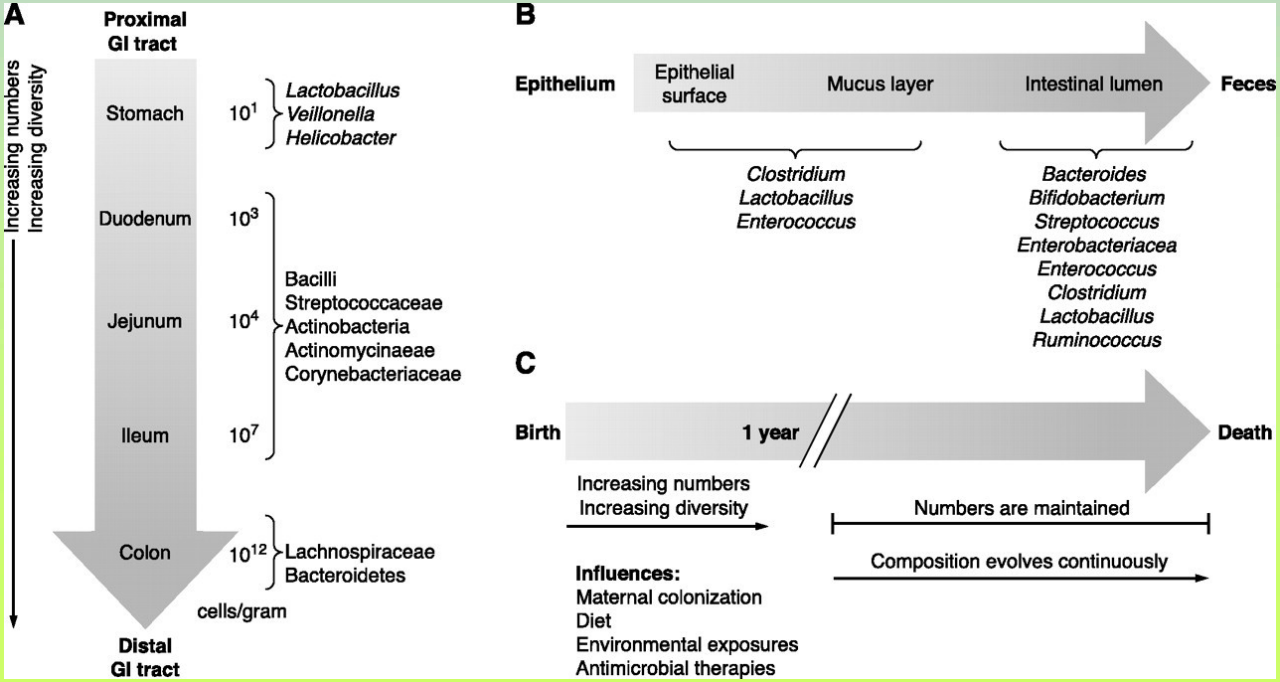
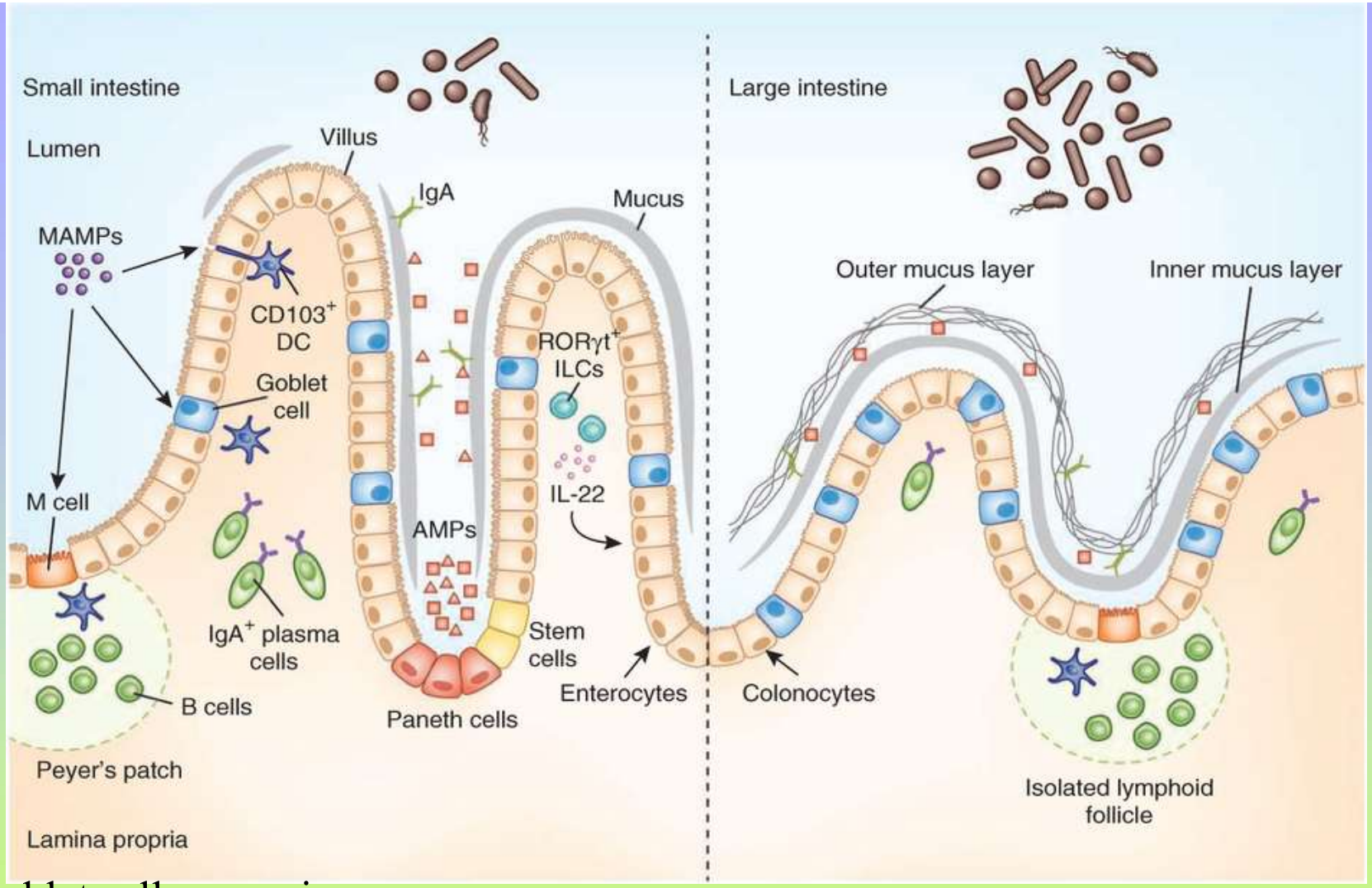


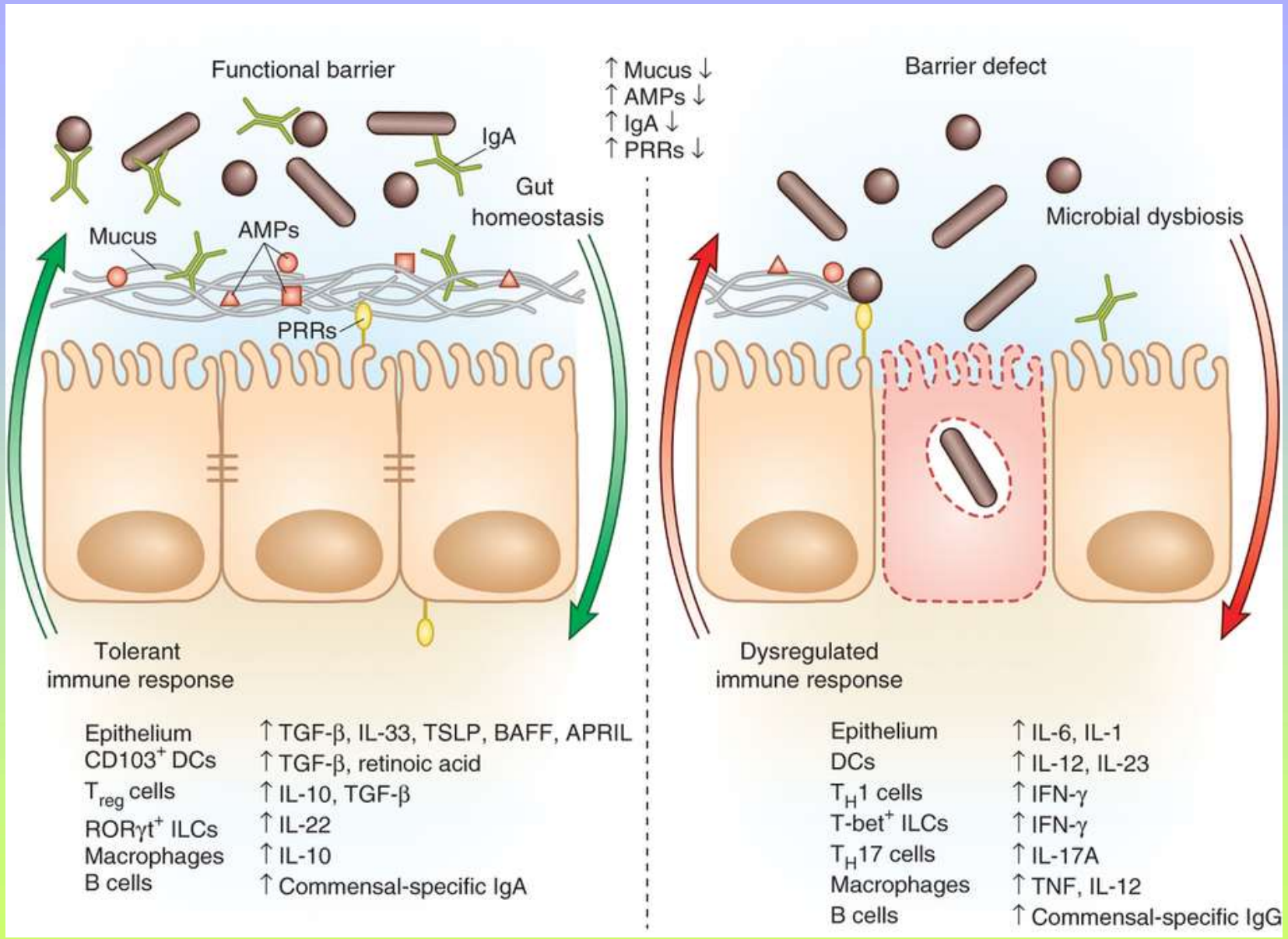
Figure 3 Structural components of gastric mucosal defense: surface epithelial cells, progenitor cells and blood microvessels. Reproduced with permission from Laine, Takeuchi and Tarnawski[4]. A: Histology of upper part of human gastric mucosa visualizing surface epithelial cells (SEC), foveoli (F), and upper gland area. (Hand E staining; original magnification, × 50). Blood microvessels with erythrocytes in the lumen are present in the lamina propria (arrows); B: Scanning electromicrograph of human gastric mucosal luminal surface. The unstirred mucus gel layer is not seen because of dissolution during fixation. Individual *SEC* are clearly visible as are lumina of the gastric pits (white arrows). Reproduced with permission from Tarnawski *et al*[7]; C: Immunostaining of human gastric mucosa with survivin (anti-apoptosis protein) antibody. Survivin is strongly expressed (brown-red staining) in the epithelial progenitor cells located in the foveolar/neck area (arrowheads). Reproduced with permission from Tarnawski *et al*[1]; D: Vascular cast study of capillary blood vessels in the gastric mucosa using Mercox resin. The remaining components of the mucosa were dissolved with concentrated NaOH. Reproduced with permission from Ichikawa, Tarnawski *et al*[8]; E: Transmission electron micrograph of normal human gastric mucosa. SEC contain dark mucus granules (MG, arrows). Below the surface epithelial cells, a capillary blood vessel (CAP) with erythrocytes (E) in the lumen is present in the lamina propria. N, nucleus of endothelial cell lining capillary vessel (original magnification, × 2000). Reproduced with permission from Tarnawski *et al*[9]; F: Transmission electron micrograph of a portion of human gastric capillary blood vessel. The structure of the capillary wall and endothelial cell cytoplasm is normal with a characteristic fenestration (arrows) allowing transport. BM: Basement membrane; E: Erythrocytes in the capillary lumen; J: Junction between two neighboring endothelial cells; CF: Collagen fibers. Original magnification, × 17400. Reproduced with permission from Tarnawski *et al*[9].


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

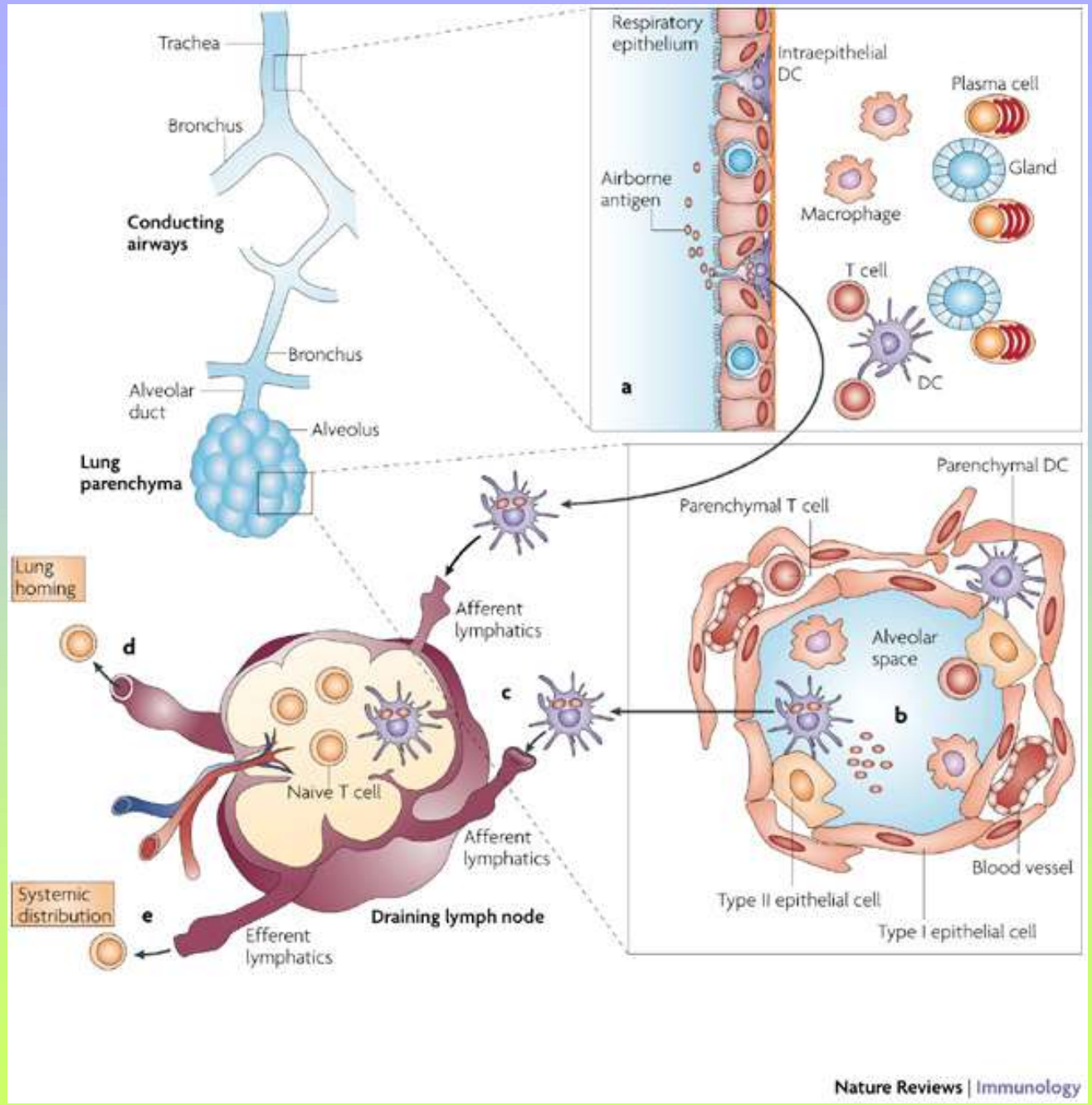

Functional barrier
↑ Mucus ↓
↑ AMPs ↓
↑ IgA ↓
↑ PRRs ↓
Barrier defect
IgA
Gut homeostasis
Mucus
AMPs
PRRs
Microbial dysbiosis
Tolerant immune response
Dysregulated immune response
Epithelium ↑ TGF-β, IL-33, TSLP, BAFF, APRIL
CD103+ DCs ↑ TGF-β, retinoic acid
Treg cells ↑ IL-10, TGF-β
RORγt+ ILCs ↑ IL-22
Macrophages ↑ IL-10
B cells ↑ Commensal-specific IgA
Epithelium ↑ IL-6, IL-1
DCs ↑ IL-12, IL-23
TH1 cells ↑ IFN-γ
T-bet+ ILCs ↑ IFN-γ
TH17 cells ↑ IL-17A
Macrophages ↑ TNF, IL-12
B cells ↑ Commensal-specific IgG

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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Think of the human body as a hollow plastic tube…

The food is digested within the hole in the tube, but it never actually enters into the solid plastic material.

Tube inner surface ~Digestive System~

Tube outer surface ~Skin~

Plastic interior ~Body~

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.

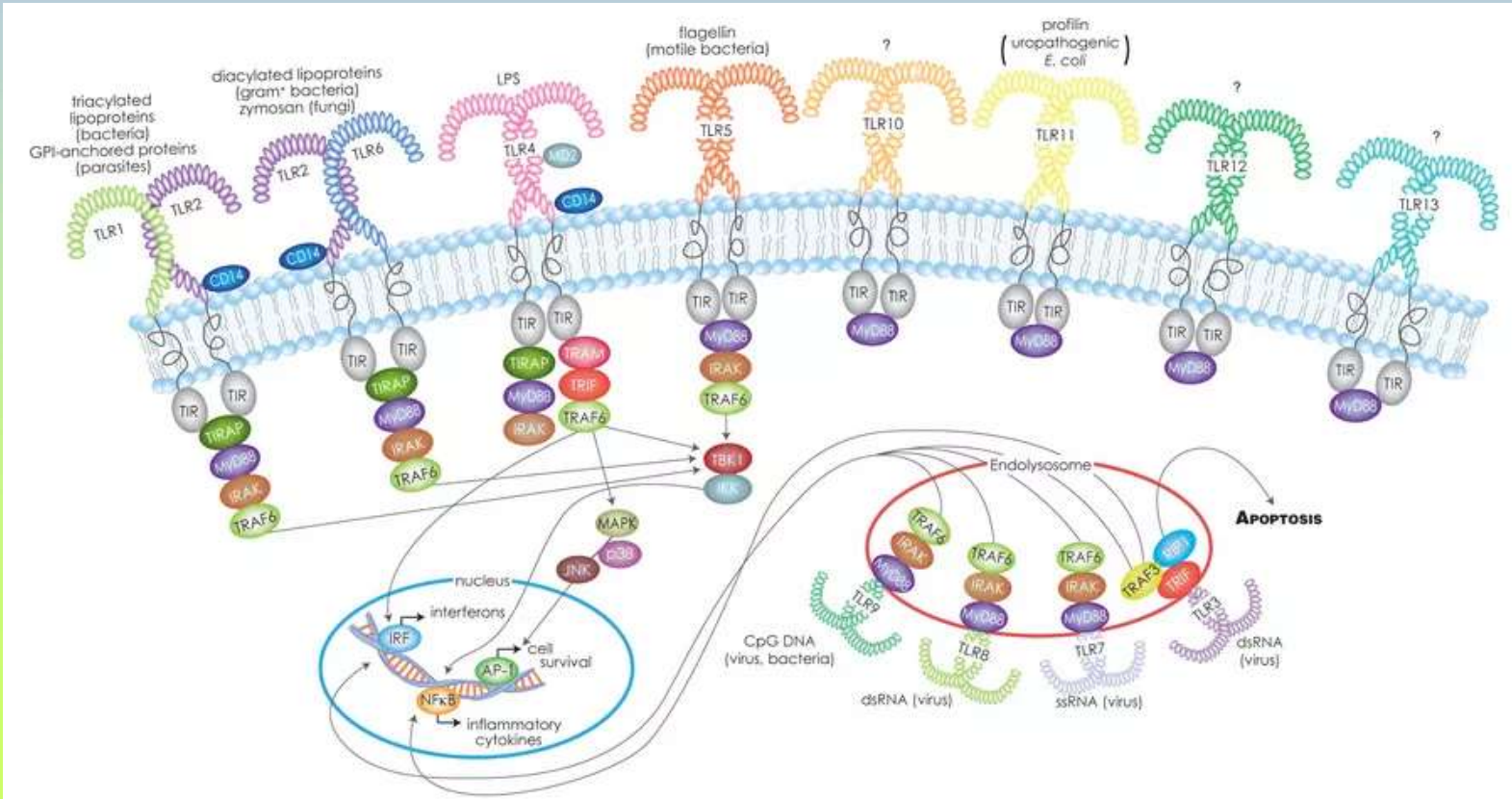
Acquired Immunity:Immunity that an organism *develops* during lifetime.

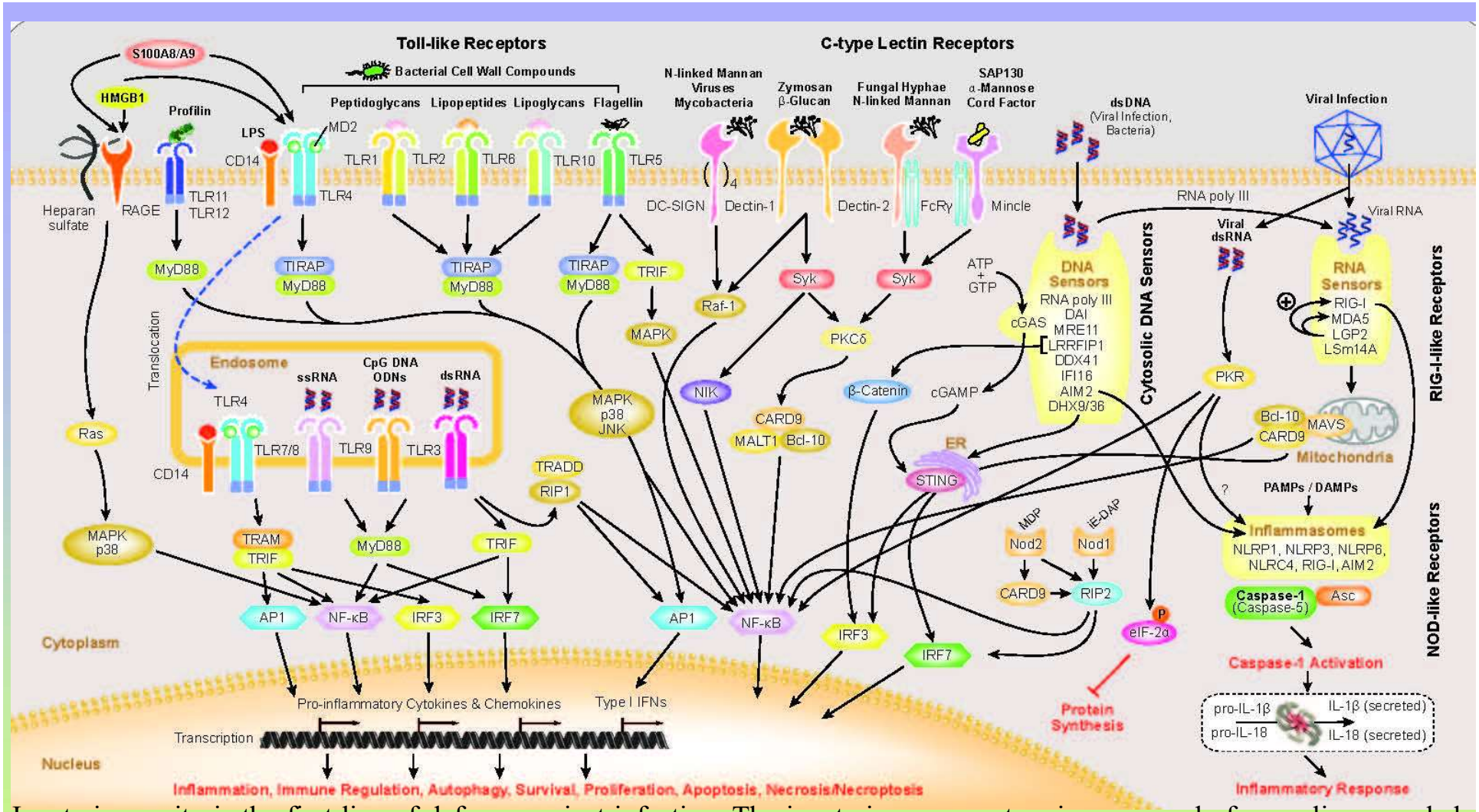
- Not genetically determined.
- May be acquired naturally or artificially.
  - Development of immunity to measles in response to infection or vaccination.

Innate versus acquired immunity

Innate immunity

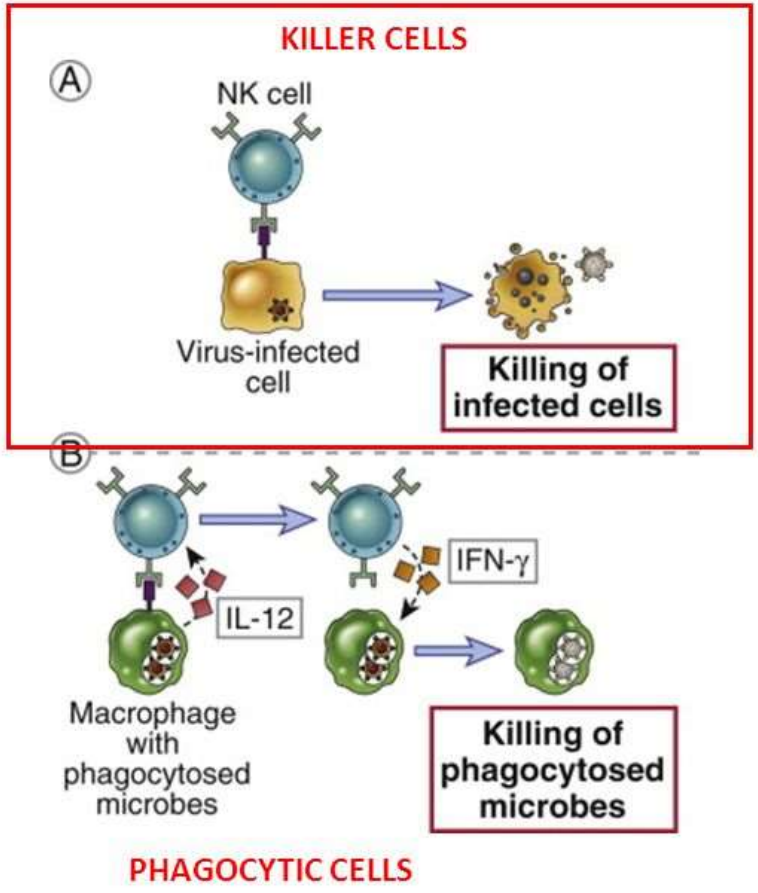
- neutrophils, macrophages, NK cells
- Toll and toll-like receptors = affinity to bacterial lipopolysaccharides, lipoproteins, peptidoglycans, DNA = molecular patterns expressed by pathogens

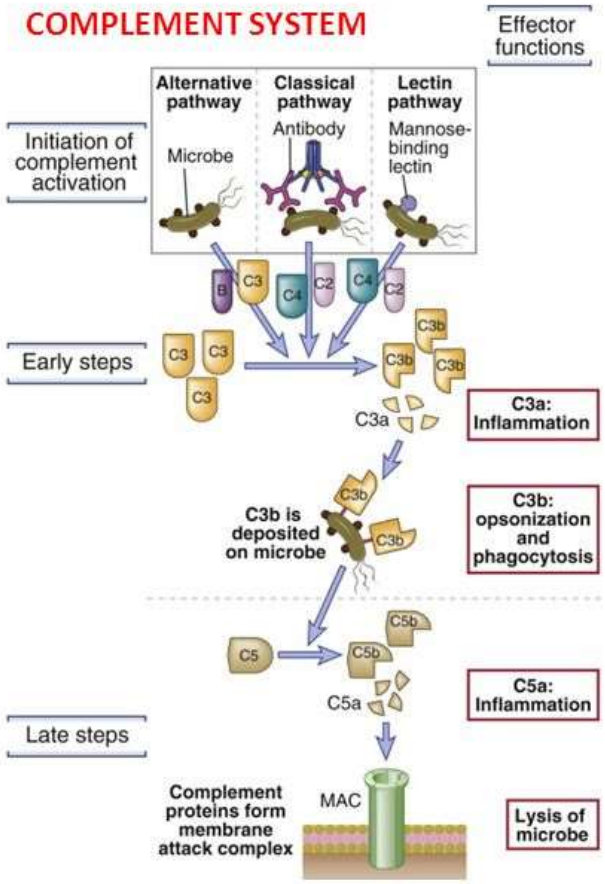




Innate immunity is the first line of defense against infection. The innate immune system is composed of germ-line encoded receptors that collectively serve as a sensor to monitor extracellular and intracellular compartments for signs of infection or tissue injury. Since the discovery linking Toll in the fly to anti-fungal defense, seminal discoveries have identified families of mammalian Toll-like receptors (TLRs), Nod-like receptors, Rig-I like receptors, C-type lectins, Aim2-like receptors and other DNA sensors and highlighted their ability to recognize microbial products. Activation of innate immune sensing receptors leads to the transcription of hundreds of genes involved in antimicrobial defense, phagocytosis, cell migration, metabolic reprogramming, tissue repair and regulation of adaptive immunity. These responses curb pathogen growth and spread and also mobilize the T-cells and B-cells of the adaptive immune system. The ability of the innate immune system to mobilize, instruct and regulate adaptive immunity is well established.

EFFECTOR MECHANISMS OF INNATE IMMUNITY





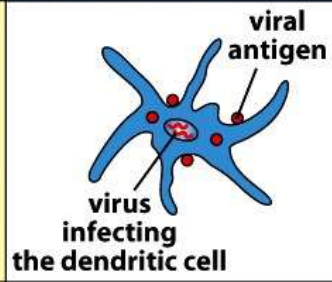
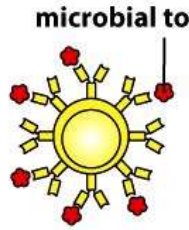
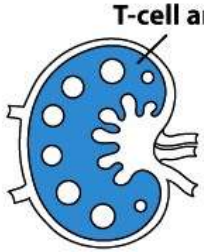
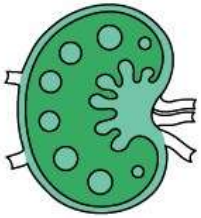
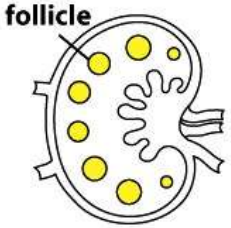
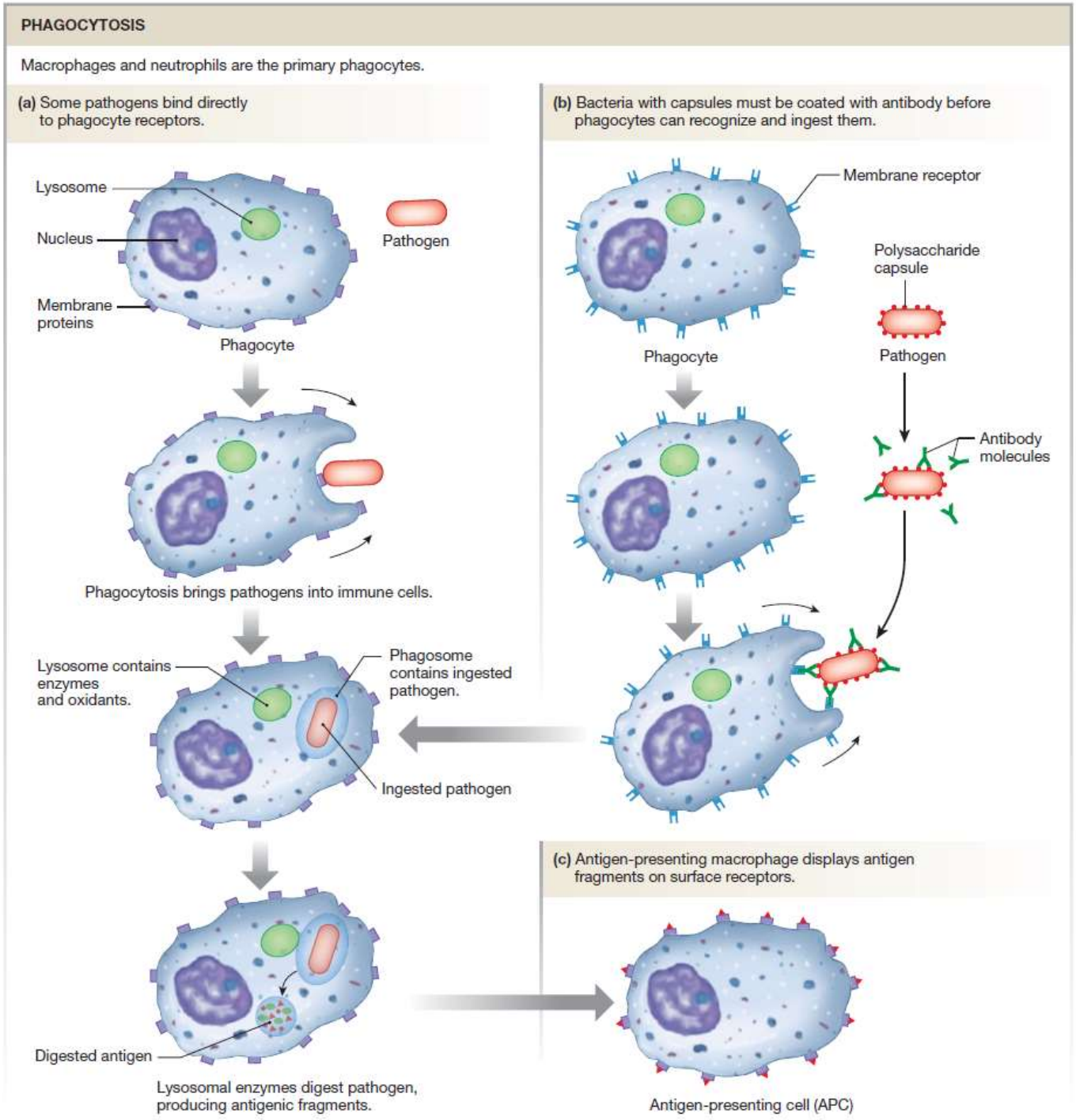
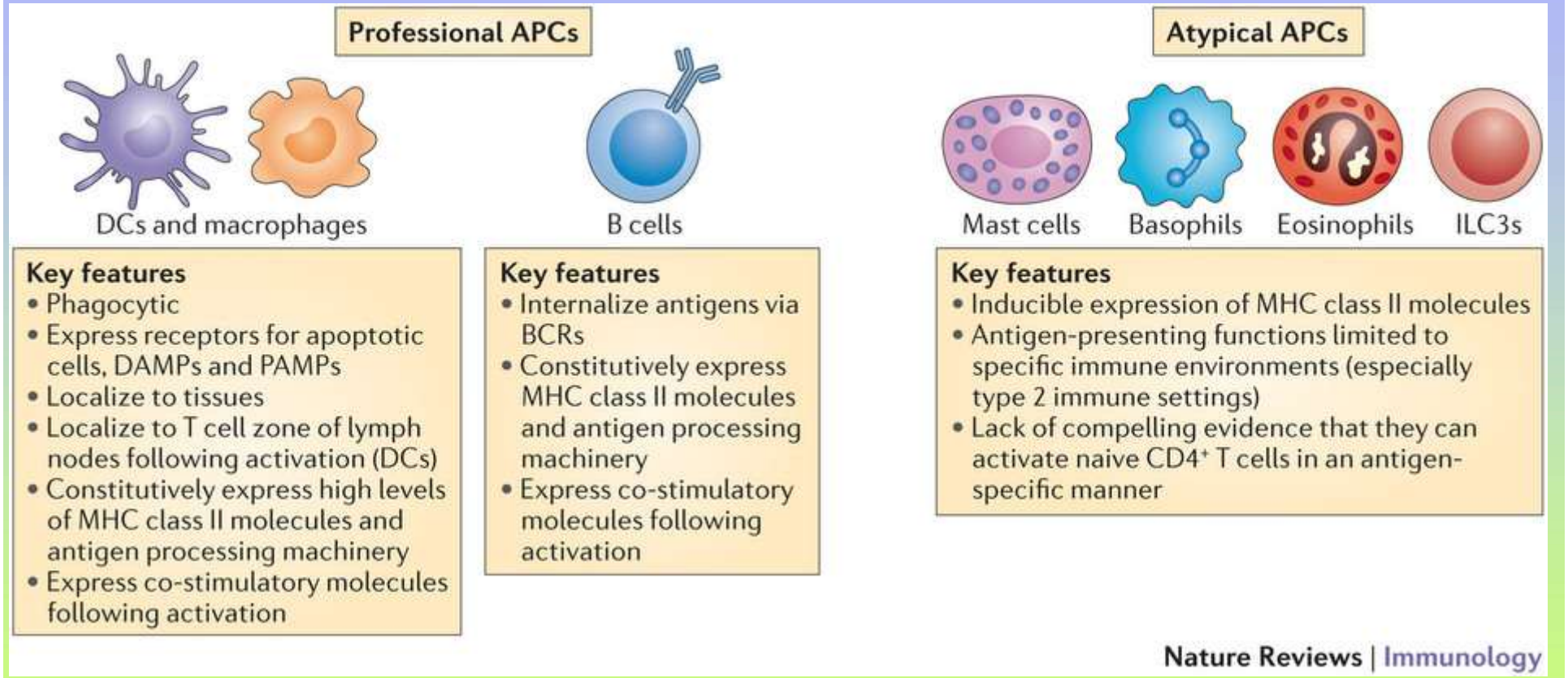
	Professional antigen-presenting cells		
	Dendritic cell	**Macrophage**	**B cell**
Cell type			
Location in lymph node			
Antigen uptake	+++ Macropinocytosis and phagocytosis by tissue dendritic cells Viral infection	Phagocytosis +++	Antigen-specific receptor (Ig) ++++
MHC expression	Low on tissue dendritic 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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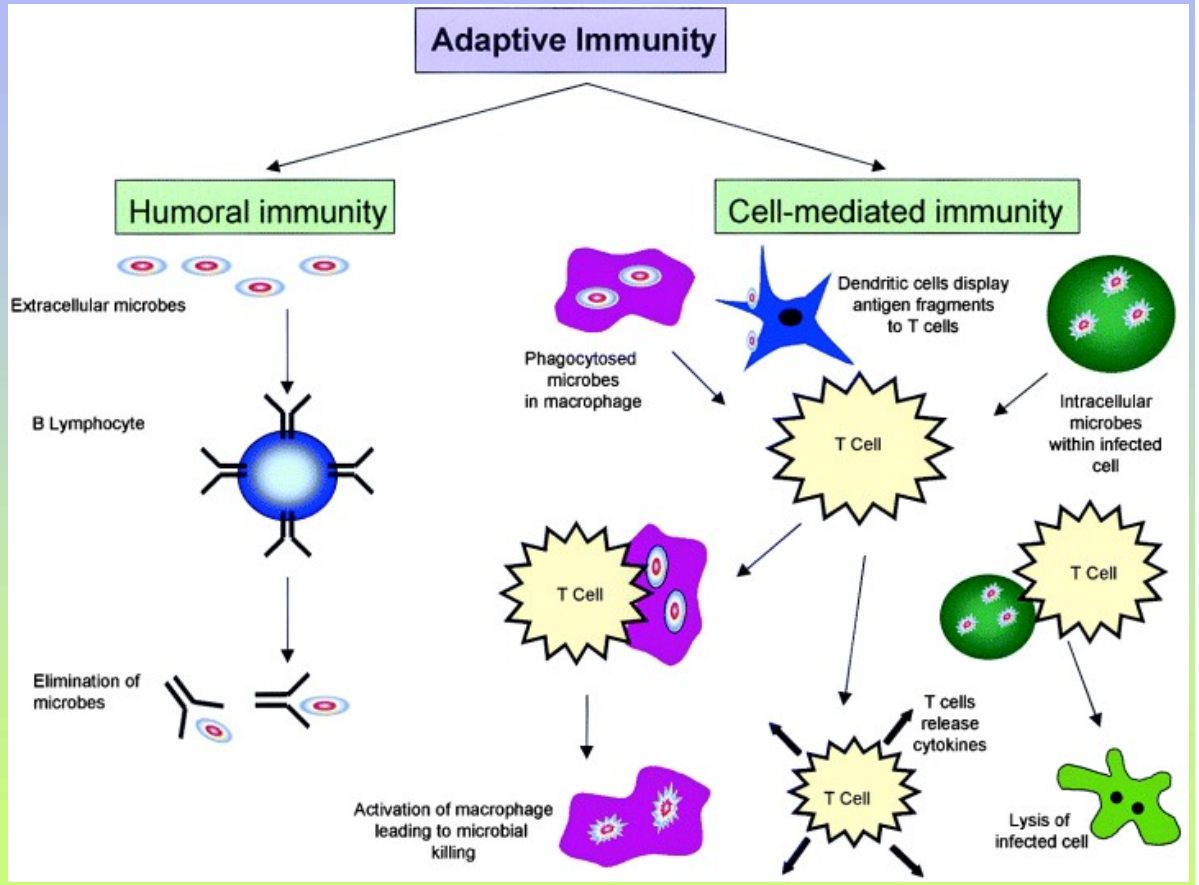
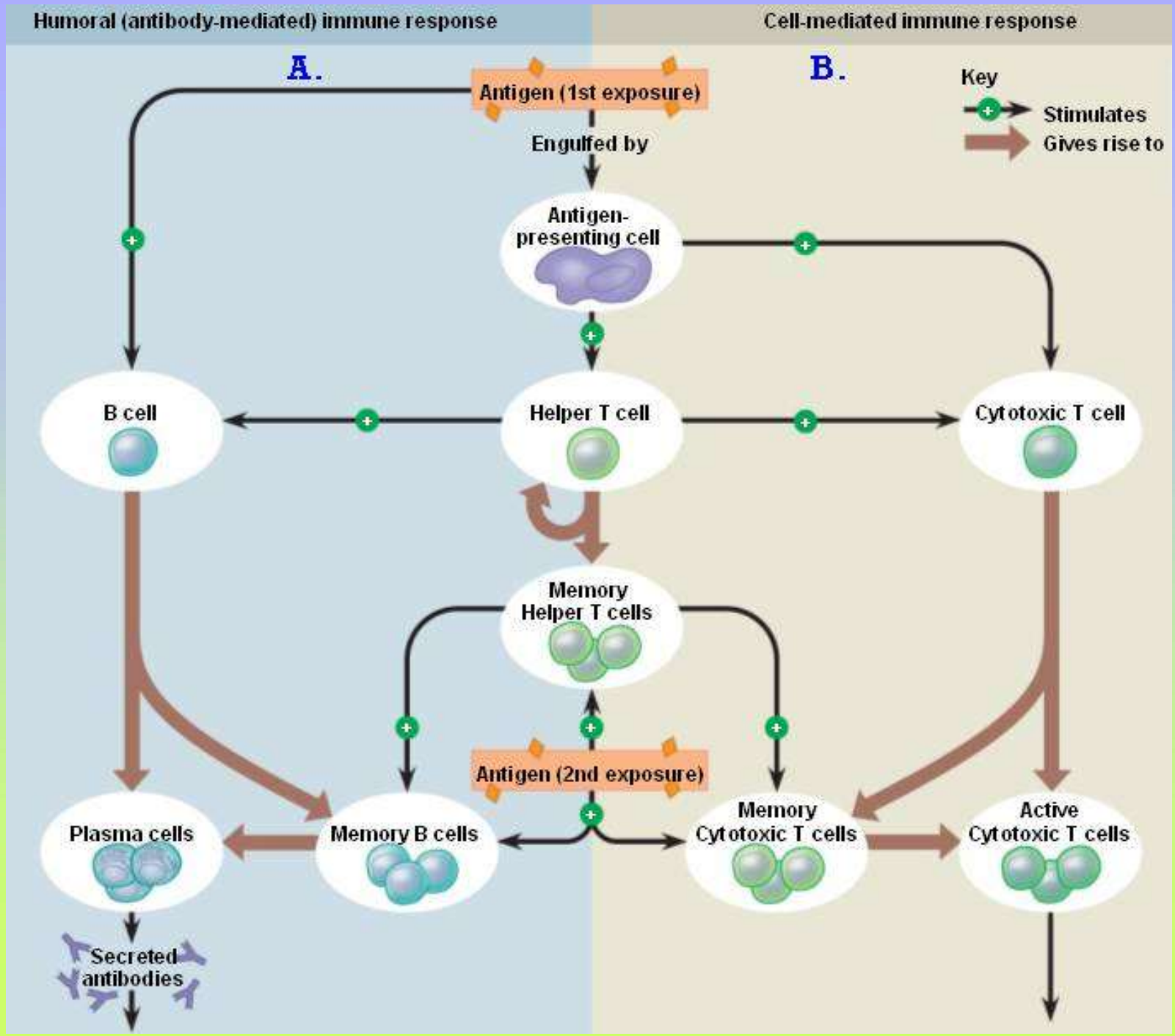
Innate versus acquired immunity

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

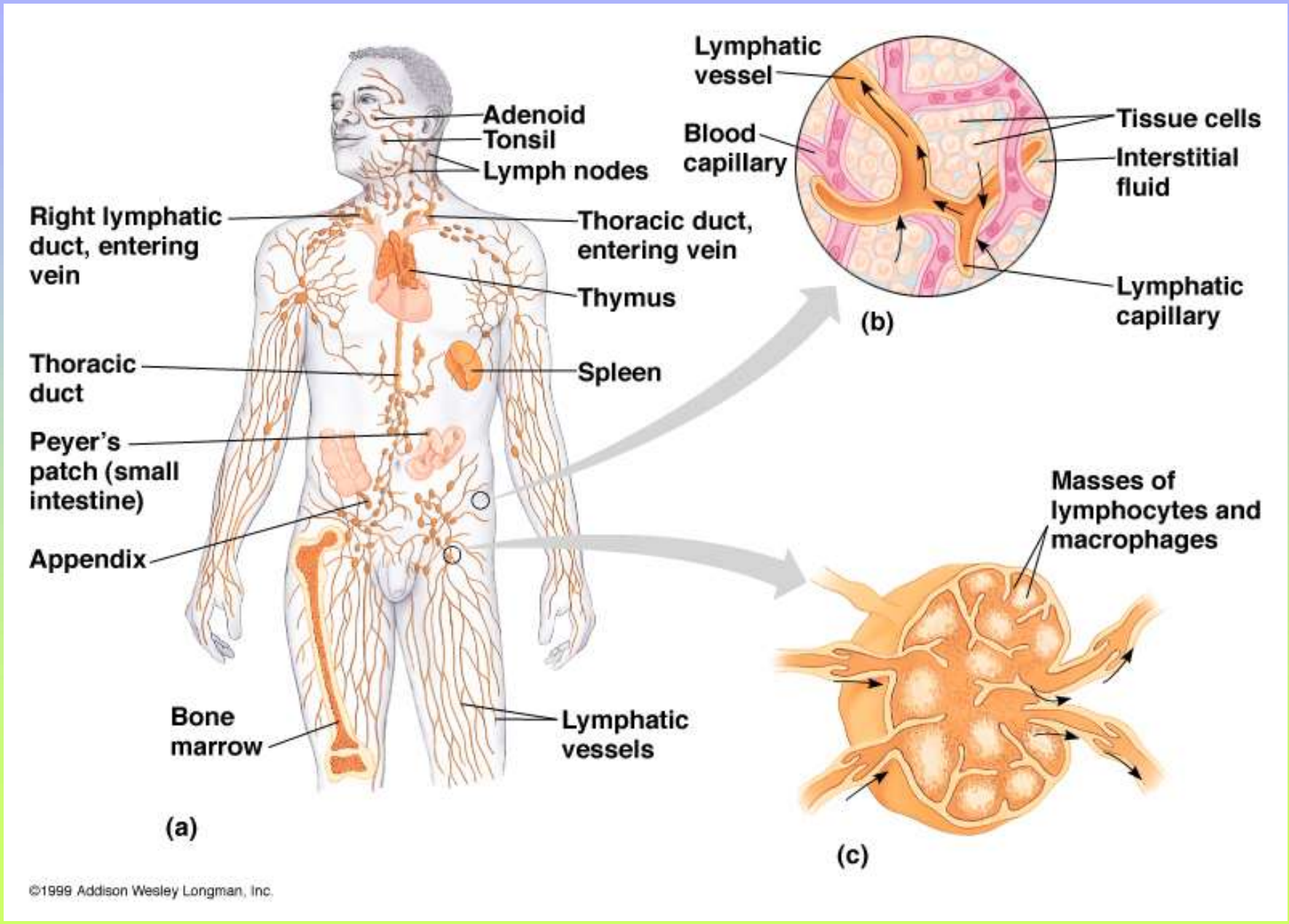



Humoral (antibody-mediated) immune response
Cell-mediated immune response
A.
B.
Key
Stimulates
Gives rise to
Antigen (1st exposure)
Engulfed by
Antigen-presenting cell
B cell
Helper T cell
Cytotoxic T cell
Memory Helper T cells
Antigen (2nd exposure)
Plasma cells
Memory B cells
Memory Cytotoxic T cells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

Innate versus Adaptive immunity

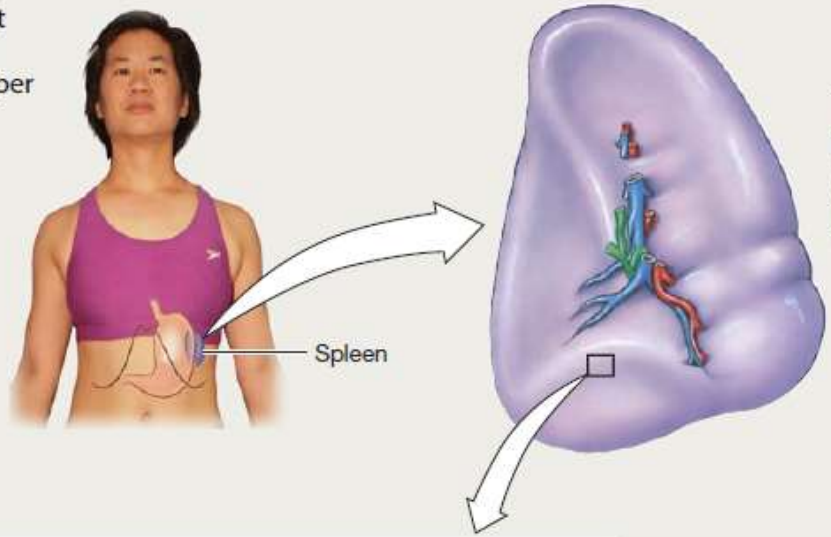
	Innate	Adaptive
Receptors	Primitive and broad	Highly specific (T and B cell receptors)
Kinetics	Fast (hours-days)	Slow (days-wks)
Regulation	+/-	++++
Amplification	No (insignificant)	Yes
Self discrimination	-	++++
Duration	Short (days)	Long (months/yrs)
Memory	-	++++

Components of Human Immune System

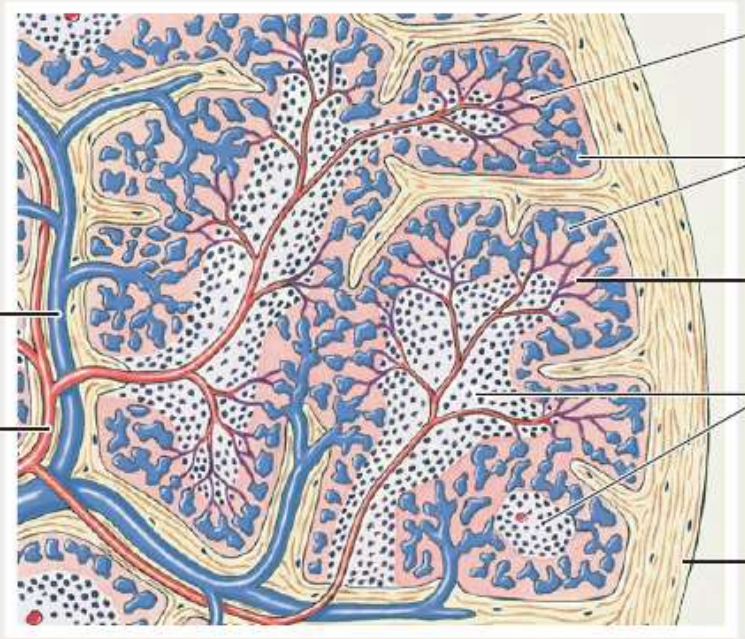


The Spleen

The spleen is the largest lymphoid organ in the body, located in the upper left quadrant of the abdomen close to the stomach.

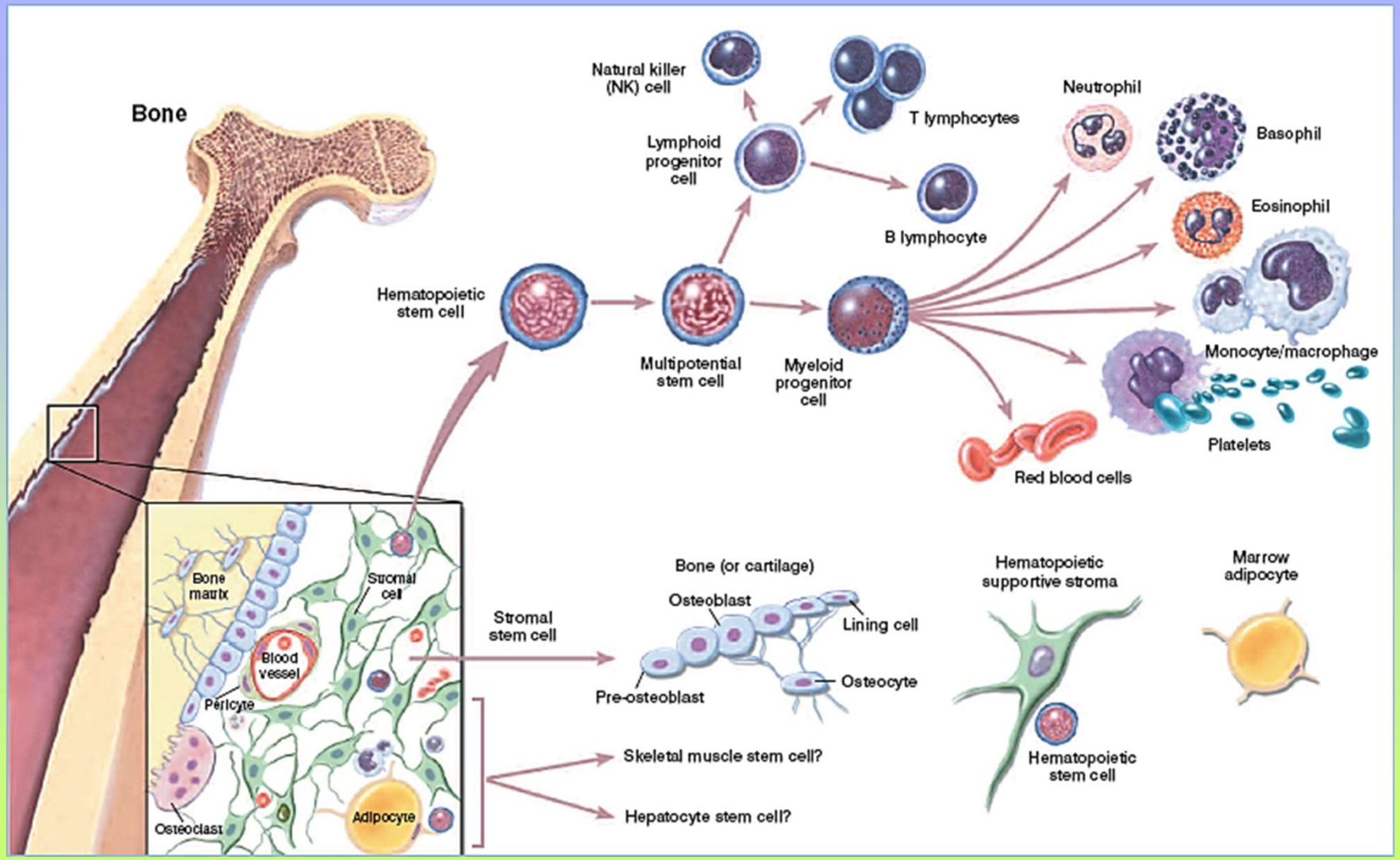


The outer surface of the spleen is a connective tissue capsule that extends into the interior to create an open framework that supports the blood vessels and lymphoid tissue.

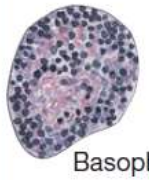
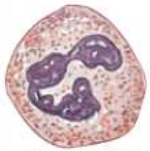
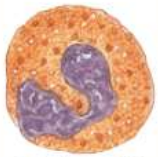
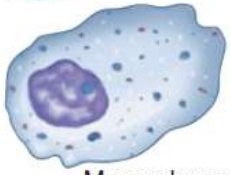
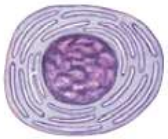


Darker regions of **red pulp** are closely associated with extensive blood vessels and open venous sinuses.The red pulp contains many macrophages that act as a filter by trapping and destroying foreign material circulating in the blood. In addition, the macrophages ingest old, damaged, and abnormal red blood cells, breaking down their hemoglobin molecules into amino acids, iron, and bilirubin that is transported to the liver for excretion.

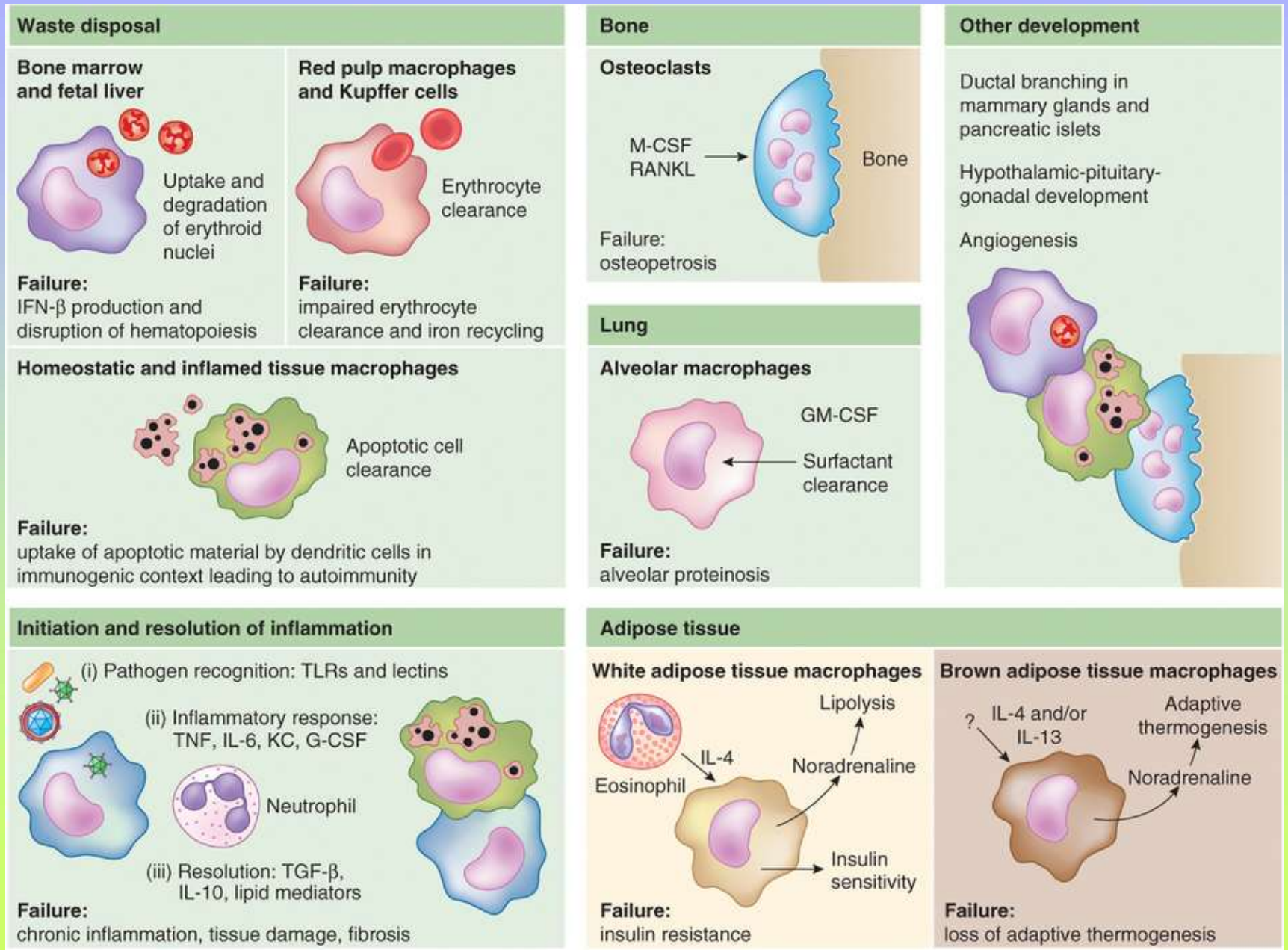
Regions of **white pulp** resemble the interior of lymph nodes and are composed mainly of lymphocytes.


Bone
Natural killer (NK) cell
T lymphocytes
Lymphoid progenitor cell
B lymphocyte
Neutrophil
Basophil
Eosinophil
Monocyte/macrophage
Platelets
Red blood cells
Hematopoietic stem cell
Multipotential stem cell
Myeloid progenitor cell
Bone matrix
Stromal cell
Blood vessel
Pericyte
Osteoclast
Adipocyte
Stromal stem cell
Bone (or cartilage)
Osteoblast
Lining cell
Osteocyte
Pre-osteoblast
Skeletal muscle stem cell?
Hepatocyte stem cell?
Hematopoietic supportive stroma
Hematopoietic stem cell
Marrow adipocyte

CELLS OF THE IMMUNE SYSTEM Circulating leukocytes, tissue macrophages, and dendritic cells are the body's immunocytes.

Types of cells	 Basophils  Mast Cells	 Neutrophils	 Eosinophils	 Monocytes  Macrophages	 Lymphocytes  Plasma Cells	 Dendritic Cells
Classifications		Phagocytes				
	Granulocytes					
			Cytotoxic cells		Cytotoxic cells (some types)	
				Antigen-presenting cells		
% of WBCs in blood	Rare	50–70%	1–3%	1–6%	20–35%	N/A
Subtypes and nicknames		Called "polys" or "segs." Immature forms called "bands" or "stabs."		Called the mononuclear phagocyte system	B lymphocytes Plasma cells Memory cells T lymphocytes Cytotoxic T cells Helper T cells Natural killer cells	Also called Langerhans cells, veiled cells
Primary function(s)	Release chemicals that mediate inflammation and allergic responses	Ingest and destroy invaders	Destroy invaders, particularly antibody-coated parasites	Ingest and destroy invaders. Antigen presentation	Specific responses to invaders, including antibody production	Recognize pathogens and activate other immune cells by antigen presentation

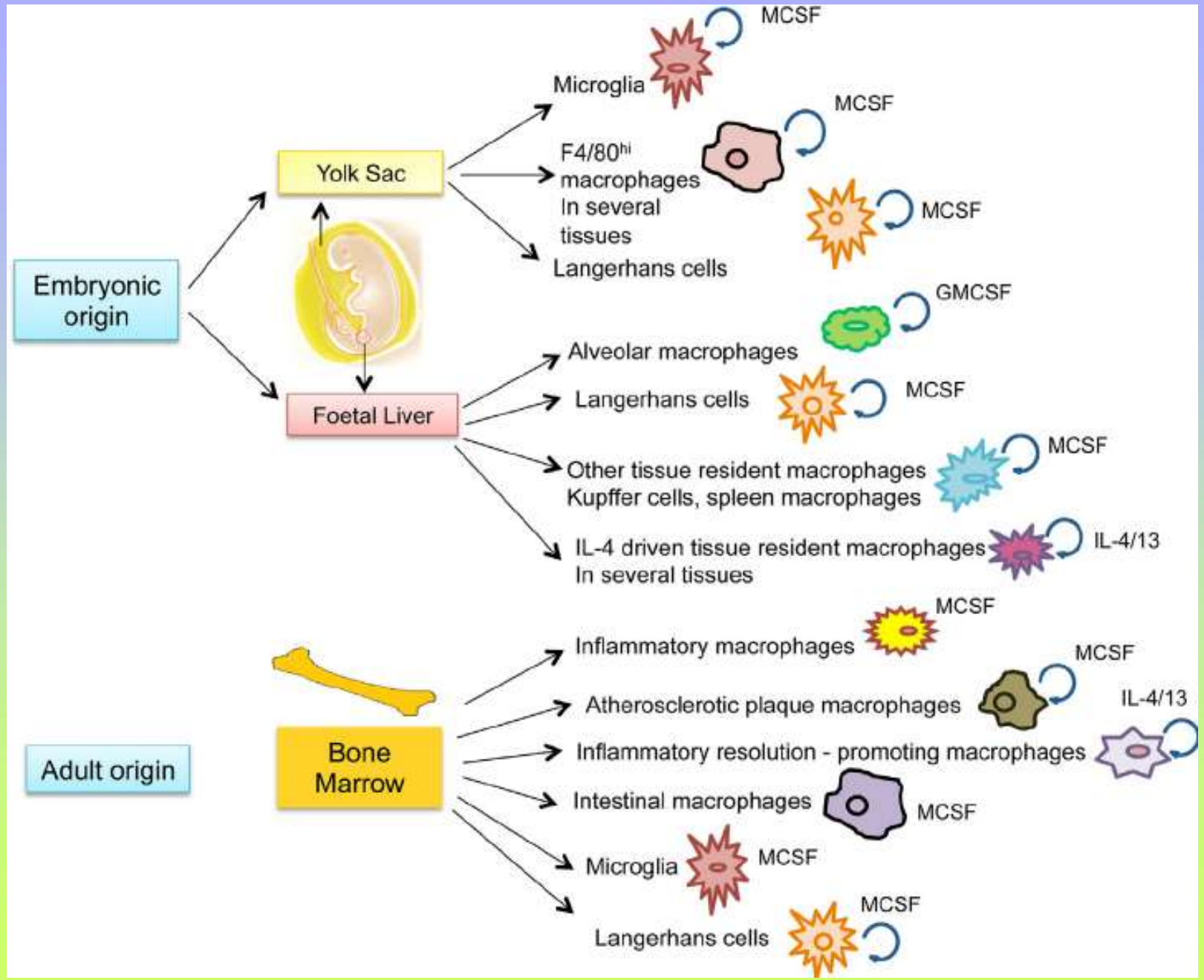
Reticuloendothelial system – tissue macrophage system



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.*


Embryonic origin
Yolk Sac
Foetal Liver
Microglia
MCSF
F4/80hi macrophages In several tissues
MCSF
Langerhans cells
MCSF
GMCSF
Alveolar macrophages
Langerhans cells
MCSF
Other tissue resident macrophages Kupffer cells, spleen macrophages
MCSF
IL-4 driven tissue resident macrophages In several tissues
IL-4/13
Adult origin
Bone Marrow
Inflammatory macrophages
MCSF
Atherosclerotic plaque macrophages
MCSF
IL-4/13
Inflammatory resolution - promoting macrophages
Intestinal macrophages
MCSF
Microglia
MCSF
Langerhans cells
MCSF

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.

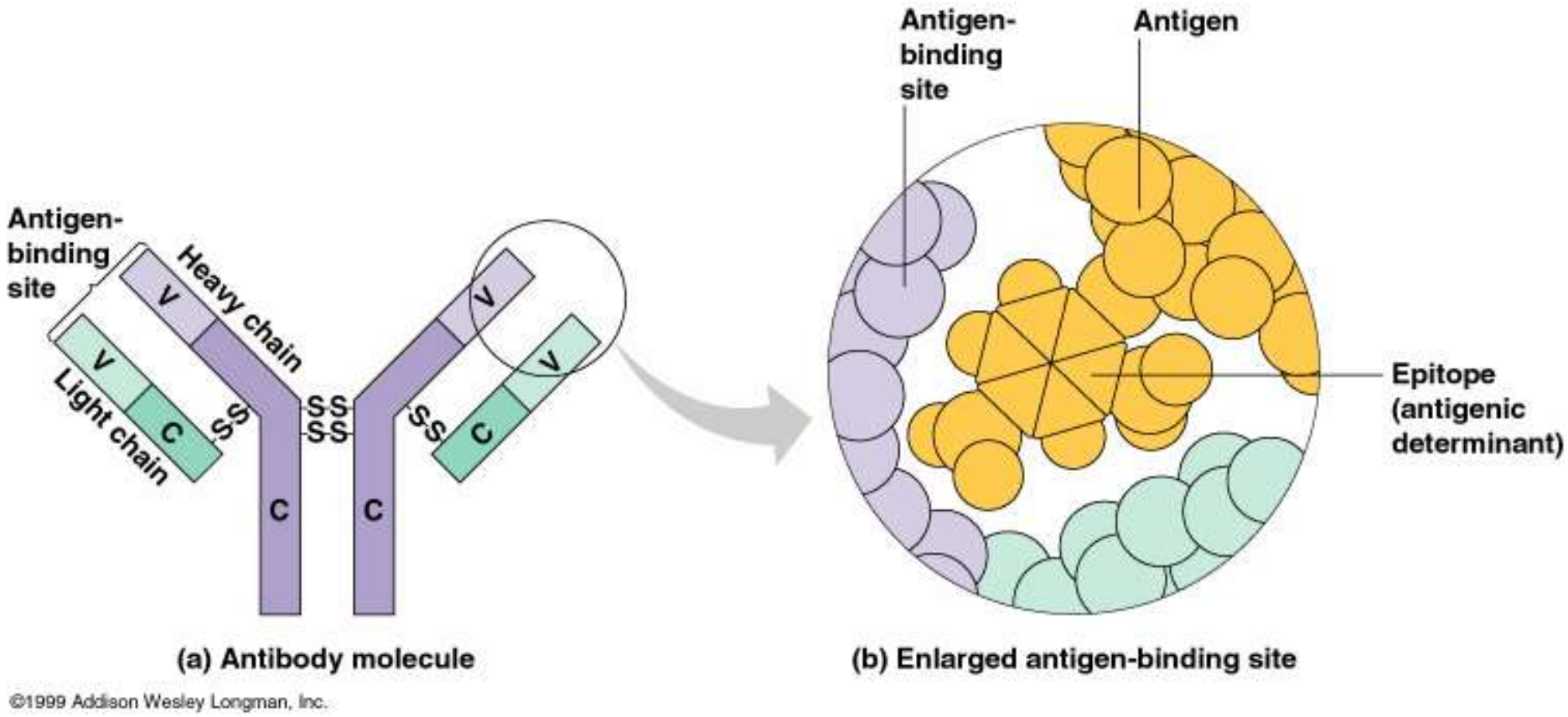
- **Serum: Fluid that remains after blood has clotted and cells have been removed.**
- **Antiserum: Serum containing antibodies to a specific antigen(s). Obtained from injecting an animal (horse, rabbit, goat) with antigen (snake venom, botulism or diphtheria toxin).**
- **Serology: The study of reactions between antibodies and antigens.**
- **Gamma Globulins: Fraction of serum that contains most of the antibodies.**
- **Serum Sickness: Disease caused by multiple injections of antiserum. Immune response to foreign proteins. May cause fever, kidney problems, and joint pain. Rare today.**

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.

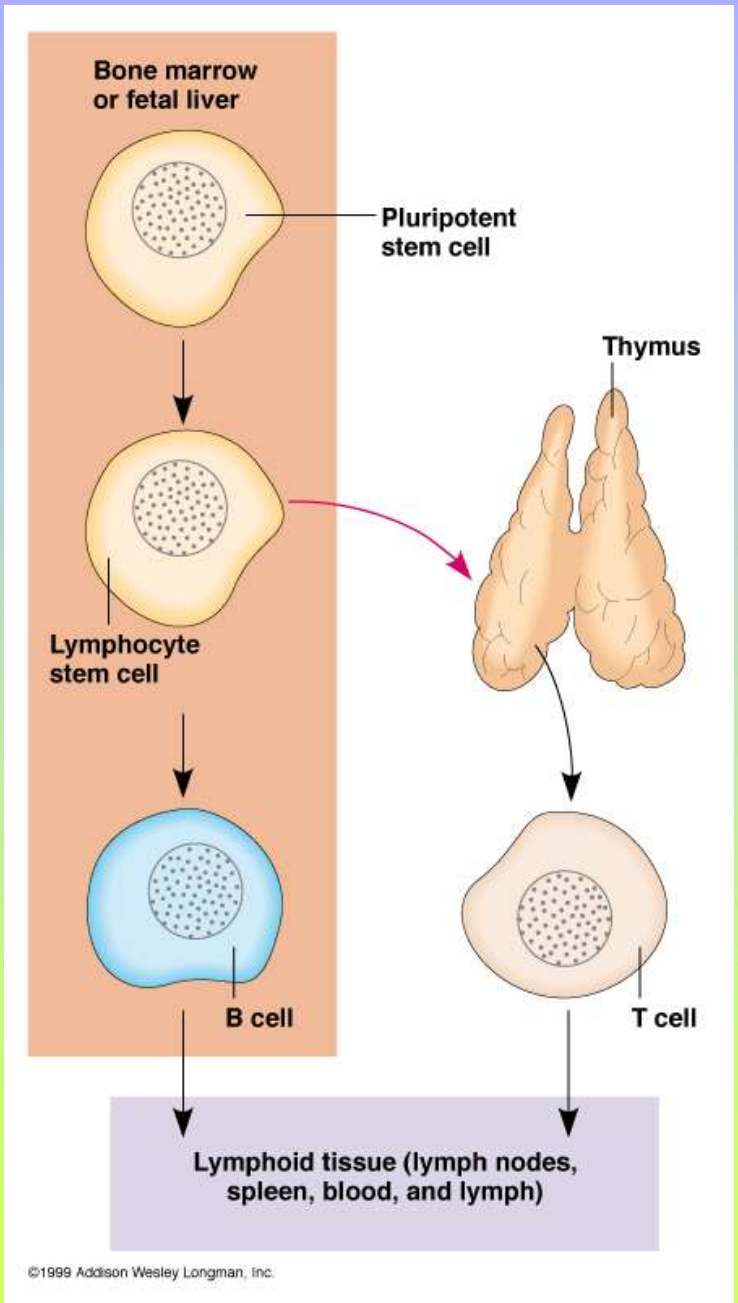
Antibodies are Proteins that Recognize Specific Antigens



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

Cell Mediated Immunity is Carried Out by T Lymphocytes

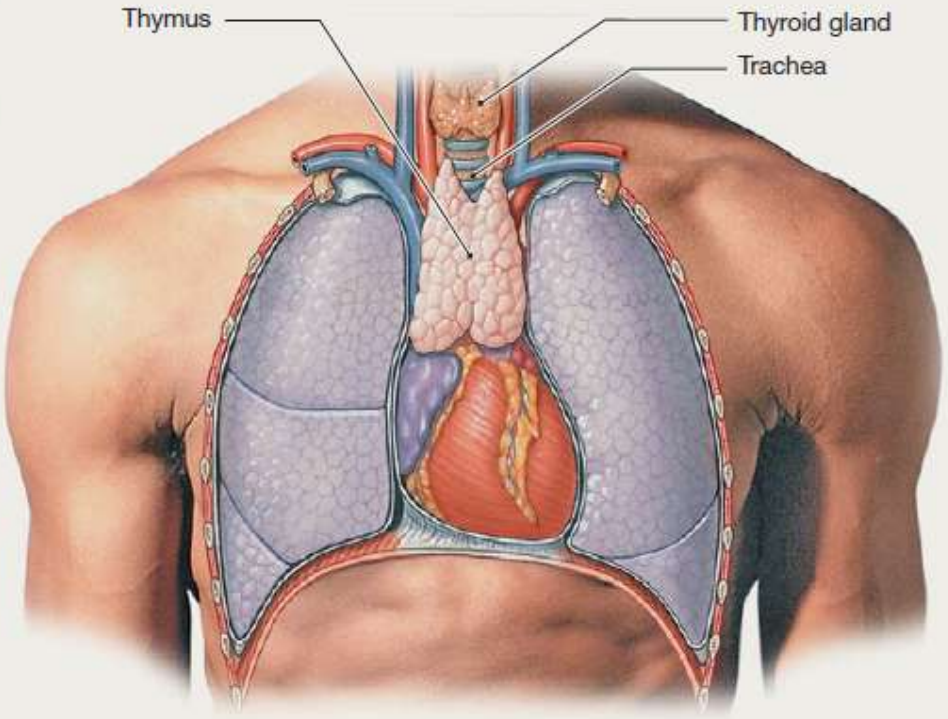


The Thymus Gland

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.

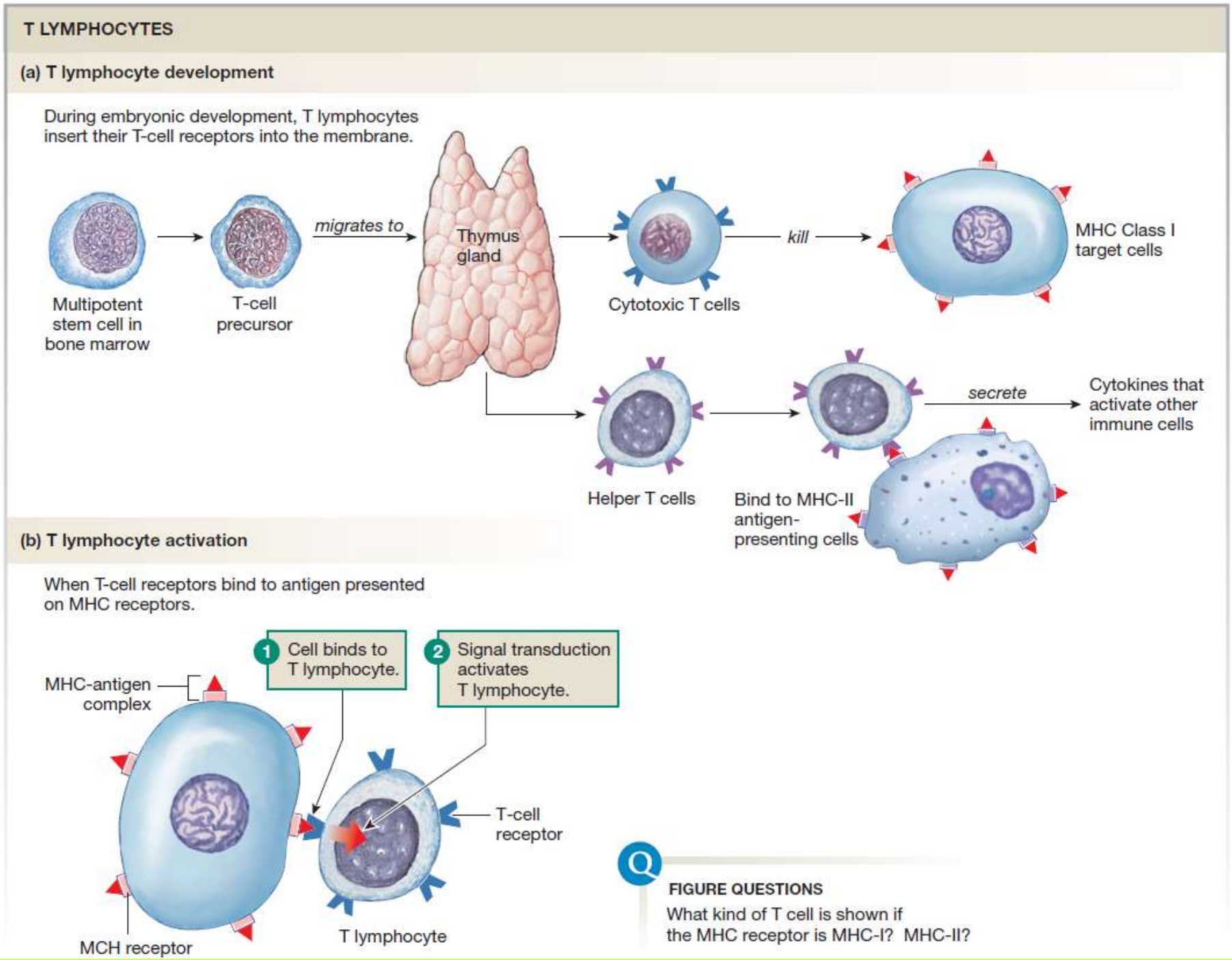


The thymus gland produces:

- 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

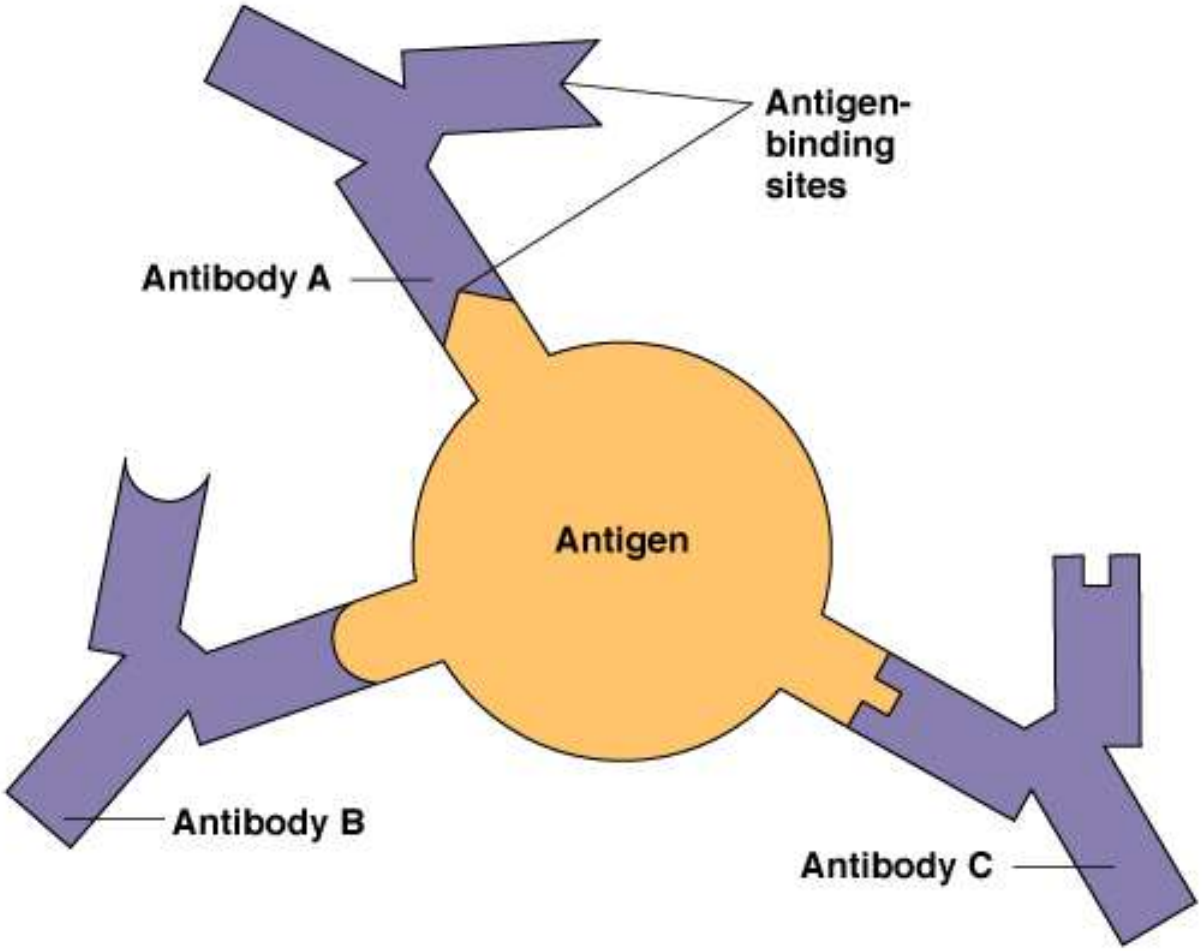
- Most are proteins or large polysaccharides from a foreign organism.
  - Microbes: Capsules, cell walls, toxins, viral capsids, flagella, etc.
  - Nonmicrobes: Pollen, egg white , red blood cell surface molecules, serum proteins, and surface molecules from transplanted tissue.
- Lipids and nucleic acids 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.

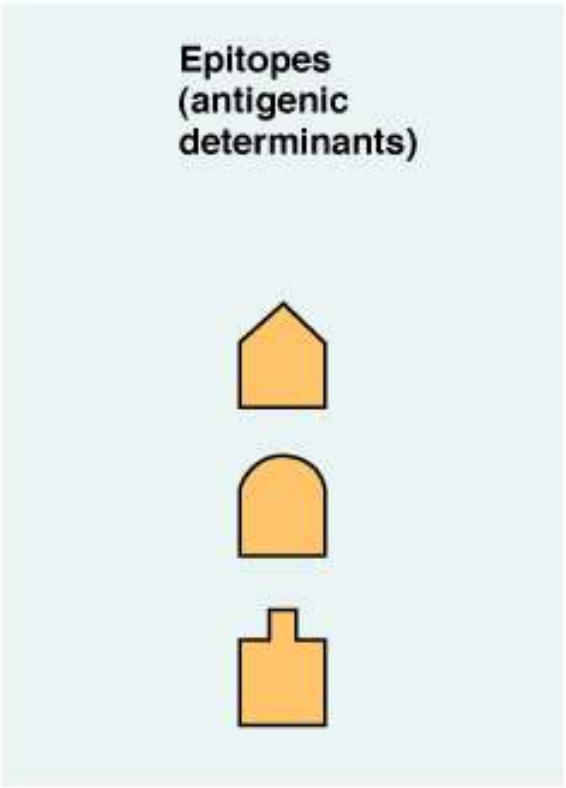
Antigens

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





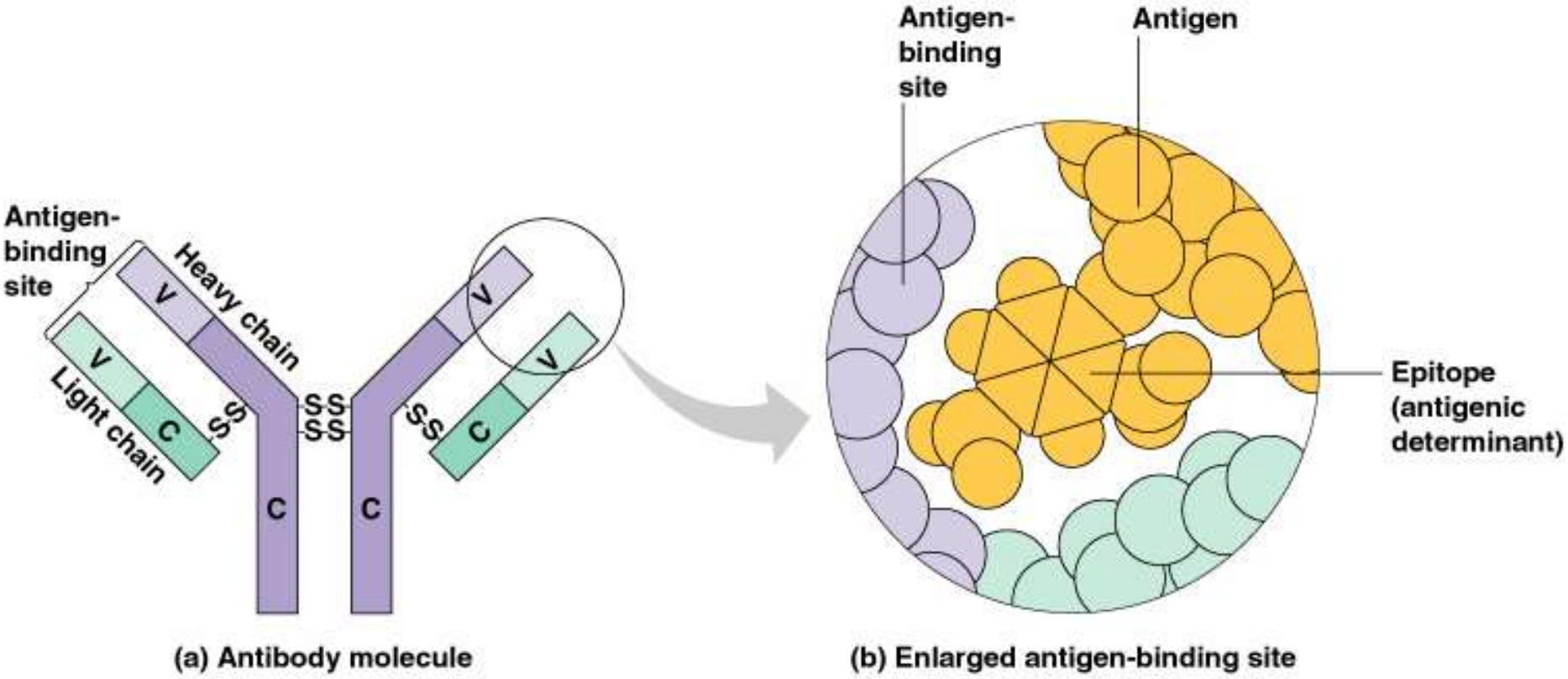
Antibodies

- **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.**

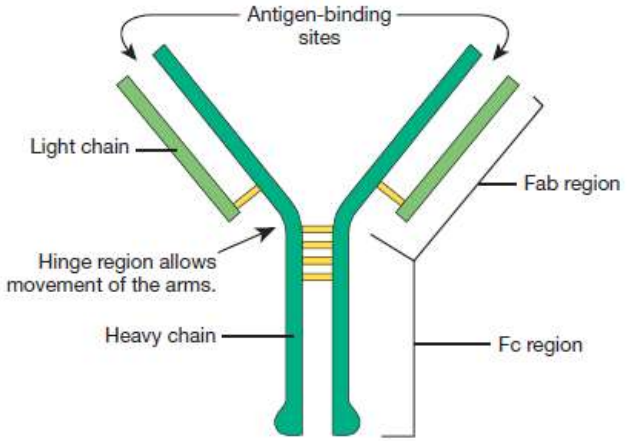
Antibody Structure



ANTIBODIES

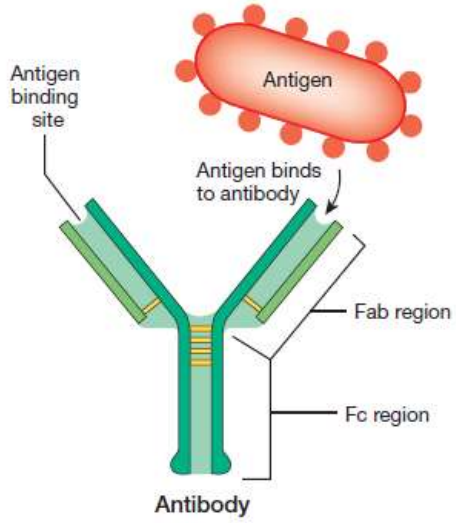
(a) Antibody structure

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

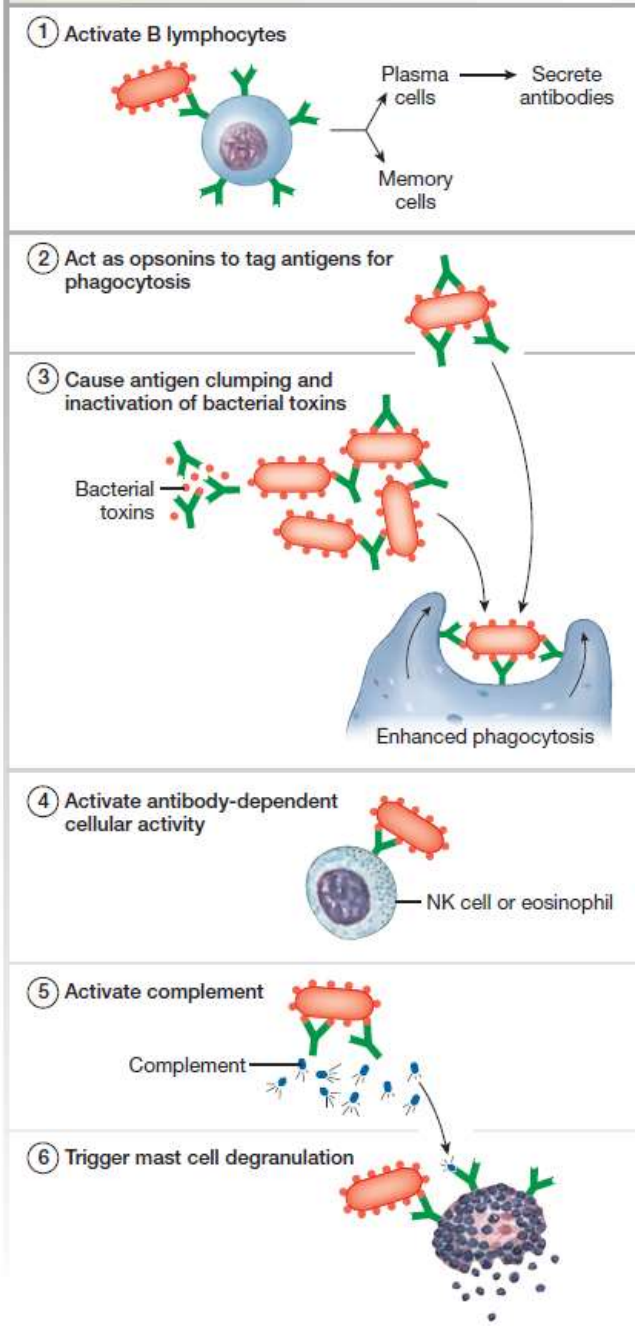


(b) Antigen binding

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

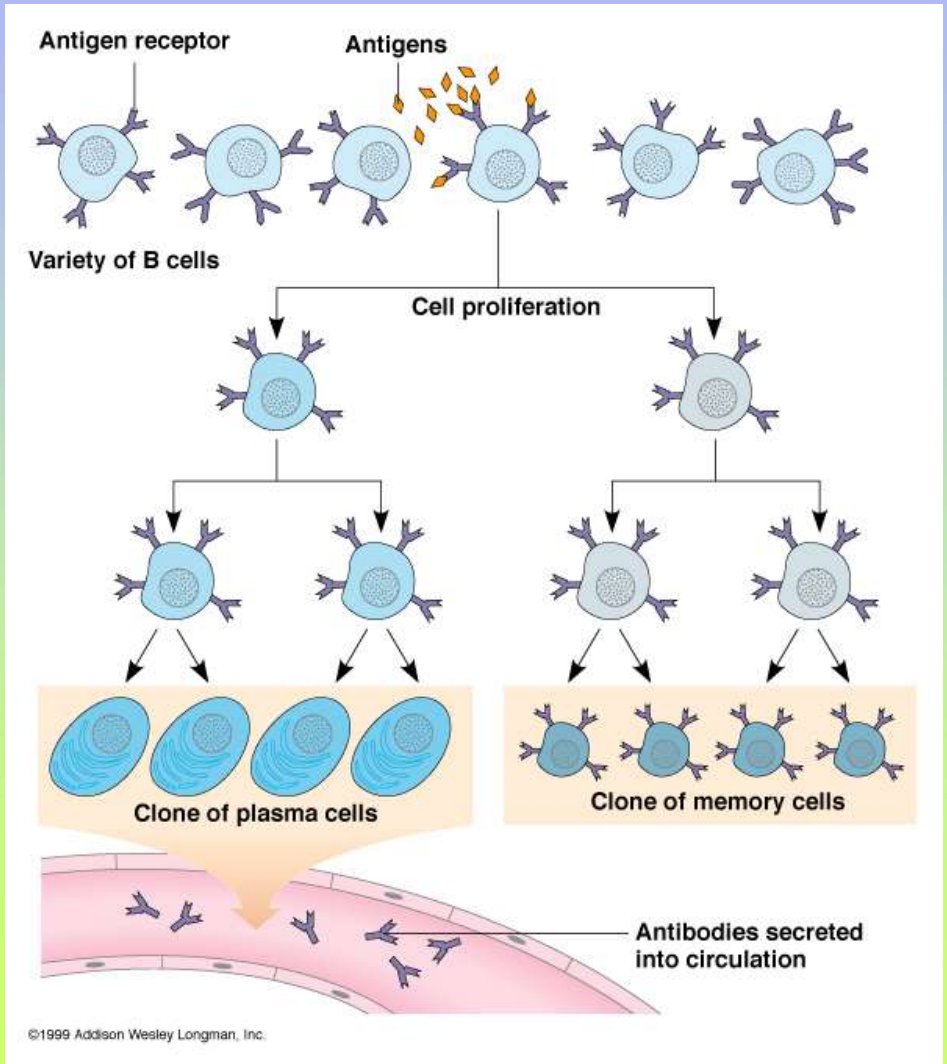
V. IgE

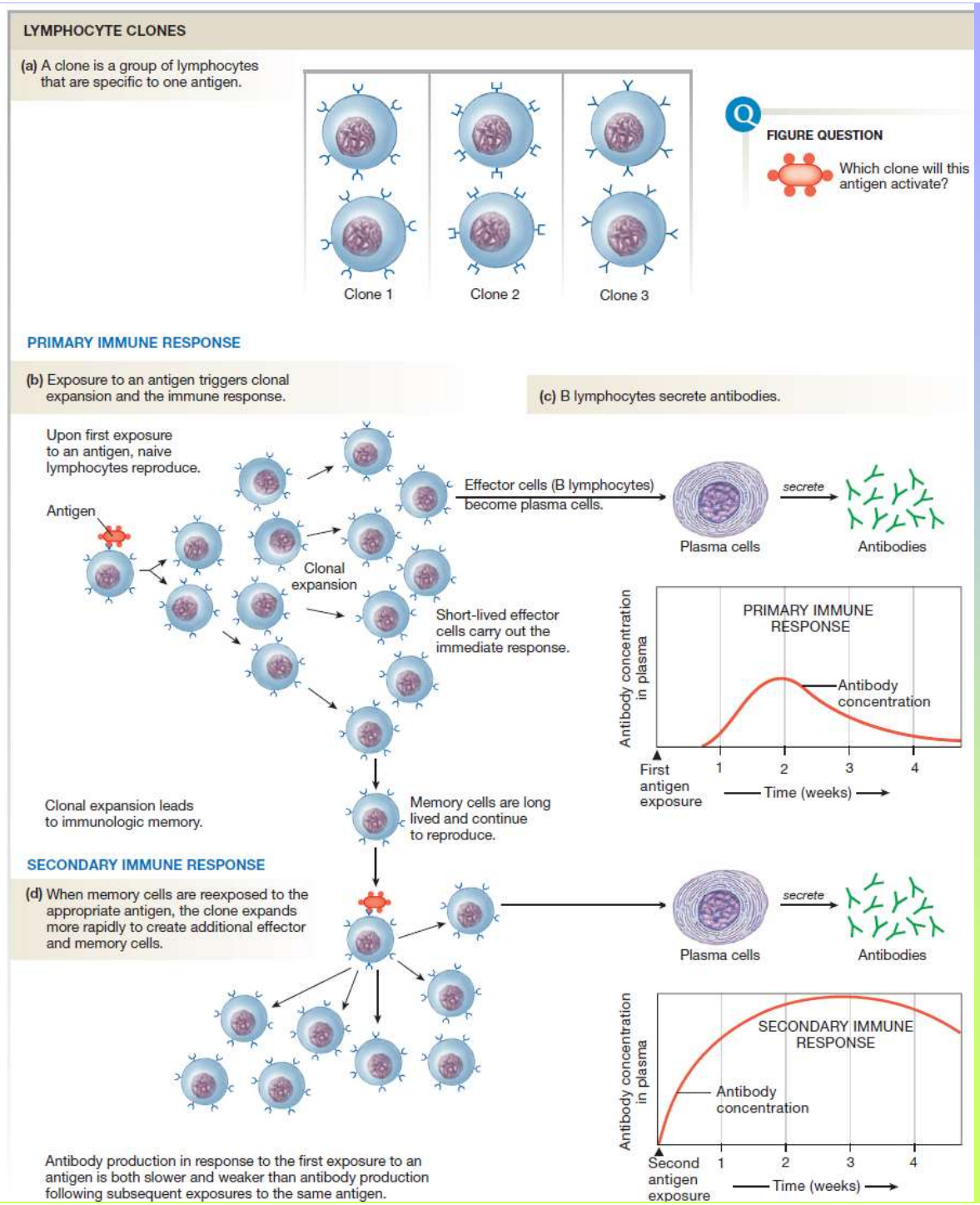
- Structure: Monomer
- Percentage serum antibodies: 0.002%
- Location: Bound to mast cells and basophils throughout body. Blood.
- Half-life in serum: 2 days
- Complement Fixation: No
- Placental Transfer: No
- Known Functions: Allergic reactions. Possibly lysis of worms.

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.

Clonal Selection of B Cells is Caused by Antigenic Stimulation




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.

Humoral Immunity

Clonal Selection

- **Clonal Selection: B cells (and T cells) that encounter stimulating antigen will proliferate into a large group of cells.**
- **Why don't we produce antibodies against our own antigens? We have developed *tolerance* to them.**
- **Clonal Deletion: B and T cells that react against *self* antigens appear to be destroyed during fetal development. Process is poorly understood.**

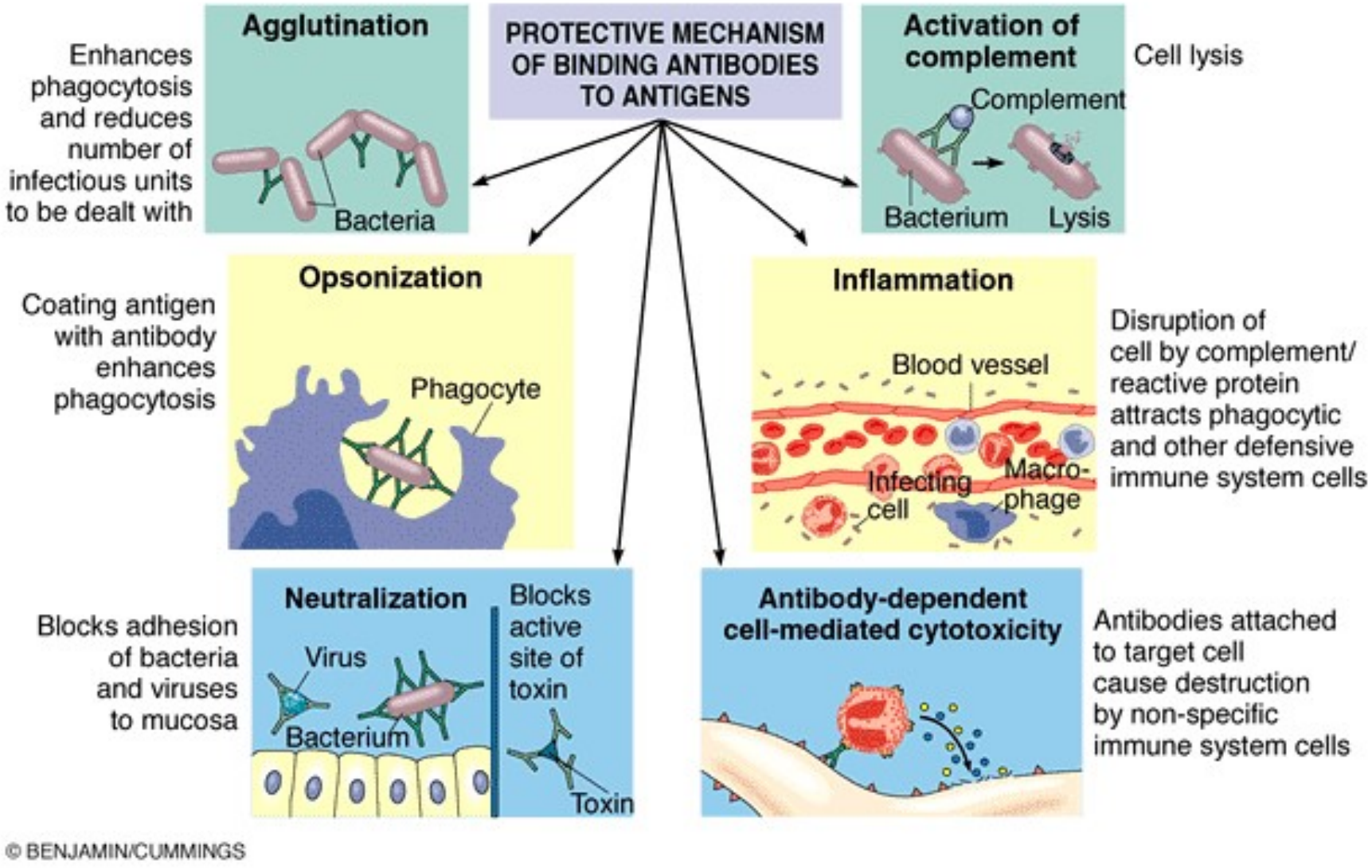
Consequences of Antigen-Antibody Binding

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.**

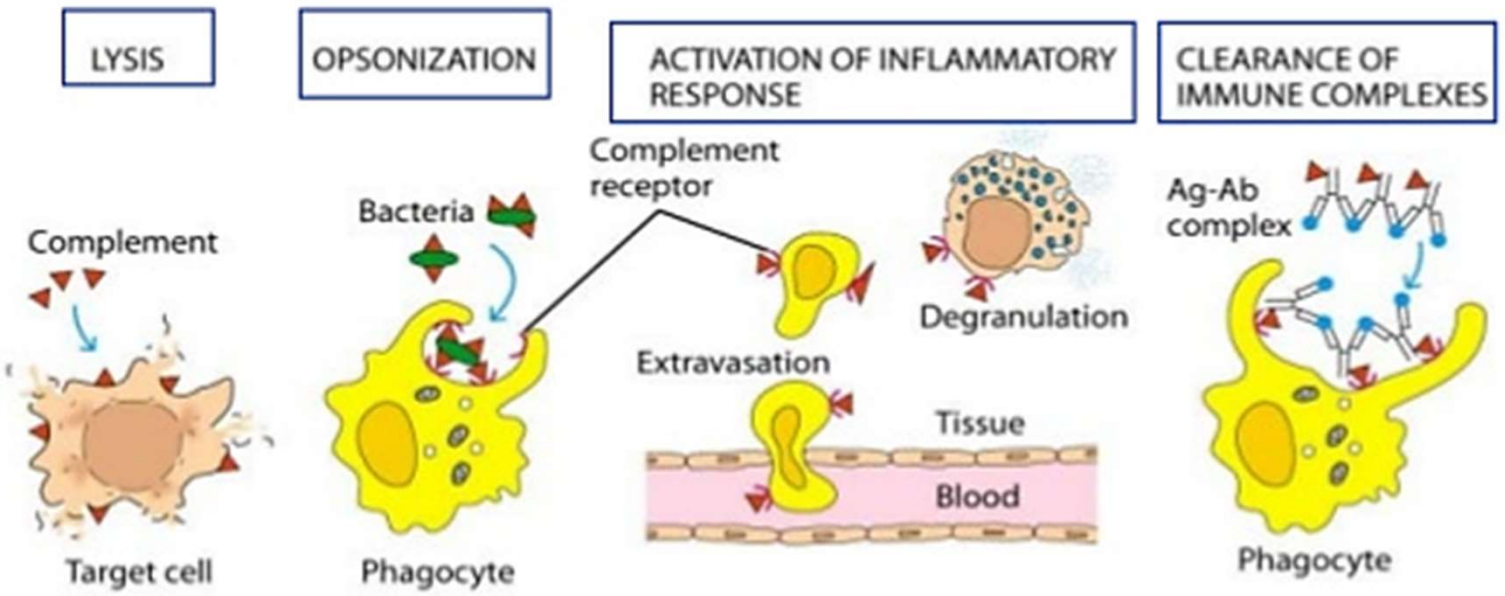
Consequences of Antibody Binding



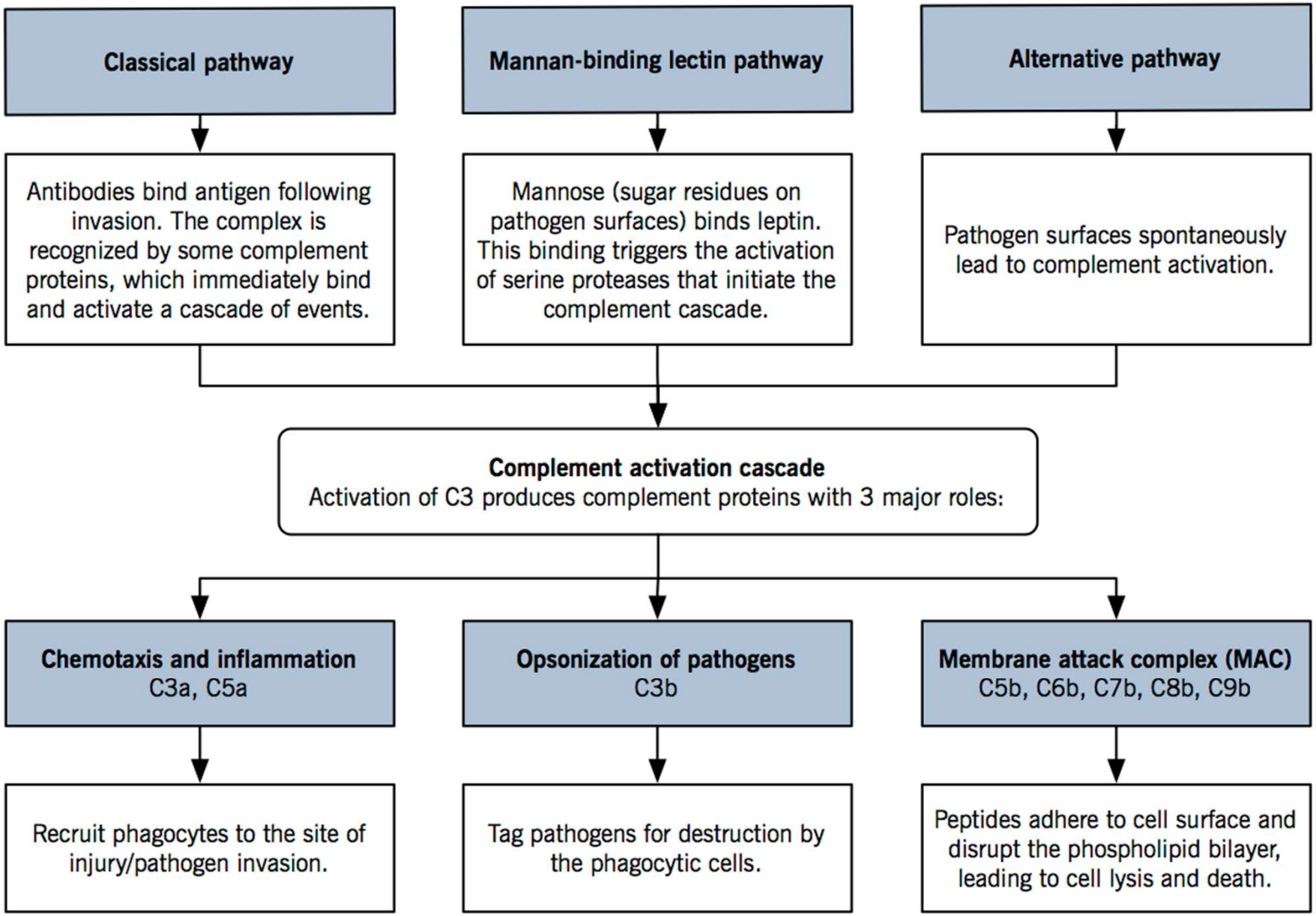
Humoral Immunity

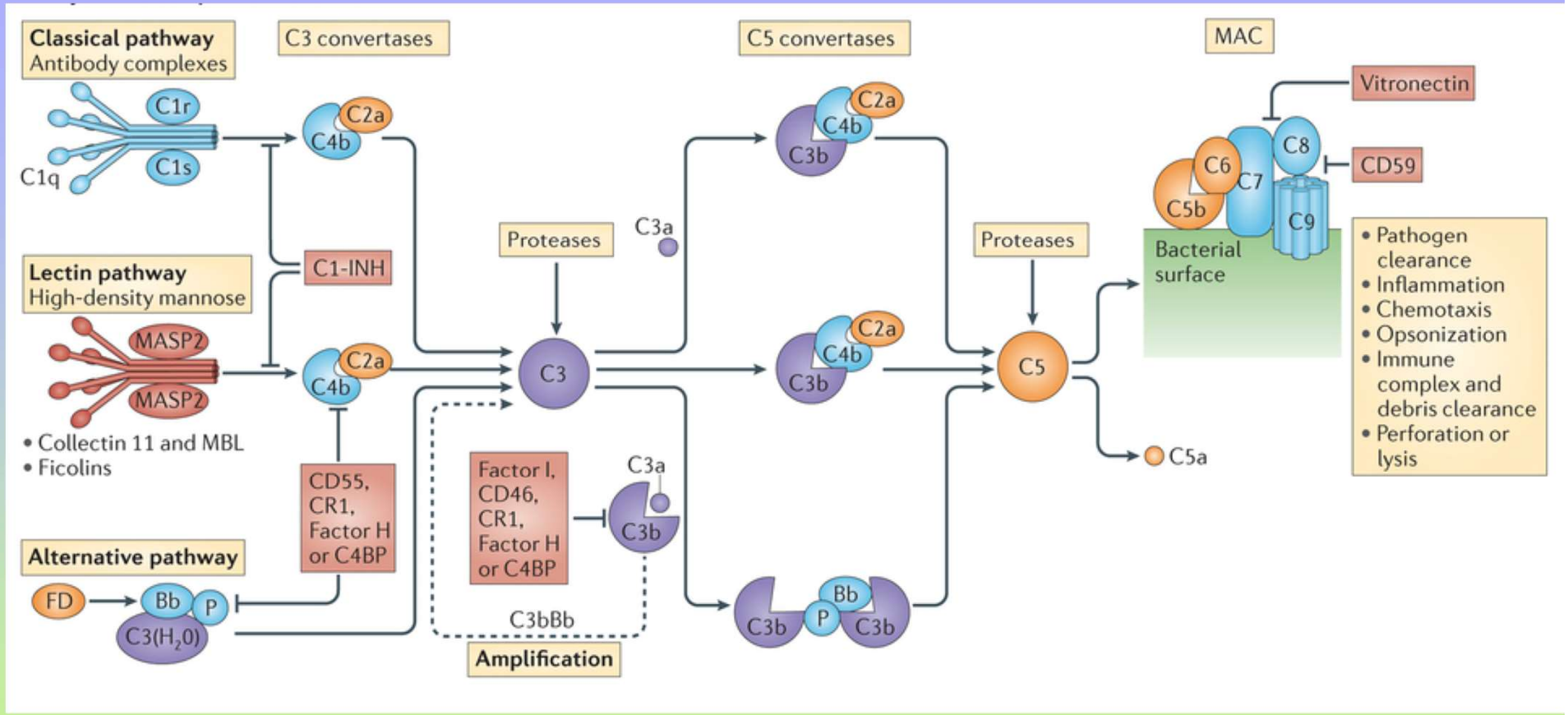
3. Neutralization: IgG inactivates viruses by binding to their surface and neutralize toxins by blocking their active sites.
4. Antibody-dependent cell-mediated cytotoxicity: Used to destroy large organisms (e.g.: worms). Target organism is coated with antibodies and bombarded with chemicals from nonspecific 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.



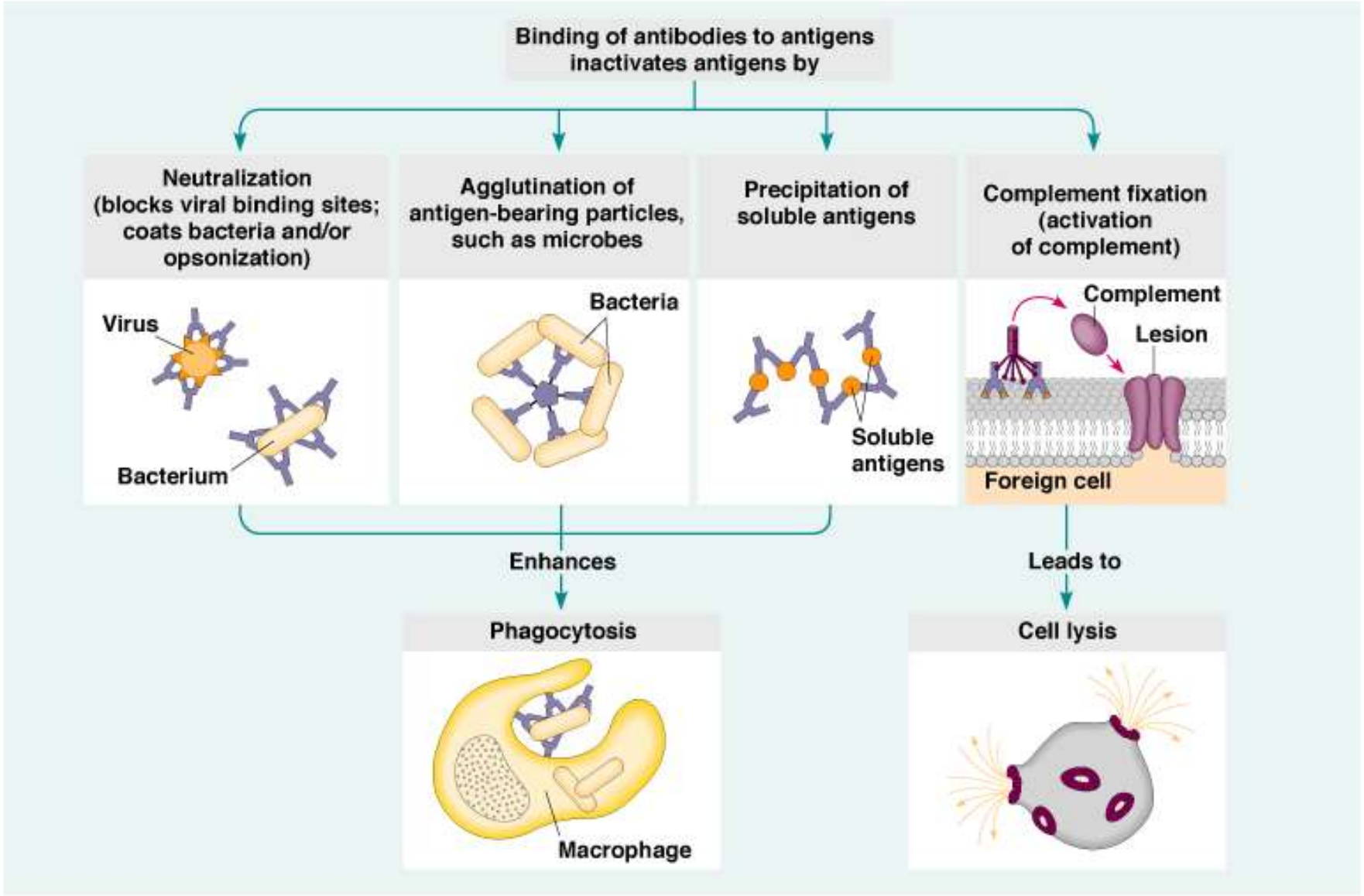
Complement pathways





All three of these pathways converge on generating C3 and C5 convertase enzyme complexes, which cleave C3 into the anaphylatoxin C3a and the opsonin C3b, and C5 into the anaphylatoxin C5a and into C5b, respectively. Deposition of C5b onto a target site initiates formation of the membrane attack complex (MAC) and blasts apart the target.

Consequences of Antibody Binding



Immunological Memory

Antibody Titer: The amount of antibody in the serum.

Pattern of Antibody Levels During Infection

Primary Response:

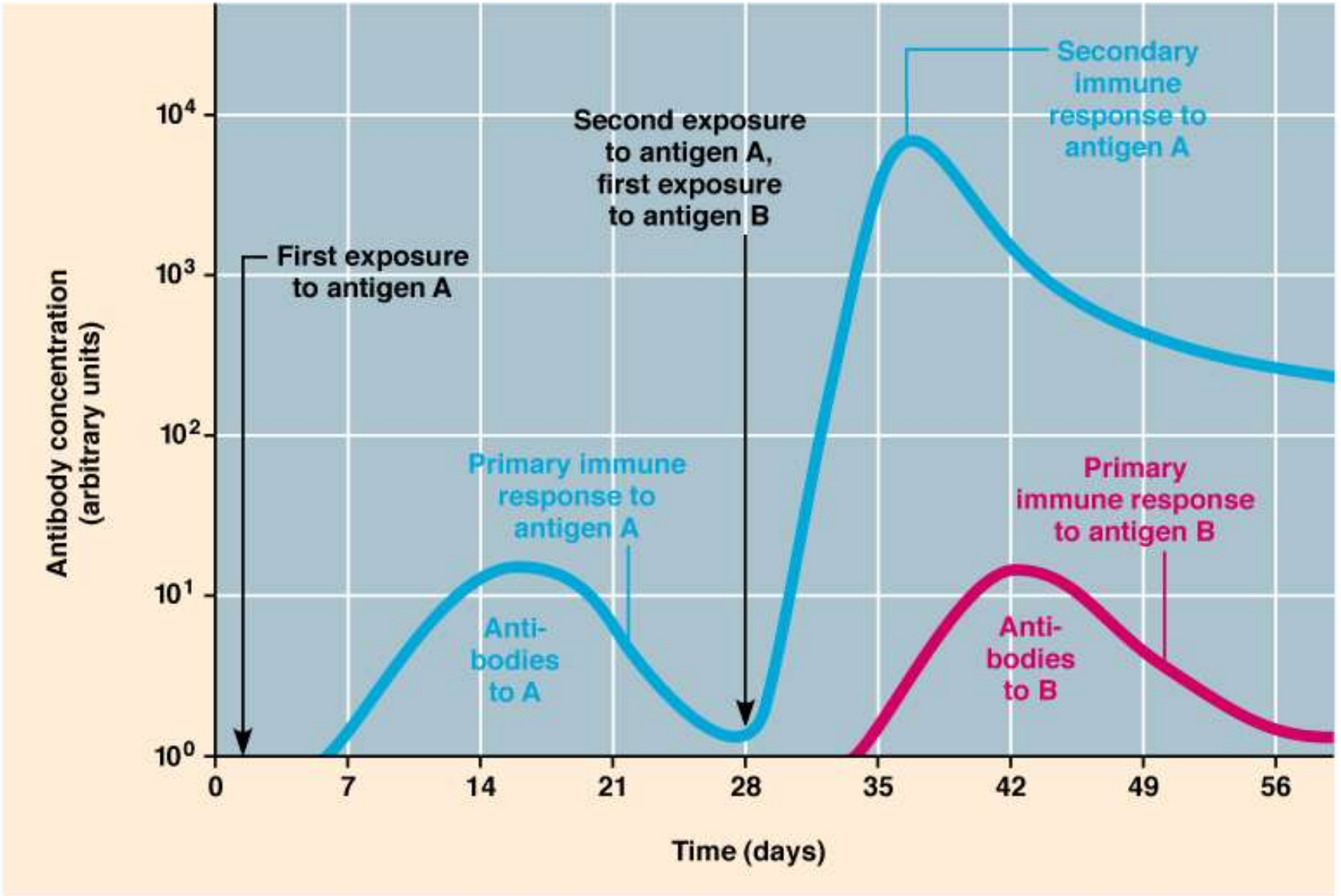
- **After *initial* exposure to antigen, no antibodies are found in serum for several days.**
- **A gradual increase in titer, first of IgM and then of IgG is observed.**
- **Most B cells become plasma cells, but some B cells become long living *memory cells*.**
- **Gradual decline of antibodies follows.**

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*.

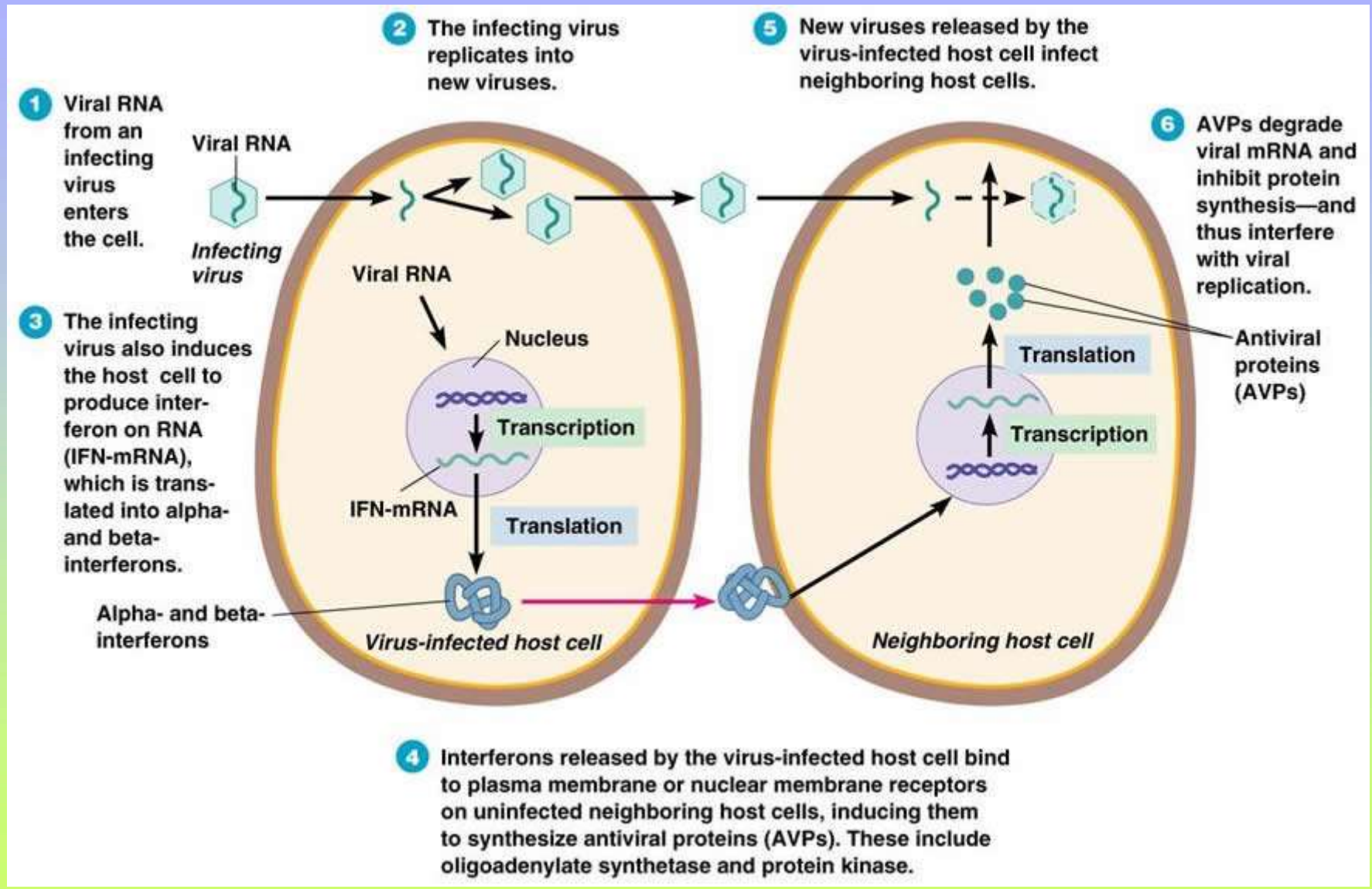
Requires constant presence of antigen to remain effective.

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

Cytokines: Chemical messengers of immune cells.

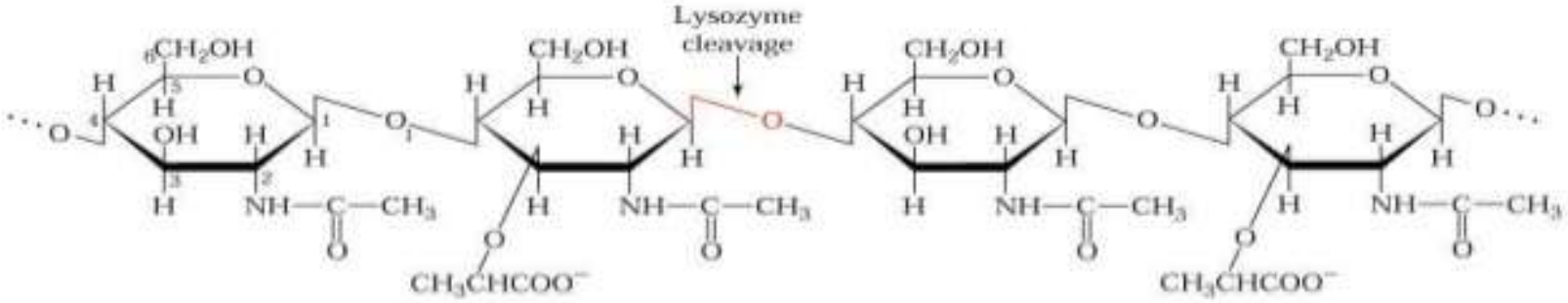
- **Over 100 have been identified.**
- **Stimulate and/or regulate immune responses.**
  - **Interleukins: Communication between WBCs.**
  - **Interferons: Protect against viral infections.**
  - **Chemokines: Attract WBCs to infected areas.**

Cytokine	Cellular Sources	Major Activities	Clinical Relevance
Interleukin-1	Macrophages	Activation of T cells and macrophages; promotion of inflammation	Implicated in the pathogenesis of septic shock, rheumatoid arthritis, and atherosclerosis
Interleukin-2	Type 1 (TH1) helper T cells	Activation of lymphocytes, natural killer cells, and macrophages	Used to induce lymphokine-activated killer cells; used in the treatment of metastatic renal-cell carcinoma, melanoma, and various other tumors
Interleukin-4	Type 2 (TH2) helper T cells, mast cells, basophils, and eosinophils	Activation of lymphocytes, monocytes, and IgE class switching	As a result of its ability to stimulate IgE production, plays a part in mast-cell sensitization and thus in allergy and in defense against nematode infections
Interleukin-5	Type 2 (TH2) helper T cells, mast cells, and eosinophils	Differentiation of eosinophils	Monoclonal antibody against interleukin-5 used to inhibit the antigen-induced late-phase eosinophilia in animal models of allergy
Interleukin-6	Type 2 (TH2) helper T cells and macrophages	Activation of lymphocytes; differentiation of B cells; stimulation of the production of acute-phase proteins	Overproduced in Castleman's disease; acts as an autocrine growth factor in myeloma and in mesangial proliferative glomerulonephritis
Interleukin-8	T cells and macrophages	Chemotaxis of neutrophils, basophils, and T cells	Levels are increased in diseases accompanied by neutrophilia, making it a potentially useful marker of disease activity
Interleukin-11	Bone marrow stromal cells	Stimulation of the production of acute-phase proteins	Used to reduce chemotherapy-induced thrombocytopenia in patients with cancer
Interleukin-12	Macrophages and B cells	Stimulation of the production of interferon γ by type 1 (TH1) helper T cells and by natural killer cells; induction of type 1 (TH1) helper T cells	May be useful as an adjuvant for vaccines
Tumor necrosis factor α	Macrophages, natural killer cells, T cells, B cells, and mast cells	Promotion of inflammation	Treatment with antibodies against tumor necrosis factor α beneficial in rheumatoid arthritis
Lymphotoxin (tumor necrosis factor β)	Type 1 (TH1) helper T cells and B cells	Promotion of inflammation	Implicated in the pathogenesis of multiple sclerosis and insulin-dependent diabetes mellitus
Transforming growth factor β	T cells, macrophages, B cells, and mast cells	Immunosuppression	May be useful therapeutic agent in multiple sclerosis and myasthenia gravis
Granulocyte-macrophage colony-stimulating factor	T cells, macrophages, natural killer cells, and B cells	Promotion of the growth of granulocytes and monocytes	Used to reduce neutropenia after chemotherapy for tumors and in ganciclovir-treated patients with AIDS; used to stimulate cell production after bone marrow transplantation
Interferon-α	Virally infected cells	Induction of resistance of cells to viral infection	Used to treat AIDS-related Kaposi sarcoma, melanoma, chronic hepatitis B infection, and chronic hepatitis C infection
Interferon-β	Virally infected cells	Induction of resistance of cells to viral infection	Used to reduce the frequency and severity of relapses in multiple sclerosis
Interferon-γ	Type 1 (TH1) helper T cells and natural killer cells	Activation of macrophages; inhibition of type 2 (TH2) helper T cells	Used to enhance the killing of phagocytosed bacteria in chronic granulomatous disease


1 Viral RNA from an infecting virus enters the cell.
Viral RNA
Infecting virus
2 The infecting virus replicates into new viruses.
Viral RNA
3 The infecting virus also induces the host cell to produce interferon on RNA (IFN-mRNA), which is translated into alpha- and beta-interferons.
Nucleus
Transcription
IFN-mRNA
Translation
Alpha- and beta-interferons
Virus-infected host cell
4 Interferons released by the virus-infected host cell bind to plasma membrane or nuclear membrane receptors on uninfected neighboring host cells, inducing them to synthesize antiviral proteins (AVPs). These include oligoadenylate synthetase and protein kinase.
5 New viruses released by the virus-infected host cell infect neighboring host cells.
6 AVPs degrade viral mRNA and inhibit protein synthesis—and thus interfere with viral replication.
Translation
Transcription
Antiviral proteins (AVPs)
Neighboring host cell

LYSOZYME

- **Lysozyme:** is 129 aminoacid residues enzyme
- (EC 3.2.1.17), hydrolase which catalyzes hydrolysis of 1,4-beta-linkages between N-acetylmuramic acid and N-acetyl-D-glucosamine residues in peptidoglycan and between N-acetyl-D-glucosamine residues in chitodextrins.
- Molecular weight of Lysozyme is an approximately 14.7 kDa.

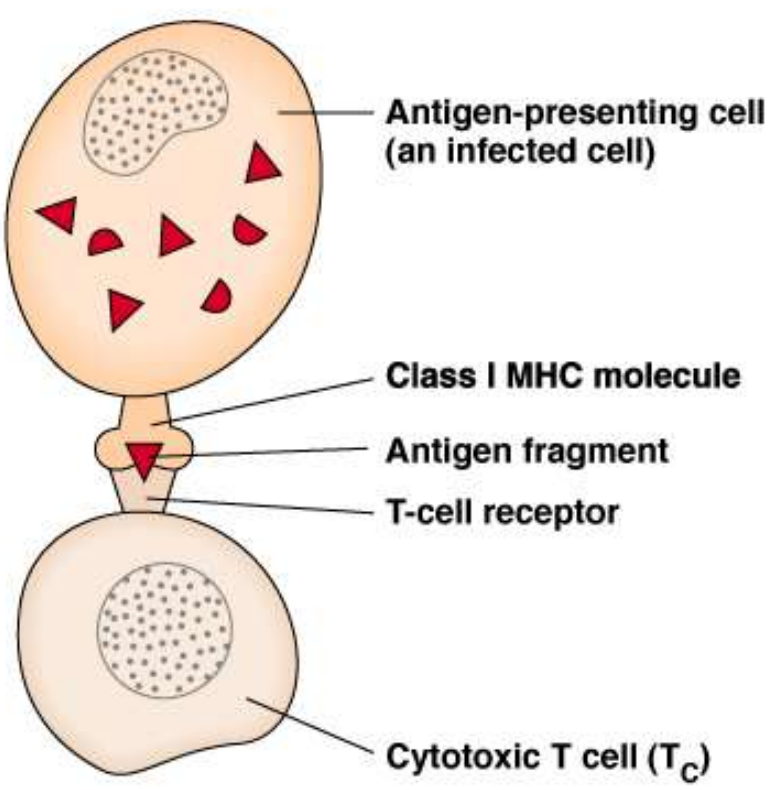


T Cells and Cell Mediated Immunity

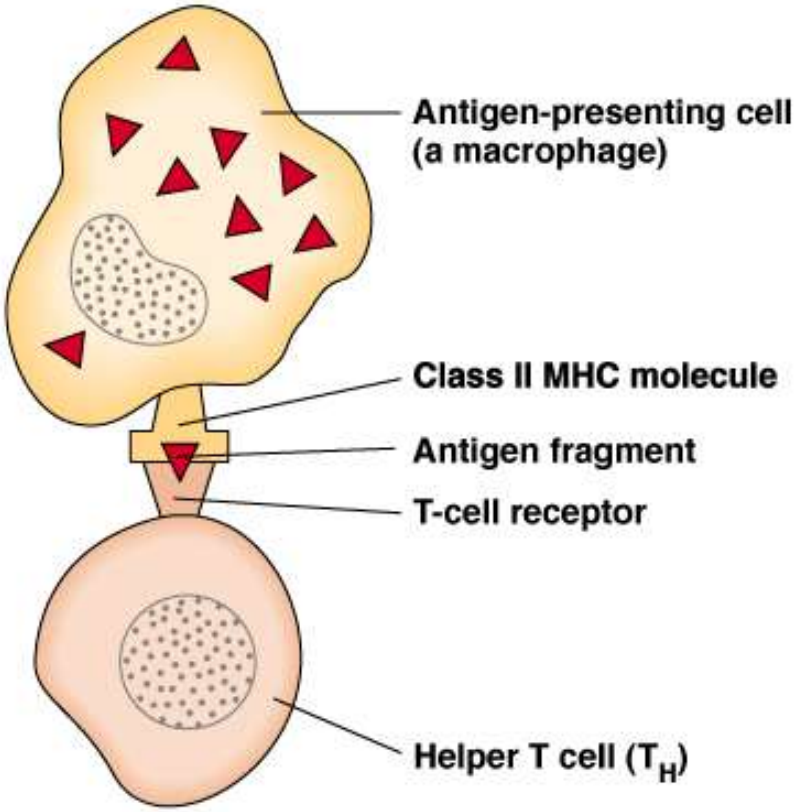
Cellular Components of Immunity:

- **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)



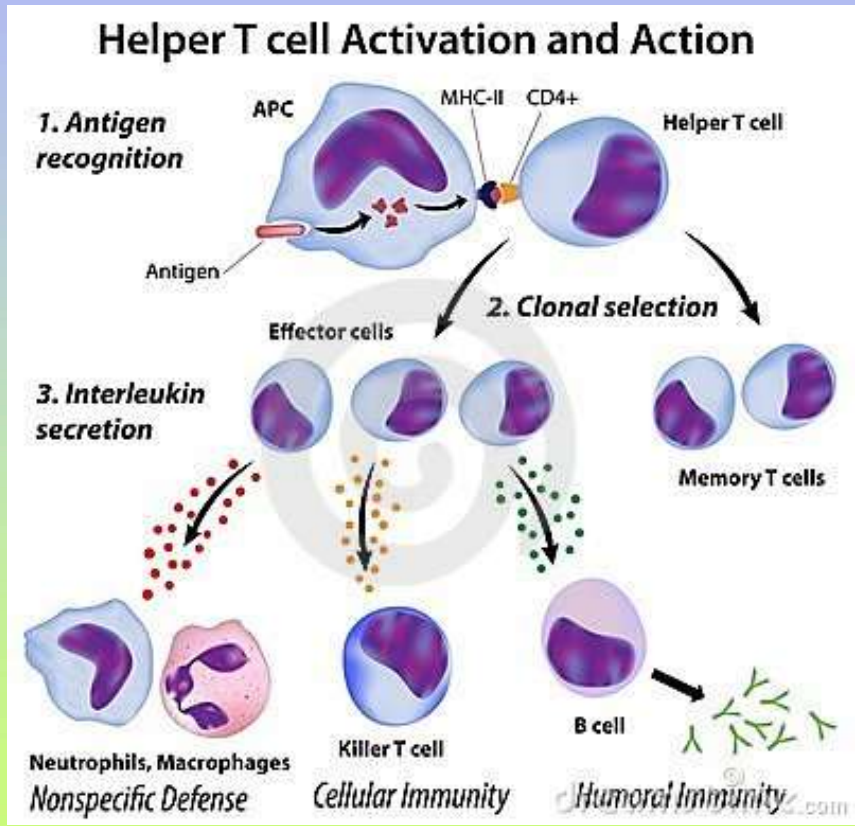
(b)

T Cells and Cell Mediated Immunity

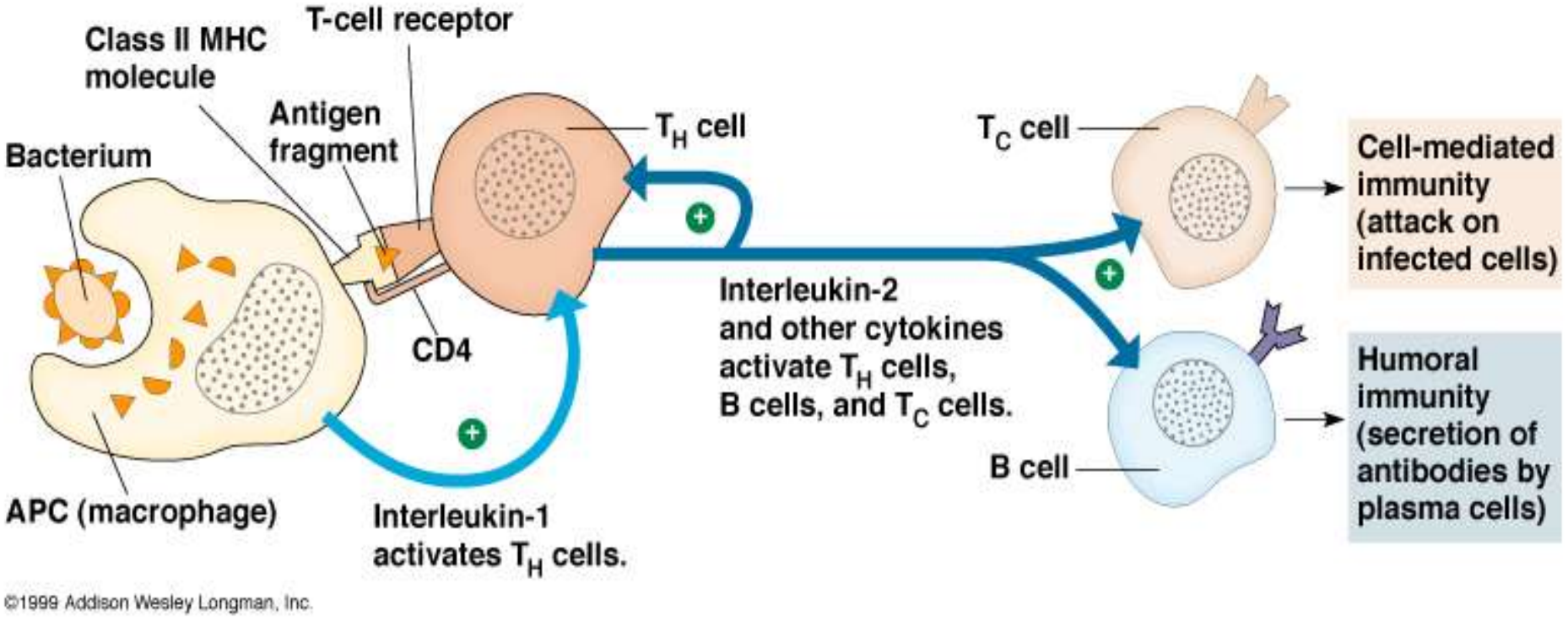
Types of T cells

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.



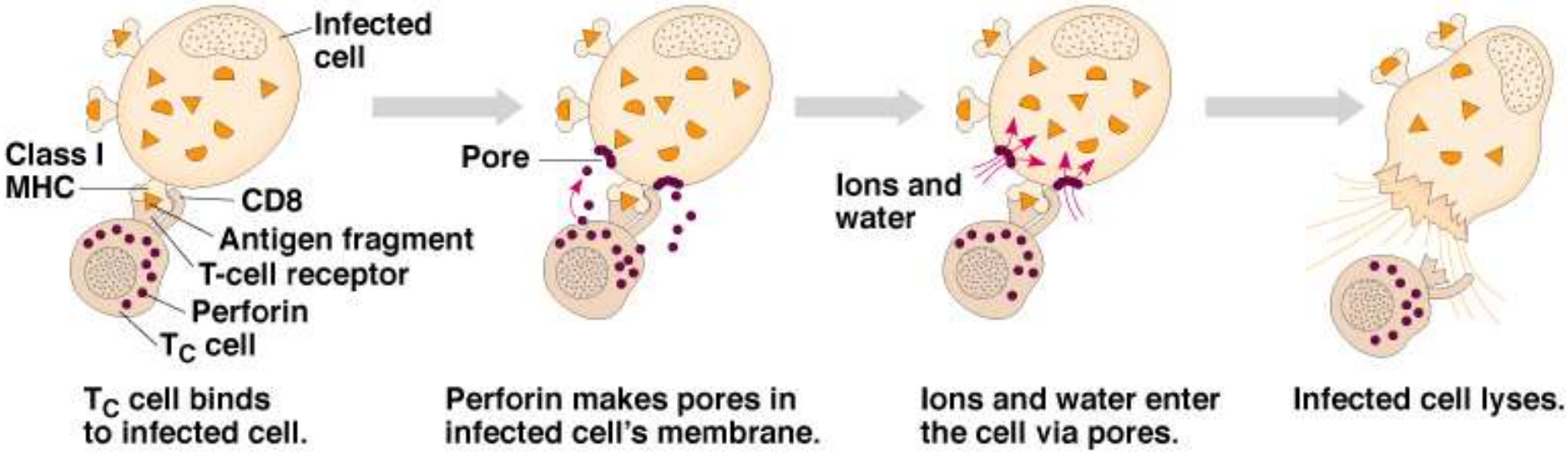
Central Role of Helper T Cells



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.**

Nonspecific Cellular Components

1. Activated Macrophages: Stimulated phagocytes.

- Stimulated by ingestion of antigen
- Larger and more effective phagocytes.
- Enhanced ability to eliminate intracellular bacteria, virus-infected and cancerous cells.

2. Natural Killer (NK) Cells:

- Lymphocytes that destroy virus infected and tumor cells.
- Not specific. Don’t require antigen stimulation.
- Not phagocytic, but must contact cell in order to lyse it.

Relationship Between Cell-Mediated and Humoral Immunity

1. Antibody Production

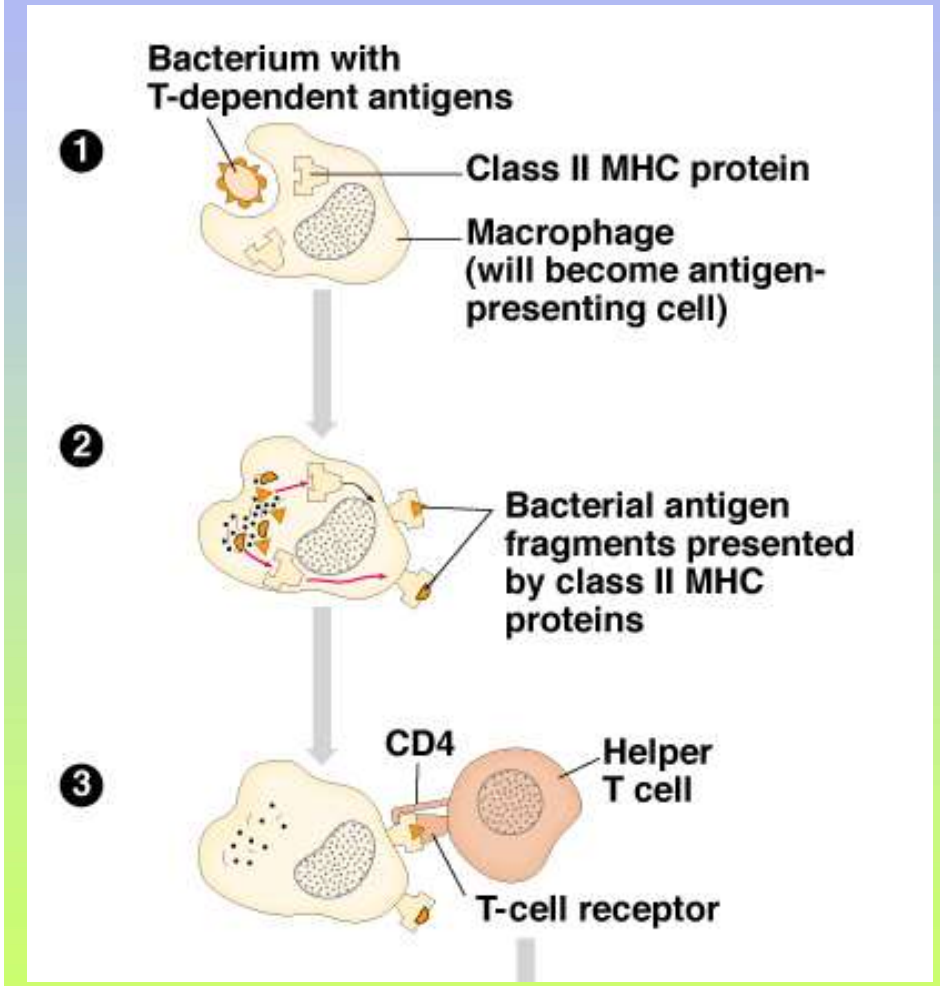
T-Dependent Antigens:

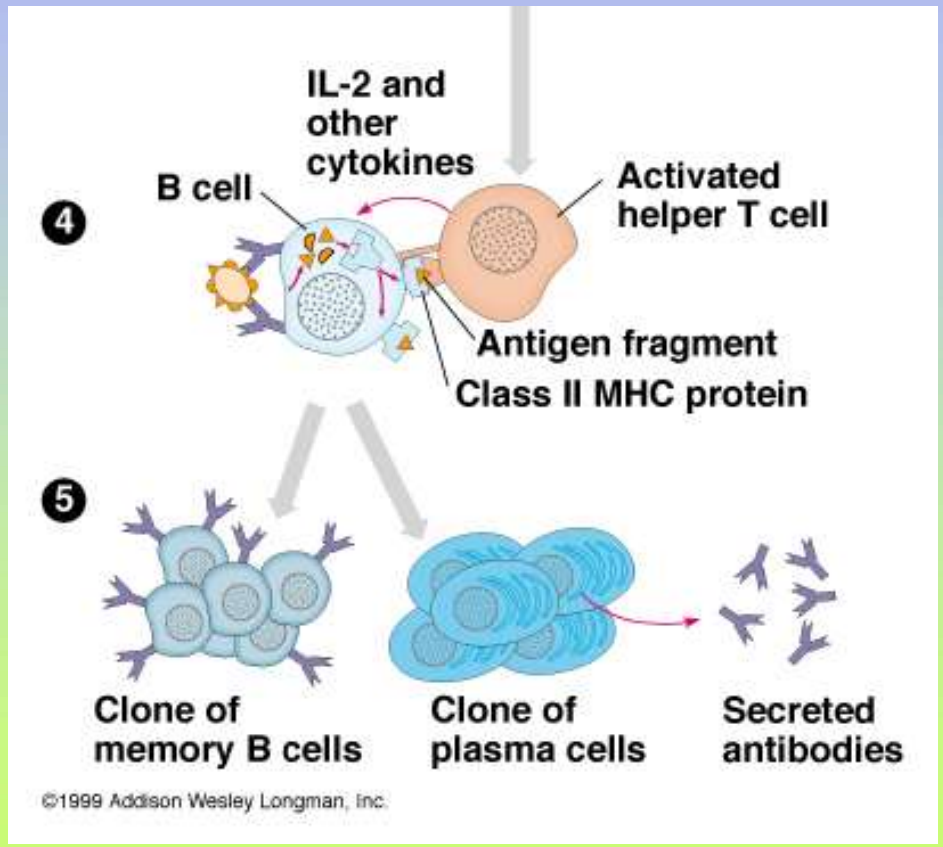
- Antibody production requires assistance from T helper cells.
- A macrophage cells ingest antigen and presents it to T_H cell.
- T_H cell stimulates B cells specific for antigen to become plasma cells.
- Antigens are mainly proteins on viruses, bacteria, foreign red blood cells, and hapten-carrier molecules.

T-Independent Antigens:

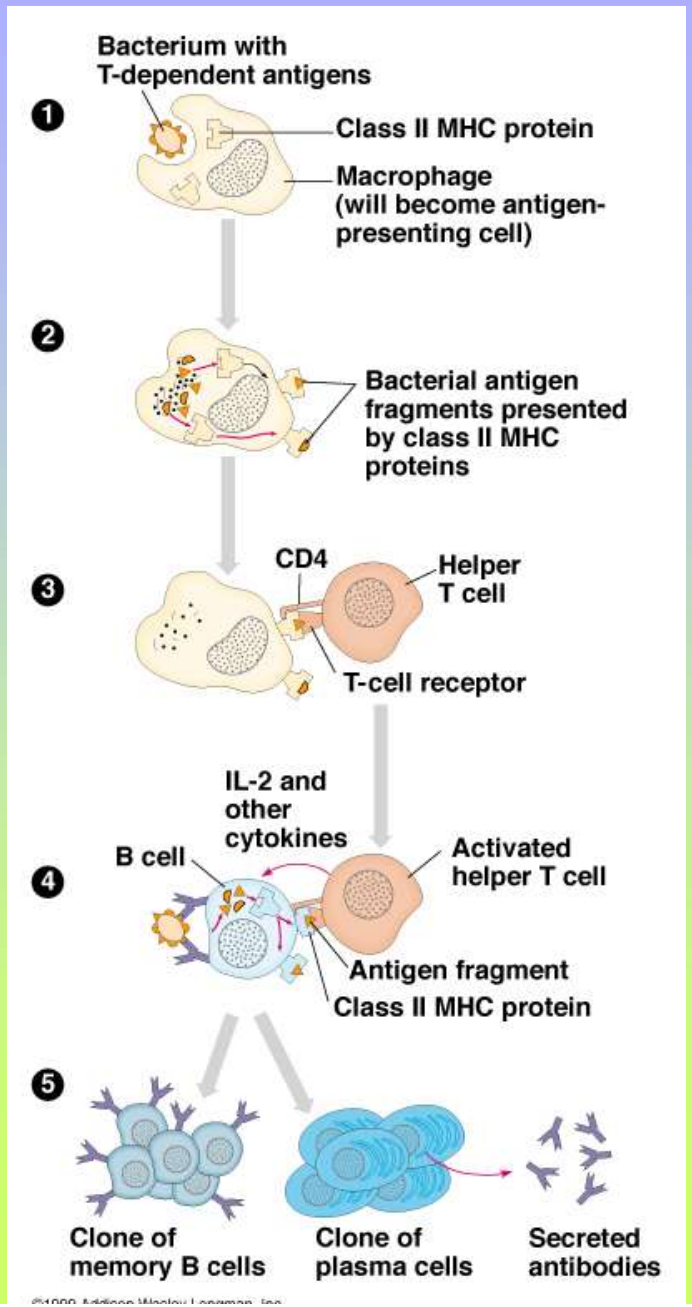
- Antibody production does not require assistance from T cells.
- Antigens are mainly polysaccharides or lipopolysaccharides with repeating subunits (bacterial capsules).
- Weaker immune response than for T-dependent antigens.

Humoral Response to T Dependent Antigens





Humoral Response to T Dependent Antigens

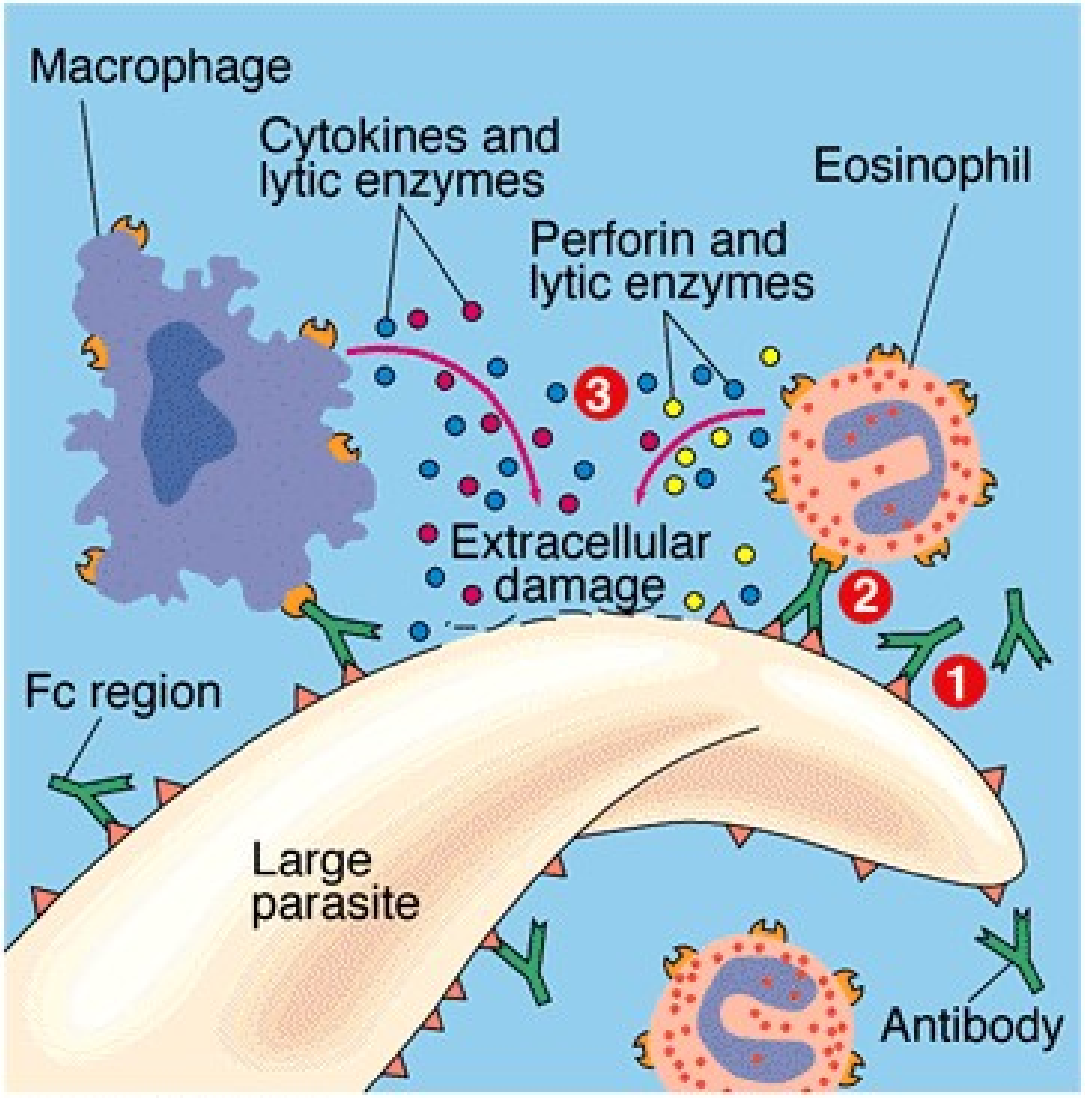


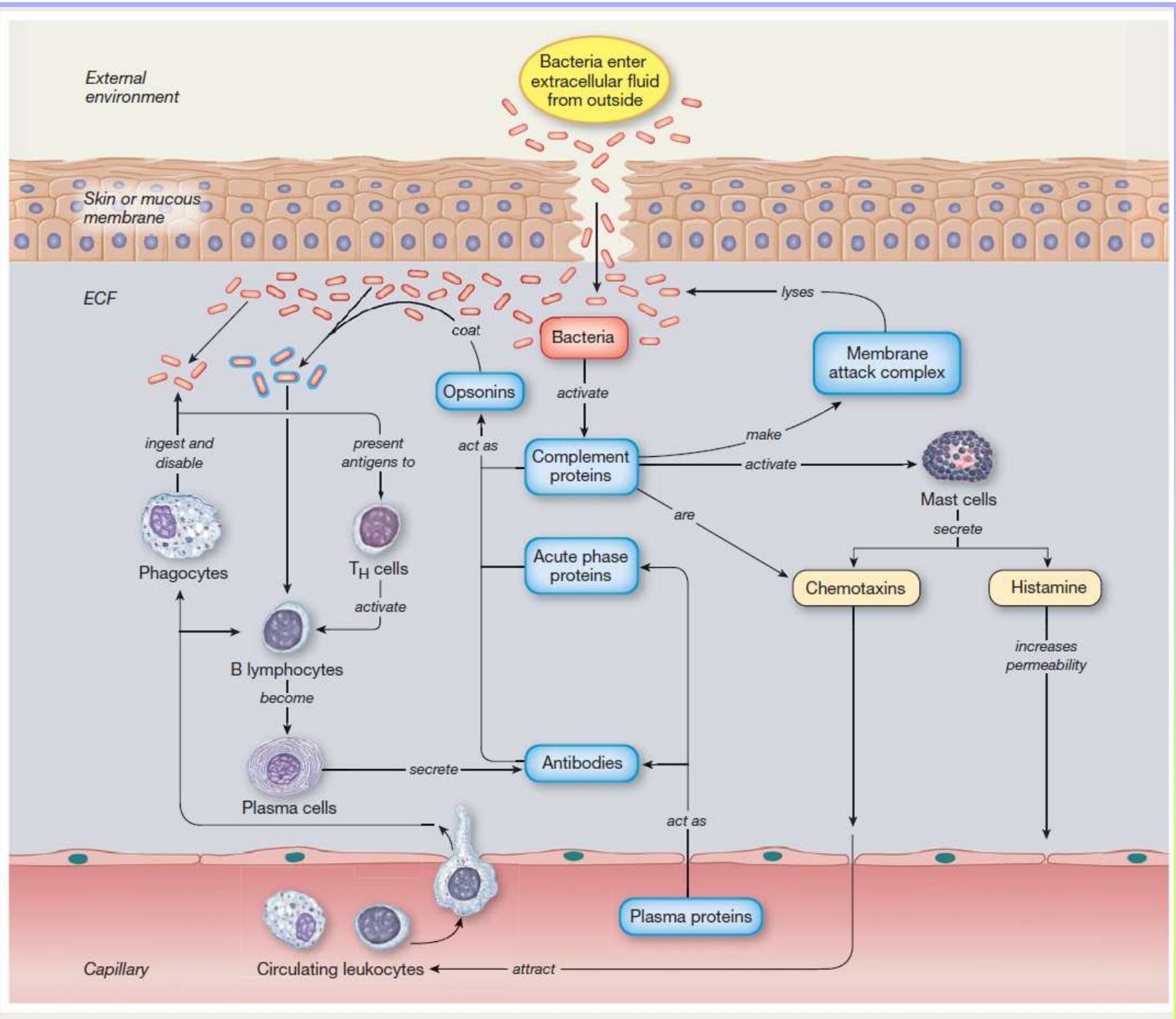
Relationship Between Cell-Mediated and Humoral Immunity

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.

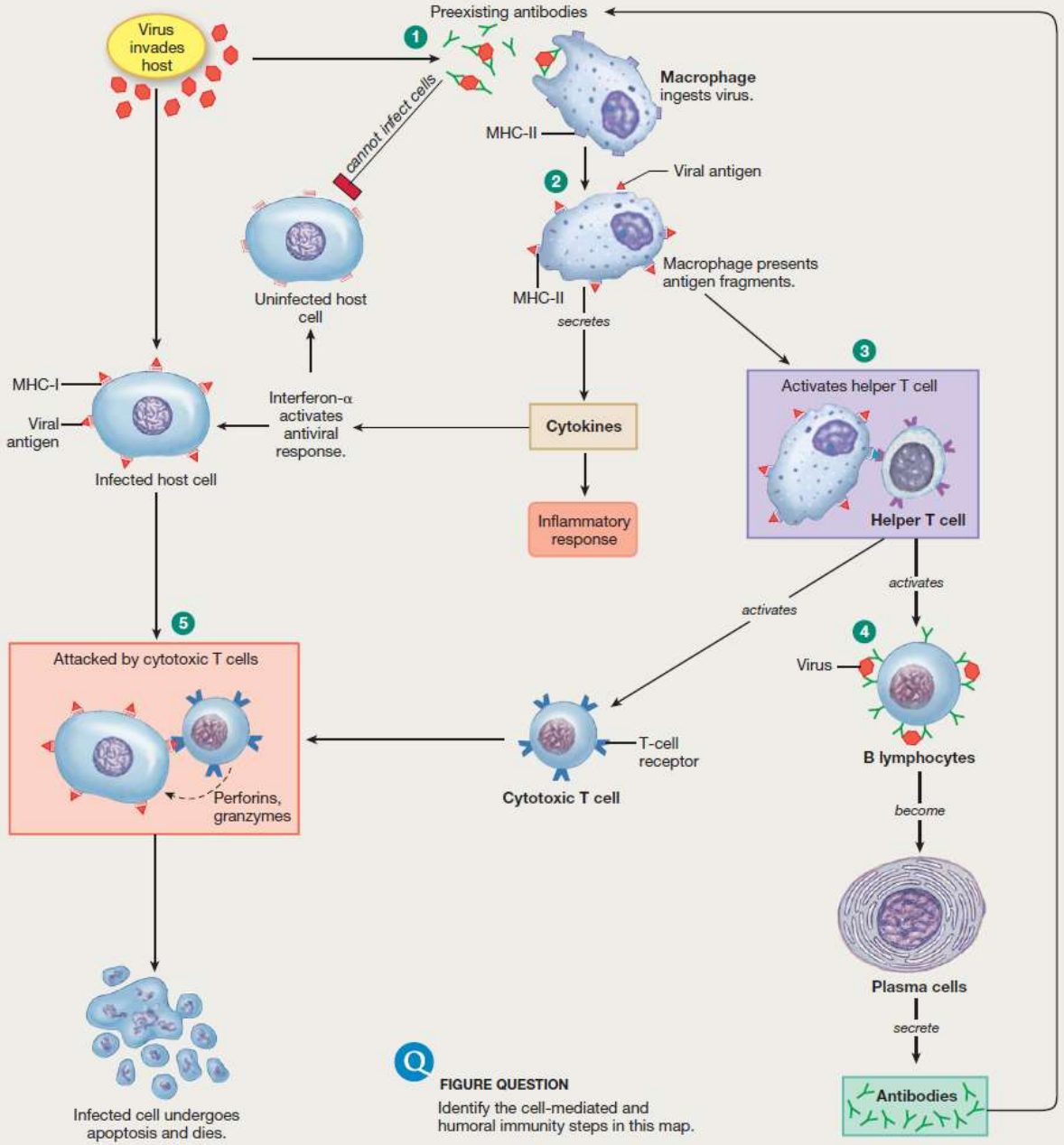
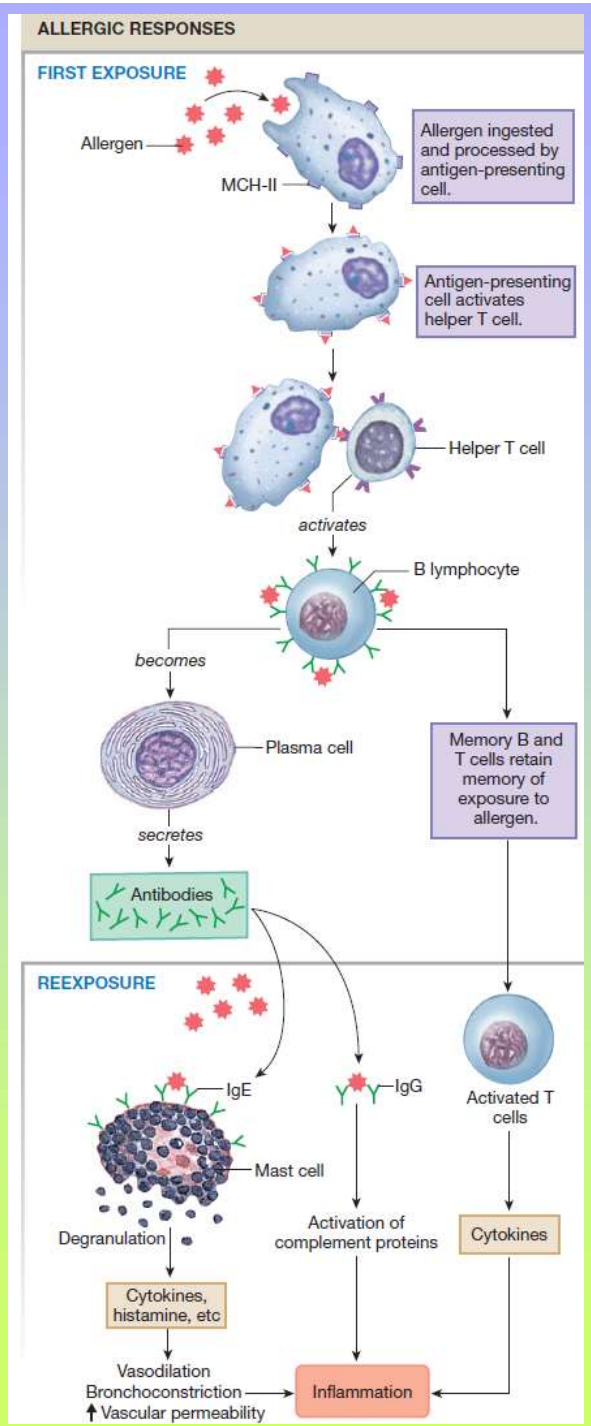


FIGURE QUESTION

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