Overview of the immune system and innate immunity

Prof. Dr. Hazem Aqel AL-Rimawi

Lecture 1

This is a presentation given by Mohamed Alzobi

The Objectives

- What is Immunology?
- What are the Components of the Immune System?
- What is the difference between innate & adaptive immunity
- What is the difference between cellular and humoral immunity
- What is Phagocytosis

History



Edward Jenner infects a boy with cow pox to protect against small pox.





Robert Koch showed that microorganism cause infectious diseases and that different organisms cause different diseases

discovered Bacillus bacteria









Louis Pasteur first showed how vaccines could be made to a variety of bacterial and viral pathogens.





In 1796 Edward Jenner infects a boy with cow pox to protect against small pox

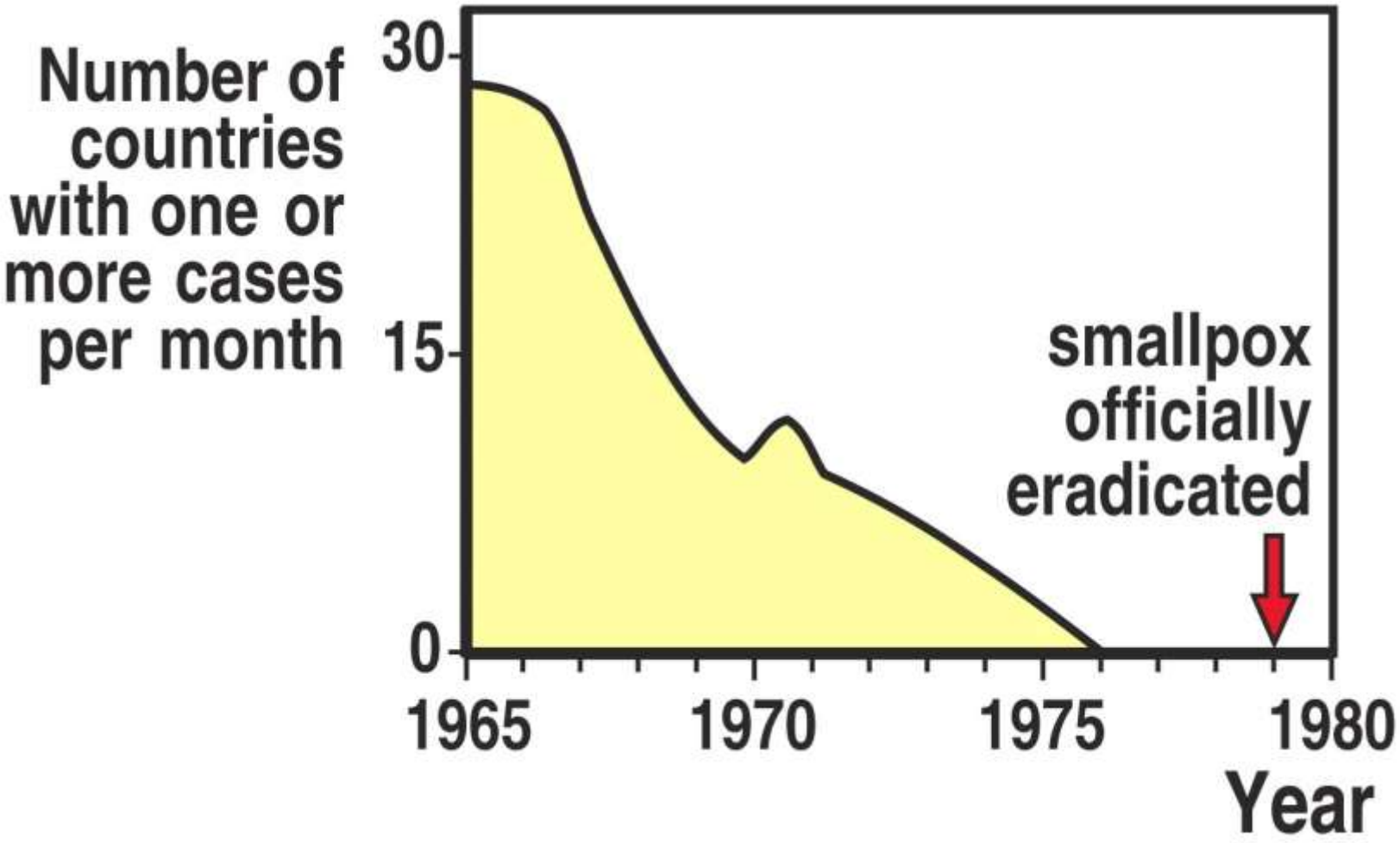
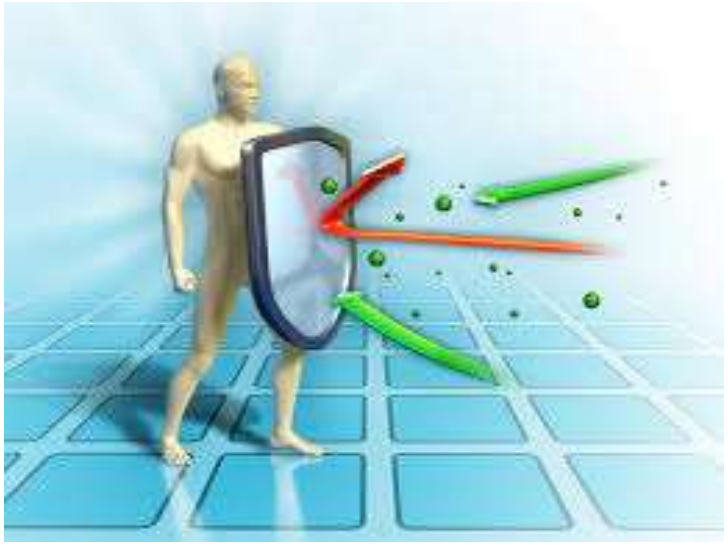


Figure 1-2 Immunobiology, 6/e. (© Garland Science 2005)

Immunology

Immunology: is the study of the body's defense mechanisms against foreign agents such as pathogens



viruses have no treatments!

it is different among individual, affected by nutrition, stress, age, drugs ..

sometimes we induce low immunity status like in transplant to avoid rejection

What is immunity?

- when a microorganism tries to infect us, we firstly defend through physical barriers (skin, mucous membranes)
- if it was able to bypass this barrier, phagocytic cells come to place and try to get rid of the MO
- if it was able to avoid phagocytosis, B cells come and start to secrete antibodies, which fight in many ways
- if it is a virus, T cells help through identification and killing of infected cells
- if the cell fails to present the virus for T cells, NK will work by destructing those cells.

Immunity: is derived from the word *immunitas:* Latin for exemption. It means protection from disease especially infectious diseases.

some immunity is transferred from the mother to the baby in the form of immunoglobulins during pregnancy and lactation, this is called passive immunity

Immunity is mediated by variable cells and molecules.

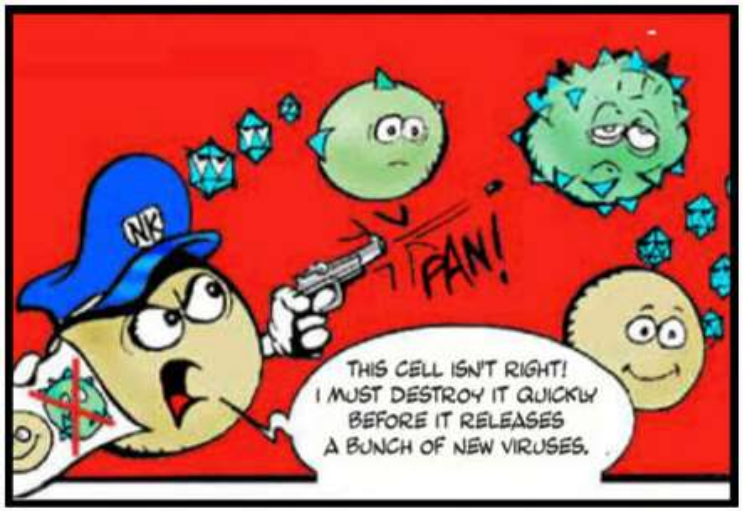
The response to introduction of a foreign agent is known as the **immune response**.

Immune response: is the response we make against a vast range of substances such as:

- Proteins, glycoproteins and polysaccharides (pathogens)
- Metals (nickel)
- Drugs (penicillin)
- Organic chemicals (poison ivy)

What are the main tasks of the immune system

1. Recognition: Recognize the presence of an infection
2. Distinction: Distinguish between self and non-self
3. Control: Eliminate the infection
4. Regulation: Regulate the response
5. Protect against recurring infection "Immunological memory"



What are the components of the immune system?

- Organs: Bone marrow, thymus, lymph nodes and spleen.
  maturation of T cells
- Cells: Myeloid (macrophages, granulocytes, mast cells and dendritic cells) and Lymphoid (T cells, B cells and NK cells)
  monocyte in blood --> macrophages in tissues
- Molecules: complement components, C reactive proteins and defensins

What are types of an immune response?

- Innate immune response: Immediate, first line of defense, usually effective, not specific and does not lead to lasting immunity (e.g., macrophages, neutrophils, certain molecules).

or natural

no memory

NK cells are part of the innate response, comes from lymphoid lineage

- Adaptive immune response (acquired): Slower than innate (7days) develops during lifetime, Specific, highly effective and usually results in lifelong protection (mediated by B and T cells).

innate
fast
non specific
no memory

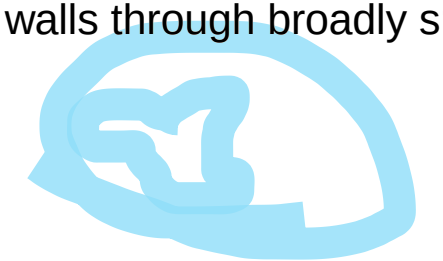
adaptive
slow
specific
memory
more effective

Mechanisms that protect against infectious pathogens

Innate (or natural) immunity

is made up of several components.

- **Physical barriers are the first line of defense against infection.** The skin and mucous membranes provide a continuous surface. stomach acidity inhibits bacterial growth
- **Physiological factors** such as pH, temperature and oxygen tension limit microbial growth.
- **Proteins** secretions into external body fluids such as lysozyme also help resist invasion.
- **Soluble factors** within the body such as **complement**, **interferons** and **collectins** and other "broadly specific" molecules such as C-reactive protein are of considerable importance in protection against infection.
- **Phagocytic cells** are critical in the defense against bacterial and simple eukaryotic pathogens. **Macrophages** and **Polymorphonuclear leukocytes (PMN)** can recognize bacterial and yeast cell walls through broadly specific receptors (usually for carbohydrate structures).





Cells of innate and adaptive immune systems differ in receptor specificity

- Cells in innate immune system have receptors that bind pathogen-associated molecular patterns (PAMPs) expressed on microbes, and not in mammalian cells (host): A global recognition system!

- PAMPs are found on many bacterial or viral species including gram-negative bacterial lipopolysaccharide (LPS), gram-positive bacterial peptidoglycan (PGN), viral double-stranded RNA, unmethylated bacterial CpG nucleotides.

Toll-Like Receptors

are pattern recognition receptors

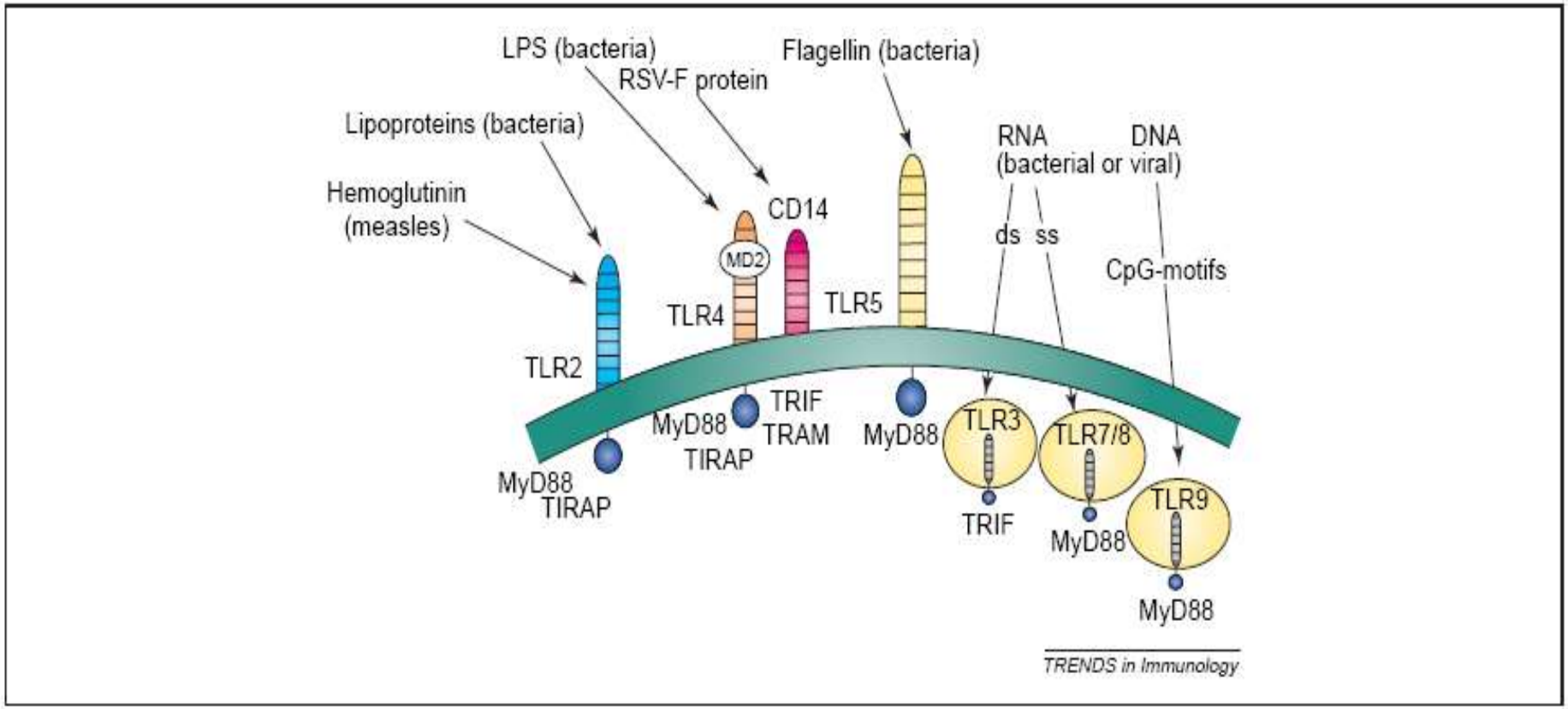


Figure 1. Toll-like receptors (TLRs) segregate into a subgroup expressed at the cell membrane (TLR2, 4, 5) or at the endosome (TLR3, 7–9). Altogether, they donate to innate immune cells a germ line-encoded repertoire specific for ligands of bacterial and viral origin. Whereas TLRs expressed at endosomal membranes recognize RNA- and DNA-motifs, cell membrane-bound TLRs recognize primarily proteins, lipoproteins and lipopolysaccharide. Upon ligand driven activation of TLRs, different adaptor molecules (MyD88, TRIF, TIRAP, TRAM) become recruited to the respective cytoplasmic TIR domain (blue), which in turn control the emanating signaling pathways. Abbreviations: ds, double stranded; LPS, lipopolysaccharide; RSV, respiratory syncytial virus; ss, single stranded; TIR, Toll–interleukin-1 receptor; TIRAP, TIR domain-containing adaptor protein; TRAM, TRIF-related adaptor molecule; TRIF, TIR domain-containing adaptor inducing interferon-β.

Cells of innate and adaptive immune systems differ in receptor specificity

- Lymphocytes, the cells of the adaptive immune system, have antigen-specific receptors: a subtle recognition system!

- Lymphocytes can somatically create 10^9 to 10^{16} different antigen receptors (Antibodies or T cell receptors).

Types of adaptive immunity

- **Humoral immunity**
  - Immunity that is mediated by B cells producing antibodies

first response -- IgM
second response -- IgG

antibodies do:
- neutralization
- opsonization

- **Cell Mediated Immunity**
  - Immunity that is mediated by antigen specific T cells

cytokines

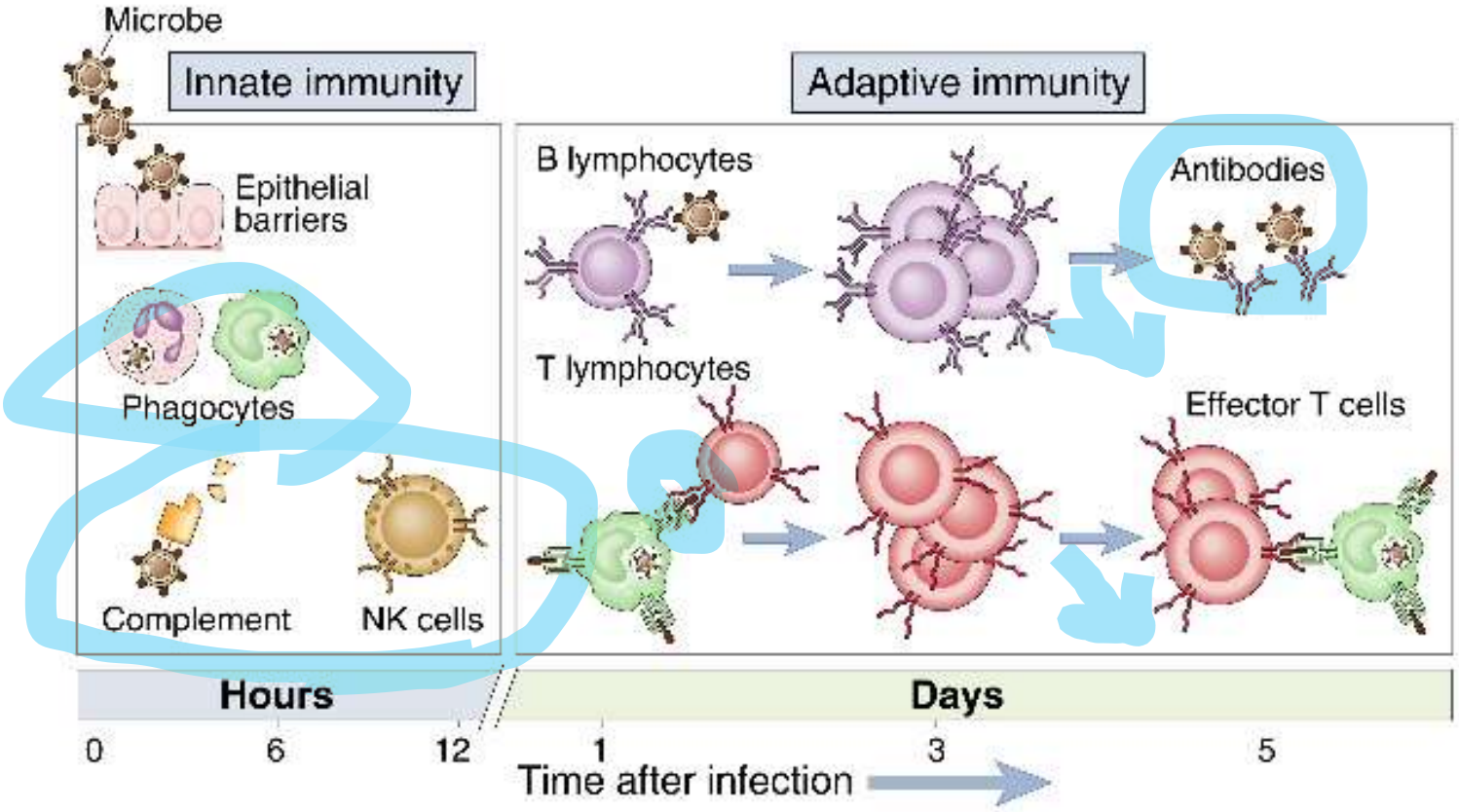
Components of Innate & Adaptive Immunity

Innate Immunity	Adaptive Immunity
physical barriers	
skin, gut villi, lung cilia	none
cells	
phagocytes, NK cell eosinophils	T lymphocytes and B lymphocytes
soluble factors	
many protein (cytokines) and non-protein secretions	Immunoglobulins (antibodies) secreted by B cells or plasma cells

Comparing innate & adaptive immunity

Innate Immunity	Adaptive Immunity
Antigen independent	Antigen dependent
No time lag immediate	A lag period
Not antigen specific (Pathogen associated molecular patterns)	Antigen specific (T cell and B cell receptors)
No Immunologic memory	Development of memory

Innate and adaptive immunity



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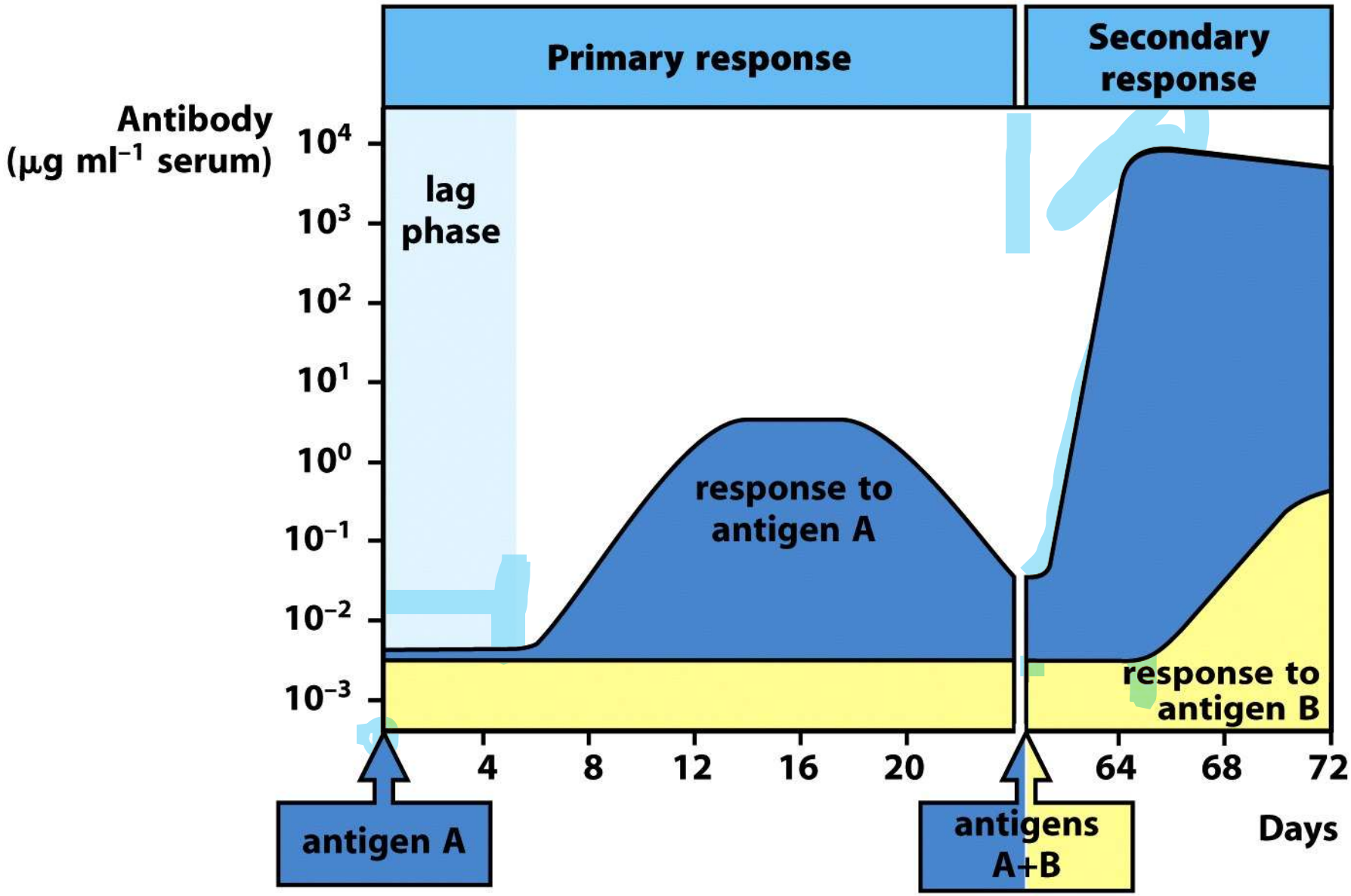
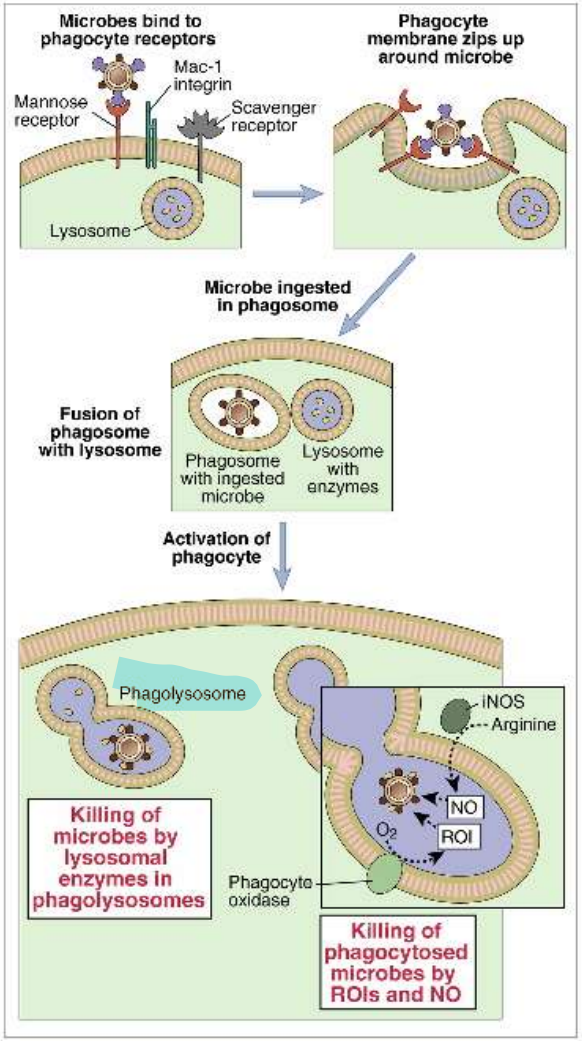


Figure 1-24 Immunobiology, 7ed. (© Garland Science 2008)

Phagocytosis and intracellular destruction of microbes

- Macrophages and neutrophils ingest microbe by phagocytosis (phagocytosis = eating by cells) (macrophage = big eater!)
- Microbes may be ingested by different membrane receptors of phagocytes; The microbes are internalized into phagosomes, which fuse with lysosomes to form phagolysosomes, where the microbes are killed.



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Thank you

ANY QUESTIONS

Cells and organs of the immune system I

Prof. Dr. Hazem Aqel AL-Rimawi

Lecture 2

This is a presentation given by Mohamed Alzobi

The Objectives

- List the cells of the immune system and discuss their function.
- Differentiate between primary and secondary lymphoid organ.
- State the general organization found in the lymph node and spleen, and the predominant cells in each area.
- Differentiate between T and B lymphocytes in terms of site of maturation.
- Explain what is a cluster of differentiation (CD).
- Identify the immune cells by their characteristic marker, e.g., CD19 (B cell), CD3 (T cell) & CD56 (NK cell).

Types of Immunity

- **Innate Immunity**
  - Not specific (Recognize “patterns’ of amino acids, polysaccharides, etc..)
  - Immediate.
  - Mediated by cells such as neutrophiles and macrophages and also by molecules such as complements.

- **Adaptive (Acquired) Immunity**
  - Specific
  - Takes 4-7 days
  - Immunological memory.
  - Mediated by T lymphocytes (cellular) and B lymphocytes (humoral).

- Both innate and adaptive immune responses depend upon the activities of white blood cells or leukocytes which are the main cells of the immune system.

- These cells originate in the bone marrow then migrate to guard peripheral tissues.

- Some reside in tissues, and some circulate in the blood or lymph.

Components of blood

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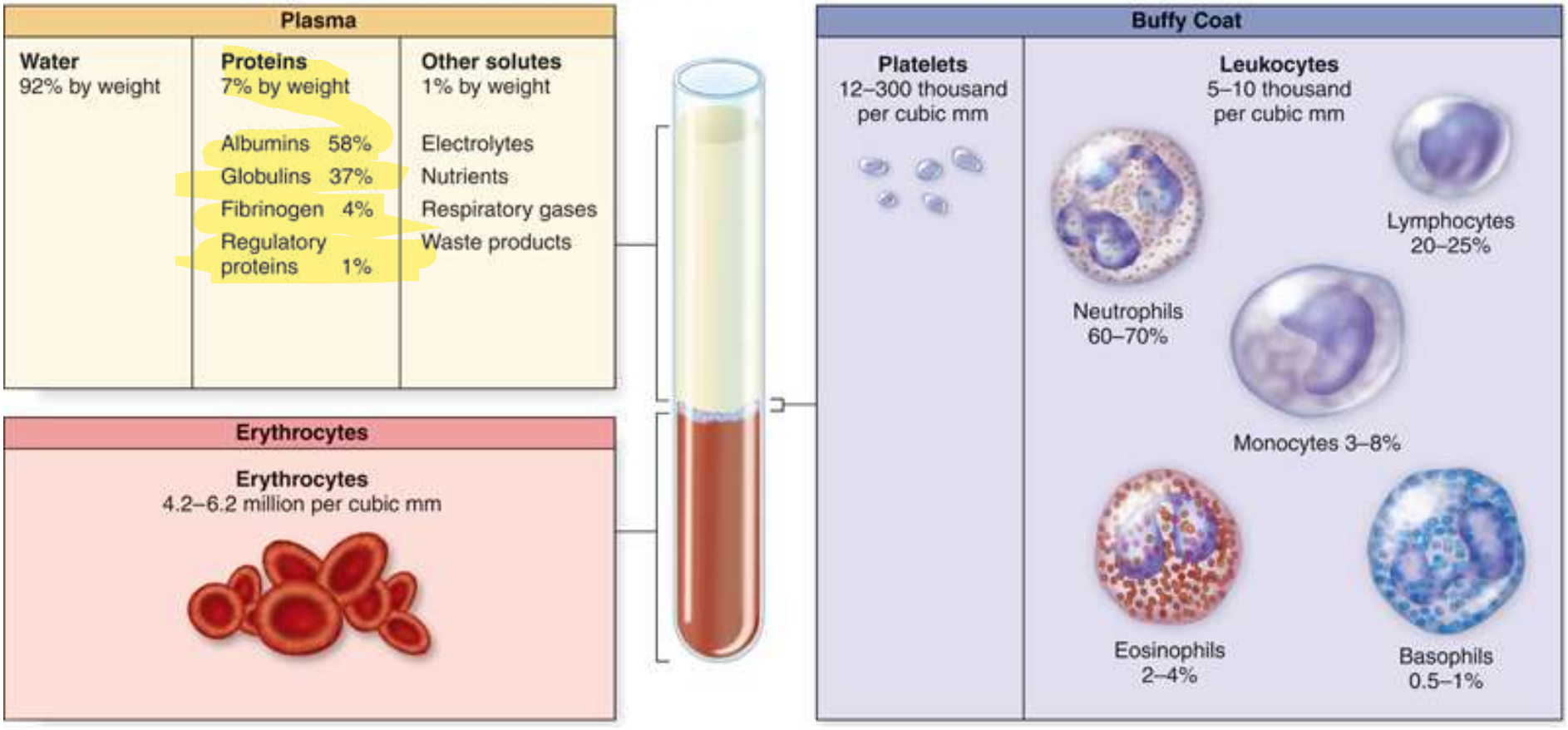


Serum = plasma - clotting factors

Serum vs. plasma:

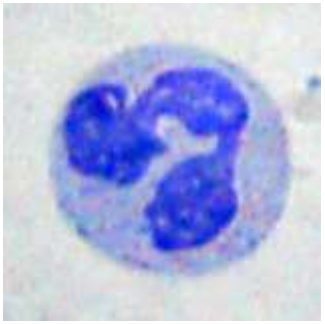
Serum: cell-free liquid, minus the clotting factors mostly used in labs

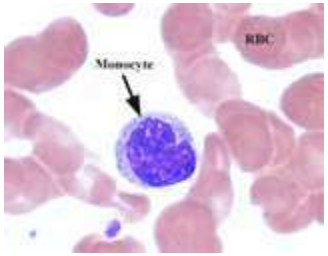
Plasma: cell-free liquid with clotting factors in solution (must use an anticoagulant)

Cell Histology

with CBC, we can not differentiate between types of lymphocytes (B,T,NK), So they can be differentiated by flow cytometry. sometimes this is important when considering transplantation

- **Polymorphonuclear**
  - ✓ Lobed nucleus
- **Mononuclear**
  - ✓ Non-lobed nucleus
- **Granulocyte**
  - ✓ Many granules seen in cytoplasm
- **Neutral**
  - ✓ Does not stain to acidic or basic compounds
- **Acidic (red-pink)**
  - ✓ Stains to acidic compounds (Eosin)
- **Basic (blue-purple)**
  - ✓ Stains to basic compounds







The cells of the immune system

•The cells of the immune system arise from pluripotent hematopoietic stem cells.

•These cells divide to produce 2 types of cells:

- A common lymphoid progenitor cell which give rise to the lymphoid lineage of white blood cells.

- A common myeloid progenitor cell which give rise to the myeloid lineage of white blood cells.

all cells except lymphocytes

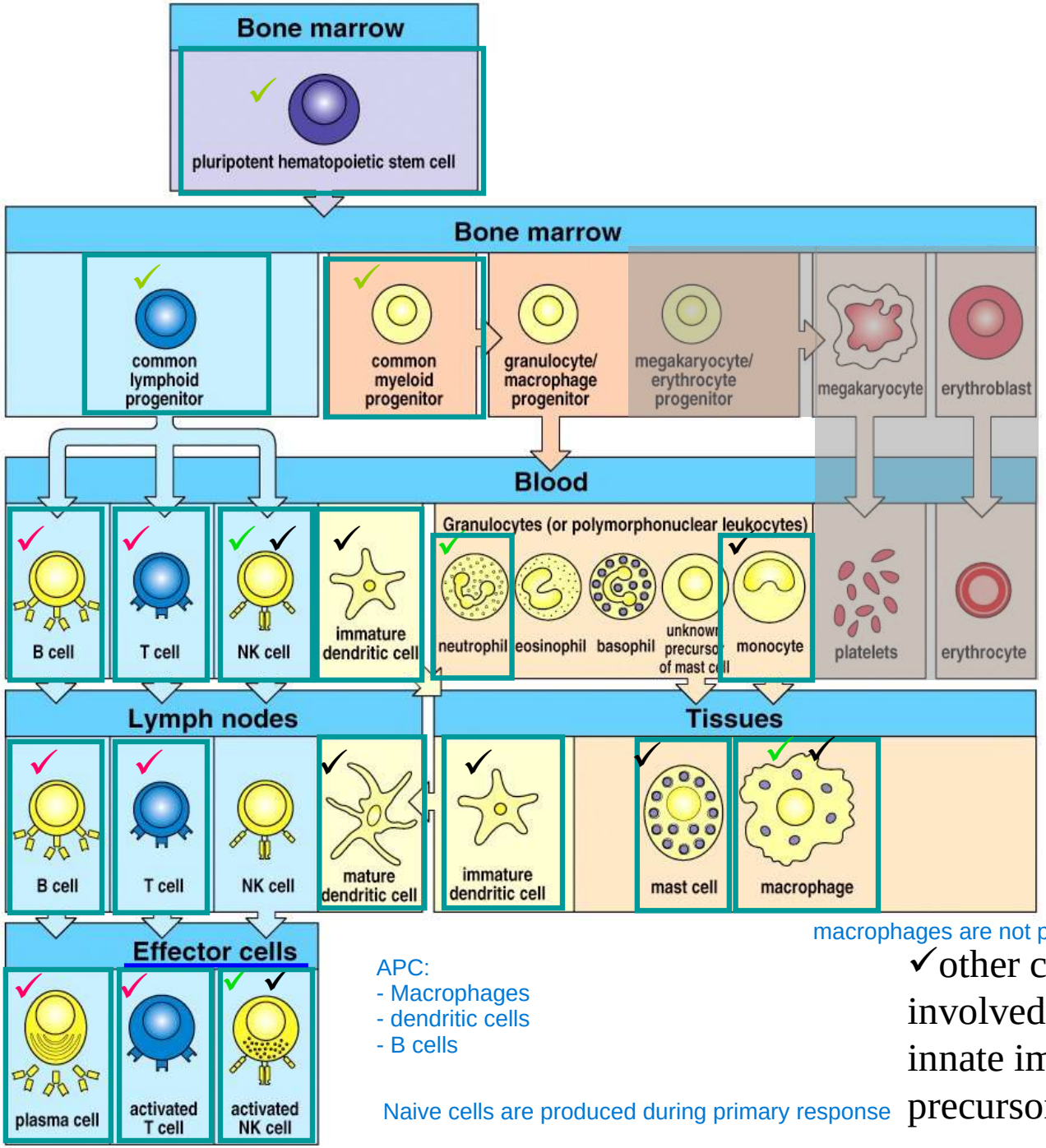


Figure 1-3 Immunobiology, 6/e. (© Garland Science 2005)

✓ progenitors

✓ Innate immunity largely involves granulocytes and macrophages (although macrophages can influence adaptive immunity)

✓ Adaptive immunity is mediated primarily by B and T lymphocytes

macrophages are not produced DIRECTLY from Bone marrow

✓other cells are regulatory or involved with both adaptive and innate immunity and/or are precursors of another cell type

APC:
- Macrophages
- dendritic cells
- B cells

Naive cells are produced during primary response

The lymphoid lineage

- Comprises most of the cells of the adaptive immune response.
- The common lymphoid progenitor is the precursor of:
  - T lymphocytes } Adaptive
  - B lymphocytes }
  - Natural killer (NK) cells Innate

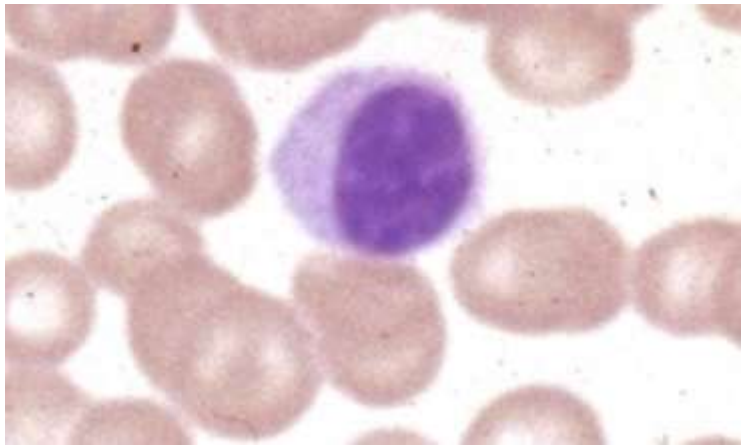
HIV infects and destructs T cells (CD4 cells)
NK cells try to fight in this case

HIV has very slow growth rate inside T lymphocytes, so it needs time to develope into AIDS, which is defined by CD4 <200.
we can detect HIV infection by measuring IgG levels

Lymphocytes

•The major subtypes of lymphocytes are T and B lymphocytes (or cells).
•They are responsible for the adaptive immune response and immunological memory.
•T cells mature in the thymus.
•B cells mature in the bone marrow.
•T cells participate in cell-mediated immunity and immunoregulation
•B cells synthesize antibodies.
• NK cells are morphologically like T and B cells they are cytotoxic in absence of prior-stimulation

NK does Not need the antigen to be presented on MHC



T lymphocytes

•T cells mature in the thymus.
•They posses a high variety of antigen receptors.
•T cells participate in cell-mediated immunity.
•When T lymphocytes get activated by an antigen they proliferate and differentiate into one of the different functional types of effector cells including:

- Cytotoxic T lymphocytes (CD8): destroy tumor cells and cells infected with intracellular pathogens such as viruses recognize MHC I
- Helper T lymphocytes (CD4): help activated B cells to differentiate and produce Abs, they also activate macrophages to become more efficient in killing recognize MHC II
- Memory T lympocytes (CD4 or CD8): responsible for long-lasting immunity naive --> memory
- Regulatory T lymphocytes: suppress the activity of other lymphocytes and help to control the immune response
- γδ T lymphocytes: : present mainly in the gut, skin , lung

- classical CD4 and CD8 have alpha beta TCR, while this type is defined by expression of heterodimeric T-cell receptors (TCRs) composed of and chains.
- activated in an MHC-independent manner

B lymphocytes

- B cells originate from the bone marrow
- B cells mature in the bone marrow.
- B cells mediate in humeral immunity.
- B cells require help from T cells. when the antigen is a protein
- Once activated B cells they proliferate and differentiate into plasma cells that produce antibodies (Ab).

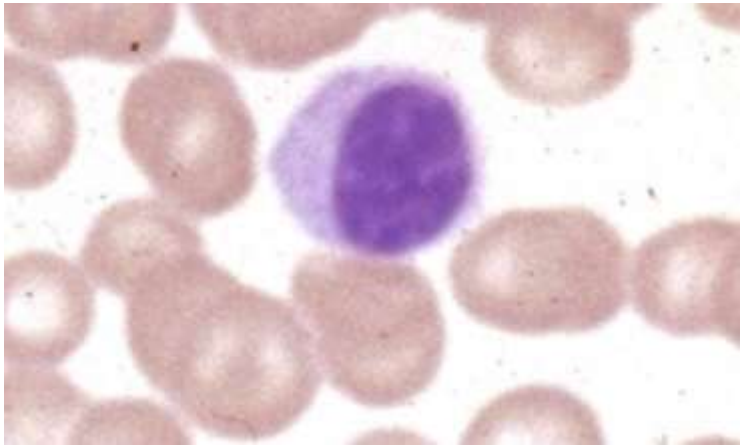
MAGED

Natural killer cells (NK cells)

- NK cells are cells of the innate immune response.

- They are a type of lymphocytes that respond to the presence of infection but not antigen specific.

- They can kill viral infected cells as well as tumor cells.



Lymphocyte classes

Table 2-2. Lymphocyte Classes

Class	Functions	Antigen receptor	Selected phenotype markers	Percent of total lymphocytes		
T lymphocytes				Blood	Lymph node	Spleen
$CD4^+$ (Helper T lymphocytes)	Stimuli for B cell growth and differentiation (humoral immunity)	αβ heterodimers	$CD3^+$, $CD4^+$, $CD8^-$	50-60*	50-60	50-60
	Macrophage activation by secreted cytokines (cell-mediated immunity)					
$CD8^+$ (Cytolytic T lymphocytes)	Killing of virus-infected cells, tumor cells; rejection of allografts (cell-mediated immunity)	αβ heterodimers	$CD3^+$, $CD4^-$, $CD8^+$	20-25	15-20	10-15
B lymphocytes	Antibody production (humoral immunity)	Surface antibody (immunoglobulin)	Fc receptors; class II MHC; CD19; CD21	10-15	20-25	40-45
Natural killer cells	Killing of virus-infected cells, tumor cells; antibody-dependent cellular toxicity	Killer cell Ig-like receptor	Fc receptor for IgG (CD16) CD56	~10	Rare	~10

CD: cluster of determinant, marker of cells recognized by monoclonal antibodies

T cells versus B cells

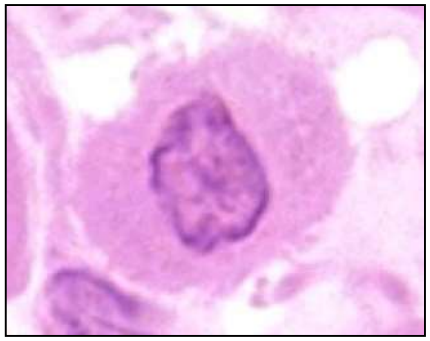
	T cells	B cells
Ag receptor	T cell receptor (**TCR**)	B cell receptor (**BCR**) is membrane-bound Ig (Ab)
Ag recognition	in context of **MHC** on antigen presenting cells (APC) or accessory cells	can recognize Ag alone
Functional subsets	Th (helper) and Tc (cytotoxic)	no specific subsets of B cells
Secrete	Cytokines	Ig **(Ab)** and cytokines
When activated	Become (proliferating) **lymphoblasts**	Become lymphoblasts, then become **plasma cells** (Ab producing cells)
	matures in Thymus	matures in BM

The Myeloid lineage

- Comprises most of the cells of the innate immune response.
- The common myeloid progenitor is the precursor of:
  - Macrophages
  - Monocytes
  - Granulocytes

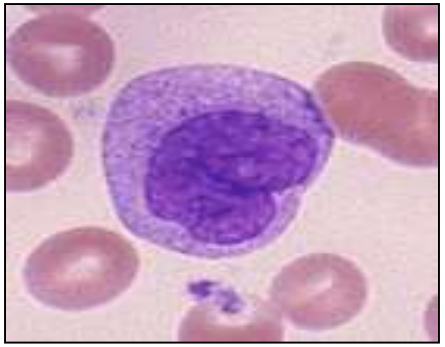
    (Neutrophils, Eosinophils and Basophils)
  - Mast cells
  - Dendritic cells

Macrophages



- Macrophages are resident in almost all tissues
- They are the mature form of monocytes
- Both macrophages and monocytes express CD14 which can bind to a wide variety of bacteria cell wall components
- They are phagocytic
- They posses microbiocidal activity (degradative enzymes, nitrogen and oxygen free radical ..)
- Long-lived cells
- Orchestrate the immune response by activating other immune cells and recruiting them
- They express receptors for Abs and complements
- They are scavenger cells by clearing dead and aged cells as well as cell debris
- They are also antigen presenting cells

Monocytes



bilobed nucleus (kidney shaped)

no abundant granules

- Monocytes circulate in the blood

- They continually migrate to the tissues to differentiate into macophages

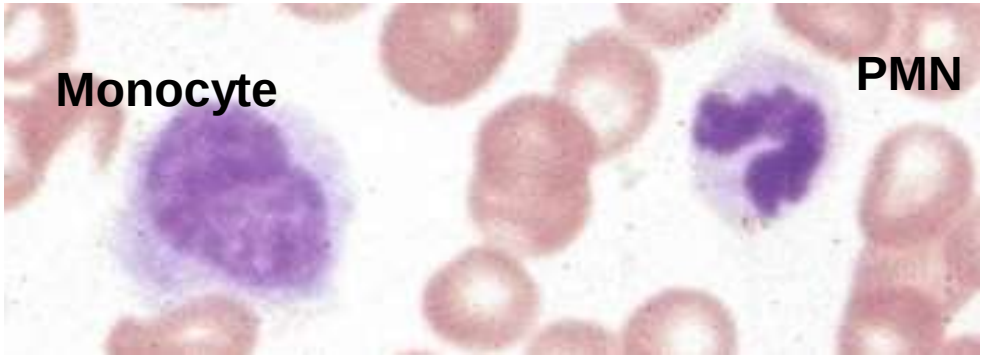
- They are the immature form of macrophages

- They are phagocytic

- They posses microbiocidal activity (degradative enzymes, nitrogen and oxygen free radical ..)

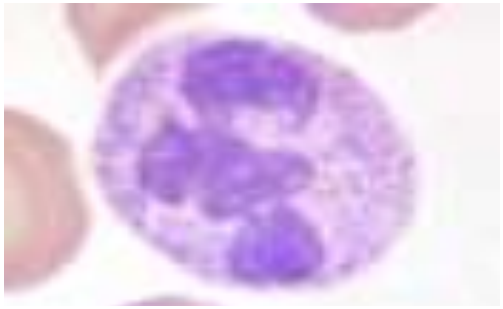
Granulocytes

- Granulocytes are called so because they have densely staining granules in their cytoplasm
- They are also called polymorphonuclear leukocytes (PMN) because of their oddly shaped nuclei
- They are short-lived cells
- They are 3 types:
  1. Neutrophils
  2. Eosinophils
  3. Basophils



Comparison of monocyte to PMN

1. Neutrophils

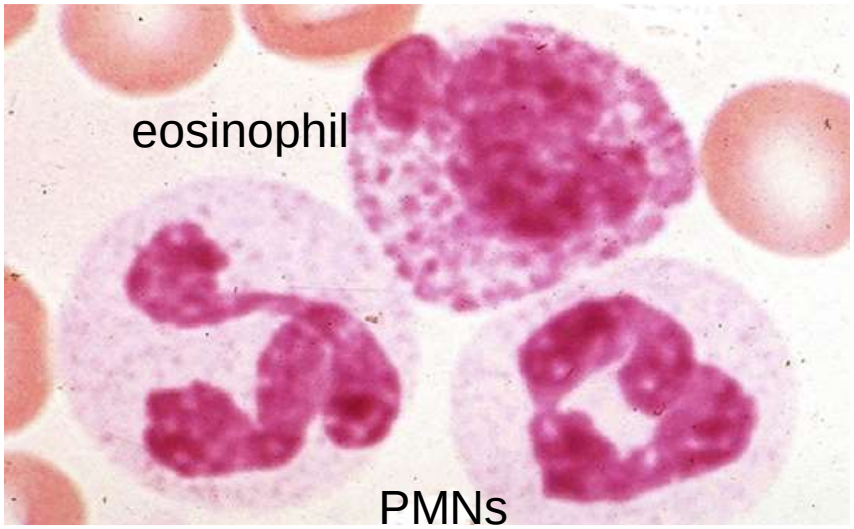


Tri-lobed nucleus

- Neutrophils are the most numerous and most important type of white blood cell in innate immune responses.
- They rapidly migrate to sites of infection or inflammation.
- They are phagocytic
- They destroy microorganisms in intracellular vesicles using special enzymatic pathways for enhanced bacteriocidal action and antimicrobial substances stored in their granules.

2. Eosinophils

- Eosinophils circulate in the blood.
- Their granules stain red with eosin.
- Mediate late phase of allergic response.
- They are active in immune responses to parasites and tumors.



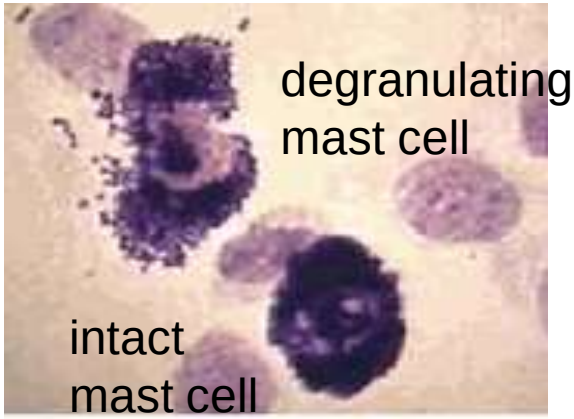
3. Basophils

- Basophils circulate in the blood.
- Basophils have basophilic granules, which are released when activated.
- Important in defense against parasites.
- Their granules contain allergic mediators.
- Play a role in allergic inflammatory reactions



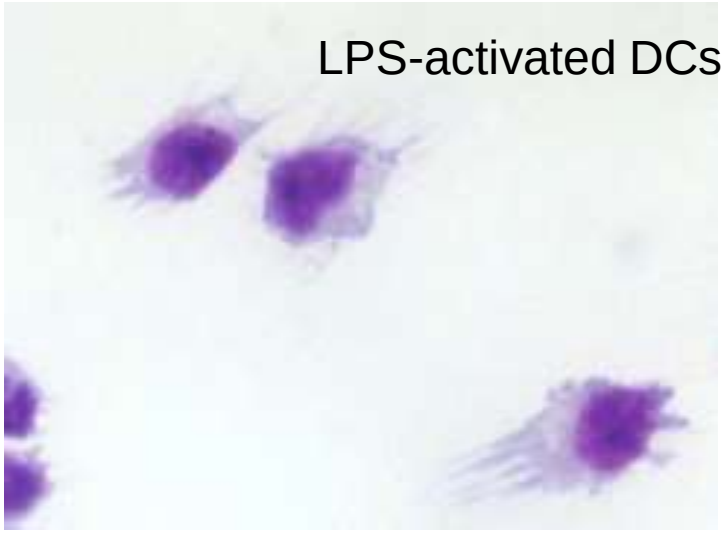
Mast cells

- Mast cells are present in many tissues such as the skin.
- Mast cells are like basophiles, they play a major role allergic responses.
- They play a role in responses against parasitic worms.
- Their granules contain allergic substances such as histamine.



Dendritic cells

- Dendritic cells are the most efficient antigen presenting cells.
- They are phogocytic
- They have long finger-like processes (dendrities)
- They are immature in the blood
- They migrate from the blood to the lymph nodes where they activate T lymphocytes
- There are several types for example
  - Myloid Dendritic cells
  - Plasmacytoid
  - Langerhans cell (in the skin)
  - Folicular dendritic cells (in lymph nodes)



THANK YOU

ANY QUESTIONS??

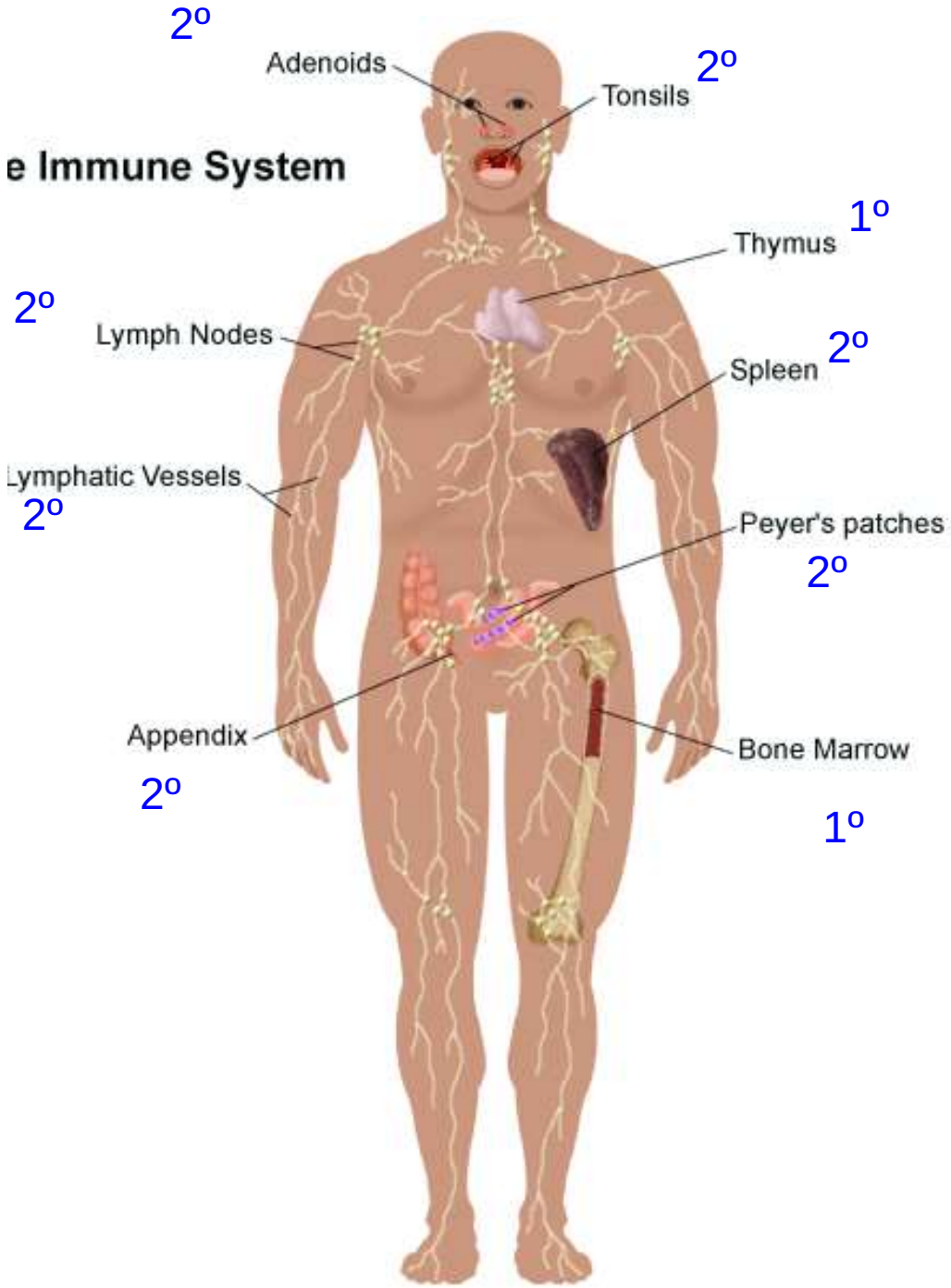
Cells & organs of the immune system II

Prof. Dr. Hazem Aqel AL-Rimawi

Lecture 3

Lymphatic Organs

- Primary lymphatic organs:
  - Bone marrow
  - Thymus
- Secondary lymphatic organs:
  - Lymph nodes
  - Spleen
  - Tonsils
  - Adenoids
  - Lymphoid tissues associated with the gut, skin and mucosa



Major Tissues:

- Primary Lymphoid Tissues
  - Cells originate or mature
- Secondary Lymphoid Tissues
  - Cells are maintained and initiate immune responses

The primary lymphoid organs

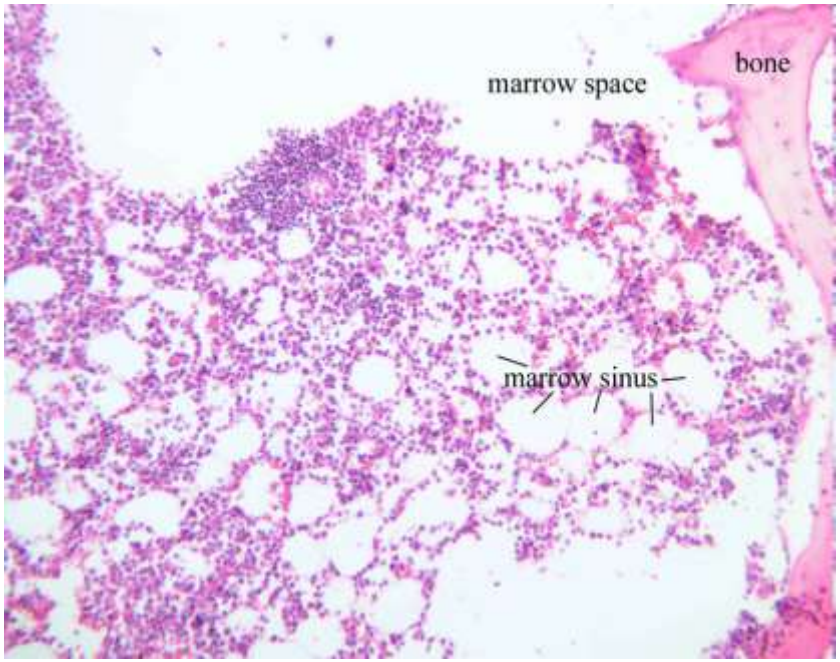
- Also known as the central lymphoid organs or tissues.
- It is the cite where lymphocytes originate and mature in the absence of antigenic stimuli.
- It includes:
  - Bone marrow
  -- Thymus

The Bone Marrow

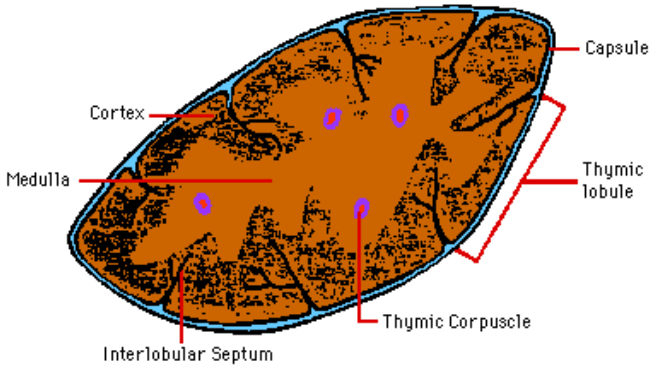
A source of all hematopoietic progenitor (stem) cell

T lymphocyte and B lymphocyte are **produced**

B lymphocytes **mature**

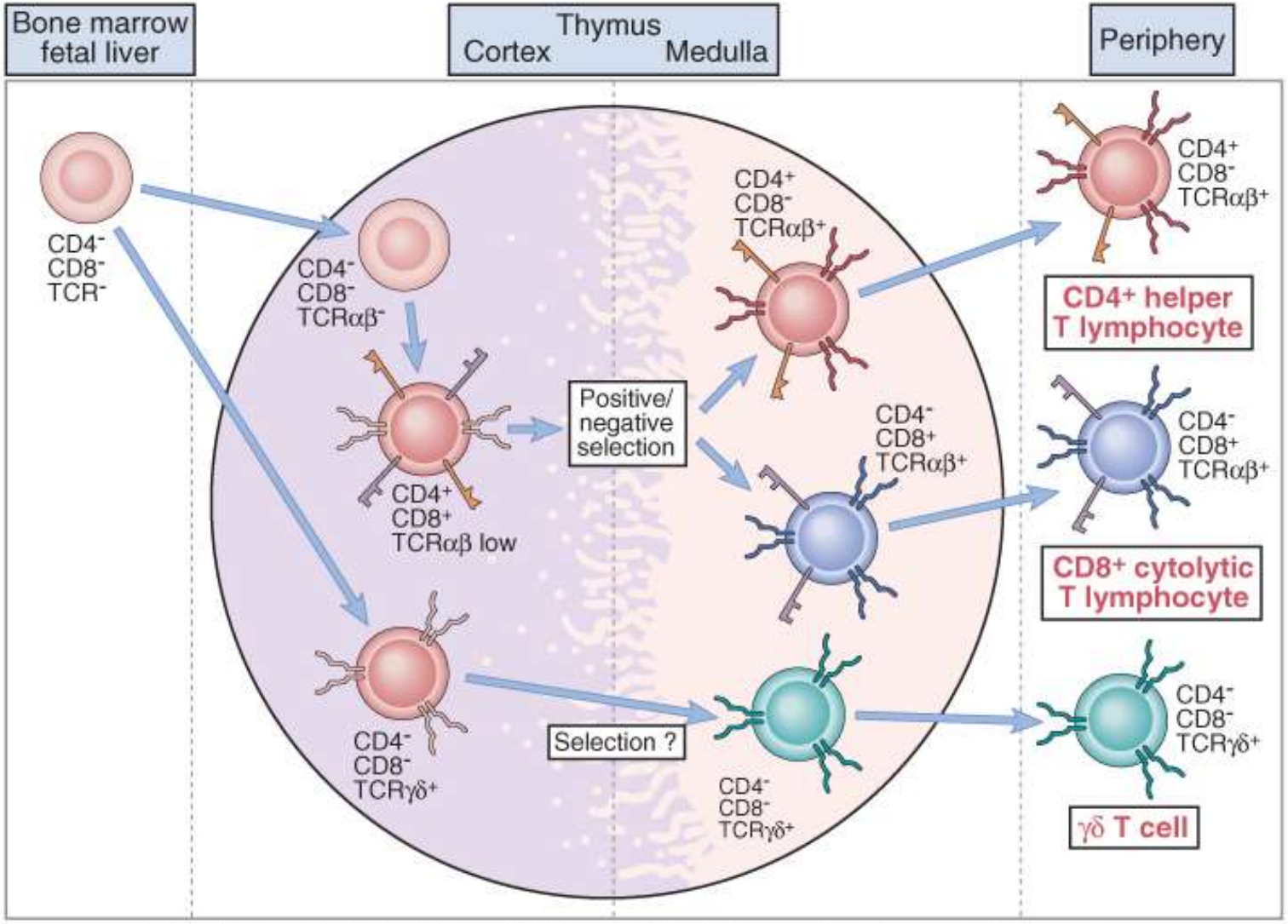


The Thymus



- An organ in the upper chest above the heart, where T cell develop and mature.
- It gradually enlarges during childhood but after puberty it undergoes a process of involution
- The thymus is arranged into an outer cortex and an inner medulla.
- Immature lymphoid cells in the cortex. Mature T cells are in the medulla
- Pre - T cells come from bone marrow and develop into T cells
- Mature T lymphocytes enter the circulation from the medulla.
- T cells then go to other lymphatic tissues

T cell development in the Thymus



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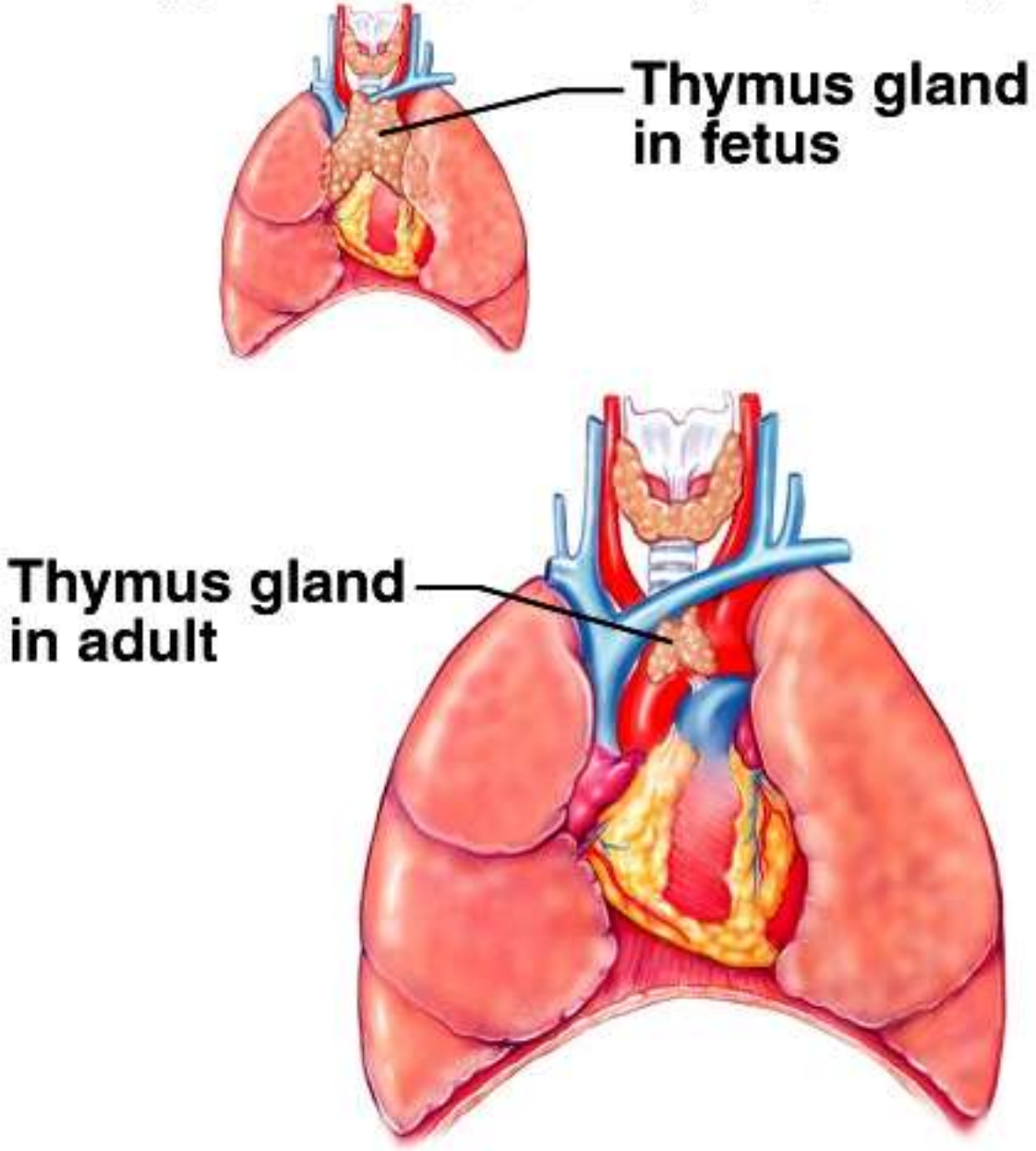


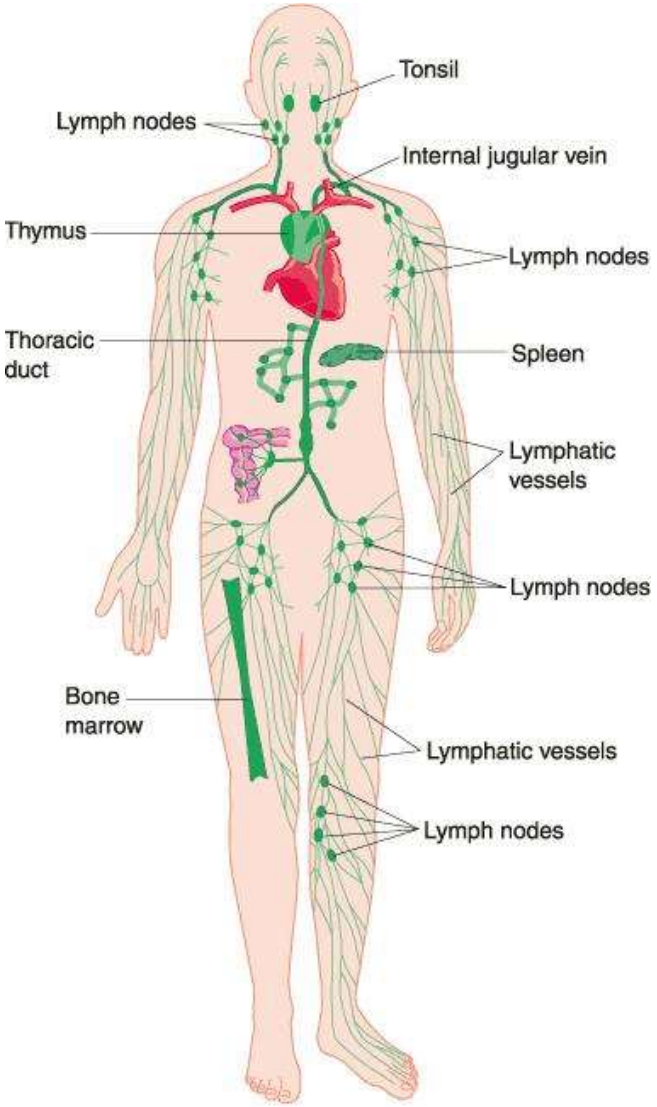
The secondary lymphoid organs

- Also known as the peripheral lymphoid organs or tissues.
- Composed of aggregations of lymphocytes in a framework of non-leukocytes stromal cells
- They also contain resident macrophages and dendritic cells.
- Lymphocytes re-circulate between the blood and these organs until they encounter their specific antigen.
- The site of lymphocyte activation by an antigen.
- It is the cite where adaptive immune responses are initiated.

The secondary lymphoid organs cont'd

- Includes:
  - Lymph nodes
  - Spleen
  - Mucosa-Associated Lymphoid Tissue (MALT)
  - Gut-Associated Lymphoid Tissue (GALT)

    This includes:
    - Adenoids
    - Tonsils
    - Appendix
    - Peyer's Patches
  - Skin-Associated Lymphoid Tissue (SALT)



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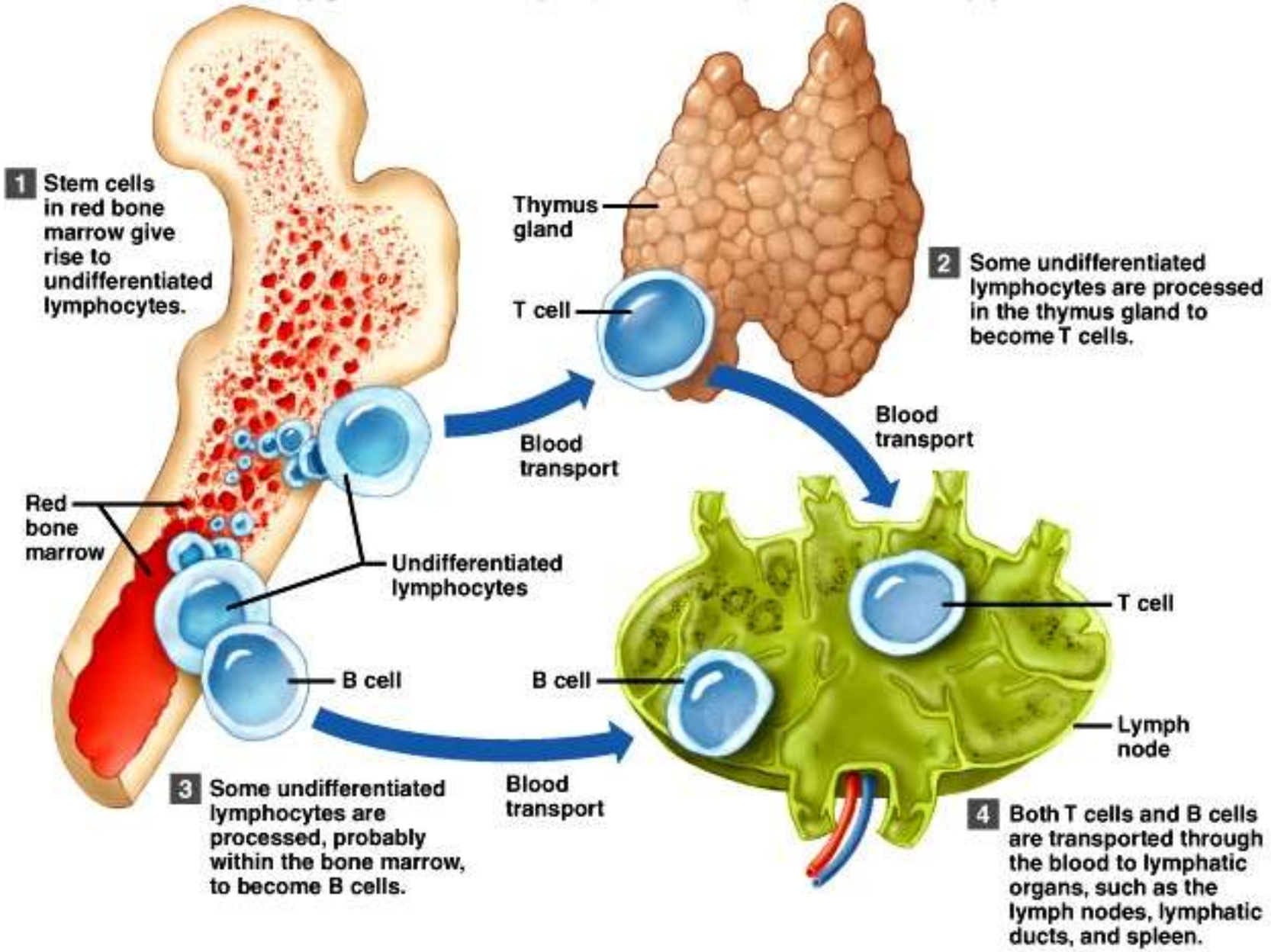


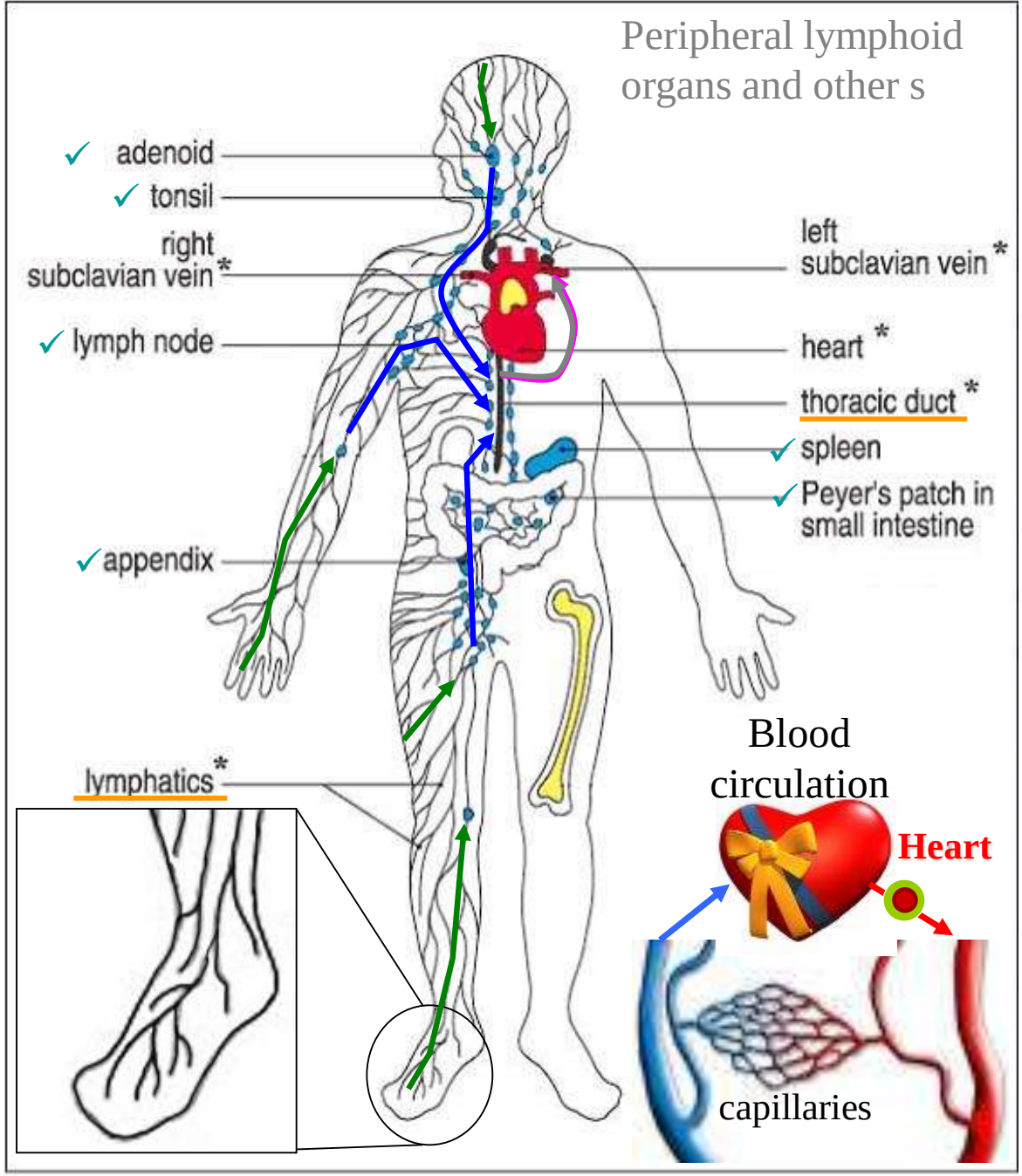


Fig 1.7 © 2001 Garland Science

✓ Peripheral lymphoid organs

1. trap antigens
2. are the sites for initiation of most immune response
3. provide signals for recirculation of lymphocytes

*others (not peripheral lymphoid organs)

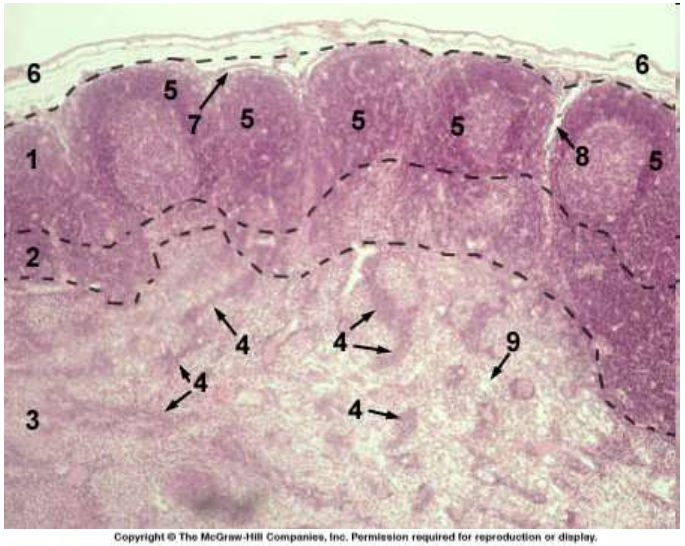
Lymph Nodes

- It is the site of antigen presentation
- Lymph nodes filter the lymph
- Found in clusters
- Interconected by a system of lymphatic vessels.
- Vary in size
- Principal groupings in cervical, axillary and inguinal regions.
- Provide biological filtration

Lymph Nodes Structure

Lymph node consist of:

1 - cortex (B Cells)
2 - paracortical zone (T Cells)
3 – medulla(T, B, Mac)
4 - medullary cords
5 - lymphoid follicle of the cortex
6 - capsule
7 - subcapsular sinus
8 - cortical sinus
9 - medullary sinus



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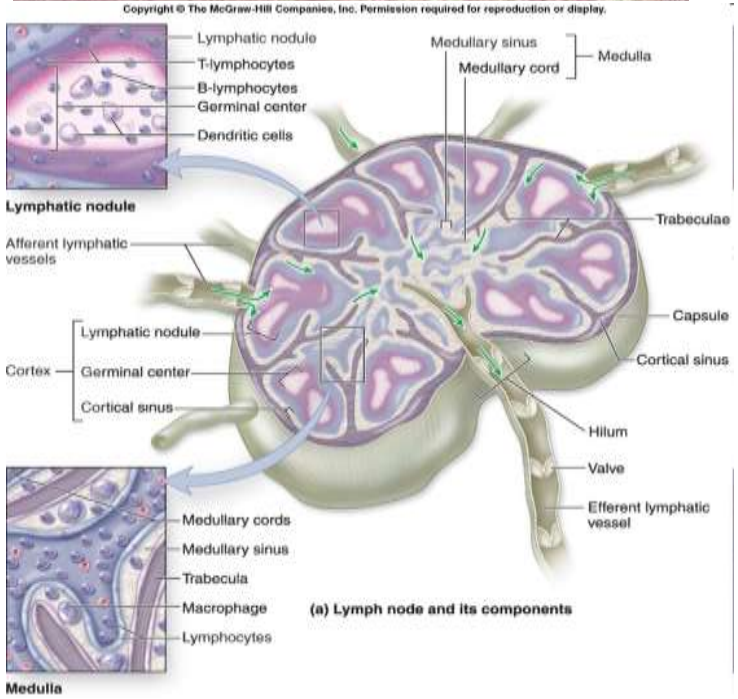


Lymph nodes cont'd

Functions of structural elements of lymph nodes:

Lymph → afferent lymphatics, →sinuses lined with macrophages → efferent lymphatic.

Lymphocytes enter the node primarily from the blood via HEV → efferent lymphatics.

DCs migrating from tissue enter the node into the T cell areas.

B cells entering nodes from blood must cross the T rich area in transit to the B cell rich areas thus optimizing T-B cooperation.

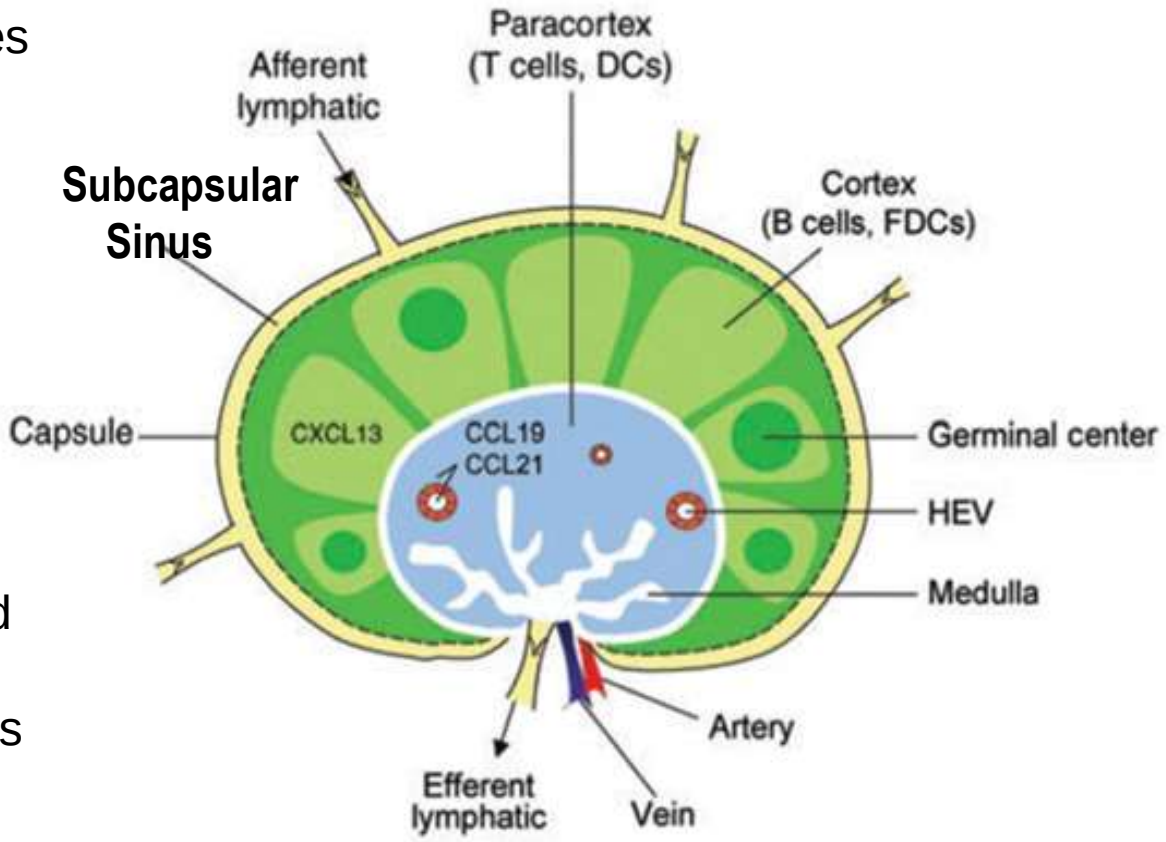
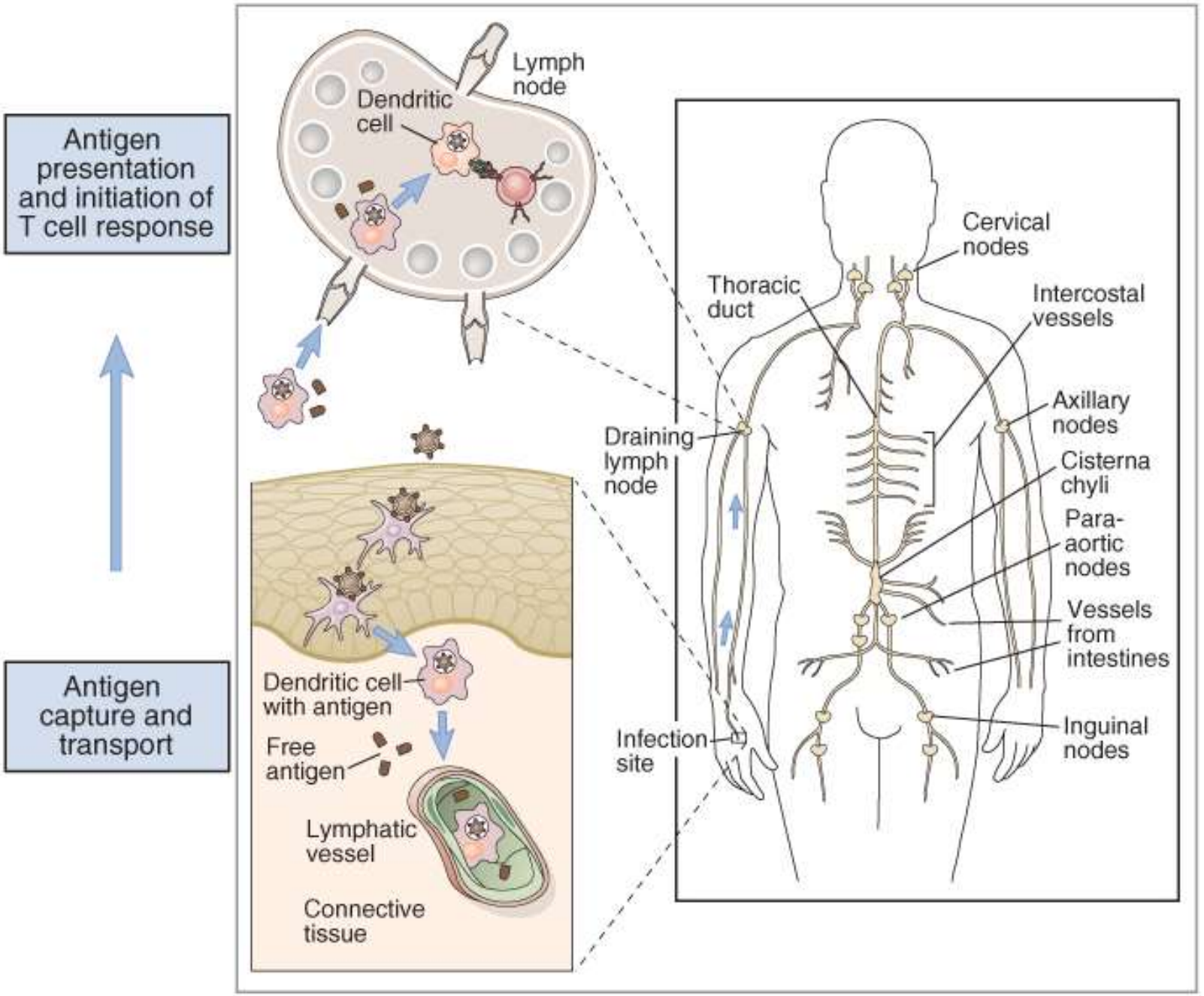


Figure 2-12 **The lymphatic system.**

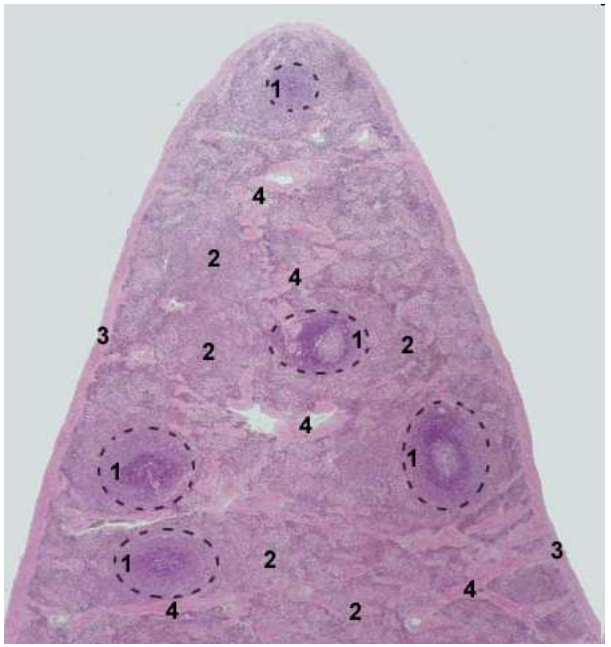


Spleen

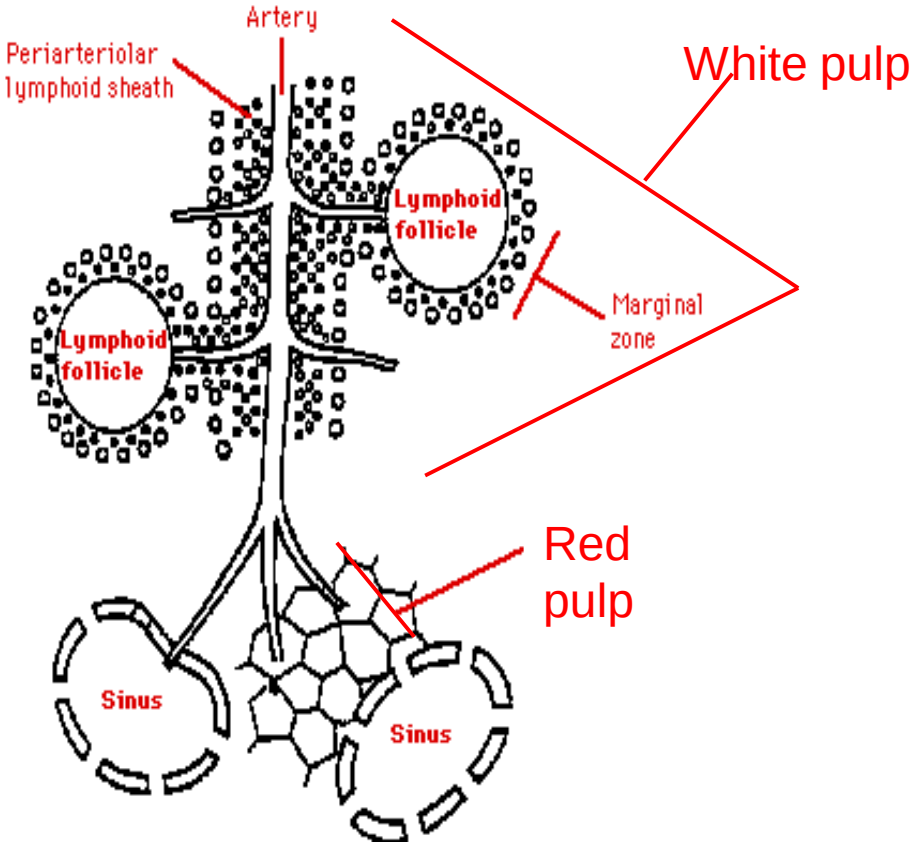
- Largest lymphoid organ.
- Filters the blood.
- Site of removing blood-borne antigens.
- Site of removing and destruction of old/defective blood cells (RBCs).
- It is a major site for mounting the immune response.
- Site of hematopoiesis (blood formation) in the fetus.
- It stores a large amount of blood.

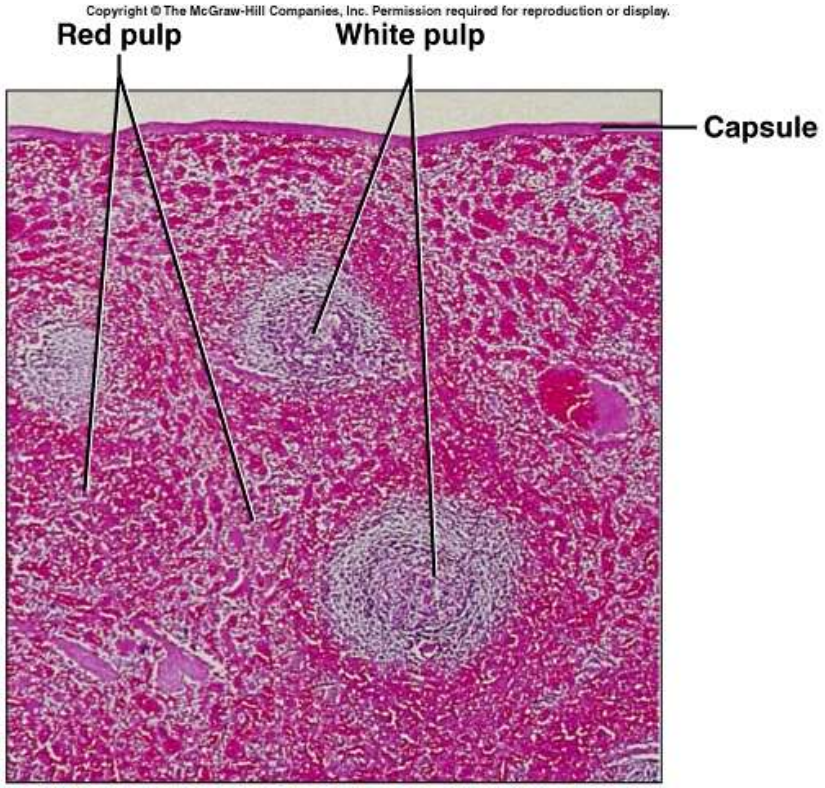
The spleen cont'd

The spleen (stained with haematoxylin and eosin) consist of:
1 - white pulp: mostly contain B lymphocytes
2 - red pulp: site of RBC disposal
3 - capsule
4 - trabeculae (connective tissue)



The spleen cont’d





Mucosa-Associated Lymphoid Tissue (MALT)

- Lymphoid tissue found at the gastrointestinal tract, respiratory tract and urogenital tract.

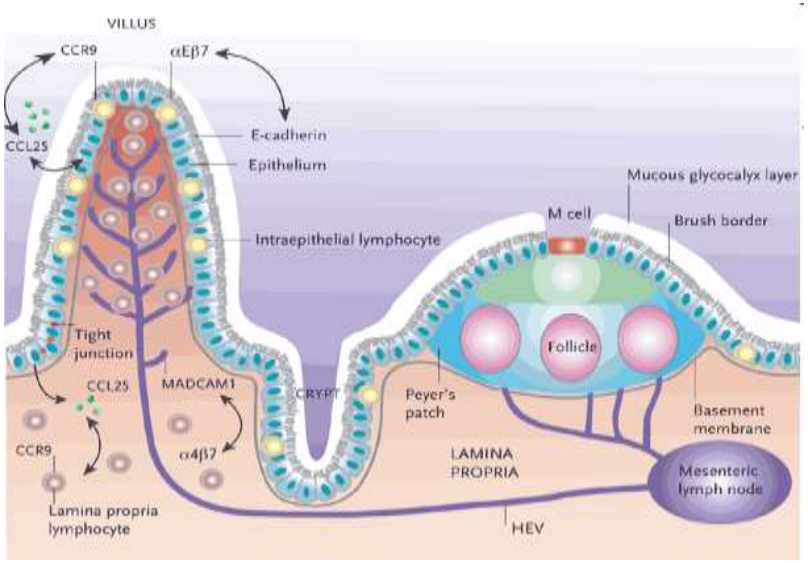
- It protects the body mostly from antigens that enter the body from the air and food.

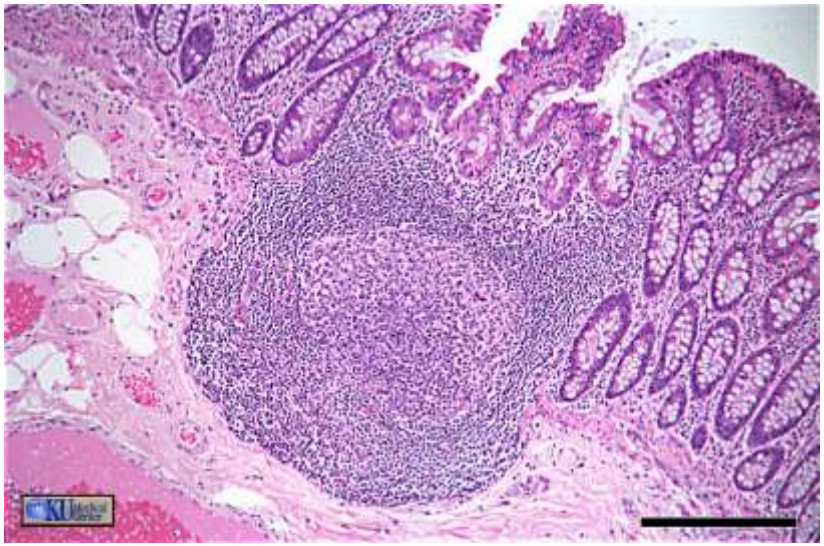
- MALT consists of aggregates of lymphocytes, macrophages, dendritic cells, and other accessory cells.

Gut-Associated Lymphoid Tissue (GALT)

This is comprised of:

- Tonsils
- Adenoids
- Appendix
- Peyer's patches which are lymphoid aggregates in the small intestine



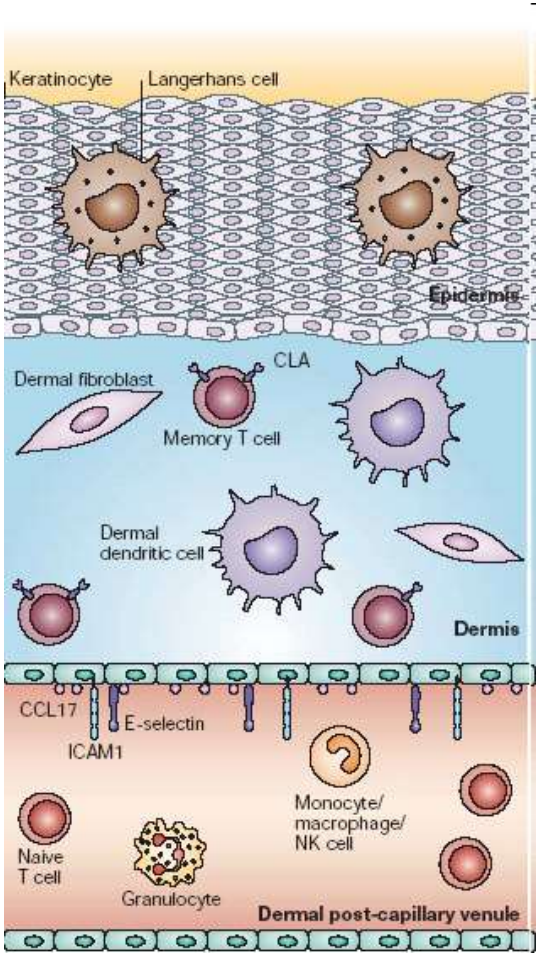


Skin-Associated Lymphoid Tissue (SALT)

•Skin is an active participant in host defense. It has the capability to generate and support local immune and inflammatory responses to foreign Antigens that enter the body via the skin.

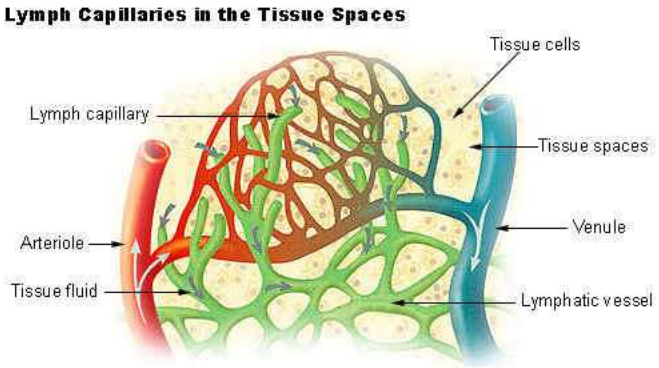
•Cells of SALT include keratinocytes, Langerhans cells (immature DCs found in skin), intraepiethelial T cells, and melanocytes.

•Langerhans cells form a continuous epidermal meshwork: they capture Ag, then migrate to draining lymph nodes, where they act as Ag-presenting cells.



The Lymphatic System

- An extensive system that collects extracellular fluid from the tissues and returns it to the blood.
- NOT A CIRCULATING FLUID
- The extracellular fluid is called lymph.
- The transportation is carried by lymphatic vessels
- Its main function is protection.



Lymphatic Pathways

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Lymphatic capillary

↓

Lymphatic vessel

↓

Lymph node

↓

Lymphatic vessel

↓

Lymphatic trunk

↓

Collecting duct

↓

Subclavian vein

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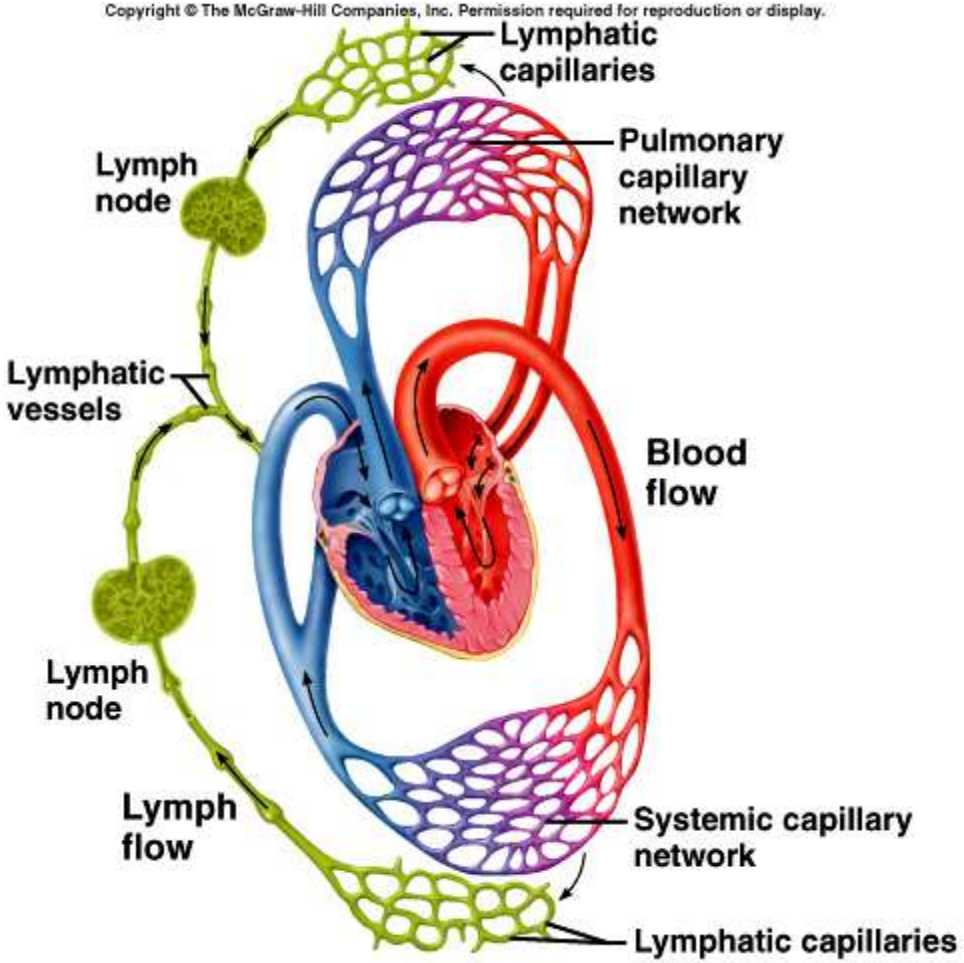
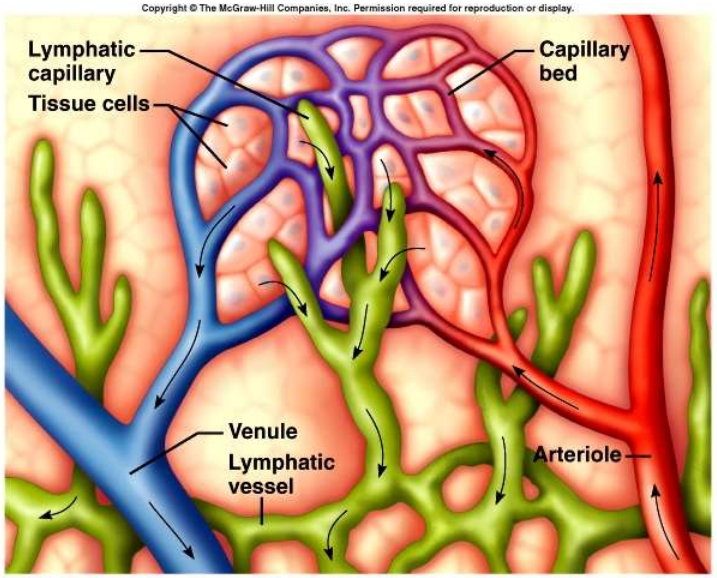


Lymphatic Capillaries

- Made of a single layer of squamous epithelial cells
- Slightly larger than blood capillaries
- Cells overlap and act as one-way valves
- Opened by pressure of interstitial fluid that drains into lymphatic capillaries, forming lymph.



Lymphatic Vessels

- Begin as closed ended lymph capillaries in tissue spaces between cells.
- Lymph capillaries merge to form lymphatic vessels.
- Lymphatic vessels carry lymph into and out of lymph nodes and finally back to the vascular system.
- Resemble veins
- Found throughout body **except**:
  - Avascular tissues
  - Central nervous system
  - Splenic pulp
  - Bone marrow

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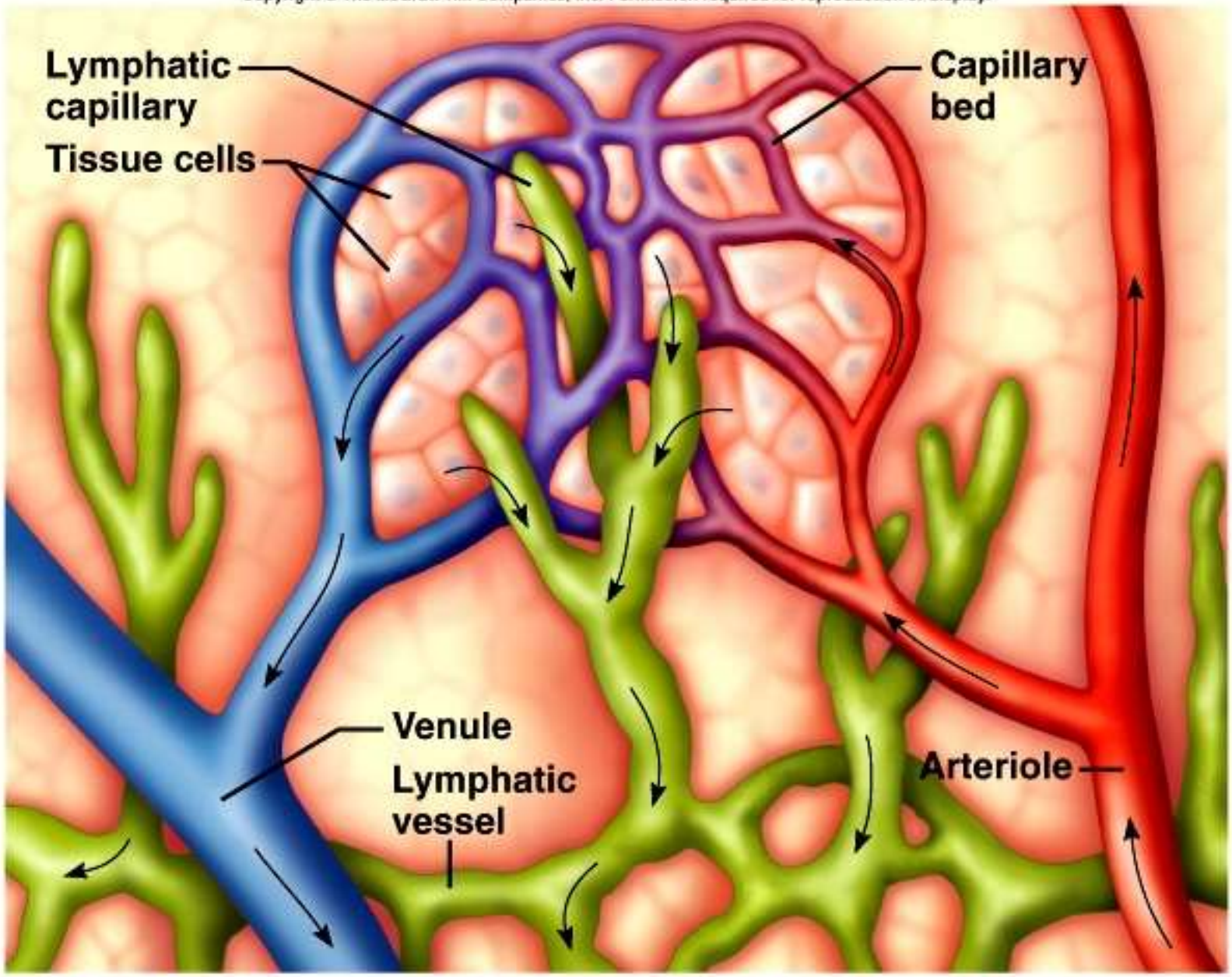

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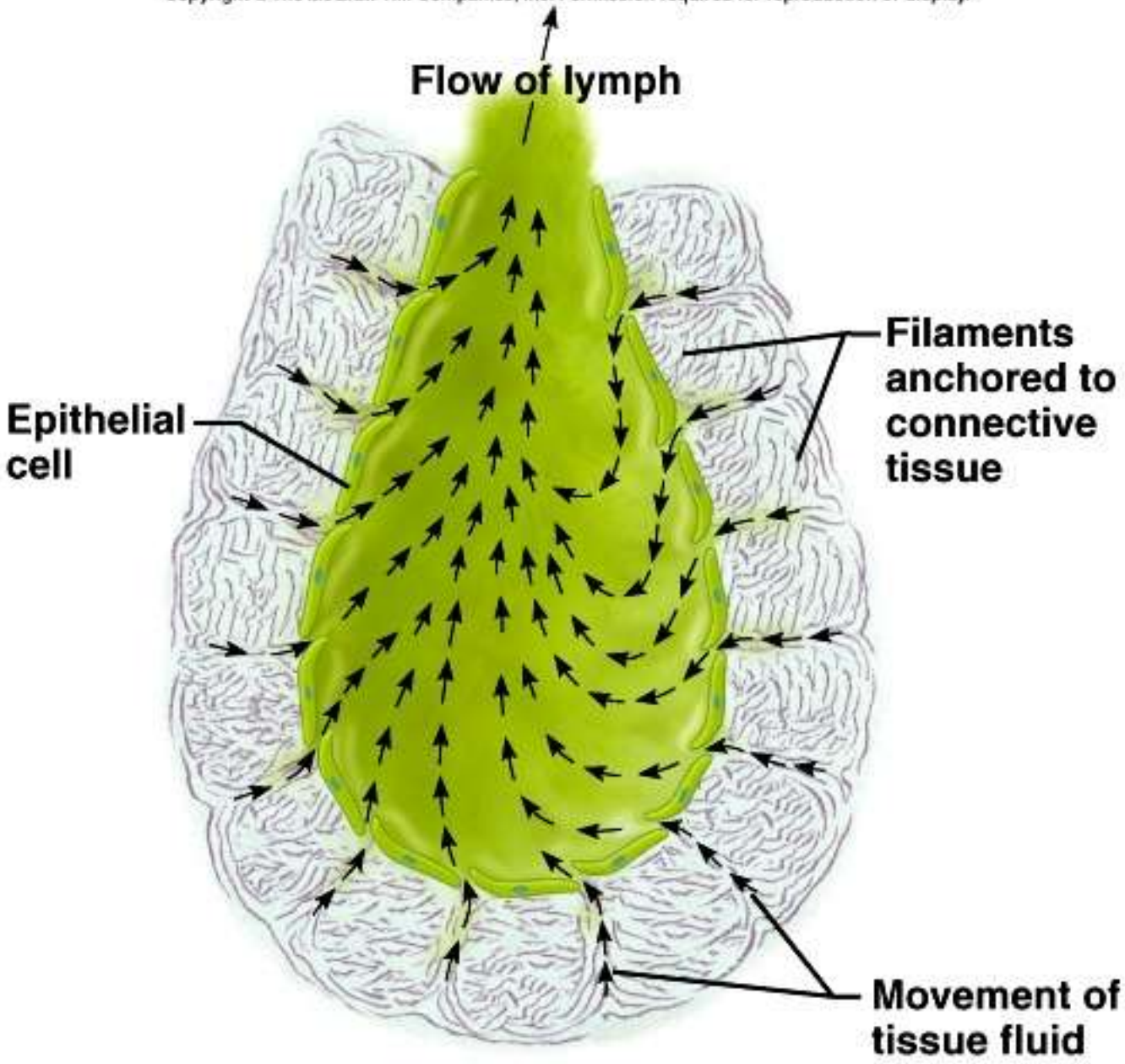

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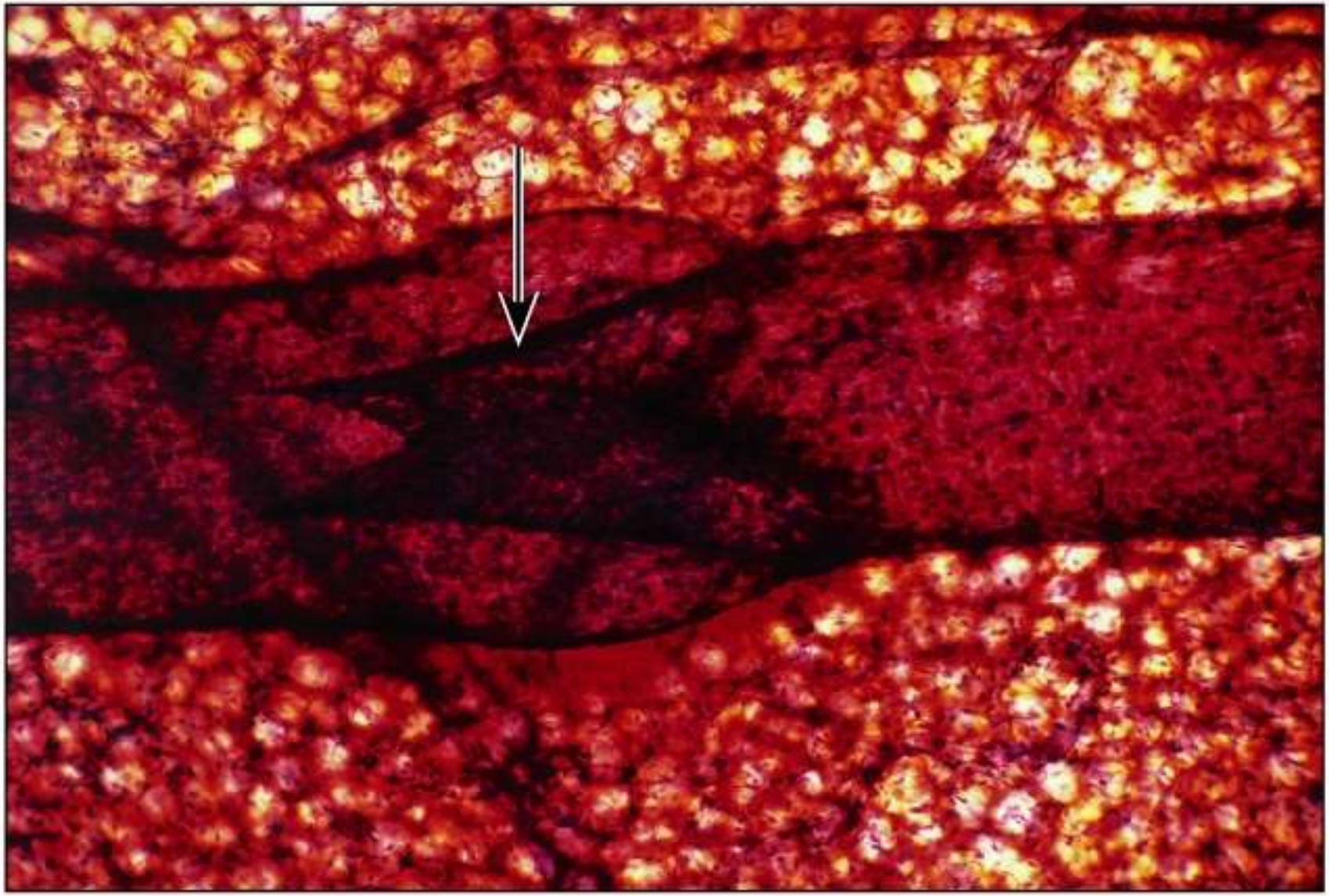
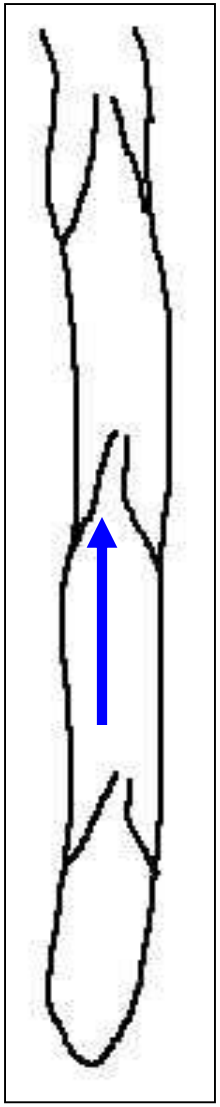
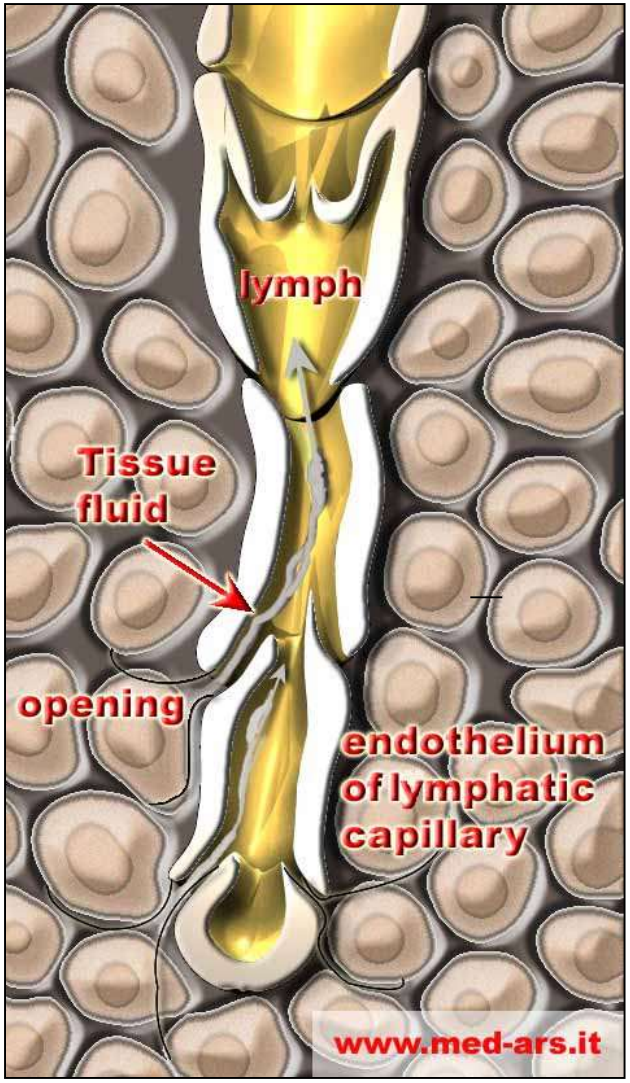
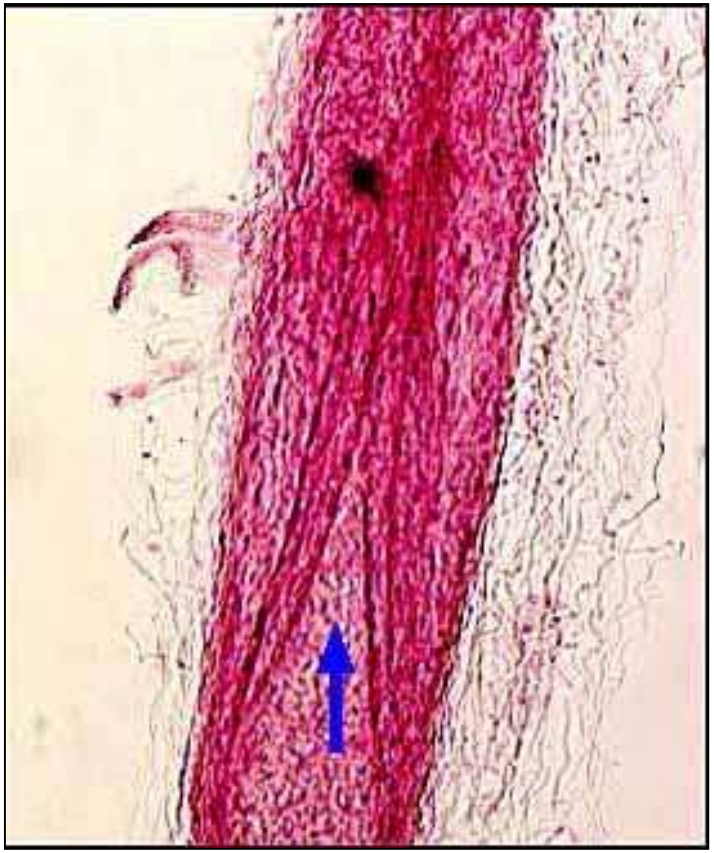


The flow of lymph through lymphatic vessels







THANK YOU

ANY QUESTIONS??

Antigens/Antibodies I & II

Prof. Dr. Hazem Aqel AL-Rimawi

Lecture 4

Antigens

Are substances capable of inducing a specific immune response

Antigen vs. Immunogen

- Antigen
  - Any substance that can bind to an antibody or T cell receptor
- Immunogen
  - Any substance that can elicit an immune response

•All immunogens are antigens

•Not all antigens are immunogens, i.e. haptens

Immunogenicity: is the ability to induce a humoral and/or cell-mediated immune response.

Antigenicity: is the ability to combine specifically with antibodies and/or cell surface receptor.

plasma cells

B cells + Antigen → effector B cells + memory B cells

T cells + Antigen → effector T cells + memory T cells

sometimes found in the skin

* It is more appropriate to call a substance that induces a specific immune response immunogen instead of antigen

Immunogenicity of Antigens

- Determined by
  - Foreignness
    ideally only foreign molecules are immunogenic
  - Molecular Size
    in general, the larger the molecule the more immunogenic it is likely to be.
  - Chemical Composition
    In general, the more complex the substance is chemically the more immunogenic it will be.
  - Degradability
    Antigens that are easily phagocytosed are generally more immunogenic.

- Influenced by
  - Host genotype
    some substances are immunogenic in one individual but not in others
  - Dose and route of administration
  - Presence of ***adjuvants***

Adjuvants (taken from the Latin, "adjuvare," meaning "to help")
A substance that enhances body's immune response to antigen.

Exogenous antigens

- Exogenous antigens are antigens that have entered the body from the outside, for example by inhalation, ingestion, or injection.
- Exogenous antigens are taken by phagocytosis into the antigen-presenting cells (APCs) and processed into fragments. T helper does Not kill by its own
- APCs then present the fragments to T helper cells (CD4+) by the use of MHC class II molecules on their surface.
- T helper cells will then activate B lymphocytes to produce antibodies.

Endogenous antigens

- Endogenous antigens are antigens that have been generated within previously-normal cells as a result of normal cell metabolism, or because of viral or intracellular bacterial infection. such as: chlamydia, rickettsia
- The fragments are then presented on the cell surface in the complex with MHC class I molecules. If activated cytotoxic CD8+ T cells recognize them, the T cells begin to secrete various toxins that kill the infected cell.

some wild type viruses prevent the expression of MHC I

Epitopes

- Also called Antigen determinants
- Discrete sites on immunogens recognized by antibodies or T cell receptors
- Macromolecules contain many epitopes with different immunogenicities carbs, proteins(most common), lipids, nucleic acids
- Immunogenicity can vary between individuals and populations.

Antigen

[only the part of the antigen that fills the binding site is shown. The antigen can be much much bigger such that only a small part of the whole antigen is in contact with the antigen binding site]

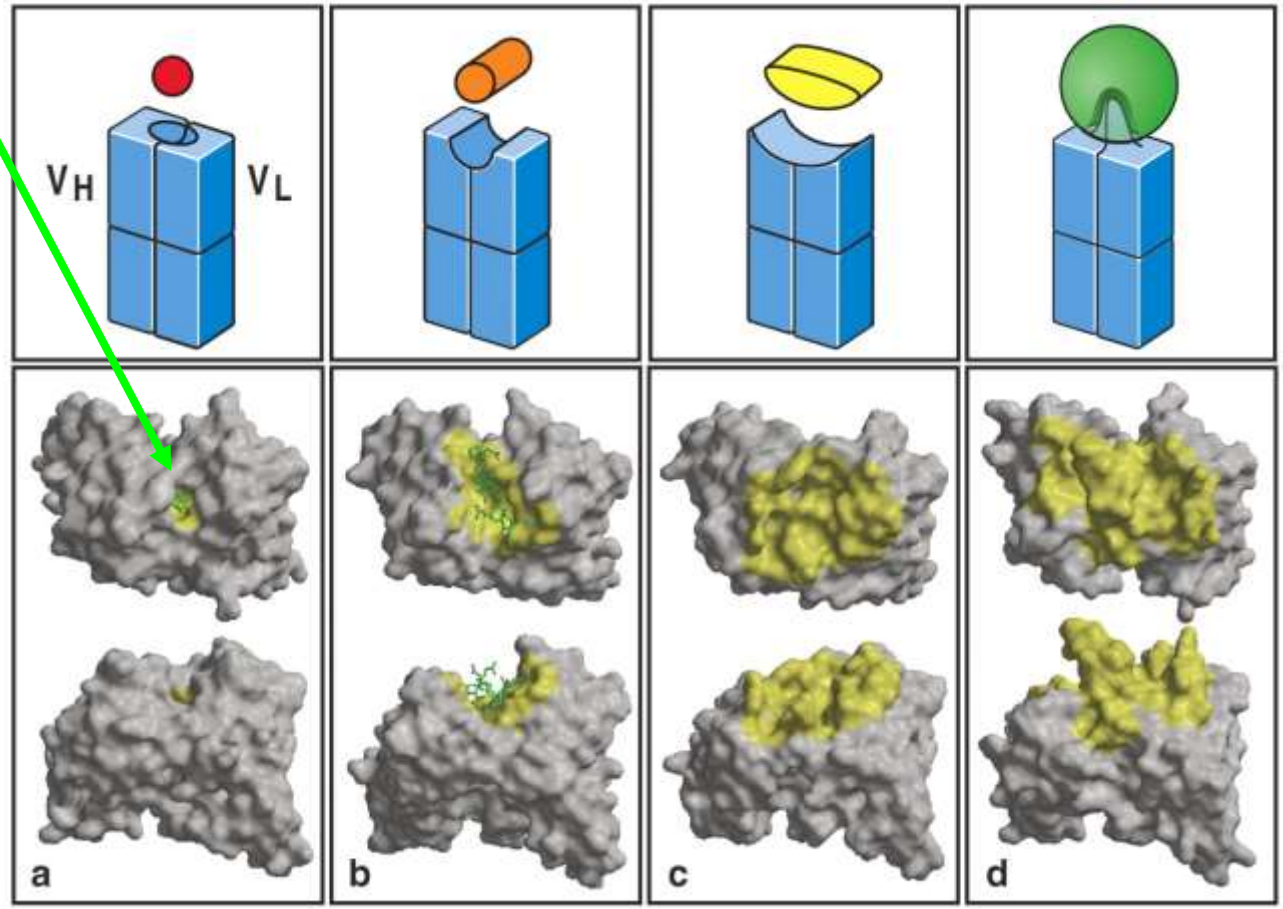
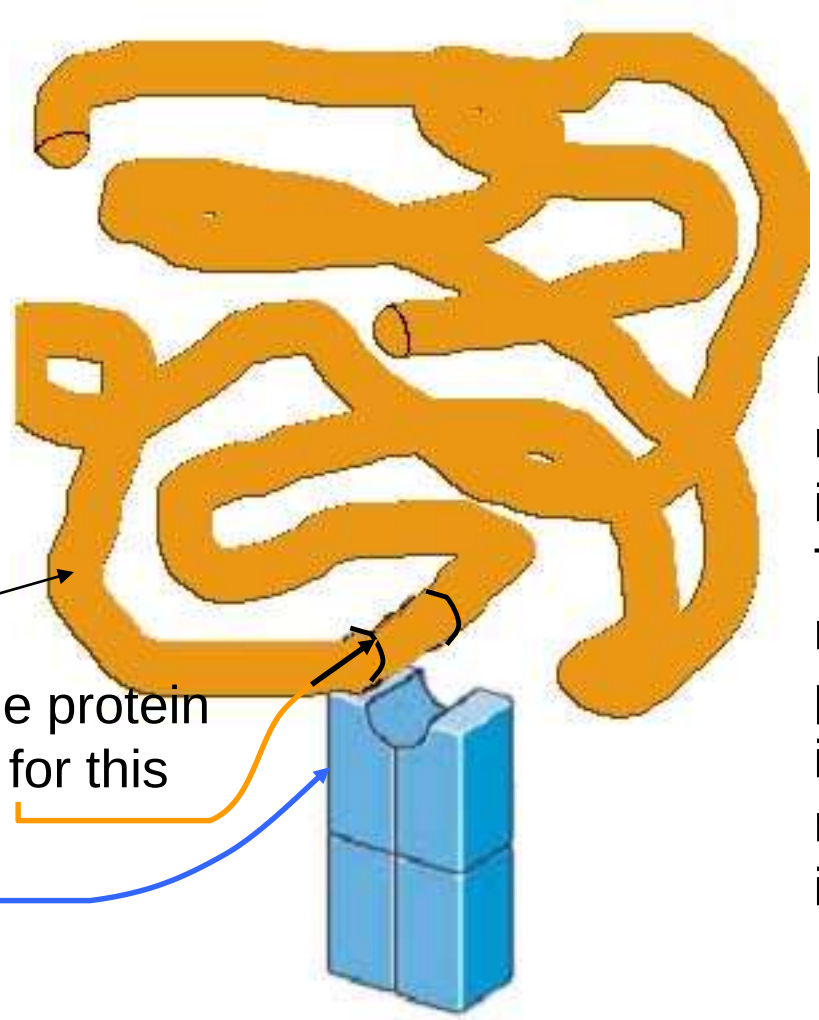


Figure 3-8 Immunobiology, 6/e. (© Garland Science 2005)

This antigen is a protein.

This part of the protein is the epitope for this antibody.



Peptides, and other small molecules, will usually not induce an immune response. Thus, although the antibody recognizes and binds a small part of a big molecule, the isolated small part of the molecule cannot induce an immune response.

Free peptides are not recognized by T cells, rather the peptides associate with molecules coded for by the major histocompatibility complex (MHC) and it is the complex of MHC molecules + peptide that is recognized by T cells

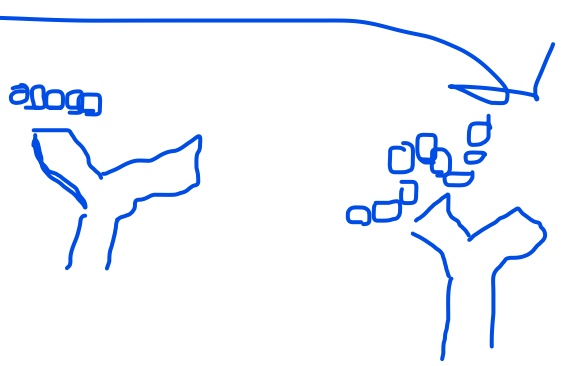
Properties of B cell epitopes

- The ~~size~~ recognizability is determined by the size, shape and amino acid residue of the Ag-binding site on the Ab molecule
- The binding involves weak non covalent interaction

antibodies can activate complement system by the classical pathway

- Sequential or non-sequential amino acids

linear conformational



- Located in accessible region

Properties of T cell epitopes

- T cell recognize Ag that has been processed in antigenic peptides with MHC
- Antigenic peptides recognized by T cells form trimolecular complexes with a T cell receptor and MHC molecules
- Internal peptides

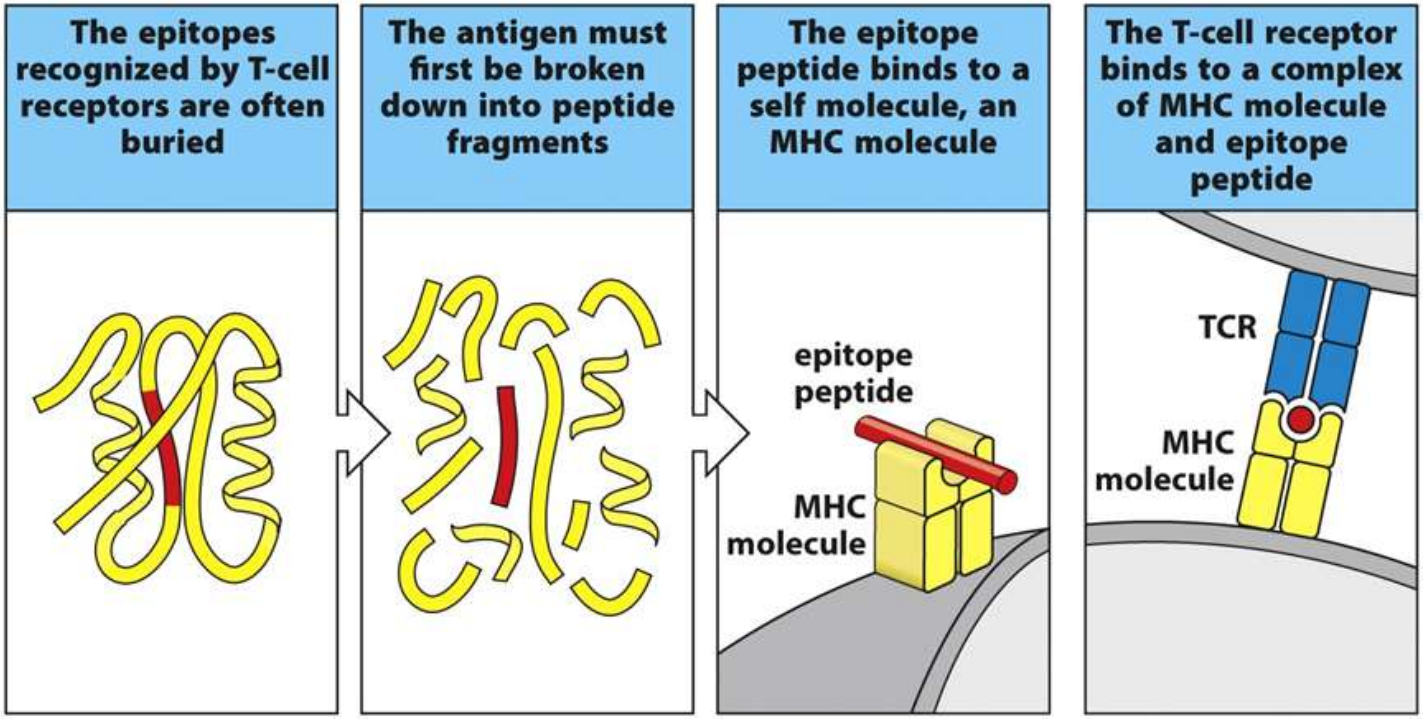
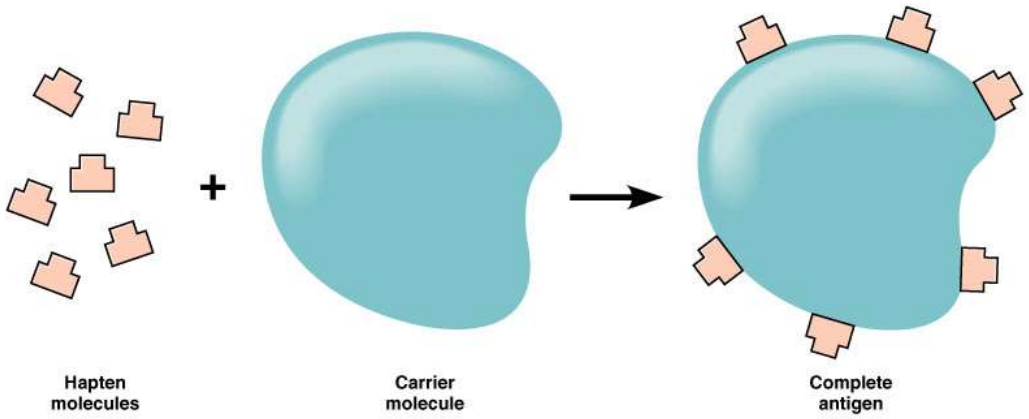


Figure 1.16 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Haptens

- Small molecules that are antigenic but not immunogenic
- Chemical coupling of a hapten to a large protein “called a carrier” yields an immunogenic **hapten-carrier conjugate**



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- **Allergen** - A substance capable of causing an allergic reaction.
- **Superantigen** - A class of antigens that cause non-specific activation of T-cells. antigens which polyclonally activate a large fraction of the T cells
- **Immunoglobulin binding protein** - These proteins are capable of binding to antibodies at positions outside of the antigen-binding site.
- **Autoantigen** is usually a normal protein that is recognized by the immune system of patients suffering from a specific autoimmune disease.
- **Native antigen** is an antigen that is not yet processed by an APC to smaller parts. T cells cannot bind native antigens, but require that they be processed by APCs, whereas B cells can be activated by native ones.

Antibodies

- Antibodies are the antigen-recognition molecules of B lymphocytes
- Antibodies function as "antigen binding proteins"
- They are produced by B cells in a large range of antigen specificities
- Each B cell produce antibodies of a single specificity
- Membrane-bound antibodies on B cell serves as the cell's receptor for the antigen

Antibodies Con’t

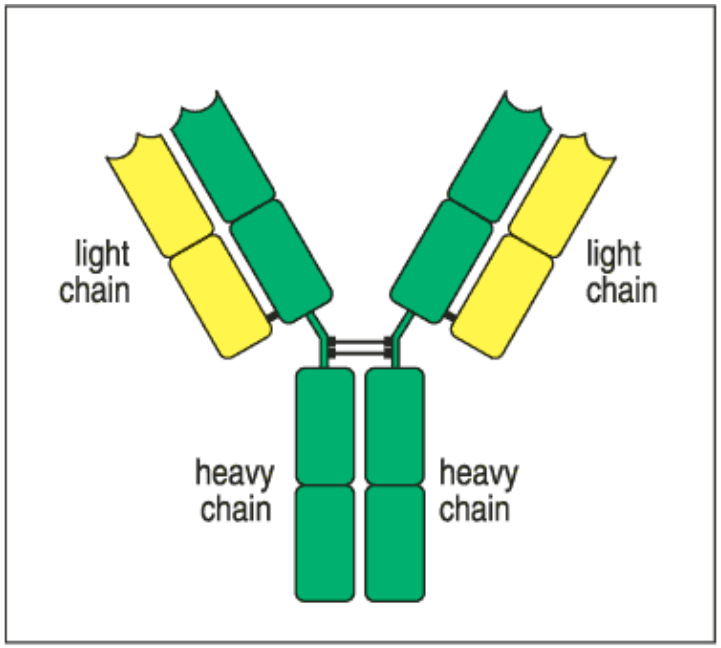
- Interaction of antigen with membrane-bound antibody elicit antigen specific B-cell proliferation
- Antibodies are secreted by plasma cells “terminally differentiated B cells”
- The serum antibodies produced in response to a particular antigen are heterogenous consists of populations of molecules with different physical, chemical or immunochemical properties
- All immunoglobulins share certain structural features, bind antigens and have effector functions

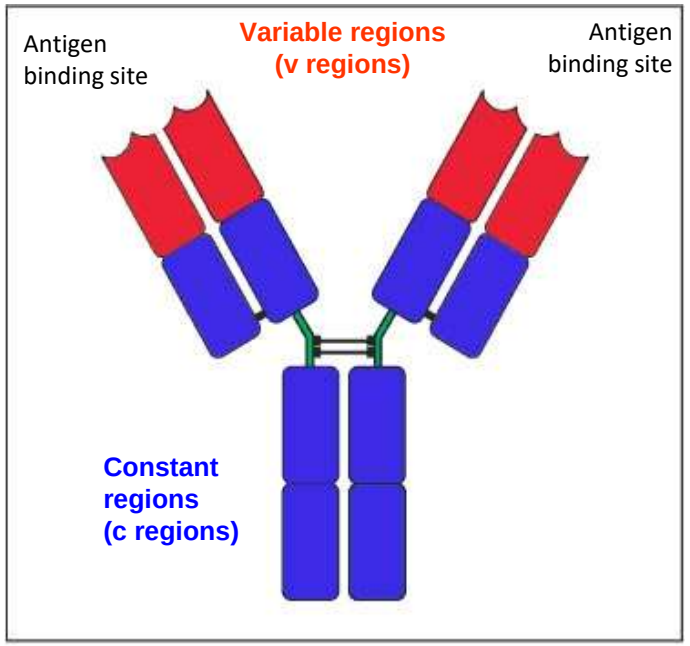
Antibody structure

antibody isotype is determined by the constant region of heavy chain

- **2 identical light (L) chains (~25kD) with variable and constant regions**
- **2 identical heavy (H) chains (~50kD) with variable and constant regions**
- **Linked by disulfide bound**

the isotype is determined based on the heavy chain they consist of.





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Antibody structure

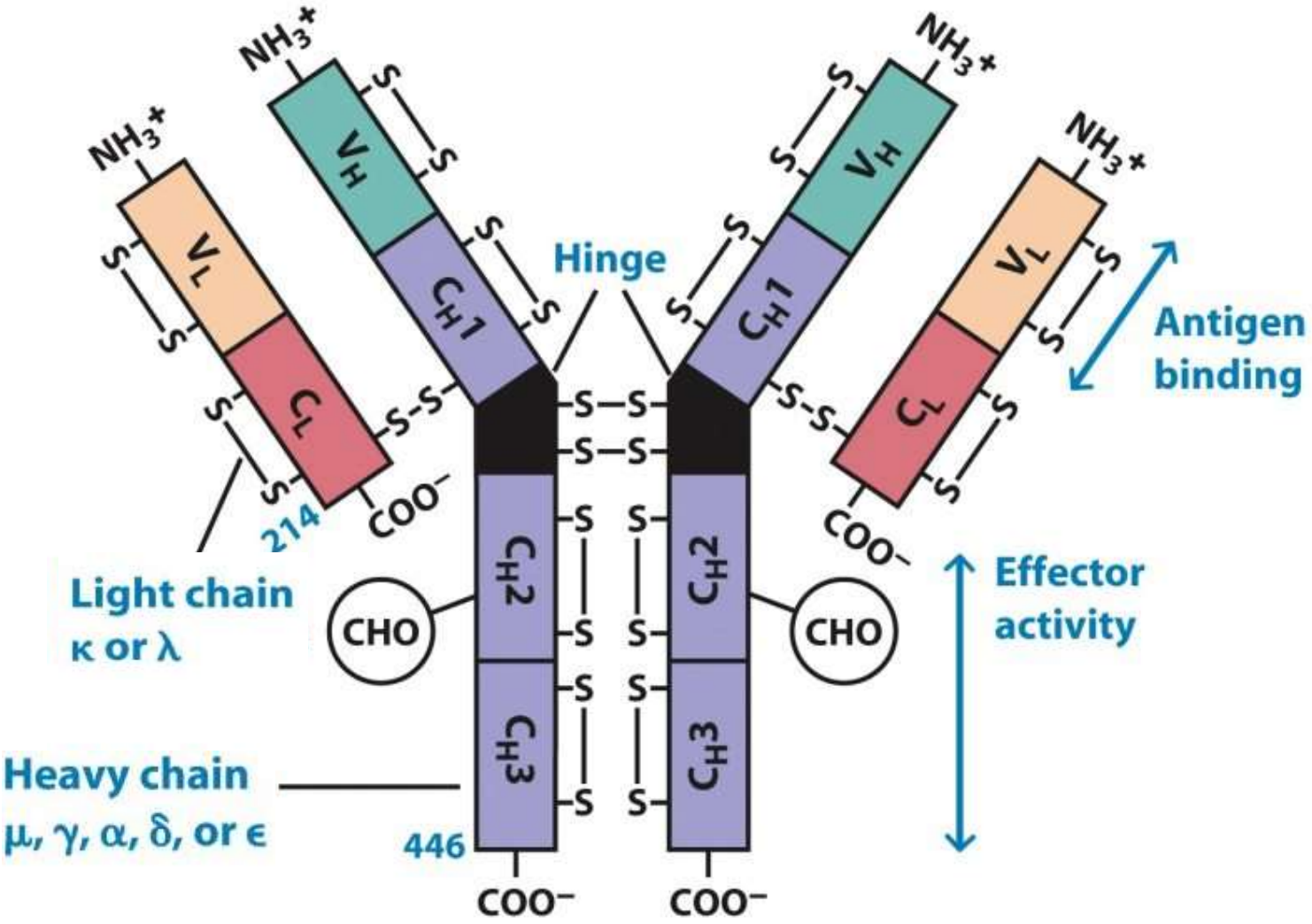

Figure 4-6
Kuby IMMUNOLOGY, Sixth Edition
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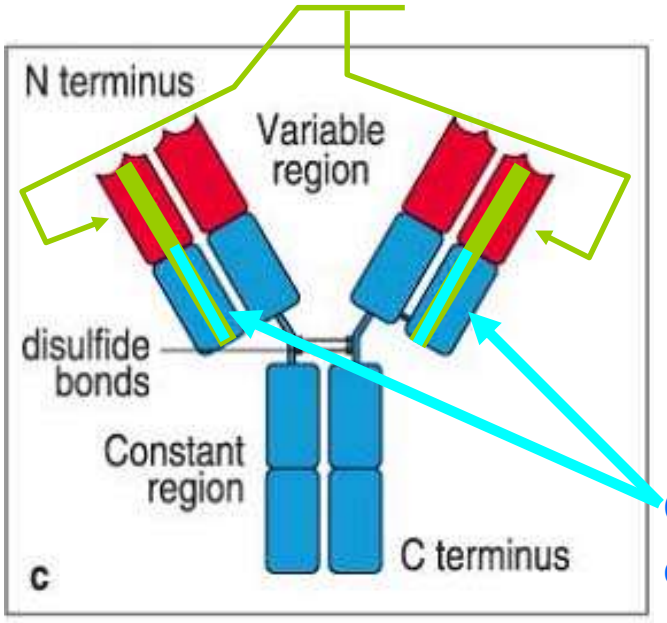
The light chains Constant regions

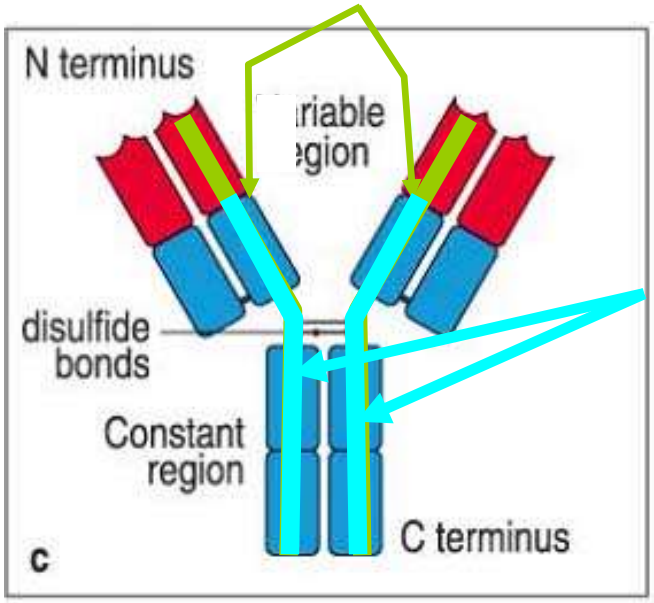


Constant region of the light chain = C_L

•There are **two** major Ig light chain constant region types. These DO NOT determine the class/isotype of the Ig and are not known to link the molecule to specific effector functions

•The 2 major Ig light chain types are **k** (kappa) and **l** (lambda). k and l are encoded at different genetic loci.

The heavy chains Constant regions

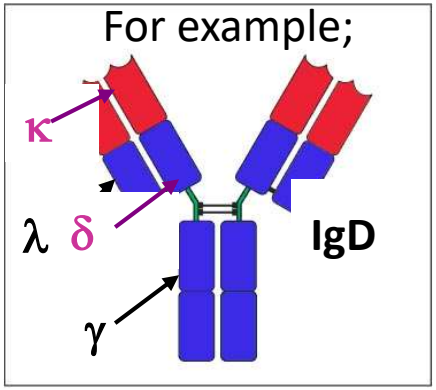


Constant region of the heavy chain = C_H

- The class of an antibody is defined by the structure of its heavy chain. Their are 5 main classes IgM, IgD, IgA, IgG and IgE.
- Each class determine the functional activity of an antibody molecule

Greek letters are used to name the heavy and light chain constant regions

γ, μ, α, δ, ε for the heavy chains
κ, λ for the light chains



The heavy chain determines the class of the Ig, thus

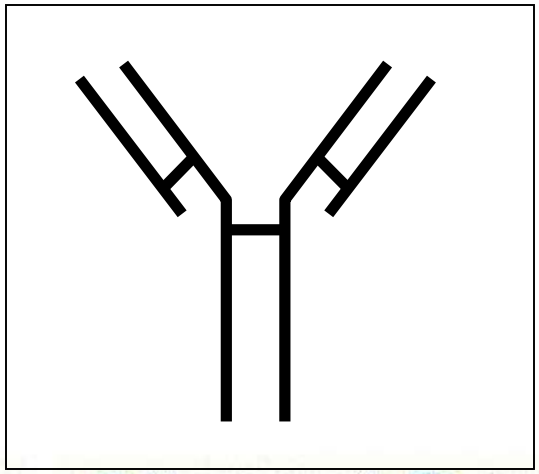
If the heavy chain is γ the class is IgG (and γ1 for IgG1, etc.)

If the heavy chain is μ the class is IgM

If the heavy chain is α the class is IgA

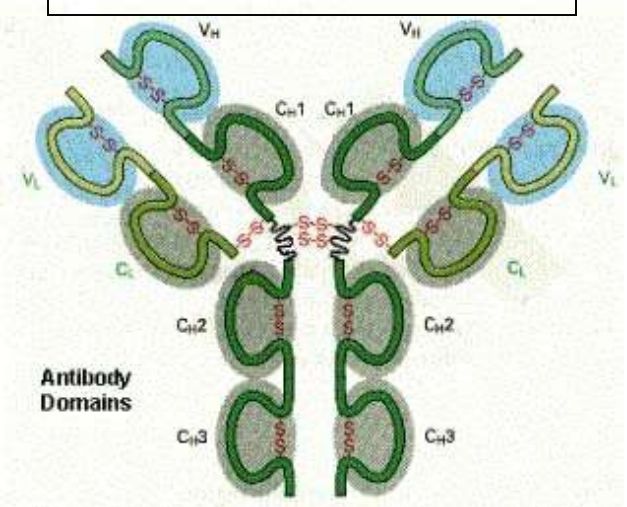
If the heavy chain is δ the class is IgD

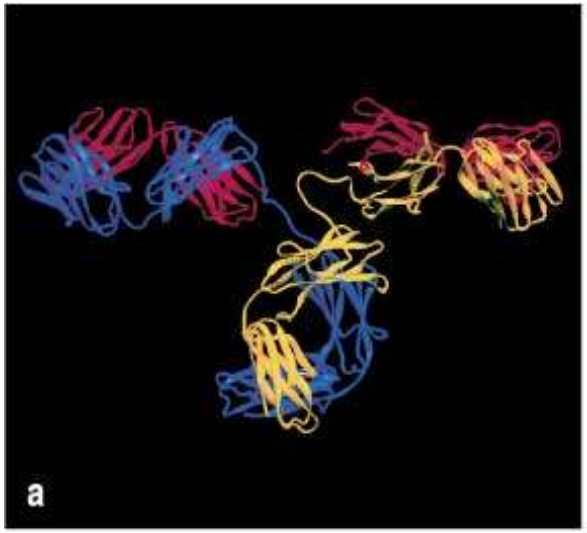
If the heavy chain is ε the class is IgE

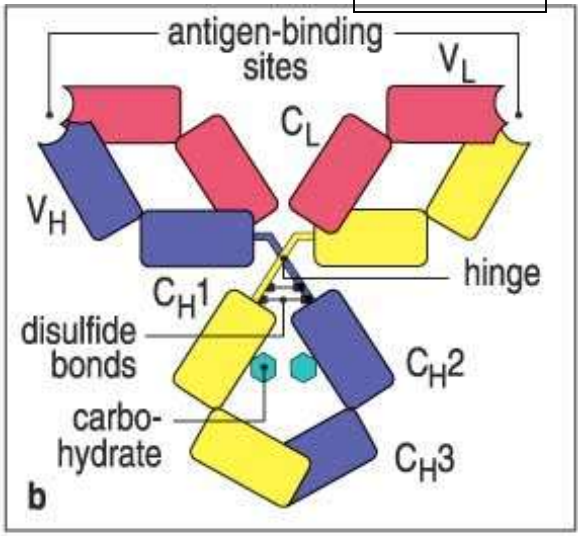


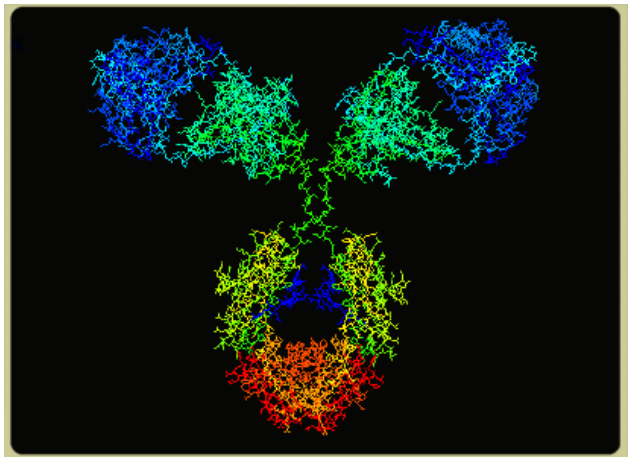
Different way to depict an Ig molecule

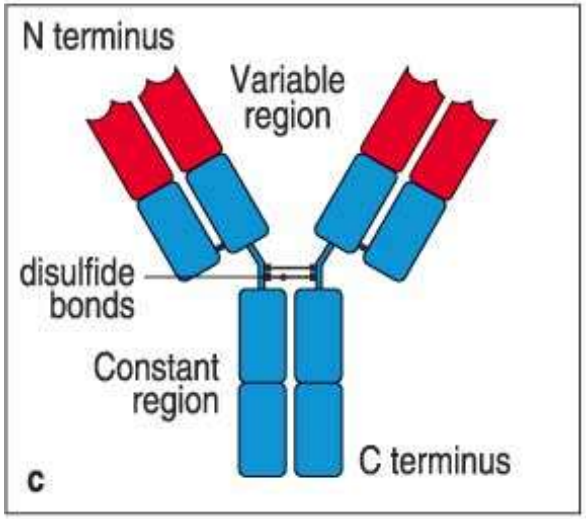
Y











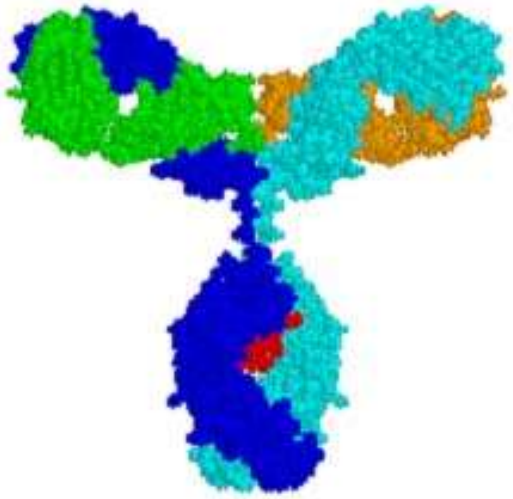


Fig 3.1 © 2001 Garland Science

THANK YOU

ANY QUESTIONS??

Antigens/Antibodies II

Prof. Dr. Hazem Aqel AL-Rimawi

Lecture 5

this presentation is given by Mohamed Alzobi

Immunoglobulin classes

5 classes:

- **Immunoglobulin G (IgG)**
- **Immunoglobulin M (IgM)**
- **Immunoglobulin A (IgA)**
- **Immunoglobulin E (IgE)**
- **Immunoglobulin D (IgD)**

They differ in size, charge, amino acid composition and carbohydrate content

- in the secondary infection
- long term immunity
- the only type which crosses the placenta
- passive immunity to the fetus through the placenta
- passive immunity through antibodies transference
- can be detected easily in serum

Immunoglobulin G (IgG)

•Is the most abundant Ig in normal human serum (75-80%)

•It has 4 subclasses IgG1, IgG2, IgG3 and IgG4

•IgG1, IgG3 and IgG4 can cross the placenta

IgG TWO does no cross TO placenta

one and three bind Fc

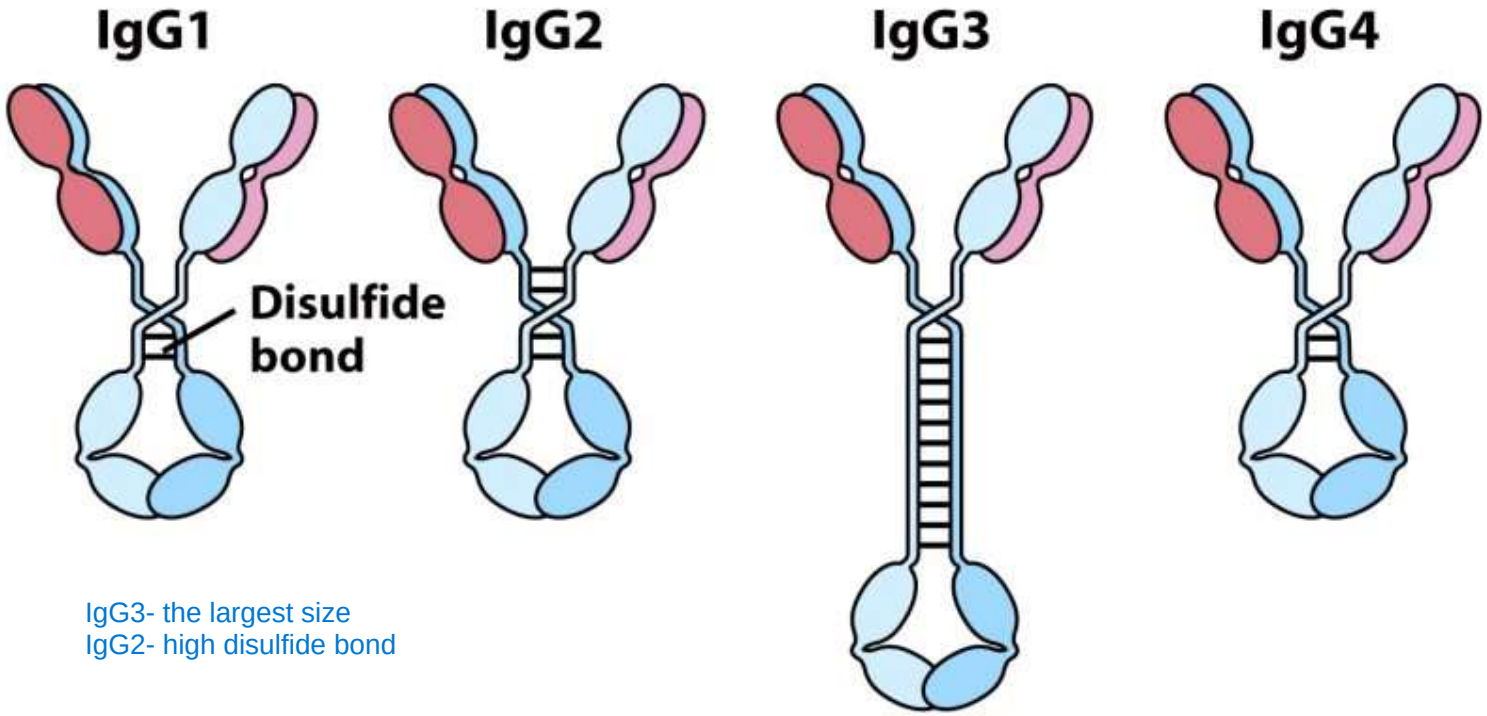
IgG FOUR does not anCHOR to complement

•It confers a high degree of passive immunity

•IgG3 is the most effective complement activator, followed by IgG1 and IgG2 while IgG4 can not activate complement

•IgG1 and IgG3 bind to with high affinity to Fc receptors on phagocytic cells and mediate opsonization.

The structure of the four subclasses of human IgG



IgG3- the largest size
IgG2- high disulfide bond

Figure 4-18
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Immunoglobulin M (IgM)

mainly during primary infection, fast response then disappears

- It accounts for approximately 5-10% of Ig
- It is expressed as a membrane-bound antibody on B cells
- It is secreted as a pentamer (5 monomer units)

can bind to 10 epitopes
bound together by J chain

- It is the first Ig produced in a primary response to an antigen
- More efficient than IgG in activating complement.

Immunoglobulin A (IgA)

Longe term immunity in secretory organs

- Consist of 15-20% of Ig
- Mostly exists as monomers but is also seen as polymeric forms
- It is the predominant Ig in external secretions such as saliva, tears, breast milk, tracheobronchial and genitourinary secretions.
- It has 2 subclasses IgA1 and IgA2
- The IgA in secretions is called “secretory IgA” which consists of a dimer or tetramer
- It can crosslink large antigens with multiple epitopes
- It provides an important line of defense against bacteria and viruses

Structure of secretory IgA

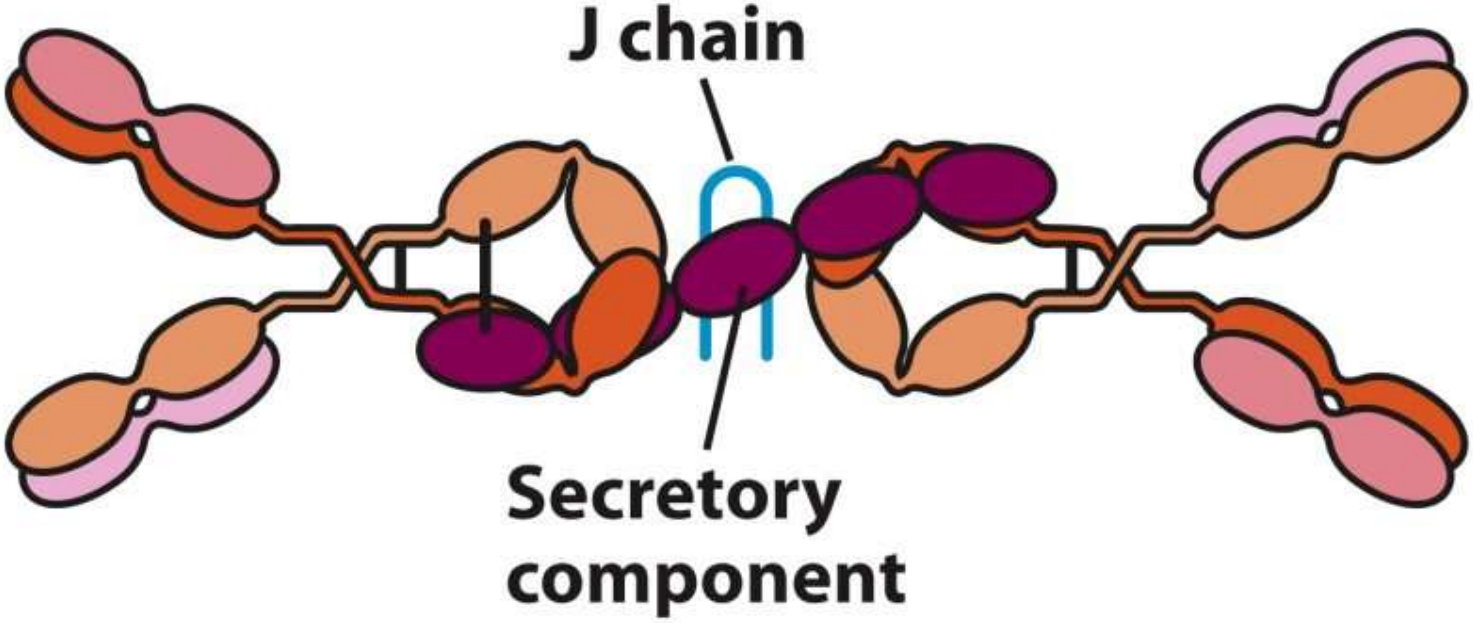

Figure 4-19a
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Immunoglobulin E (IgE)

•It is found on the surface membrane of mast cells and basophils (Fc receptor)

•Crosslinkage of Fc receptor bound IgE by antigen induces degranulation of mast cells and basophils which leads to the release of many pharmacologically active mediators and thus allergic manifestations

•It mediates allergic diseases such as asthma and hay fever

•It plays a role in immunity to helminthic parasites

Immunoglobulin D (IgD)

- Consists 1% of Ig

- Present in large quantity on the membrane of mature B cells

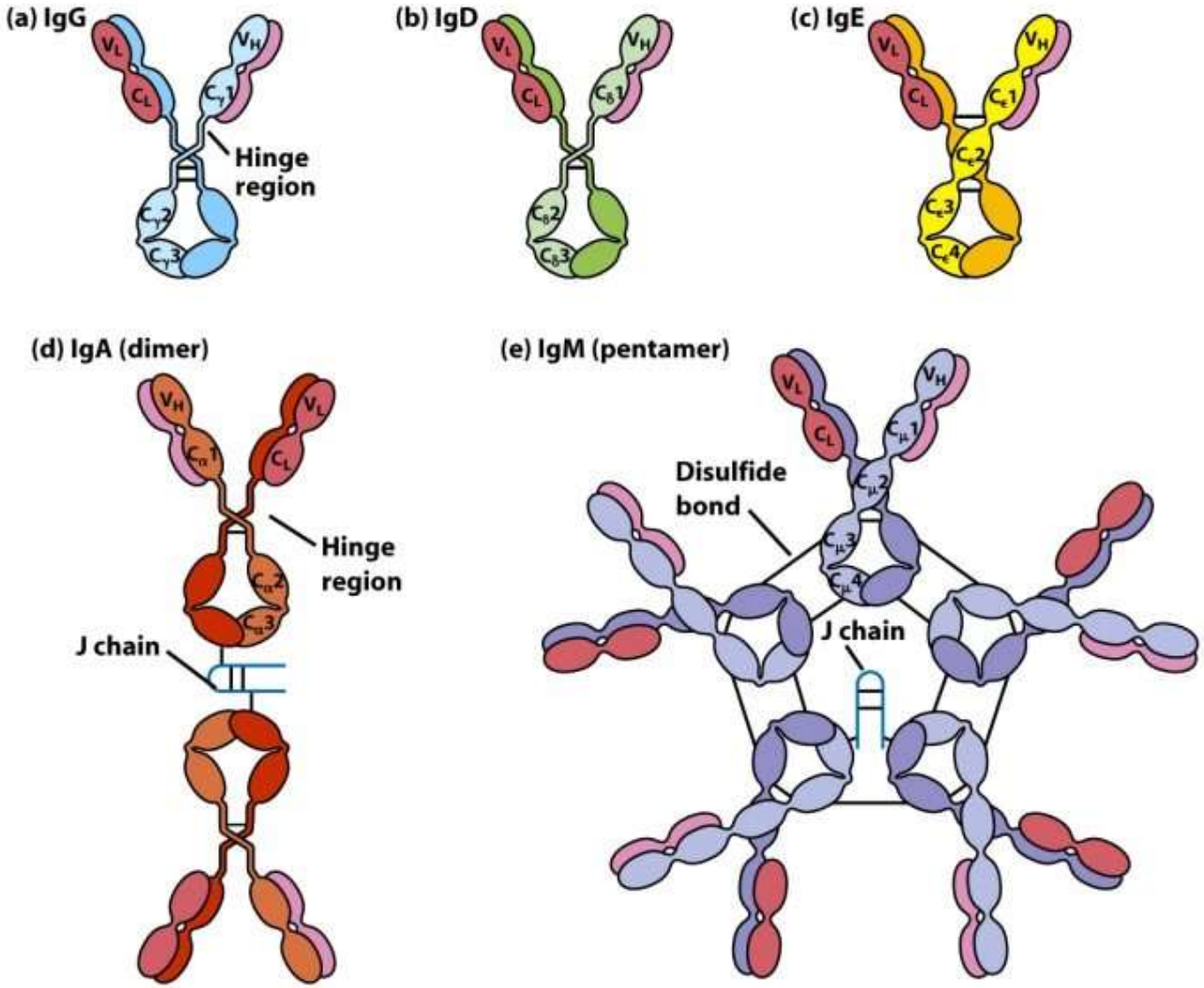

Figure 4-17
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Immunoglobulin effector functions

- Recognizing and binding to the Ag
- This binding will invokes responses that will remove the Ag and kill the pathogen
- The variable regions of the Ab binds the Ag
- The constant regions of the Ab are responsible for collaborative interaction with proteins, cells and tissues that result in the effector function of the humoral response

What are these effector functions?

- **Opsonization**: phagocytosis of the Ag by macrophages and neutrophils through the binding of their Fc receptor to the constant region of the Ab

- **Neutralization** of Microbes and Microbial Toxins: Most neutralizing antibodies in blood are of the IgG isotype; in mucosal organs, IgA isotype.

- **Complement activation**

  IgM>IgG

- **Activation of other immune cells**
  - NK cells Ab-dependent cell-mediated cytotoxicity (ADCC)
  - Mast cells

TABLE 4-4 Properties and biological activities* of classes and subclasses of human serum immunoglobulins

	IgG1	IgG2	IgG3	IgG4	IgA1	IgA2	IgM‡	IgE	IgD
Molecular weight†	150,000	150,000	150,000	150,000	150,000 – 600,000	150,000 – 600,000	900,000	190,000	150,000
Heavy-chain component	γ1	γ2	γ3	γ4	α1	α2	μ	ϵ	δ
Normal serum level (mg/ml)	9	3	1	0.5	3.0	0.5	1.5	0.0003	0.03
In vivo serum half-life (days)	23	23	8	23	6	6	5	2.5	3
Activates classical complement pathway	+	+/−	++	−	−	−	++	−	−
Crosses placenta	+	+/−	+	+	−	−	−	−	−
Present on membrane of mature B cells	−	−	−	−	−	−	+	−	+
Binds to Fc receptors of phagocytes	++	+/−	++	+	−	−	?	−	−
Mucosal transport	−	−	−	−	++	++	+	−	−
Induces mast cell degranulation	−	−	−	−	−	−	−	+	−

*Activity levels indicated as follows: ++ = high; + = moderate; +/− = minimal; − = none; ? = questionable.
†IgG, IgE, and IgD always exist as monomers; IgA can exist as a monomer, dimer, trimer, or tetramer. Membrane-bound IgM is a monomer, but secreted IgM in serum is a pentamer.
‡IgM is the first isotype produced by the neonate and during a primary immune response.

- the largest is IgM
- the most abundant in plasma is IgG
- the least abundant is IgE
- highest half life is IgG
- on mature B cells - IgD, IgM
-

Table 4-4
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Function	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	–	++	++	++	++	++	–
Opsonization	–	–	+++	*	++	+	+	–
Sensitization for killing by NK cells	–	–	++	–	++	–	–	–
Sensitization of mast cells	–	–	+	–	+	–	–	+++
Activation of complement system	+++	–	++	+	+++	–	+	–
Transport across epithelium	+	–	–	–	–	–	+++ (dimer)	–
Transport across placenta	–	–	+++	+	++	+/–	–	–
Diffusion into extravascular sites	+/–	–	+++	+++	+++	+++	++ (monomer)	+
Mean serum level (mg ml^{-1})	1.5	0.03	9	3	1	0.5	2.1	$5x10^{-5}$

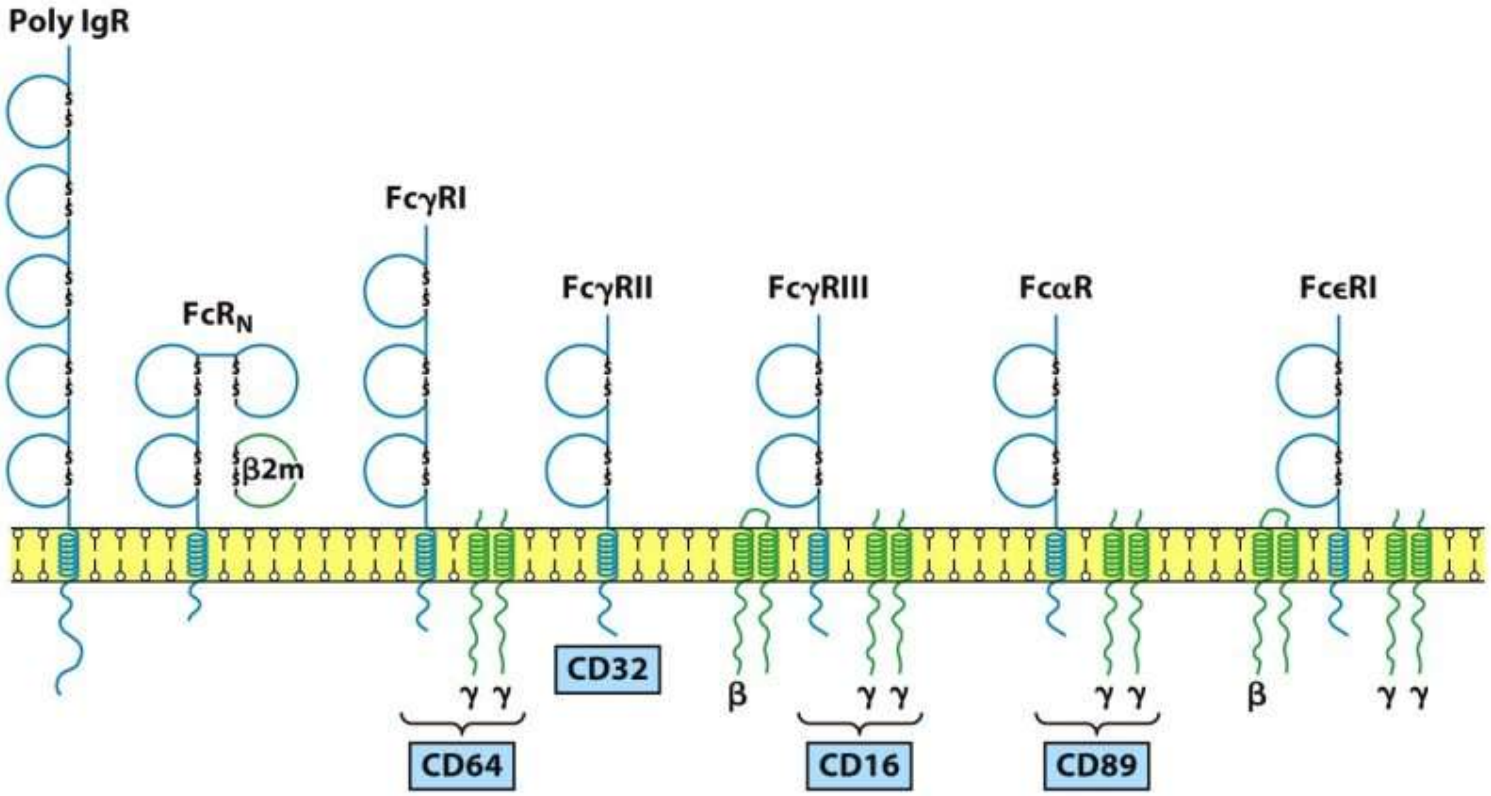

Figure 4-23
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- A memory B cell can express a variety of Ig classes, including mIgM, mIgG, mIgA or mIgE

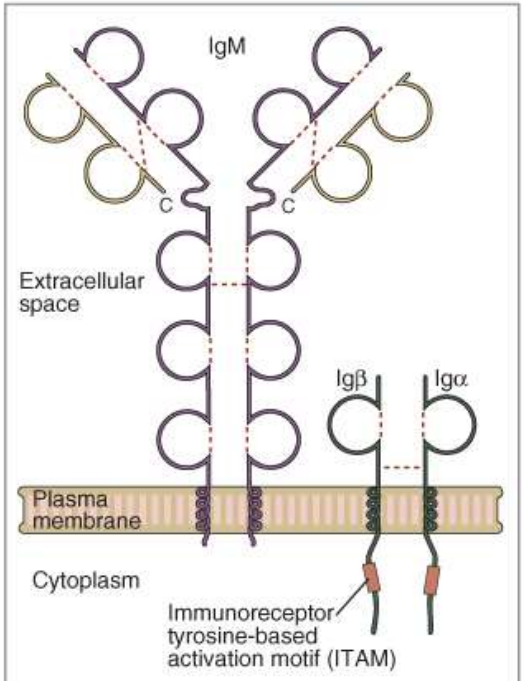
- Even when different classes are expressed on a single cell, the antigenic specificity of all the mIg is **identical** (bind the same epitope)

The B cell receptor

The B cell receptor consist of:

-The mIg which has short cytoplasmic tail (no signaling)

- 2 heterodimer disulfid linked called Ig-α and Ig-β with long cytoplasmic tail to interact with intracellular signalling



Antigenic determinants on immunoglobulins

- Antibodies are glycoproteins they can themselves function as potent immunogens to induce an Antibody response
- Such anti-Ig antibodies are great tools to study B cell development and humoral immune responses

Antigen-antibody complexes are held together by **non-covalent** forces (therefore, antigen binding by antibody is reversible)

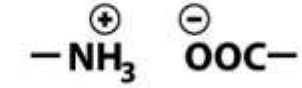
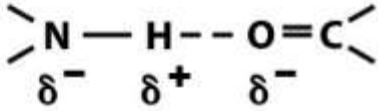
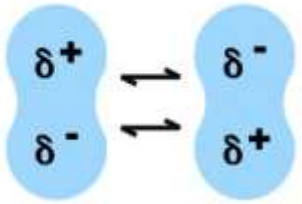
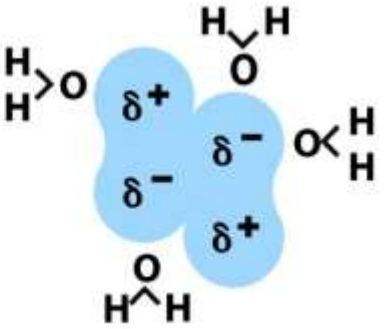
Noncovalent forces	Origin	
Electrostatic forces	Attraction between opposite charges	
Hydrogen bonds	Hydrogen shared between electronegative atoms (N,O)	
Van der Waals forces	Fluctuations in electron clouds around molecules oppositely polarize neighboring atoms electron clouds just barely touch	
Hydrophobic forces	Hydrophobic groups interact unfavorably with water and tend to pack together to exclude water molecules. The attraction also involves van der Waals forces	

Figure 3-9 Immunobiology, 7ed. (© Garland Science 2008)

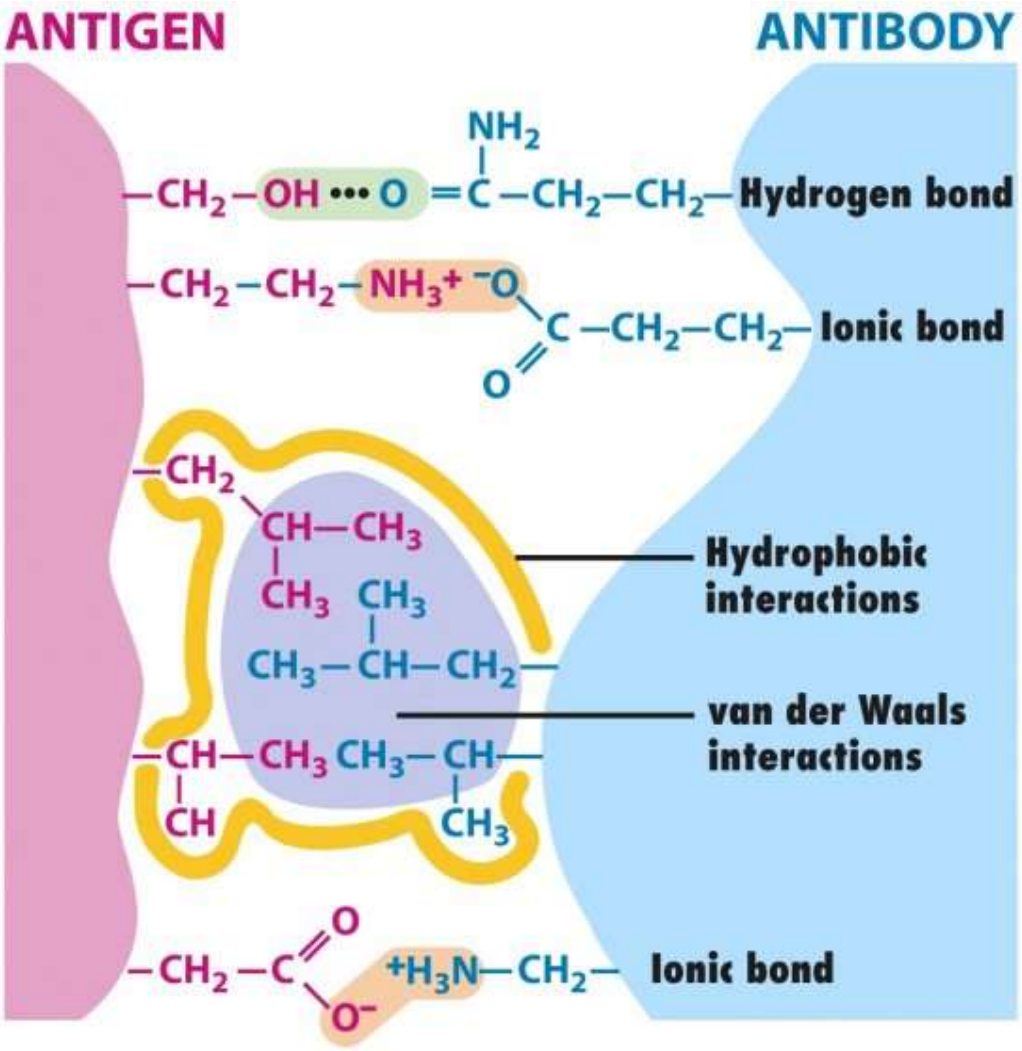


Figure 6-1
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Monoclonal Antibodies

A homogenous preparation of antibodies secreted from a single B cell lineage specific for a single epitope

Polyclonal Antibodies

A collection of different antibodies secreted by different B cell lineages specific for different epitopes

THANK YOU

ANY QUESTIONS??

The Complement System

Prof. Dr. Hazem Aqel AL-Rimawi

Lecture 6

This presentation is given by Mohamed Alzobi

The Objectives

1. Describe the nature of the complement components
2. Describe the classical and the alternate pathways
3. Describe the biological consequences of complement activation
4. List the antibodies that are effective in activating Complement

The complement system

inactive till it gets activated during inflammation/by antigen-antibody complex

- The complement system is made up of a large number of different plasma proteins that interact with each other.

- The majority of complements are soluble but some of them are membrane bound but inactive

- Complements are widely distributed in body fluids and tissues.-

- Complements can kill pathogens directly or help in pathogen removal by phagocytosis

- Complement augment opsonization and killing of pathogens by antibodies “it complements antibacterial activity”.

The complement system cont'd

- Complements circulate in an inactive state.

- Complement activation needs the presence of a pathogen.

- Complement activation can happen by binding to antibodies bound to - pathogens or by binding directly to pathogens

- Several complements are proteases that become activated after cleavage by another protease.

- They become activated through a triggered-enzyme cascade.-

- Each protein must be activated sequentially for the reaction to proceed

the Dr talked about complement fixation test (please turn on my video to listen for the explanation)

Complement Activation

- The site of complement activation is usually the surface of pathogens.

- Complement activation result in an enzymatic cascade that is highly regulated.

- Once a complement is activated, it cleaves its substrate to its active enzymatic form, this in turn will cleave and activate the next complement in the pathway and so on.

Activation of the complement system

Occurs through **3 distinct pathways**

1- Classical pathway starts from C1

2- Mannan-binding lectin pathway Starts from c2, c4

3- Alternative pathway starts from C3

The Complement Activation Pathways

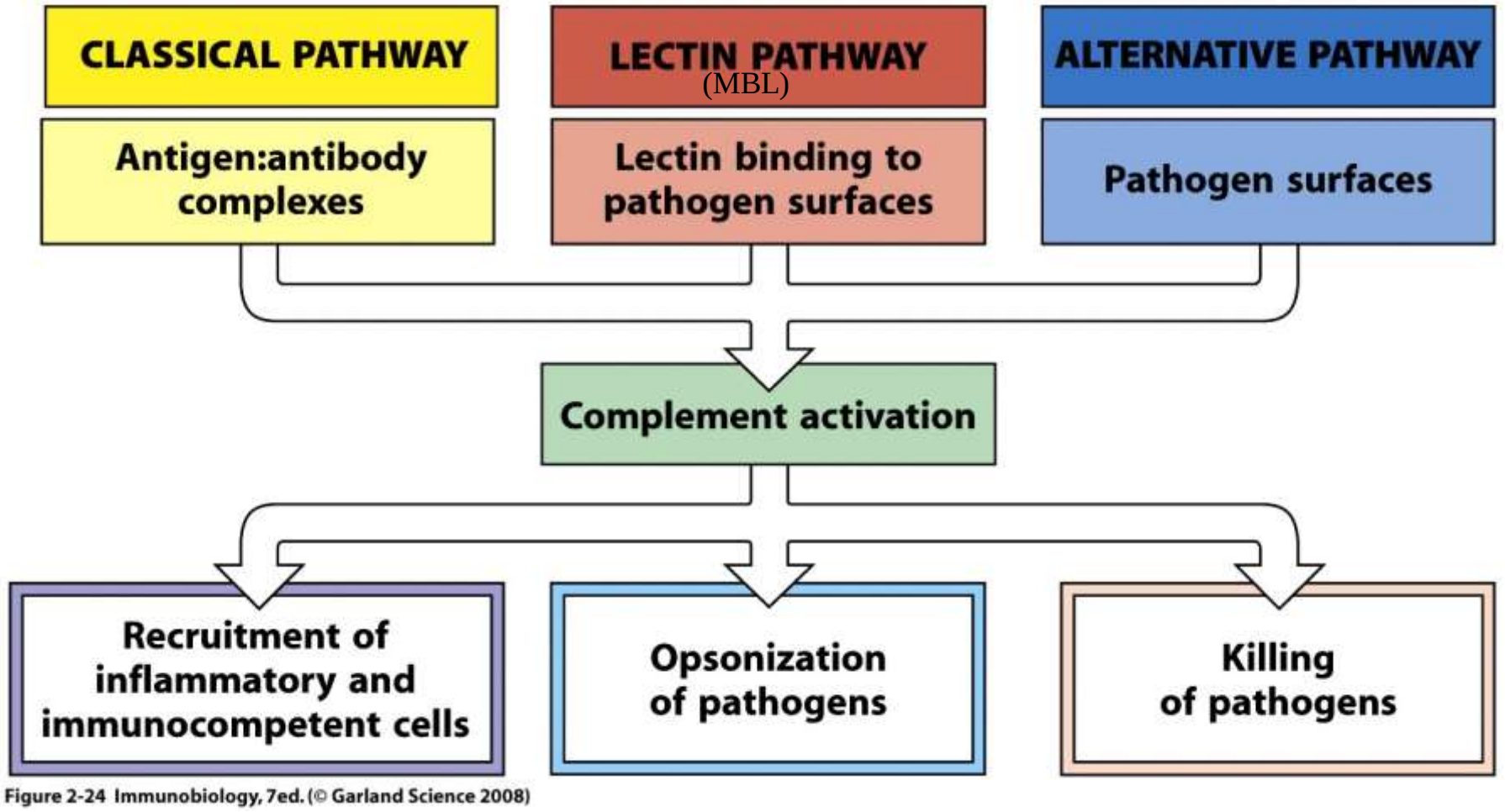


Figure 2-24 Immunobiology, 7ed. (© Garland Science 2008)

The Classical Pathway

- Is usually activated by antigen: antibody complexes.

- Is initiated by the binding of the first protein in the complement cascade "C1" to the pathogen surface.

- C1 comprises C1q + C1s + C1r

C1 can bind to the Fc region of the antigen: antibody complex on the pathogen or directly to the pathogen.

- Binging of C1q to the pathogen causes conformational changes that activates C1r which will then cleave C1s to generate its active form.

- C1s will then act on C4 and C2 generating C4b and C2a which together form C4b2a the C3 convertase.

- C3 convertase then cleave C3 molecules to produce C3b to coat the pathogen and C3a to induce inflammation.

Initiation of the classical pathway is with **C1**

C1 is activated by antibody and can be activated by itself on the surface of certain bacteria

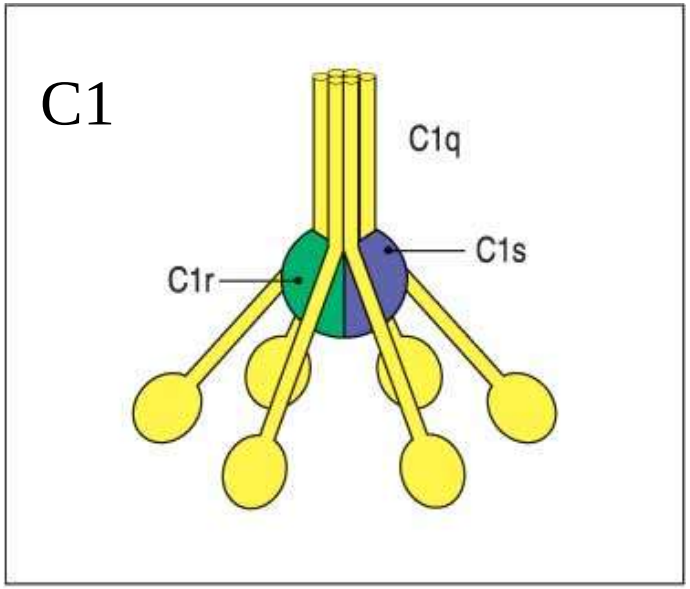




Fig 2.10 © 2001 Garland Science

C1=C1q+C1r+C1s

Binding of two of the C1q heads to the surface of a bacteria activate C1r to cleave and activate C1s

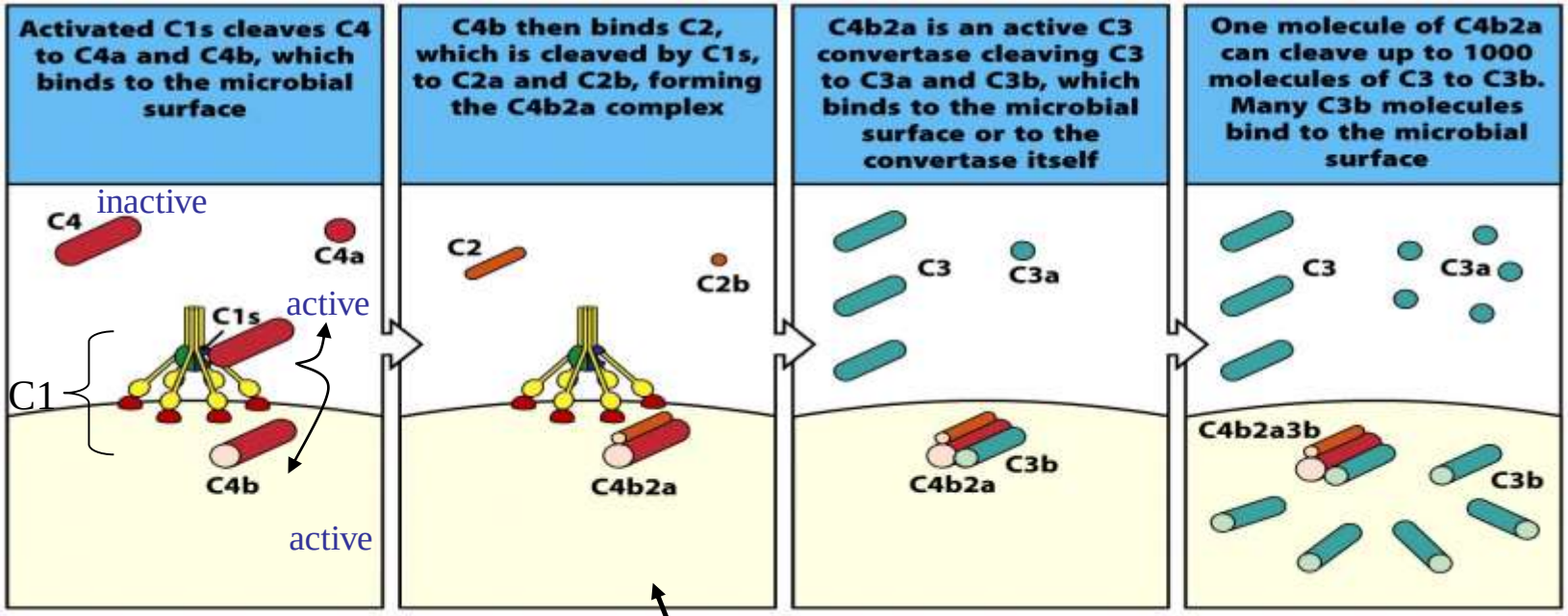


Figure 2-28 Immunobiology, 7ed. (© Garland Science 2008)

$$C4 \xrightarrow{C1s} C4a + C4b$$

inactive → active + active

C4b and C2a combine to form C4b2a

$$C2 \xrightarrow{C1s} C2a + C2b$$

inactive → active + active

$$C3 \xrightarrow{C4b2a} C3a + C3b$$

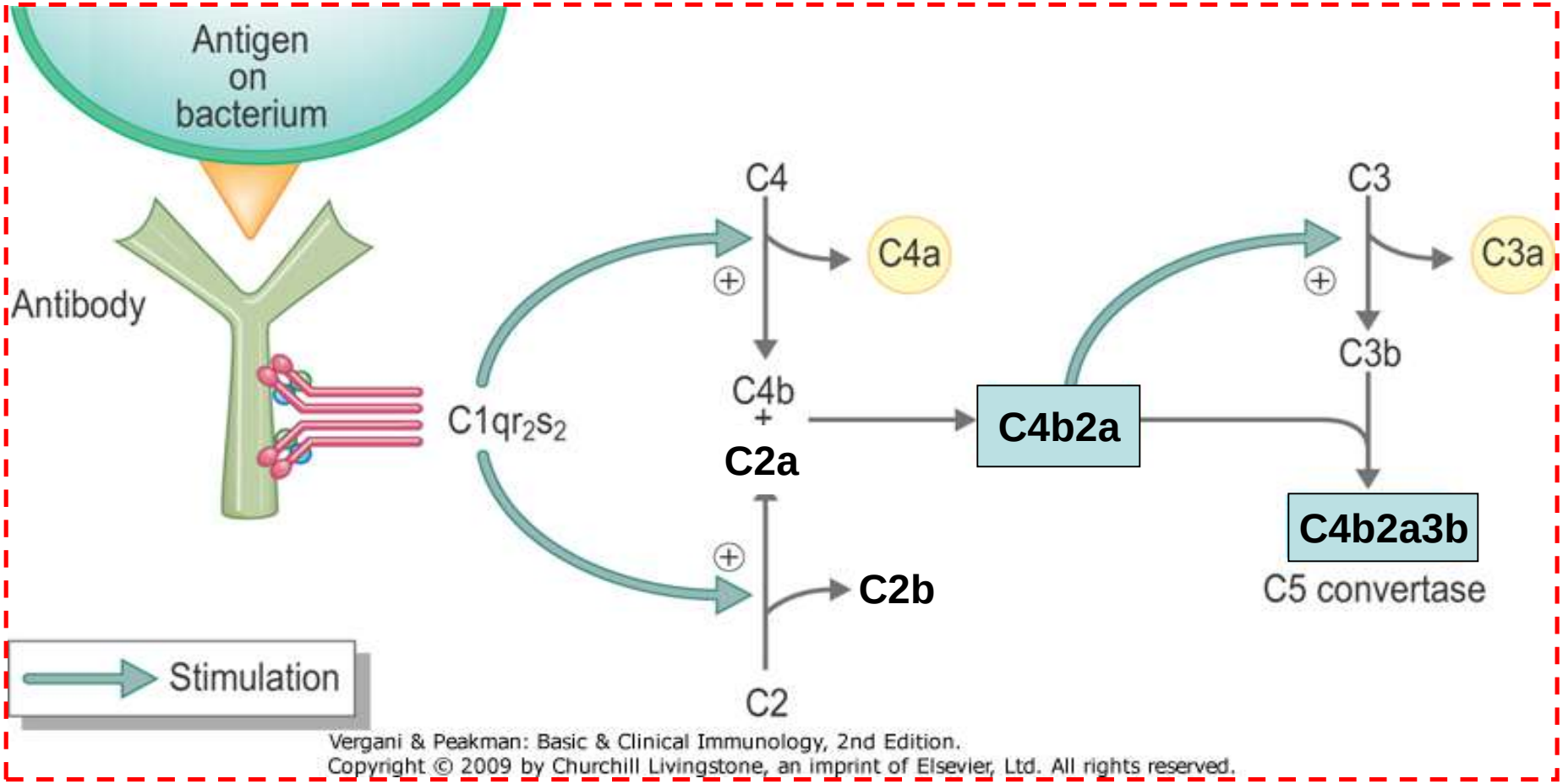
inactive → active + active

C4b2a is a **C3 convertase** (there are others)

- **C1s** cleave **C4** to **C4a** & **C4b**
- **C1s cleave C2 to C2a & C2b**

----→ **C4b2a**

- **C4b &C2a** continues the **reaction** process whereas **C4a** & C2b has other **biological** properties



Vergani & Peakman: Basic & Clinical Immunology, 2nd Edition.
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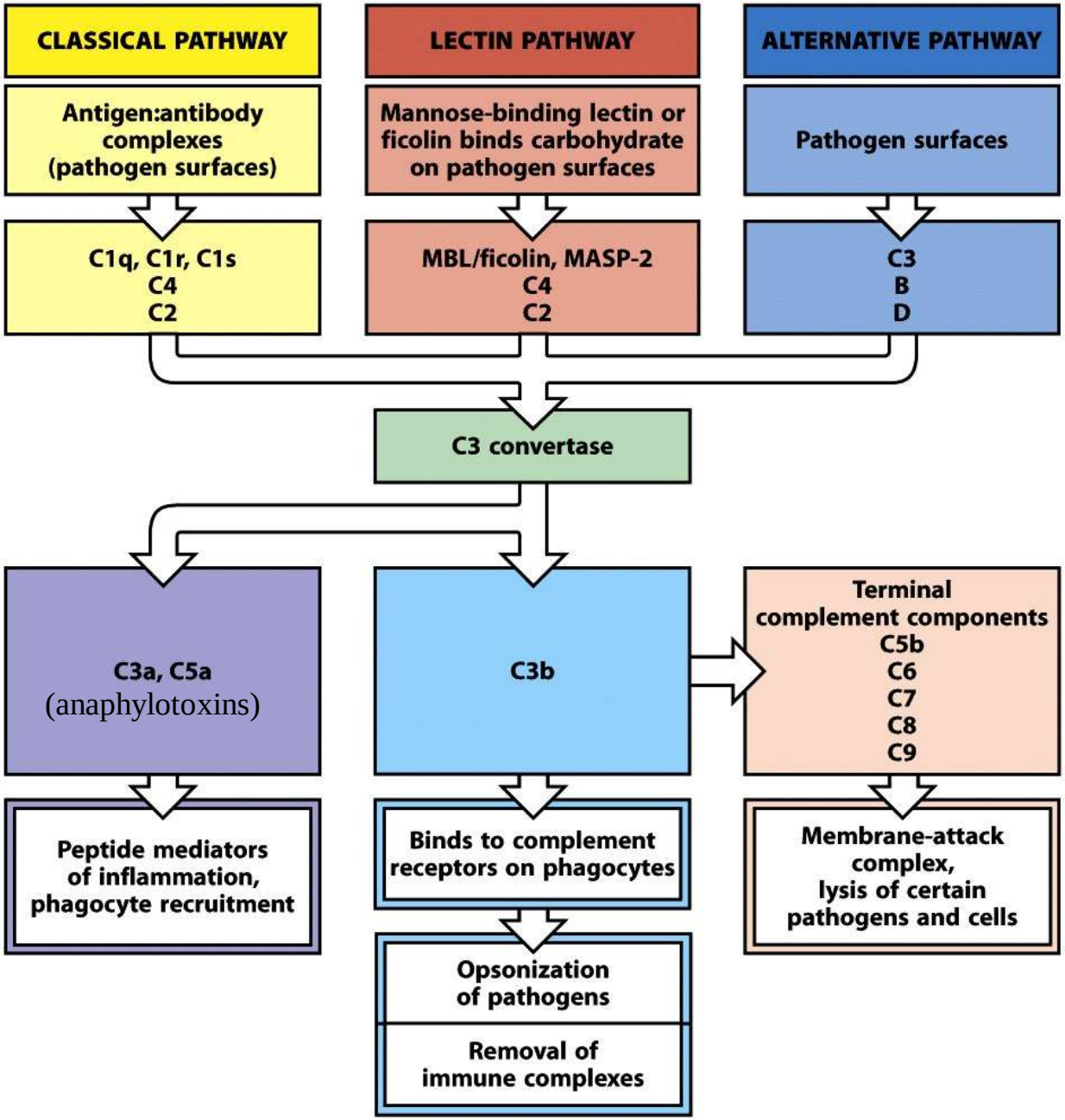


Figure 2-25 Immunobiology, 7ed. (© Garland Science 2008)

C3 convertase is an enzyme that activates C3

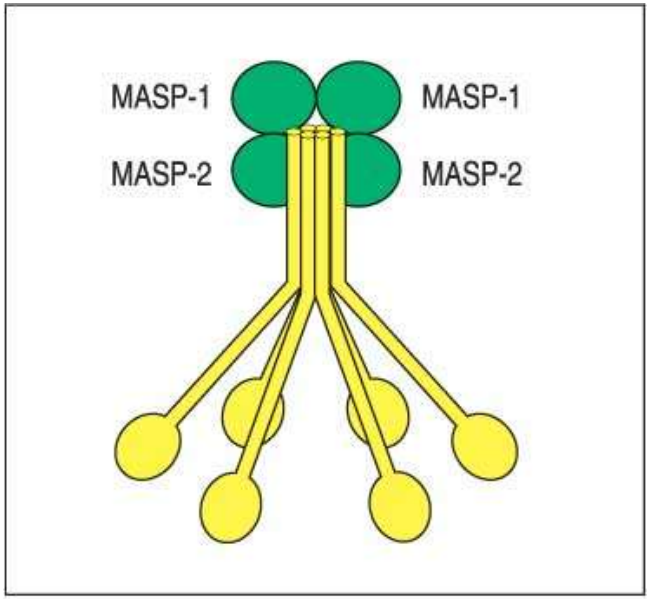
$$C3 \xrightarrow{\text{C3 convertase}} C3a + C3b$$

The lectin Pathway

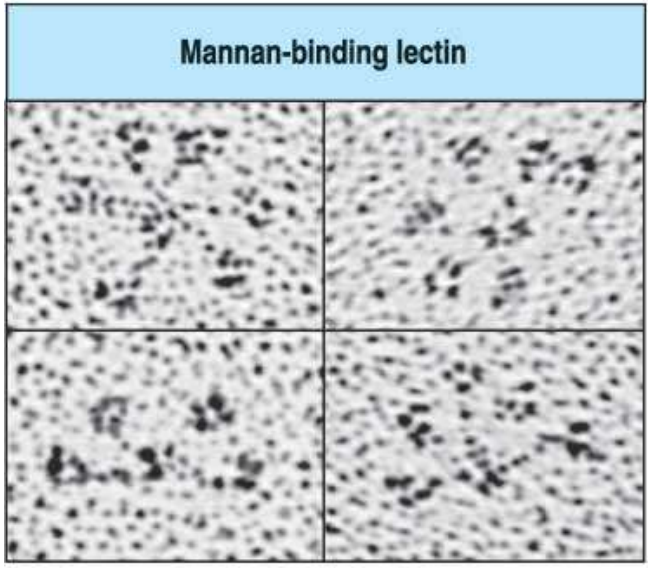
- Is initiated by the mannose-binding lectin.
- MBL binds to mannose residues on pathogen surfaces.
- MBL forms a complex with 2 zymogens MASP-1 and MASP-2. inactive protein Mannan-binding lectin serine protease
- Once MBL complex binds to a pathogen MASP-2 is activated to cleave C4 and C2.
- Activation and cleaving C2 and C4 will then generate C2a and C4b which together form the C3 convertase.
- C3 convertase then cleave C3 molecules to produce C3b to coat the pathogen and C3a to induce inflammation.

Mannan-binding lectin (MBL) is similar to C1 but it binds to mannose then activates C4 and C2.

MB-lectin pathway is particularly important in children that do not have much antibody



MASP-1 and MASP-2 are serine proteases



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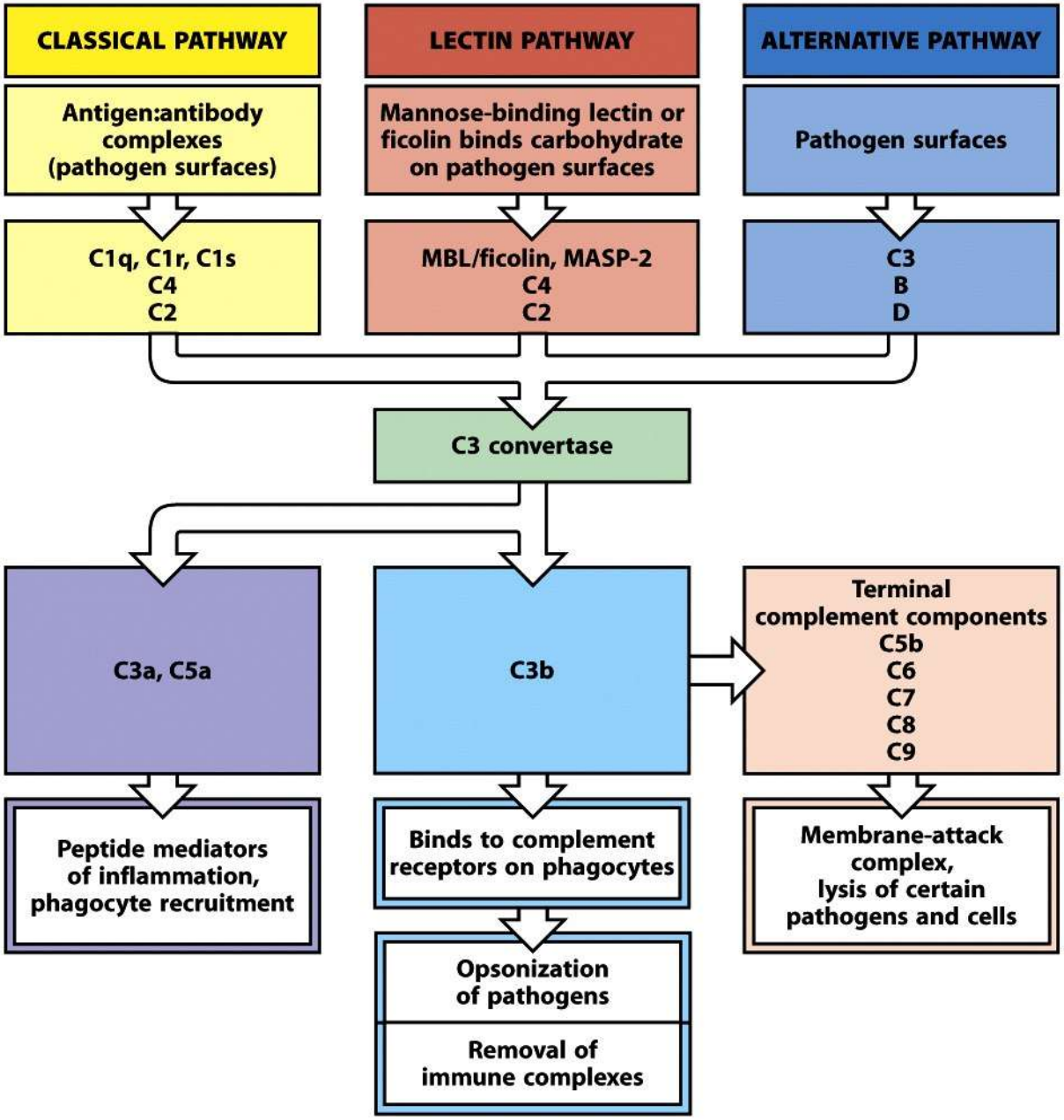


Figure 2-25 Immunobiology, 7ed. (© Garland Science 2008)

The alternative Pathway

- Is not initiated by the binding of proteins to the pathogen surface.

- It is initiated by the spontaneous hydrolysis of C3 into C3(H_2O).

- C3 is abundant in the plasma and producing C3(H_2O) by hydrolysis allows the binding to factor B.

- Binding factor B to C3(H_2O) allows the plasma protease factor D to cleave factor B to Ba and Bb.

- Bb will associate with C3(H_2O) and form C3(H_2O)Bb complex.

- C3(H_2O)Bb is a C3 convertase.

- C3 convertase then cleave C3 molecules to produce C3b to coat the pathogen and C3a to induce inflammation.

- C3b will bind to factor B that will cleaved by factor D into Bb and Ba.

- C3bBb is a C3 convertase acting on C3.

Complement activation by the Alternative Pathway

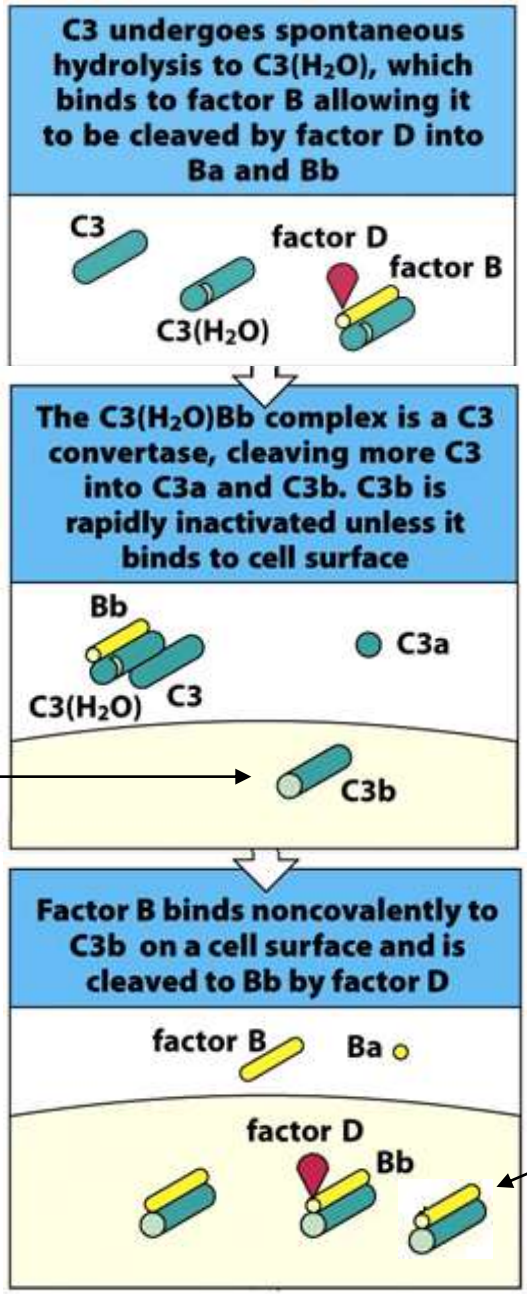


Figure 2.32

For C3, there is spontaneous hydrolysis that occurs whether bacteria are present or absent

C3b is quickly inactivated in solution but is stabilized when it binds to bacteria surfaces

C3bBb is a C3 convertase

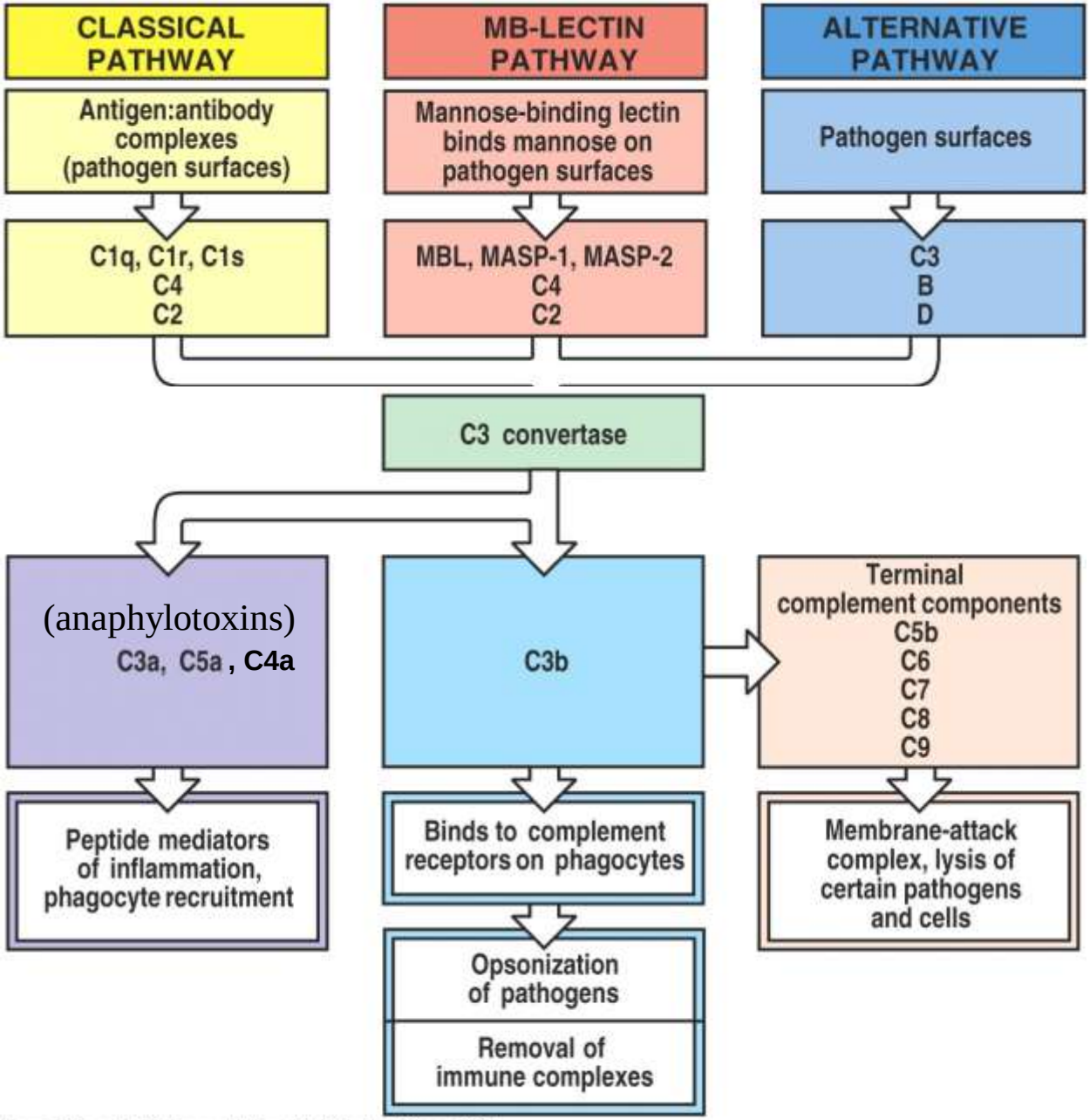


Figure 2-19 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

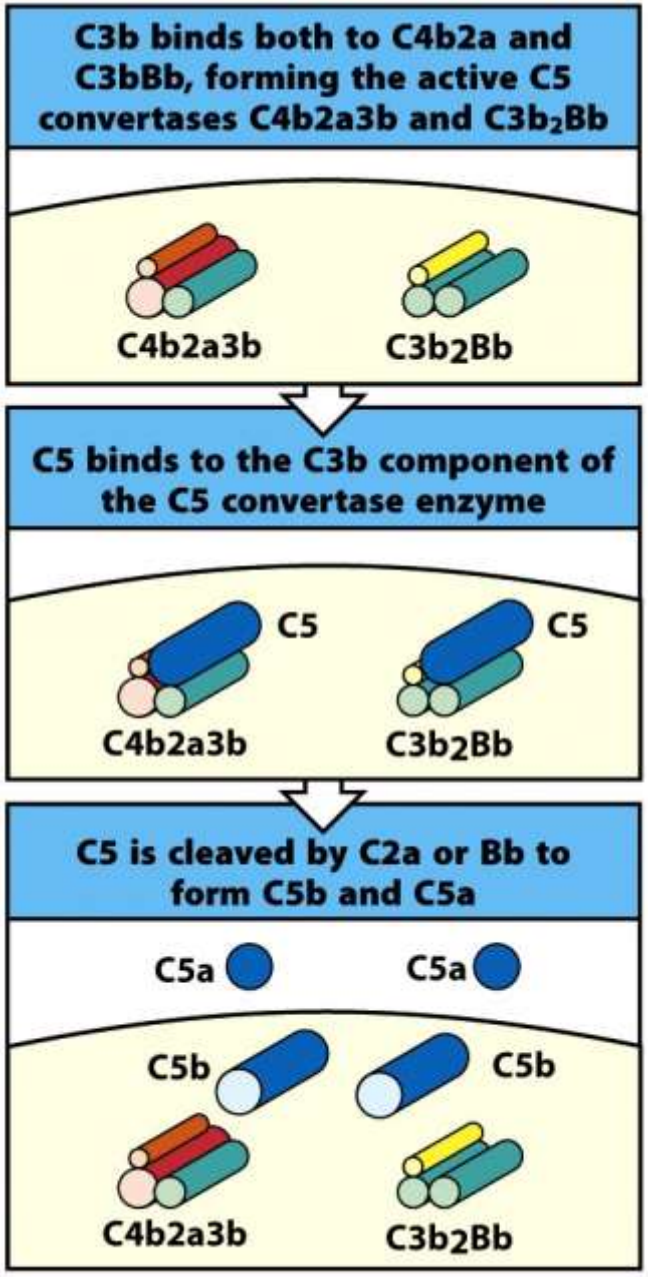


Figure 2-36 Immunobiology, 7ed. (© Garland Science 2008)

C4b2a and C3bBb are C3 convertases but if you add another C3b then:

C4b2a3b and $C3b_2Bb$ are **<u>C5 convertases</u>**

$$C5 \xrightarrow{\text{C5 convertase}} C5a + C5b$$

The membrane attack complex (MAC)

C5 convertase starts the final part of the complement activation pathways.

The cascade ends by the formation of the **'killer molecule'** of the **system**

This is known as **membrane** attack **complex (MAC),** since it **provokes** membrane **damage**

How is the MAC formed?

- Cleavage of C5 by the classical, MBL or alternative pathway convertases gives C5a & C5b
- C5b binds to C6 & inducing it to express a labile reactive site for C7
- C5b67 complex is highly lipophilic & binds to membranes, where it acts as a receptor for C8
- C8 has 3 chains, one of which inserts into the membrane, anchoring the C5b678 complex
- C5b678 binds & polymerises C9, forming MAC, the final component of the system

The Main Functions of Complement System

1. Opsonization by coating the pathogens and enhancing phagocytosis.

2. Direct killing of certain bacteria by the membrane attack complex (MAC) which creates pores in the bacteria cell membrane.

3. Inducing inflammation by recruiting phagocyte to the site of infection.

1. Complement-mediated opsonization

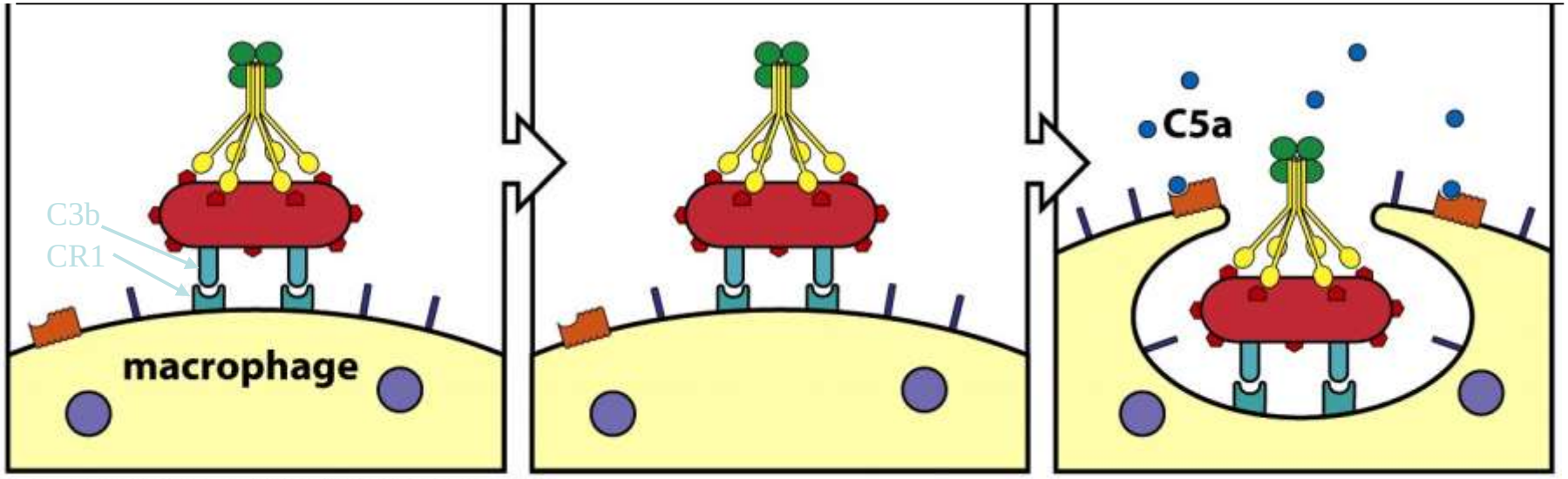


Figure 2-38 Immunobiology, 7ed. (© Garland Science 2008)

Opsonisation: coat bacteria to facilitate their removal

C3b accounts for most of the complement opsonic activity

2. Complement direct killing by the formation of the membrane attack complex (MAC)

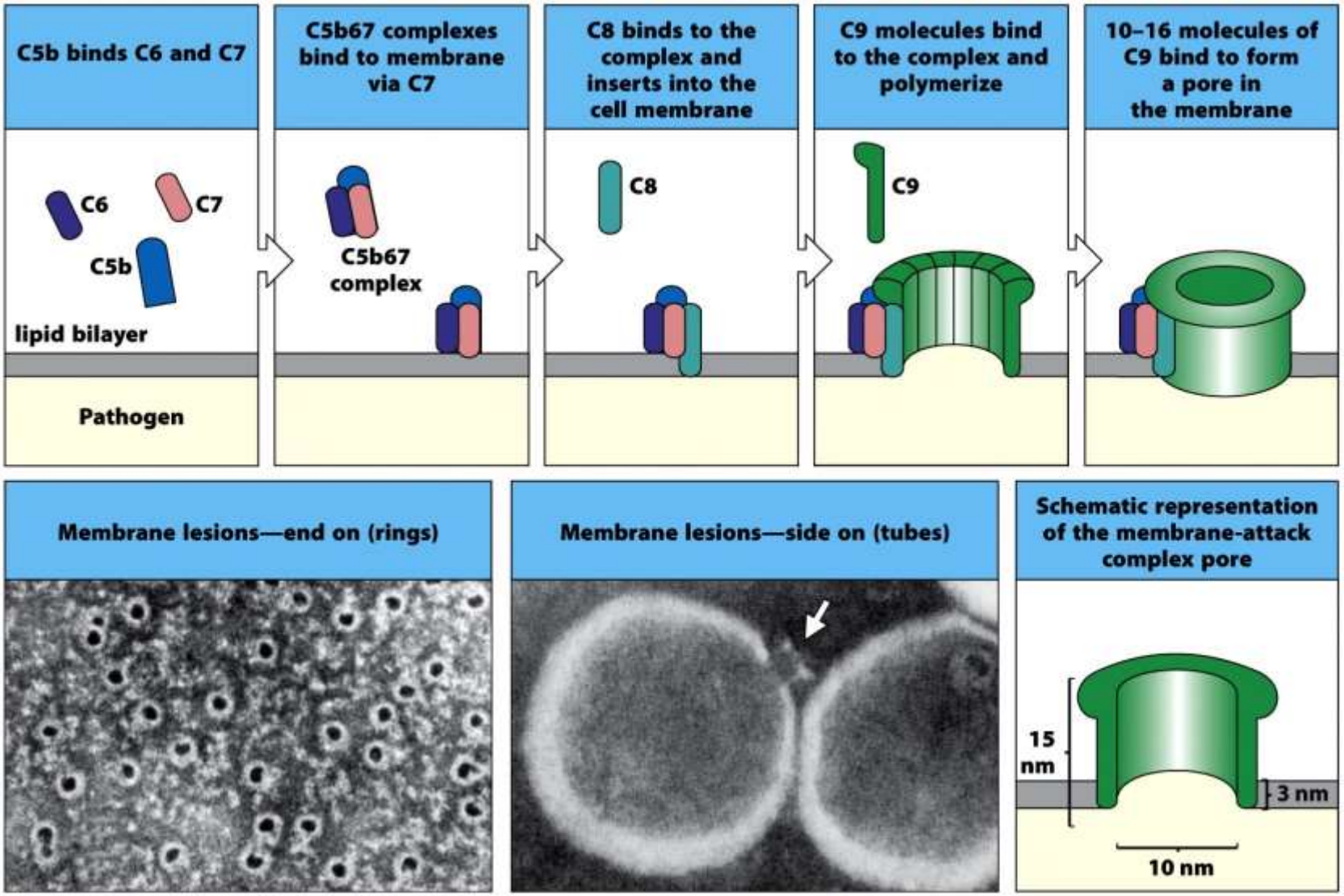
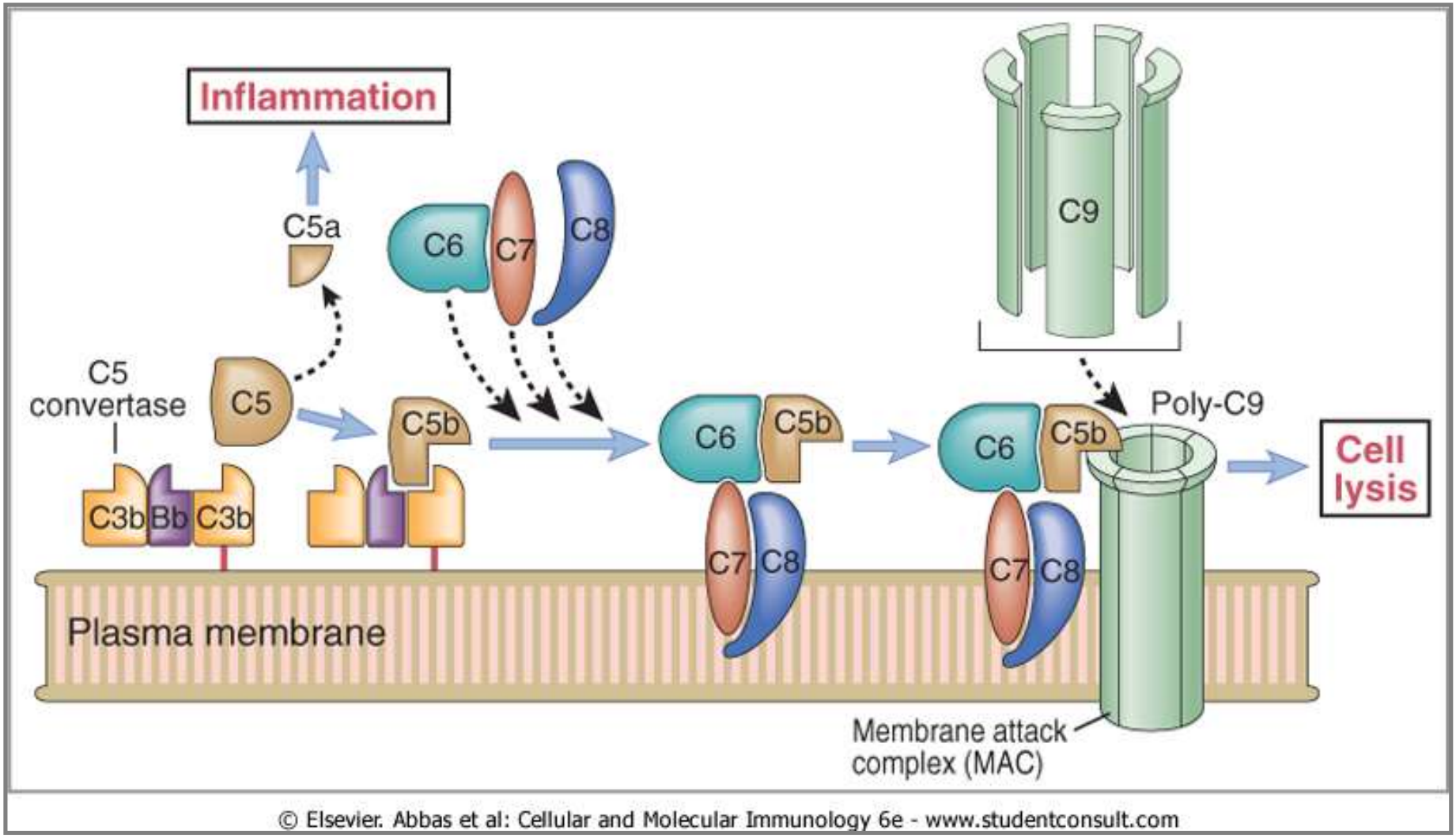


Figure 2-41 Immunobiology, 7ed. (© Garland Science 2008)



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3. Complement mediated inflammation

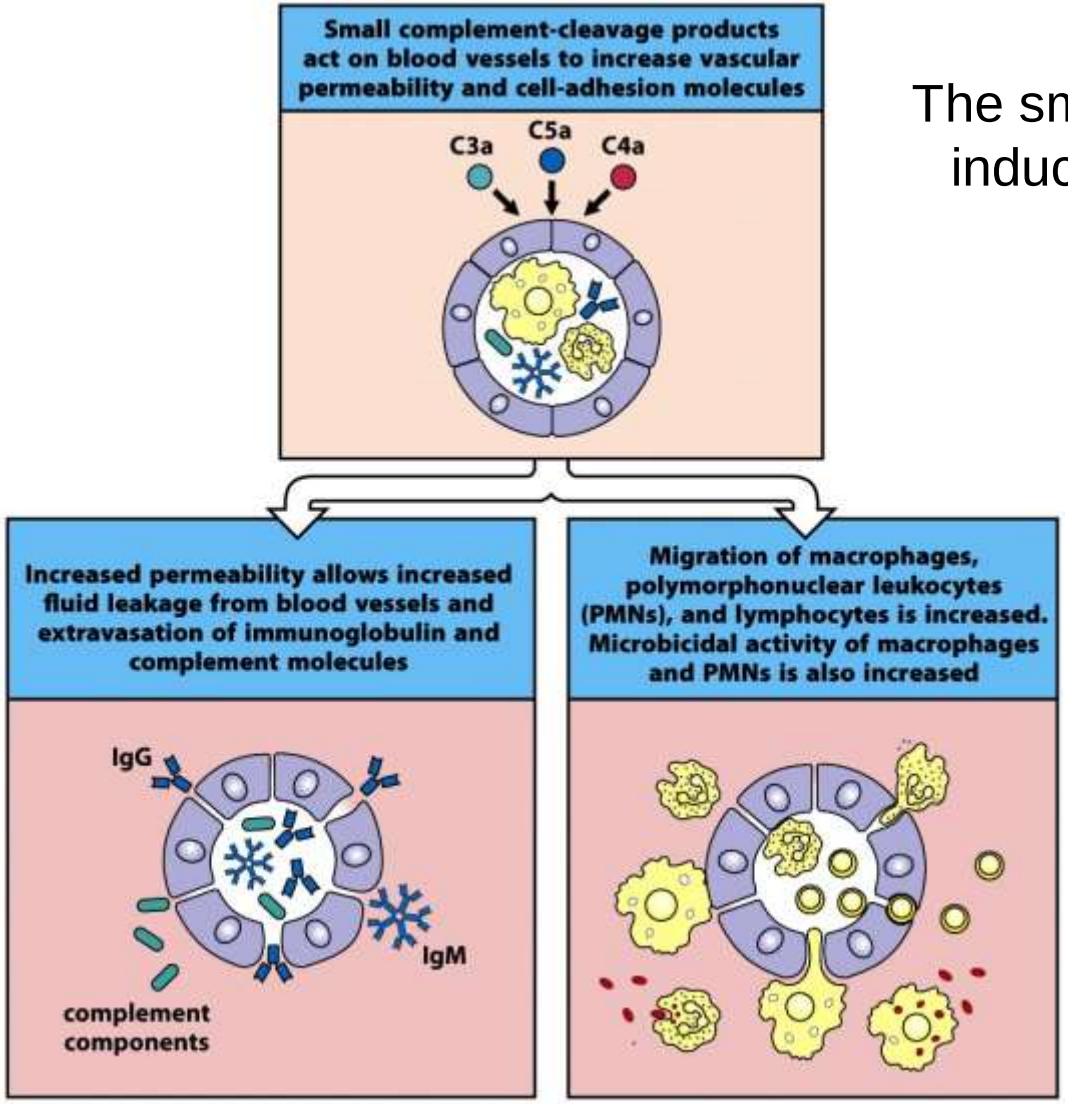


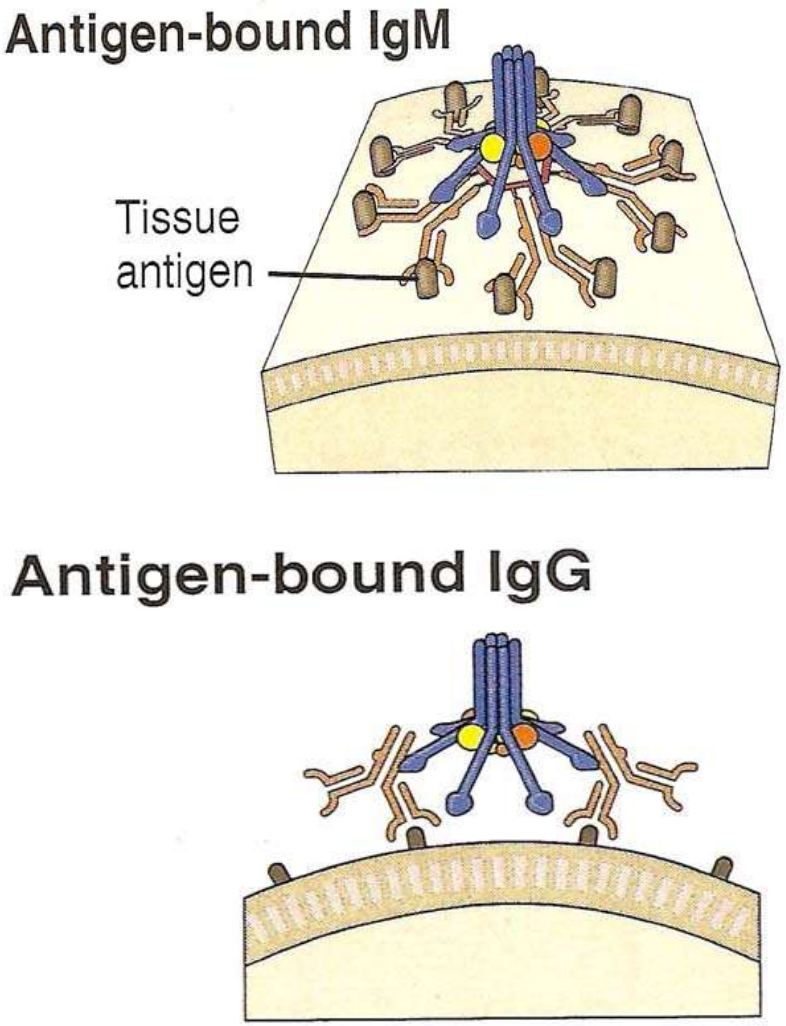
Figure 2-39 Immunobiology, 7ed. (© Garland Science 2008)

The small fragments (C3a, C4a, C5a) induce inflammation, they are also called anaphylatoxins

Anaphylactic shock can be caused by systemic distribution of anaphylatoxins and mast cell degranulation

Which antibodies can activate complements?

- IgM and IgG



Antibodies and their functional activities

Functional activity	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	-	++	++	++	++	++	-
Opsonization	+	-	+++	*	++	+	+	-
Sensitization for killing by NK cells	-	-	++	-	++	-	-	-
Sensitization of mast cells	-	-	+	-	+	-	-	+++
Activates complement system	+++	-	++	+	+++	-	+	-

ADCC
figure 9.34

Figure 9.35

Opsonin in 30% of Caucasians (appropriate Fc receptor)

THANK YOU

ANY QUESTIONS??

CYTOKINES

Prof. Dr. Hazem Aqel AL-Rimawi

Lecture 7

This presentation is given by Mohamed Alzobi

The Objectives:

- Define what a cytokine is?
- Describe the general function of cytokines.
- Explain the role of Interleukin-1 in mediating the immune response.
- Describe the effect of Interleukin -2 on target cells.

Definition of Cytokines

SIGNALS

Cytokines: are a group of **small proteins** secreted by leukocytes as well as a variety of other cells in the body in response to stimuli.

Cytokine release is a mechanism by which leukocytes communicate with one another.

Cytokines modulate the functional activities of individual cells and tissues both under normal and pathologic conditions

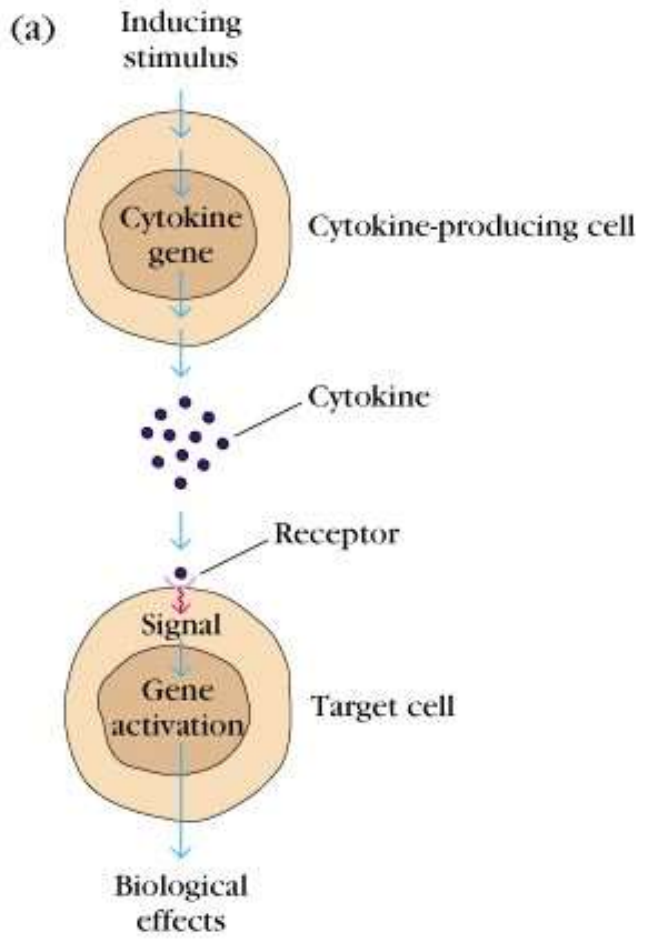
Cytokines mediate and regulate the intensity and duration of immune responses and inflammatory reactions.

could initiate and terminate

Almost all cells secrete at least a few cytokines.

The main function of cytokines

1. Stimulation
2. Inhibition
3. Proliferation
4. Differentiation
5. Cell death
6. Chemoattraction recruiting



Properties of cytokines:

1. Most cytokines are low molecular weight polypeptides or glycoproteins (8~80 KD), and most of them are monomers.

2. Cytokines are secreted by activated cells.

3. One kind of cytokines can be produced by different cells.

4. One kind of cells can secrete different cytokines.

5. Cytokines initiate their actions by binding to specific membrane receptors on target cells

Properties of cytokines con't:

6. Cytokines act on target cells through 3 major routes: Autocrine, Paracrine or Endocrine

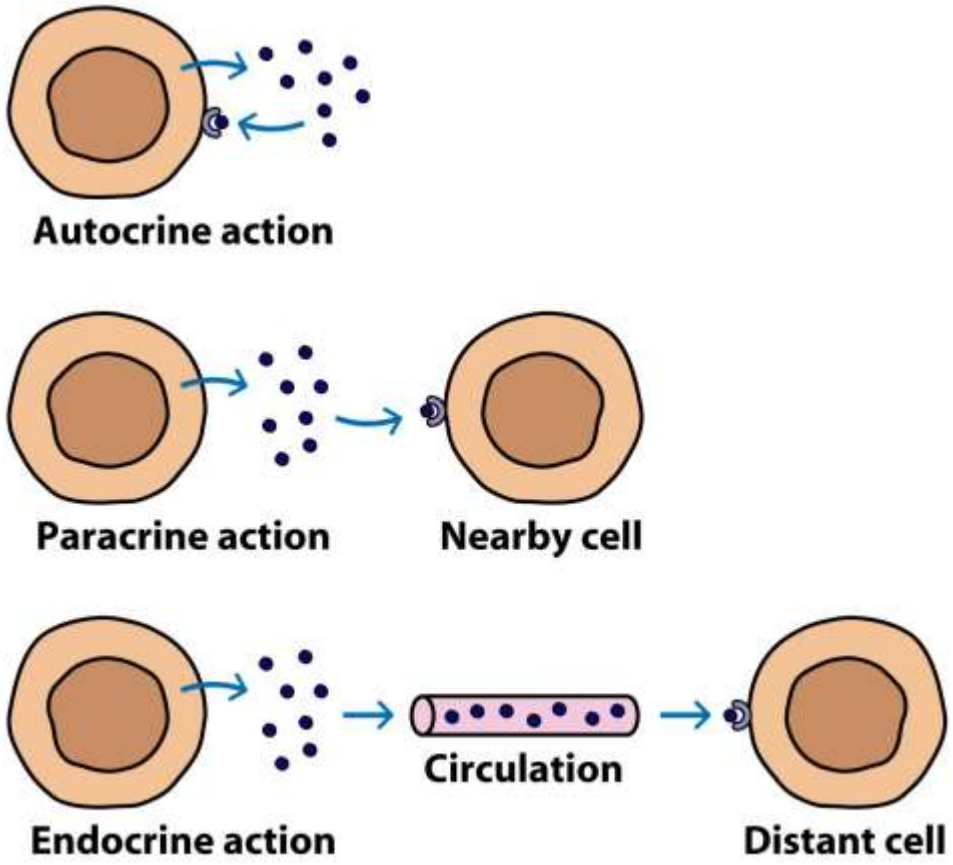


Figure 12-1b
Kuby IMMUNOLOGY, Sixth Edition
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Self such as IL-2 on T cells – clonal expansion

Nearby such as T cell cytokines act on B cells - isotype switching

Distance such as IL-1 & TNF and fever

Properties of cytokines con't:

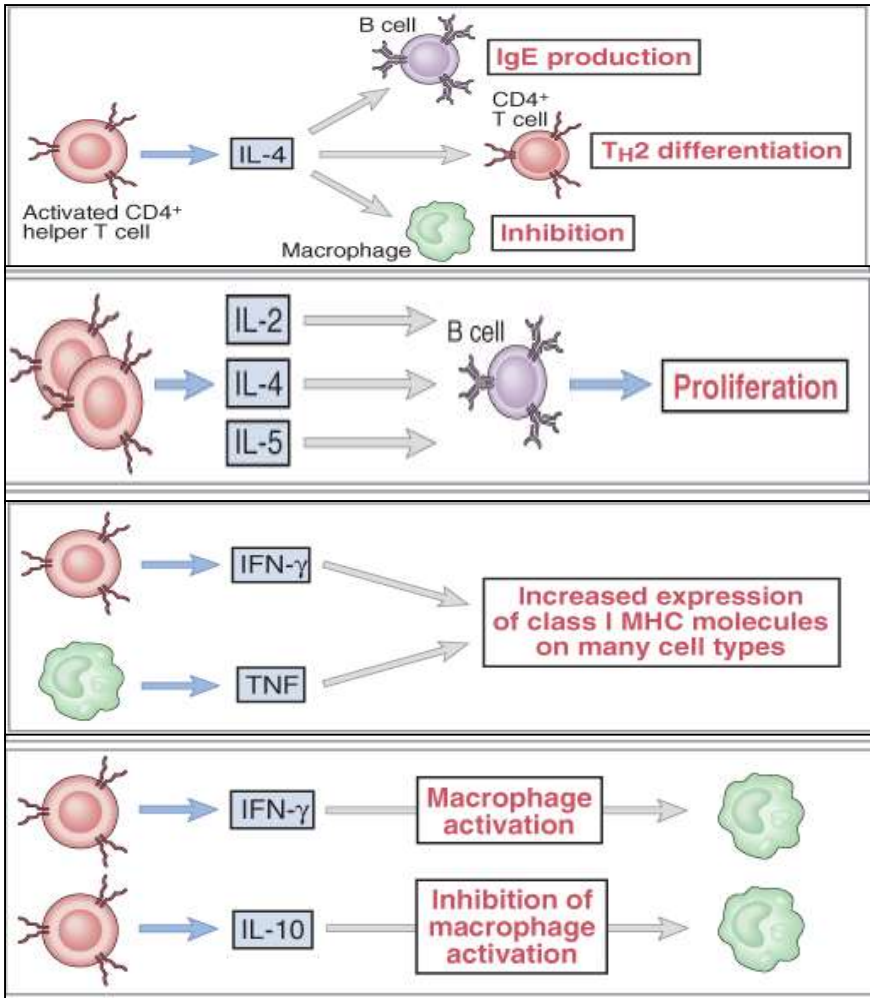
7. The effects of cytokines are:
Pleiotropism, Redundant, Synergy or Antagonism

Pleiotropism the ability of one cytokine having multiple effects on diverse cell types.

Redundant the property of multiple cytokines having the same or overlapping functional effects.

Synergy the property of two or more cytokines having greater effect than alone.

Antagonism the ability of one cytokine inhibiting the action of another



Classification of Cytokines

- Interleukin (IL) especially in bacterial infection
- Interferon (IFN) especially in viral infections and in tumors
- Tumor necrosis factor (TNF)
- Colony stimulating factor (CSF)
- Chemokine
- Transforming growth factor (TGF)

Interleukins (ILs): are cytokines secreted by leukocytes that have the ability to act as signal molecules between different population of leukocytes.

For example IL-1 and IL-2.

Hot T- Bone stEAK

Interferons (IFN): A group of glycoproteins that are produced by cells usually following viral infections or tumors. They also play an important role in immune regulation.

Including:

- IFN-α
- IFN-β

→ by virally infected cell

- IFN-γ → secreted by Th1 cells (adaptive)

Tumor Necrosis Factor (TNF): were originally thought of as selective antitumor agents, but are now known to have a multiplicity of actions.

Including:

- TNF-α
- TNF-β

Colony-stimulating factors (CSF): are cytokines that stimulate proliferation or differentiation of pluripotent hematopoietic stem cell and different progenitors.

Including:

- Multi-CSF (IL-3)
- Granulocyte macrophage-CSF(GM-CSF)
- Monocyte-CSF(M-CSF)
- Granulocyte-CSF(G-CSF)
- Stem cell factor(SCF)
- Erythropoietin(EPO)

Chemokines: are cytokines that attracts or recruits cells such as granulocytes, lymphocytes or monocytes from the blood to the sites of inflammation.

Including:

CXC chemokines(αsubgroup):IL-8

CC chemokines(β subgroup):MCP-1

C chemokines(γ subgroup)

CX_3C chemokines(δ subgroup)

Transforming growth factor: are cytokines which stimulate the growth of their target cells.

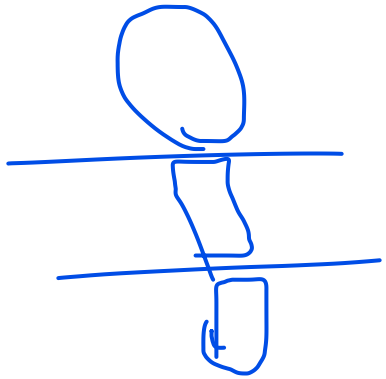
Including:

- Transforming growth factor-β (TGF- β)
- Epithelia growth factor (EGF)
- Vascular endothelia cell growth factor (VEGF)
- Fibroblastic growth factor (FGF)

Cytokine Receptors:

Cytokine receptors are membrane binding receptors, consisting of:

- an extra-cellular region
- a trans-membrane region
- a cytoplasmic region



Examples Cytokine Receptors:

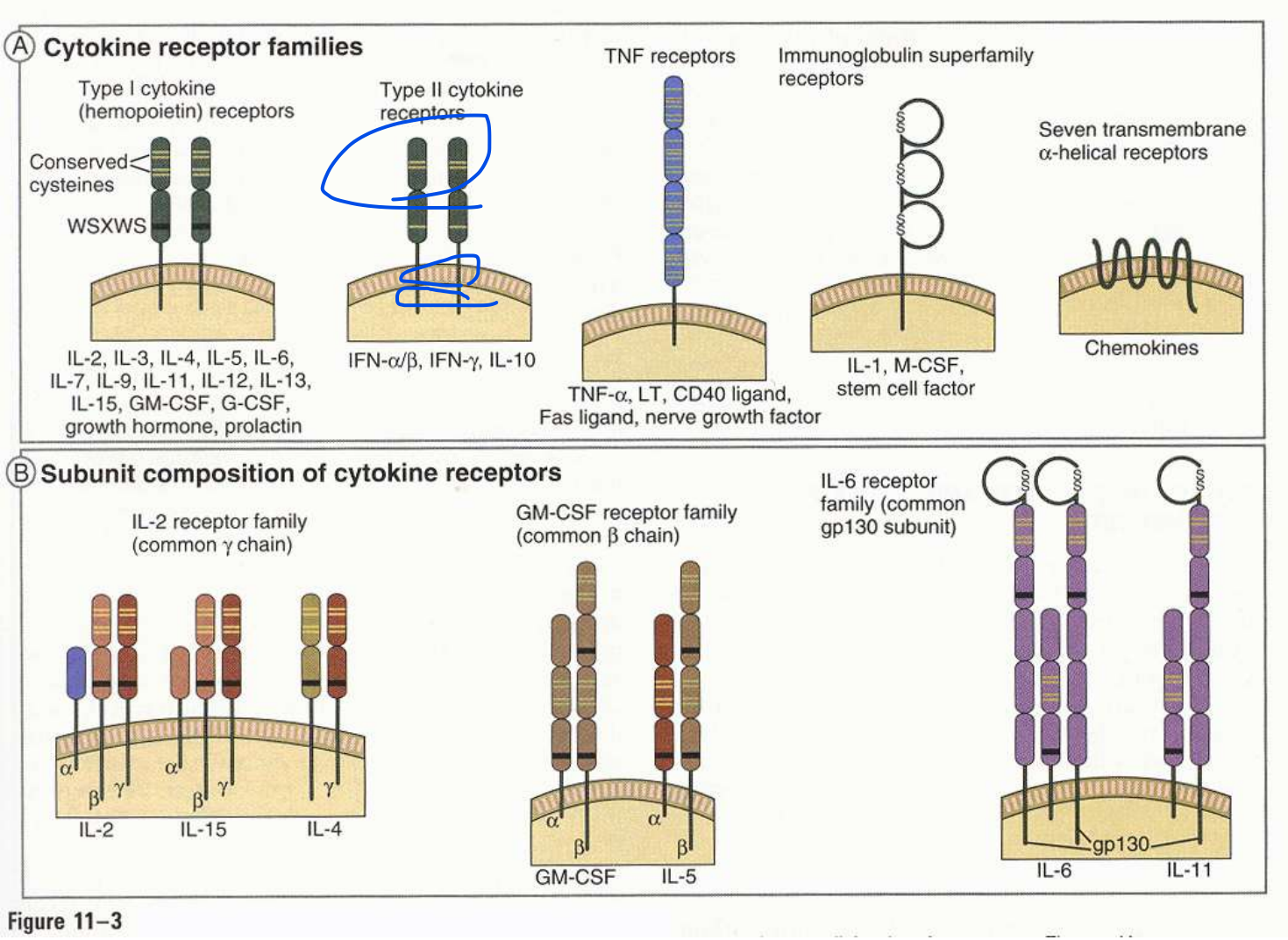


Figure 11–3

Interleukin-1 (IL-1)

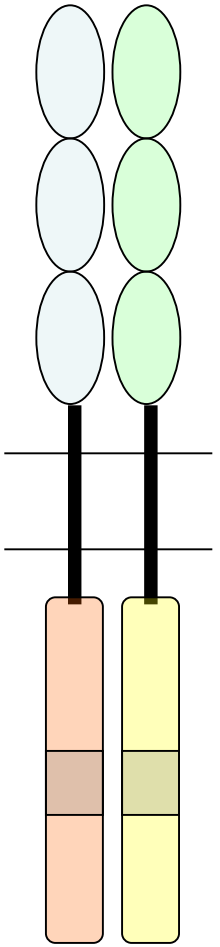
-IL-1 is mainly secreted by macrophages and keratinocytes

-Has potent inflammatory effects

-IL-1 induces TNF, IL-6 as well as Inflammatory mediators from various cells

-IL-1 is an endogenous pyrogen (fever inducer).

-Important in innate immunity



RI

Interleukin-2 (IL-2)

- IL-2 is secreted primarily by CD4+ T helper lymphocytes

- IL-2 is a central regulator of immune responses

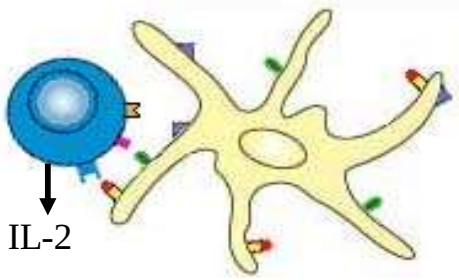
- IL-2 act as an autocrine factor on T_H cells by which IL-2 is released by T_H cells to activate T_H cells and induce the release of IL-2 and high affinity receptors for IL-2 and, subsequently, clonal expansion of antigen-specific T cells.

- IL-2 also acts as a paracrine factor, influencing the activity of other cells.

- IL-2 also augments the cytolytic activity of natural killer (NK) cells

- IL-2 induces with IL-4 B cell proliferation

IL-2 is key to antigen-induced T cell proliferation and differentiation



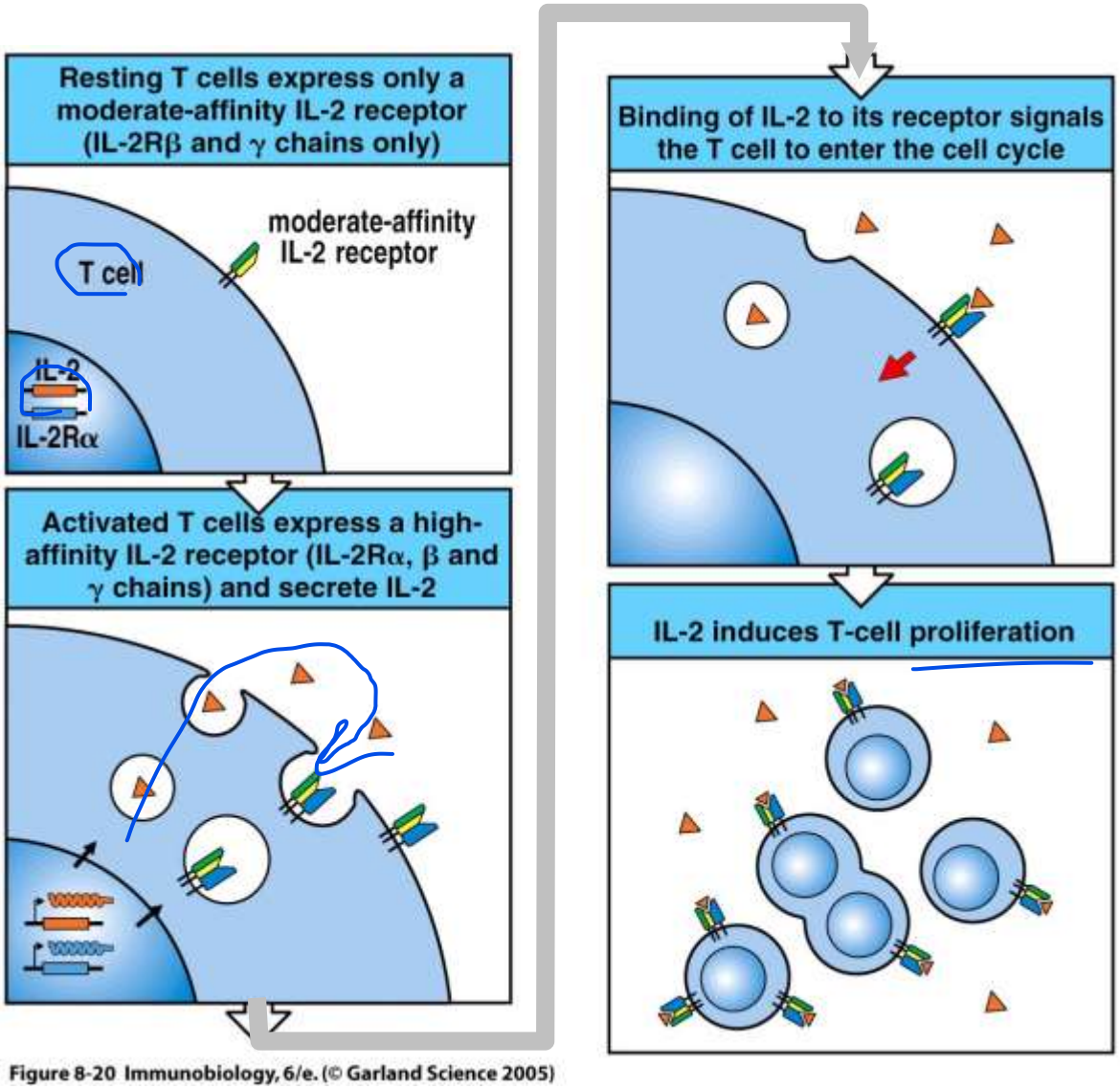


Figure 8-20 Immunobiology, 6/e. (© Garland Science 2005)

Autocrine stimulation (a cell makes a protein that is secreted and stimulate the cell that made it)

Cells divide 2-3 times per day for 4 or 5 day ($2^{12} = 4096$)

IL-2 used to be called "T cell growth factor"

Cytokines by function

CYTOKINES THAT MEDIATE AND REGULATE INNATE IMMUNITY:

IL-1, IL- 6, IL-10, IL-12 , and more

Interferons-α and Interferone-β

Tumor necrosis factor-α (TNF-α)

Chemokines

CYTOKINES THAT MEDIATE AND REGULATE ADAPTIVE IMMUNITY:

IL-2, IL-4, IL-5, IL-13, and more

Interferon-γ

Tumor necrosis factor-β (TNF-β)

Chemokines

Functional subsets of CD4 cells based on cytokine profile.

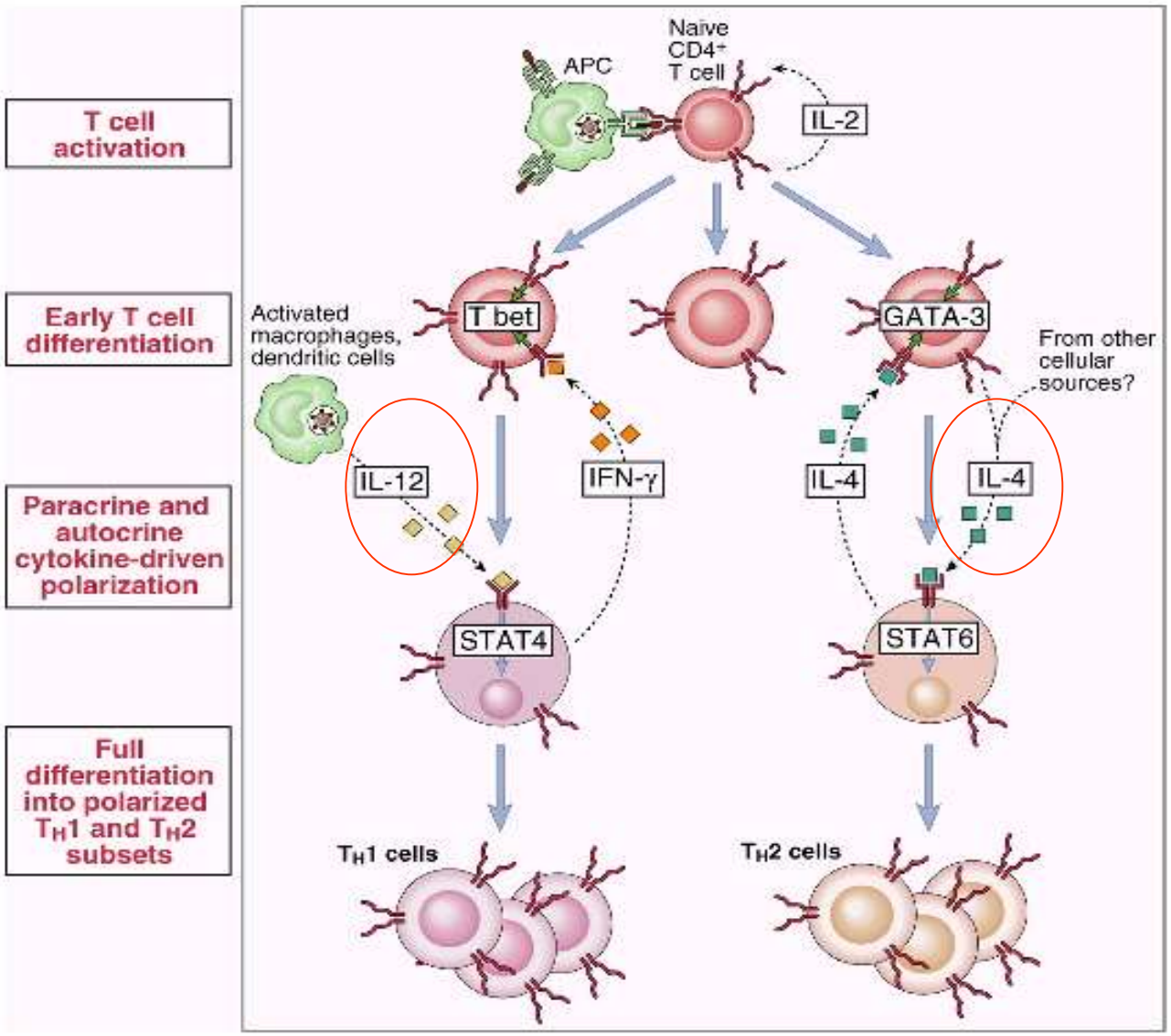
- TH1 release= IL-2, IFN-γ (promote cell mediated immunity)

- TH2 release= IL- 2, IL-3, IL-4 (promote humoral immunity)

- Subset control:
  - TH1 polarization is promoted by IL-12 and IFN-γ while IL-4 & IL-10 inhibit TH1 polarization.
  - TH2 polarization is promoted by IL-4 while IFN-γ inhibitsTH2 polarization.



IL4 makes Th2, while IL12 makes Th1 cells



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THANK YOU

ANY QUESTIONS??

MHC and Antigen Presentation

Prof. Dr. Hazem Aqel AL-Rimawi

Lecture 8

presented by: Mohamed Alzobi, immunology final course

The Objectives

- Compare the structure and expression of MHC class I and II (proteins).
- Describe the role MHC in regulating the immune response.
- Discuss the source and types of antigen processed by class I and II molecules.
- List professional antigen presenting cells.
- Discuss the role of the T helper cell in both cell-mediated and humoral immunity.

endogenous Vs exogenous
Th Vs Tc

What is Major Histocompatability Complex (MHC)?

the problem is that some microbes (wild-type viruses) prevent the expression of MHC, from here the idea of vaccines is derived, we introduce an attenuated virus so it could not prevent the expression of MHC

MHC is a set of cell surface molecules encoded by a large genetic complex with multiple loci.

The MHC loci encode 2 major classes of membrane-bound glycoprotiens:

1. MHC class I
2. MHC class II

MHC function:

- The major function of MHC is to bind to “processed antigen peptides” displayed on the cell surface to be recognized by specific T lymphocytes to initiate an immune response.

  cells capable of destructing the infected cell are Tc and NK, the difference is that NK does not need antigen expression on MHC and there is no memory

- Also MHC determines compatibility of donors for organ transplant,

matching is required for transplant

MHC Structure

determine paternity

MHC class I:

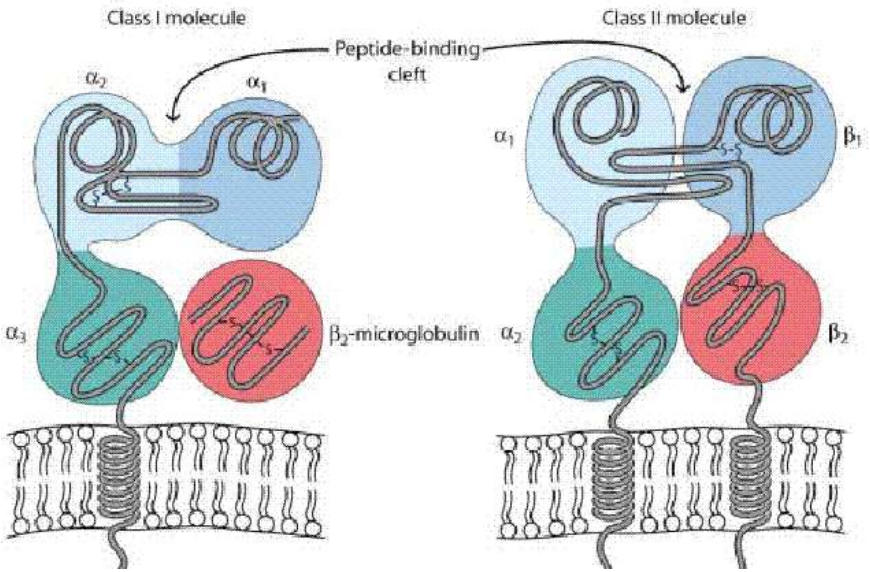
Consist of 4 domains (α1, α2, α3 and β2-microglobuline)

MHC class II:

Consist of 4 domains (α1, α2, β1and β2)

cleft: where antigen is found

MHC class I



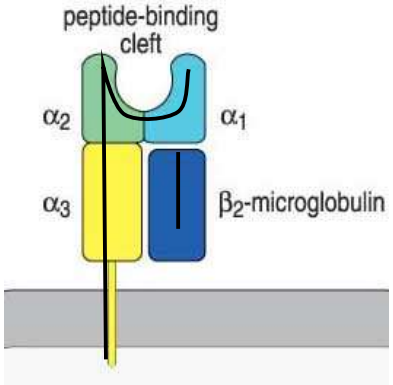
MHC class II

MHC Expression

- MHC class I:

Is expressed on all cell types

And is recognized by CD8+ cytotoxic T cells (CTL).

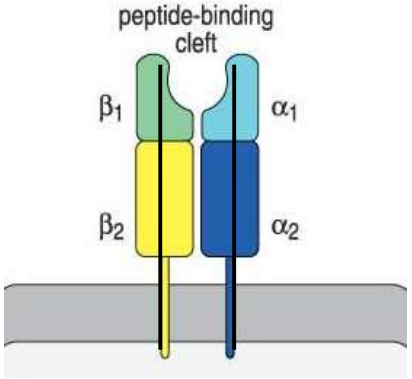


- MHC class II:

Is only expressed on antigen presenting cells

(Dendritic cells, Macrophages, B lymphocytes)

And is recognized by CD4+ helper T cells (Th).



Human Leukocyte Antigen (HLA)

The Major Histocompatibility Complex in human is known as the human leukocyte antigen (HLA). MHC class I in human is known as HLA class I and MHC class II is known as HLA class II

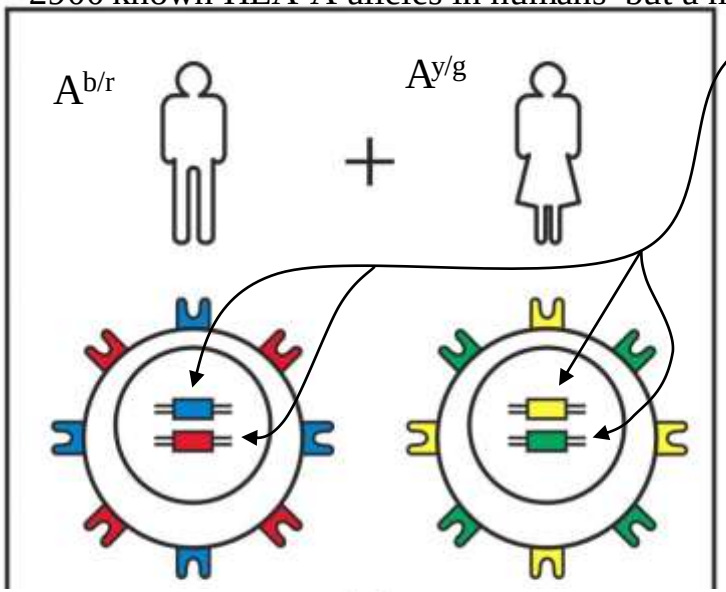
HLA class I and class II are polygenic (several loci encoding products with essentially the same function)

- HLA class I: HLA-A, HLA-B and HLA-C
- HLA class II: HLA-DR, HLA-DP and HLA-DQ

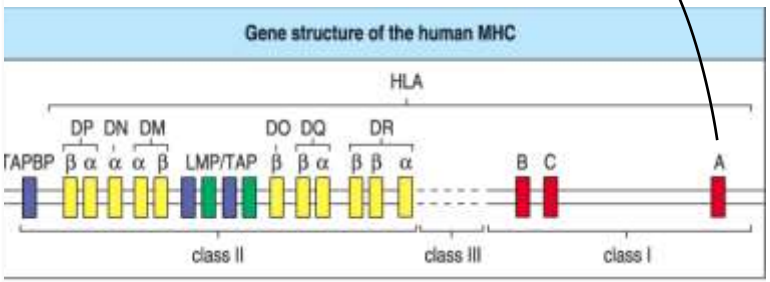
HLA class I and class II are polymorphic (variability of alleles in the species)

There are > 2000 HLA-A alleles , > 3000 HLA-B alleles and > 2000 HLA-C alleles. For example HLA-A2, HLA-A26 and HLA-B50

2900 known HLA-A alleles in humans but a maximum of 2 per person



for example, here is HLA class I A gene expression



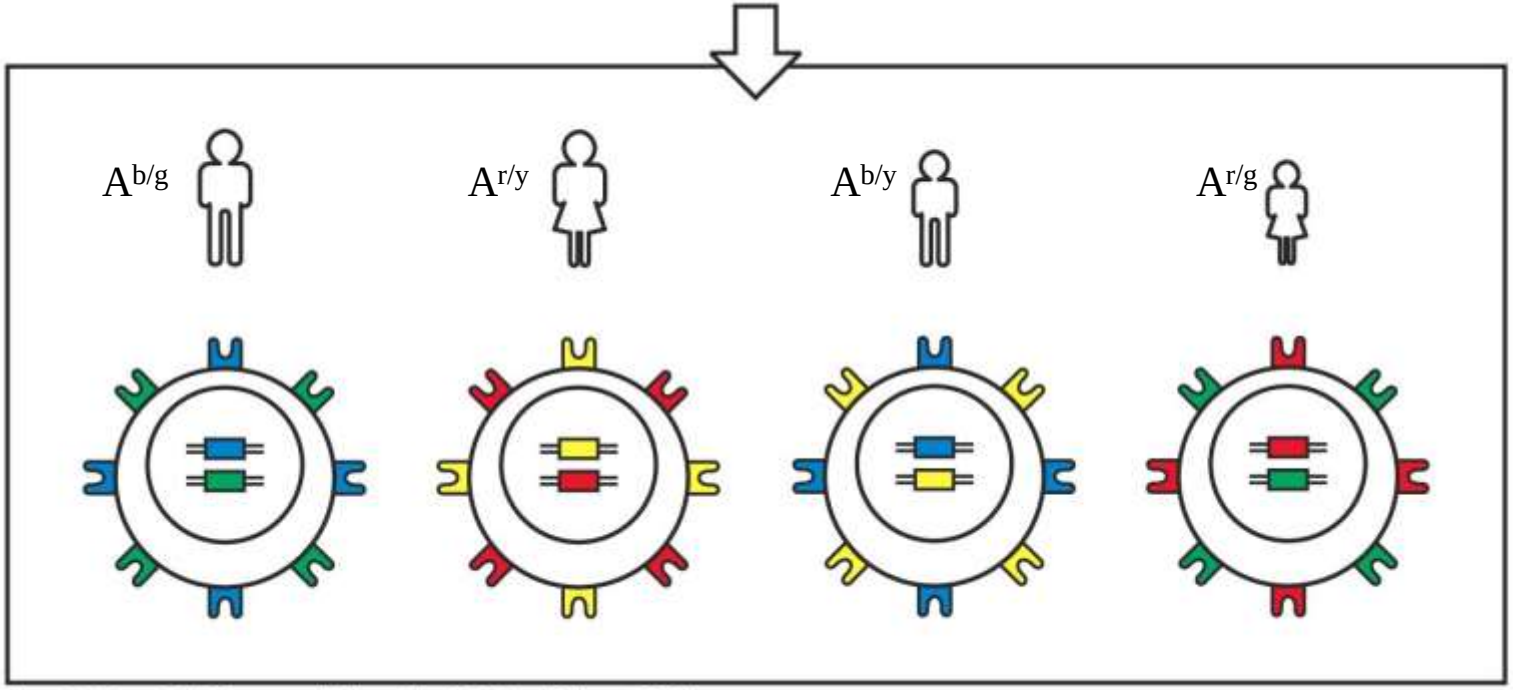


Figure 5-14 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Although there are thousands of combinations in the population*, there are only 4 combinations among siblings

What does Antigen Capture Mean?

- It means getting the pathogen and its products inside the cell

- There are different methods of capturing an antigen leading to its appearance either in the cytosol or in a vesicle.

What does Antigen Processing Mean?

- Once a pathogen is inside a cell it needs to be degraded into protein peptides in a sequence event and associate with an MHC molecule.

What does Antigen Presentation Mean?

- Once an antigen is degraded it needs to be transported to the surface of the cell and displayed within a cleft of an MHC molecule in order to be recognized by a T lymphocyte.

Which cells are antigen presenting cells (APC) ?

A variety of cells can function as APC, their distinguishing features is:

- Their ability to express MHC II
- To deliver co-stimulatory signals.

Including: Dendritic cells

Macrophages

B cells

What are the types of antigens?

Endogenous antigens are degraded into peptides within the cytosol by proteasomes and assembled with MHC class I.

For example: viruses and tumors.

Exogenous antigens are internalized and degraded within endocytic compartments and subsequently assembeled with MHC class II.

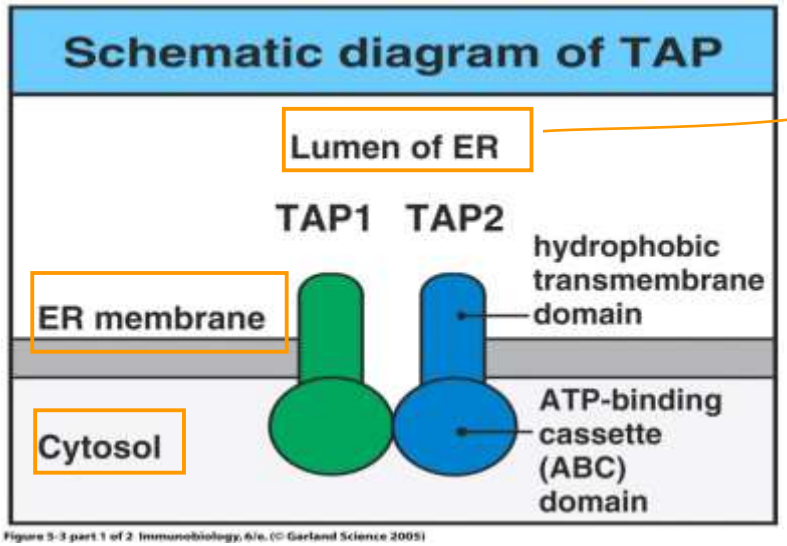
For example: bacteria

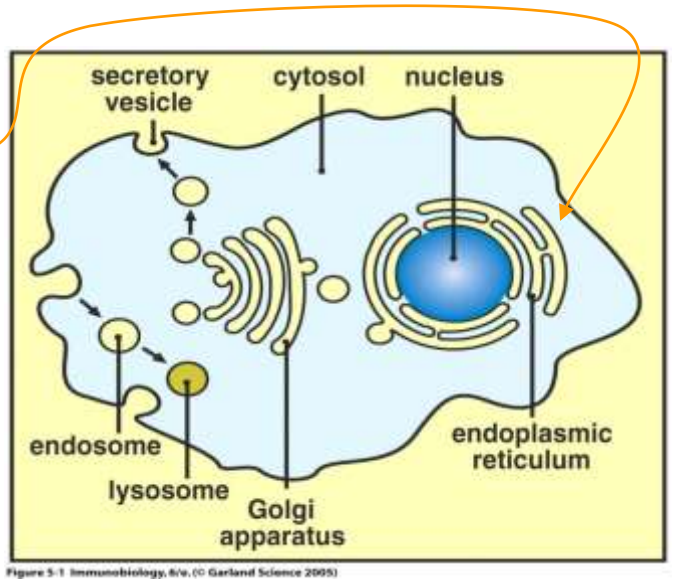
Processing and presenting endogenous antigens

•Endogenous antigens (made from proteins) are degraded into peptides within the cytosol by proteasomes.

•Then they are pumped from the cytosol into the endoplasmic reticulum (ER) by **t**ransporters **a**ssociated with antigen **p**rocessing (**TAP**) molecules,

•Then they get loaded into MHC class I and transported to the surface of the cell.





Processing and presenting endogenous antigens cont'd

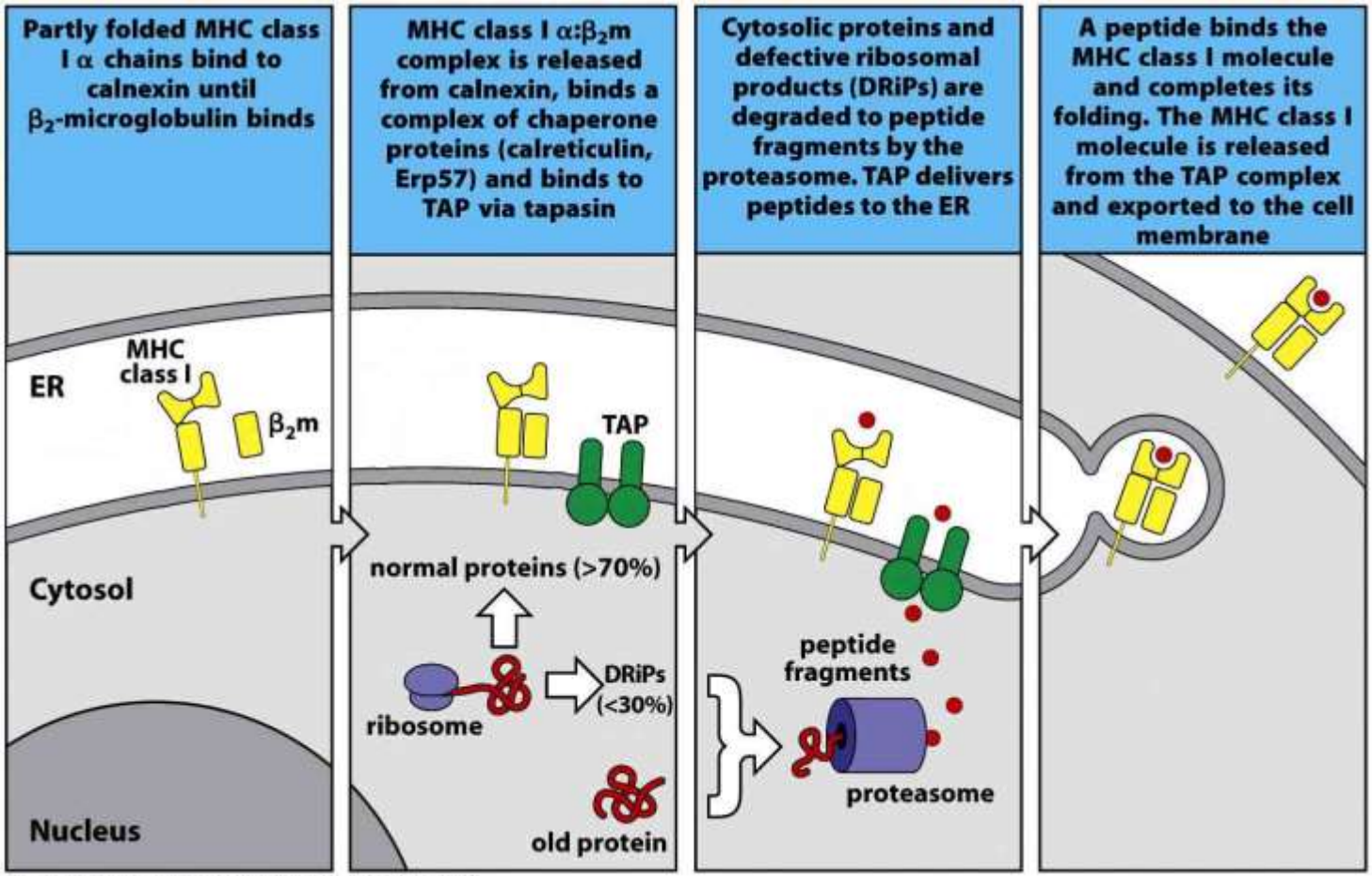


Figure 5-5 Immunobiology, 7ed. (© Garland Science 2008)

Which cells do this? ALL cells

Processing and presenting exogenous antigens

- Exogenous antigens are taken up from the outside of the cell into vesicles and degraded into peptides by the acidity of these vesicles
- The vesicles then fuse with vesicles containing MHC class II molecules
- A small molecule known as CLIP blocks the binding site of the MHC molecule, until HLA-DM binds to the MHC and release the CLIP
- The degraded peptides then bind to the MHC and get transported to the cell surface

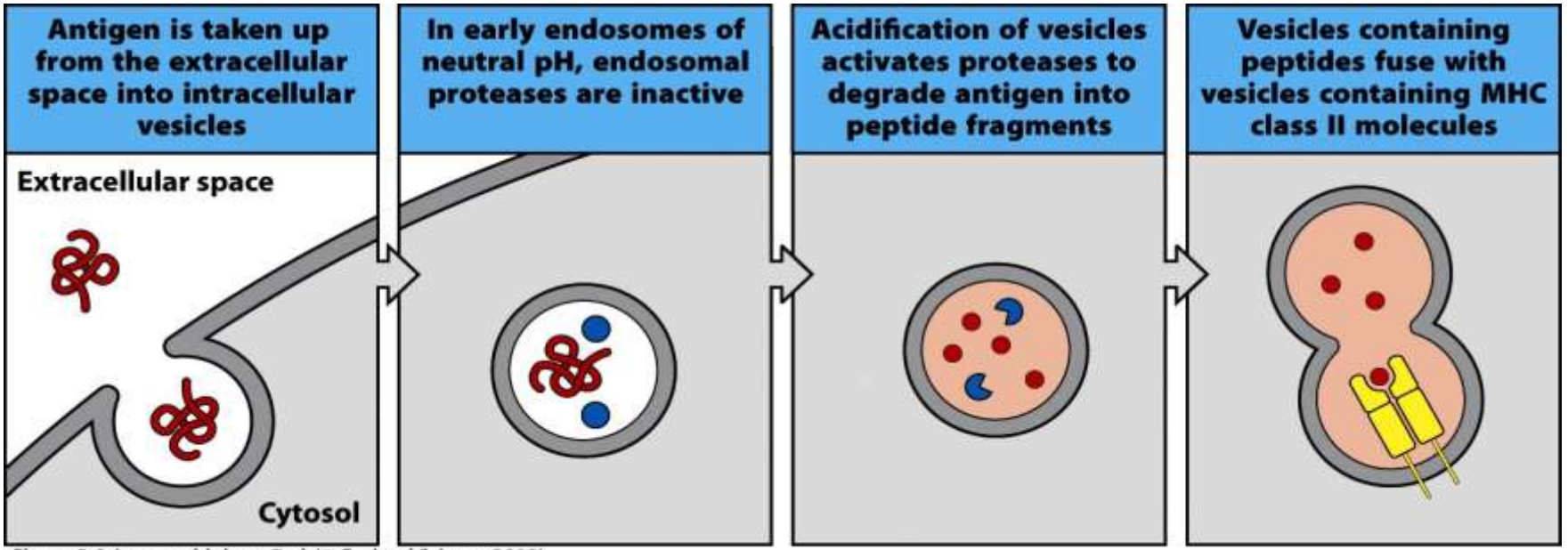


Figure 5-8 Immunobiology, 7ed. (© Garland Science 2008)

Processing and presenting <u>exogenous</u> antigens cont'd

NO TAP

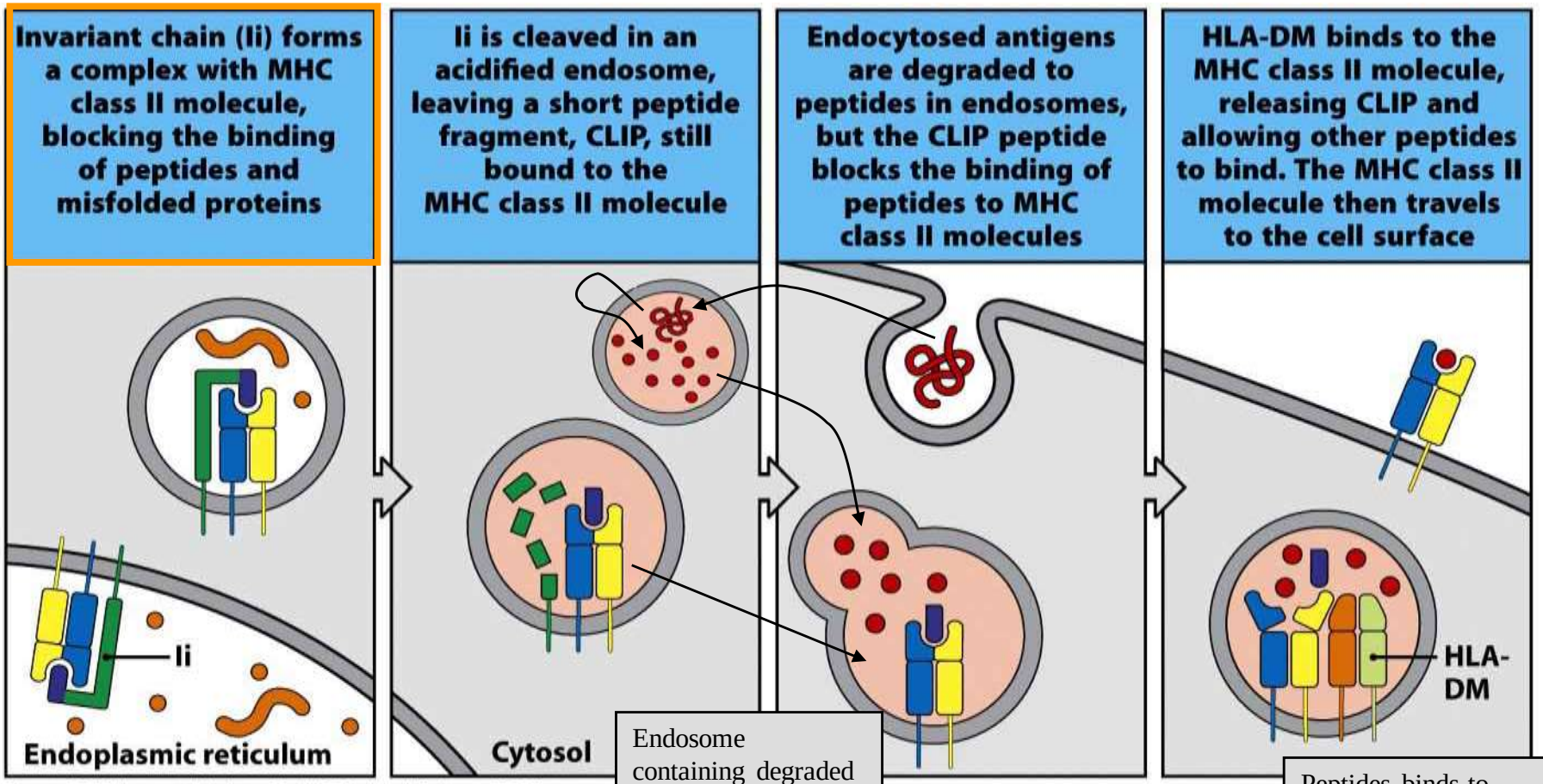


Figure 5-11 Immunobiology, 7ed. (© Garland Science 2008)

Endosome containing degraded protein (i.e., peptides) fuses with endosome containing MHC class II

Peptides binds to MHC class II. MHC class II + peptide are displayed on the cell surface

Which cells do this? APC

MHC I and II associate with peptides that have been processed in different intracellular compartments.

- **MHC class I** presents processed proteins* that were in the **cytosol.**

- **MHC class II** presents processed proteins* that were in **endocytic vesicles**.

- **MHC class I** presented-antigens are recognized by **$CD8^+$ T cells (CTL).**

- **MHC class II** presented-antigens are recognized by **$CD4^+$ T cells (T_H).**

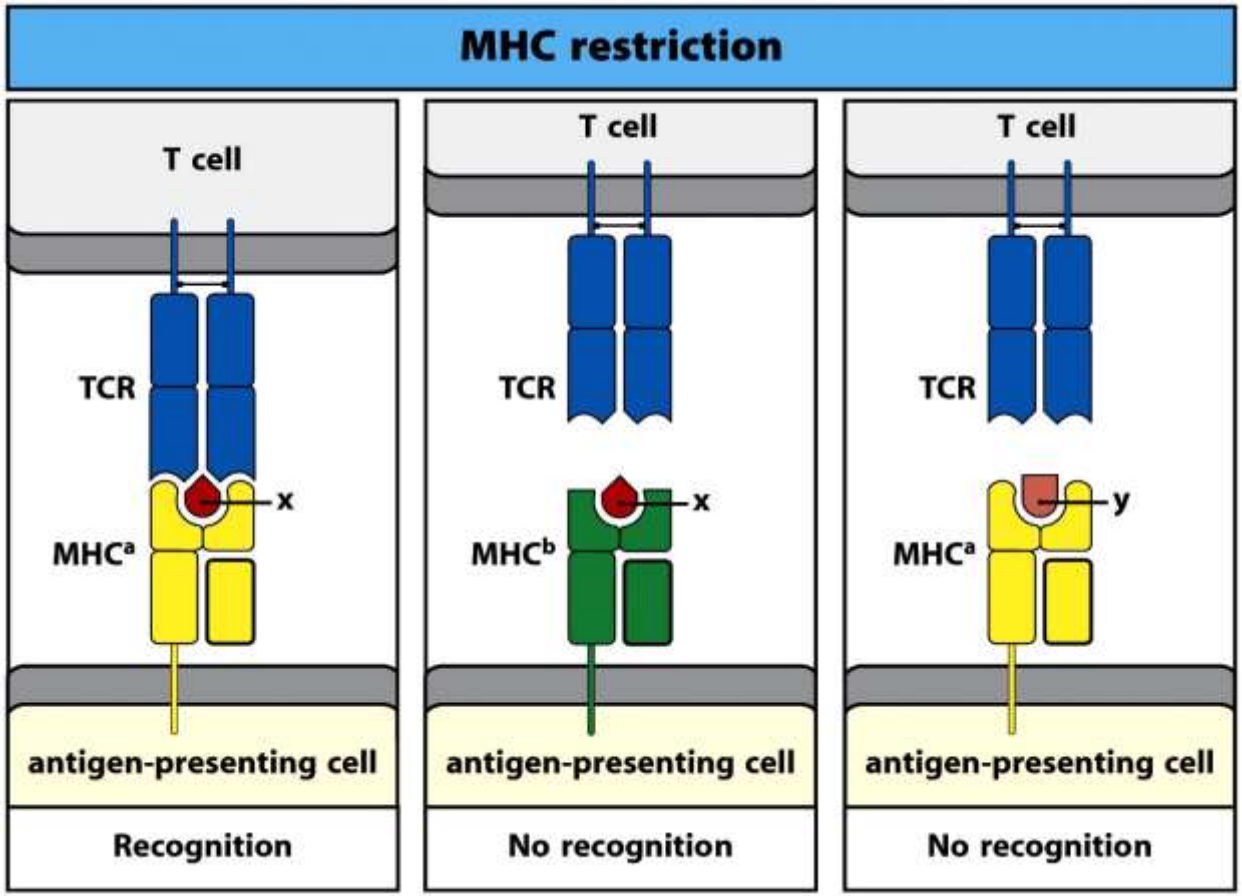


Figure 5-20 Immunobiology, 7ed. (© Garland Science 2008)

T cells only recognize Ag in context of MHC

T cells are restricted to recognizing Ag in the context of self MHC

MHC polymorphism affects which antigens can be presented and which T cells can recognize antigen

THANK YOU

ANY QUESTIONS??