

Biochemistry of the immune system

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Immunity = protection

- The immune system – integrated body system of organs, tissues, cells, and products that interact with many different pathogens.
- Specificity of immune response – ability of discriminate and recognition between “self” and “non-self”.
- Ability to „remember“ – imprinting of some information about organisms previously encountered.

Antigen

A substance that can induce an immune response

Antibody

A protein produced as a result of introduction of antigen

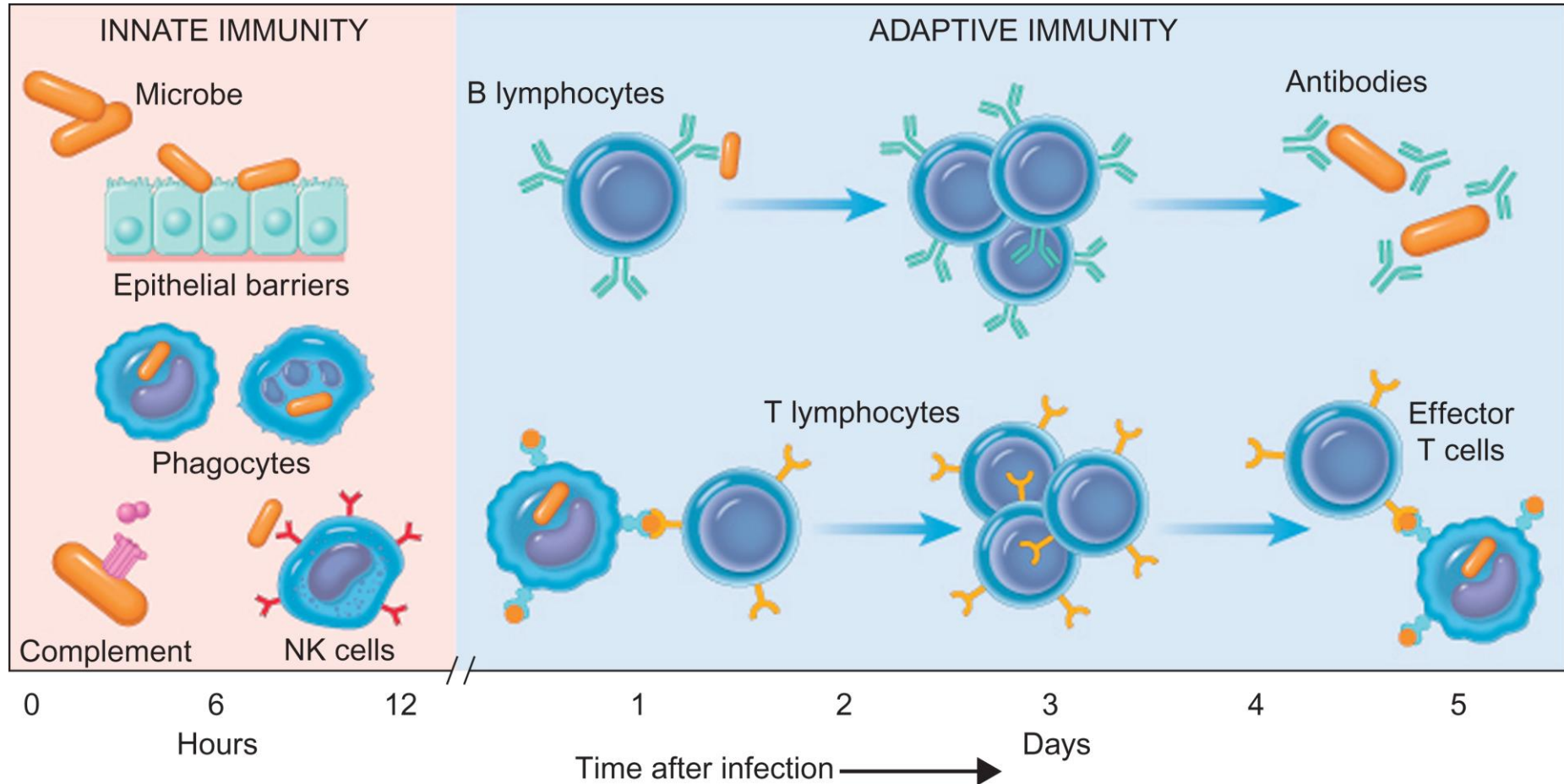
Antibody has the ability to combine with the antigen that stimulated its production.

What generates the immune response?

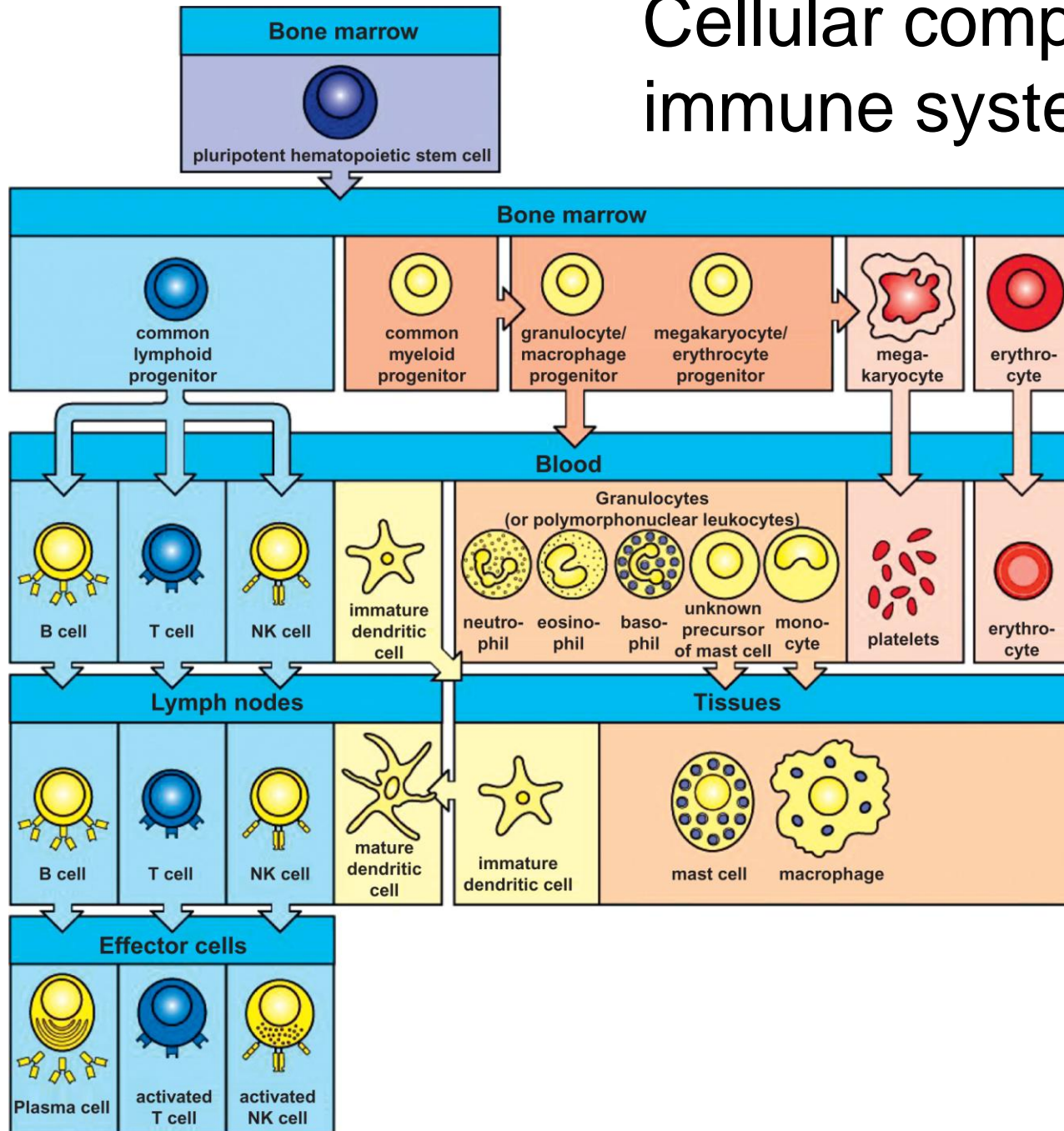
Immune system beginning of the external surface – mechanical and chemical barrier:

- skin – low pH , antimicrobial peptides (β -defensins)
- epithelium of the respiratory and gastrointestinal tract
- tears, saliva, breast milk – enzyme lysozyme and phospholipase A
- stomach – gastric acid and proteases
- cells – neutrophils and macrophages – phagocytosis of potential pathogens

The innate and adaptive immune response



Cellular components of immune system



Cellular components of immune system

– lymphoid cells

- *B cells* (B lymphocytes) – recognition of antigen, antibody secreted plasma cells, act as antigen presenting cells (APC). Some B cells differentiate into memory cells

Characteristic receptors:

express CD (cluster of differentiation) molecules, antigen receptors CD1, CD2 etc., surface IgM, IgD MHC Class II, complement receptors CD3, CD19, CD20, CD21 etc.

- *T cell* (T lymphocytes) – regulation of adaptive immune system, play a central role in initiation, propagation, and control of antigen-specific immune response
 - recognize a "non-self" target (a pathogen), only after antigens (small fragments of the pathogen) have been processed and presented in combination with a "self" receptor - a major histocompatibility system (MHC) molecule.

Cellular components of immune system

– lymphoid cells

2 major subtypes (subclasses) of T cells:

- *T helper cell* - regulate both the innate and adaptive immune responses, release necessary cytokines for cells stimulation and differentiation
- *cytotoxic T lymphocytes* and *natural killer cells* (NK cells)
 - cytotoxic T cells are cytotoxic against tumor cells, virus infected cells. Produce $\text{TNF}\alpha$ and $\text{TNF}\beta$, recognize antigen/MHC Class I
 - NK cells are granular lymphocytes, destroy tumor cells, virus infected cells

Cellular components of immune system

- myeloid cells

Neutrophils – first cells recruit into the site of inflammation, dominant phagocytic cells, use respiratory burst to kill cells, are attracted to site of complement activation by C5a (chemoattractive peptide from complement component C5)

Basophils – blood „analogues“ of tissue mast cells, stimulated by complement C3

Mast cells – resident in tissues, tissue granulocytes, produce cytokines, release heparin and histamine

Eosinophils – attack parasites too large for phagocytosis, adhere to foreign organisms via C3b, release enzymes, use respiratory burst

Cellular components of immune system

Monocytes

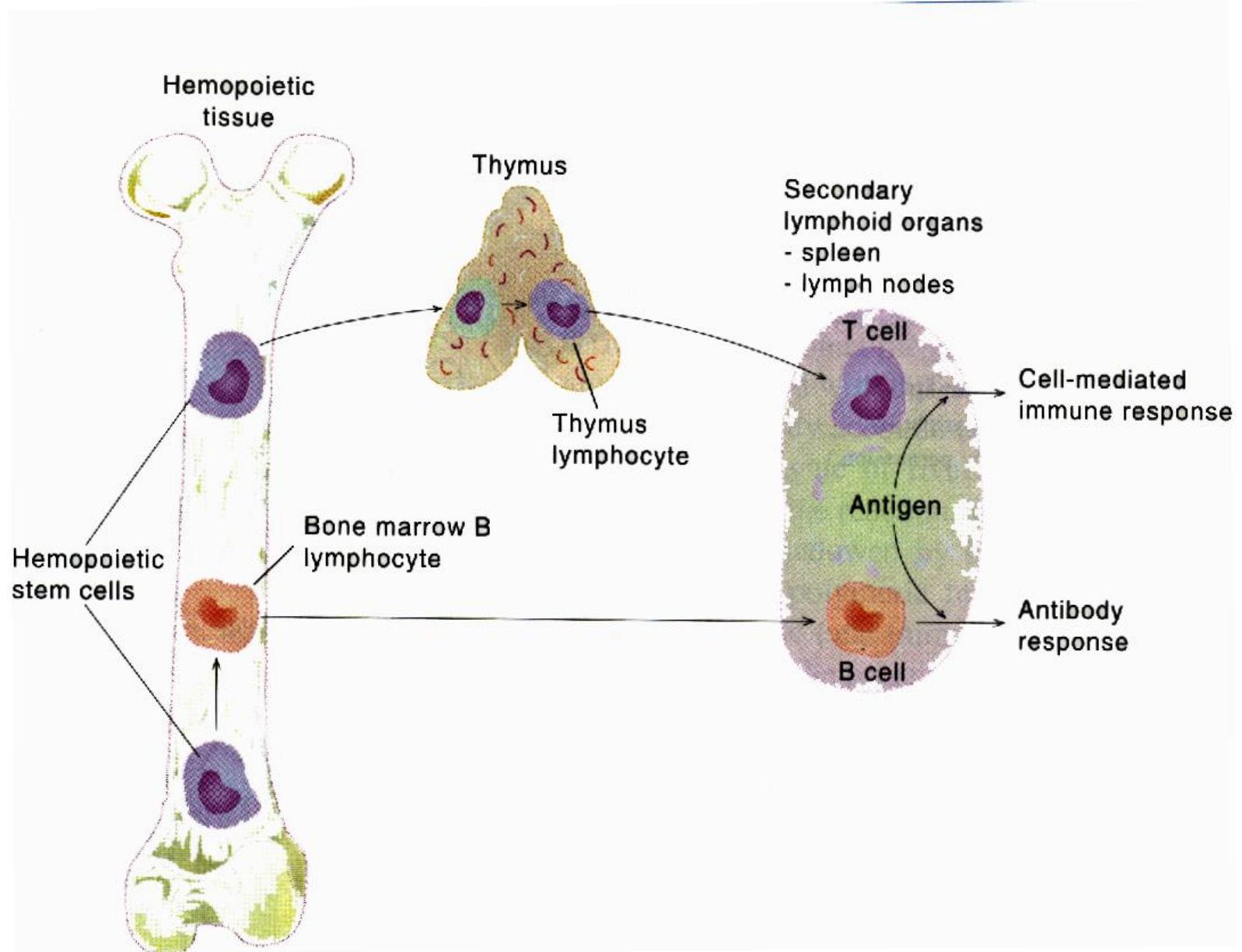
Mononuclear phagocyte in blood, mature in bone marrow, precursor of tissue macrophages, process antigens to peptides, present peptides to T cells

Macrophages

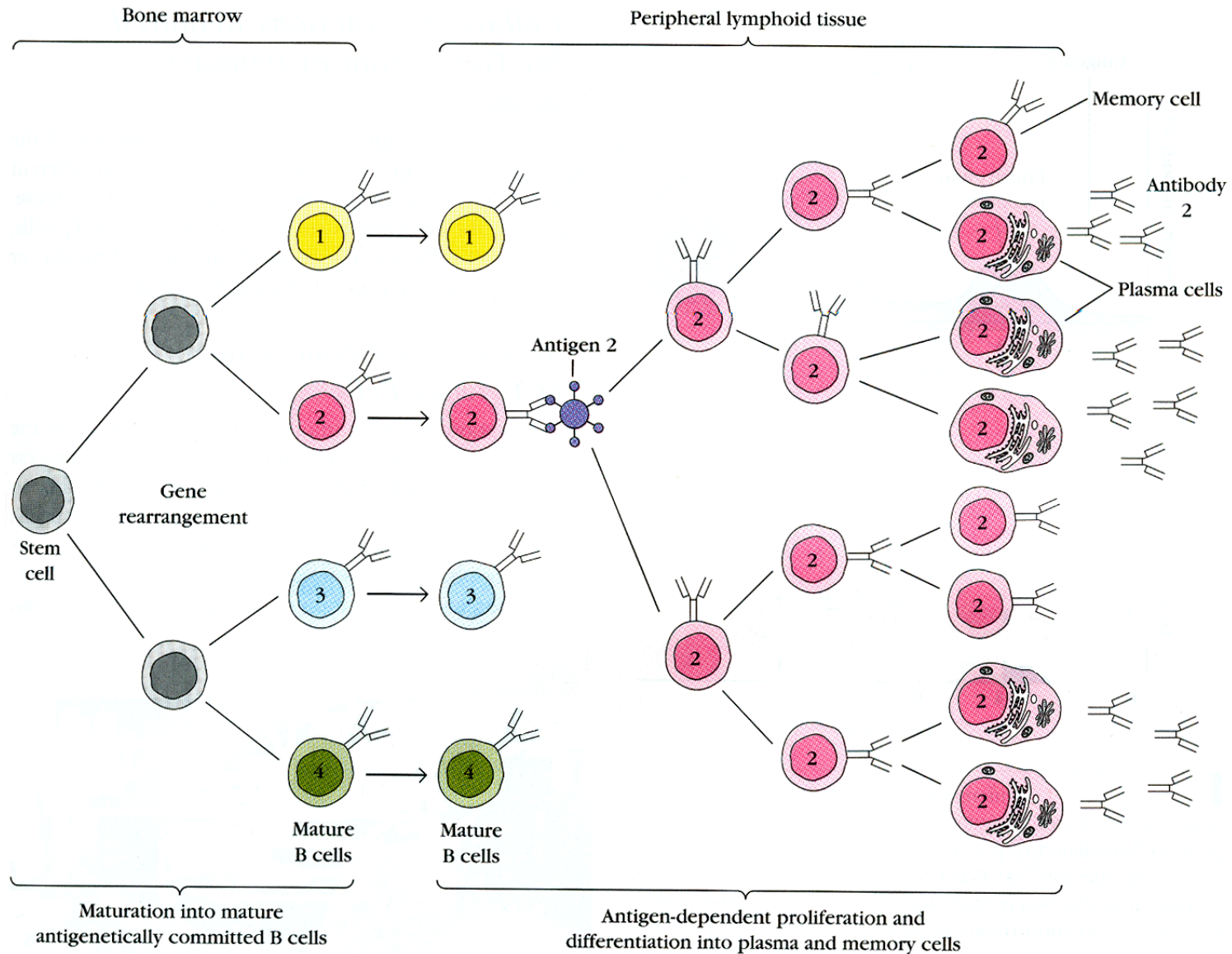
Tissue phagocytes, process antigens for presentation to T cells, principal attack in bacteria, viruses, protozoa

Dendritic cells – skin, Langerhans cells and lymph nodes and spleen. Recognize and endocytose foreign carbohydrate antigens

Adaptive immunity



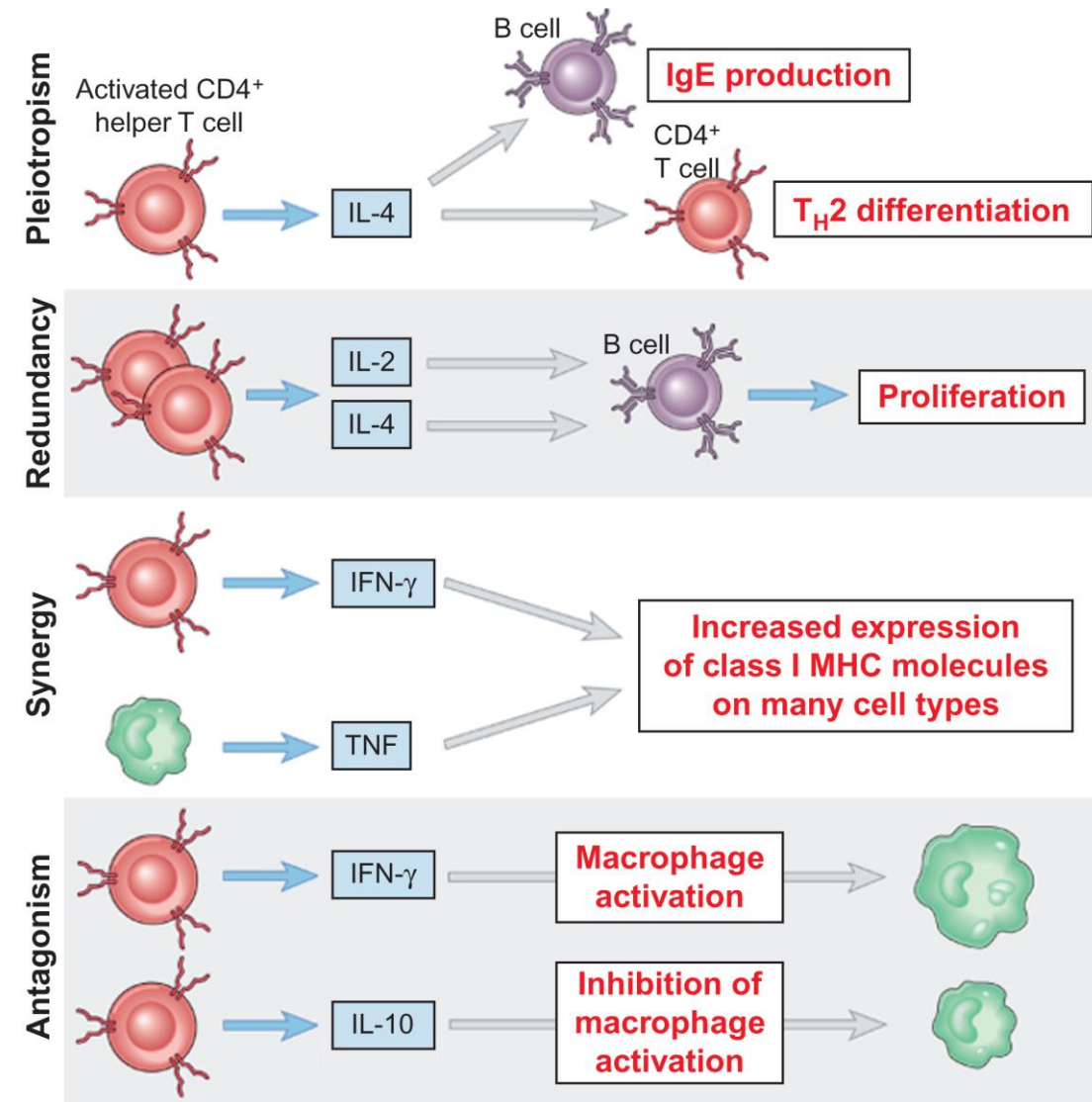
Maturation and selection of B lymphocytes



Communication within the immune response

- Signal activating or inhibiting a cell to perform its function in immune response
 - surface proteins – T cell receptors, major histocompatibility complex (MHC), co-stimulatory molecules
- Cells communicate by direct cell-to-cell contact or through the production of soluble factors – cytokines with wide range of different effects
 - endocrine, paracrine or autocrine manner

Communication within the immune response



Functionality of cytokines

1. Pleiotropic – different effect
2. Redundant – many different cytokines with the same function
3. Synergistic – increase effects of one another
4. Antagonistic – one negates the function of the other

Cytokines

- *Chemokines* - specific class of cytokines. Mediates chemoattraction (*chemotaxis*) between cells, stimulate leukocyte movement and regulate the migration of leukocytes from the blood to tissues.
- *Interleukins* - presumed targets are principally **leukocytes**.
- *Lymphokines* - produced by activated **T lymphocytes** direct the immune system response by signaling between its cells
- *Monokines* - derived primarily from mononuclear cells such as **macrophages**.

Major histocompatibility system (MHC)

- Cell surface molecule encoded by a large set of highly polymorphic evolutionary related genes
- The function of MHC – to process and bind antigenic peptide fragment during the immune response
- MHC surface bound proteins present this peptide fragments (antigens)
- The presented antigen can be either *self* or *nonself*
- MHC determines compatibility of donors for organ transplant, susceptibility to an autoimmune disease
- In human - the complex is also called the *human leukocyte antigen – HLA system*.
- The proteins encoded by HLAs are those on the outer part of body cells that are (in effect) unique to that person.

Humal leukocyte antigens (HLA)

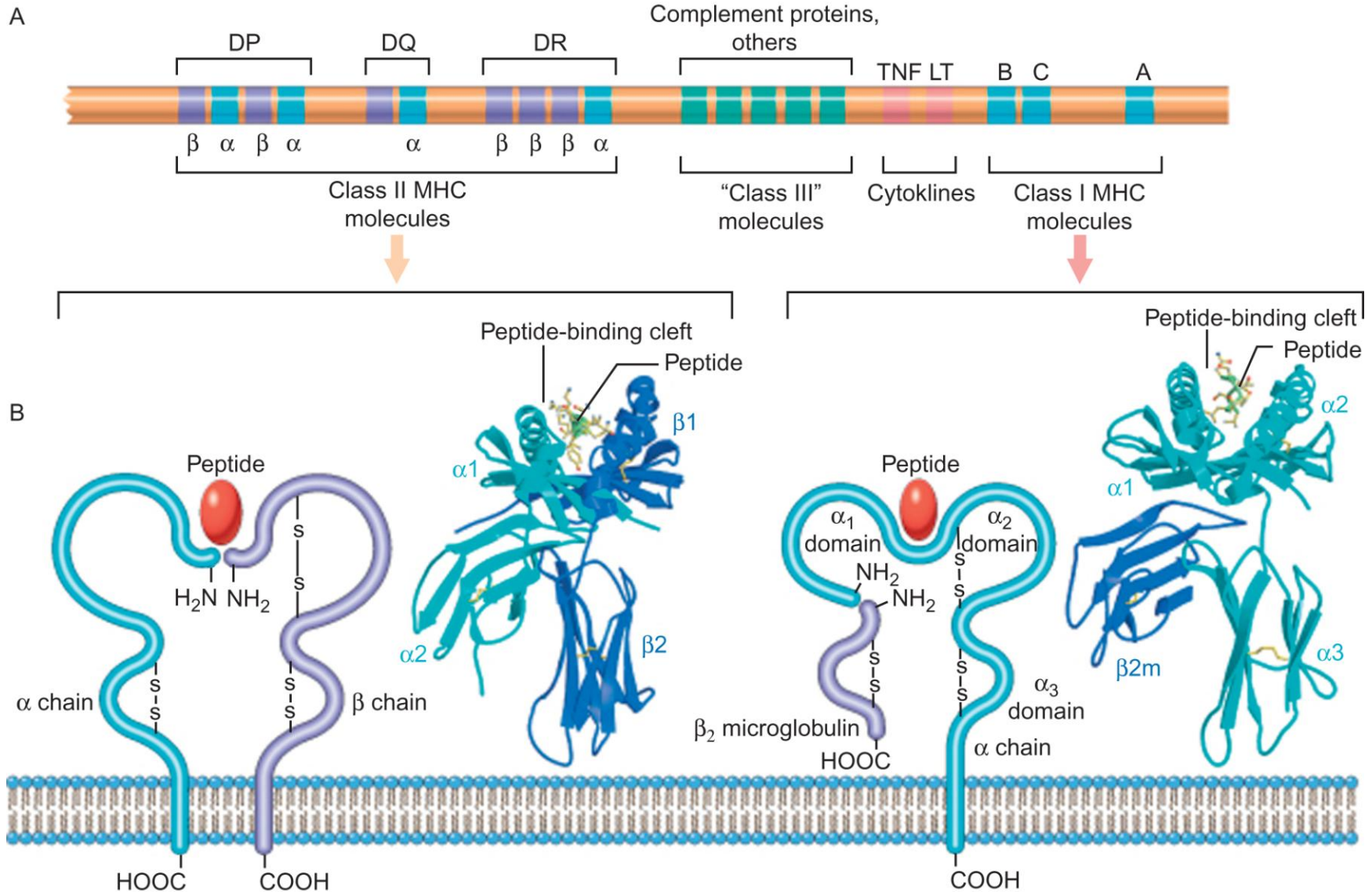
Class I – membrane-bound glycoproteins, found on every nucleated cell of the body, function is to display fragments of proteins processed from intracellular protein and present HLA/protein complex to cytotoxic T cells; cells containing foreign proteins will be attacked by the immune system; healthy cells will be ignored

class II - membrane-bound glycoproteins are restricted to cells of the immune - macrophages and lymphocytes

- proteins from the pathogen are digested into small peptides
- peptides are loaded onto HLA antigens → then displayed by the antigen-presenting cells to T-cells → variety of effects to eliminate the pathogen.

class III – other proteins such as complement proteins, cytokines (chemical messengers), and enzymes

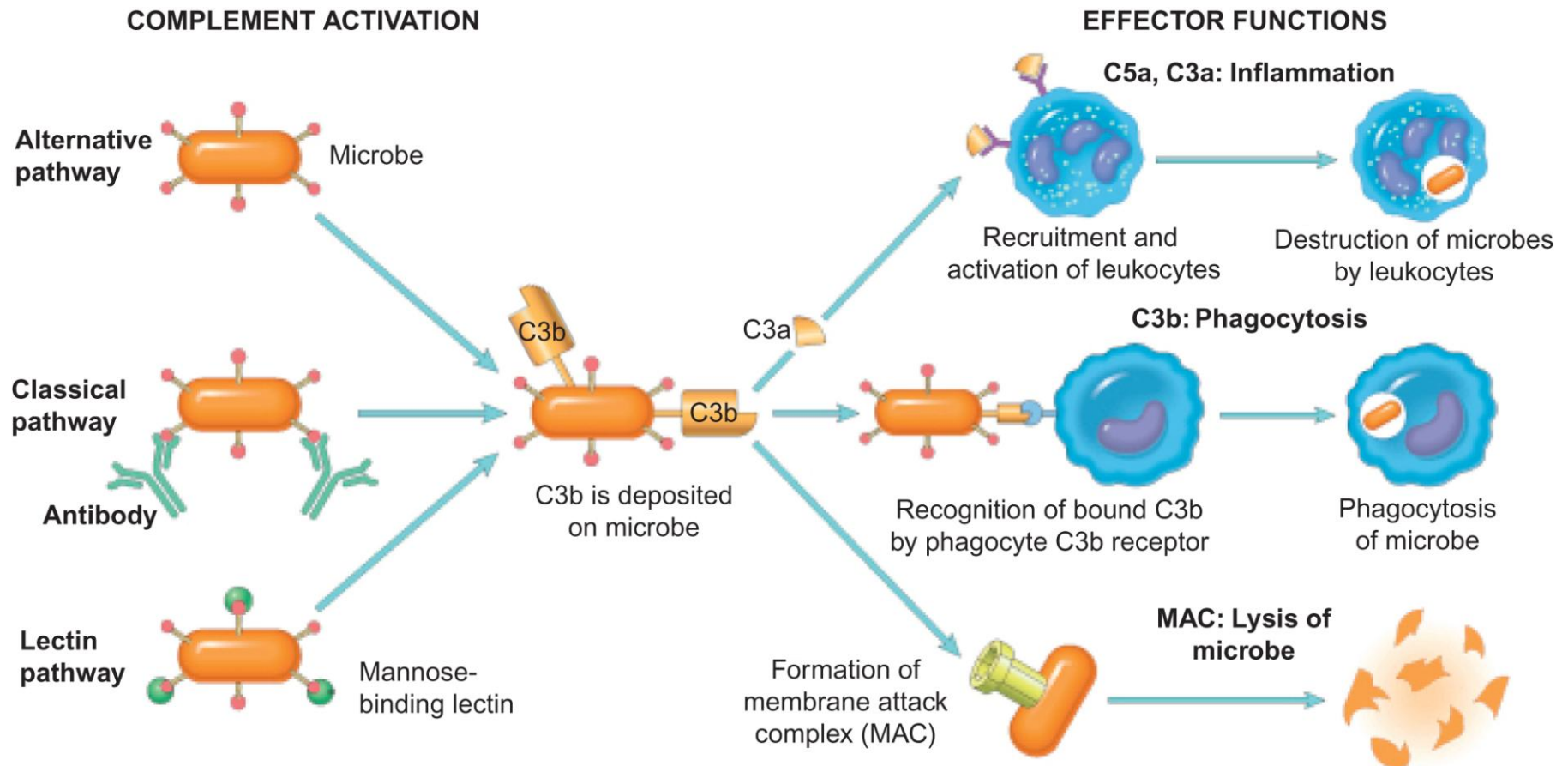
The HLA complex, structure of HLA molecules



The complement system

- The innate immunity system (the immunity one is born with).
- The initial response by the body to eliminate microbes and prevent infection.
- One of the major effector pathway of the inflammation.
- The biochemical cascade of proteins C1 to C9 (enzymes) normally circulate in constant concentration in the blood (inactive form).
- In response to the recognition of specific molecular component of the pathogen → activation of cascade → each enzyme acts as a catalyst for the next.
- Mechanism for augmenting (complementing) the biological activities in antibody response.

The complement system



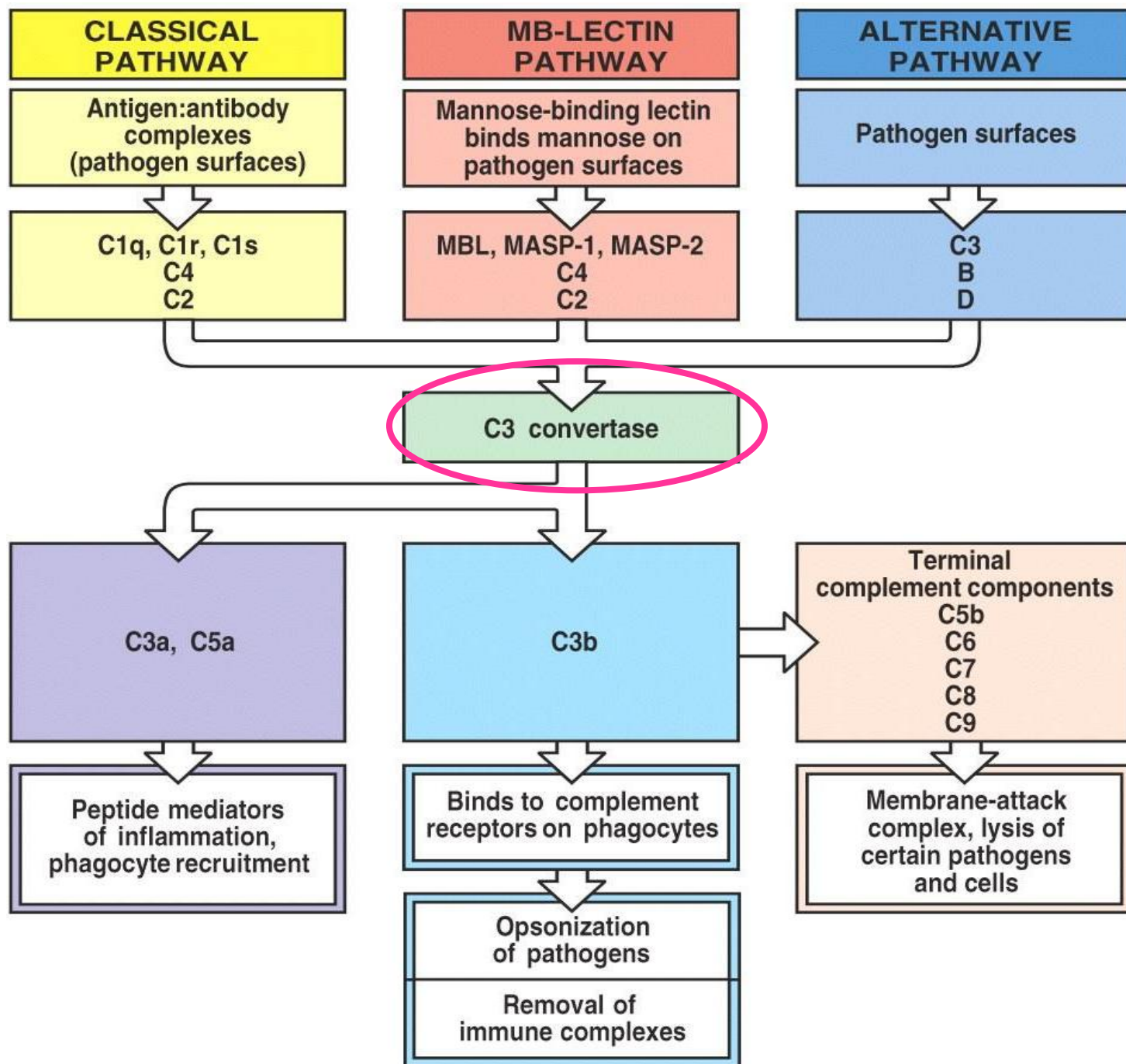


Figure 2-19 Immunobiology, 6/e. (© Garland Science 2005)

The function of major proteins of complement system

- 1. *Opsonisation:*** C3b and, to a lesser degree, C4b molecules are opsonins. They coat foreign organisms, enhancing their phagocytosis because phagocytes have receptors that recognize complement proteins bound to pathogen.
- 2. *Inflammation:*** The C5a and, less potently, the C4a and C3a fragments are important inflammatory activators inducing vascular permeability, recruitment and activation of phagocytes.

The function of major proteins of complement system

3. Lysis

C5b begins formation of a membrane pore (binds C6 to C9 components) which forms a transmembrane pore of ~ 10nm diameter causing lysis of the cell.

This macromolecular assembly is known as the Membrane Attack Complex (MAC).

Main function of component cleavages:

Complement-mediated chemotaxis

C5a is chemotactic for all types of phagocytic cells

- (neutrophils, eosinophils, macrophages, basophils)
- stimulates “respiratory burst” of neutrophils

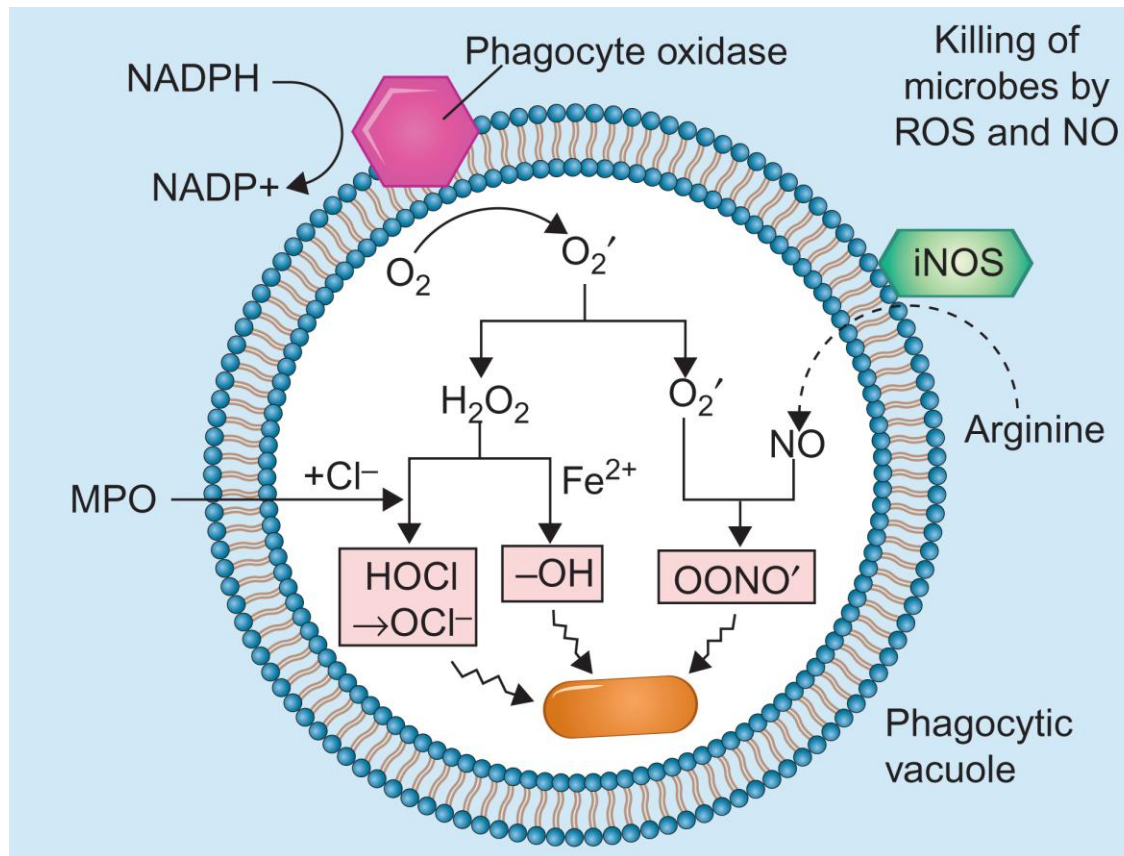
C3a, C4a and C5a are anaphylatoxins

hormone like peptides cause smooth muscle contraction, vascular permeability, release of *histamin* from mast cells and basophils and *lysosomal enzymes* release from granulocytes.

Inflammatory mediators

- Inflammatory mediators released from different leukocytes – initiation and modulation of inflammation;
- proinflammatory cytokines released from macrophages – IL1, IL6, TNF- α are endogenous pyrogens; production of C-reactive protein (CRP) by liver;
- mast cells, basophils, neutrophils, platelets in connective tissue produce – release vasodilators (histamin, kinins, leukotriens, prostaglandins).

Production of microbicidal reactive oxygen intermediates within phagocytic vesicles



Antibodies

Immunoglobulin structure

4 polypeptide chains:
2 identical heavy
(H)
2 identical light (L)

H chains: μ , δ , γ , α , ϵ
(different amino acid composition)

L chains: κ , λ

Izotypes = classes of

IgG:

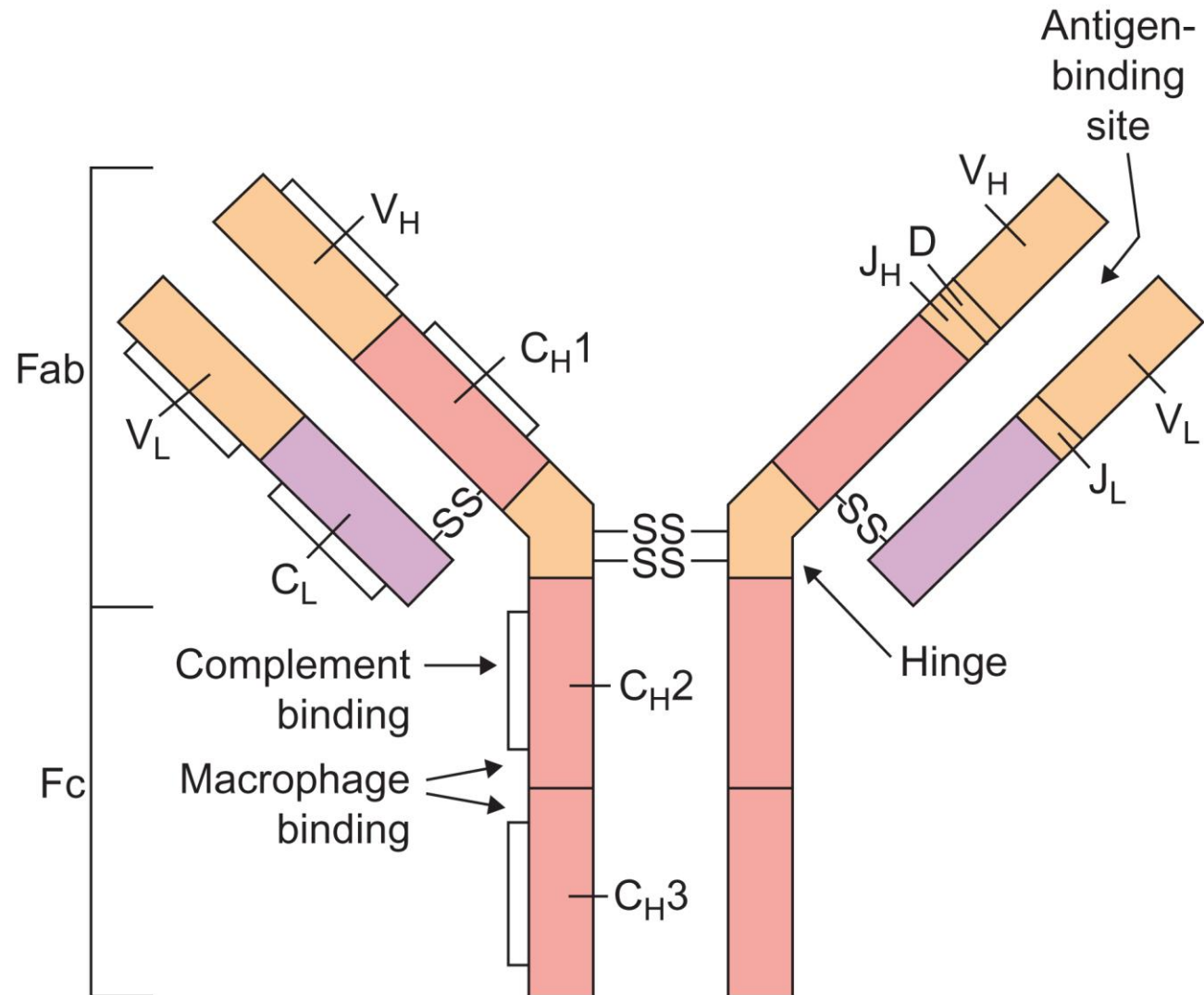
IgM (μ)

IgD (δ)

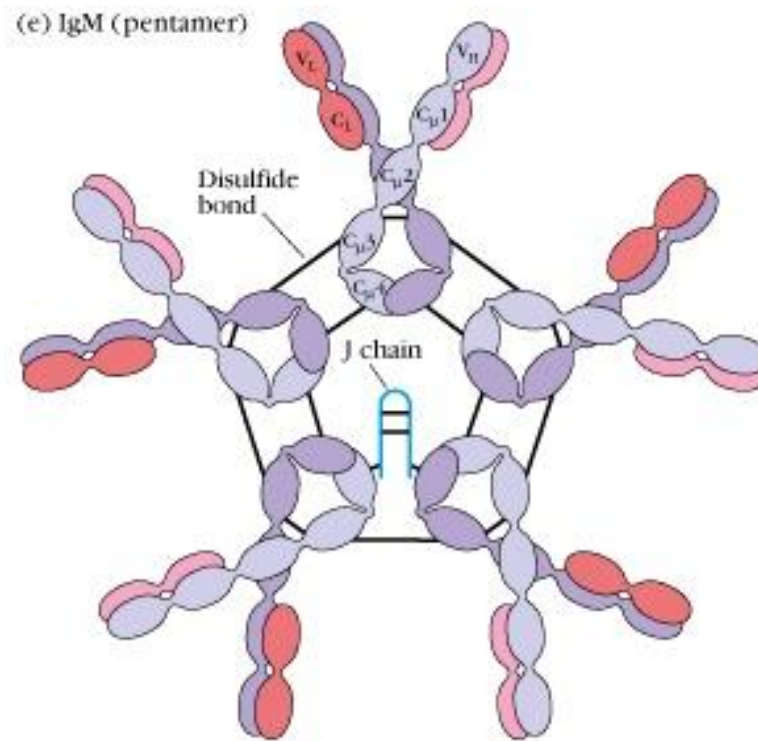
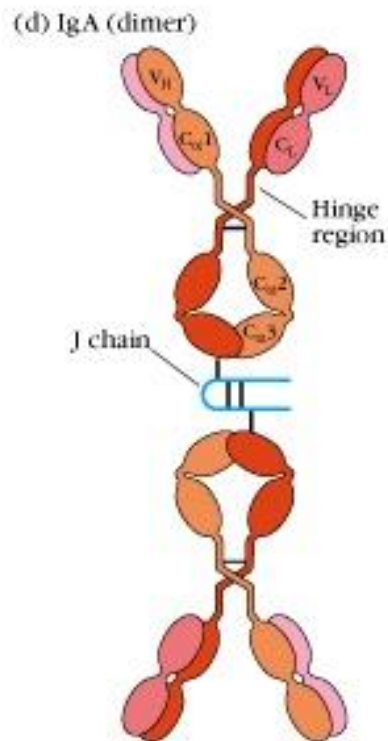
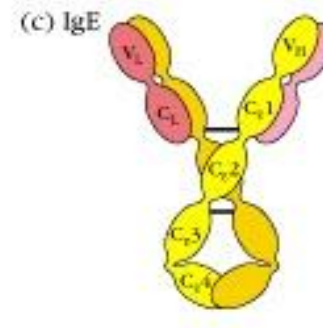
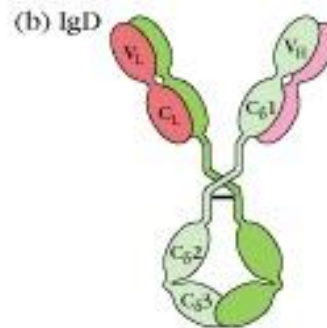
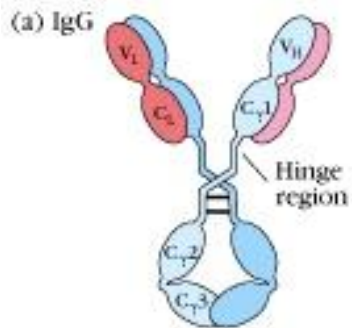
IgG (γ)

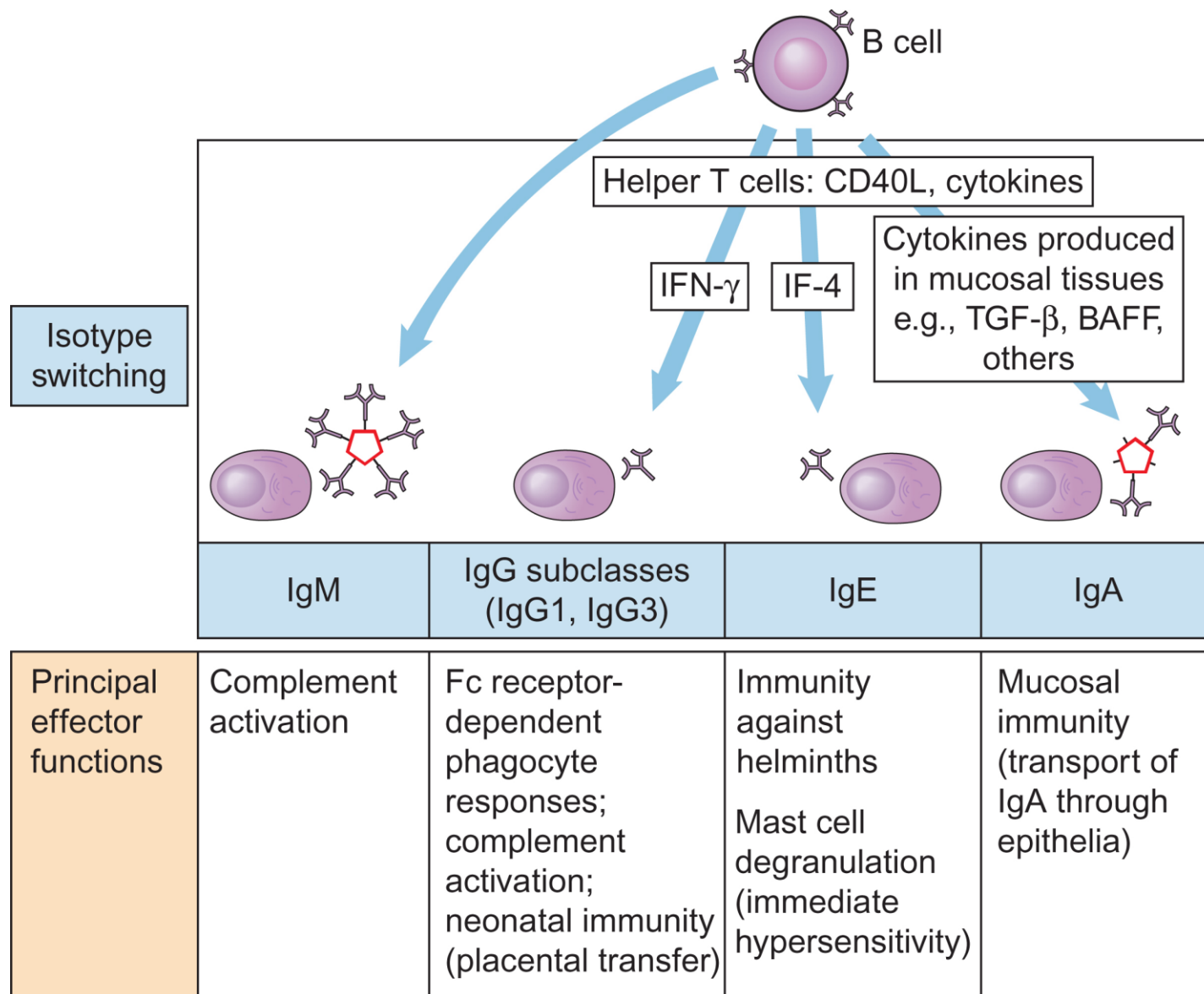
IgA (α)

IgE (ϵ)



Immunoglobulin classes



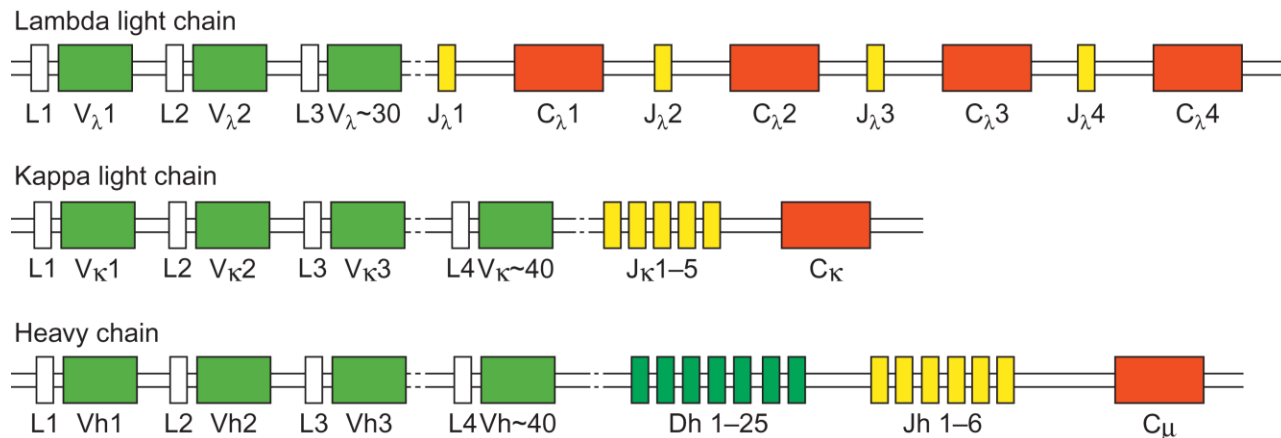


Immunoglobulin diversity

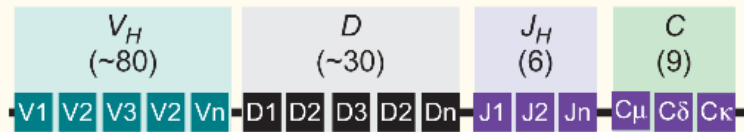
- The human immune response must be able to provide antibodies against any and all non-self antigens.
- Problem...the immune system makes over one billion different antibody proteins.
- B cells create this vast antibody diversity by randomly selecting from a number genes.
- These are spliced together.

Immunoglobulin gene arrangements

- The heavy chain locus – ~80 Variable (V_H) genes, 27 Diversity (D_H) genes, 6 Joining (J_H) genes for producing the wide range of antigen-binding sites, 9 Constant (C_H) genes for the constant region.
- The light chain loci (κ and λ) – V genes and J genes, no D genes



Heavy-chain genes



$D \rightarrow J_H$ rearrangement

Exonuclease deletion
N addition (TdT)



$V_H \rightarrow D-J_H$ rearrangement

Exonuclease deletion
N addition (TdT)



Rearranged DNA

Transcription
RNA splicing



mRNA
Translation

Variable region

Heavy-chain polypeptide

Light-chain genes



$V_\kappa \rightarrow J_\kappa$ rearrangement



DNA rearrangement



Rearranged DNA

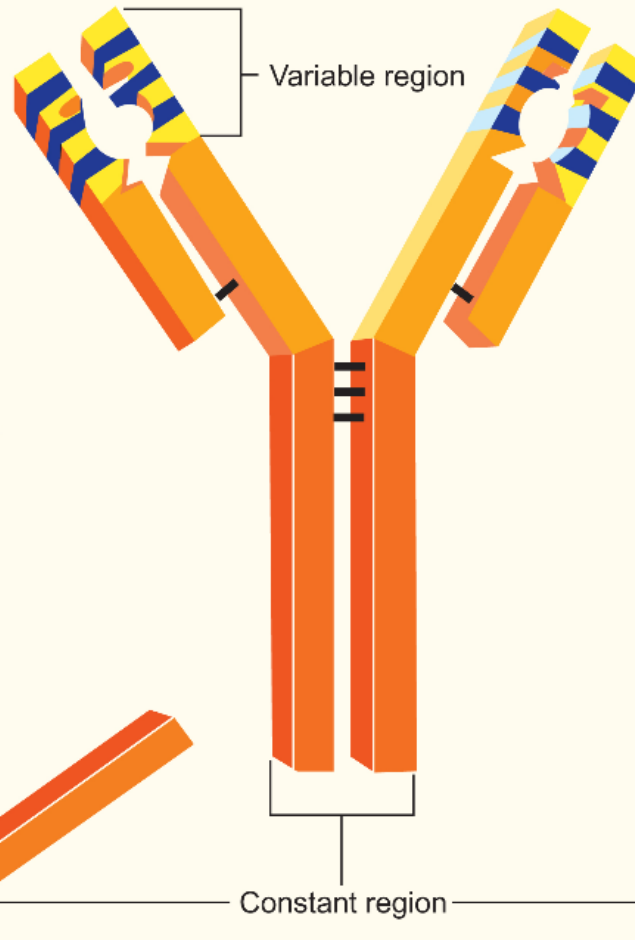
Transcription
RNA splicing



mRNA
Translation

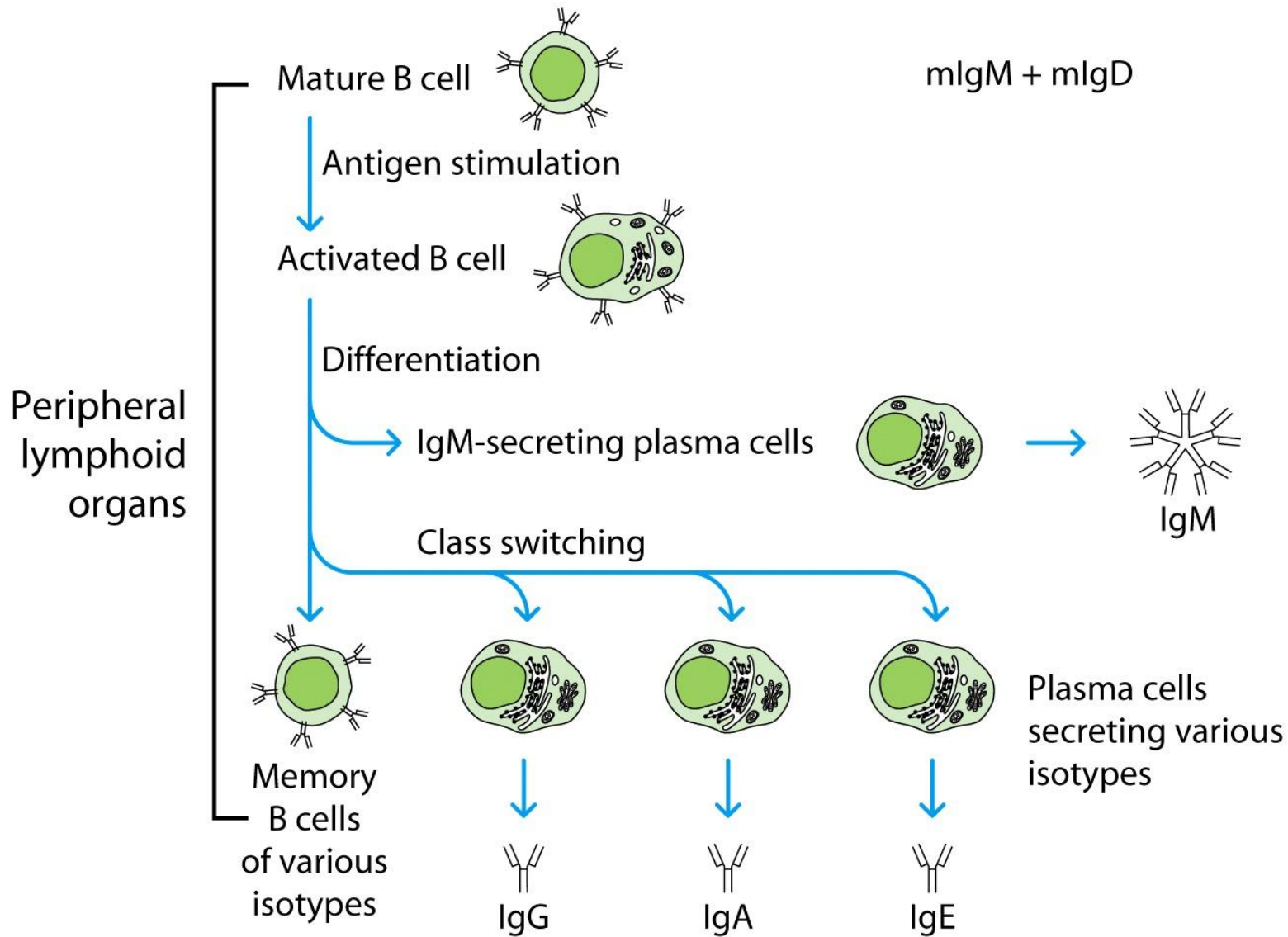
Variable region

Light-chain polypeptide



Isotype rearrangement

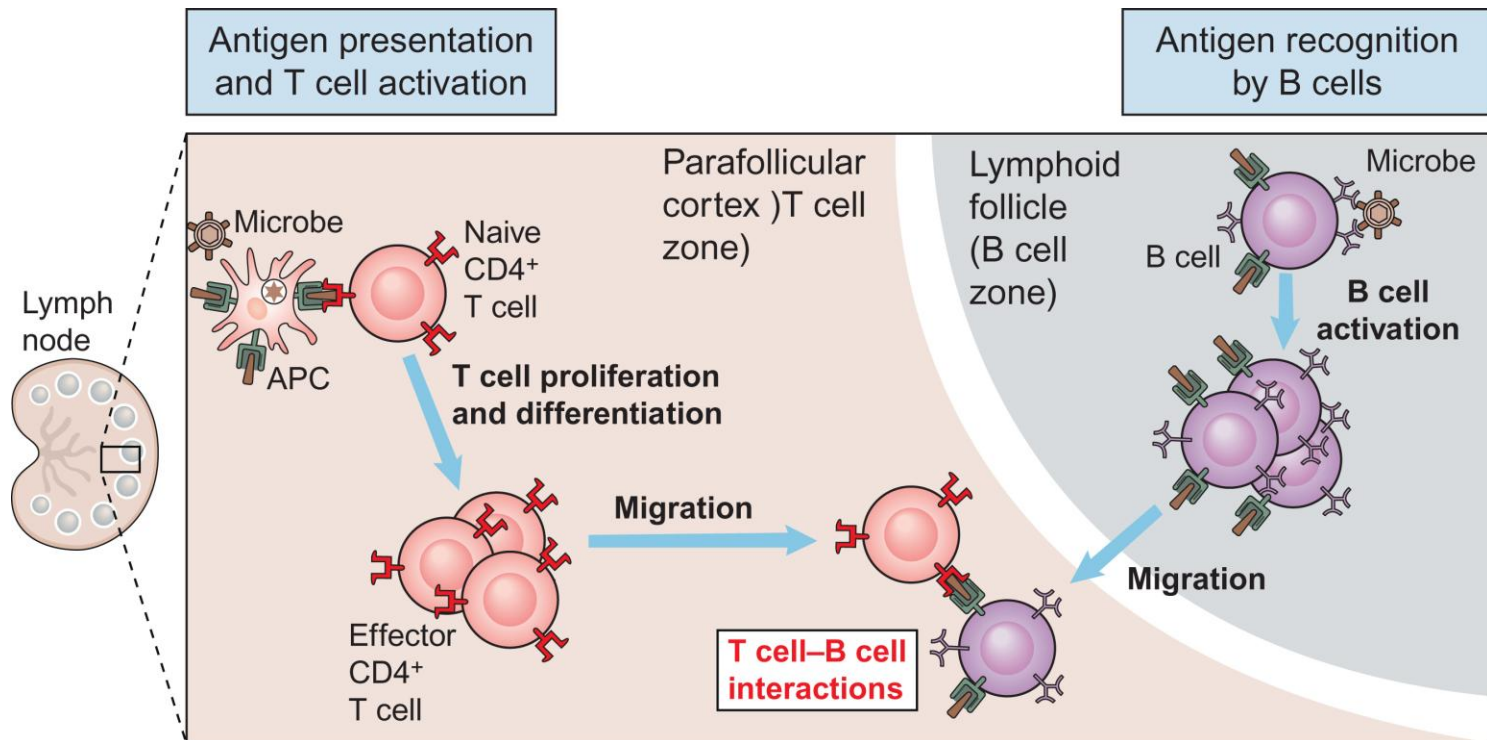
- In the course of the immune response to the antigen there is a switch from IgM to IgG production or to other classes of Ig.
- Mechanism: the C μ segment is cut out and in its place in order is received the next segment, e.g. C γ (production of antibodies IgG).
- Direction of rearrangement (option isotype) is regulated by cytokines - especially IL-4 (stimulates production of IgG, IgE), TGF- β , IL-10.
- Change concerns only the constant domain of H-chain; **antigenic specificity is maintained.**



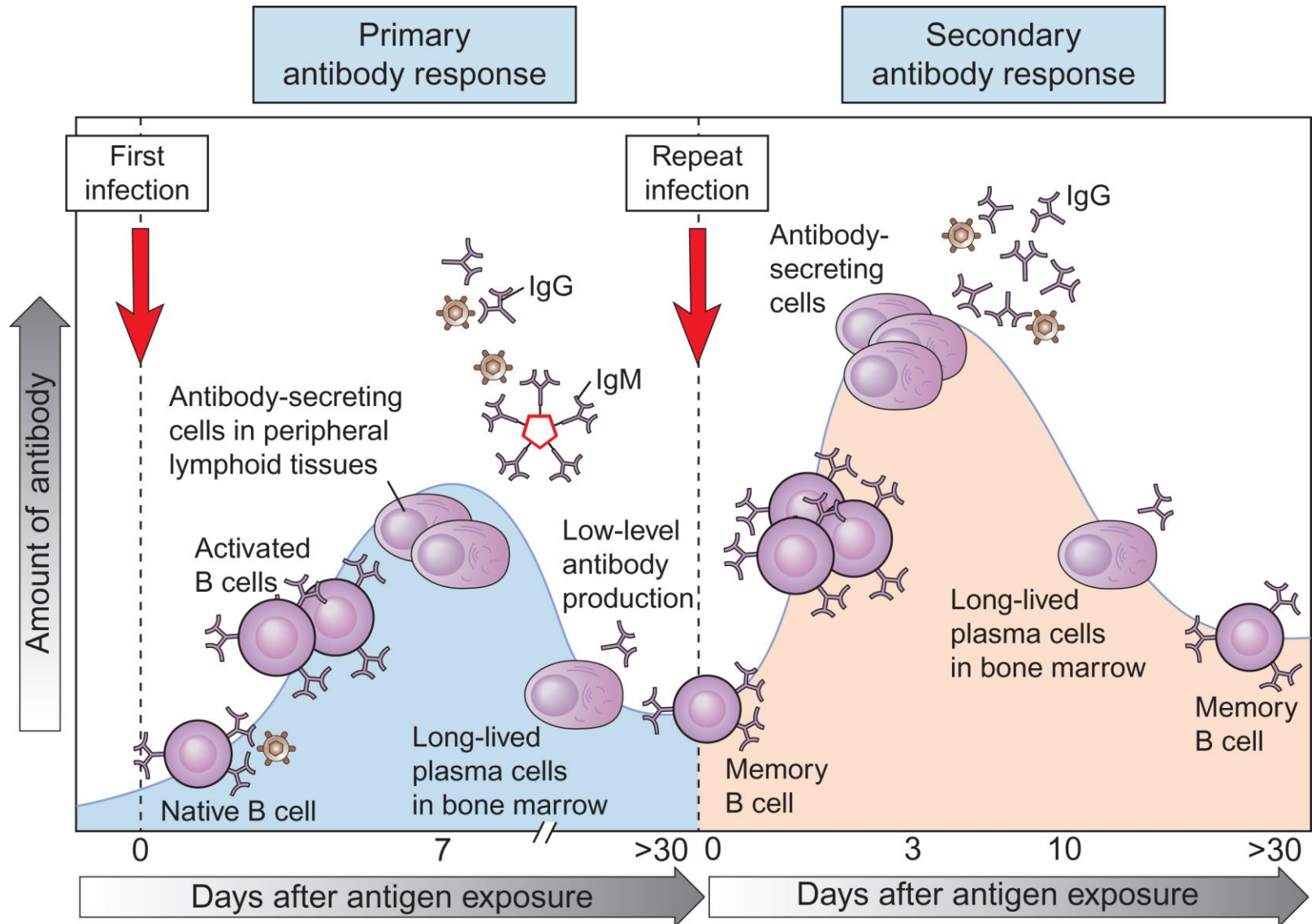
Antigen recognition by T and B cells in lymph node

B cells recognize specific antigen in the soluble form using membrane-bound immunoglobulin

T cells recognize specific antigen as a peptide fragment presented by an antigen-presenting cell (macrophage)



Primary and secondary antibody response



Reference

N.V. Bhagavan, Chung-Eun Ha:
Essentials of **Medical Biochemistry**
With Clinical Cases