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Tiruchirappalli – 620 024,
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Programme: M.Sc., Biotechnology (Marine)

Course Title : Immunology

Course Code : 21 CC7

Unit: IV
Cell mediated Immune response

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CONTENTS :

- Organization of immune system, cells, antibody, regulation of immune response
- Hypersensitivity reactions
- Autoimmune disease

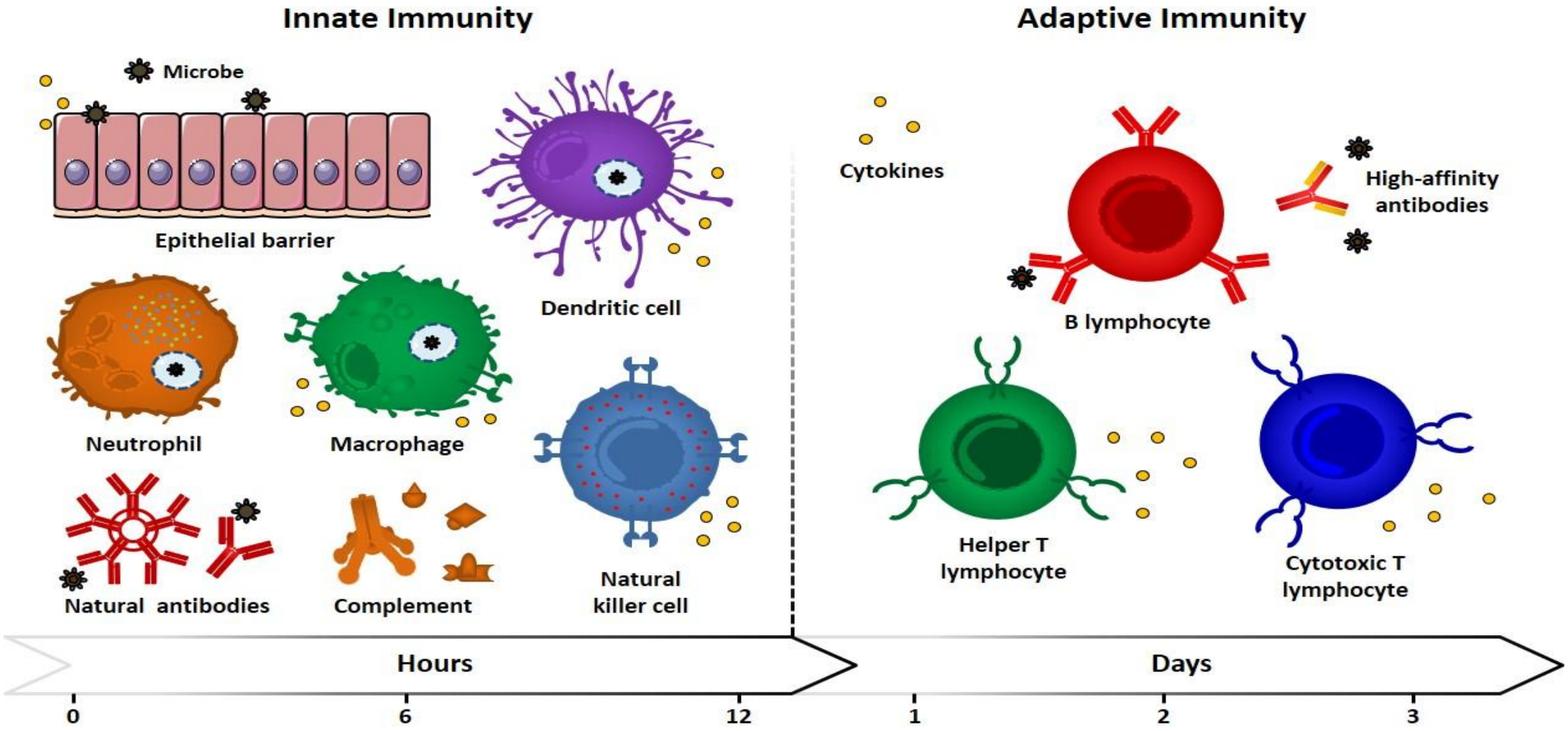
INTRODUCTION :

The immune system protects the host from invasion by foreign and potentially harmful agents.

Characteristics :

1. Distinguish self from non-self
2. Discriminate among potential invaders (Specificity)
3. Maintain the presence of immune memory (anamnesis)
4. Recall previous exposure and mount an amplified response to them.
5. Immune response can be elicited by a wide range of agents (termed antigens) including microorganisms, chemicals, toxins, drug, and transplanted tissues.

- Innate immunity – Does not demonstrate immune memory and lacks the exacting specificity of adaptive immunity.
- Adaptive immunity – immune responses that show antigen specificity and immune memory.



Source: https://www.youtube.com/watch?v=eBE804Ut_eo

Innate and Adaptive Immunity :

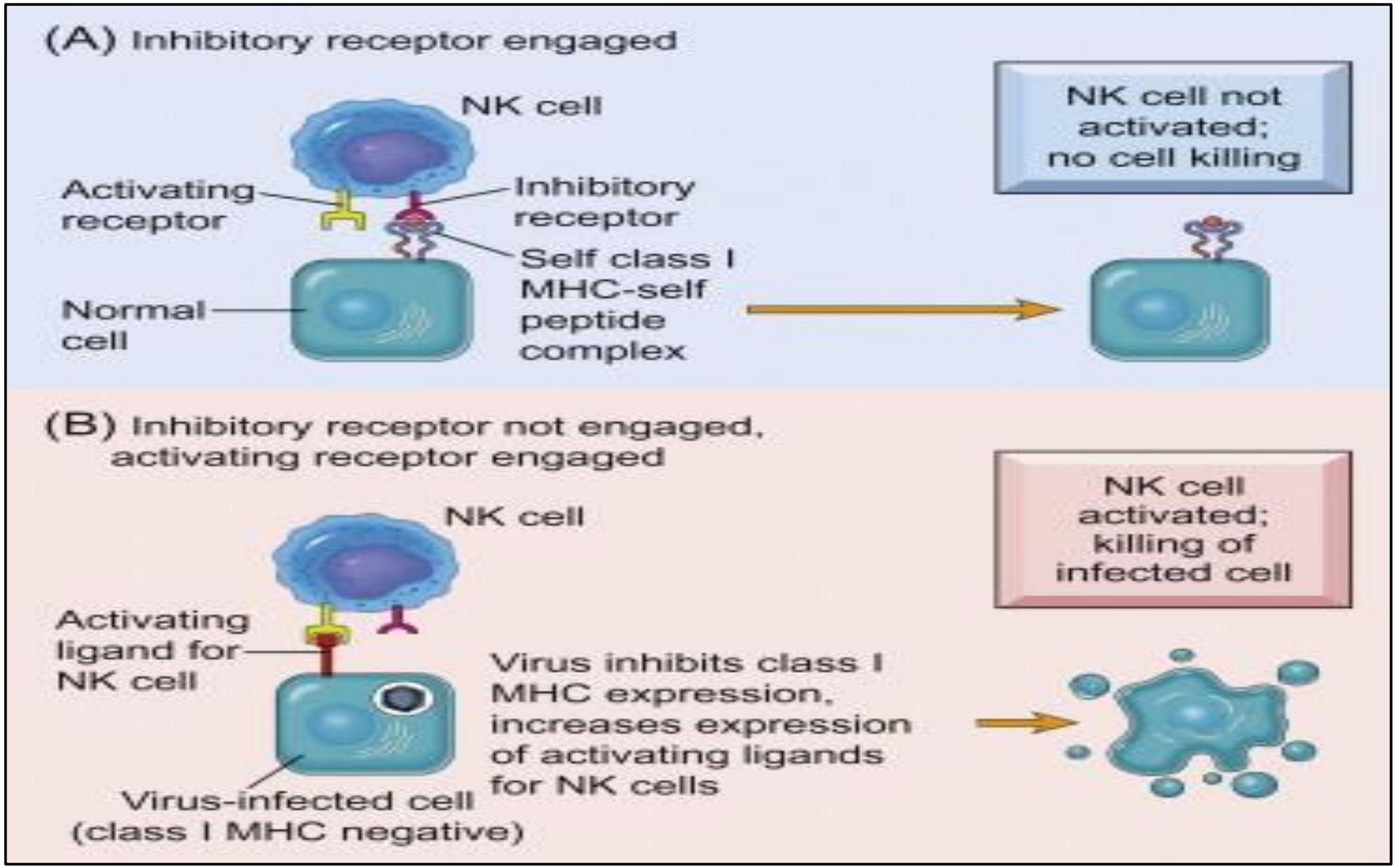
- Innate immunity
- Natural or native immunity
- Defense mechanisms present even before infection
- First line of defense

Two most important cellular reactions

1. **Inflammation** – Phagocytic leukocytes are recruited and activated to kill microbes
2. **Anti-viral defense** – Mediated by dendritic cells and NK cells

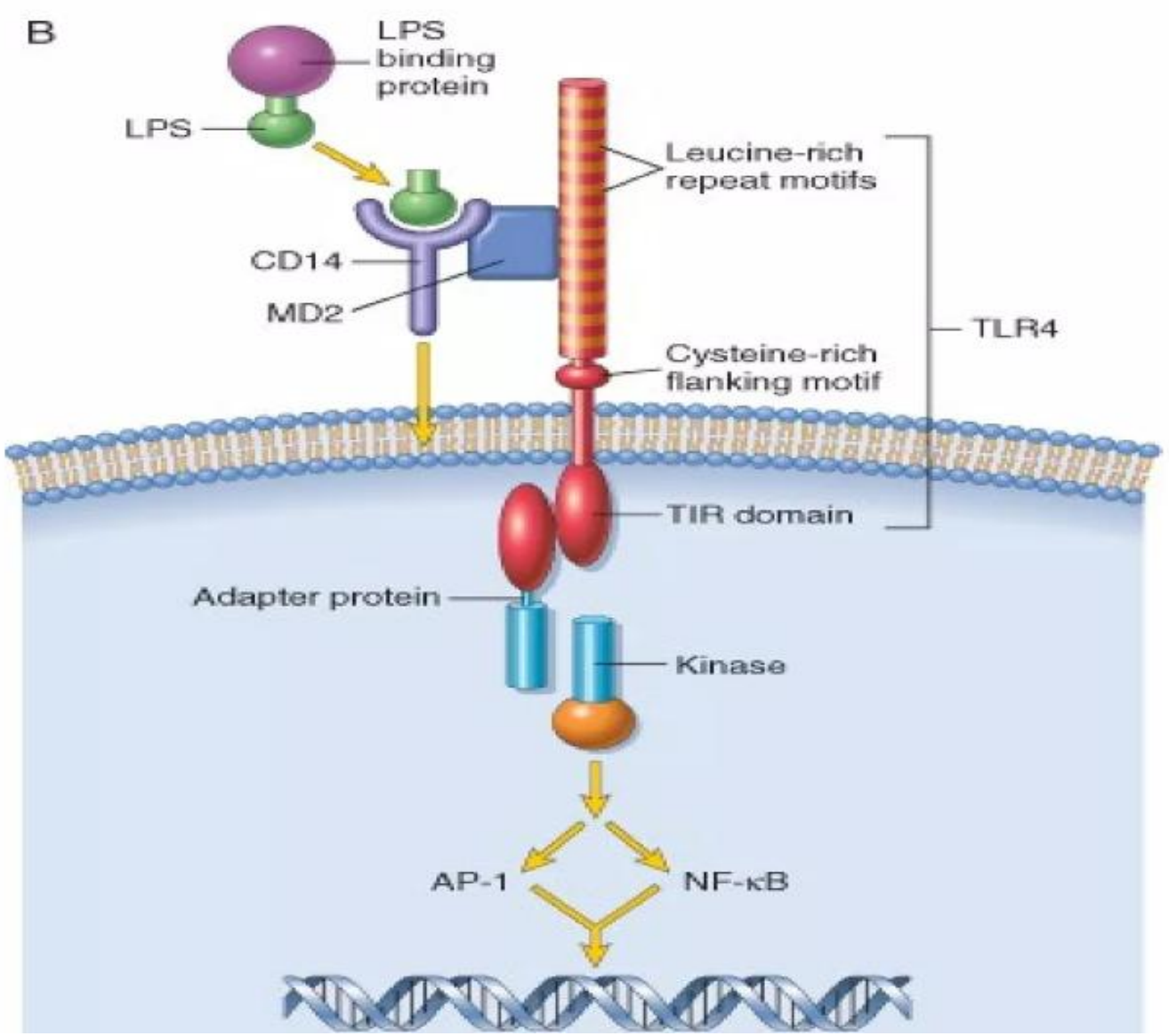
Components

1. Epithelial barriers
2. Phagocytic cells (PMN's and Macrophages), Dendritic cells, NK cells
3. Several plasma proteins, including the Complement system.


(A) Inhibitory receptor engaged
NK cell
Activating receptor
Inhibitory receptor
Self class I MHC-self peptide complex
Normal cell
NK cell not activated; no cell killing
(B) Inhibitory receptor not engaged, activating receptor engaged
NK cell
Activating ligand for NK cell
Virus inhibits class I MHC expression, increases expression of activating ligands for NK cells
Virus-infected cell (class I MHC negative)
NK cell activated; killing of infected cell

- Pathogen - associated molecular patterns Microbial structure recognized by leukocytes and epithelial cells
- Danger – associated molecular patterns Molecules released by injured and necrotic cells that are recognized by leukocytes pattern recognition receptors Toll – like receptors (TLR's)
- Toll – like Receptors (TLR's) homologous to the drosophila protein
  - ✓Specific for components of different bacteria and viruses located on the cell surface and in endosomes
  - ✓Recognize and initiate cellular responses

TLR	Ligand	Microbial source
TLR2	Lipoproteins Peptidoglycan Zymosan LPS GPI anchor Lipoarabinomannan Phosphatidylinositol dimannoside	Bacteria Gram positive bacteria Fungi Leptospira Trypanosomes Mycobacteria
TLR3	Double-Stranded RNA	Viruses
TLR4	LPS HSF00	Gram negative bacteria Chlamydia
TLR5	Flagellin	Various bacteria
TLR6	CpG DNA	Bacteria, Protizoans



- Epithelial (skin, respiratory, GIT) provided mechanical barriers to the entry of microbes
- Produce anti – microbial molecules = *defensins*
- Monocytes and Neutrophils phagocytes in the blood recruited at the site of infection, monocytes that enter the tissues and mature are called *macrophages.*

Adaptive Immunity

Consists of lymphocytes and their products, including antibodies.

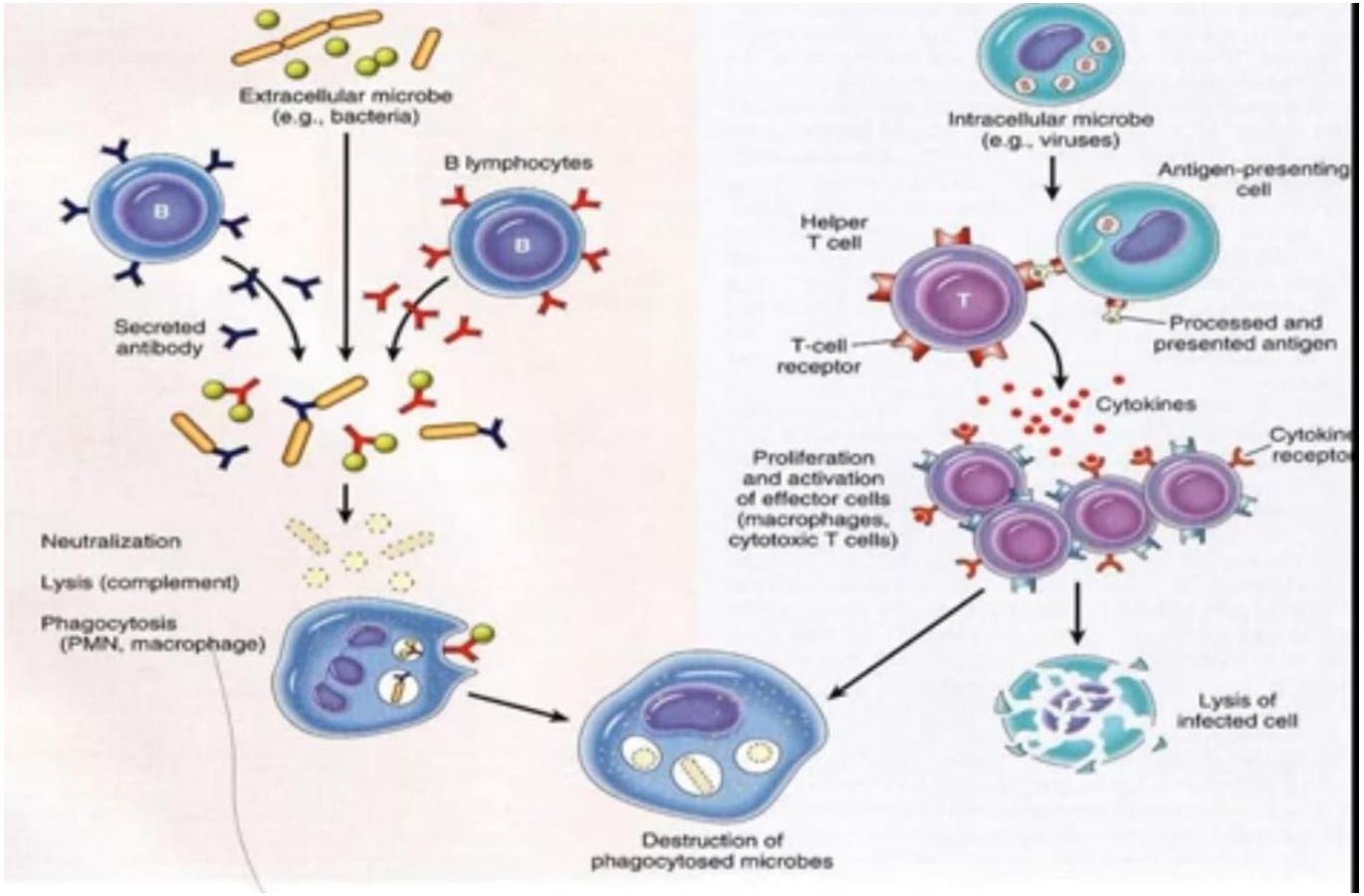
Cell-mediated (cellular) immunity:

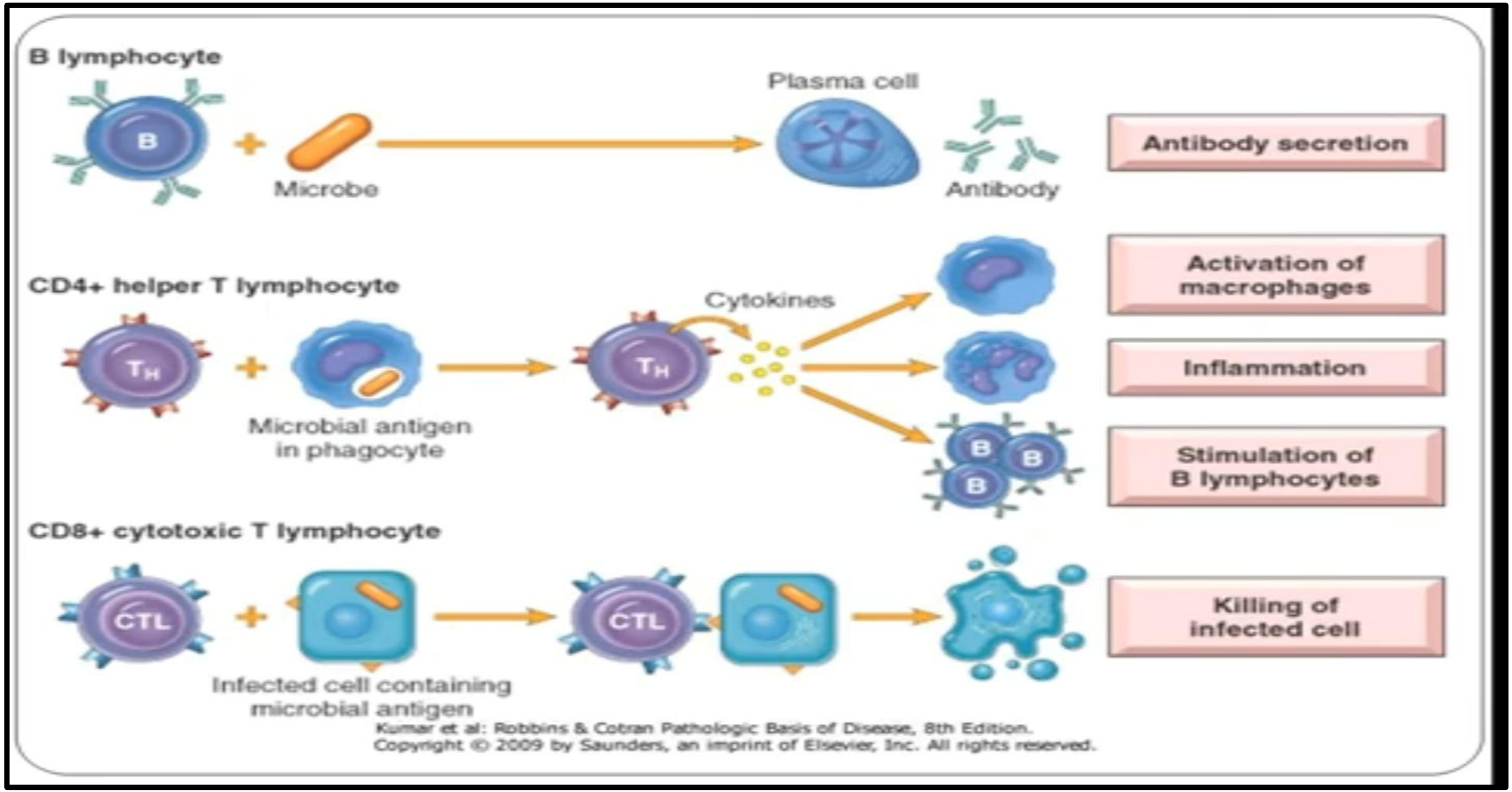
Responsible for defense against intracellular microbes mediated by T (Thymus-derived) lymphocytes.

Humoral immunity :

Protects against extracellular microbes and their toxins.

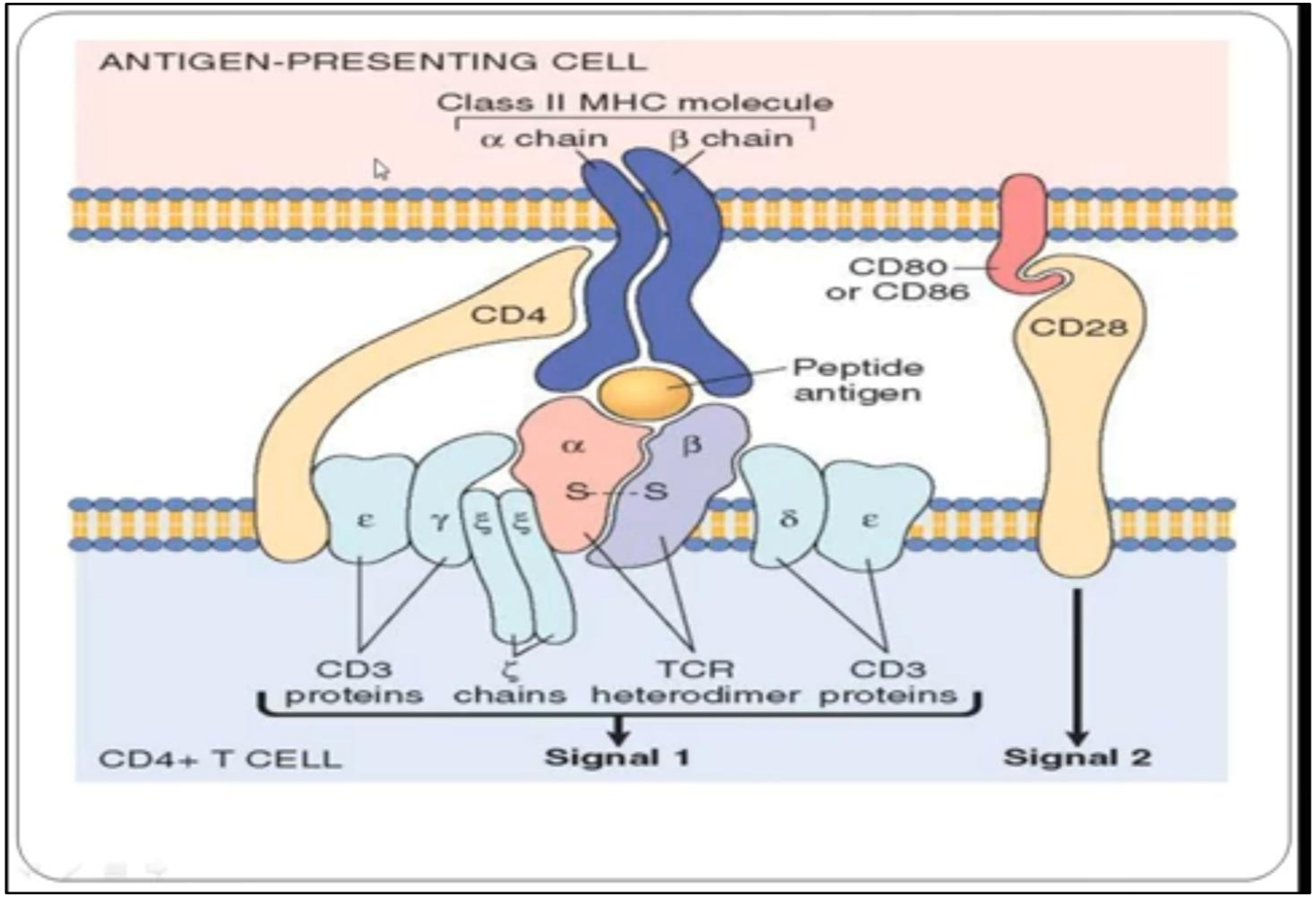
Mediated by B (Bone-marrow derived) lymphocytes and their secreted products and antibodies.





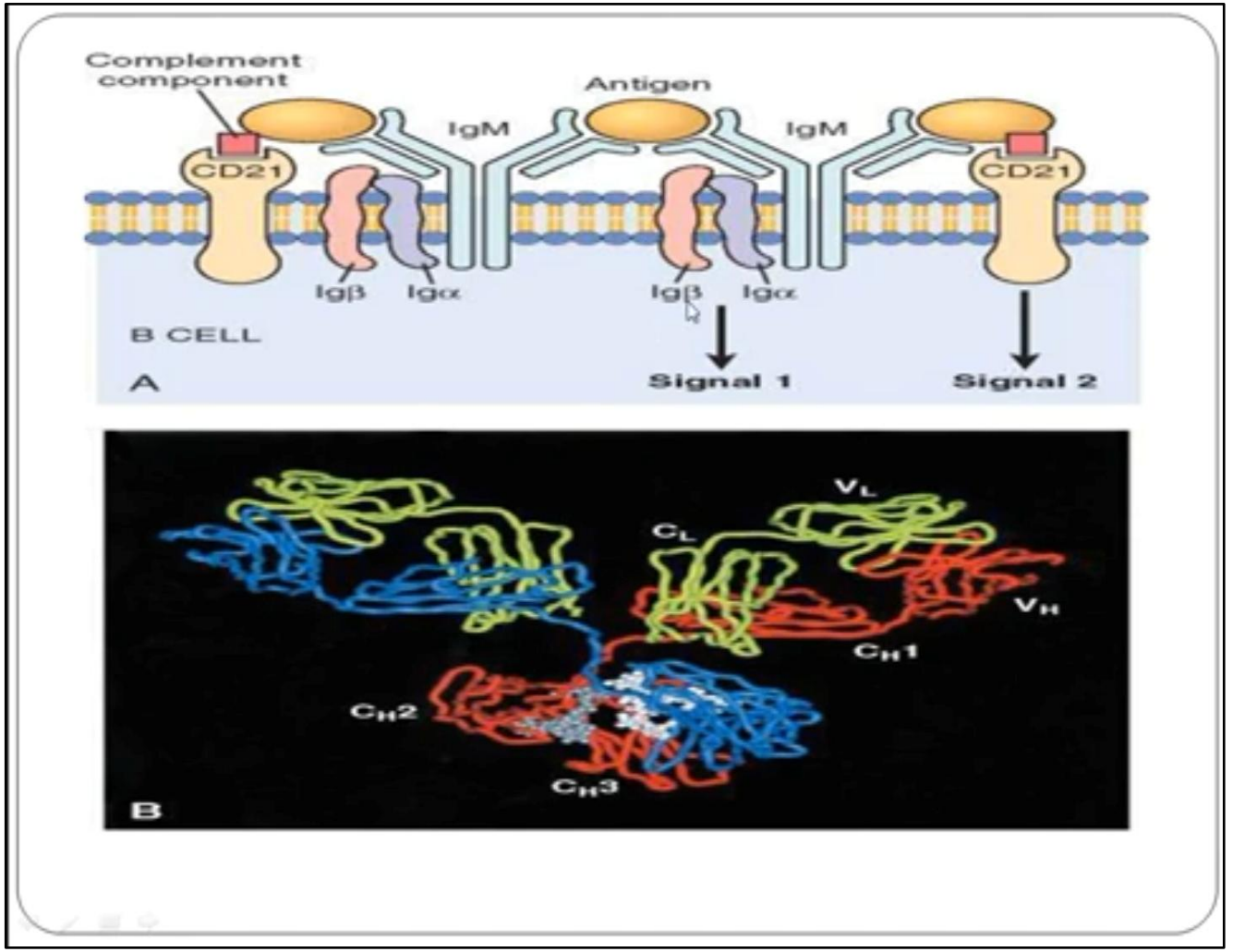
T Lymphocytes

- Generated from immature precursors in the thymus.
- Mature, naïve T cells enters the circulation, consisting 60-70% of lymphocytes.
- Found in the paracortical areas of LN and periarteriolar sheaths of spleen.
- Each T cell is genetically programmed to recognize a specific cell-bound antigen by means of an antigen specific T cell receptor (TCR).



B Lymphocytes

- Develop from immature precursors in the bone marrow.
- Mature B cells constitute 10-20% of the circulating peripheral lymphocytes.
- Also seen in the LN (superficial cortex), spleen (white pulp), tonsils, and extralymphatic organs (eg. GIT).
- Recognizes antigen via the B-cell antigen receptor complex, has unique antigen specificity derived partly from somatic rearrangements of immunoglobulin gene.



Cytokines

- Short-acting soluble mediators.
- Includes lymphokines, monokines and other polypeptides that regulate immunologic, inflammatory responses.
- Molecularly defined cytokines-Interleukins.

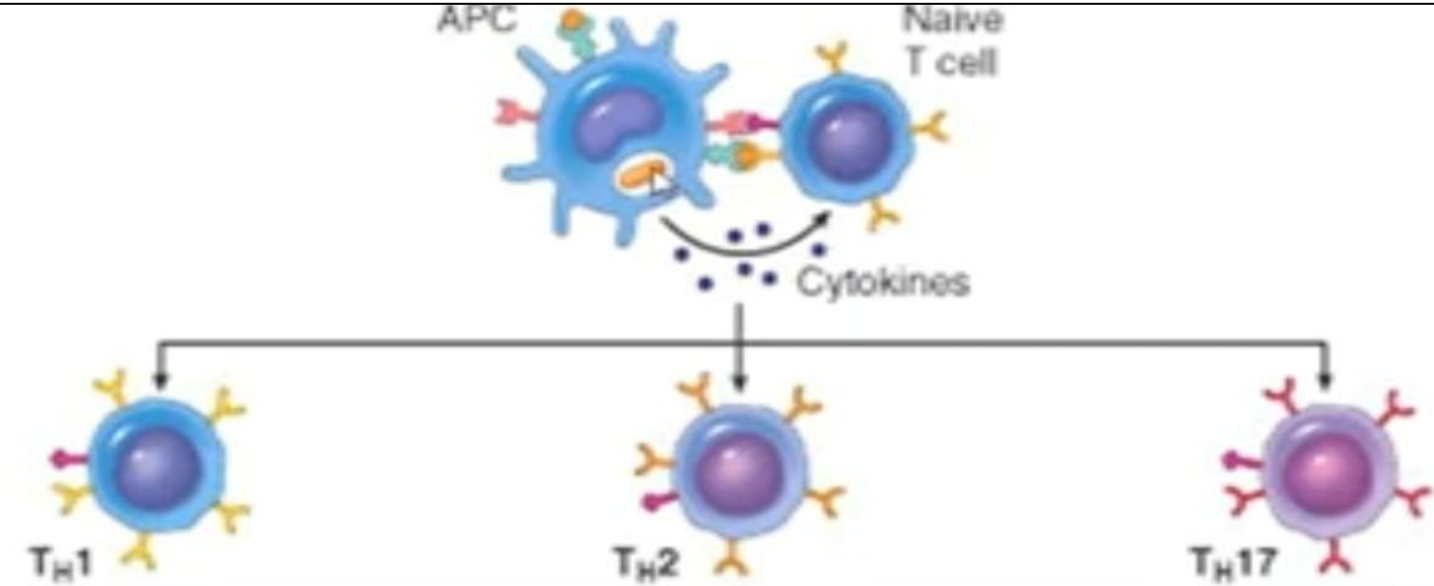
1. Mediate innate (natural) immunity

   IL-1, TNF, type 1 IFN, IL-6, IL-12 and IFN-γ (innate and adaptive immunity).

2. Regulate lymphocyte growth, activation and differentiation

   IL-2, IL-4, IL-12, IL-15 and TGF-8

3. Activate inflammatory cells- IFN-γ→ macrophages, IL-5 → eosinophils, TNF and TNF-B → PMNs and endothelial cells.
4. Affect leukocyte movement (Chemokines) C-C and C-X-C chemokines.
5. Stimulate hematopoiesis derived from lymphocytes or stromal cells, colony-stimulating factors.



	T_H1	T_H2	T_H17
Cytokines produced	IFN-γ	IL-4, IL-5, IL-13	IL-17, IL-22, chemokines
Cytokines that induce this subset	IFN-γ, IL-12	IL-4	TGF-β, IL-6, IL-1, IL-23
Immunological reactions triggered	Macrophage activation, stimulation of IgG antibody production	Stimulation of IgE production, activation of mast cells and eosinophils	Recruitment of neutrophils, monocytes
Host defense against	Intracellular microbes	Helminthic parasites	Extracellular bacteria, fungi
Role in disease	Immune-mediated chronic inflammatory diseases (often autoimmune)	Allergies	Immune-mediated chronic inflammatory diseases (often autoimmune)

Histocompatibility Molecules

- Important for the induction and regulation of the immune response.
- Principal physiologic function is to bind peptide fragments of foreign proteins for presentation to antigen-specific T cells.
- Encoding genes are found in chromosome 6.
- MHC or HLA complex
- Class I and Class II genes encode cell surface glycoproteins involved in antigen presentation.
- Class III genes encode components of the complement system.

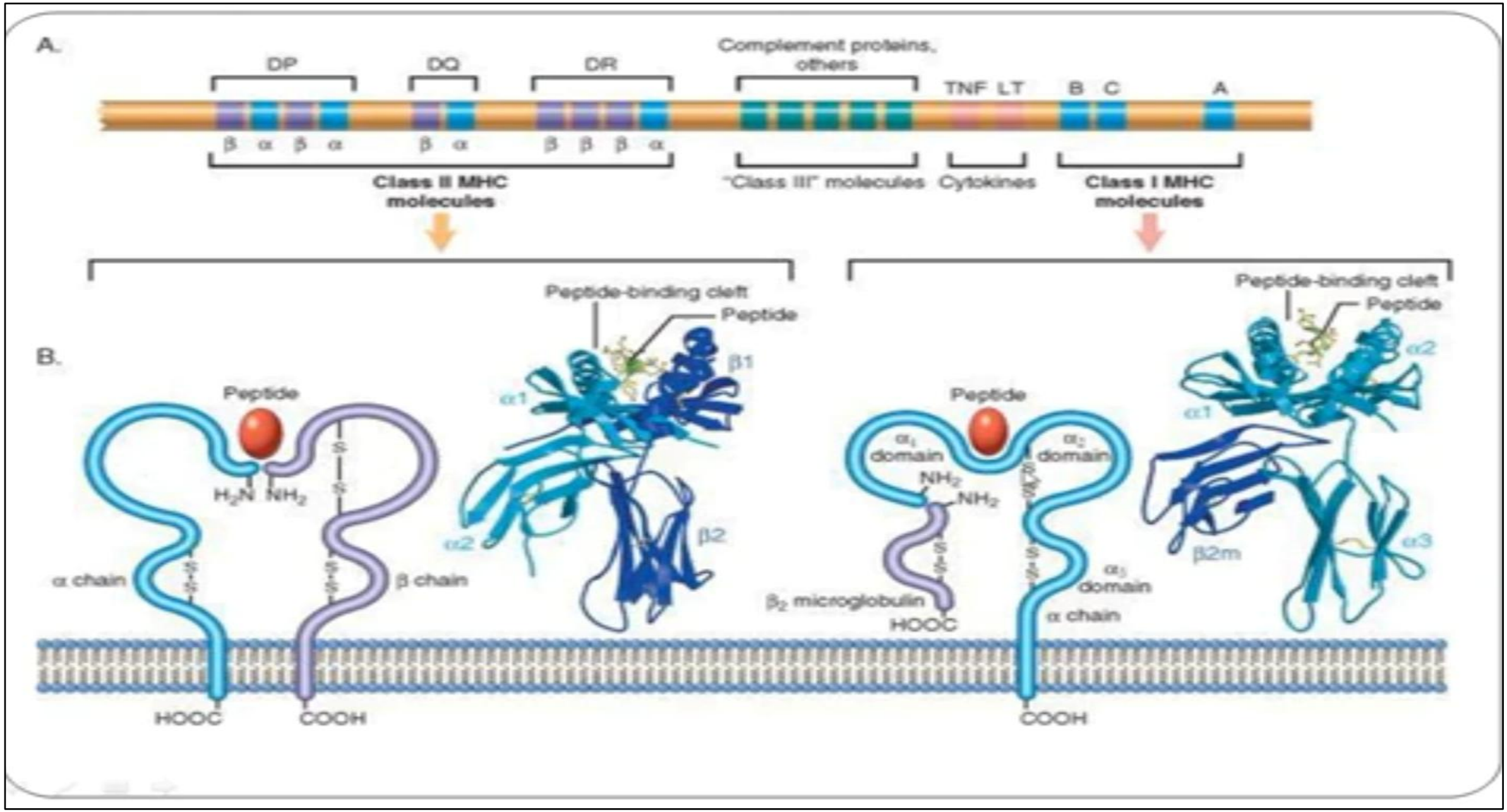
1. Class I MHC molecules

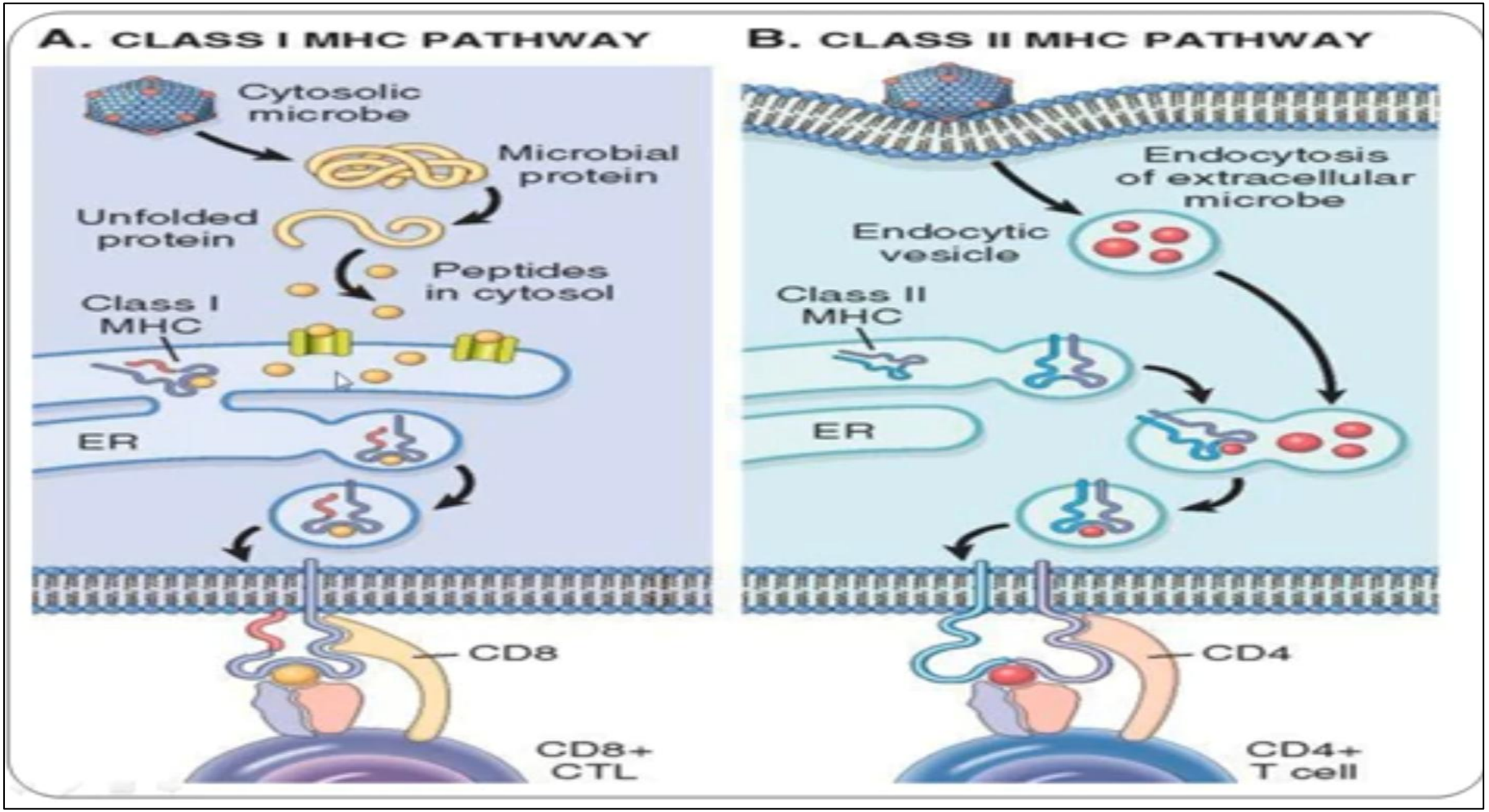
expressed on *all nucleated cells and platelets.*

- Encoded by 3 closely linked loci – HLA-A, HLA-B, and HLA-C, heterodimer molecules- polymorphic α linked noncovalently to nonpolymorphicpeptide β-2 macroglobulin.
- CD8 Tcells

2. Class II MHC molecules

- Coded in the HLA-D region (HLA-DP, HLA-DQ, and HLA-DR) heterodimer, noncovalently binded α and β chains CD4 Tcells.


A.
DP
DQ
DR
Complement proteins, others
TNF LT
B C
A
β α β α
β α
β β β α
Class II MHC molecules
"Class III" molecules
Cytokines
Class I MHC molecules
B.
Peptide-binding cleft
Peptide
β1
α1
α2
β2
α chain
β chain
HOOC
COOH
α1 domain
α2 domain
NH2
β2 microglobulin
α3
β2m



Source: https://www.sciencedirect.com/science/article/abs/pii/B9780123751584000043

- HLA and Disease Association.
- Mechanisms not fully understood grouped into the following categories ;
    1. Inflammatory diseases.
    2. Inherited errors of metabolism.
    3. Autoimmune disorders.
- Ankylosing spondylitis – B27
- Type I diabetes – DR3, DR4, DR3 /DR4
- Rheumatoid arthritis – DR4.

Hypersensitivity Reaction :

- Hypersensitivity is a misnomer.
- These diseases result from normal immune responses.
- Not excessive or “Hyper” responses.
- Classification based on immunologic mechanisms.

Characteristics :

- May be immediate or delayed hypersensitivity.
- Release of vasoactive substances.
- Phagocytosis or lysis of cells.
- Activation of inflammatory and cytolytic components of complement system.
- Release of cytokines, proteolytic enzymes and other mediator of tissue injury or inflammation.

- Both exogenous and endogenous antigens may elicit hypersensitivity reactions.
- The development of hypersensitivity diseases (both allergic and auto immune disorders) is often associated with the inheritance of particular susceptibility genes.
- Hypersensitivity reflects an imbalance between the effector mechanisms of immune response and the control mechanisms that serve to normally limit such responses.

TABLE 6–2 Mechanisms of Immunologically Mediated Diseases

Type	Prototype Disorder	Immune Mechanisms	Pathologic Lesions
Immediate (type I) hypersensitivity	Anaphylaxis; allergies; bronchial asthma (atopic forms)	Production of IgE antibody → immediate release of vasoactive amines and other mediators from mast cells; recruitment of inflammatory cells (late-phase reaction)	Vascular dilation, edema, smooth muscle contraction, mucus production, inflammation
Antibody-mediated (type II) hypersensitivity	Autoimmune hemolytic anemia; Goodpasture syndrome	Production of IgG, IgM → binds to antigen on target cell or tissue → phagocytosis or lysis of target cell by activated complement or Fc receptors; recruitment of leukocytes	Cell lysis; inflammation
Immune complex–mediated (type III) hypersensitivity	Systemic lupus erythematosus; some forms of glomerulonephritis; serum sickness; Arthus reaction	Deposition of antigen–antibody complexes → complement activation → recruitment of leukocytes by complement products and Fc receptors → release of enzymes and other toxic molecules	Necrotizing vasculitis (fibrinoid necrosis); inflammation
Cell-mediated (type IV) hypersensitivity	Contact dermatitis; multiple sclerosis; type I, diabetes; transplant rejection; tuberculosis	Activated T lymphocytes → i) release of cytokines and macrophage activation; ii) T cell–mediated cytotoxicity	Perivascular cellular infiltrates; edema; cell destruction; granuloma formation

Hypersensitivity reactions	Type I	Type II	Type III	Type IV
Synonym	Anaphylaxis (immediate type)	Cytotoxic (Antibody dependent).	Immune complex initiated	Cell – mediated (delayed)
Time elapsed	Seconds to minutes	Hours to a day	Hours to day	2 – 3 days
Specific immune	Ig E	Ig G, Ig M	Ig G, Ig M	T cell reactant
Chemical mediators of tissue injury and inflammation.	Vasoactive products of mast cells/basophils	Complement (C’)	Cytolytic, chemotactic, vasoactive components.	Lymphokines/monokines
Cell pathology/Pathophysiology.	Accumulation of neutrophils, eosinophils, smooth muscle contraction	Phagocytosis, lysis of target, receptor dysfunction.	Accumulation of neutrophils, macrophages, release of lytic lysosomal enzymes.	Lymphocytes and Macrophages.
Clinical examples.	Anaphylaxis, Urticartia Angioedema.	Hemolytic disease of new born, Graves diseases.	SLE, Serum sickness.	Granulomatous diseases,Organ allograft rejection.

Autoimmune diseases :

Definition : Autoimmune diseases are conditions in which the immune system fails to distinguish between self and non-self, leading to an abnormal immune response against the body own cells, tissues, and organs.

Autoimmunity – immune reaction against ‘self antigens’.

Common in females.

Three requirements :

1. The presence of an immune reaction specific for some self-antigen or self-tissue.
2. Evidence that such a reaction is not secondary to tissue damage but is of primary pathogenic significance.
3. The absence of another well- defined cause of the disease.

Types of autoimmune diseases	Description
Rheumatoid arthritis	A chronic inflammatory disorder affecting many joints including those in the hands and feet. In severe cases, it attacks internal organs.
Lupus	An inflammatory disease caused when the immune system attacks its own tissues and it also affects the joints, skins, kidney, brain, heart.
Celiac diseases	The immune reaction to eating glutan creates inflammation that damages the small intestine lining, leading to medical complication.
Multiple sclerosis	A disease in which the immune system damages the protective covering of nerves.
Ankylosing spondylitis	An inflammatory arthritis affecting the spine and large joints and it is more common among men and in early adulthood.
Alopecia areata	It occurs when the immune system attacks hair follicles and may be brought on by severe stress.
Vasculitis	It can cause vessel walls to thicken and narrow, cutting of vital blood supply to tissue and organs.