Immune System and Immunological mechanisms in health

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Learning objectives

At the end of the session, the students will be able to understand:

- Central and peripheral lymphoid organs
- Cells of immune system
- Major Histocompatibility Complex
- Cytokines and diseases caused by them

Structure of immune system

Lymphoid organs: Consist of central and peripheral lymphoid organs

- Central or primary lymphoid organs, e.g. thymus and bone marrow: They host the development of immune cells (hematopoiesis)
- Peripheral or secondary lymphoid organs, e.g. lymph node, spleen, and mucosa-associated lymphoid tissue (MALT)

Lymphoid cells: Consist of lymphocytes such as T cells, B cells and NK cells

Other cells of immune system: Include phagocytes, such as macrophage and microphages (neutrophil, eosinophil and basophil), dendritic cells, mast cells and platelets

Cytokines: They are the soluble products secreted from various cells of immune system. They include interleukins, interferons, tumor necrosis factors, colony-stimulating factors, etc.

CENTRAL LYMPHOID ORGANS

Bone Marrow

- All the cells in blood are originated from pluripotent hematopoietic stem cells of *bone marrow* and the process is called a **hematopoiesis.**
- In early fetal life, hematopoiesis occurs in liver; gradually the stem cells migrate to bone marrow.
- By birth, the stem cells occupy most of the bone marrow space of large bones.

Bone Marrow (Cont..)

- **After puberty** hematopoiesis is mostly **confined to axial bones** such as pelvis, vertebrae, sternum, skull & ribs.
- Progenitor T and B cells originate in bone marrow.
  - Further development of B cells occurs in bone marrow itself.
  - Progenitor T cells migrate to thymus for further proliferation.

Thymus

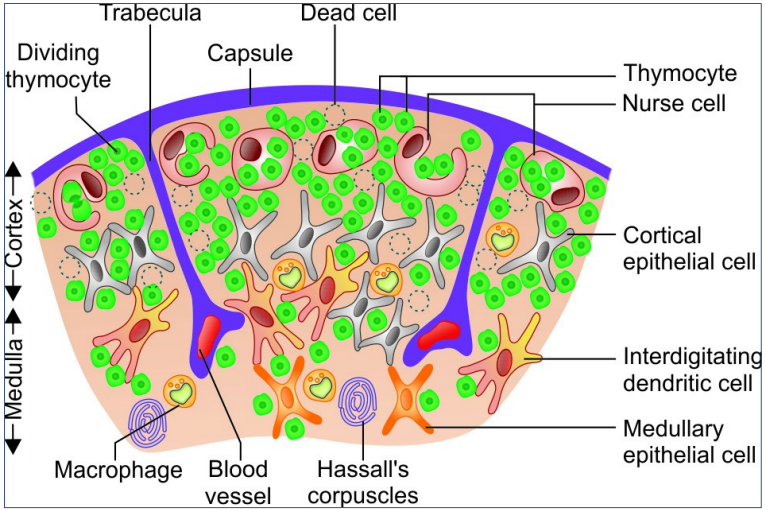
- Site of proliferation and maturation of T cells.

Development

- Developed in the embryonic life (third month) from third/fourth pharyngeal pouch.
- Highly active at birth, continues to grow for many years, reaches its peak size at puberty, and then it degenerates.

Structure

- Thymus has two lobes surrounded by a fibrous capsule.
- Septa arising from capsule divide thymus into lobules, and each lobule is differentiated into an outer cortex & an inner medulla



Cortex

- Densely populated and contains:
  - Thymocytes- Lymphocytes of thymus (immature and many in number).
  - Cortical epithelial cells and
  - Nurse cells (specialized epithelial cells with long membrane extensions that surround many thymocytes)

Medulla

- Sparsely populated and contains:
  - Thymocytes which are relatively more mature and fewer in number
  - Medullary epithelial cells
  - Interdigitating dendritic cells
  - Hassall’s corpuscles (concentric layers of degenerating epithelial cells)

Thymic Hormones

- Produced from the epithelial cells of thymus.
- They are believed to attract the precursor T cells (progenitor T cells) from bone marrow.
  - Thymulin
  - Thymopoietin
  - Thymosin

Maturation of T Cells

- Cell-to-cell interaction between thymocytes and thymic stromal cells (including epithelial cells, dendritic cells and macrophages) and the effect of thymic hormones help in maturation of T cells in thymus

Central Tolerance

- Only 2-5% of the developing T cells become mature and released out from thymus.
- Remaining T cells are destroyed as they are either not capable of recognizing MHC or are believed to be self-reacting in nature.
- Destruction of such self-reacting T cells prevents development of autoimmunity (immune response against self-antigens).
- Such tolerance to self-antigens mediated by thymus that occurs in embryonic life is called as central tolerance.

Defect in Thymus

- Leads to defect in maturation of T lymphocytes that in turn results in severe life threatening cell mediated immunodeficiency disorders.
- **DiGeorge syndrome** (immunodeficiency disorder) - congenital aplasia of thymus.
- **Nude mice-** Mice with congenital absence of thymus.

PERIPHERAL LYMPHOID ORGANS

Lymph Node

- Small bean shaped organs.
- Occur in clusters or in chains, distributed along the length of lymphatic vessels.
- Lymph nodes act as physiological barriers - filter the microbial antigens carried to lymph node by activating the T and B cells.

Structure

- Thymus is divided into three parts:
  - Cortex
  - Medulla (both are B cell areas)
  - Paracortex (T cell area).
- Bears the lymphatic vessels (efferent and afferent) and blood vessels.

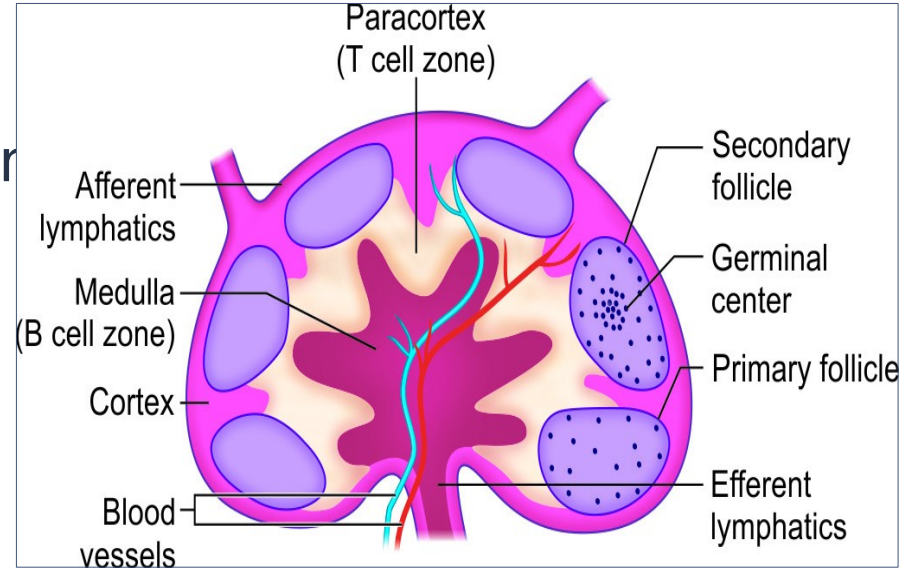
Cortex

- Contains lymphoid follicles that are composed of:
  - B cells
  - Few special type of dendritic cells (called follicular dendritic cells)
  - Occasional T cells.
- Lymphoid follicles are mainly of two types:
  - Primary lymphoid follicles
  - Secondary lymphoid follicles

Cortex (Cont..)

Primary lymphoid follicles:

- Found before the antigenic stir
- Smaller in size
- Contain the resting B cells.



Cortex (Cont..)

Secondary lymphoid follicles:

- Following contact with an antigen - resting B cells starts dividing and become activated.
- Activated B cells differentiate rapidly in to *plasma cells* and *memory B cells.*
- Follicles become larger called secondary lymphoid follicles.

Cortex (Cont..)

Secondary lymphoid follicles (Cont..):

- Has two areas:
  - Central area - **germinal center**
  - Peripheral zone - **mantle area**; contains activated B cells.

Paracortical area

- Present in between cortex and medulla.
- T cell area of lymph node (rich in naive T cells).Contains macrophages and interdigitating dendritic cells, which trap the antigens and present to T cells.

Medulla

- Innermost area of lymph node.
- Rich in B-lymphocytes (mainly plasma cells).

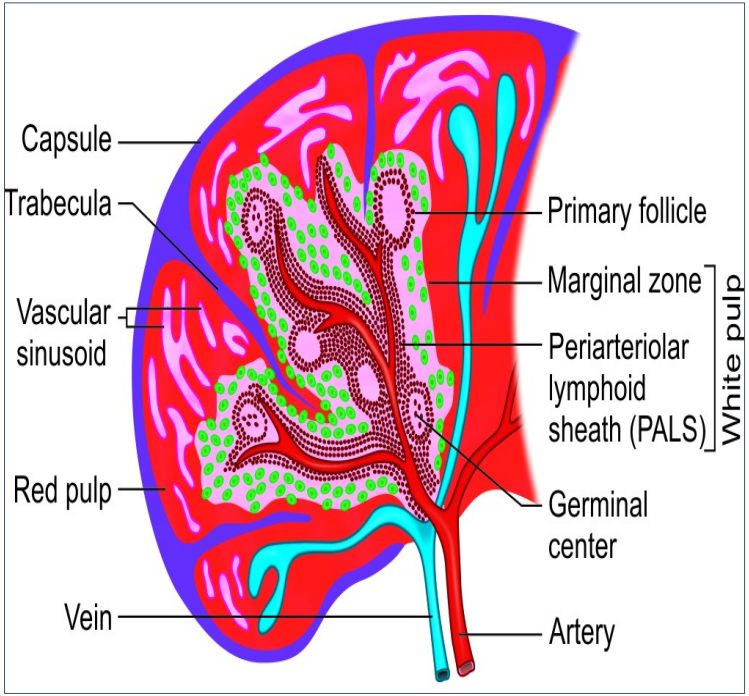
Spleen

- Largest secondary lymphoid organ.
- Acts as **physiological barrier** similar to lymph node in clearing the microbial antigens through the antigenic stimulation of T and B cells.

Structure

- Situated below the diaphragm on left side of the abdomen.
- Adult spleen measures about 5-inch in length & weighs around 150gm.
- Divided into two compartments: central *white pulp* and outer *red pulp*, surrounded by capsule and intervened by trabeculae.

Structure


Capsule
Trabecula
Vascular sinusoid
Red pulp
Vein
Primary follicle
Marginal zone
Periarteriolar lymphoid sheath (PALS)
White pulp
Germinal center
Artery

White pulp

- Central densely populated area.
- Contains T cells and B cells.
- It has two parts:
  - Periarteriolar lymphoid sheath (PALS), which is T cell area
  - Marginal zone is located peripheral to the PALS and is populated by B cell lymphoid follicles

Red pulp

- Area that surrounds the sinusoids.
- Filled with red blood cells (RBCs).
- Older and defective RBCs are destroyed here.

Defect in Spleen

- Increased incidence of bacterial sepsis caused primarily by capsulated bacteria such as:
  - *Streptococcus pneumoniae*
  - *Neisseria meningitides*
  - *Haemophilus influenzae*.

Mucosa-associated Lymphoid Tissue (MALT)

- Defense mechanisms in the mucosal sites to prevent the microbial entry.
- Group of lymphoid tissues lining these mucosal sites are collectively known as mucosa associated lymphoid tissue (MALT).

Mucosa-associated Lymphoid Tissue (MALT)
(Cont..)

- Structurally, MALT may be arranged in two types-
  - Loose clusters of lymphoid cells (usually found in the lamina propria of intestinal villi)
  - Lymphoid tissues arranged as organized structures (such as tonsils, appendix and Peyer’s patches)

Submucosa

- Contains Peyer’s patches.
- **Peyer’s patch -** nodule of 30–40 lymphoid follicles (both primary and secondary follicles similar to that of lymph node)

Lamina propria

- Contains loose clusters of lymphocytes (B cells, plasma cells, T helper cells) and macrophages

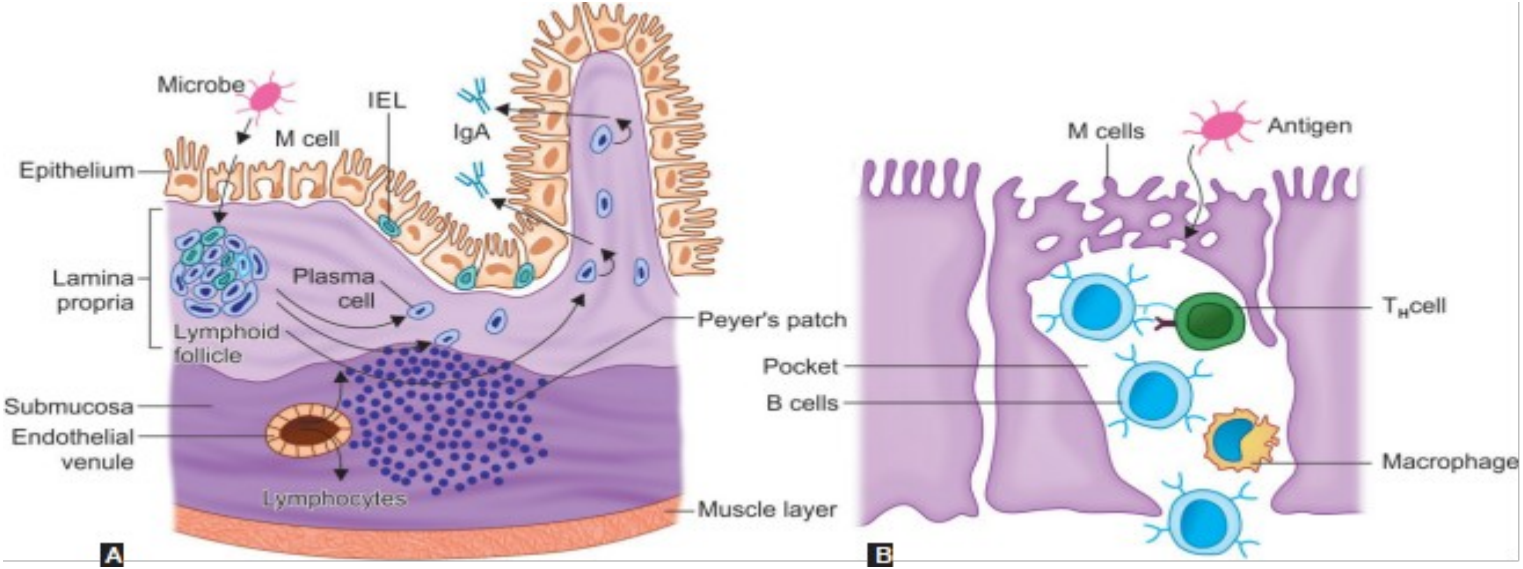
Epithelial layer

- Contains few specialized lymphocytes called intraepithelial lymphocytes (IELs) and modified epithelial cells (called M cells)
  - **Intraepithelial lymphocytes (IELs)** are the γδ T cells.
  - **M cells**
  - **Secretory IgA:** Dimeric IgA antibodies - present in the submucosa as well as in the lining epithelium.

M Cells

- Specialized flattened epithelial cells.
- Do not have microvilli; instead they bear deep invaginations or *pockets* in the basolateral side.
- Contains B cells, T cells and macrophages.
- Portal of entry of a number of microbes such as *Salmonella, Shigella, Vibrio,* and Poliovirus.

M Cells (Cont..)



A. MALT; **B.** Structure of M cell

M Cells (Cont..)

- Invading microbes are taken-up by M cells (by endocytosis) - transported in a vesicle and are delivered to the basolateral pockets
- B lymphocytes in MALT once activated at a site by antigenic exposure, migrate to other parts of the intestine, secrete the dimeric IgA, and thus extend the local immunity

Cutaneous-associated Lympho Tissue

- Similar to MALT.
- Skin also contains a few loose lymphocytes and specialized antigen presenting cells in epidermis called *Langerhans cells*.

LYMPHOID CELLS

LYMPHOID CELLS

- Lymphocytes are the major components of cells of immune system.
- Approximately 10^{11} lymphocytes in the body, accounting for 20-40% of the total white blood cells (WBCs) in blood and 99% of the cells in the lymph.

Distribution of lymphocytes (%) in organs/blood

Tissues	T cell	B cell	NK cell
Bone marrow	5-10	80-90	5-10
Thymus	99	<1	<1
Lymph node	70-80	20-30	<1
Spleen	30-40	50-60	1-5
Peripheral blood	70-80	10-15	10-15

CD molecules (cluster of differentiation)

- Cell surface markers useful for the identification of cells of immune system.
- Numerous functions, often act as surface receptors or some CD proteins may help in cell adhesion.
- As of 2015, CD molecules for humans are numbered up to 364, important examples are CD4 and CD8 molecules—expressed by helper T cells and cytotoxic T cells

TYPES OF LYMPHOCYTES

TYPES OF LYMPHOCYTES

- **Based on function and cell membrane structure:**
  - T lymphocytes
  - B lymphocytes
  - NK (natural killer) cells.
- Lymphocytes can also be classified into:
  - Naive lymphocytes
  - Lymphoblasts.

Naive Lymphocytes

- Resting B and T lymphocytes that have not interacted with antigen (unprimed lymphocytes).
- Also known as *small lymphocytes* (6µm); having thin rim of cytoplasm, larger nucleus with dense chromatin; fewer mitochondria, ribosomes, and lysosomes.
- Short life span (1-3 months).

Lymphoblasts

- Naive cells interact with antigen in the presence of certain cytokines (e.g. interleukin-7) - become activated - transform into lymphoblasts - eventually differentiate into effector cells or memory cells.

Effector cells

- Function in various ways to eliminate antigen.
- Short life span (few days to few weeks)
- *Large lymphocytes* (15 µm in size), having wider rim of cytoplasm with more organelles.
  - Effector B cells - Antibody producing *plasma cells*
  - Effector T cells - *Helper* T cells and *cytotoxic* T cells.

Memory cells

- Remain dormant like naive cells.
- Capable of transforming into effector cells rapidly on subsequent antigenic challenge.
- Longer life span; providing long term immunity to may pathogens.

Differences between naive, effecto and memory cells

	Naive cell	Effector cell	Memory cell
Location (present mostly in)	Secondary lymphoid organs	Inflamed tissues & mucosal surfaces	Both the locations of naive & effector cell
Cell cycle	Dormant (G0 phase)	Active	Dormant (G0 phase)
Morphology	Small lymphocyte	Large lymphocyte	Small lymphocyte
Life span	Short	Short	Long
Function	Transforms to effector cell on primary exposure to antigen; Occurs slow due to lag period	Eliminate antigen	Transforms to effector cell on secondary exposure to antigen, Occurs fast without lag period

Differences between naive, effector and memory cells (Cont..)

	Naive cell	Effector cell	Memory cell
Surface markers			
CD127 (IL-7R)	High	Low	High
CD45 isoform	CD45RA	CD45RO	CD45RO
CD25 (IL-2R α) on T cells	No	Yes	Yes
CD27 on B cells	No	Yes	Yes
B cells producing Ig types & their affinity	IgM and IgD Low affinity	IgG, IgA, IgE High affinity	IgG, IgA, IgE High affinity

T LYMPHOCYTES

T LYMPHOCYTES

- T cells constitute 70–80% of blood lymphocytes.
- Unlike B cells, they do not have microvilli on their surface.
- Bear specialized surface receptors called T cell receptors (TCR).

T Cell Receptor

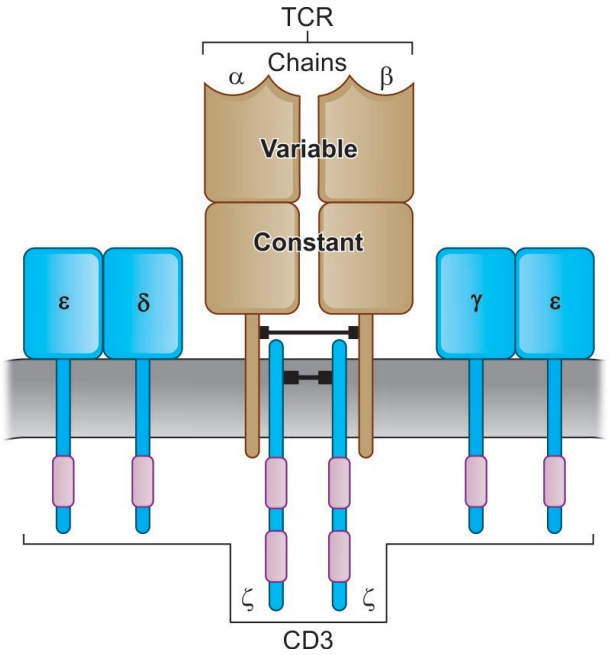
- Main function - antigen recognition.
- Unlike B cell receptor which binds to antigen directly, TCR does not recognize antigen by itself.
- Can only respond to an antigen which is processed and presented by the antigen presenting cells such as macrophages.

TCR–CD3 Complex

- Most T cell receptors (95%) comprise of two chains (α & β) which in turn have three regions:
  - Extracellular domain
  - Transmembrane domain
  - Cytoplasmic tail.
- Extracellular domain of each polypeptide chain has 2 regions (variable and constant region).

TCR–CD3 Complex *(Cont..)*

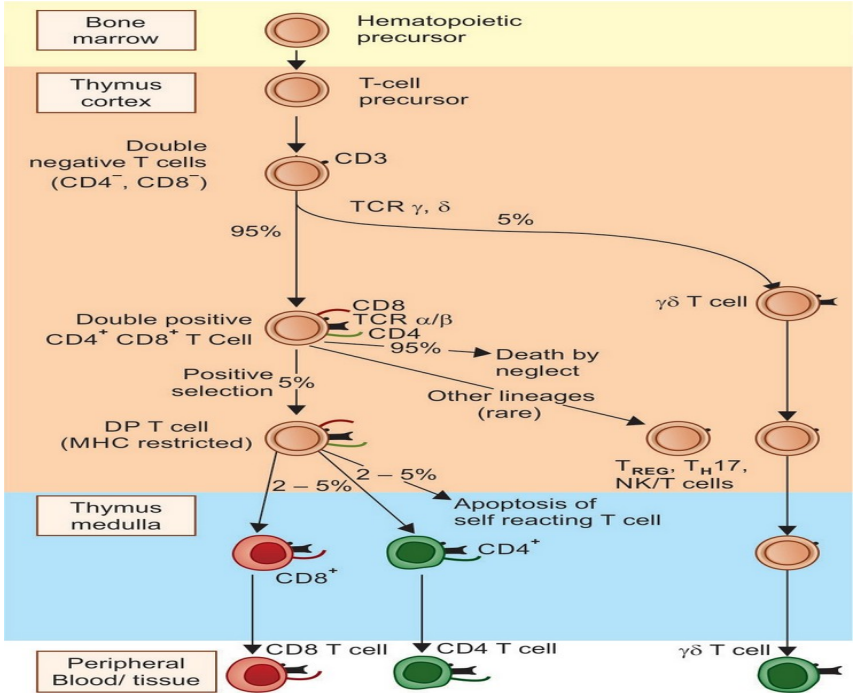
- TCR is active only when both the chains (α & β) complexes with CD3 molecule.



T Cell Development

- Major events of T cell maturation take place in thymus.
- Progenitor T cells are originated from the fetal liver or in adults from the bone marrow and seed the thymus through blood stream.

T Cell Development (Cont..)



Types of T Cells - *Effector T C*

- Two types of effector T cells:
  - $CD4^+$ helper T cells
  - $CD8^+$ cytotoxic T cell.

Helper T cells (T_H)

- Possess CD4 molecules as surface receptors.
- Recognize the antigenic peptides that are processed by antigen presenting cells and presented along with MHC-II molecules.
- Following antigenic stimulus, the helper T cells differentiate into either of the two types of cells- T_H1 and T_H2 subset.
- Each secrete specific cytokines which modulate the cellular and humoral immune responses respectively.

Helper T cells (T_H) (Cont..)

***T_H17 cells*:**

- Recently a third subset of T helper cells.
- Produces IL-17 & IL-22 - primarily involved in recruiting neutrophils which in turn kill the microbes as well as induce inflammation.
- Contribute to the pathogenesis of many autoimmune inflammatory diseases.

Cytotoxic T cells

- Possess CD8 molecules
- Recognize the intracellular antigens processed by any nucleated cells and presented along with MHC-I.
- T_C cells are involved in destruction of virus infected cells and tumor cells.

Regulatory T cells (TREG cells)

- Subpopulation of T cells which regulate the immune system.
- Provide tolerance to self-antigens (known as peripheral tolerance), and prevent the development of autoimmune disease.
- **Surface markers** -T_{REG} cells possess surface markers such as CD4, CD25 and Foxp3 (a forkhead family transcription factor)
- **Deficiency of Foxp3** receptors leads to a severe form of autoimmune disease known as **I**mmune dysregulation, **P**olyendocrinopathy, **E**nteropathy **X**-linked (**IPEX**)

γδ T cells

- Small subset of T cells (5%) that possess a distinct TCR composed of γ & δ chains; instead of α/β chains.
- Lack both CD4 and CD8 molecules.
- Do not require antigen processing and MHC presentation of peptides.

γδ T cells (Cont..)

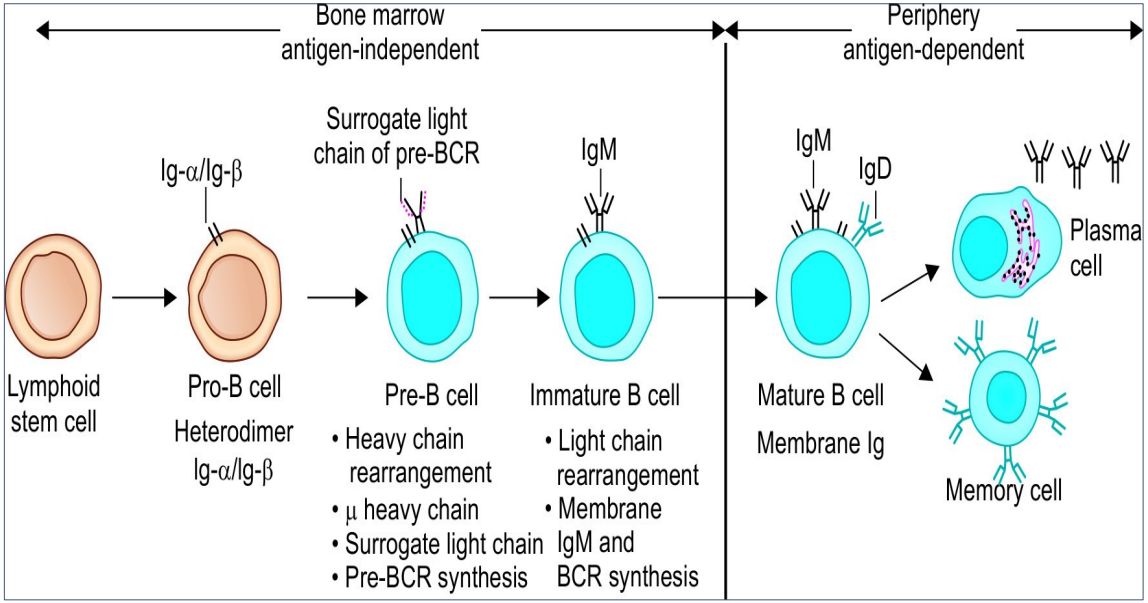
- Part of innate immunity.
- Found in the gut mucosa, within a population of lymphocytes known as *intraepithelial lymphocytes* (IELs).
- Encounter the lipid antigens that enter through the intestinal mucosa.

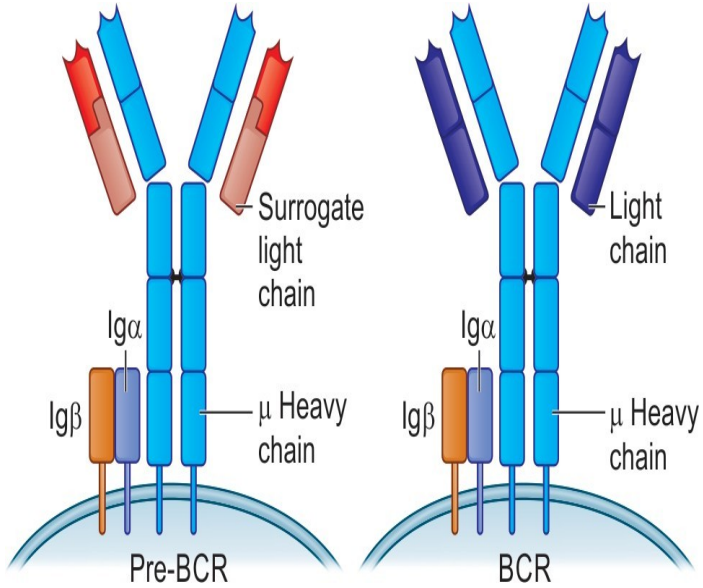
B LYMPHOCYTES

B LYMPHOCYTES

- Mediators of humoral immunity; constitutes 10-15% of blood lymphocytes.
- Named after their site of maturation (*b*ursa of Fabricius in birds and *b*one marrow in human and other mammals).

Development of B Lymphocyt





Development of B Cells in Peripheral Lymphoid Organs

- Immature B cells migrate from bone marrow to peripheral lymphoid organs (lymph node and spleen).
- Transform into mature B cells following contact with appropriate antigen.

Mature or Naive B Cells

- Most mature B cells (95%) belong to the follicular B cell type and produce surface receptor IgD in addition to IgM.
- Play an important role in humoral immune response.
- Following antigenic stimulus, the mature B cells transform into activated B cells (lymphoblasts).
- Which further differentiate into either effector B cells i.e. plasma cells (majority) or memory B cells.

Mature or Naive B Cells (Cont..)

- **Plasma cells** (antibody secreting cells):
  - Oval, large (15µm size), with an eccentrically oval nucleus containing large blocks of peripheral chromatin (*cartwheel* appearance)
  - Cytoplasm contains abundant organelles.
  - Short life span of two or three days.

Rare mature B cell types

- **B-1 cells:**
  - Found mostly in the peritoneal cavity.
  - Coated by surface markers IgM (natural antibodies) and CD5 molecules, but lack IgD.
- **Marginal-zone B cells**:
  - Present at the edges of lymphoid follicles of spleen.
  - Produced in response to the polysaccharide antigens.

Differences between T cell and B cell

Property	T-cell	B-cell
Origin	Bone marrow	Bone marrow
Maturation	Thymus	Bone marrow
Peripheral blood	70-80% of total lymphocytes	10-15% of total lymphocytes
Antigen recognition receptors	T cell receptors complexed with CD3	B cell receptor-Surface IgM or IgD complexed with Igα/Igβ
CD markers	CD 3,4,8	CD19, 21, 24
Thymus specific Ag	Present	Absent
Microvilli on the surface	Absent	Present

NATURAL KILLER CELLS

NATURAL KILLER CELLS

- Large granular lymphocytes.
- Constitute 10-15% of peripheral blood lymphocytes.
- Derived from a separate lymphoid lineage.
- Similar to cytotoxic T cells, NK cells also are involved in destruction of virus infected cells and tumor cells.

OTHER CELLS OF IMMUNE SYSTEM

Macrophage

- First described - Russian scientist Metchnikoff (1883)
- Monocytes/macrophages originate from bone marrow, from a separate lineage; i.e. from the granulocyte-monocyte progenitor cells.

Macrophage (Cont..)

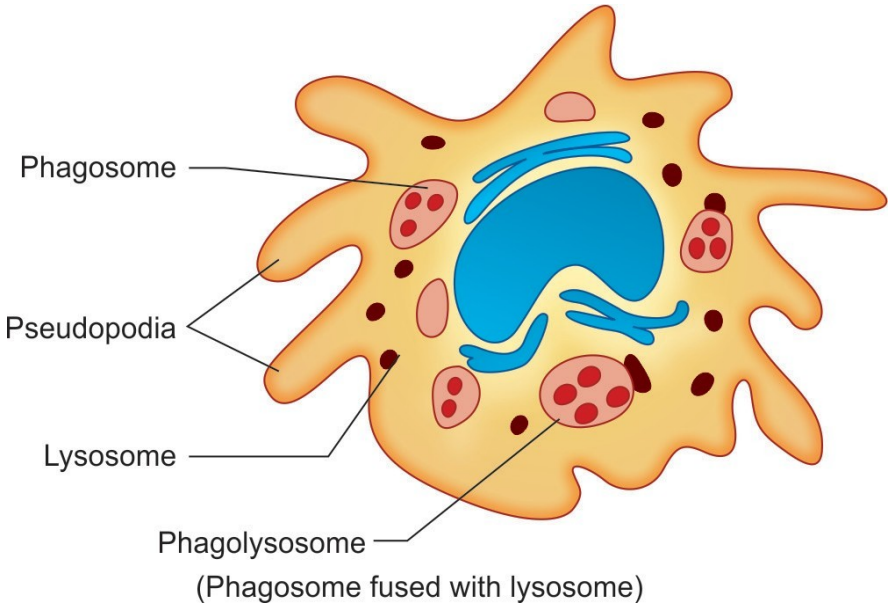
- **Monocytes:**
  - Present in blood.
  - Largest blood cells measuring 12-20µm size.
  - Do not divide.
  - Average transit time -8 hours in blood; then they migrate to tissues.

Macrophage (Cont..)

Macrophages:

- When monocytes migrate to tissues, they transform into macrophages
- Macrophages differ from monocytes in the following:
  - 5-10 folds larger than monocytes
  - Contain more lysozymes and cell organelles
  - Produce more lytic enzymes and cytokines
  - Possess greater phagocytic activity
  - Have a longer life in tissues (months to years)

Macrophage (Cont..)



Types of macrophages

Body sites		Macrophage designation
Peripheral blood		Monocytes
Tissues		Macrophages
	Liver	Kupffer cells
	Brain	Microglial cells
	Kidney	Mesangial cells
	Lungs	Alveolar macrophages
	Bone	Osteoclasts

Types of macrophages (Cont..)

Body sites		Macrophage designation
	Inflammation site	Epithelioid cells Multinucleated cell (Langhans giant cells)
	Connective tissues	Histiocytes
	Placenta	Hofbauer cell
	Lymphoid follicle	Tingible body macrophage

Secretory products of activated macrophages

Secretory Products	Examples
Enzymes	Lysozyme, acid hydrolases, elastases, Phosphatases, lipases, collagenases
Free radicals	Reactive oxygen intermediates ➢ Superoxide anion (O2-) ➢ Hydroxyl radicals (OH) ➢ Hydrogen peroxide (H2O2) ➢ Hypochlorite anion(ClO-) Reactive nitrogen intermediates- ➢ Nitric oxide (NO) ➢ Nitrogen dioxide (NO2) ➢ HNO2(nitrous acid)

Secretory products of activated macrophages
(Cont..)

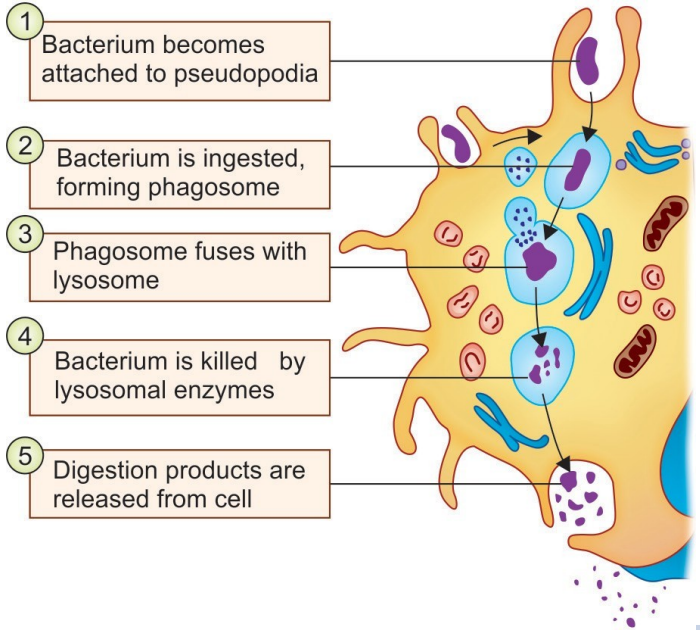
Secretory Products	Examples
Cytokines	Interferon α,β Interleukins (IL-1, IL-6, IL-8, IL-12) Tumor necrosis factor- α (TNF- α)
Growth factors	Colony stimulating factors (CSF) Platelet derived growth factor (PDGF) Platelet activating factor (PAF) Transforming growth factor β (TGF-β)
Coagulation factors	Factor V,VII,IX,X Prothrombin
Complement factors	C5, C8 properdin, Factor B, D, I

Functions of Macrophage

- Phagocytosis
- Antigen presentation
- Activated macrophages
- Secretory products

Phagocytosis

- Macrophages are the principle cells involved in phagocytosis.
- Steps:



Antigen presentation

- Macrophages also promote adaptive immunity, by acting as antigen presenting cells (APCs).
- Macrophages capture the antigen - process into smaller antigenic peptides and present the antigenic peptides along with the MHC class II molecules to the helper T cells.
- Facilitating helper T cell activation.

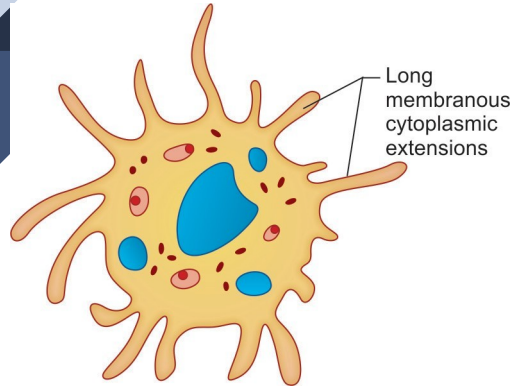
Activated macrophages

- On exposure to cytokines such as *interferon-γ*, macrophages become activated ▭ greater phagocytic ability ▭ produce many cytokines ▭ act against intracellular bacteria, virus infected cells and tumor cells.
- Also express higher level of MHC class II, hence can act as efficient APCs.

Secretory products

- Interleukin 1 (IL-1):Promotes inflammatory responses, fever and activate helper T cells.
- IL-6 & TNF-α:Promote innate immunity, (inflammation & fever) and eliminate the pathogens.
- Interferon α & β -have *antiviral* activity.
- TNF-α: Lyse the tumor cells (*anti-tumor* activity)
- Growth factors such as CSF (colony stimulating factor): promote hematopoiesis.
- Following tissue injury, various mediators are secreted from macrophage; which help in *tissue repair* and *scar formation.*

Dendritic Cells



- Possess long membranous cytoplasmic extensions resembling dendrites of neurons - hence named as dendritic cells.
- Originate from bone marrow, but the pathway is uncertain.
- Develop as a separate lineage from stem cells or may originate from the macrophage lineage.

Distribution and functions of dendritic cells

Types of dendritic cells	Site	Function
Langerhans cells	Skin and mucosa	Antigen presentation, express high MHC-II and B7 molecules
Interstitial dendritic cells	Organs (lungs, liver, spleen etc)	
Interdigitating dendritic cells	Thymus	
Circulating dendritic cells	Blood & lymph	
Follicular dendritic cells	Lymph nodes	➢ B cells maturation, and differentiation ➢ MHC-II and B7 molecules absent ➢ Coated with Ag-Ab complex

Functions of dendritic cells

- Non-phagocytic in nature.
- Most efficient APCs.
- Main function is to capture, process and present the antigenic peptides on their cell surface to the helper T cells.
- Carry high level of MHC class II and co-stimulatory B7 molecules.
- Act as messengers between the innate and the adaptive

Follicular dendritic cells

- Present in lymphoid follicles are an exception in the sense that they recognize antigen-antibody complex rather than antigen alone.
- Do not act as APCs
- Do not express MHC class II or B7 molecules.

Granulocytic Cells

- Granulocytes are a category of white blood cells characterized by the presence of granules in their cytoplasm.
- E.g. neutrophils, eosinophils and basophils.
- Differ from each other by cell morphology and cytoplasmic staining and function.

Neutrophils

- Possess multilobed nucleus and a granulated cytoplasm that stains with both acid and basic dyes.
- Cytoplasm - heavily granular; contains several granules such as myeloperoxidase, lysozyme, defensins, elastase, gelatinase, etc.
- Constitute 50%–70% of the circulating WBCs.

Neutrophils *(Cont..)*

- Level is greatly increased in presence of infection under the influence of certain cytokines such as ***IL-8.***
- Principal phagocytes of innate immunity.
- Mechanism of microbial killing:
  - Both by oxygen dependent and independent mechanisms.

Eosinophils

- Bilobed nucleus and a granular cytoplasm that stains red with the acid dye eosin.
- Phagocytic.
- Constitute only 1-3% of total leukocytes.
- Number is greatly increased in certain allergic conditions and helminthic infections.
- Interleukin-5 is believed to be the eosinophil chemotactic factor.

Basophils

- Non-phagocytic granulocytes.
- Function – secretes contents of granules.
- Lobed nucleus and heavily granulated cytoplasm that stains with the basic dye methylene blue.
- Resemble mast cells in their function.
- Granules are rich in histamine & other mediators that play a major role in certain allergic responses.

Mast Cells

- Present in various body sites such as skin, connective tissues of various organs, and mucosa (respiratory and intestinal).
- Contain cytoplasmic granules rich in histamine and other active substances.
- Play an important role in the development of certain allergic (type I hypersensitivity) reactions.

MAJOR HISTOCOMPATIBILITY COMPLEX

MAJOR HISTOCOMPATIBILITY COMPLEX

- Complex is a group of genes.
- Coding for a set of host cell surface molecules that bind to peptide fragments derived from pathogens
- Display them on the host cell surface for recognition by the appropriate T-cells.

MAJOR HISTOCOMPATIBILITY COMPLEX
(Cont..)

- Present in almost all the human cells, but first discovered on the surface of leukocytes; hence in humans, the MHC coded proteins are also called as **human leukocyte antigens (HLA).**
- Serve as a unique identification marker for every individual.
- Following transplantation of a graft, the recipient mounts an immune response against the graft's MHC molecule and

MAJOR HISTOCOMPATIBILITY COMPLEX
(Cont..)

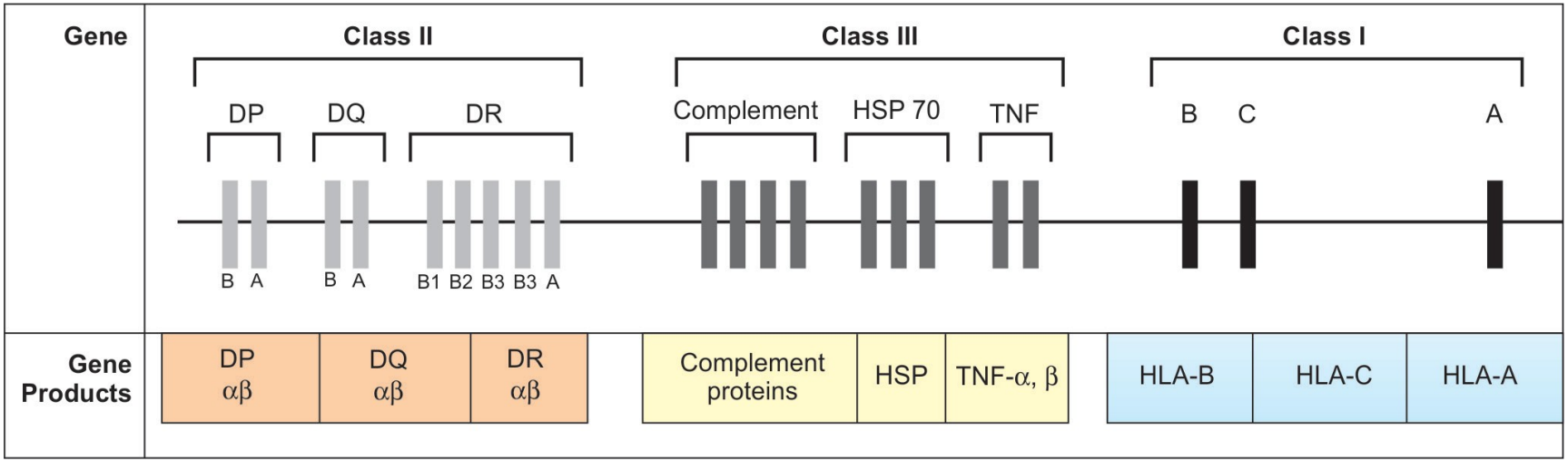
- The acceptance or rejection of the graft is directly dependent on the MHC molecules of the graft and the recipient.
- As the MHC molecules determine the compatibility between the graft and host tissues, they are named as **histocompatibility antigens**.

MHC GENES AND THEIR PRODUCTS

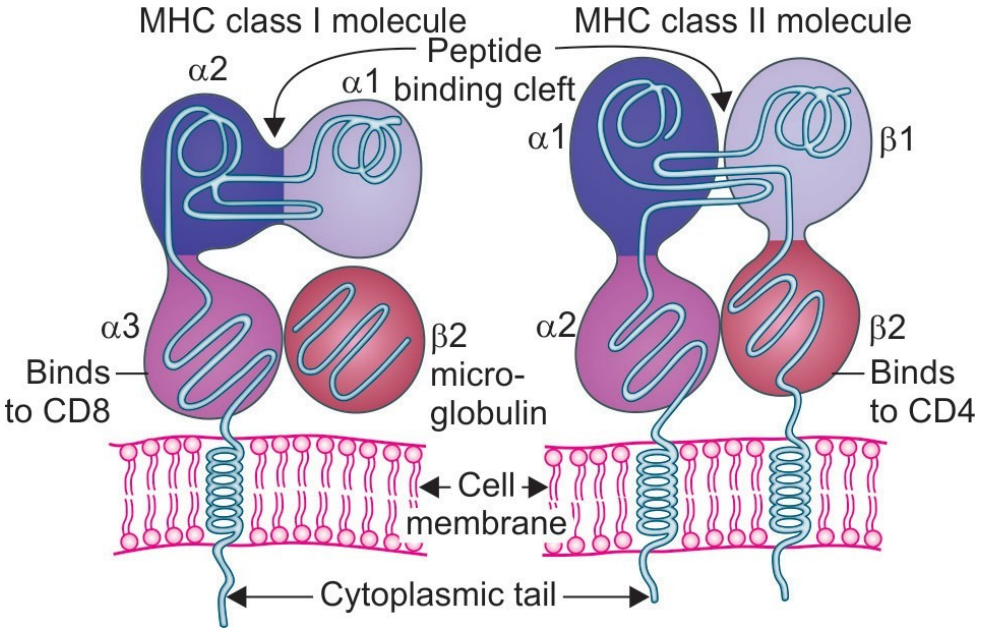
MHC GENES AND THEIR PRODUCTS

- Located in *short arm of chromosome-6*.
- HLA complex extends over 4000kbp length covering >100 genes.
- Genes are clustered in three regions named as MHC region-I, II and III.

Structure of human MHC complex



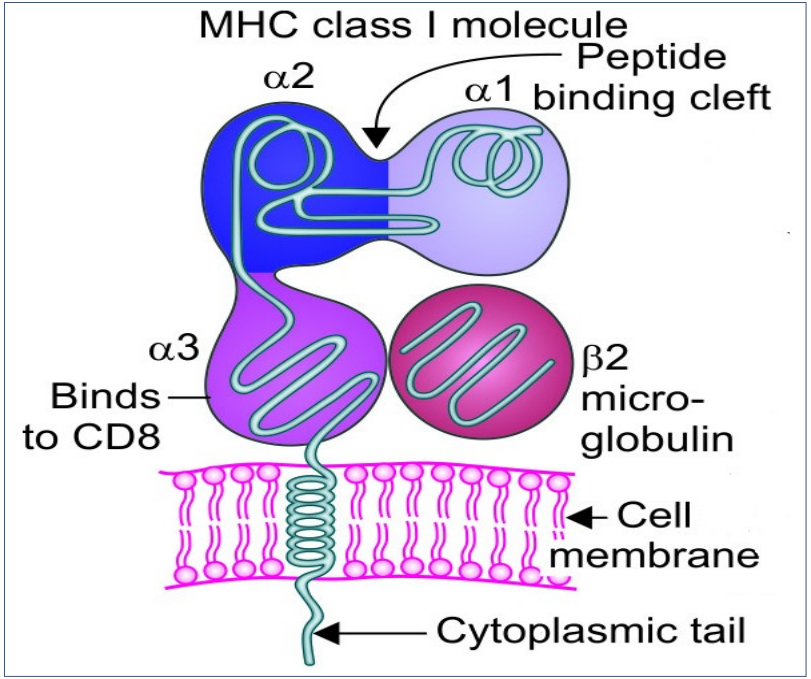
Structure of MHC molecule



MHC Class I Molecule

- Association of β2 microglobulin with α chain is necessary for the expression of MHC I molecules on to the cell surface.
- In **Daudi cells** (a type of human B cell tumor cell which are not able to produce β2 microglobulin) - observed that they synthesize MHC-I but do not express them on cell surface.

Structure of MHC Class I molecule



Role of MHC Class I Molecule

- Antigen peptide groove of class I MHC molecule (i.e. the site, where the antigen peptide binds) is formed by the cleft between α1 and α2 domains.
- α3 domain binds to CD8 molecule present on cytotoxic T cells during antigen presentation.

MHC Class II Molecule

- Comprises of one α chain (33 kDa) and one β chain (28 kDa).
- The α and β chains in turn consist of two domains each—(1) α1 and α2 and (2) β1 and β2, respectively and cytoplasmic tails.

MHC Class II Molecule (Cont..)

- The antigen peptide binding groove is formed by the cleft between α1 and β1 domains
- β2 domain interacts with CD4 molecule of helper T cells during antigen presentation.

Differences between MHC class I a
MHC
class II molecules

	MHC class I	MHC class II
Present on	All nucleated cells (except sperms) and platelets	Antigen presenting cells (APCs)
Peptide antigen is	presented to CD8 T cells	presented to CD4 T cells
Nature of peptide antigen	Endogenous or intracellular (viral / tumor antigen)	Exogenous
Peptide antigen (size)	8-10 amino acid long	13-18 amino acid long
Antigen presentation pathways	Cytosolic pathway	Endocytic pathway
Peptide-binding site	α1/α2 groove	α1/β1 groove
CD4 or CD8 binding site	α3 binds to CD8 molecules on T_C cells	β2 binds to CD4 on T_H cells

Regulation of MHC Expressio

- **Transcription factors-**MHC genes have promoter sequences at their 5’ end which are regulated by certain transcription factors such as **CIITA, and RFX** (both bind to MHC II promoter genes and increase their transcription). Defects in CIITA, and RFX cause one of the form of **bare lymphocyte syndrome**.

Regulation of MHC Expression
(Cont..)

- **Cytokines** also influence MHC expression.
  - Interferon γ activates both MHC-I & II promoter genes.
  - IL-4 increases expression of class II MHC molecules on resting B cells.

Regulation of MHC Expression
(Cont..)

- **Corticosteroid and prostaglandins** decrease the expression of MHC II molecules.
- **In many viral infection**, the viral antigens inhibit various components of MHC-I (e.g., adenovirus proteins inhibit TAP, cytomegalovirus proteins inhibit β2 microglobulin). As a result, MHC-I expression is suppressed.

Diseases associated with certain HLA alleles

HLA allele	Associated disease
HLA B27	Ankylosing spondylitis, Reactive arthritis (Yersinia, Salmonella, Gonococcus) and Reiter's syndrome
DR-2	Multiple sclerosis, Goodpasture's syndrome, Narcolepsy
DR-3	Myasthenia gravis, systemic lupus erythematosus (SLE)
DR-3/DR-4	Insulin-dependent diabetes mellitus
DR-4	Rheumatoid arthritis
A3/B14	Hereditary hemochromatosis

SOLUBLE PRODUCTS OF LYMPHOID CELLS

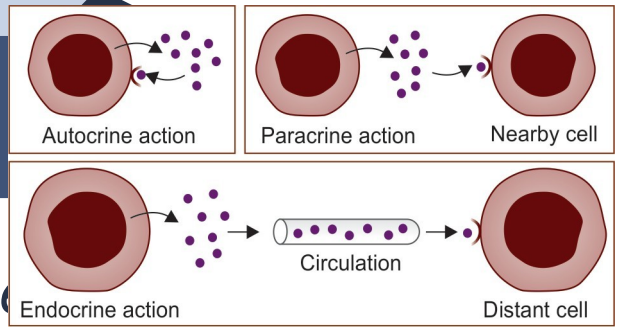
CYTOKINES

- Cytokines are chemical substances which serve as messengers, mediating interaction and communication between the various cells of immune system.

Major Classes of Cytokines

- Lymphokines- produced by lymphocytes
- Monokines- produced by monocytes & macrophages
- Interleukins- produced by WBCs and acting on the same or different WBCs
- Chemokines- involved in chemotaxis and other leukocyte behavior

Properties of Cytokines

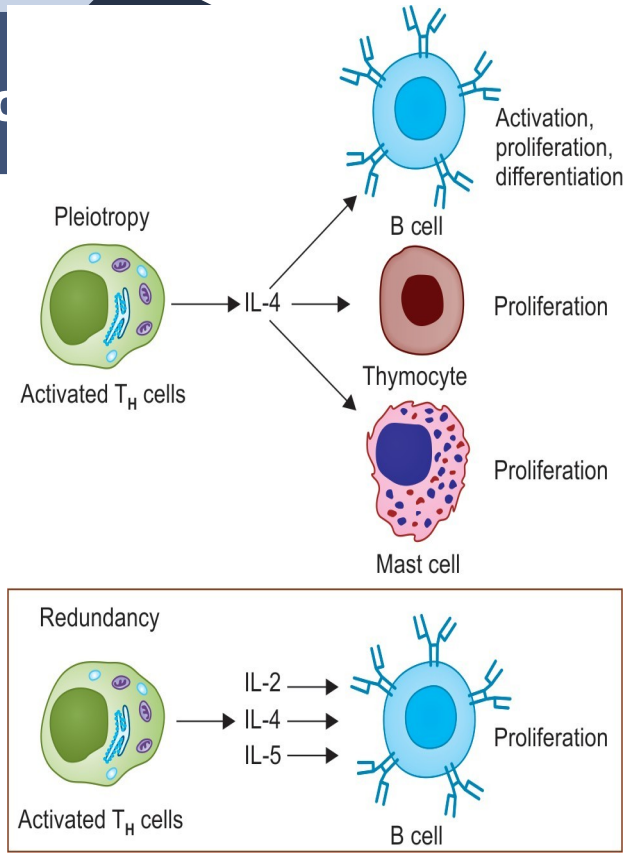


- Growth factors are produced *constitutive* while cytokines are *inducible* i.e. produced only after the activation of their cells of origin.
- Cytokines have broad range of effects; which include:
  - Autocrine effect- Act on the same cell
  - Paracrine effect- Act on the adjacent cell
  - Endocrine effect- Act on a cell present

Properties of Cytokines (Co

Various types of interactions occurring between cytokines

- **Pleiotropy and redundancy effect:**
  - Pleiotropy - Same cytokine having different actions on different target cells
  - Redundancy - Different cytokines producing the same effect on the same target cell.



Properties of Cytokines (Cont..)

Various types of interactions occurring between cytokines (Cont..)

- **Synergy and antagonism effect-** Two cytokines may augment each other's action producing a larger effect (*synergism*) or may oppose each other's action (*antagonism*).
- **Cascade effect** - series of effects mediated by different cytokines. One cytokine acts on a target cell to produce

Structure of Cytokines

- Cytokines are glycoproteins with molecular weight less than 30kDa.
- Most cytokines display high degree of α-helix structure but no β-structure.
- Cytokines characterized so far belong to one of the four groups: the hematopoietin family, the interferon family, the chemokine family, or the tumor necrosis factor family.

Sources and functions of cytokines

Cytokine	Cytokine secreting cells	Target cells & Functions
Interleukins (IL)		
IL-1	Produced by all nucleated cells, but principal sources are APCs such as- Macrophages, monocytes dendritic cell, B cells & endothelial cell	1. T_H cells - IL1 produced by APCs stimulates T_H cells activation & proliferation ➢ Promotes IL2 secretion by T_H cells ➢ Induces IL-2 receptor expression on T_H cells ➢ Induces ↑MHC-II expression on APCs 1. B cell -Promotes B cell development & maturation 2. Liver- Induces synthesis of acute phase reactant proteins 3. Hypothalamus- induction of fever 4. Macrophage & neutrophil activation-↑ expression of ICAM
IL-2	T_H 1 cells	Induces proliferation activated T_H cells, T_C cells and some NK cells (Previously called as T cell growth factor)

Sources and functions of cytokines *(Cont..)*

Cytokine	Cytokine secreting cells	Target cells & Functions
Interleukins (IL)		
IL-4	T_H 2 cells	1. T_H cells -Promote T_H 2 cell activity and inhibit T_H 1 cell 2. B cell- Promote B cells activation & proliferation and induce B cell class switch over to produce IgE, IgG4, IgG1;previously called as B cell growth factor 3. Macrophage & APCs- Induce ↑MHC-II expression
IL-5	T_H 2 cells	Promote eosinophil growth and differentiation
IL-6	T_H 2 cells, macrophages	IL-1 & TNF like effects (synergistic effect) Promotes B cell proliferation and antibody production
IL-7	Bone marrow/thymic stromal	Serves as a growth factor for T cell and B cell

Sources and functions of cytokines *(Cont..)*

Cytokine	Cytokine secreting cells	Target cells & Functions
Interleukins (IL)		
IL-8	Macrophages, endothelial cells	Attracts neutrophils, NK cells, eosinophils and basophils.
IL-9	T_H cells	Hematopoietic & thymopoietic effects
IL-10	T_H 2 cells	Reduces cytokine production by T_H1 cell.
IL-11	Bone marrow stromal cells	Hematopoietic effect (B cell and platelet development) Liver- Induce synthesis of acute phase reactant protein
IL-12	Macrophages	Promote T_H 1 cell induction and inhibit T_H 2 activity; promotes CMI responses NK cell stimulatory factor
IL-13	T_H 2 cells	Mimic IL-4 function
IL-17	$CD4^+$ activated memory T_H	Initiates and maintains inflammation

Sources and functions of cytokines *(Cont..)*

Cytokine	Cytokine secreting cells	Target cells & Functions
Interferons (IFN)		
IFN-α	Leukocytes	Antiviral activity
IFN-β	Fibroblasts	Antiviral activity
IFN-γ	T_H &T_C cells, NK cells	1. Macrophage -Activates the resting macrophages into activated macrophage 2. B cells -Activate B cells to produce IgG 3. Promotes inflammation of delayed type of hypersensitivity (along with TNF-β) 4. T_H 2 cell - Inhibits T_H 2 cell proliferation

Sources and functions of cytokines *(Cont..)*

Cytokine	Cytokine secreting cells	Target cells & Functions
Tumor necrosis factors (TNF)		
TNF-α	Macrophage	1. IL-1 like effect 2. Tumor cells- Promote vascular thrombosis and tumor necrosis 3. Inflammatory cells- Induce cytokine secretion 4. Induces lipolysis, causes extensive weight loss associated with chronic inflammation
TNF- β	T_H 1 cell and T_C cell	Tumor cells- Similar effect like TNF-α Macrophage-Enhance phagocytic activity

Sources and functions of cytokines *(Cont..)*

Cytokine	Cytokine secreting cells	Target cells & Functions
Colony stimulating factor(CSF)		
GM-CSF	Fibroblasts, endothelium, T cells, macrophages	Macrophage and granulocyte growth stimulation
G-CSF	Bone marrow stromal cells, macrophages	Granulocyte growth stimulation
M-CSF	Fibroblasts, endothelium	Macrophage growth stimulation
Others		
TGF- β	Macrophages, mast cells T and B cells, platelet	1. Inhibit T and B cell proliferation and hematopoiesis: 2. Promote wound healing 3. Promotes class switching of B cells to the IgA class

Cytokines and Diseases

- Pathogenesis of many diseases is characterized by increased expression of cytokines or their receptors.
- Common examples include:
  - Septic shock
  - Toxic shock syndrome
  - Cancers
  - Chaga’s disease
  - Cytokine storm

Cytokine Storm

- Condition, where the cytokines are produced in excess leading to **hypercytokinemia** which can cause significant damage to body tissues and organs.
- Normally, the production of cytokines is kept in check by the body.
- However, in some instances, the reaction becomes uncontrolled, and too many immune cells are activated in a

Cytokine Storm

- Precise reason for this is not entirely understood but may occur in a number of infectious and noninfectious diseases, including graft versus host disease (GVHD), acute respiratory distress syndrome (ARDS), sepsis, Ebola, avian influenza, smallpox, and systemic inflammatory response syndrome (SIRS).

Cytokines used in Therapy

Many strategies have been followed to create a cytokine or anticytokine state in the body depending on the need.

- **Use of cytokines (e.g. interferons) as drug:**
  - Interferon-α - treatment of hepatitis B, hepatitis C, hairy cell leukemia, multiple myeloma and chronic myeloid leukemia (CML)
  - Interferon-β - treatment of multiple sclerosis
  - Interferon-γ - treatment of chronic granulomatous disease.