بسم الله الرحمن الرحيم

IMMUNOLOGY

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Clinical Immunology

REFRENCES:

-Medical Microbiology by Jawetz
-Immunology by Roitt
-Immunology by kuby

Objectives:

- Introduction
- Function and types of immune system
- Anatomy of immune system
- Antigen
- Cytokines

Immunity: is a specific resistance to infection caused by different pathogens.

Immune system: collection of cells ,tissues, receptors, organs and molecules that mediate response and function properly .

Immune response: Coordinated reaction of cells and molecules to infectious disease.

Immunology: Is the science that study immune system and its response to pathogens

Function of the immune system:

1. Prevent infection
2. Eradicate established infection
3. self/non-self discrimination

TYPES OF IMMUNITY

Innate immunity
Adaptive immunity

Innate immunity: Exterior defense mechanism

Characteristics of innate immunity:

1. **Pre exist**
2. **Not specific**
3. **No memory**
4. **Response minutes or hours**
5. **No diversity**
6. **Not discriminate between self cell and non self cell**

1-Anatomic Barriers

1-Skin

epidermis, dermis

low pH due to lactic and fatty acids secreted from sebaceous glands associated with hair follicles

2-Mucous membranes: ciliated epithelial cells; saliva, tears and mucous secretions - GIT, urogenital, respiratory tracts

2- *Physiologic Barriers*

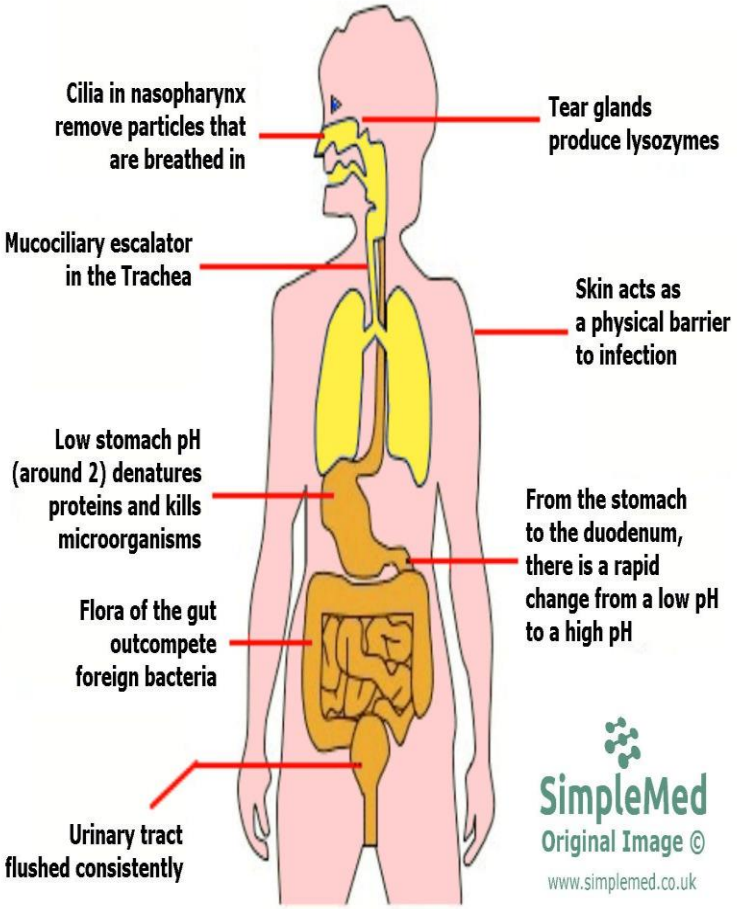
*1-***Temperature** - normal body temperature inhibits growth of most microorganisms and

Elevated body temperature

fever can have a direct effect on pathogenic microorganisms.

2- **pH** - low pH of stomach, skin, microbial growth

3- Presence of **Oxygen**



3-chemical barriers:

1. **Lysozyme: hydrolytic enzyme found in mucous secretions able to cleave the petidoglycan layer of the bacterial cell wall**
2. **Defensins: Low molecular weight protein produced in base of crypts of small intestine and respiratory tract.**
3. **Lactoferrin: it is mucosal secretion present in the milk and mucosal secretion**

4-Cellular barrier

Neutrophil,Macrophages,Natural killer cells,Dendritic cells

- **The mechanism that cells can kill pathogen is phagocytosis**
- **Phagocytosis is triggered by specific receptors**

1- pattern recognition receptors like Toll like receptors

2-Opsonin receptors like Ig Fc receptors and complement receptors

5-Toll-like receptors

- Phagocytic cells have a variety of Toll-like receptors which recognize broad molecules on pathogens so called PAMPs (pathogen associated molecular patterns). Binding of infectious agents toToll-like receptors results in phagocytosis and the release of inflammatory mediators by the cell.

Adaptive immunity include:

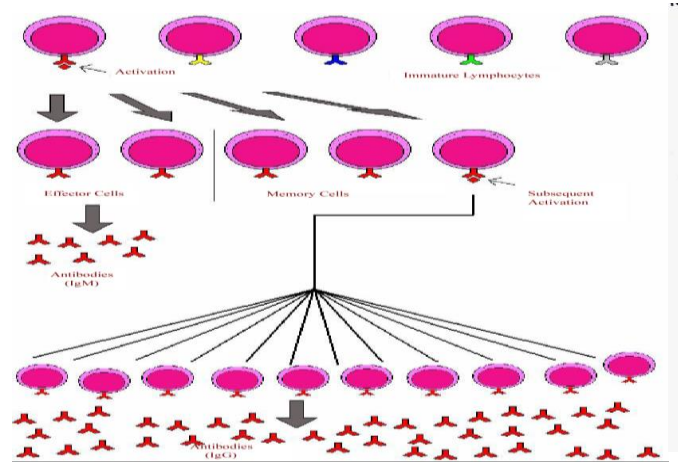
1- Lymphocytes

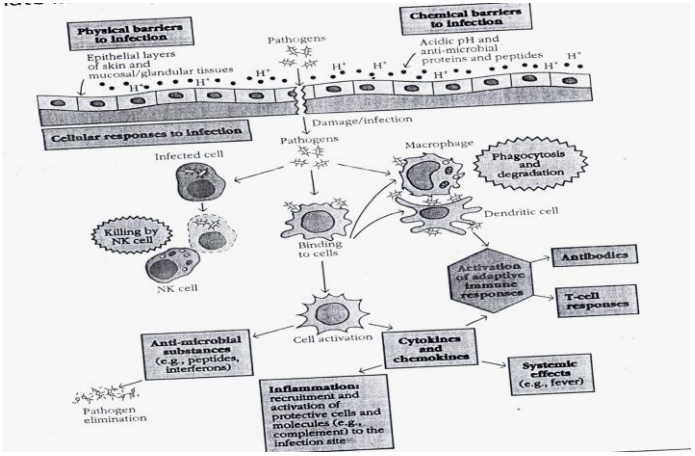
T lymphocytes-----cell mediated immunity

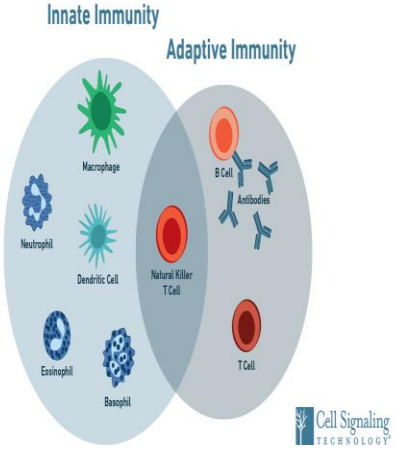
B lymphocytes-------humoral immunity production of antibodies

2- Characteristics of Adaptive immunity

1. Specificity: Virus, bacteria, fungus and helminthes
2. Diversity: very large number of receptors
3. Memory
4. Self cell non self cell recognition
5. Clonal expansion:an immunological response in which lymphocytes stimulated by antigen proliferate and amplify the population of relevant cells
6. Delay response time (Days)



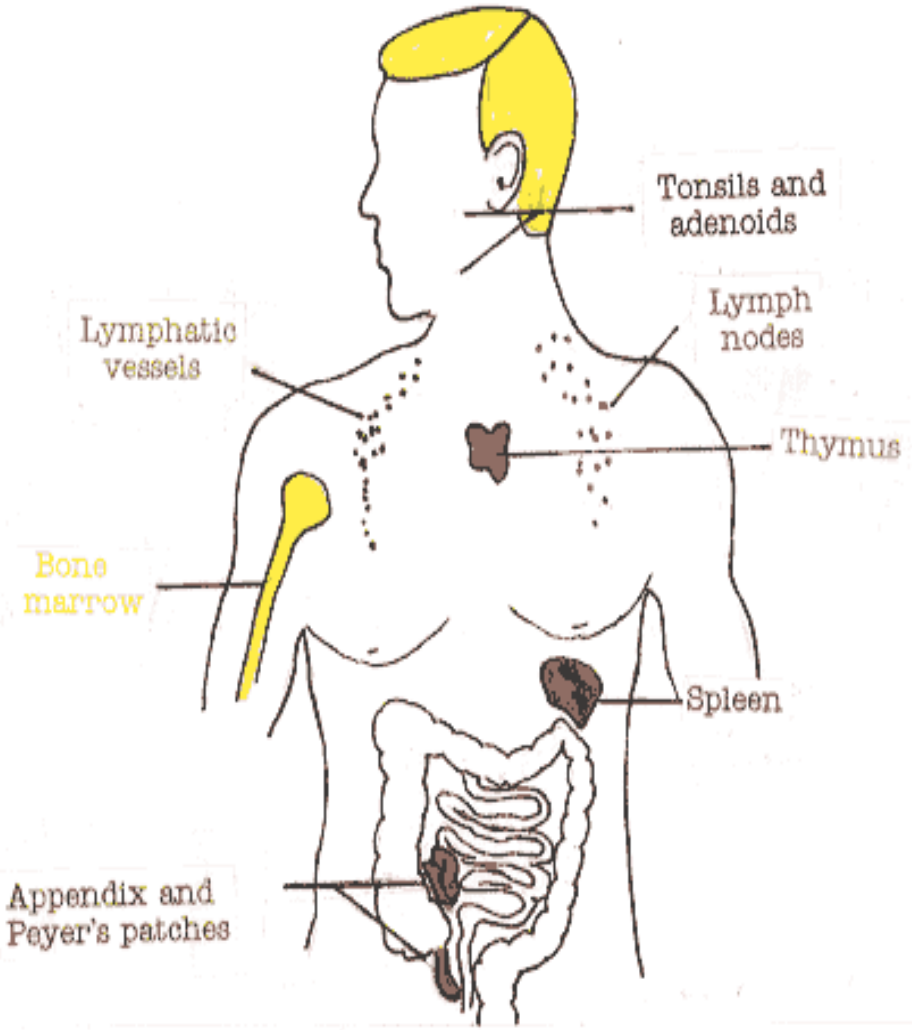




ANATOMY OF THE IMMUNE SYSTEM

1. Primary:
- thymus,
- Bone Marrow,
- bursa of Fabricius

2- Secondary:
- Spleen
- Lymph Node,
- Tonsils,
- adenois,
- GALT,MALT



- Generation of mature lymphocytes first occurs in the embryo in
  -yolksac
  -fetal liver and spleen
  -fetal bone marrow

  and continues through out life in birds (lymphoid organs called Bursa of fibricius (primary site of B-cell maturation)
  In humans –Bone Marrow and other lymphoid tissue serve as Bursa equivalent

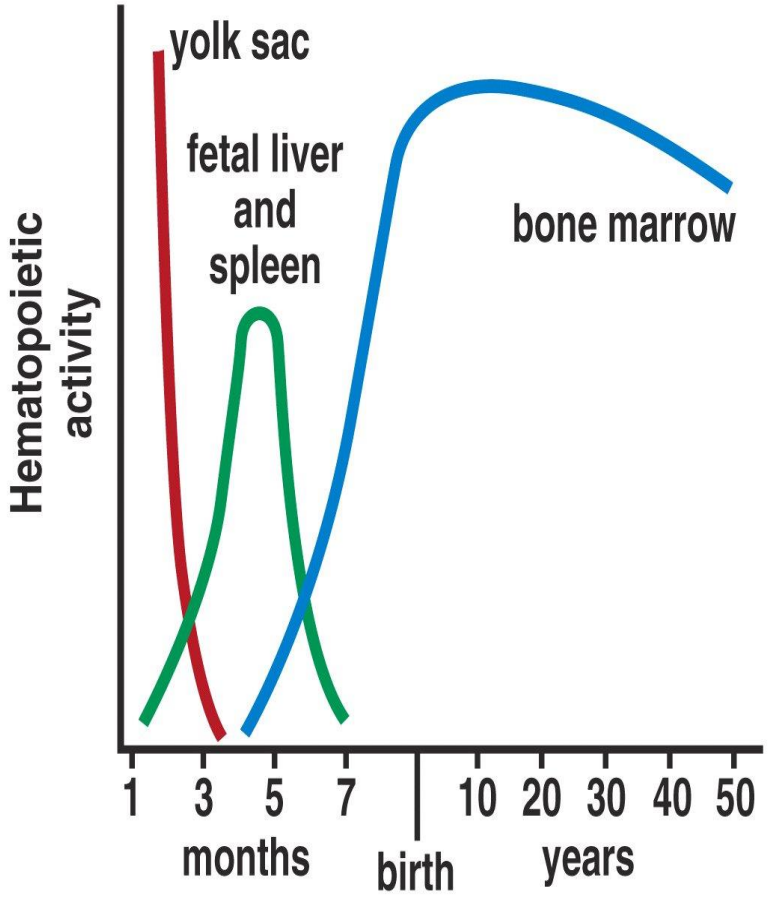
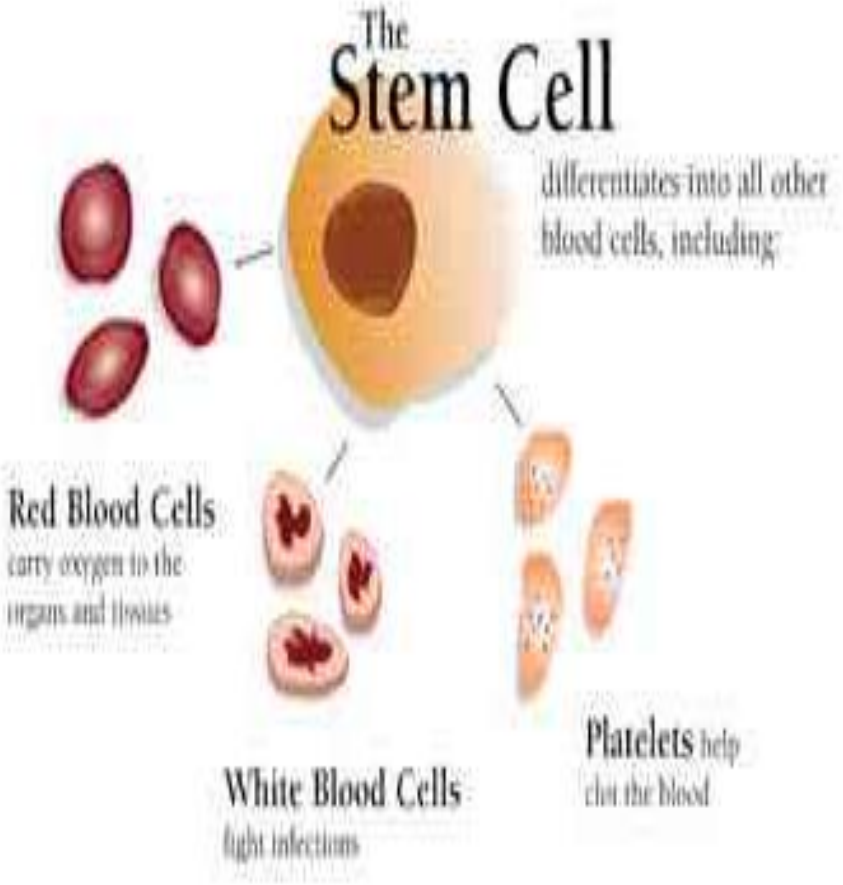


Figure 1-10 The Immune System, 2/e (© Garland Science 2005)

Bone marrow

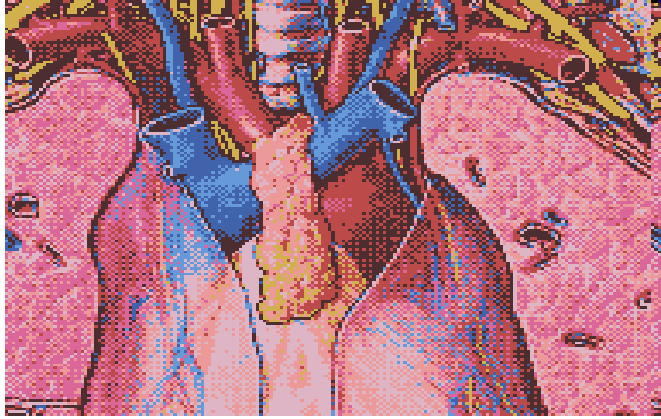
The bone marrow is where the lymphatic process begins. Stem cells in the soft tissue in the shafts of the long and pelvis produce white blood cells and red blood cells. The white blood are transported in a whitish medium called the lymph throughout the lymphatic distribution system.



In BM a selection process occurs and elimination of B-ells that react with self antigens

There are thousands of lymph vessels or channels throughout the body that transport and distribute lymph-containing white cells. This network of channels is parallel to and connects to the blood vessels. The lymphatic system also scavenges dead cells from the blood and distributes and re-absorbs the various cells of the immune system to and from the blood.

Thymus



- Its flat , bilobed organ situated above the heart. Each lobe is surrounded by a capsule divide into lobule and separated from each other by a trabeculae.Each lobule is organized into cortex and medulla.
- Hormones (thymosin, thymulin)and (enzymes like adenosine deaminase)

In the thymus:

1-differentiation occur

1- Progenitor T cells (hematopoiesis)leave bone marrow then enter thymus and undergo differentiation by acquiring differentiation markers during development calld CD markers (CD =Cluster of Differentiation) markers.

1-Immature double negative

(CD3+ CD4- CD8-) then

2-immature double positive thymocytes

(CD3+ CD4+ CD8+) then

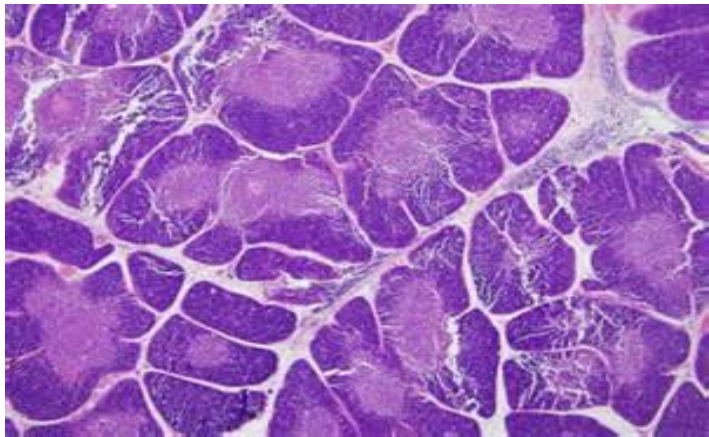
3-mature single positive single negative thymocytes

(CD3+ CD4+ CD8-)

(CD3+ CD4 – CD8+)

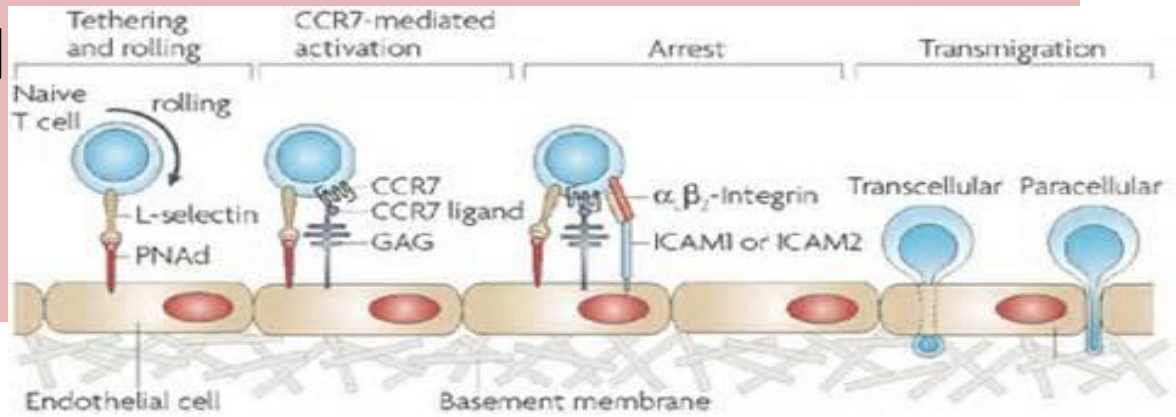
2-Thymic education and selection

- The property of mature T cells is recognized only foreign Ag (non self)+self MHC molecule. This can be achieved by selection process
- Negative selection:Any lymph. Acquire receptors with high affinity for self Ags will be die by a programmed cell death (apoptosis). This occurs in the medulla by macrophages and dendretic cells. (95-99%)
- Positive selection:Any lymph. Acquire receptors recognize foreign Ags+ self MHC molecule will allow to mature and expand and survive (1-5%). This occurs in the cortex of the thymus by epithelial cells.
- The two processes called
- lymphocytes teachings or education.



Lymphocytes homing

- Lymphocytes leave thymus to sec. lymphoid organs (LN) and to sites of inflammations through high endothelial venules (HEV) by binding to specific receptors on lymphocytes and cell adhesion molecules on HEV after that lymphocytes . homing to different tissues (GALT, MALT, skin dermal endothelial venules) by a cascade of interactions between adhesions molecul



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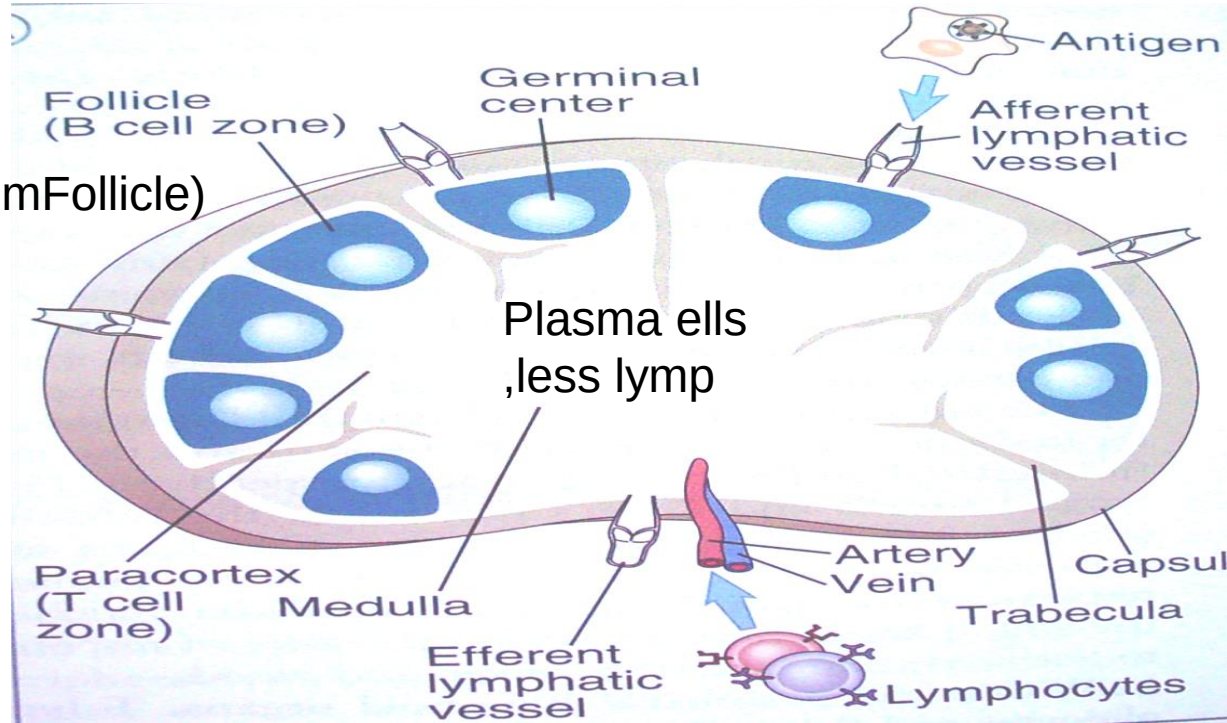
Lymph nodes

- Bean shaped , encapsulated ,containing a reticular network packed with lymp., macrophages and dendretic cells .
- Cortex. populated with B cell
- Paracortex. populated with T cell
- Medulla .

Macr,follicular dendritic cells (primFollicle)

Dendritic cells wih MHC class II

Sec folllicle with germinal centr



Spleen

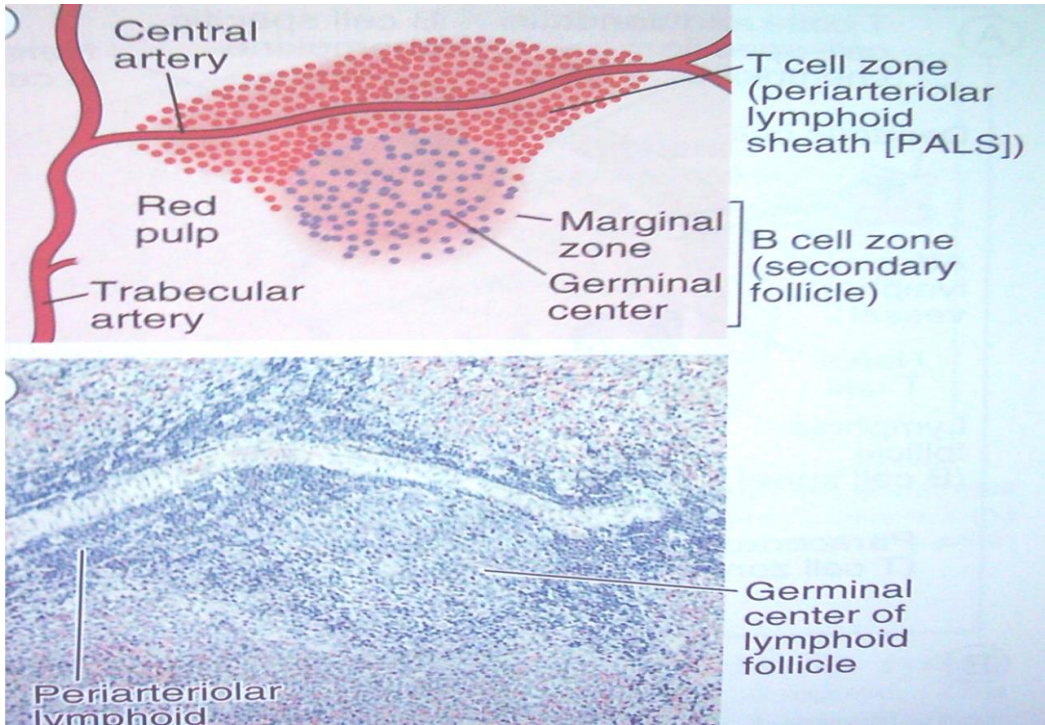
- Function: filtration of blood
- Consisted from:

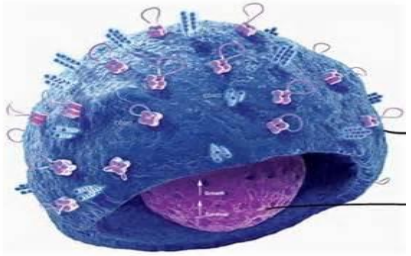
- white pulp (thymus dependant area)

    T cell zone (PALS)

    B cell zone

- red pulp



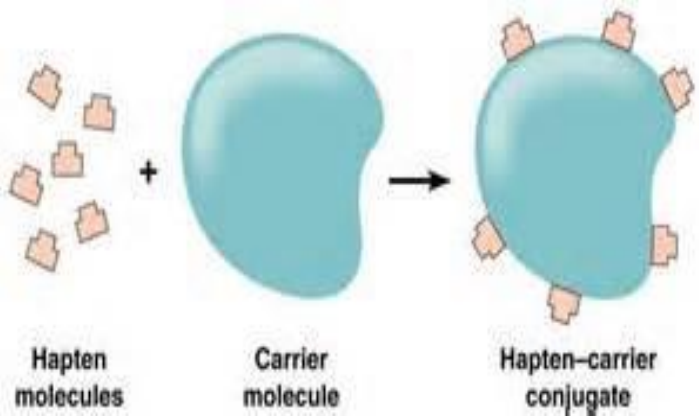


ANTIGEN

Antigens (Ag): any molecule that can be specifically recognized by the adaptive immune system

2- Epitope: is a restricted part of Ag (short sequence of sugars , a.a. , that bind with antibodies (Abs).

3-**Hapten**: a small molecule had a low molecular weight that can not initiate an immune response unless its coupled with a large carrier molecule



MAJOR HISTOCOMPATIBILITY COMPLEX *(MHC)*

- Each mammalian species possesses a tightly linked **cluster of genes (MHC),** Consisted of three classes:

1- class I

2-class II

3-class III

their products play a major role in :

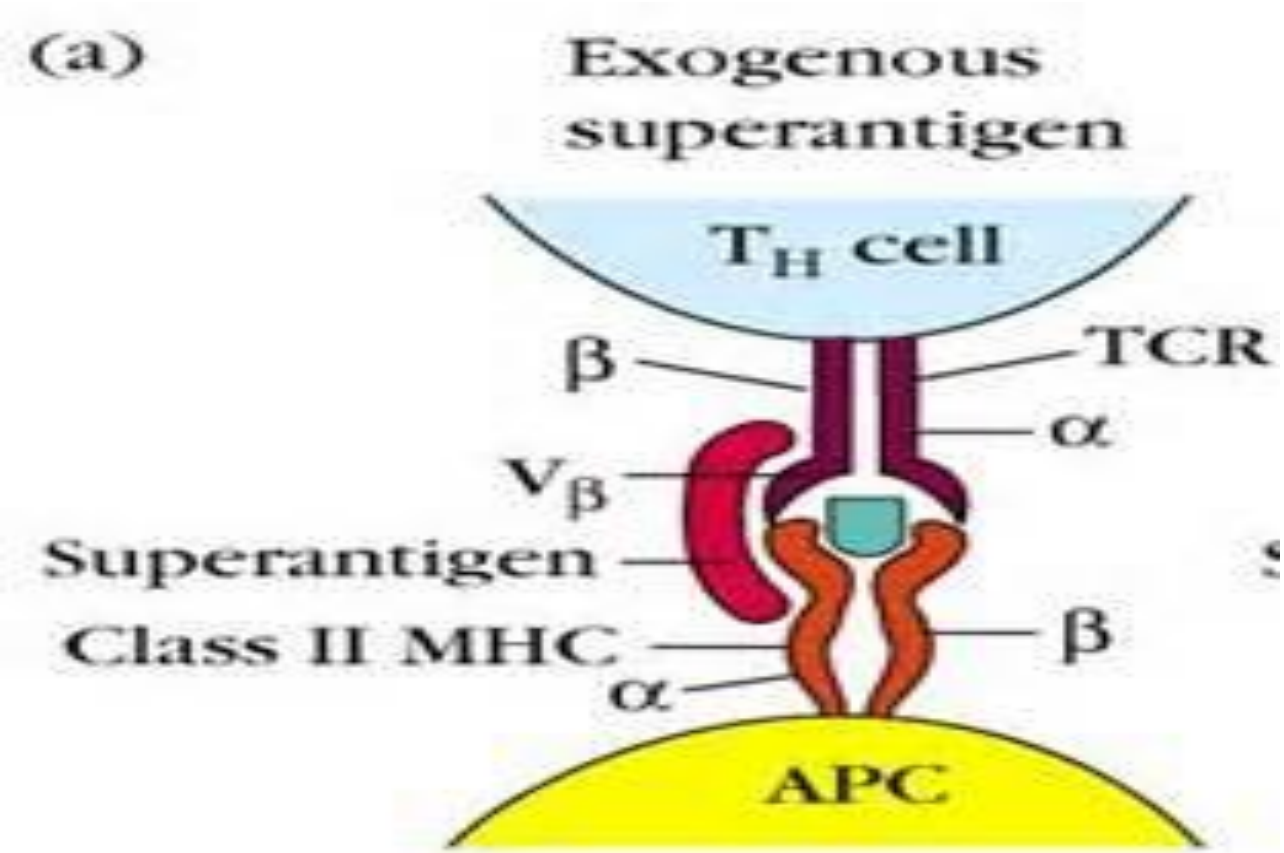
1- cellular recognition

2- determining the transplanted tissue is accepted or rejected.

- The product of these genes were expressed as **antigens** on the cell surface of the cells. its also called human leukocyte antigens (HLA).

Super antigen:

Is an antigen like Staphylococcal enterotoxins that binds Tcell receptor variable beta regions to alpha chain of class II major histocompatibility complex on antigen presenting cells. This leads to stimulation multiple T cells



Factors determining antigenicity

1. Degree of foreignness
2. Molecular size:100000 Dalton
3. Chemical compositions:
   proteins-polysaccharide-lipid-nucleic acids
1. Susceptibility to antigen processing
2. Genotype
3. Dose of immunogens
4. Route of administration
5. Adjuvant: substance mix with Ag to enhance immunogenicity (Alum-Aluminum potassium sulfate)

Cytokines

Are regulatory proteins or glycoproteins of low molecular weight secreted by white blood cells and other cells in response to a number of stimuli. They are either soluble or membrane bound form

Function as intercellular messenger that evoke particular biological activity after binding to a specific receptor.

Interlukines: cytokines are secreted by some leukocytes and act upon other leukocytes.

Chemokines: are molecules that communicate among immune cells that mobilize them from one organ or from one part of organ to other organ

Chemoattractants: molecules that attract the cells by expression of cell surface adhesion molecules

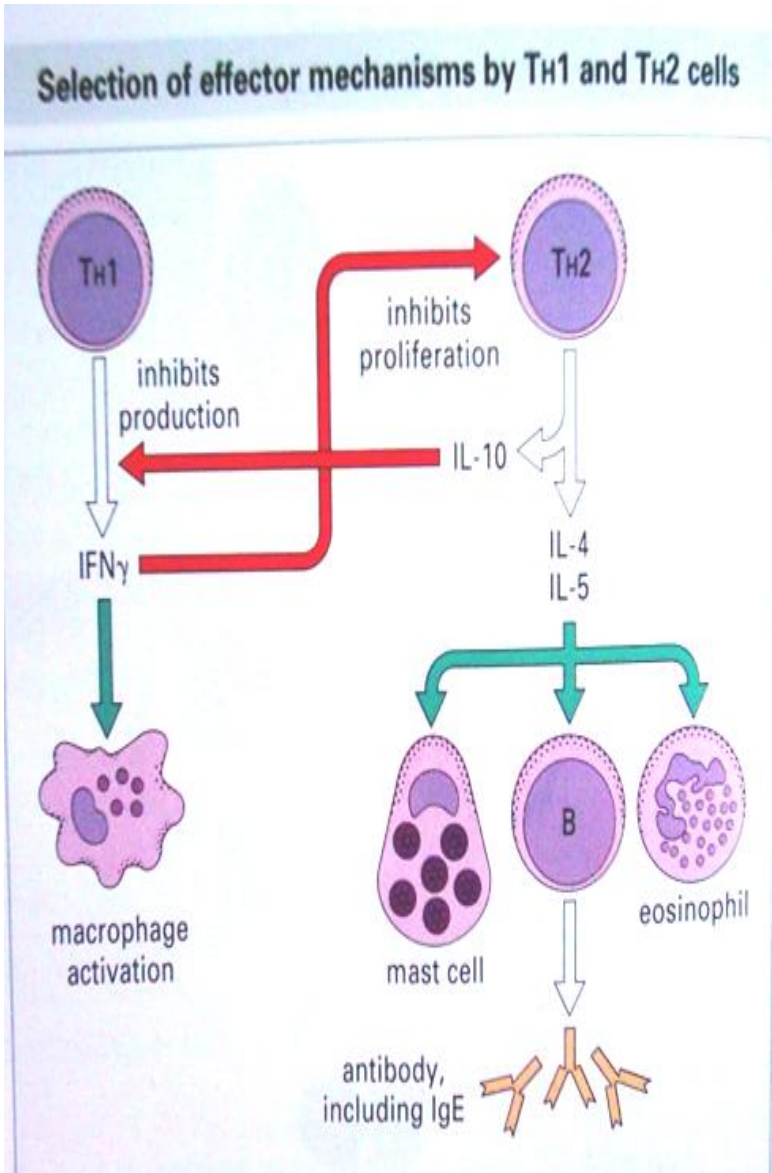
- IL-1
- Secreted by macrophages
- Act on lymphocytes Induce lymphocytes maturation , activation and clonal expansion
- Acts on hypothalamus inducing fever
- Acts on liver induce acute phase protein synthesis

IL-2

- Secreted from Th1
- Acts on Ag specific T-cell supporting its growth
- Acts on NK cell increasing activity
- Acts on Tc cell increasing cytotoxicity
- Leads to development cell mediated immunity
- Suppress cytokines secreted from Th2 cells.

IL-3

- Secreted from Th2
- Supports growth and differentiation of hematopoietic cells



IL4 and IL-5

- Secreted from TH2
- Its up-regulate classII MHC expression
- Stimulate growth of mast cell
- Stimulate proliferation of activated B-cell
- Stimulate Abs secretions from plasma cell
- Stimulates humoral immune response
- Down regulates Th1
- IL-4 promotes class switch to IgE
- IL-5 promotes Eosinophil activation and generation

IL-6

- Secreted by macrophages and endothelial cells and TH2 cells.
- Effect liver induces acute phase protein synthesis and proliferation and antibody secretion of B-cells.

IL-10

- Secreted from Th2
- Antagonizes generation of Th1 subsets and cytokines production by TH1
- Anti-inflammatory cytokine
- Mediate regulation of the immune system

IL-17

-secreted from TH17

-promotes inflammation and increase production of proinflammatory cytokines

-Family of IL-17 include (A,B,C,D,E,F)

-It binds to specific receptors

-Type I Interferon (IFN) consisted from:

- **IFN α and IFN β:secreted by activated macrophages, dendritic cells and viral infected cell and inhibit viral replication**
- **Type II interferon include IFN γ:secreted from Th1, Tc, NK cell and inhibit viral replication,**

  enhance activity of macrophages, increase MHC class-II expression, inhibits Th2 proliferation

-Type III interferon include IFNλ : It is up-regulates the expression of genes controlling viral replication and host cell proliferation

Tumor necrosis factor (TNF)

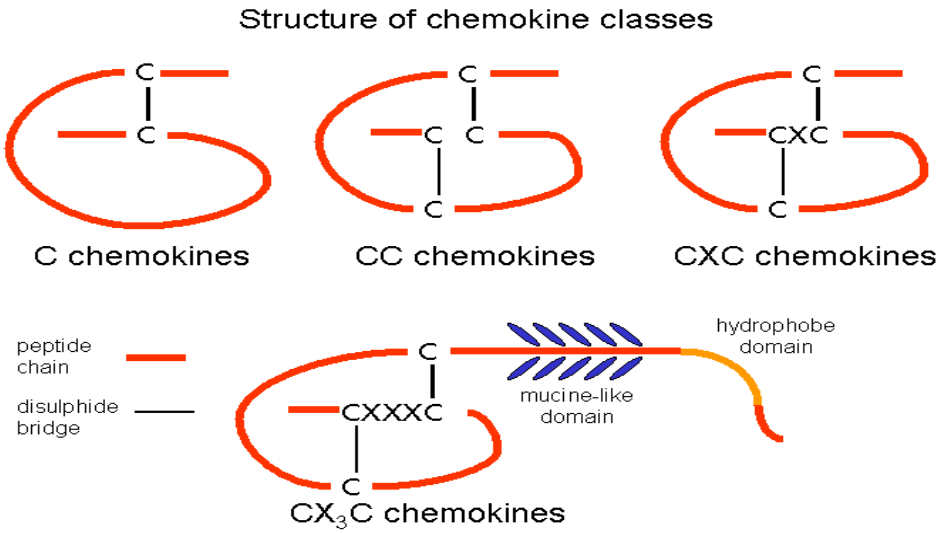
- TNF :secreted from macrophages NK cell and act on tumor cells
- Had direct cytotoxic effect on tumor cells and tumor undergoes visible hemorrhagic necrosis and regression by inhibition angiogenesis, there by decreasing the flow of blood that is necessary for progressive tumor growth.
- Causes extensive loss weight, loss

of muscle and body fat (cachexia) by suppression lipogenetic metabolism

Chemokines

- **Chemokines** are a family of small cytokines, or signaling proteins secreted by cells. Their name is derived from their ability to induce directed chemotaxis in nearby responsive cells; they are **chemo**tactic cyto**kines**
- Some chemokines are considered pro-inflammatory and can be induced during an immune response to recruit cells of the immune system to a site of infection,
- while others are considered homeostatic and are involved in controlling the migration of cells during normal processes of tissue maintenance or development.
- Chemokines have been classified into four main subfamilies based on their structural characteristics, :
- CXC, CC, CX3C and XC.
- All of these proteins exert their biological effects by interacting with transmembrane receptors called chemokine receptors, that are selectively found on the surfaces of their target cells.

- Members of the chemokine family are divided into four groups depending on the spacing of their first two cysteine residues. Thus the nomenclature for chemokines is, e.g.: CCL1 for the ligand 1 of the CC-family of chemokines, and CCR1 for its respective receptor.
- three amino acids between the two cysteines and is termed CXXXC



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