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Step 1 lecture Notes

Microbiology and Immunology

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SMASH USMLE Step 1 High Yield Review

(First Edition)

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High Yield Review

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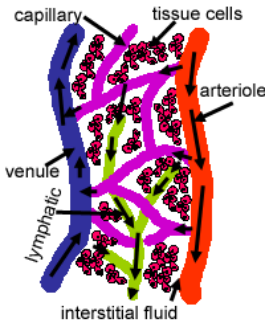
-This book is dedicated to the Almighty God, the Master physician, entrepreneur, author and finisher of my faith.

-To my lovely wife and children, Olufunmilayo, Olamide and Oluwadamola, and my parents, for your love and encouragement.

Chapter 3

Immunology step 1 notes

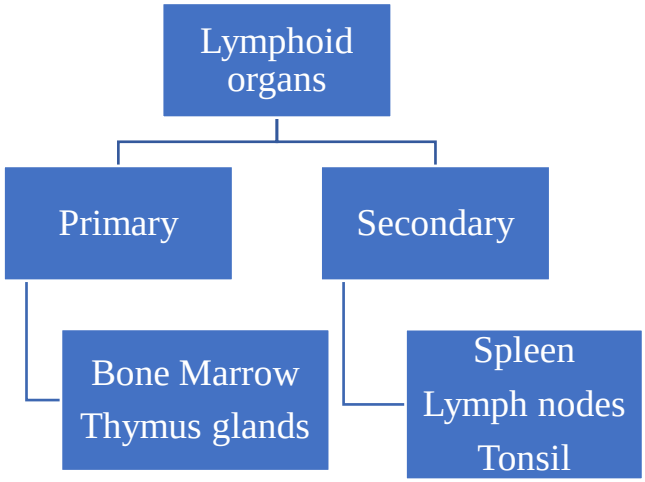
Lymphoid structures



What's lymphoid tissue?

- Lymph means clear fluid
- This fluid flows in in lymphatic vessels, lymphatic tissue and red bone marrow.
- The main function is to filter out of capillaries and drains into lymphatic vessels to become lymph.
- Lymph eventually drains into venous blood.
- Lymph drains interstitial fluid, transports dietary lipids and facilitates immune responses.

Primary& Secondary lymphoid organs:



- Provide the right environment for immature progenitor cells to generate, mature
- Function as the house for stem cells to divide and mature into B- and T- cells
- Both T-cell and B-cells are 'born' in the bone marrow.

Bone marrow:

- Red marrow is the bone marrow parenchyma and contains the hematopoietic stem cells, which function in the formation of all blood cell lines, including B and T cells.
- Yellow marrow is the bone marrow stroma (supportive tissue) and contains mostly fat.
- Note: Orthopedic injuries especially fractures of the long bones are the most common cause of fat embolism syndrome, characterized by rapid breathing and shortness of breath. Following trauma, fat is released directly from the bone marrow into the circulation.
- This is because after trauma, an elevated pressure in the medullary cavity of the bone causes the release of fat globules into venous system supplying the bone.
- This explains the obstruction of the fat emboli in the lung capillaries.

Thymus

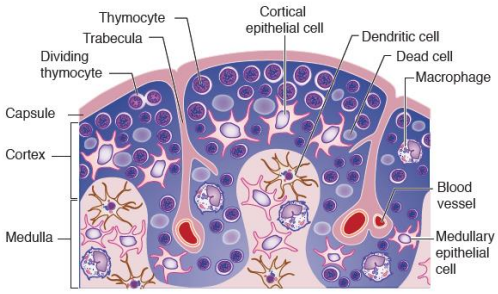
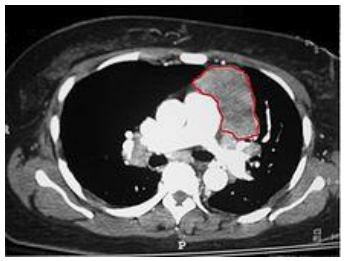


Figure I-3-9. Structure of the Thymus

- Encapsulated, bilobed organ, located in the anterior mediastinum
- Derived from the third pharyngeal pouch
- Morphologically thymus changes during development, during early childhood, the thymus is large and is easily seen on a chest radiograph. However, during adulthood it becomes invisible on a chest film.
- Provide an adequate condition for T cell differentiation and maturation
- They are called T cells because they mature in the thymus from thymocytes

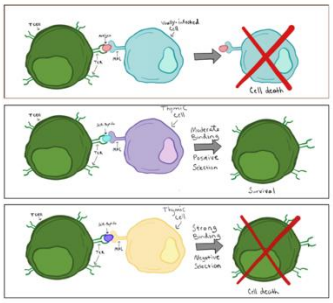


CT scan of the chest revealing a large necrotic mass in the left anterior mediastinum (indicated by the red line). Histology later established the diagnosis of a thymoma.

- Thymoma is considered the most common tumor associated with the thymus
- Thymoma is usually associated with myasthenia gravis
- Removal of thymus glands in myasthenia gravis associated with better prognosis

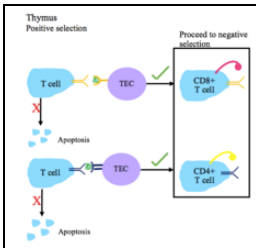
Thalamus composed of 2 areas:

Cortex

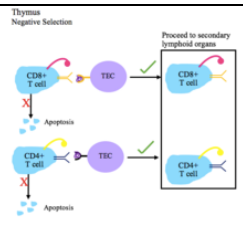


- High cellular density with packed immature T cells awaiting positive (functional) selection.

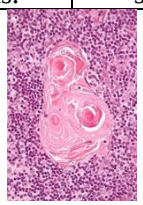
- The immature T cells undergo positive selection where it binds (reversibly/Not strong binding) to the cell surface proteins major histocompatibility complex class I (MHC I) or II.
- T cells which bind strongly to MCH I/II will undergo apoptosis.
- The majority of developing thymocytes will die during this process.
- Thymocytes that interact well with MHC I mature into $CD8^+$ cells.
- Thymocytes that interact well with MHC II mature into $CD4^+$ cells.
- Thymocytes that survive positive selection migrate towards the boundary of the cortex and medulla in the thymus.
- Don't bind to human body antigens
- Some immature T cells mange to pass through the periphery
- If the peripheral system didn't recognize the escaped T cells, the patient is going to progress to autoimmune disease
- The autoimmune cells are removed by the process of negative selection, which occurs in the corticomedullary junction
- Negative selection destroys cells that see the body's own normal antigens as foreign invaders.



This figure depicts the process of positive selection for T cells.



This figure depicts the process of negative selection for T cells.

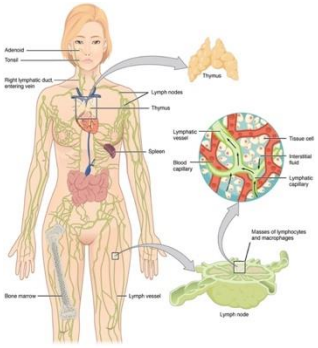


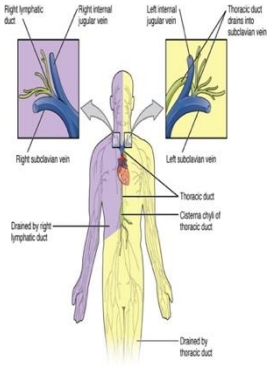
Medulla:

- low cellular density with mature T cells having already gone through positive and negative selection.
- This area also contains Hassall corpuscles, which are remnants of apoptosed T cells seen on histology.

Lymphatic drainage

Overview:

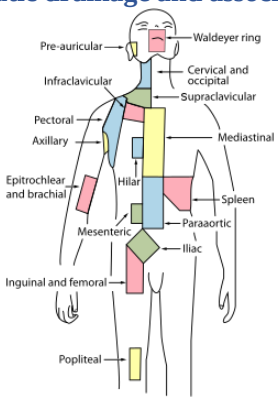




- The overall drainage system of the body is **asymmetrical**
- **The** right lymphatic duct receives lymph from only the upper right side of the body (right arm, chest, half of head)
- The lymph from the rest of the body enters the bloodstream through **the thoracic duct** via all the remaining lymphatic trunks.
- The thoracic duct drains a much larger portion of the body than does the right lymphatic duct

Lymph node	Area of body drained
Upper limb and lateral breast	Axillary
Stomach	Celiac
superior mesentery	Duodenum
Inferior mesenteric	Sigmoid colon
Internal iliac	Lower rectum to anal canal (above pectinate line), bladder, vagina (middle third), cervix, prostate
Superficial inguinal	Anal canal (below pectinate line), skin below umbilicus (except popliteal area), scrotum, vulva
Popliteal	Dorsolateral foot, posterior calf
Para-aortic	Testes, ovaries, kidneys, uterus

Lymphatic drainage and associations



- Axillary lymph nodes
- Celiac lymph nodes
- Paraaortic lymph nodes
- Internal iliac and Superficial inguinal
- Popliteal

Cervical lymph node:

- Located in the neck region and divided into two groups:
- Anterior superficial and deep nodes include submental and submaxillary (tonsillar) nodes located under the chin and jawline.
- Posterior lymph nodes are located along the back of the neck.

Associated pathology:

- Bronchitis
- Tonsillitis
- Sore throat
- Infectious mononucleosis
- Kawasaki disease

Mediastinal lymph nodes:

- Glands that are located in the part of the chest that lies between the sternum and the spinal column
- Mediastinal lymphadenopathy generally suggests a problem related to lungs, whether benign or malignant.

Associated pathology:

- Anthracosis (Miner`s lung)
- Cystic fibrosis
- Lung cancer
- Tuberculosis
- Chronic obstructive pulmonary disease
- Acute Lymphoblastic Leukemia
- Granulomatous disease

Hilar lymph nodes:

- located in the retrotracheal region or the area posterior to the trachea.

Associated pathology:

- Enlargement of the hilum may occur due to:
- Tumors (such as lung cancer)
- pulmonary hypertension
- Enlarged hilar lymph nodes due to conditions such as infections (especially tuberculosis and fungal infections)
- Cancer (either local or metastatic)
- Sarcoidosis

Axillary

- Lymph nodes located in the armpits.
- Drain lymph vessels from the lateral quadrants of the breast

Associated pathology:

- A local infection of the arm or breast, including skin and wound infections and cellulitis. The bacteria are carried in the lymph to the axillary lymph nodes, causing a reaction there.
- An infection that is affecting your whole body, such as strep throat, measles, mononucleosis, herpes or AIDS.
- Cancers, including lymphomas, leukemias, and breast cancer.
- **Immune disorders** such as lupus or rheumatoid arthritis.

Celiac

- The celiac lymph nodes are grouped into three sets: the gastric, hepatic and splenic lymph nodes.

Associated pathology:

- Mesenteric lymphadenitis
- Typhoid fever
- Ulcerative colitis
- Celiac disease

Paraaortic lymph nodes

- Group of lymph nodes that lie in front of the lumbar vertebrae near the aorta. These lymph nodes receive drainage from the gastrointestinal tract and the abdominal organs

Associated pathology:

- Metastasis especially colorectal cancer

Internal iliac and Superficial inguinal:

- Inguinal lymph nodes are the lymph nodes in the inguinal region

Associated pathology:

- Sexually transmitted infections
- The presence of swollen inguinal lymph nodes is an important clinical sign because lymphadenopathy (swelling) may indicate an infection, or spread as a metastasis from cancers, such as anal cancer and vulvar cancer.

Popliteal:

- Dorsolateral foot/ posterior calf Foot

Associated pathology:

- leg cellulitis
- Popliteal artery entrapment syndrome

Secondary lymphoid structures

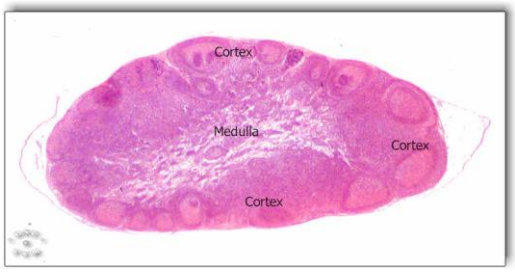
Overview:

- Sites where lymphocytes undergo differentiation (increase specificity) and clonal expansion (increase number) in antigen- dependent manner.
- Examples of secondary lymphoid organs
- lymph nodes, spleen, tonsils, adenoids, and mucosa-associated lymphoid tissue (MALT).

Lymph nodes:

- T cells undergo maturation in the thalamus then through the circulation to lymph nodes and other organs
- Lymph nodes are spread throughout the body and present in group where lymphatic vessels come together to form larger vessels such as in the groins, neck and axilla.
- Lymph nodes are also part of the lymphatic system that includes the lymphatic vessels, lymphoid tissue and lymphoid organs.
- Lymph nodes filter and purify the lymph before it flows into the venous system.
- Encapsulated and trabeculated secondary lymphoid organs with many afferent vessels (Many ways in and one way out)

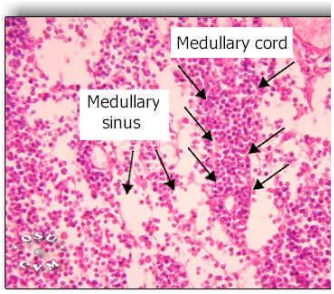
Functions of lymph nodes:

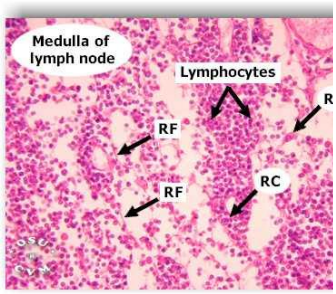


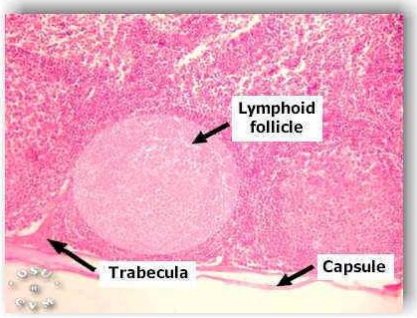
- Filtration of debris and microorganisms via phagocytosis
- facilitate the interaction between antigen presenting cells and circulating lymphocytes to initiate an immune response
- Activation and proliferation of B lymphocytes
- Activation of T lymphocytes to become T helper and T cytotoxic cells

Medulla

- The medulla of a lymph node is composed of medullary cords (densely packed lymphocytes) interspersed between medullary sinuses. The medullary sinuses are composed primarily of reticular fibers, reticular cells and macrophages.

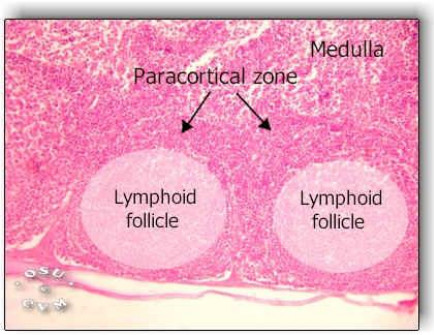






Cortex:

- The cortex is composed of the cortical sinuses surrounded by dense accumulations of lymphocytes.
- Arranged into spherical follicles, lymphoid follicles.
- Where that B lymphocytes are activated and undergo proliferation.



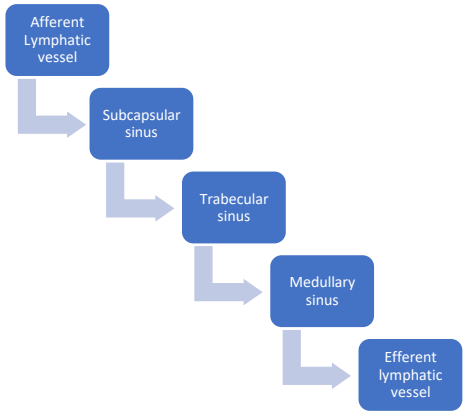
Paracortex

- Contains high endothelial venules
- T cells are concentrated within the paracortex
- Paracortex enlarges in an extreme cellular immune response (eg, viral infection).

Thymic hypoplasia (DiGeorge syndrome):

- Lymphoid follicles are usually present, but lymph node paracortical areas and thymus-dependent regions of the spleen show variable degrees of depletion.

Flow Through a Lymph Node:



Spleen:

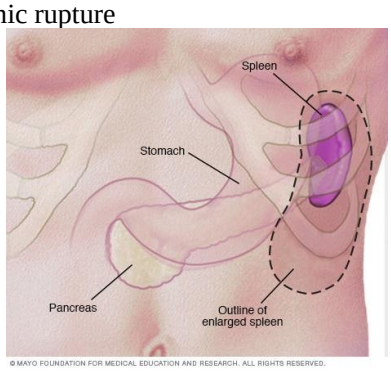
- Located between the stomach, left kidney and diaphragm, the spleen is the largest lymphoid organ in the body

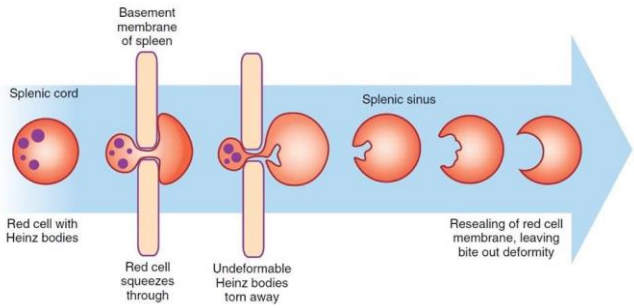
The spleen is divided into two pulps:

- Red pulps: Filtration of red blood cells.
- Composed of macrophages and the rest of the red pulp is occupied by numerous venous sinuses (VS).
- RBCs undergo phagocytosis by splenic macrophages
- Also encapsulated bacteria are removed by splenic macrophages
- White pulps: Reservoir for T cells
- Contains the periarterial lymphatic sheath (PALS), which contains T cells and follicles that contain B cells.
- B cells are found in the marginal zone between red pulp and white pulp

Cases of splenic dysfunction:

- Splenic macrophages remove Heinz bodies from RBC leading to characteristic bite cells
- In case of patients with G6PD deficiency, large number of Heinz bodies are produced
- Patients with infectious mononucleosis (EBV infection) develops splenomegaly increase risk of splenic rupture

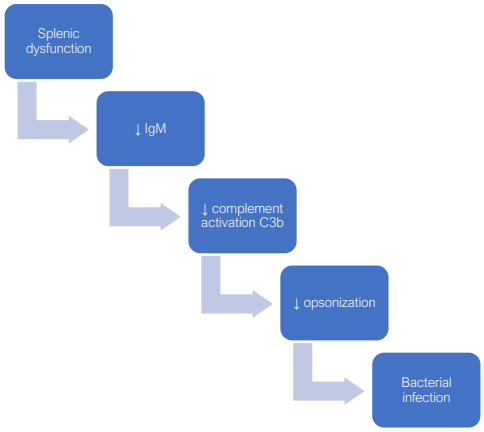




Enlarged spleen

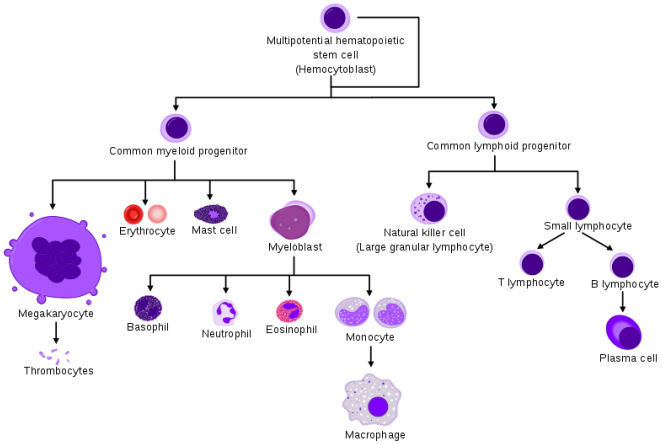
- The spleen contains macrophage
- These macrophages are activated when bacteria bound by IgG antibodies or the complement component C3b.
  Note: IgM is produced by plasma cells in the spleen and lymph nodes
- These types of antibodies and complement are immune substances called opsonizes, molecules that bind to the surface of bacteria to facilitate phagocytosis
- In cases of splenic dysfunction, IgG and C3b are still bound to bacteria, but they cannot be removed from the blood circulation due to the loss of the splenic macrophages. Hence the bacteria are free to cause infection (encapsulated bacteria) such as:

  - Streptococcus pneumonia
  - Haemophilus influenza type B
  - Neisseria meningitidis
  - Salmonella
  - Klebsiella pneumonia
  - Group B streptococcus

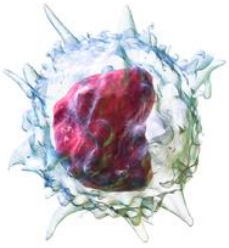


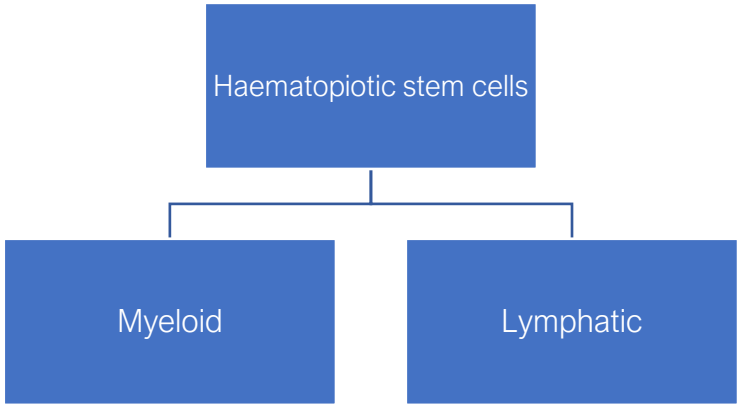
Cells of the immune system

Overview:



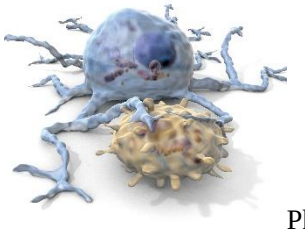
- Hematopoietic stem cells located in the bone marrow and capable of differentiating into all different mature blood cells types and tissues which considered the immune cells
- Multipotent and self-renewal





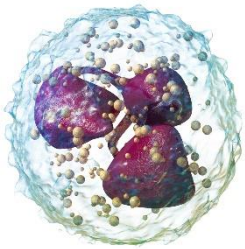
Myeloid linage:

- **Monocytes:**
  - Circulate in the blood, differentiate to macrophages in the tissues



  - Phagocytose pathogens
  - Produce cytokines that initiate inflammation (Il-1, IL8, IL-12, IL-6 and TNF α)
  - Play an important role in tissue repair
  - Large, kidney-shaped nucleus with frosted glass cytoplasm

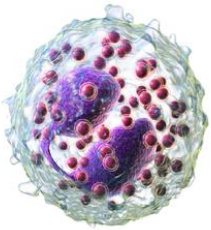
- **Dendritic cells:**



  - Cells with long cytoplasmic arms, found in all tissues
  - Express MHC II and Fc receptors on the surface
  - Three major functions:

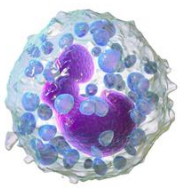
1. Efficient antigen presentation to lymphocytes (professional antigen- presenting cell (APC)
2. Stimulate adaptive immune response
3. Initiate inflammatory response

- **Neutrophils:**



  - Mature cells with multilobed nucleus
  - Contains toxic cytoplasmic granules
  - Number increases in bacterial infection
  - Main function: Circulating phagocytes

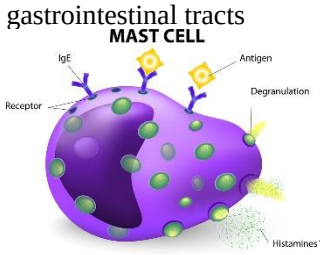
- **Eosinophils:**
  - Mature cells with a bilobed nucleus
  - Contain the major basic proteins



  - Packed with large eosinophilic granules of uniform size
  - Main function: Protect against parasitic and helminthic infections

- **Basophils:**
  - Mature cells with large blue granules

- **Mast cells:**
  - These cells release histamine in response to antigen exposure
  - Concentrated within the respiratory and gastrointestinal tracts



  - Like Basophil (contain large cytoplasmic granules) with small nucleus
  - Cromolyn sulphate is used as mast cells stabilizer (used for asthma prophylaxis)

Lymphoid linage:

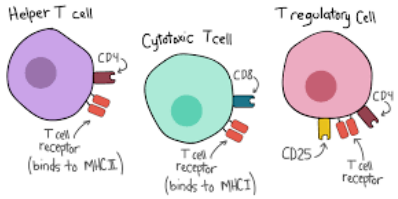
- Lymphocytes:

Divided into 3 classes:

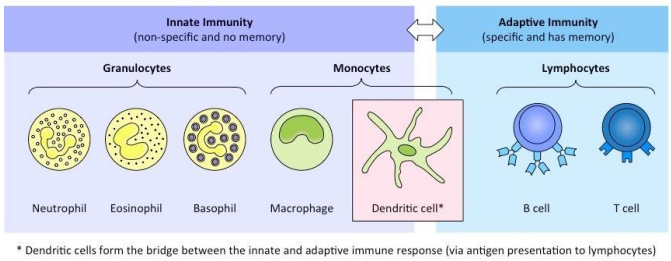
A. B cells
- Belongs to adaptive immune system (Humoral immune response)
- Differentiate into either memory B cells or plasma cells (circulating antibodies)

B. T cells
- Belongs to white blood cells and plays a role in cell mediated immunity
- T cells differentiate into either CD4+, helper T cells, CD8+ cytotoxic T cells, regulatory T cells or memory T cells

C. Natural killer cells



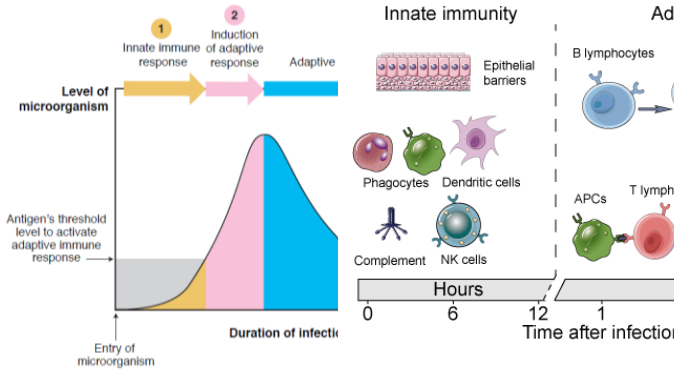
  - Named like this because they don't require activation to kill cells that lack MHC
  - CD56+ lymphocyte that contains cytoplasmic toxic granules (such as granzymes)
  - Activity enhanced by Il-2, Il-12, IFN-β, IFN-α
  - Able to recognize stressed cells in the absence of antibodies and MHC allowing for faster immune response
  - Able to kill malignant cells, virus-infected cells, or antibody-coated (opsonized) cells



Innate and adaptive immunity

Overview:

- The innate and adaptive immune response work together to stop an infection.
- Initially, once a pathogen has broken through the anatomic and physiologic barriers, the innate immune response is immediately activated, oftentimes it is able to contain and eliminate the infection.
- BUT, when the innate immune response is unable to handle an infection, the adaptive immune response is engaged and activated by the innate immune response in an antigen-specific manner.
- Typically, it takes 1-2 weeks after the primary infection for the adaptive immune response to begin clearance of the infection through the action of effector cells and antibodies.
- Once an infection has been cleared, both the innate and adaptive immune responses cease.
- Antibodies and residual effector cells continue to provide protective immunity, while memory cells provide long-term immunologic protection from subsequent infection.



Innate immunity:

- Innate immunity provides the body's first line of defense against infectious agents.

Characterized by:

- Fast (Minutes to hours)
- nonspecific response to infection
- Lack of immune memory.
- Does not improve after exposure to antigen
- Always present
- Available on short notice to protect
- It allows for an individual to have basic immunity

Functions:

- Fight against microbes
- Activation of adaptive immunity

Components:

1. Anatomical barrier:
   Physical barrier (skin, cilia, mucosal tissue and normal flora), chemical barrier (enzymes, antimicrobial peptides)
2. Cell response
   Recognize pathogen by receptors
3. Soluble proteins
   - Such as Natural killer cells (in case of viral infection and malignancy)
   - Phagocytic cells (Macrophages, Neutrophil)
   - Dendritic cell activates adaptive immune response

Specificity:

- Has limited specificity. Different microbes could be recognized by the identical mannose receptor

Receptors:

- Included in germline with limited diversity

Receptor distribution:

- Non- clonal: Identical receptors are found at cells of the same lineage such as Neutrophils

Mechanisms of pathogen recognition:

- Phagocytic cells (monocytes/macrophages, neutrophils and dendritic cells) are considered the first line of defense mechanism against infection
- They recognize pathogens via shared molecules that are not expressed on host cells.
- Receptors of the innate immune system are referred to as pattern recognition receptors (PRRs).
- PRRs recognize pathogen-associated molecular patterns (PAMPs), such as LPS, flagellin (bacteria), nucleic acids (viruses).
- PPRs could also recognize damage-associated molecular patterns (DAMPs) released from dying or damaged cells.
- Receptors of innate immune system examples: Toll like receptors (TLR), Nod like receptors (NLR), Rig like receptors (RLR)
- These receptors are present intrinsically, encoded in the germline genes, and are not generated through somatic recombination as the lymphocyte receptors are generated.

Adaptive immunity:

Characterized by:

- Increased with each repeat exposure— immunologic memory
- Capable of distinguishing self from non-self
- Self-limiting

Functions:

- Protect against persistent or recurrent challenge (immunologic memory-specificity)

- Protect against several pathogens
- Protect against auto immune reaction. Ability to distinguish between self (host cells) and non-self (pathogens)

Components:

- T cells, B cells and circulating antibody

Specificity:

- Different microbes could be recognized by different antibody molecules

Receptors:

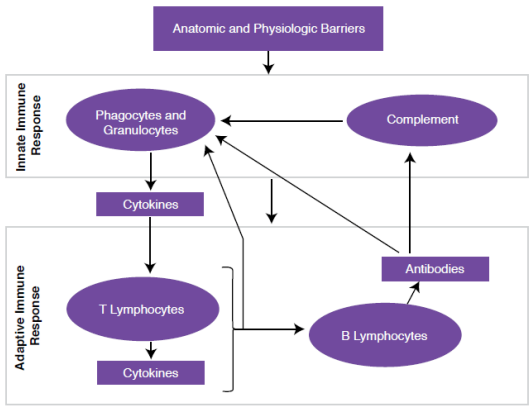
- Encoded by genes produced by somatic recombination of gene segments; greater diversity

Innate Immunity	Adaptive Immunity
Antigen independent	Antigen dependent
No time lag	A lag period
Not antigen specific	Antigen specific
No immunologic memory	Development of memory
Present at birth	Developed after birth

Receptor distribution:

- Variation through V(D)J recombination during lymphocyte development

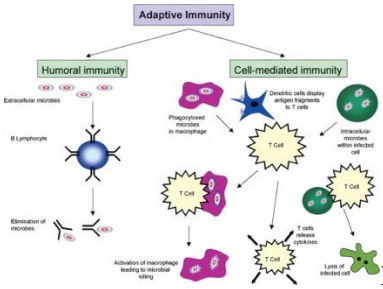
Crosslink between innate and adaptive immune response



- The responses of both innate and adaptive are overlapped in a positive feedback mechanism
- Phagocytic cells recognize pathogens by binding PAMPs leading to phagocytosis.
- Phagocytic cells present antigen to facilitate stimulation of specific T lymphocytes with subsequent release of cytokines that trigger initiation of specific immune responses.
- T lymphocytes produce cytokines that enhance phagocytosis
- Cytokines will drive differentiation of B lymphocytes into plasma cells and isotype switching.
- Antibodies will aid in the destruction of pathogen through opsonization, complement activation and antibody-dependent cellular cytotoxicity.

Types of adaptive immunity:

1. Humoral immunity is mediated by antibodies that are produced by B lymphocytes.

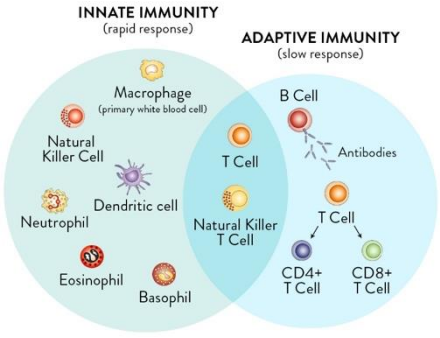


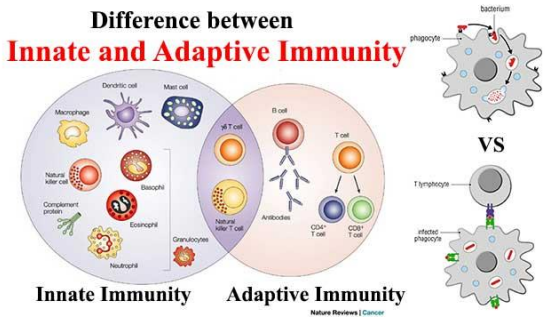
- It is the principal defense mechanism against extracellular microbes and their toxins, with secreted antibodies binding to microbes and toxins to assist in their elimination.

2. Cell mediated immunity is mediated by T cells, with dendritic cells playing important roles in antigen presentation.
T cells can function by various methods:

A. Activating macrophages to kill phagocytosed microbes
B. Directly destroy infected cells
C. Releasing cytokines and alter the milieu around them.

Innate versus Adaptive immunity:





MHC class I and II

Overview:

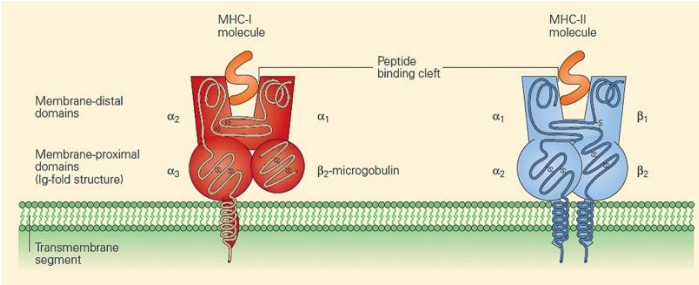
- T lymphocyte development (origin of MHC):

- Immature lymphocytes leave the **bone marrow** and proceed to the **thymus**, the second primary lymphoid organ dedicated to the maturation of T cells (double negative T lymphocytes since they do not express CD4 or CD8 on their surface

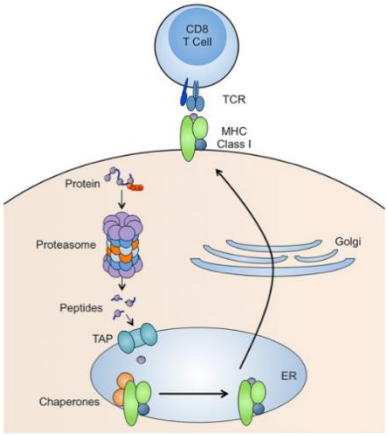
- Within the thalamus, cortex packed with immature T cells, while the inner medulla receives ONLY mature T cells.
- As the developing thymocytes begin to express their T cells receptors (TCRs), they are subjected to a rigorous 2-step selection process (positive and negative selection)
- TCRs designed to bind to antigen presenting cells (APCs)
- **Major histocompatibility complex (MHC) antigens** is necessary to remove those cells that would bind to normal self-antigens and cause autoimmunity.
- MHC is a cell surface protein which is essential for acquired immune system
- Binds to antigens derived from pathogens and display them on the cell surface to be recognized by T cells
- Able to differentiate between self and non-self-antigens
- Detects when the body's own cells are either infected or subjected to malignancy
- There are 2 major classes of cell-bound MHC gene products: I and II.
- Both class I and class II molecules are structurally and functionally distinct from one another
- MHC gene products are also called human leukocyte antigens (HLA).

Class I and Class II gene products:

Class I gene products			Class II gene products			
HLA-A	HLA-B	HLA-C	HLA-DM	HLA-DP	HLA-DQ	HLA-DR



MHC I



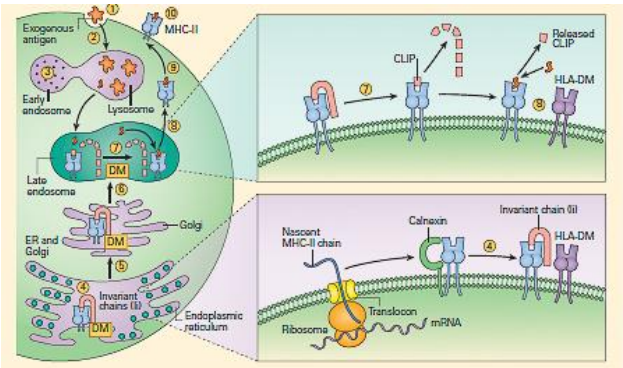
- Class I molecules are expressed on all nucleated cells in the body, as well as platelets EXCEPT RBCs

Note: Pathogens within red blood cells can go undetected by cytotoxic T cells, e.g., malaria.

- Functionally, antigen is loaded into the MHC I in the endoplasmic reticulum before the MHC I is inserted into the cell membrane.
- Normally the antigen that is loaded onto MHC I is self-antigen, and cytotoxic T cells (CD8+ T cells) will not react to it.
- In case of viral infection, viral proteins will also be loaded onto MHC I. This is how cytotoxic T cells confer immunity to viral infection.
- They recognize MHC I with loaded viral antigen and targets it for **cytotoxic destruction.**

MHC II

- Class II MHC molecules are expressed on the professional antigen-presenting cells of the body (primarily the macrophages, B lymphocytes, and dendritic cells).
- After APCs phagocytose microbes, they process and load these antigens onto MHC II. Then the MHC II is inserted into the cell membrane for binding and recognition by helper T cells (CD4+ T cells).
- Helper T cells can then activate B cells and/or trigger local inflammation.



Previously discussed:

- TCRs capable of binding with low affinity will receive a **positive selection signal** to divide and migrate into medulla

- TCRs that bind too strongly to self MHC molecules will be induced to undergo apoptosis (negative selection) because these cells would have the potential to cause **autoimmune disease**.
- Double positive thymocytes co-express CD4 and CD8
- If TCR binds MHC class I named as CD8 positive
- If TCR binds MHC class II named as CD4 positive
- CD4+ cells that recognize class II MHC are destined to become “helper T cells (Th)
- CD8+ cells that recognize class I MHC are destined to become cytotoxic T lymphocytes (CTLs).

HLA and disease associations

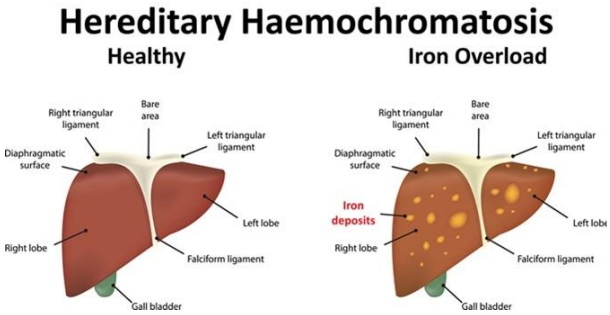
Overview (previously discussed):

- There are 2 major classes of cell-bound MHC gene products: I and II.
- Both class I and class II molecules are structurally and functionally distinct from one another
- MHC gene products are also called human leukocyte antigens (HLA).

HLA and disease associations

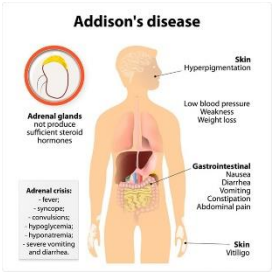
HLA subtypes	Disease
A3	Hemochromatosis
B8	Addison disease, myasthenia gravis, Graves’s disease
B27	Psoriatic arthritis, Ankylosing spondylitis, IBD-associated arthritis, Reactive arthritis
DQ2, DQ8	Celiac disease
DR2	Multiple sclerosis, hay fever, SLE, Goodpasture syndrome
DR3	Diabetes mellitus type 1, SLE, Graves’ disease, Hashimoto thyroiditis, Addison disease
DR4	Rheumatoid arthritis, diabetes mellitus type 1, Addison disease
DR5	Hashimoto thyroiditis

Hemochromatosis:



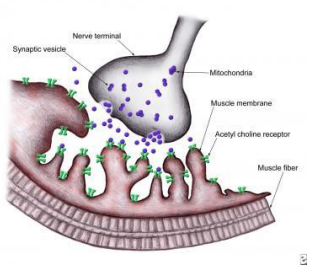
- Hemochromatosis is the abnormal accumulation of iron in parenchymal organs, leading to organ toxicity.
- It is the most common autosomal recessive genetic disorder and the most common cause of severe iron overload
- Mutations in human leukocyte antigen A3 (HLA-A3) and human leukocyte antigen B7 (HLA-B7) were linked to Hemochromatosis

Addison disease:



- Is adrenocortical insufficiency due to the destruction or dysfunction of the entire adrenal cortex.
- It affects glucocorticoid and mineralocorticoid function
- Highest genetic risk is associated with the Major Histocompatibility region (MHC), specifically human leukocyte antigen (HLA)-DR3 haplotypes (containing HLA-B8)
- Addison disease is also associated with HLA-DR3&4

Myasthenia Gravis:

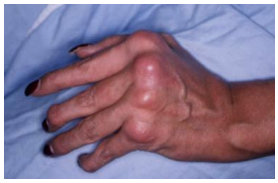


- Myasthenia gravis (MG) is a relatively rare acquired, autoimmune disorder caused by an antibody-mediated blockade of neuromuscular transmission resulting in skeletal muscle weakness.
- The autoimmune attack occurs when autoantibodies form against the nicotinic acetylcholine postsynaptic receptors at the neuromuscular junction of skeletal muscle
- People with certain human leukocyte antigen (HLA) types have a genetic predisposition to autoimmune diseases.
- The histocompatibility complex profile includes HLA-B8.

Graves’s disease:

- Graves' disease is an immune system disorder that results in the overproduction of thyroid hormones (hyperthyroidism).
- Although a number of disorders may result in hyperthyroidism, Graves' disease (GD) is a common cause.
- HLA-B8 was reported to be associated with GD in many studies

Psoriatic Arthritis:



- Psoriatic arthritis is most commonly a seronegative oligoarthritic found in patients with psoriasis,
- Characterized by differentiating features of distal joint involvement and arthritis mutilans
- Human leukocyte antigen (HLA)-B27 associated, psoriatic arthritis has also been classified among the seronegative spondyloarthropathies.

Celiac disease:

- Celiac disease is a chronic disorder of the digestive tract that results in an inability to tolerate gliadin
- When patients with celiac disease ingest gliadin, an immunologically mediated inflammatory response occurs that damages the mucosa of their intestines, resulting in maldigestion and malabsorption of food nutrients.
- A strong association exists between celiac disease and two human leukocyte antigen (HLA) haplotypes (DQ2 and DQ8).
- Damage to the small intestinal mucosa occurs with the presentation of gluten-derived peptide gliadin, consisting of 33 amino acids, by the HLA molecules to helper T cells that mediates the inflammatory response.

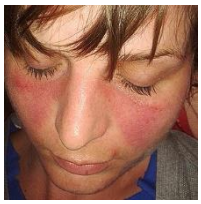
Multiple sclerosis:

- Multiple sclerosis (MS) is a potentially disabling disease of the brain and spinal cord (central nervous system)
- The immune system attacks the protective sheath (myelin) that covers nerve fibers and causes communication problems between your brain and the rest of your body.
- Characterized by Numbness, Slurred speech, Fatigue and Dizziness
- It has been shown that, T cells infiltrating the central nervous system and of myelin basic protein-reactive T cells found in HLA-DR2 MS patients.

Hay fever:

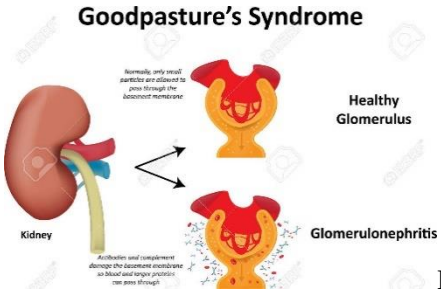
- Hay fever, also known as allergic rhinitis, is a type of inflammation in the nose which occurs when the immune system overreacts to allergens in the air.
- Signs and symptoms include a runny or stuffy nose, sneezing, red, itchy, and watery eyes, and swelling around the eye.

Systemic lupus erythematosus (SLE)

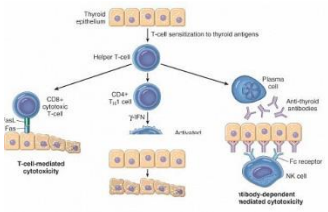


- Is an autoimmune disease in which the body's immune system mistakenly attacks healthy tissue in many parts of the body.
- Symptoms vary between people and may be mild to severe.
- Common symptoms include painful and swollen joints, fever, chest pain, hair loss, mouth ulcers, swollen lymph nodes, feeling tired, and a red rash which is most commonly on the face

Goodpasture syndrome (GPS):



- Known as anti-glomerular basement membrane disease, is a rare autoimmune disease in which antibodies attack the basement membrane in lungs and kidneys, leading to bleeding from the lungs and kidney failure.
- It is thought to attack the alpha-3 subunit of type IV collagen, which has therefore been referred to as Goodpasture's antigen.



Hashimotos Thyroiditis

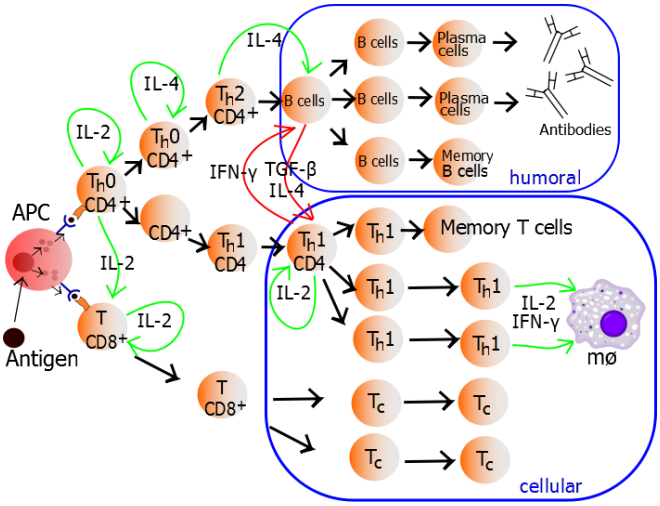
- Hashimotos Thyroiditis is an autoimmune disorder whereby the body produces antibodies against itself that leads to the destruction of the thyroid gland thereby causing a Thyroid Disease known as Thyrotoxicosis in the early phase of Hashimotos Thyroiditis or Hypothyroidism in the late phase.

T cells activation and immunity

Characteristics	T cells	B cells
Origin of undifferentiated cells	Red bone marrow	Red bone marrow
Site of differentiation	Thymus	Red bone marrow
Primary Locations	Lymphatic tissues 70-80% of the circulating lymphocytes in blood	Lymphatic tissues 20-30% of the circulating lymphocytes in blood
Primary functions	• Provide cellular immune response in which T cells interact with the antigens to destroy them • CD4+ T cells help B cells make antibodies and produce cytokines to recruit phagocytes and activate other leukocytes. • CD8+ T cells directly kill virus-infected cells.	• Provide humoral immune response in which B cells interact indirectly, producing antibodies that destroy the antigens • Maintain immunologic memory

- T-cell precursors move from the bone marrow (born) to the thymus (maturate) where they are selected for self-tolerance by exposure to **major histocompatibility complex (MHC)**
- Most T-cell precursors entering the thymus are destined to die there (apoptosis)

- Only those with TCRs appropriate to protect the host from foreign invaders will be permitted to exit to the periphery.
- CD4+ cells that recognize class II MHC are destined to become **"helper" T cells (Th)**.
- CD8+ cells that recognize class I MHC are destined to become **cytotoxic T lymphocytes (CTLs)**.



CD4+ T cells known as Helper T cells

- Helper T cells release cytokines into bloodstream to warn the immune system of the presence of a dangerous cell or virus
- when an antigen-presenting (APC) cells expresses an antigen on MHC class II, a $CD4^+$ cell will aid those cells through a combination of cell to cell
- Stimulation of helper T cells by interleukins become either Th1 or Th2 cells with specific functions to help regulate both the humoral and cell-mediated immune system

Note:

- In the advanced stages of **HIV infection**, loss of functional $CD4^+$ T cells leads to the symptomatic stage of infection known as the acquired immunodeficiency syndrome AIDS.

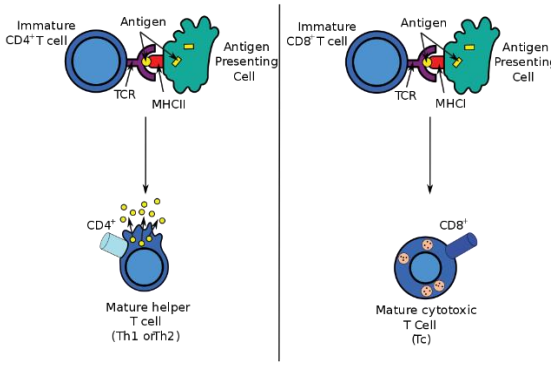
Subtypes

- **T_h1 helper cells** lead to an increased cell-mediated response, typically against intracellular bacteria and protozoa.
- They are triggered by IL-12 and their effector cytokines are IFN-γ and IL-2.
- They also secrete IL-2, which activates CD8+ (cytotoxic T cells) to kill virally infected cells.
- Main partner cell types: include Macrophage, CD8+ T cell
- **Th2 helper cells** lead to a humoral immune response, typically against extracellular parasites including helminths.
- They are triggered by IL-4 and IL-2, and their effector cytokines are IL-4, IL-5, IL-9, IL-10, IL-13 and IL-25.
- Main partner cell types: include eosinophils, mast and B cells

CD8+ T cells

- A type of cells that kills cancer cells, cells that are infected (particularly with viruses), or cells that are damaged in other ways.

- Cytotoxic T cells have CD8, which binds to MHC I on virus-infected cells.
- Destruction mechanism either by forcing the cell to commit suicide, or
- Secret enzymes that kill the cells (**perforin, granzyme B**)



Activations of T cells

- Several surface molecules are involved in the activation of mature, naive T lymphocytes:
- **First (primary) signal**: recognition of the MHC: peptide complex by the T cell receptor and coreceptors (CD4 and CD8)
- Second (costimulatory) signal: recognition of B7 by CD28

1. Once T cells leave the thymus, they circulate throughout the body until they recognize their antigen on the surface of **antigen presenting cells (APCs)**.
2. The T cell receptor (TCR) on both CD4+ helper T cells and CD8+ cytotoxic T cells binds to the antigen as it is held in a structure called the MHC complex, on the surface of the APC. This trigger initial activation of the T cells
3. Besides T cells, both CD4 and CD8 molecules then bind to the MHC molecule too
4. This normally takes place in the secondary lymphoid organs.
5. In addition to TCR binding to antigen-loaded MHC, both helper T cells and cytotoxic T cells require several secondary signals to become activated and respond to the threat.
6. The costimulatory molecules B7-1 (CD80) and B7-2 (CD86) on APCs bind to CD28 on the mature, naïve T cells, providing the second signal necessary for successful activation.
7. The activated CD4+ (helper) T lymphocytes will begin to produce and secrete cytokines and increase surface expression of cytokine receptors.

- The CD4+ T cell will also release IL-2 which lead to:

A. activation and proliferation of CD8+ cytotoxic T cells to kill virally infected host cells
B. Cause CD4+ T cell proliferation and differentiation in an autocrine manner

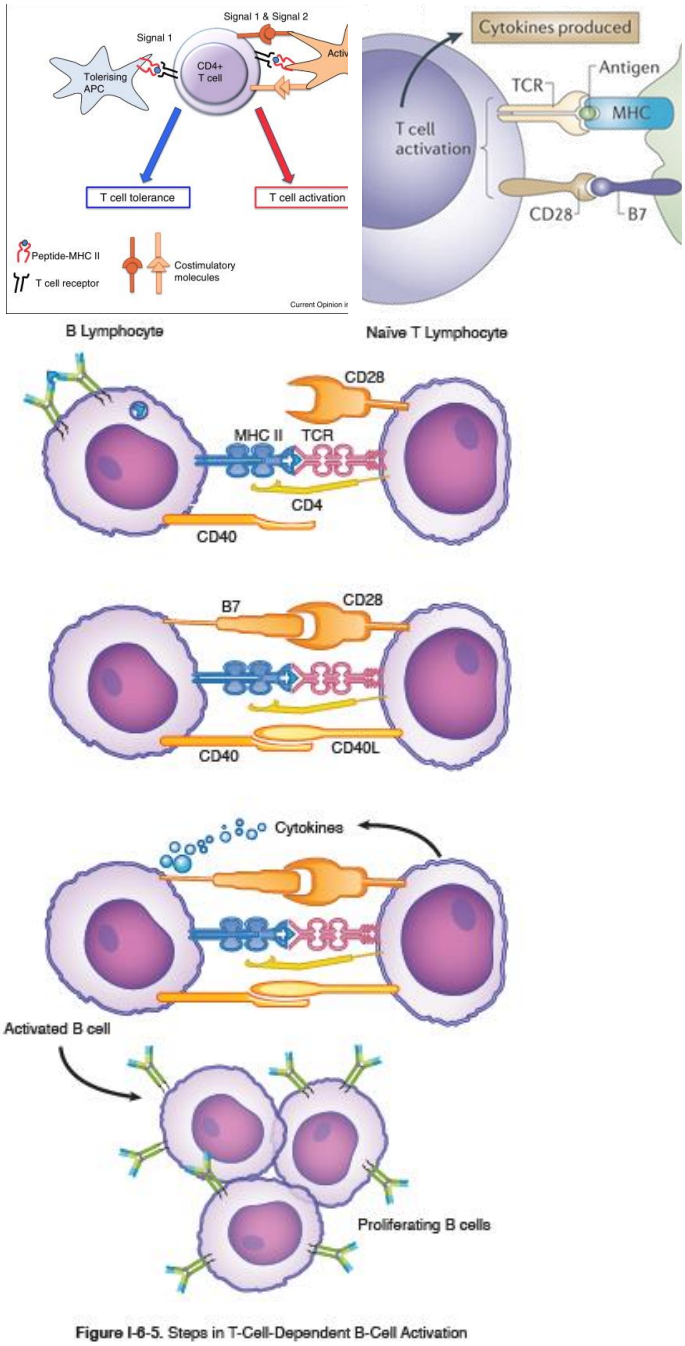
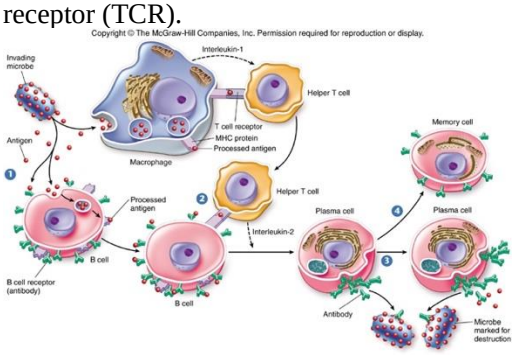


Figure I-6-5. Steps in T-Cell-Dependent B-Cell Activation

B cell activation and class switching

- A helper T cell subtype 2 (Th2 cell) can then recognize the antigen on the MHC II with its T cell receptor (TCR).



  The Th2 cell will then secrete specific cytokines (IL-4, IL-5, and IL-6) to stimulate B cell proliferation, hypermutation, and isotype switching.
- Once a B cell becomes a plasma cell, it is no longer able to proliferate because it is designed for maximal immunoglobulin secretion.
- Two signals to make a Th2 cell secrete B cell activating cytokines:

A. The TCR–MHC II antigen interaction
B. CD40–CD40 ligand interaction.

B cells, antibodies and Humoral immunity

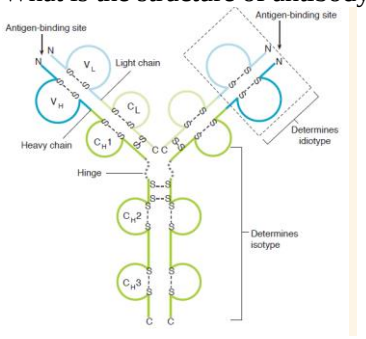
Overview:

- Antibody formation is accomplished by mature plasma B cells, which synthesize and release antibodies
- Antibody is a large protein, constitutes γ-globulin produced by plasma cells.
- It is used by the immune system to identify and neutralize pathogens such as bacteria and viruses
- Antibodies are also called Immunoglobulins

Humoral immunity antibodies synthesis (immunoglobulins)

Antibody structure and function:

- What is the structure of antibody molecule?



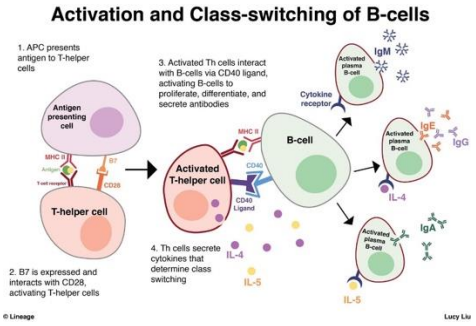
- Each antibody consists of four polypeptides; two heavy chains and two light chains joined to form a "Y" shaped molecule.
- Both heavy and light chains bonded via interchain of di-Sulphide linkages
- Each heavy chain composed of one constant and one variable region
- The trunk of the "Y" is the constant fragment (Fc) and the two branches are antigen-binding fragments (Fab)
- The Fc region is the constant region:
- Include the carboxy terminal and various carbohydrate side chains and play an important role in both complement factor binding and determining **the isotype** of the immunoglobulin (IgM, IgA, IgE or IgD).
- Fab region:
- Determine **the idiotype** of the immunoglobulin

Generation of antibody diversity:

Antigen dependent	Antigen Independent
Somatic hypermutation and affinity maturation (variable region)	Random recombination of VJ (light-chain) or V(D)J (heavy-chain) genes
Isotype switching (constant region)	Random addition of nucleotides to DNA during recombination by terminal deoxynucleotidyl transferase (TdT)
	Random combination of heavy chains with light chains

Isotype switching:

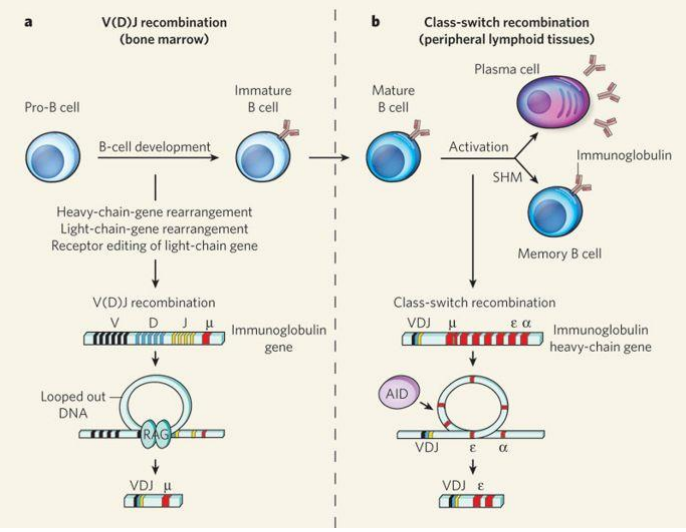
- Biological mechanism that changes a B cell's production of immunoglobulin from one type to another.
- During this process, the constant-region portion of the antibody heavy chain is changed, but the variable region of the heavy chain stays the same
- The antibody retains affinity for the same antigens, but can interact with different effector molecules.



Mechanism of Isotype switching:

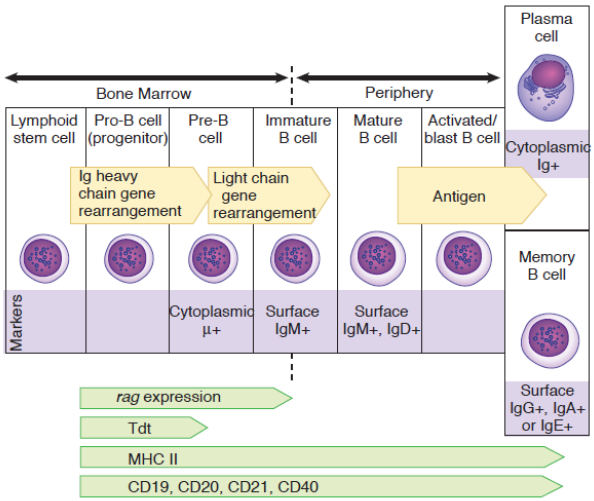
- Isotype switching occurs after mature B cell activation
- Generation of different classes of antibodies (with constant variable domains but include changes at the antibody heavy chain)

- mature B cells produce both IgM and IgD, which are the first two heavy chain segments in the immunoglobulin locus
- After activation by antigen, these B cells proliferate.
- If these activated B cells encounter specific signaling molecules via their CD40 and cytokine receptors (both modulated by T helper cells), they undergo antibody class switching to produce IgG, IgA or IgE antibodies



Types of Antibodies

- Antibodies of primary humoral response (IgM)
- Antibodies of secondary immune response
- All isotypes can exist as monomers.
- Mature, naive B cells prior to activation express IgM and IgD on their surfaces.
- They may differentiate in germinal centers of lymph nodes by isotype switching into plasma cells that secrete IgA, IgE, or IgG.



B cell differentiation

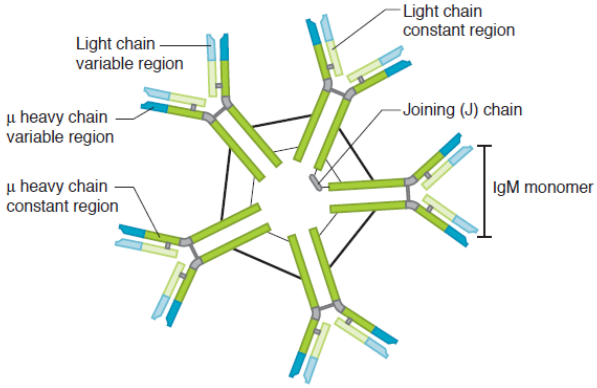
IgD (Immunoglobulin D class)

- Expressed on the surface of mature B cells
- Unknown function **BUT**, IgD works with IgM in B cell development.
- IgD is found in very low levels in serum and does not activate the complement pathway

IgM (immunoglobulin M):

- The first isotype of immunoglobulin that can be produced by a B cell **with or without T-cell help**.
- Therefore, considered the fast-antigenic response
- The IgM molecule on the surface of the B cell is a monomer, but the secreted form of this molecule is a **pentamer.**
- The design of the IgM pentamer maximizes its effect critical to the body early during antigenic challenge. Because of its multimeric structure (5 of the Y shaped monomers joined into one unit), plasma IgM has 5 times the capacity for binding antigenic epitopes.
- The multimeric structure of IgM also makes **it the most effective antibody at activating complement**, a set of serum proteases important in mediating inflammation and antigen removal.
- However, the pentamer is very bulky and therefore **does not cross the placenta**.

IgG



- The preponderant isotype of immunoglobulin that begins to be produced **after IgM during the primary immune response.**
- Most abundant isotype in serum
- IgG has the following characteristics:

1. Activates complement
2. Acts as an opsonin, enhancing phagocytosis
3. Neutralizes pathogen and toxins
4. Mediates antibody dependent cellular toxicity (ADCC)

- IgG is also actively transported **across the placenta** and thus plays a crucial role in protection of the fetus during gestation (passive immunity).

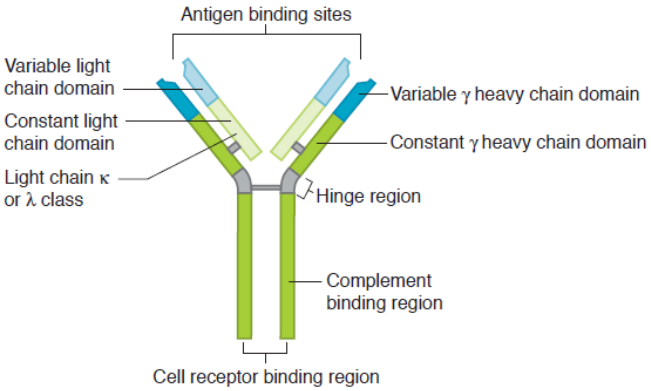


Figure I-7-3. Basic Structure of IgG

IgA

- More commonly produced in the submucosa than in the lymph nodes and spleen
- Prevents attachment of bacteria and viruses to mucous membranes; does not fix complement.
- Occurs as a monomer in the bloodstream and as a dimer when secreted
- Uses transepithelial transport for navigation
- IgA is secreted onto mucosal surfaces (gastrointestinal, genitourinary, and respiratory) to block attachment of pathogens to mucous membranes.
- Most produced antibody overall but has lower serum concentrations.
- Released into secretions **(tears, saliva, mucus) and breast milk**. Picks up secretory component from epithelial cells, which protects the Fc portion from luminal proteases.

Functions of IgA

- Serves as a major protective defense of the mucosal surfaces of the body Any pathogen that infects the mucosa will induce
- Functions as a neutralizing antibody by inhibiting the binding of toxins or pathogens to the mucosa of the digestive, respiratory, and urogenital systems

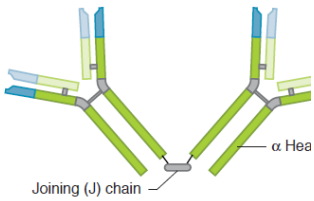


Figure I-7-4. The IgA Dimer

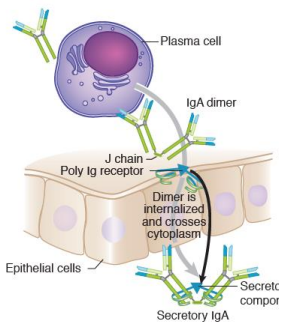
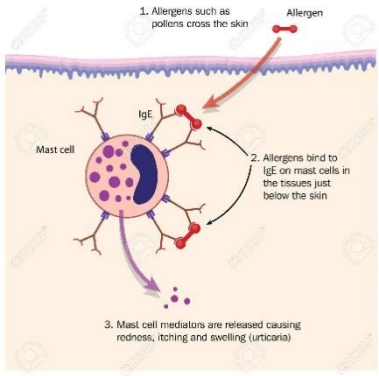


Figure I-7-5. Secretory IgA

IgE

- Binds directly to Fc receptors present on mast cells, eosinophils and basophils
- Involved in elicitation of protective immune responses against parasites and allergens **(Type I hypersensitivity)**
- It does not activate complement or act as an opsonin.



Bilogical Functions of the antibody isotypes

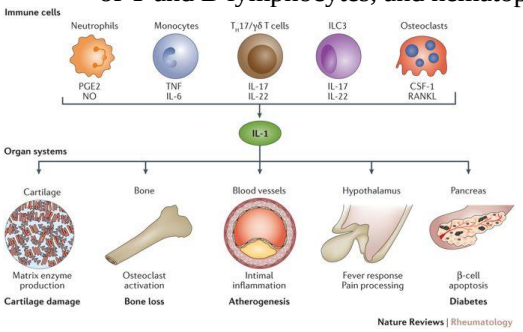
Functions	IgM	IgM	IgA	IgD	IgE
Complement activation	+	+	-	-	-
Neutralization	+/-	+	+	-	-
Opsonization	-	+	-	-	-
Antibody-dependent mediated cytotoxicity	-	+	_	_	+/-
Placental transport	-	+	-	-	-
Triger mast cells and granule release	_	_	_	_	+
Naïve B cells antigen receptor	+	_	_	+	_
Memory B cell antigen receptor	_	+	+	-	+

Interleukins Overview

Overview:

- Interleukins are a group of cytokines (secreted proteins and signaling molecules) that were first seen to be expressed by **white blood cells** (leukocytes).
- The function of the immune system depends in a large part on interleukins.
- Deficiencies of several of them were linked to **autoimmune diseases or immune deficiency**.

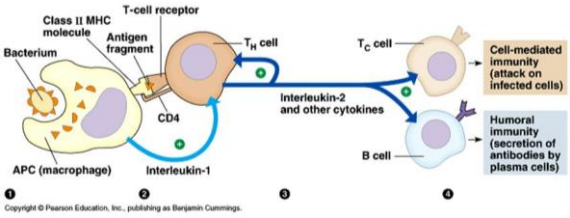
- Most interleukins are synthesized by **helper CD4 T lymphocytes**, as well as through monocytes, macrophages, and endothelial cells.
- They promote the development and differentiation of T and B lymphocytes, and hematopoietic cells



Interleukin 1:

- Produced by activated macrophages- participate in the regulation of immune responses and **inflammatory reactions**
- Enhance corticosteroid release, leukocyte recruitment
- Induce fever and shivering
- Induces chemokine secretion to recruit WBCs.

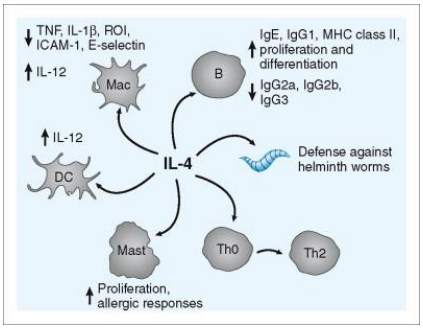
Interleukin 2:



- Stimulates growth of helper, cytotoxic, and regulatory T cells, and NK cells.
- T Lymphocytes regulate the growth and differentiation of **T cells and certain B cells** through the release of secreted protein factors.
- IL2 is a lymphokine that induces the proliferation of responsive T cells.

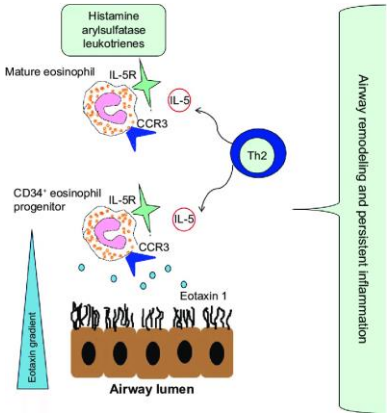
Interleukin 3:

- Interleukin that stimulates **bone marrow**
- regulates blood-cell production by controlling the production, differentiation and function of granulocytes and macrophages



Interleukin 4:

- produced by CD4 T cells specialized in providing help to B cells to proliferate and to undergo class switch recombination (IgE and IgG) and somatic hypermutation.
- IL-4 also promotes **CD8+ Cell growth** and
- promotes TH2 Cell differentiation

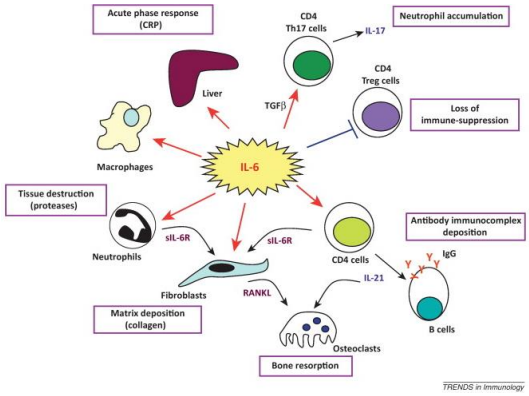


Interleukin 5:

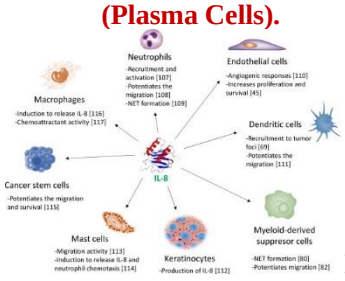
- It regulates eosinophil growth and activation, and thus plays an important role in diseases associated with increased levels of eosinophils, including asthma.
- Secreted by Th2 cells that enhances immunoglobulin class type switching to IgE

Interleukin 6:

- Is produced by many cell types, including T- Cells, Macrophages, B-Cells, Fibroblasts, and Endothelia Cells.



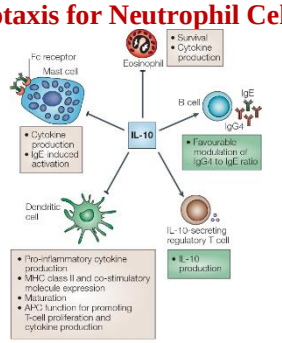
- IL-6 stimulates several types of Leukocytes, and the production of **acute Phase Proteins in the Liver**.
- IL-6 is particularly important in inducing B- Cells to differentiate into **antibody Forming Cells (Plasma Cells).**



Interleukin 8:

- Produced by most cells of the body, especially Macrophages and Endothelia Cells.

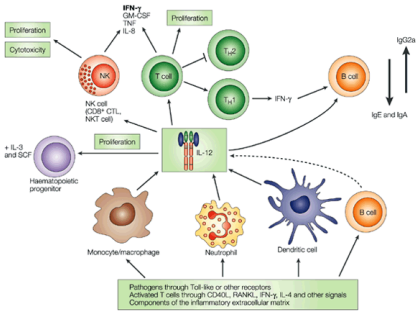
- • IL-8 enhances Inflammation, by enabling Immune Cells to migrate into tissue, & is a powerful inducer of **Chemotaxis for Neutrophil Cells**



Interleukin 10:

- Secreted by regulatory T cells to suppress cell-mediated immunity and stimulate humoral immunity.
- Decreases expression of MHC class II and Th1 cytokines.
- Inhibits activated macrophages and dendritic cells
- Attenuates inflammatory response.

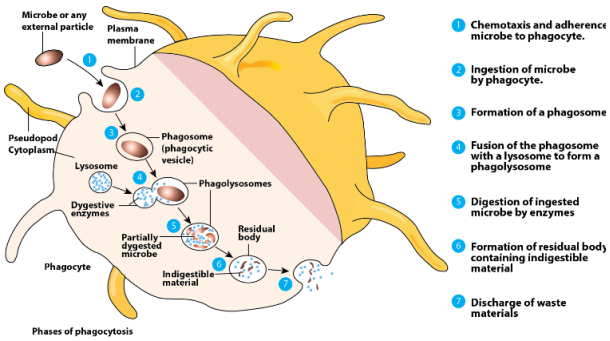
Interleukin 12:



- Secreted by macrophages with functions to enhance **NK cells and T cells**.
- It is involved in the stimulation and maintenance of Th1 cellular immune responses, including the normal host defense against various intracellular pathogens, such as Leishmania, Toxoplasma, Measles virus, and Human immunodeficiency virus 1 (HIV).
- IL-12 also has an important role in pathological Th1 responses, such as in **inflammatory bowel disease and multiple sclerosis**

Oxidative Burst

Overview:



- When molecular oxygen (O2) is partially reduced, unstable products called reactive oxygen species (ROS) are formed.
- Reactive oxygen species include:

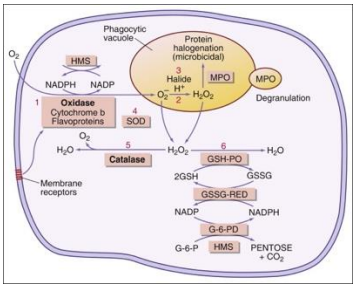
1. Superoxide (O2–)
2. Hydrogen peroxide (H2O2)
3. Hydroxyl radical (OH)

- The polymorphonuclear neutrophil produces these substances to kill bacteria in the protective space of the phagolysosome during the oxidative burst accompanying **phagocytosis.**
- Phagocytosis is an Innate defense mechanism is ingestion of extracellular particles
- Performed by specialized cells such as Blood Monocytes, Neutrophils and tissue Macrophages
- During phagocytosis, a metabolic process known as the respiratory burst activates a membrane-bound oxidase that generates oxygen metabolites, which are toxic to ingested microorganisms.
- Oxygen uptake increase greatly, undergoes a series of changes **"Respiratory Burst"**

Respiratory Burst

- Respiratory Burst" occurs during:

1. Activation of macrophages during phagocytosis
2. Abrupt rise in Oxygen consumption
3. Activation of NADPH oxidase/Phagocyte oxidase



- Respiratory burst Plays an important role in the immune response that initiate the rapid release of reactive oxygen species (ROS).
- Two oxygen-dependent mechanisms of intracellular digestion are activated because of this process.

1. **NADPH oxidase** reduces oxygen to superoxide anion, which generates hydroxyl radicals and hydrogen peroxide, which are microbicidal.

2. **Myeloperoxidase** in the lysosomes acts on hydrogen peroxide and chloride ions to produce hypochlorite (the active ingredient in household bleach), which is microbicidal.

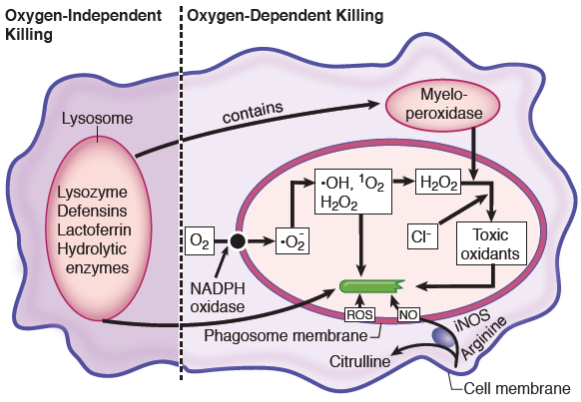


Figure I-4-11. Metabolic Stimulation and Killing Within the Phagocyte

NADPH oxidase

- Present in membrane associated of phagocytic cells
- NADPH oxidase catalyzes the production of a superoxide free radical by transferring one electron to oxygen from NADPH.
- During this process O2 is transported from the extracellular space to the cell interior and the H+ is exported.

Superoxide dismutase

- Catalyzes the dismutation of the superoxide(O_2-) radical into either molecular oxygen (O_2) or hydrogen peroxide (H_2O_2).

Myeloperoxidase

- Abundantly expressed in **neutrophil granulocytes**
- produces hypochlorous acid (HOCl) from hydrogen peroxide(H2O2) and chloride anion (Cl−) during the neutrophil's respiratory burst.
- Hypochlorous acid is cytotoxic to bacteria
- Myeloperoxidase contains a blue-green heme-containing pigment that gives sputum its color.

Glutathione peroxidase

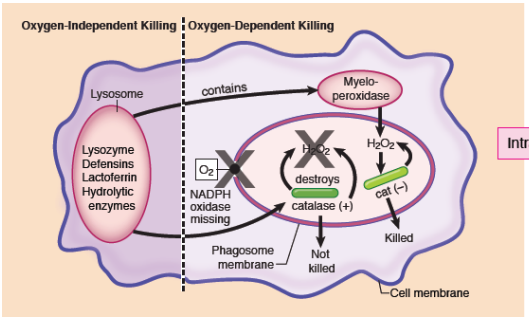
- Glutathione (GSH) is crucial for the detoxification of H_2O_2 that has diffused into the cytosol

Glutathione reductase

- Catalyzes the reduction of glutathione disulfide (GSSG) to the sulfhydryl form glutathione (GSH)

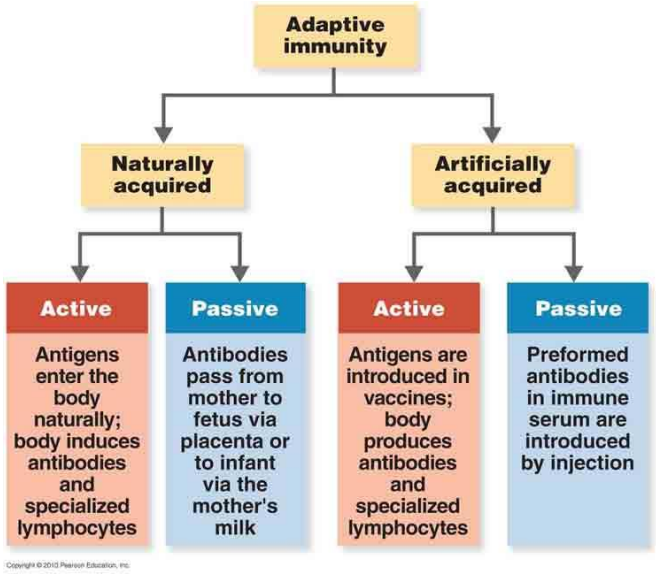
Chronic granulomatous disease

- Chronic granulomatous disease is most frequently caused by genetic deficiency of NADPH oxidase in the polymorphonuclear neutrophils (PMN).
- This defect eliminates the phagocyte's ability to produce many critical oxygen-dependent intracellular metabolites ($\cdot O2^-$, OH, $^1O_2$, and H_2O_2).
- The 2 other intracellular killing mechanisms remain intact (myeloperoxidase + H_2O_2 → HOCl and lysosomal contents).
- If the patient is infected with a catalase-positive organism (e.g., Staphylococcus, Klebsiella, Serratia, Aspergillus), the myeloperoxidase system lacks its substrate (because these organisms destroy H_2O_2),
- Thus, CGD patients suffer from chronic, recurrent infections with catalase-positive organisms. Such as:
- Staphylococcus aureus, Klebsiella, Escherichia coli, Candida, and Aspergillus.
- These species neutralizing their own H2O2, leaving phagocytes without ROS for fighting infections
- The patient is subjected to recurrent pulmonary infection
- Skin, lymphatic tissue Hepatic infection
- Fever induced by prostaglandin Il-1, PGE1, TNF alpha
- Diagnosis: Failures of phagocytic cells to generate oxygen radicals are easily detected by the **nitroblue tetrazolium (NBT) reduction test** or neutrophil oxidative index



Intracellular Killing in CGD

Active and passive immunity



	Artificial Active immunity	Artificial Passive immunity
Duration of immunity	Long lasting immunity	Short lasting immunity half-life 3 weeks
Time taken to achieve immunity	Body needs time to synthesis antibody after exposure to antigen	Ready-made antibodies
Time of injection	Before the person is infected	At the time when the person is infected or at high risk of getting the disease
Type of injection	Vaccines containing dead or weakened antibody	Serum containing specific antibody
Necessity of booster dose	Required because the first injection usually induces a slow & low level of antibody	Not required The first injection usually enough
	• Natural infections • Vaccines • Toxoid	• Antitoxin • Immunoglobulin for intravenous (Kawasaki disease) • Digitalis antibody fragment • Humanized monoclonal antibody

		• Maternal Ig crossing the placenta
		• After exposure to Tetanus toxin, Botulinum, toxin, HBV, Varicella, Rabies virus, or diphtheria toxin • unvaccinated patients are given preformed antibodies (passive)

Types of vaccines:

Attenuated

- Comprised of live organisms which lose capacity to cause disease but still replicate in the host
- Attenuated vaccines are comprised of live organisms, there is slight potential to revert to a virulent form
- Stimulating both a humoral and cell mediated immune response, as they mimic the natural infection and typically elicit lifelong immunity
- Not safe-dangerous for immunocompromised patients/pregnancy because even attenuated viruses can cause them significant disease.

Examples

- Polio (sabin), Varicella (chickenpox), Smallpox, BCG, Yellow fever, Influenza (intranasal), MMR, Rotavirus

Nonattenuated

- Used by U.S. military against adenovirus types 4 and 7

Killed vaccines

- Utilize organisms that are killed so they can no longer replicate in the host
- Inactivated by chemicals rather than heat, as heat will often denature the immunogenic epitopes
- Typically require several doses to achieve desired response
- Safer but weaker immune response
- Produce humoral immunity

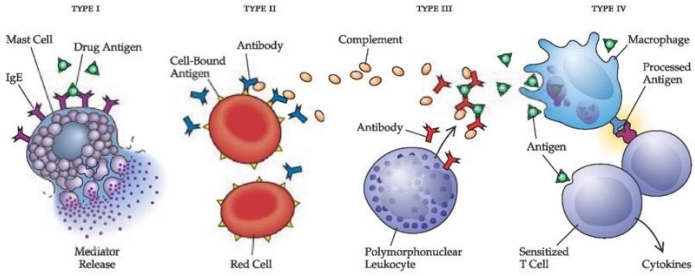
Examples

- Rabies, Influenza, Polio (Salk) and Hepatitis A

Hypersensitivity response

Overview:

- Hypersensitivity diseases are conditions in which tissue damage is caused by immune responses.
- They may result from uncontrolled or excessive responses against foreign antigens or from a failure of self-tolerance, in which case they are called **autoimmune diseases**.



Type I hypersensitivity:

- When someone is exposed to an allergen, it can lead to a rapid immune response that occurs almost immediately. Such a response is called an allergy and is classified as a type I hypersensitivity.
- The first exposure activates a primary IgE antibody response that sensitizes an individual to type I hypersensitivity reaction upon subsequent exposure.

Immune mechanism:

- Allergen-specific IgE antibodies bind to mast cells via their Fc receptor

Mechanisms of tissue injury:

Immediate reaction

- Degranulation and release of vasoactive amines (ie. histamine) and proteases
- Degranulation: a reaction in which the contents of the granules in the mast cell are released into the extracellular environment.

Late phase reaction

- Synthesis and secretion of prostaglandins and leukotrienes
- Cytokine-induced inflammation and leukocyte recruitment

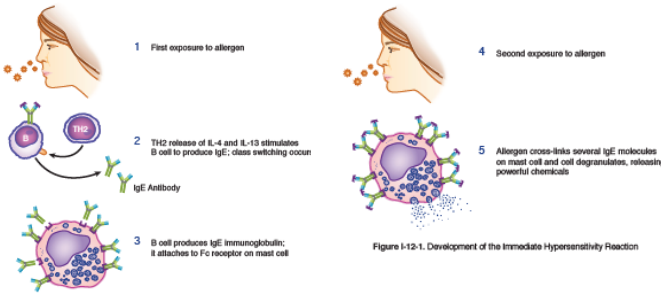
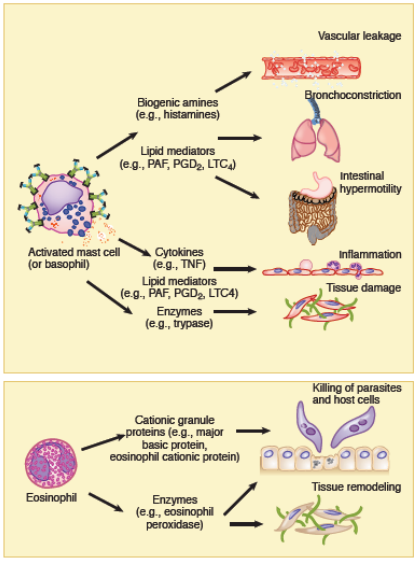


Figure I-12-1. Development of the Immediate Hypersensitivity Reaction

Source of allergy:

- Food allergy milk, egg, fish and peanuts
- Dust, cats, dogs, pet dander, pollen
- Bee stings

Clinical presentations:



- **Allergic rhinitis (hay fever)**: Histamine stimulates mucus secretion in nasal passages and tear formation from lacrimal glands, promoting the runny nose and watery eyes of allergies. Interaction of histamine with nerve endings causes itching and sneezing.
- The vasodilation caused by several of the mediators can result in hives, headaches, angioedema (swelling that often affects the lips, throat, and tongue), and hypotension (low blood pressure).
- **Systemic anaphylaxis** Bronchiole constriction (**Asthma**) caused by some of the chemical mediators leads to wheezing, dyspnea (difficulty breathing), coughing, and, in more severe cases, cyanosis (bluish color to the skin or mucous membranes).
- **Gastrointestinal problems:** Vomiting can result from stimulation of the vomiting center in the cerebellum by histamine and serotonin. Histamine can also cause relaxation of intestinal smooth muscles and diarrhea

Diagnosis:

- The main test used by allergists is scratch testing in which a positive test result in a wheal and flare reaction of the scratched skin site.

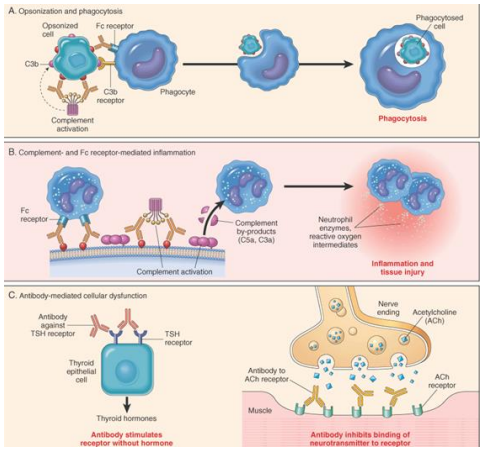
Type II hypersensitivity (cytotoxic hypersensitivity):

- Mediated by IgG and IgM antibodies (**autoantibodies**) binding to cell-surface antigens or matrix-associated antigens on basement membranes.
- These antibodies can either activate complement, resulting in an inflammatory response and lysis of the targeted cells,
- They can be involved in antibody-dependent cell-mediated cytotoxicity (ADCC) with cytotoxic T cells.

- These antibodies can cause tissue destruction by 3 main mechanisms:

1. Opsonization of cells leading to either phagocytosis/activation of complement system/ NK cell killing
2. Activation of the complement system which recruit neutrophils and macrophages that cause tissue damage
3. Cellular dysfunction

- In some types of type II hypersensitivity, complement is activated and/or ADCC is active (hemolytic disease of the newborn).
- In other types, cell function is altered in the absence of complement activation and ADCC (myasthenia gravis).
- During Type II antigen and antibody interaction may cause localized damage, but they do not circulate so the damage is localized to the specific tissue.



Disorders associated with type II hypersensitivity

Cytotoxic	Mechanism	Clinical manifestations
Autoimmune hemolytic anemia	Opsonization, phagocytosis, and complement-mediated destruction of RBCs	Hemolysis, anemia
Acute rheumatic fever	Inflammation, macrophage activation	Myocarditis, arthritis
Goodpasture syndrome	Complement- and Fc receptor– mediated inflammation	Nephritis, lung hemorrhage, linear Ab deposits
Transfusion reaction	opsonization + complement activation	Hemolysis
Autoimmune thrombocytopenic purpura	opsonization and complement activation	Bleeding
Non-cytotoxic		
Myasthenia gravis	Ab inhibits acetylcholine binding, downmodulates receptors	Muscle weakness, paralysis
Graves' disease	Ab-mediated stimulation of TSH receptors	Hyperthyroidism followed by hypothyroidism
pemphigus vulgaris	Autoimmune disease	Oral blisters
Bullous pemphigoid	Formation of anti-hemidesmosome antibodies.	Skin lesions

Other common Type II hypersensitivities:

Hemolytic disease of the newborn (HDN)

- IgG from mother crosses the placenta, targeting the fetus' RBCs for destruction
- Characterized by Anemia, edema, enlarged liver or spleen, hydrops (fluid in body cavity), leading to death of newborn in severe cases

Hemolytic transfusion reaction

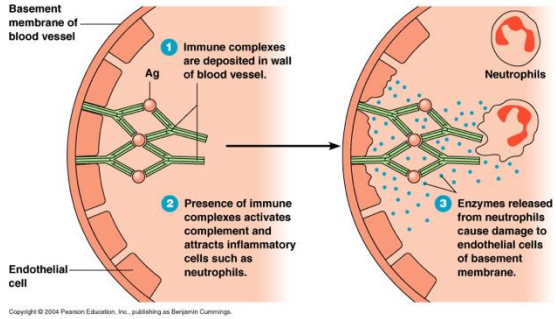
- IgG and IgM bind to antigens on transfused RBCs, targeting donor RBCs for destruction
- Characterized by Fever, jaundice, hypotension, disseminated intravascular coagulation, possibly leading to kidney failure and death

Diagnosis:

- Direct and indirect coombs test of RBC for hemolytic anemia.
- Direct immunofluorescence of the glomerular basement membrane for Goodpasture syndrome

Type III hypersensitivity (Antigen-Antibody-Complement):

- Antigen-antibody complexes are deposited in tissues lead to:



1. Complement activation with production of pro-inflammatory C3a and C5a
2. IgG binding to antibody receptors on localized mast cells, resulting in **mast-cell degranulation**
3. Increased blood-vessel permeability **(vasculitis)** with chemotactic recruitment of neutrophils and macrophages

Note: neutrophil degranulation results in the release of lysosomal enzymes that cause extracellular destruction of the immune complex, damaging localized cells in the process.

Clinical presentations:

- Fever, urticaria, arthralgia, proteinuria, lymphadenopathy occur 1–2 weeks after antigen exposure

Serum sickness

- **Systemic type** occurs when immune complexes deposit in various body sites, resulting in a more generalized systemic inflammatory response (within 1-2 weeks)

Examples:

- These immune complexes involve non-self-proteins such as antibodies produced in animals for artificial passive immunity such as **Tetanus vaccine**
- Certain drugs such as haptens, **penicillin**
- Microbial antigens that are continuously released over time during chronic infections:
  - Subacute bacterial **endocarditis**
  - chronic viral **hepatitis**

Arthus reaction

- **Localized type** occurs within 3-10 hours after intradermal injection of antigen into a pre-sanitized person (has circulating IgG) causing necrosis, edema and local pain

Disorders associated with type III hypersensitivity

Disease	Clinical Manifestations
Systemic lupus erythematosus	Nephritis, arthritis, vasculitis, butterfly facial rash
Poststreptococcal glomerulonephritis	Nephritis, "lumpy-bumpy" deposits
Polyarteritis nodosa	Systemic vasculitis

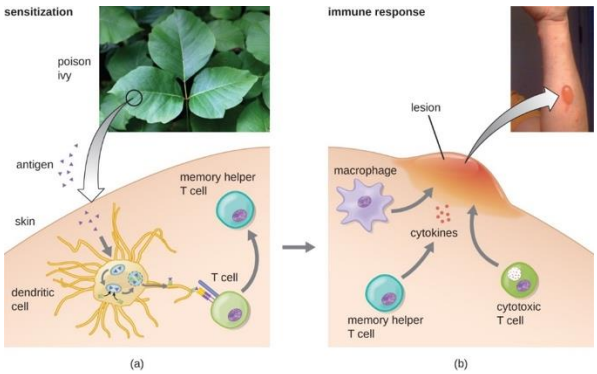
Diagnosis:

- immunofluorescent staining

Type IV hypersensitivity

- Known as delayed- type hypersensitivity or antibody-independent cytotoxicity
- Can be organized into three subcategories based on T-cell subtype, type of antigen, and the resulting effector mechanism.

1. The antigen presenting cells activate **helper T cells**, stimulating differentiation into memory **TH1 cells**.
   - These sensitized memory **TH1 cells** release cytokines that activate macrophages
   - Activated macrophages are responsible for much of the tissue damage
2. Effector CD4+ T cells recognize antigen and release inflammation-inducing cytokines
3. Directly killing target cells through CD8+ cytotoxic T cells
   - T-cell-mediated tissue injury is common during the protective immune response against persistent intracellular microbes.



Disorders associated with type IV hypersensitivity

Disease	Clinical manifestations
Tuberculin test PPD	Indurated skin lesion (granuloma)
Contact dermatitis	Vesicular skin lesions, pruritus, rash
Multiple sclerosis	Progressive demyelination, blurred vision, Paralysis
Rheumatoid arthritis	Rheumatoid factor (IgM against Fc region of IgG), alpha-cyclic

	citrullinated peptide (a-CCP) antibodies, chronic arthritis, inflammation, destruction of articular cartilage and bone
Guillain-Barré syndrome	Ascending paralysis, peripheral nerve demyelination
Contact dermatitis	Nickel allergy, exposure to urushiol oil from poison ivy/oak
graft-versus-host disease (GVHD)	Abdominal swelling, yellow discoloration of the skin and/or eyes,
Celiac disease	Gluten-sensitive enteropathy
Corhn disease	Chronic intestinal inflammation due to Th1 and Th17 cells, obstruction

Blood transfusion reactions

Allergic reactions

- **Type I hypersensitivity reaction** against plasma proteins in transfused blood
- The primary antigen exposure stimulates plasma cells to produce specific IgE.
- This IgE binds to mast cells via its Fc receptor and sensitizes them.
- Causes crosslinking of surface IgE stimulating degranulation of mast cells.

Signs and symptoms:

- Itching, pruritis, fever, wheezing, urticaria

Treatment:

- Antihistaminic

Anaphylactic reactions

- Less common but sever reactions
- IgA-deficient recipient who is transfused with **IgA-containing blood products**

Signs and symptoms:

- Type I hypersensitivity symptoms include:
  - Generalized flushing
  - laryngeal edema
  - bronchospasm and dyspnea
  - profound hypotension, shock and potential cardiopulmonary arrest

Treatment:

- The transfusion should be stopped immediately and adrenaline 1 in 1000 (0.3-0.5 mL) given immediately.
- Supportive therapy for the circulation and respiratory system may be necessary

Diagnosis:

- Diagnosis must be made by demonstrating deficiency of IgA and the detection of an anti-IgA.
- Those patients should receive only IgA-deficient components which are collected from a special panel of IgA-deficient donors.

Febrile non-hemolytic transfusion reactions (FNHR)

- Caused by cytokines from leukocytes in transfused red cell or platelet components, causing fever, chills, or rigors.
- Host antibodies attack donor HLA antigens and leukocytes

Signs and symptoms:

- Type II hypersensitivity symptoms include:
  - Fever
  - Chills
  - Headache

Acute hemolytic transfusion reactions (HTR)

- Intravascular hemolysis due to ABO blood group incompatibility
- Extravascular hemolysis host antibody reacts against foreign antigens

Signs and symptoms:

- Flank pain, hemoglobinuria
- Fever, hypotension

B cells immunodeficiency disorders

Selective IgA deficiency

Molecular defects

- Most common immunodeficiency
- Unknown cause but mostly multiple genetic causes

Clinical presentations

- Mostly asymptomatic
- ↓ IgA levels and **normal** IgM and IgG with ↑ of IgE.
- Repeated sinopulmonary and gastrointestinal infections
- ↑ atopy
- Susceptibility to giardiasis
- Prone to autoimmune disease
- Anaphylaxis to **IgA**-containing products.

Example: Patient with bloody diarrhea and needed blood transfusion BUT few minutes later, the patient develops itching (anaphylaxis) to **IgA containing blood products**

Diagnosis:

- Blood test analysis reveal that IgA <7 mg
- Heterophilic antibodies have been reported in **IgA-deficient individuals**

X-linked (Bruton) agammaglobulinemia

Molecular defects

- Deficiency of the Bruton tyrosine kinase (btk) which promotes pre-B cell expansion
- Lack of B-cell development

- X linked recessive in boys

Clinical presentations

- Recurrent bacterial infection after **6 months**
- Increased susceptibility to encapsulated bacteria and bloodborne viruses
- ↓ circulating B-cells, ↓ immunoglobulins of all isotypes
- ↓ Maternal IgG
- B-cell maturation does not progress past the pre-B cell stage while maintaining cell-mediated immunity.

Common variable immunodeficiency:

Molecular defects

- Several associated genetic defects

Clinical presentations

- Most common form of primary B cell deficiency
- ↓measurable IgG and IgA (occasionally IgM) resulting in immunodeficiency
- Onsets in late teens, early twenties
- B cells present in peripheral blood
- Associated with higher rates of lymphomas, gastric cancer and↑ **autoimmunity**

Hyper IgM syndrome:

Molecular defects

- Deficiency of CD40L on activated T cells with inability for class switching

Clinical presentations

- High serum titers of IgM with diminished levels of IgG and IgA
- Normal level of B cells
- Normal level of B cells but with diminished levels of IgG and IgA and with high levels of IgM
- Associated with higher risk for Pneumocystis infection.

T cells disorders

Thymic aplasia (DiGeorge syndrome)

Molecular defect:

- Heterozygous deletion of chromosome 22q11.
- Failure of formation of **3rd and 4th** pharyngeal pouches
- Lack of thymus and parathyroid development

Clinical presentations

- Characteristic facies and a clinical triad of cardiac malformations, **hypocalcemia** and hypoplastic thymus
- **Tetany** (Hypocalcemia is the primary cause of tetany)
    - Low ionized calcium levels in the extracellular fluid increase the permeability of neuronal membranes to sodium ion, causing a progressive depolarization (contraction of peripheral skeletal muscles)
    - Tetany is characterized by contraction of distal muscles of the hands (carpal spasm with extension of interphalangeal joints) and feet (pedal spasm) and is associated with tingling around the mouth and distally in the limbs.
    - Recurrent fungal and viral infection
- Congenital heart & great vessel defects (**tetralogy of Fallot**, **truncus arteriosus**)
- Thymic aplasia

Diagnosis

- ↓T cells, ↓ PTH, ↓Ca^{2+}
- Thymic shadow absent on CXR.

Il-2 receptor deficiency (severe combined immunodeficiency):

Molecular defect

- IL-2 Is the major cytokine that is produced during the primary response of Th cells
- Upon differentiation into one of the two types of Th effector cells, Th1 and Th2, IL-2 production declines and is replaced by production of Th1-like (IFN-γ) or Th2-like (IL-4) cytokines
- Therefore, deficiency in Il-2 receptor is associated with ↓ Th1 response & ↓IFN-□

Clinical presentations

- Characterized by disseminated mycobacterial and fungal infection

Hyper IgE syndrome (Job syndrome):

Molecular defect

- Defects in **JAK-STAT signaling** pathway leading to impaired Th17 function
- Decreased IFN-gamma production
- Unresponsive neutrophils and chemotaxis

Clinical presentations

- Characterized by:

1. Coarse facies
2. Cold (noninflamed) staphylococcal abscesses
3. Increased IgE and eosinophils, eczematous rash
4. Pathological bone fractures
5. Retained primary teeth

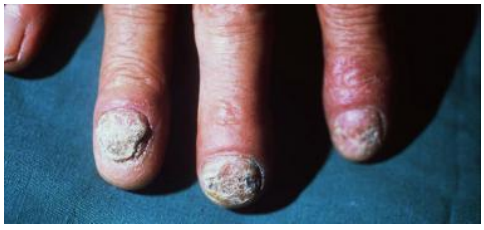
Chronic mucocutaneous candidiasis

Molecular defect

- A type of T-cell dysfunction.
- Result from congenital genetic defects in IL-17 or IL-17 receptors.

Clinical presentations

- Candida albicans infections of skin and mucous membranes
- Hyperkeratosis, skin ulcer, dyspareunia, endocardium abnormality, vision problems, hepatitis, seizures, hematuria and meningitis.



T& B cells disorders

Severe combined immunodeficiency (SCID)

Molecular defect:

- Known as bubble boy disease and bubble baby disease
- Defects in common γ chain of IL-2 receptor
- Cause widespread defect in interleukin signaling with low or absent T cells and NK cells and non-functional B cells.
- X-linked recessive disorder
- Associated with adenosine deaminase deficiency

Clinical presentations:

- Recurrent viral, bacterial, fungal, protozoal infection
- Chronic diarrhea; skin, mouth, and throat lesions; opportunistic (fungal) infections

Diagnosis

- ↓ T cells recombinant excision circles
- Absence of **thymic shadow** (CXR), **germinal centers** (lymph node biopsy), and T cells (flow cytometry).
- low levels of circulating lymphocytes

Treatment

- Bone marrow transplant

Ataxia telangiectasia

Molecular defect:

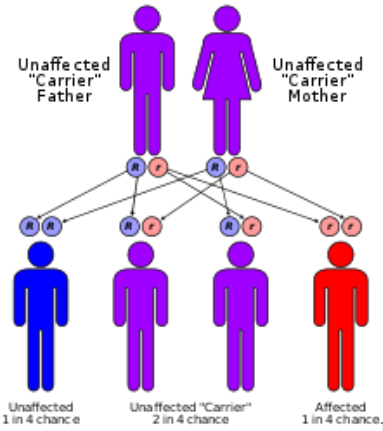
- Known as ataxia–telangiectasia syndrome or Louis–Bar syndrome
- ATM gene defects (Defect in the ATM kinase involved in the detection of DNA damage and progression through the cell cycle
- Autosomal recessive disorder

Clinical presentations

- Ataxia (gait abnormalities)
- Telangiectasia (capillary distortions in the eye)
- Deficiency of IgA and IgE production

Diagnosis

- Increased AFP
- Decreased IgA, IgG, and IgE.



- Lymphopenia, cerebellar atrophy
- Increased risk of lymphoma and leukemia

Hyper IgM disorder

Molecular defect

- Defective CD40L on helper T-cell
- Normal level of B cells but with diminished levels of IgG and IgA and with high levels of IgM
- X-linked recessive
- This condition usually results from an inability to undergo isotype class switching secondary to deficiency in **CD40 ligand** on Th2 cells.

Clinical presentations

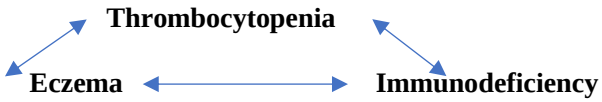
- Associated with higher risk for Pneumocystis infection, CMV and cryptosporidium

Wiskott-Aldrich syndrome:

Molecular defect

- Defect in the WAS protein which plays a critical role in actin cytoskeleton rearrangement
- T cells can NOT recognize actin cytoskeleton

Clinical Presentations



Diagnosis

- ↑IgA and IgE and ↓ IgM
- Low platelets
- Increased risk of autoimmune disorders and cancers

Transplant rejections and grafts

Overview

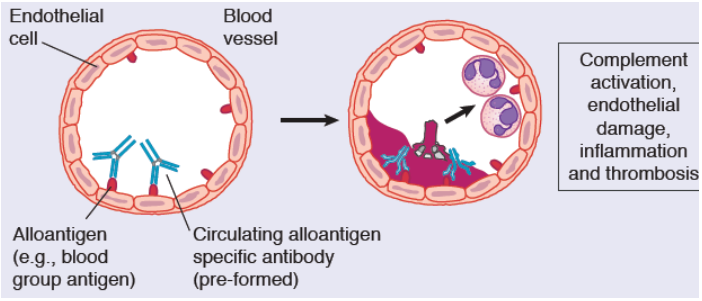
- Transplantation is the process of taking cells, tissues, or organs (a graft) from one individual (the donor) and implanting them into another individual or another site in the same individual (the host or recipient).

Types of grafts:

- **Autologous grafts (or autografts)** are those where tissue is moved from one location to another in the same individual (skin grafting in burns or coronary artery replacement with saphenous veins).
- **Isografts (or syngeneic grafts)** are those transplanted between genetically identical individuals (monozygotic twins).
- **Allogeneic grafts** are those transplanted between genetically different members of the same species (kidney transplant).
- **Xenogeneic grafts** are those transplanted between members of different species (pig heart valves into human).

Mechanism of graft rejection:

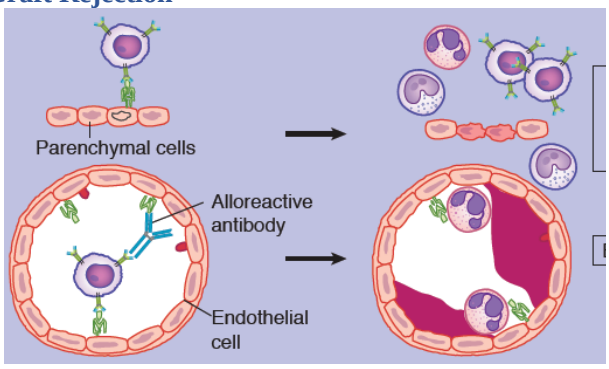
- As the graft becomes vascularized, **CD4+ and CD8+** cells that migrate into the graft from the host become sensitized and proliferate in response to both major and minor histocompatibility differences
- The cytokines play a critical role in stimulating macrophage, cytotoxic T cell.
- Interferons and TNF-α and -β all increase the expression of **class I MHC** molecules in the graft, **while** IFN-γ increases the expression of **class II MHC** as well
- These processes increase the susceptibility of cells in the graft o MHC-restricted killing.



Hyper acute Graft Rejection

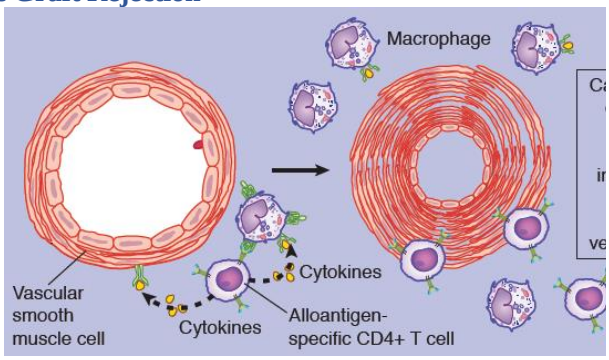
- Occurs immediately within minutes to hours
- Type II cytotoxic hypersensitivity
- Antibodies bind to the grafted tissue and **activate complement** and the clotting cascade resulting in thrombosis and ischemic necrosis
- Due to pre-formed antibodies
- Graft must be removed.

Acute Graft Rejection



- Occurs within days to weeks
- Develop type **IV hypersensitivity** reaction
- Both **CD4 and CD8 T** cells play a role as well as antibodies against donor MHCs
- Reversible by **Immunosuppressive therapy** (Interleukins inhibitors, D-cyclosporine)
- Characterized by **Vasculitis of graft vessels** with dense interstitial lymphocytic infiltrate
- Diagnosis by graft biopsy

Chronic Graft Rejection



- Occurs within months to years
- Predominantly **T cell mediated** (CD4+ T cells respond to recipient)
- **Type III and Type IV hypersensitivity** directed against the foreign MHC molecules which look like self-MHC presenting a foreign antigen
- Difficult to treat and usually results in graft rejection
- Chronic rejection appears as fibrosis and scarring in all transplanted organs
- In heart transplants, chronic rejection manifests as **accelerated coronary artery atherosclerosis**. In transplanted lungs, it manifests as bronchiolitis obliterans

Graft-versus-host disease

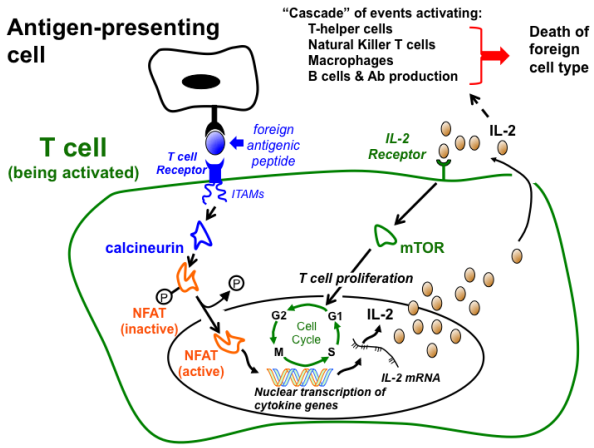
- Timeline varies
- When the grafted tissue is bone marrow.
- Bone marrow transplantation applicable in cases of cancer patients (leukemia), since **the bone marrow** is the source of pluripotent hematopoietic stem cells, it can be used to reconstitute myeloid, erythroid, and lymphoid cells
- Grafted immune-competent T cells proliferate in the irradiated immunocompromised disease host and reject cells with foreign proteins and cause organ dysfunction
- It is necessary to remove these cells before transplantation to avoid the appearance of graft-versus-host disease in the recipient.
- Type IV hypersensitivity reaction.
- **Signs and symptoms** include: Maculopapular rash, jaundice, hepatomegaly, diarrhea, and gastrointestinal hemorrhage.

General treatment in graft rejections:

- Daclizumab, basiliximab (anti-IL-2 receptor antibody)
- Muromonab (anti-CD3)
- Belatacept (CTLA-4-Ig)
- Alemtuzumab (anti-CD52) **CD52** is a marker found on all lymphocytes
- Monoclonal antibodies are used in the treatment and prevention of graft rejection along with the classic therapies (corticosteroids, cyclosporine A, rapamycin, etc.).

Cyclosporine

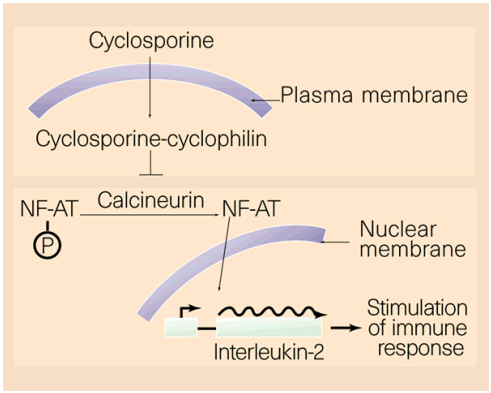
Overview



- Activation of T cells in response to a foreign antigen presented by an antigen-presenting cell (which include dendritic cells, macrophages & B lymphocytes).
- This induces "adaptive immune responses" involving multiple cell types that are involved in cell-mediated immunity involving activated **macrophages, natural killer T cells and cytotoxic T cells**, as well as stimulation of humoral immunity involving **B cells & plasma cells** that produce antibodies that bind to foreign antigens and enhance phagocytosis and cellular toxicity of the foreign cells

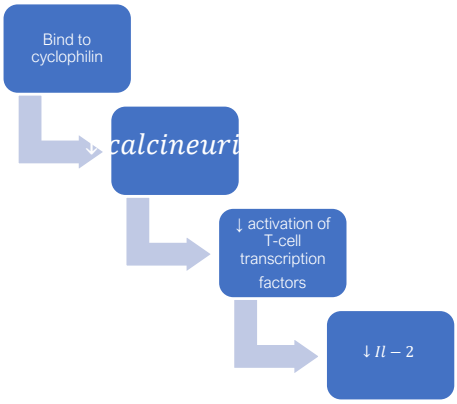
- Interleukin 2 (IL-2) plays a critical role in the initial activation of T cells
- Many other cytokines (e.g. IFN- γ, TNF-β, IL-4 & IL-5) are involved in later steps in the pathways resulting in activation of other cell types such as **macrophages & B cells**

Cyclosporine:



Cyclosporine (CsA) binds to **cyclophylin** (CpN), forming a complex that binds and blocks the function of the enzyme calcineurin (CaN). As a result, CaN **fails to dephosphorylate** the cytoplasmic component of the nuclear factor of activated T cells (NF-ATc), and the transport of NF-ATc to the nucleus and the binding of NF-ATc to the nuclear component of the nuclear factor of activated T cells (NF-ATn). The NF-ATc–NF-ATn complex binds to the promoter of the interleukin 2 (IL-2) gene and initiates IL-2 production.

Mechanism of action:



Clinical use:

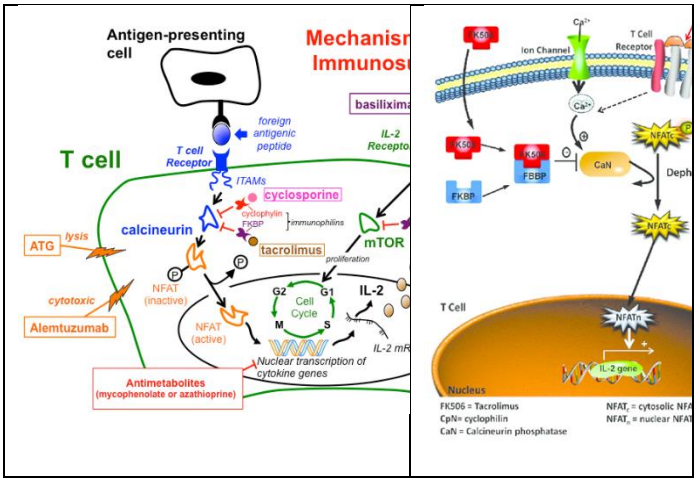
- Cyclosporine is DOC for organ or tissue transplantation (+/– mycophenolate, +/– steroids, +/– cytotoxic drugs)
- Other uses: Psoriasis, rheumatoid arthritis.

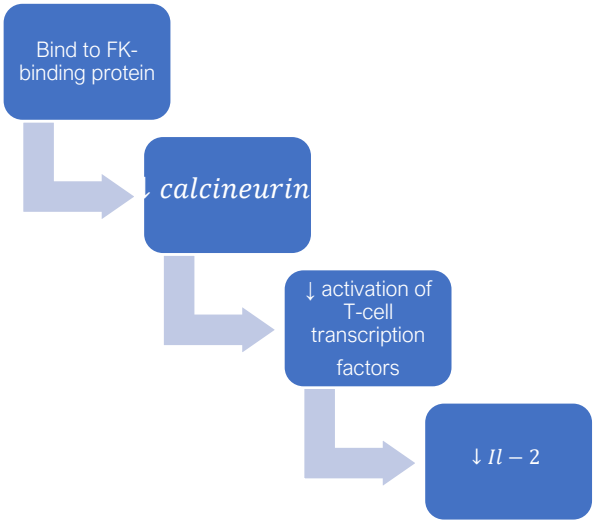
Toxicity:

- Nephrotoxicity due to vasoconstriction
- Hyperglycemia: reduce in pancreatic cells
- Hypertension
- Hyperlipidemia
- Neurotoxicity
- Gingival hyperplasia
- Hirsutism

Tacrolimus

Mechanism of action:





Clinical use:

- Tacrolimus used alternatively to cyclosporine in renal and liver transplants

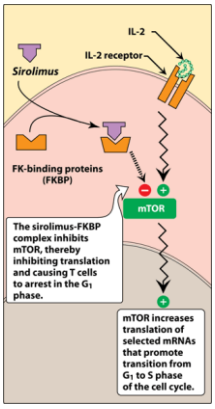
Toxicity:

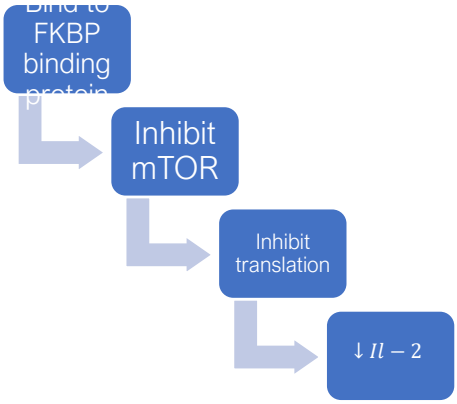
- Nephrotoxicity due to vasoconstriction
- Hyperglycemia: reduce in pancreatic cells
- Hypertension
- Hyperlipidemia
- Neurotoxicity
- Gingival hyperplasia
- Hirsutism

Sirolimus (Rapamycin)

Mechanism of action:

- **mTOR inhibitor**: binds to FKBP- Blocks T-cell activation and B-cell differentiation thereby preventing response to IL-2.





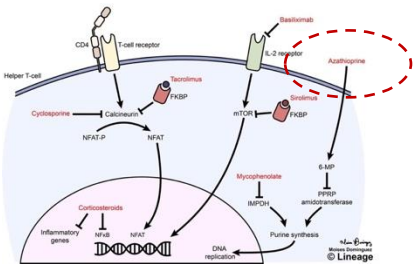
Clinical use:

- **Immunosuppressant post**- kidney transplant in conjunction with cyclosporine and corticosteroids
- Used with drugs eluting stents to prevent ischemia

Toxicity:

- Pancytopenia
- Insulin resistance
- Hyperlipidemia
- **NOT** nephrotoxic

Azathioprine



- Toxicity

Mechanism of action:

- **Purine antimetabolite**: Azathioprine inhibits DNA and RNA synthesis by preventing interconversion among the precursors of purine synthesis and suppressing de novo purine synthesis
- **Azathioprine** is a prodrug metabolized into 6-mercaptopurine

Clinical use:

- Used in cardiac and kidney transplantations
- Rheumatoid arthritis, Crohn disease, glomerulonephritis, other autoimmune conditions

Toxicity:

- Leukopenia
- Allopurinol and azathioprine should not be co-prescribed unless the combination cannot be avoided.
- Allopurinol interferes with the metabolism of azathioprine, increasing plasma levels of 6-mercaptopurine which may result in potentially fatal blood dyscrasias.
- The dose of azathioprine should be reduced to **25% of the recommended dose** and the patient's blood count should be monitored assiduously

Recombinant cytokines

Aldesleukin:

- Used for treatment of renal cell carcinoma, metastatic melanoma
- **MOA**: Aldesleukin binds to the **IL-2 receptor** which leads to stimulate growth and differentiation of T cells.

Epoetin alfa (EPO analog):

- **Erythropoietin**: used to treat anemias due to:

A. Chronic kidney disease
B. Zidovudine in patients with HIV-infection
C. The effects of concomitant myelosuppressive chemotherapy

- **MOA**: Erythropoietin or exogenous epoetin alfa binds to the erythropoietin receptor (EPO-R) and activates intracellular signal transduction pathways

Colony stimulating factors:

- Sargramostim (GM-CSF) granulocyte macrophage colony-stimulating factor
- Filgrastim (G-CSF) granulocyte colony-stimulating factor

Shared the following characteristics:

- Secreted by Macrophages and Th cells Bone marrow
- **Clinical uses**: Induces proliferation; used to counteract neutropenia following ablative chemotherapy
- **MOA**: Sargramostim binds to the Granulocyte-macrophage colony stimulating factor receptor (GM-CSF-R-alpha or CSF2R). This leads to the production of hemopoietic cells and neutrophil
- **MOA**. Filgrastim also stimulates the release of neutrophils from **bone marrow** storage pools and decreases their time to maturation. Filgrastim acts to increase the phagocytic activity of mature neutrophils, thus allowing them to prevent infection.

Interferon:

- **IFN-α** Chronic hepatitis C (not preferred) and B, renal cell carcinoma
- **IFN-β** Multiple sclerosis
- **IFN-γ** Chronic granulomatous disease

Oprelvekin (Interleukin 11):

- Oprelvekin binds to the **interleukin 11 receptor** which leads to a cascade of signal transduction events.

- IL-11 is a thrombopoietic growth factor that directly stimulates the proliferation of hematopoietic stem cells
- **Clinical uses**: Autoimmune thrombocytopenia

Thrombopoietin:

- **Clinical uses:** The procurement of platelets for donation, and recovery of platelet counts after myelosuppressive chemotherapy.

Summary

Cytokine	Clinical uses
Aldesleukin (Interleukin-2)	↑ lymphocyte differentiation and ↑ NKs—used in renal cell cancer and metastatic melanoma
Oprelvekin (Interleukin 11)	↑ platelet formation—used in thrombocytopenia
Filgrastim (G-CSF)	↑ granulocytes—used for marrow recovery
Sargramostim (GM-CSF)	↑ granulocytes and macrophages—used for marrow recovery
Thrombopoietin	Thrombocytopenia
Interferon-α	Hepatitis B and C, renal cell carcinoma, melanoma
Interferon- β	Multiple sclerosis
Interferon- γ	Chronic granulomatous disease →↑ TNF

Therapeutic antibodies

Cancer therapy

Alemtuzumab

- Binds to the **CD52 antigen** present on most B and T lymphocytes. This binding leads to antibody-dependent lysis of leukemic cells.

Clinical uses:

- Chronic leukocytic leukemia
- Multiple sclerosis
- Auto immune hemolytic anemia

Rituximab

- Monoclonal antibody that targets the **CD20 antigen**, which is expressed on the surface of pre-B and mature B-lymphocytes.
- After binding to **CD20**, rituximab mediates B-cell lysis (or breakdown).

Clinical uses:

- Non-Hodgkin's Lymphoma
- Rheumatoid arthritis
- Multiple sclerosis
- Chronic lymphocytic leukemia
- Pemphigus Vulgaris

Trastuzumab

- Trastuzumab is a recombinant humanized IgG1 monoclonal antibody against **the HER-2** receptor, a member of the epidermal growth factor receptors which is a photo-oncogene and over-expressed in breast tumor cells.

Clinical uses:

- Metastatic breast cancer

Cetuximab

- Cetuximab binds to the epidermal growth factor receptor (EGFR) on both normal and tumor cells.
- EGFR is over-expressed in many colorectal cancers.

Clinical uses:

- Treatment of EGFR-expressing, metastatic colorectal carcinoma
- Metastatic squamous cell carcinoma of the head and neck

Bevacizumab

- Bevacizumab is an antineoplastic agent and prevents or reduces the formation of blood vessels (angiogenesis) thereby preventing or reducing metastatic disease progressing.
- Bevacizumab binds VEGF and prevents vascular endothelial growth and endothelial cell proliferation

Clinical uses:

- Glioblastoma
- Colorectal cancer
- Renal cell carcinoma
- Cervical cancer
- Lung cancer

Autoimmune disease therapy

Eculizumab

- Treatment of patients with **paroxysmal nocturnal hemoglobinuria** (PNH) to reduce hemolysis.
- Eculizumab is a monoclonal antibody directed against the complement protein C5.
- This antibody blocks the cleavage of C5

Clinical uses:

- Atypical hemolytic uremic syndrome
- Paroxysmal nocturnal hemoglobinuria

Daclizumab

- Inhibits (anti-CD25) IL-2-mediated activation of lymphocytes, a critical pathway in the cellular immune response involved in allograft rejection.

Clinical uses:

- Relapsing multiple sclerosis

Ustekinumab

- Blocks interleukin IL-12 and IL-23

Clinical uses:

- Psoriasis, psoriatic arthritis

Natalizumab

- Block **α4-integrin** which expressed by inflammatory cells with VCAM-1 on vascular endothelial cells, and with CS-1 and/or osteopontin expressed by parenchymal cells in the brain.
- **α4-integrin** is required for white blood cells to move into organs, therefore, natalizumab prevents these immune cells from crossing blood vessel walls to reach affected organs thereby decreasing inflammation.

Clinical uses:

- Treatment of multiple sclerosis.

Other applications

Abciximab

- Binds to the intact platelet GPIIb/IIIa receptor, which is a member of the integrin family of adhesion receptors and the major platelet surface receptor involved in platelet aggregation

Clinical uses:

- The prevention of cardiac ischemic complications

Denosumab

- Designed to target **RANKL** (RANK ligand), a protein that acts as the primary signal to promote bone removal/resorption.
- In many bone loss conditions, RANKL overwhelms the body's natural defense against bone destruction.

Clinical uses:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture

Digoxin immune Fab

- Binds excess digoxin or digitoxin molecules circulating in the blood (making them unavailable for binding at their site of action on cells in the body)

Clinical uses:

- Digitoxin toxicity
- Digitoxin overdose

Omalizumab

- Inhibits the binding of **IgE** to receptors on mast cells and basophils, blocking the IgE-mediated secretion of inflammatory mediators from these cells

Clinical uses:

- Severe Asthma
- Chronic Urticaria

Palivizumab

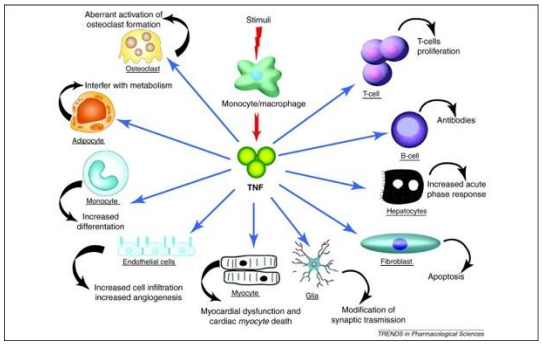
- Binds to the fusion **glycoprotein of RSV**. This prevents its binding and uptake by host cellular receptors.

Clinical uses:

- Prophylaxis of respiratory diseases caused by respiratory syncytial virus.

TNF alfa inhibitors

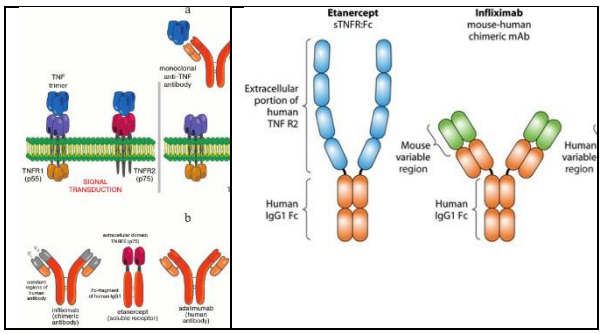
Overview:



- Produced by **activated macrophages**, although it can be produced by many other cell types such as CD4+ lymphocytes, NK cells, neutrophils, mast cells, eosinophils, and neurons.
- The primary role of TNF is in the regulation of immune cells.
- TNF is able to induce fever, to induce apoptotic cell death, to induce sepsis (through IL1& IL6 production), to induce cachexia, induce inflammation, and to inhibit tumorigenesis and viral replication.
- Dysregulation of TNF production has been implicated in a variety of human diseases, including Alzheimer's disease, cancer, major depression, and inflammatory bowel disease (IBD).
- Anti- TNF-α agents have been successfully introduced into the treatment of inflammatory diseases such as RA, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, and Behçet's disease

Etanercept:

- Etanercept is made from the combination of two naturally occurring soluble human 75-kilodalton TNF receptors linked to an Fc portion of an IgG1
- The effect is an artificially engineered dimeric fusion protein (decoy receptor for TNF-α + IgG1 Fc)
- **Clinical uses:** Rheumatoid arthritis, psoriasis and ankylosing spondylitis



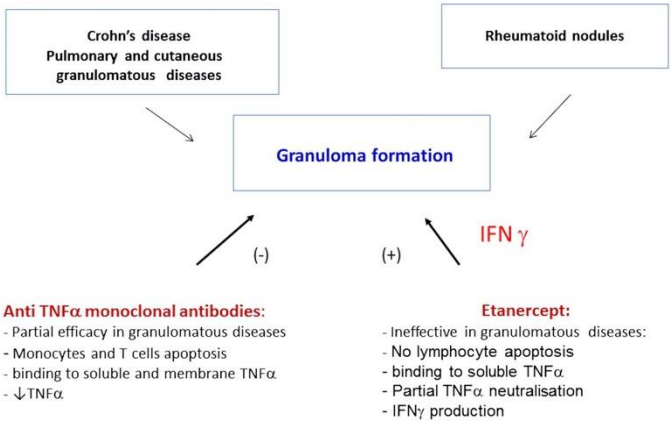
Drug interaction:

- Drug-induced lupus

Infliximab, adalimumab, certolizumab, golimumab

- They are **monoclonal antibodies** and have identical structures and affinities to the target
  - Infliximab, adalimumab and golimumab are full IgG1 monoclonal antibodies against human TNF-α.
  - **Infliximab** is a chimeric mouse/human anti-TNF-α. monoclonal antibody (mAb) composed of a murine variable region and a human IgG1 constant region.
  - **Adalimumab and golimumab** are fully humanized anti- TNF-α mAbs, which is indistinguishable from the normal human IgG1.
- **Certolizumab** is a Fab' fragment of an anti- TNF-α mAb and lacks the Fc portion. The hinge region of certolizumab is covalently linked to 2 cross-linked chains of a 20-kDa of poly- ethylene glycol, which is named as certolizumab pegol
- **MOA:** Anti-TNF-α monoclonal antibody

Differences between Etanercept and other Anti-TNF-α monoclonal antibody:



Muromonab

Mechanism of action:

- Blocks function of **CD3** in T lymphocytes (involved in Ag recognition & signal transduction), resulting in a transient activation of T cells, **release of cytokines**, and blocking of T-cell proliferation and differentiation

Clinical use:

- Acute Allograft Rejection or Acute Graft-Vs-Host Disease Treatment
- Cardiac or Hepatic Allograft Rejection, Steroid Resistant

Toxicity:

- Cytokine release syndrome typically 45 min. after injection
- Hypersensitivity reactions