BHARATHIDASAN UNIVERSITY

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Programme: M.Sc., Biochemistry

Course Title : Immunology

Course Code : BC301CR

Unit-III

Major Histocompatibility complex

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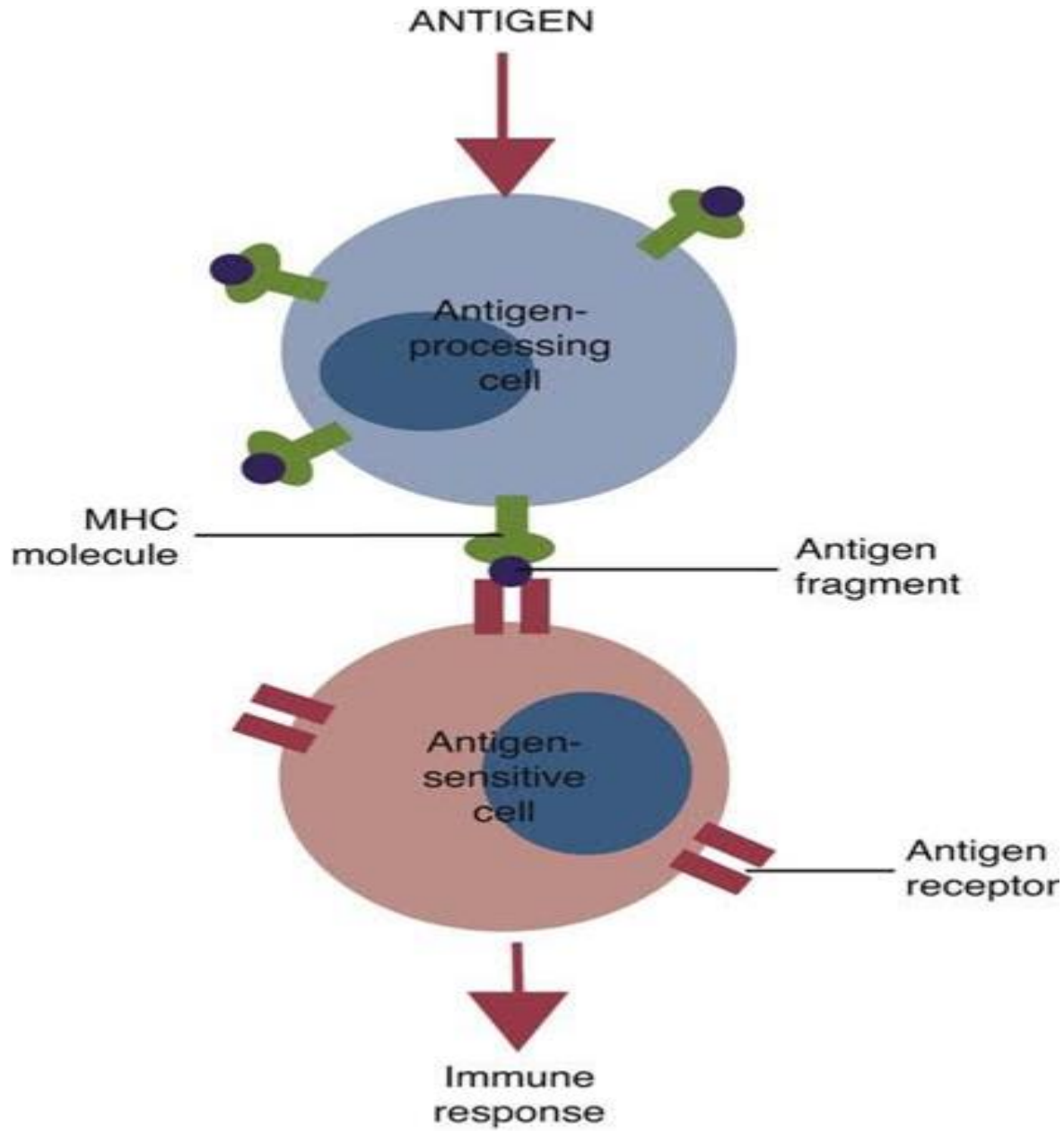
Major Histocompatibility complex

Major Histocompatibility complex (MHC)

- Major Histocompatibility complex (MHC) is set of surface proteins located on the cell membrane of nucleated cells.
- It plays more important work to indentify the antigen between self and non self body, intracellular recognization and responsible for antigen presentation.
- Histo refers to tissues.
- Compatibility refers to getting along or agreeable
- They are glycoproteins in chemical nature



Source:veteriankey.com

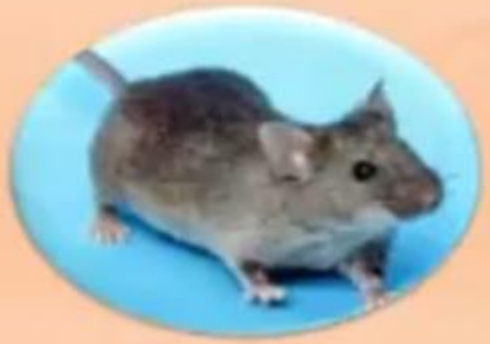
HISTORY

- In 1930s, Peter Gorer, a British geneticist, identified that certain antigens were responsible for the rejection of transplanted tissues in mice.
- In 1940s,George Snell, an American geneticist established that tissue graft rejection was controlled by a group of linked genes.
- Snell coined the term "histocompatibility genes."

Major Histocompatibility Complex (Genes)

Encode proteins

Major Histocompatibility Antigens



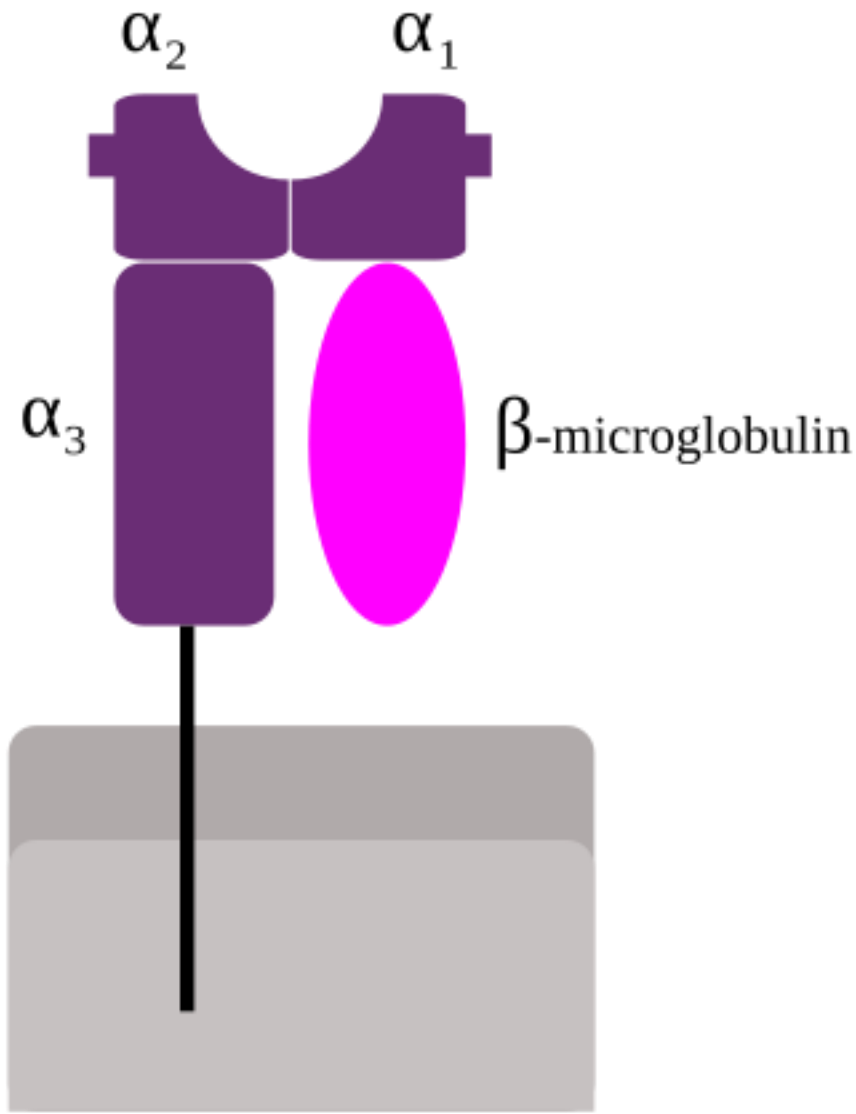
Donor

Recipient

Source: sciencedirect.com

MHC Class I Molecules

- MHC Class I molecules consist of a heavy alpha (α) chain that is non-covalently associated with a smaller protein called beta-2 microglobulin (β2m).
- The alpha chain has three extracellular domains (α1, α2, and α3), a transmembrane domain, and a cytoplasmic tail
- The α1 and α2 domains form the peptide-binding groove that can accommodate peptides typically 8-10 amino acids long.
- Peptide Binding Groove: The groove is closed at both ends, limiting the



Source: wiki

Location and Role

Location: MHC Class I molecules are expressed on the surface of almost all nucleated cells in the body.

Role: They present endogenous antigens (derived from within the cell, such as tumor antigens) to CD8+ cytotoxic T cells.

Antigen Processing

Proteasome: Proteins from within the cell (like viral proteins or abnormal cellular proteins) are degraded by the proteasome into small peptides.

Transporter Associated with Antigen Processing (TAP): Peptides are transported into the endoplasmic reticulum (ER) by TAP.

Loading: In the ER, peptides are loaded onto newly synthesized MHC Class I molecules.

Transport to Cell Surface: The peptide-MHC Class I complexes are then transported to the cell surface, where they can be recognized by CD8+ T cells.

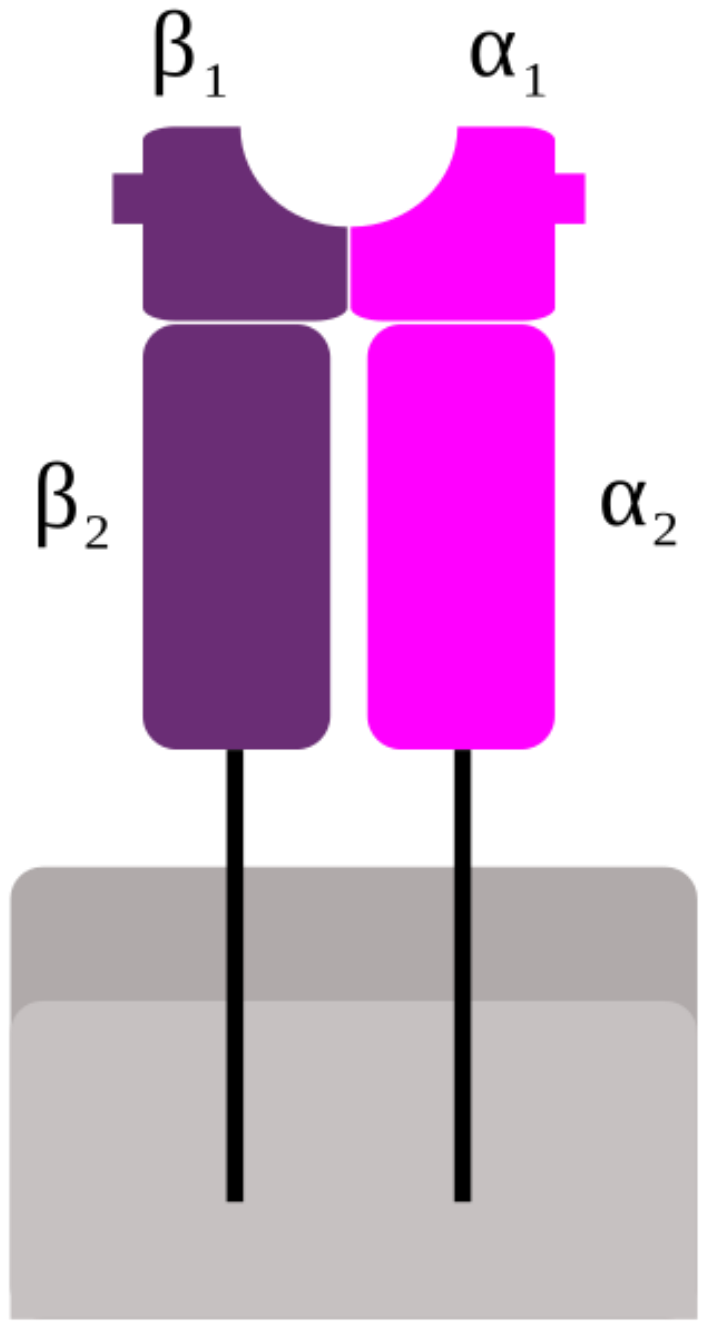
Function

Immune Surveillance: MHC Class I molecules enable CD8+ T cells to monitor the intracellular environment of cells for signs of infection or malignancy.

Cytotoxic Response: When CD8+ T cells recognize a foreign peptide presented by MHC Class I, they can directly kill the infected or cancerous cell.

MHC Class II Molecules

- MHC Class II molecules consist of two chains: an alpha (α) chain and a beta (β) chain, both of which are transmembrane proteins.
- Each chain has two extracellular domains (α1, α2, β1, β2), a transmembrane domain, and a cytoplasmic tail.
- The α1 and β1 domains form the peptide-binding groove, which is open at both ends and can accommodate longer peptides (typically 13-18 amino acids).



Source: wiki

Location and Role

Location: MHC Class II molecules are primarily expressed on professional antigen-presenting cells (APCs), such as dendritic cells, macrophages, and B cells.

Role: They present exogenous antigens (derived from outside the cell, such as bacterial or extracellular viral antigens) to CD4+ helper T cells.

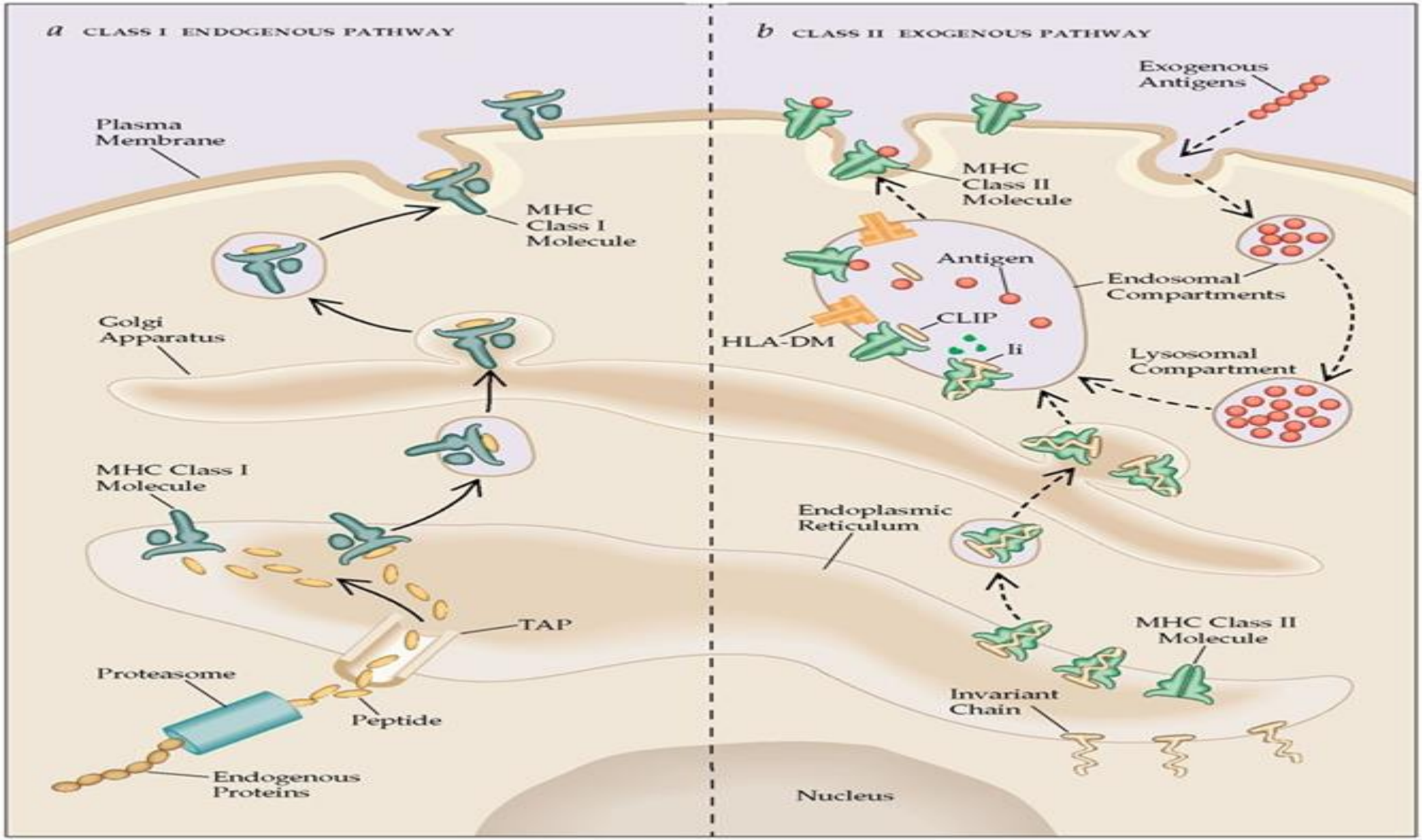
Antigen Processing:

Endocytosis/Phagocytosis: Exogenous antigens are taken up by the APCs via endocytosis or phagocytosis.

Endosomal Degradation: The antigens are degraded into peptides within endosomes or lysosomes.

Loading in MIIC: MHC Class II molecules, synthesized in the ER, are transported to endosomes known as MHC Class II compartments (MIIC).

In the MIIC, the invariant chain (Ii) that initially occupies the MHC Class II peptide-binding groove is degraded, leaving a small fragment called CLIP.



Source: onlinesciencenotes.com

Functions

HLA-DM: This molecule facilitates the removal of CLIP and the loading of antigenic peptides onto the MHC Class II molecules.

Transport to Cell Surface: The peptide-MHC Class II complexes are transported to the cell surface.

Function:

Activation of CD4+ T Cells: MHC Class II molecules present antigens to CD4+ helper T cells, which then orchestrate an immune response by activating other immune cells, such as B cells, macrophages, and cytotoxic T cells.

Immune Regulation: MHC Class II is crucial for initiating and regulating adaptive immune responses, particularly against extracellular pathogens.

MHC Class I Genes and Products

The MHC Class I genes are located on the short arm of chromosome 6 in humans

Genes: The primary MHC Class I genes are HLA-A, HLA-B, and HLA-C in humans (Human Leukocyte Antigen). Each of these genes encodes a separate MHC Class I molecule.

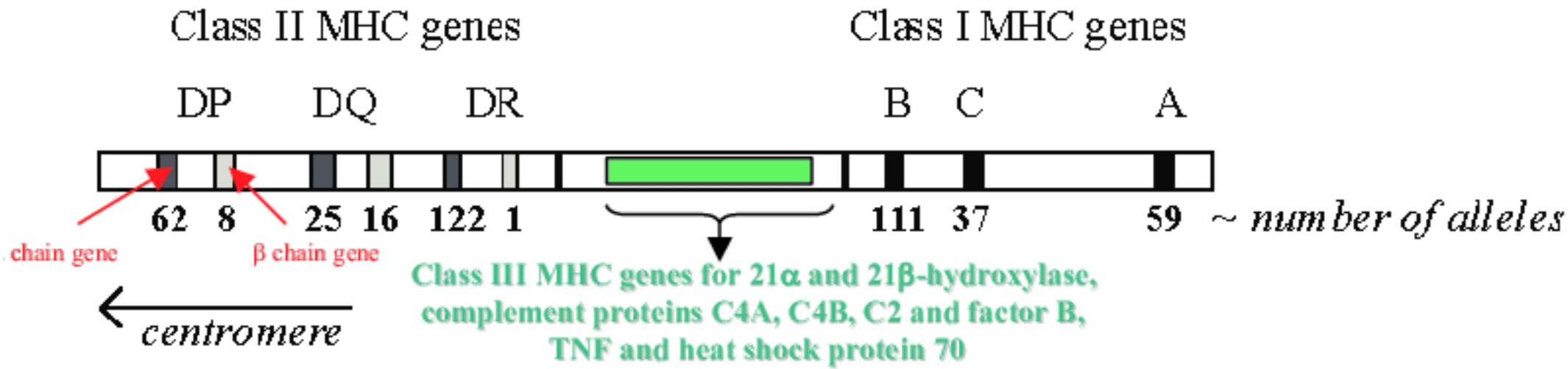
HLA-A, HLA-B, HLA-C: These are highly polymorphic, with hundreds of alleles that contribute to individual variation in immune responses

MHC Class II Genes and Products

The MHC Class II genes are also located on the short arm of chromosome 6

HLA-DQ: Consists of two genes, HLA-DQA1 (α chain) and HLA-DQB1 (β chain).

HLA-DR: Consists of one α-chain gene (HLA-DRA) and multiple β-chain genes (HLA-DRB1, and sometimes HLA-DRB3, -DRB4, -DRB5 in certain haplotypes).e primary MHC Class II genes are HLA-DP, HLA-DQ, and HLA-DR.



Source:http://dx.doi.org/10.13140/RG.2.1.5161.9924

Polymorphism of MHC Genes

- Polymorphism refers to the existence of multiple alleles (variations) of a gene within a population.

Features:

- High Allelic Diversity
- Concentrated Polymorphism in Peptide-Binding Regions
- Codominant Expression
- Balanced Selection

Mechanisms Contributing to MHC Polymorphism

- Point mutations (single nucleotide changes) contribute to the generation of new MHC alleles. Over evolutionary time, these mutations accumulate in the peptide-binding regions of MHC genes, resulting in a wide array of alleles.
- Gene conversion (the non-reciprocal transfer of genetic material between homologous sequences) and recombination (exchange of genetic material between chromosomes) are key mechanisms that introduce new variations into MHC genes.
- Balancing selection is an evolutionary force that maintains multiple alleles in a population
- Pathogen-Driven Selection

TRANSPLANTATION – INTRODUCTION
TYPES OF TRANSPLAN
MHC ANTIGENS IN TRANSPLANTATION
IMMUNOLOGY OF TRANSPLANTATION
ALLOGRAFT REJECTION

TRANSPLANTATION

- Transplantation - surgical transfer of a cells , tissue or organ from one person or site to another with the goal of replacing a damaged or missing part.

- The person who provides graft is called DONOR
- The person who receive the graft is called RECIPIENT

The major limitation of the transplantation is the immune response of the recipient to the donor tissue .

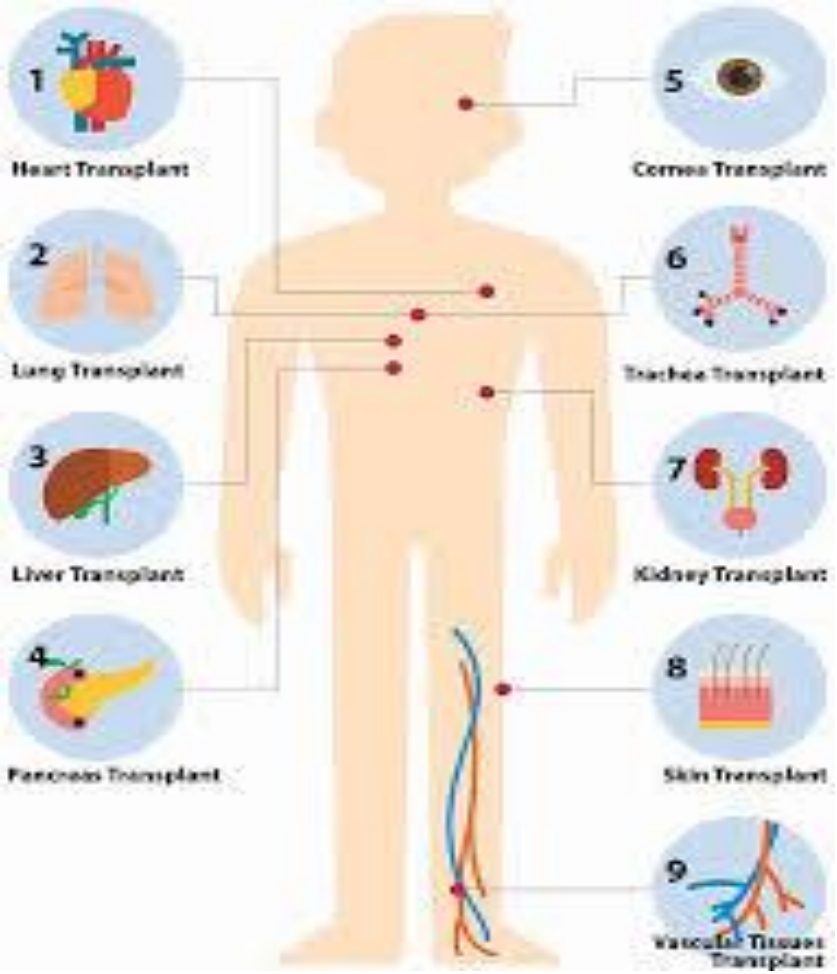
ORGAN FAILURE
CANCER TREATMENT
RECONSTRUCTIVE SURGERY

TYPES OF TRANSPLANTATION

1. **Organ transplantation**: This involves transplanting a whole organ, such as a kidney, liver, heart, lung, or pancreas, from a donor to a recipient.
2. **Tissue transplantation**: This involves transplanting smaller amounts of tissue, such as skin, bone, or cartilage, from a donor to a recipient.
3. **Stem cell transplantation**: This involves transplanting stem cells from one person to another, which can help to repair or replace damaged cells or tissues.

ORGAN TRANSPLANTATION

- It involves transplanting a whole organ from a donor to a recipient.
- This type of transplantation is often performed to treat patients with organ failure, such as kidney failure, liver failure, or heart failure.
- The most common organs transplanted are kidneys, livers, hearts, lungs, and pancreas.



Source:barahealhcare.com

TISSUE TRANSPLANTATION

Tissue transplantation involves transplanting smaller amounts of tissue from one person to another. This type of transplantation is often performed to repair damaged or deformed tissues.

1.Skin Grafting: Skin grafting involves transplanting skin from one person to another to repair damaged or deformed skin.

2.Bone Grafting: Bone grafting involves transplanting bone tissue from one person to another to repair damaged or deformed bones.

3.Cartilage Transplantation: Cartilage transplantation involves transplanting cartilage tissue from one person to another to repair damaged or deformed joints.

4.Corneal Transplantation: Corneal transplantation involves transplanting corneal tissue from one person to another to repair damaged or deformed eyes.

STEM CELL TRANSPLANTATION

- Stem cell transplantation involves transplanting stem cells from one person to another. Stem cells are undifferentiated cells that have the ability to differrentiate into different cell types.

1. **Bone Marrow Transplantation**: Bone marrow transplantation involves transplanting stem cells from the bone marrow of a donor to a recipient.
2. **Peripheral Blood Stem Cell Transplantation**: Peripheral blood stem cell transplantation involves transplanting stem cells from the peripheral blood of a donor to a recipient.
3. **Cord Blood Transplantation**: Cord blood transplantation involves transplanting stem cells from the umbilical cord blood of a donor to a recipient.

ROLE OF MHC ANTIGENS IN TRANSPLANTATION

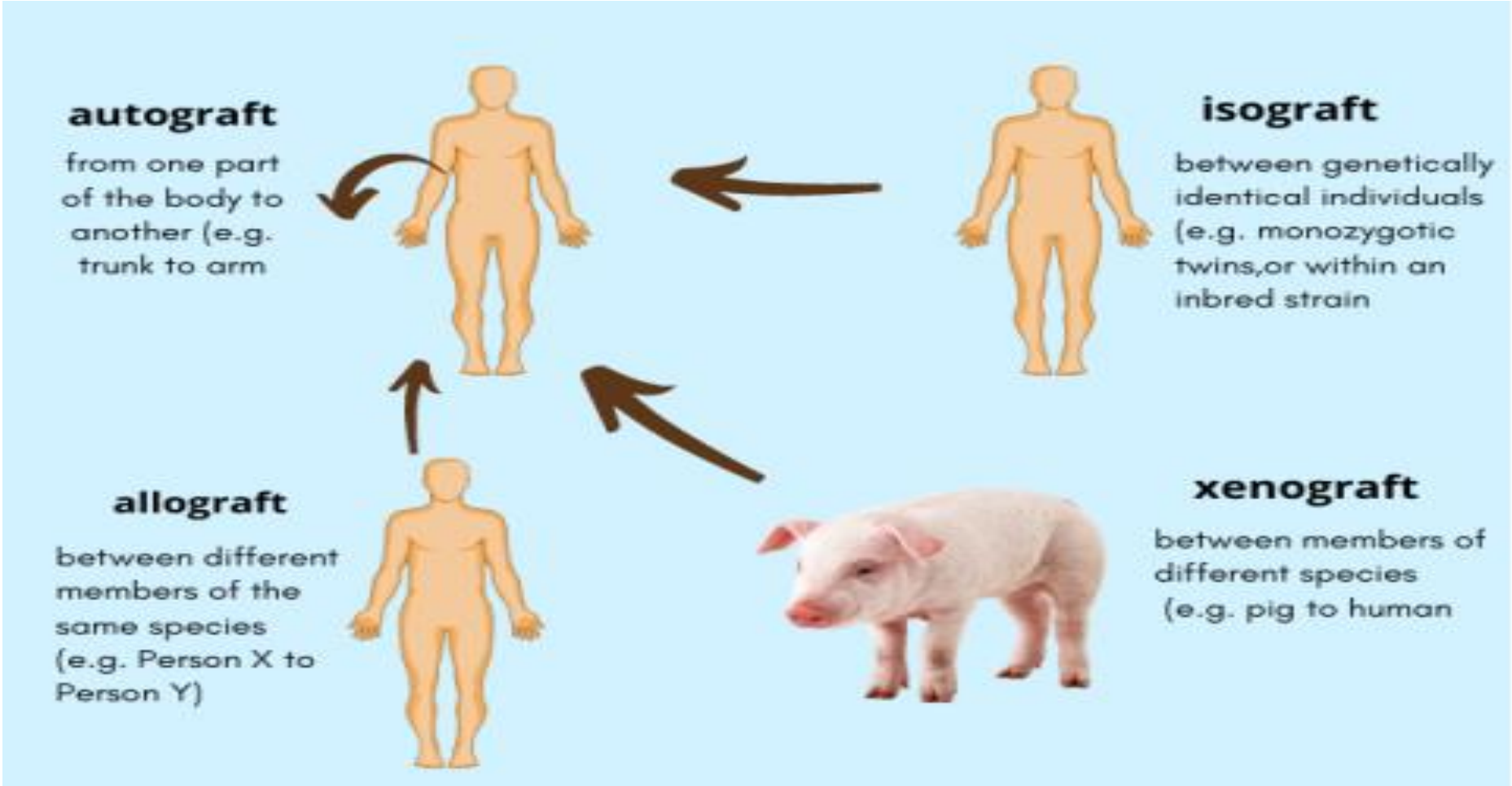
There are two main types of MHC antigens - MHC class I and II.

1. **MHC class I antigens**: MHC class I antigens present peptides from the donor organ to the recipient's CD8+ T cells. They are also highly polymorphic and are used to determine compatibility between donors and recipients.
2. **MHC class II antigens**: MHC class II antigens present peptides from the donor organ to the recipient's CD4+ T cells. They are less polymorphic than HLA and MHC class I antigens.

- MHC antigens play a crucial role in transplantation by triggering the immune response and determining the compatibility between the donor organ and the recipient's immune system.

1. **Immune response**: When a donor organ is transplanted into a recipient, the recipient's immune system recognizes the MHC antigens on the donor organ as foreign. This triggers an immune response, which can lead to rejection of the transplanted organ.
2. **Compatibility**: The compatibility between the donor organ and the recipient's immune system is determined by the MHC antigens present on both parties. If the MHC antigens are identical or very similar, the risk of rejection is lower.
3. **Matching**: To minimize the risk of rejection, transplant centers perform HLA typing to match the donor organ with the recipient's HLA type. This is done by comparing the HLA alleles of the donor and recipient.

TYPES OF TRANSPLANT



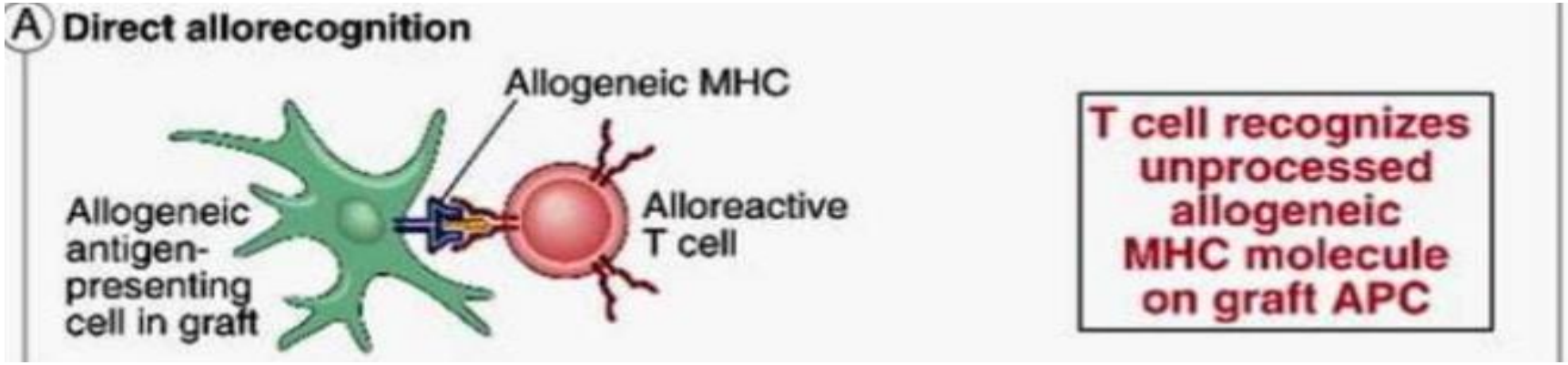
Source:patientengage.com

RECOGNITION OF ALLOANTIGENS

- DIRECT PRESENTATION

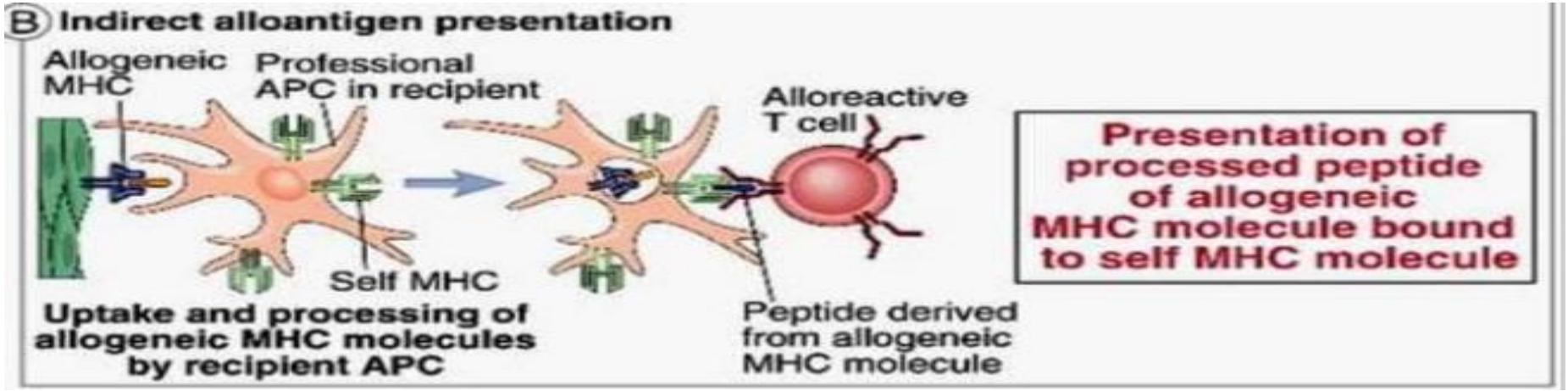
Recognition of an intact MHC molecule displayed by donor antigen presenting cells

- basically self molecules recognizes the structure of an intact allogenic MHC molecule
- Involves both CD8+and CD+4 T cells

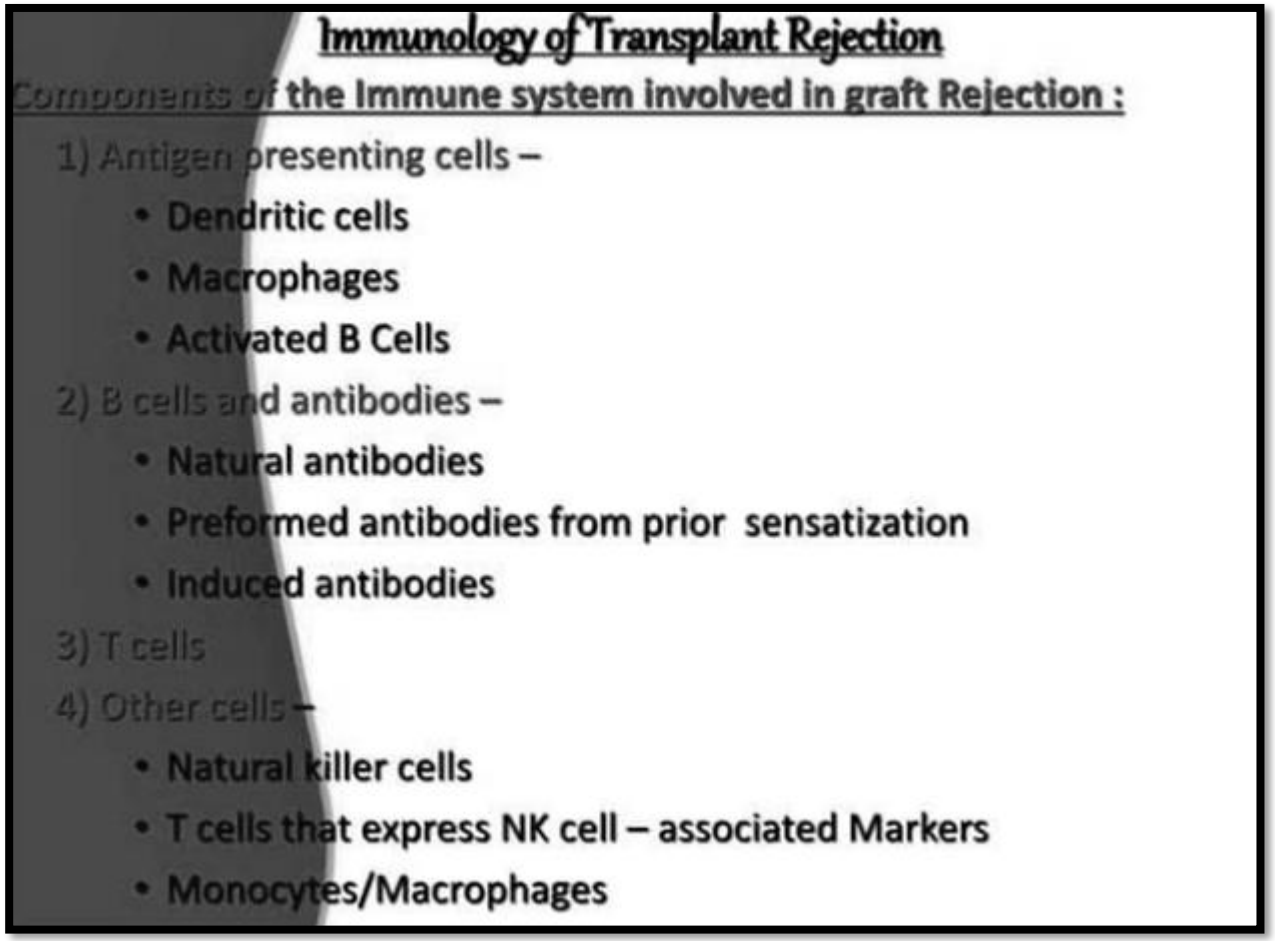


INDIRECT PRESENTATION

- Donor MHC is processed and presented by recipient APC
- Basically donor MHC molecules is handled like anyother foreign antigen
- Involve only CD4+ T cells
- Antigen presentation by class II MHC molecules



Immunology of transplant Rejection



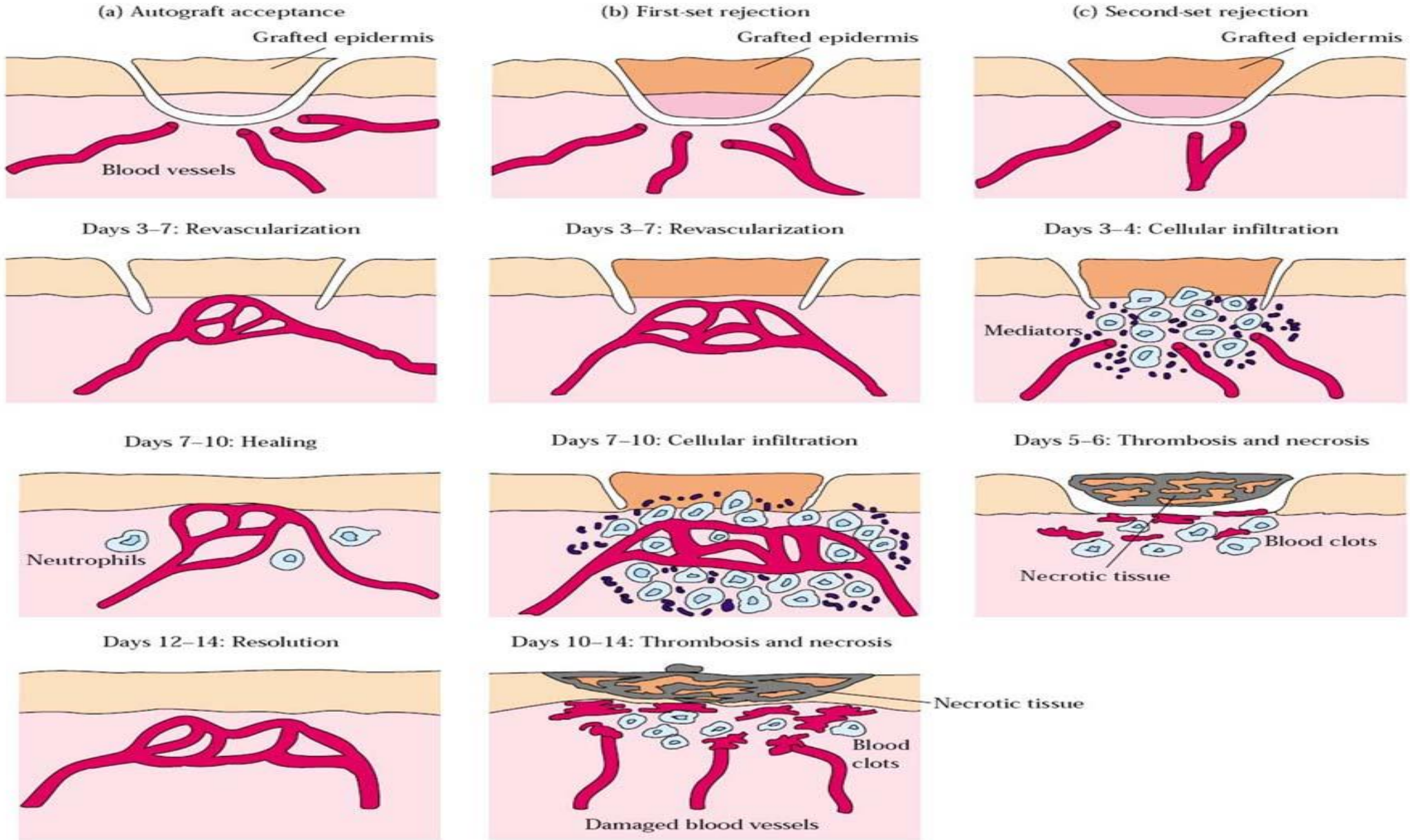
The recoginition of the foreign antigen that is self or nonself is
Determined by the polymorphic genes (MHC) that is expressed from both the parents codominantly .

Alloantigens elicit express both cell mediated and antibody mediated immune response

RESPONSES TO ALLOANTIGEN IN IMMUNE RESPONSE

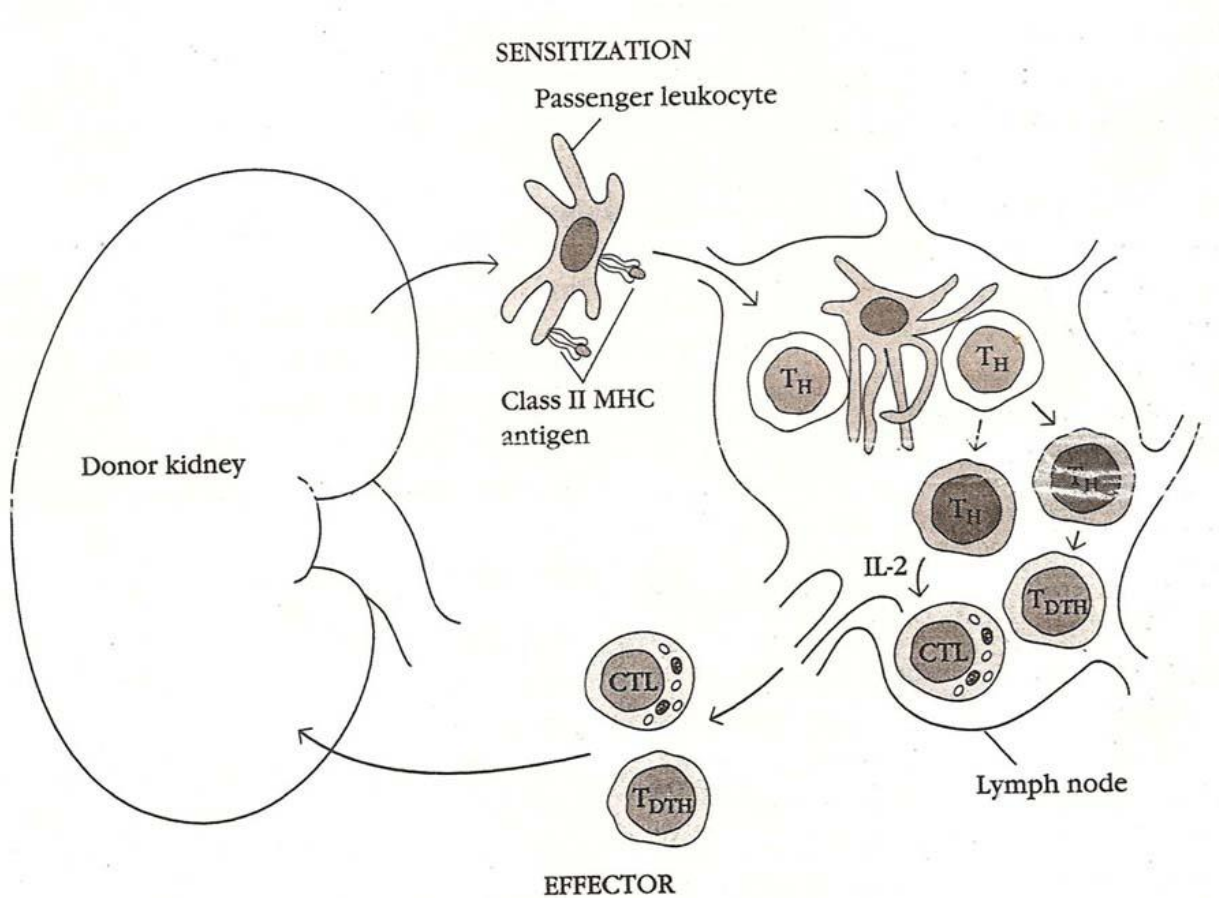
- The time sequence of allograft rejection varies according to tissue involved.
- Graft rejection always displays the attributes of specificity and memory

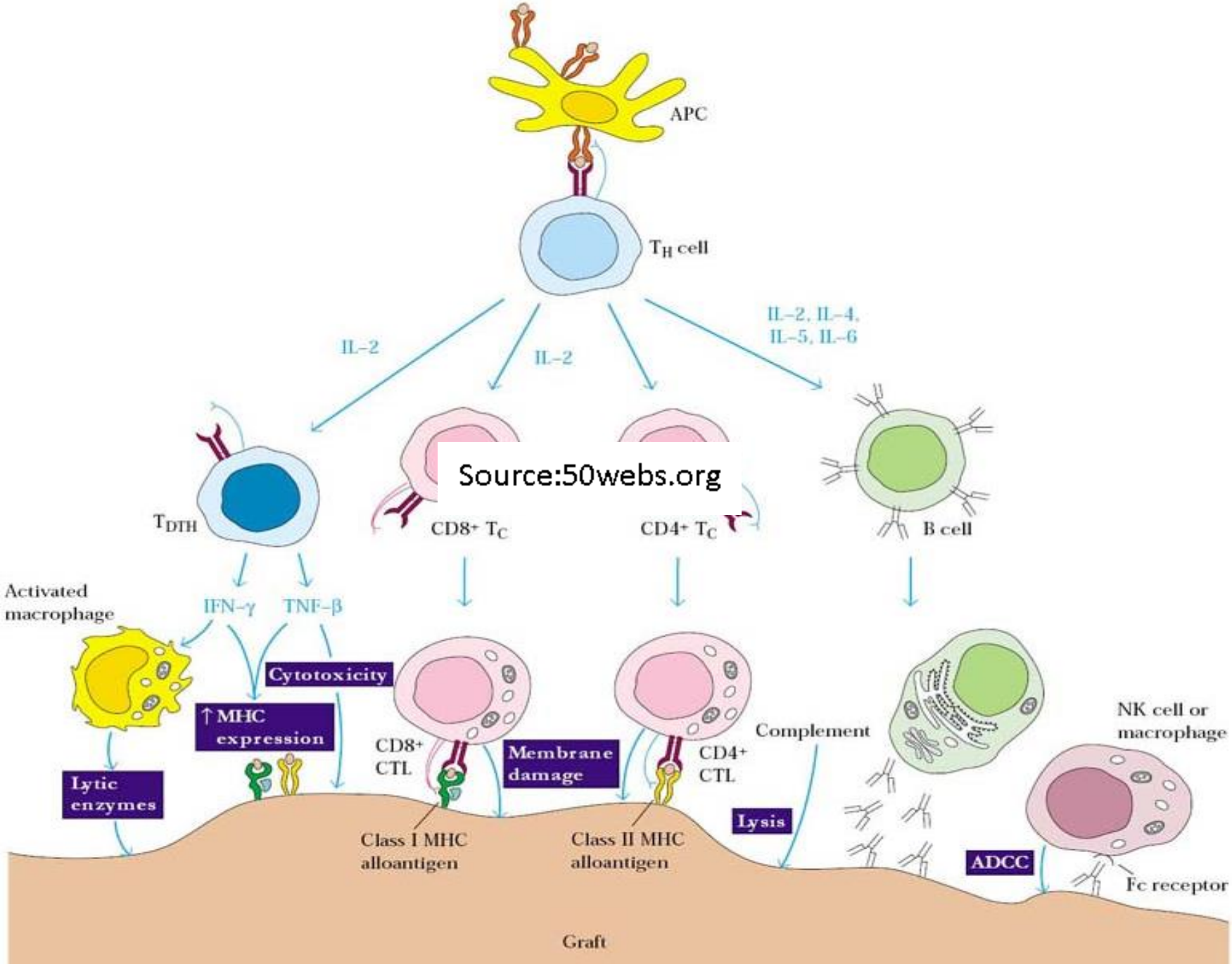
- When a graft is transplanted first time, it is referred as primary graft.
- If the primary graft is allograft type then it is rejected within 14 days of transplantation. The rejection type is known as first set of rejection.
- When another graft from same donor is transplanted second time or more then the graft is said to be secondary graft and it is rejected with 5-6 days.
- The rejection type is known as second set of rejection.
- The variation in the rejection time periods is because of immunologic memory and specificity between grafts.



MECHANISM OF GRAFT REJECTION

- Graft rejection is caused principally by a cell-mediated immune response to alloantigens primarily, MHC molecules) expressed on cells of the graft.
- Both delayed-type hypersensitive and cell-mediated cytotoxicity reactions have been implicated.
- The process of graft rejection can be divided into two stages:
- (1) a sensitization phase, in which antigen-reactive lymphocytes of the recipient proliferate in response to alloantigens on the graft
- (2) an effector stage, in which immune destruction of the graft takes place.





Role of Cytokines in Graft Rejection

- IL – 2, IFN – γ, and TNF - β are important mediators of graf rejection.
- IL – α promotes T-cell proliferation and generation of T – Lymphocytes.
- IFN - γ is central to the development of DTH response.
- TNF - β has direct cytotoxic effect on the cells of graft.
- A number of cytokines promote graft rejection by inducing expression of class – I or class – II MHC molecule on graft cell.
- The interferon (α, β and γ), TNF – α and TNF - β all increases class – I MHC expression, and IFN - γ increases class – II MHC expression as well.

TIME COURSE IN GRAFT REJECTION:

• Graft rejection reactions have various time courses depending upon the type of tissue or organ grafted and the immune response involved.

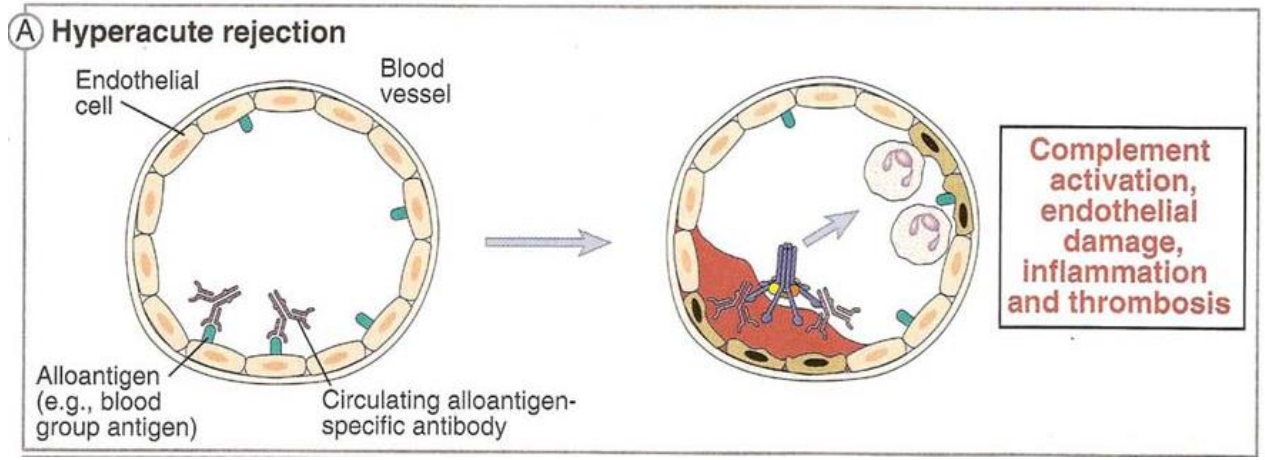
• Hyperacute rejection reaction occur within the first 24hr after transplantation
• Acute rejection reactions usually begin in the first few weeks after transplantation
• Chronic rejection reaction can occur from months to years after transplantation.

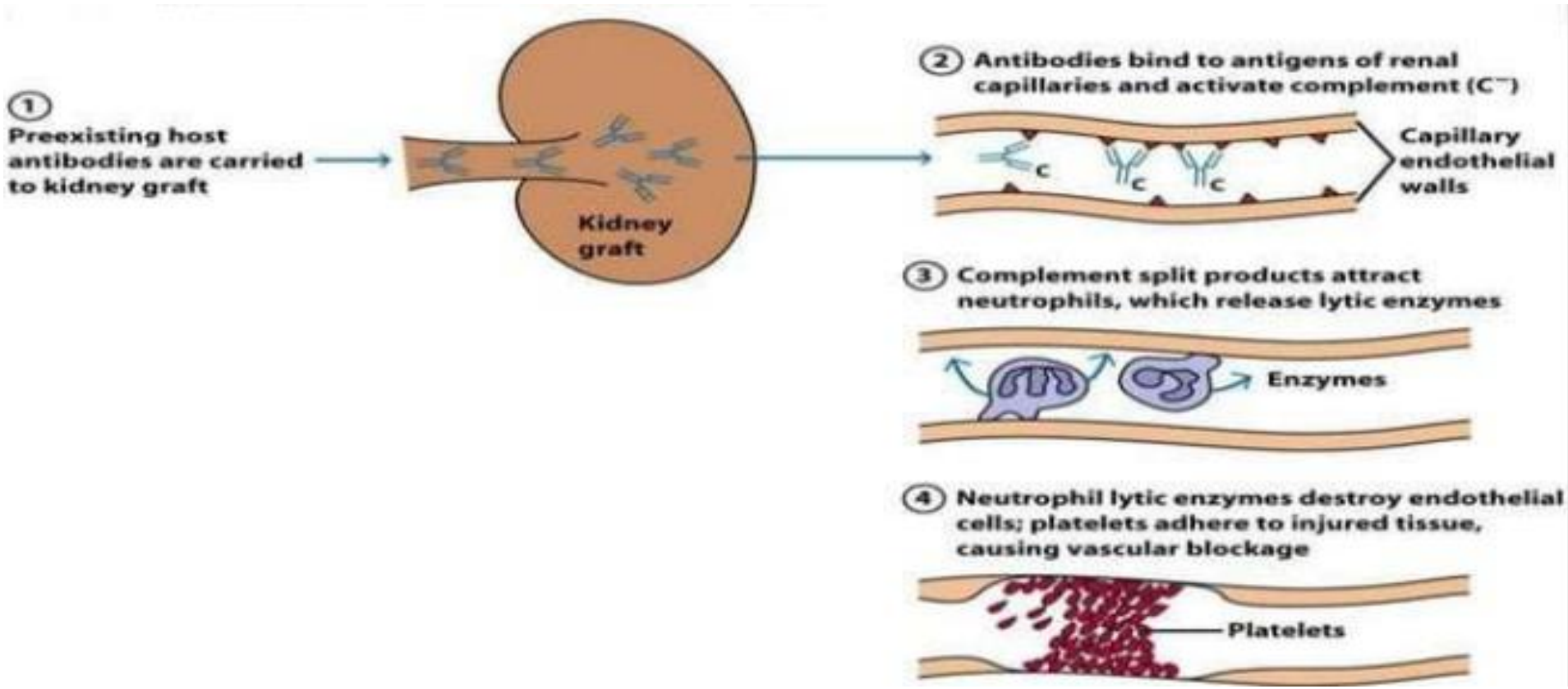
Hyperacute Rejection

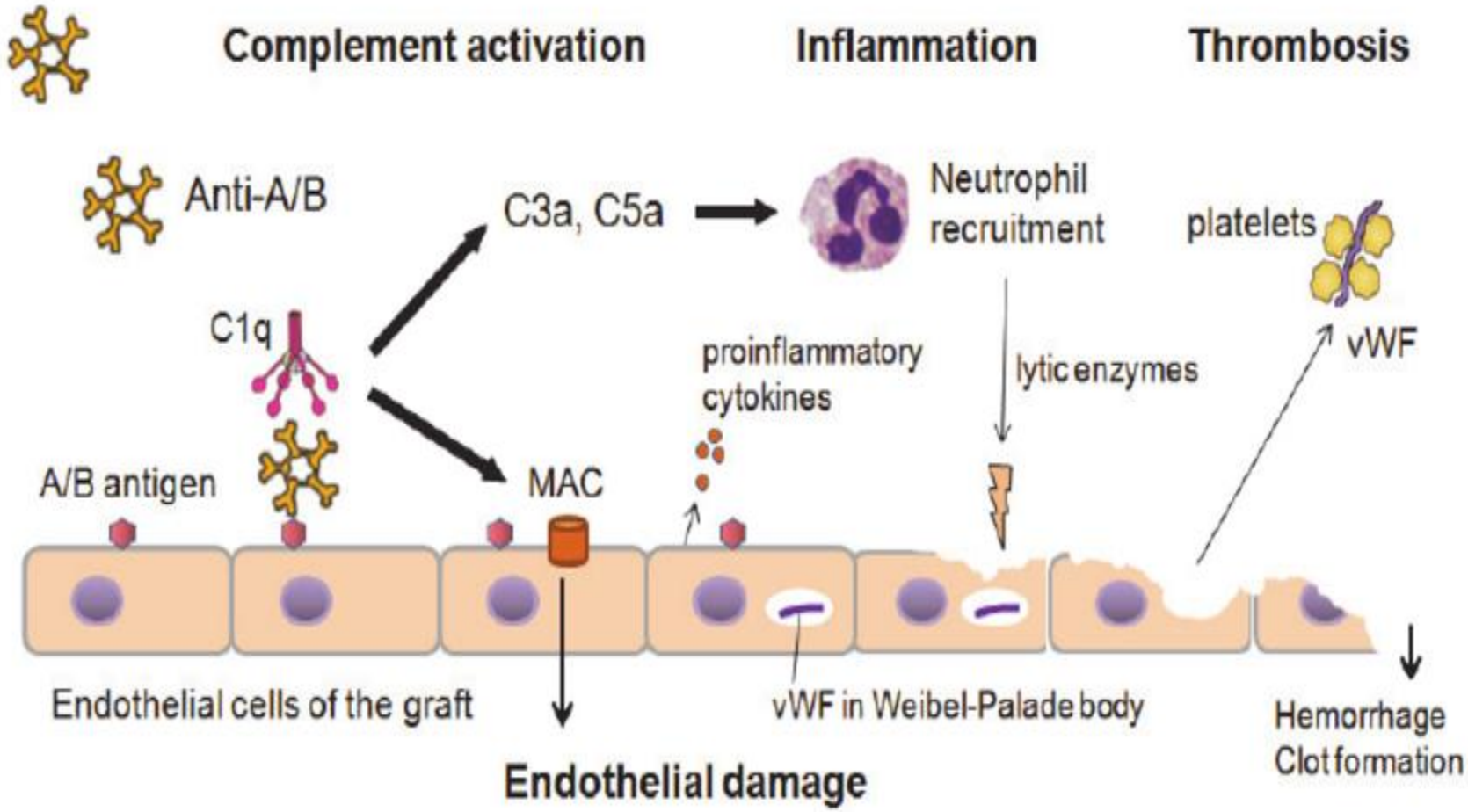
- Hyperacute Rejection is characterized by thrombotic occlusion of the graft vasculature that begins with minutes to hours after host blood vessels are anastomosed to graft vessels and is mediated by preexisting antibodies in the host circulation that bind to donor endothelial antigens.
- Binding of antibody to endothelium activates complement and antibody and complement induce a number of changes in the graft endothelium that promote intravascular thrombosis.
- Complement activation leads to endothelial cell injury and exposure of subendothelial basement membrane proteins that activate platelets. The endothelial cells are stimulated to secrete high molecular weight forms of von Willebrand factor that mediate platelets adhesion and aggregation. Both endothelial cells and platelets undergo membrane vesiculation leading to shedding of lipid particles that promote coagulation.

- Endothelial cells lost the cell surface heparin sulfate proteoglycans that normally interact with antithrombin III to inhibit coagulation. These processes contribute to thrombosis and vascular occlusion and the grafted organ suffers irreversible ischemic damage. When a graft is applied to an animal possessing the specific antibodies in high titres, hyperacuterejection takes place.

- The graft remains pale and is rejected within hours even without an attempt at vascularization. This was known as the white graft response. Humoral antibodies may sometimes act in opposition to cell mediated immunity, by inhibiting graft rejection. This phenomenon called immunological enhancement. It was originally described by kaliss in tumor transplants.





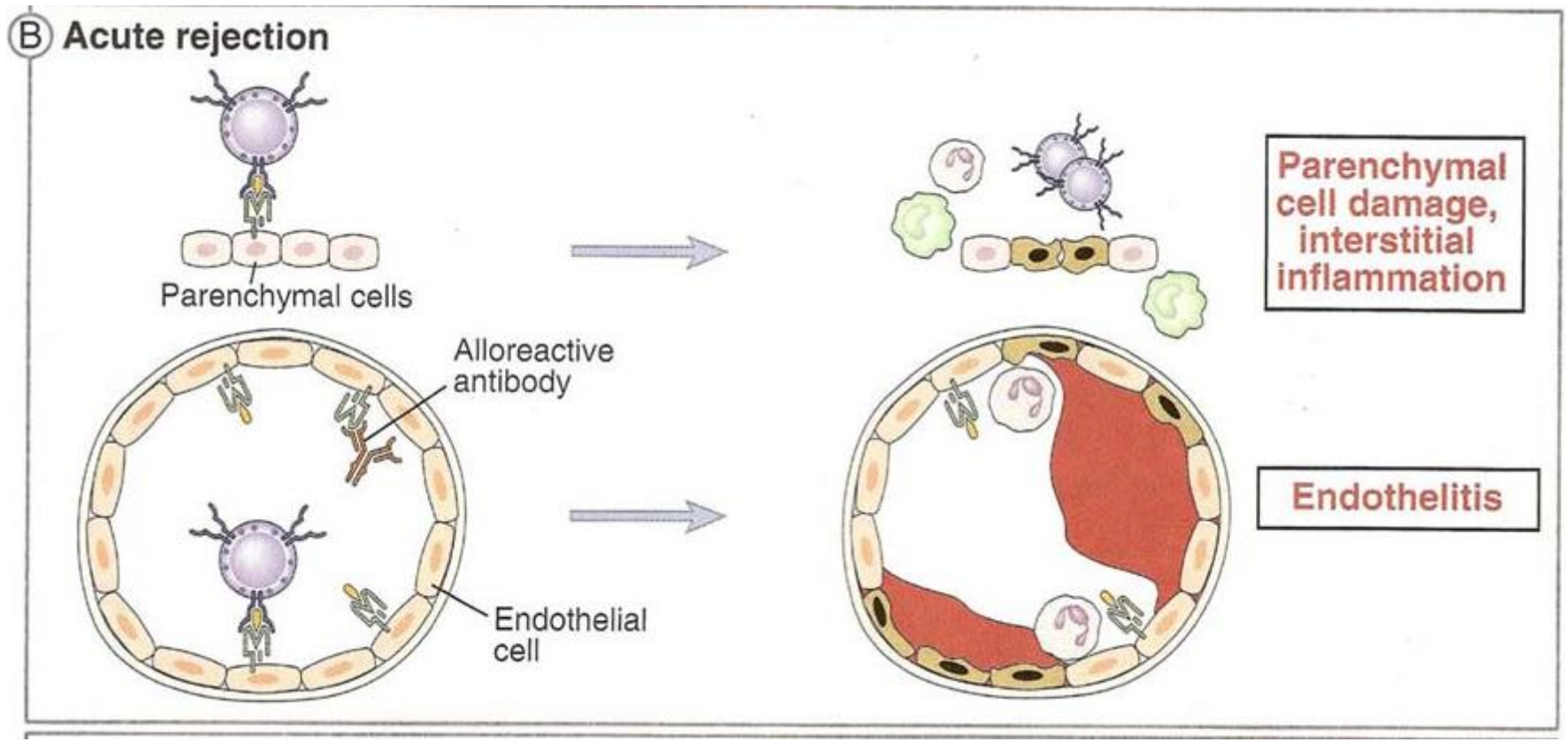


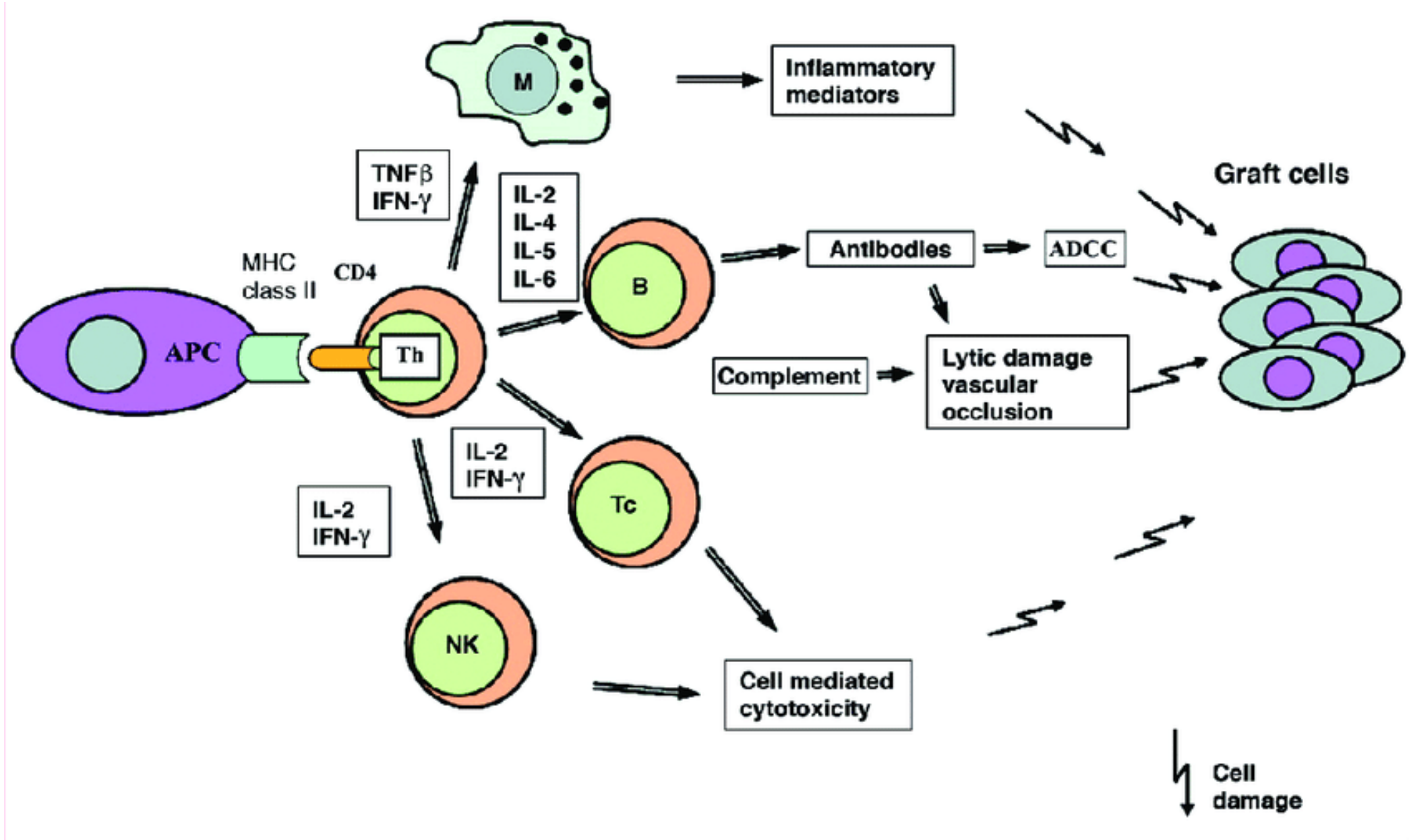
Source:Ravi Kant Upadhyay

Acute Rejection

- Acute rejection is a process of vascular and parenchymal injury mediated by T cells and antibodies that usually begins after the fist week of transplantation. Effector T cells and antibodies that mediate acute rejection develop during a few days or weeks in response to the graft, accounting for the time at onset of acute rejection.
- The activated T cells cause direct lysis of graft cells or produce cytokines that recruit and activate inflammatory cells, which injure the graft. In vascualrized grafts such as kidney grafts, endothelial cells are the earliest targets of acute rejection. Microvascular endothelitis is a frequent early finding in acute rejection episodes. Endothelitis or intimal arteritis in medium-sized arteries also occurs at an early stage of acute rejection and is indicative of severe rejection, which left untreated, will likely result in acute graft failure.

• Antibodies can also mediate acute rejection if a graft recipient mounts a humoral immune response to vessel wall antigens and the antibodies that are produced bind to the vessel wall and activate complement. The histologic pattern of this form of acute rejection is one of transmural necrosis of graft vessel walls with acute inflammation, which is different from the thrombotic occlusion without vessel wall necrosis seen in Hyperacute rejection.


B Acute rejection
Parenchymal cells
Alloreactive antibody
Endothelial cell
Parenchymal cell damage, interstitial inflammation
Endothelitis

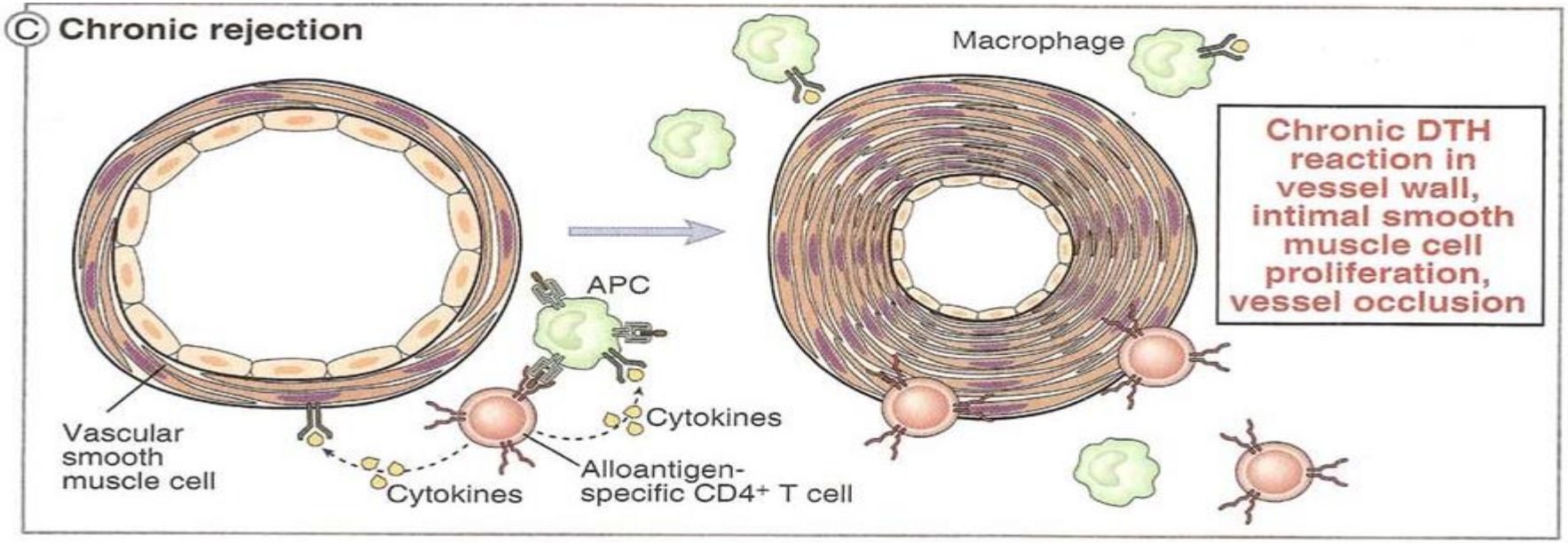


Source: govt arts and science college,cbe

Chronic Rejection

- Chronic rejection is characterized by fibrosis and vascular abnormalities with loss of graft function occurring during a prolonged period. The firbrosis of chronic rejection may result from immune reactions and the production of cytokines that stimulate fibroblasts, or it may represent would heal after parenchymal cellular necrosis of acute rejection. Perhaps the major cause of chronic rejection of vascularised organ grafts is arterial occlusion as a result of the proliferation of intimal smooth muscle cells
- This process called accelerated or graft arteriosclerosis.

- Graft arteriosclerosis is frequently seen in failed cardiac and renal allografts and can develop in any vascularlized organ transplant within 6 months to a year after transplantation. Chronic rejection of different transplanted organs is associated with distinct pathologic changes. Lung transplants undergoing chronic rejection show thickened small airways and liver transplants show fibrotic and nonfunctional bile ducts



IMMUNE RESPONSES

Role of Innate Immunity in Controlling Viral Infection

Innate immunity combats the virus immediately after its entry to prevent viral invasion and replication.

- Cytokines
- Toll-like receptors
- NK cell-mediated cytotoxicity

Adaptive immune responses to viral infection

- Both HI and CMI can control viral infections.

CYTOKINES

- Cytokines and Chemokines participating in innate defense of the host are produced by several cells of the host in response to viral infection.
- IFNs are the principle cytokines involved in antiviral response.
- Type 1 IFNs include multiple forms of IFN-a and a single IFN-B. These IFNs share the same signalling pathway. They can be produced by all nucleated cells in response to viral infection.
- IFNs have pleiotropic functions. They increase expression of intrinsic proteins, induce apoptosis of virus-infected cells, induce an antiviral state in neighbouring cells, and induce activation of adaptive immune response.

TOLL- LIKE RECEPTOR

- Viruses enter the cells by receptor-mediated endocytosis.
- As they enter the endosome, unfortunately for them, they get surveyed by the innate immune system.
- The endosomal TLRs such as TLR 3, 7, 8 and 9 get activated by the viral nucleic acids. Their expression is enhanced by type 1 IFNs.
- TLR3 recognizes double-stranded RNA (ds RNA) and triggers antivirus response by signalling . dsRNA activates macrophages and DCs via TLR3 to secrete pro-inflammatory cytokine IL-12.
- dsDNA of viral origin is recognized by TLR8 located in the endosomes in humans.
- TLR9 recognizes unmethylated viral DNA with CpG motifs of DNA viruses such as HSV1, HSV2 and CMV.
- TLR2 and TLR4 recognize the viral components at the cell surface. TLR2 recognizes components of (measles virus, hepatitis C virus and HSV), while TLR4 signals for the presence of retrovirus and respiratory syncytial virus (RSV).
- These TLRs trigger production of pro-inflammatory cytokines.

NK CELLS

- NK cells are the important killer cell type in innate immunity and keep the infection in control until adaptive immunity takes over .
- Viral infection can also induce expression of stress proteins , which give positive signal to activation receptor for NK cell-mediated lysis (by granzymes & perforins) of virus-infected targets.
- IFN-Y and IL-2 are the potent activators of NK cells.

HUMORAL IMMUNE RESPONSE

- Some viral products are expressed on the surface of infected cells which can elicit humoral immune response.
- Antibodies block the infectivity of the virus by neutralizing the virus (neutralizing antibodies).
- The isotypes of antibodies mainly involved in viral neutralization are IgM, which takes care of the fresh infection, and IgG, which takes care of the established infection and also generates memory response.

NEUTRALIZATION

Neutralization is the ability of antibodies to decrease the infectious titre of the virus. Interaction between the virion and neutralizing antibody depends on the following factors.

- Structure and location of the virion (intracellular virus particles are generally not affected by neutralizing antibodies)
- The target antigen
- Mutations in the virions, that cause change in the expression of the antigens against which the neutralizing antibodies were directed.
- Isotype of the antibodies
- Number of antibody molecules attached to a virus particle (If the number is too less, which happens if the virus is already attached to the cell surface, the neutralization can be inhibited)

CELLULAR IMMUNE RESPONSES

- Cytotoxic cells are important in localizing infections and recovery from the disease.
- Three cell types exert cytotoxicity on virus-infected cells.

1. Cytotoxic Tlymphocytes (CTLs) - Cytotoxic T lymphocytes (CTLs) are generated by the activation of CD8 T cells which recognize virus-specific antigens expressed on the membrane of virus-infected cells in the context of class I MHC molecules.
2. K (killer) cells the effector cells which can perform antibody-dependent cellular cytotoxicity (ADCC)- using IgG antibodies.
3. NK cells which are the constitutively lytic cells, a major component of innate immunity.

IMMUNE RESPONSE IN INFLUENZA

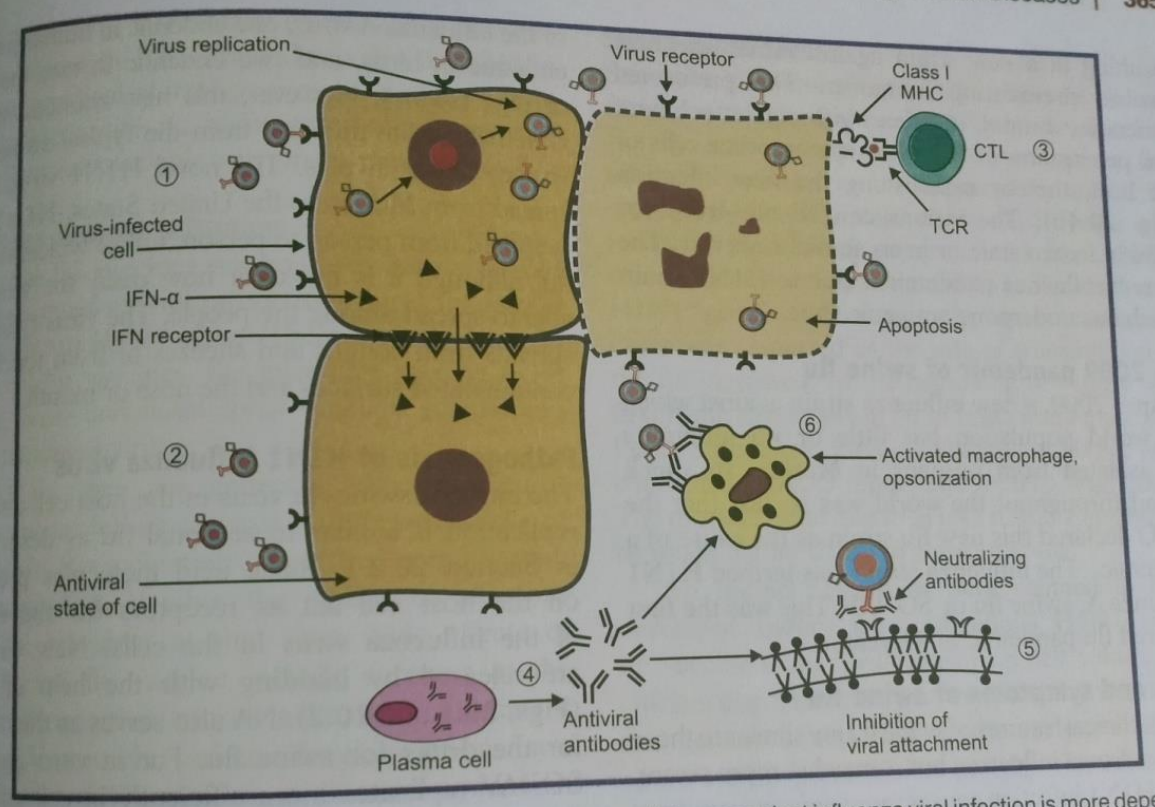


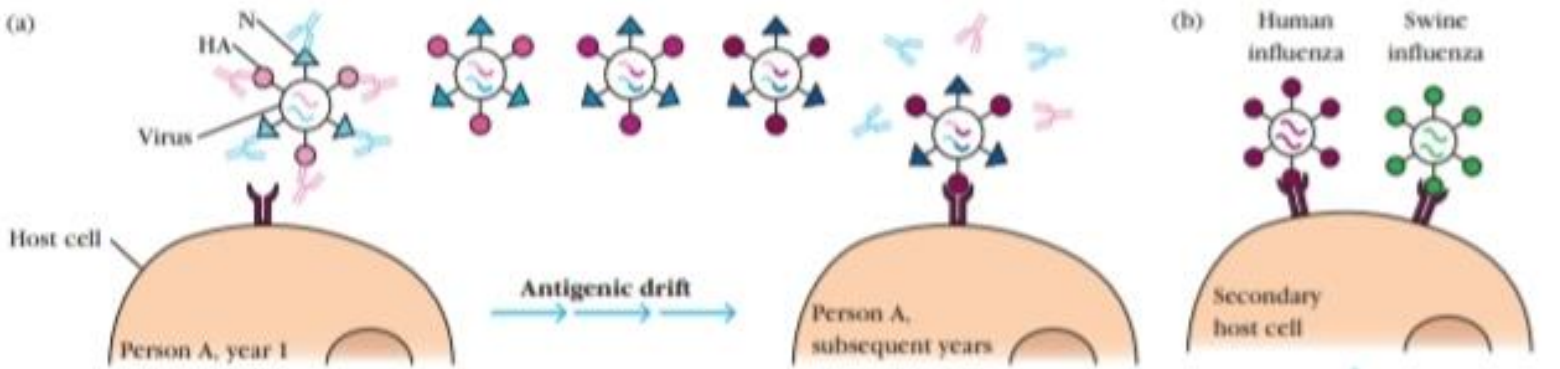
Fig. 20.3 Immune response in influenza infection The immune defence against influenza viral infection is more dependent on T cells than the antibodies. Influenza virus enters the cell and begins to replicate. The presence of viral proteins in the cytoplasm causes the production of interferon-α (1), which confers antiviral state on neighbouring cells (2). Some viral proteins are degraded and displayed on class I MHC molecules. Cytotoxic T cells sense the class I MHC molecules presenting viral antigens and get activated with the help of T_H1 cytokines. Activated cytotoxic T cells kill the infected cells displaying viral antigens (3). Viral antigens are also presented to B cells which get activated and differentiated into plasma cells producing antibodies (4). These antibodies inhibit the entry of the virus in the host cell (5). Macrophages can phagocytose viruses via Fc receptors and other receptors and kill them (6).

strains during pandemics and epidemics

Source: sciencedirect.com

ANTIGENIC DRIFT & SHIFT

- In antigenic drift, a series of spontaneous mutations occur which gradually result in minor changes in HA. The new strains which evade host's immunity.
- Antigenic shift is the result of sudden emergence of new subtypes with considerable differences in HA(Hemagglutinin) & NA(Neuraminidase). This occurs when two influenza strains infect the same host, and enter in the same cell.



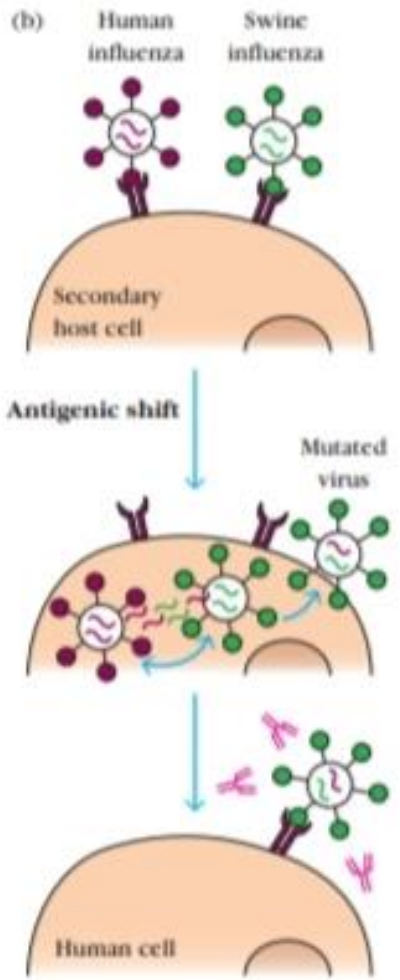


FIGURE 17-3 Two mechanisms generate variations in influenza surface antigens. (a) In antigenic drift, the accumulation of point mutations eventually yields a variant protein that is no longer recognized by antibody to the original antigen. (b) Antigenic shift may occur by reassortment of an entire ssRNA between human and animal virions infecting the same cell. For clarity, only the HA surface antigens of the virus are shown in part b. Only two of the eight RNA strands are depicted.

TABLE 17-2 Some influenza A strains and their hemagglutinin (H) and neuraminidase (N) subtype

Species	Virus strain designation	Antigenic subtype
Human	A/Puerto Rico/8/34	H0N1

Source: https://triyambak.org/

STRUCTURE OF HIV AND ITS GENOME

- HIV is an oval-shaped enveloped retrovirus with two copies of ssRNA as a genome.
- The envelope Contains two protruding proteins gp41 and gp120 which are involved in the recognition and entry of HIV in T cells and macrophages.
- Within the capsid, p10 protease and p32 integrase are present. In addition, one copy of reverse transcriptase is associated with each strand of the RNA.
- HIV has three major genes: gag, pol and env. gag codes for a 53 kDa precursor which forms matrix and capsid proteins. pol codes for p64 reverse transcriptase, p32 integrase, p10 protease and P32.

ROUTE OF HIV INFECTION AND STAGES OF INFECTION

- HIV is carried mainly by CD4 T cells. The CD4 molecule acts as a receptor for the virus, along with coreceptors CCR5 and CXCR4. Viral glycoproteins involved in the tropism are gp120 and gp41. gp120 binds to CD4 molecules present on T cells, DCs and macrophages.
- In acute phase, influenza-like illness is seen in the majority of patients. In this phase, there is abundant viremia in the peripheral blood, and decrease in the number of CD4 T cells. The acute phase does show antibody production and activated CD8 T cells (Tc), which kill virus-infected cells.
- By 3-4 months, acute viremia subsides and the disease goes into a quiescent asymptomatic period. In this period there is continuous replication of the virus and a steady decrease in the CD4 T cells

- The long latency period when there are no evident signs or symptoms of n the disease is the most dangerous period. During this period an infected individual may infect others. Antibodies to gp120 are present in the latency x period. The antibody production declines as the viral load increases.

The reduction in CD4 cells could be due to

1. killing of virus-infected CD4 cells,
2. increased susceptibility of CD4 cells to apoptosis, and
3. defective generation of new CD4 T cells from progenitors in the thymus.

- At the end of the asymptomatic period, opportunistic infections appear, viremia increases and fall in CD4 count continues. This is the stage of full-blown AIDS.

IMMUNE RESPONSE TO HIV

Both antibodies and cytotoxic T cells are generated against HIV in the infected host. However, the immune response is incapable of controlling HIV spread because of the rapid increase in the growth of the virus and rapid mutation occurring during viral infection. Cytidine transaminase helps in causing mutation.

IMMUNE RESPONSE TO BACTERIAL DISEASES

- When bacteria enter the host, they are first attacked by the innate immune system, mainly by macrophages and NK cells. Macrophages phagocytes the pathogens and NK cells get rid of the pathogens by exerting cytotoxic effect.

TABLE 17-3 Host immune responses to bacterial infection and bacterial evasion mechanisms

Infection process	Host defense	Bacterial evasion mechanisms
Attachment to host cells	Blockage of attachment by secretory IgA antibodies	Secretion of proteases that cleave secretory IgA dimers (*Neisseria meningitidis, N. gonorrhoeae, Haemophilus influenzae*) Antigenic variation in attachment structures (pili of *N. gonorrhoeae*)
Proliferation	Phagocytosis (Ab- and C3b-mediated opsonization)	Production of surface structures (polysaccharide capsule, M protein, fibrin coat) that inhibit phagocytic cells Mechanisms for surviving within phagocytic cells Induction of apoptosis in macrophages (*Shigella flexneri*)
	Complement-mediated lysis and localized inflammatory response	Generalized resistance of gram-positive bacteria to complement-mediated lysis Insertion of membrane-attack complex prevented by long side chain in cell-wall LPS (some gram-negative bacteria)
Invasion of host tissues	Ab-mediated agglutination	Secretion of elastase that inactivates C3a and CSa (*Pseudomonas*)
Toxin-induced damage to host cells	Neutralization of toxin by antibody	Secretion of hyaluronidase, which enhances bacterial invasiveness

EXTRACELLULAR BACTERIA

These bacteria live and multiply outside host cells (blood, mucus, tissues)

EG: *Streptococcus pneumoniae, Escherichia coli & Staphylococcus aureus*.

The extracellular bacteria induce antibody production. The antibodies act in several ways to curtail the infection such as those listed below.

- Neutralization of toxins produced by the bacteria
- Formation of immune complexes with the surface antigens on the bacteria facilitating their phagocytosis by opsonization
- Activation of complement system, the end point being MAC formation on the surface of the pathogen, causing death of the pathogens by cytolysis
- Activation of complement leading to release of chemotactic factors C3a and C5a , which are responsible for recruiting neutrophils and macrophages to the site of infection, generating inflammatory response

INTRACELLULAR PATHOGENS

- EG: *Mycobacterium tuberculosis*, *Salmonella*, *Chylamydia trachoatis*
- The response induced by intracellular pathogens is a delayed-type hypersensitivity response (DTH) and granuloma formation. Cytokines like IFN-y released by CD4+ T cells activate macrophages and increase their ability to kill intracellular bacteria.
- Bacterial antigens expressed on membranes of infected cells induce antibody response. These antibodies get attached to the infected cells and simultaneously bring non-specific cytotoxic cells bearing Fc receptors, namely, neutrophils, monocytes, eosinophils and NK cells, closer to infected cells.
- TLR 3 recognize lipopolysaccharides found in the outer membrane of gram negative bacteria.
- On contact with the targets (infected cells), the cytotoxic cells release lytic enzymes, TNF(Tumour necrosis factor), perforins and granzymes to kill the infected cells and the intracellular bacteria, by the process called ADCC (antibody-dependent cellular cytotoxicity).

IMMUNE RESPONSE TO PARASITES

- Parasitic diseases are mostly chronic in nature.
- Parasites depend on the host for their survival. Usually, they derive all the benefits from the host while exerting detrimental dffects on it. Parasites may secrete toxic wastes which may be partly responsible for causing the disease in the host.
- There are over a hundred types of parasites that can infect and reside in the human body. They are mainly classified as protozoans and helminths.
- Protozoans are unicellular eukaryotes that usually live and multiply in host cells. Some common protozoan diseases are amoebiosis, African sleeping sickness (trypanosomiasis), malaria, leishmaniasis and toxoplasmosis.
- Helminths are multicellular parasitic worms which live inside the host. They cause long-lived chronic infections and have complex multistage lifecycles. They are classified as follows
- Cestodes(Tapeworms)
- Nematodes(Roundworms)
- Trematodes (flukes)

VECTORS

- Vectors are organisms which carry pathogens from one individual to another and transmit the disease. The most common vectors for parasitic diseases are arthropods that assist in transmitting parasites to humans or other mammals. A vector not only transmits the parasites, but is also required to be a part of the parasite's developmental cycle.

IMMUNE RESPONSE TO PARASITIC INFECTIONS

- Immune response of the host to parasitic infection depends on the nature of the parasite. Unicellular parasites live inside the host cells and avoid the immune surveillance by hiding in the cells of the infected host.
- Role of eosinophils and IgE antibodies
- Role of cytokines

ROLE OF EOSINOPHILS AND IGE ANTIBODIES

- Parasitic worms, such as helminths are too large and therefore, cannot be ingested by phagocytic cells. Such parasitic infection induces IgE antibody response.
- IgE antibodies bind to the surface antigens of the parasites. Eosinophils have Fc receptors for IgE antibodies and attach themselves to the worms through the interaction of FcERI on eosinophils and IgE antibodies bound to parasites.
- Contents of lytic granules in the eosinophils are released directly on the parasite surface and can attack the parasites.
- Infections by helminths are strongly associated with the increased production of IgE antibodies and presence of abnormally large number of eosinophils in blood and tissues.

ROLE OF CYTOKINES

- Cell-mediated immune response is essential to kill the cells harbouring the parasites and the intracellular parasites. Cytokines play a major role in the differentiation of CD4 T cells into TH1 cells(activate the macrophages) in preference to TH2 cells.
- In response to parasitic infection, toll-like receptors (TLRs) signal DCs to produce the cytokines IL-12 and IFN-y. These cytokines favour the development of TH1 cells that participate in induction of CMI response for killing the parasites.

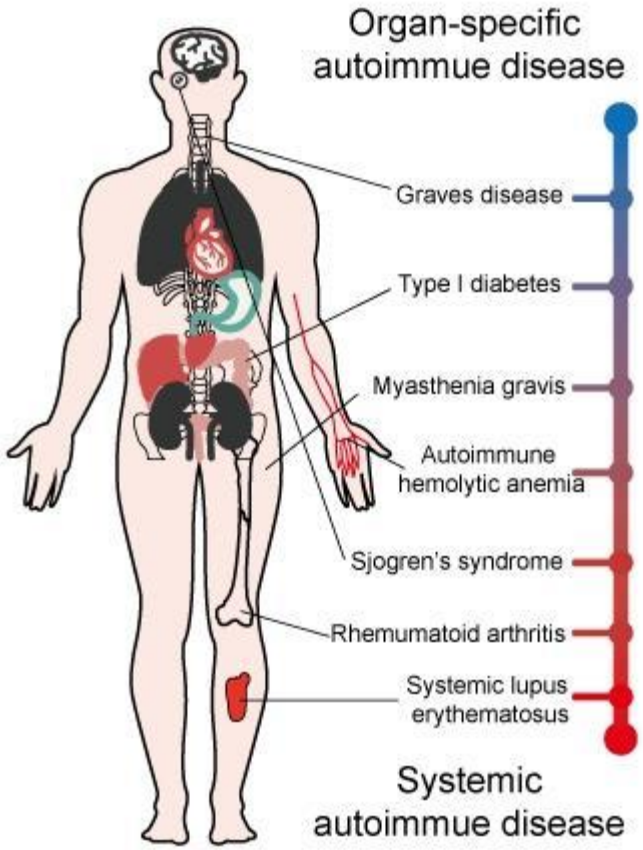
AUTOIMMUNITY: MECHANISMS OF INDUCTION OF ORGAN –SPECIFIC AND SYSTEMIC AUTOIMMUNE DISEASE

AUTOIMMUNITY

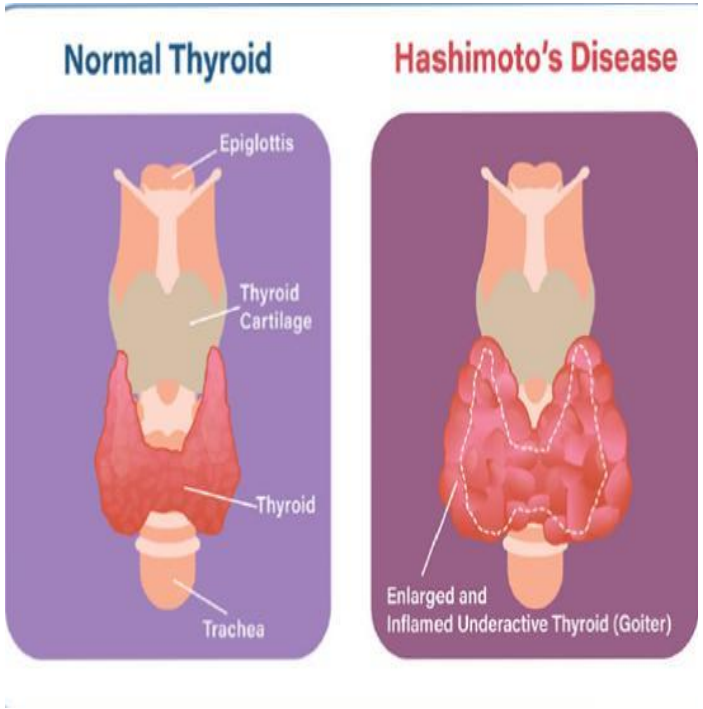
- Autoimmunity is a condition where the immune system mistakenly attacks and damages the body's **own cells, tissues, and organs.**
- It occurs when the immune system fails to distinguish between self and non-self, leading to an immune response against the body's own cells and tissues.
- They are broadly divisible into two groups
- **Organ specific disease, and**
- **Generalized systemic disease**

MECHANISMS OF INDUCTION OF ORGAN – SPECIFIC

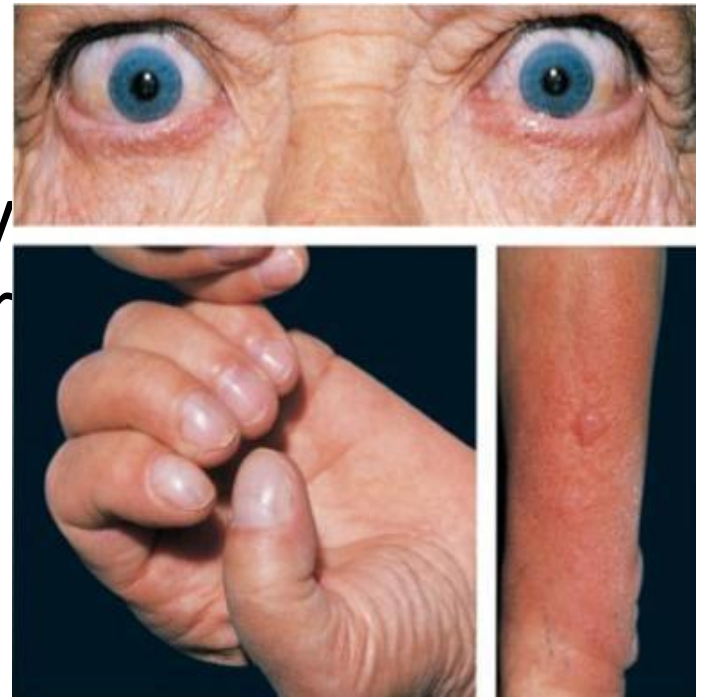
Organ-specific autoimmune diseases are conditions where the immune system mistakenly attacks a **specific organ or tissue, leading to damage** and dysfunction.



- **Type 1 Diabetes Mellitus:**
- **Target organ:** Pancreas (beta cells)
- **Mechanism**: The immune system attacks insulin-producing beta cells in the pancreas, leading to insufficient insulin production.
- **Hashimoto's Thyroiditis**:
- **Target organ**: Thyroid gland
- **Mechanism**: Autoimmune destruction of the thyroid tissue, resulting in hypothyroidism (reduced thyroid hormone production)

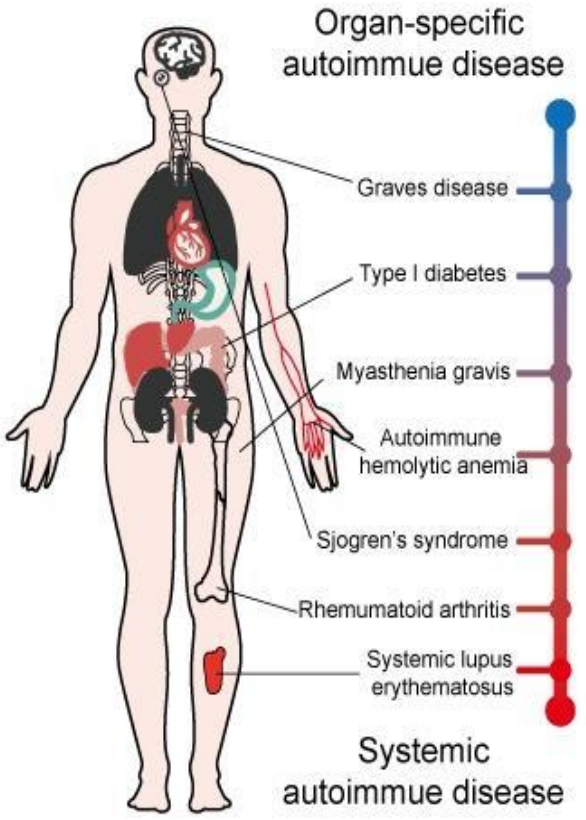


- **Graves' Disease:**
- **Target organ**: Thyroid gland
- **Mechanism**: Autoimmune activation of the thy
  causing hyperthyroidism (excessive thyroid hor
  production).
- **Addison's Disease:**
- **Target organ**: Adrenal glands
- **Mechanism**: The immune system attacks the
  adrenal cortex, leading to reduced production of
  cortisol and aldosterone.



SYSTEMIC AUTOIMMUNE DISEASES:

- Systemic autoimmune diseases are conditions in which the immune system mistakenly attacks the **body's own tissues and organs**.
- Typical systemic autoimmune diseases are **rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and dermatomyositis.**

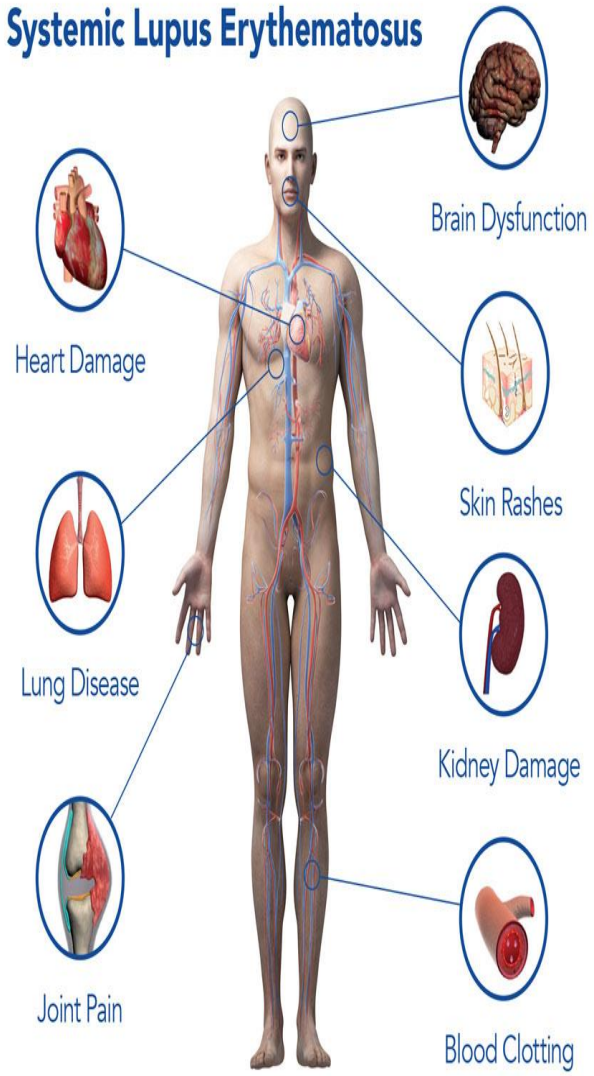


CAUSES:

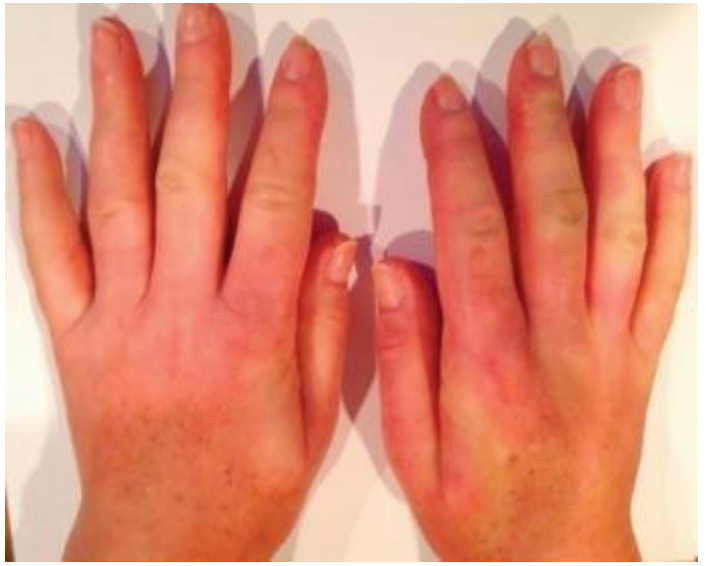
- SADs are caused by a dysregulated immune system that attacks autoantigens, which can be found in almost any type of cell in the body.
- SADs can be caused by genetic predisposition, environmental factors, chemicals, and infectious agents.

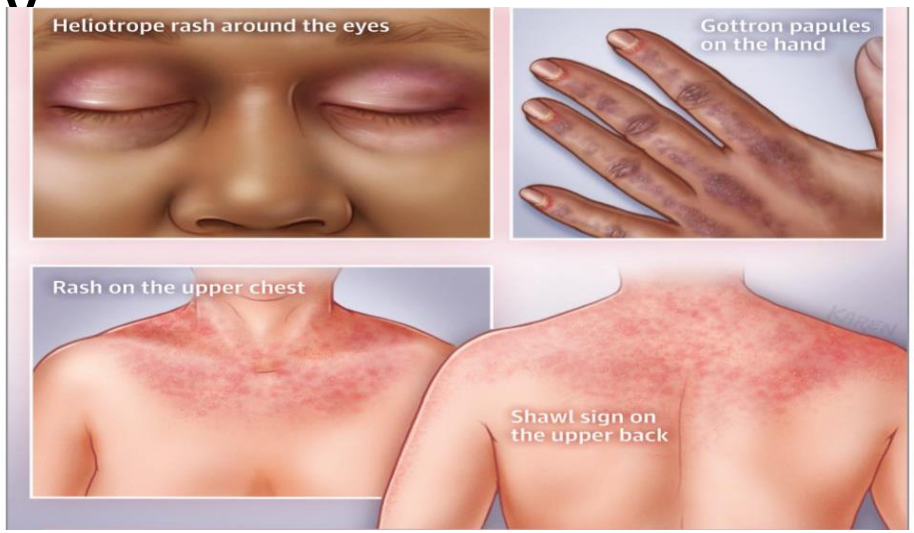
- **Treatment**:
- Corticosteroids
- Lifestyle modification
- Organ specific treatment
- **Diagnosis** :
- SADs involves a combination of medical history evaluation, physical examination, laboratory tests, and sometimes imaging

- **Systemic Lupus Erythematosus** (SLE): Affects various organs, including the skin, kidneys, heart, lungs, and joints. Symptoms include fatigue, joint pain, rashes, and organ inflammation.
- **Rheumatoid Arthritis (RA):** Primarily affects the joints, leading to inflammation, pain, and deformities. It can also affect other organs such as the lungs and heart.



- **Scleroderma**: Characterized by hardening and tightening of the skin and connective tissues, scleroderma can affect the skin, blood vessels, and internal organs.
- **Dermatomyositis**: Causes inflammation and weakness in muscles, often accompanied by skin rashes in the case of dermatomyositis.





Source: https://rheumnow.com/node/38745

HYPERSENSITIVITY, CANCER AND IMMUNOTHERAPY

Hypersensitivity

Definition of Hypersensitivity:

- Hypersensitivity refers to an exaggerated **immune response** that causes tissue damage and pathology.
- These reactions occur when the immune system responds inappropriately or excessively to antigens (allergens), causing harm to the body.

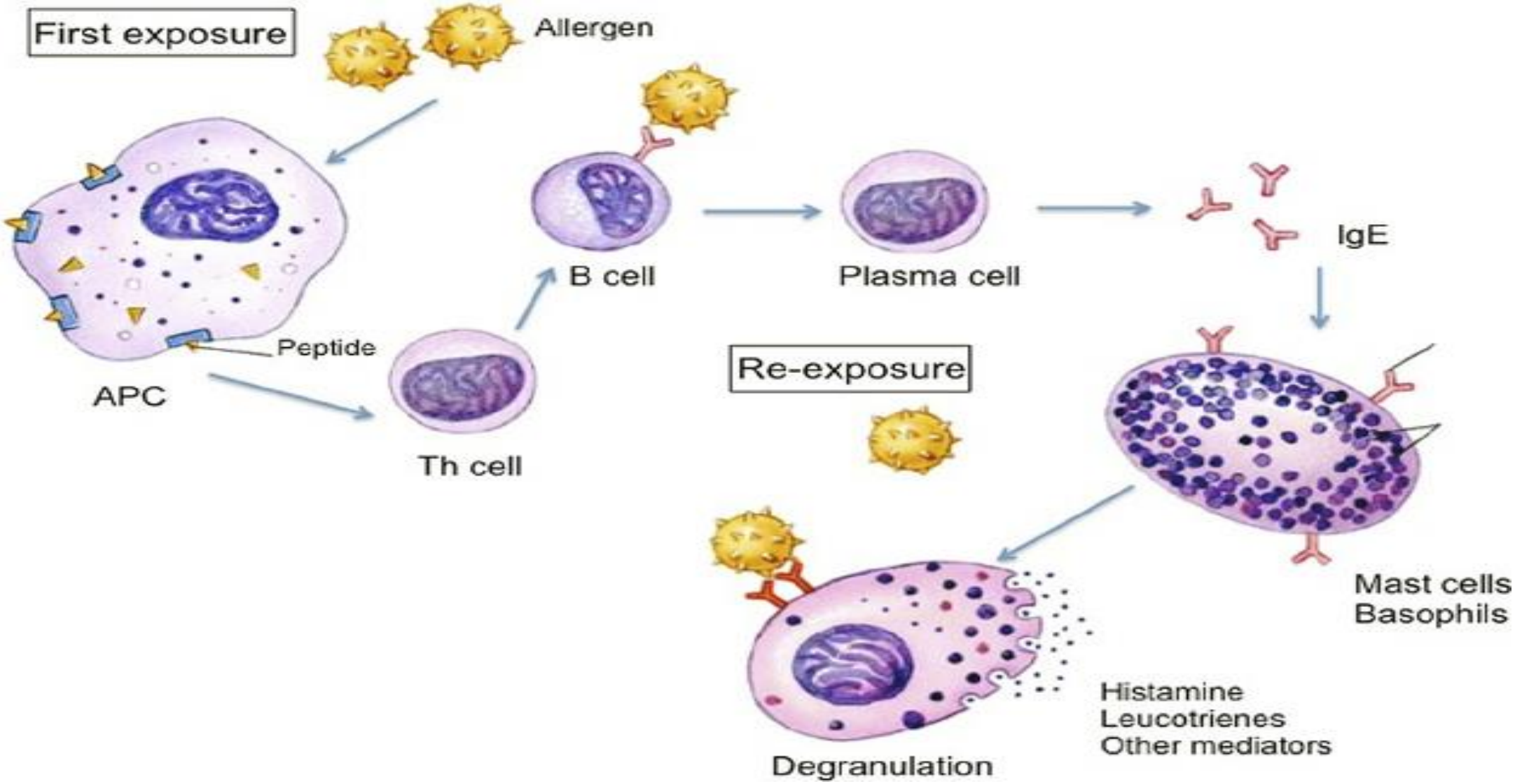
Classification of Hypersensitivity

- Hypersensitivity reactions are classified into **four main types**, based on the mechanisms involved and the time taken for the reaction to develop.
- These types are referred to as
  - **Type I,**
  - **Type II,**
  - **Type III and**
  - **Type IV hypersensitivity**.

Type I Hypersensitivity (Immediate or Anaphylactic Hypersensitivity)

- **Mechanism**: This type involves IgE antibodies binding to allergens. When exposed to the allergen, mast cells and basophils release histamine and other mediators.
- **Time period** : Immediate, usually within minutes to hours.
- **Examples**:
  - Allergic rhinitis (hay fever)
  - Asthma
  - Anaphylaxis
  - Food allergies
- **Mediation** :
  - **IgE-mediated**: Antigen binds to IgE on mast cells/basophils.
  - Release of inflammatory mediators (e.g., histamine).

TYPE 1

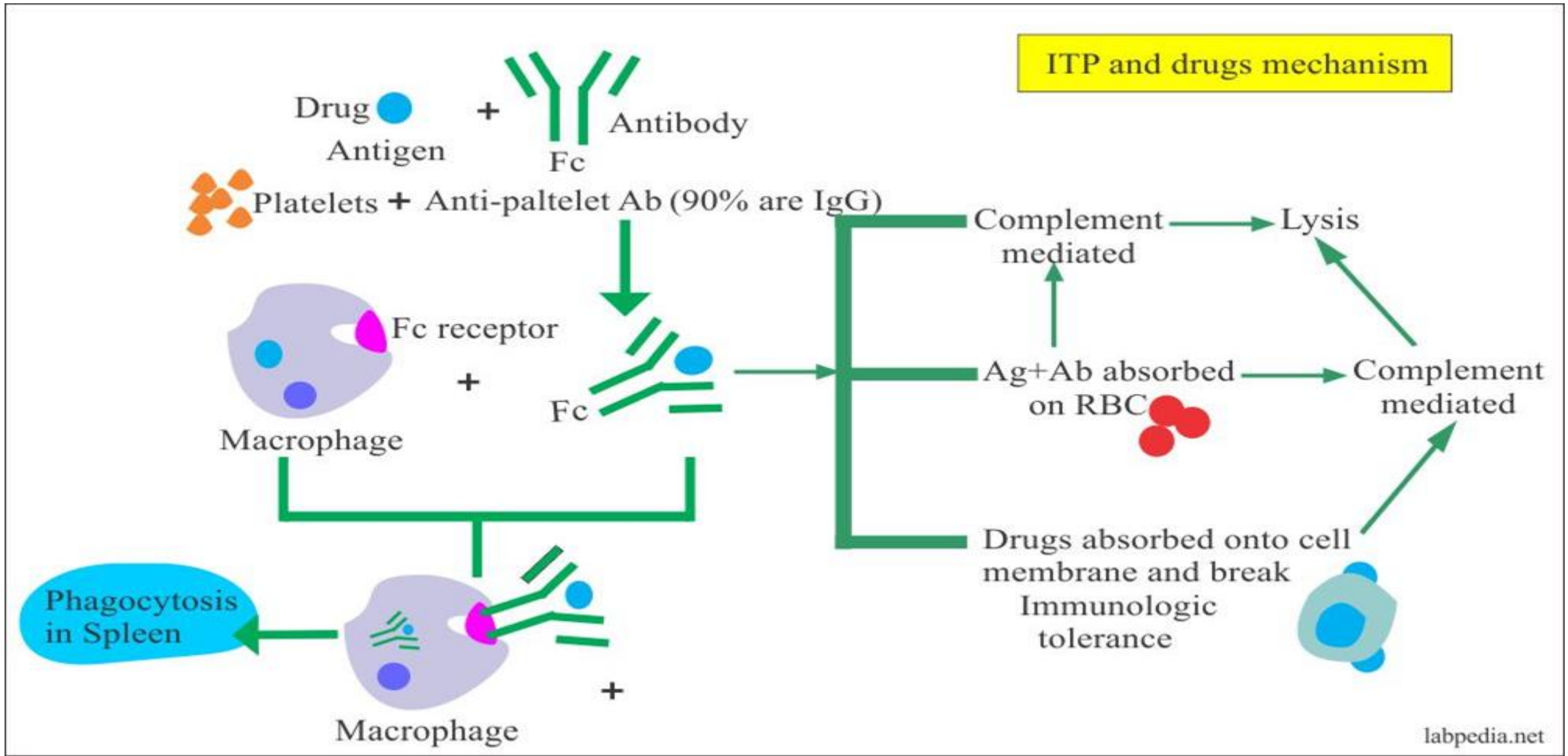


Source: https://microscopiaiwm.wordpress.com/2020/08/24/hypersensitivity/

Type II Hypersensitivity (Cytotoxic Hypersensitivity)

- **Mechanism**: Involves IgG or IgM antibodies directed against antigens on cells or extracellular matrix, leading to cell destruction via complement activation or antibody-dependent cell-mediated cytotoxicity (ADCC).
- **Time period** : Hours to days.
- **Examples**:
  - Hemolytic anemia
  - Blood transfusion reactions
  - Rh incompatibility (hemolytic disease of the newborn)

- **Mediation** :
  - **Antibody-mediated** : Targeting cells or tissue.
  - Activation of the complement system or direct phagocytosis.


ITP and drugs mechanism
Drug
Antigen
+
Antibody
Fc
Platelets + Anti-paltelet Ab (90% are IgG)
Fc receptor
+
Fc
Macrophage
Complement mediated
Lysis
Ag+Ab absorbed on RBC
Complement mediated
Drugs absorbed onto cell membrane and break Immunologic tolerance
Phagocytosis in Spleen
+
Macrophage
labpedia.net

Type III Hypersensitivity (Immune Complex-Mediated Hypersensitivity)

- **Mechanism**: Involves immune complexes (antigen-antibody complexes) that deposit in tissues, leading to complement activation and inflammation.
- **Time period** : Hours to days.
- **Examples**:
    - Systemic lupus erythematosus (SLE)
    - Rheumatoid arthritis
    - Post-streptococcal glomerulonephritis

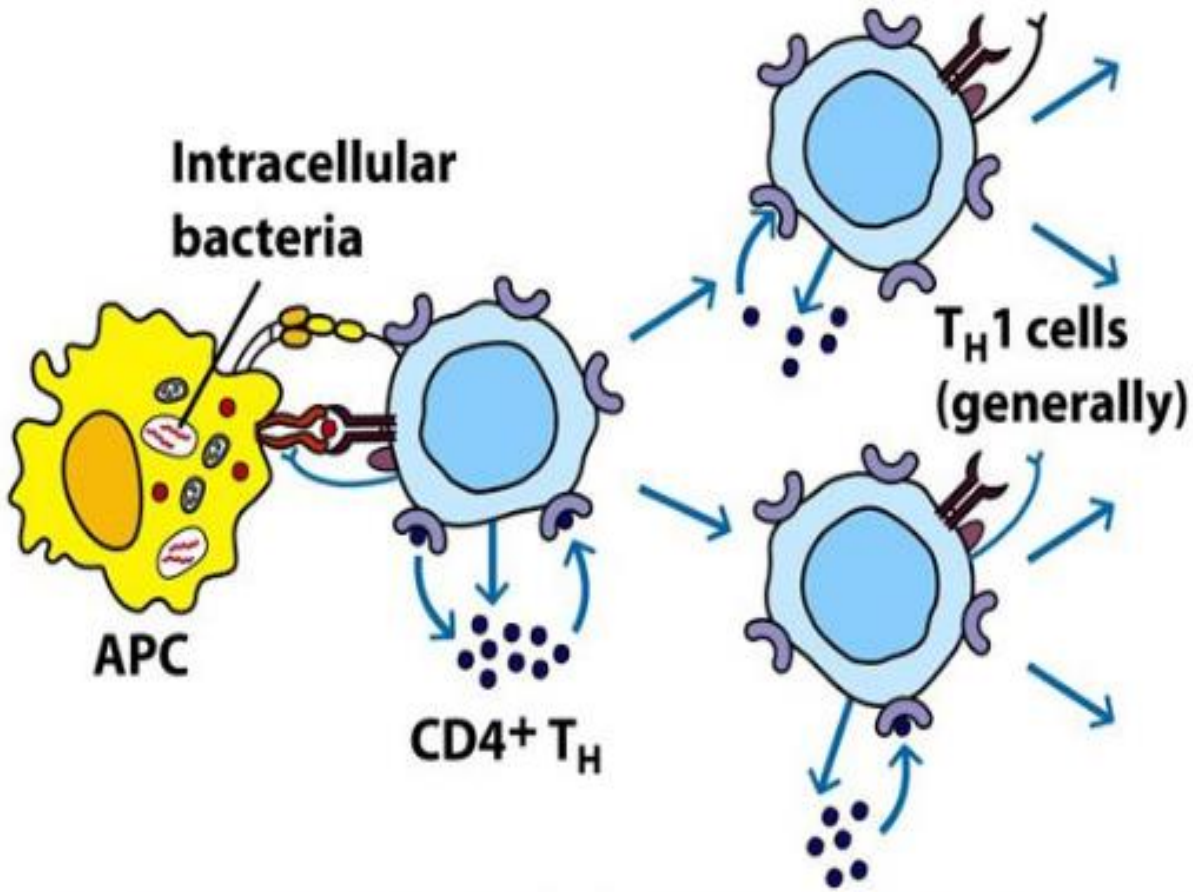
Mediation :

- **Immune complex-mediated**: Antigen-antibody complexes circulate and deposit in various tissues.
- Results in inflammation and tissue damage

Type IV Hypersensitivity (Delayed-Type Hypersensitivity)

- **Mechanism**: Involves T cell-mediated immune responses. Sensitized T cells recognize antigens and release cytokines, which recruit macrophages and cause inflammation.
- **Time period** : 48-72 hours (delayed).
- **Examples**:
  - Contact dermatitis (e.g., poison ivy)
  - Tuberculin skin test (PPD)
  - Type 1 diabetes (autoimmune destruction of insulin-producing cells)
  - Multiple sclerosis
- **Mediation** :
  - **T-cell mediated**: Does not involve antibodies.
  - Delayed onset of response.

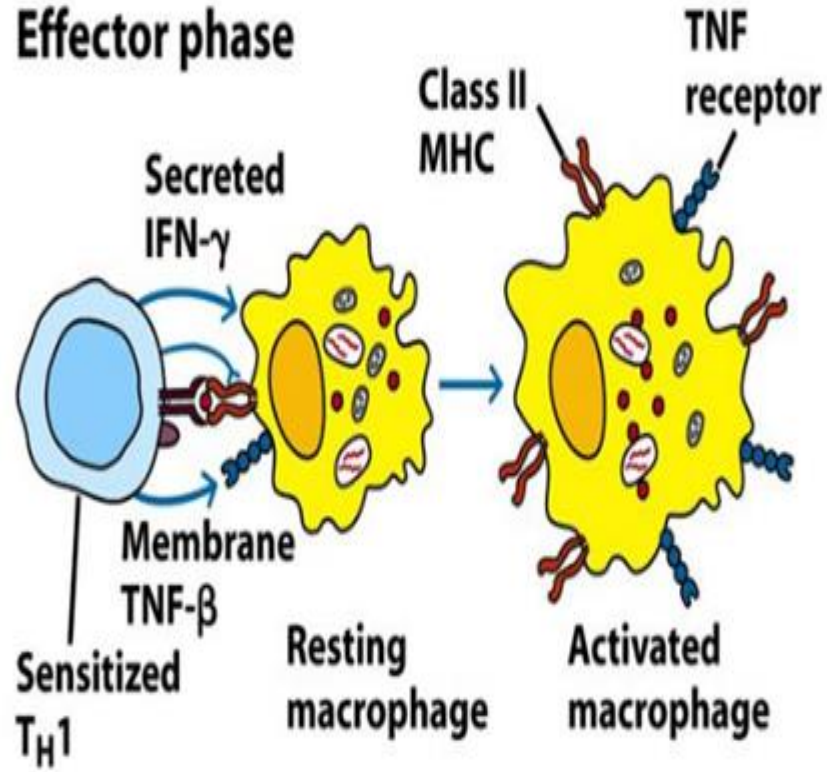
Sensitization phase



Antigen-presenting cells: Macrophages, Langerhans cells

DTH-mediating cells: T_H1 cells generally, CD8 cells occasionally

Effector phase



T_H1 secretions:

Cytokines: IFN-γ, TNF-β, IL-2, IL-3, GM-CSF, MIF

Chemokines: IL-8/CXCL8, MCP-1/CCL2

Effects of macrophage activation:

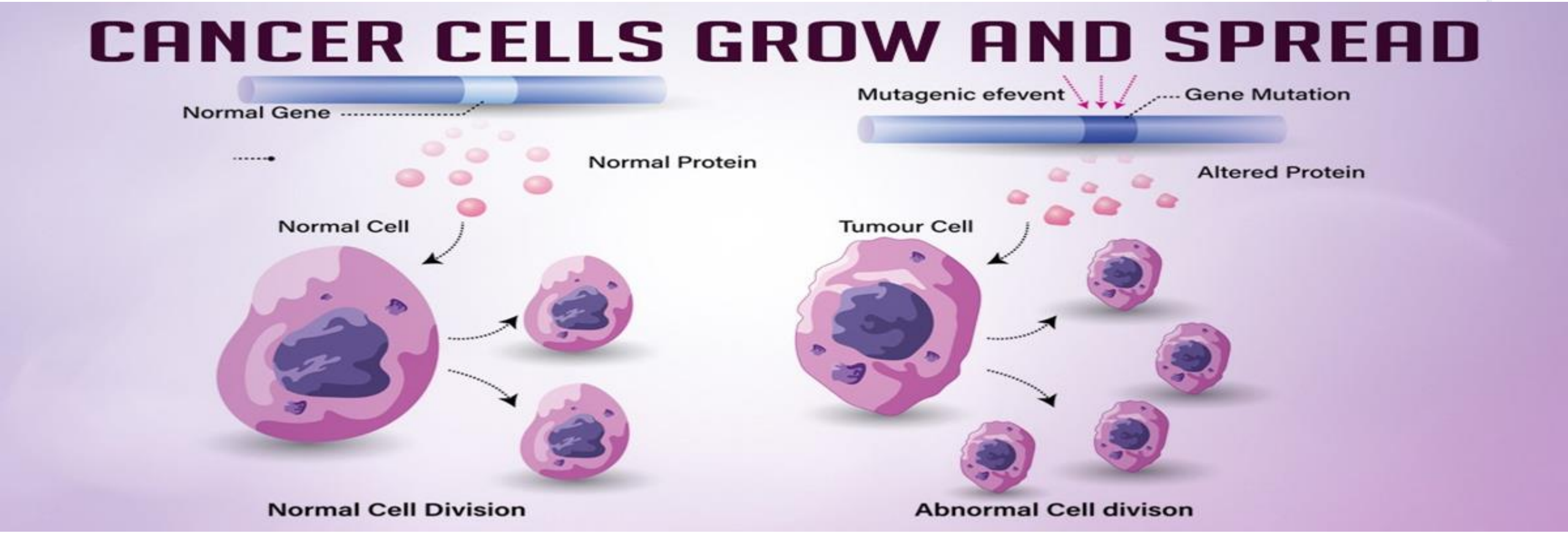
- ↑ Class II MHC molecules
- ↑ TNF receptors
- ↑ Oxygen radicals
- ↑ Nitric oxide

Source:biologynotesonline.com

Type	Immune Components	Onset	Examples	Mechanism
Type I	IgE, Mast cells	Minutes to hours	Anaphylaxis, Asthma, Food allergies	Release of histamine and other mediators
Type II	IgG/IgM, Complement	Hours to days	Hemolytic anemia, Rh incompatibility	Antibody-mediated cell destruction
Type III	Immune complexes	Hours to days	SLE, Rheumatoid arthritis	Immune complex deposition and inflammation
Type IV	T cells	48-72 hours	Contact dermatitis, Type 1 diabetes	T cell-mediated inflammation

Cancer

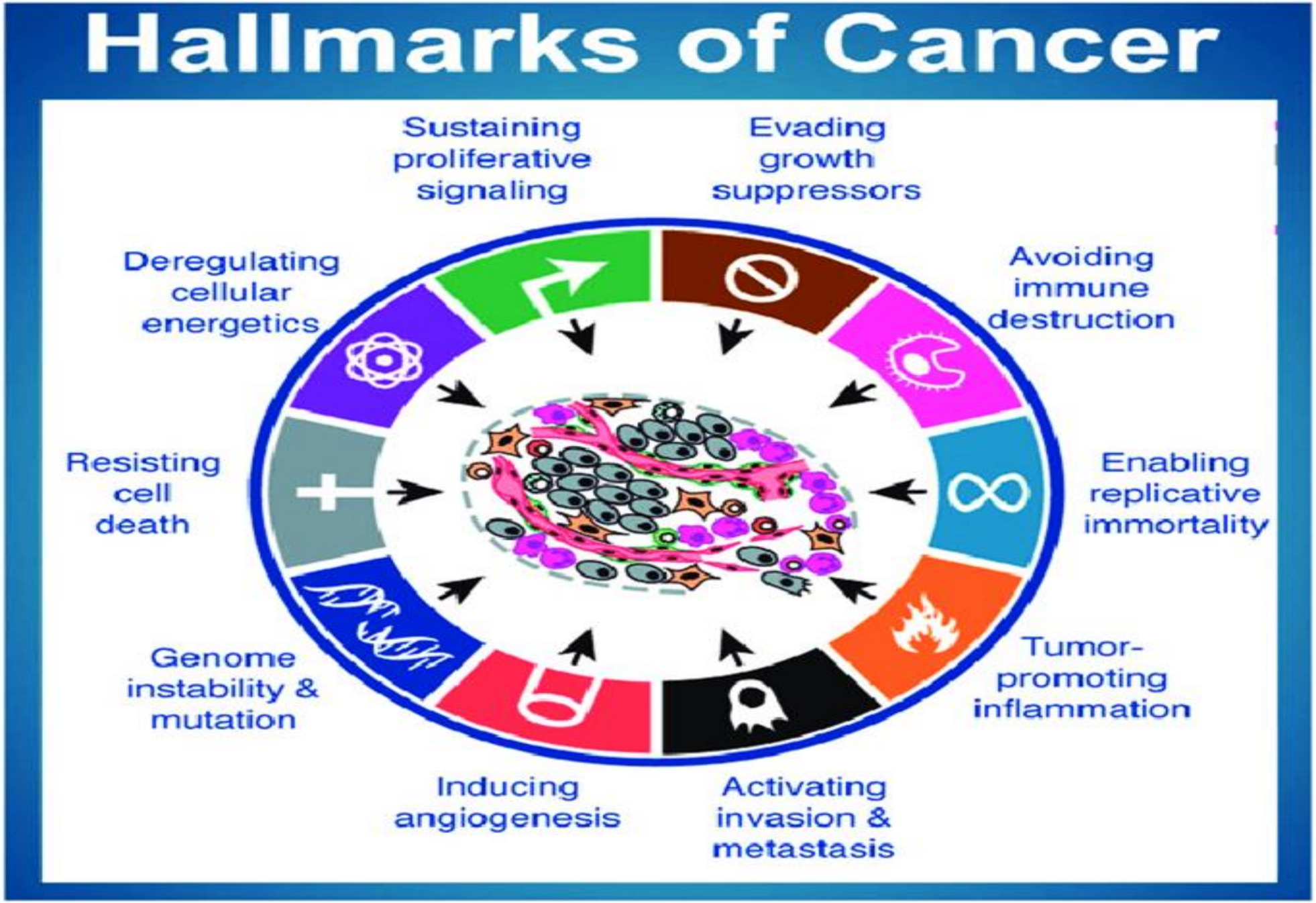
- **Cancer** is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body.



Characteristics of Cancer Cells:

1. **Uncontrolled Proliferation**: Cancer cells bypass normal growth signals, leading to rapid and uncontrolled cell division.
2. **Resistance to Cell Death (Apoptosis)**: Cancer cells evade programmed cell death, allowing damaged cells to survive and proliferate.
3. **Invasion and Metastasis**: Cancer cells invade surrounding tissues and can spread to distant organs via the bloodstream or lymphatic system.
4. **Angiogenesis**: Tumors induce the formation of new blood vessels to supply the growing mass with oxygen and nutrients.
5. **Genomic Instability**: Mutations accumulate in cancer cells, promoting genetic diversity within the tumor.
6. **Evasion of the Immune System**: Cancer cells may hide from or inhibit the immune system's ability to recognize and destroy them.

Hallmarks of Cancer



Source:https://www.cell.com/fulltext/S0092-8674(11)00127-9

CATEGORIES OF CANCER

Carcinoma

- Arises from the epithelial cells lining the internal surface of various organs (e.g. mouth, esophagus, uterus)

Sarcoma

- Arises from the mesodermal cells constituting the various connective tissues (e.g. fibrous tissue, bone)

Lymphoma, myeloma and leukemia

- Arising from the cells of the bone marrow and immune system

3. OCCUPATIONAL EXPOSURES

- These includes exposure to benzene, cadmium, arsenic, chromium, vinyl chloride, asbestos, polycyclic hydrocarbons, etc.
- Occupational exposure is usually reported 1-5% of human cancer

4. VIRUS

- Hepatitis B & C - hepato-carcinoma
- HIV infection – kaposi's carcinoma
- AIDS – Non Hodgkin's lymphoma
- Epstein – bar virus – Burkitts lymphoma and naso – pharyngial carcinoma
- Cytomegalovirus – Kaposi's Sa
- Pappiloma virus – cervix cancer
- Human T cell leukemia virus – T cell leukemia

5. Parasite

Schistosomiasis can produce Cancer of bladder

6. Customs, habits and life style May be associated with an increased risk of cancer.

7. Genetic factors

- Retinoblastoma occurs in children of the same parent
- Mongols are more likely to develop leukemia
- There is probably a complex relationship between hereditary susceptibility and environmental carcinogenic stimuli in the causation of cancer

8. Others

- Sunlight, radiation, water and air pollution, medication and pesticides

CANCER IMMUNOTHERAPY

Definition: Cancer immunotherapy is a type of cancer treatment that harnesses and enhances the body's immune system to recognize and destroy cancer cells. Unlike conventional therapies like chemotherapy and radiation, immunotherapy specifically targets the immune system to fight cancer, often with fewer side effects.

Types of Immunotherapy

- Checkpoint Inhibitors
- CAR-T Cell Therapy
- Monoclonal Antibodies (mAbs)
- Cancer Vaccines
- Cytokine Therapy
- Oncolytic Virus Therapy

1. Checkpoint Inhibitors:

- **Mechanism**: These drugs block immune checkpoints, proteins on immune cells that act as brakes, preventing them from attacking normal cells. Cancer cells often exploit these checkpoints to avoid detection. Checkpoint inhibitors release these brakes, allowing the immune system to recognize and attack cancer cells.
- **Examples**:
  - **PD-1/PD-L1 inhibitors** (e.g., Pembrolizumab, Nivolumab): Prevent cancer cells from "turning off" T-cells.
  - **CTLA-4 inhibitors** (e.g., Ipilimumab): Boost the immune response against cancer cells.
- **Cancers Treated**: Melanoma, lung cancer, bladder cancer.

2. CAR-T Cell Therapy:

- **Mechanism**: In CAR-T therapy, a patient's T cells are collected and genetically engineered to express a receptor (chimeric antigen receptor, CAR) that specifically targets cancer cells. These modified T cells are then infused back into the patient to attack the cancer.
- **Examples**:
  - Approved for certain types of leukemia and lymphoma.
- **Cancers Treated**: Acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma.

Monoclonal Antibodies (mAbs):

- **Mechanism**: Monoclonal antibodies are laboratory-made molecules that can bind to specific targets on cancer cells. They can mark cancer cells for destruction by the immune system or block growth signals.
- **Examples**:
  - **Rituximab** (targets CD20 in lymphoma),
  - **Trastuzumab** (Targets HER2-positive breast cancer).
- **Cancers Treated**: Breast cancer, lymphoma, colorectal cancer.

Cancer Vaccines:

- **Mechanism**: These vaccines work by stimulating the immune system to attack cancer cells. They can be **preventive** (e.g., HPV vaccine) **or therapeutic,** designed to treat existing cancers by enhancing the immune response to tumor antigens.
- **Examples**:
  - **Provenge** (treatment for prostate cancer).
  - **HPV Vaccine** (prevention of cervical and other HPV-related cancers).
- **Cancers Treated**: Prostate cancer, cervical cancer (preventive).

Cytokine Therapy:

- **Mechanism**: Cytokines are signaling proteins that help regulate the immune system. In cancer therapy, synthetic versions of these proteins (such as interleukins and interferons) are used to boost immune responses against cancer cells.
- **Examples**:
  - **Interleukin-2 (IL-2)Stimulate immune cells to attack cancer.**,
  - **Interferon-alpha**(Increase the number and activity of white blood cells.)
- **Cancers Treated**: Kidney cancer, melanoma.

Oncolytic Virus Therapy:

- **Mechanism**: Oncolytic viruses are genetically engineered or naturally occurring viruses that selectively infect and kill cancer cells. These viruses can also stimulate an immune response against the tumor.
- **Example**:
  - **Talimogene laherparepvec (T-VEC)**, used for melanoma.

Benefits of Immunotherapy:

1. **Targeted Action**: Immunotherapy targets cancer cells more specifically compared to chemotherapy or radiation.
2. **Durability**: Immune memory allows for long-term protection against cancer recurrence.
3. **Combination Potential**: Can be combined with other therapies like chemotherapy, radiation, or targeted therapies to enhance overall efficacy.

Limitations and Side Effects:

1. **Autoimmune Reactions**: Since immunotherapy boosts the immune system, it can sometimes lead to the immune system attacking normal cells, causing autoimmune-like symptoms.
    - **Examples of Side Effects**:
        - Fatigue
        - Skin rashes
        - Diarrhea
        - Inflammation of organs (e.g., colitis, pneumonitis)
2. **Not Effective for All Cancers**: Some cancers are less responsive to immunotherapy, and response rates can vary based on tumor type and individual immune system variability.
3. **Delayed Response**: Immunotherapy may take longer to show effectiveness compared to traditional therapies.