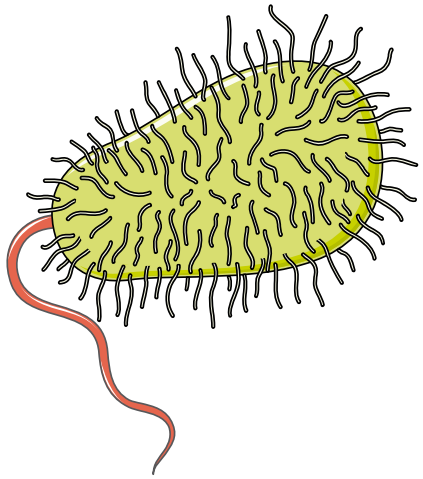
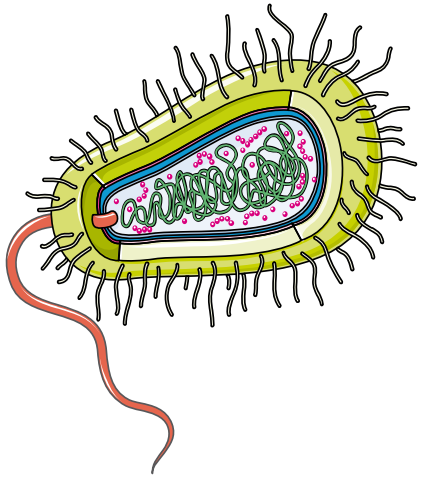
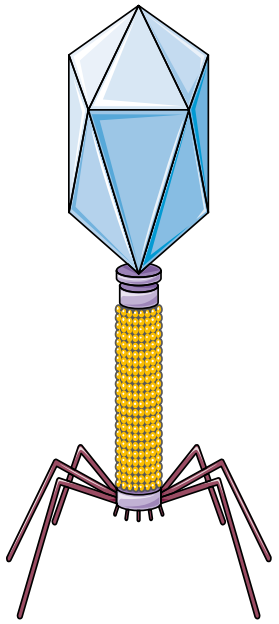
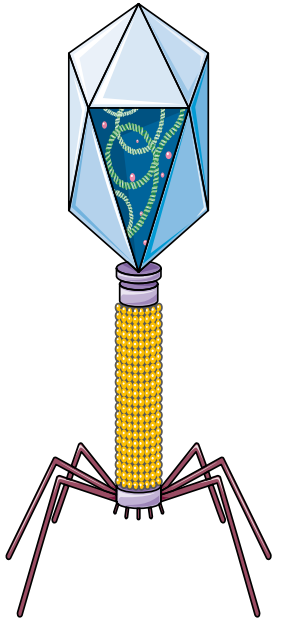
Chapter 6: Role and Components of Immune System

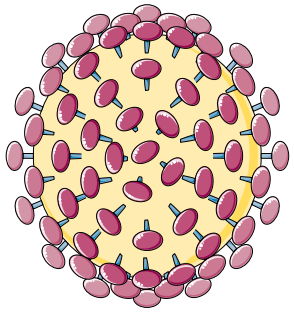
Introduction:

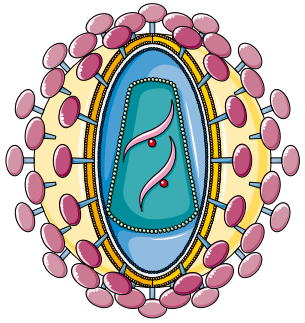












Introduction:

- Pathogens, which are infectious particles such as bacteria, viruses, worms and parasites exist enormously all around us. However, it is very rare we fall ill. Why?
- **Body 1st line of defense!**
  - skin,
  - Saliva
  - tears
  - acid in stomach
  - Normal flora

What if the pathogen crossed the 1st line of defense?

- If the infectious particle crossed the natural barrier, the immune system intervenes.

What is immune system made up of and what is its function?

- Immune System is made up of **organs** and **cells** that secrete **molecules**.
- **Role:** The immune system **distinguishes between self and non self**, and **neutralizes and/or eliminates non-self-antigens** recognized as foreign.

How the immune system does distinguish the self from non-self?

- The body possess self-markers, which present the identity of individual. There are 2 types of markers: **MHC** and **Blood group**

Document 1: HLA: a major “self” marker

- **Types of Graft**
  - **What are the 3 types of graft?**
  - Auto graft: the donor and the recipient are the same individual
  - Isograft: the donor and the recipient are genetically identical (example: identical twins)
  - Allograft: the donor and the recipient are genetically different

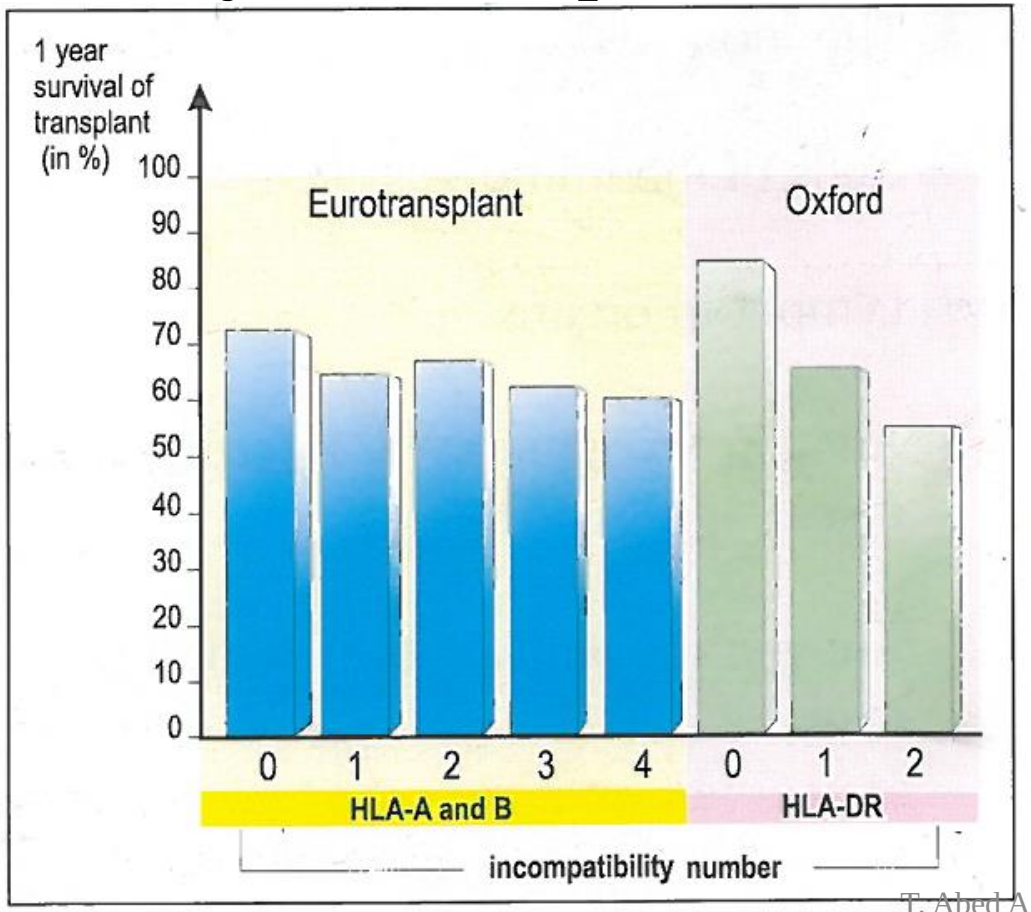
Interpret doc.a p:114

types of the graft	aspects of the graft		
	2 days later	one week later	15 days later
Autograft 	vascularization appears around the graft (pinkish aspect)	graft is integrated into neighboring cells	graft is accepted
Isograft 	vascularization appears around the graft (pinkish aspect)	graft is integrated into neighboring cells	graft is accepted
Allograft 	vascularization appears around the graft (pinkish aspect)	redness and edemas appear around the graft	graft turns black, dry and is rejected

- In the 3 cases, autograft, isograft and allograft, the grafts show vascularization around them after 2 days of grafting. while after one week, only in case of auto and isograft the graft is integrated with the neighboring cells while redness and edema appear in the case of allograft; leading finally to acceptance in case of autograft and isograft while rejected in allograft
- **This means that** grafted organ is accepted only in case of autograft and isograft (between genetically identical individuals) while rejected in allograft (between genetically different individuals), and the reaction of body toward graft starts after 7 days.

What is the factor responsible of graft acceptance/rejection?

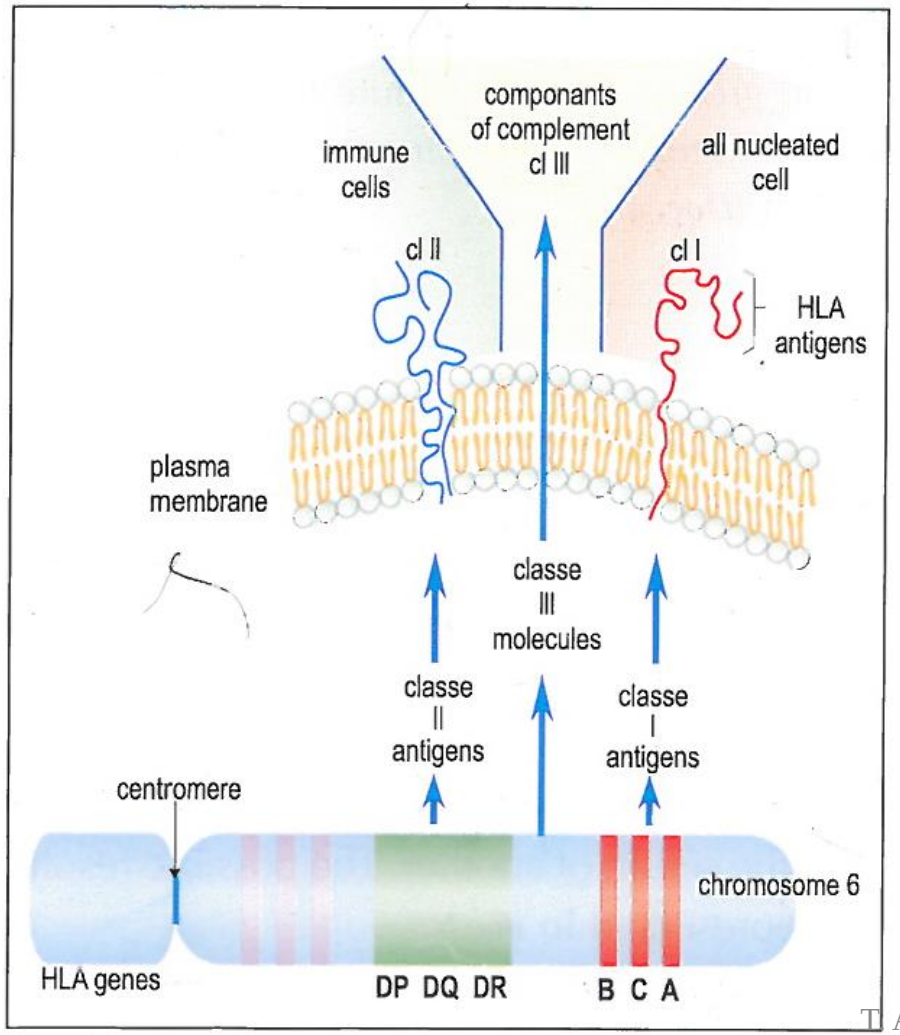
- **Analyze doc. b: p: 114 + Conclude**



- In Euro-transplant study, the percentage of survival of transplant is 73% when the number of incompatibilities in HLA-A and HLA-B between the donor and the recipient is zero. When the number of incompatibilities increases to 4, the percentage of transplant survival decreases to 60%.
- **Similarly**, in Oxford study, the percentage of survival of transplant is 85% when the number of incompatibilities in HLA-DR between the donor and the recipient is zero. When the number of incompatibilities increases to 2, the percentage of transplant survival decreases to 55%. T
- his indicates that the percentage of transplant survival is inversely proportional to the number of incompatibilities in HLA-DR between the donor and recipient.

- **Conclusion:** We can conclude that the graft acceptance (as in autograft and isograft) or rejection (as in allograft) depends on the percentage of compatibility of HLA between the donor and the recipient

Organization and Expression of MHC:

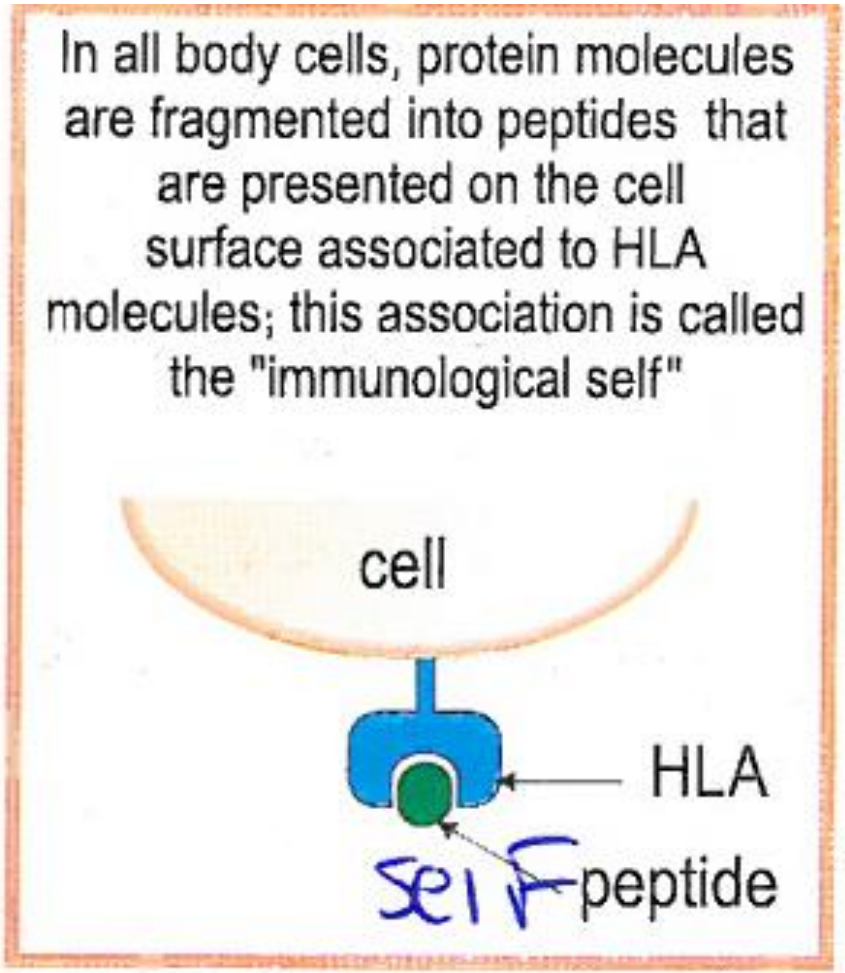


- MHC is membrane glycoprotein coded by 6 highly polymorphic genes.
- There are 2 classes of MHC:
  - **MHC class I:**
    - **coded by genes:** A, B and C.
    - **Expressed by:** all <u>nucleated</u> cells.
  - **MHC class II:**
    - **coded by genes:** D_P, D_Q, $D_{R:}$
    - **Expressed by: some** immune cells (macrophage)

Organization and Expression of MHC:

- MHC is highly polymorphic since:
  - Each gene of the genes coding for MHC have high number of alleles
  - All these alleles are codominant.
- The genes of MHC are absolutely linked on chromosome 6 and are transmitted from parents to children as a block.
- Each set of MHC genes on a chromosome is called haplotype. So each individual inherits 1 haplotype from each of his parents
- That is why probability for 2 siblings to have same MHC is ¼.

What is immunological self?



Doc.f Immunological "self".

Document 3: The non self

Introduction:

- The non- self are every that are not considered as a self

So what is a self?

What is an immunological self?

- An immunological self is considered as self by immune system and thus is tolerated.
- In all nucleated body cells protein molecules are fragmented into peptides that are presented on the cell surface associated to HLA molecules: this association is called “immunological self”
- **So immunological self = HLA + self-peptide associated to it**
- Moreover, **agglutinogens present on self-red blood** cells are self-molecules

Pathogens:

- **Definition:** Pathogens are infectious agents that can cause infect other living organism (invade and grow)

- **Types of pathogens:**
  - Non microscopic such as worms
  - Microscopic: bacteria, viruses, fungi, protozoa. **Note:** virus is not a living thing.

Pathogens:

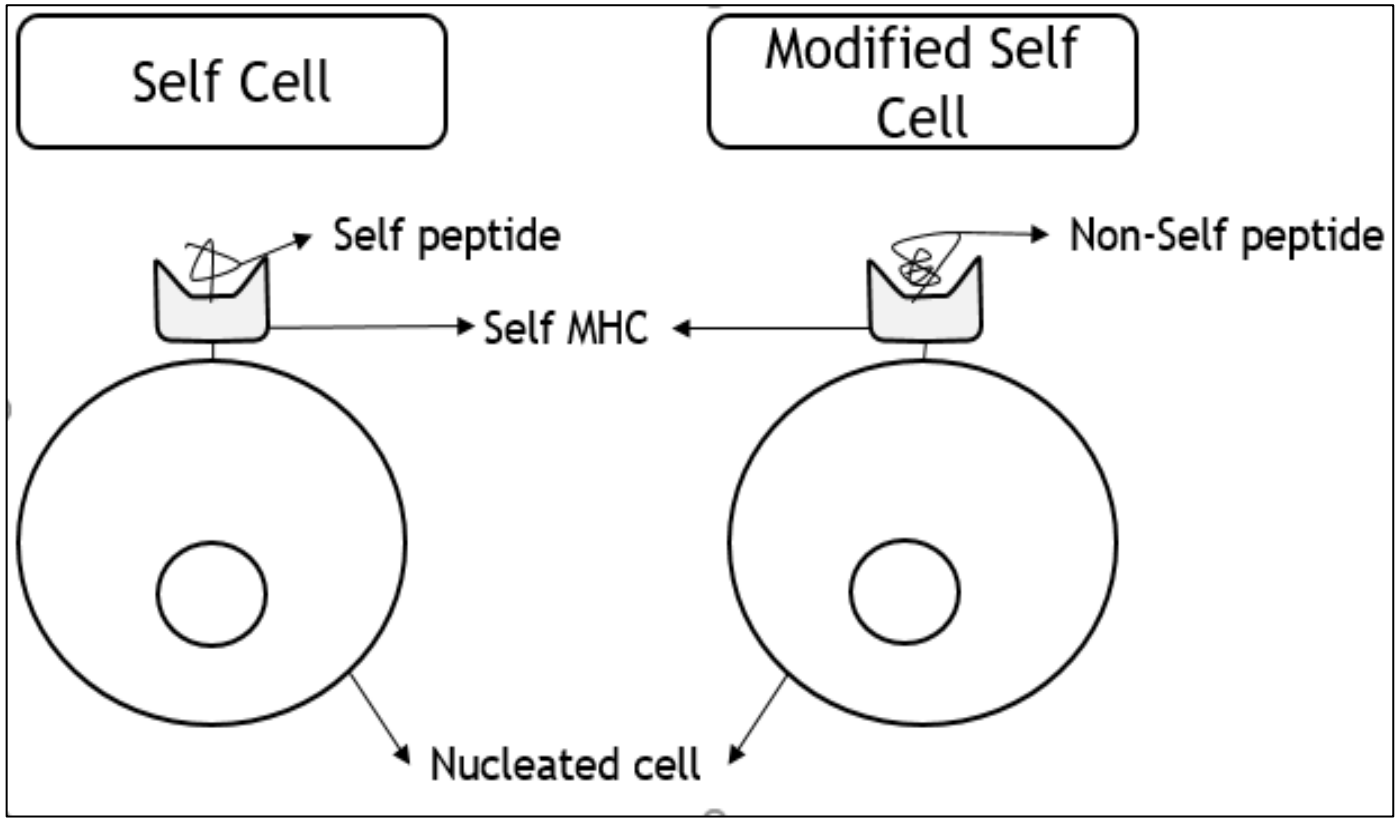
- **Ways of transmission of pathogens:**
  - **Direct:**
    - Through blood
    - Direct skin contact
    - Placenta (from mother to fetus)
    - Sexual contact
  - **Indirect:**
    - Food
    - Air
    - Water

Antigen:

- **Definition:** Is a large molecule (protein or complex carbohydrate) that can trigger an immune response
- **Types of antigens:**

Free:	**Carried by a cell:**	**Carried by particle**
Toxin, snake venom, vaccine	• MHC (in case of allograft) • Agglutinogen (RBC) in case of wrong blood transfusion • Antigen carried by bacteria • Important: Ag by modified self. Example: tumor cell, infected cell. These cells carry self MHC + non- self peptide (see figure below)	Virus Pollen grain

Modified Self cell: is considered as non- self since it expresses a non- self peptide, or a peptide that is not usually expressed by body cell (due to mutation)



Document 4: Cells of the Immune System

Pluripotent stem cell

Myeloid stem cells

Lymphoid stem cells

Granulocytes:
- Rich in granules which could be acidic basic or neutral
- They have multilobed nucleus

Basophil

Role: Amplification of allergic reaction

neutrophil

Role: Phagocytosis of bacteria

Eosinophil

Role: Phagocytosis of immune complex (antigen-antibody complex)

Mast cells:

- Rich in granules called histamine
- They have round nucleus
- **Role:** Secrete histamine which play role in allergic reaction

Monocytes

Horse shoe shaped nucleus

Macrophage

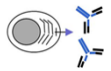
Monocytes are transformed into macrophage which are
Role: involved in pahgocytosis

Lymphocytes: round nucleus

B-Lymphocytes

has membrane bound antibody.

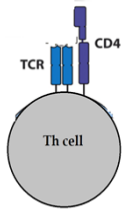
Plasma cell:



which has developed organelles (RER and golgi body)
Role: secrete antibodies

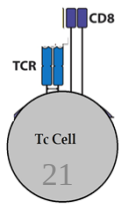
T- Lymphocytes

T helper (T4)
has TCR receptor and CD4.
Role:
Activation of T8 and B lymphocytes



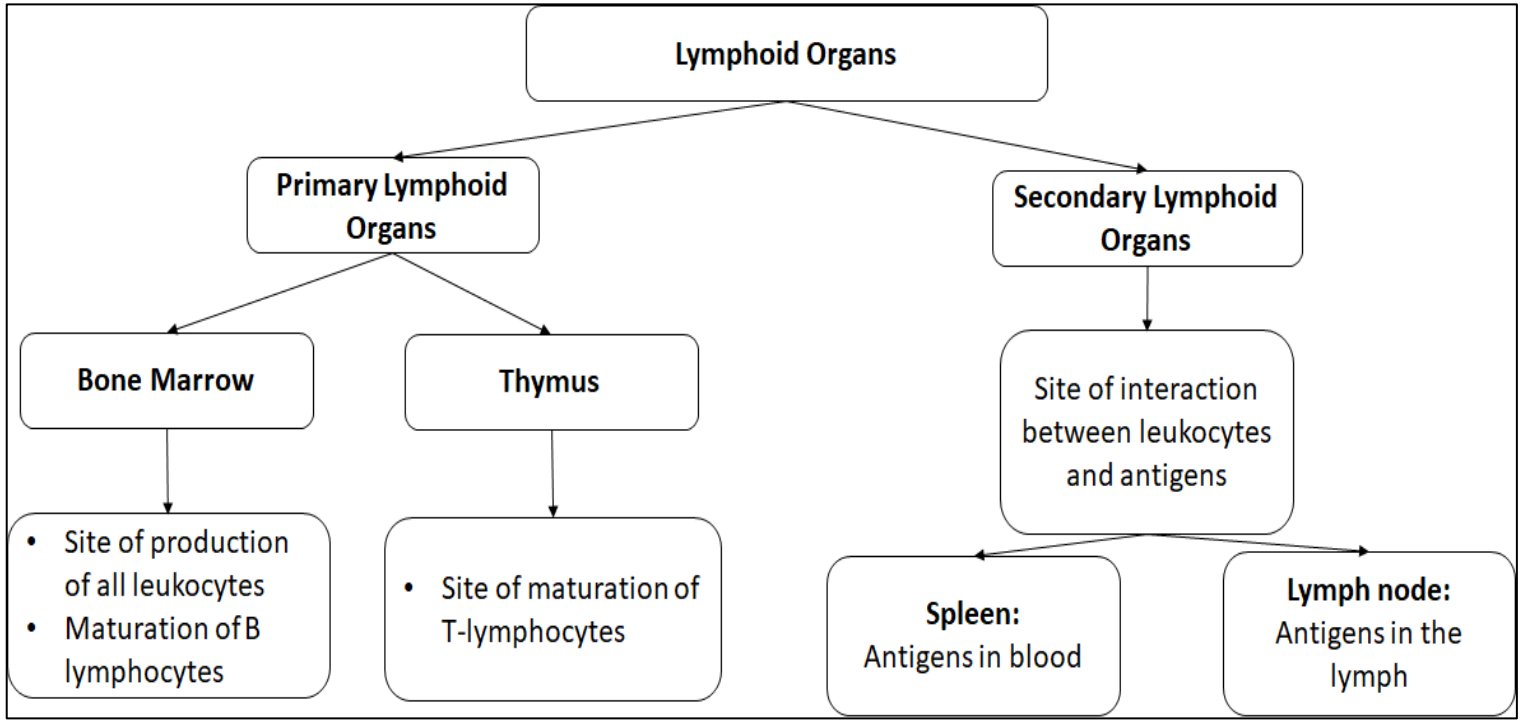
Tc (T8)
Has TCR receptor and CD8

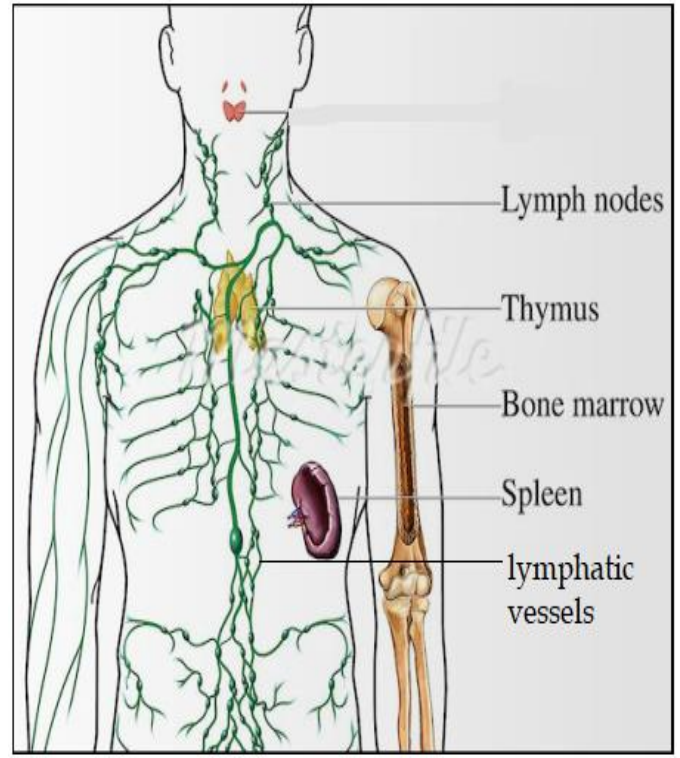
Role: Secrete chemicals that kill infected cells



The plasma cell has more Golgi body, more RER (rough endoplasmic reticulum) and larger cytoplasm. Thus it is more adapted to protein synthesis (it is now able to produce antibodies or immunoglobulins)

Document 5: Lymphoid Organs





Functions of primary lymphoid organs.

- **Interpret document (a) p: 123 then conclude**

Mice	Experiment realized	Result obtained
A	Irradiation + graft of bone marrow	Production of B and T lymphocytes
B	Ablation of the thymus + rradiation + graft of bone marrow	Production of immature T lymphocytes and mature B lymphocytes
C	Ablation of the thymus + irradiation + graft of thymus	There is no production of T or B lymphocytes

- Exp. 1 & 2: Mice of lot A, which still have their thymus, and which were subject to bone marrow graft, produce B and T lymphocytes, whereas mice of lot B, which only have bone marrow grafted, produce mature B lymphocytes and immature T lymphocyte. **This indicates that T lymphocyte maturation occurs in the thymus**, **while that of B lymphocytes occurs in the bone marrow.**
- Exp. 1 & 3: unlike lot A, mice of lot c, which were deprived of the bone marrow but have a grafted thymus, do not produce T or B lymphocytes. **This indicates that T and B lymphocytes are produced in the bone marrow**.

- **Conclusion:**
- We conclude that bone marrow is responsible of production of B and T lymphocytes in addition to maturation of B lymphocytes. And Thymus is responsible of maturation of T lymphocytes.

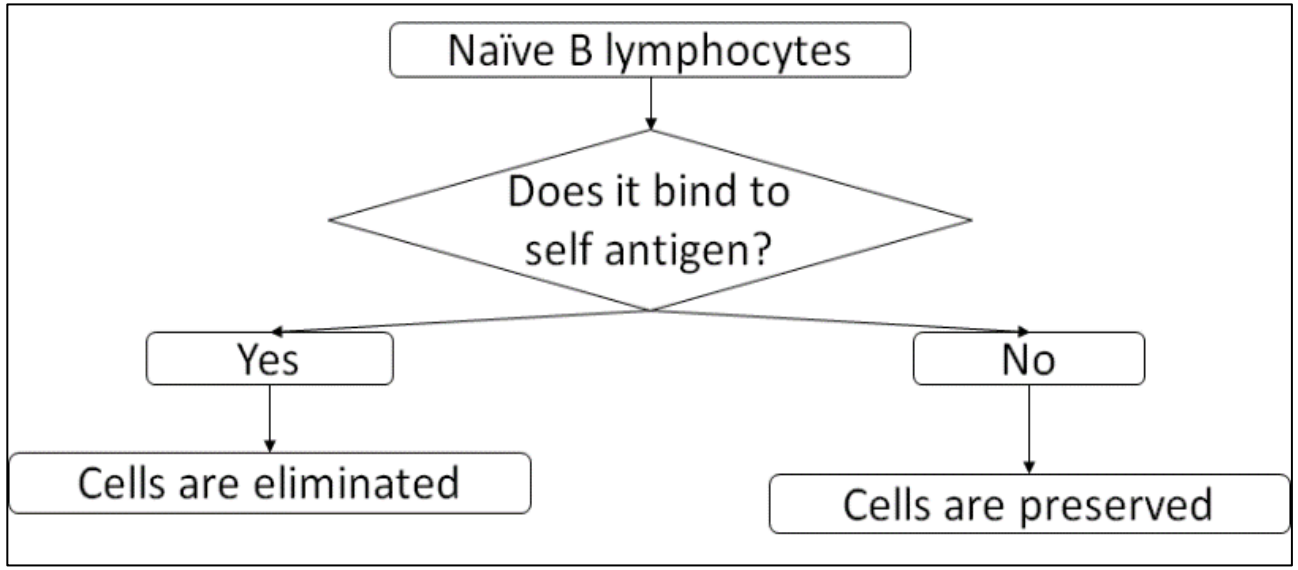
- **Note: Nude mice do not have a thymus: they will have mature B cells since their bone marrow is normal but due to the absence of thymus, their T cells are not matured.**

Maturation of lymphocytes

- **Definition:**
- Genetic mechanism by which lymphocytes become **immunocompetent, that is functional. Their receptors (Ab or TCR) bind only to non-self-antigens or peptides. Tolerate self and attack non-self.**

Mechanism of maturation

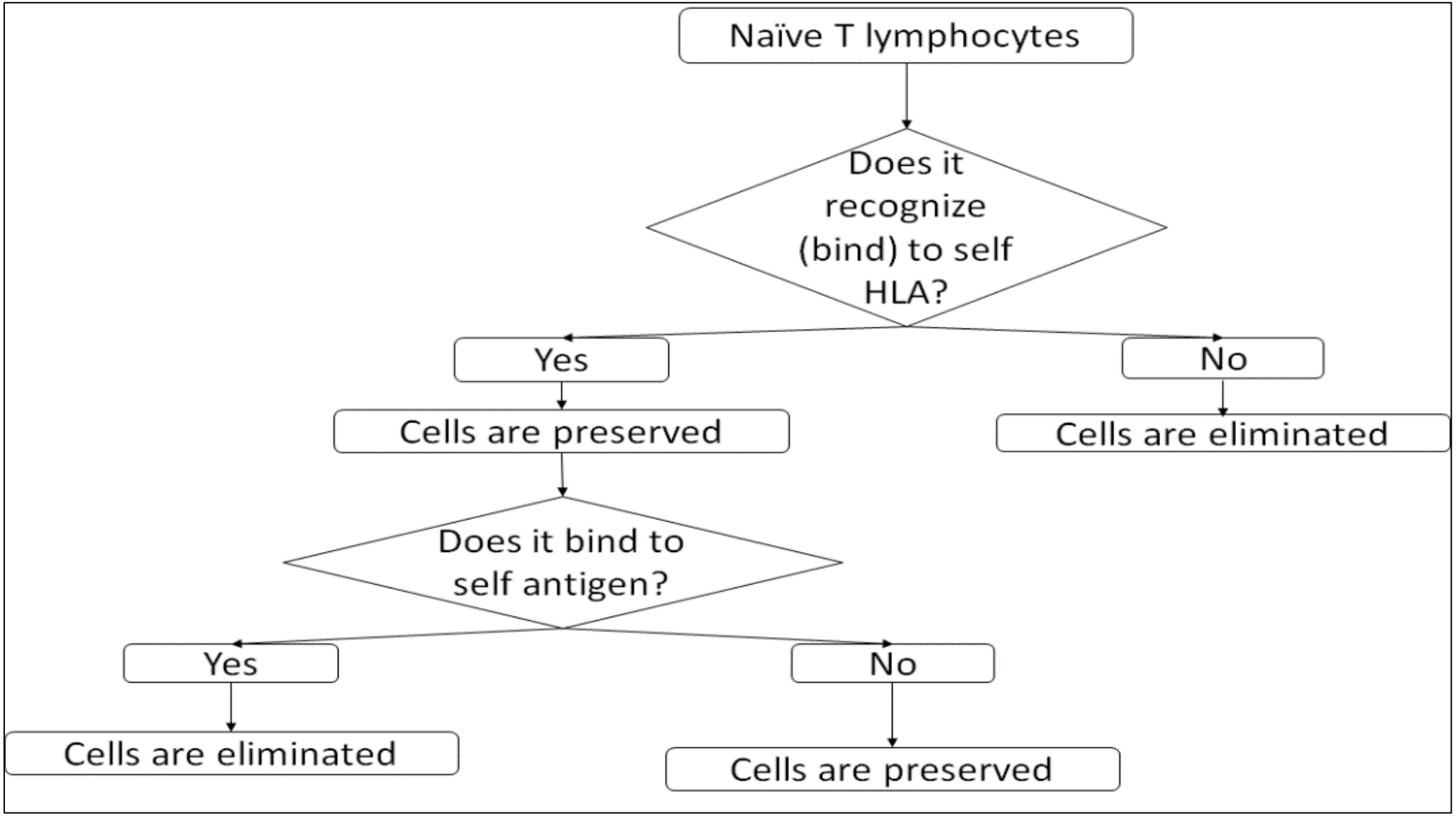
- **Maturation of B lymphocytes**
- Maturation of B lymphocytes occur in bone marrow by one step of selection: B lymphocytes that have receptors against self-antigens are eliminated, while others are preserved



Mechanism of maturation

- **Maturation of T lymphocytes: By double selection**
- T lymphocytes present in the body should recognize **self-HLA** and should not recognize **self-peptide**. If T lymphocytes can bind against cells having self-HLA and self-peptide then they can react against self. That is why the maturation of T lymphocytes occurs by a **double selection:**

  - 1st T-lymphocytes whose receptors can bind to HLA molecules of self are preserved while the others are eliminated.
  - 2nd The remained T lymphocytes are selected in second step: if they bind to self-peptide, they will be eliminated while others are preserved.


Naïve T lymphocytes
Does it recognize (bind) to self HLA?
Yes
No
Cells are preserved
Cells are eliminated
Does it bind to self antigen?
Yes
No
Cells are eliminated
Cells are preserved

Secondary lymphoid organs:

- **Lymph nodes:** lymph nodes are distributed around lymphatic vessel that contain lymph which is a colorless liquid collected from between the cells .
- **Role:** lymph nodes are the site of triggering of the specific immune response against the antigens brought by the lymph from the infected tissues.

- **Spleen:** Is the secondary lymphoid organ that is connected to the blood vessels.
- **Role:** The site of triggering of the Immune reactions against the antigens brought by the blood circulation

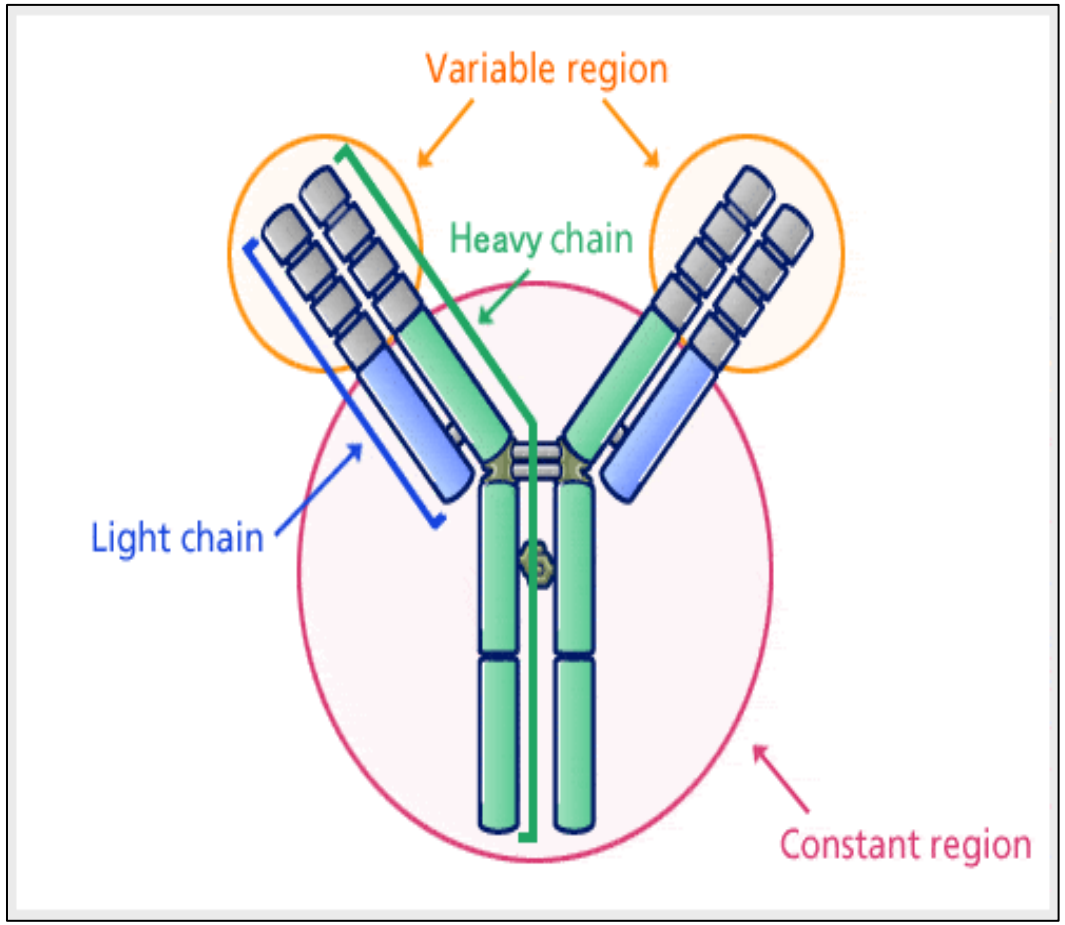
Document 6: Antigen Recognition by B-lymphocytes:

- B-lymphocytes carry a **membrane receptor** called antibody **(immunoglobulin)** which **can recognize cellular antigen** (such as antigens on bacteria) or **on a particle** (virus), **or soluble antigens** (such as bacterial toxins)

- Antibodies **can’t** recognize the antigens within HLA.

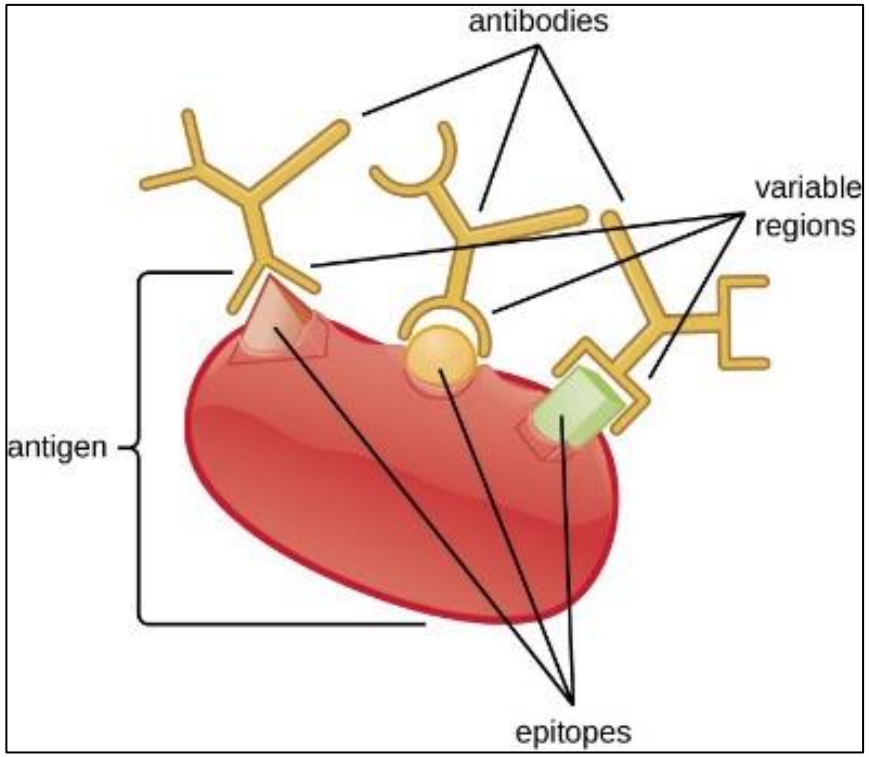
Structure of an antibody and its classes

- Consists of four polypeptide chains: 2 heavy and 2 light
- It has (more or less) constant region (lower part) and variable region (upper part)
- The variable region differ from one antibody to recognize specifically a part of an antigen called **epitope (antigenic determinant)** and binds to it
- It has two antigen binding sites **(the binding sites recognize the same epitope)**
- The constant region has slight variations that determine the different classes of antibodies **IgM, IgA, IgG, IgE, IgD** (document d p: 126)**.**



Specificity of Antibody:

- **antibody** does not recognize the whole body of antigen but it **recognizes only the epitope**.
- An antigen may have many different epitopes, so different types of antibodies can bind to it



Application:

1. **2 different antibodies can bind to the same antigen. Explain**

2. **The same antibody can bind to 2 different antigens. Explain**

1. **2 different antibodies can bind to the same antigen. Explain**

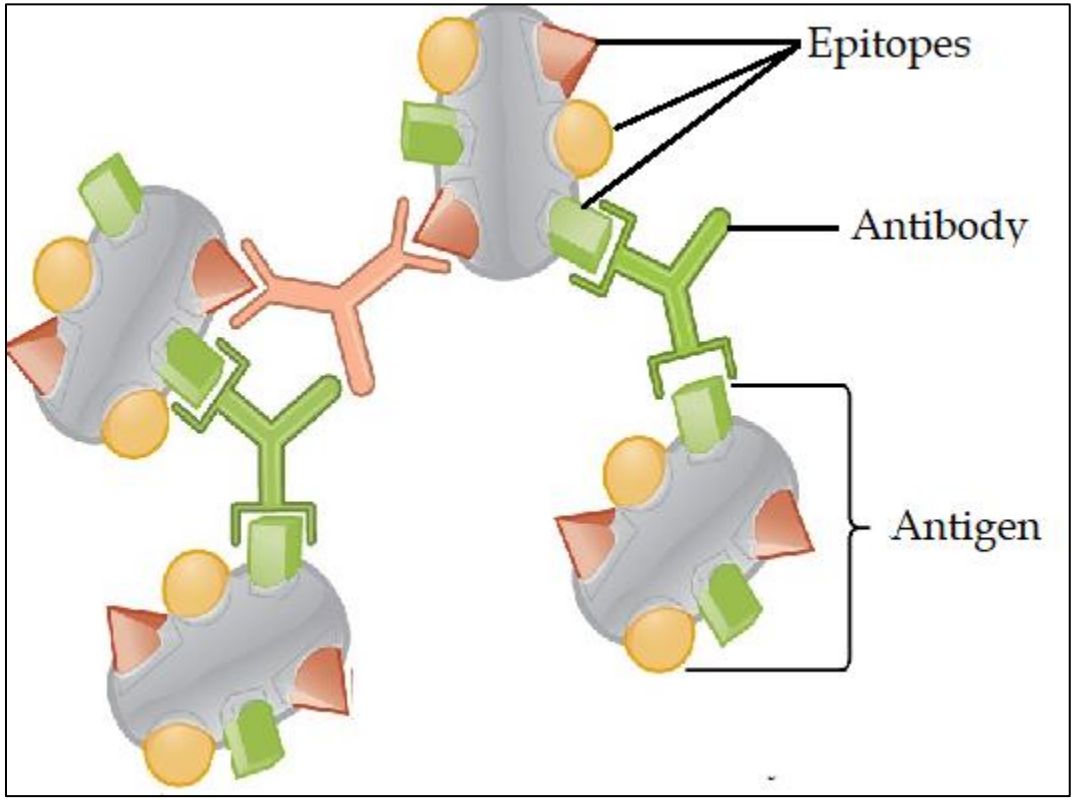
Because this antigen has 2 different epitopes so 2 different antibodies each that is specific to one epitope can bind.

2. **The same antibody can bind to 2 different antigens. Explain**

Because the 2 different antigens have a common epitope which can be recognized by the same antibody.

- **Note: The same B lymphocyte can produce only an antibody that is specific to one epitope.**
  So all antibodies secreted by same B lymphocyte have same variable region

- **Immune Complex:**
  Agglutination is the binding of many antibodies on many antigens leading to formation of the immune complex

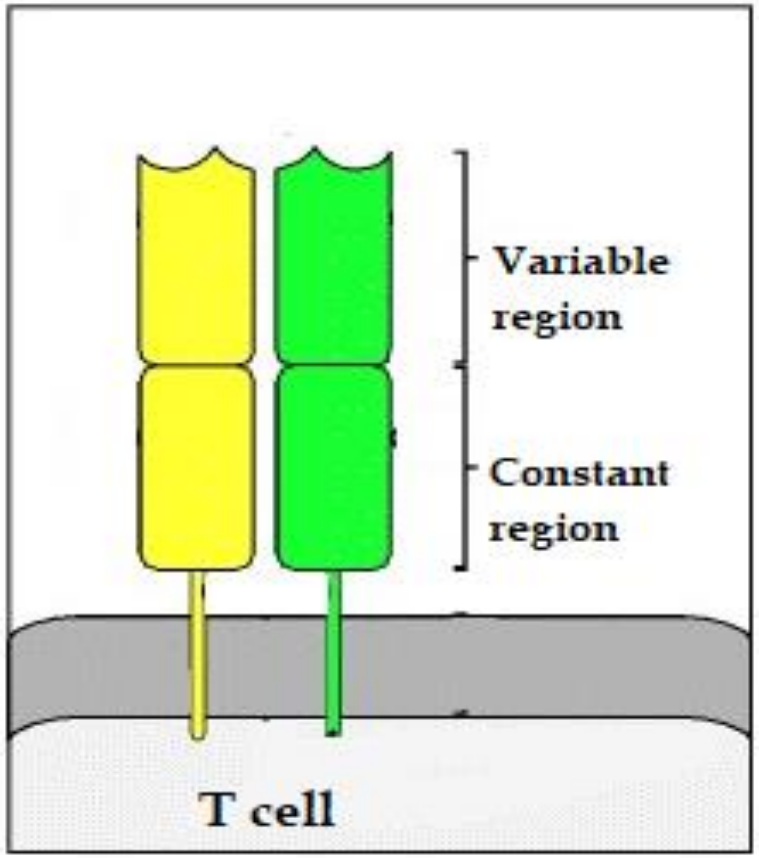


Document 7: Antigen Recognition by T lymphocytes

- T lymphocytes can’t recognize the free antigens, they **can recognize only the antigens present within HLA markers**

Molecular Structure of TCR

- TCR consists of two polypeptide chains, the upper region is variable and the lower one in constant. The 2 chains together **form a single antigen binding site**

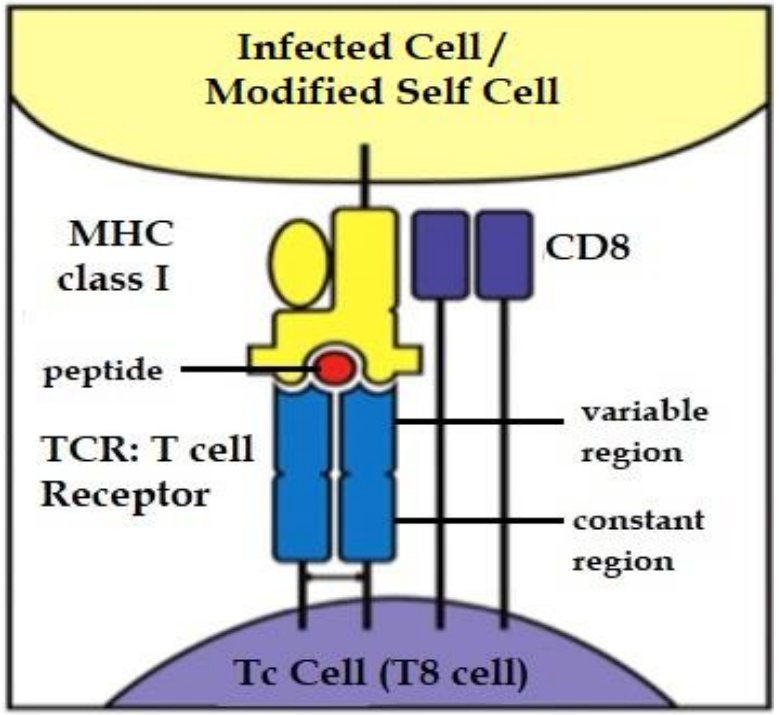


Double Recognition by TCR:

- Unlike antibody, a TCR can’t recognize a soluble or free antigens, it can only recognize the antigen or the peptide present within HLA in a way that the **TCR binds the HLA and peptide within it.** This is known as **double recognition**

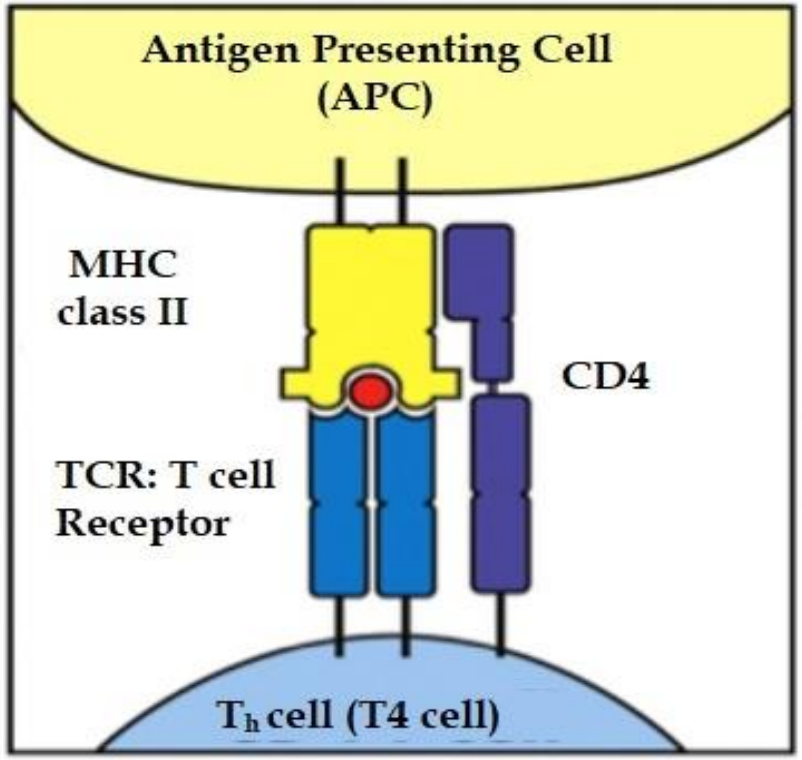
Double recognition by T8 cell

- CD8 of Tc cell binds selectively to class I HLA, and this is why T8 (Tc) cells recognize class I HLA displaying the peptide.



Double recognition of T4 cells

- CD4 binds selectively to Class II HLA and this is why T4 (T_h) recognize class II HLA displaying the peptide

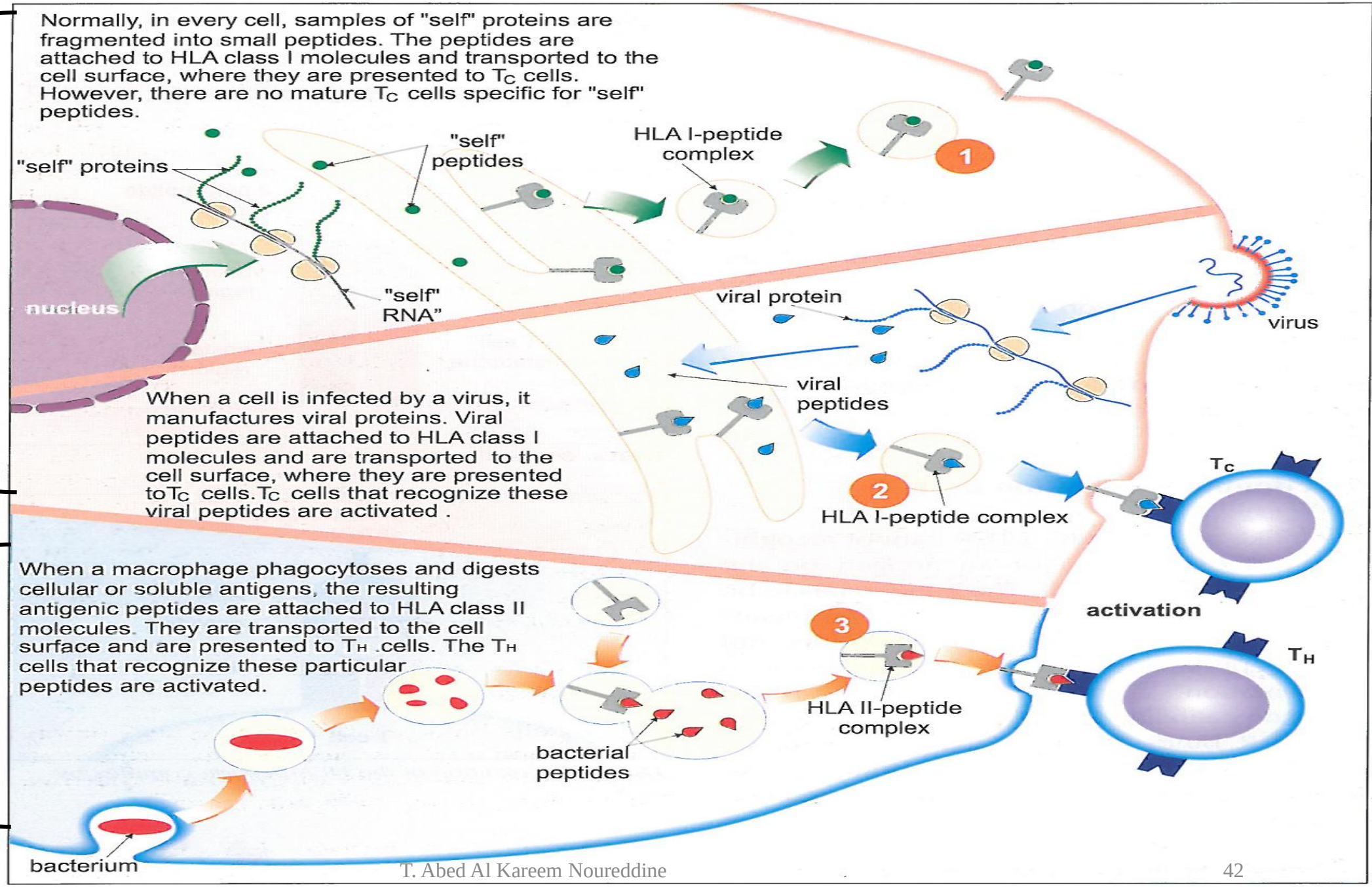


Peptide Presentation to T lymphocyte: Refer to doc. d p: 128

- How does a cell know where to express the non self peptide, on MHC I or MHC II?
- There are 2 cases depending on the pathway of peptide presentation:
  - **Endogenous**
  - **Exogenous**

Endogenous pathway

Exogenous pathway



- **Peptide presentation from Endogenous Pathway:** Peptide presented on HLA is synthesized within cell
  - **In case of self-cell:** Any nucleated self-cell has on its surface HLA I markers and self-peptide within it, but there is no mature T_C cells that can recognize and attack these cells. (Because during maturation process all T cell reactive against self-peptides are eliminated).
  - **In the case virus infected cell, or modified self:** In this case, self-cells start secretion of viral peptides or non-self-peptide instead of self-peptide, which are then associated within HLA I on the surface. Such cells are recognized through double recognition of T_C cells to destroy them

- **Peptide presentation from Exogenous pathway:** The peptide is synthesized outside the cell
  - **In case of phagocytosis:** When macrophage digests a bacterium or antigen, the remaining peptide of the digested bacterium or antigen is carried to the surface of macrophage HLA II to be recognized by T_H cells through double recognition. **Note: macrophage that expresses the non-self-peptide on its HLA II is called Antigen Presenting Cell (APC).**

Application:

- We add to a mixture of B_L and T_L a radioactive Antigen. The radioactivity appears on the surface of some lymphocytes (they become labelled) and not the others.
    - **Identify these labelled lymphocytes (are they B_L or T_L?)**
- We add macrophages to the preceding medium; these macrophages become labeled then after certain time some lymphocytes become also labelled.
    - **Explain then identify these labeled lymphocytes**

1) They are the B_L since only B_L can bind to native antigen without being processed and presented while T_L cant bind to a native Ag but it should be presented on MHC.
2) Macrophages become labeled because it phagocytes this labeled antigen then after fragmentation the resulting labeled peptide is presented on its MHC II becoming an APC. Some lymphocytes become labeled; these are the T4 lymphocytes that make a double recognition using their TCR with the specific peptide presented on these macrophages