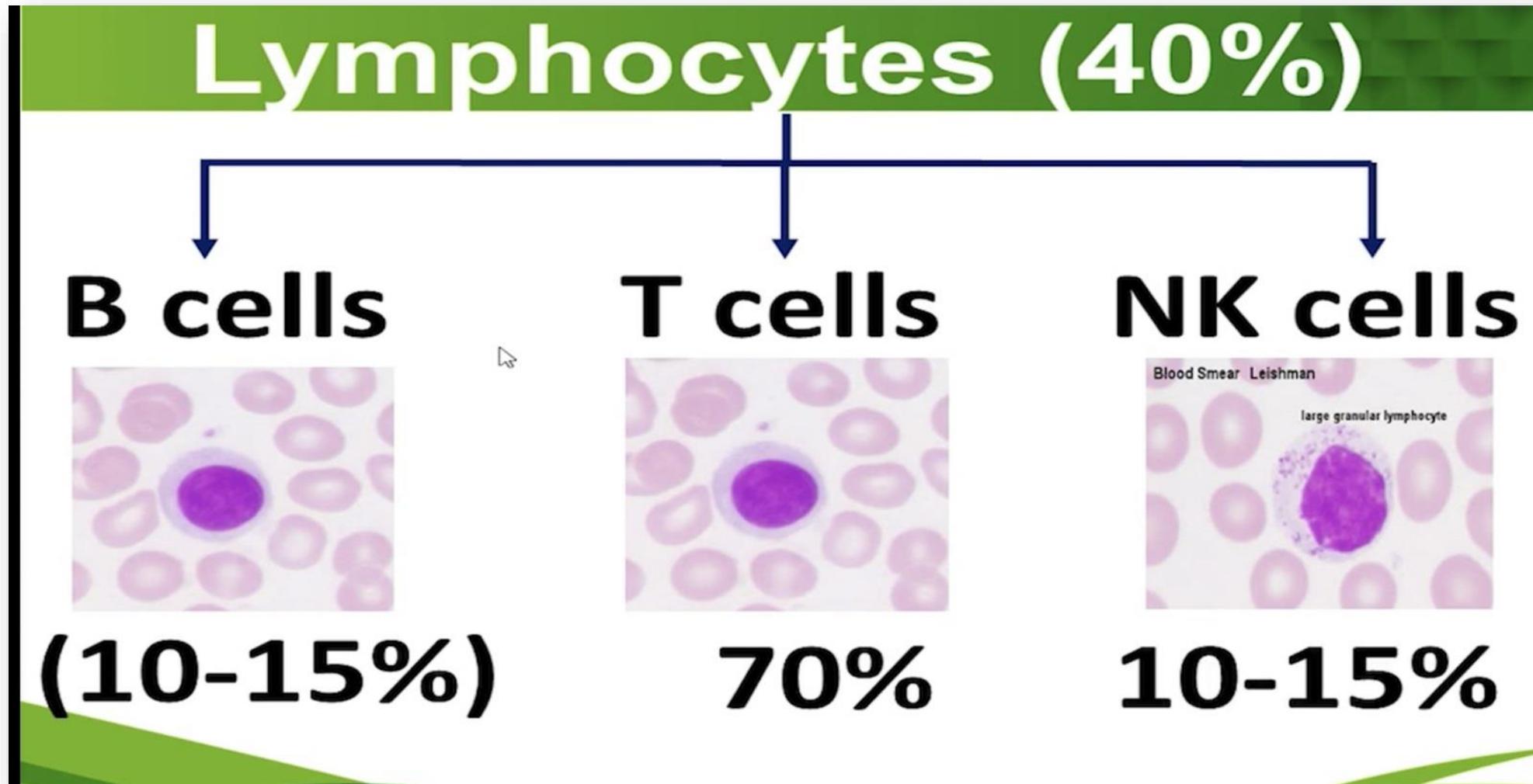
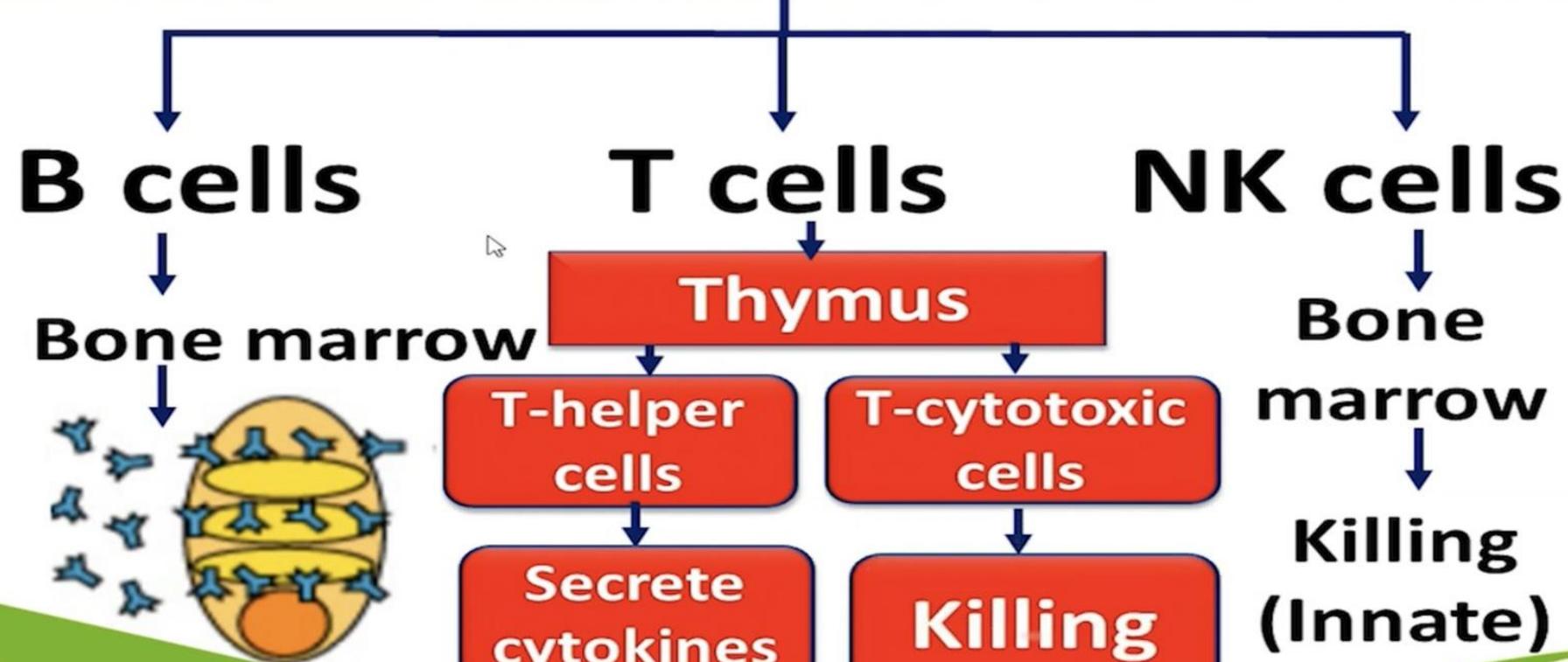


If you want to understand the development and function of three types of lymphocytes (B cells, T cells and NK cells), please read this lecture.



Lymphocytes



Journey of lymphocytes

I) B cells

- Development
- Located
- Life span
- Receptor
- Function



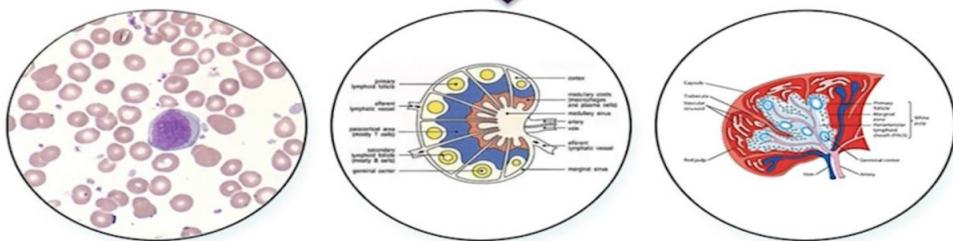
□ B cell development

Maturation in
Bone Marrow



Reside in

□ B cells



□ B cell development

Stem cell



Pro B cell



Pre B cell

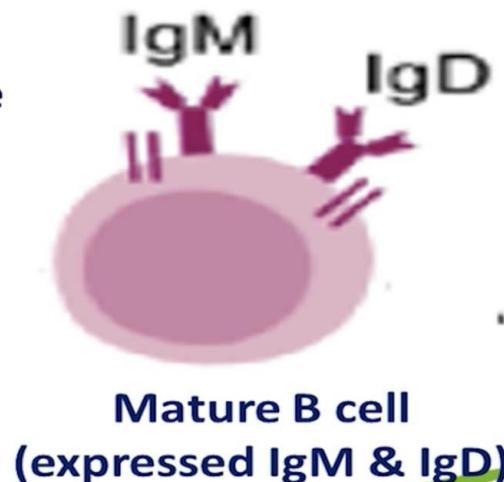


Immature

B cell (Expressed
IgM)



Tyrosine kinase



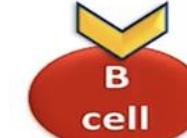
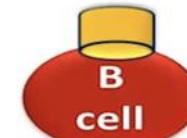
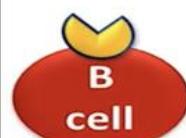
□ B cell development



➤ Each B cell has
unique
antibody

□ B cell development

➤ DNA
rearrangement



B cell development

- Antibody
- Heavy chain



- Light chain



B cell development

- Heavy chain (VDJ)

V1 V2 V3 vn D1 D2 Dn J1 J2 Jn C

RAG1 & RAG2

(Recombinant activating gene



Recombinase enzyme

- Light chain VJ

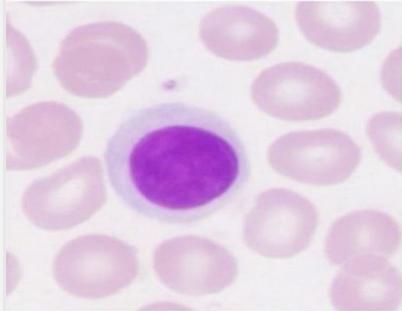
V1 V2 V3 vn J1 J2 Jn C



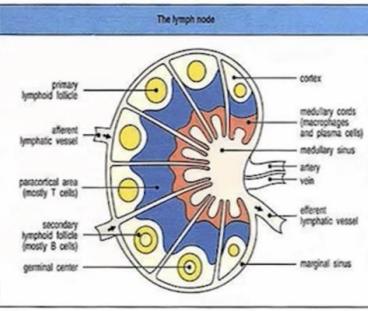
In bone marrow B cells will be synthesized (millions) and pass through different stages to become mature (diverse) due to DNA arrangement in genes responsible for variable region of both heavy and light chain of BCR (IgM and IgD). These mature B cells require to be educated or selected before leaving B.M. The process of B cell education is called negative selection. There are cells in bone marrow which present all self proteins on their surfaces and presented to mature B cells, so mature B cells which not bind with these self proteins will be selected and leave B.M, while those will bind will be killed by apoptosis and this process called negative selection

Located of B cells

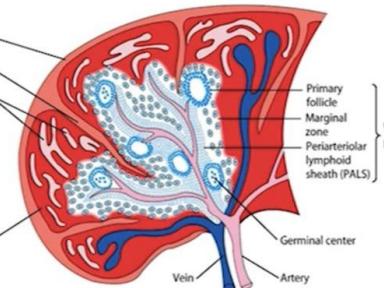
Peripheral blood



Lymph nodes

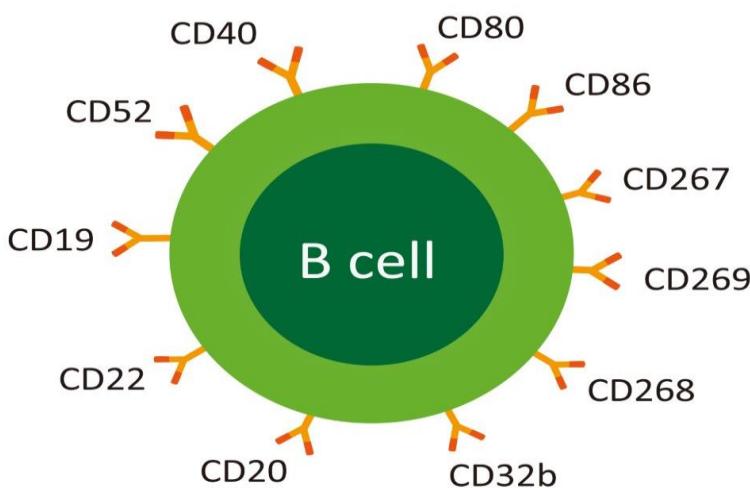
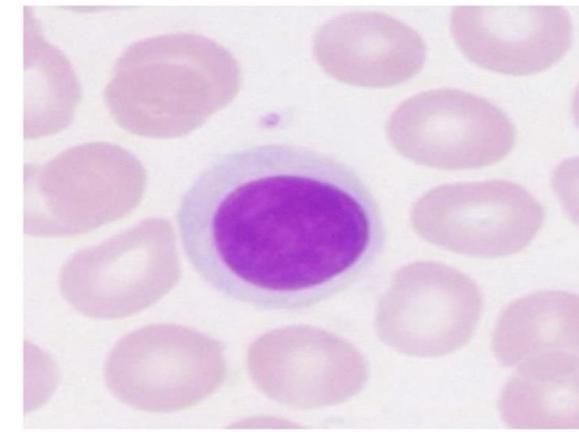


Spleen



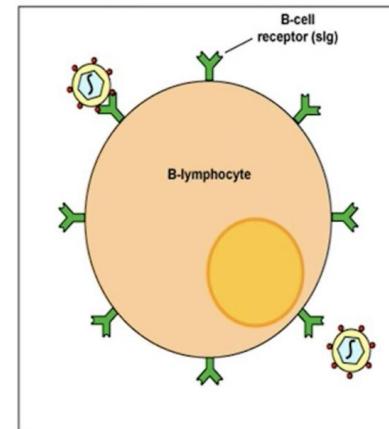
Life span of B cells

From 4 to 9 days!



Receptors of B cells

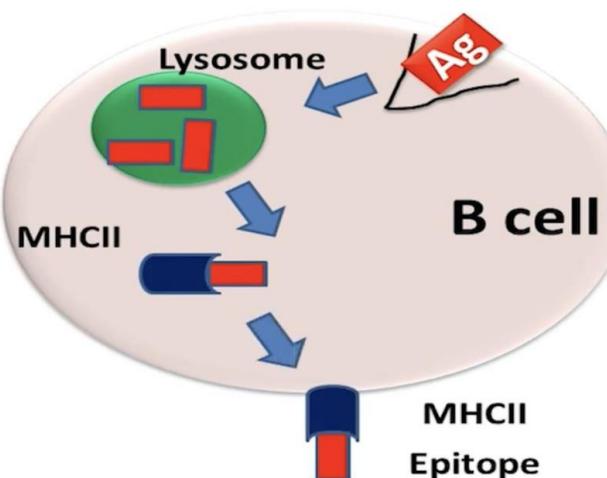
- 1) IgM & IgD (BCR)
- 2) R of complement
- 3) Fc of Ig
- 4) MHC-II
- 5) B7



Function of B cell

1

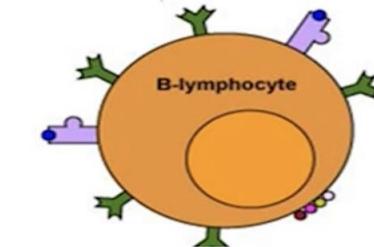
Antigen
Presentation
(APC)



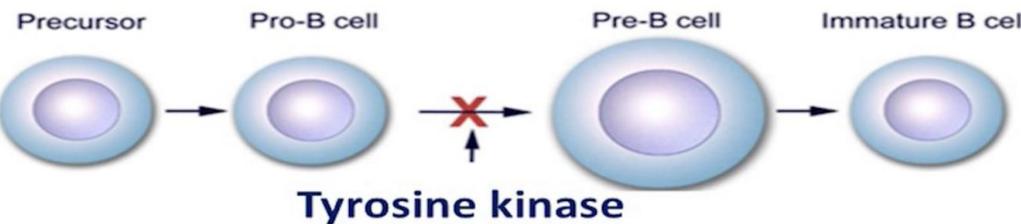
Function of B cell

2

They differentiate
into plasma cells
and producing
antibody.

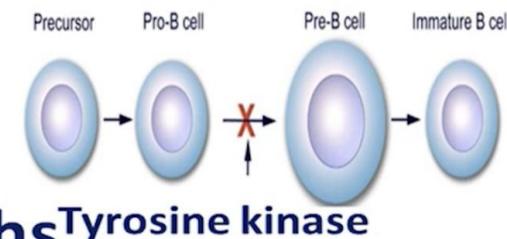


Predict what will happen if there is an absence of tyrosine kinase?



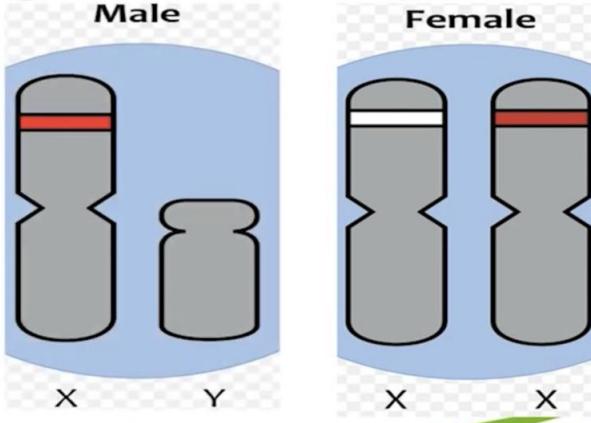
Bruton Agammaglobulinemia
(X-linked agammaglobulinemia)

- No antibodies
- Repeated bacterial infection after 9 months



Bruton Agammaglobulinemia (X-linked agammaglobulinemia)

**Infect boy
not girl**



Journey of lymphocytes

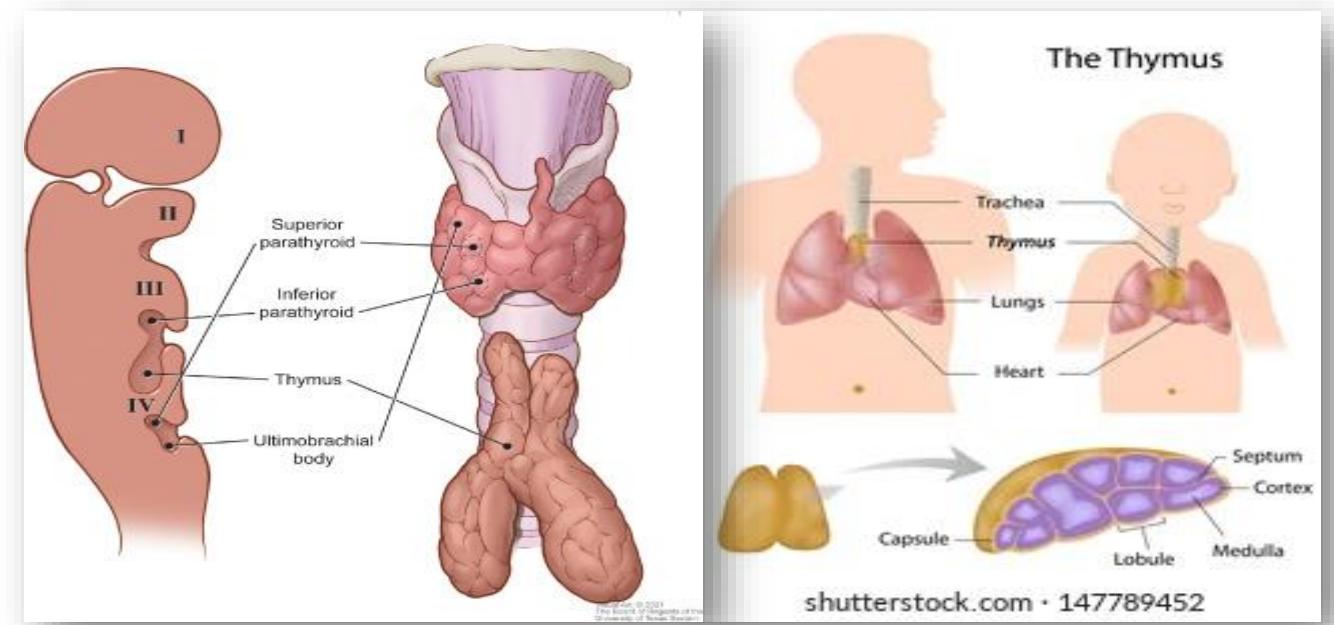
II) T cells

- Development**
- Located**
- Life span**
- Types**
- Receptor**
- Function**



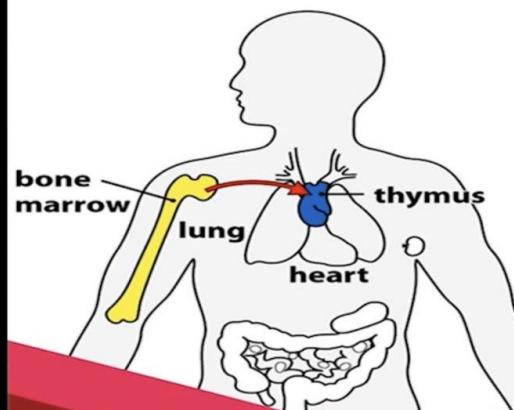
Primary lymphoid organ (Thymus)

Bilobed gland located above the heart. Active before puberty and becomes less functional after puberty (involution). Important organ for T cell development and maturation. Its absence can lead to severe immunodeficiency both humoral and cellular (DiGeorge syndrome) T cell development and maturation is very important function because many autoimmune diseases come from defective T cell function.

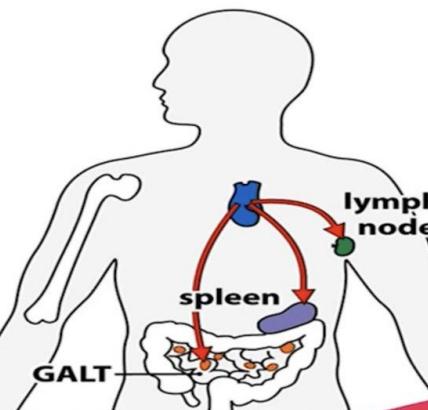


□ Development of T cells

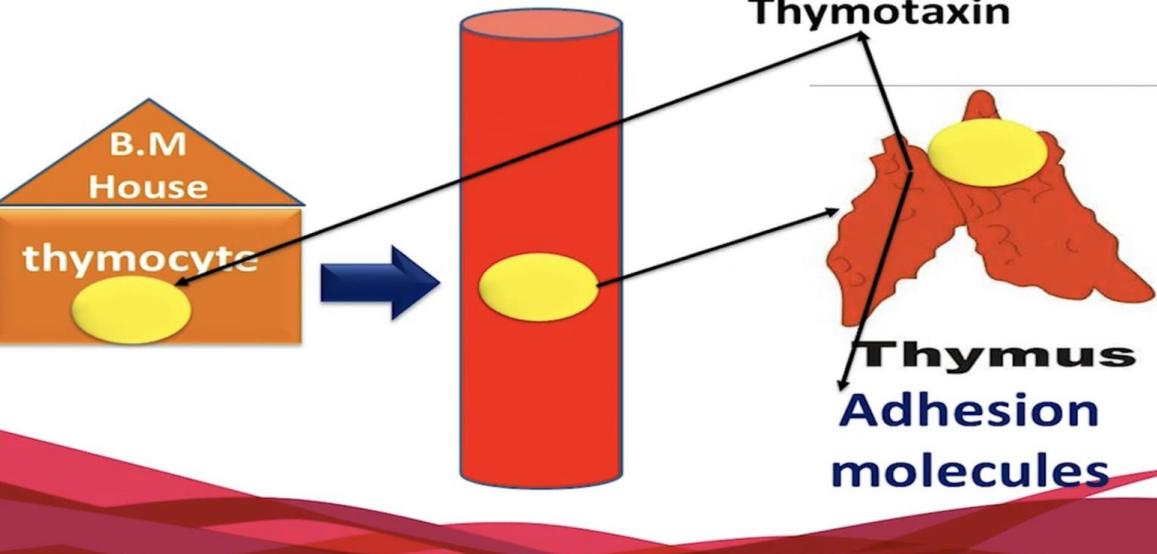
T-cell precursors travel from the bone marrow to develop in the thymus



Mature T cells leave the thymus and travel to secondary lymphoid tissues



□ Development of T cells

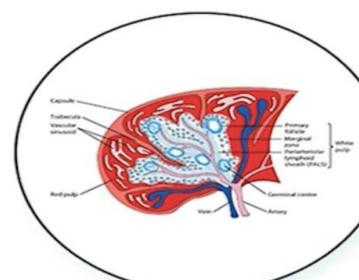
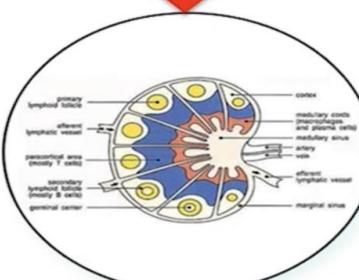
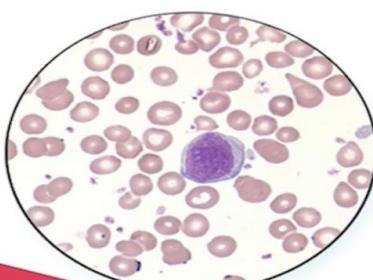


□ Development of T cells

Maturation in Thymus



Reside in



Immature thymocytes come from Bone marrow
(CD44 +, CD25-)

Enter thymus at medullocortical area. These are Double negative (CD4- and CD8 -) as well as negative for TCR

These immature thymocytes passes through different stages known DN-ve 1,2,3,4,

At DN –ve stage 3, TCR begins to be expressed but still not expressed on the cell membrane at DN-ve 4 TCR receptors expressed on the surface.

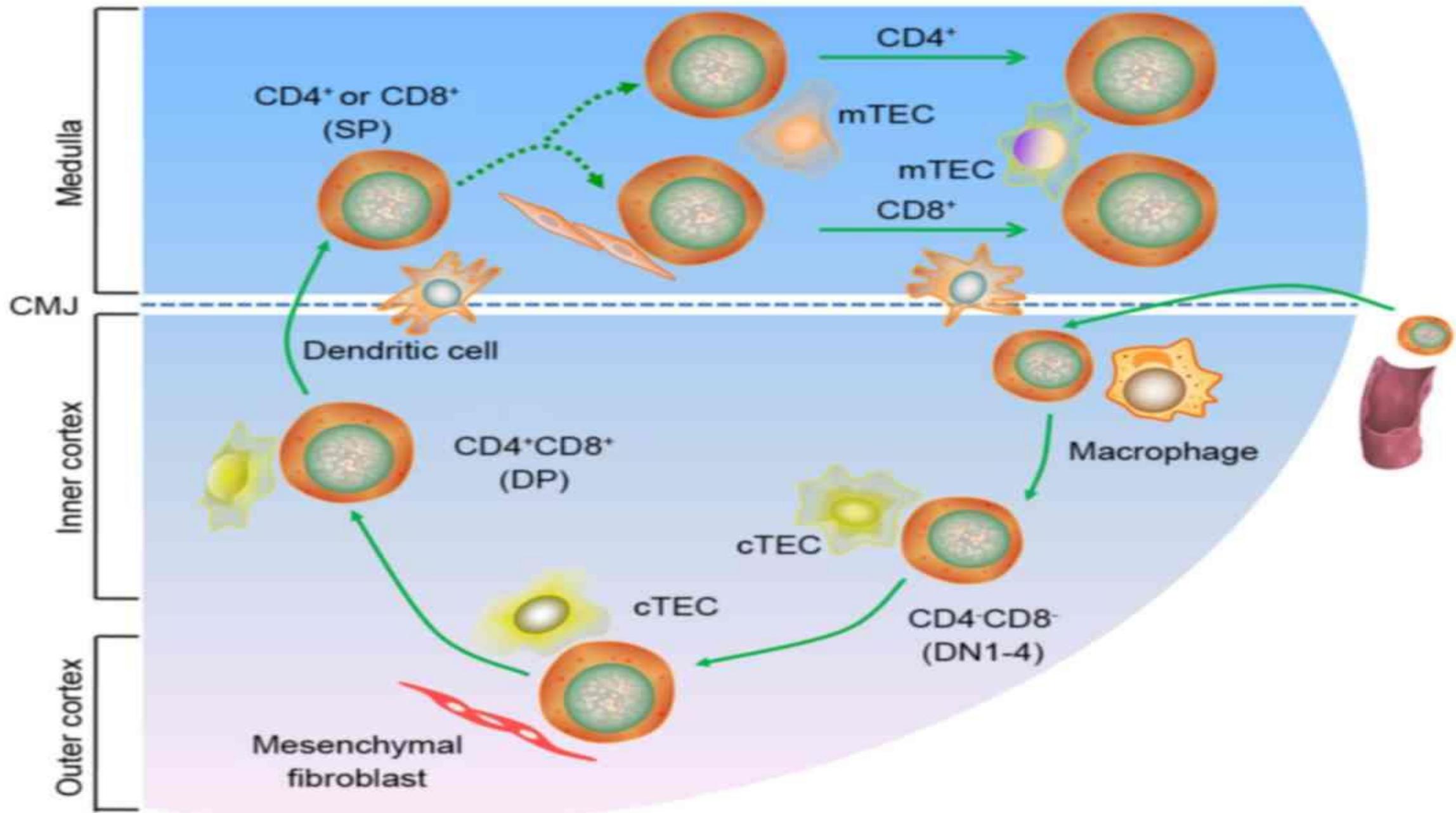
There are 2 types of epithelial cells, those in cortex are called cortical epithelial cells ,while in medulla called medullary epithelial cells

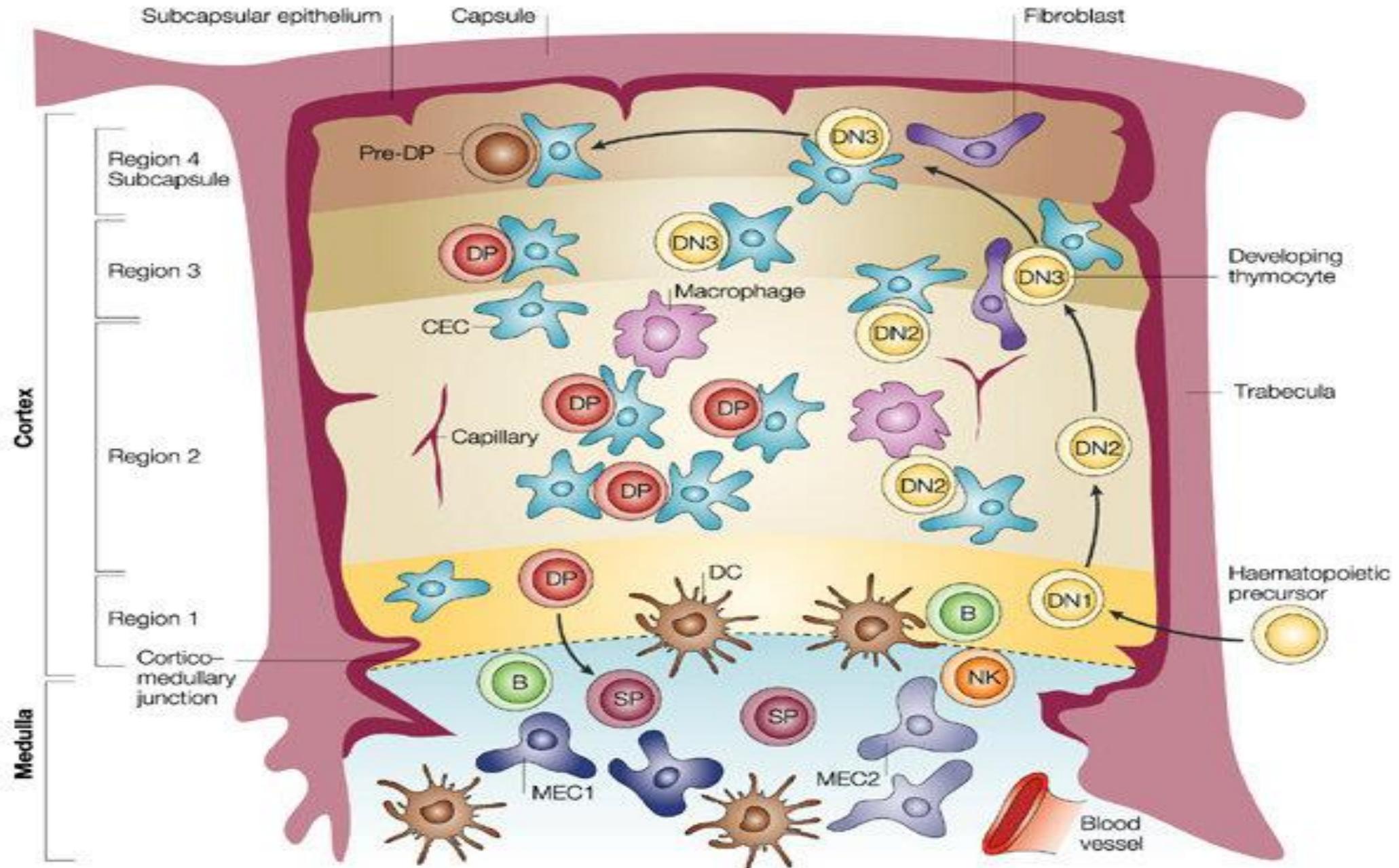
These thymocytes secrete a hormone called thymosin which help immature cells to be matures during the journey from DN1 to DN4 zone.

Then T cells will become double positive at **zone 4** then interact with cortical epithelial cells which expose both MHC- I and MHC –II on their surfaces. If positively bind with these molecules, they will pass the examination (**Positive selection**) if not bind will die by apoptosis (clonal deletion).

So T cells that bind with MHC-I more firmly will downregulate CD4 molecules and have only CD8 and vise versa.

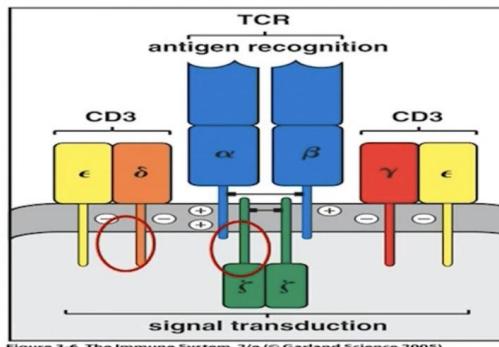
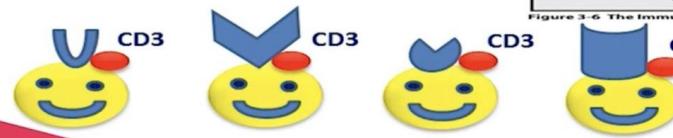
These cells CD4+ and CD8+ cells will pass through another examination which is the most difficult in the medulla where medullary epithelial cells express all body proteins via AIRE (Activation induced transcription factors) so if the T cells recognize self antigens will be killed (**negative selection**). This step is crucial because if self reacted T cells pass and go to the circulation will produce autoimmune diseases.





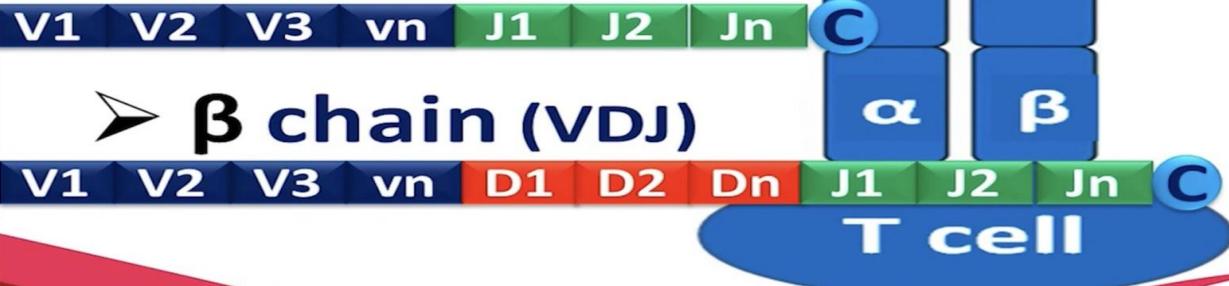
□ Development of T cells

□ DNA rearrangement



□ Development of T cells

➤ **α chain (VJ)**



➤ **β chain (VDJ)**



□ Development of T cells

RAG1 & RAG2

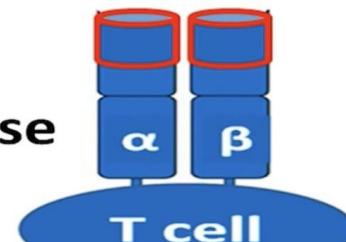
(Recombinant activating genes)



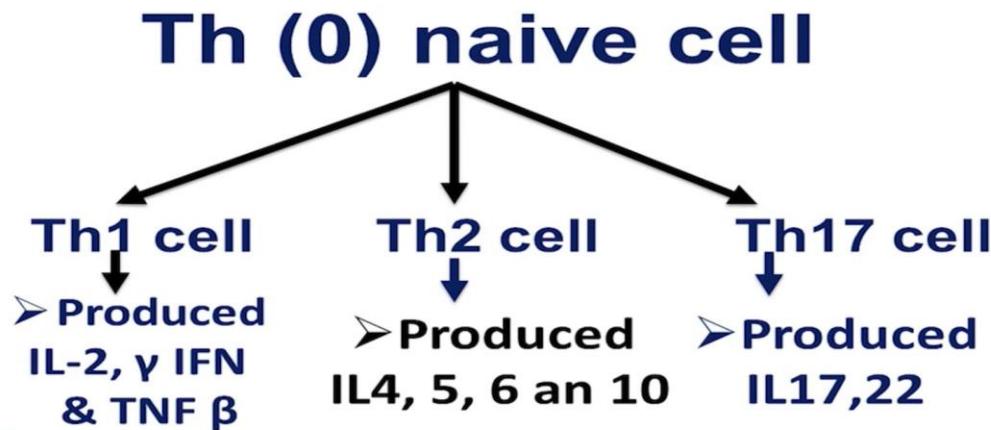
Recombinase
enzyme

V9 J4 C

V8 D6 J4 C



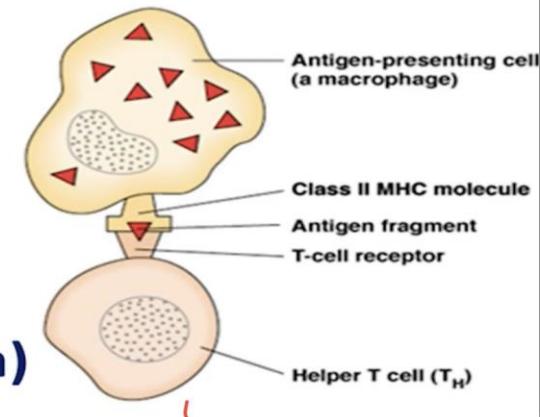
A) T helper cell (CD4)



A) Function of T helper cell (CD4)

1

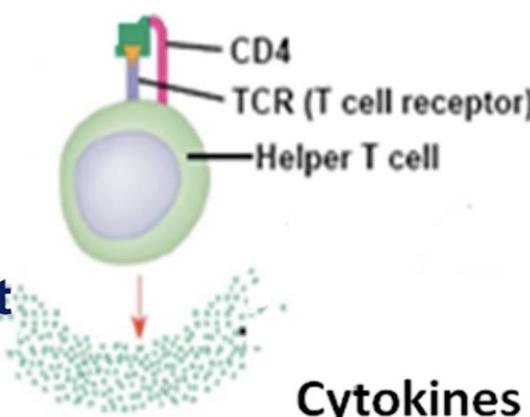
Recognition of epitope presented by APC with MHC II
(Exogenous antigen)



A) Function of T helper cell (CD4)

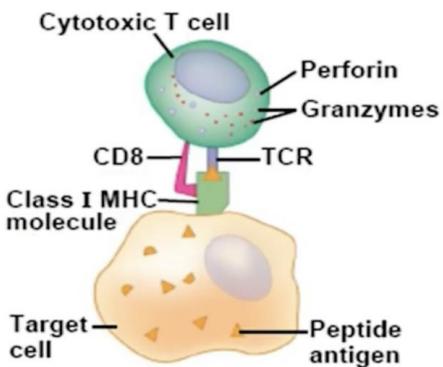
2

Production of cytokines that activated different cells.



3

Activate T-cytotoxic cells

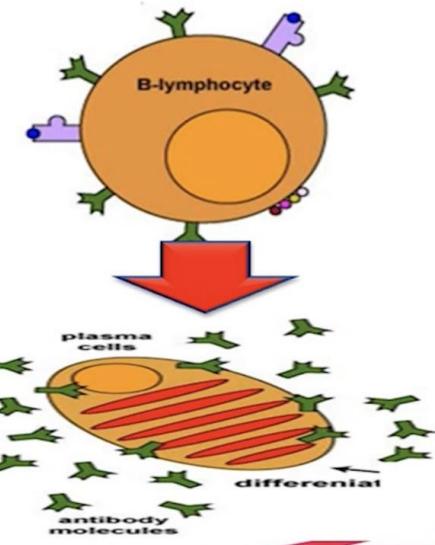


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A) Function of T helper cell (CD4)

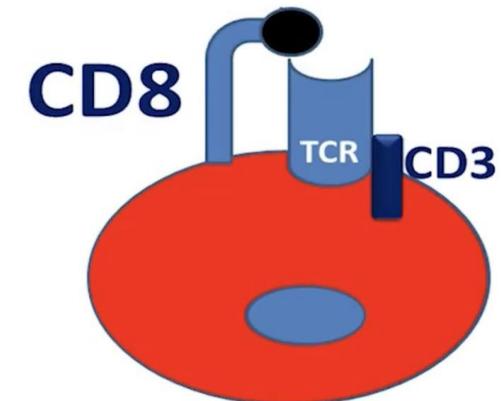
4

Activate
B cells



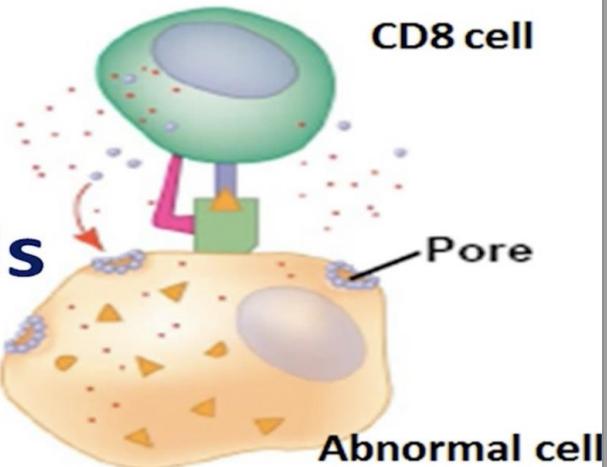
B) T cytotoxic T cell (CD8)

CD8



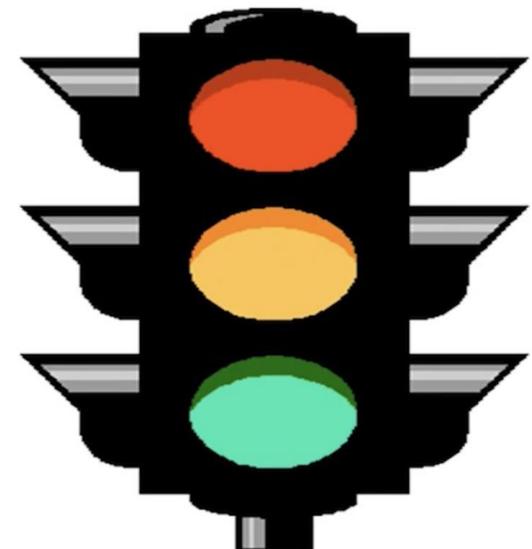
B) T cytotoxic T cell (CD8)

Killing the
abnormal cells
(Apoptosis)



C) T-reg. T cells (CD4 OR CD8)

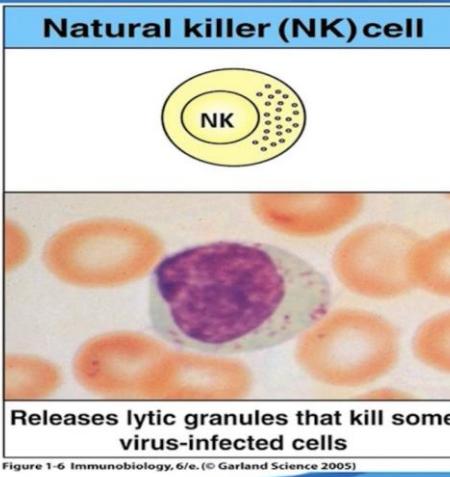
T-reg. T cell



III) NK cells

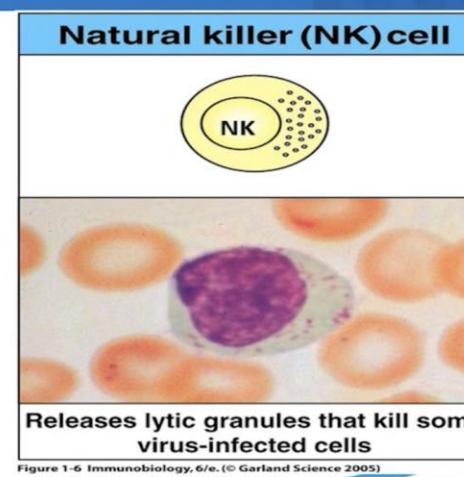
❑ Large granular lymphocytes

They comprise 10-15% of the peripheral lymphocytes.



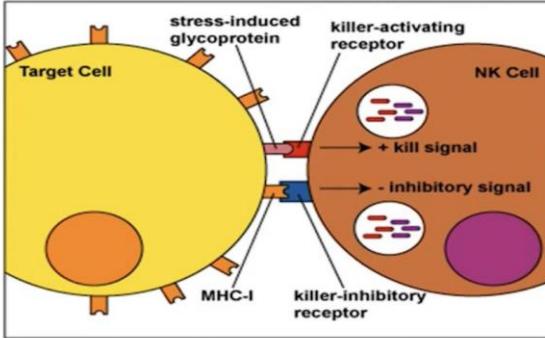
III) NK cells

- No TCR
- CD3 -ve
- CD16 +ve (Fc IgG)
- CD56+ve



III) NK cells

1 Kill cell without MHC-I



III) NK cells

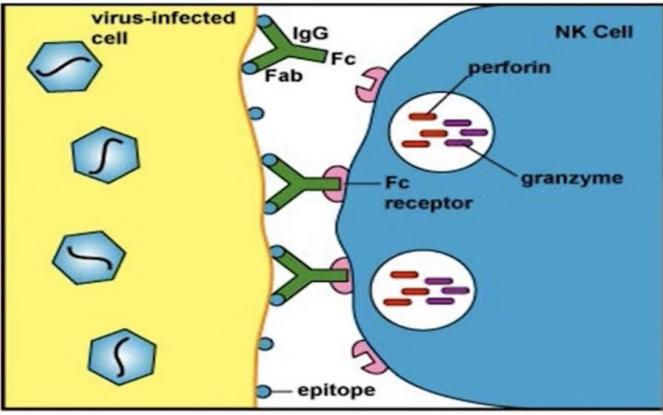
2 Kill cancer cell Through MIC protein



III) NK cells

3

Killing by ADCC



Answer of Exercise 5

Characters	T cells	B cells
1) Production		
2) Maturation		
3) Comprise		
4) Function		
5) Main receptor		

Characters	T cells	B cells
1) Production	BM	BM
2) Maturation	Thymus	BM
3) Comprise	70%	10%
4) Function	TH cells- Secrete cytokines help other cells Tc cells - Killing	Antibody production
5) Main receptor	TH- CD4 Tc-CD8	Antibody

	NK cells	T cytotoxic cells
1) CD Markers	CD16 & CD56	TCR & CD3&CD8
2) Ag recognition	No TCR (contact)	By specific TCR
3) MHC I required	No	Yes
4) Effectors molecules	Perforin & Granzyme	Perforin & Granzyme
5) Enhanced by	IL-2 & INF	IL-2
6) ADCC	Yes	No
7) Act in	Innate	Acquired

Digeorge syndrome is due to faulty development of

Adenine deaminase

Tyrosine kinase

Integrins

3,4 pharyngeal pouches

Bruton Agammaglobulinemia is characterized by

- X linked disease**
- T cells are normal**
- No antibodies**
- Recurrent bacterial infection**

T helper cells are characterized by

- Production cytokines, effect other cells**
- Activates B cells**
- Activated T cytotoxic cells**
- Killing abnormal cells**

T helper cells are Recognize

- Exogenous antigen**
- Endogenous antigen**
- Antigen presented with MHC II**
- Antigen presented with MHC I**

Positive selection is characterized by

- It occurs in cortex of thymus**
- The cells bind with self protein through MHC**
- Any cell can not bind, it will die**
- Any cell binds, it will select**

Negative selection is characterized by

It occurs in medulla of thymus

The cells bind with self protein through MHC

Any cell not bind, it will select

Any cell binds, it will die

T Cytotoxic cells are Recognize

Exogenous antigen

Endogenous antigen

Antigen presented with MHC II

Antigen presented with MHC I

T cells

About 70 % of leukocytes (Th1 cells=IL-2,IFN-gamma, TNF -Beta), Th2 cells (IL-4,5,6,10). Th17 cells (IL-17 and 22)

Synthesized in bone marrow as immature cells (Thymocytes) ---blood---Thymus---Maturation and education-----blood -----

2dry L.organs (effectors).

During Synthesis in B.M genetic recombination occurs in the genes of alpha chain (light chain) and Heavy chain (Beta chain) of the TCRs creating huge diversity of T cells.

What will happen if thymus is not developed ?

(Digeorge syndrome= Fish mouth and flat face)

1- Severe T cells deficiency

2- Recurrent viral and fungal infections

3- **Neonatal hypocalcemia tetany** (no parathyroid gland)

Receptors of T helper cells

1- TCR

2-CD3

3- CD4

4- CD40L

5-CD28

Functions of Th cells

1- Recognize exogenous peptides with MHC-11 on APCs

2-Production of cytokines that activate different cells (Cytotoxic cells and B cells).

DiGeorge syndrome/CATCH22

- **microdeletion on chromosome 22**
- birth defect that affects the immune system
- absence of or underdevelopment of the thymus and parathyroid glands
- facial features include low-set ears, wide-set eyes, small jaw, and bowing up of upper lip



Fish mouth & flat face

What will happen if both RAG1 & RAG 2 are defective ?

Severe combined immunodeficiency (SCID) due to the failure of differentiation of B & T cells.