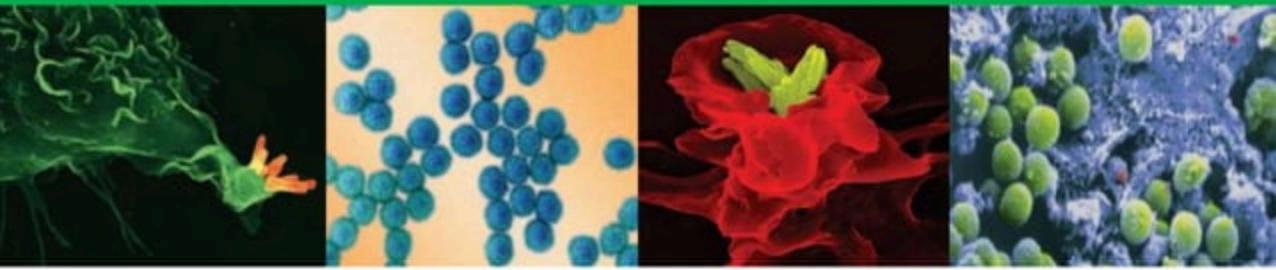
Adaptive Immune Response to Viral Infections



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Outline

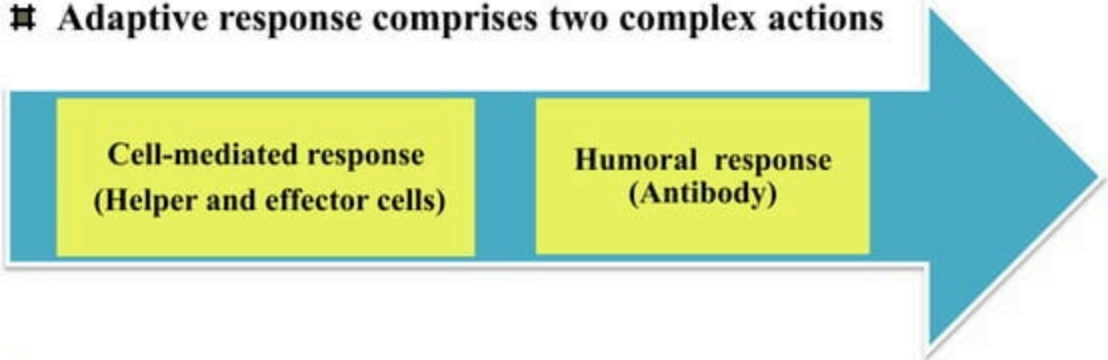
- Introduction
- General features of adaptive immune response
- The hematopoietic lineage
- Cells of the adaptive immune response
- The CMI
- The Humoral Immune Response

Introduction

- The principle cells of the immune system:
  Antigen-presenting cells , Lymphocytes, Effector cells
- All immune cells are derived from **"Hematopoietic stem cells"** in **Bone Marrow** (Fetal liver during fetus)
- Immune cells are divided into two major lineages:
  Lymphoid and Myeloid
- Multiple cell types express distinct **"Surface molecules markers"**
- Development and differentiation of different cell types depend on **"Cell Interactions and Cytokines"**

Features of adaptive immune response

- **Adaptive response comprises two complex actions**

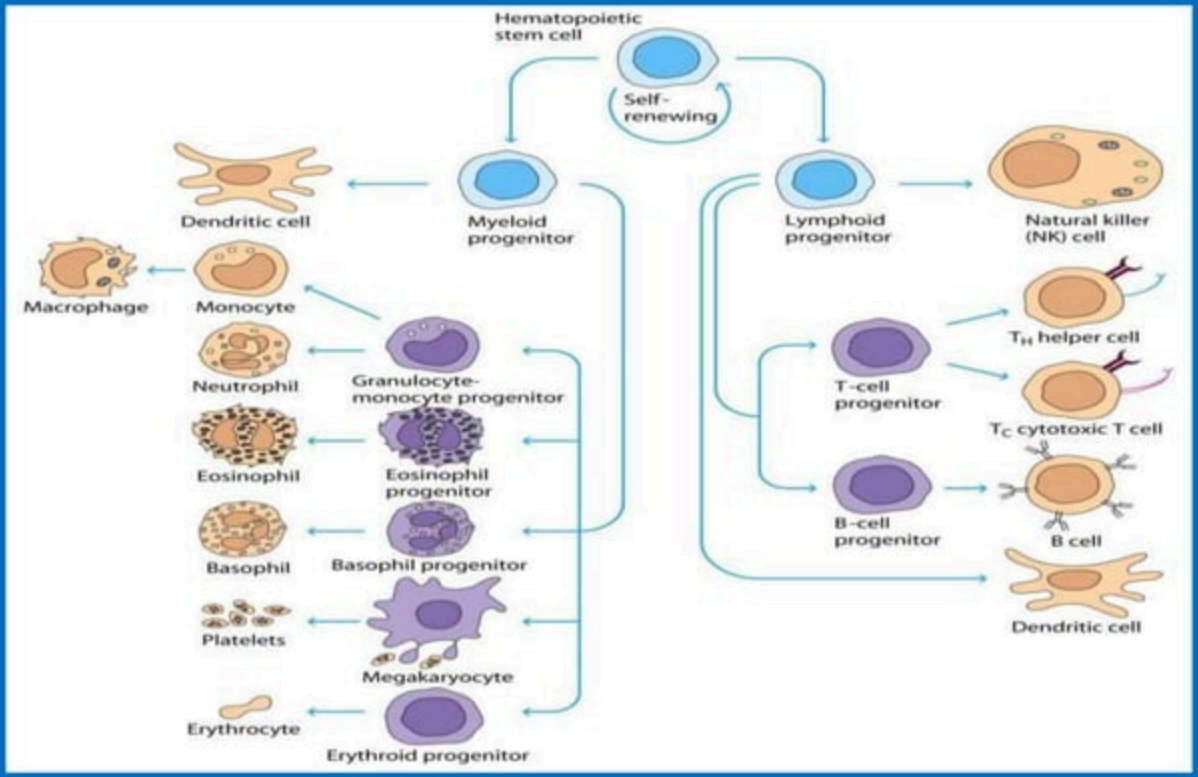


- Highly specific molecular recognition is mediated by two antigen receptors :

1. **Membrane-bound antibody on B cells or the T-cell receptor**

2. **One of two membrane glycoprotein oligomers that display fragments of internal cellular proteins on the cell surface**

Hematopoietic lineage



Cells of the adaptive immune response

- The principle cells of the immune system:
  Antigen-presenting cells, Lymphocytes, Effector cells
- During the early maturation of T and B cells, cells that react against self tissues and proteins die
- Remaining T and B cells have the capacity to recognize non-self molecules, remain in a dormant state
- These lymphocytes **(called professional antigen-presenting cells)** move back and forth from peripheral tissues to lymphoid tissues
- Function is to expose the peptides and proteins on their surfaces gathered from the peripheral tissues so that they can be **bound by T- and B-cell receptors**

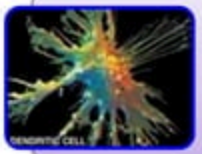
Cells of the adaptive immune response cont..

- **Dendritic cells are crucial professional antigen-presenting cells**
- Immature B cells and cells of the monocyte lineage (macrophages) are also considered to be professional APCs

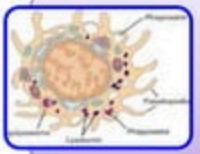
Cells of the adaptive immune response cont..

- Adaptive response depends on two important cell groups:

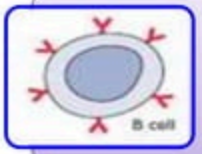
Antigen-presenting cells



Dendritic cells



Macrophages

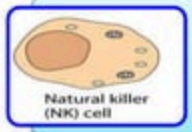


B cells

Lymphocytes

T lymphocytes

B lymphocytes



NK cells

Effector lymphocyte

Cells of the adaptive immune response cont..

The Nobel Prize in Physiology or Medicine 2011

Bruce A. Beutler

Jules A. Hoffmann

Ralph M. Steinman

The Nobel Prize in Physiology or Medicine 2011 was divided, one half jointly to **Bruce A. Beutler** and **Jules A. Hoffmann** ***"for their discoveries concerning the activation of innate immunity"*** and the other half to **Ralph M. Steinman** ***"for his discovery of the dendritic cell and its role in adaptive immunity"***

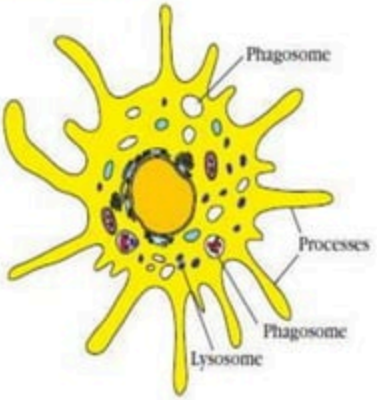
The Antigen Presenting Cells (APCs)

Dendritic cell (DC)

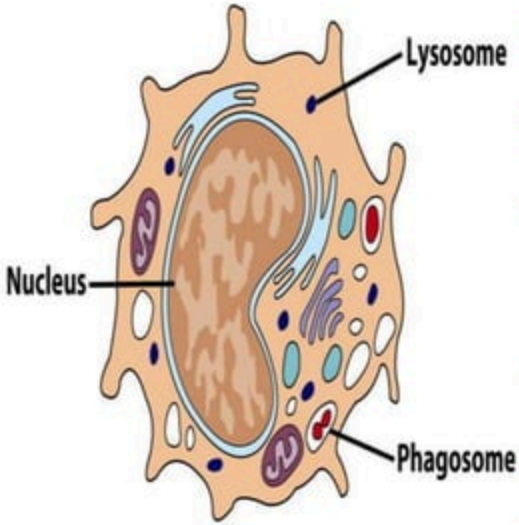
- First cells of the immune system to be discovered (1868).
- Lineage - myeloid
- Posses long, thin cytoplasmic processes called **dendrites**
- Life span-months
- DCs are found in all organs except **brain, parts of eye and testes**
- Especially prominent in LN, skin and mucosal surfaces
- **DC are 100 times more potent as APCs than Macrophages and B cells**
- DCs are the only APCs that can activate the naive T cells.

Dendritic cell (DC) cont...

- **Two major populations called MDCs & PDCs**
- **MDCs** = tissue DCs derived from blood monocyte
- **PDCs** = found in blood and lymphoid organs
- Primary function : **Immune surveillance**
  Antigen processing and presentation
- MOA= **Endocytosis**
  Phagocytosis
  Release of inflammatory mediators



Macrophage



- Lineage-myeloid
- **Kidney shaped nucleus**
- Size-15 μm
- 5% of total leukocytes population in blood
- Life span : months
- Exhibits sustained phagocytosis
- Two subsets- M1 and M2

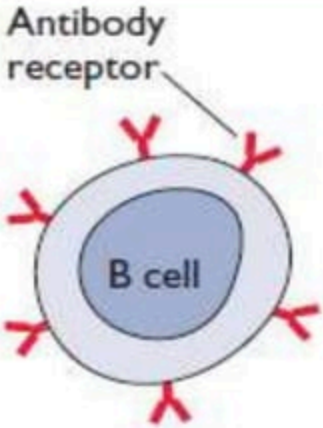
Macrophage cont..

- Major surface receptors: TLRs, CD64 (Cattle-Fcγ2R), CD35, CD11b/CD18, CD206, CD40
- **CD14 membrane marker protein**
- Primary function : Immune surveillance
  Moderate antimicrobial capacity
  Antigen presentation
- MOA : Phagocytosis and release of inflammatory mediators

Kuffer cells	**:**	**Liver MQ**
Microglia	**:**	**Brain MQ**
Osteoclast	**:**	**Bone MQ**
Mesengial cells	**:**	**Kidney MQ**
Histiocytes	**:**	**MQ in Connective tissue**
Alveolar MQ	**:**	**MQ in alveoli of lungs**
Pulmonary I/V MQ	**:**	**MQ in capillaries of lungs**

B cells

- Distribution- Spleen and lymph node
- Maximum in bone marrow and least in peripheral blood
- **Surface marker : most imp is mIg (BCR)**
- Other markers:CD40, B7, ICAM-1, LFA-1, MHC II, CD32 CD35, CD19, CD20, CD21 and CD22, CD27 (marker for B memory cells)
- **Signal transduction: Igα & Igβ (CD 79a and CD79b)**



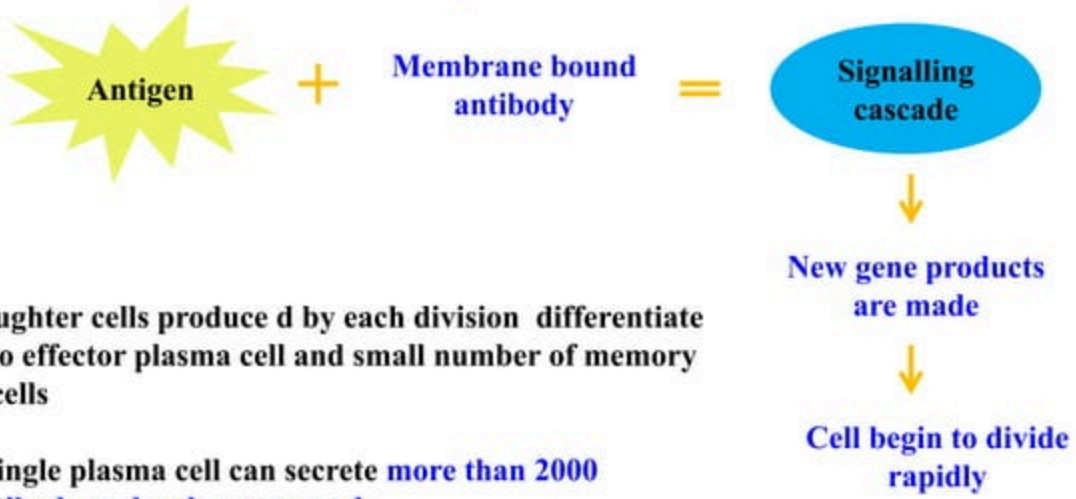
B cells cont…

- Functions of B-cells
  - **Direct antigen recognition and antigen presentation**
  - **B cells may differentiate into plasma cells**
- Plasma cells: effector B-cells with no surface Ig (short life span)
- Demonstration of B-cells by **EAC Rosettes**
- Mitogen-**Pokeweed**
- BAFF/BlyS-B-cell surviving factor

The lymphocytes

B cells

- Mature in the bone marrow
- As they mature, each synthesizes an antigen receptor which is a **membrane bound antibody**



✓**Daughter cells produce d by each division differentiate into effector plasma cell and small number of memory B cells**

✓**A single plasma cell can secrete more than 2000 antibody molecule per second**

T cells

- T cell precursors - produced in **Bone marrow**
- T cell precursor must migrate to the thymus gland to mature
- T cells can be distinguised by the presence of T-cell receptor on their surface
- Maturation process of T cell comprises of :

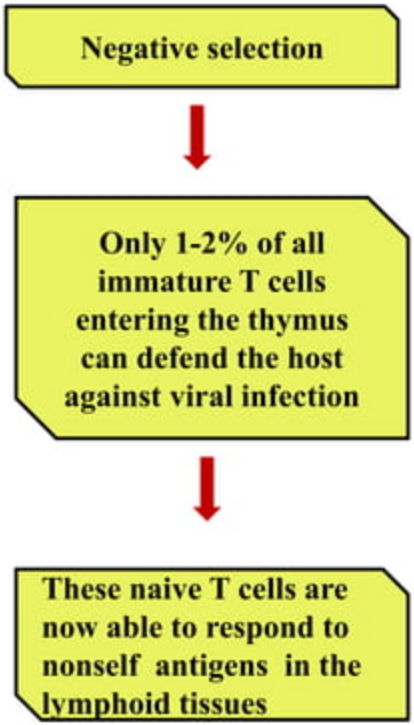
Positive selection

Negative selection

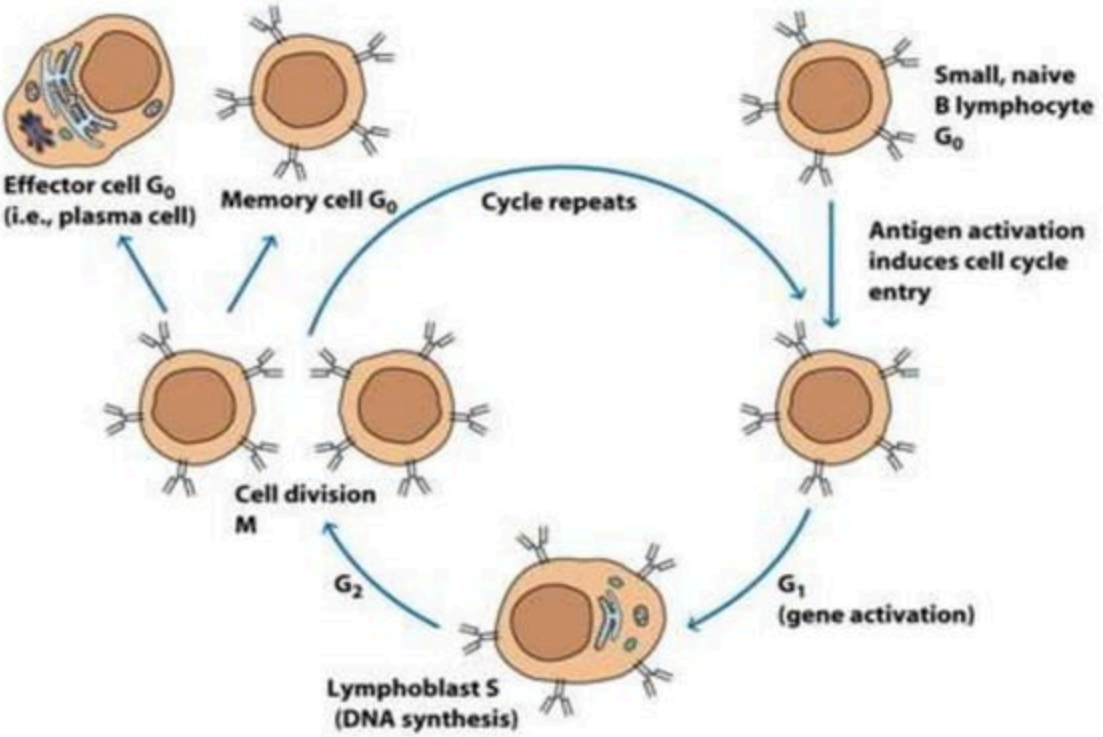
✓**Positive selection of T cells bind appropriate surface molecules via the T-cell receptor**

✓**Negative selection efficiently kills T-cell receptor that recognise target cells displaying self-peptides**

T cells cont..


Negative selection
Only 1-2% of all immature T cells entering the thymus can defend the host against viral infection
These naive T cells are now able to respond to nonself antigens in the lymphoid tissues

Lymphocyte proliferation



Th cells and CTLs

- **Th cells and CTLs** can be distinguised by presence of specific protein on their surfaces
- **Cluster of differentiation (CD) markers**

- Presence of these proteins can be detected with antibodies raised against them called **CD antigens** in heterologous organisms

- Subpopulations of T cells are defined by the presence of :

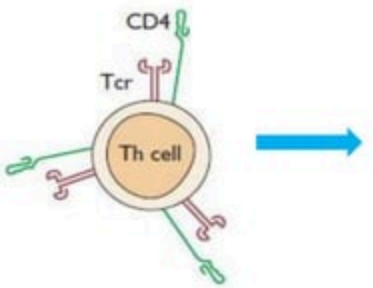
✓ Either the CD4 or the CD8 surface proteins which are coreceptors for MHC class II and MHC class I, respectively

Th cells and CTLs cont…

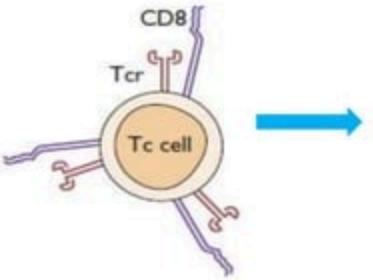
Selection of lymphocytes

Double negative	Double positive	Single positive
When immature T cells leave the bone marrow, they do not synthesize CD4 or CD8 proteins	Differentiate sequentially in the thymus, initially producing both CD4 and CD8 proteins	Differentiate sequentially in the thymus producing either CD4 or CD8

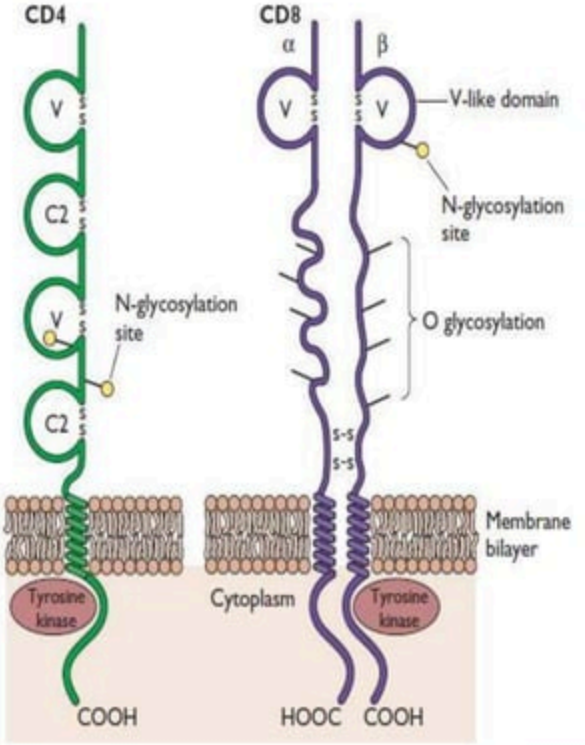
Th cells and CTLs cont..



Th 1 and
Th 2 cells

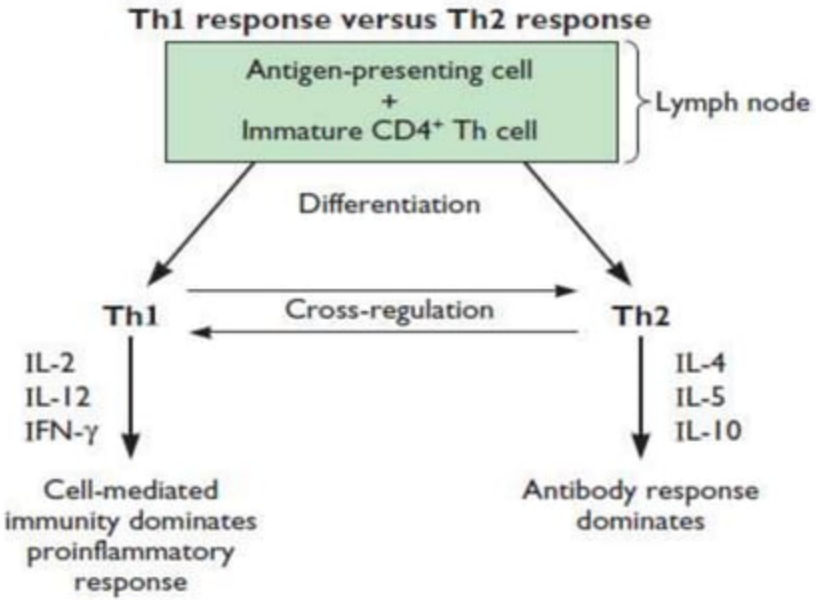


CTLs



Th1 and Th2 cells

- When **naive Th cells engage mature DCs** in lymphoid tissue cytokines and receptor ligand interactions stimulate the T cell to differentiate into one of two Th cell types :

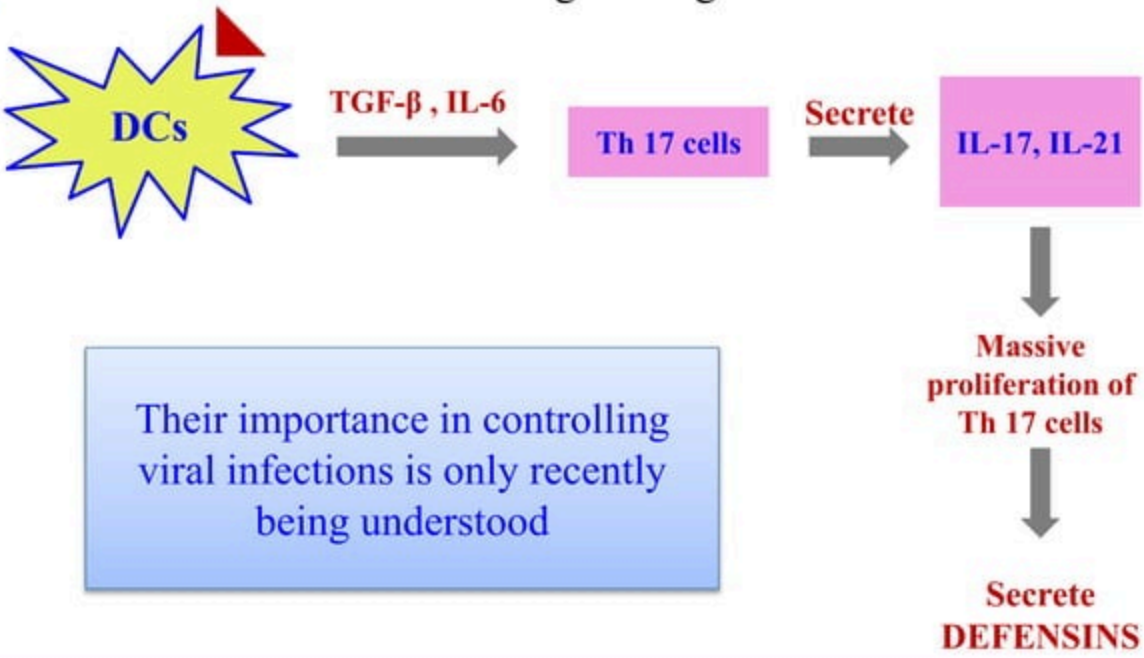


Th1 and Th2 cells cont…

Immune cross-regulation by cytokines			
Th1 response		Th2 response	
Enhance	Suppress	Enhance	Suppress
IL-2 IL-12 IFN-γ	IL-4 IL-10	IL-4 IL-5 IL-6 IL-10	IFN-γ IL-12

Th 17 cells

- Plays central roles in control of the **inflammatory response**
- Found in the skin and the lining of the gastrointestinal tract



Memory T cells

- **Long lived, mature T cells**

  Each of their T-cell receptors binds to a specific non-self peptide

  ⬇

  The cells divide rapidly producing active effector T cells

- Memory T cells can carry either CD8 or CD4 surface proteins

Regulatory T cells

- The primary function is to terminate the immune response and bring the immune system back to ground state **(Immune homeostasis)**
- **These cells are also important for :**

✓ **Immune suppression**

✓ **Self-tolerance**

✓ **Control of the inflammatory response**

- Treg cells serve to maintain a balance between protection and immune pathology

NKT Cells

- NKT cells have a T-cell receptor
- Play critical roles in early innate and adaptive responses
- NKT cells recognize glycolipid molecules bound to **CD1d**
- NKT cell can act as a Th cell or a cytotoxic cell
- NKT cells account for 20 to 30% of lymphocytes present in the liver
- Capable of **releasing IFN-γ** after viral infection

γδ T cells

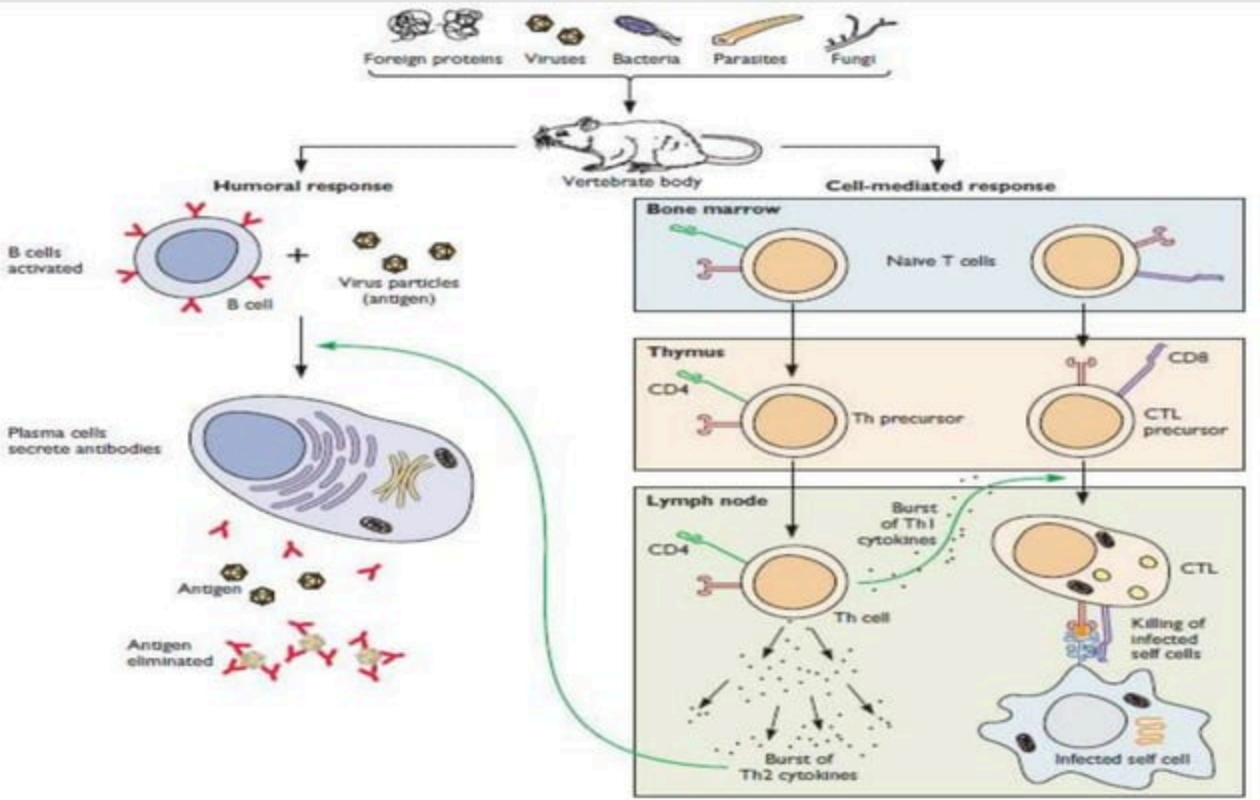
- Subset of T cells
- Develop in the thymus
- Their name derives from their unique cell surface γδ T-cell receptor
- Abundant in epithelial cell layers

✓**Antigens recognized by γδ T cells are not bound to classical cell surface MHC proteins**

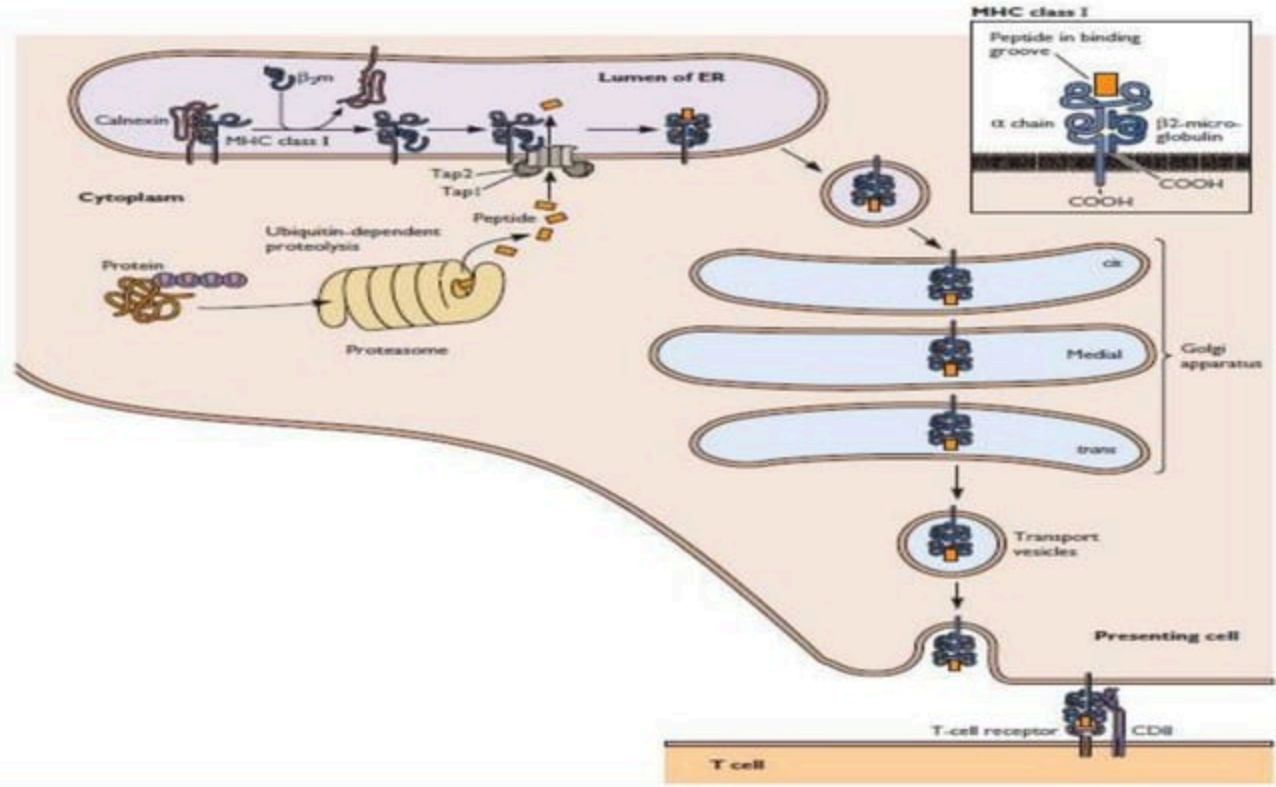
✓**Do not interact with professional antigen-presenting cells**

✓**Do not express CD8 or CD4 proteins on their cell surface.**

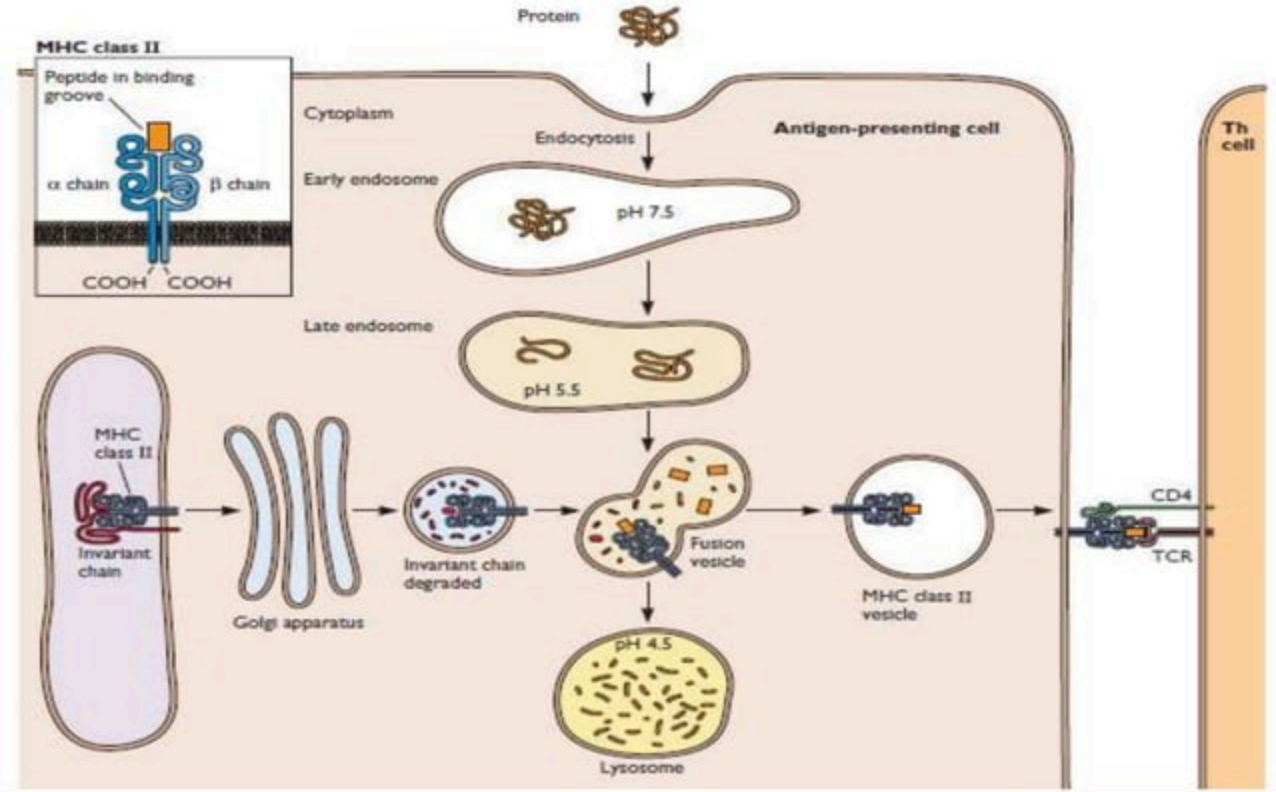
Antigen Presentation and Activation of Immune Cells



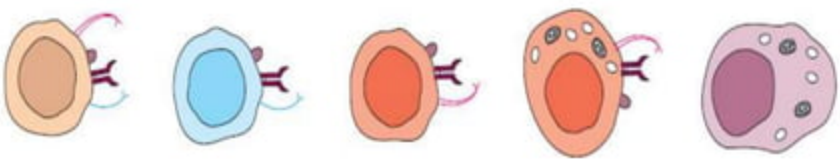
T Cell recognision of infected cells by engaging the MHC Class I Receptors



T Cells Recognize Professional APCs by Engaging the MHC Class II Receptors



The Cell Mediated Immune Response



CMI response

- The cell-mediated response facilitates recovery from a viral infection
- Antibodies have little or no effect in many natural infections that spread by cell-to-cell contact :

- **Infections by neurotropic viruses such as Alphaherpesviruses**
- **Infections by viruses that infect circulating immune cells (Lentiviruses and Paramyxoviruses)**

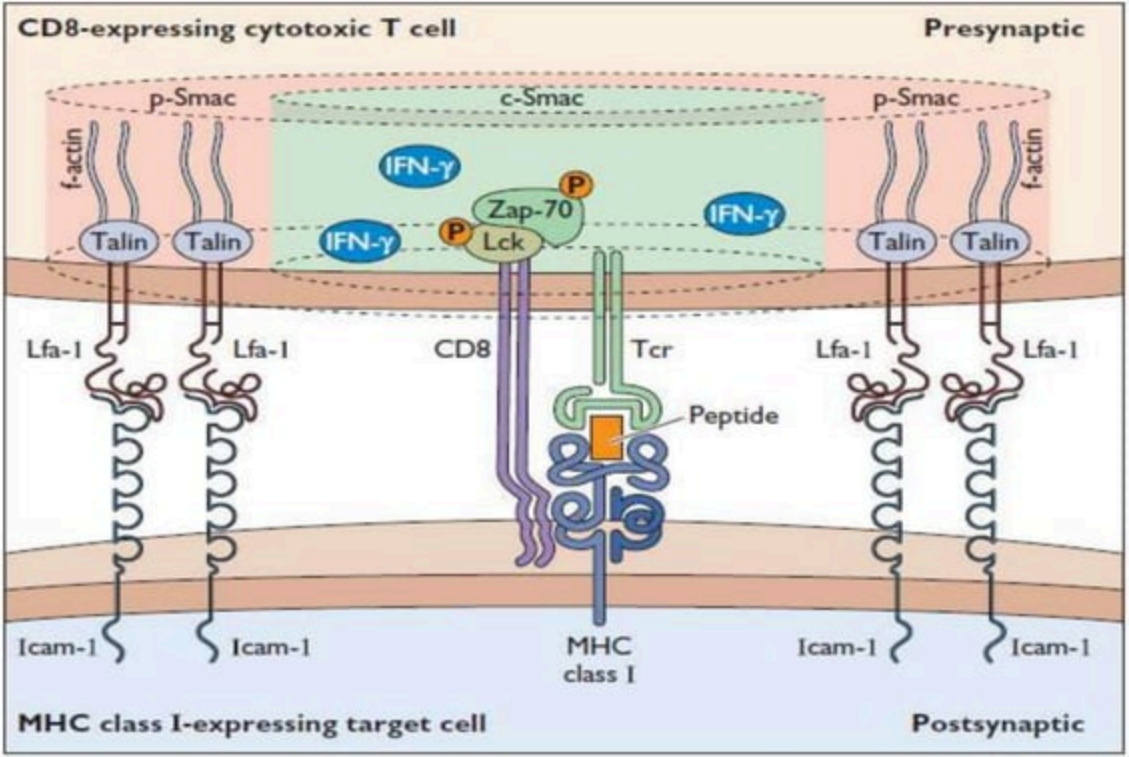
The CTLs

- Equipped to kill virus-infected cells
- Two reactions are required for their full killer potential

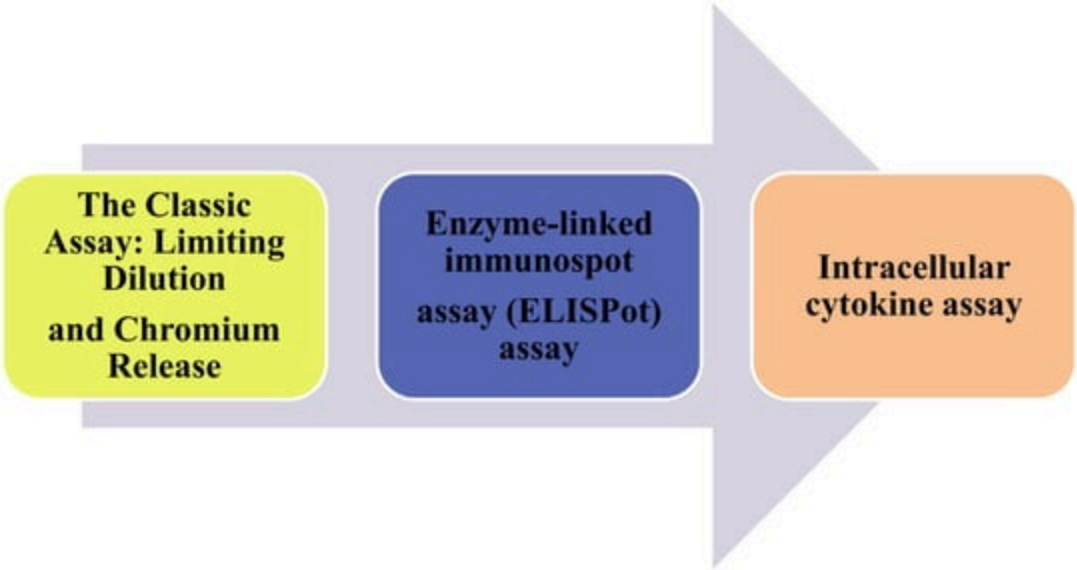
1. **Interaction of their T-cell receptor with foreign antigens presented by MHC class I molecules**
2. **Binding of additional surface proteins (the coreceptors) on the precursor CTL to their ligands on the infected cell**

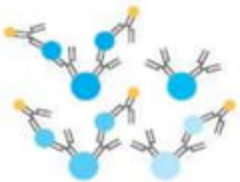
- Signalling from the T-cell receptor requires clustering of a number of T-cell receptors and reorganization of the T-cell cytoskeleton in a particular structure called the **immunological synapse**

The Immunological synapse

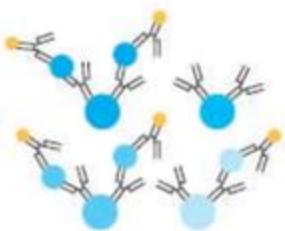


Measuring the antiviral cellular immune response





The Humoral Immune Response

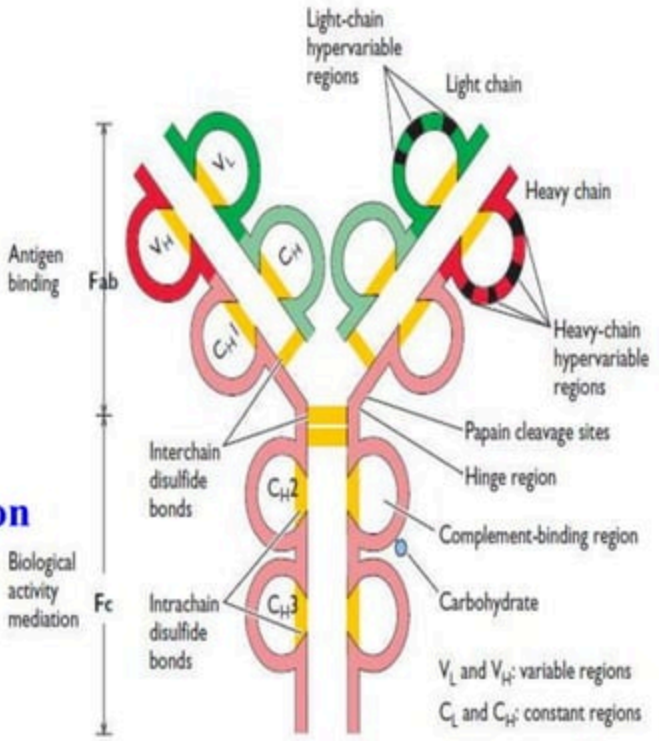


Specific antibodies are made by activated B cells

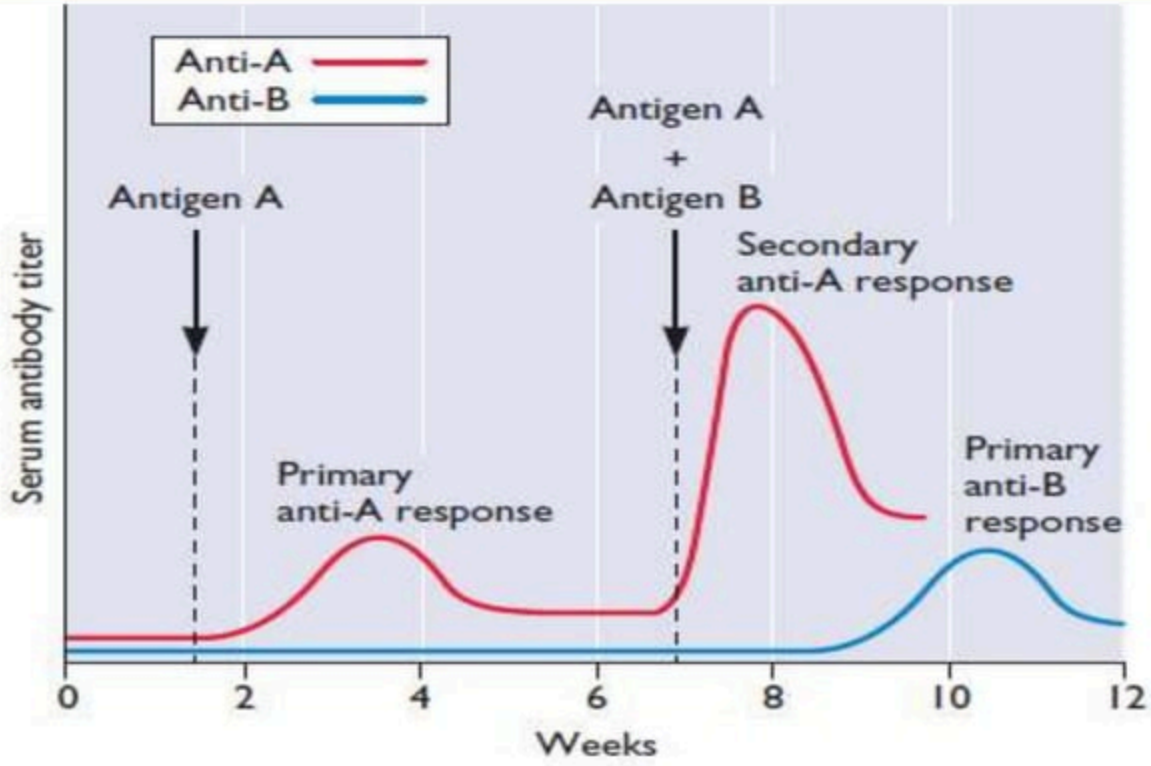
- B -cell differentiates and synthesizes antibody only when its surface antibody receptor is bound to the cognate antigen
- The activating signal requires clustering of receptors complexed with antigen
- B-cell coreceptors, such as **CD19, CD21**, and **CD8** enhance signaling by recruiting **tyrosine kinases**
- The engagement of **CD40 ligand** with its B-cell receptor facilitates exchange of cytokines that stimulates proliferation of the activated B cell and promotes its differentiation
- Rate of synthesis of IgG can be as high as **30 mg/kg of body weight/day**

Antibodies

- Five classes of immunoglobulin: IgA, IgD, IgE, IgG, and IgM
- **IgG, IgA, and IgM** are commonly produced after viral infection
- During B-cell differentiation, **"switching"** of the constant region of heavy-chain genes occurs by **somatic recombination**
- Each cell produces a specific type of antibody after such switching



Antibody response



Properties of Antibodies

Property	IgA	IgD	IgE	IgG	IgM
Function	Mucosal; secretory	Surface of B cell	Allergy; anaphylaxis; epithelial surfaces	Major systemic immunity; memory responses	Major systemic immunity; primary response; agglutination
Subclasses	2	1	1	4	1
Light chain	κ, λ	κ, λ	κ, λ	κ, λ	κ, λ
Heavy chain	α	δ	ε	γ	μ
Concn in serum (mg/ml)	3.5	0.03	0.00005	13	1.5
Half-life (days)	6	2.8	2	25	5
Complement activation					
Classical	-	-	-	+	++
Alternative	-/+	-	+	-	-

Mucosal and cutaneous arm of the immune system

- The mucosal immune system is usually the first adaptive defense to be engaged after infection

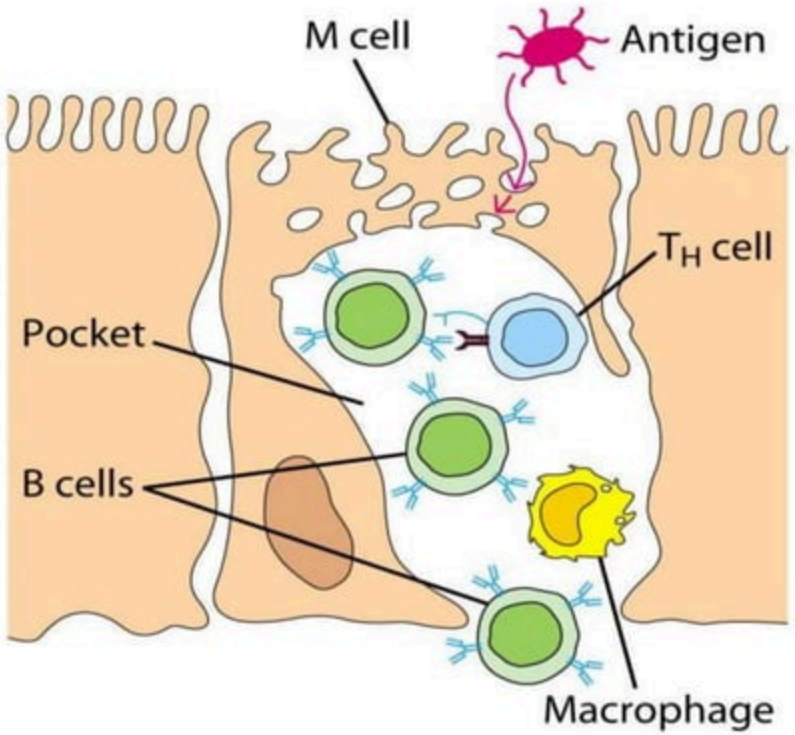
- **Mucosa-associated lymphoid tissue** are vital in antiviral defense

- These clusters of lymphoid cells include the collection called-
  - ✓ **Peyer's patches** in the lamina propria of the small intestine
  - ✓ **Tonsils** in the pharynx
  - ✓ **Submucosal follicles** of the upper airways

- A specialized epithelial cell of mucosal surfaces is the **M cell (microfold or membranous epithelial cell),** which samples and delivers antigens to the underlying lymphoid tissue by transcytosis

- M cells have invaginations of their membranes (pockets) that harbour **immature DC, B cells, CD4+ T lymphocytes and macrophages**

Mucosal and cutaneous arm of the immune system



Mucosal and cutaneous arm of the immune system

- **T lymphocytes** and **Langerhans cells** comprise the **cutaneous immune system (skin-associated lymphoid tissue)**
- Langerhans cells -predominant scavenger APCs of the epidermis
- Certain T cells in the circulation have tropism for the skin and after binding to the vascular endothelium can enter the epidermis to interact with **langerhans cells** and **keratinocytes**
- Virus particles can interact with lymphoid cells associated with mucosal and cutaneous immune systems at the primary site of infection
- The M cells have been implicated in the spread from the pharynx and the gut to the lymphoid system of a variety of viruses, including ***Poliovirus,*** **enteric** ***Adenoviruses,*** **HIV-1** and ***Reovirus***

THANK YOU