(Lecture 8)

→ 1: Epithelial barrier

- Found in the skin and the mucosal surfaces of the gastrointestinal, respiratory, and genitourinary
- Maintain immune functions by 6 Ways:

1) Forms an intact surface preventing pathogens from passing into the body by: a. Tight junctions: formed mainly by occludin/ b. Gap junctions/ c. Desmosomes

2) Secrets mucus: viscous so impairs microbial invasion because it contains lactoferrin and mucins/ Contains immunoglobulins (IgA) & anti-microbial enzymes (lysozomes)

3) Removes this mucus recurrently by ciliary action in the bronchial tree and peristalsis in the gut.

4) Secretes anti-microbial peptides, two types:

a) Defensins: are small cationic peptides, produced by epithelial cells of mucosal surfaces and by granule-containing leukocytes, including neutrophils, natural killer cells, and cytotoxic T lymphocytes.

b) Cathelicidins are produced by neutrophils and various barrier epithelia, after cleavage they have bactericidal and immunomodulatory functions.

How do they attack the pathogen?

Antimicrobial peptides possessing a net positive charge are attracted and incorporated into negatively charged bacterial membranes thus disturbing them.

5) Contains γδ T lymphocytes (intraepithelial lymphocyte):

- Part of the innate immune response
- Recognize limited number of PAMPs & DAMPs (Not necessary proteins)
- Don't need antigen presenting cells to present antigens on MHC molecules
- do not express CD4 nor CD8
- Mature in the thymus
- Secretes perforin and granzymes to kill infected cells

6) Allow benefit microbiota to colonize: don't allow bad microbes to colonize/ stimulating the epithelial cells to produce antimicrobial peptides.

- Infections related to interrupted epithelial barrier:

1) Cystic fibrosis: Defective CFTR transmembrane protein making mucous more thick and viscous.

2) primary ciliary dyskinesia, an inherited disorder that leads to impaired mucociliary clearance because of defects in the Cilla that causes repeated chest infections.

3) eczema: a defective skin barrier leads to recurrent infections mainly with staph aureus./ Eczema itself is not infectious, but infections with bacteria related to eczema maybe infectious

→ 2: Migration of leukocytes into tissue

Why a WBC want to migrate from a blood vessel to a tissue?

1) Innate leukocytes (e.g. neutrophils) migrate into infected tissue for immune response

2) Lymphocytes migrate from endothelial venules in the lymph nodes to sit in their places waiting for their antigens

3) Lymphocytes migrate into infected tissues after they're activated by antigens

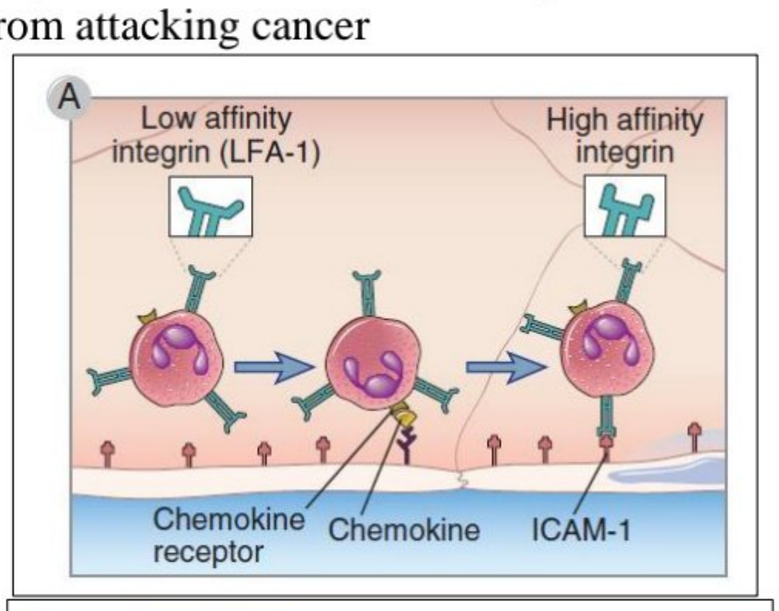
- Before we study the previous 3 points, we need to know some important points:

What are chemokines (Chemoattractant cytokines)?

cytokines that stimulate leukocyte movement & migration / 50 human chemokines/ very small/ two major families/ CC chemokines, in which the cysteine residues are adjacent, and the CXC family, in which these residues are separated by one amino acid/ produced by leukocytes and by several types of tissue cells, such as endothelial cells, epithelial cells, and fibroblasts/ effects GPCR on leukocytes causing their: growth, motility & migration

- Strange important info: some chemokines were found to be produced by cancer cells to help them for metastasis, an important example is Interleukin-8 (CXCL8) that acts on CXCR1/2 on leukocytes preventing them from attacking cancer

◦ Notes about cytokines: redundant & polytropic



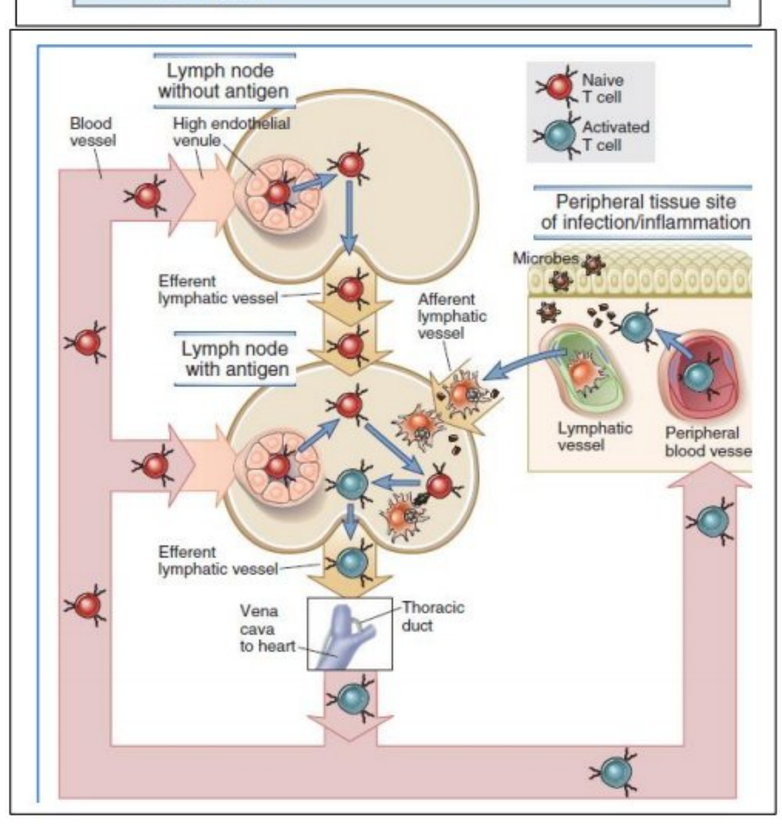
1) Innate leukocytes (e.g. neutrophils) migrate into infected tissue for immune response :
PRRs sense the danger and induce production of some cytokines such as il-1 & TNF-α that will produce adhesion molecules on endothelial cells and chemokines that will attract leukocytes

a- Leukocytes are attracted to the site of injury by chemokines

b- Weak adhesion is formed between some ligands (e.g. complex sialylated carbohydrate) on the leukocytes and selectins (e.g e-selectins and p-selectins) on the blood vessels.

C- Strong adhesion between integrins on leukocytes and ICAM-1 on the blood vessels: Integrins respond to chemokine signals by rapidly increasing their affinity for their ligands, Chemokines also induce membrane clustering of integrins leading to increased avidity of integrin interactions with ligands on the endothelial cells, and therefore tighter binding of the leukocytes to the endothelium.

D- Leukocytes will migrate into the blood vessels by diapedesis



2) Lymphocytes migrate from endothelial venules in the lymph nodes to sit in their places waiting for their antigens

3) Lymphocytes migrate into infected tissues after they're activated by antigens

• Each lymphocyte goes through one node once a day on average. Peripheral tissue inflammation, which usually accompanies infections, causes a significant increase of blood flow into lymph nodes and consequently an increase in T cell influx into lymph nodes draining the site of inflammation.

• Naive B cells use the same basic mechanisms as do naïve T cells to home to secondary lymphoid tissues throughout the body, which enhances their likelihood of responding to microbial antigens in different sites

- **(Lecture 9)** (Note: most information in this lecture & lecture 7 are mentioned in previous lectures, so just understand pictures in those lectures and go ahead)

→ 1: Immune response against extracellular pathogens

◦ Parts of the immune system that response against extracellular pathogens: 1) Complement system 2) Phagocytes: including neutrophils & macrophages 3) Antigen-presenting cells: Macrophages & Dendritic cells 4) Humoral immunity 5) Helper t cells

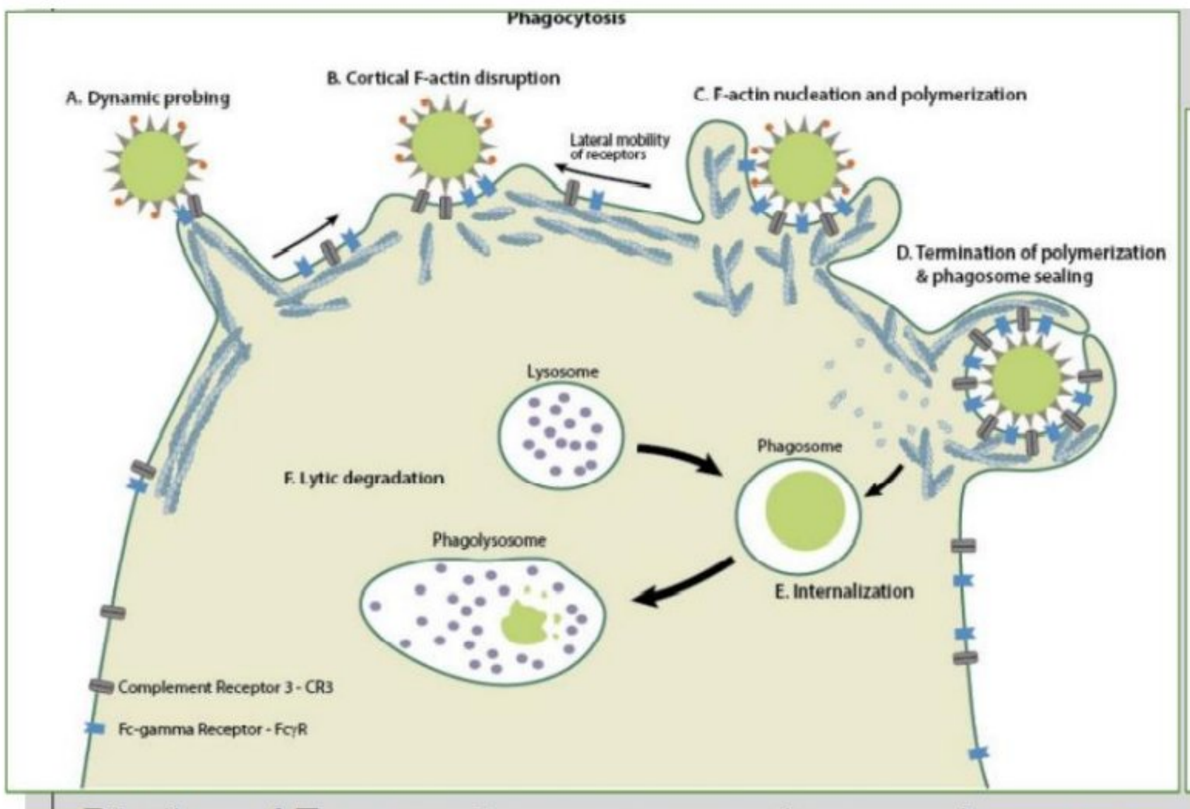
-> Macrophages: IgG subtypes that bind best to Fc receptors (IgG1 and IgG3) are the most efficient opsonins for promoting phagocytosis. Binding of FcγRI receptors on phagocytes to multivalent antibody-coated particles leads to engulfment of the particles and the activation of phagocytes.

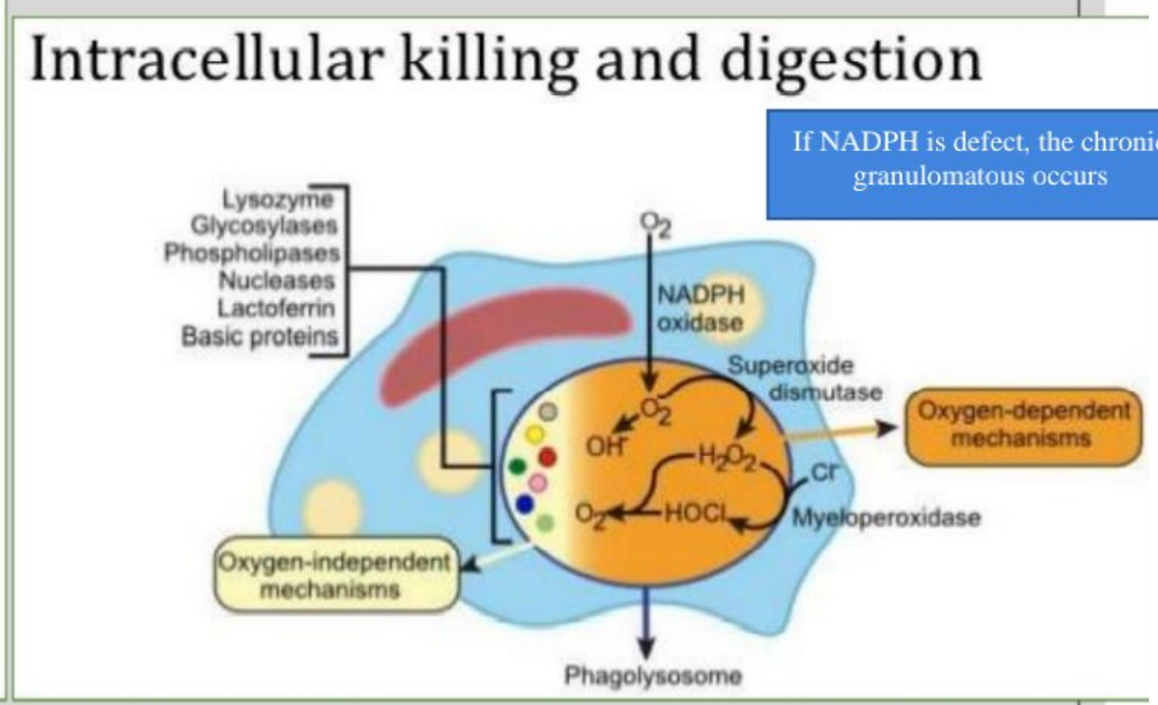
• Activation leads to:

Production of the enzyme phagocyte oxidase, which catalyzes the intracellular generation of reactive oxygen species that are cytotoxic for phagocytosed microbes. This process is called the respiratory burst (Oxygen dependent)

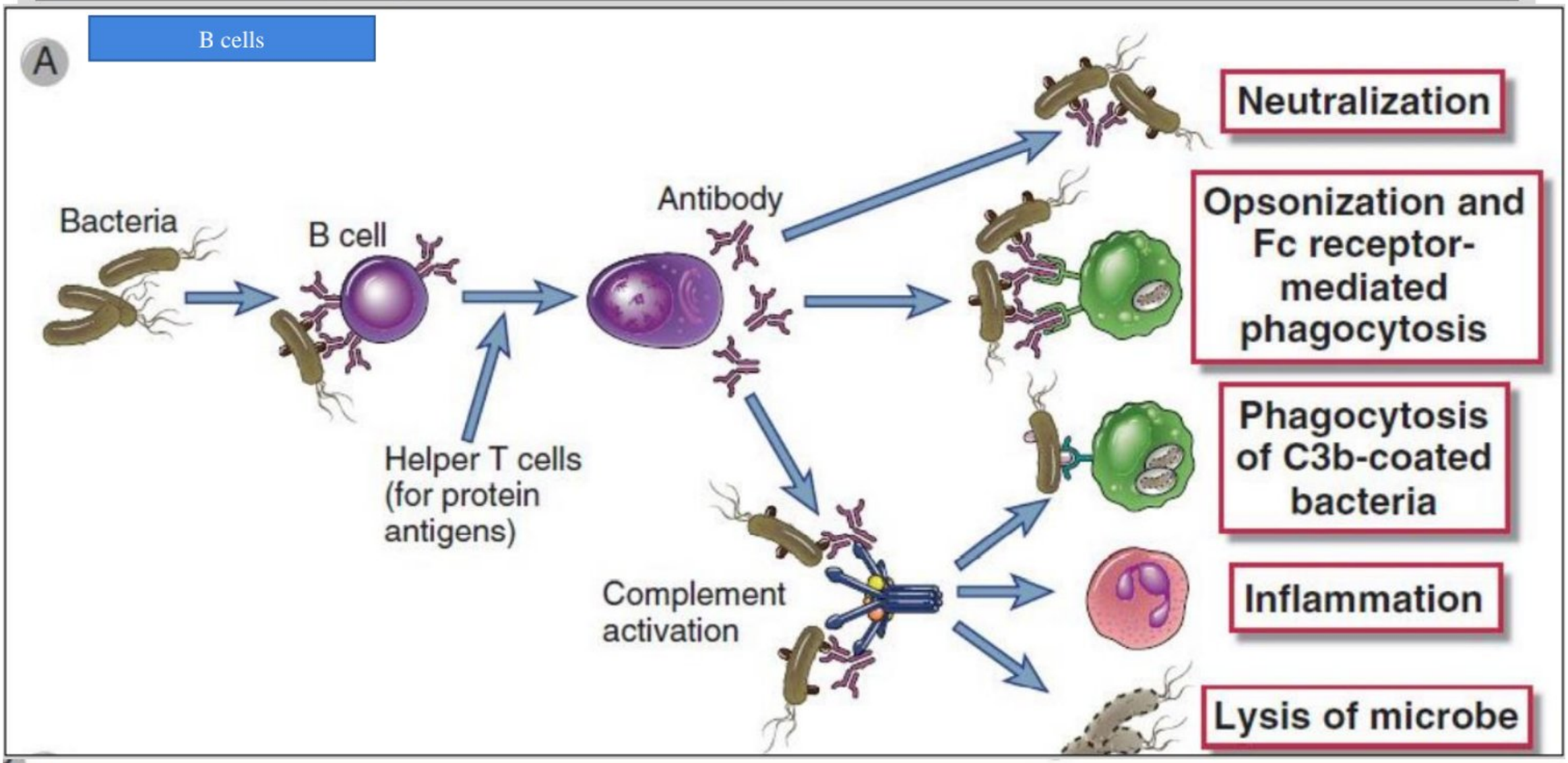
Activation of an enzyme called inducible nitric oxide synthase (iNOS), which triggers the production of nitric oxide that also contributes to the killing of pathogens.

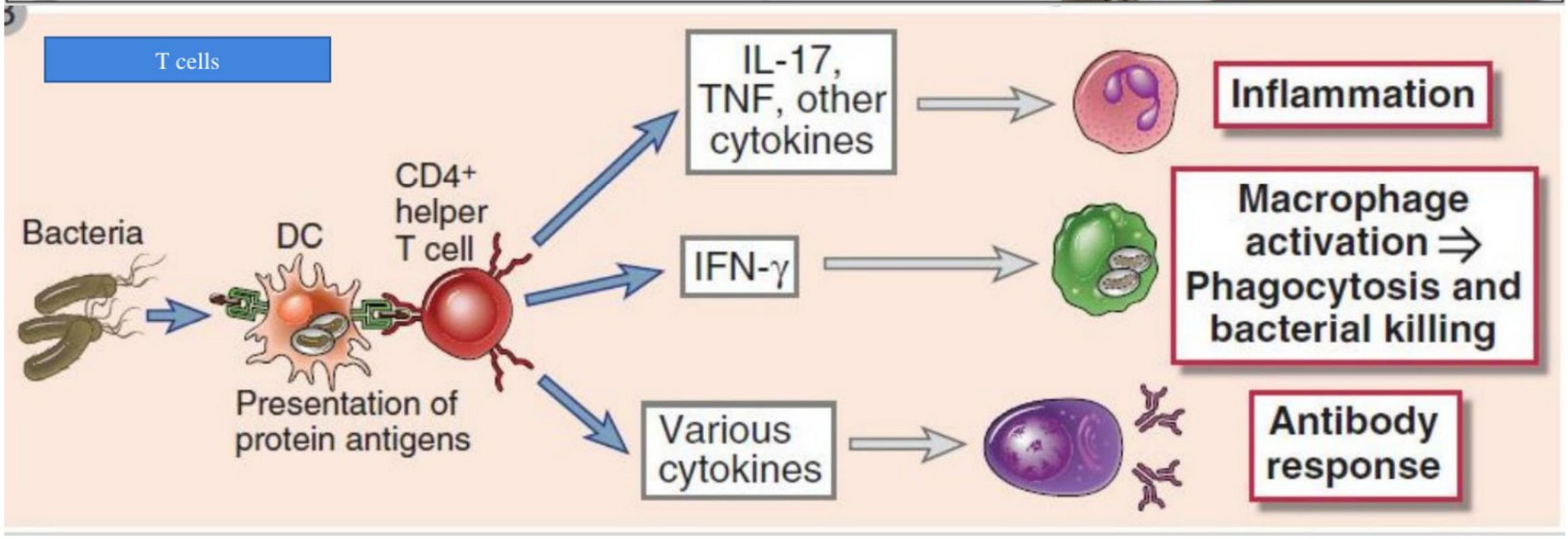
Secretion of hydrolytic enzymes and reactive oxygen intermediates into the external milieu that are capable of killing extracellular microbes too large to be phagocytosed. The same toxic products may damage tissues. (Oxygen independent)





Binding of **Fc receptors** causes an increase in **oxygen uptake** by the phagocyte called the **respiratory burst**. This influx of oxygen is used in a variety of mechanisms to cause damage to microbes inside the phagolysosome, but the common theme is the creation of **highly reactive small molecules** that damage the biomolecules of the pathogen.





Certain bacterial toxins stimulate all the T cells in an individual that express a particular family of Vβ T cell receptor (TCR) genes. Such toxins are called superantigens

→ 2: Defence against intracellular pathogens:

Parts of the immune system that response against intracellular pathogens: 1) Phagocytes (sometimes) 2) Natural killer cells (have 3 mechanisms) 3) t cells 4) Interferons

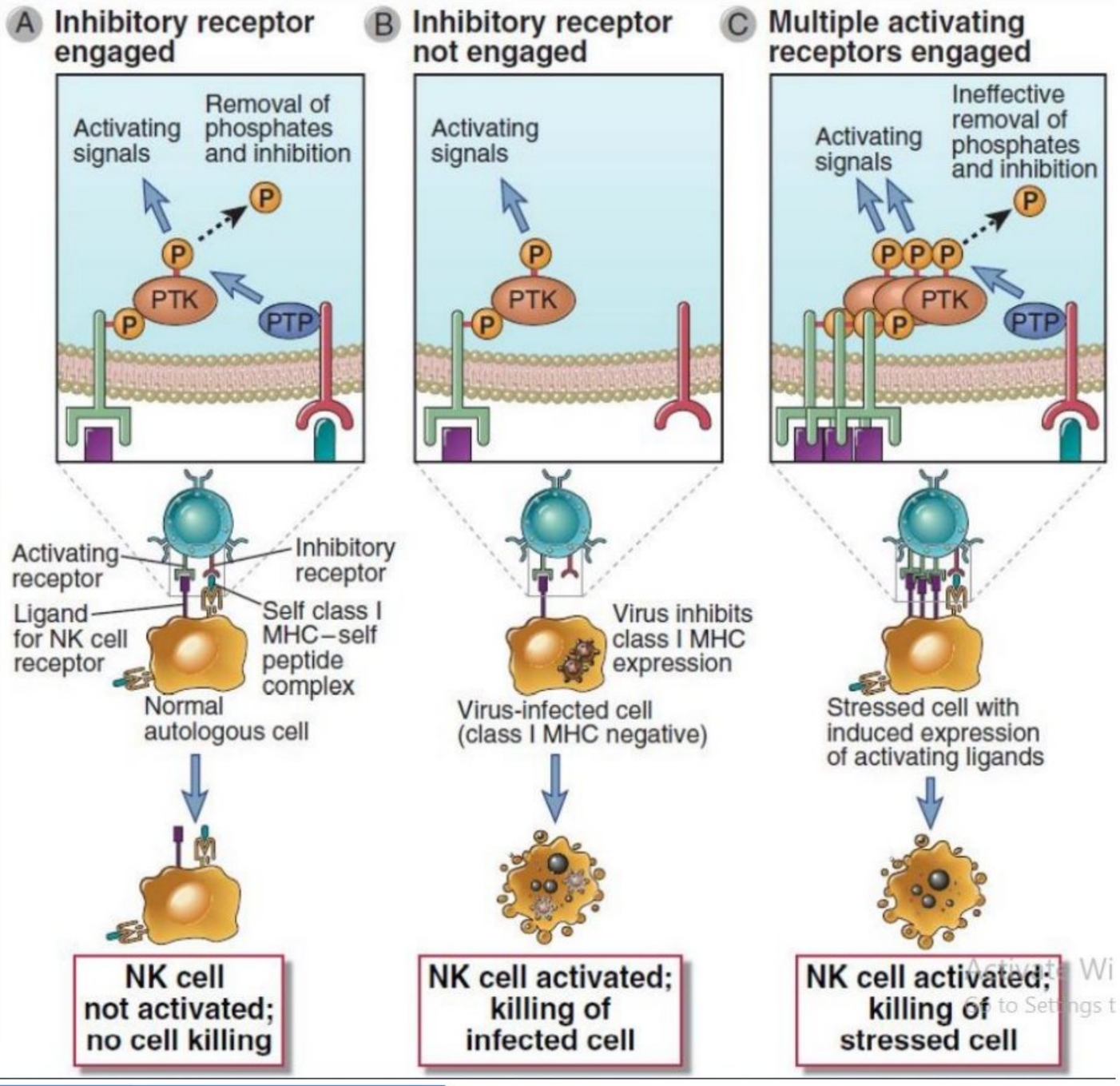
• Antibodies that bind to antigens can be recognised by FcϒRIII (CD16) receptors expressed on NK cells, resulting in NK activation, release of cytolytic granules and consequent cell apoptosis. This allows NK cells to target cells against which a humoral response has been gone through and to lyse cells through antibody-dependant cytotoxicity (ADCC).

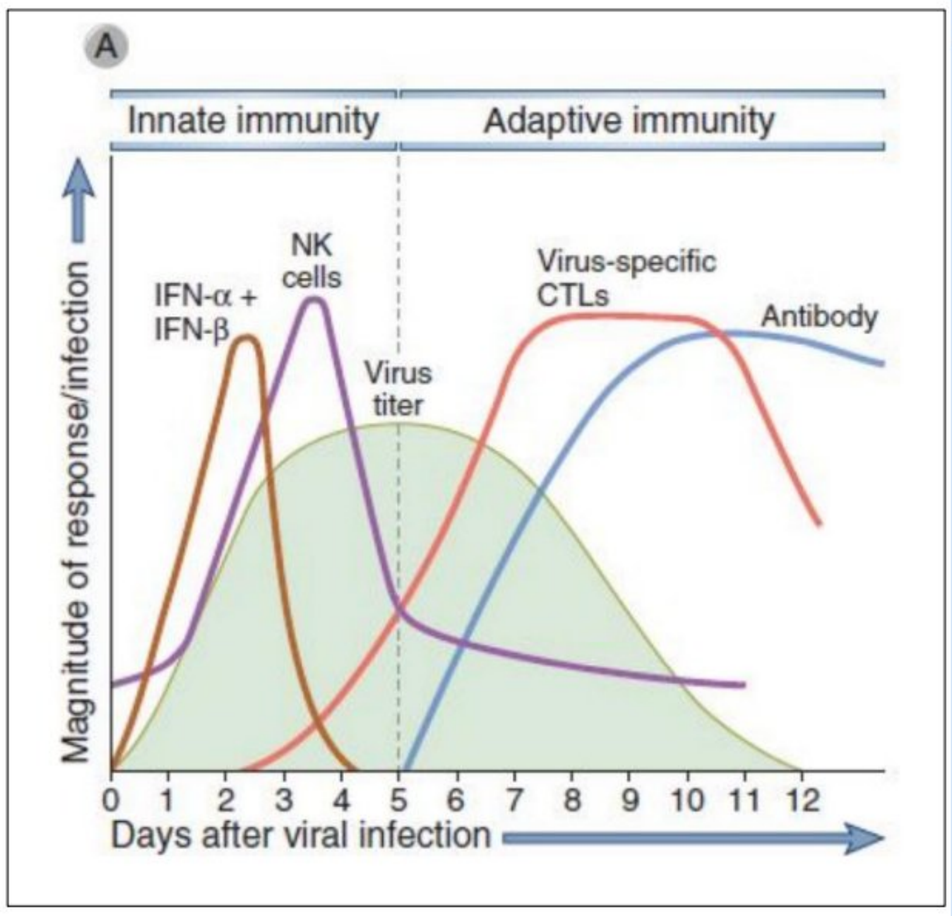
• NK cells work to control viral infections by secreting IFNγ and TNFα. IFNγ activates macrophages for phagocytosis and lysis, and TNFα acts to promote direct NK tumor cell killing.

A, Activating receptors of NK cells recognize ligands on target cells and activate protein tyrosine kinase (PTK), whose activity is inhibited by inhibitory receptors that recognize class I MHC molecules and activate protein tyrosine phosphatases (PTP). NK cells do not efficiently kill class I MHC–expressing healthy cells.

B, If a virus infection or other stress inhibits class I MHC expression on infected cells and induces expression of additional activating ligands, the NK cell inhibitory receptor is not engaged and the activating receptor functions unopposed to trigger responses of NK cells, such as killing of target cells and cytokine secretion.

C. Cells stressed by infection or neoplastic transformation may express increased amounts of activating ligands, which bind NK cell activating receptors and induce more tyrosine phosphorylation than can be removed by inhibitory receptor associated phosphatases, resulting in killing of the stressed cells





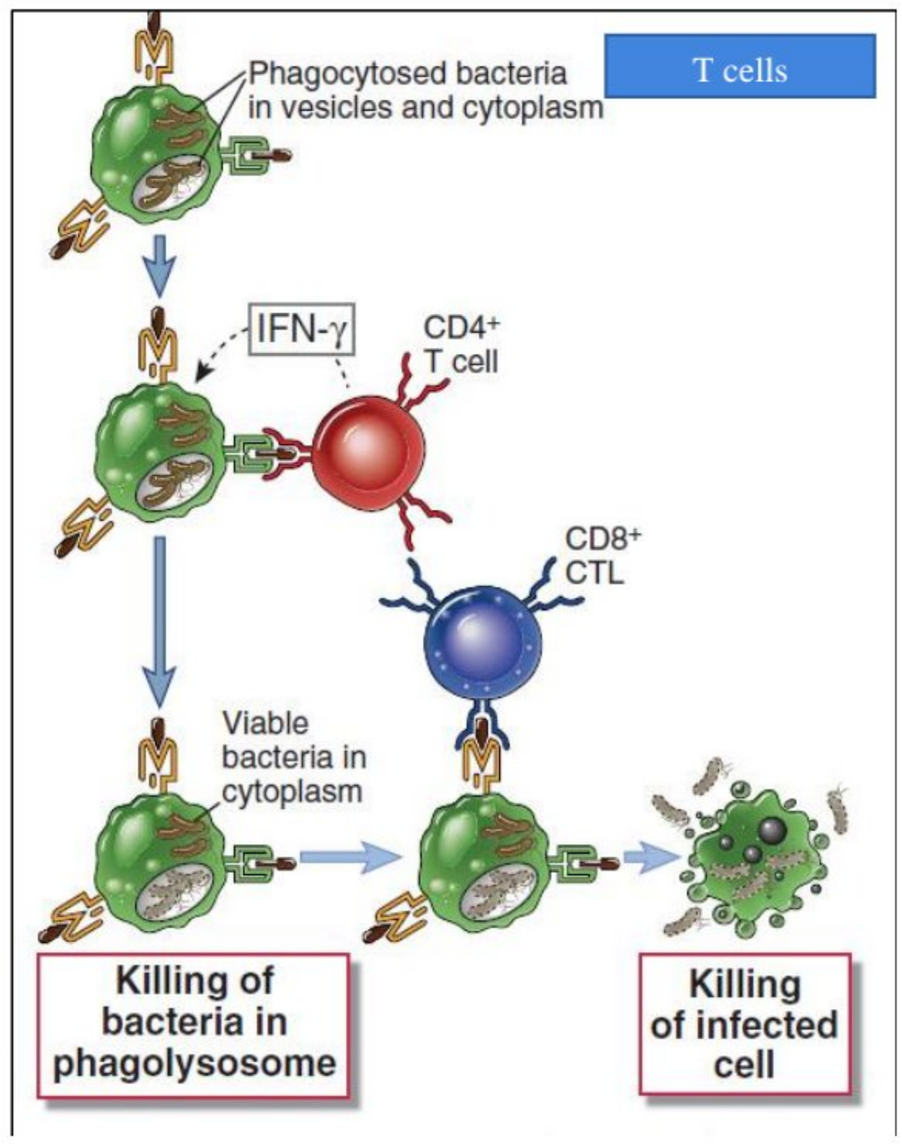
Interferons

• The major way by which the innate immune system deals with viral infections is to induce the expression of type I interferons. Type I interferons are a large family of structurally related cytokines that mediate the early innate immune response to viral infections.

• Type I interferons, signaling through the type I interferon receptor, activate transcription of several genes that confer on the cells a resistance to viral infection, called an antiviral state.

• Type I interferons cause sequestration of lymphocytes in lymph nodes, thus maximizing the opportunity for encounter with microbial antigens.

• Type I interferons increase the cytotoxicity of NK cells and CD8+ CTLs • Upregulate expression of class I MHC molecules and thereby increase the probability that virally infected cells will be recognized and killed by CD8+ CTLs



(Lecture 7)

→ 1: Introduction

• serology: The study of antibodies and their reactions with antigens

• Serum: Blood plasma with it's proteins without coagulation factors.

• antiserum : Any serum sample that contains detectable antibody molecules that bind to a particular antigen.

• A healthy 70-kg adult human produces about 2 to 3 g of antibodies every day. (large amount)

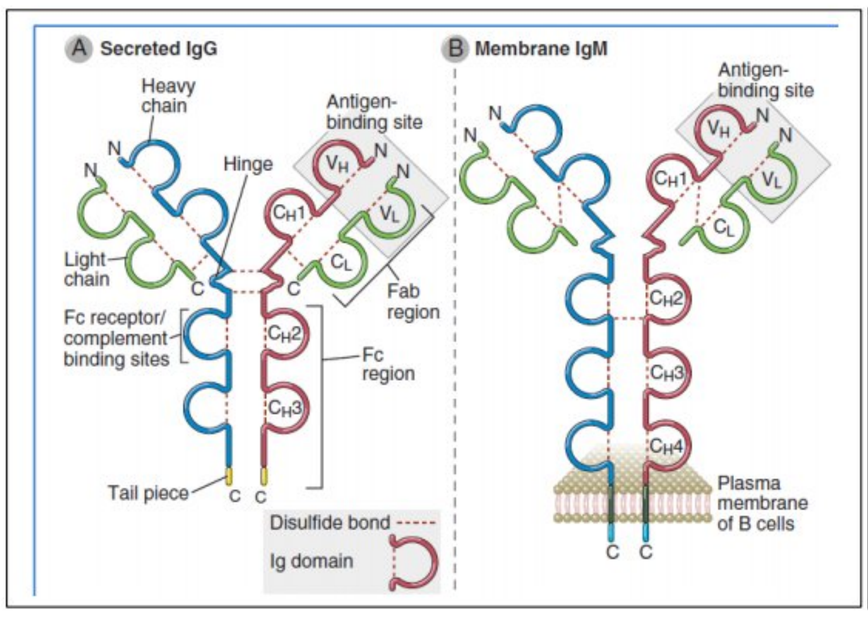
• affinity: The strength of the binding between a single site of an antibody and an epitope of an antigen

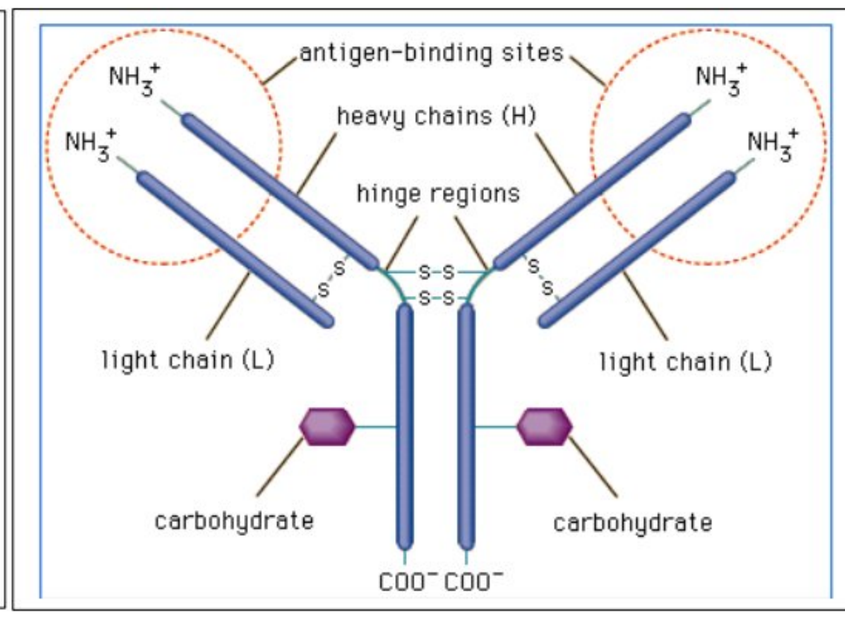
• avidity: a single antibody may attach to a single multivalent antigen by more than one binding site. the strength of attachment of the antibody to the antigen must take into account binding of all the sites to all the available epitopes. This overall strength of attachment is called the avidity

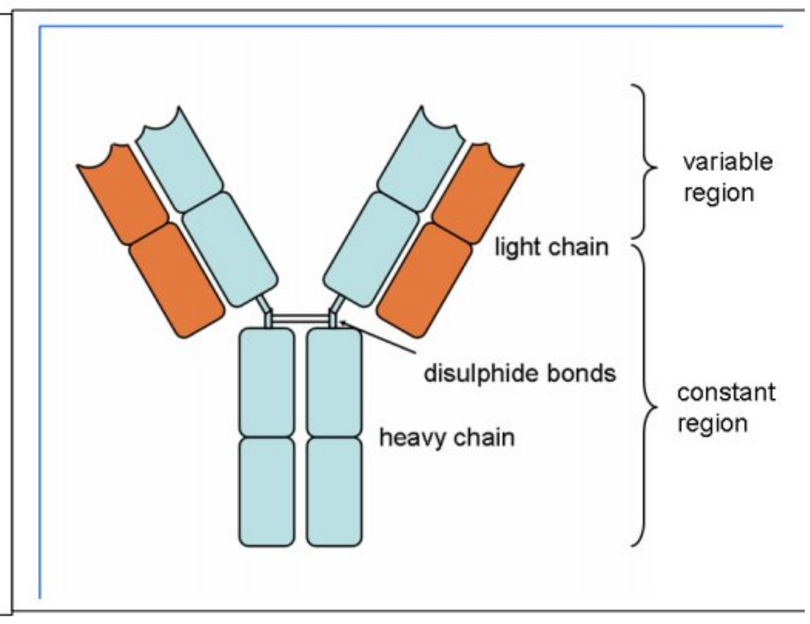
→ 2: Differences between antibodies

Types of differences between antibodies: 1) Cell bound or free 2) Different in class (isotype) 3) Different in affinity to a specific antigen among different B cells 4) Different in affinity to a specific antigen through affinity maturation for the same b cell

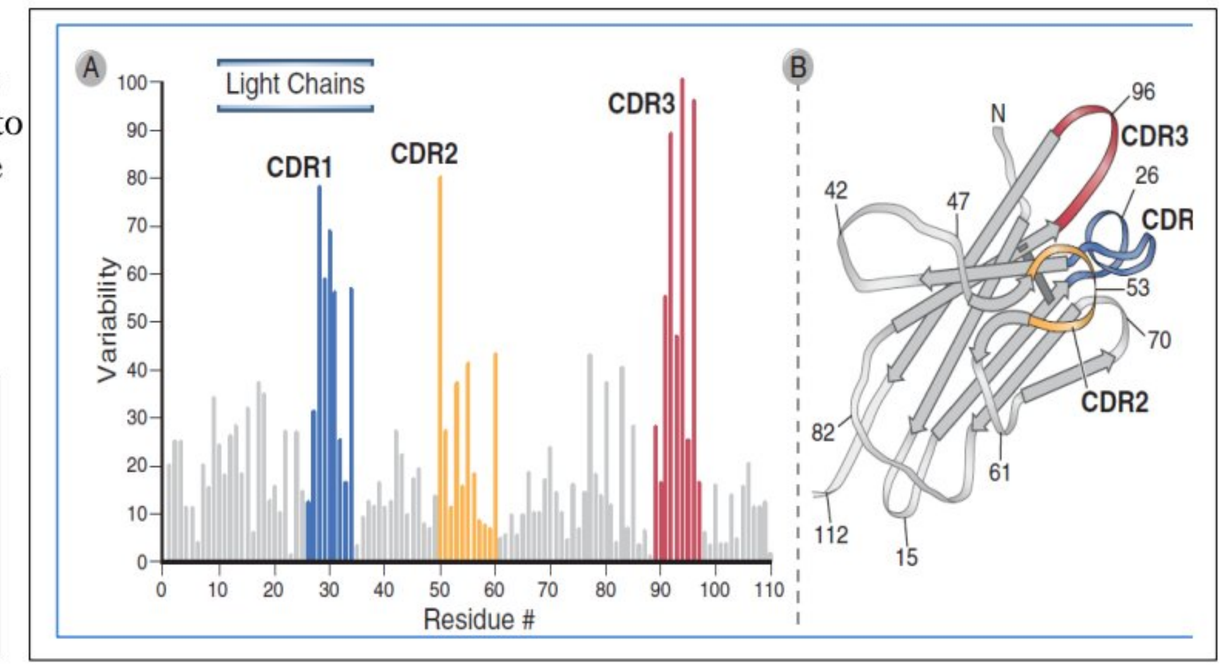
→ 3: Structure of antibody





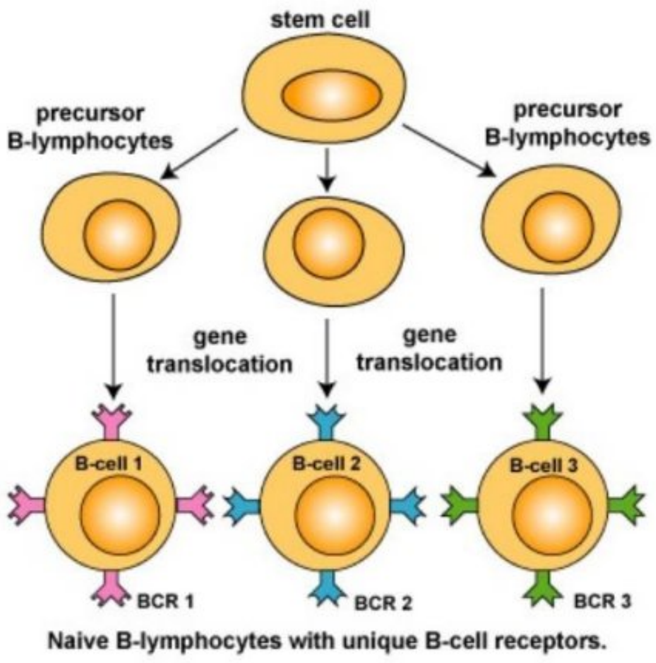


Most of the sequence differences and variability among different antibodies are confined to three short stretches in the V region of the heavy chain and to three stretches in the V region of the light chain. These diverse stretches are known as hypervariable segments, Because these sequences form a surface that is complementary to the three-dimensional structure of the bound antigen, the hypervariable regions are also called complementarity-determining regions (CDRs).



→ 4: Functions of antibodies:
1.Neutralization of infectivity
2.Phagocytosis
3.Antibody-dependent cellular cytotoxicity (ADCC)
4.Complement-mediated lysis of pathogens or of infected cells
5.Transcytosis, mucosal immunity & neonatal immunity

→ 5: Formation & maturation of B cells (Just understand those pictures)



Naive B-lymphocytes with unique B-cell receptors.

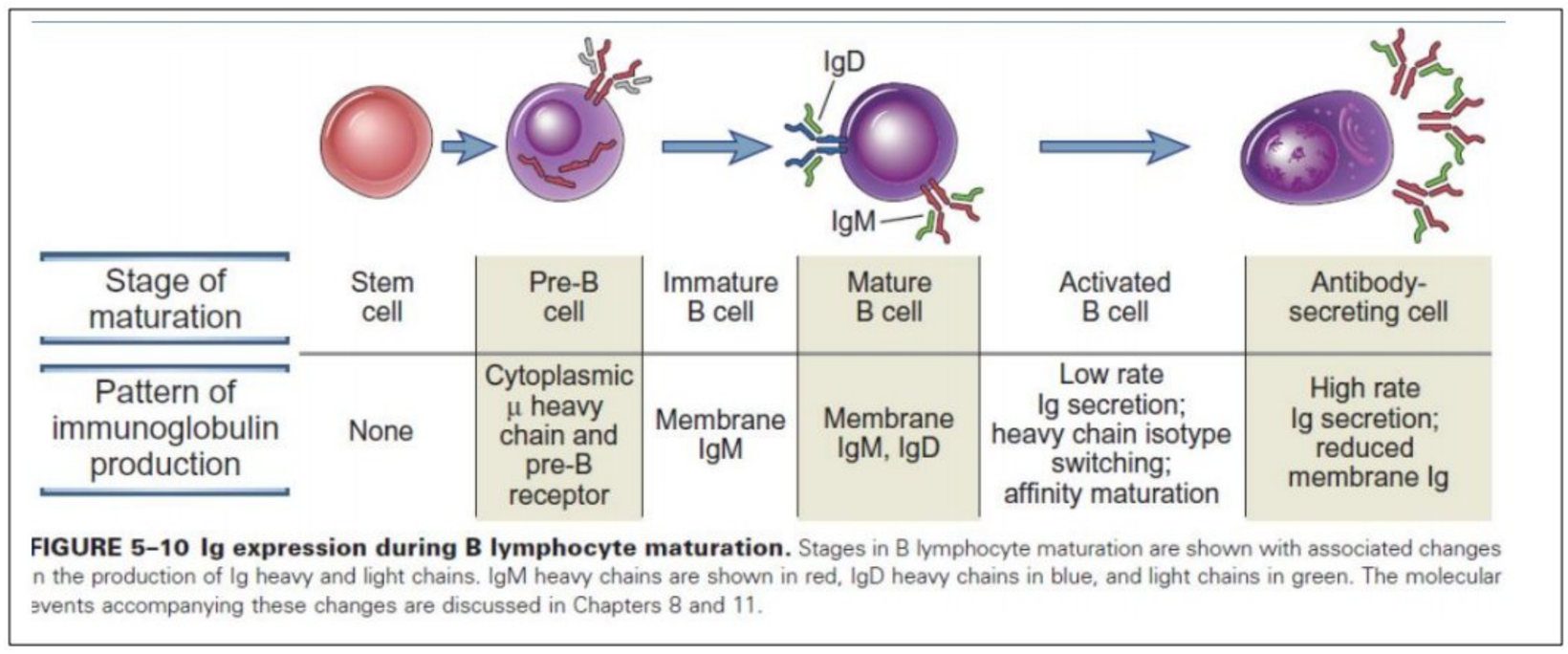
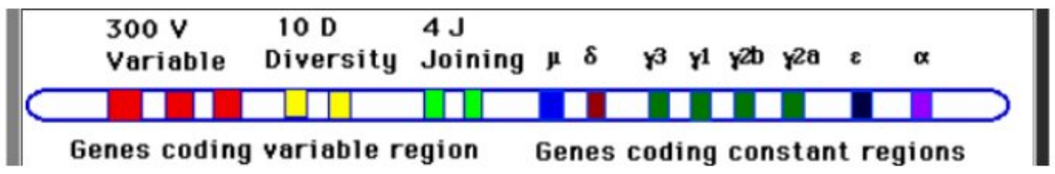
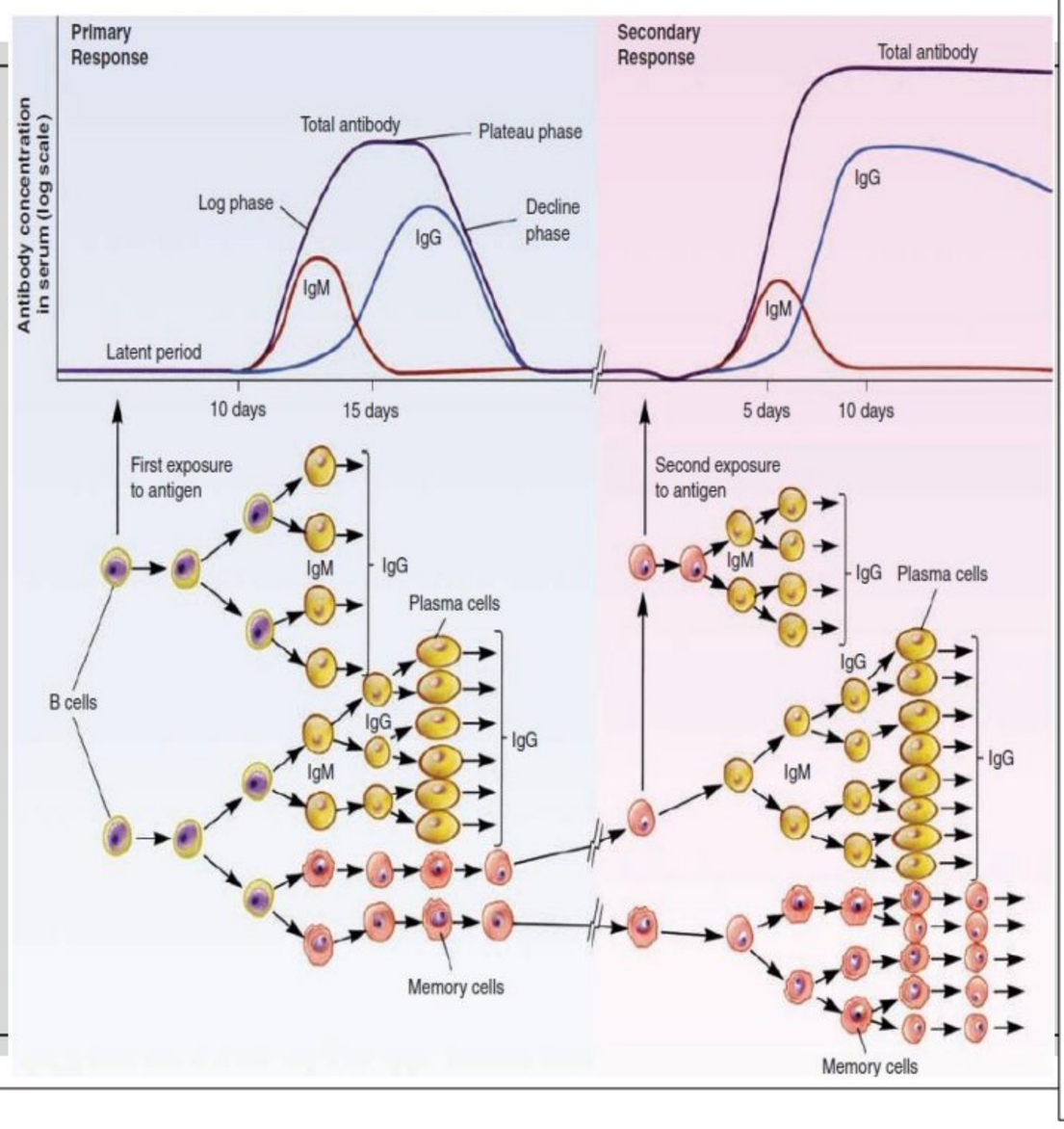
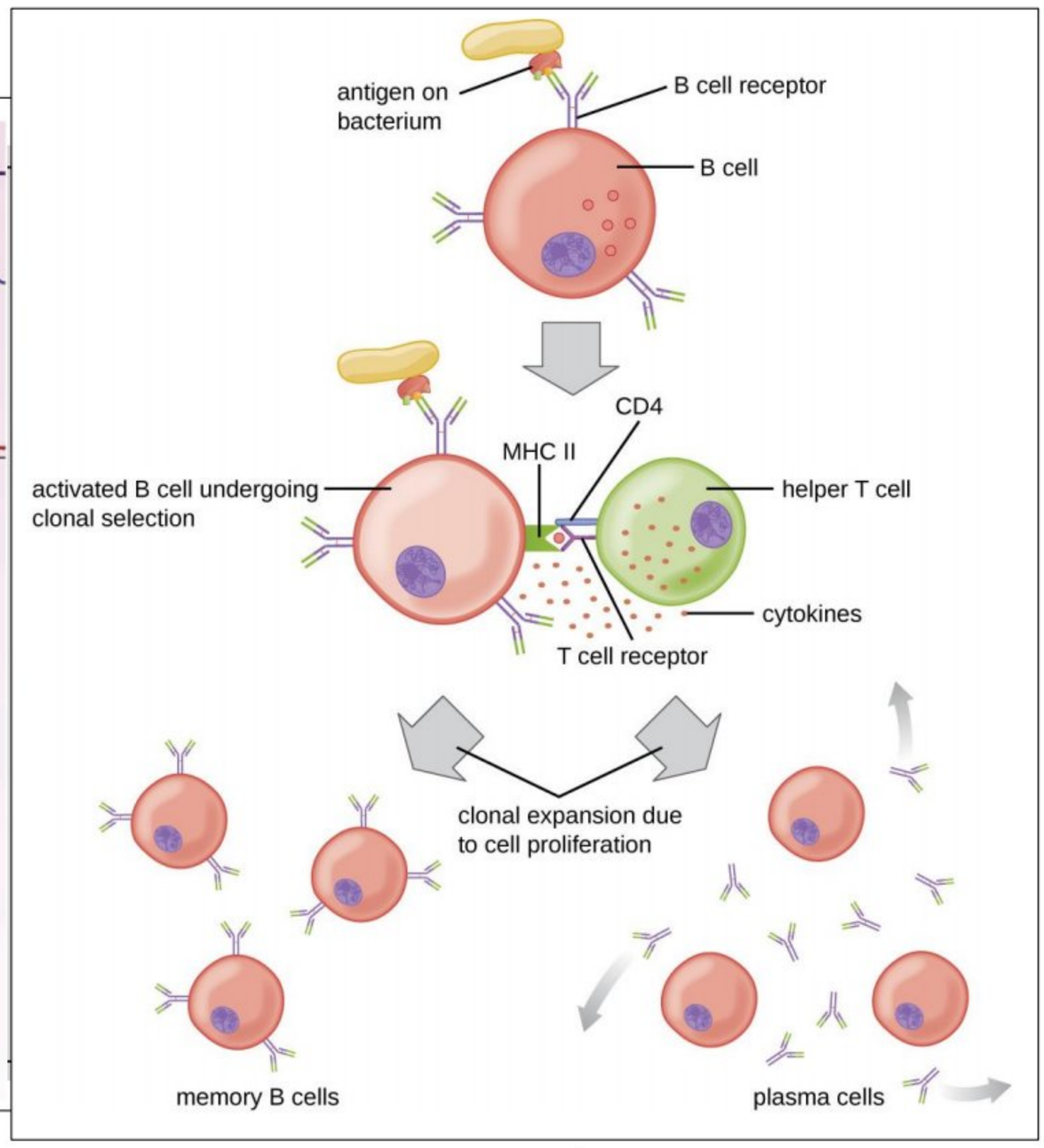


FIGURE 5–10 Ig expression during B lymphocyte maturation. Stages in B lymphocyte maturation are shown with associated changes n the production of Ig heavy and light chains. IgM heavy chains are shown in red, IgD heavy chains in blue, and light chains in green. The molecular events accompanying these changes are discussed in Chapters 8 and 11.



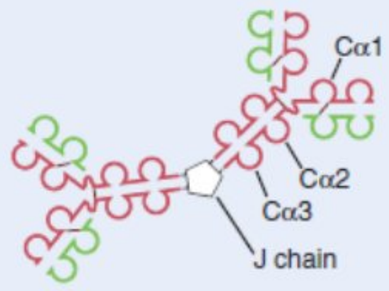
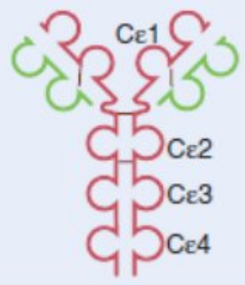
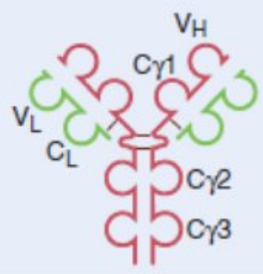
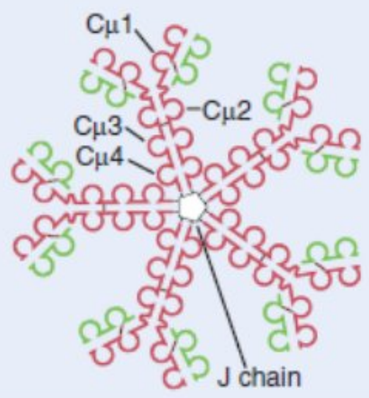




• After initial secretion of IgM, cytokines secreted by T- cells stimulate the plasma cells to switch from IgM production to production of IgG, IgA, or IgE.
• This process, called class switching or isotype switching, allows plasma cells cloned from the same activated B cell to produce a variety of antibody classes with the same antigen specificity.
• Class switching is accomplished by genetic rearrangement of gene segments encoding the constant region, which determines an antibody's class. The variable region is not changed, so the new class of antibody retains the original antigen specificity.

→ 6: Types of antibodies

TABLE 5–2 Human Antibody Isotypes

Isotope of Antibody	Subtypes (H Chain)	Serum Concentration (mg/mL)	Serum Half-life (days)	Secreted Form		Functions
IgA	IgA1,2 (α1 or α2)	3.5	6	IgA (dimer) Monomer, dimer, trimer		Mucosal immunity
IgD	None (δ)	Trace	3	None		Naive B cell antigen receptor
IgE	None (ε)	0.05	2	IgE Monomer		Defense against helminthic parasites, immediate hypersensitivity
IgG	IgG1-4 (γ1, γ2, γ3, or γ4)	13.5	23	IgG1 Monomer		Opsonization, complement activation, antibody-dependent cell-mediated cytotoxicity, neonatal immunity, feedback inhibition of B cells
IgM	None (μ)	1.5	5	IgM Pentamer		Naive B cell antigen receptor, complement activation

(Lecture 10)

→ 1: How the antigen is arrived into B cells?

First of all, how B cells reach and stay in lymph nodes?

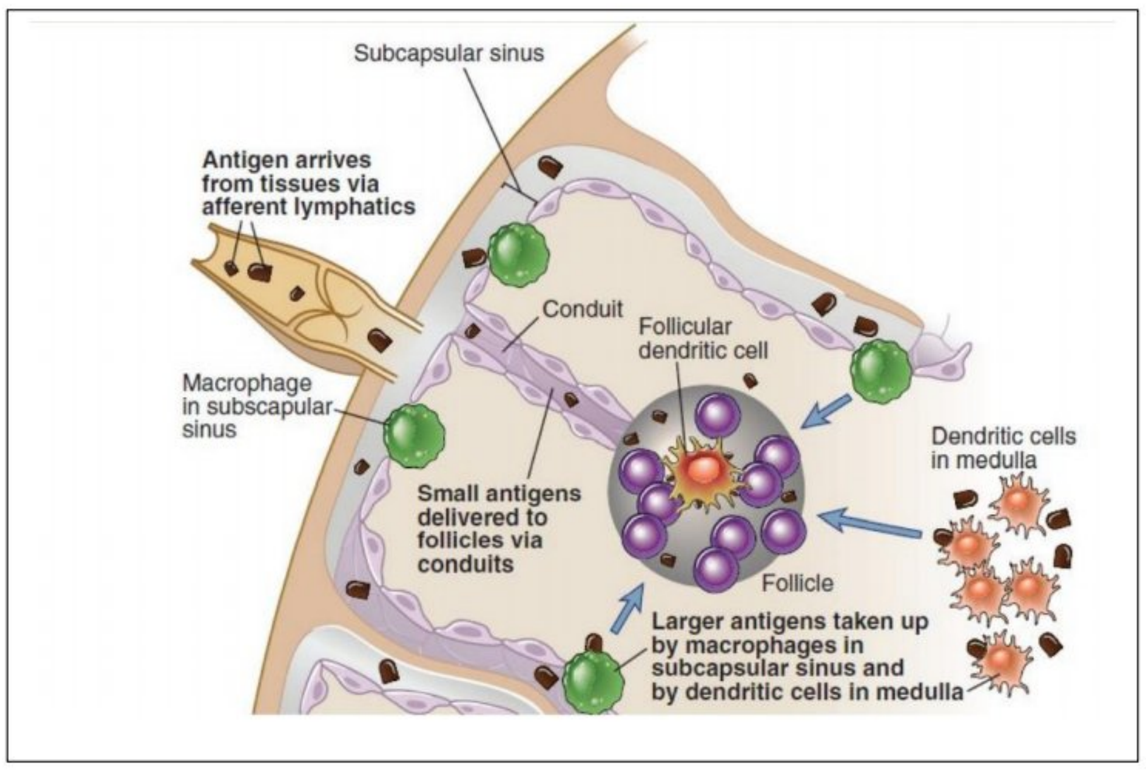
o Most B cells enter follicles guided by the chemokine CXCL13 secreted by follicular dendritic cells and are called follicular B cells or recirculating B cells. CXCL13 binds to the CXCR5 chemokine receptor on recirculating naive B cells and attracts these cells into the follicles

o Naive follicular B cells survive for limited periods until they encounter antigen, survival depends on signals from the BCR as well as on inputs received from a cytokine called BAFF (B cell–activating factor of the TNF family, also known as BLyS, for B lymphocyte stimulator), which provides maturation and survival signals through the BAFF receptor.

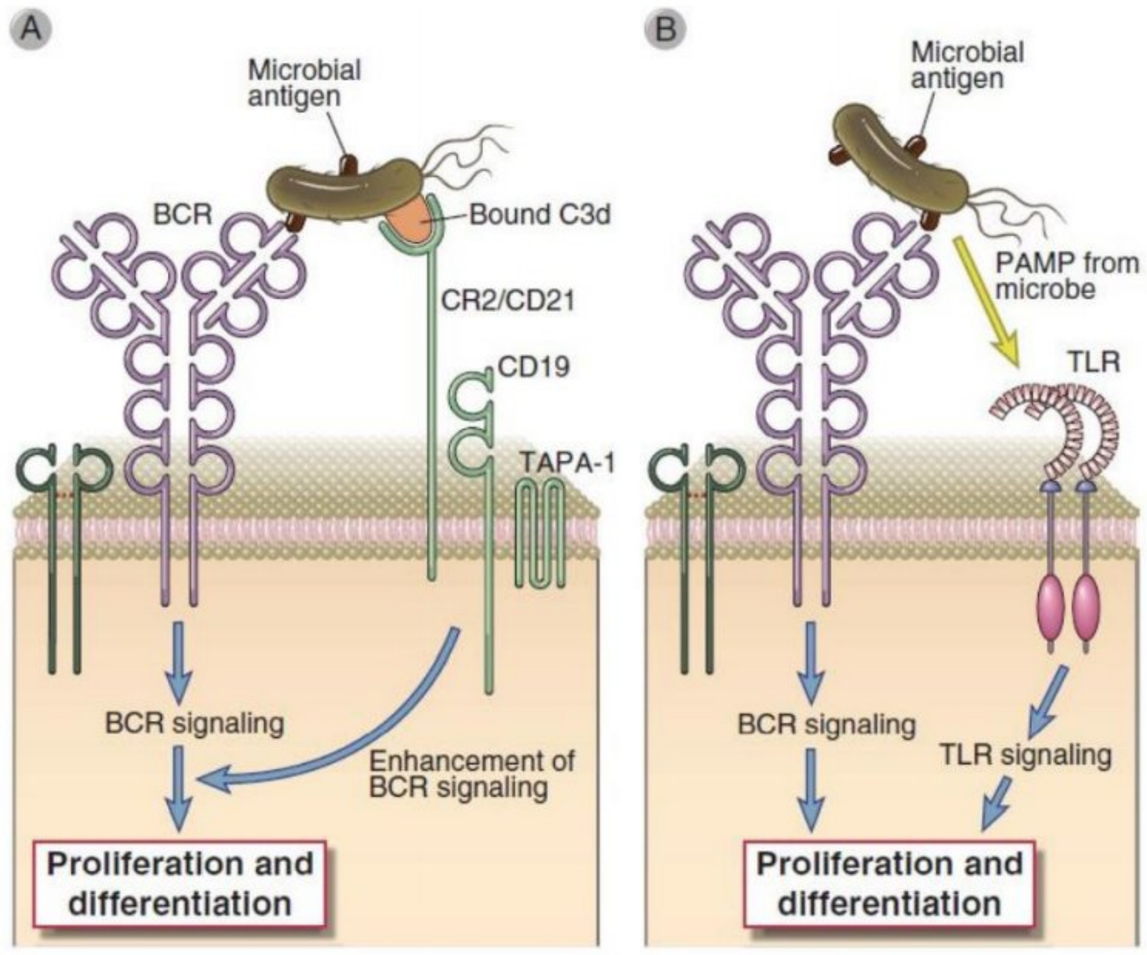
o Now let's answer our question: How the antigen is arrived into B cells?

For follicular B cells: 1) Soluble antigens, generally smaller than 70 kD, may reach the B cell zone interact directly with specific B cells. 2) Subcapsular sinus macrophages capture large microbes and antigen-antibody complexes 3) Medium sized antigens may be captured in the medullary region by resident dendritic cells

For marginal zone B cells: Antigens in immune complexes may bind to complement receptors on marginal zone B cells, and these cells can transfer the immune complex–containing antigens to follicular B cells



→ 2: Role of CR2 & TLRs in B cell activation



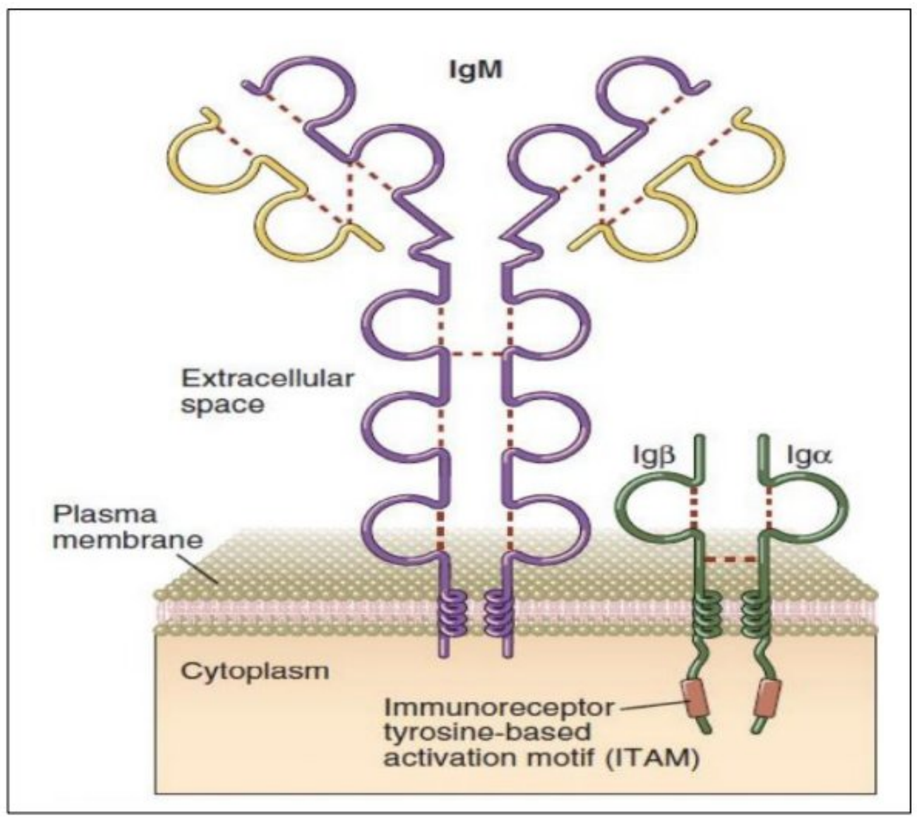
→ 3: Structural notes about B cells

• Membrane IgM and IgD, the antigen receptors of naïve B cells, have short cytoplasmic tails consisting of only three amino acids

• Ig-mediated signals are transduced by two other molecules, called Igα and Igβ, that are disulfide linked to one another and are expressed in B cells noncovalently associated with membrane Ig

• B cell receptor complexes in class-switched B cells, including memory B cells, contain membrane immunoglobulins that may be of the IgG, IgA, or IgE classes

• After an antigen binds to a B cell, it enters into the G1 stage of the cell cycle, and this is accompanied by increases in cell size, cytoplasmic RNA, and biosynthetic organelles such as ribosomes. The survival of the stimulated B cells is enhanced as a result of the production of various antiapoptotic proteins, notably Bcl-2 (Overexpression of this gene is associated with cancers)



→ 4: activation of B cells can take two pathways (very very important):

T independent B cells activation	T dependent B cells activation
B-1 B cells & marginal zone b cells	Follicular b cell
Weak activation	Strong activation
Short	Long
Non-protein antigens(e.g. polysaccharides)	Protein antigens
Antibodies are usually IgM	Antibodies are usually IgG
No need for helper t cells	Need helper t cells

◦ a. T independent B cells activation: occurs in B1 b cells and marginal zone b cells, antigen bind and cross link their receptors activating them

• B-1 B cells, differs from the majority of B lymphocytes and develops in a unique manner. These cells develop from fetal liver–derived HSCs. B-1 cells as well as marginal zone B cells spontaneously secrete IgM antibodies that often react with microbial polysaccharides and lipids. B-1 cells contribute to rapid antibody production against microbes in particular tissues, such as the peritoneum. At mucosal sites, as many as half the IgA-secreting cells in the lamina propria may be derived from B-1 cells.

• Marginal zone B cells are located primarily in the vicinity of the marginal sinus in the spleen and are similar to B-1 cells in terms of their limited diversity and their ability to respond to polysaccharide antigens and to generate natural antibodies

b) T dependent B cell activation:

• Steps of activation:

1) Binds to antigen then internalizes it into endosomal vesicles, and if the antigen is a protein, it is processed into peptides that may be presented on the B cell surface for recognition by helper T cells.

2) The expression of receptors for several T cell–derived cytokines is also increased.

3) On the other side in the parafollicular zone, the same antigen is presented to CD4+ t cells on antigen-presenting cells to activate them

 Now: The frequency of naive B cells or T cells specific for a given epitope of an antigen is as low as 1 in 105 to 1 in 106 lymphocytes, and both populations have to be activated and the specific B and T cells have to find each other and physically interact to generate strong antibody responses, How this will happen?

• Helper T cells that have been activated by antigen and costimulation are induced to proliferate, express CD40L, and secrete cytokines. They also downregulate the chemokine receptor CCR7 and increase the expression of CXCR5 and as a result leave the T cell zone and migrate toward the follicle. CXCL13, the ligand for CXCR5, is secreted by follicular dendritic cells and other follicular stromal cells, and it contributes to the migration of activated CD4+ T cells toward the follicle.

• BCR engagement by these antigens results in reduced cell surface expression of the chemokine receptor CXCR5 and increased expression of CCR7, which is normally expressed on T cells. As a result, activated B cells migrate toward the T cell zone drawn by a gradient of CCL19 and CCL21, the ligands for CCR7.

• A protein antigen that elicits a T-dependent B cell response therefore makes use of at least two epitopes when activating specific B cells. A surface epitope on the native protein is recognized with high specificity by a B cell, and an internal linear peptide epitope is subsequently released from the protein, binds class II MHC molecules, and is recognized by helper T cells.

• The antibodies that are subsequently secreted are usually specific for conformational determinants of the native antigen.

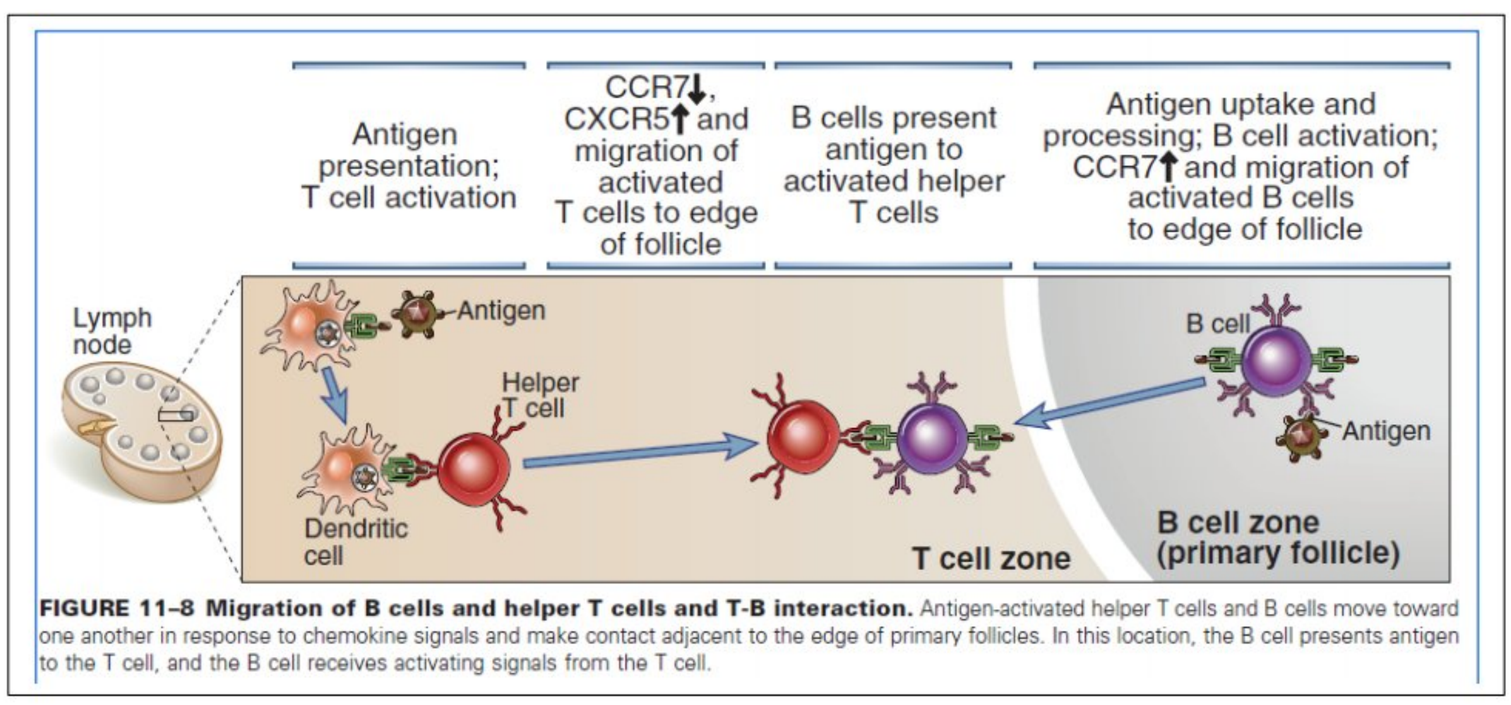
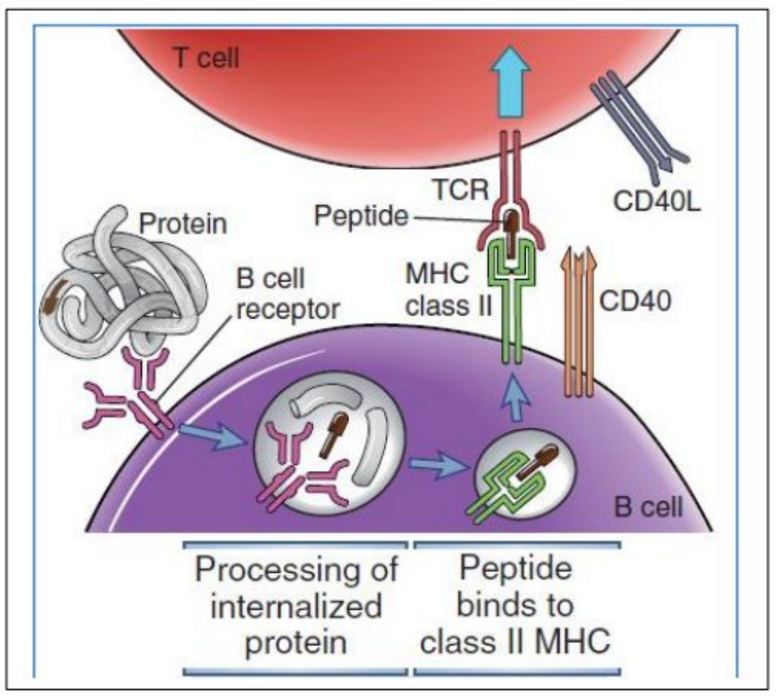


FIGURE 11–8 Migration of B cells and helper T cells and T-B interaction. Antigen-activated helper T cells and B cells move toward one another in response to chemokine signals and make contact adjacent to the edge of primary follicles. In this location, the B cell presents antigen to the T cell, and the B cell receives activating signals from the T cell.



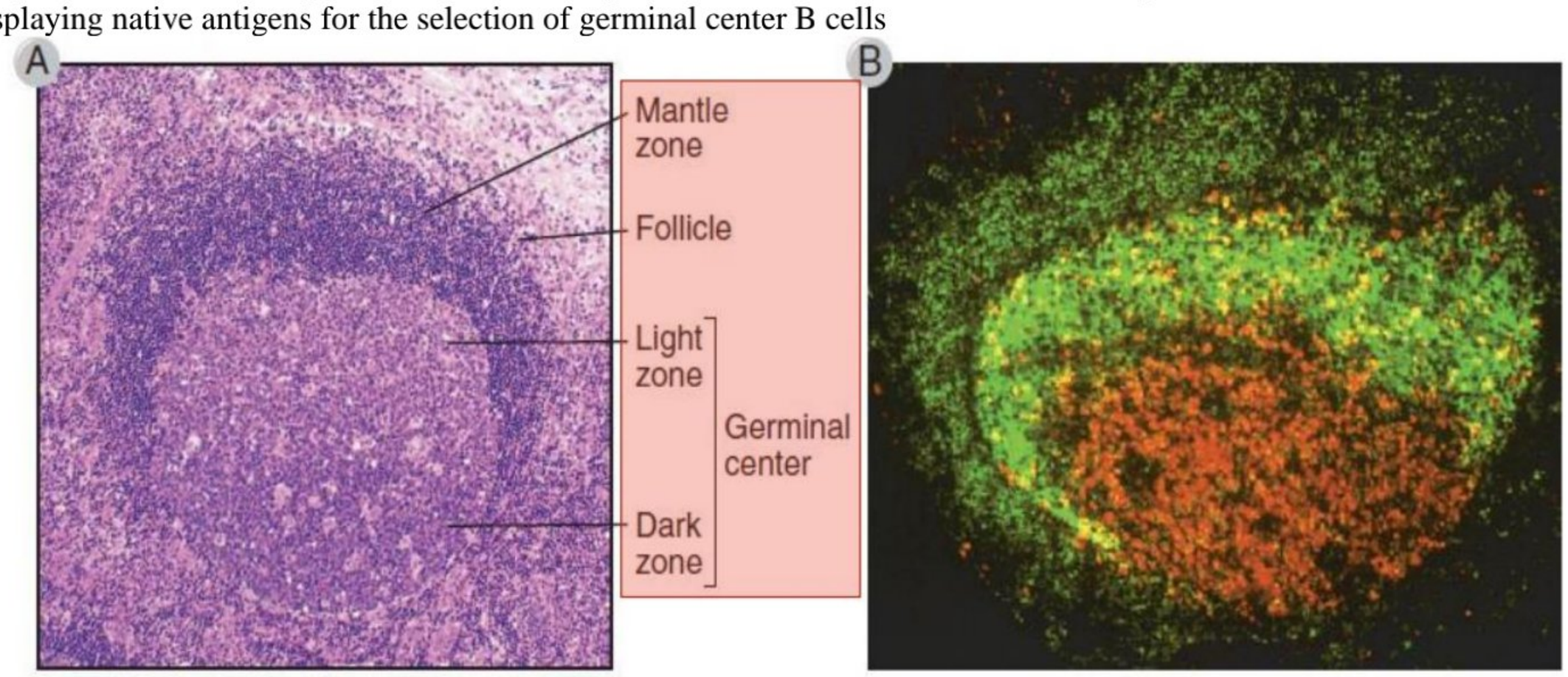
The activation of B cells results in their proliferation, leading to clonal expansion, followed by differentiation, culminating in the generation of memory B cells and antibody-secreting plasma cells. (will be discussed in next lecture)

Hapten-carrier effect:

Haptens are small chemicals that can be bound by specific antibodies but are not immunogenic by themselves. If, however, haptens are coupled to proteins, which serve as carriers, the conjugates are able to induce antibody responses against the haptens. o This can be used in the production of conjugate vaccines. A conjugate vaccine consists of a polysaccharide antigen that is conjugated to a carrier molecule.

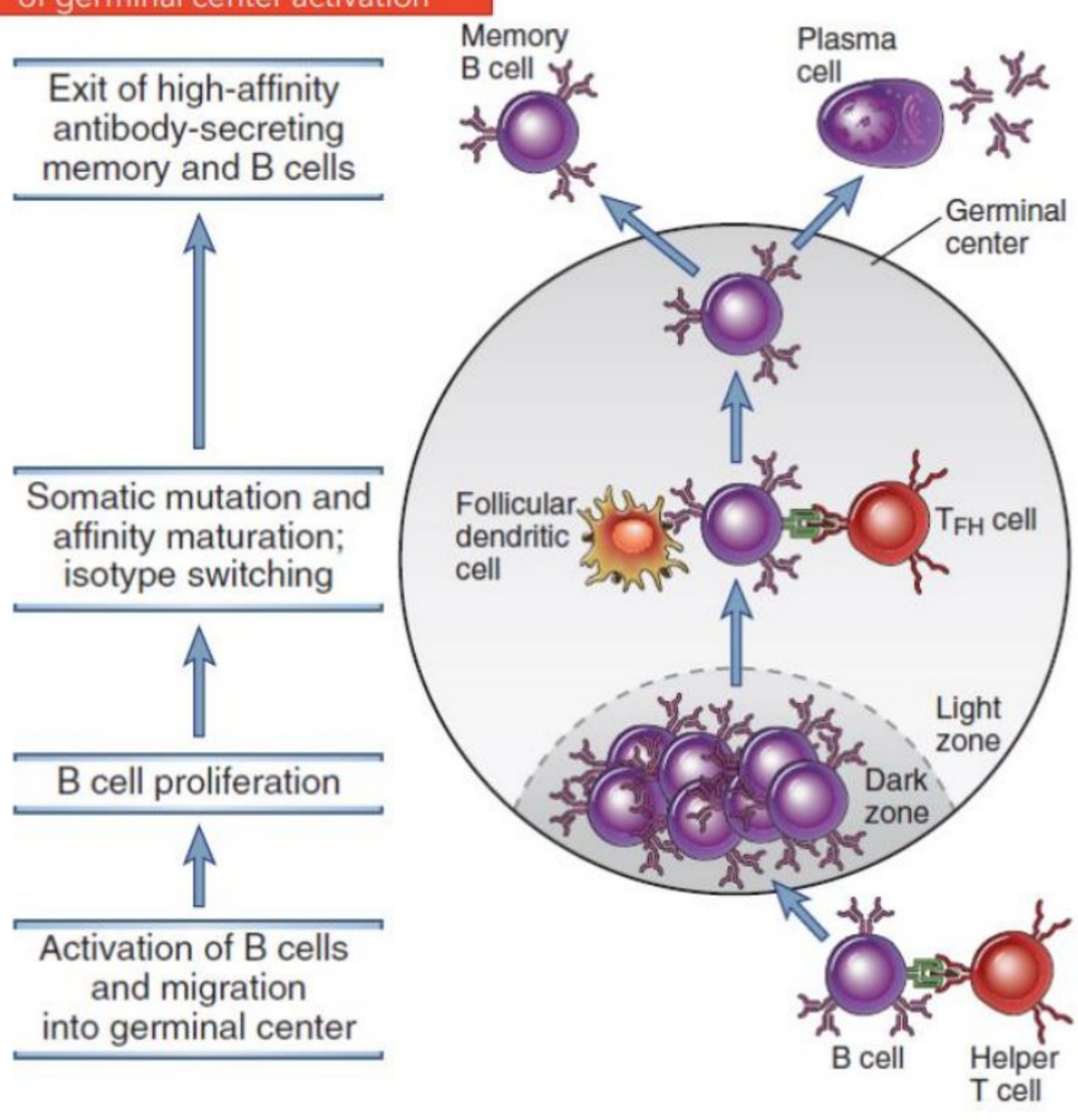
(Lecture 12)

→1: Types of T dependent b cells activation
→ There are two types of T dependent b cell activation:
1) Germinal center activation: appear a few days later, occurs by formation of a germinal center inside a follicle and include specialized follicular helper T (TFH) that have numerous effects
2) Extrafollicular foci of T-dependent B cell activation: generated relatively early in an immune response. - We will start speaking about the germinal center activation
→ There are 4 characteristic events of helper T cell–dependent antibody responses that occur primarily in the germinal centers of lymphoid follicles:
a) affinity maturation: to have antibodies with better affinities
b) isotype switching: switching from IgM to IgG, IgE or IgA
c) long-lived plasma cell differentiation.
d) generation of memory B cells.
→ Let's speak about the structure of the germinal center before we discuss the 4 events mentioned up:
- Each fully formed germinal center contains cells derived from only one or a few antigen-specific B cell clones
- Remember that primary follicle (before formation of germinal center) contains different naïve B-cells along with follicular dendritic cells.
-germinal center has 3 main cells: 1. Activated B-cells 2. Follicular T-helper cells: 3. Follicular dendritic center: are found only in lymphoid follicles and express complement receptors (CR1, CR2, and CR3) and Fc receptors. These molecules are involved in displaying native antigens for the selection of germinal center B cells

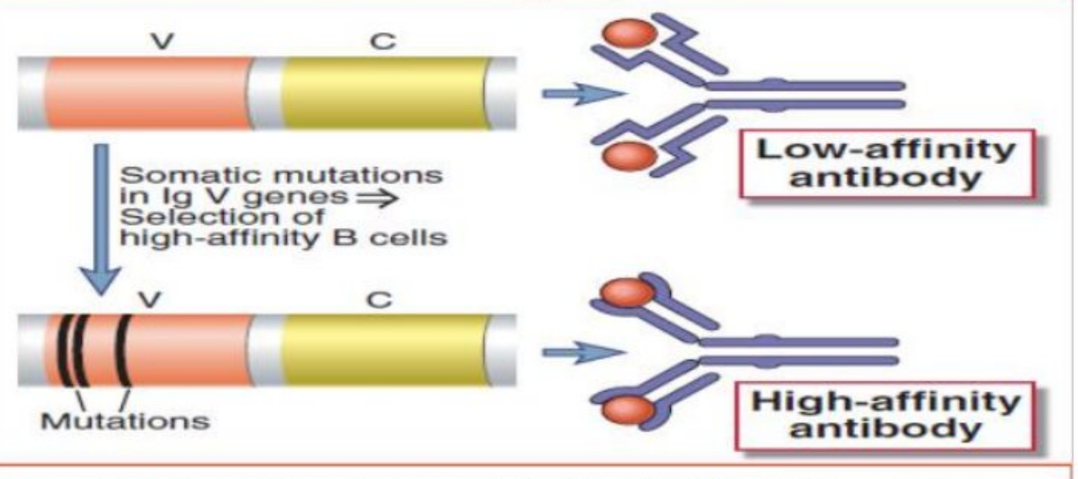


-Now, with immunofluorescence, we label cells with certain tags:
1. Green stain: labeled with Anti-CD23 antibody which is found on naïve B-cells with dimly green stain outside the germinal center.
2. Bright green (light zone): here there is higher density of CD23 found on Follicular dendritic cells.
3. Red (Dark zone): Detect cycling cells or mitotic active B-cells. Part of these B-cell migrate to light zone>>Yellow stain (due to mixing red with green stain), which may indicate B-cells that express CD23(Green)and highly mitotic(Red).

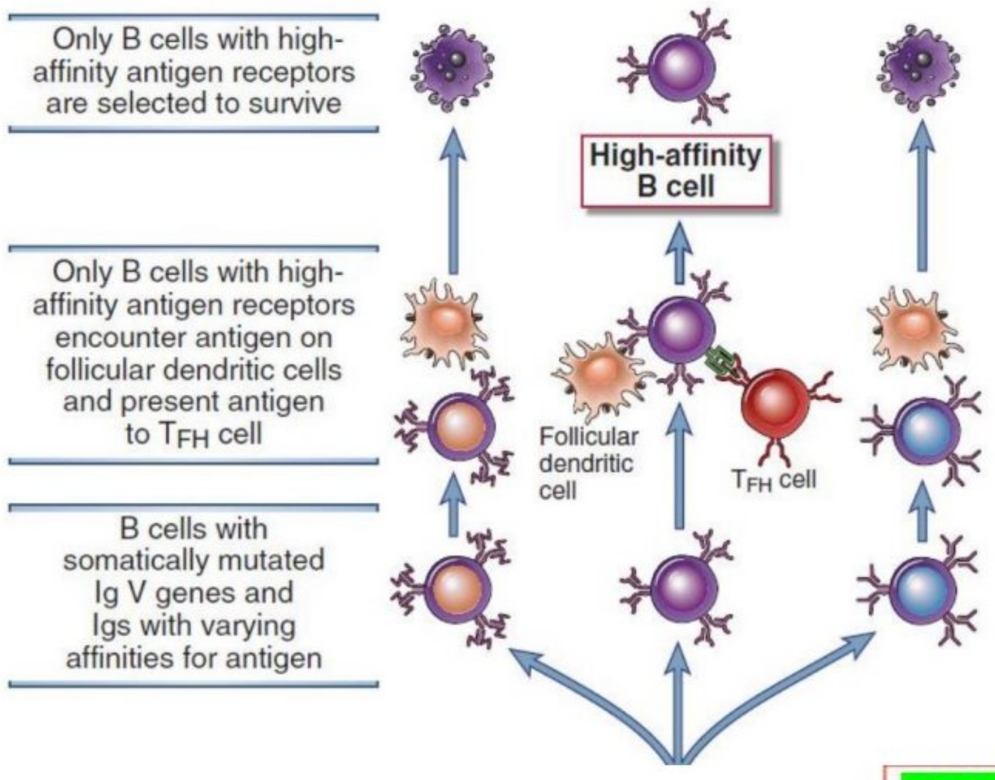
This picture summarize the 4 steps of germinal center activation

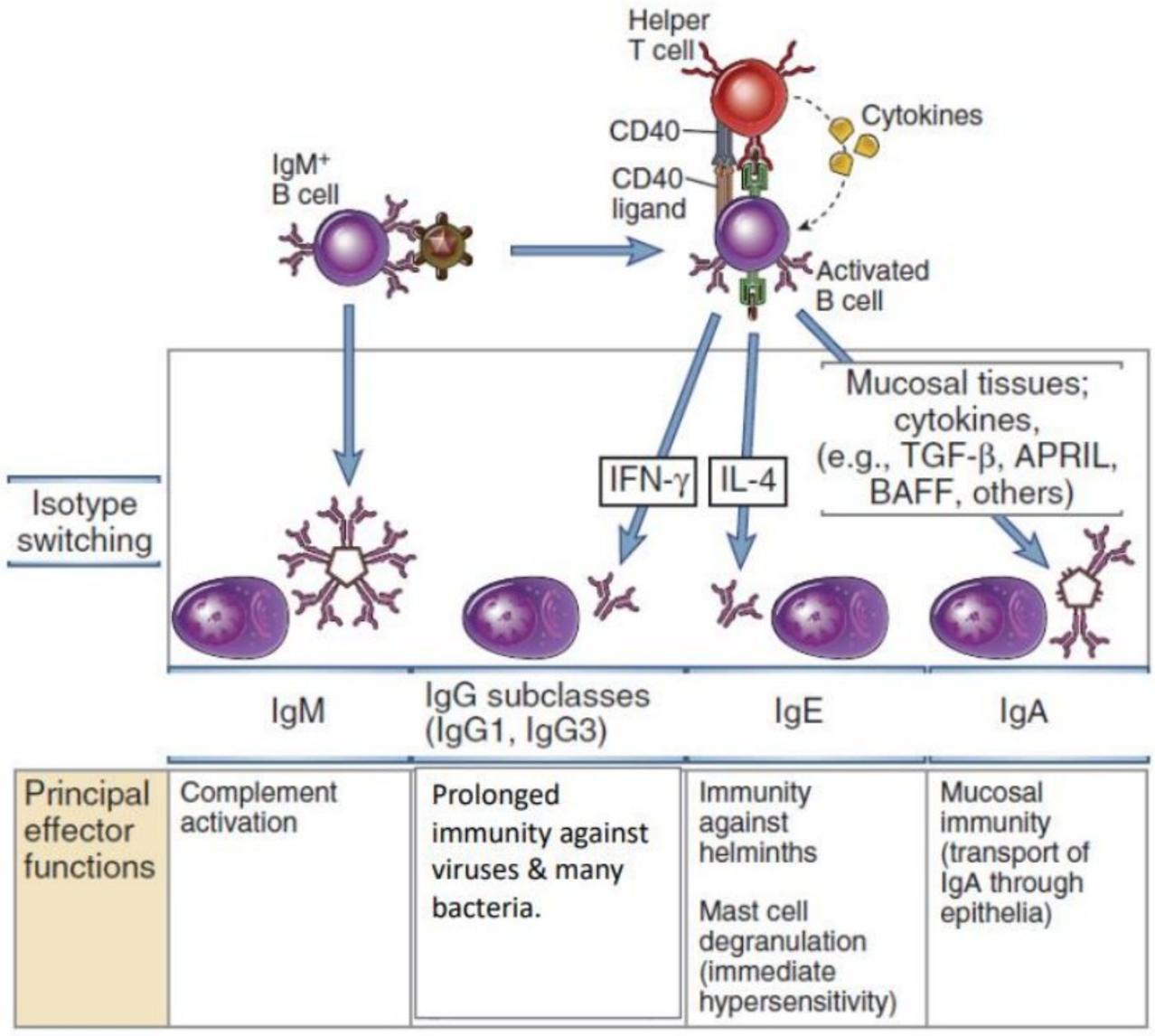


→ So what occurs in the germinal center? Let's start with:
a) affinity maturation!
1) Activated B cell enters the germinal center
2) B cells undergo proliferation in the dark zone & mutate about 1000 times more than normal cells in the body when replicating , especially in the variable region of the Ig genes, which will produce either high or low affinity antibodies.
3) B-cells with antibodies with different affinities when they migrate to light zone, there will be Follicular TH-cell that releases IL-21 cytokine which induce apoptosis of B-cells, unless these B-cells are rescued by a survival signal, which is binding of **HIGH AFFINITY** B-cell to antigens found on FCDs and also bind to Follicular T helper cell that release cytokines to keep them alive. So low affinity B-cells can't bind these cells and will undergo apoptosis.



Note: Helper T cells and CD40:CD40L interactions are required for somatic mutation to be initiated





b) Isotype switching

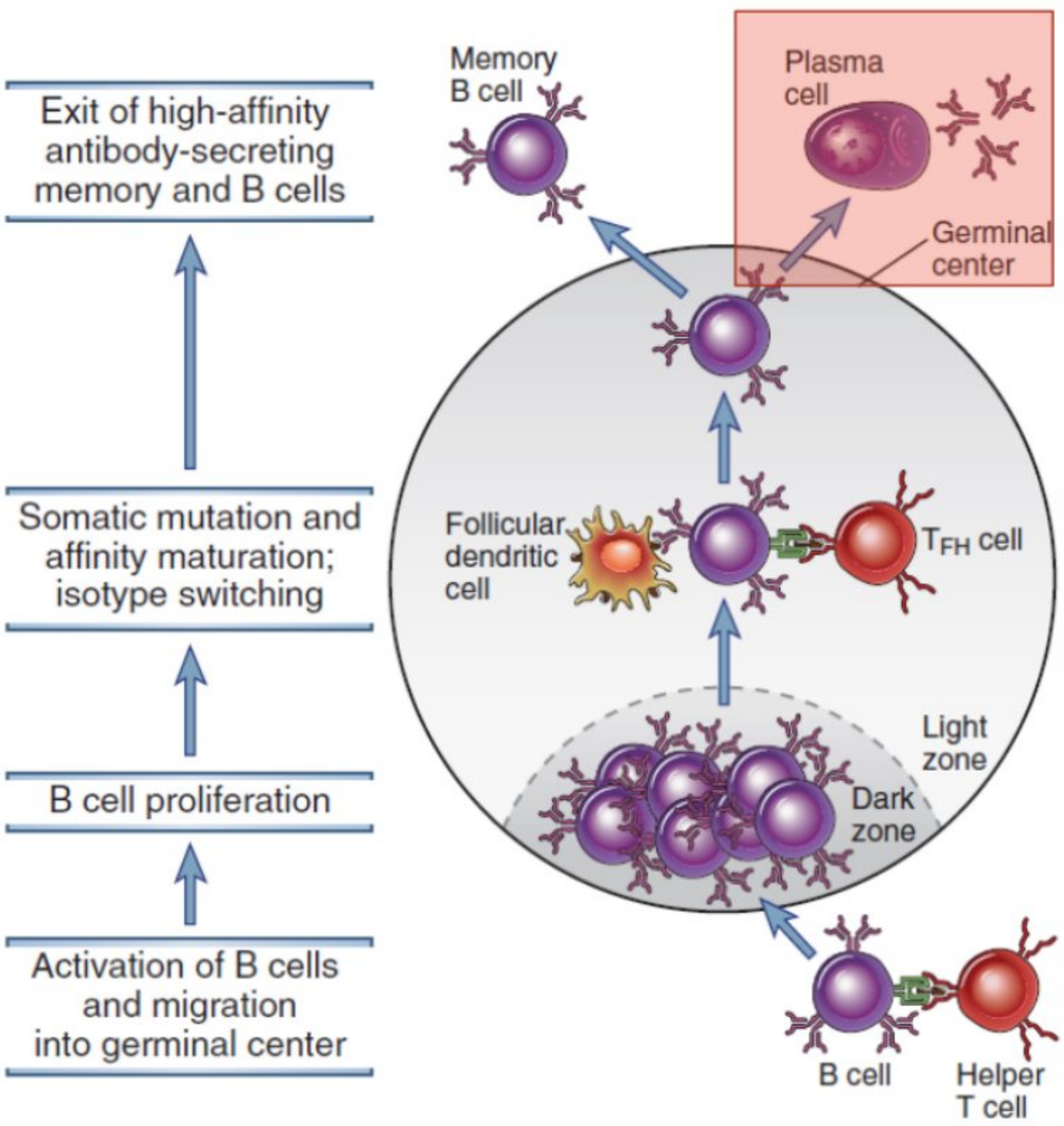
→ Isotype switching in response to differen types of microbes is regulated by cytokines produced by the helper T cells that are activated by these microbes.

→ Polysaccharide antigens, which do not elicit T cell help, stimulate mainly IgM antibodies, with little if any isotype switching to some IgG subclasses

→ Viruses and many bacteria activate helper T cells of the TH1 subset, which produce the cytokine IFN-γ.

→ Helminths activate the TH2 subset of helper T cells, which produces IL-4, the cytokine that induces switching to IgE (Also happens in hypersensitivity reactions).

→ B cells in different anatomic sites switch to different isotypes. Specifically, B cells in mucosal tissues switch to IgA, which is the antibody class that is most efficiently transported through epithelia into mucosal secretions, where it defends against microbes that try to enter through the epithelia



c) long-lived plasma cell differentiation:

→ Plasma cells are morphologically distinct, terminally differentiated (can't go back and do isotype switching for example) B cells committed to abundant antibody production.

→ Long lived plasma cells are generated after the activation of B cells through signals from the BCR, CD40, TLRs, and other receptors including cytokine receptors.

→ **Long-lived plasma cells (for life time)** : generated in T-dependent germinal center responses to protein antigens. Signals from the B cell antigen receptor and IL-21 cooperate in the generation of plasma cells, acquire the ability to home to the bone marrow, where they are maintained by cytokines of the BAFF family (B Cell activating factor of TNF family) which keep giving them survival signals. They set in the bone marrow for 20-30 years and they never go out again. Typically, 2 to 3 weeks after immunization with a T cell–dependent antigen, the bone marrow becomes a major site of antibody production.

→ Plasma cells in the bone marrow may continue to secrete antibodies for months or even years after the antigen is no longer present. That's why if you test different people you will find different pool of antigens depending on the antigens that they have encountered.

→ It is estimated that almost half the antibody in the blood of a healthy adult is produced by long-lived plasma cells and is specific for antigens that were encountered in the past.

Changes during differentiation of b cells include:

➢ the cell enlarges dramatically, and the ratio of cytoplasm to nucleus also undergoes a striking increase. The endoplasmic reticulum becomes prominent, and the cell is transformed into a secretory cell that bears little or no resemblance to a B cell.

➢ The change in Ig production from the membrane form (characteristic of B cells) to the secreted form (in plasma cells)

d) Generation of memory b cells: A non-terminally activated b cell that is produced from the germinal center, they have done some affinity maturation, their function is: when the infection is eliminated and the body face the same antigen again, they undergo rapid activation and propagation, and enter germinal centers to improve affinity of antibodies, to change finally into plasma cells.

◦ They express high levels of the antiapoptotic protein Bcl-2.

◦ Some memory B cells may remain in the lymphoid organ where they were generated, whereas others exit germinal centers and recirculate (same as naïve cells as they look to encounter the antigen again) between the blood and lymphoid organs.

◦ They are produced in T cell dependent responses and usually emerge in parallel with memory helper T cells.

◦ The production of large quantities of isotype-switched, high-affinity antibodies is greatly accelerated after secondary exposure to antigens, because they don't have to repeat the cycle and go to the extra follicular foci, germinal center, isotype switching and so on.

◦ Note: Memory b cells usually emerge in parallel with memory helper T cells.

→ 2)Extrafollicular foci of T-dependent B cell activation: Occurs outside the germinal center, it produces short lived plasma cells are generally found in secondary lymphoid organs and in peripheral nonlymphoid tissues (like the skin), and sometime a little amount of memory b cells are generated

TABLE 11–1 Extrafollicular and Germinal Center B Cell Responses

Feature	Follicular/Germinal Center	Extrafollicular
Localization	Secondary follicles	Medullary cords of lymph nodes and at junctions between T cell zone and red pulp of spleen
CD40 signals	Required	Required
Specialized T cell help	T_{FH} cells in germinal center	Extrafollicular T helper cells
AID expression	Yes	Yes
Class switching	Yes	Yes
Somatic hypermutation	High rate	Low rate
Antibody affinity	High	Low
Terminally differentiated B cells	Long-lived plasma cells and memory cells	Short-lived plasma cells (life span of ~3 days)
Fate of plasma cells	Bone marrow or local MALT	Most die by apoptosis in secondary lymphoid tissues where they were produced
B cell transcription factors	Bcl-6	Blimp-1

AID, activation-induced cytidine deaminase; Bcl-6, B cell lymphoma 6; Blimp-1, B lymphocyte–induced maturation protein 1; IL-21R, interleukin-21 receptor; MALT, mucosa-associated lymphoid tissue; T_{FH}, follicular helper T cell.
Data from Vinusa CG, I Sanz, and MC Cook. Dysregulation of germinal centres in autoimmune disease. Nature Reviews Immunology 9:845-857, 2009.

→ 2: General overview of antibodies: include antibodies feedback, functions of antibodies, types of antibodies

- Secreted antibodies **inhibit continuing B cell activation** by forming antigen-antibody complexes that simultaneously bind to antigen receptors and inhibitory Fcγ receptors on antigen-specific B cells.
- The antigen-antibody complexes simultaneously interact with the antigen receptor (through the antigen) and with **FcγRIIB** (through the antibody), and this brings the inhibitory phosphatases close to the antigen receptors whose signaling is blocked.

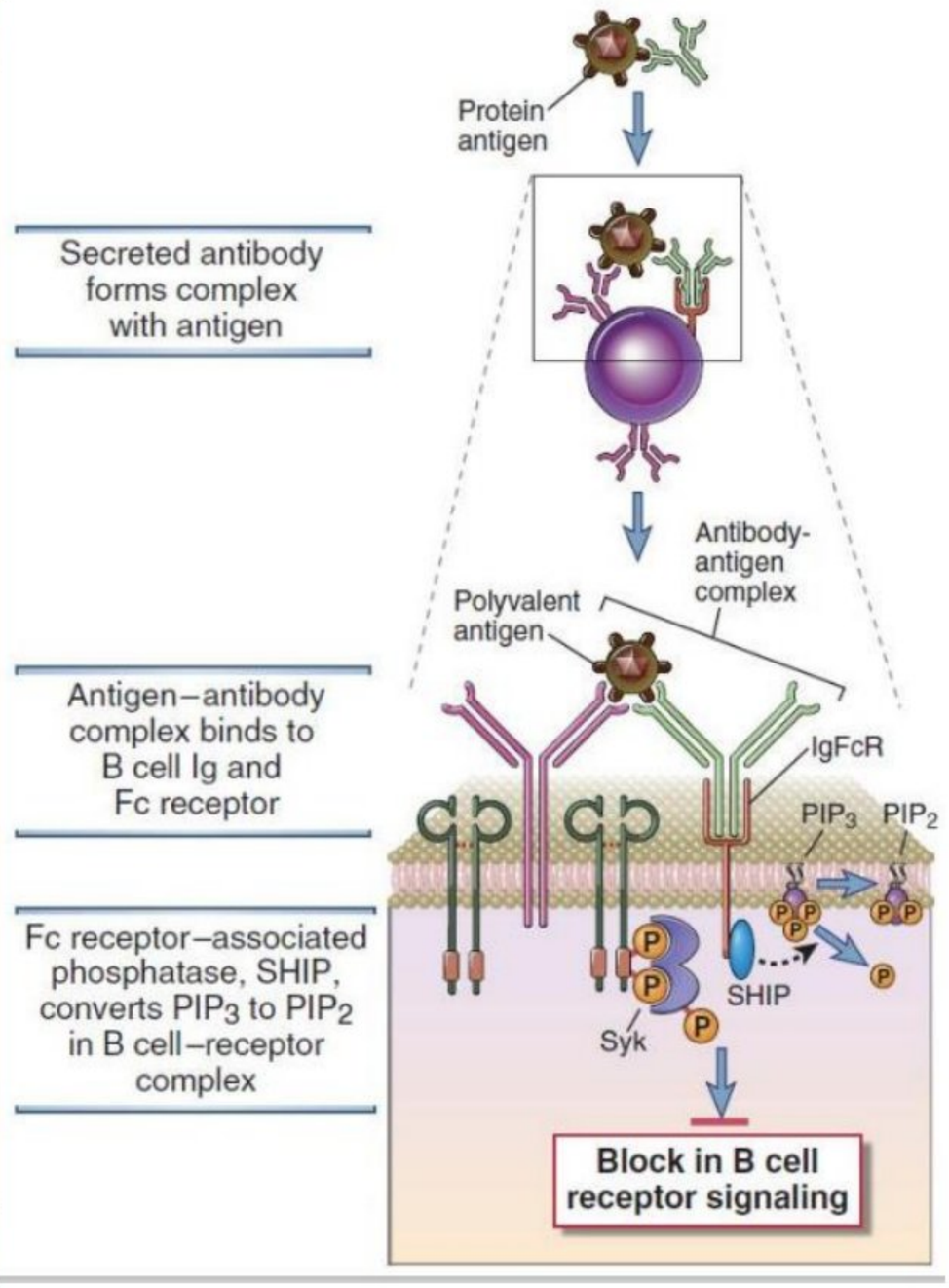


TABLE 12–3 Fc Receptors

FcR	Affinity for Immunoglobulin	Cell Distribution	Function
FcγRI (CD64)	High ($K_d < 10^{-9}$ M); binds IgG1 and IgG3, can bind monomeric IgG	Macrophages, neutrophils; also eosinophils	Phagocytosis; activation of phagocytes
FcγRIIA (CD32)	Low ($K_d > 10^{-7}$ M)	Macrophages, neutrophils; eosinophils, platelets	Phagocytosis; cell activation (inefficient)
FcγRIIB (CD32)	Low ($K_d > 10^{-7}$ M)	B lymphocytes	Feedback inhibition of B cells
FcγRIIC (CD32)	Low ($K_d > 10^{-7}$ M)	Macrophages, neutrophils, NK cells	Phagocytosis, cell activation
FcγRIIIA (CD16)	Low ($K_d > 10^{-6}$ M)	NK cells	Antibody-dependent cell-mediated cytotoxicity
FcγRIIIB (CD16)	Low ($K_d > 10^{-6}$ M); GPI-linked protein	Neutrophils	Phagocytosis (inefficient)
FcεRI	High ($K_d > 10^{-10}$ M); binds monomeric IgE	Mast cells, basophils, eosinophils	Cell activation (degranulation)
FcεRII (CD23)	Low ($K_d > 10^{-7}$ M)	B lymphocytes, eosinophils, Langerhans cells	Unknown
FcαR (CD89)	Low ($K_d > 10^{-6}$ M)	Neutrophils, eosinophils, monocytes	Cell activation?

GPI, glycophosphatidylinositol; NK, natural killer.

TABLE 12–1 Functions of Antibody Isotypes

Antibody Isotype	Isotype-Specific Effector Functions
IgG	Opsonization of antigens for phagocytosis by macrophages and neutrophils Activation of the classical pathway of complement Antibody-dependent cell-mediated cytotoxicity mediated by natural killer cells Neonatal immunity: transfer of maternal antibody across the placenta and gut Feedback inhibition of B cell activation
IgM	Activation of the classical pathway of complement Antigen receptor of naive B lymphocytes*
IgA	Mucosal immunity: secretion of IgA into the lumens of the gastrointestinal and respiratory tracts Activation of complement by the lectin pathway or by the alternative pathway
IgE	Mast cell degranulation (immediate hypersensitivity reactions)
IgD	Antigen receptor of naive B lymphocytes*

*These functions are mediated by membrane-bound and not secreted antibodies.

(Lecture 11)

Topics discussed In this lecture

1. MHC I & MHC II

→ MHC II: found on APCs and present extracellular linear peptide antigens to CD4+
→ cells that present MHC II are
1. Classical dendritic cells (active naïve t cells) (there is another type of dendritic cells which is plasmacytoid that functions in secreting IFNs)
2. Macrophages
3. B lymphocytes
4. Thymic epithelial cells
5. Vascular endothelial cells.

Uptake of extracellular proteins into vesicular compartments of APC	Processing of internalized proteins in endosomal/ lysosomal vesicles	Biosynthesis and transport of class II MHC molecules to endosomes	Association of processed peptides with class II MHC molecules in vesicles	Expression of peptide-MHC complexes on cell surface

→ MHC I: found on almost all cells and present intracellular proteins to CD8+

Production of proteins in the cytosol	Proteolytic degradation of proteins	Transport of peptides from cytosol to ER	Assembly of peptide-class I complexes in ER	Surface expression of peptide-class I complexes

Migration of dendritic cells

2. T cells

→ Cytotoxic T cells have CD4 / Helper T cells have CD8

TABLE 6–1 Features of Antigens Recognized by T Lymphocytes

Features of Antigens Recognized by T Cells	Explanation
Most T cells recognize peptides and no other molecules.	Only peptides bind to MHC molecules.
T cells recognize linear peptides and not conformational determinants of protein antigens.	Linear peptides bind to clefts of MHC molecules, and protein conformation is lost during the generation of these peptides.
T cells recognize cell-associated and not soluble antigens.	T cell receptors recognize only MHC-like shapes, and MHC molecules are membrane proteins that display stably bound peptides on cell surfaces.
$CD4^+$ and $CD8^+$ T cells preferentially recognize antigens sampled from the extracellular and cytosolic pools, respectively.	Pathways of assembly of MHC molecules ensure that class II molecules display peptides that are derived from extracellular proteins and taken up into vesicles in APCs and that class I molecules present peptides from cytosolic proteins; CD4 and CD8 bind to nonpolymorphic regions of class II and class I MHC molecules, respectively.

3. Important notes:

→ NKT (Natural Killer) T cells and γδ (gamma-delta) T cells can detect non-protein antigens that aren't presented on MHC
→ Sometimes, extracellular antigen can escape from phagosome and presented on MHC I

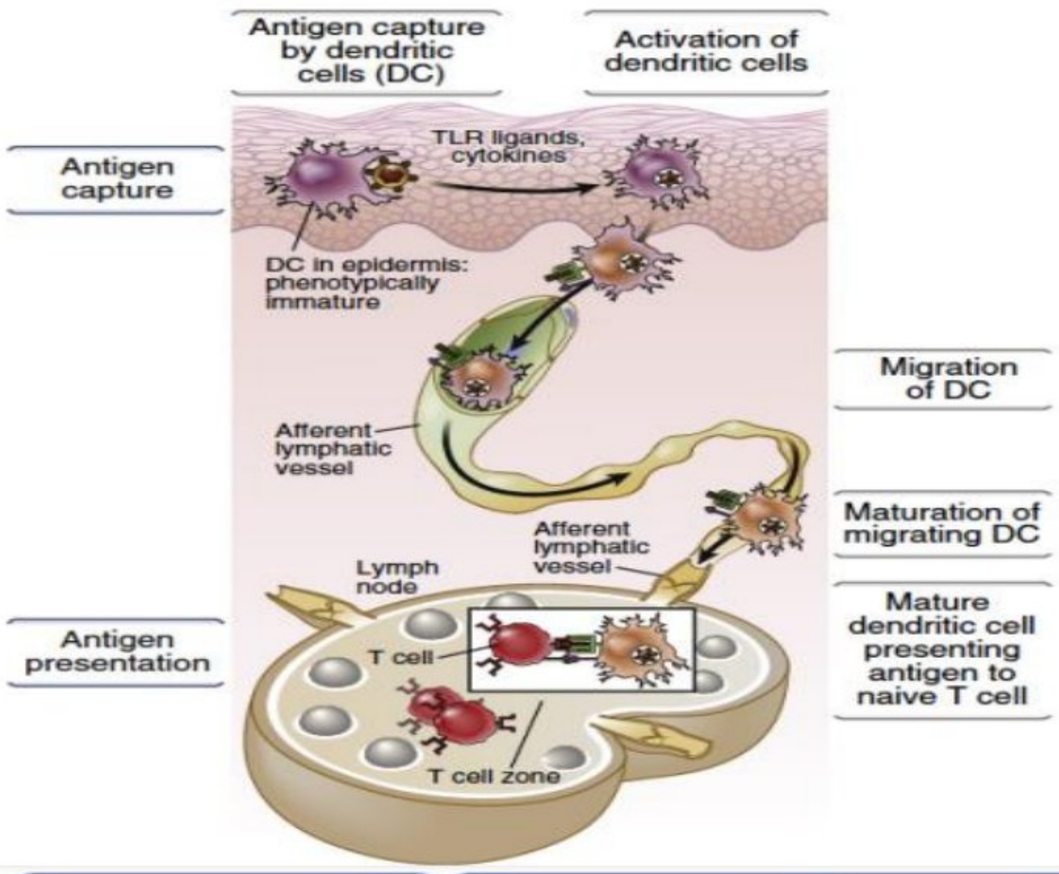
→ 1: MHC 1 & 11

1.Let's talk in details about dendritic cells:

Feature	Classical dendritic cells	Plasmacytoid dendritic cells
Surface markers	CD11c high CD11b high	CD11c low CD11b negative B220 high
Major location	Tissues	Blood and tissue
Expression of Toll-like receptors	TLRs 4, 5, 8 high	TLRs 7, 9 high
Major cytokines produced	TNF, IL-6, IL-12	Type I interferons (Anti-viral)
Postulated major functions	Induction of T cell responses against most antigens	Antiviral innate immunity and induction of T cell responses against viruses

◦What makes a dendritic cell migrate?

 The activated DCs (also called mature DCs) because of some cytokines & TLRs lose their adhesiveness for epithelia or tissues and migrate into lymph nodes. The DCs also begin to express a chemokine receptor called CCR7 that is specific for two chemokines, CCL19 and CCL21, that are produced in the T cell zones of lymph nodes. CCR7 is also called "homing receptor" because it HOMES dendritic cells toward their targets.



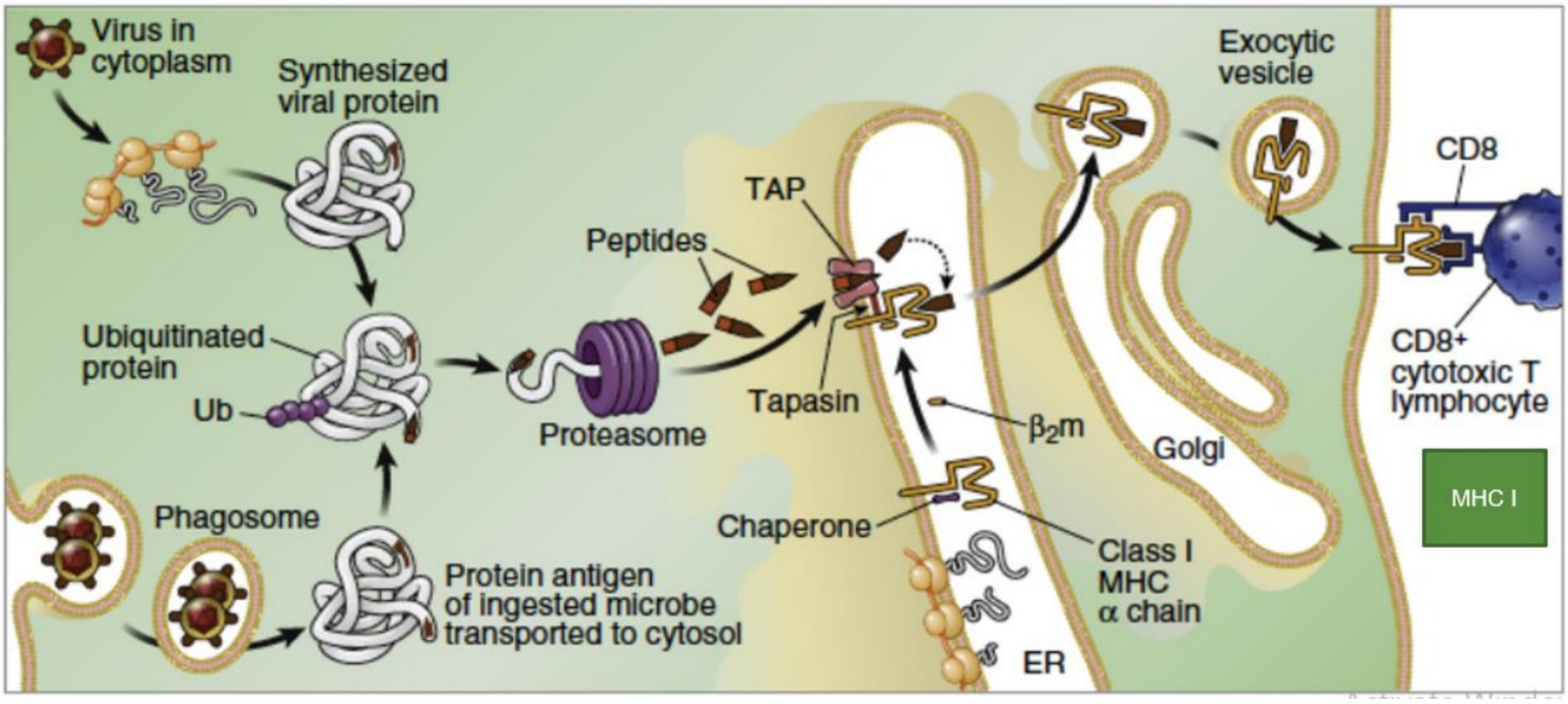
T cell zone

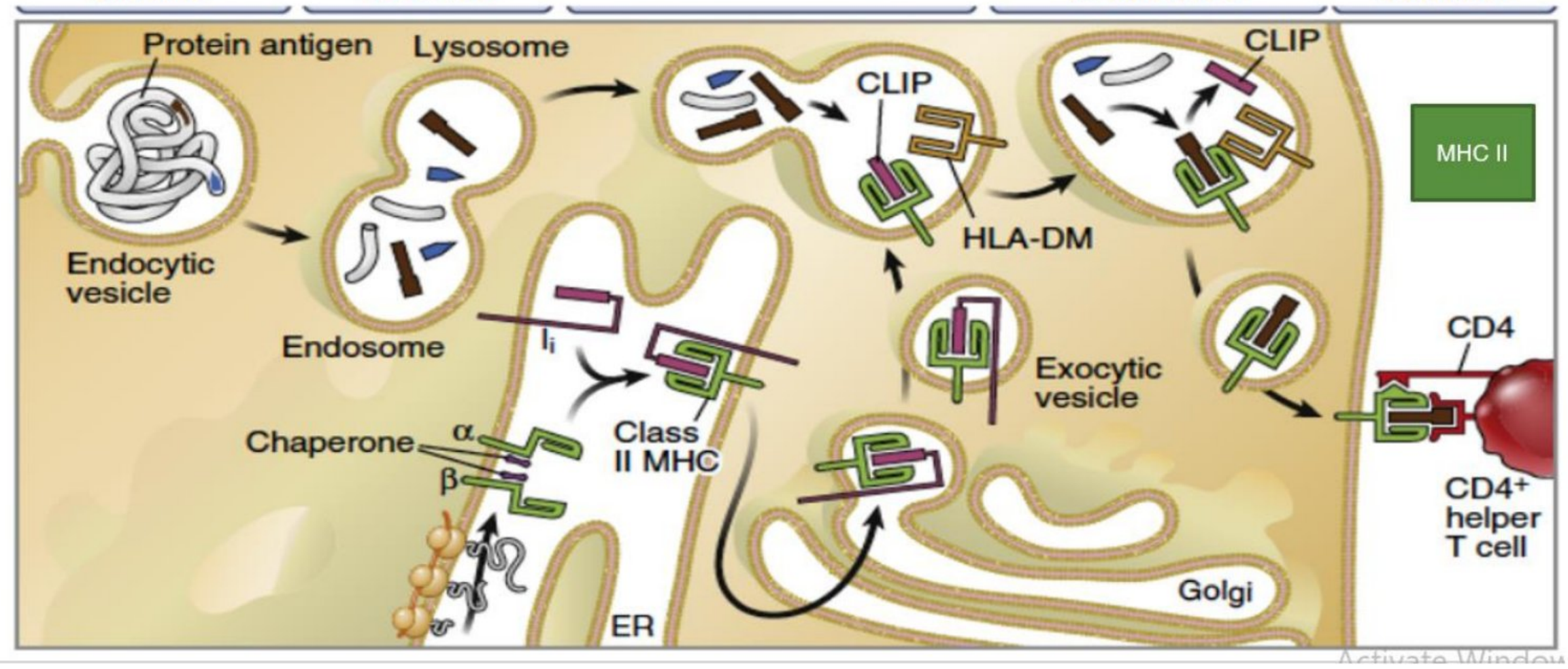
	Immature dendritic cell	Mature dendritic cell
Principal function	Antigen capture	Antigen presentation to T cells
Expression of Fc receptors, mannose receptors	++	–
Expression of molecules involved in T cell activation: B7, ICAM-1, IL-12	– or low	++
Class II MHC molecules		
Half-life	~10 hr	>100 hr
Number of surface molecules	~10^6	~7×10^6

Cell type	Expression of		Principal function
	Class II MHC	Costimulators	
Dendritic cells	Constitutive; increases with maturation; increased by IFN-γ	Constitutive; increases with maturation; increased by TLR ligands, IFN-γ, and T cells (CD40-CD40L interactions)	Antigen presentation to naive T cells in the initiation of T cell responses to protein antigens (priming)
Macrophages	Low or negative; inducible by IFN-γ	Low, inducible by TLR ligands, IFN-γ, and T cells (CD40-CD40L interactions)	Antigen presentation to CD4+ effector T cells in the effector phase of cell-mediated immune responses
B lymphocytes	Constitutive; increased by cytokines (e.g., IL-4)	Induced by T cells (CD40-CD40L interactions), antigen receptor cross-linking	Antigen presentation to $CD4^+$ helper T cells in humoral immune responses (T cell–B cell interactions)

Thymic epithelial cells: have a role in lymphocytes' maturation, development and selection in thymus (also called nursery cells)

Just one page is remaining, let's go !





- GOLDEN RULES:
  1- Rule of 8: MHC I activates CD8+ T cells, while MHC II activate CD4+ T cells. (+ means this CD is present on its surface)
  2- Extracellular antigens go through MHC II pathway, while intracellular antigens go through MHC I pathway