

Adaptive immunity: second line of response

- Based upon resistance acquired during life
 - comes into action after innate immunity fails to get rid of microbe
- Relies on genetic events and cellular growth
- Responds more slowly, over few days

Three major functions

- Recognize nonself
- Respond to nonself
- Remember nonself

Four Characteristics of Adaptive (Specific) Immunity

- **Discrimination between self and non-self**
 - usually responds selectively to non-self, producing specific responses against the stimulus
- **Diversity**
 - generates enormous diversity of molecules
- **Specificity**
 - can be directed against one specific pathogen or foreign substance among trillions
- **Memory**
 - response to a second exposure to a pathogen is so fast that there is no noticeable pathogenesis

Adaptive Immunity

The resistance that an individual acquires during life

Active Immunity

Resistance developed as a result of antigenic stimulus

Natural active immunity

Type of specific immunity a host develops after exposure to foreign substance

Artificial active immunity

(vaccination)
Intentional exposure to a foreign material

Passive Immunity

Resistance transmitted passively in ready made form

Natural passive immunity

Transfer of antibodies, e.g., mother to fetus across

Artificial acquired passive immunity

Preformed antibodies or lymphocytes produced by one host are introduced into another host

Adaptive Immunity

Active immunity	Passive immunity
Produced actively by host immune system	Immunoglobulins received passively
Induced by <ul style="list-style-type: none">• clinical, sub-clinical Infection (natural)• Vaccination (artificial) Live, killed, purified antigen vaccine	Acquired by- <ul style="list-style-type: none">• Mother to fetus IgG transfer, breast milk, (natural)• Readymade antibody transfer immune serum, immune cells (artificial)
Long lasting	Lasts for short time

Types of Adaptive(Acquired)

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Acquired Immunity

Natural immunity

is acquired through the normal life experiences of a human and is not induced through medical means.

Active immunity

is the consequence of a person developing his or her own immune response to a microbe.

Passive immunity

is the consequence of one person receiving preformed immunity made by another person.

Artificial immunity

is that produced purposefully through medical procedures (also called immunization).

Active immunity

is the consequence of a person developing his or her own immune response to a microbe.

Passive immunity

is the consequence of one person receiving preformed immunity made by another person.



Infection



Maternal antibody



Vaccination

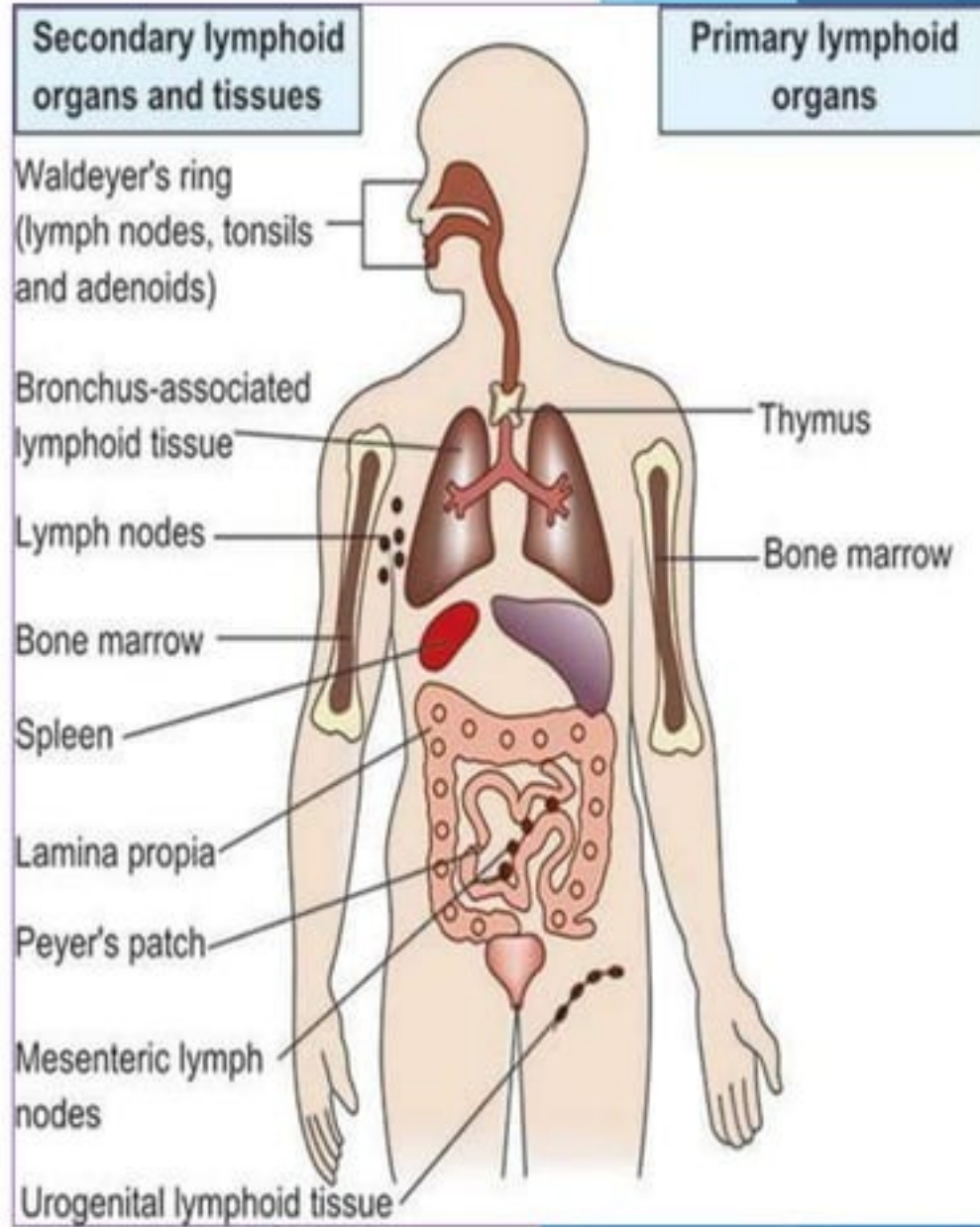
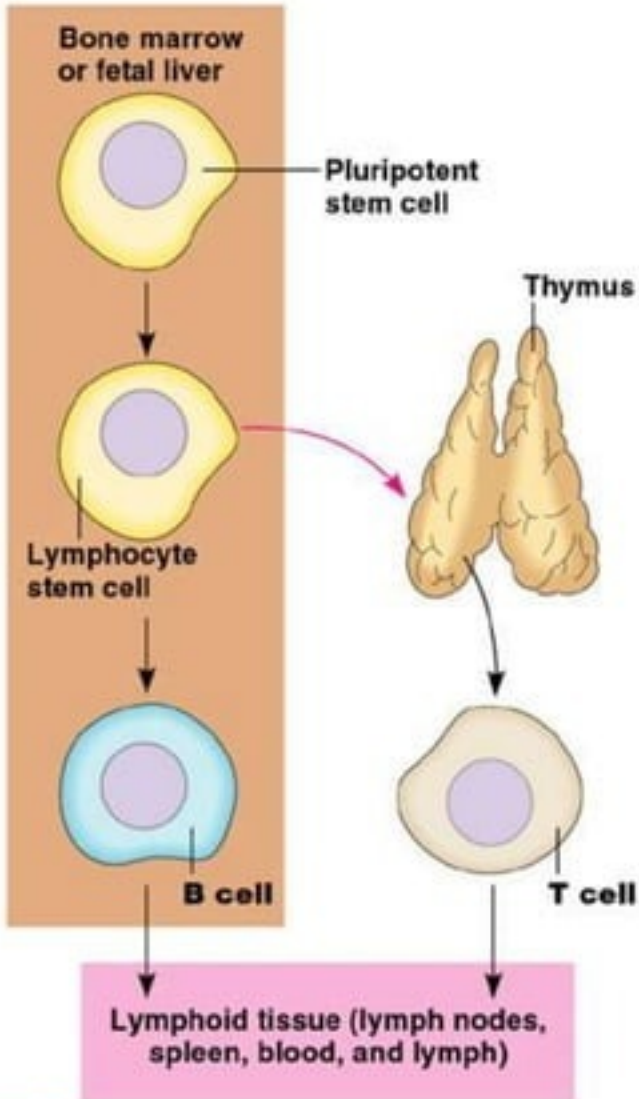


Immune globulin therapy

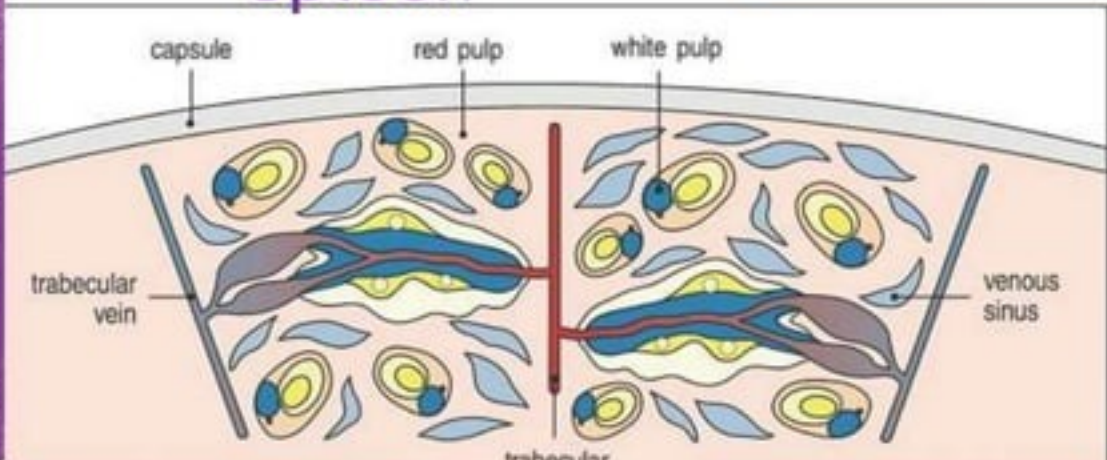
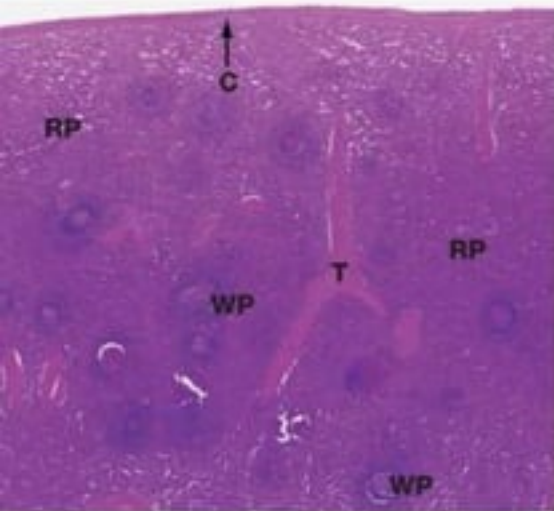
Adaptive immunity: mechanisms

- ▶ Cell-mediated immune response (CMIR)
 - Mediated by T cells via:
 - Direct lysis of target (infected) cells
 - Production of cytokines that activate infected cells to kill pathogens
 - Eliminate intracellular microbes that survive within phagocytes or other infected cells
- ▶ Humoral immune response (HIR)
 - Mediated by antibodies produced by B cells
 - Antibodies bind to whole or fractions of antigens outside cells
 - Eliminate extra-cellular microbes and their toxins

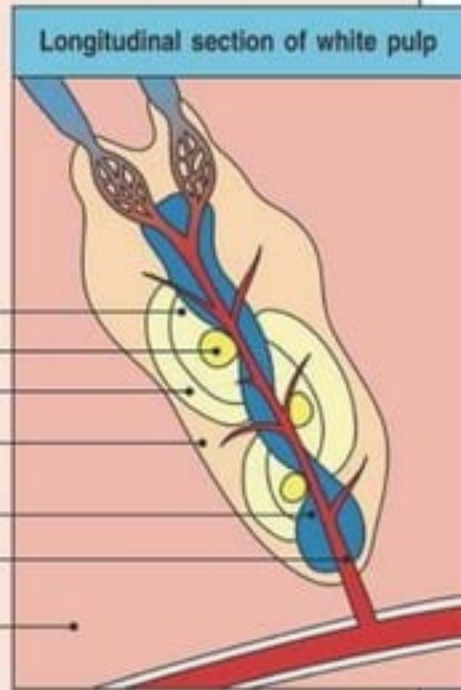
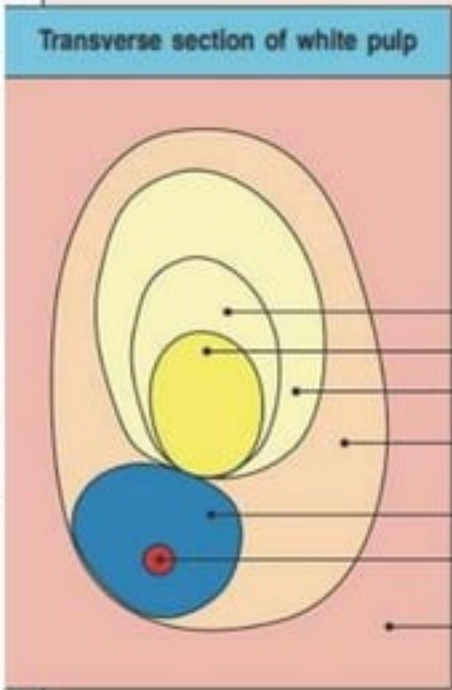
Lymphocyte Formation



Spleen

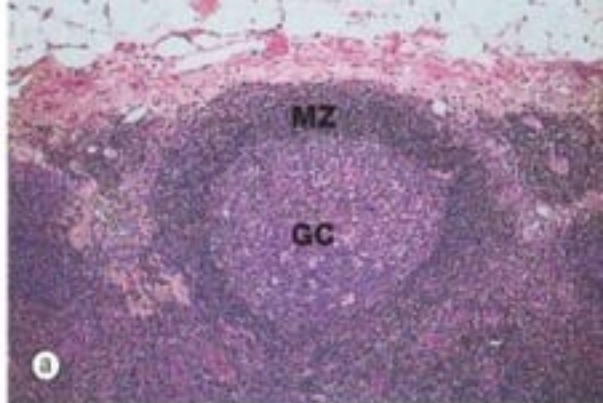
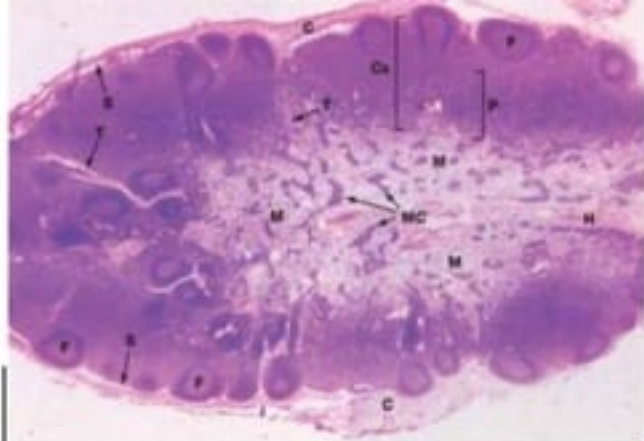


- From central arteriole smaller blood vessels fan out, eventually terminating in a specialized zone -- perifollicular zone (PFZ),
- Cells and antigen then pass into the white pulp through open blood-filled spaces in the perifollicular zone.

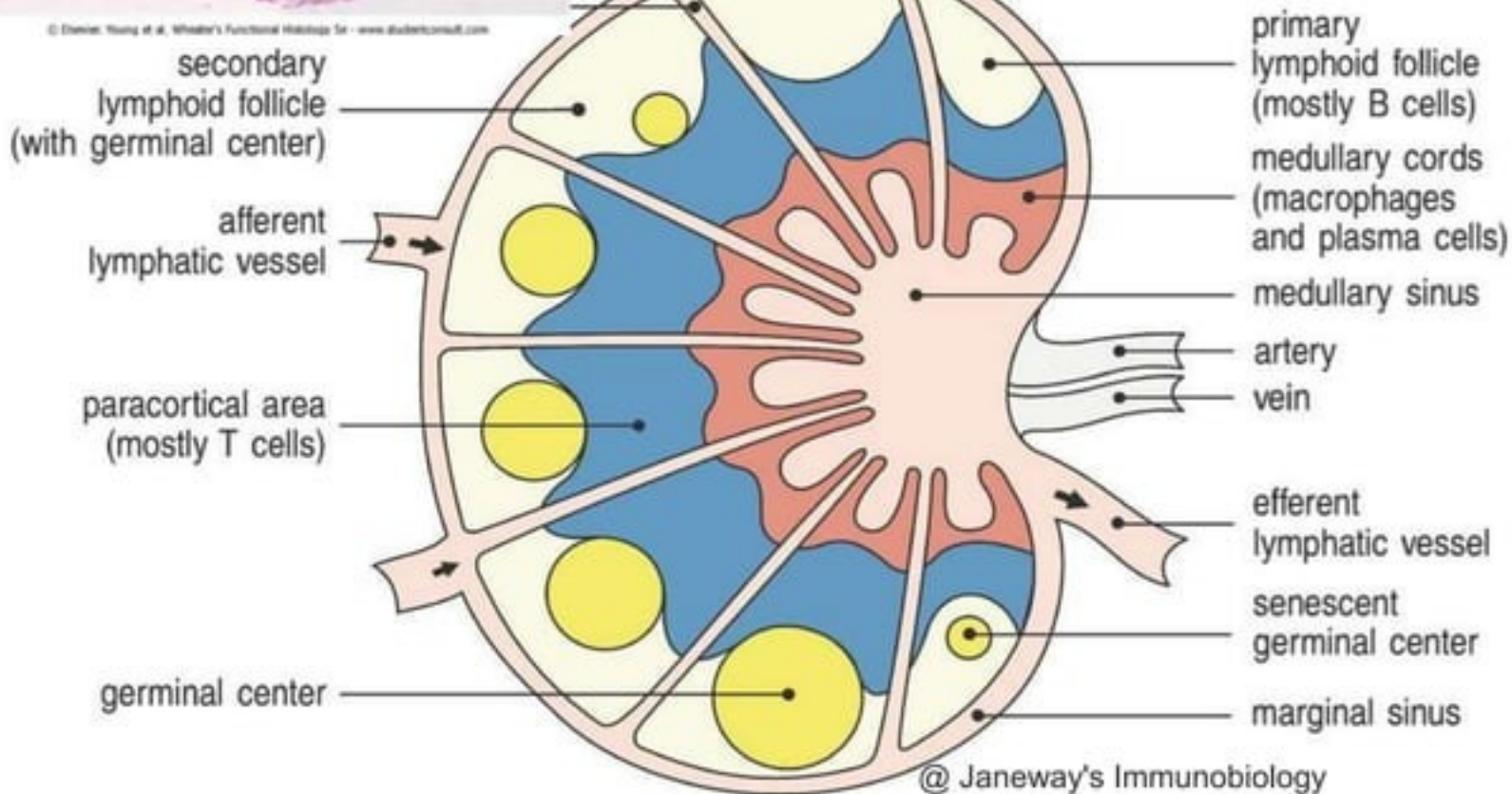


- B-cell corona
- germinal center
- marginal zone
- perifollicular zone
- periarteriolar lymphoid sheath
- central arteriole
- red pulp

Lymph Node

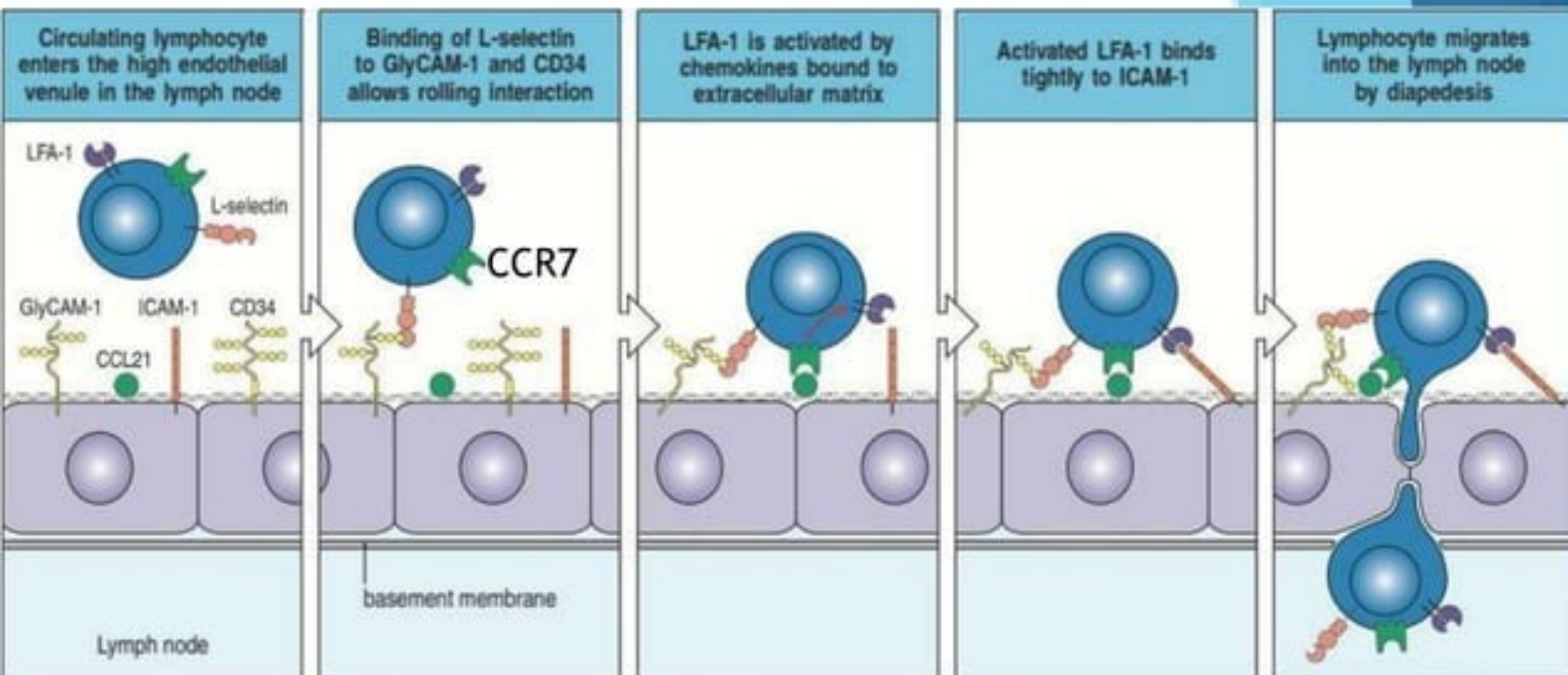


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@ Janeway's Immunobiology

Lymphocytes in the blood enter lymphoid tissue



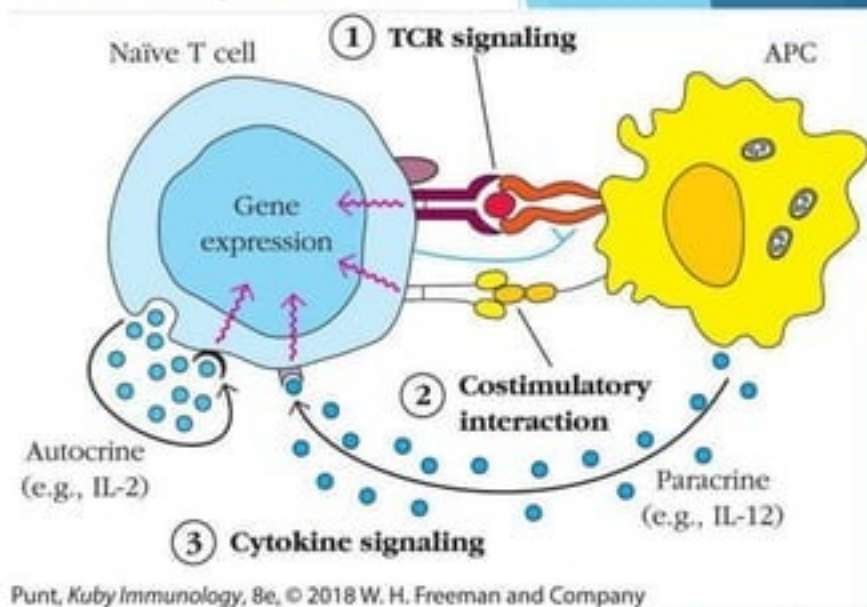
▶ Lymphocytes in the blood enter lymphoid tissue by crossing the walls of high endothelial venules.

- ▶ Binding of L-selectin on the lymphocyte to sulfated carbohydrates of GlyCAM-1 and CD34 on the HEV.
- ▶ Local chemokines such as CCL21 bound to a proteoglycan matrix on the HEV surface stimulate chemokine receptors on the T cell, leading to the activation of LFA-1.
 - ▶ This causes the T cell to bind tightly to ICAM-1 on the endothelial cell, allowing migration across the endothelium.

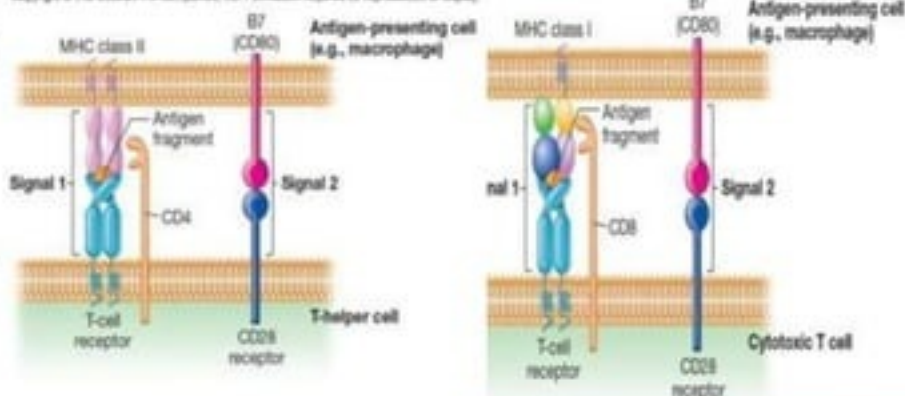
Cell-mediated immune response

T-cell

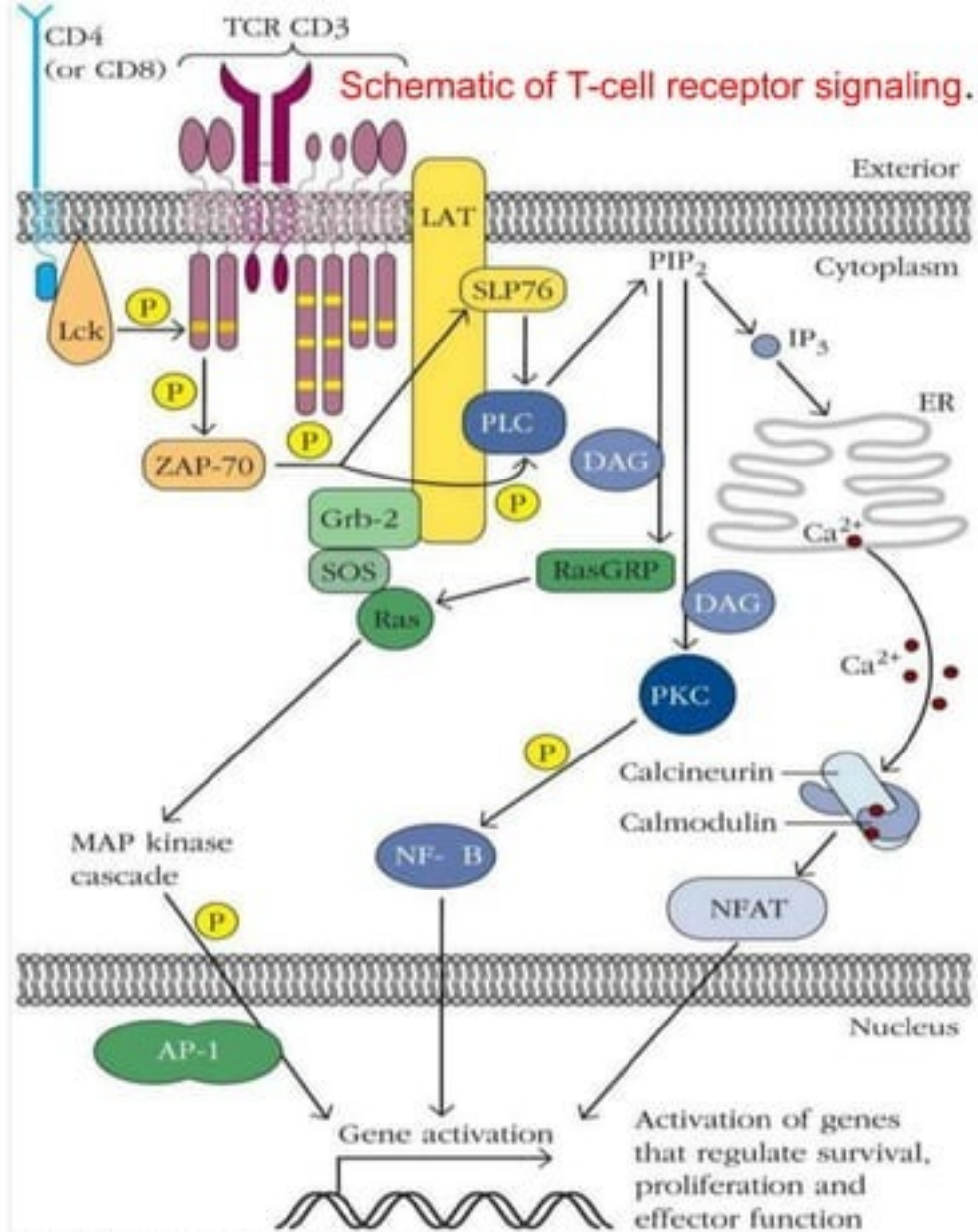
- recognizes peptide antigen on (macrophage)APC in association with major histo-compatibility complex (MHC) class
- distinguish self from non-self antigens
- T cells with CD4 molecule are restricted to recognizing antigen bound to class II MHC molecules,
- T cells expressing CD8 are restricted to recognition of antigen bound to class I MHC molecules.
- T-cell goes into effectors cells stage that is able to kill infected cells



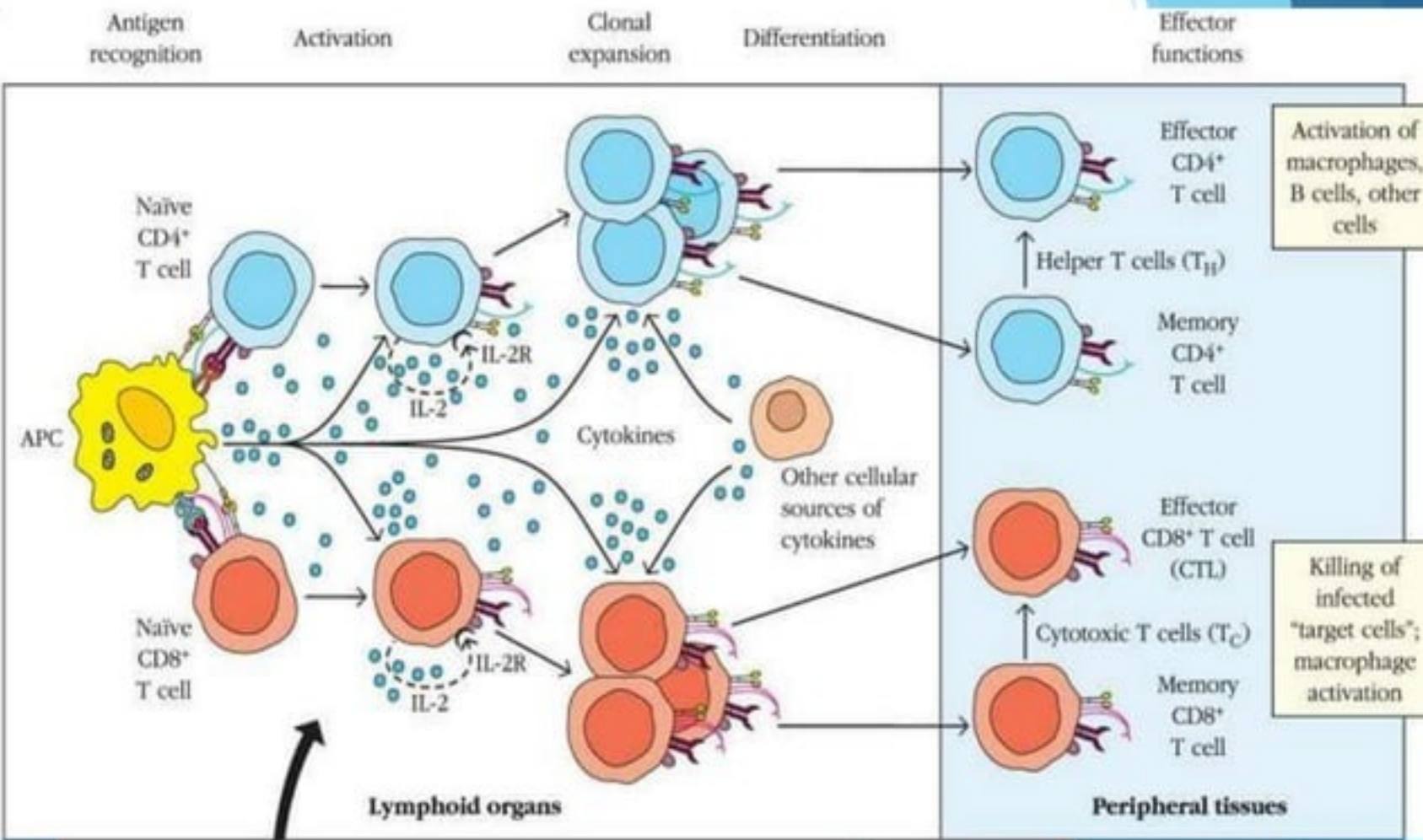
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- Once a TCR engages MHC-peptide on the surface of an APC, the co-receptor CD4 or CD8 steps in
 - to stabilize this interaction
- The tyrosine kinases Lck and ZAP-70 initiate
 - TCR signaling
 - And phosphorylate (ITAMs) CD3 tail as well as adapter molecules LAT and SLP-76.
- Phosphorylation generates docking sites for the assembly and organization of signaling molecules,
 - which lead to the activation of transcription factors.



Activation of a naïve T cell in the secondary lymphoid tissues results in the generation of effector and memory T cells



Cell mediated immune response

Primary response

- ▶ production of specific clones of effector T cells and memory clones
- ▶ develops in several days
- ▶ does not limit the infection

Secondary response

- ▶ more pronounced, faster
- ▶ more effective at limiting the infection

Example - cytotoxic reactions against intracellular parasites, delayed hypersensitivity (e.g., Tuberculin test) and allograft rejection

T lymphocytes

- Once T cells activated they proliferate into effector cells and memory cells
- 2 types cells
 - Helper T- lymphocytes (CD4+)
 - Cytotoxic T-lymphocyte (CD8+)
- Helper T- lymphocytes (CD4+)
 - CD4 T cells differentiate into several subsets of effector T cells with a variety of different functions.
 - Main functional classes
 - T_H1
 - T_H2 ,
 - T_H17 ,
 - T_H9
 - T_H22
 - T follicular helper cell(T_{FH})
 - Regulatory cell(Treg)

T Helper Cells

- **T_H1 cells**

- promote cytotoxic T cell activity and activate macrophages
- mediate inflammation and delayed hypersensitivity by producing a specific set of cytokines
 - IL-2, IFN- γ , tumor necrosis factor (TNF)- β

- **T_H2 cells**

- stimulate antibody responses and defend against helminth parasites
- involved in promoting allergic reactions
- produce a specific set of cytokines
 - IL-5, IL-6, IL-10, and IL-13

T Helper Cells

T_H9 cells

- Protects against extracellular pathogensInvolved in mucosal autoimmunity
- Producing a specific set of cytokines--- IL-9

T_H17 cells

- Protects against fungal and extracellular bacterial infections
- Contributes to inflammation, autoimmunity
- produce a specific set of cytokines--IL-17A,IL-17F

T Helper Cells

T_H 22cells

- Protects against extracellular pathogens
- Involved in inflammatory skin disease
- produce a specific set of cytokines---IL22

T follicular helper cell(T_{FH})Cells

- TFH cells contribute to humoral immunity by stimulating the production of antibodies by B cells and inducing class switching,
- can produce cytokines characteristic of either TH1 or TH2 cells
- produce a specific set of cytokines--IL-4 , IL-21

Regulatory T Cells

- **Treg cells**

- Has an inhibitory manner to suppress immune responses and inflammation.
- Suppress T-cell activity and help prevent the development of autoimmunity during immune responses
- IL-10 induces regulatory function by inhibiting T helper cell function.
 - Activates transcription factor Foxp3
 - Foxp3 upregulated CD25 and CTLA-4
 - CTLA-4 binds to B7 on APCs, blocking the 2nd signal required for lymphocyte activation
- Tregs also suppress/regulate functions by secretion of IL-9 and TGF- β

- **Regulatory T-cell immunotherapy** has recently become a reality in clinical trials.
 - Treg effectiveness in preventing graft-versus-host disease (GvHD) after bone marrow transplantation



Engineering

Volume 5, Issue 1, February 2019, Pages 98-105



Research Immunology—Review

Immune Regulatory Cell Biology and Clinical Applications to Prevent or Treat Acute Graft-Versus-Host Disease

Review | [Open Access](#) | Published: 17 July 2020

Regulatory T cells in tumor microenvironment: new mechanisms, potential therapeutic strategies and future prospects

[Chunxiao Li](#) , [Ping Jiang](#), [Shuhua Wei](#), [Xiaofei Xu](#) & [Junjie Wang](#) 

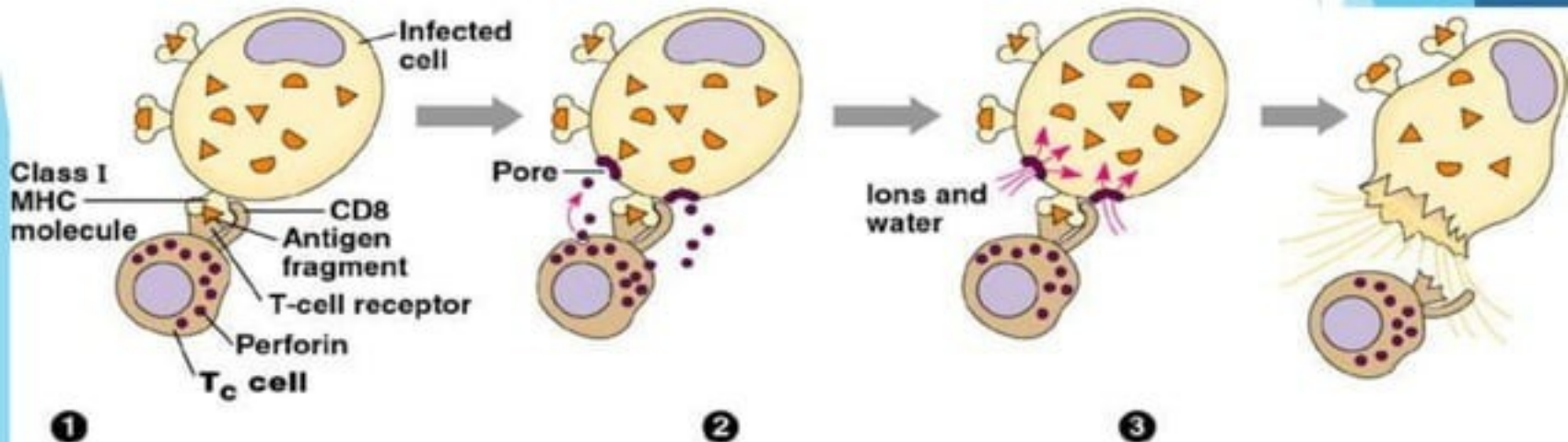
Molecular Cancer **19**, Article number: 116 (2020) | [Cite this article](#)

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Cytotoxic T Cells (T_C s)

- ▶ T cells that express CD8 molecule on their surface
- ▶ 30% of T cells in the periphery
- ▶ Destroy cells infected by intracellular pathogens and cancer cells Class I MHC molecules (nucleated body cells) expose foreign proteins
- ▶ Releases perforin and granzymes, proteins that form pores in the target cell membrane; causing cell lysis and/or apoptosis

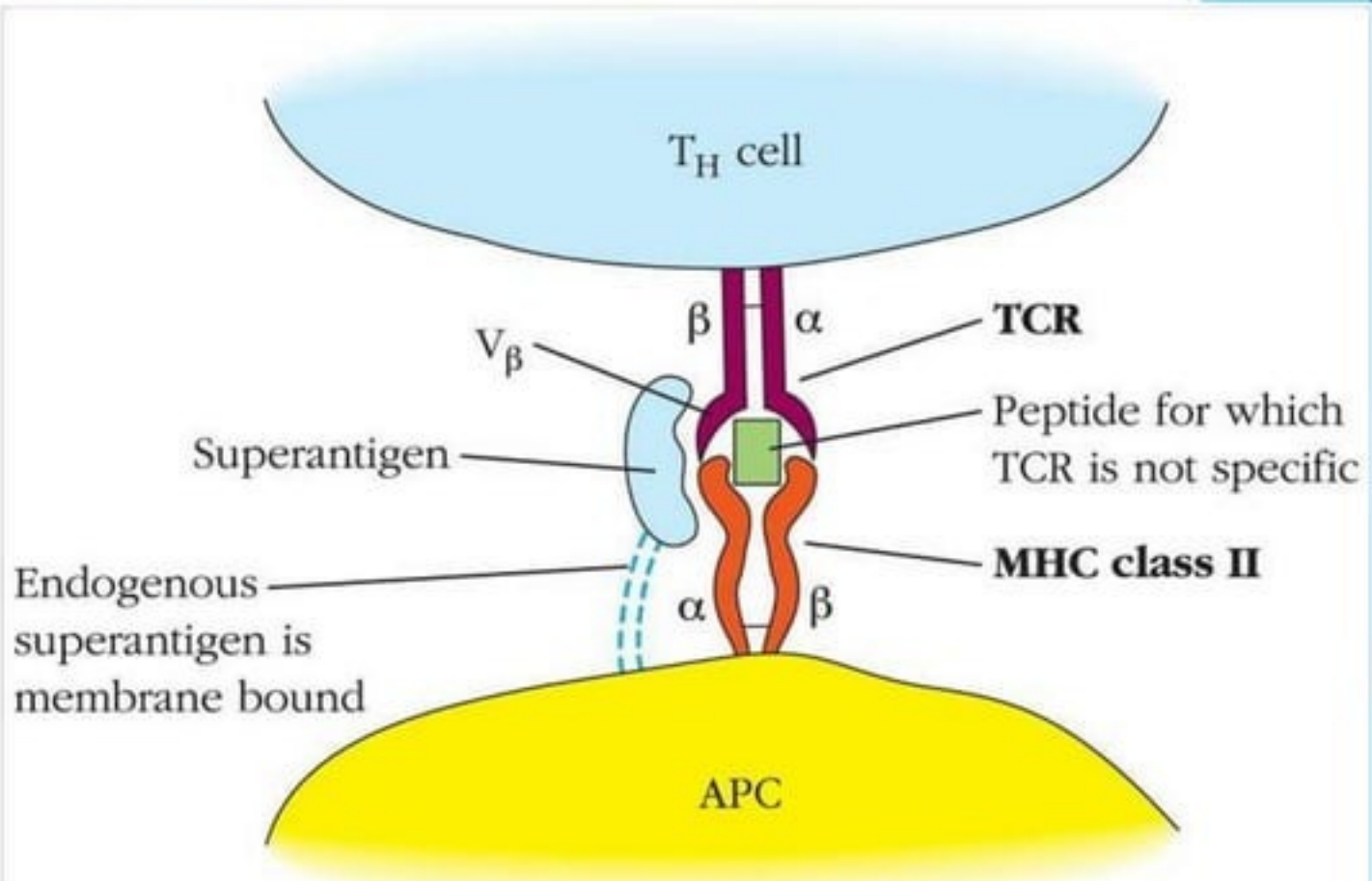


(a)

Superantigens

- Bacterial and viral proteins
 - staphylococcal enterotoxin B
 - the toxin that causes toxic shock syndrome
 - mouse tumor virus superantigen
 - putative proteins from Epstein-Barr and rabies viruses
- Stimulate stronger immune response than normal antigens by “tricking” T cells into activation although they have not been triggered by a specific antigen
- Stimulate T cells to proliferate nonspecifically
- Contribute to microbial pathogenicity
- stimulate release of massive quantities of cytokines from T cells
 - may result in circulatory shock and multiorgan failure

Superantigens Are a Special Class of T-Cell Activators



Humoral immune response

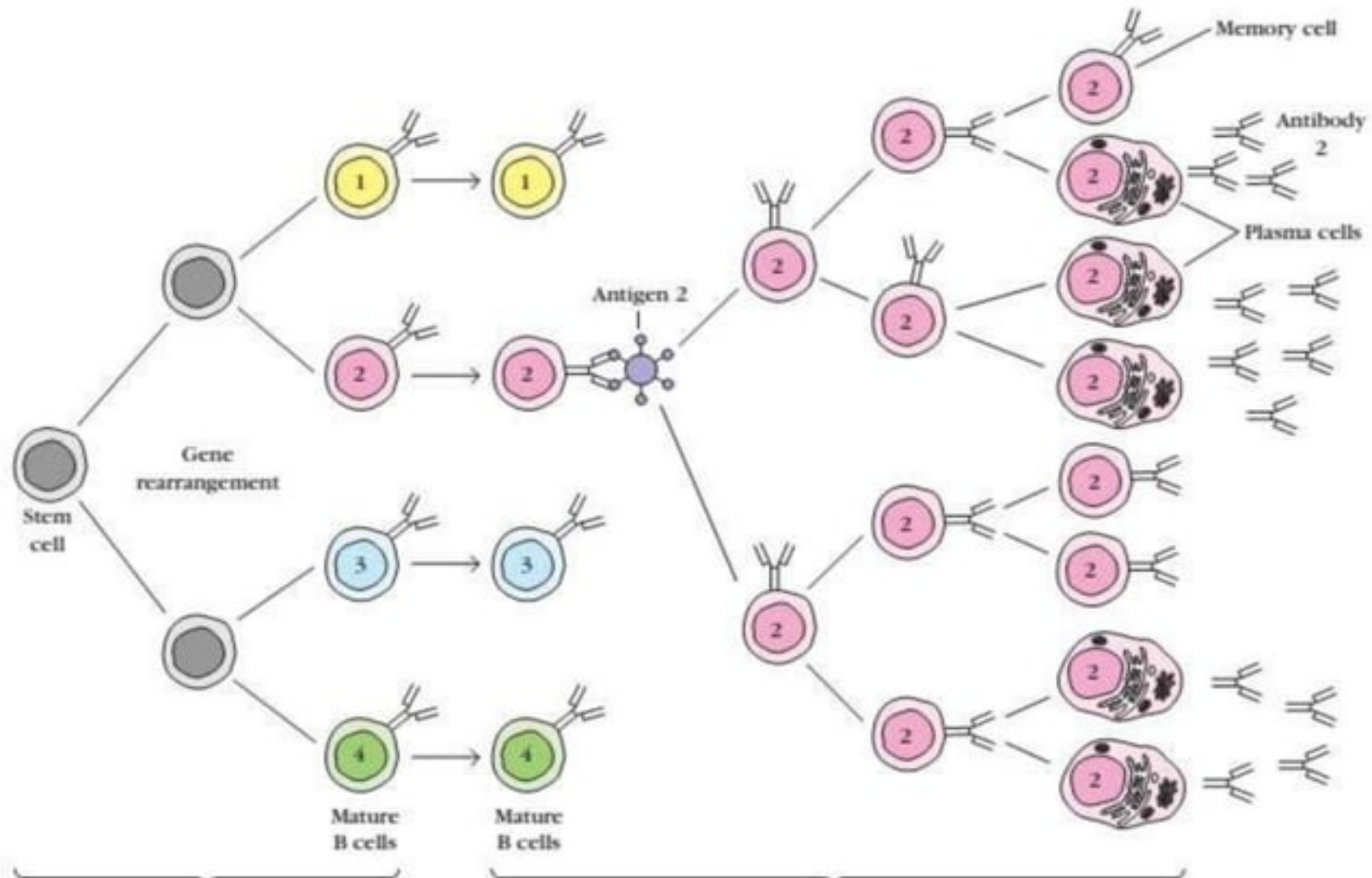
- ▶ Mediated by B cells

B cell

- ▶ Mature in bone marrow
 - ▶ Contain B cell receptors (BCRs) that bind to antigens.
-
- B lymphocytes recognize specific antigens
 - proliferate and differentiate into antibody-secreting plasma cells
 - Antibodies bind to specific antigens on microbes; destroy microbes via specific mechanisms
 - Some B lymphocytes evolve into the resting state - memory cells

Bone marrow

Peripheral lymphoid tissue



Memory cell

Antibody

Plasma cells

Antigen 2

Gene rearrangement

Stem cell

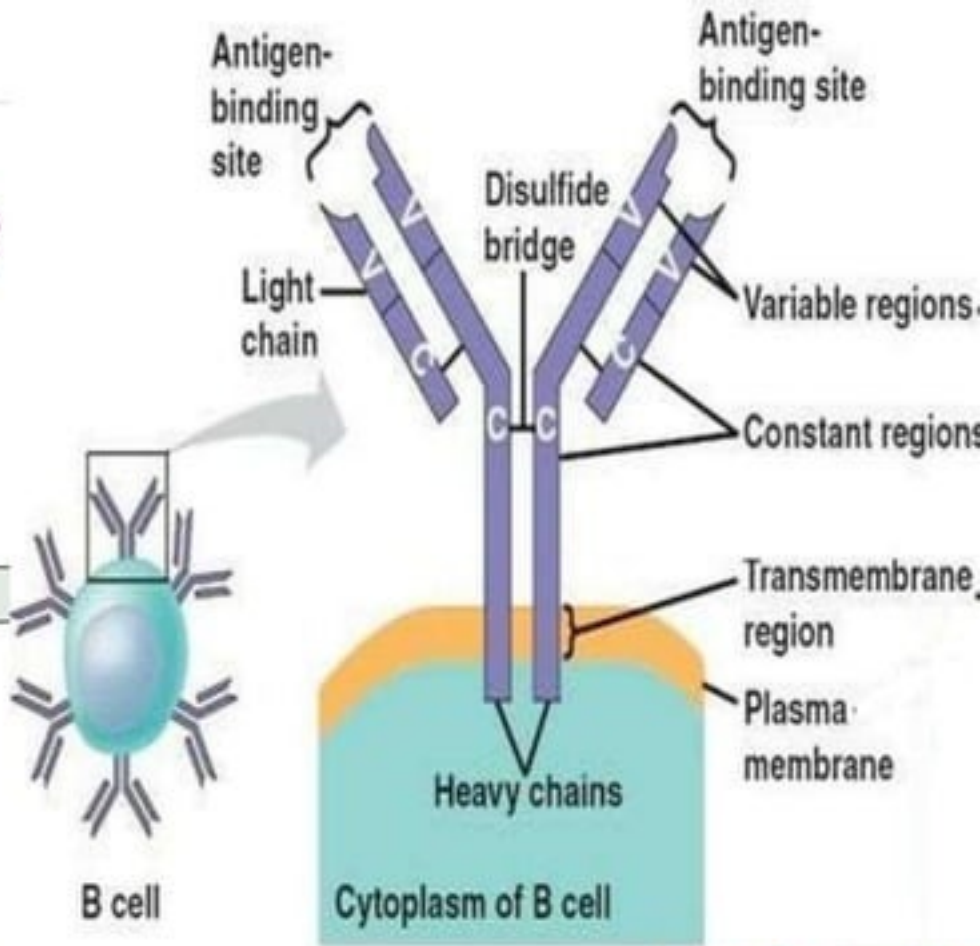
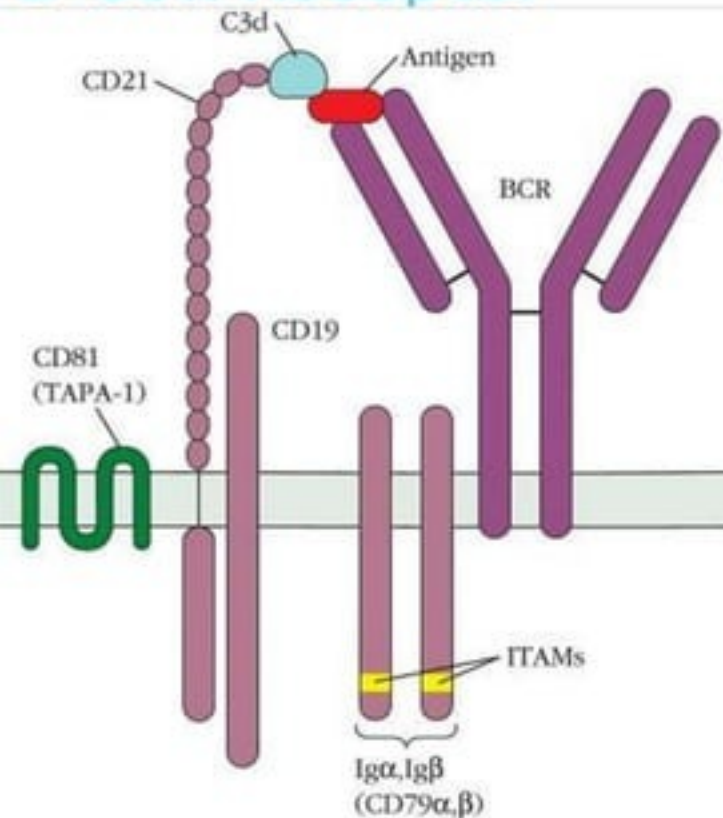
Mature B cells

Mature B cells

Maturation into mature antigenetically committed B cells

Antigen-dependent proliferation and differentiation into plasma and memory cells

B-Cell Receptor



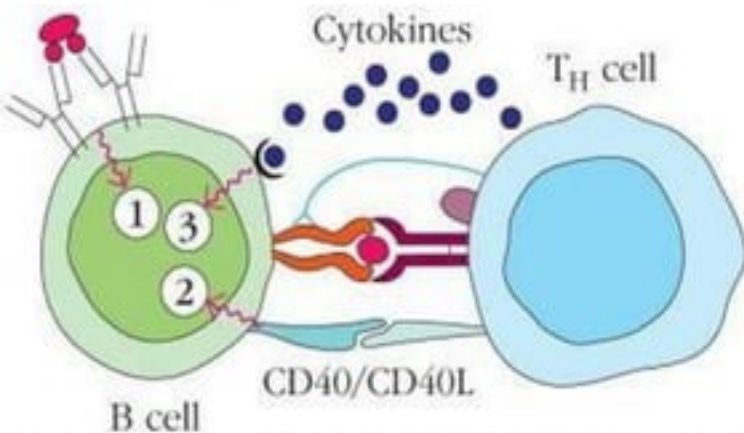
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- BCR is unique the receptors
- Surface-bound immunoglobulin functions as the epitope-specific BCR.
- All BCRs expressed by a single B cell have identical epitope specificity.
- Epitope binding causes conformational change in the BCR that transduces a signal to the cytoplasm via $Ig\alpha$ and $Ig\beta$ accessory molecules.

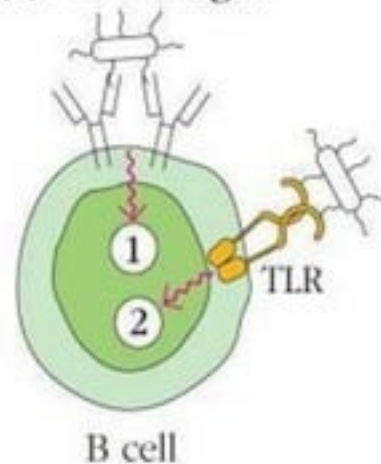
B- cells

- Activation of **naive B cells** is triggered by antigen.
 - leads to generation of **plasma cells** and **memory B cells**.
- In the **absence of** antigen-induced activation
 - Naive B cells in the periphery have a short life span, dying within a few weeks by apoptosis
- Depending on the nature of the antigen, B-cell activation proceeds by two different routes
 - one dependent upon TH cells and other not.
- The B-cell response to **thymus-dependent (TD) antigens**
 - requires direct contact with TH cells, not simply exposure to TH -derived cytokines.
- Antigens that can activate B cells in the absence of direct participation by TH cells are known as **thymus independent (TI) antigens**.

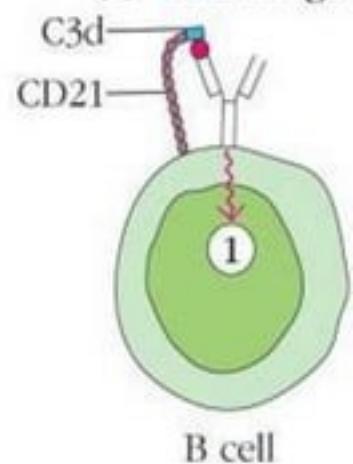
(a) TD antigen



(b) TI-1 antigen



(c) TI-2 antigen



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(a) TD antigens bind to the Ig receptor of B cells. Some of the antigen is processed and presented to helper T cells.

- After binding to T cell, secretes cytokines such as IL-2 and IL-4, which are recognized by receptors on the B cell surface.
- Cytokines deliver differentiation, proliferation, and survival signals to the B cells.

(b) T-independent-type 1 (TI-1) antigens bind to B cells through both Ig and innate immune receptors.

- For example, LPS from gram-negative organisms binds to B cells via both membrane-bound immunoglobulin (mIg) and TLR4, resulting in signaling from both receptors.

(c) T-independent-type 2 (TI-2) antigens are frequently bound by C3d complement components and cross-link both mIg and CD21 receptors on B cells.

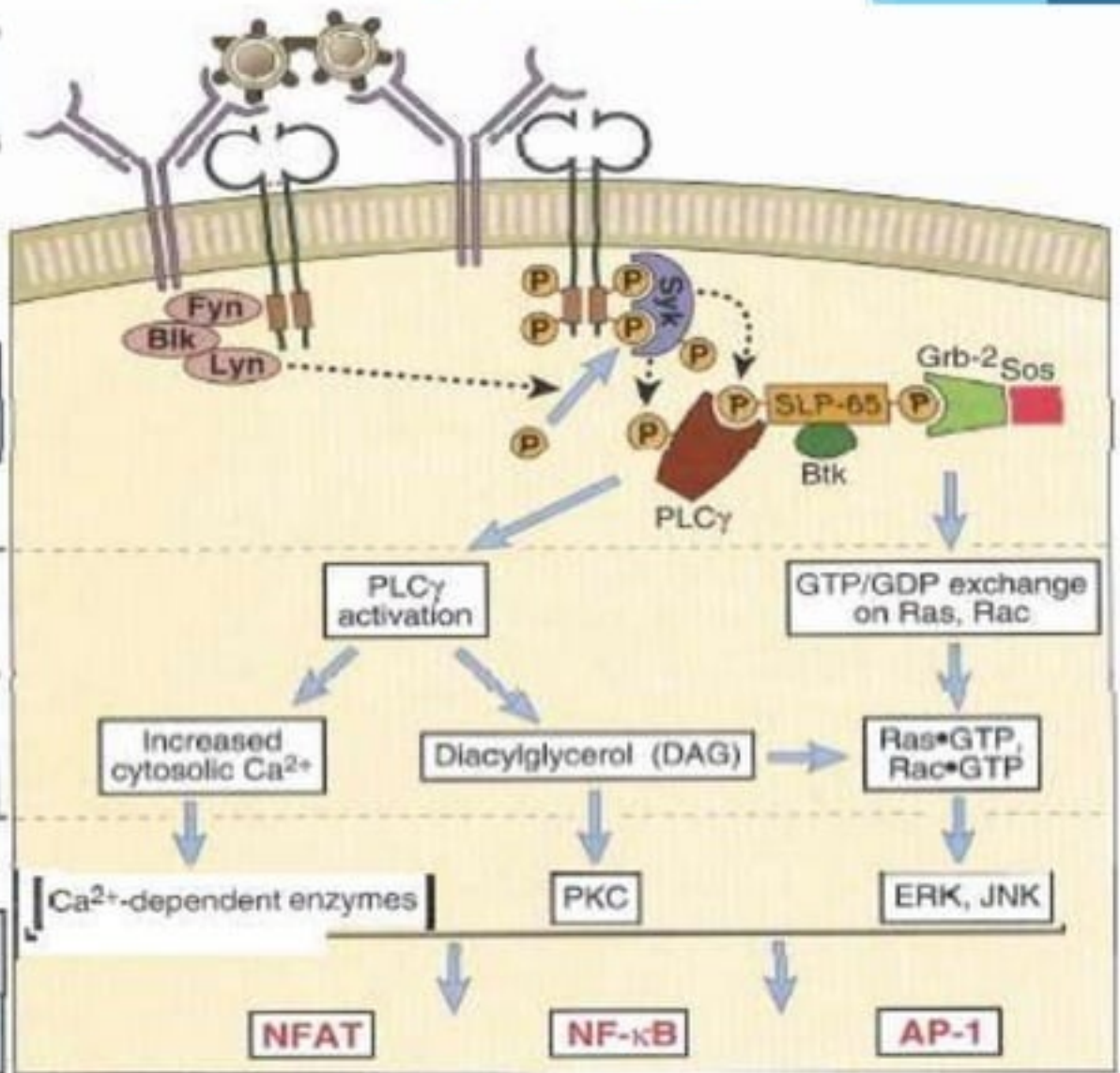
B cell signaling

Cross-linking of membrane Ig by antigen

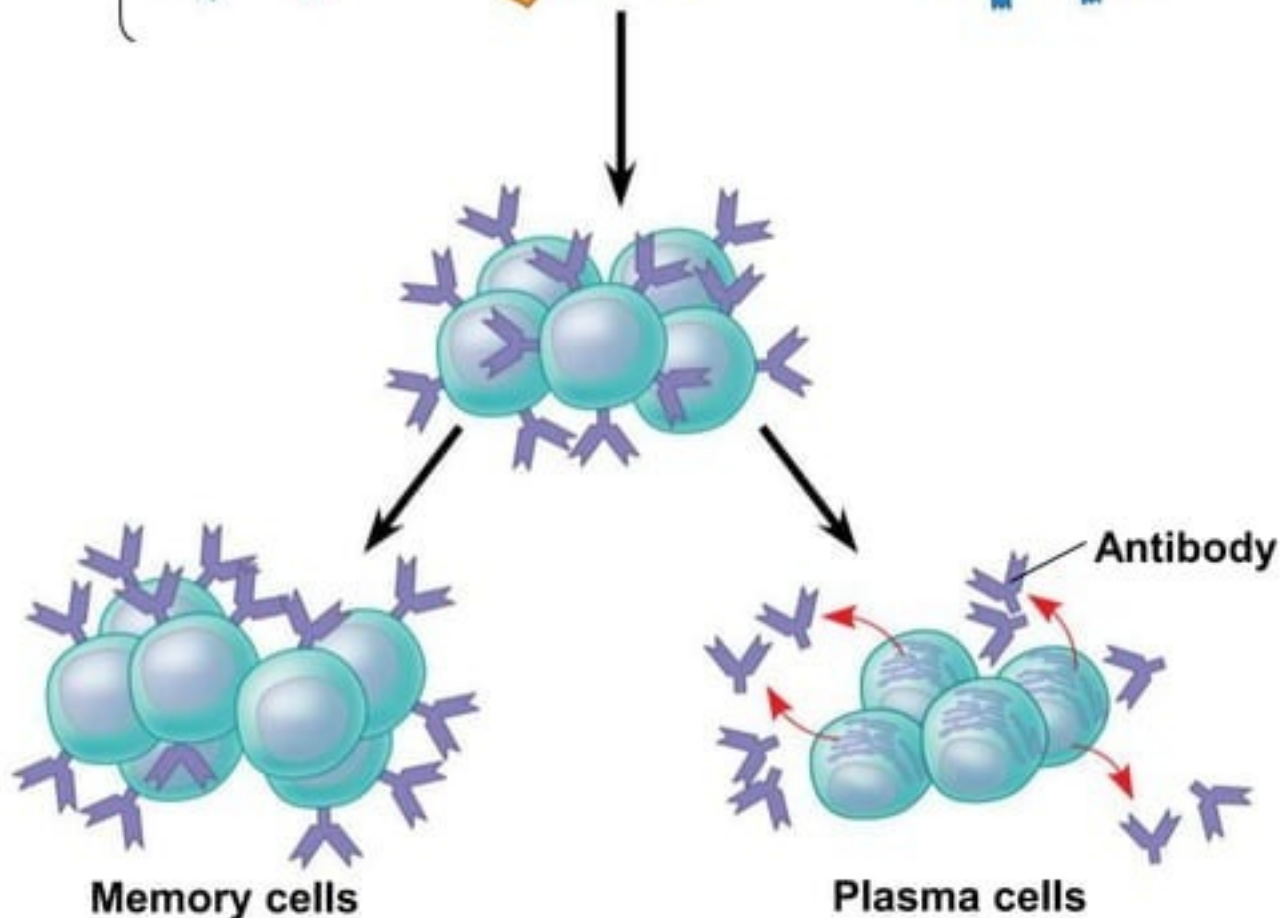
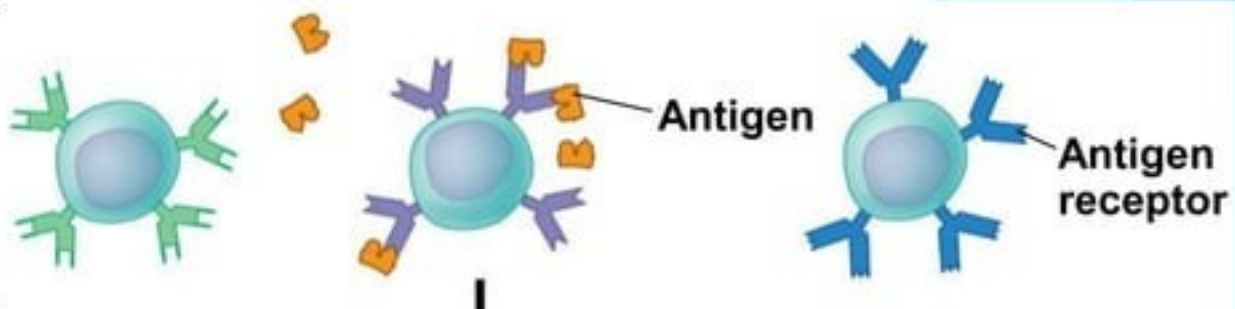
Tyrosine phosphorylation events

Biochemical intermediates

Active enzymes
Transcription factors



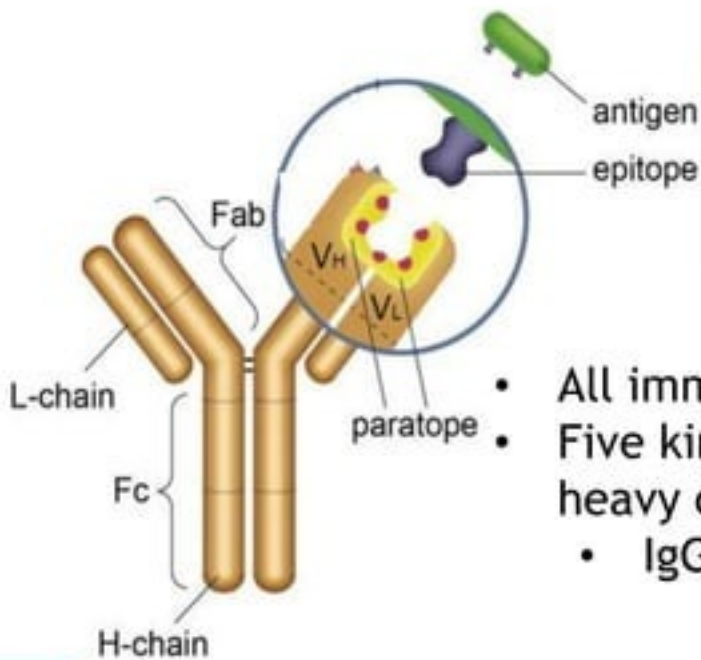
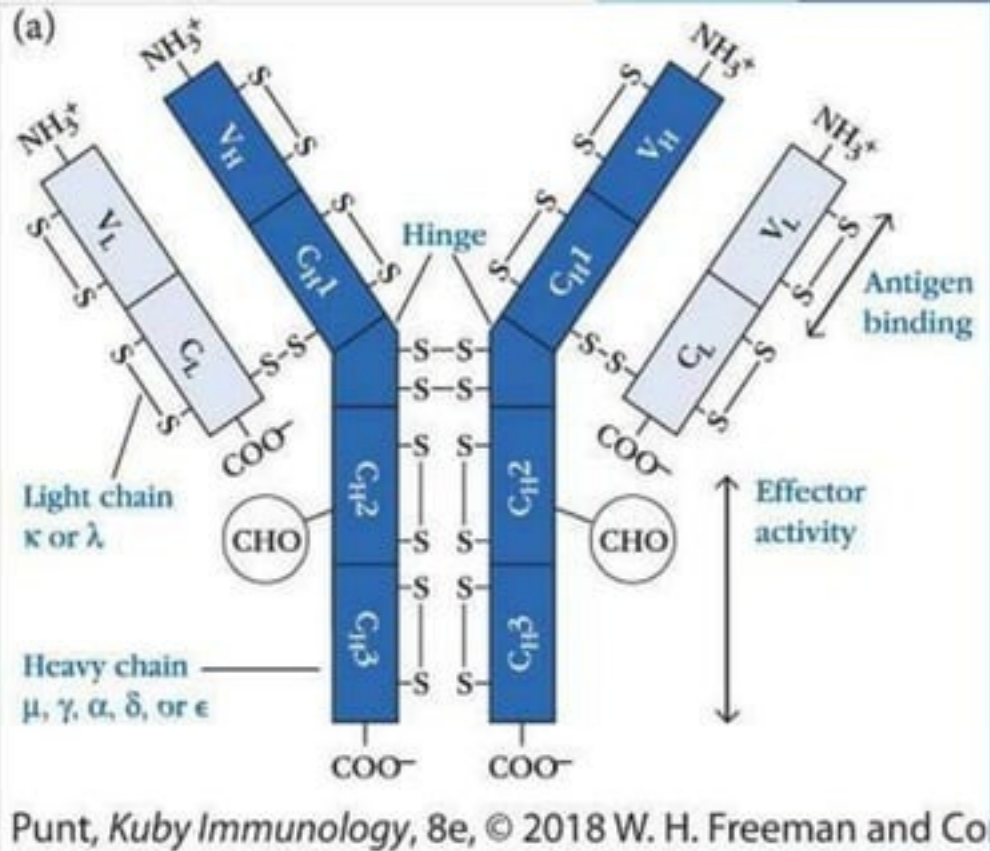
B cells that differ in antigen specificity



Activation of B Cells

- ▶ Activation of B cells formed Plasma cells in response to cytokines.
- ▶ Plasma cell produce antibody molecules
 - ▶ Antibodies are versatile effector molecules that, through a variety of mechanisms,
 - ▶ play direct roles in protecting us from
 - ▶ pathogens
 - ▶ pathogen-derived toxins,
 - ▶ and cells that have become dangerous through infection or malignant transformation

- Two identical light (L) chain molecular weight about 25000 Da
- two identical heavy (H) chain of larger polypeptide of about 50000 Da or more.



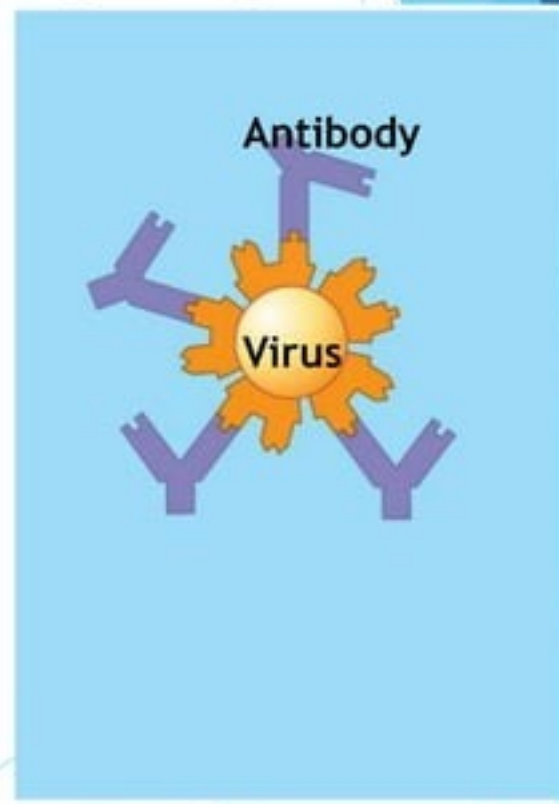
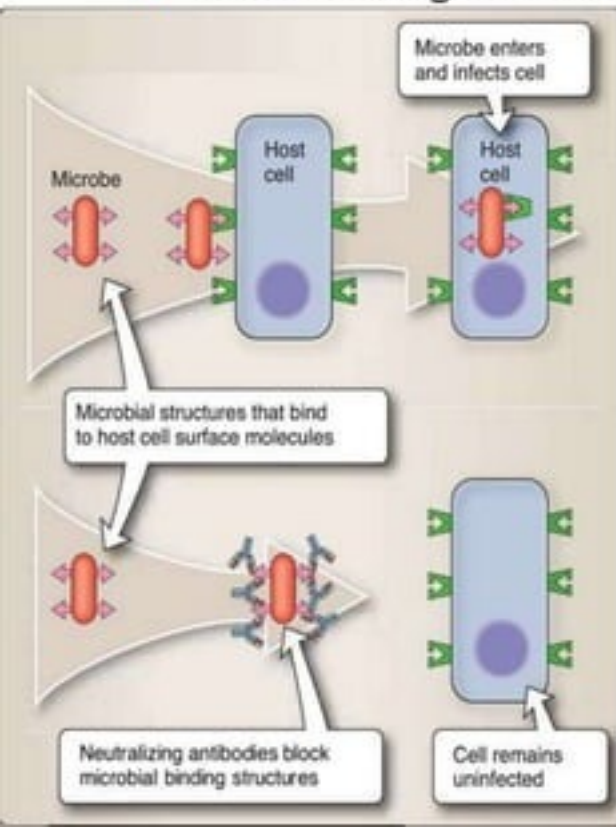
- All immunoglobulins are not antibodies
- Five kinds of antibodies based on constant region of heavy chain
 - IgG, IgM, IgA, IgD, IgE

Antibody-mediated effector function

- ▶ Antibodies contribute to immunity in following ways
 - ▶ Neutralization
 - ▶ Opsonization
 - ▶ Antibody-dependent cell-mediated cytotoxicity (ADCC)
 - ▶ Activation of classical complement pathway.

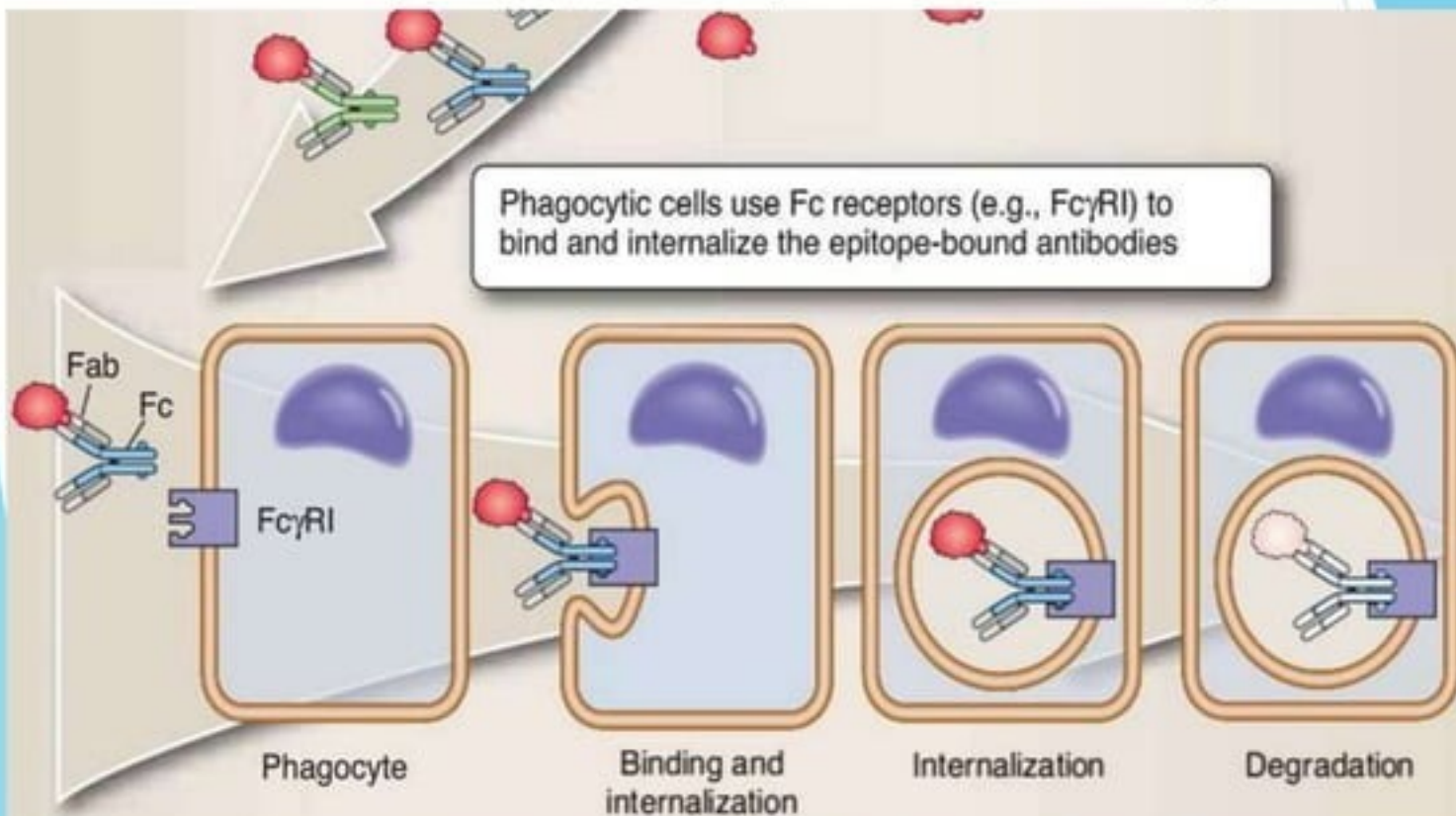
Neutralization

- ▶ Antibodies bind to viral surface proteins preventing infection of a host cell
- ▶ Antibodies may also bind to toxins in body fluids and prevent them from entering body cells
- ▶ Neutralizing antibodies are usually of the IgG and IgA isotypes.



Opsonization

- ▶ Antibodies bind to antigens on bacteria creating a target for macrophages or neutrophils, triggering phagocytosis
 - ▶ As macrophages, dendritic cells, and neutrophils bear surface receptors (FcR) for the Fc portion of bound immunoglobulin.



Antibody-dependent cell-mediated cytotoxicity (ADCC)

Antibody bound to target cells (virus infected cells of the host) with the Fc receptors of a number of cell types, particularly natural killer (NK) cells

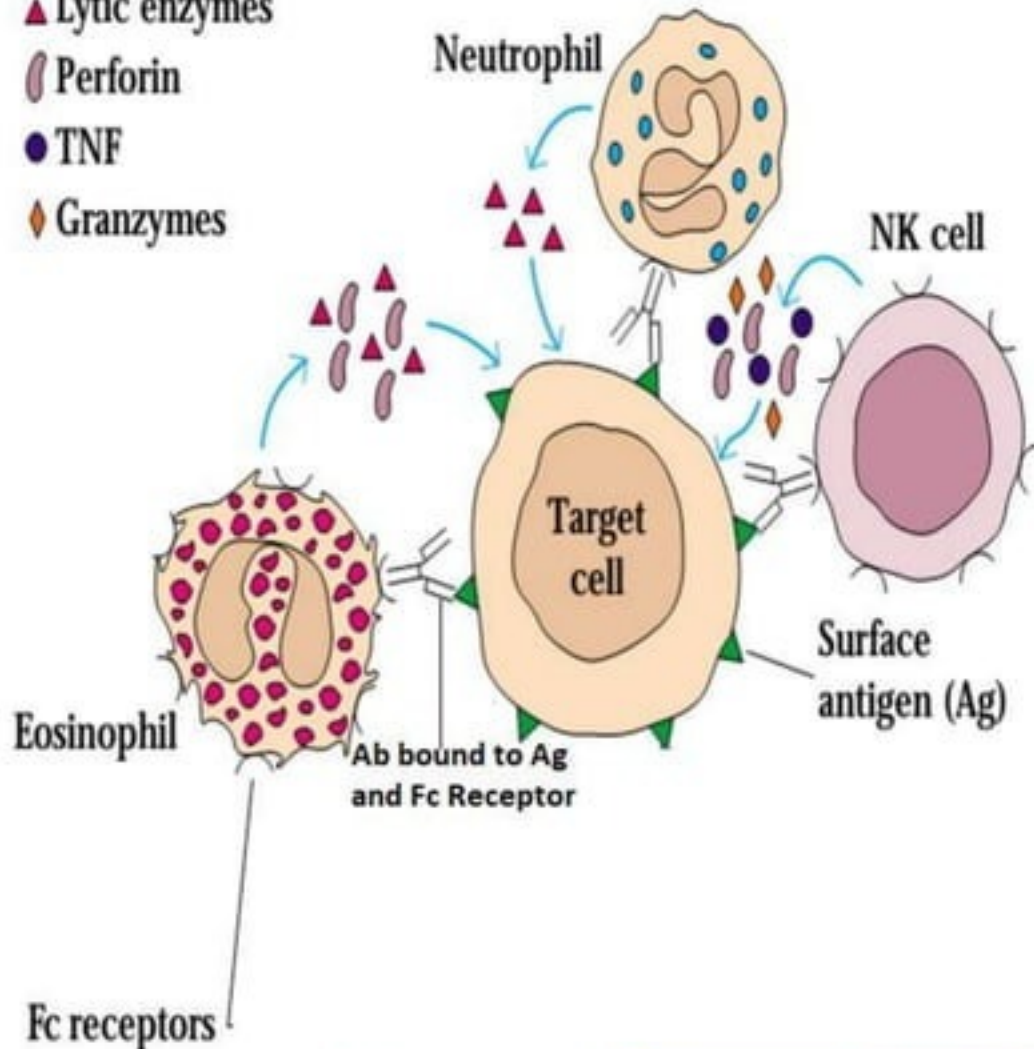
- can direct the cytotoxic activities of the effector cell against the target cell.
- FcRs on NK cells and eosinophils are IgG-, IgE-, and IgA-specific.

▲ Lytic enzymes

● Perforin

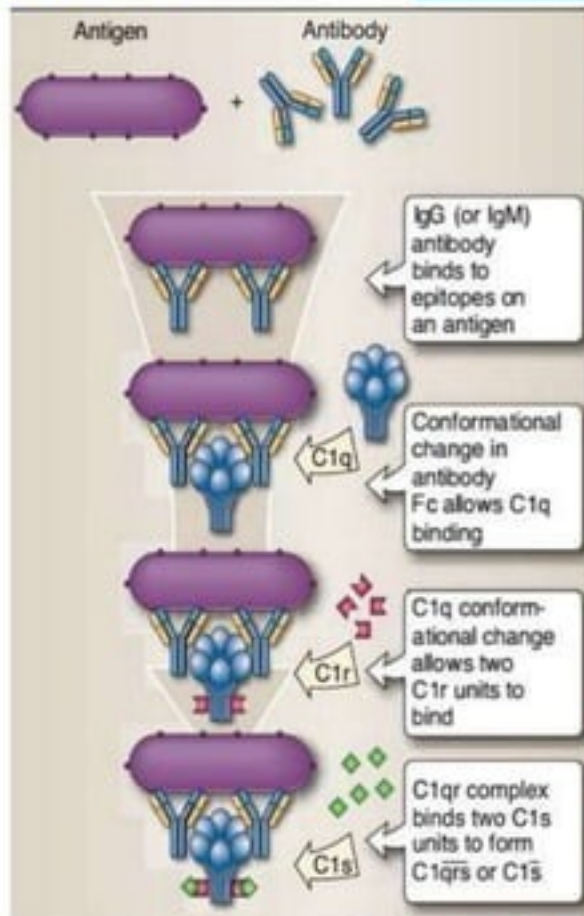
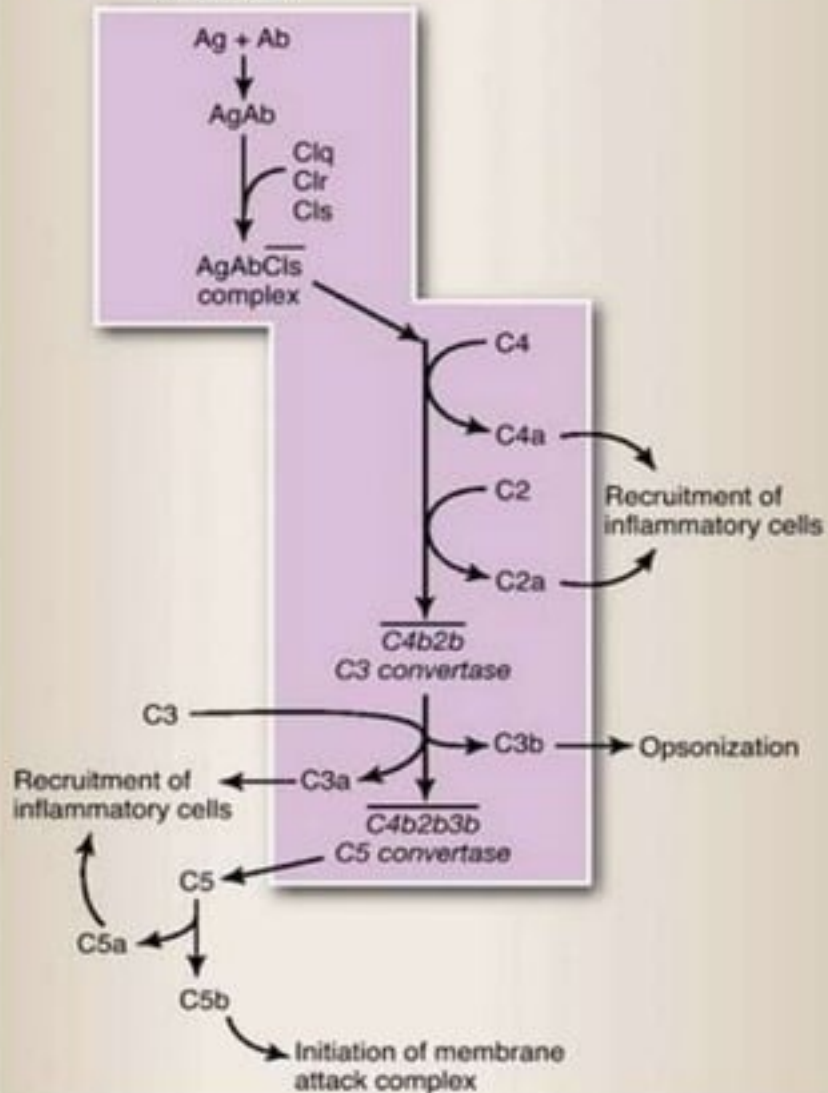
● TNF

◆ Granzymes



Complement activation

Classical



The classical pathway of complement is activated by **conformational changes that occur in the Fc portion of antibodies upon epitope binding.**

Function of Antibody Isotypes

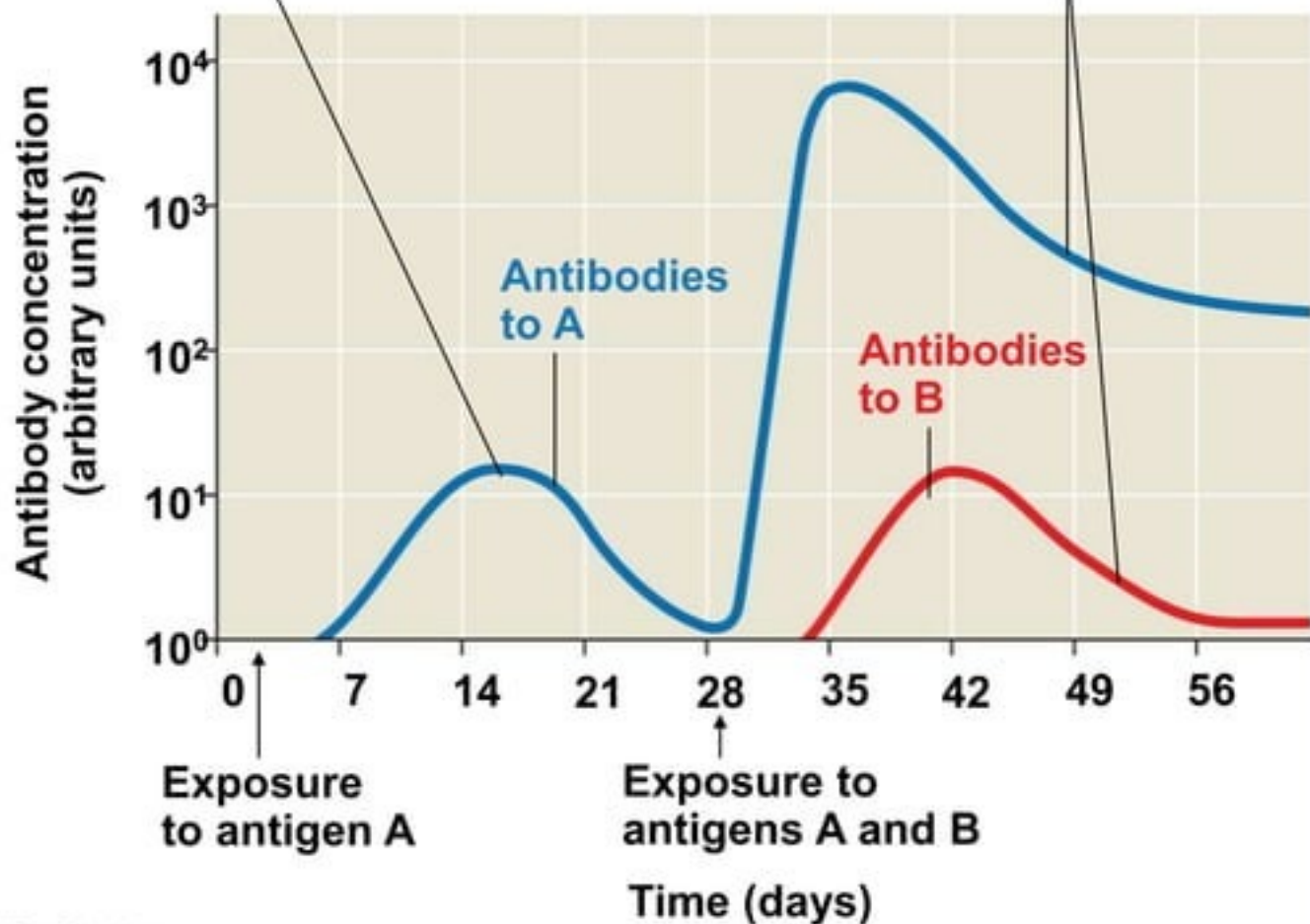
Antibody Isotypes	Isotype -specific Effector function
IgG	<ul style="list-style-type: none">• Opsonization of antigens for phagocytosis by macrophages and neutrophils (IgG1 and IgG3)• Activation of the classical pathways of Complements. IgG3 is the most effective complement activator, followed by IgG1; IgG2 is less efficient, and IgG4 is not able to activate complement at all.• Antibody dependent cell mediated cytotoxicity mediated by natural killer cells• Neonatal immunity: transfer of maternal antibody across placenta (IgG1, IgG3, and IgG4)• Feedback inhibition of B-cell activation
IgM	<ul style="list-style-type: none">• first immunoglobulin produced in a primary response to an antigen• Activation of the classical pathway of complements• Antigen receptor of naïve B lymphocytes• Endocytosis, phagocytosis
IgA	<ul style="list-style-type: none">• Mucosal immunity : secretion of IgA into lumens of the GI and Respiratory tracts• Antibody-dependent cell-mediated cytotoxicity
IgE	<ul style="list-style-type: none">• Mast cell degranulation(immediate hypersensitivity reaction)• Antibody-dependent cell-mediated cytotoxicity
IgD	<ul style="list-style-type: none">• Antigen receptor of naïve B lymphocytes

Immunological Memory (memory B cell)

- ▶ Immunological memory is responsible for long-term protections against diseases, due to either a prior infection or vaccination
- ▶ The first exposure to a specific antigen represents the **primary immune response**
- ▶ During this time, selected B and T cells give rise to their effector forms
- ▶ In the **secondary immune response**, memory cells facilitate a faster, more efficient response

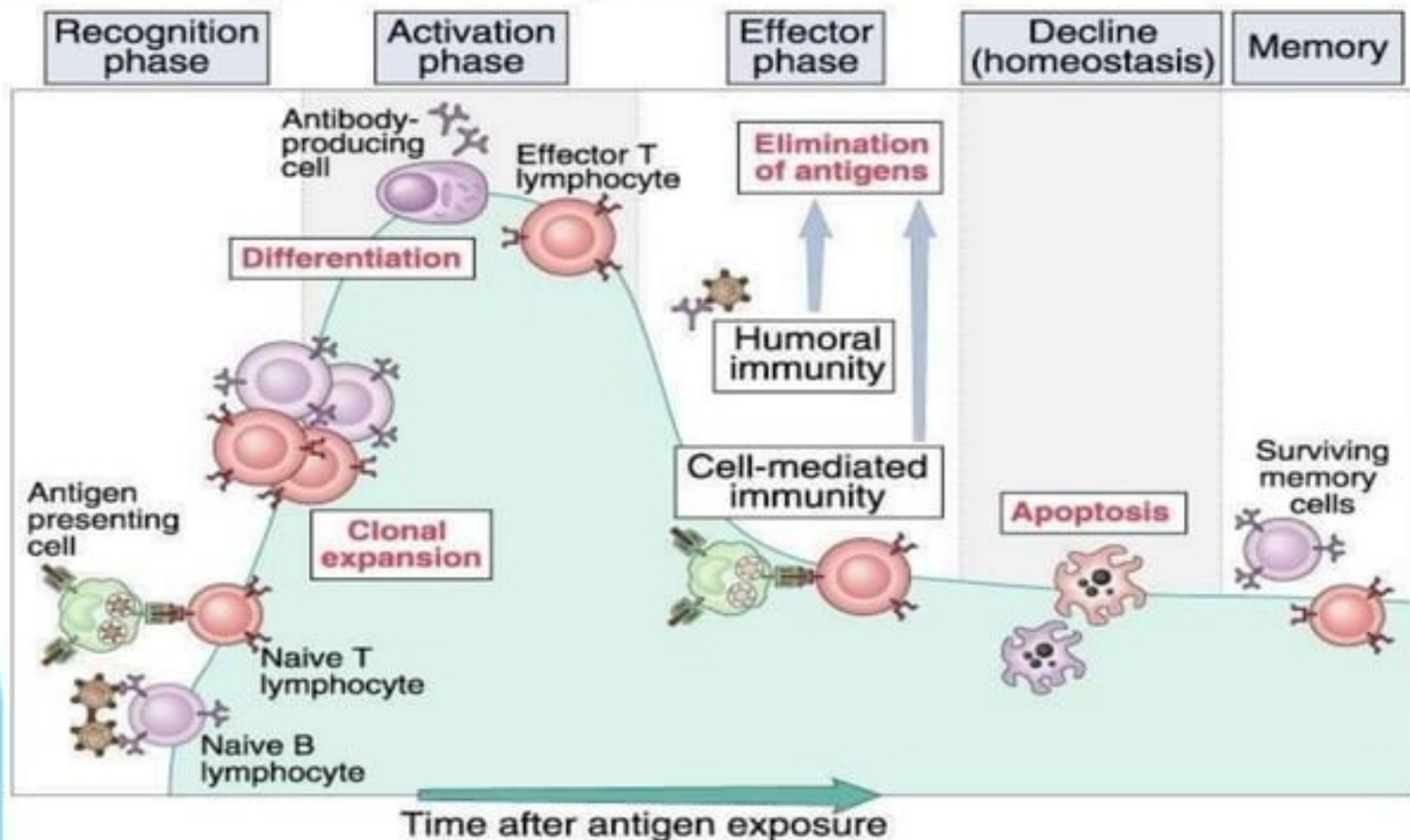
Primary immune response to antigen A produces antibodies to A.

Secondary immune response to antigen A produces antibodies to A; primary immune response to antigen B produces antibodies to B.



Stages in adaptive immune response

Phases of adaptive immune responses.



Attribute	Innate immunity	Adaptive immunity
Response time	Minutes/hours	Days
Specificity	Specific for molecules and molecular patterns associated with pathogens and molecules produced by dead /damaged cells	Highly specific; discriminates between even minor differences in molecular structure of microbial or non microbial molecules
Diversity	A limited number of conserved, germ line-encoded receptors	Highly diverse; a very large number of receptors arising from genetic recombination of receptor genes in each individual
Memory responses	Some (observed in invertebrate innate responses and mouse/human NK cells)	Persistent memory, with faster response of greater magnitude on subsequent exposure
Self/nonsel self discrimination	Very good; no microbe-specific self/non self patterns in host	Very good; occasional failures of discrimination result in autoimmune disease
Major cell types	Phagocytes , natural killer (NK) cells, other leukocytes, epithelial and endothelial cells	T cells, B cells, antigen-presenting cells

Herd immunity

- ▶ **Herd immunity** is defined as the overall immunity of a community (or herd) towards a pathogen.
- ▶ Elements that contribute to create a strong herd immunity are-
 - Occurrence of clinical and subclinical cases in the herd
 - On-going immunization programme
 - Herd structure i.e. type of population involved
 - Type of pathogen-Herd immunity may not be strong in a community against all the pathogens.

Herd immunity

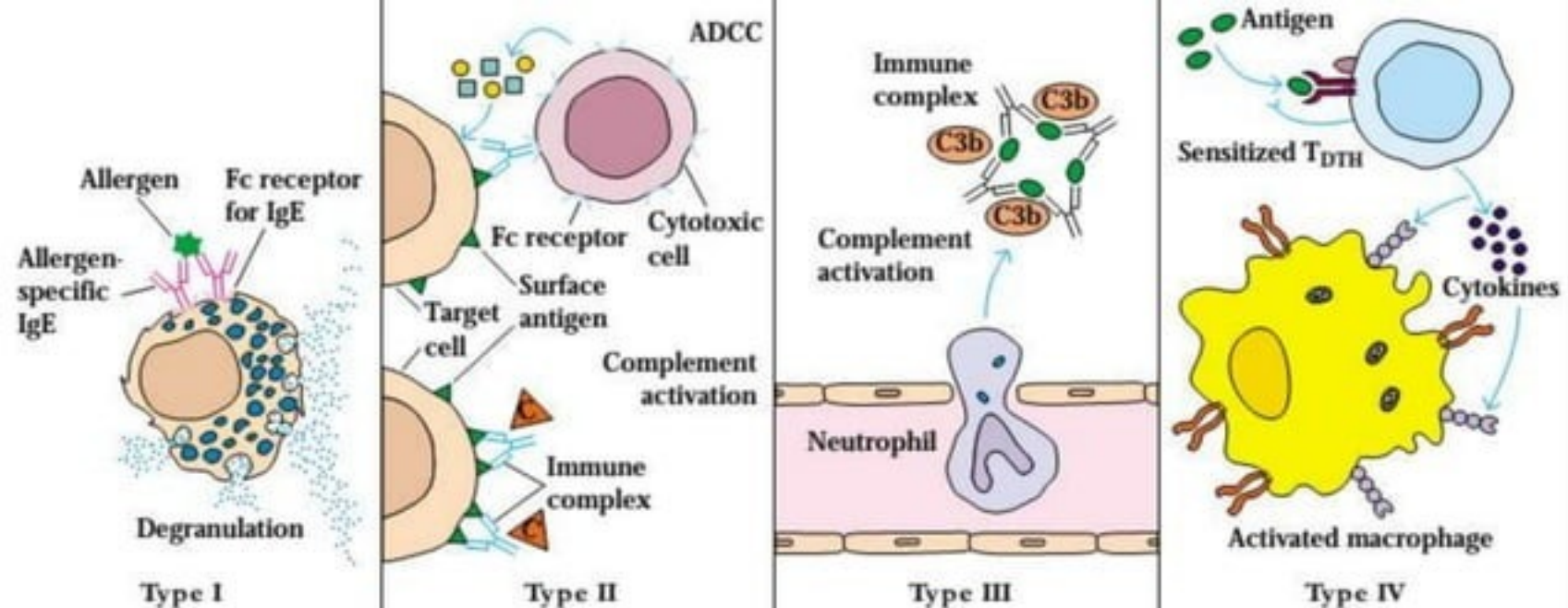
- ▶ Herd immunity develops following effective vaccination against some diseases like:
 - Diphtheria and Pertussis vaccine
 - Measles, Mumps and Rubella (MMR) vaccine
 - Polio (Oral polio vaccine)
 - Smallpox vaccine
- *“Herd immunity against COVID-19 should be achieved by protecting people through vaccination, not by exposing them to the pathogen that causes the disease.”* Director-General’s 12 October media briefing speech from WHO.

Failure of immune response

- Immune response helps individuals defend against
 - microbes and some cancers
- Immune response can fail in
 - hypersensitivity reactions
 - immunodeficiency

Hypersensitivity Reaction

- Cause cell damage through excessive immune response to antigens
 - Hypersensitivity
 - overreaction to infectious agents
 - Allergy
 - overreaction to environmental substances
 - Autoimmunity
 - overreaction to self



<p>IgE-Mediated Hypersensitivity</p>	<p>IgG-Mediated Cytotoxic Hypersensitivity</p>	<p>Immune Complex-Mediated Hypersensitivity</p>	<p>Cell-Mediated Hypersensitivity</p>
<p>Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators</p>	<p>Ab directed against cell surface antigens mediates cell destruction via complement activation or ADCC</p>	<p>Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils</p>	<p>Sensitized T_{H1} cells release cytokines that activate macrophages or T_C cells which mediate direct cellular damage</p>
<p>Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema</p>	<p>Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia</p>	<p>Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus</p>	<p>Typical manifestations include contact dermatitis, tubercular lesions and graft rejection</p>

Immunodeficiency

- **Loss or inadequate** function of various components of the immune system
- Can occur in **any part or state** of the immune system
 - physical barrier, phagocytes, B lymphocytes, T lymphocytes, complement, natural killer cells
- The immuno-compromised host
 - has an impaired function of immune system
 - is at high risk of infection

Types of Immunodeficiency

- **Congenital (primary) immunodeficiency**
 - genetic abnormality
 - defect in lymphocyte maturation
- **Acquired (secondary) immunodeficiency**
 - results from infections, nutritional deficiencies or treatments
 - AIDS, chronic leukemia

Altered immunity: immuno-compromised

Disorder

Compromised function

Immune
system

**Adaptive
immunity**

Reduction of T cells

Activation of macrophages

**Activation of B
lymphocytes**

Hypo-gammaglobulinemia

**Neutralizes pathogens and
toxins, opsonization,
complement activation**

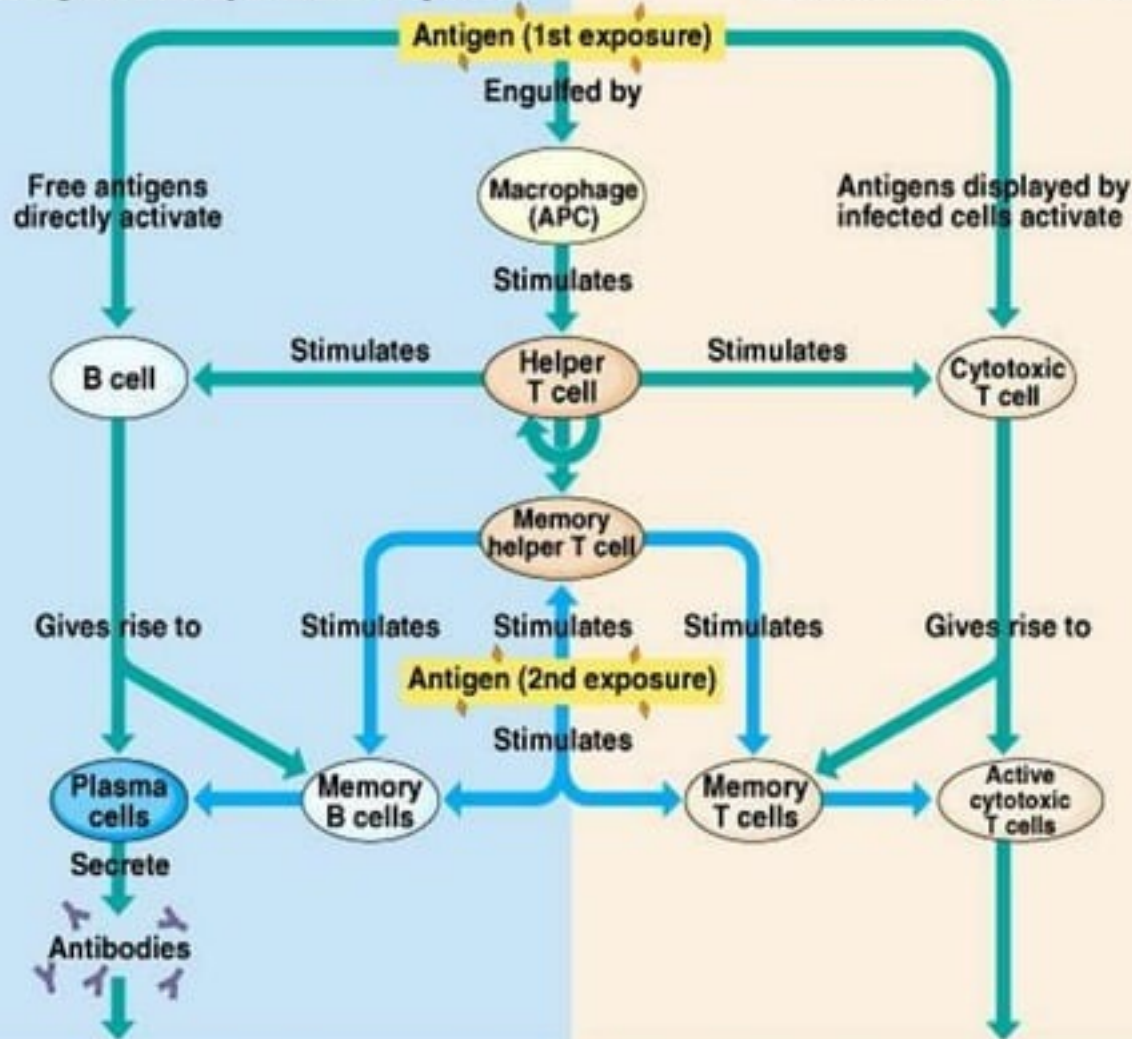
Summary

- **Evolutionary need for adaptive immunity:**
 - Self/non-self discrimination, specificity, amplification, regulation, duration and memory
- **T and B cells are mediators of adaptive immunity**
 - T cells: cell-mediated immunity
 - B cells: humoral immunity
 - Cells of innate immunity also participate (DCs, Macrophages)
- **Activation of T and B cells are different:**
 - T cells: specific recognition of peptide/MHC complex (signal 1) and costimulatory signals by APC (Signal 2)
 - B cells: recognize native proteins (signal 1). May/may not require signal 2 from CD4⁺ Th cells (TD and TI antigens)
- **Immunological memory: an important hallmark**
 - Faster and rapid response on a second antigen encounter
- **Innate immune response shapes the adaptive immunity**

Overview of Immune System Responses

Humoral (antibody-mediated) immune response

Cell-mediated immune response



Defend against extracellular pathogens by binding to antigens and making the pathogens easier targets for phagocytes and complement.

Defend against intracellular pathogens and cancer by binding to and lysing the infected cells or cancer cells.

Thank you

