NEUROIMMUNOLOGY

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IMMUNITY

INNATE

ACQUIRED

DR AMR HASAN AL HASANY

IMMUNITY

INNATE

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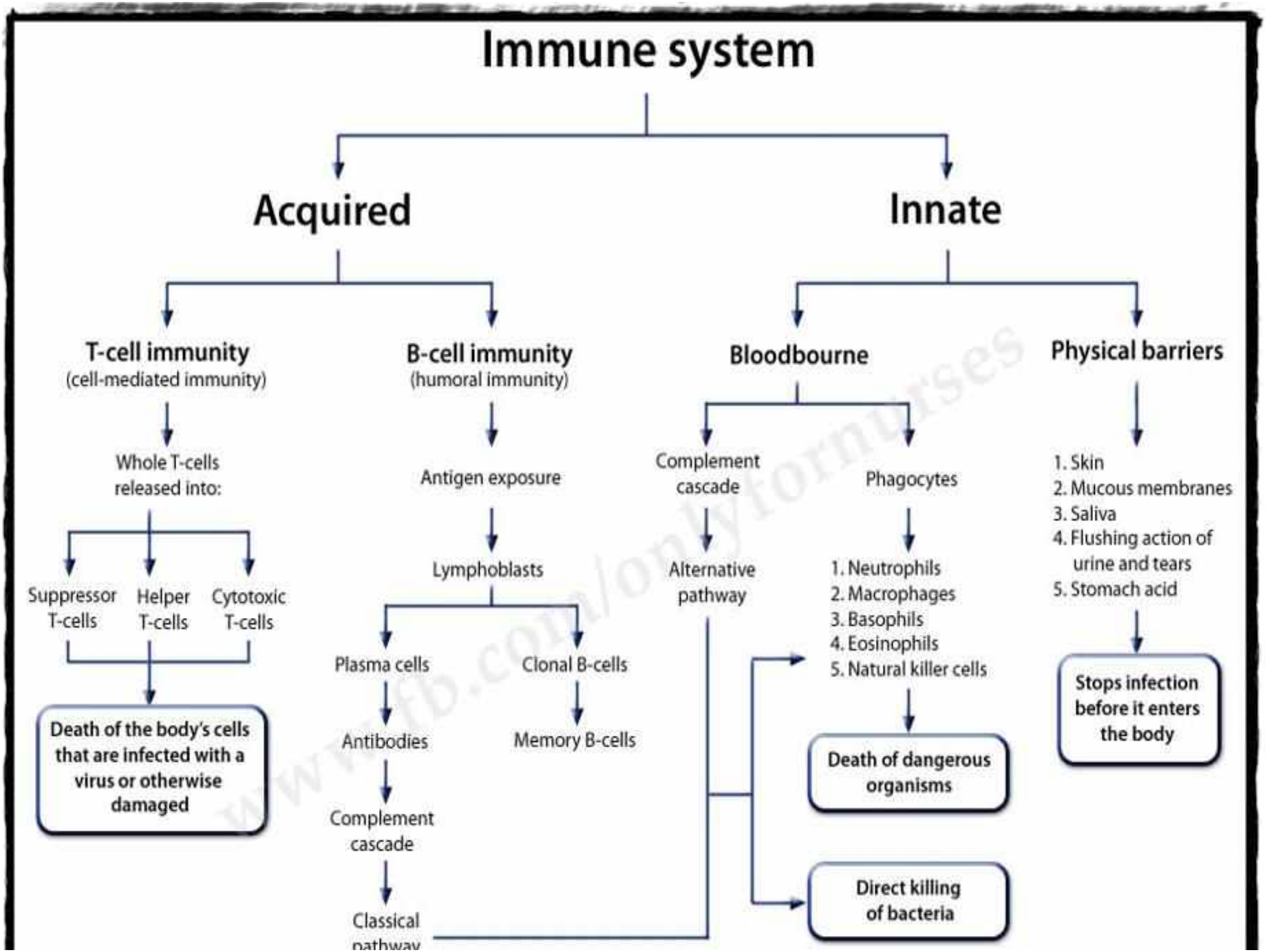

Immune system
Acquired
Innate
T-cell immunity
(cell-mediated immunity)
B-cell immunity
(humoral immunity)
Bloodbourne
Physical barriers
Whole T-cells released into:
Antigen exposure
Complement cascade
Phagocytes
1. Skin
2. Mucous membranes
3. Saliva
4. Flushing action of urine and tears
5. Stomach acid
Suppressor T-cells
Helper T-cells
Cytotoxic T-cells
Lymphoblasts
Alternative pathway
1. Neutrophils
2. Macrophages
3. Basophils
4. Eosinophils
5. Natural killer cells
Plasma cells
Clonal B-cells
Death of the body's cells that are infected with a virus or otherwise damaged
Antibodies
Memory B-cells
Stops infection before it enters the body
Complement cascade
Death of dangerous organisms
Classical pathway
Direct killing of bacteria

INNATE IMMUNITY

I. Mechanical barriers and surface secretions

1. ***S***kin
2. The ***S***ticky mucus
3. Blinking, ***S***neezing and coughing.
4. ***S***weat and ***S***ebaceous secretions
5. ***S***aliva, tears and mucous secretions
6. The ***F***lushing action of saliva, tears and urine helps in washing microbes from the body.
7. ***G***astric and vaginal acidity inhibit growth of microorganisms.
8. Cilia of the ***R***espiratory tract epithelium sweep foreign material out.

INNATE IMMUNITY

II. Normal bacterial flora

1. Bacteria of the normal flora produce bacteriocins and acids that destroy microorganisms.
2. They compete with pathogens for essential nutrients.

N.B.: Suppression of normal flora by antibiotics may lead to infection with potential pathogens (superinfection).

INNATE IMMUNITY

III. Humoral defence mechanisms

1. **Lysozyme:** It is an enzyme that lyses bacteria by destroying the peptidoglycan of their cell wall.

2. **Complement**

3. **Acute phase proteins**

4. **Interferons.**

INNATE IMMUNITY

IV.Cellular Defence Mechanisms:

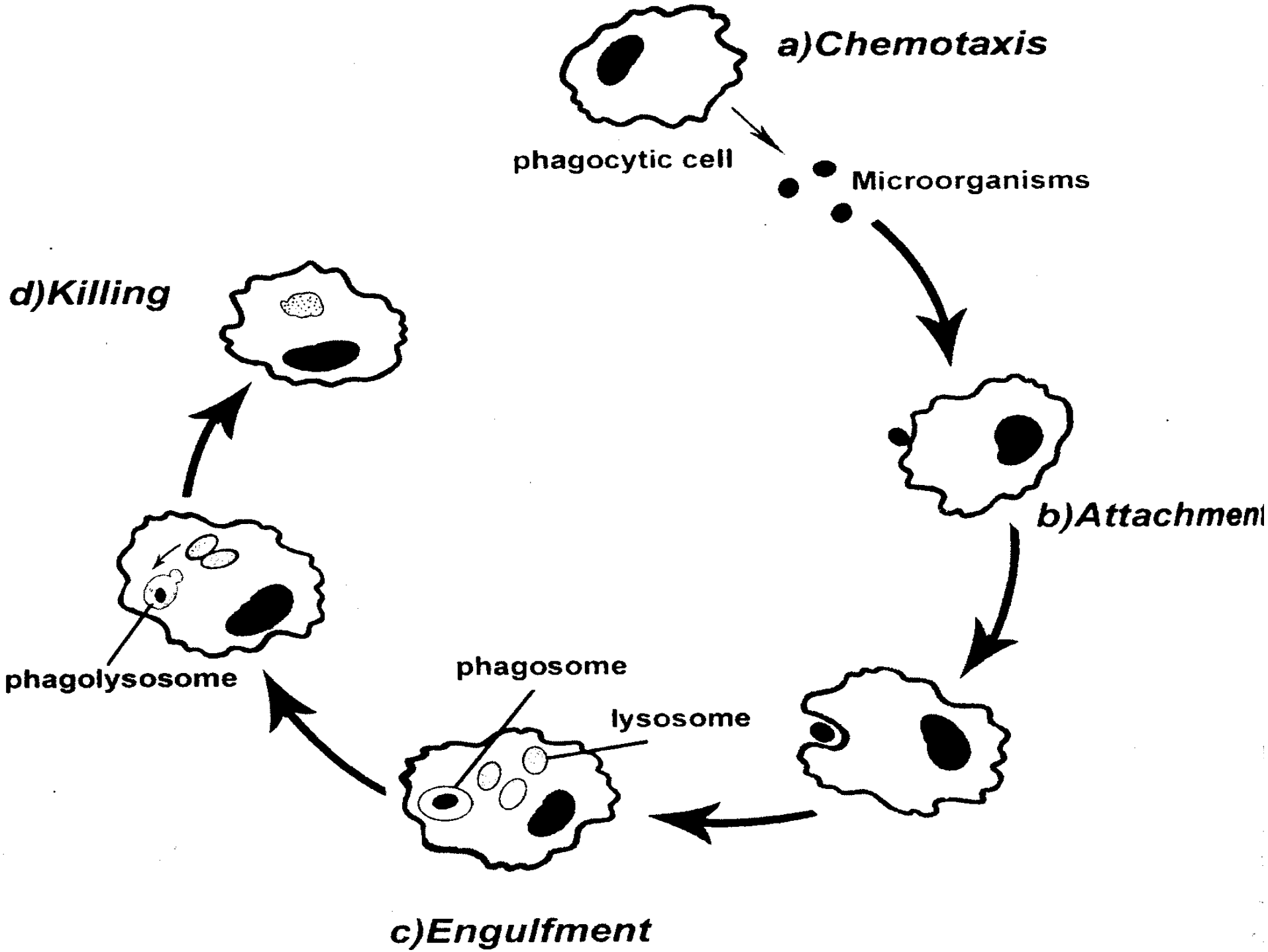
1. Phagocytes

Particles, e.g. bacteria, entering the tissue fluids or blood are rapidly engulfed by phagocytic cells.

This process of engulfment (internalization) of particulate matter is termed **phagocytosis.**

There are 2 main types of phagocytic cells:
Polymorphonuclear leucocytes (especially neutrophils)

Mononuclear phagocytes (monocytes in the blood and macrophages in the tissues).


a)Chemotaxis
phagocytic cell
Microorganisms
b)Attachmen
c)Engulfment
phagosome
lysosome
phagolysosome
d)Killing

2. Natural Killer cells (NK cells)

Large granular lymphocytes which can be distinguished from B and T lymphocytes.

They constitute 10-15% of peripheral blood lymphocytes.

They are capable of non-specific killing of tumour cells and virus-infected cells a manner similar to cytotoxic T cells, but differ from them in the way they recognize their target

3.Eosinophils (PAP)

	Innate	Acquired
Presence	Since birth	Following exposure to pathogens
Onset of action	Immediately after infection	Relatively delayed
Main cells	Granulocytes, monocytes/ macrophages & NK cells	B & T lymphocytes
Memory	Absent	Present
Efficiency	Less efficient	More efficient and improves with each exposure
Specificity	Non-specific: Present in all individuals, against all microorganisms, without previous exposure	Specific: Occurs in a given person, against a particular pathogen
Interaction	Interact with acquired immunity through: e.g. - Antigen presentation	Interact with innate immunity through: e.g. - Opsonization

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II. ACQUIRED IMMUNITY (ADAPTIVE IMMUNITY)

A) T lymphocytes are produced in the bone marrow, but complete their maturation in the Thymus. They comprise around 75% of peripheral blood lymphocytes.

There are two main kinds of T cells:

1. Cytotoxic T (Tc) cells

These recognize body cells infected with virus.

Antigens from replicating viruses are displayed on the surface of infected cells → recognized by the cytotoxic T cells → kill the infected cells before viral replication.

Can kill tumour cells

II. ACQUIRED IMMUNITY (ADAPTIVE IMMUNITY)

A) T lymphocytes are produced in the bone marrow, but complete their maturation in the Thymus. They comprise around 75% of peripheral blood lymphocytes.

There are two main kinds of T cells:

1. **Cytotoxic T (Tc) cells**
2. **Helper T (Th) cells**

II. ACQUIRED IMMUNITY (ADAPTIVE IMMUNITY)

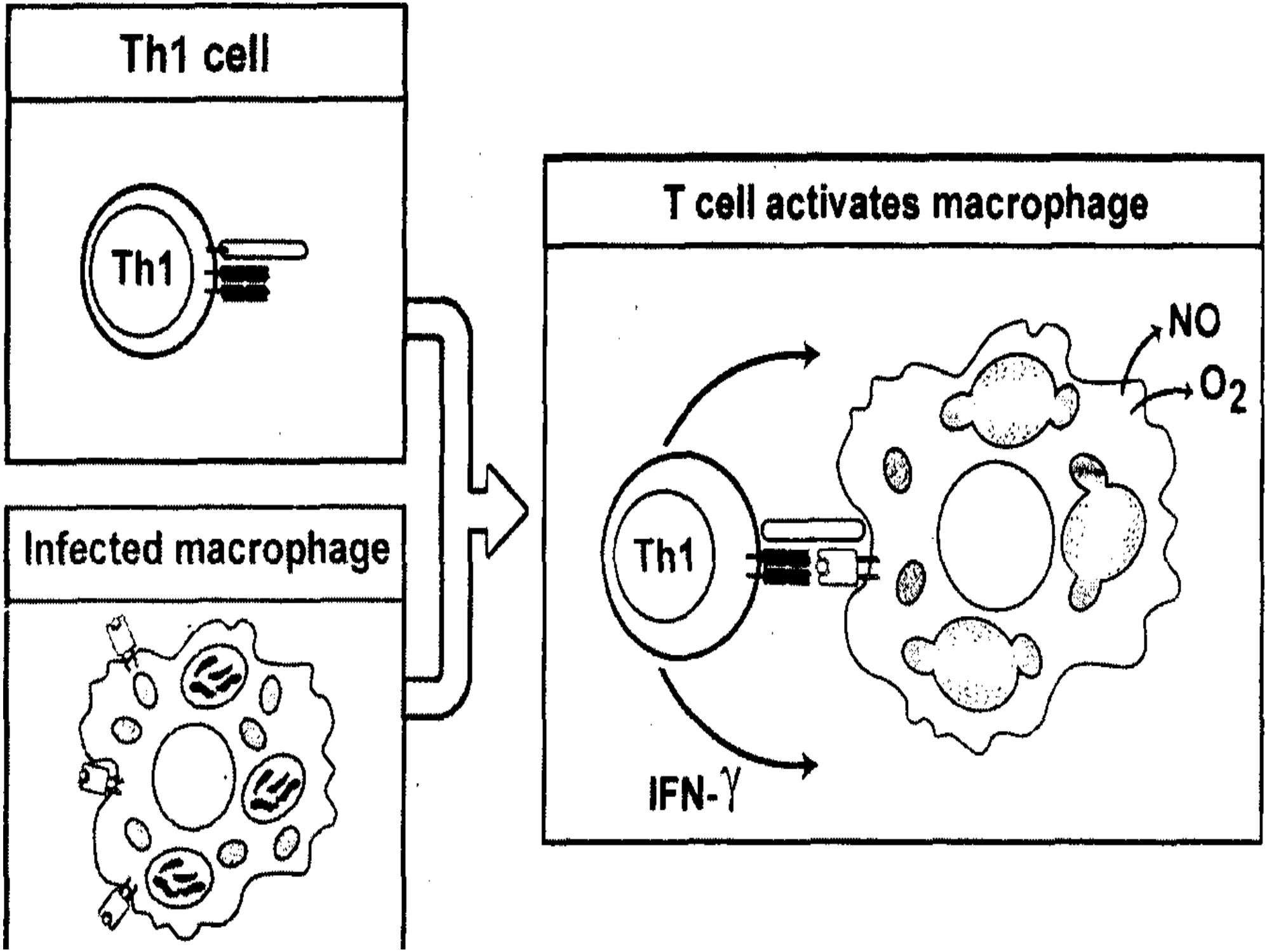
2. Helper T (Th) cells

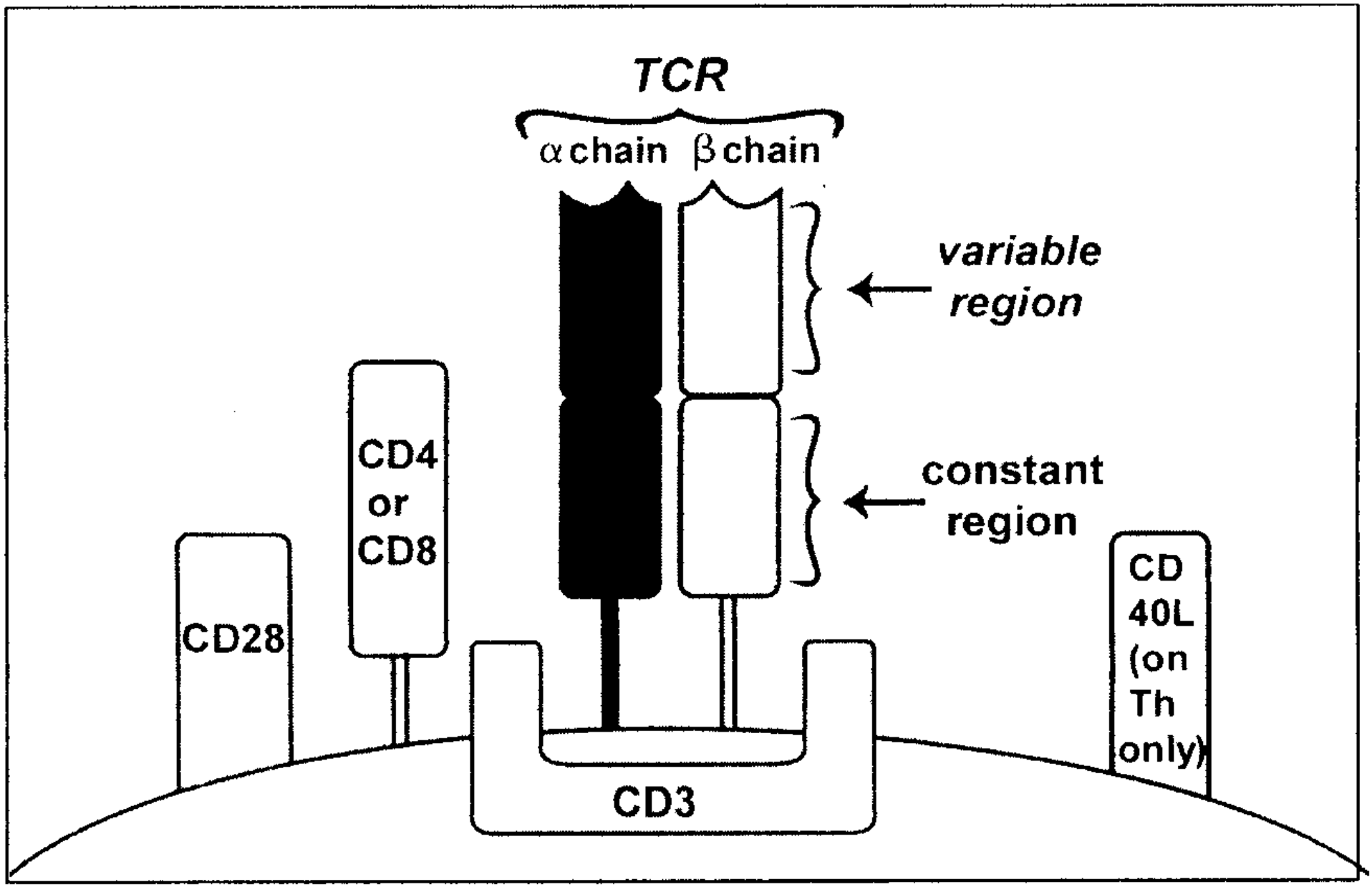
a-T helper 1 (Th1) cells

Secrete cytokines which help in **activation** of **Macrophages ------→** making macrophages more capable of killing any bacteria inside them.

b- T helper 2 (Th2) cells

Secrete certain cytokines which help in **activation of B cells ---→** plasma cells ----> produce antibodies to deal with those extracellular pathogens.

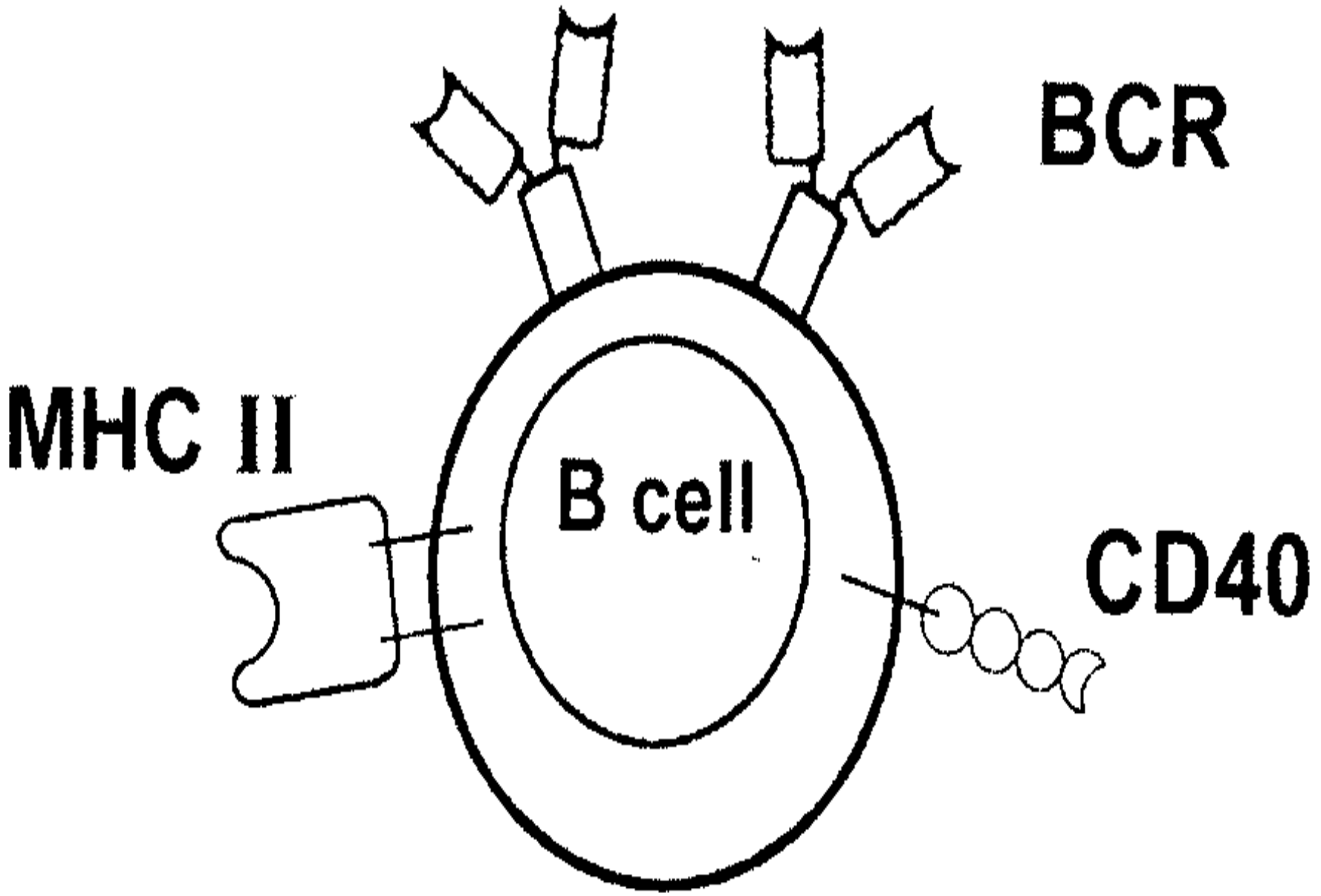

Th1 cell
Th1
Infected macrophage
T cell activates macrophage
Th1
NO
O_2
IFN-γ


TCR
α chain
β chain
variable region
constant region
CD4 or CD8
CD28
CD 40L (on Th only)
CD3

II. ACQUIRED IMMUNITY (ADAPTIVE IMMUNITY)

B) B lymphocytes are produced in the **B**one marrow, where they complete their maturation. They comprise around 10% of peripheral blood lymphocytes.

When B cells become active -----→ plasma cells -----→**antibodies,** or **immunoglobulins**


BCR
MHC II
B cell
CD40

II. ACQUIRED IMMUNITY (ADAPTIVE IMMUNITY)

II.The Lymphoid Organs:

They are defined as organized tissues where lymphocytes interact with other non-lymphoid cells that are important either in their maturation or in starting an acquired immune response. They are divided into:

A. Primary (central) lymphoid organs

This is where lymphocytes complete their maturation, becoming **mature** (adult) lymphocytes. They are:

The Bone marrow: where the **B** cells complete their maturation.

The Thymus: where the **T** cells complete their maturation.

II. ACQUIRED IMMUNITY (ADAPTIVE IMMUNITY)

B. Secondary (peripheral) lymphoid organs

They are the places where lymphocytes can meet **antigens,** leading to

activation of the lymphocytes. The secondary lymphoid organs include the ***spleen, lymph nodes and various mucosal associated lymphoid tissue (MALT):***

II. ACQUIRED IMMUNITY (ADAPTIVE IMMUNITY)

C)Circulation of Lymphocytes between Blood and Lymph:

Naive lymphocytes :Small B and T lymphocytes that have matured, but have not yet met antigen.

They leave the bone marrow and thymus--→ the blood ---→ secondary lymphoid organs, such as the lymph nodes.

Microbial antigens are drained from the site of infection through the afferent lymphatic vessels into the lymph nodes.

Not any lymphocyte seeing an antigen will recognize it,because lymphocytes are very specific for the antigens they recognize.

II. ACQUIRED IMMUNITY (ADAPTIVE IMMUNITY)

C)Circulation of Lymphocytes between Blood and Lymph:

Lymphocytes which **recognize** a certain antigen undergo a series of changes ----→ready to start working against the antigen .

The changes which occur are:

a. **Activation:** they become lymphoblasts.

b. **Proliferation:** rapid multiplication.

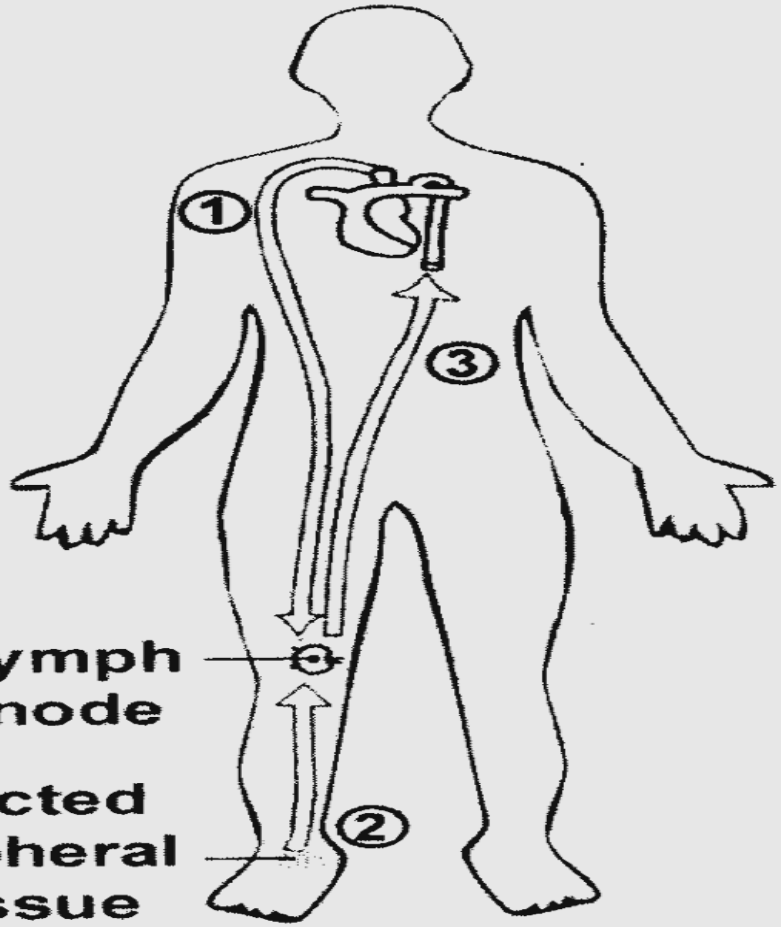
c. **Differentiation:** they change into **Effector cell**

1

Naive lymphocytes enter lymph nodes from blood

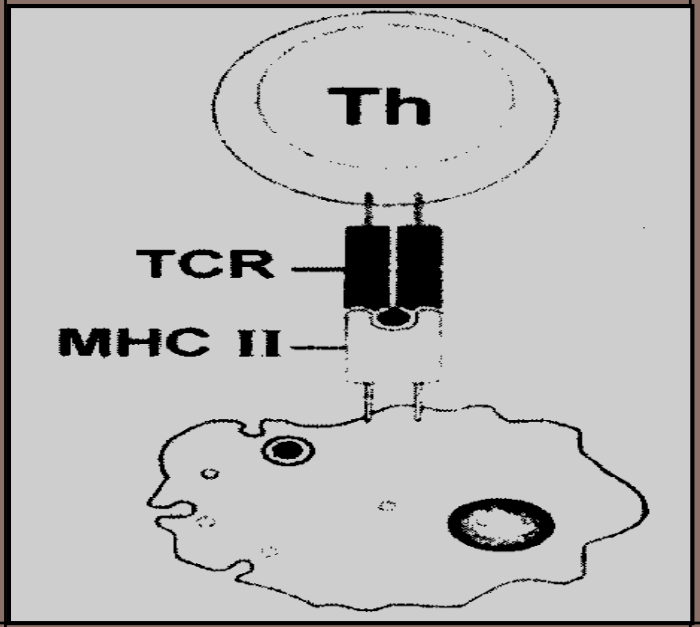
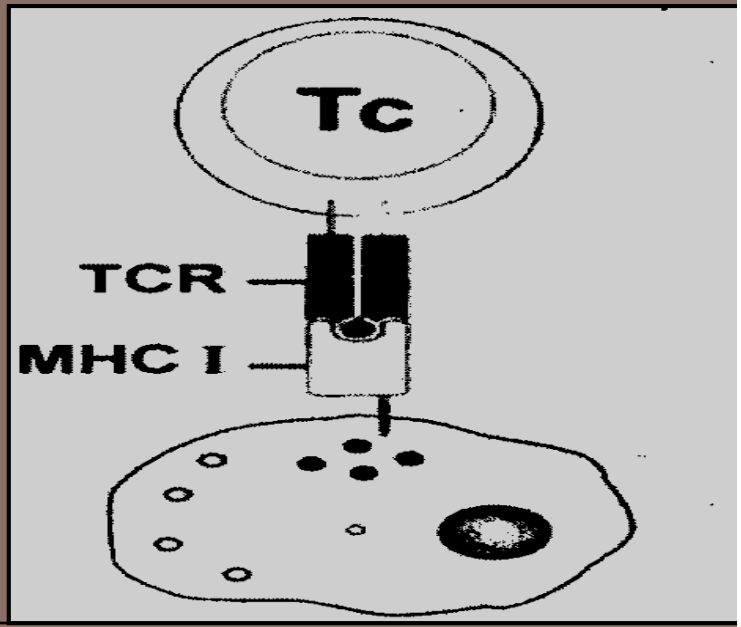
3

Lymphocytes return via thoracic duct to blood and from there to tissues

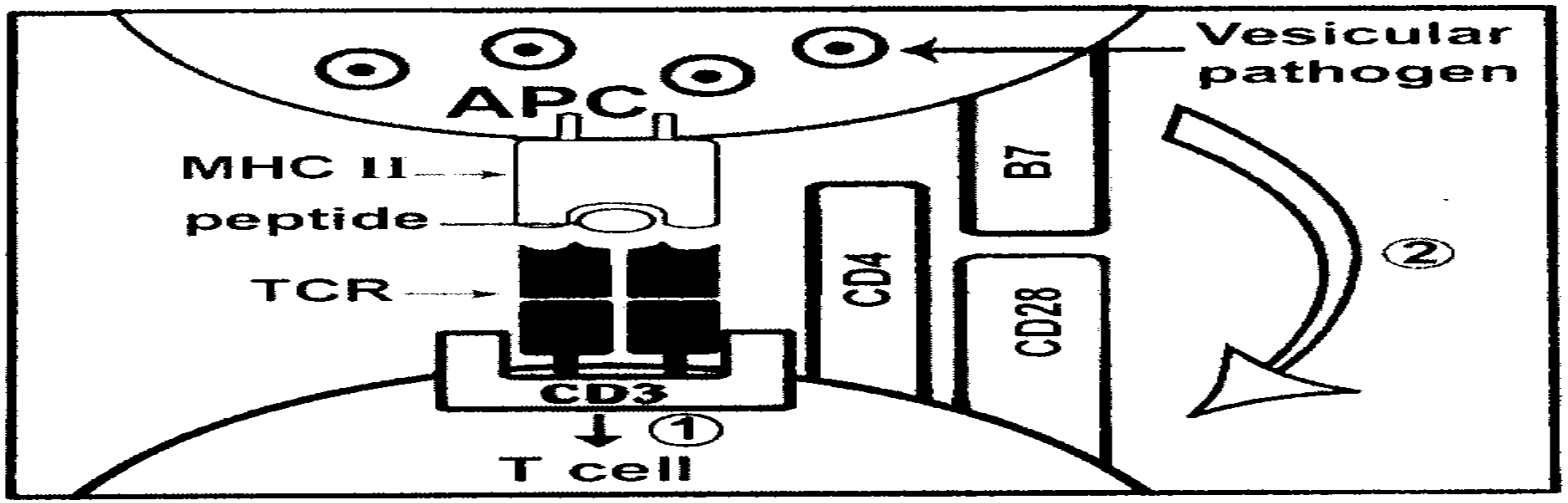


2

Antigens from sites of infection reach lymph nodes via lymphatics

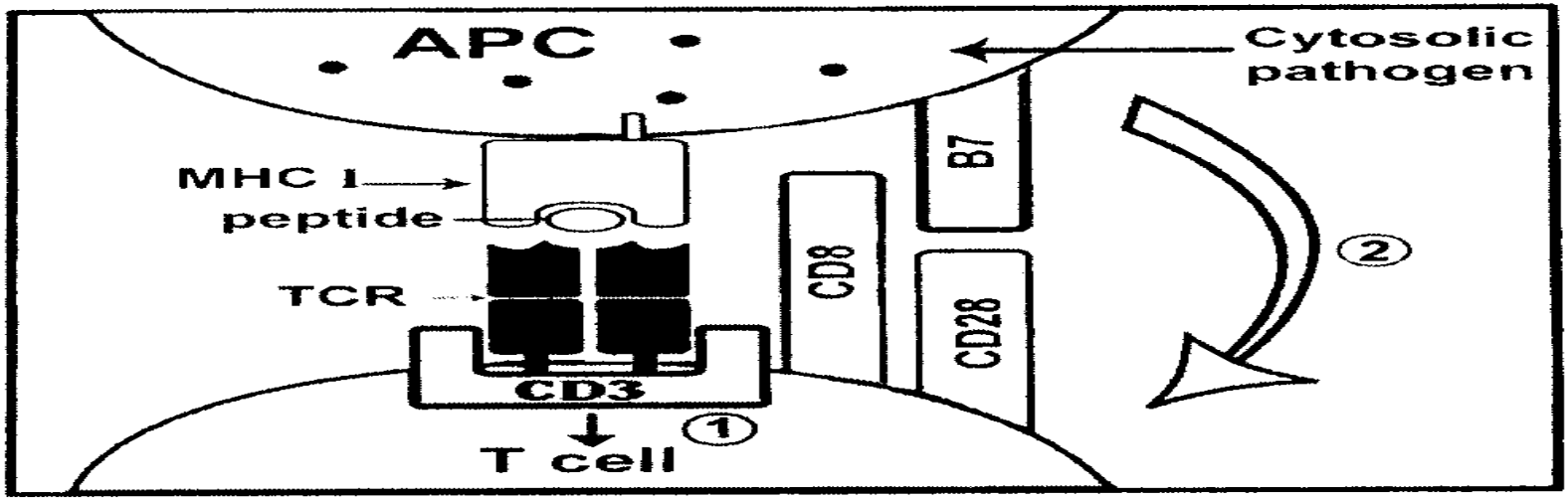
	Cytosolic "endogenous"	Vesicular "exogenous"
		
Examples	All viruses, few bacteria	-Intracellular bacteria e.g.T.B. -Extracellular bacteria and their products when internalized
Degraded in	Cytoplasm	Vesicles
Peptides bind to	MHC I molecules	MHC II molecules
Presented to	CD8 T cells	CD4 T cells
Result	Cytotoxic killing of presenting cell by CD8 T cell	Secretion of cytokines by CD4 T cells, giving help to macrophages, B cells and others

(a)



activation
proliferation
differentiation
→ memory T cell
→ effector Th cell
→ Th1 ⇶ cytokines
→ Th2 ⇶ cytokines

b)



activation
proliferation
differentiation
→ memory T cell
→ effector Tc cell ⇶ killing of target cells

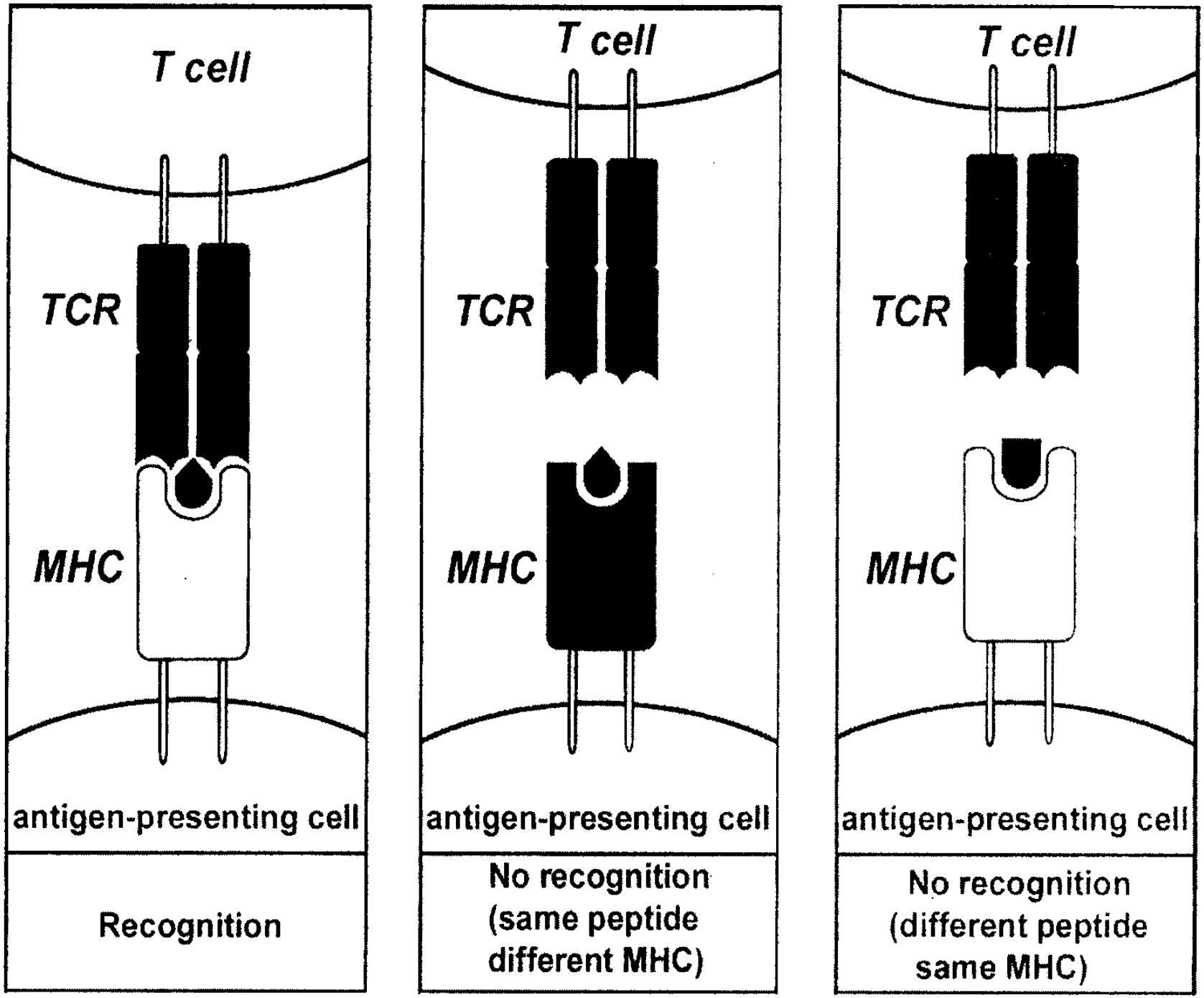
MHC Restriction

This means that antigen recognition by T cells is restricted by the MHC

molecules. This is true on two levels:

1. Since CD8 T cells recognize peptides bound to MHC I molecules and CD4 T cells recognize peptides bound to MHC II molecules, it is said that **CD8 Tcells are "MHC I restricted", and CD4 T cells are "MHC II restricted".**

2. There is a variety of different possible shapes of MHC I and MHC II molecules (**MHC polymorphism**). Thus, one cell may have many differentMHC I and MHC II molecules, and there are even more differences between MHC molecules on cells of different people.


T cell
TCR
MHC
antigen-presenting cell
Recognition
T cell
TCR
MHC
antigen-presenting cell
No recognition
(same peptide
different MHC)
T cell
TCR
MHC
antigen-presenting cell
No recognition
(different peptide
same MHC)

I. Antigen(=immunogen) is a substance that can stimulate the immune system to produce an immune response (humoral and/or cell-mediated) and reacts specifically with the product of this response.

Antigenic Determinants or Epitopes

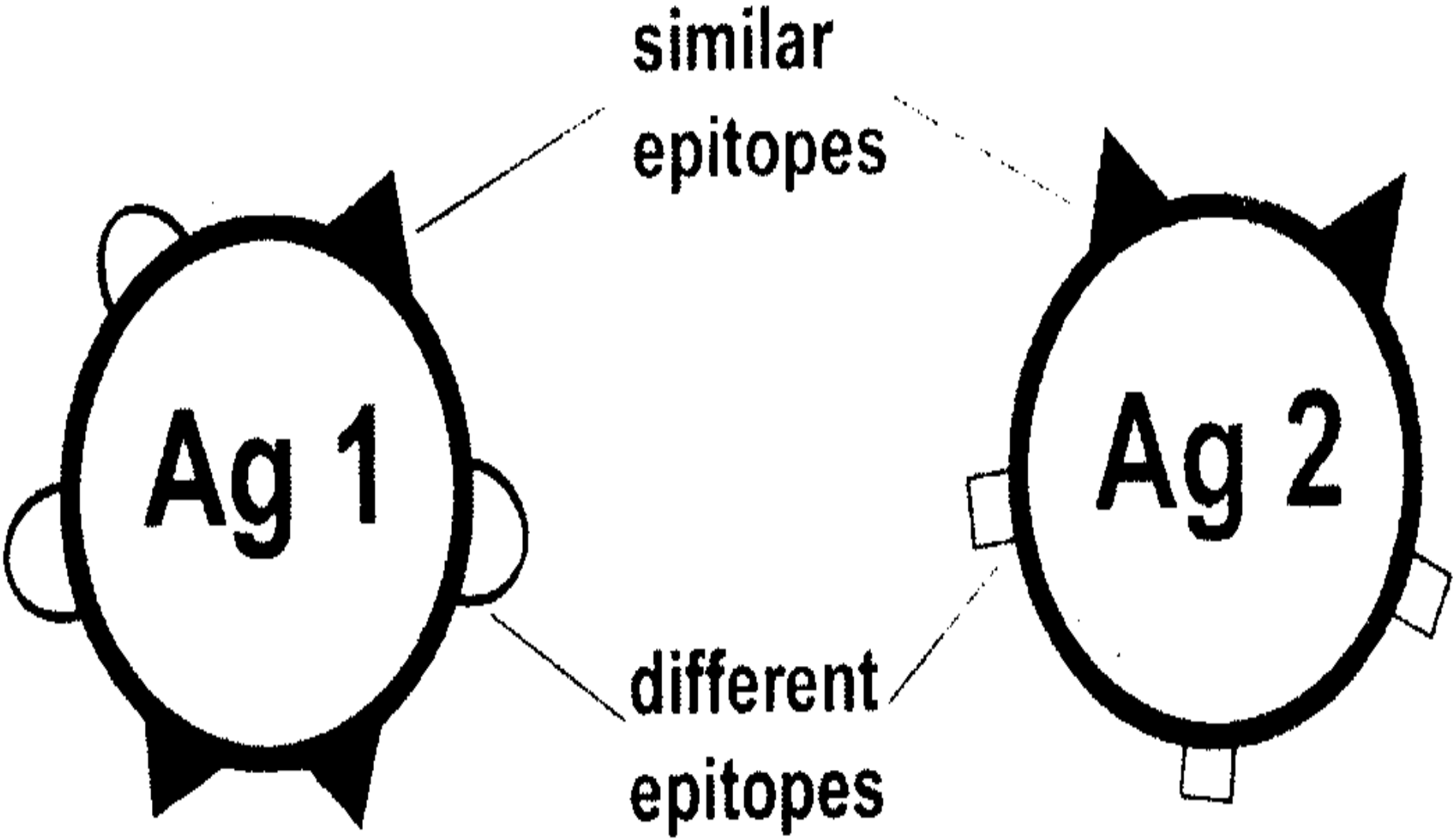
The immune system does not recognize the antigen molecule as a whole but reacts to structurally limited parts of the molecule called epitopes.

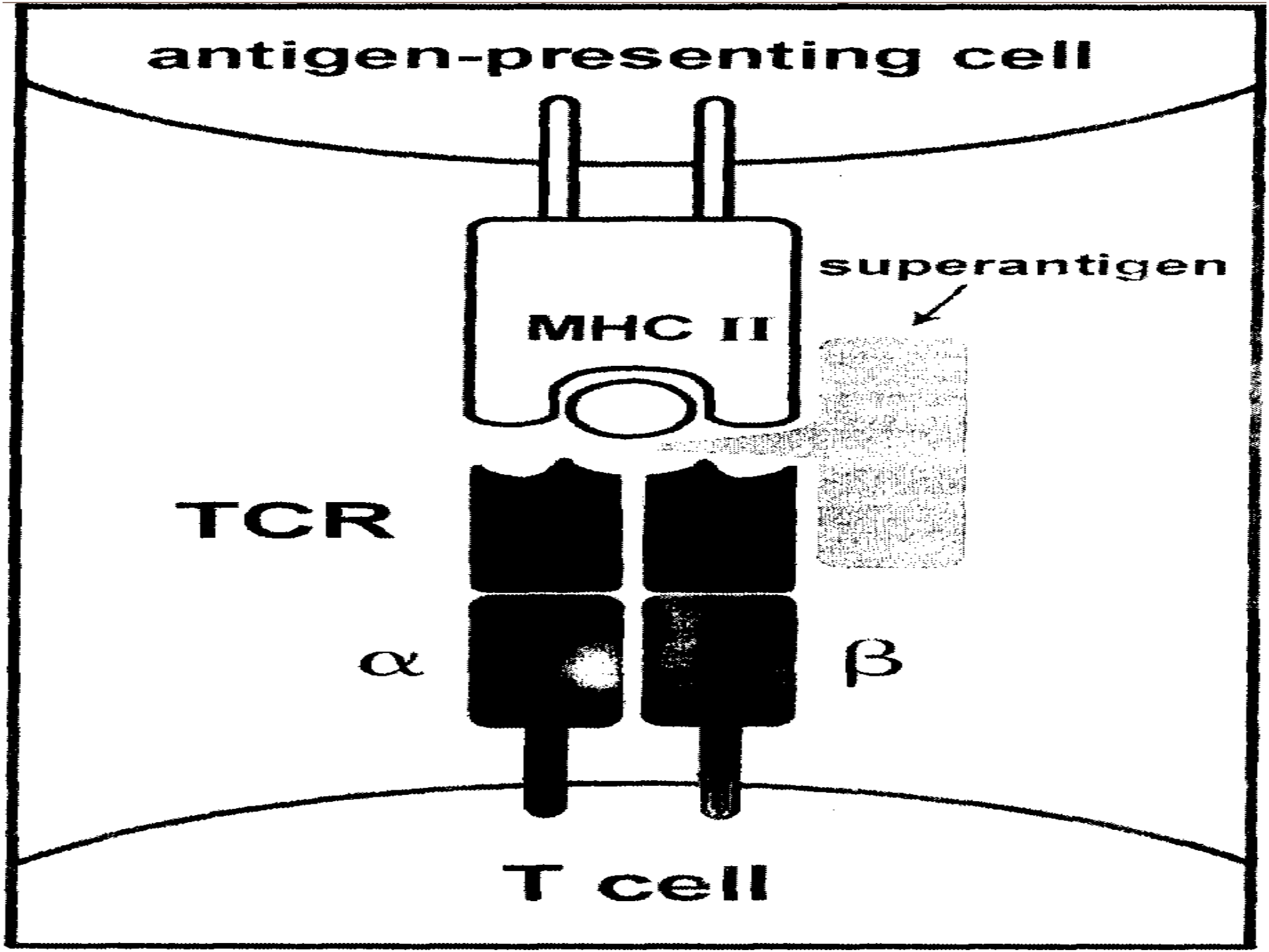
They are very small, composed of just four to five amino acids or monosaccharide residues.

They determine the specificity of the antigen.

The same antigen may possess different epitopes.

Antigens that share one or more similar epitopes are known as cross-reactive (heterophil) antigen


similar
epitopes
Ag 1
Ag 2
different
epitopes


antigen-presenting cell
MHC II
superantigen
TCR
α
β
T cell

MHC

- MHC antigens are a group of molecules expressed on cell surface membranes.

- They are also called ***HLA*** because they were first discovered on the surface of ***H***uman ***L***eucocytes.

- **MHC genes are divided into *3* major classes; class I, II and class III**

II. MHC

Class I

There are **three** class I loci (HLA-A, B and C). Each locus is highly polymorphic i.e. a single HLA locus contains one of many possible alleles(Alleles: variants of a single genetic locus)

The various possible alleles are given consecutive numbers, e.g. HLA- A1, HLA-A2, etc.

II. MHC

Class II

- Molecules are encoded by three principal loci (HLA-DP, -DQ and -DR), which also show polymorphism.

- MHC molecules have a much more limited cellular distribution.

- They are mainly found on the surface of (APCs).

Class III

- The class III genes code for a number of complement components and are grouped together in a region between HLA-D and HLA-B.

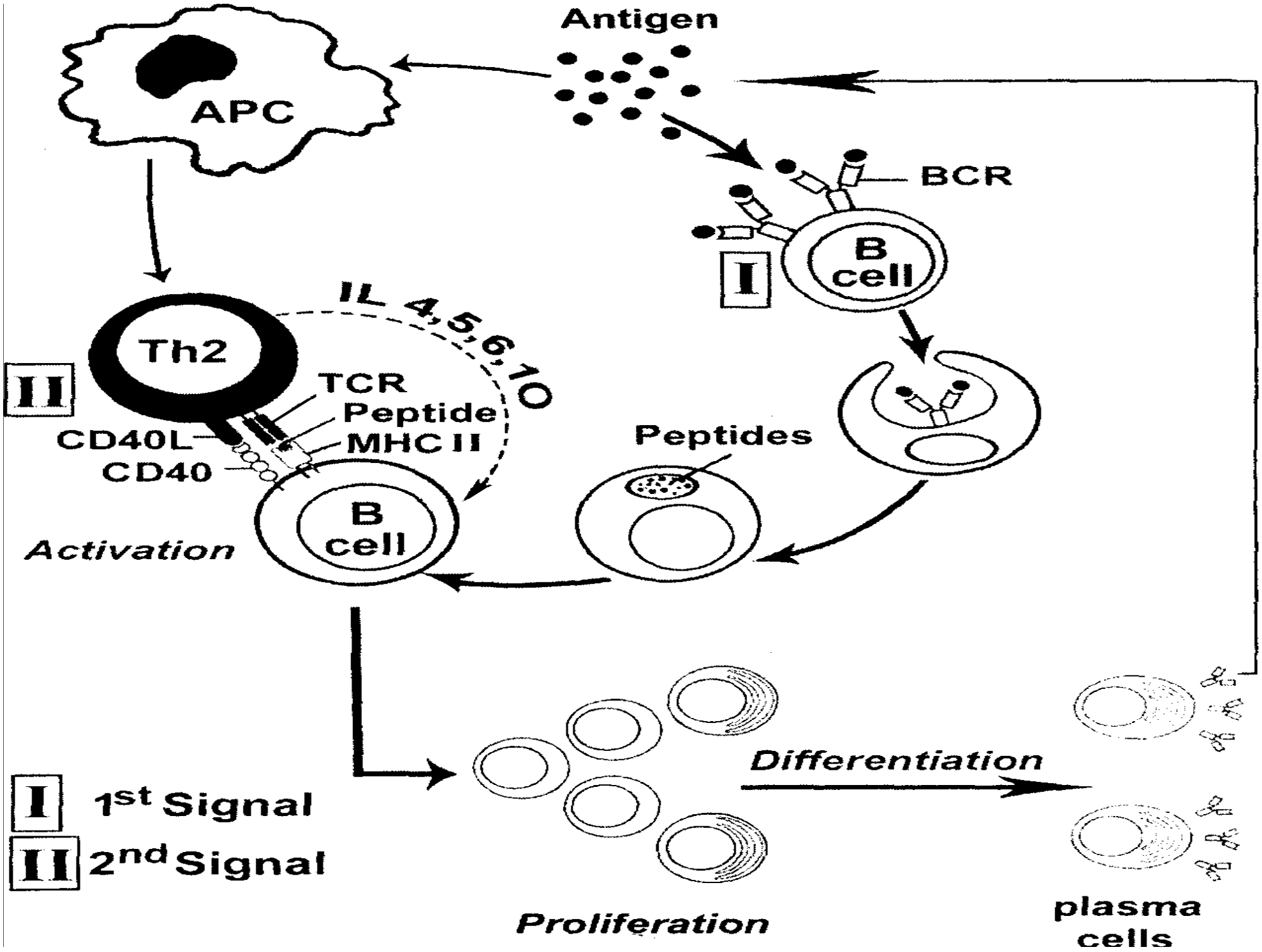
II. Superantigens

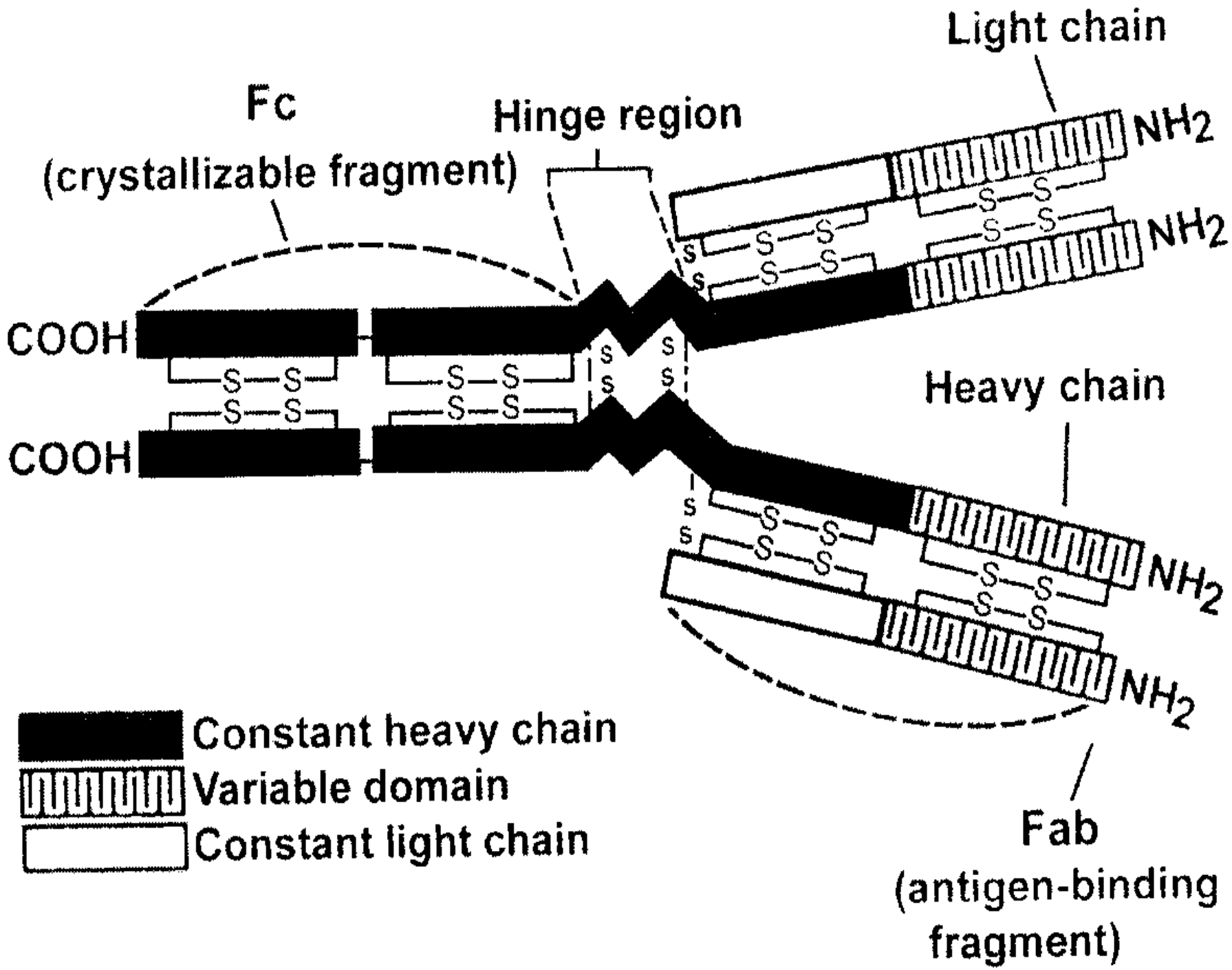
Certain proteins secreted by some pathogens do not act like ordinary antigens

They are not processed and presented to T cells like ordinary antigens, but have the ability to bind directly to the MHC II molecule on the surface of the APC without entering the cell

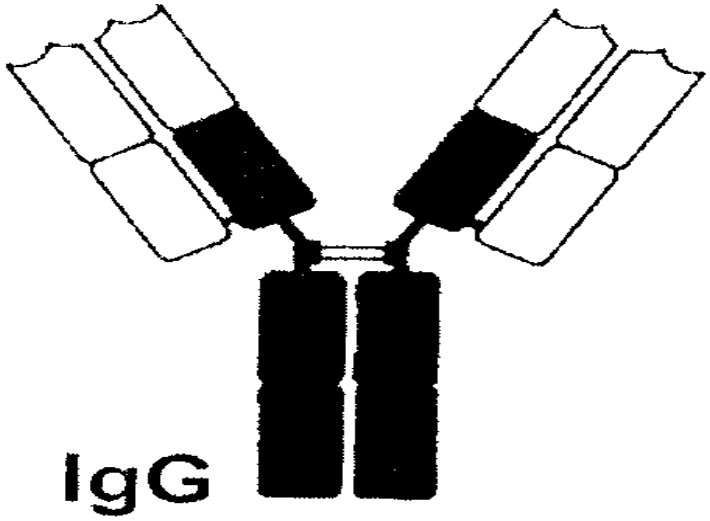
As in ordinary activation of T cells and, consequently, very large numbers- of Th cells can be activated by one kind of superantigen.

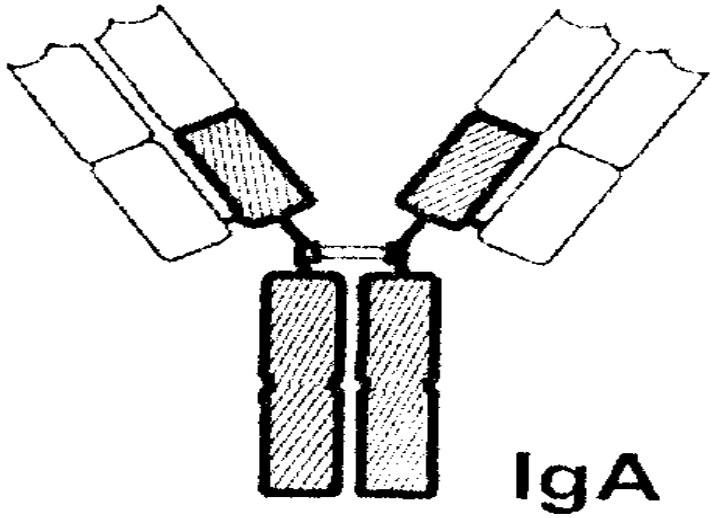
That is why these antigens are called 'superantigens'. The result is release of huge amounts of cytokines, which is not beneficial to the host and even causes systemic toxicity.

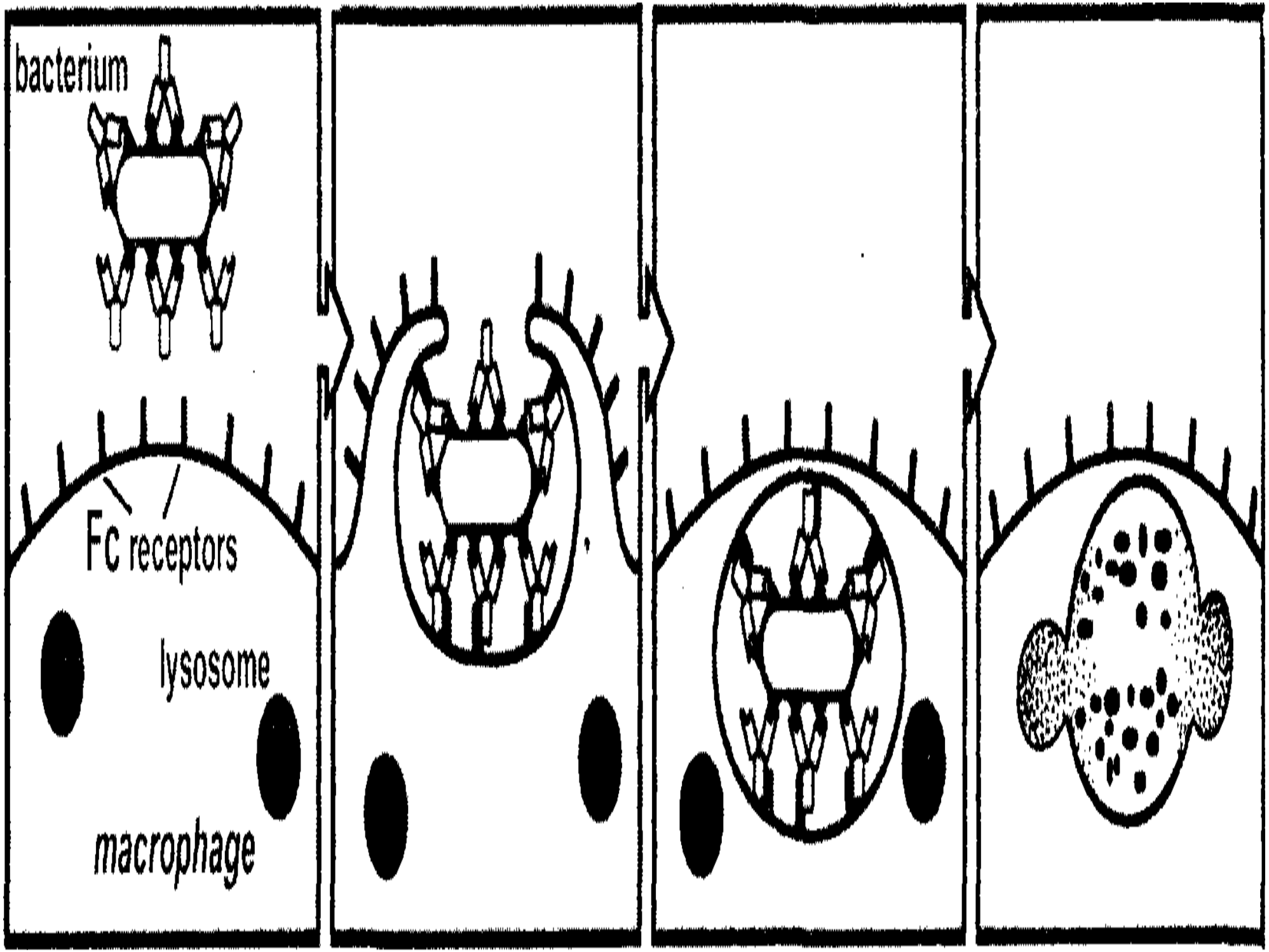

Antigen
APC
BCR
I
B cell
IL 4,5,6,10
Th2
II
TCR
Peptide
MHC II
CD40L
CD40
Peptides
B cell
Activation
Differentiation
I 1st Signal
II 2nd Signal
Proliferation
plasma cells


Light chain
Fc
(crystallizable fragment)
Hinge region
NH2
NH2
COOH
COOH
Heavy chain
NH2
NH2
Constant heavy chain
Variable domain
Constant light chain
Fab
(antigen-binding
fragment)

There are 5 main types: **gamma (γ), alpha (α), mu (u), delta (δ) and epsilon (ε),** corresponding to the 5 isotypes of Igs IgG, IgA, IgM, IgD and IgE respectively.





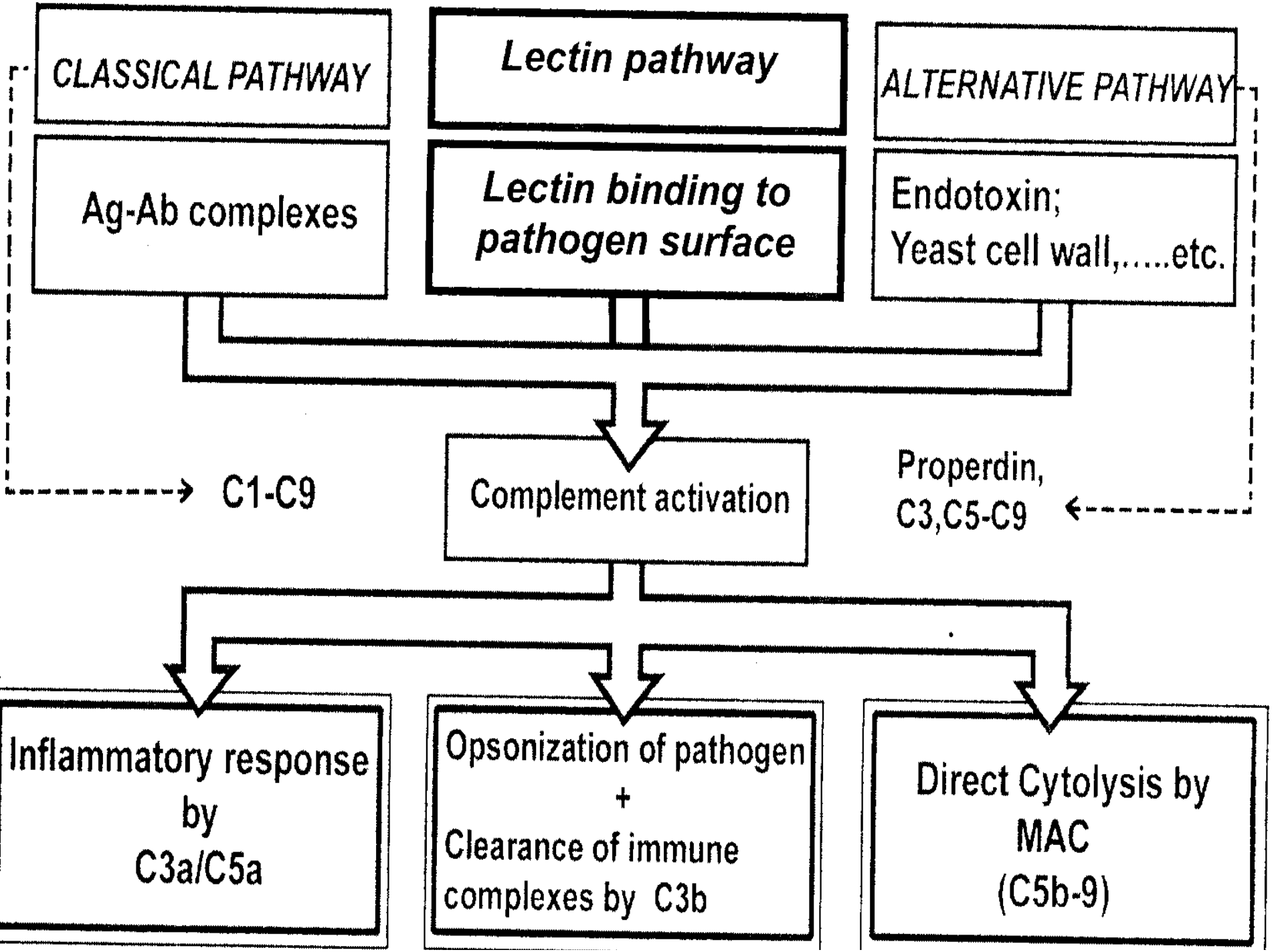

bacterium
Fc receptors
lysosome
macrophage

COMPLEMENT

The complement system is a group of heat-labile proteins produced by the liver normally found in blood and tissue fluids **(except urine and CSF).**

These proteins are termed complement factors because they are required to **'complement'** the bactericidal effects of antibodies.

Termed C1 to C9, in addition to factor B, D and properdin and some complement regulatory proteins.


CLASSICAL PATHWAY
Lectin pathway
ALTERNATIVE PATHWAY
Ag-Ab complexes
Lectin binding to pathogen surface
Endotoxin;
Yeast cell wall,.....etc.
C1-C9
Complement activation
Properdin,
C3,C5-C9
Inflammatory response by C3a/C5a
Opsonization of pathogen + Clearance of immune complexes by C3b
Direct Cytolysis by MAC (C5b-9)

AUTOIMMUNITY

It is an adaptive immune response to self-antigens. Normally, this is prevented by ***autotolerance.***

Breakdown in autotolerance leads to production of autoantibodies and/or self-reactive T cells which may cause ***autoimmune diseases***.

Aetiology of Autoimmune Diseases(4)

Multifactorial aetiology

E

1. (اللى ما يعرفك يجهلك)
   that are normally sequestered within organs, e.g. eye lens and sperms.

2. **Structural modification or alteration** of tissue proteins by drugs, chemicals or viruses, so that such antigens are no longer recognized as self. (New look ت)

3.Cross reactivity

4. **Breakdown in the immune network** which may)الشبكة واقعه(occur as a result of:

- Interference with the mechanisms which normally suppress surviving self- reactive T cells.
- Polyclonal activation of lymphocytes: Certain agents (e.g. viruses or bacteria) are capable of non-specifically stimulating many clones of lymphocytes, including self-reactive clones.
- Over production of IL-2 by Th1 cells.

TOLERANCE

Tolerance = the absence of specific immune response against some antigens in an otherwise fully immunocompetent person.

It includes: ***autotolerance and aquired (induced) tolerance***.

I. Autotolerance

It is a tolerance to self antigens that is acquired early in life, probably *in utero*.

Failure of autotolerance may result in autoimmune disease.

Mechanism of Autotolerance

1. Central tolerance

During development in the primary lymphoid organs, B and T lymphocytes go through a phase in which contact with antigen leads to their death or permanent inactivation.

Such antigens are most likely to be ***self-antigens***. The elimination of immature self-reactive lymphocytes during their maturation is called **negative selection (clonal deletion).**

2. Peripheral tolerance

IMMUNOPATHOGENESIS OF MG

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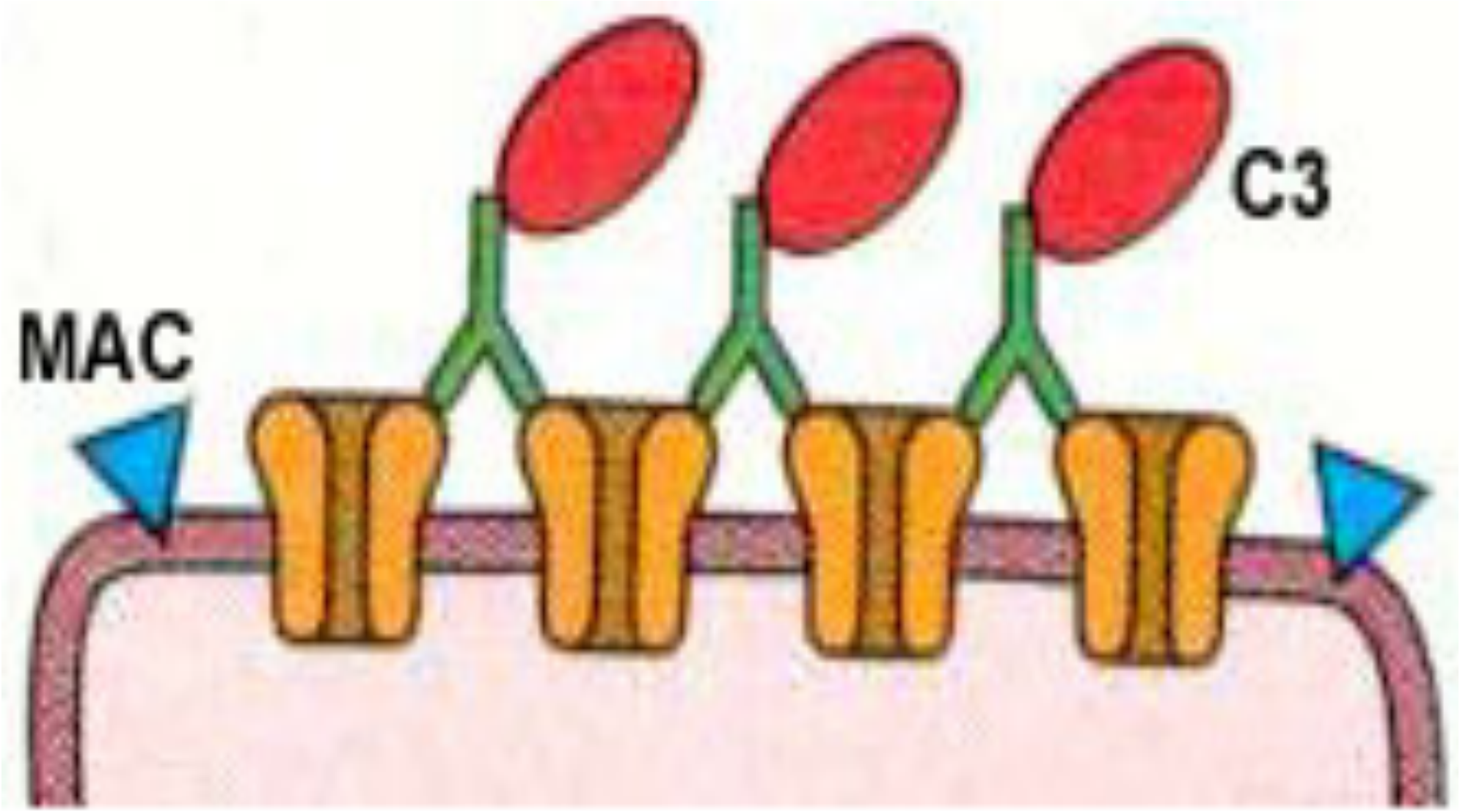
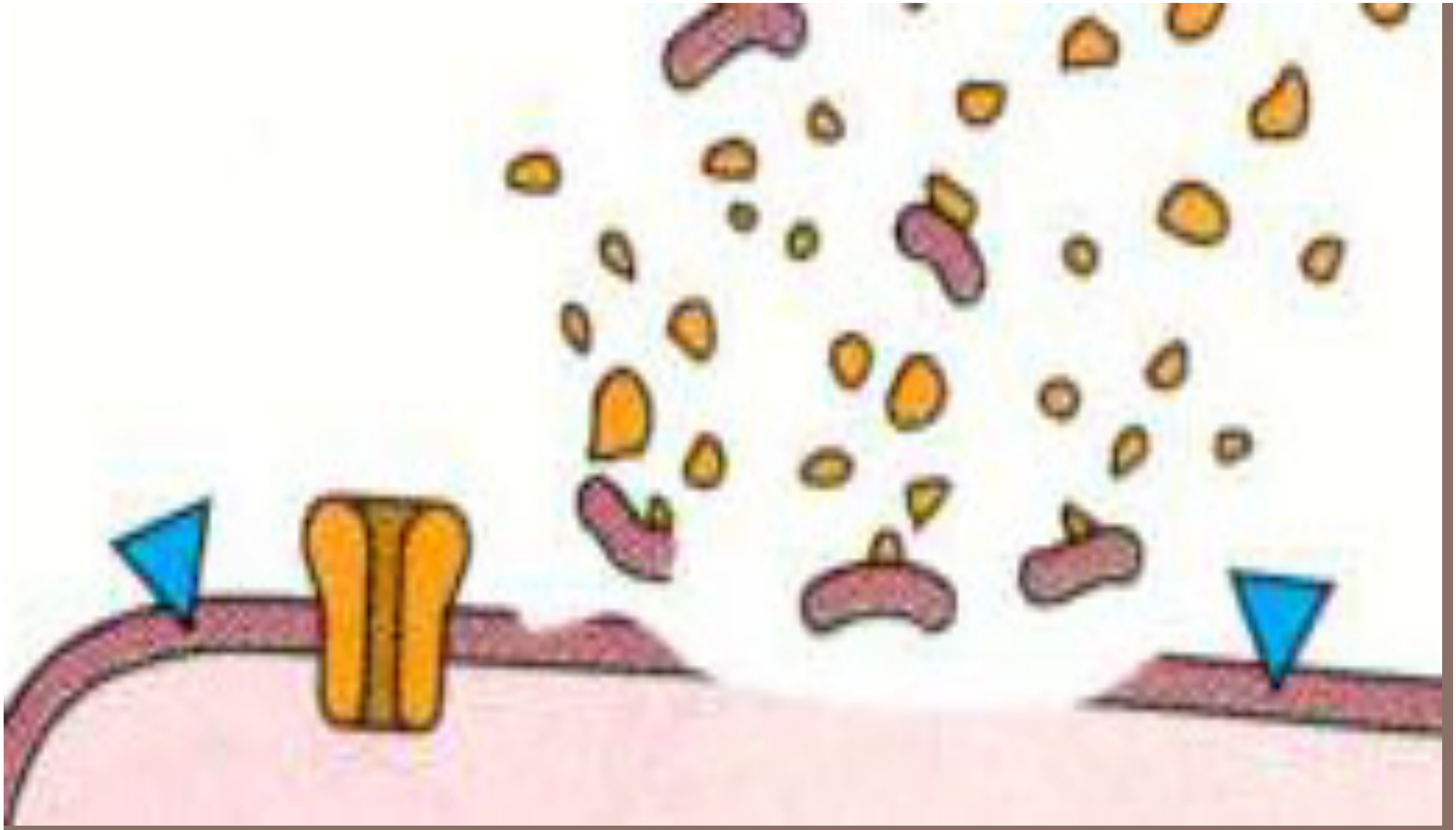


- Complement binds to the Antibody-AChR complex
- Membrane-attack complex (MAC) forms on the membrane

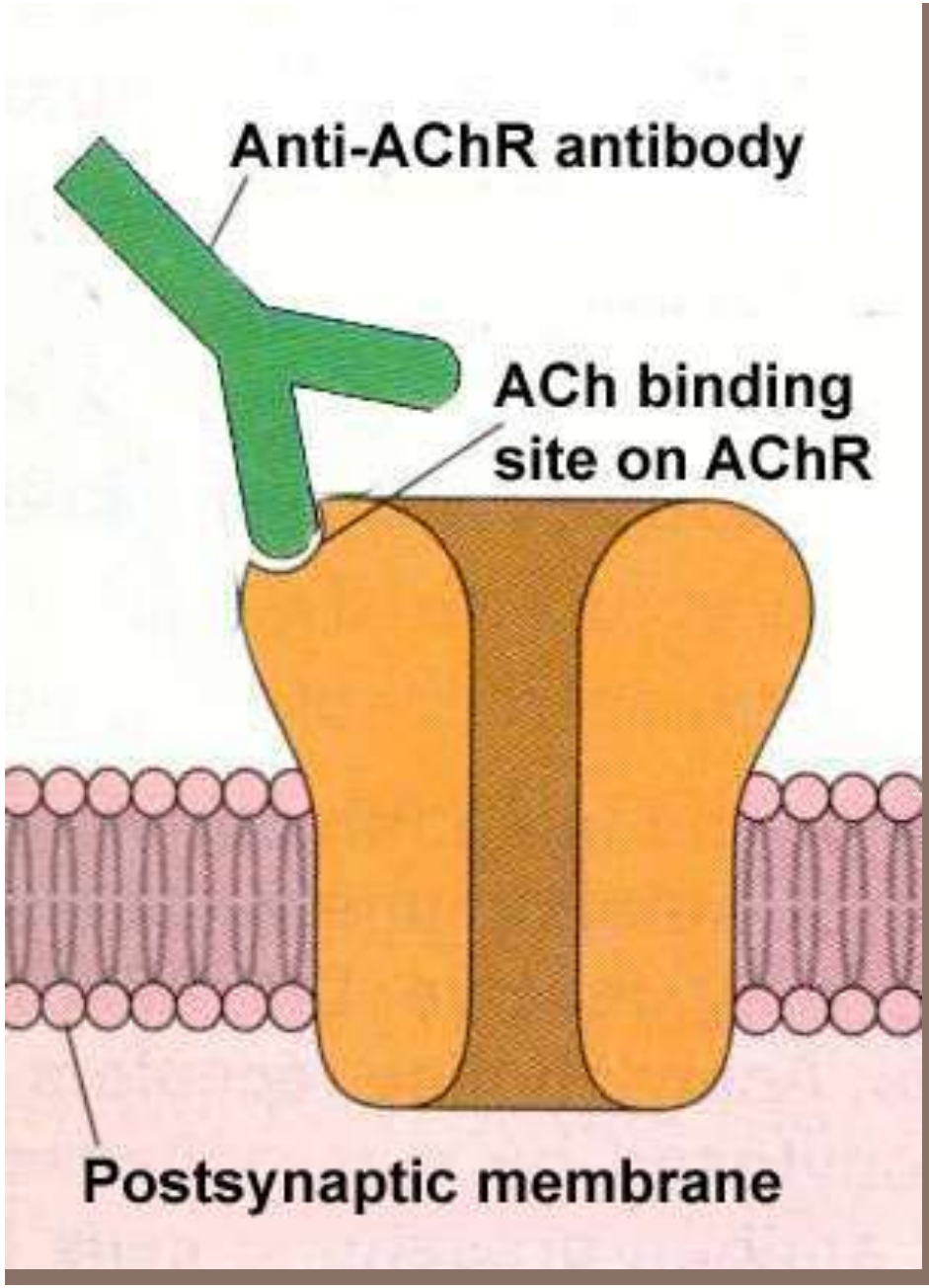


The post-junctional membrane is damaged

Fewer post-synaptic membrane folds

Reduced numbers of AChRs

Widened synaptic cleft



Blockade of ACh binding site

- Acquired immune MG: No prominent blockade of ACh binding to AChRs
- Recurrent arthrogryposis: Blocking antibodies identified

Altered AChR channel function

- Acquired immune MG: No prominent change in AChR ion channel function

Acquired Slow Channel syndrome: Antibodies to adult AChR alter AChR ion channel function

THANK YOU

IMMUNOPATHOGENESIS OF CIDP

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IMMUNOPATHOGENESIS OF LGB

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IMMUNOPATHOGENESIS OF DM

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IMMUNOPATHOGENESIS OF PM

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