

# MIRACLE Academy

قال تعالى (يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ)

تفريغ المناةة  
زميلتكم جنين الخطيب



لجان الرفعات

# Antigen Structure, Processing and Presentation

**A Presentation by**

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# Objectives

- Definition of antigens and epitopes
- Types and sources of antigens
- Antigen processing and presentation
- The roles of Major Histocompatibility Complex (MHC)
- Discuss the role of antigen presentation in generating immunity

*Based on the previous lecture, what are the cells that work as Antigen presenting cells?*

- 1- macrophages*
- 2- Dendritic cells.*

الantigen هو اي جسم غريب قادر على تحفيز جهاز المناعة لحتى يكون اجسام مضادة

الvaccine مبدأه اني بعطي للانسان antigen هاد الantigen بيكون اما killed او مضعف بحيث يكون قادر على انه يحفز جهاز المناعة ويكون اجسام مضادة اله بدون ما يسبب ضرر كبير للانسان

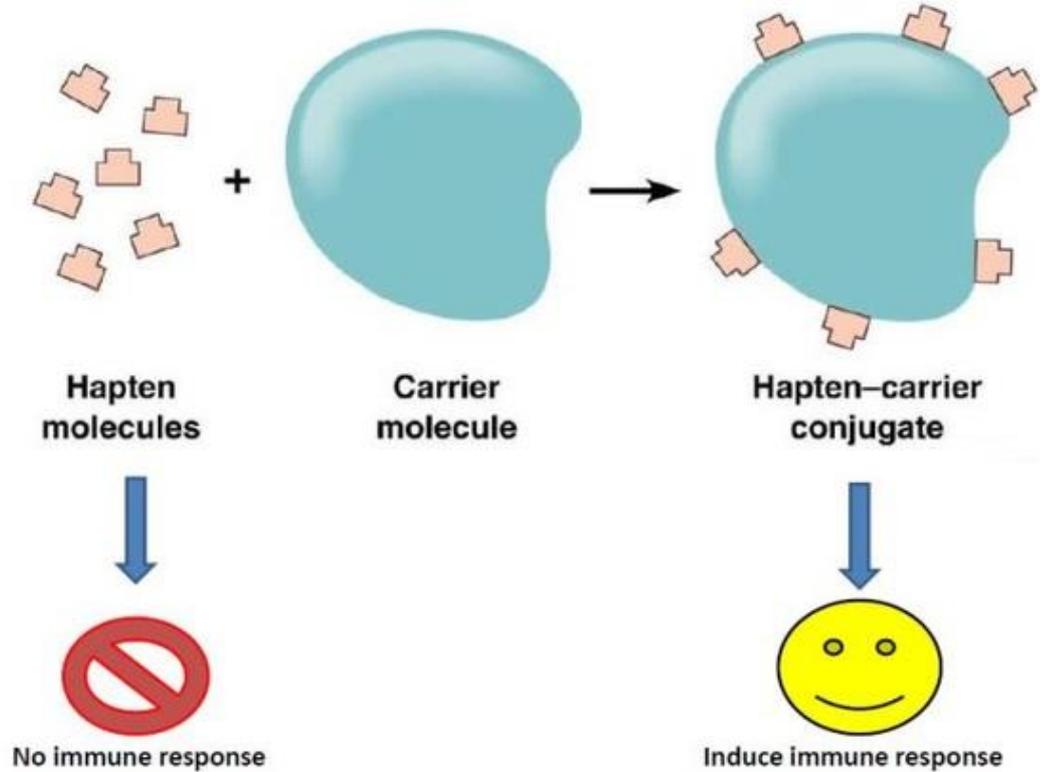
# Definitions

- **Antigen:** الimmunogen هي اي مادة قادرة على تحفيز المناعة وهو مصطلح اعم واشمل من الantigen

is any substance that causes your immune system to prompts the generation of antibodies

- **Immunogen:** a stimulus that produces a humoral or cell-mediated immune response

- **Haptens:** Low molecular weight substances, these substances not immunogenic by itself, if it couples to a larger carrier molecule (albumin, globulins), they become immunogenic



الhapten هي مادة لحالها اله low molecular weight فهي غير قادرة على تحفيز جهاز المناعة (not immunogenic) لكن اذا ارتبطت مع carrier اله higher molecular weight وقتها بيصير immunogenic

# Definitions

- Antigen can be proteins, polysaccharides, conjugates of lipids with proteins (lipoproteins) and glycolipids.
- An antigen may be a foreign substance from the environment such as chemicals, bacteria, viruses, or pollen
- An antigen may also be formed within the body, as with bacterial toxins or tissue cells  
*endotoxins*

# Definitions

ال complete antigen هو قادر على تحفيز جهاز المناعة لحاله بدون ما يحتاج انه يرتبط باشي

## • Complete Antigen or Immunogen

- Posses antigenic properties denovo, i.e. there are able to generate an immune response by themselves.
- High molecular weight (more than 10,000)
- May be proteins or polysaccharides  
*the majority of antigens is proteins.*

## • Incomplete Antigen or Hapten

- These are the foreign substance, usually non-protein substances
- Unable to induce an immune response by itself, they require carrier molecule to act as a complete antigen.
  - Serum Protein such as Albumin or Globulin.
- Low Molecular Weight (Less than 10,000)

# Properties that make molecules more effective antigens include:

كل ما كان الantigen غريب عن الجسم كل ما كان أقوى

- 1. Foreignness:** foreignness means substances that never contact with lymphocytes in embryo period.
- 2. Stable molecules,** ie, molecules that assume and maintain a definite shape.

كل ما كان stable اكثر يعني شكله ثابت ما يغير كل ما كان أقوى لانه جهاز المناعة رح يكون أجسام مضادة بناء شكل الantigen

- 3. Larger molecules** with molecular masses between 5000 and 100,000 daltons.

- 4. Molecules** that are structurally **complex**, with distinctive shapes and novel subunit combinations

كل ما كان الantigen اكبر وتركيبته complex اكثر كل ما كان أقوى مثل لدغة الأفعى هي تعتبر قوية ومخيفة لأنها بتدخل على جسمنا protein والprotein مادة معقدة جدا

- 5. Route of administration:** Parenteral routes are more immunogenic to oral route

دخول الantigen عن طريق parental route يعتبر اقوى كمحفز لجهاز المناعة عشان هيك أغلب الvaccines اللي بنوخذها يتم اعطاءها parentaly

# Antigenic Determinants-epitopes

- **Epitope** is immunologically active regions of an immunogen (or antigen) that binds to antigen-specific membrane receptors on lymphocytes or to secreted antibodies. It is also called **antigenic determinants**.

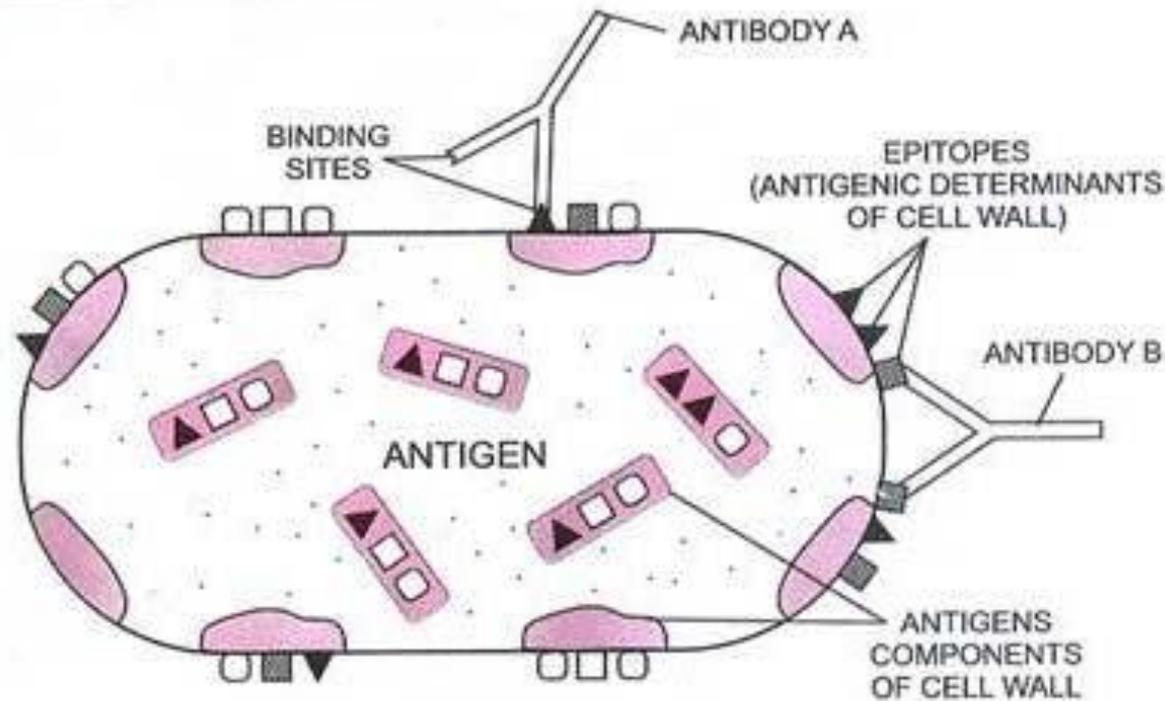


Diagram showing an antigen with epitopes (antigenic determinants).  
Two attached antibodies are also shown.\

# Determinants of Antigenicity

- The whole antigen does not evoke immune response and only a small part of it induces B and T cell response.
- The small area of chemical grouping on the antigen molecule that determines specific immune response and reacts specifically with antibody

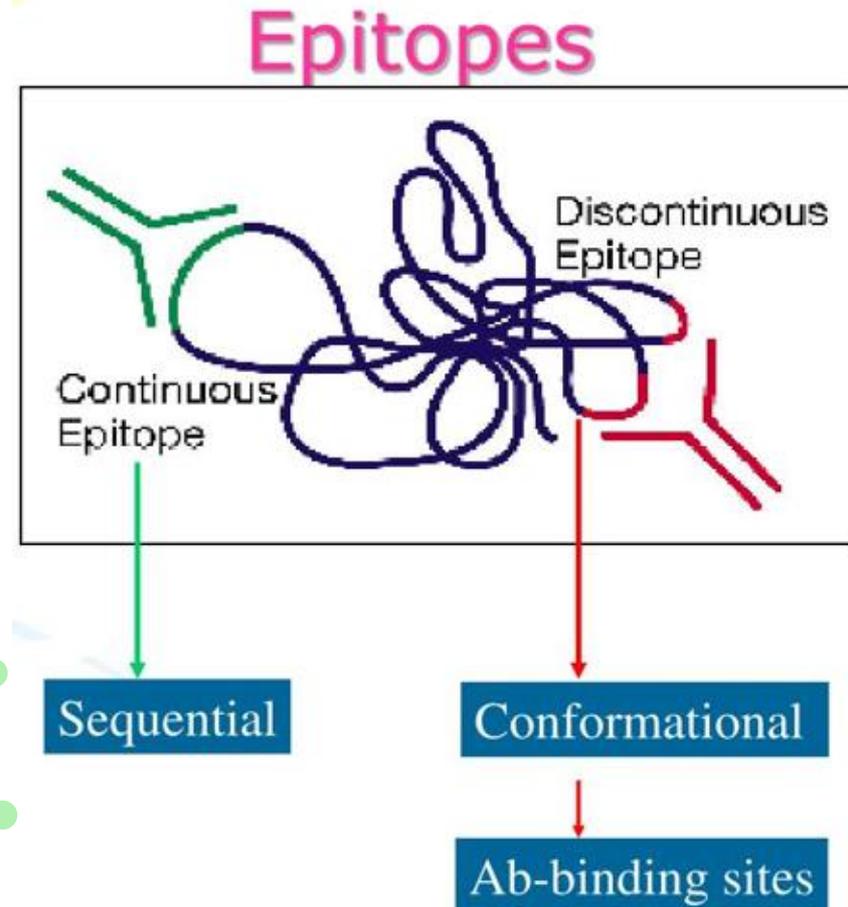
هسا ال antibodies كيف بترتبط بال antigen ؟  
في منطقة على سطح ال antigen اسمها ال epitop هاي المنطقة بيكون الها شكل معين وبيكون specific لهاد ال antigen فلما يدخل ال antigen على الجسم لأول مرة ويسبب استجابة مناعية رح يتم تكوين اجسام مضادة شكلها متناسب مع شكل ال epitop الموجود على سطح ال antigen فيرتبط الجسم المضاد مع ال epitop ويقضي على ال antigen وبيكون هاد النوع من الاجسام المضادة specific بس لهاد النوع من ال antigen

هسا احنا الاشبي اللي بنخاف منه هو ال mutation اللي ممكن يصير على ال antigen بحيث بيتغير شكل ال epitop على سطحه فبيبطل الجسم المضاد المكون داخل الجسم لهاد ال antigen قادر على الارتباط فيه والقضاء عليه وهي احدى المشاكل اللي كان عليها دراسات ايام كورونا لانهم كانوا خايفين انه يصير mutation بالفيروس ويتغير شكل ال epitop اللي كان على شكل spikes واللي تم تصنيع كل ال vaccines بناء عليه

# Antigenic Determinants-epitopes

بِس (المخطط المطلوب معرفة)

- The body recognizes antigens by the three-dimensional shapes or regions called antigenic determinants or epitopes. Sites on or within antigen with which antibodies react
- **2 types of antigenic determinants**
  1. **Conformational determinants:** amino acid residues that aren't in a sequence but become spatially juxtaposed in the folded protein. They are recognized by B cells or antibody.
  2. **Sequential (or linear) determinants:** They are mainly recognized by T cells, but some also can be recognized by B cells.



# Chemical Nature of Antigens

## • **Proteins**

- The **vast** majority of immunogens
- Pure proteins or glycoproteins or lipoproteins.
- Very good immunogens.

## • **Polysaccharides**

- Pure polysaccharides and lipopolysaccharides are good immunogens. *but less potent than proteins*

## • **Nucleic Acids**

- Poorly immunogenic.
- Become immunogenic when single stranded or when complexed with proteins.

## • **Lipids**

- Non-immunogenic, although they may be haptens.

# Types of Antigens

- **Exogenous antigens** (*Formed outside the body*)
- **Endogenous antigens** (*Formed inside the body*)
- **Autoantigens**

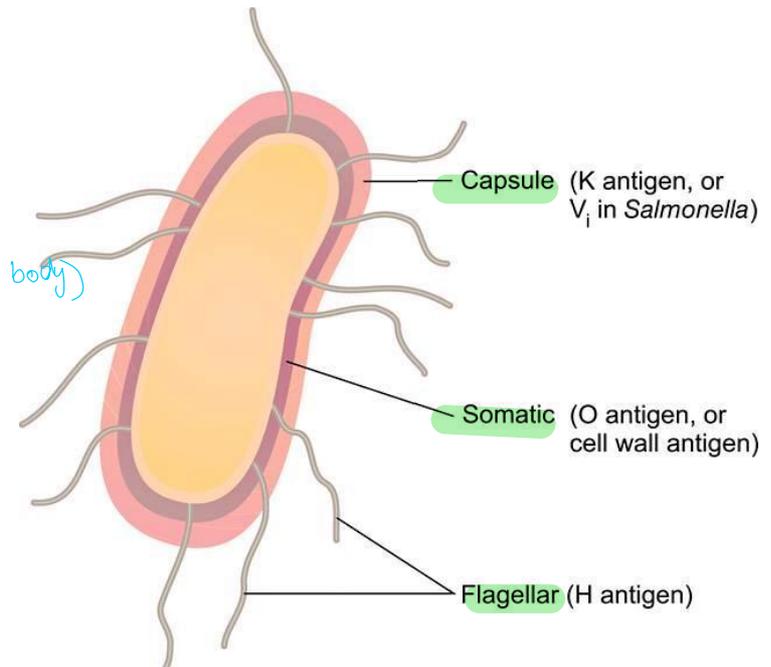
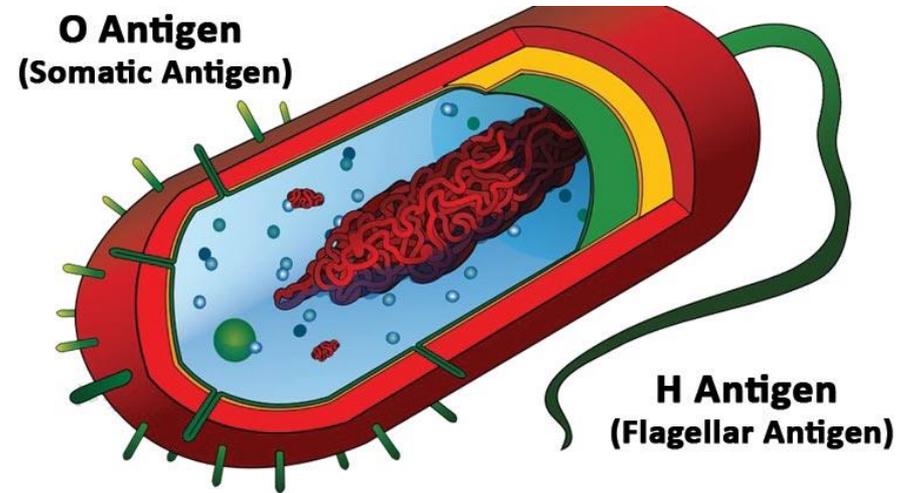
بعض الantigens بيكونو exogenous بعدين بيصيرو endogenous مثل البكتيريا اول اشئ لما حدا يتناول طعام ملوث بالبكتيريا والمواد السامة اللي صنعتها خارج الجسم بيكون exo لكن بعد ما تدخل وتبلش تصنع toxins داخل الجسم هاي الtoxins تعتبر endo وبرضو الفيروسات لما تدخل عالجسم بتكون exo لكن لما تبلش تتكاثر داخل الجسم وتكون toxins داخل الجسم بتصير endo

# 1. Exogenous Antigens

- Exogenous antigens are antigens that have entered the body from the outside, for example by inhalation, ingestion, or injection

## A. Bacterial antigens:

- Antigen related to bacterial cells: Somatic antigen (O), Capsular antigen, Flagellar Ag (H), etc
- Antigen secreted by bacteria: for ex Exotoxins (Toxins formed outside the host body)

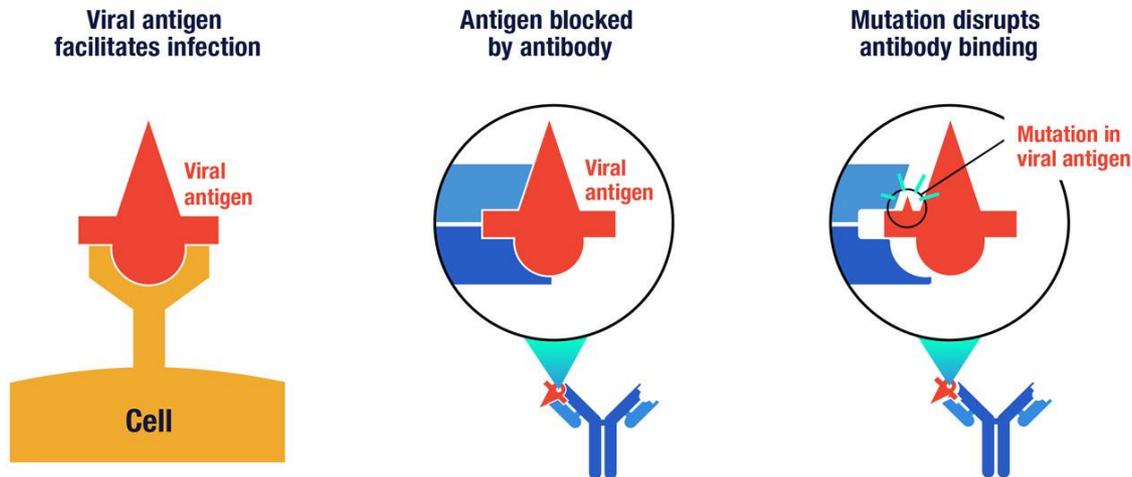


# 1. Exogenous Antigens

## B. Viral antigens:

- These antigens enter the body or system and start circulating in the body fluids and are trapped by the **APCs** (Antigen processing cells such as macrophages, dendritic cells, etc.)
- The uptake of these exogenous antigens by APCs is mainly mediated by phagocytosis

**Viral mutations may reduce the effectiveness of antibodies**



# 2. Endogenous Antigens

- Endogenous antigens are antigens that have been generated within cells as a result of normal cell metabolism, or because of viral or intracellular bacterial infection

- **Human tissue antigens:**

1. **Blood group antigens:** A, B and Rh antigens

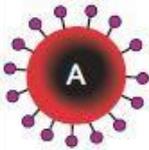
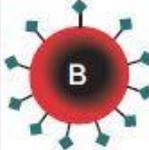
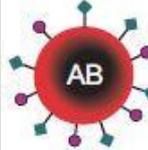
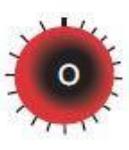
2. **Histocompatibility antigens:** Glycoprotein molecules on all nucleotide cells:

- Major histocompatibility complex antigens (MHC)
- Human leucocyte antigen (HLA)

3. **Cells infected with viruses**

- Some antigens start out as exogenous antigens, and later become endogenous (for example, intracellular viruses)

ABO blood group system

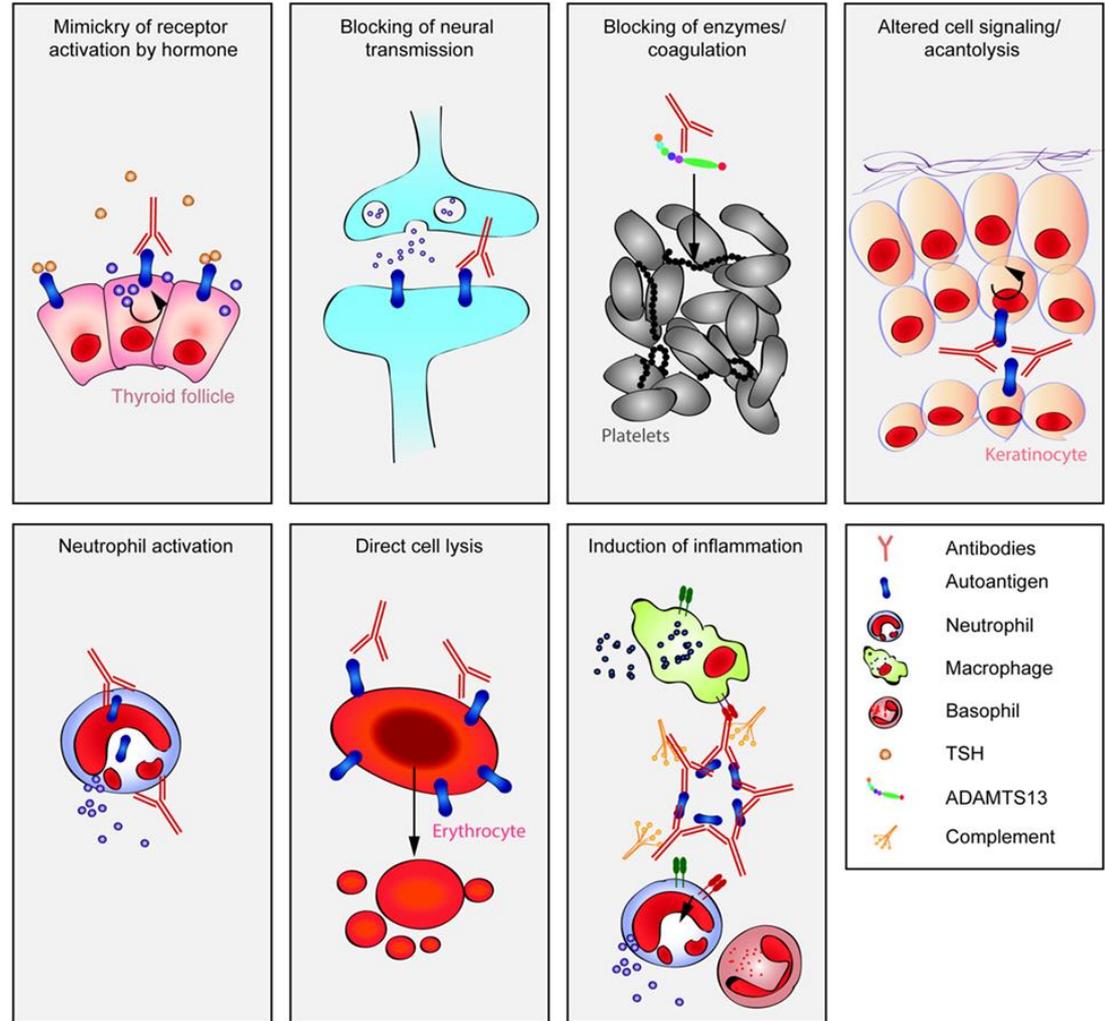
	Group A	Group B	Group AB	Group O
Red blood cell type				
Antibodies in Plasma	 Anti-B	 Anti-A	None	 Anti-A and Anti-B
Antigens in Red Blood Cell	 A antigen	 B antigen	 A and B antigens	None

الblood group antigens هي normal antigens موجودة بأجسامنا جميعا لكنها تختلف في نوعها والها antibodies برضه بتختلف حسب فصيلة الدم عند كل انسان فمثلا اذا كانت فصيلة الدم عند واحد A رح يكون موجود بدمه anti B فالبتالي اذا انا نقلت لهاد الانسان دم من فصيلة B رح يهاجمها الantibodies اللي بدمه ويعمل clotting لهاد الدم وممكن اذا كانت كمية الدم كبيرة يسبب وفاة المريض وبنفس الطريقة اللي فصيلة دم B رح يكون بدمه anti A فما بيصير انقله دم من فصيلة A . هسا اللي فصيلة دم AB ما رح يكون عنده antibodies بدمه فبسميه مستقبل عام يعني بيستقبل دم من اي فصيلة ،واللي فصيلة دم O هاد ما عنده antigen على سطحه فهو ما يسبب اي استجابة مناعية فبسميه معطي عام يعني بتقديري تعطيه لاي انسان بغض النظر عن نوع فصيلة دم

الhistocompatibility وهاد كتير بيهمنا في حالات زراعة أعضاء من أشخاص آخرين دائما بنسمع عن اي حدا بدو يزرع عضو انه لازم يكون في تطابق بينه وبين والشخص اللي بده يتبرع اله لحتى الجهاز المناعي ما يتعرف على هاد العضو على انه جسم غريب ويهاجمه وهاد التطابق بالعادة بيكون اكثر اشي بين الأقارب

# 3. Autoantigens

- An autoantigen is usually a normal protein or complex of proteins (and sometimes DNA or RNA) that is recognized by the immune system of patients suffering from a specific autoimmune disease
- These antigens under normal conditions, not be targeted of the immune system, but due to mainly genetic and environmental factors, the normal immunological tolerance for such an antigen has been lost in these patients



ال autoantigen هو عبارة عن مادة طبيعية موجودة بشكل طبيعي بالجسم ما بتشكل اي ضرر عليه ولكن بسبب مشكلة في جهاز المناعة بتخليه يتعرف على هاي المواد الطبيعية على انها غريبة ويكون لها اجسام مضادة ويصير يهاجمها ويمنعها من القيام بعملها ، مثال عليه مرض ال diabetes type 1 اللي جهاز المناعة فيه بيتعرف على البنكرياس على انه جسم غريب وبيبلش يهاجم فيه لحتى يدمره فبالتالي وظيفة البنكرياس في الجسم واللي هي افراز ال insulin رح تبطل موجودة

في كثير دراسات اثبتت انه النساء اكثر اصابة بالامراض المناعية وهاد الاشئ بسبب الطبيعة الحساسة للنساء لانه الحزن احد اسباب الاصابة بالامراض المناعية

# Superantigens (SAgs)

- **SAgs** are a class of antigens that result in excessive activation of the immune system. Specifically it causes:
  - non-specific activation of multiple clones of T-cells (polyclonal T cell activation) resulting in massive cytokine release. *الcytokine هي مادة بتحفز جهاز المناعة بشكل عنيف جدا*
- They are active at very low concentration causing release of large amounts of cytokines
- The massive T-cell activation and release of large amounts of cytokines cause **systemic toxicity**
- It **does not** lead to acquired immunity i.e no memory *يعني اذا الجسم رجع تعرض لنفس الsuperantigen مرة ثانية ما رح يرجع يتذكره ويقضي عليه بشكل اسرع مثل ماكان يصير مع الantigen العادي*
- SAgs are produced by some pathogenic viruses and bacteria most likely as a defense mechanism against the immune system

# Superantigens (SAgs)

- **Conventional T-dependent antigen,**

- only a small fraction (1 in  $10^4$  -  $10^5$ ) of the T cell population is able to recognize the antigen and become activated (monoclonal/oligoclonal response).

- **Superantigens**

- Polyclonally activate a large fraction of the T cells (up to 25%).

- Examples of superantigens **Bacterial toxins** include:

- **Staphylococcal enterotoxins** (food poisoning),  
يمكن يكون ضيف ويمكن يكون severe ، وفاد الشيء يعتمد على العوامل الجينية المختلفة عند كل مريض
- **Staphylococcal aureus toxic shock syndrome toxin (TSST)**
- **Staphylococcal exfoliating toxins** (scalded skin syndrome) and
- **Streptococcal pyrogenic exotoxins** (shock).

# Requirement of T Cells Response

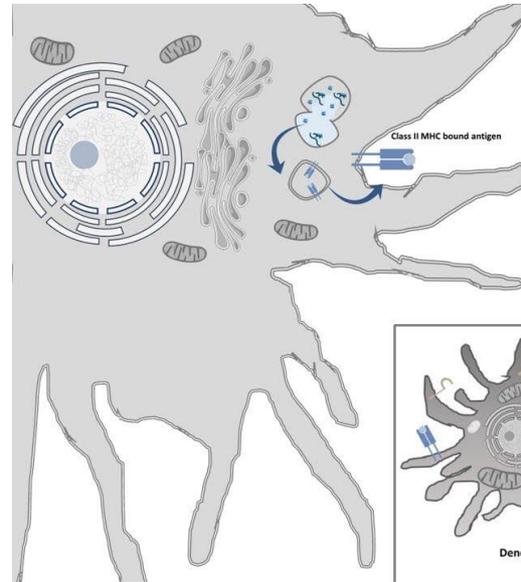
مثل ما حكينا بالشباتر اللي قبل الantigens لما يدخلو الجسم بيتجمعو بالperipheral immune system اللي همه الlymph nodes والspleen بعدها بيتتم استدعاء كميات كبيرة من الT cells (اللي بيكونو موجودين بالcentral immune system) لمكان تجمع الantigens عشان يهاجموهم ويقضو عليهم

- 1. T cells present mainly in lymph and lymphoid organs,** however, microbes usually enter through epithelial cells (like skin, respiratory sys, alimentary track..etc) where T cells number is very low. According, microbial antigens needs to be transported to lymph nodes to enhance chances of encounter with T cells.
- 2. T cells can not interact with complex microbial antigen,** antigens need to be captured, processed, and then presented for T cells in a specific way in order to allow interactions  
برضه حكينا انه الantigen ما بيتفاعل عطول مع الT cell لازم بالاول نعمل processing و antigen presentation ، على عكس الB cells اللي بترتبط بالantigen عطول ما بيكون بحاجة اعمله processing
- 3. T cells respond only to protein antigens and not to other types of chemical antigens.**

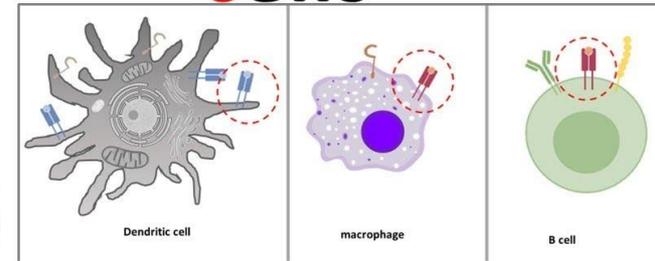
# Antigen Presenting Cells (APC)

- A group of immune cells, whose role is to take up, process and present antigenic peptides to T cells.
- **Professional APC:** Macrophages, dendritic cells, and B cells, which can express MHC class II molecules
- **Non-professional APC:**

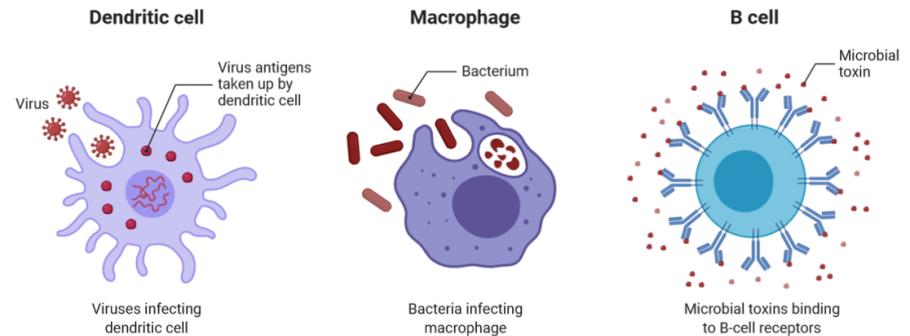
Other cell type capable of expressing MHC class II molecules eg. Endothelial cells, fibroblasts, activated T cell.



## Antigen presenting cells



Different Types of Antigen Presenting Cells



هأ كيف بدي أعمل أنا processing و presentation لantigen عشان احضره لحتى يتفاعل مع ال T cell؟؟  
هاد الانشي بيصير عن طريق خلايا بالجسم اسمها antigen presenting cells (APC)

# Major Histocompatibility Complex (MHC)

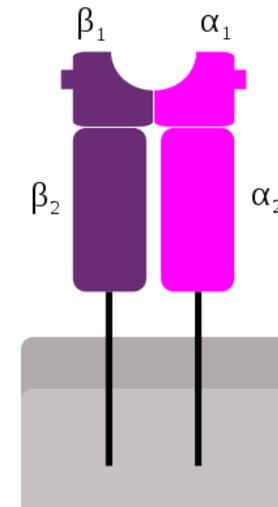
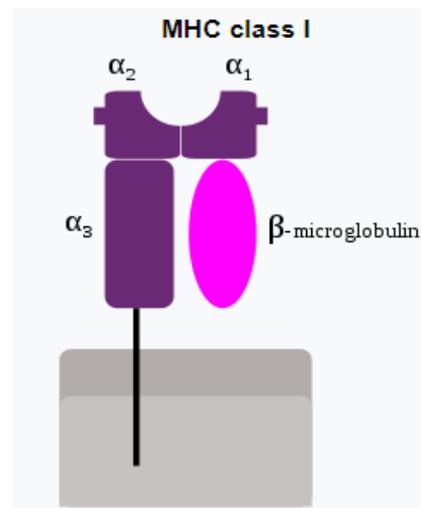
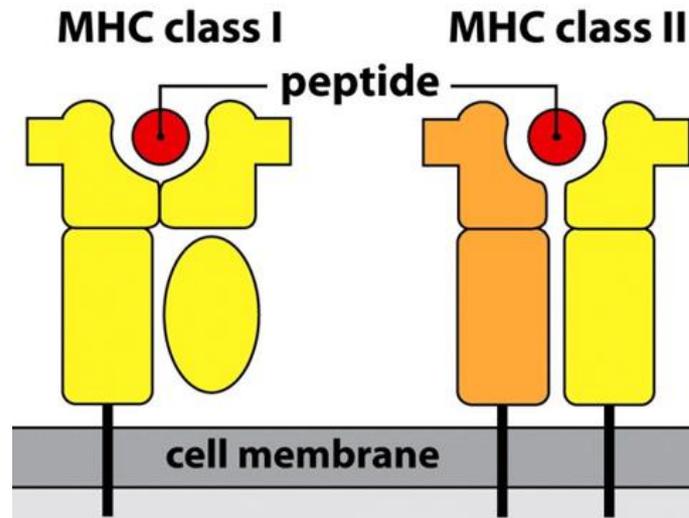
- **MHC molecules:**

- ✓ are membrane proteins on APCs that displays peptide antigen for recognition by T cells.

- MHC molecules are the **principle** determinants of **acceptance or rejection** of tissue graft

- **Two main classes of MHC**

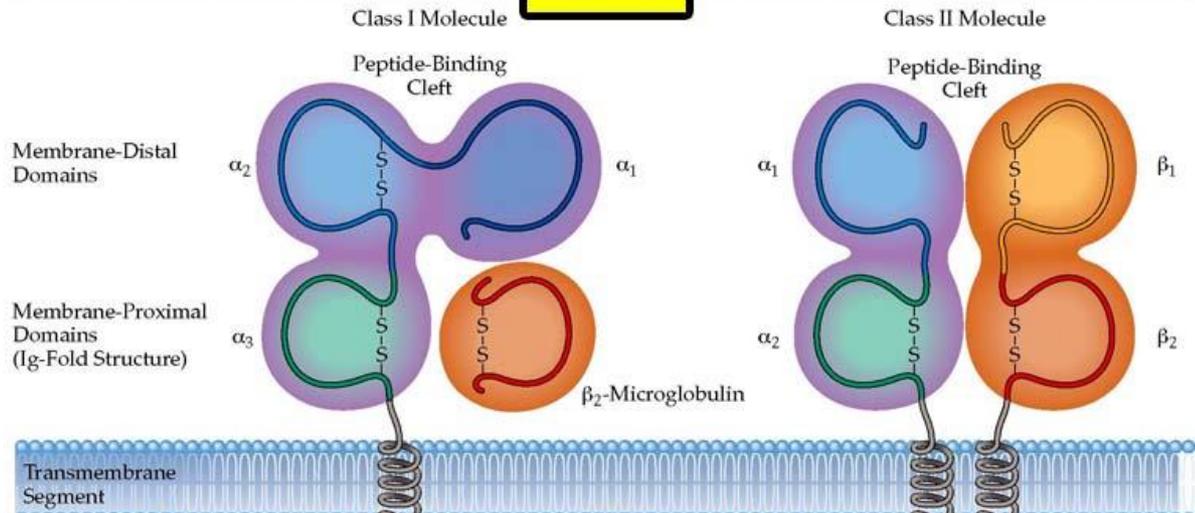
1. **MHC class I**
2. **MHC class II**



# Major Histocompatibility Complex (MHC)

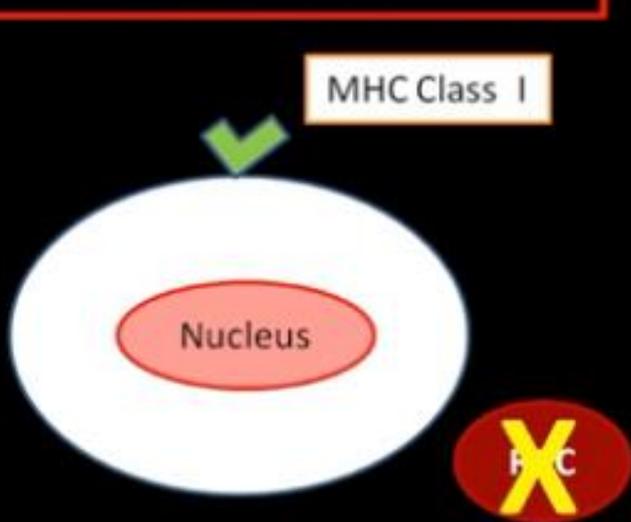
- **MHC class I:** الفرق بين class 1 و class 2 مهم نعرفه
  - **Function:** Regulation of immune responses to **intracellular** parasites (**endogenous antigens**) such as viruses
  - **All cells** can be infected by viruses, therefore **all cells express MHC class I**
  - **Structure:**  $\alpha 1$ ,  $\alpha 2$ ,  $\alpha 3$ , and  $\beta 2$  macroglobulin
  - Contain a peptide binding cleft that accommodate **8-11 aa**
  - Necessary for **CD8+ T cells** activation (cytotoxic T cell)
- **MHC class II:**
  - Regulation of immune responses to **exogenous antigens**, **few cells** are specialized to take up extracellular antigens, and so the **distribution of MHC class II expression is restricted to APCs**
  - **Structure:** 2  $\alpha$  chains ( $\alpha 1$ ,  $\alpha 2$ ) and 2  $\beta$  ( $\beta 1$ ,  $\beta 2$ )
  - Contain peptide binding cleft of **10-30 residues**
  - Important for binding and activation of **CD4+ T cells**

## MHC Class I vs MHC Class II



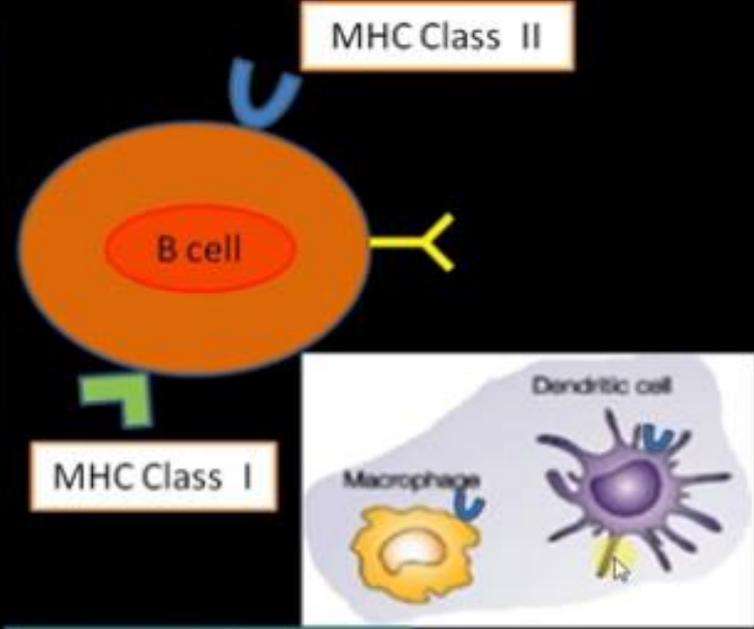
حكيينا عن ال  
CD8+ وال CD4+  
في اخر شابتر 2

# Difference No: 1



## MHC Class I

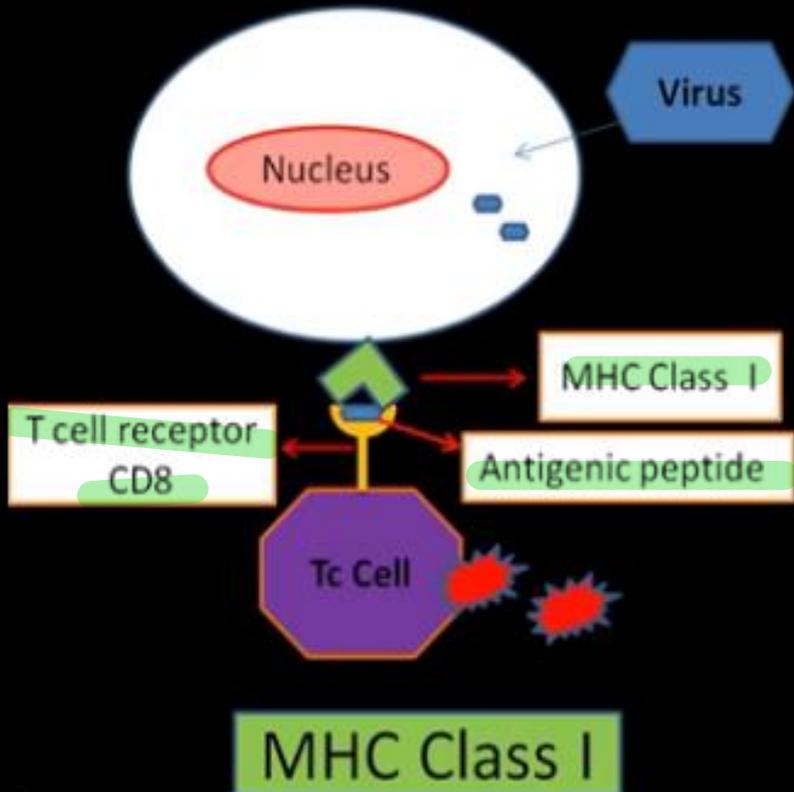
Present on the surface of all nucleated cells



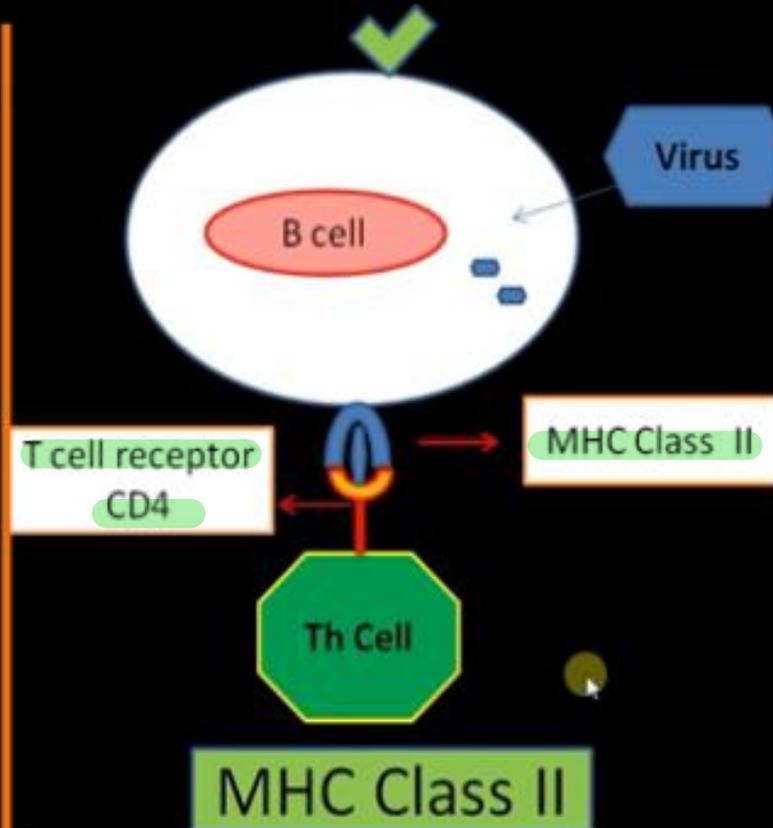
## MHC Class II

Present on the surface of antigen presenting cells such as macrophages, B cells, dendritic cells etc. هون المتاد على ال B cells

### Difference No: 3



Mainly interact with cytotoxic T cells



Mainly interact with helper T cells

# Features of Peptides Binding to MHC Molecules

- Each MHC molecule display one peptide at a time

- Peptides are acquired during intracellular assembly

ال peptide بتتكون من تكسير ال antigen واعادة تجميعه بعدين هاد ال peptide مع ال MHC بيطلعو على سطح ال APC عشان يصير الهم recognition على ال T cell

- Low affinity and broad specificity binding so many different peptides can bind to the same MHC molecule, and even can bind self peptides

- Very low off rate: MHC display bound peptides long enough to be located by T cells

الارتباط بين ال peptide وال MHC لازم يكون ضعيف كفاية انه يكون reversible ويكون قوي كفاية انه يتحمل لوقت ما توصل ال T cells وترتبط فيه وتقوم بعملها

- Stable expression of MHC molecules require peptides displaying

- MHC molecules bind only to peptides (protein antigen) so T cells can only respond to protein antigens

# Steps in Antigen Preparation for T cells

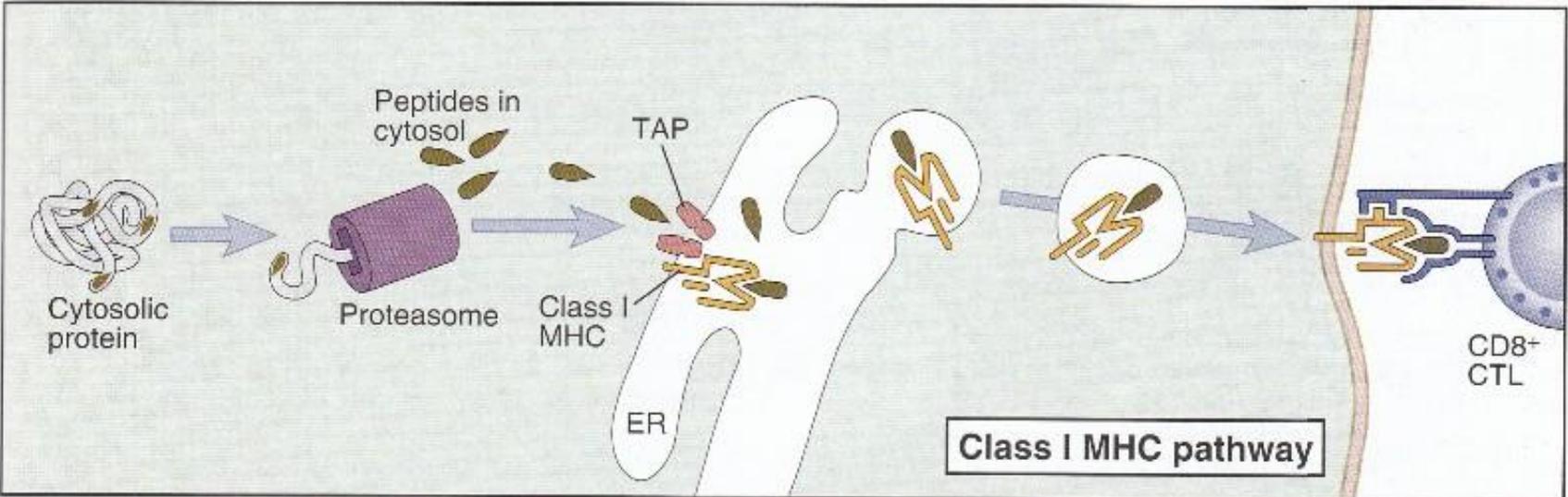
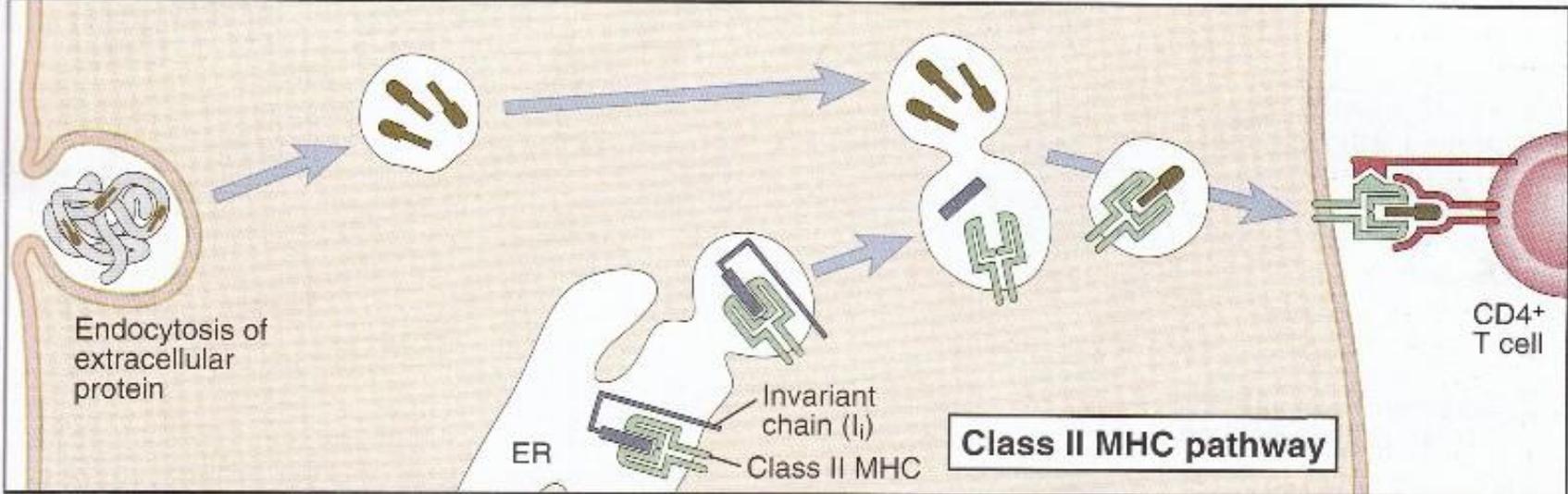
- Antigens must be prepared in order to be recognized by T cells
- 1. **TRANSPORT:** Antigen must be transported to lymph node for proper interaction with T cells
- 2. **UPTAKE:** Access of native antigens and pathogens to intracellular pathways of degradation بيصير الة uptake عن طريق ال APC
- 3. **DEGRADATION:** Limited proteolysis of antigens to peptides
- 4. **ANTIGEN-MHC COMPLEX FORMATION:** Loading of peptides onto MHC molecules
- 5. **ANTIGEN PRESENTATION:** Transport and expression of peptide-MHC complexes on the surface of cells for recognition by T cells

Antigen uptake

Antigen processing

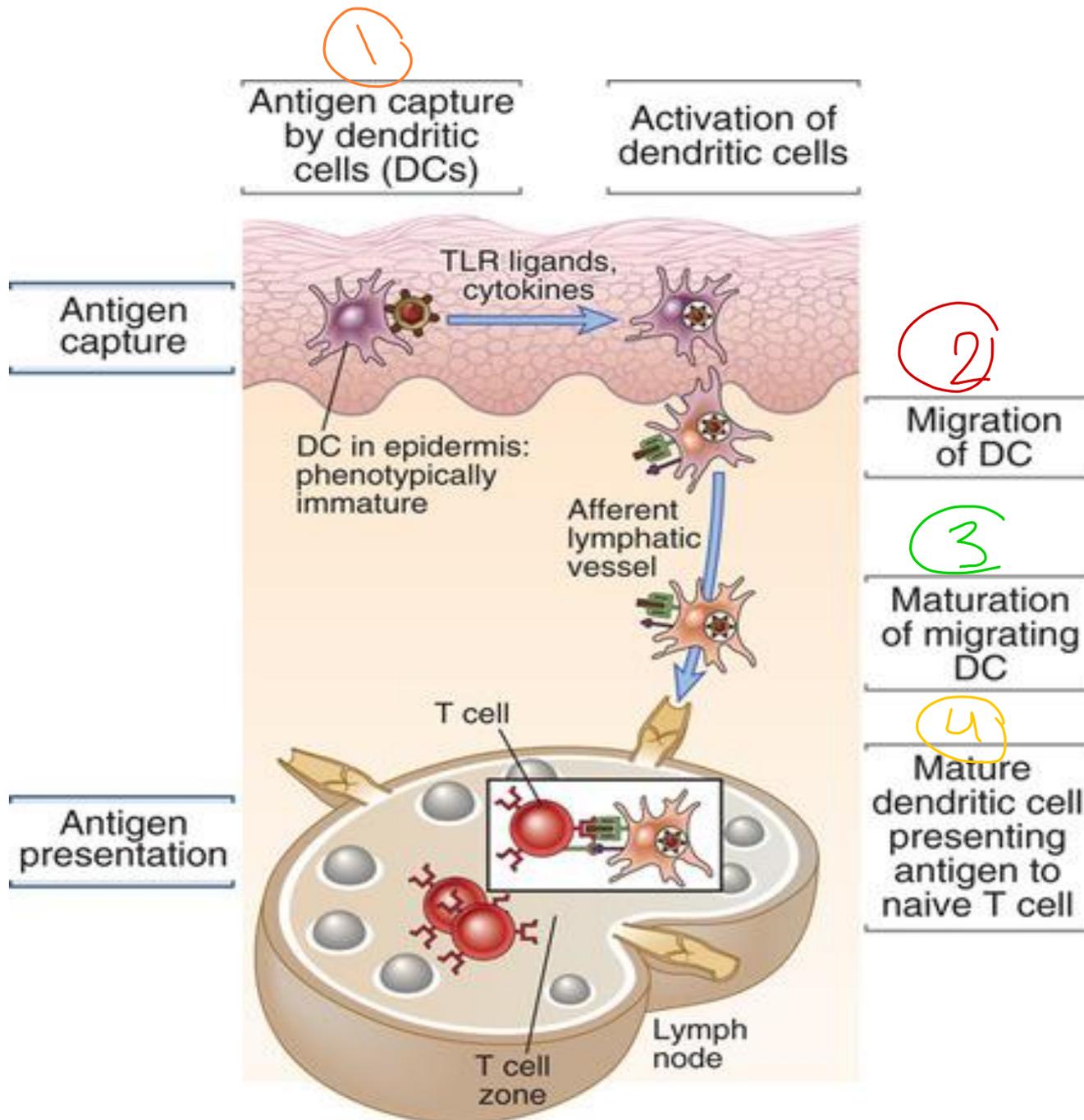
MHC biosynthesis

Peptide-MHC association



# 1. Antigen Capture and Transport to Lymph Node

- 1 • **Immature dendritic cells (DCs)** in the epithelium capture microbial antigens and leave the epithelium
- 2 • The DCs **migrate** to draining lymph nodes being attracted by chemokines produced in the nodes
- 3 • During their migration the DCs **mature**
- 4 • Once at the lymph nodes the DCs start the processing of presenting the antigen to T cells
  - DCs at their maturation **express** different membrane proteins, for example **immature DCs express** surface receptors essential for **microbial** binding and capture, while **mature DCs express MHC** molecules necessary for antigen processing



## 2. Uptake of Antigen

- The process of entering the antigens into the cells (mainly APCs) this is important for exogenous antigen processing, while endogenous antigens are already inside the cells.

- Uptake by immature DCs

- Pinocytosis: Liquid or small granule

- Receptor-mediated endocytosis

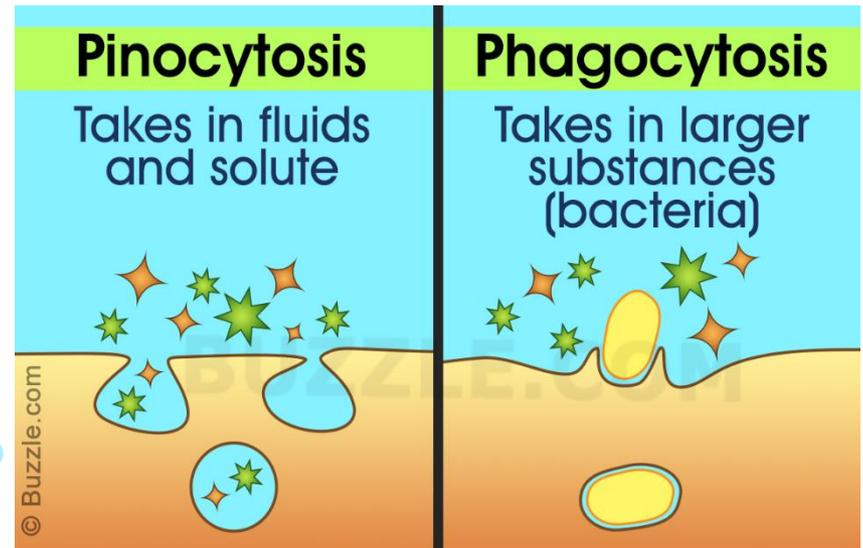
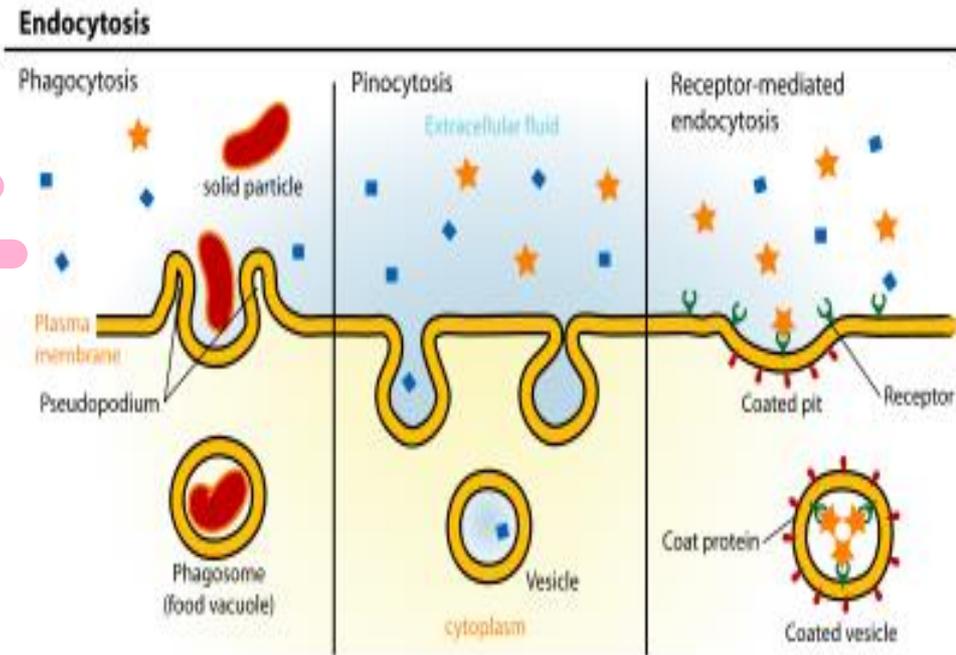
- Phagocytosis: Large molecular or microbe

- Uptake by Macrophage

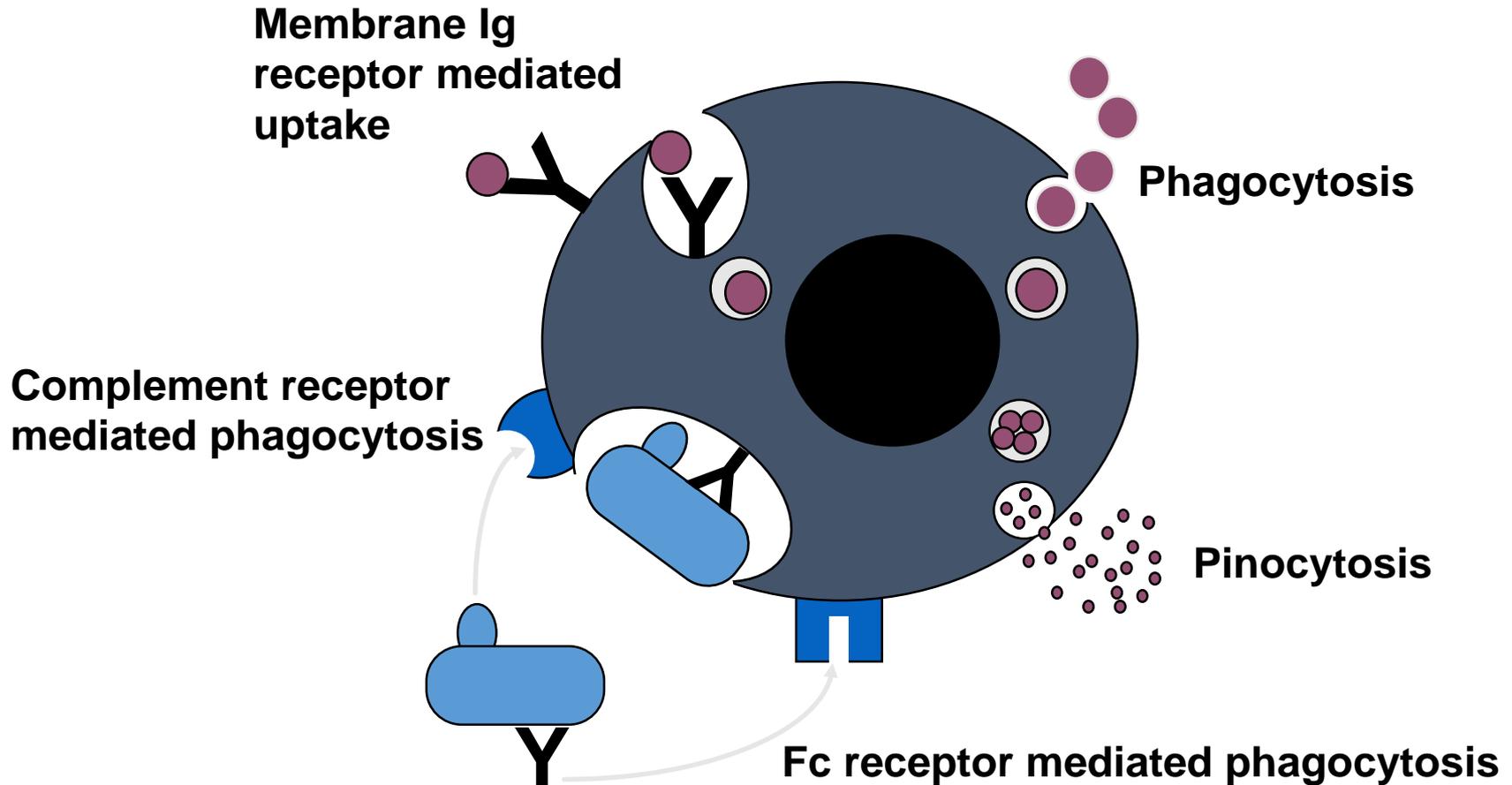
- Phagocytosis: Large solid or molecular complex

- Pinocytosis: Receptor-mediated pinocytosis

- Endocytosis: Low levels of particulate or soluble antigens



# Uptake of exogenous antigens



Uptake mechanisms direct antigen into intracellular vesicles for exogenous antigen processing

### 3. Antigen Processing

- Antigen must be processed in order to be recognized by T cells, require 2 main steps

- ① • Degradation of externally- or internally-derived antigen into short peptide sequences

- ② • Association of the peptide with MHC molecules

# Two antigen-processing pathways

	MHC class I	MHC class II
Major antigen sources	endogenous antigen	exogenous antigen
Processing machinery	proteasome	lysosomal enzymes
Cell type where active	all nucleated cells	professional APCs
Site of antigen-MHC binding	endoplasmic reticulum	lysosome and endosome
MHC utilized	MHC class I	MHC class II
Presents to	CD8+ T cell (Tc)	CD4+ T cells (Th)

## 4. Antigen Presentation

- The activation of T cells via T cell receptors, which specifically recognize antigenic peptide in association with either MHC class I or II molecules on the surface of APC.

## 5. Antigen Recognition

- Antigenes are recognized by and bind to:

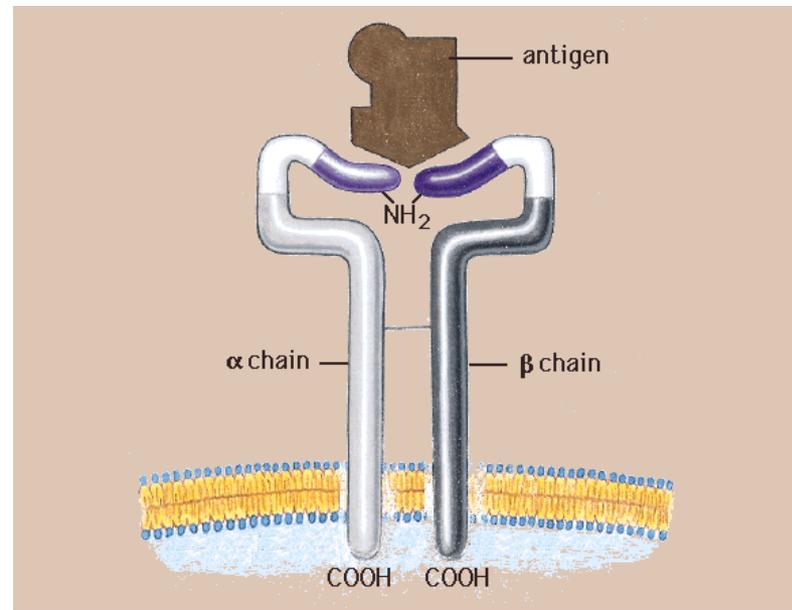
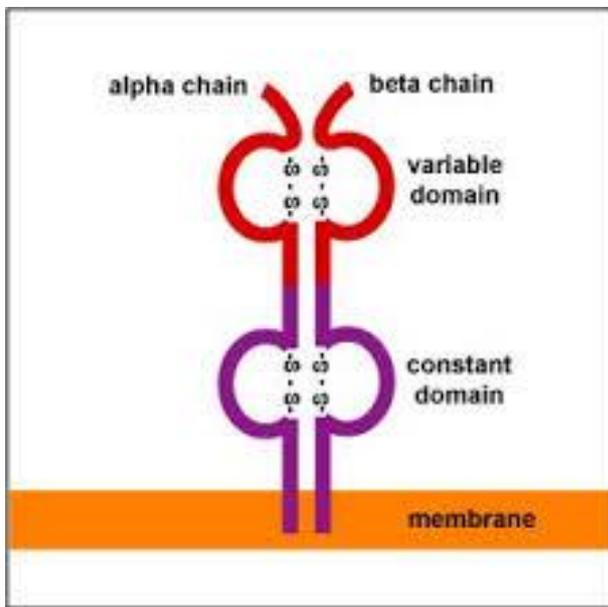
### 1. B-cell receptors (BCR) :

- These are membrane-bound immunoglobulins (IgM and IgD) on B-cells
- BCRs can be secreted in plasma as antibodies

### 2. T-cell receptors (TCR)

- $\alpha$  and  $\beta$  chains anchored to T-cells
- There is a groove which binds small peptides presented by MHC on surface of APCs  
*عشان فيك للزما أكسز الـ antigen small peptides*

TCR



BCR

