

# Basic Immunology

*Lecture 3<sup>rd</sup> and 4<sup>th</sup>*

**Structure, classes and functions of immunoglobulins and T cell receptors.**

**Recognition and presentation of antigen by MHC.**

**Antigen presentation and MHC restriction.  
Superantigens and toxic shock.**

# Antigen recognition in adaptive immunity

Native antigens are recognized by immunoglobulins or B cell receptors.

T cells can recognize exclusively in denatured (presented) forms of the antigens.

# Basic terms

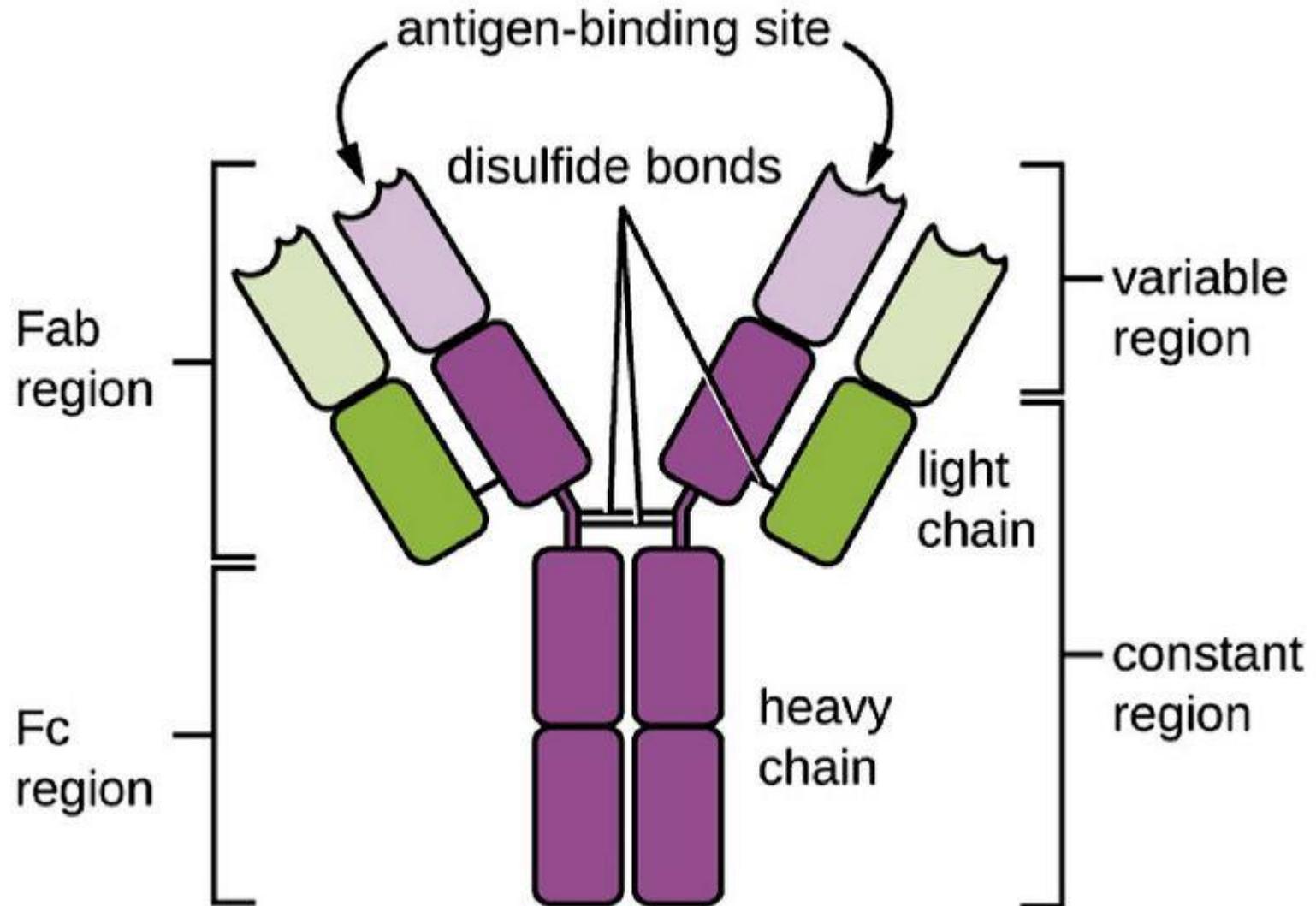
**immunogen** (fine chemical structure can induce specific immune response)

**epitope** (antigen determinant) well circumscribed region (molecular shape) of the antigen molecule targeted by Ig/BcR or TcR

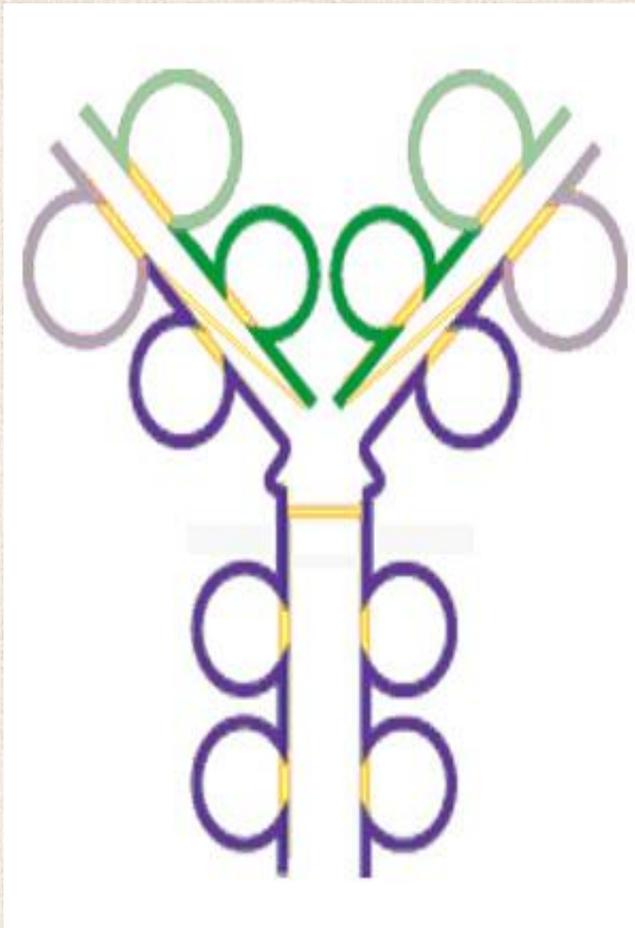
**hapten** (small molecular weight antigen can not induce immune reaction itself, but specifically recognized by immunoglobulins)

**carrier** (indifferent, large molecular weight molecule, hold on the surface hapten molecules; carrier molecules did not participate in the anti-hapten immune reaction only hapten)

# Immunoglobulin molecule

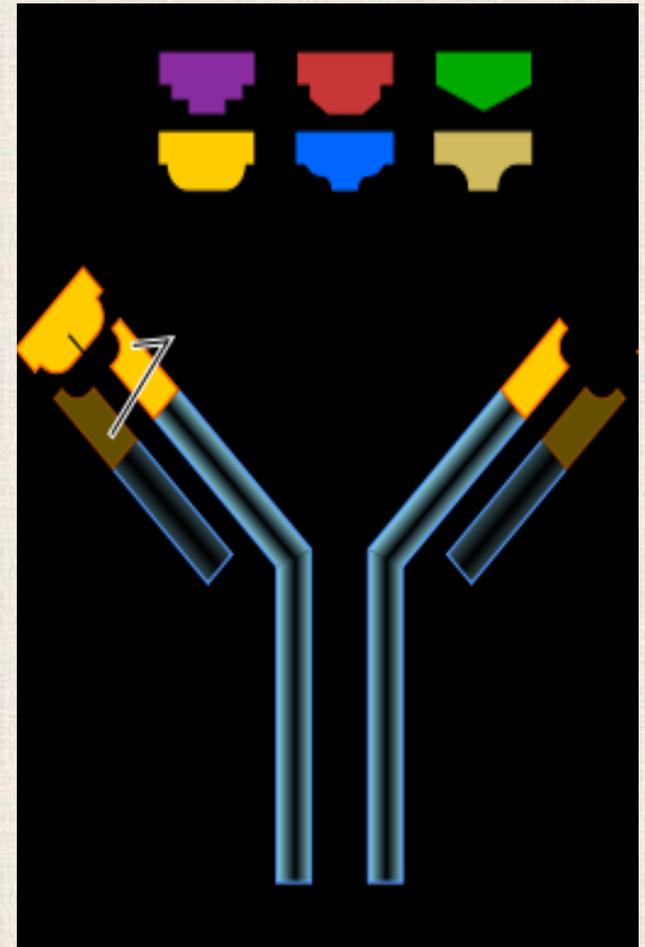


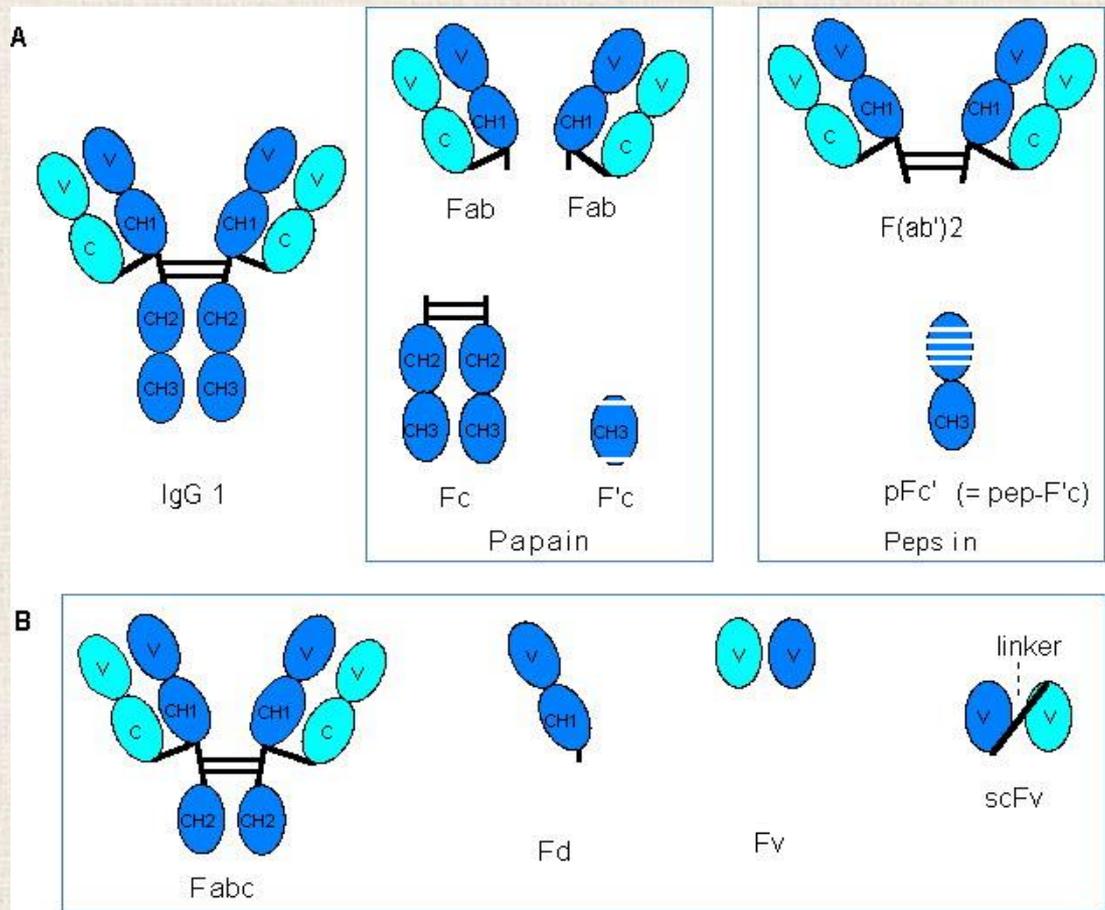
# Immunoglobulin molecule



**CDR**  
**Variable region**  
**Idiotyp**  
**Fab fragment**

**Constant region**  
**Isotype**  
**Fc fragment**





**Ig domains: intra-chain disulphide bonds form loops in the peptide chain, the loops are globular, constructed from beta-plated sheets and beta-turn loops.**

# Immunoglobulins

***Monofunctional*** character (specific antigen recognition and binding) ***before*** the antigen administration. **Fab** dependent function.

***Polyfunctional*** character ***after*** the antigen administration (signal transduction, complement fixation, opsonization, immunocomplex formation, FcR binding, etc). **Fc** dependent functions.

# Immunoglobulin isotypes

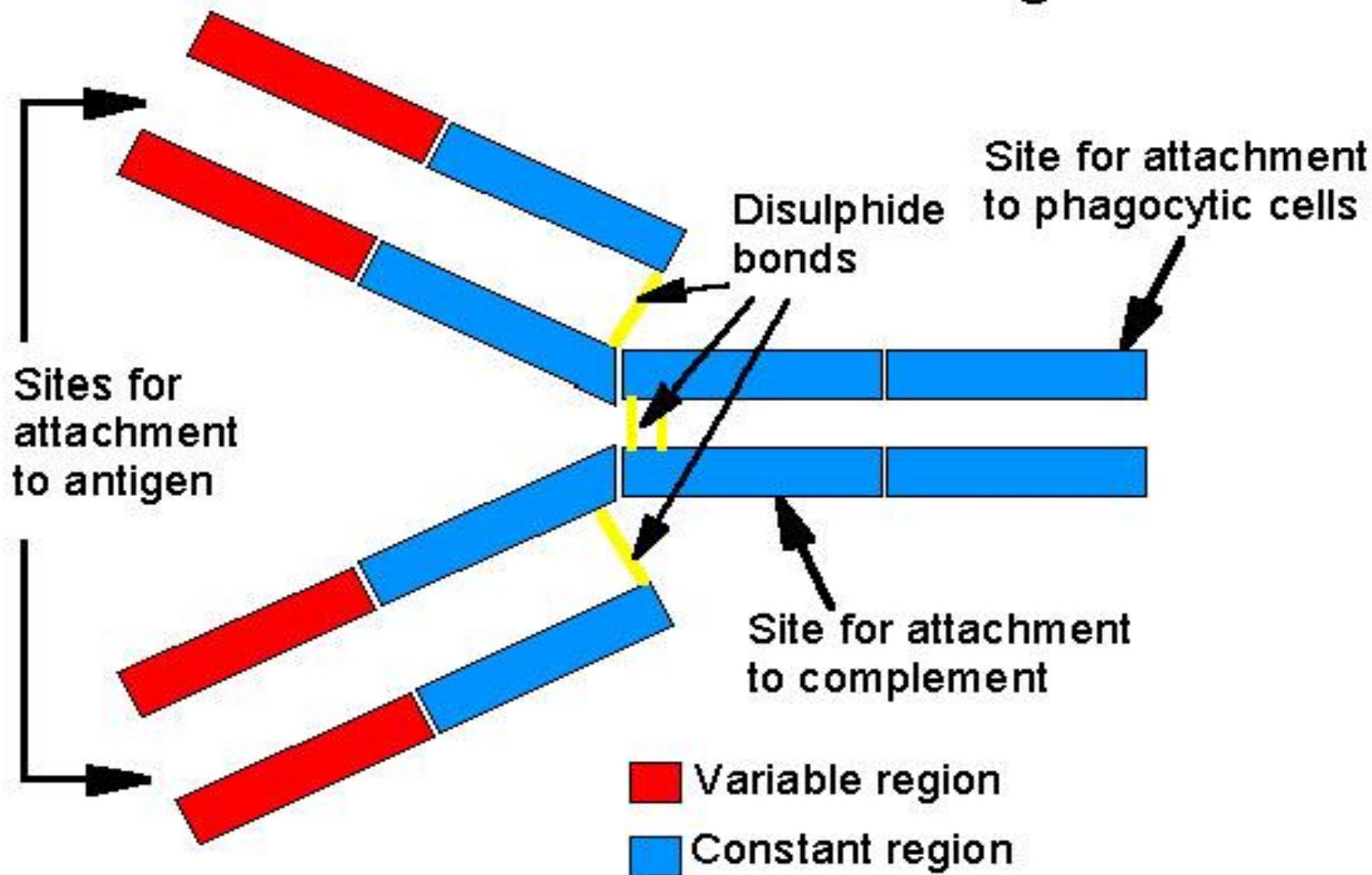
- Based upon the constant structures of heavy (H) and light (L) chains
- **CH isotypes:** called Ig classes and subclasses as **IgG, IgM, IgA, IgD** and **IgE**. All classes are represented in a normal serum (except the membrane bound IgD) as isotype variants.
- **CL** chain exists in two **isotypic forms:** kappa ( $\kappa$ ) and lambda ( $\lambda$ ), which can associate with all heavy chain isotypes.

<b>Heavy chain</b>	<b>Light chain</b>	<b>Immuno-globulin Class</b>	<b>Immuno-globulin Subclass</b>
$\gamma 1$	$\kappa$ or $\lambda$	IgG	IgG1
$\gamma 2$	$\kappa$ or $\lambda$		IgG2
$\gamma 3$	$\kappa$ or $\lambda$		IgG3
$\gamma 4$	$\kappa$ or $\lambda$		IgG4
$\alpha 1$	$\kappa$ or $\lambda$	IgA	IgA1
$\alpha 2$	$\kappa$ or $\lambda$		IgA2
$\mu$	$\kappa$ or $\lambda$	IgM	
$\delta$	$\kappa$ or $\lambda$	IgD	
$\epsilon$	$\kappa$ or $\lambda$	IgE	

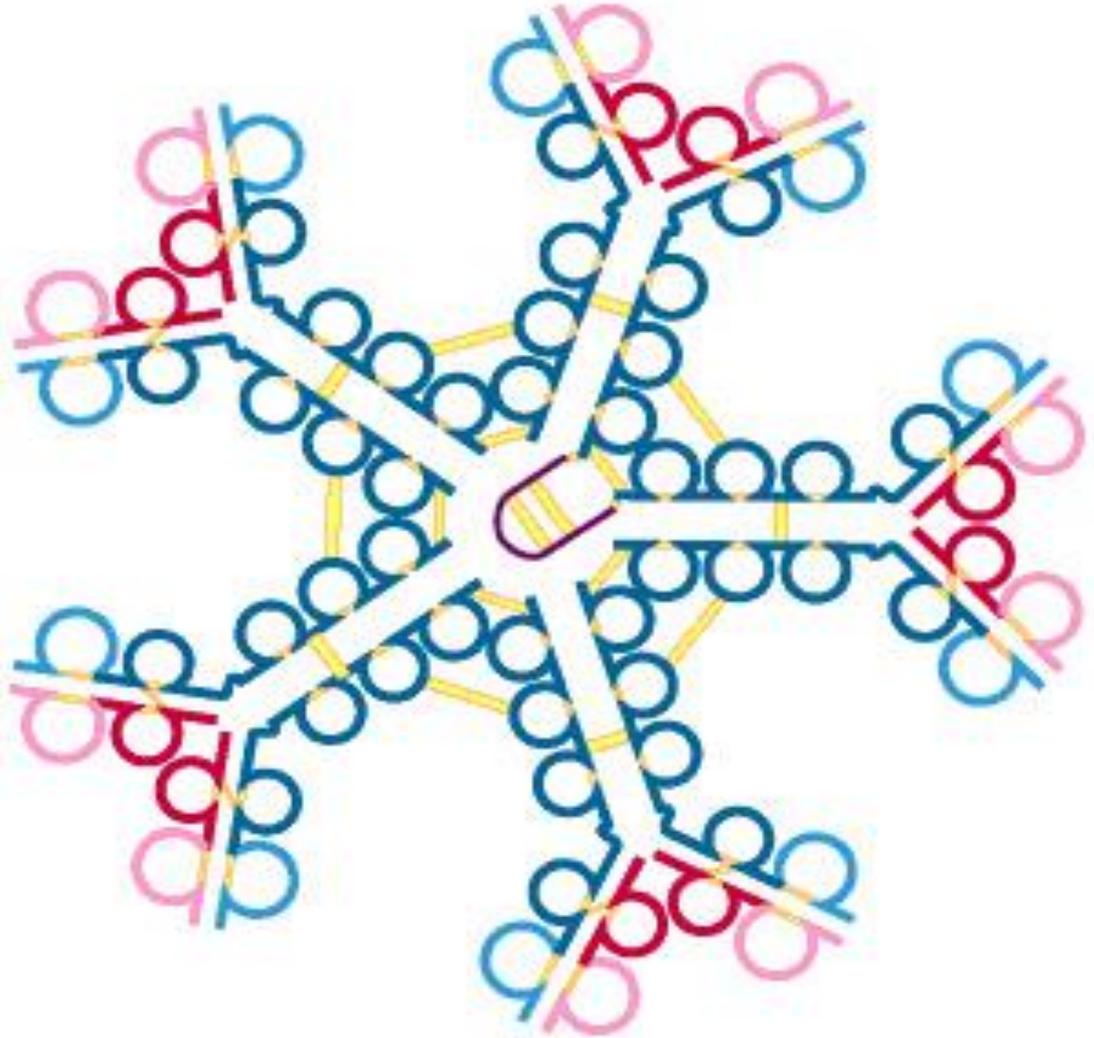
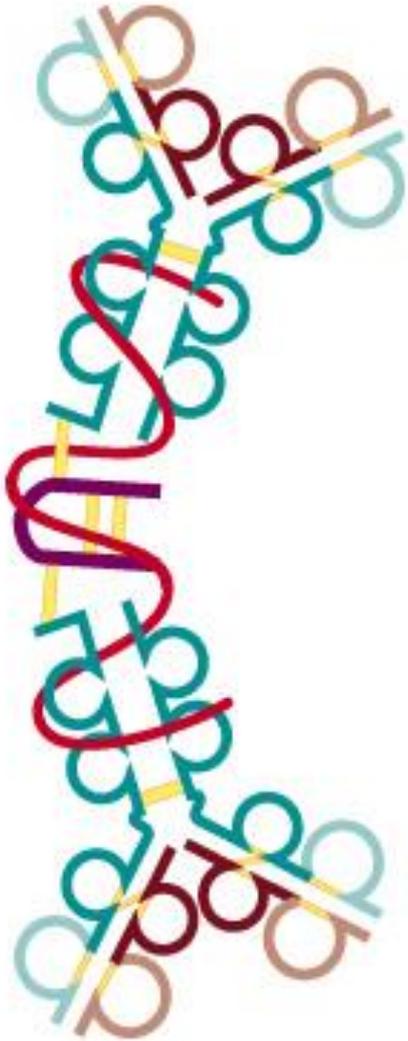
Pronunciation of Greek letters:

$\gamma$  gamma     $\alpha$  alpha     $\mu$  mu     $\delta$  delta  
 $\epsilon$  epsilon     $\kappa$  kappa     $\lambda$  lambda

# Structure of Immunoglobulin G1



# IgA and IgM



# Immunoglobulin E with name of each domain

Sites for attachment to antigen

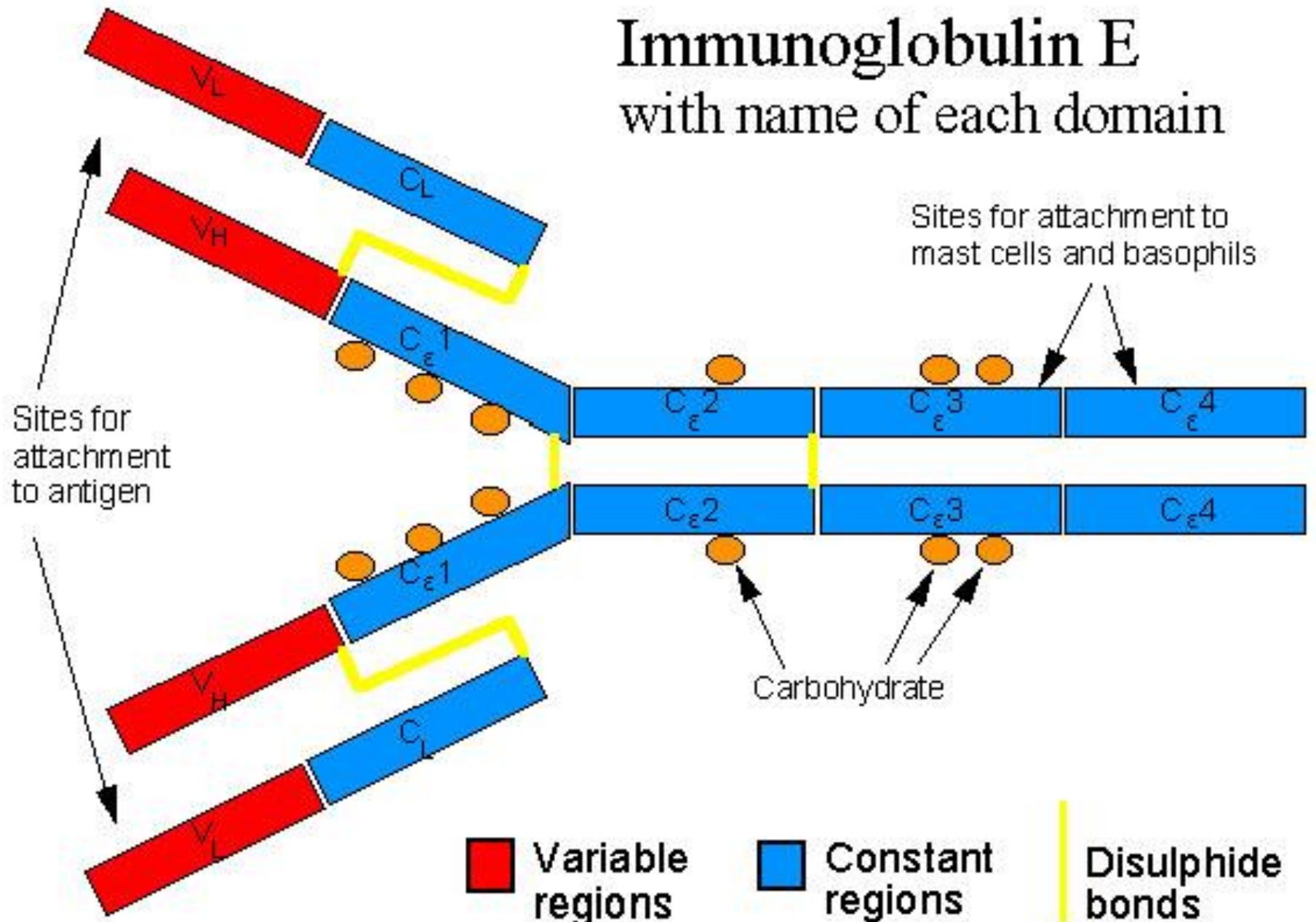
Sites for attachment to mast cells and basophils

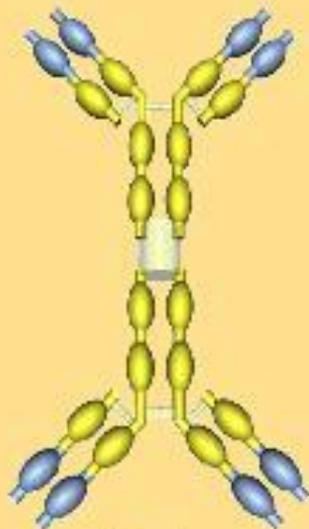
Carbohydrate

 Variable regions

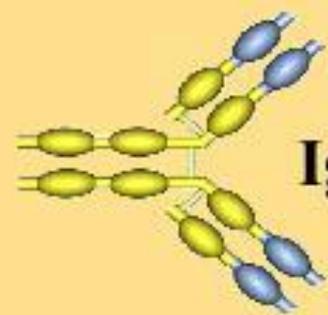
 Constant regions

 Disulphide bonds

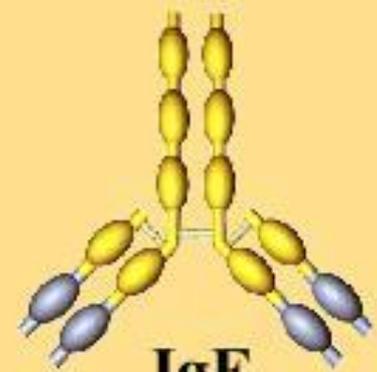




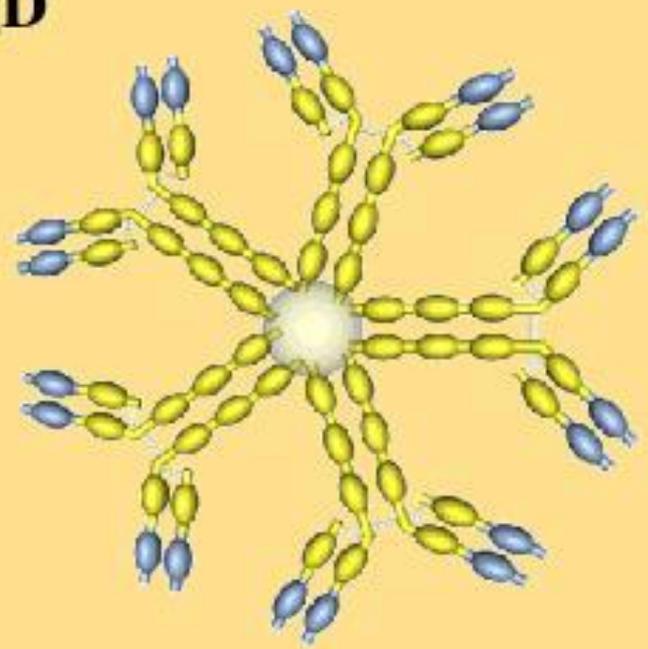
**IgA**



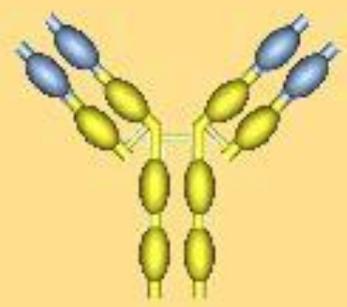
**IgD**



**IgE**



**IgM**

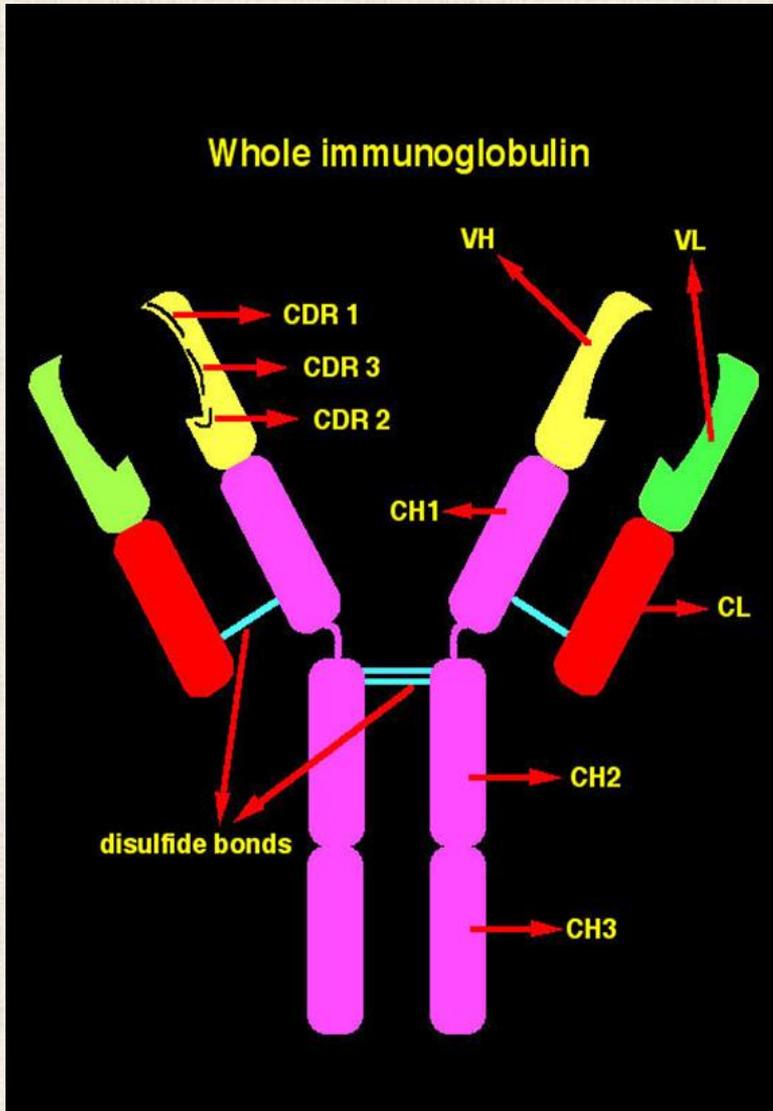


**IgG**

# Immunoglobulin idiotype

Individual determinants in **V regions**, specific for each antibody.

The N terminal Ig domain contains V region forming the antigen binding site: clustering the 3 hyper variable sequences close to each other on both chains - the variation of 3 x 3 results tremendous diversity.



# Construction of idiotype by immunoglobulin rearrangement

Génátrendeződés



\*\*\*

1 2 3 Szomatikus hipermutációk

Gene rearrangement

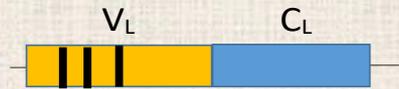


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1 2 3

Somatic hypermutations

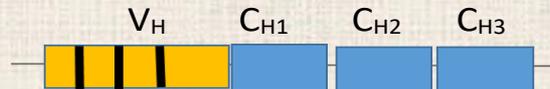
Hírvivő RNS



CDR

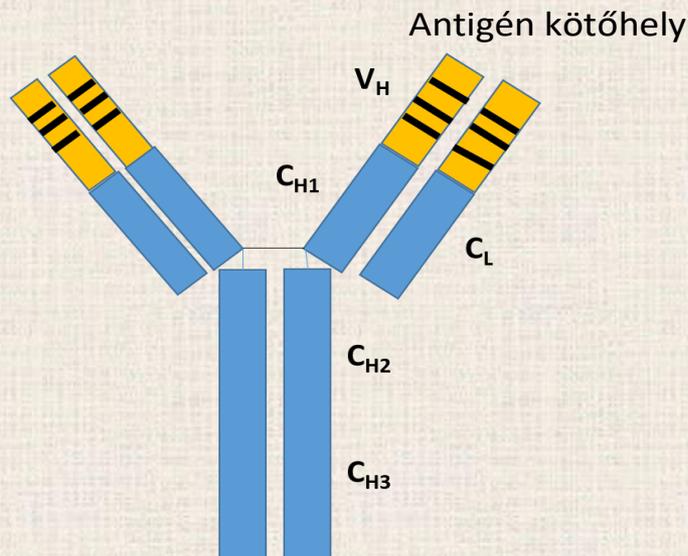
1 2 3

Messenger RNA



1 2 3

Immunglobulin fehérje



Immunoglobulin protein

Antigen binding site

# Human immunoglobulins

**IgG** – blood, lymph, make up 80% of Ig only Ig of maternal origin to pass the placenta wall give newborns (Mw 150 kD) neutralize toxins and viruses

**IgM** – Blood, lymph (cell surface) pentamer structure (Mw 900 kD) first antibodies formed in response to initial infection.

**IgA** – Mucosal surfaces, blood (active in dimeric or tetrameric form)  
(Mw 150-600 kD)

**IgD** – only membrane-bounded form in B-cell surfaces (Mw 150 kD)  
may function in initiation of antibody-antigen response

**IgE** – blood, in periphery can bound to basophiles and mast cells  
(Mw 190 kD) plays role in defence against parasites and initiation  
allergic reactions

**IgG** - vér, nyirok, az Ig 80%-át teszik ki. Az egyetlen anyai eredetű Ig, amely áthalad a placenta falán.

(Mw 150 kD) Semlegesítik a toxinokat és vírusokat.

**IgM** - vér, nyirok (sejtfelszíni), pentamer szerkezetű (Mw 900 kD), az első antitestek a fertőzésre adott kezdeti válaszban.

**IgA** - Nyálkahártya felületek, vér (dimer vagy tetramer formában aktív) (Mw 150-600 kD)

**IgD** - csak membránhoz kötött forma a B-sejtek felszínén (Mw 150 kD)/ Az antitest-antigén válasz beindításában játszhat szerepet.

**IgE** - a vérben, a periférián a bazofilokhoz és hízósejtekhez kötődhet (Mw 190 kD) szerepet játszik a paraziták elleni védekezésben és az allergiás reakciók kiváltásában.

# **Antigen – antibody reactions**

- **Neutralization (e.g. viruses, toxins)**
- **Precipitation (soluble molecules)**
- **Agglutination (particles, cells)**
- **Opsonization (large particles)**
- **Complement fixation**



# T Cell receptor

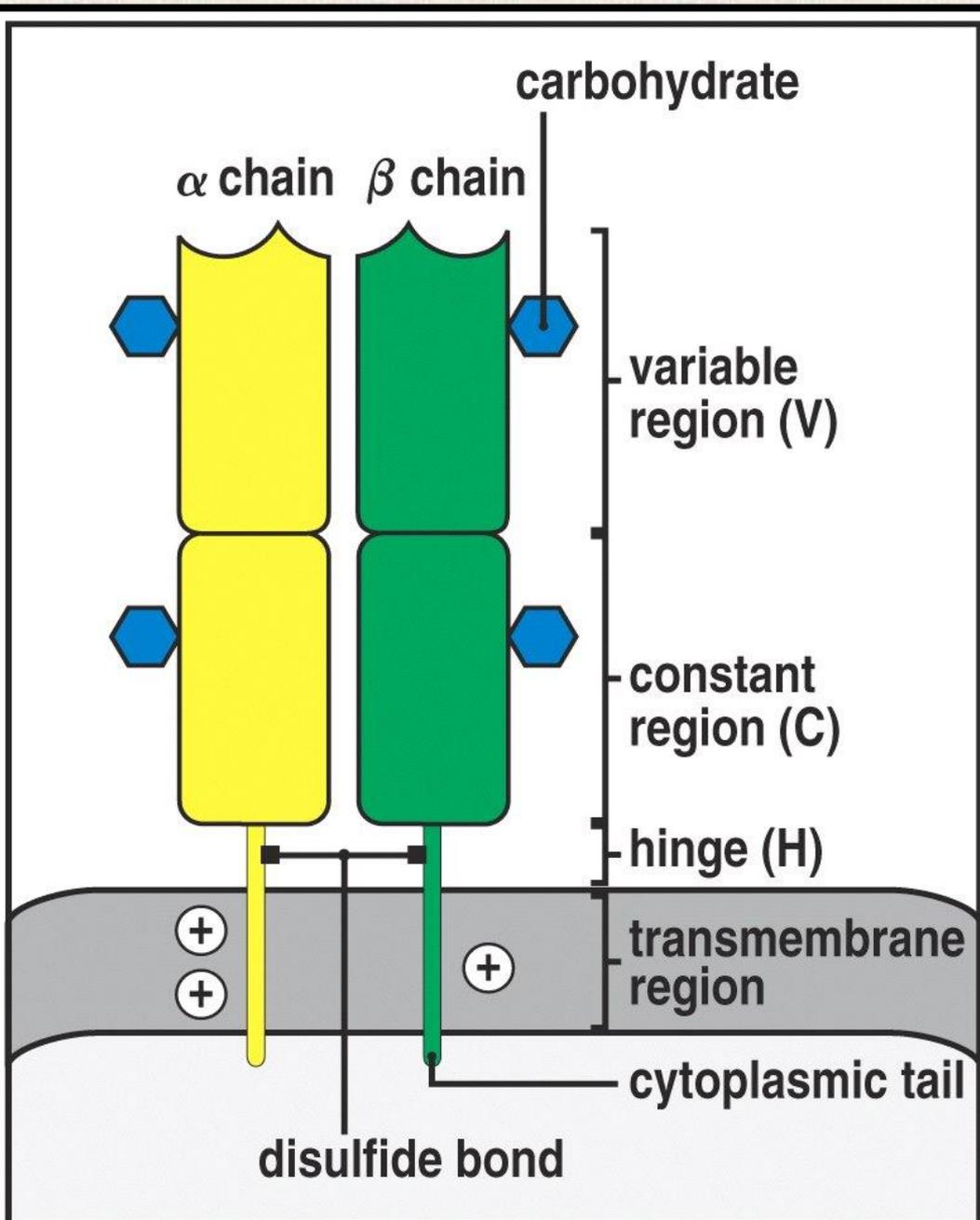
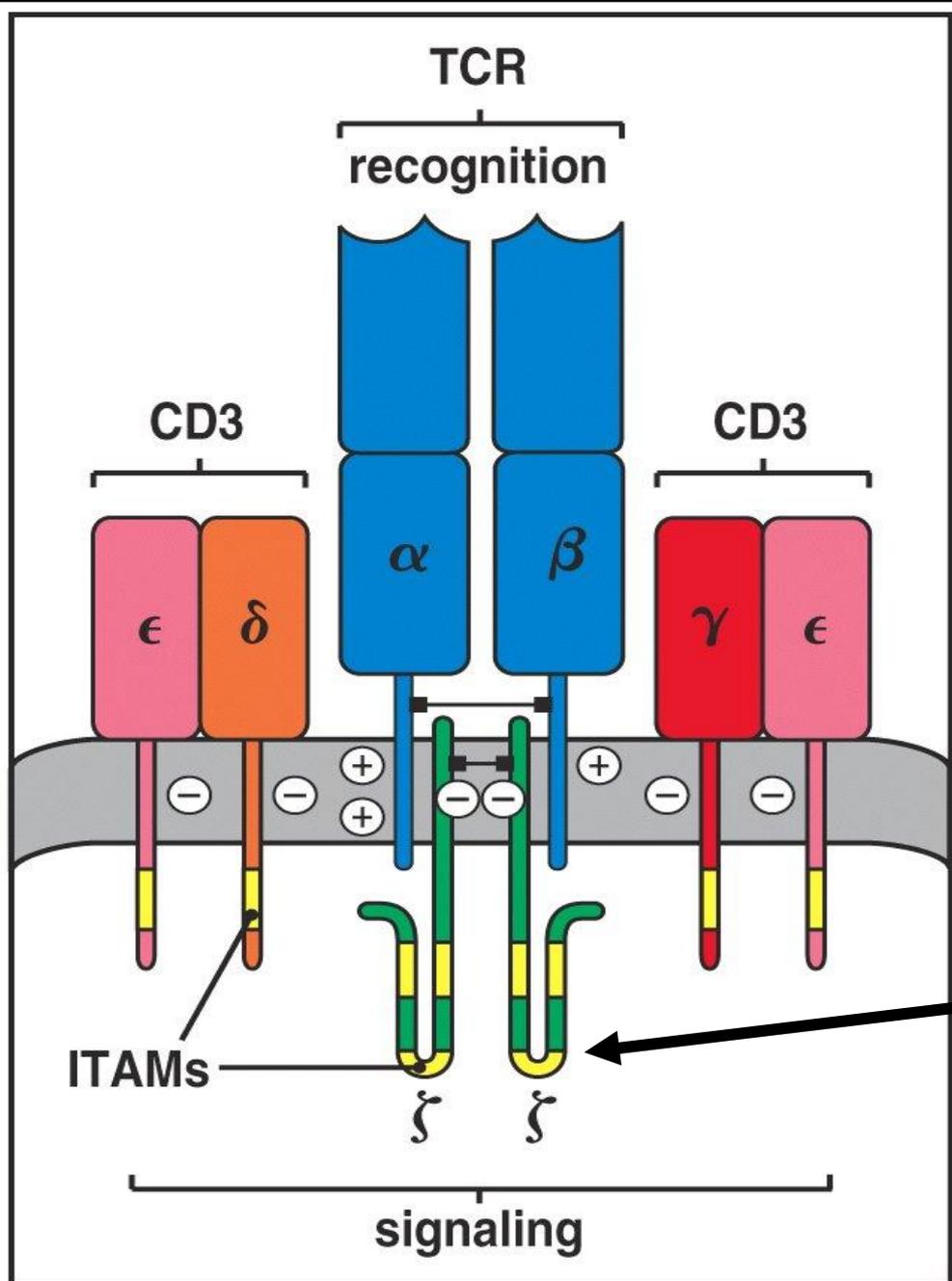


Figure 3-12 Immunobiology, 6/e. (© Garland Science 2005)

# T Cell Receptor complex



ITAMs  
Immunoreceptor  
Tyrosine-based  
Activation  
Motifs

# Antigen Recognition by T Cells

-T cells recognize antigens exclusively displayed on surfaces of the body's own cells as MHC and peptide complexes

## Main T cell types:

**-CD8+ (cytotoxic) T-cells**

recognizes **MHC Class I - peptide complex**

**-CD4+ (helper) T-cells**

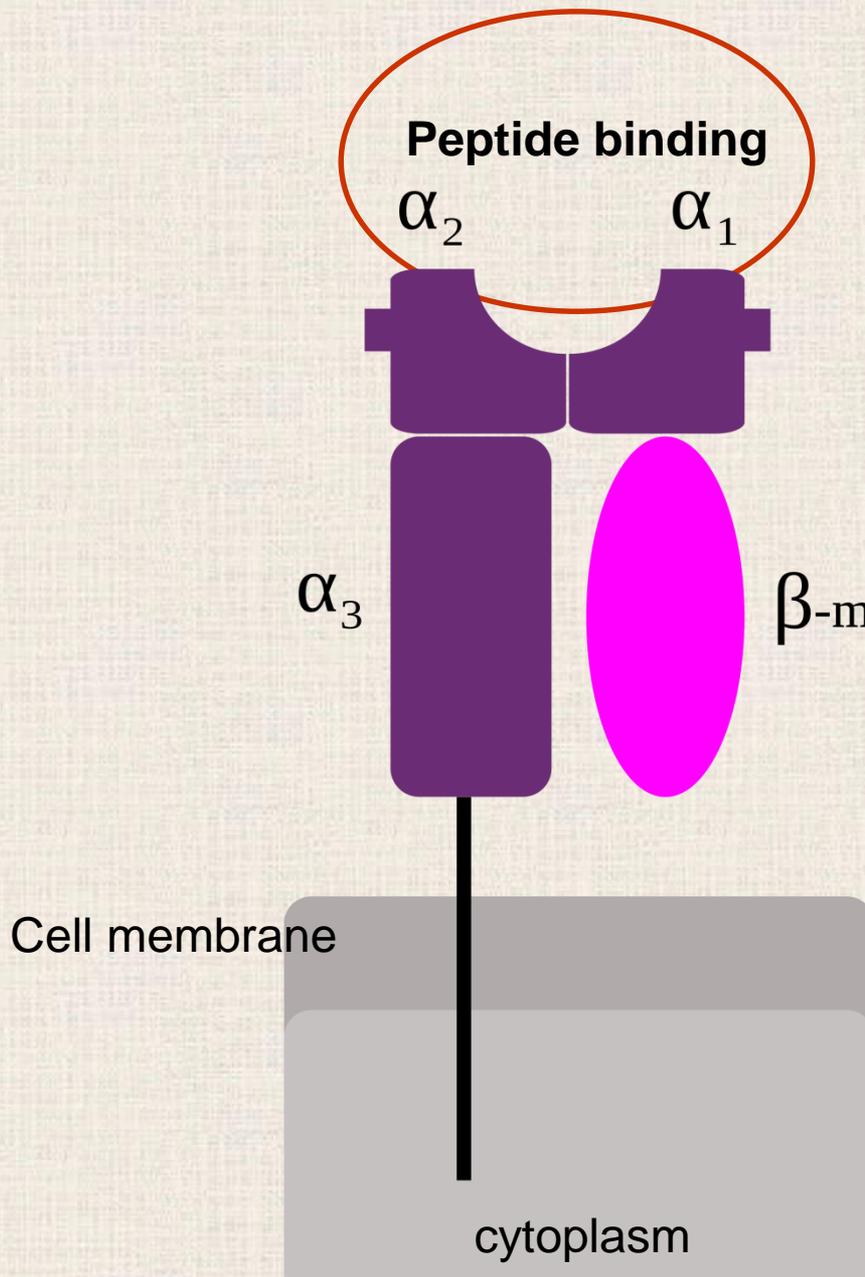
recognizes **MHC Class II - peptide complex**

# Major Histocompatibility Complex

Self and foreign antigens are presented on the cell surface by specialized host-cell glycoproteins encoded in a large cluster of genes that were first identified by their effects on the immune response to transplanted tissues. For that reason, the gene complex was termed the **M**ajor **H**istocompatibility **C**omplex (MHC). The antigen binding glycoproteins are called MHC molecules/antigens. (MHC vs. HLA, H2, BoLA, ChLA etc.)

# Inbred strains of mice

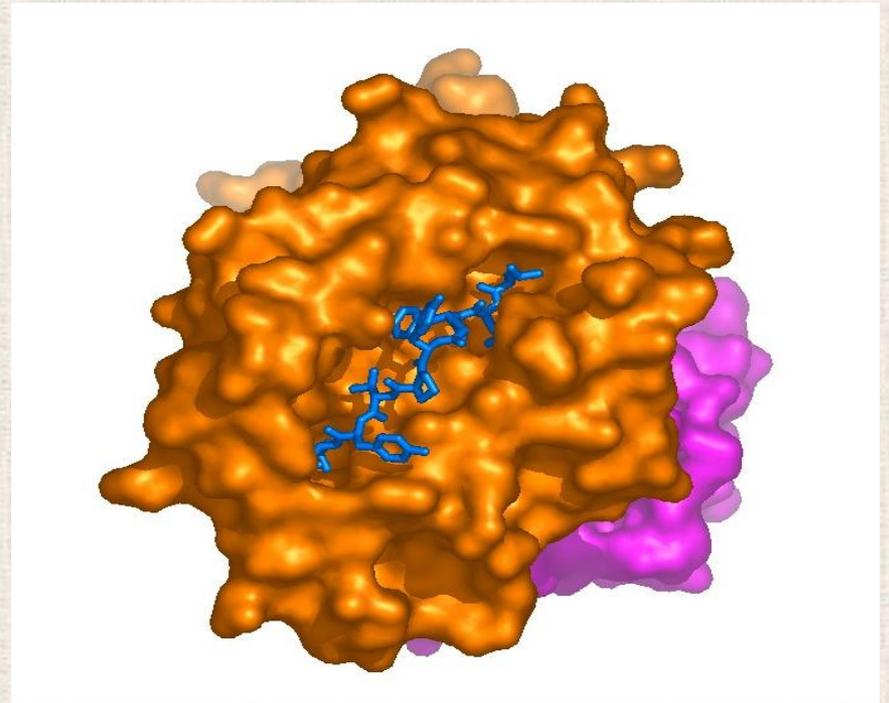
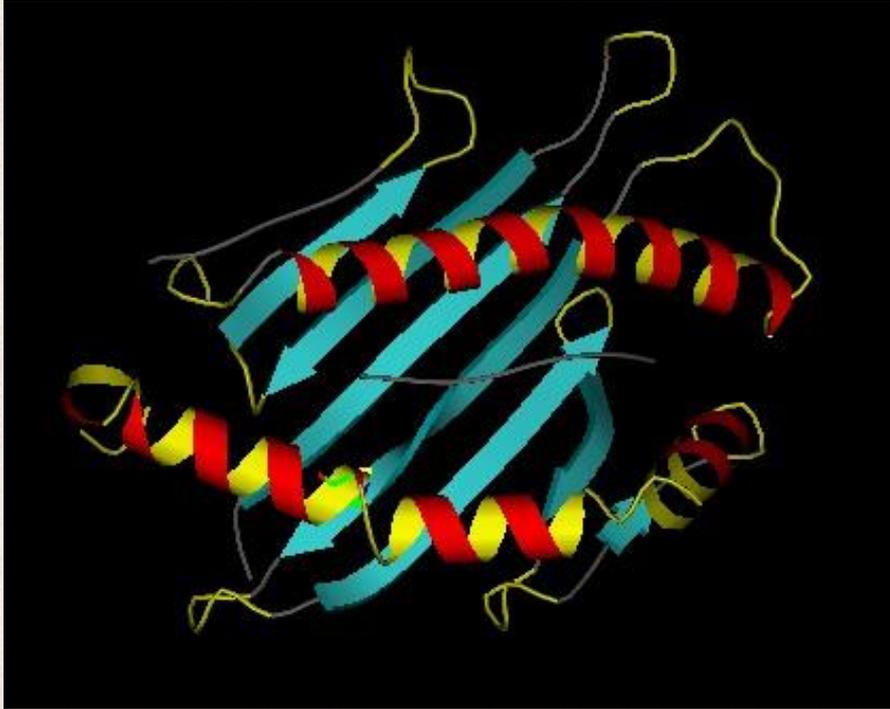




# MHC Class I

**Present in all nucleated cells and platelets**

# Antigen binding site of MHC class I

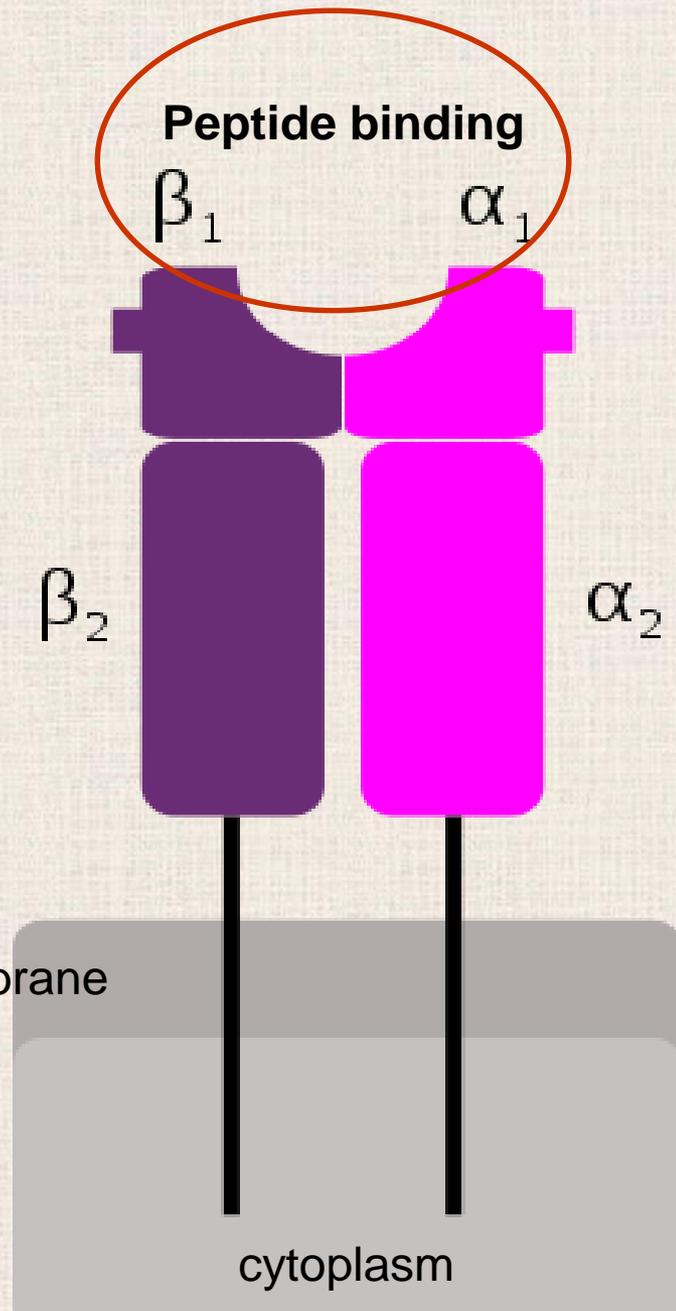


# MHC Class II

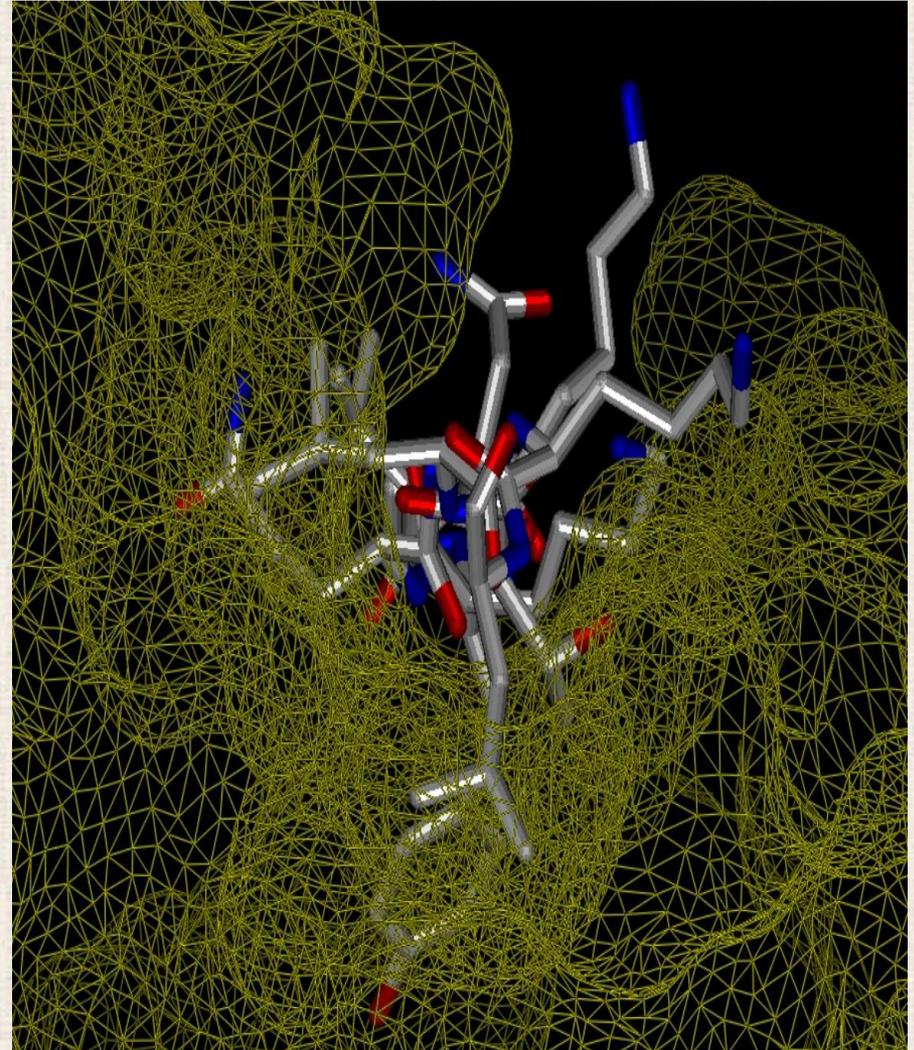
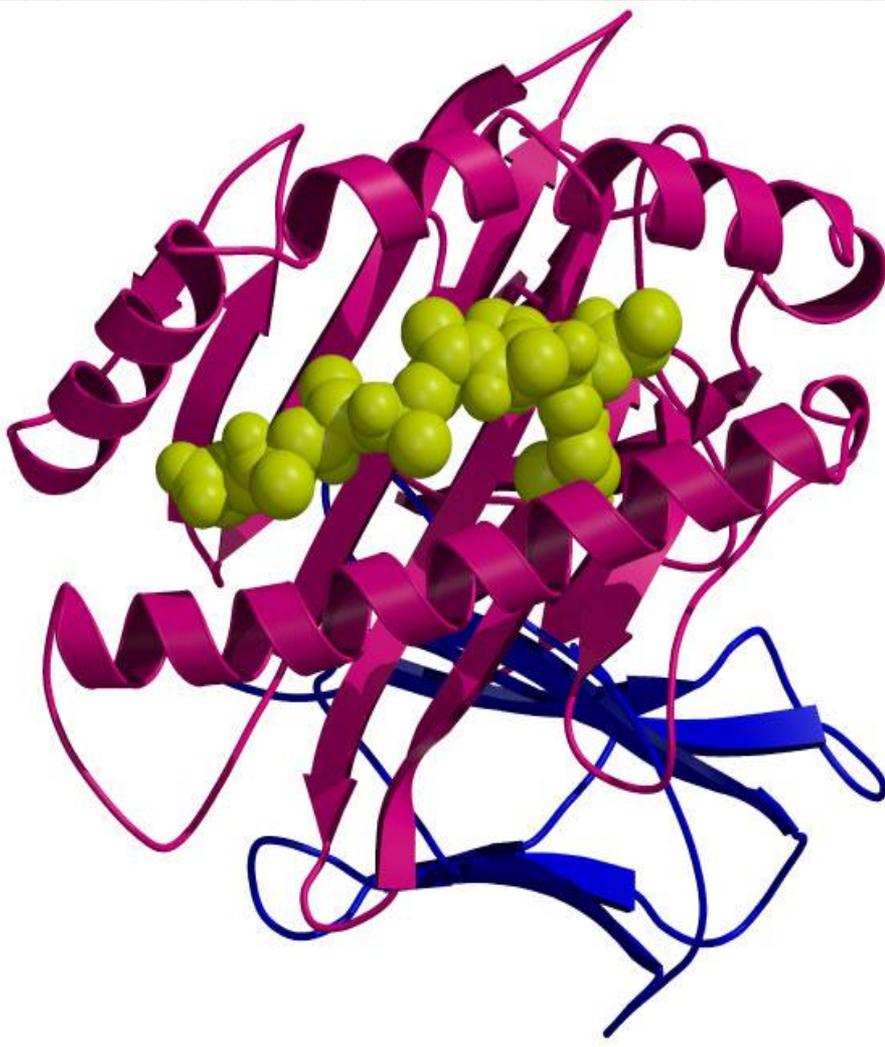
Present in professional or facultative antigen presenting cells (APC)

**Professional antigen presenting cells:** dendritic cells, monocytes, macrophages, B cells, thymus epithelial cells

**Facultative antigen presenting cells:** inflammatory epithel and endothel in pathologic conditions

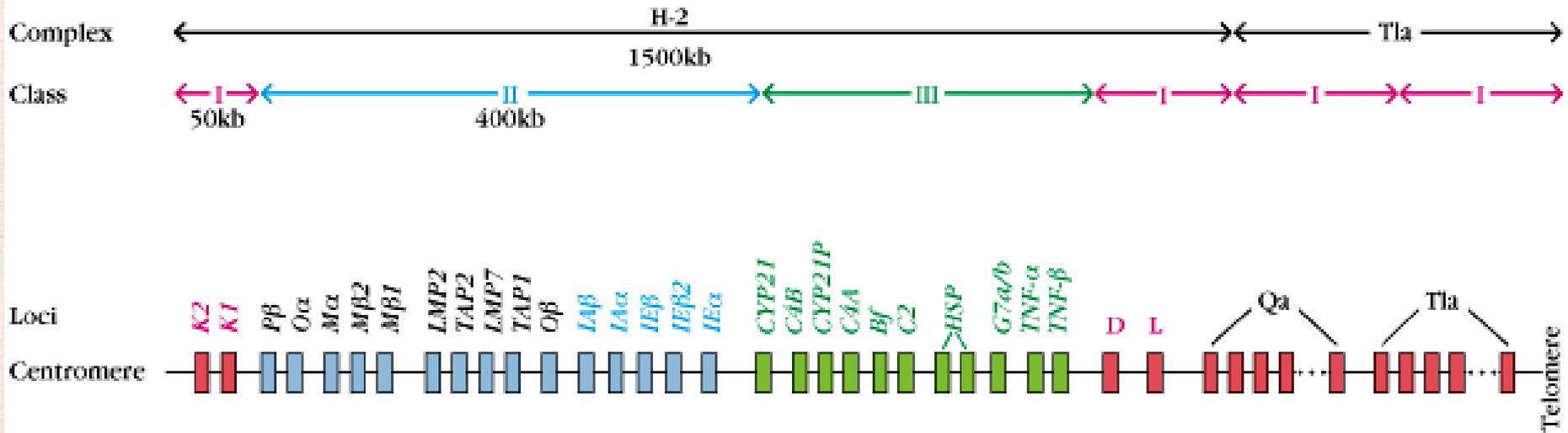


# Antigen binding site of MHC class II

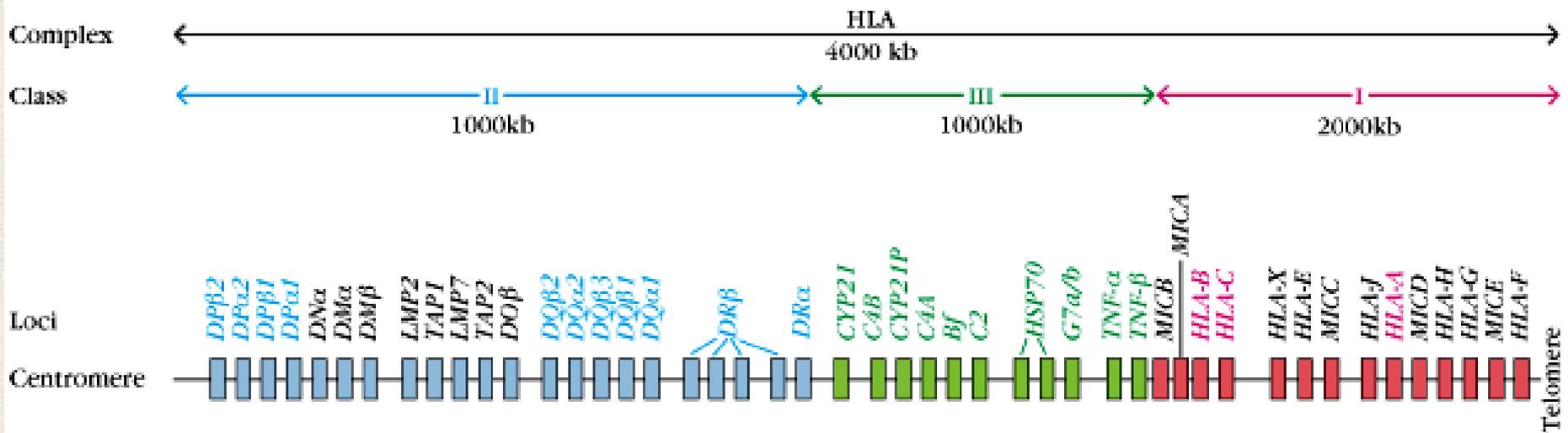


# Structure of MHC genes

## MOUSE CHROMOSOME 17

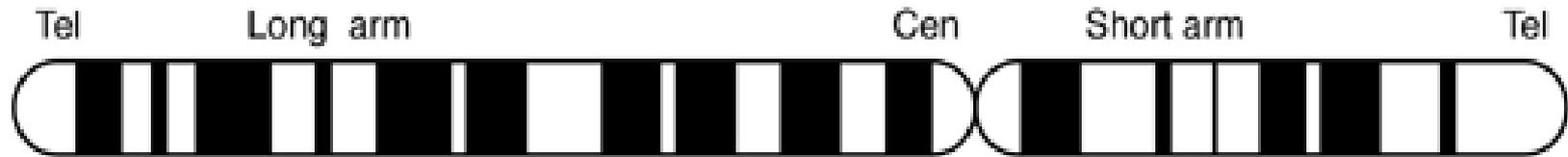


## HUMAN CHROMOSOME 6

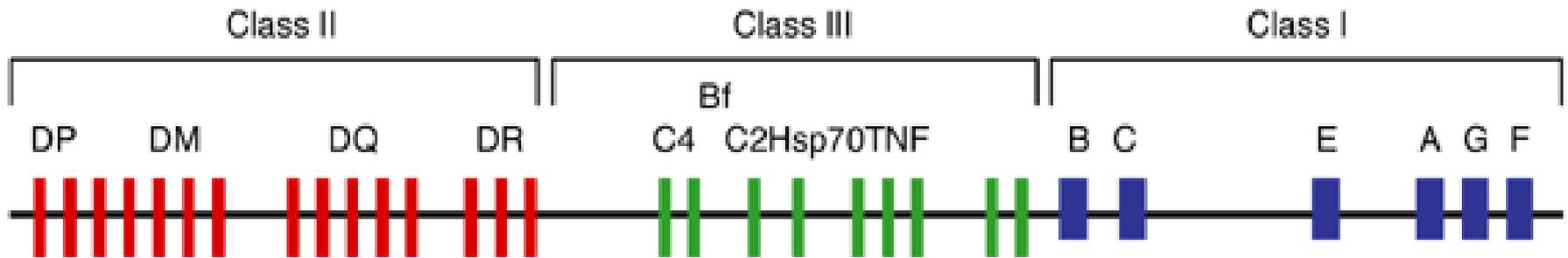


# HLA map

Chromosome 6



HLA region  
6p21.1-21.3



Gene map of the human leukocyte antigen (HLA) region

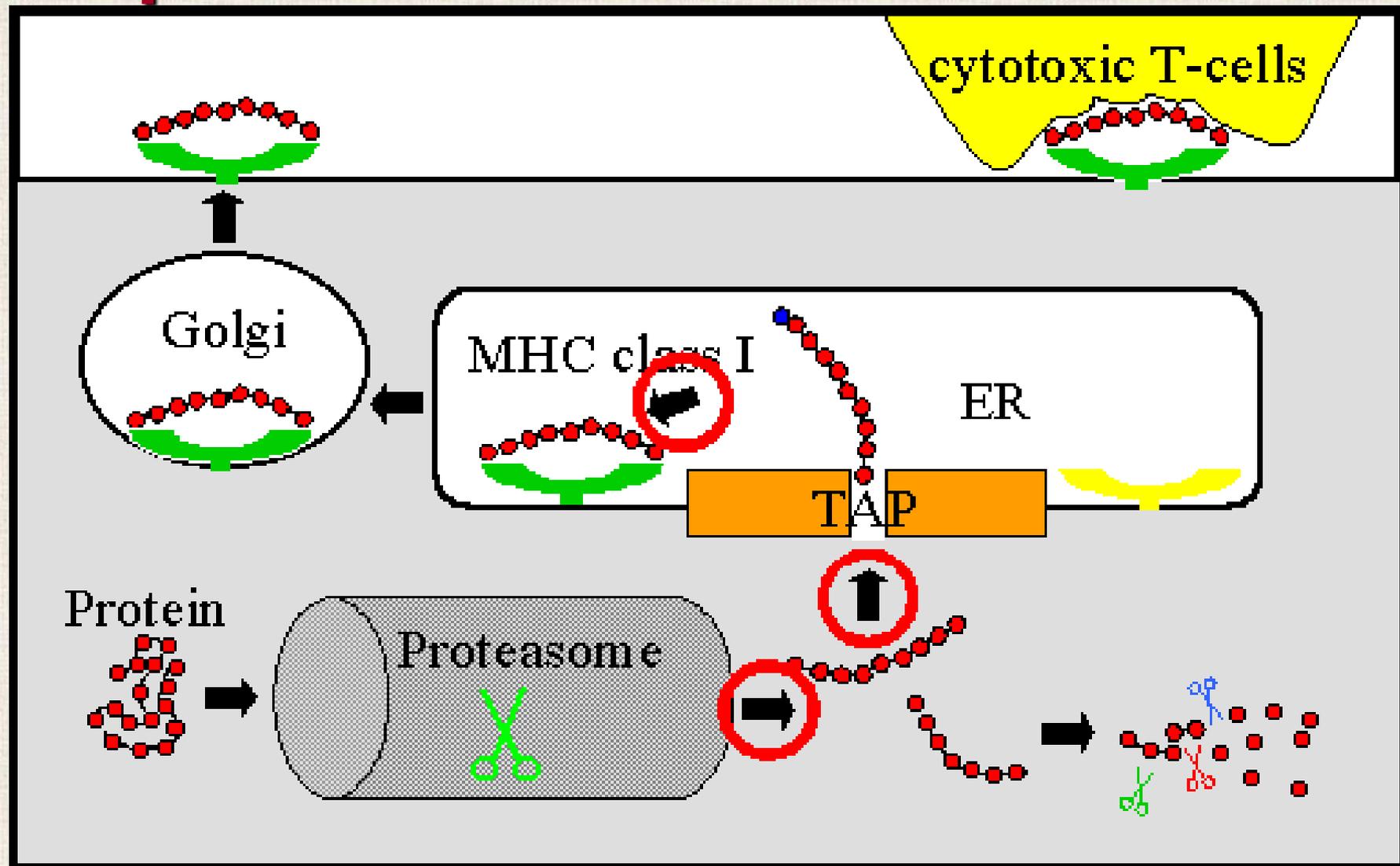
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The MHC is **polygenic** (there are *several* different class I and class II ***genes*** encoding proteins with different specificities) and highly **polymorphic** (there are ***multiple alleles of each gene***) that most individuals are likely to be heterozygous at each locus. Alleles are expressed from both MHC haplotypes in any one individual (**co-dominant**), and the products of all alleles are found on all expressing cells.

In human there are three classical class I molecules (**HLA-A, B, C**) and three classical class II molecules (**HLA-DR, DP, DQ**). The HLA-A has more than 20, B has more 50, and C more than 10 alleles. HLA-DR has 20, and HLA-DP has 6, HLA-DQ has 9 alleles.

Az MHC **poligénes** (több különböző I. és II. osztályú gén létezik, amelyek különböző specifitású fehérjéket kódolnak) és erősen **polimorf** (minden génnek több allélja van), így a legtöbb egyén valószínűleg heterozigóta az egyes lókuszokon. Az allélok mindkét szülői MHC-haplotípusból kifejeződnek egy egyénben (**ko-domináns**), és az összes allél termékei megtalálhatók az összes expresszázó sejtben. Emberben három klasszikus I. osztályú molekula (HLA-A, B, C) és három klasszikus II. osztályú molekula (HLA-DR, DP, DQ) létezik. A HLA-A több mint 20, a B több mint 50, a C több mint 10 alléllal rendelkezik. A HLA-DR 20, a HLA-DP 6, a HLA-DQ pedig 9 alléllal rendelkezik.

# Antigen processing and presentation on MHC Class I



# Transporter Associated with Antigen Processing

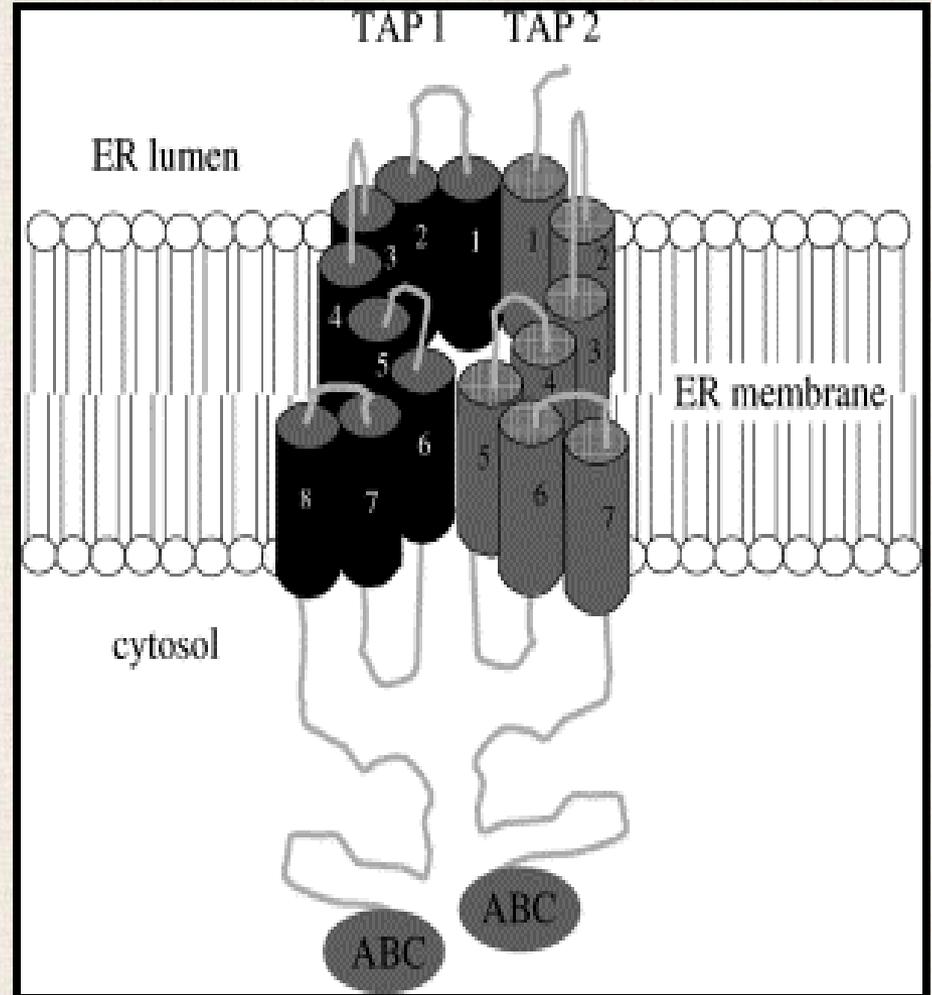
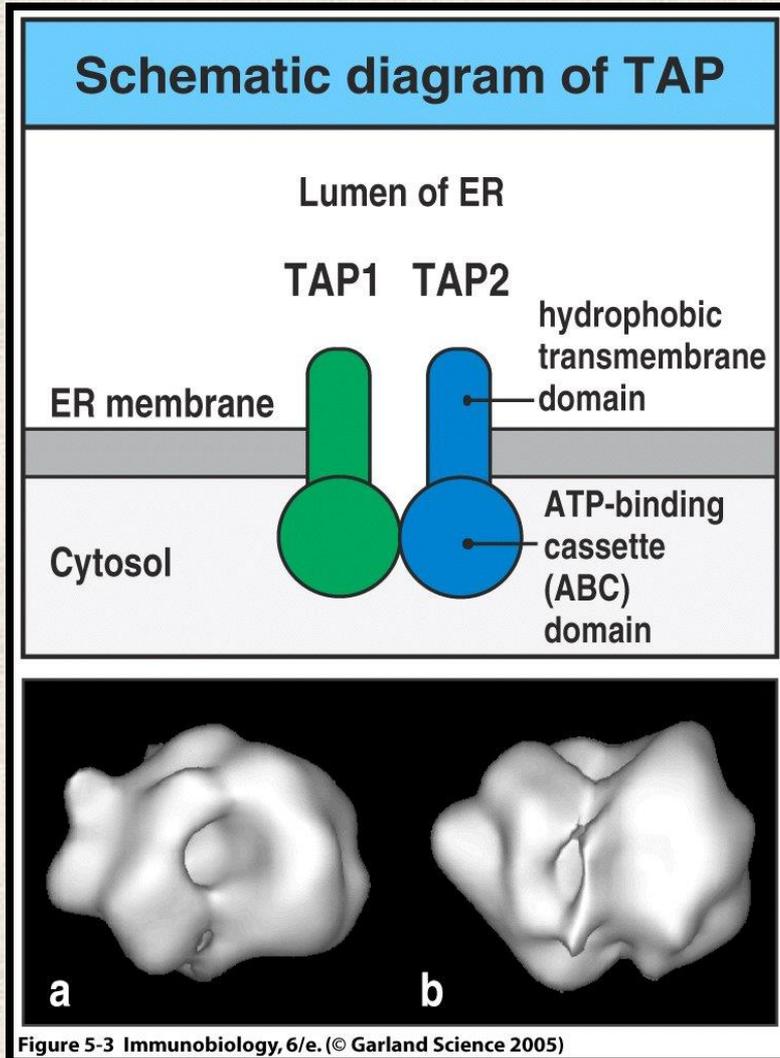
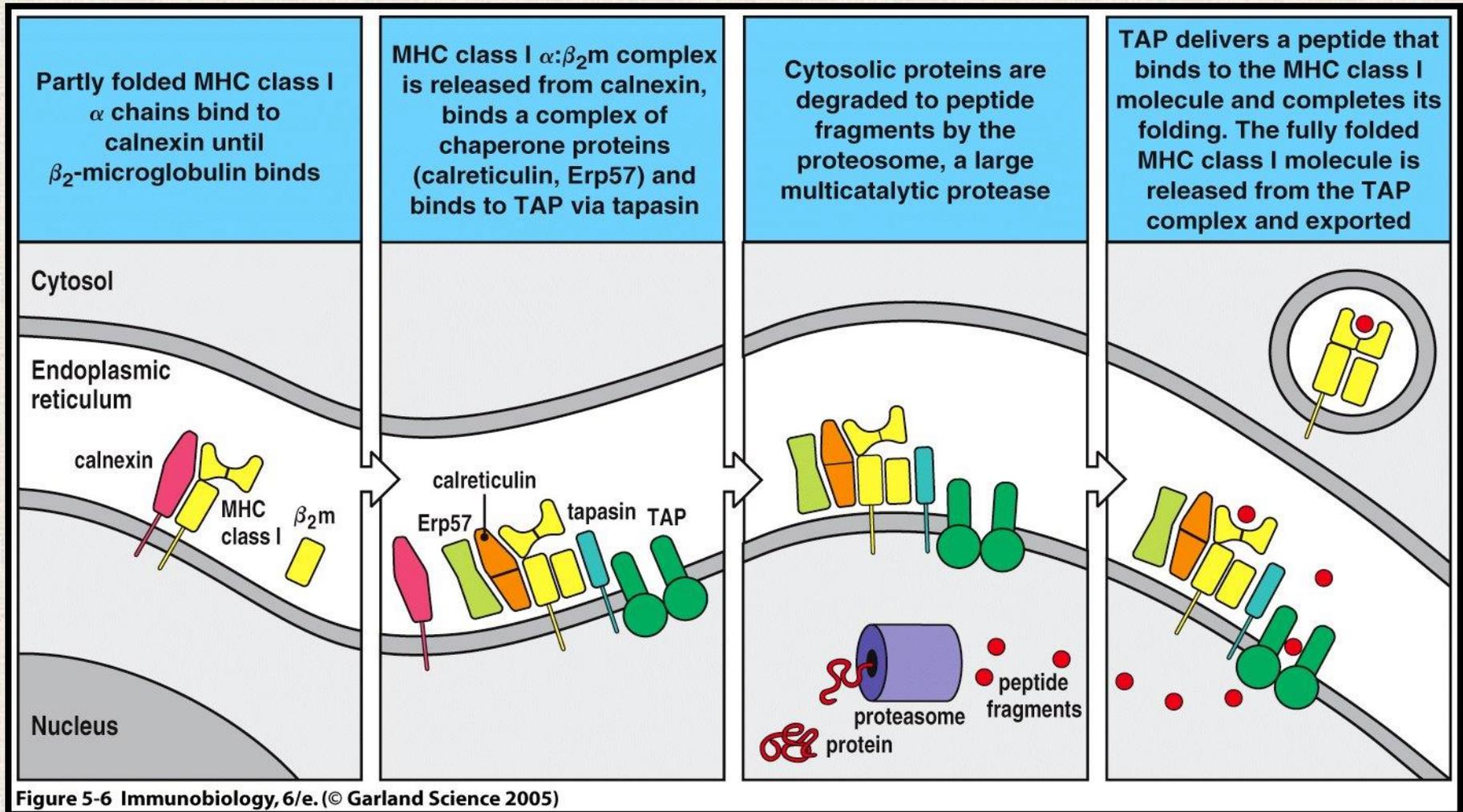


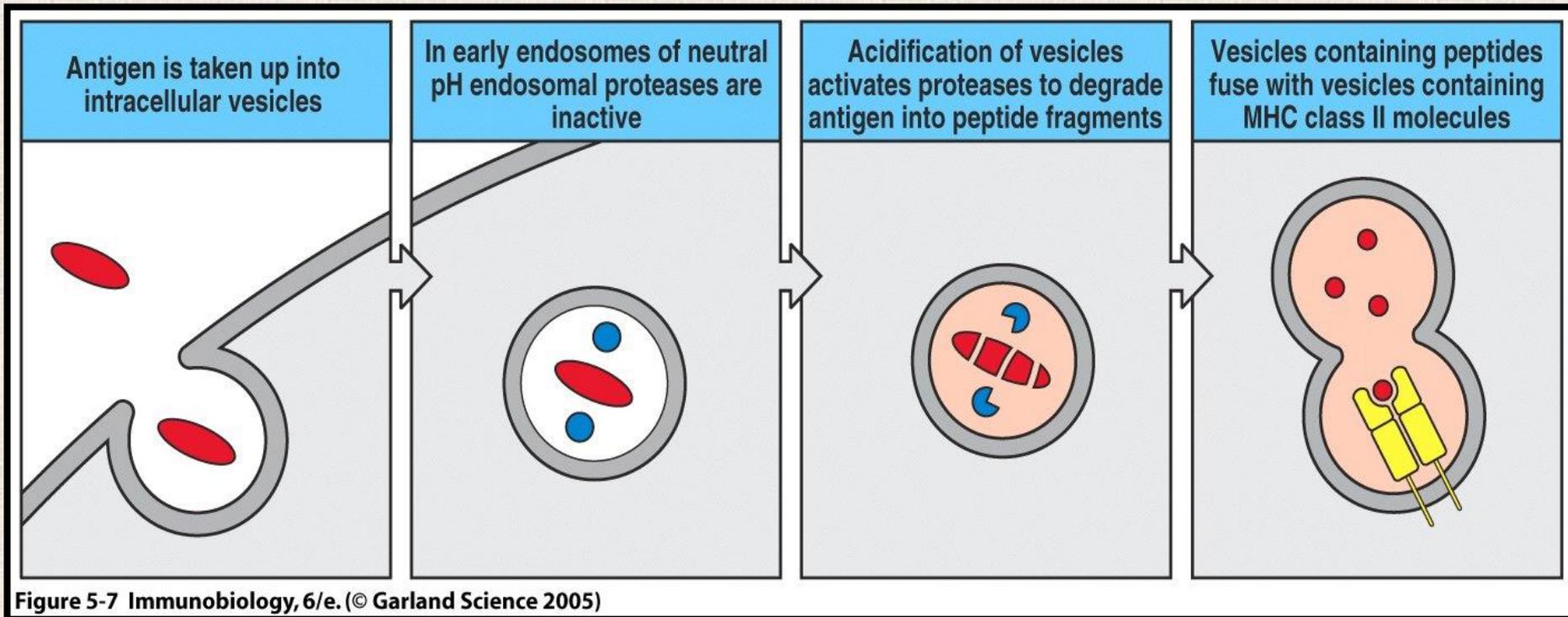
Figure 5-3 Immunobiology, 6/e. (© Garland Science 2005)

# Chaperons in the MHC Class I antigen presentation

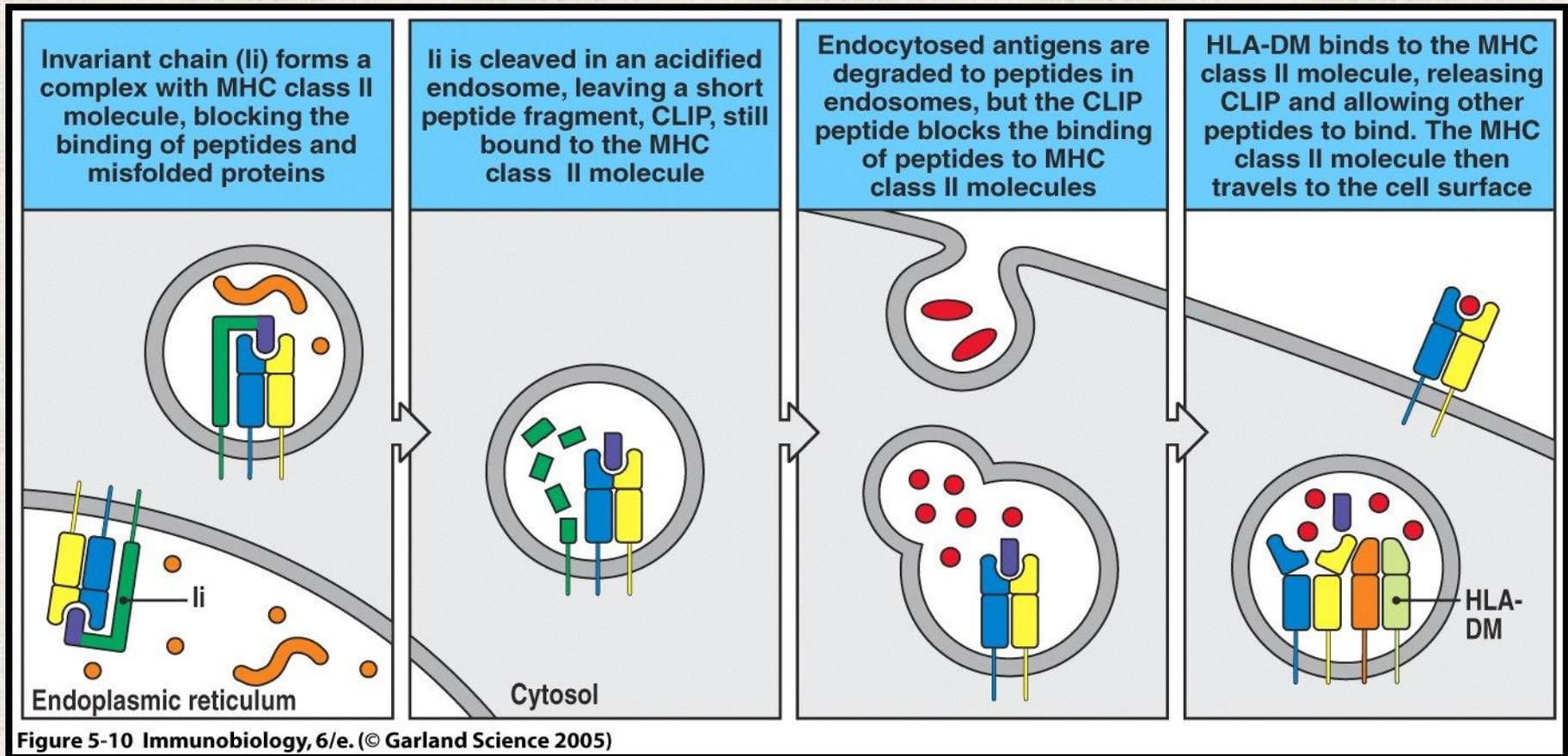
## Calnexin, calreticulin, Erp57, tapasin



# Generation of antigenic peptides in the endocytic pathway for presentation by MHC II



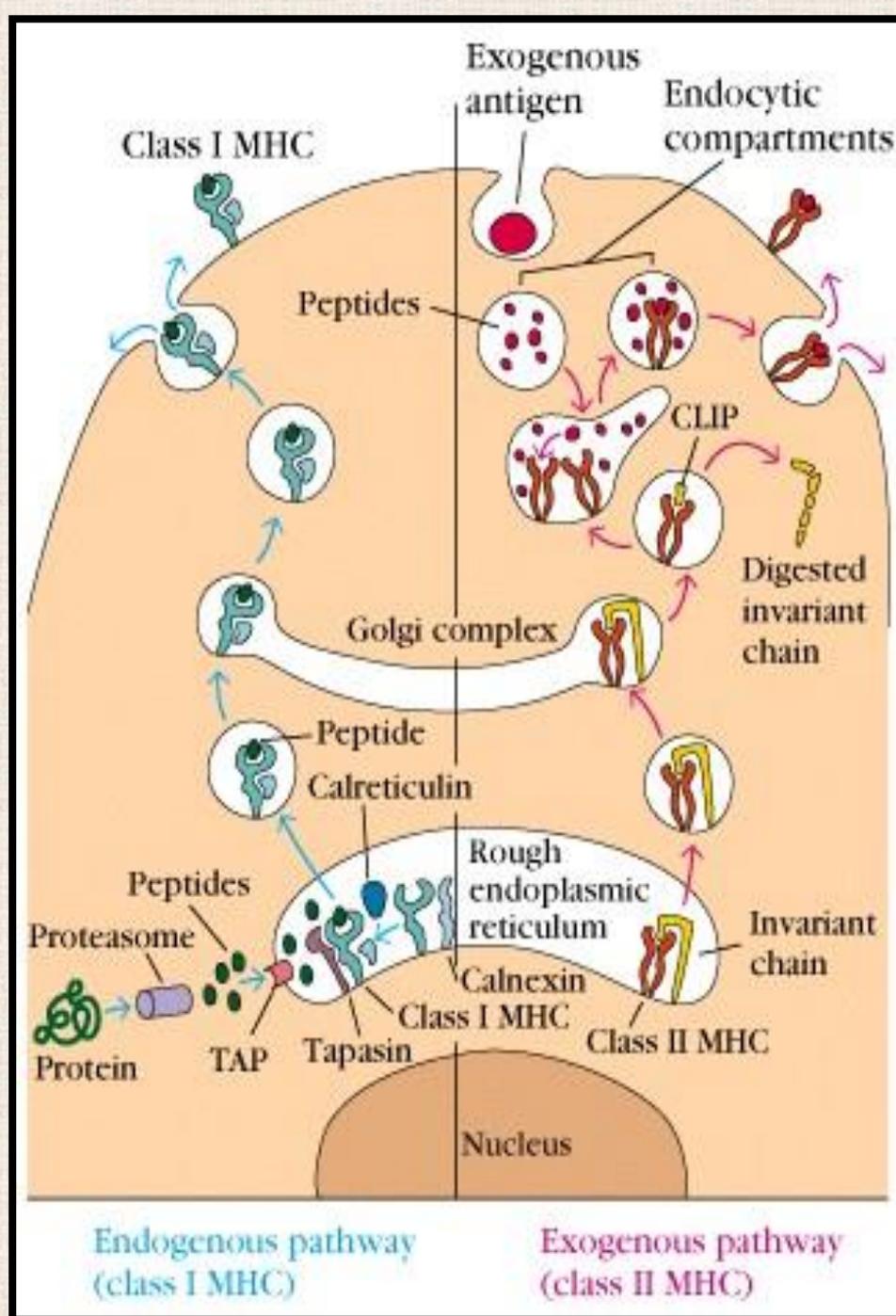
# Peptide loading of MHC Class II molecules



**HLA-DM: MHCII chaperon**

**CLIP=class II associated invariant chain peptide**

**Presentation  
of  
intracellular  
antigens by  
MHC I:  
continuous in  
all cells and  
platelets**



**Presentation  
of  
extracellular  
antigens by  
MHC II:  
in APCs,  
after  
phagocytosis**

# MHC Restriction

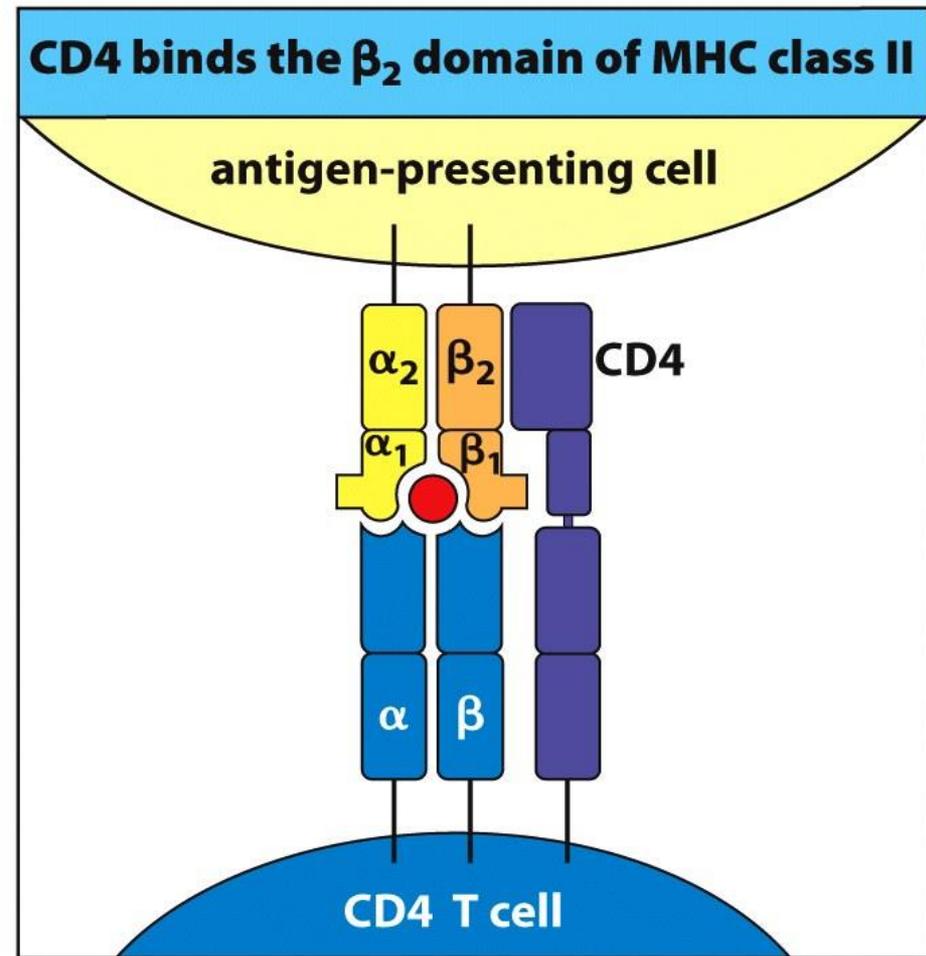
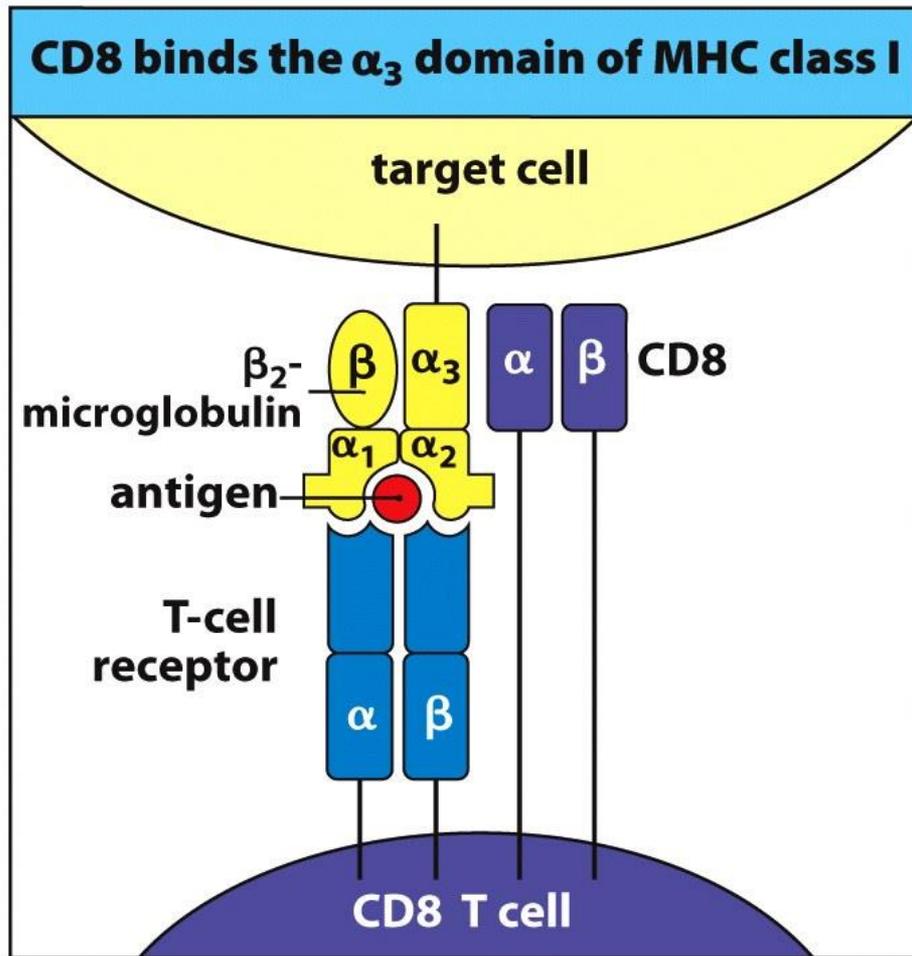


Figure 5.14 The Immune System, 3ed. (© Garland Science 2009)

**MHC I – CD8**

**MHC II – CD4**

# How do pathogens avoid detection?

## MHC-I

*Herpes simplex* – produces a protein which inhibits TAP

*Adenovirus* – produces a protein, which binds to and retains MHC-I in the ER

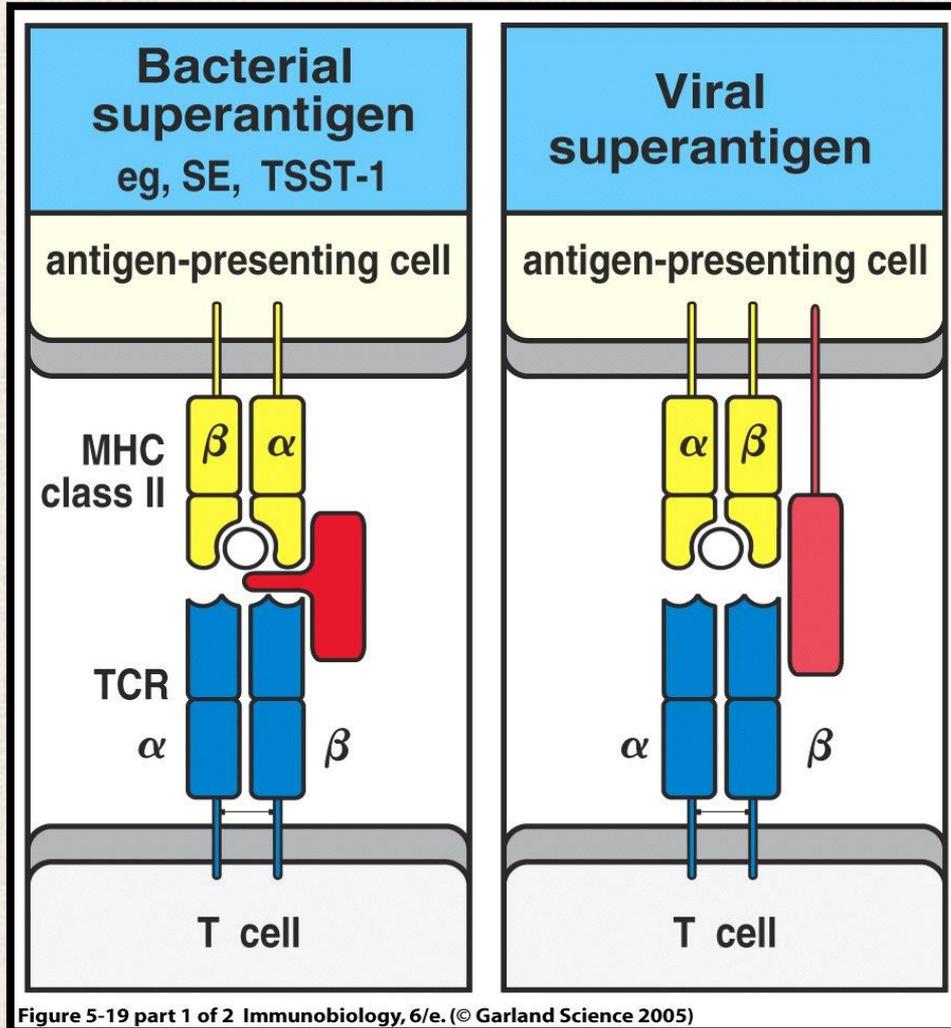
*Cytomegalovirus* – accelerates MHC-I translocation to the cytosol for degradation

*HIV* – accumulate mutations faster than the adaptive immune system can cope with

## MHC-II

*Helicobacter pylori* – encodes a 95kD protein toxin, which increases the pH of the lysosomes, inhibiting protease activity

# Septicemia (toxic shock syndrome) caused by superantigens



Compared to a normal antigen-induced T-cell response the endotoxins (Sags) are capable of activating much higher number of the T-cells in nonspecific manner. This causes a massive immune response with irregular cytokine production (toxic shock syndrome) that is not specific to any epitope on the SAg.

**T cells activated nonspecifically overproduce cytokines resulting systemic toxicity with general catastrophe of bioregulation, („Cytokine tsunami”)**

# Definition of Toxic Shock Syndrome (septicemia, blood-poisoning)

Toxic shock syndrome (septicemia/blood-poisoning) is a life-threatening complication of certain types of bacterial or viral infections. Often toxic shock syndrome results from toxins produced by *Staphylococcus aureus* and *group A Streptococcus* bacteria, or some viral toxins (SARS-CoV-2). First description of toxic shock syndrome has been associated primarily with the use of superabsorbent tampons, but risk factors now include skin wounds and surgery. Physiological T cell activation is antigen-specific and well controlled, however, the T cell activation in toxic shock syndrome is none-specific and irregular. Clinical symptoms caused by irregular and mass production of cytokines („cytokine-tsunami”).

A **toxikus sokk szindróma** (szepszis/vérmérgezés) bakteriális v. vírusfertőzések bizonyos típusainak életveszélyes szövődménye. Gyakran a *Staphylococcus aureus* és a *Streptococcus A* baktériumok által termelt toxinok, vagy egyes vírustoxinok (SARS-CoV-2) okozzák. A toxikus sokk szindróma első leírása elsősorban a szuperabszorbens tamponok használatával volt összefüggésbe hozható, de a kockázati tényezők ma már inkább a bőrsebek és a műtétek. A fiziológiás T-sejtaktiváció antigénspecifikus és jól kontrollált, szemben a toxikus sokk szindrómával, ahol a T-sejtek aktivációja nem-specifikus és rendszertelen. A klinikai tüneteket a citokinek szabálytalan és tömeges termelődése okozza („citokin-cunami”).