Basic Immunology

Lecture *3rd and 4th*

Structure, classes and functioins 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

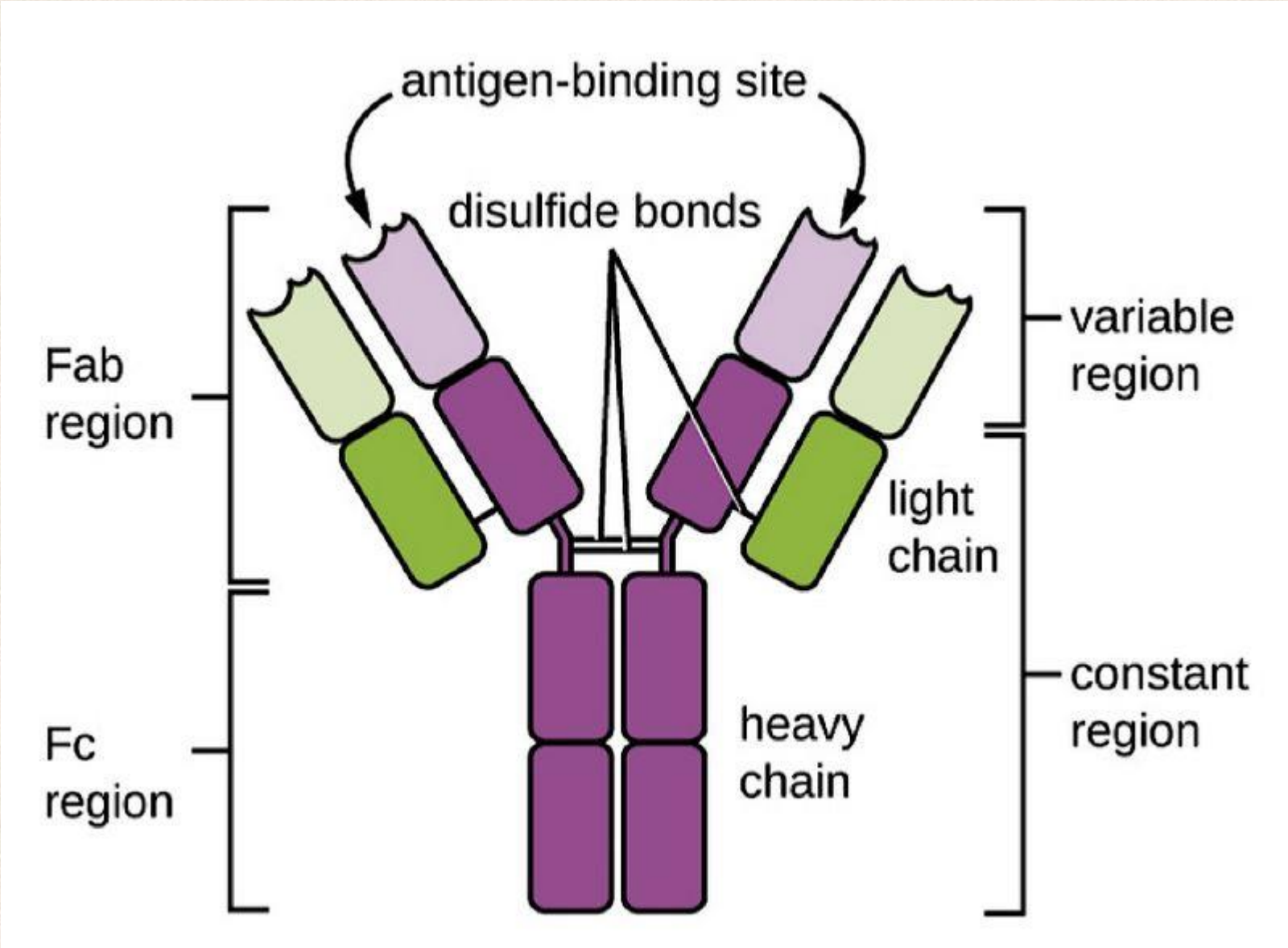
immunogen (fine chemical structure can induce specific immune response)

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

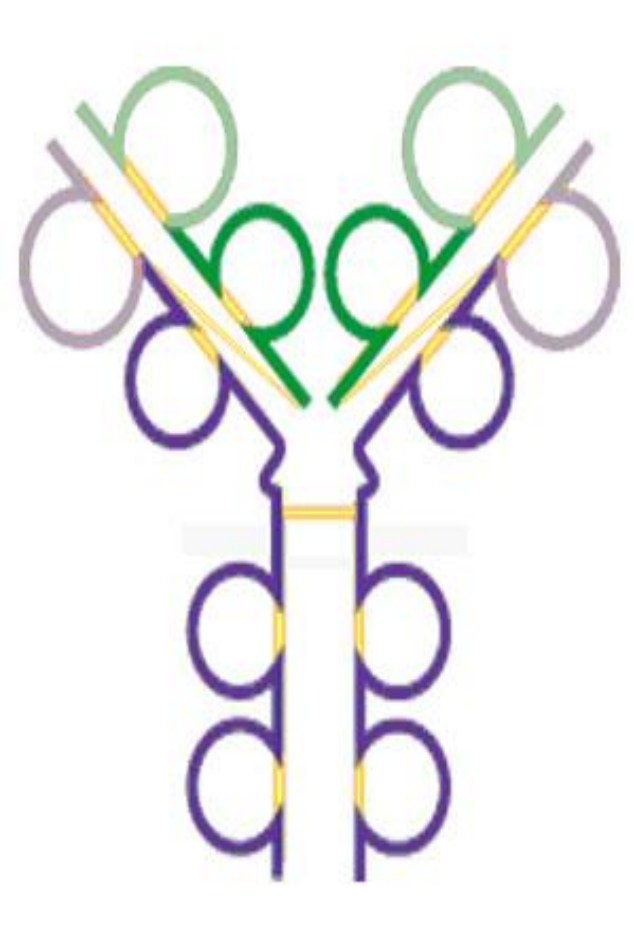
hapten (small molecular weight antigen can not induce immune reaction itself, but specifically recognized by immunoglobulins)

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

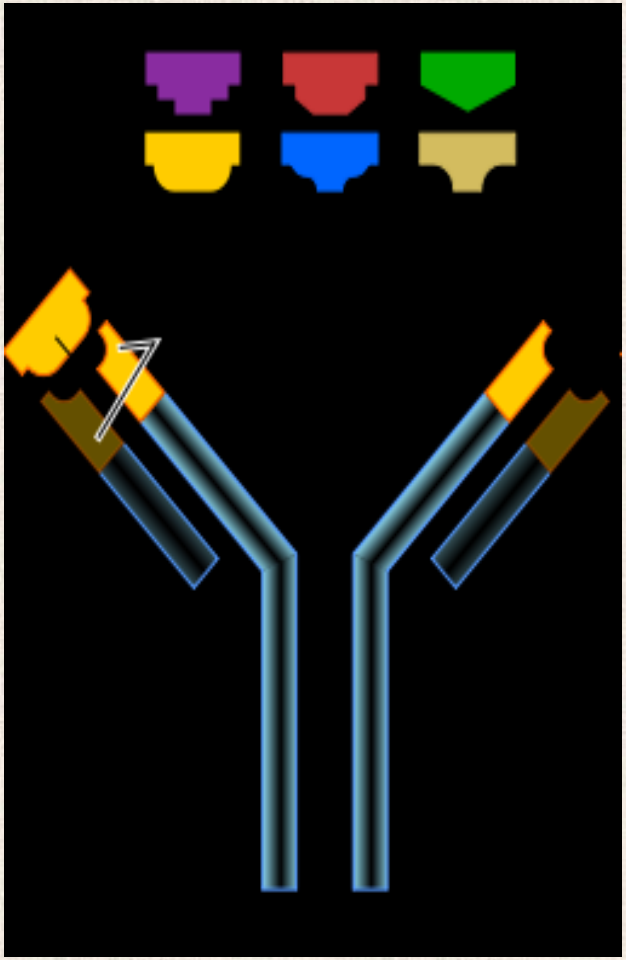
Idiotype

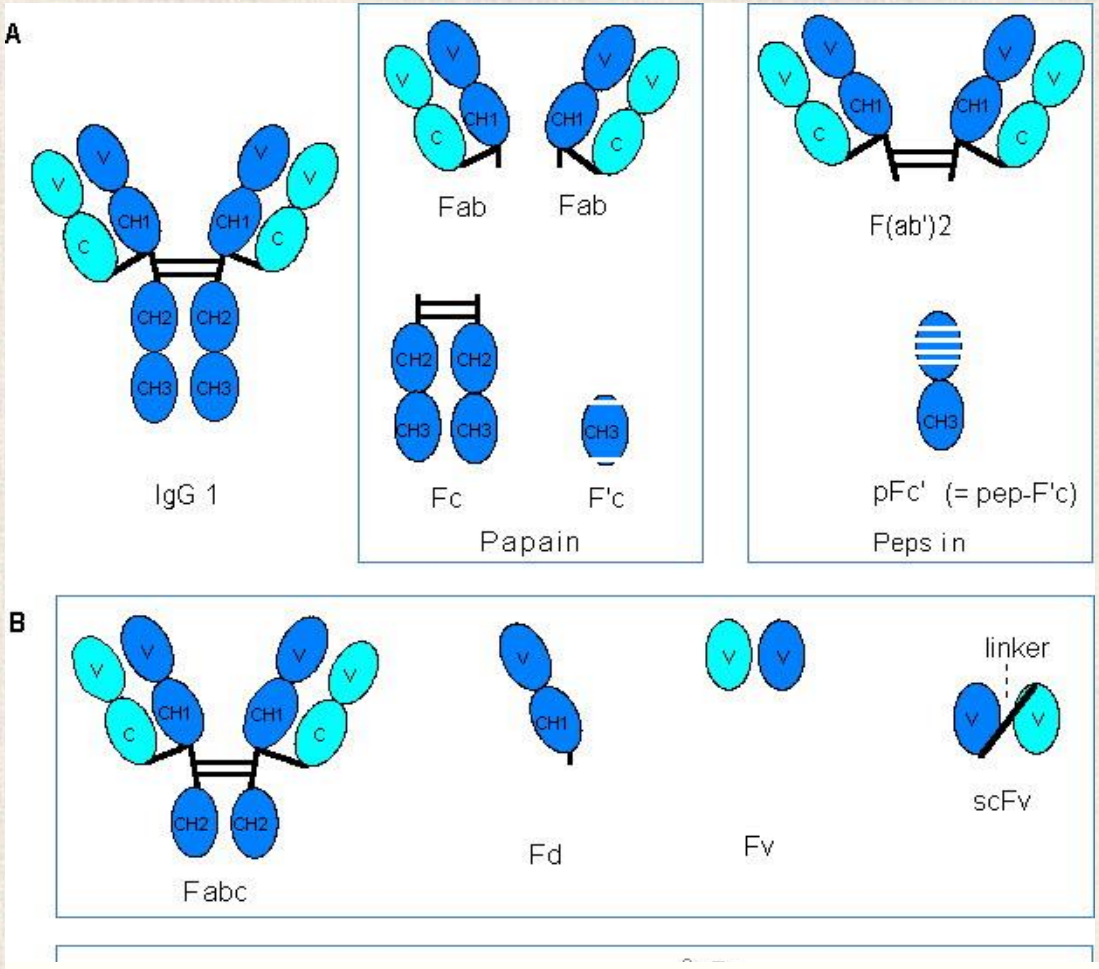
Fab fragment

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.

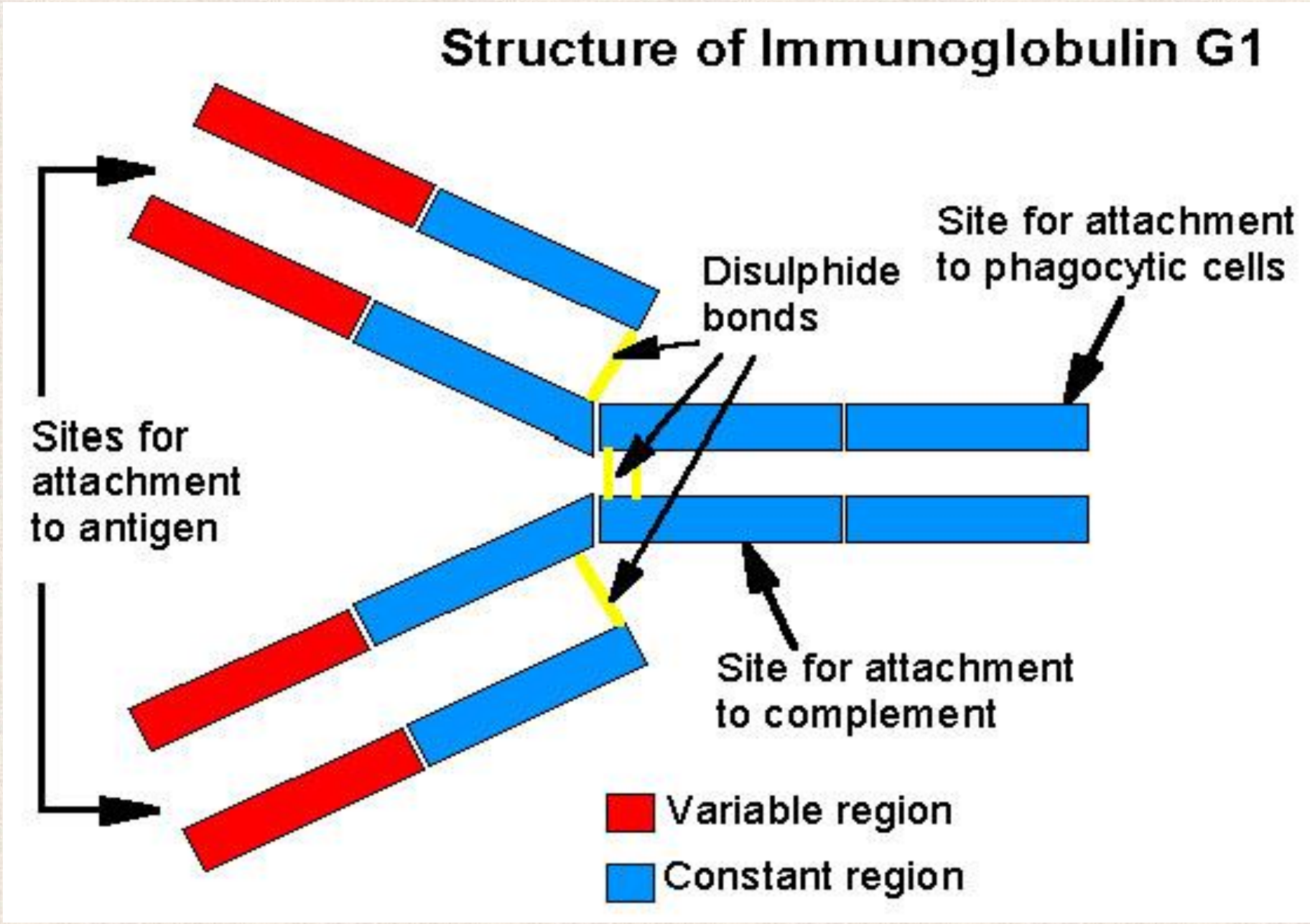
Immunoglobulin isotypes

- 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 **(κ)** and lambda **(λ),** which can associate with all heavy chain isotypes.

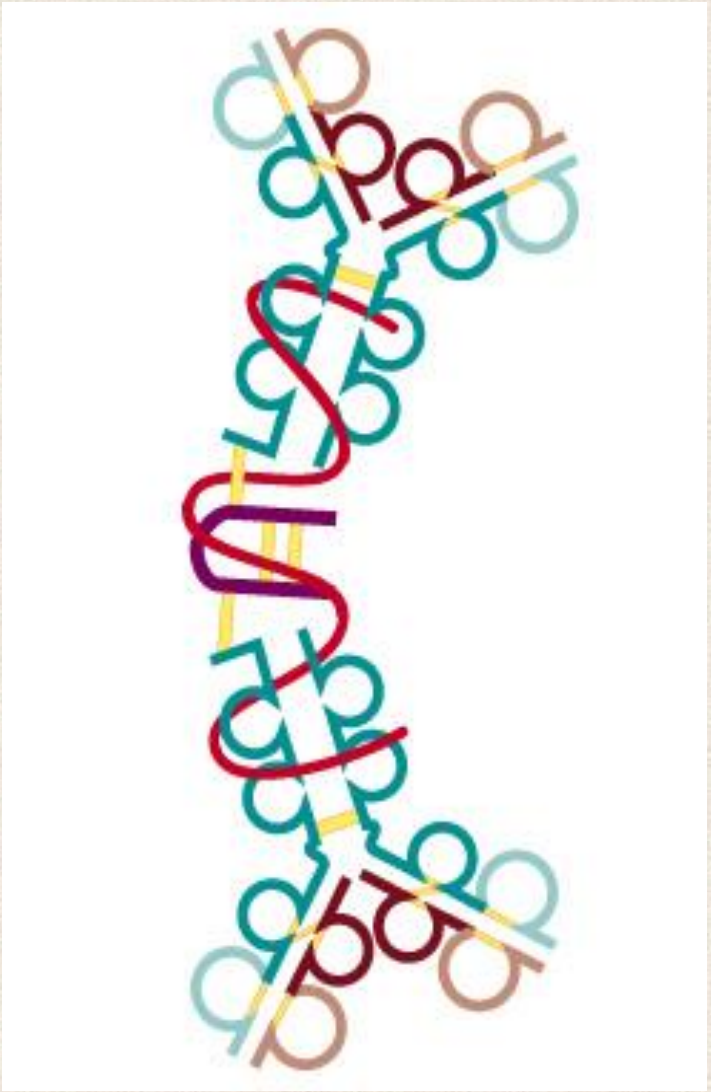
Heavy chain	Light chain	Immuno-globulin Class	Immuno-globulin Subclass
γ1	κ or λ	IgG	IgG1
γ2	κ or λ		IgG2
γ3	κ or λ		IgG3
γ4	κ or λ		IgG4
α1	κ or λ	IgA	IgA1
α2	κ or λ		IgA2
μ	κ or λ	IgM	
δ	κ or λ	IgD	
ε	κ or λ	IgE	

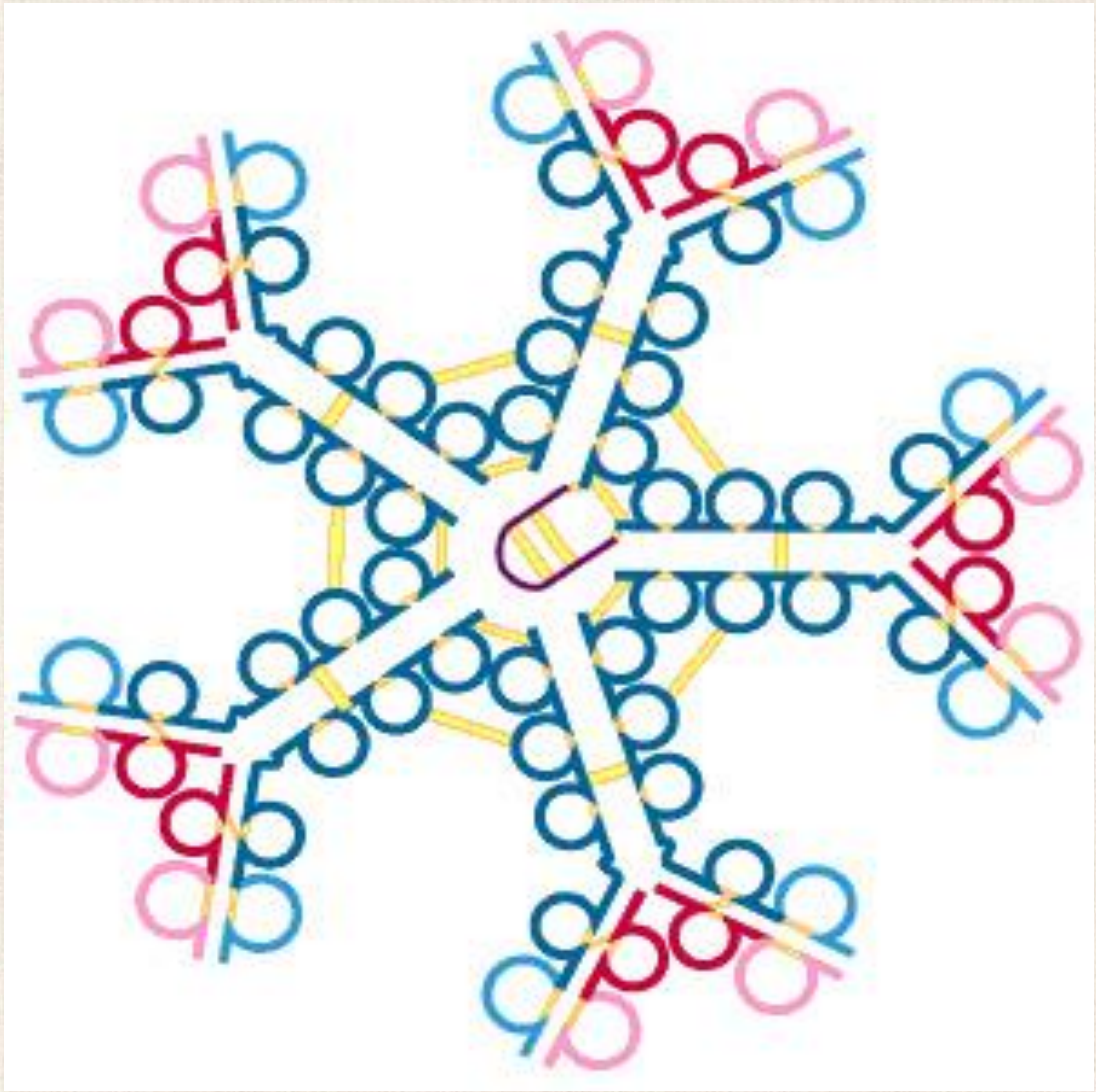
Pronunciation of Greek letters:

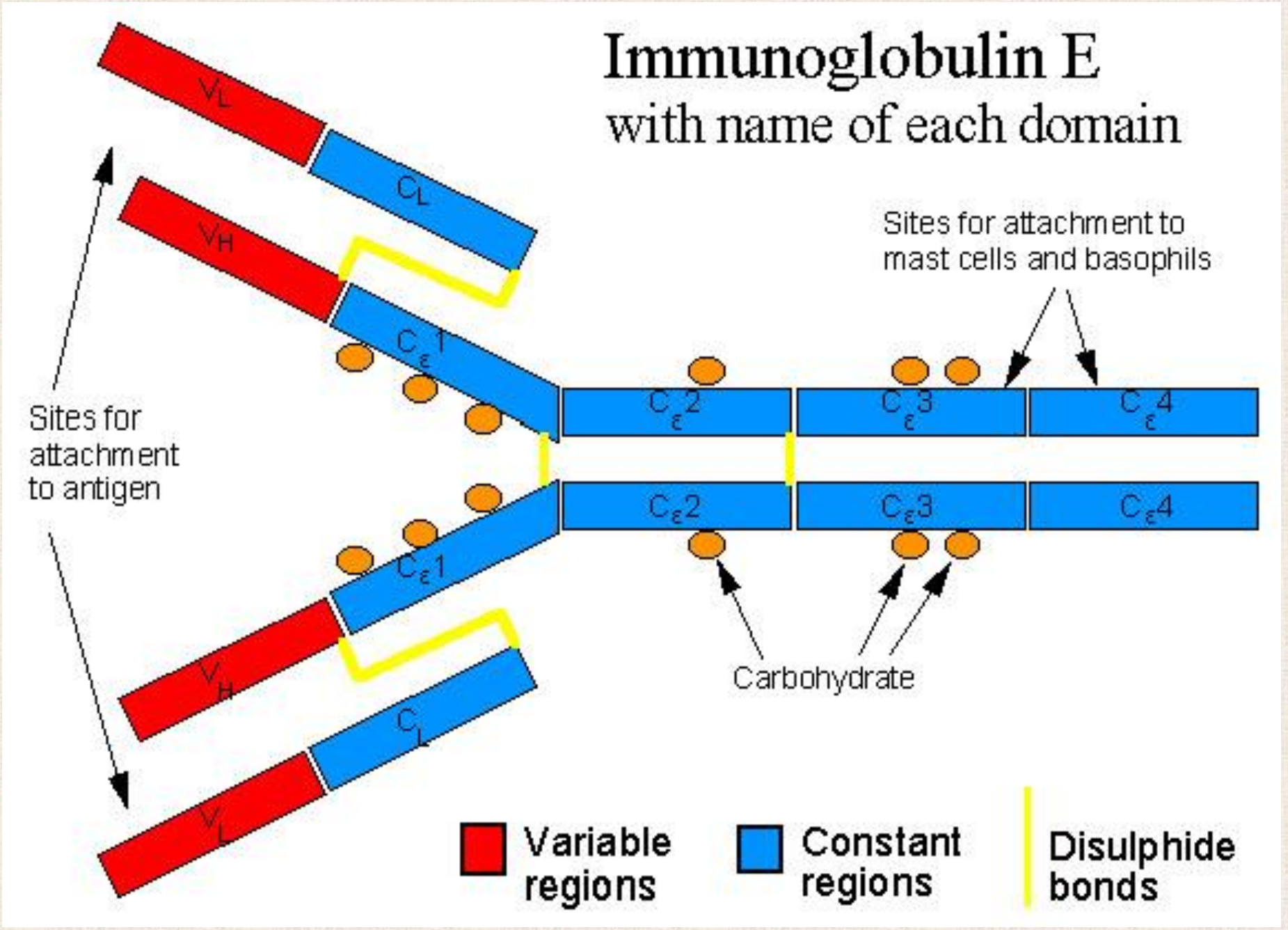
γ	gamma	α	alpha	μ	mu	δ	delta
ε	epsilon	κ	kappa	λ	lambda		

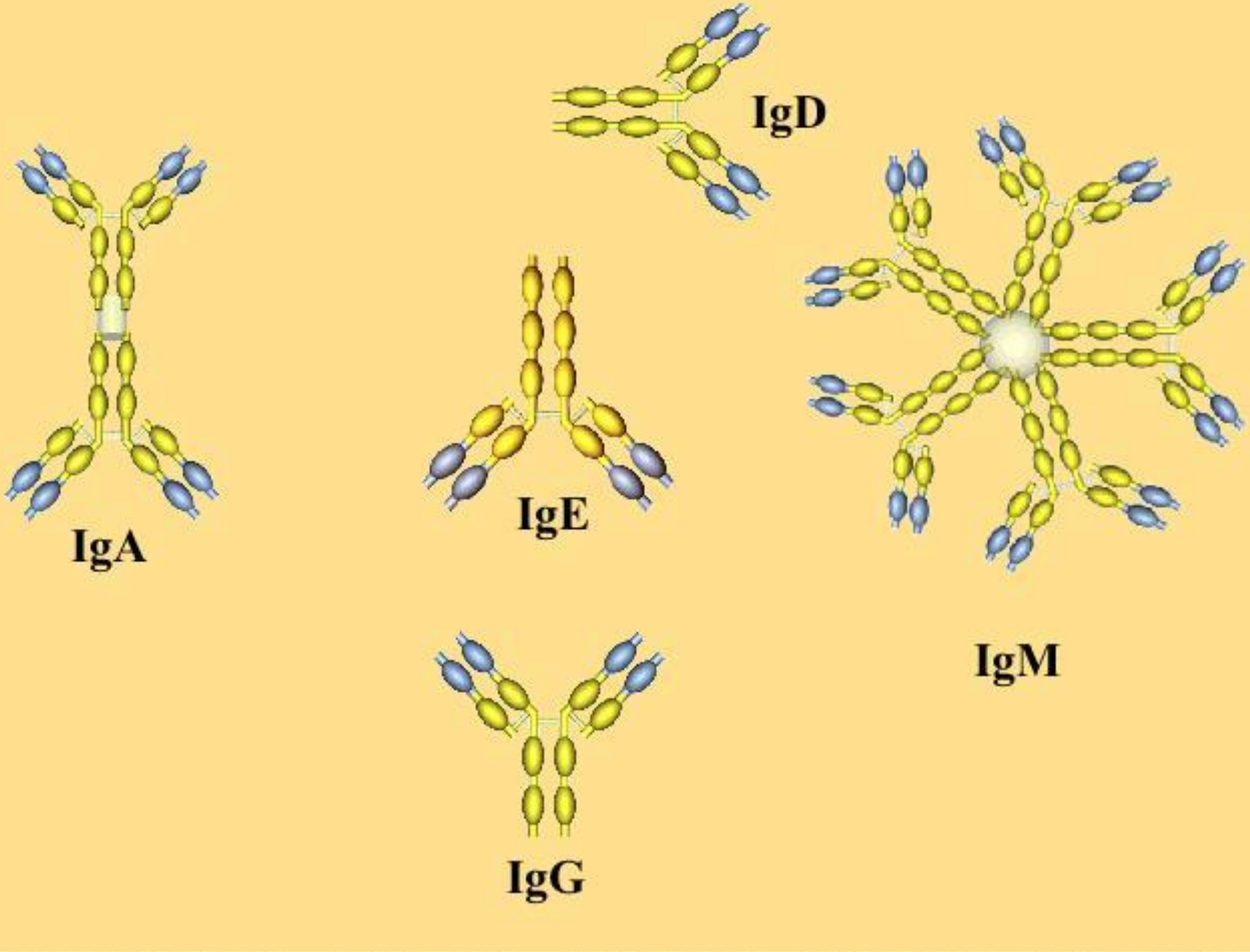

Structure of Immunoglobulin G1
Site for attachment to phagocytic cells
Disulphide bonds
Sites for attachment to antigen
Site for attachment to complement
Variable region
Constant region

IgA and IgM

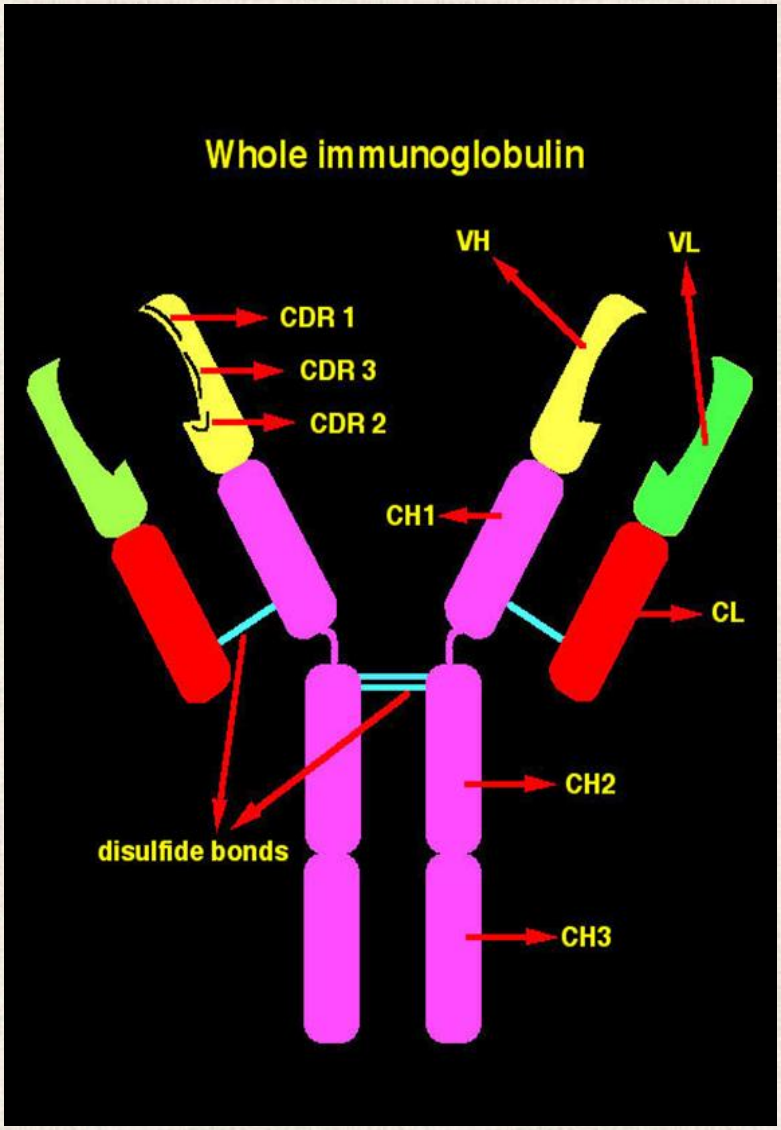





Immunoglobulin E
with name of each domain
V_L
C_L
V_H
$C_\varepsilon 1$
$C_\varepsilon 2$
$C_\varepsilon 3$
$C_\varepsilon 4$
Sites for attachment to mast cells and basophils
Sites for attachment to antigen
Carbohydrate
Variable regions
Constant regions
Disulphide bonds


IgD
IgA
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

Gene rearrangement

Somatic hypermutations

Hírvivő RNS

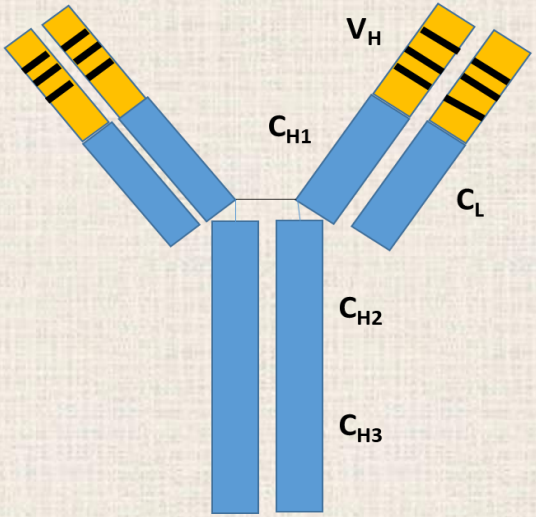
Messenger RNA

Immunglobulin fehérje

Immunoglobulin protein

Antigén kötőhely

Antigen bindingsite



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

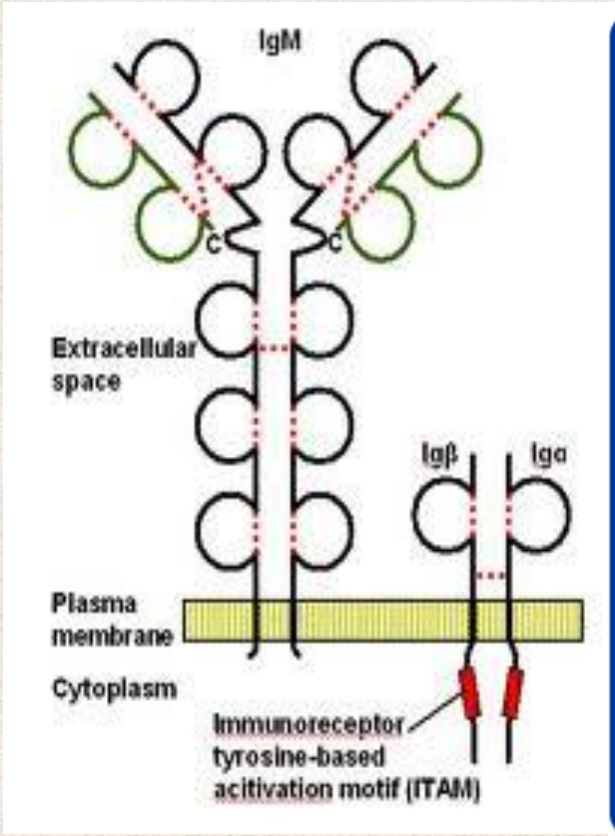
IgE – blood, in perifery can bound to basophiles and mast cells (Mw 190 kD) plays role in defence agains parasites and initiation allergic reactions

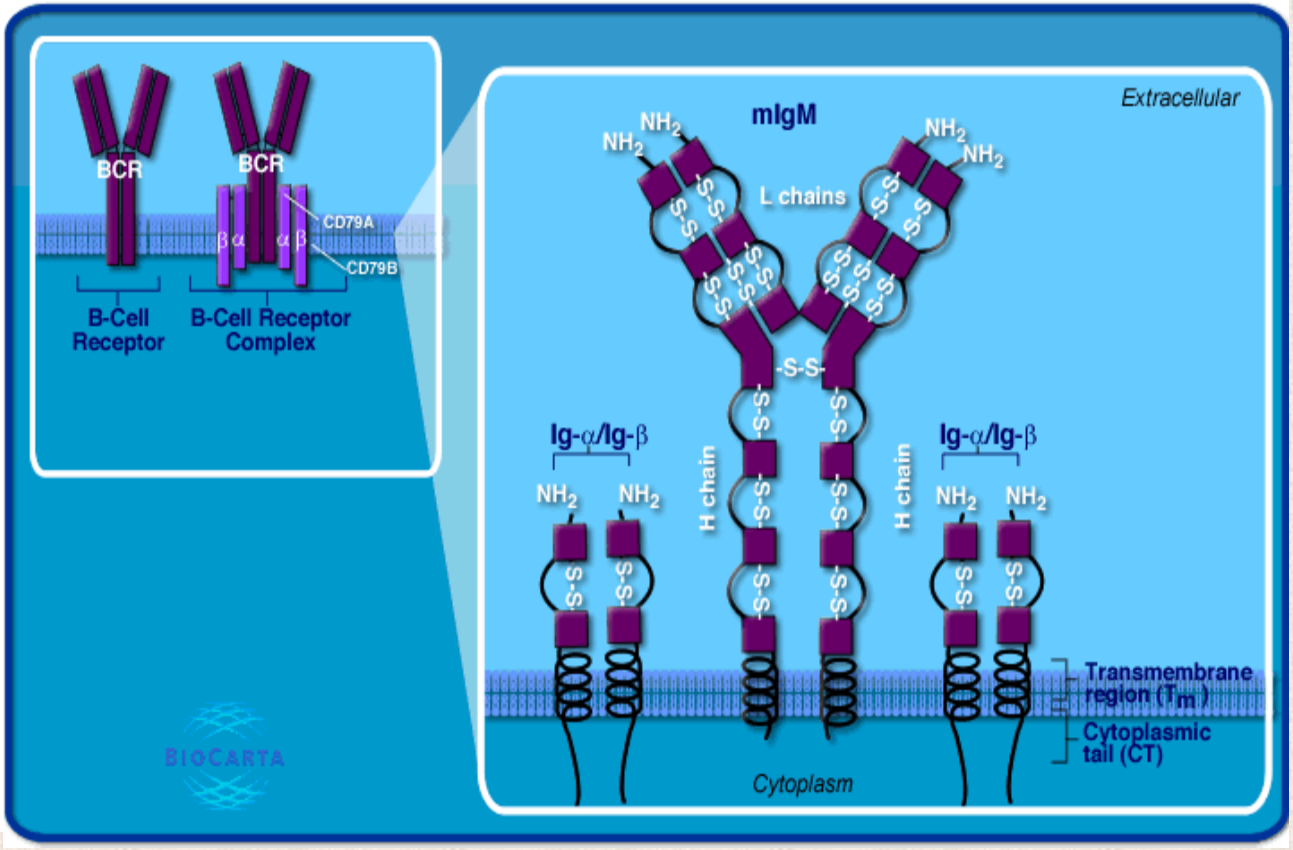
IgG - vér, nyirok, az Ig 80%-át teszik ki. Az egyetlen anyai eredetű Ig, amely áthalad a placenta falán. (Mw 150 kD) Semlegesítik a toxinokat és vírusokat.
IgM - vér, nyirok (sejtfelszíni), pentamer szerkezetű (Mw 900 kD), az első antitestek a fertőzésre adott kezdeti válaszban.
IgA - Nyálkahártya felületek, 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

B cell Receptor (BcR) Complex





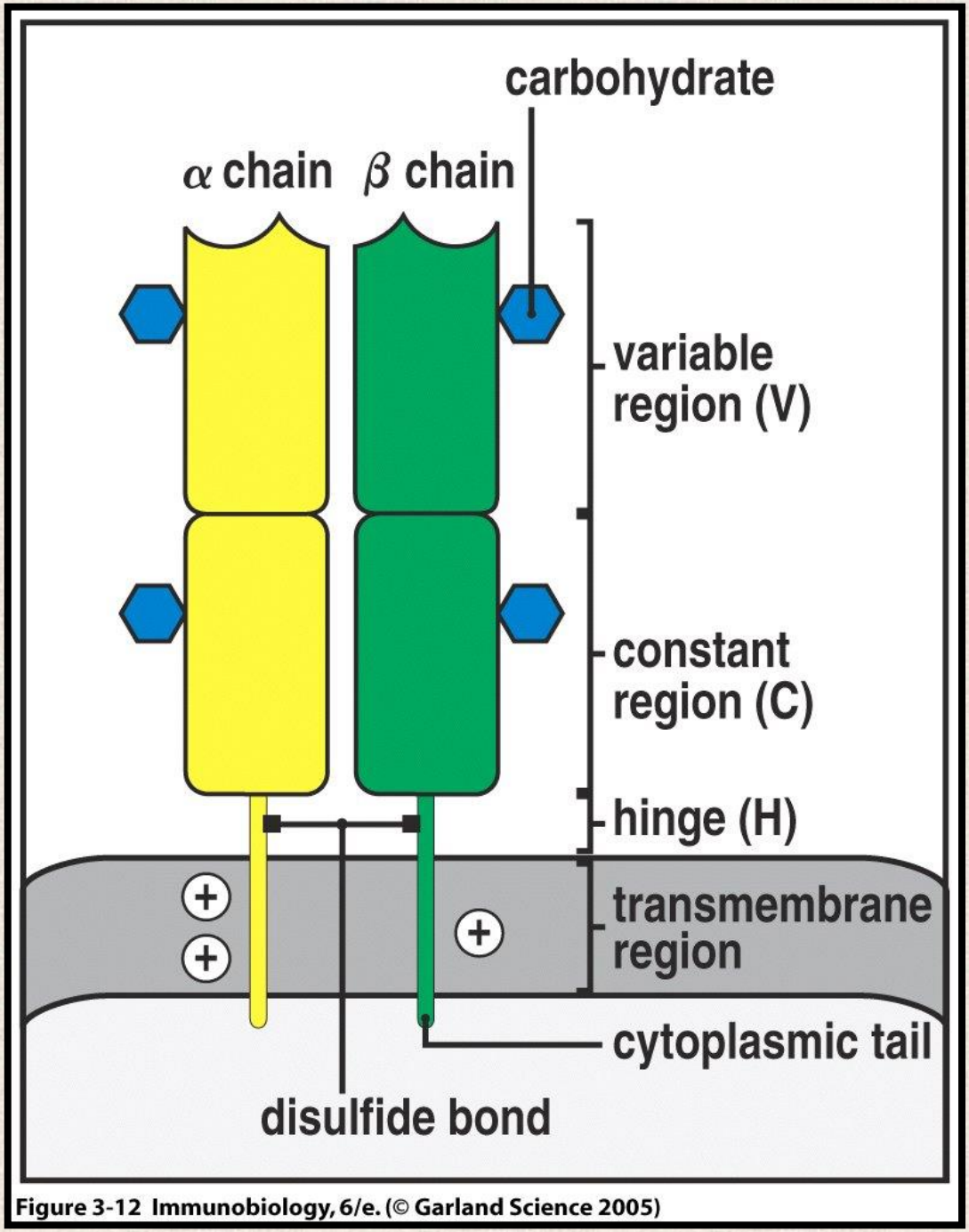


Figure 3-12 Immunobiology, 6/e. (© Garland Science 2005)

T Cell receptor

T Cell Receptor complex

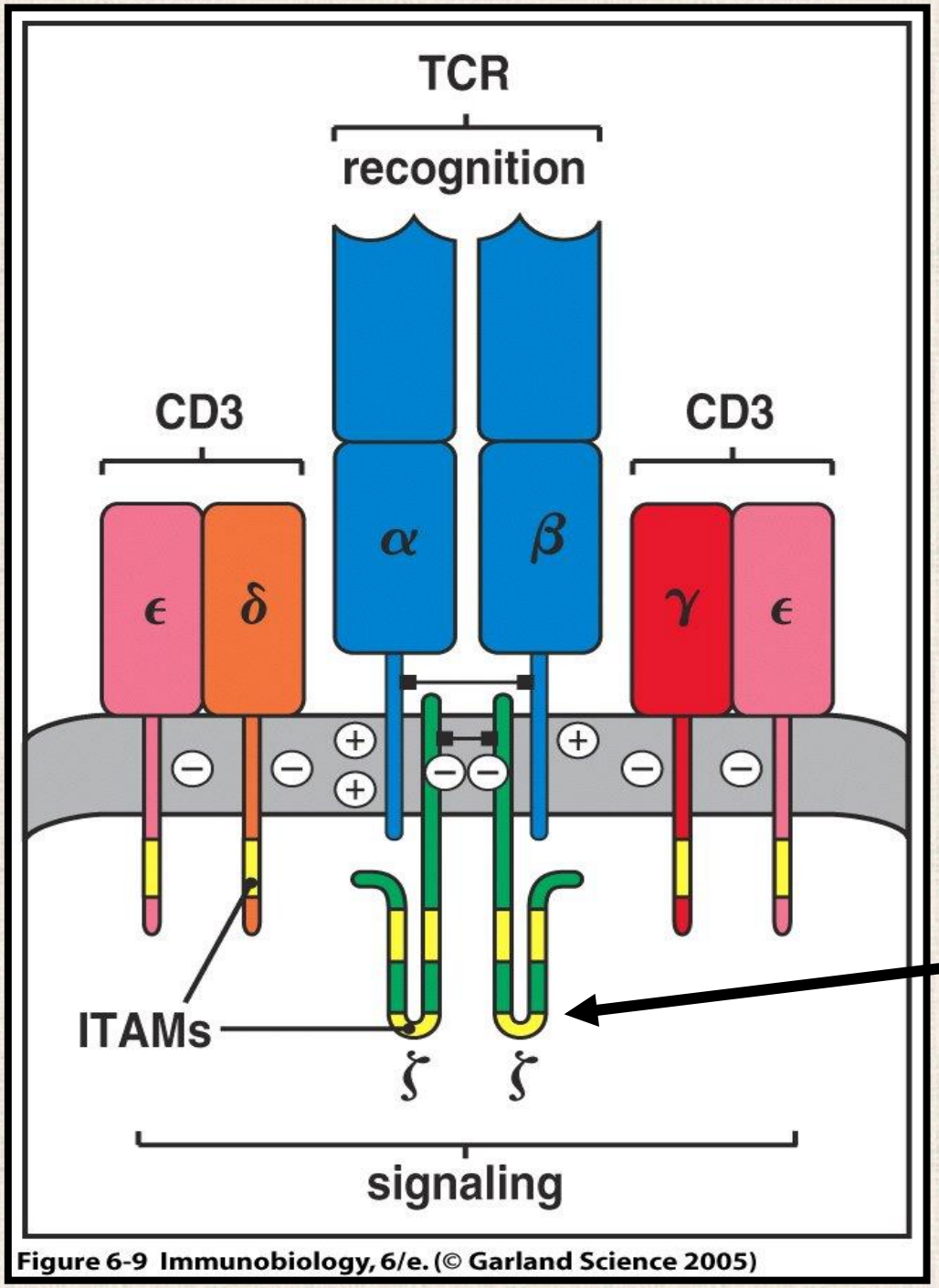


Figure 6-9 Immunobiology, 6/e. (© Garland Science 2005)

ITAMs
Immunoreceptor
Tyrosine-based
Activation
Motifs

Antigen Recognition by T Cells

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

Main T cell types:

-CD8+ (cytotoxic) T-cells

MHC Class I - peptide complex

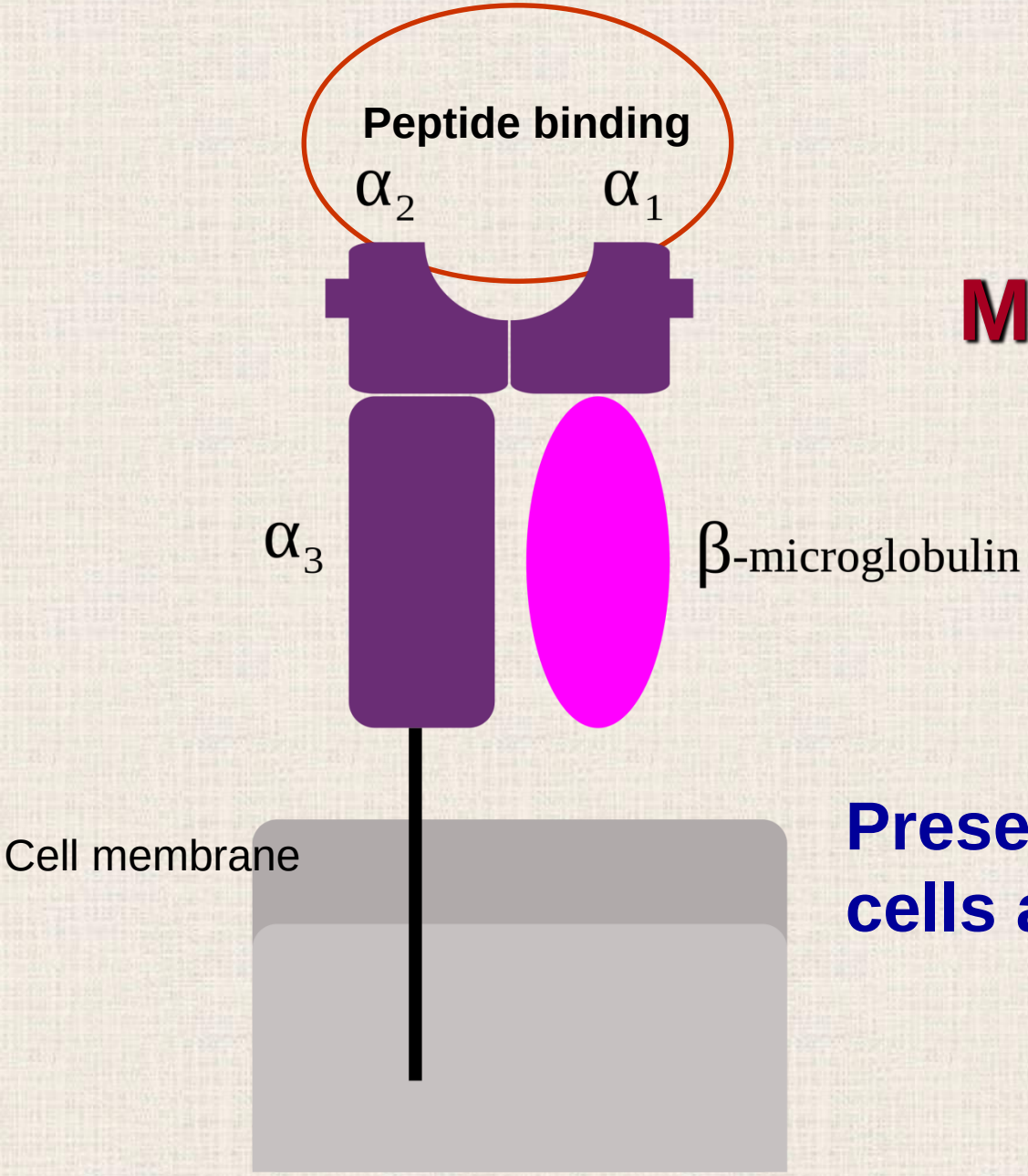
-CD4+ (helper) T-cells

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 Major Histocompatibility Complex (MHC). The antigen binding glycoproteins are called MHC molecules/antigens. (MHC vs. HLA, H2, BoLA, ChLA etc.)

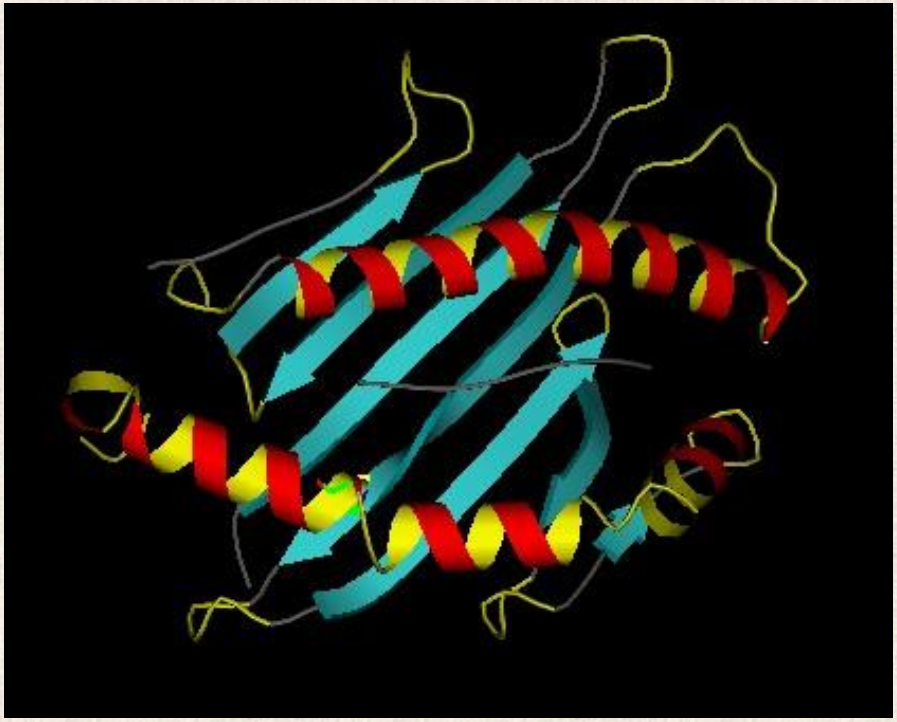
Inbred strains of mice

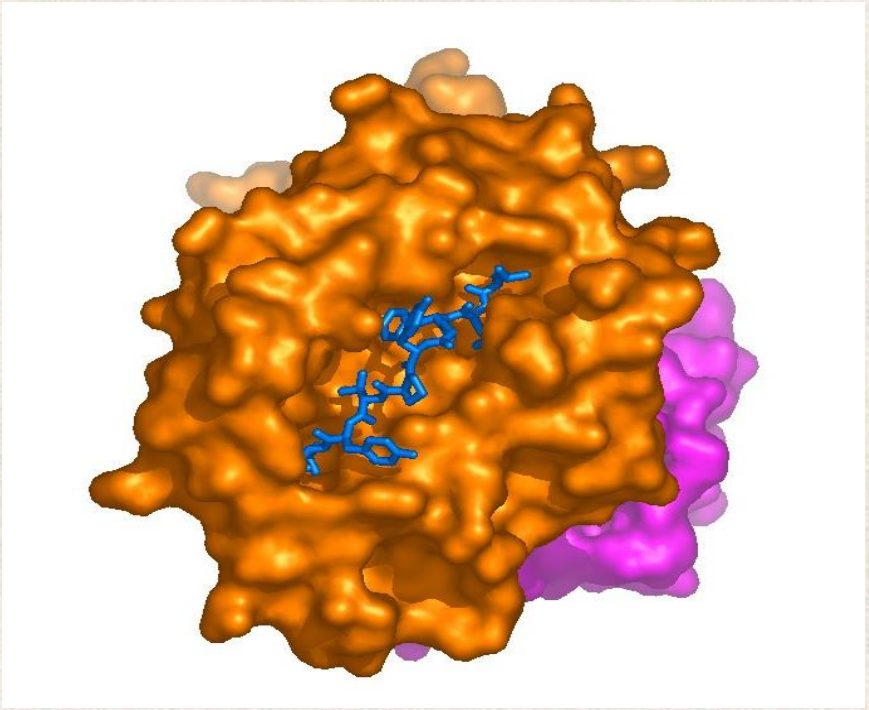


MHC Class I

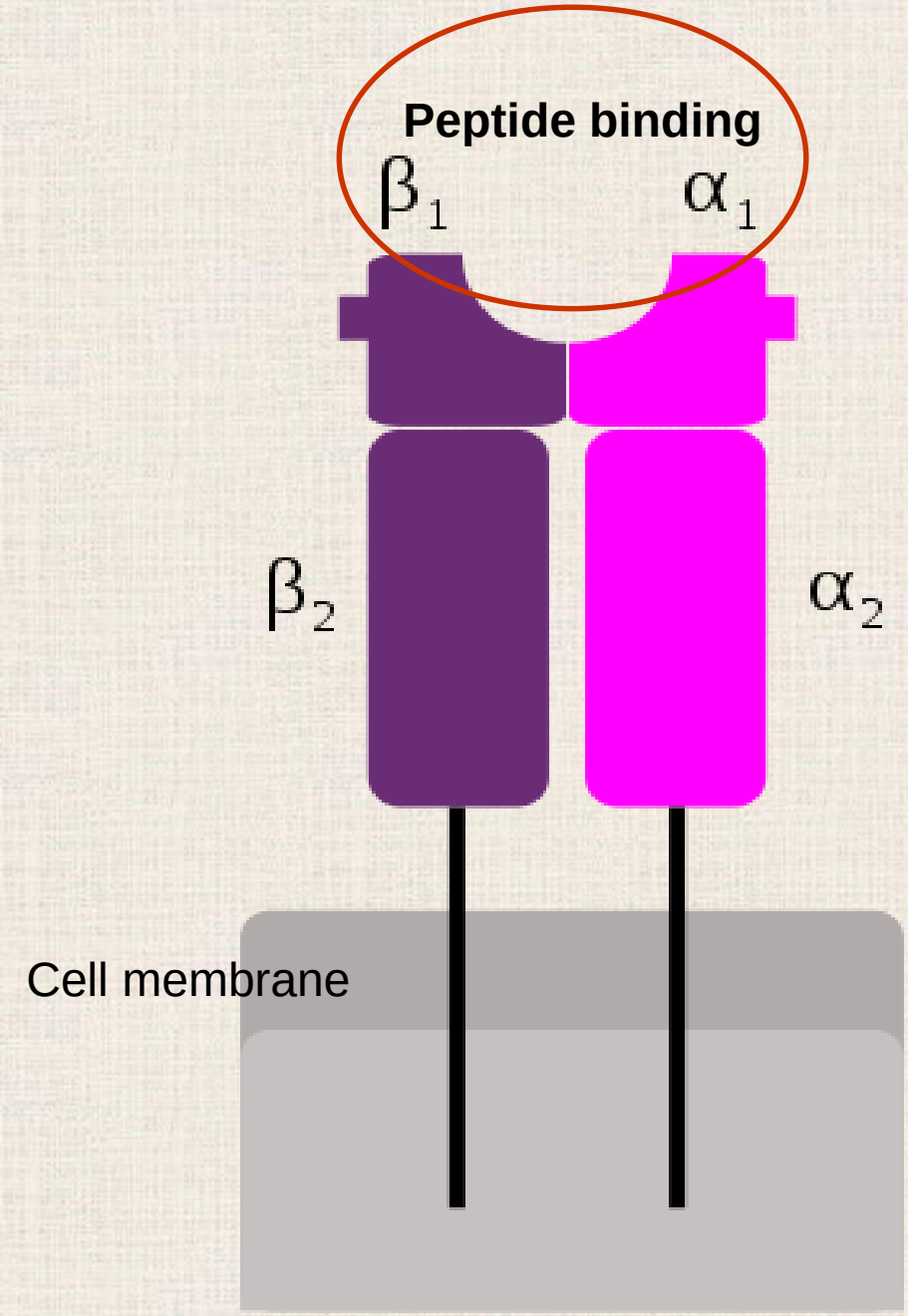
Present in all nucleated cells and platelets

Antigen binding site of MHC class I





MHC Class II

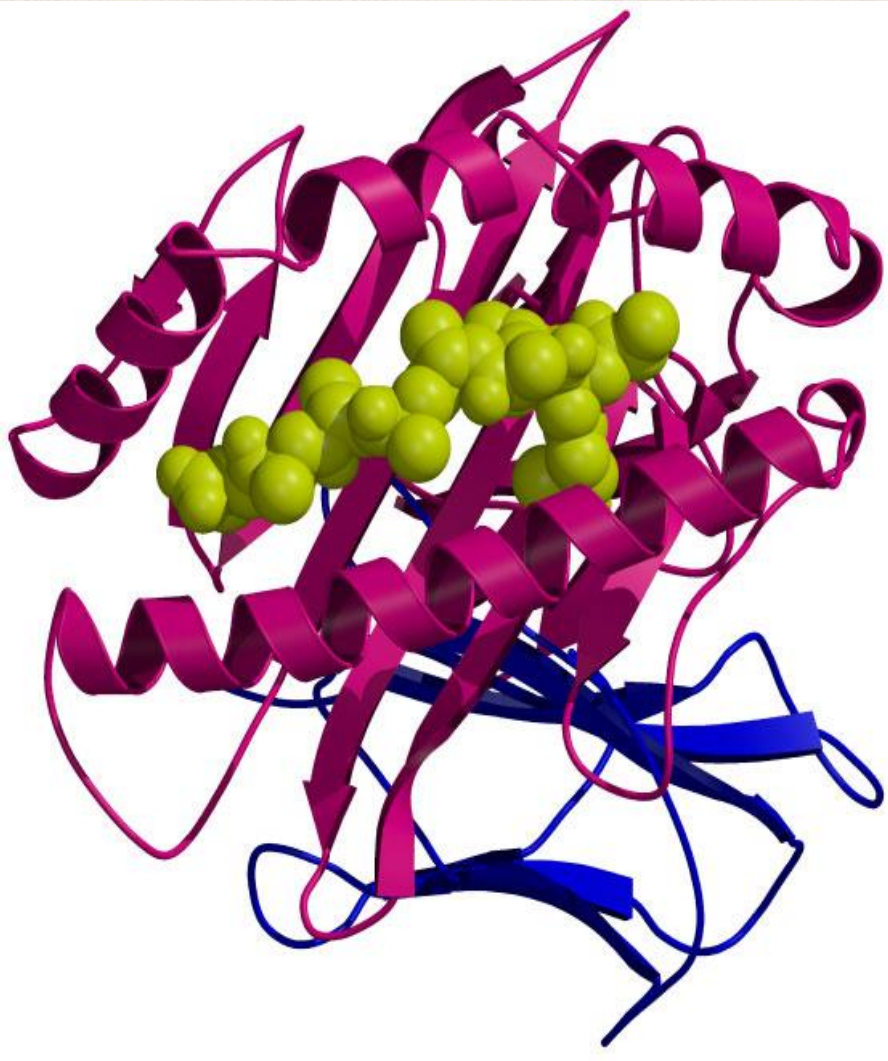


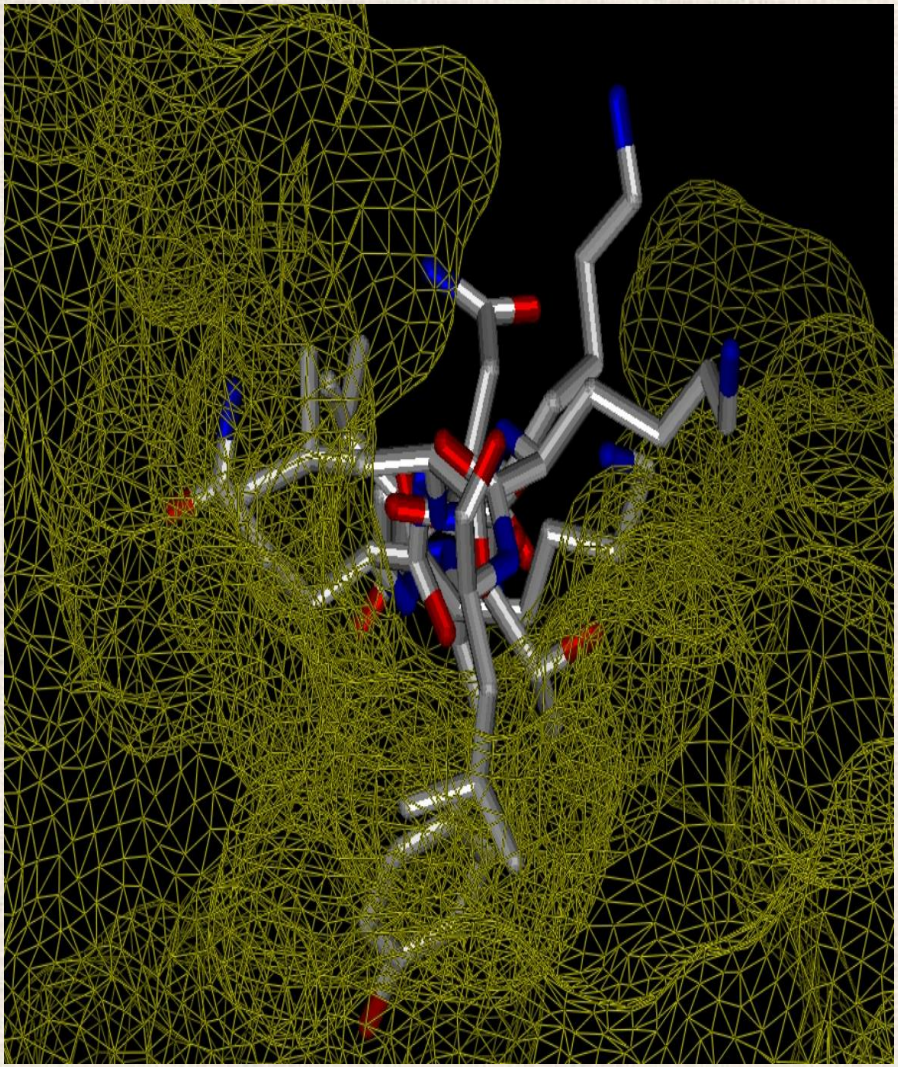
Present in professional or facultative antigen presenting cells (APC)

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

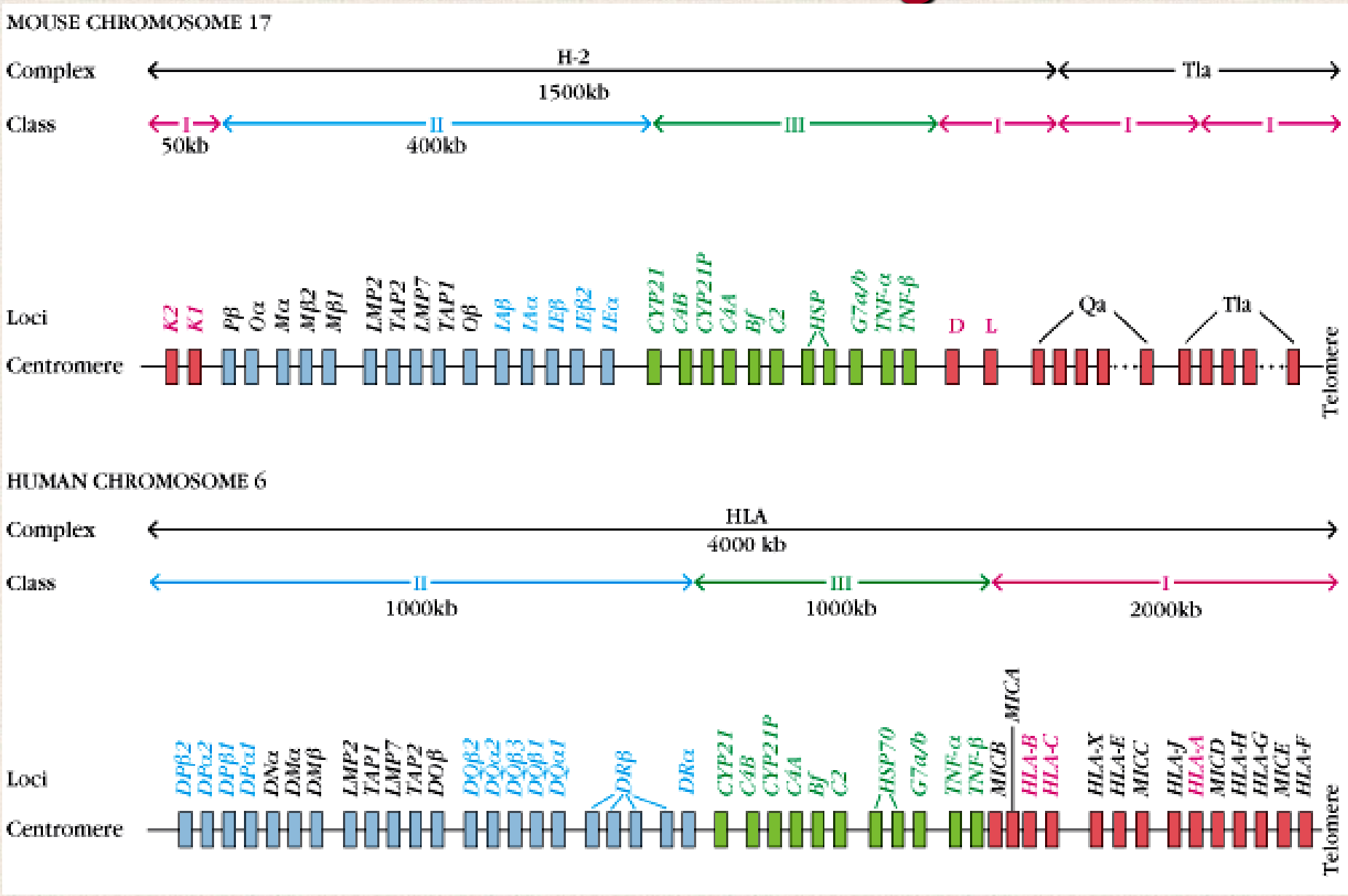
Facultative antigen presenting cells: inflammatory epithel and endothel in pathologic conditions

Antigen binding site of MHC class II

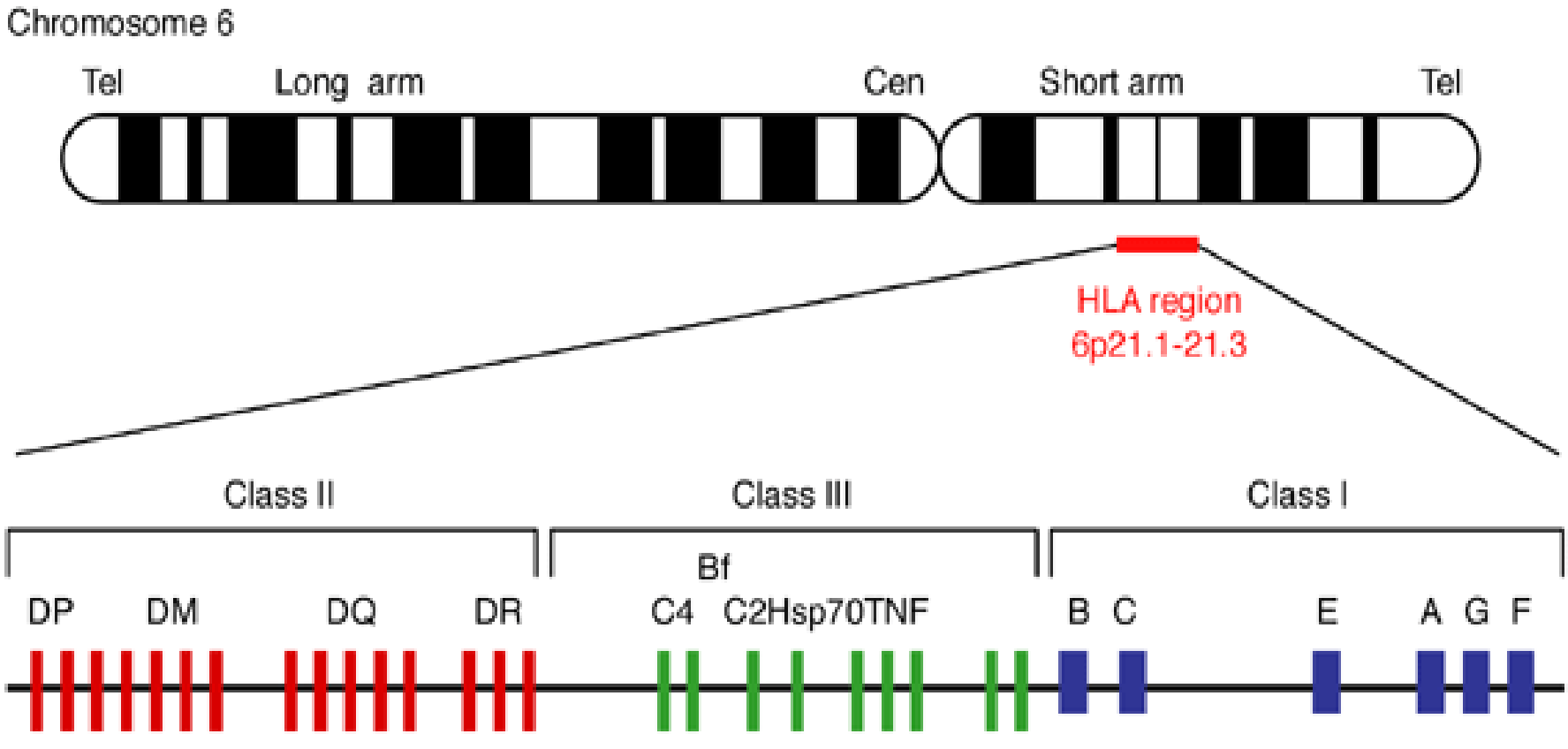




Structure of MHC genes



HLA map



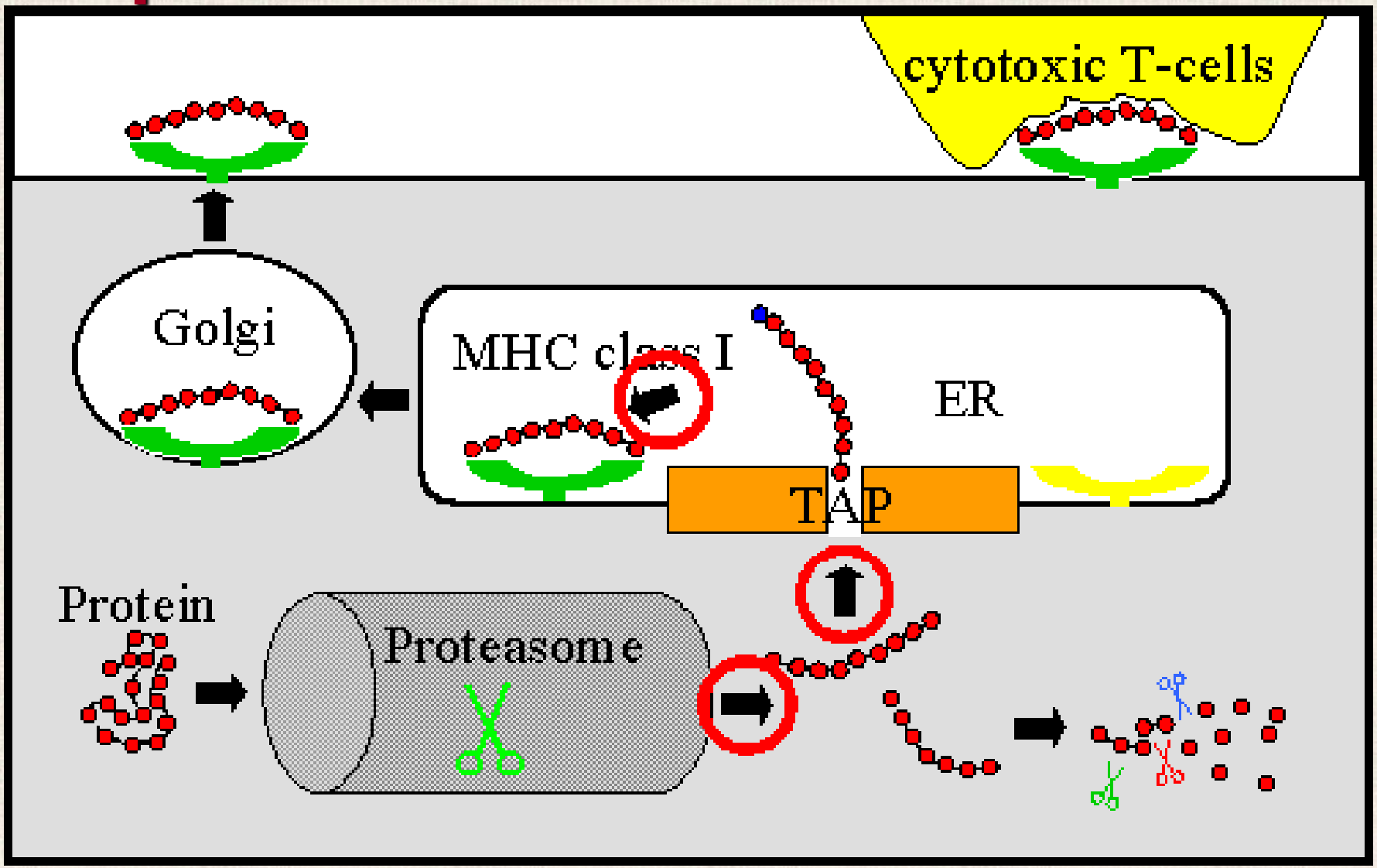
Gene map of the human leukocyte antigen (HLA) region

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.

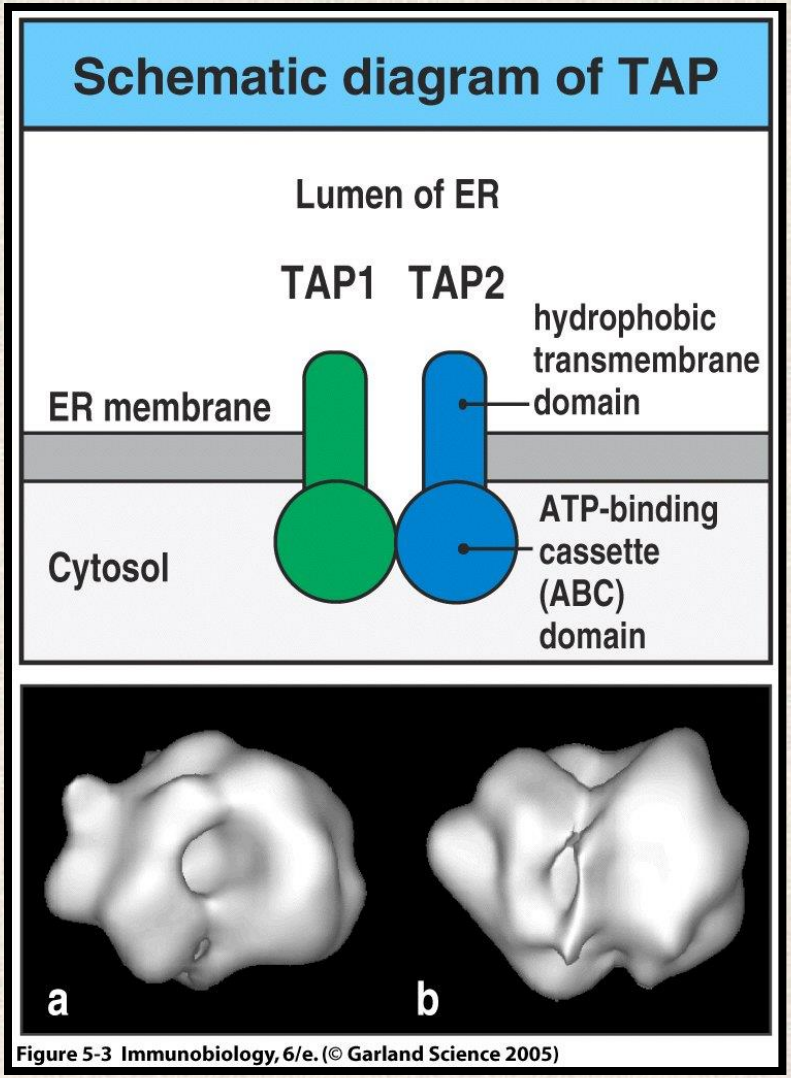
In human there are three classical class I molecules (**HLA-A, B, C**) and three classical class II molecules (**HLA-DR, DP, DQ**). The HLA-A has more than 20, B has more 50, and C more than 10 alleles. HLA-DR has 20, HLA-DQ has 9, and HLA-DP has 6 alleles.

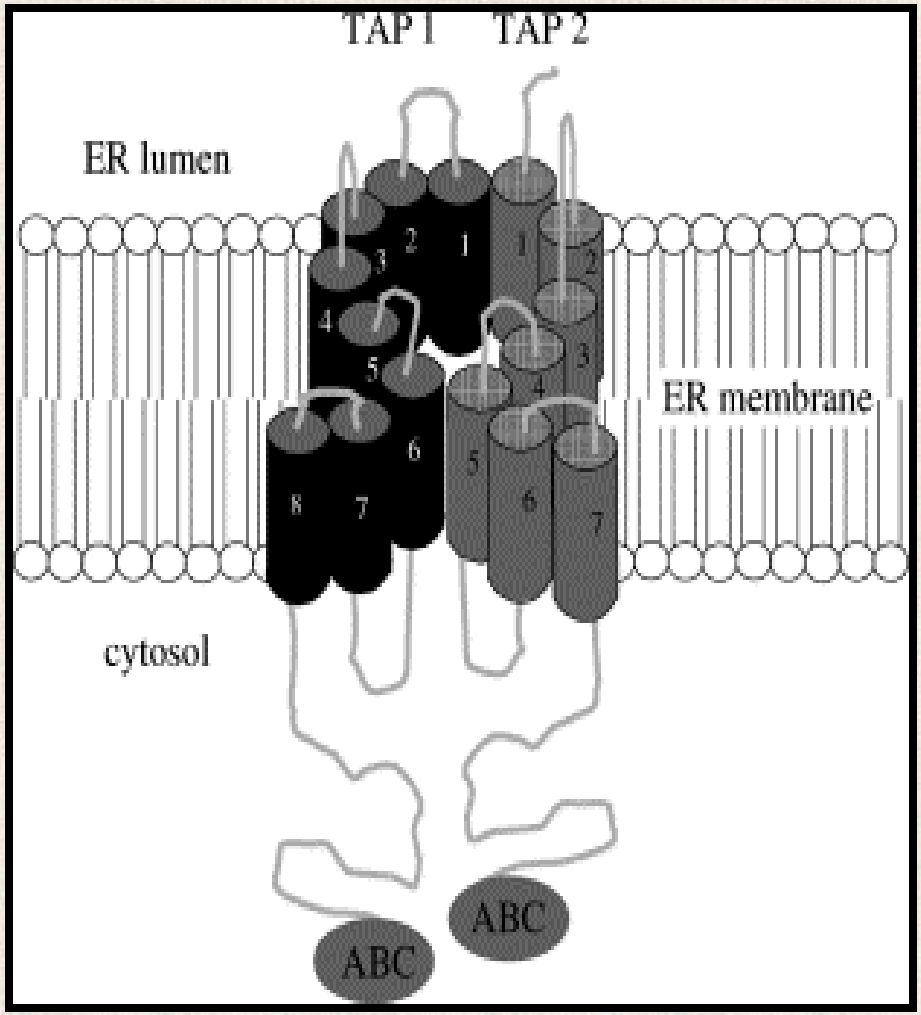
Az MHC poligénes (több különböző I. és II. osztályú gén létezik, amelyek különböző specifitású fehérjéket kódolnak) és erősen polimorf (minden génnek több allélja van), így a legtöbb egyén valószínűleg heterozigóta az egyes lókuszokon. Az allélok mindkét szülői MHC-haplotípusból kifejeződnek egy egyénben (ko-domináns), és az összes allél termékei megtalálhatók az összes expresszáló 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-DQ 9, a HLA-DP pedig 6 alléllal rendelkezik.

Antigen processing and presentation on MHC Class I



Transporter Associated with Antigen Processing





Molecular Immunol. 2002

Chaperons in the MHC Class I antigen presentation

Calnexin, calreticulin, Erp57, tapasin

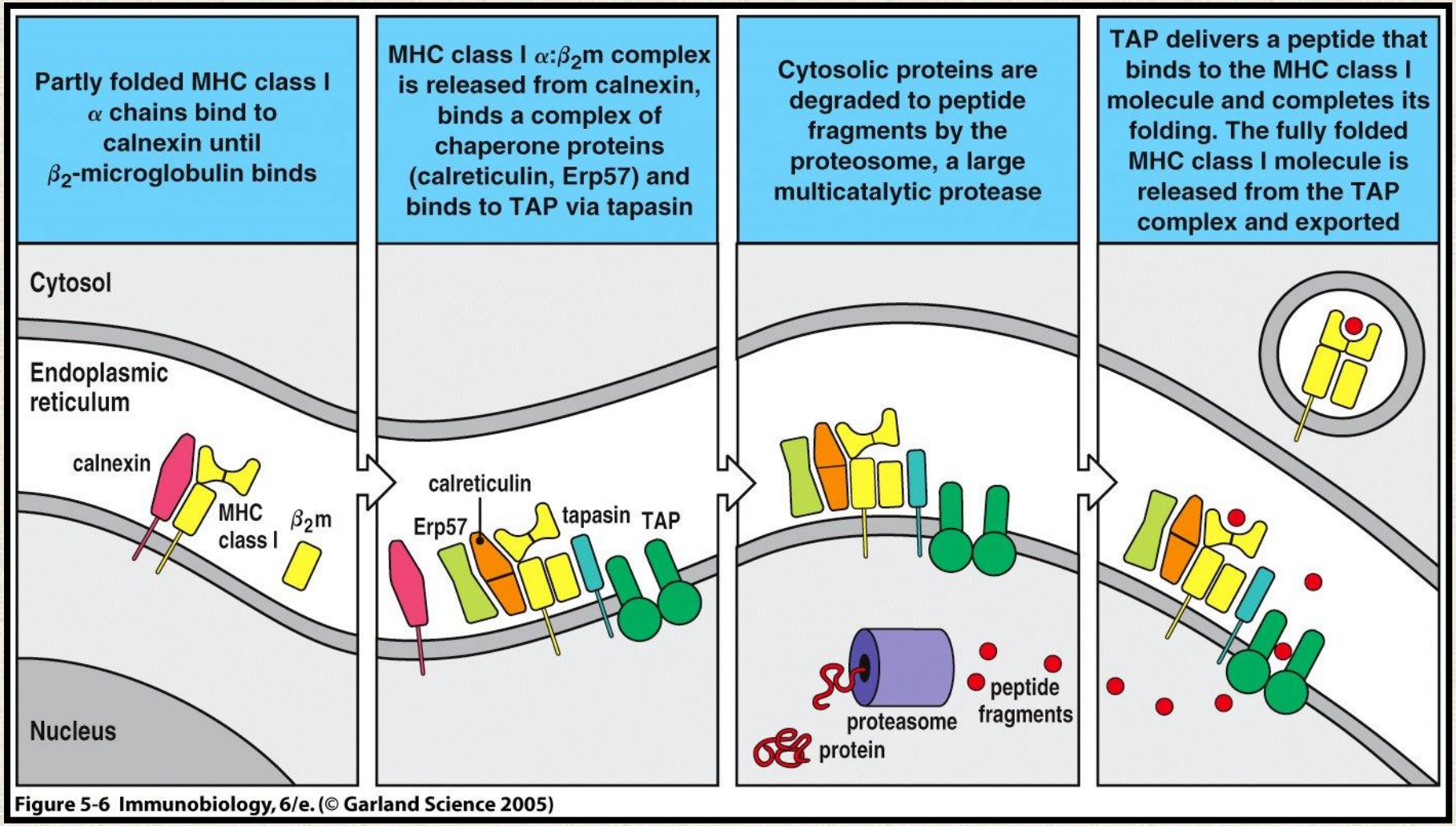


Figure 5-6 Immunobiology, 6/e. (© Garland Science 2005)

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

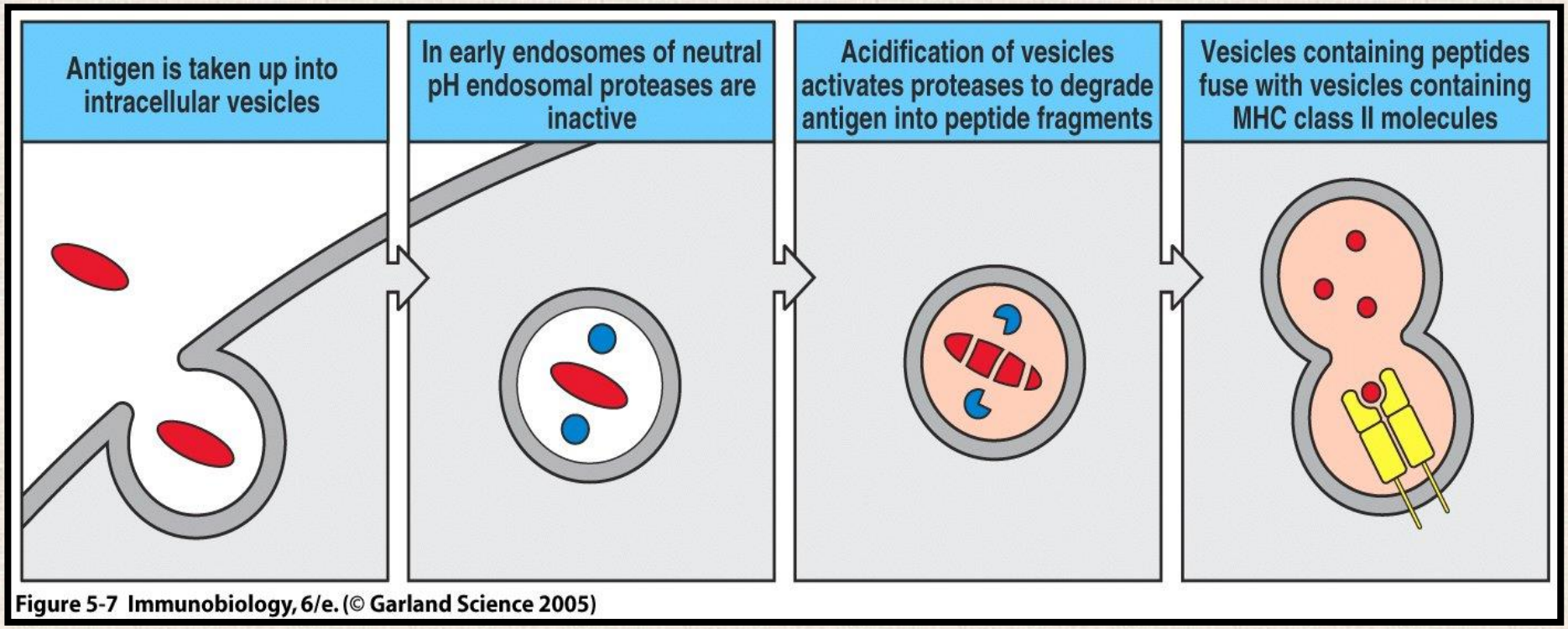
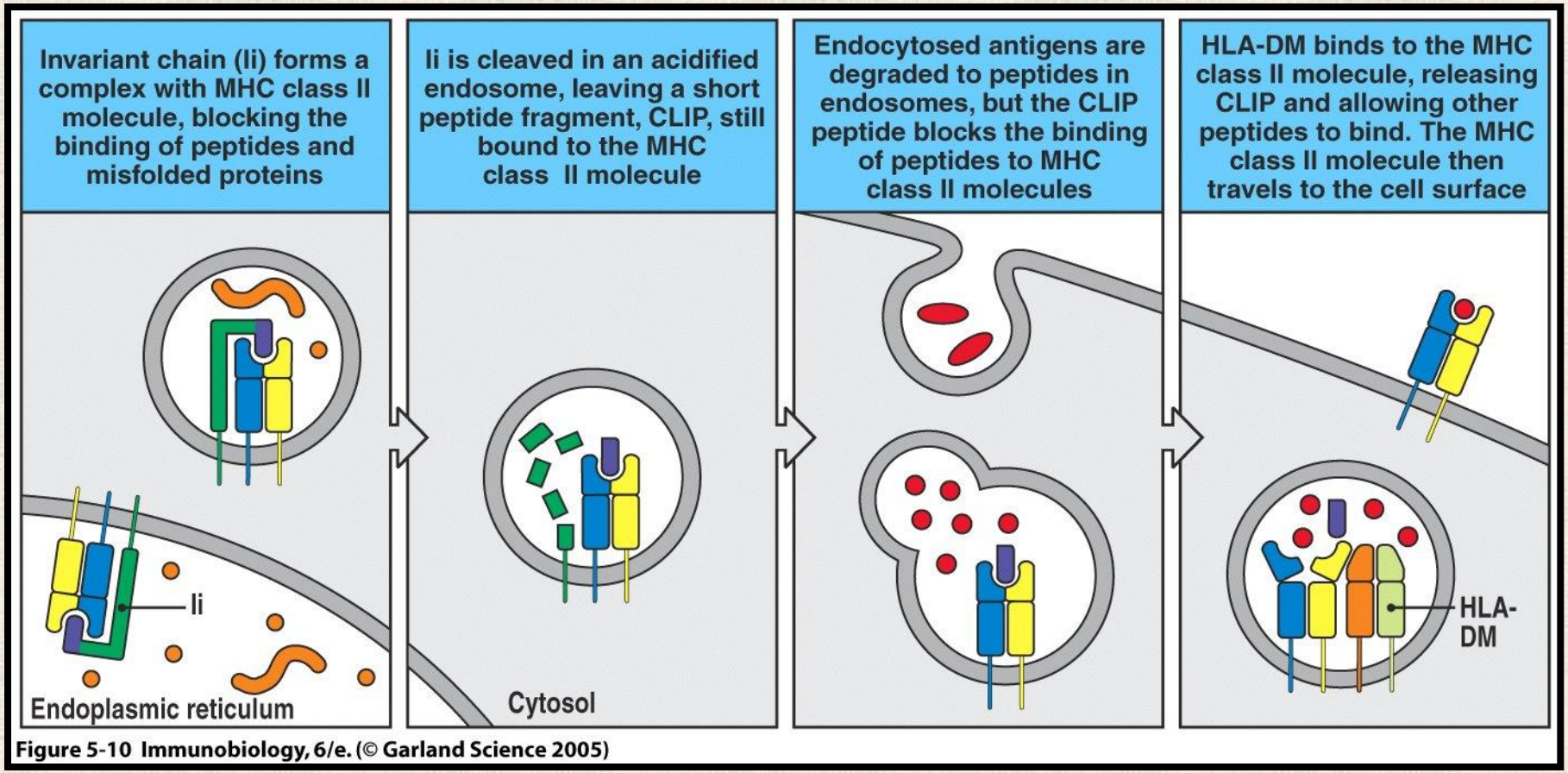


Figure 5-7 Immunobiology, 6/e. (© Garland Science 2005)

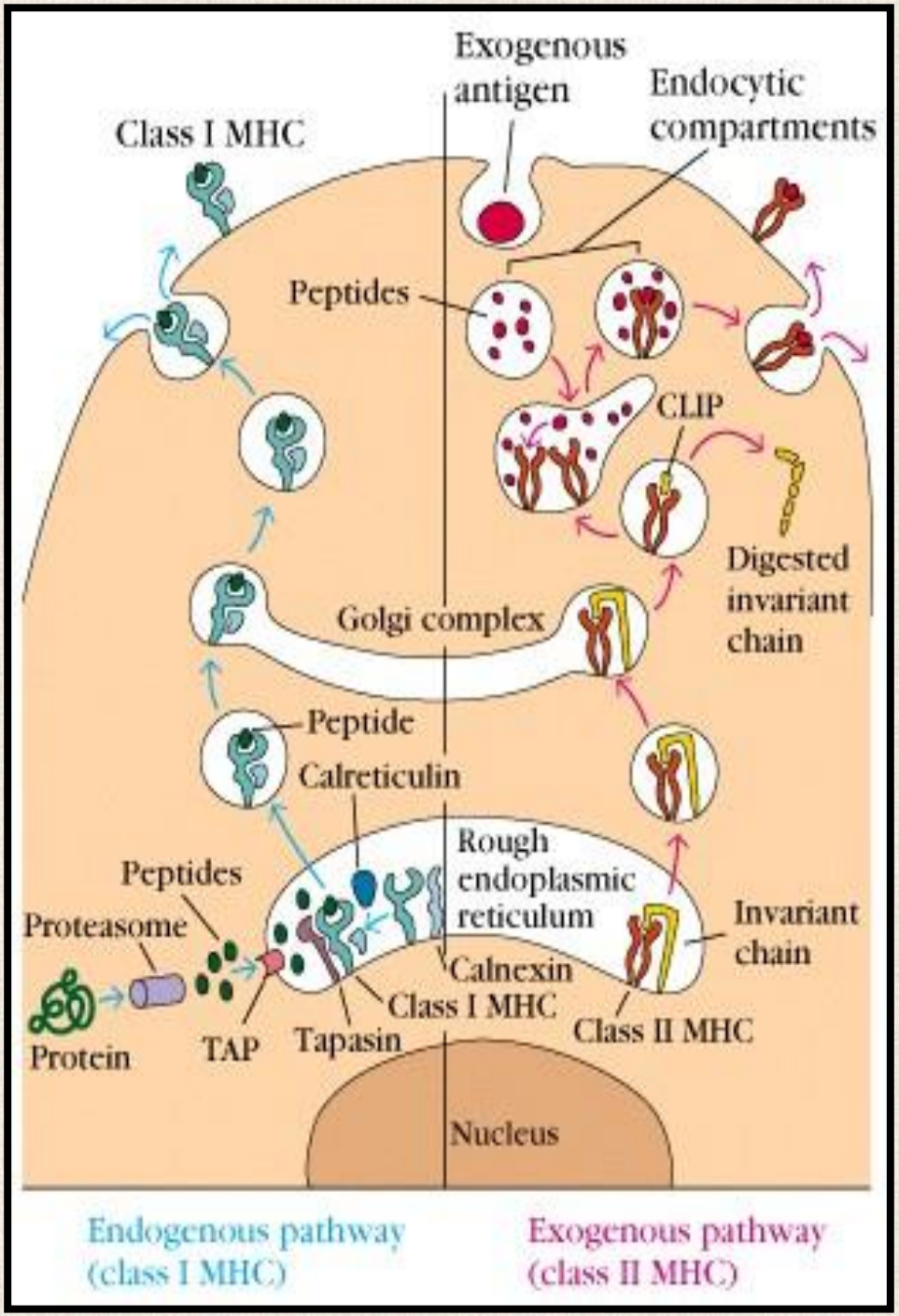
Peptide loading of MHC Class II molecules



HLA-DM: MHCII chaperon

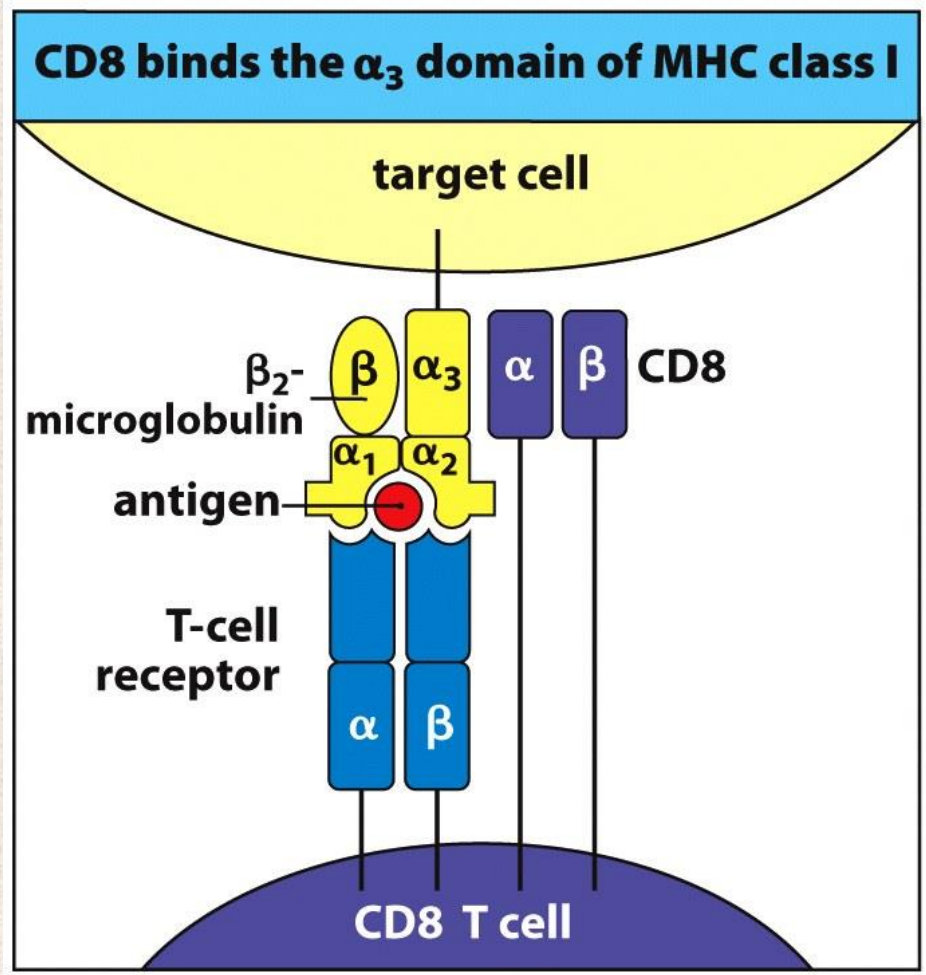
CLIP=class II associated invariant chain peptide

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



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

MHC Restriction



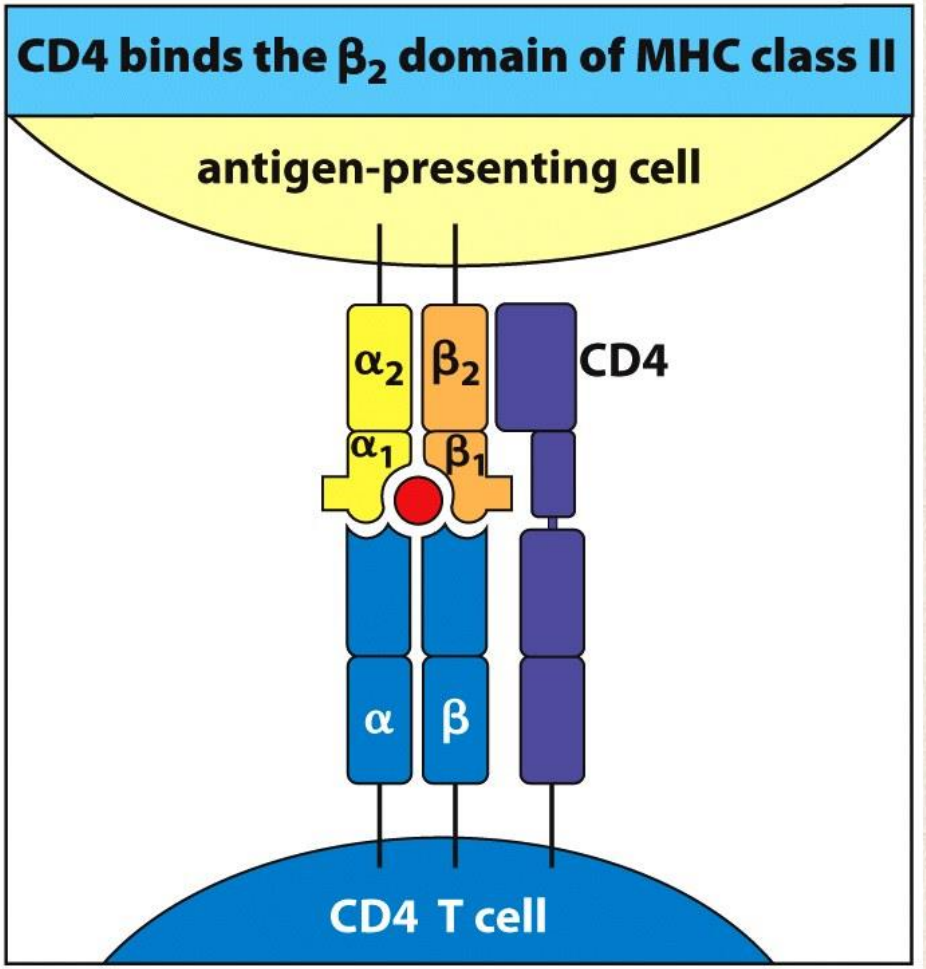


Figure 5.14 The Immune System, 3ed. (© Garland Science 2009)

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

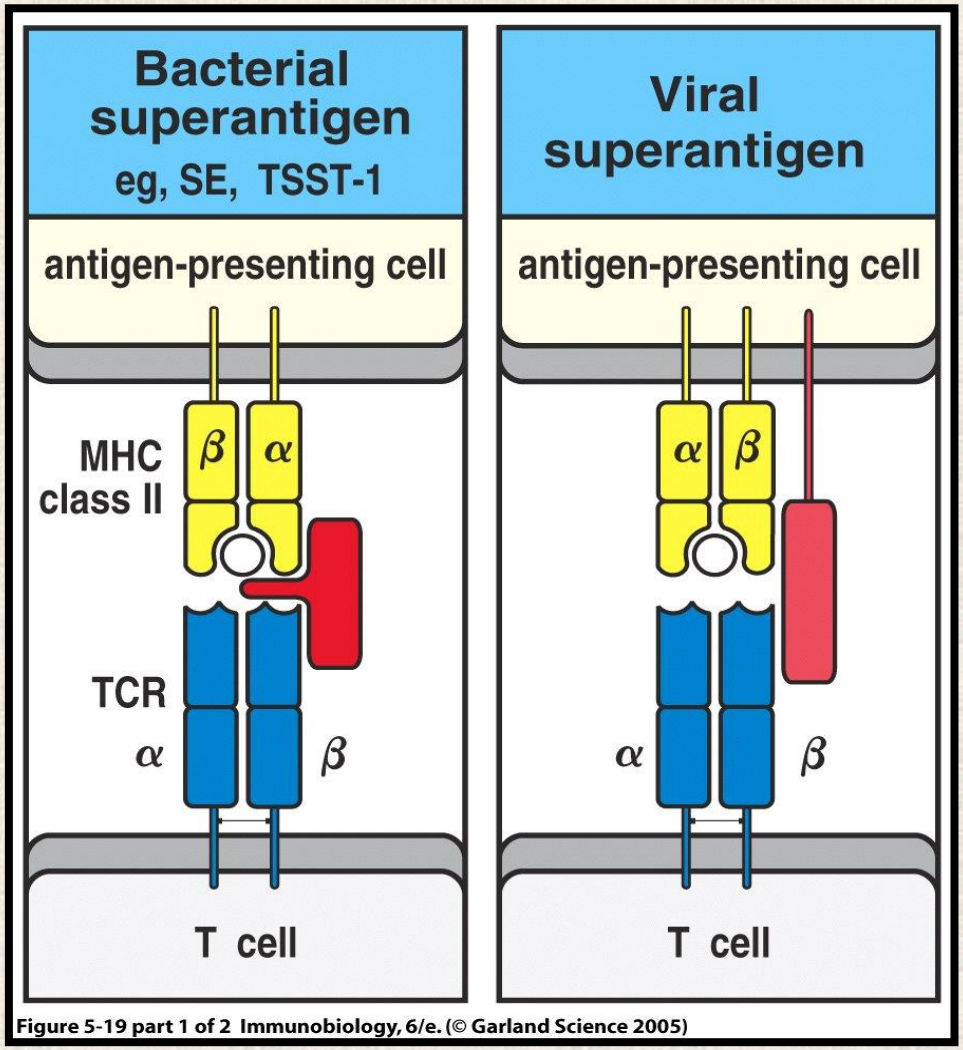


Figure 5-19 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

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 Toxis 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”).