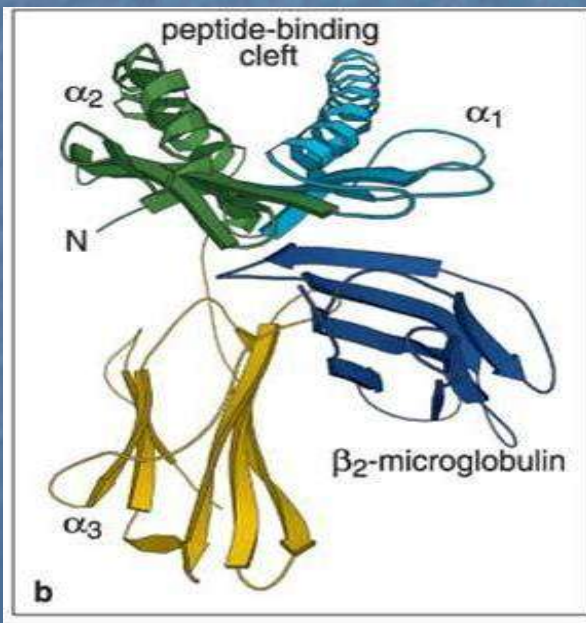
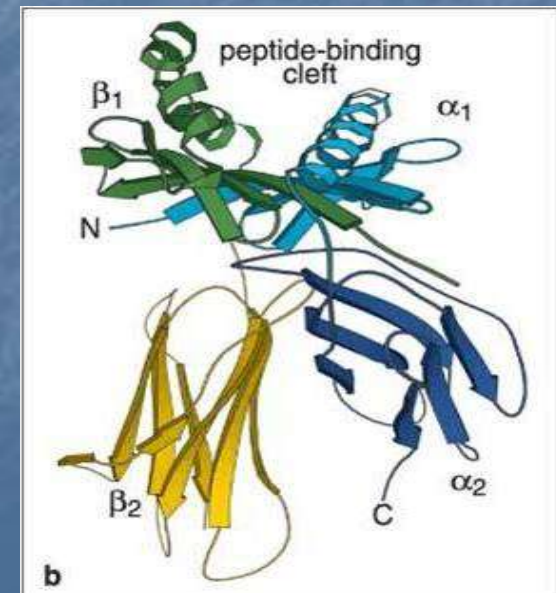


MAJOR HISTOCOMPATIBILITY COMPLEX AND ANTIGEN PRESENTATION

DEPARTMENT OF BIOCHEMISTRY



Dr Jyoti



MHC

- Major Histocompatibility Complex
 - Cluster of genes found in all mammals
 - Its products play role in discriminating self/non-self
 - Participant in both humoral and cell-mediated immunity
- MHC Act As Antigen Presenting Structures
- In Human MHC Is Found On Chromosome 6
 - Referred to as HLA complex
- In Mice MHC Is Found On Chromosome 17
 - Referred to as H-2 complex

History



Gorer (1930s):

1. Rejection of foreign tissue is the result of an immune response to cell-surface molecules.
2. Identification of I, II, III and IV groups of genes.

Gorer and Snell (1940s & 1950s):

1. Antigens encoded by the genes in the group II took part in the rejection of transplanted tumors and other tissues.
2. Snell called these genes "histocompatibility genes" (currently called H-2 genes)
3. Snell was awarded the Nobel Prize in 1980.

Earlier studies were done in inbred strain of mice.

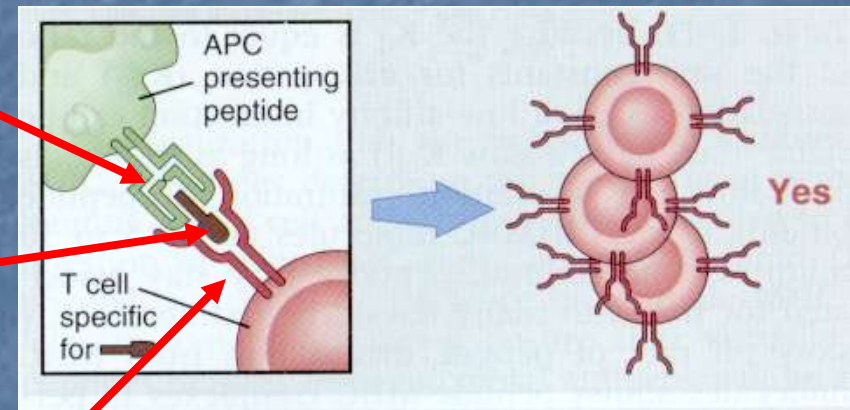
Pioneering studies were done by **R.zinkernagel and P.Doherty,B. benacerraf etc**

Aspects of MHC

1. MHC molecules are membrane-bound. Recognition by T cells requires cell-cell contact.
2. Peptide from cytosol associates with class I MHC and is recognized by Tc cells. Peptide from vesicles associates with class II MHC and is recognized by Th cells.
3. Although there is a high degree of polymorphism for a species, an individual has maximum of six different class I MHC products and only slightly more class II MHC products.

4. A peptide must associate with a given MHC of that individual, otherwise no immune response can occur. That is **one level** of control.

Mature T cells must have a T cell receptor that recognizes the peptide associated with MHC. This is the **second level** of control.



5. Each MHC molecule has only one binding site. The different peptides a given MHC molecule can bind all bind to the same site, but only one at a time.
6. MHC polymorphism is determined only in the germline. There are no recombinational mechanisms for generating diversity.
7. Because each MHC molecule can bind many different peptides, binding is termed degenerate.
8. Cytokines (especially interferon- γ) increase level of expression of MHC.

9 Alleles for MHC genes are **co-dominant**. Each MHC gene product is expressed on the cell surface of an individual nucleated cell.

10 Why the high degree of polymorphism?
Survival of species!

11 The control of transplantation, autoimmunity, and the other immune responses are the phenotypic consequences of the function of molecules encoded in the *MHC*.

12. MHC follows :

- 1. Polymorphism*
- 2. Polygenism*
- 3. linkage disequilibrium*
- 4. Co- Dominance*

MHC .

■ Genes Of MHC Organized In 3 Classes

■ **Class I MHC genes**

- Glycoproteins expressed on all nucleated cells
- Major function to present peptide Ags to T_C

■ **Class II MHC genes**

- Glycoproteins expressed on MΦ, B-cells, DCs
- Major function to present processed Ags peptides to T_H

■ **Class III MHC genes**

Class III molecules are not membrane proteins, are not related structurally to class I and class II molecules, and have no role in Ag presentation, although most play some role in immune responses. e.g., C2, C4a, C4b, factor B, 21-hydroxylase enzymes, TNF α , TNF β , heat shock proteins (HSP)(include secreted proteins)

Mouse H-2 complex

Complex	H-2						
MHC class	I	II		III		I	
Region	K	IA	IE	S		D	
Gene products	H-2K	IA $\alpha\beta$	IE $\alpha\beta$	C' proteins	TNF- α TNF- β	H-2D	H-2L

Human HLA complex

Complex	HLA							
MHC class	II			III		I		
Region	DP	DQ	DR	C4, C2, BF		B	C	A
Gene products	DP $\alpha\beta$	DQ $\alpha\beta$	DR $\alpha\beta$	C' proteins	TNF- α TNF- β	HLA-B	HLA-C	HLA-A

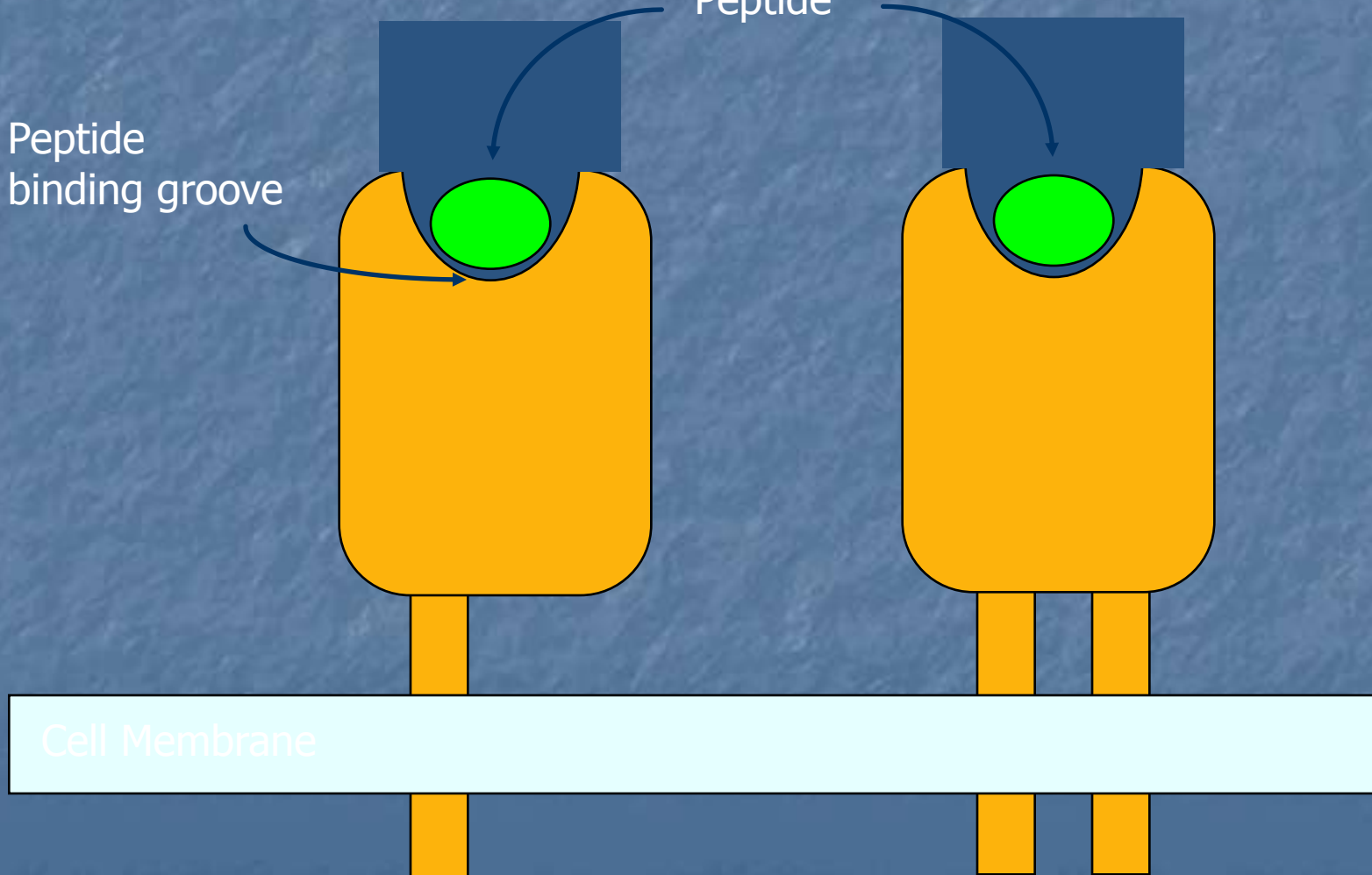
MHC molecules

MHC class I

MHC class II

Peptide

Peptide binding groove



Differential distribution of MHC molecules

Cell activation affects the level of MHC expression.

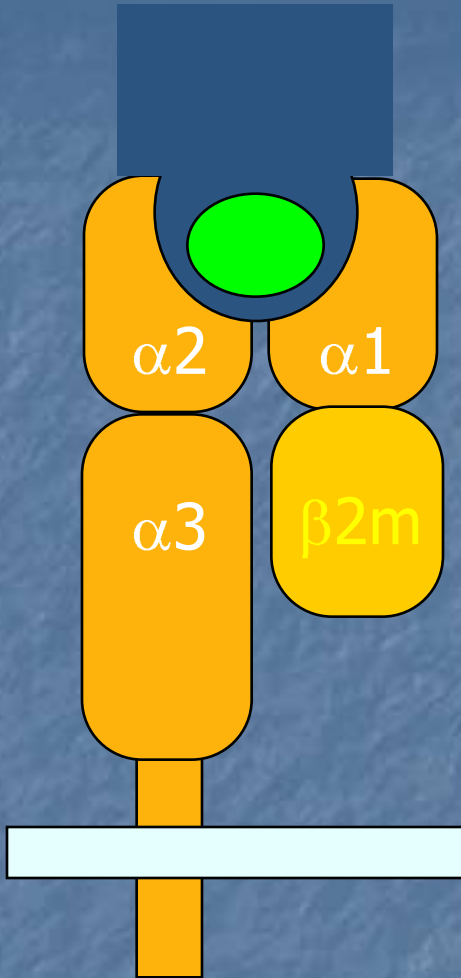
Tissue	MHC class I	MHC class II
T cells	+++	+/-
B cells	+++	+++
Macrophages	+++	++
Other APC	+++	+++
Thymus epithelium	+	+++
Neutrophils	+++	-
Hepatocytes	+	-
Kidney	+	-
Brain	+	-
Erythrocytes	-	-

The highest level of class I molecules are expressed on lymphocytes: 1 % of the total plasma membrane proteins or 5×10^5 molecules / cell.

A few cell types (e.g., neurons and sperm cells at certain stages of differentiation) appear to lack class I MHC molecules altogether.

Thymic epithelial cells and some other cell types can be induced to function as APC and then express class II molecules under certain conditions.

Overall structure of MHC class I molecules



MHC-encoded α -chain of 43kDa ,Made Up Of 3 Domains ($\alpha 1$, $\alpha 2$ and $\alpha 3$)

α -chain anchored to the cell membrane

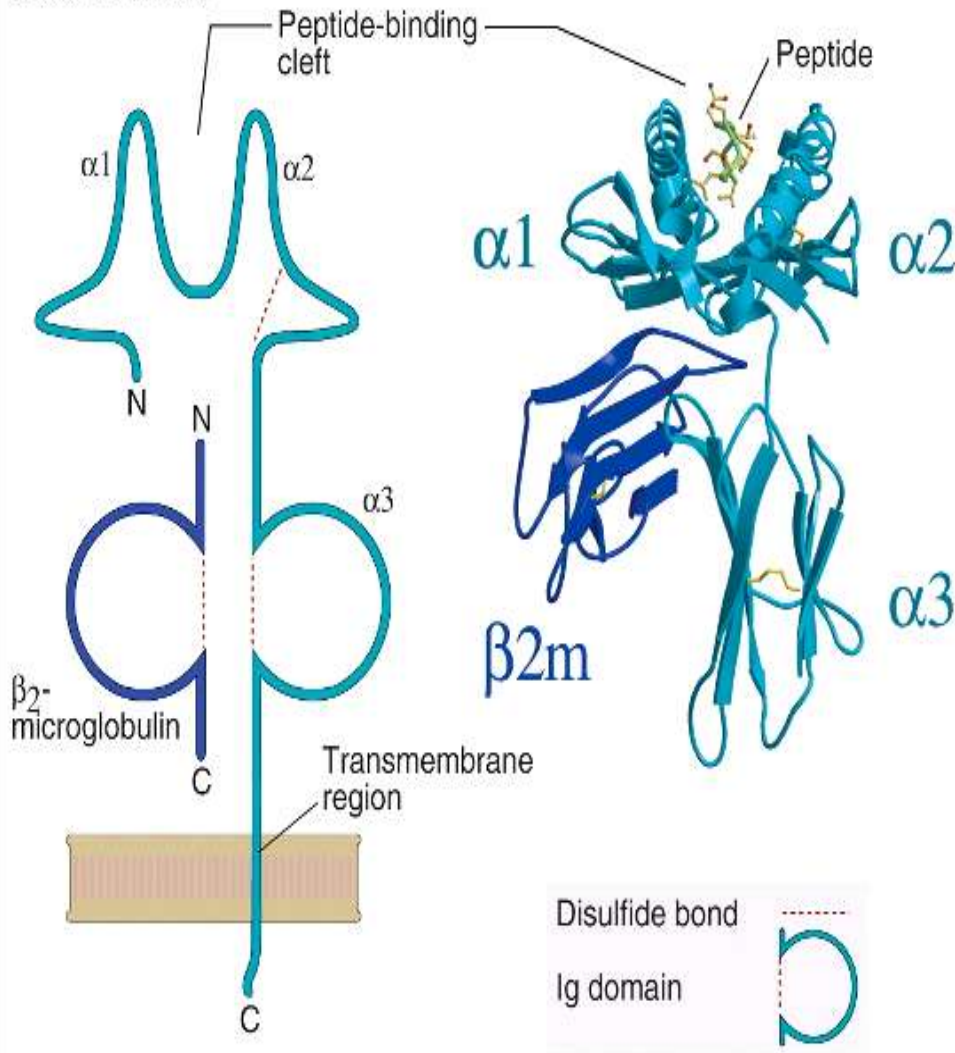
Peptide antigen in a groove formed from a pair of α -helices on a floor of anti-parallel β strands

$\beta 2$ -microglobulin, 12kDa, non-MHC encoded, non-transmembrane, non covalently bound to $\alpha 3$ domain

The $\alpha 3$ segment of the MHC I , is highly conserved among MHC1 & serves as a binding site for CD8

The α chain the HLA-A, -B, -C and $\beta 2m$ on different chromosome

Class I MHC



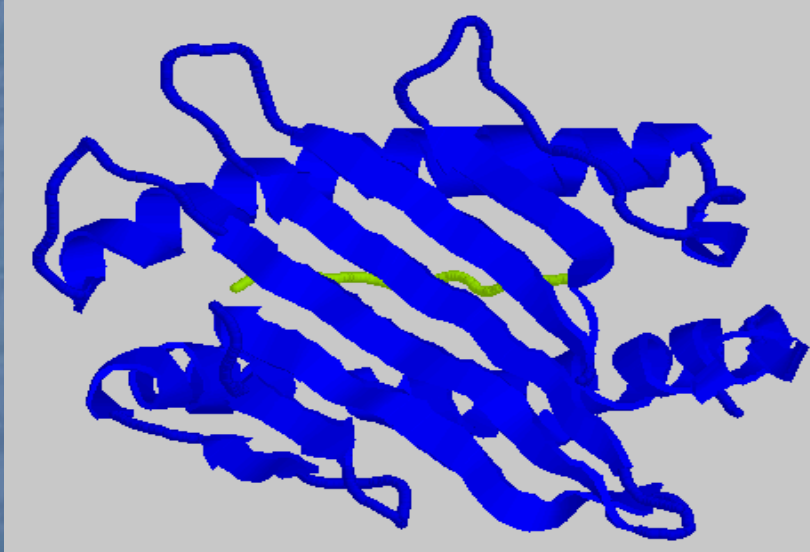
$\alpha 1$, $\alpha 2$ and $\alpha 3$ contains 90 amino acid, tm domain 25 hypho AA, followed by short stretch of hyphi AA and cytoplasm anchor of 30 aa

$\alpha 3$ domain & $\beta 2m$ have structural & amino acid sequence homology with Ig C domains **IG GENE SUPERFAMILY**

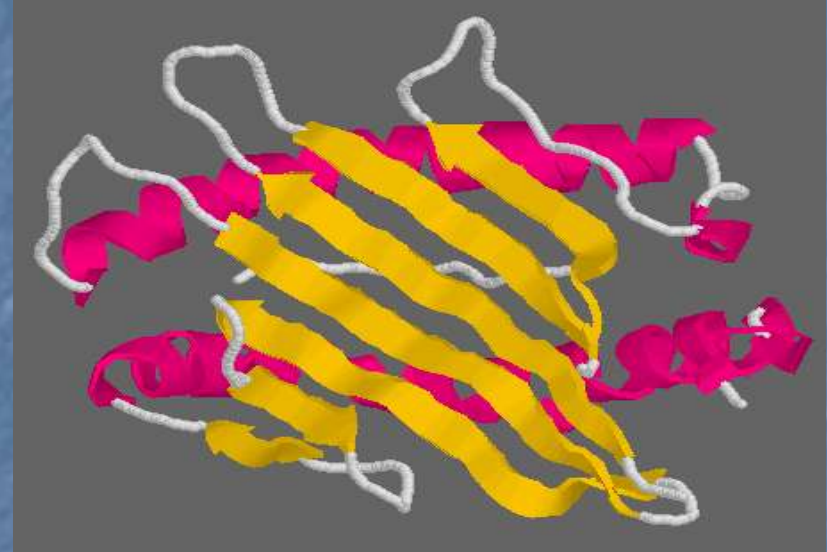
Association Of α Chain and β_2 Is Required For Surface Expression

Duadi tumours absence $\beta 2$ -m, cell is unable to express mhc 1 on the membrane

$\alpha 1$ and $\alpha 2$ domains form two segmented α -helices on eight anti-parallel β -strands to form an antigen-binding cleft.



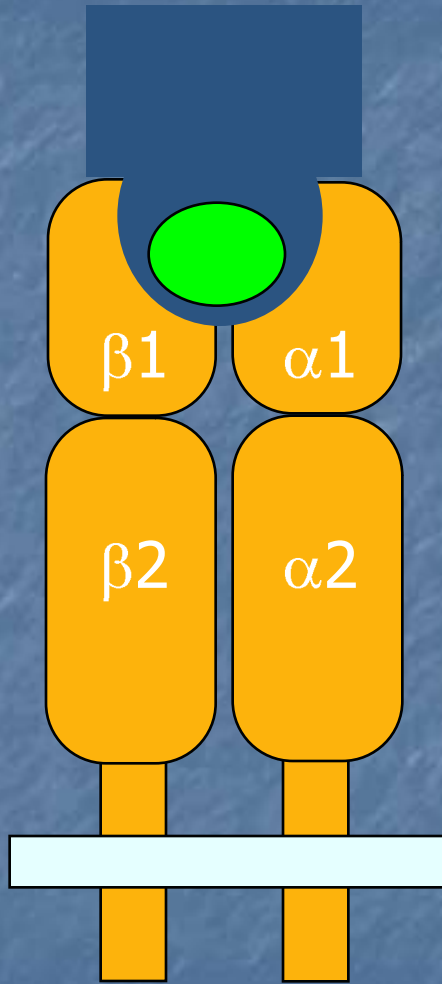
Chains



Structures

Properties of the inner faces of the helices and floor of the cleft determine which peptides bind to the MHC molecule
The formed cleft can bind peptides of 8 -10 amino acids in a flexible extended conformation.

Overall structure of MHC class II molecules



MHC-encoded, α -chain of 34kDa, $\alpha 1$ and $\alpha 2$
and a β -chain of 29kDa $\beta 1$ and $\beta 2$

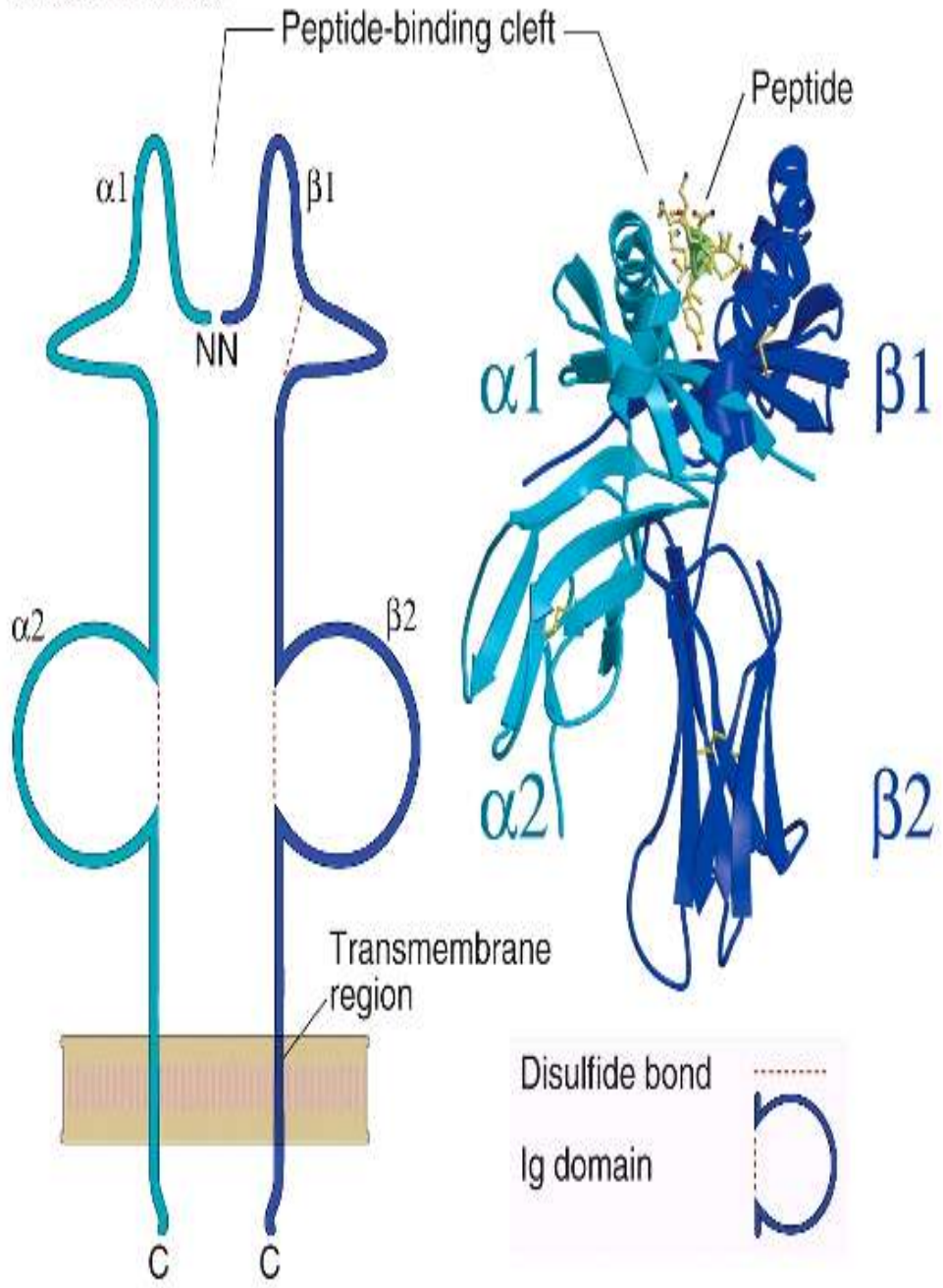
No β -2 microglobulin

α and β chains anchored to the cell membrane
These chains are non-covalently associated
peptides

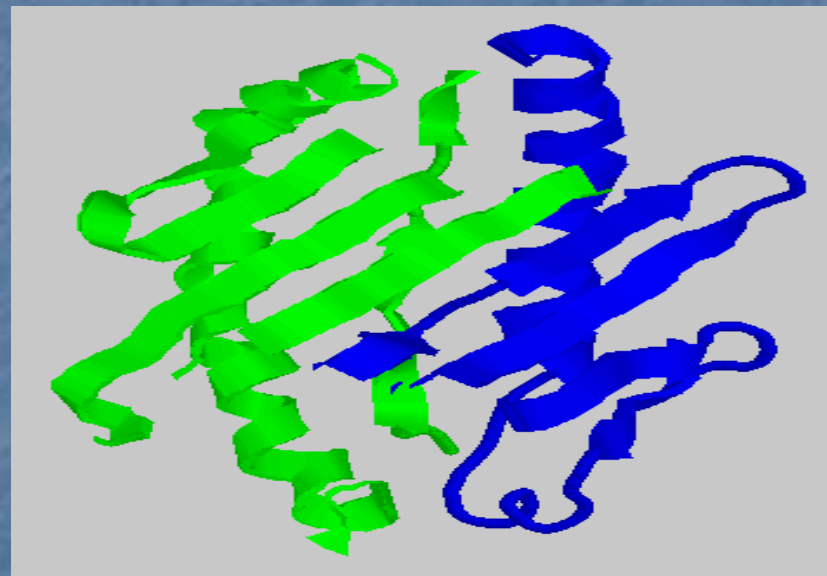
Peptide antigen in a groove formed from a pair
of α -helices on a floor of anti-parallel β
strands

$\alpha 2$ & $\beta 2$ domains have structural & amino acid sequence
homology with Ig C domains **Ig GENE SUPERFAMILY**

Class II MHC



- CD4 Molecule Binds α 2/ β 2 domains
- The α chains are the HLA DR
- The β chains are the HLA DQ and DP



Cleft is made of both α and β chains

Table 4-1. Features of Class I and Class II MHC Molecules

Feature	Class I MHC	Class II MHC
Polypeptide chains	α (44-47 kD) β_2 -Microglobulin (12 kD)	α (32-34 kD) β (29-32 kD)
Locations of polymorphic residues	α 1 and α 2 domains	α 1 and β 1 domains
Binding site for T cell coreceptor	α 3 region binds CD8	β 2 region binds CD4
Size of peptide-binding cleft	Accommodates peptides of 8-11 residues	Accommodates peptides of 10-30 residues or more
Nomenclature		
Human	HLA-A, HLA-B, HLA-C	HLA-DR, HLA-DQ, HLA-DP
Mouse	H-2K, H-2D, H-2L	I-A, I-E

Abbreviations: CD, cluster of differentiation; H-2K, H-2D, genes identified as determinants of graft rejection in mice; HLA, human leukocyte antigen; I-A, I-E, immune response genes of mice; kD, kilodalton; MHC, major histocompatibility complex.

Class I MHC Peptides

- Peptides Presented Through MHC I Are Endogenous Proteins
- As Few As 100 Peptide/MHC Complex Can Activate T_C
- Peptide Features
 - size 8-10 a/a, preferably 9
- Peptides Bind MHC Due To Presence Of Specific a/a Found At The Ends Of Peptide. Ex. Glycine @ Position 2

Class II MHC Peptides

- Peptides Presented Through MHC II Are Exogenous
 - Processed through endocytic pathway
- Peptides Are Presented To T_H
- Peptides Are 13-18 a/a Long
- Binding Is Due To Central 13 a/a
- Longer Peptides Can Still Bind MHC II
 - Like A long hot dog
- MHC I Peptides Fit Exactly, Not The Case With MHC II Peptides

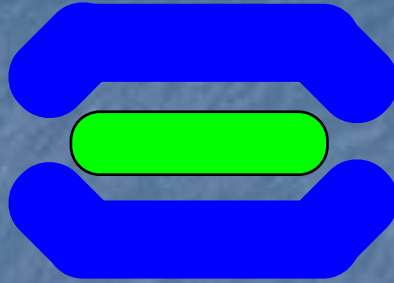
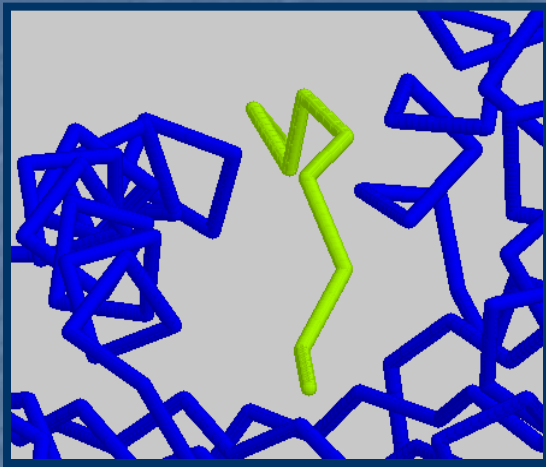
TABLE 7-2

Peptide binding by class I and class II MHC molecules

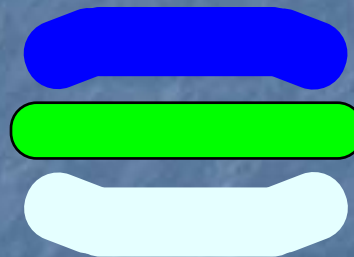
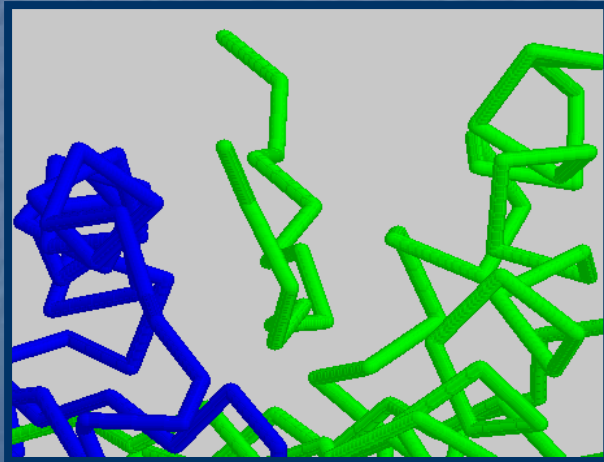
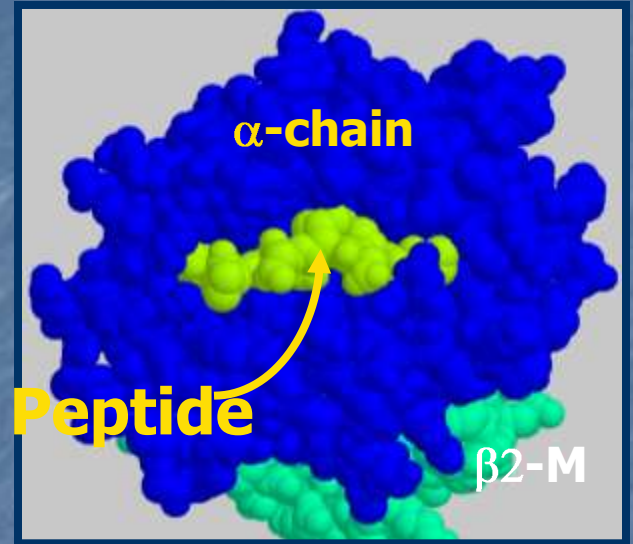
	Class I molecules	Class II molecules
Peptide-binding domain	$\alpha 1/\alpha 2$	$\alpha 1/\beta 1$
Nature of peptide-binding cleft	Closed at both ends	Open at both ends
General size of bound peptides	8–10 amino acids	13–18 amino acids
Peptide motifs involved in binding to MHC molecule	Anchor residues at both ends of peptide; generally hydrophobic carboxyl-terminal anchor	Anchor residues distributed along the length of the peptide
Nature of bound peptide	Extended structure in which both ends interact with MHC cleft but middle arches up away from MHC molecule	Extended structure that is held at a constant elevation above the floor of MHC cleft



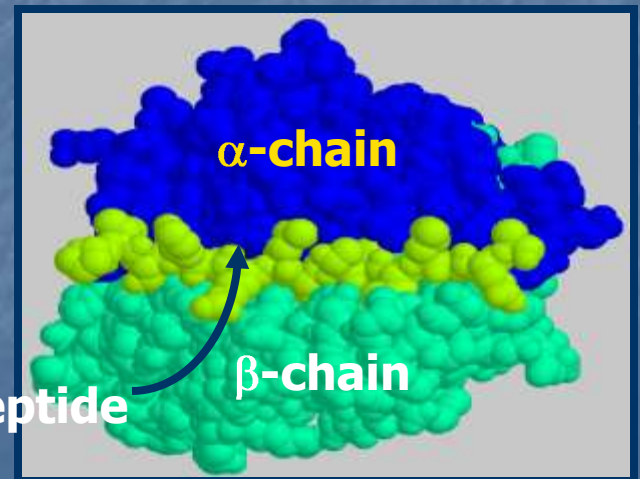
Cleft geometry



MHC class I



MHC class II



Peptide is held in the cleft by non-covalent forces

MHC-binding peptides

Each human usually expresses:

3 types of MHC class I (A, B, C) and

3 types of MHC class II (DR, DP, DQ)



The number of different **T cell antigen** receptors is estimated to be **1,000,000,000,000,000**

Each of which may potentially recognise a different peptide antigen.

How can 6 invariant molecules have the capacity to bind to 1,000,000,000,000,000 different peptides?

A flexible binding site?

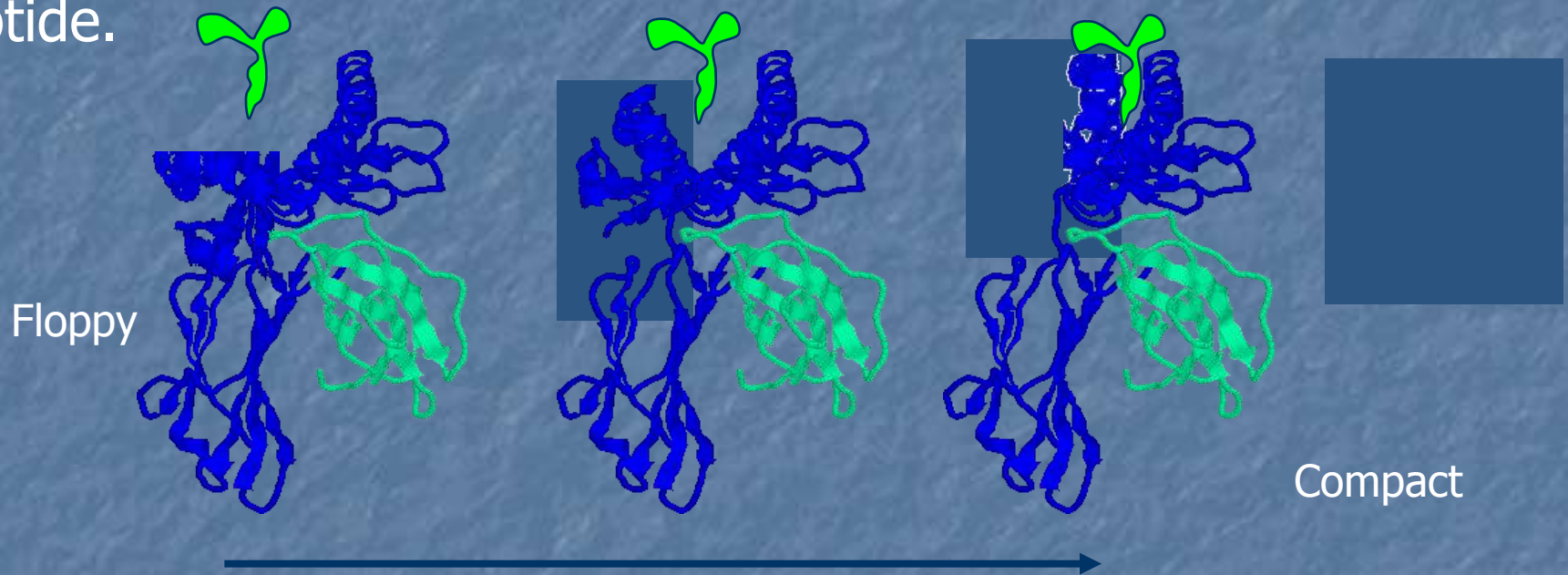
A binding site that is flexible enough to bind any peptide?



NO because: at the cell surface, such a binding site would be unable to allow a high enough binding affinity to form a trimolecular complex with the T cell antigen receptor & prevent exchange of the peptide with others in the extracellular milieu

So , here the answer lies

A binding site that is flexible at an early, intracellular stage of maturation Formed by folding the MHC molecules around the peptide.



Allows a single type of MHC molecule to

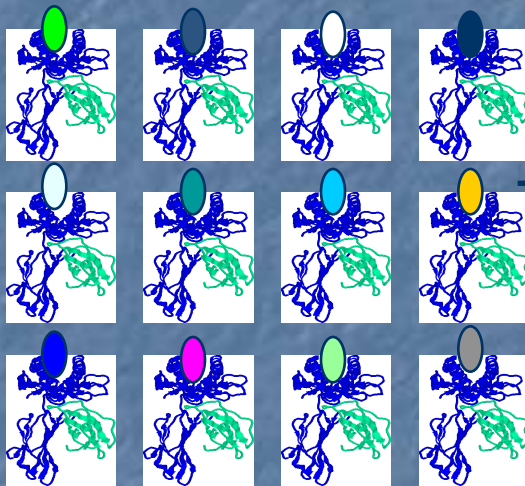
- bind many different peptides
- bind peptides with high affinity
- form stable complexes at the cell surface
- Export only molecules that have captured a peptide to the cell surface

Binding affinity of MHC to peptides

- The association constant K_D of the peptide-MHC molecule complex is approximately 10^{-6} .
- The rate of association is low, but the rate of dissociation is even lower.
- Thus, the peptide-MHC molecule association is very stable under physiological conditions and most of the MHC molecules expressed on the membrane of a cell are associated with a peptide of self or nonself origin.

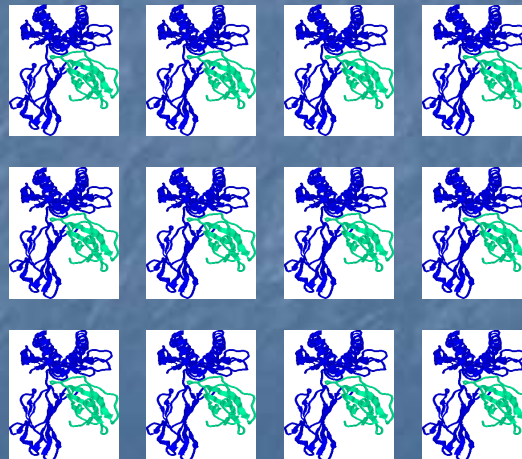
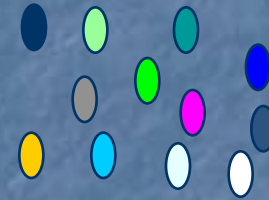
Peptides can be eluted from MHC molecules

Purify stable MHC-peptide complexes



Fractionate and microsequence peptides

Acid elute peptides



Peptides after elution

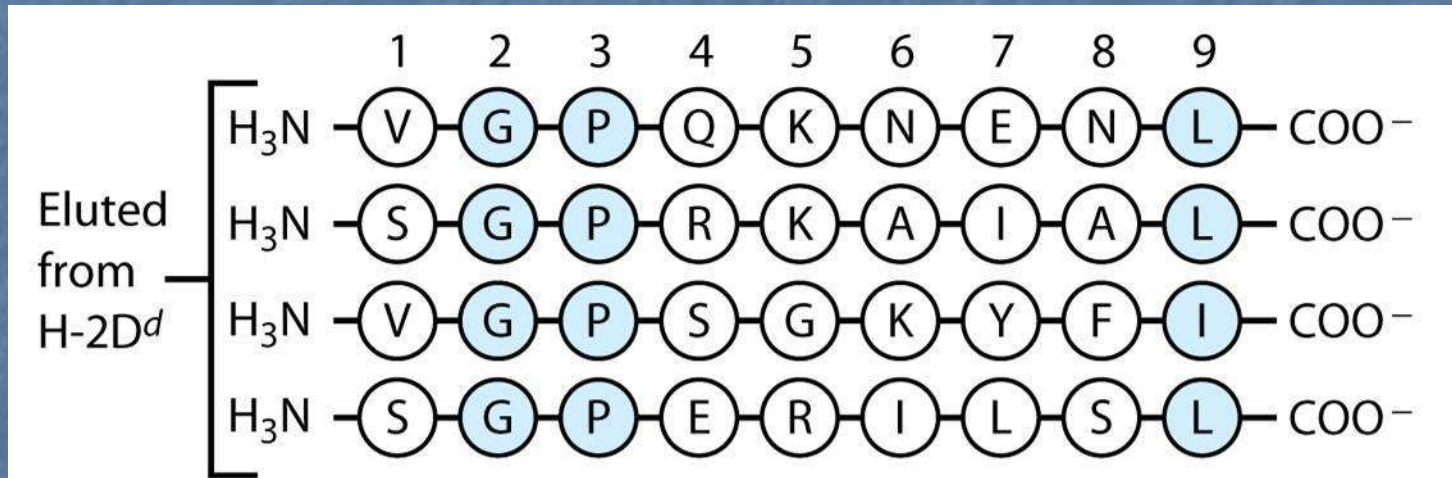
E.g. for class 1 MHC

Because a single nucleated cell express about 10^5 copies of each class 1 molecule, many different peptides will be expressed simultaneously on the surface of nucleated cell by class 1 MHC molecule.

It is also estimated that each of 2000 distinct peptide (found after elution & HPLC) is presented with a frequency of 100 to 4000 copies per cell.

Evidence also suggest that even a single peptide- MHC complex may be sufficient to target a cell for recognition and lysis by a cytotoxic T lymphocyte with a receptor specific for that target structure.

Eluted peptides from MHC molecules have different sequences but contain motifs



Peptides bound to a particular type of MHC class I molecule have conserved patterns of amino acids

A common sequence in a peptide antigen that binds to an MHC molecule is called a **MOTIF**

R G Y V Y Q Q L

S I I N F E K L

A P G N Y P A L

Amino acids common to many peptides tether the peptide to structural features of the MHC molecule **ANCHOR RESIDUES**

Tethering amino acids need not be identical but must be related

Y & F are aromatic

V, L & I are hydrophobic

Side chains of anchor residues bind into **POCKETS** in the MHC molecule

Different types of MHC molecule bind peptides with different patterns of conserved amino acids

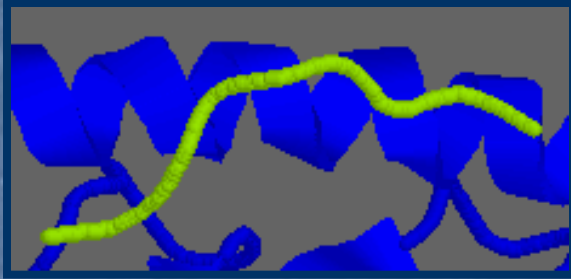
In all peptides examined to date that bind to class 1 molecule contains 2 anchors :

1. carboxy terminal anchor. These anchors are generally hydrophobic residue (eg leucine, isoleucine).
2. anchor is reported at 2nd or 2nd or 3rd positions at the amino terminal end end of the peptide .

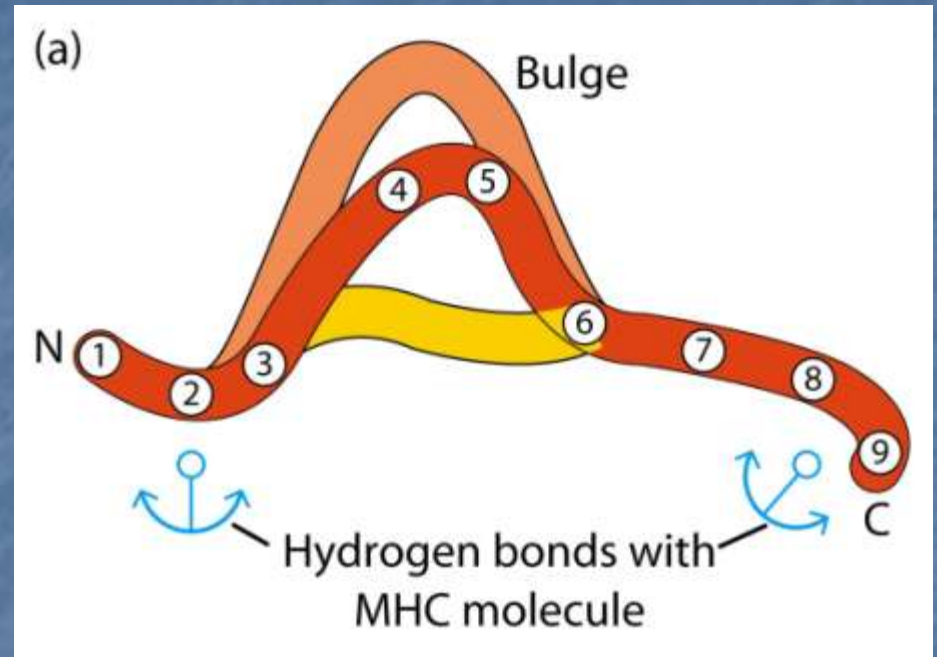
In general any , peptide of correct length that contains the same or similar anchor residue will bind to same class 1 MHC molecule.

The main contacts between class 1 MHC molecule and peptide involves the anchors(residue 2 at the aminoterminal end and residue 9 at the carboxyl terminus of the nanomeric peptide)

MHC molecules can bind peptides of different length

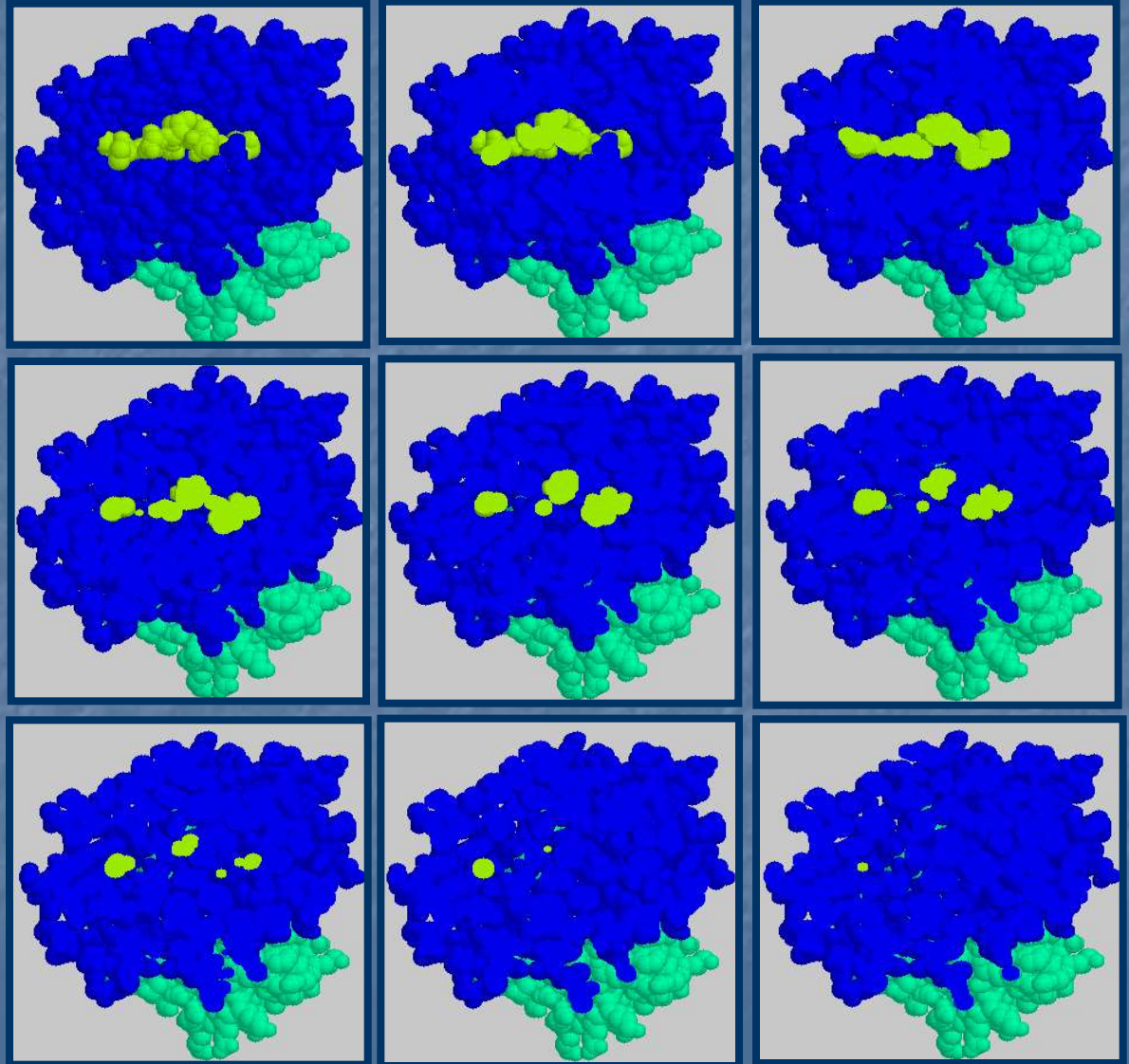
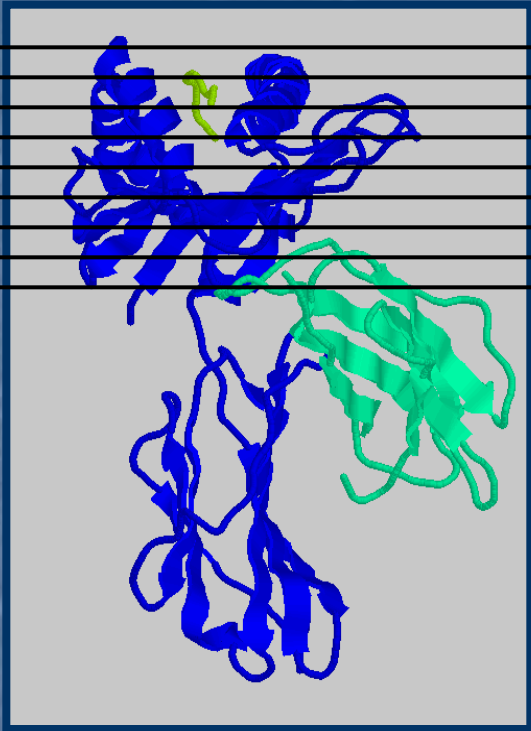


Arched peptide



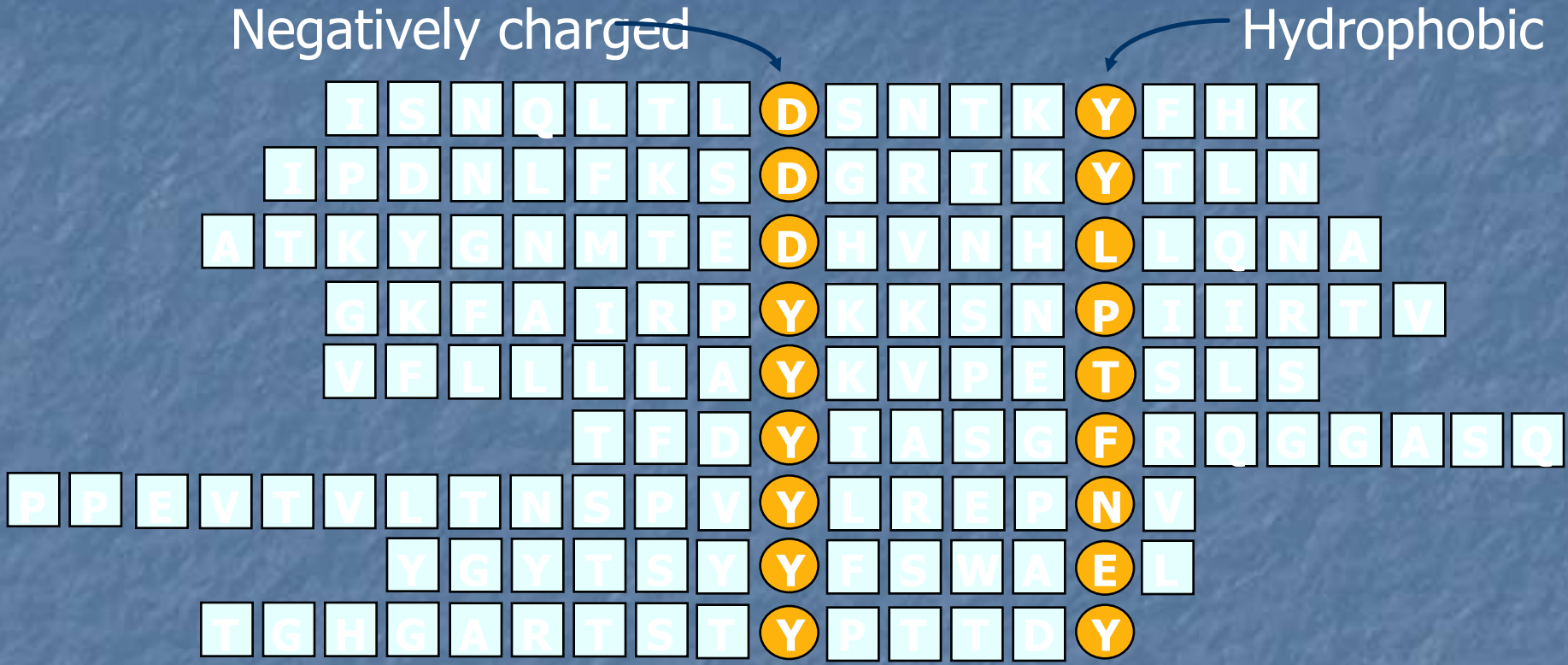
B/w the anchors, the peptides arches away from the floor of the cleft in the middle allowing peptides that are slightly longer or shorter to accommodate. Amino acids that are away from the MHC molecule are more exposed and presumably can interact more directly with the T cell receptor.

Peptide binding pockets in MHC class I molecules



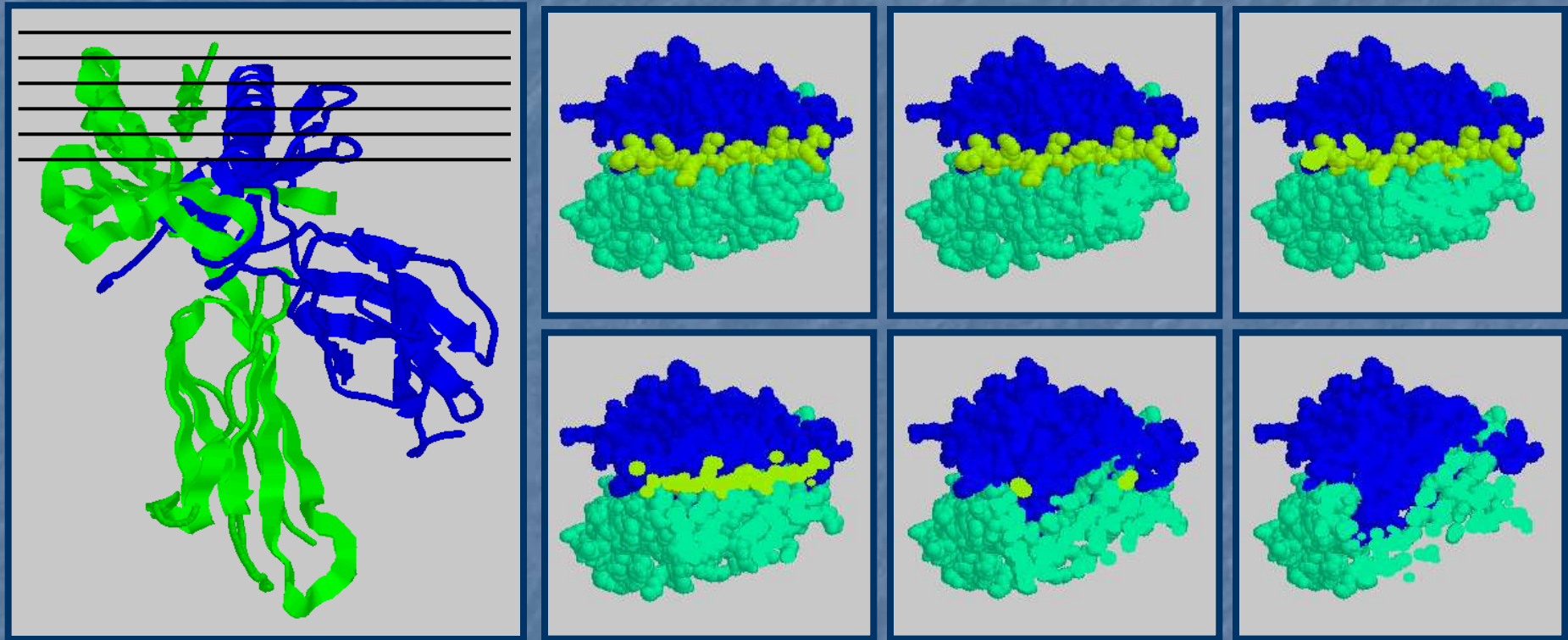
Slices through
MHC class I
molecules, when
viewed from above
reveal deep, well
conserved pockets

Peptide antigen binding to MHC class II molecules



- Anchor residues *are not* localised at the N and C termini
- Ends of the peptide are in extended conformation and are not conserved
- Motifs are less clear than in class I-binding peptides
- Pockets are more permissive

Peptide binding pockets in MHC class II molecules



Slices through MHC class II molecules, when viewed from above reveal shallow, poorly conserved pockets compared with those in MHC class I molecules

of the question.....

ation until a peptide binds
stability of the complex
ber of anchor residues
anchors and different

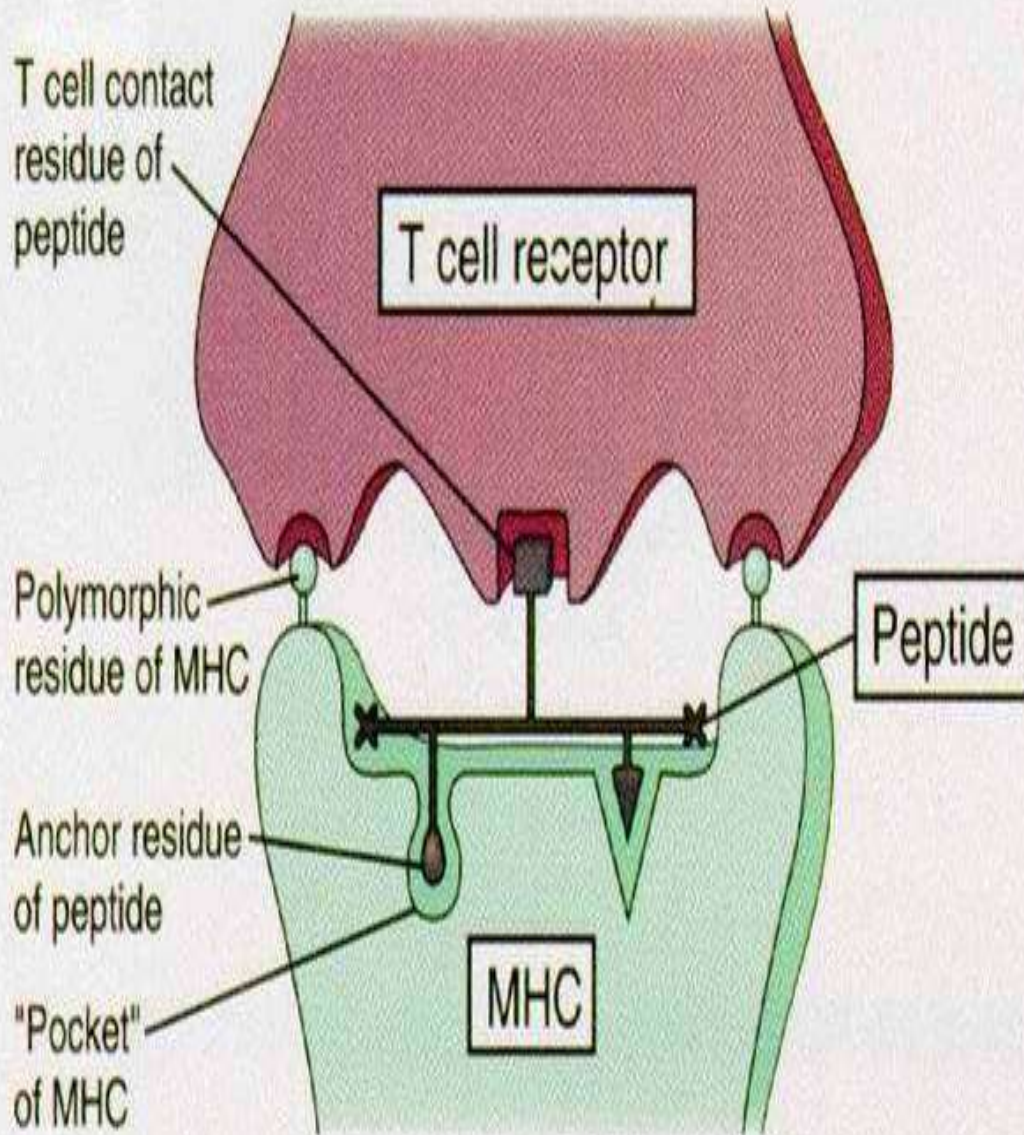


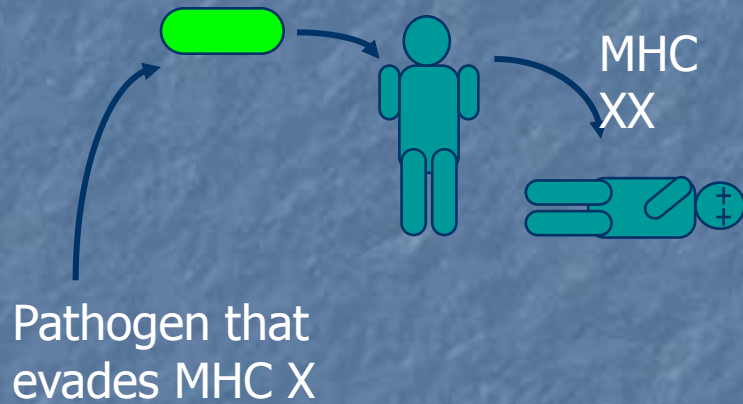
Figure 4-1 T cell recognition of a peptide-MHC complex.

This schematic illustration shows an MHC molecule binding and displaying a peptide and a T cell receptor recognizing two polymorphic residues of the MHC molecule and one residue of the peptide. Details of the interactions among peptides, MHC molecules, and T cell receptors are described in Chapters 4, 5, and 6. MHC, major histocompatibility complex.

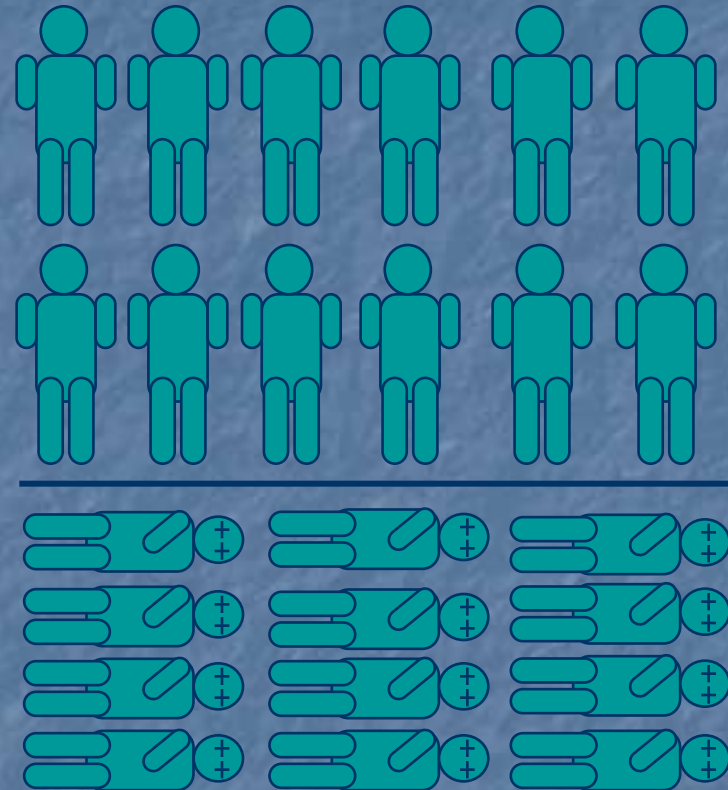
MHC molecules are targets for immune evasion by pathogens

- Without T cells there is no effective immune response
- Ag-specific T cells are activated by peptide/MHC complexes
- There is therefore strong selective pressure for pathogens to mutate genes encoding antigens so that they can evade the formation of peptide/MHC complexes
- The MHC has two strategies to prevent evasion by pathogens
 1. More than one type of MHC molecule in each individual
 2. Extensive differences in MHC molecules between individuals

Example: If MHC X was the only type of MHC molecule

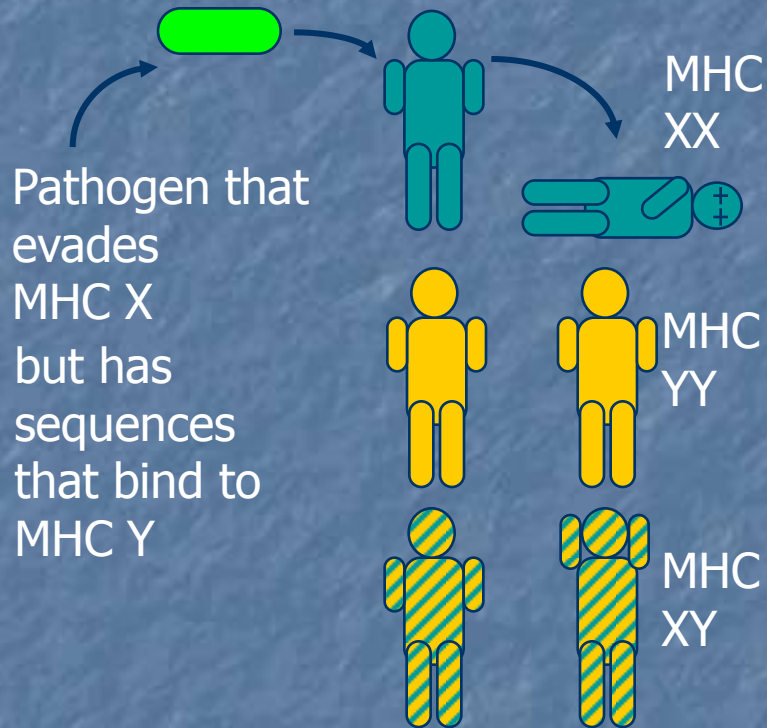


Survival of individual threatened

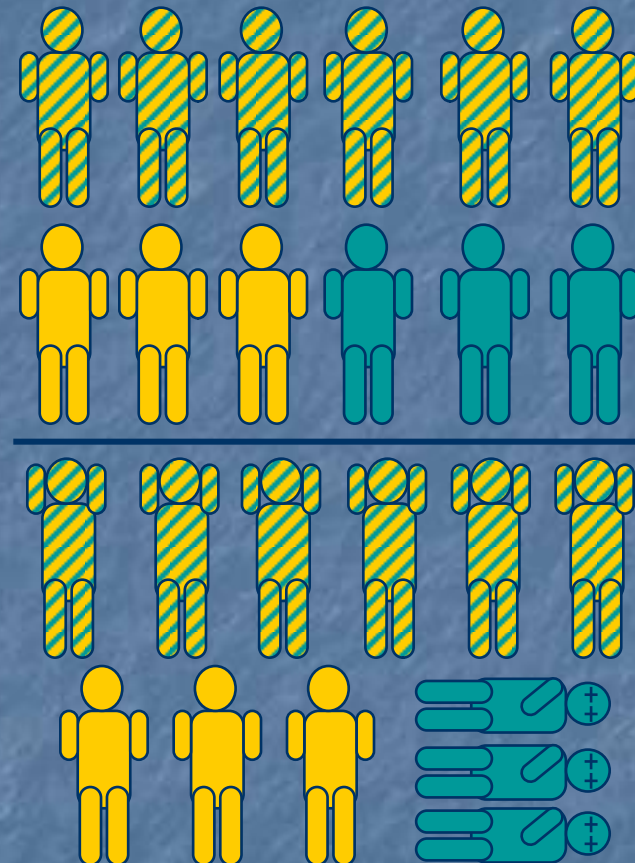


Population threatened with extinction

Example: If each individual could make two MHC molecules, MHC X and Y



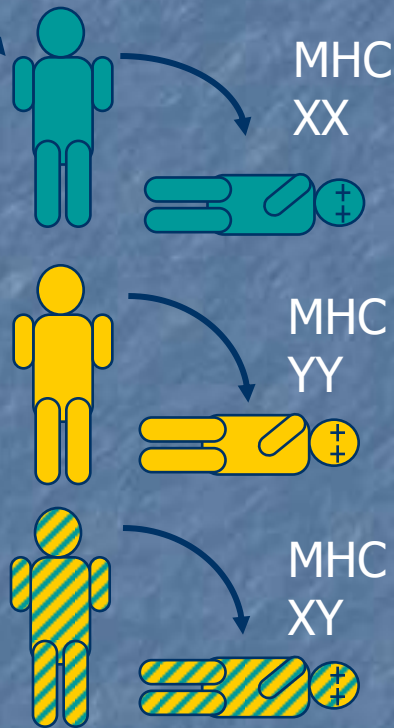
Impact on the individual depends upon genotype



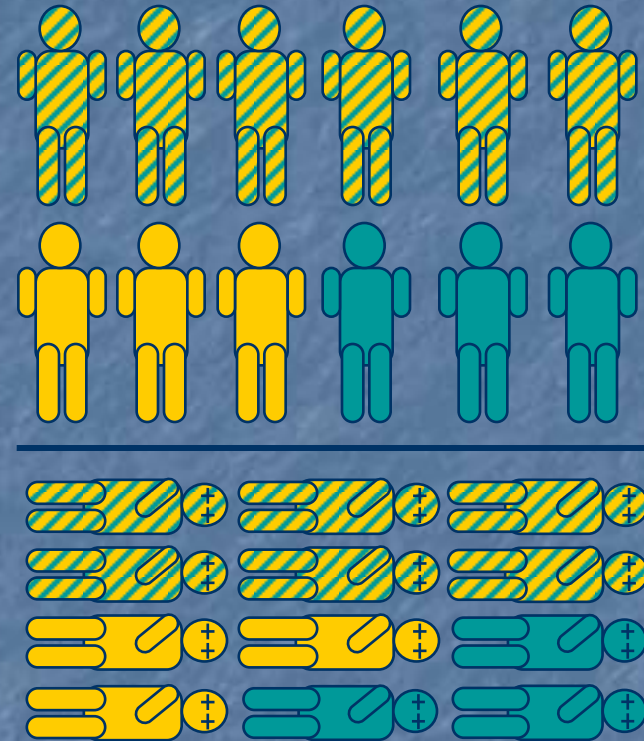
Population survives

Example: If each individual could make two MHC molecules, MHC X and Y.....and the pathogen mutates

Pathogen that evades MHC X but has sequences that bind to MHC Y
....until it mutates to evade MHC Y



Survival of individual threatened



Population threatened with extinction

The number of types of MHC molecule can not be increased *ad infinitum*

Populations need to express variants of each type of MHC molecule

- Populations of microorganisms reproduce faster than humans
- Mutations that change MHC-binding antigens or MHC molecules can only be introduced to populations after reproduction
- The ability of microorganisms to mutate in order to evade MHC molecules will always outpace counter evasion measures that involve mutations in the MHC
- The number of types of MHC molecules are limited

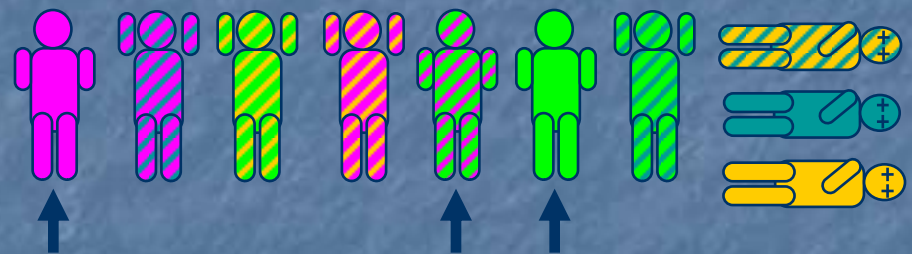
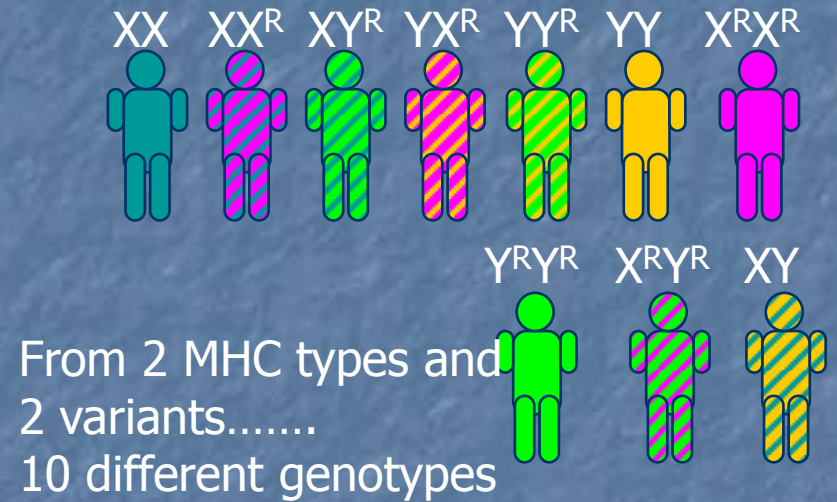
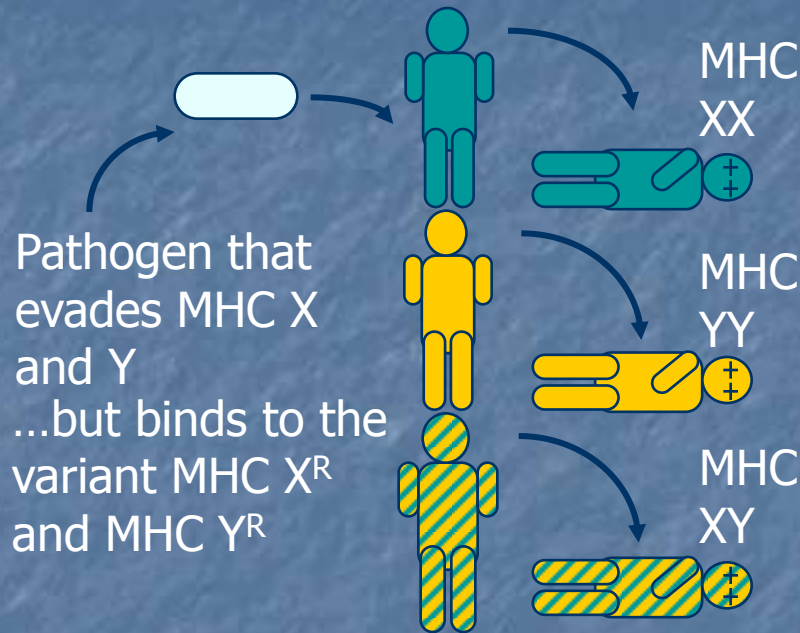
To counteract the superior flexibility of pathogens:

Human populations possess many variants of each type of MHC molecule

Variant MHC may not protect every individual from every pathogen.

However, the existence of a large number of variants means that the population is prevented from extinction

Variant MHC molecules protect the population



Variants – alleles - of each type of MHC gene encode proteins that increase the resistance of the population from rapidly mutating or newly encountered pathogens without increasing the number of types of MHC molecule

Molecular basis of MHC types and variants

MHC genes are the most polymorphic known.

The type and variant MHC molecules do not vary in the lifetime of the individual. This sharply contrasts diversity in T and B cell antigen receptors which are in a constant state of flux within the individual

Diversity in MHC molecules exists at the population level

.

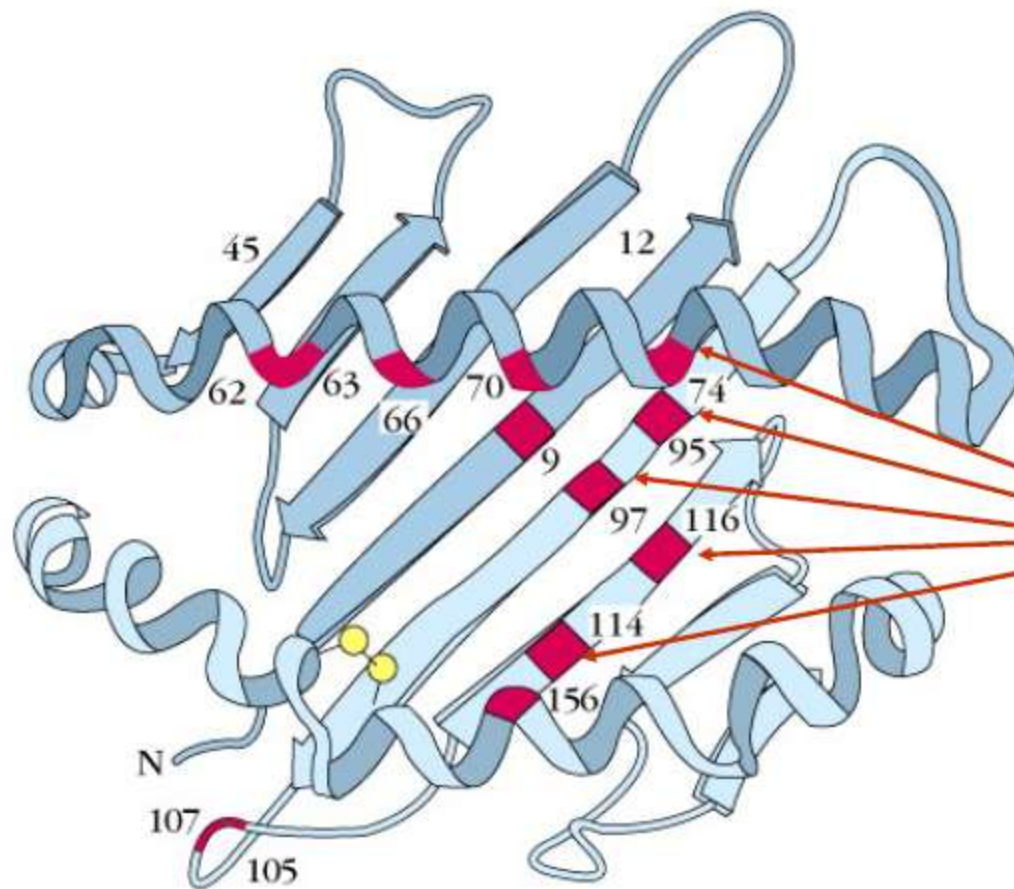
POLYMORPHISM

The presence of multiple alleles at a given genetic locus within species

POLYGENISM

Several MHC class I and class II genes encoding different types of MHC molecule with a range of peptide-binding specificities.

Location of polymorphic amino acid residues



Most of the residues with significant polymorphism are located in the peptide-binding cleft

Detailed Genomic Map of MHC genes

The MHC spans 4000 Kb of human DNA at chromosome no 6

The human class 1 region span about 2000 kb at the telomeric end of HLA complex.

1. MHC classical HLA- A, HLA-B & HLA C.
2. **MHC Class 1b genes**

Encoding MHC class I-like proteins that associate with β -2 microglobulin:
HLA -E,F,G,J & X (some are pseudogenes)

HLA-G binds to CD94, an NK-cell receptor. Inhibits NK attack of foetus/
tumours

HLA-E binds conserved leader peptides from HLA-A, B, C. Interacts with
CD94

HLA-F function unknown

3. MIC region , which include MICA through MICE. MIC gene product are expressed at low levels in epithelial cells and are induced by heat or other stimuli that influence heat shock proteins. MICA are highly polymorphic.

CLASS 2 MHC GENES are located at the centromeric end of HLA

1. HLA DR, DP&DQ multiple α & β chain DR= 3-4 functional β chain, 1 α chain. DP & DQ region each contains two of each α & β chain

MHC Class II genes NON CLASSICAL GENES

Encoding several antigen processing genes:

HLA-DM α and β (loading of antigenic peptide), proteasome components LMP-2 & 7, peptide transporters

TAP-1 & 2, HLA-DO α and DO β (thymus & mature B cells regulators of loading antigen peptide)

Many pseudogenes

MHC Class III genes

CLASS 3 genes are between CLASS 1 & 2

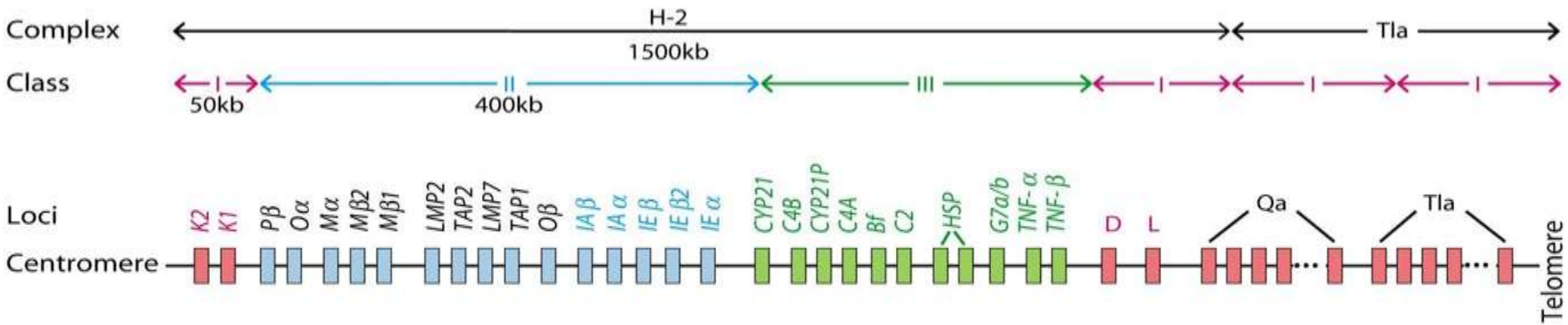
Encoding complement proteins C4A and C4B, C2 and FACTOR B
TUMOUR NECROSIS FACTORS α AND β

Immunologically irrelevant genes

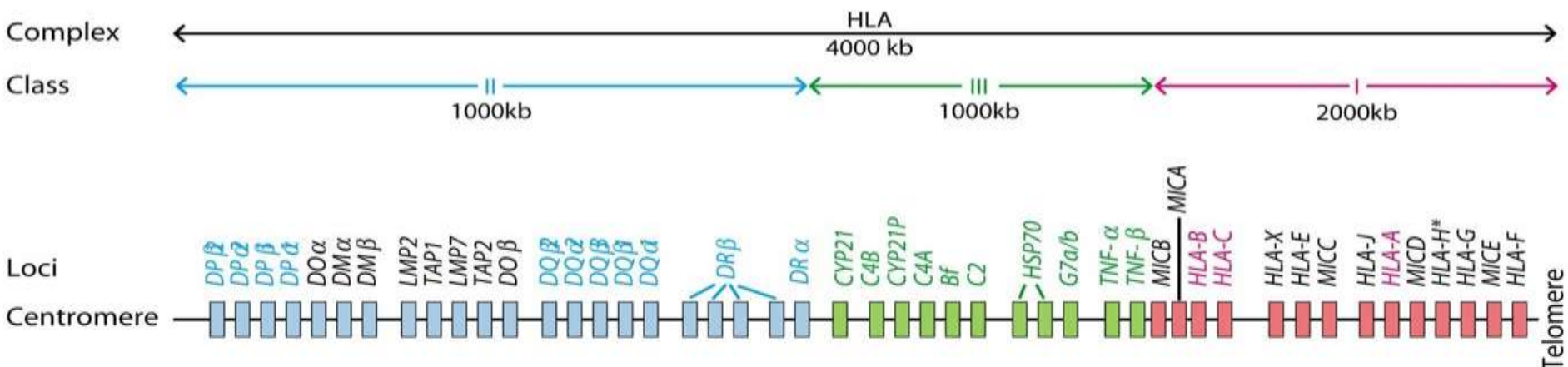
Genes encoding 21-hydroxylase, RNA Helicase, Caesin kinase
Heat shock protein 70, Sialidase

Congenital adrenal hyperplasia , mutation in gene encoding 21
hydroxylase. The presence of linked class 3 genes is cluster is
conseved in all species with MHC

MOUSE CHROMOSOME 17



HUMAN CHROMOSOME 6



KEY

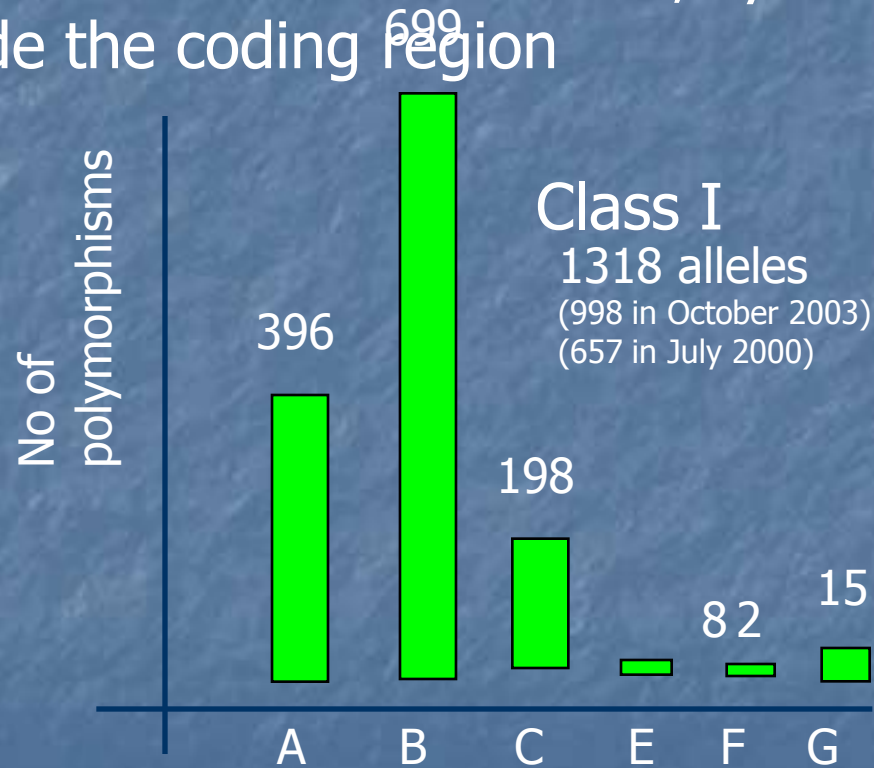
Gene	Encoded protein
C2, C4A, C4B, Bf	Complement components
CYP21, CYP21P	Steroid 21-hydroxylases
G7a/b	Valyl-tRNA synthetase
HSP	Heat-shock protein
LMP2, LMP7	Proteasome-like subunits
TAP1, TAP2	Peptide-transporter subunits
TNF-α, TNF-β	Tumor necrosis factors α and β

*Now designated HFE

Polymorphism in MHC Class I genes

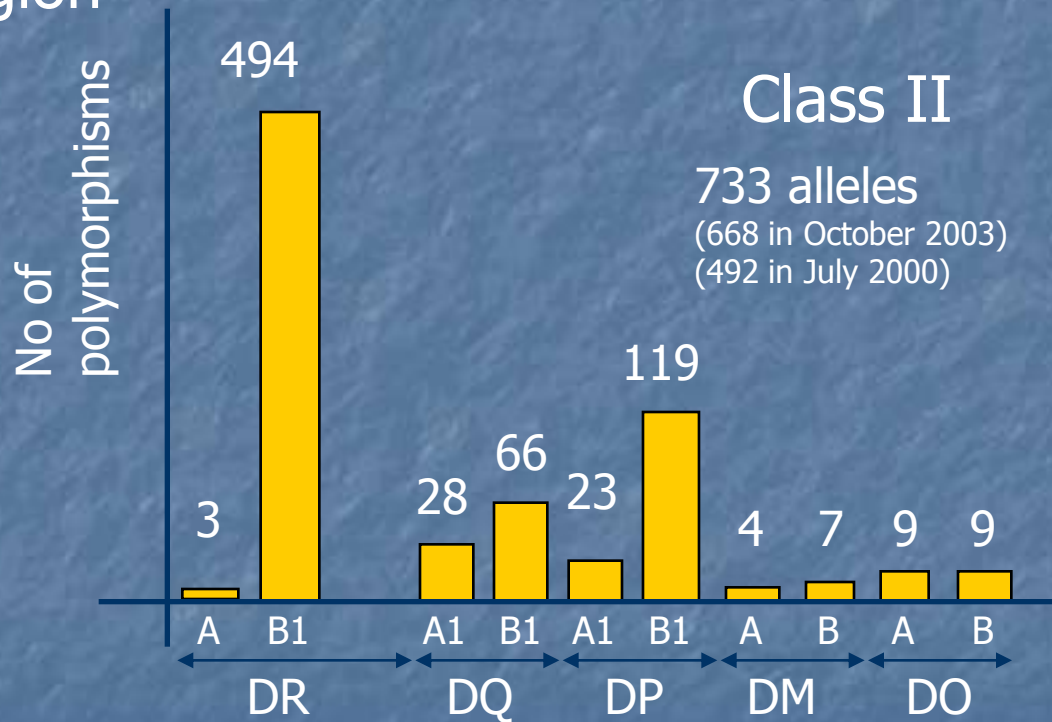
Variation $>1\%$ at a single genetic locus in a population of individuals

In the human population, over 1300 MHC class I alleles have been identified - some are null alleles, synonyms or differ in regions outside the coding region



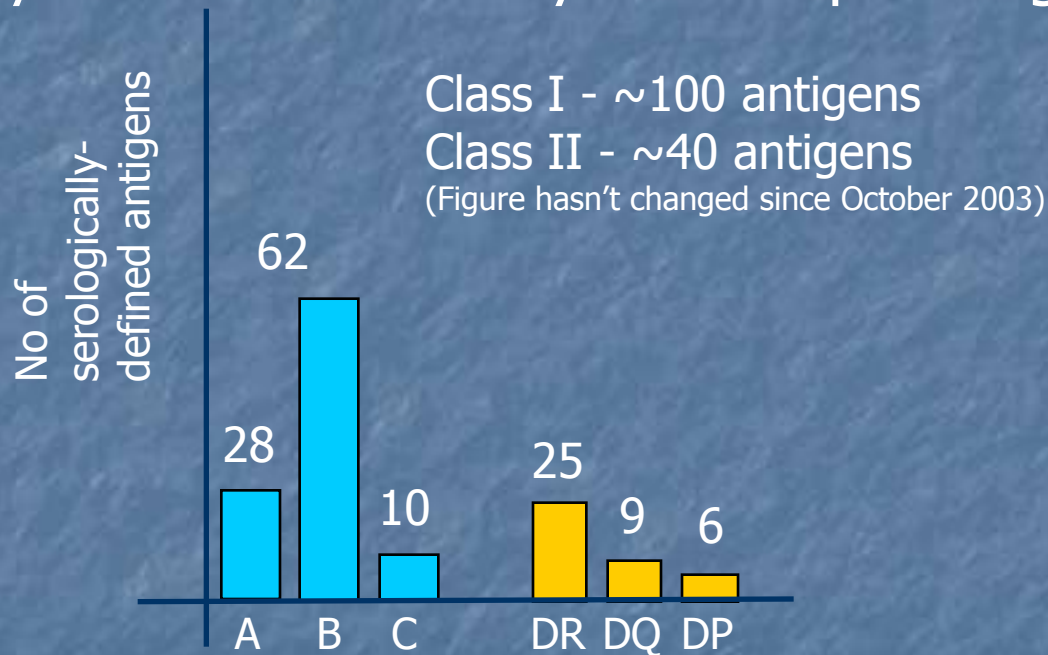
Polymorphism in MHC Class II genes

Over 700 human MHC class II alleles have been identified - some are null alleles, synonyms or differ in regions outside the coding region



Diversity of MHC Class I and II antigens

Because so many MHC class I & II alleles are null, or contain synonymous mutations, the diversity of MHC molecules that can be identified by antibodies i.e. **SEROLOGICALLY**, is considerably fewer than that by DNA sequencing



Data from www.anthonynolan.org.uk/HIG/index.html September 2005

Most polymorphisms are point mutations

Replacement substitutions occur at a higher frequency than silent substitution

Suggests that selective pressures may operate on MHC polymorphism

Evolution of pathogens to evade MHC-mediated antigen presentation

60% of individuals in south east China & Papua New Guinea express HLA-A11

HLA-A11 binds an important peptide of Epstein Barr Virus

Many EBV isolates from these areas have mutated this peptide so that it can not bind to HLA-A11 MHC molecules

Evolution of the MHC to eliminate pathogens

In west Africa where malaria is endemic HLA-B53 is commonly associated with recovery from a potentially lethal form of malaria

How diverse are MHC molecules in the population?

- IF*
- each individual had 6 types of MHC
 - the alleles of each MHC type were randomly distributed in the population
 - any of the 1,200 alleles could be present with any other allele

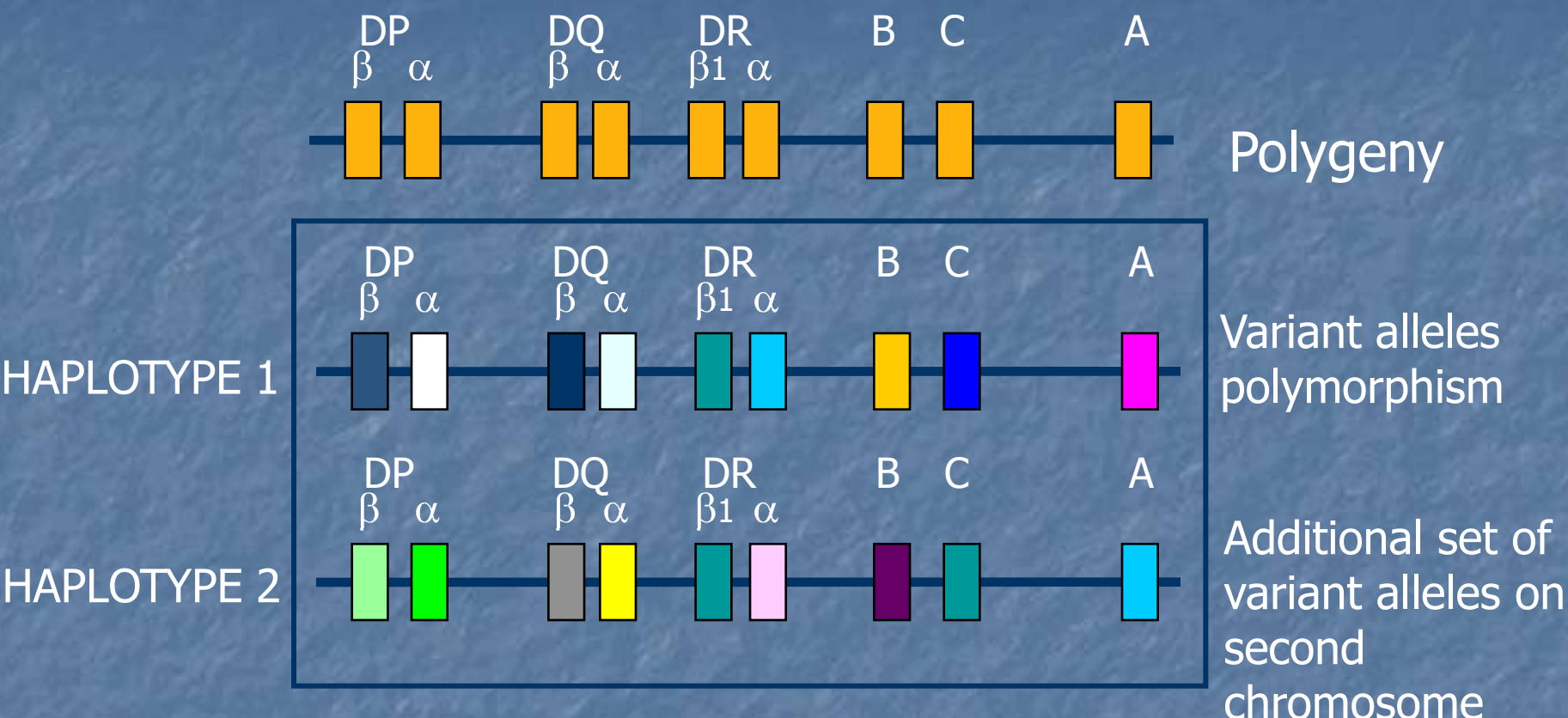
~6 x 10¹⁵ unique combinations

Group of alleles	Frequency (%)		
	CAU	AFR	ASI
HLA-A1	15.18	5.72	4.48
HLA- A2	28.65	18.88	24.63
HLA- A3	13.38	8.44	2.64
HLA- A28	4.46	9.92	1.76
HLA- A36	0.02	1.88	0.01

In reality MHC alleles are NOT randomly distributed in the population

Alleles segregate with lineage and race

Diversity of MHC molecules in the individual

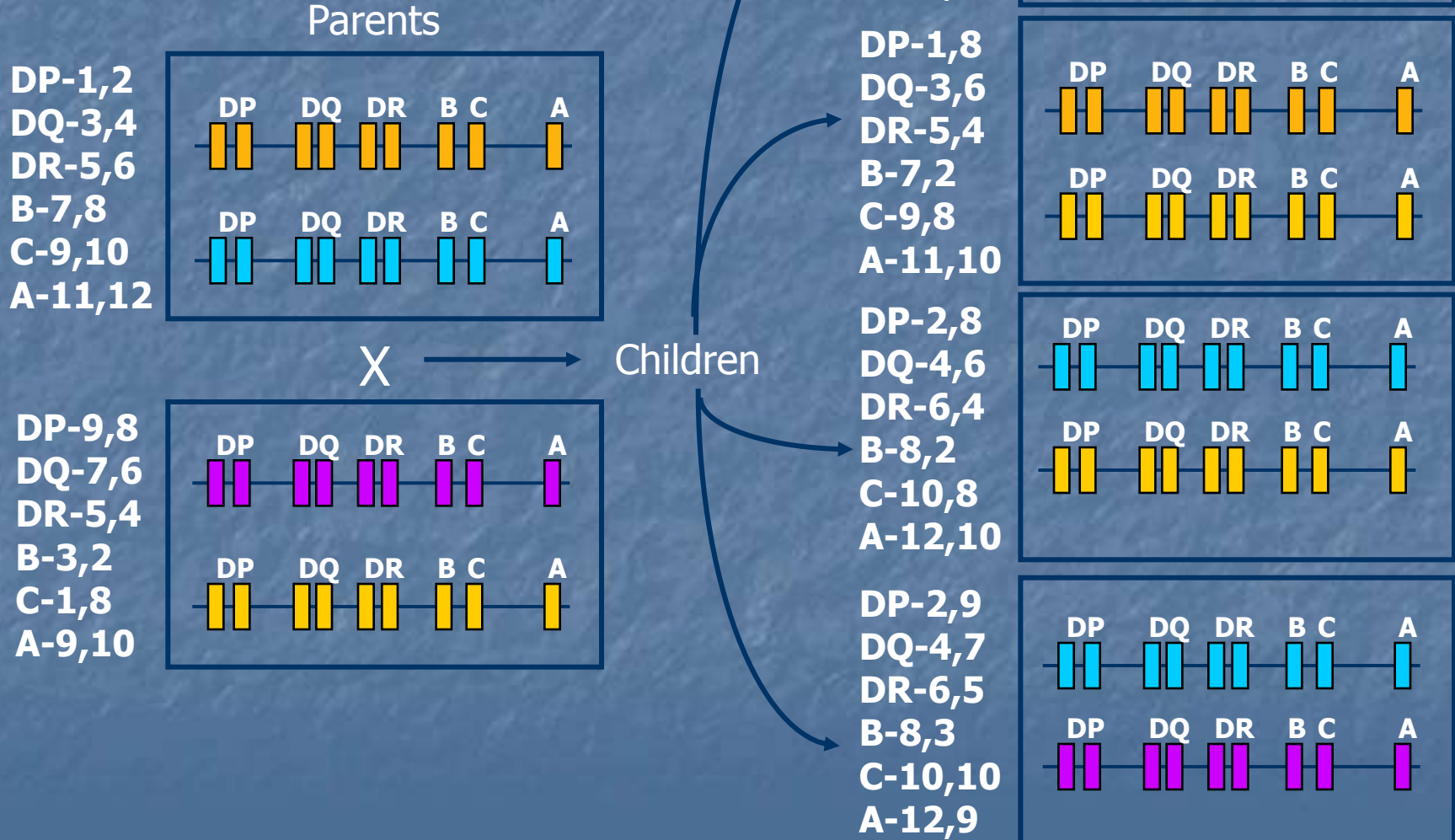


MHC molecules are **CODOMINANTLY** expressed
 Two of each of the six types of MHC molecule are expressed

Genes in the MHC are tightly **LINKED** and usually inherited in a unit called an **MHC HAPLOTYPES**

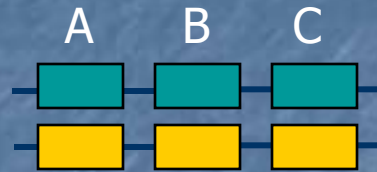
Inherited as 2 sets (one from father, one from mother)

Inheritance of MHC haplotypes

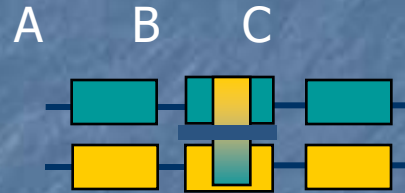


Errors in the inheritance of haplotypes generate polymorphism in the MHC by gene conversion and recombination

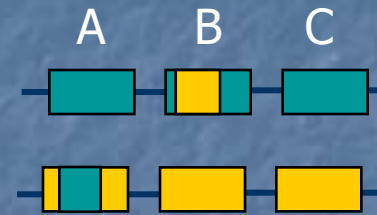
GENE CONVERSION



Multiple distinct but closely related MHC genes

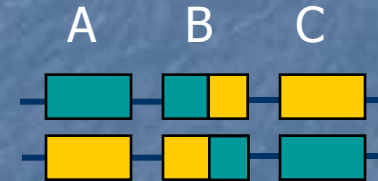
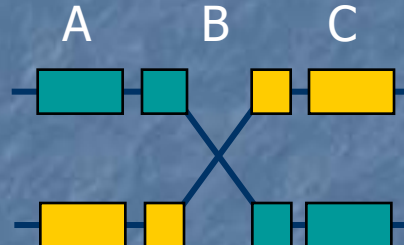
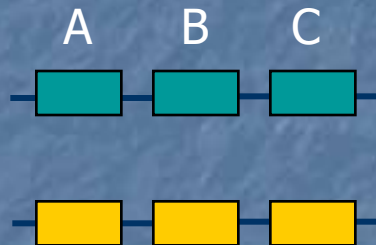


During meiosis chromosomes misalign



Chromosomes separate after meiosis DNA is exchanged between haplotypes

RECOMBINATION between haplotypes



In both mechanisms the **type** of MHC molecule remains the same, but a new allelic variant may be generated.

However, Crossover Rate Is Low 0.5%

MHC polymorphism and Organ Transplants & Autoimmune disorders

- Developing T cells that recognize complexes of peptide and MHC molecules on HEALTHY tissue (self-peptides presented by self MHC) are DESTROYED
- This results in the preservation of T cells that recognize non-self MHC (allogenic MHC). Called alloreactive T cells (1-10%) of total T-cell repertoire
- It is primed for REJECTION OF FOREIGN ORGANS that express allogenic MHC
- Those MHC of healthy tissue that are unable to present peptides to developing T cells, leads to the production of T & B cells that are autoreactive causing AUTOIMMUNE DISORDERS

A clinically relevant application of MHC genetics: Matching of transplant donors and recipients

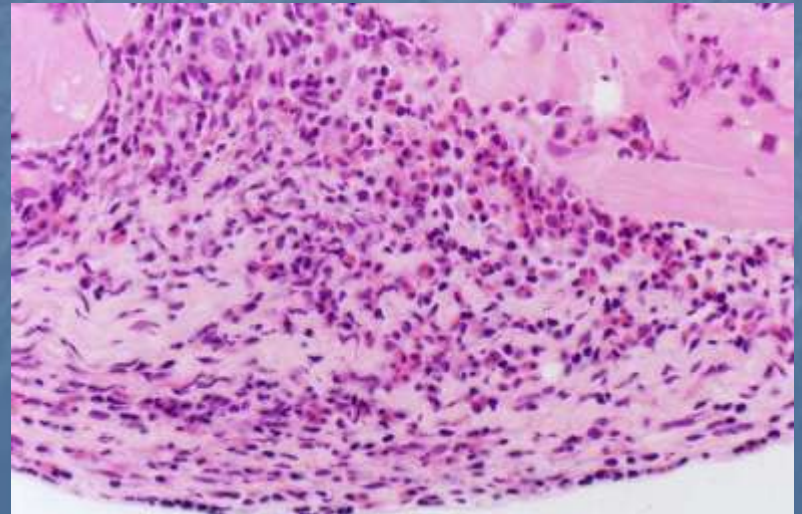
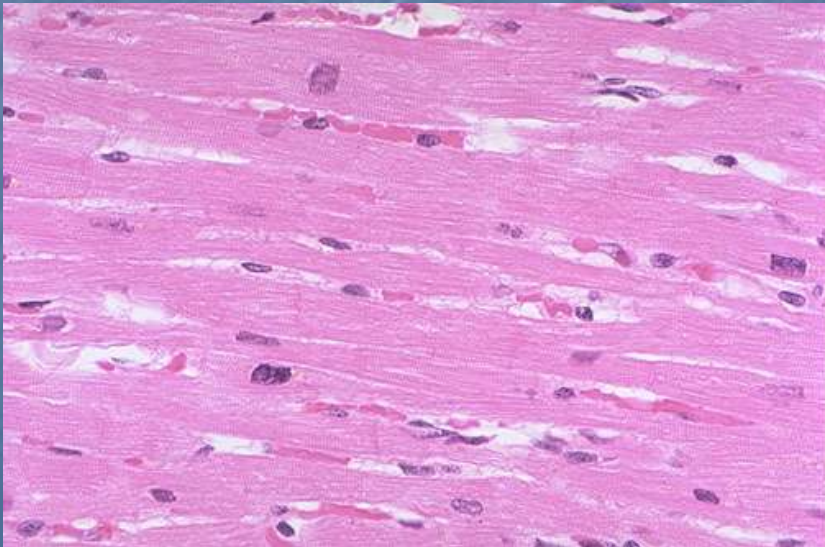
The biology, diversity and complexity of the MHC locus and its pattern of inheritance explains:

- The need to match the MHC of the recipient of a graft with the donor
- The difficulties faced in matching unrelated donors with recipients
- The ~20% chance of finding a match in siblings

IMMUNE GRAFT REJECTION

If unmatched MHC transplantation takes place, then T cells recognize them as foreign and generate an immune response, that can lead to graft failure.

Rejection of transplanted tissue was associated with inflammation and lymphocyte infiltration



AUTOIMMUNITY AND MHC

- It is well recognized that certain immune disorders predominate in families.
- Determined by family studies.
- Genetic links have occurred between diseases and HLA antigens
- Sometimes,,, there is another non MHC gene cause that is related to a specific MHC gene that is related to autoimmune disease.
- The mechanisms of tissue damage in autoimmune diseases are essentially the same as those that operate in protective immunity.

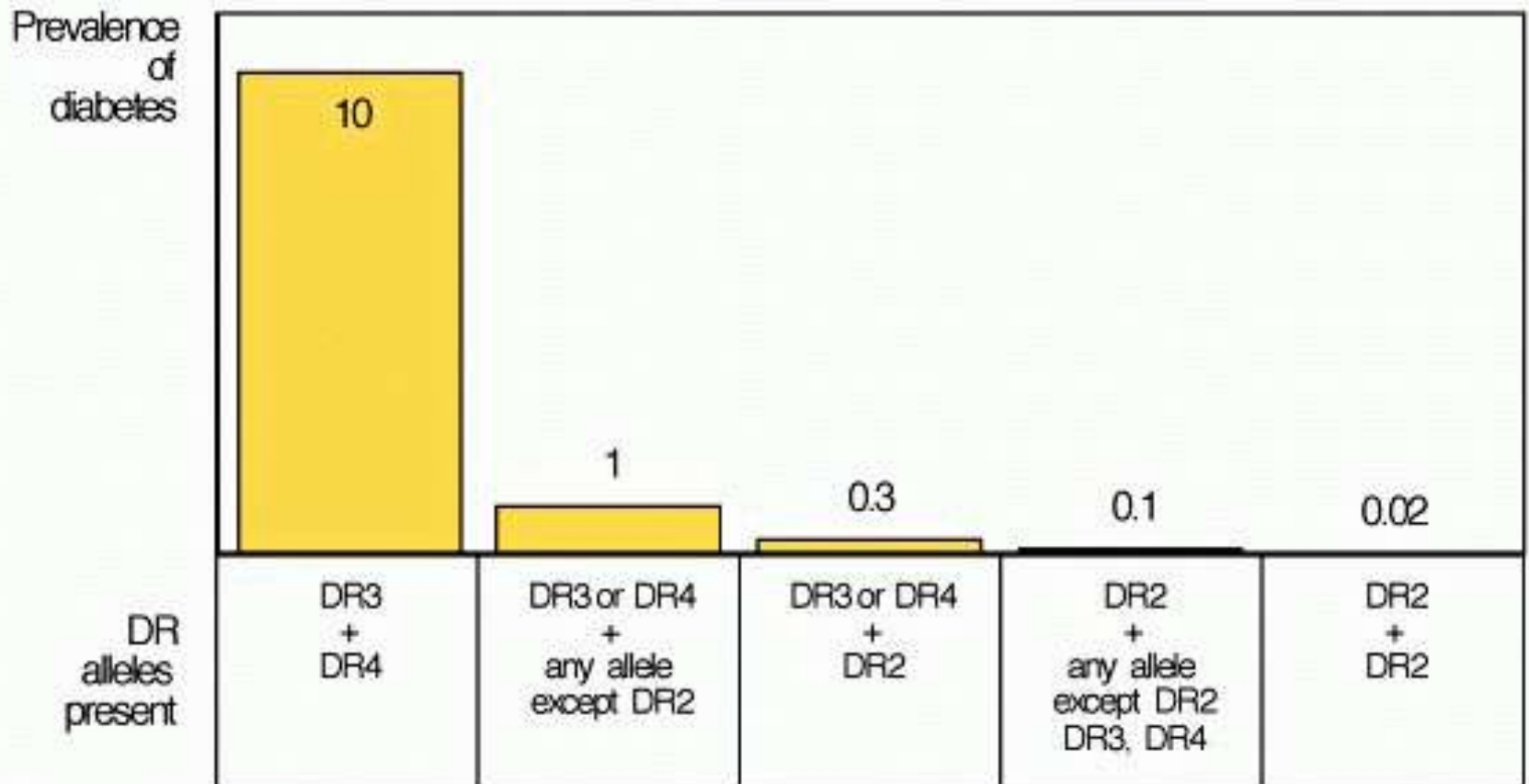
Association of HLA Serotype with Susceptibility to Autoimmune Diseases

Disease	HLA allele	Relative risk	Sex ratio (♀: ♂)	
Hip joints Eyes	Ankylosing spondylitis	B27	87.4	0.3
	Acute anterior uveitis	B27	10	<0.5
Kidneys	Goodpasture's syndrome	DR2	15.9	~1
CNS	Multiple sclerosis	DR2	4.8	10
Thyroid	Graves' disease	DR3	3.7	4-5
Muscles	Myasthenia gravis	DR3	2.5	~1
Systemic	Systemic lupus erythematosus	DR3	5.8	10-20
Pancreas	Type 1 (insulin-dependent) diabetes mellitus	DR3/DR4 heterozygote	~25	~1
Small joints	Rheumatoid arthritis	DR4	4.2	3
Skin	Pemphigus vulgaris	DR4	14.4	~1
Thyroid	Hashimoto's thyroiditis	DR5	3.2	4-5

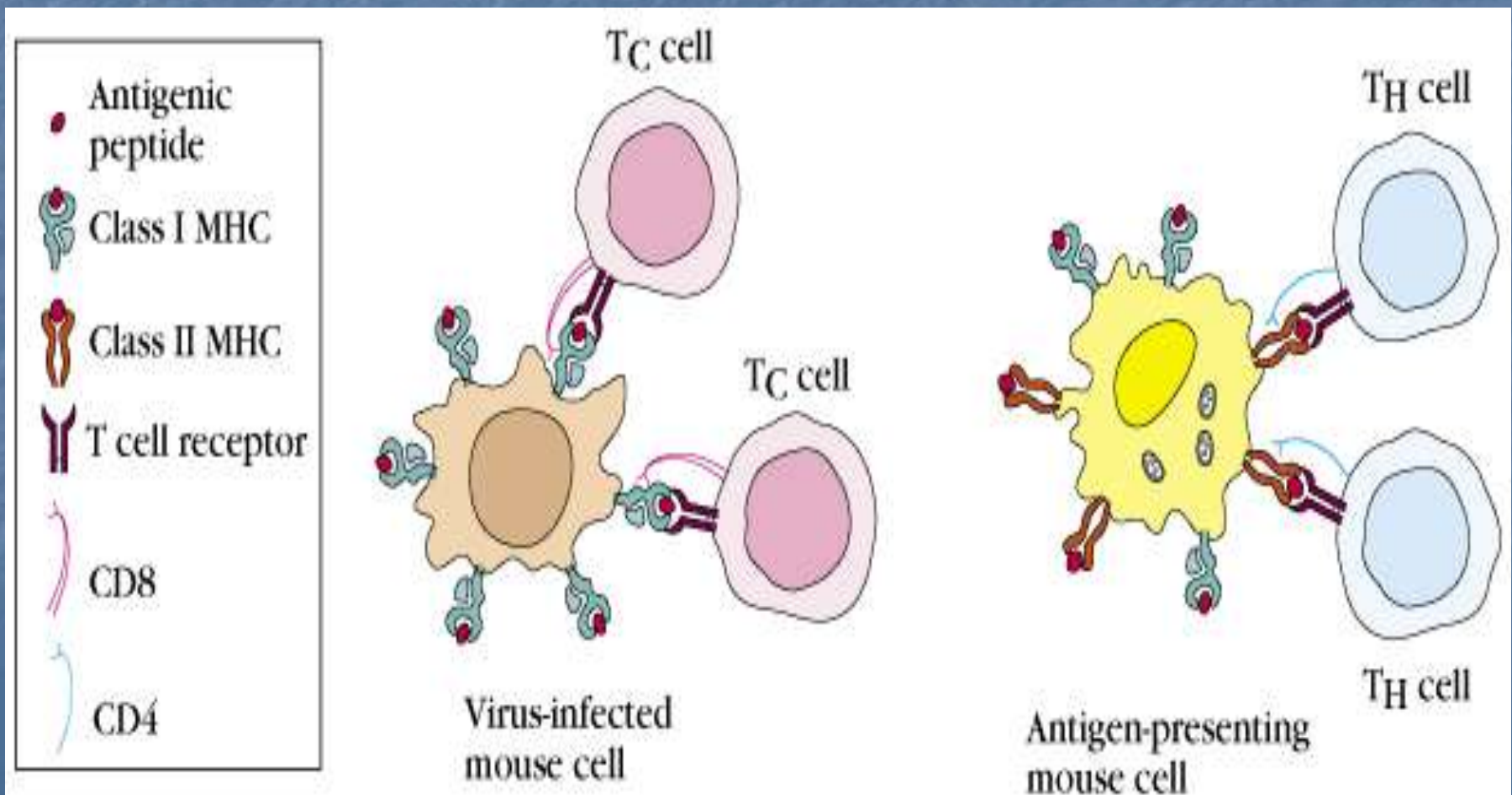
Figure 14-33 Immunobiology, 7ed. (© Garland Science 2008)

Population studies show association of susceptibility to insulin-dependent diabetes mellitus (IDDM) with HLA genotype

Population studies of HLA-DR alleles in insulin-dependent diabetes mellitus



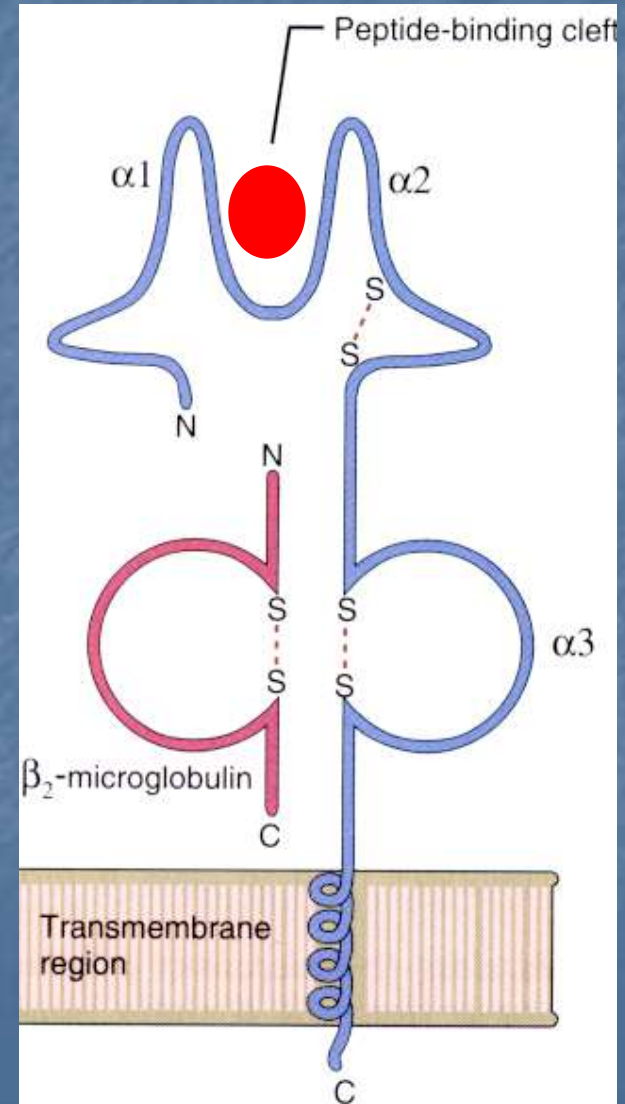
Antigen processing and presentation pathways



MHC I

In particular, cell surface **MHC class I** glycoproteins gather from the cell's biosynthetic pathway fragments of proteins derived from infecting viruses, intracellular parasites, or self molecules, either normally expressed or dysregulated by tumorigenesis, and then display these **molecular fragments** at the cell surface.

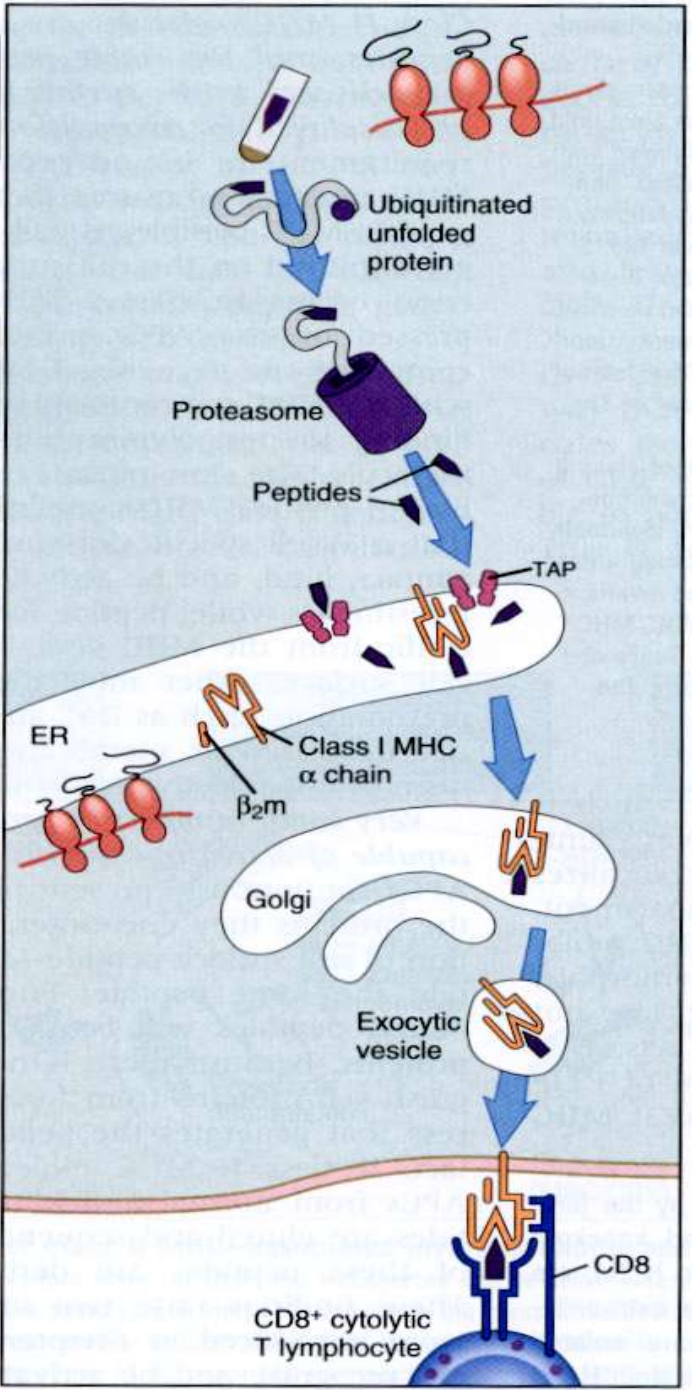
Anucleate erythrocytes can not support virus replication - hence no MHC class I. Some pathogens exploit this - e.g. *Plasmodium* species.



MHC I

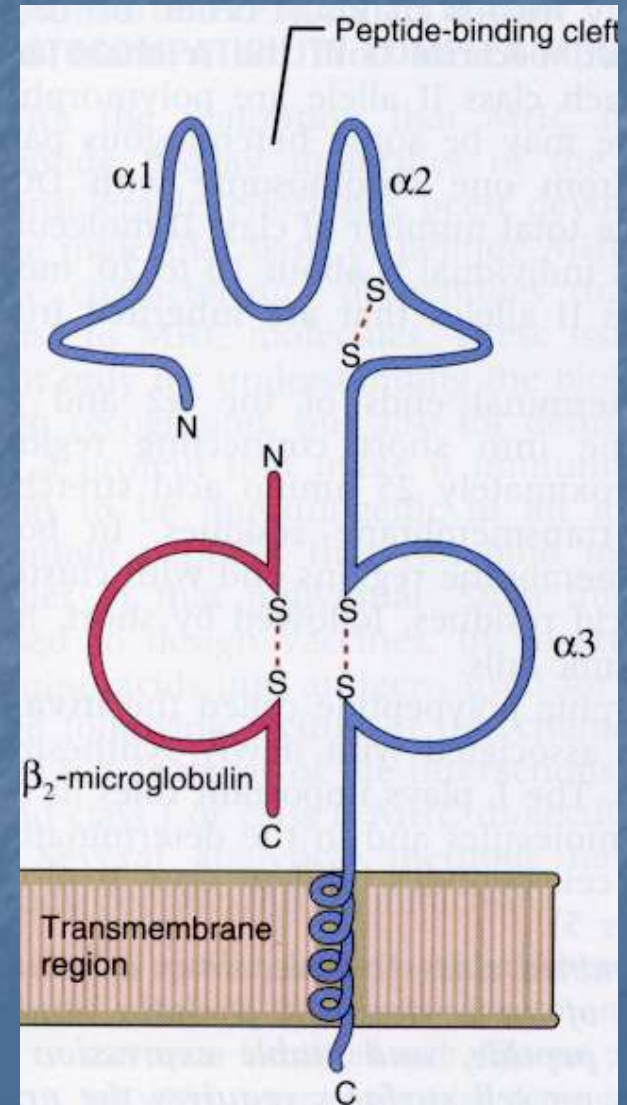
Peptides derived from proteins found in the cytosol that are then degraded by the multiproteolytic **proteasome** complex into peptides. As Few As 100 Peptide/MHC Complex Can Activate T_C

- 1 Production of proteins in the cytosol
- 2 Proteolytic degradation of cytosolic proteins
- 3 Transport of peptides from cytosol to ER
- 4 Assembly of peptide-class I complexes in ER
- 5 Surface expression of peptide-class I complexes



MHC I

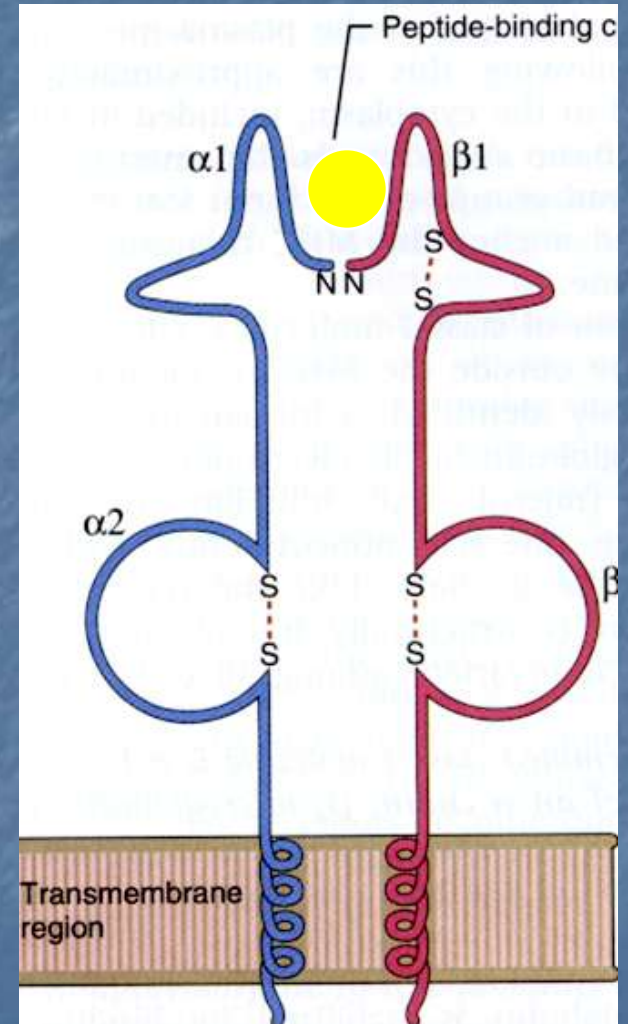
- The MHC-I molecule, the ability to interact with **TCR**, then allows the APC bearing a particular MHC–peptide complex to engage an appropriate **$\alpha\beta$ TCR** as the first step in the activation of a CD8⁺ cellular program that might lead to cytolysis of the APC as a target and/or to the secretion of lymphokines by the T cell.



Vedio

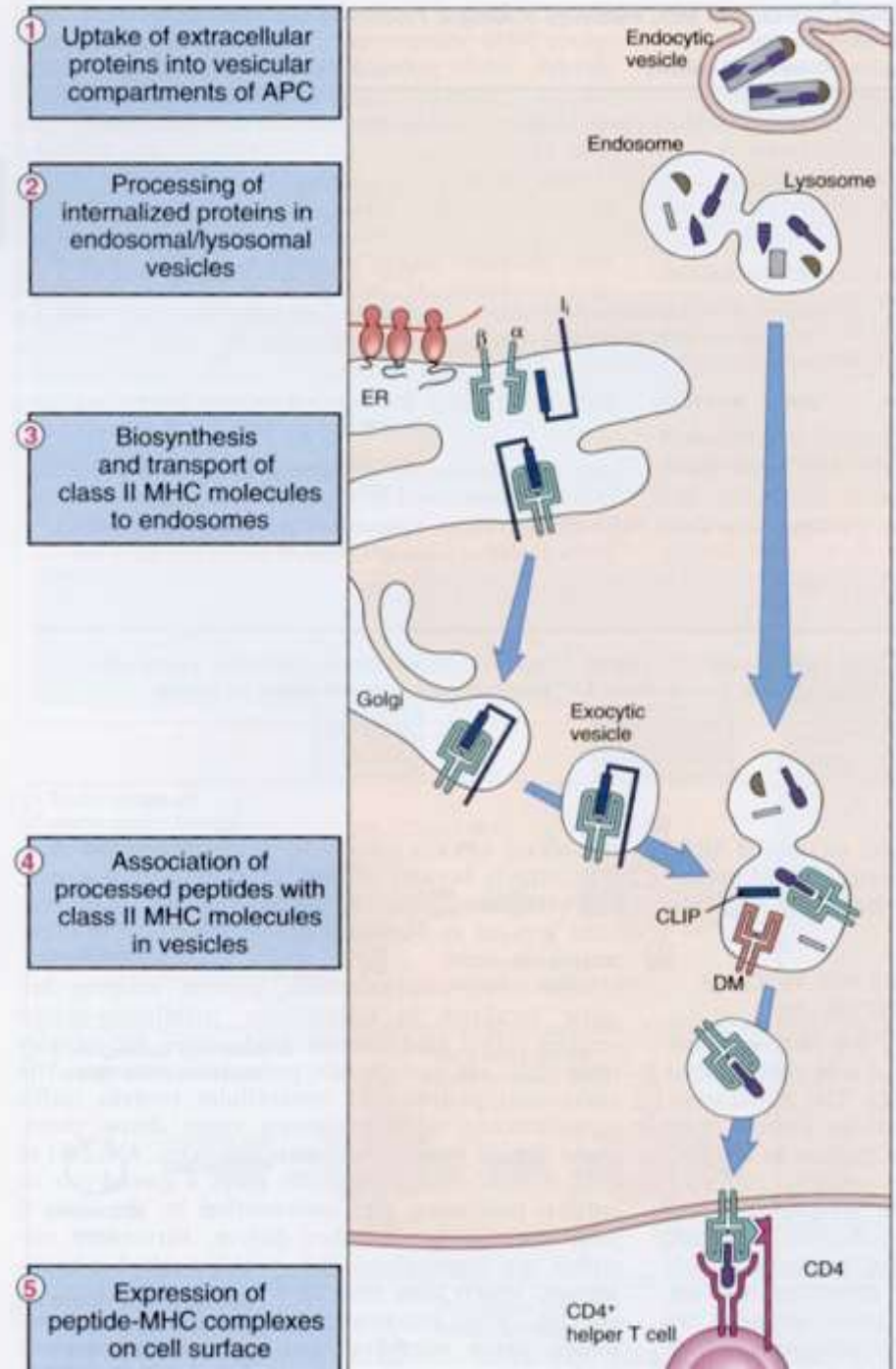
MHC II

- **MHC class II** molecules bind peptides derived from the degradation of proteins **ingested** by MHC-II-expressing APC, and display them at the cell surface for recognition by specific T-lymphocytes.



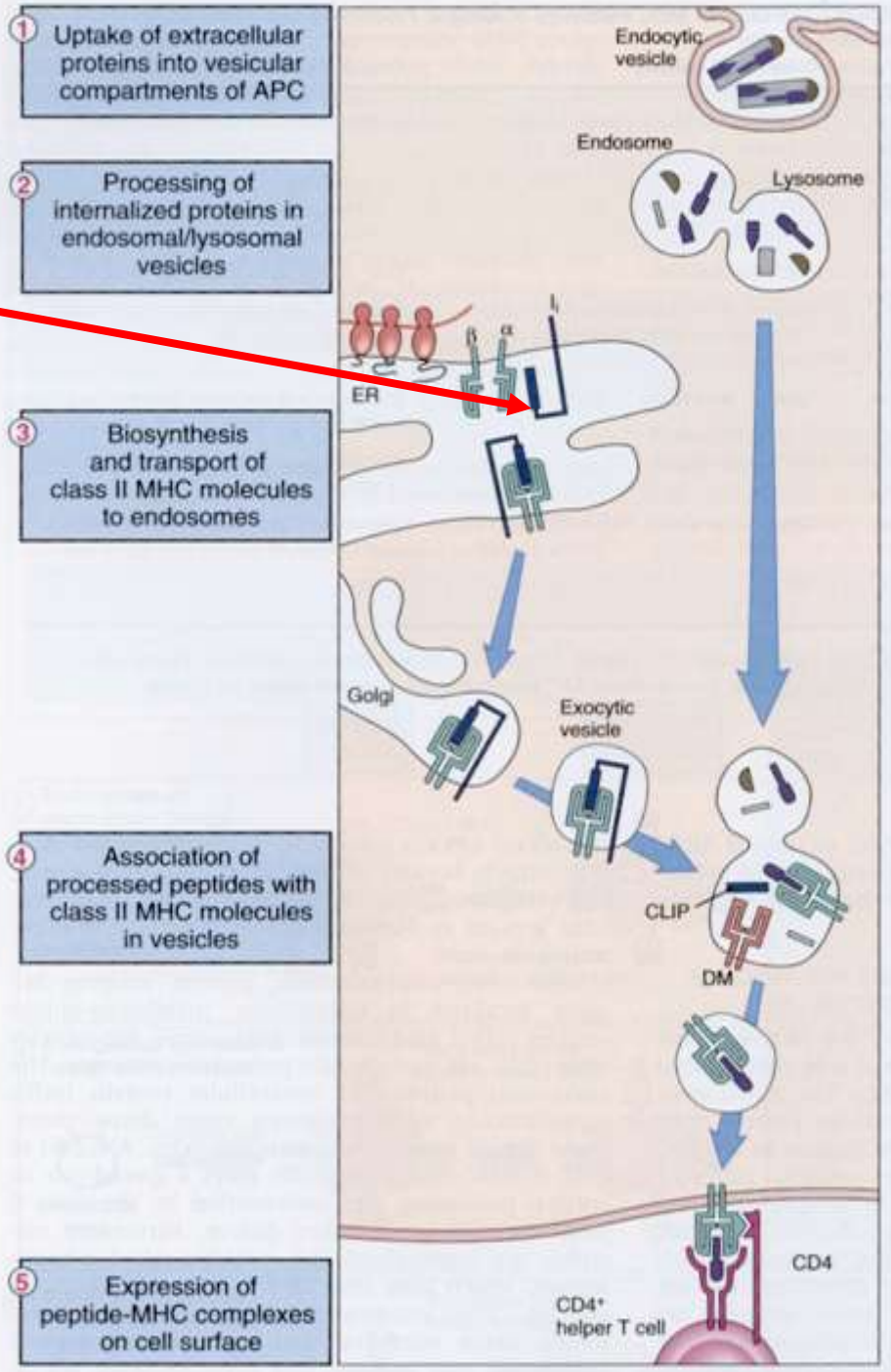
MHC II

The MHC-II antigen presentation pathway is based on the initial assembly of the MHC-II $\alpha\beta$ heterodimer with a dual function molecule.



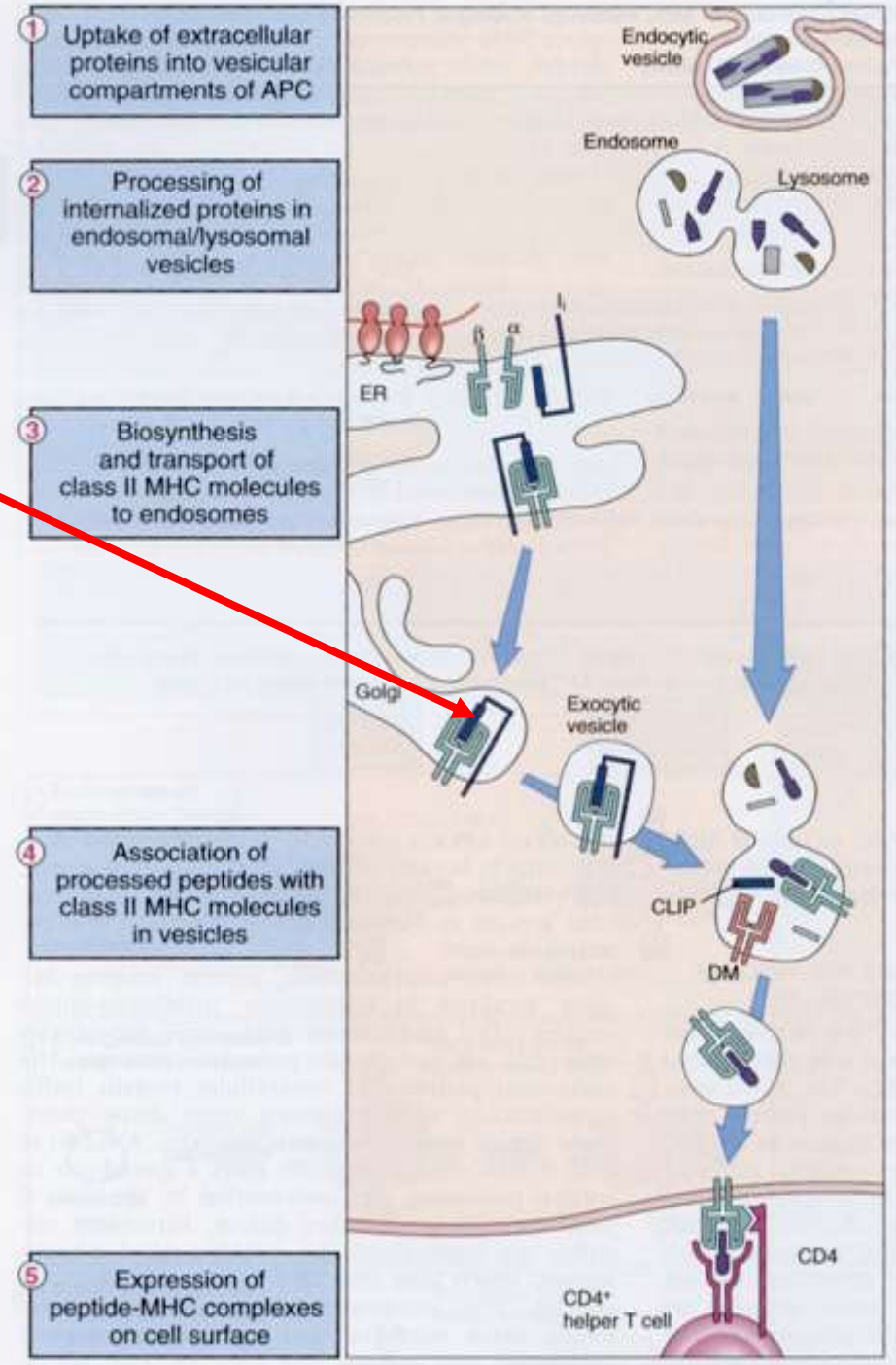
MHC II

The **invariant chain (Ii)** that serves as a chaperone to direct the $\alpha\beta$ heterodimer to an endosomal, acidic protein-processing location.



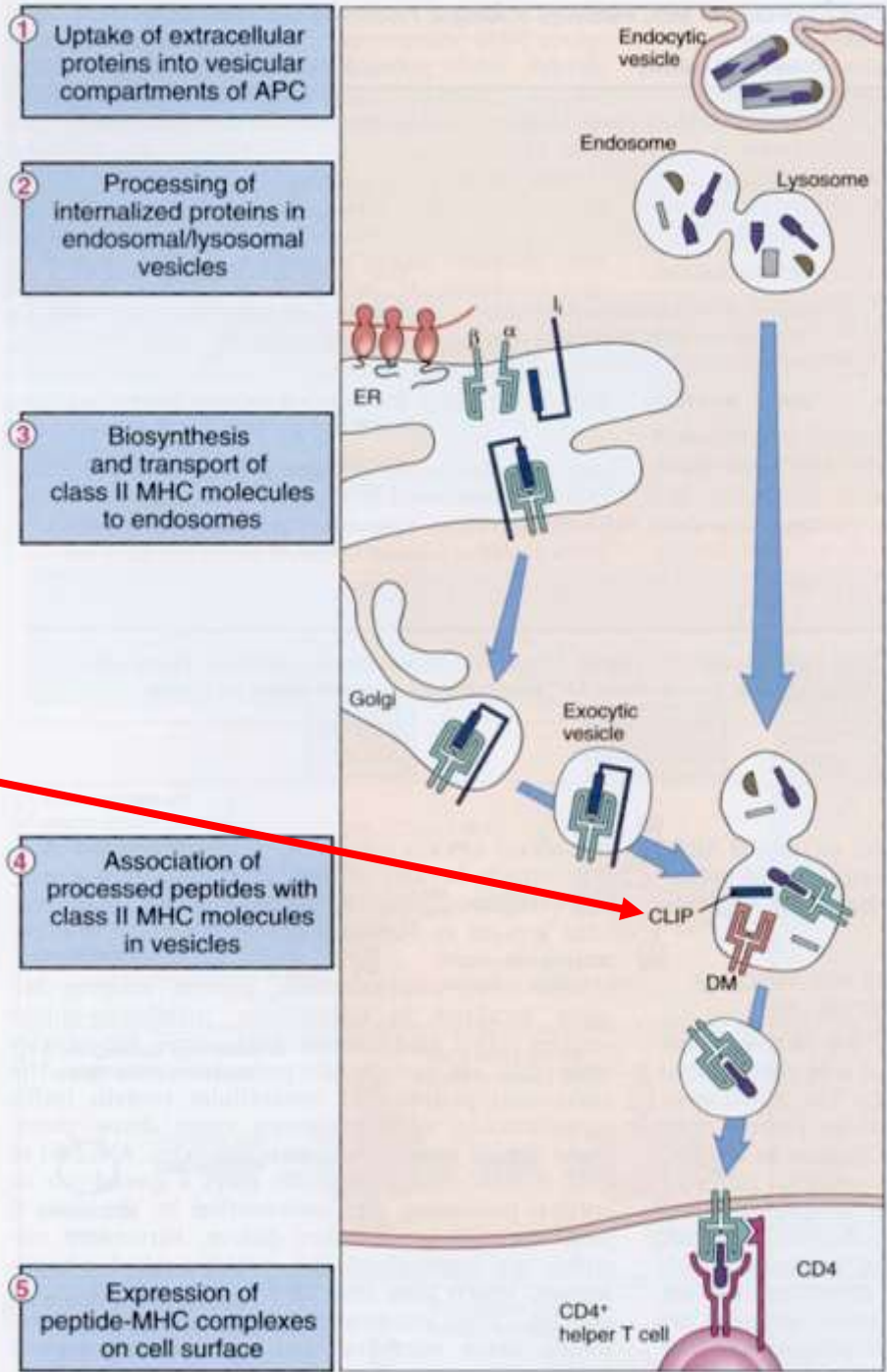
MHC II

Where **Ii** encounters antigenic peptides, it serves to protect the antigen-binding site of the MHC-II molecule so that it preferentially will be loaded with antigenic peptides in this endosomal-lysosomal location.



MHC II

The loading of the MHC-II molecule with antigenic peptide, a process dependent on the release of the Ii-derived **CLIP** peptide, in part dependent on the MHC-II-like molecule leads to the cell surface expression of MHC-II peptide complexes.



MHC molecules on the cell surface display peptide fragments

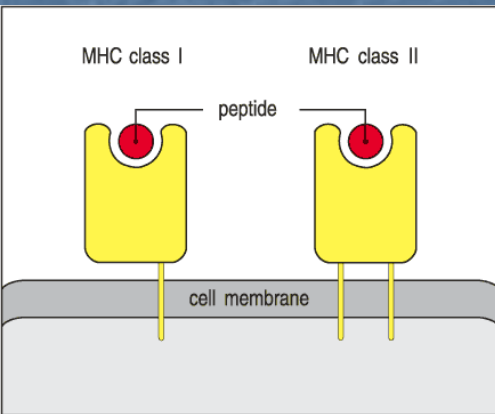


Fig 1.27 © 2001 Garland Science

Eg HIV

Cytotoxic T cell recognizes complex of viral peptide with MHC class I and kills infected cell

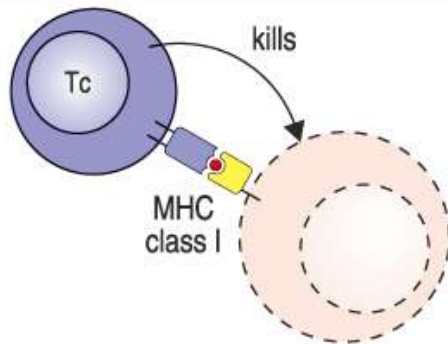


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T_H1 cell recognizes complex of bacterial peptide with MHC class II and activates macrophage

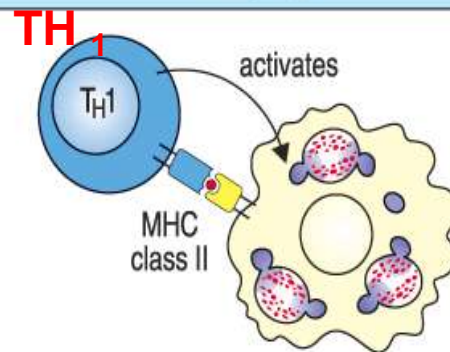
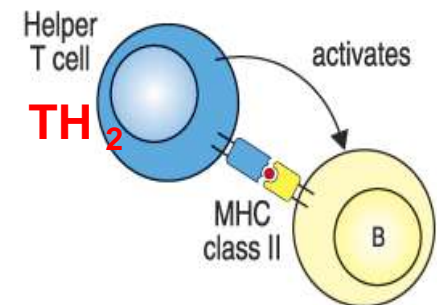


Fig 1.31 © 2001 Garland Science

Helper T cell recognizes complex of antigenic peptide with MHC class II and activates B cell



vedio

MHC Expression

- Expression Is Regulated By Many Cytokines
 - $IFN\alpha$, $IFN\beta$, $IFN\gamma$ and TNF Increase MHC expression
- Transcription Factors That Increase MHC gene Expression
 - CIITA (Transactivator), RFX (Transactivator)
- Some Viruses Decrease MHC Expression
 - CMV, HBV, Ad12
- Reduction Of MHC May Allow For Immune System **Evasion**

Thank you!
Jim

