HLA and antigen presentation

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MHC in adaptive immunity

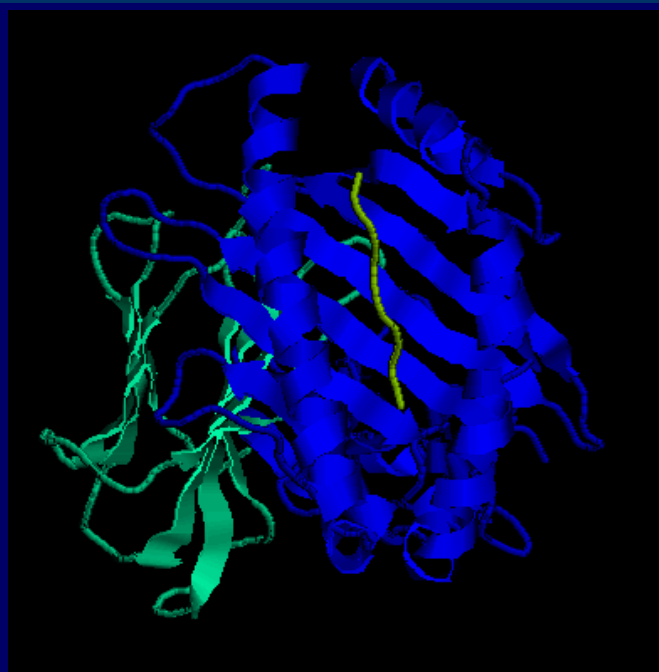
	Innate	Adaptive
Characteristics		
Specificity	For structures shared by groups of related microbes	For antigens of microbes and for nonmicrobial antigens
Diversity	Limited; germline-encoded	Very large; receptors are produced by somatic recombination of gene segments
Memory	None	Yes
Nonreactivity to self	Yes	Yes
Components		
Physical and chemical barriers	Skin, mucosal epithelia; antimicrobial chemicals	Lymphocytes in epithelia; antibodies secreted at epithelial surfaces
Blood proteins	Complement	Antibodies
Cells	Phagocytes (macrophages, neutrophils), natural killer cells	T and B Lymphocytes

T cells recognise cell-associated antigens displayed on

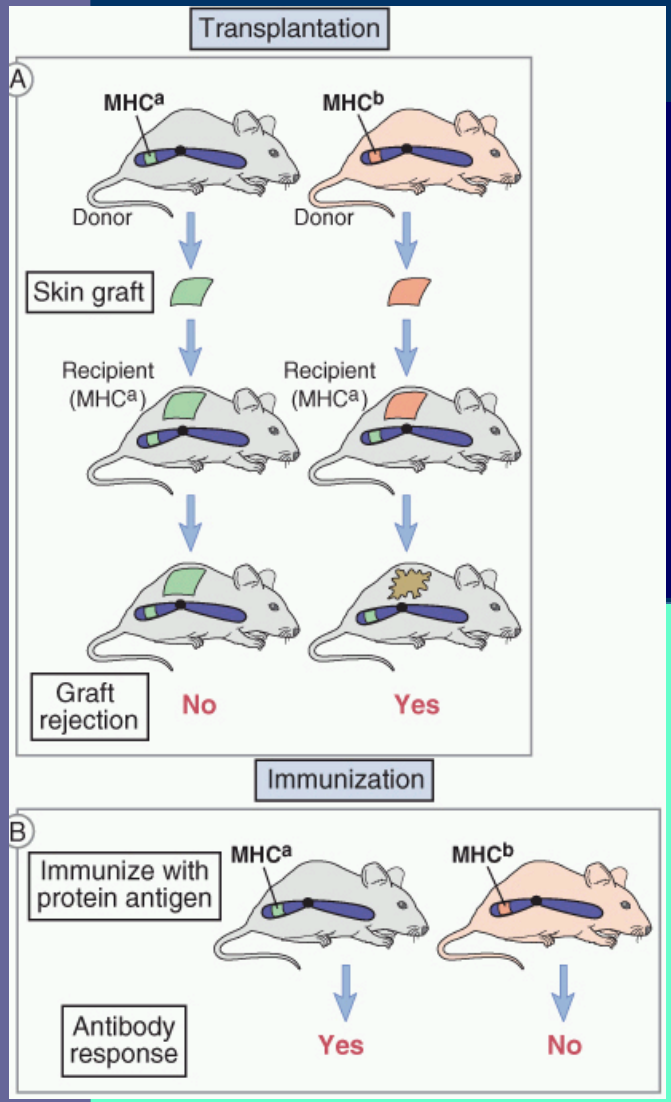
MHC = major histocompatibility complex

Topics

- Adaptive immunity, role of MHC (HLA)
- discovery of HLA genes
- structure of HLA genes and molecules
- polymorphism of HLA molecules
- nomenclature of HLA system
- HLA association with disease
- antigen presentation



Discovery of Human MHC



- Recognition of a graft as self or foreign is an inherited trait
- histocompatibility genes: differences between self and foreign were attributed to their genetic polymorphisms
- Mouse study: identification of MHC locus

- Human MHC

  In study with transplanted patients discovered „human leukocyte antigens“ HLAs

  HLA-A, HLA-B, HLA-C (class I MHC genes)

  In study of mixed leukocyte reaction identified HLA-DR, HLA-DP, HLA-DQ (class II MHC genes

HLA – MHC: basic facts

- Two groupes of MHC genes:

  structurally and functionally distinct

  class I recognition by CD8+ T cells

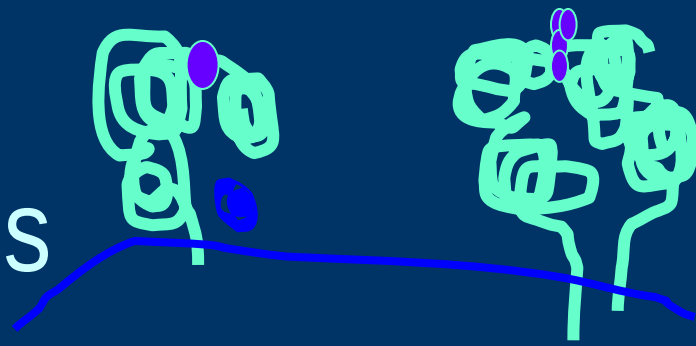
  class II recognition by CD4+ T cells

- HLA molecules are responsible for the compatibility of the tissues of genetically different individuals and for the rejection of transplant

- MHC genes are codominantly expressed in each individual
- monozygotic twins have the same histocompatibility molecules on their cells
- MHC genes are the most polymorphic genes present in the genome!

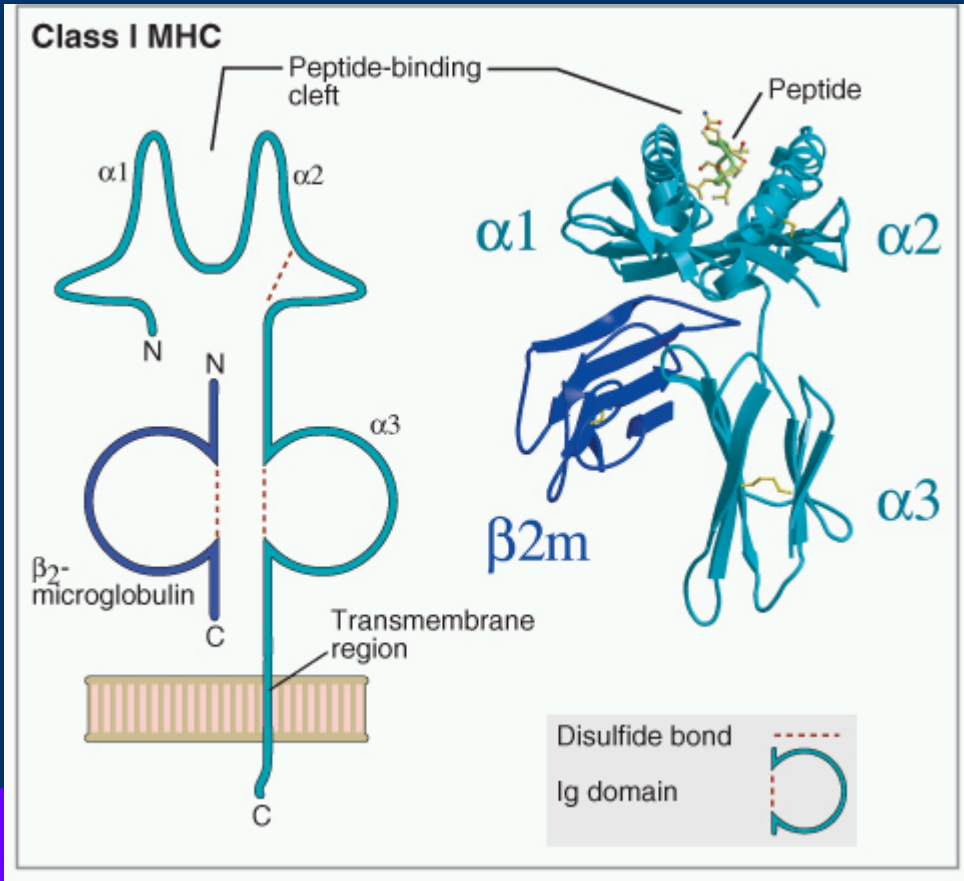
  (Up to 250 alleles identified for some loci)

structure of HLA molecules



- glycoproteins, heterodimers (two chains)
- Structure of HLA molecules of both classes enables antigen binding and contact with T cell receptors. Extracellulary located peptide binding cleft
- polymorphic (predominantly in the cleft).
- Nonpolymorphic part of the molecule contain binding sites for the T cell molecules CD4 and CD8

HLA class I. molecules



1. Heavy chain

α1, α2 domain: polymorphic sites

α3 domain: binding of CD8

2. β-2 microglobulin
3. peptide

Structure of HLA class II. molecules

1. α chain

α1: polymorphic sites

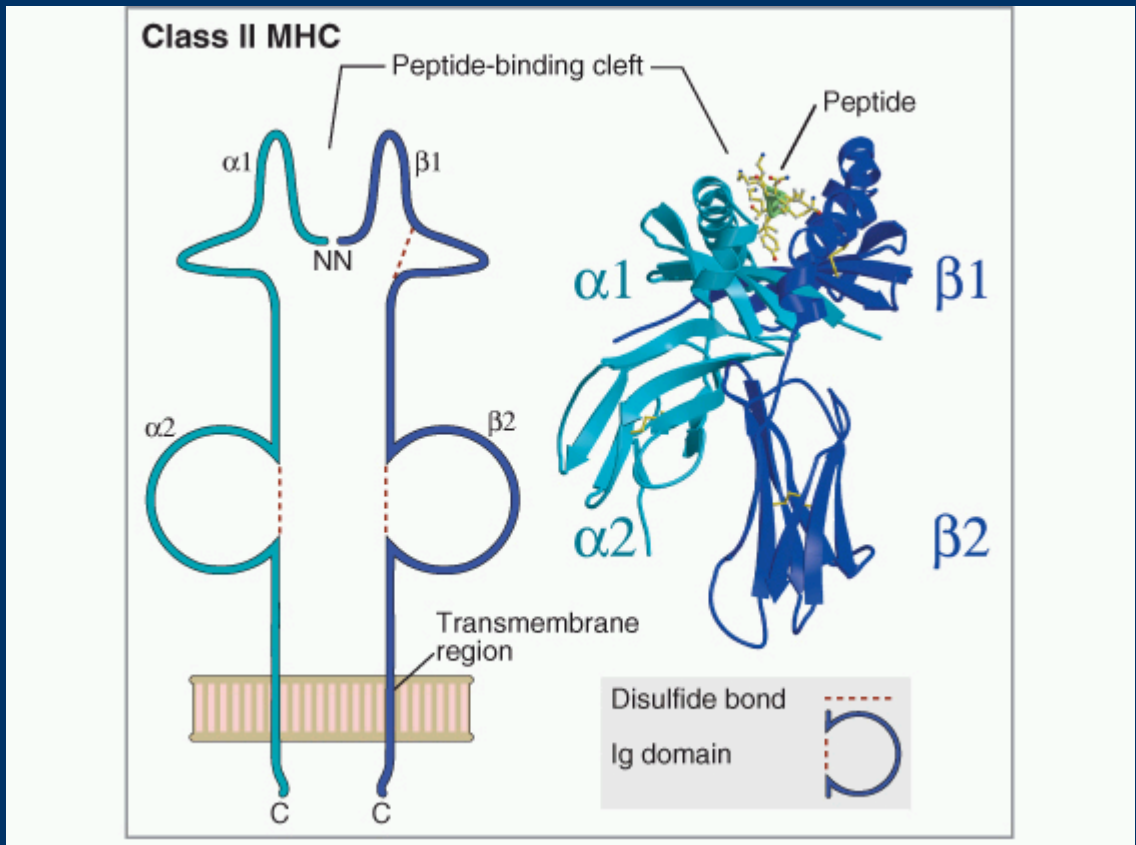
α2: binding of CD4

2. β chain

β1: polymorphic sites

β2: binding of CD4

3. peptide

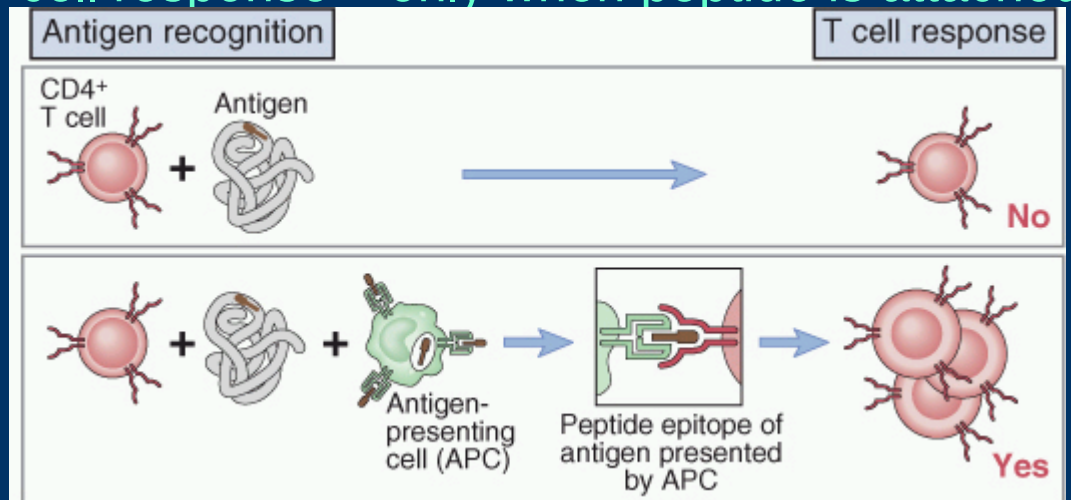


HLA and antigens

- Most T lymphocytes recognize only peptides
- T cells are specific for amino acid sequences of peptides - TCR
- Intracellular antigens are presented in connection with HLA class I. - CD8+ T cells recognition
- Extracellular antigens are presented in connection with HLA class II.
  – CD4+ T cells recognition

Experiment:

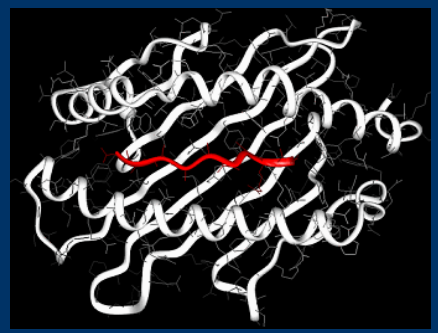
- T cell response – only when peptide is attached to APC

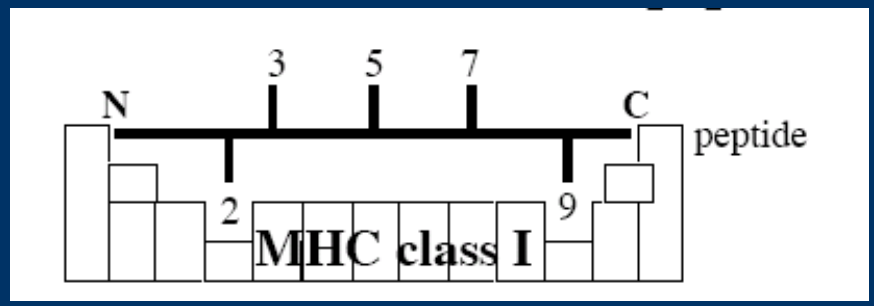


HLA and peptides

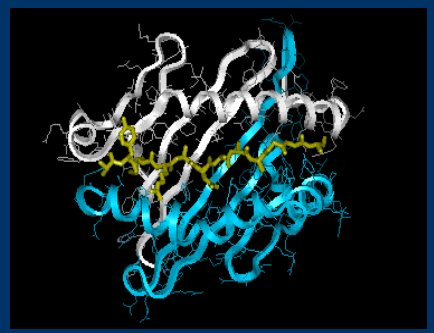
- antigenic peptides in the binding sites of HLA molecules
- One MHC - many peptides sharing structural features can bind
- Interaction has a very slow on- and off-rate (very stable)

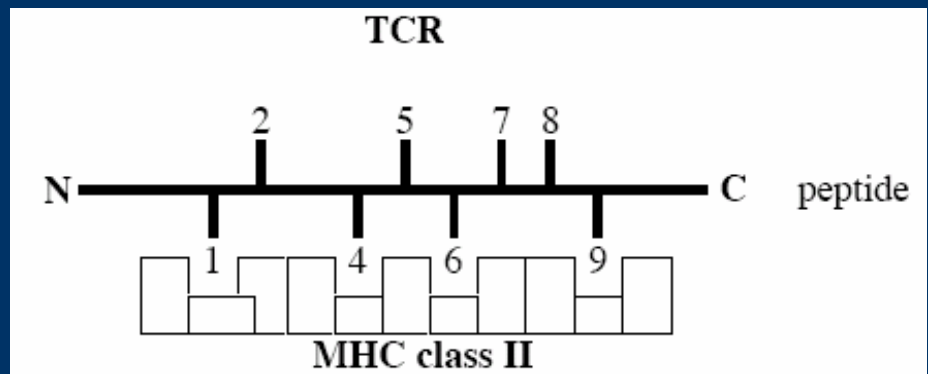
- class I.





- class II.





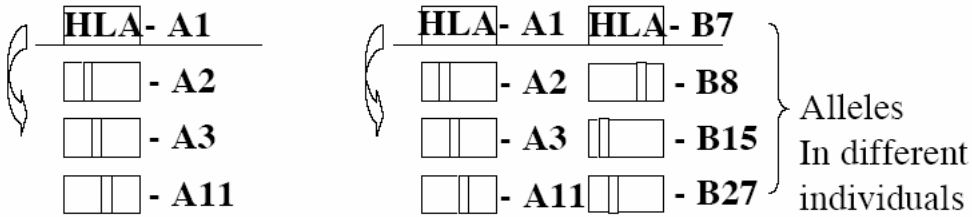
Diversity of MHC class I and II genes

Diversity of MHC class I and II genes

Arises from two mechanisms:

Duplication of a gene locus in an individual resulting in multiple loci, *polygeny*

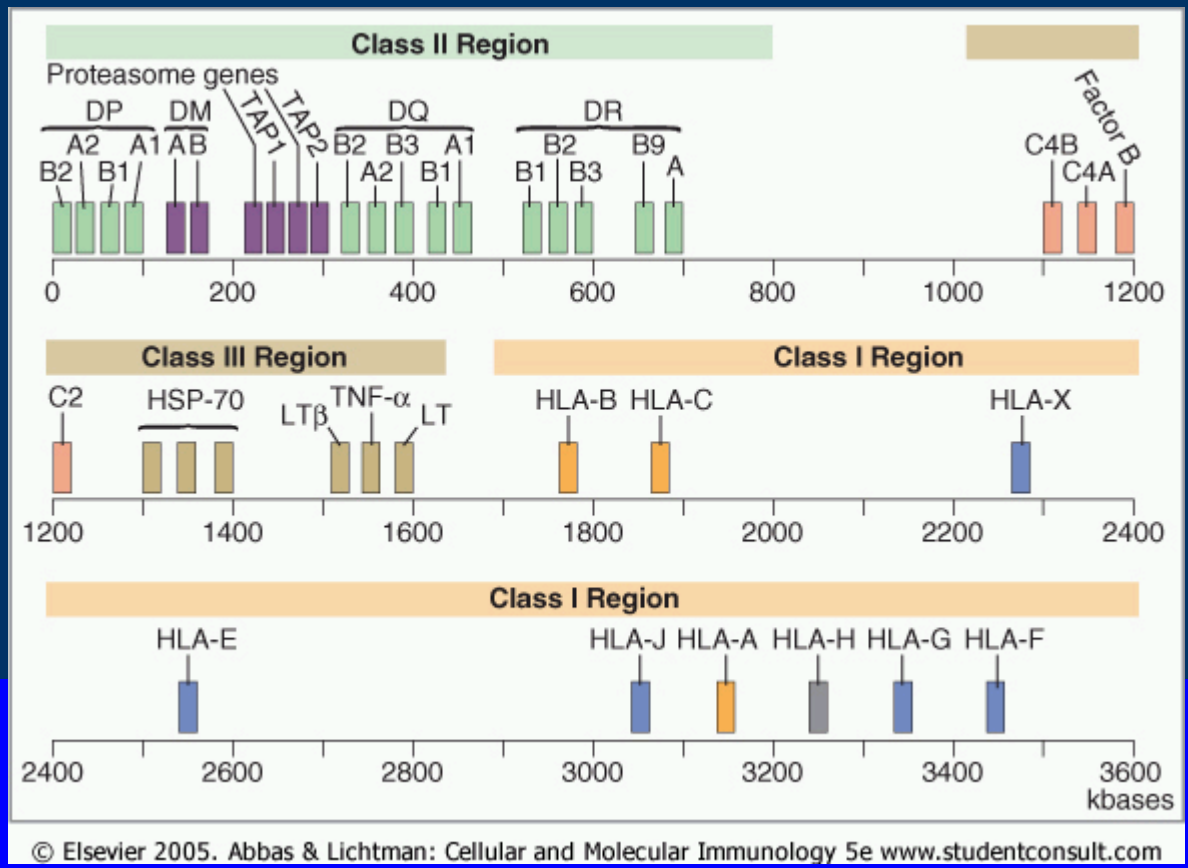
Development of multiple alleles at a locus among individuals in the species, *polyallelism*



HLA genes

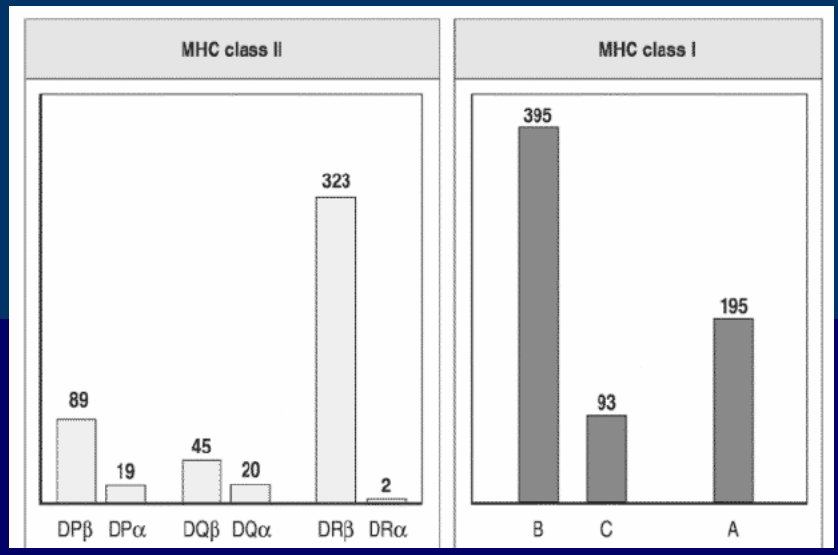
MHC locus

- On chromosome 6
- HLA class III. are soluble molecules as complement, TNF, HSP
- Many other proteins involved in antigen presentation



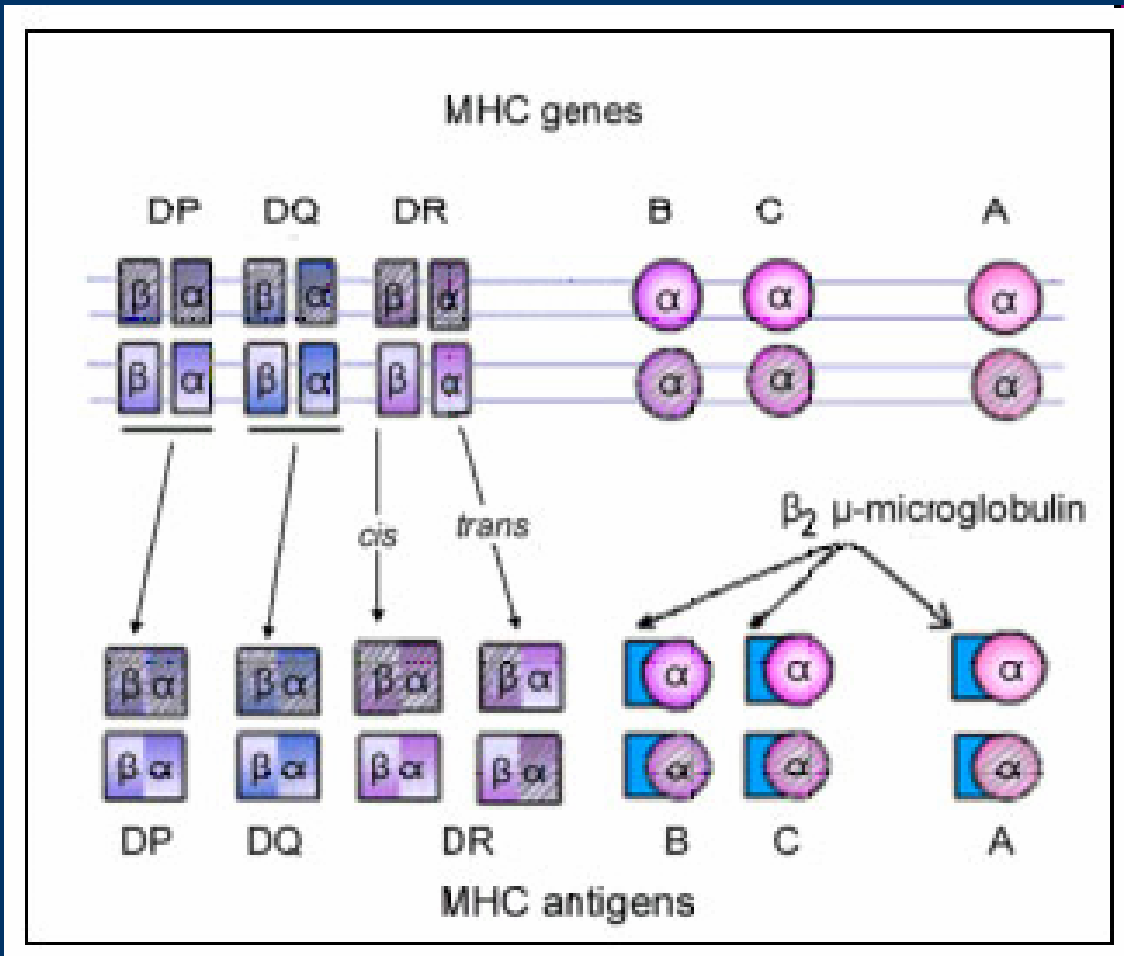
HLA polymorphism

- most polymorhic structures from all known systems.



- human study: 1000 donors, HLA-A, B genotyping
  - Over half the group had a combination that was unique.
  - Another 111 donors had a set of these molecules that they shared with only one other person in the group.
  - The most frequent phenotype (HLA-A1, HLA-A3, HLA-B7, and HLA-B8) was found in 11 donors.

Co-dominant expression of MHC alleles



HLA polymorphism – why?

Pathogen driven mechanisms

- Pathogens tend to escape
- Heterozygotes have advantage
- Frequency-dependent selection: the individual with the rarest allele has the best chance to survive an infection

cheetahs (low polymorphism): extremly susceptible to infectious diseases

vertebrate species can detect MHC genotype by smell!

HLA nomenclature

Nomenclature: The genetic "unit" of the HLA system is the allele, with each defined by its own DNA nucleotide sequence

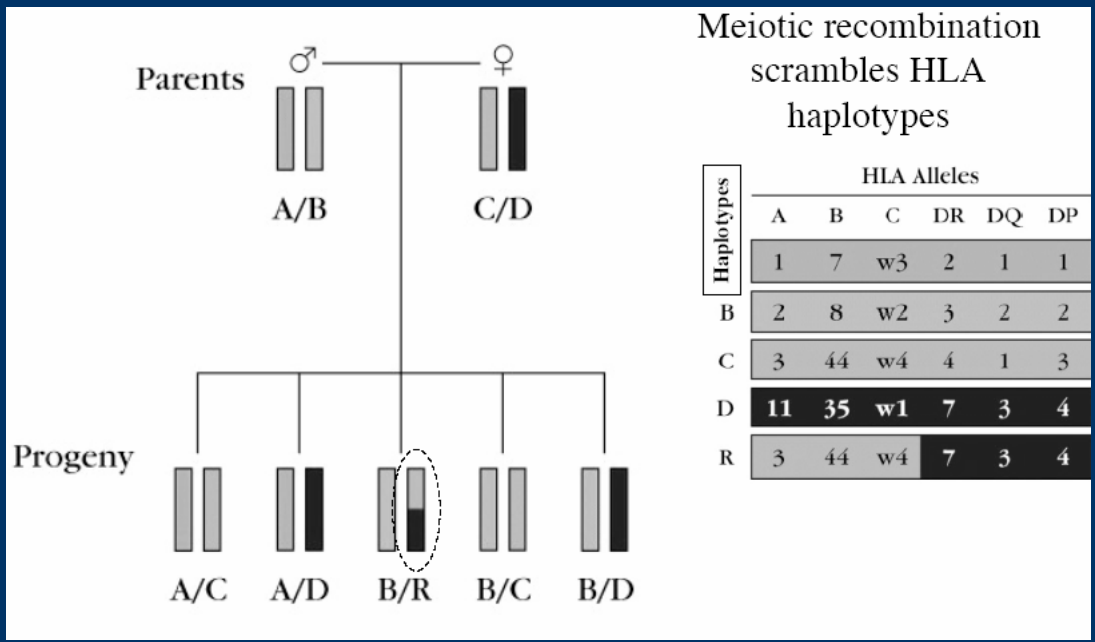
Allele	E.g. HLA-B*0801	}	"Specificity"
	*0802		HLA-B8
	…		
	*0821		
	*2701	}	
	*2702		
	*2703		HLA-B27
	…		
	*2725		

But to make things "simpler", alleles can be grouped in families, e.g. HLA-B*27

"specificity", is an old nomenclature used when human alloantibodies were used to first detect HLA serologic "specificities" or "antigens"

HLA haplotypes in a typical family

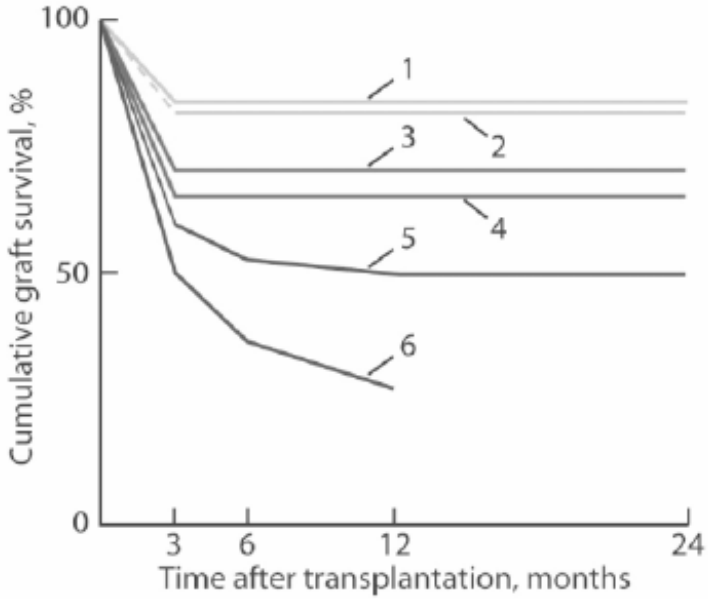
- Haplotype is combination of allelic forms of HLA molecules on one chromosome.
- We inherit 3 types of heavy chains for HLA class I. molecules from each parent .
- Everybody expresses 6 different types of HLA class I. molecules unless honmozygous status for some of the types was inherited.



Meiotic recombination scrambles HLA haplotypes

Haplotypes	HLA Alleles					
	A	B	C	DR	DQ	DP
	1	7	w3	2	1	1
B	2	8	w2	3	2	2
C	3	44	w4	4	1	3
D	**11**	**35**	**w1**	**7**	**3**	**4**
R	3	44	w4	**7**	**3**	**4**

MHC control transplantat survival

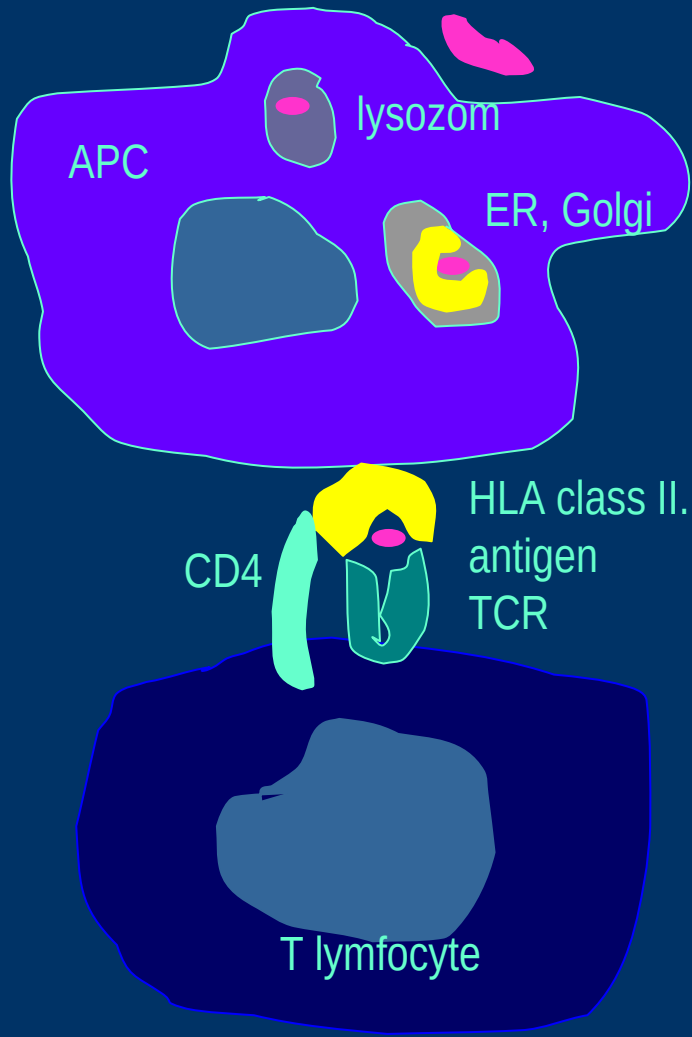


Curve no.	HLA mismatches (no.) Class I	Class II
1	0	0
2	1 or 2	0
3	3 or 4	0
4	0	1 or 2
5	1 or 2	1 or 2
6	3 or 4	1 or 2

- A graft is compatible only if there is a complete match at all MHC alleles, i.e. a two haplotype match for all MHC loci

Function of MHC

- The recognition of antigen by T cells is necessary for induction of the immune response.
- The nature of the outcome of the immune response is directed according to the nature of presented antigen.
  - exogenic antigen presentation



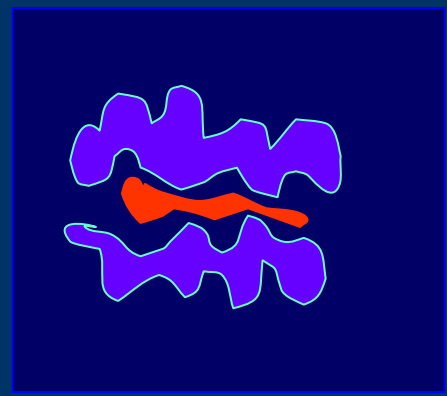
MHC expression

Class I

On all nucleated cells (no MHC on red blood cells, weak expression on cells in brain)

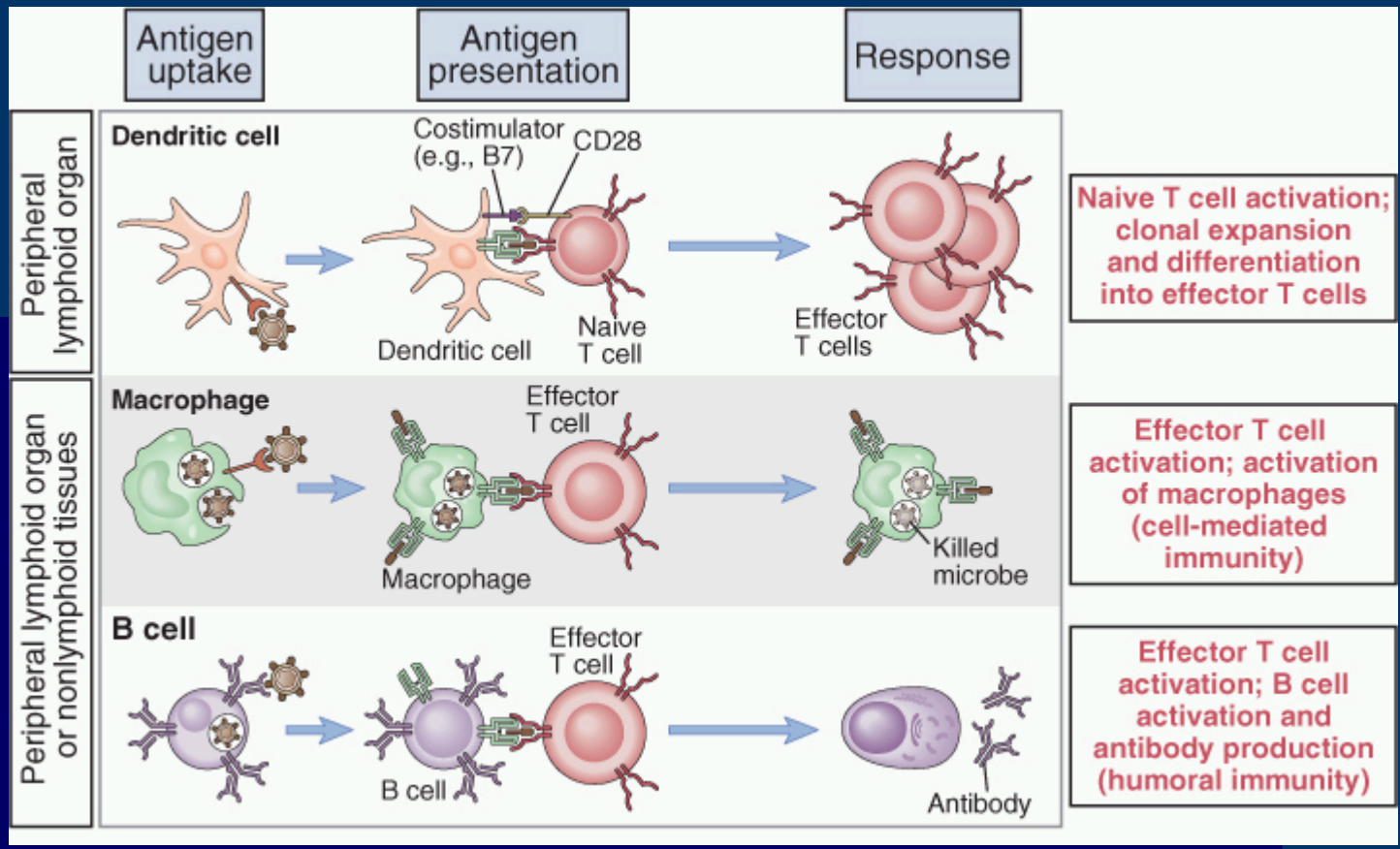
Class II

Found on antigen presenting cells



Antigen presenting cells

Most important population of APC



Other population of APC

- Vascular endothelial cells: function as APC is inducible
- Various epithelial and mesenchymal cells: inducible

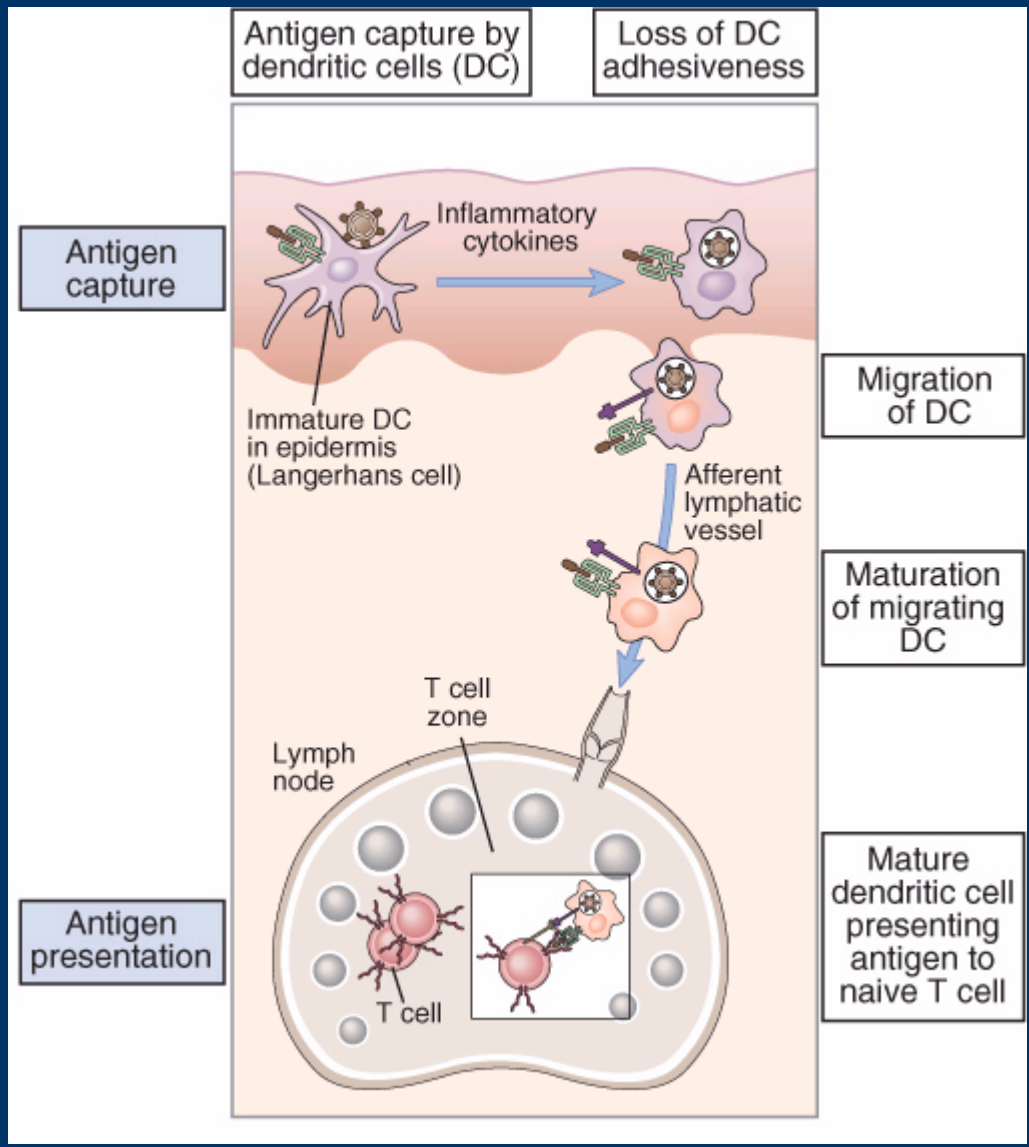
Dendritic cells in antigen presentation

Dendritic cells

- most effective population in T cell activation
- used as immunoterapeutic tools in cancer vaccines

Immature DC: capture antigens in periphery

Mature DC: activation of T lymphocytes in lymphatic nodes



Exogenous antigens

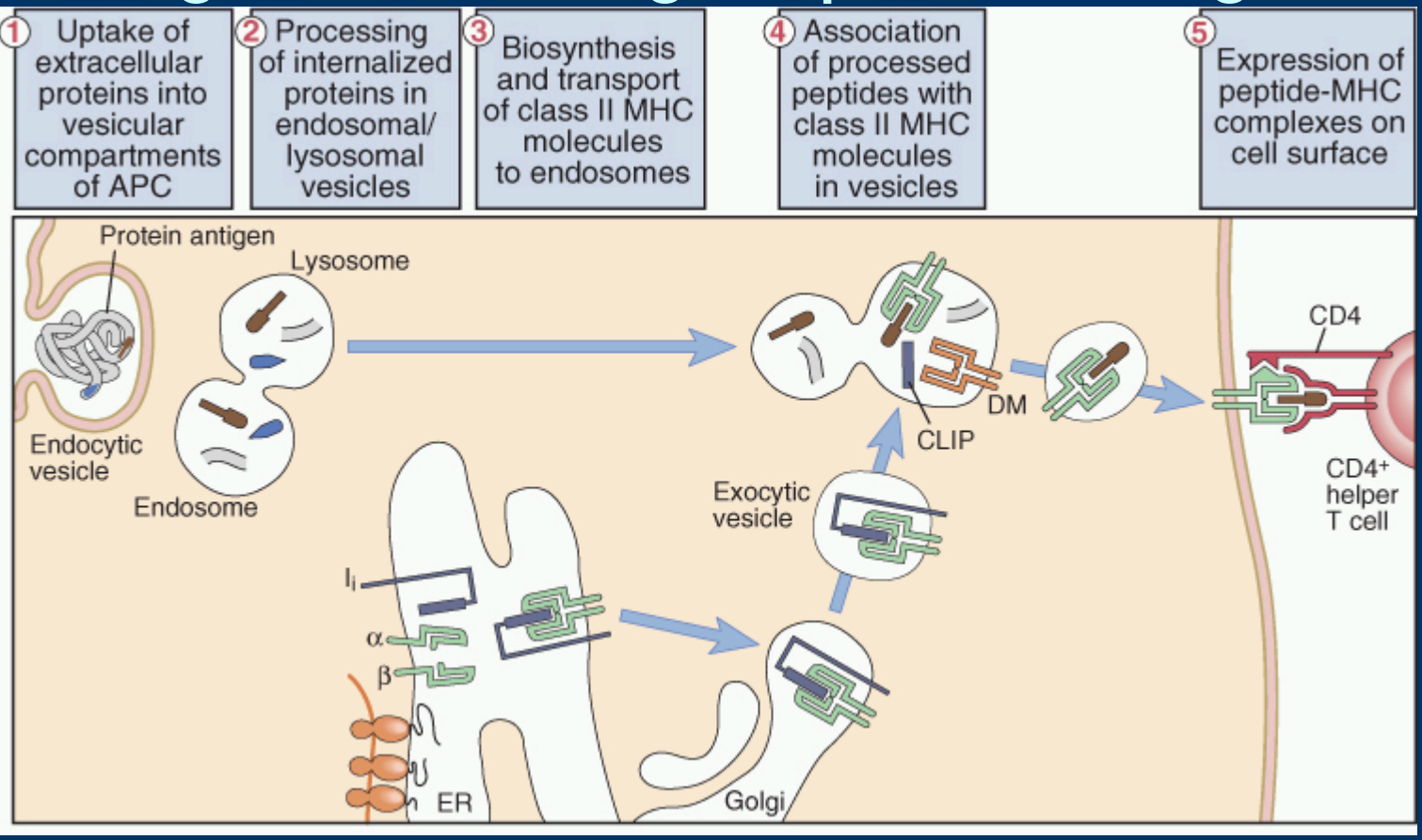
- Exogenous antigens (inhaled, ingested, or injected) are taken up by "professional" antigen-presenting cells
- These include:

  phagocytic cells like macrophages and dendritic cells

  B lymphocytes which are responsible

  for producing antibodies against the antigen.
- All these cells express HLA class II. molecules

Exogenous antigen processing



Invariant Chain (Ii)-Contributes to:

1.proper folding of the alpha and beta chains in the ER

2.preventing in advertent association with endogenous peptides

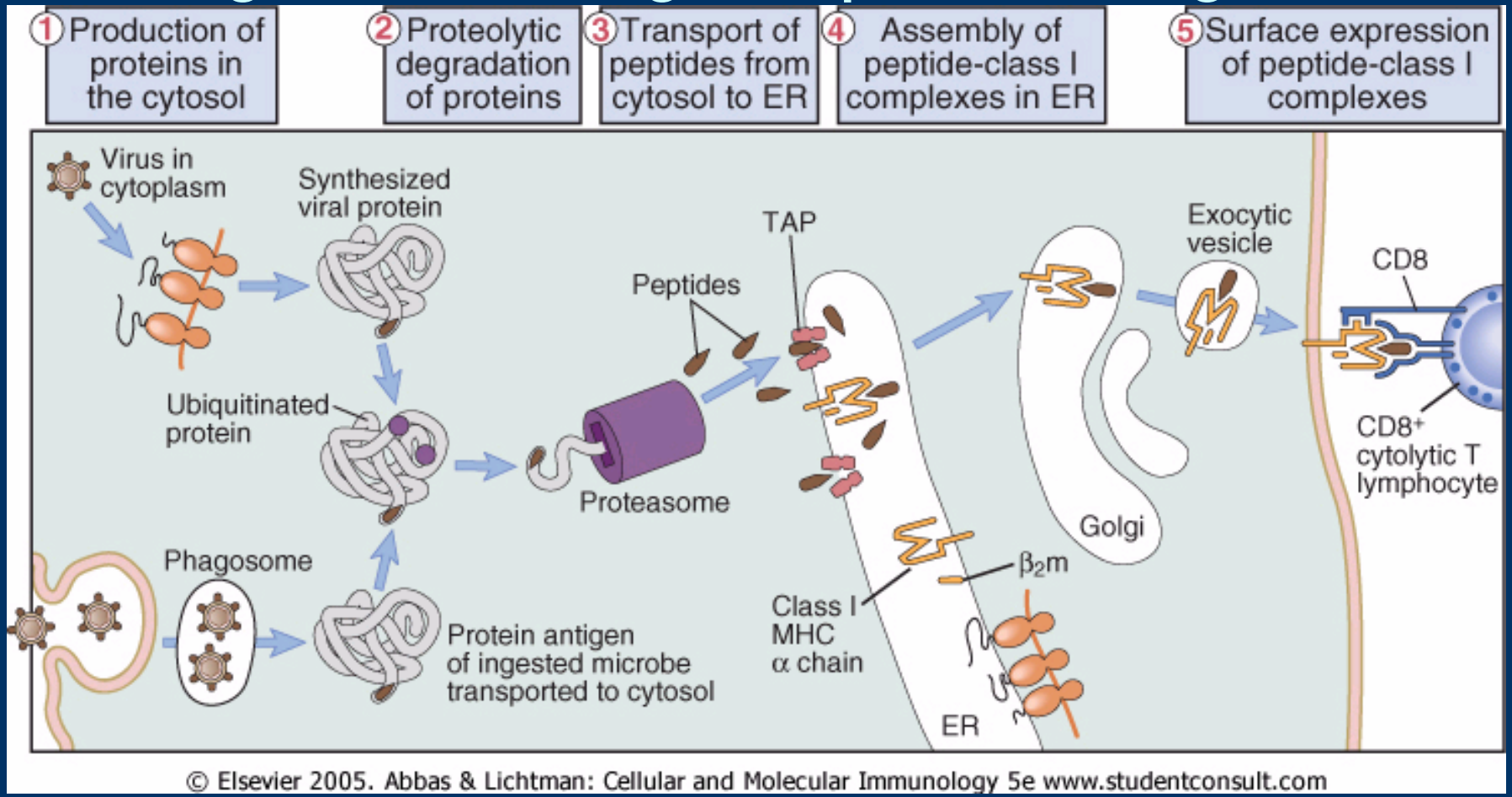
3.directing immature MHC II through the secretory pathway

CLIP (Class II-associated invariant chain peptide)-Degradation product derived from the Invariant chain.

HLA-DM Responsible for displacing CLIP and allowing peptide to bind once MHC has reached the endosome.

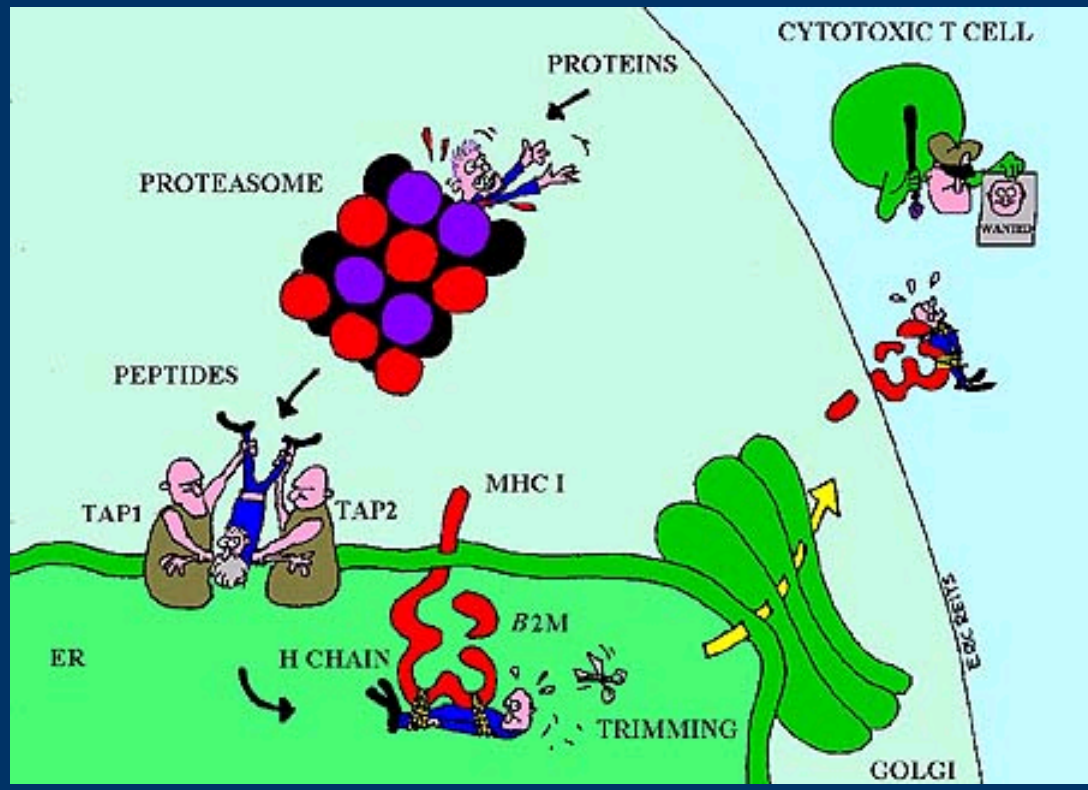
HLA-DO Negative regulator of HLA-DM activity

Endogenous antigens processing



TAP (transporter associated with antigen presentation)

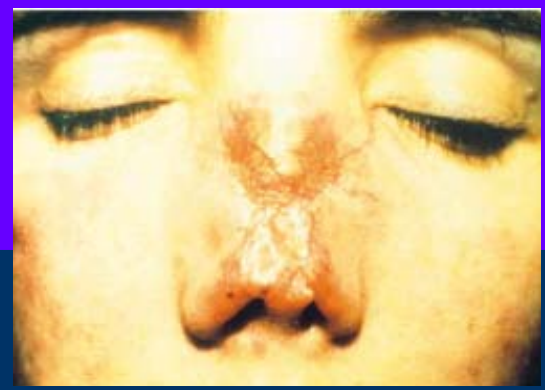
- Transport associated protein - TAP is responsible for the peptide transport from cytoplasm to ER.
- Proteins are degraded to peptide in proteasome.
- The peptides are picked up by TAP proteins and transported from the cytosol into the RER where they assemble with



  - the transmembrane polypeptide and beta-2 microglobulin.
  - this trimolecular complex then moves through the Golgi apparatus and is inserted in the plasma membrane

Imunodeficiences - MHC defect

- Bare lymphocyte syndrome:
  mutation in genes regulating class II MHC transcription
  - reduced number of CD4+ T cells in periphery
  - defective activation of CD4+ T cells
  - fatal, treatment: BM transplantation

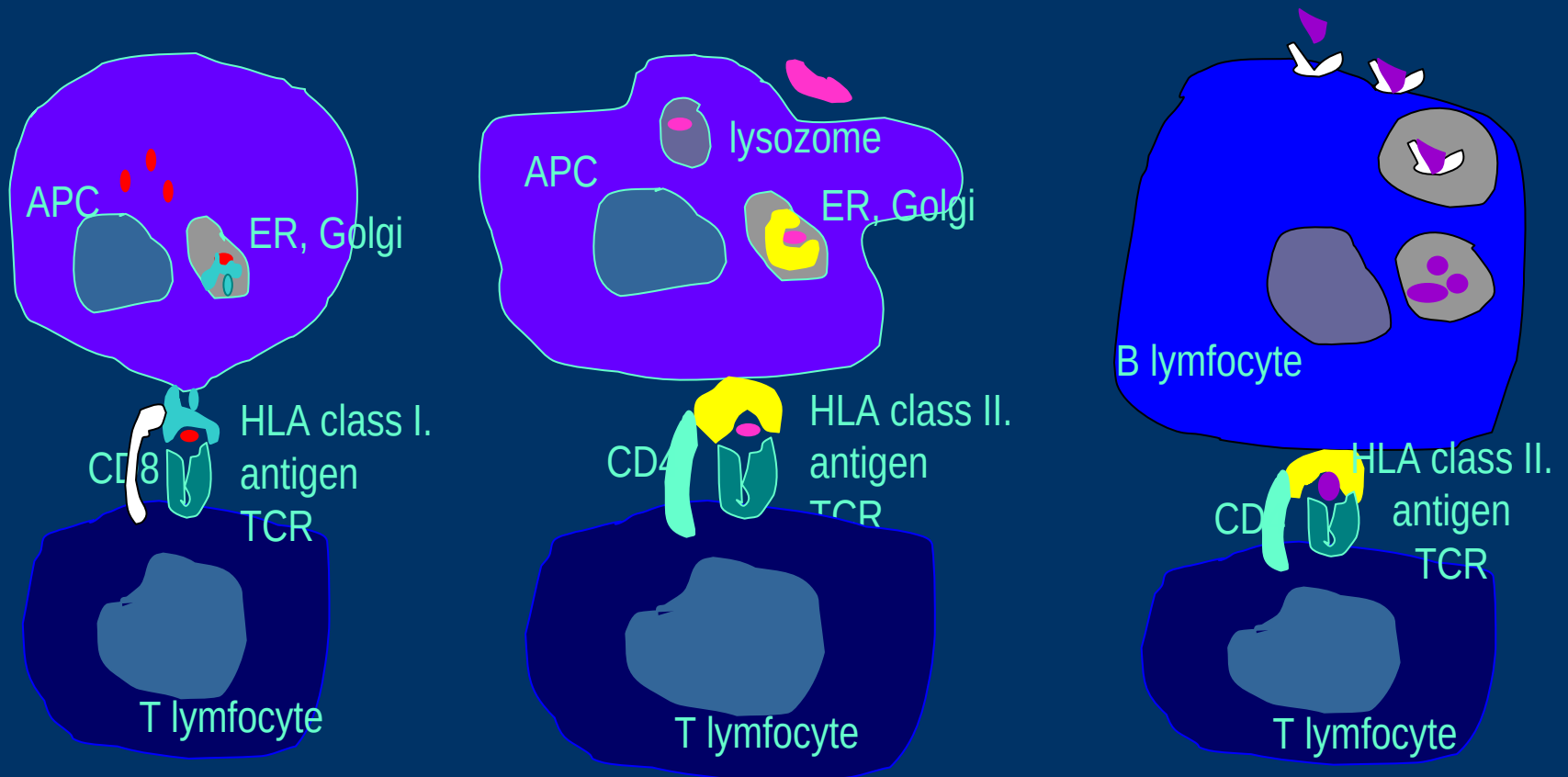


- Class I MHC deficiencies:
  - decreased number of CD8+ T cells in periphery
  - caused by TAP1, TAP2
  - patients suffer from respiratory tract bacterial infection

HLA-associated diseases

	HLA	Patients	Controls
Ankylosing spondylitis	*B27*	90%	9%
Type 1 diabetes	*DR3*	52%	23%
	DR4	74%	24%
	DR3 or *DR4*	93%	43%
Multiple sclerosis	*DR2*	86%	33%
Rheumatoid arthritis	*DR4*	81%	24%
Narcolepsy	*DR2*	>95%	33%

Summary - antigen presentation pathways



endogenous
cell destruction

exogenous
immune response

B lymfocytes
antibody production