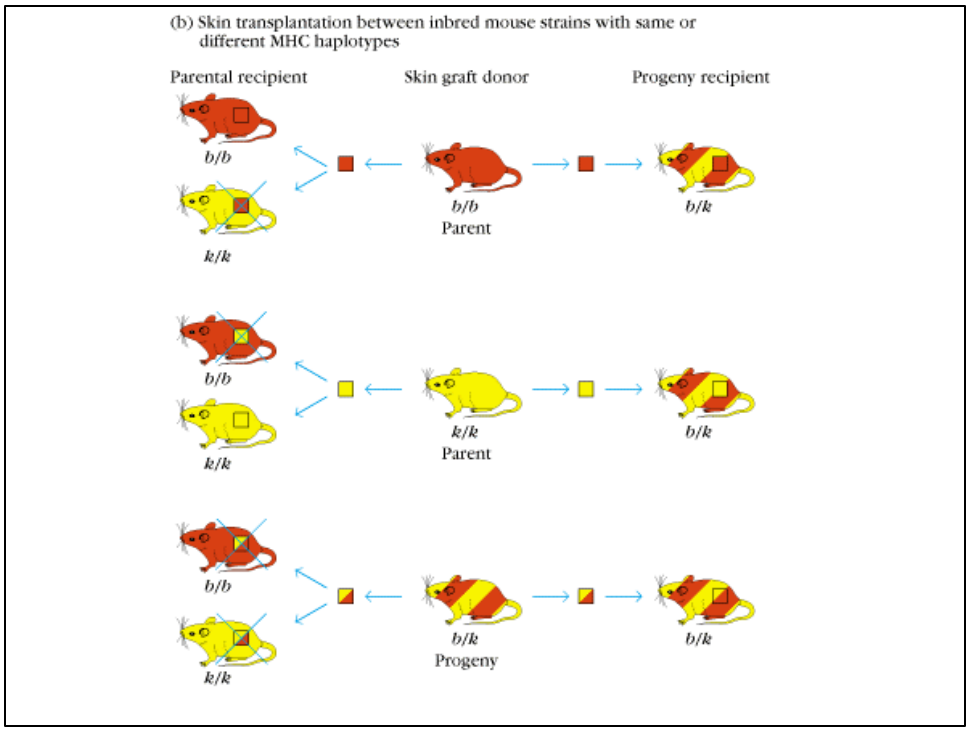
Chapter 7: MHC

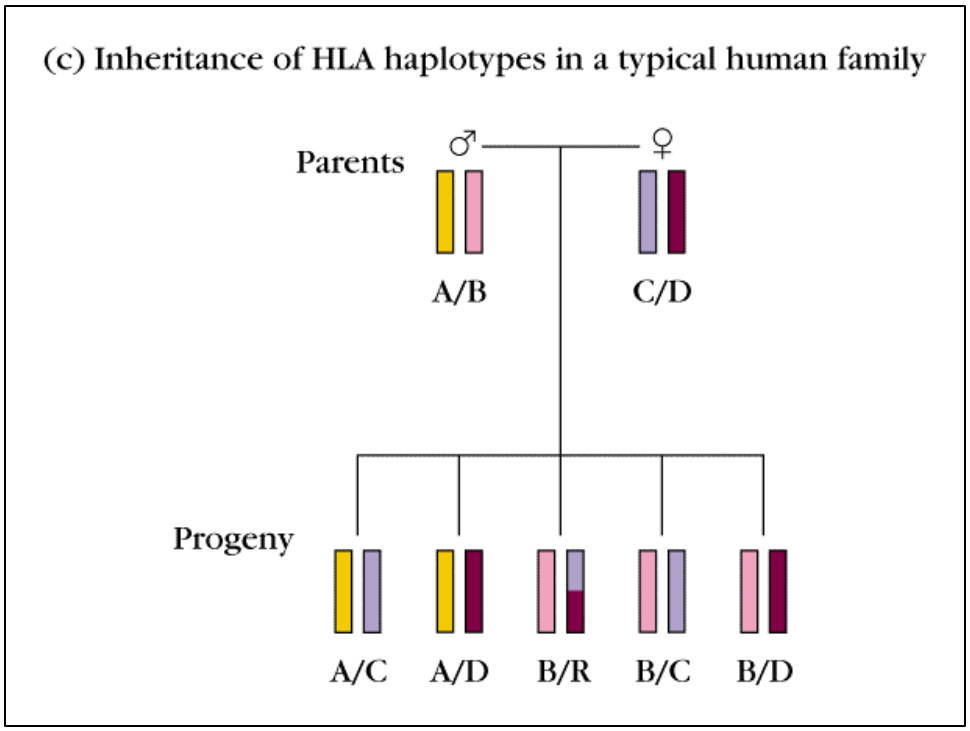
Mouse H-2 complex

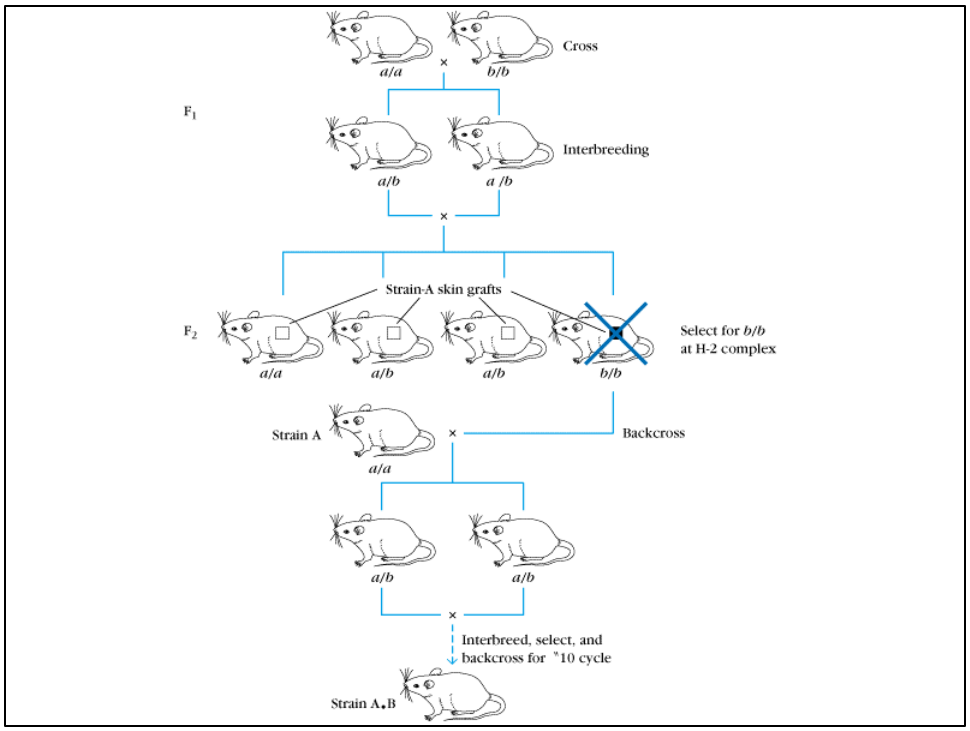
Complex	H-2						
MHC class	I	II		III		I	
Region	K	IA	IE	S		D	
Gene products	H-2K	IA αβ	IE αβ	C′ proteins	TNF-α TNF-β	H-2D	H-2L

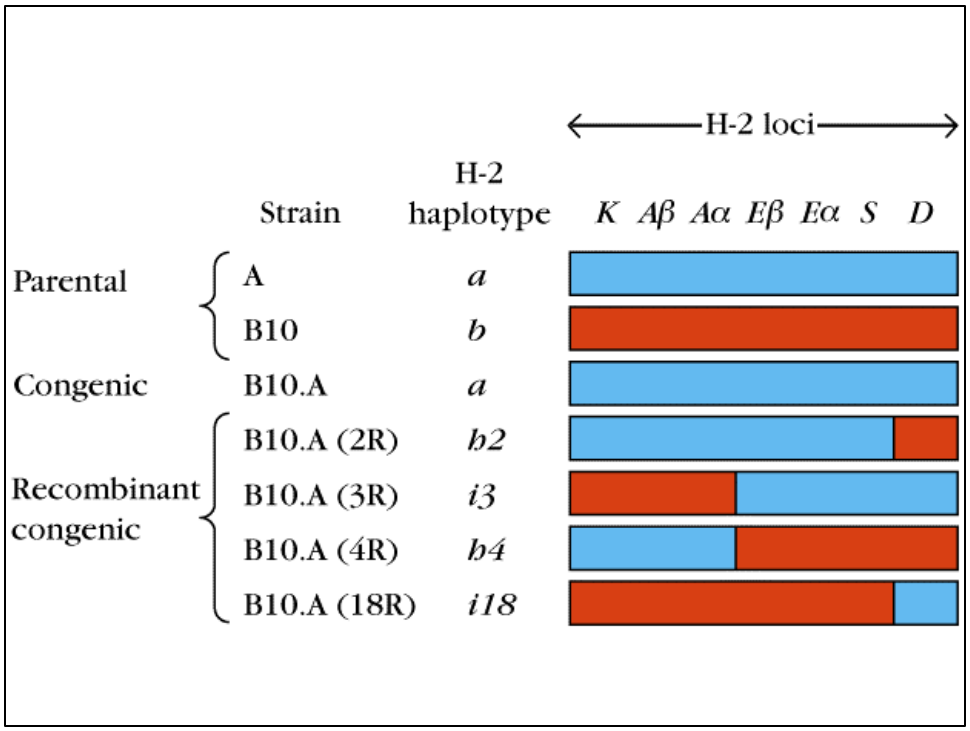
Human HLA complex

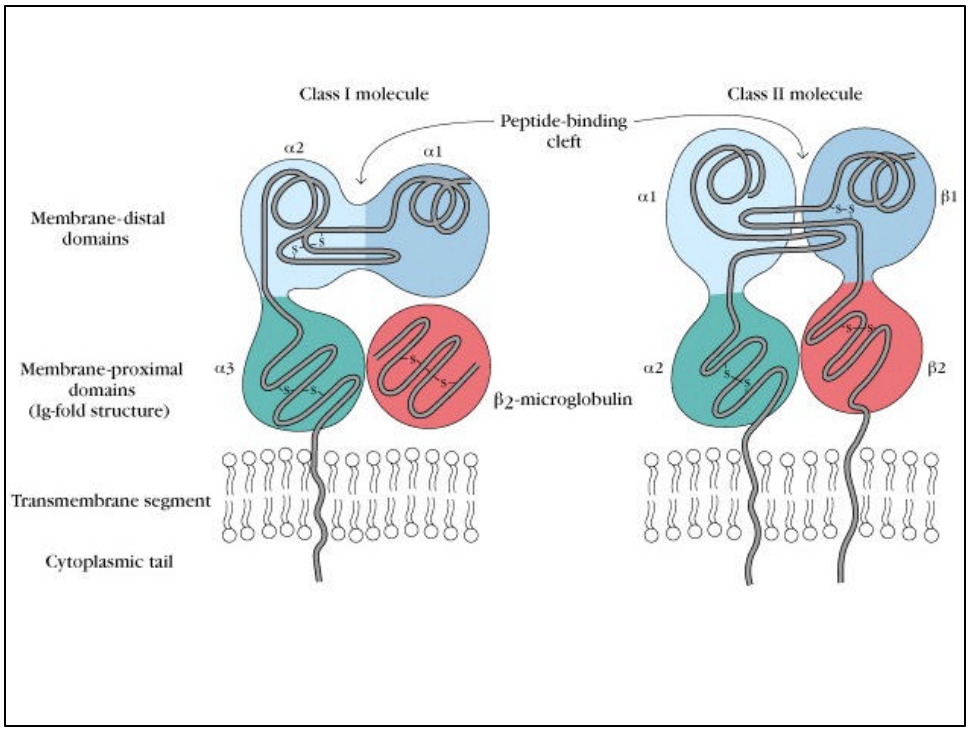
Complex	HLA							
MHC class	II			III		I		
Region	DP	DQ	DR	C4, C2, BF		B	C	A
Gene products	DP αβ	DQ αβ	DR αβ	C′ proteins	TNF-α TNF-β	HLA-B	HLA-C	HLA-A

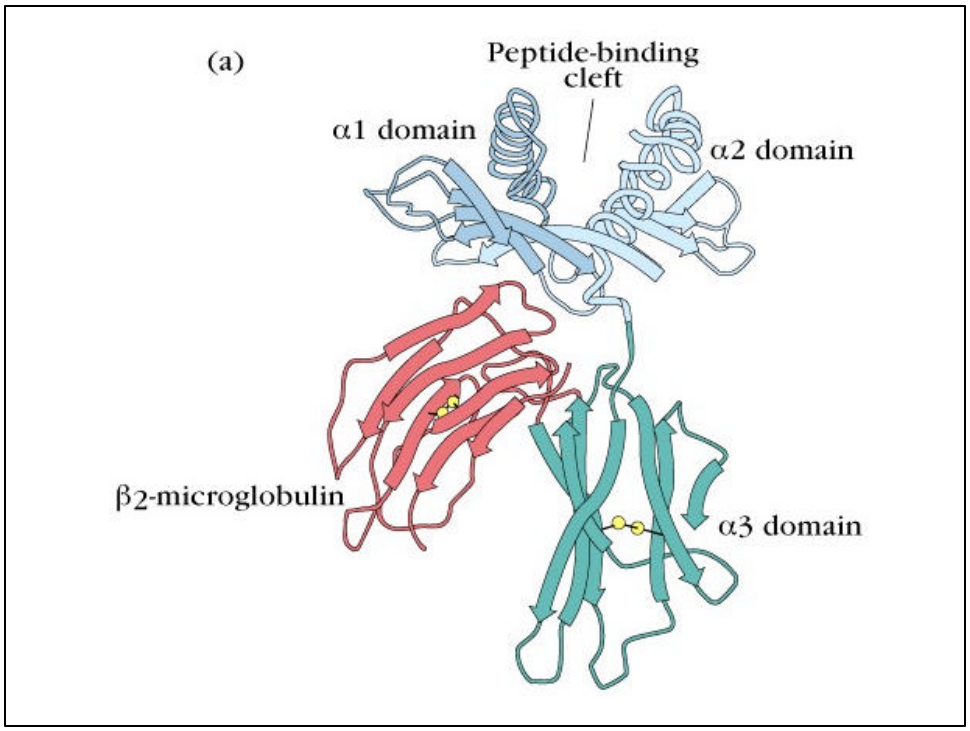

(b) Skin transplantation between inbred mouse strains with same or different MHC haplotypes
Parental recipient
Skin graft donor
Progeny recipient
b/b
k/k
b/b
Parent
b/k
b/b
k/k
k/k
Parent
b/k
b/b
k/k
b/k
Progeny
b/k

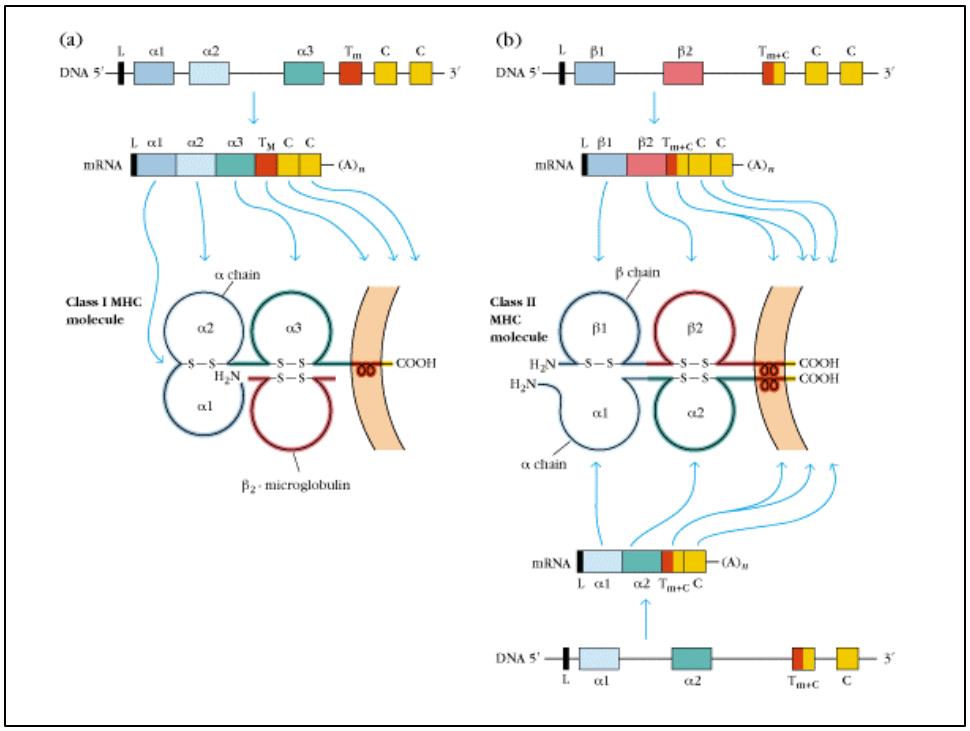

(c) Inheritance of HLA haplotypes in a typical human family
Parents
♂
♀
A/B
C/D
Progeny
A/C
A/D
B/R
B/C
B/D

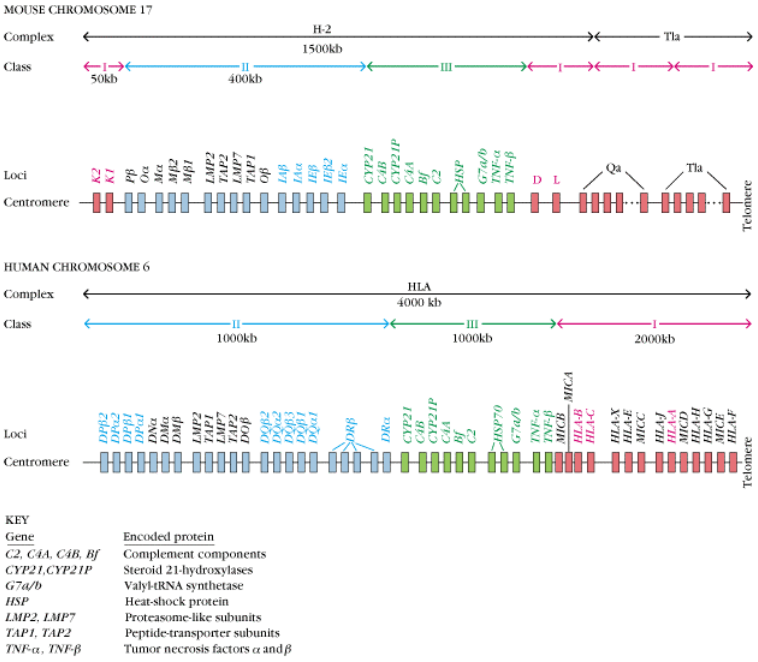

Cross
a/a
b/b
F1
Interbreeding
a/b
a /b
Strain-A skin grafts
F2
Select for b/b
at H-2 complex
a/a
a/b
a/b
b/b
Strain A
Backcross
a/a
a/b
a/b
Interbreed, select, and
backcross for ~10 cycle
Strain A.B


H-2 loci
Strain
H-2
haplotype
K Aβ Aα Eβ Eα S D
Parental
A
a
B10
b
Congenic
B10.A
a
Recombinant
congenic
B10.A (2R)
b2
B10.A (3R)
i3
B10.A (4R)
b4
B10.A (18R)
i18


Class I molecule
Class II molecule
Peptide-binding cleft
α2
α1
α1
β1
Membrane-distal domains
Membrane-proximal domains (Ig-fold structure)
α3
α2
β2
β2-microglobulin
Transmembrane segment
Cytoplasmic tail


(a)
Peptide-binding cleft
α1 domain
α2 domain
β2-microglobulin
α3 domain


(a)
DNA 5′
L α1 α2 α3 Tm C C 3′
mRNA
L α1 α2 α3 TM C C (A)n
α chain
Class I MHC molecule
α2 α3
S—S S—S
H2N S—S COOH
α1
β2-microglobulin
(b)
DNA 5′
L β1 β2 Tm+C C C 3′
mRNA
L β1 β2 Tm+C C C (A)n
β chain
Class II MHC molecule
β1 β2
H2N S—S S—S COOH
H2N COOH
α1 α2
α chain
mRNA
L α1 α2 Tm+C C (A)n
DNA 5′
L α1 α2 Tm+C C 3′


MOUSE CHROMOSOME 17
Complex
H-2
1500kb
Tla
Class
I
50kb
II
400kb
III
I
I
I
Loci
K2 K1 Pβ Oα Mα Mβ2 Mβ1 LMP2 TAP2 LMP7 TAP1 Oβ Iaβ Iaα Ieβ Ieβ2 Ieα CYP21 C4B CYP21P C4A Bf C2 HSP G7a/b TNF-α TNF-β D L Qa Tla
Centromere
Telomere
HUMAN CHROMOSOME 6
Complex
HLA
4000 kb
Class
II
1000kb
III
1000kb
I
2000kb
Loci
DPβ2 DPα2 DPβ1 DPα1 DNα DMα DMβ LMP2 TAP1 LMP7 TAP2 DOβ DQβ2 DQα2 DQβ3 DQβ1 DQα1 DRβ DRα CYP21 C4B CYP21P C4A Bf C2 HSP70 G7a/b TNF-α TNF-β MICB MICA HLA-B HLA-C HLA-X HLA-E MICC HLA-J HLA-A MICD HLA-H HLA-G MICE HLA-F
Centromere
Telomere
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

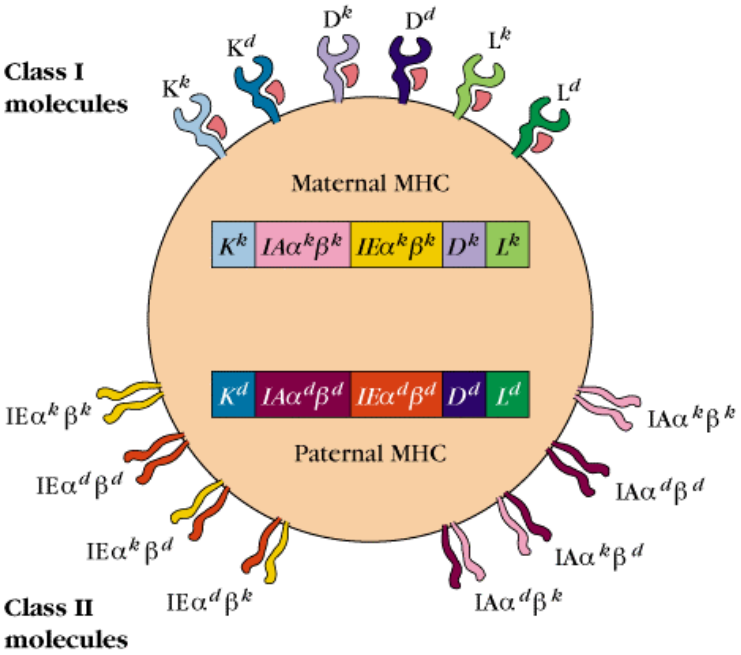

Class I molecules
K^k
K^d
D^k
D^d
L^k
L^d
Maternal MHC
K^k $IA\alpha^k\beta^k$ $IE\alpha^k\beta^k$ D^k L^k
K^d $IA\alpha^d\beta^d$ $IE\alpha^d\beta^d$ D^d L^d
Paternal MHC
$IE\alpha^k\beta^k$
$IE\alpha^d\beta^d$
$IE\alpha^k\beta^d$
$IE\alpha^d\beta^k$
$IA\alpha^k\beta^k$
$IA\alpha^d\beta^d$
$IA\alpha^k\beta^d$
$IA\alpha^d\beta^k$
Class II molecules

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

TABLE 7-3 DIFFERENTIAL BINDING OF PEPTIDES TO MOUSE CLASS II MHC MOLECULES AND CORRELATION WITH MHC RESTRICTION

Labeled peptide*	MHC restriction of responders†	Percentage of labeled peptide bound to‡			
		IA^d	IE^d	IA^k	IE^k
Ovalbumin (323–339)	IA^d	**11.8**	0.1	0.2	0.1
Influenza hemagglutinin (130–142)	IA^d	**18.9**	0.6	7.1	0.3
Hen egg-white lysozyme (46–61)	IA^k	0.0	0.0	**35.2**	0.5
Hen egg-white lysozyme (74–86)	IA^k	2.0	2.3	**2.9**	1.7
Hen egg-white lysozyme (81–96)	IE^k	0.4	0.2	0.7	**1.1**
Myoglobin (132–153)	IE^d	0.8	**6.3**	0.5	0.7
Pigeon cytochrome *c* (88–104)	IE^k	0.6	1.2	1.7	**8.7**
λ repressor (12–26)§	$IA^d + IE^k$	1.6	**8.9**	0.3	2.3

*Amino acid residues included in each peptide are indicated by the numbers in parentheses.

†Refers to class II molecule (IA or IE) and haplotype associated with a good response to the indicated peptides.

‡Binding determined by equilibrium dialysis. Bold-faced values indicate binding was significantly greater ($p < 0.05$) than that of the other three class II molecules tested.

§The λ repressor is an exception to the rule that high binding correlates with the MHC restriction of high-responder strains. In this case, the T_H cell specific for the λ peptide–IE^d complex has been deleted; this is an example of the hole-in-the-repertoire mechanism.

SOURCE: Adapted from S Buus et al, 1987, *Science* **235**:1353.

TABLE 7-4 SOME SIGNIFICANT ASSOCIATIONS OF HLA ALLELES WITH INCREASED RISK FOR VARIOUS DISEASES

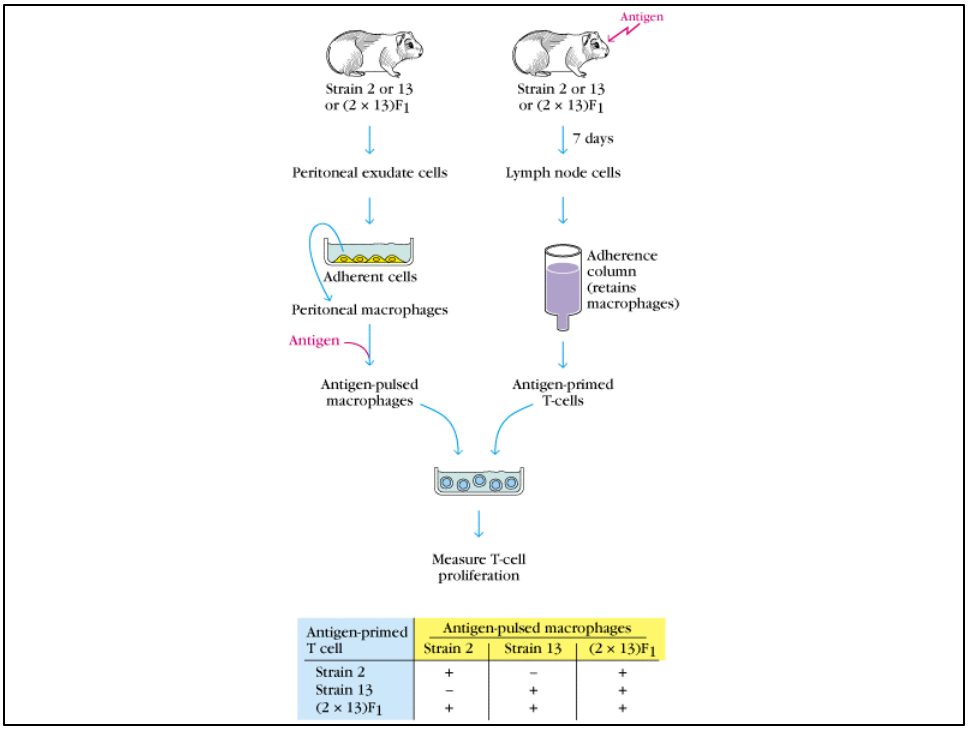
Disease	Associated HLA allele	Relative risk*
Ankylosing spondylitis	*B27*	90
Goodpasture's syndrome	*DR2*	16
Gluten-sensitive enteropathy	*DR3*	12
Hereditary hemochromatosis	*A3*	9.3
	B14	2.3
	A3/B14	90
Insulin-dependent diabetes mellitus	*DR4/DR3*	20
Multiple sclerosis	*DR2*	5
Myasthenia gravis	*DR3*	10
Narcolepsy	*DR2*	130
Reactive arthritis (*Yersinia, Salmonella, Gonococcus*)	*B27*	18
Reiter's syndrome	*B27*	37
Rheumatoid arthritis	*DR4*	10
Sjogren's syndrome	*Dw3*	6
Systemic lupus erythematosus	*DR3*	5

*Relative risk is calculated by dividing the frequency of the HLA allele in the patient population by the frequency in the general population:

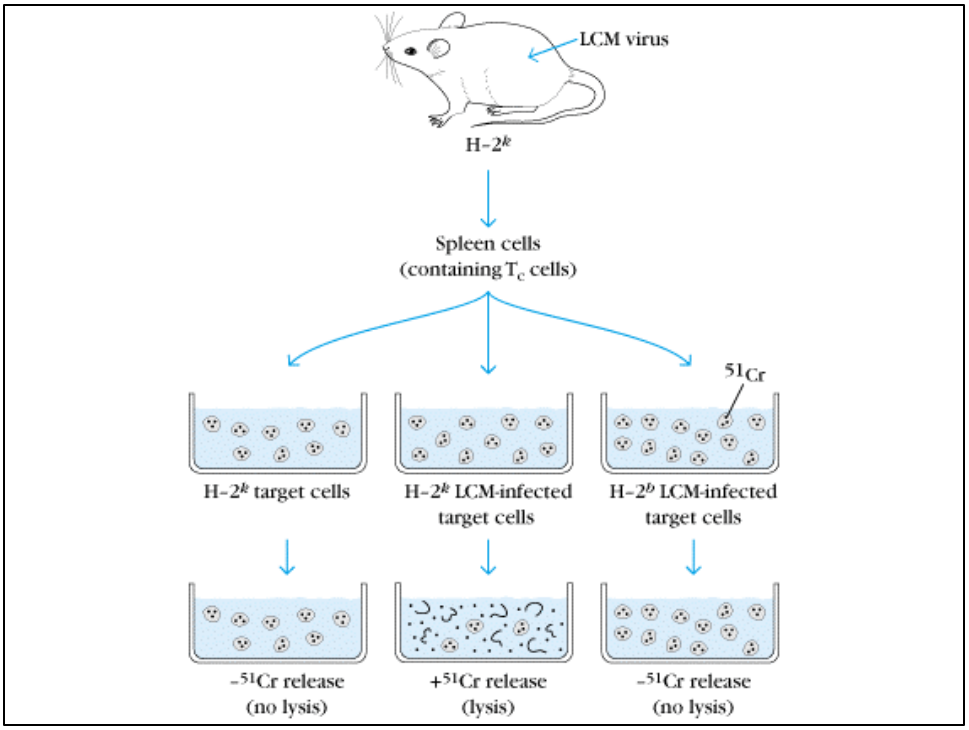
$$RR = \frac{(Ag^+/Ag^-)\ \text{disease}}{(Ag^+/Ag^-)\ \text{control}}$$

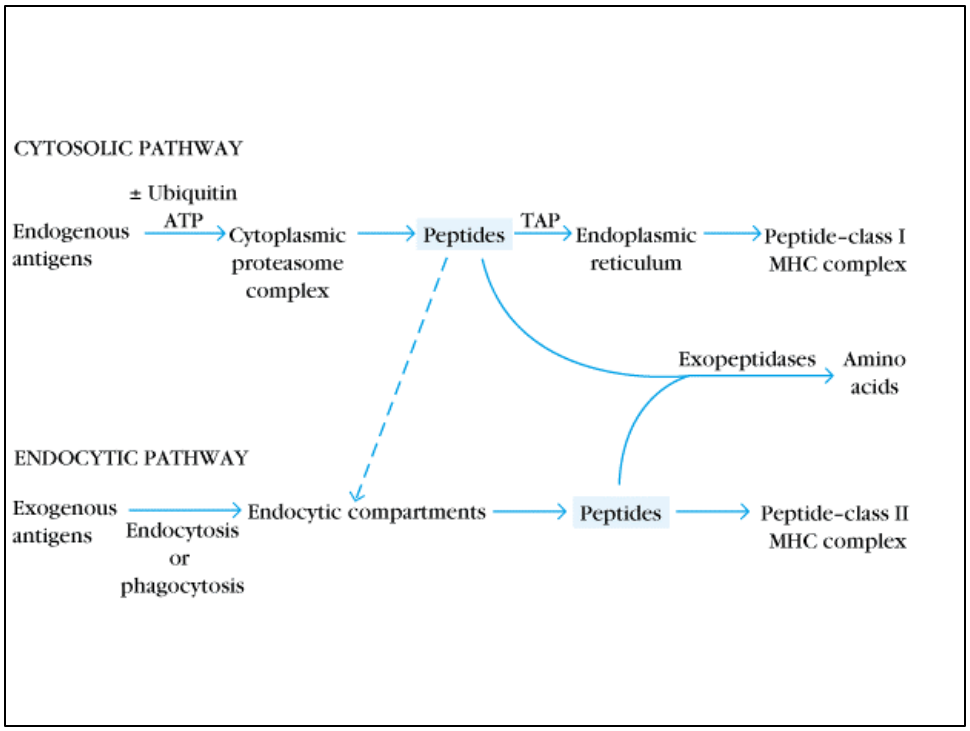
SOURCE: SAM CD: A Comprehensive Knowledge Base of Internal Medicine, DC Dale and DD Federman, eds., 1997, Scientific American, New York.

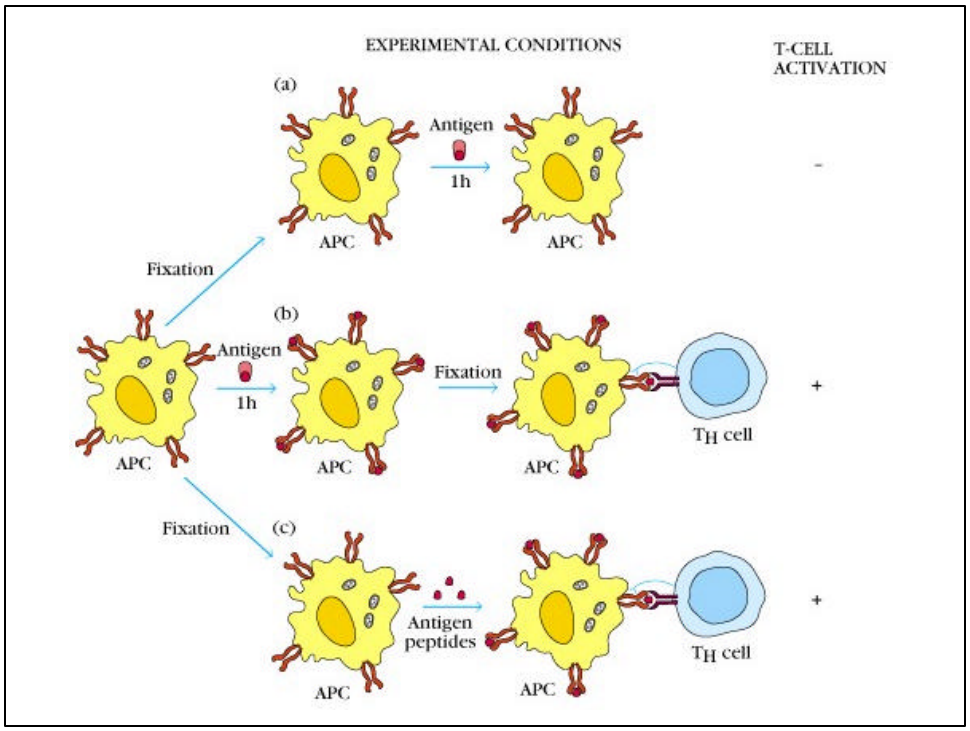
Chapter 8: Antigen Processing

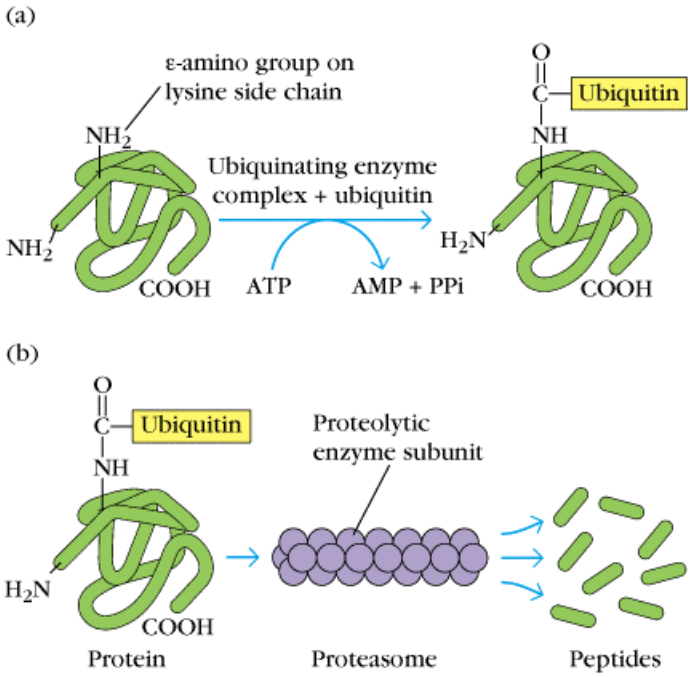


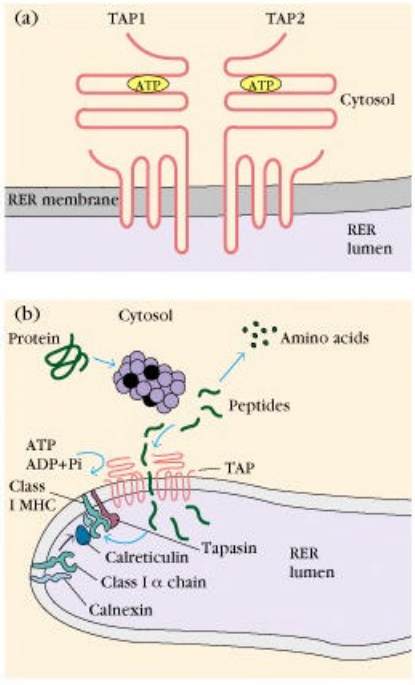
Antigen-primed T cell	Antigen-pulsed macrophages		
	Strain 2	Strain 13	(2 × 13)F1
Strain 2	+	–	+
Strain 13	–	+	+
(2 × 13)F1	+	+	+

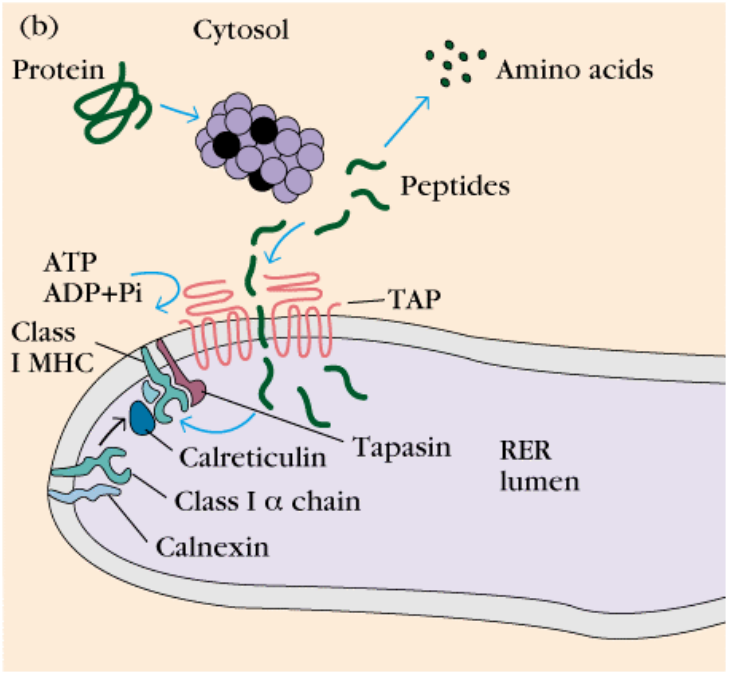


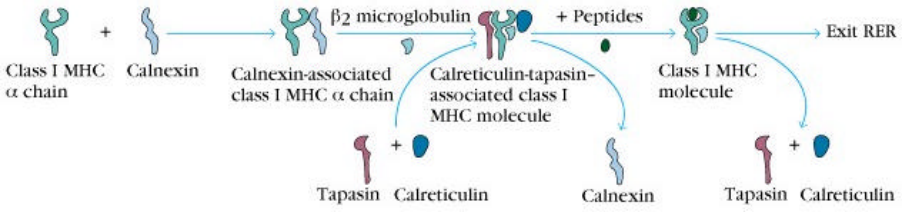

CYTOSOLIC PATHWAY
± Ubiquitin
ATP
Endogenous antigens
Cytoplasmic proteasome complex
Peptides
TAP
Endoplasmic reticulum
Peptide–class I MHC complex
Exopeptidases
Amino acids
ENDOCYTIC PATHWAY
Exogenous antigens
Endocytosis or phagocytosis
Endocytic compartments
Peptides
Peptide–class II MHC complex

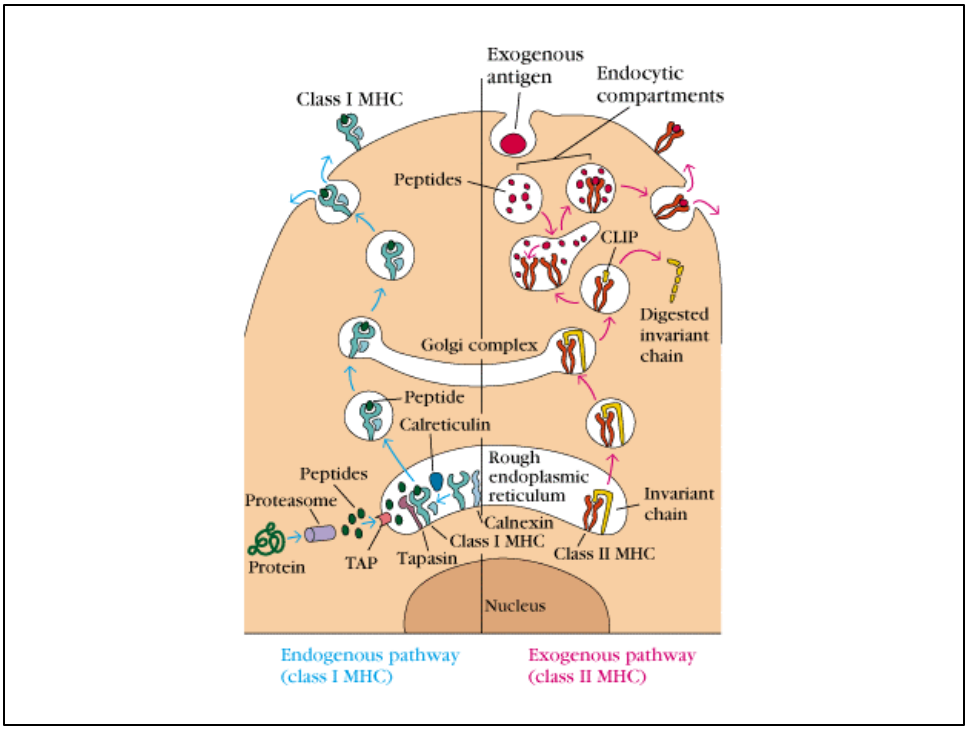

EXPERIMENTAL CONDITIONS
T-CELL ACTIVATION
(a)
Antigen
1h
APC
APC
-
Fixation
(b)
Antigen
1h
Fixation
APC
APC
APC
TH cell
+
Fixation
(c)
Antigen peptides
APC
APC
TH cell
+

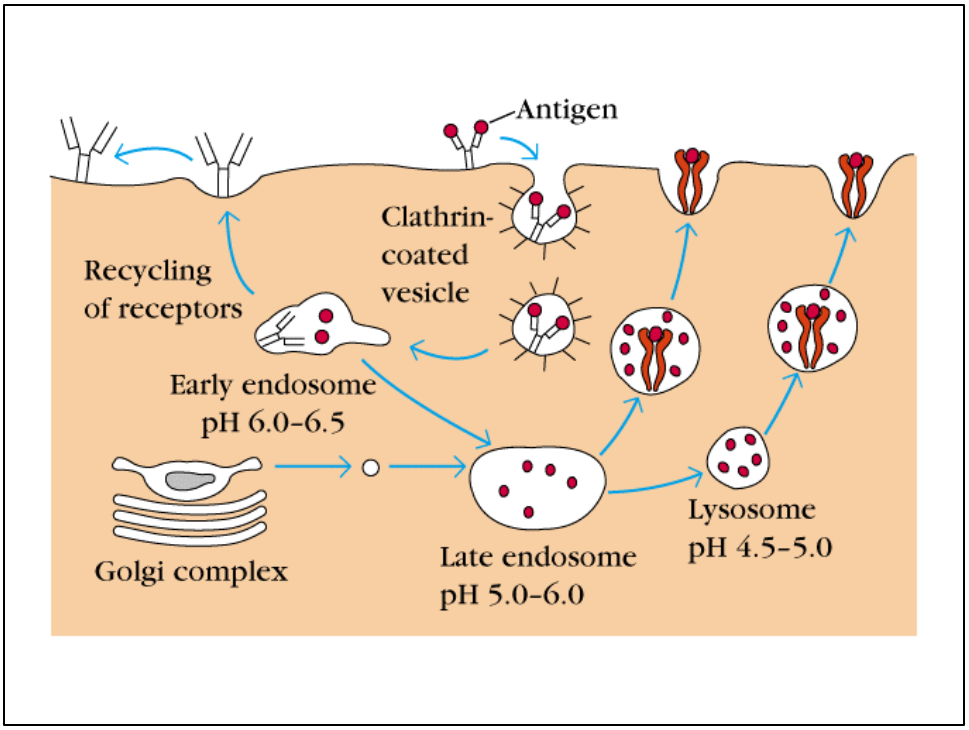

(a)
ε-amino group on
lysine side chain
NH2
NH2
COOH
Ubiquinating enzyme
complex + ubiquitin
ATP
AMP + PPi
O
C
Ubiquitin
NH
H2N
COOH
(b)
O
C
Ubiquitin
NH
H2N
COOH
Protein
Proteolytic
enzyme subunit
Proteasome
Peptides

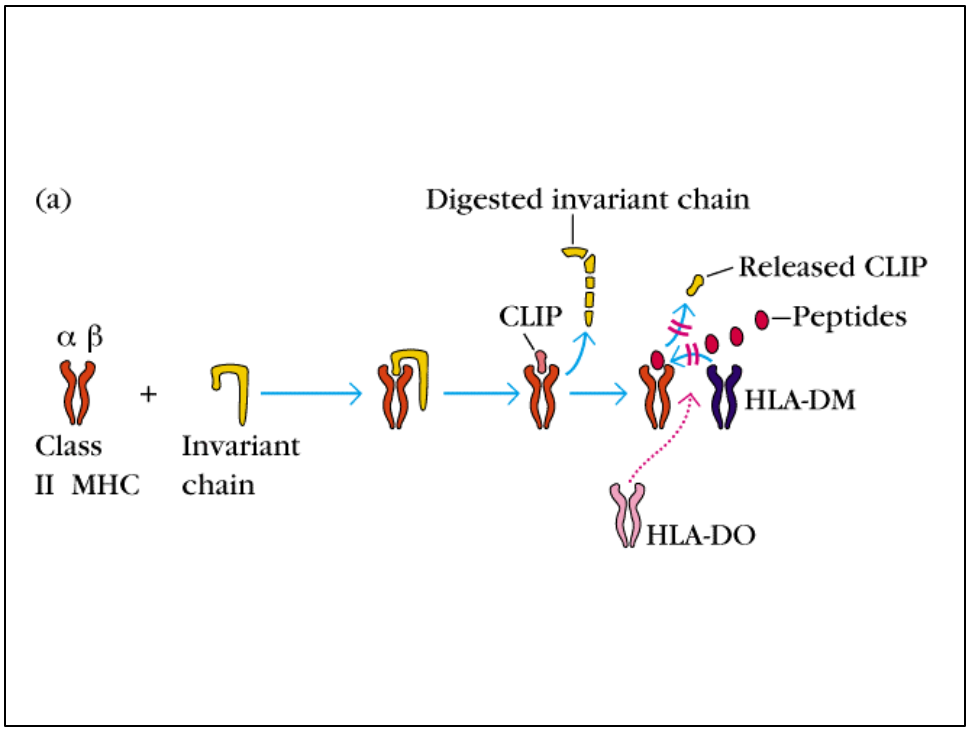

(a)
TAP1
TAP2
ATP
ATP
Cytosol
RER membrane
RER
lumen
(b)
Cytosol
Protein
Amino acids
Peptides
ATP
ADP+Pi
TAP
Class
I MHC
Tapasin
Calreticulin
Class I α chain
Calnexin
RER
lumen


(b)
Cytosol
Protein
Amino acids
Peptides
ATP
ADP+Pi
TAP
Class
I MHC
Calreticulin
Tapasin
RER
lumen
Class I α chain
Calnexin


Class I MHC
α chain
+
Calnexin
Calnexin-associated
class I MHC α chain
β2 microglobulin
Calreticulin-tapasin-
associated class I
MHC molecule
+ Peptides
Class I MHC
molecule
Exit RER
Tapasin
+
Calreticulin
Calnexin
Tapasin
+
Calreticulin


Exogenous antigen
Endocytic compartments
Class I MHC
Peptides
CLIP
Digested invariant chain
Golgi complex
Peptide
Calreticulin
Rough endoplasmic reticulum
Peptides
Proteasome
Invariant chain
Calnexin
Class I MHC
Protein
TAP
Tapasin
Class II MHC
Nucleus
Endogenous pathway (class I MHC)
Exogenous pathway (class II MHC)


Antigen
Clathrin-coated vesicle
Recycling of receptors
Early endosome pH 6.0–6.5
Golgi complex
Late endosome pH 5.0–6.0
Lysosome pH 4.5–5.0


(a)
Digested invariant chain
Released CLIP
CLIP
Peptides
α β
HLA-DM
+
Class
II MHC
Invariant
chain
HLA-DO

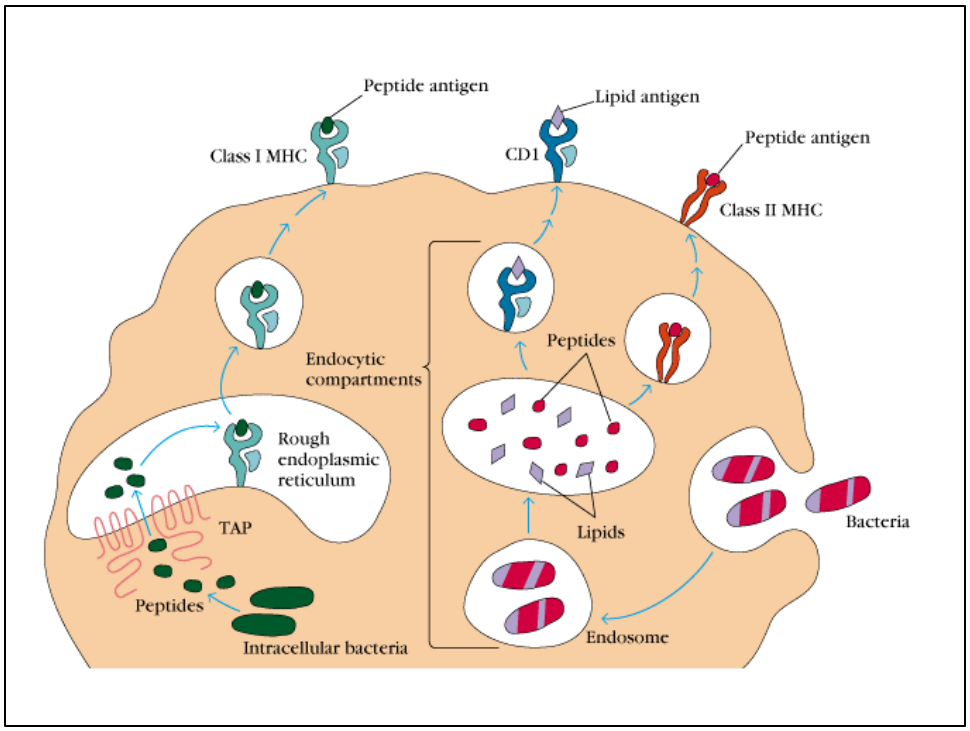

Peptide antigen
Lipid antigen
Class I MHC
CD1
Peptide antigen
Class II MHC
Endocytic
compartments
Peptides
Rough
endoplasmic
reticulum
TAP
Lipids
Bacteria
Peptides
Endosome
Intracellular bacteria

TABLE 8-2 EFFECT OF ANTIGEN PRESENTATION ON ACTIVATION OF CLASS I AND CLASS II MHC-RESTRICTED T_C CELLS

	CTL activity†	
Treatment of target cells*	Class I restricted	Class II restricted
Infectious virus	+	+
UV-inactivated virus (noninfectious)	−	+
Infectious virus + emetine	−	+
Infectious virus + chloroquine	+	−

*Target cells, which expressed both class I and class II MHC molecules, were treated with the indicated preparations of influenza virus and other agents. Emetine inhibits viral protein synthesis, and chloroquine inhibits the endocytic processing pathway.

†Determined by lysis (+) and no lysis (−) of the target cells.

SOURCE: Adapted from TJ Braciale et al., 1987, *Immunol. Rev.* **98**:95.