Antigen Processing and Presentation

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抗原被什么细胞捕获?

抗原被什么分子识别?

抗原经什么途径加工?

抗原被什么分子递呈?

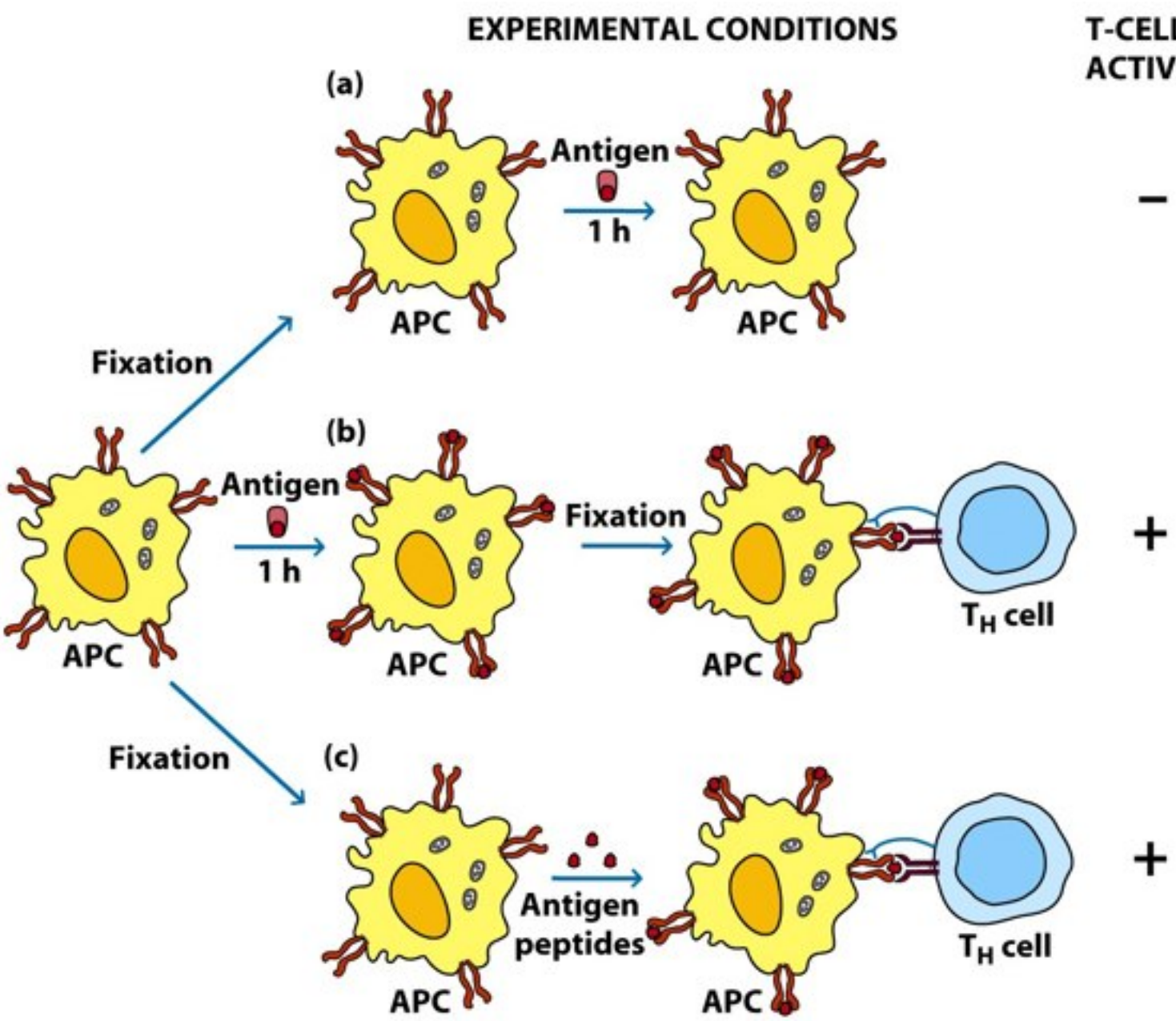
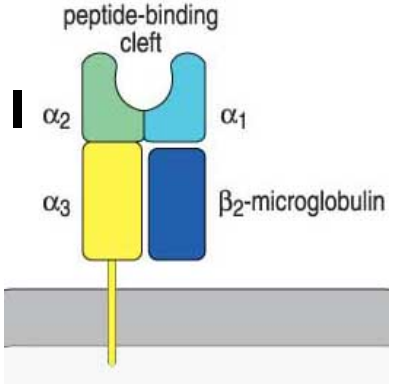
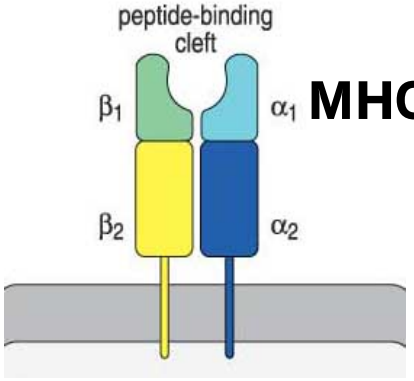


Figure 8-16
Kuby IMMUNOLOGY, Sixth Edition

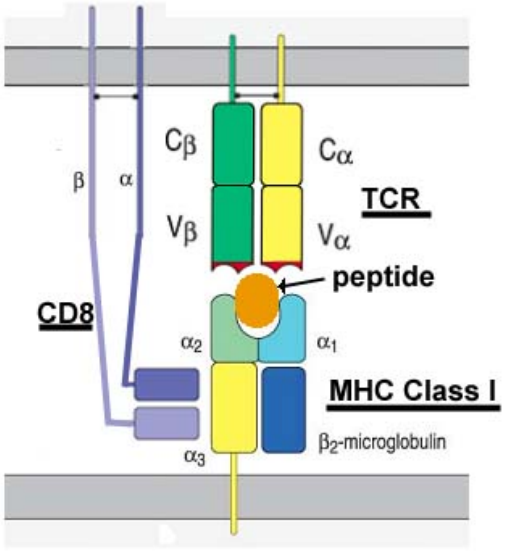
More on the Major Histocompatibility Complex Genetics and Function

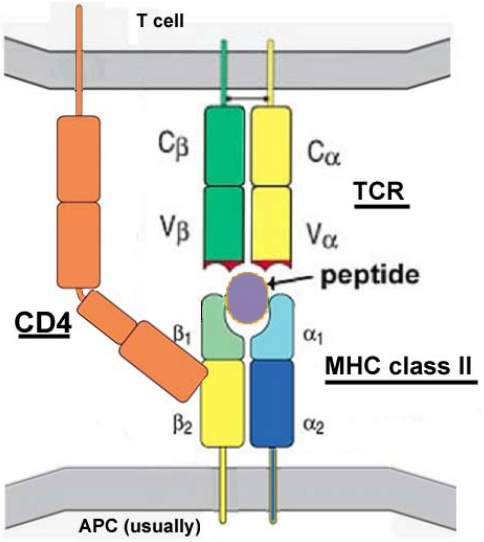
MHC class I





MHC class II





1. MHC-I endogenous antigens Processing pathway

1.1 Production of endogenous antigens

Polyubiquitination of endogenous antigens

Function of Proteosome

20S proteosome { X→LMP7; Y→LMP2; Z→MECL-1 } Immune proteosome

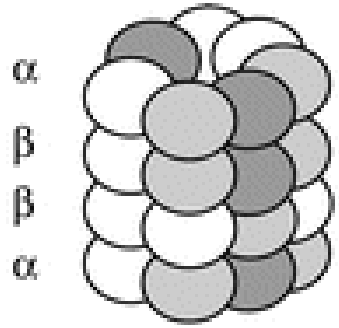
LMP7=PSMB9; LMP2=PSMB2

1.2 Transport of endogenous antigens

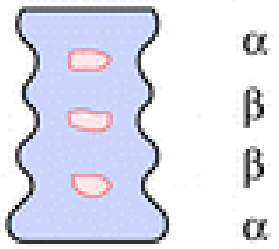
transporter associated with antigen processing, TAP1,2

1.3 Peptides are stably bound to MHC-I molecules

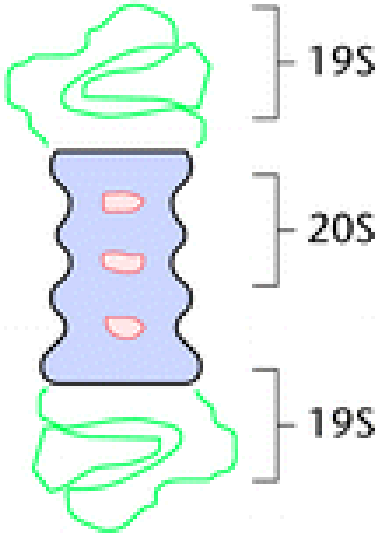
calnexin, tapasin, calreticulin



(a) 20S proteasome

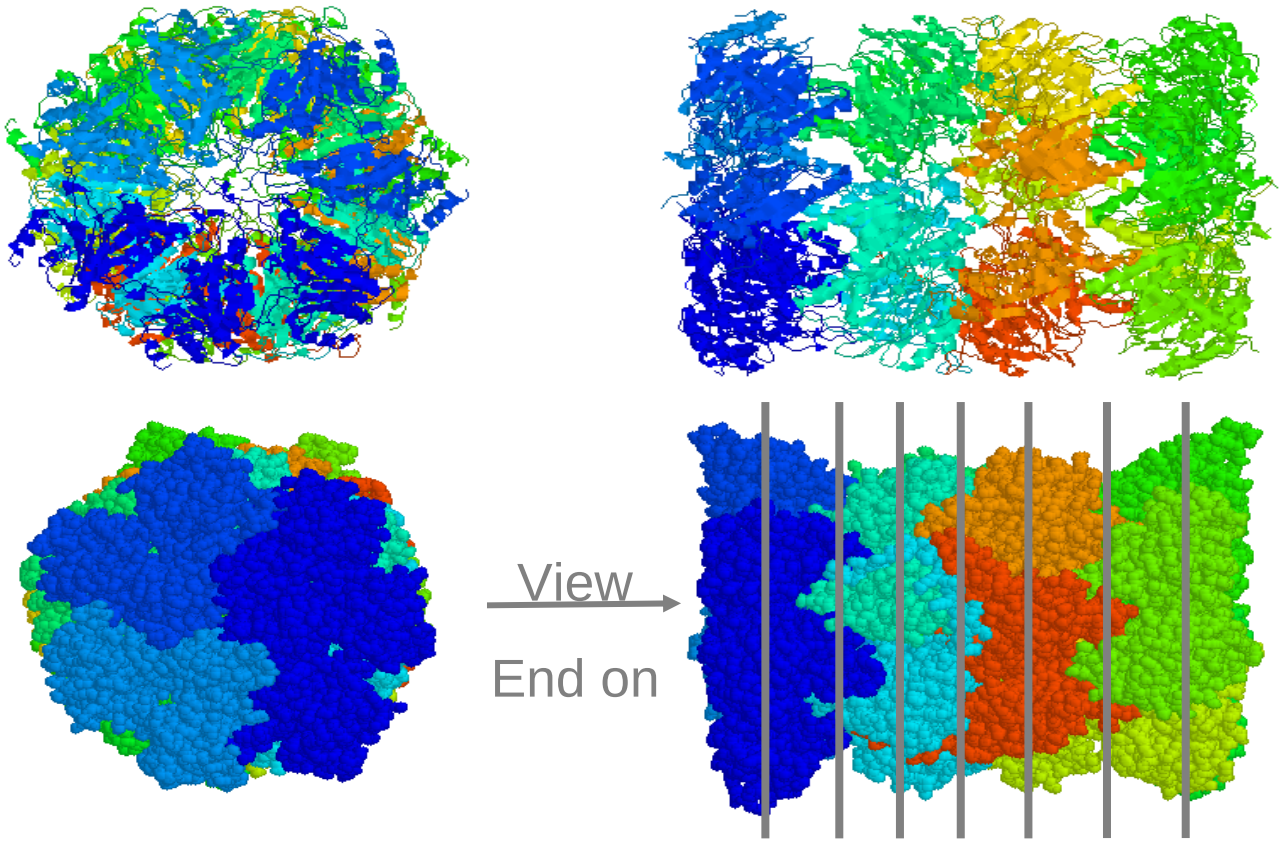


(b) 20S proteasome



26S proteasome

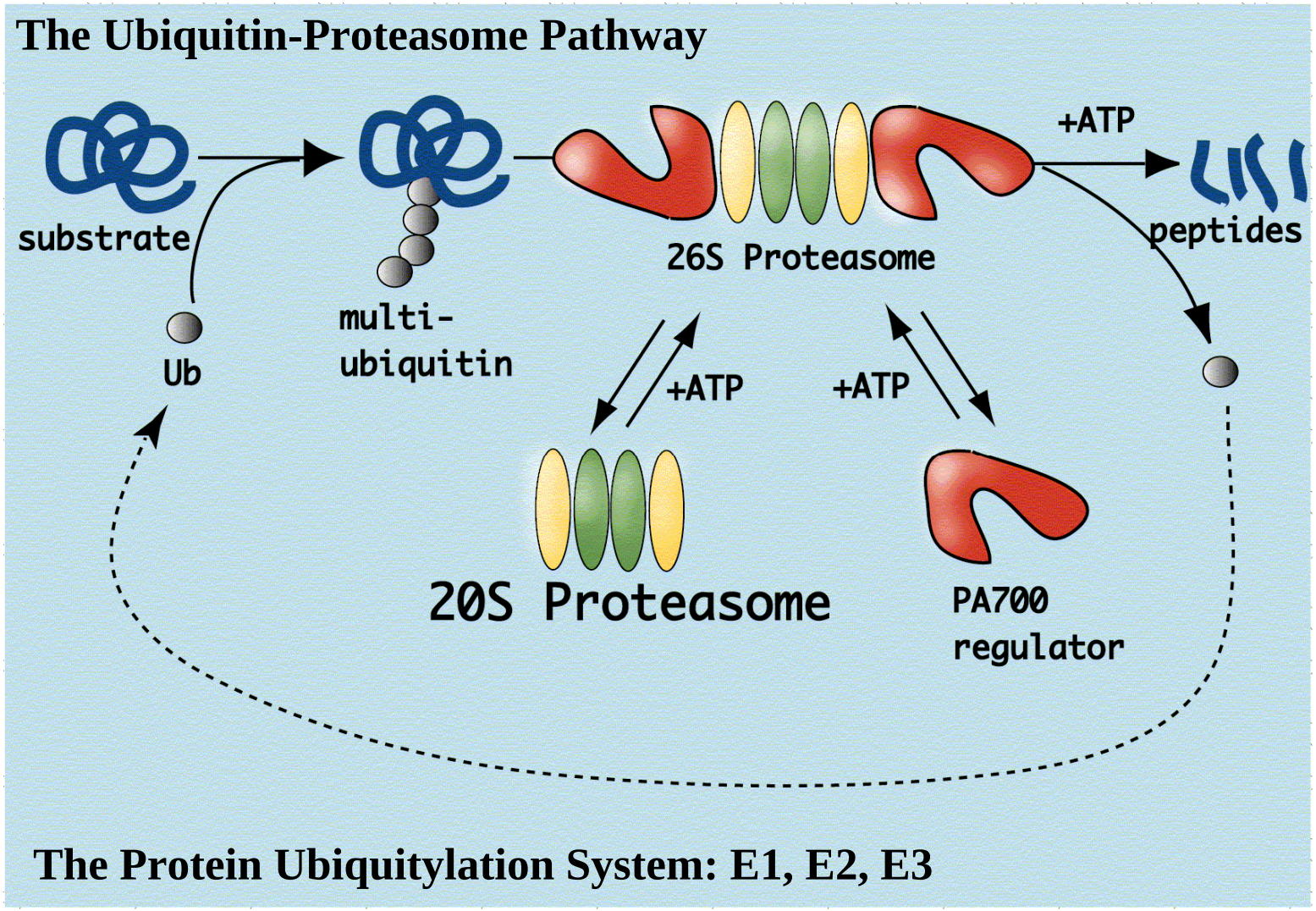
Crystal Structure Of The 20s Proteasome From Yeast



20S proteosome { **X→LMP7**, **Y→LMP2**, **Z→MECL-1** } **Immune proteosome**

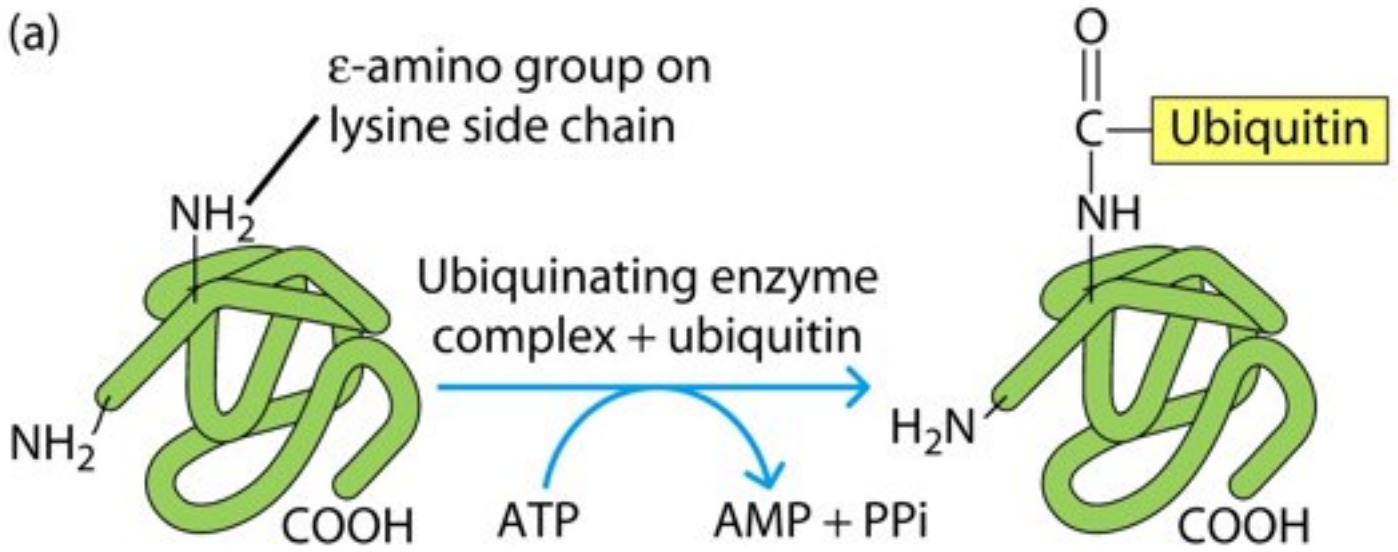
LMP7=PSMB9; LMP2=PSMB2

In the cytosol, proteins are degraded into peptides by **proteasomes**



2004 Nobel Prize in chemistry for the role of ubiquitin in protein recycling

Proteasomes are multicatalytic protease complexes made of ~28 subunits



The Protein Ubiquitylation System:

E1:泛素激活酶

E2:泛素结合酶

E3:泛素-靶蛋白连接酶

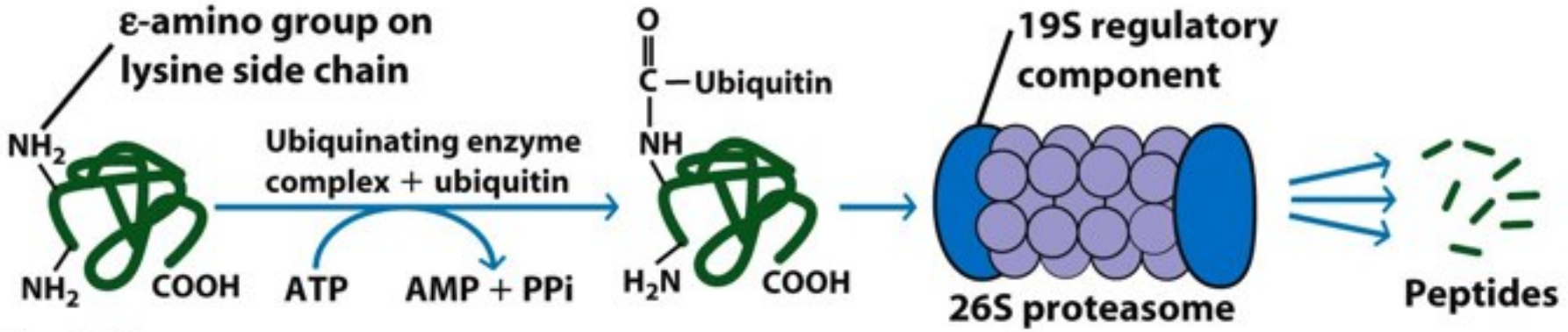
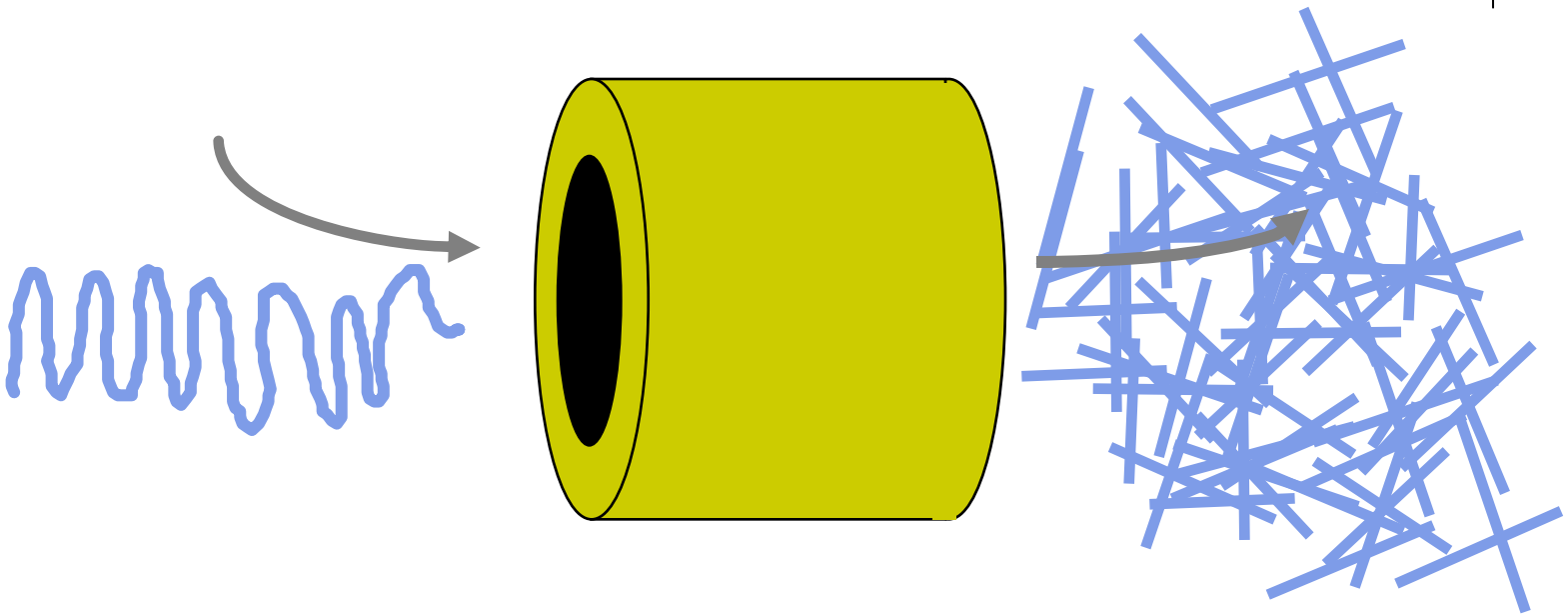


Figure 8-18b
Kuby IMMUNOLOGY, Sixth Edition

Degradation in the proteasome

Cytoplasmic cellular proteins, including non-self proteins are degraded continuously by a multicatalytic protease of 28 subunits

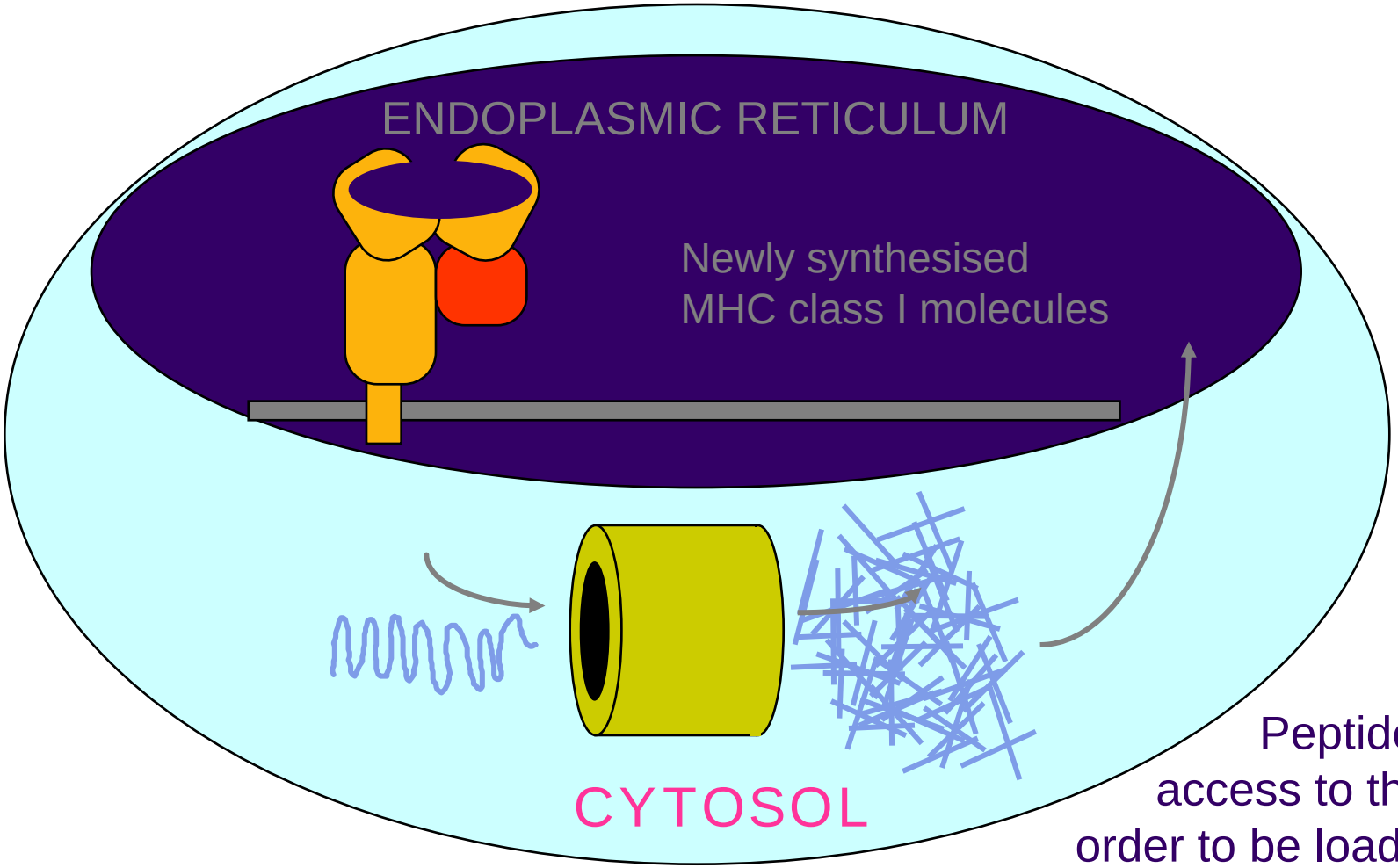


The components of the proteasome include MECL-1, LMP2, LMP7
These components are induced by IFN-γ and replace constitutive components to confer proteolytic properties.

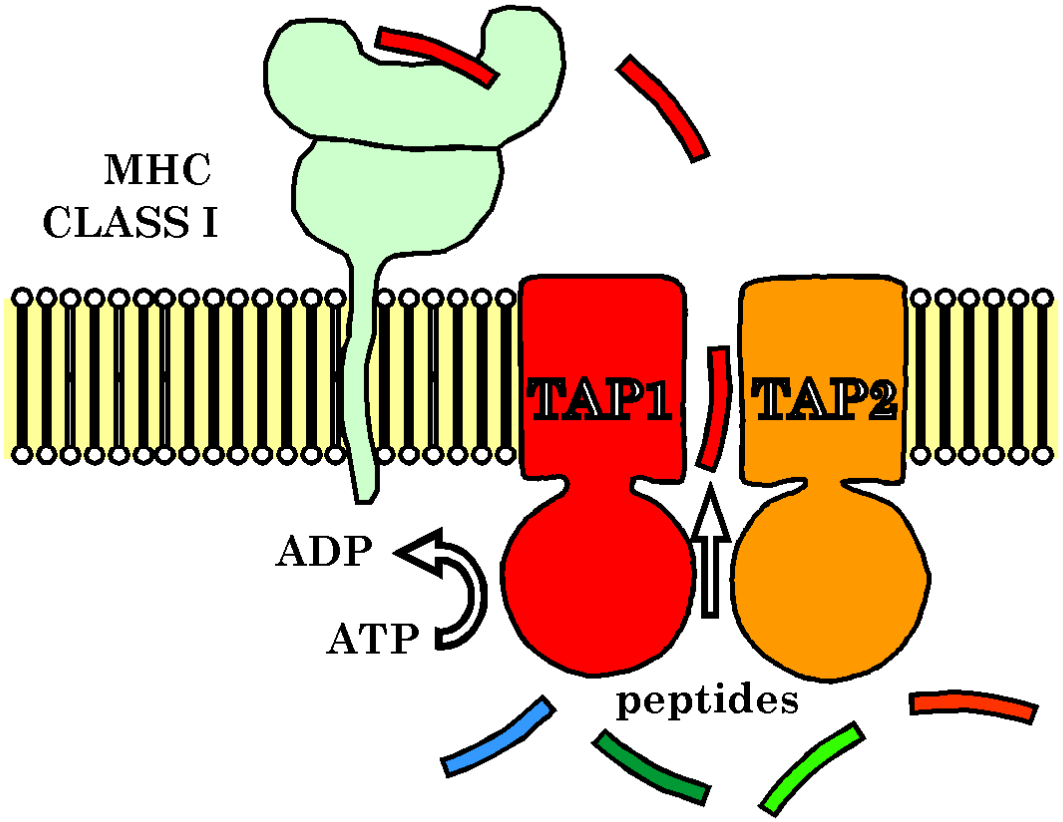
LMP2 & 7 encoded in the MHC

Proteasome cleaves proteins after hydrophobic and basic amino acids and releases peptides into the cytoplasm

Peptide antigens produced in the cytoplasm are physically separated from newly formed MHC class I



Peptides need access to the ER in order to be loaded onto MHC class I molecules



The two MHC-linked genes, TAP1 [embl: X57522] and TAP2 [embl: M84748] (for **T**ransporter **A**ssociated with antigen **P**rocessing), are required for normal presentation of intracellular antigens to T cells. These genes encode the polypeptides that form a heteromeric "peptide pump". The TAP1 (also known as RING4 or PSF1) and TAP2 (also known as RING11 or PSF2) genes possess an ATP binding cassette and 6 to 8 transmembrane helical segments. They are responsible for peptides selection and movement across the ER membrane to the binding site of MHC class I molecules.

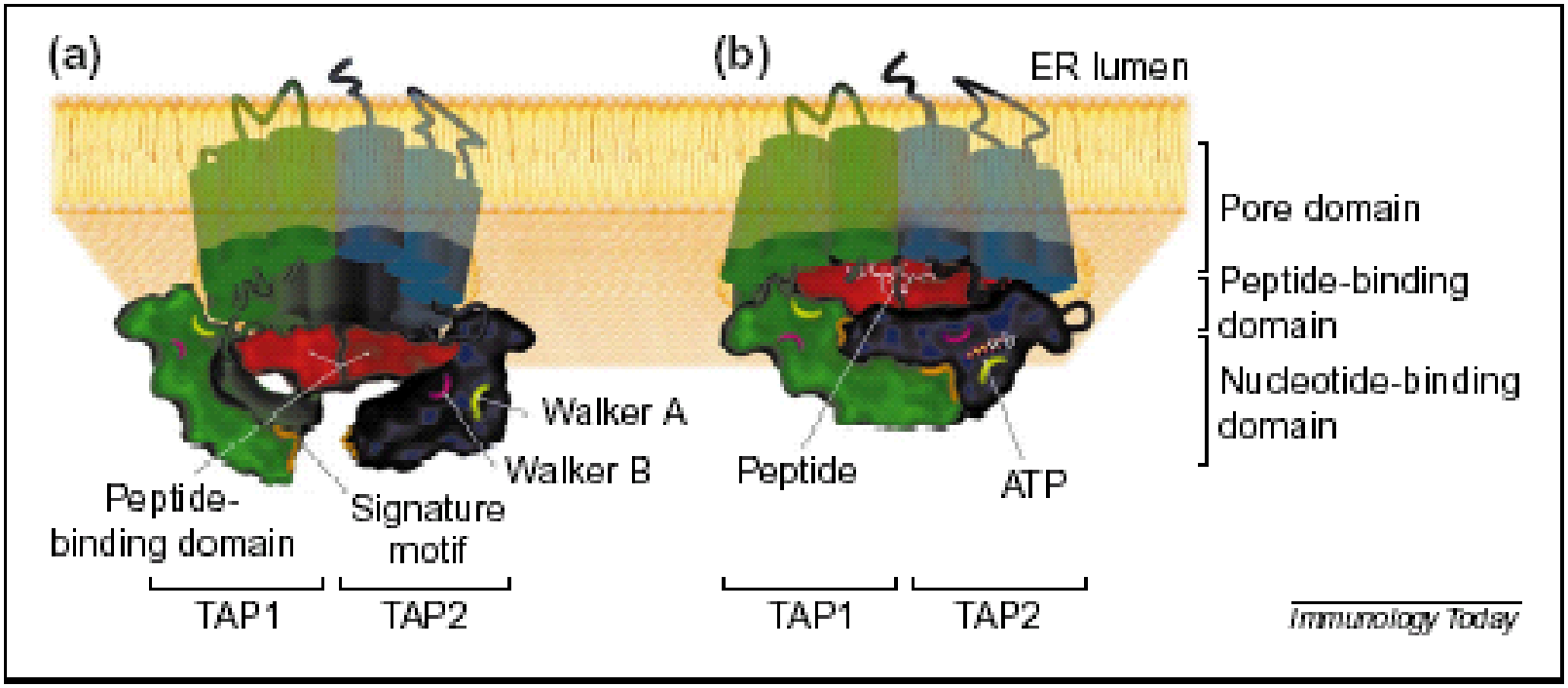
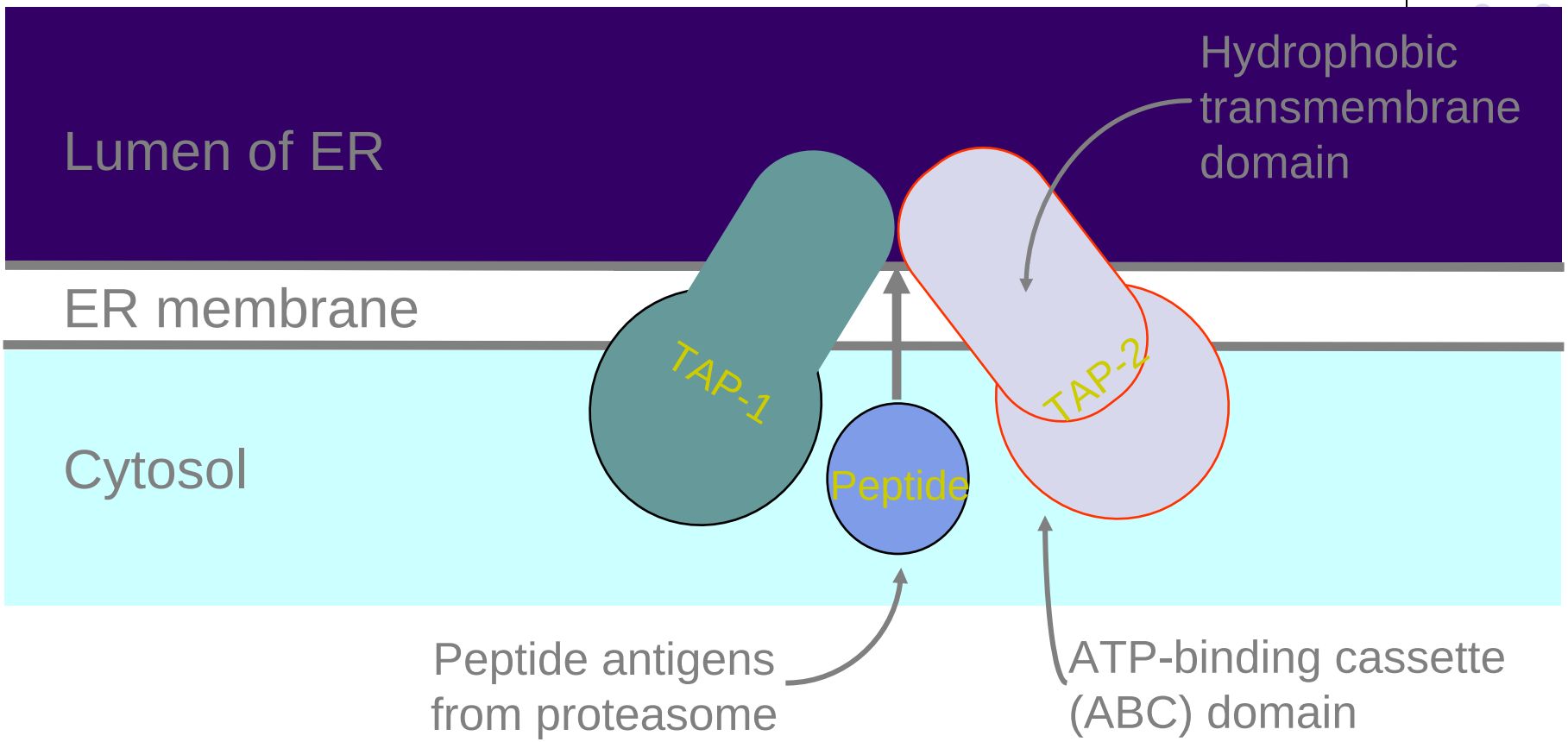


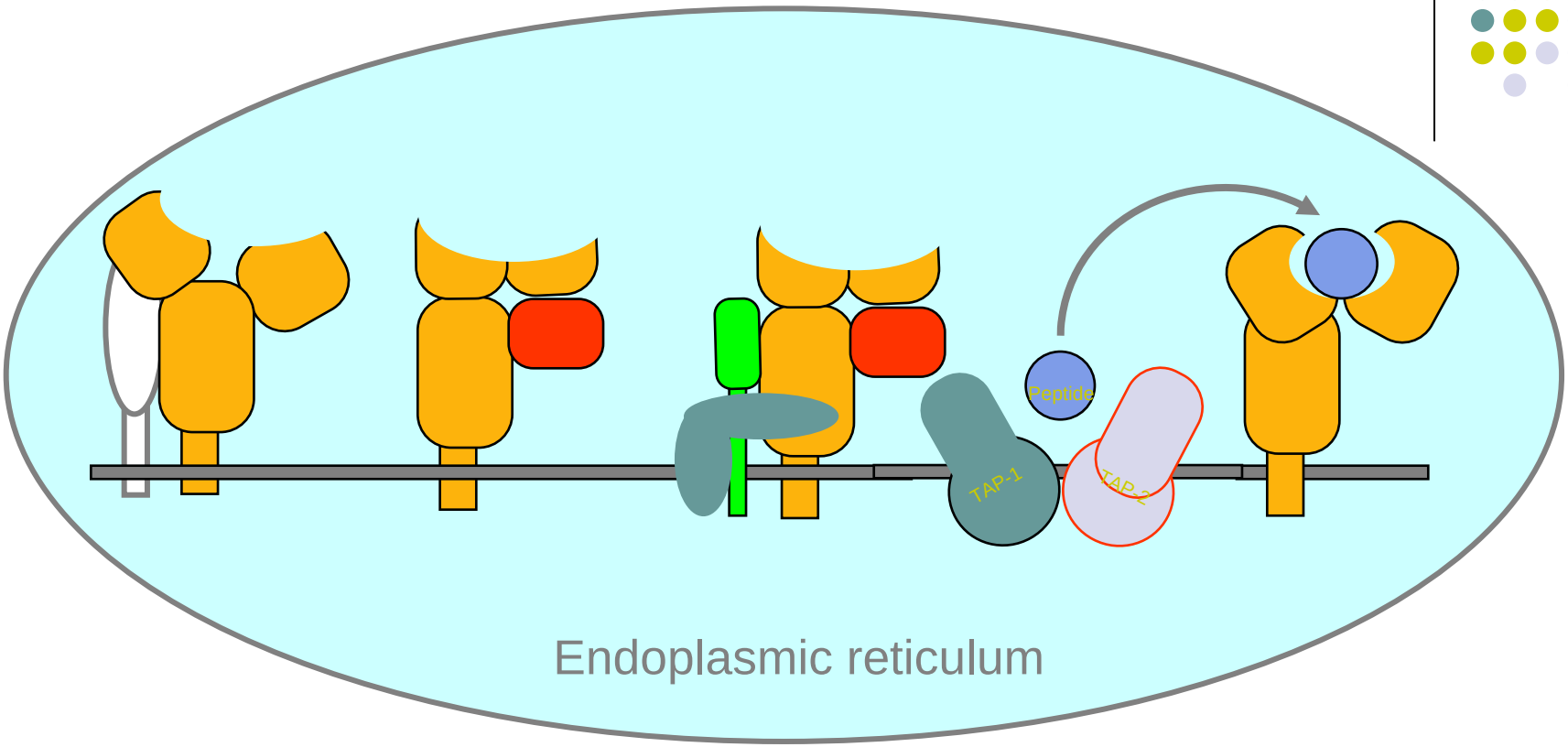
Fig. 2. *Model for peptide binding and translocation by TAP based on the topology and domain definition of TAP and the NBD domain structure of Rad50. (a) TAP is viewed from the cytosolic side as approached by the cytosolic peptide. (b) Upon peptide binding to the peptide-binding domain (red), ATP binding by the Walker A (yellow) and Walker B (purple) motifs is sensed by the signature motif (orange) of the partner NBD. This results in dimerization of the NBDs, with the signature motif of one NBD contacting the ATP bound to the other NBD. ATP hydrolysis induces a conformational change in the TAP complex, positioning the peptide beneath the opening pore, allowing peptide diffusion into the ER lumen. The outer radius of the transmembrane pore is approximately 90 Å (based on P-glycoprotein), and the NBD dimer is approximately 40 × 40 × 90 Å (based on Rad50). The topology and relative orientation of the TAP subunits, the dimerizing pore and the peptide-binding segments, and the localization of the pore and peptide-binding segments, have all been biochemically validated.*

Transporters associated with antigen processing (TAP1 & 2)



Transporter has preference for >8 amino acid peptides with hydrophobic C termini.

Maturation and loading of MHC class I



Calnexin binds to nascent class Iα chain until β2-M binds

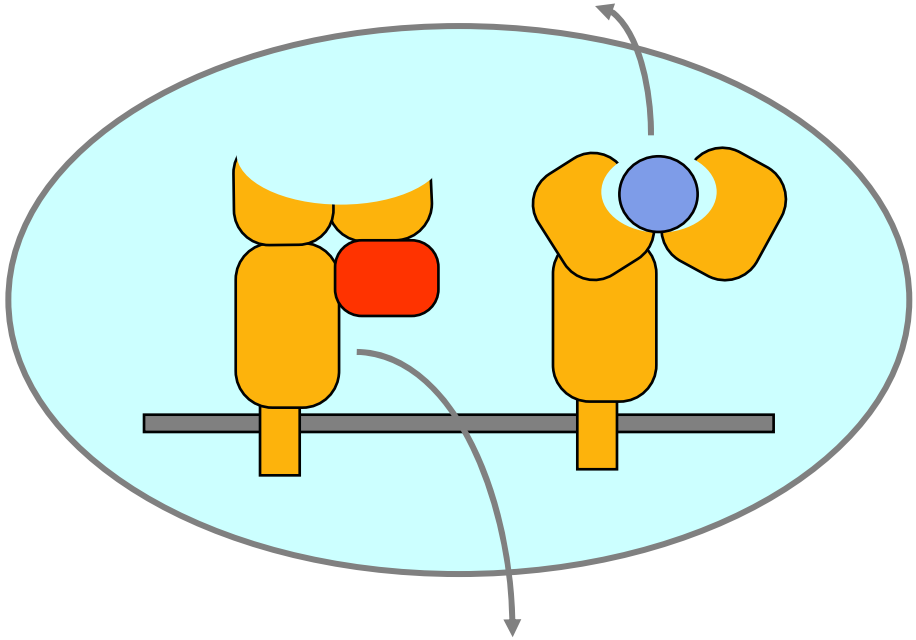
B2-M binds and stabilises floppy MHC

Tapasin, calreticulin, TAP 1 & 2 form a complex with the floppy MHC

Cytoplasmic peptides are loaded onto the MHC molecule and the structure becomes compact

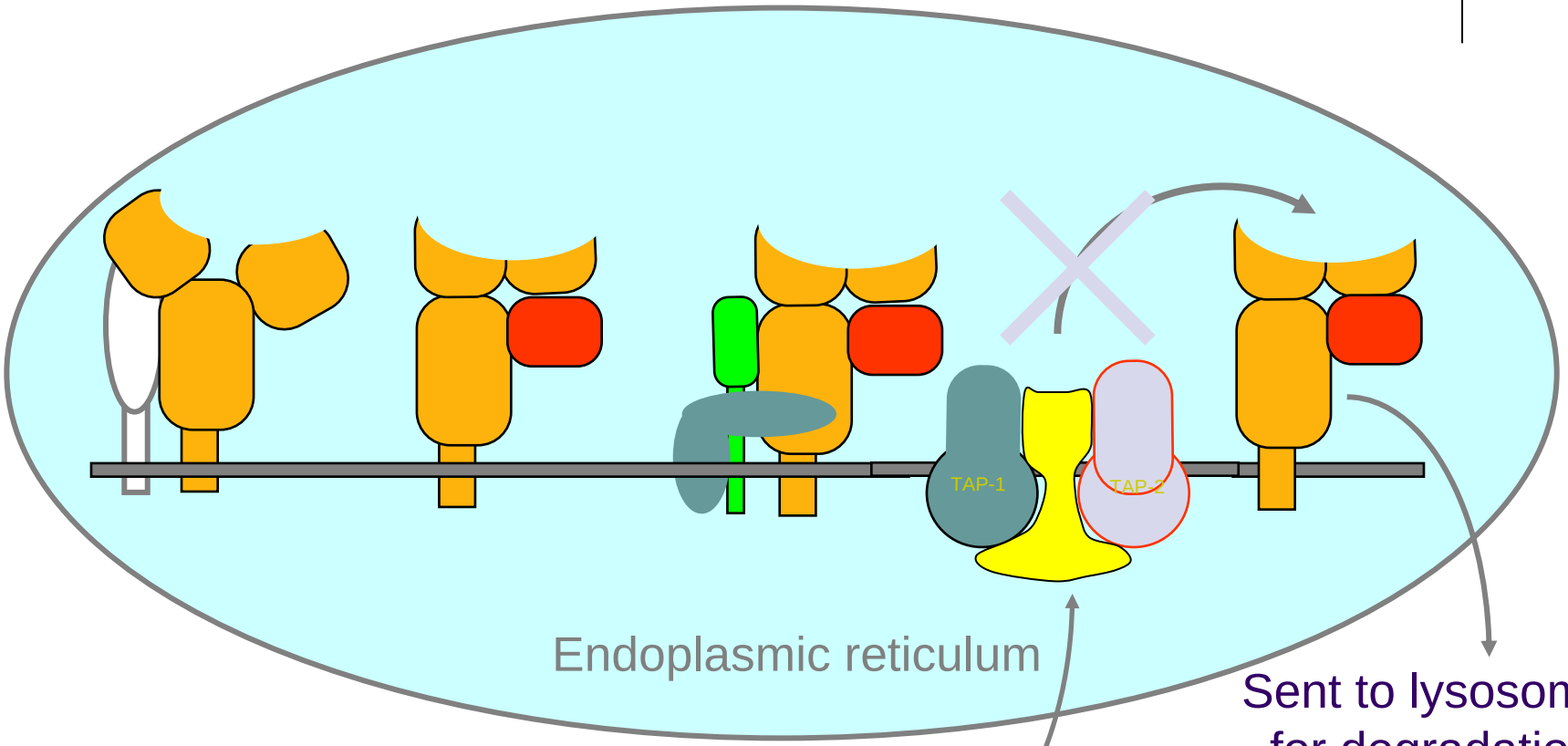
Fate of MHC class I

Exported to the cell surface

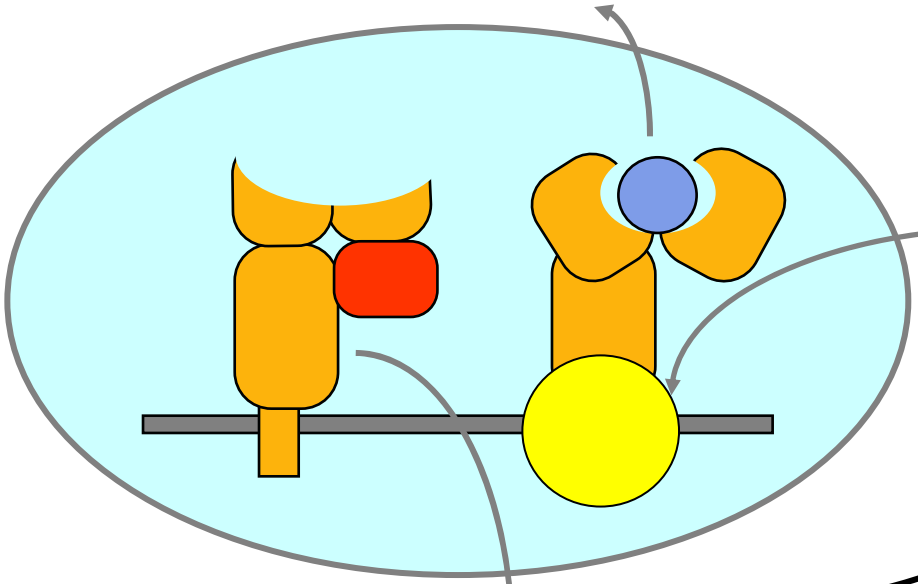


Sent to lysosomes for degradation

Evasion of immunity by interference with endogenous antigen processing



Evasion of immunity by interference with endogenous antigen processing



Normally exported to the cell surface

Adenoviral protein retains MHC class I in the ER

Sent to lysosomes for degradation

CYTOSOL PATHWAY

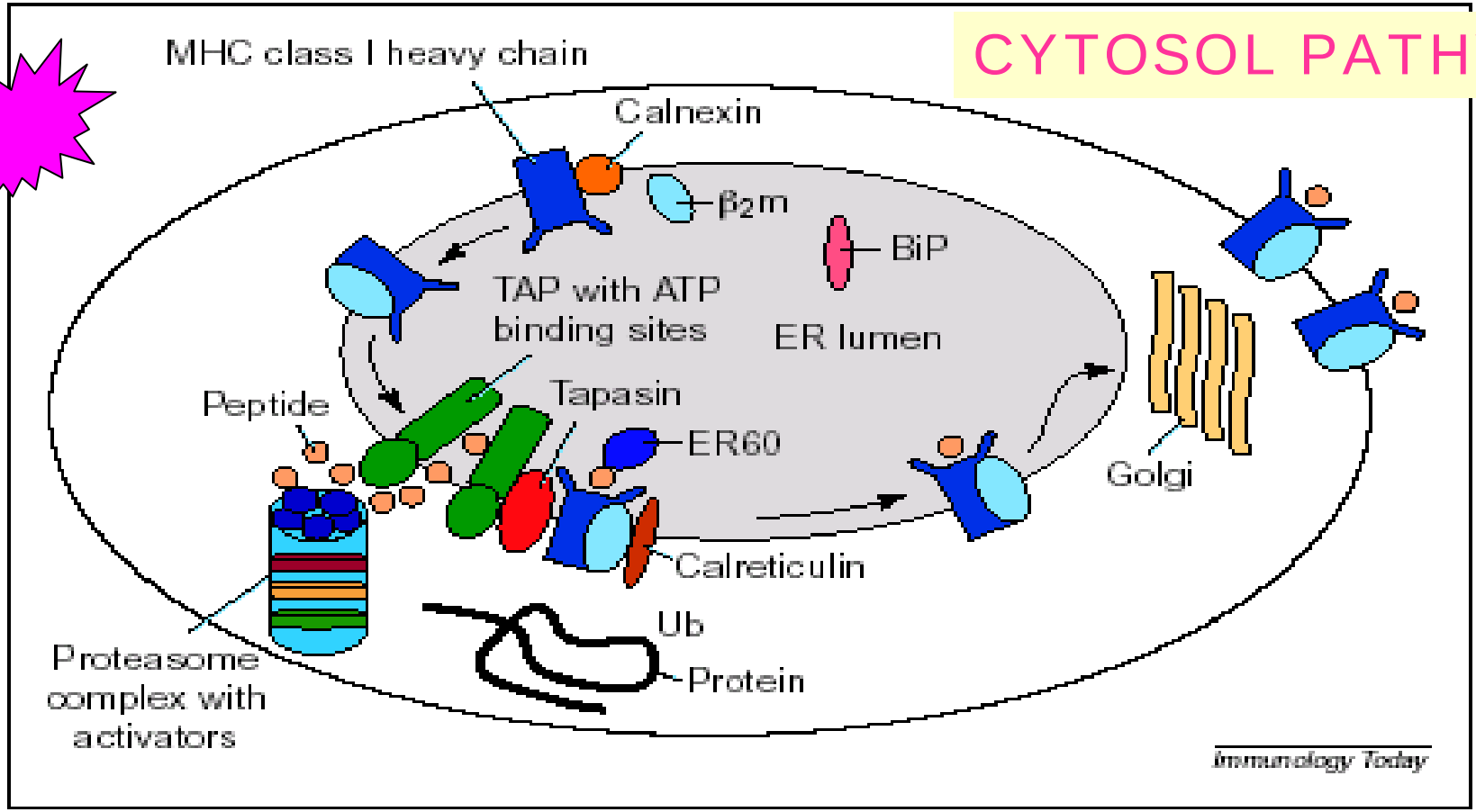
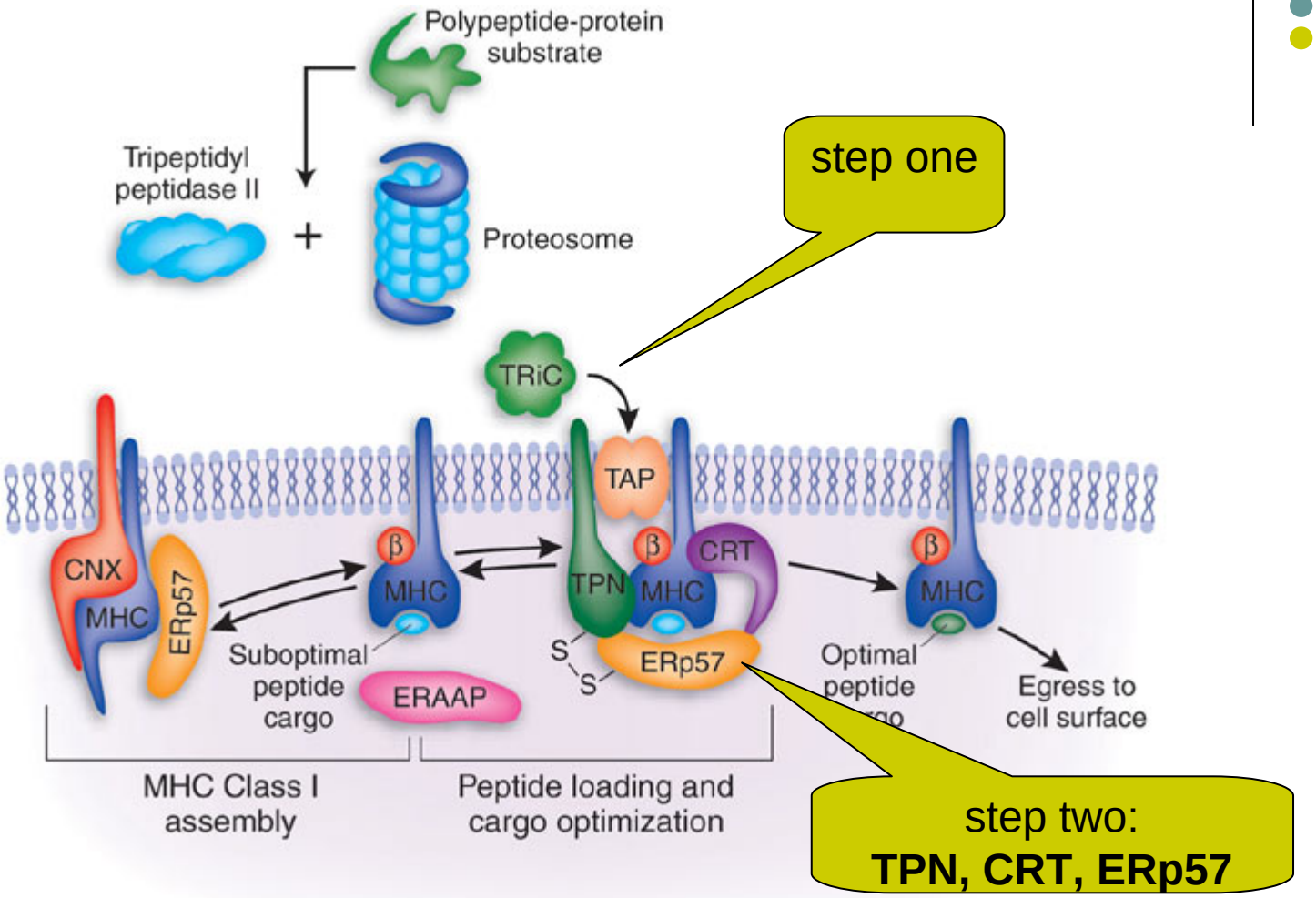


Fig. 1. *The MHC class I antigen-processing pathway. Processing and presentation of peptides by MHC class I antigen processing machinery requires three major steps: (a) the generation of antigenic peptides by the proteasome and other cytosolic proteases; (b) peptide transport mediated by the TAP dimer from the cytosol into the ER; and (c) the assembly of peptides with HLA class I molecules, which is assisted by various chaperones, such as calnexin, calreticulin, ER60 and tapasin. The trimeric complex comprising HLA class I H chains, β_2m and peptide is then transported through the Golgi directly to the cell surface for presentation to CD8$^+$ T cells. Abbreviations: β_2m, β_2-microglobulin; BiP, immunoglobulin H-chain-binding protein; ER, endoplasmic reticulum; H, heavy; MHC, major histocompatibility complex; TAP, peptide transporter associated with antigen processing; Ub, ubiquitin.*

MHC-I类抗原加工递呈的亲和力“编辑”

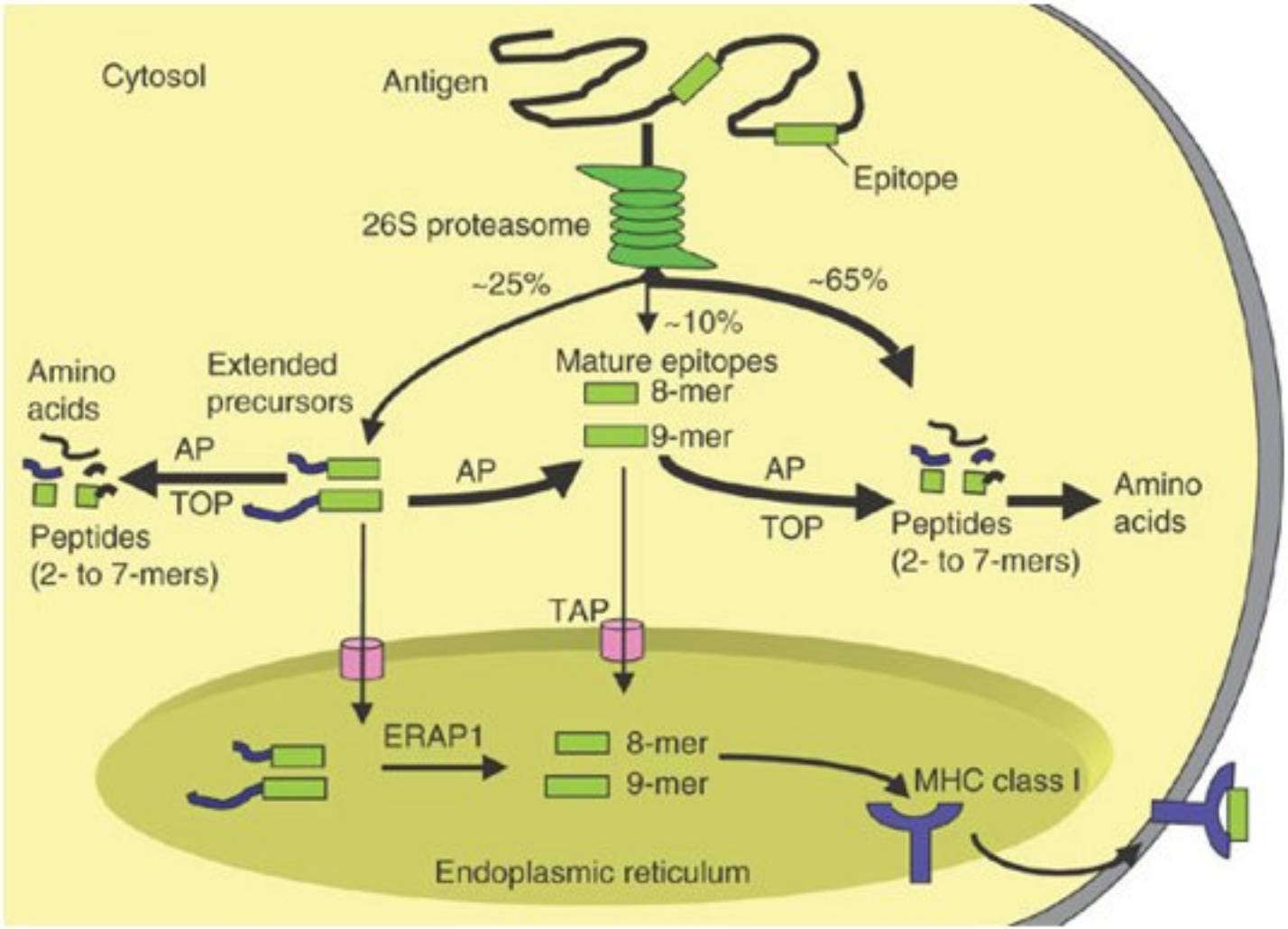


Nature Immunology **7**, 7 - 9 (2006)
The 'chop-and-change' of MHC class I assembly

Antigens destined for presentation by MHC class I molecules are degraded by the combined action of proteasome and tripeptidyl peptidase II as well as other proteases in the cytosol.

The peptides thus generated are then transported into the lumen of the endoplasmic reticulum by TAP. Peptides may be chaperoned between proteases and TAP by the cytosolic hsp60 homolog TRiC. Once in the lumen of the endoplasmic reticulum, peptides can bind to newly assembled MHC class I molecules. Assembly of MHC class I from a constituent heavy chain and 2-microglobulin is assisted by calnexin (CNX), possibly in complex with ERp57. Peptide loading proceeds in a two-step process. In step one, peptide-receptive molecules load with peptide cargo that is not refined in terms of its affinity (off-rate). A subsequent step involving tapasin (TPN), calreticulin (CRT) and ERp57 results in the 'editing' of this peptide cargo in favor of high-affinity ligands. This process happens while MHC class I molecules are incorporated into the peptide-loading complex. ERAAP is also involved in this peptide editing step by trimming long, low-affinity peptide precursors to a size more suited to binding to MHC class I molecules with high affinity.

Epitope Destruction vs. Production



The Nobel Prize in Chemistry 2004

"for the discovery of ubiquitin-mediated protein degradation"

Aaron Ciechanover
1/3 of the prize
Israel
Technion –
Israel Institute of
Technology
Haifa, Israel
b. 1947

Avram Hershko
1/3 of the prize
Israel
Technion –
Israel Institute of
Technology
Haifa, Israel
b. 1937
(in Karcag, Hungary)

Irwin Rose
1/3 of the prize
USA
University of California
Irvine, CA, USA
b. 1926

Thanks to the work of the three Laureates it is now possible to understand at molecular level how the cell controls a number of central processes by breaking down certain proteins and not others. Examples of processes governed by ubiquitin-mediated protein degradation are cell division, DNA repair, quality control of newly-produced proteins, and important parts of the immune defence. When the degradation does not work correctly, we fall ill. Cervical cancer and cystic fibrosis are two examples. Knowledge of ubiquitin-mediated protein degradation offers an opportunity to develop drugs against these diseases and others.

‘kiss of death'

The label consists of a molecule called *ubiquitin*. This fastens to the protein to be destroyed, accompanies it to the proteasome where it is recognised as the key in a lock, and signals that a protein is on the way for disassembly. Shortly before the protein is squeezed into the proteasome, its ubiquitin label is disconnected for re-use.

2. MHC-II Exogenous antigens Processing pathway

2.1 Endosomes and Compartments for antigen processing

2.2 Antigen degradation

multi-catalytic unit,

immunodominant site

2.3 MHC-II transport

ER→ α chain and β chain

Calnexin, Cx

Ia-associated invariant chain, Ii

Class II- associated invariant chain peptide, CLIP

$Ii_3 \alpha_3 \beta_3$

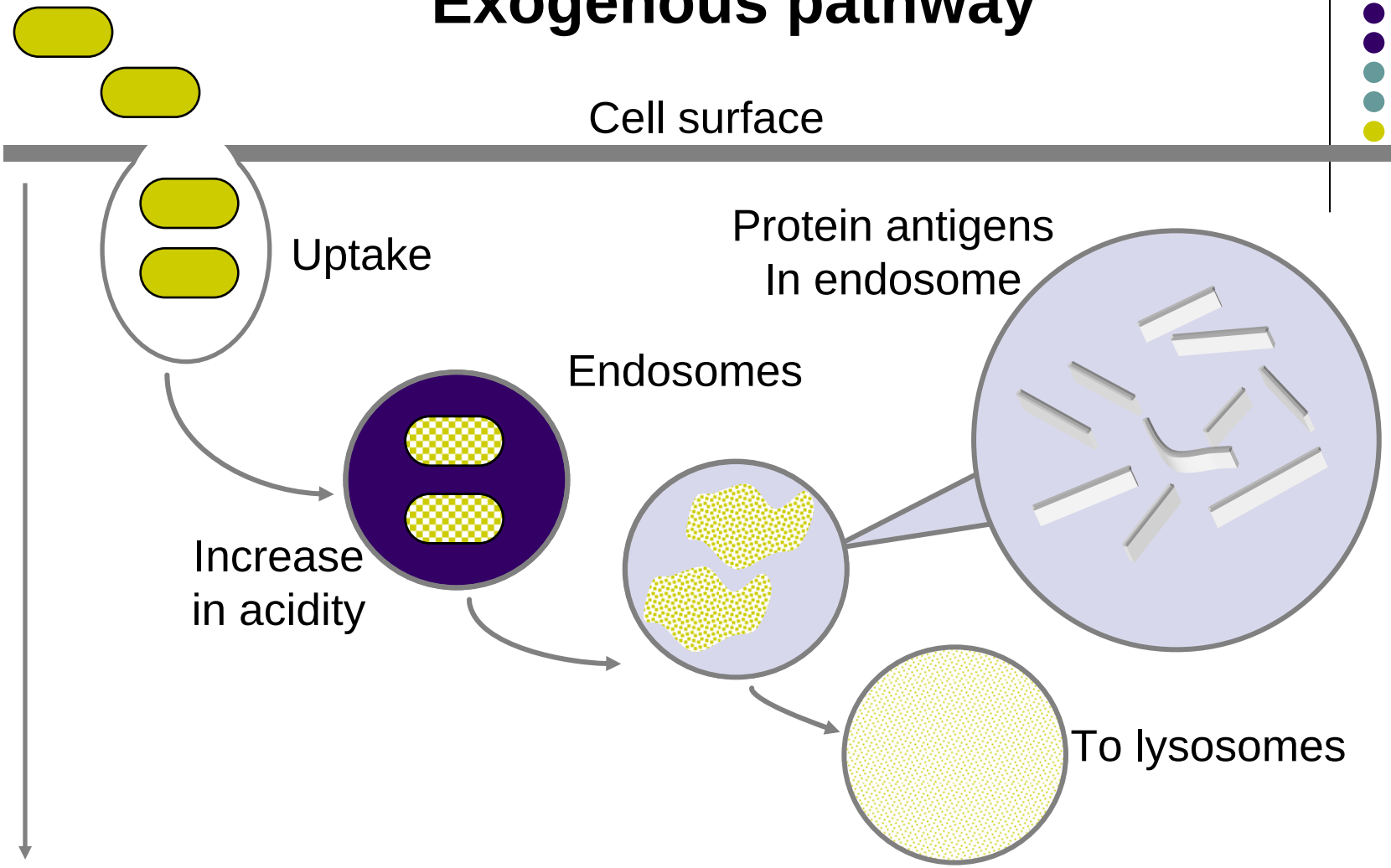
Trans-Golgi network→endosome

2.4 Ii degredation in endosome

2.5 Peptides are stably bound to MHC-II molecule/HLA-DM

2.6 Antigen presentation

Exogenous pathway



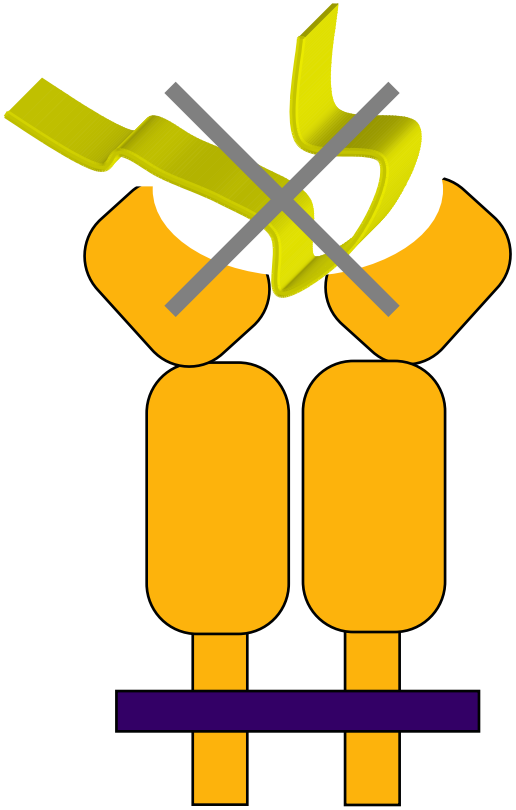
Cathepsin B, D and L proteases are activated by the decrease in pH

Proteases produce ~24 amino acid long peptides from antigens

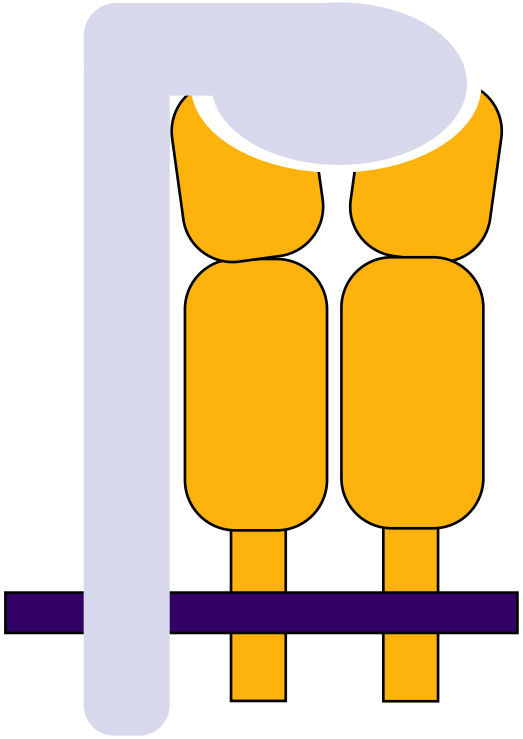
Drugs that raise the pH of endosomes inhibit antigen processing

MHC class II maturation and invariant chain

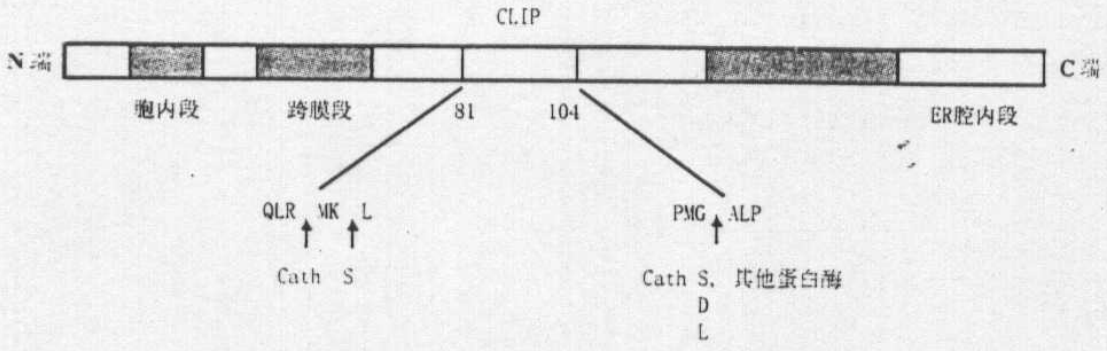
In the endoplasmic reticulum



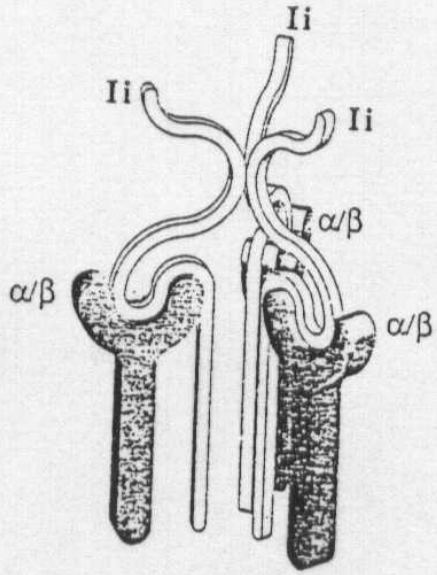
Need to prevent newly synthesised, unfolded self proteins from binding to immature MHC



Invariant chain stabilises MHC class II by non- covalently binding to the immature MHC class II molecule and forming a nonomeric complex



(A)



(B)

Invariant chain structure

The invariant chain

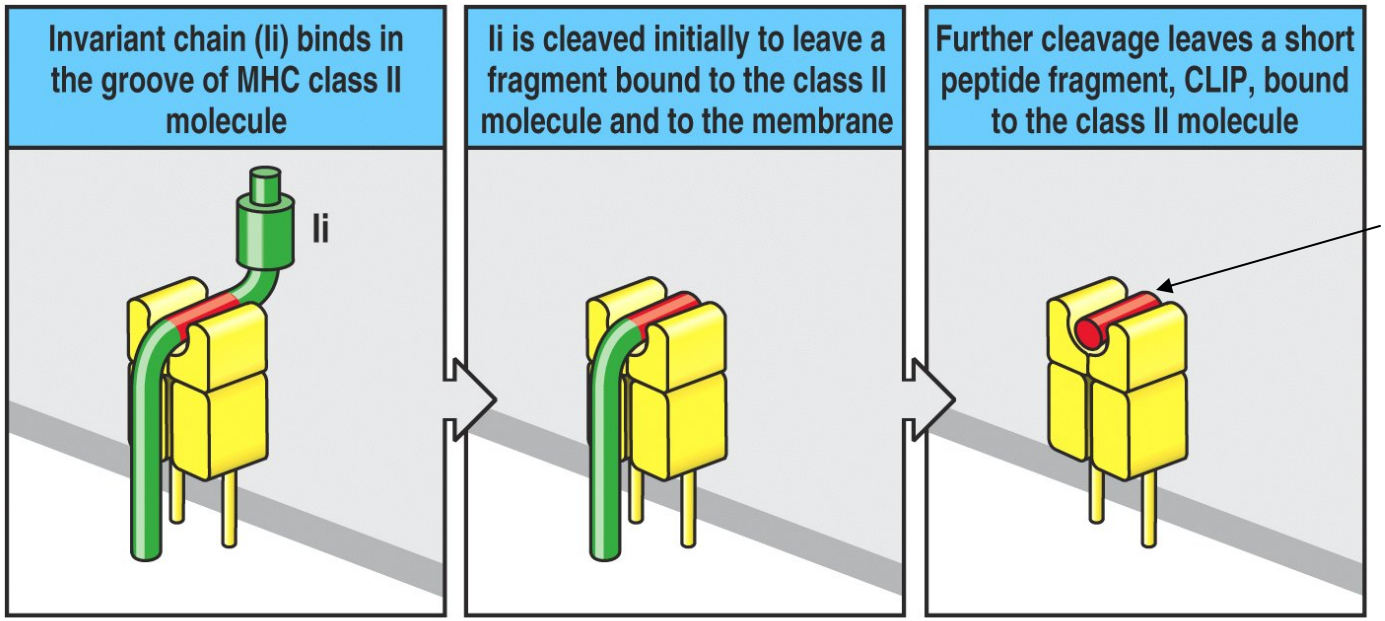


Figure 5-8 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Class II-associated invariant-chain peptide (CLIP)

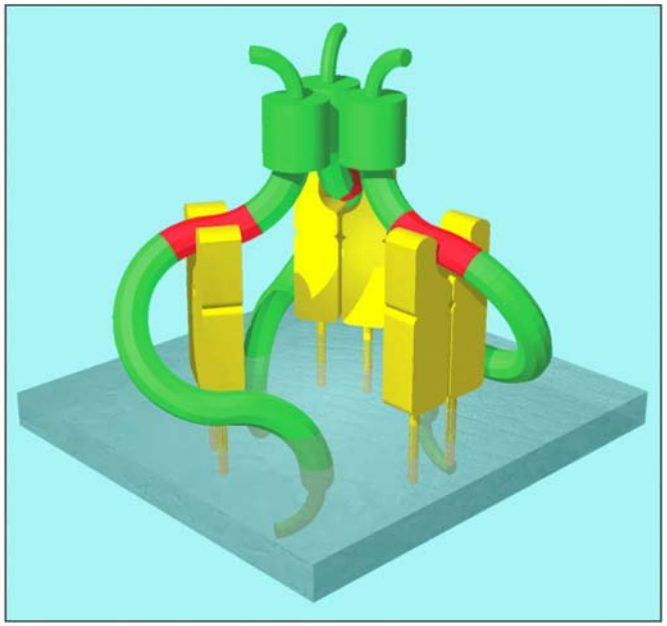
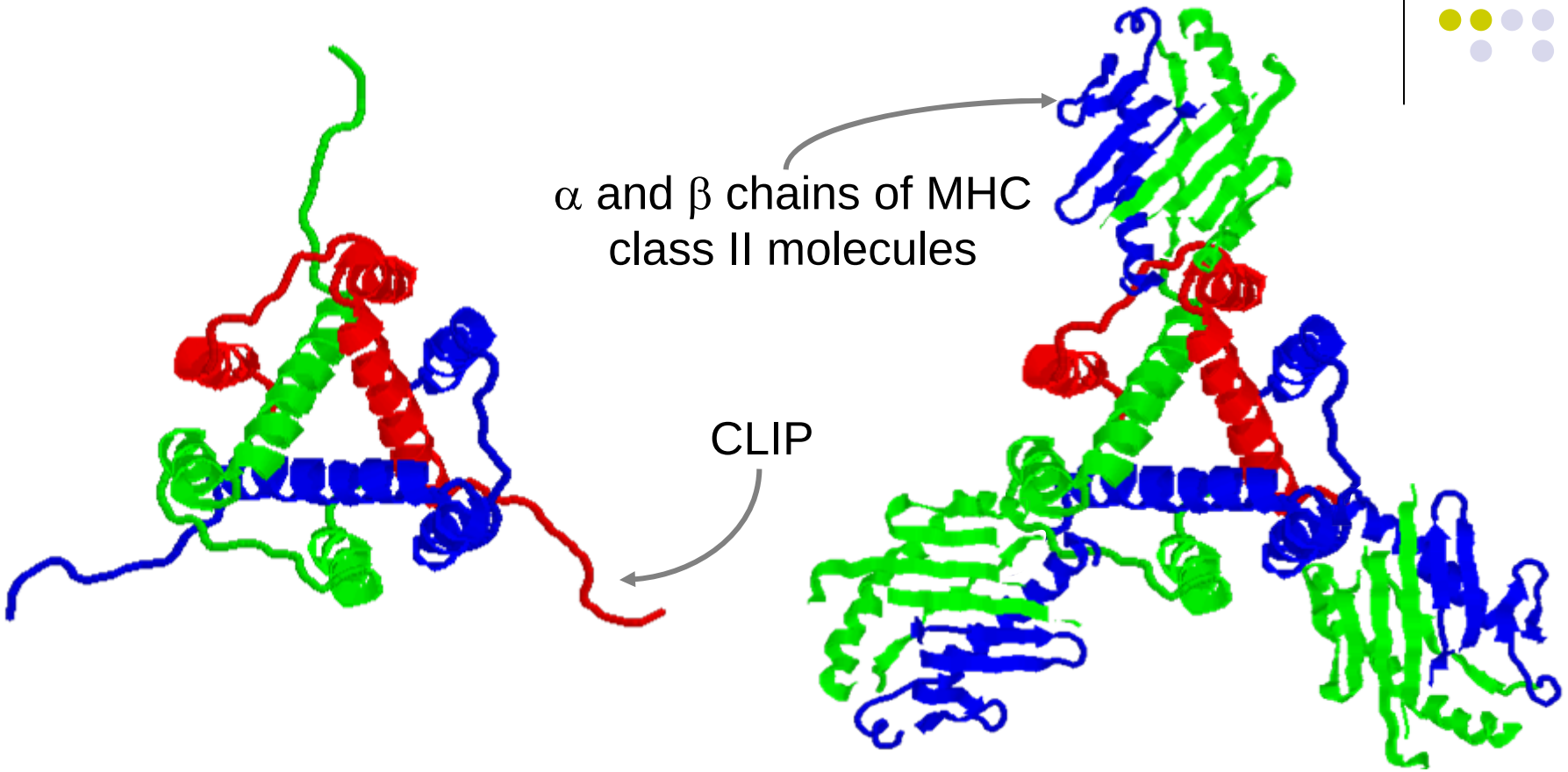


Figure 5-8 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Invariant chain structure

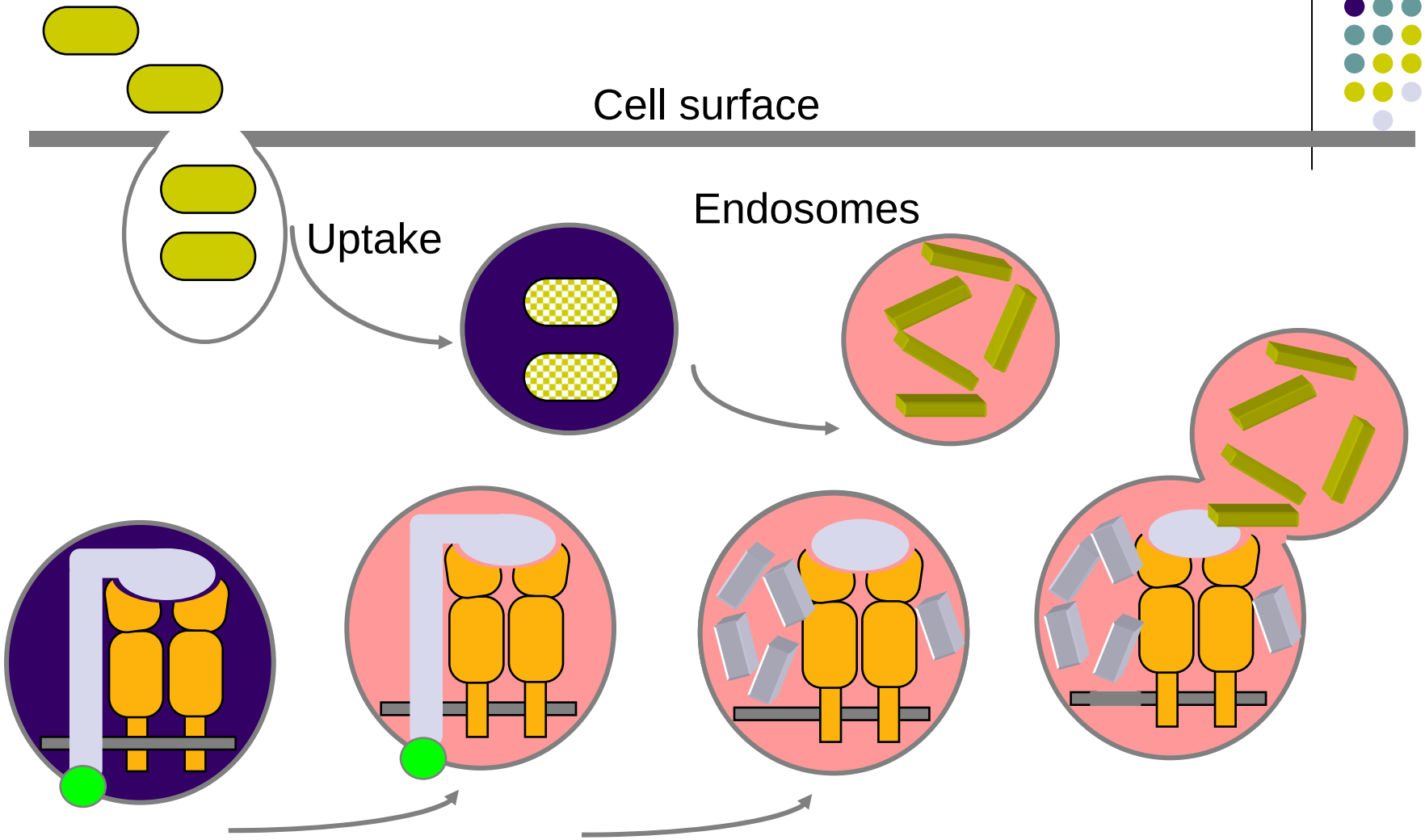
Three extended peptides each bind into the grooves of three MHC class II molecules to form the nonomeric complex

Invariant chain CLIP peptide



A peptide of the invariant chain blocks the MHC molecule binding site. This peptide is called the CLass II associated Invariant chain Peptide (CLIP)

Class II associated invariant chain peptide (CLIP)

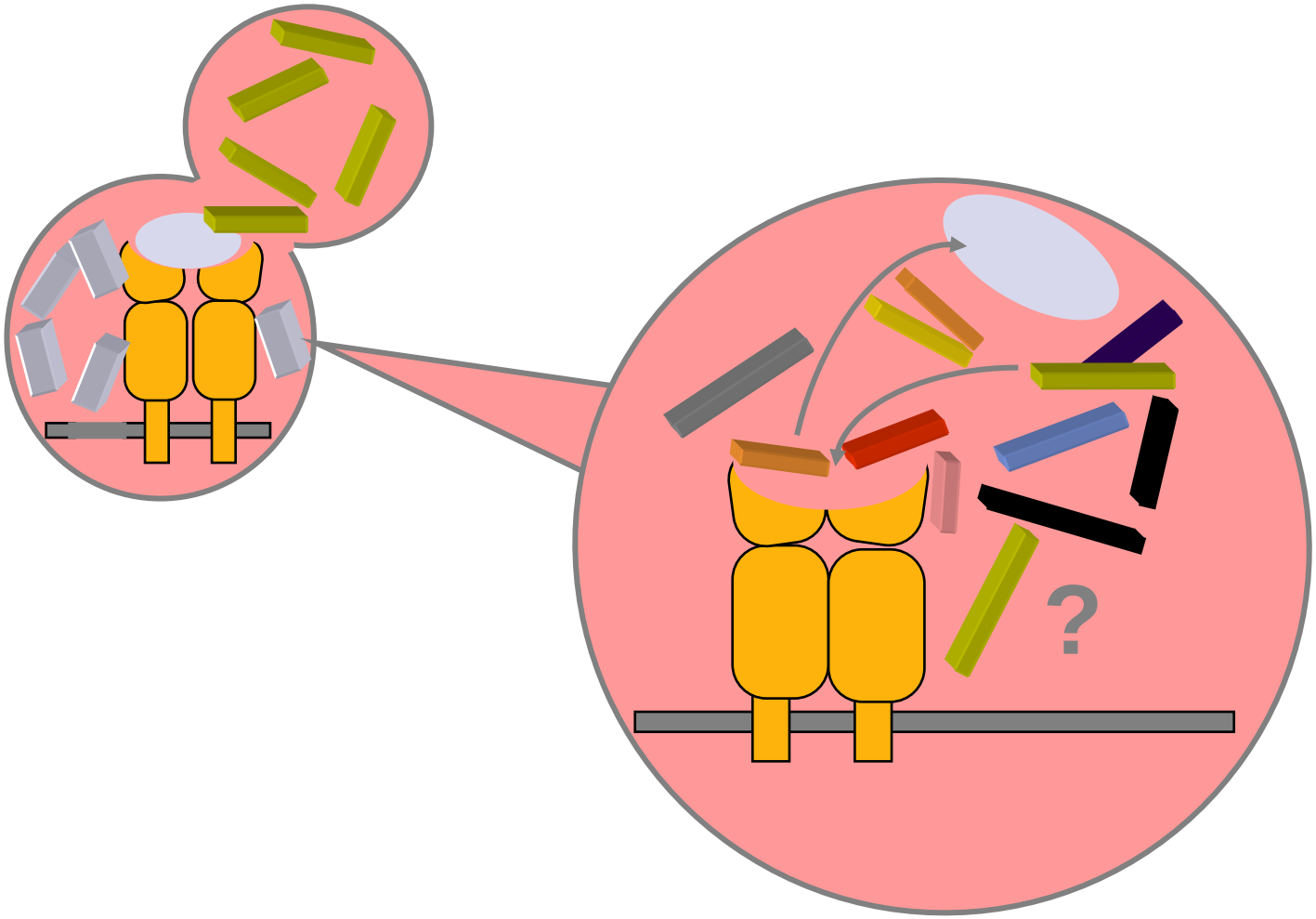


(αβinv)3 complexes directed towards endosomes by invariant chain

Cathepsin L degrades Invariant chain
CLIP blocks groove in MHC molecule

MHC Class II containing vesicles fuse with antigen containing vesicles

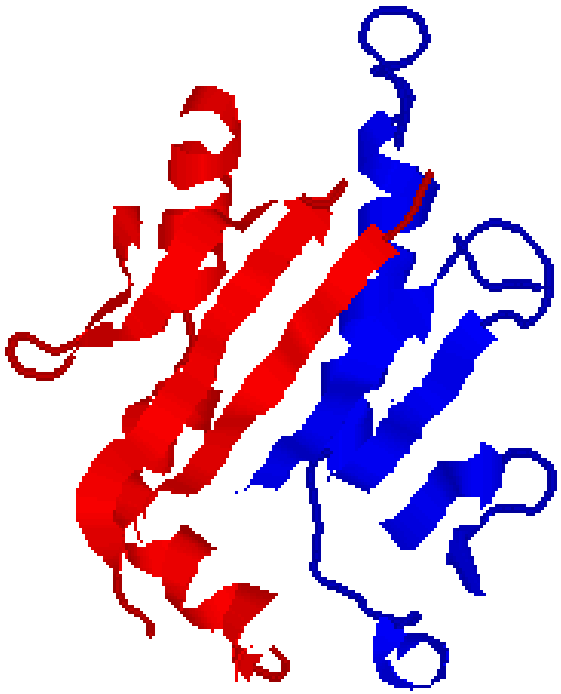
Removal of CLIP

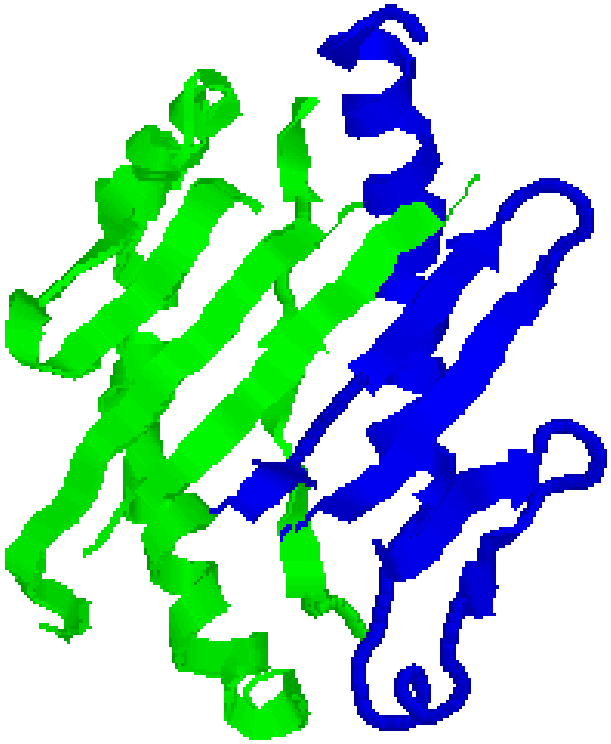


How can the peptide stably bind to a floppy binding site?

Competition between large number of peptides

HLA-DM assists in the removal of CLIP





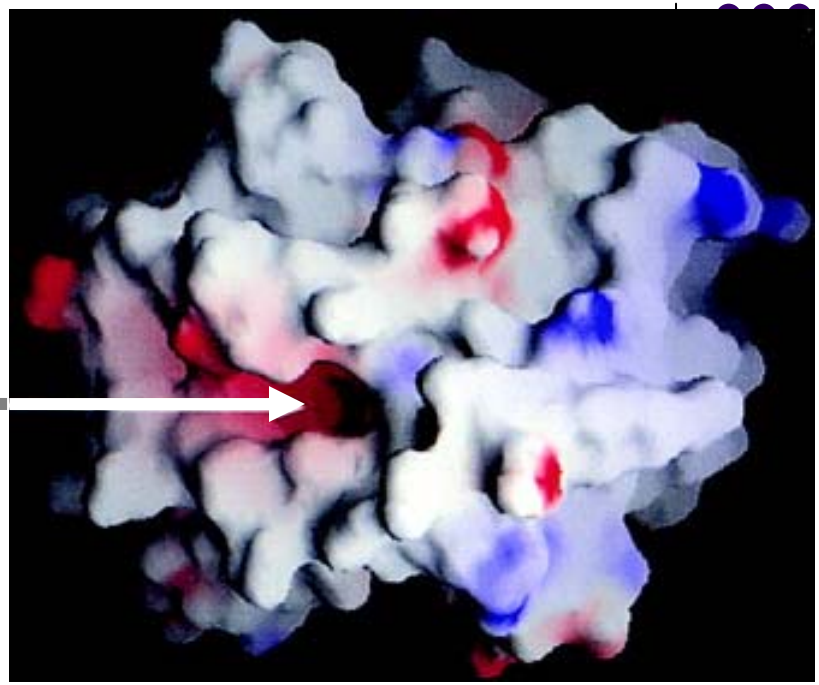
HLA-DM

HLA-DR

HLA-DM: Crystallised without a peptide in the groove
In space filling models the groove is very small

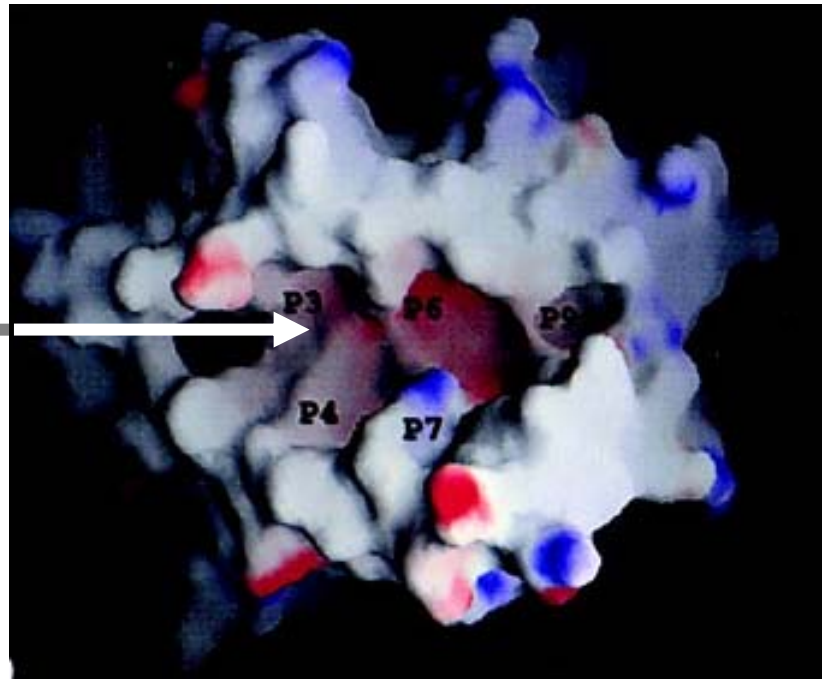
HLA-DM

Single pocket in “groove” insufficient to accommodate a peptide

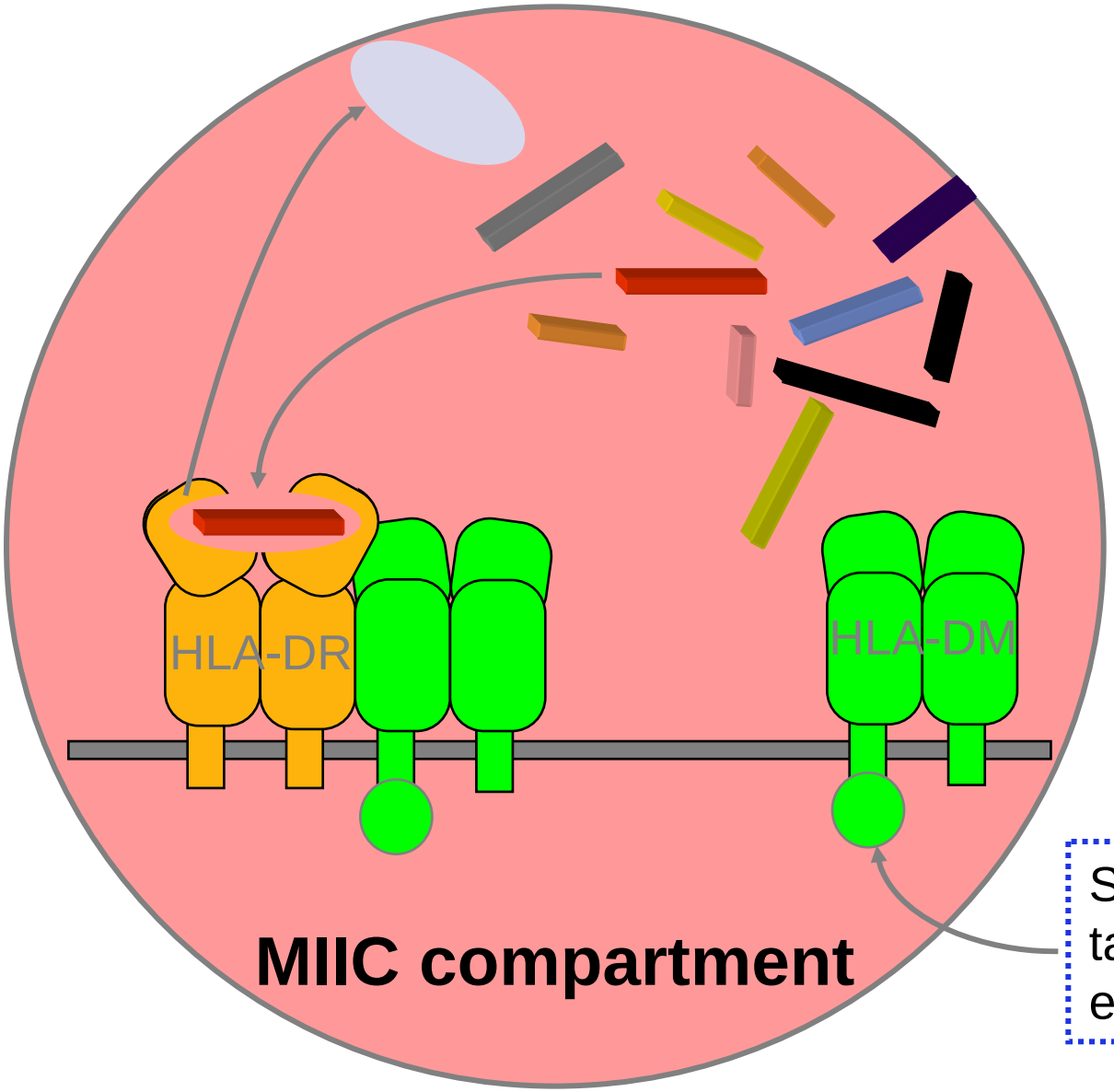


HLA-DR

Multiple pockets in groove sufficient to accommodate a peptide



HLA-DM catalyses the removal of CLIP



HLA-DM

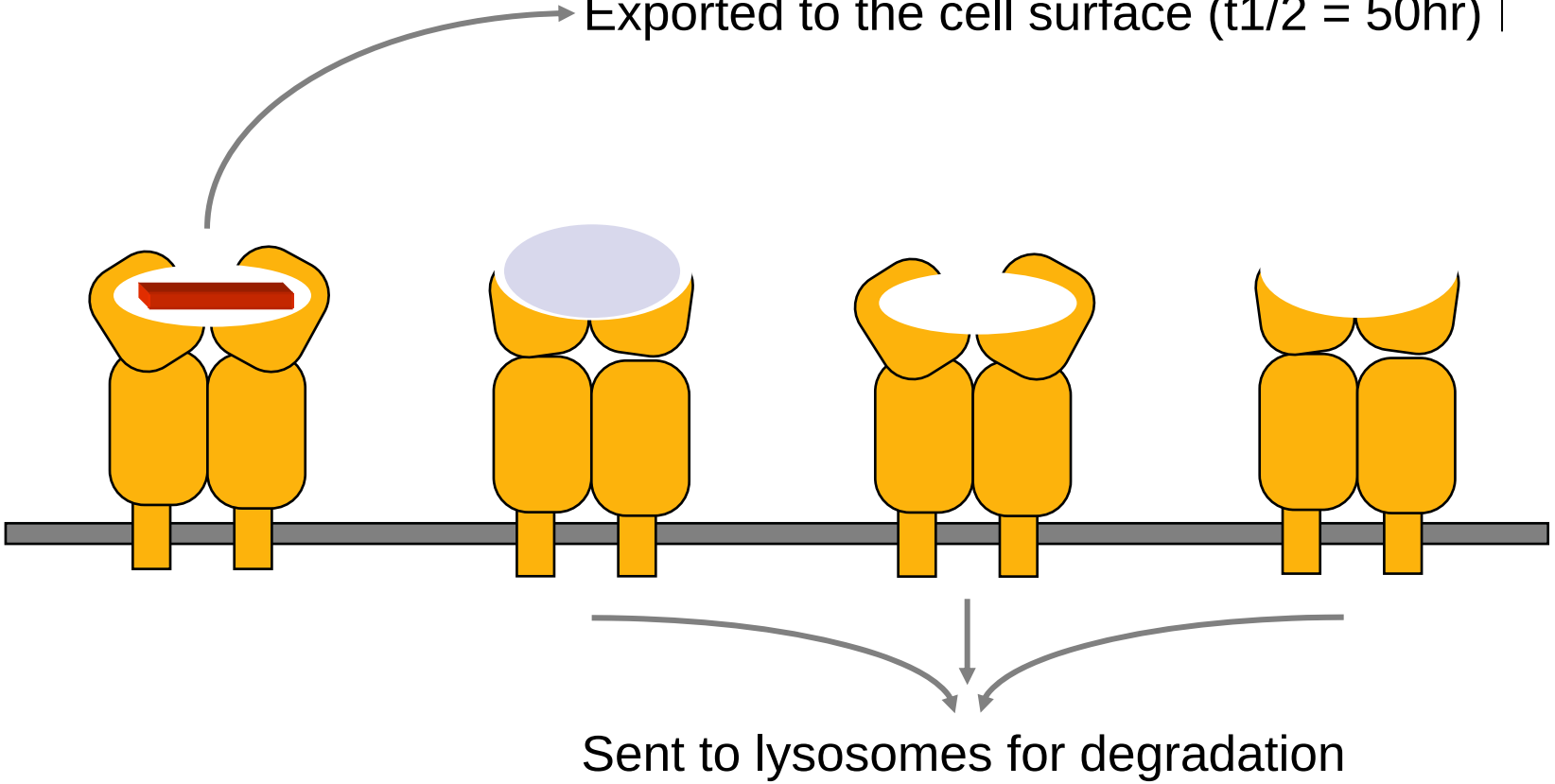
Replaces CLIP with a peptide antigen using a catalytic mechanism (i.e. efficient at sub-stoichiometric levels)

Discovered using mutant cell lines that failed to present antigen

HLA-DO may also play a role in peptide exchange

Sequence in cytoplasmic tail retains HLA-DM in endosomes

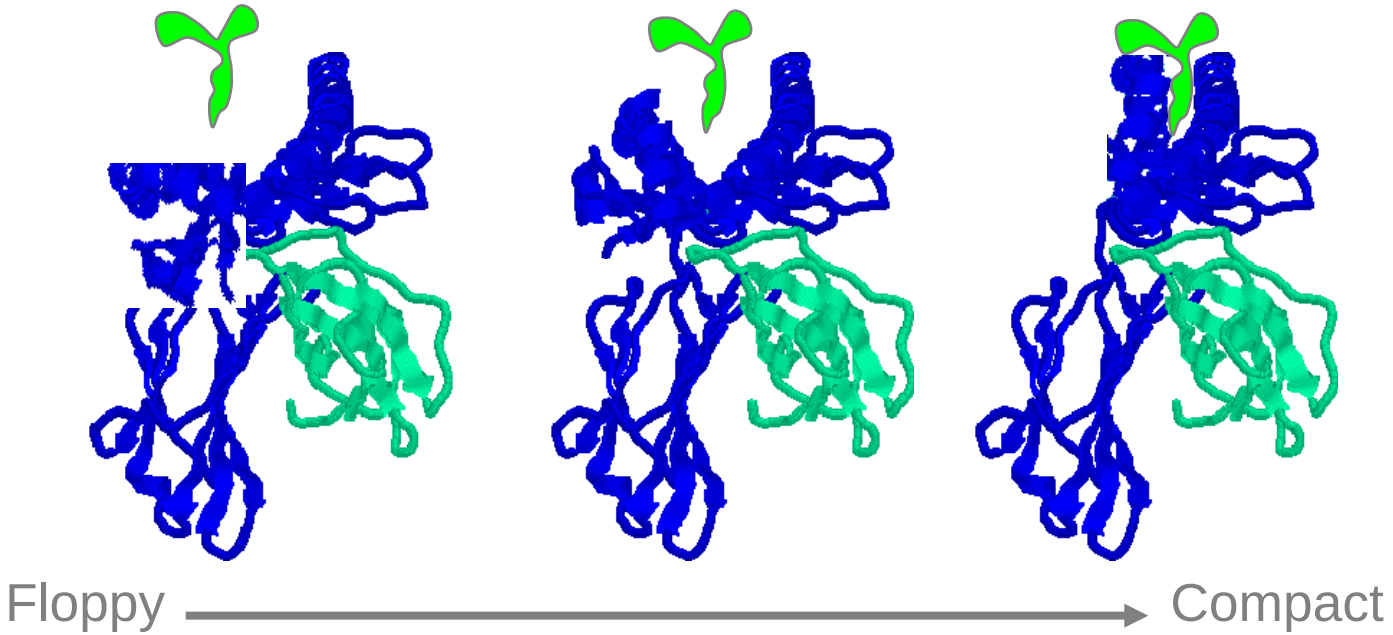
Surface expression of MHC class II-peptide complexes



MIIC compartment sorts peptide-MHC complexes for surface expression or lysosomal degradation

Flexibility of the peptide binding site in MHC molecules

MHC molecules possess binding sites that are flexible at an early, intracellular stage of maturation



Although this example shows MHC class I molecules, the flexibility in the peptide binding site of MHC class II molecules also occurs at an early stage of maturation in the endoplasmic reticulum

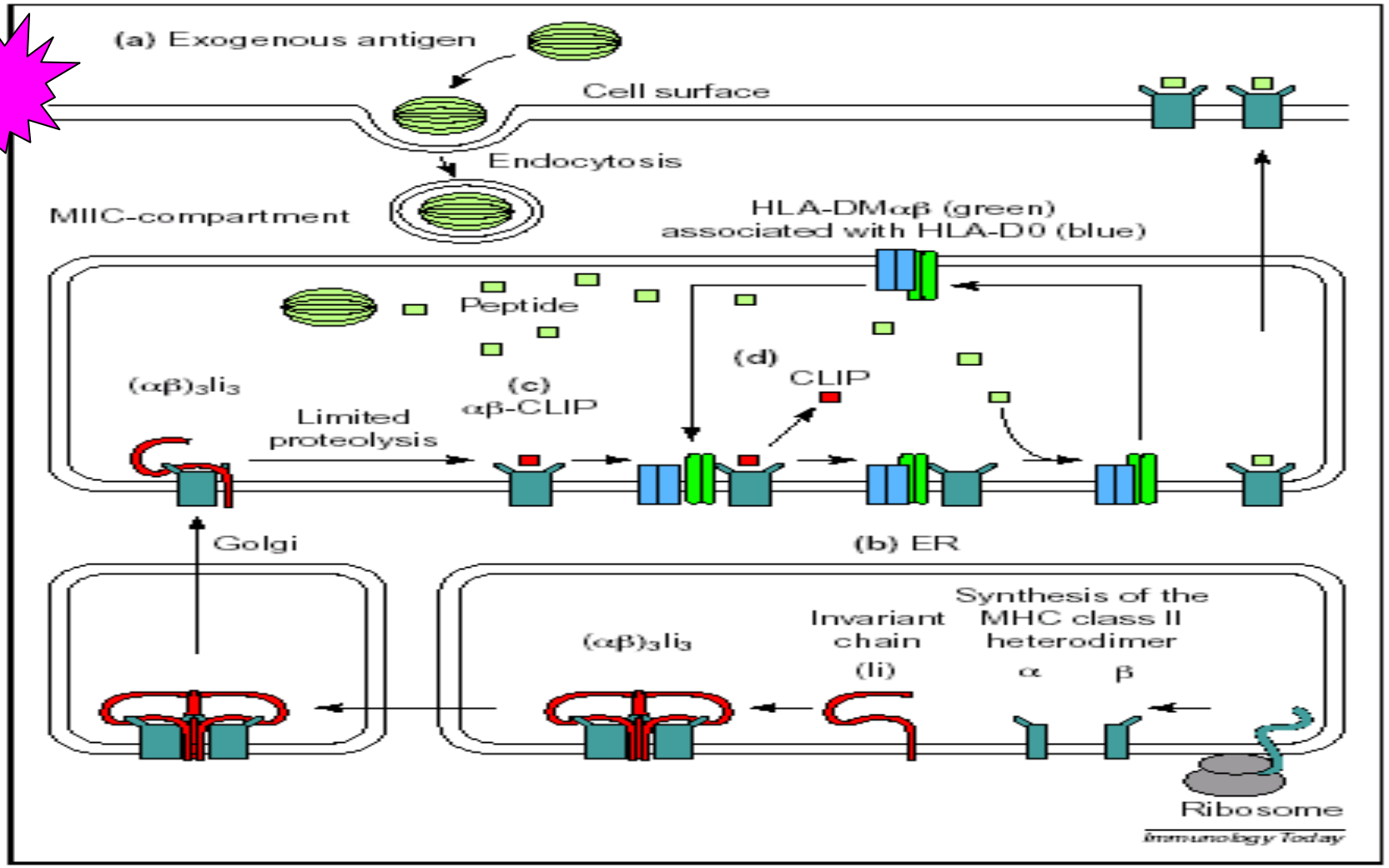
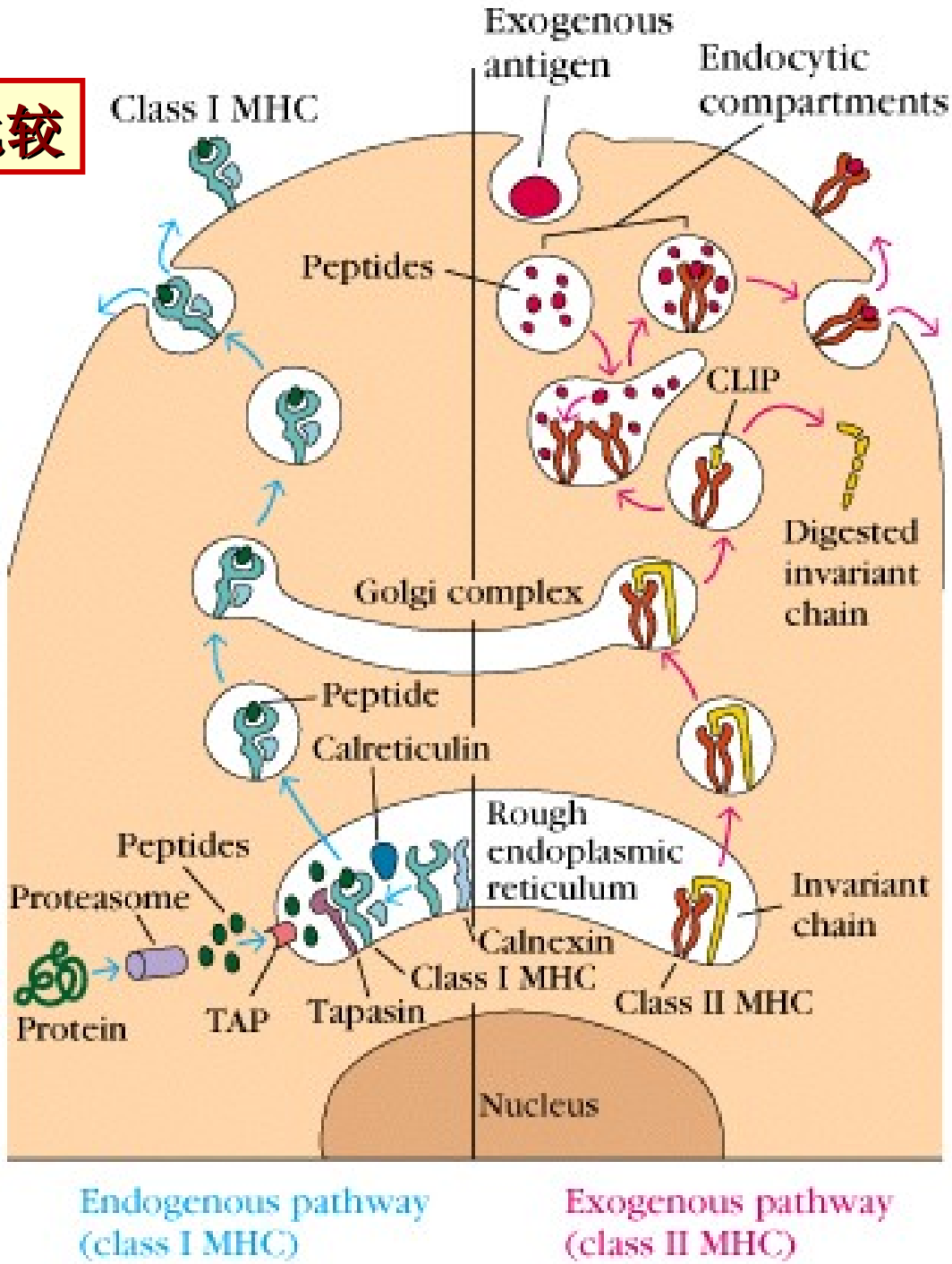


Fig. 2. *The MHC class II antigen-processing pathway. MHC class II molecules present peptides derived from exogenous antigens internalized in the endocytic pathway (a). HLA class II heterodimers assemble in the ER (b) with the invariant chains (Ii) to form nonameric α/β–Ii complexes [$(\alpha\beta)_3Ii_3$], which are targeted to MHC class II compartments (MIIC) in the endocytic pathway. The HLA class II-associated Ii is degraded in distinct steps, leaving class II-associated Ii peptide (CLIP) within the HLA class II binding groove (c). CLIP can then be exchanged for antigenic peptides and this exchange is catalysed by HLA-DM molecules (d). The HLA-DM-dependent peptide loading is regulated by HLA-DO molecules. Peptide-loaded HLA class II molecules are then transported to the cell surface for presentation to $CD4^+$ T cells. Abbreviations: ER, endoplasmic reticulum; MHC, major histocompatibility complex.*

两类抗原加工递呈途径的比较



MHC-I类抗原的交叉递呈途径

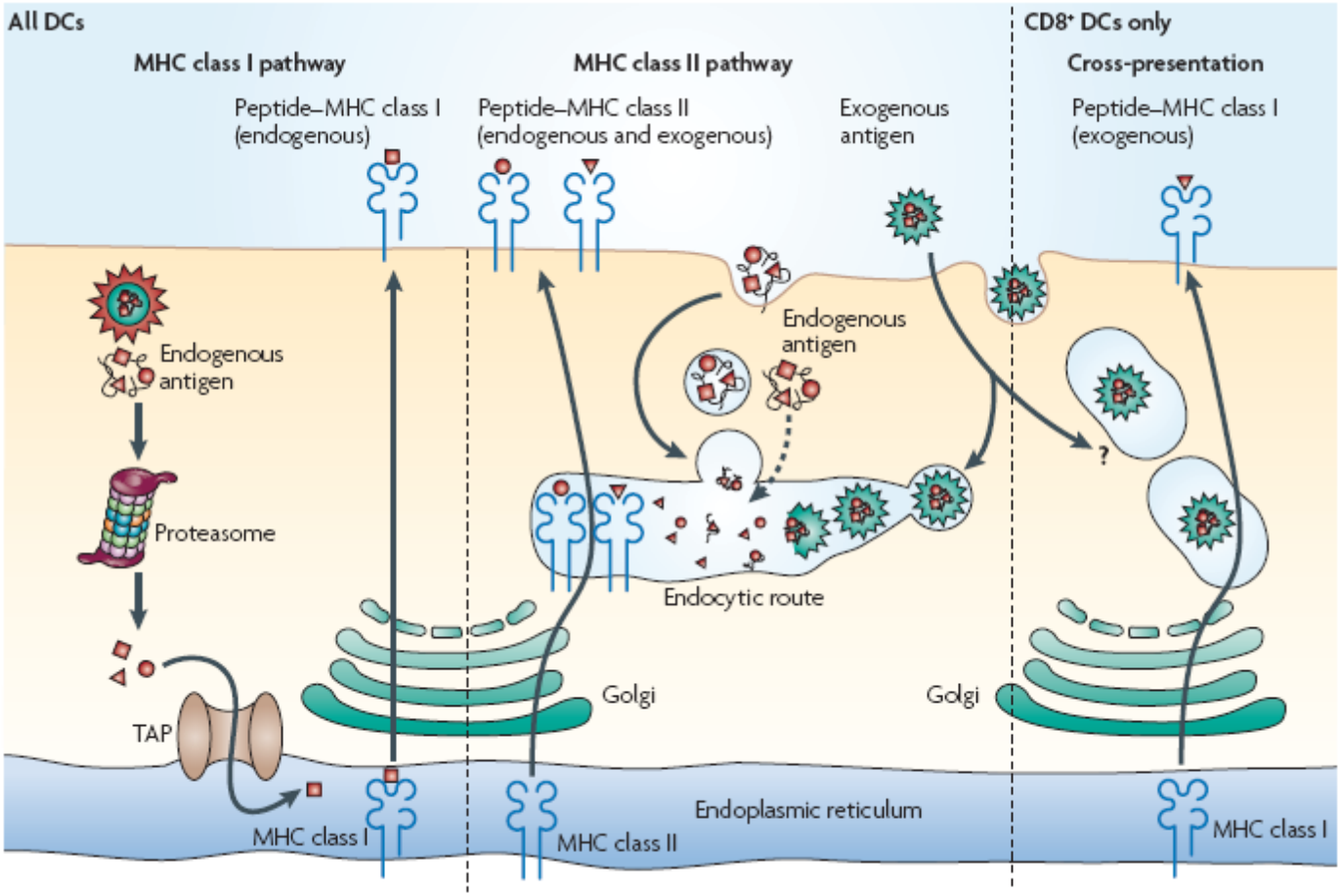


Figure 2 | **The antigen-presentation pathways in dendritic cells.** All dendritic cells (DCs) have functional MHC class I

Nature Reviews Immunology 7, 543-555 (2007);

Christian Münz. **Autophagy and antigen presentation**
Cellular Microbiology, Volume 8 Page 891 - June 2006

Christian Münz

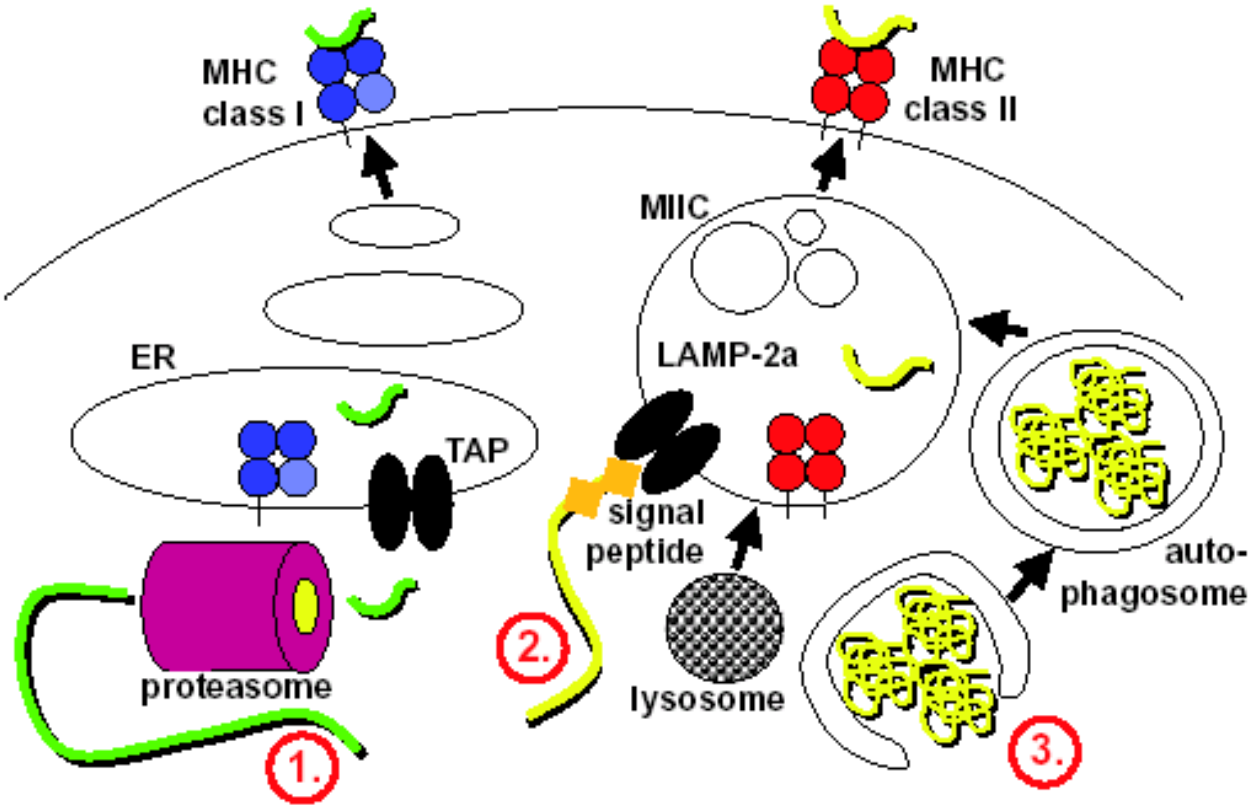


Fig. 1. The degradation behaviour of three distinct cytosolic/nuclear protein pools might determine preferential processing onto MHC class I or II. 1. Soluble short-lived proteins are primarily degraded by the proteasome and peptide products of this proteolysis gain access to the endoplasmic reticulum (ER) via the transporter associated with antigen processing (TAP). In the ER, newly synthesized MHC class I molecules load some of these ligands and migrate to the cell surface via the secretory pathway to be recognized by $CD8^+$ T cells. 2. Soluble proteins or peptides that contain a lysosomal targeting signal peptide get imported into the MHC class II loading compartment (MIIC) via the LAMP-2a transporter under the assistance of cytosolic and lysosomal Hsc70 members. In MIICs, they get degraded by lysosomal proteases and their fragments get loaded onto MHC class II molecules, which then migrate to the cell surface for $CD4^+$ T cell stimulation. 3. Aggregate-prone long-lived proteins get incorporated into autophagosomes, which then fuse with MIICs. Their content is also degraded by lysosmal hydrolases and peptides derived thereof are loaded onto MHC class II. Stable MHC class II/ligand complexes then move to the cell surface and display their cargo to $CD4^+$ T cells.

自噬加工递呈途径

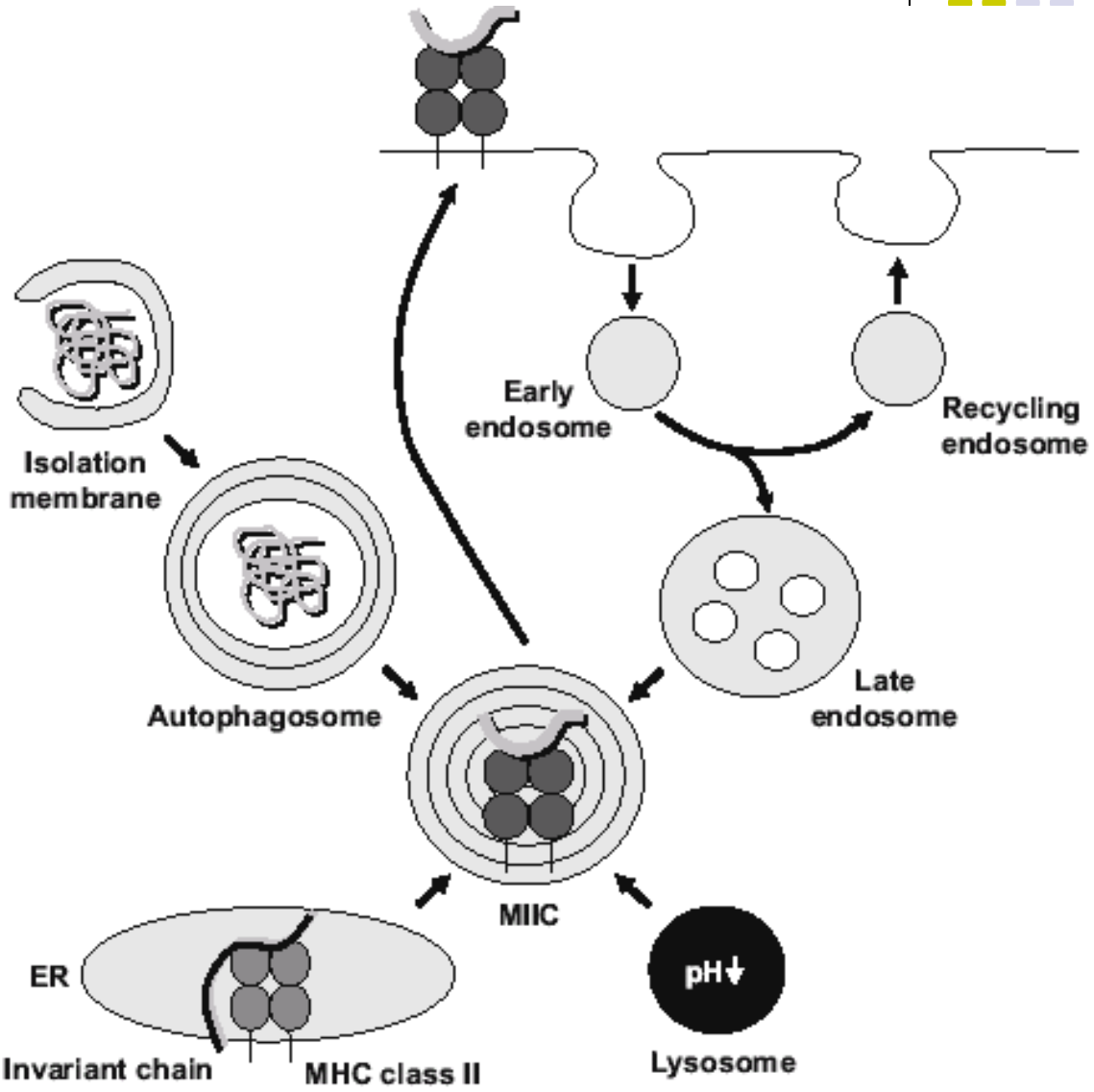
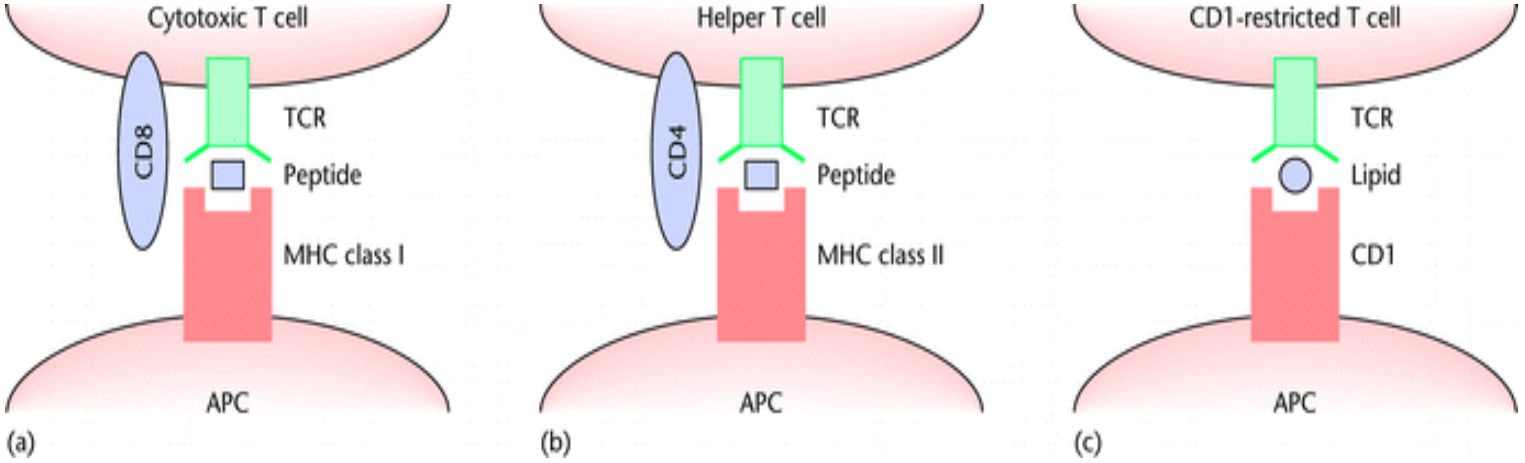


Fig. 2 Autophagy might be involved in the formation of multilamellar MHC class II loading compartments. Autophagosomes fuse with late endosomes for the generation of multilamellar vesicles. MHC class II is targeted to this late endosomal compartment (MIIC), and lysosomal proteases degrade autophagy substrates for loading on MHC class II molecules. MHC class II/peptide complexes then migrate to the cell surface for recognition by $CD4^+$ T cells

J Mol Med (2006) 84: 194–202

CD1d加工递呈途径: Lipid antigen



NKT细胞的识别与活化

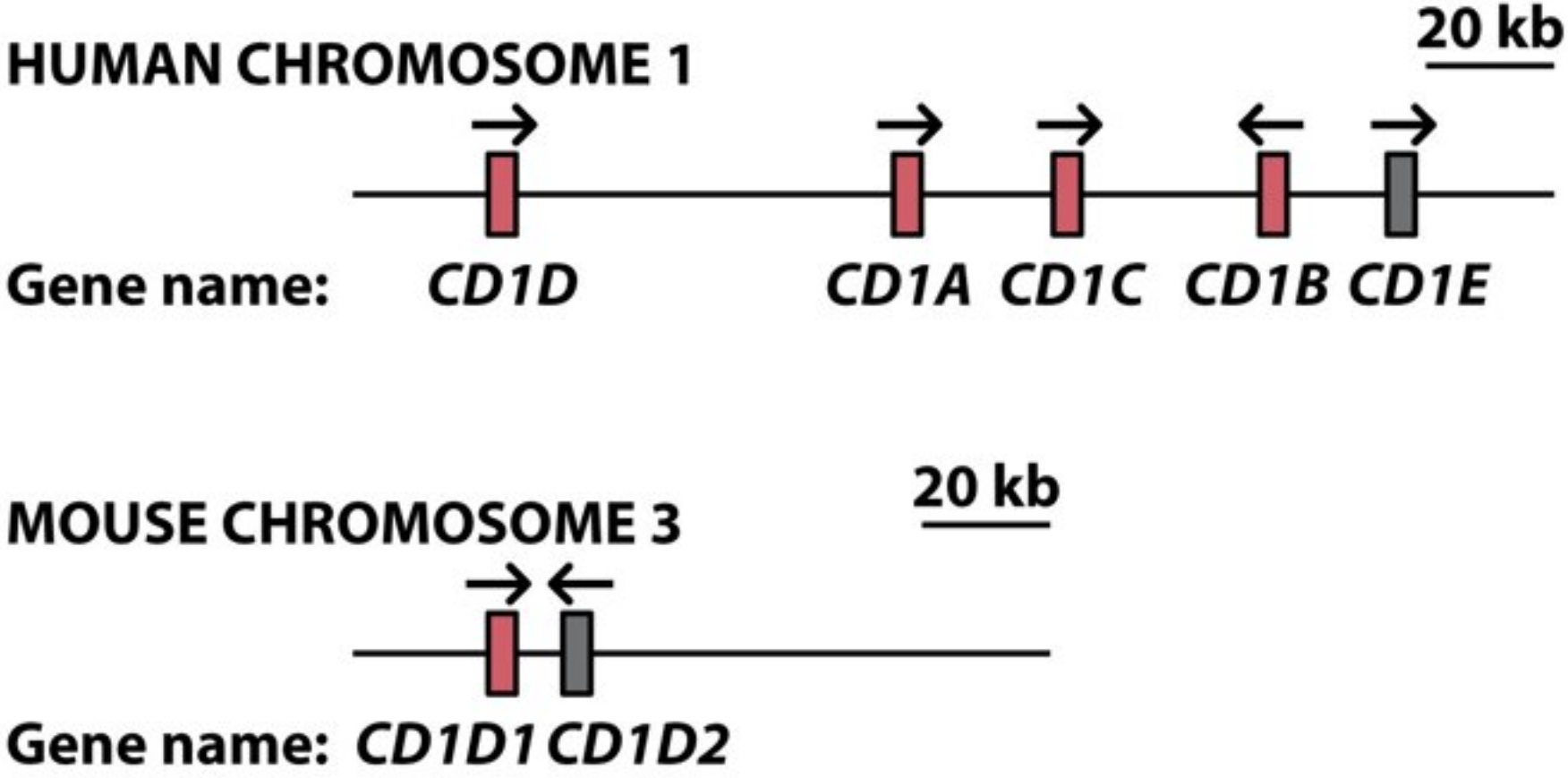


Figure 8-25a
Kuby IMMUNOLOGY, Sixth Edition

Nature reviews immunology 2007;7(12) : 933

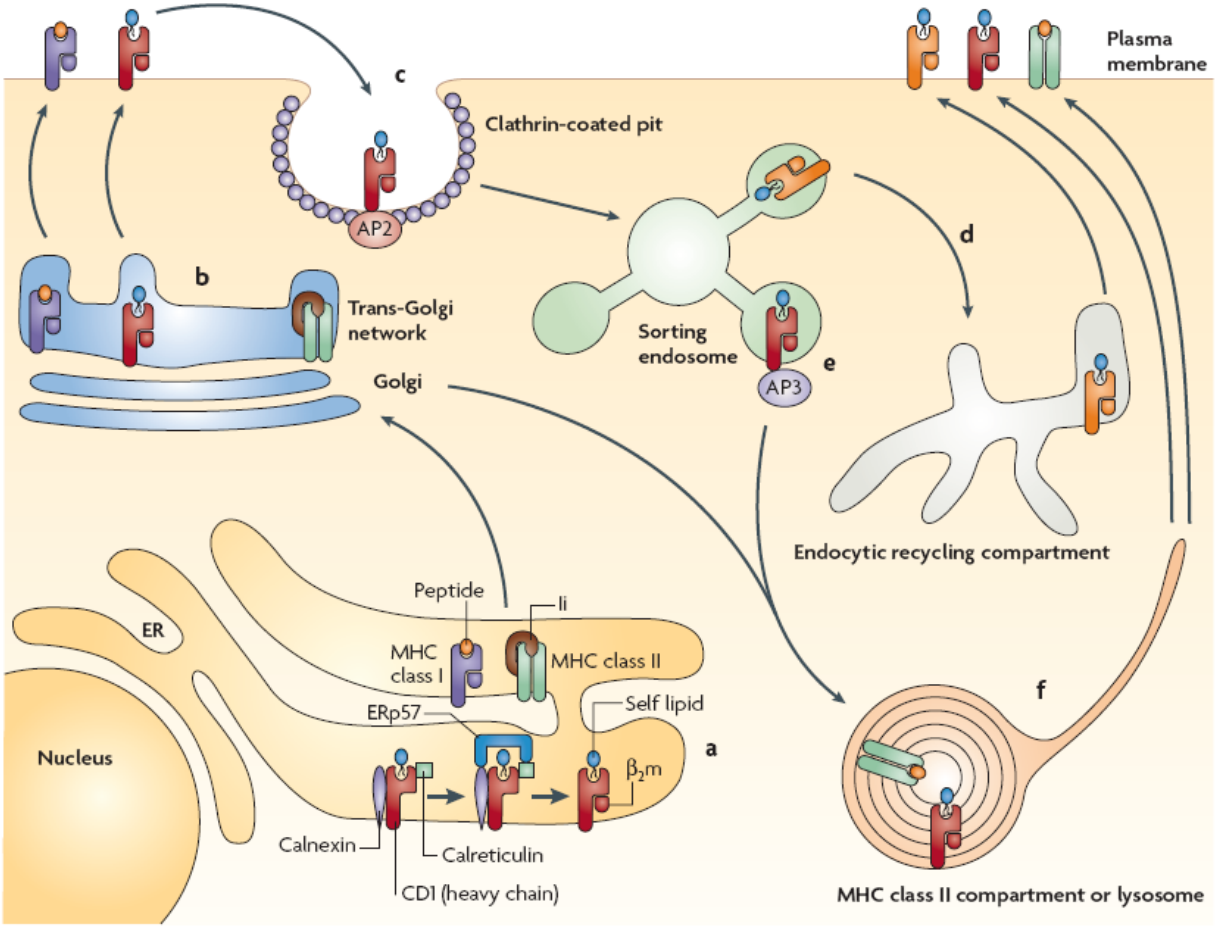


Figure 2 | **Intracellular trafficking of CD1 molecules. a** | CD1 heavy chains are assembled in the endoplasmic reticulum (ER), where they bind the chaperones calnexin, calreticulin and ERp57. They also bind β_2-microglobulin (β_2m) non-covalently in the ER. **b** | CD1 molecules then follow the secretory route through the Golgi apparatus to the plasma membrane. MHC class I and II molecules also assemble in the ER and follow a similar route, with MHC class II molecules (in complex with invariant chain (Ii)) being diverted from the trans-Golgi network to the endosomes. **c** | CD1 molecules are internalized in clathrin-coated pits via the interaction of the adaptor complex AP2 with tyrosine-based sorting motifs present in the cytoplasmic tails of CD1. From the sorting endosome, CD1 molecules can follow two main routes. **d** | CD1 molecules such as CD1a and CD1c can follow the slow recycling pathway, back to the plasma membrane, through the endocytic recycling compartment. **e** | CD1 molecules such as CD1b and mouse CD1d can traffic to late endosomal and lysosomal compartments via the interaction of AP3 also with tyrosine-based motifs contained in the cytoplasmic tails of these CD1 molecules. **f** | CD1 and MHC class II molecules recycle from lysosomal compartments to the plasma membrane. During their trafficking, CD1 molecules are thought to be loaded with a lipid molecule.

CD1d:

Synthetic glycolipid:

α -GalCer

Endogenous ligand:

iGb3

Bacterial glycosphingolipids:

GSL-1,GSL-1'

Bacterial cell wall antigens:

PBS 30, PBS59, PBS 50

Gram-LPS+

↓

DC

↓

MyD88

↓

hexb

↓

iG3b

↓

NKT

↓

IFN- γ

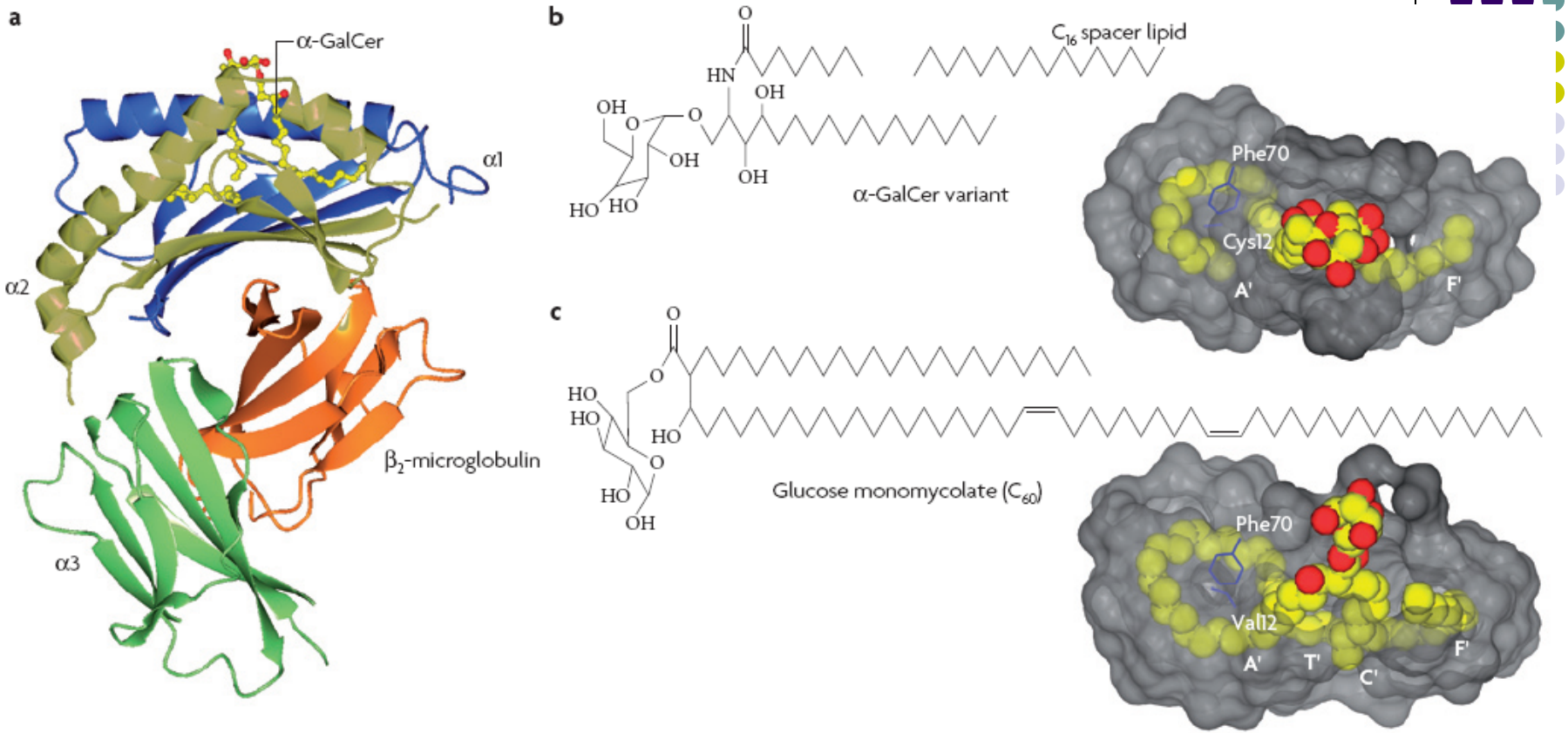
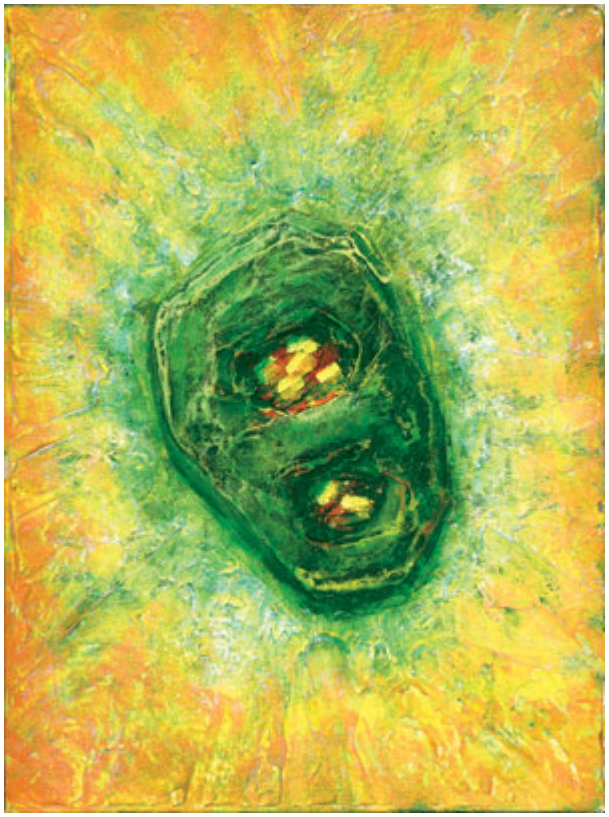
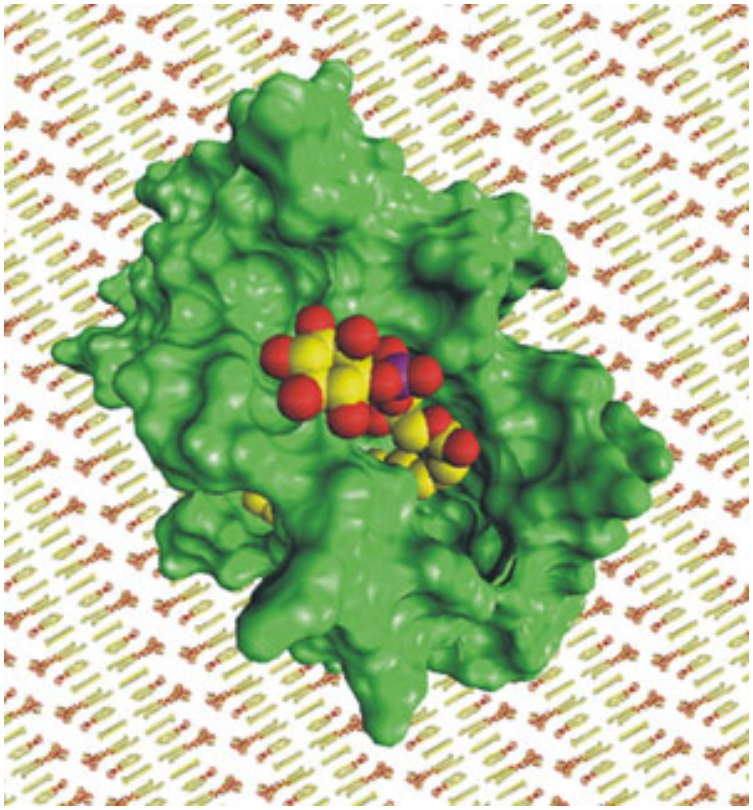


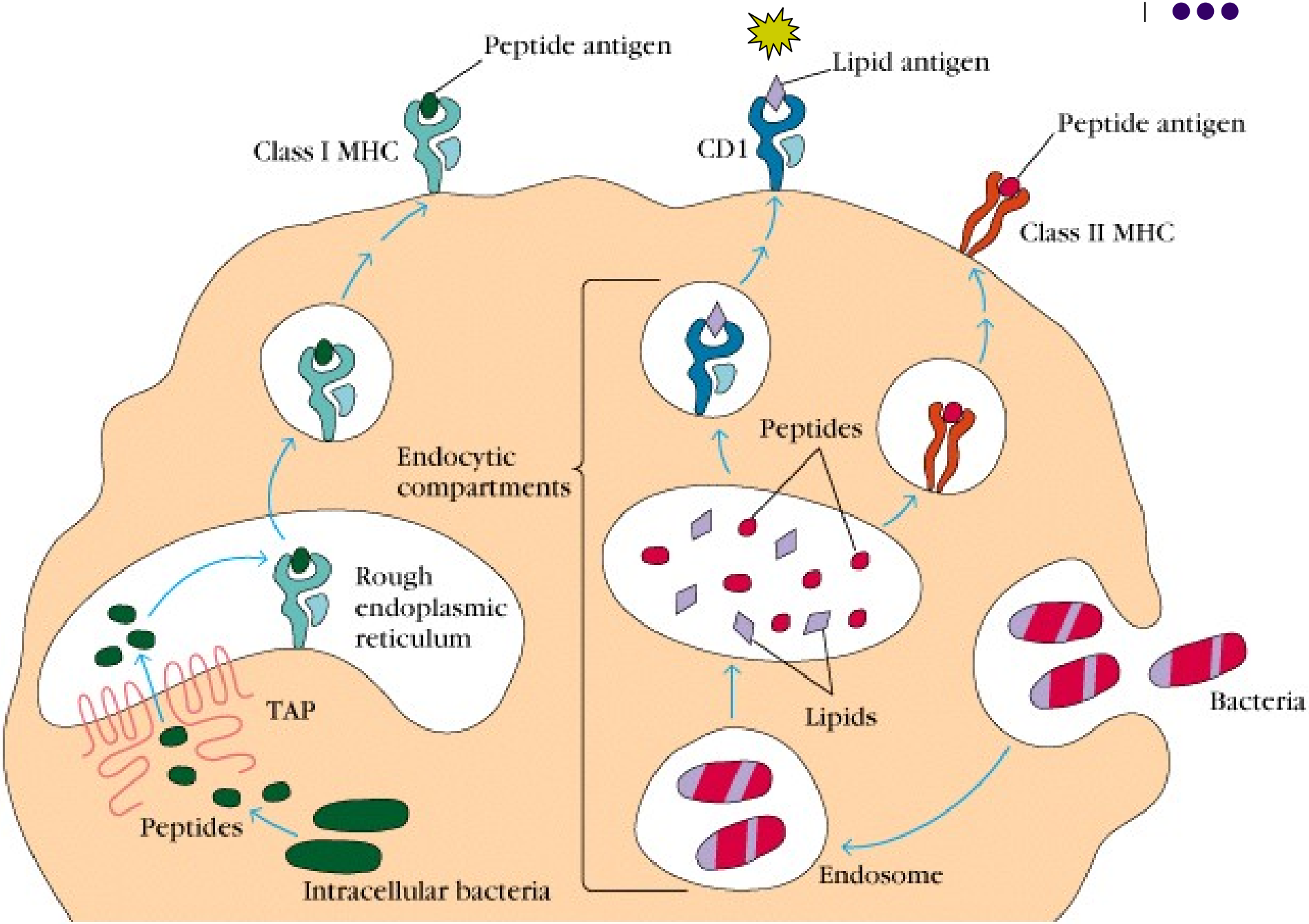
Figure 1 | **Crystal structures of CD1b and mouse CD1d loaded with lipids. a** | A ribbon diagram of the mouse CD1d crystal structure loaded with a synthetic variant of α-galactosylceramide (α-GalCer) that contains a shorter fatty acid chain (the α-GalCer variant is shown in stick representation with the carbon backbone in yellow and oxygen atoms in red)[130]. A C_{16} spacer lipid was found to fill the empty space in the A′ channel of CD1d, which would be occupied by the longer fatty acid of the non-variant α-GalCer. **b** | Surface representation of the mouse CD1d antigen-binding groove loaded with the same lipids as in **a**. The A′ and F′ hydrophobic channels are shown, as well as two amino-acid residues that form the A′ pole (Cys12 and Phe70) and divert the channel containing the lipid alkyl chain around them. The short fatty acid chain of the lipid inserts into the A′ channel, whereas the sphingosine chain is inserted into the F' channel. **c** | Surface representation of CD1b loaded with the C_{60} species of glucose monomycolate[47]. The long fatty acid chain sequentially traverses the A′, T′ and F′ superchannel and the α-branched chain inserts into the C′ channel. The diagrams were generated using CCP4MG software[131].

Nature reviews immunology 2007;7(12) : 932

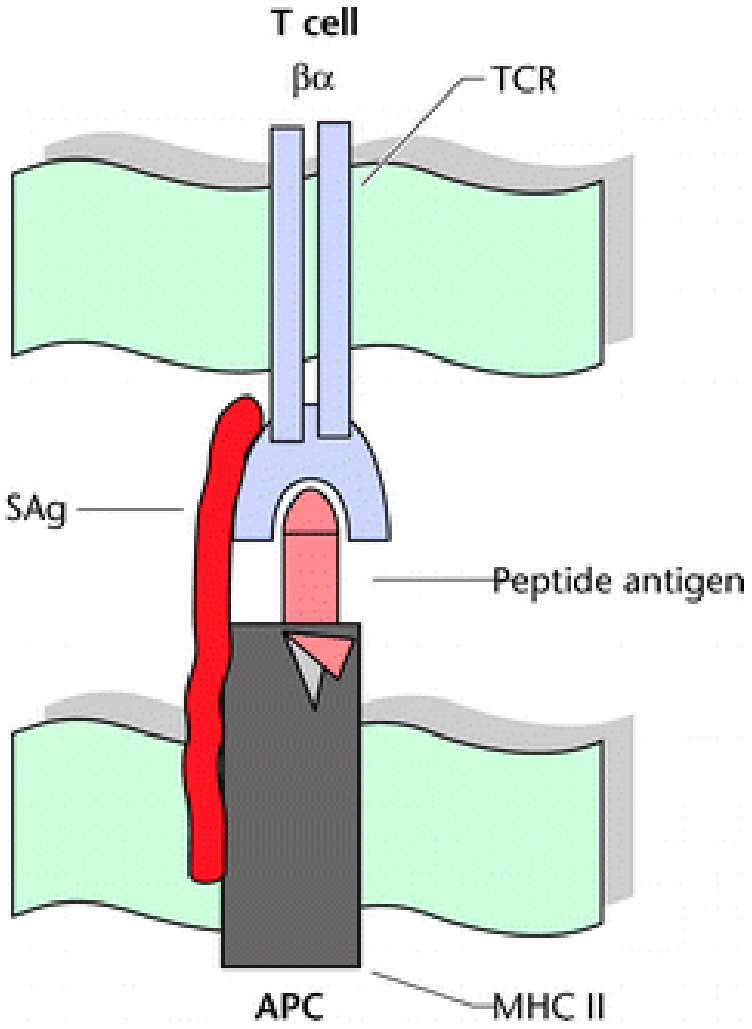




The structure of human CD1b has now been solved by Gadola et al. (page 721), revealing a fascinating set of tunnels and tubes that explains how one protein can bind lipids of such variety. See also the News & Views by Niazi et al. (page 703) Painting is acrylic on canvas by Michael Malicki.


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

超抗原递呈途径



'Chain of events'
Nature Reviews Immunol
July 2008 Vol 8 No 7

The End