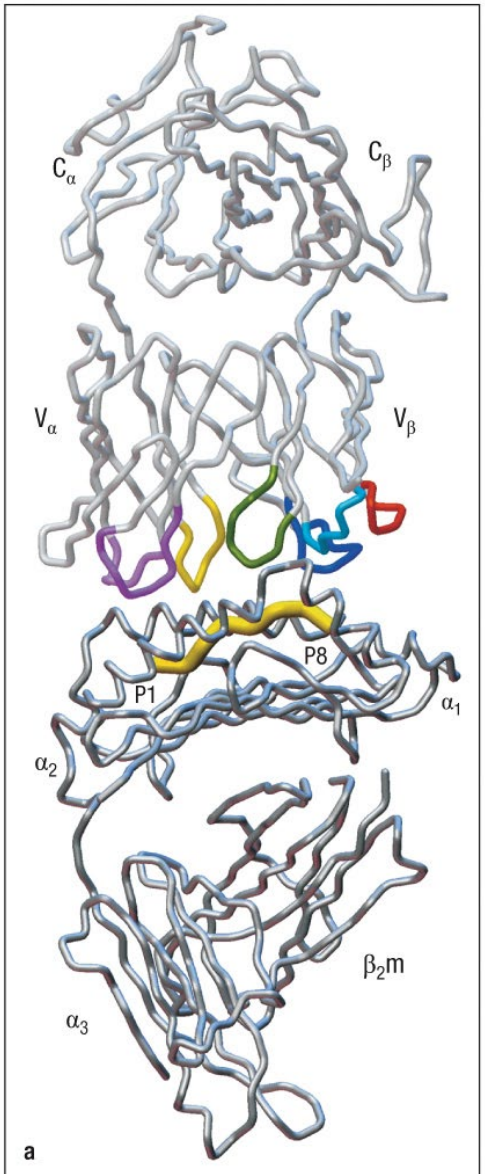
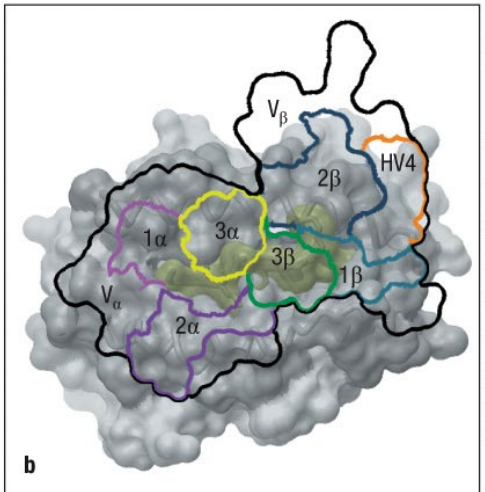
TCR Binds to Peptide:MHC Complex



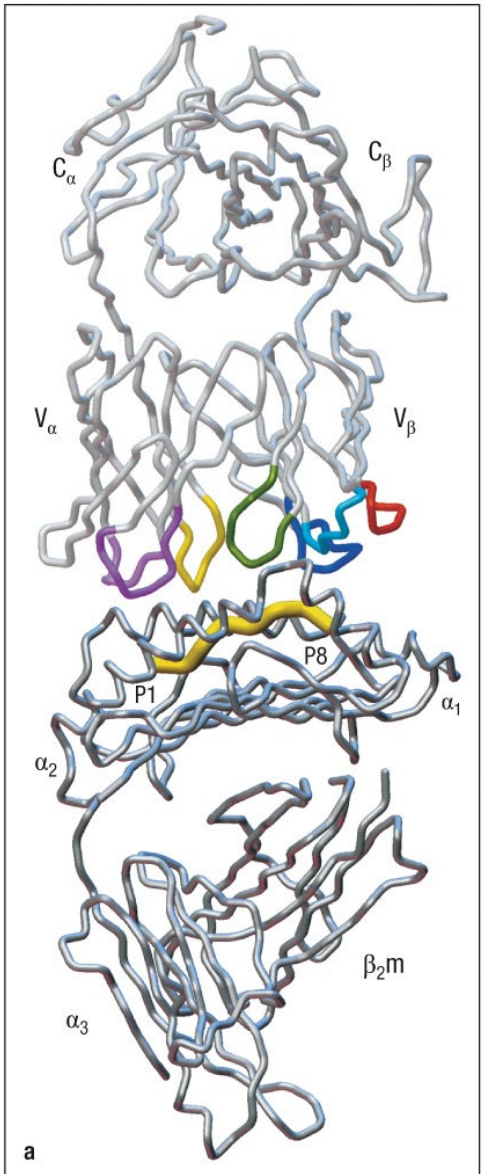
complementarity determining regions

Peptide



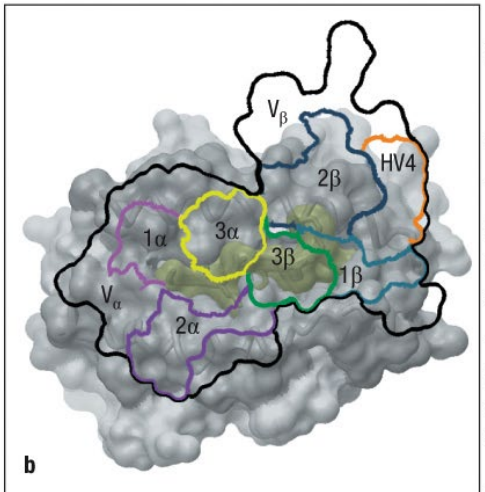
From K. Christopher Garcia, Massimo Degano, Robyn L. Stanfield, et al., "An αβ T cell receptor structure at 2.5 Å and its orientation in the TCR-MHC complex," *Science* 274(5285): 209–219, 1996. Reprinted with permission from AAAS.

TCR Binds to Peptide:MHC Complex



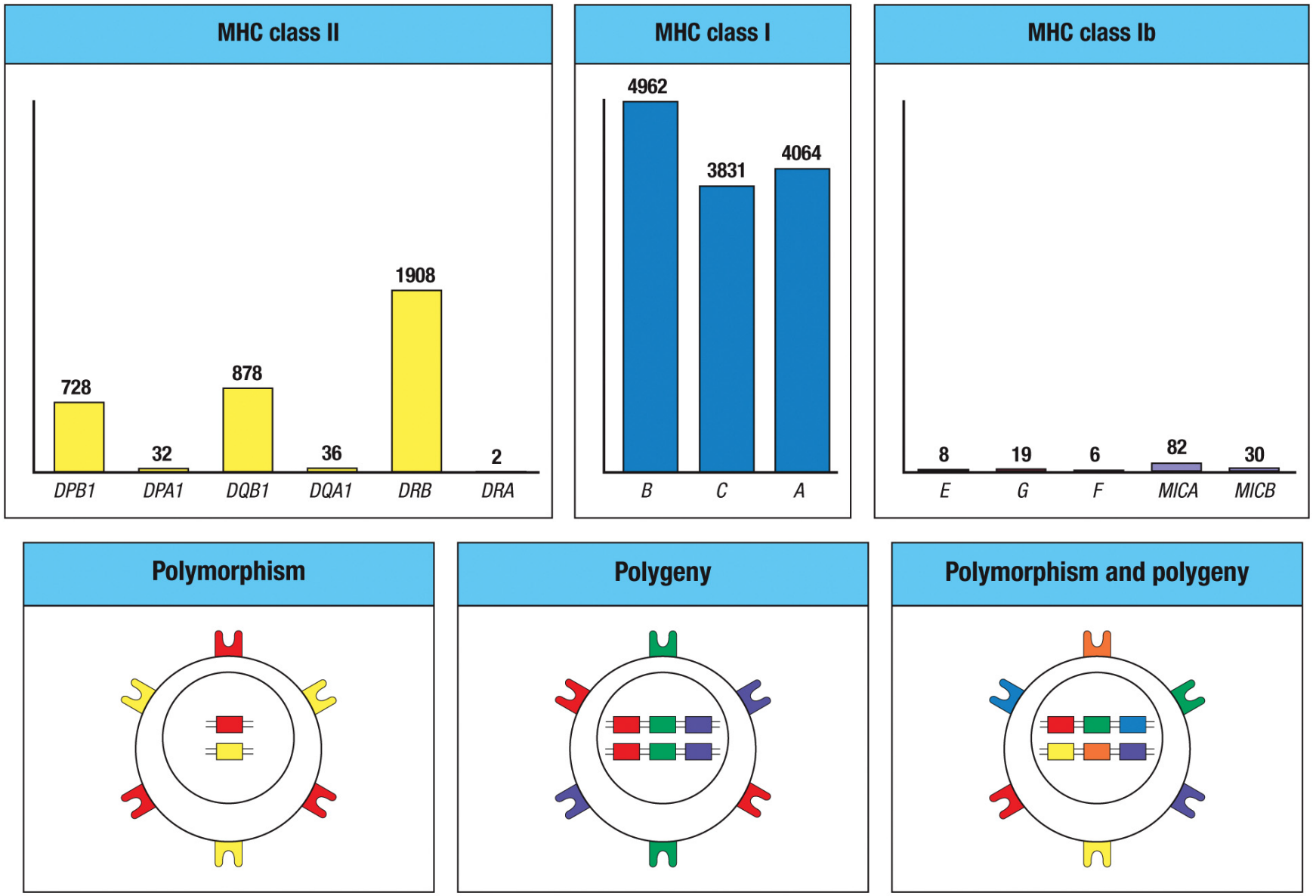
complementarity determining regions

Peptide



From K. Christopher Garcia, Massimo Degano, Robyn L. Stanfield, et al., "An αβ T cell receptor structure at 2.5 Å and its orientation in the TCR-MHC complex," *Science* 274(5285): 209–219, 1996. Reprinted with permission from AAAS.

Polymorphism and Polygeny Contribute to MHC Diversity



Outline

- Major histocompatibility complex
- MHC complex and its functions
- Generation of TCR ligands
  - Generation and processing of MHC class I peptides
  - Generation and processing of MHC class II peptides

MHC Class I and Class II

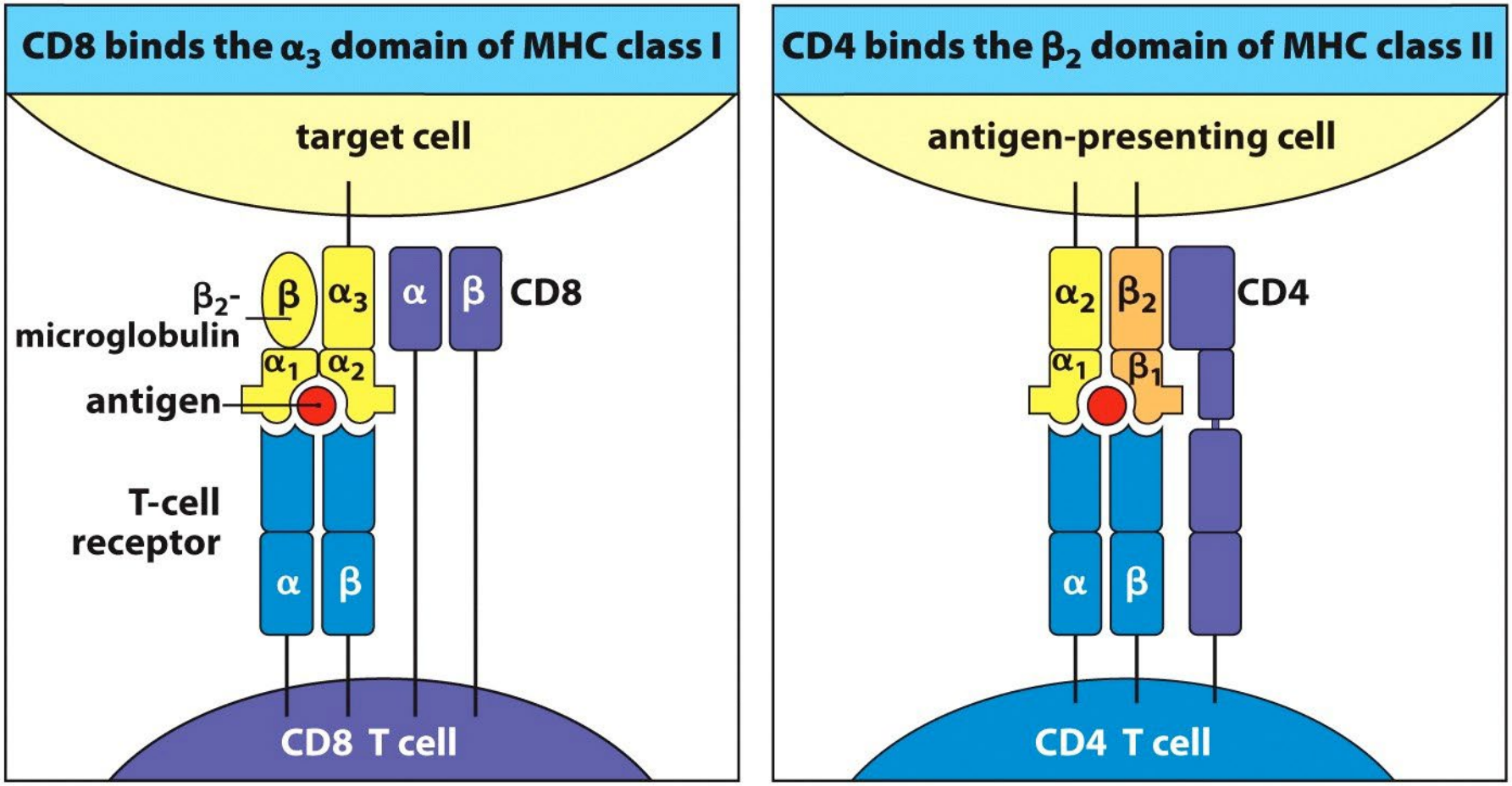
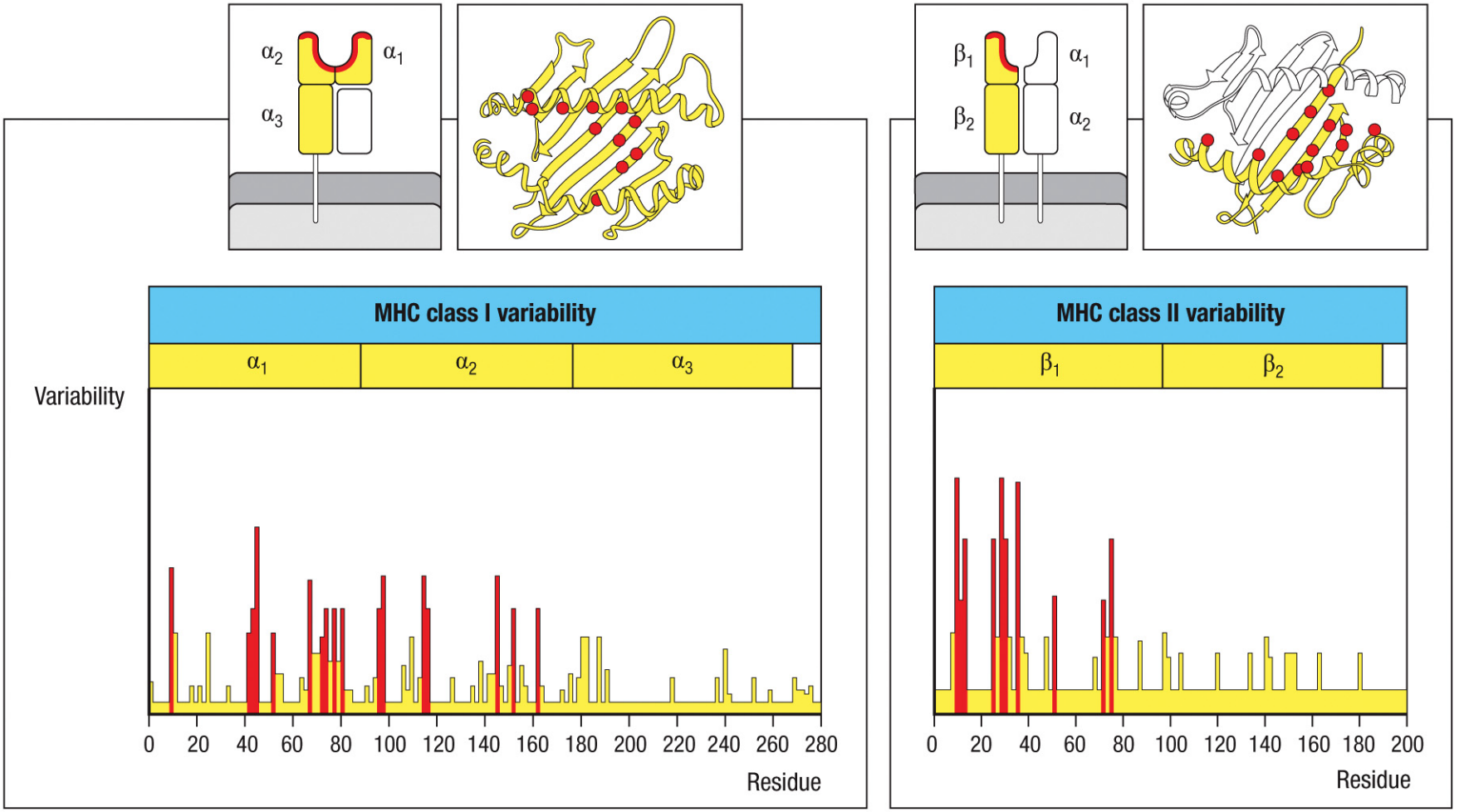
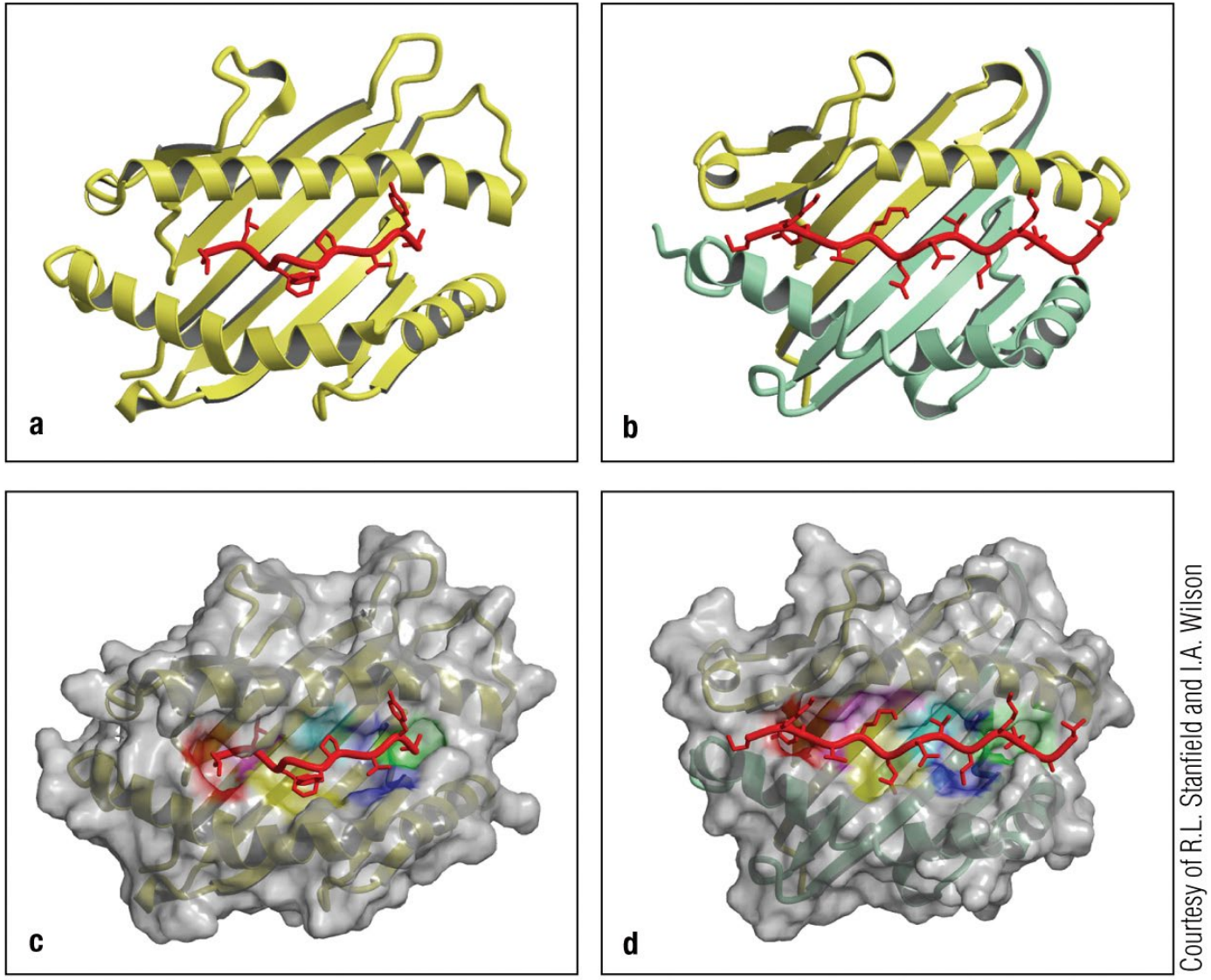


Figure 5.14 The Immune System, 3ed. (© Garland Science 2009)

Allelic Variation Occurs at Specific Sites within MHC

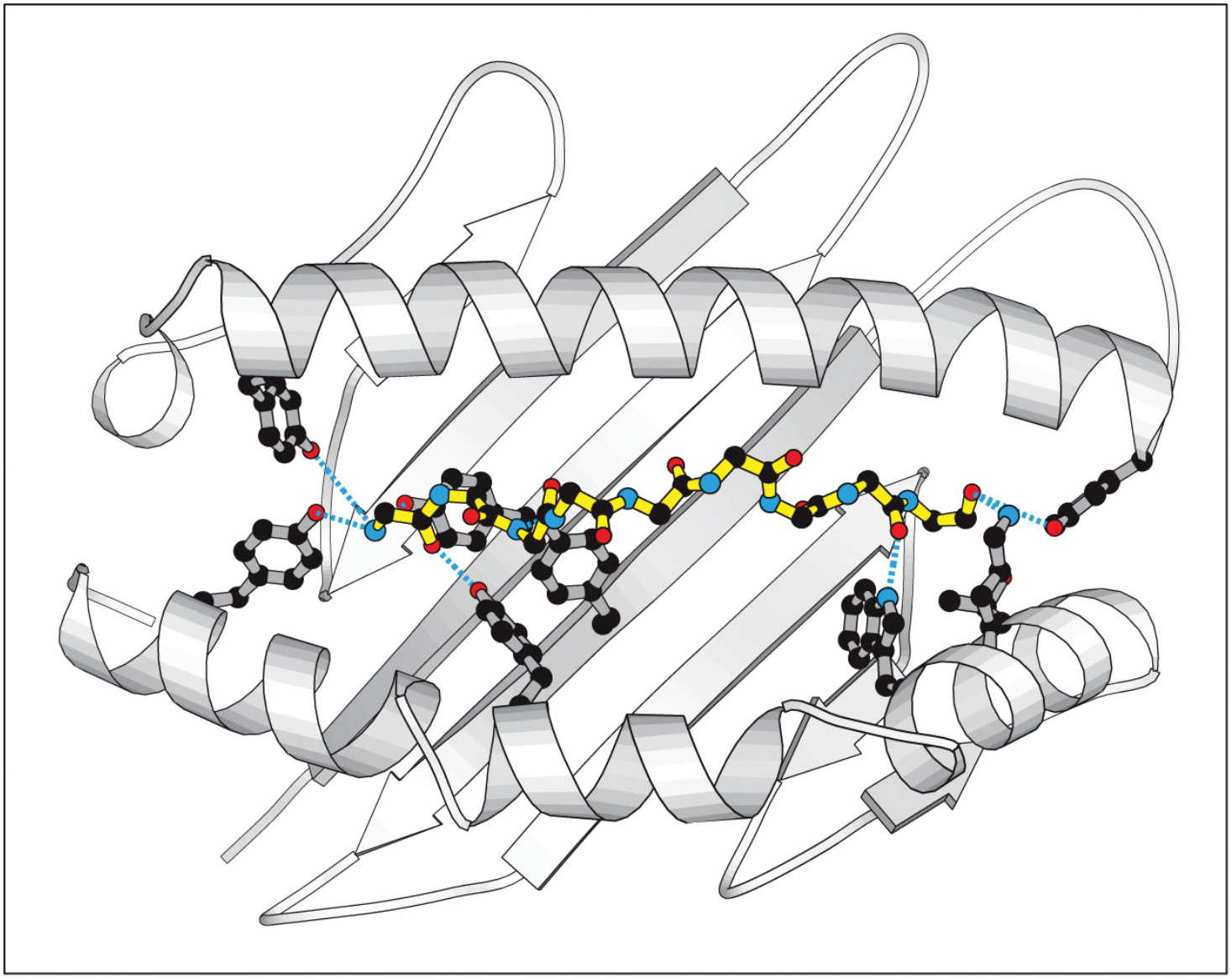


MHC Molecules Bind Peptides Within the Cleft

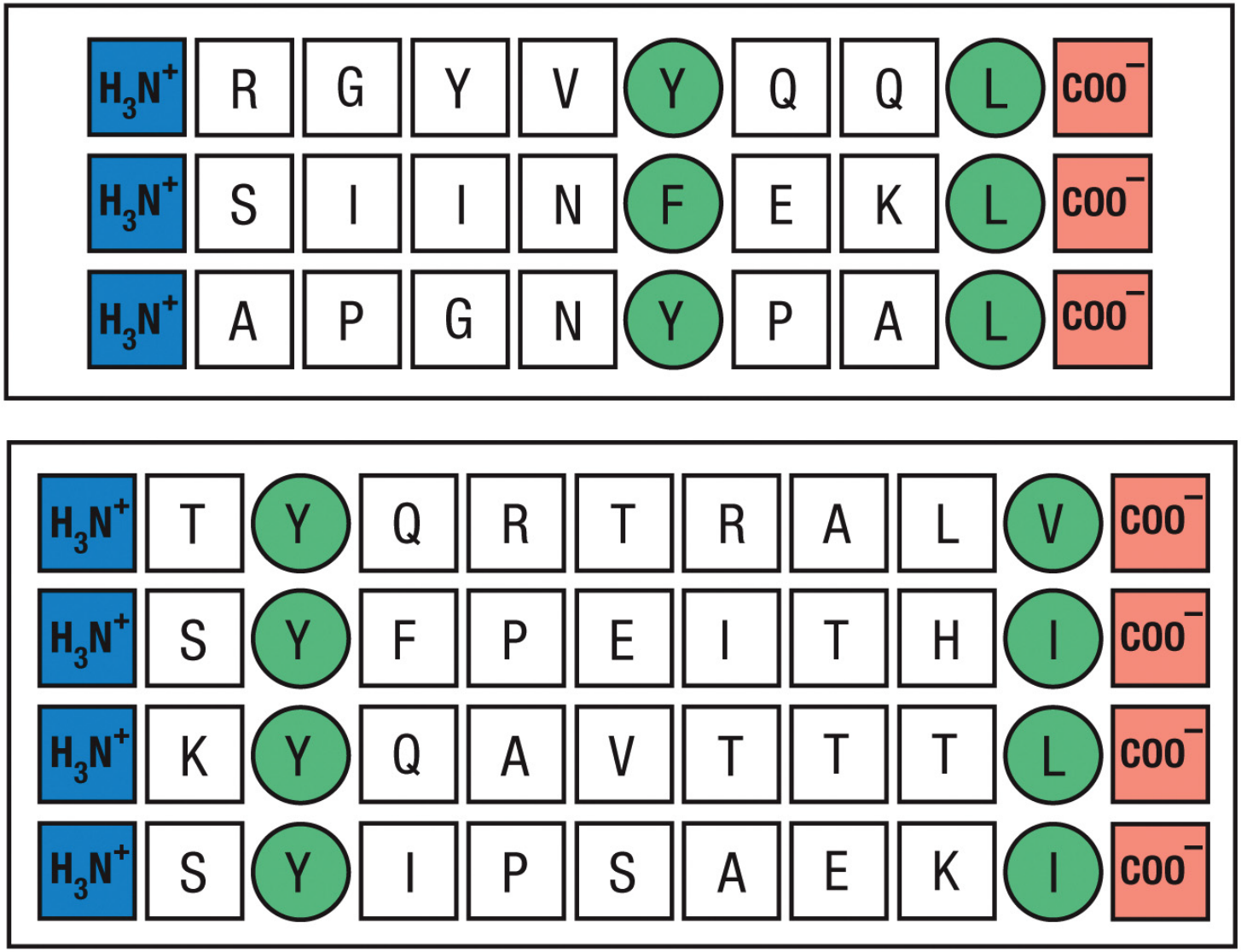


Courtesy of R.L. Stanfield and I.A. Wilson

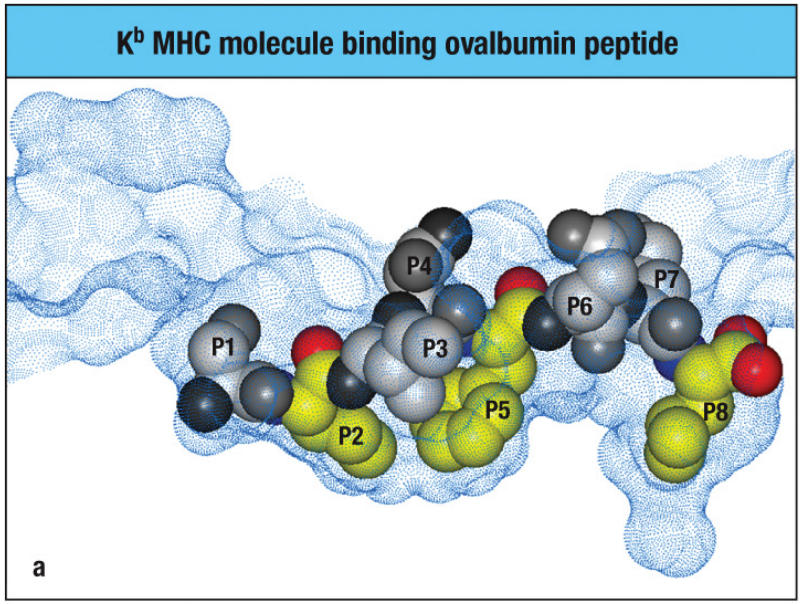
MHC Class I Molecules Bind Short Peptides 8-10 Amino Acids by Both Ends

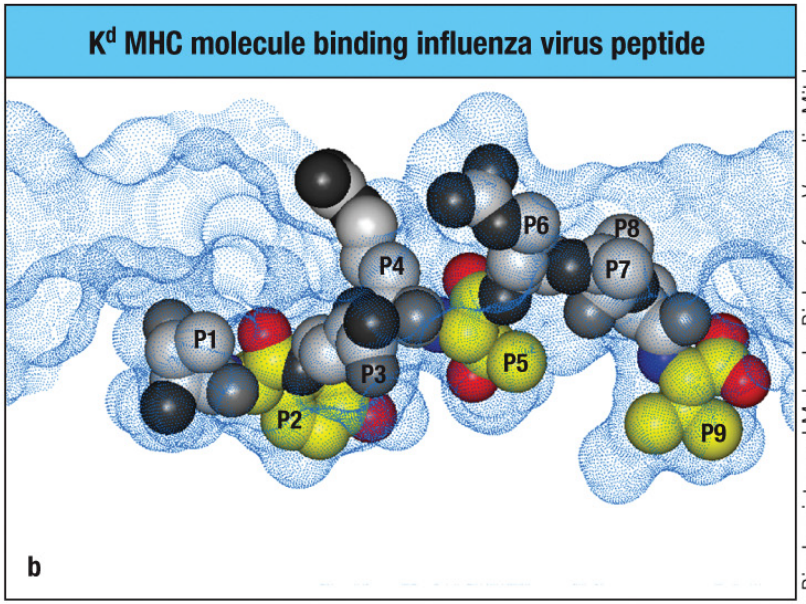


A Given MHC I Binds to Similar Peptides



A Given MHC I Binds to Similar Peptides

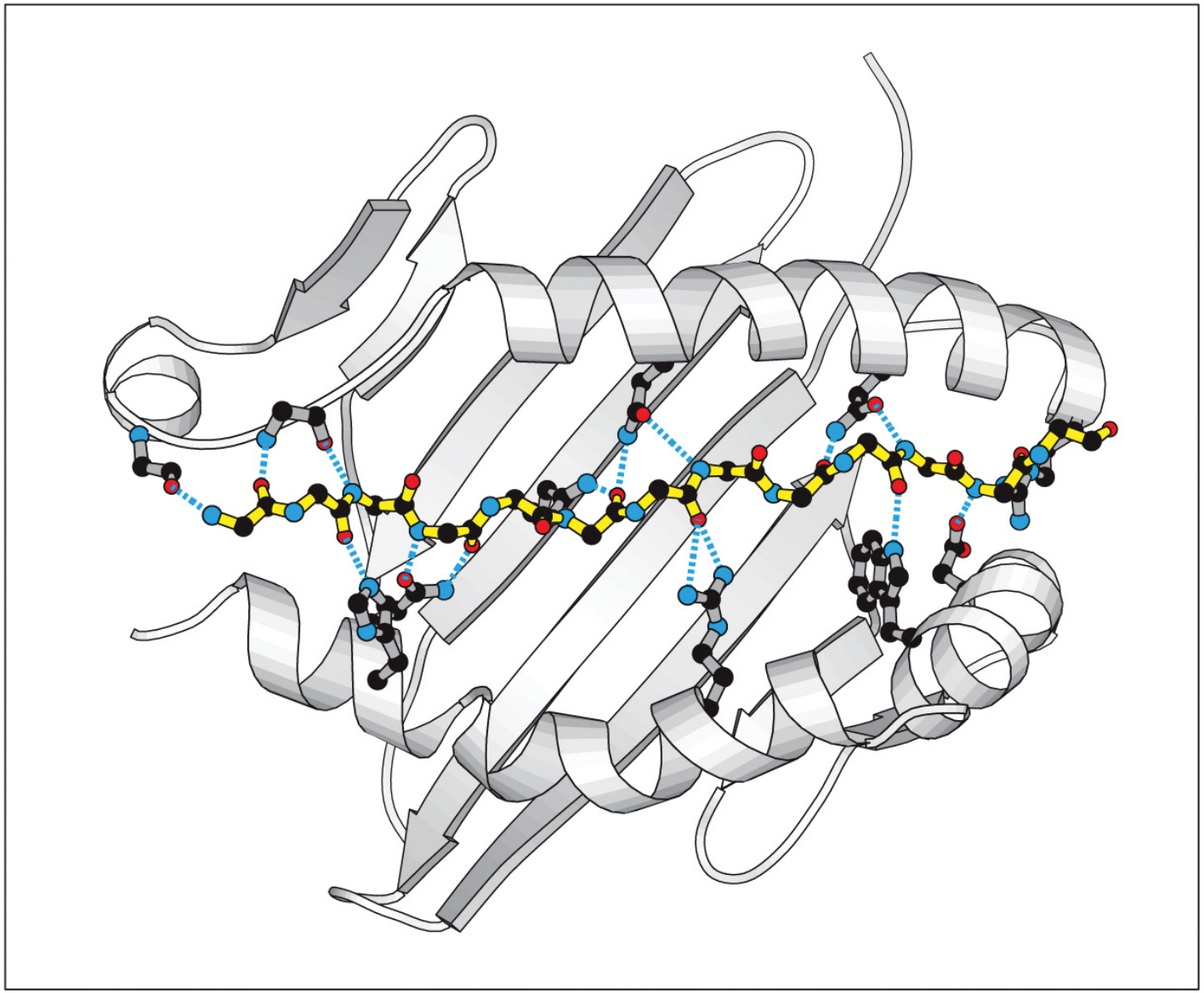




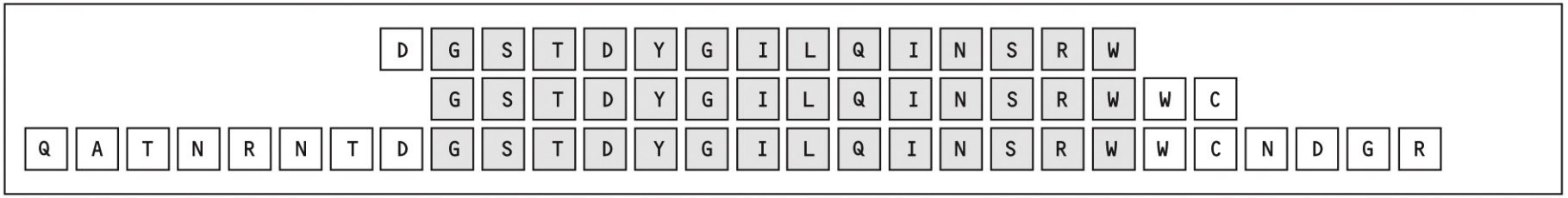
	P1	P2	P3	P4	—	P5	P6	P7	P8
Ovalbumin (257–264)	S	I	I	N		F	E	K	L
HBV surface antigen (208–215)	I	L	S	P		F	L	P	L
Influenza NS2 (114–121)	R	T	F	S		F	Q	L	I
LCMV NP (205–212)	Y	T	V	K		Y	P	N	L
VSV NP (52–59)	R	G	Y	V		Y	Q	G	L
Sendai virus NP (324–332)	F	A	P	G	N	Y	P	A	L

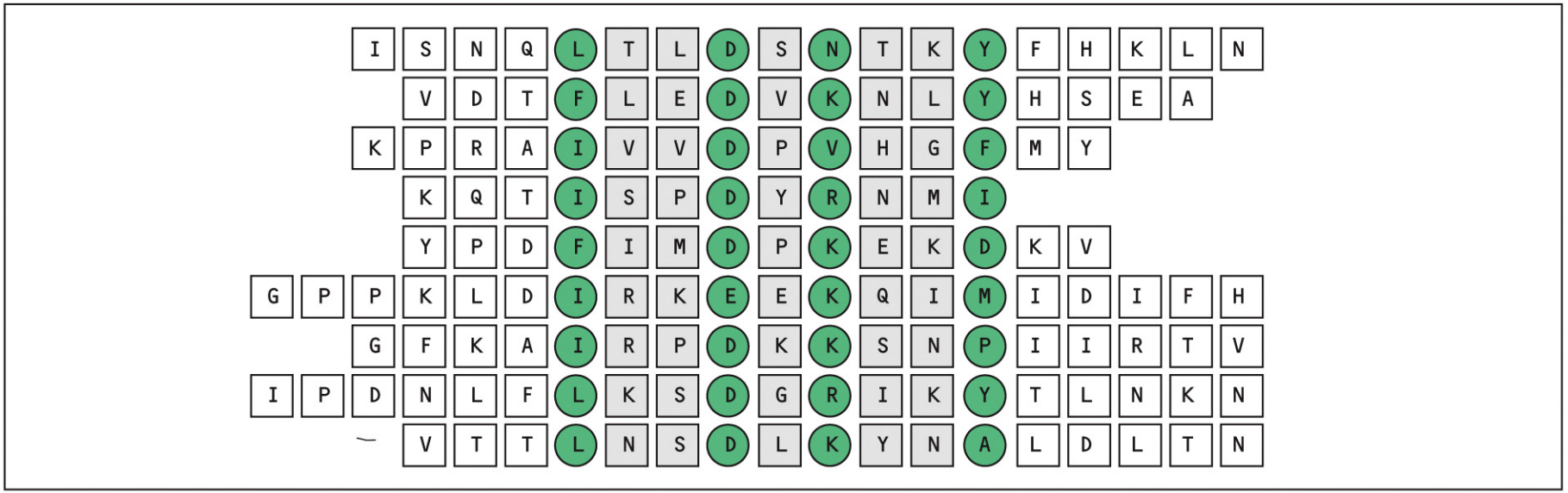
	P1	P2	P3	P4	P5	P6	P7	P8	P9
Influenza NP (147–155)	T	Y	Q	R	T	R	A	L	V
ERK4 (136–144)	Q	Y	I	H	S	A	N	V	L
P198 (14–22)	K	Y	Q	A	V	T	T	T	L
P. yoelii CSP (280–288)	S	Y	V	P	S	A	E	Q	I
P. berghei CSP (25)	G	Y	I	P	S	A	E	K	I
JAK1 (367–375)	S	Y	F	P	E	I	T	H	I

MHC Class II Molecules Bind Peptides 13 Amino Acids and Larger along the Cleft



Peptides Binding to Two MHC II Molecules





MHC-peptide form stable complexes

- MHC molecules bind to both T cell receptor and CD4/CD8 co-receptors on T lymphocytes, and the antigen epitope held in the peptide-binding groove of the MHC molecule interacts with the variable Ig-Like domain of the TCR to trigger T-cell activation.

- Stable long lived complex:
  - Efficient antigen presentation
  - Killing of infected cells
  - No empty complex on cell surface

TCR Binds to Peptide:MHC Complex

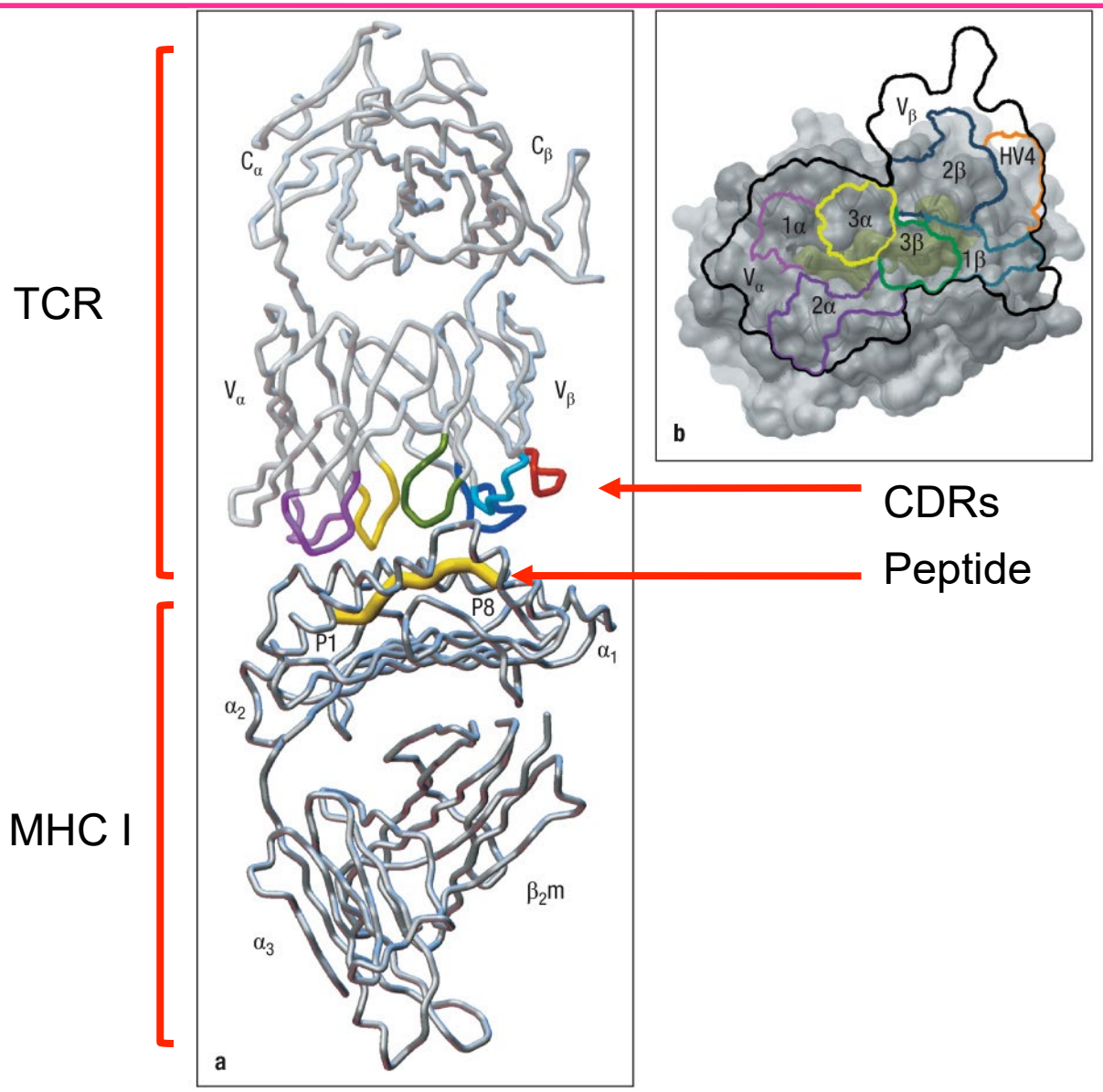
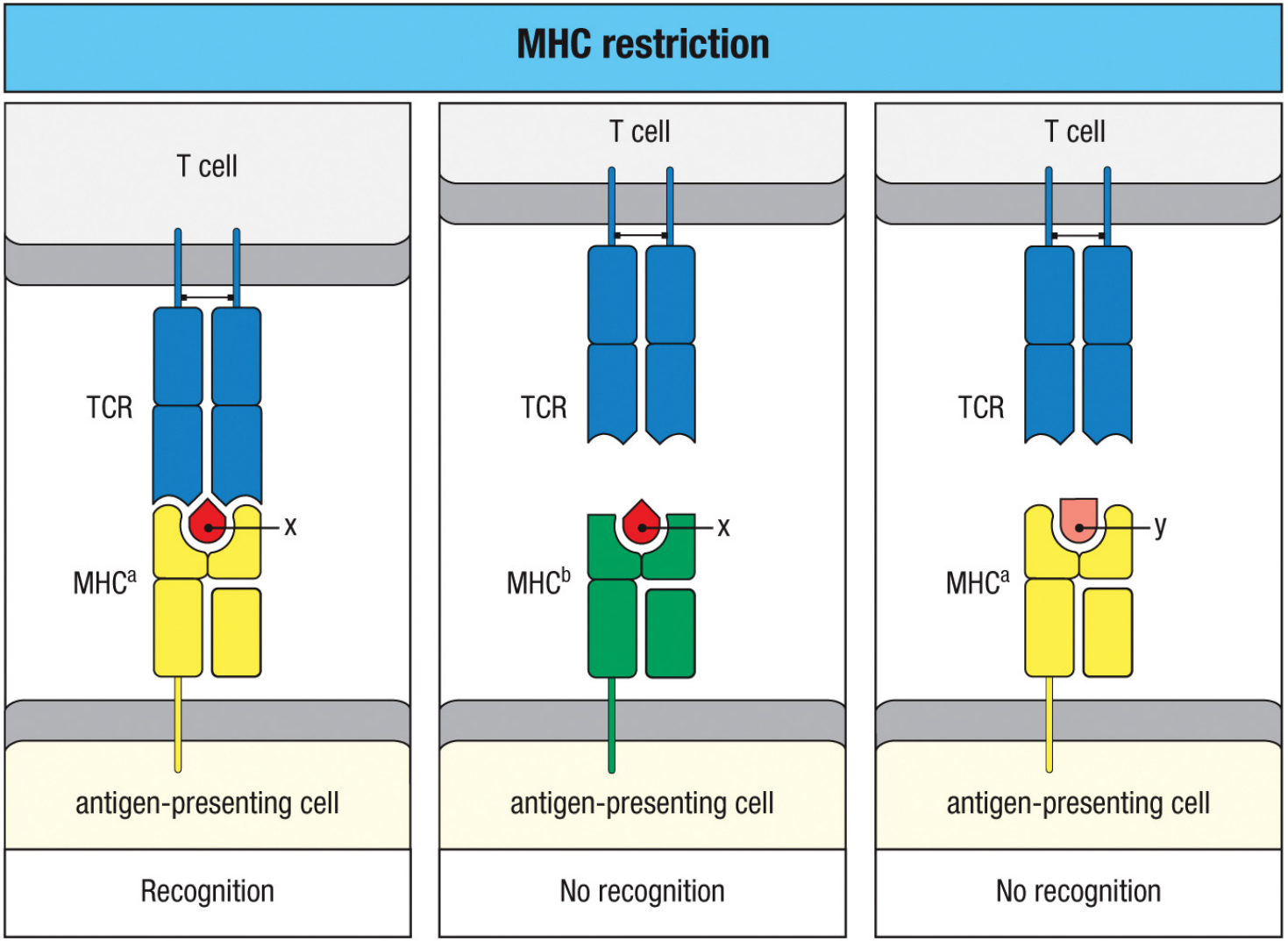
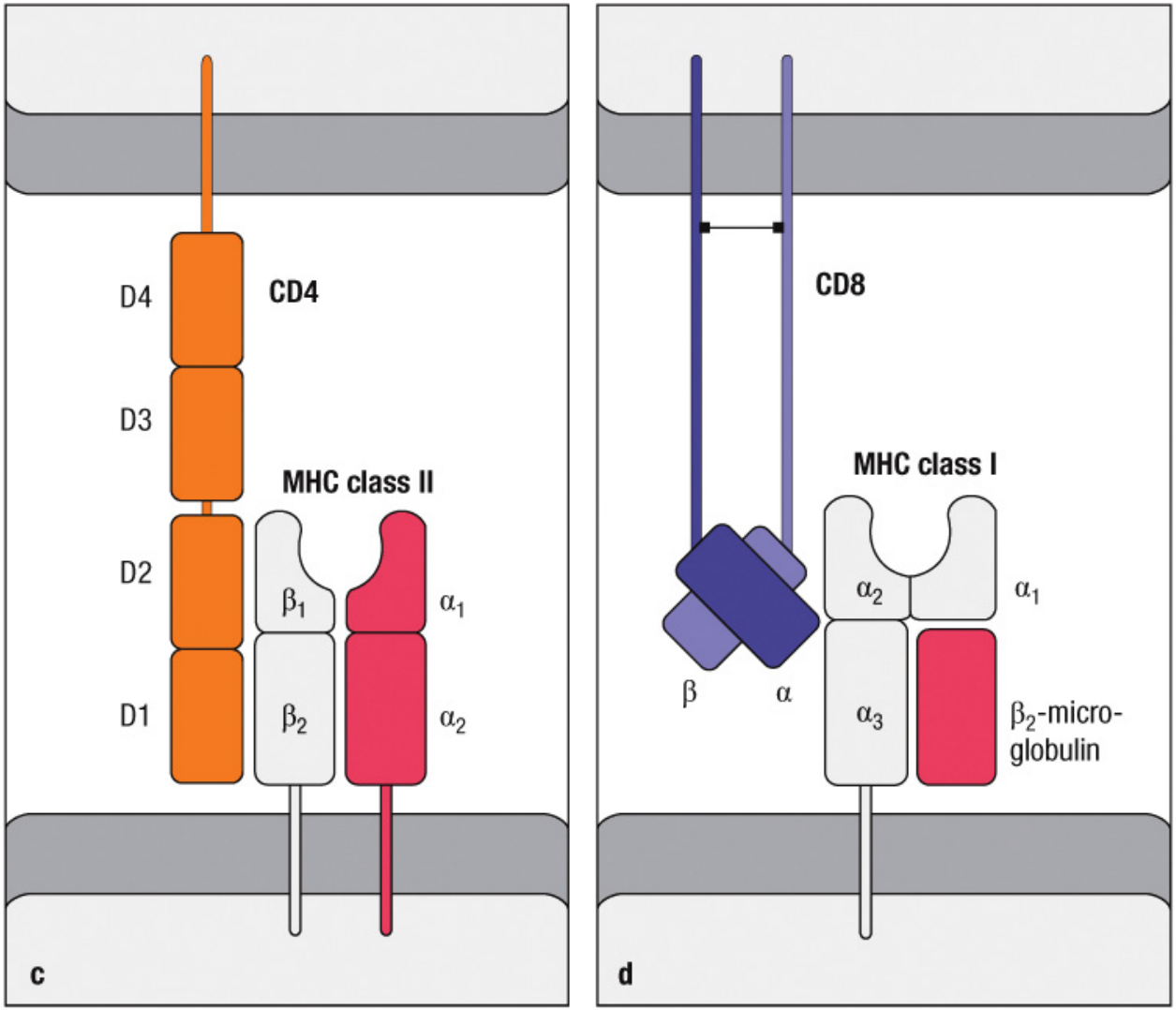


Figure 4.24 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

MHC Restriction



MHC Molecules Display Antigens



Question

- If infected by the same virus, the same epitopes are presented by different individuals.
- A) True
- B) False

Expression of MHC I/II Molecules

Tissue	MHC class I	MHC class II
Lymphoid tissues		
T cells	+++	+*
B cells	+++	+++
Macrophages	+++	++
Dendritic cells	+++	+++
Epithelial cells of thymus	+	+++
Other nucleated cells		
Neutrophils	+++	–
Hepatocytes	+	–
Kidney	+	–
Brain	+	–†
Nonnucleated cells		
Red blood cells	–	–

Antigen Presenting Cells

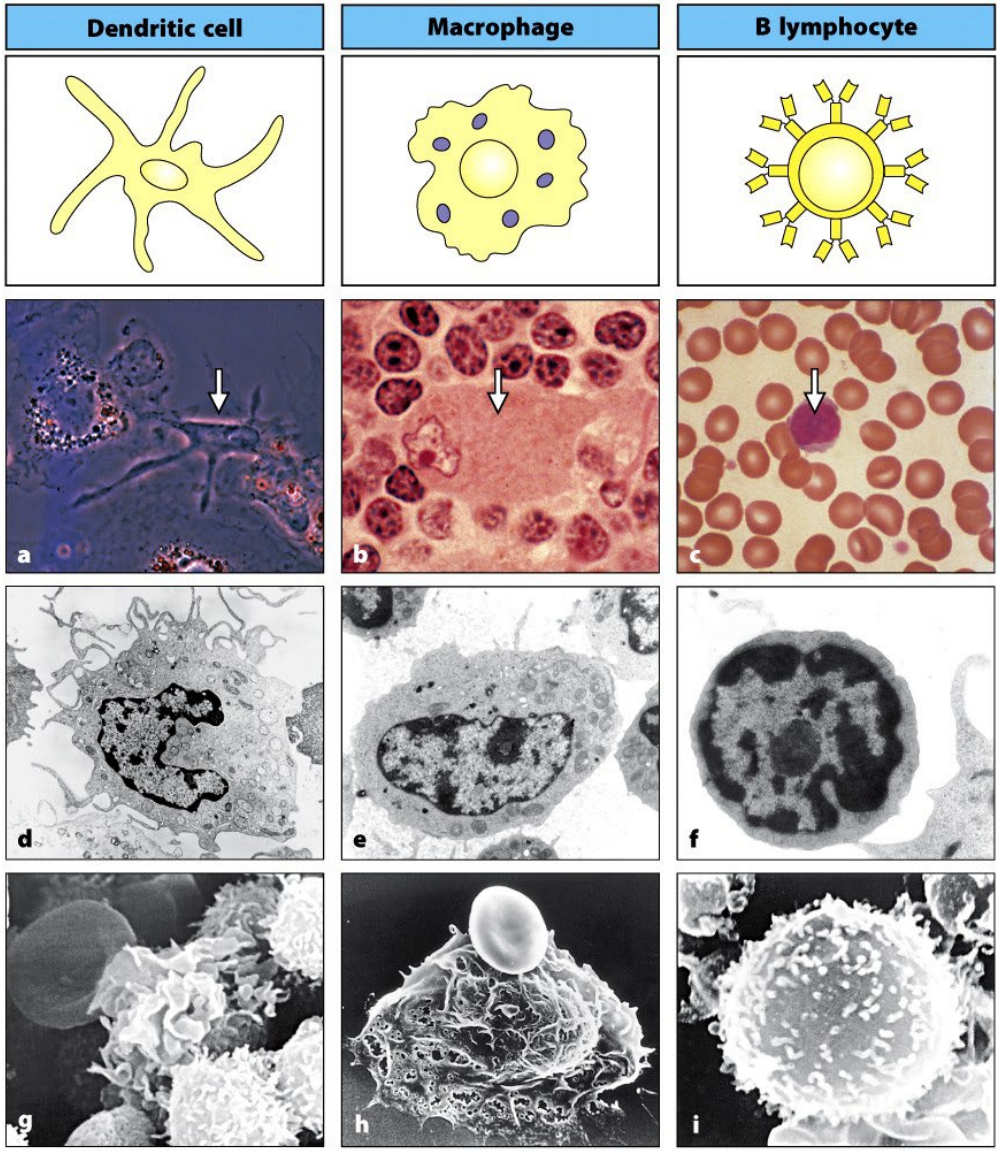
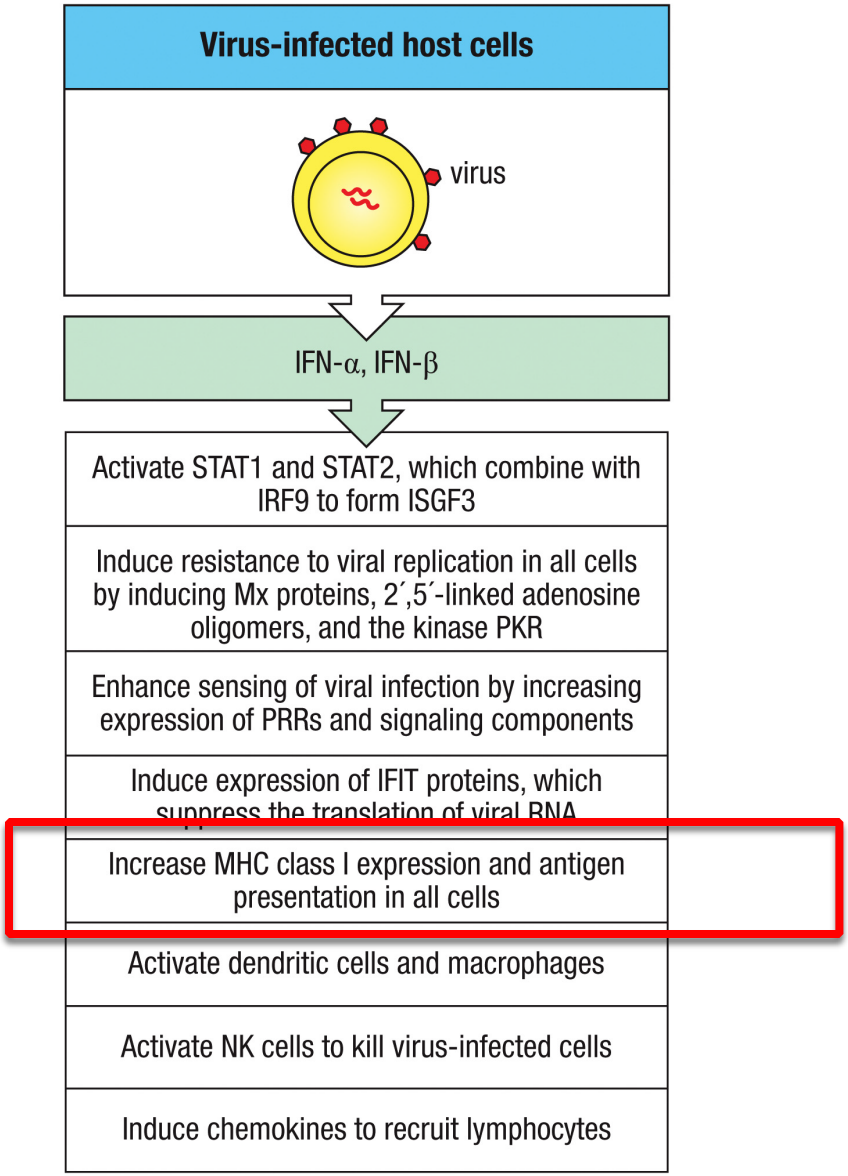


Figure 1.22 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Interferons Induce MHC I expression



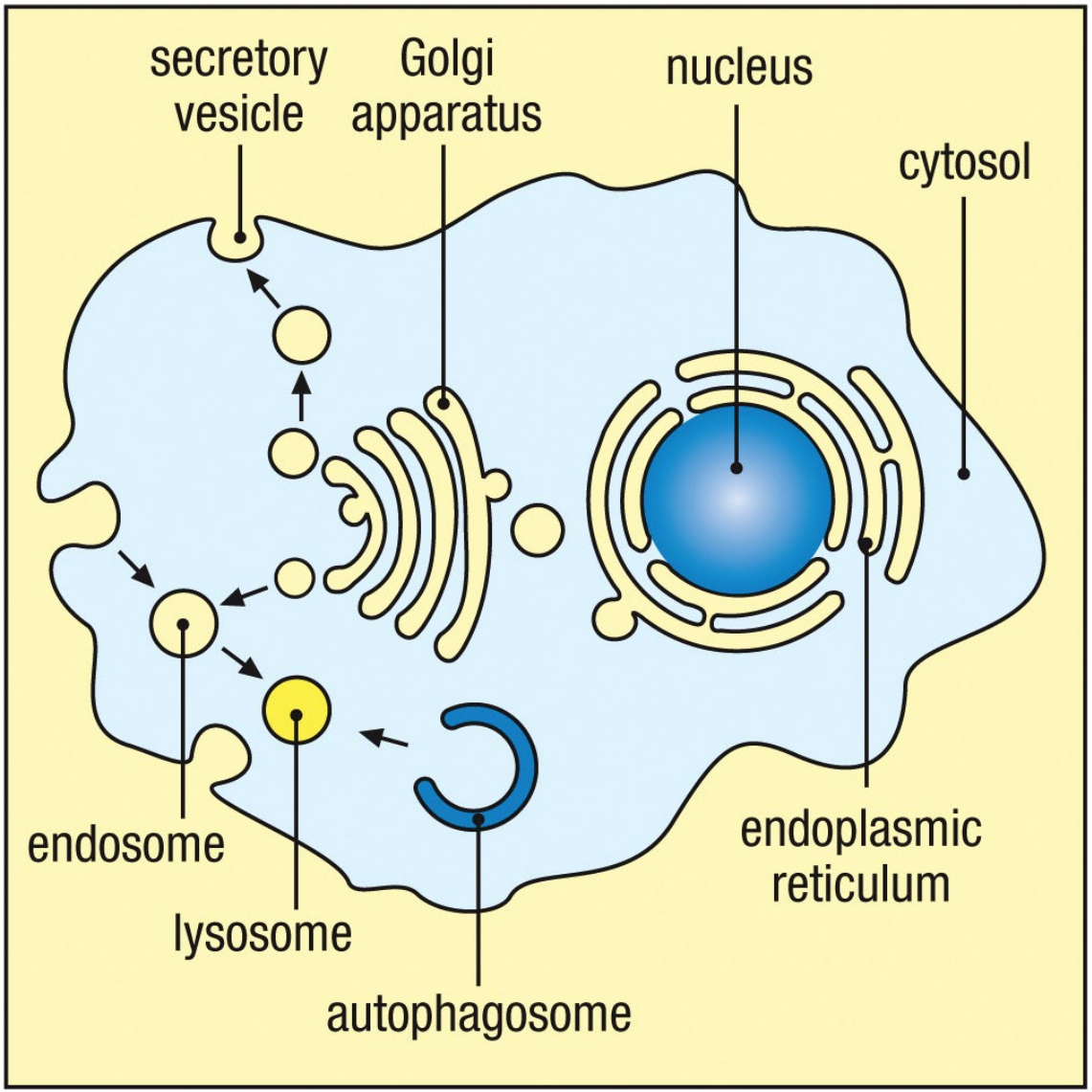
Outline

- MHC complex and its functions
- Generation of TCR ligands
  - Generation and processing of MHC class I peptides
  - Generation and processing of MHC class II peptides

Antigen Presentation Is a Two Step Process

- Antigen processing
  - generation of peptides
- Antigen presentation
  - loading of peptides onto MHC molecules
  - presentation of peptides on the surface of APCs (antigen presenting cells)

Cytosol and Vesicular System Are Two Major Intracellular Compartments



Cytosolic Antigens Are Presented by MHC Class I

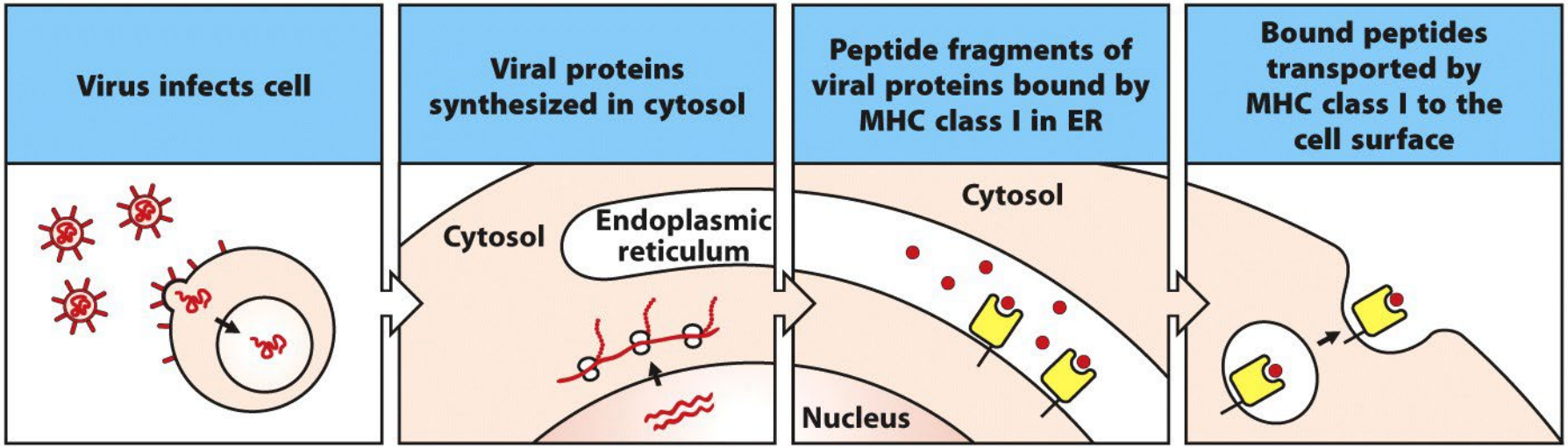
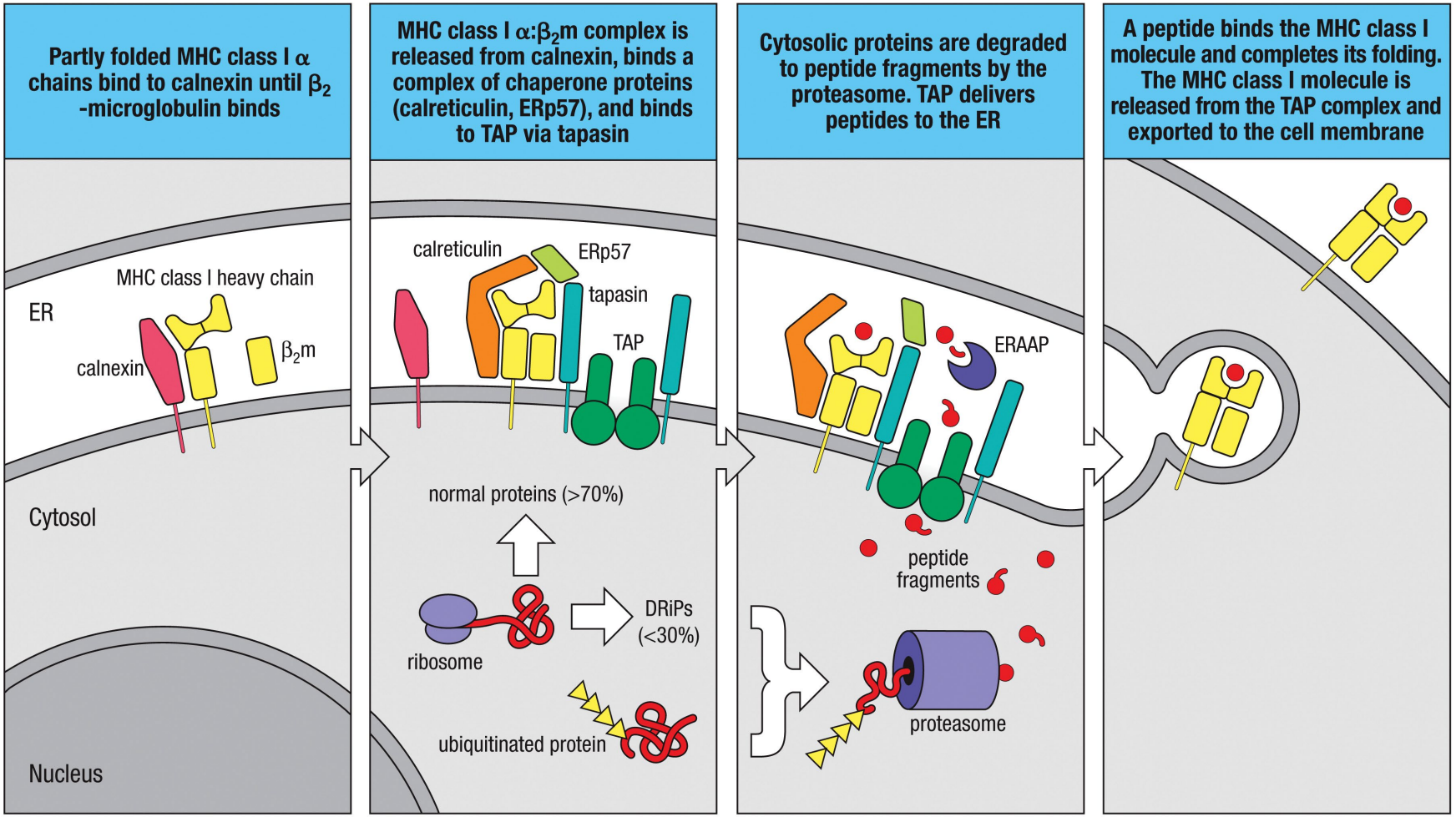


Figure 1.29 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

To Leave ER, MHC Class I Molecules Must Bind Peptides



Formation and Transport of MHC Class I Peptides

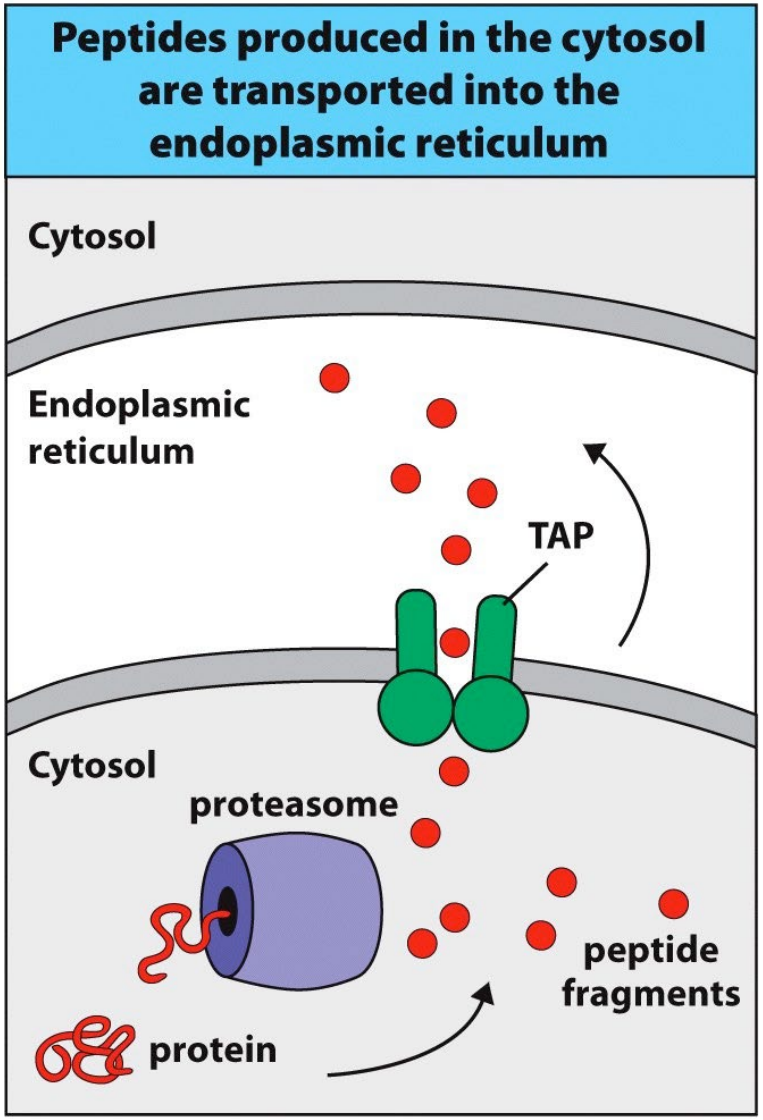


Figure 5.17 The Immune System, 3ed. (© Garland Science 2009)

TAP: transporter associated with antigen processing

Viral Immunoevasins Target ER Peptide Loading Complex

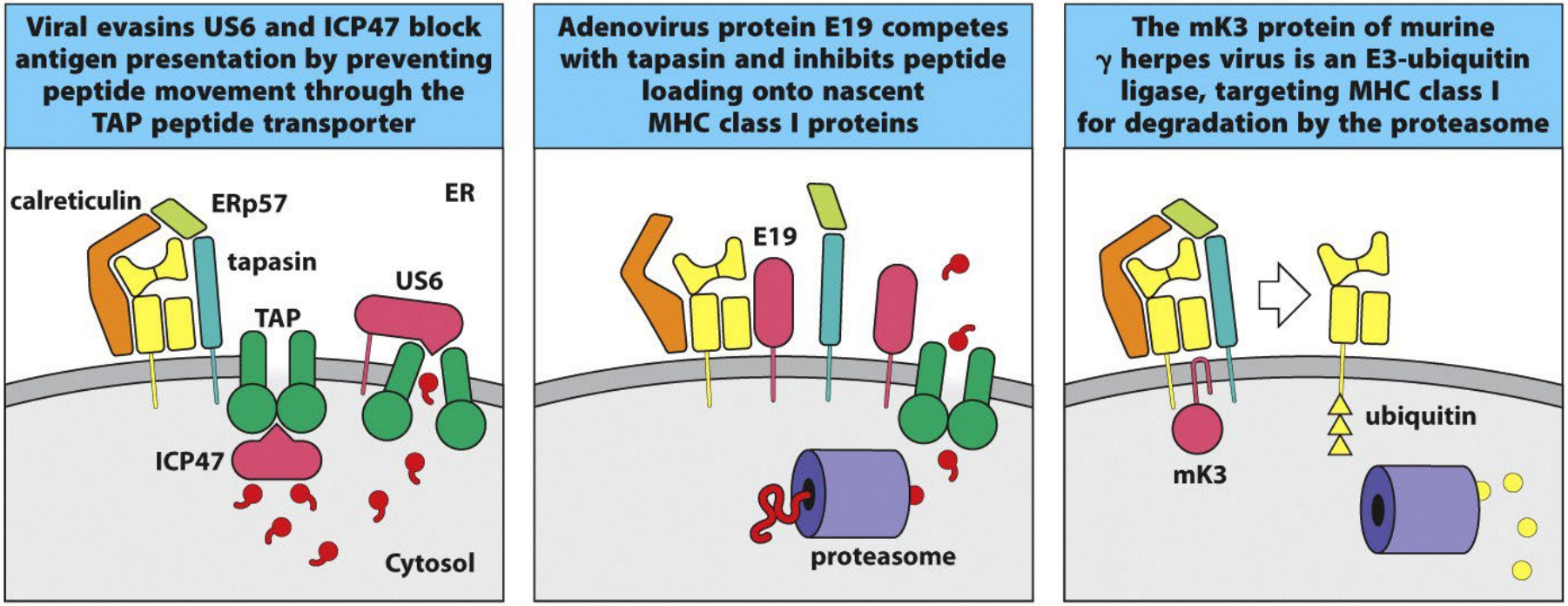


Figure 6.8 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

MHCI will not be displayed on cell surface without peptide loaded.

Question

- Describe how antigens are presented on MHCI molecule
- What if TAP is absent?

Outline

- MHC complex and its functions
- Generation of TCR ligands
  - Generation and processing of MHC class I peptides
  - Generation and processing of MHC class II peptides

Intravesicular Antigens Are Presented by MHC Class II

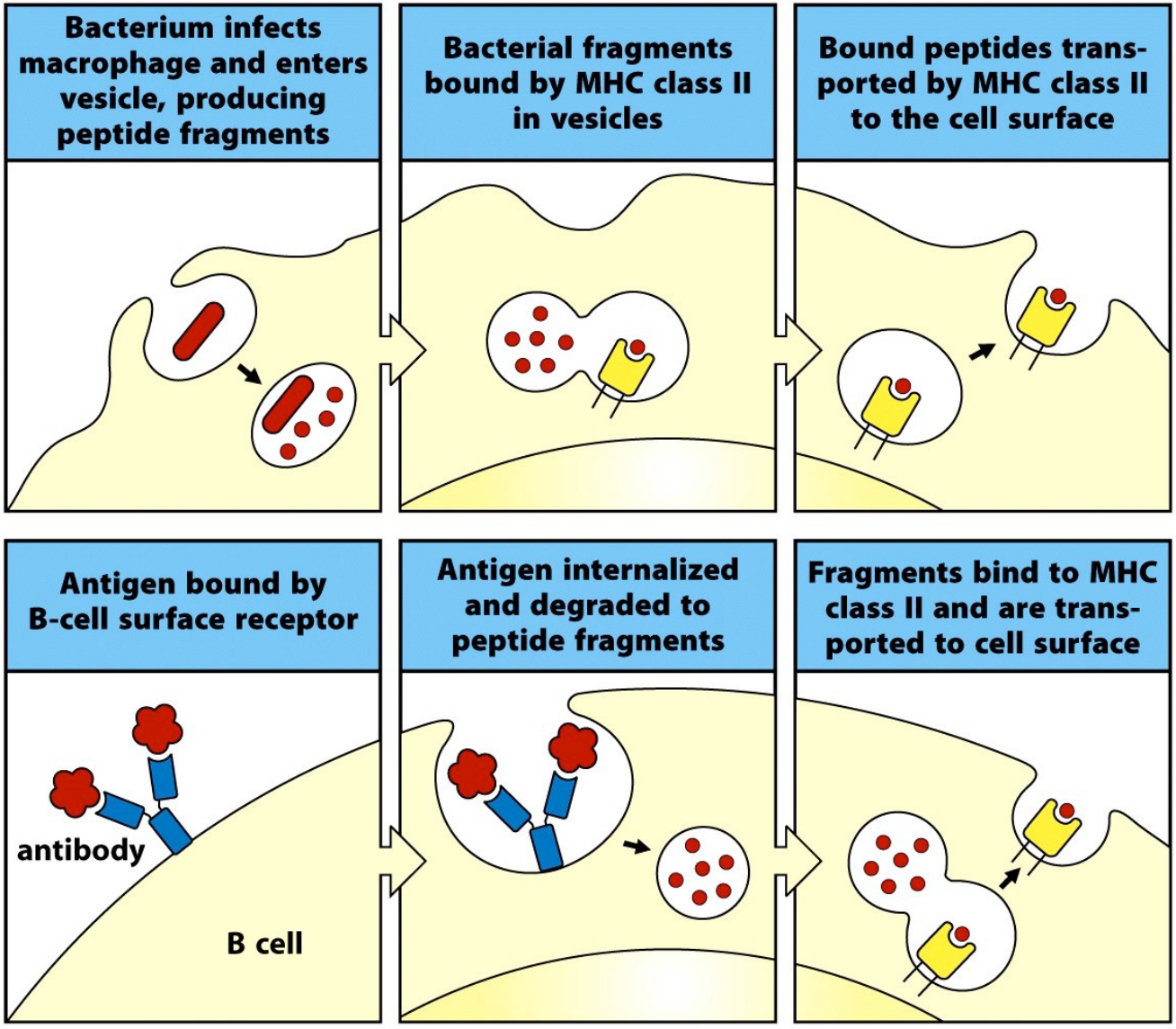
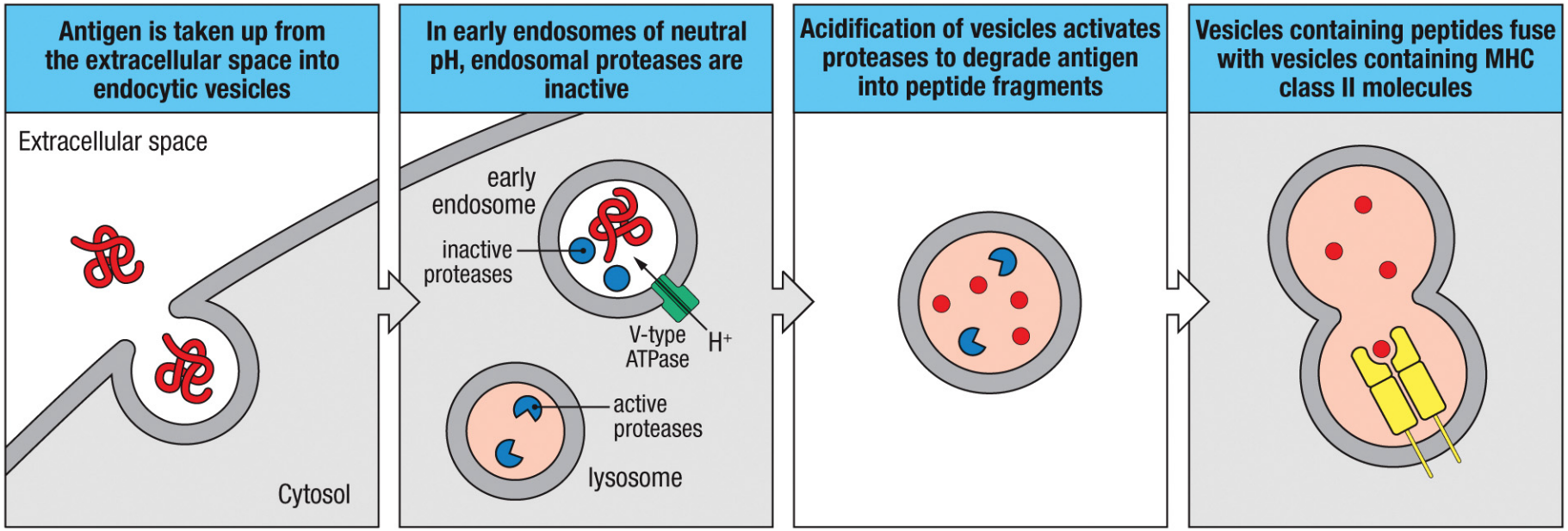
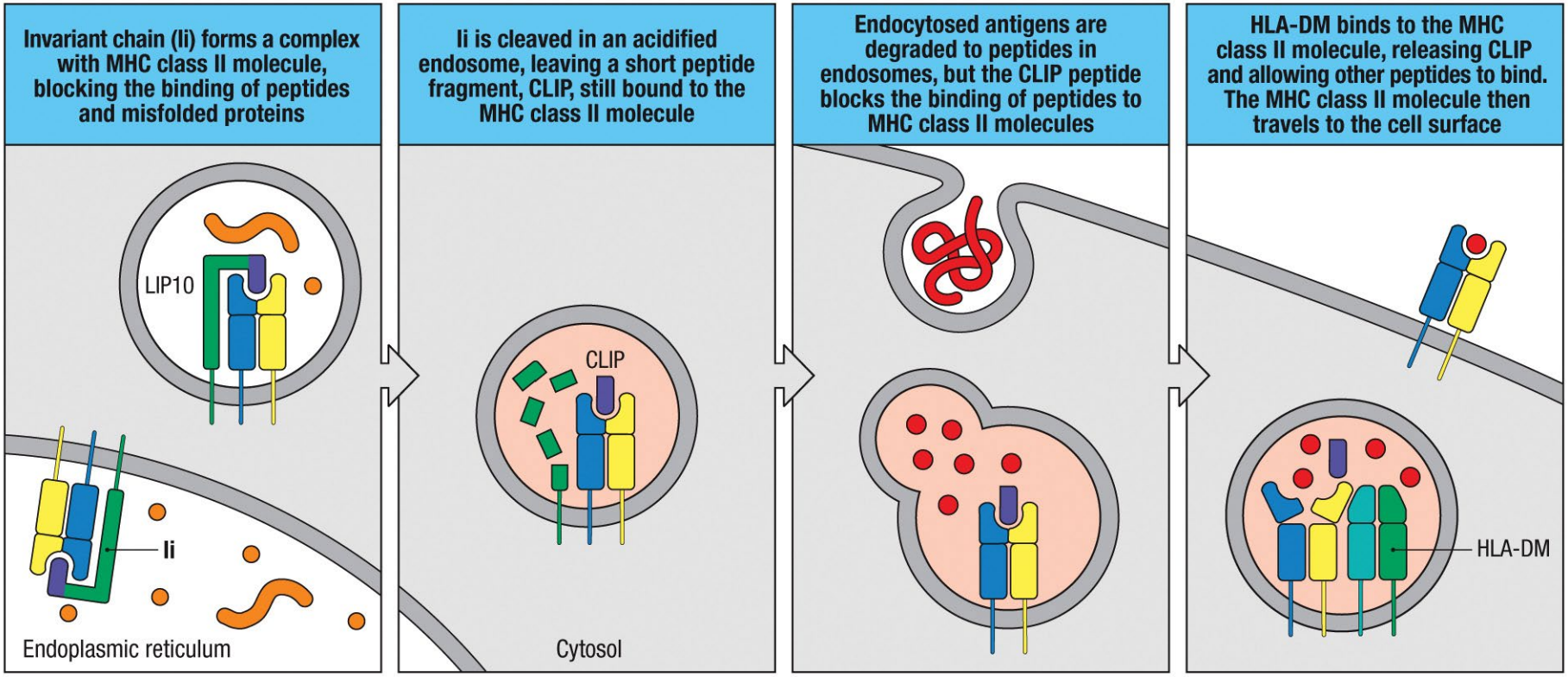


Figure 1-31 Immunobiology, 7ed. (© Garland Science 2008)

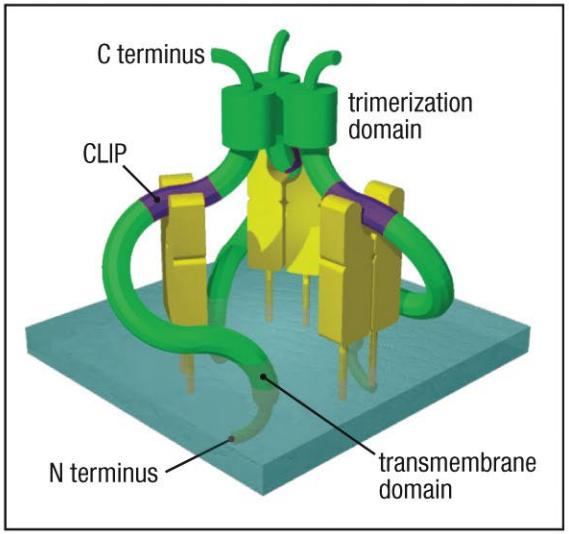
MHC Class II Peptides Are Generated in Acidified Endocytic Vesicles



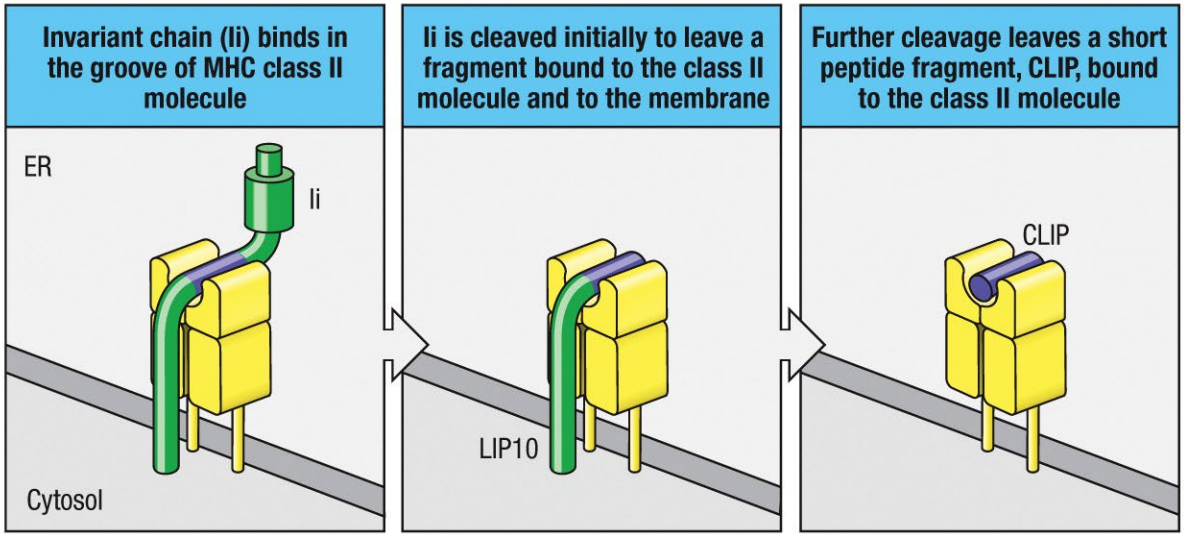
HLA-DM Facilitates Loading of Antigenic Peptides onto MHC Class II Molecules



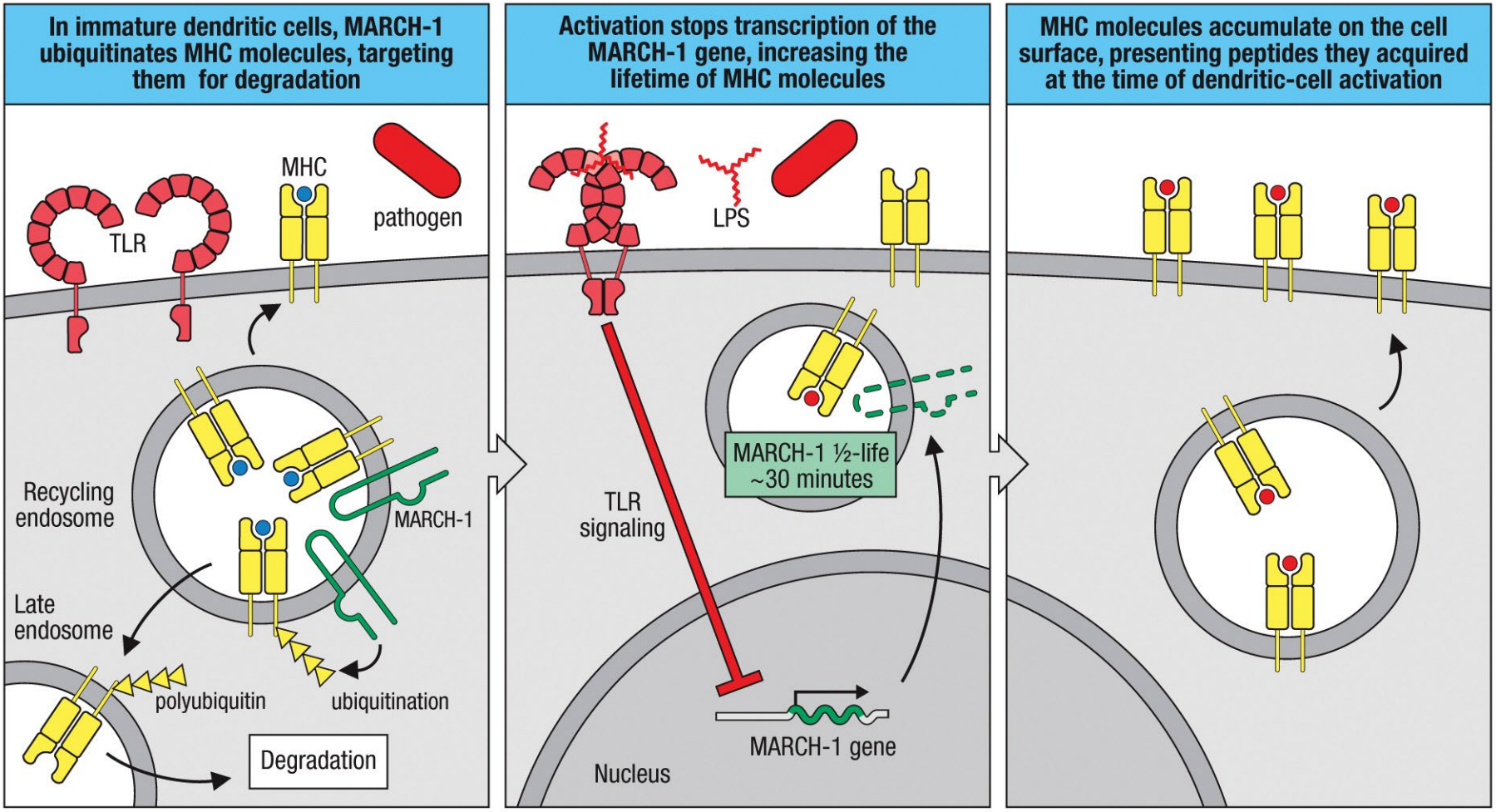
Processing of the Invariant Chain



Courtesy of Peter Cresswell



Increased Surface Level after Infection



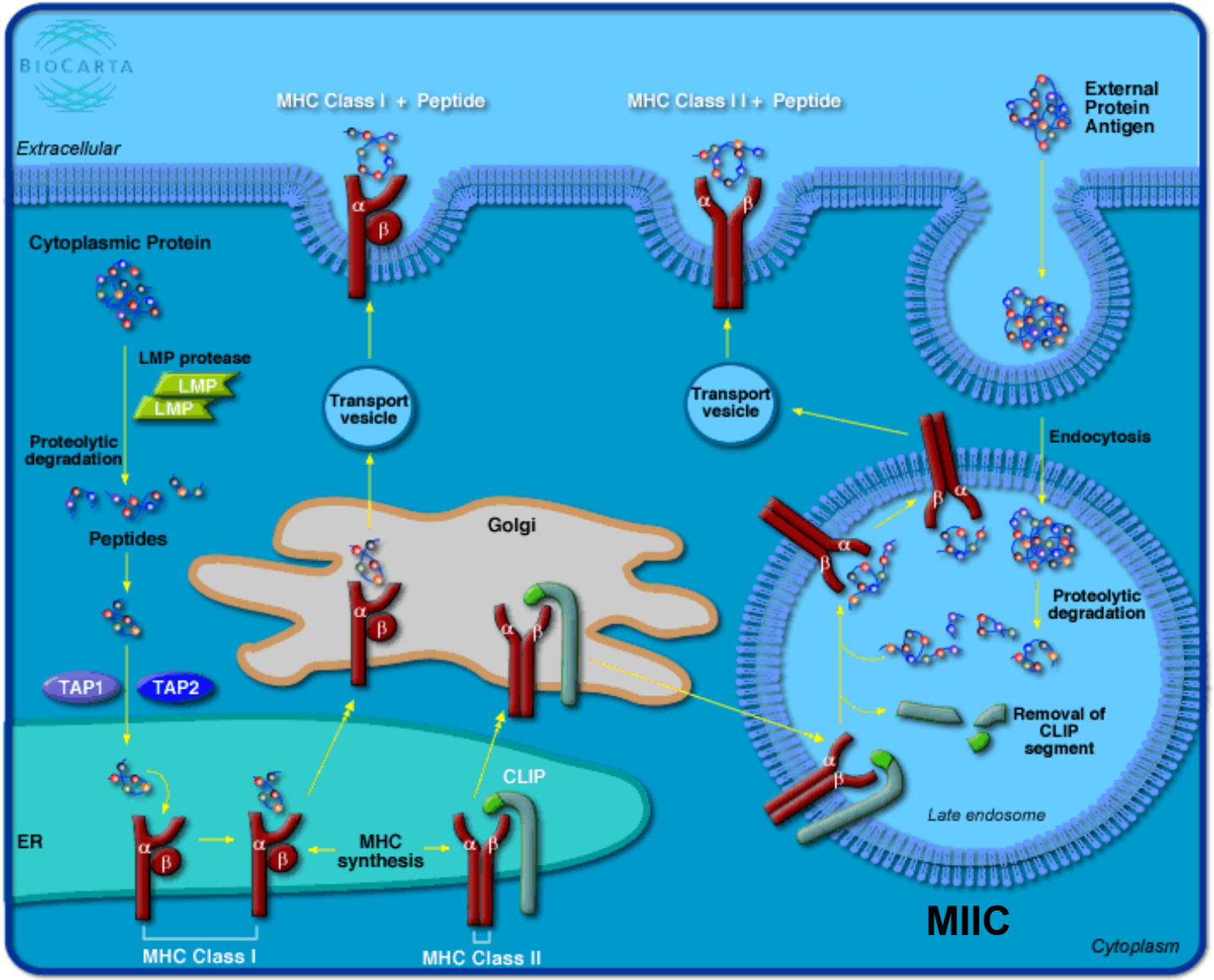
Function of the Invariant Chain

- Prevent antigen loading in the ER
- Facilitate transportation out of the ER

Question

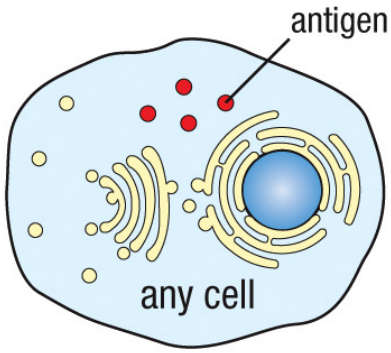
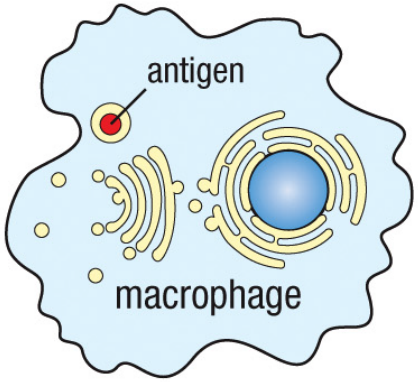
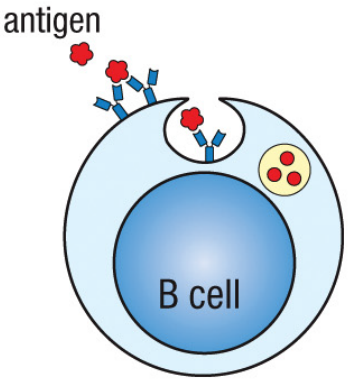
- Describe how antigens are presented on MHCII molecule
- What if CLIP is absent?

MHC Class I and II Life Cycle

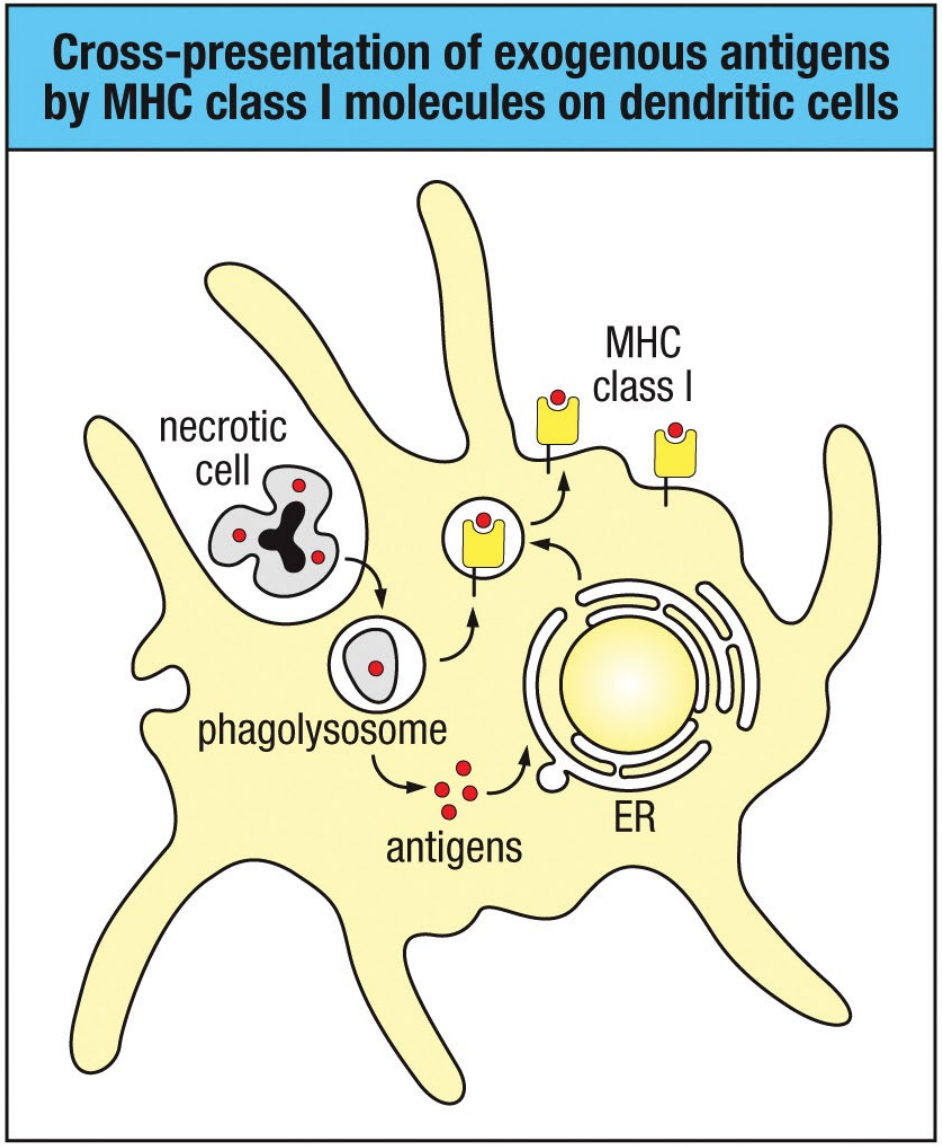


http://dri-constant.slavoljubpenkala.hr/wp-content/uploads/2009/09/h_mhcPathway-BETTER-ONE.gif

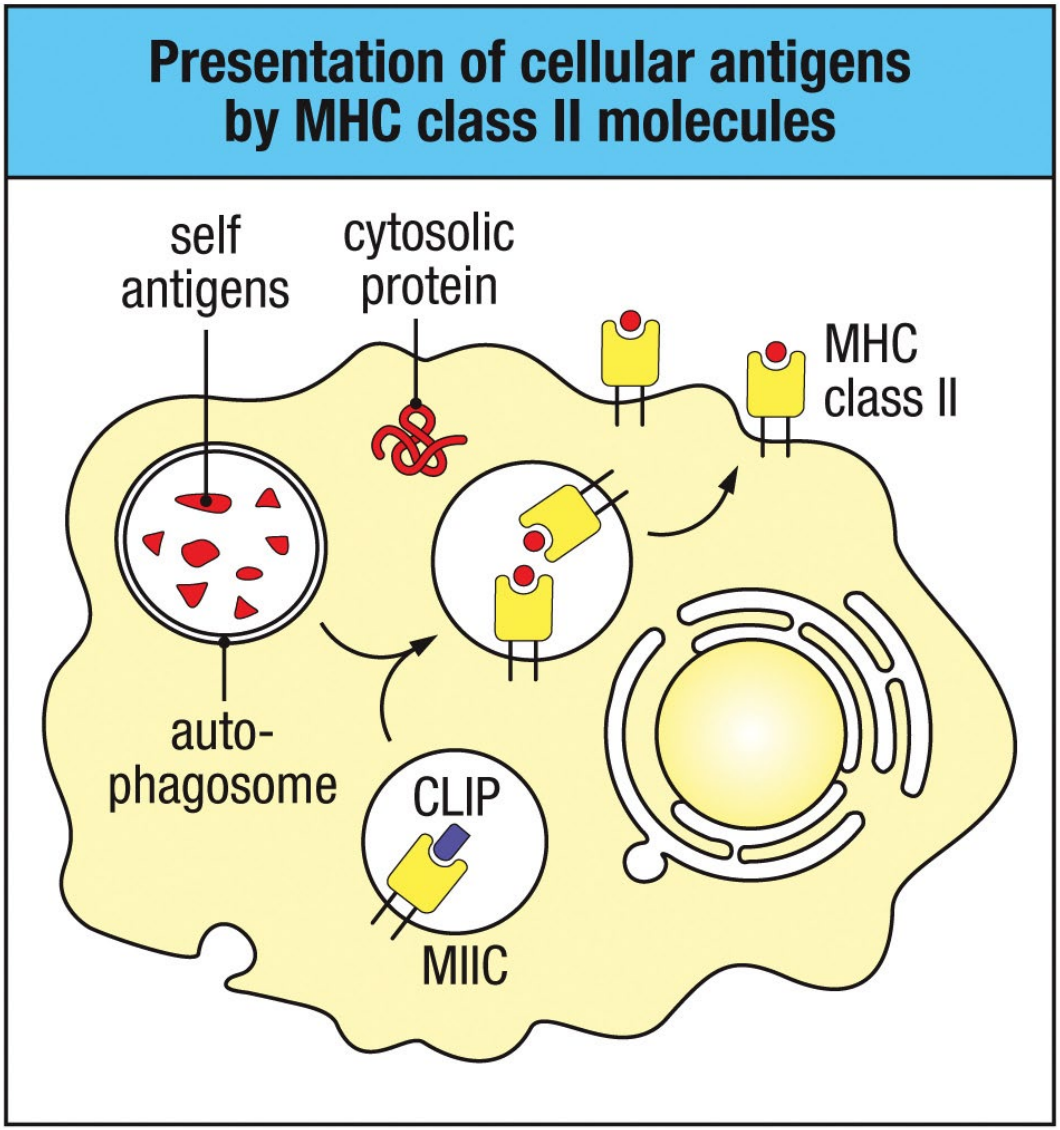
Target Cells of Activated T Cells

	Cytosolic pathogens	Intravesicular pathogens	Extracellular pathogens and toxins
			
Degraded in	Cytosol	Endocytic vesicles (low pH)	Endocytic vesicles (low pH)
Peptides bind to	MHC class I	MHC class II	MHC class II
Presented to	Effector CD8 T cells	Effector CD4 T cells	Effector CD4 T cells
Effect on presenting cell	Cell death	Activation of macrophage to kill intravesicular bacteria and parasites	Activation of B cells to secrete Ig to eliminate extracellular bacteria/ toxins/viruses

Cross-presentation



Cross-presentation



Outline

- MHC complex and its functions
- Generation of TCR ligands
  - Generation and processing of MHC class I peptides
  - Generation and processing of MHC class II peptides

MHC Class I Deficiency

Patient:

- 17 years old female
- Chronically ill since 4
- Repeated infections from respiratory viruses
- cultures positive for *H. influenza and Streptococcus in sputum* (bacterial)

Family history:

- Brother, 7 years old, chronic respiratory infections
- Three other children, healthy

Tests:

- 90% CD4 positive and 10% CD8 positive
- Very low antibody titer to influenza despite previous immunization
- Very small amount of MHC class I molecule on cell surface
- Normal mRNA levels for the alpha chain
- Defect in TAP2 gene.

Autosomal Recessive

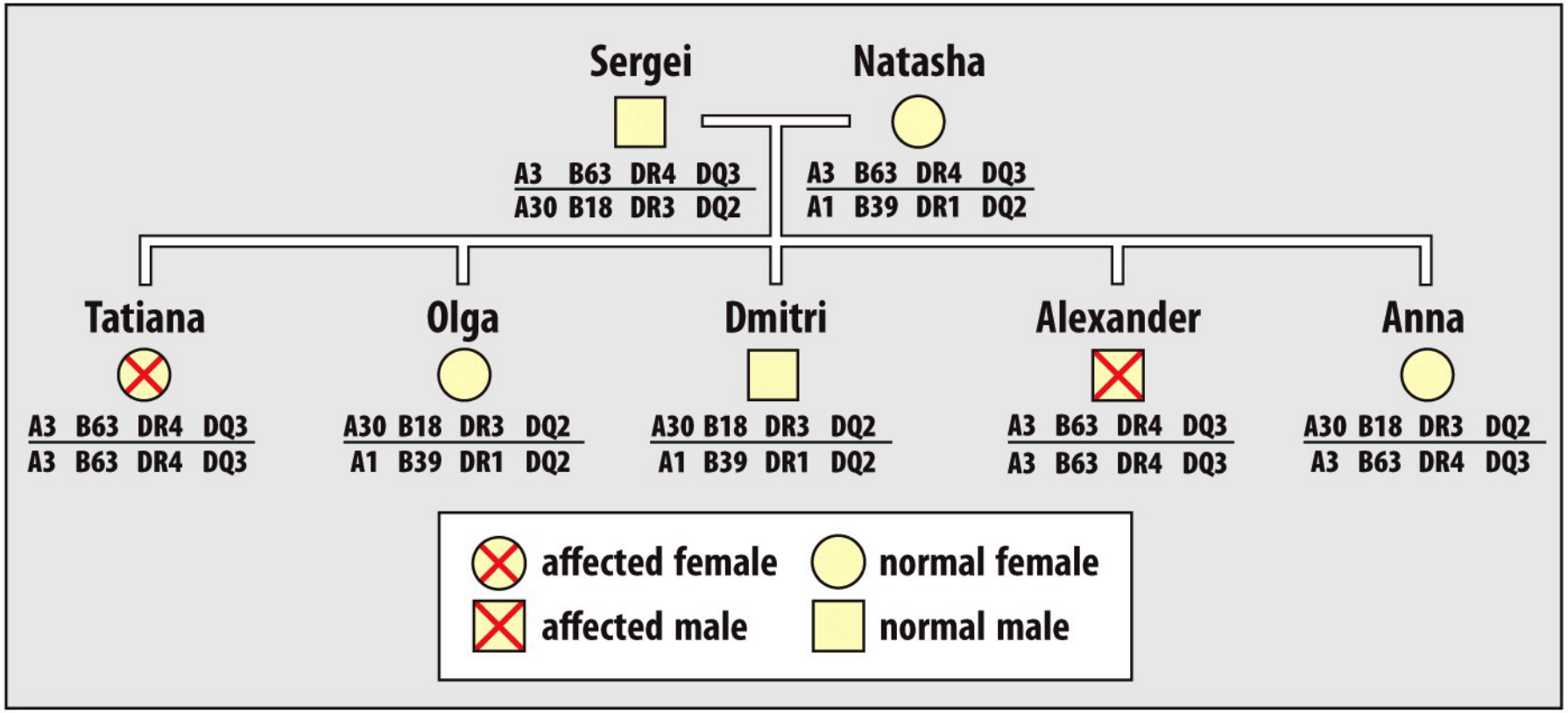
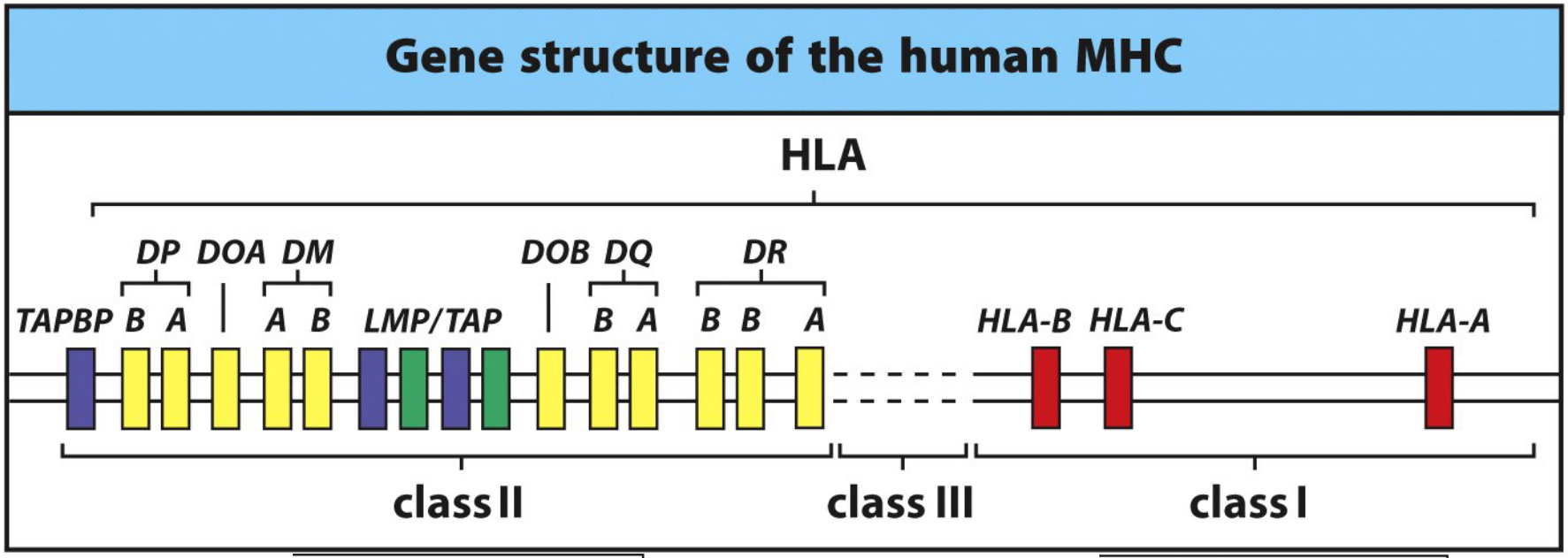
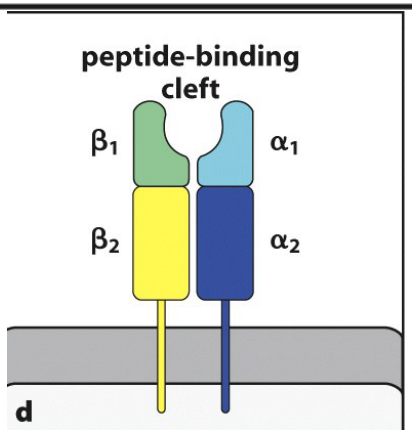


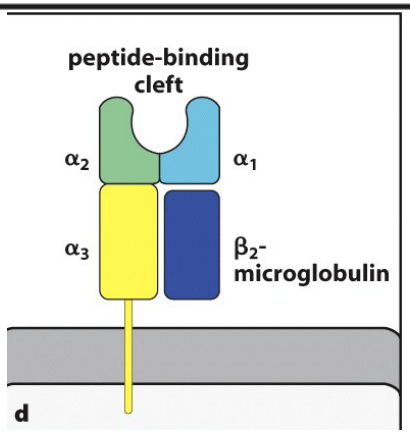
Figure 12.7 Case Studies in Immunology, 6ed. (© Garland Science 2012)

Genetic Organization of MHC Locus

human leukocyte antigen







Low MHC class I on cell surface

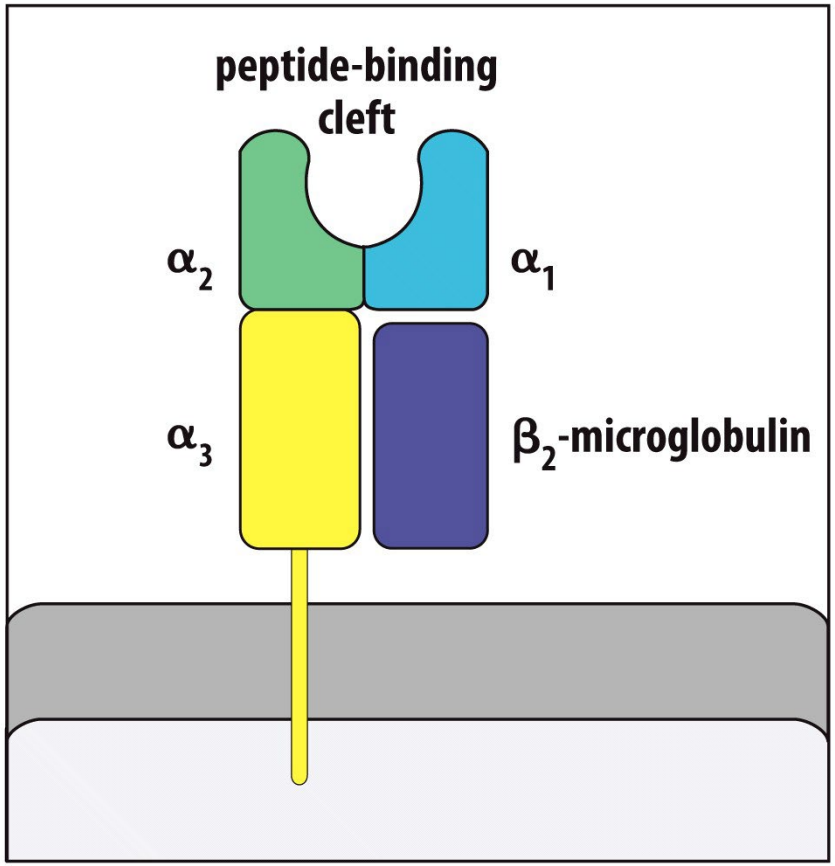


Figure 12.2 Case Studies in Immunology, 6ed. (© Garland Science 2012)

HLA-A3

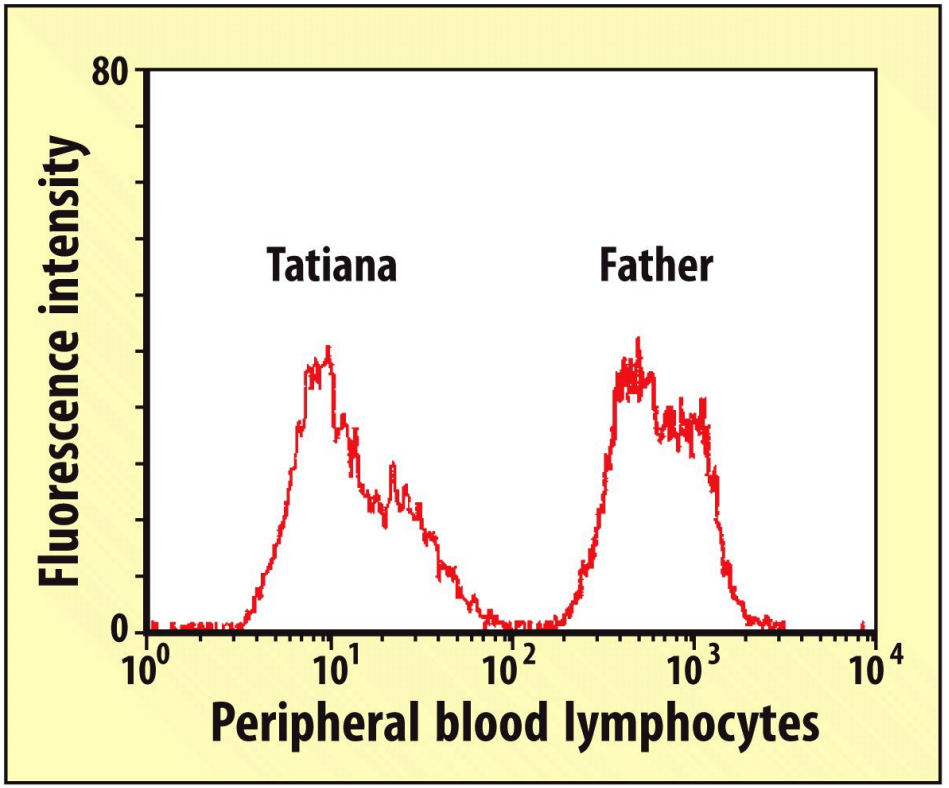


Figure 12.6 Case Studies in Immunology, 6ed. (© Garland Science 2012)

TAP

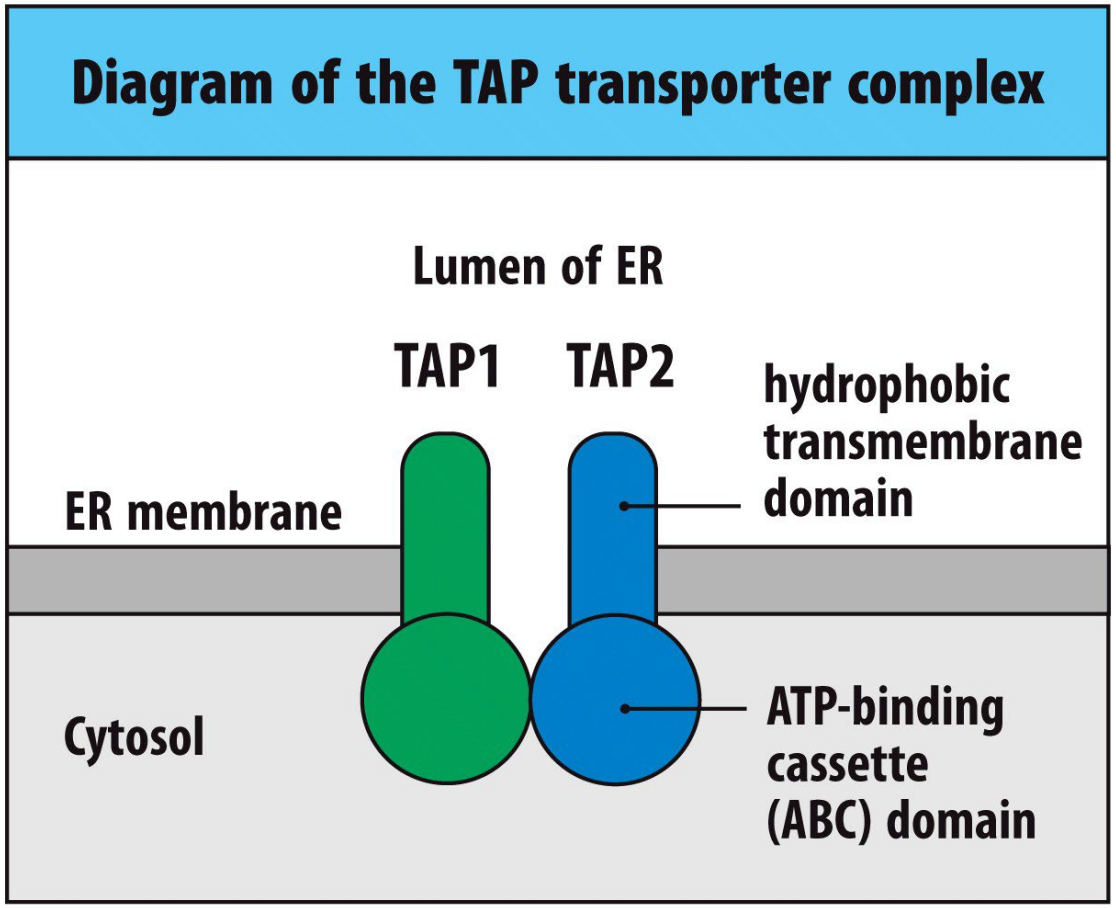


Figure 12.4 Case Studies in Immunology, 6ed. (© Garland Science 2012)

TAP is Required for Peptide Loading on MHC I

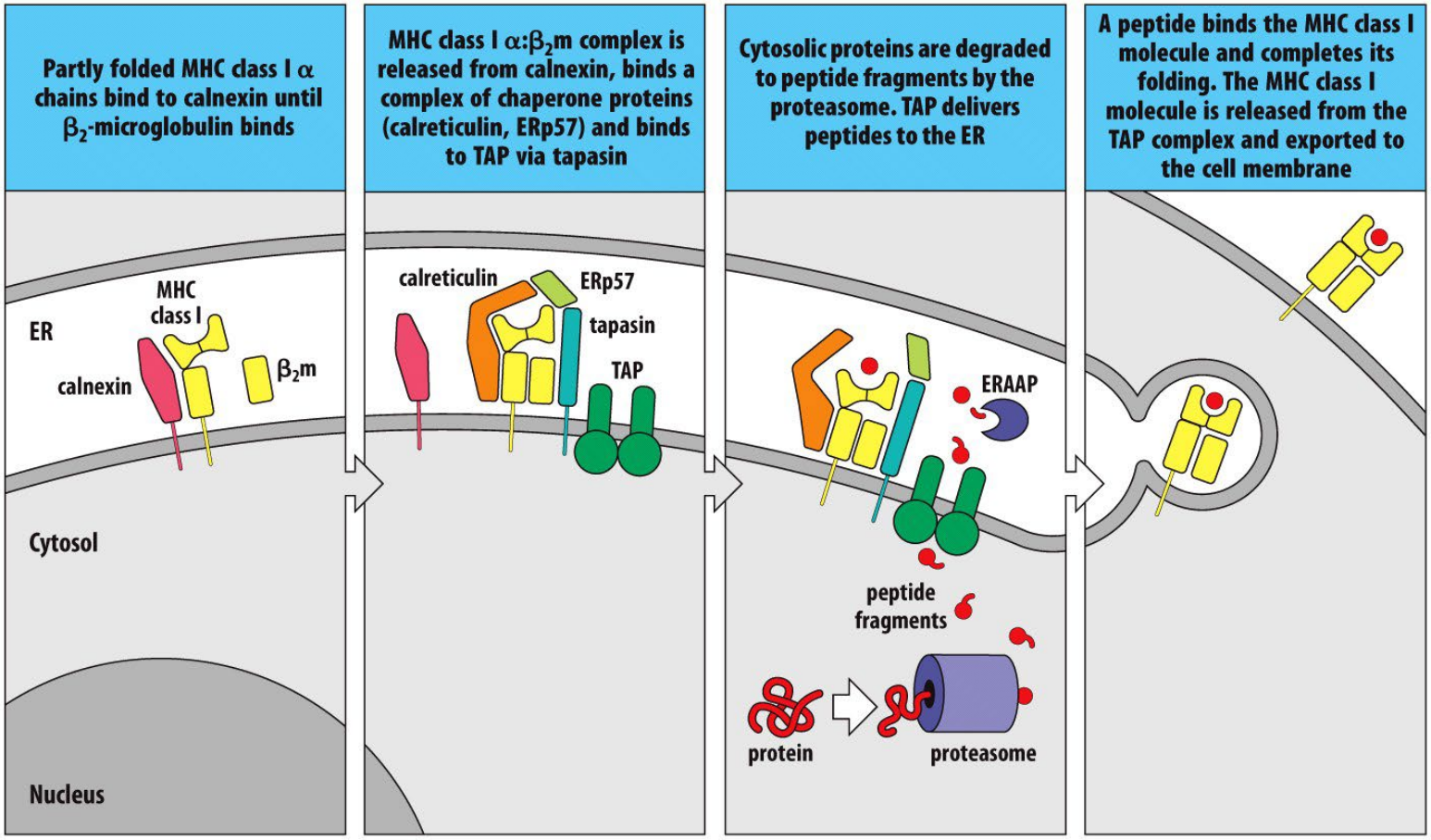


Figure 12.5 Case Studies in Immunology, 6ed. (© Garland Science 2012)

Activation of Cytotoxic T cells

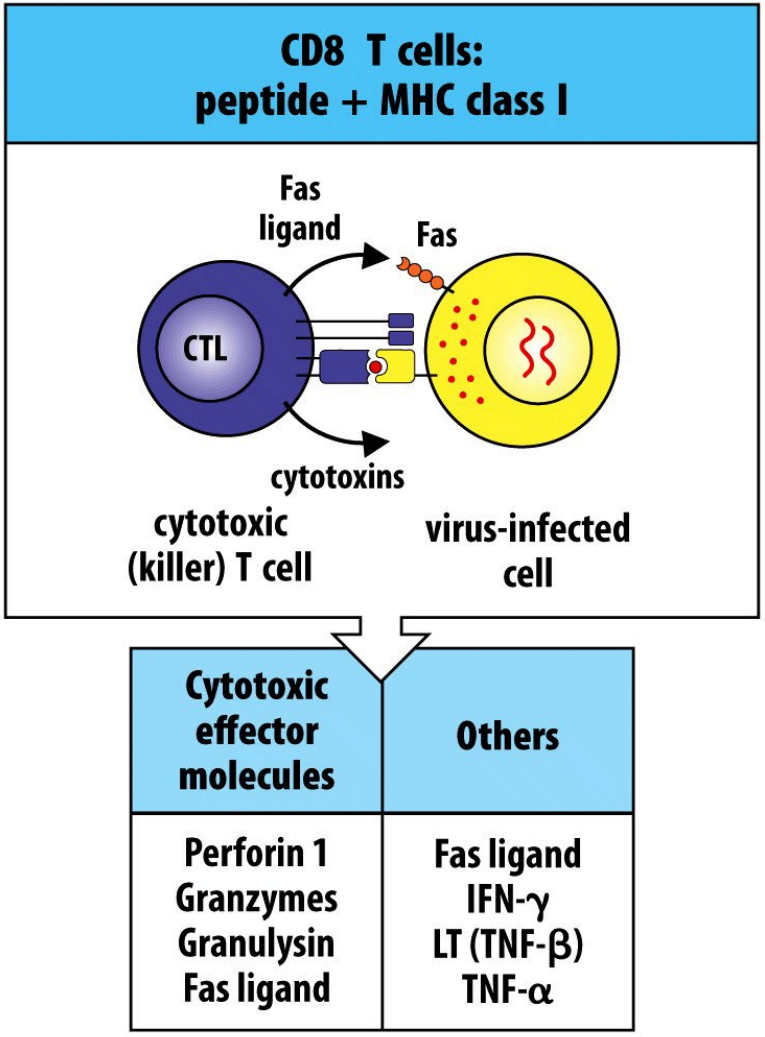


Figure 12.1 Case Studies in Immunology, 6ed. (© Garland Science 2012)

MHC Class I Deficiency

- What's wrong with the patient?
- Defect in TAP results in defect in peptide transportation into the ER for peptide loading. Unloaded MHC I is unstable and quickly degraded.
- Susceptible to viral infection

Question

- What is the consequence of a genetic defect in HLA-A?

A) MHC I deficiency

B) MHC II deficiency

C) Both

D) Neither

MHC Class II Deficiency

Patient:

- 6 month old female
- Pneumonia, severe cough and fever
- cultures positive for *Pneunocystic jirovecli* in tracheal aspirate (opportunistic bacteria)

Tests:

- Low serum immunoglobulin
- 34 % CD8 positive and 10% CD4 positive lymphocytes
- T cell proliferate with PHA—signaling can be activated
- T cells don't respond to tetanus toxoid despite previous immunization
- Respond normally to allogeneic B cells
- Can not obtain a DR type

Treatment:

- Bone marrow transplantation and cured

CD4 T Cells Recognize MHC II

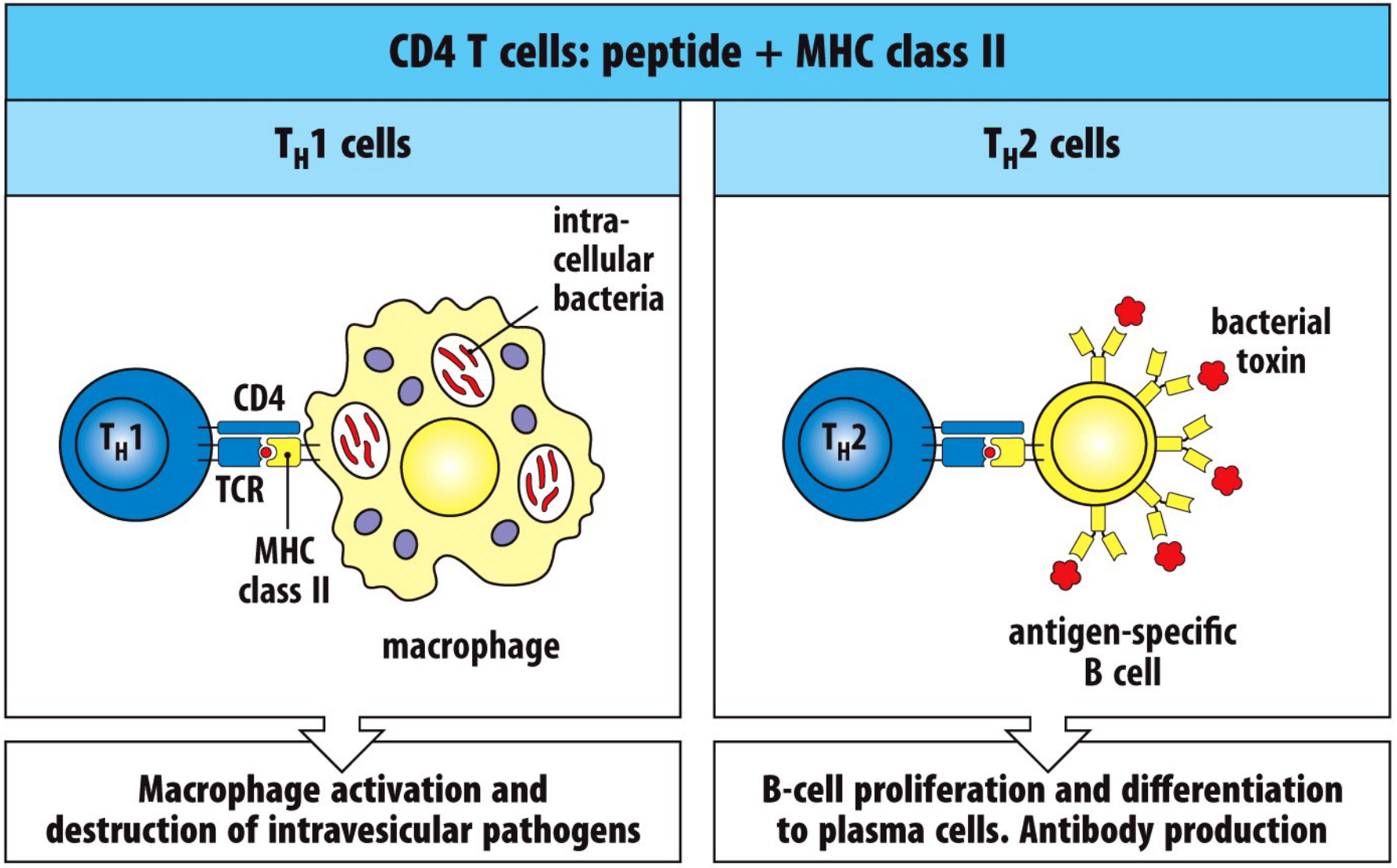


Figure 8.3 Case Studies in Immunology, 6ed. (© Garland Science 2012)

Low Level Cell Surface MHC II

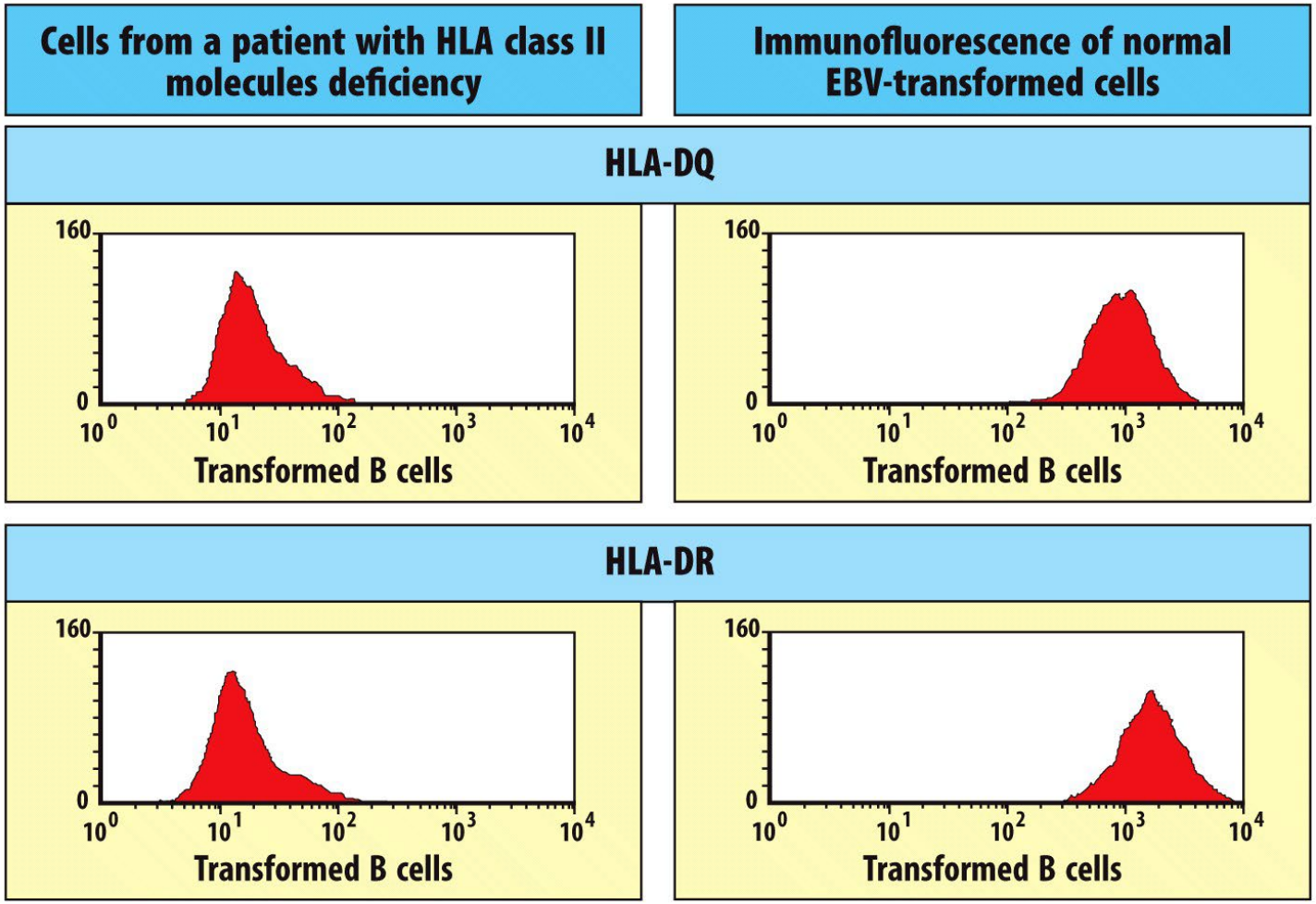


Figure 8.4 Case Studies in Immunology, 6ed. (© Garland Science 2012)

MHC Class II Deficiency

- What's wrong with the patient?
- Low level cell surface MHC II due to defects in upstream transcription factors.
- Defect in macrophage killing of intracellular bacteria and antibody production

True or False?

- MHC class I/II deficiency is usually a defect in MHC class I/II genes themselves

- A) True
- B) False