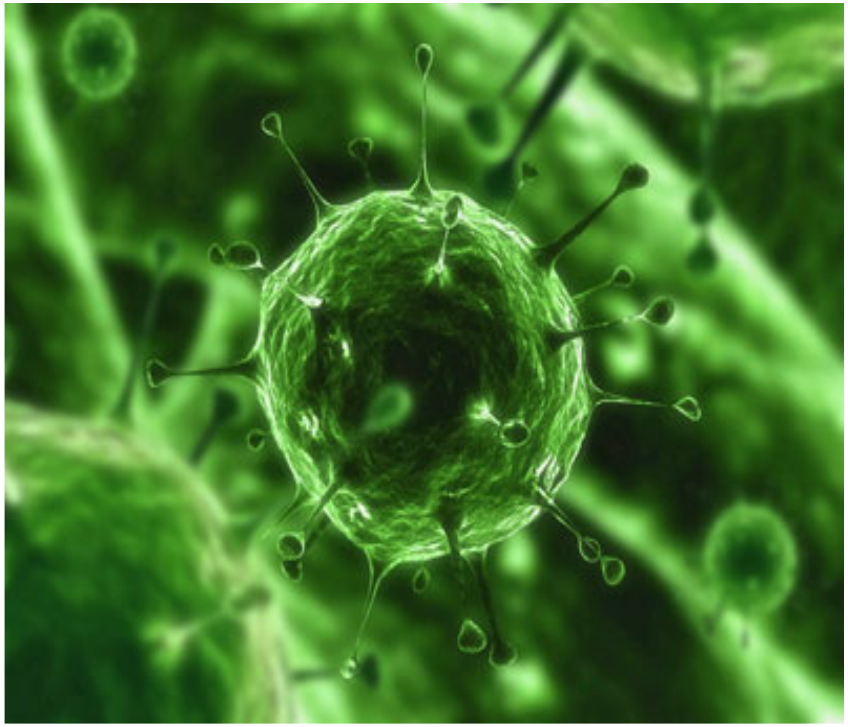
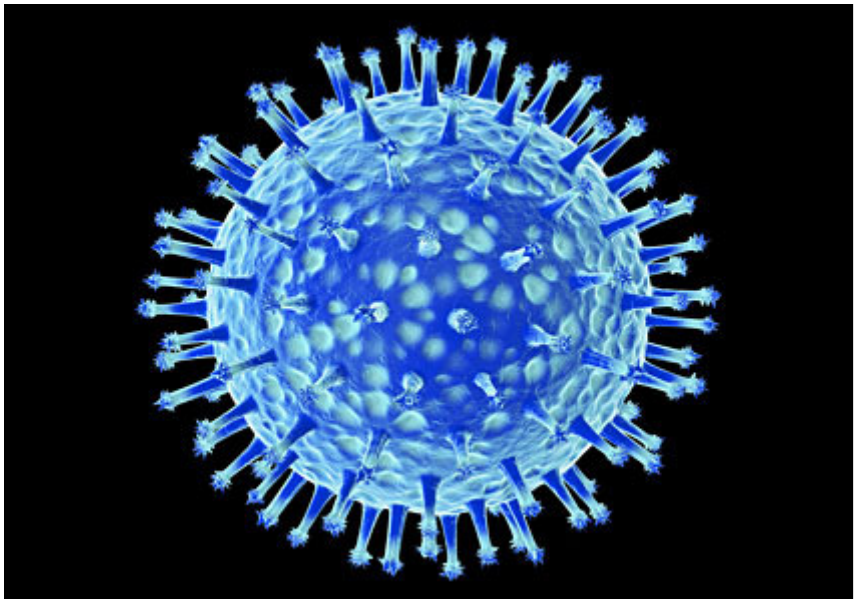
INMUNOPATOLOGÍA

Inmunología de las infecciones virales

2010





Elisa Beraja

Características generales de los virus

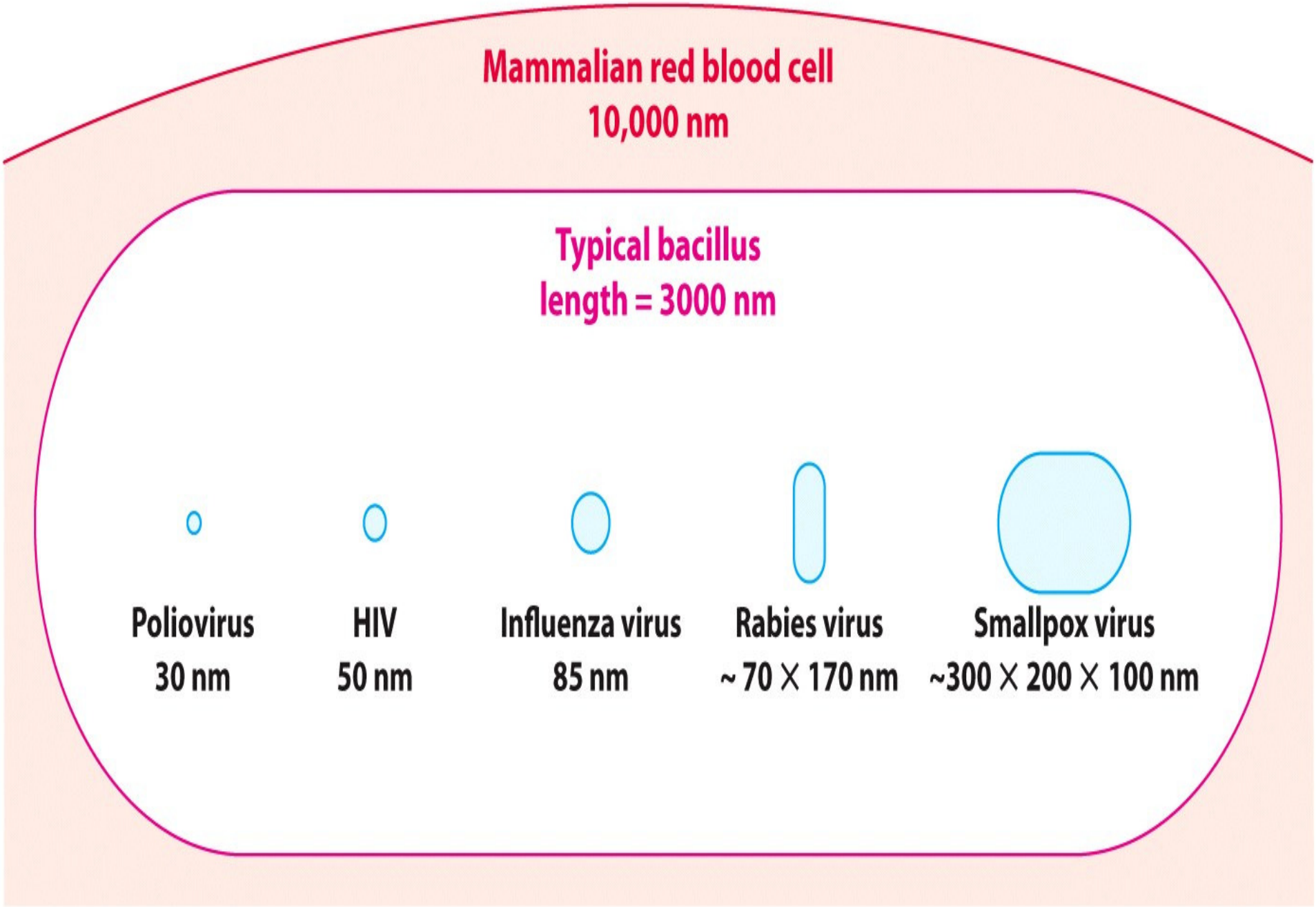


Figure 4.25 Living in a Microbial World (© Garland Science)

Some common causes of disease in humans

Viruses	DNA viruses	Adenoviruses	Human adenoviruses (e.g., types 3, 4, and 7)
		Herpesviruses	Herpes simplex, varicella zoster, Epstein–Barr virus, cytomegalovirus, HHV8
		Poxviruses	Variola, vaccinia virus
		Parvoviruses	Human parvovirus
		Papovaviruses	Papilloma virus
		Hepadnaviruses	Hepatitis B virus
	RNA viruses	Orthomyxoviruses	Influenza virus
		Paramyxoviruses	Mumps, measles, respiratory syncytial virus
		Coronaviruses	Cold viruses, SARS
		Picornaviruses	Polio, coxsackie, hepatitis A, rhinovirus
		Reoviruses	Rotavirus, reovirus
		Togaviruses	Rubella, arthropod-borne encephalitis
		Flaviviruses	Arthropod-borne viruses, (yellow fever, dengue fever)
		Arenaviruses	Lymphocytic choriomeningitis, Lassa fever
		Rhabdoviruses	Rabies
		Retroviruses	Human T-cell leukemia virus, HIV

Figure 2-2 part 1 of 3 Immunobiology, 7ed. (© Garland Science 2008)

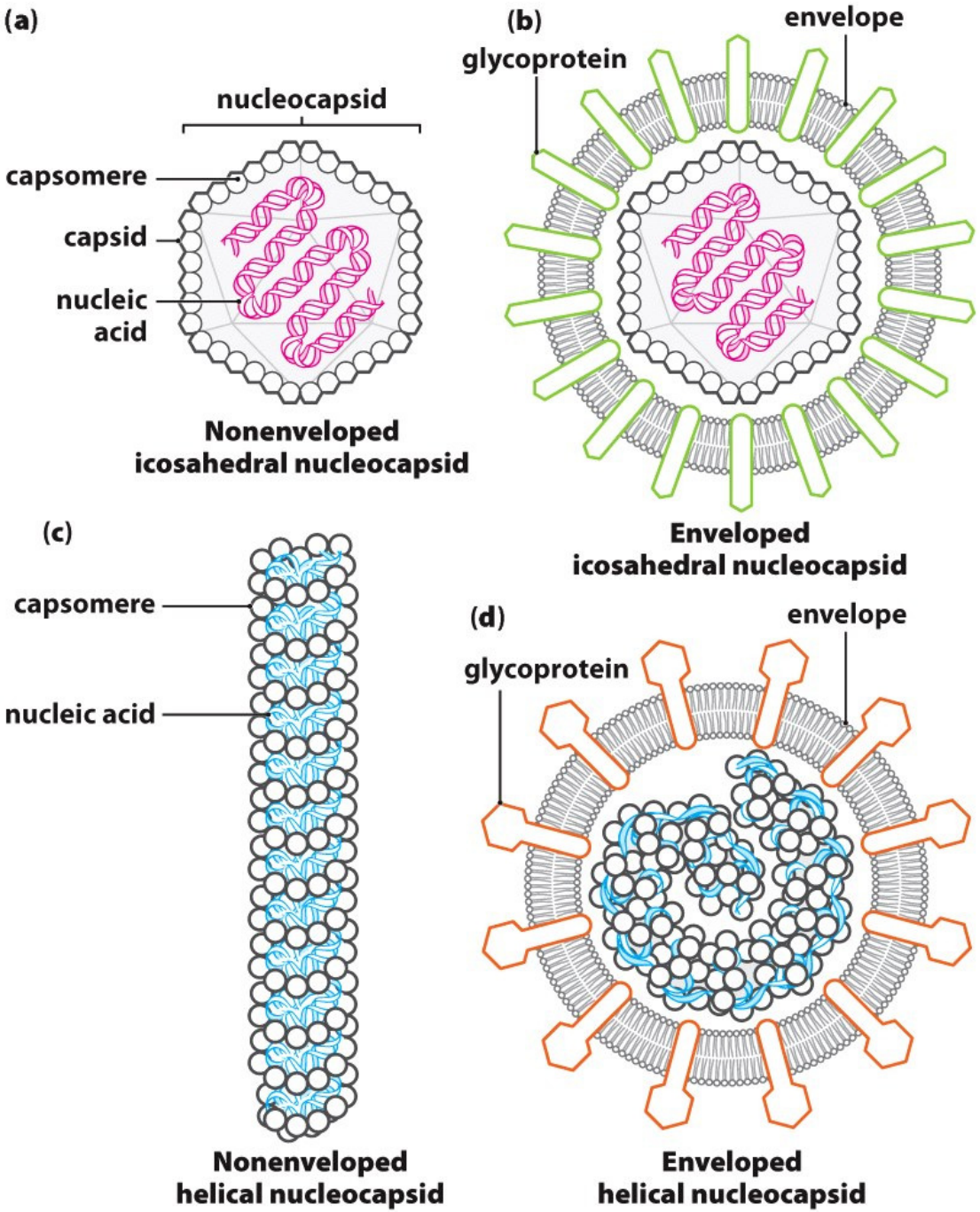


Figure 4.26 Living in a Microbial World (© Garland Science)

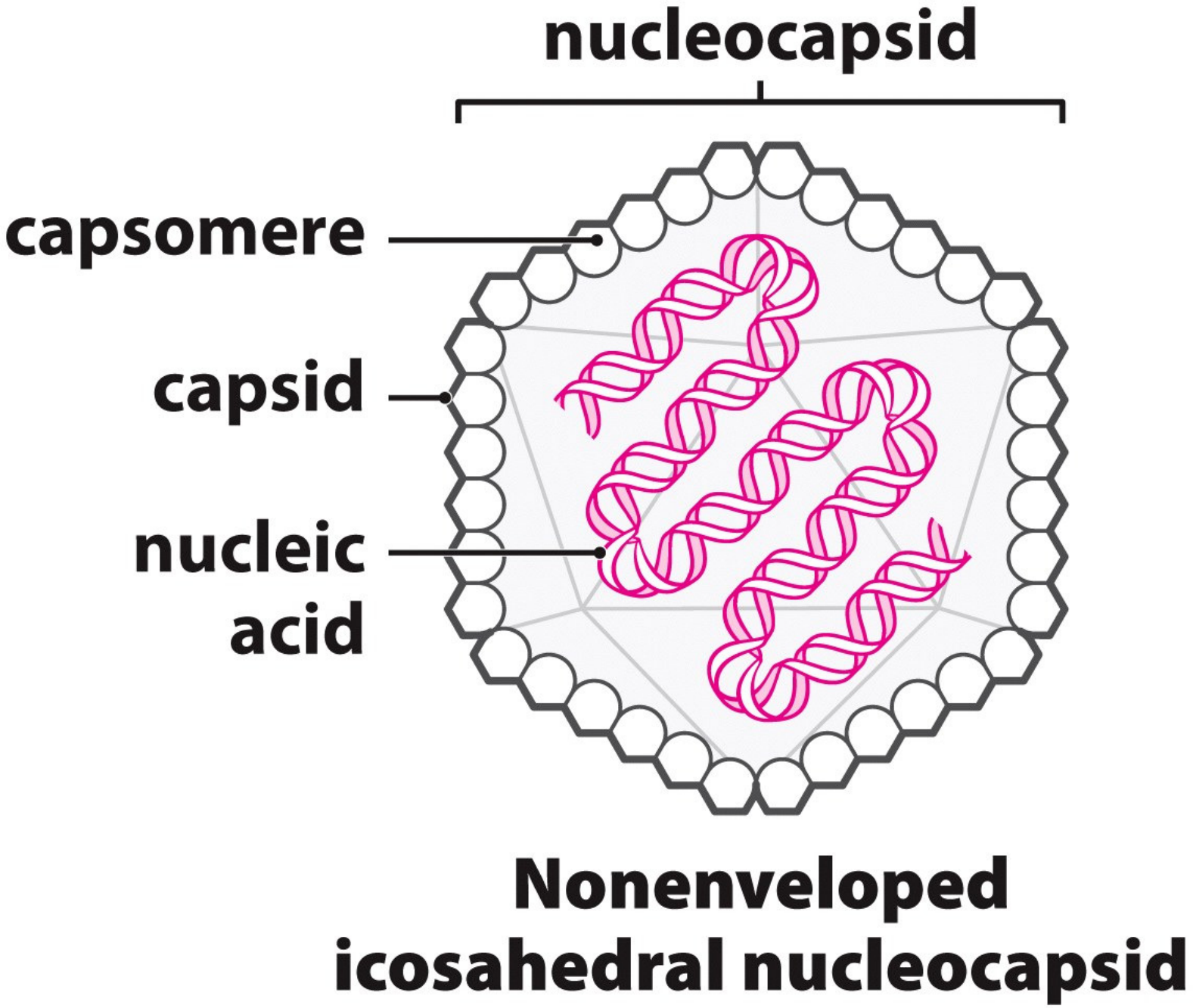


Figure 4.26a Living in a Microbial World (© Garland Science)

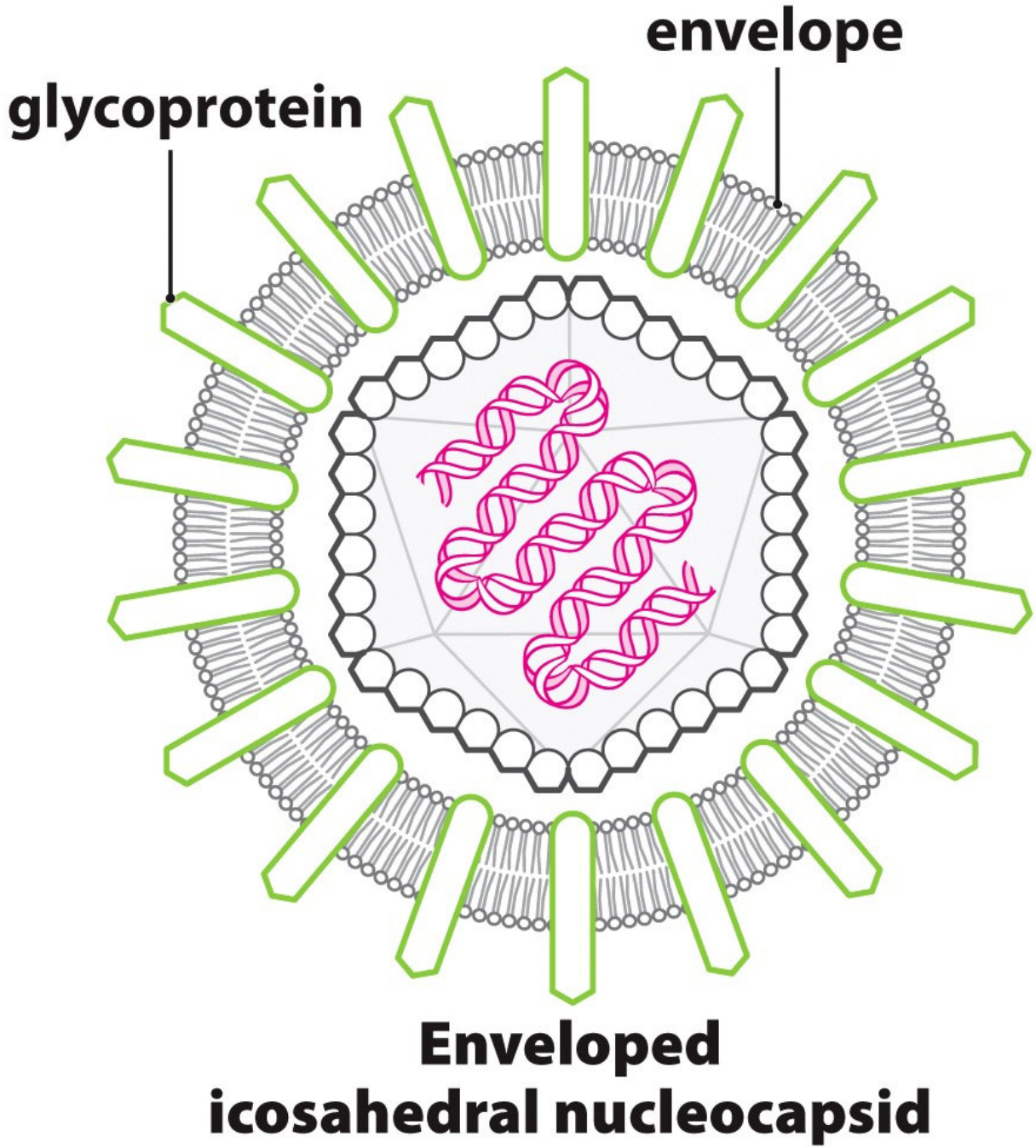


Figure 4.26b Living in a Microbial World (© Garland Science)

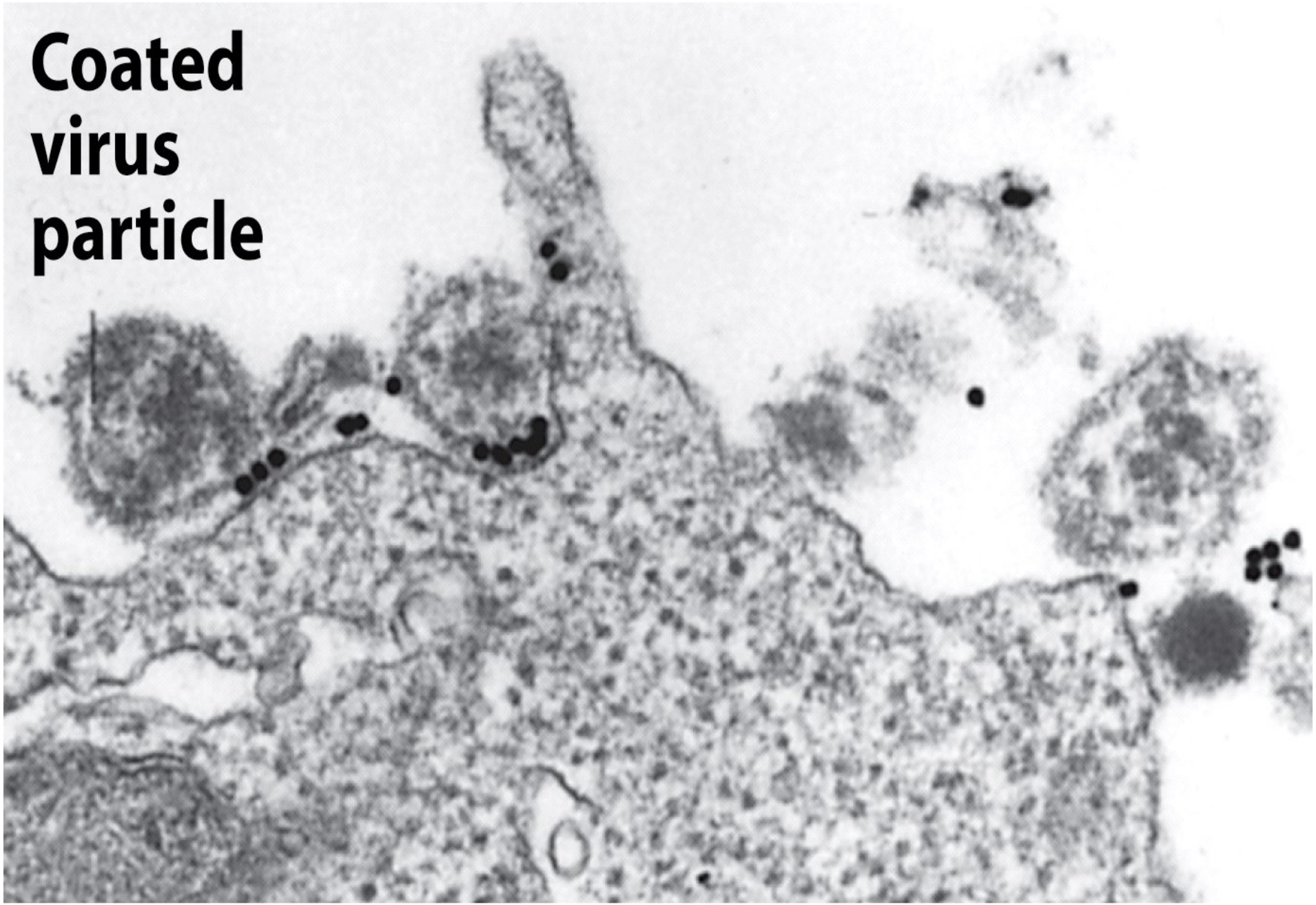


Figure 7-13b
Kuby IMMUNOLOGY, Sixth Edition

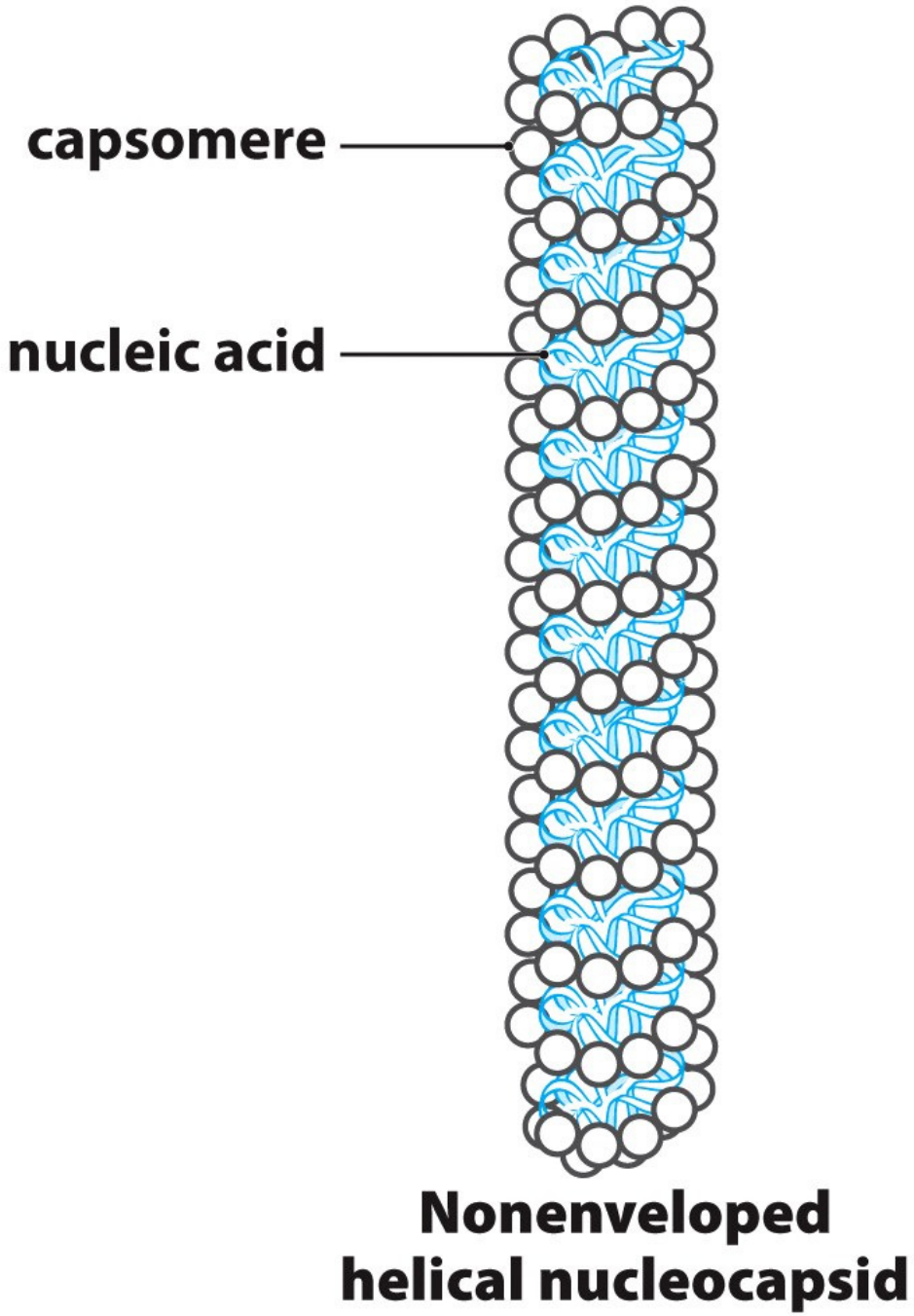


Figure 4.26c Living in a Microbial World (© Garland Science)

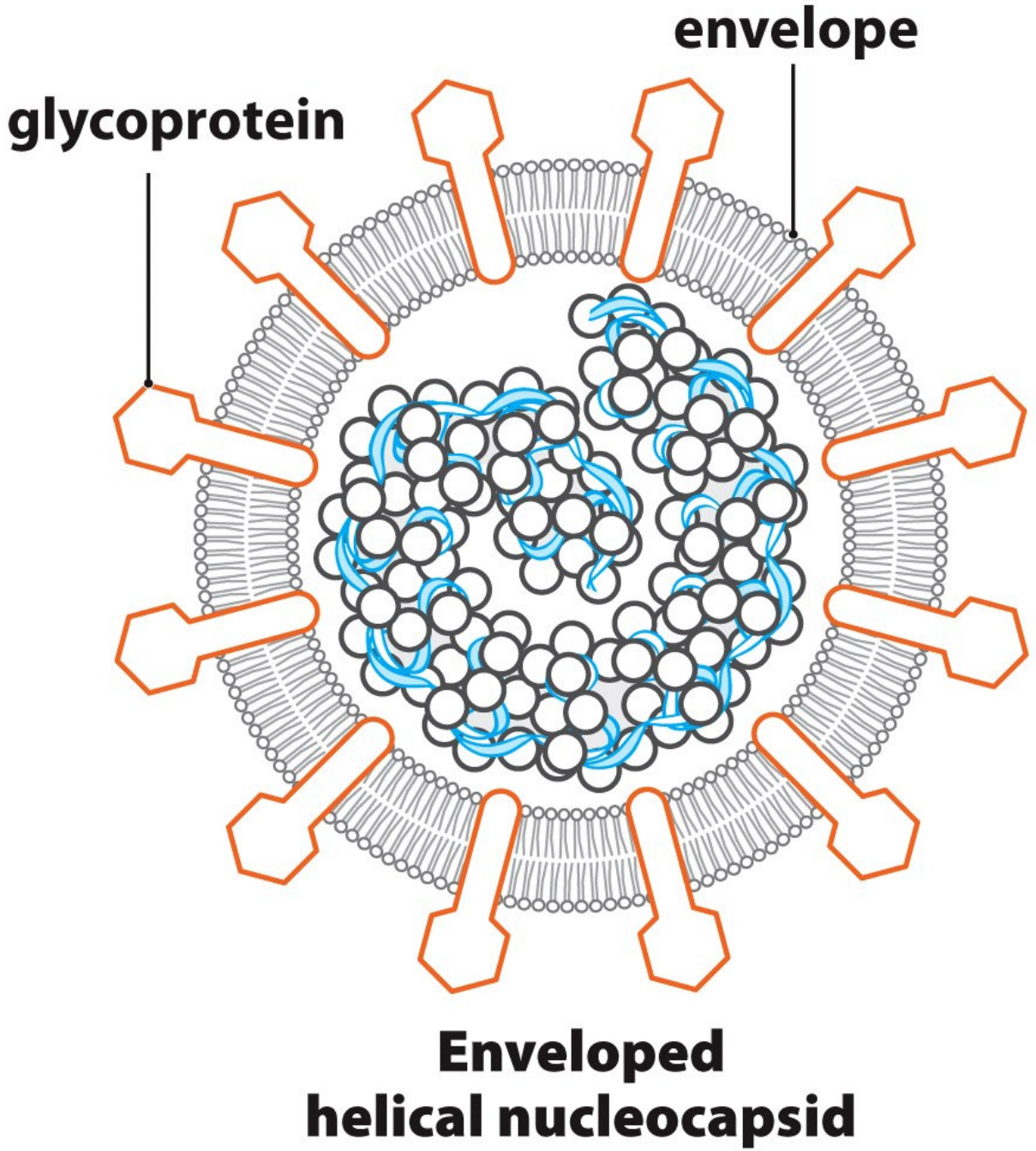


Figure 4.26d Living in a Microbial World (© Garland Science)

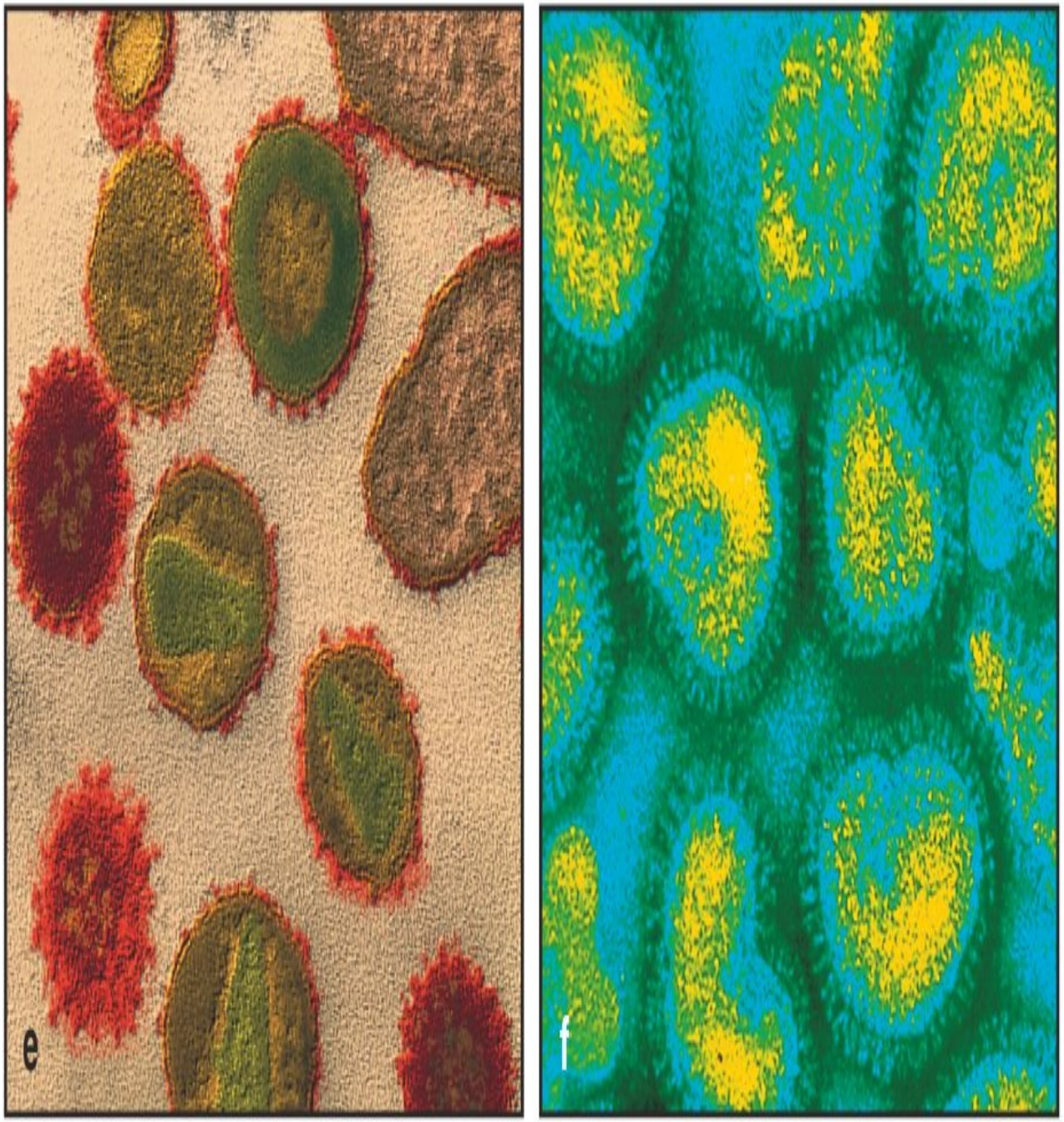


Figure 1-3 part 2 of 4 The Immune System, 2/e (© Garland Science 2005)

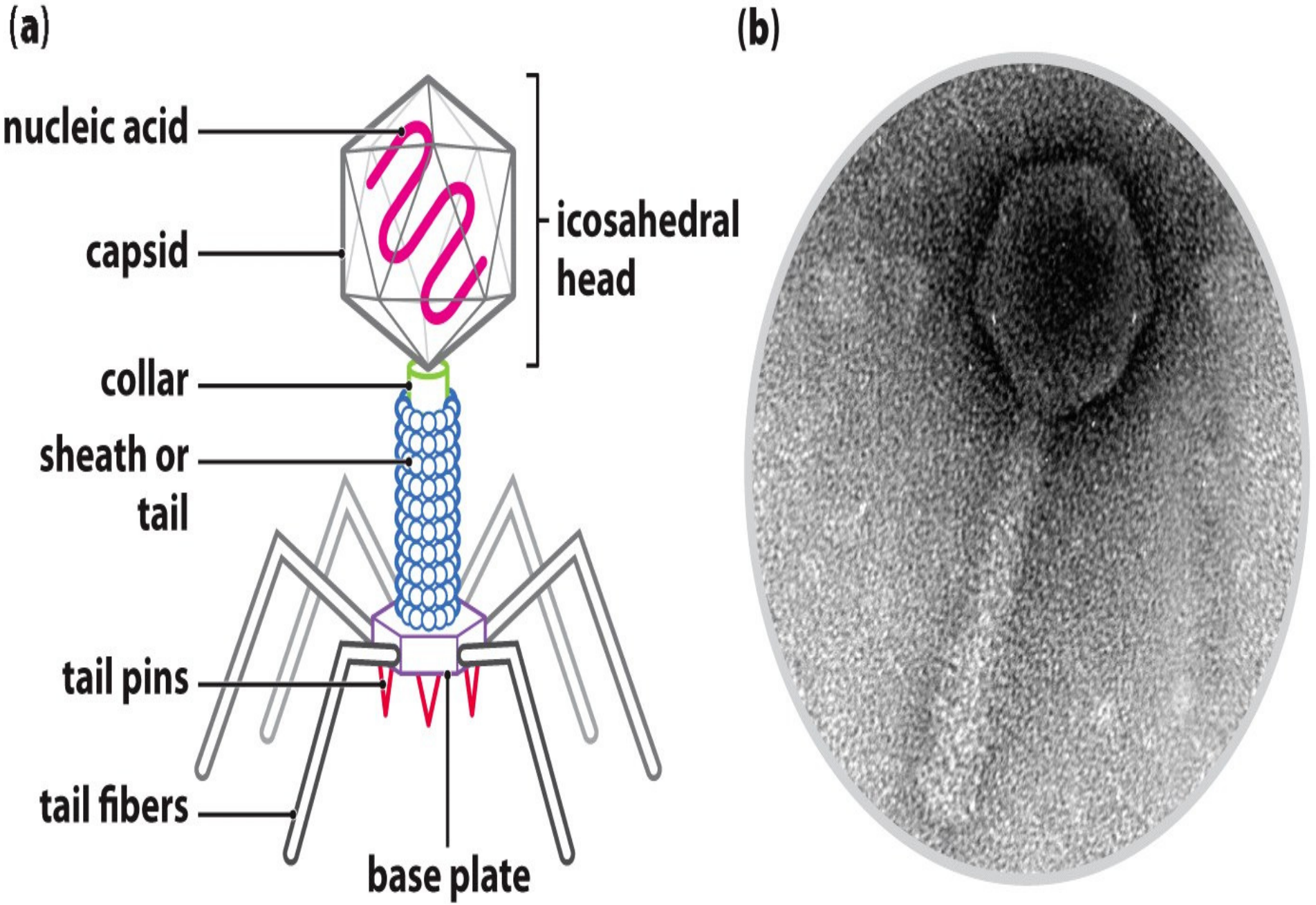


Figure 4.35 Living in a Microbial World (© Garland Science)

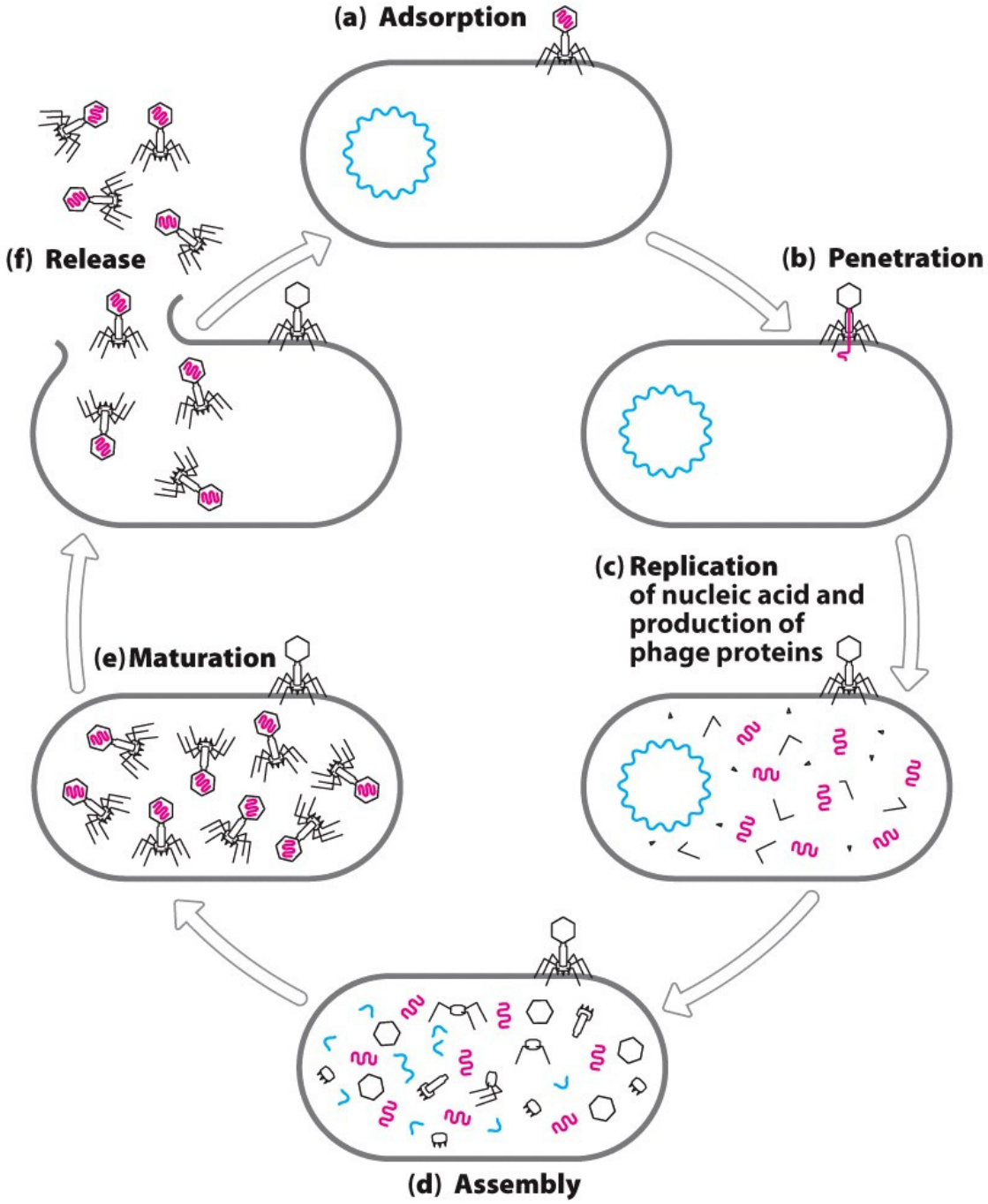


Figure 4.36 Living in a Microbial World (© Garland Science)

Ciclo de replicación viral

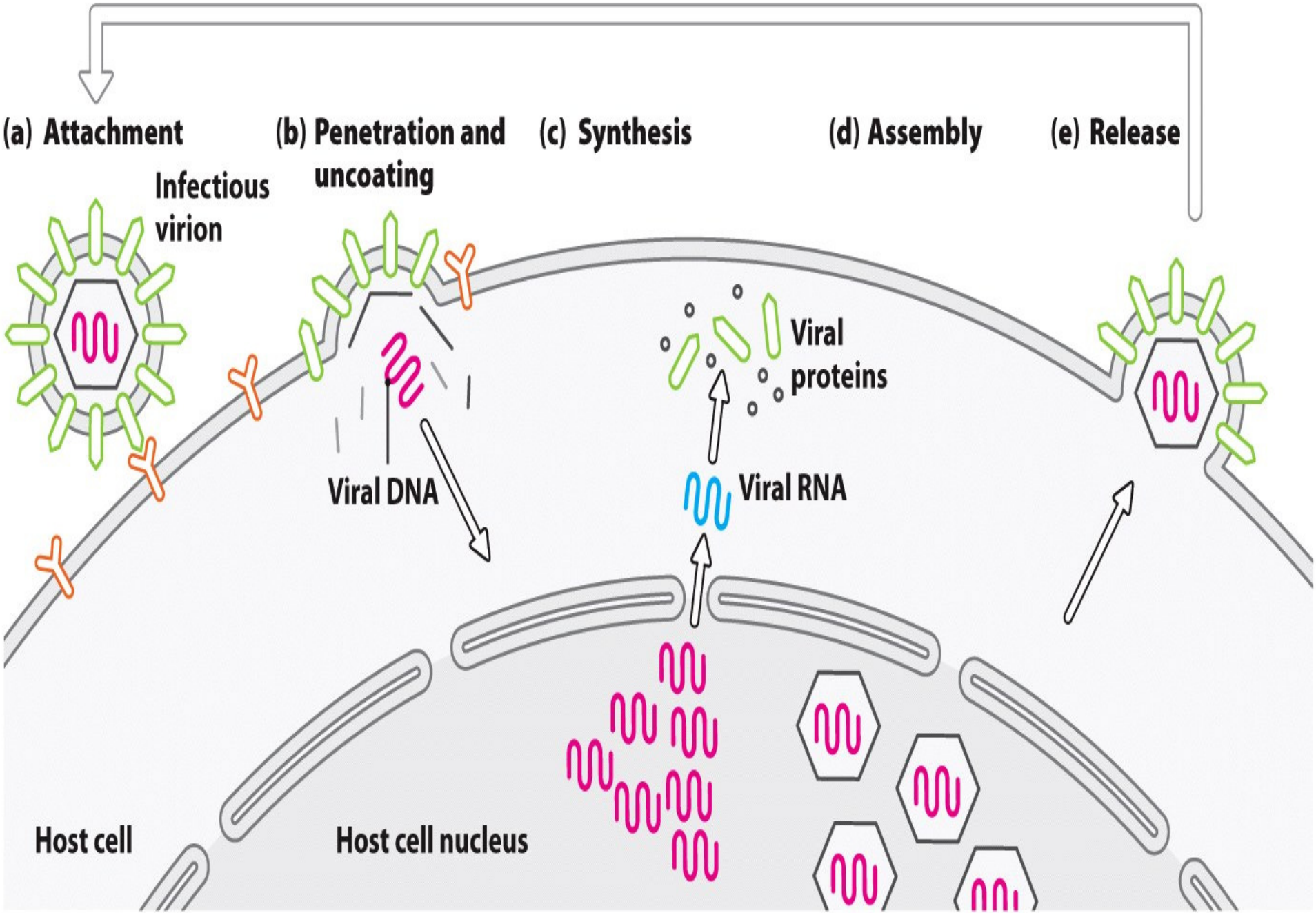


Figure 4.29 Living in a Microbial World (© Garland Science)

Adsorción

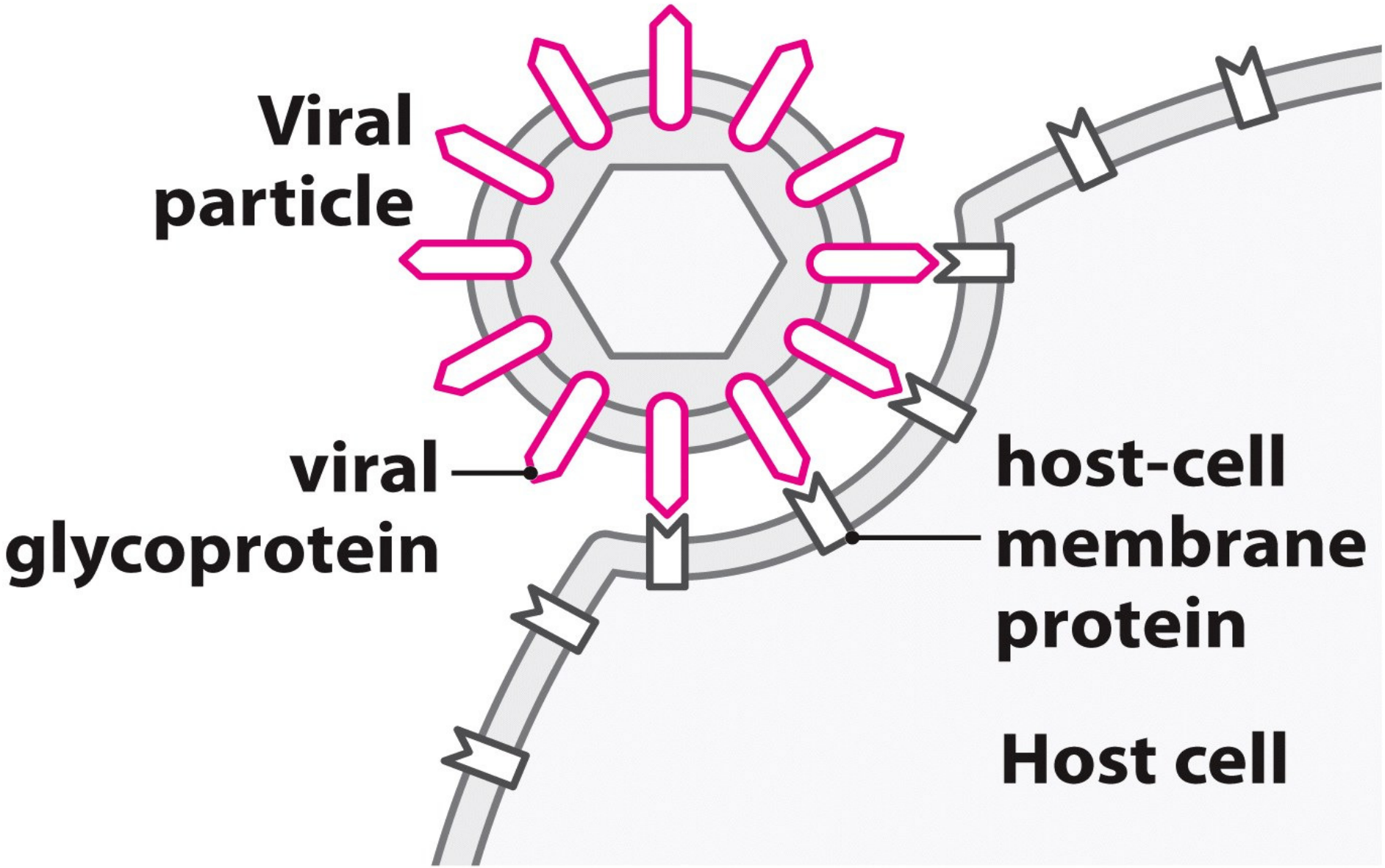


Figure 10.13c Living in a Microbial World (© Garland Science)

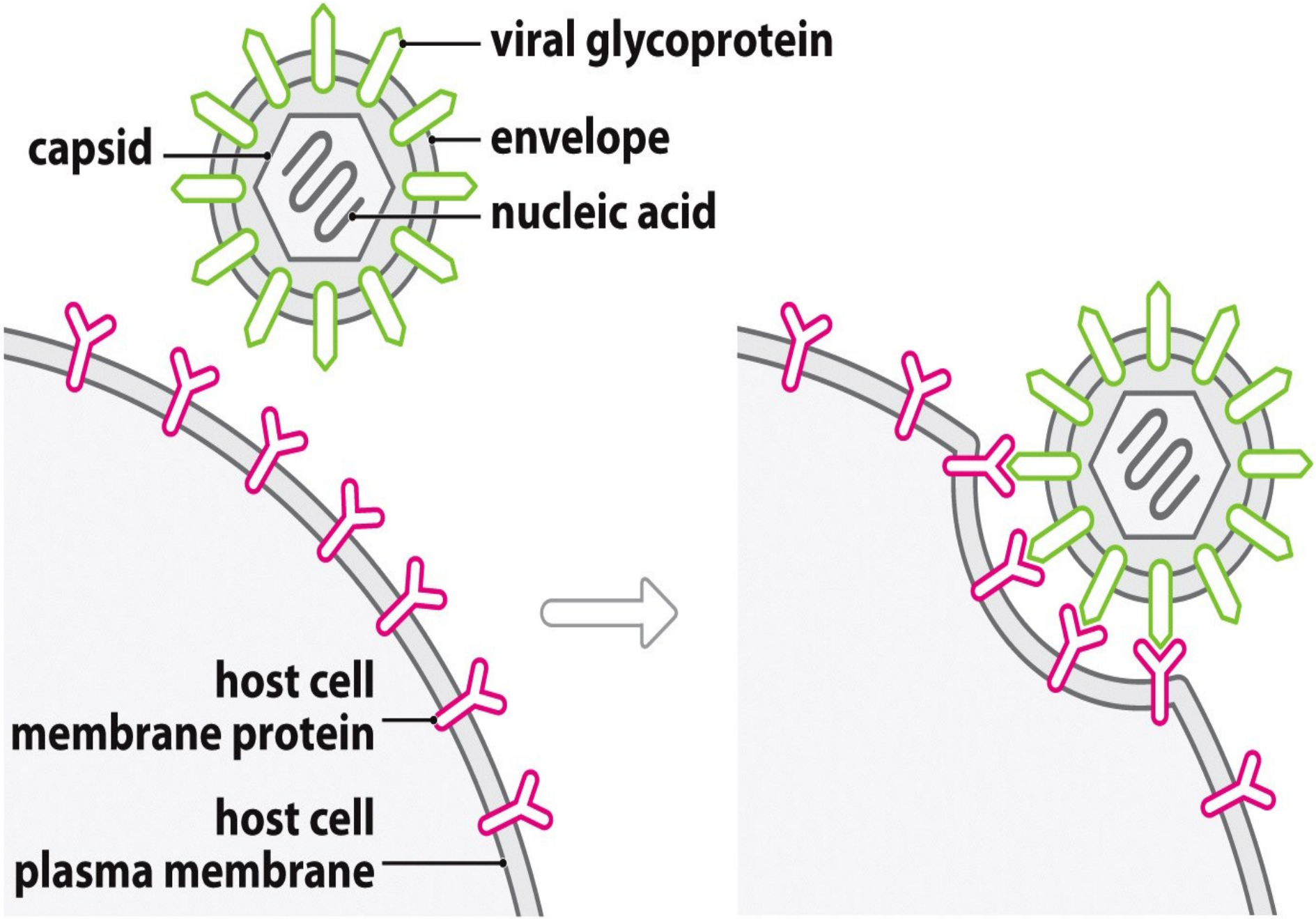


Figure 4.27a Living in a Microbial World (© Garland Science)

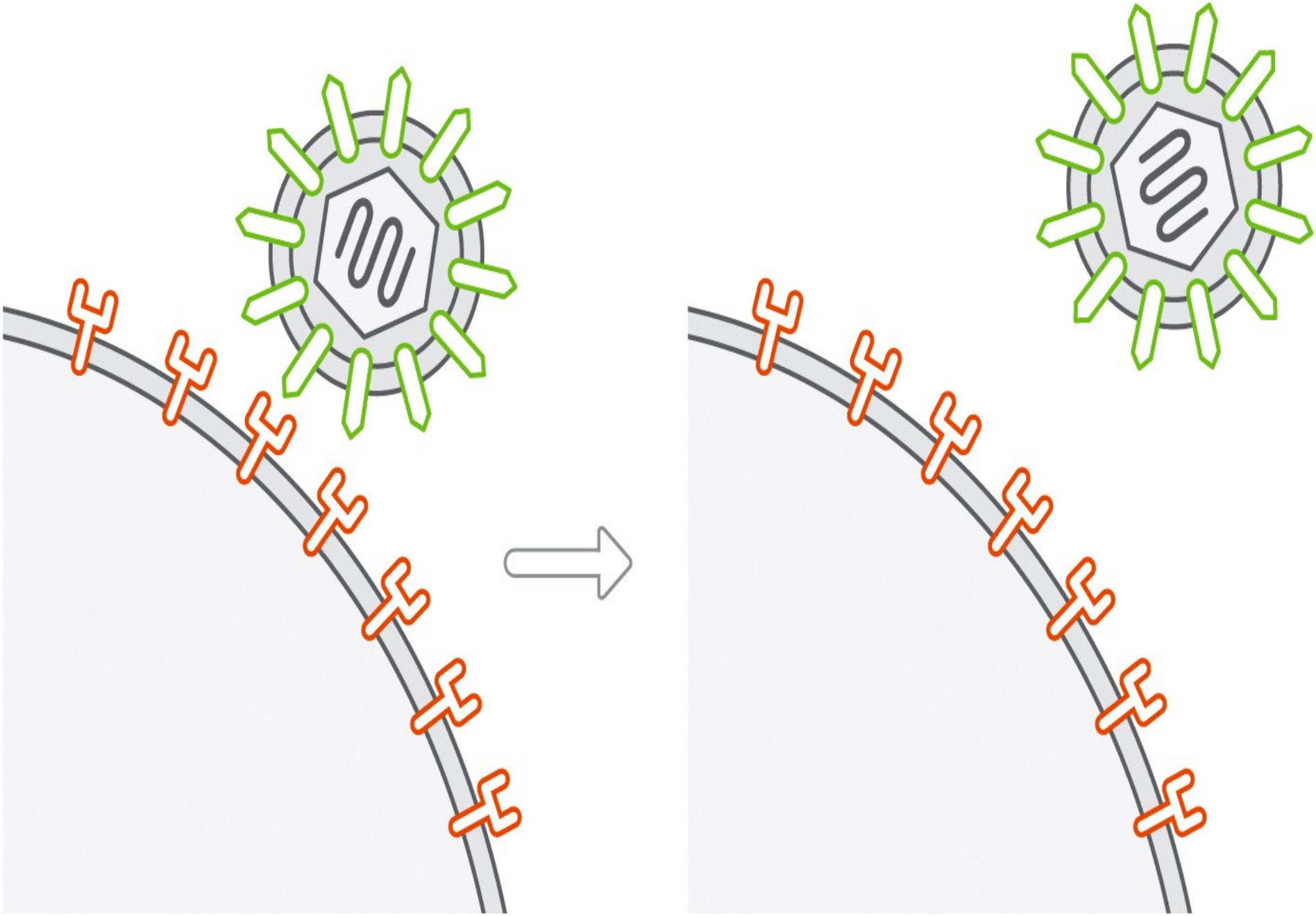


Figure 4.27b Living in a Microbial World (© Garland Science)

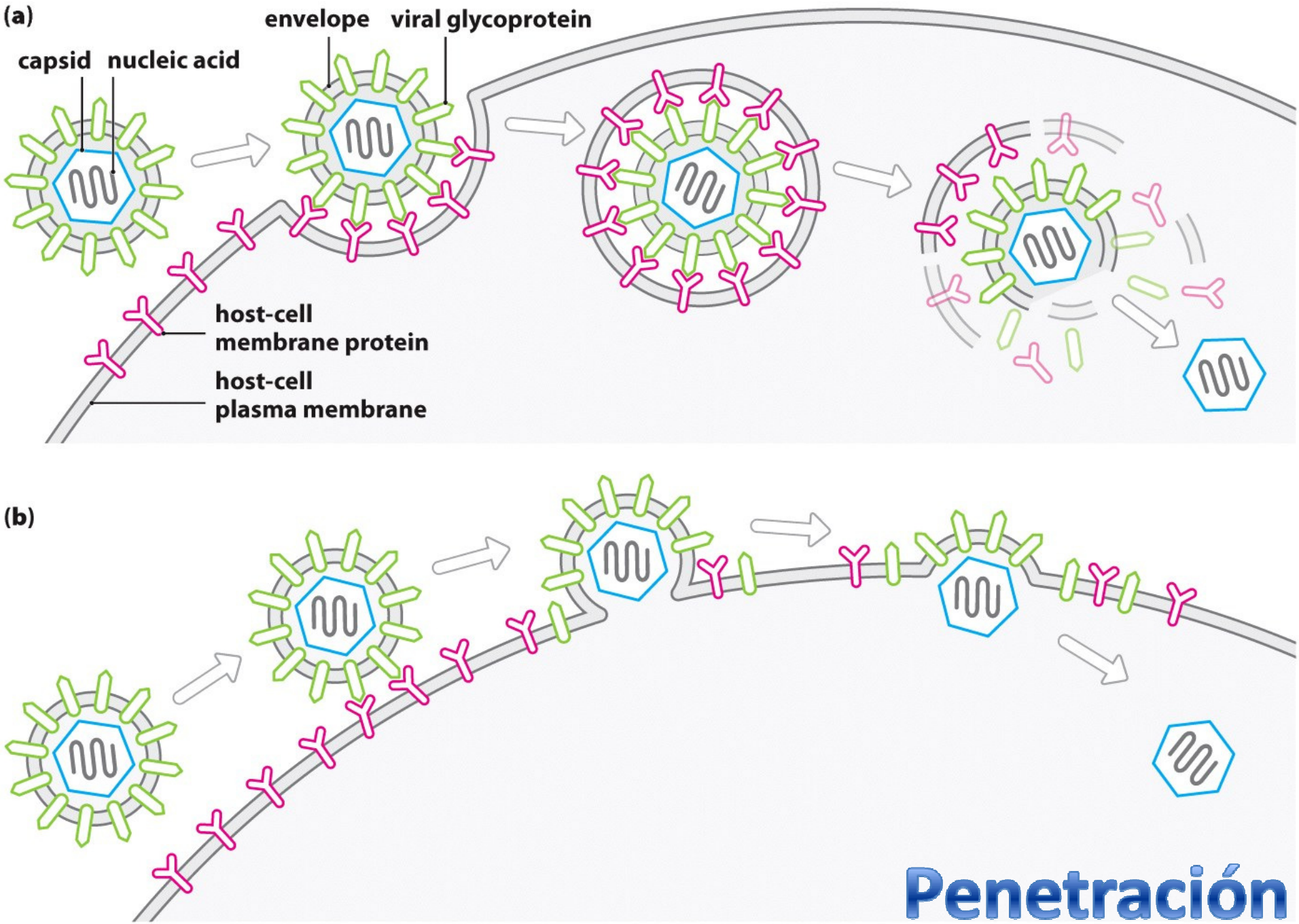


Figure 4.28 Living in a Microbial World (© Garland Science)

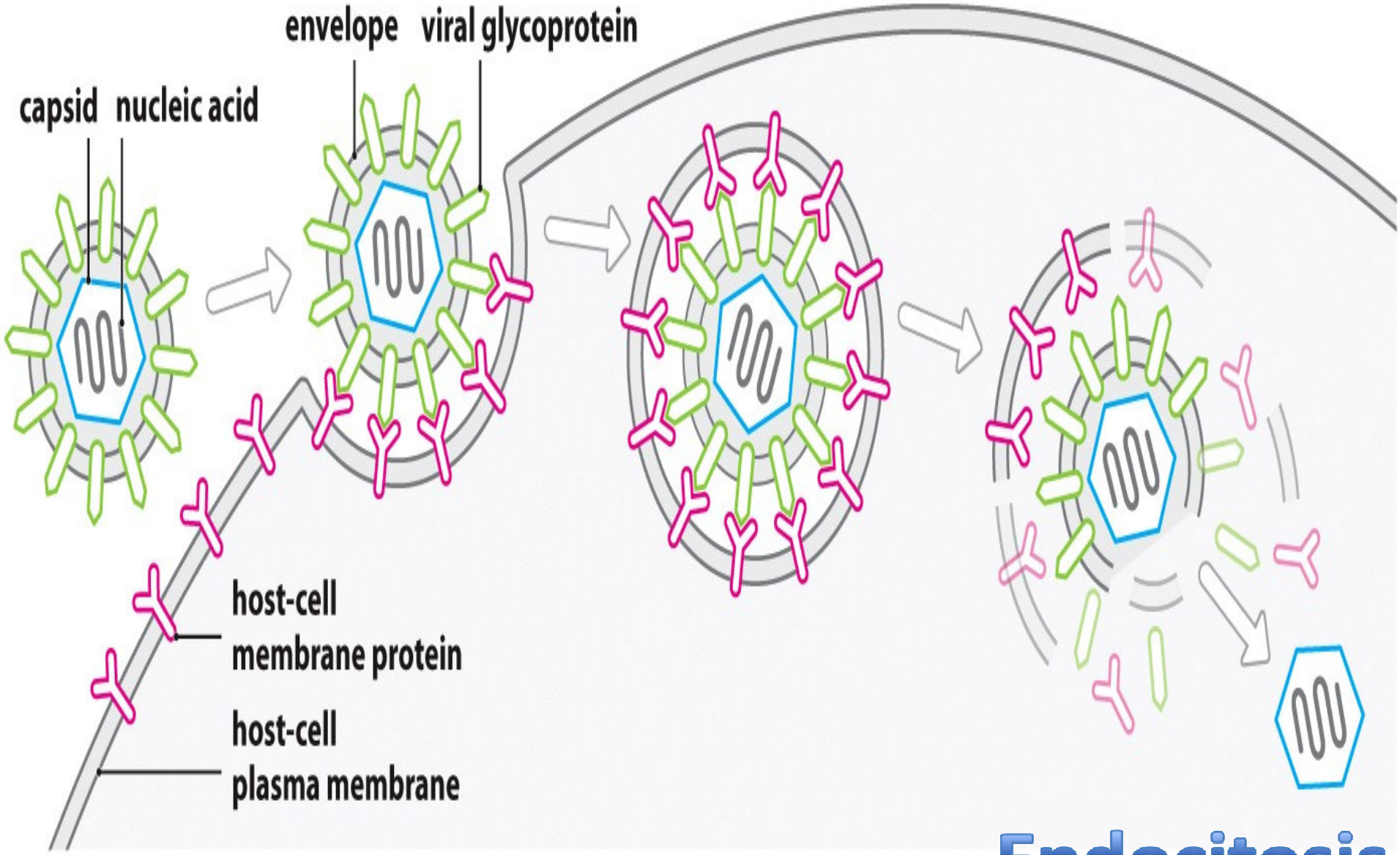


Figure 4.28a Living in a Microbial World (© Garland Science)

Fusión

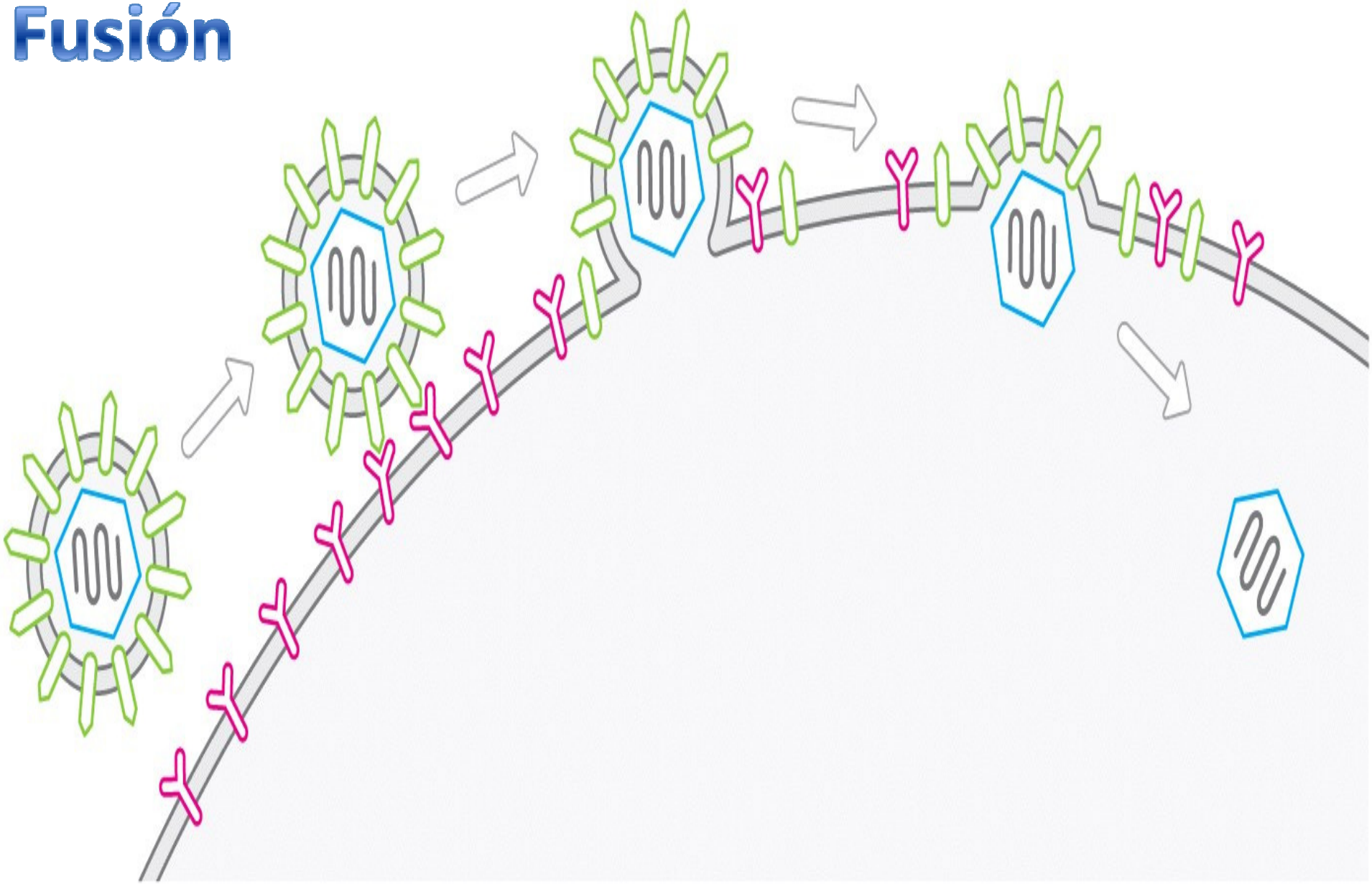


Figure 4.28b Living in a Microbial World (© Garland Science)

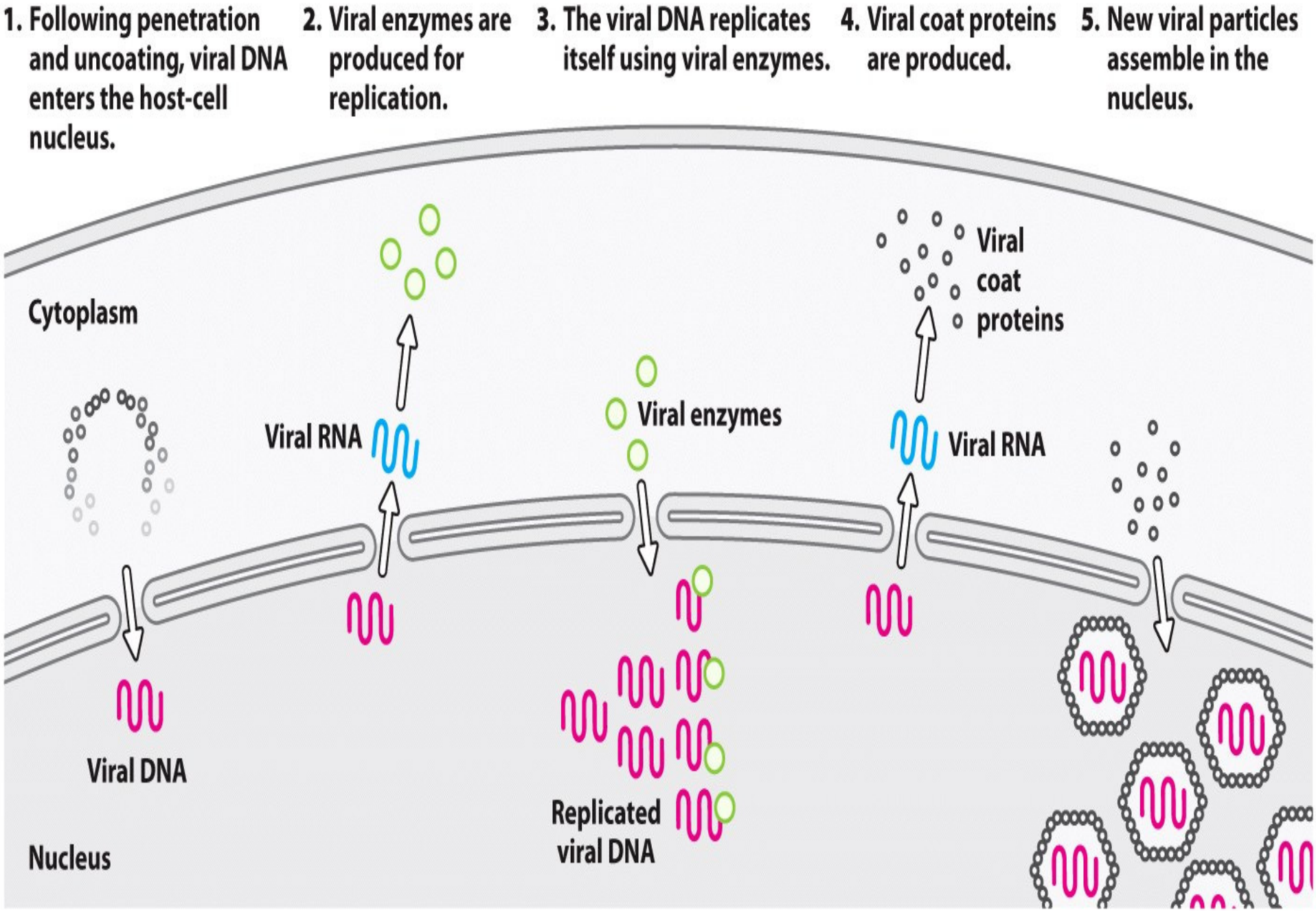


Figure 4.31 Living in a Microbial World (© Garland Science)

Liberación: Brotación o Lisis

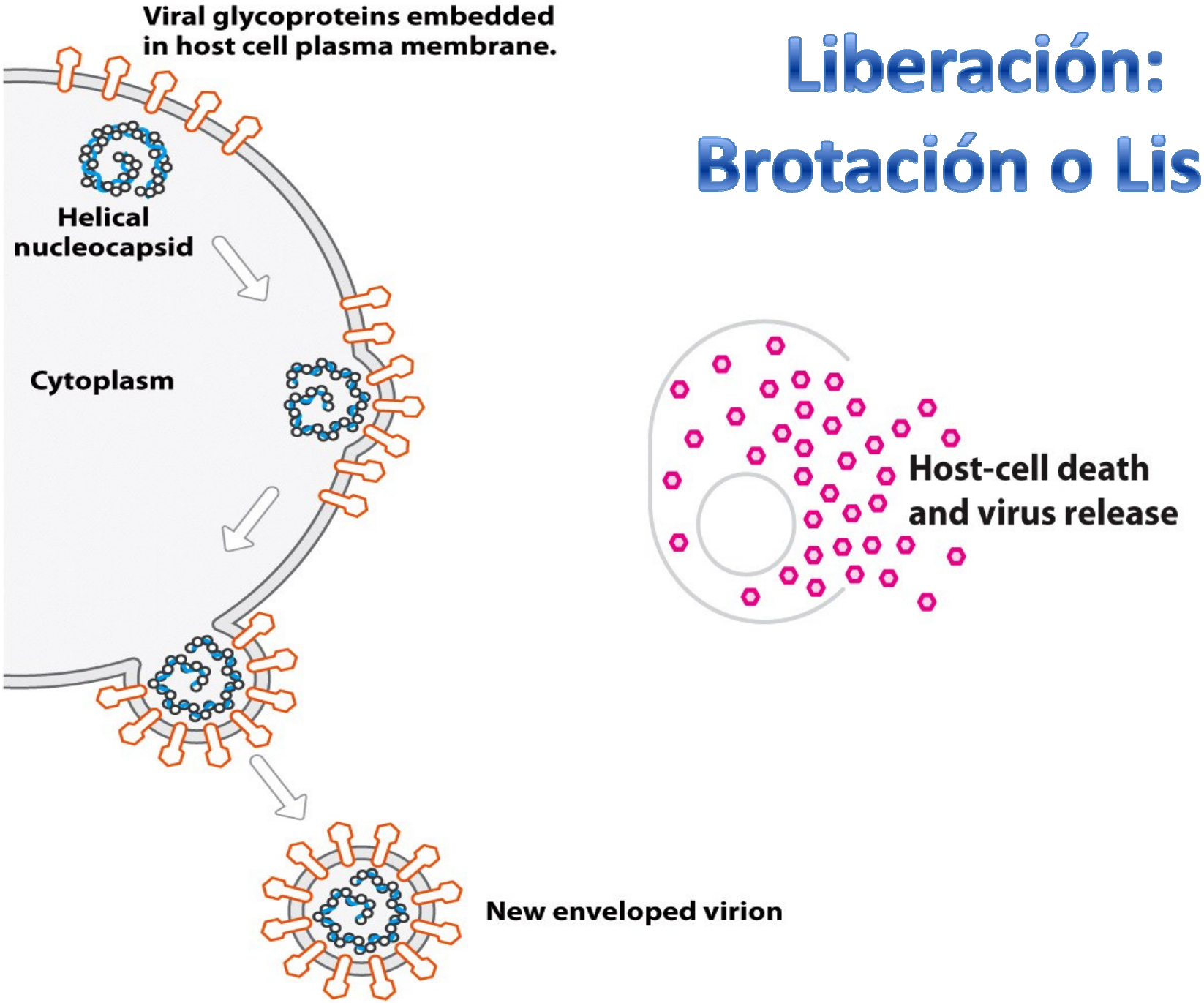


Figure 4.30 Living in a Microbial World (© Garland Science)

Modelos de infección viral

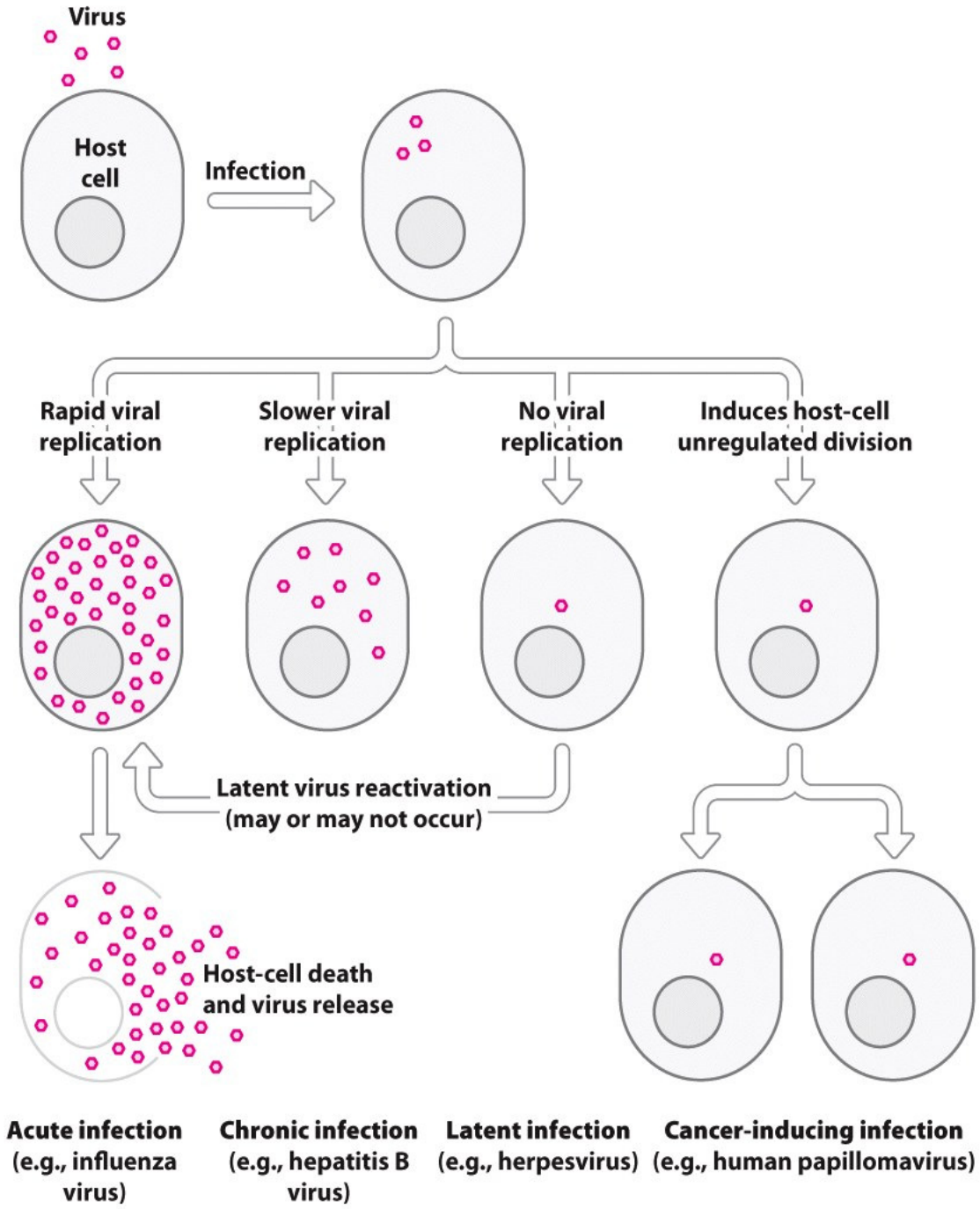


Figure 10.22 Living in a Microbial World (© Garland Science)

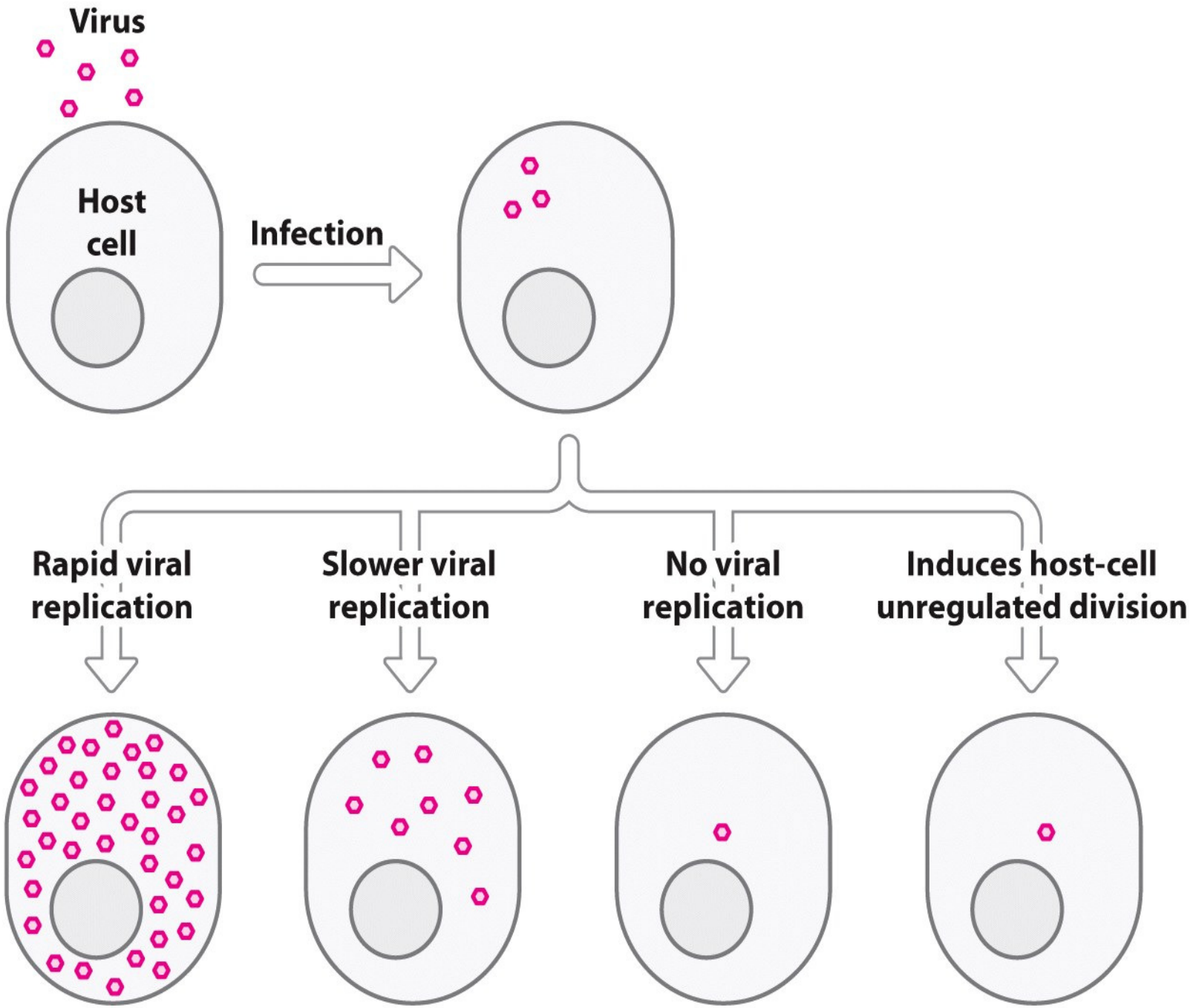


Figure 10.22 part 1 of 2 Living in a Microbial World (© Garland Science)

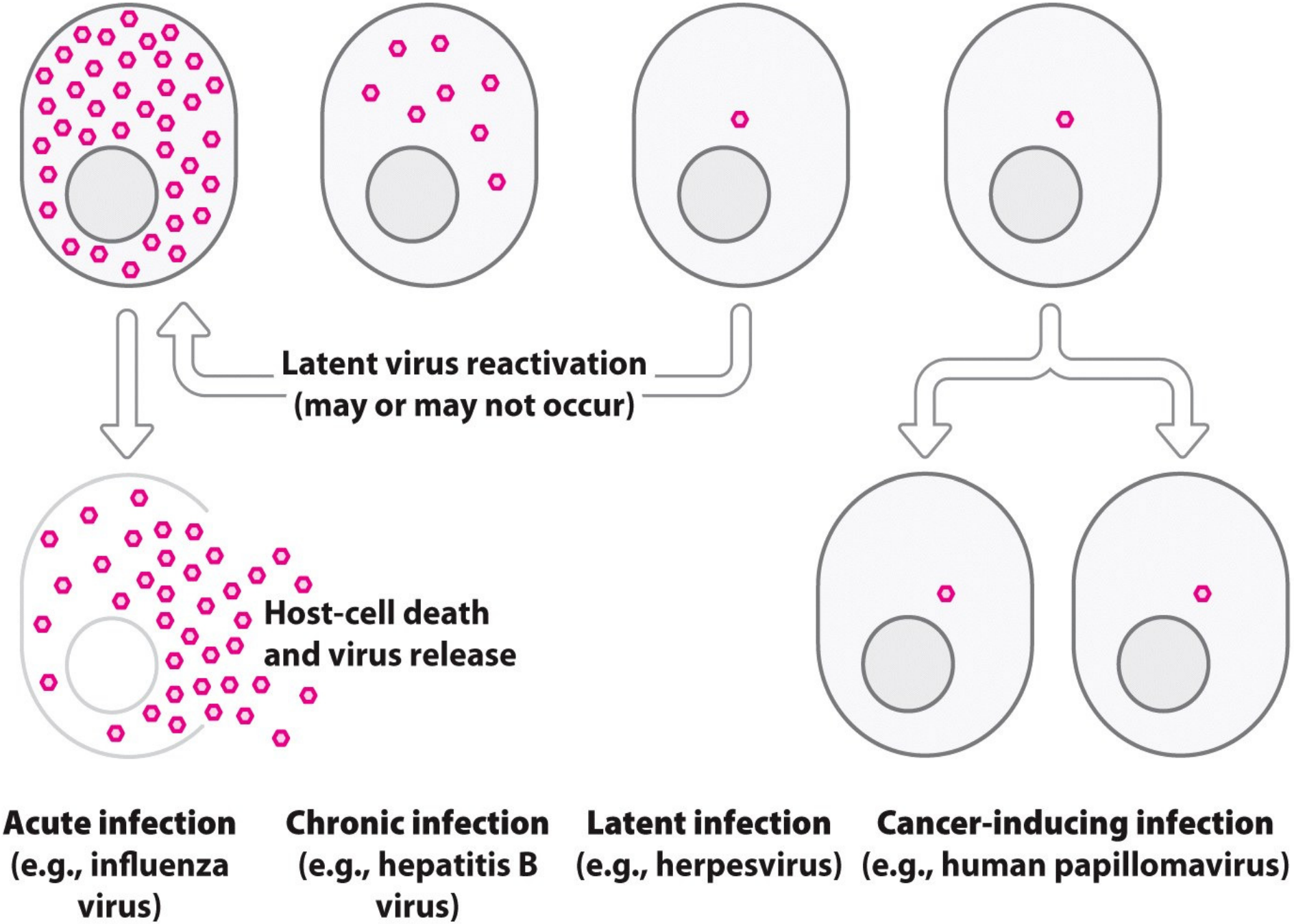


Figure 10.22 part 2 of 2 Living in a Microbial World (© Garland Science)

Time highlighted in pink corresponds to when signs and symptoms of disease are apparent.

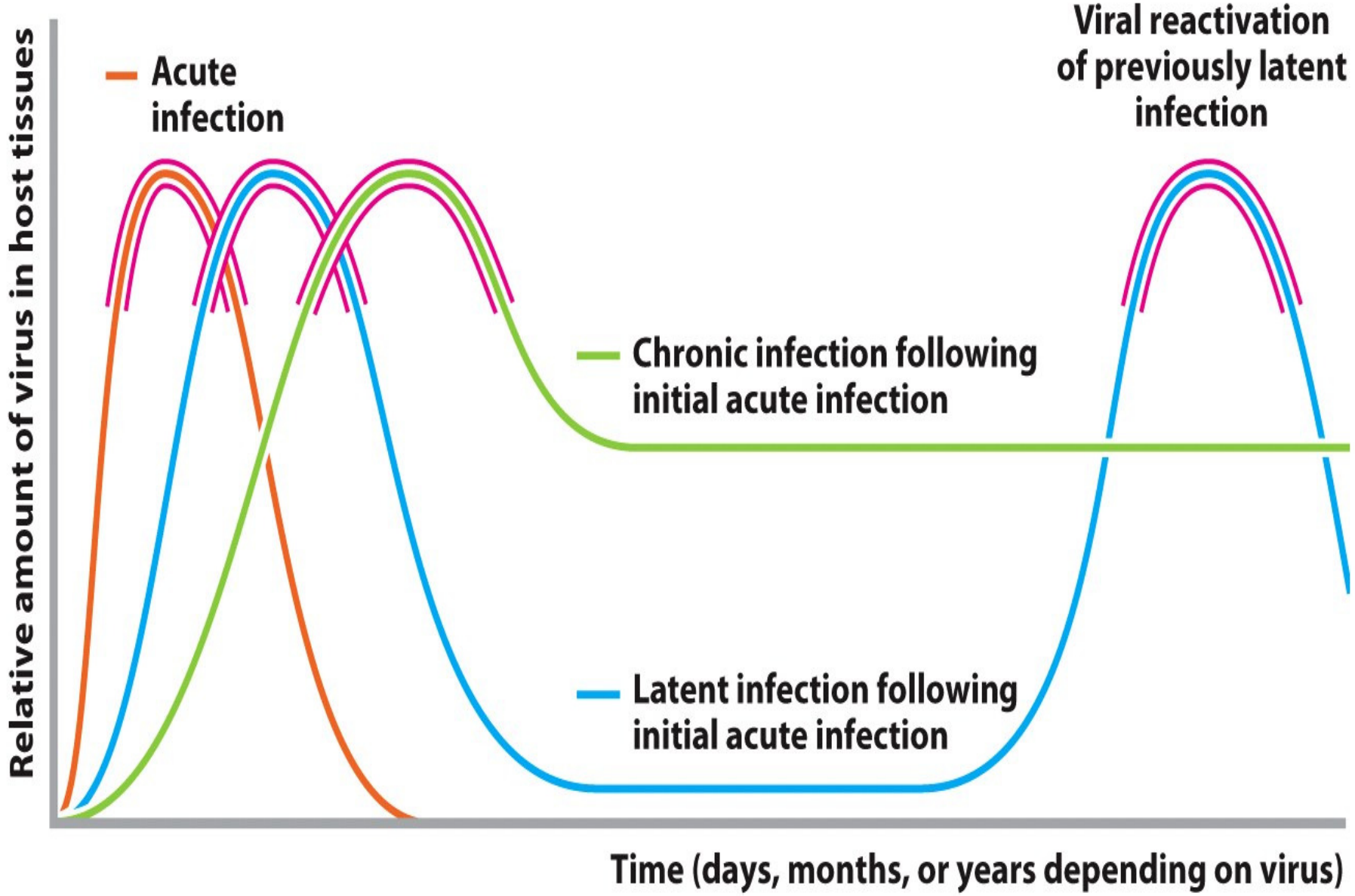


Figure 4.33 Living in a Microbial World (© Garland Science)

INMUNIDAD INNATA

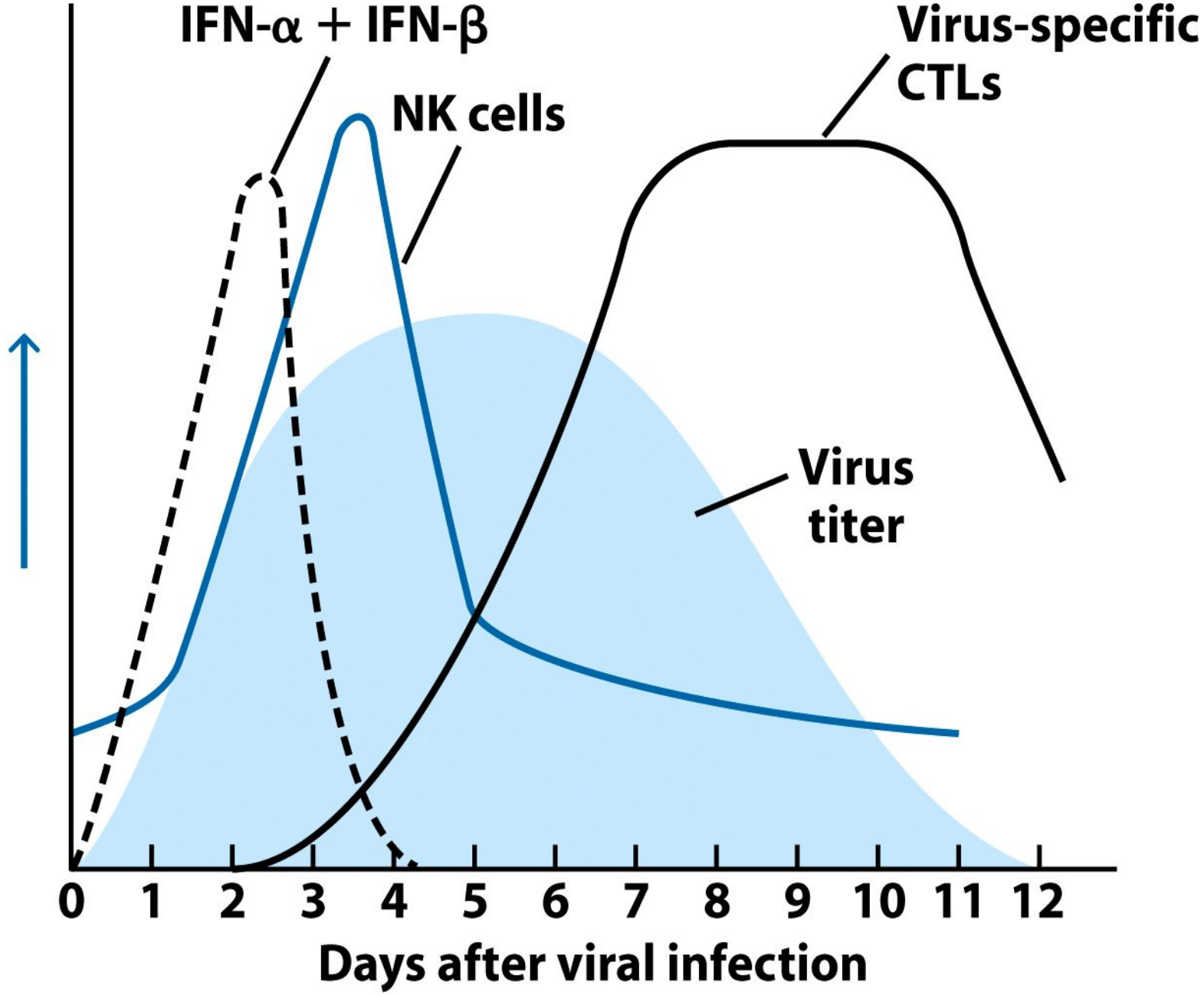


Figure 14-12
Kuby IMMUNOLOGY, Sixth Edition

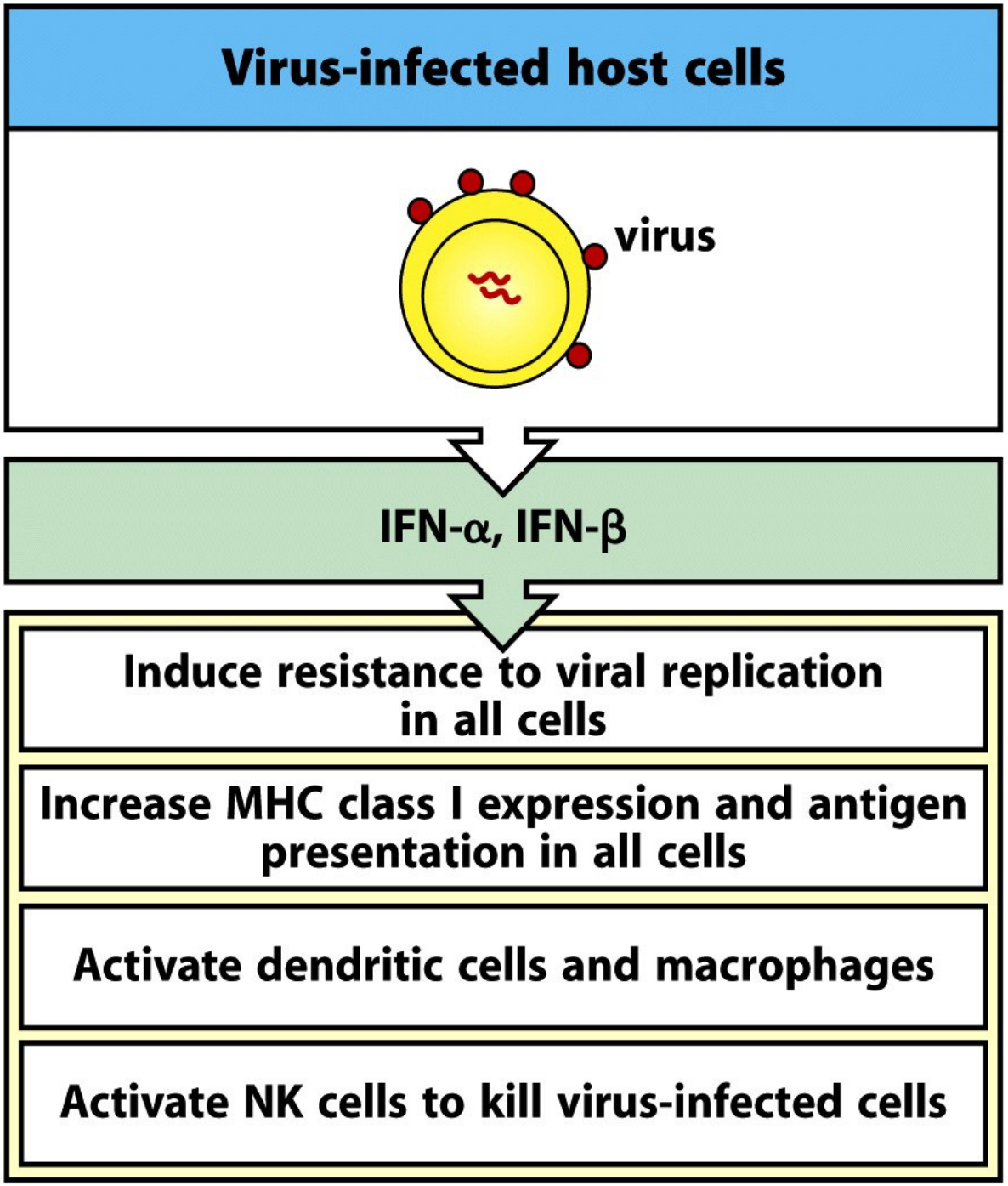


Figure 2-54 Immunobiology, 7ed. (© Garland Science 2008)

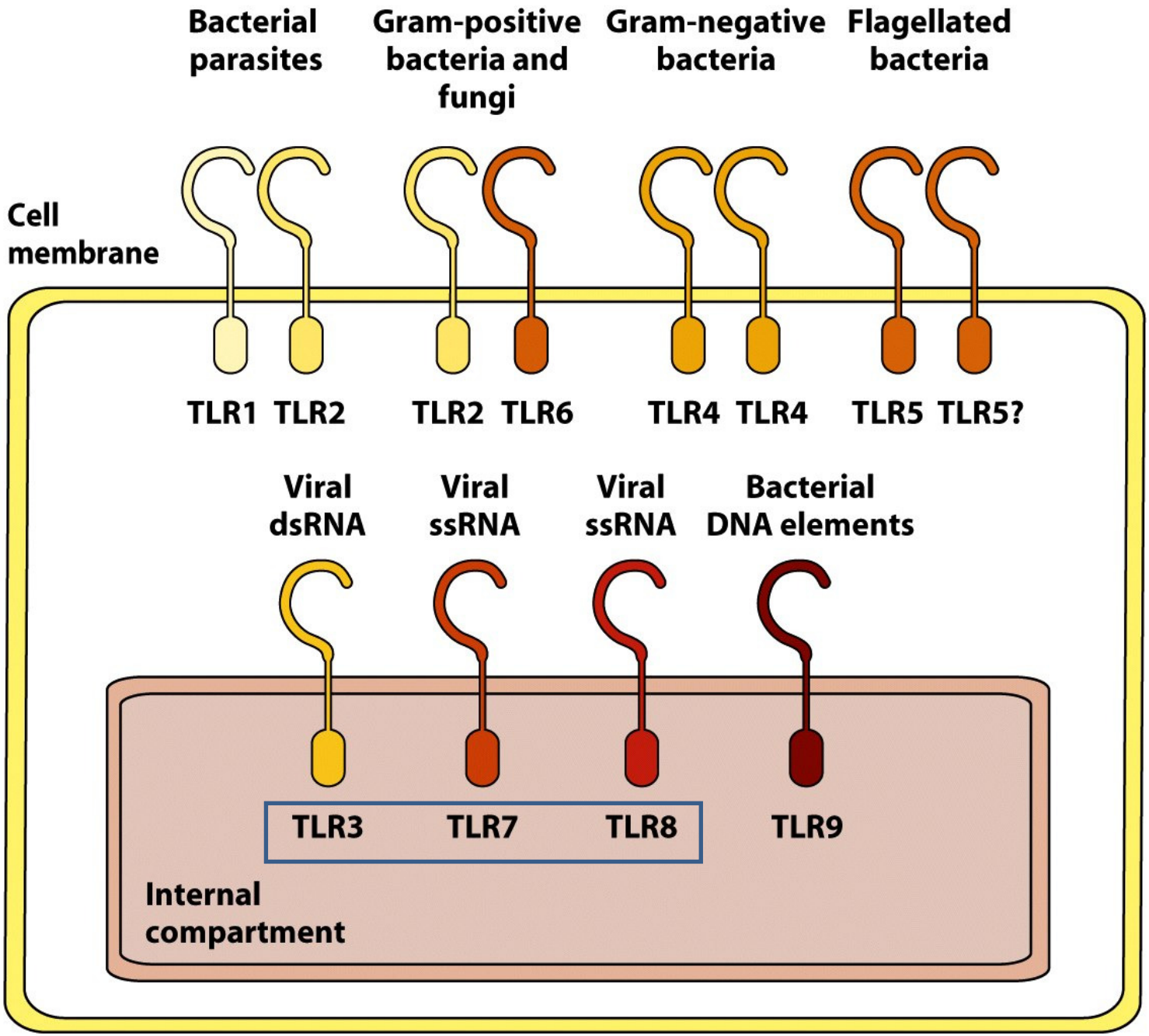


Figure 3-11 part 1
Kuby IMMUNOLOGY, Sixth Edition

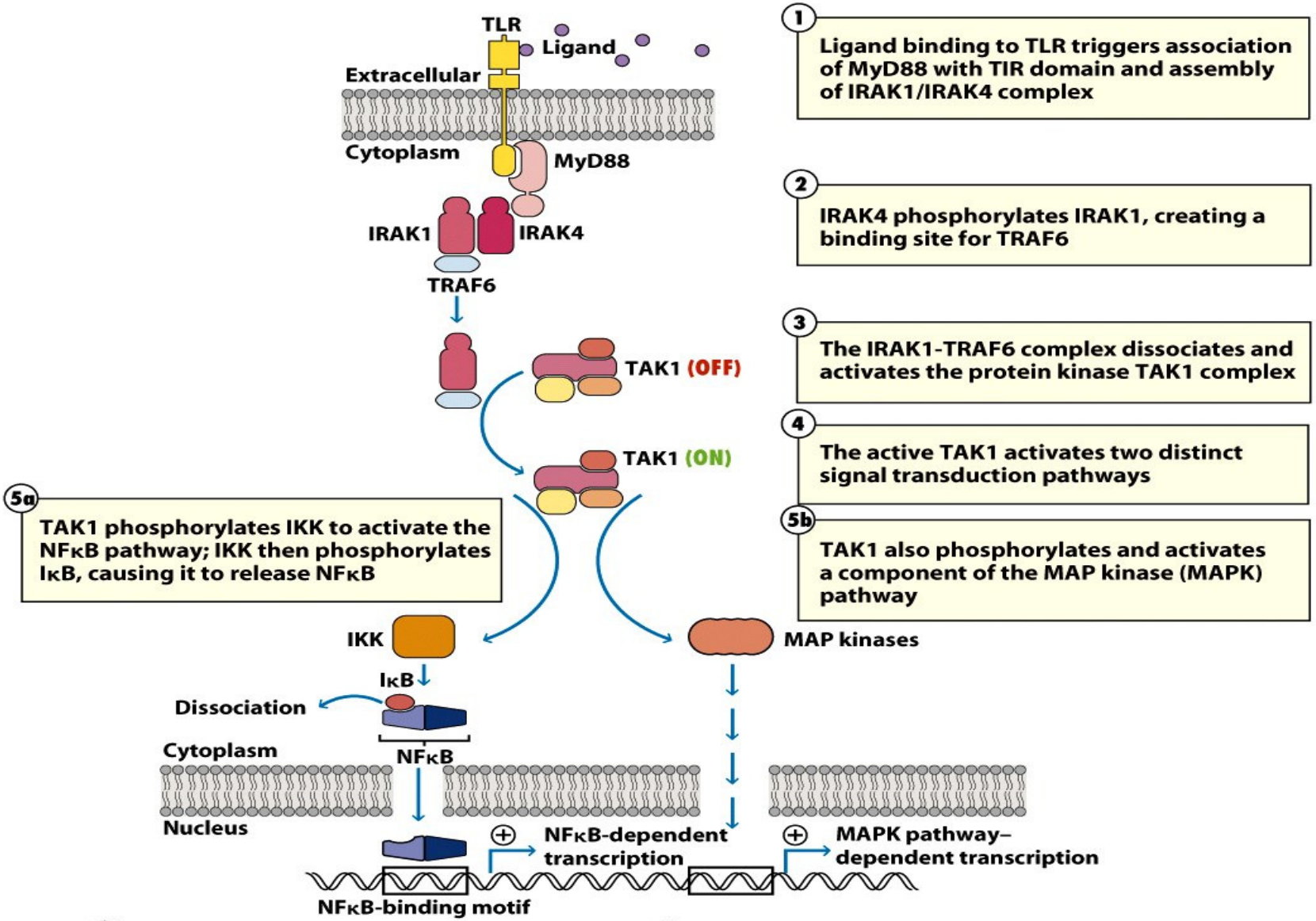
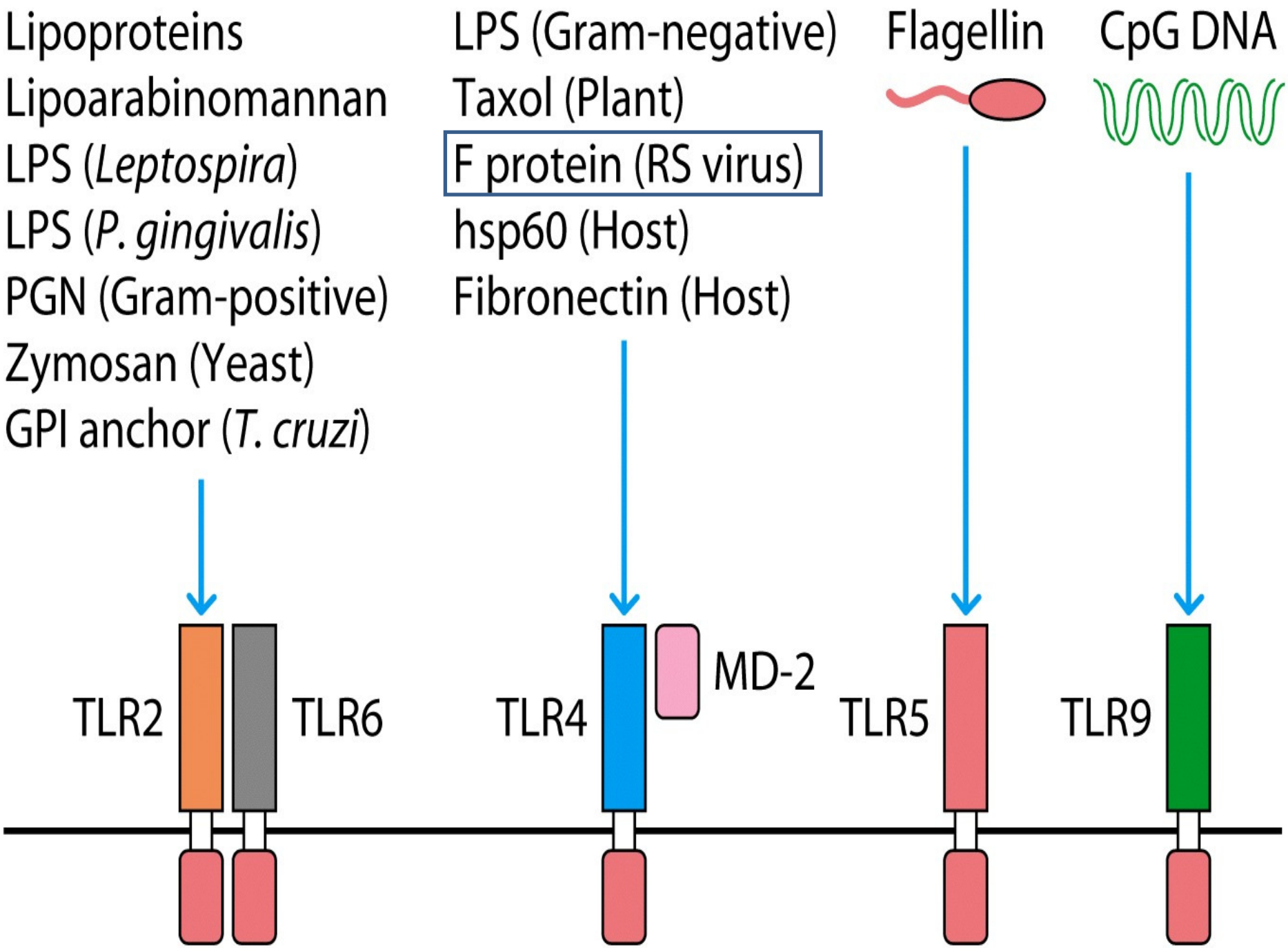


Figure 3-14
Kuby IMMUNOLOGY, Sixth Edition

TLRs	Ligands	Target microbes
TLR1	Triacyl lipopeptides	Mycobacteria
TLR2	Peptidoglycans GPI-linked proteins Lipoproteins Zymosan	Gram-positive bacteria Trypanosomes Mycobacteria Yeasts and other fungi
TLR3	Double-stranded RNA (dsRNA)	Viruses
TLR4	LPS F-protein	Gram-negative bacteria Respiratory syncytial virus (RSV)
TLR5	Flagellin	Bacteria
TLR6	Diacyl lipopeptides Zymosan	Mycobacteria Yeasts and fungi
TLR7	Single-stranded RNA (ssRNA)	Viruses
TLR8	Single-stranded RNA (ssRNA)	Viruses
TLR9	CpG unmethylated dinucleotides Dinucleotides Herpesvirus infection	Bacterial DNA Some herpesviruses
TLR10,11	Unknown	Unknown

Figure 3-11 part 2
Kuby IMMUNOLOGY, Sixth Edition


Lipoproteins
Lipoarabinomannan
LPS (*Leptospira*)
LPS (*P. gingivalis*)
PGN (Gram-positive)
Zymosan (Yeast)
GPI anchor (*T. cruzi*)
LPS (Gram-negative)
Taxol (Plant)
F protein (RS virus)
hsp60 (Host)
Fibronectin (Host)
Flagellin
CpG DNA
TLR2
TLR6
TLR4
MD-2
TLR5
TLR9

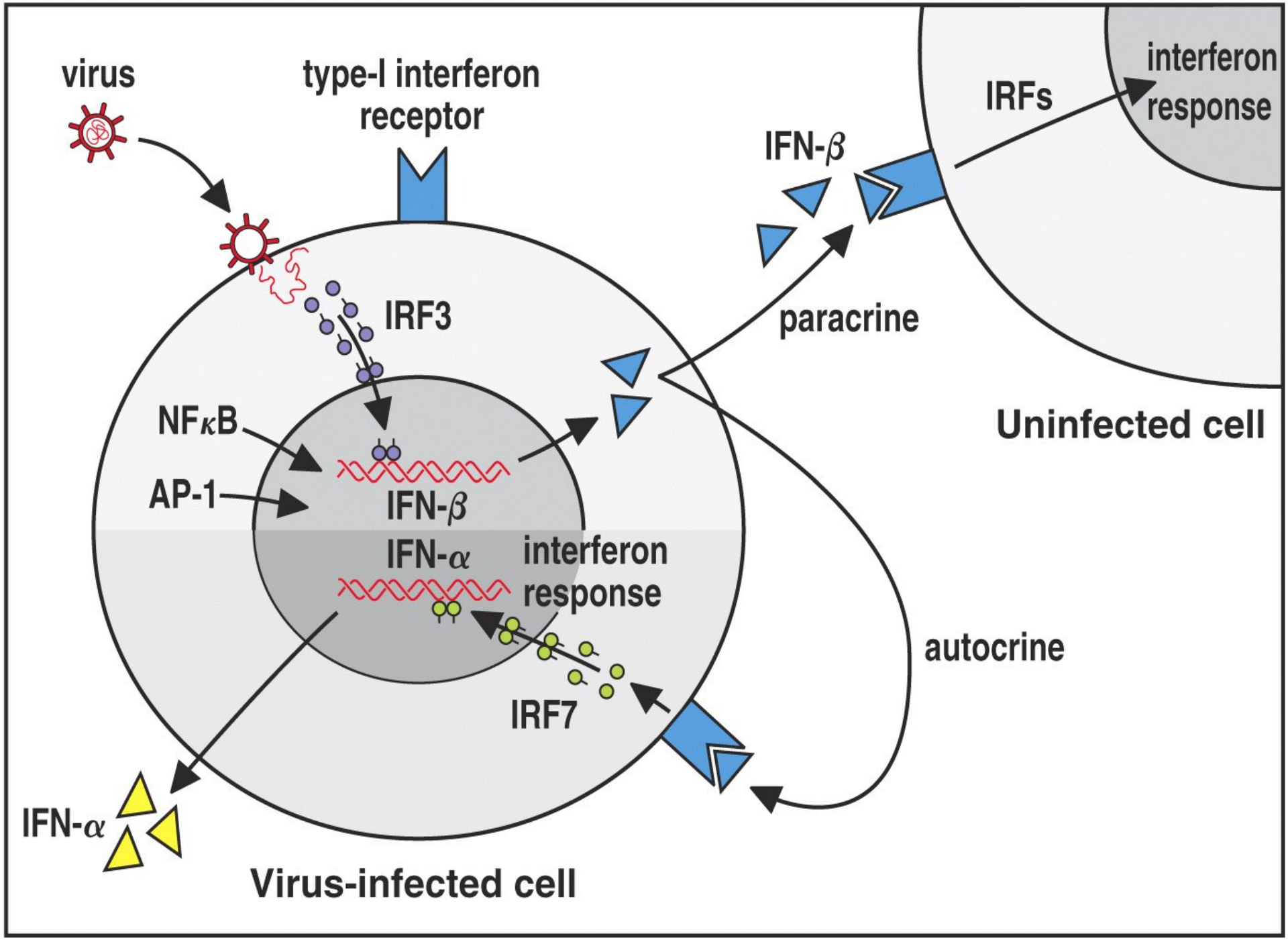
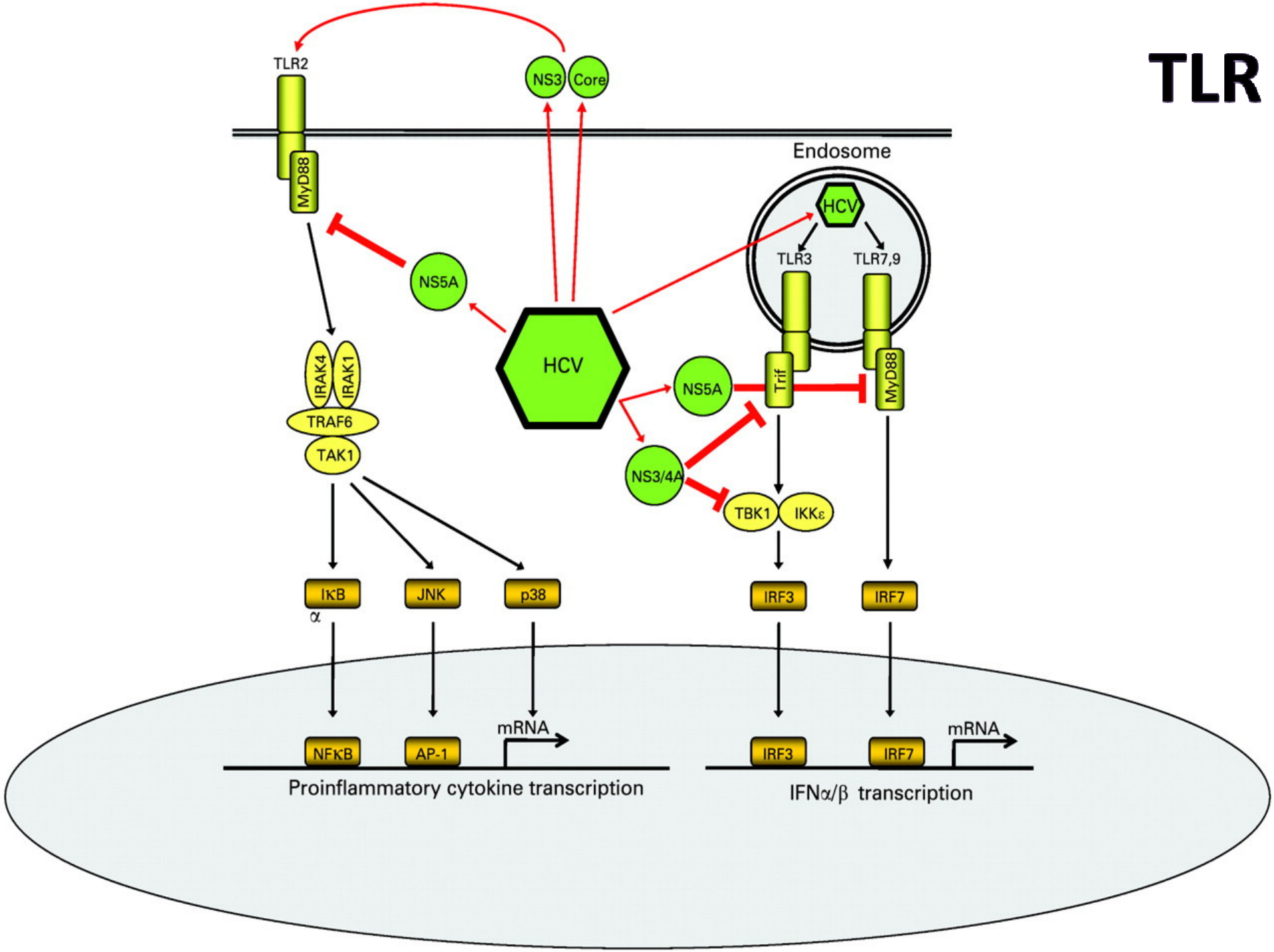


Figure 8-25 The Immune System, 2/e (© Garland Science 2005)

TLR


TLR2
NS3
Core
MyD88
Endosome
HCV
TLR3
TLR7,9
NS5A
HCV
IRAK4
IRAK1
TRAF6
TAK1
NS5A
Trif
MyD88
NS3/4A
TBK1
IKKε
IκB
α
JNK
p38
IRF3
IRF7
mRNA
NFκB
AP-1
IRF3
IRF7
mRNA
Proinflammatory cytokine transcription
IFNα/β transcription

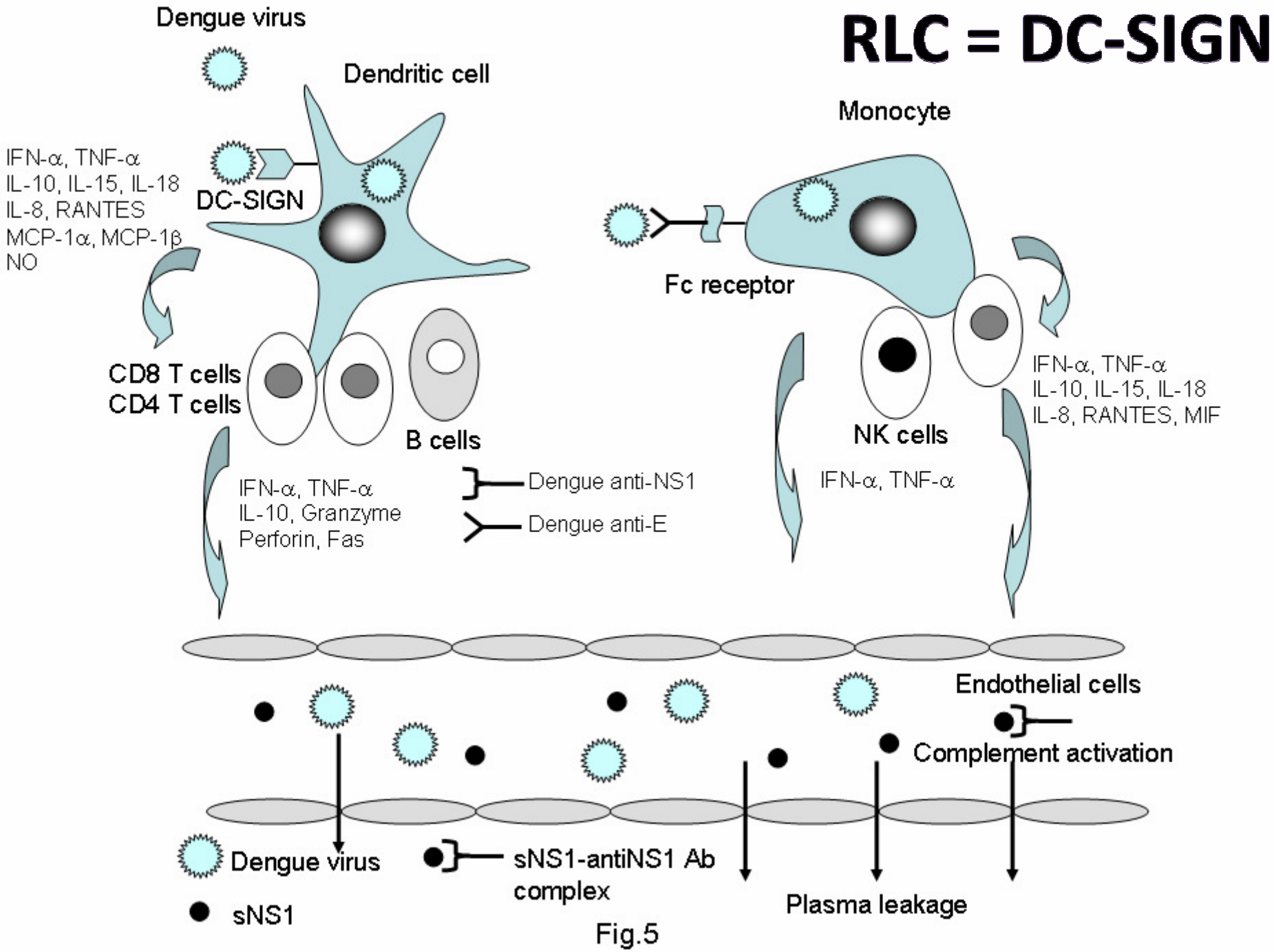
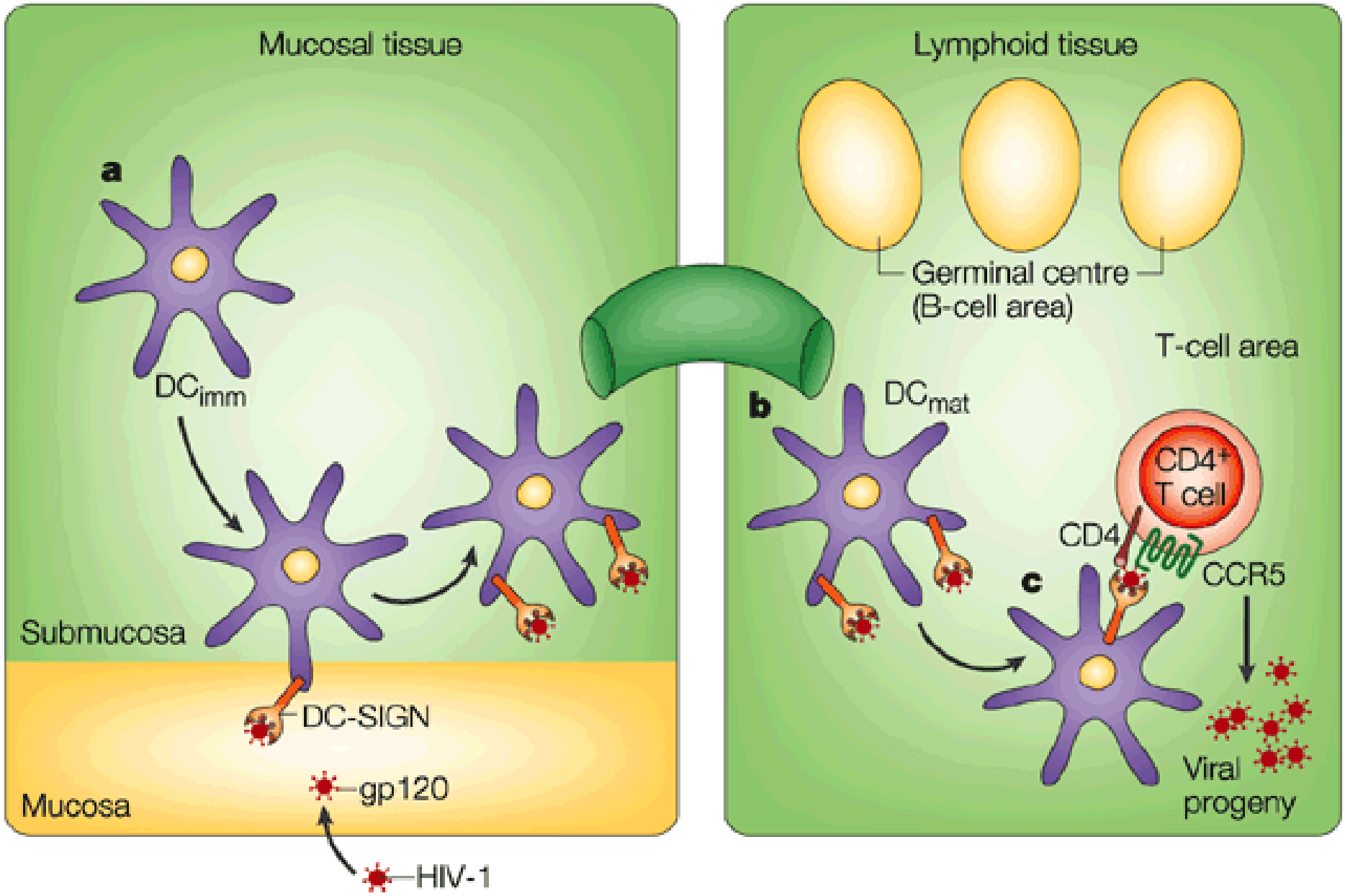

RLC = DC-SIGN
Dengue virus
Dendritic cell
DC-SIGN
IFN-α, TNF-α
IL-10, IL-15, IL-18
IL-8, RANTES
MCP-1α, MCP-1β
NO
CD8 T cells
CD4 T cells
B cells
IFN-α, TNF-α
IL-10, Granzyme
Perforin, Fas
Dengue anti-NS1
Dengue anti-E
Monocyte
Fc receptor
NK cells
IFN-α, TNF-α
IFN-α, TNF-α
IL-10, IL-15, IL-18
IL-8, RANTES, MIF
Endothelial cells
Complement activation
Dengue virus
sNS1
sNS1-antiNS1 Ab
complex
Plasma leakage

Fig.5


Mucosal tissue
Lymphoid tissue
a
DC$_{imm}$
Germinal centre
(B-cell area)
T-cell area
b
DC$_{mat}$
CD4$^+$
T cell
CD4
CCR5
c
Submucosa
DC-SIGN
gp120
Mucosa
HIV-1
Viral
progeny

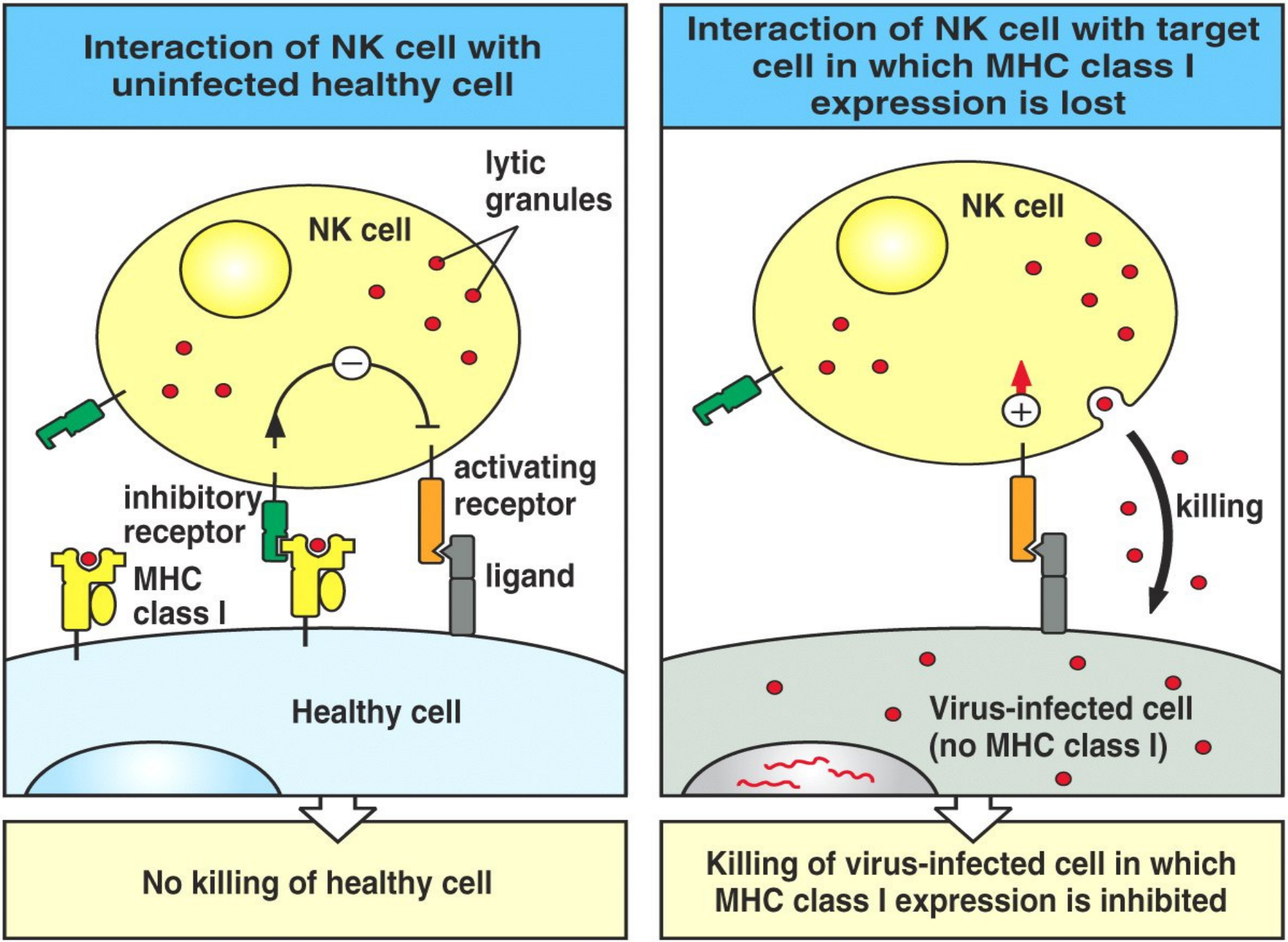


Figure 8-32 The Immune System, 2/e (© Garland Science 2005)

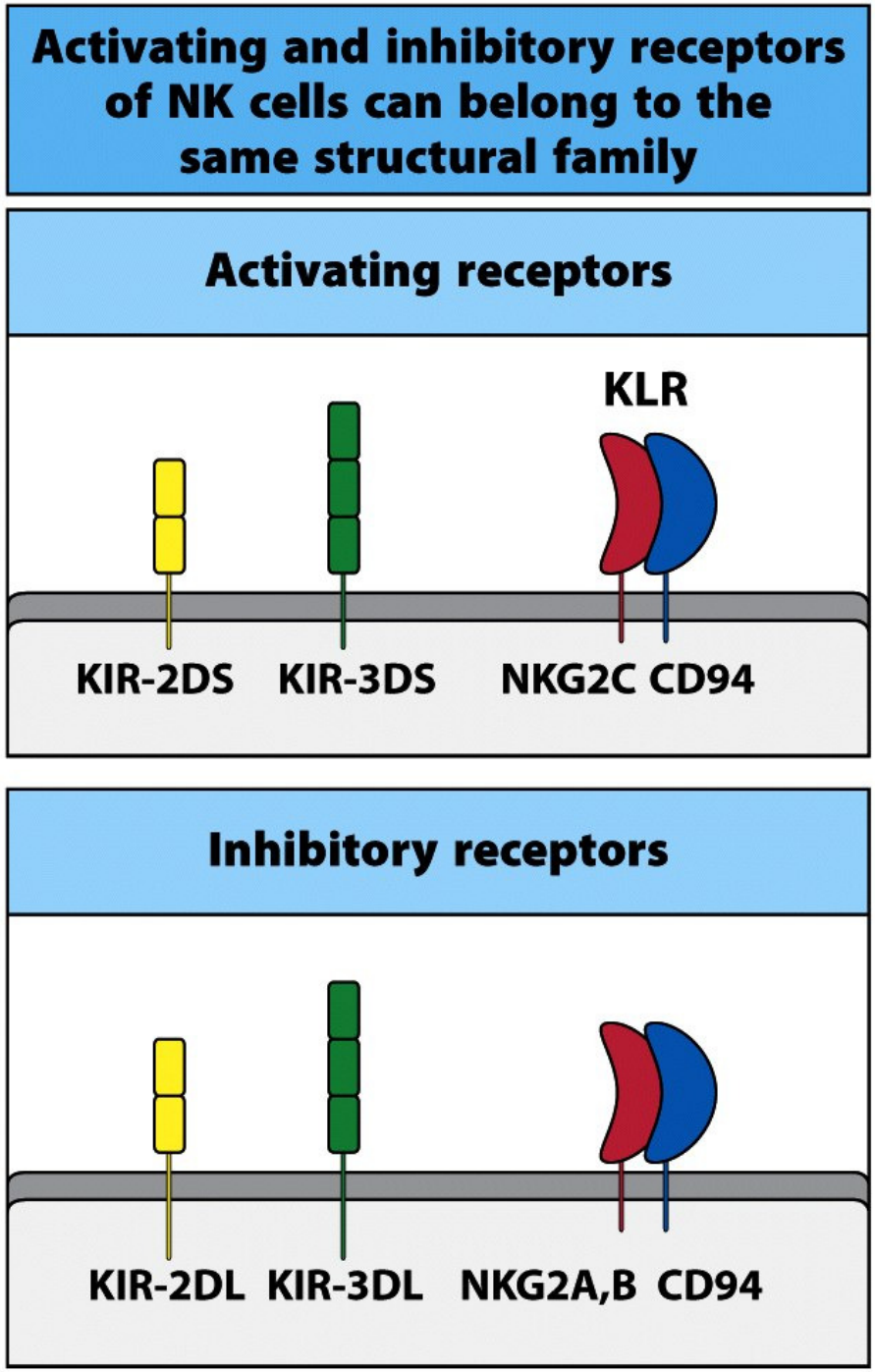


Figure 2-58 Immunobiology, 7ed. (© Garland Science 2008)

The major activating receptors of NK cells

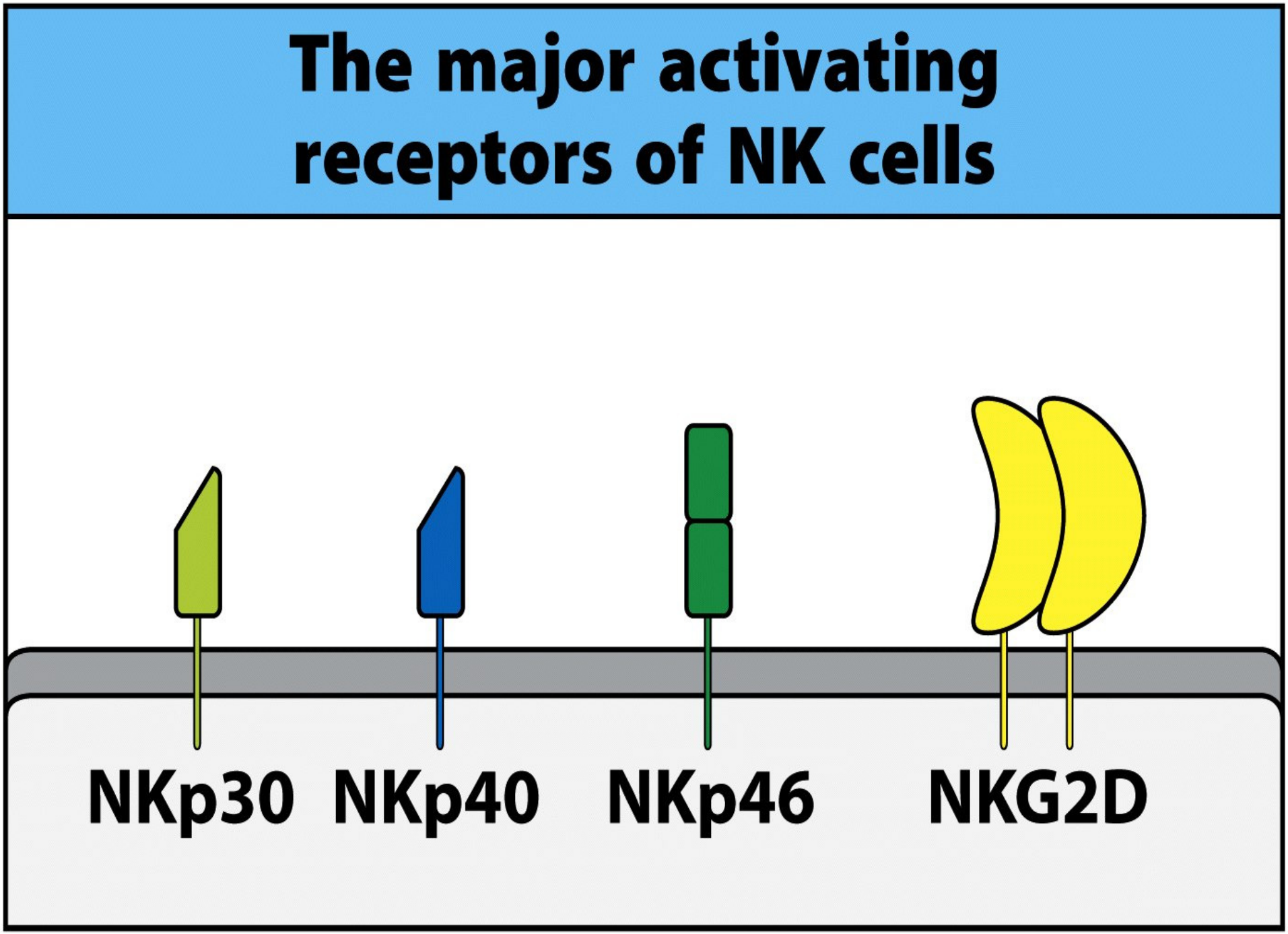
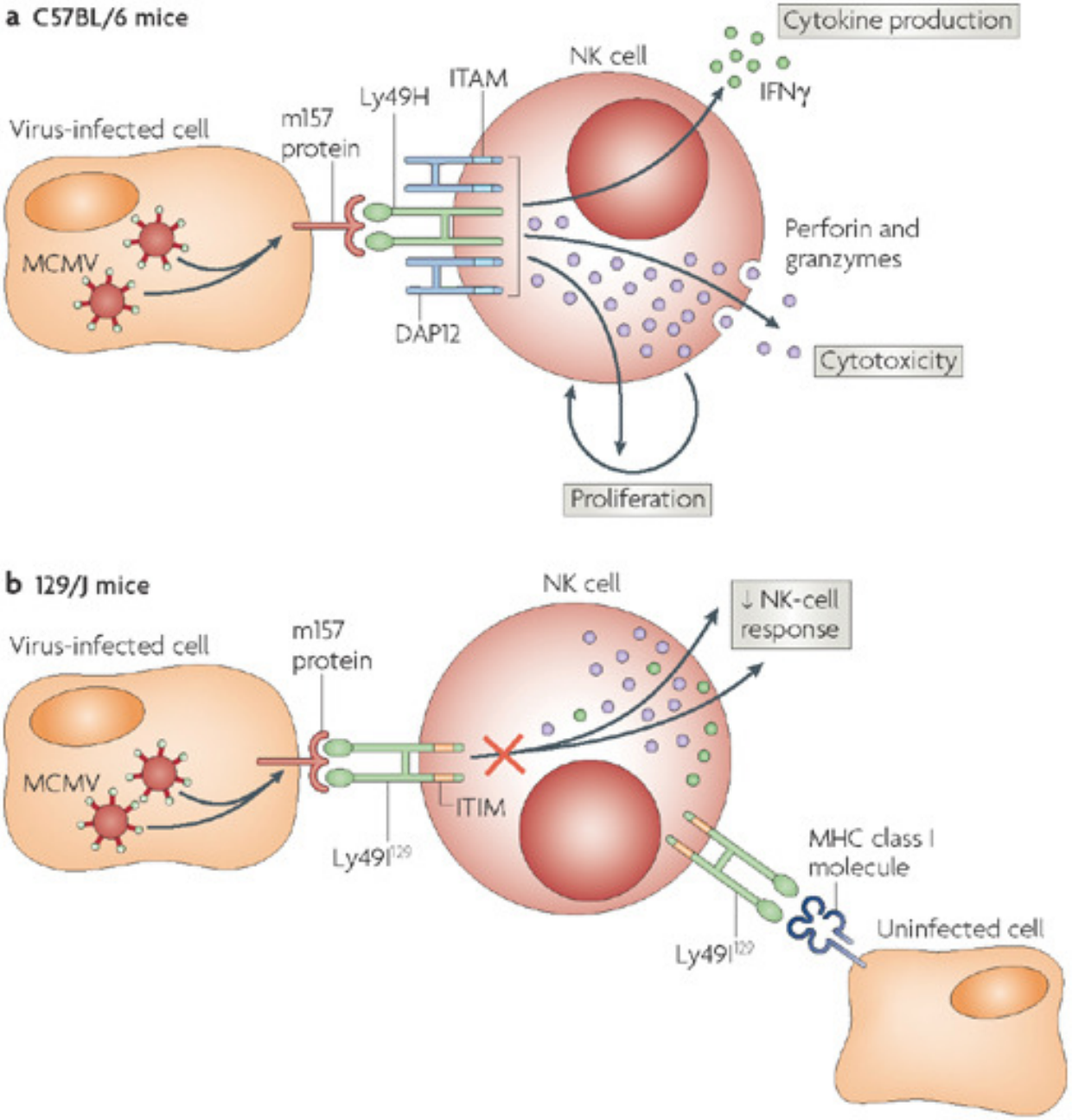
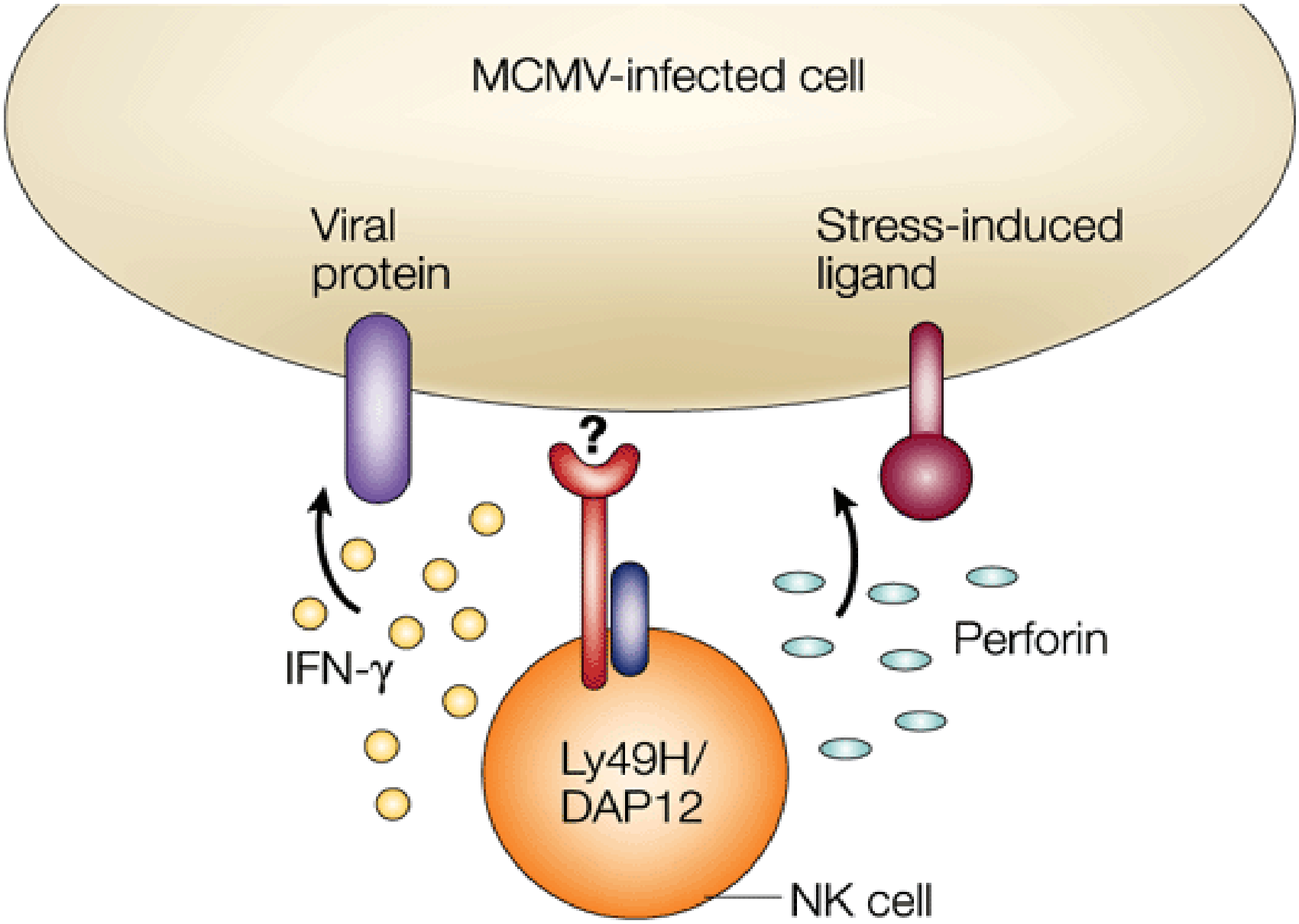


Figure 2-59 Immunobiology, 7ed. (© Garland Science 2008)

NK-cell receptors					
Inhibitory			Activating		
Receptor	Structural type	Ligand	Receptor	Structural type	Ligand
KIR2DL	Ig	HLA-C	KIR2DS	Ig	HLA-C
KIR3DL	Ig	HLA-B,C	KIR3DS	Ig	HLA-B?
LILRB1,2	Ig	HLA class I	LILRA3	Ig	?
CD94:NKG2A	Lectin	HLA-E	CD94:NKG2C/E	Lectin	HLA-E
LAIR-1	Ig	?	LAIR-2	Ig	?
			NKG2D	Lectin	MIC-A,B and others
			NKp30	Ig	?
			NKp44	Ig	?
			NKp46	Ig	?
			CD16	Ig	Fc

Figure 8-29 The Immune System, 2/e (© Garland Science 2005)


a C57BL/6 mice
Cytokine production
NK cell
ITAM
Ly49H
IFNγ
Virus-infected cell
m157
protein
MCMV
Perforin and
granzymes
DAP12
Cytotoxicity
Proliferation
b 129/J mice
NK cell
↓ NK-cell
response
Virus-infected cell
m157
protein
MCMV
ITIM
MHC class I
molecule
Ly49I129
Ly49I129
Uninfected cell

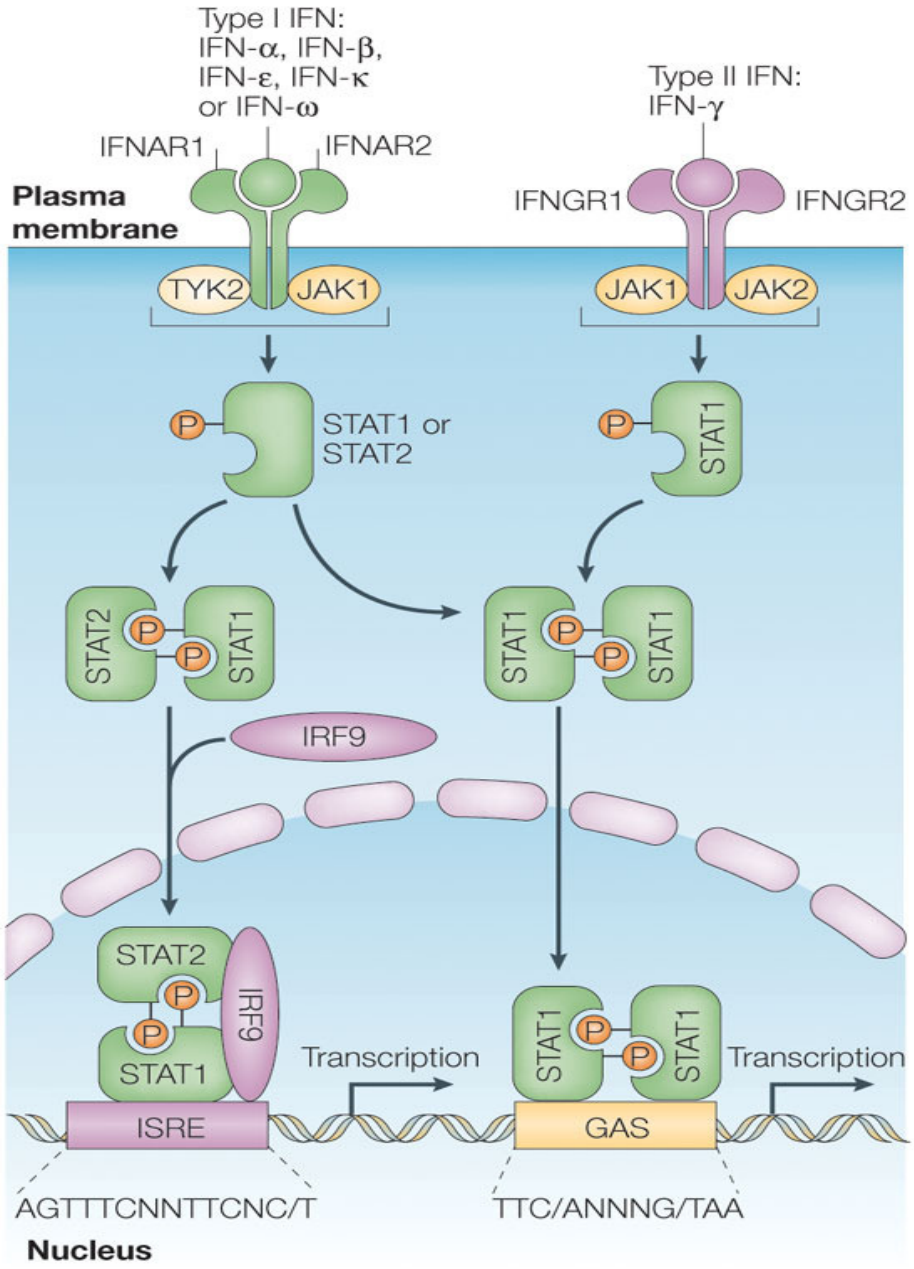

MCMV-infected cell
Viral protein
Stress-induced ligand
?
IFN-γ
Perforin
Ly49H/ DAP12
NK cell

Célula infectada por virus

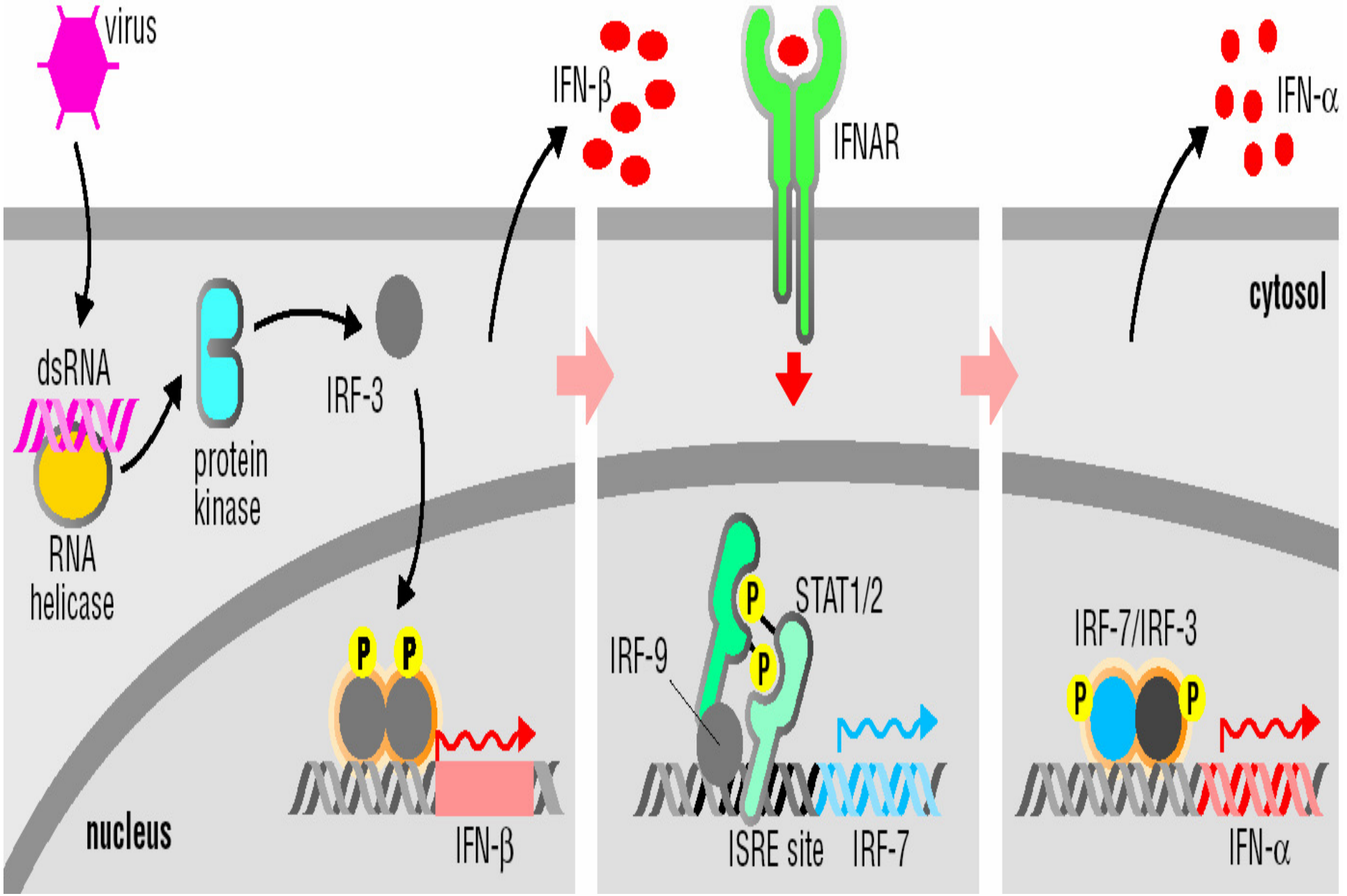
↓ Expresión de MHC I

↑ Expresión de ligandos para Rc activadores

El sistema INF como agente antiviral

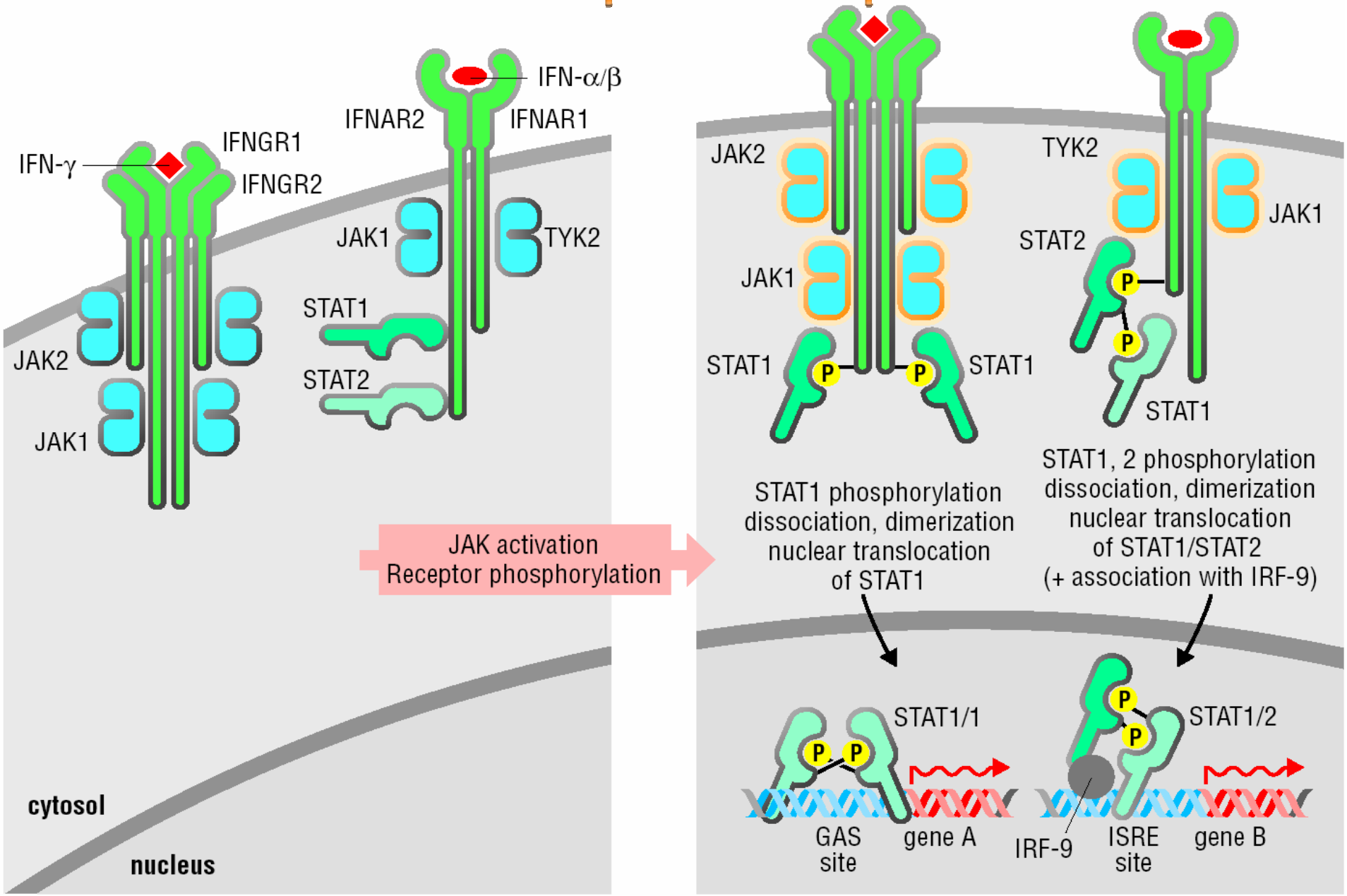


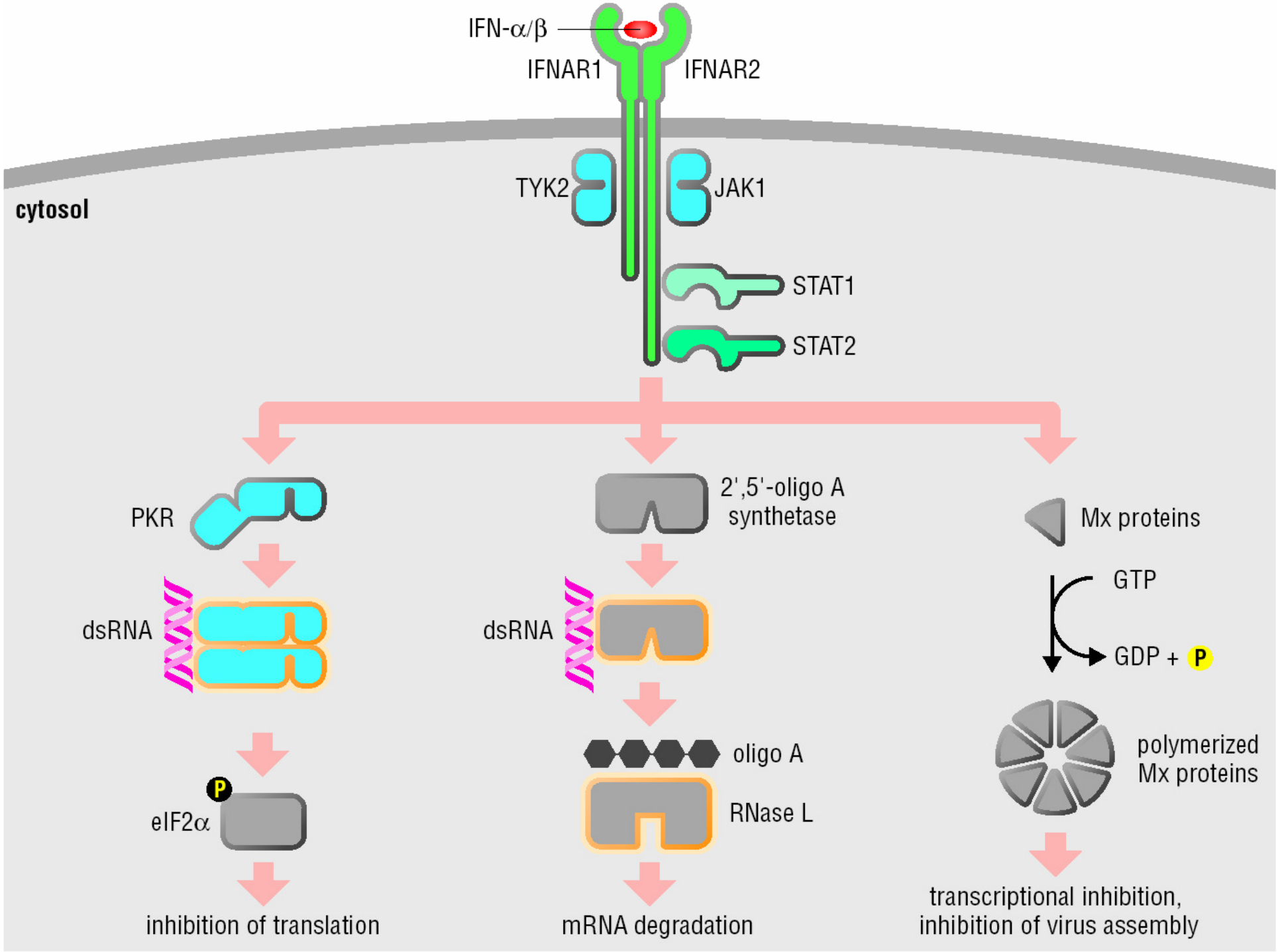
Nature Reviews | Immunology

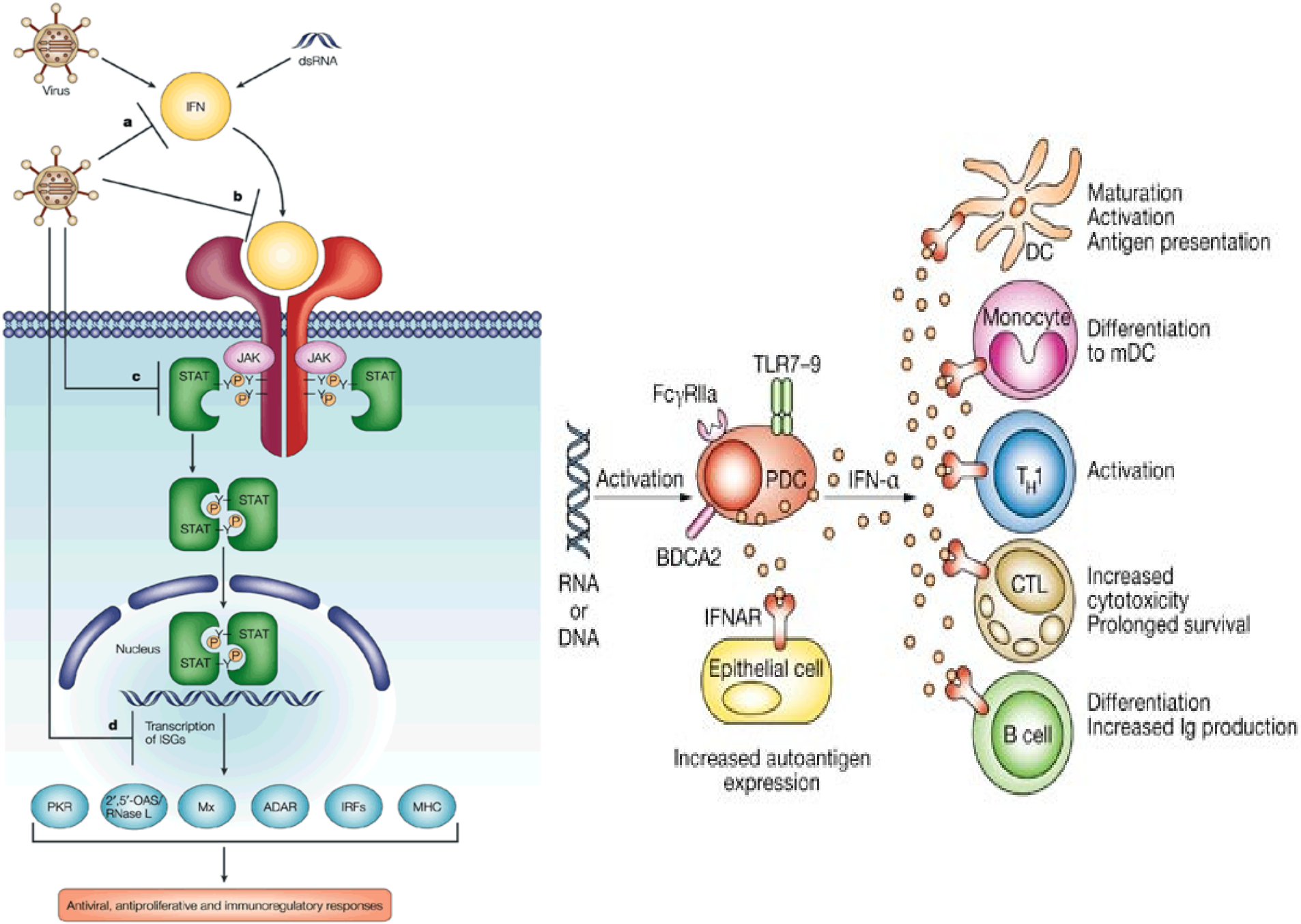


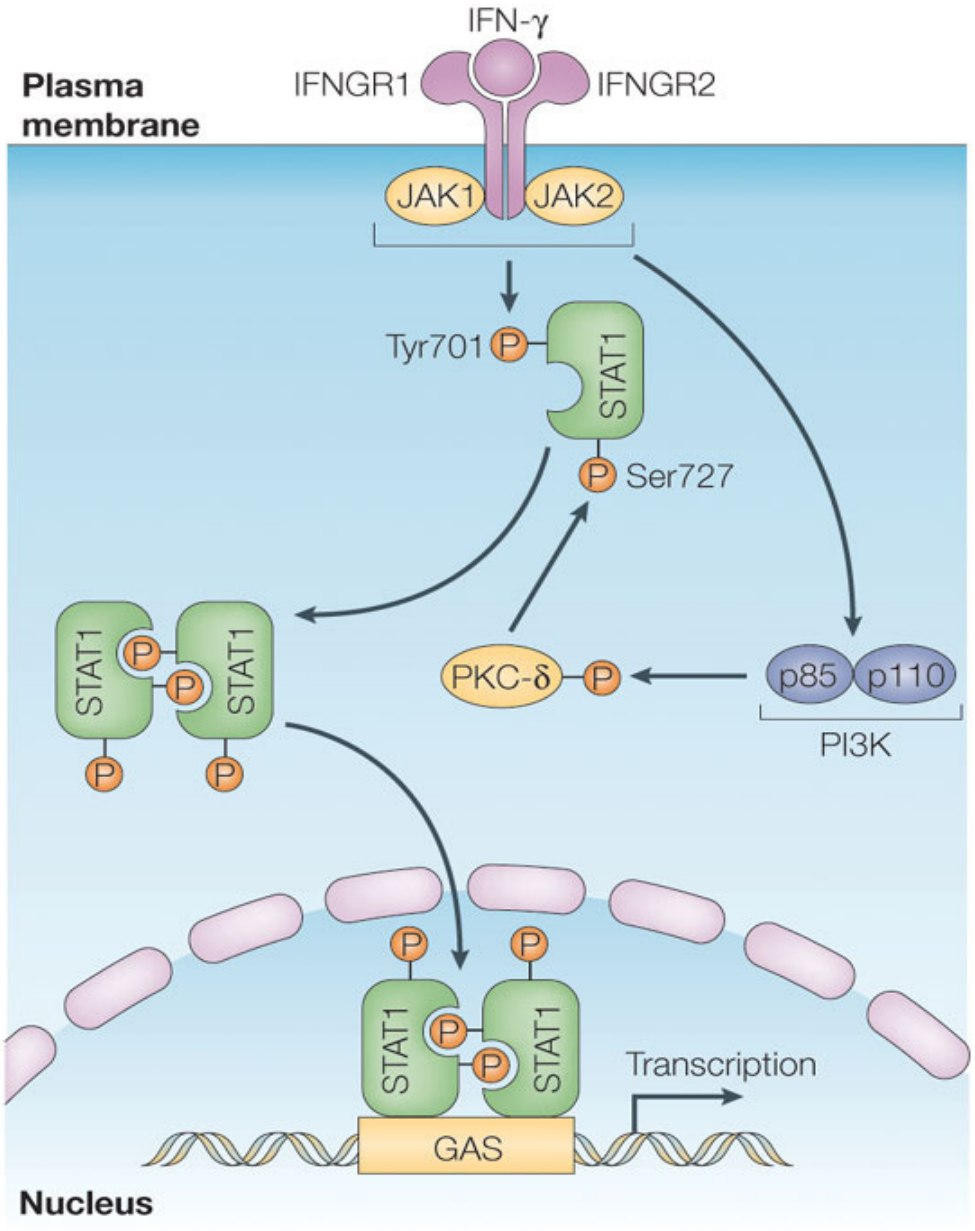
Regulación transcripcional del sistema INF α/β

Traducción de señales y activación transcripcional de genes inducidos por INF de tipo I




IFN-α/β
IFNAR1
IFNAR2
TYK2
JAK1
STAT1
STAT2
cytosol
PKR
dsRNA
eIF2α
P
inhibition of translation
2',5'-oligo A synthetase
dsRNA
oligo A
RNase L
mRNA degradation
Mx proteins
GTP
GDP + P
polymerized Mx proteins
transcriptional inhibition, inhibition of virus assembly


Virus
dsRNA
IFN
a
b
c
JAK
JAK
STAT
STAT
STAT
STAT
Nucleus
STAT
STAT
d
Transcription of ISGs
PKR
2′,5′-OAS/ RNase L
Mx
ADAR
IRFs
MHC
Antiviral, antiproliferative and immunoregulatory responses
TLR7–9
FcγRIIa
Activation
PDC
IFN-α
BDCA2
IFNAR
Epithelial cell
RNA or DNA
Increased autoantigen expression
DC
Maturation
Activation
Antigen presentation
Monocyte
Differentiation to mDC
T_H1
Activation
CTL
Increased cytotoxicity
Prolonged survival
B cell
Differentiation
Increased Ig production



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INMUNIDAD ADAPTATIVA

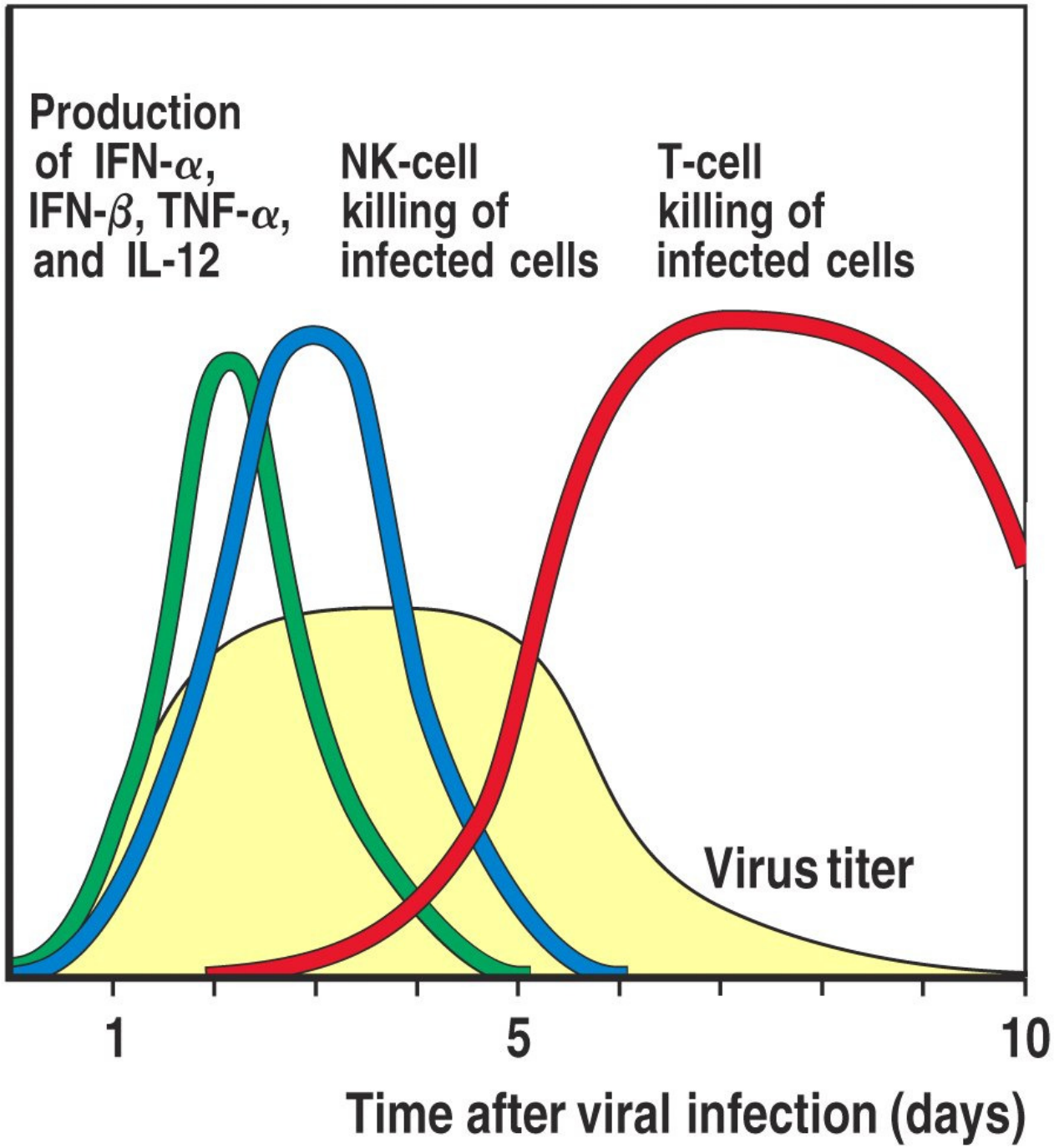


Figure 8-28 The Immune System, 2/e (© Garland Science 2005)

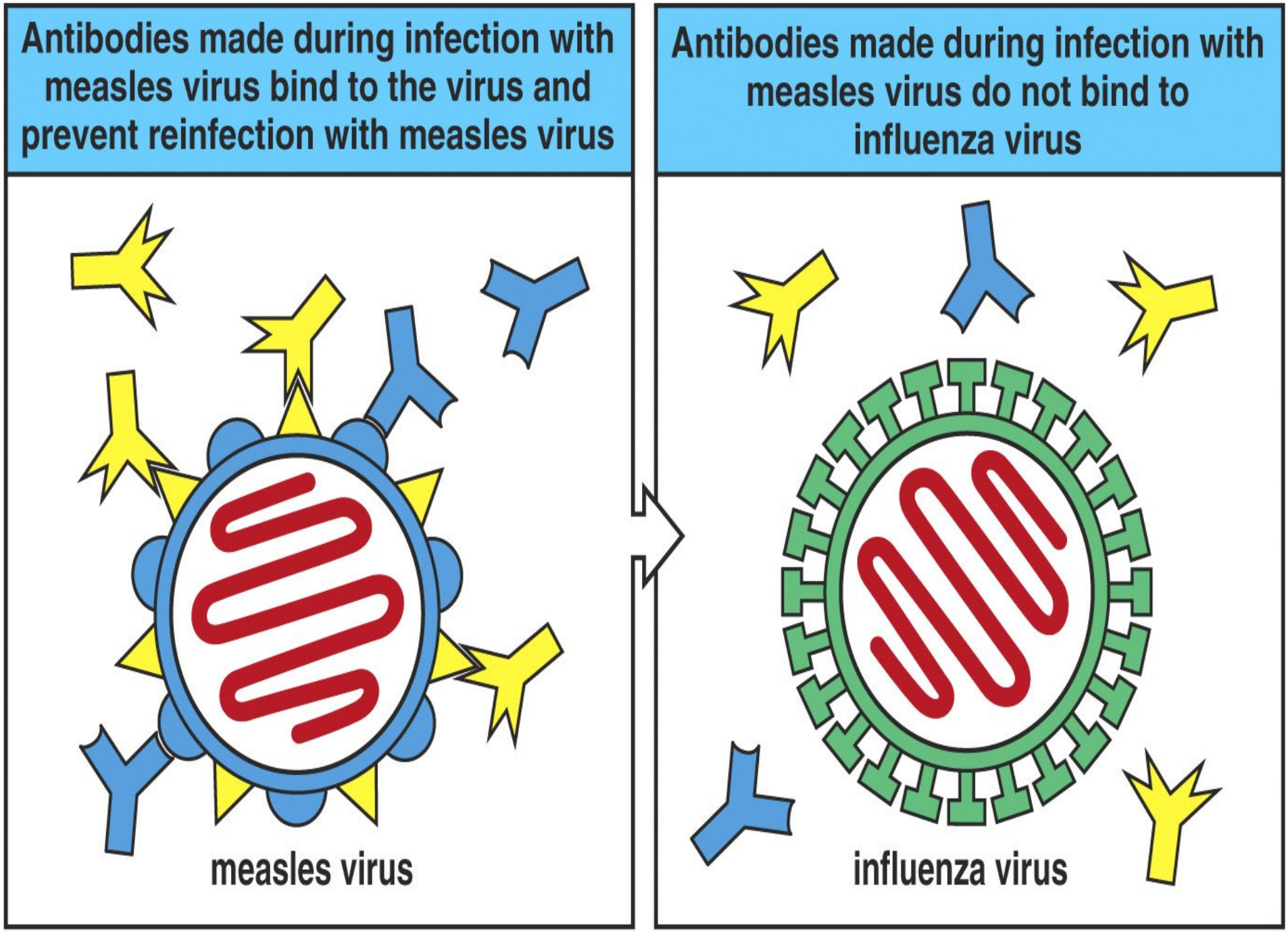
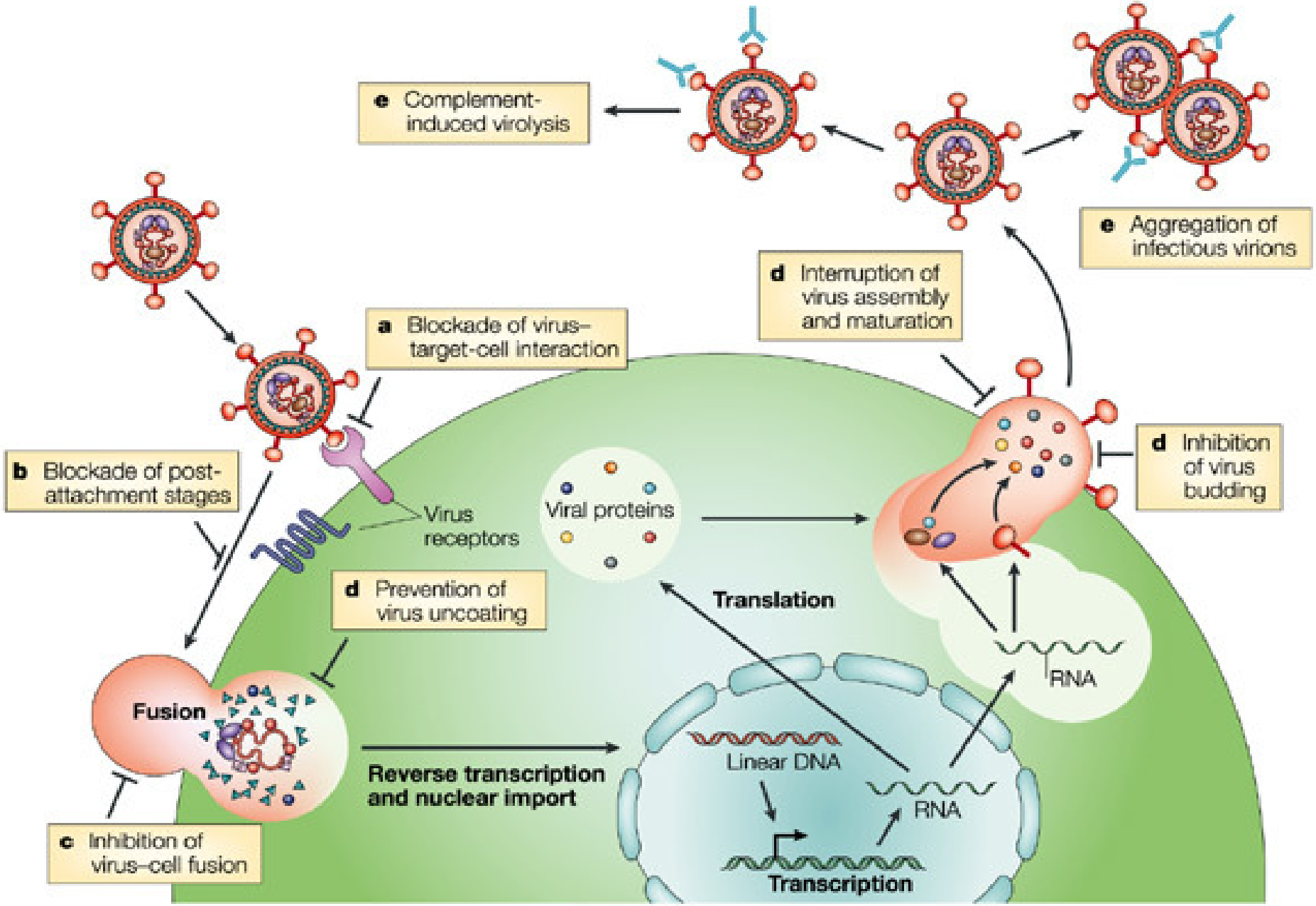
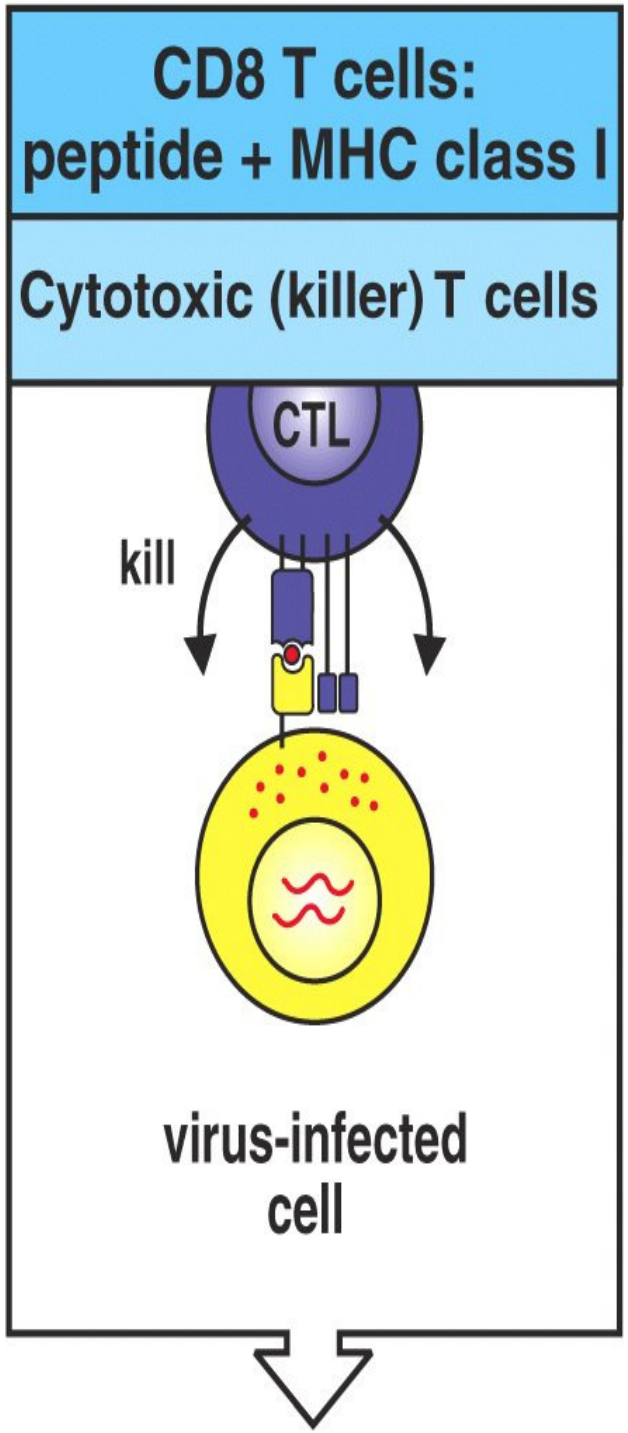


Figure 1-22 The Immune System, 2/e (© Garland Science 2005)


e Complement-induced virolysis
e Aggregation of infectious virions
d Interruption of virus assembly and maturation
a Blockade of virus–target-cell interaction
b Blockade of post-attachment stages
Virus receptors
Viral proteins
d Inhibition of virus budding
d Prevention of virus uncoating
Translation
Fusion
RNA
Linear DNA
Reverse transcription and nuclear import
RNA
Transcription
c Inhibition of virus–cell fusion


CD8 T cells:
peptide + MHC class I
Cytotoxic (killer) T cells
CTL
kill
virus-infected
cell

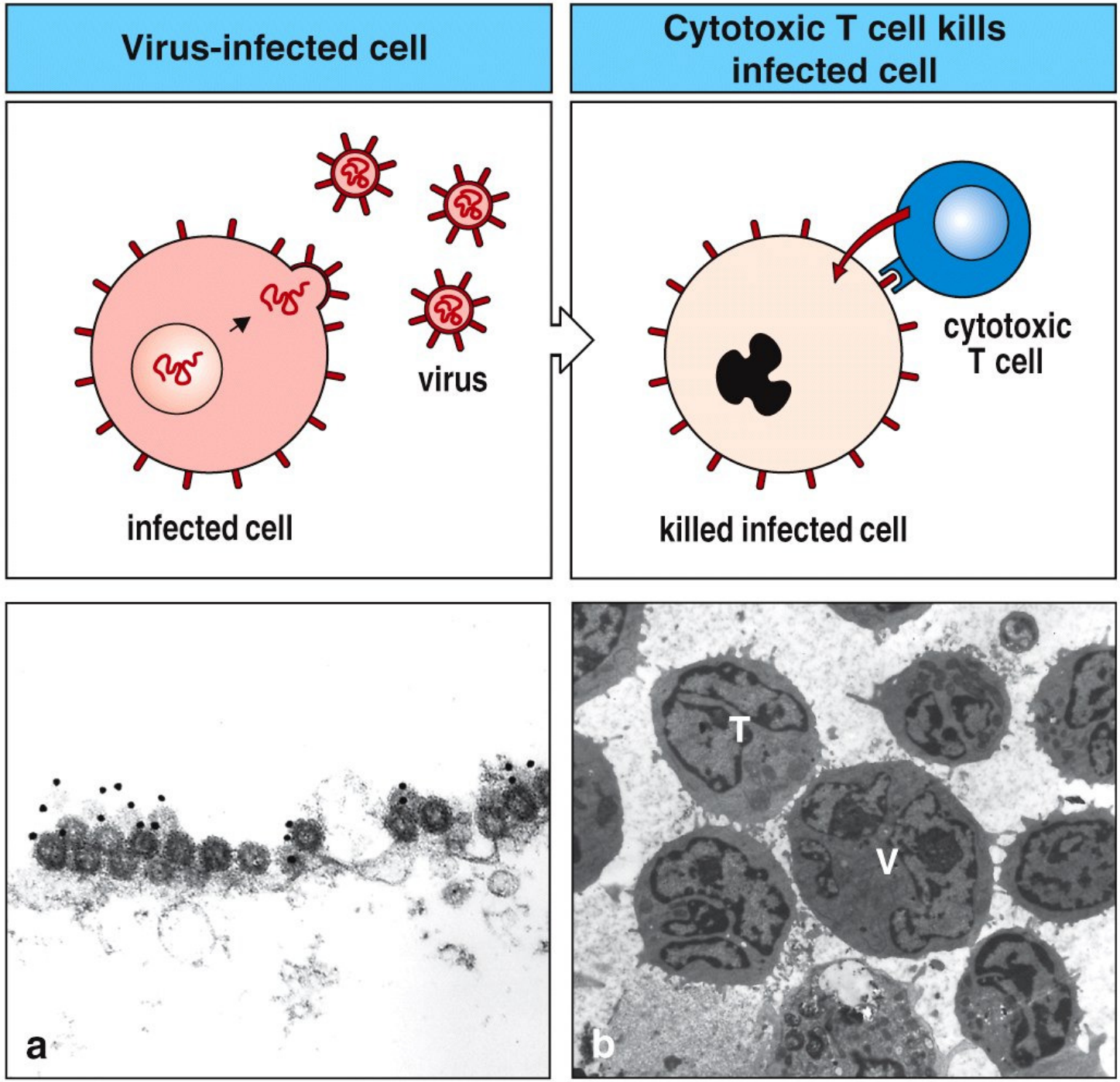


Figure 1-25 Immunobiology, 6/e. (© Garland Science 2005)

DCs: Maduración, Procesamiento y Presentación de Ag virales

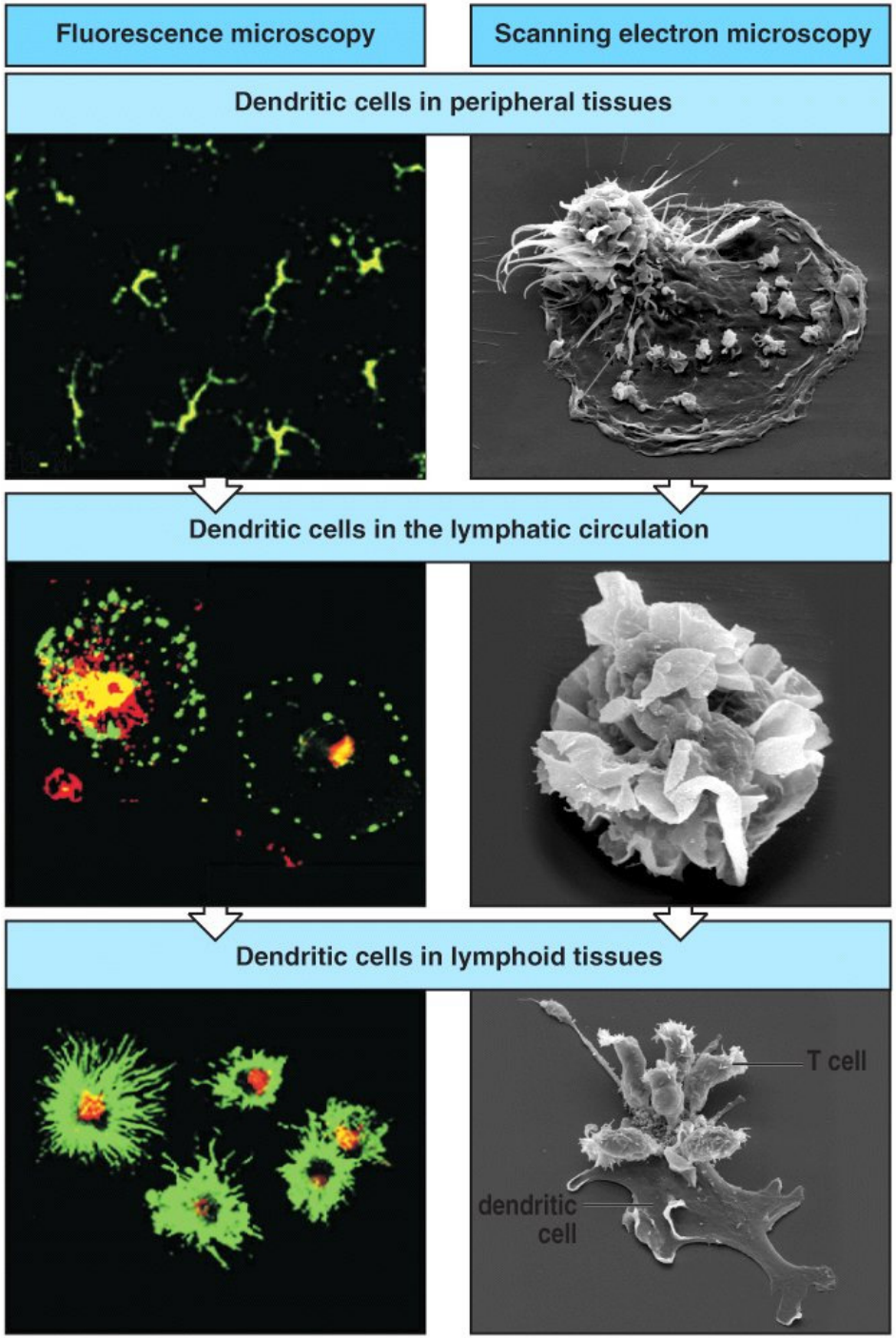
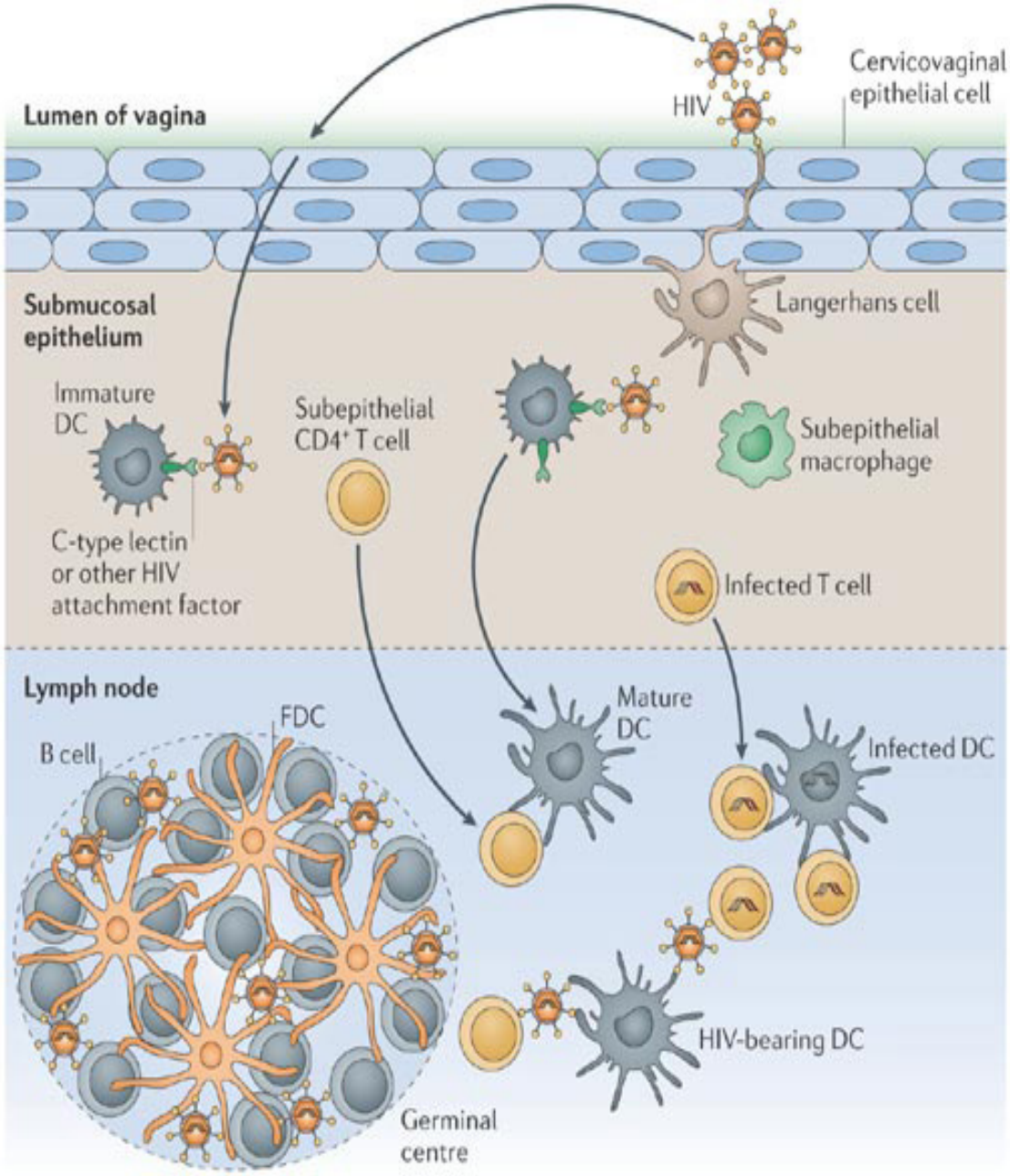
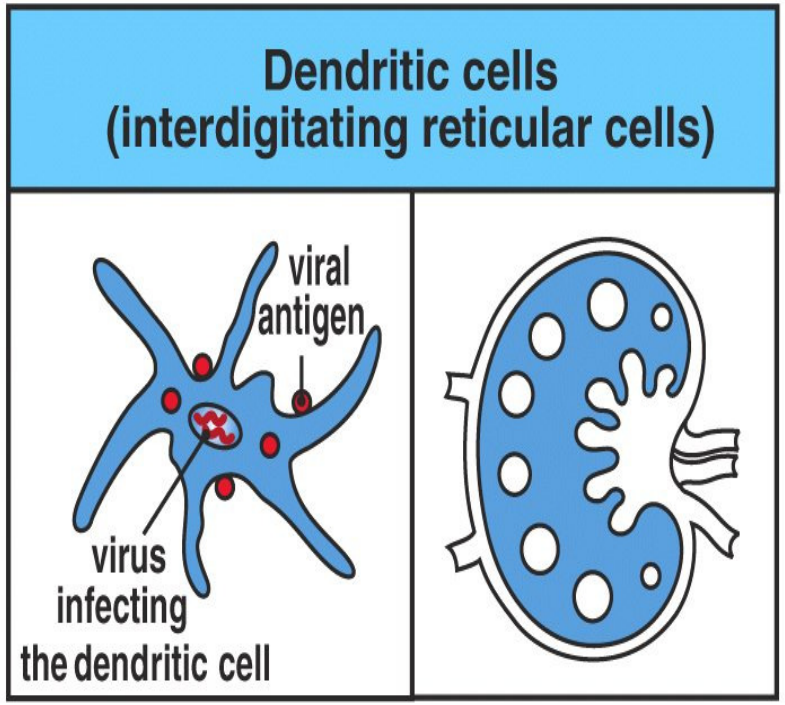
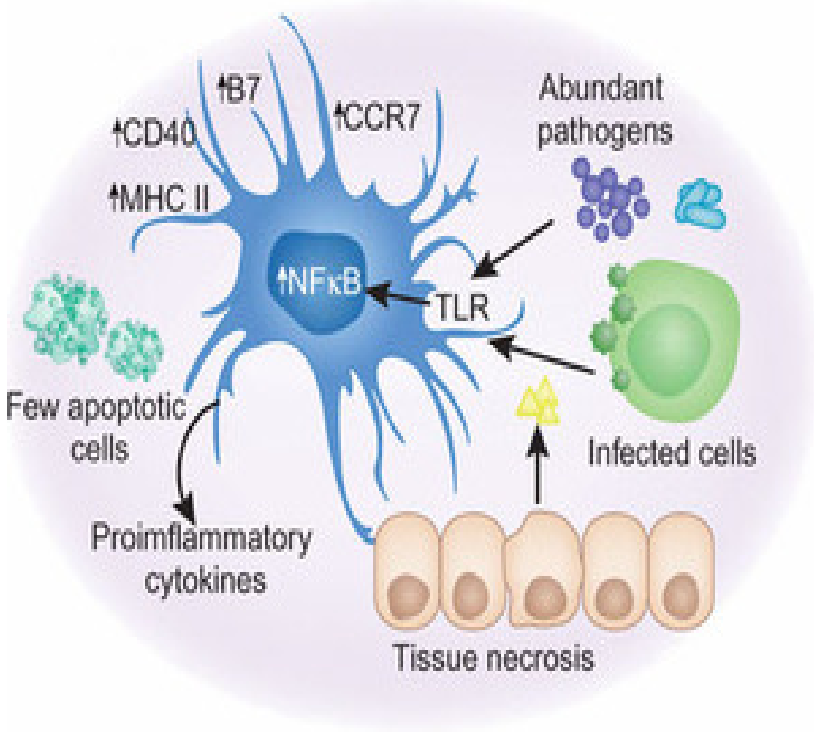


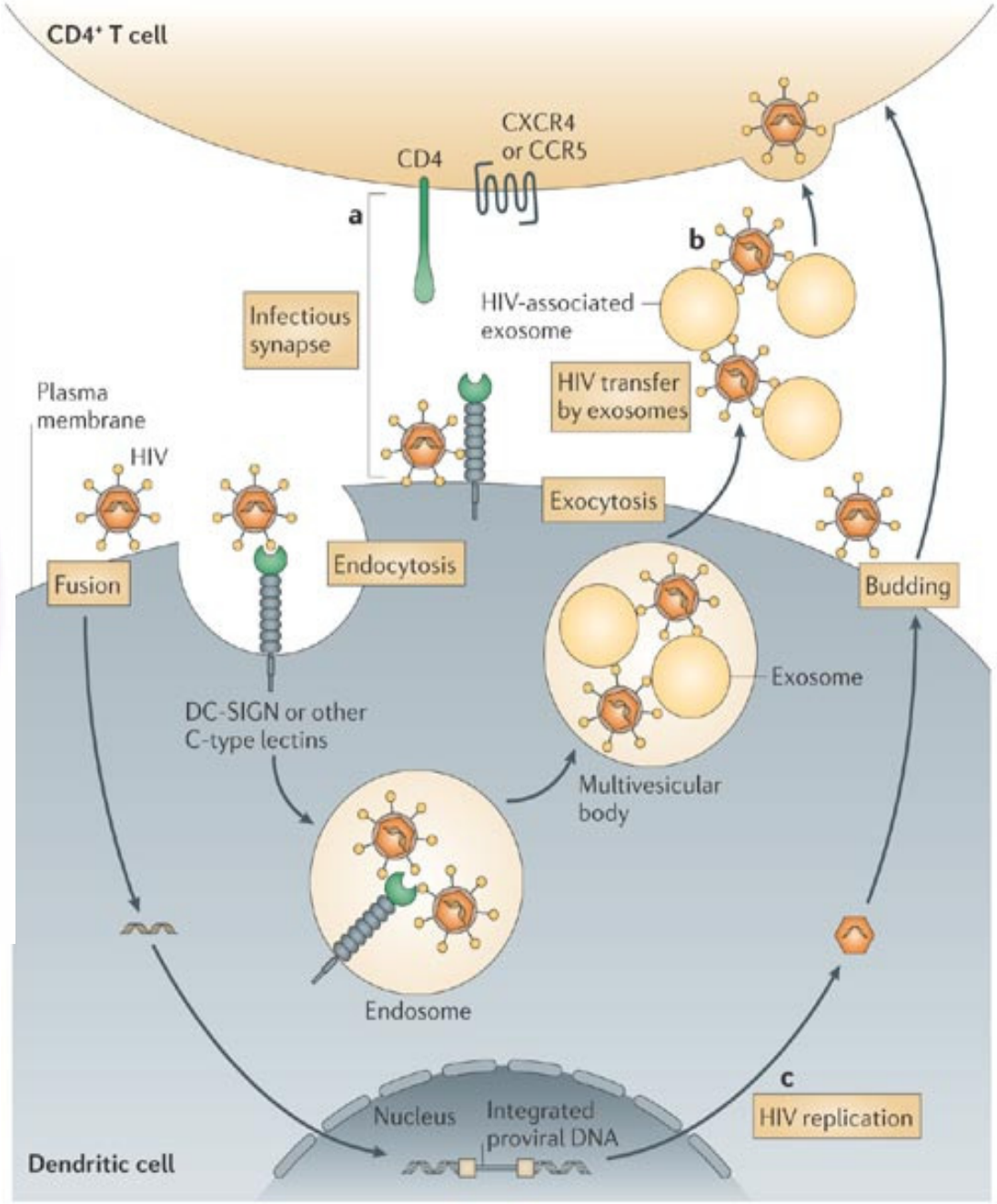
Figure 8-2 Immunobiology, 6/e. (© Garland Science 2005)

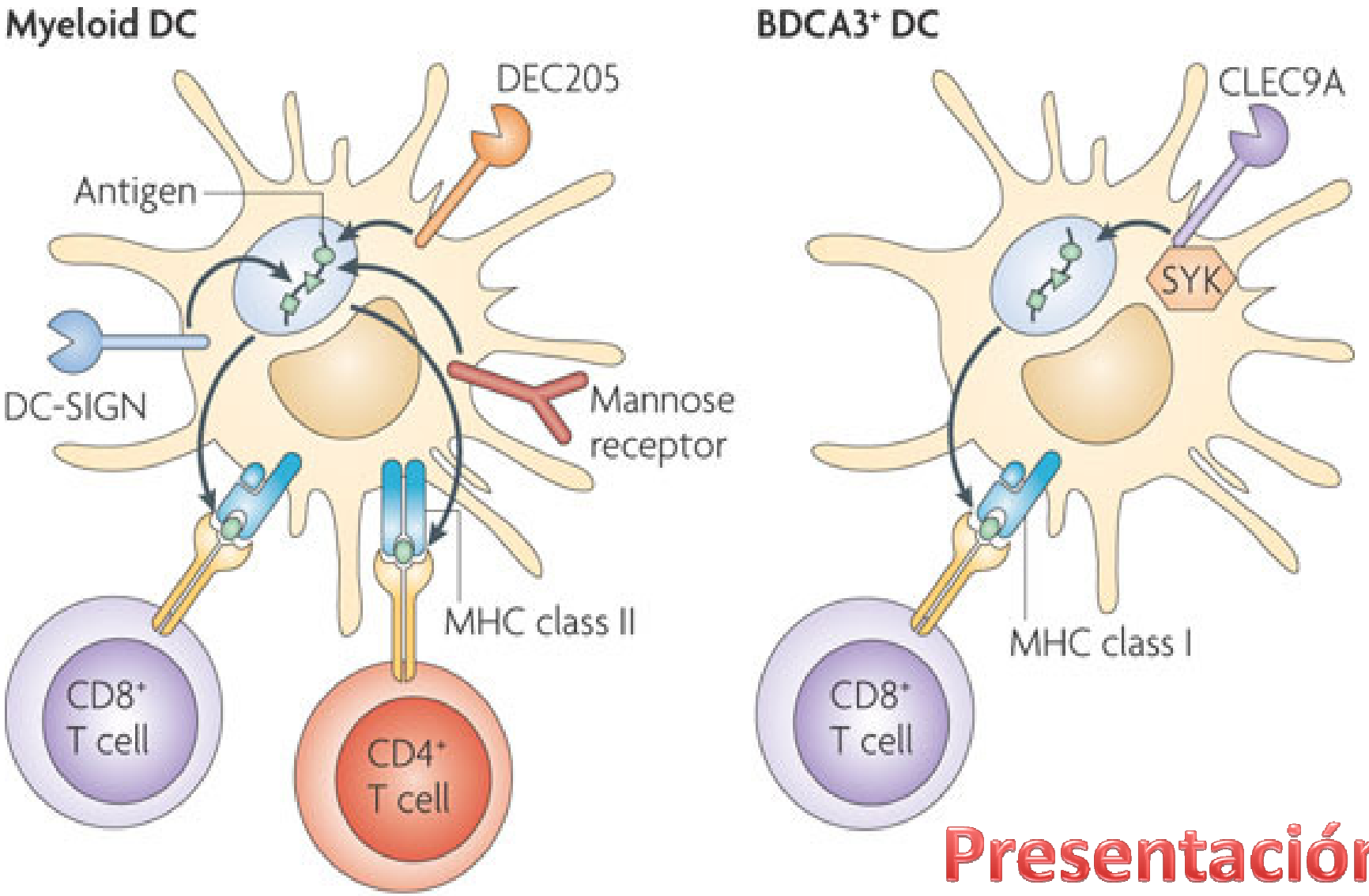
Maduración











Presentación de Ag

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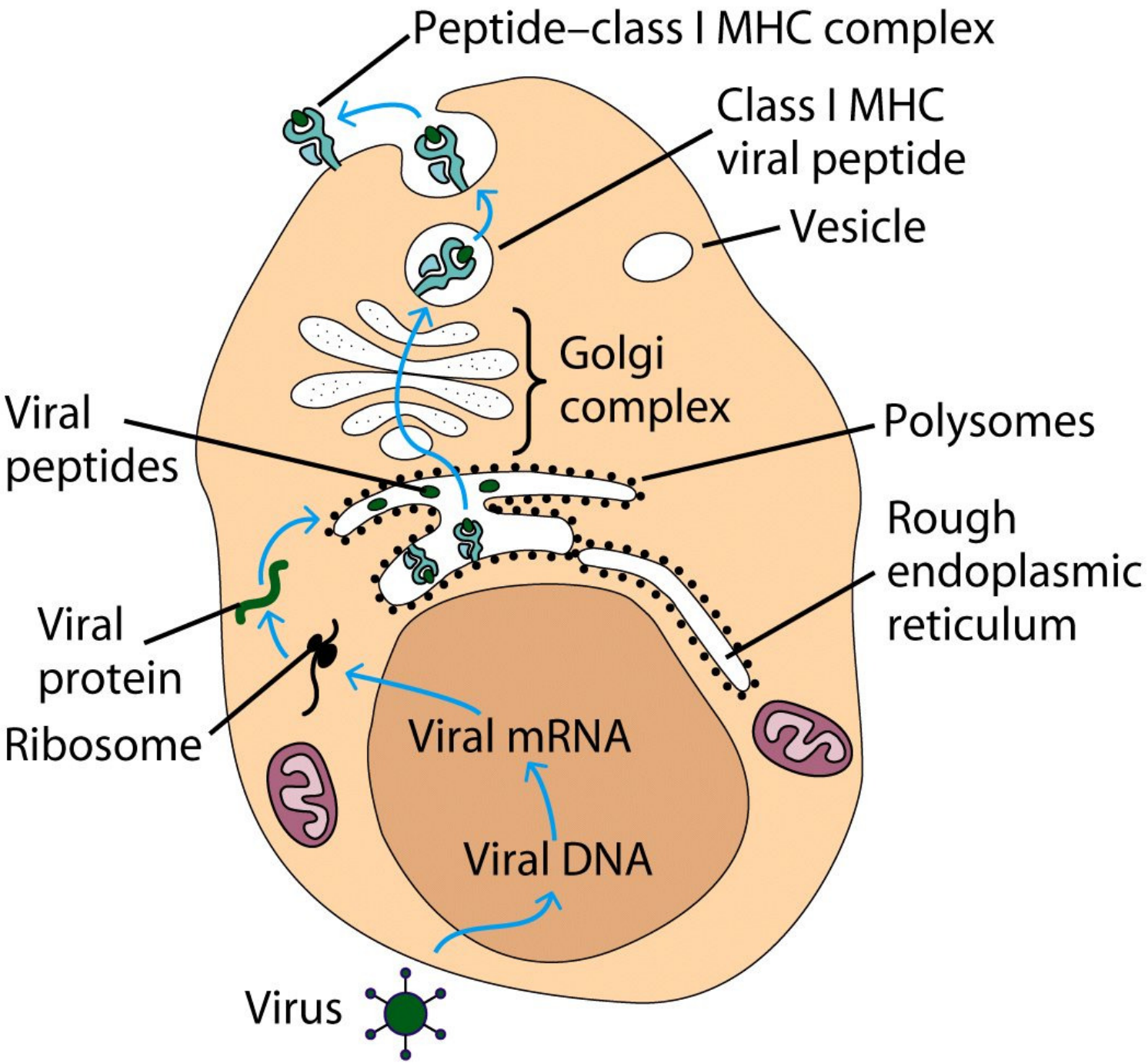

Peptide–class I MHC complex
Class I MHC viral peptide
Vesicle
Golgi complex
Viral peptides
Polysomes
Rough endoplasmic reticulum
Viral protein
Ribosome
Viral mRNA
Viral DNA
Virus

Activación de Linfocitos T $CD8^+$

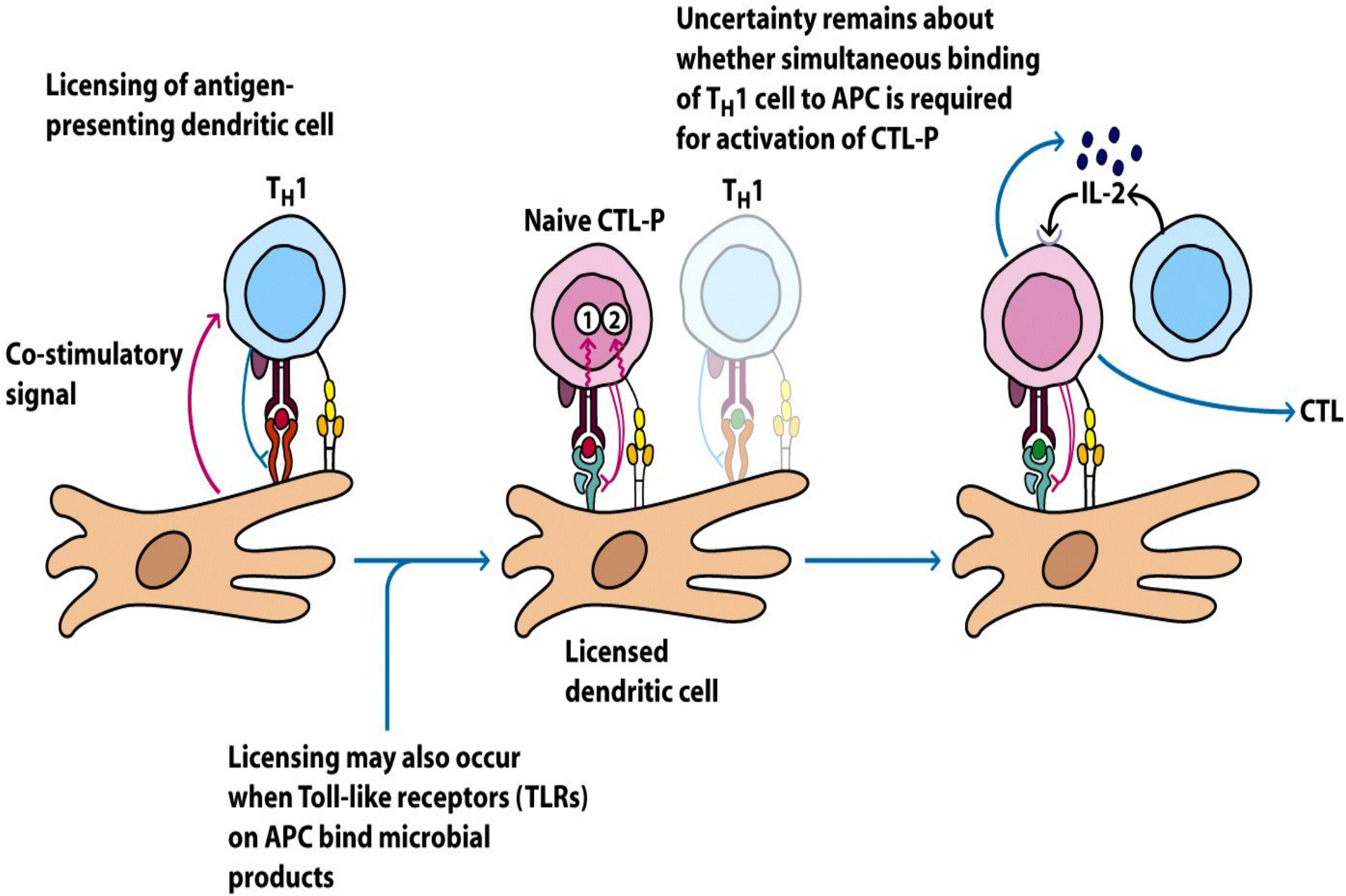


Figure 14-1
Kuby IMMUNOLOGY, Sixth Edition

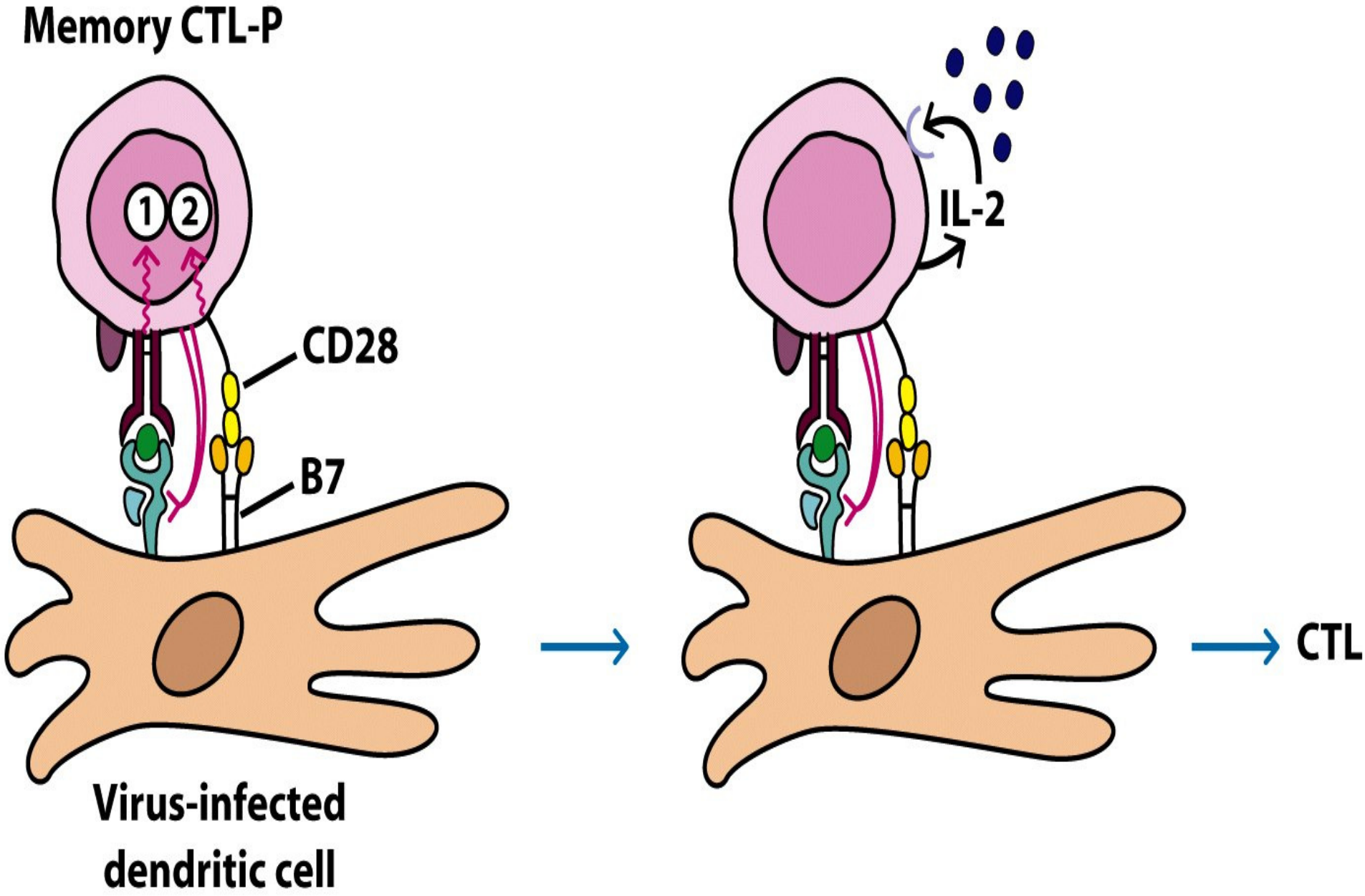
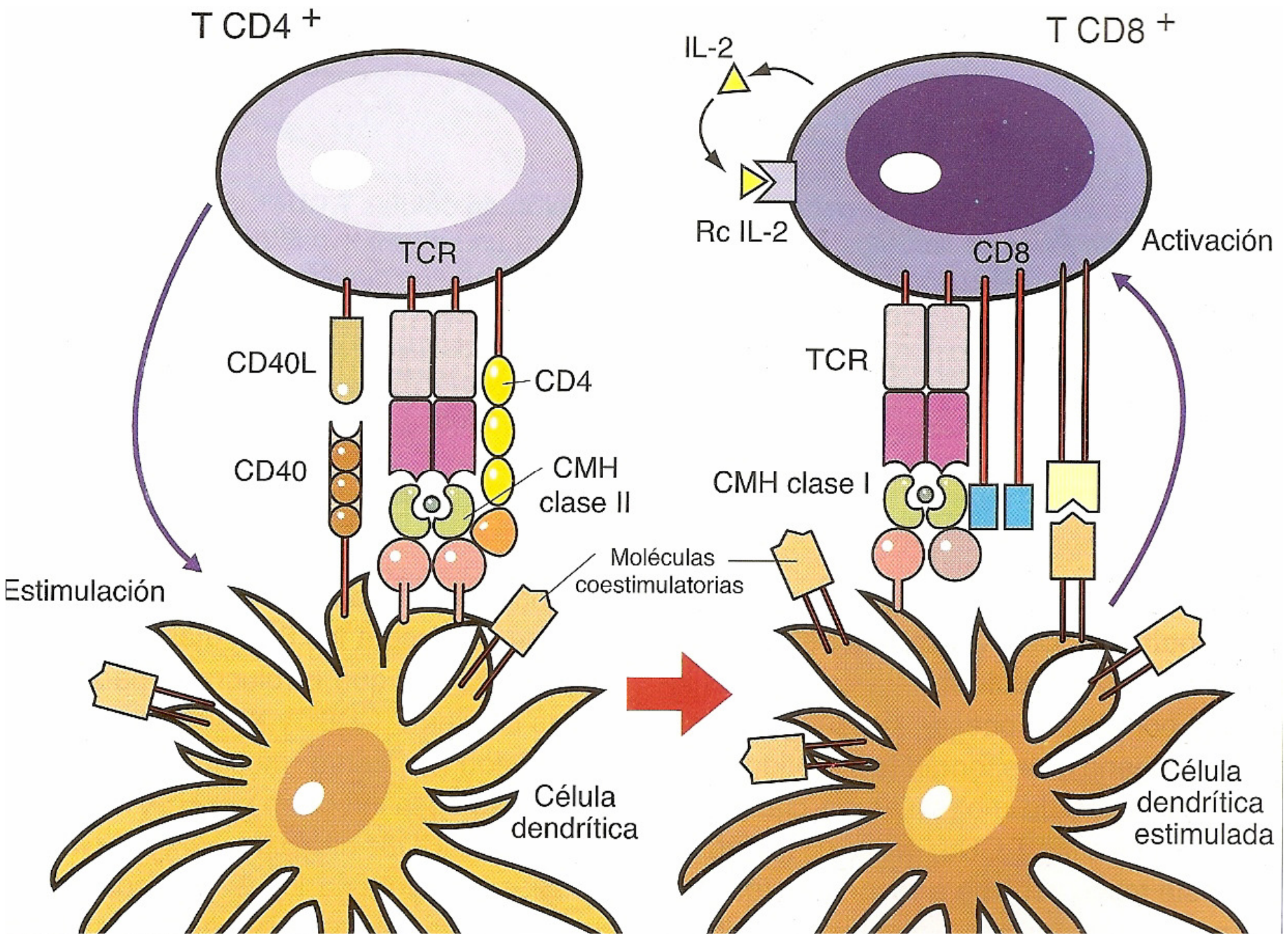


Figure 14-2
Kuby IMMUNOLOGY, Sixth Edition


T CD4 +
TCR
CD40L
CD4
CD40
CMH
clase II
Estimulación
Moléculas
coestimulatorias
Célula
dendrítica
T CD8 +
IL-2
Rc IL-2
CD8
Activación
TCR
CMH clase I
Célula
dendrítica
estimulada

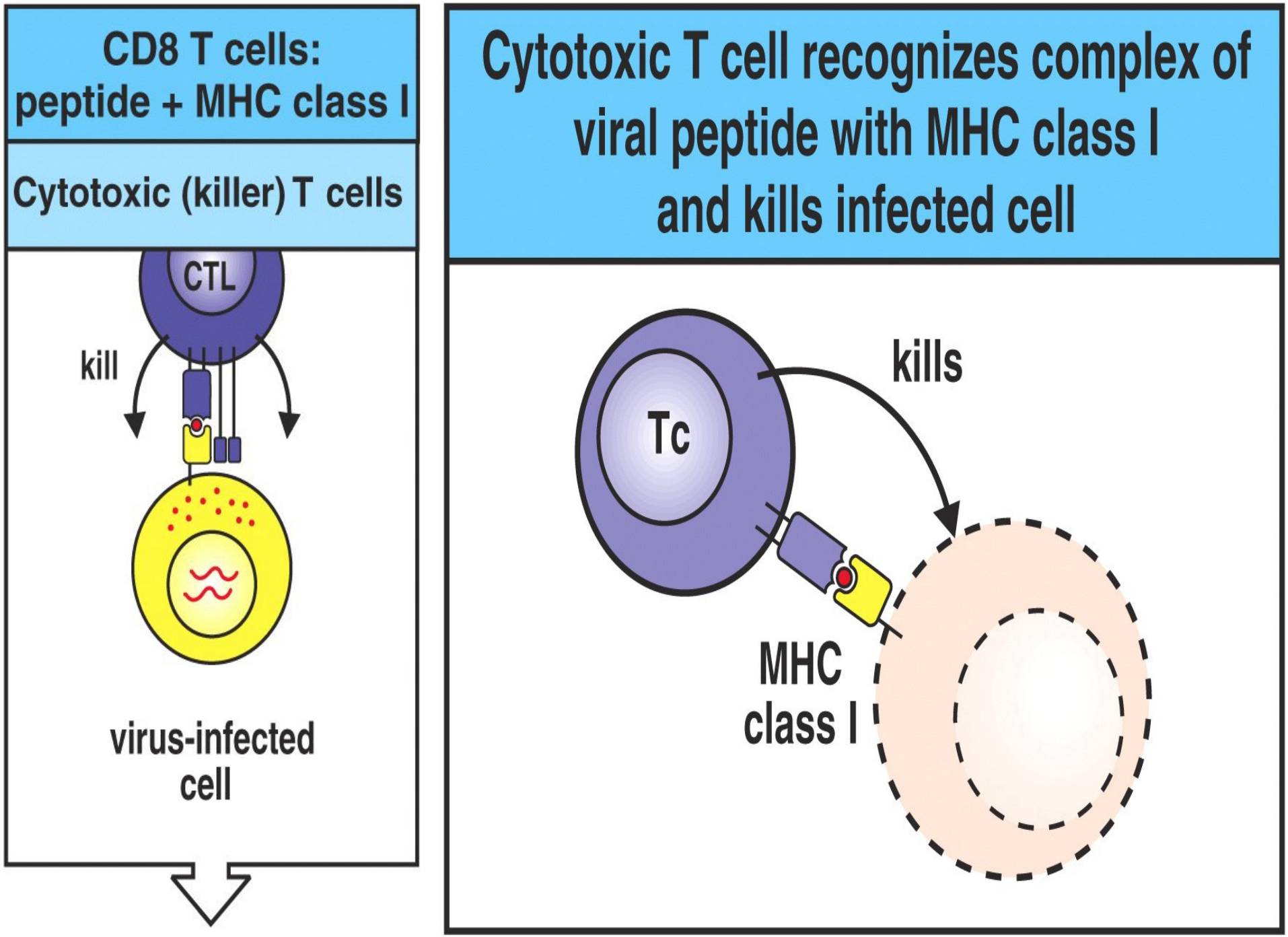


Figure 1-30 Immunobiology, 6/e. (© Garland Science 2005)

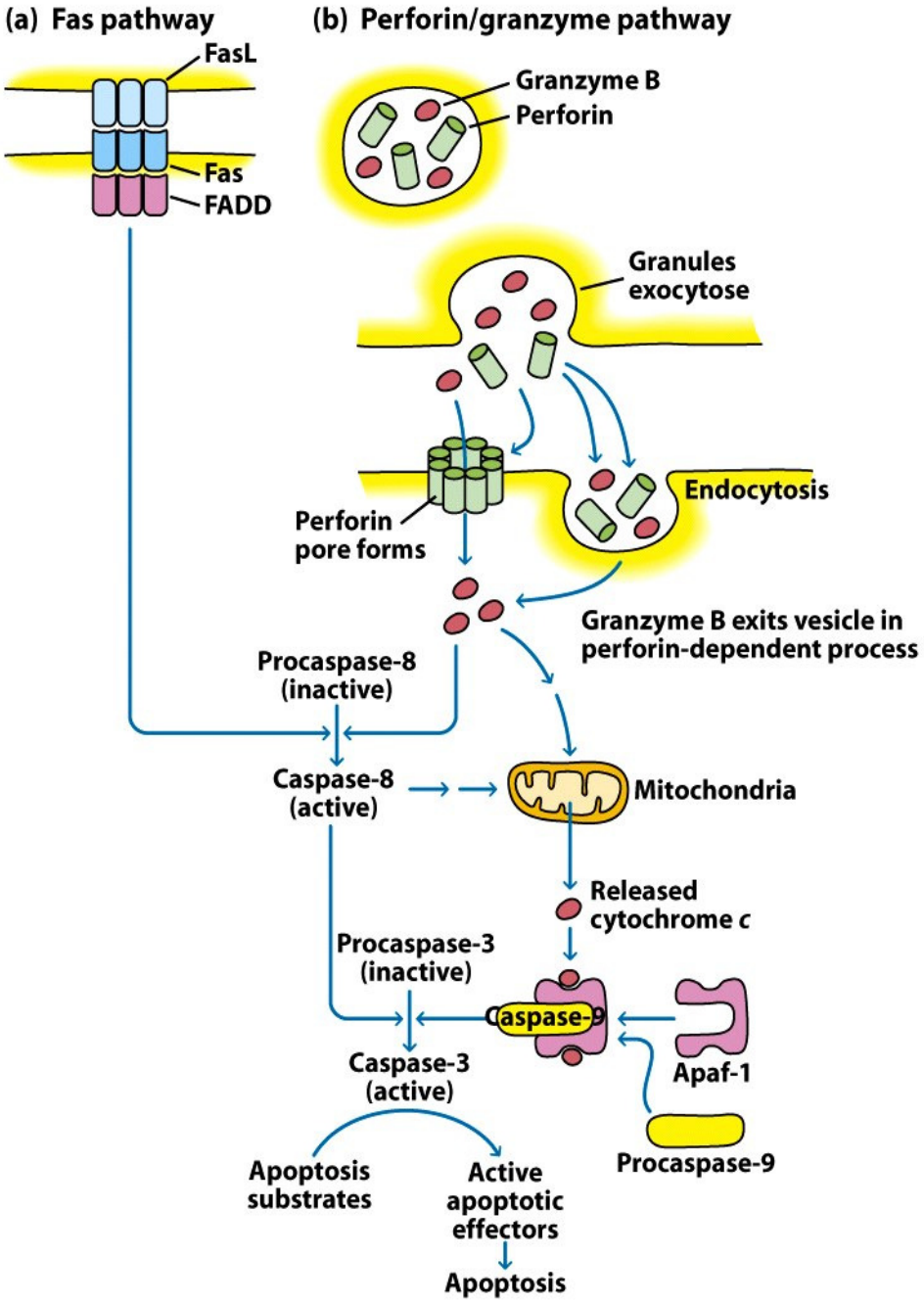


Figure 14-11
Kuby IMMUNOLOGY, Sixth Edition

Respuesta B frente a la infección viral

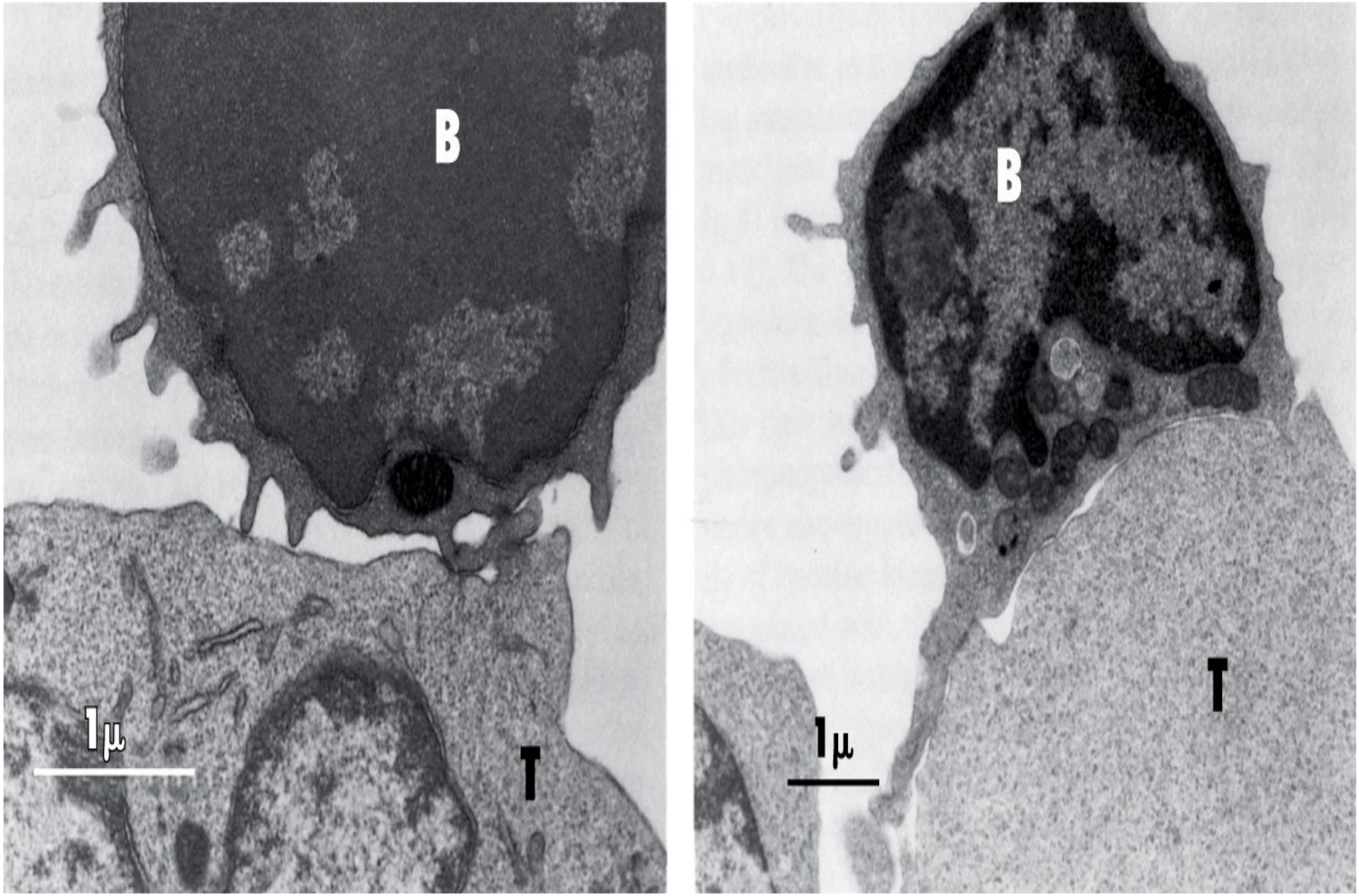


Figure 11-13
Kuby IMMUNOLOGY, Sixth Edition

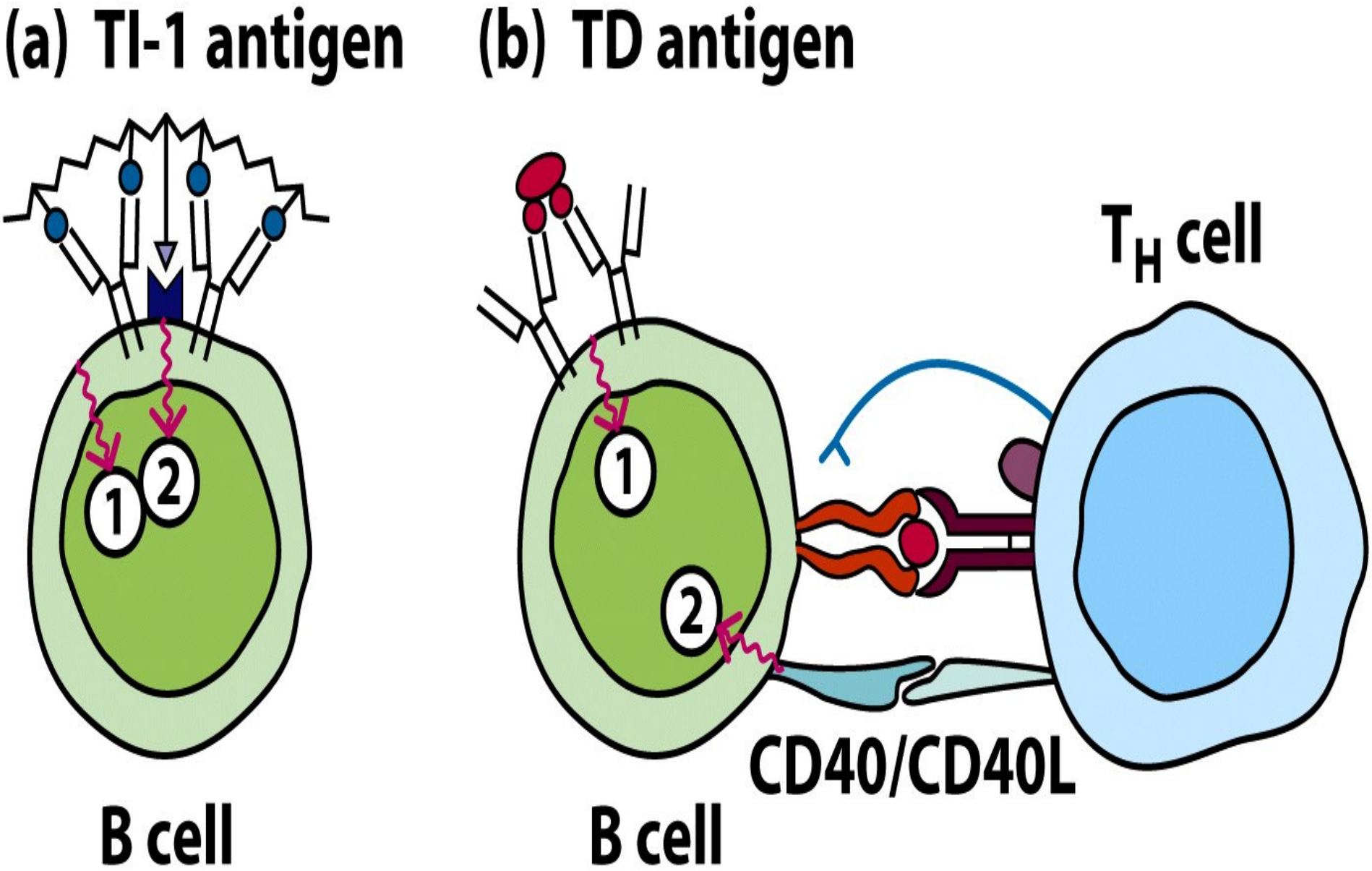
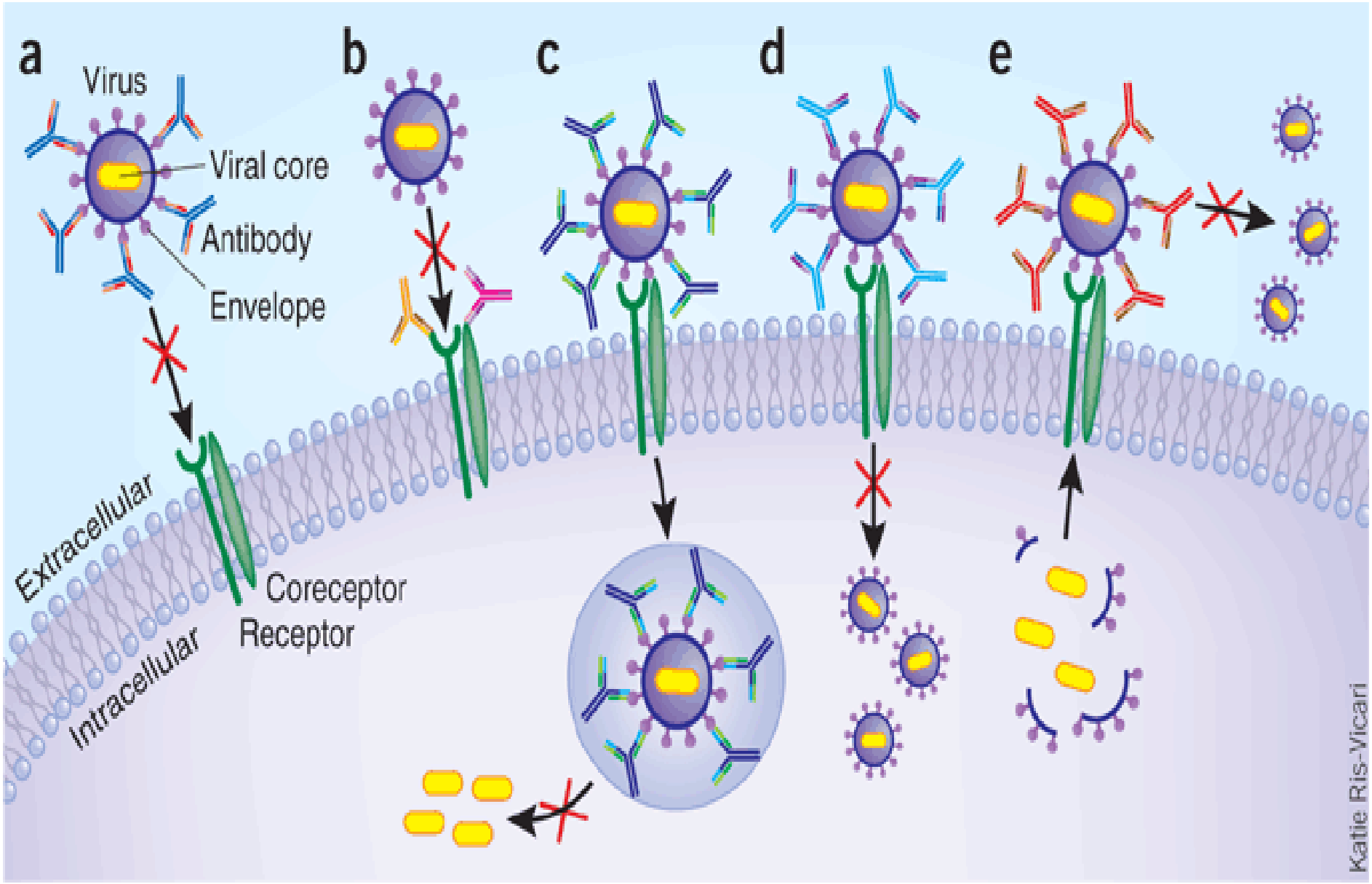


Figure 11-7
Kuby IMMUNOLOGY, Sixth Edition

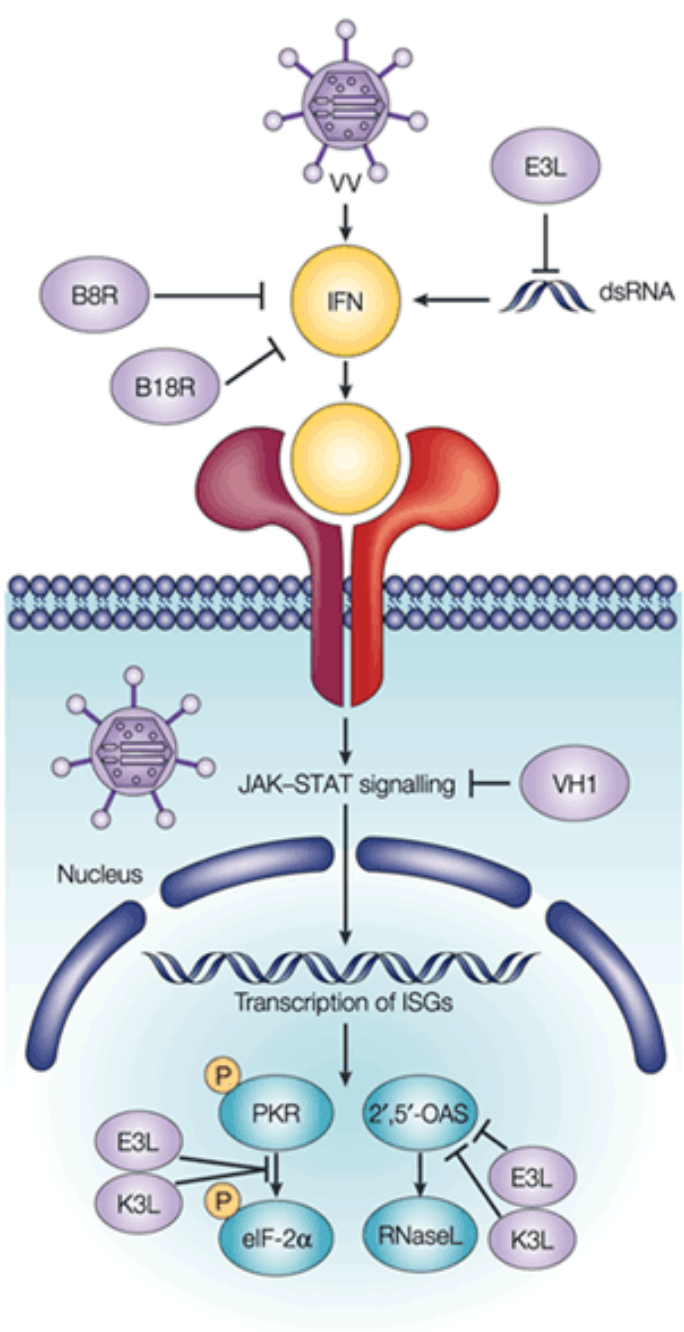


Ac neutralizantes

MECANISMOS DE EVASIÓN DE LA RESPUESTA INMUNE

Interferencia en la actividad mediada por citocinas

Virus	Proteínas	Funciones
Vaccinia	B18R soluble	Homóloga al Rc IFNAR
	E3L y K3L	Inhiben activación de PKR y de 2'5'-OAS
HHV-8	vIRF-1 – 4	Homólogas de IRF
	vIRF-1	Une e inhibe p300 → inhibición de expresión de genes
	vIRF-2	Bloquea PKR
	ORF-74	Homólogo de Rc de citocinas
	vMIP-1	Recluta L Th2 y disminuye Th1/Th2
Adenovirus	E1A	Inhibe formación de ISGF3 y disminuye expresión de STAT1 e IRF-9
	VAI (dsRNA)	Inhibe acción de PKR
Influenza A	NS1	Inhibe activación de PKR y de 2'5'-OAS
	p58	Reprime PKR
HSV	ICP34.5	Inhibe acción de PKR
	derivados de 2'5'-OAS	Inhiben RNAsa L



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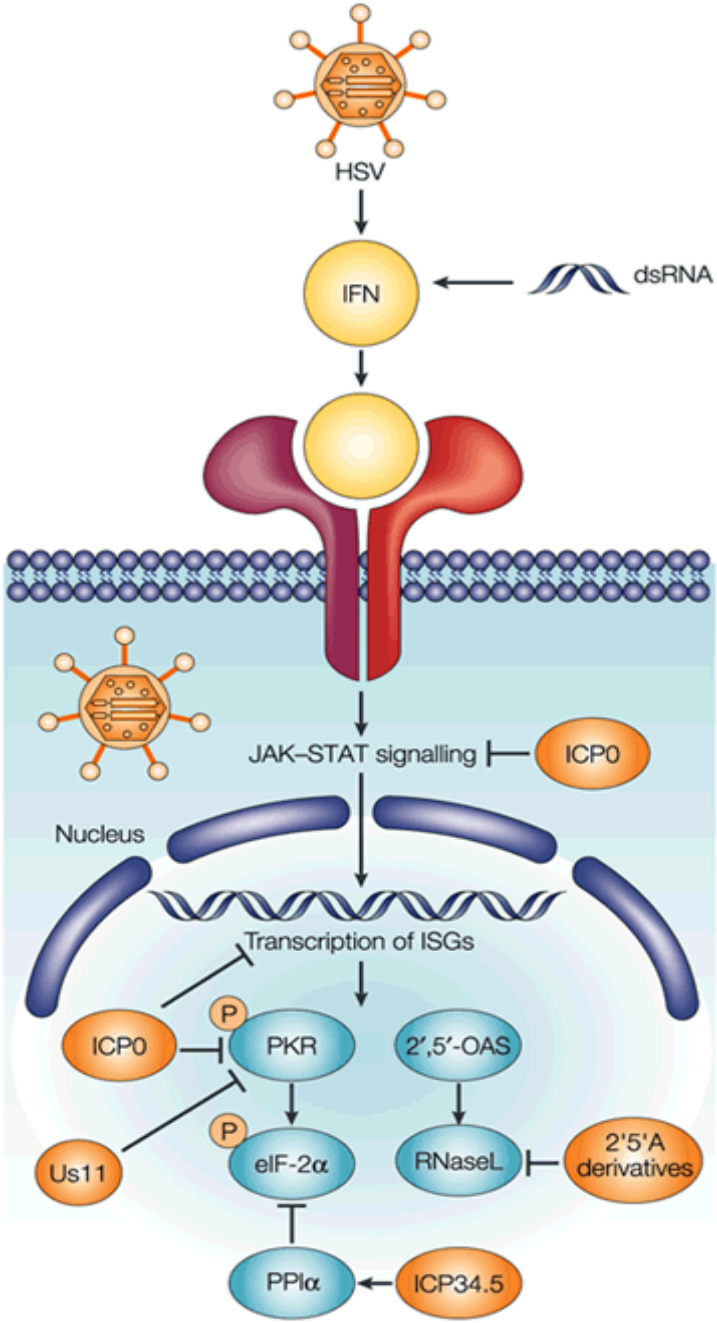

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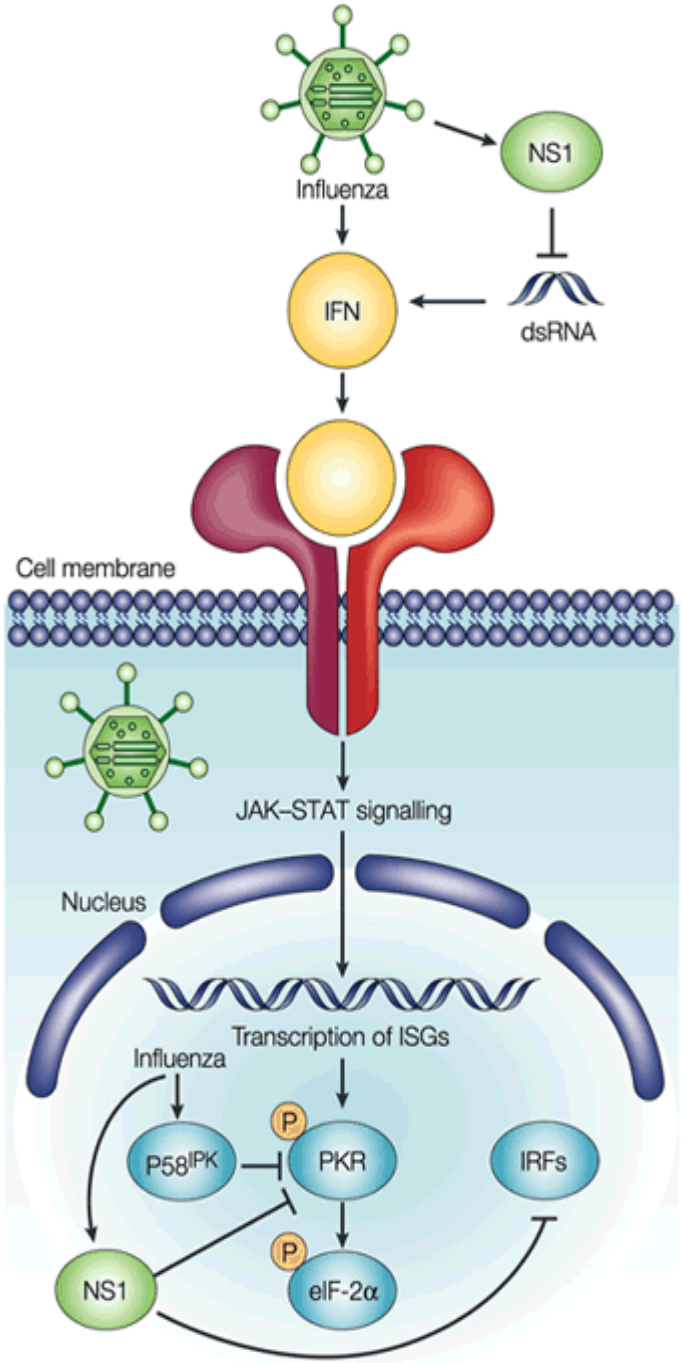

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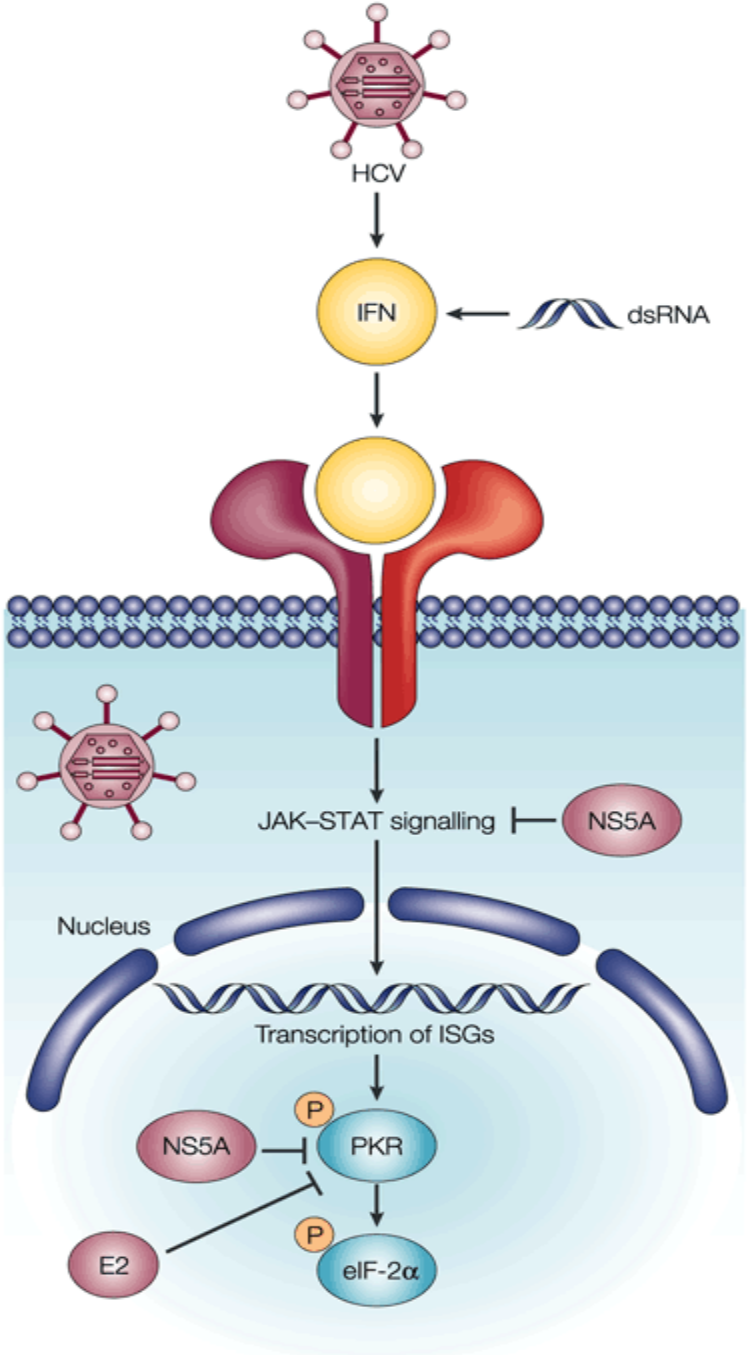

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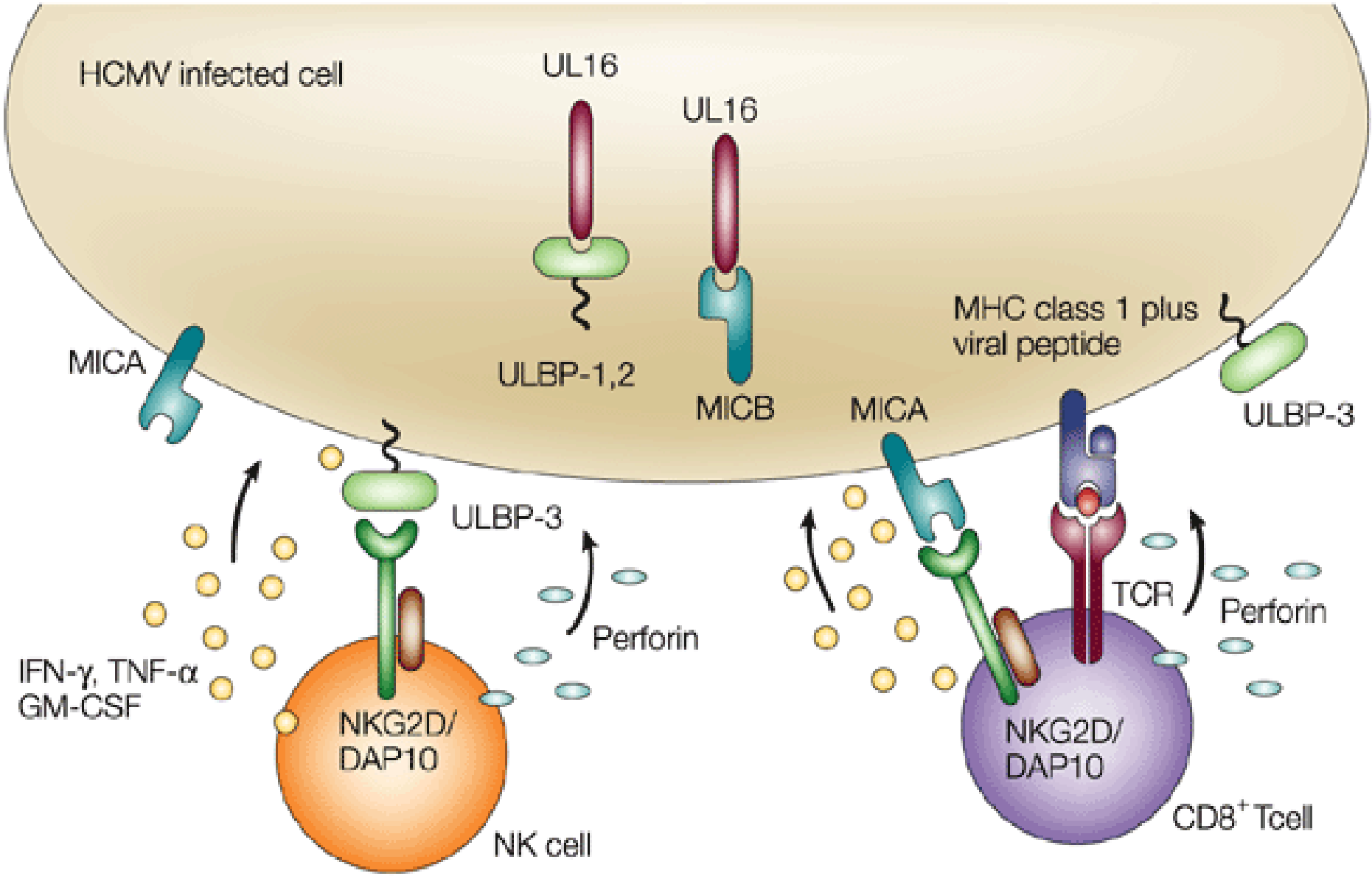
Virus	Proteínas	Funciones
HCV	NS5A E2	Inhibe acción de PKR Compite con eIF-2α por el sitio de unión en PKR
Sarampión	HA	Se une a CD46 y suprime producción de IL-12 → INF-γ
CMV	US28	Homólogo de Rc de citocinas RANTES y MCP-1
Herpesvirus	vMIPII	Homóloga de citocinas. Bloquea quimiotaxis de monocitos
HHV-6	U83	Homóloga de citocinas. Facilita diseminación viral
EBV	Homóloga de IL-10	Antagoniza perfil Th1

Interferencia en la expresión y función de MHC

Virus	Proteínas	Funciones
Adenovirus	E3-19K	Retiene MHC I en el RE
	E1A	Interfiere en la expresión de MHC II
EBV	BZLF2	Interfiere en la presentación antigénica mediada por MHC II
HCMV	US2	Marca las cadenas pesadas de MHC I y las cadenas DRα para su degradación
	US3	Retiene MHC I en el RE
	US6	Inhibe el complejo TAP 1/2
	US11	Marca las cadenas pesadas de MHC I para su degradación
	UL18	Homólogo de MHC I, inhibe la activación de NK
HIV	Nef	Induce una endocitosis rápida de MHC I y CD4 e interfiere en el procesamiento de MHC II
	Vpu	Desestabiliza MHC I sintetizadas de novo y marca CD4 para su degradación
HPV	E5 y E6	Interfieren en el procesamiento de MHC II
HSV	ICP47	Inhibe el complejo TAP 1/2
RSV	?	Disminuye la transcripción de MHC I
Vaccinia	?	Disminuye la expresión de MHC I sobre la superficie celular


HCMV infected cell
UL16
UL16
ULBP-1,2
MICB
MICA
MHC class 1 plus
viral peptide
ULBP-3
MICA
ULBP-3
Perforin
IFN-γ, TNF-α
GM-CSF
NKG2D/
DAP10
NK cell
TCR
Perforin
NKG2D/
DAP10
CD8+ Tcell

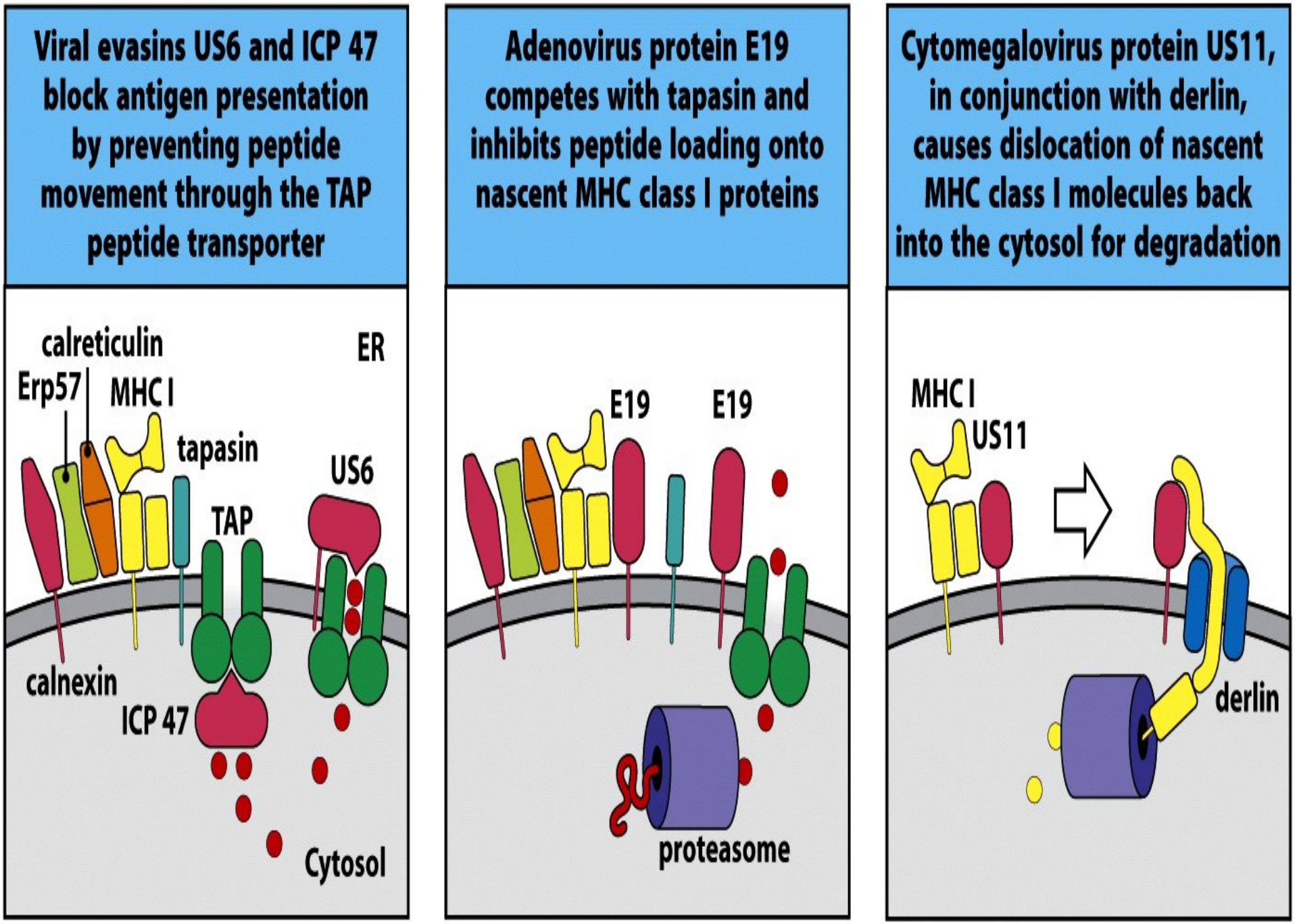
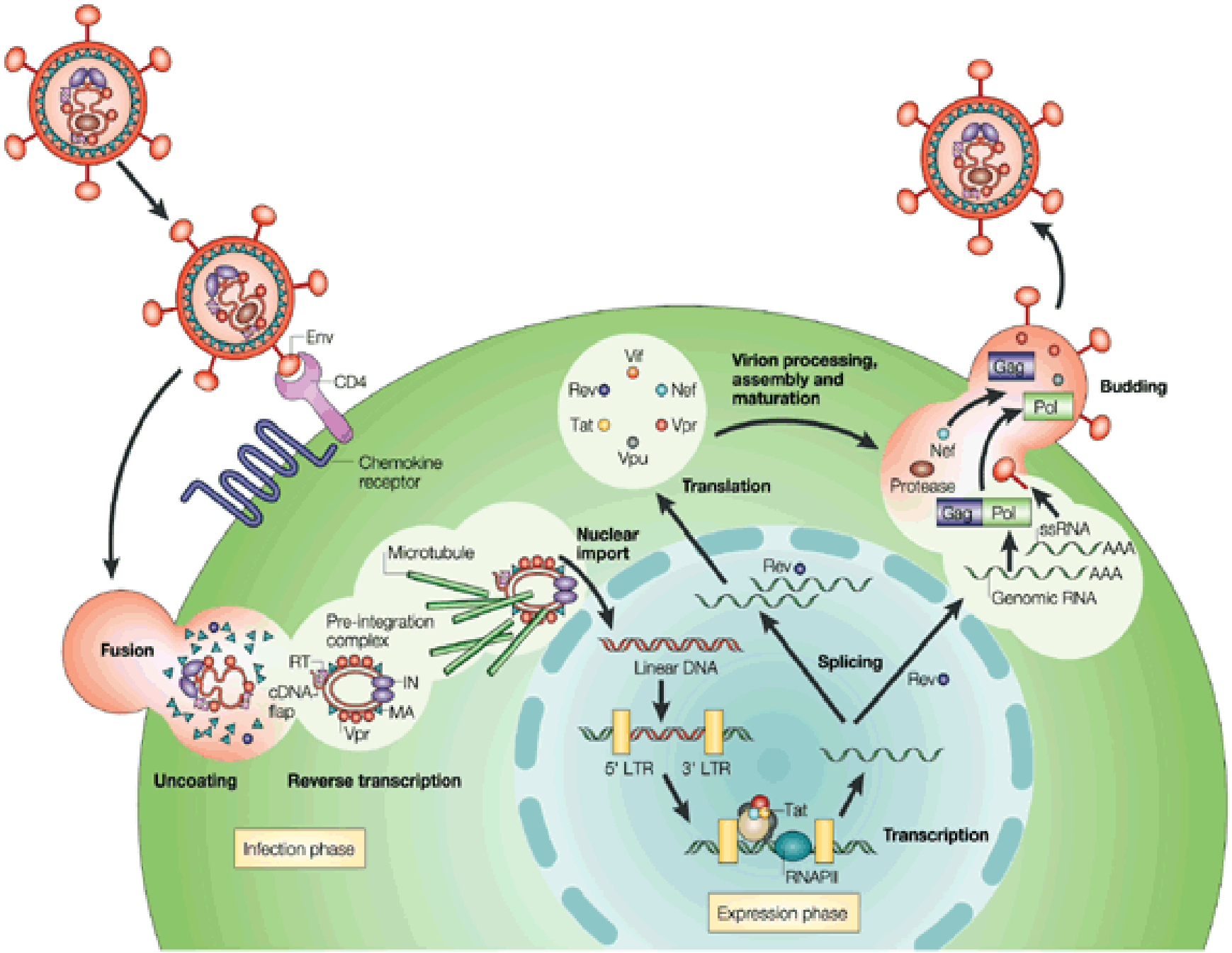
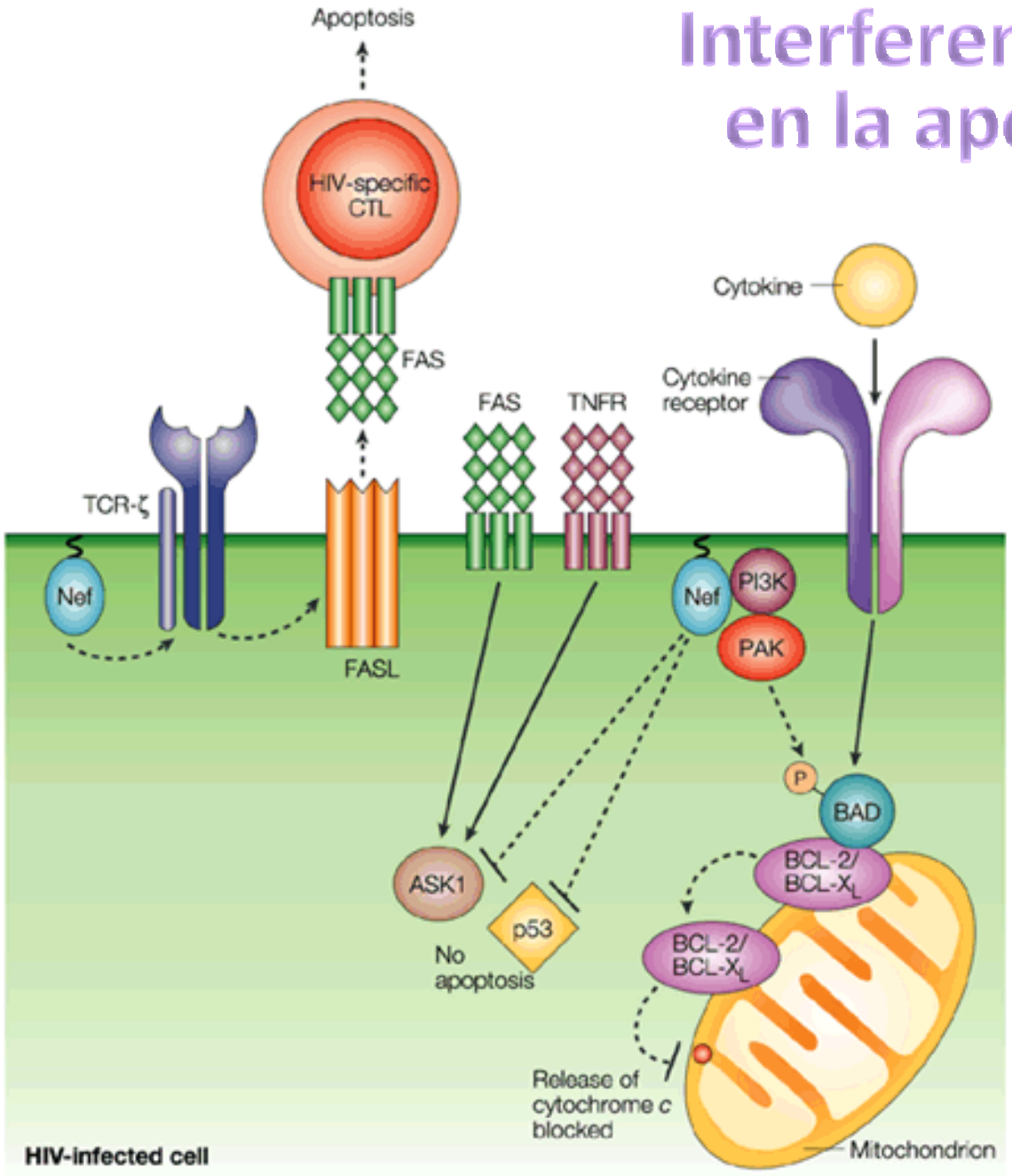


Figure 5-7 Immunobiology, 7ed. (© Garland Science 2008)


Env
CD4
Chemokine receptor
Fusion
Uncoating
Microtubule
Pre-integration complex
RT
cDNA flap
IN
MA
Vpr
Reverse transcription
Nuclear import
Infection phase
Vif
Rev
Nef
Tat
Vpr
Vpu
Translation
Virion processing, assembly and maturation
Linear DNA
5' LTR
3' LTR
Tat
RNAPII
Transcription
Rev
Splicing
Rev
Expression phase
Gag
Pol
Budding
Nef
Protease
Gag
Pol
ssRNA
AAA
AAA
Genomic RNA

Interferencia viral en la apoptosis



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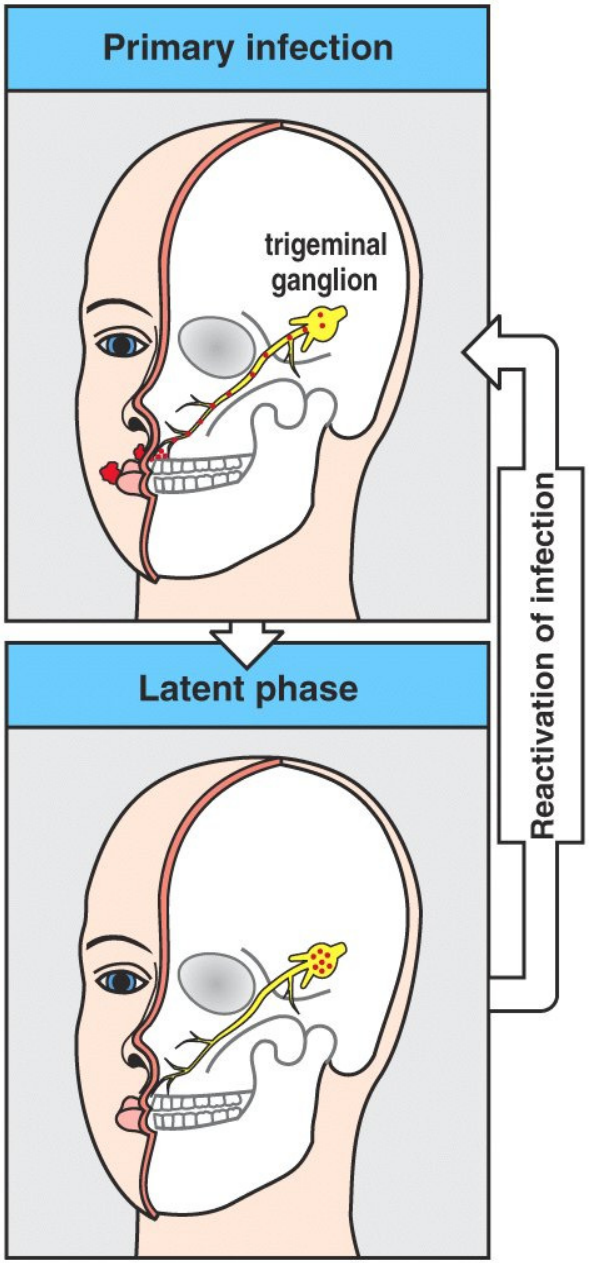
Virus	Proteínas	Funciones
Adenovirus	E3-10.41/14.5K	Internalización y degradación de Fas
	14.7K	Interactúa con la caspasa 8 e inhibe la activación de otras caspasas
HCMV	UL144	Retención intracelular de Fas
Cowpox	crmA	Potente inhibidor de caspasas 1 y 8
	crmB	Neutraliza a TNF-α
	crmC	Neutraliza a TNF-α
	crmD	Bloquea a la linfotoxina alfa y al TNF-α
HHV-8	K13	Inhibe la activación de las caspasas por Rc de muerte
	Ksbcl-2	Homólogo de Bcl-2
EBV	BHRF1	Homólogo de Bcl-2
	BALF1	Homólogo de Bcl-2
	LMP	Aumenta la expresión de Bcl-2 y otros miembros de su familia que promueven la supervivencia celular

Sitios inmunológicamente "ocultos"



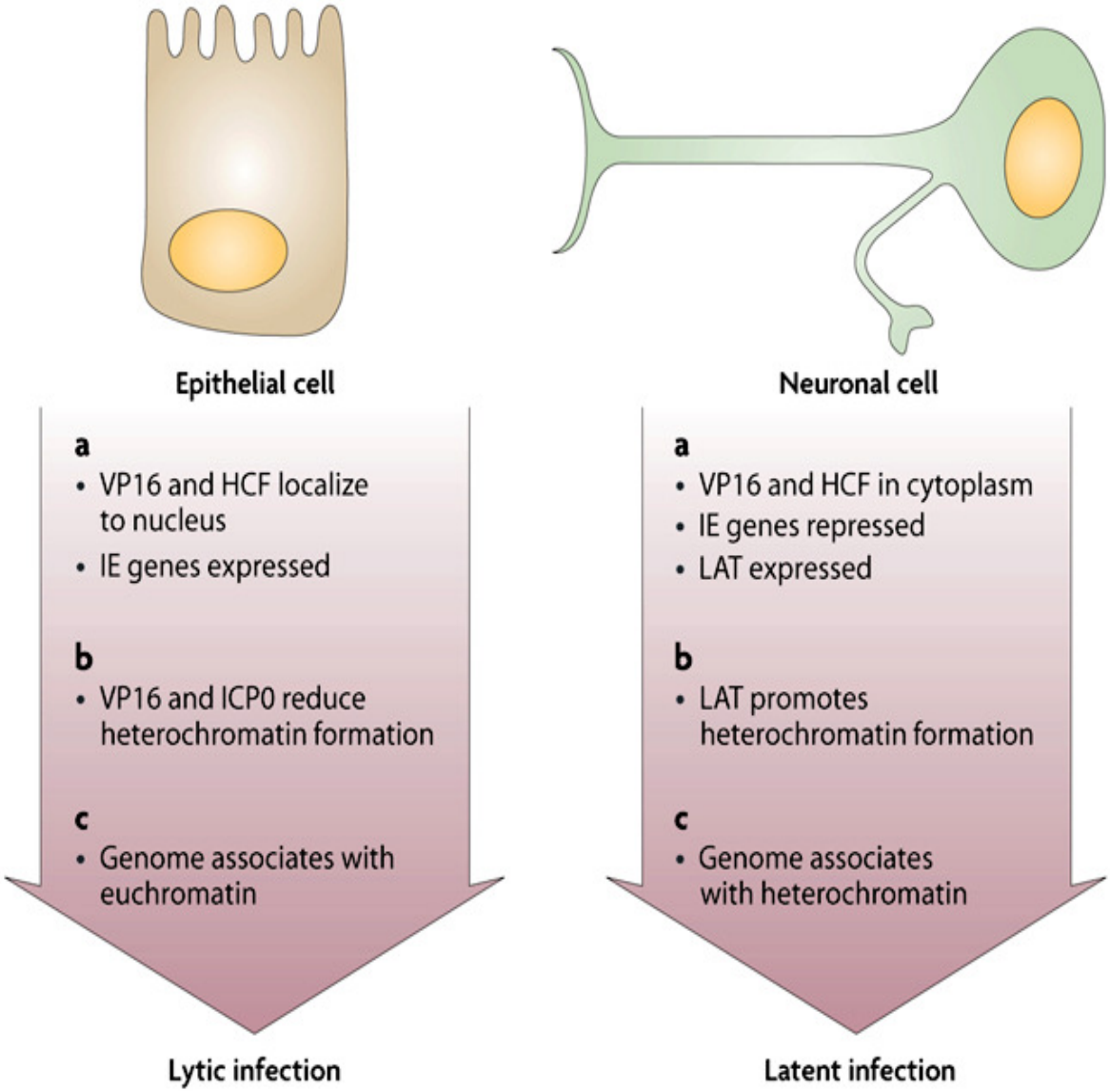


Figure 9-4 The Immune System, 2/e (© Garland Science 2005)

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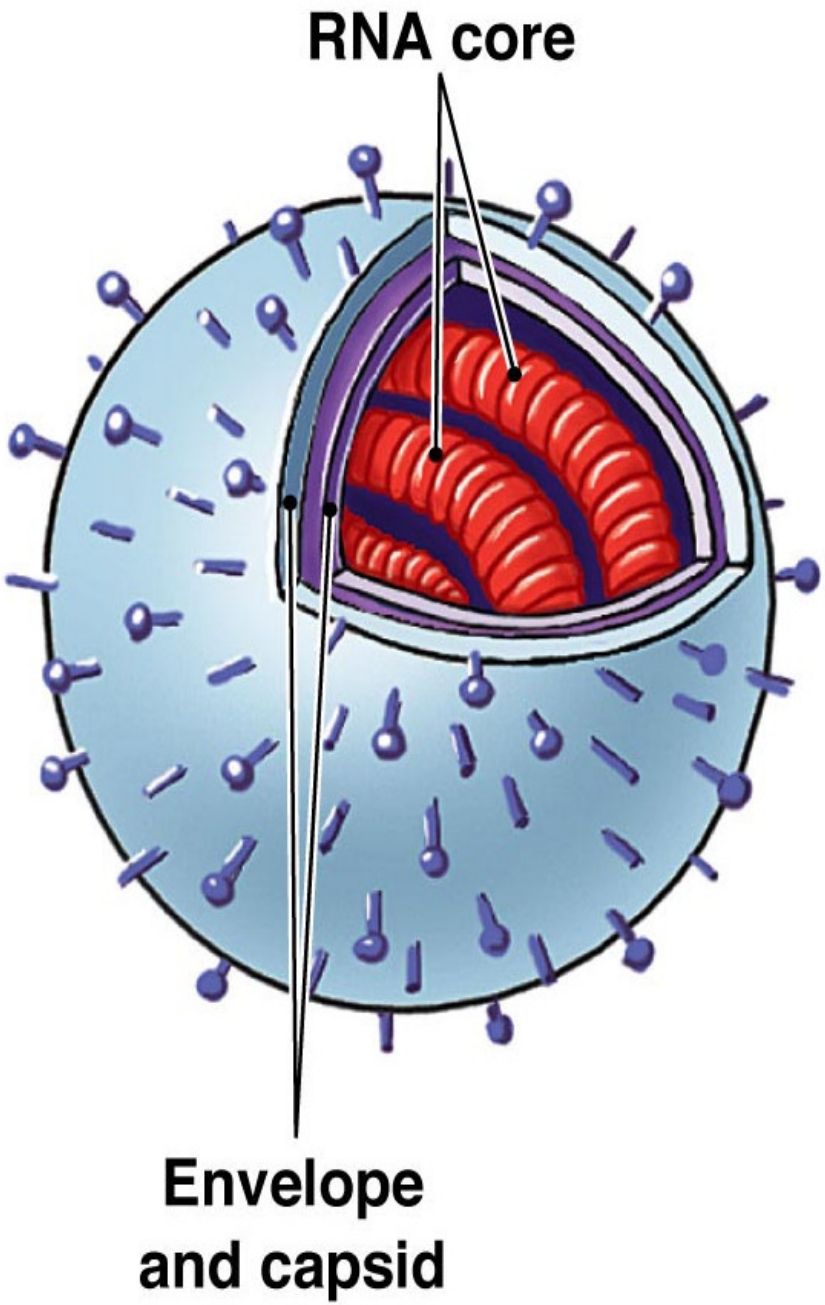
Viral strategy	Specific mechanism	Result	Virus examples
Inhibition of humoral immunity	Virally encoded Fc receptor	Blocks effector functions of antibodies bound to infected cells	Herpes simplex Cytomegalovirus
	Virally encoded complement receptor	Blocks complement-mediated effector pathways	Herpes simplex
	Virally encoded complement control protein	Inhibits complement activation of infected cell	Vaccinia

Figure 9-5 part 1 of 3 The Immune System, 2/e (© Garland Science 2005)

Variación antigénica

(a) Influenza, an RNA virus



(b) General steps of viral replication

Viral invasion of host cell

↓

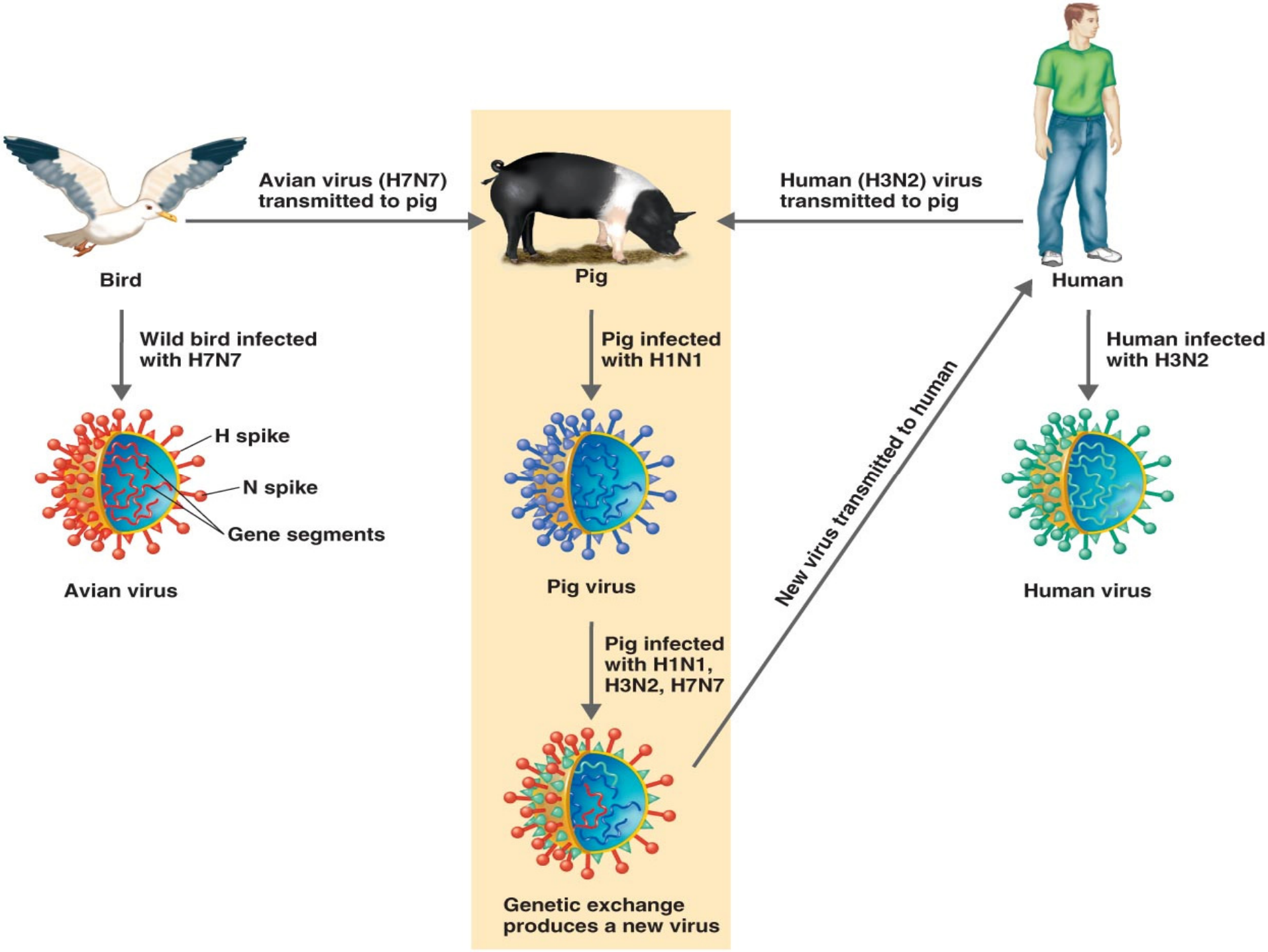
Synthesis of new viral nucleic acids and proteins

↓

Self-assembly of new viral macromolecules into new virus particles

↓

Virus particles released from host cell


Avian virus (H7N7) transmitted to pig
Human (H3N2) virus transmitted to pig
Bird
Pig
Human
Wild bird infected with H7N7
Pig infected with H1N1
Human infected with H3N2
H spike
N spike
Gene segments
Avian virus
Pig virus
Human virus
New virus transmitted to human
Pig infected with H1N1, H3N2, H7N7
Genetic exchange produces a new virus

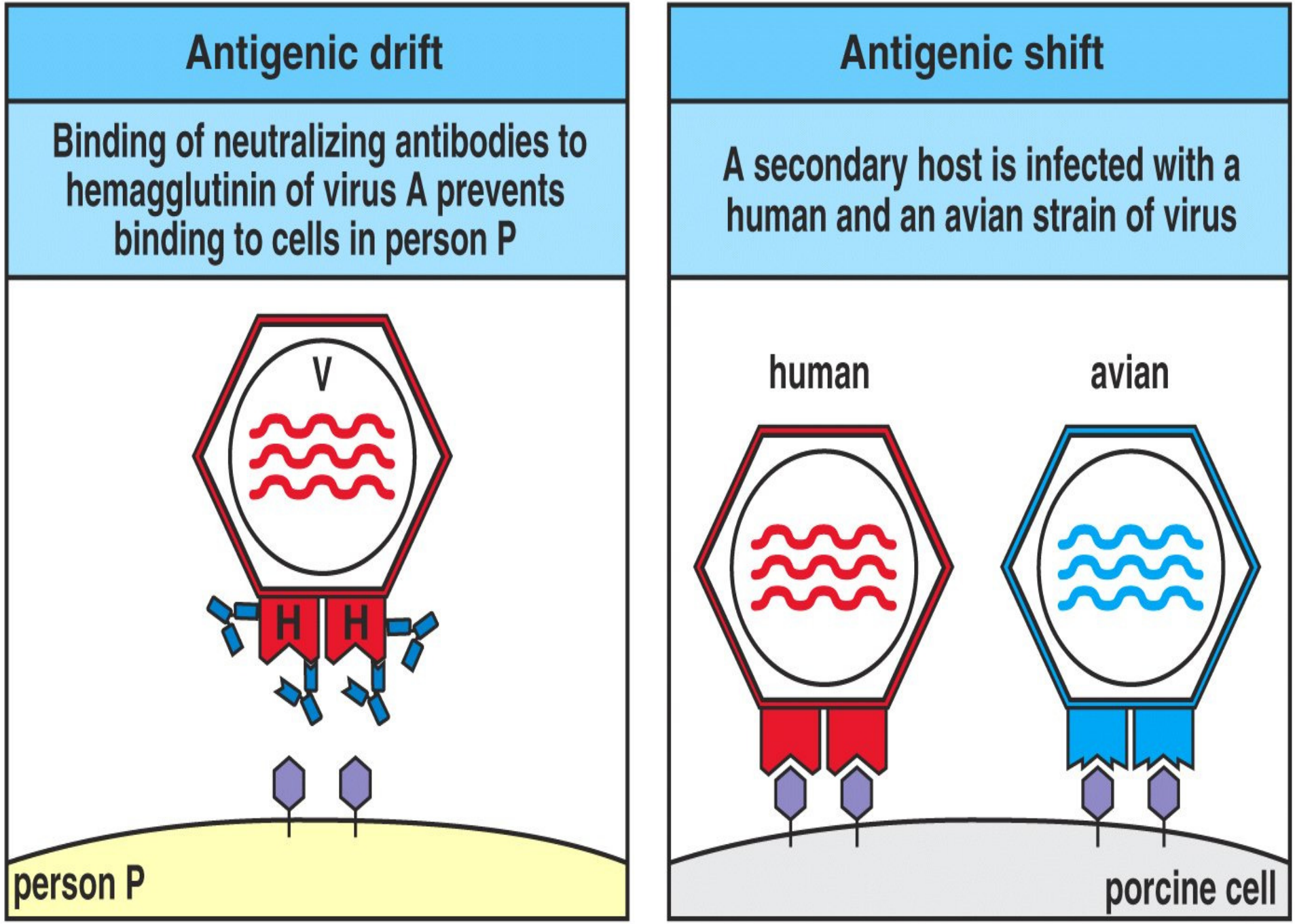


Figure 9-2 part 1 of 3 The Immune System, 2/e (© Garland Science 2005)

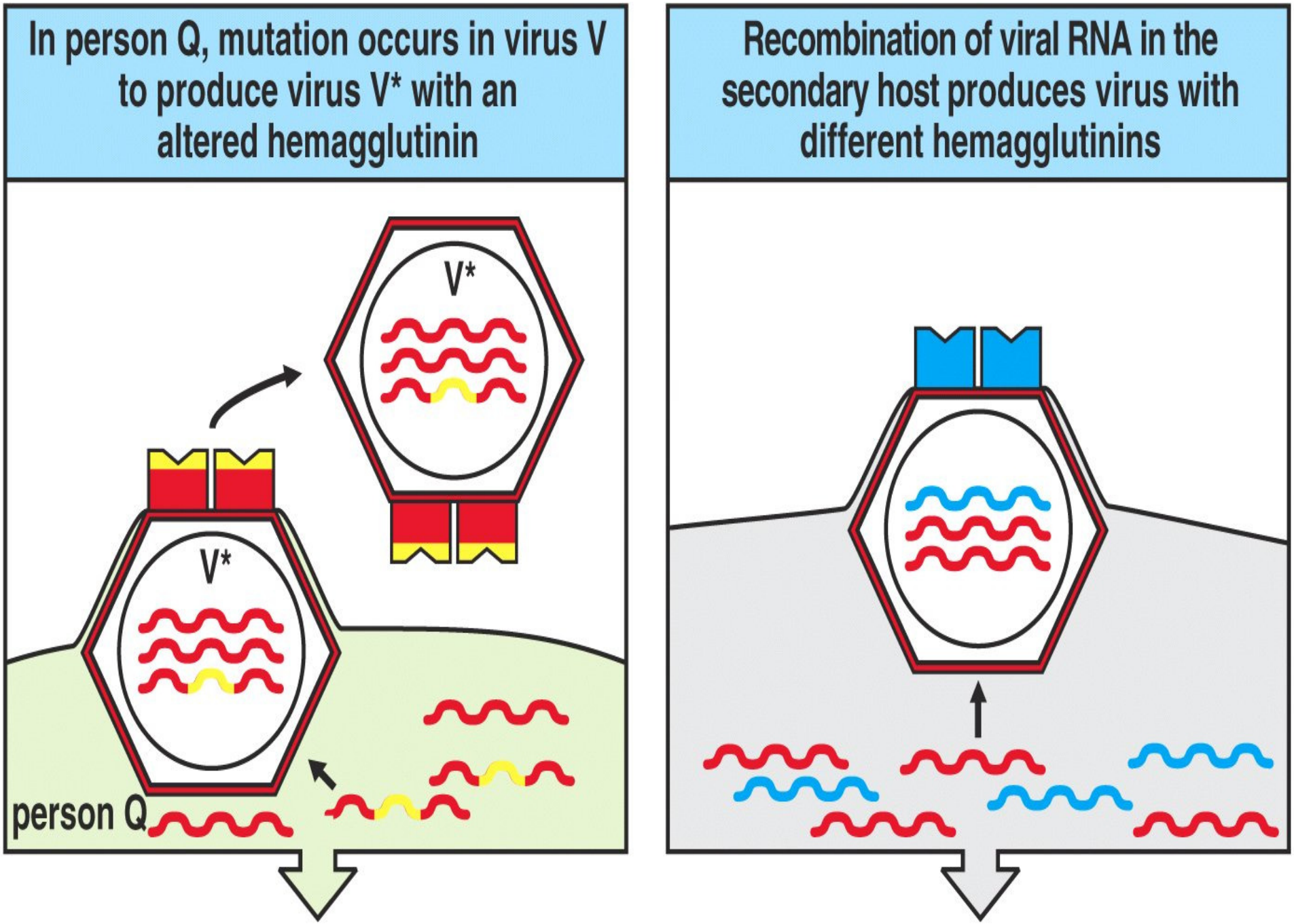


Figure 9-2 part 2 of 3 The Immune System, 2/e (© Garland Science 2005)

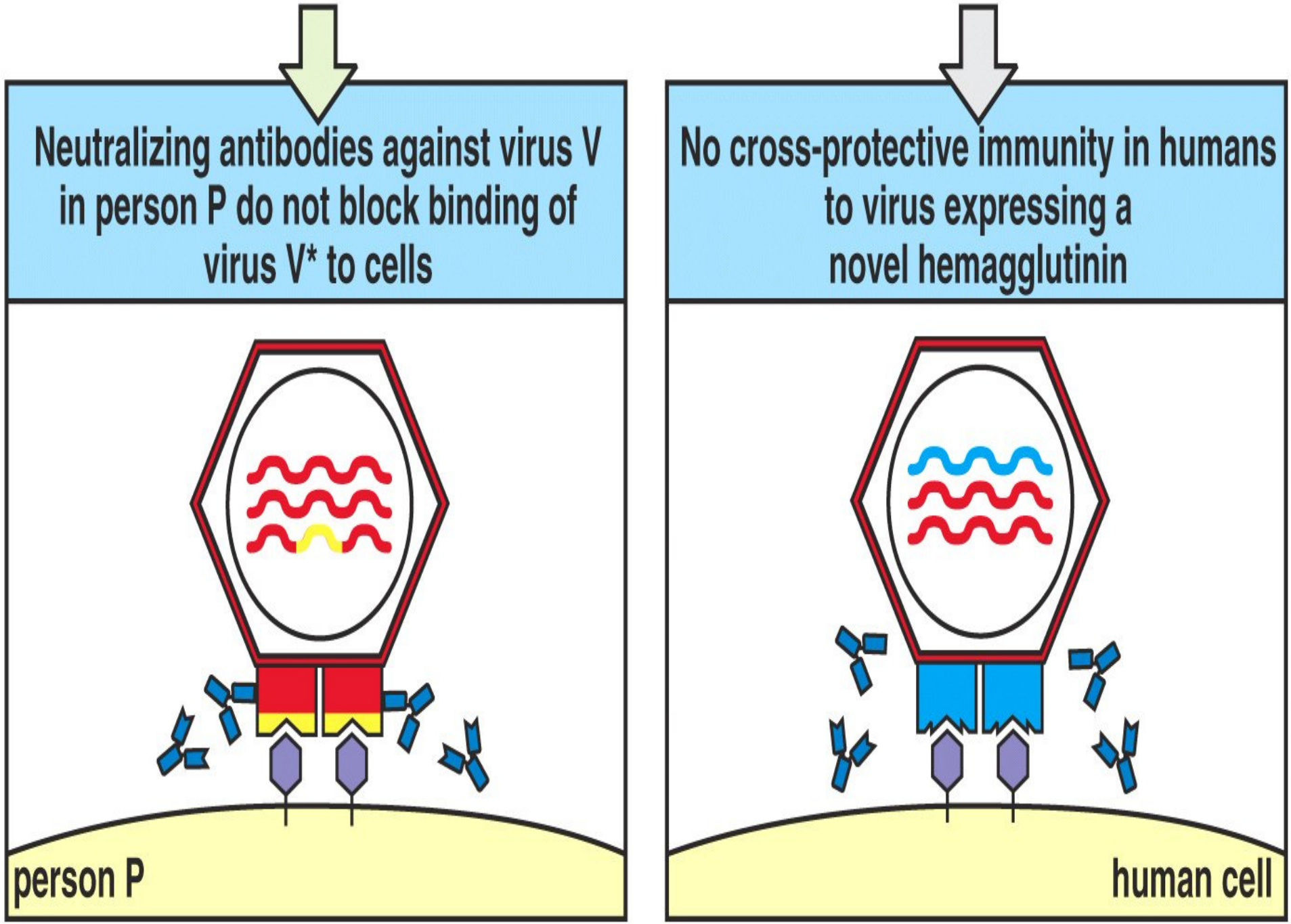


Figure 9-2 part 3 of 3 The Immune System, 2/e (© Garland Science 2005)

Resumiendo…

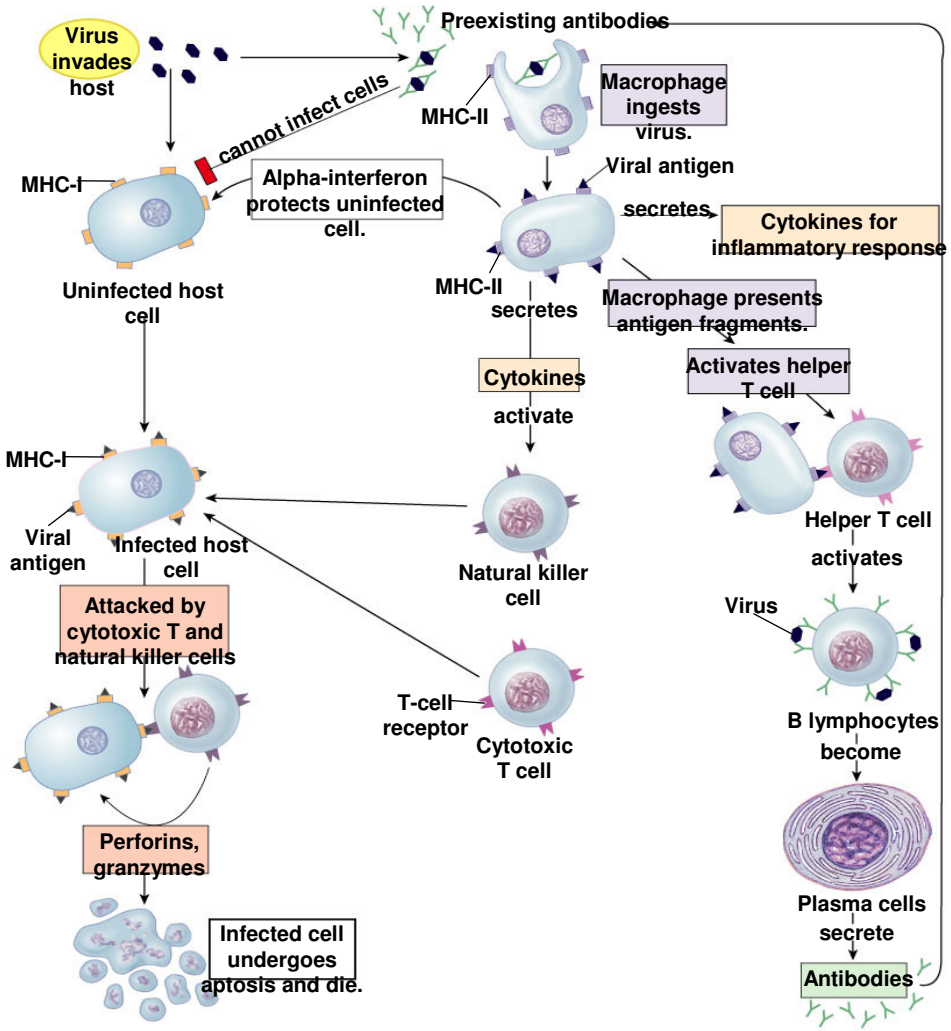


Figure 24-18

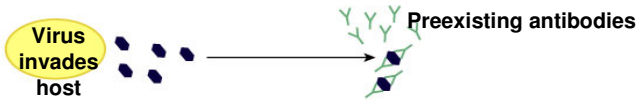


Figure 24-18 (1 of 5)

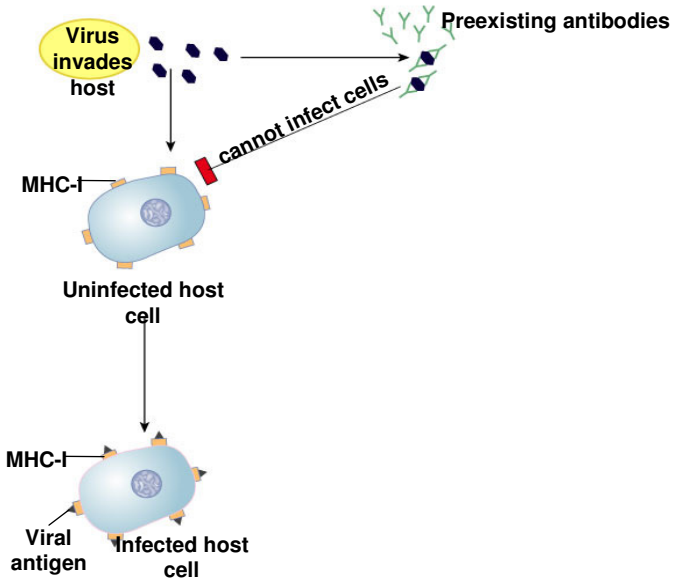


Figure 24-18 (2 of 5)

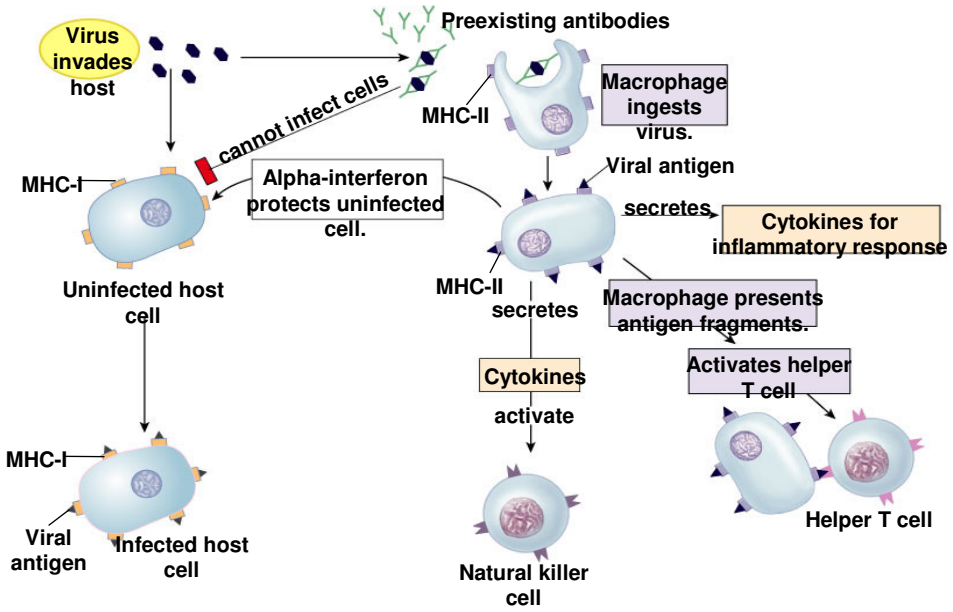


Figure 24-18 (3 of 5)

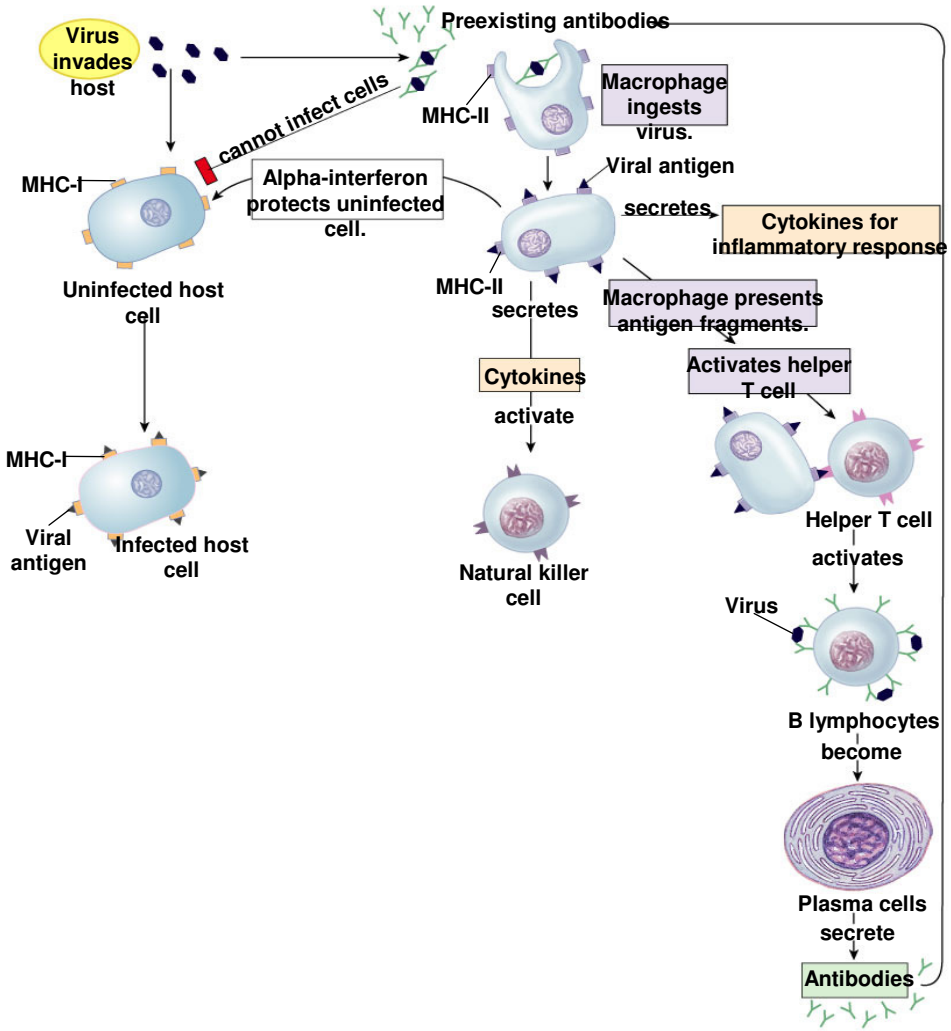


Figure 24-18 (4 of 5)

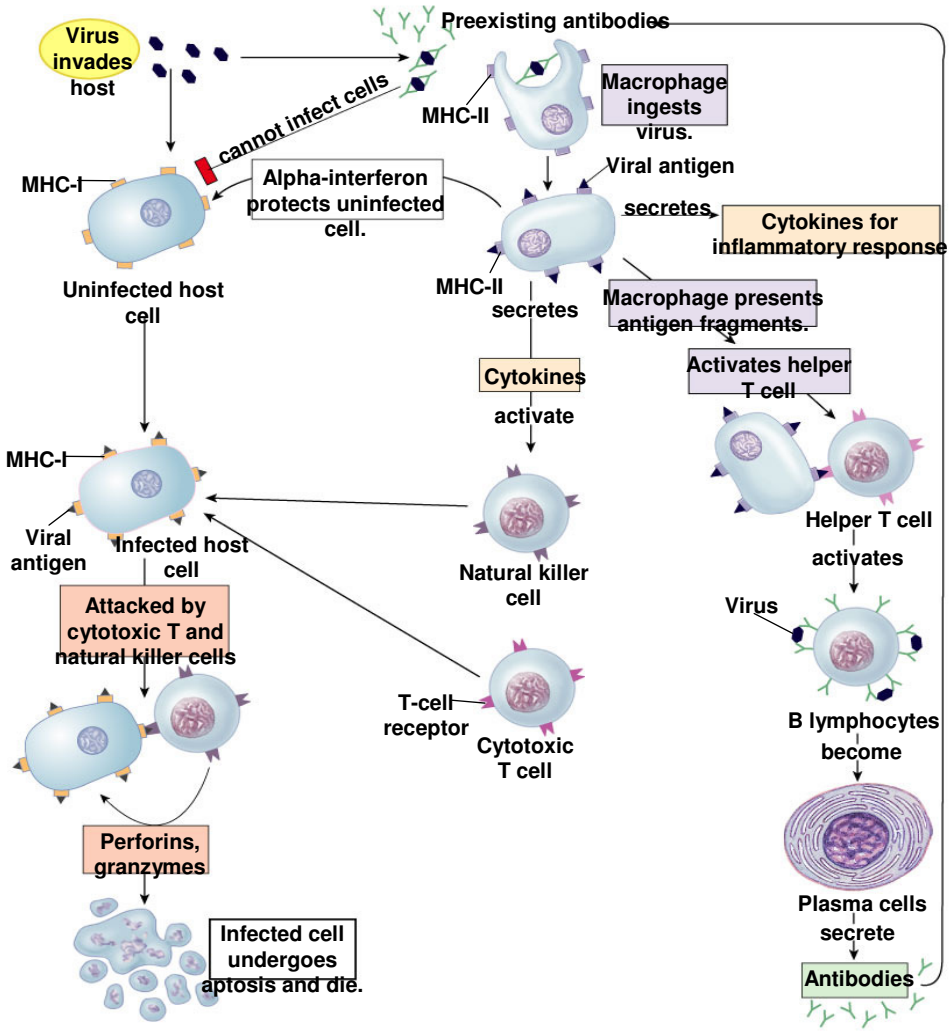


Figure 24-18 (5 of 5)