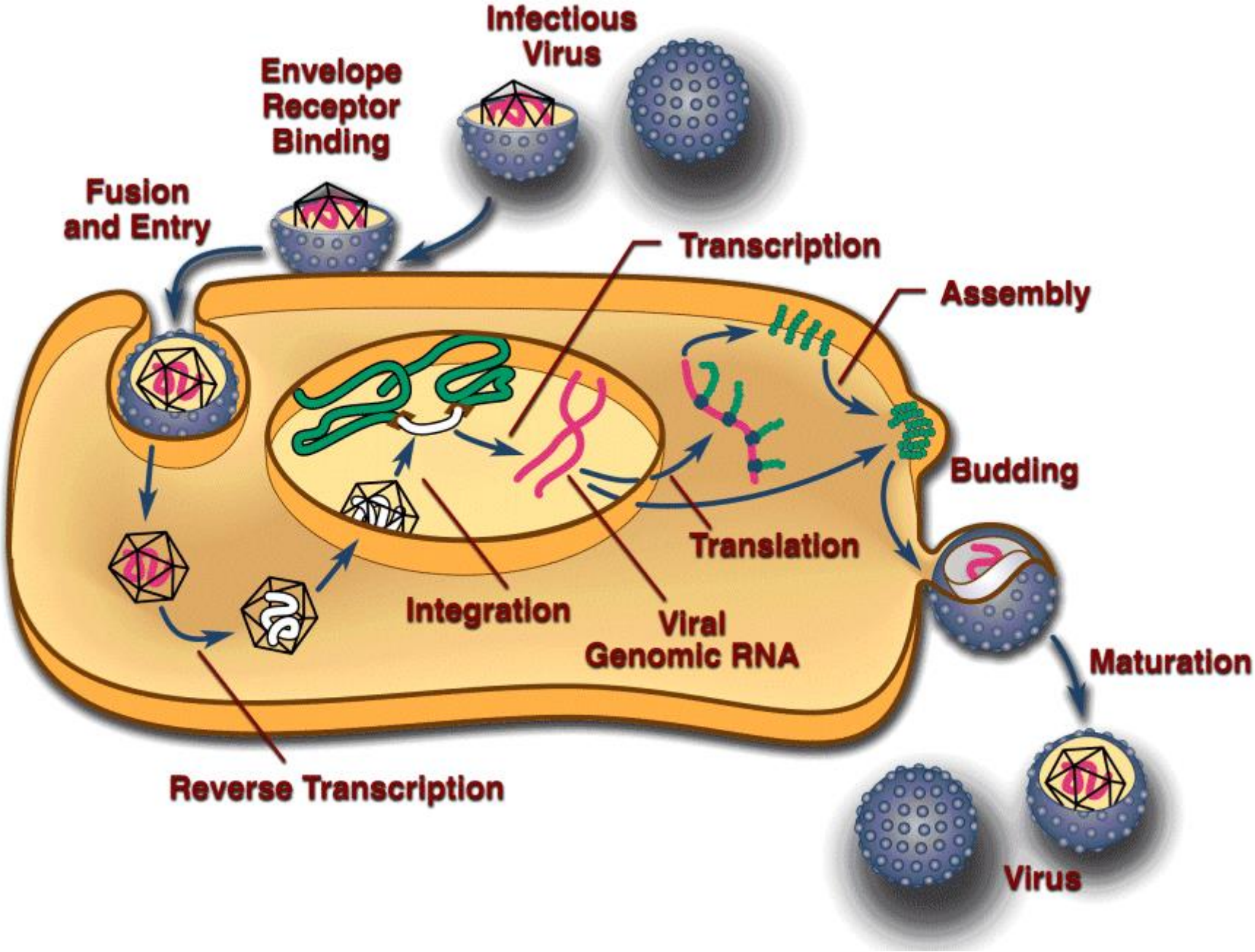

Infectious Virus
Envelope Receptor Binding
Fusion and Entry
Transcription
Assembly
Budding
Translation
Integration
Viral Genomic RNA
Reverse Transcription
Maturation
Virus

VIRAL LIFE CYCLE

- **ATTACHMENT**
- **ENTRY**
- **UNCOATING**

- **GENOME REPLICATION**

- **ASSEMBLY**
- **RELEASE**

VIRAL LIFE CYCLE

- **ATTACHMENT**
- **ENTRY**
- **UNCOATING**

- **GENOME REPLICATION**

- **ASSEMBLY**
- **RELEASE**

On the surface membrane of all living cells are protein structures called "receptors". Some viral proteins “antireceptors” usually expressed on the enveloped or on the capsid are able to interact with them.

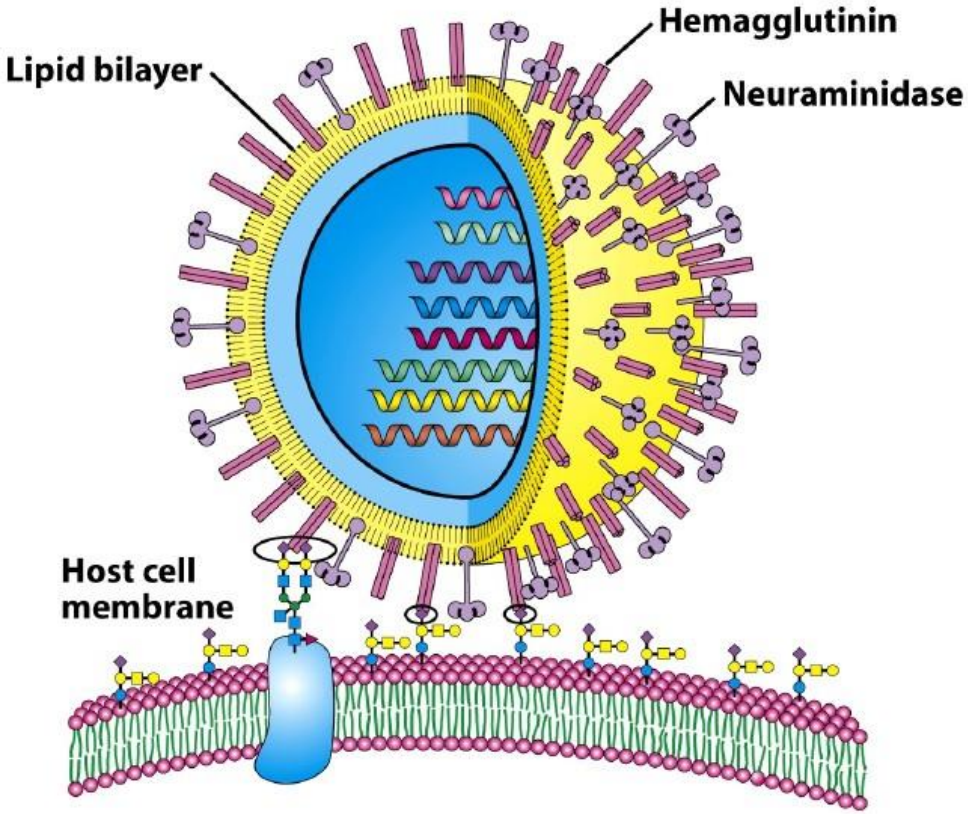
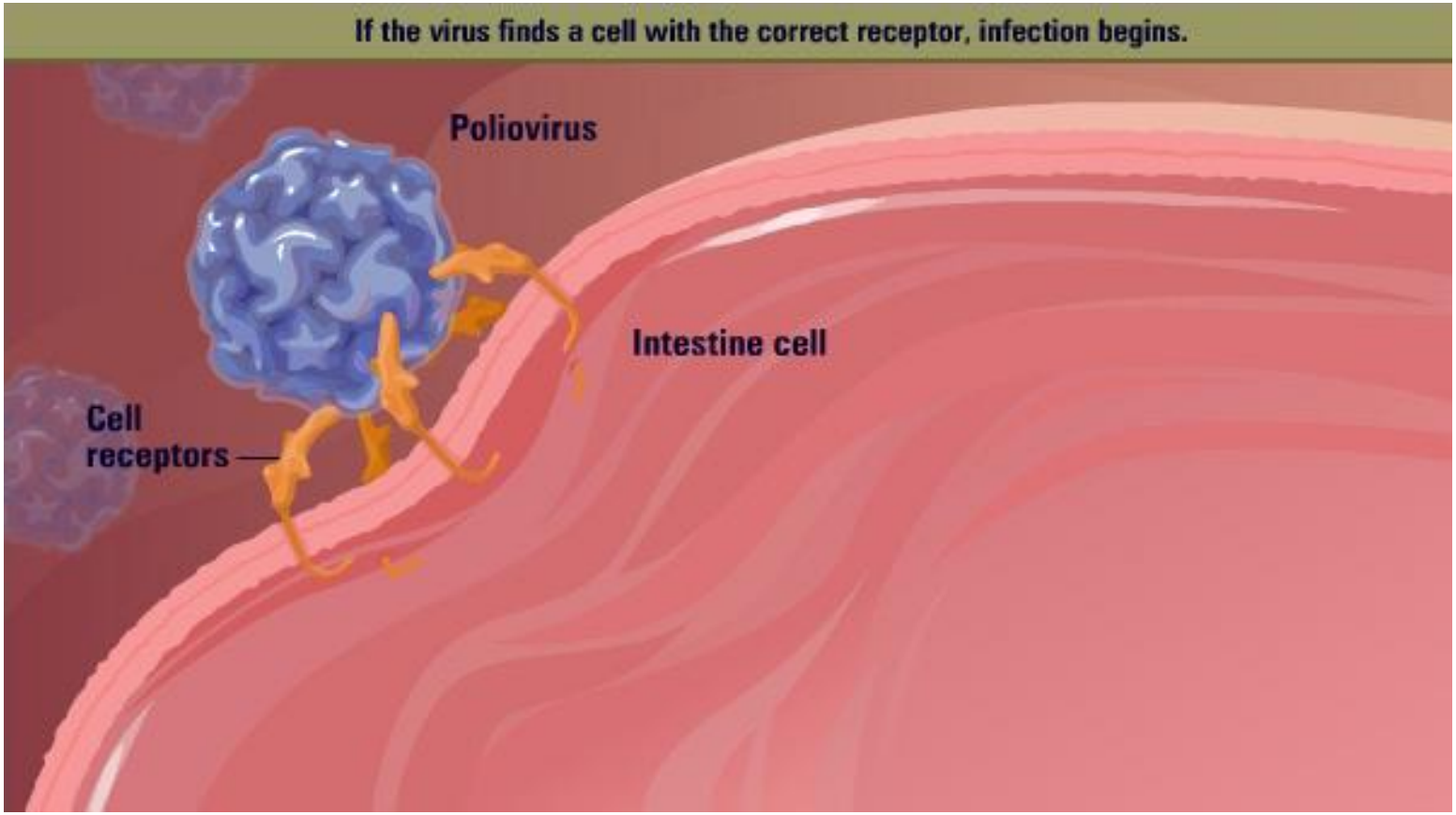


Figure 11-29
Biochemistry, Sixth Edition


If the virus finds a cell with the correct receptor, infection begins.
Poliovirus
Intestine cell
Cell receptors

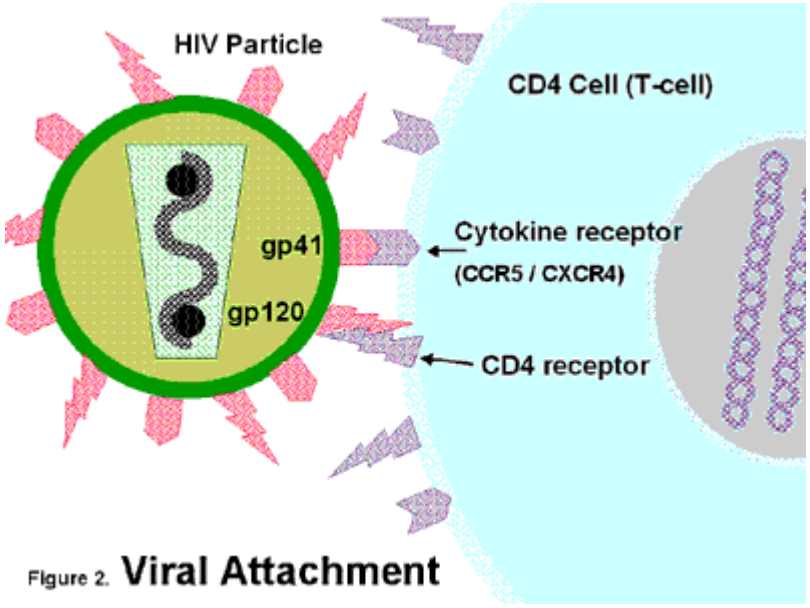


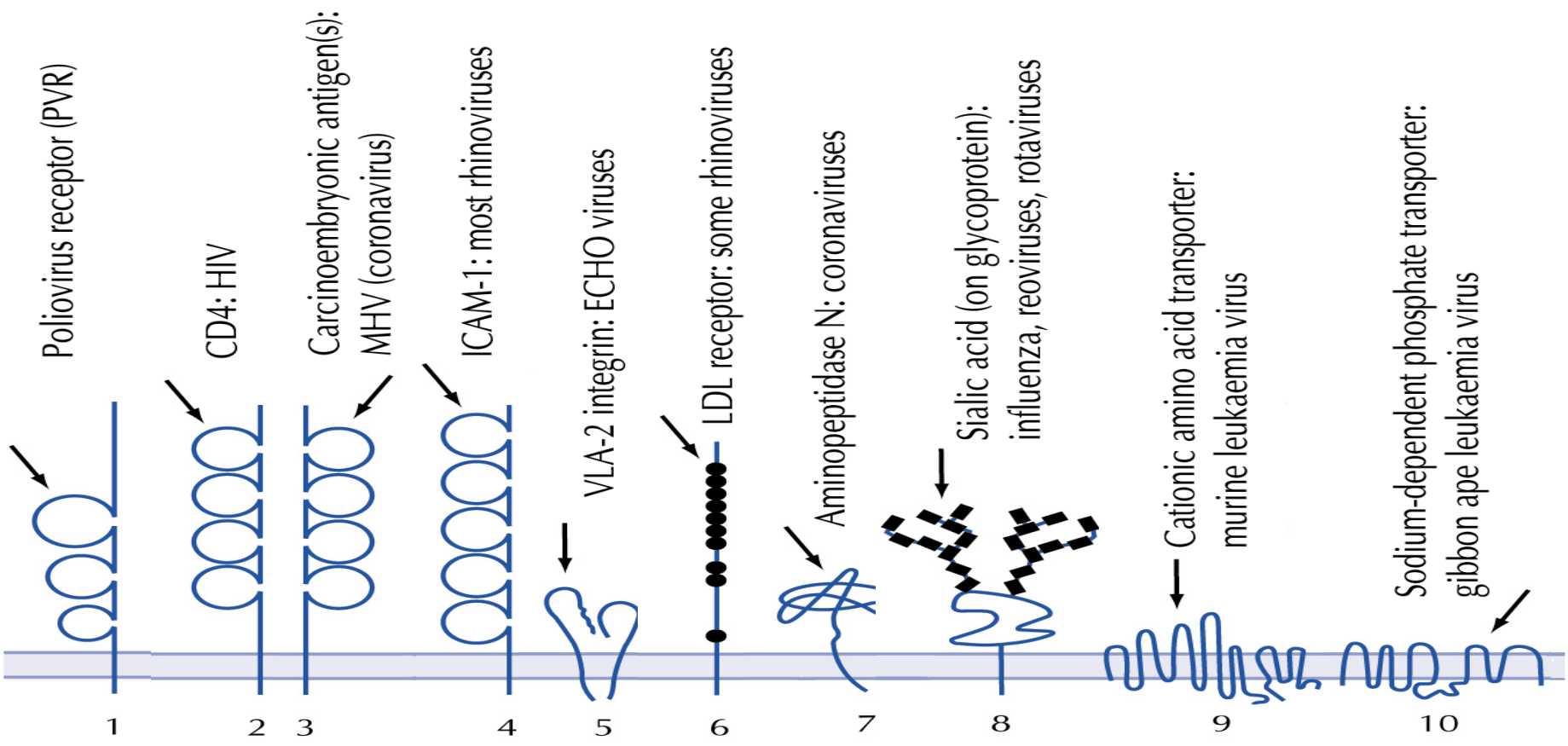
Figure 2. **Viral Attachment**

There are at least two receptors on T-lymphocytes to which the human immunodeficiency virus (HIV) sticks. The primary receptor, called "CD4" and a second receptor that loops through the cell membrane (chemokine receptor) . Both are critical for infection to occur.

HIV infection of a lymphocyte requires attachment of the virus to the cell membrane through both of these "ligand-receptor" links. In cells whose the transmembrane receptor is different, the HIV "key" no longer matches the lymphocyte "lock" and attachment is incomplete.

Those cells may avoid infection by HIV.

Virus Binding to the Cell Surface



VIRAL LIFE CYCLE

- **ATTACHMENT**
- **ENTRY**
- **UNCOATING**

- **GENOME REPLICATION**

- **ASSEMBLY**
- **RELEASE**

On the surface membrane of all living cells are protein structures called "receptors". Some viral proteins “antireceptors” usually expressed on the enveloped or on the capsid are able to interact with them.
This event turns on the life replication cycle of the virus

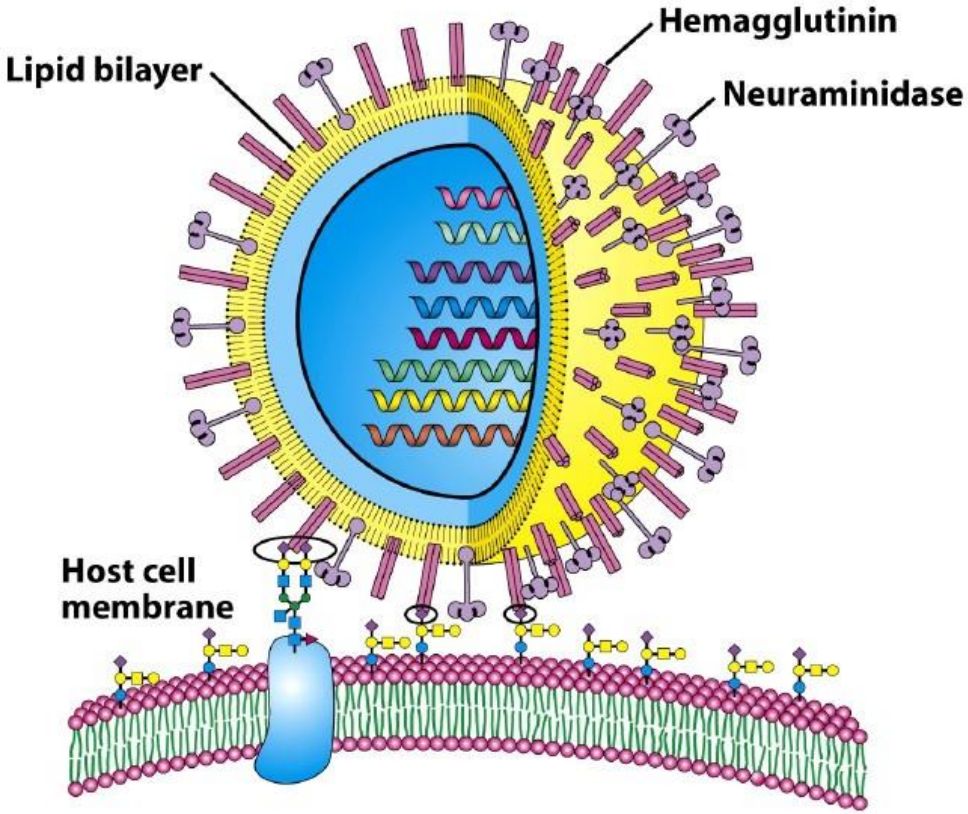
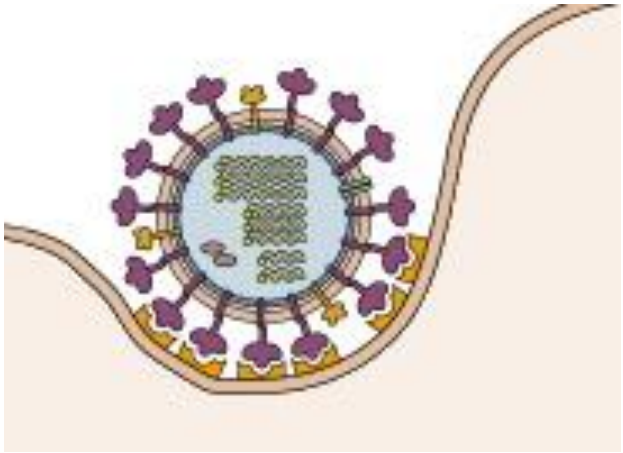
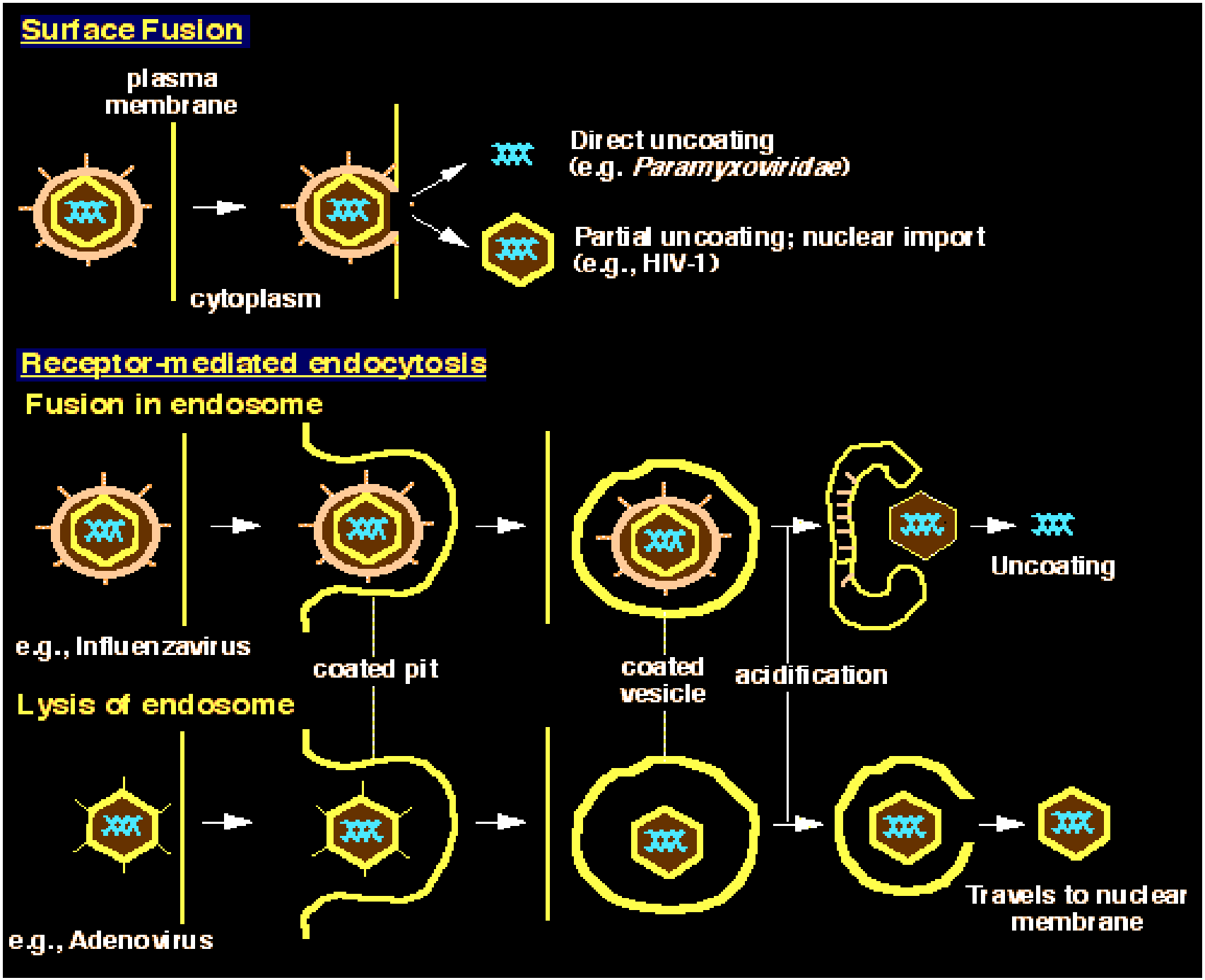


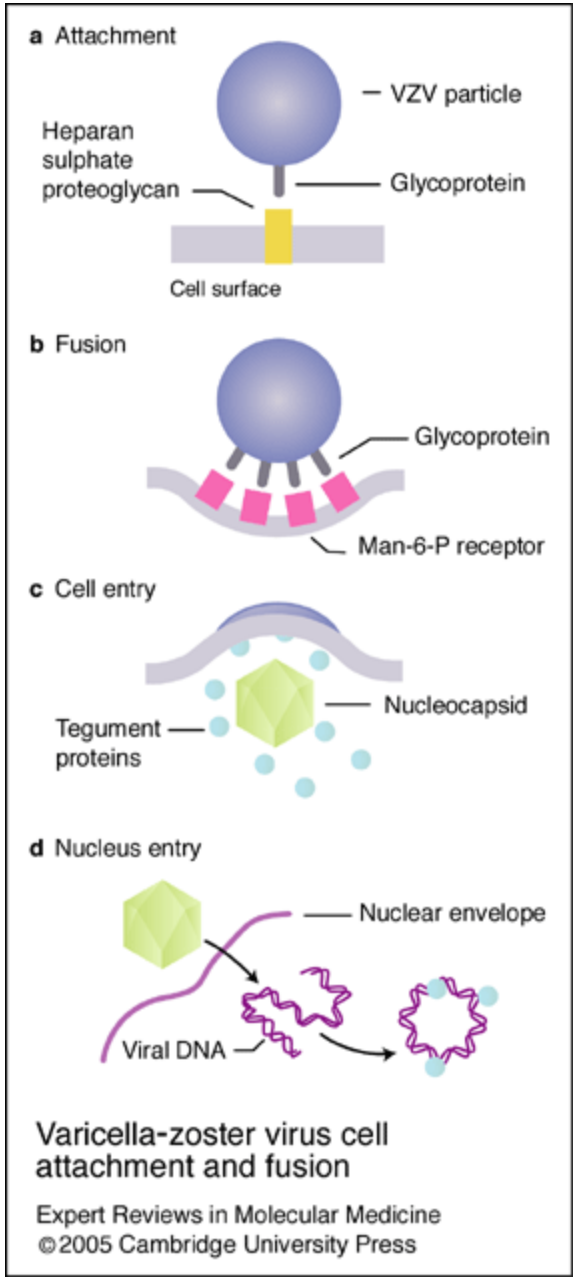
Figure 11-29
Biochemistry, Sixth Edition



VIRUS ENTRY

- Penetration by Membrane Fusion
- Endocytic Pathways
- Penetration of Nonenveloped Viruses
  - Membrane puncture
  - Perforation


Surface Fusion
plasma membrane
cytoplasm
Direct uncoating
(e.g. Paramyxoviridae)
Partial uncoating; nuclear import
(e.g., HIV-1)
Receptor-mediated endocytosis
Fusion in endosome
e.g., Influenzavirus
coated pit
coated vesicle
acidification
Uncoating
Lysis of endosome
e.g., Adenovirus
Travels to nuclear membrane



Varicella-zoster virus cell attachment and fusion

Expert Reviews in Molecular Medicine

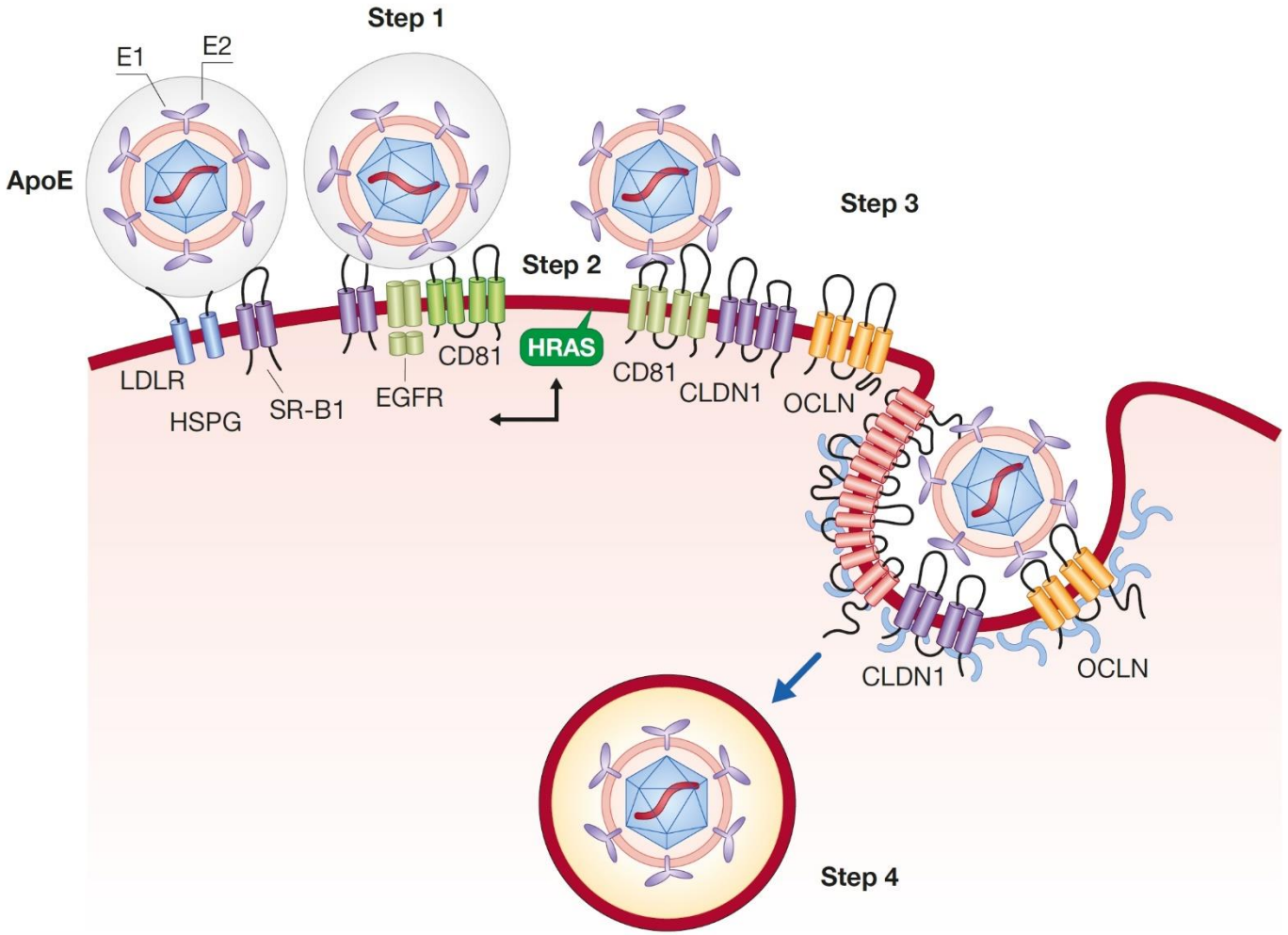
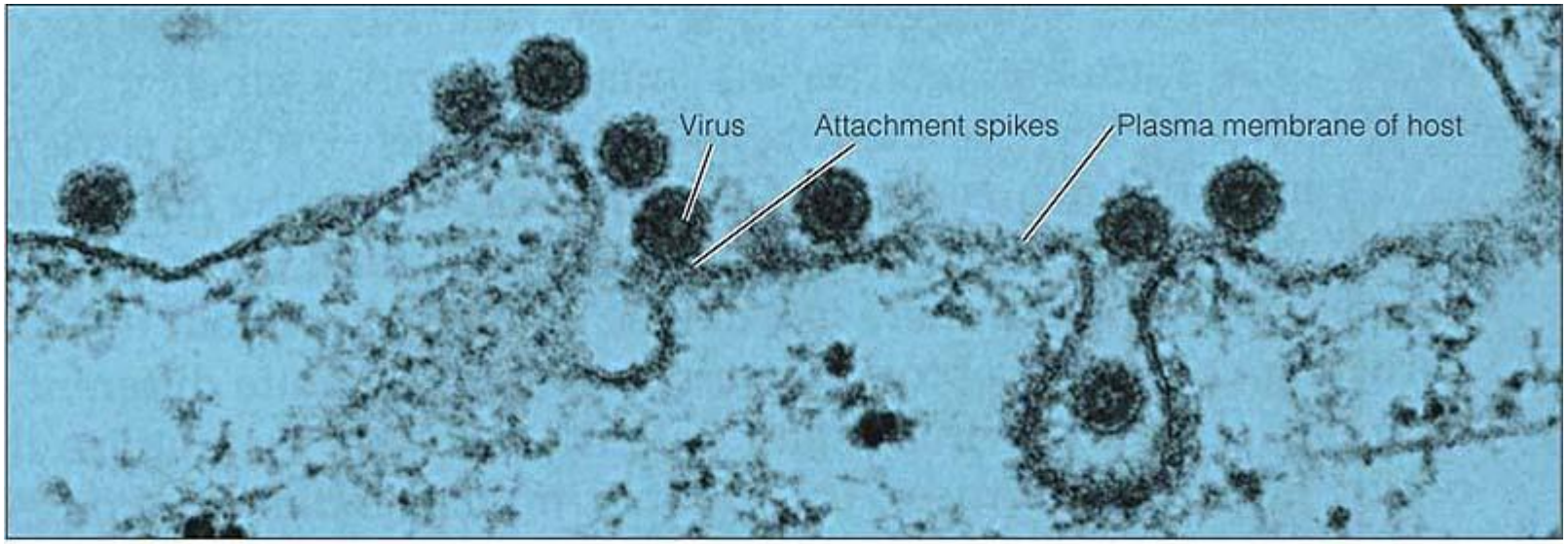
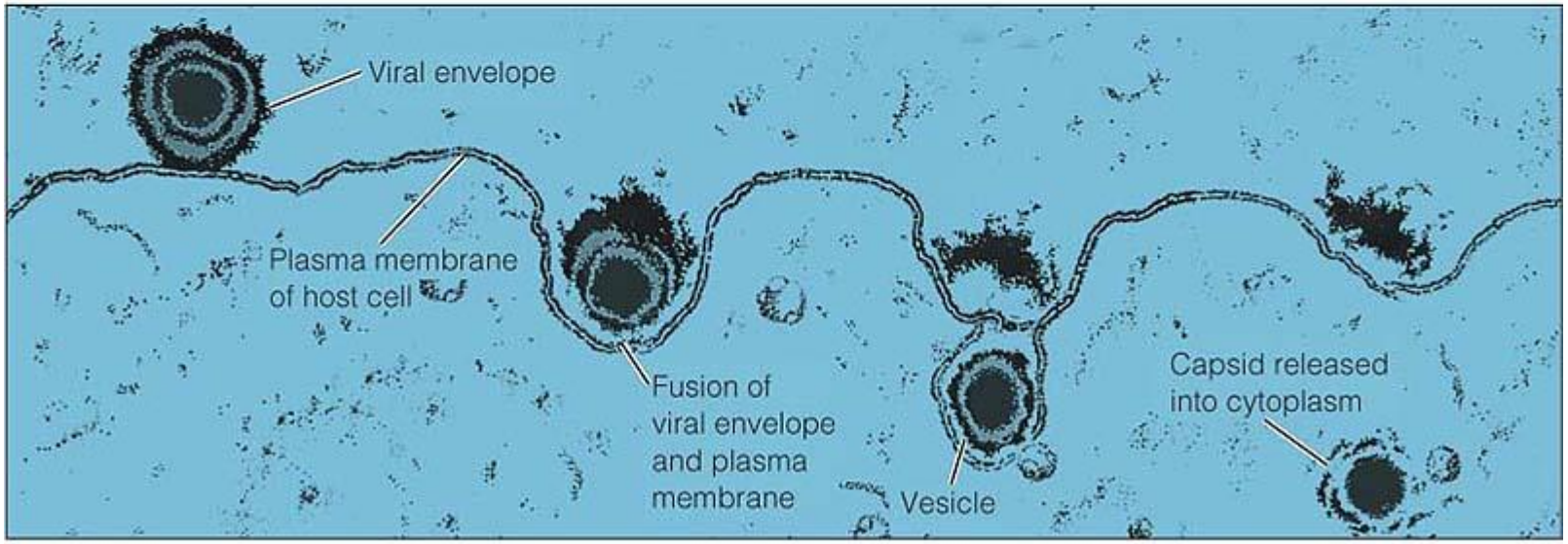


Figura 36.1 Il capside di HCV è circondato da lipidi, in cui sono incorporate le glicoproteine E1 ed E2, ed è associato a lipoproteine sieriche quali l'apolipoproteina E (ApoE). L'attacco alla superficie della cellula richiede l'interazione tra ApoE e una serie di molecole cellulari quali eparansolfati proteoglicani (HSPG), recettori per le proteine a bassa densità (LDLR) e il recettore scavenger di classe B di tipo 1 (SR-B1). Questa interazione induce un cambiamento conformazionale della glicoproteina E2 che gli permette di legarsi al CD81 (step 1). L'interazione tra E2 e CD81 porta all'attivazione delle vie di segnale mediante il recettore per il fattore di crescita epidermico (EGFR) e la via HRAS (step 2) che promuovono il movimento laterale del complesso CD81-HCV verso la *tight junctions protein* claudina-1 (CLDN1) (step 3). Il CD81 interagisce con CLDN1 per formare un complesso co-recettore che insieme con la particella HCV viene internalizzato negli endosomi (step 4).



(a) Entry of togavirus



(b) Entry of herpesvirus

VIRUS ENTRY

- Penetration by Membrane Fusion
- Endocytic Pathways
- Penetration of Nonenveloped Viruses
  - Membrane puncture
  - Perforation

VIRUS ENTRY

- Penetration by Membrane Fusion
- Endocytic Pathways

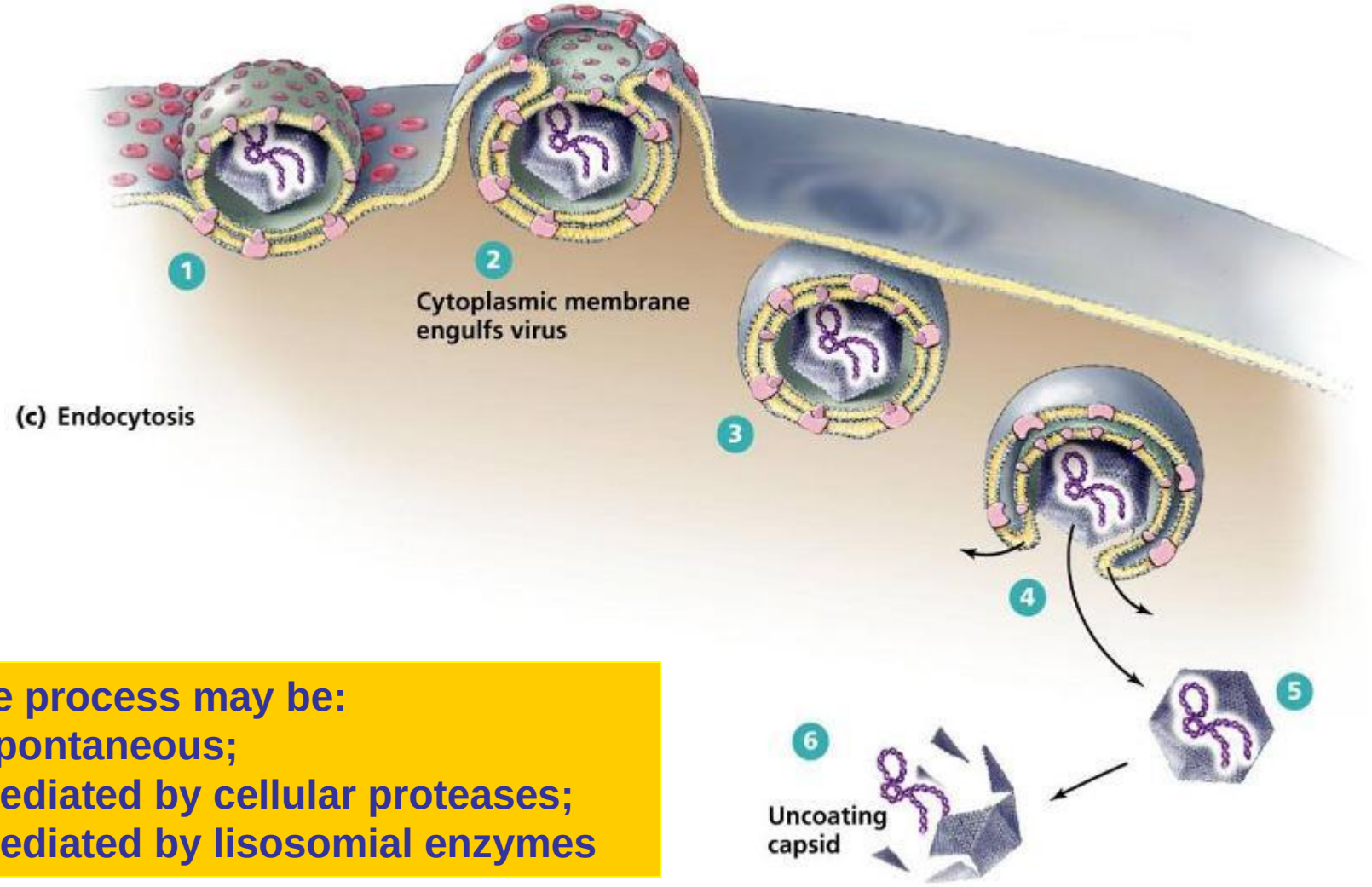
Nonenveloped viruses can use three distinct, general strategies:
(a) Membrane puncture. The virus particle generates a pore in the membrane through which the genome is selectively released into the cytosol.
(b) Perforation. The entire capsid is transferred through the membrane without major lysis of the membrane.

VIRAL LIFE CYCLE

- **ATTACHMENT**
- **ENTRY**
- **UNCOATING**

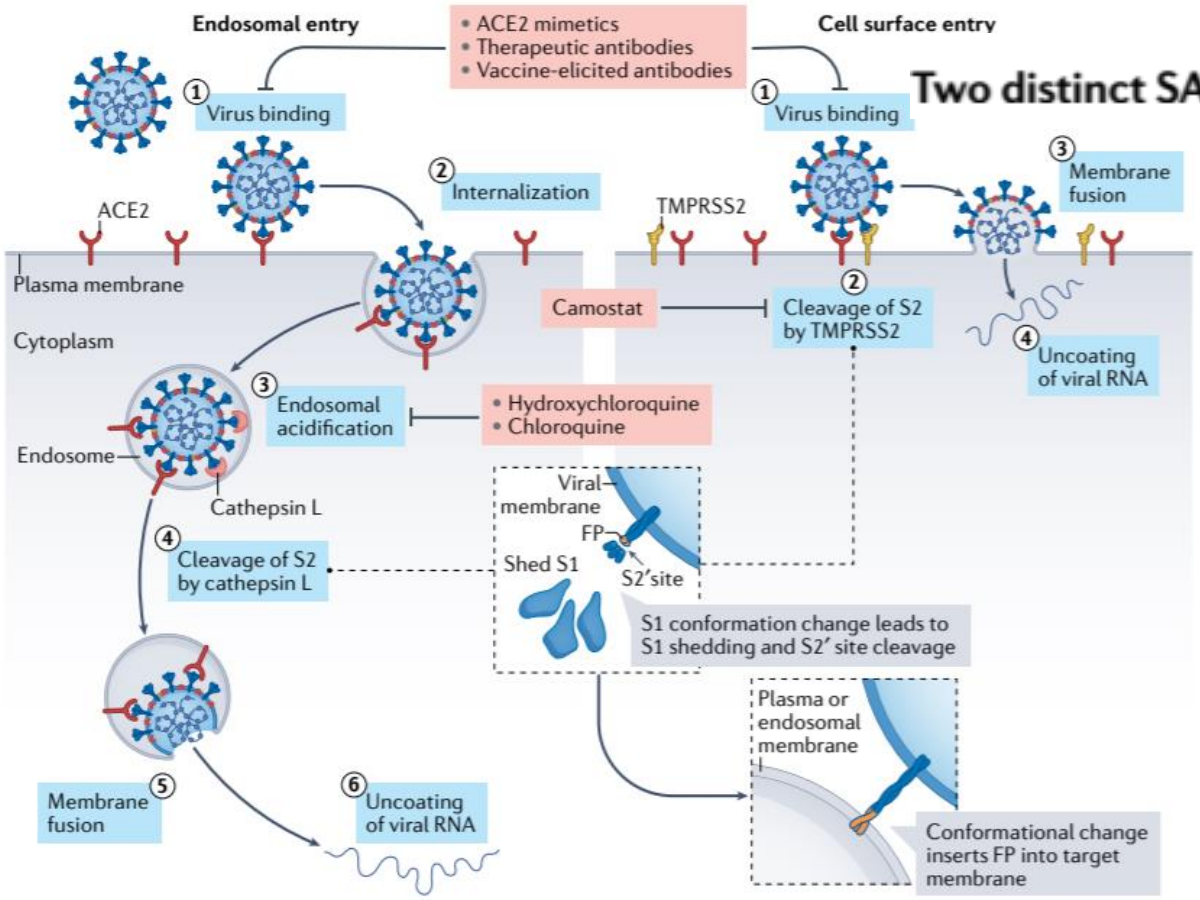
- **GENOME REPLICATION**

- **ASSEMBLY**
- **RELEASE**



The process may be:
- **Spontaneous;**
- **Mediated by cellular proteases;**
- **Mediated by lisosomial enzymes**

Why coronavirus and SARS-CoV-2 are so successful -2B-
PRODUCTIVE VIRAL LIFE CYCLE



Other co-receptors (for example, neuropilin 1) and proteases (for example, cathepsin L, TMPRSS11D and TMPRSS13) have been proposed to be involved in SARS-CoV-2 entry as well but their respective contribution to SARS-CoV-2 pathogenesis remains unclear1.

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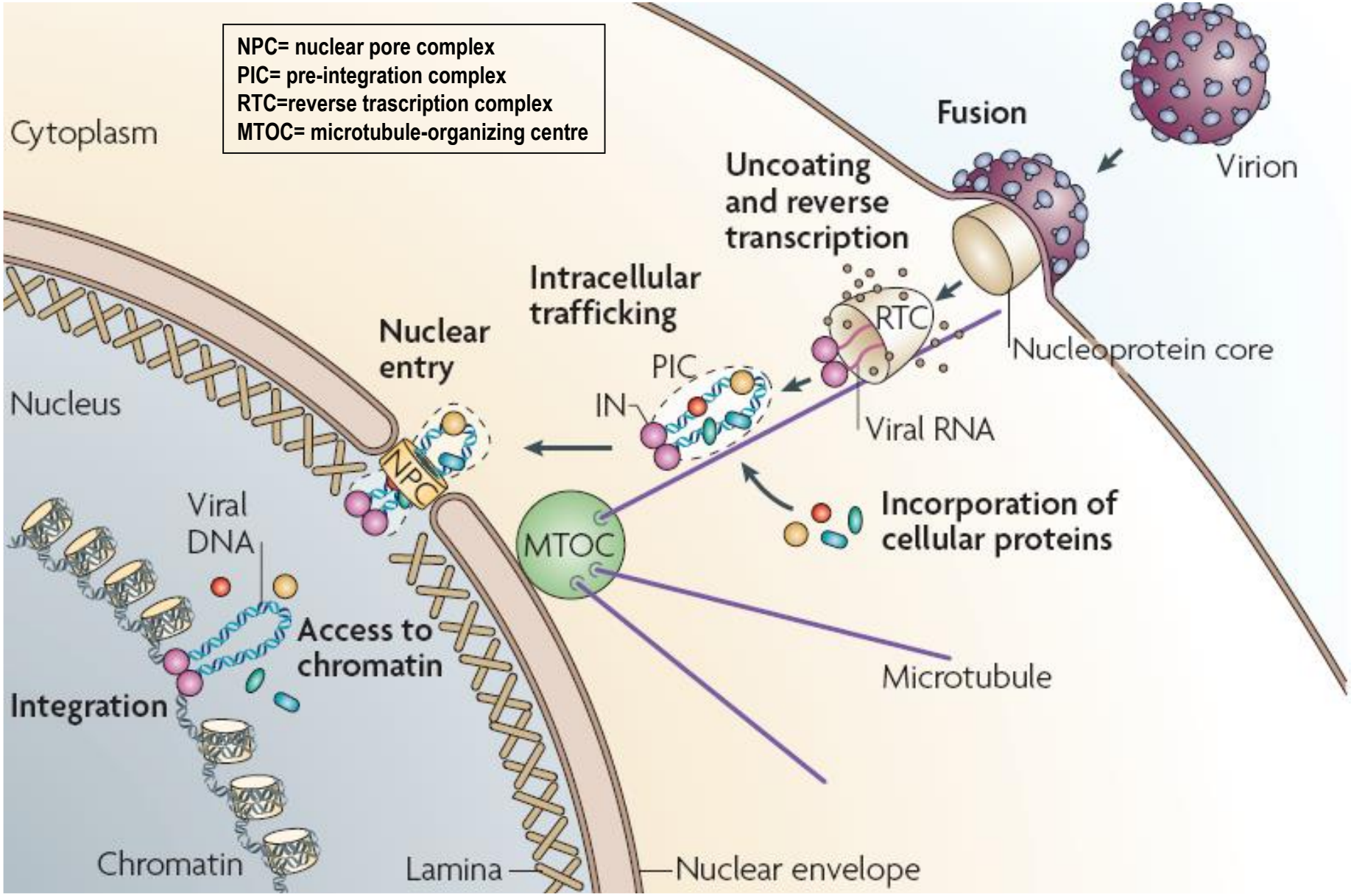

NPC= nuclear pore complex
PIC= pre-integration complex
RTC=reverse trascription complex
MTOC= microtubule-organizing centre
Cytoplasm
Fusion
Virion
Uncoating and reverse transcription
Intracellular trafficking
Nuclear entry
RTC
Nucleoprotein core
PIC
IN
Viral RNA
Nucleus
NPC
Viral DNA
MTOC
Incorporation of cellular proteins
Access to chromatin
Integration
Microtubule
Chromatin
Lamina
Nuclear envelope

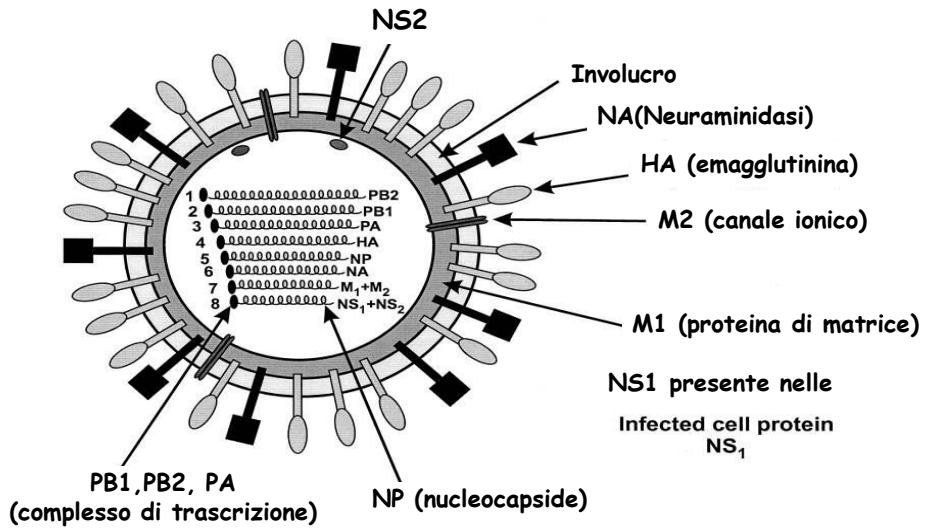
VIRAL LIFE CYCLE

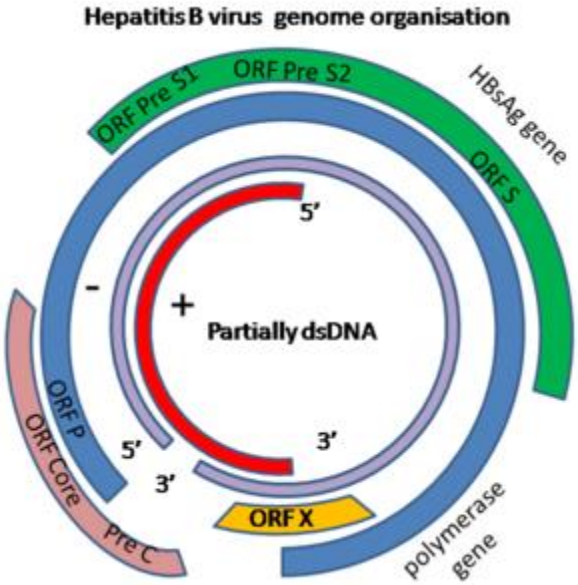
- **ATTACHMENT**
- **ENTRY**
- **UNCOATING**

- **GENOME REPLICATION (and Expression)**

- **ASSEMBLY**
- **RELEASE**

Influenza

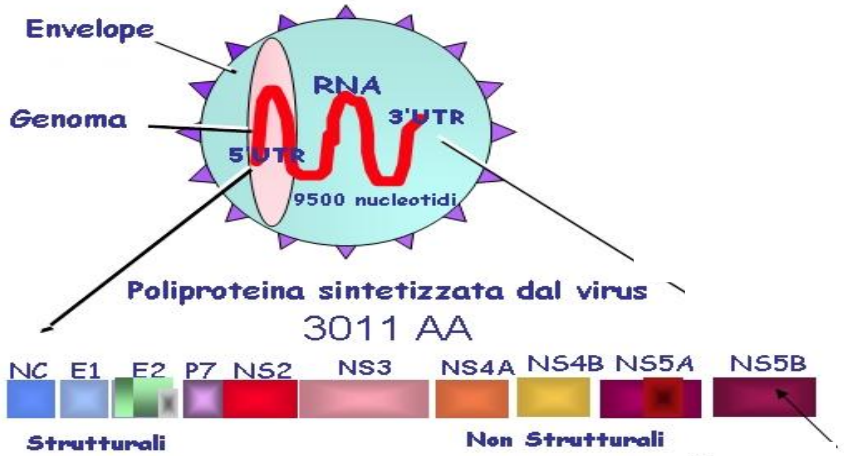




DNA ds circolare

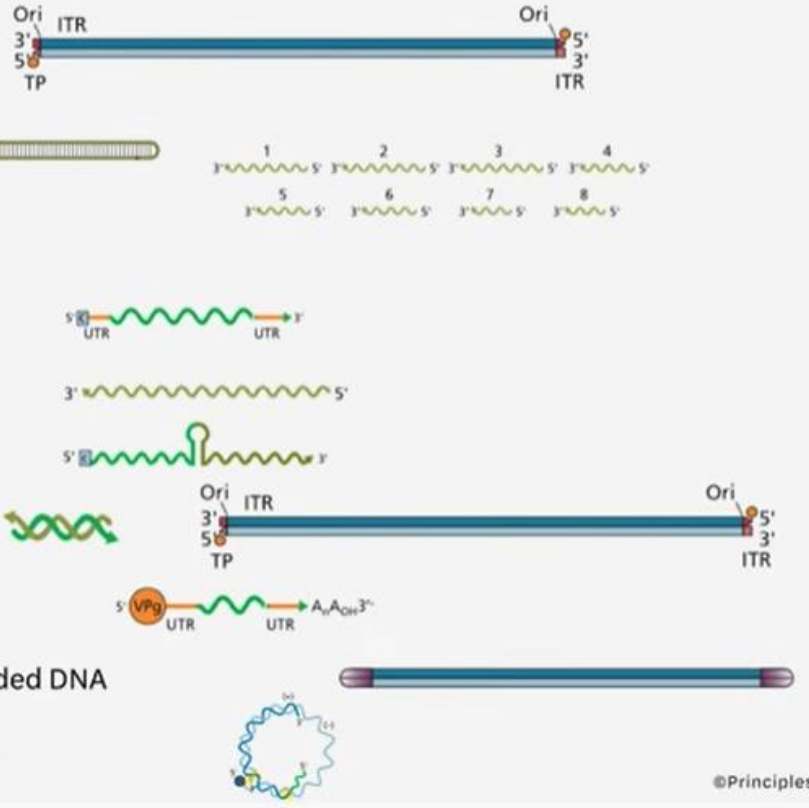
RNA (–) segmentato

HCV RNA ss +

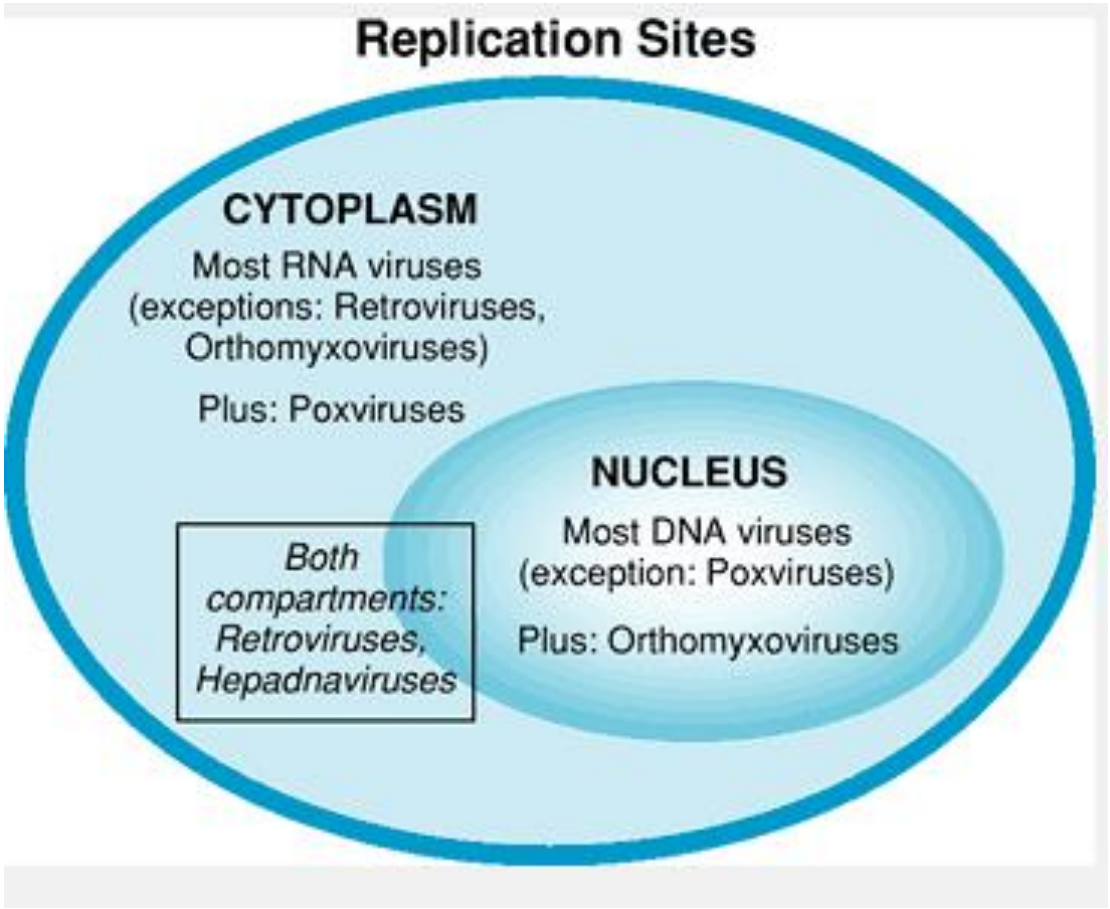


Viral DNA or RNA genomes are structurally diverse

- Linear
- Circular
- Segmented
- Gapped
- Single-stranded (+) strand
- Single-stranded (-) strand
- Single stranded, ambisense
- Double-stranded
- Covalently attached proteins
- Cross-linked ends of double-stranded DNA
- DNA with covalently attached RNA



Replication sites for major families of viruses



Fields Virology, V ed., Lippincott Williams and Wilkins

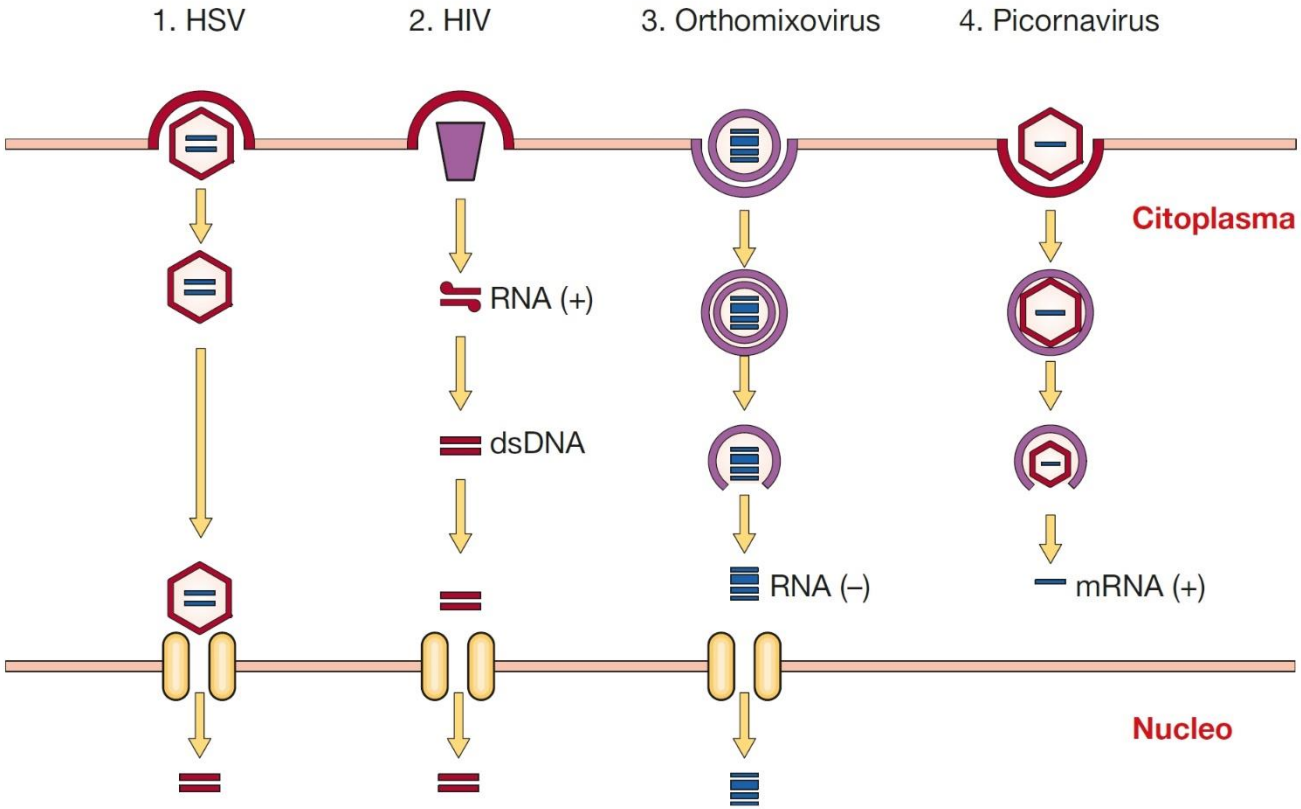


Figura 36.2 Meccanismi di entrata per diverse classi di virus. I virus rivestiti possono entrare o mediante fusione (**1** e **2**) oppure mediante endocitosi seguita da un processo di fusione con la membrana endosomiale (**3**). I virus nudi, come i picornavirus (**4**), penetrano all'interno della cellula mediante un processo di endocitosi.

RNA Virus Genome Strategies

RNA VIRUSES

- Most RNA viruses replicate **in the cytoplasm**

- **Notable exceptions** are the **orthomyxo-** and **bornaviruses**, whose linear negative-sense RNA genomes replicate in the nucleus, **retroviruses** (that integrate DNA copies of their genomes into cellular chromosomes) and the circular RNA genome of **hepatitis delta virus**

- RNA virus can derive several separate protein products from a single genome through **fragmentation** at the level of:
  - proteins (processing of polyprotein precursors)
  - mRNAs (production of several different monocistronic mRNAs from a single RNA template)
  - genes (multiple genome segments)

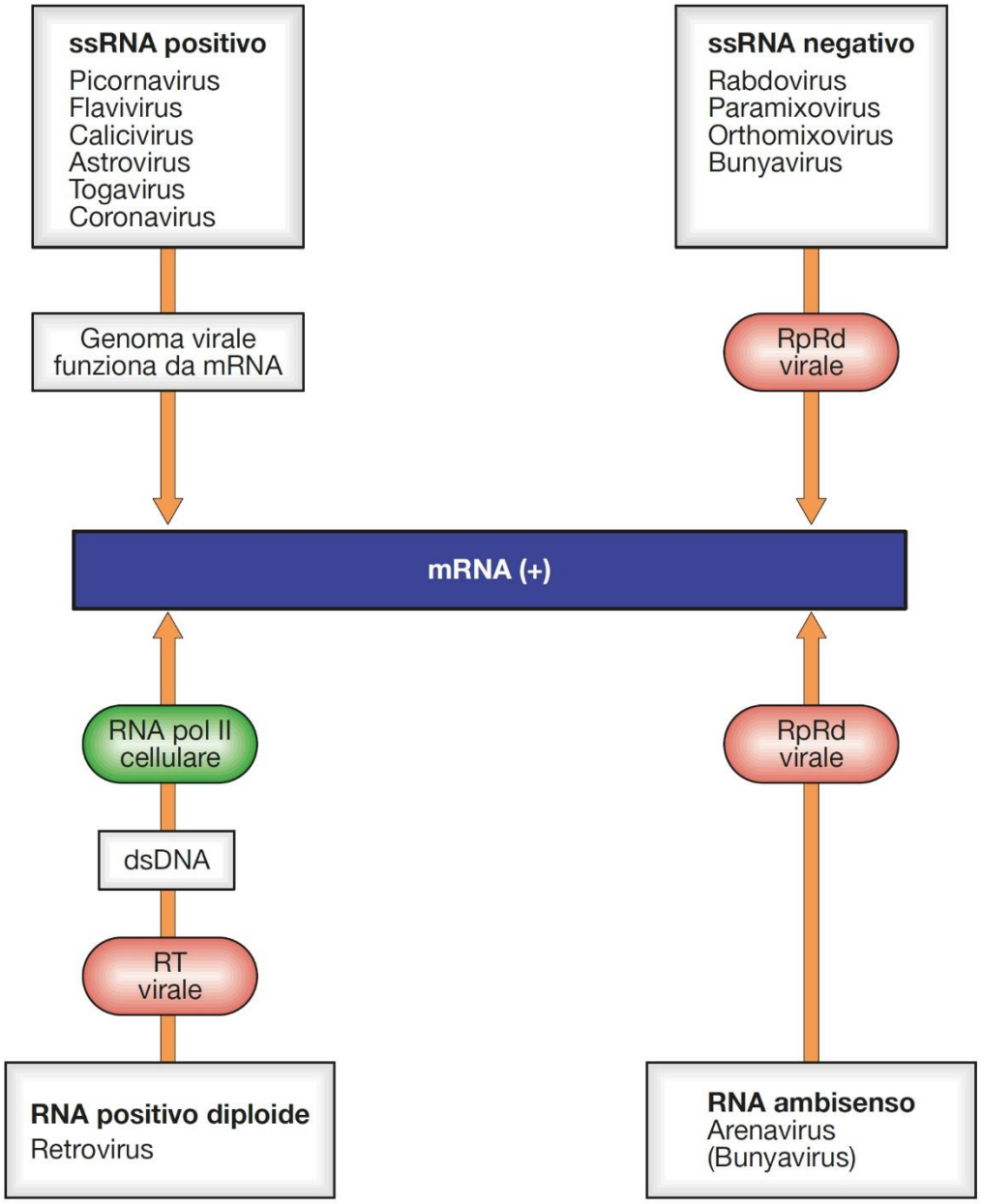


Figura 36.3 Principali strategie replicative dei virus a RNA. L'RNA virale monofilamento (ssRNA) a polarità positiva viene immediatamente tradotto; l'RNA virale a polarità negativa necessita di essere trascritto da una RNA polimerasi-RNA dipendente (RpRd). Nei retrovirus la trascrittasi inversa (RT) retrotrascrive l'RNA virale in una doppia catena di DNA (dsDNA).

The type of RNA genome largely determines whether the first step of macromolecular synthesis is translation, transcription, or RNA replication.

Positive-sense RNA genomes

- Viruses with positive-sense ssRNA genomes (**except the retroviruses**) deliver their genomic RNAs directly to cellular ribosomes and begin the infectious cycle with translation.

- Positive-sense RNA viruses fall into two groups: those that produce subgenomic mRNAs and those that do not.

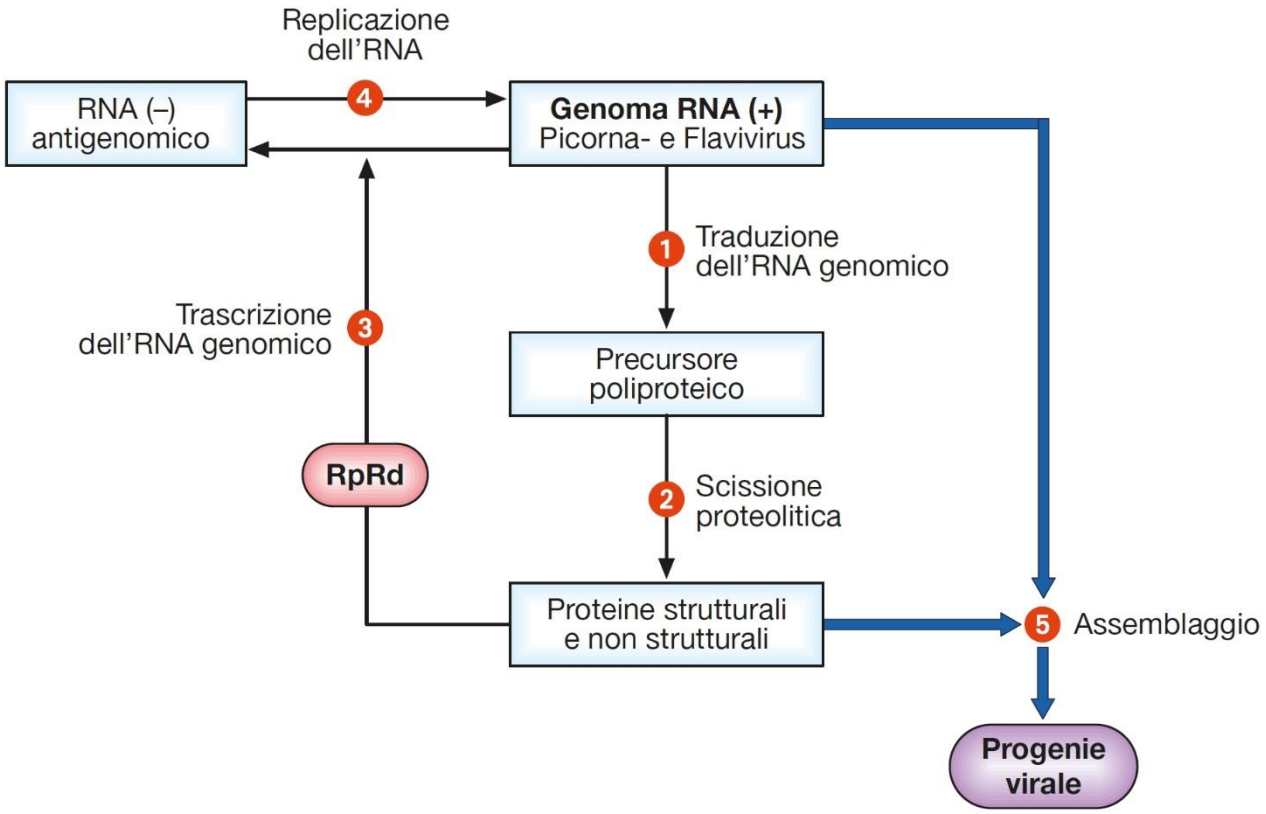


Figura 36.4 Replicazione di alcuni virus con genoma a RNA (+). 1. Traduzione dell'RNA genomico in un precursore poliproteico; **2.** scissione proteolitica e formazione delle proteine strutturali e funzionali; **3.** trascrizione dell'RNA genomico in RNA (–) (antigenoma) a opera dell'RNA polimerasi-RNA dipendente (RpRd) neoformata; **4.** sintesi di nuovo RNA (+); **5.** assemblaggio delle proteine strutturali e dei nuovi genomi.

Negative-sense RNA genomes

- Viral genomes that consist of negative- or ambisense ssRNA or dsRNA are not infectious by themselves because they must begin the infectious cycle by transcribing viral mRNAs, and uninfected cells do not contain an appropriate RdRp. In general, primary transcription is catalyzed by enzymes that are carried into cells by the infecting virions, producing individual mRNAs for the viral proteins

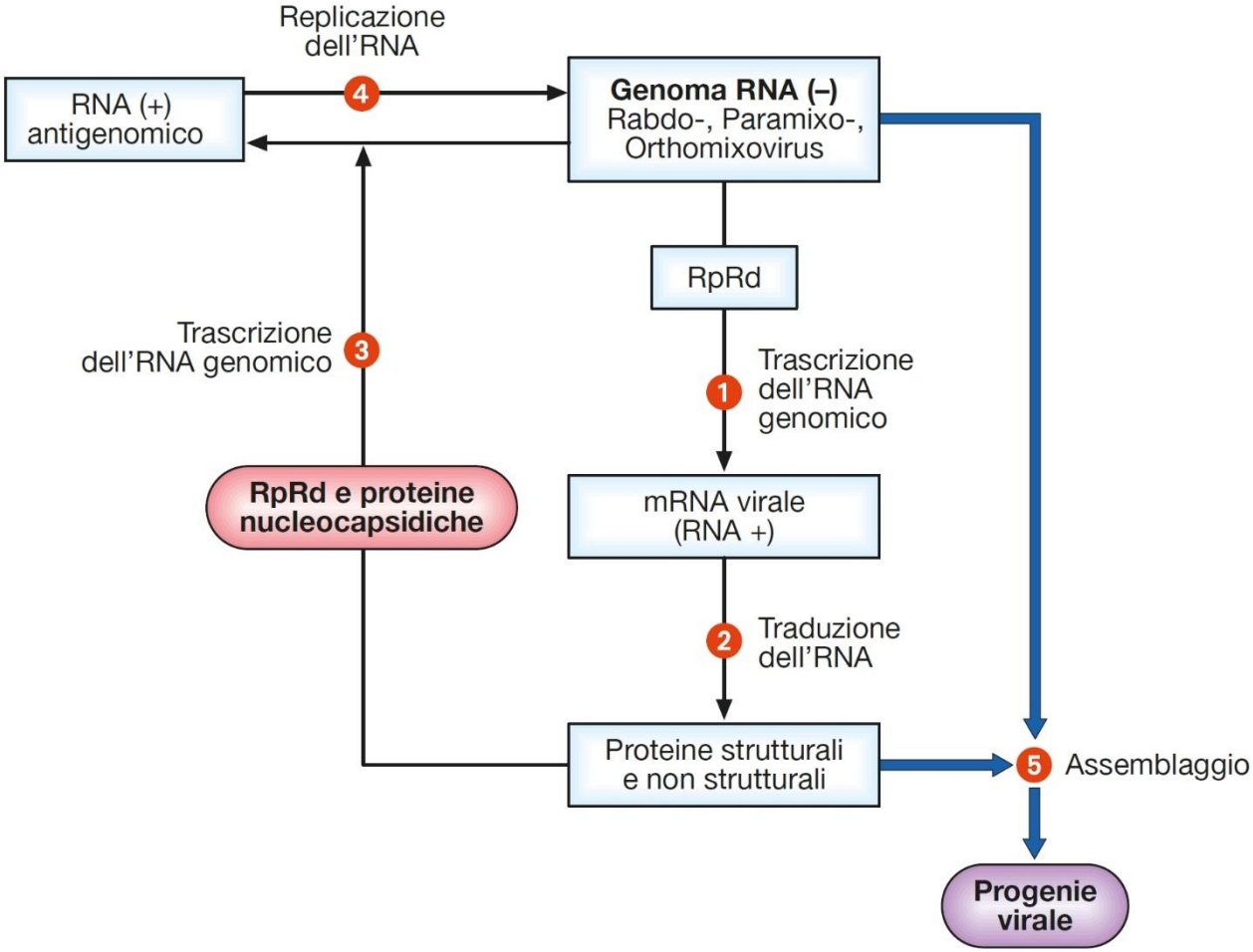
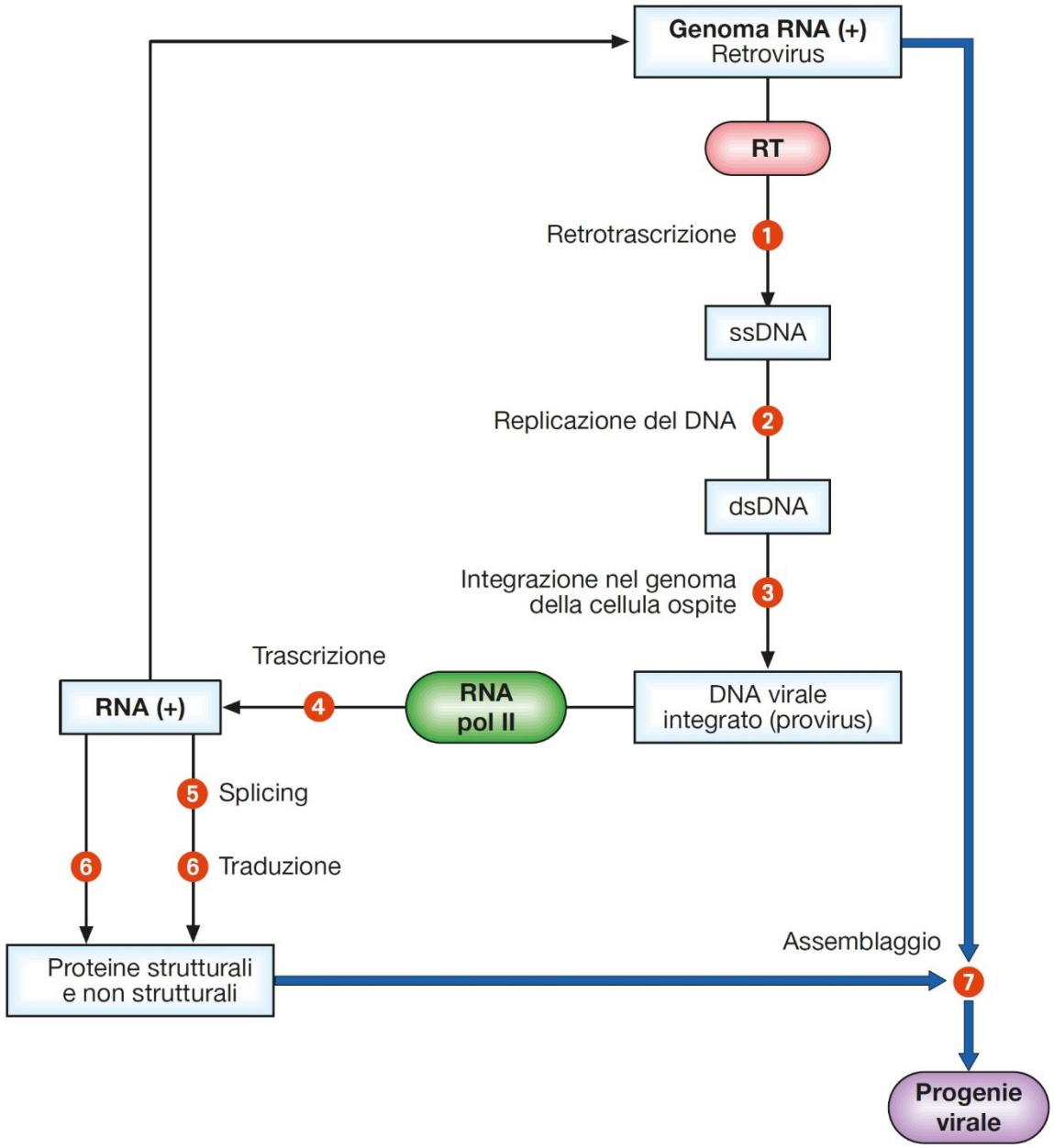
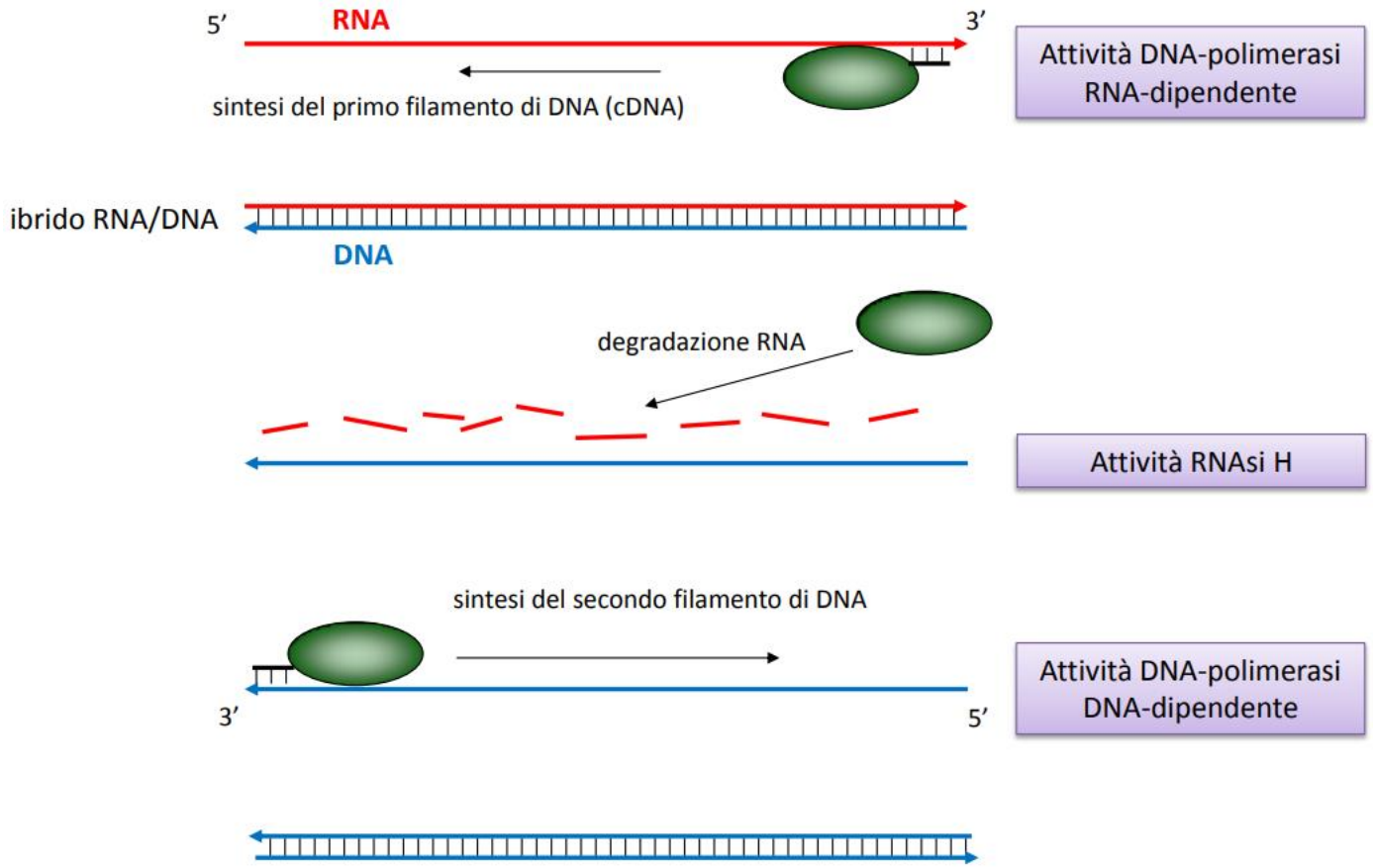


Figura 36.5 Replicazione di alcuni virus con genoma a RNA (–). 1. Trascrizione dell'RNA (–) in RNA (+) a opera della RNA polimerasi-RNA dipendente (RpRd) associata al virione; **2.** traduzione dell'RNA (+) neoformato; **3.** trascrizione dell'RNA genomico in RNA (+) (antigenoma) a opera della RpRd virale; **4.** sintesi del nuovo RNA di progenie; **5.** assemblaggio delle proteine strutturali e dei nuovi genomi.

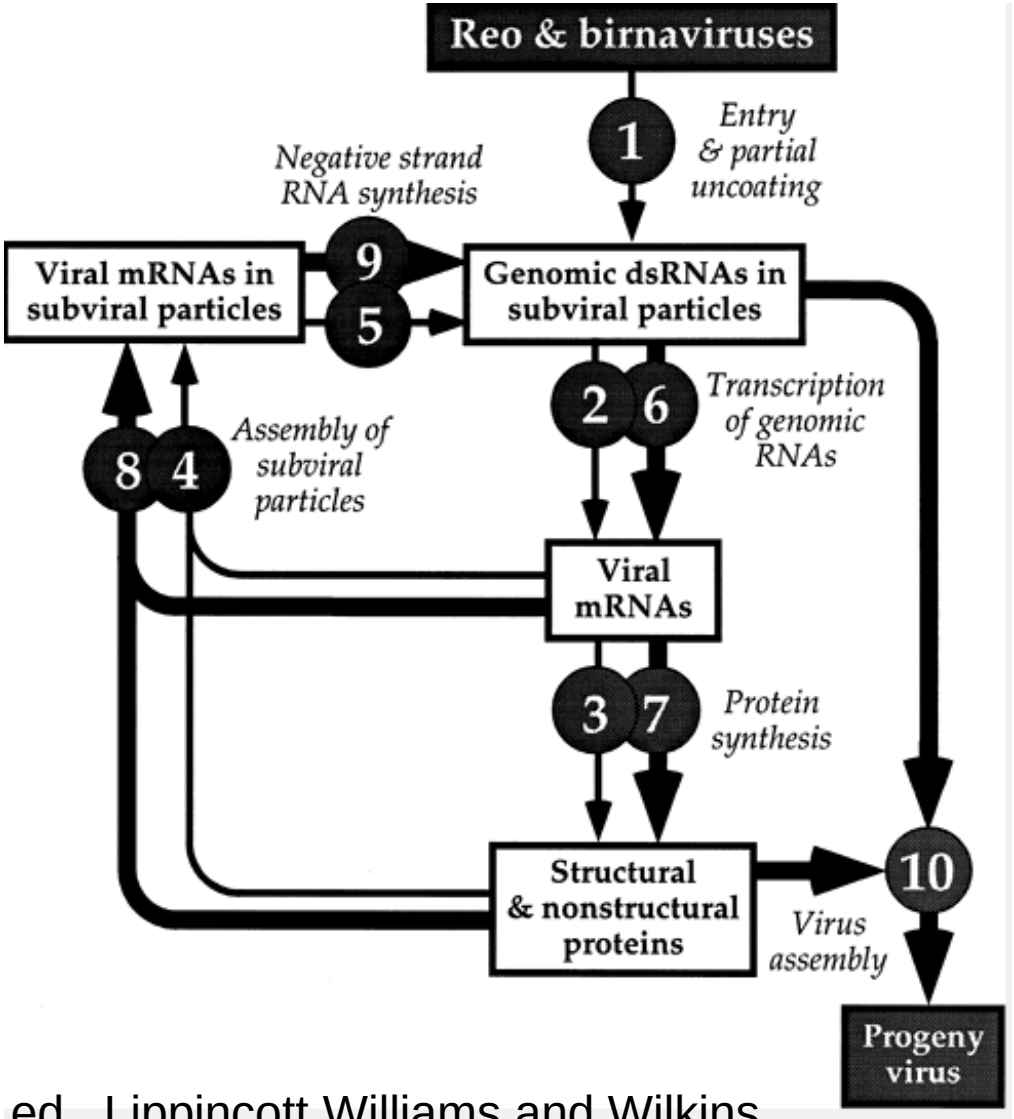
Positive-sense RNA genomes which are transcribed into DNA (Retroviridae)

Figura 36.6 Replicazione dei retrovirus. 1. e **2.** Retrotrascrizione dell'RNA genomico in DNA ad opera della trascrittasi inversa (RT) virale; **3.** integrazione del genoma virale nel DNA cellulare; **4.** trascrizione del genoma virale ad opera dell'RNA polimerasi II; **5.** splicing dell'RNA; **6.** traduzione dell'mRNA (sottoposto e non a splicing); **7.** assemblaggio delle proteine strutturali e dei nuovi genomi.




5'
RNA
3'
sintesi del primo filamento di DNA (cDNA)
Attività DNA-polimerasi RNA-dipendente
ibrido RNA/DNA
DNA
degradazione RNA
Attività RNAsi H
sintesi del secondo filamento di DNA
3'
5'
Attività DNA-polimerasi DNA-dipendente

Double-stranded RNA viruses



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DNA Virus Genome Strategies

DNA VIRUSES (1)

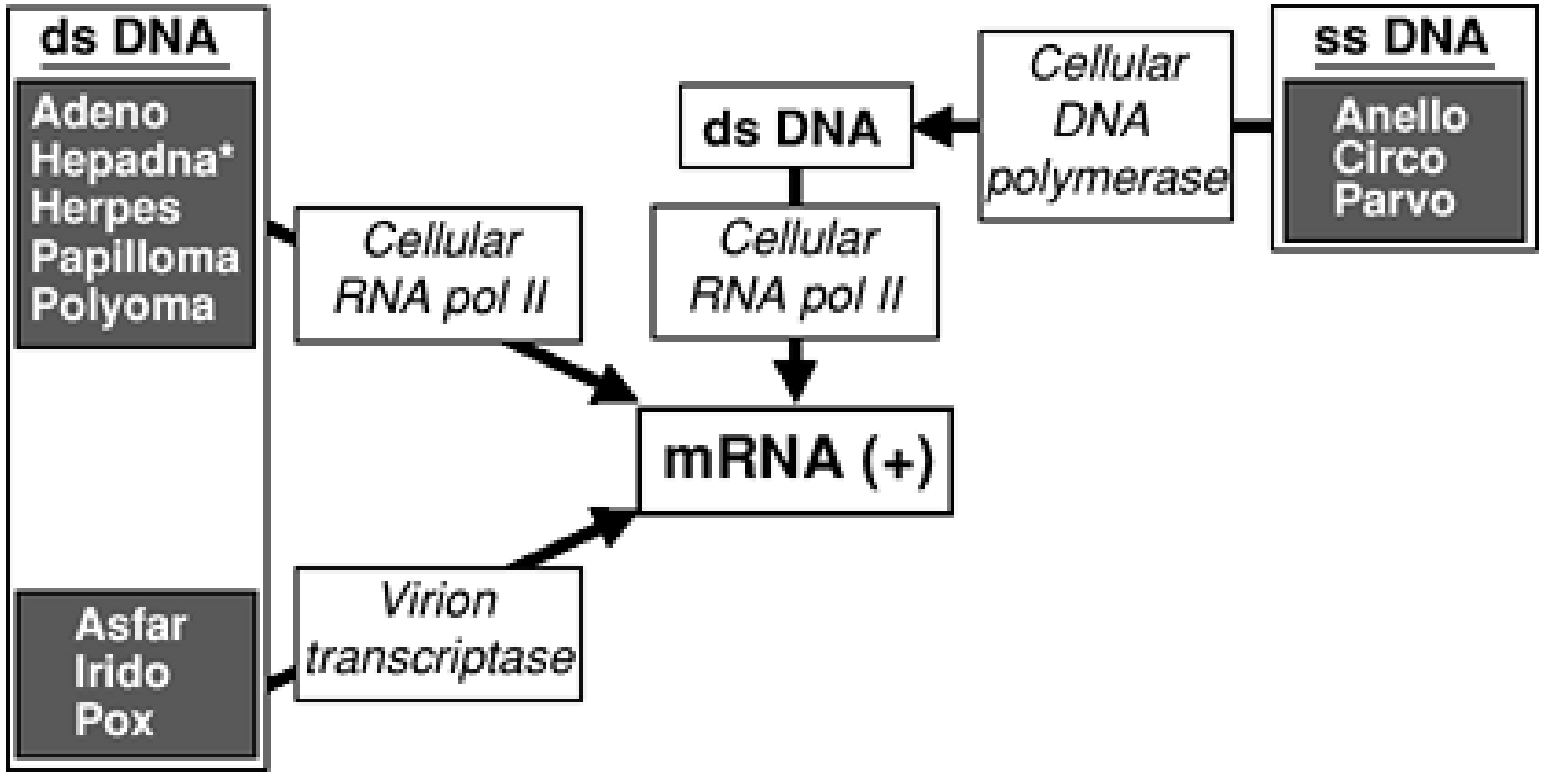
- Most DNA viruses of eukaryotes transcribe and replicate their genomes and assemble progeny **in the nucleus**, the site of cellular DNA transcription and replication. The exceptions are the poxviruses, iridoviruses, and African swine fever virus, which replicate their DNA genomes partly or completely in the cytoplasm.
- DNA virus use **host cell enzymes for transcription**
- **Early in infection**, a subset of so-called immediate early viral genes is expressed to produce mostly catalytic amounts of the **nonstructural proteins** required for DNA replication and modulation of the intracellular environment
- Sometimes these early events can lead to **neoplastic transformation**
- Most viruses with small DNA genomes use host cell enzymes for **DNA replication**; those with intermediate and large size genomes have sufficient genetic capacity to encode DNA polymerases
- After genome replication, a different subset of genes is expressed (**late genes**) that directs synthesis of stechiometric amounts of the **structural proteins** required for progeny virus assembly

DNA VIRUSES (2)

- Because cellular DNA synthesis occurs only **during the S-phase of the cell cycle** and not at all in terminally differentiated G0 cells, **viruses that depend on the DNA polymerases of the host must either wait** for infected cells to enter S-phase spontaneously, **as do parvoviruses**, **or** early in infection **they must express one or more viral oncogenes to** override the regulation imposed by the cell cycle control proteins p53 and pRb and thereby **stimulate infected cells to enter S-phase** prematurely, **as do polyoma- and papillomaviruses**, among others.

- **Viruses with large DNA genomes** (e.g., **herpes-** and **poxviruses**) **encode some of these enzymes themselves**, **and can thus replicate in nondividing cells** and other environments that would otherwise be inhospitable for DNA replication, such as terminally differentiated cells of the nervous system (some herpesviruses) or even the cytoplasm (poxviruses).

Pathways of primary mRNA synthesis by DNA viruses of animals.



*Hepadnaviruses replicate via reverse transcription of an ssRNA intermediate

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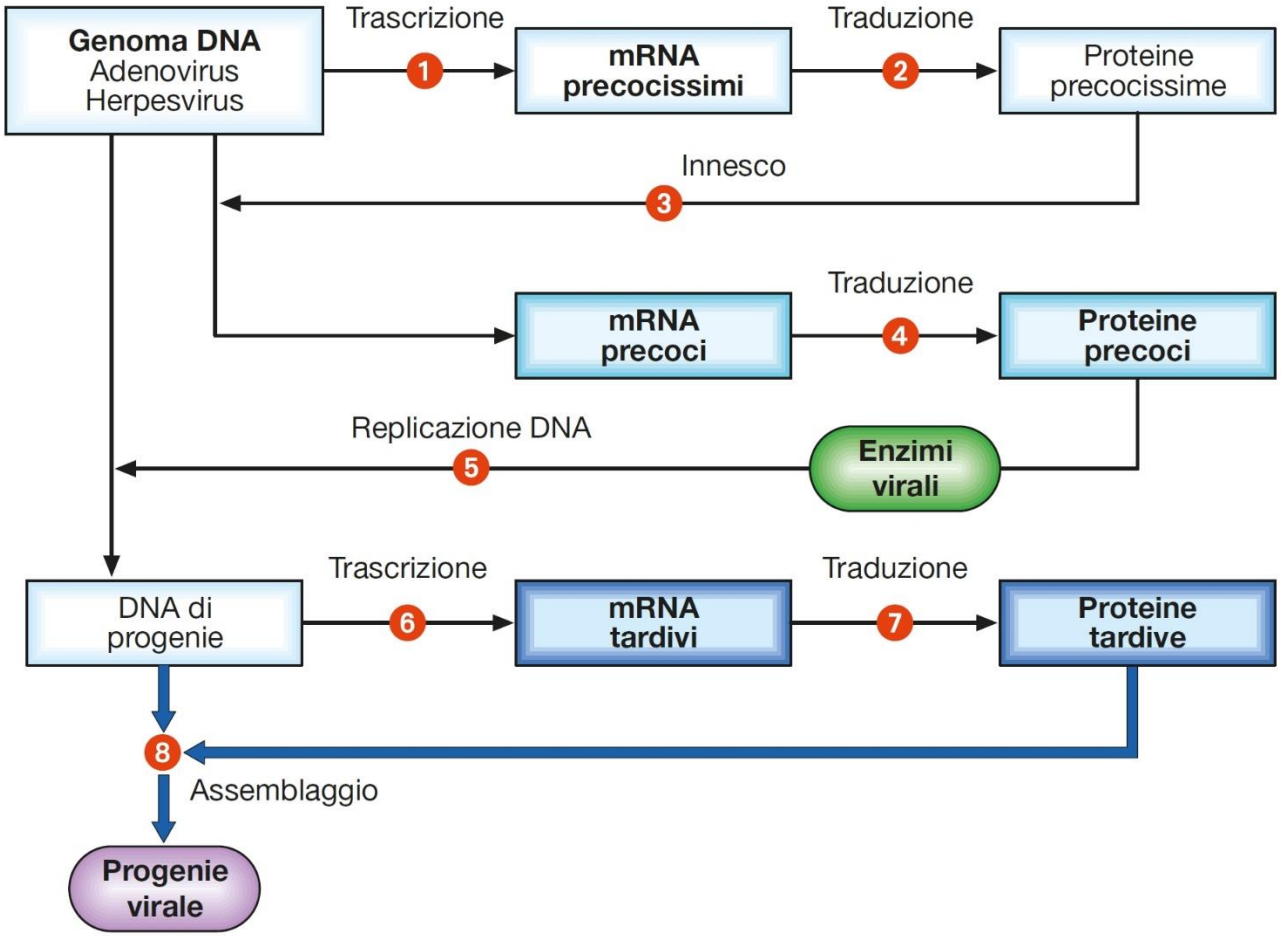
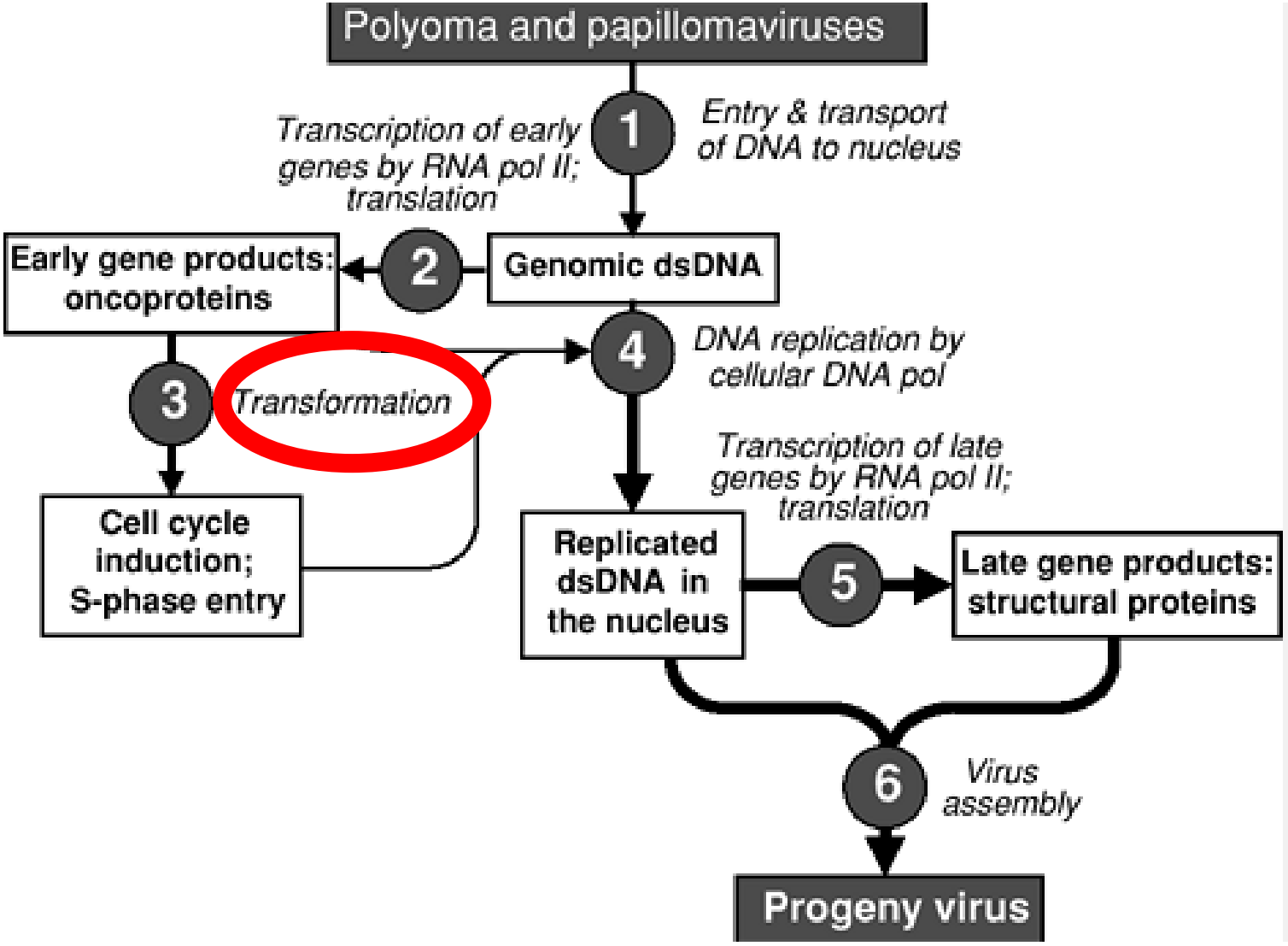


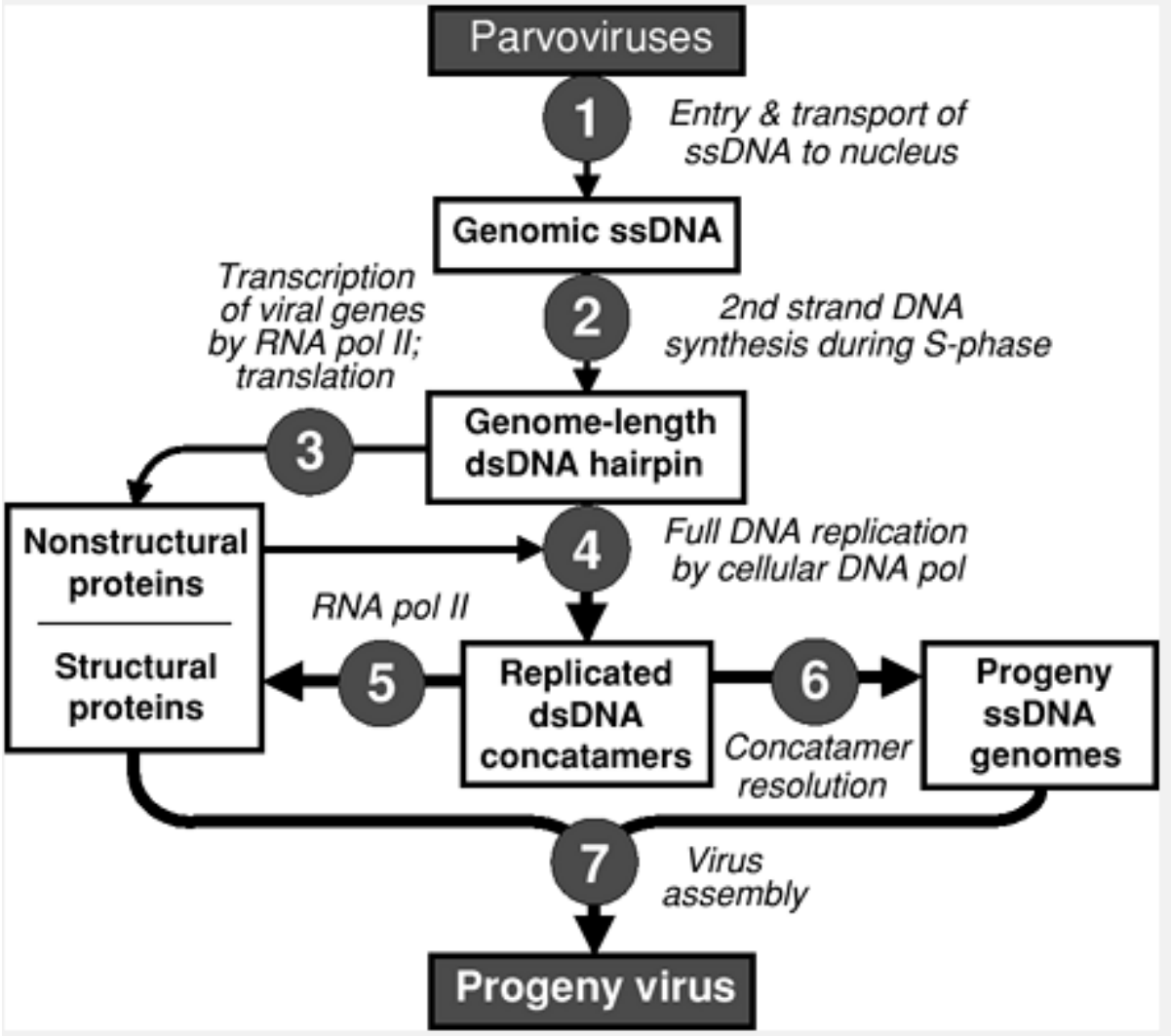
Figura 36.7 Replicazione di alcuni virus con genoma dsDNA. **1.** Trascrizione del DNA in mRNA precocissimi; **2.** traduzione dei messaggeri precocissimi; **3.** innesco della sintesi dei messaggeri precoci da parte delle proteine precocissime; **4.** traduzione degli mRNA precoci; **5.** replicazione del DNA virale a opera di enzimi virali neoformati; **6.** e **7.** trascrizione e successiva traduzione degli mRNA tardivi dal DNA neoformato; **8.** assemblaggio delle proteine strutturali e dei nuovi genomi.

Small DNA genomes use host cell enzymes for both transcription and DNA replication



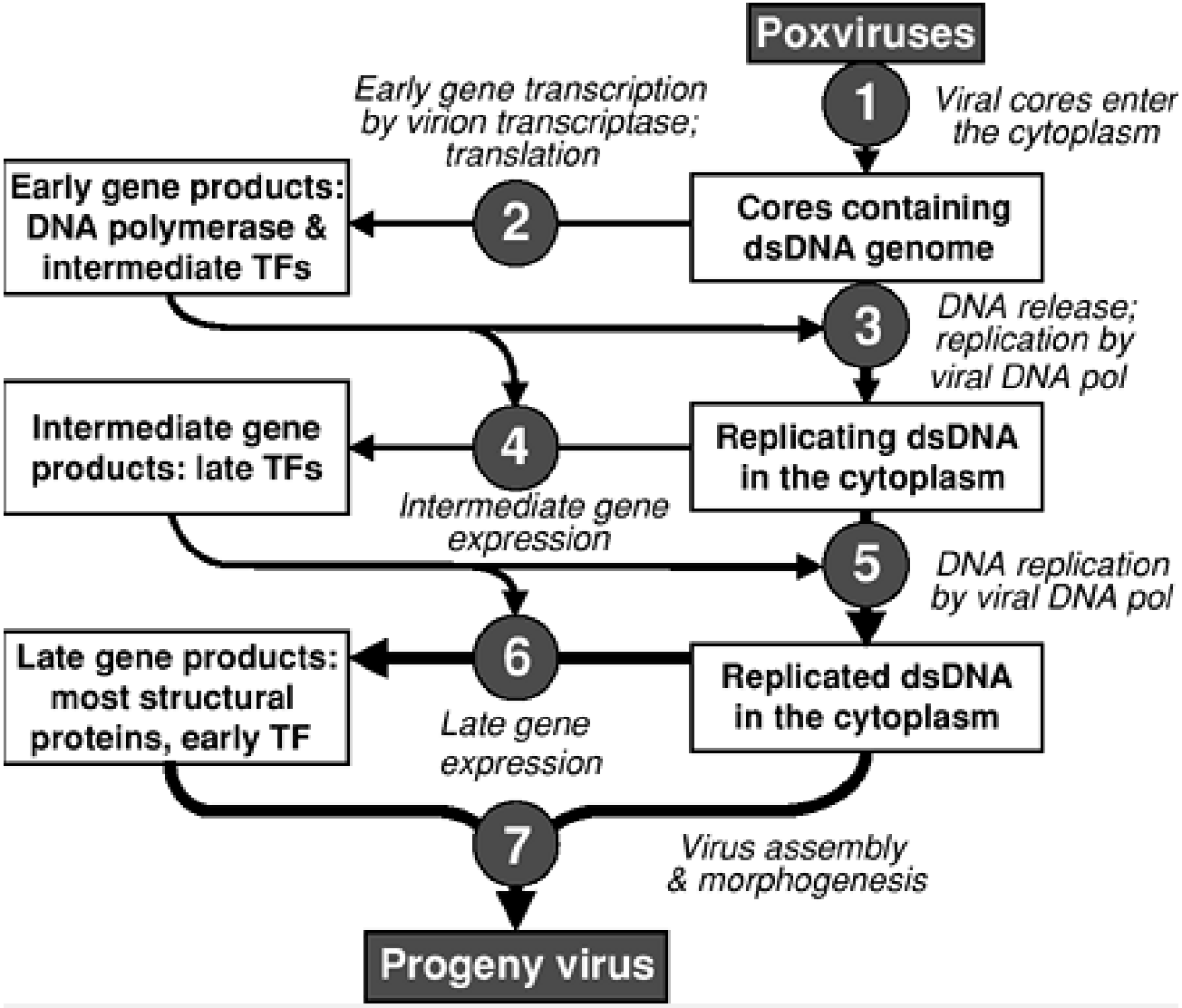
Fields Virology, V ed., Lippincott Williams and Wilkins

Small DNA genomes use host cell enzymes for both transcription and DNA replication



Fields Virology, V ed., Lippincott Williams and Wilkins

Virus with large (130-350 kb) genomes have sufficient genetic capacity to encode DNA polymerases and binding proteins, and have entire multisubunit virus-specific RNA polymerases that mediate all viral transcription



Fields Virology, V ed., Lippincott Williams and Wilkins

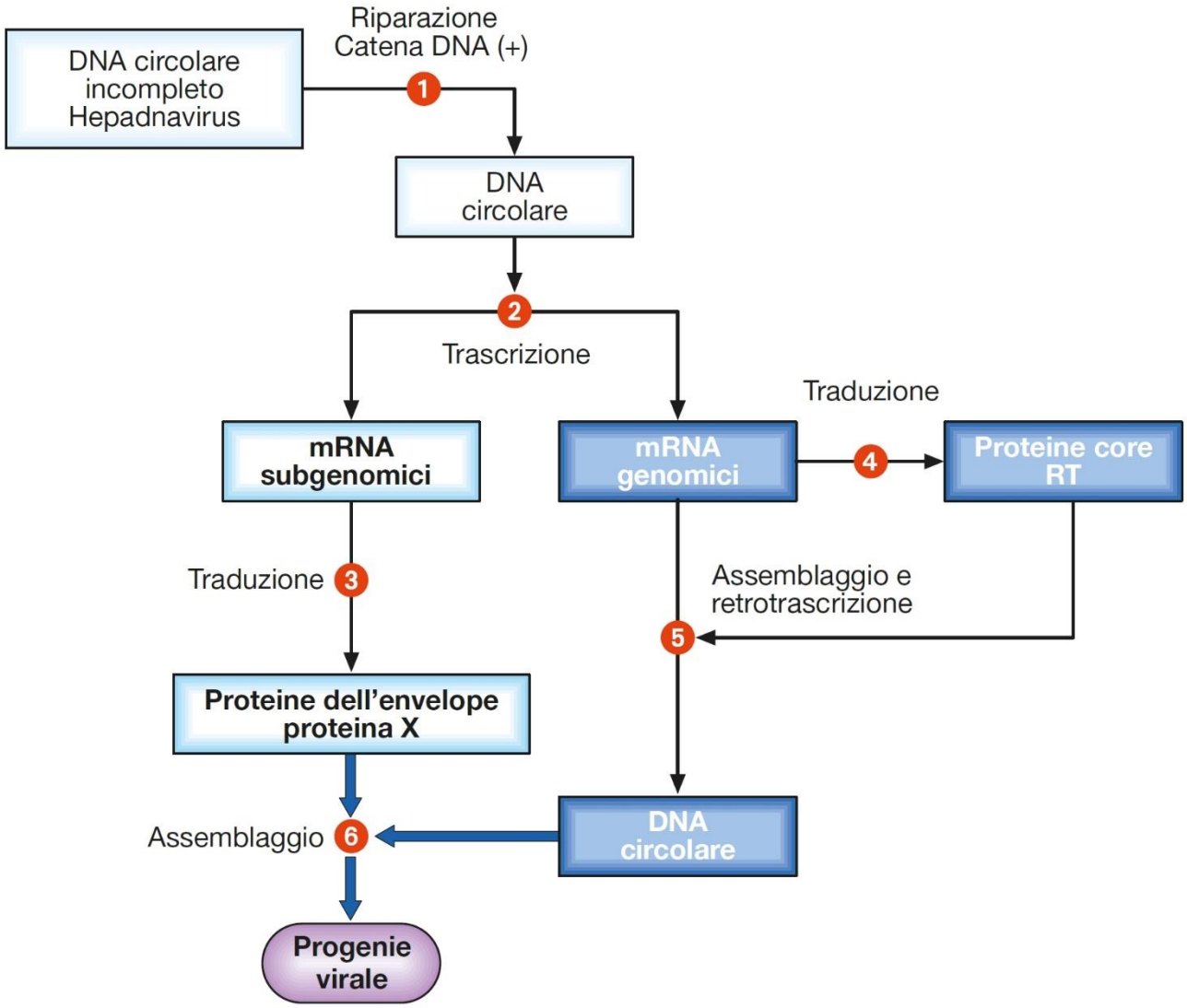


Figura 36.8 Replicazione degli hepadnavirus. 1. Riparazione della catena di DNA (+) interrotta; **2.** trascrizione del DNA in RNA genomici e subgenomici; **3.** traduzione degli mRNA subgenomici; **4.** traduzione degli mRNA genomici; **5.** retrotrascrizione dell'RNA genomico in DNA a opera della trascrittasi inversa (RT) virale; **6.** assemblaggio delle proteine strutturali e dei nuovi genomi.

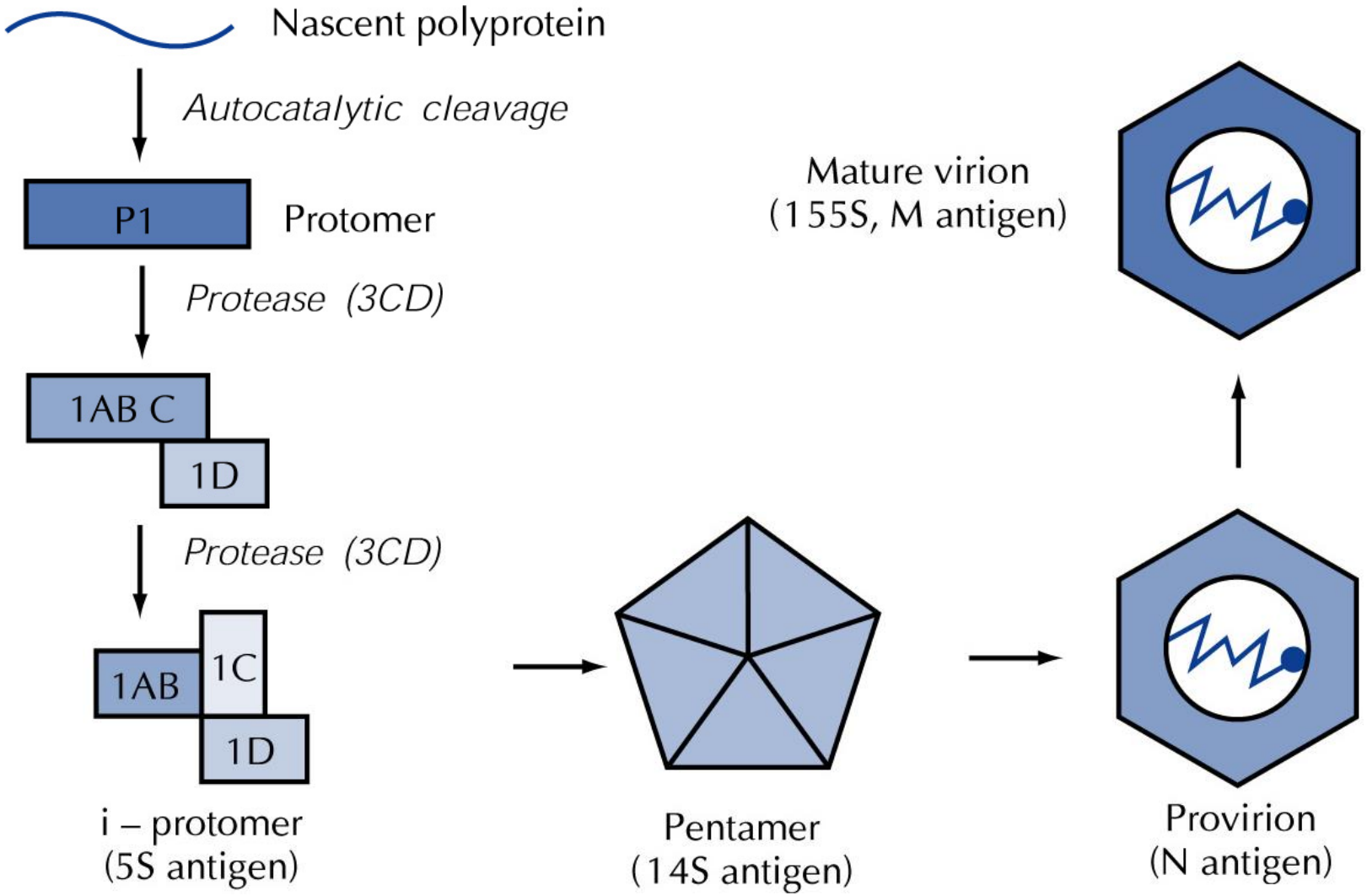
VIRAL LIFE CYCLE

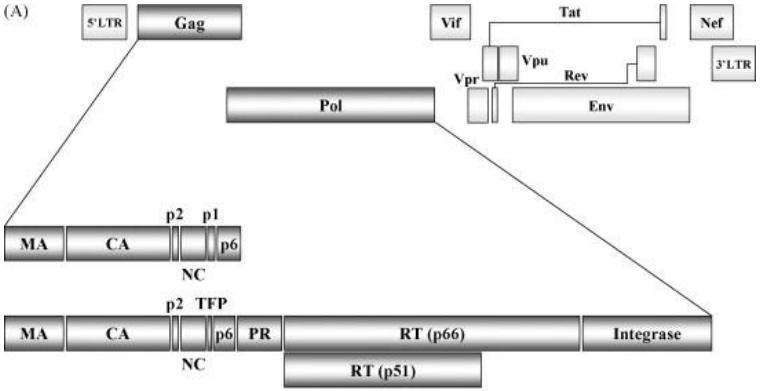
- **ATTACHMENT**
- **ENTRY**
- **UNCOATING**

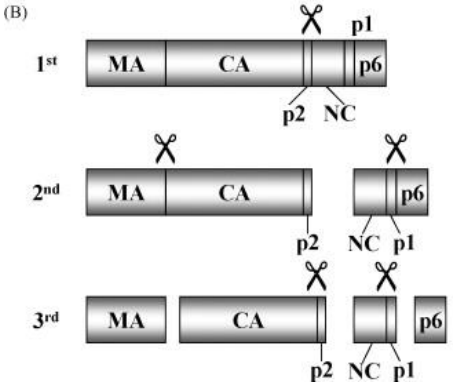
- **GENOME REPLICATION**

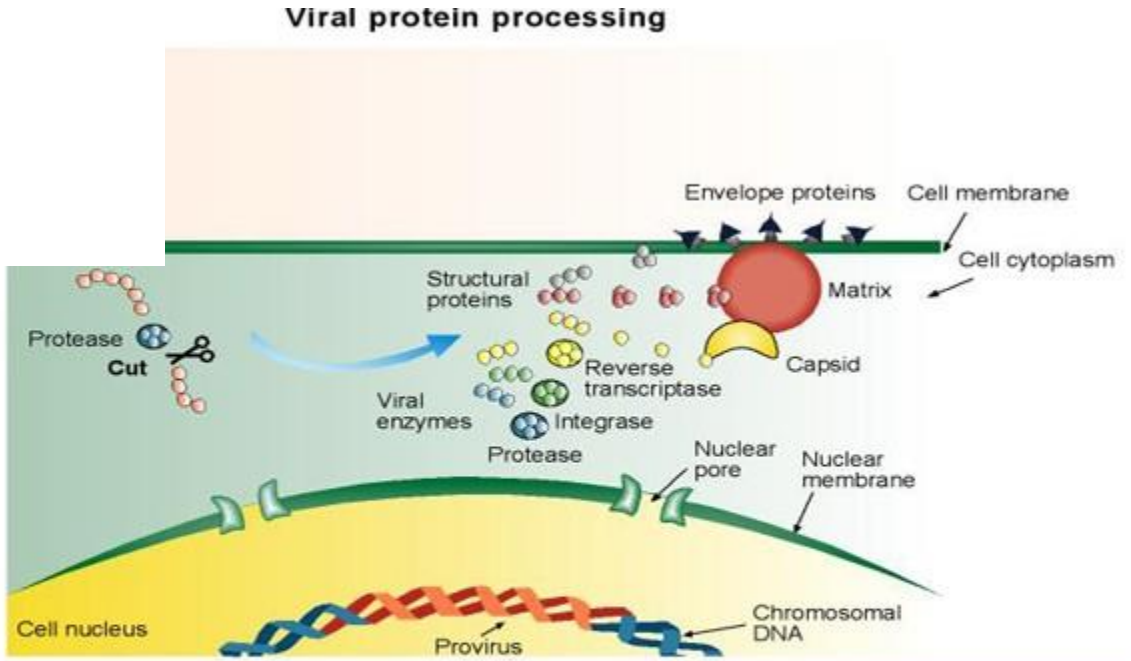
- **ASSEMBLY**
- **RELEASE**

Assemby of Picornavirus





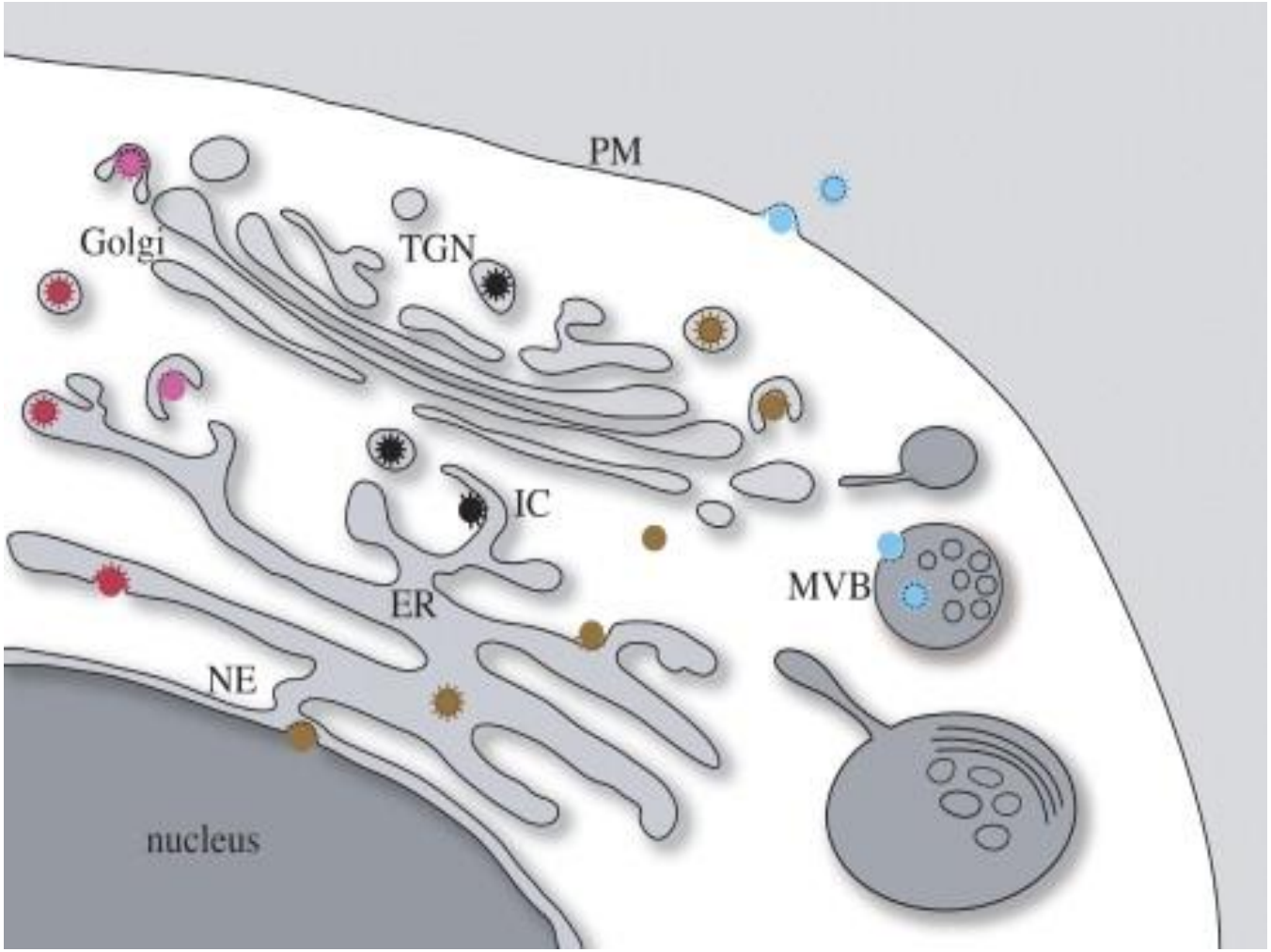


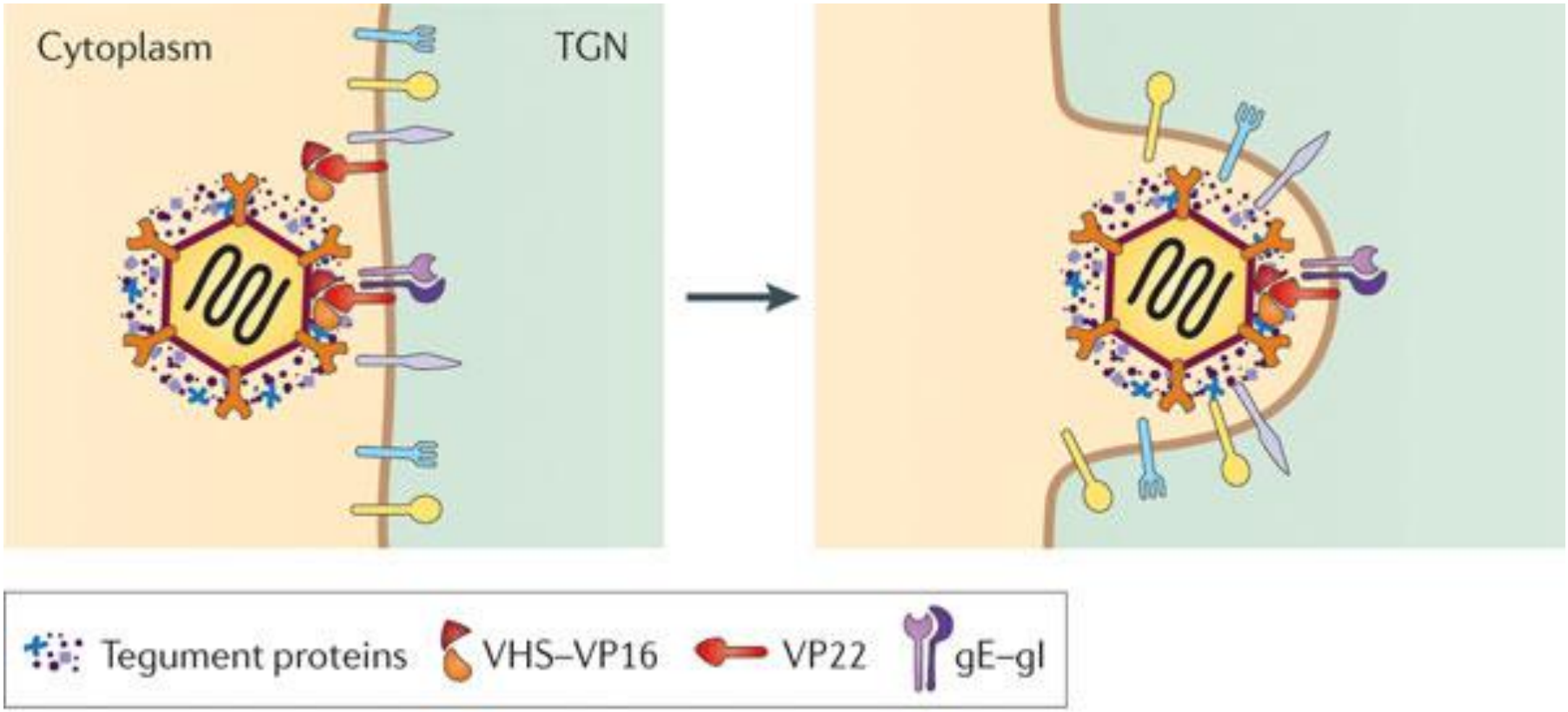


Virus particles are assembled at the cell membrane by recruitment of the newly synthesised viral proteins. Viral genomic RNA is also transcribed for incorporation into the virus core.

Various membrane systems are implicated in budding of enveloped viruses

nuclear envelope (NE), endoplasmic reticulum (ER), endosomes, intermediate or pre-Golgi compartment (IC), Golgi cisternae and the *trans*-Golgi-network (TGN) multivesicular body (MVB) have been proposed to serve as platforms for virus budding





Nature Reviews | Microbiology

Herpes simplex virus

VIRAL LIFE CYCLE

- **ATTACHMENT**
- **ENTRY**
- **UNCOATING**

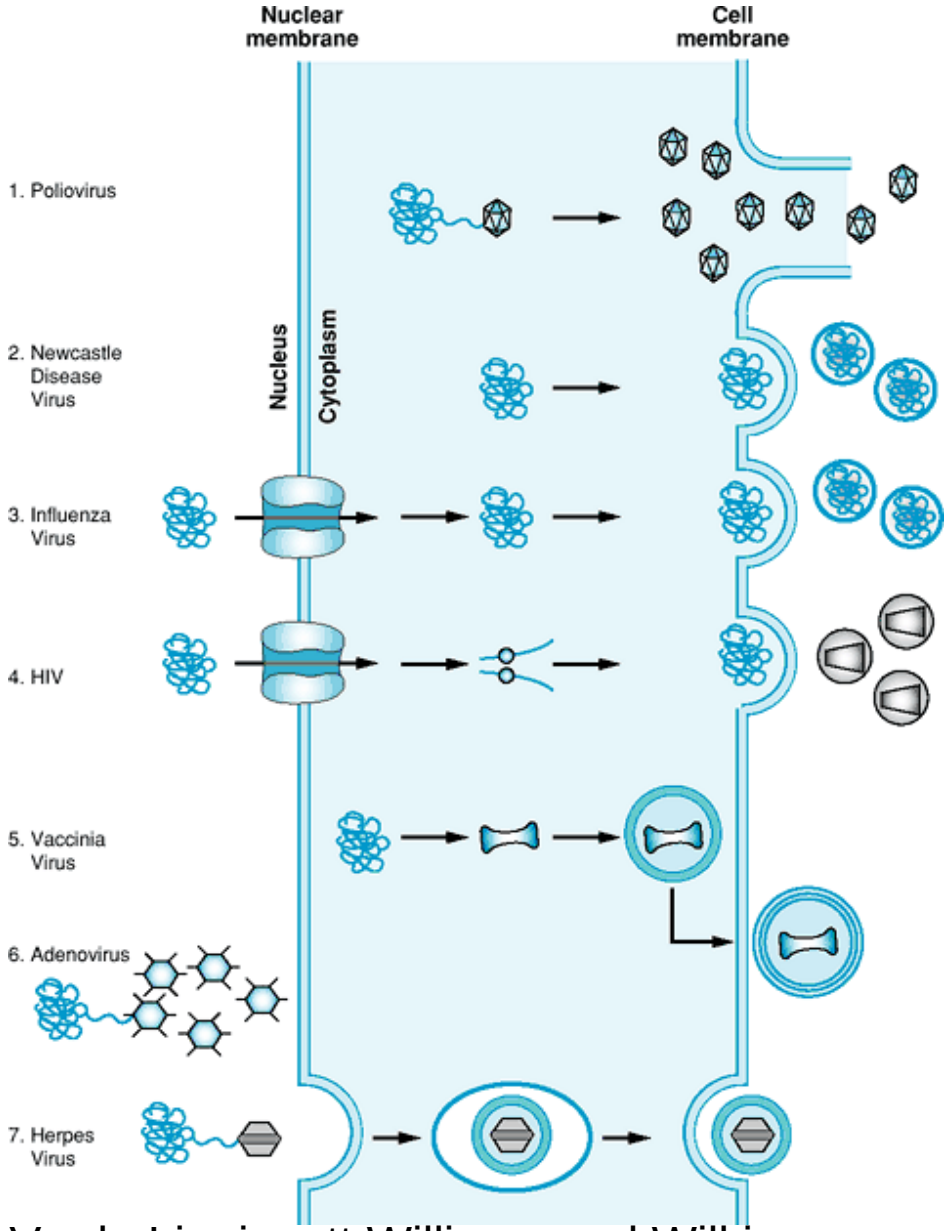
- **GENOME REPLICATION**

- **ASSEMBLY**
- **RELEASE**

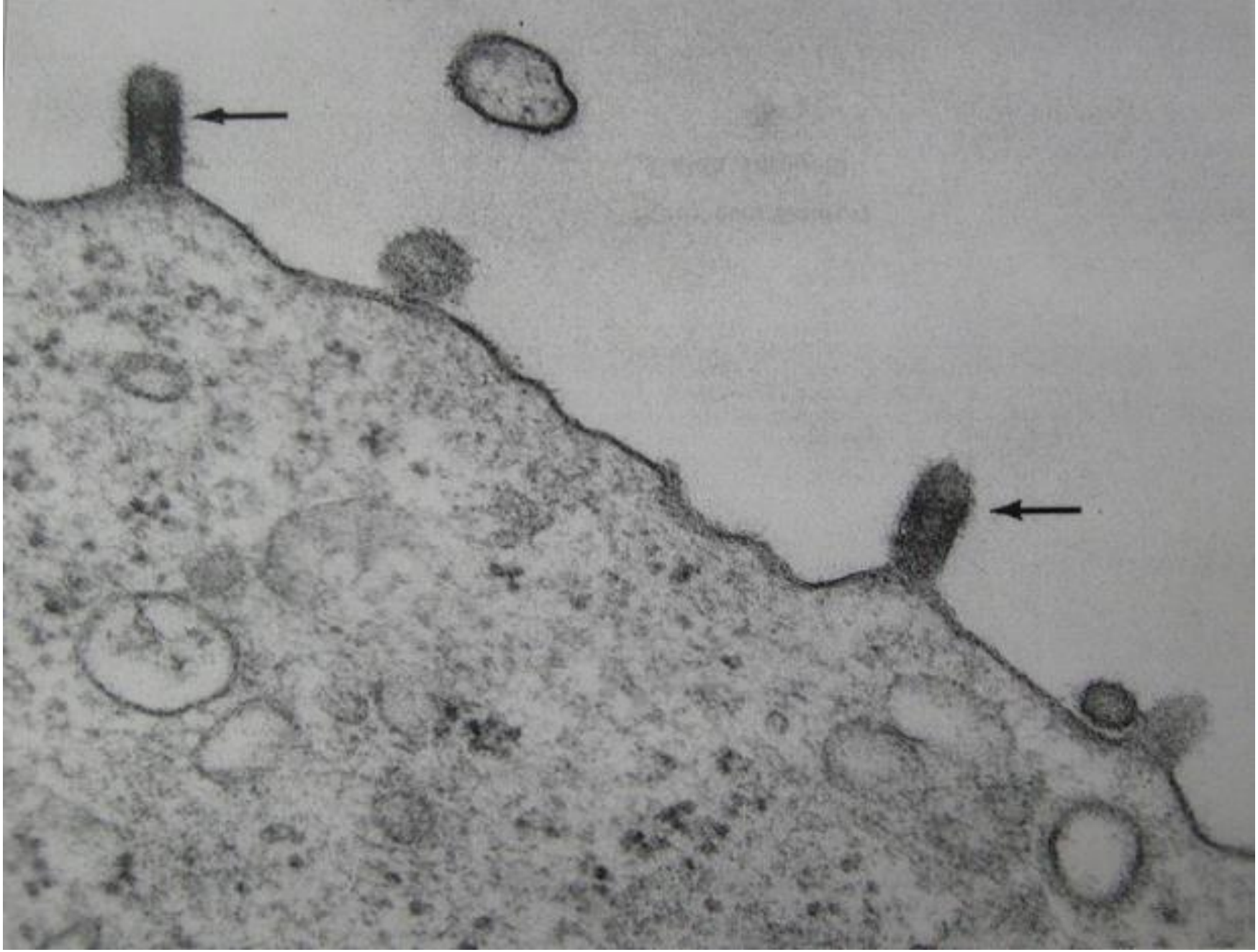
VIRUS RELEASE

- CELL LYSIS
- BUDDING

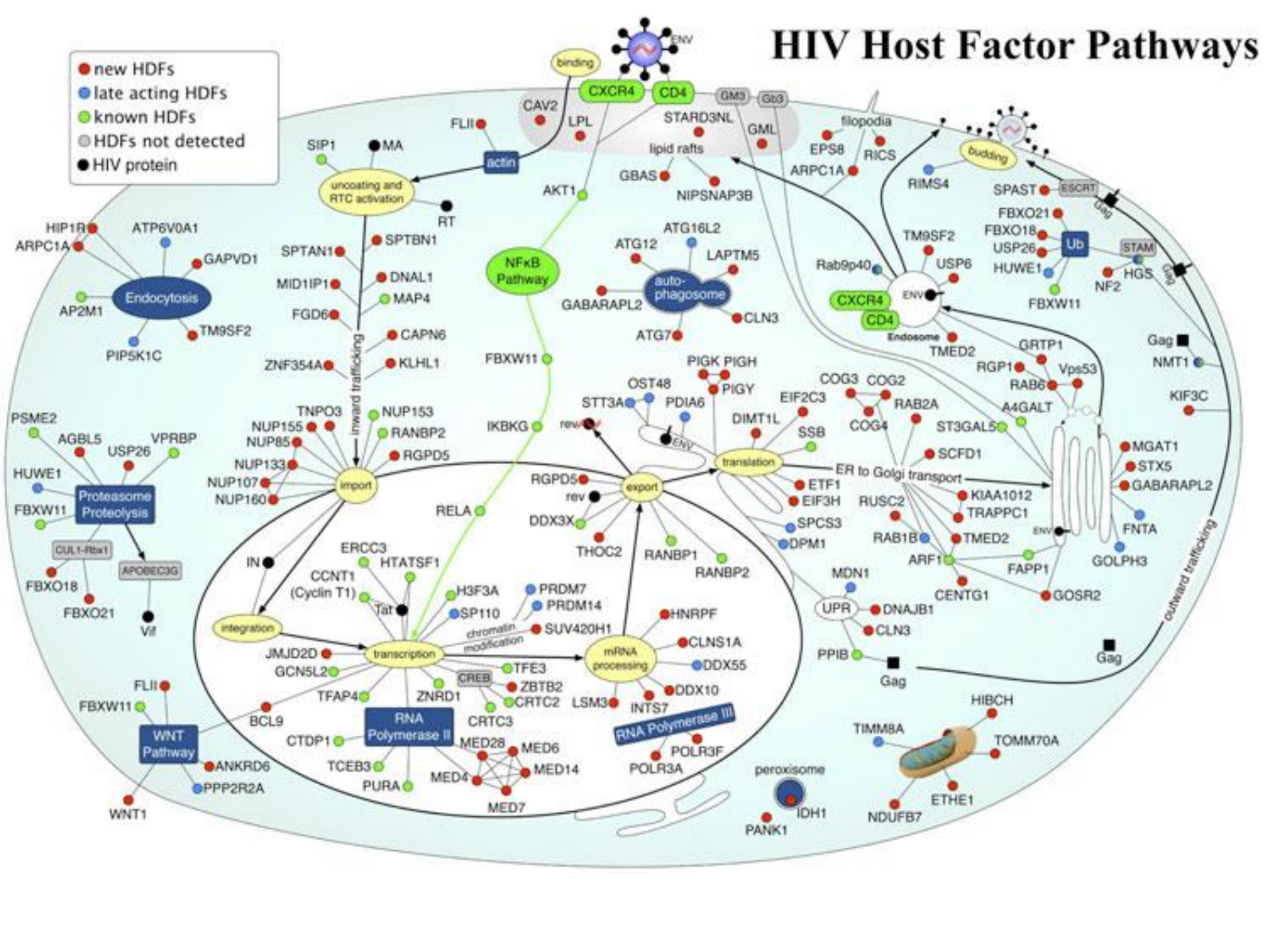
Pathways of exit from cells for different viruses



Fields Virology, V ed., Lippincott Williams and Wilkins



Electron micrograph of enveloped virus particles budding from the infected cell surface


HIV Host Factor Pathways
new HDFs
late acting HDFs
known HDFs
HDFs not detected
HIV protein
ENV
binding
CXCR4
CD4
GM3
Gb3
CAV2
LPL
FLII
STARD3NL
GML
lipid rafts
actin
SIP1
MA
uncoating and RTC activation
RT
AKT1
GBAS
NIPSNAP3B
filopodia
EPS8
RICS
ARPC1A
budding
RIMS4
SPAST
ESCRT
Gag
FBXO21
FBXO18
USP26
Ub
STAM
HUWE1
HGS
NF2
FBXW11
TM9SF2
Rab9p40
USP6
CXCR4
CD4
ENV
Endosome
TMED2
HIP1R
ARPC1A
ATP6V0A1
GAPVD1
Endocytosis
AP2M1
TM9SF2
PIP5K1C
SPTAN1
SPTBN1
MID1IP1
DNAL1
MAP4
FGD6
CAPN6
KLHL1
ZNF354A
inward trafficking
NFκB Pathway
FBXW11
ATG16L2
ATG12
LAPTM5
auto-phagosome
GABARAPL2
CLN3
ATG7
PIGK PIGH
PIGY
OST48
STT3A
PDIA6
IKBKG
rev
ENV
DIMT1L
SSB
translation
EIF2C3
ETF1
EIF3H
SPCS3
DPM1
RGPD5
rev
export
DDX3X
THOC2
RANBP1
RANBP2
RELA
COG3
COG2
COG4
RAB2A
A4GALT
ST3GAL5
GRTP1
RGP1
RAB6
Vps53
KIF3C
Gag
NMT1
MGAT1
STX5
GABARAPL2
FNTA
GOLPH3
ER to Golgi transport
SCFD1
KIAA1012
TRAPPC1
TMED2
RUSC2
RAB1B
ARF1
FAPP1
CENTG1
GOSR2
ENV
outward trafficking
PSME2
AGBL5
USP26
VPRBP
HUWE1
Proteasome Proteolysis
FBXW11
CUL1-Rbx1
APOBEC3G
FBXO18
FBXO21
Vif
TNPO3
NUP155
NUP85
NUP133
NUP107
NUP160
NUP153
RANBP2
RGPD5
import
IN
integration
ERCC3
HTATSF1
CCNT1
(Cyclin T1)
Tat
H3F3A
SP110
PRDM7
PRDM14
SUV420H1
chromatin modification
transcription
JMJD2D
GCN5L2
TFE3
CREB
ZBTB2
CRTC2
CRTC3
ZNRD1
TFAP4
BCL9
RNA Polymerase II
CTDP1
TCEB3
PURA
MED28
MED6
MED14
MED4
MED7
mRNA processing
HNRPF
CLNS1A
DDX55
DDX10
LSM3
INTS7
RNA Polymerase III
POLR3F
POLR3A
FLII
FBXW11
WNT Pathway
ANKRD6
PPP2R2A
WNT1
MDN1
UPR
DNAJB1
CLN3
PPIB
Gag
HIBCH
TIMM8A
TOMM70A
ETHE1
NDUFB7
peroxisome
IDH1
PANK1

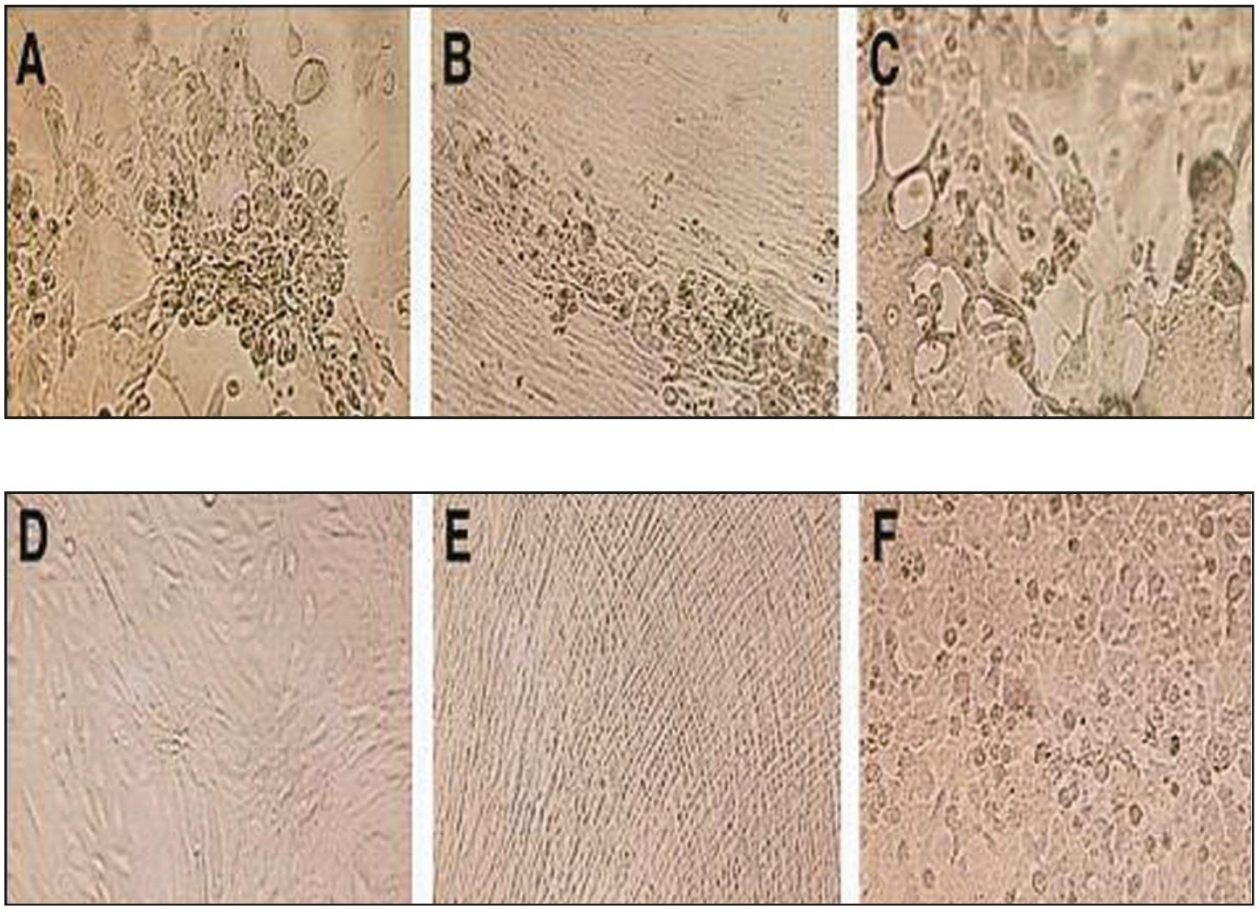


Figura 36.9 Effetto citopatico causato da diversi virus. **A.** Effetto della replicazione del virus herpes simplex in cellule di rene di scimmia (in **D**, cellule di rene di scimmia non infette); **B.** effetto della replicazione di citomegalovirus in fibroblasti embrionali (in **E**, fibroblasti embrionali umani non infetti); **C.** effetto della replicazione del virus respiratorio sinciziale in una linea cellulare di carcinoma laringeo umano (in **F**, cellule di carcinoma laringeo non infette).