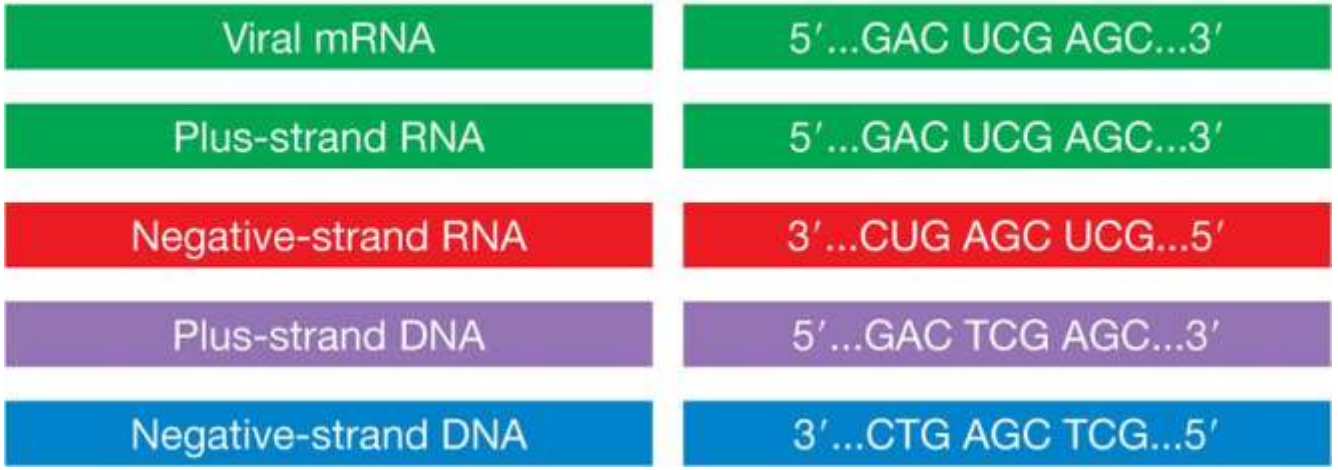
27

Viruses

Virus Classification

- Classification based on numerous characteristics
  - nucleic acid type
  - presence or absence of envelope
  - capsid symmetry
  - dimensions of virion and capsid



Alternative Classification Scheme

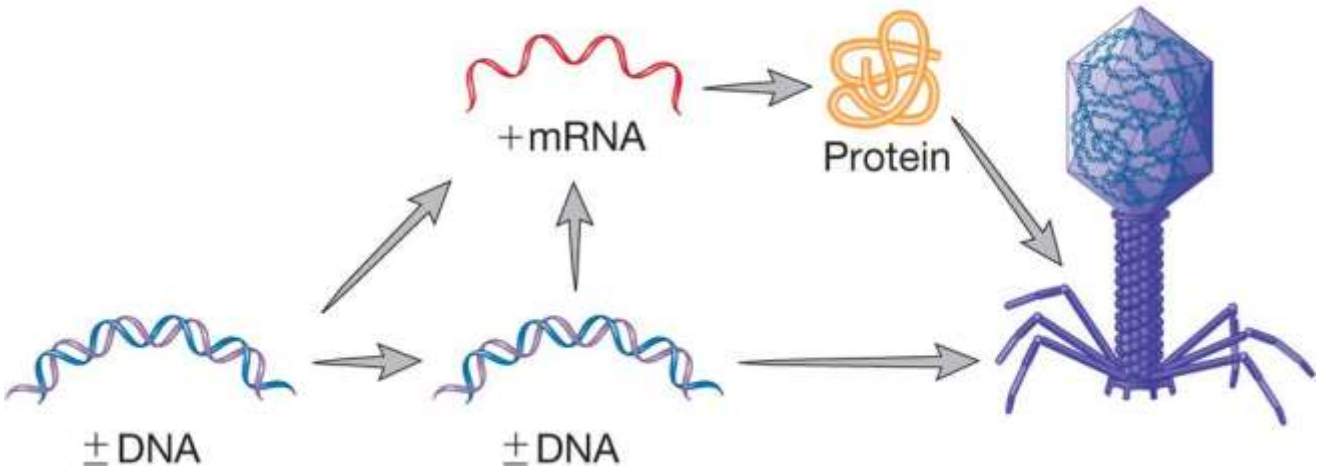
- David Baltimore
  - focuses on viral genome and process used to synthesize viral mRNA
  - 7 life cycle groups based on
    - double stranded (ds) DNA
    - single stranded (ss) DNA
    - dsRNA
    - ssRNA (+ or – strand)
    - retrovirus

Table 27.1 The Baltimore System

Group	Description
Double-stranded (ds) DNA viruses	Genome replication: dsDNA → dsDNA mRNA synthesis: dsDNA → mRNA
Single-stranded (ss) DNA viruses	Genome replication: ssDNA → dsDNA → ssDNA mRNA synthesis: ssDNA → dsDNA → mRNA
Double-stranded RNA viruses	Genome replication: dsRNA → ssRNA → dsRNA mRNA synthesis: dsRNA → mRNA
Plus-strand RNA (+RNA) viruses	Genome replication: +RNA → −RNA → +RNA mRNA synthesis: +RNA = mRNA → −RNA → mRNA
Negative-strand RNA (−RNA) viruses	Genome replication: −RNA → +RNA → −RNA mRNA synthesis: −RNA → mRNA
Retroviruses	Genome replication: ssRNA → dsDNA → ssRNA mRNA synthesis: ssRNA → dsDNA → mRNA
Reverse transcribing DNA viruses	Genome replication: dsDNA → ssRNA → dsDNA mRNA synthesis: dsDNA → mRNA

Double-stranded DNA Viruses

- Largest group of known viruses
- Most bacteriophages have dsDNA
- Important vertebrate viruses
  - herpesviruses, poxviruses
- Insect viruses
- Some rely on host's DNA/RNA polymerases

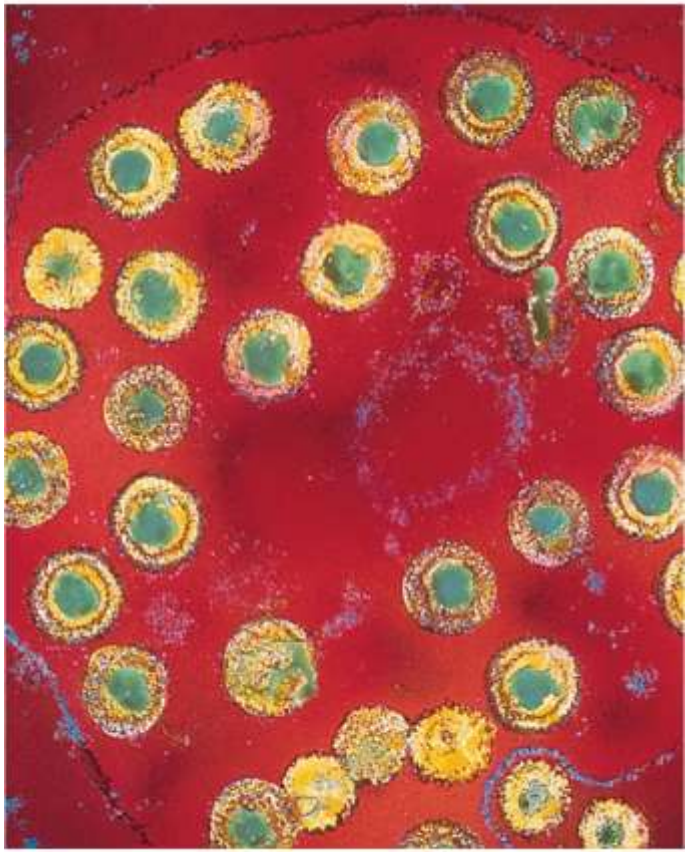


Eukaryotic Viruses

- Herpesviruses
- Nucleocytoplasmic Large DNA Viruses

Herpesvirus Virons

- Icosahedral, 120–200 nm, pleomorphic(متعدد الأشكال), enveloped, surface spikes
- Envelope surrounds tegument (layer of proteins) which surrounds nucleocapsid
- Linear genomes, 50–100 genes
- Targets are epithelial or nerve cells



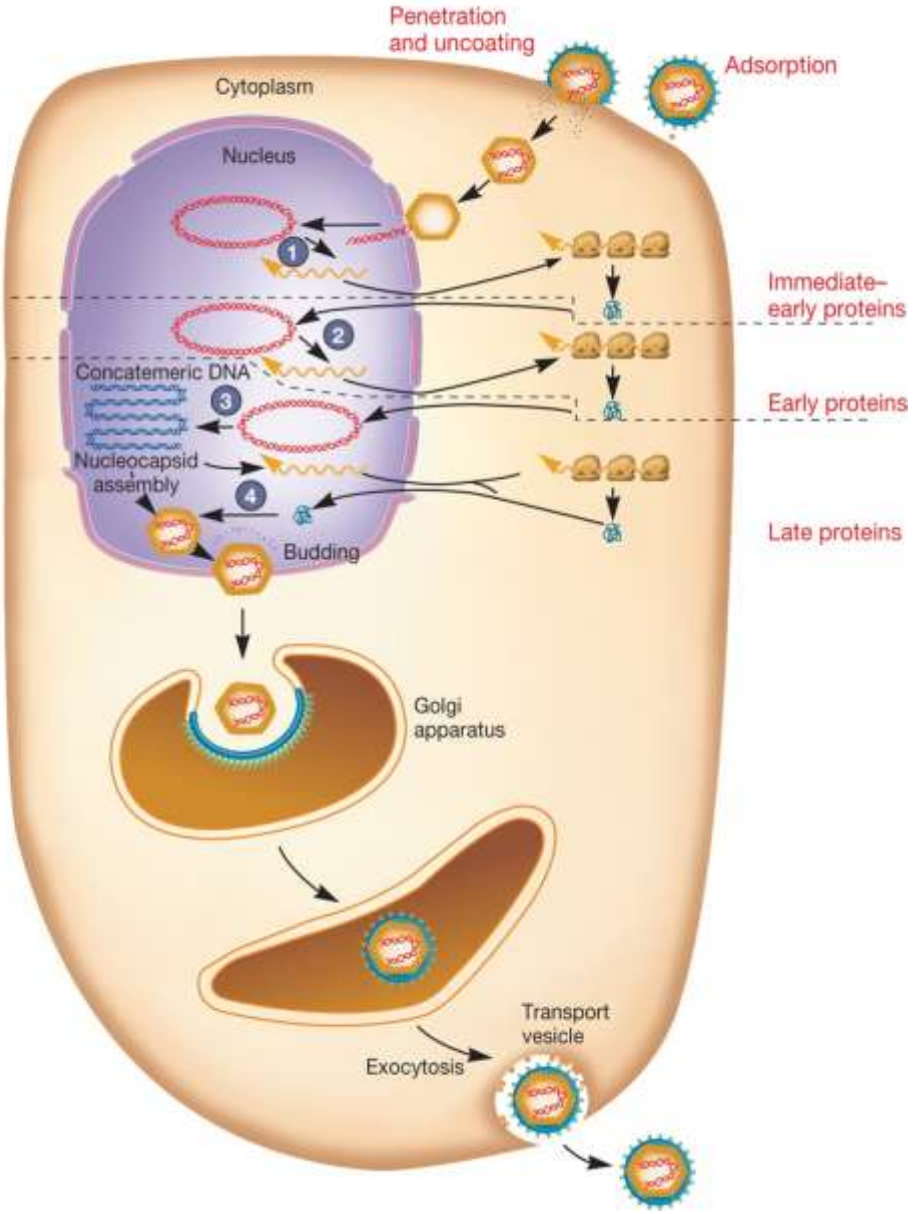
Herpesvirus Infections

- Productive (primary) infections
  - 50,000–200,000 virions produced/cell
  - cell dies due to degraded DNA
- Latent infections
  - occurs in neuronal cells
  - infectious virus not detected
  - can be reactivated in neurons
  - production infection recurs(يتكرر)

Herpesvirus Productive Infection

- Receptor mediated attachment
- Virus envelope fuses with host cell membrane
- Linear dsDNA enters nucleus, circularizes
  - immediate early and early proteins made
    - used for viral DNA replication
  - late gene transcription
    - viral structural proteins

1. Circularization of genome and transcription of immediate-early genes
2. Immediate-early proteins (products of immediate-early genes) stimulate transcription of early genes.
3. Early proteins (products of early genes) function in DNA replication, yielding concatemeric DNA. Late genes are transcribed.
4. Late proteins (products of late genes) participate in virion assembly.



Herpesvirus Productive Infection…

- Nucleocapsid assembles and leaves nucleus
- Tegument proteins associate with nucleocapsid
- Virus envelope is generated by Golgi apparatus
- Mature enveloped virion leaves cell

How do RNA viruses replicate their genomes?

- Methods vary from group to group
  - dsRNA, + sense, and - sense ssRNA viruses use an RNA-dependent RNA polymerase to create a template intermediate of their genome
    - This template can then be used by the same enzyme to create more genome copies
  - Retroviruses use reverse transcriptase enzymes to convert their RNA genome into a DNA intermediate
    - This intermediate is transcribed into more genome copies by a DNA-dependent RNA polymerase (often cellular in nature)

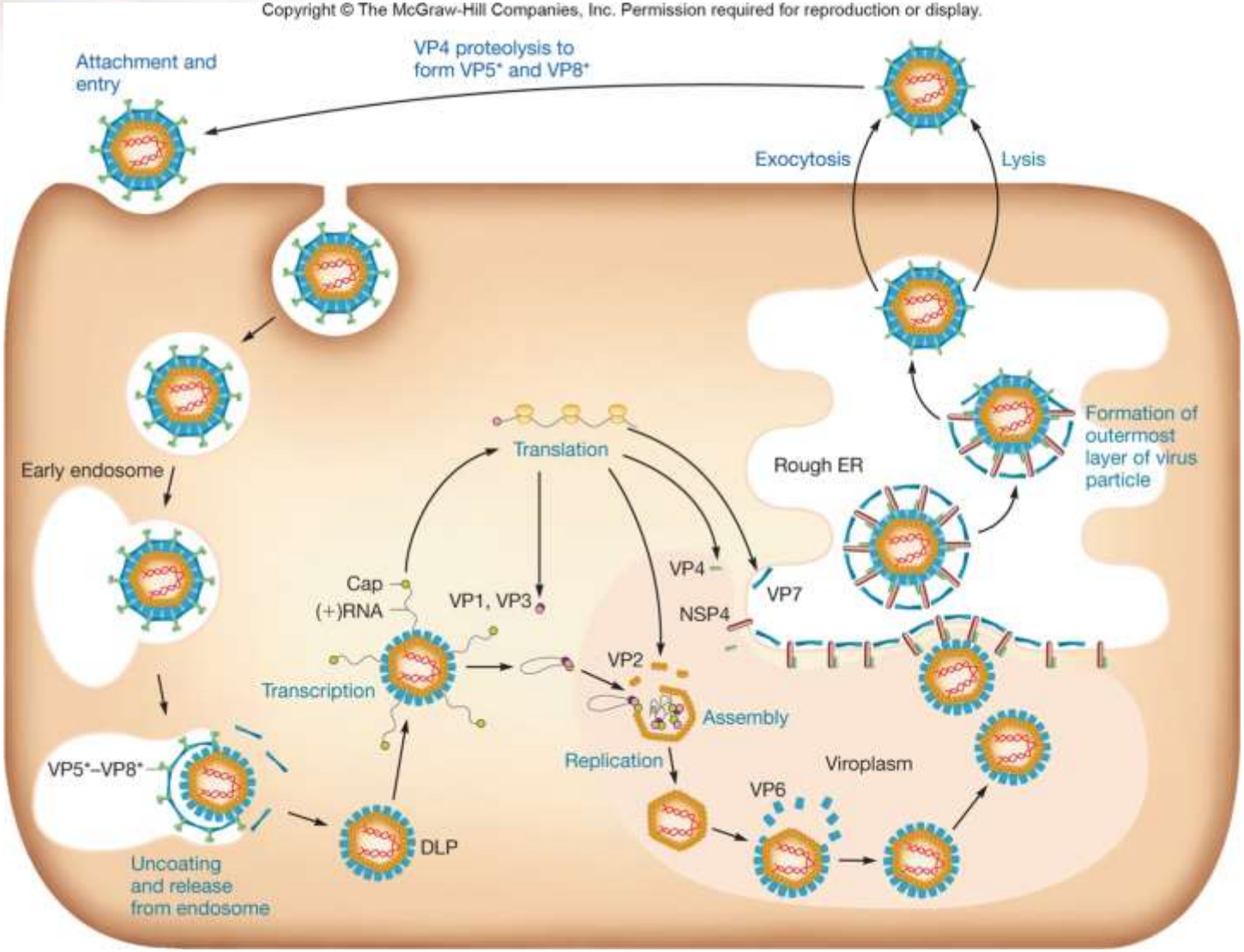
How do viruses use the least genetic material to create their proteins?

- Methods vary
  - RNA levels
    - polycistronic mRNA
    - shorter length subgenomic RNA molecules
    - alternative splicing of RNA molecules
  - Translational levels
    - overlapping coding regions with independent start/stop signals
    - different reading frames
    - production of large polyproteins, cleaved by proteases
    - ‘read-through,’ not stopping at a stop codon

Rotavirus

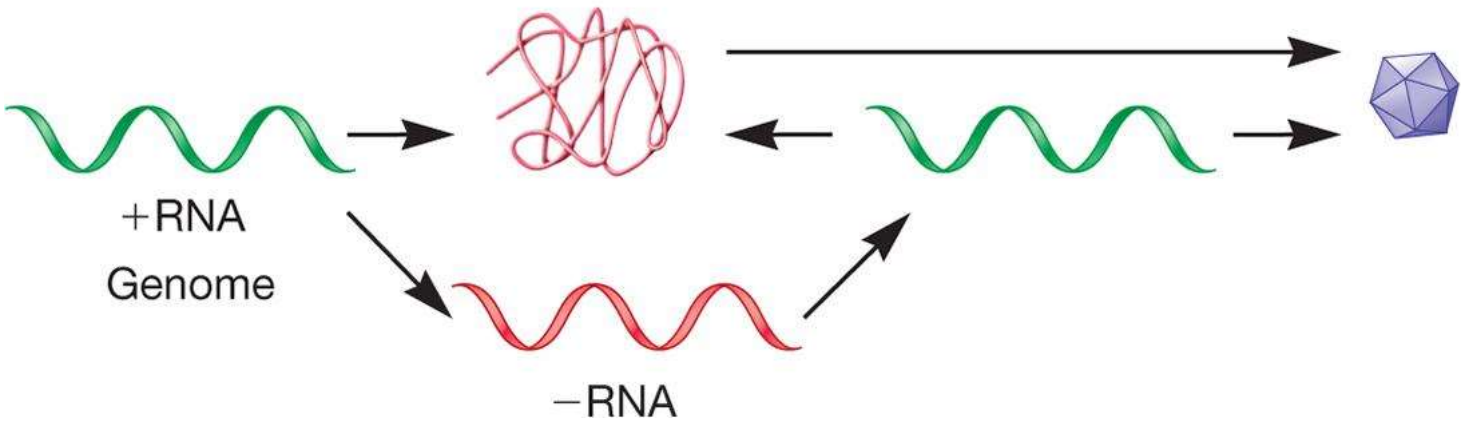
- Human rotavirus kills >600,000 children worldwide each year
  - transmitted by fecal material
  - virus stable in environment
- Virion
  - wheel-like appearance, non-enveloped, segmented genome, dsRNA, three concentric layers of proteins
  - virus loses outer layer of protein when it enters host cell – double layered particle (DLP)
    - mRNA transcription, translation
    - proteins form inclusion called viroplasm
    - RNA genome replication occurs here
    - third layer added in ER

Rotavirus…



Plus-Strand RNA Viruses

- Nonsegmented plus-strand RNA genomes
- Replicate in cytoplasm and synthesize RNA-dependent RNA polymerase
  - synthesizes negative strand RNA
- Replication complex for assembly
  - derived from different cell organelles

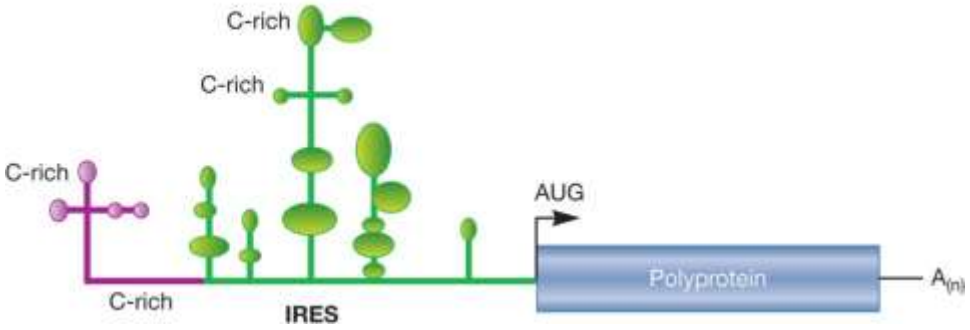


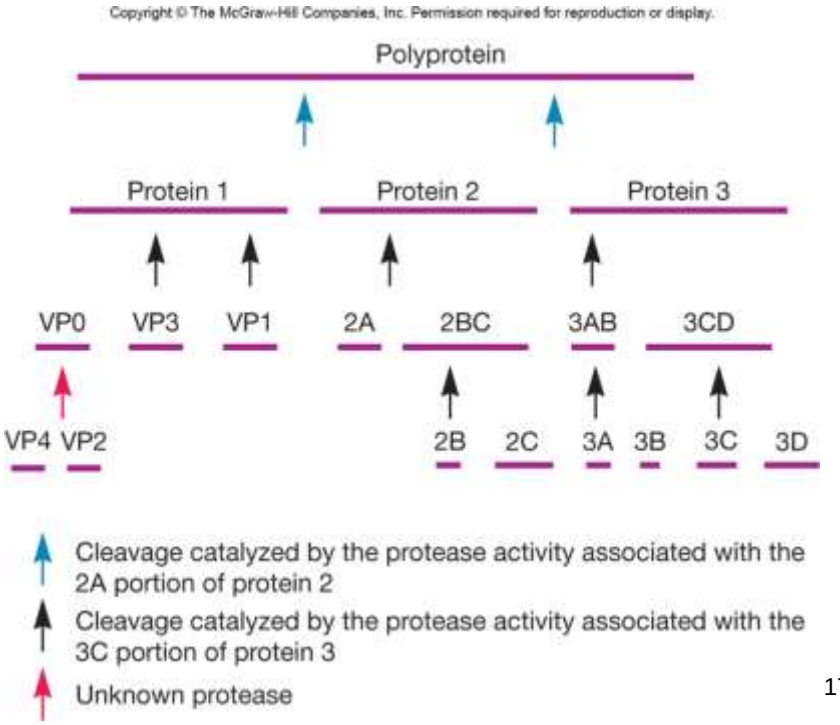
Poliovirus

- Causative agent of poliomyelitis
  - transmitted by ingestion(تنتقل عن طريق الابتلاع)
  - may cripple and paralyze
  - vaccine is eradicating the disease (اللقاح هو القضاء على المرض)
- Virion
  - nonenveloped

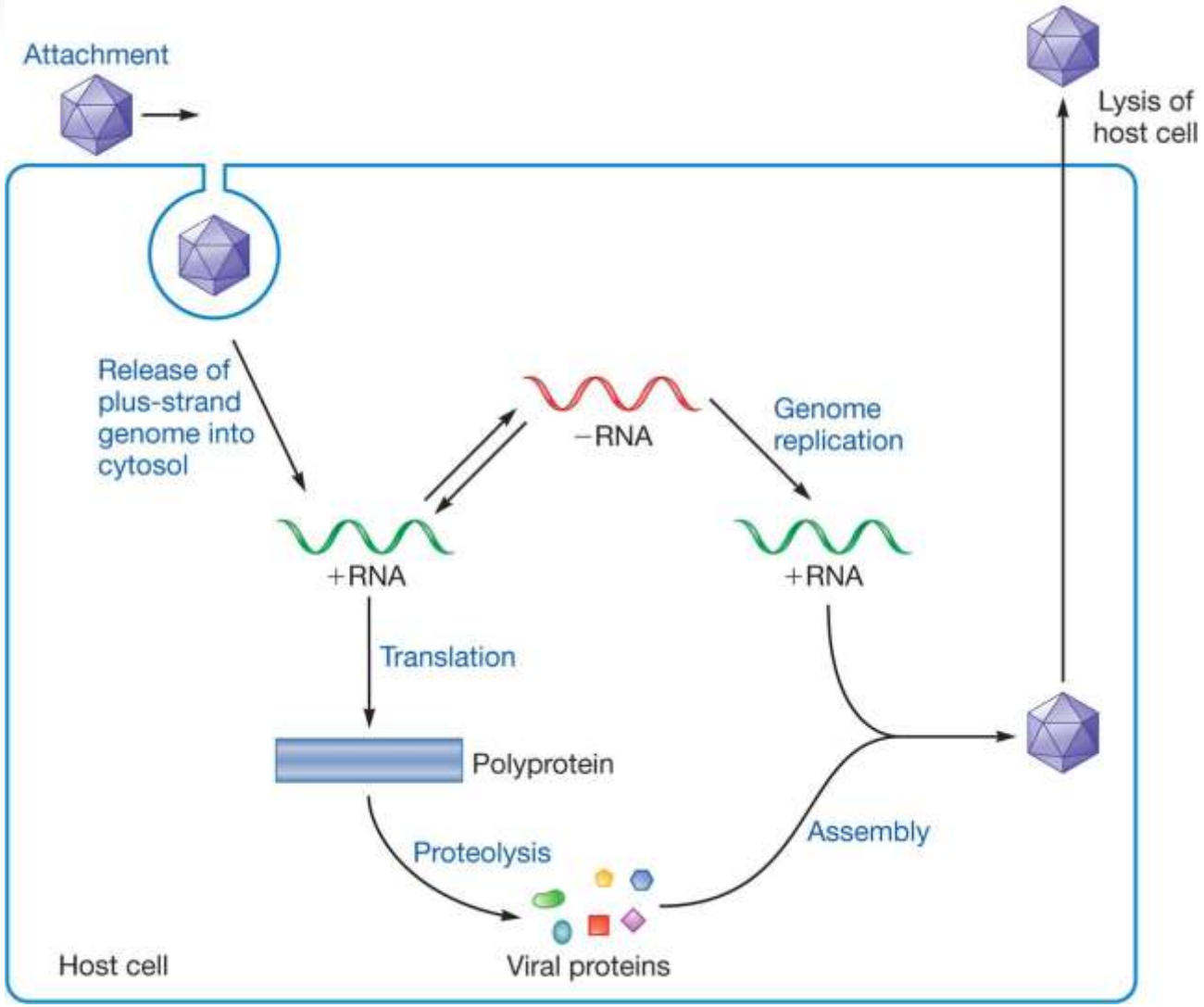
Poliovirus Life Cycle

- Attaches to human PV receptor
- Viral genome acts as mRNA
  - virus uses internal ribosome binding site (IRBS) instead of 5’ cap
  - polyprotein translated, cleaves itself into small proteins
  - genomic RNA synthesized
  - assembly, lysis





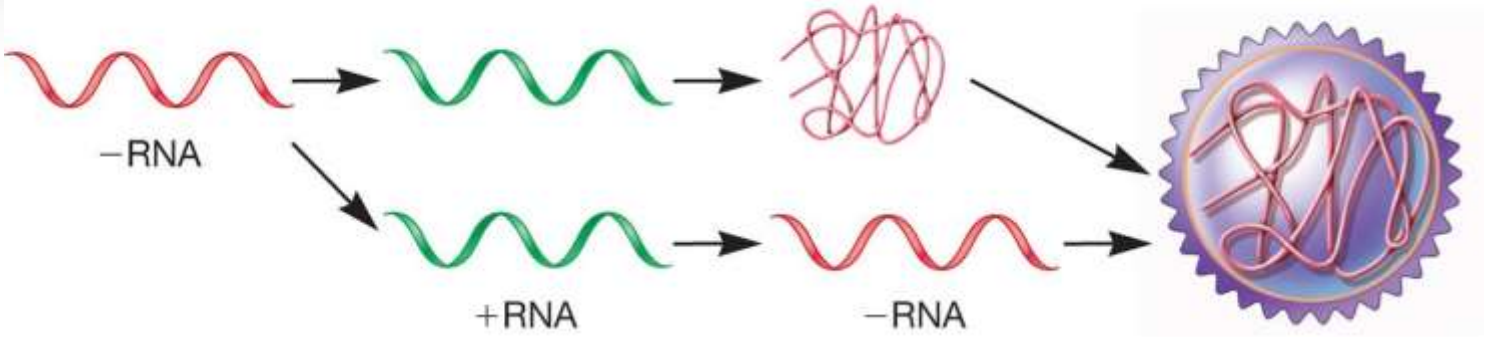
Poliovirus Life Cycle



Minus-Sense RNA Viruses

- More recent evolutionary development
- Enveloped virions, pleomorphic shape
- Segmented and nonsegmented genomes
  - segmented may have evolved from nonsegmented genomes by reduction of redundant(زائد) genetic regions
  - nonsegmented arranged in highly conserved order, tandemly linked separated by nontranscribed intergenic sequences

Negative-Strand Viruses



- Cannot serve as mRNA to form viral proteins
- Must bring into cell preformed RNA-dependent RNA polymerase
  - new plus strand intermediates synthesized
  - the newly synthesized plus strand serves as template for genome synthesis and mRNA as well

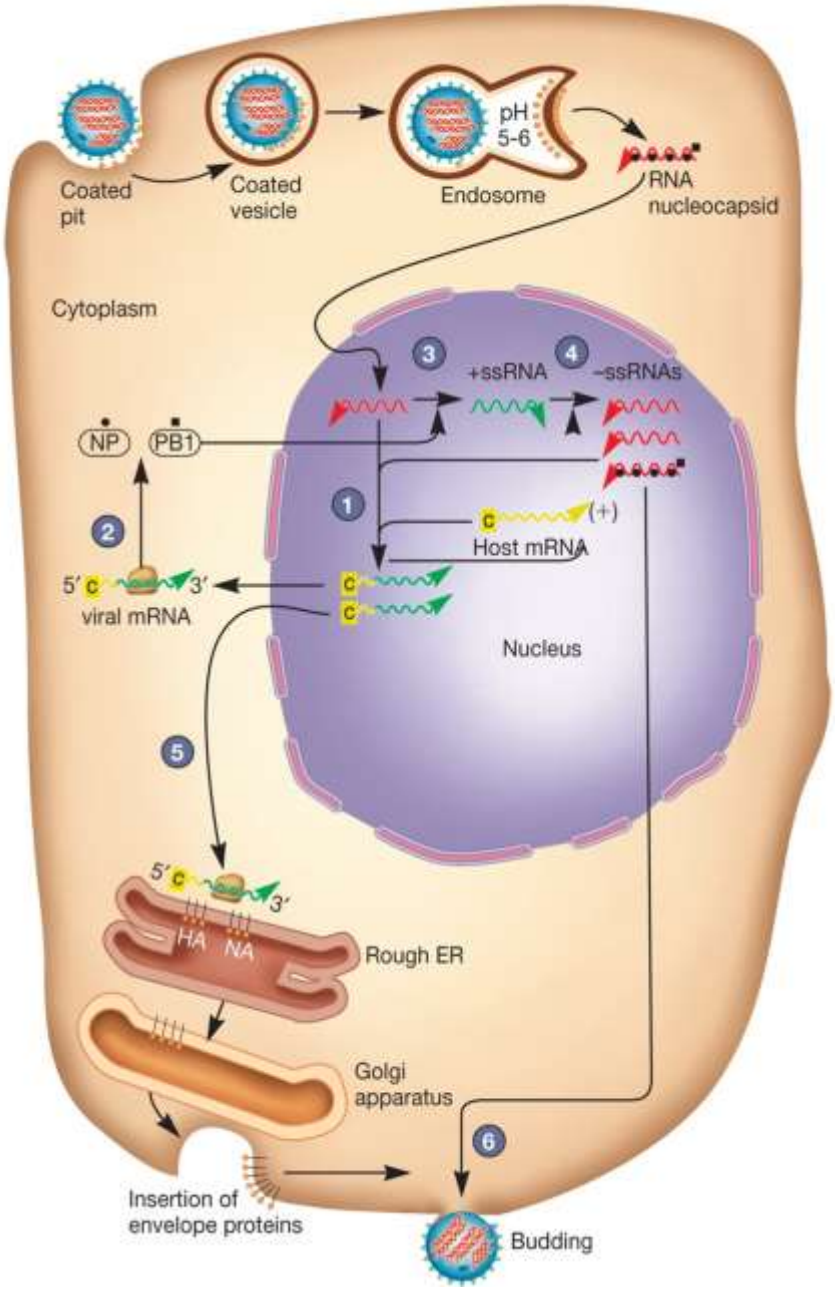
Influenza Virus

- Causative agent of the flu
  - transmitted by inhalation or ingestion
- Three types of viruses – A, B, and C
- Seven to eight segments of linear RNA
  - hemagglutinin binds host receptors
  - neuraminidase hydrolyzes mucus, cleaves virus from host receptor

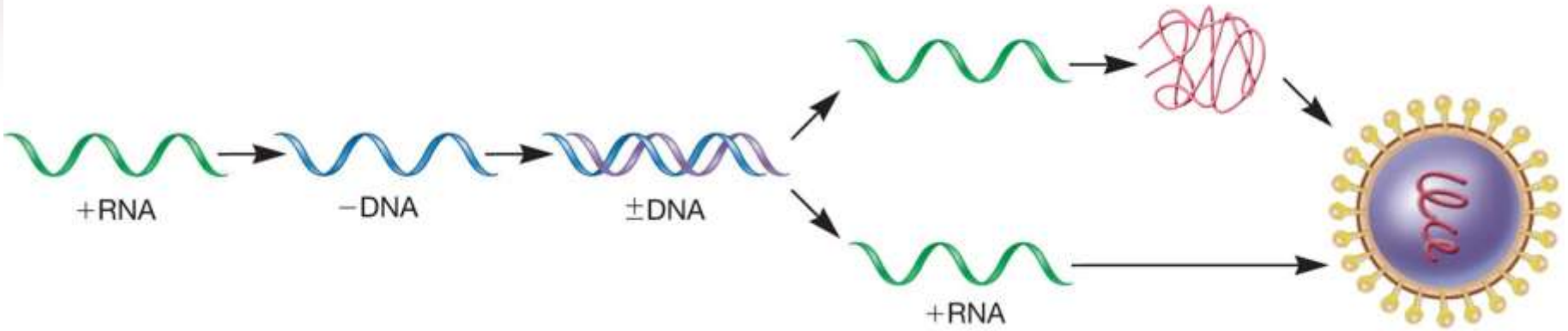
Influenza Virus Life Cycle

- Enters in endosome
  - low pH causes conformational change in hemagglutinin protein
    - hydrophobic ends swing outward and fusion of membranes
    - nucleocapsid released
- Genome template for genome synthesis and mRNA synthesis
- Virus buds from host cell acquiring envelope

1. The endonuclease activity of the PB1 protein cleaves the cap and about 10 nucleotides from the 5′ end of host mRNA (cap snatching). The fragment is used to prime viral mRNA synthesis by the RNA-dependent RNA polymerase activity of the PB1 protein.
2. Viral mRNA is translated. Early products include more NP and PB1 proteins.
3. RNA polymerase activity of the PB1 protein synthesizes +ssRNA from genomic −ssRNA molecules.
4. RNA polymerase activity of the PB1 protein synthesizes new copies of the genome using +ssRNA made in step 3 as templates. Some of these new genome segments serve as templates for the synthesis of more viral mRNA. Later in the infection, they will become progeny genomes.
5. Viral mRNA molecules transcribed from other genome segments encode structural proteins such as hemagglutinin (HA) and neuraminidase (NA). These messages are translated by ER-associated ribosomes and delivered to the cell membrane.
6. Viral genome segments are packaged as progeny virions bud from the host cell.



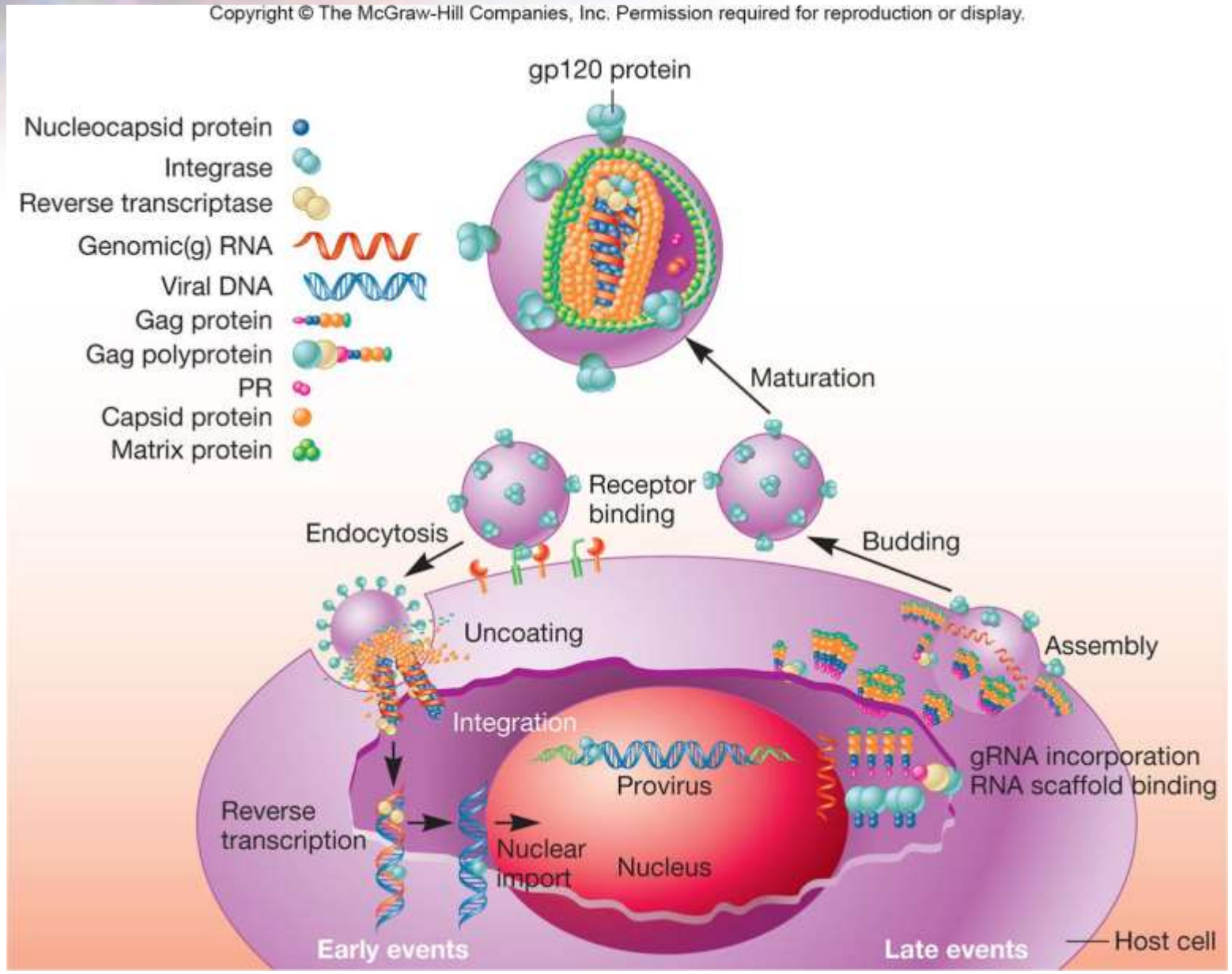
Retroviruses



- Convert ssRNA into dsDNA using reverse transcriptase
- dsDNA integrates into host cell genome and serves as template for mRNA synthesis and genome synthesis

Retroviruses - HIV

- Human immunodeficiency virus (HIV)
  - cause of acquired immunodeficiency syndrome (AIDS)
  - globally important pandemic(وباء مهم عالمياً)
- Member of genus *Lentivirus*
  - HIV-1 (most common cause of AIDS in US), HIV-2 (common in Africa)
- HIV-1
  - enveloped virus
    - two copies of RNA genome
    - reverse transcriptase and integrase

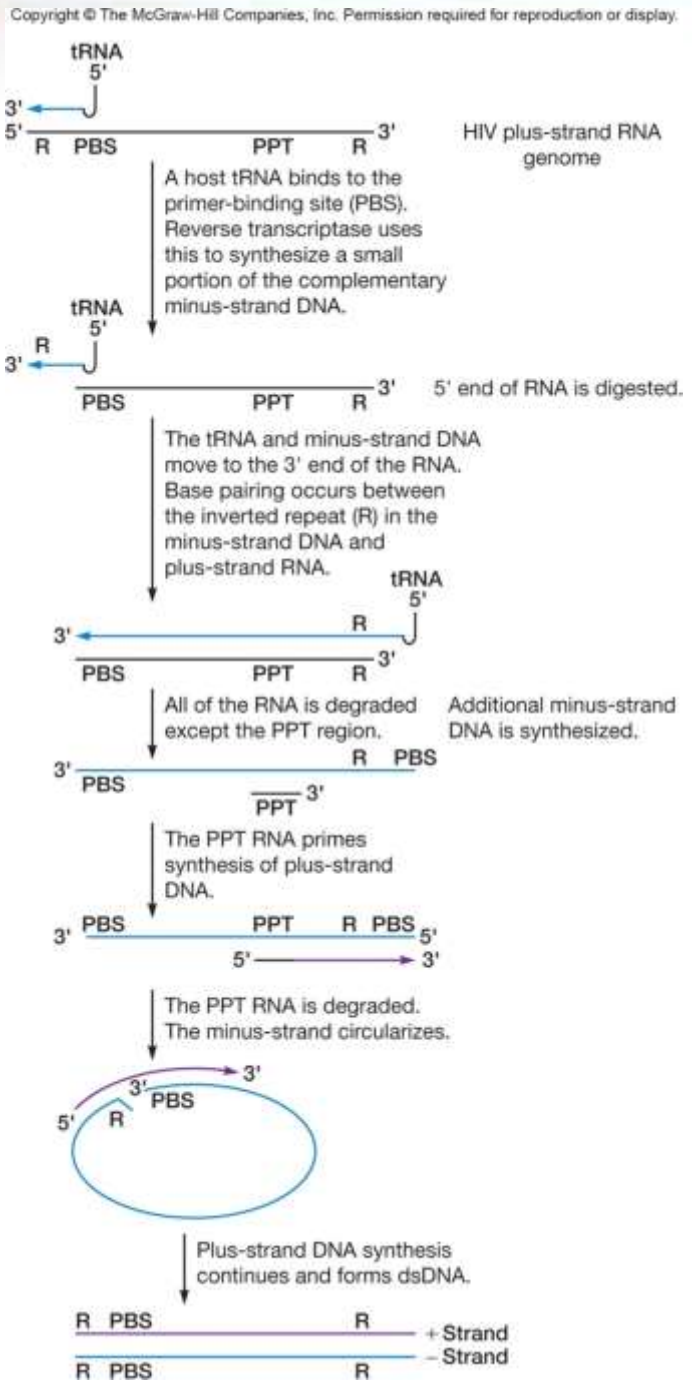


HIV…

- gp120 binds $CD4^+$ T cells, macrophages, dendritic cells, and monocytes
  - coreceptor (which can vary) also required to gain entry into cell
  - virus enters by receptor-mediated endocytosis
- Reverse transcriptase
  - RNA dependent DNA polymerase
  - DNA dependent DNA polymerase
  - ribonuclease RNase H
  - error prone, has no proofreading capability

HIV Life Cycle

- Reverse transcriptase
  - RNA dependent DNA polymerase
  - DNA dependent DNA polymerase
  - ribonuclease RNase H
  - error prone, has no proofreading capability



HIV Life Cycle…

- dsDNA is moved to the nucleus
  - integrase and other proteins integrate proviral DNA
  - forces cell to synthesize viral mRNA
  - splicing forms 10 viral transcripts
- Cleavage forms viral proteins
- Assembly and budding occurs
- Eventually cell dies