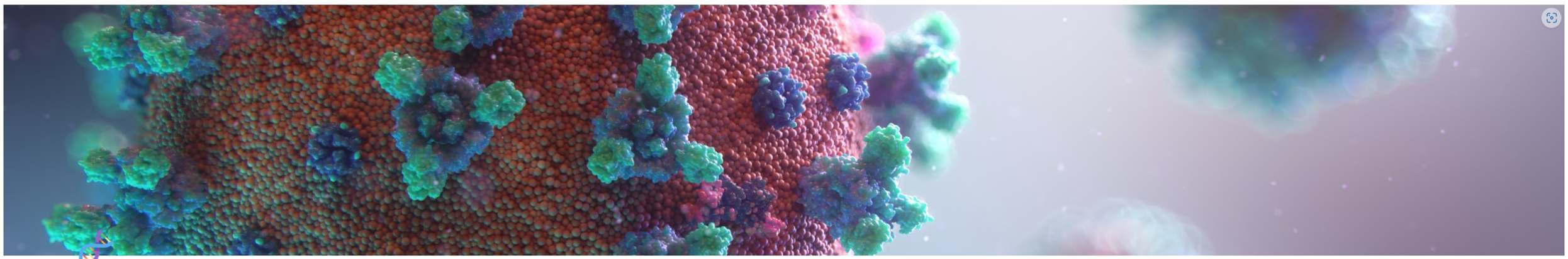


M5 - Virus & Prions

3 more properties

Learning Objectives

- Define the terms “virus” & “prion”
- Explain how viruses & prions differ from other organisms
- Classification of the viruses
- Describe the structure and life cycle of a typical virus & a prion
- List some medically important viruses & prions
- Discuss reasons for studying viruses & prions

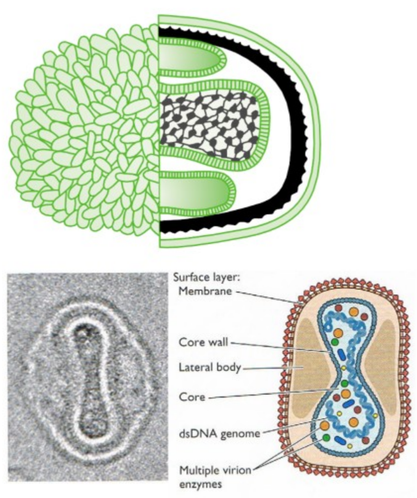
Differentiate Virus from Other Microbes

Characteristics of Virus

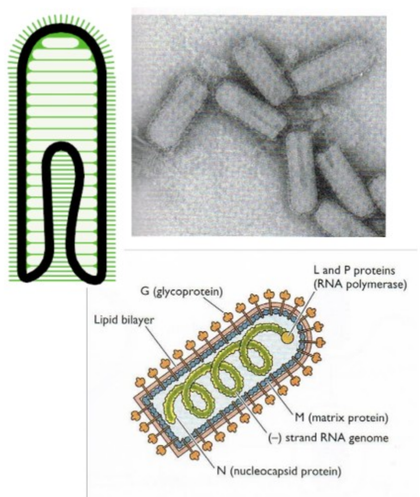
- **Small, infectious, obligate intracellular parasite.**
  - **Molecular building blocks.**
  - **Machinery and energy.**
- **Replicates itself in a host cell.**
- **Genome is enclosed in a protein coat.**
- **Non-cellular organism.**
- *Approximately 20-200 nm (Electron Microscopy).*

Genome Size

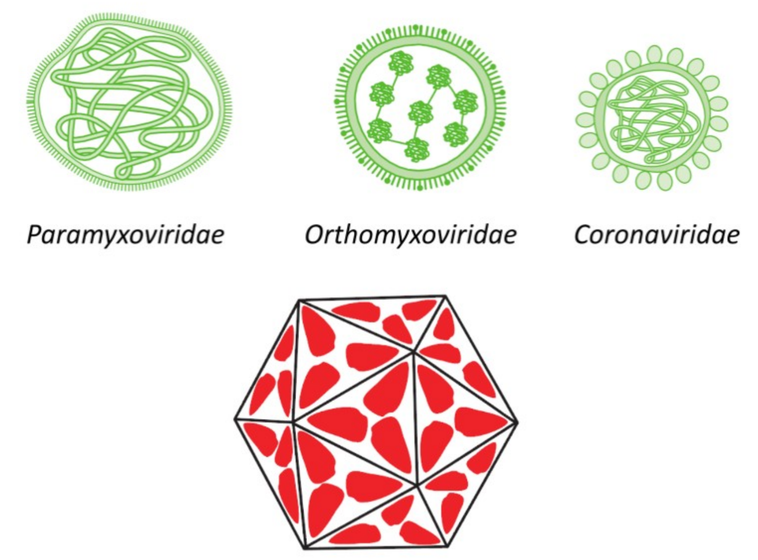
Organism	Genome size (b = Base pair)	No. of Protein Coding Genes*
Human	3 Gb	~ 21,000
Yeast (S. cerevisiae)	12.1 Mb	~ 6,300
E. coli	4.6 Mb	~ 4,000
Pandoraviruses	**1.9 - 2.5 Mb (dsDNA)**	**-1,500 - 2,500**
Herpes viruses	120 - 230 kb (dsDNA)	60 - 120
Coronaviruses	**27 -32kb - (+ssRNA)**	**14 -16**
Influenza virus	14 kb (-ssRNA)	14
Hepatitis B virus	3 kb (dsDNA-RT)	4
Hepatitis D virus	**~ ~1.7 kb (-ssRNA)**	**1 (with 2 isoforms)**



Poxviridae



Rhabdoviridae



Structure of Viruses

Component	Description
Nucleic acid (genome)	★ Segmented or in one piece; ★ **Inside the capsid** (often with virus proteins)
Capsid (protein shell, matrix)	★ Made of protein subunit called **capsomeres (protomeres)** ★ **Accounts for the major mass of virus**
Envelope (with or without)	★ **Lipid bilayer** lying outside of the capsid ★ Providing **antigenic structures of lipid, protein and carbohydrate molecules**
Viral Spikes [Made of **glycoprotein**]	★ **Protruding from (突出于) the envelope or matrix** ★ **Have enzymatic and/or adsorption and/or hemagglutinating activity (血凝活性)** ★ **Highly antigenic (bind to cell)** ★ Targeted by the immune response

Classification of Viruses

Method	Mechanism
Morphology	Helical Icosahedral Complex morphologies
Envelop	(Non-)Enveloped
Genome	dsDNA ssDNA dsRNA ssRNA Linear; Circular
Mechanism of mRNA production	**Baltimore classification (mechanism of mRNA production)**

Morphology

Virus Structure	Shape	Morphology	Examples
Helical-structured viruses	Spiral capsid	★ **Paramyxoviridae** ★ **Orthomyxoviridae** ★ **Coronaviridae**	★ Measles, Mumps ★ Influenza ★ SARS / MERS, Common Colds
Icosahedral-structured viruses (二十面体)	Closed shell	Robust viruses pack lots of Genes	HPV Dengue Virus
Poxviridae	**Brick-shaped/oval-shaped**	Complex Envelope dsDNA genome	**Variola virus → Small pox**
Rhabditida	**Bullet-shaped**	Complex Envelope RNA genome	**Rabies virus**

Enveloped Virus

- Capsid (Inner: **genome + virus proteins.**)
- Envelop (Outer: **Holds Antigenic glycoproteins**)
  - **Hemagglutinin** (HA) - *Help Entering Cell*
  - **Neuraminidase** (NA) - *Help Spreading*
- Spreading Method:
  - **Take a lipid layer → “bud” from it**

Non-Envelop Virus (Naked)

- Virus Protein
  - VP2: icosahedral capsomers
  - VP1/3: Virus Proteins(VP) with dsRNA in the capsid
  - VP4/6/7: “Spike” protein
- Spreading Method:
  - **Lyse** infected cell membrane

Genome

Virion Structure	dsDNA	ssDNA	dsRNA	ssRNA
Naked Icosahedral	√	√	√	√
Enveloped Icosahedral	√		√	√
Naked Helical	√	√		√
Enveloped Helical				√

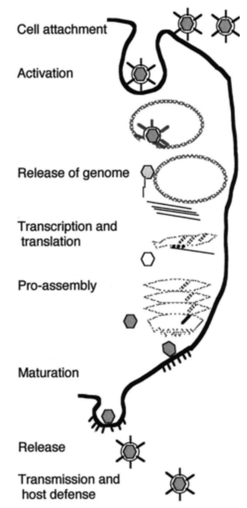
Remarks:
Shape of Genome can be **Linear & Circular**
ds: double-strands ; ss: single-strands

Transcription - Baltimore classification

Class (mechanism of mRNA production)	Type Virus
I (ds):	★ Adenovirus ★ Herpesvirus ★ Poxvirus
II (ss):	★ Parvovirus
III (ds)	★ Reovirus (e.g. rotavirus)
IV(+ss):	★ Picornavirus (eg EV71) ★ Astrovirus Coronavirus (eg SARS-CoV)
V(-ss):	★ Orthomyxovirus (eg flu) ★ Paramyxovirus (eg Nipah) ★ Rhabdovirus (eg rabies) ★ Deltavirus (eg HDV)
VI (RT)	★ Retroviruses (e.g. HIV)
VII (RT)	★ Hepadnaviruses (e.g. HBV)

Virus Life Cycle - AETTGAE

- Contacts a cell receptor for attachment (adsorption) → penetration
  - Virus surface protein can attach to receptors from specific type of host cells
  - Key (virus) fits → Unlock and enter the cell.
- Extract viral genome in the cytoplasm
  - cellular proteolytic enzymes digest the viral capsid → nucleic acid
- Protein synthesis
  - Uses the host cell's machinery → Protein Needed for replication of new virions.
    - Transcription Protein
    - Translation structural Protein
    - Functional proteins
- Replication of the virus' genome
  - Uses the host's cellular machinery to replicate.
- Maturation of virus particle
  - Assembly of synthesized nucleic acid, proteins, capsid, envelopes
- Release of particles from the host cell
  - lysis of cell or virus "buds" from cell



💡 **AETTGAE:** **A**ttachment, **E**ntry, **T**ranscription, **G**enome replication, **A**ssembly, **E**xit

Some Chemically Important Viruses

Disease	Virus
Gastroenteritis	Rotavirus, norovirus, adenovirus, astrovirus
Common cold	Rhinovirus and enteroviruses, coronavirus, influenza viruses, adenoviruses, respiratory syncytial virus, parainfluenza viruses, metapneumovirus
Seasonal epidemics (A, B, C)	Influenza virus
Liver failure / Cancer	Hepatitis virus (A, B, C, others)
AIDS	Human Immunodeficiency Virus
SARS/MERS	SARS/MERS coronavirus
COVID-19	SARS-CoV-2
Zika, Dengue, Yellow fever, Japanese encephalitis	Vector (mosquito) borne viruses (Flaviviruses)
Pandemics (influenza A)	Influenza A virus

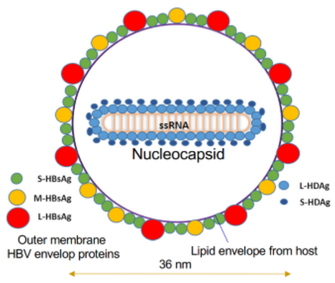
▼ Strategy used by Virus

- Δ receptors & transmission routes
- Δ Host
- Integrate within chromosome → *replicate at a slow rate*
  - Symptomless carriers → Wait lowered host defense （e.g.: HIV）
- RNA viruses have ↑ mutation rates & evolve rapidly
  - Type of Evolution:
  - ▼ Recombination:
    - Genome from two different viruses (that have infected the same cell) combine to form a new virus
  - ▼ Reassortment:
    - Segmented genomes in viruses like influenza can lead to the mixing and matching of genome segments from two different viruses.
    - This process can create a new virus with new combinations of genetic material.
  - ▼ Mutation:
    - RNA viruses are prone to mutations due to lack of proofreading ability during genome replication
    - Mutations can lead to creation of new strains or variants
  - Escape treatment or immune response
  - Δ clinical illness spectrum
- **Reassortment** & **recombination** → generate novel variants

▼ Recap: Diagnosis of Viral Infection

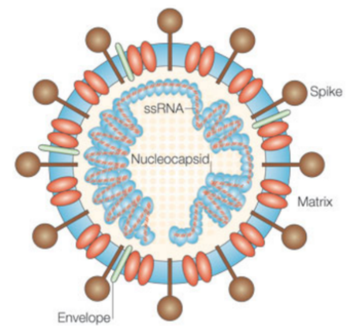
- Virus detection
  - Antigen detection — hours
  - Nucleic acid detection — hours-days
  - Shell viral cultures — days
  - Culture — weeks
  - Inclusion bodies — days
  - Direct electron microscopy — days
- Serology (acute infection)
  - IgM — Days
  - Rinsing antibody titres — Weeks
- Serology (post-infection/serostatus)
  - IgG — Hours

▼ Remarks: HDV - Smallest Virus



- Subviral satellite depending on HBV
- Closed circular ssRNA of 1679nt
- 200 molecules of HDAg (hepatitis D antigen)
- 2 Isoforms of HDAg (L, S)
- Envelope from host
- Envelope proteins from HBV

▼ Remarks: SARS-CoV-2



- Group: Group IV((+)ss RNA)
- Order: Nidovirales
- Family: Coronaviridae
- Viral genome encoding >29 protein

▼ Differentiate Prions from Other Microbes

💡 Definition: **A prion is an infectious agent composed entirely of protein material, called PrP (prion protein)**

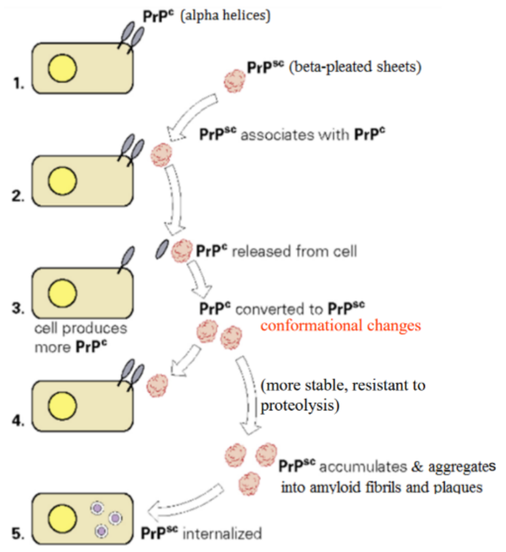
▼ Characteristic of Prions - Proteinaceous infectious particles

- Misfolded of a normal cellular protein - **Host-derived glycoproteins**
- Neurodegenerative disorders
  → **Transmissible Spongiform Encephalopathies (TSEs).**
  - Degenerative
  - Large vacuoles in the CNS
  - **Motor disturbances.**
- Both PrPSc & PrPc:
  - Highly similar sequence
  - Differ in structure & protease resistance
- **PrPSc**
  - A 30-35 kDa (Size) glycoprotein derived from PrPc
  - Associated with **intracellular fibrils** in *diseased tissue*
  - @ **lymphoreticular system** (淋巴网状系统)
    - Tonsils, Spleen & Neurological tissue
  - **Carried in the blood by lymphocytes**
- **PrPc - with unknown function**
  - a naturally occurring cellular prion protein
  - *coded by a single copy gene on chromosome 20 in humans*
- ▼ Prion caused diseases
  - Kuru
  - Creutzfeldt–Jakob disease (CJD)
  - Variant CJD (vCJD)
  - Bovine spongiform encephalopathy (BSE, mad cow disease)
- Most infectious agents have **mutations** at **a.a. residue 129**

Small size (< 100 nm)	Lack of a nucleic acid genome
Cannot be cultured in vitro (體外)	Not elicit immune & inflammatory responses
Slow Replication Rate (Except Variant CJD [vCJD])	Long incubation period (Except Variant CJD [vCJD])
Extreme resistance: heat, disinfectants & irradiation	Susceptible to ↑ Conc.: NaOH, NaOCl, Phenol, Periodate
Ingestion of contaminated tissues & medical procedures	**Interspecies transmissible**

PrPSc (Prion protein scrapie)	**PrPc (Cellular Prion Protein)**
True Prions	Normal Prion
Misfolded induce Misfold	Function natively
@ Lymphoreticular system	@ Surface of nerve cells
Insoluble globular (β-sheet)	Soluble, linear (α-helices)
Enzyme Resistant	Enzyme Susceptible

$$PrP^{c} \xrightarrow{\text{misfold}} PrP^{Sc} \xrightarrow{\text{Induce}} n * PrP^{Sc} \xrightarrow{\text{accumulate}} \beta\text{-sheet rich amyloid fibrils} \rightarrow \text{Neurodegeneration}$$



▼ Chemically Important Prions

Transmission

- alimentary tract :
  prions survive digestion → taken up **across the intestinal mucosa** →
  carried in **lymphoid cells** → transferred into **neural tissues & enter the CNS**

Treatment

- *chemotherapeutic strategies* → **reduce, stop or destabilize PrPSc formation**
  - **polyanionic compounds**
  - **tricyclic compounds**
- **Immunomodulation & mucosal immunization**
  - *Potential therapeutic*

Confirmed histologically post mortem [尸檢]

- Tonsillar tissue
  - source of PrPSc in clinical cases
  - By immunoblotting or immunohistochemistry
- Tissue homogenates
  - By enzyme immunoassays

Name	Target
Scrapie	Sheep
Creutzfeldt-Jakob diseases (CJD)	Humans
Gerstmann-Sträussler-Scheinker disease	Humans
Kuru	Humans
Fatal familial insomnia	Humans
Sporadic CJD	Humans
Bovine spongiform encephalopathy (BSE)	Cattle
Variant CJD (vCJD) - From BSE	Humans