An Introduction to Viruses

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Virus infections are Universal ......
Introduction to Virology

• A virus is an obligate intracellular parasite containing genetic material surrounded by protein

• Virus particles can only be observed by an electron microscope
Introduction to Virology

- Recognizing the shape, size, and structure of different viruses is critical to the study of disease
  - Viruses have an inner core of nucleic acid surrounded by protein coat known as an envelope
  - Most viruses range in sizes from 20 – 450 nanometers
Viral Properties

- Viruses are inert (nucleoprotein) filterable Agents
- Viruses are obligate intracellular parasites
- Viruses cannot make energy or proteins independent of a host cell
- Viral genome are RNA or DNA but not both.
- Viruses have a naked capsid or envelope with attached proteins
- Viruses do not have the genetic capability to multiply by division.
- Viruses are non-living entities
# Virus vs. cells

<table>
<thead>
<tr>
<th>Property</th>
<th>Viruses</th>
<th>Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of nucleic acid</td>
<td>DNA or RNA</td>
<td>DNA and RNA</td>
</tr>
<tr>
<td>Proteins</td>
<td>Few</td>
<td>Many</td>
</tr>
<tr>
<td>Lipoprotein membrane</td>
<td>Enveloped present in some viruses</td>
<td>Cell membrane present in all cells</td>
</tr>
<tr>
<td>Ribosomes</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>Absent</td>
<td>Present in eukaryotic cells</td>
</tr>
<tr>
<td>Enzymes</td>
<td>None or few</td>
<td>Many</td>
</tr>
<tr>
<td>Multiplication by binary fission</td>
<td>No</td>
<td>Yes (most cells)</td>
</tr>
</tbody>
</table>
Viruses are Ultramicroscopic

The size of viruses

Meters

10^{-2} (1 cm)
10^{-3} (1 mm)
10^{-4}
10^{-5} (1 \mu m)
10^{-6}

Light microscope

10^{-7}
10^{-8}
10^{-9} (1 nm)
10^{-10} (1 \AA)

Electron microscope

X ray

NMR

Plant cells
Animal cells
Bacteria
Poxvirus
Viruses
Ribosomes
Proteins
Small molecules
Atoms
VIRAL STRUCTURE – SOME TERMINOLOGY

• virus particle = virion
• protein which coats the genome = capsid
• capsid usually symmetrical
• capsid + genome = nucleocapsid
• may have an envelope
Virion

- The complete infectious unit of virus particle
- Structurally mature, extracellular virus particles.
Viral Structure - Overview

Fig 1. Schematic overview of the structure of animal viruses

** does not exist in all viruses
Distinguishing characteristics of viruses

• Obligate intracellular parasites
• Extreme genetic simplicity
• Contain DNA or RNA
• Replication involves disassembly and reassembly
• Replicate by "one-step growth"
Naming viruses

• No taxa above Family (no kingdom, phylum, etc)
• Classified based on structures, size, nucleic acids, host species, target cells.
• 19 families of animal viruses (6 DNA, 13 RNA)
• Family name ends in – viridae
• Subfamily ends in — virinae
• Genus name ends in – virus
• Species
  ➢ Example
    – Family – Herpesviridae
    – Subfamily - Herpesvirinae
    – Genus – Simplex virus
    – Common name – herpes virus (Herpes simplex virus I (HSV-I))
    – Disease – fever blisters, cold sores
How are viruses named?

• Based on:
  - the disease they cause
    poliovirus, rabies virus
  - the type of disease
    murine leukemia virus
  - geographic locations
    Sendai virus, Coxsackie virus
  - their discovers
    Epstein-Barr virus
  - how they were originally thought to be contracted
    dengue virus (“evil spirit”), influenza virus (the “influence” of bad air)
  - combinations of the above
    Rous Sarcoma virus
Virus particle = virion
5 BASIC TYPES OF VIRAL STRUCTURE

ICOSAHEDRAL

ENVELOPED ICOSAHEDRAL

HELICAL

ENVELOPED HELICAL

ICOSAHEDRAL nucleocapsid

HELICAL nucleocapsid

COMPLEX
Viral Structure

• Varies in size, shape and symmetry

• 3 types of capsid symmetry:
  – Cubic (icosahedral)
    • Has 20 faces, each an equilateral triangle. Eg. adenovirus
  – Helical
    • Protein binds around DNA/RNA in a helical fashion eg. Coronavirus
  – Complex
    • Is neither cubic nor helical eg. poxvirus
1. Protect genome during passage from one cell to another
2. Aid in entry process
3. Package enzymes for early steps of infection
1. Helical capsid

- Rod-shaped capsomeres
- Coil around hollow center
- Nucleic acid is kept inside – wound-up within tube (Helix)
Helical – capsid surrounds DNA like hollow tube
Ex: Influenza, measles, rabies (enveloped)
Helical symmetry
Helical symmetry

Pitch of helix
\( P = 22.8 \text{Å} \)

\( p = 1.4 \text{Å} \)
(axial rise/subunit)

\( \mu = 16.3 \)
(subunits/helix turn)

How to assemble
In 1955, Fraenkel, Conrat, and Williams demonstrated that tobacco mosaic virus (TMV) spontaneously formed when mixtures of purified coat protein and its genomic RNA were incubated together.
2. icosahedral

- 20-sided with 12 corners
- Vary in the number of capsomers
- Each capsomer may be made of 1 or several proteins
- Some are enveloped
Icosahedral capsids

a) Crystallographic structure of a simple icosahedral virus.

b) The axes of symmetry
Cubic or icosahedral symmetry
ICOSAHEDRAL SYMMETRY

5-FOLD  3-FOLD  2-FOLD
ICOSAHEDRAL SYMMETRY
ICOSAHEDRAL SYMMETRY

CAPSOMER
= PENTON (pentamer)
ICOSAHEDRAL SYMMETRY

CAPSOMER = PENTON

CAPSOMER = HEXON
Adenovirus
Adenovirus

12 PENTONS

240 HEXONS
Enveloped helical virus

Enveloped icosahedral virus
Helical

- California Encephalitis Virus
- Coronavirus
- Hantavirus
- Influenza Virus (Flu Virus)
- Measles Virus (Rubeola)
- Mumps Virus
- Para influenza Virus
- Rabies Virus
- Respiratory Syncytial Virus (RSV)
Icosahedral

- Adeno-associated Virus (AAV)
- Adenovirus B19
- Coxsackievirus - A
- Coxsackievirus - B
- Cytomegalovirus (CMV)
- Eastern Equine Encephalitis Virus (EEEV)
- Echovirus
- Epstein-Barr Virus (EBV)
- Hepatitis A Virus (HAV)
- Hepatitis B Virus (HBV)
- Hepatitis C Virus (HCV)
- Hepatitis Delta Virus (HDV)
- Hepatitis E Virus (HEV)

- Herpes Simplex Virus 1 (HHV1)
- Herpes Simplex Virus 2 (HHV2)
- Human Immunodeficiency Virus (HIV)
- Human T-lymphotrophic Virus (HTLV)
- Norwalk Virus
- Papilloma Virus (HPV)
- Polio virus
- Rhinovirus
- Rubella Virus
- Saint Louis Encephalitis Virus
- Varicella-Zoster Virus (HHV3)
- Western Equine Encephalitis Virus (WEEV)
- Yellow Fever Virus
Complex viruses

• Have additional or special structures
• Examples:
  • **Poxviruses** – lack normal capsid – instead, layers of lipoproteins and fibrils on surface
A bacteriophage

• A bacteriophage is any one of a number of viruses that infect bacteria. They do this by injecting genetic material, which they carry enclosed in an outer protein capsid. The genetic material can be ssRNA, dsRNA, ssDNA, or dsDNA ('ss-' or 'ds-' prefix denotes single-strand or double-strand) along with either circular or linear arrangement.
Phage - viruses have a polyhedral head, helical tail and fibers for attachment.
Classification of viruses

- Nucleic acid
- Capsid
- Presence of envelope
- Replication strategy
CLASSIFICATION
NUCLEIC ACID

• RNA or DNA
• segmented or non-segmented
• linear or circular
• single-stranded or double-stranded
• if single-stranded RNA
  – is genome mRNA (+) sense or complementary to mRNA (-) sense
ENVELOPE

• OBTAINED BY BUDDING THROUGH A CELLULAR MEMBRANE (except poxviruses)
• POSSIBILITY OF EXITING CELL WITHOUT KILLING IT
• CONTAINS AT LEAST ONE VIRALLY CODED PROTEIN
  – ATTACHMENT PROTEIN
• LOSS OF ENVELOPE RESULTS IN LOSS OF INFECTIVITY
Properties of naked viruses

- Stable in hostile environment
- Not damaged by drying, acid, detergent, and heat
- Released by lysis of host cells
- Can sustain in dry environment
- Can infect the GI tract and survive the acid and bile
- Can spread easily via hands, dust, fomites, etc
- Can stay dry and still retain infectivity
- Neutralizing mucosal and systemic antibodies are needed to control the establishment of infection
Naked viruses (Non Enveloped)

- Adeno-associated Virus (AAV)
  adenovirus
  B19
  coxsackievirus - A
  coxsackievirus - B
  echovirus
  hepatitis A virus (HAV)
  hepatitis E virus (HEV)
  norwalk virus
The Baltimore classification system

Based on genetic contents and replication strategies of viruses. According to the Baltimore classification, viruses are divided into the following seven classes:

1. dsDNA viruses
2. ssDNA viruses
3. dsRNA viruses
4. (+) sense ssRNA viruses (codes directly for protein)
5. (-) sense ssRNA viruses
6. RNA reverse transcribing viruses
7. DNA reverse transcribing viruses

where "ds" represents "double strand" and "ss" denotes "single strand".
Virus Classification
- the Baltimore classification

- All viruses must produce mRNA, or (+) sense RNA
- A complementary strand of nucleic acid is (−) sense

- The Baltimore classification has + RNA as its central point

- Its principles are fundamental to an understanding of virus classification and genome replication, but it is rarely used as a classification system in its own right
Viral genome strategies

- dsDNA (herpes, papova, adeno, pox)
- ssDNA (parvo)
- dsRNA (reo, rota)
- ssRNA (+) (picorna, toga, flavi, corona)
- ssRNA (-) (rhabdo, paramyxo, orthomyxo, bunya, filo)
- ssRNA (+/-) (arena, bunya)
- ssRNA (+RTase) (retro, lenti)
Sub-viral agents

• **Satellites**
  – Contain nucleic acid
  – Depend on co-infection with a helper virus
  – May be encapsidated (satellite virus)
  – Mostly in plants, can be human e.g. hepatitis delta virus
  – If nucleic acid only = virusoid

• **Viroids**
  – Unencapsidated, small circular ssRNA molecules that replicate autonomously
  – Only in plants, e.g. potato spindle tuber viroid
  – Depend on host cell polII for replication, no protein or mRNA

• **Prions**
  – No nucleic acid
  – Infectious protein e.g. BSE
Viroids & Prions

• Viroids
  – ss RNA genome and the smallest known pathogens.
  – Affects plants

• Prions
  – Infectious particles that are entirely protein.
  – No nucleic acid
  – Highly heat resistant
  – Animal disease that affects nervous tissue
  – Affects nervous tissue and results in
    • Bovine spongiform encephalitis (BSE) “mad cow disease”,
    • scrapie in sheep
    • kuru & Creutzfeld-Jakob Disease (CJD) in humans
Viroids

- Viroids are small (200-400nt), circular RNA molecules with a rod-like secondary structure which possess no capsid or envelope which are associated with certain plant diseases. Their replication strategy like that of viruses - they are obligate intracellular parasites.
- Viroids do not encode any proteins and unlike satellites they are not dependent on the presence of another virus.
Viroid replication

- Viroids utilize cellular RNA polymerases for their replication
- Replication is performed by “rolling circle mechanism”
- The resulting long RNA molecule is cut in pieces and ligated either autocatalytically or by cellular factors (depending on a viroid)
- So in a sense, at least some viroids are ribozymes...
Examples of plants, infected with various viroids
Hepatitis δ virus – a chimeric molecule, half viroid, half satellite

- Viroid like properties
  - Rod-like RNA molecule
  - Rolling circle replication
  - Self-cleaving activity

- Satellite like properties
  - Encodes a protein, which is necessary both for encapsidation and replication
  - Dependent on presence another virus – HBV
  - Genome larger than for viroids (1640 nt)
Prions

• Prions are rather ill-defined infectious agents believed to consist of a single type of protein molecule with no nucleic acid component. Confusion arises from the fact that the prion protein & the gene which encodes it are also found in normal 'uninfected' cells. These agents are associated with diseases such as Creutzfeldt-Jakob disease in humans, scrapie in sheep & bovine spongiform encephalopathy (BSE) in cattle.
Prions

Prions are proteinaceous transmissible pathogens responsible for a series of fatal neurodegenerative diseases (in humans, Creutzfeld-Jakob disease and kuru, in animals, bovine spongiform encephalopathy).

A prion (proteinaceous infectious particle, analogy for virion) is a type of infectious agent that does not carry the genetic information in nucleid acid!

Prions are proteins with the pathological conformation that are believed to infect and propagate the conformational changes of the native proteins into the abnormally structured form.
<table>
<thead>
<tr>
<th>Disease name</th>
<th>Natural host</th>
<th>Prion name</th>
<th>PrP isoform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scrapie</td>
<td>Sheep, goat</td>
<td>Scrapie prion</td>
<td>OvPrP&lt;sup&gt;Sc&lt;/sup&gt;</td>
</tr>
<tr>
<td>Transmissible mink encephalopathy (TME)</td>
<td>Mink</td>
<td>TME prion</td>
<td>MkPrP&lt;sup&gt;Sc&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chronic wasting disease (CWD)</td>
<td>Elk, mule deer</td>
<td>CWD prion</td>
<td>MDePrP&lt;sup&gt;Sc&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bovine spongiform encephalopathy (BSE)</td>
<td>Cattle</td>
<td>BSE prion</td>
<td>BovPrP&lt;sup&gt;Sc&lt;/sup&gt;</td>
</tr>
<tr>
<td>Feline spongiform encephalopathy (FSE)</td>
<td>Cat</td>
<td>FSE prion</td>
<td>FePrP&lt;sup&gt;Sc&lt;/sup&gt;</td>
</tr>
<tr>
<td>Exotic unguale encephalopathy (EUE)</td>
<td>Greater kudu, nyala</td>
<td>EUE prion</td>
<td>NyaPrP&lt;sup&gt;Sc&lt;/sup&gt;</td>
</tr>
<tr>
<td>Kuru</td>
<td>Human</td>
<td>Kuru prion</td>
<td>HuPrP&lt;sup&gt;Sc&lt;/sup&gt;</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease (CJD)</td>
<td>Human</td>
<td>CJD prion</td>
<td>HuPrP&lt;sup&gt;Sc&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gerstmann-Straussler-Scheinker syndrome (GSS)</td>
<td>Human</td>
<td>GSS prion</td>
<td>HuPrP&lt;sup&gt;Sc&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fatal familial insomnia (FFI)</td>
<td>Human</td>
<td>FFI prion</td>
<td>HuPrP&lt;sup&gt;Sc&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Prion diseases: rare neurodegenerative disorders (one person per million)

1. Sporadic (85 %)
   
   In the sixth or seventh decade, rapidly progressive (death in less than a year)
   
   Creutzfeldt-Jakob disease (CJD)

2. Familial (inherited-15%)

   Mutations in the PrP gene that favour the transition from the cellular form to the pathological form of PrP

   Gerstmann-Straussler-Scheinker disease (GSS), fatal familial insomnia (FFI)

3. Transmissible (rare; a source of great concern)

   Propagation of kuru disease in New Guinea natives (ritualistic cannibalism)

   Recently, it has been discovered that BSE had been transmitted to humans in Europe after consumption of infected beef, producing a variant of the CJD called vCJD
Transmissible spongiform encephalopathy (TSE)=prion disease

A group of progressive conditions that affect the brain and nervous system of humans and animals and are transmitted by prions

The pathology: vacuolar degeneration, neuronal loss, astrocytosis and amyloid plaque formation

The clinical signs: loss of motor functions (lack of coordination, ataxia, involuntary jerking movements), personality changes, depression, insomnia, confusion, memory problems, dementia, progressive tonic paralysis, death

Definitive diagnostic test: biopsy of brain tissue (histopathological examination and immunostaining for PrP\text{Sc})

There is no cure
Conformational change

Normal protein (folded structure)  →  Disease-associated protein (misfolded structure)

- Gain of toxic activity
- Loss of biological function
- Aggregation
<table>
<thead>
<tr>
<th><strong>PrP&lt;sub&gt;C&lt;/sub&gt;</strong></th>
<th><strong>PrP&lt;sub&gt;Sc&lt;/sub&gt;</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>The normal protein</td>
<td>The abnormal, disease-producing protein</td>
</tr>
<tr>
<td>is called PrP&lt;sub&gt;C&lt;/sub&gt; (for cellular)</td>
<td>is called PrP&lt;sub&gt;Sc&lt;/sub&gt; (for scrapie)</td>
</tr>
<tr>
<td>is a transmembrane glycoprotein (neurons, lymphocytes); its function is unknown; it binds Cu&lt;sup&gt;2+&lt;/sup&gt; (regulation its homeostasis)</td>
<td>has the same amino acid sequence (primary structure)</td>
</tr>
<tr>
<td>has dominant secondary structure α-helix</td>
<td>has dominant secondary structure β-sheets</td>
</tr>
<tr>
<td>is easily soluble</td>
<td>is insoluble</td>
</tr>
<tr>
<td>is monomeric and easily digested by proteases</td>
<td>is multimeric and resistant to digestion by proteases</td>
</tr>
<tr>
<td>is encoded by a gene designated PRNP located on the chromosome 20</td>
<td></td>
</tr>
</tbody>
</table>

When PrP<sub>Sc</sub> comes in contact with PrP<sub>C</sub>, it converts the PrP<sub>C</sub> into more of itself. These molecules bind to each other forming aggregates.
Molecular models of the structure of:

**PrP^C**
Predominantly α-helix (3)

**PrP^Sc**
β-sheets (40%), α-helix (30%)
Replication cycle

The presence of an initial \( \text{PrP}^{\text{Sc}} \): exogenous (infectious forms) or endogenous (inherited or sporadic forms)

This first prion will initiate \( \text{PrP}^{\text{Sc}} \) accumulation by sequentially converting \( \text{PrP}^{\text{C}} \) molecules into \( \text{PrP}^{\text{Sc}} \) in replication cycle

\( \text{PrP}^{\text{Sc}} \) molecules aggregate
Summary

The prions are proteins that carry information for self-reproduction (contradict the central dogma of modern biology)

The prions are expressed in cells of healthy humans and animals; their abnormal conformations (PrP\textsuperscript{Sc}) are insoluble, resistant to digestion and aggregate

The PrP\textsuperscript{Sc} attacks the native prion PrP\textsuperscript{C}, changes its conformation into an abnormal form and causes an exponential production of insoluble proteins; they aggregate and form the fibrillar structure

Prion disease are rare fatal degenerative disorders; a portion of them can be transmitted; this mechanism is not clear (e.g. transmission of BSE to human)

One part of the prion protein can cause apoptosis, or programmed cell death

Prions induce no immune reactions within the human
DNA VIRUSES

DOUBLE STRANDED

ENVELOPED
HERPESVIRIDAE

NON-ENVELOPED

PAPILLOMAVIRIDAE

SINGLE STRANDED
NON-ENVELOPED

PARVOVIRIDAE

COMPLEX
ENVELOPED
POXVIRIDAE

CIRCULAR

LINEAR

ADENOVIRIDAE

All families shown are icosahedral except for poxviruses

(formerly grouped together as the PAPOVAVIRIDAE)
DNA viruses

- Icosahedral DNA viruses
  - Naked DNA viruses
    - ss linear (+) or (−)
    - ds circular
    - ds linear
  - Enveloped DNA viruses
    - ds circle gapped
    - ds linear

- Helical DNA viruses
  - Naked/Env. (cytoplasmic)
  - Enveloped (cytoplasmic)

- Complex DNA viruses
  - Enveloped (x linked)

- Parvo: (-), 18–26, 5
- Papova: (-), 45–55, 5–8
- Adeno: (-), 70–90, 36–38
- Hepadna: (+), 42
- Herpes: (-), 150–200, 120–200
- Irido: (-), 125–300, 150–350
- Baculo: (-), 60 x 300
- Pox: (+), 170–200 x 300–450

From Principles of Virology, Flint et al, ASM Press, 66
RNA VIRUSES

- SINGLE STRANDED
  - positive sense
    - ENVELOPED
      - ICOSAHEDRAL
        - FLAVIVIRIDAE
        - TOGAVIRIDAE
        - RETROVIRIDAE
    - NONENVELOPED
      - HELICAL
        - CORONAVIRIDAE
        - PICORNAVIRIDAE
        - CALICIVIRIDAE
        - ASTROVIRIDAE
- SINGLE STRANDED
  - negative sense
    - ENVELOPED
      - HELICAL
        - ORTHOMYXOVIRIDAE
        - PARAMYXOVIRIDAE
        - RHABDOVIRIDAE
        - FILOVIRIDAE
        - BUNYAVIRIDAE
        - ARENAVIRIDAE
    - NONENVELOPED
      - ICOSAHEDRAL
        - REOVIRIDAE

DOUBLE STRANDED

RNA VIRUSES
RNA viruses

From Principles of Virology Flint et al ASM Press
BASIC STEPS IN VIRAL LIFE CYCLE

• ADSORPTION
• PENETRATION
• UNCOATING AND ECLIPSE
• SYNTHESIS OF VIRAL NUCLEIC ACID AND PROTEIN
• ASSEMBLY
• RELEASE