Viruses – Molecular Parasites

- Causal Agents of Numerous Human Diseases Spanning the Cold to Cancer
  Incl. Hepatitis, Flu, Ebola, Smallpox, Measles, Herpes, HIV, Polio, West Nile

- Relatively Small Genomes (DNA or RNA) Amenable to Genetic Analyses
  - Relatively Simple Bipartite Gene Expression Program
    “Early” Genes Expressed Before Viral Genome Replication
    “Late” Genes Expressed After Viral Genome Replication
  - Utilize Host Cell Biosynthetic Processes During Infection
    Provide Excellent Models to Study Basic Molecular & Cellular Events

- Typically Proliferate By 1 of 2 Life Cycles – Some Viruses Exhibit Both
  “Lytic” or “Productive” Infection Lyses & Usually Kills Infected Cell
  Cells supporting Lytic Cycle Termed “Permissive”

- “Lysogenic” or “Nonproductive” Infection
  Results in Integration of Viral DNA Into Host Cell Genome “Provirus”
  Infectious Viral Progeny Usually Not Generated
  Cells supporting Lysogenic Cycle Termed “Nonpermissive”

- Viruses Can Be Inhibited by Anti-viral Therapies or Vaccines, but *not* Antibiotics!

![Canonical Gene Expression Program for Typical DNA Viruses](image)

Primary Functions

- Viral genome
  - Transcription
    - mRNA
  - Translation
    - Viral proteins
    - Lysis proteins

**Early genes**
- Primary Functions Of Early Gene Products
  1. Shut down host cell gene expression.
  2. Activate viral DNA replication
  3. Activate viral late gene expression by "redirecting" RNA polymerase to late gene promoters

**Late genes**
- Primary Functions Of Late Gene Products
  1. Encode viral “coat” or “capsid proteins
  2. Assemble virus particles
  3. Release virus particles & (usually) lyse infected cell

Lytic & Lysogenic Cycles of Bacteriophage λ.
Also Applicable to Certain Mammalian DNA Tumor Viruses

λ Phage binds maltose receptor
Viral DNA inserted into chromosome
Prophage
Viral DNA copied & propagated ea. cell division
All Viral Genes Expressed
Favored by good growth conditions
Phage DNA Replicated
Coat & Lysis Genes Expressed
Host DNA Degraded
Under certain conditions, (e.g., DNA damage or favorable growth conditions) viral genome excised from chromosome & phage enters lytic cycle

Few Viral Genes Expressed
Favored by poor growth conditions
Viral DNA inserted into chromosome
Viral DNA copied & propagated ea. cell division
All Viral Genes Expressed
Favored by good growth conditions
Phage DNA Replicated
Coat & Lysis Genes Expressed
Host DNA Degraded
Under certain conditions, (e.g., DNA damage or favorable growth conditions) viral genome excised from chromosome & phage enters lytic cycle

The "Race" Between Cro & cl Determines the Lytic vs Lysogenic Decision for Bacteriophage λ.
 Favorable growth conditions
Cro "wins"
cl is repressed
lytic genes turned on
LYTIC

Both Cro & cl are "dual function"
DNA binding proteins encoded by early genes expressed immediately upon infection. Whichever protein attains a higher concentration 1st & can occupy its binding sites "wins"

Both cl & Cro activate their own transcription but repress each other

Poor growth conditions cl "wins"
Cro is repressed lysogenic genes turned on LYSOGENY

DECISION PT

HOST DNA DEGRADATION

Phage DNA Replicated
Coat & Lysis Genes Expressed

DNA Enters Cell
Shades of Hershey-Chase

Viral DNA inserted into chromosome
Prophage
Viral DNA copied & propagated ea. cell division
All Viral Genes Expressed
Favored by good growth conditions
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Poor growth conditions cl "wins"
Cro is repressed lysogenic genes turned on LYSOGENY
Variation on the Lytic Cycle: Influenza Virus - RNA Genome & Life in the Cytoplasm

Virus infects cell by binding to a cell surface receptor sialic acid, (which unfortunately is found on virtually all cells) & enters cell via endocytosis same process by which cholesterol is imported by LDL receptor. Virus enclosed in vesicle.

Acidic pH of vesicle promotes dissociation of viral capsid proteins.

Viral genome transcribed by viral-encoded RNA-dependent RNA polymerase into viral mRNA.

Viral mRNA translated into proteins including RNA replicases to generate more viral genomes.

Viral capsids & RNA genomes fuse with viral envelope proteins expressed on cell surface.

Virus particles "bud" off from surface surrounded with portion of plasma membrane "envelope".

Infected cells typically die due to a combination of inhibiting host cell gene expression during infection & damage to membrane during virus release.

Electron Micrograph of Enveloped Influenza Virion

Electron Micrograph of Influenza Virions Budding Off From Infected Cell.
gp120 envelope protein (knobs) binds to CD4 receptor on “Helper” T Cells & Macrophages

HIV Infection Incorporates Features From Both Lysogenic & Lytic Cycles

Reverse transcriptase is Extremely error-prone. No proofreading capacity therefore vast majority of Proviral DNAs are nonfunctional owing to mutations. But this also explains how drug-resistant HIV strains emerge rapidly. Therefore, virus production requires a given cell to be simultaneously infected by numerous viruses so mutants can complement each other to generate viral progeny.

Viral RNA Genomes reverse transcribed by Viral-encoded Reverse Transcriptase which is packaged along with viral RNA in capsids. Proviral DNA enters nucleus & integrates into host chromosome. Duplicated & segregated into daughter cells w/ ea. cell division.

Viral genes may or not be expressed accounting for latency of HIV Infection. Viral mRNAs transcribed in nucleus exported to cytoplasm & viral proteins synthesized & processed virus assembled & emerges from cell as with influenza.