Viral Replication: Basic Concepts

- Viruses are obligate intracellular parasites
- Viruses carry their genome (RNA or DNA) and sometimes functional proteins required for early steps in replication cycle
- Viruses depend on host cell machinery to complete replication cycle and must commandeer that machinery to successfully replicate

Steps in Viral Replication: Attachment (First Step)

- Surface protein on virus attaches to specific receptor(s) on cell surface
  - May be specialized proteins with limited tissue distribution or more widely distributed
  - Virus-specific receptor is necessary but not sufficient for viruses to infect cells and complete replicative cycle

Selected Virus Receptors

- Adenovirus: CAR
- Coxsackievirus: CAR, CD55
- Echovirus: Integrin VLA-2, CD55
- Epstein-Barr Virus: CD21
- HIV-1: CD4, CCR5, CXCR4
- Measles virus: CD45
- Parvovirus: Erythrocyte P Ag
- Poliovirus: PVR
- Rhinovirus: ICAM-1

Steps in Viral Replication: Penetration (Second Step)

- Enveloped viruses penetrate cells through fusion of viral envelope with host cell membrane
  - May or may not involve receptor-mediated endocytosis
- Non-enveloped viruses penetrate by
  - Receptor-mediated endocytosis
  - Translocation of the virion across the host cell membrane

Viral Replication: Basic Concepts

- Replication cycle produces
  - Functional RNA's and proteins
  - Genomic RNA or DNA and structural proteins
- 100's-1,000's new particles produced by each cycle
  - Referred to as burst size
  - Many are defective
  - End of 'eclipse' phase
- Replication may be cytopathic or non-cytolytic
Influenza Virus Replication Cycle

Steps in Viral Replication: Uncoating
(Third Step)
- Makes viral nucleic acid available for transcription to permit multiplication to proceed
- Mechanism variably understood depending upon the virus

Steps in Viral Replication: Basic Strategies of Transcription and Translation
(Fourth and Fifth Steps)
- (+) RNA \rightarrow Proteins
- (-) RNA \rightarrow (+) RNA \rightarrow Proteins
- RNA \rightarrow DNA \rightarrow RNA \rightarrow Proteins
- DNA \rightarrow RNA \rightarrow Proteins

Steps in Viral Replication:
Assembly and Release
(Sixth and Seventh Steps)
- Process involves bringing together newly formed genomic nucleic acid and structural proteins to form the nucleocapsid of the virus
- Nonenveloped viruses exhibit full maturation in the cytoplasm or nucleus with disintegration of cell

Steps in Viral Replication:
Assembly and Release
(Sixth and Seventh Steps)
- Many enveloped viruses exhibit full maturation as the virion exits the cell
  - Viral proteins are inserted into the host cell membrane
  - Nucleocapsids bind to these regions and bud into the extracellular space
  - Further cleavage and maturation of proteins may occur after viral extrusion
  - Cytolytic activity of these viruses varies
Steps in Viral Replication: Assembly and Release
(Sixth and Seventh Steps)

- Herpesviruses (enveloped) assemble nucleocapsids in the nuclei of infected cells and mature at the inner lamella of the nuclear membrane
  - Virions accumulate in this space, in the ER and in vesicles
  - Virion release is associated with cytolysis
**Schematic of Nonsegmented (-) RNA Strand Virus Replication Cycle**

Transcription of (-) strand occurs after entry and mediated by virion packaged transcriptase

(-) strand RNA's produced; proteins synthesized

Full length (-) strand RNA's produced and packaged into new virions

Transcription and translation take place entirely in cytoplasm

*From Fields Virology*

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**Schematic of Segmented (-) RNA Strand Virus Replication Cycle**

mRNA's are synthesized from each segment

Viral proteins are synthesized

(+/-) strand RNA's are synthesized and serve as templates for (-) strand genomic RNA's

*From Fields Virology*

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**HIV-1 Virion**

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**HIV-1: Genetic Organization**

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**HIV Life Cycle**

Tat = transcriptional activator
Rev = regulator of mRNA nuclear export

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**HIV Entry**
Primary HIV Infection: Pathogenetic Steps

- Virus – dendritic cell interaction
  - Infection is typically with R5 (M-tropic) strains
  - Importance of DC-SIGN
- Delivery of virus to lymph nodes
- Active replication in lymphoid tissue
- High levels of viremia and dissemination
- Downregulation of virus replication by immune response
- Viral set point reached after approximately 6 months

Primary HIV Infection: Clinical Characteristics

- 50-90% of infections are symptomatic
- Symptoms generally occur 5-30 days after exposure
- Symptoms and signs
  - Fever, fatigue, myalgias, arthralgias, headache, nausea, vomiting, diarrhea
  - Adenopathy, pharyngitis, rash, weight loss, mucocutaneous ulcerations, aseptic meningitis, occass. oral/vaginal candidiasis
  - Leukopenia, thrombocytopenia, elevated liver enzymes
- Median duration of symptoms: 14 days

Primary HIV Infection: Determinants of Outcome

- Severity of symptoms
- Viral strain
  - SI (X4) vs. NSI (R5) viruses
- Importance of GI tract associated lymphoid tissue (GALT)
- Immune response
  - CTL response
  - Non-CTL CD8 responses
  - Humoral responses?
- Viral set point at 6-24 months post-infection
- Other host factors
  - Chemokine receptor and HLA genotype
  - Gender and differences in viral diversity?
- Antiviral therapy
  - Near vs. long-term benefit?
To Be Continued...