Retroviruses

TRACO
Frank Maldarelli
HIV Dynamics and Replication Program
NCI
Retroviruses

- Introduction
- Molecular Biology/Replication
- Retroviruses in Human Populations
- Emergence/Spread
- HIV Therapy and Beyond
- Lessons
The Disease is Widespread: Global Burden of HIV-1 Infection

Total: 36.7 million [34.0–39.8 million]

UNAIDS, 2015

WHO, 2015
Global Burden of HIV-1 Infection
People undergoing antiretroviral therapy: 17 million
The Need is Great:
HIV is a Challenge on Numerous Levels

HIV Infection - USA

HIV Prevalence is INCREASING
New cases of HIV diagnosed = 38,000
Deaths from HIV = 6465

Gardner State of Engagement in HIV Care: USA
The Need is Great: Research Priorities Office of AIDS Research 2018
Retroviruses

• Introduction
• **Molecular Biology/Replication**
• Retroviruses in Human Populations
• Emergence/Spread
• Lessons
Retroviruses
A group of RNA viruses that replicate via a DNA intermediate using Reverse Transcriptase.
Retroelements

Reverse Transcriptase and Retroelements are all around you

Avian Retroviruses

Human
  - Primate
  - Rodent

Porcine

Fish

Bacterial retroplasmids

Plant

Fruit fly

Roundworm retrovirus
Retrovirus classification

Retroviruses
Classification by RT Sequence into Seven Families

Spumavirus  exog. infection from primates, no oncogene
MLV  endo/exo oncogene  numerous mammals

Lentiviruses  HIV-1,-2, SIV, EIAV, CAEV, VISNA

D-type viruses  Primates-MPMV, SAIDS

B-type viruses  endog/exogen milk-borne agent-mouse
  Some T cell lymphoma in mice

ALV-related  endog/exogen avian oncogene

BLV-HTLV  exog, no oncogenes, neoplasms

Line length not to scale  AND THERE IS NO UNIFORM TIME SCALE
Lentivirus Relationships

HIV-2
SIV-smm
SIV-syk
HIV-1
SIV-cpz
SIV-agm
SIV-mnd
VMV
CAEV
EIAV
BIV
FIV

1 % difference
Retrovirus conventions

Names of genes in lower case *italics*, e.g., *pol, env*
Protein gene products are capitalized, e.g., Reverse Transcriptase, Gp120
Retrovirus conventions

The viral genome is RNA

Retrovirus Conventions

Poly A Coding Sequences Promoter

The integrated genome is called the provirus

Names of genes in lower case italics, e.g., pol, env
Protein gene products are capitalized, e.g., Reverse Transcriptase, Gp120
Retroviruses Glossary

- **gag**: group antigen
- **pol**: polymerase
- **env**: envelope
- **tat**: Transactivator
- **rev**: Regulator of Expression of Virion proteins

- U3: unique sequence in 3’ region
- U5: Unique sequence in 5’ region
- R: Repeat sequence
- PBS Primer binding site for initiation of RT
- Ppt: polypurine tract primer for RT
- TAR: Tat activating sequence
- RRE: Rev responsive element
- Provirus: copy of retrovirus that is integrated into host genome
HIV replication

- Attachment and Entry
- Reverse Transcription
- Integration
- Transcription
- RNA Processing
- Translation
- Assembly
- Maturation

HIV virion

CYTOPLASM

Maturation
Assembly
Translation
RNA Processing
Integration
Reverse Transcription
Attachment
HIV Attachment and Entry

• Virus Factors
  • Attachment: Env glycoprotein gp120
  • Entry: Env glycoprotein gp41

• Host Cell Factors
  • Receptor
    • CD4
  • Co-receptor (major)
    • CXCR4
    • CCR5
Blocking the HIV Receptor: Ibalizumab
Blocking the HIV coreceptor

Blaocing the HIV Coreceptor: Maraviroc

- Multiple binding domains predicted
- Binding disrupts structure generally
- Does not require blocking CCR5-gp120 interaction
- Potential for simultaneous inhibition
- Resistance emerges by reducing affinity for drug
Blocking HIV Fusion

Blocking HIV Fusion: Enfuvirtide Blocking a Spring-Loaded Mechanism

Native cell membrane

Pre-Hairpin Intermediate

Hairpin

Fusion

Post-Fusion
HIV replication

HIV Replication

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HIV virion

Attachment

Uncoating

Reverse Transcription

Integration

RNA Processing

Translation

Assembly

Maturation

Cytoplasm
HIV replication
HIV Post-Entry events

HIV Post – Entry Events

• Uncoating is a fundamental step in virus replication
  • Restricts replication
  • Source of host range restriction

• Requires interactions between viral and cellular factors

• Virus
  • Gag

• Cell
  • Trim 5 – alpha
HIV Post-Entry events

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>Host Trim5 Alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Human</td>
</tr>
<tr>
<td>HIV</td>
<td>Infection</td>
</tr>
<tr>
<td>SIV Chimp</td>
<td><strong>INFECTION</strong></td>
</tr>
<tr>
<td>SIV Monkey</td>
<td><strong>INFECTION</strong></td>
</tr>
</tbody>
</table>
Positive Selection in Trim 5-alpha

• Trim 5 alpha undergoes genetic change faster than many genes

• Working hypothesis
  • human populations undergo waves of pandemics
  • Humans that survive have trim 5alpha variant that excludes infection
HIV Reverse Transcription and Integration
Reverse Transcriptase
Enzymatic Activities

• RNA-dependent DNA Polymerase
• RNase H
• DNA-dependent DNA Polymerase
• Error rate on order of 1-4 / 100,000 bases synthesized
• Recombination occurs during reverse transcription permitting reassortment of sequences
• Replication rapid and error prone
Error-Prone HIV replication

Error-Prone HIV Replication is a Pathogenic Determinant

- Each round of HIV replication generates numerous mutants.
- The ability of the mutants to replicate (viral “fitness”) may vary greatly.
- The virus population can respond rapidly to a selective pressure
HIV Reverse Transcription and Integration
Integration

Multistep reaction

Dolutegravir

Chemical structures:
- L-731,968 (1)
- Diketo acid (2)
- Diketone (3)
- Naphthyridine ketone (4)
- L-870,810

Hazuda 2005
Late events
Translation

Translation of HIV *gag/pol* and *env* Paradigm: Process Polyprotein Precursors

mRNA → Polyprotein
- **Gag**
- **Pol**
- **env**

Intracellular processing:
- **Gp120**
- **Gp41**
HIV particle maturation

HIV Particle Maturation

Immature Particle
Noninfectious

HIV Protease

Mature Particle
Infectious
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Lentivirus Relationships

- HIV-2
- SIV-smm
- SIV-syk
- HIV-1
- SIV-cpz
- SIV-agm
- SIV-mnd
- VMV
- CAEV
- EIAV
- BIV
- FIV

1% difference
HTLV distribution

HTLV DISTRIBUTION

HTLV-I Sporadic
HTLV-I High endemicity
HTLV-II Endemic (AmerIndian and Pygmy tribes)
HTLV-I ATL

- Long Latency (>30 years)
  - Small pediatric series in SA
- Epidemiology
  - Approximately 1% of HTLV- I infected adults
- Associated syndromes
  - Infectious
    - TB, MAC, Leprosy
    - PCP
    - Strongyloides
    - Scabies esp. Norwegian scabies
  - Noninfectious-hypercalcemia+lytic bone lesions
- Therapy-Chemotherapy, Ifn, anti-Tac
HIV-1 origins
Bushmeat trade

Bushmeat Trade in Central and West Africa

Potential opportunities for Zoonotic Events

Poacher  Chophouse  Bushmeat market

Phylogenetic Analyses Date Introduction to Late 1800’s-Early 1900’s

BUT WHY THEN?
HIV Spread

• Biologic
  • Blood and body fluid
  • Iatrogenic
    • Blood transfusion
    • Vaccination – needles not vaccine
  • Mother to Child

• Non-Biologic
  • Political
  • Economic
  • Multiple Epidemics
HIV spread

HIV Spread

- Modes of Transmission
  Political

Consequences of large political upheaval are population movement and potential for malnutrition and immunodeficiency
Zoonotic Transmission of HIV Coincides with Population Expansion in Africa

http://www.populstat.info/
HIV spread

HIV Spread

• Modes of Transmission
  Trans Africa Highway
HIV Spread

Worobey et al.
AIDS in 1983

Cumulative U.S. AIDS Cases as of 2/83 N~1,000

Each point = 30 cases
AIDS in 1985

Cumulative U.S. AIDS Cases as of 5/85  N~10,000

Each point = 30 cases
AIDS in 1989

Cumulative U.S. AIDS Cases
as of 7/89  N~100,000

Each point = 30 cases
AIDS in 1995

Cumulative U.S. AIDS Cases as of 12/95 N~500,000

Each point = 30 cases
New cases of HIV/AIDS

**Geographic spread from metropolitan areas**
- ~12% of cases in locations with population <50,000

**Women**
- comprise > 25% of all AIDS cases

**Age**
- 11% of AIDS cases are 50+ years old
- c.50% of persons living with HIV are >50 yo
HIV Therapy and Beyond
Expiration

If you get the AIDS virus now, you and your license could expire at the same time.
Treatment for all

90-90-90: TREATMENT FOR ALL
Worlds AIDS day
The need is great

The Need is Great: HIV is a Challenge on Numerous Levels

HIV Infection - USA

HIV Prevalence is INCREASING
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Key Advances in HIV Therapy

• PrEP
  • Adherent prophylaxis is effective

• SMART Study
  • Continuous therapy essential to avoid AIDS and other complications

• START Study
  • Earlier therapy is initiated, greater preservation of therapy
Next Advances in HIV Therapy

• Vaccines
• Cures
Lessons

• Viruses are bad and should be avoided
• Except when they save the planet
• And maybe if it saves you from the next virus
• Epidemics are not single events
• Epidemics evolve
• Detailed understanding of replication leads to new therapy
• Antivirals are useful
  • Instituted as early as possible
  • Adherence is essential