The role of viral fitness in HIV-1 disease progression

Eric Hunter
Emory Vaccine Center
Rwanda Zambia HIV Research Group

Follow-up after HIV-1 transmission in discordant couples

Follow-up newly infected partner for up to 8 years with longitudinal CD4 and viral load (VL).
Allows us to analyze the impact of immune selection in the donor on virus replication and disease progression in the recipient over more than 5 years.

The more CTL escape mutations in Gag results in lower set-point viral loads in newly infected linked recipients.

Extension of analysis of Goepfert et. al.

To what degree does the viral replicative capacity, defined by the gag gene, of the transmitted virus contribute to the set-point viral load and early pathogenesis of a newly infected individual?

Experimental Design

1. Clone gag from 127 acutely infected patients into pMJ4
2. Transfect 293T cells
3. Collect virus stocks
4. Calculate titer via β-Gal expression in TZM-BL cells
5. Infect 5x10^5 CEM-CCR5 cells at an MOI of .05
6. Quantify via radio-labeled RT assay

Viral replicative capacity is a heritable component affecting viral load

VRC is positively correlated with plasma VL in 149 linked transmission pairs

How does VRC affect pathogenesis in terms of CD4+ T cell decline?

Prince, Claiborne et al. PLoS Pathogens 2012

Prince J, Claiborne D et al., Plos Path., 2012
Influence the early inflammatory cytokine response and microbial translocation

Determine how high vRC is associated (albeit weakly) with early set point VL. Could the impact of vRC on CD4 decline just be a result of the higher VL associated with high vRC.

1. Measure levels of inflammatory cytokines and markers of microbial translocation in plasma at 0 (seroconversion, 45 days post EDI) months post-infection.
1. Determine levels of cellular immune activation and exhaustion, specifically in the T cell compartment.
1. Evaluate viral burden and cellular depletion of different memory CD4 T cell compartments.

**Experimental Approach**

**vRC of the transmitted Gag sequence influences CD4+ T cell decline**

We hypothesized that infection with high vRC viruses could:

- Influence the early inflammatory cytokine response and microbial translocation
- Result in increased activation, exhaustion, and proliferation of key T cell populations
- Give rise to elevated infection and/or depletion of key memory CD4+ T cell subsets

**Set point VL is an established predictor of CD4+ T cell decline**

Early viral replication before host responses: Irreversible damage with no turning back?

We hypothesized that infection with high vRC viruses could:

- Influence the early inflammatory cytokine response and microbial translocation
- Result in increased activation, exhaustion, and proliferation of key T cell populations
- Give rise to elevated infection and/or depletion of key memory CD4+ T cell subsets

**High vRC is associated with increased levels of pro-inflammatory cytokines early in infection**

- *High RC is significantly associated with an increase in inflammatory cytokine levels at an early time point post-infection (45 days)*
- The expression levels of many of these inflammatory mediators are highly correlated – we have therefore employed Principal Component analysis to define “inflammatory profiles” associated with different variables

Gisela Scully and Marcus Ahmed, Regan Institute
Principal component analysis (PCA) of cytokines at seroconversion

PC#1 and PC#2 describe distinct cytokine profiles associated with vRC and set point VL, respectively.

Eileen Scully and Marcus Altfeld, Ragon Institute

Experimental Approach

1. Measure levels of inflammatory cytokines and markers of microbial translocation in plasma at 0 (seroconversion, 45 days post EDI) months post-infection.

1. Determine levels of cellular immune activation and exhaustion, specifically in the T cell compartment.

1. Evaluate viral burden and cellular depletion of different memory CD4 T cell compartments.

High vRC associated with increased activation and reduced cytotoxic potential

Gladys Macharia, Jakub Kopycinski, Jill Gilmour, IA VI

The aberrant CD4+ T cell phenotypes are associated with rapid CD4 decline

• These activation and proliferation phenotypes are highly deleterious

Gladys Macharia, Jakub Kopycinski, Jill Gilmour, IA VI
Experimental Approach

1. Measure levels of inflammatory cytokines and markers of microbial translocation in plasma at 0 (seroconversion, 45 days post EDI), 3 and 6 months post-infection.

1. Determine levels of cellular immune activation and exhaustion, specifically in the T cell compartment.

1. Evaluate viral burden and cellular depletion of different memory CD4 T cell compartments.

Conclusions from current study

- We show that infection by high vRC virus is:
  - linked to an inflammatory state early in infection that is characterized by elevated levels of key inflammatory cytokines known to drive pathogenesis.
  - associated with aberrant CD8 and CD4 T cell phenotypes characterized by increased levels of cellular activation, exhaustion, and proliferation.
  - characterized by increased viral burden in naïve CD4+ T cells and CD4+ Tcm cells.

Thus the nature of the virus initiating infection has a dramatic impact on immune control of virus and disease progression.

Acknowledgements

EMORY:
- EVC
- Dan Claiborne
- Jessica Prince
- Paul Farmer
- Malinda Schaefer
- Ling Yue
- Cynthia Derdeyn
- Biostatistics
- Tianwei Yu

IAVI-RZHRG:
- Susan Allen
- Shabir Lakhi
- William Kilembe
- Mubiana Inambao
- Elienne Karita
- Staff & study participants
- International AIDS Vaccine Initiative

Microsoft Research:
- Jonathan Carlson
- David Heckerman

Ragon Institute:
- Marcus Altfeld
- Eileen Scully

UAB
- Paul Goepfert
- Anju Bansal
- Richard Kaslow
- James Tang
- Heather Prentice

Funding:
- NIH/NIAID R01 AI-64060/R37 AI-51231 (EH)
- IAVI, CIDA, USAID (SA)