In Vivo Analysis of the Replication Capacity and Pathogenic Potential of HIV Primary Isolates from Elite Suppressors

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Elite Suppressors (ES)

- ES= Infected Individuals with viral RNA ≤ 50 copies per ml and sustained levels CD4⁺ T cells
- Mechanism: Increased immune recognition and/or attenuated virus
  - HLA*B57
    - Commonly found in ES
  - Mutations resulting in decreased fitness
    - nef deletions
- Few isolates from ES have been characterized (limited in vivo studies)
Is the superior suppression of viral replication by ES attributed to infection with a defective virus?

- *In vitro* assays may not be representative of *in vivo* results
- Are HIV isolates from ES replicative and pathogenic *in vivo*?
  - BLT Humanized Mouse Model
BLT Humanized Mice

- Systemically reconstituted with human immune cells
- Susceptible to natural routes of HIV infection
- Sustain HIV replication
- HIV infection results in CD4⁺ T cell depletion

Generation of BLT Mice

NOD/SCID γc⁻ → Isolate CD34⁺ Cells From Liver → Implant Tissue → Transplant CD34⁺ Cells

Nat. Med. 12, 1316 (2006)
HIV Isolates from ES

ES38

- Viral load below 50 copies per mL
- 935 CD4\(^+\) T cells per µL
- Not on ART
- HLA-B*57:03
- WT ccr5

- Two HIV isolates: ES38-5 & ES38-9
  - Subtype B
  - No drug resistance mutations, intact nef orf

Joel Blankson, Maria Salgado, Christopher Polymeyer, Robert Buckheit III

HIV Isolates from ES

- ES8
  - Viral load 26 copies per mL
  - 626CD4+ T cells per µL
  - Not on ART
  - HLA-B*57:03
  - WT CCR5
    - HIV isolates: ES8
      - Subtype B
      - No drug resistance mutations, intact nef orf

Joel Blankson, Maria Salgado, Christopher Polymeyer, Robert Buckheit III
Experimental Outline

Inject Virus Via Tail Vein

Non-HLA*B57 BLT Mice

Obtain Blood/Plasma (Several Weeks)

qRT-PCR

Flow Cytometry

ATCG

Harvest Tissues

Sequencing

Flow Cytometry

Flow Cytometry
ES Isolates are Replication Competent In Vivo

ES38-5

ES38-9

ES8

Viral Load (per ml) vs. Days Post Exposure
ES Isolates decrease blood CD4+ T levels

Days Post Exposure

% of Blood CD3+ CD4+ Positive Cells

ES38-5

Days Post Exposure

% of Blood CD3+ CD4+ Positive Cells

ES38-9

Days Post Exposure

% of Blood CD3+ CD4+ Positive Cells

ES8
Systemic Depletion of CD4+ T cells

- Bone Marrow
- Liver
- Lung
- Lymph Nodes
- Spleen

% of T Cells Expressing CD4

- ES38-5
- ES38-9
- ES8
- Noninfected

International AIDS Society
Stronger Together Against HIV
ES Isolates Do Not Mutate to Become Pathogenic and Replicative

ES38-5 and ES38-9 Mice were HLA*B18 and HLA*B51

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ES38-5 and ES38-9 Mice were HLA*B18 and HLA*B51
ES38-5, ES38-9, and ES8 sustain viral replication in BLT mice

All isolates tested demonstrate *in vivo* CD4⁺ T cell depletion in the peripheral blood and tissues

Mutations are not required for ES isolates to become replicative and pathogenic
Conclusions

- Host genetics are sufficient to achieve HIV suppression below clinical limits of detection
Acknowledgements

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