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Our Issues, Our Drugs, Our Patients

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HIV acute infections and elite controllers- what can we learn?

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Outline

• Acute HIV infection- public health importance and challenges of research

• Some lessons on HIV immunopathogenesis from acute infection studies (host restriction factors and CD8+ T cells)

• Elite and viremic controllers

• Lessons from viremic and elite controllers on viral control mechanisms
Acute HIV-1 infection - what lessons can we learn?

Viral set point is a predictor for:
- Rate of disease progression
- Risk of transmission

Key questions:
- What behavioural, socioeconomic and biomedical factors are responsible for continuing high incidence especially among young women?
- What is the nature of the transmitted/founder virus?
- What do immune responses in acute HIV-1 infection look like and why do they ultimately fail in most cases?
2 Parallel Rapid Tests: Unigold & Determine

Positive -> Participant infected

Negative or discordant

HIV-1 RNA testing (individual or pooled)

Positive

Viral load < 2,000 copies/ml -> Re-draw blood and repeat tests

Negative or discordant

Negative

Participant uninfected

Viral load ≥ 2,000 copies/ml -> Enroll patient as acutely infected
Acute HIV infection viral load trajectory and set point
Sites of Host Restriction Activity in HIV Life Cycle

APOBEC3G: an intrinsic block to HIV

Producer Cell

Target Cell

HIV-1 Vif

HIV- RNA

APOBEC3G

Reverse Transcription

mutations

Vif

Viral replication disabled

APOBEC3G

APOBEC3G

Viral replication disabled
APOBEC3G H186R is associated with high viral load and rapid CD4 decline

Reddy et. al., 2010, AIDS
Patient derived Vif clonal sequences cluster independently of APOBEC3G H186R genotype
APOBEC3G variants: hypothesis and aims

Hypothesis: The Vif protein adapts to APOBEC3G immune pressure according to APOBEC3G haplotypes with differential ability to inhibit HIV replication

Specific Aims:
1. Assessment of Vif genetic diversity according to genotypes with different infection outcomes
2. Functionally characterize Vif variants from patients with different APOBEC3G genotypes and their ability to degrade APOBEC3G variants
Vif activity is independent of patient A3G genotype and A3G WT restricts HIV more efficiently than 186R

Vif derived from patient A3G
- A3G WT
- A3G 186R/R
Conclusions I

• A3G WT and A3G-H186R are equally susceptible to counteraction by Vif.

• A3G-H186R variant intrinsically displayed lower antiviral activity.

• We speculate that A3G-H186R may have:
  • reduced deaminase activity.
  • inefficient packaging into virions.

• Understanding sites of host/virus interaction can be targeted by novel therapy approaches for the treatment of HIV.
Evidence for role of CTLs in HIV control

- In animal models, depletion of CTLs results in uncontrolled viral replication
- Breadth of Gag CTLs in chronic infection correlates with better viral control
- GWAS and importance of HLA in HIV
- Viral escape can occur that abrogates immune recognition
ELISPOT assay

Antigen presenting cell/virus infected cell

HLA class I

Cytokine secretion e.g. IFN-γ

Proliferation, other antiviral factors

CTL
Protein-specificity of CD8 T cell responses and association with viral load

Breadth of Gag responses at 8 weeks

Breadth of Gag responses at 26 weeks

Breadth of Gag responses at 56 weeks

Viral set point (RNA copies/ml)

Viral set point (RNA copies/ml)

Viral set point (RNA copies/ml)

\( R = 0.3 \)
\( P = 0.2 \)

\( R = 0.7 \)
\( P = 0.0003 \)

\( R = 0.5 \)
\( P = 0.01 \)
Persistent Gag responses correlate with lower viral load set point

Persistent responses were defined as:

- Responses that persisted over time and
- Were detected in at least 3 time-points 4w, 6w, 8w, 14w, 26w, and 52w post infection

$p = 0.0001; r = -0.8$
HIV-specific CD8+ T cells are numerous but defective

B

Kruskal-Wallis p=0.0001

CD38+HLA-DR+Tetramer+ CD8 T cells

HIV | CMV | EBV | Flu

C

% OF TERAMER + CELLS SECRETING IFNγ

P=0.01

HIV | CMV
Conclusions II

• Nef-specific CD8+ T cell responses are immunodominant in acute HIV-1 infection but do not correlate with viral control.

• Gag-specific immune responses associate with viral control in early (but not acute) HIV-1 infection.

• Limited immunogenicity, transient and defective immune responses may explain the failure of the immune system to contain the virus.

HIV controllers: a model of successful viral control?

Transmission/Progression Threshold
2,000 RNA copies/ml

CD4 Cell Count

RNA copies/ml plasma

30 years
Distinction between elite controllers and long-term non-progressors

- **EC** defined by VL <50 copies/ml
- **LTNP** defined by ability to maintain normal CD4 counts for long period
- 5%-15% of infected persons are LTNP
- Less than 0.15% of infected individuals are elite controllers
Genome-wide association studies: host HLA is the most significant determinant of outcome

HLA B*57:01

Controllers without protective HLA class I alleles more likely to maintain viral control

Controllers with protective HLA alleles

Controllers without protective HLA alleles
Viremic controllers with protective HLA alleles have broad anti-Gag responses compared to non-controllers.
CD8+ T cells from controllers without protective HLA alleles have poor viral inhibition capacity

Co-culture
CD8 and CD4 T-cells
E:T ratio 1:1

Inhibition of HIV
Replication measured by p24 in supernatants

CD4+ T-cells + HIV + CD8+ T-cells

p= 0.02*

Log10 p24 Inhibition

protective HLA class I alleles

non-protective HLA class I alleles
Conclusions III

• HIV controllers with protective HLA alleles appear to have a CD8+ T cell-mediated mechanism of control.

• Controllers without protective alleles have an alternative, more durable mechanism of HIV control.

• Understanding the mechanisms of control in acute HIV infection and in controllers may lead to novel prophylactic or therapeutic interventions.
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