CTL and the Control of HIV-1 Replication

Or

Lessons learned from mixing HIV-1 and CTL

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Evidence that CTL are protective in HIV-1 infection:

- Temporal associations with reduction in acute viremia and AIDS
- SIV-macaque model: CD8+ T cell depletion leads to sharply increased viremia, and recovery with decreased viremia
- HIV-1 sequence evolution in CTL epitopes \textit{in vivo}: selective pressure (escape)
New technologies offer amazingly precise characterizations of CTL

- **ELISpot**: rapid, robust, validated measurements using few cells
- **ICS**: ability to examine phenotypes and functional markers in remarkable detail
- Such assays tell us about CTL: how many, what specificity, and what functional potentials
- How do these correlate to antiviral activity? These assays offer a detailed picture of the effector end of the CTL interaction, but what about CTL-HIV-1 interaction and the upstream events in infected cells?
Questions about the antiviral activity of HIV-1-specific CTL

• Do they kill HIV-1-infected cells?
• Do they suppress HIV-1 replication (via what mechanisms?), and what factors influence efficiency?
• Why do they fail in vivo, and how can a vaccine prevent that failure?
CTL recognize cells displaying foreign protein epitopes

CTL
Release of Cytolytic Granules
And Signal for Apoptosis, Cytokines

Target Cell
HIV-1 replicates rapidly, posing a challenge to CTL

Initial Infection

CD4+ T Cell

First Virion Produced

CD4+ T Cell

~1 Day

~1 Day

Cell Death
(Last Virion Produced)

Killing Would Result in:

Prevention of Virion Production

Reduction of Virion Production
HIV-1-infected cells early in viral replication are susceptible to CTL

HIV-1-specific CTL can potently inhibit viral replication

Suppression of HIV-1 by CTL can be irreversible

CTL can suppress HIV-1 via cytokines and direct cytolysis

CTL recognizing different epitopes can vary in their antiviral efficiency

Note that T.J. Tsomides and H.N. Eisen et al (JEM 1994, 180:1294) showed that IV9 is presented ~12/cell and SL9 is presented ~400/cell.

Unpublished data
Both Nef-mediated HLA-I downregulation and epitope kinetics affect CTL antiviral activity

Adapted from A. Ali and O.O. Yang et al. J. Virol 2004, 78:561
The impact of Nef on CTL antiviral activity can be quantitated

WT Nef

M20A Nef

Nef Impact Ratio = \( \frac{(6.3-5.5)}{(6.3 -0.9)} = 0.15 \)

The impact of Nef on CTL antiviral activity can vary dramatically

**WT Nef**

**M20A Nef**

Nef Impact Ratio = \( \frac{(6.3 - 3.2)}{(6.3 - 2.6)} = 0.84 \)

Nef does not affect the antiviral activity of HLA-I C-restricted CTL

Other epitope factors may also affect Nef susceptibility (?)
HIV-1-specific CTL lose antiviral function with senescence


Summary of factors determining CTL antiviral efficiency

- Epitope levels (adequacy for recognition)
- Epitope kinetics (timing of recognition in relation to viral production)
- Impact of Nef-mediated HLA-I downregulation
- Effector status of CTL
- *What is the relative importance of these factors???
An example that antiviral assays can give different results than standard CTL assays (Implications for escape and cross-clade studies?)

CTL killing of peptide-loaded versus HIV-infected cell

Clade A1 consensus
Clade A2 and F2 consensus
Clade F1 consensus

Epitope Sequence

Peptide 10µg/ml

Infected

MS Bennett and OO Yang, Submitted
CTL detection does not predict virus suppression

RPAEPVPLQL
(Consensus B/C/G)

-S-------
(Consensus A1)

--T-------
(Consensus A2/F2)

--E-------
(Consensus F1)

MS Bennett and OO Yang, Submitted
Implications for analysis of current vaccine trials?

- ELISpot is the major validated surrogate marker for CTL immunogenicity of vaccines
- Most likely, ELISpot responses are necessary but not sufficient to reflect the antiviral activity of CTL (recognition of infected cells)
- If current vaccine trials fail to demonstrate clinical benefit despite “immunogenicity,” it may be premature to discount a CTL-based vaccine approach based on lack of protection in vaccine “responders”
A more important question about HIV-1-specific CTL:

Why do they fail *in vivo*?
Multiple mechanisms have been observed and proposed to explain failure \textit{in vivo}

- Abnormal differentiation and activation
- Exhaustion/senescence
- Hypofunctional profile
- Lack of CD4 help
- Epitope escape mutation

Can a single process explain these diverse events (Ockham’s razor)????
Single amino acid changes in epitopes can allow HIV-1 to completely avoid CTL
HIV-1 Infection

Immunodominance of Poorly Conserved Epitopes

Early Escape and Poor Containment

Original Antigenic Sin

Decreasing CTL Quantity and Quality

Ongoing HIV-1 Replication

Abnormal CTL Activation and Differentiation

Ongoing Escape

Early Massive Irreversible CD4+ T Cell Loss

Eventual Complete Failure

A hypothesis....
A hypothesis....

HIV-1 Infection → Immunodominance of Poorly Conserved Epitopes

Vaccine Priming → Targeting of Conserved Epitopes

Early Reduction of HIV-1 → Preserved CD4+ T Helper Cells

Effective CTL → Containment of HIV-1
What strategies can prevent escape?

All randomly generated epitope mutants

Viable mutants

Unrecognizable mutants

Escape Mutants
A mutation must be both non-recognized and viable to allow escape.
Bypassing immunodominance to focus CTL on very constrained epitopes?

All randomly generated epitope mutants

Viable mutants

Unrecognizable mutants

Escape Mutants
Focus immunity on constrained sequences?

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.

From entropy calculations generously provided by B Korber
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