LAIR-1 is a negative regulator of SIV-specific CD8 T cells during chronic SIV infection

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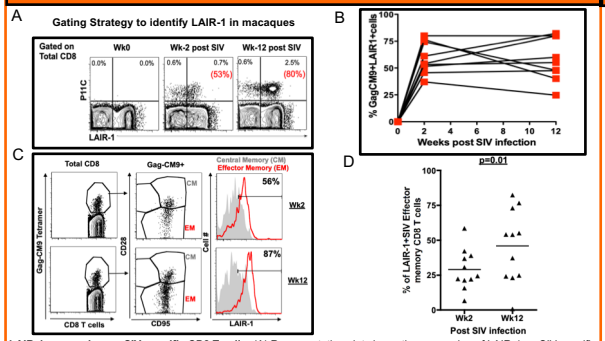
BACKGROUND: Human Immunodeficiency virus (HIV)-1- specific CD8 T cells play an important role in controlling HIV infection. However, during chronic HIV infection, HIV-specific CD8 T cells undergo functional exhaustion, lose effector function, and fail to inhibit viral replication. Here, we report the expression of Leukocyte-associated Ig-like receptor (LAIR-1) on Simian virus-specific CD8+ T cells during chronic SIV infection and the effect of LAIR-1 blockade on the proliferation and cytokine function of these cells.

METHODS: A total of 14 macaques were infected with simian immunodeficiency virus (SIVmac251) and studied the temporal dynamics of LAIR-1+ SIV-specific CD8 T cells for their phenotypic and functional profiles using multicolor flow cytometry. We performed immunohistochemistry IHC to stain for LAIR-1 in LN tissues and used RNA sequencing to study the transcriptomic profile of LAIR-1+ CD8 T cells.

RESULTS: LAIR-1 expression was found to be low on naive CD8+ T cells and increased on total SIV-specific and SIV-specific effector memory CD8+ T cells during chronic infection. In addition, the level of LAIR-1 expression in the lymph node during chronic infection was higher compared to naïve animals. Transcriptionally, these LAIR-1+ CD8 T cells exhibited a unique transcriptome characterized by heightened IFN signaling coupled with reduced TCR signaling, cell cycling, and cell metabolism pathways. Importantly, the expression of LAIR-1 on SIV-specific effector memory CD8 T cells correlates directly with the SIV viral load levels. Indeed, In vitro blockade of LAIR-1 using LAIR-1-Fc/anti-LAIR-1 antibody resulted in enhanced proliferation of SIV-specific CD8 T cells with cytotoxic function.

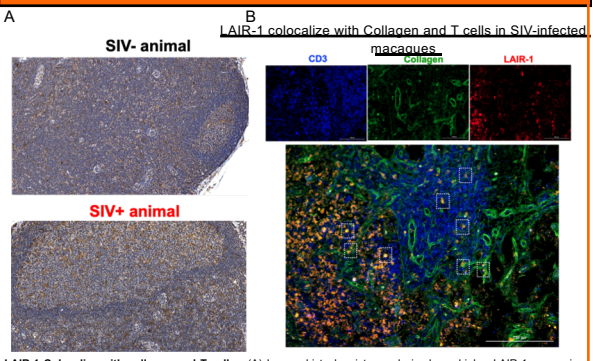
CONCLUSION: These results serve as a foundation for future in vivo trials of the use of rMamu-LAIR-1 to potentially enhance and/or restore antiviral immune responses in vivo, especially in secondary lymphoid tissues which may be important for the HIV cure strategy.

LAIR-1 expression on SIV-specific CD8 T cells during chronic SIV infection



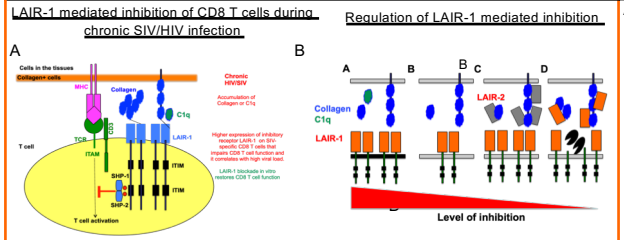
LAIR-1 expression on SIV-specific CD8 T cells: (A) Representative plot shows the expression of LAIR-1 on SIV-specific CD8 T cells. (B). Temporal kinetics of LAIR-1 expression on SIV-specific CD8 T cells during chronic SIV infection. (A) Representative plot shows the expression of LAIR-1 on SIV-specific memory CD8 T cells. (B). Cumulative plot showing frequency of LAIR-1 expression on SIV-specific memory CD8 T cells during chronic SIV infection.

LAIR-1 expression increased in Lymph node during chronic SIV infection



LAIR-1 Colocalize with collagen and T cells : (A) Immunohistochemistry analysis shows higher LAIR-1 expression during chronic SIV infection. (B). LAIR-1 (red) colocalize with collagen (green) and T cells (blue) in chronic SIV infection.

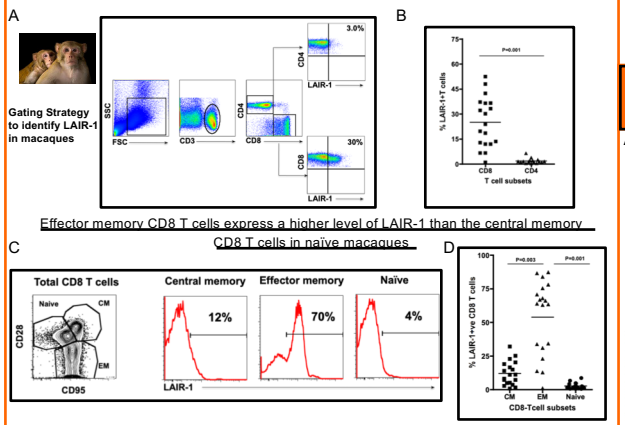
LAIR-1 mediated inhibition and regulation of CD8 T cells during chronic SIV/HIV infection



LAIR-1 mediated inhibition and regulation: (A) Schematic figure shows LAIR-1 mediated inhibition of CD8 T cells during chronic SIV/HIV infection. (B) Schematic figure shows the regulation of LAIR-1 mediated inhibition.

LAIR-1 expression in CD4 and CD8 T cells in Naïve Rhesus Macaques

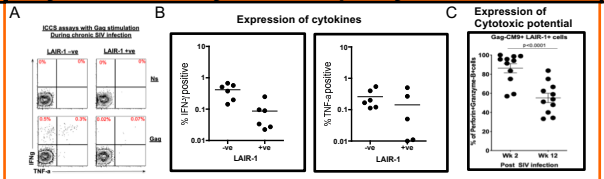
Expression of LAIR-1 is high in CD8 T cells compared to CD4 T cells (Naïve Macaques)



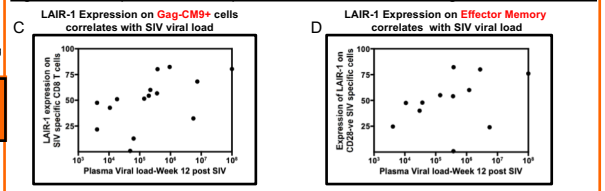
Effector memory CD8 T cells express a higher level of LAIR-1 than the central memory CD8 T cells in naïve macaques

LAIR-1 mediated inhibition and regulation: (A) Representative plots for the expression of LAIR-1. (B) Cumulative data plots showing the frequency of LAIR-1 in CD4 and CD8 T cells in Naïve macaques. (C) Representative plots for identifying different memory subsets in CD8 T cells. (D) Cumulative data plots showing the expression of LAIR-1 in different memory subsets in CD8 T cells in Naïve macaques.

SIV-specific LAIR-1+ CD8 T cells produce lower cytokines and cytotoxic capacity in chronic SIV

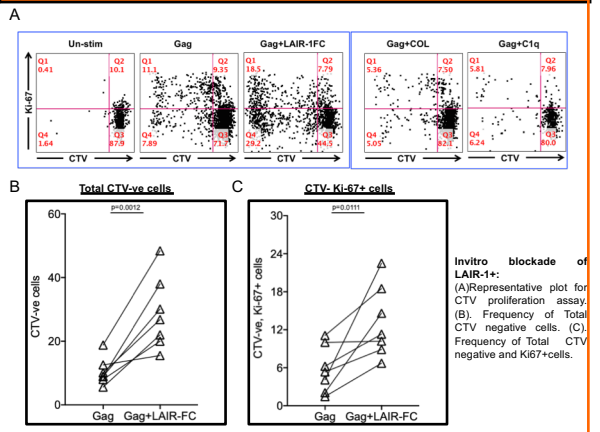


Higher LAIR-1 Expression on SIV-specific CD8 T cells is associated higher viral RNA Levels



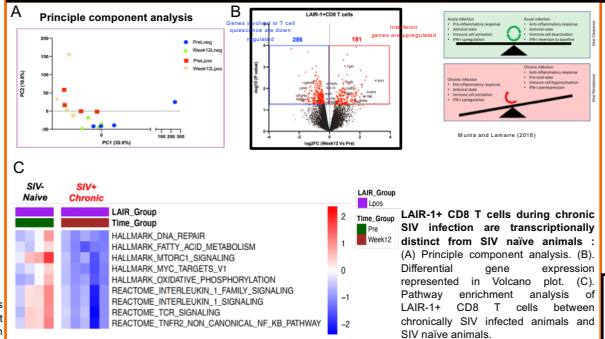
(A) Representative plots for the expression of LAIR-1, (B). Graphs represent cytokines expression. (C). LAIR-1 expression on Gag-CM9+ cells directly correlates with SIV viral load. (D). LAIR-1 expression on effector memory cells directly correlates with SIV viral load.

In vitro blockade of LAIR-1 results in Enhanced Proliferation of SIV-specific CD8 T Cells



Invitro blockade of LAIR-1+: (A)Representative plot for CTV proliferation assay. (B). Frequency of Total CTV negative cells. (C). Frequency of Total CTV negative and Ki67+cells.

Exhaustion pathways are enriched in LAIR-1+ CD8 T cells during chronic SIV infection



LAIR-1+ CD8 T cells during chronic SIV infection are transcriptionally distinct from SIV naïve animals : (A) Principle component analysis. (B). Differential gene expression represented in Volcano plot. (C). Pathway enrichment analysis of LAIR-1+ CD8 T cells between chronically SIV infected animals and SIV naïve animals.

Conclusions

- LAIR-1 expression is elevated in SIV-specific CD8 T cells following SIV infection.
- SIV-specific effector memory CD8 T cells express more LAIR-1 and demonstrate a strong correlation with viral load.
- LAIR-1+ SIV-specific CD8 T cells produce a lower level of cytokines
- Exhaustion pathways are enriched in LAIR-1+ CD8 T cells during chronic SIV infection
- Imaging studies show LAIR-1 expression increased in chronic SIV infection and LAIR-1+ T cells colocalized with collagen
- Blocking LAIR-1 in vitro enhances the proliferation of SIV-specific CD8 T cells

Support testing for the safety and therapeutic potential of in vivo blockade of LAIR-1 to control HIV infection-

If it works in vivo there is a possibility to combine this with another co-inhibitory receptor blockade for HIV cure strategy as well as in cancer therapy

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