TLR8 Regulation of LILRA3 Is Abrogated in HIV Infection and Correlates to CD4 Counts and Virus Loads

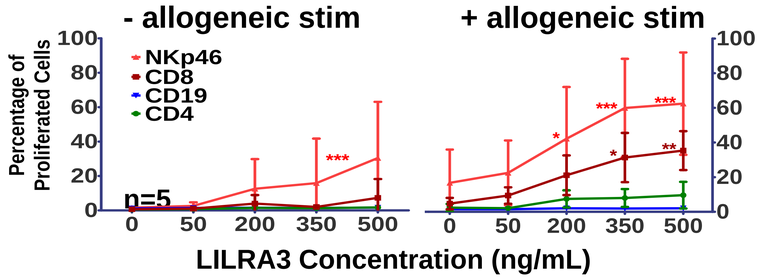
Hui Zhi Low, Gerrit Ahrenstorf, Torsten Witte
Department of Clinical Immunology and Rheumatology, Hannover Medical School

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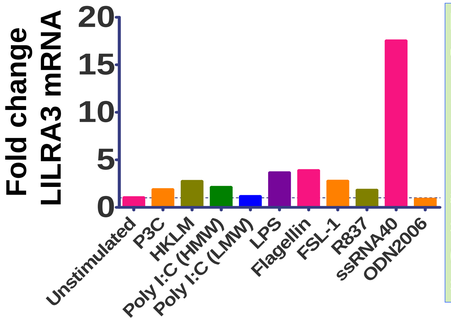
Introduction

Functional studies performed in our group have shown that LILRA3, by binding to monocytes, is an activatory molecule that induces proliferation of CD8 T-cells and NK cells (Figure below), as well as inducing various proinflammatory cytokines, implicating involvement in the cytotoxic immune response. LILRA3 genetic deletion is a risk factor for HIV (in revision). In this study, we analyzed regulation upstream of LILRA3, and its significance in the context of HIV.

LILRA3 induced NK and CD8 proliferation



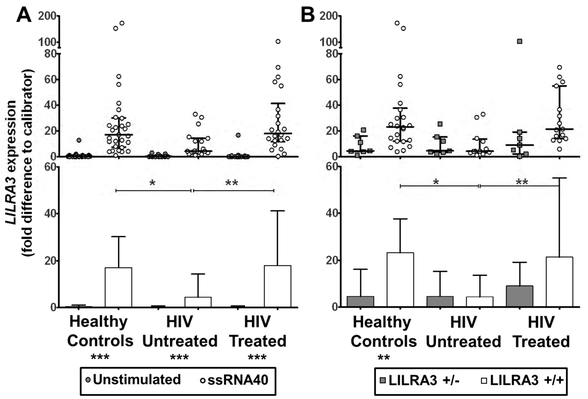
Screening of TLRs for LILRA3 induction



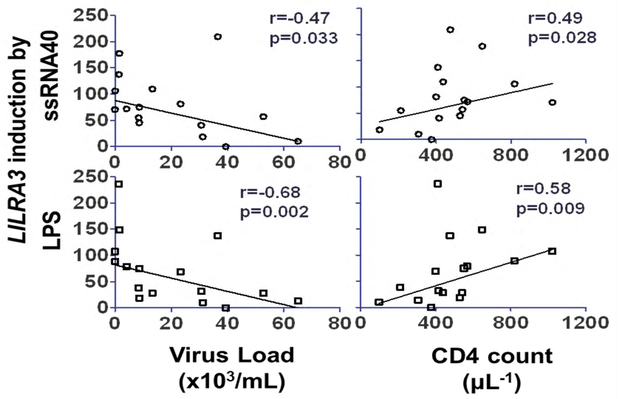
If LILRA3 is involved in viral defence, it should be regulated by TLRs which are important for virus recognition. Among a panel of 10 TLR agonists, TLR8 agonist ssRNA40 induced the strongest LILRA3 expression (Figure 2, 1 of 4 donors shown).

Abrogation of ssRNA40-induced LILRA3 in HIV

LILRA3 expression by monocytes in untreated HIV patients was significantly reduced compared to healthy controls, which appears to be partially restored in treated patients (A). Gene dosage is vital to LILRA3 expression as *LILRA3*$^{+/+}$ individuals have higher expression than those that are *LILRA3*$^{+/-}$ among the healthy controls and HIV treated patients (B).



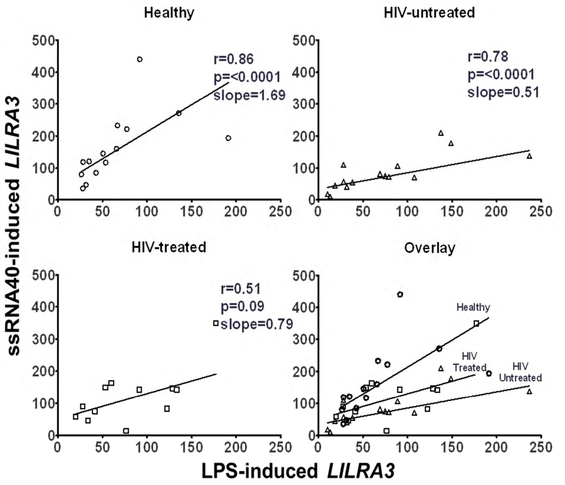
Correlation with viral load and CD4 counts



We hypothesize that higher expression of LILRA3 should lead to better immune status of the patients. Among the HIV untreated patients, higher expression of both ssRNA40 and LPS induced LILRA3 was significantly correlated with lower virus load of HIV-untreated patients as well as higher CD4 T-cell count.

Selective dysregulation of ssRNA40-induced LILRA3 in HIV

ssRNA40-induced *LILRA3* correlated well with LPS-induced *LILRA3* expression across the 3 groups. However, while TLR8 stimulation gave a more robust LILRA3 response than TLR4 stimulation in healthy controls, this trend is paradoxically skewed towards LPS in HIV patients, who might actually benefit from the TLR8-ssRNA response rather than TLR4-LPS response.



Conclusion

- ssRNA40 prominent inducer of LILRA3
- LILRA3$^{+/-}$ heterozygotes express less LILRA3
- LILRA3 induction is abrogated in HIV
- LILRA3-induction correlated to virus load and CD4 counts in untreated patients

KFO 250 Auto Immunität Klinische Forschergruppe

Email:
low.huizhi@mh-hannover.de
witte.torsten@mh-hannover.de