HIV-induced modifications of TIGIT expression impair CD8 T cell polyfunctionality

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Upon HIV infection, CD8 T cells become severely exhausted, which correlates with the accumulation of inhibitory receptors and loss of co-stimulatiors, as seen for the complementary co-inhibitor/co-stimulator pair T cell immunoglobulin and ITIM domain (TIGIT) and CD226.

We observed an elevated frequency of TIGIT-positive CD8 T cells in chronically infected patients, both long-term treated and treatment-naïve, and a longitudinal accumulation despite early initiation of ART. We found elevated levels of TIGIT as well as decreased CD226 expression on CD8 T cells recognizing HIV compared to CMV-specific cells. In addition, we detected an upregulation of poliovirus receptor (PVR) on CD4 T cells in blood and lymph nodes, especially on follicular T helper cells (Tfh).

Our results suggest increased TIGIT signaling during HIV infection as one mechanism of CD8 T cell deterioration.

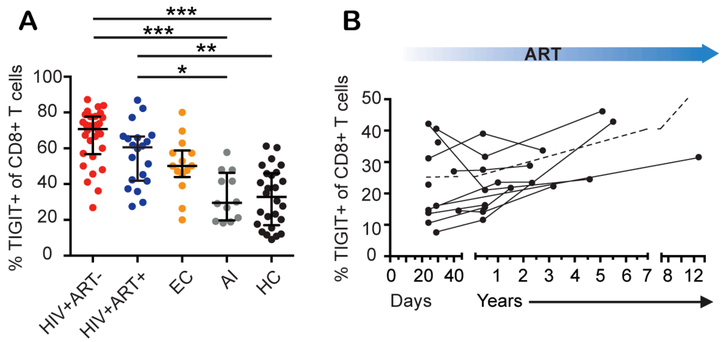

Figure 1. TIGIT is elevated in chronic HIV infection and accumulates over time. (A) In comparison to healthy control subjects, both treatment-naïve and long-term treated HIV-positive patients have elevated frequencies of TIGIT+ CD8 T cells. (B) Despite successful control of viremia by early initiated ART, the frequency of TIGIT+ CD8 T cells increases during chronic infection.

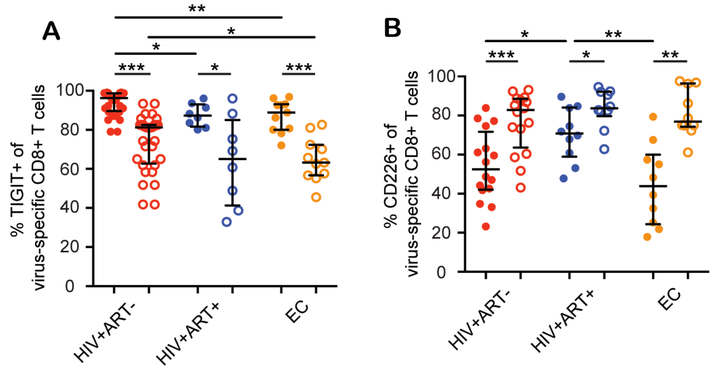

Figure 2. HIV-specific CD8 T cells comprise more TIGIT⁺ and less CD226⁺ cells compared to CMV-specific cells. CD8 T cells of patients infected with both, HIV and CMV, were compared regarding TIGIT and CD226 expression. In contrast to the CMV-reactive T cells (open circles), those specific for HIV (full circles) display higher frequencies of TIGIT+ cells and lower frequencies of CD226+ cells.

Introduction

In the context of chronic viral infections, CD8 T cells undergo changes that are referred to as CD8 T cell exhaustion. Amongst others, these changes comprise upregulation of inhibitory receptors (e.g. TIGIT) and downregulation of co-stimulators (e.g. CD226), dysregulation of transcription factors and consequently loss of functional features.

TIGIT inhibits immune cells via multiple mechanisms, most importantly ITIM signaling and decreasing CD226-mediated co-stimulation. TIGIT and CD226 are both activated upon binding to PVR for which TIGIT has a higher affinity. Upon dysregulation in the TIGIT/CD226 expression, the expression of PVR becomes therefore relevant, especially on CD4 T cells as potential target cells.

Aim

Detailed characterization of the TIGIT/CD226/PVR axis in CD8 T cell exhaustion during HIV infection.

Methods

The sample material included peripheral blood mononuclear cells (PBMCs) and lymph node mononuclear cells (LMNCs) from

- treatment-naïve (HIV+ART-)
- long-term treated (HIV+ART+)
- acutely infected patients (AI)
- healthy control subjects (HC)

The cells were analyzed by flow cytometry. HIV- and CMV-reactive T cells were identified by peptide stimulation (HIV gag p55 or CMV pp65, respectively) and IFNγ detection.

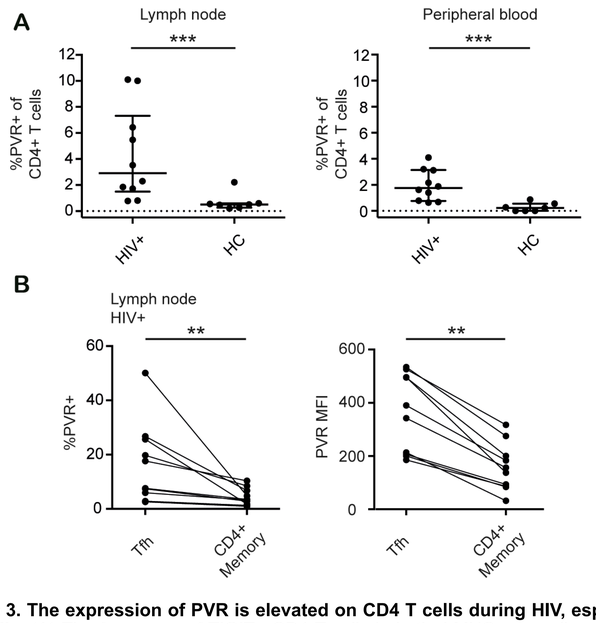

Figure 3. The expression of PVR is elevated on CD4 T cells during HIV, especially on Tfh cells. (A) The frequency of TIGIT+ CD4 T cells in both, LMNCs as well as PBMCs, is significantly elevated in HIV-positive patients when compared to healthy control subjects. (B) Among LMNCs, frequency of positive cells and expression levels of TIGIT are significantly higher in Tfh cells, compared to CD4 memory T cells.

Conclusion

Our results suggest that not only TIGIT expression, but also signaling is enhanced during HIV infection.

- Accumulation of TIGIT
- Decreased CD226 expression
- PVR upregulation, especially on Tfh

Tfh cells represent a major compartment of active HIV production and latency. Given the inhibitory functions of TIGIT, this mechanism is likely to contribute to the deterioration of CD8 T cells and viral persistence seen in HIV infection. Thus, representing a major obstacle in finding a cure for HIV infection.

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