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Investigating the role of the immune checkpoint receptor TIGIT in T cells during HIV disease progression and as a target for immune restoration

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Background: HIV infection induces a series of phenotypic and functional changes to T cells that eventually results in a state of T cell exhaustion and failure to control viral replication. T-cell-Ig-and-ITIM-domain (TIGIT) is a recently described negative checkpoint receptor expanded on CD8$^+$ T cells during LCMV infection in mice and inhibits anti-viral effector CD8$^+$ T cell activity. We hypothesized that during progressive HIV infection, TIGIT surface expression will mark an expanded population of dysfunctional T cells, and that novel monoclonal antibodies targeting TIGIT would restore anti-HIV-specific T cell responses.

Methods: Surface expression of TIGIT and PD-1 on T cells were measured by flow cytometry from 103 HIV-infected participants [non-controllers (n=20), elite controllers (n=20), antiretroviral (ART) suppressed (n=39), acutely infected (n=24)] and 20 age and gender matched HIV-uninfected controls. Quantified cell associated HIV (CA-HIV) DNA and RNA from purified CD4$^+$ T cells. Functional characterization of TIGIT+ T cells was performed and ex-vivo HIV-specific cytokine and proliferative responses were assessed in the presence monoclonal antibodies (mAb) targeting TIGIT and/or PD-1 pathways (anti-TIGIT mAb and anti-PD-L1 mAb).

Results: In controls a median of 28.05% of CD8$^+$ T cells were TIGIT$^+$ (IQR 24.43,39.15). In comparison, we found a significant expansion of TIGIT$^+$CD8$^+$ T cells during chronic (median 57.1%, IQR 42.6,63.45; p< 0.0001) and a non-significant trend in acute HIV infection (40.40%, 28.3,47.8; p=0.08). TIGIT expression remained elevated despite viral suppression and associated with CD4$^+$ CA-HIV DNA. TIGIT$^+$ and TIGIT$^+$PD-1$^+$ CD8$^+$ T cells inversely correlated with CD4 count (p=0.0016, r=-0.658; p=0.0024, r=-0.385 respectively). TIGIT was expressed on >50% HIV-specific CD8$^+$ T cells, however TIGIT+ T cells failed to produce cytokines in response to HIV antigens. Single blockade of TIGIT led to a significant increase of interferon gamma response to HIV Gag compared to no blockade (p=0.027). Co-blockade of TIGIT and PD-L1 lead to greater restoration of HIV-specific CD8$^+$ T cell proliferative responses (4.10%, IQR 1.46,22.28) than single blockade of TIGIT (3.47, IQR 1.11,10.08; p=0.0078) or PD-L1 (3.945%, IQR 1.15,17.53; p=0.039).

Conclusions: These findings identify TIGIT as a novel marker of dysfunctional HIV-specific T cells and suggest TIGIT along with other checkpoint receptors may be novel curative HIV targets.

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