Retrovirology

Poster presentation

P16-30. Induction of Tim-3 expression by the common gamma-chain cytokines IL-2, IL-7, IL-15 and IL-21

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Background

Tim-3 expression is upregulated in HIV-1-infected individuals, and has been implicated in driving T cell exhaustion. While expression is disproportionately high on HIV-1-specific CD8+ T cells, >70% of total CD8+ T cells in the peripheral blood of infected individuals have been observed to express Tim-3, suggesting the existence of a more general mechanism of induction. Thus, Tim-3 may contribute not only to an impairement of virus-specific responses, but also tp a more generalized immunosuppression. The mechanisms leading to this global upregulation of Tim-3 expression remain unknown.

Methods

Isolated CD4+ T cells were infected with HIV-1 in vitro. Whole PBMC, and isolated CD4+ or CD8+ T cells were treated with stimuli including LPS, and cytokines. Tim-3 expression was analyzed at various time-points by flow cytometry, in conjunction with a number of phenotypic markers and CFSE. Upon removal of cytokine, apoptosis (annexin-V) was analyzed along with Tim-3 expression.

Results

In vitro HIV-1-infection had no effect on the Tim-3 expression levels of CD4+ T cells. The common gamma-chain cytokines induced high levels of Tim-3 expression with IL-15>IL-2>IL-21>IL-7, while LPS and IL-4 had no effect. The gamma-chain cytokines induced distinct profiles of Tim-3/PD-1 co-expression with some driving a dual-positive population, and other preferentially upregulating either Tim-3 or PD-1. Tim-3 expression was primarily limited to cells that had undergone proliferation in response to cytokine, and these cells preferentially underwent apoptosis upon cytokine removal.

Conclusion

We provide evidence against the direct exposure of T cells to virus, or exposure to LPS as etiologies for global Tim-3 upregulation in HIV-1 infected individuals. Potent upregulation of Tim-3 is however driven by exposure of T cells to common-gamma chain cytokines. Physiologically, this upregulation likely serves to balance the survival signals provided by these cytokines, and to drive the elimination of these activated cells upon removal of cytokine (resolution of infection).