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HTLV-1 Tax induces Th1 master regulator T-bet and thus IFN-γ in CD4+CCR4+ T-cells of virus-associated myelopathy patients

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The plasticity inherent to the CD4+ T cell differentiation program especially as it pertains to regulatory T (Treg) cells has been implicated in the pathogeneses of multiple inflammatory diseases. Human T-lymphotropic virus type 1 (HTLV-1) is thought to effect transcriptional changes in infected T cells via HTLV-1 Tax that can cause once suppressive CD4+CD25+CCR4+ Treg cells to lose FOXP3 expression and produce IFN-γ. We hypothesized that spawning of such inflammatory Th1-like cells from infected CCR4+ T cells plays a key role in the pathogenesis of the neurodegenerative inflammatory disease HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). In this study, we demonstrated that Tax in cooperation with specificity protein 1 (Sp1) boosts the expression of the Th1 master regulator T box transcription factor (T-bet/Tbx21) and consequently IFN-γ. We established the presence of abundant CD4+CCR4+ T cells co-expressing the Th1 marker CXCR3 and producing T-bet/Tbx21 and IFN-γ in the CSF and spinal cord lesions of HAM/TSP patients. Finally, we tested treatments on ex vivo cell cultures from patients and found evidence that a therapy targeting CCR4+ T cells via antibody-dependent cellular cytotoxicity may represent a viable treatment option for HAM/TSP.

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