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Superior antiviral and antiproliferative activity of IFN-beta vs. IFN-alpha in primary ATL cells occurs downstream of STAT1 signaling

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Adult T-cell leukemia (ATL) is an aggressive $CD4^+CD25^+$ leukemia with poor prognosis, which usually develops several decades after HTLV-1 infection. In contrast to HIV-infection, the treatment of HTLV-1-associated diseases rely on a limited number of drugs. For ATL, combination therapy with IFN-alpha+AZT has shown clinical benefit in the non-lymphoma subtypes. Type I IFNs (IFN-alpha/beta) are essential cytokines with proved anticancer and antiviral action in vitro and in vivo. Nonetheless, their mechanisms of action in HTLV-1 infection remain unclear and a side-by-side comparison of both type I IFNs has not been performed in ATL. We show, in short-term culture of primary mononuclear cells from ATL patients, that both IFNs cause increased apoptosis, exert an anti-proliferative and antiviral effect, and decrease pro-inflammatory cytokine levels. However, IFN-beta treatment was significantly more effective in inhibiting viral p19 protein levels and lymphoproliferation, as compared to IFN-alpha. This pronounced effect of IFN-beta was explained by an induction of a higher number of known IFN-stimulated genes and antiviral genes by microarray analysis (76 vs. 26 genes were selected with $p<0.001$ and >2-fold difference vs. control). In PBMCs from healthy donors, ATL patients as well as in HTLV-1-infected cell lines, both IFNs have comparable activity in phosphorylating STATs 1 through 5 (PhosFlow), although phospho-STAT1 levels were up to tenfold higher than phospho-STAT2 through 5. This predominant STAT1-mediated antiviral gene signature was confirmed by Ingenuity Pathway analysis. In conclusion, our data suggest the superior antiviral and antiproliferative activity of IFN-beta vs. IFN-alpha occurs downstream of STAT1 signaling.

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