Proteomic profiling of HTLV-1 carriers and ATL patients reveals sTNFR2 as a novel diagnostic biomarker for acute ATL

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Abstract

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Abstract

Adult T-cell leukemia/lymphoma (ATL) is a human T-cell leukemia virus type-I (HTLV-1)-associated T-cell malignancy with generally poor prognosis. Although only about 5% of HTLV-1 carriers progress to ATL, early diagnosis is challenging due to the lack of ATL biomarkers. In this study, we analyzed blood plasma profiles of asymptomatic HTLV-1 carriers (AC), untreated ATL patients including acute, lymphoma, smoldering, and chronic types, and ATL patients in remission. Through SOMAscan, expression levels of 1305 plasma proteins were analyzed in 85 samples (40 AC, 40 ATL, 5 remission). Using Gene Set Enrichment Analysis and Gene Ontology, overrepresented pathways in ATL versus AC included angiogenesis, inflammation by cytokines and chemokines, IL6/JAK/STAT3, and notch signaling, among others. During the selection of candidate biomarkers, we focused on soluble tumor necrosis factor receptor 2 (sTNFR2) due to its active role in the enriched pathways, extreme significance (Welch's t-test, $p<0.00001$), high discrimination capacity (area under the curve >0.90), and novelty to ATL research. Quantification of sTNFR2 in 102 plasma samples (30 AC, 68 ATL, 4 remission) using ELISA showed remarkable elevations in acute ATL, at least 10-times that of AC, and a return of sTNFR2 to AC state levels after achieving remission. Flow cytometry and immunostaining validated the expression of TNFR2 in ATL cells. No correlation between sIL-2 and sTNFR2 levels in acute ATL was found, suggesting the possibility of sTNFR2 as an independent biomarker. Our findings represent the first extensive blood-based proteomic analysis of ATL, suggesting the potential clinical utility of sTNFR2 in diagnosing acute ATL.