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Identification of Potential Biomarkers for Adult T-Cell Leukemia/Lymphoma through Proteomic Analysis

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Commentary

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DESCRIPTION

Adult T-cell leukemia/lymphoma (ATL), a malignancy caused by Human T-cell Leukemia Virus type-1 (HTLV-1) infection, poses significant challenges in treatment. To address this, a biomarker identification strategy was developed using total cell proteomics of cultured ATL cells to uncover potential novel biomarkers for ATL. Four distinct protocols, varying in lysis buffers and additional agents, were employed to perform a comparative analysis among three groups: ATL cell lines, HTLV-1-infected cell lines and HTLV-1-negative cell lines. The analysis revealed 24 proteins significantly increased (ratio ≥ 2.0, $p<0.05$) and 27 proteins significantly decreased (ratio ≤ 0.5, $p< 0.05$) in the ATL group. Notably, previously reported biomarkers CCL3 and CD30/TNFRSF8 were among the significantly increased proteins. Moreover, correlation analysis between identified proteins and Tax, a key protein in HTLV-1 infection, highlighted RASSF2 and GORASP2 as potential novel Tax-regulated factors. The biomarker identification strategy established in this study holds promise for advancing the understanding and identification of biomarkers not only for ATL but also for other diseases.

Biomarkers play a crucial role in diagnosing diseases, assessing treatment efficacy, and predicting prognosis. While genome and transcriptome analyses *via* Next-Generation Sequencing (NGS) have unveiled numerous disease-related abnormalities, it's essential to note that genetic anomalies don't always translate directly to protein alterations. Moreover, mRNA expression levels only weakly correlate with protein expression. Additionally, post-translational modifications to proteins, vital for functional diversity, remain undetectable by NGS

methods. Proteomics, employing Mass Spectrometry (MS), offers a distinct advantage by directly analyzing proteins themselves. This approach enables the comprehensive study of protein profiles, including post-translational modifications, providing valuable insights into disease mechanisms and potential biomarkers.

Adult T-cell Leukemia/Lymphoma (ATL) is a severe hematologic malignancy instigated by Human T-cell Leukemia Virus type-1 (HTLV-1) infection of $CD4^+$ T cells. With an estimated 10 to 20 million individuals infected globally, ATL typically manifests in adults 20-30 years post-infection, with carriers facing a lifetime risk of 6% -7% for men and 2%-3% for women in Japan. Despite uncertainties surrounding ATL's molecular mechanisms, pivotal roles are attributed to two viral proteins, Tax and HBZ. Tax, prevalent in the early phase, prompts HTLV-1-infected T cell proliferation, but is often suppressed or absent later on. Conversely, HBZ is constitutively expressed throughout infection, with higher expression in ATL patients, correlating positively with HTLV-1 proviral load. Studies on transgenic mice suggest Tax suppression and HBZ expression are critical for ATL pathogenesis, with HBZ alone capable of inducing T-cell lymphomas and inflammatory diseases. Thus, understanding the proteome of ATL cells expressing HBZ while Tax is suppressed can illuminate ATL-specific biomarkers.

Previous proteomic analyses, including investigations into ATL, have yielded insights. Notably, complement C3f emerged as a potential biomarker in ATL patient sera. Another study elucidated the pentose-phosphate pathway's role in carnosol-induced apoptosis in ATL cells. However, these analyses fell short in identifying low-abundance and functionally obscure proteins, emphasizing the need for broader coverage, quantification, and focus on target molecules. Past efforts leveraged shotgun analysis and Normalized Spectral Abundance Factors (NSAFs) for enhanced coverage and quantification, respectively.

In this study developed a biomarker identification strategy for ATL, concentrating on optimizing protein solubilization and in-solution digestion steps to enhance coverage. Through this approach, 24 significantly increased and 27 significantly decreased proteins were identified in ATL cell lines. Notably, previously reported chemokines CCL3/MIP-1α and CD30/TNFRSF8 were among the proteins found to be increased. This proteomic-based biomarker identification strategy holds promise for unveiling biomarkers not only for ATL but also for other diseases.