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Chronic lymphocytic leukemia and Chronic Lymphoproliferative Disorders

ANALYSIS OF THE EXPRESSION PROFILE OF LONG NON-CODING RNAS (LNCRNAS) IN PATIENTS AFFECTED BY T-CELL LARGE GRANULAR LYMPHOCYTE LEUKEMIA (T-LGLL)

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Introduction: Large Granular Lymphocyte Leukemia (LGLL) is a rare chronic lymphoproliferative disorder, most commonly found in the T-cell form (T-LGLL). Activating *STAT3* and *STAT5B* mutations are associated with symptomatic cytopenias in CD8+ T-LGLL and a milder course in CD4+ T-LGLL, respectively. The disease ranges from indolent to aggressive conditions, with low-dose immunosuppressive drugs often giving only transient responses, revealing the need for targeted therapies. With the goal of discovering potential diagnostic markers and therapeutic targets, this study investigates long non-coding RNAs (lncRNAs), including key regulators of gene expression and oncogenesis, a matter still unexplored in T-LGLL.

Methods: For lncRNA identification and quantification, RNA-sequencing (RNA-seq) was performed on purified CD57+ LGLs from a pilot cohort of 20 T-LGLL patients, subdivided by immunophenotype (CD8+/CD4+) and mutational status (*STAT3*/*STAT5B*), and 5 healthy donors (HD). To test whether lncRNA changes in *STAT3*-mutated patients were dependent on JAK2/STAT3 activation, primary T-LGLs were stimulated with IL-6 (20 ng/mL) and treated with STATTIC (3.5 µM). Treatment efficacy was assessed by western blot to measure STAT3 phosphorylation and by RT-qPCR to evaluate lncRNA expression levels following treatment.

Results: Transcriptome profiling identified 5,543 differentially expressed genes (*p-adj<0.05*), of which 1,182 were lncRNAs, revealing lncRNAs dysregulated in T-LGLL patients compared to HD. CD8+ *STAT3*-mutated T-LGLL patients showed marked transcriptomic remodeling, with a unique lncRNA signature clearly separating symptomatic from indolent cases. RT-qPCR analysis confirmed that LINC00461, PVT1, LINC002422 and MSC-AS1 were overexpressed, whereas FIRRE downexpressed in symptomatic CD8+ *STAT3*-mutated T-LGLL patients compared to asymptomatic patients and HD. HOTAIRM1 expression was higher in T-LGLL cases relative to HD. Correlation analysis between deregulated lncRNAs and clinical features showed interesting associations: PVT1 and LINC00461 were inversely correlated with absolute neutrophil count (*p<0.05*), while FIRRE showed a positive relationship (*p<0.05*). Functional data demonstrated that PVT1 and FIRRE expression were modulated through STAT3 activation, suggesting a STAT3-dependent regulation. Due to the rarity of T-LGLL and limited viability of primary cells, hematologic cell lines were screened for the expression of the validated lncRNAs. MOTN-1 expressed LINC00461, PVT1, and HOTAIRM1; JURKAT expressed LINC002422; and HDMAR expressed FIRRE, making them suitable models for future studies aimed at revealing their mechanism of action.

Conclusions: This study identifies lncRNA dysregulation in T-LGLL, highlighting their potential role in disease pathogenesis. In particular, RNA-seq revealed a distinct lncRNA profile in symptomatic CD8+ *STAT3*-mutated T-LGLL patients, suggesting their involvement also in the development of T-LGLL clinical manifestations.