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Differential Expression of *LEF1* Isoforms in Adult Lymphoid and Myeloid Malignancies

Yetişkin Lenfoid ve Miyeloid Malignitelerde *LEF1* İzoformlarının Farklı Ekspresyonu

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ABSTRACT

Objective: Lymphoid enhancer-binding factor-1 (LEF1) is one of the key regulators of lymphocyte proliferation and its aberrant expression is a prognostic factor for lymphoid or myeloid malignancies. In this study, we focused on the expression of *LEF1* isoforms in several hematological malignancies and found tissue-specific differential expression for the full-length (FL)-*LEF1* gene and its tumor suppressor (Δ*LEF1*) variant.

Material and Method: Fifty-three leukemia/lymphoma patients were included in this study. Diagnostic samples of "lymphoid group" patients: Chronic Lymphoblastic Leukemia (CLL) (n=10), B-cell Acute Lymphoblastic Leukemia (B-ALL) (n=9) and "myeloid group" patients: Chronic Myeloblastic Leukemia (CML) (n=12), Acute Myeloid Leukemia (AML) (n=13), and Multiple Myeloma (MM) (n=9) were studied. Healthy bone marrow, peripheral blood cells, and CD34 positive cells were used as controls. Total (T) and *FL-LEF1* transcript levels were examined by using quantitative real-time polymerase chain reaction (qRT-PCR). T and *FL-LEF1* mRNA ratios were also evaluated for calculation of Δ*LEF1*.

Results: *LEF1* levels were significantly high in lymphoid malignancies, but MM and AML patients have decreased *LEF1* levels. Although CLL patients have high *FL-LEF1* levels, the ratio of the T/FL levels was significantly decreased.

Conclusion: *LEF1* is a proliferation factor for lymphocytes and not only its differential overexpression but also the ratio of T/FL isoforms seem to accompany leukemia progress.

Keywords: *LEF1*, alternative splicing, lymphoid, myeloid, leukemia

ÖZ

Amaç: Lenfositlerin çoğalmasındaki önemli düzenleyicilerden biri olan lenfoid güçlendirici bağlama faktörü-1 (LEF1)'in anormal ekspresyonu, lenfoid veya miyeloid maligniteler için prognostik bir faktördür. Bu çalışmada, farklı *LEF1* izoformlarının çeşitli hematolojik malignitelerdeki ekspresyonu incelenmiş ve tüm uzunluktaki *LEF1* (*FL-LEF1*) anlatımı ile tümör baskılayıcı özelliğe sahip kısa izoformu (Δ*LEF1*) için dokuya özgü farklılıklar tespit edilmiştir.

Gereç ve Yöntem: Çalışmaya 53 yetişkin lösemi/lenfoma hastasının tanı anı örnekleri dahil edilmiştir. Çalışmaya dahil edilen hastalar, "lenfoid grubu"; Kronik Lenfoblastik Lösemi (KLL) (n=10), B hücreli Akut Lenfoblastik Lösemi (B-ALL) (n=9) ve "miyeloid grubu"; Kronik Miyeloblastik Lösemi (KML) (n=12), Akut Miyeloid Lösemi (AML) (n=13) ve Multipl Miyelom (MM) (n=9) gruplarından oluşmaktadır. Sağlıklı kemik iliği, periferik kan hücreleri ve CD34 pozitif hücreler kontrol olarak kullanılmıştır. Total (T) ve FL-LEF1 transkript seviyeleri, gerçek zamanlı kantitatif polimeraz zincir reaksiyonu (qRT-PZR) ile incelenmiştir. T ve FL-LEF1 oranları da ΔLEF1 hesaplaması için değerlendirilmiştir.

Bulgular: *LEF1*'in lenfoid malignitelerde anlamlı derecede yüksek olduğu, MM ve AML hastalarında ise *LEF1* seviyelerinde azalma olduğu görülmüştür. KLL hastalarında *FL-LEF1* seviyeleri yüksek olmasına rağmen, *T/FL-LEF1* seviyelerinin önemli ölçüde azaldığı tespit edilmiştir.

Sonuç: *LEF1*, lenfositler için bir çoğalma faktörüdür ve sadece aşırı ekspresyonu değil, aynı zamanda *T/FL-LEF1* izoformlarının oranının da lösemi ilerlemesine eşlik ettiğini düşündürmektedir..

Anahtar Kelimeler: *LEF1*, alternatif kırpılma, lenfoid, miyeloid, lösemi

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INTRODUCTION

Lymphoid enhancer binding factor-1 (LEF1), a member of the regulatory proteins called high mobility group proteins, is one of the key regulators in the proliferation of lymphocytes (1,2). *LEF1* is a downstream target of the WNT pathway involved in regulating cellular proliferation, differentiation, and organ development (3). Deregulated *LEF1* expression was observed in specific cancer types such as colon and prostate cancer or various hematological malignancies like acute lymphoblastic leukemia (ALL), Burkitt lymphoma (BL), and Chronic Lymphocytic Leukemia (CLL) (4-6).

LEF1 has different isoforms caused by alternative splicing and these alternative isoforms can change transcriptional activity (7). The full-length *LEF1* (*FL-LEF1*) isoform derives from selective activation of a promoter that can bind to beta catenin, and the other short isoform of *LEF1 (ΔLEF1)*, located within the intronic promoter of *LEF1* and acts as a dominant-negative isoform (8). *FL-LEF1* is expressed in mitotically active cells and behaves as a growth-promoting isoform; *ΔLEF1* uses an alternative translation start site and lacks exons 1 and 2, resulting from the loss of the beta catenin binding site and acts as an inhibitory isoform and suppresses cell growth (9). Different *LEF1* isoforms are transcribed in harmony under normal circumstances. Studies have shown that aberrant *LEF1* activity and differential expression patterns in different *LEF1* isoforms were important in leukemia development (6, 10). *FL-LEF1* was shown as a pro-survival factor in B-cell CLL cells, expressing abundant *LEF1*, but the expression of *LEF1* gene is much lower or absent in low-grade B-cell non-Hodgkin's lymphoma (NHL), suggesting differences in the activity of the *LEF* genes/isoforms between different malignancies (11,12).

Our previous study showed that pediatric T-cell and B-cell ALL patients have differential expression of *LEF1* variants (13). Therefore, in this study, we focused on *LEF1* isoforms' expression in a group of adult lymphoid and myeloid hematological malignancies and found tissue-specific differential expression for *LEF1* gene variants.

MATERIAL AND METHOD

Study Population

Fifty-three newly diagnosed patients in the hematology clinics were enrolled in this study. Diagnostic samples of "lymphoid group" patients: CLL (4) (n=10), B-cell ALL (n=9), and "myeloid group" patients: AML (n=13), Chronic Myeloblastic Leukemia (CML) (n=12), and Multiple Myeloma (MM) (n=9) patients were diagnosed according to WHO criteria (14) at Hacettepe University, Faculty of Medicine, Hematology Department. Twenty-six males and twenty-seven females with a mean age of 58.5±13.3 for the lymphoid group and 56.6±14.1 for the myeloid group were selected. Diagnostic samples whose white blood cell (WBC) count was above $20x10^3$/μL were included. Patients who received chemotherapy prior to the study were excluded. The control group comprised of the bone marrow samples of 10 healthy individuals, and the CD34 positive cells of nine healthy donors for allogeneic peripheral stem cell transplantation. Additionally, peripheral blood cells (n=5) were also studied. The study was approved by Hacettepe University Ethics Boards and Commissions (Project number: LUT 10/45) and all patients and healthy individuals signed written informed consent.

RNA Isolation and cDNA Synthesis

Mononuclear cells were collected, and total RNA was isolated according to the manufacturer's instructions (Qiagen, Germany). RNA quantity was measured by Nanodrop (ND-1000, Nanodrop Technologies, Inc., USA). 1000 ng RNA was used for cDNA synthesis by using random primers (20 μM, Roche Diagnostics, Germany).

Quantitative Real-time Polymerase Chain Reaction (qRT-PCR) Analysis

Total (T)-LEF and *FL-LEF1* mRNA levels were determined in patients and controls by qRT-PCR. To measure the balance between the isoforms, the ratio of *T- LEF1/ FL- LEF1* was also calculated for each hematologic malignancy. The primer sequences of *LEF1* isoforms and the qRT-PCR protocol were shown previously (13). *CYPA* and *BACT* genes were used as housekeeping genes. All runs were performed twice and each sample was run in duplicate. qRT-PCR analyses were performed on LightCycler 480 (Roche Diagnostics).

Statistical Analysis

The $2^{-\Delta\Delta Ct}$ method was used for relative quantification (15). Groups were compared by using the Mann-Whitney U test and p-value of ≤ 0.05 was considered significant.

RESULTS

We determined both *LEF1* isoforms' expression in control CD34 positive cells, bone marrow cells, and peripheral blood cells and showed *LEF1* variants at variable levels. Each patient sample was evaluated for *T* and *FL-LEF1* expression levels. *T-LEF1* including long and *ΔLEF1* isoforms and *T/FL LEF1* ratio gives us *ΔLEF1* isoforms levels. The ratio of *total LEF1/ FL LEF1* in the lymphoid group (CLL and ALL) and myeloid group (AML, CML, and MM) patients were also evaluated.

In general analysis, lymphoid group patients had aberrant *FL-LEF1* expression (p=0.01), but T-*LEF1* levels and the T/FL ratio were normal compared to healthy control samples. Myeloid group patients showed decreased T-*LEF1* (p=0.0009) and *FL-LEF1* (p=0.003) expression, but the T/FL ratio was found to be similar compared to the controls. When we compared leukemia groups, the myeloid leukemia patients showed significantly decreased T (p=0.008) and FL-*LEF1* (p=0.004) expression compared to lymphoid leukemia patients, and this deregulated T and FL-*LEF1* expression levels caused decreased T/FL ratio (p=0.03) in these patients.

Although there is no significant difference in T-*LEF1* expression, the oncogenic isoform *FL-LEF1* showed increased expression (p<0.0001) compared to healthy bone marrow and

peripheral blood cells in CLL patients. The ratio of T/FL-*LEF1* was also found to decrease in CLL patients (p=0.002) (Figure 1). Differently from CLL patients, adult B-ALL patients showed increased total (p=0.02) and *FL-LEF1* (p<0.001) expression levels (Figure 1).

T-*LEF-1* and *FL-LEF1* mRNA expression levels were found to be significantly decreased in AML patients compared to CD34 positive healthy controls. In addition, the T/FL ratio was found to be similar when compared to the controls (Figure 2A). CML patients showed slightly decreased *FL-LEF1* expression, but the ratio of T/*FL-LEF1* was similar when compared to the controls (Figure 2).

The total expression levels of the *LEF1* gene and the ratio of *T/FL-LEF1* were found to be decreased in MM samples (p=0.02, p=0.02, respectively) (Figure 2).

DISCUSSION

LEF-1 plays a role in the canonical Wnt signaling pathway by β-catenin and the LEF1/TCF complex, and activation of Wnt-target genes (16). Up-to-date studies point to activation of the

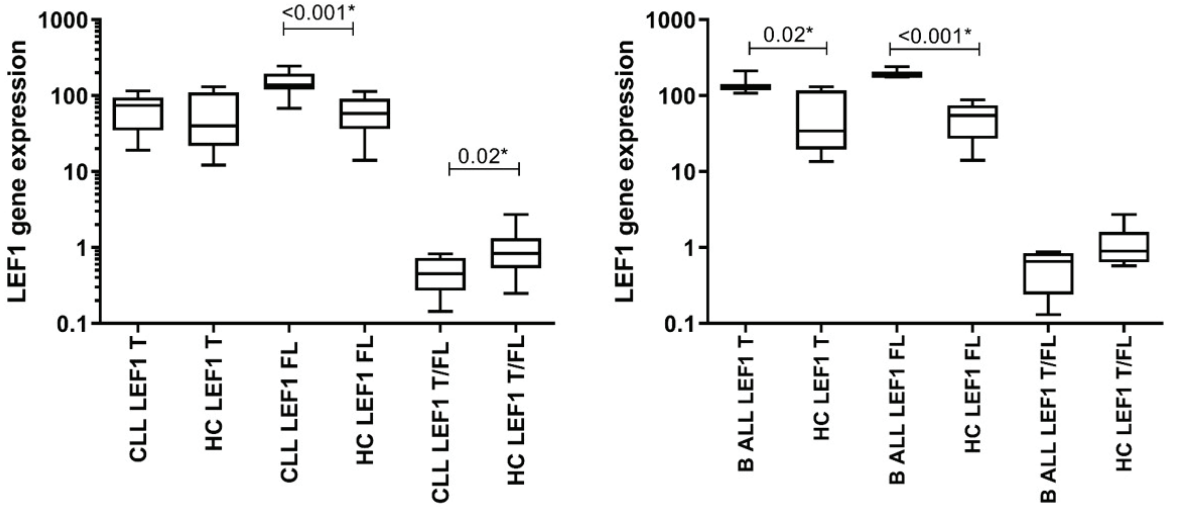

Figure 1. Expression analysis of *LEF1* isoforms in lymphoid group patients. *LEF1* expression in chronic lymphoblastic leukemia and adult B-cell acute lymphoblastic leukemia (B-ALL).

T represents the total expression of *LEF1*, FL represents full-length *LEF1* expression and T/FL represents the total and full-length ratio of *LEF1* expression. T/FL ratio was used for calculating short (ΔLEF1) isoform. CLL: Chronic Lymphoblastic Leukemia; B-ALL: Adult B-cell Acute Lymphoblastic Leukemia, HC: Healthy control sample. Statistical significance is shown by *.

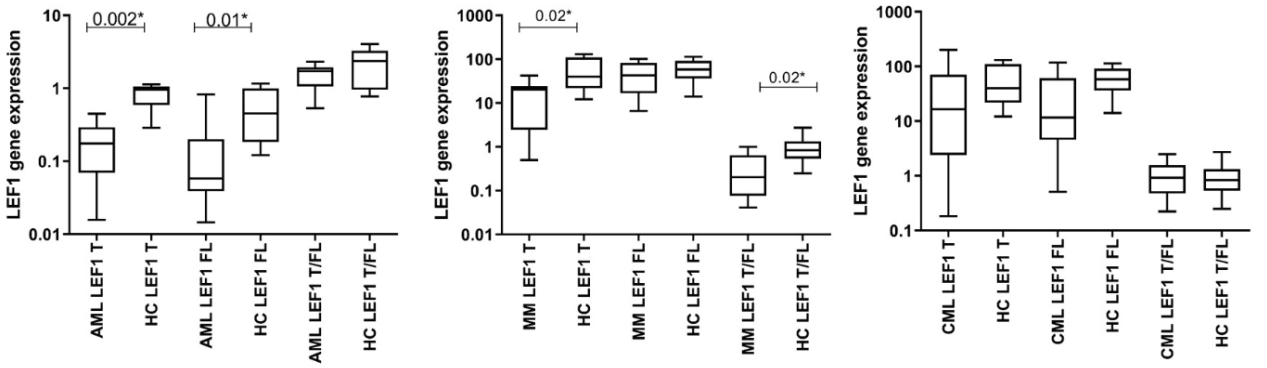

Figure 2. Expression analysis of *LEF1* isoforms in myeloid group and multiple myeloma patients.

T represents the total expression of *LEF1*, FL represents full-length *LEF1* expression and T/FL represents the total and full-length ratio of *LEF1* expression. T/FL ratio was used for calculating short (ΔLEF1) isoform. AML: Acute Myeloid Leukemia; MM: Multiple Myeloma; CML: Chronic Myeloid Leukemia; HC: Healthy control sample. Statistical significance is shown by *.

WNT pathway, and increased *LEF1* expression as being associated with the pathogenesis of different leukemia types (17-21). Not only high *LEF1* expression levels, but the existence of different isoforms and their heterogeneous contribution may also explain its role in malignancy development. The imbalance between the *LEF1* isoforms was shown in the transformation of malignancies (22,23). The role of the *LEF1* gene in cell growth is not restricted upon the WNT pathway; studies have shown that *ΔLEF1* stimulates the TCR alpha enhancer as strongly as *FL-LEF1*, which indicates that beta catenin has independent transactivation of the *LEF1* gene (24). In human CD34 positive cells, inhibition of *FL-LEF1*, but not beta catenin, affects proliferation and apoptosis of these progenitor cell populations, which supports that WNT is an independent function of *LEF1* in early hematopoiesis (25).

In our previous study, we showed that pediatric ALL patients have increased *FL-LEF1* expression and an abnormal ratio of long and short *LEF1* isoforms have been found in B and T cell ALL (13). Here we defined the different expression patterns of *LEF1* isoforms among adult lymphoid and myeloid malignancies and showed that although lymphoid and myeloid malignancies had significantly increased *LEF1* expression, lymphoid group patients have significantly aberrant *LEF1* activity according to the myeloid patients' group. We also further compared the lymphoid and the myeloid cohort and found that myeloid patients (including AML, CML, and MM) have decreased T-*LEF1* expression levels. These results indicate that although imbalanced *LEF1* isoforms were seen in both lymphoid and myeloid series, *LEF1* activation is more related to lymphoid leukemia.

Guiterrez *et. al* reported *LEF-1* expression in B-cell lymphocytosis previously (11). Recently, we have established that *LEF1* is a highly specific marker for the diagnosis of B-CLL (26) and/or *LEF1* expression is related to atypical CLL (27). In our study, CLL cases showed differences in oncogenic *FL-LEF1* and *ΔLEF1* variants leading to the instability between long and short transcript ratio. These findings indicate that *LEF1* oncogenic activity might have a role in CLL but due to the limited number of CLL patients, our results did not show any subtype differences.

Adult B-ALL patients have upregulated total and *FL-LEF1* isoforms, but the T/FL ratio was not changed indicating that the upregulation of T-*LEF1* expression is related to high *FL-LEF1* expression. Kühnl et al., identified that high *LEF1* expression is a prognostic factor for adult B- ALL patients, and high *LEF1* levels were associated with the outcome of the patients (28). While full length *LEF1* acts as an oncogene, a short transcript of the *LEF1* gene functions as a tumor suppressor (29). Our results showed that adult B-ALL patients have increased *FL-LEF1* isoform expression beside high *ΔLEF1* isoform and the balance of T/*FL-LEF1* were not changed.

In addition to the lymphoid group patients, our CML patients have unaffected *LEF1* gene expression and *LEF1* variant ratios. CML is a type of cancer resulting mostly from a reciprocal translocation t(9;22)(q34;q11), which caused the accumulation of an active fusion kinase protein called BCR-ABL. The oncogenic role of BCR-ABL is the dominant causative genetic defect in adult CML patients, but the WNT pathway activity is associated with tyrosine kinase inhibitory resistance and acute blast phase in leukemic stem cells in CML (30). Further studies are needed to understand the role of the *LEF1* gene in CML patients.

Unlike CML patients, multiple myeloma patients have decreased *T-LEF1* expression, resulting in an abnormal T/*FL-LEF1* isoform ratio, but no change in *FL-LEF1* expression. These findings point to a reduced T/*FL-LEF1* ratio occurring by impaired *ΔLEF1* levels. In addition, AML patients showed decreased total and *FL-LEF1* and a slightly decreased level in *ΔLEF1* expression. Recent studies reported that abnormal *ΔLEF1* levels, but normal *FL-LEF1* levels, were found in AML patients (31). Our results showed MM patients have similar results compared to AML patients in the literature.

In conclusion, we reported the *LEF1* isoform levels in adult lymphoid and myeloid leukemia patients and observed impaired full-length or *ΔLEF1* expression. Our results point to aberrant *LEF1* expression is mostly associated with lymphoid leukemia.

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