Original Article

ELANE is highly expressed in leukemia patients and predicts poor survival

Yanli Zhao\(^1,3\)*, Lining Si\(^2,3\)*, Weihua Zhang\(^3\), Wei Huang\(^4\), Rong Wang\(^1\)

\(^1\)Department of Medicine, Qinghai University, Xining, Qinghai Province, China; \(^2\)Department of Critical-Care Medicine, Affiliated Hospital of Qinghai University, Xining, Qinghai Province, China; \(^3\)Department of Pathophysiology, Harbin Medical University, Harbin, Heilongjiang Province, China; \(^4\)Division of Cellular Therapy, Duke University, Durham, USA. \(*\)Equal contributors.

Received March 18, 2018; Accepted October 11, 2018; Epub April 15, 2019; Published April 30, 2019

Abstract: ELANE (Elastase, Neutrophil Expressed), which has been identified as an oncogene in various tumors, is associated with neutropenia, both cyclic and autosomal dominant forms. However, little is known about ELANE on leukemia progression. To better understand the role of ELANE in leukemia progression, the expression level of ELANE, as well as correlation and survival analyses, was performed in patients with leukemia. Gene expression of ELANE on the normal monocytes and myeloid leukemia samples was obtained and compared via Oncomine. Correlation of ELANE and proto-oncogenes includes MYC and TP53 was assessed. The clinical prognostic value of ELANE was found to be elevated using Metzeler Acute myeloid leukemia microarray. As a result, ELANE was found to be highly expressed in the leukemia samples compared to normal monocytes. ELANE was found to be positively correlated with MYC expression, whereas it was negatively correlated with TP53 expression. Additionally, high expression of ELANE was associated with a relatively shorter survival time in leukemia patients, suggesting that ELANE is an oncogene in leukemia development. In conclusion, ELANE acts as a pro-oncogene in leukemia, which provides a potential therapeutic target.

Keywords: ELANE, leukemia, expression, correlation, survival rate

Introduction

Leukemia occurs in 2.3 million people and has caused 353,500 deaths by 2018 [1]. Four main types of leukemia - acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML) have been identified in clinic. Epidemic studies revealed that many risk factors, such as smoking, ionizing radiation, chemicals, prior chemotherapy, and even Down syndrome can be ascribed to the carcinogenesis and progression of leukemia [2]. However, the exact cause of leukemia is still unknown.

ELANE is a serine protein-coding gene that provides instructions for making a protein called neutrophil elastase [3]. Previously, numerous studies have reported roles for the ELANE mutation in pathological processes such as inflammatory diseases [4] and cancers [5]. Pharmacological inhibitors such as alpha 2-antiplasmin and some natural products (curcumin and EGCG) have been well documented to counteract and decrease damage caused by neutrophil elastase [6, 7]. However, whether ELANE can be used as a marker for leukemia diagnostics is still unclear. In this present study, to clarify gene expression changes that are common in cancer tissues or differ among cancer tissues, we analyzed leukemia patient samples downloaded from GEO database. Expression, correlation, and survival analyses of ELANE associated with leukemia were performed and ELANE was identified as a potential therapeutic target against leukemia.

Material and methods

ELANE expression analysis

The expression value of ELANE in normal and lymphoblastic leukemia patients was queried
ELANE predicts leukemia progression

Figure 1. ELANE mRNA levels in the Stegmaier leukemia microarray. Expression analysis for ELANE was performed using student t-test method via comparing acute myeloid leukemia (n = 9, group 3) and monocyte samples (n = 3, group 1). P value and fold change were extracted directly without any manual modification. In this figure, p value was 2.34E-5 and the fold change of ELANE in acute myeloid leukemia was 28.425 compared with monocyte samples in Stegmaier leukemia microarray.

Figure 2. ELANE mRNA levels in the Coustan-Smith leukemia microarray. Expression analysis for ELANE was performed using student t-test method via comparing T-cell childhood acute lymphoblastic leukemia (n = 46, group 2) and CD10 positive CD19-positive hematogone (n = 4, group 1) samples. P value and fold change were extracted directly without any manual modification. In this figure, p value was 4.63E-5 and the fold change of ELANE in acute myeloid leukemia was 6.774 compared with monocyte samples in the Stegmaier leukemia microarray.

Microarray correlation analysis

To address the role of ELANE in leukemia, MYC and TP53 were used as internal references for the Pearson correlation analysis of ELANE.

Clinical significance of ELANE in leukemia patients

Overall survival (OS) of ELANE in leukemia patients was accessed using a data set of patients originally derived from Metzeler acute myeloid leukemia microarray as previously described [8, 9].

Statistical analysis

Gene expression was considered to be dramatically changed if the p-value was less than 5%. For survival analysis, the overall survival rate was performed using a log-rank test and considered to be different if the p-value
ELANE predicts leukemia progression

**Results**

**ELANE mRNA is highly expressed in patients with leukemia**

To compare ELANE expression in leukemia patient samples, the original Series Matrix. txt File(s) of Stegmaier leukemia [10] and Coustan-Smith leukemia [11] were downloaded from Gene Expression Omnibus (GEO). Original intensity files were performed MAS 5.0 normalization before further analysis. As shown in Figure 1, mRNA level of ELANE was highly expressed in acute myeloid leukemia samples compared to the normal monocyte cells, with a total of 28.428 fold change in Stegmaier leukemia.

Furthermore, mRNA level of ELANE was also found to be significantly increased in T- and B-cell childhood acute myeloid leukemia samples compared to the CD10+ and CD19+ hematogone (Figures 2 and 3).

**ELANE is positively correlated with pro-oncogene MYC expression and negatively correlated with tumor suppressor TP53 expression in leukemia samples**

To address the role of ELANE in leukemia progression, correlation analysis of ELANE and MYC/TP53 was conducted using Herold [12, 13], Kirschner [14] and Metzeler [8] datasets. As a tumor suppressor that governed tumor progression, TP53 has been reported to suppress leukemia cell growth and increase the overall survival time in leukemia patient. As shown in Figures...
**ELANE predicts leukemia progression**

**Figure 5.** Correlation analysis of **ELANE** and **MYC** or **TP53** expression in Kirschner-Schwabe, acute lymphoblastic leukemia (n = 60). In this figure, the best-fit values of the slopes were 0.01652 ± 0.06522 (A. ELANE ID 206871_at vs. MYC ID 202431_s_at), -0.06860 ± 0.06239 (B. ELANE ID 206871_at vs. TP53 ID 201746_at) and -0.05521 ± 0.04437 (C. ELANE ID 206871_at vs. TP53 ID 211300_s_at), which indicated that **ELANE** was negatively correlated with **TP53**, but positively correlated with **MYC** in Kirschner-Schwabe, acute lymphoblastic leukemia microarray.
ELANE predicts leukemia progression

4-6, expression of ELANE was found to be consistently negatively correlated with TP53 expression. Additionally, ELANE was positively correlated with the expression of MYC (Figure 5A). In conclusion, our data strongly suggested that ELANE served as an oncogene in leukemia patients.

Low expression of ELANE suggested a good prognosis in leukemia patients

The clinical significance of ELANE was further validated by Metzeler acute myeloid leukemia patients [8]. Both of Figures 7 and 8 indicated that mRNA level of ELANE with a relatively lower expression predicted a good survival in leukemia patients compared to the high expression group.

Discussion

Microarrays have enabled researchers to conduct large-scale quantitative assessments of gene expression, defining the transcriptome of a multitude of cellular types and states [15]. In addition, gene expression microarrays provide a snapshot of all the transcriptional activity in a biological sample. Collectively, the Gene Expression Omnibus (GEO) at the National Center for Biotechnology Information (NCBI) has emerged as the leading fully public repository for gene expression data. To better address the role of ELANE in leukemia progression, in this present study, we delineated the expression, correlation and survival of ELANE using the datasets downloaded from GEO. As a result, ELANE was found to be highly expressed in leukemia sample. In addition, mRNA level of ELANE was positively correlated with pro-oncogene MYC and negatively correlated with tumor suppressor TP53, suggesting that ELANE may act as an oncogene in leukemia. Finally, this prediction was validated by the survival analysis in Metzeler acute myeloid leukemia patients.

TP53 [16] (tumor protein with MW ~53 kDa) is a tumor suppressor gene found on chromo-
ELANE predicts leukemia progression

Maximally selected rank statistics

<table>
<thead>
<tr>
<th>Expression of 206871_at (ELANE)</th>
</tr>
</thead>
</table>

206871_at (ELANE)

<table>
<thead>
<tr>
<th>Expression signal</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Samples</th>
</tr>
</thead>
</table>

GenomicScape=2.0

Metzeler, Acute myeloid leukemia 1 (Affy_133 plus 2)

| n = 79, OSID: OS-DY-26 |

P = 0.019, HR = 2.1

ELANE Expression Signal <= 9607.86: n = 62 (78.5%)

ELANE Expression Signal > 9607.86: n = 17 (21.5%)

Figure 8. Overall survival analysis of ELANE in the Metzeler acute myeloid leukemia 1 dataset. Survival analysis was performed using a log-rank test. In this figure, high and low groups of ELANE were defined using the expression of ELANE (ID: 206871_at) in Metzeler acute myeloid leukemia 1 microarray with a cut-off of 9607.86. For the high expression of ELANE group (expression > 9607.86, red line), the overall survival time was shorter compared with the low expression group (expression ≤ 9607.86, blue line) with p value of 0.019.

ELANE predicts leukemia progression

Some 17 that is involved in DNA repair [17, 18], cell cycle arrest [19], and apoptosis [20], and its overexpression is a hallmark of many human cancers [21]. TP53 drew initial attention from cancer community because its expression was frequently detected in acute myeloid leukemia (AML) patients and closely connected with the prognosis in leukemia patients [22, 23]. It has been validated that a higher expression of the wild-type TP53 in leukemia may accelerate the apoptotic process. In our study, ELANE was found to be negatively correlated with TP53 expression, which indicated that ELANE was an oncogenic gene in leukemia progression.

Unlike TP53, MYC (c-MYC) is a tumor suppressor that codes for a transcription factor. A mutated version of MYC is found in cancers [24], which finally causes MYC to be constitutively expressed. Malfunctions in MYC have also been found in carcinoma of the cervix, colon, breast, lung and stomach [25]. MYC is thus viewed as a promising target for anti-cancer drugs. In our study, ELANE was found to be positively correlated with MYC expression, which further validated our hypothesis of the oncogenic role of ELANE in leukemia progression.

Microarray technology is essentially a measurement tool for measuring expressions of genes and gene expressions could be employed as predictors of patient survival. In this study, the clinical significance of ELANE was further validated by Metzeler acute myeloid leukemia patients. Finally, we discovered that low expression of ELANE predicted a good survival in leukemia patients.

In conclusion, in this study, the role of ELANE in leukemia patients was determined using the public available microarray datasets and demonstrate that ELANE might be a potential therapeutic target against leukemia.

Acknowledgements

We would like to thank Gene Expression Omnibus (GEO) and Oncomine for making their data readily available to the scientific community. This work was supported by National Natural Science Foundation of China (No. 8106-0162, No. 81460284, No. 81460051, No. 31-560039), National Science Foundation of Qinghai Provincial (No. 2014-ZJ-944Q, No. 2015-ZJ-744, 2015-ZJ-929Q, 2015-ZJ-731), Construction of Laboratory of Qinghai Province (No. 2015-ZY-23). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure of conflict of interest

None.

Address correspondence to: Rong Wang, Department of Biochemistry, Medical College of Qinghai University, No. 16 Kunlun Road, Chengxi District, Xining 810001, Qinghai Province, China. Tel: +86-971-6108393; Fax: +86-971-6108393; E-mail: qhwr2007@163.com
ELANE predicts leukemia progression

References


ELANE predicts leukemia progression

G and Hilal G. Different TP53 mutants in p53 overexpressed epithelial ovarian carcinoma can be associated both with altered and unaltered glycolytic and apoptotic profiles. Cancer Cell Int 2018; 18: 14.


