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Original Article

Overexpression of TIGAR predicts poor prognosis in elderly patients with cytogenetically normal acute myeloid leukemia (CN-AML)

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Abstract: Background: Elderly patients with acute myeloid leukemia (AML) have poor clinical outcomes and cytogenetically normal (CN)-AML shows great heterogeneity. Leukemic cells exhibit increased aerobic glycolysis. TP53-induced glycolysis and apoptosis regulator (TIGAR) decreases glycolysis and correlates with tumor survival. The objectives of this study were to investigate *TIGAR* expression in elderly patients with *de novo* CN-AML and correlate the results with clinical features and outcomes. Patients and Methods: We explored the expression of *TIGAR* by real-time quantitative PCR and its correlation with other prognostic factors, overall survival (OS) and disease-free survival (DFS) in 75 elderly patients with *de novo* CN-AML. Results: No significant differences were observed between patients with high and low expression of *TIGAR* for most clinical features, while patients with low expression of *TIGAR* were more prone to have high incidence of *CEBPA* mutations (P=0.0383). Patients with low expression of *TIGAR* had significantly longer OS (P=0.0054) and DFS (P=0.0124) compared to patients with high expression of *TIGAR*. The overexpression of *TIGAR* was associated with a significantly higher relapse rate (P=0.0138) and cumulative incidence of relapse (P=0.004). A multivariate analysis revealed that high *TIGAR* expression was associated with shorter OS (P=0.029) and DFS (P=0.045). Conclusion: Our study identified that the overexpression of *TIGAR* was closely correlated with worse clinical outcome in elderly patients with CN-AML, suggesting that TIGAR may be an independent prognostic factor and a therapeutic target of this devastating and heterogenetic malignancy.

Keywords: TP53-induced glycolysis and apoptosis regulator (TIGAR), glycolysis, cytogenetically normal acute myeloid leukemia (CN-AML), prognosis, relapse

Introduction

Acute myeloid leukemia (AML) presents in all ages, but is mainly a disease of the elderly with a median age of 65 to 70 years [1, 2]. Survival for many elderly patients with AML is only 2-6 months, because of the high degree of resistance to conventional chemotherapy, high frequency of adverse cytogenetics, decreased performance status, and comorbid conditions [3-5]. Even though risk stratification based on cytogenetic characteristics divides AML patients into three subgroups, favorable, intermediate and unfavorable risk cytogenetics, as well as numerous molecular markers (e.g. *NPM1, FLT3, CEBPA, c-kit, LEF1, ID1* and *GATA2*), have been proven to predict the outcome of CN-AML. Furthermore, among these, *NPM1* and *FLT3-ITD* mutations represent the most frequent molecular aberrations [6-8] and cytogenetically normal-AML (CN-AML) shows great heterogeneity [9]. Additionally, myeloid leukemogenesis may involve the abnormal expression of transcription factors regulating the proliferation, differentiation and survival of myeloid progenitors [10]. Thus, there is an increasing need to improve the risk stratification in elderly patients with CN-AML using molecular biomarkers.

The metabolic properties of cancer cells diverge significantly from those of normal cells. Over the past decade, cancer metabolism has received a substantial amount of interest.

Metabolic reprogramming in cancer has been increasingly recognized, as numerous connections between oncogenic signaling pathways and metabolic activities emerge [11, 12].

Leukemic cells exhibit increased aerobic glycolysis and take advantage of this metabolic pathway to generate ATP. TP53-induced glycolysis and apoptosis regulator (TIGAR) has been directly implicated in cellular metabolism by altering the concentration of fructose 2, 6-bisphosphate (Fru-2, 6-BP) in cells, which subsequently lowers the activity of phosphofructosekinase-1 (PFK1). This is a key step in the control of glycolysis. P53 negatively regulates glycolysis through the activation of TIGAR [13]. TIGAR blocks glycolysis and promotes cellular metabolism *via* the pentose phosphate pathway (PPP). It promotes the production of cellular nicotinamide adenine dinucleotide phosphate (NADPH), which leads to the enhanced scavenging of intracellular reactive oxygen species (ROS) and the inhibition of oxidative stress-induced apoptosis in normal cells [14]. Hence, TIGAR expression results in slowing down the glycolysis pathway. Moreover TIGAR has been found to be elevated in several human tumor types [15-20]. However, molecular changes leading to altered metabolic activity and the role of *TIGAR* in elderly patients with CN-AML remains poorly understood. In this study, we sought to investigate *TIGAR* expression in elderly patients with CN-AML, and correlated these results with clinical features and outcomes.

Patients and methods

Patients and samples

Our study enrolled 75 previously untreated de novo AML patients aged ≥60 years with newly diagnosed de novo AML between September 2004 and May 2015, according to the 2008 WHO classification [21]. All patients were diagnosed, treated and followed-up at the Department of Hematology, the First Affiliated Hospital of Nanjing Medical University. Complete clinical data was available in all enrolled patients and enough cryopreserved bone marrow (BM) samples were taken at diagnosis for analysis. Twenty normal donors were enrolled for comparison. This study was approved by the Institutional Review Board of the First Affiliated Hospital of Nanjing Medical University, and was carried out in accordance with the Declaration of Helsinki. All patients and normal donors provided written informed consent.

Measurement of TIGAR mRNA expression by real-time quantitative PCR (qPCR)

TIGAR mRNA expression was detected by real-time quantitative PCR. Total RNA was isolated from BM mononuclear cells (MNCs). RNA was reverse-transcribed using random hexamers, and cDNA was added to the final PCR reaction mixture of fluorescent dye SYBR Green I, PCR Master Mix, TIGAR primers (forward primer: 5'-GAGCCCACATTACACTGAC-3', reverse primer: 5'-GCCTCGGACTAAACCTAAC-3'), or β-actin internal control primers (forward primer: 5'-AGCGAGCATCCCCCAAAGTT-3', reverse primer: 5'-GGGCACGAAGGCTCATCATT-3'). Reactions for qPCR were conducted in triplicate using the Applied Biosystems ABI 7300 Real-time PCR system (Applied Biosystems software: SDSv-2.0). Each reaction mixture contains 2 μL of cDNA, 10 μL of SYBR Green PCR Master Mix (Applied Biosystems), 1 μL of TIGAR or β-actin primers, and deionized water, to a total volume of 20 μL. Cycle conditions for TIGAR and β-actin were one cycle for five minutes at 95°C, 35 cycles for 30 seconds at 95°C, 30 seconds at 58°C, 30 seconds at 72°C, and finally, one cycle for 10 minutes at 72°C. The threshold cycle (Ct) was defined as the fractional cycle number at which the fluorescence passes the fixed threshold, and each sample was normalized based on its endogenous β-actin RNA content. The relative amount of TIGAR mRNA was calculated by the Ct comparison method, using the equation $2^{-\Delta\Delta Ct}$. Patients with TIGAR expression values above the median of all patients were defined as having high TIGAR expression ($TIGAR^{high}$), while the remaining patients were considered to have low TIGAR expression ($TIGAR^{low}$).

Cytogenetic and mutation analyses

BM cells were harvested directly or after 1-3 days of unstimulated culture, as previously described [22]. Metaphase cells were banded via an improved heat treatment and Giemsa R-banding method. The diagnosis of a normal karyotype was based on conventional cytogenetic examination of at least 20 metaphases. Genomic DNA was isolated from BM specimens. The mutation analysis of four relevant

Table 1. Clinical characteristics of the elderly patients with CN-AML according to their TIGAR expression levels

	All cases	$TIGAR^{high}$	$TIGAR^{low}$	*P*
Age (years), median (range)	66 (60~86)	66 (60~80)	67 (61~86)	> .05
Sex, male/female	39/36	20/18	19/18	> .05
WBC, median (range)	21 (0.8~291)	19 (0.8~291)	21 (1.3~169)	> .05
Hb, median (range)	87 (49~148)	79 (39~154)	87 (39~148)	> .05
PLT, median (range)	50 (2~295)	42 (10~190)	37 (2~295)	> .05
PB blasts (%), median (range)	64 (0~98)	64 (0~98)	56 (0~96)	> .05
BM blasts (%), median (range)	73.6 (11.6~96.2)	75 (11.6~96.2)	72 (24~93.6)	> .05
NPM1 (+)	23.9% (17/71)	23.5% (8/34)	24.3% (9/37)	> .05
CEBPA (+)	21.1% (15/71)	8.8% (3/34)	32.4% (12/37)	.0383
FLT3-ITD (+)	14.1% (10/71)	14.7% (5/34)	13.5% (5/37)	> .05
c-kit (+)	7.0% (5/71)	5.9% (2/34)	8.1% (3/37)	> .05

Abbreviations: BM = bone marrow; Hb = hemoglobin; PB = peripheral blood; PLT = platelets; WBC = white blood cells.

molecular marker genes (NPM1, CEBPA, FLT3-ITD and c-kit) was carried out as previously described [23, 24].

Statistical analyses

Data in our study was statistically analyzed using the Statistical Package for Social Science (SPSS version 16.0). The primary endpoints were overall survival (OS; duration from diagnosis to last follow-up or death), disease-free survival (DFS; time from achievement of complete remission [CR] until last follow-up, relapse or death), and morphologic leukemia relapse (hematologic and/or extramedullary). Statistical significance was considered at $P<0.05$. Possible differences between continuous variables were analyzed using the Mann-Whitney U-test. Chi-square or Fisher's exact tests were performed to compare incidences. The Kaplan-Meier method was employed to estimate survival probabilities, and the log-rank test was employed for univariate comparisons. The probabilities of relapse were calculated by cumulative incidence curves. The association between TIGAR expression or other characteristics and OS were studied using the Cox's proportional hazards regression model.

Results

TIGAR expression and clinical characteristics of elderly patients with CN-AML

The clinical characteristics of the 75 patients are shown in **Table 1**. Among these patients, 23 patients were with M_1, 31 patients were with M_2, seven patients were with M_4, 10 patients were with M_5, and four patients were with M_6, respectively. The median age of patients was 66 years (range: 60-86 years), with a male/female ratio of 1.08:1. Among those patients, 29 patients (38.7%) were ≥70 years of age. Performance status score of patients according to the Eastern Cooperative Oncology Group (ECOG) was 0-2. All patients in this study had normal karyotypes and received a combination of cytarabine and anthracycline-based induction or D-CAG regimen, as previously described; and none of these patients underwent hematopoietic stem cell transplantation [25]. Furthermore, no significant differences were observed between the $TIGAR^{high}$ and $TIGAR^{low}$ groups for most clinical characteristics, including white blood cell (WBC) count, hemoglobin (Hb) level, platelet count, the percentage of peripheral blood (PB) blasts and BM blasts. In addition, no association was found between TIGAR expression and mutations in the NPM1, FLT3-ITD or c-kit genes. Notably, patients in the $TIGAR^{low}$ group were more prone to have high incidences of CEBPA mutations (P=0.0383).

Impact of TIGAR expression level on survival in elderly patients with CN-AML

Median follow-up period of the entire cohort was 11 months (range: 0.5-93 months). Median OS for all the patients was 12 months (**Figure 1A**). Median DFS for the 48 patients that achieved CR was 12 months (**Figure 1B**). Median OS and DFS were similar between patients aged ≥70 years and patients aged

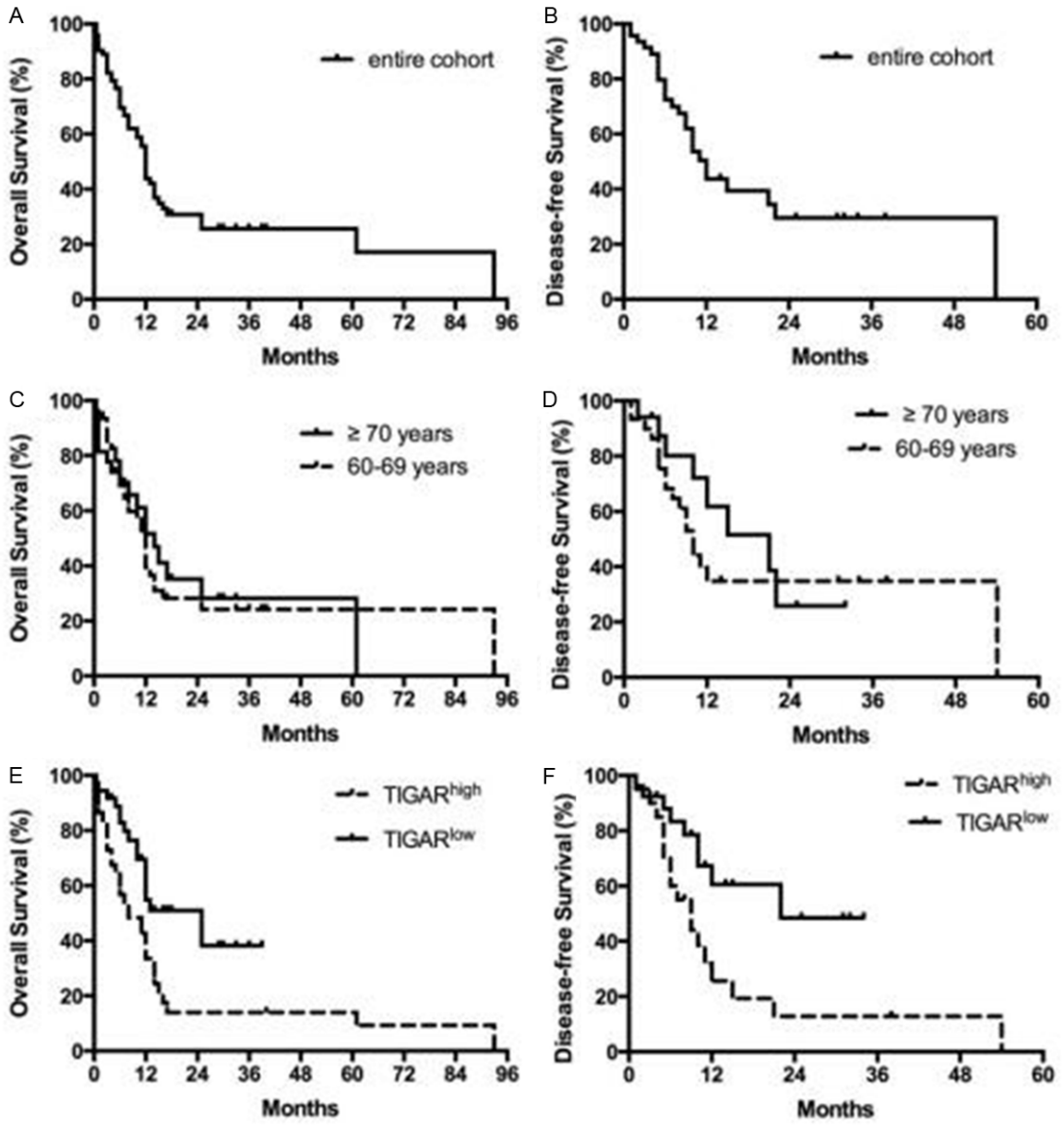

Figure 1. Overall survival (OS) and disease free survival (DFS) in elderly patients with CN-AML. (A) OS and (B) DFS of the entire cohort. (C) OS and (D) DFS of the patients aged ≥ 70 years or 60-69 years. (E) OS and (F) DFS of the patients with high or low expression of TIGAR.

60-69 years (**Figure 1C** and **1D**; P=0.7377 and P=0.3682). Patients in the $TIGAR^{high}$ group revealed a trend towards a lower CR rate than patients in the $TIGAR^{low}$ group (54.1% vs. 74.3%), but the difference was not statistically significant (P=0.0898). This was possibly due to the relatively small cohort. Patients in the $TIGAR^{high}$ group revealed a significantly higher relapse rate than patients in the $TIGAR^{low}$ group (37.8% vs. 11.4%, P=0.0138). Noticeably, patients in the $TIGAR^{low}$ group had a significantly longer OS (8 months vs. 25 months, P=0.0054, **Figure 1E**) and DFS (9 months vs. 22 months, P=0.0124, **Figure 1F**), and a significantly lower cumulative incidence of relapse (P=0.004), compared with patients in the $TIGAR^{high}$ group (**Figure 2**).

Prognostic impact of TIGAR expression level in elderly patients with CN-AML

A multivariate analysis was conducted to determine the prognostic significance of TIGAR expression after adjustment for other known

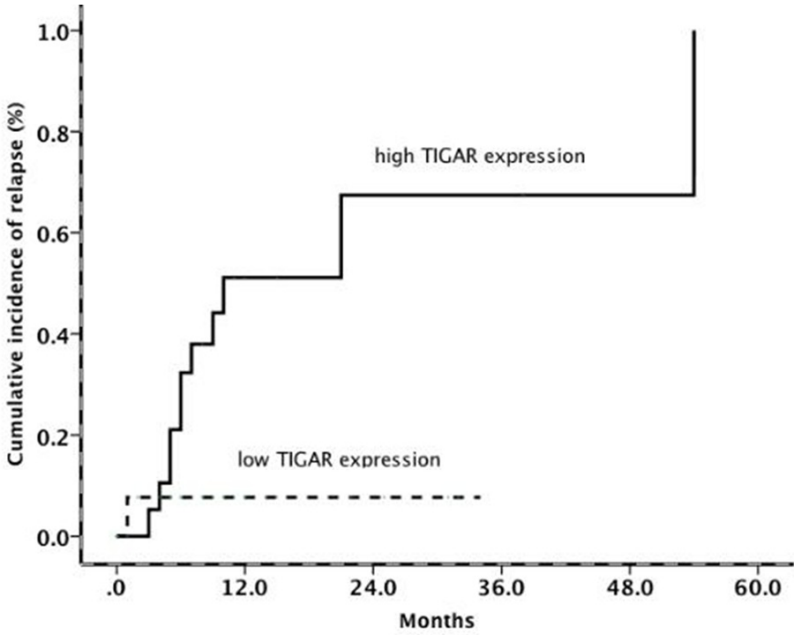

Figure 2. Cumulative incidence of relapse in patients with high or low TIGAR expression.

risk factors including WBC count, Hb level, platelet count, the percentage of BM and PB blasts, and NPM1, CEBPA, FLT3-ITD and c-kit mutations (**Table 2**). High TIGAR expression was associated with shorter OS (P=0.029) and DFS (P=0.045). Another prognostic factor associated with longer OS was CEBPA mutations (P=0.017).

Discussion

Elderly patients with AML are consistently associated with worse survival, which is attributable for tumor biology including a higher incidence of high-risk genetics and secondary leukemia, unique patterns of deregulated signaling pathway variations, and decreased treatment tolerance [2, 26, 27]. However, the prognostic factors of CN-AML in the elderly have not been sufficiently explained. To the best of our knowledge, the present study is the first to examine the prognostic relevance of *TIGAR* expression in elderly patients with *de novo* CN-AML. Our data revealed that *TIGAR* overexpression correlated with OS, DFS and the cumulative incidence of relapse. This represents an independent prognostic factor, and is irrespective of most of the other molecular factors. Patients in the *TIGAR*^{low} group were more prone to have high incidences of *CEBPA* mutations, possibly indicating that low expression levels of *TIGAR* and *CEBPA* mutations were both good risk factors.

Energy production in cancer cells is abnormally dependent on aerobic glycolysis. TIGAR, as a p53 target, functions to lower Fru-2, 6-BP levels and upregulates glucose-6-phosphate dehydrogenase in cells. This results in the inhibition of glycolysis and the enhancement of PPP to produce NADPH and ribose-5-phosphate, which are crucial for nucleotide synthesis and DNArepair [28]. Increased glycolysis has been associated with resistance to chemotherapy and poorer clinical outcomes that concern solid cancers and acute lymphoblastic leukemia (ALL) [29-31]. Similarly, enhanced glycolysis was observed in AML; and altered metabolic activity has opened a window of opportunity for therapeutic intervention in AML [11, 32]. Highly glycolytic AML blasts including cell lines and primary cells are more resistant to apoptosis induced by all-trans retinoic acid and/or arsenic trioxide *in vitro* [33, 34]. Glycolysis inhibitor treatment resulted in growth arrest and cell death in pre-B ALL, T-ALL and AML cell lines [35]. Our clinical observation revealed that the overexpression of *TIGAR* was associated with a relatively lower CR rate, significantly poorer survival, and higher incidences of relapse; which is in line with several previous studies that reported elevated *TIGAR* expression levels in human cancers [15-20]. Taken together, we speculate that glycolysis can induce TIGAR expression; and in turn, this higher TIGAR expression can inhibit glycolysis. Nevertheless, contrary to previous held views, Herst *et al.* demonstrated that high levels of glycolytic metabolism at diagnosis of AML were predictive of a significantly improved duration of CR1 and OS, following remission induction chemotherapy [34]. It may be interpreted that highly glycolytic cells have a limited energy budget, which is sensitive to nutrient stress. Hence, highly glycolytic AML blasts are sensitized to chemotherapy-induced apoptosis *in vivo* as a result of their position in the hypoxic and nutri-

Table 2. Multivariable analysis with overall survival (OS) and disease-free survival (DFS) in elderly patients with CN-AML

Variable	OS		DFS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
WBC	1.006 (0.995-1.017)	0.264	1.003 (0.994-1.012)	0.572
Hb	1.005 (0.974-1.036)	0.758	0.988 (0.961-1.015)	0.370
PLT	0.997 (0.990-1.005)	0.496	0.997 (0.990-1.005)	0.484
PB blast (%)	0.986 (0.952-1.021)	0.420	0.990 (0.958-1.024)	0.558
BM blast (%)	1.019 (0.979-1.062)	0.356	1.019 (0.981-1.059)	0.335
NPM1, wild type *VS* mutated	7.488 (0.940-59.644)	0.057	3.659 (0.622-21.525)	0.151
CEBPA, wild type *VS* mutated	9.471 (1.484-60.425)	0.017	2.329 (0.485-11.183)	0.291
FLT3-ITD, wild type *VS* mutated	1.314 (0.361-4.783)	0.679	0.812 (0.252-2.621)	0.728
c-kit, wild type *VS* mutated	2.005 (0.177-22.643)	0.574	0.472 (0.048-4.693)	0.522
TIGAR expression, high *VS* low	3.089 (1.120-8.519)	0.029	2.416 (1.021-5.721)	0.045

Abbreviations: OS = overall survival; DFS = disease-free survival; WBC = white blood cells; Hb = hemoglobin; PB = peripheral blood; PLT = platelets; BM = bone marrow.

ent-poor endosteal BM niche. These *in vitro* experiments were performed in cell culture medium, where glucose and other nutrients with excess supply do not sufficiently mimic the *in vivo* microenvironment of the BM niche. Moreover, many cancer cells are still able to use mitochondrial oxidative phosphorylation for ATP production, which may lead to resistance to glycolysis inhibitors [35]. Therefore, the correlation of glycolysis with the prognosis of AML remains unclear. Hence, future studies would permit mechanisms on the metabolic activity of AML.

In summary, our study identified that high *TIGAR* expression is closely correlated with worse clinical outcome in elderly patients with *de novo* CN-AML; suggesting that *TIGAR* may be an independent prognostic factor and a therapeutic target for this devastating and heterogenetic malignancy. Admittedly, our analysis was limited by its retrospective nature and the relatively small number of samples available for testing; which precludes subset analysis. Further larger scale investigations are needed.

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Disclosure of conflict of interest

None.

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