Overexpression of lncRNA *PANDAR* predicts adverse prognosis in acute myeloid leukemia

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Background and purpose: Abundant studies have shown that lncRNA *PANDAR* plays an oncogenic role in human solid tumors. Although abnormal expression of *PANDAR* has been well investigated in solid tumors, it was rarely studied in hematologic diseases. Hence, the aim of this study was to determine the *PANDAR* expression level and its clinical significance in patients with acute myeloid leukemia (AML).

Materials and methods: For detecting the expression level of *PANDAR* in 119 AML patients and 26 controls, real-time quantitative PCR was used in this study. The prognostic values were evaluated by using Kaplan–Meier analysis, Cox regression analyses, and logistic regression analysis.

Results: *PANDAR* was significantly overexpressed in AML and might be a promising biomarker which could distinguish AML from normal samples ($P < 0.001$). Patients with high expression of *PANDAR* (*PANDAR*^{high}) were older and showed higher bone marrow blasts than patients in *PANDAR*^{low} group ($P = 0.029$ and 0.032 , respectively). Significant differences between these groups were also detected regarding risk group and karyotype finding ($P = 0.009$ and 0.041 , respectively). Importantly, *PANDAR*^{high} patients presented a significant lower complete remission rate compared to *PANDAR*^{low} patients ($P < 0.001$). Furthermore, Kaplan–Meier analysis showed that *PANDAR*^{high} patients had shorter overall survival compared to *PANDAR*^{low} patients observing the whole AML cohort, and also in the non-M3 group of patients ($P < 0.001$ and $P = 0.005$, respectively). Multivariate analysis of Cox and logistic regression analysis confirmed that high *PANDAR* expression was an independent unfavorable risk factor for overall survival and complete remission in both observed patient groups.

Conclusion: These results revealed that *PANDAR* was overexpressed in AML, and that higher *PANDAR* expression was associated with poor clinical outcome. Our study therefore suggests that *PANDAR* expression is a promising biomarker for prognostic prediction for AML.

Keywords: long noncoding RNA, *PANDAR* expression, acute myeloid leukemia, complete remission, overall survival

Introduction

Acute myeloid leukemia (AML) is a cytogenetically and molecularly heterogeneous disease which is marked by uncontrolled clonal expansion of blast cells.¹ Although the new treatment strategies based on molecular biology of AML have been adopted in recent years, the prognosis of the disease remains poor.^{2–4} It has become apparent that karyotype abnormalities have important value for AML diagnosis classification, prognostic evaluation, and guiding individual treatment.^{5,6} Cytogenetic aberrations together with several gene mutations including *NPM1*, *CEBPA*, *TP53*, *TET2*, *DNMT3A*,

and *FLT3-ITD* have a strong impact on clinical outcome of AML patients.⁷ In addition to genetic abnormalities, the aberrant expression of some genes, such as overexpression of *ERG*, *BAALC*, and *EVII*, also has been proven to affect prognosis for AML patients.⁷ These important findings open up a new field for discovering novel promising biomarkers for AML patients, especially for those who are at risk of poor outcome, so that these patients can be treated with optimized treatment strategies.

Long noncoding RNAs (lncRNAs) are regarded as a kind of noncoding RNA, which are longer than 200 nucleotides. Recently, many studies have reported that lncRNAs play vital roles in gene expression regulation through association with key transcription factors and microRNAs.^{8,9} lncRNAs could act as an important component in every step of cell biology, which includes the adjustments of transcription initiation and transcription and posttranscriptional level.¹⁰ Recently, increasing number of research papers revealed that lncRNAs were relevant to many human diseases, especially to human cancers, and many studies began to explore the molecular mechanisms of lncRNA function in the pathogenesis of these disease or cancers.¹¹ With the deepening of the research, it is becoming increasingly apparent that most of the susceptibility to cancer is not caused by the variation of coding sequences of DNA but by the noncoding regulatory sequences, especially by lncRNAs.¹⁰

lncRNA *PANDAR*, which is located at 6p21.2, plays a vital role in regulation of apoptosis by inhibiting the expression of proapoptotic genes through interaction with the transcription factor *NF-YA*.¹² To date, the abnormal expression of *PANDAR* has been reported in various solid cancers, such as hepatocellular carcinoma, gastric cancer, and breast cancer.¹³ However, there are few reports about the expression of *PANDAR* in blood cancer. Therefore, we focused on exploring the *PANDAR* expression level and its connection with clinical implication in AML patients.

Materials and methods

Patients and treatment

A total of 119 de novo AML patients and 26 healthy donors were included in the present research, which was approved by the Ethics Committee and Institutional Review Board of the Affiliated People's Hospital of Jiangsu University. Bone marrow (BM) was collected from all the participants after they signed the informed consents. BM mononuclear cells (BMMNCs) were extracted from BM specimen using Lymphocyte Separation Medium (TBD Sciences, Tianjin,

People's Republic of China). Treatment protocols for AML were described previously.¹⁴

Cytogenetics and mutation analysis

By conventional R-banding method, karyotype was analyzed at the time of initial diagnosis. Risk classification based on the karyotype findings has been done as previously reported.¹⁵ Mutations in *C-KIT*, *NPM1*, *DNMT3A*, *N/K-RAS*, and *U2AF1* were detected by high-resolution melting analysis,^{16–20} whereas *FLT3-ITD* and *CEBPA* mutations were detected by direct DNA sequencing.^{21,22}

RNA isolation and reverse transcription

Total RNA was extracted by using Trizol reagent (Invitrogen, Carlsbad, CA, USA). The specific procedure of reverse transcription was conducted as previously reported.²³

Real-time quantitative PCR

The primers for *PANDAR* are as follows: forward: 5'-CTCCATCATGCCAA GTTCTGC-3' and reverse: 5'-GAAGGCAGGCAAGACTCGAA-3'. *PANDAR* expression was detected by real-time quantitative PCR using AceQ qPCR SYBR Green Master Mix (Vazyme Biotech Co., Piscataway, NJ, USA). The reaction condition of real-time quantitative PCR was conducted as reported earlier.^{24,25} Relative *PANDAR* expression levels were calculated by $2^{-\Delta\Delta CT}$ method.

Statistical analysis

SPSS software version 20.0 (IBM Corporation, Armonk, NY, USA) was used to carry out the statistical analysis. Meanwhile, receiver operating characteristic (ROC) curve and area under the ROC were applied to assess the value of *PANDAR* expression. Besides, Pearson's chi-squared analysis was conducted to detect the difference of categorical variables between *PANDAR*^{high} group and *PANDAR*^{low} group. Through Kaplan–Meier method and Cox regression analysis, the effect of *PANDAR* expression on prognosis was analyzed. Logistic regression analysis was used to identify the independent risk factors of complete remission (CR). In all tests, $P < 0.05$ was defined as statistically significant.

Results

PANDAR expression in AML

The expression level of *PANDAR* in controls ranged from 0.000 to 2.926 (median 0.294). *PANDAR* transcript level in AML patients ranged from 0.005 to 306.109 (median 1.862). Through nonparametric test, *PANDAR* was found to be sig-

nificantly upregulated in AML ($P<0.001$, Figure 1). Besides this, significant upregulation of *PANDAR* was also found in non-M3-AML and cytogenetically normal AML subgroup of patients (Figure 1).

Distinguishing capacity of *PANDAR* expression

The ROC curve analysis was applied to evaluate whether *PANDAR* expression could be used as a biomarker for the diagnosis of AML. The results showed that area under the curve value was 0.800 (95% CI: 0.716–0.883), which suggested the *PANDAR* expression level might be a potential biomarker in discriminating AML from controls ($P<0.001$, Figure 2A). In addition, when the cutoff value was 0.840, the sensitivity and specificity of diagnosis of AML were 65.5% and 80.8%. For non-M3-AML and CN-AML patients, significant differences also existed (Figure 2B and C, respectively).

The connection between *PANDAR* expression level and clinical characteristics in AML

By the set cutoff value based on the basis of ROC curve, the whole cohort of AML patients was divided into two groups.

Figure 1 Expression of *PANDAR* in controls, whole-cohort AML patients, non-M3 AML patients, and CN-AML patients.

Notes: The distributions of the *PANDAR* expression in controls, whole-cohort AML patients, non-M3 AML patients, and CN-AML patients are presented with scatter plots. The median level of *PANDAR* expression in each group is shown with horizontal line.

Abbreviations: AML, acute myeloid leukemia; CN-AML, cytogenetically normal AML.

Figure 2 Discriminative capacity of *PANDAR* expression by ROC curve analysis.

Notes: (A) For whole-cohort AML. (B) For non-M3 AML. (C) For CN-AML.

Abbreviation: AML, acute myeloid leukemia; AUC, area under the curve; CN-AML, cytogenetically normal AML; ROC, receiver operating characteristic.

Clinical features and laboratory parameters representation between *PANDAR*^{high} and *PANDAR*^{low} groups is separately shown in Table 1. No significant differences were observed in sex, white blood cells (WBCs), hemoglobin, and platelets between two groups ($P>0.05$). However, patients with *PANDAR* high expression were older than patients in the *PANDAR* low-expressed group ($P=0.029$). Patients in *PANDAR*^{high} group showed higher BM blasts than patients in *PANDAR*^{low} group ($P=0.032$). Moreover, significant differences between these two groups were also detected regarding risk group and karyotype finding ($P=0.009$ and 0.041 , respectively). Patients in *PANDAR*^{high} group had higher frequency of poor karyotypes (15%, 12/78) than patients in *PANDAR*^{low} group (2%, 1/41). There was no correlation between *PANDAR* expression and the common gene mutations (Table 1, $P>0.05$).

Effect of *PANDAR* expression on chemotherapy response in AML

In order to explore the impact of *PANDAR* expression in clinical prognosis with AML patients, we analyzed 115

AML patients with available follow-up data. Compared with *PANDAR*^{low} group, patients in *PANDAR*^{high} group had a lower CR rate ($P<0.001$, Table 1). We then analyzed the expression level of *PANDAR* in AML patients who achieved CR and those without CR, and showed it in scatter plots ($P<0.001$, Figure 3). Additionally, clinical characteristics of patients with CR and non-CR were further compared. Significant differences were found in *PANDAR* expression, age, WBCs, BM blast, risk group, and karyotype finding ($P<0.05$, Table 2). Logistic regression analysis including the most predictive factors was further performed which revealed that *PANDAR* expression was an independent risk factor that affected CR in whole-cohort AML and non-M3 AML patients ($P=0.010$ and 0.005 , respectively, Tables 3 and 4).

The relationship between *PANDAR* expression and prognosis in AML patients

The survival analysis indicated that in the whole-cohort AML patients with high *PANDAR* expression had a shorter

Table 1 Comparison of clinical manifestations and laboratory features between AML patients with low and high *PANDAR* expression

Patient's parameters	High (n=78)	Low (n=41)	P-value
Sex, male/female	52/26	27/14	1.000
Median age, years (range)	57 (15–86)	51 (17–80)	0.029
Median WBC, $\times 10^9/L$ (range)	13.2 (7–185.4)	5.7 (3–528)	0.214
Median hemoglobin, g/L (range)	78 (32–138)	76 (34–126)	0.569
Median platelets, $\times 10^9/L$ (range)	40 (5–415)	34 (4–264)	0.160
BM blasts, % (range)	49.8 (5.0–94.5)	30 (1.0–97.5)	0.032
Risk classification			0.009
Favorable	18 (23%)	18 (44%)	
Intermediate	42 (54%)	22 (54%)	
Poor	12 (15%)	1 (2%)	
No data	6 (8%)	0 (0%)	
Karyotype			0.041
Normal	34 (44%)	16 (39%)	
t(8;21)	4 (5%)	3 (8%)	
t(15;17)	14 (18%)	14 (34%)	
t(16;16)	0 (0%)	1 (2%)	
Complex	11 (14%)	1 (2%)	
Others	9 (12%)	6 (15%)	
No data	6 (7%)	0 (0%)	
Gene mutation			
<i>CEBPA</i> (+/-)	7/56	5/31	0.735
<i>NPM1</i> (+/-)	8/55	1/35	0.149
<i>FLT3-ITD</i> (+/-)	9/54	3/33	0.528
<i>C-KIT</i> (+/-)	2/61	1/35	1.000
<i>N/K-RAS</i> (+/-)	3/60	2/34	1.000
<i>IDH1/2</i> (+/-)	5/58	0/36	0.155
<i>DNMT3A</i> (+/-)	6/57	1/35	0.417
<i>U2AF1</i> (+/-)	3/60	0/36	0.552
CR (-/+)	53/21	14/27	<0.001

Abbreviations: AML, acute myeloid leukemia; BM, bone marrow; CR, complete remission; WBC, white blood cell.

Figure 3 Expression of *PANDAR* in CR and non-CR AML patients receiving induction therapy.

Notes: The distributions of the *PANDAR* expression in CR and non-CR groups are illustrated with scatter plots. The median level of *PANDAR* expression in each group is shown with horizontal line.

Abbreviations: AML, acute myeloid leukemia; CR, complete remission.

overall survival (OS) time than those who were in *PANDAR* low-expressed group ($P < 0.001$, Figure 4A). In non-M3 AML, patients with *PANDAR* high expression also had a shorter OS compared with those with *PANDAR* low expression ($P = 0.005$, Figure 4B). Regrettably, patients with *PANDAR* high expression did not presented a significant shorter OS than patients with *PANDAR* low expression among CN-AML ($P = 0.238$, Figure 4C). Multivariate analysis which included variables in univariate analysis with $P < 0.2$ (WBC [$\geq 30 \times 10^9/L$ vs $< 30 \times 10^9/L$], age [≤ 60 vs > 60 years], risk group [favorable vs intermediate vs poor], *PANDAR* expression [high vs low], gene mutations [mutant vs wild type]). Multivariate analysis further showed that *PANDAR* expression was a significant independent risk factor in affecting OS among whole-cohort AML patients and non-M3 AML patients ($P = 0.033$ and 0.032 , respectively, Tables 3 and 4).

Discussion

Lately, more and more researchers are devoted to exploring noncoding RNA and AML.²⁶ Many studies have proved

Table 2 Comparison of clinical manifestations and laboratory features between CR and non-CR in AML patients receiving induction therapy

Patient's parameters	CR (n=48)	Non-CR (n=67)	P-value
<i>PANDAR</i> expression	0.639 (0.005–190.798)	3.500 (0.051–306.109)	<0.001
Sex, male/female	30/18	46/21	0.551
Median age, years (range)	46.5 (18–81)	62 (17–86)	<0.001
Median WBC, $\times 10^9/L$ (range)	4.95 (0.3–528)	28.8 (0.7–185.4)	0.001
Median hemoglobin, g/L (range)	77.5 (34–126)	81 (32–138)	0.748
Median platelets, $\times 10^9/L$ (range)	32 (4–153)	42 (5–415)	0.073
BM blasts, % (range)	27 (1.0–97.5)	56 (5.0–94.5)	0.003
Risk classification			<0.001
Favorable	25 (52%)	8 (12%)	
Intermediate	20 (42%)	43 (64%)	
Poor	3 (6%)	10 (15%)	
No data	0 (0%)	6 (9%)	
Karyotype			<0.001
Normal	16 (34%)	33 (49%)	
t(8;21)	4 (8%)	3 (4%)	
t(15;17)	21 (44%)	4 (6%)	
t(16;16)	0 (0%)	1 (2%)	
Complex	3 (6%)	9 (13%)	
Others	4 (8%)	11 (17%)	
No data	0 (0%)	6 (9%)	
Gene mutation			
<i>CEBPA</i> (+/-)	5/37	7/48	1.000
<i>NPM1</i> (+/-)	3/39	6/49	0.728
<i>FLT3-ITD</i> (+/-)	4/38	8/47	0.545
<i>c-KIT</i> (+/-)	2/40	1/54	0.577
<i>N/K-RAS</i> (+/-)	0/42	5/50	0.067
<i>IDH1/2</i> (+/-)	0/42	5/50	0.067
<i>DNMT3A</i> (+/-)	3/39	4/51	1.000
<i>U2AF1</i> (+/-)	0/42	3/52	0.256

Abbreviations: AML, acute myeloid leukemia; BM, bone marrow; CR, complete remission; WBC, white blood cell.

Table 3 Univariate and multivariate analyses of variables for CR and OS in whole-cohort AML patients

Variables	CR			OS		
	Univariate analysis		Multivariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value	HR (95% CI)	P-value
WBC	0.261 (0.109–0.623)	0.002	0.442 (0.160–1.222)	0.116	2.361 (1.525–3.655)	<0.001
Age	0.138 (0.054–0.353)	<0.001	0.165 (0.058–0.467)	0.001	2.546 (1.639–3.956)	<0.001
PANDAR expression	0.205 (0.091–0.466)	<0.001	0.248 (0.109–0.742)	0.010	2.367 (1.453–3.856)	0.001
Risk classification	0.219 (0.107–0.451)	<0.001	0.307 (0.142–0.664)	0.003	2.091 (1.611–2.714)	<0.001
FLT3-ITD mutation	0.618 (0.173–2.211)	0.460	–	–	1.061 (0.526–2.140)	0.868
NPM1 mutation	0.628 (0.148–2.674)	0.529	–	–	1.871 (0.894–3.916)	0.096
CEBPA mutation	0.927 (0.272–3.155)	0.903	–	–	1.196 (0.593–2.415)	0.617
c-KIT mutation	2.700 (0.237–30.824)	0.424	–	–	0.684 (0.167–2.796)	0.597
N/K-RAS mutation	Undetermined	0.999	–	–	4.240 (1.625–11.064)	0.003
IDH1/2 mutation	Undetermined	0.999	–	–	4.859 (1.879–12.564)	0.001
DNMT3A mutation	0.981 (0.207–4.639)	0.980	–	–	1.123 (0.485–2.597)	0.787
UZAF1 mutation	Undetermined	0.999	–	–	5.353 (1.608–17.819)	0.006

Notes: Variables including WBC ($\geq 30 \times 10^9$ vs $< 30 \times 10^9$ /L), age (≤ 60 vs > 60 years), PANDAR expression (low vs high), risk classification (favorable vs intermediate vs poor), and gene mutations (mutant vs wild type). Multivariate analysis includes variables with $P < 0.200$ in univariate analysis.

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; HR, hazard ratio; OR, odds ratio; OS, overall survival; WBC, white blood cell.

Table 4 Univariate and multivariate analyses of variables for CR and OS in non-M3 AML patients

Variables	CR			OS		
	Univariate analysis		Multivariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value	HR (95% CI)	P-value
WBC	0.368 (0.138–1.001)	0.050	0.382 (0.126–1.164)	0.090	1.710 (1.083–2.699)	0.021
Age	0.190 (0.064–0.569)	0.003	0.221 (0.069–0.707)	0.011	1.780 (1.125–2.816)	0.014
PANDAR expression	0.223 (0.083–0.596)	0.003	0.210 (0.070–0.624)	0.005	2.063 (1.206–3.530)	0.008
Risk classification	0.435 (0.188–1.002)	0.051	0.633 (0.254–1.578)	0.327	1.692 (1.223–2.340)	0.001
FLT3-ITD mutation	0.467 (0.092–2.386)	0.360	–	–	1.138 (0.556–2.331)	0.723
NPM1 mutation	1.023 (0.234–4.478)	0.976	–	–	1.462 (0.695–3.075)	0.317
CEBPA mutation	1.571 (0.444–5.559)	0.483	–	–	0.905 (0.446–1.836)	0.781
c-KIT mutation	2.083 (0.125–34.750)	0.609	–	–	0.414 (0.057–2.992)	0.382
N/K-RAS mutation	Undetermined	0.999	–	–	4.023 (1.520–10.649)	0.005
IDH1/2 mutation	Undetermined	0.999	–	–	4.529 (1.736–11.811)	0.002
DNMT3A mutation	1.602 (0.330–7.781)	0.559	–	–	0.816 (0.349–1.907)	0.639
UZAF1 mutation	Undetermined	0.999	–	–	5.375 (1.596–18.102)	0.007

Notes: Variables including WBC ($\geq 30 \times 10^9$ vs $< 30 \times 10^9$ /L), age (≤ 60 vs > 60 years), PANDAR expression (low vs high), risk classification (favorable vs intermediate vs poor), and gene mutations (mutant vs wild type). Multivariate analysis includes variables with $P < 0.200$ in univariate analysis.

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; HR, hazard ratio; OR, odds ratio; OS, overall survival; WBC, white blood cell.

Figure 4 Prognostic value of *PANDAR* expression in AML.

Notes: (A) For whole-cohort AML patients. (B) For non-M3 patients. (C) For CN-AML patients. Overall survival was analyzed between *PANDAR*^{high} and *PANDAR*^{low} groups and performed by Kaplan–Meier method.

Abbreviations: AML, acute myeloid leukemia; CN-AML, cytogenetically normal AML; cum, cumulative.

that lncRNAs indeed played an important regulatory role in human cancers, and it was closely related with the occurrence and the development of various tumors.^{14,27} Also, increasing number of research papers have shown that the abnormal expression of *PANDAR* was connected with the tumorigenesis of various solid tumors.^{28–32} In the first report published by Hung et al, it was indicated that *PANDAR* inhibited the expression of proapoptotic genes by interacting with the transcription factor *NF-YA*.¹² Thereafter, Li et al²⁸ found

that *PANDAR* was upregulated in thyroid cancer. Further investigating the regulatory mechanism of *PANDAR*, Li et al²⁸ also found that knockdown of *PANDAR* could promote apoptosis of thyroid cells by reducing the expression of *Bcl2* and activating *Bax*. In addition, Sang et al³⁰ also reported that *PANDAR*, which was obviously upregulated in breast cancer tissues and cell lines, could affect the cell cycle by regulating its downstream target p16^{INK4A}. In summary, *PANDAR* played a significant role in various cancers, including in

cancer initiation and progression, and it could serve as an oncogene in these cancers.

In the studies examining the expression level of *PANDAR*, many reports showed that *PANDAR* was associated with the prognosis of cancers. For instance, Li et al found that *PANDAR* was upregulated in thyroid cancer tissue and cell lines, and it could be a promising therapeutic target and important biomarker for thyroid cancer.²⁸ Similarly, an article reported that the expression level of *PANDAR* in hepatocellular carcinoma was crucially associated with the size of tumor nodule, vascular invasion, and TNM stage.²⁹ Moreover, overexpression of *PANDAR* was relevant to the poorer survival and shorter recurrence duration for the disease in hepatocellular carcinoma patients, and it could be recognized as a potential tumor biomarker and therapeutic target.²⁹ However, the effect of *PANDAR* expression on prognosis in blood malignancies remains poorly defined. Findings from our study demonstrated that high expression of *PANDAR* indicated a poor prognosis in AML patients. *PANDAR* expression level influenced CR rate, with the *PANDAR*^{high} group having lower CR rate in comparison to the *PANDAR*^{low} group. Logistic regression analysis showed that *PANDAR* expression was an independent prognostic factor for CR. More importantly, Kaplan–Meier survival analyses clearly showed that patients with higher expression of *PANDAR* had a shorter OS than those patients with lower expression. Univariate and multivariate Cox regression analyses revealed the increased *PANDAR* expression was an independent unfavorable risk factor in AML patients.

Our study was the first to report that *PANDAR* was upregulated in AML and was also the first to demonstrate the prognostic value of *PANDAR* in AML.

Conclusion

Expression of *PANDAR* was frequently upregulated in AML, and high expression of *PANDAR* as an independent unfavorable risk factor for CR and OS in whole-cohort and non-M3 AML patients. Therefore, our findings indicated that *PANDAR* was a potential biomarker for AML and it might effectively predict the outcome of AML patients.

Acknowledgments

This work was supported by National Natural Science Foundation of China (81270630), Medical Innovation Team of Jiangsu Province (CXTDB2017002), 333 Project of Jiangsu Province (BRA2016131), Six Talent Peaks Project in Jiangsu Province (2015-WSN-115), Zhenjiang Clinical Research Center of Hematology (SS2018009), China Postdoctoral

Science Foundation funded project (2016M601748), Youth Medical Talents Project of “Ke Jiao Qiang Wei” project of Jiangsu province (QNRC2016450, QNRC2016449), and Key Medical Talent Program of Zhenjiang City.

Disclosure

The authors report no conflicts of interest in this work.

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