MEDICAL SCIENCE MONITOR

LAB/IN VITRO RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 4952-4959
DOI: 10.12659/MSM.914352

Received: 2018.11.03
Accepted: 2019.02.22
Published: 2019.07.04

Low Expression of Pseudogene *POU5F1B* Affects Diagnosis and Prognosis in Acute Myeloid Leukemia (AML)

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Source of support: This study was supported by National Natural Science Foundation of China (20120016), the Medical Innovation Team of Jiangsu Province (CXTDB2017002), the Zhenjiang Clinical Research Center of Hematology (SS2018009), and the Jiangsu Provincial "Innovative & Entrepreneurial Talent Team" Program

Background: The transcription factor *Oct-4* is necessary for maintaining pluripotency and self-renewal of embryonic stem cells, and *POU5F1B* is a processed pseudogene of *Oct-4* with coding capacity. The purpose of this study is to evaluate the expression and clinical implication of *POU5F1B* in AML.

Material/Methods: The expression of the *POU5F1B* transcript was evaluated in 175 newly diagnosed AML patients and 39 healthy controls by use of real-time quantitative PCR (RQ-PCR).

Results: *POU5F1B* was underexpressed in AML compared with controls ($P<0.001$). The receiver operating characteristic (ROC) curve revealed that the *POU5F1B* transcript level was able to differentiate AML patients from healthy individuals (AUC=0.682). In non-APL AML patients, the *POU5F1B*^{low} group had significantly higher WBC than the *POU5F1B*^{high} group (20.2×10^9 *vs.* 4.6×10^9 L^{-1}, $P=0.021$). Among whole-cohort AML, non-APL AML, and intermediate-risk AML, *POU5F1B*^{high} patients had obviously higher complete remission (CR) rates than *POU5F1B*^{low} patients ($P=0.012$, $P=0.012$ and $P=0.027$). In addition, Kaplan-Meier analysis demonstrated better overall survival (OS, $P=0.019$, $P=0.007$ and $P=0.046$, respectively) in *POU5F1B*^{high} patients compared with *POU5F1B*^{low} patients. Furthermore, in multivariate survival analysis, *POU5F1B* was independently associated with OS in non-APL AML patients and intermediate-risk AML as a favorable prognostic factor.

Conclusions: *POU5F1B* was frequently underexpressed in AML, and might contribute to the diagnosis and prognosis of AML.

MeSH Keywords: Biological Markers • Diagnosis • Leukemia, Myeloid, Acute • Prognosis • Pseudogenes

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/914352

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Background

Acute myeloid leukemia (AML) is a malignant clonal disorder distinguished by differentiation block of myeloid and accumulation of abnormal myeloid progenitors in the bone marrow (BM) and blood [1]. In adults, AML is the most common form of acute leukemia [2], and the incidence increases with age [3]. Patients may present with bleeding, anemia, and infection complications due to bone marrow failure, but often only have fatigue on initial presentation [3–5]. The evolving molecular genetics facilitate discernment of AML prognostic indicators, especially in cytogenetic results and molecular abnormalities [6].

In the past decade, non-coding RNAs (ncRNAs), involving microRNAs, small interfering RNAs (siRNAs), long non-coding RNAs (lncRNAs), and pseudogenes, have attracted intense attention [7]. There is an increasing focus on the relationship between non-coding RNA and cancer, especially as a diagnostic and prognostic biomarker of cancer from early detection to monitor recurrence or treatment progression [8]. Pseudogenes were defined as 'junk DNA' that no longer possess biological functions due to nonsense or frameshift mutations in coding genes, whereas some pseudogene-derived RNAs have been shown to have unique regulatory roles, and some pseudogene fragments can be translated [9]. Increasing evidence indicates that pseudogenes show important biological functions in human cancers [10]. Kong et al. demonstrated that the pseudogene *PDIA3P1* is overexpressed in HCC tissues and is associated with tumor size and TNM stage, and knockdown of *PDIA3P1* decreases HCC cell proliferation and promotes apoptosis [11].

The *POU* family possesses a *POU* DNA-binding domain, and *Oct-4* is one of the transcription factors of the family. As a master transcription factor for pluripotent cell self-renewal, *Oct-4* plays a critical role in the embryonic development of mammals [12]. Alternative splicing of *Oct-4* produces 3 isoforms: *Oct-4A*, *Oct-4B,* and *Oct-4B1* [13]. *Oct-4A (Oct-4)* can maintain stem cell self-renewal, while *Oct-4B* cannot [14]. Two of the 6 highly homologous pseudogenes of human *Oct-4* – *Oct-4-pg1* and *Oct-4-pg5* – were found to be transcribed in somatic cancers [15]. Overexpression of *POU5F1B (Oct-4-pg1)* is reported in gastric cancer and is associated with unfavorable prognosis in stage IV patients [16]. The aim of this study was to evaluate expression of *POU5F1B* in patients with an initial diagnosis of AML, as well as to explore the correlation between *POU5F1B* and AML.

Material and Methods

Patient samples

The study was subject approved by the Institutional Ethics Committee of the Affiliated People's Hospital of Jiangsu University. Bone marrow samples were collected from 214 adults, including 39 healthy donors and 175 newly diagnosed AML patients before chemotherapy. The patients were diagnosed according to the WHO and French-American-British (FAB) classification [17,18]. All participants signed written informed consent. Previous articles have described treatment protocols for AML patients [19].

RNA isolation, reverse transcription, and RQ-PCR

Lymphocyte Separation Medium (TBD Sciences, Tianjin, China) was used to separate bone marrow mononuclear cells (BMNCs). Trizol reagent (Invitrogen, Carlsbad, CA) was used to separated total RNA. We used 10 mM of dNTPs, 2 μg of total RNA from each sample, 10 μM of random hexamers, 80 U of RNase inhibitor, and 200 U of MMLV reverse transcriptase (MBI Fermentas, Hanover, MA) and reverse-transcribed them into single-stranded complementary DNA (cDNA), and then stored them at –20°C.

We used a 7500 Thermal cycler (Applied Biosystems, CA) to perform RQ-PCR. The forward primer used for *POU5F1B* transcript detection was 5'-GCGATCAAGCAGCGACTA-3', and the reverse primer was 5'-AGGGAAAGGGACTGAGGAG -3'. *POU5F1B* transcript level detection was quantified by RT-qPCR as follows: 95°C for 30 s, and then 40 cycles at 95°C for 5 s, 58.1°C for 30 s, 72°C for 30 s, and 80°C for 31 s to collect fluorescence, and finally, the melting program at 95°C for 15 s, 60°C for 60 s, 95°C for 15 s, and 60°C for 15 s. The amount of *POU5F1B* transcript was calculated by analyzing expression of the housekeeper gene *ABL* using $2^{-\Delta\Delta CT}$ method.

Gene mutation detection

Mutations of *DNMT3A, N/K-RAS, NPM1, c-KIT, IDH2 R140, IDH1/2, U2AF1, and SRSF2* were detected by PCR and high-resolution melting analysis (HRMA) [20–24]. Mutations of *CEBPA* and *FLT3-ITD* genes and all positive samples were detected in genomic DNA by PCR and direct sequencing [25].

Statistical analyses

SPSS22.0 software was used for statistical analysis. $P<0.05$ was considered statistically significant for all analyses. Continuous variables between the 2 groups were compared using the Mann-Whitney U test. The Fisher exact test or Pearson chi-square analysis was used, as appropriate, to compare categorical variables across groups. The diagnostic accuracy of *POU5F1B* expression in discriminating AML patients from normal controls was calculated by ROC curve and area under the ROC curve (AUC). Kaplan-Meier curves were used to estimate the effect of *POU5F1B* expression on survival, and Cox regression models were used to independently assess the prognostic value of *POU5F1B* expression.

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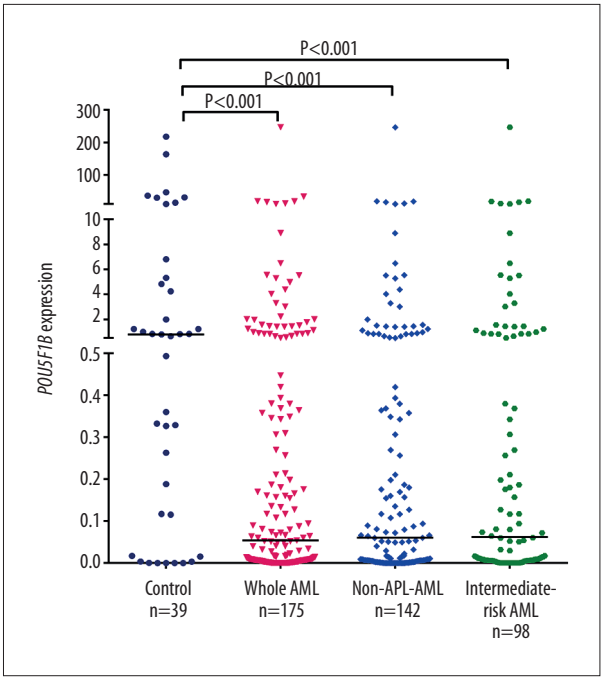

Figure 1. Relative expression levels of *POU5F1B* in AML patients and controls. The transcript level of *POU5F1B* in controls, whole-cohort AML patients, non-APL patients, and intermediate-risk AML patients were evaluated by RQ-PCR. Horizontal lines represent the median level of *POU5F1B* expression in each group.

Results

POU5F1B expression in controls and AML patients

Assessment of *POU5F1B* transcript levels in AML patients (0–246.92, median 0.0536) detected underexpression compared to controls (0–217.99, median 0.7991) (*P*<0.001, Figure 1). Moreover, the level of *POU5F1B* expression was lower in non-APL AML patients and in intermediate-risk AML patients (*P*<0.001 and *P*<0.001, Figure 1).

Diagnostic accuracy of *POU5F1B* expression

ROC was utilized to analyze the differentiating value of *POU5F1B* expression. It indicated that *POU5F1B* can act as a potential marker to distinguish whole-cohort AML patients from controls, with an AUC of 0.682 (95%CI: 0.579-0.786, *P*<0.001). Meanwhile, the level of *POU5F1B* expression might be used to segregate non-APL AML (AUC=0.683, 95%CI: 0.579–0.786, *P*<0.001) from normal controls, and a similar result was found in the intermediate-risk group (AUC=0.663, 95%CI: 0.556–0.770, *P*=0.003) (Figure 2).

Association of *POU5F1B* expression with clinical and laboratory features in AML

We divided the AML patients into 2 groups using a cutoff value of mean minus 2SD obtained in normal controls: $POU5F1B^{high}$ (>1.005) and $POU5F1B^{low}$ (≤1.005). None of these differences between the 2 groups were statistically significant, such as sex, age, white blood cells (WBC), hemoglobin (HB), platelets (PLT), BM blasts, FAB subtypes, karyotypes, and gene mutations. However, the results, as shown in Table 1, indicated that the CR of $POU5F1B^{high}$ patients was significantly higher than that of $POU5F1B^{low}$ patients (*P*=0.012, Table 1). When M3 patients were excluded, the comparison of laboratory characteristics and clinical data between the 2 groups (Table 1), patients with lower expression of *POU5F1B* had significantly higher WBC than those with higher expression of *POU5F1B* (20.2×10^9 *vs.* 4.6×10^9 L^{-1}, *P*=0.021). As with whole AML, in non-APL and intermediate-risk AML patients, the CR was strikingly higher in $POU5F1B^{high}$ patients than in $POU5F1B^{low}$ (*P*=0.012 and *P*=0.027, Tables 1, 2). The intermediate-risk AML patients with lower *POU5F1B* were older (P=0.038, Table 2).

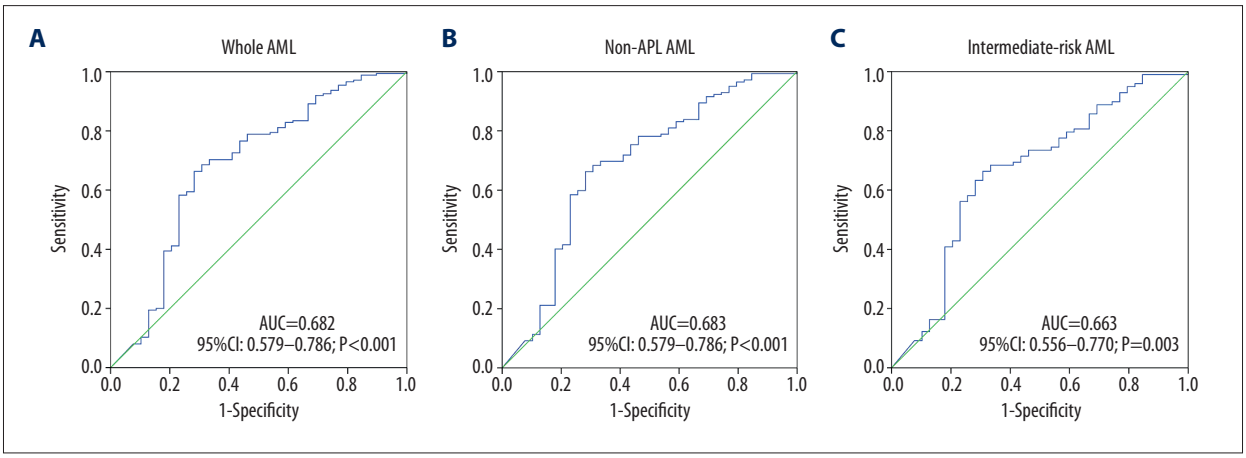

Figure 2. ROC curve analysis for distinguishing AML patients from controls. (**A**) Whole AML patients; (**B**) Non-APL patients; (**C**) Intermediate-risk AML.

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Table 1. Comparison of clinical and laboratory features between whole-cohort AML and non-APL AML patients with low and high expression.

Patient parameters	Whole-cohort AML			Non-APL AML		
	POU5F1B^{low} (n=145)	*POU5F1B*^{high} (n=30)	*P* value	*POU5F1B*^{low} (n=118)	*POU5F1B*^{high} (n=24)	*P* value
Sex, Male/Female	90/55	20/10	0.683	75/43	15/9	1.000
Median age, years (range)	57 (20–93)	54 (21–83)	0.105	61 (20–93)	57 (28–83)	0.135
Median WBC, ×10^9/L (range)	16.3 (0.4–528.0)	5.5 (0.3–203.6)	0.103	20.2 (0.4–528.0)	4.6 (0.8–203.6)	0.021
Median hemoglobin, g/L (range)	77.5 (32.0–144.0)	77.0 (34.0–131.0)	0.893	76.0 (32.0–144.0)	77.5 (34.0–131.0)	0.963
Median platelets, ×10^9/L (range)	40.0 (3.0–447.0)	46.5 (4.0–415.0)	0.937	42.0 (3.0–447.0)	50.0 (4.0–415.0)	0.714
BM blasts,% (range)	46.7 (3.0–99.0)	37.5 (1.0–93.0)	0.203	56.5 (10.5–99.0)	43.0 (6.0–93.0)	0.193
CR (+/–)	50/83	18/10	0.012	29/78	13/10	0.012
FAB			0.956			0.904
M0	2	1		2	1	
M1	10	1		10	1	
M2	56	13		56	13	
M3	27	6		–	–	
M4	29	5		29	5	
M5	16	3		17	3	
M6	5	1		5	1	
Karyotype classification			0.353			0.329
Favorable	37	8		12	2	
Intermediate	78	20		77	20	
Poor	21	1		21	1	
No data	9	1		8	1	
Karyotype			0.320			0.209
Normal	57	18		56	18	
t(8;21)	9	2		9	2	
t(15;17)	25	6		0	0	
+8	6	0		6	0	
Others	23	1		23	1	
Complex	16	2		16	2	
No data	9	1		8	1	
Gene mutation						
CEBPA (+/–)	14/106	3/23	1.000	14/85	3/18	1.000
NPM1 (+/–)	13/107	4/22	0.506	13/86	4/17	0.496
FLT3-ITD (+/–)	16/104	2/24	0.742	13/86	2/19	1.000
c-KIT (+/–)	6/114	1/25	1.000	5/94	1/20	1.000
NRAS or *KRAS (+/–)*	7/113	3/23	0.384	7/92	3/18	0.377
IDH1/2 (+/–)	6/114	1/25	1.000	6/93	1/20	1.000
IDH2 R140(+/–)	4/116	1/25	1.000	4/95	1/21	1.000
DNMT3A (+/–)	10/110	0/26	0.209	10/89	0/21	0.206
U2AF1 (+/–)	5/115	1/25	1.000	5/94	1/20	1.000
SRSF2 (+/–)	7/117	0/26	0.605	7/94	0/21	0.600

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Table 2. Comparison of clinical and laboratory features between patients with intermediate-risk AML low and high expression.

Patient parameters	Intermediate-risk AML		
	***POU5F1B*^{low} (n=78)**	***POU5F1B*^{high} (n=20)**	***P* value**
Sex, Male/Female	49/29	13/7	1.000
Median age, years (range)	61 (20–93)	57 (21–83)	0.038
Median WBC, ×10^9/L (range)	21.3 (0.4–528.0)	7.7 (0.3–203.6)	0.129
Median hemoglobin, g/L (range)	81.5 (32.0–144.0)	77.5 (34.0–131.0)	0.988
Median platelets, ×10^9/L (range)	42.5 (3.0–399.0)	52.5 (4.0–415.0)	0.547
BM blasts,% (range)	55.0 (21.5–99.0)	48.5 (6.0–93.0)	0.506
CR (+/–)	20/52	11/8	0.027
FAB			0.883
M0	1	1	
M1	6	1	
M2	39	9	
M3	1	0	
M4	17	5	
M5	11	3	
M6	3	1	
Gene mutation			
CEBPA (+/–)	11/57	3/14	1.000
NPM1 (+/–)	11/57	4/13	0.487
FLT3-ITD (+/–)	10/58	2/15	1.000
c-KIT (+/–)	1/67	1/16	0.362
NRAS or *KRAS (+/–)*	7/61	3/14	0.411
IDH1/2 (+/–)	5/63	1/16	1.000
IDH2 R140(+/–)	3/65	1/16	1.000
DNMT3A (+/–)	9/59	0/17	0.194
U2AF1 (+/–)	4/64	1/16	1.000
SRSF2 (+/–)	6/64	0/17	0.593

Prognostic value of *POU5F1B* in AML

OS and leukemia-free survival (LFS) were estimated according to Kaplan-Meier methods. OS (*P*=0.019, median 7 *vs.* 17 months; *P*=0.007, median 5 *vs.* 12 months, respectively) was significantly worse in the whole-cohort AML patients and non-APL AML patients with low *POU5F1B* expression. Kaplan-Meier analysis showed that intermediate-risk AML patients with *POU5F1B* low expression had significantly shorter OS (*P*=0.046, median 4.5 *vs.* 12 months, Figure 3F). There was no significant association between *POU5F1B* expression and LFS (*P*=0.510, *P*=0.131, and *P*=0.672, respectively) among the 3 AML groups (Figure 3).

In multivariate analyses, *POU5F1B* overexpression remained a significant favorable prognostic factor for OS (*P*=0.014 and *P*=0.023) in non-APL and intermediate-risk AML patients. However, improved OS was not observed among whole-cohort AML patients (Table 3).

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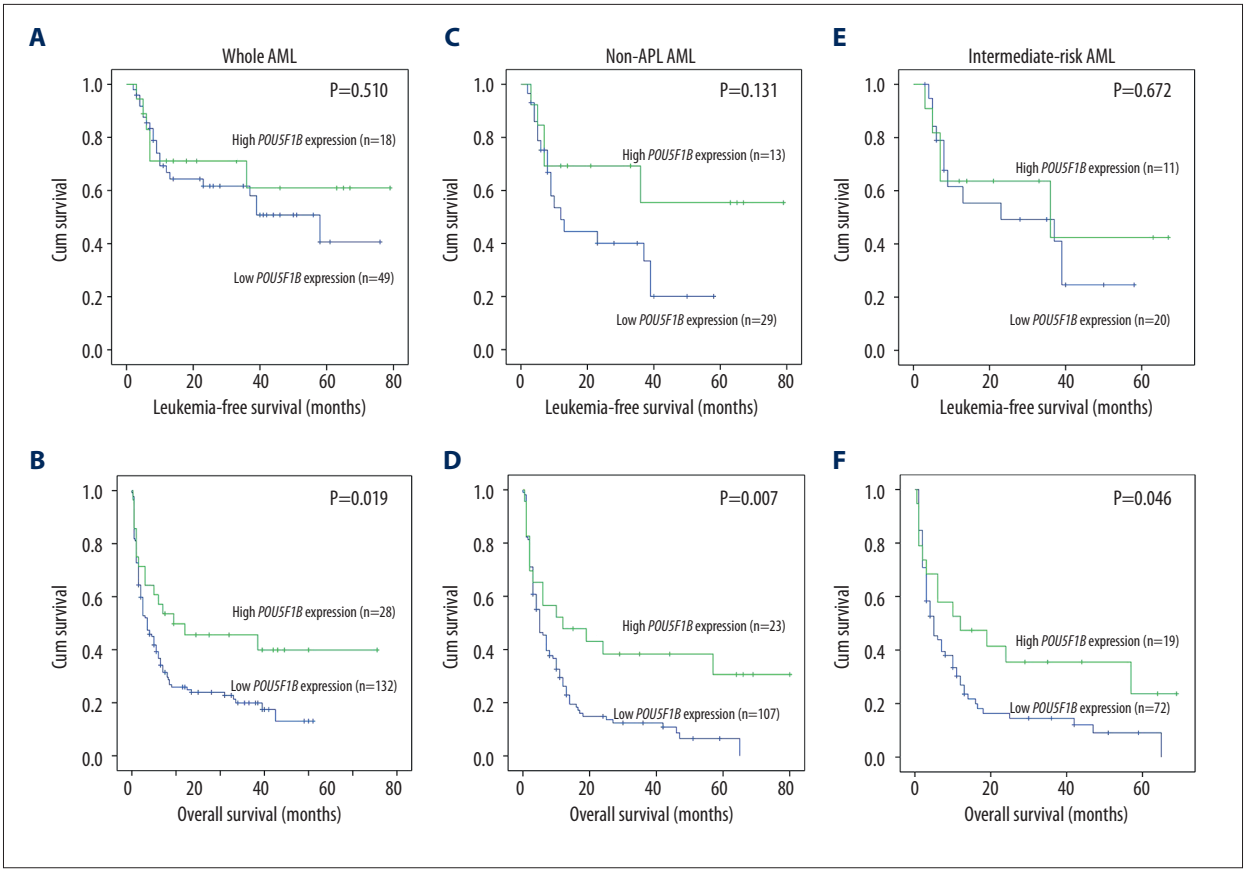

Figure 3. Differences in leukemia-free survival and overall survival between the *POU5F1B*^{high} group and the *POU5F1B*^{low} group were estimated using to Kaplan-Meier method. (**A**) LFS for whole AML patients; (**B**) OS for whole AML patients; (**C**) LFS for non-APL patients; (**D**) OS for non-APL patients; (**E**) LFS for intermediate-risk patients; (**F**) OS for intermediate-risk patients.

Table 3. Multivariate analyses of prognostic factors for overall survival in non-APL and intermediate-risk AML cases.

Prognostic factors	Non-APL AML		Intermediate-risk AML	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Sex (Male *vs.* Female)	1.136 (0.713–1.812)	0.591	0.876 (0.512–1.498)	0.629
Age (≤60 *vs.* >60 years)	1.384 (0.905–2.117)	0.134	1.116 (0.642–1.939)	0.698
WBC (≥30×10^9/L *vs.* <30×10^9/L)	1.209 (0.776–1.884)	0.401	1.499 (0.882–2.548)	0.134
PLT (100×10^9/L *vs.* 100×10^9/L)	1.340 (0.766–2.343)	0.305	1.074 (0.528–2.184)	0.845
Karyotypic classifications (favorable *vs.* intermediate *vs.* poor)	1.683 (1.251–2.266)	0.001	–	–
POU5F1B expression (high *vs.* low)	0.453 (0.241–0.852)	0.014	0.448 (0.225–0.896)	0.023
IDH1/2 mutation (mutant *vs.* wild-type)	4.470 (1.860–10.740)	0.001	5.732 (2.197–14.960)	0.000
IDH2 R140 mutation (mutant *vs.* wild-type)	0.650 (0.118–3.585)	0.621	0.636 (0.102–3.948)	0.627
U2AF1 mutation (mutant *vs.* wild-type)	2.452 (1.013–5.931)	0.047	2.206 (0.831–5.858)	0.112
SRSF2 mutation (mutant *vs.* wild-type)	1.339 (0.540–3.321)	0.529	2.032 (0.766–5.390)	0.154

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Discussion

Oct-4 was reported to be overexpressed in several types of cancers, such as bladder cancer [26], hepatocellular carcinoma [27], primary endometrioid endometrial and ovarian carcinomas [28], and non-small-cell lung cancer [29]. *Oct-4* high expression in AML was a common molecular event, and AML patients with high expression of *Oct-4* showed a shorter overall survival rate [30]. *POU5F1B* was reported as a susceptibility gene in breast cancer [31], prostate cancer [32], and gastric cancer [33]. Hayashi et al. reported that overexpression of *POU5F1B* induces overexpression of GC cell growth factors, which in turn promotes cell proliferation and inhibits apoptosis [16]. *POU5F1B* promotes HCC proliferation by activating AKT, and patients with high *POU5F1B* level have shorter survival times [34]. HPV integrated in *POU5F1B* in cervical tumor cells survives during radiotherapy and may lead to resistance to radiation therapy [35]. To date, abnormal expression of a few pseudogenes in AML have been reported, including *Vim2p, DUSP5P1,* and *BMI1P1* [36–38]. However, there has been no research focused on pseudogene *POU5F1B* in AML. In this study, *POU5F1B* transcript was expressed at lower levels in AML patients compared with the control group. ROC analysis revealed that low *POU5F1B* expression is a prospective biomarker for use in discriminating AML patients, including non-APL AML and intermediate-risk AML patients, from healthy controls. AML patients with high WBC count have a particularly poor prognosis [39]. Similarly, our finding suggested that non-APL AML patients with lower *POU5F1B* expression had higher WBC counts and worse survival.

Furthermore, CR rates and OS were significantly better in the $POU5F1B^{high}$ group than in the $POU5F1B^{low}$ group in total AML, non-APL, and intermediate-risk AML patients. Multivariate analyses demonstrated that *POU5F1B* was an independent prognostic factor for OS in non-APL and intermediate-risk AML patients. Collectively, these results showed that detecting the expression of the *POU5F1B* transcript in AML patients, especially non-APL AML and intermediate-risk patients, might have important prognostic and curative implications. *POU5F1B* expression has no significant correlation with LFS, and we considered that it was caused by the differences in consolidation and intensification therapy. A more comprehensive study including all the subgroups is needed, such as different treatment and age groups, CR and non-CR groups, and the cases need to be expanded.

Competing endogenous RNA (ceRNAs) are RNA transcripts, including long non-coding RNAs, pseudogenes, and circular RNAs [40], and they regulate each other by competing to bind to shared microRNA (miRNA) recognition elements (MREs) [41]. Pseudogenes show sequence similarity to their parental genes, with many identical MREs in its sequence [42]. Pseudogenes regulate their parental transcripts by competing for shared miRNAs [43]. A number of studies have found that ceRNAs abundance and activity are underexpressed in cancer; therefore, these ceRNAs may be potential diagnostic biomarkers in cancer [44]. Previous studies have reported that 2 pseudogenes of *HMGA1* – *HMGA1P6* and *HMGA1P7* – act as competitive endogenous RNA decoys for carcinogenesis genes *HMGA1, H19,* and *Igf2*, and pseudogene overexpression increases oncogenes levels, inhibiting their mRNA suppression by miRNAs that target *HMGA1P7* gene [45]. Scarola et al. showed that the lncRNA produced by *Oct-4-pg4* (X-linked *Oct-4* pseudogene) during transcription is overexpressed during mESC differentiation and forms a complex with *SUV39H1 HMTase* to regulate the ancestral *Oct-4* gene promoter, resulting in *Oct-4* gene silence and reduced mESC self-renewal [46]. In hepatocellular carcinoma cells (HCC) and endometrial carcinoma, *Oct-4-pg4* and *pg5* function as miRNA sponges protecting *Oct-4* transcript by competing with miR-145 [47]. To date, the function of the pseudogene *POU5F1B* in AML remains largely unknown. Combined with the expression of *Oct-4* in AML, an interesting pattern emerges: the transcript levels of *Oct-4* and *POU5F1B* showed the exact opposite trend. We anticipate that the pseudogene-derived lncRNAs may regulate the promoter of the parental gene *Oct-4*, resulting in reduced *Oct-4* gene silencing. *POU5F1B* was found to have 95% homology with *Oct-4* [48]; therefore, *POU5F1B* may serve as ceRNA, allowing *Oct-4* to evade miRNA inhibition. More research on this topic is needed, including *in vivo* and *in vitro* functional assays, correlation analysis with *Oct-4* and *POU5F1B* expression levels, prediction and detection of pseudogene-derived lncRNAs and *POU5F1B*-targeted miRNAs, and stemness potential assays.

Conclusions

Expression of the *POU5F1B* transcript is significantly decreased in AML patients and is associated with unfavorable clinical variables and poor prognosis. *POU5F1B* has promise as a potential novel biomarker and target for future therapy.

Conflicts of interest

None.

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References:

1. Grove CS, Vassiliou GS: Acute myeloid leukaemia: A paradigm for the clonal evolution of cancer? Dis Model Mech, 2014; 7: 941–51
2. Perna F, Berman SH, Soni RK et al: Integrating proteomics and transcriptomics for systematic combinatorial chimeric antigen receptor therapy of AML. Cancer Cell, 2017; 32: 506–19
3. Abelson S, Collord G, Ng SWK et al: Prediction of acute myeloid leukaemia risk in healthy individuals. Nature, 2018; 559(7714): 400–4
4. Boyd AL, Reid JC, Salci KR et al: Acute myeloid leukaemia disrupts endogenous myelo-erythropoiesis by compromising the adipocyte bone marrow niche. Nat Cell Biol, 2017; 19(11): 1336–47
5. Lacourt TE, Kavelaars A, Ohanian M et al: Patient-reported fatigue prior to treatment is prognostic of survival in patients with acute myeloid leukemia. Oncotarget, 2018; 9: 31244–52
6. Li W, Zhong C, Jiao J et al: Characterization of hsa_circ_0004277 as a new biomarker for acute myeloid leukemia via circular RNA profile and bioinformatics analysis. Int J Mol Sci, 2017; 18(3): 597–610
7. Groen JN, Capraro D, Morris KV: The emerging role of pseudogene expressed non-coding RNAs in cellular functions. Int J Biochem Cell Biol, 2014; 54: 350–55
8. Anfossi S, Babayan A, Pantel K, Calin GA: Clinical utility of circulating non-coding RNAs-an update. Nat Rev Clin Oncol, 2018; 15(9): 541–63
9. Prieto-Godino LL, Rytz R, Bargeton B et al: Olfactory receptor pseudo-pseudogenes. Nature, 2016; 539(7627): 93–97
10. Shi X, Nie F, Wang Z, Sun M: Pseudogene-expressed RNAs: A new frontier in cancers. Tumour Biol, 2016; 37(2): 1471–78
11. Kong Y, Zhang L, Huang Y et al: Pseudogene PDIA3P1 promotes cell proliferation, migration and invasion, and suppresses apoptosis in hepatocellular carcinoma by regulating the p53 pathway. Cancer Lett, 2017; 407: 76–83
12. Radzisheuskaya A, Chia Gle B, dos Santos RL et al: A defined Oct4 level governs cell state transitions of pluripotency entry and differentiation into all embryonic lineages. Nat Cell Biol, 2013; 15(6): 579–90
13. Gao Y, Wei J, Han J et al: The novel function of OCT4B isoform-265 in genotoxic stress. Stem Cells, 2012; 30(4): 665–72
14. Wang X, Dai J: Concise review: Isoforms of OCT4 contribute to the confusing diversity in stem cell biology. Stem Cells, 2010; 28(5): 885–93
15. Zhao S, Yuan Q, Hao H et al: Expression of OCT4 pseudogenes in human tumours: Lessons from glioma and breast carcinoma. J Pathol, 2011; 223(5): 672–82
16. Hayashi H, Arao T, Togashi Y et al: The OCT4 pseudogene POU5F1B is amplified and promotes an aggressive phenotype in gastric cancer. Oncogene, 2015; 34(2): 199–208
17. Giagounidis AA, Hildebrandt B, Heinsch M et al: Acute basophilic leukemia. Eur J Haematol, 2001; 67(2): 72–76
18. Arber DA, Orazi A, Hasserjian R et al: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood, 2016; 127(20): 2391–405
19. Li Y, Lin J, Yang J et al: Overexpressed let-7a-3 is associated with poor outcome in acute myeloid leukemia. Leuk Res, 2013; 37(12): 1642–47
20. Lin J, Yao DM, Qian J et al: Recurrent DNMT3A R882 mutations in Chinese patients with acute myeloid leukemia and myelodysplastic syndrome. PLoS One, 2011; 6(10): e26906
21. Lin J, Yao DM, Qian J et al: IDH1 and IDH2 mutation analysis in Chinese patients with acute myeloid leukemia and myelodysplastic syndrome. Ann Hematol, 2012; 91(4): 519–25
22. Yang X, Qian J, Sun A et al: RAS mutation analysis in a large cohort of Chinese patients with acute myeloid leukemia. Clin Biochem, 2013; 46(7–8): 579–83
23. Qian J, Yao DM, Lin J et al: U2AF1 mutations in Chinese patients with acute myeloid leukemia and myelodysplastic syndrome. PLoS One, 2012; 7(9): e45760
24. Skrdlant L, Lin RJ: Characterization of RNA-protein interactions: lessons from two RNA-binding proteins, SRSF1 and SRSF2. Methods Mol Biol, 2016; 1421: 1–13
25. Wen XM, Lin J, Yang J et al: Double CEBPA mutations are prognostically favorable in non-M3 acute myeloid leukemia patients with wild-type NPM1 and FLT3-ITD. Int J Clin Exp Pathol, 2014; 7(10): 6832–40
26. Zhou J, Dong D, Cheng R et al: Aberrant expression of KPNA2 is associated with a poor prognosis and contributes to OCT4 nuclear transportation in bladder cancer. Oncotarget, 2016; 7(45): 72767–76
27. Huang PZ, Lu CL, Li BK et al: OCT4 expression in hepatocellular carcinoma and its clinical significance. Chin J Cancer, 2010; 29(1): 111–16
28. Zhang R, Jiao J, Chu H et al: Expression of microRNA-145, OCT4, and SOX2 in double primary endometrioid endometrial and ovarian carcinomas. Histol Histopathol, 2018; 33(8): 859–70
29. Li X, Wang J, Xu Z et al: Expression of Sox2 and Oct4 and their clinical significance in human non-small-cell lung cancer. Int J Mol Sci, 2012; 13(6): 7663–75
30. Yin JY, Tang Q, Zhai LL et al: High expression of OCT4 is frequent and may cause undesirable treatment outcomes in patients with acute myeloid leukemia. Tumour Biol, 2015; 36(12): 9711–16
31. Wei W, Jiang M, Luo L et al: Colorectal cancer susceptibility variants alter risk of breast cancer in a Chinese Han population. Genet Mol Res, 2013; 12(4): 6268–74
32. Breyer JP, Dorset DC, Clark TA et al: An expressed retrogene of the master embryonic stem cell gene POU5F1 is associated with prostate cancer susceptibility. Am J Hum Genet, 2014; 94(3): 395–404
33. Shen L, Du M, Wang C et al: Clinical significance of POU5F1P1 rs10505477 polymorphism in Chinese gastric cancer patients receiving cisplatin-based chemotherapy after surgical resection. Int J Mol Sci, 2014; 15(7): 12764–77
34. Karreth FA, Reschke M, Ruocco A et al: The BRAF pseudogene functions as a competitive endogenous RNA and induces lymphoma *in vivo*. Cell, 2015; 161(2): 319–32
35. Yang D, Zhang W, Liu Y et al: Single-cell whole-genome sequencing identifies human papillomavirus integration in cervical tumour cells prior to and following radiotherapy. Oncol Lett, 2018; 15(6): 9633–40
36. Zhai LL, Zhou J, Zhang J et al: Down-regulation of pseudogene Vimentin 2p is associated with poor outcome in *de novo* acute myeloid leukemia. Cancer Biomark, 2017; 18(3): 305–12
37. Zhou LY, Yin JY, Tang Q et al: High expression of dual-specificity phosphatase 5 pseudogene 1 (DUSP5P1) is associated with poor prognosis in acute myeloid leukemia. Int J Clin Exp Pathol, 2015; 8(12): 16073–80
38. Zhou LY, Zhai LL, Yin JY et al: Pseudogene BMI1P1 expression as a novel predictor for acute myeloid leukemia development and prognosis. Oncotarget, 2016; 7(30): 47376–86
39. Ganzel C, Manola J, Douer D et al: Extramedullary disease in adult acute myeloid leukemia is common but lacks independent significance: Analysis of patients in ECOG-ACRIN Cancer Research Group Trials, 1980–2008. J Clin Oncol, 2016; 34(29): 3544–53
40. Thomson DW, Dinger ME: Endogenous microRNA sponges: Evidence and controversy. Nat Rev Genet, 2016; 17(5): 272–83
41. Li LJ, Zhao W, Tao SS et al: Competitive endogenous RNA network: Potential implication for systemic lupus erythematosus. Expert Opin Ther Targets, 2017; 21(6): 639–48
42. Karreth FA, Reschke M, Ruocco A et al: The BRAF pseudogene functions as a competitive endogenous RNA and induces lymphoma *in vivo*. Cell, 2015; 161(2): 319–32
43. Chan JJ, Kwok ZH, Chew XH et al: A FTH1 gene: Pseudogene: MicroRNA network regulates tumorigenesis in prostate cancer. Nucleic Acids Res, 2018; 46(4): 1998–2011
44. Qi X, Zhang DH, Wu N et al: ceRNA in cancer: Possible functions and clinical implications. J Med Genet, 2015; 52(10): 710–18
45. De Martino M, Forzati F, Marfella M et al: HMGA1P7-pseudogene regulates H19 and Igf2 expression by a competitive endogenous RNA mechanism. Sci Rep, 2016; 6: 37622
46. Scarola M, Comisso E, Pascolo R et al: Epigenetic silencing of Oct4 by a complex containing SUV39H1 and Oct4 pseudogene lncRNA. Nat Commun, 2015; 6: 7631
47. Villodre ES, Kipper FC, Pereira MB, Lenz G: Roles of OCT4 in tumorigenesis, cancer therapy resistance and prognosis. Cancer Treat Rev, 2016; 51: 1–9
48. Wezel F, Pearson J, Kirkwood L, Southgate J: Differential expression of Oct4 variants and pseudogenes in normal urothelium and urothelial cancer. Am J Pathol, 2013; 183(4): 1128–36

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