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Original Article

Prognostic value of the PDLIM family in acute myeloid leukemia

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Abstract: Acute myeloid leukemia (AML) is a genetically complex, highly aggressive hematological malignancy. Prognosis is usually with grim. PDZ and LIM domain proteins (PDLIM) are involved in the regulation of a variety of biological processes, including cytoskeletal organization, cell differentiation, organ development, neural signaling or tumorigenesis. The clinical and prognostic value of the PDLIM family in AML is unclear. To understand the role of PDLIM expression in AML, The Cancer Genome Atlas (TCGA) database was screened and 155 de novo AML patients with complete clinical information and the expression data of the PDLIM family were included in the study. The clinical and molecular characteristics associated with the expression of different members of the PDLIM family were summarized using various statistical methods. In 84 patients who only received chemotherapy, univariate analysis indicated that high expression of PDLIM2 or PDLIM7 was associated with shorter EFS and OS (both $P<0.05$ for PDLIM2, and both $P<0.01$ for PDLIM7). Multivariate analysis suggested that high expression of PDLIM7 was an independent risk factor for EFS and OS (both $P<0.05$). In the other 71 patients who underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT), survival was unaffected by PDLIM expressions. In summary, high expression of *PDLIM2* and *PDLIM7*, especially the latter, could serve as adverse prognostic factors for AML, but their prognostic effects could be reversed by allo-HSCT.

Keywords: Acute myeloid leukemia, PDLIM, prognosis, next generation sequencing, mutational spectrum

Introduction

Acute myeloid leukemia (AML) is caused by dysregulated clonal expansion of mutant hematopoietic progenitor cells. It is a very heterogeneous disease with various clinical and laboratory manifestations. Despite advances in AML research and treatment, it is still a deadly disease, with a survival rate of 35% to 40% in patients younger than 60 years old, and only 5% to 15% in patients older than 60 [1]. In the past decade, lots of work have been done to improve AML prognostication and individualized targeted therapy. Our team and many other groups have identified that FLT3-ITD and DNMT3A mutations, or high expressions of DOK4/5, PDK2/3, FHL2, and iASPP, are associated with adverse prognosis, whereas mutations of NPM1 and CEBPA, or high expression of DOK7 are indicative of favorable prognosis [2-4]. Many studies are underway to find new epigenetic or genetic factors that participate in leukemogenesis, affect prognosis or can be potential therapeutic targets.

The PDZ and LIM domains (PDLIM) are interacting structural modules shared by various proteins [5]. There are five genes encoding five dif-

ferent PDLIM isoforms, PDLIM1, 2, 4, 5, and 7. The PDZ domain interacts with certain peptide domains on various proteins, to exert different functions, particularly those related to cell polarity, intercellular junctions, recognition of immune cells, and control of proliferation and cellular migration [6, 7]. PDLIM4 plays crucial roles in many fundamental biological processes and reduced activities have been observed in some pathological processes including oncogenesis [8]. PDLIM5 and PDLIM1 are up-regulated in papillary thyroid carcinoma and PDLIM5 can promote this malignancy via activating the Ras-ERK pathway [9]. PDLIM7 is an important stabilizer of MDM2. After binding to the latter, it prevents the autoubiquitination of MDM2, which enables MDM2 to trans-ubiquitinate p53. MDM2 stabilization has been proposed to be one of the mechanisms of resistance to CDK4/6 inhibitors [10-12]. One study showed that AML patients were more likely to have low PDLIM4 expression than healthy controls; interestingly, among the AML patients, those with lower PDLIM4 expression had relatively longer overall survival than normal expressors [13]. Research is still limited on the prognostic impact of the expression of the other PDLIM members on AML, which we aimed to help elucidate with this study.

Methods

Patients

The Cancer Genome Atlas (TCGA) database was screened for de novo AML patients with complete clinical and PDLIM expression data. A total of 155 patients who met the criteria were included in the study, among which 84 were treated only with chemotherapy, and 71 later received allogeneic hematopoietic stem cell transplantation (allo-HSCT). Clinical features at diagnosis were described, including age, peripheral blood (PB) white blood cell (WBC) counts, blast percentages in the PB and the bone marrow (BM), French-American-British (FAB) subtypes, cytogenetic risk, and the frequencies of known recurrent genetic mutations. Event-free survival (EFS) and overall survival (OS) were the primary endpoints of this study. EFS was defined as the time from diagnosis to withdrawal of the study due to lack of complete remission, relapse, or death, or was censored at the last follow-up. OS was defined as the time from diagnosis to death from any cause, or was censored at the last follow-up. All patients provided informed consent. The study protocol of TCGA database was approved by the University of Washington Human Research Committee.

Statistical analysis

Patients' clinical and molecular characteristics were outlined by descriptive statistical methods. Numerical data was described with median and/or range; intergroup comparison was done by the Mann-Whitney *U*-test. For categorical data, we used the chi-square test to perform intergroup comparisons. Survival of each group or subgroup was estimated using the Kaplan-Meier method and compared using the log-rank test. The multivariate Cox proportional hazard models of EFS and OS were constructed using a limited backward elimination process. The statistical significance level (*P*) was less than (≤) 0.05 for a two-tailed test. All statistical analyses were performed using the SPSS software 20.0 and the GraphPad Prism software 7.0.

Results

Prognostic significance of PDLIM family expression in AML

Both chemotherapy-only and allo-HSCT groups were divided into subgroups based on the median expression levels of each of the five PDLIM members, respectively. The high expression of PDLIM2 or PDLIM7 was noted to be associated with inferior EFS and OS in the chemotherapy-only group (all P<0.05, **Table 1** and **Figure 1**). In the allo-HSCT group, survival was independent of the expression levels of any PDLIM member.

To assess the prognostic significance of PDLIM2, PDLIM7, and other clinical and molecular factors in the chemotherapy-only group, we chose the expression levels of PDLIM2 and PDLIM7 (high vs. low), WBC count (≥15 vs. <15×10^9/L), BM blasts (≥70 vs. <70%), FLT3-ITD (positive vs. negative), and other common genetic mutations (NPM1, RUNX1 and NRAS/KRAS; mutated vs. wild) to construct Cox proportional hazard models for multivariate analysis (**Table 2**). Based on the results, there were two independent risk factors for both EFS and

Table 1. Comparison of EFS and OS between different expression levels of *PDLIM* members

Variables	EFS		OS	
	χ^2	*P*-value	χ^2	*P*-value
Chemotherapy-only group				
PDLIM1 (high vs. low)	0.512	0.474	0.643	0.423
PDLIM2 (high vs. low)	4.796	0.029	6.134	0.013
PDLIM4 (high vs. low)	2.864	0.091	2.098	0.147
PDLIM5 (high vs. low)	0.707	0.401	0.955	0.328
PDLIM7 (high vs. low)	6.830	0.009	7.759	0.005
Allo-HSCT group				
PDLIM1 (high vs. low)	0.020	0.888	1.157	0.282
PDLIM2 (high vs. low)	2.236	0.135	0.644	0.422
PDLIM4 (high vs. low)	0.008	0.928	0.298	0.585
PDLIM5 (high vs. low)	0.236	0.627	1.077	0.299
PDLIM7 (high vs. low)	1.505	0.220	1.126	0.289

Abbreviations: EFS, event-free survival; OS, overall survival; Allo-HSCT, allogeneichematopoietic stem cell transplantation.

OS, which were high PDLIM7 expression and BM blasts ≥70% (all P<0.05). *RUNX1* mutation was an independent risk factor only for OS (P=0.042).

Comparison of the other clinical and molecular characteristics of the patients with different PDLIM2 and PDLIM7 expression levels

The comparison of clinical and molecular characteristics between high and low PDLIM2 and PDLIM7 expression subgroups in the chemotherapy-only group were shown in **Table 3**. Firstly, the PDLIM2^{high} subgroup were older (P= 0.029), had fewer patients with FAB-M2 (P= 0.006), more patients with complex karyotype (P=0.004), less frequent *RUNX1-RUNX1T1* (P= 0.011) but more NRAS/KRAS mutations (P= 0.004) than the PDLIM2^{low} group. No significant differences were found in gender distribution, WBC count, BM blasts, PB blasts, cytogenetic risk group distribution, and the frequencies of other recurrent genetic mutations (FLT3, NPM1, DNMT3A, IDH1/IDH2, RUNX1, TET2 and TP53) between the two subgroups. Meanwhile, comparing with the PDLIM7^{low} subgroup, PDLIM7^{high} patients had higher WBC count (P=0.045), fewer good-risk (P=0.016), and more frequent *DNMT3A* mutation (P=0.028). No significant differences were found in age, gender distribution, BM blasts, PB blasts, FAB subtypes, karyotype, and the frequencies of other recurrent genetic mutations (FLT3, NPM1, IDH1/IDH2, RUNX1, NRAS/KRAS, TET2 and TP53) between the two subgroups.

Discussion

PDLIMs are important peptide modules that controls and mediates various cellular and intercellular activities. We postulated that some of the PDLIMs could play roles in AML leukemogenesis and have prognostic meanings. In this registration-based study, we were able to find that that high expression of PDLIM2 and PDLIM7 were poor prognostic factors for AML, but their effects on survival were not observed in those who underwent allo-HSCT, indicating that allo-HSCT might prevail over the deleterious influence of PDLIM2 and PDLIM7 on AML.

PDLIM2 regulates the stability of a variety of transcription factors in the hematopoietic and epithelial cells [14]. Previous work suggested that its role in oncogenesis might be complex, with distinctive behavior in different cancer types. In some, its expression is epigenetically suppressed, such as adult T-cell lymphoma [15-17], colorectal carcinoma [18, 19], and breast cancer [20, 21]. In these tumors, in vitro and in vivo studies have observed inhibition of tumorigenicity and increasing tumor cell death after inducing PDLIM2 expression. On the other hand, PDLIM2 may have oncogenic role in other malignancies, such as prostate cancer. It is highly expressed in cell lines derived from metastatic prostate cancer and its expression is associated with tumor progression and metastasis [22]. Another study showed that PDLIM2 was capable of activating the COP9 signaling pathway, and its high expression could promote tumor growth [23]. The contradicting functions of PDLIM2 could be explained by the evolution of tumor cells when they were grown in vitro; it also highlights the complexity of oncogenesis. In this study, high PDLIM2 expression was more likely to coexist with complex karyotype and NRAS/KRAS mutations and was a poor prognostic factor for AML. Whether and how does PDLIM2 participate in the formation and thriving of AML, and if interactions exist between PDLIM2 and NRAS/KRAS, remain to be answered by future investigations.

Studies on PDLIM7 have more uniform conclusions than those on PDLIM2, that PDLIM7 often acts as a pro-oncogenic or oncogenic factor in cancers. A gene expression analysis of skin

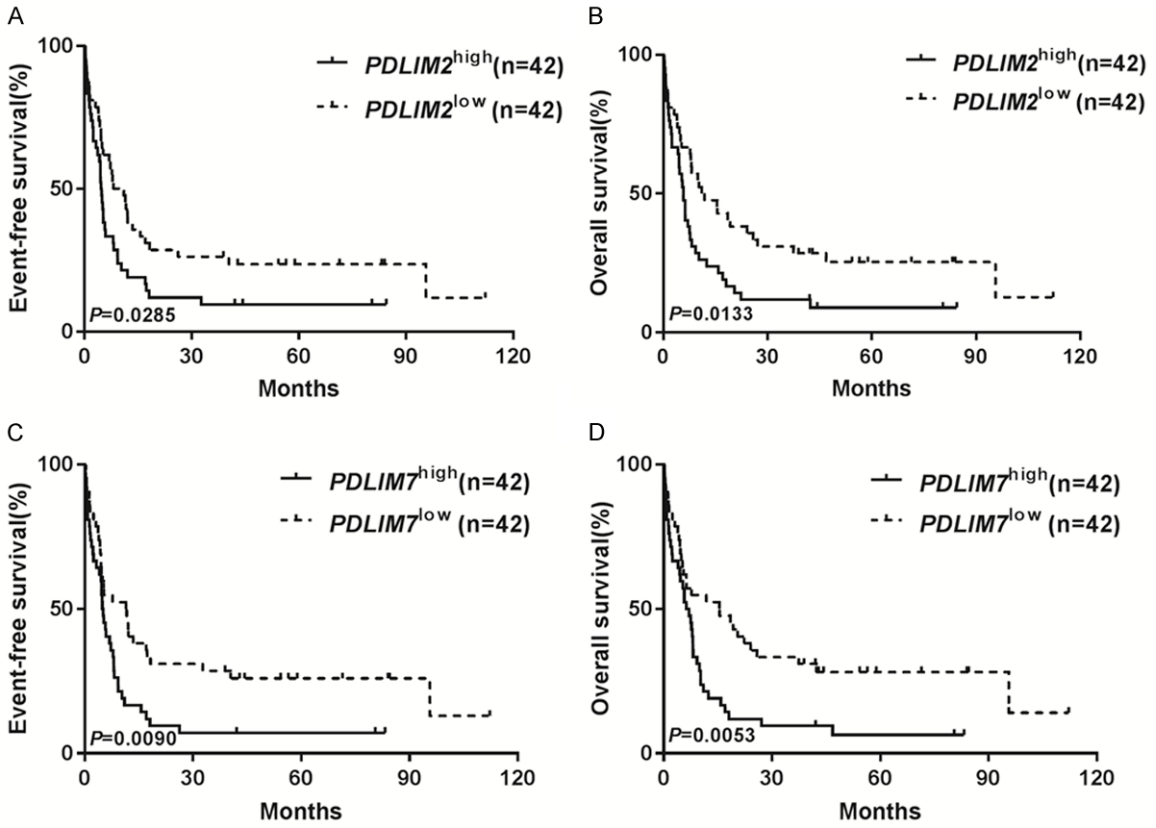

Figure 1. Kaplan-Meier curves of event-free survival (EFS) and overall survival (OS) in different expression levels of *PDLIM2* or *PDLIM7*. A, B. High *PDLIM2* expressers had shorter EFS and OS than the low expressers; C. D. High *PDLIM7* expressers had shorter EFS and OS than the low expressers.

Table 2. Multivariate analysis of EFS and OS

Variables	EFS		OS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
PDLIM2 (high vs. Low)	1.605 (0.917-2.809)	0.098	1.688 (0.965-2.952)	0.066
PDLIM7 (high vs. Low)	1.878 (1.062-3.320)	0.030	1.995 (1.139-3.495)	0.016
WBC (≥15 vs. <15×10^9/L)	0.767 (0.441-1.333)	0.346	0.819 (0.476-1.407)	0.470
BM blasts (≥70 vs. <70%)	2.073 (1.189-3.613)	0.010	2.014 (1.155-3.514)	0.014
FLT3-ITD (positive vs. negative)	0.960 (0.488-1.886)	0.905	1.042 (0.523-2.076)	0.906
NPM1 (mutated vs. wild)	0.943 (0.495-1.797)	0.859	0.842 (0.437-1.621)	0.606
RUNX1 (mutated vs. wild)	1.977 (0.877-4.457)	0.100	2.338 (1.032-5.296)	0.042
N/KRAS (mutated vs. wild)	0.719 (0.332-1.561)	0.405	0.774 (0.357-1.678)	0.516

Abbreviations: EFS, Event-free survival; OS, Overall survival; HR, hazard ratio; CI, confidence interval; WBC, white blood cell; BM, bone marrow.

tumors has shown that PDLIM7 expression is higher in metastatic compared with nonmetastatic tumors [24]. PDLIM7 is a suppressor of p53, decreasing the latter's proapoptotic activity and triggering mitosis [11]. In breast cancer, high expression level of PDLIM7 has been associated with low survival rate [25]. One explanation involves Afadin, a protein that interacts with Claudin-2 via the PDLIM7 domain, and such interaction promotes breast cancer cell growth and metastasis [26]. Another proposed mechanism of PDLIM7's oncogenic property is that as one of the major *SRF/IGF2BP1*-enhanced genes, it has conserved

Table 3. Comparison of clinical and molecular characteristics in different groups

Characteristics	*PDLIM2*		*P*	*PDLIM7*		*P*
	High (n=42)	Low (n=42)		High (n=42)	Low (n=42)	
Age/years, median (range)	68 (35-88)	63.5 (22-82)	0.029*	66.5 (35-81)	66.5 (22-88)	0.946*
Age group/n (%)			0.102§			0.483§
<60 years	10 (23.8)	17 (40.5)		12 (28.6)	15 (35.7)	
≥60 years	32 (76.2)	25 (59.5)		30 (71.4)	27 (64.3)	
Gender/n (%)			0.126§			0.512§
Male	26 (61.9)	19 (45.2)		24 (57.1)	21 (50.0)	
Female	16 (38.1)	18 (54.8)		18 (42.9)	21 (50.0)	
WBC/$\times10^9$/L, median (range)	15 (0.7-134.4)	13.7 (1-297.4)	0.872*	38 (1.5-171.9)	11 (0.7-297.4)	0.045*
BM blasts/%, median (range)	73.5 (30-98)	71.5 (32-99)	0.655*	75 (30-98)	71.5 (32-99)	0.823*
PB blasts/%, median (range)	20 (0-97)	47 (0-98)	0.058*	22.5 (0-91)	32 (0-98)	0.613*
FAB subtypes/n (%)						
M0	5 (11.9)	2 (4.8)	0.236§	4 (9.5)	3 (7.1)	0.693§
M1	10 (23.8)	10 (23.8)	1.000§	7 (16.7)	13 (31.0)	0.124§
M2	5 (11.9)	16 (38.1)	0.006§	11 (26.2)	10 (23.8)	0.801§
M4	12 (28.6)	8 (19.0)	0.306§	9 (21.4)	11 (26.2)	0.608§
M5	8 (19.0)	4 (9.5)	0.212§	8 (19.0)	4 (9.5)	0.212§
M6	1 (2.4)	0 (0.0)	0.314§	0 (0.0)	1 (2.4)	0.314§
M7	1 (2.4)	2 (4.8)	0.557§	3 (7.1)	0 (0.0)	0.078§
Karyotype/n (%)						
Normal	21 (50.0)	19 (45.2)	0.662§	22 (52.4)	18 (42.9)	0.382§
Complex	10 (23.8)	1 (2.4)	0.004§	8 (19.0)	3 (7.1)	0.106§
inv(16)/CBFβ-MYH11	3 (7.1)	3 (7.1)	1.000§	1 (2.4)	5 (11.9)	0.090§
t(8;21)/RUNX1-RUNX1T1	0 (0.0)	6 (16.3)	0.011§	1 (2.4)	5 (11.9)	0.090§
11q23/MLL	1 (2.4)	2 (4.8)	0.557§	1 (2.4)	2 (4.8)	0.557§
-7/7q-	2 (4.8)	3 (7.1)	0.645§	3 (7.1)	2 (4.8)	0.645§
t(9;22)/BCR-ABL1	0 (0.0)	1 (2.4)	0.314§	1 (2.4)	0 (0.0)	0.314§
Others	5 (11.9)	7 (16.7)	0.533§	5 (11.9)	7 (16.7)	0.533§
Risk/n (%)						
Good	3 (7.3)	9 (22.0)	0.061§	2 (5.0)	10 (23.8)	0.016§
Intermediate	23 (56.1)	23 (56.1)	1.000§	23 (56.1)	23 (56.1)	0.803§
Poor	15 (36.6)	9 (22.0)	0.145§	15 (37.5)	9 (21.4)	0.110§
FLT3/n (%)			0.137§			0.567§
FLT3-ITD	4 (9.5)	11 (26.2)		7 (16.7)	8 (19.0)	
FLT3-TKD	5 (11.9)	4 (9.5)		6 (14.3)	3 (7.1)	
Wild type	33 (78.6)	27 (64.3)		29 (69.0)	31 (73.8)	
NPM1/n (%)			0.815§			0.102§
Mutation	14 (33.3)	13 (31.0)		17 (40.5)	10 (23.8)	
Wildtype	28 (66.7)	29 (69.0)		25 (59.5)	32 (76.2)	
DNMT3A/n (%)			0.807§			0.028§
Mutation	12 (28.6)	11 (26.2)		16 (38.1)	7 (16.7)	
Wildtype	30 (71.4)	31 (73.8)		26 (61.9)	35 (83.3)	
IDH1/*IDH2*/n (%)			0.266§			0.266§
Mutation	6 (14.3)	10 (23.8)		6 (14.3)	10 (28.8)	
Wildtype	36 (85.7)	32 (76.2)		36 (85.7)	32 (76.2)	
RUNX1/n (%)			1.000§			0.137§
Mutation	4 (9.5)	4 (9.5)		2 (4.8)	6 (14.3)	

Wildtype	38 (90.5)	38 (90.5)		40 (95.2)	36 (95.7)	
NRAS/KRAS/n (%)			0.004§			0.746§
Mutation	10 (23.8)	1 (2.4)		6 (14.3)	5 (11.9)	
Wildtype	32 (76.2)	41 (97.6)		36 (85.7)	37 (88.1)	
TET2/n (%)			0.365§			0.763§
Mutation	5 (11.9)	8 (19.0)		6 (14.3)	7 (16.7)	
Wildtype	37 (88.1)	34 (81.0)		36 (85.7)	35 (83.3)	
TP53/n (%)			0.061§			0.061§
Mutation	9 (21.4)	3 (7.1)		9 (21.4)	3 (7.1)	
Wildtype	33 (78.6)	39 (92.9)		33 (78.6)	39 (92.9)	

Abbreviations: WBC, white blood cell; BM, bone marrow; PB, peripheral blood; FAB, French American British. '*' denotes Mann-Whitney *U* test; '§' denotes chi-square test.

upregulation with SRF and IGF2BP1, and together they promote tumor cell growth and invasion [27]. We found that high PDLIM7 expression was more likely to coexist with high WBC count and DNMT3A mutations and was also associated with inferior prognosis of AML. In contrast to PDLIM2, PDLIM7 had an independent prognostic effect, and could be a better marker than the former.

In multivariate analysis, BM blasts ≥70% was an independent risk factor for EFS and OS. This was consistent with former finding that abnormal proliferation of BM blasts could exert significant negative effect on AML survival [28]. RUNX1 mutation was also an independent risk factor for EFS and OS in AML, in line with former findings that somatic mutation of RUNX1 was an indicator of low OS in patients with myelodysplastic syndrome, and that RUNX1 mutation would predict poor outcomes in AML [29].

Conclusions

In conclusion, our study indicated that high expression of PDLIM2 and PDLIM7 were poor prognostic factors for AML, which could be overcome by allo-HSCT. The study was limited by its registration-based, retrospective nature and a small sample size. Therefore, larger subsequent clinical studies and laboratory investigations are needed to verify our findings and decipher the role of the PDLIM family in tumorigenesis.

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Disclosure of conflict of interest

None.

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