Overexpression of PDK2 and PDK3 reflects poor prognosis in acute myeloid leukemia

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ARTICLE

Overexpression of PDK2 and PDK3 reflects poor prognosis in acute myeloid leukemia

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Abstract

Acute myeloid leukemia (AML) is a hematological malignancy characterized by the proliferation of immature myeloid cells, with impaired differentiation and maturation. Pyruvate dehydrogenase kinase (PDK) is a pyruvate dehydrogenase complex (PDC) phosphatase inhibitor that enhances cell glycolysis and facilitates tumor cell proliferation. Inhibition of its activity can induce apoptosis of tumor cells. Currently, little is known about the role of PDKs in AML. Therefore, we screened The Cancer Genome Atlas (TCGA) database for de novo AML patients with complete clinical information and *PDK* family expression data, and 84 patients were included for the study. These patients did not undergo allogeneic hematopoietic stem cell transplantation (allo-HSCT). Univariate analysis showed that high expression of *PDK2* was associated with shorter EFS ($P = 0.047$), and high expression of *PDK3* was associated with shorter OS ($P = 0.026$). In multivariate analysis, high expression of *PDK3* was an independent risk factor for EFS and OS ($P < 0.05$). In another TCGA cohort of AML patients who underwent allo-HSCT ($n = 71$), *PDK* expression was not associated with OS (all $P > 0.05$). Our results indicated that high expressions of *PDK2* and *PDK3*, especially the latter, were poor prognostic factors of AML, and the effect could be overcome by allo-HSCT.

Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia in adults and is a heterogeneous hematopoietic stem cell disorder characterized by disordered proliferation of bone marrow precursor cells, resulting in impaired production of normal blood cells [1]. The backbone of the standard induction therapy consists of cytarabine and an anthracycline antibiotic. In patients 65 years or younger, ~80% of AML

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cases can achieve complete remission [2, 3]. However, without consolidation, relapse can occur in more than half of the cases with increased resistance to treatment. Therefore, individualized prognostic stratification is crucial in choosing the appropriate candidates for hematopoietic stem cell transplantation. Chromosomal or genetic abnormality is by far the most important prognostic factor. Intermediate-risk AML comprises more than half of adult cases, but the survival within this group is heterogeneous, meaning more room for further risk stratification [4, 5]. In recent years, several recurrent genetic mutations have been associated with the survival of intermediate-risk AML, such as FMS-like tyrosine kinase 3 internal tandem duplication (*FLT3-ITD*), nucleophosmin 1 (*NPM1*) mutation, and CCAAT/enhancer-binding protein alpha (*CEBPA*) mutation [6–10]. However, the frequency of these anomalies are observed in only about 30% of the intermediate-risk group, indicating the need to discover other prognostic factors [11, 12].

According to the Warburg effect, tumor cells primarily utilize glycolysis instead of aerobic oxidation to produce energy. Pyruvate dehydrogenase kinase (PDK) is an inhibitor of the pyruvate dehydrogenase complex (PDC), and is involved in the pathophysiology of many disorders with abnormal metabolism, including cancer [13]. While PDC facilitates aerobic oxidation, PDK inhibits its activity by phosphorylation, thereby diverting cell metabolism towards glycolysis [14]. High expression of PDKs may be responsible for the aberrant activation of glycolysis observed in tumors [15]. There are four PDK isoenzymes (1–4) in human cells [16]. Overexpression of PDK1 is one of the common features of AML, and it can promote the formation of monocyte colonies and participate in the regulation of human leukemia lineage [17]. Additionally, PDK1 is an activator of the PI3K/AKT pathway, and inhibition of PDK1 expression can reduce the activity of this pathway, thereby affecting the AML cell cycle [18]. The inhibitory effect of tumor cell proliferation exerted by inhibiting PDK isoenzyme activity has been observed in lung, prostate and breast cancer [19]. The role of PDKs in the prognosis of leukemia, on the other hand, is still poorly understood. Our study aimed to analyze the prognostic impact of *PDK* gene expression in AML and gain new insights into individualized prognostic stratification.

Patients and Methods

Patients

A total of 155 adult de novo AML patients with complete clinical data and *PDK* expression information from The Cancer Genome Atlas (TCGA) database were included in the study. Eighty-four patients were treated with chemotherapy only, and 71 further received allogeneic hematopoietic stem cell transplantation (allo-HSCT) as consolidation. Chemotherapy-only patients age ranged from 22 to 88. Clinical features at diagnosis were described, including peripheral blood (PB) white blood cell counts (WBC), blast percentages in PB and bone marrow (BM), French-American-British (FAB) subtypes, and the frequencies of known recurrent genetic mutations. Detailed clinical and molecular characteristics could be found on the TCGA website. 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 or was censored at the last follow-up. Informed consent was provided to all patients and the study protocol was approved by the University of Washington Human Research Committee.

Statistical analysis

The clinical and molecular characteristics of the patients were summarized using descriptive statistical methods. Data sets were described by median and/or range. The Mann–Whitney *U* test was used as appropriate to compare numerical comparison and X^2 test for comparison of categorical data. Survival rates were estimated using the Kaplan–Meier method and the log-rank test. The univariate and multivariate Cox proportional hazard models of EFS and OS were established using a limited backward elimination process. The statistical significance level was 0.05 for a two-tailed test. All statistical analyses were performed using SPSS software 20.0 and GraphPad Prism software 7.0.

Results

Prognostic significance of *PDK* family in AML

According to the median expression levels of the four *PDK* members, all patients were divided into two groups. Kaplan–Meier analysis demonstrated that the chemotherapy-only patients with high *PDK2* expression had shorter EFS than those with low expressions ($P = 0.047$, Table 1, Fig. 1A); the high *PDK3* expression group had shorter OS than the low expression group ($P = 0.026$, Table 1, Fig. 1D). But in allo-HSCT patients, only the difference in EFS between $PDK3^{low}$ group and $PDK3^{high}$ group was statistically significant ($P = 0.010$, Table 1). Allo-HSCT could have overcome the adverse effect on OS brought by the high expressions of *PDK2* and *PDK3* (all $P > 0.05$). Following these initial results, we then focused the statistical analysis on the chemotherapy-only patients.

Clinical and molecular characteristics of the patients

All chemotherapy-only patients ($n = 84$) were divided by *PDK2* and *PDK3* median expression levels respectively (Table 2). Comparing to the $PDK2^{low}$ group, the $PDK2^{high}$ group had more FAB-M1 ($P = 0.040$) and fewer FAB-M4 ($P = 0.040$), fewer patients with inv(16)/*CBFβ-MYH11* ($P = 0.011$) and more with other karyotypes ($P = 0.013$), and fewer good-risk patients ($P = 0.012$). No significant differences were found in age, gender distribution, race, WBC count, BM blasts, PB blasts, and frequency of other recurrent genetic mutations (*FLT3-ITD*, *NPM1*, *DNMT3A*, *IDH1/IDH2*, *RUNX1*, *NRAS/KRAS*, *TET2* and *TP53*) between the two groups. Meanwhile, comparing to the $PDK3^{low}$ group, $PDK3^{high}$ group had more FAB-M0 patients ($P = 0.048$), fewer patients with *RUNX1-RUNX1T* ($P = 0.011$), and fewer good-risk patients ($P = 0.002$). No significant differences were found in age, gender distribution, race, WBC count, BM blasts, PB blasts, and frequency of other recurrent genetic mutations (*FLT3-ITD*, *NPM1*, *DNMT3A*, *IDH1/IDH2*, *RUNX1*, *NRAS/KRAS*, *TET2* and *TP53*) between the two groups.

Table 1 Comparison of EFS and OS between different expression levels of *PDK1-4*

Variables	EFS		OS	
	χ^2	*P* value	χ^2	*P* value
Chemotherapy-only group				
PDK1 (high vs. low)	1.122	0.289	0.784	0.376
PDK2 (high vs. low)	3.948	0.047	3.277	0.070
PDK3 (high vs. low)	3.721	0.054	4.928	0.026
PDK4 (high vs. low)	1.698	0.192	2.330	0.127
Allo-HSCT group				
PDK1 (high vs. low)	1.042	0.307	0.062	0.803
PDK2 (high vs. low)	0.918	0.338	1.485	0.223
PDK3 (high vs. low)	6.660	0.010	1.735	0.188
PDK4 (high vs. low)	0.043	0.835	0.021	0.884

EFS event-free survival, *OS* overall survival

Multivariate analyses of EFS and OS

To assess the prognostic significance of the aforementioned clinical and molecular characteristics in the chemotherapy-only patients, we chose the expression levels of *PDK2* and *PDK3* (high vs. low), WBC count (≥15 vs. $<15 \times 10^9$/L), BM blasts (≥70 vs. <70%), *FLT3-ITD* (positive vs. negative), and other common genetic mutations (*NPM1*, *DNMT3A*, *RUNX1* and *TP53*; mutated vs. wild) to construct multivariate analyses (Table 3). Three independent risk factors were identified for EFS and OS, including high *PDK3* expression, BM blasts ≥ 70% and *TP53* mutation (all $P < 0.05$).

Discussion

In our study, we found that high expressions of *PDK2* and *PDK3* had adverse prognostic effects on AML, especially the latter. Zabkiewicz, et. al. had shown that overexpression

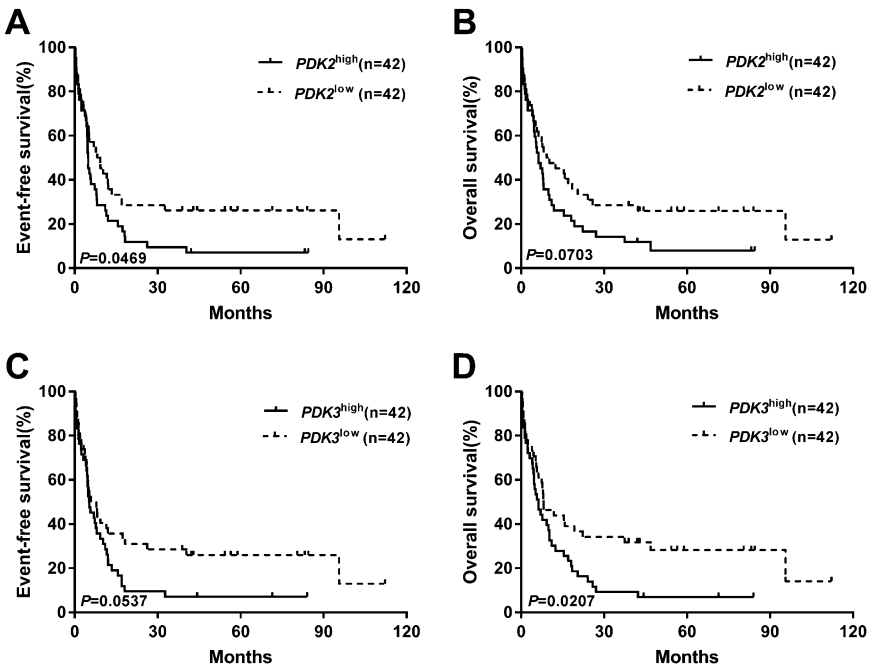

Fig. 1 Kaplan–Meier curves of event-free survival (EFS) and overall survival (OS) in different expression levels of *PDK2* or *PDK3*. A, B. High *PDK2* expressers had shorter EFS and OS than the low expressers. C, D. High *PDK3* expressers had shorter EFS and OS than the low expressers.

Table 2 Comparison of clinical and molecular characteristics in different groups

Characteristics	*PDK2*			*PDK3*		
	High ($n = 42$)	Low ($n = 42$)	*P* value	High ($n = 42$)	Low ($n = 42$)	*P* value
Age/years, median (range)	67 (35–88)	66 (22–81)	0.730*	67 (33–81)	63 (22–88)	0.522*
Age group/*n* (%)			0.483§			0.483§
<60 years	12 (28.6)	15 (35.7)		12 (28.6)	15 (35.7)	
≥60 years	30 (71.4)	27 (64.3)		30 (71.4)	27 (64.3)	
Gender/*n* (%)			0.827§			0.827§
Male	22 (52.4)	23 (54.8)		23 (54.8)	22 (52.4)	
Female	20 (47.6)	19 (45.2)		19 (45.2)	20 (47.6)	
Race/*n* (%)			0.450§			0.450§
Caucasian	30 (71.4)	33 (78.6)		30 (71.4)	33 (78.6)	
Others	12 (28.6)	9 (21.4)		12 (28.6)	9 (21.4)	
WBC/$\times 10^9$/L, median (range)	8.55 (0.7–134.4)	19.6 (1–297.4)	0.154*	8.8 (0.7–297.4)	17 (1.4–116.2)	0.370*
BM blasts/%, median (range)	73 (30–97)	71.5 (35–99)	0.674	71 (30–99)	72 (32–98)	0.982*
PB blasts/%, median (range)	24 (0–97)	21 (0–98)	0.713*	17 (0–98)	37 (0–97)	0.415*
FAB subtypes/n (%)						
M0	4 (9.5)	3 (7.1)	0.693§	6 (14.3)	1 (2.4)	0.048§
M1	14 (33.3)	6 (14.3)	0.040§	8 (19.0)	12 (28.6)	0.306§
M2	8 (19.0)	13 (31.0)	0.208§	9 (21.4)	12 (28.6)	0.450§
M4	6 (14.3)	14(33.3)	0.040§	11 (26.2)	9 (21.4)	0.608§
M5	7 (16.7)	5 (11.9)	0.533§	5 (11.9)	7 (16.7)	0.533§
M6	1 (2.4)	0 (0.0)	0.314§	0 (0.0)	1 (2.4)	0.314§
M7	2 (4.8)	1 (2.4)	0.557§	3 (7.1)	0 (0.0)	0.078§
Karyotype/*n* (%)						
Normal	21 (50.0)	19 (45.2)	0.662§	21 (50.0)	19 (45.2)	0.662§
Complex	6 (14.3)	5 (11.9)	0.746§	7 (16.7)	4 (9.5)	0.332§
inv(16)/CBFβ-MYH11	0 (0.0)	6 (14.3)	0.011§	1 (2.4)	5 (11.9)	0.090§
t(8;21)/RUNX1-RUNX1T1	2 (4.8)	4 (9.5)	0.397§	0 (0.0)	6 (14.3)	0.011§
11q23/MLL	0 (0.0)	3 (7.1)	0.078§	1 (2.4)	2 (4.8)	0.557§
-7/7q-	3 (7.1)	2(4.8)	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	10 (23.8)	2 (4.8)	0.013§	8 (19.0)	4 (9.5)	0.212§
Risk/*n* (%)						
Good	2 (4.9)	10 (24.4)	0.012§	1 (2.5)	11 (26.2)	0.002§
Intermediate	27 (65.9)	19 (46.3)	0.075§	16 (40.0)	20 (47.6)	0.487§
Poor	12 (29.3)	12 (29.3)	1.000§	15 (37.5)	9 (21.4)	0.110§
FLT3/*n* (%)			0.513§			0.333§
FLT3-ITD	7 (16.7)	8 (19.0)		6 (14.3)	9 (21.4)	
FLT3-TKD	3 (7.1)	6 (14.3)		3 (7.1)	6 (14.3)	
Wild type	32 (76.2)	28 (66.7)		33 (78.6)	27 (64.3)	
NPM1/n (%)			0.483§			0.815§
Mutation	15 (35.7)	12 (28.6)		14 (33.3)	13 (31.0)	
Wild type	27 (64.3)	30 (71.4)		28 (66.7)	29 (69.0)	
DNMT3A/n (%)			0.807§			0.807§
Mutation	11 (26.2)	12 (28.6)		12 (28.6)	11 (26.2)	
Wild type	31 (73.8)	30 (71.4)		30 (71.4)	31 (73.8)	

Table 2 (continued)

Characteristics	*PDK2*			*PDK3*		
	High ($n = 42$)	Low ($n = 42$)	*P* value	High ($n = 42$)	Low ($n = 42$)	*P* value
IDH1/*IDH2*/n (%)			0.578§			0.266§
Mutation	7 (16.7)	9 (21.4)		10 (23.8)	6 (14.3)	
Wild type	35 (83.3)	33 (78.6)		32 (76.2)	36 (85.7)	
RUNX1/n (%)			0.137§			0.137§
Mutation	6 (14.3)	2 (4.8)		6 (14.3)	2 (4.8)	
Wild type	36 (85.7)	40 (95.2)		36 (85.7)	40 (95.2)	
NRAS/*KRAS*/n (%)			0.746§			0.746§
Mutation	5 (11.9)	6 (14.3)		5 (11.9)	6 (14.3)	
Wild type	37 (88.1)	36 (85.7)		37 (88.1)	36 (85.7)	
TET2/n (%)			0.763§			0.763§
Mutation	7 (16.7)	6 (14.3)		7 (16.7)	6 (14.3)	
Wild type	35 (83.3)	36 (85.7)		35 (83.3)	36 (85.7)	
TP53/n (%)			1.000§			0.212§
Mutation	6 (14.3)	6 (14.3)		8 (19.0)	4 (9.5)	
Wild type	36 (85.7)	36 (85.7)		34 (81.0)	38 (90.5)	

WBC white blood cell, *BM* bone marrow, *PB* peripheral blood, *FAB* French American British

* denotes Mann–Whitney *U* test, § denotes X^2 test

Table 3 Multivariate analysis of EFS and OS

Variables	EFS		OS	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
PDK2 (high vs. Low)	0.651 (0.381–1.115)	0.118	0.640 (0.371–1.105)	0.109
PDK3 (high vs. Low)	0.559 (0.329–0.951)	0.032	0.523 (0.304–0.900)	0.019
WBC (≥ 15 vs. $< 15 \times 10^9$/L)	1.419 (0.808–2.491)	0.223	1.491 (0.845–2.631)	0.168
BM blasts (≥ 70 vs. $< 70\%$)	1.803(1.038–3.132)	0.037	1.657 (0.953–2.878)	0.073
FLT3-ITD (positive vs. negative)	1.179 (0.777–1.790)	0.439	1.208 (0.797–1.830)	0.373
NPM1 (mutated vs. wild)	0.929 (0.462–1.865)	0.835	0.784 (0.389–1.578)	0.495
DNMT3A (mutated vs. wild)	1.556 (0.846–2.863)	0.155	1.550 (0.847–2.839)	0.156
TP53 (mutated vs. wild)	3.055 (1.372–6.804)	0.006	2.909 (1.305–6.485)	0.009
RUNX1(mutated vs. wild)	1.880 (0.791–4.469)	0.153	1.988 (0.841–4.703)	0.118

EFS event-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *WBC* white blood cell, *BM* bone marrow, *PB* peripheral blood

of *PDK1* was seen in over 40% of myelomonocytic acute leukemia patients, which was associated with poorer treatment outcome [20]. We did not observe a similar effect of *PDK1* in our study. This might be explained by the focus on the myelomonocytic subtypes of the previous study, while our study did not have a specific focus on leukemia subtypes.

The unique metabolic pathway of aerobic glycolysis has become a major target for cancer treatment [21]. PDKs are clearly overexpressed in a variety of human tumors, promoting glucose-dependent oxidative phosphorylation, and inhibiting such activity is one of the important directions in therapy [22, 23]. There is also evidence that PDKs can at least indirectly affect the cell cycle and they can be regulated by oncogenes [24–27]. Targeted inhibition of the isoenzyme may reverse the Warburg effect of tumor cells, reduce lactic acid concentration in the tumor microenvironment, increase mitochondrial reactive oxygen species (ROS) production, and decrease HIF1a expression and caspase-mediated apoptosis [28]. In several experimental models, inhibiting PDKs can reduce the risk of tumor angiogenesis and metastasis, and prolong survival [29]. Among them, *PDK2* has the widest tissue distribution and is particularly sensitive to the PDC reaction products, acetyl-CoA and NADH [30]. The expression of *PDK3* in colon cancer was found to be directly related

to metastasis and inversely correlated with survival [24]. During hypoxia, *PDK3* was overexpressed in glioblastoma multiforme; inhibition of *HIF1α* expression reduced *PDK3* expression, leading to tumor cell apoptosis [31]. Nucleus accumbens-1 (NAC1), a nuclear protein of the BTB/POZ gene family, mediates suppression of mitochondrial function in hypoxia through inducing expression of *PDK3* by *HIF-1a* at the transcriptional level, thereby inactivating pyruvate dehydrogenase and attenuating mitochondrial respiration [32]. In sporadic clear-cell renal cell carcinoma, the von Hippel-Lindau tumor suppressor gene was easily inactivated and also caused a decrease in the expression of *PDK3* [33]. The molecular mechanism of the adverse prognostic effect of *PDK3* on AML is yet to be elucidated.

In multivariate analyses, *TP53* mutation also had unfavorable effects on EFS and OS. *TP53* is a multifunctional transcription factor that is activated during DNA damage and hypoxia [34]. It's the main genetic controller of apoptosis. It regulates the G1 to S phase of the cell cycle and maintains the integrity of the genome [35]. Abnormal mutation and expression of *TP53* is associated with the tumorigenesis of various cancers [36]. There are few studies on the relationship between *PDK3* expression and *TP53* mutation. There may be some interplay between these two genes in the case of AML, which is worth studying in the future.

In conclusion, our study indicated that the overexpression of *PDK2* and *PDK3* conferred poor prognosis in AML, especially the latter. The study used registry data with a small sample size. Therefore, larger prospective study would be needed for further verification.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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