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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.

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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 χ^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)/CBF β -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.

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 $\geq 70\%$ and *TP53* mutation (all $P < 0.05$).

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				
<i>PDK1</i> (high vs. low)	1.122	0.289	0.784	0.376
<i>PDK2</i> (high vs. low)	3.948	0.047	3.277	0.070
<i>PDK3</i> (high vs. low)	3.721	0.054	4.928	0.026
<i>PDK4</i> (high vs. low)	1.698	0.192	2.330	0.127
Allo-HSCT group				
<i>PDK1</i> (high vs. low)	1.042	0.307	0.062	0.803
<i>PDK2</i> (high vs. low)	0.918	0.338	1.485	0.223
<i>PDK3</i> (high vs. low)	6.660	0.010	1.735	0.188
<i>PDK4</i> (high vs. low)	0.043	0.835	0.021	0.884

EFS event-free survival, OS overall survival

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	<i>PDK2</i>			<i>PDK3</i>		
	High (<i>n</i> = 42)	Low (<i>n</i> = 42)	<i>P</i> value	High (<i>n</i> = 42)	Low (<i>n</i> = 42)	<i>P</i> value
Age/years, median (range)	67 (35–88)	66 (22–81)	0.730*	67 (33–81)	63 (22–88)	0.522*
Age group/ <i>n</i> (%)			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/ <i>n</i> (%)			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/ <i>n</i> (%)			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/× 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/ <i>n</i> (%)						
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/ <i>n</i> (%)						
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/ <i>n</i> (%)						
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§
<i>FLT3</i> / <i>n</i> (%)			0.513§			0.333§
<i>FLT3</i> -ITD	7 (16.7)	8 (19.0)		6 (14.3)	9 (21.4)	
<i>FLT3</i> -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)	
<i>NPM1</i> / <i>n</i> (%)			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)	
<i>DNMT3A</i> / <i>n</i> (%)			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	<i>PDK2</i>			<i>PDK3</i>		
	High (<i>n</i> = 42)	Low (<i>n</i> = 42)	<i>P</i> value	High (<i>n</i> = 42)	Low (<i>n</i> = 42)	<i>P</i> value
<i>IDH1/IDH2</i> /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)	
<i>RUNX1</i> /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)	
<i>NRAS/KRAS</i> /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)	
<i>TET2</i> /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)	
<i>TP53</i> /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 χ^2 test

Table 3 Multivariate analysis of EFS and OS

Variables	EFS		OS	
	HR (95%CI)	<i>P</i> value	HR (95%CI)	<i>P</i> value
<i>PDK2</i> (high vs. Low)	0.651 (0.381–1.115)	0.118	0.640 (0.371–1.105)	0.109
<i>PDK3</i> (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
<i>FLT3</i> -ITD (positive vs. negative)	1.179 (0.777–1.790)	0.439	1.208 (0.797–1.830)	0.373
<i>NPM1</i> (mutated vs. wild)	0.929 (0.462–1.865)	0.835	0.784 (0.389–1.578)	0.495
<i>DNMT3A</i> (mutated vs. wild)	1.556 (0.846–2.863)	0.155	1.550 (0.847–2.839)	0.156
<i>TP53</i> (mutated vs. wild)	3.055 (1.372–6.804)	0.006	2.909 (1.305–6.485)	0.009
<i>RUNX1</i> (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 HIF1 α 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 *HIF1 α* 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-1 α* 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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References

- De Kouchkovsky I, Abdul-Hay M. Acute myeloid leukemia: a comprehensive review and 2016 update. *Blood Cancer J*. 2016;6:e441.
- Tallman MS, Gilliland DG, R JM. Drug therapy for acutemyeloid leukemia. *Blood*. 2005;106:1154–63.
- Ohtake S, Miyawaki S, Fujita H, Kiyoi H, Shinagawa K, Usui N, et al. Randomized study of induction therapy comparing standard-dose idarubicin with high-dose daunorubicin in adult patients with previously untreated acute myeloid leukemia: the JALSG AML201 Study. *Blood*. 2011;117:2358–65.
- Wu S, Dai Y, Zhang Y, Wang X, Wang L, Ma D, et al. Mutational spectrum and prognostic stratification of intermediate-risk acute myeloid leukemia. *Cancer Gene Ther*. 2018;25:207–13.
- Byrd JC, Mrózek K, Dodge RK, Carroll AJ, Edwards CG, Arthur DC, et al. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). *Blood*. 2002;100:4325–36.
- Schnittger S1, Schoch C, Kern W, Mecucci C, Tschulik C, Martelli MF, et al. Nucleophosmin gene mutations are predictors of favorable prognosis in acute myelogenous leukemia with a normal karyotype. *Blood*. 2005;106:3733–9.
- Preudhomme C, Sagot C, Boissel N, Cayuela JM, Tigaud I, de Botton S, et al. Favorable prognostic significance of CEBPA mutations in patients with de novo acute myeloid leukemia: a study from the Acute Leukemia French Association (ALFA). *Blood*. 2002;100:2717–23.
- Pabst T1, Eyholzer M, Fos J, M BU. Heterogeneity within AML with CEBPA mutations; only CEBPA double mutations, but not single CEBPA mutations are associated with favourable prognosis. *Br J Cancer*. 2009;100:1343–6.
- Kottaridis PD, Gale RE, Frew ME, Harrison G, Langabeer SE, Belton AA, et al. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. *Blood*. 2001;98:1752–9.
- Döhner K, Schlenk RF, Habdank M, Scholl C, Rücker FG, Corbacioglu A, et al. Mutant nucleophosmin (NPM1) predicts favorable prognosis in younger adults with acute myeloid leukemia and normal cytogenetics: interaction with other gene mutations. *Blood*. 2005;106:3740–6.
- Ryotokuji T, Yamaguchi H, Ueki T, Usuki K, Kurosawa S, Kobayashi Y, et al. Clinical characteristics and prognosis of acute myeloid leukemia associated with DNA-methylation regulatory gene mutations. *Haematologica*. 2016;101:1074–81.
- Terada K, Yamaguchi H, Ueki T, Usuki K, Kobayashi Y, Tajika K, et al. Usefulness of BCOR gene mutation as a prognostic factor in acute myeloid leukemia with intermediate cytogenetic prognosis. *Genes Chromosomes Cancer*. 2018;57:401–8.
- Gudi R, Bowker-Kinley MM, Kedishvili NY, Zhao Y, P KM. Diversity of the pyruvate dehydrogenase kinase gene family in humans. *J Biol Chem*. 1995;270:28989–94.
- Korotchikina LG, P MS. Site specificity of four pyruvate dehydrogenase kinase isoenzymes toward the three phosphorylation sites of human pyruvate dehydrogenase. *J Biol Chem*. 2001;276:37223–9.
- Pouyssegur J, Dayan F, M NM. Hypoxia signalling in cancer and approaches to enforce tumour regression. *Nature*. 2006;441:437–43.
- Bowker-Kinley MM, Davis WI, Wu P, Harris RA, P KM. Evidence for existence of tissue-specific regulation of the mammalian pyruvate dehydrogenase complex. *Biochem J*. 1998;329(Pt 1): 191–6.
- Pearm L, Fisher J, Burnett AK, D RL. The role of PKC and PDK1 in monocyte lineage specification by Ras. *Blood*. 2007;109:4461–9.
- Yoon JS, Won YW, Kim SJ, Oh SJ, Kim ES, Kim BK, et al. Anti-leukemic effect of 2-pyrone derivatives via MAPK and PI3 kinase pathways. *Invest New Drugs*. 2012;30:2284–93.
- Wigfield SM, Winter SC, Giatromanolaki A, Taylor J, Koukourakis ML, H AL. PDK-1 regulates lactate production in hypoxia

- and is associated with poor prognosis in head and neck squamous cancer. *Br J Cancer*. 2008;98:1975–84.
20. Zabkiewicz J, Pearn L, Hills RK, Morgan RG, Tonks A, Burnett AK, et al. The PDK1 master kinase is over-expressed in acute myeloid leukemia and promotes PKC-mediated survival of leukemic blasts. *Haematologica*. 2014;99:858–64.
 21. Yang J, Cao Q, Zhang H, Hao L, Zhou D, Gan Z, et al. Targeted reversal and phosphorescence lifetime imaging of cancer cell metabolism via a theranostic rhenium(I)-DCA conjugate. *Bio-materials*. 2018;176:94–105.
 22. Christofk HR, Vander Heiden MG, Harris MH, Ramanathan A, Gerszten RE, Wei R, et al. The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. *Nature*. 2008;452:230–3.
 23. Zhang SL, Hu X, Zhang W, Yao H1, T KY. Development of pyruvate dehydrogenase kinase inhibitors in medicinal chemistry with particular emphasis as anticancer agents. *Drug Discov Today*. 2015;20:1112–9.
 24. Kaplon J, Zheng L, Meissl K, Chaneton B, Selivanov VA, Mackay G, et al. A key role for mitochondrial gatekeeper pyruvate dehydrogenase in oncogene-induced senescence. *Nature*. 2013;498:109–12.
 25. Pate KT, Stringari C, Sprowl-Tanio S, Wang K, TeSlaa T, Hoverter NP, et al. Wnt signaling directs a metabolic program of glycolysis and angiogenesis in colon cancer. *EMBO J*. 2014;33:1454–73.
 26. Kamarajugadda S, Stemboroski L, Cai Q, Simpson NE, Nayak S, Tan M, et al. Glucose oxidation modulates anoikis and tumor metastasis. *Mol Cell Biol*. 2012;32:1893–907.
 27. Lu CW, Lin SC, Chien CW, Lin SC, Lee CT, Lin BW, et al. Overexpression of pyruvate dehydrogenase kinase 3 increases drug resistance and early recurrence in colon cancer. *Am J Pathol*. 2011;179:1405–14.
 28. Bonnet S, Archer SL, Allalunis-Turner J, Haromy A, Beaulieu C, Thompson R, et al. A mitochondria-K⁺ channel axis is suppressed in cancer and its normalization promotes apoptosis and inhibits cancer growth. *Cancer Cell*. 2007;11:37–51.
 29. Kankotia S, S PW. Dichloroacetate and cancer: new home for an orphan drug? *Biochim Biophys Acta*. 2014;1846: 617–29.
 30. S PW. Therapeutic targeting of the pyruvate dehydrogenase complex/pyruvate dehydrogenase kinase (PDC/PDK) axis in cancer. *J Natl Cancer Inst*. 2017;109:11.
 31. Han JE, Lim PW, Na CM, Choi YS, Lee JY, Kim Y, et al. Inhibition of HIF1 α and PDK Induces Cell Death of Glioblastoma Multiforme. *Exp Neurobiol*. 2017;26:5.
 32. Ren YJ, Wang XH, Ji C, Guan YD, Lu XJ, Liu XR, et al. Silencing of NAC1 expression induces cancer cells oxidative stress in hypoxia and potentiates the therapeutic activity of elesclomol. *Front Pharmacol*. 2017;8:804.
 33. Ilic BojanaB, Antic JadrankaA, Bankovic JovanaZ, Milicevic IvanaT, Rodic GordanaS, Ilic DusanS, et al. VHL dependent expression of redd1 and PDK3 proteins in clear-cell renal cell carcinoma. *J Med Biochem*. 2018;37:31–8.
 34. Siddamalla S, Reddy TV, Govatati S, Guruvaiiah P, Deenadayal M, Shivaji S, et al. Influence of tumour suppressor gene (TP53, BRCA1 and BRCA2) polymorphisms on polycystic ovary syndrome in South Indian women. *Eur J Obstet Gynecol Reprod Biol*. 2018;227:13–8.
 35. Shim U, Kim HN, Lee H, Oh JY, Sung YA, K HL. Pathway analysis based on a genome-wide association study of polycystic ovary syndrome. *PLoS ONE*. 2015;10:e0136609.
 36. Duffy MJ, Synnott NC, C J. Mutant p53 in breast cancer: potential as a therapeutic target and biomarker. *Breast Cancer Res*. 2018; 170:213–9.