PLK1, A Potential Target for Cancer Therapy

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Zhixian Liu*, Qingrong Sun† and Xiaosheng Wang*

*Department of Basic Medicine, School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing 211198, China; †School of Science, China Pharmaceutical University, Nanjing 211198, China

Abstract

Polo-like kinase 1 (PLK1) plays an important role in the initiation, maintenance, and completion of mitosis. Dysfunction of PLK1 may promote cancerous transformation and drive its progression. PLK1 overexpression has been found in a variety of human cancers and was associated with poor prognoses in cancers. Many studies have showed that inhibition of PLK1 could lead to death of cancer cells by interfering with multiple stages of mitosis. Thus, PLK1 is expected to be a potential target for cancer therapy. In this article, we examined PLK1's structural characteristics, its regulatory roles in cell mitosis, PLK1 expression, and its association with survival prognoses of cancer patients in a wide variety of cancer types, PLK1 interaction networks, and PLK1 inhibitors under investigation. Finally, we discussed the key issues in the development of PLK1-targeted cancer therapy.

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Introduction

Polo-like kinases (PLKs) are a family of serine/threonine protein kinases which are widespread in eukaryotic cells [1]. Human PLK family includes five members: PLK1, PLK2, PLK3, PLK4, and PLK5. Among them, PLK1 was the most investigated [2]. PLK1 plays multiple roles in the cell cycle: controls mitotic entry and the G2/M checkpoint, coordinates the centrosome and cell cycles, regulates spindle assembly and chromosome segregation, exerts multiple functions at the spindle midzone and during abscission, facilitates DNA replication, and is involved in cytokinesis and meiosis [3]. PLK1 is essential for precisely regulating the cell division and maintaining genome stability in mitosis, spindle assembly, and DNA damage response [2,4]. Previous studies have shown that PLK1 is highly expressed in most of human cancers, and its overexpression is associated with poor prognosis in cancer patients [5–7]. Several reports have shown that blocking the expression of PLK1 by antibody, RNA interference (RNAi), or kinase inhibitors can effectively inhibit the proliferation of tumor cells and induce apoptosis of tumor cells [8,9]. Thus, it has been suggested that PLK1 could be an attractive target for cancer therapy [10]. In this article, we reviewed PLK1's functions in cell cycle progression, its roles in human cancers, and the development of potential inhibitors targeting PLK1 in cancer treatment.

The Structure Characteristics of PLK1

As the other members in PLK family, PLK1 protein involves a highly conserved N-terminal kinase catalytic domain (harboring 252 amino acids), C-terminal polo-box domain (harboring 60-70 amino acids), and the connecting region in the middle. The N-terminal kinase domain is a Ser/Thr kinase domain with a T-loop whose phosphorylation is directly related to the kinase activity of PLK1 [11]. The polo-box domain is a notable feature of PLK family. It is located in the C-terminal, each of which contains two polo-box structures, and a flexible structure is in the middle (Figure 1). The crystal structure of PLK1 shows that the polo-box domain is similar to two clips, and the phosphopeptide is clamped in the middle [12]. Differing from the other members of PLK family, PLK4 has only one polo box in the C-terminal polo-box domain [11].

PLK1 protein can bind to phosphopeptide of certain proteins through the polo-box domain. When it is recruited to a particular cell position by interacting with different phosphopeptide, its kinase domain is released. As a result, different proteins or the different sites of the same protein can be phosphorylated. In a normal condition, the

Figure 1. The domain structure of *PLK1*. PB1: polo-box 1; PB2: polo-box 2; PBD: polo-box domain.

polo-box domain always combines with the N-terminal kinase domain to inhibit the phosphorylation of T210 in the kinase, thereby inhibiting the kinase activity of *PLK1*. *PLK1* is activated when the polo-box domain binds to its ligand, and separates with the T-loop of kinase domain [13].

PLK1 and Mitosis

In eukaryotic organisms, cell cycle progression is regulated by proteolysis and phosphorylation, and the precise regulation is necessary for the replication of the genetic information in offspring. Any mistakes in the mitotic or DNA replication process may result in apoptosis or mutation to form tumors. *PLK1* expression is elevated in actively proliferating cells and is significantly different among different stages of the cell cycle [14]. The expression of *PLK1* is cell cycle dependent, usually gathers in the centrosome of the spindle poles in early period of mitosis, and then migrates gradually from spindle poles to the equatorial plate after entering into middle and late period of mitosis. At the end of mitosis, *PLK1* gathers in the midbody. Therefore, *PLK1* expression is barely detectable in G1 and S phase, gradually increases in G2 phase, and peaks in M phase [14]. After the completion of cell division, *PLK1* expression would get a sharp decline and then move into the next loop of cell cycles (Figure 2).

PLK1 is a key regulator of mitosis initiation. It can drive the transformation of G2/M phase by controlling the activity of the *CDK1/Cyclin B* complex which is necessary for cells' transition from the G2 phase into the M phase [15]. *PLK1* regulates cytoplasmic separation and membrane formation in mitosis telophase via phosphorylating mitotic kinesin-like protein l [16]. *PLK1* also regulates cytokinesis [17]. In late mitosis, *PLK1* protein is gradually inactivated because of the protein hydrolysis and finally enters into a quiescent state when mitosis ends.

PLK1 and Human Cancer

PLK1 Expression in Cancer

Carcinogenesis depends both on the activation of proto-oncogenes and on the deactivation of tumor suppressor genes [18]. Oncogenes and tumor suppressor genes are mostly related to cell cycle regulation, and dysregulation of the cell cycle is the main cause of cancer [19]. Since *PLK1* was found to be highly expressed in primary tumor tissues more than two decades ago [20], its role as an oncogene has been identified by many studies [21,22]. A number of studies have revealed that *PLK1* is overexpressed in cancers compared with normal controls in
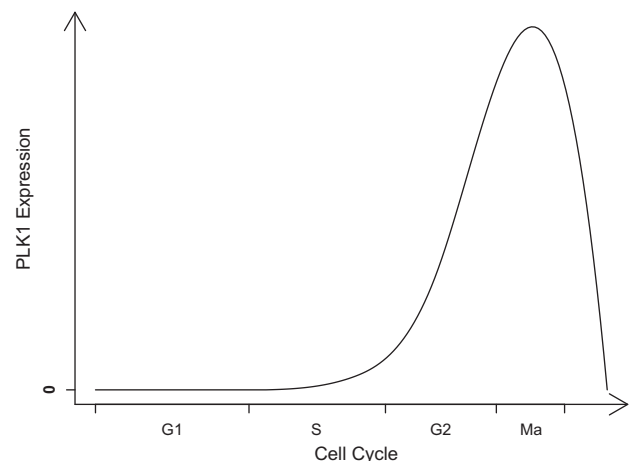
Figure 2. The tendency for *PLK1* expression in different phases of mitosis.

various types of human cancers such as glioma [23], thyroid carcinoma [24], head and neck squamous cell carcinoma [25], melanoma [26], colorectal cancers [27], esophageal carcinoma [28], ovarian carcinoma [29], breast cancer [30], and prostate cancer [31].

To examine the expression of *PLK1* in various types of human cancers, we downloaded the RNA-Seq gene expression (Level 3), gene somatic mutation (Level 2), and clinical data for all of the 33 cancer types from The Cancer Genome Atlas (TCGA) data portal (https://gdc-portal.nci.nih.gov/). We compared *PLK1* expression between cancers and normal tissue in 19 cancer types (14 cancer types were excluded from the analysis because of their small numbers or lack of normal samples) and found that *PLK1* has significantly higher expression levels in cancers than in normal tissue in 18 of the 19 cancer types (Student's *t* test, *P* value < .05) (Table 1). Besides the TCGA data, *PLK1* gene and protein expression has been reported to be elevated in a wide variety of human cancers compared with normal tissue in a number of previous studies and to be associated with poor prognoses of cancers (Table 2). These results confirm that the overexpression of *PLK1* gene and protein is a common feature of human cancers.

PLK1 Expression and Prognosis of Cancer

We compared the overall survival (OS) time between *PLK1* higher-expression-level and *PLK1* lower-expression-level cancers in 25 cancer types (8 cancer types were excluded from the analysis because of very few samples having both *PLK1* expression and OS data). *PLK1* higher-expression-level and lower-expression-level cancer patients were determined by the median values of *PLK1* expression. If the *PLK1* expression level in a patient was higher than the median value, the patient was classified as *PLK1* higher expression level; otherwise, patient was classified as *PLK1* lower expression level. Kaplan-Meier survival curves (Figure 3) show that patients with higher expression levels of *PLK1* have significantly worse OS prognoses than those with lower expression levels of *PLK1* in 10 cancer types: adrenocortical carcinoma (ACC), BLCA, BRCA, KIRC, KIRP, brain lower-grade glioma (LGG), LUAD, PAAD, skin cutaneous melanoma (SKCM), and UCEC. In the other cancer types, both groups of cancer patients show no significant OS time differences (log-rank test, *P* value < .05). We also compared the disease-free survival (DFS) time between *PLK1* higher-expression-level and *PLK1* lower-expression-level cancers in 26 cancer types (7 cancer types were excluded from the analysis because of very few

Table 1. Comparison of *PLK1* Expression between Cancers and Normal Tissue

Cancer Type	Full Name	*P* Value	Fold Change[*]
LUSC	Lung squamous cell carcinoma	7.41E-157	20.8
BRCA	Breast invasive carcinoma	5.88E-126	11.3
LUAD	Lung adenocarcinoma	1.18E-63	9.7
KIRC	Kidney renal clear cell carcinoma	2.33E-55	6.1
HNSC	Head and neck squamous cell carcinoma	6.52E-50	4.2
LIHC	Liver hepatocellular carcinoma	3.59E-40	11.7
UCEC	Uterine corpus endometrial carcinoma	1.96E-36	21.3
COAD	Colon adenocarcinoma	5.97E-33	2.5
STAD	Stomach adenocarcinoma	8.45E-27	4.8
ESCA	Esophageal carcinoma	9.52E-27	10.2
BLCA	Bladder urothelial carcinoma	4.96E-26	9.1
PRAD	Prostate adenocarcinoma	1.29E-22	3.3
KIRP	Kidney renal papillary cell carcinoma	6.76E-22	4.7
CHOL	Cholangiocarcinoma	6.97E-14	24.3
GBM	Glioblastoma multiforme	5.63E-12	12.4
KICH	Kidney chromophobe	1.63E-06	3.3
READ	Rectum adenocarcinoma	1.06E-05	2.3
PAAD	Pancreatic adenocarcinoma	0.04	2.2

[*] Mean *PLK1* expression in cancers/mean *PLK1* expression in normal tissue.

Table 2. Overexpression of *PLK1* mRNA and Protein in Human Cancers Reported in Previous Studies

Cancer Type	Reference
Lung cancer	[32,33]
Breast cancer	[30,34–36]
Melanoma	[26,37]
Renal cancer	[38,39]
Head and neck cancer	[25,40,41]
Hepatocellular carcinoma	[42–44]
Endometrial carcinoma	[45]
Colorectal cancer	[6,27,46,47]
Gastric carcinoma	[48,49]
Esophageal carcinoma	[50,51]
Bladder urothelial carcinoma	[52]
Prostate cancer	[31]
Cholangiocarcinoma	[53]
Glioblastoma	[54,55]
Glioma	[23,56]
Ovarian cancer	[29,57]
Pancreatic cancer	[58–60]
Thyroid cancer	[24]

samples having both *PLK1* expression and DFS data). Kaplan-Meier survival curves (Figure 4) show that patients with higher expression levels of *PLK1* have significantly worse DFS prognoses than those with lower expression levels of *PLK1* in seven cancer types: ACC, KIRC, KIRP, LGG, LUAD, SKCM, and uveal melanoma (UVM). In the other cancer types, both groups of cancer patients show no significant DFS time differences (log-rank test, *P* value < .05). These results confirm that overexpression of *PLK1* leads to poor clinical outcomes in cancer [5,7].

Moreover, we compared *PLK1* expression levels between early and late stage of cancer patients in 11 TCGA cancer types which have relatively complete records of the clinical phenotype. The 11 cancer types include ACC, BLCA, BRCA, cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), CHOL, COAD, lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), ESCA, GBM, HNSC, and KICH. We found that *PLK1* has significantly higher expression levels in late stage of cancers than in early stage of cancers in four cancer types: ACC (Student's *t* test, *P* value = $2*10^{-5}$, fold change = 3.3), BRCA (*P* value = .03, fold change = 1.9), KIRC (*P* value = $1.7*10^{-6}$, fold change = 1.6), and KIRP (*P* value = .0005, fold change = 1.6). In the other seven cancer types, *PLK1* expression levels have no significant differences between early and late stage of cancers, although the mean expression levels of *PLK1* are higher in late stage of cancers than in early stage of cancers in six of the seven cancer types (except COAD). These results indicate that *PLK1* upregulation may be involved in cancer progression and invasion. This is in line with the results of previous studies [60–62].

Interactions between PLK1 and Other Molecules

PLK1 interacts with a number of gene products (proteins) (Figure 5, generated by the BioGRID [63]). For example, *RSF1* directly binds to *PLK1* to play an important role in *PLK1* deposition and function at mitotic kinetochores [64]; *PLK1* phosphorylates *PAX3-FOXO1* to stabilize the protein and has been proposed as a rational target for treating alveolar rhabdomyosarcoma [65]; *CLIP-170* recruits *PLK1* to kinetochores during early mitosis for chromosome alignment [66]. Among the interactive partners with *PLK1*, tumor suppressor genes are noteworthy considering the oncogenic role of *PLK1* in human cancers. The tumor suppressor *p53* acts as the "guardian of the genome" and plays an important role in antiproliferation [67]. *TP53* mutations and
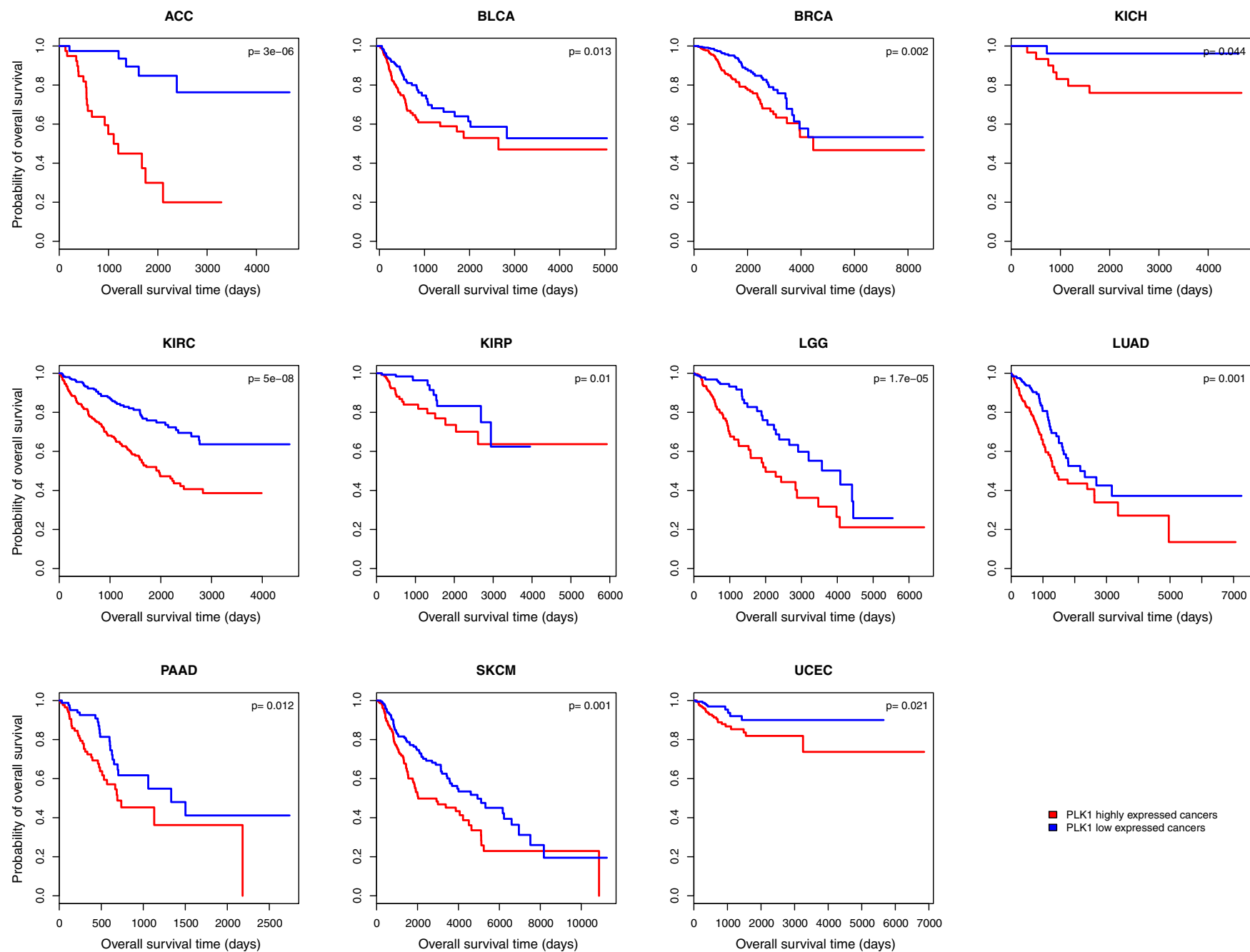
Figure 3. Kaplan-Meier survival curves show significant overall survival (OS) time differences between *PLK1* higher-expression-level and *PLK1* lower-expression-level cancer patients (log-rank test, *P* value < .05).
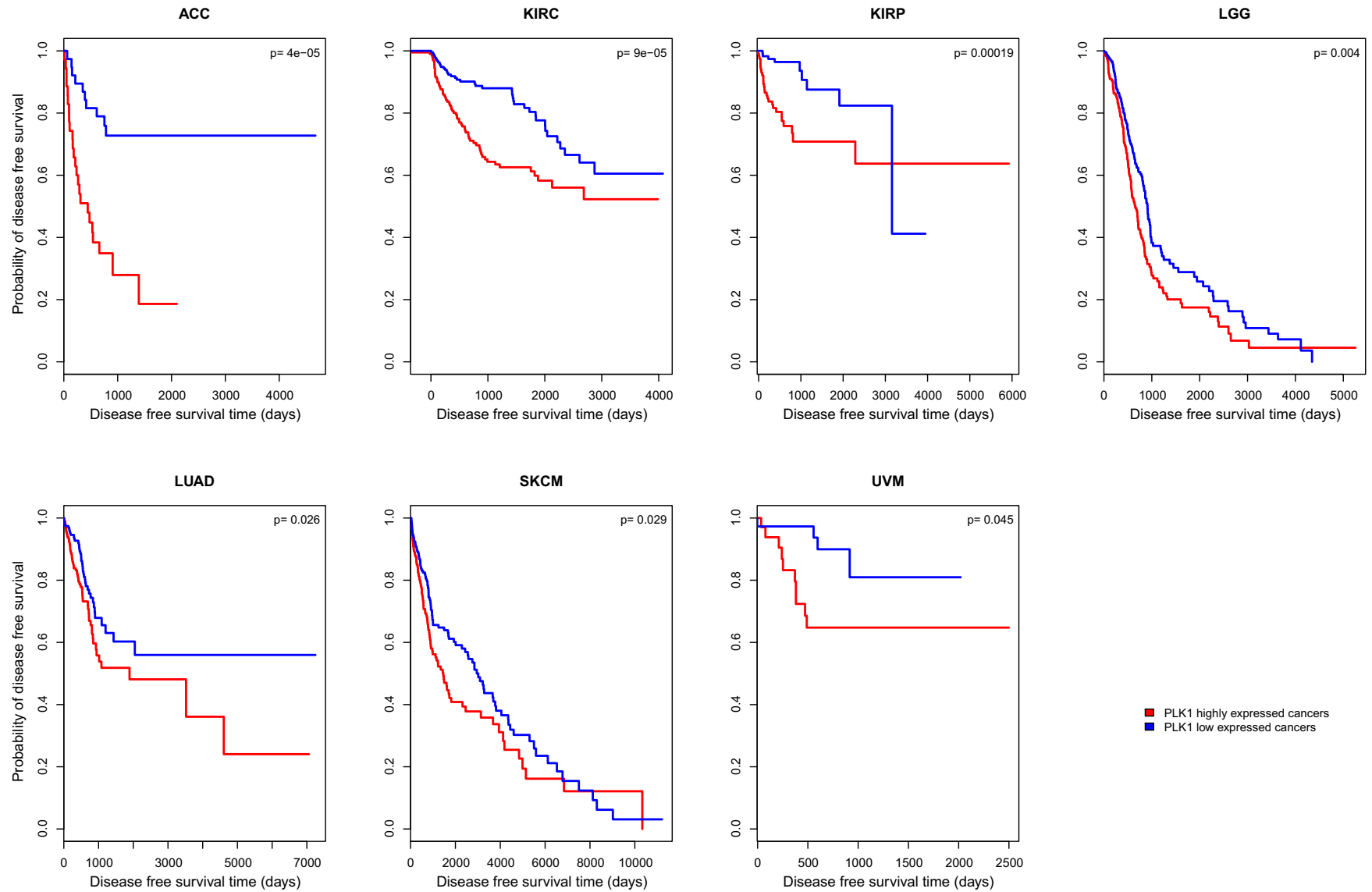
Figure 4. Kaplan-Meier survival curves show significant disease-free survival (DFS) time differences between *PLK1* higher-expression-level and *PLK1* lower-expression-level cancer patients (log-rank test, *P* value < .05).
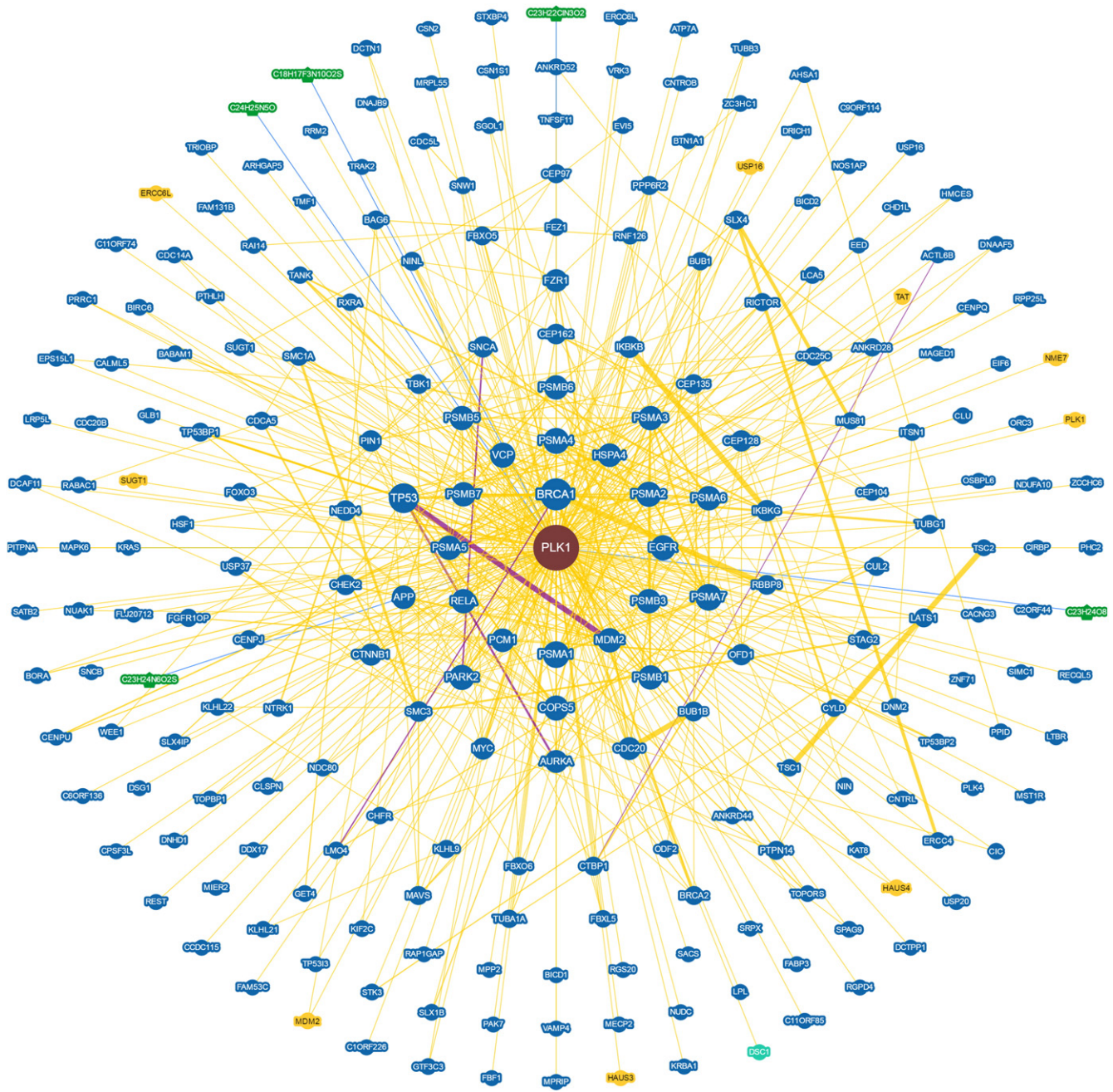
Figure 5. *PLK1* interaction networks.

dysfunction occur in more than half of all human cancer cases [68]. Previous studies have shown that *PLK1* can bind to the sequence-specific DNA-binding domain of *p53* and inhibit the *p53*-dependent transcriptional activation as well as proapoptotic activity by physical interaction and phosphorylation [69]. *P53* in turn can repress expression of *PLK1* [70]. By analyses of the TCGA datasets, we found that *PLK1* expression levels are significantly higher in *TP53*-mutated cancers than in *TP53*–wild-type cancers in 17 of the 29 cancer types (4 cancer types were excluded from the analysis because of their small numbers of *TP53*-mutated samples), as shown in Table 3. These results suggest that *p53* may repress *PLK1* expression, and once *TP53* mutations result in loss of the *p53* transcriptional repression function, *PLK1* would have elevated expression in *TP53*-mutated cancers compared with *TP53*–wild-type cancers.

When we focused on the aforementioned 19 cancer types each of which has a sufficient number of normal control samples, we found that in 11 of the 19 cancer types, *PLK1* expression follows this pattern: *TP53*-mutated cancers > *TP53*–wild-type cancers > normal controls. The 11 cancer types include BRCA, LUAD, UCEC, BLCA, LIHC, PRAD, STAD, KIRC, LUSC, KICH, and CHOL (Figure 6). This pattern indicates that *PLK1* has an elevated expression level in cancers relative to normal tissue and further has an elevated expression level in *TP53*-mutated cancers than in *TP53*–wild-type cancers, suggesting that the interaction between the oncogene *PLK1* and the tumor suppressor gene *TP53* may play an important role in carcinogenesis.

Some other tumor suppressors such as *CHK2* [71], *BRCA1/2* [72–75], *ATM* [76] and *ATR* [77], *BUB1B* [78,79], *CYLD* [80],

Table 3. Comparison of *PLK1* Expression between *TP53*-Mutated and *TP53*–Wild-Type Cancers

Cancer Type	Full Name	*P* Value	Fold Change*
BRCA	Breast invasive carcinoma	6.45E-52	2.5
LUAD	Lung adenocarcinoma	5.14E-23	2.1
UCEC	Uterine corpus endometrial carcinoma	1.10E-15	2.2
BLCA	Bladder urothelial carcinoma	2.44E-14	1.8
LIHC	Liver hepatocellular carcinoma	6.72E-13	2.5
PRAD	Prostate adenocarcinoma	1.12E-07	1.8
STAD	Stomach adenocarcinoma	1.57E-07	1.5
ACC	Adrenocortical carcinoma	2.85E-07	5.4
PAAD	Pancreatic adenocarcinoma	6.15E-06	1.7
KIRC	Kidney renal clear cell carcinoma	0.0004	2.3
SKCM	Skin cutaneous melanoma	0.0004	1.4
SARC	Sarcoma	0.001	1.5
LUSC	Lung squamous cell carcinoma	0.01	1.3
CESC	Cervical squamous cell carcinoma and endocervical adenocarcinoma	0.02	1.4
KICH	Kidney chromophobe	0.03	1.9
DLBC	Lymphoid neoplasm diffuse large B-cell Lymphoma	0.03	1.8
CHOL	Cholangiocarcinoma	0.05	2.4

* Mean *PLK1* expression in *TP53*-mutated cancers/mean *PLK1* expression in *TP53*–wild-type cancers.

REST [81], and *TSC1/2* [82,83] all have been shown to interact with *PLK1*. The imbalance between these interactions for regulating proliferation could be a leading cause of cancer.

In addition to the tumor suppressors, *PLK1* interacts with other classes of genes or proteins such as kinases: *AURKA* [84,85], *BUB1* [86,87], and *WEE1* [88]; oncogenes: *MDM2* [89] and *FOXO3* [90]; and transcriptional factors: *HSF1* [91–93], *RELA* [94], *TRIOBP* [95], and *FOXM1* [62,96–98], etc. These interactions may be essential for *PLK1* to play an important role in regulation of the cell cycle, and dysfunction of the interactions could be associated with cancer and other diseases.

PLK1 and Tumor Sensitivity to Chemotherapy and Radiotherapy

Drug resistance of cancer cells is one of the main reasons for the failure of chemotherapy in clinic [99,100]. A number of studies have revealed that targeting *PLK1* may be a novel approach for overcoming drug resistance in cancer chemotherapy. For example, Jimeno et al. confirmed that *PLK1* mediated the resistance to gemcitabine of pancreatic cancer cells [101]; Tyagi et al. reported that *PLK1* silencing could enhance the sensitivity to cisplatin in human *TP53*-mutated epidermal squamous carcinoma cells by upregulating *p73a* [102]; Gleixner et al. found that BI2536, a small molecule inhibitor of *PLK1*, could enhance the inhibition of imatinib and nilotinib on chronic myeloid leukemia cell growth [103].

In addition, many studies have suggested that *PLK1* is potentially important for radiation sensitizer. For example, Rodel et al. showed that *PLK1* silencing could enhance the sensitivity of rectal cancer to radiotherapy [47]; Gerster et al. revealed that targeting *PLK1* enhanced radiation efficacy for HNSC [40]; Harris et al. found that using BI2536 before radiotherapy could enhance radiotherapy sensitivity in medulloblastoma cells [104]. Thus, the inhibition of *PLK1* may overcome drug resistance in cancer chemotherapy and enhance sensitivity of cancer radiotherapy.

PLK1 as a Target for Cancer Therapy

PLK1 could be a new therapeutic target for cancer because *PLK1* knockout can decrease cancer cell survival, induce apoptosis, and increase the sensitivity to chemotherapy drugs, whereas it has little effect on normal cells [9,105–107]. A number of studies have shown that inhibiting *PLK1*

expression or function by RNAi or small molecule inhibitors was effective in control of cancer cell proliferation [38,50,108,109].

RNAi or small interfering RNA (siRNA) technology is used to inhibit certain gene expression by human intervention. Spänkuch-Schmitt et al. showed that siRNAs targeting *PLK1* reduced cancer cell proliferation, whereas they had almost no effect on human mammary epithelial cells [110]. McCarroll et al. targeted *PLK1* by RNA-interfering nanoparticle-7 that reduced non–small cell lung cancer cell proliferation in a mouse model [22]. A number of studies have suggested that targeting *PLK1* by siRNA could be a viable approach to cancer therapy [9,60,111]. However, as the synthesis of antisense oligonucleotides is susceptible to ribozymes' attack and RNAi has security and stability issues, small molecule inhibitors may be a better option in targeting *PLK1* for cancer therapy than RNAi. *PLK1* structure provides two targets: kinase domain of N-terminal and polo-box domain of C-terminal. Thus, we can divide *PLK1* inhibitors into two classes, *ATP*-competitive inhibitors and non–*ATP*-competitive inhibitors, based on their different action mechanisms [112] (Table 4).

ATP-competitive inhibitors target the deep groove in the kinase *ATP* binding domain [112]. BI2536 is a representative *ATP*-competitive inhibitor with strong selective inhibition on *PLK1* [103]. It can inhibit the proliferation of various cancer cell lines from different tissue sources by blocking cancer cells in the metaphase of mitosis and leading to apoptosis [130,131]. Volasertib (BI6727) is another promising *PLK1* inhibitor. Several preclinical experiments have demonstrated that BI6727 is highly efficacious in inducing tumor regression [116,132–134]. As a result, this agent has recently been awarded the "Breakthrough Therapy Status" by the Food and Drug Administration for its significant benefit in treating acute myeloid leukemia patients [135]. However, because of the high conservation of *ATP* binding domains of different kinases and the frequent mutation in *ATP* binding sites, cancer patients always develop resistance to *ATP*-competitive inhibitors [136]. In addition, the *ATP*-competitive inhibitors can often also act on other kinases and therefore are not specific for *PLK1*.

In contrast, the polo-box domain is specific to *PLKs* and therefore could be a more suitable target for development of selective *PLK1* inhibitors. Poloxin, thymoquinone, and purpurogallin are selective *PLK1* inhibitors targeting the polo-box domain of *PLK1* [137]. Poloxin and thymoquinone can block the correct orientation of *PLK1*, thereby preventing the mitosis of cancer cells [126]. A recent study showed that Poloxin-2, an optimized analogue of poloxin, has significantly improved potency and selectivity over poloxin in inducing mitotic arrest and apoptosis in cultured human cancer cells [128].

However, so far, the small molecule inhibitors of *PLK1* including BI2536 have not achieved a satisfactory therapeutic effect in clinical trials [138]. One main reason is the dose-limiting toxicities of *PLK1* inhibitors [10]. A recent study revealed that reduced efficacy of the *PLK1* inhibitor BI2536 on progressive hepatocellular carcinoma was due to low intratumoral drug levels [139].

Concluding Remarks

PLK1 is a key regulator of the cell cycle and an important oncogene in cancer initiation, progression, and drug resistance. Its overexpression is a common feature of human cancers (Tables 1 and 2) and is an important marker for prognosis in cancer (Figures 3 and 4). Inhibition of *PLK1* expression could reverse the drug resistance of cancer cells and increase sensitivity to radiotherapy and chemotherapy. Thus, *PLK1* could be a promising target for cancer treatment. Particularly, Wang and Simon have proposed that *PLK1* is a promising target for treating *TP53*-mutated
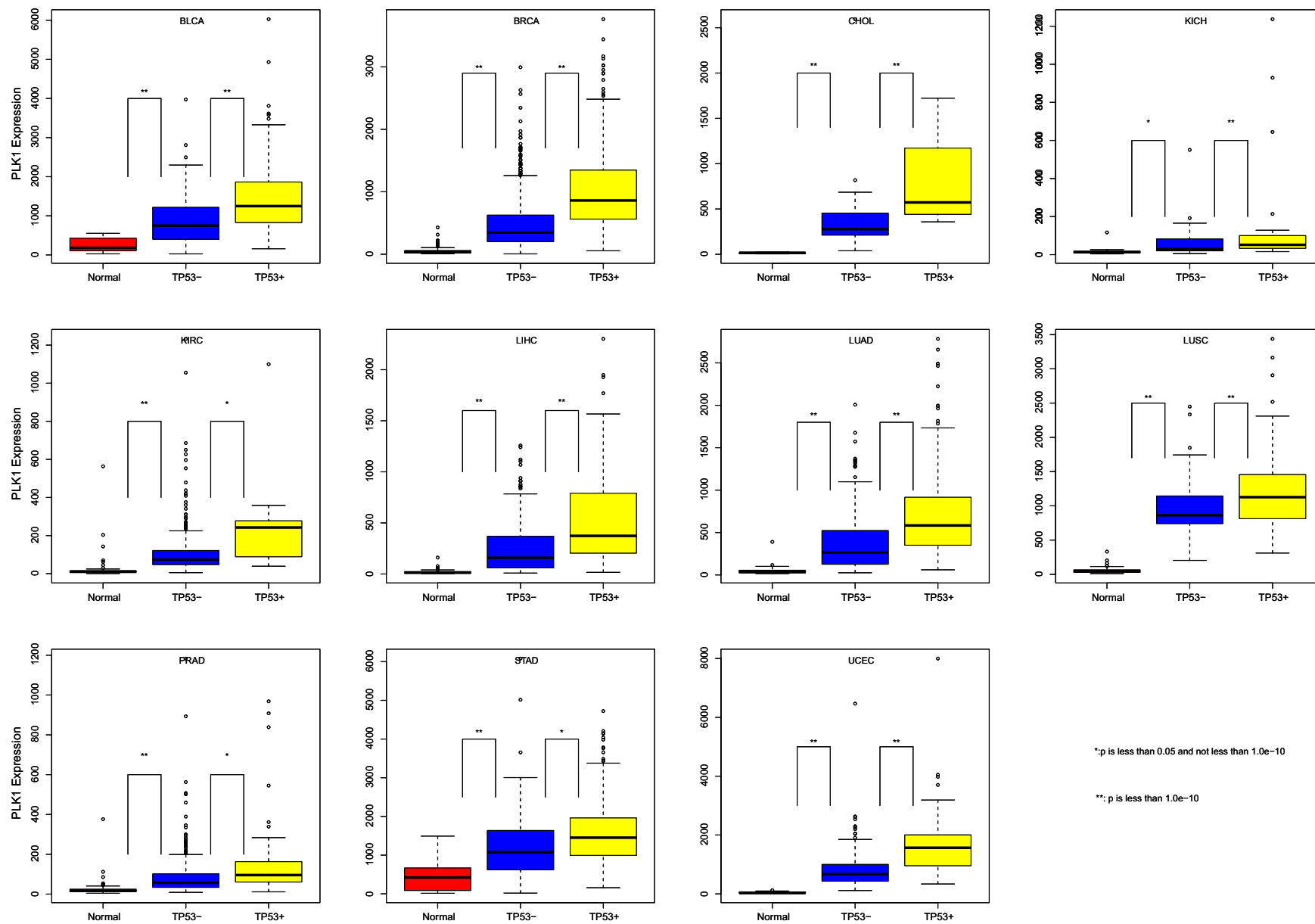
Figure 6. *PLK1* gene expression level pattern: *TP53*-mutated cancers > *TP53*–wild-type cancers > normal controls, in 11 cancer types. *TP53+*: *TP53*-mutated cancers; *TP53−*: *TP53*–wild-type cancers.

Table 4. A List of *PLK1* Inhibitors

Inhibitor	Status	Reference	Company or Lab	Class
BI2536	Experimental	[113]	Boehringer Ingelheim	*ATP*-competitive
GSK461364	Experimental	[114,115]	GlaxoSmithKline	*ATP*-competitive
Volasertib (BI6727)	Experimental	[115,116]	Boehringer Ingelheim	*ATP*-competitive
ZK-thiazolidinone	Experimental	[115,117]	Bayer Schering Pharmacy	*ATP*-competitive
Rigosertib (ON01910)	Experimental	[118]	Onconova Therapeutics Inc.	Non–*ATP*-competitive
Cyclapolin 9	Experimental	[119,120]	Cyclacel	*ATP*-competitive
GW 843682X	Experimental	[121]	GlaxoSmithKline	*ATP*-competitive
SBE 13 hydrochloride	Experimental	[122,123]	Institute of Organic Chemistry & Chemical Biology, Goethe-University	*ATP*-competitive
TAK960 hydrochloride	Experimental	[124,125]	Takeda Pharmaceutical Company	*ATP*-competitive
Poloxin	Experimental	[126,127]	Max Planck Institute of Biochemistry and Munich Center for Integrated Protein Science	Non–*ATP*-competitive
Poloxin-2	Experimental	[128]	Institute of Organic Chemistry, University of Leipzig	Non–*ATP*-competitive
RO3280	Experimental	[129]	Hoffmann-La Roche	*ATP*-competitive

cancers because of its potential synthetic lethality relationship with *TP53* [140]. However, to translate the cancer biology of *PLK1* into clinical application, we need to resolve some important issues such as the following: Is the overexpression of *PLK1* in cancer the cause of cancer or just a consequence of cancer cells' proliferation [141]? What is the key interactive network of *PLK1* underlying the carcinogenesis? What is the true relationship between *p53* and *PLK1* in cancer? How can we develop effective *PLK1* inhibitors or improve the clinical efficacy of current *PLK1* inhibitors? We believe that the solution to these issues would bring significant progress in cancer treatment by targeting *PLK1* and its related network or pathway.

Competing Interests
The authors declare that they have no competing interests.

Acknowledgements

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