PLK1, A Potential Target for Cancer Therapy

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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.

Translational Oncology (2017) 10, 22–32

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
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 1 [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
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.

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-117 | 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 | 3.95E-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                  | 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 cancer/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 cancer| [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]               |

PLK1 interacts with a number of gene products (proteins) (Figure 5, generated by the BioGRID [63]). For example, RSK1 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 \textit{PLK1} higher-expression-level and \textit{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).
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],
and transcriptional factors: HSF1 [95], and [86,87], and cancer and other diseases. PLK1 may overcome drug resistance in cancer chemotherapy and enhance sensitivity of cancer radiotherapy. Gleixner et al. found that BI2536, a small molecule inhibitor of PLK1, could enhance the inhibition of imatinib and nilotinib on chronic epidermal squamous carcinoma cells by upregulating TRIO-BP [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]; oncopgenes: 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 p73α [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 PLK5 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 cancer and other diseases.
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.
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? 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

This work was supported by the startup funds to X. W. from the China Pharmaceutical University.

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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 |
| Cyclaplatin 9     | Experimental   | [119,120] | Cyclacal                         | 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 |
| TAK906 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 |
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