Original Article

Up-regulation of Polo-like Kinase 1 in nasopharyngeal carcinoma tissues: a comprehensive investigation based on RNA-sequencing, gene chips, and in-house tissue arrays

Xia Yang1#, Weijia Mo1#, Yeying Fang2, Ganguan Wei1, Minda Wei1, Yiwu Dang1, Gang Chen1, Kai Hu2*, Danming Wei1*  
1Department of Pathology, First Affiliated Hospital of Guangxi Medical University, 6 Shuangyong Road, Nanning 530021, Guangxi Zhuang Autonomous Region, China; 2Department of Radiation Oncology, Radiation Oncology Clinical Medical Research Center of Guangxi, First Affiliated Hospital of Guangxi Medical University, 6 Shuangyong Road, Nanning 530021, Guangxi Zhuang Autonomous Region, China; 3Department of ENT and HN Surgery, NO. 303 Hospital of PLA, 52 Zhiwu Road, Nanning, Guangxi Zhuang Autonomous Region, China. *Equal contributors and co-first authors.  

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Abstract: Background: Nasopharyngeal carcinoma (NPC) is a highly invasive malignancy which has unique characteristics when found among individuals from certain ethnic or geographic populations. The role and molecular mechanism of Polo-like kinase 1 (PLK1) in NPC remain yet to be clarified. Hence, the aim of this study is to identify the clinical implications of PLK1 in NPC based on gene chip, tissue microarray, and other silico approaches. Methods: Relevant data related to PLK1 levels in NPC was screened for by searching in SRA, GEO, ArrayExpress, Oncomine and throughout the existing literature on this topic. The raw data about gene chips were normalized by using an RMA algorithm provided by “Limma” package. Furthermore, the “SVA” package of R software was used to remove the batch effect and data from the same platform were merged into one part. The differential expression levels of PLK1 between NPC and non-NPC tissues were extracted and analyzed with the Student’s t-test. Meta-analyses were used to calculate the standard mean difference and sROC. Furthermore, in-house immunohistochemistry was performed with tissue microarrays. Weighted correlation network analysis was used to identify the PLK1-related genes. Several bioinformatic evaluations, including the Gene Ontology, Kyoto Encyclopedia of Genes and Genomes, and protein-protein interactions, were also performed to assess the PLK1-related pathways. Results: The tissue microarray and gene chips indicated that the PLK1 levels clearly had an up-regulating trend as compared to the non-cancerous controls. These trends were observed in both the single study and the comprehensive meta-analysis. The area under the sROC curve in the NPC tissues was 0.87, with pooled sensitivity and specificity at 0.950 and 0.710, respectively, based on 393 NPC tissues and 83 non-cancerous controls. A total of 144 genes were identified as co-expressed genes of PLK1 in NPC and were mainly enriched in the “cell cycle” pathway. Among the genes related to the cell cycle, CDK1, CCNA2 and CCNB2 were all closely related to PLK1 expression level. Conclusions: PLK1 may play a potential oncogenic role in the tumorigenesis and development of NPC. Since several PLK1 inhibitors have been developed, it is believed that the PLK1 inhibitors have great therapeutic potential in clinic applications for NPC patients.

Keywords: Polo-like Kinase 1, nasopharyngeal carcinoma, RNA-sequencing, gene chip, tissue microarrays

Introduction

Nasopharyngeal carcinoma (NPC) is a highly invasive malignancy which is disproportionately found among certain ethnic and geographic populations [1, 2]. A predominantly high occurrence of NPC takes place in the Southeast regions of Asian countries, especially in the Southern areas of China, including the districts of Guang Dong, Guang Xi and Fu Jian [3, 4]. NPC has complex pathogenic mechanisms and a series of molecular events that occur during the process of the tumorigenesis. However, the exact molecular mechanisms of NPC remain
broadly abstruse, which greatly restrains the clinical manipulation of NPC [5-7]. Thus, there is an urgent need to carry out studies that explore the genetic levels of NPC.

Among all the cancer-related genes, the family of Polo-like kinases (PLKs) are principally serine/threonine kinase enzymes that regulate the cell cycles of different cells. Polo-like kinase 1 (PLK1), one member of the PLKs family, has been reported to play an essential role in the intracellular processes in different cancers [8]. By far, the relationship between PLK1 and the progression and efficient treatment of NPC has been reported only by one group. That other study found that a decrease in PLK1 led to mitotic catastrophe with substantial cytotoxicity when using both in vitro and in vivo experiments. Clinically, PLK1 protein expression levels were detected through immunohistochemistry on 40 cases of NPC samples, of which 28 cases showed an over-expressed pattern [9]. However, the sample size of 40 in that study was quite small, and the findings still need to be validated. Additionally, the exact molecular mechanism of PLK1 in the development of NPC still needs to be clarified. Hence, to identify the clinical role of PLK1 in NPC, we performed data-mining based on RNA-sequencing and gene chip data, further validated by an in-house tissue microarray and immunohistochemistry. We also collected the relative genes of PLK1 in NPC and determined the possible signaling pathways of PLK1 via in silico approaches.

Materials and methods

mRNA expression level of PLK1 in NPC tissues

mRNA expression level of PLK1 in NPC tissues based on RNA-sequencing and microarray data: To collect the mRNA expression level of PLK1 in NPC tissues assessed by RNA-sequencing and gene chip technique, related studies were screened for in SRA, GEO, ArrayExpress and Oncomine. The search keywords used were “nasopharyngeal carcinoma” OR “NPC”. The inclusion criteria were as follows: (1) the PLK1 expression profiles in NPC and non-NPC controls could be achieved and (2) more than five tumors and controls were enrolled in the study. Four authors (Xia Yang, Wei-jia Mo, Min-da Wei and Dan-ming Wei) carried out the screening independently and discussed all discrepant opinions to reach a consistent agreement about the inclusion of possible data.

The raw data of gene chips were produced by Affymetrix or other platforms and were downloaded and normalized by using the RMA algorithm provided by “Limma” package (http://bioconductor.org/packages/limma/). Furthermore, the “SVA” package of R software was used to remove the batch effect.

The microarray data were normalized according to each platform, and the PLK1 mRNA level was extracted. The differential expression level of PLK1 between NPC and non-NPC tissues were analyzed with the Student’s t-test by using the SPSS software version 22.0 for each study. Scatterplots were drawn by using GraphPad version 7.0. The area under the curve (AUC) of receiver operating characteristic (ROC) was further calculated to examine the potential for PLK1 to separate NPC from non-NPC tissues.

mRNA expression level of PLK1 in NPC tissues based on previous reports: To gather the reported data of PLK1 mRNA in NPC, a literature search and data extractions were performed as previously reported [10]. The keywords for NPC mentioned above were used. The keywords “PLK1” or “Polo-like Kinase 1” were added to the search. The inclusion and exclusion criteria followed was consistent with the previous studies performed by our group [10, 11]. The PLK1 mRNA levels were presented using enumeration data, instead of ranked data.

mRNA expression level of PLK1 in NPC tissues based on meta-analyses: To have a comprehensive depiction of the expression levels of PLK1 in NPC, meta-analyses calculating the standard mean difference (SMD) and sROC were performed using Stata software version 14.0. The heterogeneity status of the data decided whether a random- or fixed-model was preferred. The heterogeneity of I² > 50% or P < 0.05 led to a random-effects model, and vice versa. Publication bias was detected by using the Begg’s and Egger’s tests. Sensitivity, specificity and sROC were also calculated [12, 13].

Protein expression level of PLK1 in NPC tissues

In-house immunohistochemistry with tissue microarray and clinical samples: Two tissue arrays (NPC1507 and NPC1504) were purchased from Pantomics, Inc (Richmond, CA). These arrays included 18 cases of non-cancerous na-

3925

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Figure 1. Flowchart of the present study. The present study mainly includes two parts: validation of the expression level of PLK1 and exploration of its potential molecular mechanisms in NPC.
Up-regulation of PLK1 in NPC

Another 26 cases of non-cancerous nasopharyngeal tissues and 10 NPCs were collected from the Department of Pathology, First Affiliated Hospital of Guangxi Medical University from July 1st to August 1st, 2018. The Ethical Committee of First Affiliated Hospital of Guangxi Medical University approved this study. All the patients signed the informed consents for the use of these samples for research. Altogether, the current immunohistochemistry study included 44 non-cancerous controls, including nasopharyngeal polyp and chronic mucosa inflammation, as well as 292 cases of NPCs.

In the immunohistochemistry, the primary antibody used was a rabbit polyclonal antibody, anti-PLK1 antibody (at 1/500 dilution) (Abcam's RabMab technology), as previously reported [14]. The immunostaining results of PLK1 expression was assessed according to the following two factors: first, the proportion of stained cells among total cells (0: < 5%; 1: 5%-25%; 2: 25%-50%; 3: 50%-75%; 4: > 75%); second, the staining degree of the positive cells.

![Figure 2](image_url). PLK1 protein expression in tissues from nasopharyngeal region. Non-cancerous nasopharyngeal tissues (A, C): Only a small portion of the epithelial cells was positive for PLK1 immunostaining. Red arrow: simple columnar epithelium; Green arrow: squamous metaplasia. Nasopharyngeal carcinoma (NPC: B, D): Major part of NPC were positively stained for PLK1. ×400.

![Table 1](image_url). General characteristics of included microarrays

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Up-regulation of PLK1 in NPC

(0: no staining; 1: light yellow or yellow; 2: brown; 3: dark brown). Two numbers were multiplied to generate the final score for each sample, which was shown as enumeration data. The minimum of the immunohistochemical score was 0, and the maximum was 12. We also catalyzed the samples into positive staining (≥ 6) and negative staining (< 6) based on the medium value of the score. All the assessments for immunohistochemical staining were carried out by three authors independently (Wei-jia Mo, Gang Chen and Dan-ming Wei).

All the statistical analysis for IHC was performed using SPSS 22.0. A student’s t-test was performed to analyze the enumeration data. The frequencies and percentages were calculated for the classified variables, and a Chi-square test was used to assess the difference of PLK1 expression between two groups. All the \( P \)-values in the statistical analysis were two-tailed, and \( P < 0.05 \) was considered to be statistically significant.

**Protein expression level of PLK1 in NPC tissues based on previous reports:** The literature was searched to collect data related to PLK1 protein expression levels in NPC. The procedure was followed as previously described [10]. The search strategies used were consistent with the aforementioned procedures. The protein expression level of PLK1 was divided into positive and negative groups based on detailed rules. Hence the positive and negative ratios were obtained or calculated.

**Protein expression level of PLK1 in NPC tissues based on meta-analyses:** Similar to the meta-analyses for the mRNA level mentioned above, a meta-analysis calculating odds ratios (OR) was performed to summarize the comprehensive protein level of PLK1 in NPC. The procedure was performed as previously described [15].

**Potential relative genes and signaling pathways of PLK1 in NPC**

**Relative genes of PLK1 in NPC as assessed by using weighted correlation network analysis (WGCNA):** To explore the potential molecular mechanisms of PLK1 in NPC, “WGCNA” package of R software was conducted to identify the PLK1-related genes [16]. Genes with correlation coefficient more than 0.4 and \( P \)-value < 0.05 were identified as the PLK1-related genes. Then, PLK1-related genes were submitted to “clusterprofiler” for gene functional enrichment analysis [17].

**Relative signaling pathways of PLK1 in NPC:** The PLK1-related genes in NPC underwent several bioinformatic evaluations, including the

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Figure 3. Integration of included Affymetrix gene chips. A. Box plot displays the overall expression profiles of four Affymetrix gene chips before normalization. B. The batch effect of the four gene chips was removed by using “SVA” package of R software.
Up-regulation of PLK1 in NPC

Results

The flowchart of the present study

The present study mainly includes two parts: investigation of the expression profiles of PLK1 and the exploration of the potential molecular mechanism in NPC (Figure 1).
Up-regulation of PLK1 in NPC

Figure 5. Validation of the upregulation of PLK1 in NPC tissues based on meta-analysis. (A) Forest plot of standard mean difference indicates that PLK1 has a tendency for overexpression in NPC tissues. (B) Area under curve of summary receiver operating characteristic curve was 0.870, which indicates that PLK1 could have ideal performance in distinguishing NPC from non-NPC tissues. Forest plots of pooled sensitivity (C) and specificity (D) are also used to show the pooled result.
PLK1 was upregulated in NPC tissues

We first examined the protein expression level of PLK1 in NPC with tissue microarray. The IHC results showed that PLK1 was markedly upregulated in NPC tissues compared with non-NPC tissues (Figure 2). When the ranked data were used to define the protein level of PLK1 in NPC, the apparently higher positive ratio could be observed. In NPC, 272 cases were PLK1 positive stained with a ratio of 93.2%; however, the positive ratio was only 4.5% for the non-NPC controls (P < 0.001).

The mRNA expression level of PLK1 was validated when using public microarray datasets. Altogether, there were five microarray studies enrolled in the current study (Table 1), including four Affymetrix and one Agilent microarrays. The microarrays produced by Affymetrix were merged into one part. The batch effect was removed for further analysis (Figure 3). The dif-
Up-regulation of PLK1 in NPC

The expression level of PLK1 protein detected by tissue microarray and IHC was also presented using enumeration data. The PLK1 level was 8.56 ± 2.612 in NPC cases, pronouncedly higher than that in the non-NPC controls (1.66 ± 1.829, P < 0.001, Figure 4A). The AUC of ROC was 0.979 (Figure 4B). Since the mRNA level of PLK1 in NPC had never previously been studied, there was no relevant existing literature with which to compare. The current meta-analysis of PLK1 level contained only data from microarrays with 393 NPC tissues and 83 non-cancerous controls. Finally, an SMD of 1.08 was achieved, and the AUC of sROC was 0.87, with pooled sensitivity and specificity at 0.950 and 0.710, respectively (Figure 5).

**Discussion**

This study combined multiple methods to examine the expression level of PLK1 in NPC tissues, the term most significantly found. “Chromosome region” and “ATPase activity” were the most frequent marked terms for cellular component and molecular function, respectively (Figure 8; Table 2). As expected, these PLK1-related genes were most significantly enriched in the “cell cycle” pathway (Figure 9A; Table 2). Disease ontology analysis was conducted to find related diseases triggered by these genes (Figure 9B; Table 2). The top ten hub genes in the PPI network were significantly correlated with each other. CDK1, CCNA2 and CCNB2 were all closely related to PLK1 expression level (Figure 10A).
Up-regulation of PLK1 in NPC

Figure 8. Gene ontology analysis of PLK1-related genes in NPC. A. Biological process; B. Cellular component; C. Molecular function.
Table 2. Gene functional enrichment analysis of PLK1-related genes

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Figure 9. Kyoto Encyclopedia of Genes and Genomes (KEGG) and disease ontology (DO) analysis of PLK1-related genes. A. KEGG analysis revealed that “cell cycle” was the most significant pathway; B. Several relevant DO terms of PLK1-related genes.
Up-regulation of PLK1 in NPC

including tissue microarray, IHC, gene chip, and meta-analyses. Interestingly, both PLK1 mRNA and protein levels were observed to be apparently up-regulated in NPC tissues. The silico approaches indicated that PLK1 may exert its function in a cell cycle by influencing certain key genes. Since PLK1 inhibitors have great potential to be clinically applied for cancer treatment, PLK1 could be a promising target for precision treatment of NPC too.

PLK1 has been well documented to be over-expressed in different malignant tumor cells, which have generally high mitotic ratios [19]. The oncogenic role of PLK1 has been clarified in multiple types of cancers, including non-small lung cancer [20, 21], pancreatic cancer [22, 23], esophageal squamous cell carcinoma [24], hepatocellular carcinoma [25], bladder cancer [26], gastric cancer [14, 27], and etc. However, so far only one group has studied the expression level of PLK1 in NPC tissue. In that study, forty cases of NPC were collected and stained with PLK1 by IHC. The positive ratio of PLK1 protein was 70% [9]. But no non-NPC nasopharyngeal tissues were included in that study as controls. In our current study, the PLK1 levels from both tissue microarray and gene chips were observed to clearly have an up-regulating trend as compared to the non-cancerous controls. This has also been supported by our subsequent meta-analysis, where the AUC of sROC reached 0.87 based on 393 cases of NPC. This finding suggests that PLK1 may also play a vital role in the tumorigenesis and development of NPC as a potential oncogene. However, our conclusions still need to be validated by research using larger cohorts.

Most recently, the subversive tumor-suppressive role of PLK1 has been reported in a subtype of breast cancer, even though PLK1 has been verified to be up-regulated in most of the breast cancers [28-30]. PLK1 up-regulation was found to lead to aberrant chromosome segregation and cytokinesis, which in turn generates polyploid cells with suppressed proliferative potential. In animal models, the up-regulation of PLK1 stops the progress of a subtype of breast cancer induced by KRAS and HER2 with an augmented rate of chromosome instability. Surprisingly, PLK1 up-regulation was also related to a more favorable outcome in this special subtype of breast cancer [28]. Similarly, PLK1 has also been reported to have tumor-suppressive potential in APC-truncated colon cancer cells [31]. Hence, despite the acknowledged therapeutic benefits of suppressing PLK1 due to its role in cancer cell cycles, PLK1 up-regulation may also have tumor-suppressive capacities through other mechanisms. As for the function of PLK1 in NPC, PLK1 knock-down was found to decrease Cdc25c levels in NPC cell lines in vitro and in vivo, which led to the inhibition of cell growth in C666-1 cells, as well as G2/M arrest, increased DNA double-strand breaks, apoptosis, and caspase activation. However, the effect of PLK1 in different subtypes of NPC still needs to be tested.

Figure 10. Correlations of the top 10 hub PLK1-related genes. (A) Relationships in merged Affymetrix chips dataset and (B) GSE53819 dataset.
Considering the possible molecular mechanisms of PLK1 in NPC cells, we performed WG-CNA based on different microarray data to collect the co-expressed genes and relative signaling pathways of PLK1 in NPC. Not surprisingly, the co-expressed genes were enriched in pathways closely related to cell cycles. Especially the well-known cell cycle genes CDK1,
Up-regulation of PLK1 in NPC

CCNA2 and CCNB2, are all positively related to the PLK1. CDK1 and PLK1 have been shown to support mitotic nuclear pore complexes disintegration by hyperphosphorylation of Nup98 together [32, 33]. However, the exact molecular mechanism of PLK1 in the modulation of NPC cell cycle still requires further investigation.

The potential to target PLK1 as a tool to treat cancers has been noted. Different ways to inhibit PLK1 have been tested, including using antibodies, RNA interference, or small molecule inhibitors [19, 34, 35]. For instance, BI2536, a potent and selective inhibitor of PLK1, has been verified to gain a synergistic effect on stomach cancer cells when combined with cisplatin [36]. The combination of the PI3K/Akt pathway suppression and PLK1 inhibition was also able to improve the chemosensitivity of pancreatic cancer cells to gemcitabine treatment [37]. Besides, PLK1 inhibitor BI-6727 could cause an increase in the radiosensitivity of NSCLC cells [38]. The similar role of PLK1 in the radiosensitivity of esophageal squamous cell carcinoma cells has also been reported [39]. While radiation therapy is currently the primary standard of treatment for NPC, regrettably the rates of failure range from 7% up to 58% [40, 41]. Targeting PLK1 may have the potential to enhance the efficiency of radiation therapy in NPC. However, the effect of PLK1 inhibition may have in assisting radiosensitivity needs to be tested in the future.

Based on our findings, more research must be conducted to address the shortcomings of our study. First, a larger cohort is needed to confirm the clinical role and prognostic value of PLK1 in NPC patients. Second, the biological effects of PLK1 inhibition and over-expression need to be verified in more NPC cell lines that cover different subtypes of NPC. Third, the therapeutic potential of PLK1 inhibition, alone or with other treating methods, must be carried out.

In conclusion, both PLK1 mRNA and protein levels were observed to be evidently up-regulated in NPC tissues, which suggest its potential oncogenic role in the tumorigenesis and development of NPC. Since several PLK1 inhibitors have been developed, PLK1 inhibitors may have important therapeutic potential in clinic application for NPC patients.

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Disclosure of conflict of interest

None.

Address correspondence to: Kai Hu, Department of Radiation Oncology, Radiation Oncology Clinical Medical Research Center of Guangxi, First Affiliated Hospital of Guangxi Medical University, 6 Shuangyong Road, Nanning 530021, Guangxi Zhuang Autonomous Region, China. Tel: +86 771 5356509; Fax: +86 771 5302797; E-mail: hukaigxmu@163.com; Danming Wei, Department of Pathology, First Affiliated Hospital of Guangxi Medical University, 6 Shuangyong Road, Nanning 530021, Guangxi Zhuang Autonomous Region, China. Tel: +86 771 5352194; Fax: +86 771 5352194; E-mail: danmingwei08@163.com

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Up-regulation of PLK1 in NPC


Up-regulation of PLK1 in NPC


