Research Article

Analysis of the Expression of Cell Division Cycle-Associated Genes and Its Prognostic Significance in Human Lung Carcinoma: A Review of the Literature Databases

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Background. Lung cancer (LC) has become the top cause responsible for cancer-related deaths. Cell division cycle-associated (CDCA) genes exert an important role in the life process. Dysregulation in the process of cell division may lead to malignancy.

Methods. Transcriptional data on CDCA gene family and patient survival data were examined for lung cancer (LC) patients from the GEPIA, Oncomine, cBioPortal, and Kaplan–Meier Plotter databases. Results. CDCA1/2/3/4/5/6/7/8 expression levels were higher in lung adenocarcinoma tissues, and the CDCA1/2/3/4/5/6/7/8 expression levels were increased in squamous cell LC tissues compared with those in noncarcinoma lung tissues. The expression levels of CDCA1/2/3/4/5/8 showed correlation with tumor classification. The Kaplan–Meier Plotter database was employed to carry out survival analysis, indicating that increased CDCA1/2/3/4/5/6/7/8 expression levels were obviously related to poor overall survival (OS) and progression-free survival (PFS) (P < 0.05). Only LC patients with increased CDCA3/4/5/8 expression were significantly related to lower post-progression survival (PPS) (P < 0.05). The following processes were affected by CDCA genes’ alteration: R-HAS-2500257: resolution of sister chromatid cohesion; GO:0015301: cell division; CORUM: 1118: chromosomal passenger complex (CPC, including CDCA8, INCENP, AURKB, and BIRC5); CORUM: 127: NDC80 kinetochore complex; M129: the PID PLK1 pathway; and GO: 0007080: mitotic metaphase plate congression, all of which were remarkably modulated since the alterations affected CDCA genes. Conclusions. Upregulated CDCA genes’ expression levels in LC tissues probably play a crucial part in LC oncogenesis. The upregulated CDCA genes’ expression levels are used as the potential prognostic markers to improve patient survival and the LC prognostic accuracy. CDCA genes probably exert their functions in tumorigenesis through the PLK1 pathway.

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1. Introduction

In the United States, lung cancer (LC) has turned into the top cause responsible for cancer-related deaths. According to estimation, there are over 200 thousand new LC cases and over 100 thousand deaths in 2019 [1]. LC can be classified as small-cell lung cancer (SCLC) as well as non-small-cell lung cancer (NSCLC). Among them, squamous cell carcinoma (SCC) and adenocarcinoma represent the two major NSCLC types. Nowadays, some studies have found that the platinum-based chemotherapy regimens generate a plateau, and the median overall survival (OS) is 8–14 months [2, 3]. Great progress has been made in gene-targeted therapies and immunotherapies in treating NSCLC patients, and metastatic LC patients treated with these therapies can survive for a longer period than before (over 2 years) [2, 3]. Mutations in epidermal growth factor receptor (EGFR), as well as rearrangement of ROS1 and anaplastic lymphoma kinase (ALK), are suggested as the first-line treatment for metastatic LC, which contribute a lot to cancer patient OS. [2, 3]. Besides, remarkable progress has been made in a new gene study, which has been recommended in the clinical guidelines, like neurotrophic tyrosine kinase receptor (NTRK) gene fusion. Larotrectinib has been added as the treatment option for metastatic NSCLC patients, which is sensitive to the NTRK gene fusion [4].

There are 8 respective members in the cell division cycle-associated (CDCA) gene and protein families, namely, CDCA1-8. Cell division takes an important role in the life process. It has been suggested in numerous reports that any dysregulation in the process of cell division may lead to malignancy [5–7]. CDCA2 plays a role in modulating the response of DNA injury in the cell cycle, which is achieved through binding onto protein phosphatase 1 y (PP1y) [8, 9]. CDCA3 functions modulate the progression of the cell cycle, and the expression level is regulated via protein degradation and transcription at the G1 phase in the cell cycle [10]. Moreover, CDCA4 can regulate the cell cycle, which is associated with the transition of the G1/S phase [11] and regulates the expression of p53 [12]. CDCA5 serves as a primary regulatory factor for the sister chromatid separation and cohesion [13]. In the undifferentiated hematopoietic populations, CDCA7 can be triggered in the precursors of hematopoietic stem cells in the murine embryo and is maintained afterwards. Additionally, CDCA8 plays an essential role in regulating mitosis [14].

This study aimed to evaluate systematically the association of CDCA s mRNA expression with LC patient survival. The CDCA s mRNA expression was detected in both normal and LC tissues. Then, the significance of all CDCA family members in predicting the prognosis for LC was analyzed based on the Kaplan–Meier Plotter database, and later the gene–gene interaction network of CDCA s was established to examine the underlying mechanisms of action. This study explored the CDCA s clinical value, so as to provide a certain theoretical foundation for making an early diagnosis, prognosis evaluation, and specific treatment for LC.

2. Materials and Methods

Each dataset used in the current work was searched based on the published literature. Gene Expression Omnibus (GEO) datasets and The Cancer Genome Atlas (TCGA) dataset were used for the analysis in the Oncomine dataset, the Gene Expression Profiling Interactive Analysis (GEPIA) dataset, and the Kaplan–Meier Plotter dataset. Additionally, the informed consent of participated subjects has been submitted by the researchers, which could be searched in the TCGA database and GEO datasets.

2.1. Oncomine Analyses. The transcription levels of CDCA s among various cancer types were examined based on the online cancer microarray database, namely, the Oncomine gene expression array dataset (www.oncomine.org). Moreover, CDCA s mRNA expression was compared between the clinical tumor samples and normal specimens. The P value was generated by Student’s t-test. The threshold fold change and P value were set at 2 and 0.01, respectively.

2.2. The Gene Expression Profiling Interactive Analysis (GEPIA) Dataset. As the latest designed interactive web server, GEPIA was used to analyze RNA sequencing materials based on the GTEx and TCGA projects with the normalized processing pipeline. GEPIA allows us to offer the differential expression analyses on normal and tumor tissues, as well as the access to the profiling of cancer type and pathologic stage, analysis of patient survival, detection of a similar gene, and dimensionality reduction and correlation analyses.

2.3. The Kaplan–Meier Plotter. Kaplan–Meier Plotter (http://www.kmplot.com), the online database, was used to evaluate the prognostic significance of CDCA s mRNA expression, which offered the data on LC patient survival and gene expression. To examine the postprogression survival (PPS), progression-free survival (PFS), and overall survival (OS) of LC cases, all patient specimens were divided into two groups (namely, high and low expression groups) according to the median expression. Afterwards, the Kaplan–Meier survival plot was used for the evaluation on the basis of hazard ratio (HR) and the corresponding 95% confidence intervals (CI), as well as the log-rank P value. The Kaplan–Meier plots were obtained through the CDCA s Jetset best probe set alone, where the number at risk was suggested under the major plot.

2.4. Bioinformatic Analysis and Functional Enrichment. The online database Metascape (http://metascape.org) has integrated more than 40 bioinformatic knowledge bases, which enables us to extract rich annotations, identify the enriched pathways, and construct the protein-protein interaction (PPI) network based on the lists of protein and gene identifiers. The CDCA genes were analyzed using the Kyoto Encyclopedia of Genes and Genomes (KEGG) and
Gene Ontology (GO) approaches of Metascape, so as to search for linked genes with the highest alteration frequency.

3. Results

Eight CDCA factors are recognized in mammalian cells. In the present study, the Oncomine databases were used to compare CDCA transcriptional levels between cancer tissues and normal specimens (Figure 1). According to our results, the mRNA expression of CDCA2 was remarkably upregulated in LC patients of many databases. In terms of the Garber dataset, CDCA1 overexpression was detected in SCLC and SCC tissues, with the fold changes of 13.086 and 9.240, respectively [15]. In Hou et al.’s dataset, CDCA1 was overexpressed in SCC, large-cell LC, and adenocarcinoma, and the fold changes were 10.202, 13.352, and 5.248, respectively [16]. According to Okayama’s dataset, CDCA1 overexpression was detected in lung adenocarcinoma, and the fold change was 3.267 [17]. For CDCA2, Hou et al.’s dataset showed that the fold changes in lung adenocarcinoma, SCC, and large-cell LC were 2.752, 4.844, and 5.076, separately [16]. Okayama et al.’s dataset also indicated CDCA2 overexpression in lung adenocarcinoma, and the fold change was 2.511 [17]. CDCA3 overexpression was found in lung adenocarcinoma, and the fold change was suggested to be 4.143 by Su et al.’s dataset [18], 2.828 by Okayama et al.’s dataset [17], and 3.551 by Hou’s dataset. In Hou’s dataset, CDCA3 was also expressed, and the fold change in SCC was 7.717 and that in large-cell LC was 4.431 [16]. CDCA4 was found to be overexpressed in Hou’s dataset, and the fold change in SCC was 3.354 [16]. For CDCA5, the fold changes in Garber Lung’s dataset were shown to be 7.928, 5.343, and 3.557 in large-cell LC, SCC, and lung adenocarcinoma in comparison with the common tissues, respectively [15]. Hou’s dataset demonstrated the fold changes of 5.533, 6.249, and 2.853 in SCC, large-cell LC, SCC, and lung adenocarcinoma, respectively [16]. In addition, the CDCA5 fold changes in lung adenocarcinoma were 3.324 and 2.291 in Selamat et al.’s [19] and Okayama et al.’s datasets [17], respectively. For CDCA6, the fold changes presented in Hou’s dataset were 5.371, 3.744, and 2.267 in large-cell LC, SCC, and lung adenocarcinoma compared with common tissues, respectively [16]. For CDCA7, the fold changes displayed in Hou’s dataset were 5.997, 9.075, and 7.392 in lung adenocarcinoma, SCC, and large-cell LC, respectively [16]. Okayama’s dataset showed that the fold change was 9.000 in lung adenocarcinoma [17]. Besides, Selamat’s dataset indicated that the fold change was 2.935 in lung adenocarcinoma. For CDCA8, in Hou’s dataset, the fold changes in lung adenocarcinoma, SCC, and large-cell LC were 2.935, 3.743, and 4.913, respectively, compared with normal tissues [16]. Selamat et al.’s dataset showed a fold change of 2.000 in lung adenocarcinoma [19], while Okayama et al.’s dataset presented a fold change of 5.763 in lung adenocarcinoma [17] (Table 1).

3.1. Associations of CDCA mRNA Expression with Clinico-pathological Variables in LC Patients. The GEPIA dataset (http://gepia.cancer-pku.cn/) was performed to compare the mRNA expression of CDCA in LC tissues with that in normal lung tissues. According to our findings, the CDCA1/2/3/4/5/6/7/8 expression levels were upregulated in LC tissues relative to that in noncarcinoma ones (Figures 2 and 3). Additionally, the association of the expression of CDCA genes with the LC stage was analyzed. There were significant differences in CDCA1/2/3/4/5/8 expression (Figure 4).

3.2. Relationship between Elevated CDCA 2/3/4/5/7/8 mRNA Expression and Dismal Prognosis for LC Cases. The crucial CDCA efficiency in LC patient survival was also found. The Kaplan–Meier Plotter approach was utilized to examine the relationship of mRNA expression of CDCA with LC patient survival based on the public datasets. Our results suggested that increased CDCA 1–8 showed a significant relationship with poorer OS and PFS (P < 0.05). Only LC patients with upregulated CDCA3/4/5/8 expression were significantly correlated with the lower PPS (P < 0.05) (Figure 5).

3.3. Genetic Alteration and Correlation

3.3.1. Pathway Enrichment Analyses and Predicted Functions of CDCA Genes among LC Cases. Genes showing coexpression with CDCA genes would be examined using the String and Functional protein association networks. NUF2, CDCA2, CDCA3, CDCA4, CDCA5, CDCA, CDCA7, CDCA8, CDC20, AURKB, CBX2, CDK1, ZWINT, BUB1, NDC80, SPC24, SPC25, BIRC5, and INCENP were discovered in our results (Figure 6). Then, the lists of all the CDCA genes expressed, together with linked genes displaying the highest alteration frequency, were compiled before they were analyzed by the KEGG and GO approaches in Metascape (Figure 7). According to our results, the processes below were subjected to the influence of CDCA gene alteration: R-HAS-2500257: resolution of sister chromatid cohesion; GO:0051301: cell division; CORUM: 1118: Chromosomal passenger complex (CPC, including CDCA8, INCENP, AURKB, and BIRC5); CORUM: 127: NDC80 kinetochore complex; M129: PID PLK1 pathway; and GO: 0007080: mitotic metaphase plate congression.

4. Discussion

CDCA1, one of the Ndc80 complex members, plays a role in regulating mitosis [20], which is coexpressed with the known cell cycle genes [21] (such as cyclin and topoisomerase II). Some studies demonstrate that CDCA1 overexpression is related to the dismal prognosis for patients with colorectal cancer (CRC) [22, 23]. Moreover, the study conducted by Hayama, et al. [21] showed that CDCA1 knockdown using small interfering RNA remarkably suppressed the growth of NSCLC cells. Furthermore, CDCA1 has been used as the vaccination for patients with advanced biliary tract cancer and prostate cancer, and well toleration is achieved in these phase I clinical trials [24, 25]. The current study suggested that The Cancer Genome Atlas and the Oncomine datasets
### Table 1: The significant changes of CDCA expression in transcription level between types of lung cancer and normal lung tissues (Oncomine Database)

| Type of lung cancer versus normal lung tissue | Fold change | P value | t-test | Source and/or reference |
|--------------------------------------------|-------------|---------|--------|-------------------------|
| CDCA1 Smooth muscle cell lung carcinoma     | 1.03E – 5   | 8.546   |        | Garber et al. [15]      |
| Squamous cell lung carcinoma               | 4.40E – 6   | 6.905   |        | Garber et al. [15]      |
| Squamous cell lung carcinoma               | 1.55E – 19  | 18.306  |        | Hou et al. [16]         |
| Lung adenocarcinoma                        | 5.248       | 10.550  |        | Hou et al. [16]         |
| Large-cell lung carcinoma                  | 3.267       | 10.264  |        | Okayama et al. [17]     |
| CDCA2 Smooth muscle cell lung carcinoma     | 2.752       | 10.285  |        | Hou et al. [16]         |
| Squamous cell lung carcinoma               | 4.844       | 12.093  |        | Hou et al. [16]         |
| Large-cell lung carcinoma                  | 5.076       | 6.586   |        | Hou et al. [16]         |
| Lung adenocarcinoma                        | 2.511       | 10.242  |        | Okayama et al. [17]     |
| CDCA3 Smooth muscle cell lung carcinoma     | 4.143       | 8.366   |        | Su et al. [18]          |
| Squamous cell lung carcinoma               | 7.717       | 21.275  |        | Hou et al. [16]         |
| Lung adenocarcinoma                        | 3.551       | 10.511  |        | Hou et al. [16]         |
| Large-cell lung carcinoma                  | 4.431       | 9.131   |        | Hou et al. [16]         |
| Lung adenocarcinoma                        | 2.828       | 10.001  |        | Okayama et al. [17]     |
| CDCA4 Squamous cell lung carcinoma         | 3.354       | 12.179  |        | Hou et al. [16]         |
| Large-cell lung carcinoma                  | 7.928       | 10.744  |        | Garber et al. [15]      |
| Squamous cell lung carcinoma               | 5.343       | 8.173   |        | Garber et al. [15]      |
| Lung adenocarcinoma                        | 3.557       | 7.382   |        | Garber et al. [15]      |
| Squamous cell lung carcinoma               | 5.533       | 21.214  |        | Hou et al. [16]         |
| Large-cell lung carcinoma                  | 6.249       | 8.843   |        | Hou et al. [16]         |
| Lung adenocarcinoma                        | 2.853       | 9.704   |        | Hou et al. [16]         |
| CDCA5 Squamous cell lung carcinoma         | 3.324       | 13.055  |        | Selamat et al. [19]     |
| Large-cell lung carcinoma                  | 6.249       | 8.843   |        | Hou et al. [16]         |
| Lung adenocarcinoma                        | 2.853       | 9.704   |        | Hou et al. [16]         |

**Figure 1:** CDCA expression at transcription level among various cancer types (the ONCOMINE).
revealed higher CDCA1 expression in LC tissues than in noncarcinoma tissues. A high CDCA1 level revealed a significant correlation with worse OS in all LC patients.

CDCA2 acts as the PP1 expression regulator, which inhibits the activation of DNA damage response [8, 9]. Recent research results demonstrate that CDCA2 methylation in HeLa cells promotes cell proliferation and suppresses apoptosis [26]. Additionally, CDCA2 overexpression promotes the proliferation of CRC cells and oral squamous cell carcinoma (OSCC) cells [27, 28]. Furthermore, a study on lung adenocarcinoma suggests that CDCA2 proliferates lung adenocarcinoma cells and predicts the poor prognosis for these patients [29]. Our results indicated that CDCA2 expression level in LC tissues was upregulated relative to that in noncarcinoma tissues. The expression of CDCA2 showed a correlation with the LC stage. High CDCA2 expression level displayed a significant correlation with the improved OS for all LC patients.

CDCA3 controls the G1 phase [30], which acts as one of the prognostic genes for hepatocellular carcinoma (HCC) [31] and is also involved in LC cell proliferation, migration, invasion, and apoptosis [30], as well as CRC cell proliferation [32]. Moreover, it has been reported that CDCA3 expression is related to prognosis for bladder cancer cases [33] and luminal A breast cancer [34]. Current studies show that overexpression of CDCA3 frequently occurs in the process of oral carcinogenesis [35]. It was discovered that CDCA3 expression was upregulated among LC tissues.

Table 1: Continued.

| Type of lung cancer versus normal lung tissue | Fold change | P value | t-test | Source and/or reference |
|---------------------------------------------|-------------|---------|--------|-------------------------|
| Large-cell lung carcinoma                    | 5.371       | 7.64E-7 | 6.902  | Hou et al. [16]          |
| Squamous cell lung carcinoma                 | 3.744       | 5.28E-10| 8.850  | Hou et al. [16]          |
| Lung adenocarcinoma                          | 2.267       | 1.35E-8 | 6.564  | Hou et al. [16]          |
| Squamous cell lung carcinoma                 | 5.997       | 9.23E-17| 6.009  | Hou et al. [16]          |
| Large-cell lung carcinoma                    | 9.075       | 1.91E-19| 15.046 | Hou et al. [16]          |
| Lung adenocarcinoma                          | 7.392       | 6.18E-6 | 5.779  | Hou et al. [16]          |
| Lung adenocarcinoma                          | 6.000       | 1.26E-16| 15.108 | Okayama et al. [17]      |
| CDCA7                                        |             |         |        |                         |
| Lung adenocarcinoma                          | 2.935       | 3.18E-15| 10.818 | Hou et al. [16]          |
| Squamous cell lung carcinoma                 | 3.743       | 3.32E-17| 15.713 | Hou et al. [16]          |
| Large-cell lung carcinoma                    | 4.913       | 1.07E-8 | 9.151  | Hou et al. [16]          |
| Lung adenocarcinoma                          | 2.000       | 4.40E-17| 11.529 | Selamat et al. [19]      |
| Lung adenocarcinoma                          | 5.763       | 5.05E-10| 9.625  | Okayama et al. [17]      |

Figure 2: CDCA expression in LC (GEPIA).
CDCA4 protein expression is found in some human cells, which can be induced when cells enter the G1/S phase in the cell cycle [11]. In a previous study, Hayashi et al. showed that CDCA4 participated in cell proliferation [11]. Moreover, CDCA4 is involved in the triple-negative breast cancer (TNBC) cells [36], and it is shown that RNA interference of CDCA4 markedly increases cell apoptotic rate. In addition, one recent study suggests that CDCA4 enhances human BC cell proliferation and reduces their apoptosis [37]. In this study, we found that CDCA4 expression was increased in human LC tissues relative to that in noncarcinoma tissues, and such expression showed a correlation with the LC stage. The upregulated CDCA4 expression showed a marked correlation with the improved PFS and OS of all LC patients.

A recent study shows that CDCA5 probably serves as a biomarker for the prognosis, treatment, and diagnosis for HCC [38–40]. It also exerts a vital part in the proliferation of HCC cells [41, 42], OSCC [41, 42], and bladder cancer [43]. For digestive system cancer, CDCA5 is found to play crucial
Number at risk
Low 298 238 186 122 34 11 3 1
High 298 207 139 64 26 7 2 0

Number at risk
Low 69 25 11 2 0
High 69 24 8 5 1

Number at risk
Low 572 324 63 15 3
High 573 222 76 31 3

Number at risk
Low 572 325 75 17 2
High 573 221 64 29 4

(a)

Figure 5: Continued.
Figure 5: Continued.
Figure 5: Continued.
roles in the proliferation of gastric cancer cells [44]. Moreover, CDCA5 is also differentially expressed in patients with localized and locally advanced prostate cancer [45]. Regarding LC, the transactivation of CDCA5 and its phosphorylation exert vital parts in the proliferation of LC cells [13]. Wu et al. [46] also indicated that CDCA5 acted as a novel promising target for NSCLC diagnosis and treatment. In this study, the CDCA5 expression level was downregulated in LC tissues compared with that in noncarcinoma counterparts. Besides, such expression showed an association with the LC stage. Obviously, the high CDCA5 expression displayed a significant correlation with the improved OS for all LC patients.

CDCA7 has been recognized as an MYC-target gene [47]. A recent study shows that CDCA7 is overexpressed in lymphoid tumors, and CDCA7 knockdown decreases the growth rate of the lymphoid tumor, without inhibiting the proliferation of normal cells [48]. In this study, the CDCA7 expression level was upregulated in human LC tissues compared with that in noncarcinoma counterparts, and such expression showed no correlation with the LC stage. Obviously, the high CDCA7 expression displayed a remarkable correlation with the improved PFS and OS in all LC patients.

CDCA8 protein has been identified as an integral part of the vertebrate chromosomal passenger complex (cPc) [49]. The expression of CDCA8 is closely associated with tumor progression, N stage, T stage, and grade of bladder cancer [50]. CDCA8 is related to the distant metastasis risk of breast cancer [51, 52]. With regard to renal cancer, CDCA8 has also certain prognostic value [53]. CDCA8 promotes the malignant progression of cutaneous melanoma [54]. Furthermore, CDCA8 also exerts a vital part during lung carcinogenesis [55]. In this study, the CDCA8 expression level was upregulated in LC tissues relative to that in noncarcinoma counterparts, and such expression exerted no correlation with the LC stage. Obviously, the high CDCA8 expression showed a close association with the improved PFS and OS of all LC patients.

Besides, KEGG and GO analyses were also carried out to find the correlations between CDCA genes’ expression and linked genes of the highest alteration frequency and
Figure 6: Gene coexpression among LC cases (STRING).

- R-HSA-2500257: resolution of sister chromatid cohesion
- GO:0051301: cell division
- CORUM:1118: chromosomal passenger complex CPC (INCENP, CDCA8, BIRC5, AURKB)
- CORUM:127: NDC80 kinetochore complex
- M129: PID PLK1 PATHWAY
- G:0007080: mitotic metaphase plate congression

(a)

Figure 7: Continued.
the prognosis for LC. According to our results, attention should be paid to some pathways including R-HAS-2500257: resolution of sister chromatid cohesion; GO: 0051301: cell division; CORUM: 1118: chromosomal passenger complex (CPC, including CDCA8, INCENP, AURKB, and BIRC5); CORUM: 127: NDC80 kinetochore complex; M129: PID PLK1 pathway; and GO: 0007080: mitotic metaphase plate congression. Previous studies show that the Polo-like kinase 1 (PLK1) is highly expressed in LC, which predicts the poor survival in metastatic LC patients [56, 57]. In addition, the PLK1 pathway plays a certain role in the progression of HCC [58], glioma [59], and lung adenocarcinoma [60].

The current research systemically examines the expression of CDCA genes and its prognostic significance in LC, which sheds more light on the complexity and heterogeneity of LC biological properties at the molecular level. Based on our results, CDCA upregulation in LC tissues probably exerts a crucial part during LC oncogenesis. Besides, CDCA upregulation can serve as a potential prognostic marker to improve the survival and prognostic accuracy for LC. Moreover, CDCA genes probably exert their functions in tumorigenesis through the PLK1 pathway.

Data Availability
The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest
All authors declare no conflicts of interest.

Authors’ Contributions
HL and LJL designed the research protocol, analyzed data, and revised the manuscript. CXC and SLC searched and analyzed the data. CXC and LLP wrote the manuscript and participated in analyzing data. QYZ made a lot of work in reviewing and revising the manuscript. All authors read and approved the final manuscript. Chongxiang Chen and Siliang Chen contributed equally to this work.

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