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Expression analysis of cytoskeleton regulator RNA and Cyclin Dependent Kinase Inhibitor 2B genes in Lung cancer

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Abstract.
BACKGROUND: Breast cancer has been found to be associated with deregulation of several non-coding genes and mRNA coding genes.
OBJECTIVE: To assess expressions of CYTOR and CDKN2B in breast cancer and adjacent samples and find their relevance with clinical data.
METHODS: We enumerated expression level of CDKN2B and CYTOR in 43 newly diagnosed breast cancer samples and their adjacent specimens using real-time PCR method Expression data was judged using Wilcoxon matched-pairs signed rank test.
RESULTS: CYTOR level was higher in tumors compared with adjacent tissues. Nevertheless, there was no difference in expression of CDKN2B between these two sets of tissues. ROC curve analysis showed that CYTOR levels can differentiate between tumoral and adjacent tissues with AUC, specificity and sensitivity values of 0.65, 37% and 92% ($P = 0.017$). There was a positive correlation between expression levels of CYTOR and CDKN2B genes in breast cancer tissues ($r = 0.5$ and $P = 0.0008$) as well as adjacent tissues ($r = 0.79$ and $P < 0.0001$). Relative expression level of CDKN2B in normal tissues was associated with clinical stage ($P = 0.014$). Moreover, relative expression level of CDKN2B in tumor tissues was associated with the body weight. There was no other association between expressions of CYTOR and CDKN2B and clinical or pathological variables. CONCLUSIONS: Cumulatively, this study offers evidence for involvement of these genes in the pathoetiology of breast cancer.

Keywords: Breast cancer, CYTOR, CDKN2B

1. Introduction

Breast cancer is the utmost frequently diagnosed malignancy among females. With an expected 2.3 million new cases, it accounts for more than 11% of all diagnosed cancers among both sexes [1]. Moreover, this malignancy is the fifth principal source of cancer death

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among both sexes [1]. The mortality of female breast cancer is significantly higher in developing countries versus developed ones [1]. High mortality and morbidity rates associated with this malignancy necessitate identification of molecular pathways that are altered in this context to find appropriate therapeutic targets and diagnostic markers.

In the current study, we have focused on Cyclin Dependent Kinase Inhibitor 2B (CDKN2B) and a long non-coding RNA (lncRNA), namely cytoskeleton regulator RNA (CYTOR) to find their contribution in the pathoetiology of breast cancer. CDKN2B encodes a tumor suppressor which is named $p15^{INK4b}$. It resides near to the tumor suppressor gene CDKN2A. The genomic area corresponding to these genes is commonly altered or deleted in human cancers [2–5]. The encoded protein by this gene establishes a complex with CDK4 or CDK6, and inhibits induction of these kinases by cyclin D, therefore suppresses cell cycle progression at G1 point [6,7].

CYTOR has been to affect pathogenesis of several kinds of cancers, such as colon cancer [8], stomach cancer [9] and hepatocellular carcinoma [10]. Expression of CYTOR has also been demonstrated to be elevated in tissue and plasma samples of breast cancer patients [11]. Moreover, CYTOR has promoted tamoxifen resistance in breast cancer cells via serving as a sponge for miR125a5p. This lncRNA can up-regulate SRF levels and enhance activity of Hippo and MAPK/ERK pathways [12]. CYTOR also stimulates cell cycle transition via the miR-193a/b-3p/CCND1 route [13]. Although these genes have important functions in the carcinogenesis, they are under-investigated in terms of sample expression [14].

According to the aforementioned evidence, we conducted the current expression assay to evaluate expression of CYTOR and CDKN2B in breast cancer samples in relation with clinical and pathological features.

2. Materials and methods

2.1. Patients

Expressions of CYTOR and CDKN2B were quantified in 43 pairs of breast cancer samples and adjacent non-tumoral samples. Cases included in the current study had undergone surgery in Farmanieh and Sina centers, Tehran, Iran. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Science (IR.SBMU.MSP.REC.1399.287). All patients signed informed consent form. Breast samples were gathered during surgery prior to chemotherapy or radiotherapy. Patients' medical records were also assessed to find relevant data.

Table 1
Nucleotide sequences of primers

Gene	Primer sequence		Primer length	Product size
CDKN2B	F	CCCAACTCCACCAGATAGCA	20	186
	R	CTCCACTCCACCACCTCAT	19	
CYTOR	F	AAAATCACGACTCAGCCCCC	20	183
	R	AATGGGAAACCGACCAGACC	20	
B2M	F	AGATGAGTATGCCTGCCGTG	20	105
	R	GCGGCATCTTCAAACCTCCA	20	

2.2. Experiments

RNA was obtained from all gathered tissues using the RiboEx kit (GeneAll, South Korea). After that, around 80 ng of RNA was subjected to cDNA production using the ExcelRT^{TM} Reverse Transcription Kit II (SMOBIO, Taiwan, China). Expression of CYTOR and CDKN2B was measured in all specimens in the ABI step one plus PCR machine. Expressions of CYTOR and CDKN2B were normalized to B2M. Primers were designed by authors. Reactions were formulated using RealQ Plus 2x PCR Master Mix (Ampliqon, Denmark). Details about primers are shown in Table 1. A 2-step thermo-cycling protocol (merging annealing and extension steps) was applied.

2.3. Statistical analysis

SPSS v.22.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Graphs were depicted using GraphPad Prism version 9.0 (La Jolla, California, USA). Expressions of CYTOR and CDKN2B were evaluated in tumor and adjacent tissues using the Wilcoxon matched-pairs signed rank test. The correlation between expressions of these two genes was measured using Spearman correlation coefficient. Association between expression of genes and clinical/pathological data was calculated using Mann-Whitney and one-way ANOVA tests (Kruskal-Wallis). In addition, the receiver operating characteristic (ROC) curve was plotted by the GraphPad Prism v.9 software. P value < 0.05 was considered as significant.

3. Results

3.1. General information

General information of patients is summarized in Ta-

Table 2
Clinicopathological data of 43 patients with breast cancer

Case no	Abortion	Stage	Grade	Tumor size (cm)	Mitotic rate	First pregnancy age (year)	Breast feeding duration (month)	OCP	HRT	Obesity	Lymph node	ER (Estrogen receptor)	PR (Progester-one receptor)	HER-2/neu receptor	Ki67
1	−	3	2	2	1	17	28	+	−	ND	ND	+	−	−	+
2	−	4	2	3	2	17	32	−	−	Normal	+	+	+	−	ND
3	−	3	3	ND	2	22	33	+	−	ND	+	−	−	−	ND
4	−	1	ND	ND	ND	15	12	+	−	Normal	+	−	−	+	+
5	−	ND	ND	ND	ND	18	72	+	−	Underweight	ND	−	−	−	+
6	−	2	2	2.5	1	24	29	−	−	Overweight	ND	+	+	−	+
7	−	1	1	1.5	1	24	18	−	−	Normal	ND	+	+	−	−
8	−	1		1.5	ND	22	12	−	−	Overweight	ND	+	+	+ + +	+
9	+	2	3	2.5	2	34	4	+	−	Normal	ND	+	+	+ + +	+
10	−	3	1	3	ND	24	48	−	−	Normal	ND	+	+	−	+
11	−	2	ND	7	ND	24	73	−	−	Normal	ND	+	+	++	+
12	−	0	ND	2	ND	15	168	−	−	Normal	+	+	−	+ + +	+
13	−	1	2	ND	ND	23	35	+	−	Overweight	−	−	−	+	+
14	+	1	2	2	1	20	12	+	−	Normal	+	+	+	−	+
15	−	1	1	0.5	2	15	84	+	−	Overweight	−	+	+	+ + +	+
16	−	2	1	2.5	1	ND	0	+	+	Overweight	+	+	+	+	−
17	−	1	ND	2	ND	17	127	+	−	Normal	+	+	+	−	+
18	−	1	2	1.5	2	ND	0	−	+	Overweight	−	+	+	+	+
19	−	1	2	1.8	2	28	0	+	−	Overweight	+	+	−	++	+
20	+	3	3	1	3	37	25	+	−	Normal	+	−	ND	+ + +	ND
21	−	2	1	2	1	27	32	+	−	Normal	−	+	+	+	+
22	−	4	3	2	3	0	0	−	+	Overweight	ND	+	+	++	+
23	−	3	2	2	1	18	192	−	−	Overweight	−	+	+	−	+
24	−	3	3	1	2	28	3	−	−	Overweight	ND	+	+	+ + +	+
25	−	2	2	2	2	18	32	−	−	Overweight	ND	+	+	−	+
26	−	2	3	2	2	19	96	+	−	Underweight	−	−	+	−	+
27	−	3	1	1.5	1	24	48	−	−	Normal	−	+	+	+ + +	+
28	−	2	1	3	ND	14	240	−	−	Overweight	+	+	+	++	+
29	−	3	2	1.5	1	21	72	+	−	Normal	−	−	−	−	+
30	−	1	2	2	2	27		+	−	Overweight	+	+	+	+ + +	+
31	−	3	2	2	1	25	36	+	−	Overweight	−	+	+	+	−
32	+	3	3	2.8	ND	ND	0	+	−	Normal	−	+	+	+	+
33	++	4	3	2	ND	18	68	+	−	Normal	−	+	+	++	+
34	−	1	ND	1.5	ND	0	ND	−	−	Normal	+	+	+	−	+
35	++	3	2	2	2	22	31	+	−	Normal	ND	+	+	+	+
36	−	3	3	3	2	0	0	−	−	Normal	+	+	+	++	+
37	−	2	3	4	3	17	38	+	−	Overweight	ND	+	+	++	+
38	+	4	3	2	2	19	76	+	+	Overweight	ND	+	+	+	+
39	−	2	3	3	1	18	36	−	−	Normal	−	+	+	++	+
40	−	1	1	1	2	19	48	−	−	Normal	+	+	+	++	ND
41	−	1	1	0.5	ND	15	84	+	−	Overweight	−	+	+	+ + +	+
42	−	4	3	5	2	27	25	−	−	Normal	−	+	+	−	+
43	−	3	3	1	3	23	ND	−	+	Overweight	+	+	+	+	+

OCP = Oral contraceptives; HRT = Hormone replacement therapy; ND = Not determined.

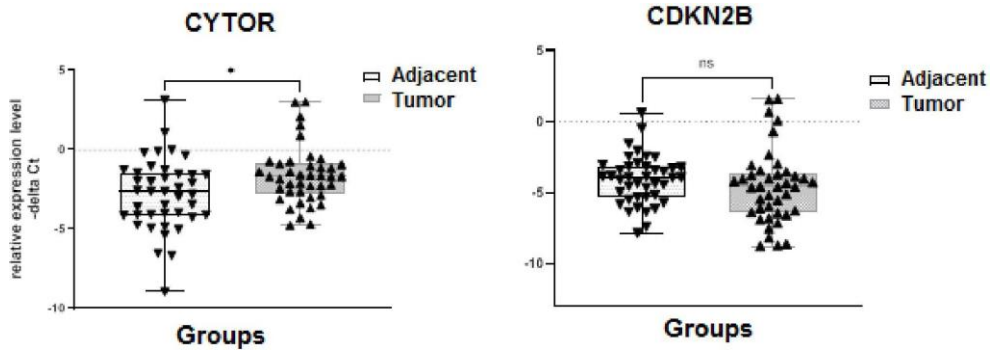

Fig. 1. Levels of CYTOR and CDKN2B genes in breast cancer tissues versus adjacent tissues. Asterisk indicates significant difference between groups (P 6 0.05).

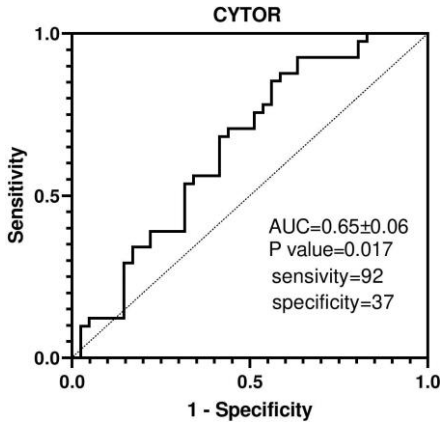

Fig. 2. Receiver operating characteristic (ROC) curve of CYTOR expression for separation of tumor samples from adjacent tissues. AUC signifies area under the ROC curve.

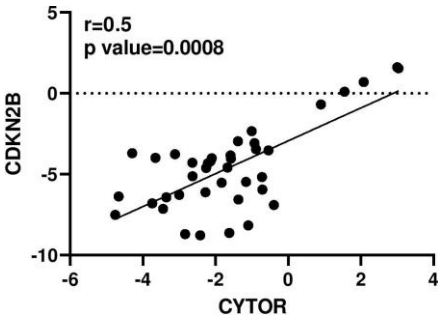

Fig. 3. Correlations between expressions of CYTOR and CDKN2B genes in breast tumor samples. There was a significant positive correlation between CYTOR and CDKN2B genes expression ($r = 0.5$ & $P = 0.008$).

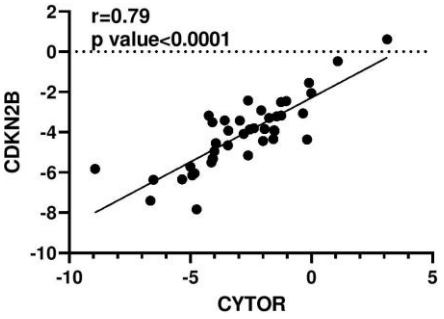

Fig. 4. Correlations between expressions of CYTOR and CDKN2B genes in adjacent tumor tissue samples. There was a positive correlation between CYTOR and CDKN2B genes expression ($r = 0.79$ & $P < 0.0001$).

ble 2. Patients had stage 0 (1 case), stage 1 (13 cases), stage 2 (10 cases), stage 3 (12 cases) and stage 4 (5 cases) breast cancer. They were also classified according to the presence of ER, PR and HER-2/neu markers in the breast tumors.

3.2. Expression assays

Expression of CYTOR was significantly higher in tumor tissues compared with adjacent tissues. However, there was no significant difference in expression of CDKN2B between these two sets of tissues (Fig. 1).

ROC curves showed that CYTOR levels can differentiate between tumoral and adjacent tissues with AUC, specificity and sensitivity values of 0.65, 37% and 92% ($P = 0.017$) (Fig. 2).

There was a statistically significant positive correlation between expression levels of CYTOR and CDKN2B genes in breast cancer tissues ($r = 0.5$ & $P = 0.0008$) as well as adjacent tissues ($r = 0.79$ & $P < 0.0001$) (Figs 3 and 4, respectively).

We detected no significant correlation between relative expressions of aforementioned genes in tumors and their level in adjacent non-tumoral specimens (Fig. 5).

We detected positive associations between histological grade and mitotic rate ($\chi^2 = 13.3$, $P = 0.038$)

Table 3
The association between gene expression and clinicopathological features of breast cancer patients (Neg: negative, Pos: positive)

Parameters	Subclasses	Numbers (%)	Expression of CYTOR in tumor tissue (mean ± SD)	P	Expression of CDKN2B in tumor tissue (mean ± SD)	P	Expression of CYTOR in normal tissue (mean ± SD)	P	Expression of CDKN2B in normal tissue (mean ± SD)	P
Clinical stage	I	14 (34.14)	−1.73 ± 0.51	0.6	−4.56 ± 0.66	0.46	−1.54 ± 0.5	0.056	−2.91 ± 0.4	0.014*
	II	9 (21.95)	−1.93 ± 0.48		−5.38 ± 0.88		−3.44 ± 0.87		−4.56 ± 0.34	
	III	13 (31.7)	−2.01 ± 0.42		−5.19 ± 0.64		−3.69 ± 0.36		−4.85 ± 0.33	
	IV	5 (12.19)	−0.78 ± 0.82		−3.25 ± 1.02		−3.26 ± 1.37		−4.51 ± 0.99	
Histological grade	Low	8 (19.04)	−2.31 ± 0.45	0.53	−6.13 ± 0.5	0.067	−2.46 ± 1.05	0.60	−3.88 ± 0.71	0.15
	Moderate	12 (28.5)	−1.34 ± 0.54		−4.08 ± 0.75		−2.56 ± 0.38		−3.55 ± 0.32	
	High	14 (33.3)	−1.41 ± 0.43		−4.06 ± 0.63		−3.22 ± 0.54		−4.58 ± 0.35	
Tumor size (cm)	≥ 2 cm	24 (57.14)	−1.52 ± 0.36	0.69	−4.35 ± 0.5	0.40	−2.69 ± 0.39	0.69	−3.87 ± 0.33	0.45
	< 2 cm	12 (28.57)	−1.85 ± 0.42		−5.2 ± 0.7		−2.96 ± 0.78		−4.32 ± 0.34	
Mitotic rate	Slow	10 (23.8)	−2.22 ± 0.41	0.68	−4.6 ± 0.48	0.98	−3.02 ± 0.55	0.68	−4.54 ± 0.48	0.68
	Moderate	15 (35.7)	−1.36 ± 0.56		−4.2 ± 0.77		−3.18 ± 0.45		−4.24 ± 0.32	
	Quick	4 (9.5)	−1.96 ± 0.85		−4.65 ± 0.95		−2.12 ± 1.42		−4 ± 1.15	
Oral contraceptives	No	20 (47.6)	−1.51 ± 0.48	0.58	−4.32 ± 0.6	0.61	−3.18 ± 0.61	0.65	−4.37 ± 0.39	0.12
	Yes	21 (51.2)	−1.69 ± 0.35		−4.81 ± 0.57		−2.43 ± 0.4		−3.68 ± 0.33	
Body weight	Underweight	2 (4.8)	−1.18 ± 0.18	0.14	−2.64 ± 0.31	0.05*	−3.59 ± 0.64	0.55	−3.29 ± 0.12	0.59
	Normal	21 (51.2)	−2.05 ± 0.37		−5.2 ± 0.5		−2.47 ± 0.44		−4 ± 0.33	
	Overweight	17 (41.4)	−1.05 ± 0.47		−3.99 ± 0.72		−3.07 ± 0.64		−4.06 ± 0.45	
ER (Estrogen receptor)	Neg	7 (17)	−2.28 ± 0.43	0.36	−5.43 ± 0.77	0.48	−2.48 ± 0.98	0.65	−3.31 ± 0.78	0.32
	Pos	34 (83)	−1.47 ± 0.33		−4.41 ± 0.47		−2.83 ± 0.38		−4.14 ± 0.26	
PR (Progesterone receptor)	Neg	8 (19.5)	−1.49 ± 0.68	0.82	−4.36 ± 0.99	0.75	−2.17 ± 0.78	0.75	−3.26 ± 0.62	0.21
	Pos	32 (80.5)	−1.64 ± 0.32		−4.65 ± 0.45		−2.94 ± 0.39		−4.2 ± 0.27	
HER-2/neu receptor	Neg	15 (36.5)	−2 ± 0.31	0.56	−5.13 ± 0.39	0.37	−2.95 ± 0.47	0.7	−3.88 ± 0.36	0.49
	Pos	26 (63.4)	−1.4 ± 0.41		−4.29 ± 0.59		−2.67 ± 0.48		−4.05 ± 0.34	

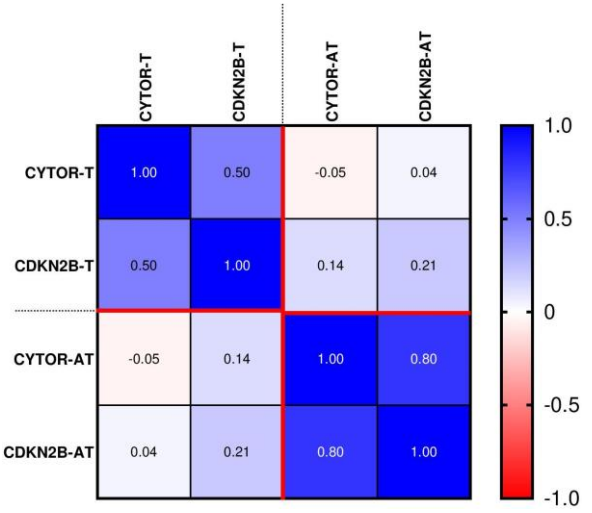

Fig. 5. Spearman r correlation between levels of CYTOR and CDKN2B genes in tumors, adjacent non-tumoral samples and between expressions of genes in tumors versus non-tumoral samples. There was no significant correlation between levels of CYTOR and CDKN2B genes in tumors and their expression in adjacent non-tumoral specimens. T; Tumor, AT; adjacent tissues.

and between clinical stage and tumor size ($\chi^2 = 12.16$, $P = 0.007$). Also, we reported a positive association between clinical stage and histological grade ($\chi^2 = 14.82$, $P = 0.02$). Besides, there was a positive association between estrogen receptor and progesterone receptor ($\chi^2 = 11.83$, $P = 0.01$).

Relative expression level of CDKN2B in normal tissues was associated with clinical stage ($P = 0.014$). Moreover, relative expression level of CDKN2B in tumor tissues was associated with the body weight. There was no other significant association between expression levels of CYTOR and CDKN2B and clinicopathological features (Table 3).

4. Discussion

Several transcripts have been shown to be dysregulated during the course of breast carcinogenesis. Expression profiles have revealed intertumor and intratumor heterogeneity in this type of cancer [15]. These dysregulated transcripts represent potential therapeutic target for this type of common malignancy as well as biomarkers for its diagnostic purposes. With the aim of finding new markers for breast cancer, we evaluated expression of two transcripts in breast cancer. Expression of CYTOR was elevated in tumor tissues compared with adjacent tissues. Nevertheless, there was no significant difference in expression of CDKN2B between these two sets of tissues.

CYTOR has been found to drive carcinogenesis in different tissues. Being up-regulated in colon cancer tissues, it confers resistance to oxaliplatin-associated apoptosis [16]. In gastric cancer, CYTOR can affect expression of epithelial-mesenchymal transition (EMT) markers [9]. Another study in colon cancer has shown the impact of this lncRNA in enhancement of EMT and metastasis is related with its interaction with β-catenin [17] In nasopharyngeal carcinoma, CYTOR can affect tumor growth, migration, and invasion through modulation of miR-24-3p/GAD1 axis [18]. In breast cancer, CYTOR can promote tamoxifen resistance via functioning as a sponge for miR125a5p. This lncRNA can up-regulate SRF levels and enhance activity of Hippo and MAPK/ERK pathways [12]. Thus, this lncRNA has interactions with several cancer-related pathways through them promoting carcinogenesis.

ROC curve analysis showed that CYTOR levels can differentiate between tumoral and adjacent tissues with AUC, specificity and sensitivity values of 0.65, 37% and 92%. Moradi et al. have shown that expression of CYTOR can distinguish breast cancer patients from healthy control subjects with AUC value of 0.907 which is higher than CA 15-3 [11].

There was a statistically significant positive correlation between expression levels of CYTOR and CDKN2B genes in breast cancer tissues as well as adjacent tissues, implying the presence of an interaction network between them or a possible comparable regulatory mechanism for these genes However, further functional studies are needed for evaluation of this hypothesis.

There were also positive associations between histological grade and mitotic rate as well as between clinical stage and tumor size. Likewise, there was a positive association between clinical stage and histological grade. These observations confirm the validity of obtained clinicopathological data.

Relative expression level of CDKN2B in normal tissues was associated with clinical stage. Moreover, relative expression level of CDKN2B in tumor tissues was associated with the body weight. The underlying mechanism for these observations should be clarified in future studies. There was no other noteworthy association between expression levels of CYTOR and CDKN2B and clinicopathological parameters. Lack of such associations can be a result of small sample size of the study.

Taken together, we provided evidence for participation of these genes in the pathoetiology of breast can-

cer. Future functional studies and expression assays in larger sample sizes of patients are needed for confirmation of these results and suggestion of CYTOR as a potential marker for breast cancer.

Ethics approval and consent to participant

All procedures were in accordance with the ethical standards of the institutional research committee. Informed consent forms were obtained from all study participants. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences. All methods were performed in accordance with the relevant guidelines and regulations.

Consent of publication

Not applicable.

Availability of data and materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare they have no conflict of interest.

Funding

Not applicable.

Authors contribution

SGF wrote the draft and revised it. AR and MM designed and supervised the study. SE analyzed the data. BMH, AA and MG performed the experiment and data collection. All the authors read and approved the submitted version.

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